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32. Deutscher Krebskongress

Krebsmedizin heute: präventiv, personalisiert, präzise und partizipativ

ABSTRACTS

Berlin, 24.–27. Februar 2016

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Abstracts

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Breast Cancer

ID 0038

Osteopontin as a potential target in treatment of breast cancer skeletal metastasis

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Bone metastasis is an unfavorable event occurring in up to 70% of patients with advanced breast cancer and renders the disease virtually incurable. Therefore, it is of major importance to elucidate and validate the driver genes of breast cancer osteolytic metastasis.
Here, we investigated the role and function of osteopontin by combining the tetracycline-controlled transcription activation system ("Tet-off system") and RNA interference. We generated two MDA-MB-231 subclones, in which the tetracycline-dependent transactivator tTA in absence of doxycycline stimulates the simultaneous expression of the red fluorescent protein mCherry, firefly luciferase and a highly efficient and specific miRNA targeting OPN mRNA.
The expression of this miRNA resulted in OPN silencing, as characterized by 62–96% and 85–98% inhibition of mRNA expression after 3 and 6 days, respectively. The respective protein levels were decreased only after 6 days by 40–50%. The miRNA mediated OPN knockdown for 6 or 9 days led to a reduction in colony formation by 50–60%, but it had low to no influence on cellular proliferation after 3 and 6 days in vitro. The antimetastatic effect of conditional OPN knockdown was tested in a nude rat model for site-specific osteolytic lesions. Remarkably, complete remissions were observed within 5 weeks in 5 of 5 rats. In addition, following conditional OPN knockdown, a concomitant inhibition of genes correlated with angiogenesis (*RRM2)* or adhesion of tumor cells (PVRL3) was detected.
In conclusion, the conditional OPN knockdown led to reduced antimetastatic properties of breast cancer cells in vitro and in vivo and thus OPN can be considered as a target for treatment of breast cancer patients with skeletal metastasis.

ID 0101

Generation of human tumor specific antibodies in humanized tumor mice (HTM)

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Breast cancer is a highly inter- and intra-individual heterogeneous disease that comprises a number of subtypes for which no therapeutic antibodies are available yet. Hence we utilized the Humanized Tumor Mouse (HTM) model and evaluated its capability to generate tumor cell specific human antibodies directed against BC cells.
HTM were generated by the co-transplantation of human hematopoietic stem cells and human Her2-positive breast cancer cells into neonatal NSG mice. These mice develop a human immune system in combination with human breast cancer growth. Due to the concurrent transplantation the transfer of MHC-mismatched tumor cells causes an activation of a variety of immune ($CD4^+$, NK, myeloid) cells without evidence for rejection. Histological staining of the spleen of HTM revealed co-localization of human antigen-presenting cells together with human T- and B-cells enabling an MHC-dependent interaction and thereby the generation of T-cell dependent antibody production by B-cells.
Overall, HTM were able to generate human tumor-specific antibodies which dose dependently inhibited tumor outgrowth. Western blot analyses revealed that the tumor-specific antibodies generated in HTM recognized antigens which were different from Her2.
In conclusion, HTM offer a novel approach to generate complete human monoclonal antibodies that do not require further genetic manipulation (e. g. "humanization"). This might be of particular interest for cancer subtypes with no currently available antibody therapy.

ID 0137

Adjuvant endocrine therapy in pre- versus postmenopausal patients with steroid hormone receptor positive breast cancer – results from a large population-based cohort of a cancer registry

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Purpose: The present study evaluated the quality of steroid hormone receptor (HR) determination and adjuvant endocrine therapy (ET) in a large cohort of breast cancer patients.
Methods: Data from the population-based Clinical Cancer Registry Regensburg (Germany) were analyzed. Female patients with primary, non-metastatic invasive breast cancer diagnosed between 2000 and 2012 (n = 7,421) were included. HR status was available in 97.4% (n = 7,229) of the patients.
Results: Since 2009 almost a complete rate of 99.6% of analyzed HR-status was achieved. 85.8% of the patients (n = 6,199) were HR-positive, 14.2% (n = 1,030) were HR-negative. Overall, 85.3% (n = 5,285) of HR-positive patients received ET either alone or in combination with chemotherapy (CHT) and/or trastuzumab. The majority of premenopausal patients (n = 716, 52.3%) received CHT plus ET. In postmenopausal patients, the most frequent systemic therapy was ET alone (n = 2,670, 55.3%). Best overall survival (OS) was found in HER2/HR-positive patients receiving CHT plus ET plus trastuzumab (7-year OS of 97.2% in premenopausal vs. 86.9% in postmenopausal patients). Premenopausal patients had a reduced benefit from additional CHT than postmenopausal patients. Premenopausal patients receiving only ET had a 7-year OS rate of 95.3% compared to 92.7% of patients receiving CHT plus ET. Postmenopausal patients treated with CHT plus ET had a 7-year OS rate of 84.0% compared to those patients receiving only ET with a 7-year OS rate of 81.7%.
Conclusions: Analysis of HR in patients with early breast cancer achieved a very high quality in recent years. The vast majority of HR-positive patients received guideline adherent ET that significantly improved OS.

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ID 0143

Establishment and characterization of a 3D mamma carcinoma test system on a decellularized scaffold

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Breast cancer is the most frequent cancer among women and the second most common cause of cancer death in developed countries. As chemotherapy is often ineffective and causes severe side effects, there is an urgent need for tumor model systems that allow for reliable predictions in drug sensitivity. In this study, we established a 3D mamma carcinoma test system on the basis of a decellularized scaffold derived from porcine small intestine. Two different breast cancer cell lines (MCF-7, MDA-MB-231) were separately cultured on this scaffold under static conditions in a cell crown or under dynamic conditions in a bioreactor for 14 days with or without treatment and afterwards analyzed by immunohistochemistry.
The breast cancer cell lines MDA-MB-231 and MCF-7 are reported to be highly invasive and non-invasive, respectively. By using these cell lines, different stages of tumor progression could be modeled in order to investigate their sensitivity towards different therapeutic strategies. Our 3D models showed *in vivo*-like proliferation rates and the constant medium flow in the bioreactor system allowed the generation of models with higher cell densities and a more tumor-like morphology. With the help of our test system, different therapeutic approaches and their influence on signaling pathways can be investigated. In the future, data from this model will be integrated into a breast cancer-tailored *in silico* Boolean model, a tool for prediction of drug sensitivity according to mutational background.
Our models aim to contribute to the development of personalized treatment based on signaling analysis in different mutational backgrounds and tumor stages, which will improve the selection of patients for the most suitable therapy.

ID 0163

Final analysis of WSG-ADAPT HER2+/HR+ phase-II-trial – efficacy, safety and predictive markers for 12-weeks of neoadjuvant T-DM1 with or without endocrine therapy versus Trastuzumab+endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer

M. Braun[1], O. Gluz[2], U. Nitz[2], M. Christgen[3], S. Kümmel[4], C. Schumacher[5], J. Potenberg[6], S. Krämer[7], A. Kleine-Tebbe[8], D. Augustin[9], B. Aktas[10], H. Forstbauer[11], J. Tio[12], C. Liedtke[13], R. E. Kates[14], R. Würstlein[15], H.-H. Kreipe[3], N. Harbeck[15]

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Background: In HER2+ early breast cancer (eBC) pCR rates after standard neoadjuvant chemo+anti-HER2 therapy differ according to hormone-receptor (HR) status. Molecular analysis reveals HER2+/HR+ BC as a distinct entity within HER2+ BC. The ADAPT HER2+/HR+ phase II trial aims to identify early responders to endocrine+anti-HER2 therapy.
Methods: The trial completed recruitment in 01/2015 (n = 376). Patients were randomized to 12 weeks of neoadjuvant therapy: A: T-DM1 (3.6 mg/kg q3w) vs. B: T-DM1 with endocrine therapy (ET) (pre-: tamoxifen; postmenopausal: aromatase inhibitor) vs C: trastuzumab q3w + ET. Trial tests pCR (ypN0/ypT0/is) after T-DM1 or T-DM1+ET compared to T+ET. Biomarkers are measured at baseline and after 3 weeks.
Results: Pre-planned interim analysis (n = 130) aimed to identify an early-response biomarker and to validate trial assumptions. Median age was 49 years; 55% were premenopausal; 51% cT2; 27% cN1; 75% had G3. Median baseline Ki67 was 30%. In all arms, >95% received all 4 therapy cycles. Only 16 SAEs were reported in 13 pts (A: 7; B: 6; C: 3). Overall pCR rate was 30.8%: T-DM1: 40.5%, T-DM1+ET: 45.8%, T+ET: 6.7%. The difference between either T-DM1 arm vs. T + ET was significant (p
Conclusions: The WSG-ADAPT HER2+/HR+ phase II trial is one of the few randomized trials performed in this distinct subtype. Interim analysis demonstrated for the first time clinically meaningful pCR rates (>40%) after short therapy (12 weeks) of T-DM1 ± ET without systemic chemotherapy in HER2+/HR+ eBC. Final efficacy and safety data will be presented at the meeting together with results of the correlative science program.

ID 0258

Effective humoral immune responses improve overall survival in a comprehensive cohort of breast cancer patients

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Recent evidence for the role of B cells in breast cancer implicate a two faced mechanism of action. This includes a tumor-promoting role mediated by immune suppression and antibody secretion. However, responses to tumor-associated antigens have been thought to be the main source of B cell-mediated antitumor immunity. The present study aims to analyze level and subclasses of anti-MUC1 antibodies in regard to tumor biologic parameters, clinical characteristics and overall survival.
In 288 primary, non-metastatic breast cancer patients, pretreatment serum levels of anti-MUC1 IgG and its subclasses G1-4 as well as IgM were analyzed via ELISA. With respect to overall survival, tumor biologic parameters as hormone receptor status, Her2neu, Ki-67 expression and tumor grading have been correlated as well as clinical characteristics as nodal involvement, tumor stage and patients' age at the time of diagnosis. Median follow-up time was 148 months.
A significant increase in IgG antibody titers was correlated highly significantly with an improved overall survival. In multivariate analysis, total IgG proved to be an independent prognostic marker for overall survival (p = 0.002). IgG subclass analysis did not reveal any correlation of IgG1, IgG3 and IgG4 levels with overall survival, while increased IgG2 values, although statistically not significant, tended to correlate with prolonged patient survival. MUC1-specific IgM antibodies were shown not to be predictive of overall survival.
Considering the growing body of evidence suggesting a tumor promoting role of B lymphocytes the present results confirm the positive impact of tumor-specific IgG on prolonged overall survival in breast cancer patients. Further, MUC1-antibody testing might be a useful tool to identify high-risk patients who may need adjuvant therapy and potentially might benefit from MUC1-directed immunotherapy.

ID 0263

Pregnancy as a mechanism of natural immunization against breast cancer tumor-associated antigens

C. Domschke[1], A.-L. Krause[2], S. Stefanovic[1], Y. Ge[2], M. Wallwiener[1], S. Schott[1], C. Sohn[1], A. Schneeweiss[1], P. Beckhove[2], F. Schuetz[1]

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Introduction: Parity has a protective effect against breast cancer, but the cause remains unclear. T cells recognize transformed cells that express tumor-associated antigens (TAA) and subsequently destroy them. Since TAA levels are high in pregnant women, we asked if TAA-reactive T cells are simultaneously induced and investigated the impact of TAA-specific regulatory T cells (Treg) on anti-tumor immunity.
Methods: We collected peripheral blood from 59 healthy females and 64 women with ductal carcinoma in situ or invasive breast cancer and performed IFN-γ ELISpot analyses with TAAs. The impact of TAA-specific Treg cells was assessed before and after depletion of CD4+CD25+ T cells, followed by a Treg cell specificity assay. Results compared the reproductive history of the donors.
Results: Preexisting T cell responses against tumor-associated antigens were detected in 85% of healthy parous females, but in none of the nulliparous controls. Further analysis revealed an induction of anti-tumor immunity during the first trimenon of pregnancy. We also observed an increase of TAA-specific Treg cells during lactation in that these cells were identified in two thirds of healthy mothers. Eventually, the control of anti-tumor T cell immunity by Treg cells advanced in women with breast cancer.
Conclusions: Our findings demonstrate the induction of a long-lasting anti-tumor T cell memory during pregnancy. The potentially protective immunity is limited by TAA-specific regulatory T cells, which not only control tumor immunity, but also the autoimmune reactions in healthy tissues. A prospective study will reveal if women with preexisting TAA-specific immune responses have a reduced breast cancer risk and if a preventive vaccine is applicable.

ID 0272

Validation of a next generation sequencing (NGS)-based workflow for mutation and CNV detection in routine genetic testing using an HBOC multi-gene panel

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Reduced turnaround times and costs have led to rapid NGS technology adoption in diagnostics, enabling risk gene analysis in familial breast/ovarian cancer patients beyond *BRCA1+2*. As part of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC), we currently validate a 34 gene panel (TruRisk™) for implementation in routine genetic testing.
Sequencing libraries were generated via a transposase-based in solution capture enrichment technique (SureSelect QXT; Agilent) and analysed on the MiSeq (v2, 2×150 bps). Bioinformatic analysis for smaller variants and larger duplications/deletions (CNVs) was done via a commercial provider (Sophia Genetics, Genf).
For validation we analyze 96 DNA samples precharacterized by Sanger sequencing. So far, half of the samples have been sequenced. We observed a median of 32 million total reads per run with 38% reads on target. The median sequencing depth was 500× with 99,9% of the target regions covered at least 50×. Regarding variant detection we initially focussed on the diagnostic relevant ten panel core genes. We detected all 238 known variants, including eight CNVs (*CHK2, BRCA1, BRCA2, RAD51C*) and a deletion in *CHK2* problematic due to pseudogenes. We found additional unknown variants listed in dbSNP and/or manually confirmed in IGV, therefore not considered as false positives. One sample (2,1%) was rejected during CNV analysis. No regions were affected by pseudogenes or high homology. From current data an estimate of one million reads per sample is needed for core gene coverage with a minimum of at least 50×.
Current data suggest an accurate detection of core gene germline alterations using TruRisk™ combined with Agilent QXT technology. Complete validation data will be presented.

ID 0291

Enrichment, detection and isolation of EpCAMneg circulating tumor cells of breast cancer combining Parsortix© system and CellCelector™micromanipulator

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CTCs are epithelial cells derived from solid tumors and circulating in their peripheral blood stream with similar characteristics as the primary tumor and therefore considered informative "liquid biopsies". Main challenges in investigating these cells as predictive biomarkers are their low numbers in the blood and their heterogeneity.
Most of CTC enrichment techniques are based on EpCAM protein expression, excluding those CTCs which underwent epithelial-mesenchymal transition.
In this project we established a workflow to enrich, detect and isolate EpCAM- CTCs combining potientials of both the Parsortix© system and the CellCelector™ micromanipulator for further molecular characterizations.
A cohort of 10 metastatic breast cancer blood samples depleted for EpCAM+ CTCs was processed through the semi-automated Parsortix© system in order to isolate EpCAM- CTCs based on their size. Captured cells were stained *in situ* for cytokeratin and CD45 to identify epithelial cells and were then harvested from the system.
EpCAM- CTCs were detected by immune fluorescence microscopy and further micromanipulated as single cells into PCR tubes (CellCelector™). Six out of 10 samples were found positive for EpCAM+ CTCs (142 cells) and 5 positive for EpCAM- CTCs as well (99 cells). Sixtyone out of 99 EpCAM- cells and comparable numbers of EpCAM+ cells and leucocytes were successfully isolated. Whole genome amplification was performed to prove EpCAM- CTCs malignant origin in comparison with EpCAM+ CTCs and co-isolated leucocytes.
Our workflow allows to successfully isolate EpCAM- cells from EpCAM depleted samples and to further process them for further molecular characterization.

ID 0348

Performance of prediction programs on clearly pathogenic or neutral BRCA1/2 missense variants from GC-HBOC

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One main challenge for centers performing genetic testing in families at risk for breast and ovarian cancer is the classification of variants of unknown significance (VUS). Often VUS are extremely rare and further information for their classification is missing. Different prediction tools are widely used to forecast their functional consequences. We tested the performance of three prediction tools (SIFT, Polyphen2 and MutationTaster) using a subset of 670 *BRCA1/2* missense variants from the GC-HBOC database and compared the results with the evidence based classifications given by expert committees.
Analysis of the 119 definitely neutral variants revealed 35 variants that were predicted to be damaging by at least 2 of the chosen programs. 13 of those 35 variants were predicted to be pathogenic by all 3 programs a classification only depending on those prediction programs would lead to a false positive result in 254 families. Classification of the definitely pathogenic variants revealed 10 variants which were classified as benign by at

least one of the prediction programs. An automated classification dependent on consistent prediction of all three programs would lead to a false negative result for 327 families tested in the GC-HBOC since this subset of variants also includes the Cys61Gly founder mutation which is found in 262 families and classified neutral by the Polyphen2 algorithm.
In total the classification of 670 variants based solely on the prediction programs would lead to false positive or negative results for 581 GC-HBOC families (3.3%) in the database at the time of analysis. Classification of VUS should be carried out in an evidence based manner which takes functional, pathology, co-segregation and co-occurrence data into account.

ID 0357

Timing of (neo)adjuvant systemic therapy for breast cancer in Germany in the years 2004 to 2014 – results of surveys carried out by "Organkommission Mamma der AGO"

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Purpose: With the studies by AGO Organkommission Mamma 2004–2014 we analyzed timing of adjuvant and neoadjuvant chemotherapy (AC resp. NAC) in Germany for early breast cancer (eBC).
Method: All 1959 hospitals and medical practices for treatment of breast cancer in Germany were contacted.
Results: Data of 3962 patients eBC are valid for evaluation. 3324 patients received AC and 638 Patients NAC. For the selection of AC or NAC the parameters examined were tumor size, nodal status and grading, as well as age at first diagnosis (age < 60 vs. ≥ 60 years).
AC is applied with increasing age (≥ 60 years 28% in 2004–40% in 2014), as well as increasingly with nodal negativity (35% in 2004–50% in 2014). The share of GIII carcinoma in selection of chemotherapy is stable. Pats. < 60 years with nodal positive status received in 93% an anthracycline+taxane regime, pats. ≥ 60 in 82%. Pats. < 60 years with nodal negative status in 83% are given anthracycline+taxane and pats. ≥ 60 years in 79%. Use of NAC is expanding in pats. ≥ 60 years (doubling of the share since 2004 to 26% in 2014) and in smaller tumor sizes.
Summary: Our analysis confirms the importance of anthracycline+taxane in AC regardless of the nodal status, whereas in NA therapies with platine+taxane and anthracyline-free taxane-regimes gain in importance. NAC to a growing extent is used in elderly patients.

ID 0375

Evidence for oligogenetic traits in hereditary breast cancer

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Introduction: About 5–10% of all breast (BC) and ovarian cancers (OC) are due to hereditary factors. *CHEK2*, a moderately penetrant BC gene, initiates DNA repair in response to DNA double strand breakage. In a case control study of unselected BC cases an overall odds ratio (OR)of about 3 was calculated (Cybulski et al. 2011).Higher odds radios are described with a familial background of breast cancer. An explanation is a selection bias when focusing on risk families, probably resulting in the enrichment of an oligogenetic cohort in which more than one genetic risk factor co-segregates. As *CHEK2* mutations are relatively frequent, they appear to be an appropriate model to analyze the potential oligogenetic trait in high risk families.
Methods: In our center 5684 families with a familial background have been tested for *BRCA1*, *BRCA2* and *CHEK2* concomitantly.
Results: 132 families were identified carrying a pathogenic mutation in *CHEK2*, leading to a mutation detection rate of 2.23%. In two families a homozygous mutation in *CHEK2* has been identified. We identified one family with a *CHEK2*/ *BRCA2* co-occurrence and 3 families with a *CHEK2/BRCA1* co-occurrence. In *BRCA1/CHEK2* families the additional *CHEK2* mutation did not aggravate disease penetrance. The *BRCA2/CHEK2* mutation carrier revealed a severe phenotype with bilateral early onset breast cancer at the age of 24.
Discussion: The co- occurrence of deleterious mutations in several risk genes necessitates further research on gene-to-gene interaction and on genotype-phenotype correlation- in order to establish an appropriate prevention and prophylactic measures.

ID 0405

Prognostic significance of focal adhesion kinase (FAK) in node-negative breast cancer (microarray based gene-expression- and immunohistochemistry-data)

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Background/Aim: Focal adhesion kinase (FAK) is a cytoplasmic tyrosine kinase playing an important role as a key mediator for signal transduction. Regarding the prognostic role of FAK in breast cancer studies show different results. We analyzed the prognostic influence of FAK expression in a cohort of lymph node-negative breast cancer patients without adjuvant systemic treatment.
Patients and **Methods:** Using microarray based gene-expression data, we analysed the prognostic significance of FAK (208820_at) in three previously published cohorts (Mainz, Rotterdam, TRANSBIG) of node-negative breast cancer patients not treated with adjuvant therapy (n = 766). A meta-analysis was performed using a random effects model. Furthermore we evaluated FAK expression on protein level by immunohistochemistry (IHC) in the Mainz cohort (n = 335). Prognostic significance of FAK for metastasis-free survival (MFS) as well as for disease-free survival (DFS) and overall survival (OS) was examined.
Results: Prognostic significance of FAK for MFS was seen in the whole cohort as well as in the Mainz cohort of patients on mRNA level (HR 1.48, 95% CI 1.16-1.87, p = 0.001; HR 1.89,95% CI 1.006-3.556, p = 0.048), however, not on protein level. In both methods FAK expression was a significant prognostic factor for shorter DFS (mRNA HR 1.85, 95% CI 1.054-3.261, p = 0.032; IHC HR 1.54, 95% CI 1.043-2.284, p = 0.030), no influence was seen on OS.
Conclusion: A higher FAK expression on mRNA-level was associated with worse MFS and DFS in node-negative breast cancer. Overexpression of FAK was only associated with worse DFS.

ID 0512

Tumor-infiltrating lymphocytes and response prediction to neoadjuvant chemotherapy in HER2-positive breast cancer

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Background: Tumor infiltrating lymphocytes (TILs) show a higher prevalence in aggressive subtypes of breast cancer. We elucidated their value as an independent predictor for pathological complete response (pCR) rate in patients with HER2-positive breast cancer receiving neoadjuvant chemotherapy plus anti-HER2 treatment.
Methods: We evaluated stromal TILs in 498 centrally confirmed HER2-positive breast cancer samples of the neoadjuvant GeparQuattro and GeparQuinto trials. Levels of TILs were determined as a continuous parameter per 10% increase and as lymphocyte-predominant breast cancer type (LPBC; >= 60% TILs), and correlated to pCR rate. Furthermore, we evaluated the association of TILs and pCR according to different anti-HER2 treatment strategies, namely trastuzumab and lapatinib.
Results: In the complete cohort, LPBC cases had a significantly increased pCR rate compared to non LPBC-types (57.7% versus 40.4%, p = 0.002). Stromal lymphocytes per 10% increase were significant predictors for pCR in univariate (OR 1.12, p = 0.002) and multivariate analyses (OR 1.09, p = 0.034). This effect was also detectable in the trastuzumab treated subgroup (10%TILs: OR 1.12, p = 0.018; LPBC: OR 2.08, p = 0.013).
Conclusion: We could substantiate the predictive impact of TILs in HER2-positive breast cancer on pCR rate in the neoadjuvant setting. These results provide further evidence of the antitumoral influence of the immunological microenvironment. Therefore it might be reasonable to test the combination of conventional therapy strategies with immune-modulating regimen to improve therapy results.

Cancer Prevention

ID 0453

Building a comprehensive cervical cancer screening and triage system from bottom up – the accessing approach

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Objective: To build a bottom up cervical cancer screening programme applicable in rural areas of low-resource settings, such as the North Tongu District of Ghana.
Methods: Cervical cancer screening by self-sampling is incorporated in the work of community health workers in the rural communities. HPV DNA testing is done at the Catholic Hospital Battor, a district hospital in Ghana. Further triage is conducted via Arbor Vita OncoE6 Cervical test and colposcopy. This algorithm is accompanied by intensive capacity building for laboratory technicians, nurses and doctors, includes strong community and political engagement and acceptability analysis.
Results & Discussion: Pilot studies preceding the main screening of 2000 women (starting in August 2015) in the district tested methodology and logistical workflow. A Kick-off workshop included all stakeholders and continuous training built capacity for the main study. Epidemiological data on HPV prevalence among HIV+ women was collected and acceptability of the Evalyn brush self-sampling device analyzed.
It revealed that 100% found it "easy" or "very easy" (85.5%) to take the sample with the Evalyn brush and 92% felt "very comfortable". 92% indicated that they would get checked more often if self-sampling works as well as going to see a doctor and 73.5% stated that they would prefer it.
Among 400 pilot study patients two cases of invasive cervical cancer were detected, highlighting the importance of this approach. The pilot studies have attracted other interested clinics and received lot of media and political attention, which is essential and fruitful to build up sustainable cervical cancer screening. Initial results from screening in villages will be presented.

Central Nervous System Tumors

ID 0160

Isocitrate dehydrogenase mutant diffuse gliomas grades II and III are radiological indistinguishable and underlie only molecular alterations

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Objectives: To determine whether *IDH*-mutant diffuse gliomas grades II and III have similar radiological presentations in magnetic resonance imaging (MRI).
Methods: Clinical and radiological data of 79 patients; 40 patients with an glioma WHO grade II and 39 patients with glioma WHO grade III were collected. Sequencing of *IDH*1 codon 132, IDH2 codon 172 as well as of the *TERT*-promoter was performed. Moreover, the 1p/19q-co deletion status was determined in gliomas harboring oligodendroglial components (n = 32). Using immunohistochemistry, the MIB-1 index was detected. All molecular data were correlated to the tumor features on MRI before treatment.
Results: *IDH* mutations were present in 63 patients (79.7%; in 34 patients with grade II and 29 patients with grade III gliomas, respectively). *TERT* mutations were detected in 31.5% and a co-deleted 1p/19q status in 30% of the entire group. Both groups of glioma grades with an *IDH* mutation depicted similar radiological features – in regard to tumor size, tumor localization, insular involvement, contrast enhancement, tumor heterogeneity, local and/or bilateral infiltration pattern, midline shifting and diffusion restriction – without any significant differences. *IDH*-mutant gliomas with *TERT* mutations and/or 1p/19q co-deletion were predominantly located in the frontal lobe and did not cross the midline nor involve insular structures, making a gross total resection more amenable. A high MIB-1-index was associated with a bigger tumor size and bilateral infiltration of the hemispheres.

Conclusions: Our analysis implicates that *IDH*-mutant gliomas WHO grades II and III are MR-radiologically indistinguishable. We further elucidate that the clinical behavior of diffuse gliomas more likely underlines molecular alterations than the pathological subclasses.

ID 0221

XAF1 is a novel epigenetic marker to predict survival of high-grade brain tumor patients

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The tumor-suppressor X-linked inhibitor of apoptosis (XIAP)-associated factor 1 (XAF1) is ubiquitously expressed in normal tissue, while expression often is reduced in cancer cells. Besides its ability to interfere with the inhibitor of apoptosis protein (IAP) XIAP, also newly described interactions with p53, were shown to account for the growth inhibitory functions of XAF1. IAPs on the other hand, particularly survivin and XIAP, have a usually high expression in tumors. These proteins can cause therapy resistance and finally lead to therapy failure. In this context XAF1 functions as IAP-antagonist. High-grade gliomas (HGG) are the most common and also most aggressive brain tumors. HGG patients have a very bad prognosis and the disease remains largely incurable. Therefore, there is an urgent need for new predictive or prognostic markers and potential therapeutic targets. In this study we analyzed the epigenetic regulation of the anti-apoptotic *survivin* and the pro-apoptotic *XAF1* in HGG cell lines and tumor samples. We could show that *XAF1*, but not *survivin*, is epigenetically regulated in HGG tumors. *In vitro* a methylation of the *XAF1* promoter region was inversely correlated to mRNA and protein expression. On the basis of this data a set of HGG-tumor samples was analyzed. According to a calculated threshold of methylation, the patients were grouped and Kaplan-Meier estimates were calculated. Intriguingly overall- and progression-free survival (OS; PFS) was significantly increased for patients, whose tumor cells showed a methylated XAF1 promoter. This indicates that XAF1 promoter methylation is a promising predictive marker in high-grade glioma and might give valuable information about therapy outcome, OS and PFS.

ID 0227

Interferon-β modulates the innate immune response against glioblastoma initiating cells

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Treatment of glioblastoma remains a challenge in neuro-oncology. Glioblastoma initiating cells with stem cell properties (GIC) are considered a putative target for immunotherapy of glioblastoma. However, GIC are prone to evade immune responses and there is a need for potent adjuvants. Here, we define the modulation of the innate immunogenicity of GIC by Interferon (IFN)-β. Several genes involved in innate immune responses were regulated by IFN-β in GIC as assessed by microarrays. The results were validated by reverse transcription polymerase chain reaction and on the protein level by flow cytometry. The up-regulation of the innate immune inhibitory molecules HLA-E and MHC class I was balanced by immune stimulating effects including the up-regulation of nectin-2. In 3 out of 5 GIC lines tested we found a net immune stimulating effect of IFN-β in cytotoxicity assays using NKL cells as effectors. In 2 cell lines, the immune stimulating effect was reverted completely upon gene silencing of *nectin-2*, indicating that innate immune activation by IFN-β can in part be attributed to nectin-2 up-regulation. IFN-β warrants further investigation as an adjuvant for immunotherapy targeting GIC.

ID 0269

"Stem cell like" cells in high grade gliomas – are there other possible markers apart from CD 133?

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Objective: "Stem cell like" cells with CD133 as the most popular marker are considered an important factor for the treatment failure in high grade gliomas. But during the last years the relevance of the surface protein CD133 has become more and more an issue of discussion.
In this study we wanted to define possible new marker genes describing stem cell and proliferation properties in a tumour sphere model.
Methods: We defined 4 groups of glioblastoma cells being cultivated under different conditions. Group A (n = 6): Cells isolated according to an established tumour stem cell isolation protocol/ Group B (n = 4): Cells from a commercial cell line/ Group C (n = 6): Cells from adherent primary glioblastoma cell cultures. Group A-C were cultured in serum-free sphere medium to induce a spherical growth pattern, while the adherent primary cultures were cultured as Group D (n = 6) in serum medium.
Presuming the maximum fraction of potential stem cell like in group A we analysed the following markers RT-qPCR: CD133, Musashi-1 (Msi1), Sox2, Oct4, Nanog, Nestin, GFAP and Notch with group A as reference.
Results: There was a downregulation of Msi1**(17-680 fold), Nestin*** (10-130), Notch (5-15 fold), GFAP** (250-1900 fold) and Sox2* (4-12 fold) and an increased gene expression of the cell surface marker CD133 (12-24 fold) in the groups B-D compared to group A. Oct4 (0,5-1,4 fold) and Sox2 (in Gr. C: 1,1 fold) showed no regulation (*significant). Nanog was not representatively detected.
Conclusion: According to our data Msi1 is a more reliable marker to define tumour stem cell subpopulation compared to CD 133. Additional, the significantly increased Nestin and Notch-expression correlated with Msi1 and seems to be associated with stem cell like properties.

ID 0411

mTOR signaling in meningiomas and gliomas

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Objective: To date targeted pharmacological inhibition of the mTOR network to treat brain tumors is, due to inconsistent therapeutical results in various clinical trials, still questionable. Being aware of that, the aim of our analysis was to illustrate the expression patterns of key components of both mTOR complexes in the two most common adult brain tumor entities – meningiomas and gliomas – and their regulation by associated microRNAs.
Methods: The expression of mTORC1 associated RAPTOR, mTORC1 effectors S6K and 4E-BP1 as well as mTORC2 associated RICTOR and FoxO 1 were quantitatively analyzed in 51 surgical specimens of meningiomas (WHO I°-III°) and in 50 glioma specimens (WHO II°-IV°) using real-time polymerase chain reaction (qPCR) and subsequently evaluated applying the comparative ΔΔCt method against healthy brain or non pathological dural tissue respectively. Additionally, the expression of microRNAs (miR-99a, miR-99b, miR-100 and miR-101, miR-143, miR-144 and miR-145) associated with components of the mTOR-network were quantitatively analyzed.
Results: In meningiomas we detected a preferential expression of mTORC1 associated substrates. Anaplastic astrocytoma (WHO III°) exhibited no significant preference for mTORC1 respective 2 associated factors, whereas in glioblastoma (WHO IV°) the expression level of mTORC2 associated effectors was preferably increased.
Conclusions: Analyzing mRNA and microRNA expression of gliomas and meningiomas we detected a statistically significant different expression profile between the WHO grades within each tumor entity on the one

hand as well as intriguing differences between the neuroectodermal glial and mesodermal meningeal tumor types on the other hand.

Developmental Therapeutics: Immunotherapy/Cellular Theraphy

ID 0104

Tumorantigen-specific CD40B cells – combining enhanced antigen-presentation and antibody-secretion for tumor targeting

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Efficient antigen presentation is a prerequisite for the development of a T-cell-mediated immune response. Dendritic cells (DCs) are the most prominent professional antigen-presenting cells (APCs). However, they have several disadvantages as cellular adjuvant in cancer immunotherapy. Therefore, an alternative approach was developed, in which polyclonal B cells can serve as potent APCs by treatment with the CD40 ligand. We demonstrated that CD40-activation dramatically improves antigen presentation by B cells, efficiently inducing naive and memory CD4+ and CD8+ T-cell responses. Moreover, these CD40-activated (CD40) B cells home to secondary lymphoid organs.
However, antigen presentation by antigen-specific B cells is more effective compared to polyclonal B cells. Therefore, we use tumorantigen-specific B cells to improve the antigen-presenting function of CD40B cells. Purified human and murine tumorantigen-specific B cells highly upregulate activation markers upon CD40-stimulation resulting in an enhanced CD4+ and CD8+ T cell response in vitro and in vivo. This response is significantly lower in polyclonal CD40B cells and comparable to the stimulation induced by mature dendritic cells. Moreover, antigen-specific B cells could be stimulated in vitro to differentiate into antibody-secreting plasma cells. Treatment of E.G7 lymphoma-bearing mice with a combination of antigen-specific CD40B cells and plasma cells results in inhibition of tumor growth and prolonged survival. Moreover, antigen-specific B cells home to the tumor site and the spleen, where they encounter T cells. These results provide new insights into the role of activated antigen-specific B cells as APCs and their use for cancer immunotherapy.

ID 0196

Development of a functional humanized immune system in mice by transplantation of human hematopoetic stem cells – a model for immuno-oncology research

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Objective: The preclinical evaluation of novel immune checkpoint modulators is dependent on models with functional human immune cells (HIC). In previous experiments, we have demonstrated, that hematopoietic stem cells (HSC) can proliferate and differentiate in vivo to form a functional humanized immune system (HIS). However it has to be evaluated whether parallel xenotransplantation of patient-derived human tumors in these mice would allow to generate a panel of personalized models for immuno-oncology research. We designed a study to investigate the differentiation and function of HSC in immunodeficient mice in the presence of co-transplanted PDX.
Methods: HSC from cord blood were transplanted i.v. into 3 week (w) old irradiated nod scid gamma mice. After 4, 8 and 12w, blood was collected and screened by FACS for HIC (huCD45$^+$). PDX were s.c. co-transplanted into these humanized mice and followed for growth and tolerance by the HIC. Functionality of the HIC was evaluated by treatment with the CTLA-4 checkpoint inhibitor ipilimumab.
Results: After 8w up to 50% of leucocytes in the blood were CD45$^+$. A high percentage of B-cells was measured (up to 85%). After 12w up to 20% of the HIC in the blood were T-cells. Engraftment in different organs has been detected, with up to 15% CD45$^+$ cells in spleen and thymus and 50% in the bone marrow. PDX showed engraftment on the humanized mice. No difference was observed compared to the growth on immunodeficient mice demonstrating no innate immune response against the tumors. Treatment with ipilimumab led to a slight tumor growth delay and an increased percentage of T-cells in the blood and in the tumor.
Conclusion: Transplantation of HSC into immunodeficient mice generates a HIS. PDX can be successfully transplanted into these humanized mice. Initially results revealed the function of our model as a tool to investigate the human hematopoiesis and the efficacy of immunotherapeutics.

ID 0262

The anti-tumor function of ROR1-CAR modified T-cells against triple-negative breast cancer is enhanced by shielding from immunosuppressive TGF-ß

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Adoptive immunotherapy with genetically engineered autologous T cells expressing tumor-reactive chimeric antigen receptors (CARs) is an innovative experimental treatment for advanced malignancies. CARs are synthetic receptors that bind surface molecules via antibody moieties and confer T cell activation upon antigen encounter. We have shown in previous work that the tumor antigen ROR1 is expressed at high levels in triple-negative breast cancer (TNBC). We have thus constructed a ROR1-specific CAR that mediates recognition and destruction of TNBC cell lines *in vitro* and in pre-clinical models *in vivo*. Detailed phenotypic analysis revealed that ROR1-CAR T cells express substantial levels of TGF-b receptors, suggesting their function might be impaired by immunosuppressive TGF-b prevalent in the TNBC microenvironment. We prepared ROR1-CAR T cells and analyzed their function in the presence and absence of TGF-b. In a standardized assay we found that the cytolytic activity of CD8$^+$ CAR T cells against TNBC cell lines is reduced by about 25% in the presence of TGF-b. Proliferation of both CD8$^+$ and CD4$^+$ CAR T cells is also impaired as assessed by CFSE dilution, whereas cytokine secretion remained unaltered. Intriguingly, the functional impairment mediated by TGF-b could be reversed by pre-treatment of CAR T cells with the TGF-ß receptor I kinase inhibitor SD-208. Analyses of SMAD phosphorylation by Western blot demonstrated that SD-208 confers a near-complete block of TGF-b signaling in CAR T cells. Collectively, our data demonstrate that ROR1-CAR T cells have therapeutic potential in TNBC and suggest their efficacy in a clinical setting may be enhanced by shielding from TGF-b which could be achieved by *ex vivo* pretreatment with SD-208.

ID 0477

Cytotoxic local tumor treatment in combination with xystemic Ipilimumab enhances the efficacy of this immunotherapy and prolongs overall survival in patients with advanced malignant melanoma

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Purpose: Immune checkpoint inhibition with ipilimumab has revolutionized cancer immunotherapy and significantly improved outcomes of patients with advanced malignant melanoma. Local peripheral treatments (LPT) such as radiotherapy or electrochemotherapy have been shown to modulate systemic immune responses. Preliminary data have raised the hypothesis that the combination of systemic immune checkpoint blockade with LPT could lead to improved clinical outcomes.
Patients and Methods: Clinical data of consecutively treated melanoma patients at four cancer centers in Germany and Switzerland were analyzed. Patients either received ipilimumab or ipilimumab and LPT if indicated for local tumor control. Additional immune assessments were performed in order to identify tumor-specific immune responses during the combination treatment.
Results: A total of 127 melanoma patients were analyzed who either received ipilimumab (n = 82) or ipilimumab+LPT (n = 45). We found that the addition of LPT to ipilimumab significantly prolonged median overall survival (OS) (93 versus 42 weeks, p = 0.0028). Interestingly, adverse immune-related events were not significantly increased by the combination treatment. The clinical benefit was found irrespective of brain metastases or BRAF mutational status. Moreover, the synergy of the combination treatment also improved progression-free survival (PFS) (15 versus 11 weeks, p = 0.0138) in BRAF-mutated patients.
Conclusion: Our data suggest that the addition of LPT to ipilimumab is safe and effective in patients with metastatic melanoma irrespective of clinical disease characteristics. Synergistic induction of tumor-specific immune responses is most likely the underlying mechanism and warrants prospective validation.

Endocrine Tumor (e. g. thyroid cancer, adrenal tumor, neuroendocrine tumor …)

ID 0191

Patterns of lymphatic recurrence in adrenocortical cancer

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Background: Surgery with a complete tumor resection still remains the treatment of choice for adrenocortical carcinoma (ACC) and is the cornerstone for long-term survival. Beside complete tumor resection, loco-regional lymph node dissection (LND) seems to improve the prognosis of patients with a localized ACC. Until now, there are no recommendations about the extents of LND or required regional lymph nodes which should be removed.
Purpose: To investigate the pattern of lymph node metastases in ACC, the patient records of the *European Network for the Study of Adrenal Tumours* (ENSAT) registry were evaluated concerning imaging (CT scan, PET-CT, MRI scan). The inclusion criteria were the following: initial complete resection (R0) of a non-metastatic ACC (ENSAT I-III) and lymph node metastases in the course of the disease. The fields of lymph nodes were evaluated separately to figure out the pattern and incidence of lymph node recurrence.
Results: In total 49 patients were included for evaluation with a median age of 51 years (range 25-79) at the time of initial tumor diagnosis. The primary tumor was located on the right side in 20 (41%) and on the left side in 29 cases (59%). For left sided ACC lymphatic recurrence was detected perirenal-cranial (48%), paraaortic (45%), interaortocaval (24%), and perirenal ventro-caudal (14%). For right sided ACC the majority of lymph node metastases could be identified perirenal-cranial (55%), paracaval (10%), interaortocaval (30%), and paraaortic (10%).
Conclusion: The distribution of lymph node metastases suggests that the field of (currently recommended) loco-regional LND should be extended. Furthermore, these data suggest that the indication for a minimal invasive approach should be critically reviewed due to technical limitations for laparoscopic LND in the abovementioned fields.

ID 0273

Management of thyroid stimulating hormone (TSH) and possible impact on outcomes for patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC) receiving sorafenib or placebo on the phase III DECISION trial

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Background: One third of RAI-rDTC patients randomized to receive sorafenib in the phase III DECISION trial had increased serum TSH values. Here we examined the management of TSH for patients from the DECISION trial and conducted an exploratory post-hoc analysis to determine whether progression-free survival (PFS) was impacted based on successful TSH management.
Methods: A total of 417 patients were randomized to receive placebo (n = 210) or sorafenib (n = 207). Serum TSH and levothyroxine (LT4) levels were assessed every 28-day cycle and LT4 dosing adjusted for TSH values >0.5 mU/L so as to maintain a desired level <0.1 mU/L. Median PFS (mPFS) was assessed by independent radiologic assessment using modified RECIST 1.0 every 8 weeks.
Results: Elevated TSH values >0.5 mU/L at any cycle were reported in 69 (33.3%) and 28 (13.4%) of patients in the sorafenib and placebo arms, respectively. Most new occurrences of elevated TSH in the sorafenib arm were reported in cycle 2 (11.4% of evaluable patients), at which time mean TSH values were 0.37±1.20 mU/L compared to 0.18±1.07 mU/L in the placebo arm. Successful control of TSH (defined as >75% of TSH values <0.1 mU/L) was reported in 96 (48.0%) and 155 (76.4%) of patients in the sorafenib and placebo arms, respectively, with 82 (41.0%) and 50 (24. 6%) of patients having LT4 dose adjustment, respectively.
Conclusions: Approximately twice as many patients in the sorafenib arm compared to the placebo arm of the DECISION trial had elevated serum TSH requiring LT4 dose adjustment. In an exploratory post-hoc analysis, PFS outcomes did not appear to be negatively impacted by failure to maintain TSH target levels. These results highlight nonetheless the need

for active monitoring of TSH and LT4 dose adjustment for optimal management of RAI-rDTC patients receiving sorafenib therapy.

ID 0277

Analysis of tumor growth rate for radioiodine (RAI)-refractory differentiated thyroid cancer patients receiving placebo and/or sorafenib in the phase III DECISION study

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Background: In the phase III DECISION trial, patients were randomized to receive double-blind (DB) sorafenib (SOR) or placebo (PLC) until tumor progression, at which time PLC patients were allowed to switch to open-label (OL) SOR and SOR patients to continue OL. We conducted an exploratory analysis of target lesion size over time.
Methods: Changes in target lesions assessed by central radiologic review every 8 weeks were approximated by a parabola-like 3-parametric model and tumor growth rates (TGR) derived for DB and OL treatment periods. TGR was defined as % change per month of sum of target lesion diameters.
Results: Patients receiving SOR DB and then OL totaled 207 and 55, and patients receiving PLC DB and then SOR OL totaled 210 and 150, respectively; patients evaluable for TGR were 176, 38, 189 and 123, respectively. For SOR patients, TGR was typically negative early reflecting target lesion shrinkage from baseline [-3.9 (-4.7, -3.1), mean % change/mo (95% CI)] and then positive from nadir to progression [2.6 (1.9, 3.3)] reflecting tumor growth, as was TGR for the subgroup of SOR patients continuing OL treatment from 2nd baseline [1.7 (-0.9, 4.3)]. For PLC patients, TGR was typically positive [5.0 (2.2, 7.8)], as was TGR for the subgroup prior to switching to SOR at progression [6.1 (1.9, 10.3)]. The TGR pattern of PLC patients on OL SOR was similar to the DB SOR pattern, i.e. negative post second baseline [-4.4 (-5.6, -3.2)] and positive from nadir to progression [1.8 (0.5, 3.1)].
Conclusions: SOR reversed tumor growth (negative TGR) during the DB period and for PLC patients switching to SOR. TGR from nadir to progression for patients receiving SOR or post-progression for patients continuing on SOR was less than for patients on PLC, suggesting that despite evidence of tumor growth or prior RECIST progression, SOR continued to slow tumor growth relative to growth in its absence.

ID 0336

Assessment of the treatment situation of patients with neuroendocrine tumors (NET) by means of a retrospective survey in specialized oncological offices

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Background: Neuroendocrine tumors (NET) are rare and heterogeneous neoplasia. The aim of this survey was to obtain data on prevalence and different subpopulations of NET patients treated at office-based oncologists as well as the diagnostic measures and therapeutic approaches provided.
Methods: A questionnaire focusing on diagnostic classification and applied treatment decisions for NET patients was developed. The survey was carried out in 22 oncologists` offices and 276 NET patients were documented in total.
Results: In total 77% of all NET had a gastrointestinal origin (pNET=25%; other GI-NET=52%). In 11% the origin was found in the lung. Another anatomic location or CUP existed in 13%. Most GI-NET showed a low (G1/G2/G3 = 45/21/17%), while most pNET showed a slightly higher grading (28/39/13%). In contrast lung-NET (14/14/31%) and "other NET" (23/9/34%) were associated with a higher grading. No grading at all was documented in 21% of cases. While most patients underwent surgery (74%), further therapeutic strategies depend on tumor localization. The most prevalent treatment regimens for GI-NET were biotherapy (39%) and "watch&wait" (22%) while pNET therapies were typically biotherapy (43%), chemotherapy (Ctx, 23%) a0595nd targeted therapy (22%). Lung-NET as well as "other NET" were typically treated with Ctx (45% and 46% resp.).
Conclusion: NET patients of all sub entities and grades were treated by office based oncologists. For an optimal treatment of NET it is essential to ensure a careful diagnosis. Remarkably in 21% of all cases the most significant prognostic marker (WHO grading) was not available. Thus one conclusion of this survey could be to continue standardization efforts in everyday clinical documentation practice.

ID 0552

Identification and validation of AGTR1 as a possible anti-cancer target in neuroendocrine tumours

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Neuroendocrine tumours (NETs) have been found to overexpress somatostatin receptors (SSTRs). This led to the development of somatostatin analogs utilized for diagnostics and therapeutics. However, around 30% of all NETs do not respond to somatostatin based approaches, leading to an interest to find and characterize alternative cell surface targets.
A clear response of neuroendocrine cell lines to angiotensin II (ATII), the natural ligand of the angiotensin-II type 1 receptor (AGTR1), was observed in a screening approach using different cell-based assays. This resulted in further experiments elucidating the role of ATII and AGTR1 in NETs.
Quantitative real-time PCR showed significantly higher AGTR1 expression levels in neuroendocrine tumour tissue (n = 72) compared with mRNA levels in healthy control tissue (n = 13). For the establishment of autoradiographic protein detection and based on mRNA expression analysis, two AGTR1-positive (BON, H727) and two AGTR1-negative (LCC18, QGP-1) NET cell lines were chosen. Radioactive binding assays identified specific binding sites for ATII on BON and H727 cells respectively, with an affinity at nanomolar concentrations and a density between 50 and 200 fmol/mg protein. In vitro receptor autoradiography using tumour xenografts of BON and H727 cells confirmed these data. In a next step, patient samples will be tested for their AGTR1 protein expression. Also, altered functional consequences of an AGTR1 overexpression are currently investigated.
Up to now, AGTR1 overexpression was shown in various cancers and anti-hypertensive drugs targeting the AGTR1 that are already clinically used might be retooled. Therefore, AGTR1 might be an interesting molecule for therapeutic approaches in NETs.

Gastrointestinal (Colorectal) Cancer

ID 0014

CONSIGN – an open-label phase-3B-study of regorafenib in patients with metastatic colorectal cancer (mCRC) who failed standard therapy

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Background: CONSIGN (NCT01538680) was designed to provide regorafenib (REG) to patients (pts) with mCRC who had failed standard therapies and had no treatment alternatives, and to characterize the safety of regorafenib in a large cohort of pts.
Methods: This prospective, open-label, single-arm study was carried out at 188 sites in 25 countries and enrolled pts in ECOG PS 0–1 to receive REG 160 mg once daily for 3 weeks on/1 week off. Dose modification for toxicity was allowed. Treatment was continued until disease progression, death, or unacceptable toxicity. The primary endpoint was safety. Progression-free survival (PFS) per investigator assessment was the only efficacy variable assessed.
Results: 2864 pts were treated. Median age: 62 years; ECOG PS 0/1: 47%/53%; and 96% of pts had ≥2 prior regimens for mCRC. Median treatment duration: 2.5 mos (range: 0-30) and the mean (SD) duration was 3.6 (3.8) mos. Patients received a median of 3 cycles of regorafenib (range: 1-33). Daily dose was a median of 160 mg (range: 74–166) and a mean of 146 mg. A total of 87% of pts had treatment modifications and 46% had an adverse event (AE) requiring dose reduction. Almost all (99%) pts had at least one treatment-emergent AE, and 91% had an AE considered related to REG. AEs led to treatment discontinuation in 25%; 9% discontinued for a drug-related AE. Serious AEs (SAEs) occurred in 44% of ps; 9% had drug-related SAEs. Among the most common NCI-CTCAE v4.0 grade ≥3 AEs were fatigue (17%), hypertension (18%), HFSR (14%), hypophosphatemia (7%), and diarrhea (6%). Grade ≥3 hepatobiliary disorders occurred in 4%. Treatment-emergent laboratory toxicities with grades ≥3 included ALT (6%), AST (7%), and bilirubin (13%). Median PFS (95% CI) was 2.7 months (2.6–2.7).
Conclusion: In this large, prospective study of regorafenib in patients with mCRC who failed standard therapies, AEs were consistent with the known safety profile of regorafenib. Median PFS was in the range of that reported in phase 3 trials.

ID 0016

Pharmacokinetics of regorafenib (REG) in the phase 3 CONCUR and CORRECT trials in patients (pts) with metastatic colorectal cancer (mCRC)

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Introduction: The CORRECT trial (NCT01103323) included 760 randomized pts in North America, Europe, Israel, Australia, and Asia (China n = 4; Japan n = 100), whereas CONCUR (NCT01584830) included a broader population of Asian pts (n = 204), mostly from China. The aim of this analysis was to compare pharmacokinetic (PK) data of REG in CONCUR and CORRECT populations.
Methods: This analysis included 98 Asian pts from CONCUR and 381 pts from CORRECT. AUC(0-24),ss values for REG and its active metabolites M-2 and M-5 were calculated from sparse plasma samples determined by a previously developed population PK model for REG.
Results: The range of individual AUC(0-24),ss values for REG was similar between pts in CONCUR (20.7-184 mg·h/L) and those in CORRECT (19.2-311 mg·h/L). The geometric mean AUC(0-24),ss was 64.4 mg·h/L in the 98 Asian pts from CONCUR, 69.5 mg·h/L in the 54 CONCUR pts from mainland China, and 68.1 mg·h/L in the 45 Asian pts from CORRECT, compared with 72.9 mg·h/L in the overall CORRECT population (n = 381). Ranges of AUC values for the M-2 metabolite were similar in CONCUR (2.22-233 mg·h/L) and CORRECT (3.54-295 mg·h/L) populations. Geometric mean AUC(0-24),ss values for M-2 were 42.4 mg·h/L in the 98 Asian pts from CONCUR, 47.8 mg·h/L in the 54 CONCUR pts from mainland China, 49.7 mg·h/L in the 45 Asian pts from CORRECT, and 56.7 mg·h/L in the overall CORRECT population. M-5 exposure was highly variable in both studies. Geometric mean AUC(0-24),ss values for M-5 were 33.1 mg·h/L in the 98 Asian pts from CONCUR (range 0.66-312), 36.4 mg·h/L in the 54 CONCUR pts from mainland China (range 2.21-266), 44.9 mg·h/L in the 45 Asian pts from CORRECT (range 3.13-315), and 54.7 mg·h/L (range 1.85-555) in the overall CORRECT population. A slightly lower mean exposure of M-5 was seen in CONCUR compared with CORRECT; however, a high intersubject variability was observed in both trials.
Conclusion: REG PK (AUC(0-24),ss) for Asian mCRC patients in the CONCUR trial (including pts from Vietnam, Hong Kong, Taiwan, South Korea, and mainland China) was similar to that seen in mCRC pts in the CORRECT trial.

ID 0074

Clinical relevance of subsequent treatment procedures on overall survival in FIRE-3/AIO KRK0306 (FOLFIRI plus cetuximab [arm A] or bevacizumab [arm B]) in patients with KRAS wild-type metastatic colorectal cancer

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Background: To explore the overall survival (OS) difference in favour of arm A in the context of comparable progression-free survival (PFS) and response rates in FIRE-3.
Patients and Methods: We analyzed overall survival and treatment procedures in a time-wise (six months) fashion. Moreover, subsequent treatment procedures were evaluated concerning duration and efficacy.
Results: Efficacy of 2nd-line therapy (calculated from start of 2nd-line regimen), PFS (6.5 *v* 4.7 months; hazard ratio, 0.68; 95% CI, 0.54 to 0.85; *P*= .001) and OS (16.3 *v* 13.2 months; hazard ratio, 0.70; 95% CI, 0.55 to 0.88; *P*=.0021) were longer in patients in arm A compared with arm B. A first significant difference in overall survival by cox regression was observed between 24 and 30 months (hazard ratio: 0.48 (95%CI: 0.27-0.85)) after randomisation of patients with only a minority of patients receiving anti-tumor therapies in this interval. Updated data including RAS wild-type population might be presented at the meeting.
Conclusion: Efficacy of 2nd-line treatment seemed greater in patients of arm A compared to arm B. The small number of patients receiving anti-tumor therapy 24 months after randomisation when a signifcant difference in overall survival becomes manifest, suggests that underlying effects on OS in FIRE-3 are complex and cannot be explained by 2nd-line therapy alone.

ID 0112

Argyrin F therapy attenuates carcinogenesis of pancreatic ductal adenocarcinoma (PDAC)

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Introduction: PDAC is an aggressive disease with a 5-year survival rate of <5%. New therapeutic approaches are higly needed. Recent studies have reported that the proteasome inhibitor Argyrin A, a cyclic peptide derived from the myxobacterium Archangium gephyra, show antitumoral activities. The aim of the present study is to explore the anti-tumor activity of his analogue Argyrin F in PDAC carcinogenesis.
Methods and Materials: *In vitro*, we analyzed the effect of Argyrin F by testing different dosages on PDAC cell growth and epithelial plasticity by using WST-1-, wound healing-, invasion-, colony formation-, apoptosis- and senescence assay, as well as cell cycle analysis and Western Blot. *In vivo*, we assessed the effects of single Argyrin F therapy and combination of Argyrin F + Gemcitabine in a genetically engineered mouse model (Pdx1- Cre; LSL-KrasG12D; p53 $^{lox/+}$) of PDAC.
Results: Treatment with Argyrin F significantly impaired cell proliferation, migration, invasion and colony formation compared to therapy with DMSO. We also found that Argyrin F impairs epithelial-mesenchymal-transition (EMT) and induces apoptosis and senescence in a dose- and time-dependent manner. Argyrin F application resulted in cell cycle G1/S phase transition. Most importantly, Argyrin F + Gemcitabine treatment showed prolonged survival and caused significant tumor reduction. Ki67 expression and tumor angiogenesis marker (CD34) were diminished under Argyrin F and Argyrin F + Gemcitabine treatments.
Conclusion: Our work demonstrate that treatment with Argyrin F can successfully attenuates the carcinogenesis of PDAC cells *in vitro* and *in vivo* and might be a new and promising drug for human PDAC.

ID 0204

On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe – results from the EUROCARE-5-study

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Background: Previous studies revealed major variation in survival for patients with colorectal cancer (CRC) in Europe by age and between different regions, but also a sustained improvement in survival for CRC patients in recent years. This study aimed to update available knowledge from previous studies and to provide the latest survival estimates for CRC patients from Europe.
Methods: This study analysed data of patients diagnosed with CRC from population-based cancer registries diagnosed in 29 European countries. Estimates of 5-year relative survival (RS) were derived for patients diagnosed in 2000-2007 by European region, country and age at diagnosis. Additionally to these cohort estimates, time trends in 5-year RS were obtained for the calendar period 1999-2007, using the period analysis methodology.
Results: European average 5-year RS for patients diagnosed with colon and rectum cancer was 57% and 56%, respectively. The analyses showed persistent differences in cancer survival across Europe with lowest survival for CRC patients observed in Eastern Europe and a strong negative gradient in age-specific survival. Even though the study revealed sustained improvement in 5-year patient survival between 1999 and 2007 (absolute increase of 4 and 6 percentage points for colon and rectum, respectively), the differences observed at the beginning of the millennium persisted over time.
Conclusion: Although survival for CRC patients in Europe improved markedly in the study period, significant geographic variations and a strong age gradient still persisted. Enhanced access to effective diagnostic procedures and treatment options might be the keys to reducing the existing disparities in the survival of CRC patients across Europe.

ID 0211

Interim analysis of the non-interventional QoLiTrap-study – therapy sequences, progression-free survival and quality of life in clinical practice with FOLFIRI and Aflibercept

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Introduction: Aflibercept is approved in combination with FOLFIRI for patients with mCRC, who have already received an Oxaliplatin containing therapy. This analysis shows interim results of the non-interventional QoLiTrap-study
Methods: Patients with mCRC are included in QoLiTrap (AIO-LQ-0113) when they are treated with Aflibercept and FOLFIRI according to label. Quality of life is assessed by EORTC-QLQ C30 questionnaires that are filled in by the patients at baseline and in every other cycle.
Results: This is the interim analysis of the first 277 patients who completed at least baseline and 2 additional EORTC questionnaires. These patients received Aflibercept therapy in 1st (11%), 2nd (49%), 3rd (17%) and later lines (23%) with a median of 6 (and up to 36) cycles. Patients were treated in therapeutic sequences that contained Bevacizumab (48%), anti-EGFR (13%), both (13%) or no biological (14%) before Zaltrap/FOLFIRI (n.a.12%). Complete or partial remission was observed in 22%, SD in 52% and PD in 26% of all patients with evaluated response (n = 144). EORTC global health score moderately declined (difference mean after 8 cycles: -8.41; Osoba et. al, 1998). Serious unknown safety signals were not observed up to date.
Conclusion: QoLiTrap is a large observational study for treatment of mCRC patients with FOLFIRI/Aflibercept. This interim analysis shows that Aflibercept is used in various therapeutic sequences and provides encouraging results with a tumor control rate of 74% in patients with response documentation. The decline in global health status was moderate.
This study is supported by Sanofi

ID 0308

Neoadjuvant therapy in rectal cancer – challenges of biobanking tumor biopsies taken prior to treatment

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Introduction Aiming to improve the integration of molecular information in clinical decision making translational research strongly rely on high-quality biospecimens. In patients with rectal cancer treated preoperatively with chemoradiotherapy tissue based analyzes are challenging due to the small size of the biopsies. To assess potential pitfalls and quality challenges we analyzed tissue samples taken over the last years in a multicenter setting.
Material and Methods We retrospectively evaluated 197 patients with rectal cancer that were biopsied preoperatively and stored in RNAlater between 2001 and 2013 at the University Medical Center Göttingen as well as in 10 cooperating hospitals in Germany. A professional biobank infrastructure was established.
Results The median RNA and DNA amount of a single RNAlater biopsy was 33.16µg and 18.89µg respectively. A high amount of RNA of one single biopsy was significantly associated to good RNA quality ($p = 2.74e-07$). Also the content of tumor showed a significant correlation to high RIN-values ($p = 0.004$), whereas a high content of mucosa and necrosis turned out to be associated with RNA of poor quality ($p = 0.07$ and $p = 0.01$ respectively). There was no association between the content of stroma and RNA quality ($p = 0.20$). Correlating biopsies from the University Medical Center Göttingen and the cooperating centers showed comparable tumor content results. 65.13% were included for further molecular analyses due to a tumor content >50% and/ or RIN>5.
Conclusion By taking small sized biopsies preoperatively we could assess a clear correlation between a good RNA quality and a high amount of RNA and tumor cells as well. These results also indicate that specimens collected at different centers are of comparable quality. Tumor biopsies with inadequate quality parameters should be excluded from further molecular analyses.

ID 0324

UICC-stages of colorectal cancers – interpolation of missing data

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The Federal State Cancer Registry of Baden-Wuerttemberg (KRBW) is the first cancer registry of a German federal state which collects epidemiological and clinical data on reported cancer cases. For determination of the UICC stage full information on TNM is necessary. Its reporting is however optional. Thus, the register can generate the clinical stage only for that part of the reported cases for which TNM information has been transferred. Since further clinical data are available, the question arises whether size of the tumor, nodal status or metastasis status can be derived from these sources.
The basis for the analysis is the data on colorectal tumors of the KRBW with 2013 as year of diagnosis. In a first step, the derivation of TNM elements from pathology findings and OPS is validated in 150 cases, in which TNM information is in fact available, so that the result of the extrapolation procedure may be compared.
For the year of diagnosis 2013, a total of 6046 reported colorectal tumors are available to the KRBW. In 55.6% of cases, full information on the TNM is available, so that the UICC stage can be generated directly. In 44.4% of cases one or several TNM specifications are missing: T-stage in 21.7%, N-status in 24.3% and M-status in 42.9% of cases. The analysis of the proposed extrapolation procedure is currently in progress and will be finalized by the end of the year. The results will be presented at the congress.
Of course the primary aim is to have information on the TNM reported by the reporting institutions to the greatest possible extent. In cases of incomplete reporting, which can for sure never be completely avoided, the presented procedure might exploit the additionally available clinical data effectively. Thus, if this procedure appears working properly it may be a useful tool in the analysis of data from clinical-epidemiology cancer registries.

ID 0326

Selective AKT inhibition by MK-2206 eliminates tumor-initiating cells in colorectal cancer

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Colorectal cancer (CRC) is the second leading cause of cancer related death in Germany. Growing evidence indicates that CRC is a stem cell-driven malignancy, in which only a small population of cells are capa-

ble to initiate and promote tumor growth (tumor initiating cells, TICs). To date, conventional chemotherapeutics do not sufficiently eliminate TICs leading to tumor relapse and chemoresistance.
The aim of this study was to gain insight into TIC biology by comparing the transcriptome of primary TIC cultures and their normal stem cell counterparts in order to identify new targets for a directed therapy.
We established colonosphere cultures, enriched for TICs, derived from resection of paired tissues of primary tumor and normal mucosa in patients with CRC. These colonospheres were used for differential transcriptome analyses. Pathway analysis of the differentially regulated genes showed that genes involved in PI3K/AKT signalling were overrepresented.
Previous, we identified CD133 as a marker for an aggressive subpopulation of colon cancer SW480 cells enriched with TICs. Treatment of CRC cells with the selective AKT inhibitor MK-2206 caused a decrease in cell proliferation, mainly in the TIC fraction, resulting in a significant reduction of the stemness capacity to form tumorspheres *in vitro* and to initiate tumor formation *in vivo*. Consequently, treatment with MK-2206 of established xenograft tumors lead to a significant deceleration of tumor growth *in vivo.* Further, MK-2206 almost blocked tumorsphere formation in primary patient tissue.
In conclusion, this study reveals that AKT signalling is a critical mediator of TIC proliferation. Targeting AKT by MK-2206 represents a potential therapeutic strategy to eradicate TICs in CRC.

ID 0392

A prognostic gene signature for UICC II colorectal cancer patients with a high risk of recurrence by next generation sequencing

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Background: The group of UICC II colorectal cancer patients comprise a subgroup of 10-20% which suffer of a recurrence within five years after resection. Unfortunately, there is no reliable prognostic factor, which allows to estimate frequency of recurrence for patients without risk factors (e.g. T4, G3, tumor perforation). Therefore, new biomarkers with a prognostic value for patients with a potential risk of recurrence are needed.
Methods: To identify candidate genes which are associated with a high risk of recurrence, whole exome sequencing to identify somatic mutations was performed. We differentially analyzed FFPE primary colorectal cancer tissues from patients with recurrence and those who have the longest relapse-free survival.
Results: We identified 44 significantly mutated candidate genes, which were solely found in the primary tumors of patients who showed a relapse within five years after tumor resection. Known cancer associated genes like FOXO3 or NCOA3, and genes in regulative sites of cell proliferation, migration or metabolism like CUL4A, NOTCH2NL or FLG were identified.
Discussion: The application of whole exome sequencing has led to the identification of a mutation pattern of prognostic value. Our data suggest that the found candidates play an important role in the prognosis of recurrence for UICC II colorectal cancer patients. The potential candidate genes will be further validated on a cohort of 180 patients by a hybridization-pulldown-method in combination with Duplex-Sequencing. We aim to establish a gene signature for patients with a high risk of recurrence which may help to optimize therapeutic decisions.

ID 0403

Repeated anti-CEA radioimmunotherapy (RIT) with 131I-Labetuzumab after complete resection of colorectal liver metastases – safety, feasibility and long-term efficacy results of a prospective phase-II-study

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Background: Previously, a single dose of anti-CEA 131iodine(I)-labetuzumab radioimmunotherapy (RIT) after complete resection of colorectal liver metastases (CLM) was well-tolerated and significantly improved survival compared to a control group without RIT. In this phase II study, we examined safety, feasibility and efficacy of repeated RIT in the same setting.
Methods: Sixty-three patients (median age 64·5 years) received RIT with 40-50 mCi/m2 per dose. Prior to RIT, restaging with CT/MRI and FDG-PET was performed to confirm patients being "truly adjuvant". Patients with elevated serum CEA or suspected lesions were classified as "non-adjuvant," but also received RIT. Time to progression (TTP), overall survival (OS), and cancer-specific survival (CSS) were calculated. The median follow-up was 54 months.
Results: After the first RIT, 14/63 patients experienced NCI-CTC grade 4 hematotoxicity; 19 patients did not receive the second RIT due to impaired performance status (N=5) or metastatic relapse (N=14). 6 patients received the planned second cycle of RIT after re-resection of limited metastatic recurrence. After the second RIT, 9/44 patients experienced NCI-CTC grade 4 hematotoxicity. During follow-up, 5 patients developed a myelodysplastic syndrome 22-55 months after their last RIT. The median TTP, OS and CSS for all patients were 16, 55 and 76 months, respectively. The "truly adjuvant" patients (N=39) had an improved median TTP (NR vs. 6·1 months, HR 0·12, P<0·001), OS (75·6 vs. 33·4 months, HR 0·44, P=0·014) and CSS (NR vs. 41·4 months, HR 0·32, P=0·003) compared to "non-adjuvant" patients (N=24).
INTERPRETATION Repeated RIT is safe and feasible. Survival is very encouraging, in particular for patients deemed "truly adjuvant."

ID 0424

MRI-based indication for primary surgery for rectal cancer – a possible alternative to the standard of neoadjuvant chemoradiation? Interim analysis of the German OCUM–Studie (NCT 01325649)

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Introduction: Surgery and neoadjuvant chemoradiation entail a reduction in quality of life by functional impairment. In a prospective multi-center observational study (OCUM-Study) neoadjuvant chemoradiation was only given when circumferential tumor margin (CRM) was less than 1 mm. We aimed to determine whether adequate surgical quality was achieved regarding different surrogate parameters.
Patients and Methods: In 16 hospitals patients with rectal cancers (cT2-4, jedes cN, M0) received only chemoradiation when a cT4 tumor or a circumferential margin (CRM) of ≤ 1 mm were present in a pretherapeutic MRI. 642 patients were included. In 506 patients a UICC II oder UICC III situation was present. Independent of CRM all T3 Tumors were irradiated when located in the lower third.

Results: pCRM (p = pathology) was positive in 36/640 (5.6%) patients. pCRM+ rate was 37/642 (5,8%), while the pCRM – rate was 605/642 (94,2%). Variation between hospitals was between 90 and 96.4%, p = 0.462. 8/642 specimen were dissected in the „intramesorektal plane". Variation was 0–4%, p = 0.147. Tumor cell dissemination occurred in 25/642 patients (3.9%). Variation between hospitals was from 0 to 9%, p = 0.009. Rate of chemoradiation was 253/262 patients (39.4%). In 506 of 642 patients a UICC II oder UICC III stage was present. Standard indication for chemoradiation according to guidelines would have implied chemoradiation in 506/604 (79.1%)
Conclusions: Rate of positive margins did not increase. The number of complete specimen was high. Thus, limiting neoadjuvant chemoradiation by use of MRI appears possible without compromising short-term surgical quality.

ID 0503

Modelling effects of oncogenes in the intestine to identify target combinations for therapeutic intervention

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To develop effective cancer therapies, we need to know which changes in the wiring of signalling networks drive tumour initiation and progression. WNT, MAPK and PI3K represent the pathways most commonly affected in colorectal cancer (CRC). To model the impact of frequent oncogenes in CRC, we have established 3D intestinal organoid cultures from transgenic mice carrying inducible oncogenes. Since the 3D cultures consist of native epithelium comprising all cell types, we can directly assess the influence of individual oncogenes or combinations on signalling cascades, cellular phenotypes and cell hierarchies.
We find that oncogene-inducible organotypic cultures display distinct phenotypes upon oncogene induction (Farrall *et al.*, 2012; Riemer *et al.* 2014), e.g. shift of cell composition to a uniform, stem cell like phenotype in the case of stabilised β-Catenin, or to stem cell abrogation when oncogenic BRAF is induced. We used small molecule inhibitors and interrogated the activation state of critical signalling nodes to gather information on cellular signalling networks at multiple levels: Which cancer-related phenotypes can be induced by the oncogene? How does the respective oncogene impinge on the regulatory network? Can this impact be abolished by intervention at certain nodes? Are there bypasses to the blocks imposed? Systematic data acquired in these experiments allow computational modelling of the different states of signalling networks of CRC. Our systems biology approach will give insights into which combinations of therapeutic targets may be relevant to impair CRC cells carrying specific combinations of oncogenes.

ID 0514

The occurrence of mutant KRAS clones in the blood of RAS wild type colorectal cancer patients – impact of response or failure under anti-EGFR therapy

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Issue: Colorectal cancer (CRC) is characterized by a high level of genetic heterogeneity. In addition, changes in the genetic profile induced by chemotherapy affect treatment results. Acquired resistance of tumors is defined as a result of clonal evolution and clonal selection under systemic chemotherapy. Repeated tumor tissue biopsies are difficult to obtain and cannot be easily used for dynamic monitoring of therapy response or failure due to marked tumor heterogeneity. Promising data for circulating cell-free tumor DNA (ctDNA) as a tool for studying tumor evolution were recently published. In this study, we analyzed ctDNA from patients with metastatic CRC during treatment with anti-epidermal growth factor receptor (EGFR) antibodies (cetuximab/panitumumab).
Methods: By droplet digital PCR we performed genotyping of CRC tissue and tracking of clonal evolution of the most frequent KRAS mutations (G12A, G12C, G12D, G12R, G12S, G12V, G13C, G13D, Q61R, A146T and A59T).
Results: In initial KRAS wild type tumors several mutated KRAS clones occurred in plasma under the course of anti-EGFR-therapy indicating an increasing acquired resistance to the given therapy leading to a disease progression. Some of these mutations declined upon discontinuation of anti-EGFR therapy.
Conclusion: The initial state of KRAS wild type situation seems to be restored in some cases. This opens up the possibility to reinduce anti-EGFR therapy in later therapy lines.

Gastrointestinal (Noncolorectal) Cancer

ID 0073

A confirmatory randomized controlled trial with mistletoe extract on overall survival in patients with locally advanced or metastatic pancreatic cancer

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Background: Current second line treatments for late-stage pancreatic cancer patients are often so toxic that their risk-benefit ratios are unfavourable. Therefore, effective but non-toxic therapeutic approaches should be examined. Mistletoe extract (ME) therapy claims to be both, effective and non-toxic. The aim of this study was to assess the efficacy of ME regarding the overall survival (OS), quality of life (QoL), and safety in patients with locally advanced or metastatic adenocarcinoma of the pancreas.
Methods: In this randomized study (ISRCTN70760582) patients were stratified according to a binary prognosis index and evenly randomized to receive s.c. injections of ME (Iscador® Qu) in a dose-escalating manner from 0.01 mg up to 10 mg three times per week, or no antineoplastic therapy (control). All patients received best supportive care. The primary endpoint was 12-month OS. Secondary efficacy parameters were the QoL dimensions of the core questionnaire of the European Organization for Research and Treatment of Cancer assessed at month 1, 2, 3, 6, 9, and 12.
Results: After 220 patients a preplanned interim analysis was done. Baseline characteristics were well balanced between the ME and control group. Median OS for ME versus control patients was 4.8 vs. 2.7 months (prognosis-group adjusted hazard ratio, HR=0.49; p < 0.0001); within the 'good' prognosis subgroup 6.6 vs. 3.2 months (HR=0.43; p < 0.0001); within the 'poor' prognosis subgroup 3.4 vs. 2.0 months (HR=0.55; p = 0.0031). In thirteen of the 15 QoL dimensions ME was significantly and relevantly superior to control. Subgroup analyses as well as investigator rating and body weight support these findings. No ME-related serious or non-serious adverse events were observed.
Conclusion: ME therapy showed a significant and clinically relevant increase of OS and QoL. The independent data monitoring committee recommended the termination of the trial due to proven efficacy after the interim analysis. ME may provide an effective and non-toxic second-line therapy for patients with locally advanced or metastatic pancreatic cancer.

ID 0144

Innovative substance 2250, a derivative of taurultam, shows anti-neoplastic effects in malignant pancreatic carcinoma in vitro and in vivo

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In former studies the anti-infective agent Taurolidine (TRD) revealed anti-neoplastic properties against many tumor species *in vitro* and *in vivo*. The anti-proliferative and cell death inducing capacity of TRD is caused by several metabolities a.o. Taurultam (TRLT). In this study it is shown for the first time, that substance 2250 - a newly defined innovative derivative of TRLT – displays an anti-neoplastic effect on malignant pancreatic carcinoma *in vitro* and *in vivo,* along with a longer metabolic stability. In extensive *in vitro* analysis the anti-neoplastic potential as well as the mode of action of substance 2250 was demonstrated, followed by successful and effective *in vivo* testings using xenograft models derived from established pancreatic cancer cell lines as well as patient derived tissue.
This is the first study providing an evaluation of the newly developed substance 2250 induced cell death among several pancreatic cancer cell lines *in vitro* and inhibition of pancreatic tumor growth *in vivo*. In pursuing functional analysis of the involvement of ROS driven and caspase activated programmed cell death we were able to show, that this oxidative stress plays the major role inducing cell death in pancreatic carcinoma. Especially the inhibition of xenograft derived pancreatic cancer tumor growth in mice and the sharply higher metabolic stability of this new substance are strongly relevant towards clinical practice and provide new therapeutical opportunities in pancreatic cancer treatment. These encouraging results build the basis for further functional analysis and first clinical studies for this promising agent.

ID 0168

Rac1b negatively controls transforming growth factor (TGF)-β-induced epithelial-mesenchymal transition and cell motility in pancreatic ductal adenocarcinoma cells by inhibiting both Smad and non-Smad signaling

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Introduction: In pancreatic ductal adenocarcinoma (PDAC), TGF-β1 mediates its prooncogenic effects, e.g. epithelial-mesenchymal transition (EMT) and migration/invasion of tumor cells, in part through the small GTPase Rac1. Prompted by the recent detection of an alternatively spliced Rac1 isoform, Rac1b, in PDAC tissue, we asked whether Rac1b affects EMT and cell motility in the same or in a different way as Rac1.
Methods: Transfection of small interfering RNA (siRNA) was used to selectively knockdown Rac1b. Gene expression analysis was done by real-time PCR, and cell motility was measured by realtime cell migration assay. Results: SiRNA-mediated knockdown of Rac1b in the PDAC cell lines Panc1 and Colo357 attenuated the TGF-β1-dependent down-regulation of E-cadherin but amplified the TGF-β1 response of various other genes involved in EMT (Snail, Slug), and migration/invasion (PAI-1, MMP2, MMP9). Moreover, siRNA-mediated silencing of Rac1b enhanced the ability of TGF-β1 to stimulate cell motility, while cosilencing of Rac1 and Rac1b, or ectopic expression of Rac1b in Panc1 cells attenuated TGF-β1-induced cell migration. The promigratory effect of Rac1b depletion was alleviated by pharmacologic or siRNA-mediated inhibition of Smad3, but not Smad2, by pharmacologic inhibition of p38 mitogen-activated protein kinase, or by ectopic expression of dominant-negative mutants of either p38 or MKK6. The Rac1b-deficient cells exhibited elevated levels of phosphorylated forms of Smad3 and p38.
Conclusions: The results suggest that Rac1b counteracts TGF-β1-induced EMT and, in contrast to Rac1, acts as an antagonist of TGF-β1-dependent cell motility by negatively regulating both canonical (Smad3) and non-canonical (p38) signaling.

ID 0207

Response to 6 cycles of chemotherapy with FOLFIRINOX is predictive of overall survival in patients with locally advanced unresectable pancreatic cancer

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Aim: Retrospective monocentric analysis of outcome of patients with newly diagnosed locally advanced unresectable pancreatic cancer (cM0) after induction chemotherapy with FOLFIRINOX.
Methods: Between 4/2012 and 7/2015 27 patients (13 female, 14 male) underwent induction chemotherapy with 6 cycles FOLFIRINOX(Calciumfolinate 400mg/m²BSA d1, Irinotecan 180mg/m²BSA d1, Oxaliplatin 85mg/m² BSA d1, 5-FU 400mg/m²BSA d1 and 2400mg/m²BSA over 48h).
Median age was 65 years (range: 45–78).
Median Follow-Up was 52 weeks (range: 16–160).
Results: All patients received 6 cycles of FOLFIRINOX. In 14 patients(52%) a dose reduction was performed.
After 6 cycles of FOLFIRINOX 14 patients(52%) showed CT-morphologic partial remission, 9 patients(33%) showed stable and 4 patients(15%) progressive disease.
After 1 year cumulative overall/progression-free survival (OS/PFS) was 70,8%/56,4%.
By comparing responders (partial remission, stable disease) and non-responders (progressive disease) after 6 cycles of FOLFIRINOX the responders showed a cumulative 1year-OS of 87,9% and the non-responders of 0% (log-rank-test: $p < 0.0001$).
None of the non-responders showed a response to a second-line chemotherapy.
In the further course of treatment a tumor resection (8xR0-resection, 1xR1-resection) could be performed in 9 out of 27 patients(33%).
After 1 year patients who underwent tumor resection showed a cumulative OS of 83,3%, patients without resection showed a 1year-OS of 64% (log-rank-test: $p = 0,51$).
Conclusion: In patients with locally advanced unresectable pancreatic cancer response to 6 cycles of chemotherapy with FOLFIRINOX correlates significantly ($p < 0,0001$) with OS. In one third of patients a tumor resection could be achieved.

ID 0233

Correct decision processes are essential in curative therapy of gallbladder cancer

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Background: The S3 guidelines valid till 2015 have recommended radical re- resection (RR) in up to T2 stages. The new guidelines recommend RR even in T1b. According to the data of the German- registry the indication for RR in Germany depends more on the experience of the hospitals in liver surgery than on complying with the guidelines, so most of IGBC`s are staged and not treated oncological sufficiently. In practice there are the following questions asked. Is the biologic behavior of GC underestimated? Depends the therapy of patients with IGBC in Germany on the surgical or oncological expertise of the clinics? Which technique of liver resection (LR) is meaningful in which stage? What is important regarding lymph node ratio (LNR).
Methods: For data analysis, we used the German Registry.

Results: To date more than 900 cases of IGBC have been analyzed. There was a significant survival benefit for the 42 Tb, 228 T2 and 80 T3 patients after RR. Comparison of LR techniques showed good results for the wedge resection in T1b and T2. For T3 more radical techniques are needed. Less than 50% of T2-3 tumors in the registry have been re-resected. LR was performed significantly more often in High- volume (HV) clinics. In 212 patients the LNR could be calculated. Statistical analysis showed that LNR is a significant prognostic factor. The results show that the referral of patients from a LV to a HV has no practical relevance.
Discussion: IGBC`s up to T1b needs a radical surgery. Complying the S3-guidelines is essential even in rare tumors. The wedge resection technique is an attractive procedure for T1b and T2 IGBC due to the lower invasiveness in spite of oncological adequacy and implantation of this technique should also be possible in LV`s. Also the count of retrieved lymph nodes is of essential interest. By following the correct decision processes more patients in Germany have the possibility for cure in GBC.

ID 0249

Targeting notch for myeloid reprogramming in pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) is characterized by two major hallmarks. First, insufficient therapeutic treatment options leading to poor prognosis and short survival rates. Second, a complex stromal reaction quantitatively exceeding the one found in other tumors by far. A progressive immune cell accumulation associated with PDAC development suggests multiple potential targets for immunotherapeutic interventions. However, despite overwhelming success in many other solid tumors, therapeutic immune checkpoint blockade failed in clinical trials of human PDAC highlighting the urgent need for in-depth analysis of PDAC-associated immune networks.
We investigated the different roles and interactions of infiltrating lymphocyte as well as myeloid-derived subpopulations in the context of PDAC using genetically engineered mouse (GEM) models which particularly recapitulate human tumorigenesis and desmoplasia. Applying antibody-mediated immune cell depletion and genetic target cell manipulation we were able to specifically dissect the multifaceted immune environment of spontaneous pancreatic cancer in mice. Taking advantage of a novel combined Cre/LoxP-Flp/FRT approach we were able to activate or abolish canonical Notch-signaling genetically in a myeloid cell-restricted manner in addition to pancreas-specific Kras-driven tumorigenesis. Myeloid Notch-activation was found to diminish M2-macrophage polarization and translated in prolonged survival of GEMs.
Here we describe a genetic animal model functionally reprogramming tumor-associated myeloid cells thereby opening an avenue to overcome immunosuppression and to provoke susceptibility for potential immunotherapies in pancreatic cancer.

ID 0283

The role of Pdk1-dependent signaling pathways in pancreatic cancer

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Objective: In pancreatic ductal adenocarcinoma (PDAC) the mutation of the oncogene Kras plays a decisive role. It initiates carcinogenesis via different signaling cascades including the PI3K-Pdk1 pathway. The deletion of the 3-phosphoinositide dependent protein kinase 1 (Pdk1) entirely blocks the formation of precursor lesions and PDAC in a pancreatic cancer mouse model. The aim was to further analyse downstream kinases of Pdk1 to define novel therapeutic targets.
Methods: Pdk1 has two regulatory domains, i.e. the PH-domain activating Akt and the PIF-pocket-domain regulating Sgk, Pkc and Rsk. Using two different Pdk1 mutant alleles, $Pdk1^{K465E}$ and $Pdk1^{L155E}$, we blocked the activation of each domain particularly. For this, we crossed these alleles into the genetically engineered endogenous $Ptf1a^{Cre/+}$;$LSL\text{-}Kras^{G12D/+}$ pancreatic cancer model. Pancreatic tissue of mice at 3, 6, 9 and 12 month of age were analysed for tumor formation and compared to $Ptf1a^{Cre/+}$;$LSL\text{-}Kras^{G12D/+}$ mice.
Results: Recombination of the mutant Pdk1 alleles in the pancreas was shown by PCR using microdissected pancreatic tissues. Western blot and immunohistochemistry indicated a downregulation of targets of Pdk1 in the respective knock-in mice. Despite expression of oncogenic Kras, inactivation of each regulatory domain resulted in a reduction of preneoplastic pancreatic intraepithelial lesions (PanIN) and blocked cancer development in the animals within one year. Aged $Pdk1^{L155E}$-mutant animals evolved pancreatic atrophy.
Conclusion: These results support the pivotal role of Pdk1 and imply that both regulatory domains and their downstream kinases are essentially involved in pancreatic tumorigenesis. Further research will help to clarify their potential as targets for therapy in human PDAC.

ID 0287

Clinical validation of response and resistance factor candidates to targeted therapy in gastric cancer (GC)

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Background: 10–20% of GC overexpress HER2, a membrane-bound receptor tyrosine kinase (RTK) which belongs to the epidermal growth factor receptor (EGFR) family.
Drugs against HER2 and EGFR have shown variable success in the treatment of advanced GC. While EGFR targeting therapies failed to improve outcomes, trastuzumab addressing HER2 has been approved for stage IV HER2+ GC. Until now, primary and secondary resistance against RTK-directed treatment of GC is not well understood. The VARIANZ study, which is part of the SYS-Stomach consortium (supported by the German Federal Ministery of Education and Research, BMBF) aims to assess resistance mechanisms in HER2+ tumor samples from patients receiving trastuzumab.

Methods: HER2 status was verified centrally by two pathologists (KS and CW). In a second step, samples will be used to validate resistance factors that are identified as interesting candidates by in-vitro and in-silico modelling within the consortium.
Results: From 26 May 2014 to 31 July 2015, we have enrolled 142 patients in 30 active German sites in this ongoing project. At present, 105 samples were fully characterized for HER2 status by immunohistochemistry (IHC) and in-situ-hybridization (ISH). According to criteria from the Trastuzumab for Gastric Cancer (ToGA) study, 28 of 105 samples were HER2+ in central testing. In 16 samples that were diagnosed as HER2+ by local pathologists the HER2 status could not be verified centrally. 5 HER2-probes in local testing were characterized as HER2+ by central testing.
Conclusions: HER2-expression in GC appeared to be heterogeneous and still not easy to assess. Variability between local and central HER2 assessment was significant. Robust biomarkers predicting resistance to HER2 and other target therapies are needed. Updated results will be shown at the congress.

ID 0353

Carbohydrate restriction inhibits malignant progression and survival of sorafenib-resistant murine hepatocellular carcinoma via reduction of PI3K/Akt/mTOR signaling

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Hepatocellular carcinoma (HCC) is characterized by robust therapy resistance and poor prognosis. Detailed understanding of the molecular pathogenesis of HCC is of pivotal importance to identify new therapy targets. As enhanced glycolysis is a key feature of cancer, we tested the antiproliferative efficacy of 2-deoxyglucose (2DG), an established inhibitor of glycolysis in a murine HCC model (ASV-B mice). However, 2DG was unable to reduce HCC progression in this model. Compensatory activation of glucose uptake has been shown to mediate resistance to 2DG in vitro. In order to test the in vivo relevance of this observation, we fed our mice a carbohydrate restricted diet (15% vs. 50% in standard chow). While the efficacy of 2DG was not affected, carbohydrate restriction per se resulted in significant inhibition of tumor progression and survival. Blood as well as intratumoral glucose levels were unaffected by dietary carbohydrate, ruling out diminished glucose availability as an explanation for the observed effect. Intriguingly, mitogenic signaling via insulin receptor/PI3K/Akt/mTOR was significantly reduced by the diet. Taken together, we were able to show that a simple modification of macronutrients is able to exert significant growth inhibition in a murine HCC model. Our results are especially intriguing as ASV-B mice are resistant to sorafenib and support a critical role of macronutrient composition (especially carbohydrate content) for HCC therapy. As low carbohydrate diets have been safely used for almost a century, clinical application of these results seems feasible.

ID 0465

Survival and symptom relief after palliative radiotherapy for esophageal cancer

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Purpose: The aim of this study was to assess the 6-months dysphagia-free survival, improvement in swallowing function, complication rate, and overall survival in patients with incurable esophageal cancer treated with palliative radiotherapy.

Methods: We retrospectively reviewed data from 139 patients (median age 72 years) with advanced/recurrent incurable esophageal cancer, who were referred to 3 German radiation oncology centers for palliative radiotherapy between 1994 and 2014. Radiotherapy consisted of external beam radiotherapy (EBRT) with 30–40.5 Gy/2.5–3 Gy per fraction, brachytherapy alone (BT) with 15–25 Gy/5–7Gy per fraction/weekly and EBRT + BT (30–40.5 Gy plus 10–14 Gy with BT) in 65, 46, and 28 patients, respectively. Dysphagia-free survival (Dy-PFS) was defined as the time to worsening of dysphagia for at least one point, a new loco-regional failure or death of any cause.
Results: Median follow-up time was 6 months. Subjective symptom relief was achieved in 72% of patients with median response duration of 5 months. The 1-year survival rate was 30%. The 6-months Dy-PFS time for the whole group was 73 ± 4%. The 6-months Dy-PFS was 90 ± 4% after EBRT, 92 ± 5% after EBRT + BT and 37 ± 7% after BT, respectively ($p < 0.001$). Five patients lived for more than 2 years, all of them were treated with EBRT ± BT. Ulceration, fistula and stricture developed in 3, 6 and 7 patients, respectively.
Conclusions: Radiotherapy leads to symptom improvement in the majority of patients with advanced incurable esophageal cancer. The present results favor EBRT ± BT over BT alone. Due to the retrospective nature of this study, imbalances in baseline characteristics might have contributed to this finding, and further trials appear necessary.

ID 0478

Little evidence, big efforts – surveillance situation in Germany in resected pancreatic adenocarcinoma patients – results from an AIO-pancreatic cancer group survey

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer related deaths in Germany. Only 15–20% of patients are in a potentially curable situation. Nevertheless, there are no evidence-based or even consensus-based guidelines for surveillance strategies for these resected patients during and after adjuvant chemotherapy. In our opinion, nearly everyone does it, no one tells about it and no one knows, if high-level surveillance efforts are worth it and generate a survival benefit for patients.
Methods: We did an questionnaire-based online survey in spring 2015 among German institutions (hospitals, outpatient clinics and private practices) experienced in treatment of pancreatic cancer patients. The questionnaire included 25 questions concerning the institutions itself and their practice in adjuvant/additive setting after resection of a pancreatic cancer.
Results: In total 161 institutions replied. 29% of the institutions were certified pancreatic cancer centers of the German Cancer Society (DKG), 25% were university hospitals and 10% private practices. In 82,4% of all institutions surveillance procedures exceed only laboratory testing during adjuvant chemotherapy this includes staging imaging (CT, MRI) in 63,7% of patients after 3 months. After termination of adjuvant chemotherapy 76,5% of institutions perform CT/MRI scan, 72,3% use abdominal ultrasound and 92,9% use CA19-9 as a tumor marker. 96% of all institutions perform a surveillance and nearly half of them for 5 years.
Conclusions: Here we can present an overview of the broad spectrum of surveillance strategies used in Germany. This survey suggests that despite little evidence extensive surveillance is frequently performed after R0/R1 resection of PDAC. This calls for a prospective evaluation of the different surveillance tools.

ID 0535

ALPPS (in situ split with right portal vein ligation) – where is the perfect niche in multimodality treatment of liver tumors?

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Background: ALPPS (in situ split with right portal vein ligation enabling right extended 2-stage hepatectomy) is a tremendous evolution in modern hepatic surgery for borderline resectable malignancies. However, morbidity (25%) and perioperative mortality (3 out of 27 initial cases) was deemed far beyond acceptable thresholds. An international registry and a first international meeting of experts earlier this year, helped to define optimal indications and put them into a perspective of currently concurring and established treatment modalities.
Patients and Methods: Report of patients included in the ALPPS registry until 06/2015 with follow-up data of at least 3 months were included in this morbidity, mortality and oncology focused analysis.
Results: 372 patients (78% with colorectal liver metastasis) undergoing ALPPS were analyzed. Mean age was 59±11,8 years. Time from diagnosis to ALPPS was 368±771 days. Of 246 patients with CRLM, 194 had synchronous metastases. 208 patients underwent 7,5 cycles of different mostly FOLFIRI/FOLFOX/antibody-based chemotherapy and 103 patients underwent another 7,4 cycles. Mean time from chemotherapy to ALPPS was 120±277 days. Overall survival for CRLM was significantly better than for other primary and metastatic tumors (Chi-square: 31,1; p = 0.0001). Mean overall survival for CRLM was 648 days (95%CI: 608; 686). Time to recurrence was 222 days in 157 patients with recurrence. Morbidity represented by complications exceeding Dindo-Clavien IIIa were 19% and thus in an acceptable range.
Conclusions: ALPPS is safe and equivalent to other 2-stage procedures in patients with colorectal liver metastases in patients with a long history of disease.

Genitourinary Cancer including Prostate Cancer

ID 0057

Options for treatment of lymph node recurrence of penile cancer

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Background: Effective primary management is a prerequisite for curative therapy of penile cancer. Compromises in the treatment often lead to lymph node recurrences, which are prognostically unfavorable. Recurrences are distinguished within the first 2 years after diagnosis. Recurrences of penile cancer require a consistent multimodal treatment. The aim of this study is to investigate the effectiveness of the treatment options for lymph node recurrence.
Material and Methods: Included patients (n = 10) suffered a lymph node recurrence after a primary therapy. The average age of patients at onset of disease was 56 years. The patients showed a lymph node recurrence within 17 months after initial therapy. We admitted a neo-adjuvant chemotherapy concept followed by resection of residual tumor.
Results: A response with partial remission under systemic neo-adjuvant therapy with gemcitabine / cisplatin or paclitaxel / cisplatin or carboplatin and 5-FU was observed in 4 patients. Subsequently performed the resection of residual tumor. These patients are currently disease-free. 4 patients showed progression despite systemic therapy. In 2 patients could not achieved local control despite neo-adjuvant therapy because of disease extent.
Conclusion: Lymph node recurrences can be successfully treated by a multimodal therapy in patients with penile carcinoma. Some of the patients benefited from an aggressive approach with paclitaxel / cisplatin / 5-FU. Early detection of lymph node recurrence by a risk-adapted follow-up provides better chances for curative treatment.

ID 0120

Renal function after nephron-sparing surgery and radical nephrectomy – a 13-year single-center analysis

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Background: Over the past ten years the guidelines for therapy of localized renal cell carcinoma (RCC) have changed. The indication for nephron sparing surgery (NSS) has been extended considerably. There is still a lack of information on how pronounced the protective effect on renal function is as compared to radical nephrectomy.
Objective: In this retrospective monocentric analysis the laboratory parameters referring to nephron protection were compared for a 13 year kidney cancer cohort undergoing either partial nephrectomy (PN) or radical nephrectomy (RN).
Patients and Methods: 718 patients treated for a renal mass from 2001 to 2013 were assessed. We compared the two surgical techniques (533 RN vs. 185 PN) for pre- and postoperative serum creatinine, urea and glomerular filtration rate. We used the Mann-Whitney-U-test for interval-scaled values (median of laboratory parameter) to explore significant differences between the two surgical groups. Laboratory assessments were performed preoperatively, at hospital discharge and 3–12 months postoperatively.
Results: Preoperatively, the GFR was significantly better in the PN cohort (75 vs. 65 ml/min/1,73m^2; p = 0.012), creatinine and urea were comparable in the 2 groups.
All postoperative renal function parameters were significantly better (p < 0.001) in the PN – cohort (creatinine: PN 1,04 vs. RN 1,4 mg/dl; urea: PN 32 vs. RN 37 mg/dl; GFR: PN 71 vs. RN 43 ml/min/1,73m^2). Late postoperative creatinine and GFR were significantly better in the PN group as well (p < 0,001).
Conclusion: In patients undergoing RN, renal function decreased significantly higher as compared to patients undergoing PN. The results of our analysis support the therapeutic guidelines for localized renal cell carcinoma in favour of PN.

ID 0142

Lässt sich die Umsetzung neuer Leitlinien über das klinische Krebsregister nachvollziehen? Nierentumorchirurgie im klinischen Alltag

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Hintergrund: Während bis zum Jahr 2006 in den Leitlinien der European Association of Urology für alle Nierentumoren die radikale Tumornephrektomie als Standard empfohlen wurde, gewann die nierenerhaltende Chirurgie in den Folgejahren an Bedeutung und sollte seit 2010 - sofern technisch realisierbar – bei allen lokal begrenzten Nierentumoren angestrebt werden.
Methodik: An Hand der an das regionale klinische Tumorregister gemeldeten histologischen und Operationsdaten aus sieben urologischen Kliniken wurde die Entwicklung der Nierentumorchirurgie im Zeitraum von 2000 bis 2014 retrospektiv evaluiert.
Ergebnisse: Insgesamt erfolgten an den 7 Kliniken 3320 operative Eingriffe bei Nierenzellkarzinomen, davon 2149 (64,7%) / 195 (5,9%) / 891 (26,8%) / 35 (1,1%) bei pT1/pT2/pT3/pT4-Tumoren. Die Rate der Nie-

renteilresektionen bei pT1-Tumoren betrug 2005 27%, 2010 51,3% und 2014 73,6% Teilresektionen mit stabiler Teilresektionsrate 2013/2014. Die Teilresektionsquote bei pT1-Nierenzellkarzinomen schwankte zuletzt zwischen 48,4 und 93,8% (2014). Durch den breiten Einsatz der Nierenteilresektion nahm die Anzahl dieser Eingriffe auch bei lokal fortgeschrittenen Tumoren des Stadiums pT3 auf zuletzt 16% zu. In der retrospektiven Analyse zum Gesamtüberleben zeigt sich ein Überlebensvorteil der teilresezierten gegenüber den nephrektomierten Patienten, der altersabhängig abnimmt und in der Gruppe >70 Jahre keine statistische Signifikanz mehr erreicht.
Zusammenfassung: Die Nierenteilresektion ist als Standardeingriff beim Nierenzellkarzinom pT1 in unserer Region etabliert. Die im klinischen Tumorregister dokumentierten Daten lassen die Änderung der europäischen Leitlinie über die Jahre und deren Umsetzung im klinischen Alltag gut nachvollziehen und eignen sich daher als Instrument zur Qualitätssicherung.

ID 0299

Medication safety in patients with metastatic castrate-resistant prostate cancer treated with enzalutamide or abiraterone – the observational study ENZABI focussing on drug-drug interactions. Supported by the German Cancer Aid within the Comprehensive Cancer Center Erlangen-EMN

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Aim: The new oral anticancer drugs enzalutamide and abiraterone, used for treatment of metastatic castrate-resistant prostate cancer (mCRPC), have a major potential for various drug-drug interactions. Abiraterone is an inhibitor of CYP2D6 and enzalutamide enhances metabolism of multiple drugs due to induction of CYP3A4 and transporters. The observational study ENZABI is designed to identify potential drug-drug interactions (PDDI), occurring in clinical routine, and to improve medication safety in treatment of mCRPC.
Methods: In the urologic-oncological outpatient clinic (AURONTE), a clinical pharmacist carries out a structured interview with each patient receiving enzalutamide or abiraterone. To gather a complete medical history, patients' medical records and patients' general practitioners (GP) are consulted. An extended medication review is provided to the attending physicians. The advices regarding the patients' medication are classified in 3 categories: critical warnings are highlighted red, general recommendations blue and advices already taken into consideration green.
Results: In this ongoing study, until now 11 patients (mean age: 74 years) were recruited. On average, patients took 12.3 (8-17) drugs. Over-the-counter medication was used by 90.9%. So far, a total of 68 advices regarding the patients' medication were given: 6 (8.8%) red, 46 (67.6%) blue and 15 (22.1%) green advices. PDDI with opioids were frequently observed.
Conclusions: Healthcare professionals should always care for potential drug-drug interactions caused by enzalutamide or abiraterone. To achieve further improvements in medication safety in oncology, efforts towards an interdisciplinary medication management have to be pursued.

ID 0385

Adjuvant chemotherapy after radical cystectomy in patients with advanced bladder cancer – who benefits?

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Objective: Currently, there is still a lack of evidence regarding the value of adjuvant chemotherapy for patients with ≥ pT3 and/or pN+ bladder cancer following radical cystectomy, since randomized trials did not recruit the number of patients required and yielded divergent results.
Patients and **Methods:** 80 patients with stage ≥ pT3 and/or pN+ urothelial carcinoma of the bladder were retrospectively analyzed. 17 patients received adjuvant gemcitabine / cisplatin (GC; group A), whereas the remaining 63 patients received chemotherapy at time of relapse (group B).
Results: There was a substantially higher rate of pN+ patients in group A (88.2%) compared to group B (39.7%). Patients in group A were also significantly younger. No differences were observed with respect to gender, Charlson-Score, pT-stage, R-status and the number of removed lymph nodes.
The median overall (OS) and progression free survival (PSF) were 54.4 and 18.9 months for group A and reduced to 26.3 and 10.2 months for group B (P=0.309 ; P=0.612). The subgroup of pN+ patients showed a significant increase in OS (54.4 vs 22.4 months; p = 0.029) and PSF (18.9 vs 6.4 Mo.; p = 0.007) in favor of patients who received adjuvant GC.
Conclusion: Although this study is small and retrospective, it supports the suggestion of the latest metaanalysis that particularly patients with lymph node metastases might benefit form adjuvant GC chemotherapy.

ID 0418

Characterization of B-cell subsets in renal cell carcinoma

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Background: In contrast to the impact of T cells on the natural biology of renal cell carcinoma, the role of tumor associated B cells is poorly investigated so far. Against this backdrop, the aim of this study was to characterize functionally different B-cell subsets in renal cell carcinoma.
Methods: Peripheral blood mononuclear cells (PBMC) (n = 13), tumor samples (n = 10) and normal tissue (n = 6) from patients with a diagnosis of RCC as well as PBMC of 20 healthy controls (HC) were collected. B-cell subsets were analyzed by 10-color flow cytometry.
Results: The percentage of absolute B cells (CD19+/CD20+ in % of CD45+ cells) was similar in tumor samples, normal renal tissue and PBMC of tumor patients as well as in healthy controls. In contrast to other tumor entities, activated (CD86+) or memory B cells (IgD-/CD27+) were not elevated in renal tumor samples. Empirical data suggested an elevated fraction of plasmablasts (CD19+/CD20-/CD27+/CD38high in % of CD19+) in the tumor microenvironment. Furthermore, this subset was elevated compared to normal tissue. While regulatory CD24high/CD27+ B cells were not elevated in cancer patients, our analyses revealed an increased fraction of CD24high/CD38high regulatory B cells in PBMC of tumor patients compared to healthy controls.
Conclusion: Our analyses indicate a rather naïve B-cell infiltrate in renal cell carcinoma. Furthermore, we found increased percentages of transitional B cells. Following research has to evaluate if regulatory B-cell subsets may represent a novel therapeutic target for a highly immunogenic disease. This abstract constitutes preliminary data. Sample size will be expanded.

ID 0480

Reduced disqualification rates when MRI-targeted transperineal fusion biopsies are used instead of standard 12-core systematic biopsies for selection of prostate cancer patients for active surveillance

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Background: Active surveillance (AS) is commonly based on standard 10-12 core prostate biopsies, which misclassify approximately 50% of cases compared to radical prostatectomy.
We assessed the value of multiparametric magnetic resonance imaging (mpMRI)-targeted transperineal fusion biopsies in men under AS.
Methods: 149 low-risk prostate cancer (PC) patients were included in AS according to PRIAS criteria between 2010-2015. 45 patients were initially diagnosed by MRI/TRUS-fusion biopsy. 104 patients first underwent standard biopsy followed by MRI-targeted biopsies for restratification and follow-up. MpMRI were analyzed using PIRADS.
AS-disqualification rates for men initially diagnosed by standard or fusion-biopsy were compared using Kaplan-Meier estimates. Detection rates between systematic (SB) and targeted biopsies (TB) on MRI/TRUS-fusion biopsy were analyzed using rate differences along with 95% confidence intervals. Regression analyses were performed to predict AS disqualification.
Results: In the initial fusion-biopsy cohort, upgrading occurred significantly less frequently during two-year follow-up compared to initial 12-core TRUS-biopsy subgroup (20% vs. 48%, $p < 0.001$). TB were significantly superior compared to SB to detect Gleason score-upgrading. PSA-level, initial PIRADS score ($p < 0.001$ each) and PIRADS score-progression on consecutive MRI ($p = 0.007$) were significant predictors of AS-disqualification.
Conclusions: Standard TRUS-biopsies lead to significant underestimation of PC under AS. MRI/TRUS-fusion biopsies lead to a significantly increased probability for patients continuing AS. Cancer detection with mpMRI alone is not yet sensitive enough to omit SB on follow-up after initial 12-core TRUS biopsy. After MRI/TRUS-fusion biopsy confirmed AS, it may be appropriate to biopsy only those men with suspected progression on MRI.

ID 0486

Comparison of three or fewer sequential high-dose chemotherapy cycles as salvage treatment in germ-cell tumors

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Background: Germ-cell tumors (GC) are highly curable with the stage-dependent use of platinum-based first-line chemotherapies. Nevertheless, 10% of the pts ultimately relapse. Sequential high-dose chemotherapy (HDCT) with autologous stem cell transplantation offers a curative option in these men. However, the number of HDCT cycles needed remains controversial.
Methods: In this single-center retrospective study, we analyzed the survival rates of 36 consecutive relapsed GC pts treated with 3 or fewer than 3 sequential HDCT as salvage treatment between 01/1997–12/2013.
Results: 34/36 pts had metastases at first diagnosis, with 5 pts having CNS metastases. Histology was seminoma in 10 pts. First-line regimens were BEP (n = 32), VIP(n = 3) or TIP (n = 1). 35/36 patients received 3 or more cycles. Relapsed pts were treated with carboplatin, etoposide and cyclophosphamide until 12/2000 (n = 8), or carboplatin and etoposide since 01/2001 (n = 28). 21 pts received 3 sequential HDCT, 8 pts had 2 HDCT, and 7 pts underwent one HDCT. Reasons for not having 3 HDCT were poor performance status (n = 4), pts decision (n = 4), toxicities (n = 3), early progression (n = 2), physician decision (n = 1) and suicide (n = 1). Remission rates were CR2 (18 pts;50%), PR2 (8 pts;22%); PD2 (6 pts;16.7%) and not evaluable in 4 pts (early death;11.1%). After a Ø follow-up of 84 mo, 44% of all pts remained in CR2, and overall survival (OS) was 58.3%. OS and PFS at two years were better in pts with 3 HDCT versus fewer (85% vs 33.3%,*P*=.0034; and 70% vs. 26.7%,*P*=.0044,respectively).
Conclusion: Our data suggest that three sequential HDCT are associated with better OS and PFS than fewer than three HDCT. We currently extend this analysis to all Swiss men with relapsed GC treated in this time period.

ID 0563

Genetic alterations in specific chromosomal regions indicate metastatic potential in ccRCC patients

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Introduction: A total number of specific aberrations (TNSA) score system was established as a promising prognostic test for individual risk assessment in ccRCC. The prognostic value of the 4 most promising aberrations was verified in an independent cohort and the technique was established on FFPE tissue for tissue micro array (TMA) processing. Expression analysis of genes located in the examined regions is to be performed to further understand the metastatic process.
Methods: FISH was performed on isolated cell nuclei from 37 ccRCCs (18 metastasized/19 non-metastasized) and 60 FFPE sections on TMAs from a second cohort (10 metastasized/50 non-metastasized). For each chromosomal region (1q21.3,7q36.3,9p21.3p24.1 and 20q11.21q13.32) commercially available FISH probes were used and the cut-off values for prediction of metastatic risk were determined by ROC-curve analysis. The expression of tumor associated genes was determined by quantitative real time PCR.
Results: TNSA and loss of 9p21.3p24.1 were significantly associated with metastasis (AUC = 0.829, p-value = 0.001 and AUC =0.787, p-Wert = 0.003). FISH analysis on FFPE samples of TMAs of an independent cohort confirmed these results. Loss of chromosome 9p21 leads to reduced expression of tumor associated genes CDKN2A, MTAP and PDL1. Furthermore CDKN2A expression levels correlate with occurrence of distant metastases.
Conclusions: We could validate TNSA as a prognostic score for metastatic risk. Interphase FISH proves to be a dependable method for prognostic evaluation in primary tumor tissue on isolated cell nuclei as well as on FFPE sections. Expression analysis of selected genes on 9p21 revealed a significant correlation between CNV and expression levels.

Geriatric Oncology

ID 0086

Factors influencing global HRQOL of elderly cancer patients – first results of a secondary data analysis

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Introduction: Cancer treatment of elderly people is often complicated by impaired functioning and the severity and number of comorbidities. Patient reported health related quality of life (HRQOL) can help evaluate expected treatment benefits against presumed side effects. Knowledge about the factors influencing HRQOL is needed for the development of supportive measures and care pathways intended to improve HRQOL.
Objective: The goal of the analysis was to generate hypotheses with respect to factors influencing global HRQOL of elderly cancer patients.
Methods: An exploratory secondary data analysis was performed on a data set of 518 questionnaire assessments of HRQOL in elderly cancer patients, comprising the EORTC QLQ-C30 (core questionnaire) and QLQ-ELD14 (elderly module). Preliminary univariate analyses were performed in order to identify possible influencing factors on global HRQOL (as measured by the QLQ-C30) to include in multivariable analyses. Three multivariable linear regression models were computed separately for: 1. QLQ-C30 functioning scales, 2. QLQ-C30 symptom scales, 3. QLQ-ELD14 scales.
Results: The strongest possible influence on HRQOL shown in model 1 was physical function (regression coefficient β=0.302, 95%CI: 0.186; 0.418) followed by social function and emotional function, in model 2 fatigue (β=-0.300, 95%CI: -0.391; -0.210) followed by pain and financial difficulties and in model 3 mobility (β=-0.198, 95%CI: -0.286; -0.111) followed by burden of illness and joint stiffness.
Conclusions: Physical function, fatigue and mobility seem to have the largest impact on HRQOL of elderly cancer patients. Prospective studies are needed to test whether individual supportive measures to improve these factors maximize the HRQOL of elderly cancer patients.

Gynecologic Cancer

ID 0008

Lymph node involvement pattern and survival differences of FIGO IIIC[1] and FIGO IIIA1[2] ovarian cancer patients after primary complete tumor debulking surgery – a ten years retrospective analysis of the Tumor Bank Ovarian Cancer Network (TOC)

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Objective: The main goal of the current study is to compare survival differences among subgroups of primary epithelial ovarian cancer (EOC) patients in FIGO IIIC[1] and FIGO IIIA1[2] stages after complete tumor debulking.
Methods: A total number of 218 patients with primary EOC who received complete cytoreductive surgery were included to the current retrospective analysis of validated TOC-Database, covers the periods January 2002 until December 2012. According to their tumor spread pattern patients were divided into 3 groups; A (peritoneum only), B (peritoneum and lymph nodes) and C (lymph nodes only). Associations between groups and clinicopathological factors were analyzed using standard statistic procedures.
Results: Lymph node involvement was detected in 70.5% of the cases where peritoneal implants presented ≥2 cm beyond pelvis (group A+B). The estimated 5-year overall survival (OAS) rates were 47.4% in group A, 45.1% in group B and 91.7% in group C ($p = 0.02$). Patients with paraaortic lymph node metastasis only that were in group B had better median progression-free survival (PFS) compared to patients with pelvic lymph node affection only and pelvic and paraaortic lymph node affection (28, 16 and 18 months, respectively, $p = 0.02$). The median OAS differed significantly between patients with paraaortic lymph node affection only versus patients with both pelvic and paraaortic affection (68.5 vs. 46.7 months, respectively, $p = 0.02$). 3-year PFS was 90.0% in FIGOIIIA1(i) and 62.6% in FIGOIIIA1(ii) (HR=2.30, 95%CI=0.45-11.58).
Conclusion: *Patients in FIGO IIIC stage with lymph node affection only have the best clinical outcome compared to patients of the same stage with peritoneal affection only. Furthermore, involvement of both pelvic and paraaortic lymph nodes are the same infrequency and involvement of only paraaortic lymph node in this stage has better survival chance than pelvic only or simultaneous of them. Our study revealed that, in comparison to FIGOIIIA1(ii), FIGOIIIA1(i) is prognostically better in accordance to revised FIGO classification of 2013.*

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ID 0257

Application and compliance of complementary medicine in patients with breast and/or gynecologic carcinoma

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Introduction: 50-70% of the patients suffering from a breast- and/or gynecologic carcinoma use complementary medicine (CAM). There is only limited data / research concerning the applied complimentary medication and CAM Compliance.
Material and Method: 291 patients with gynecologic cancers that underwent surgery in the Klinikum rechts der Isar in the period 2011-2013 and 285 patients with breast cancer (year 2012) were chosen to participate in this study. Two telephone surveys, one for CAM-users and one for NON-CAM-users were conducted with 333 patients. The survey contains general questions about the current situation of their disease and questions on CAM use and compliance.
Results: 58% (194/333) of the patients use complementary medicine. The most commonly used substance was selenium (53%), followed by phytochemicals (52%), dietary supplements (51%) and homeopathy (38%). The therapeutic compliance was 87% (168/194). Patients used CAM as a supportive measure for conventional therapies (85%) as well as to improve quality of life (83%). 72% (140/194) of the patients that used complementary medicine felt that their CAM therapy was equally or even more important than their conventional therapy. 53% (73/139) of the Non-CAM-users would have liked to have received more information on CAM from their physicians.
Conclusion: 80% of the patients suffering from breast- and/or gynecologic cancer are interested in CAM. 58% use substances that can be attributed to complementary medicine. The compliance was 87%. Physicians should put an emphasis on discussing complementary medical options with their patients.

ID 0278

Analysis of disseminated tumor cells before and after platinum-based chemotherapy in primary ovarian cancer. Do stem cell like cells predict prognosis?

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Background: We recently showed that the presence of disseminated tumor cells (DTCs) in the bone marrow (BM) of primary ovarian cancer patients (POC pts) significantly correlated with reduced progression free survival (PFS) and overall survival (OS). Here we analyzed whether the negative prognostic impact a) was related to the persistence of DTCs after *platinum* based chemotherapy and/or b) may arise from a cellular phenotype, being associated with stem cell character
Methods: 79 pts with POC were studied for DTCs before (BT) and after therapy (AT) using immunocytochemistry for pan-cytokeratin (CK). Eight pts harboring at least five DTCs AT were analysed on two2 additional cytospin slides by four-plex immunofluorescence staining for DAPI, CK (FITC), LIN-28 or SOX-2 (TRITC), CD45 and CD34 (Cy5). A DTC was characterized as a tumor stem cell in case of DAPIpos, CD45neg, CD-34neg, SOX-2pos/LIN-28pos and CKpos or CKneg as evaluated by microscopy.
Results: BT DTCs were detected in 42% or the POC pts (median DTC number (mDTC): 4; range 1-37) and in 41% (mDTC: 8, range 1-100) AT no change in positivity was observed in 13 pts, 20 pts were only positive BT and 19 pts became DTCpos AT. 27 pts were DTC-negative.
Presence of DTCs BT significantly correlated with reduced OS ($p = 0.024$). Patients who became DTCpos AT had a significant shorter PFS ($p = 0.025$). The persistence of DTCs resulted in a shorter PFS and OS reaching borderline significance ($p = 0.06$; $p = 0.07$). AT, LIN-28-as well as SOX-2 positive cells (both: mDTC: 7; range 1-11) were detected in all eight pts analyzed for these two proteins separately.
Conclusion: DTCs present AT show stem cell character and seem to be associated with worse outcome. Additional therapeutic regimens may be necessary to eliminate these cells

ID 0446

Prevalence of oropharyngeal human papilloma virus (HPV) in women with high-risk HPV-positive CIN 2-3

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Objectives: A subgroup of oropharyngeal squamous cell cancers (OSCC) is Human Papilloma Virus (HPV) associated. Co-prevalence of cervical and oropharyngeal HPV infection, ways of transmission, and adequate testing methods are still unknown.
Methods: Women with abnormal Pap smear admitted to the colposcopy unit University Center Hamburg-Eppendorf (UKE) and Medical Center Asklepios Altona received HPV-testing of the uterine cervix and the oropharynx via tonsillar brush, in the cohort from the UKE additional oral lavage was performed. Greiner bio-one (GBO) - PapilloCheck HPV-PCR was used to differentiate 24 HPV types.
Results: 235 women have been included in the study. 130/235 (55.3%) were cervically high risk HPV positive with histologically verified CIN II-III (median age 30, range 21-45 years). 7/130 (5.4.%) were oropharyngeally HPV positive. In 3/7 (4.3%) the same HPV types were detected cervically and orally. Tonsillar brush was HPV positive in 6/7 (85.7%) and oral HPV lavage in 2/7 (14.3%) patients. Only 2/130 (1.5%) cervically HPV positive women were also HPV positive in the oropharyngeal lavage (HPV 16 / high risk positive). 6/130 (4.6%) cervically HPV positive women were tonsillar brush positive. In only one case the same HPV types were found in lavage and tonsillar brush test (HPV 16, cervically HPV type 51).
Conclusion: Oral HPV-prevalence in women with cervical HPV infection is very low. Simultaneous testing of oropharyngeal HPV infection in patients with cervical HPV related disease does not seem promising for screening.

Head and Neck Cancer

ID 0266

Impact of tumour hypoxia and cancer stem cells on loco-regional control after primary radiochemotherapy in locally advanced HNSCC – results of a multicentre biomarker study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG)

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Purpose: To investigate the impact of tumour hypoxia and cancer stem cell marker expression on outcome of patients with locally advanced head and neck squamous cell carcinoma (HNSCC) after primary radiochemotherapy (RCTx).
Experimental design: At six partner sites of the German Cancer Consortium (DKTK), 160 patients with HNSCC were included in this retrospective DKTK multicentre study. All patients received primary cisplatin-based RCTx between 2005 and 2011. Their median follow-up was about 29 months. HPV status and CD44 expression were analysed by immunohistochemistry. Gene expression analysis was performed for hypoxia-associated genes and the potential CSC marker *SLC3A2*. Results of the biomarker analyses and clinical parameters were correlated with the clinical outcome. Primary endpoint was loco-regional control (LRC).
Results: In univariate analysis, HPV status and CSC marker expression were significantly associated with LRC (HPV: HR 0.30, p = 0.02; CD44: HR 2.30, p = 0.04; *SLC3A2*: HR 2.08, p = 0.01). Multivariate Cox regression analysis including HPV status, tumour localisation, tumour volume and tumour hypoxia or the respective CSC marker showed a significant effect of *SLC3A2* (HR 2.03, p = 0.02) or CD44 (HR 2.52, p = 0.04) and a trend for tumour hypoxia (HR 7.86, p = 0.06) on LRC. Interestingly, the tumour volume was an independent variable in all cox models, a high tumour volume was significantly associated with poor LRC.
Conclusion: We have shown that high CSC marker expression and high tumour volume significantly correlate with poor LRC in patients with locally advanced HNSCC who received primary RCTx. For highly hypoxic tumours, a trend towards poor LRC was seen. After validation of these promising results in our ongoing prospective study of the DKTK-ROG, these biomarkers may help to further stratify patients for individualised treatment escalation or de-escalation strategies.

Health Economy/Public Health

ID 0116

Development of a program for routine implementation of shared decision-making in oncology

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Background: Shared decision-making (SDM) is important in oncology, where many preference-sensitive treatment options exist. Many cancer patients wish active engagement in treatment decision-making. Despite evidence of benefit, SDM is not widely implemented in routine practice. Research has shown that empirical and theoretical grounding are important for a successful practice implementation. The aim of this study was to foster implementation of SDM in Germany by developing a cancer-specific implementation program that is both theoretically and empirically grounded.
Method: Qualitative study in two phases: 1) analysis of the current state (analysis of quality management (QM) documents, observation of current cancer care), 2) needs assessment (interviews & focus groups with different stakeholders). Collected data were analyzed using content analysis.
Results: 1) Analysis revealed poor integration of SDM in QM documents. Observations showed that SDM rarely occurred, with more SDM when patients actively asked questions. Time pressure, rotation of clinicians and insufficient team communication were main barriers. Observation of tumor boards showed that patients' preferences were rarely discussed. 2) 6 focus groups with 42 participants (clinicians, patients, family members) and 17 interviews with managers revealed the several needs, e.g. better communication skills, better patient information and culture change. Current structure of tumor boards was seen as a barrier. Participants supported a range of interventions to implement SDM.
Discussion: Results were used to develop a multifaceted implementation program, which will be evaluated in a follow-up study, fostering implementation of SDM in German cancer care.

ID 0328

CANKADO: First open eHealth platform for Oncology

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CANKADO (*www.cankado.com*) is the first open eHealth platform for oncology. Research and development teams are welcome to realize their projects on the basis of this platform. It is meant to support standard care and research projects as well as accompanying measures which serve the patients' well-being.
Own ideas or concepts can be incorporated or realized on the basis of CANKADO. Enhancements are possible in all fields of oncology and in adjacent sectors. These enhancements can be related to one or more user groups. Further options would be the involvement of additional user groups (e.g. pharmacists, relatives, patient organisations, sport therapists, nutritionists or physical therapists) or the limitation to one separate user group (e.g. within the scope of a study). The use of user data is limited to studies.
Individual projects can be funded publicly or industrially, their services can either be free of charge or chargeable. Industrial offers are possible with CANKADO, too, if they serve the patients' well-being. In case of chargeable/industrial offers a license fee has to be paid to CANKADO. Funding applications can be submitted by the project sponsor or together with the CANKADO team. Both the scientific responsibility and the scientific use remain with the group which carries out the project(s).

ID 0463

A comparison of market access evaluations for new oncology therapies in France, Germany and the UK: An Analysis using the PrismAccess database

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Introduction: In recent years (2011-2014) various new oncology therapies were launched and evaluated by the different market access authorities. The international Prismaccess database includes all evaluations and decisions by the respective authorities in France, Germany and the UK.
Methods: All decisions for new oncology therapies which were evaluated by the authorities in France, Germany and UK were systematically searched for. A comparison was executed with a focus on reimbursement decision, basis of decision, acceptance of submitted clinical endpoints, study designs, comparator, quality of life and indirect treatment comparison (ITC).

Results: In total there were 23 new oncology therapies being evaluated in the three countries. In France 10 decisions were positive, further 6 of minor improvement, 20 were positive in Germany and 4 were positive in England and 5 in Scotland. In 2 cases, respectively the assessment was positive (different magnitude) or negative in all countries. 26% (n = 6) it was similar in at least three countries (n = 5 positive decisions; n = 1 negative decision). In case overall survival was the primary endpoint the likelihood was higher in all countries for a positive decision. Key differences in terms of decisions were given in acceptance of ITCs, comparator as standard of care and ratings for cost-effectiveness.
Conclusions: Using the Prismaccess database the analysis shows that there might be key differences in terms of evaluation criteria between the three countries analysed. In Germany a key focus is given on the appropriate comparator(s) and patient-relevant endpoints. In the UK and Scotland cost-effectiveness might trump a positive benefit assessment. In France the key drivers are not only the severity of the pathology (for tumours, 25% of SMR are not substantial), but also efficacy/adverse events ratio, Effective amount, Comparator choice and Therapeutic strategy.

Imaging

ID 0053

The development of a simulation tool for clinical use in image-guided percutaneous minimally invasive cancer treatment (MICT) – the GoSmart project

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Background: There are several common methods of image guided minimally invasive cancer treatment (MICT) including radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, brachytherapy or irreversible electroporation. However, there is no common software environment to plan and to predict the results from different types of MICT. The GoSmart project therefore develops an intervention planning system for assisting radiologists to choose the best patient specific approach in MICT.
Evaluation: GoSmart aims to create a web based open ended software to assist interventionalists to plan a patient specific procedure and to also train within an augmented reality simulation environment. The project includes the development of dedicated tools for patient specific 3D-modelling of liver, kidney and lung from CT or MRI data. New tissue heat transfer and cell death mathematical models are integrated into a finite element model based computer simulation code. This tool will help clinicians for better planning MICTs and predicting the induced tissue lesion. The results of the tools will be validated by comparing simulations with the real patient treatment results.
Results: Yet a prototype interface with possibility to plan and simulate different MICT has been developed successfully and can be tested. Furthermore an international external user forum has been set up to spread the concept to a larger group of clinicians and researchers.
Conclusion: The finalized IMPPACT project showed encouraging results for the simulation of RFA induced liver lesions. During IMPPACT a user survey among German interventional radiologists demonstrated the request of computer assistance for percutaneous MICT procedures. GoSmart proposes practical support for MICT of the liver, kidney and lung providing a powerful tool for interventional radiologists for best personalized approach in MICT. It will also allow cross validation of different MICT types. Furthermore the unification of different MICT types into a common simulation environment helps implementing standardized benchmarks and protocols for MICT.

ID 0421

Predictive value of genetically engineered endogenous mouse models in preclinical therapeutic studies

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Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies with an alarming resistance to both chemotherapeutics and targeted therapy approaches. Genetically engineered mouse models (GEMM) of PDAC reflect molecularly and pathophysiologically the carcinogenesis and cancer progression observed in humans, thus being excellent tools for preclinical evaluation of new therapies.
To successfully predict and characterize the effect of chemotherapies and targeted approaches in PDAC, we use a complex and highly aggressive GEMM of endogenous PDAC, Ptf1a +/Cre Kras +/LSL-G12D p53Lox/Lox (CKP) mice. To do so, we established a highly usable GEMM-based therapy platform including multi-parametric MR imaging using CKP mice. Animals receive a T2w scan on a 3T clinical MRI scanner for detection and staging of solid tumors for study enrolment at defined inclusion criteria. Mice get a weekly scan throughout the study until endpoint criteria are met. Upon reaching the endpoint criteria, mice are sacrificed and tumor material is processed for histopathological and RNA/Protein analysis, isolation and culturing of primary tumor cells. Tumors are assessed macro- and microscopically and graded. Proliferation, apoptosis and analysis of respective downstream effectors are characterized. Further comprehensive analysis depending on the respective phenotypical features is then carried out. Primary cell lines are generated for further functional and molecular characterization including but not limited to cell viability, drug sensitivity, expression and methylation profiling.
Through this platform, we have successfully been able to target key signaling pathways and want to highlight the vital need to develop improved preclinical tools to characterize individual tumors.

ID 0518

Preclinical whole-body PET-MRI – established functional and anatomical imaging allows to strictly discriminate between necrotic and vital tumor tissue of orthotopically grown hepatocellular carcinoma (HCC) in rats

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The aim of this study was to evaluate and characterize orthotopically growing HCC in Spraque Dawley (SD) rats using a preclinical integrated whole-body PET/MRI.
Material and Methods: Inoculation of HCC cells (N1-S1) into rat liver will be shown (movie). Multimodal imaging was performed using a nanoScan PET/MRI (1T permanent magnet, Mediso). A set of MRI sequences (T1w, high res. T2w, DWI) was established to visualize HCC in liver parenchyma and FDG-F18 PET was performed. Tumor growth was monitored on day 10, 13 and 20. To visualize liver vascularisation around the tumor, angiography was performed by MRI and CT.

Results: HCC tumors were visualized with strong liver (bright) /tumor (dark) contrast by T1w imaging. High resolution T2w imaging was used to visualize necrotic areas and oedema. While on day 10 the tumors appeared as a solid tumor mass (bright), necrotic areas started to arise from day 13 and became more distinctive on day 20. To establish ADC-mapping, initially 11 healthy rat livers were measured by DWI. While ADC-means calculated from all four b-values were similar to the calculated ADC-means resulting from b-values 0, 200 and 300. Tumor ADC-means first decreased compared with ADC-means from healthy livers, but increased and became more heterogeneous as the tumor increased in size and necrotic areas became more present (day 20). T2w imaging and DWI confirmed the increase in necrotic areas progressively. FDG-F18 turnover of the tumor was high on day 10, but started to decay from day 13. Although tumor increased in size until day 20, reduced FDG-F18 uptake demonstrates the loss of vital tumor tissue.
Conclusions: Combining high resolution T2w with ADC-mapping and FDG-F18 allows a detailed characterisation of the tumor mass identifying necrotic areas and vital tumor tissue. Using an integrated PET/MRI, workflow can be greatly optimized.

Leukemia, Myelodysplasia, and Transplantation

ID 0318

Migration of acute lymphoblastic leukemia cells into the central nervous system is regulated by VEGF A

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Molecular mechanisms leading to the entry of acute lymphoblastic leukemia (ALL) cells into the central nervous system (CNS) are barely understood. However, knowledge about these pathways is needed to improve the patient's treatment to a more CNS-directed therapy.
Here, we xenotransplanted primary B-cell precursor ALL samples into NOD/SCID mice identifying a subset of samples engrafting in spleen (S), bone marrow (BM), and CNS (CNS^{pos}), and others engrafting only in S, and BM (CNS^{neg}). Whole human genome expression arrays performed on human leukemia cells isolated from BM and CNS of CNS^{pos} samples (n = 9) identified vascular endothelial growth factor A (VEGF) to be highly upregulated in the CNS.
Cell proliferation, metabolism, and apoptosis signalling were not altered when Nalm-6 cells (CNS^{pos}) were exposed to VEGF or bevacizumab (beva), or when Nalm-6 cells overexpress or knock down (ko) VEGF, thus, arguing for an absent autocrine VEGF signalling on leukemic cells.
Transwell assays with brain endothelial cells revealed significantly increased cell migration of VEGF overexpressing Nalm-6 cells and when Nalm-6 was exposed to VEGF. In the same line, significantly decreased cell migration was observed for VEGF ko cells and when Nalm-6 cells were treated with beva.
To further show a role of VEGF on the transmigration of leukemic cells into the CNS *in vivo*, we treated CNS^{pos} samples with beva (n = 4). We identified significantly reduced tumor loads in the CNS of beva-treated mice compared to control. Importantly, tumor loads in S and BM were not changed upon treatment indicating a compartment specific role for VEGF in supporting leukemic cell entry into the CNS. Thus, targeting VEGF may be a promising novel strategy to control CNS disease in ALL patients.

ID 0450

Mutations of cytological 5´-nucleotidase II (NT5C2) predict recurrent disease and poor outcome in children with first relapse of precursor B acute Lymphoblastic Leukemia

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Acute lymphoblastic leukemia (ALL) is the most frequent cancer in children, and has good overall survival rates. Nevertheless, resistance to chemotherapy after first relapse is an unsolved challenge in the clinical management of ALL. Relapse-specific mutations activating the purine salvage pathway gene *NT5C2* (cytological 5´nucleotidase II) elevate turnover of thiopurine drugs used in ALL treatment. However, the impact of *NT5C2* mutations for outcome of patients and design of second-line therapy is unknown. Therefore, we studied *NT5C2* mutations in 466 children with first relapse of precursor B ALL enrolled in the German ALL-REZ BFM 2002 trial by Sanger and next-generation sequencing. *NT5C2* mutations occurred in 6% of patients (28/466). Of the *NT5C2* mutated cases, 50% had the T-ALL hotspot mutation p.R367Q, whereas the other half showed a spectrum of known and novel *NT5C2* mutations. Surprisingly, response to multi-agent second-line induction treatment was not significantly different between patients with and without *NT5C2* mutations. However, patients with *NT5C2* mutations showed a significantly increased cumulative incidence of second relapse (53.6% ±9.8% vs. 26.2% ±2.2%; $p < 0.001$) and accordingly, a significantly reduced event-free survival rate (28.6% ±8.5% vs. 51.3% ±2.5%; $p = 0.002$). Of note, second relapse occurred early after first relapse (median 8.8 months) and independent of hematopoietic stem cell transplantation. Multivariate analysis confirmed the predictive value of *NT5C2* mutations for disease recurrence ($p < 0.001$). In conclusion, *NT5C2* mutations are associated with aggressive leukemia. As novel biomarker for high-risk relapse, they can aid in molecular risk stratification of children with ALL.

Lung Cancer

ID 0026

Prognostic relation between changes of tumor volume and plasma levels of the hypoxia-related protein osteopontin (OPN) in the radical radiotherapy of NSCLC

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Background: Hypoxic radiation resistance compromises response to radiotherapy (RT) in cancer. In radical RT of NSCLC, we previously showed an additive prognostic effect of elevated plasma levels of the hypoxia-associated proteins osteopontin (OPN), vascular endothelial growth factor (VEGF) and carbonic anhydrase (CA) IX and that OPN plasma level changes after RT provide additional prognostic information. Since OPN is associated with tumor burden, it remains unclear whether plasma level changes are merely surrogate of tumor volume changes during RT, accounting for the prognostic effect.
Methods: OPN plasma levels of 27 patients with inoperable NSCLC (100% M0, 92% UICC III) were prospectively determined by ELISA before (t0), at the end (t1) and four 4 weeks after radical RT (t2). For each patient, tumor volume (GTV) was contoured in the initial planning CT before RT (GTV1) and re-contoured after 50 Gy in a new CT (GTV2). Correlation and prognostic relation of OPN and GTV was evaluated.

Results: Med. follow-up was 65 (28-66) months. OPN *t0* was 846 (361-2441), *t1* 777 (323-1398) and *t2* 624 (72-2248) ng/ml, GTV1 90 (3-271) and GTV2 63 (2-185) ml. During RT, GTV declined by 42% ($p < .0001$) and OPN by 8% (n.s.); after RT, OPN decreased by 21% (n.s.). Correlations were determined between GTV1 and 2 ($r=.7$, $p < .0001$), OPN t1 and t2 ($r=.6$, $p = .005$) but not between OPN and GTV. Significant predictors of overall survival (OS) in univariate analysis were GTV1 ($p = .08$), GTV2 ($p = .03$), grade ($p = .009$), T-, N-, UICC-stage ($p = .005, .03, .02$). In multivariate analysis, OPN t0 ($p = .003$) and GTV1 ($p = .04$) remained independent predictors for OS. OPN t1 ($p = .004$), GTV2 ($p = .004$), OPN level changes after (t1t2, $p = .02$) and GTV changes during RT ($p = .02$) significantly predicted OS.
Conclusion: These results suggest that OPN and GTV are independent prognostic predictors after radical RT of NSCLC.

ID 0027

Investigation of pharmaceutical targets in pulmonary neuroendocrine tumors by massive parallel sequencing and digital gene expression analysis

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Background: Lung cancer is the leading cause of cancer-related deaths worldwide. Twenty-five percent of all lung tumors belong to the group of neuroendocrine tumors, encompassing typical (TC) and atypical carcinoids (AC) as well as large-cell neuroendocrine carcinomas (LCNEC) and small-cell lung cancer (SCLC). Despite the excellent survival rates of carcinoid tumors, metastatic carcinoids are commonly not sensitive to standard chemotherapeutic regimes or radiation. Based on the WHO classification guidelines, LCNEC belongs to NSCLCs leaving it to the clinicians to treat it similarly to SCLCs or NSCLCs. For SCLC, chemotherapy with cisplatin plus etoposide is an established treatment, which is often associated with resistances occurring in early treatment stages. Therefore, novel therapeutic strategies are urgently desirable.
Material and Methods: In order to address this question, 70 representative tumor specimens were subjected to next generation sequencing analysis analyzing 14 genes related to therapy response. Additionally, mRNA-expression profiles of 61 of those tumor samples were determined for eleven selected drug targets by the NanoString nCounter technology.
Results: A number of features known to sensitize tumors for different targeted therapies could be identified, which hopefully might improve the clinical management of this subgroup of lung neoplasias. In particular, *EGFR* expression was observed in the investigated tumors in a noteworthy manner. Additionally, *MDM2* was strongly expressed in the majority of all samples whereas *CDKN2A* expression was rare in all low-grade tumors. *TP53* showed a high frequency of variants in high-grade tumors but were rare in carcinoids.
Conclusion: Based on our results, therapeutic approaches with Nutlin-3A and monoclonal anti-EGFR antibodies may be the most promising future therapeutic approaches in pulmonary carcinoid tumors.

ID 0061

Physical exercise program in non-operable lung cancer patients undergoing palliative treatment – preliminary report of recruitment rates and feasibility of the POSITIVE study (part III)

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Background: The treatment of advanced lung cancer is a challenge for both patients and their relatives as well as for the attending physicians. The approach of maintaining or improving quality of life and physical performance through an exercise intervention is promising (Kuehr/Wiskemann et al., 2014). Here we present recruitment and feasibility data of one of the largest ongoing physical exercise intervention studies at the Clinic for Thoracic Diseases in Heidelberg, Germany.
Methods: Since November 2013 (ClinicalTrials.gov: NCT02055508), patients with advanced lung cancer have been randomized either to a 24 weeks exercise intervention program plus Care Management Phone Calls (CMPC, for proper symptom and side effect management) or CMPC alone. CMPC are provided on a weekly basis, half of the participants receive an individually tailored, combined endurance and resistance exercise intervention program 3 times a week. We aim to enroll 250 patients. The primary endpoints are physical well-being and extent of fatigue after 12 weeks. Based on preliminary data, we present the current recruitment rate and feasibility.
Results: So far, 111 patients are included in the study. In total, 159 patients declined participation due to lack of interest. Reasons for decline were "high expenditure of time" (35.2%) and "lack of motivation" (11.3%), resulting in a current recruitment rate of 41.1%.
Conclusion: Overall, regarding the feasibility and implementation of study contents, the results show good adherence in 90.2%. In the exercise arm, good adherence is observed in 62.7% of the patients. The current recruitment rate of 41.1% reflects the challenging patient population. However, preliminary adherence data are very promising.

ID 0072

Individualized drug response predictions based on a combined in silico and in vitro lung cancer model on a biological scaffold

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Facing heterogeneity of cancer, individualized treatment options are emerging in therapy regimens. To identify the patient population that is most likely to benefit from a specific targeted therapy and to specify new drug targets, we developed a pre-clinical 3D lung cancer (LC) model based on a decellularized biological matrix. This kind of tumor tissue model reflects tissue characteristics such as a biological tissue architecture and ECM composition, including a preserved basement membrane that is important for modeling epithelial cancers. Additionally and in contrast to 2D conditions, we observed a lower proliferation rate that correlates to patient's tumors. These aspects of our models have major implications for drug-responses and should improve pre-clinical testing.
To represent different response groups of LC patients towards tyrosine kinase inhibitors (TKI), we used cell lines, harboring specific driver mutations. Upon gefitinib treatment, we could show an increase of apoptosis and a reduced proliferation in the cell line harboring an EGFR mutation (HCC827) which was not observed in EGFR wt cells (A549, H441). For

target predictions we connected our 3D test system with an *in silico* model based on the EGFR signaling network and determined activation changes of 49 receptor TKs and 43 phospho-kinases.
To model more advanced tumor stages, we induced epithelial to mesenchymal transition (EMT) by TGFβ1 that is connected to invasive processes. The Boolean *in silico* model correctly calculates the observed system responses such as apoptosis, proliferation and EMT. Furthermore, we generated gefitinib resistant HCC827 cells as a basis for testing drugs, that were predicted by the *in silico* model as being effective after TKI resistance.

ID 0321

Investigating the utility of circulating-free tumor-derived DNA (ctDNA) in plasma for the detection of epidermal growth factor receptor mutation (EGFRM) status in German patients (pts) with advanced non-small-cell lung cancer (aNSCLC) - ASSESS study

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Aim: ASSESS evaluated the EGFRM status in pts with aNSCLC. The here presented subgroup analysis shows the results of the German cohort.
Methods: Eligible pts had newly diagnosed local/metastatic (stage IIIA/B/IV) chemotherapy- and EGFR TKI-naïve aNSCLC. Primary endpoint: EGFRM status concordance between matched plasma and tissue/cytology samples (as per local testing).
Results: 346 pts were enrolled from 10 centres across Germany; 343 were eligible, of which 306 tumor and 338 plasma samples were collected and analysed.
Key outcomes for the 301 matched samples:

1. 94% (95% CI 90.7-96.4) concordance, 36% (18-57.5) sensitivity and 99.3% (97.4-99.9) specificity for the plasma tests. The positive predictive value (PPV) and negative predictive value were 81.8% (48.2-97.7) and 94.5% (91.2-96.8), respectively.
2. EGFRM positivity in pts with adenocarcinoma: 25 out of 306 pts (8.2%) with tumor evaluable sample (TES) and 12 out of 338 pts (3.6%) with plasma evaluable samples (PES) were EGFRM positive. In contrast, mutations del19 and L858R were detected in both tissue and plasma samples: 7 *del*19 and 4 L858R in tissue as well as in plasma samples.
3. 1st-line treatment decision for the EGFR mutation positive TES population: 19 out of 25 pts (76%) received systemic anticancer therapy. 14 out of 19 pts (73.7%) received an EGFR-TKI as 1st-line therapy.

Conclusions: The German subgroup analysis suggests that ctDNA from plasma is a feasible suitable sample for EGFRM analysis when tumor samples are unavailable. Robust and sensitive detection methods should be used to reduce false negative results in both plasma and tumour.

ID 0352

Phase 3, randomized trial (CheckMate 057) of nivolumab (NIVO) vs. docetaxel (DOC) in advanced non-squamous (non-SQ) non-small cell lung cancer (NSCLC) – subgroup analyses and patient reported outcomes (PROs)

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Aims: We report results from a phase 3 study of NIVO vs DOC in patients with advanced non-SQ NSCLC after failure on platinum-doublet chemotherapy and a tyrosine kinase inhibitor, if eligible.
Methods: Patients were randomized to NIVO 3 mg/kg Q2W (n = 292) or DOC 75 mg/m2Q3W (n = 290) until progression or discontinuation due to toxicity/other reasons. The primary objective was overall survival (OS); secondary objectives were investigator-assessed overall response rate (ORR) (per RECIST v1.1), progression-free survival (PFS), efficacy by programmed death ligand-1 (PD-L1) expression, PROs, and safety.
Results: NIVO improved median OS (12.2 [95% CI: 9.7-15.0] vs 9.4 [95% CI: 8.0-10.7] months; hazard ratio [HR]=0.73; 96% CI: 0.59, 0.89; *P*=0.00155) and ORR (19.2% vs 12.4%; *P*=0.0246) vs DOC. The 1-year OS was 50.5% (95% CI: 44.6-56.1) with NIVO vs 39.0 (95% CI 33.3-44.6) with DOC. Median PFS was shorter with NIVO (2.3 [95% CI: 2.2-3.3] vs 4.2 [95% CI: 3.4-4.9] months; HR = 0.92 [95% CI: 0.77, 1.11; *P*=0.393]) vs DOC. The 1-year PFS was 18.5 (95% CI: 14.1-23.4) vs 8.1 (95% CI: 5.1-12.0) in the NIVO vs DOC arms. Grade 3-5 treatment-related adverse events (TRAEs) occurred in 10.5% vs 53.7% of NIVO- vs DOC-treated patients. Any grade/grade 3-5 TRAEs leading to discontinuation occurred in 4.9%/3.8% vs 14.9%/6.7% of NIVO- vs DOC-treated patients. Serious treatment-related AEs were less frequent in the NIVO arm. PROs and efficacy by tumor PD-L1 expression will also be presented.
Conclusions: NIVO significantly improved OS vs DOC in patients with advanced, previously treated, non-squamous NSCLC. The safety profile of NIVO 3 mg/kg Q2W was favorable vs DOC.

ID 0454

Results of all 5 screening rounds of the randomized study on the early detection of lung cancer LUSI

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The LUSI-study (Lung Cancer Screening Intervention Trial) is a randomized controlled study on the early detection of lung cancer which is conducted in Germany since 2007. Participants in the intervention group underwent 5 annual screening rounds with low-dose-MSCT (multi-slice-CT), participants in the control group "usual care". The study design of no screening intervention in the control group contrasts LUSI and a number

of other European studies to the American National Lung Screening Trial (NLST). From the NLST, a 20% lung cancer mortality reduction was reported, but under a design with X-ray screening in the control group. Many issues crucial for screening can only be answered accurately in a comparison against a "no screening"-control group.
For LUSI, the results of all 5 screening rounds are now available and form the basis of the presentation. Additionally, at least 5 years of observation are available for almost all participants. Compliance in the intervention group was 99.9% 94.6% 93.4% 93.1% and 95% in the five screening rounds, respectively, and 99.9%, 91.5%, 94.5%, 95.5% and 91.1% in the control group. The detection rates of 1.1% in the first round and 0.5% to 0.6% in rounds 2 to 5 are comparable to rates found in other European studies. In the intervention group, the proportion of advanced lung cancer cases were 26.1%, 45.5%, 20%, 12.5% and 33.3% for the first 5 years since randomization, respectively.
The sample size of the LUSI study of 4052 study participants will be too small to confirm a reduction of lung cancer mortality by MSCT screening. The data of LUSI will however be a valuable contribution to the planned common analysis of all European studies.

Lymphoma and Plasma Cell Disorders

ID 0050

AFM13, a novel bispecific (CD30xCD16A) tetravalent antibody (TandAb®) specifically engaging NK-cells to fight Hodgkin Lymphoma (HL)

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The majority of HL patients can be cured with chemotherapy. However, since these treatments are toxic or generally unsatisfactory in relapsed/refractory disease (r/r H), immunotherapies represent encouraging alternatives.
AFM13 is a bispecific, tetravalent antibody (TandAb®) designed for the treatment of CD30+ malignancies. AFM13 specifically recruits natural killer (NK) cells via CD16A but not neutrophils.
AFM13 was investigated in a phase 1 safety study in r/r HL. 28 patients were treated at doses of 0.01 to 7mg/kg. Adverse events were generally mild to moderate. The maximum tolerated dose was not reached. Three patients had partial response (PR, 11.5%) and 13 patients had stable disease (SD, 50%). AFM13 was active in brentuximab vedotin-refractory patients. In 13 patients with doses of ≥1.5mg/kg, the rate of PR and SD was 23% and 77% with tumor shrinkage in more than 2/3 of patients.
In vitro cytotoxicity assays with AFM13 alone or in combination with different immunomodulators were performed. The combinations strongly enhanced lysis of CD30+ cell lines compared to single agents with the strongest effect for the combination with anti-PD-1. Similarly, combinations were tested *in vivo* by xenografting CD30+ HL tumor specimens followed by infusion of autologous PBMCs and ip treatment with the agents. Tumor shrinkage was significantly greater in the combination treatment compared to single agents and greatest for the combination with anti-PD-1.
Based on these data, clinical studies in r/r HL with AFM13 alone and in combination with anti PD-1 have been initiated or are in preparation.

ID 0410

Elotuzumab plus bortezomib and dexamethasone (EBd) versus bortezomib and dexamethasone (Bd) in patients (Pts) with relapsed/refractory multiple myeloma (RRMM) – 2-year follow-up

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Question: Phase 2 open-label study (NCT01478048) comparing the efficacy and safety of EBd vs Bd in RRMM pts.
Methods: Pts with 1-3 prior therapies were given EBd or Bd in 21-day (Cycles 1-8) or 28-day (Cycle 9+) cycles until disease progression/unacceptable toxicity. Primary endpoint: PFS (ITT population) using IMWG criteria. The study had 80% power to detect a HR of 0.69 with 103 events. A 2-sided 0.30 significance level was specified to test for PFS difference between arms (p≤0.3 considered significant).
Results: 152 pts (median age 66 yrs) were randomized (77 EBd; 75 Bd). Median time since diagnosis: 45 (EBd) and 44 (Bd) months. 51% (EBd) and 53% (Bd) of pts had prior proteasome inhibitor use. At data cut-off (16 April 2015), 12% (EBd) and 3% (Bd) of pts remained on therapy; discontinuation was mainly for disease progression (56% across arms). Median number of treatment cycles was 12 (EBd) and 7 (Bd). HR for PFS was 0.75 (70% CI 0.62, 0.90). 2-year PFS rate (95% CI) was 18% (10%, 28%) and 10% (4%, 18%) for EBd and Bd, respectively. Adjusting for prognostic factors, PFS HR (EBd vs Bd) was 0.60 (70% CI 0.48, 0.74; p = 0.0116). Median PFS was 9.9 months (EBd) vs 6.8 months (Bd). ORR was 65% (EBd) vs 63% (Bd). 54 deaths occurred (26 EBd; 28 Bd), mainly due to multiple myeloma. Grade 3/4 AEs occurred in 53 (71%) and 45 (60%) pts with EBd and Bd. AEs ≥ Grade 3 in ≥15% of pts (EBd; Bd) were thrombocytopenia (7 [9%]; 13 [17%]) and infections (17 [23%]; 11 [15%]). Infusion reactions (all Grade 1-2) occurred in 5% of EBd pts. Updated data including 2-year OS will be presented.
Conclusions: Longer-term follow-up demonstrates prolonged PFS with EBd, and minimal incremental toxicity, consistent over time, vs Bd alone. Longer-term PFS and OS will be presented.
Prior submission: ASH 2015

Molecular Pathology

ID 0195

Tumor infiltrating cells – cell-to-cell distances enable differentiation between functionally active and suppressed inflammatory cells

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Background: Mostly the density of tumor infiltrating inflammatory cells is investigated in tumor tissues and therefore only the presence of inflammatory cells is studied. We were interested in cell-to-cell distances of inflammatory cells as a possible indicator of inflammatory cell functionality.
Methods: Double-stainings of regulatory T cells (FoxP3+) with either dendritic cells (CD1a+) or B-cells (CD20+) were performed in anal cancer tissues of 38 patients. Whole slide scanning and image analysis software was used to determine the distances between the same cell subsets and between FoxP3+ cells and the other cell subsets, both in the intraepithelial and stromal compartment. The observed cell-to-cell distances were compared to simulated cell-to-cell distances of randomly distributed cells.
Results: We hypothesize that randomly distributed cells are non-functional cells with a lack of antigen-driven functioning leading to a random distribution pattern. Intraepithelial CD1a+ and CD20+ cells were randomly distributed and we ranked them as non-functional. In contrary stromal CD20+ cells had a non-random pattern. Additionally, short intraepithelial CD20 to FoxP3 distances had an unfavorable prognosis. It indicates that FoxP3+ cells intraepithelially suppress CD20+ cells. Observed FoxP3 to FoxP3 distances were distinctly shorter than expected and indicate the functional active state of the regulatory T cells.
Conclusions: Cell-to-cell distances have most probably the potential to distinguish between functional and non-functional inflammatory cells. We did find FoxP3+ cells and stromal CD20+ cells to be functionally active, while CD1a+ cells and intraepithelial CD20+ cells were non-functional.

ID 0426

Plasma extracellular vesicles (pEV) of Melanoma patients modulate the minimal residual disease (MRD) through the beta-Catenin pathway

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Recent work on plasma extracellular vesicles (pEV) in cancer patients suggests that (1) growing tumors secrete abundant amounts of pEV, also called tumor exosomes, that (2) modulate the tumor microenvironment in a pro-tumorigenic fashion, (3) contain a whole array of biomarkers and (4) allow the early diagnosis of cancer. We have systematically analyzed circulating pEV in 60 melanoma patients and controls, who either had (1) a growing tumor, (2) a high or (3) low risk for tumor relapse. We found that pEV are upregulated in tumor patients even with low risk for tumor relapse and can be detected in all melanoma patients even many years after primary surgery. Investigating the underlying mechanisms, we realized that these pEV to not originate from tumor cells, but likely constitute an innate immune response to the presence of circulating and disseminated tumor cells (MRD). Correlating with the clinical stage the biomarker profile of the pEV was quite distinct. Analyzing the function of these vesicles, we discovered a strong capacity to modulate the beta-Catenin pathway in tumor cells by means of specific micro-RNAs. Interestingly, this capacity to suppress tumor cells was lost in patients that had a growing tumor. Instead, beta-Catenin was strongly activated. Our findings could be confirmed by different experimental approaches and assays. The latter may be used to diagnose and monitor cancer activity in the course of the disease.

Paediatric Cancer

ID 0176

Targeting the EWS/ETS transcriptional program by BET bromodomain inhibition in Ewing sarcoma

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Background: Ewing sarcomas (ES) are highly malignant, osteolytic bone or soft tissue tumors, which are characterized by early metastasis into lung and bone. Genetically, ES are defined by balanced chromosomal EWS/ETS translocations, which give rise to chimeric proteins (EWS-ETS) that generate an oncogenic transcriptional program associated with altered epigenetic marks throughout the genome.
Methods: By use of an inhibitor (JQ1) blocking BET bromodomain binding proteins (BRDs) we strikingly observed a strong down-regulation of the predominant EWS-ETS protein EWS-FLI1 in a dose dependent manner in different ES cell lines.
Results: Microarray analysis further revealed JQ1 treatment to block a typical ES associated expression program. The JQ1 treatment effect on this expression program could be mimicked by RNA interference with BRD3 or BRD4 expression, indicating that the EWS-FLI1 mediated expression profile is at least in part mediated via such epigenetic reader proteins. Consequently, contact dependent and independent proliferation of different ES lines was strongly inhibited by JQ1. Mechanistically, JQ1 treatment of ES resulted in a partial arrest of the cell cycle as well as induction of apoptosis associated with increased caspase 3 activity. Tumor development was suppressed dose dependently in a xeno-transplant model in immune deficient mice.
Conclusion: Results overall indicate that ES may be susceptible to treatment with epigenetic inhibitors blocking BET bromodomain activity and the associated pathognomonic EWS-ETS transcriptional program in ES.

ID 0332

Long-term overall survival for patients with retinoblastoma: A report from the German referral center from 1940-2008

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Retinoblastoma is the most common eye tumor in childhood. The 5-year overall survival for children with retinoblastoma is excellent. However, 50% of patients have a heritable predisposition to retinoblastoma characterized by a germline mutation in *RB1*. These children are at risk to develop second primary malignancies later in life that are associated with high mortality. The presented study investigates the long-term survival of German patients with retinoblastoma. At the German referral center, 1194 national patients were treated for retinoblastoma between 1940 and 2008. Overall survival and the influences of *RB1* germline mutation, IRSS and TNM staging, decade of diagnosis and treatment were analyzed. The 5-year overall survival rate was 95.4% after diagnosis of retinoblastoma between 1940-2008 in Germany. Mortality correlated with IRSS and TNM staging. Despite a 5-year overall survival rate of 97.4% (95% CI: 96.0-

98.8%) for survivors of heritable retinoblastoma with tumors restricted to the eye (IRSS stage 0 or I), the 50-year overall survival rate was significantly decreased compared to patients with non-heritable disease. The treatment for intraocular retinoblastoma comprises of enucleation or eye-preserving therapies with radiotherapy or chemotherapy. Children receiving radiotherapy had a further reduced long-term overall survival compared to those treated without radiotherapy. The results of this follow-up study emphasize that long-term side effects of eye-preserving treatment need to be balanced carefully and alternative eye-preserving treatments are urgently required. For all survivors of heritable retinoblastoma, life-long regular oncological follow-up is crucial.

ID 0339

Coping with T-cell promiscuity in genomics-based immunotherapy – allorestricted T-cell receptor transgenic T-cells (ATRs) vs. chimeric antigen receptor T-cells (CARs)

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EWS/ETS dependent genes (EDG) are actionable by T cells. Perceived as specific, chimeric antigen receptor T cells (CARs) bypass evolutionary safety features and restrict recognition to surface molecules. CAR expenses are unwanted activation of innate immunity and agammaglobulinemia. We employed allorestricted T cell receptor (TCR) transgenic T cells (ATRs) from donor parents recognizing peptides presented by the non-inherited HLA haplotype (Burdach 2013). ATRs recognize intracellular targets; their target pool is unlimited. T cell activation and deregulation of innate immunity are low, while off-targets effects are more frequent. ATRs can target antigens essential for survival. Regulatory authorities require specificity of ATRs but not of CARs while TCR promiscuity is imperative, given that 10^{11} human TCRs have to recognize 10^{20} universal peptides.
Functionality of genomics based ATR targets as addiction oncogenes in Ewing Sarcoma (ES) was verified in vivo, including EDG EZH2 (Histone methyltransferase) and ChM1 (osteochondrous differentiation regulator): ChM1 specific ATRs kill ES in vivo without target down modulation, whereas EZH2 specific ATRs kill in vitro, but not in vivo. STEAP1 (ROS signaling receptor) specific humanized ATRs show off-target reactivity killing ES in vivo. ADRB2 (adrenergic receptor) specific ATRs committed fratricide. EDG ATRs killed ES irrespective of donor source, making haplodisparate transplants dispensable. We applied ChM1 specific ATRs in humans with advanced ES, detecting transgenic cells active in the relapse site.
In conclusion, some addiction oncogene peptides are actionable. Specificity is not required. Epitope spreading and alloreactivity may help to overcome resistance.

ID 0363

Oncolytic measles virus against ALL of childhood – preclinical proof-of-principle and molecular mechanisms

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Introduction: Novel therapies are needed for pediatric acute lymphoblastic leukemia (ALL) resistant to conventional therapy. While emerging data suggest leukemias as possible targets of oncolytic attenuated measles virus (MV), it is unknown whether MV can eradicate disseminated leukemia, in particular pediatric ALL.
Methods: We evaluated the efficacy of attenuated MV against a large panel of pediatric xenografted and native primary ALL *ex vivo*, and against four different ALL xenografts of B-lineage in nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice.
Results: *Ex vivo*, attenuated MV readily spread among and effectively killed ALL cells while sparing normal human blood cells and their progenitors. In NOD/SCID mice with disseminated ALL a few intravenous injections of attenuated MV sufficed to eradicate leukemic blasts in the hematopoetic system and to control central nervous system disease resulting in long-term survival in three of the four xenografted B-lineage ALL. Differential sensitivity of ALL cells did not require increased expression of the measles entry receptors CD150 or CD46 nor absence of the anti-viral retinoic acid-inducible gene I/melanoma differentiation associated gene-5 /interferon pathway.
Conclusion: Attenuated oncolytic measles virus is dramatically effective against pediatric B-lineage ALL in the preclinical setting warranting further investigations towards clinical translation.

ID 0397

BRCA-like Hallmarks Unify the Evolution of Osteosarcoma

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Background: Osteosarcomas (OS) are primary malignant tumors of bone with complex karyotypes showing abundant structural and numerical aberrations. Rapid tumor progression and early metastatic spread are the rational for multimodal treatment approaches that can achieve long-term survival in about 60% of patients. Effective treatment options are still lacking for the remaining 40% of patients suffering from refractory or recurrent disease, however. A partial explanation for treatment failure might lie in different etiologies responsible for the structural aberrations marking the onset of the disease and resulting in a variety of mutations in genes and pathways of which only few are targetable.
Methods: In this study, we sequenced exomes of 31 tumors and deciphered their evolutionary landscape by inferring clonality of the individual mutation events. Exome findings were interpreted in the context of mutation and SNP array data from a replication set of 92 tumors.
Results: We identified 14 genes including *TP53*, *RB1*, *ATRX*, *RET*, *MUTYH*, *NUMA1*, *FANCA*, *BRCA2*, and *ATM* as the main drivers, of which some were formerly unknown in the context of osteosarcoma. None of the drivers was clearly responsible for the majority of tumors and even *TP53* mutations were frequently mapped into subclones. However, >80% of osteosarcomas exhibited a specific combination of single base substitutions, LOH, or large-scale genome instability signatures characteristic for BRCA1/2-deficient tumors.
Conclusion: Our findings imply that multiple oncogenic pathways drive chromosomal instability during osteosarcoma evolution and result in acquiring BRCA-like traits, which could be therapeutically exploited.

ID 0431

Mutational dynamics between primary and relapse neuroblastoma involve genes relevant for mesenchymal transition

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Neuroblastoma is a malignancy of the developing sympathetic nervous system that is often lethal when relapse occurs, but the molecular mechanisms behind this process are poorly defined. We here used whole exome sequencing, mRNA expression, array CGH and DNA methylation analysis to holistically characterize 16 paired samples from neuroblastoma patients at diagnosis and relapse. Global allele frequencies at relapse indicated clonal mutation selection during disease progression. Promoter

methylation patterns were consistent over disease course and patientspecific. No relapse tumor acquired new mutations in previously identified neuroblastoma driver genes, but MYCN amplification was acquired in one. Inactivating mutations in the putative PTPN14 tumor suppressor and a relapsespecific activity pattern for the PTPN14 target gene, YAP, were identified, and represent the first hint for Hippo/YAP signaling involvement in neuroblastoma relapse. Recurrent new mutations in HRAS, KRAS, DOCK8, and genes mediating cell-cell interaction in 13 of 16 relapse tumors also point to disturbances in signaling pathways mediating mesenchymal transition. Our results suggest a role for mesenchymal transition processes and their modulation by genomically altered upstream signaling in neuroblastoma recurrence.

Palliative Care

ID 0183

Assessment of disease burden and palliative care needs of patients after first diagnosis of incurable cancer – Arbeitsgemeinschaft Palliativmedizin (APM) Project of the Section B of the German Cancer Society

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Introduction: Current data as well as medical experience suggest that palliative care needs should be addressed early in patients (pts) with incurable cancer. However, it has not been systematically investigated which symptoms and burden exist at the moment of first diagnosis of incurable cancer and how care needs change over time. Moreover, information is sparse on patients` actual needs as well as which needs are fulfilled and what demands exist for general and specialized palliative treatment although this information is required for early palliative care integration.
Methods: The APM project assesses needs and preferences of patients suffering from incurable cancer using validated questionnaires (FACT, SEIQoL-Q, PHQ-4, modified SCNS-SF-34, Distress Thermometer) at the time of first diagnosis and before any specific anti-cancer treatment. Patients are re-assessed regularly 3, 6, and 12 months after inclusion. Medical information is obtained from the treating physicians.
Results: 150 cancer patients were included in this ongoing study from October 2014 to August 2015. Median age of patients is 61 years (range, 29 and 85 years), ECOG performance status at first visit 0–3, underlying diagnoses are: gastrointestinal cancer (54 pts), lung cancer (53 pts), head and neck cancer (22 pts), malignant melanoma (1 pt) and gynecological cancer (20 pts). Preliminary results show a broad spectrum of patients' needs and disease burden even at the very beginning of an incurable course of disease which will be presented in detail.
Conclusion: Patients' needs and disease burden comprise a broad spectrum even at first diagnosis of an incurable cancer. These findings emphasize the need for early individualized provision of multi-faceted support, including palliative care services, beginning already at the time of diagnosis of incurability.

ID 0281

Patient information needs and treatment goals in the EPAL-Study (Ethics policy for advanced care planning and limiting treatment)

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Introduction: The aim of this prospective quantitative study is to investigate relevant factors for End-of-life decision-making in order to inform the development of an institution-wide policy on treatment limitation.
Methods: This study recruited 50 cancer patients from May 2014 to July 2015 in the Dept. of Hematology/Oncology at the LMU Hospital/Munich with treatment limitations either being discussed or decided. The patient and their respective physician and nurse completed a set of validated instruments on patient's information needs, patient's goals of care and decision-making preferences.
Results: Patients report higher information needs about diagnosis, treatment options and side effects than about prognosis and advanced directives. Information needs depend on patients' preferred role in decision-making: patients with an active role have higher information needs and are less often satisfied with their opportunities to get involved compared to those preferring shared decisions or delegating decisions to their physicians. Interestingly, 94% of the patients indicate that they agree with their physician on treatment goals. Still, they overestimate their chances for cure, as 15% say that the treatment goal is cure, 60% cure is unlikely and only 25% cure is not possible. While nurses state that 77% of the patients know their prognosis, nurses themselves do not know patients' preferences on treatment limitation in 77%.
Conclusion: These results were fed into the development of an ethics policy for advanced care planning and limiting treatments. A post-implementation study will start at the end of 2015 to evaluate the impact of the policy. For EPAL see 2nd contribution (Jaeger et al., 2015).

ID 0282

End-of-Life decision-making in patients with advanced cancer – an ethics policy for advanced care planning and limiting treatment (EPAL)

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Introduction: The aim of the EPAL study (Ethics policy for advanced care planning and limiting treatment) is to develop a clinical practice guideline about limiting treatment and to evaluate its impact on medical practice, patient involvement, patient's information needs and timing of advanced care planning in a pre-post-design.
Methods: The policy was developed between 5/14 and 7/15 according to the Appraisal of Guidelines for Research & Evaluation (AGREE): all stakeholders of the Department of Haematology/Oncology at the LMU Hospital/Munich for example were involved. Results of the pre-implementation study were fed into the process for the guideline development (see second contribution Mehlis et al., 2015). In five consensus meetings with all

stakeholder representatives the policy was discussed and also reviewed by external experts and approved in a final clinic wide consensus conference.
Results: The policy includes 20 recommendations and 3 statements as well as definitions and relevant legal information concerning end of life situations. The documentation forms within the department were newly adapted to the policy and the policy was passed as an official quality management procedure. During the process of the policy-development sensitization for the topics and cooperation between different professions could be observed.
Conclusion: The focus of the policy is to structure the decision process about limiting treatment. The overall interest of external departments shows the significant relevance of this policy and subject area. The evaluation of the impact of the guideline with a post-implementation study will start at the end of 2015.

ID 0444

Early palliative care for improving quality of life and survivaltime in adults with advanced cancer – Results from a Cochrane Review

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Background: Early palliative care has reached high international attention since the seminal work of Temel et al. (NEJM, 2010). This was the first study to show that starting with palliative care (PC) already at the time a person is diagnosed with metastatic lung cancer, can be favourable to improve quality of life and survival. As a consequence, further trials on early PC in different cancer groups have been completed during the recent years. We examined overall efficacy of early palliative care approaches within the framework of a Cochrane Review.
Method: The review was carried out in collaboration with the Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group. Following a pre-drafted protocol published in 2014 after peer-review, we conducted a highly-sensitive database search covering CENTRAL (Cochrane Library), Medline, Embase, PsycINFO, and CINAHL as well as major trial registries. Included studies, limited to RCT and cluster RCT, were selected according to pre-defined inclusion and exclusion criteria. In the absence of an evidence-based definition of early palliative care, criteria were derived on the basis of a consensus definition conceptualised in cooperation with reviewers from the PaPaS Group. Primary outcome measure were health-related quality of life, depression, symptom intensity, and survival. Data collection, analysis and assessment of risk of bias were conducted by two independent raters.
Results: Database searches together with screening of systematic review and cross-references yielded 13.683 potentially relevant records. After screening of titles and abstracts, 52 full-texts were assessed for eligibility. Finally, five studies were included into the review and subjected to quantitative synthesis in meta-analysis for the primary outcome of health-related quality of life.

ID 0462

Palliative Versorgung statt Beihilfe zum Suizid und zur Tötung auf Verlangen? Über eine mögliche Notwendigkeit lebensverkürzender Maßnahmen. Vollerhebung im Sinne empirischer Sozialforschung bei Palliativmedizinern in SAPV-Teams im Saarland und in Hessen sowie bei Kinder-SAPV-Teams in Deutschland

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Zunehmend wird über Tötung auf Verlangen und/ oder Beihilfe zur Selbsttötung als mögliche Behandlungsoptionen diskutiert. In der vorliegenden Arbeit wurden leitende Palliativmediziner aus Palliative Care Teams retrospektiv zu Lebensverkürzung befragt.
Aus den 42 Antworten der 49 befragten Palliative Care Teams (PCT) kann aufgrund der vorliegenden Ergebnisse zusammengefasst werden:
Von den PCTs wurden in den Jahren 2013 und 2014 bis zum Tod **17.772 Patienten** multiprofessionell versorgt und begleitet. Der Wunsch nach lebensverkürzenden Maßnahmen in Form von Beihilfe zum Suizid oder Tötung auf Verlangen für diese Patienten wurde in dieser Zeit meist zu Beginn von den Patienten 1.452 mal geäußert.
Es verstarben durch Suizid mit oder ohne Beihilfe **17 Patienten**, es gab keine Tötung auf Verlangen. Die Suizide geschahen aber nach Einschätzung der befragten Palliativmediziner kein einziges Mal auf Grund palliativ nicht behandelbaren Leidens.
Einen hohen Stellenwert als Behandlungsoption nahm auch gegen schwerstes Leiden die palliative Sedierung ein. Das Problem war nicht Lebensverkürzen sondern Sterbenzulassen.
Kurz: Beihilfe zur Selbsttötung bei Palliativpatienten wurde so selten zu Symptomlinderung notwendig, dass durch die Seltenheit gesetzliche Rahmenbedingungen kaum definiert werden können.
2. Für die in der SAPV durch eigenständige Teams versorgten Sterbenden kann vermutet werden, dass Palliative Care in dieser Struktur- und Prozessqualität eine Suizidprävention bewirken könnte.

ID 0476

Suizide in der spezialisierten ambulanten Palliativversorgung – Vollerhebung im Sinne empirischer Sozialforschung bei Palliativmedizinern in allen SAPV-Teams im Saarland und Hessen sowie Kinder-SAPV-Teams in Deutschland

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Aus den 42 Antworten von 49 befragten Palliative Care Teams kann aufgrund der vorliegenden Ergebnisse zusammengefasst werden:
Von den Palliative Care Teams wurden in den Jahren 2013 und 2014 bis zum Tod multiprofessionell versorgt und begleitet: **17.772 Patienten.**
Der Wunsch nach lebensverkürzenden Maßnahmen in Form von Beihilfe zum Suizid oder Tötung auf Verlangen für diese Patienten wurde in dieser Zeit meist zu Beginn von den Patienten 1.147 mal, zusätzlich von Angehörigen für die Patienten 305 mal geäußert.
Wiederholt und nachdrücklich geschah dies von den Patienten 326 mal, von Angehörigen 164 mal.
Es verstarben durch Suizid mit oder ohne Beihilfe **17 Patienten (0,09%)**.
In vom Patienten geäußerter sowohl drohender als auch bereits manifester, existenzieller Not und bei aus den verschiedensten Gründen sehr hohem Leidensdruck wird häufiger ein Wunsch nach Lebensverkürzung vorgetragen. Die Suizide geschahen aber nach Einschätzung der befragten Palliativmediziner kein einziges Mal auf Grund palliativ nicht behandelbaren Leidens und die weit überwiegende Zahl unvorhersehbar für die Versorgenden und auch ohne Vorankündigung. Im Kollektiv Patienten mit einer besonders ausgeprägten und bislang schwer behandelbaren Symptomlast, war die Prävalenz der Todesursache (Selbst)Tötung im Jahr 2013 nur 0,10% und 2014 0,09%, also um über eine ganze 10er-Potenz geringer als mit den obengenannten 1,13% in der durchschnittlich belasteten und durchschnittlich kranken Bevölkerung.

Pflegerische Beiträge

ID 0141

Das Phänomen Schlafstörung bei Menschen mit onkologischer Erkrankung – eine konzeptuelle Begriffsanalyse aus pflegewissenschaftlicher Perspektive

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Hintergrund: Schlafstörungen bei Menschen mit onkologischer Erkrankung sind ein belastendes, untererfasstes Phänomen mit einer Prävalenz bis zu 96%. Ein pflegerisches Symptom-Management findet oft nicht statt. Behandelt wird meist mit Hypnotika. Obwohl international vermehrt empirische Erkenntnisse zum Phänomen existieren, liegt bislang keine deutschsprachige Analyse vor, die Pflegende in der Praxis unterstützt, das Phänomen zu erkennen, einzuordnen und adäquat zu behandeln. Ziel war eine konzeptionelle Klärung des Phänomens, um daraus Handlungsempfehlungen für die Praxis abzuleiten.
Methode: Es wurde eine konzeptuelle Begriffsanalyse durchgeführt. Als Material diente eine systematische Literaturrecherche in den Datenbanken Cochrane, Pubmed, PsycInfo und Medpilot.
Ergebnisse: 200 Artikel der letzten 10 Jahre wurden identifiziert. Ein Konzept wurde entwickelt, das als Erleben die Repräsentation sowie seine multidimensionalen Einflussfaktoren und Auswirkungen zusammenfasst. Viele Faktoren können sowohl Einflussfaktor als auch Auswirkung der Schlafstörung sein. Assessment und Interventionen müssen an allen Punkten ansetzen. Das entwickelte Rahmenmodell „Somnus®" bettet das Konzept in den Pflegeprozess ein und unterstützt das Symptom-Management in der Pflegepraxis.
Diskussion: Das Phänomen erfordert mehr Aufmerksamkeit von professionell Pflegenden. Regelmäßiges Screening ist notwendig. Assessment und Interventionen müssen zur Repräsentation wie zu Einflussfaktoren/Auswirkungen angeboten und evaluiert werden. Eigenständiges und interprofessionelles Handeln mit kommunikativem Austausch ist erforderlich. Es besteht großer Forschungsbedarf zu pflegerischen Interventionen.

ID 0177

Brustprothetische Versorgung von Frauen nach Mastektomie in Deutschland

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Einleitung: In Deutschland werden jährlich ca. 150.000 Frauen mit externen Brustprothesen versorgt. Über Erfahrungen betroffener Frauen liegen bislang wenige Studien vor, grundlegend sind Publikationen aus Australien und Irland. Defizite zeigen sich vor allem hinsichtlich Informationen über Zugang, Entscheidungsteilnahme und Wahlmöglichkeit.
Ziel: Die vorliegende Untersuchung nimmt Einblick in das Leben von 20 Frauen mit Brustkrebs in Deutschland, die nach einer Mastektomie mit einer Prothese leben. Ergänzend wird der Kontext durch Interviews mit Sanitätsfachangestellten (n = 8), spezialisiert Pflegenden (n = 8) und Prothesenherstellern (n = 4) beleuchtet.
Methodik: Die Studie zur Dissertation an der Universität Witten/Herdecke nutzt den methodischen Ansatz der qualitativen Evaluationsforschung um Erfahrungen und Perspektiven betroffener Frauen und einzelner Akteure in der brustprothetischen Versorgung abzubilden. Die Datenerhebung erfolgte anhand leitfadengestützter Interviews, die Analyse mittels offenen und selektiven Codierens. Ausgehend von den Ergebnissen der an Krebs erkrankten Frauen werden „Stakeholder", d.h. die Gruppen der Professionellen bewertet und beide Perspektiven miteinander in Beziehung gestellt.
Ergebnisse: Bisherige Analysen zeigen, dass die Erfahrungen Betroffener mit denen der Professionellen häufig nicht übereinstimmen. Für die Mehrzahl dieser Frauen stellt das „EINseitig sein" durch den Brustverlust eine gravierende Veränderung dar, die mithilfe einer externen Brustprothese vor allem in der Öffentlichkeit ausgeglichen werden soll. Welchen Einfluss die Beratung und Versorgung auf das Erleben, das Wissen und die Zufriedenheit hat, werden weitere Analysen zeigen.

Psychooncology

ID 0036

Computer-based interactive distress assessment – feedback of screening results may support a patient's informed decision on psycho-oncological treatment offers (ePOS-react)

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Background: Current S3-guidelines recommend routine distress assessment for all cancer patients. Up to now there is no gold-standard which screening instrument should be used.
We've been able to show that the accordance of recommended instruments used for psycho-oncological treatment indications is poor and their correlation with a subjective need is small. This study investigates whether a feedback of screening results and suggestion of a specific treatment offer to the patient results in a patient's reaction which is similar to an expert's rating of psycho-oncological need of treatment.
Methods: A distress assessment using 7 recommended and often used instruments in psycho-oncology has been made for N=103 patients with breast cancer and gynaecological tumours. At the end of the computer-based questionnaire they've been given a recommendation (no treatment, information about psycho-oncological services and psycho-oncological counselling) based on their screening results. They've been asked to choose which of these options they want to receive. In an additional separate interview their distress has been assessed from blinded experts using the PO-BaDo.
Results: 71% of all patients choose the suggested treatment offer. There is a strong correlation between the expert's evaluation of a need for treatment and the screening-instruments' results. This drops to moderate level when comparing it with the patient's wish for treatment.
Discussion: A computer based screening offers automated and immediate analysis of survey data which can be used to design an interactive screening procedure. This may include the possibility to strengthen patients' autonomy and help to form an informed decision about psycho-oncological treatment.

ID 0203

Quality assurance in psychosocial cancer counselling centres in Germany – a nation-wide analysis

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Background: Tailoring psychosocial cancer care to patients' individual needs across the whole continuum of cancer care is an important goal of Germany's National Cancer Plan. As a consequence, assuring the quality of in- and out-patient psychosocial cancer counselling becomes mandatory. Therefore, we aimed to explore quality aspects of psychosocial cancer

counselling provided by out-patient cancer counselling centres in Germany. The study was funded by the German Cancer Aid (DKH).
Method: Based on a list of 152 psychosocial cancer counselling centres available from the German Cancer Information Service in Heidelberg, data on quality characteristics concerning the structures and processes of psychosocial cancer counselling as provided by these centres were collected via either internet or mail survey. 107 of the centres (70%) responded. Data analysis included frequency counts and contingency tables. The quality characteristics covered were based on a prior expert survey conducted by our study group using a Delphi-approach.
Results: Basic services offered to patients and their families by the great majority of the centres include providing information, psychosocial as well as social benefit counselling, and referring to other services (> 75% of the centres each). 75% conduct regular case conferences, 66% report regular supervision by an external supervisor. 41% use some form of quality management. 40% report screening for distress in the majority of their clients.
Discussion: Most of the centres included provide basic services of psychosocial counselling. Results concerning the quality of processes are varied, however, thus calling for further analysis and discussion before deciding on strategies for improvement.

ID 0553

Fatigue-syndrom after allogeneic stem cell transplantation – screening and effects of a standardized inpatient rehabilitation program

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Introduction: Fatigue is a frequent and relevant problem of patients after allogeneic stem cell transplantation. We aimed therefore to evaluate the effects of three weeks-rehabilitation with a structural exercise and psychoeducational program on the fatigue-syndrom of patients after stem cell transplantation.
Methods: 131 patients (median age 59 years, range 26-70) undergoing an allogeneic stem cell transplantation carried out an endurance and resistance training 5-6 times weekly for a mean of three weeks. The program included weekly group-meetings, an educational seminar about diagnose, therapy and self-care management of fatigue-syndrome and an individual psychological support.The psychological functioning has been evaluated using the Fatigue-Scores with the Linear Analog Self Assessment Scale (LASA) and the questionnaire Multidimensional Fatigue Inventory (MFI), Hospital Anxiety and Depression Scale (HADS-D and HADS-A) at the beginning and at the end of the rehabilitation. In addition we are examined the heart rate variability and its correlation with these parameter.
Results: The exercise and psychoeducational program resulted in clinical and statistical relevant improvement of psychological performance during three weeks. We observed a statistical significant reduction of the fatigue scores LASA (mean) from 5,82 to 4, 25 and MFI (subscale general fatigue, mean) from 13,92 to 12,09. The HADS-D-Score (mean) was 58,45 and the HADS-A-Score (mean) was 48,57 at the beginning of rehabilitation. The heart rate variability was correlated with the fatigue scores.
Conclusions: The psychological performance of patients after stem cell transplantation is severely impaired. A structured inpatient exercise and psychoeducational program is feasible and helps to reduced fatigue symptoms this patient group.

Quality-of-Life

ID 0209

SECOM – self-efficacy coaching, quality of life (QoL) and recurrence-free survival in patients with early breast cancer (EBC)

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Breast cancer represents the leading cause of cancer in women in Germany with around 70,000 newly diagnosed cases per year. Beside the therapy- and cancer-associated somatic illness, about one third of patients develop anxiety disorders or depression and need psychotherapeutic or psychiatric care. Women with breast cancer display the highest psychic comorbidity in Germany compared to patients with other cancer entities. To prevent the onset and manifestation of psychic distress, patients should be offered patient-oriented psycho-oncologic support (S3-Guidelines).
Several approaches of psycho-oncological interventions exist. Nagel & Schreiber have developed a patient-oriented, individualized self-efficacy coaching (SWC) to mobilize and strengthen the belief in one's own ability to deal with and fight cancer. The interventional, comparative, multicenter study SECOM investigates the effect of SWC in women diagnosed with high risk EBC (n = 945). 36 sites will be assigned 1:1 to either the experimental Group A or the control Group B. The controlled site assignment will assure a balanced site-specific QoL between both groups at baseline. All patients will be medically treated according to guidelines. The experimental Group A will in addition receive regular SWC. SECOM consists of two parts: Primary endpoint of Part 1 is to show a higher QoL in Group A than in Group B after one year (FACT-B). If the primary endpoint is met, SECOM will continue with Part 2 for another 4 years to show a lower recurrence rate after 5 years in Group A than in Group B (primary endpoint, Part 2).
Grantgeber: Patientenförderverein – Wissenschaftliche Gesellschaft zur Förderung der Patientenkompetenz e.V., Germany

Radiation

ID 0346

Toxicity of concomitant application of radiotherapy with „new targeted therapies"

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Background: New targeted therapies (nTTs) are increasingly used in virtually every type of cancer. On the other hand radiation therapy (RT) is frequently applied in the curative and palliative setting of cancer treatment, confronting clinicians with the problem, weather a previously initiated nTT-therapy could be continued during RT. The aim of this systematic literature analysis was to evaluate the toxicity of concomitant application of RT with nTTs in a qualitative descriptive manner.
Methods: Clinical studies comprising concomitant application of RT with EGFR-, VEGFR-, HDAC-, proteasom-, BRAF-, m-Tor- or immune-checkpoint-inhibitors were eligible. Using fixed search terms 215 publications were identified including more than 6000 patients. 48 studies analyzed combinations of nTTs with ZNS-RT, 45 with head and neck-RT, 59 with thoracic RT, 33 with abdominal RT and 30 with pelvic RT.

Results: In most cases combination produced no additional toxicity or a slight increase of the already known toxicity profile. Scarcely, however, combination of RT with nTTs resulted in serious side effects. These toxicities for example comprised fistulas or GI-bleeding for combinations of RT with VEGFR-inhibitors, recall phenomena with erlotinib or severe mucositis, dermatitis when combining RT with ipilimumab. Predictive risk factors could not be isolated for all of these events.
Conclusions: The currently available data seems to be not adequate to give a general recommendation, on weather RT could be combined with nTTs in clinical routine. If application is carried out on an individual basis, it should be done under close clinical surveillance. Multicentric observational studies are needed to address this clinical relevant problem.

ID 0361

Outcome and toxicity of stereotactic body radiotherapy with Cyberknife of inoperable patients with NSCLC

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Purpose: The aim of this study was to evaluate the clinical outcome and toxcicity of Cyberknife stereotactic body radiotherapy for patients with in operable NSCLC
Methods: Between April 2012 and March 2015 110 patients were treated with Cyberknife sterotactic body radiotherapy at the Cyberknife Centum Cologne, Germany. 110 inoperable Patients with clinically staged and histologically proven T1(n= 85) or T2 (n = 25) NSCLC were included. They were inoperable due to age, pulmonary disorder due to earlier operation and comorbidities. Comobiditis were valued on the basis of the Charlson comobidity index. The treatment constisted of 1-8 fractionswith 7.5 to 25 Gy per fraction prescribed to the 80-65% isodose. 22 patients received fiducals.
Results:: The overall survival rates at 1 and 2 years after stereotactic body radiotherapy with Cyberknife were 83% und 62%, respectively. T stage, mediastinal staging, age or gender have no significance impact of the overall survival. In the analysis of the comobidities, subclassified in 5 points versus >5 points it becomes apperent that the overall survival in 2 years is 83% versus 38% in favour of group < 5 points. But there was no significant (log rank p = 0.068). The freedom of local recurrence at 1 and 2 years was 90% and 73% (n = 11). The stereotactic body radiation therapy with the Cyberknife was generally well tolerated.Only 2 patient had a pneumonia who need a hospital treatment.
Conculsion: Stereotactic body radiation therapy with Cyberknife is very well tolerated in this patient cohort with significant comobidities. The result in the loacal control rate is good, although considerable number of patient develops regional and distant metastasis

ID 0408

Radiosensitizing effect of BRAF inhibitors in BRAF-mutated melanoma

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Background: Concomitant treatment with BRAF inhibitors and radiotherapy increases the risk of radiation induced adverse events. This radiosensitizing effect of BRAF inhibitors might also sensitize melanoma cells to ionizing radiation and may improve therapy outcome.
Methods: Local tumor control, survival and toxicity in patients treated concomitantly with radiotherapy and BRAF inhibitors were studied. Two primary BRAF mutated and two primary BRAF wildtype cell lines were treated with the BRAF inhibitor vemurafenib and ionizing radiation in vitro and analysed with flow cytometry after Annexin-V-APC/7AAD and Hoechst 33342 staining.
Results: Within this study, 15 patients with metastatic melanoma were treated concomitantly with BRAF inhibitors and radiotherapy . Local tumor control of the irradiated metastases after 6 and 12 months was 82% and 71% according to Kaplan Meier analysis. Overall survival after 6 and 12 months was 70% and 41%, respectively. Three patients developed grade 3-4 toxicities (1 skin toxicity, 1 intracerebral hemorrhage, 1 esophagitis). One patient developed the severe form of follicular cystic proliferations (cutis verticis gyrata). BRAF mutated cell lines induced a G1 cell cycle arrest after treatment with vemurafenib. The rate of dead cells was 7% in the control, 9% after 2Gy ionizing radiation, 16% after 1µmol/l vemurafenib and 24% in the combination of radiotherapy and vemurafenib. BRAF wildtype cell lines did not show apoptosis or necrosis.
Conclusion: Concomitant treatment with BRAF inhibitors and radiotherapy is feasible with an acceptable increase in toxicity. In vitro experiments indicate a radiosensitization especially of BRAF mutated melanoma cells, which might improve tumor control in vivo.

Rehabilitation and long term burden in social medicine (survivor)

ID 0156

Sustained Increase of Physical Activity in Breast Cancer Patients

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Although mortality and recurrence rate can be reduced by physical activity in breast cancer patients, patients even tend to be more inactive after diagnosis. Oncological rehabilitation therefore seems to be an ideal setting to modify life style towards more physical activity. The purpose of this study was to investigate the effect of an individualized training program in comparison to standard 3-week rehabilitation.
206 patients (mean age of 55,9 yrs) were included in the study. 91 pts in the control group (CG) received a usual 3-week in-patient rehabilitation program, while 115 pts in the intervention group (IG) underwent an individualized training planned jointly by physiotherapists and patients during inpatient rehabilitation, gradually enhancing training intensity and duration. The IG also took part in a home training program supervised by regular telephone coaching. After 4 and 8 months the IG received another 1-week in-patient refresher program. Physical activity was assessed in both groups after 4, 8, 12 and 24 months by the Freiburger Questionnaire for physical activity.
In the CG physical activity was increased from 1,01hours/wk to a maximum 1,77 hours/wk after 8 months. In the intervention group physical activity rose from 1,35 hours/week to 4,44hours/week after 8 months ($p < 0,001$). After 24 months patients of the IG (2,75hours/week) were still significantly more physically active than the CG (1,19hours/week) ($p < 0,001$).
In contrast to conventional rehabilitation programs individualized training with long-term supervision may result in sustained improvement of physical activity in breast cancer patients.

ID 0181

Work-related intervention for the oncological rehabilitation – a pilot-study

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Objectives: Only little knowledge exists about contents of work-related measures in oncological rehabilitation. The aim of the study was to develop and evaluate a work-related module called *Perspective Job* for the oncological rehabilitation.
Methods: *Perspective Job* was developed within a rehabilitation team. The pilot-study had a sequential control group design with an intervention group (IG: n = 120) and a control group (CG: n = 86). Participants were oncological patients with substantial work-related problems. We asked patients how helpful they estimated the work-related therapies and defined work-related outcomes (self-assessed working capacity (SWC), functional capability in occupational (FCO)) over 3 months after discharge. Non-parametric-tests and analysis of covariance were applied to investigate differences between CG and IG.
Results: *Perspective Job* consists of occupational therapies as well as job trainings. The IG emphasized that most therapies were classified as work-related ($p < 0.001$) than the CG. The IG valued both contents ($p < 0.001$) and organisation ($p < 0.001$) better than the CG. They felt better prepared for the return to work ($p < 0.05$), were considerably less limited in their FCO ($p < 0.01$) and estimated their SWC more often as re-established than the CG ($p < 0.05$).
Conclusion: The development of *Perspective Job* within a rehabilitation team is possible and successful. The pilot study provides evidence that *Perspective Job* is a useful intervention to enhance work-related outcomes until 3 months after discharge. A controlled and multi-centre study should be carried out to verify this results.

ID 0208

Improved Nutrition in Adolescents and Young Adults after childhood cancer. INAYA – a pilot study

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Background: By the use of multimodal therapies the chance of survival improves and thus the risk for long-term side effects are increasing in „Adolescents and Young Adult" cancer survivors (AYAs) . Compared to the general population AYAs have a 5 to 15-fold increased risk of cardiovascular diseases. Therefore, the improvement of modifiable lifestyle risk factors is of importance.
Methods: The INAYA trial enrolled AYAs between 18-39 years to receive an intensified individual nutrition counseling based on a 3-day dietary records at 4 defined timepoints. At week 0 and 12 AYAs got personal counseling during follow-up care and consultation hours and at week 2 and 6 by telephone. Primary endpoint was change in nutritional intake measured by HEI-EPIC.
Results: 23 AYAs (11 female, 12 male, 21.9 ± 4.3 years of age, BMI: 21.6 ± 1.7 kg/m²) after treatment for childhood malignancies (12× hodgkin lymphoma, 6× leukaemia, 2× sarcoma, 2× carcinoma, 1× blastoma) were included. At baseline 14 patients (pts) were of normal weight, 4 pts overweight and 5 pts underweight (WHO criteria). 56.5% (n = 13) reported gastrointestinal symptoms (e.g. flatulence, change in stool consistency, stomach pain). According to HEI-EPIC a good, moderate and bad nutritional intake was seen in 4.3%, 73.9% and 21.7% of the pts.
Dietary habits improved after nutrition counseling at week 0, 2 and 6. 43.7% (n = 10) took more time to eat, 47.8% (n = 11) increased their fluid intake to ≥1.5 l/d and 21.7% (n = 5) changed their weight positively. Up to now 7 pts completed the study. Median HEI-EPIC score improved from 45 points (baseline) to 66 points (week 12). Final results are expected for November 2015.
Conclusion: Intensified nutrition counselling improves dietary intake and nutrition status in AYAs.

ID 0366

Dimensions and Changes of Patient Competence in Patients with Breast, Colorectal, or Prostate Cancer during Oncological Rehabilitation and 9 Months afterwards

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Background: In the light of increasing demands for patient autonomy, increasingly complex cancer therapies, prolonged survival, and efforts to enable shared decision making, Germany's National Cancer Plan designates developing Patient Competence (PC) as an important goal in comprehensive cancer care. At the same time, it acknowledges the need for clarifying the concept of PC itself and for analysing its determinants and its effect on outcomes empirically. Therefore, the present study explores the dimensions of PC and its changes during oncological rehabilitation.
Method: In a multi-centre study, 325 patients with either breast, colorectal, or prostate cancer were surveyed at the beginning and at the end of their rehabilitation as well as 9 months later. At each time point patients filled in questionnaires covering, e.g., PC, self-efficacy, fear of progression, depression, coping, and quality of life. Data were analysed by means of factor analyses and repeated measures ANOVAs.
Results: Factor analyses support distinguishing between at least 4 dimensions of PC: information-seeking, interacting with physicians, self-regulation, and managing distressing emotions. Diagnostic groups differ primarily with respect to information-seeking. Significant (and – in terms of effect size – small) changes in PC across time are observed only for self-regulation and managing distressing emotions.
Discussion: The factor analytic results clearly support a multidimensional approach to conceptualising and measuring PC. Analyses of changes in PC during oncological rehabilitation yield mixed results. Therefore, partially refining the measure of PC used is called for. Nevertheless, the results may in part help develop strategies how to promote PC.

ID 0368

Improvement of Sleep Quality and Fatigue due to a new Multimodal and combined Multimodal-Aerobic Intervention Concept in Breast Cancer Survivors with Cancer-Related Fatigue

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Background: Cancer-related fatigue (CRF) and insomnia are burdensome symptoms in breast cancer survivors (BC). Aerobic training (AT) is the standard therapy in BC with CRF. Other interventions with positive evidence are sleep education/restriction (SE), psycho-education (PE) and mindfulness-oriented therapies. We investigated a 10-week multimodal intervention (MT) consisting of SE, PE, eurythmy- and painting-therapy or in combination with AT (CT) and compared MT and CT each with AT alone.
Methods: In a three-arm comprehensive cohort design study BC with chronic CRF (6-36 months after adjuvant treatment) were allocated by randomization or by patient preference. Main endpoint was a composite outcome of Pittsburgh Sleep Quality Index and Cancer Fatigue Scale (CFS-D) after 10 weeks (primary endpoint) and six months. We hierarchically tested for non-inferiority of MT vs. AT, and for superiority of CT and MT vs. AT. The principal intention-to-treat analysis included 2 propensity-scores (randomization/preference, preferred treatment). Here, we present the explorative results of the combined analysis of both evaluation time points.
Results: 65 BC patients with CRF were randomized and 61 allocated by preference to the treatment arms (AT: n = 22/6, MT: n = 21/23, CT: n = 22/32). Socio-demography was comparable at baseline. After significant MT-non-inferiority testing both CT and MT were significantly superior to AT (CT vs. AT:Δ=-0.034, 95%-CI [-0.064; -0.004], p = 0.027; MT vs. AT:Δ=-0.045, 95%-CI [-0.078; -0.013], p = 0.007).
Conclusion: This study supports the hypothesis that a multimodal CRF-therapy might be superior to standard therapy. A further confirmative randomized clinical trial including a long-time follow up is necessary.

ID 0546

Oscillating pole treatment – a new effective treatment option for postprostatectomy urinary incontinence

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Introduction: There is evidence that specialized continence training has an effect on the recovery of continence after prostatectomy. Aim of this prospective randomized controlled study was the development of a complementary therapeutic option improving continence recovery during rehabilitation.
Methods: 353 patients (Ø 64.1 years) with urinary incontinence after prostate cancer surgery were evaluated. All patients passed a standard treatment program (continence training, endurance training, moderate strength training). Additionally the intervention group participated in a guided training with an oscillating pole (daily, 30 minutes). Urinary incontinence was evaluated using 1-h (ICS) and 24-hour pad-test.
Results: The data of 337 participants could be evaluated.

Table 1

parameter	Intervention group (n = 252)		control group (n = 84)		significance
	begin	end	begin	end	Intervention- and control group
1h pad-test	28,1g	14,3g	22,7g	17,9g	P<0,001
24h pad-test	282,5g	152,6g	235,3g	179,3g	P<0,001

Conclusion: Results of urinary continence therapy after prostate cancer surgery were significantly improved up by complex approach combining standard continence therapy and the new training using an oscillating pole. Therefore this new treatment option should be offered to all patients suffering urinary incontinence.

Sarcoma

ID 0010

Einflussfaktoren auf die Rezidiventstehung bei Patienten mit aggressiver Fibromatose

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Fragestellung: Die Radikalität der chirurgischen Resektion bei aggressiven Fibromatosen wird seit Jahren kontrovers diskutiert, da die großen monozentrischen Verlaufsuntersuchungen bisher widersprüchliche Ergebnisse hierzu hervorbrachten. In der folgenden Studie sollten nun der Einfluss diverser Faktoren auf das Rezidivrisiko aggressiver Fibromatosen untersucht werden.
Methoden: Es erfolgte eine retrospektive Analyse an 90 Patienten, die zwischen 1998 und 2014 in unserer Klinik chirurgisch behandelt wurden. Der mediane Follow-up betrug 6,2 Jahre. Als potenzielle Prognosefaktoren wurden u.a. Alter, Geschlecht, Tumorlokalisation, -größe, -tiefe, Resektionsstatus, Trauma, Radiatio, NSAR- und antihormonelle Therapie mittels log-rank-Test untersucht.
Ergebnisse: Das mittlere Alter der Patienten bei Erstdiagnose lag bei 42,1 Jahren. 50% aller Patienten (n = 45) entwickelten während der Nachbeobachtungszeit ein Lokalrezidiv. Im Rahmen der chirurgischen Entfernung des Primärtumors erfolgte bei 50 Patienten (68,0%) eine R0-Resektion, bei 28 Patienten (25,0%) eine R1- und bei 12 Patienten (7,0%) eine R2-Resektion. Das rezidivfreie Überleben nach 5 Jahren (5-JRÜ) war bei den R0-resezierten Patienten mit 68,8% (95%-Konfidenzintervall (KI): 53,5-79,9) signifikant höher als bei den R1/R2-resezierten Patienten mit 34,1% (95%-KI: 19,9-48,9) (p = 0,001). Tumoren, die an den Extremitäten lokalisiert waren (n = 51), waren mit einem rezidivfreien 5-JRÜ von 40,0% (95%-KI: 25,9-53,8) tendenziell aggressiver als Tumoren, die an der Rumpfwand (n = 18), im Kopf-Hals-Bereich (n = 7) oder intraabdominal (n = 14) lokalisiert waren (5-JÜR: 68,0%; 95%-KI: 50,4-80,4; p = 0,074).
Schlussfolgerung: Die Erlangung einer R0-Situation nach Primäreingriff ist mit einer deutlich besseren Prognose assoziiert und sollte angestrebt werden. Ob nun die R0-Resektion selbst als beeinflussbarer Faktor die Prognose entscheidet oder es vielmehr die unkomplizierten Umstände sind, die eine R0-Resektion erlauben, kann retrospektiv jedoch nicht abschließend geklärt werden.

ID 0018

Activity of regorafenib (RE) in leiomyosarcomas (LMS) and other types of soft-tissue sarcomas (OTS) – results of a double-blind, randomized placebo (PL) controlled phase-II-trial

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Background: RE is a multikinase inhibitor that has demonstrated activity in gastrointestinal stromal tumors. We investigated its activity and safety in anthracycline pretreated metastatic soft tissue sarcomas (STS).
Methods: REGOSARC (NCT01900743) consisted of four independent cohorts of patients (pts) with LMS, OTS, synovial, and adipocytic sarcomas who were randomized (1:1) to receive either RE (160 mg/d, 21/28 d) or PL, with optional cross-over. Key-eligibility criteria were age 18, measurable progressing STS not amenable to curative-intent surgery, 3 previous lines of treatment for metastatic STS. The primary endpoint was progression-free survival (PFS) with blinded central radiological review. Statistical assumptions for LMS and OTS cohorts were PFS = 1.6 months (mo) with PL, PFS = 4.6 mo with RE, 1-sided $\alpha = 0.1$ and $\beta = 0.05$.
Results: 57 LMS and 53 OTS pts were enrolled (55 with PL, 55 with RE). The two most common OTS types were Undifferentiated Pleomorphic Sarcomas (n = 21, 40%) and Solitary Fibrous Tumors (n = 7, 13%). Eighty-four (77%) tumors were grade 3. There were 48 men (44%). The median age was 60 (20-81) years. The median number of prior lines was 2 (1-3): 106 (97%), 59 (54%), 39 (35%) and 4 (4%) pts were previously treated with doxorubicin, ifosfamide, trabectedin and pazopanib, respectively. Both arms in each cohort were well balanced. The most common Gr 3 AEs were hypertension (10 vs 2 pts; RE vs PL), skin toxicity (9 vs 1), asthenia (9 vs 3) and diarrhea (6 vs 2). There was no Gr5 AE and 1 Gr4 AE (anemia in RE arm). The median PFS of LMS pts was 4.0 mo with RE versus 1.9 mo with PL (HR = 0.49; 95CI 0.27-0.89; p = 0.017). The median PFS of OTS pts were 4.6 and 1.0 mo, with RE and PL respectively (HR = 0.38, 95CI 0.20-0.74; p = 0.002). The 6-mo OS rate of LMS pts was higher in the RE arm (87.0% vs 75.9%; HR = 0.25; 95CI 0.08-0.81; p = 0.013), this difference was not significant in the OTS cohort (79.0 vs 62.0%; HR = 0.64, 95CI 0.23-1.74; p = 0.4).
Conclusions: RE demonstrates promising activity and an acceptable toxicity profile that warrant further clinical evaluation in LMS and OTS pts.

ID 0302

Follow-up in patients with ewing sarcoma – value of an imaging protocol including FDG-PET(-CT) and MRI for recurrence detection

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Objectives: The value of follow up imaging in patients with Ewing Sarcoma has not been evaluated systematicaly, so far. Aim of our study was to evaluate a prospectively defined imaging protocol of FDG-PET(-CT), MRI, bone scintigraphy, thoracic CT/-x-ray and x-ray of the primary tumour site and to compare detection of relapse by imaging only with detection of recurrence by clinical symptoms. To additionally assess the influence of detection mode on survival.
Methods: Eighty patients received regular follow-up imaging examinations according to a prospectively defined protocol over a duration of 5 years. The number of recurrences and the modes of recurrence detection (imaging method, clinical symptom) were determined from the imaging reports and patient files.
Results: In 30 of 80 patients who were analysed in this study, a relapse was diagnosed within the first five years of followup; 14 (47%) relapsed during the first year. Recurrent tumour was detected by protocol imaging studies in 19 patients (63%) and by clinical symptoms in 11 patients (37%). Detection rate of protocol imaging was: 8/164 investigations for FDG-PET(-CT), 1/309 for MRI, 2/151 for thoracic CT, 2/318 for bone scan, 6/1052 for X-ray. FDG-PET-CT and thoracic CT detected significantly more frequently pulmonary metastases
Conclusion: Most recurrences of Ewing sarcoma were detected by protocol imaging studies, among these many with FDG-PET(-CT). Diagnosis of recurrence by protocol seems to be associated with advantage for survival.

ID 0414

Effect of regional hyperthermia (RHT) in combination with neo-adjuvant chemotherapy for treatment of locally advanced high-risk soft-tissue sarcoma (HR-STS) is not dependent on etoposide

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Introduction: In a phase 3 study, the addition of RHT to EIA (etoposide=E, ifosfamide=I, doxorubicin=A) significantly improved tumor response and survival outcome in adult patients (pts) with HR-STS (Issels et al. Lancet Oncol. 2010). Subsequently, the EIA regimen was modified due to the mutagenic potential of E. Here, we report a retrospective analysis of pts treated either with EIA or with AI both combined with RHT.
Methods: Inclusion criteria and procedures were equivalent to the reported study. Pts with localized HR-STS were treated with up to 8 cycles of EIA (E: 250mg/m², I: 6g/m²; A: 50mg/m²; 12/06–12/08) or AI (A=60mg/m², I=6-9g/m²; 01/09–12/12) both combined with RHT (Tmax 42°C, 60min). Response was evaluated according to RECIST and survival parameters using Kaplan Meier and cox regression models supplemented by backward elimination using the likelihood ratio test for possible confounders.
Results: Among 65 eligible pts (23-70y, median age 48y), 34 pts received EIA and 31 pts AI with a median follow up of 43 months and 33 months. Overall response rate (CR and PR) for EIA was 38% and 39% for AI (p = 0.50). Local progression free survival (LPFS), progression free survival (PFS) and overall survival (OS) were not significantly different. Hazard ratio [HR] for LPFS was 0.97 (CI 0.46–2.05, p = 0.94), for PFS 1.21 (CI 0.64–2.27, p = 0.55) and for OS 0.79 (CI 0.36–1.75, p = 0.57) without significant differences in HRs after adjustment for confounders. For EIA vs. AI, 3-year rates of LPFS, PFS and OS were 59% [95% CI 0.56–0.62] vs. 53% [95% CI 0.50–0.56], 44% [95% CI 0.41–0.47] vs. 37% [95% CI 0.34–0.47] and 58% [95% CI 0.55–0.61] vs. 65% [95% CI 0.62–0.69].
Conclusion: AI in combination with RHT is equally effective as EIA + RHT for the neo-adjuvant treatment of locally advanced HR-STS.

ID 0423

Stem cell rescue after irradiation of multiple tumor sites combined with high-dose chemotherapy – high long-term survival in patients with advanced translocation positive pediatric sarcomas without bone marrow involvement

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Advanced Translocation Positive Pediatric Sarcomas (ATPS) are rare and have a poor prognosis. ATPS include Ewing sarcomas (ES) with early relapse or metastatic to multiple bones (MB) or bone marrow (BM) (advanced ES; aES) as well as rhabdomyosarcomas metastatic to lymph nodes or BM (advanced RMS; aRMS). We compared toxicity, relapse free survival (RFS) and overall survival (OS) of ATPS treated with MetaEICESS vs. EICESS92 protocols.

Of 46 patients, 20 patients were enrolled between 1992 and 2014 into two subsequent MetaEICESS protocols and compared to outcomes of 26 aES patients treated with EICESS 1992. MetaEICESS 1992 consisted of induction chemotherapy, whole body imaging directed radiotherapy to the primary tumor and to all metastases followed by consolidation with tandem high-dose chemotherapy and autologous rescue. In MetaEICESS 2007 treatment was complemented by allogeneic stem cell transplantation (allo-SCT). EICESS 1992 comprised induction chemotherapy, local therapy to the primary tumor only, followed by consolidation chemotherapy. 18/20 MetaEICESS patients had aES and 2 had aRMS. All 26 EICESS 1992 patients had aES.

8/20 in MetaEICESS vs. 2/26 in EICESS 1992 are surviving in CR ($p < 0.05$). OS and RFS did not differ between MetaEICESS 2007 (5/9) versus MetaEICESS 1992 (3/11). Three MetaEICESS patients died of complications, all in MetaEICESS 1992, i.e. *without* allo-SCT. After exclusion of DOC patients (n = 3), 8/11 patients survived without BM involvement, in contrast to 0/6 patients with BM involvement at diagnosis.

The MetaEICESS protocols yield long-term survival in patients with ATPS. Allo-SCT was not associated with increased DOC. BM involvement is a risk factor beyond MB metastases in ATPS.

Skin Cancer including Melanoma

ID 0337

Phase I gene therapy trial for nonviral jet-injection gene transfer of the TNF-alpha expressing minimalistic MIDGE vector (MGN1404) in melanoma patients

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Incidence for malignant melanoma is increasing worldwide with limited therapeutic options for late stage disease. Nonviral gene therapy might represent a therapeutic alternative. In this dose-escalation phase I clinical trial the nonviral jet-injection gene transfer of the minimalistic TNF-α expressing MIDGE vector (MGN1404) is evaluated for efficiency and safety in patients with in-transit metastases of malignant melanoma.

The patients received low (10 µg) and medium dose (50 µg) of MGN1404 vector DNA by five jet-injections of 10 µL into a single metastatic lesion. 72 hours after application the treated and an untreated tumor lesion was surgically removed. In parallel to the clinical and laboratory monitoring, the analysis of TNF-expression by immunohistochemistry, intratumoral vector-load and vector-clearance from patients' blood (30 min, 3, 6, 24, 48, 72 h and 4 weeks after jet-injection) was analyzed by quantitative PCR (qPCR).

For all patients no adverse events were observed. The laboratory and clinical monitoring revealed no signs of systemic inflammation. Molecular analysis by qPCR detected MGN1404 vector-DNA in the tumors at varying amounts, which was dose dependent (max. of 4×10^7 copies/µg genomic DNA). The immunohistochemistry revealed TNF-α expression in all transfected melanoma tissues. The control lesions neither carried vector DNA nor showed TNF-expression. The qPCR-analysis of the patients' blood revealed low level peaking of vector-DNA 30 min. after jet-injection (max. 8×10^3 copies/µg genomic DNA) in all patients followed by the clearance starting 3 h after application.

These first results demonstrate the safety and feasibility of nonviral jet-injection gene transfer for the minimalistic MIDGE vector.

ID 0354

Efficacy and safety in key patient subgroups of nivolumab (NIVO) alone or combined with ipilimumab (IPI) versus IPI alone in treatment-naive patients with advanced melanoma (MEL) (CheckMate 067)

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Aims: Phase III study CheckMate 067 reported improved progression-free survival (PFS) with NIVO + IPI vs IPI alone. Here, we report results of subgroup analyses in this trial.
Methods: Treatment-naïve MEL pts (N=945) were randomized 1:1:1 to receive NIVO (3 mg/kg Q2W) + placebo (PBO), or NIVO + IPI (1 mg/kg + 3 mg/kg Q3W X 4) followed by NIVO 3 mg/kg Q2W, or to IPI (3 mg/kg Q3W X 4) + PBO until disease progression or unacceptable toxicity. PFS, a co-primary endpoint, was evaluated in predefined subgroups.
Results: In the total population, median PFS was 11.5 months for NIVO + IPI vs 2.9 months for IPI alone (hazard ratio [HR] vs IPI, 0.42; $P<0.00001$), and was 6.9 months for NIVO alone (HR vs IPI, 0.57; $P<0.00001$). Numerically longer PFS was observed with the combination vs NIVO or IPI alone in all predefined subgroups, including baseline lactate dehydrogenase >upper limit of normal (NIVO + IPI: 4.2 months [95% CI: 2.8-9.3] vs NIVO: 2.8 months [95% CI: 2.6-4.0] vs IPI: 2.6 months [95% CI: 2.6-2.8]) and age <65 (NIVO + IPI: 11.7 months [95% CI: 7.0-not reached] vs NIVO: 5.5 months [95% CI: 3.0-8.3] vs IPI: 2.8 months [95% CI: 2.8-3.1]). The incidence of drug-related grade 3-4 adverse events was 55.0%, 16.3% and 27.3% in the NIVO + IPI, NIVO and IPI groups, respectively. Across pt subgroups, the safety profile was consistent with that observed in the overall safety population.
Conclusions: In pts with treatment-naïve MEL, NIVO + IPI and NIVO alone significantly improved PFS across predefined subgroups. The safety profile of the combination was manageable across subgroups of pts.

ID 0365

Impact of skin cancer screening on the incidence of skin melanoma in Germany – a trend analysis by tumor stage and histological subtype

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Background: In 2008, skin cancer screening was introduced in Germany. We analysed its impact of on melanoma incidence by tumor stage and histological subtype.
Methods: Pooled age standardized incidence rates for the years 2003 to 2012 were calculated using the data of 13 of 16 German federal states and one district. Results were stratified by tumor size (T-stage of TNM) and histological subtype. Multiple imputations based on polytomous regression models were used to replace missing data on tumor size or unspecific codes for melanoma morphology. Relative 5- and 10- year survival rates were calculated by histological subtype for patients diagnosed before introduction of the screening (cohort analysis).
Results: After introduction of the screening, skin melanoma incidence in Germany increased by about 20% for both sexes. The increase was mainly related to early stage tumors (in situ and T1 melanoma). Until 2012, no decline in more advanced stages could be observed. Regarding histological subtypes, incidence rates considerably increased for superficial spreading melanoma, for which relative 5- and 10- year survival rates were close to 100%. Nodular, amelanotic and acral lentiginous melanoma had a less favourable prognosis with relative 10- year survival rates varying between 49% and 70%. These subtypes did not show any significant increase in incidence rates after implementation of the screening.
Conclusions: According to the data of the population based cancer registries, skin cancer screening in Germany seems to affect mainly small and superficial spreading melanoma. Because of the favourable prognosis of this subtype, a substantial impact of the screening on melanoma mortality seems unlikely, even in the long run.

Supportive Care

ID 0060

Physical condition, nutritional status, fatigue and quality of life in tumor outpatients

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Background: There is a growing number of cancer out-patients demanding more comprehensive care. Physical activity and a balanced diet are constitutional factors for cancer survivors. The early detection and management regarding deficiencies may contribute to the improvement of quality of life (QoL) and the reduction of cancer-related fatigue.
The aim of this study is to describe the physical and nutritional status in tumor out-patients and its association with fatigue and QoL.
Material and Methods: In a consecutive convenience sample of 173 cancer out-patients data on QoL (SF-36), Fatigue (Multidimensional Fatigue Inventory, MFI-20), Karnofsky Index (KI), body mass index (BMI) and stability index (MFT S3- SI) were collected. Phase angle (PA), as an indicator of cellular health and integrity, was calculated from bioelectrical impedance analysis (BIA).
Results: PA and MFT S3-SI of tumor-outpatients differ significantly from the norm. PA and MFT S3-SI are significantly interrelated and correlate with the SF-36 physical component summary scale and SF 36 'physical functioning' but not with the SF-36 mental health component. PA significantly correlates with SF-36 'role limitations physical', 'general health

perception' and MFI-20 'physical fatigue', MFI-20 'reduced activity' and KI. BMI shows no interrelation with these variables.
Conclusions: Physical condition and nutritional status (MFT S3-SI, PA) are related to the physical QoL and fatigue of oncological out-patients. These are essential and interrelated components of cancer outpatient treatment, which should all be included in tailored ambulatory multimodal intervention strategies.

ID 0089

FIBS – a self-management program for patients with cancer-related fatigue

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Objective: To evaluate a patient education program that aims at reducing perceived fatigue in cancer survivors.
Methods: In ten German centres, 261 patients with cancer-related fatigue were randomly assigned to a patient education program consisting of 6 sessions à 90 min or standard care. The primary outcome measure was cancer-related fatigue. Data were analysed using analysis of variance (ANOVA) with repeated measures.
Results: Patients were highly satisfied with the program. 95.8% of the patients achieved a subjectively perceived personal benefit, on average 8.14 of 12 possible points. The overall patient education satisfaction scores 78.72%. Patients in the intervention group showed statistically significant reduction in cancer-related fatigue ($F = 76.510$, $p < 0.001$, $\eta^2 = 0.248$). Secondary outcomes also showed significant improvements in all measures, including quality of life ($F = 29.607$, $p < 0.001$, $\eta^2 = 0.113$), general self-efficacy ($F = 27.680$, $p < 0.001$, $\eta^2 = 0.107$), exercise self-efficacy ($F = 49.230$, $p < 0.001$, $\eta^2 = 0.175$), physical activity ($F = 8.036$, $p < 0.001$, $\eta^2 = 0.033$), anxiety ($F = 33.194$, $p < 0.001$, $\eta^2 = 0.125$), depression ($F = 24.604$, $p < 0.001$, $\eta^2 = 0.096$), and fatigue knowledge ($F = 55.157$, $p < 0.001$, $\eta^2 = 0.192$).
Conclusion: The program is characterised by target group-specific contents and methods and a high satisfaction of the patients. It was effective in reducing perceived fatigue as well as further outcomes. This patient education program has the potential to fill a gap in current care of cancer survivors.

Surgical Oncology

ID 0316

Partial resection of large abdominal wall and mesenteric desmoids under protective medication – a good concept for selected patients?

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Purpose: Severe desmoid disease in FAP patients frequently comprises combined large mesenteric and large abdominal wall tumour mass. In the light of severe morbidity and mortality caused by heroic intraabdominal desmoids surgery, we investigated a less invasive approach in some selected patients.
Methodology: Patients with FAP and large desmoids tumours that requested surgery and/or had large abdominal wall desmoids without mesenteric involvement or combined desmoids were evaluated by MRI scans. All of these patients had been on medication with high-dose tamoxifen (120mg) and sulindac (300mg).
Results: A total of 5 patients were included in this series (4 males). All patients had abdominal wall mass exceeding the diameter of 15cm and additionally mesenteric desmoid tumour. In the preoperative scans, the abdominal portion of the mass appeared to have a sheath separating the tumour masses in 2 cases; in 3 cases there was a narrow connection of tissue. In 3 cases the histological margin towards the mesenteric desmoid was involved, indicating a R1 or R2 situation. In the 2 R0 cases, the margin was minimal (1mm versus 3mm).
The shortest follow-up is 12 months, the longest 23 months. No recurrence of the abdominal wall desmoids was observed – the mesenteric desmoids tumours remained stable and quiescent in all cases.
Conclusion: In this series we have demonstrated, that partial resection of large abdominal wall desmoids under protective medication with high-dose tamoxifen and sulindac does not lead to recurrence and does not have a negative impact on existing mesenteric desmoids. Therefore in a selected group on patients with large abdominal wall desmoids and distorting physical appearance partial desmoids removal may be a new and attractive concept.

ID 0369

Pilot results on effects of human hMSC in an orthotopic SCID/NOD mouse model for cholangiocarcinoma

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Introduction: The aim of our study is to evaluate whether the employment of genetically engineered human mensenchymal stem cells (hMSC) from the bone marrow can improve the therapeutic options for cholangiocarcinoma (CCC).
Methods: The effect of hMSCs on human CCC cell lines (CL-6 and HuCCT-1) was detected on proliferation, pro-angiogenic potential, chemosensitivity and apoptosis *in vitro*. A boyden chamber based system and adhesion assay were applied to evaluated the hMSC homing *in vitro*. To investigate an *in vivo* effect, an orthotopic model of CCC was established by tumor cell local-injection into the liver of SCID/NOD mice. We tested the recruitment of intravenously injected hMSCs and their homing efficacy in this model. For a therapeutic purpose, genetic modified hMSCs transfected with a suicide gene were used.
Results and Conclusion: Our *in vitro* data showed that hMSCs had a significant effect on the biological function of CCC cell lines. Cell proliferation, pro-angiogenic potential, adhesion and the chemotherapy outcome is vigorous influent by hMSCs. CCC cell supernatant is able to attract MSC transmigration and invasion. CCC tumor cells with a high mitotic index (e.g. Cl-6) are more susceptible to external interaction and they showed a stronger ability in manifesting solid tumor in the orthotopic SCID/NOD mice model with lung metastatic potential. *In vivo* experiments on "homing" of hMSCs as well as potential role of hMSCs on tumor biology will be performed in this mouse model. CXCL12/CXCR4-mediated migration of MSCs to tumor stroma and signal-transduction pathways, including phosphoinositide 3-kinase/Akt signaling were also investigated in CCC model of our study. In addition, GCV treatment after MSC administration will be further implemented.

ID 0485

Ergebnisse der radikalen Zystektomie bei cT4 „very-high risk"-Prostatakarzinom – eine multizentrische Outcome-Studie von 62 Patienten

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Einleitung: Der Krankheitsverlauf von Patienten mit T4 PCa nach radikaler Zystektomie wurde bezogen auf das Rezidiv- und Metastasierungsmuster sowie Überleben untersucht.
Methoden: 62 Männer mit T4N0-1M0 PCa wurden zwischen 1972 und 9/2011 an 4 Zentren mittels pelviner Lymphadenektomie und radikaler Zystektomie (RC) behandelt. Adjuvante- und Salvage Therapien (Radiatio RT; Androgenentzug HT) erfolgten gemäß lokaler Behandlungsprotokolle. Alle Pat. wurden in regelmäßigen Zeitintervallen mittels PSA Bestimmungen nachuntersucht. Erweiterte Staginguntersuchungen erfolgten zum Zeitpunkt eines biochemischen Rezidivs oder bei Symptomen. Rezidivlokalisation, Zeit bis zum Auftreten eines Rezidivs und Überleben wurden analysiert.
Ergebnisse: Das mittlere Alter der Pat. betrug 64.1 J. (SD+/-8.2). Das präop-PSA war für 40 Männer verfügbar und lag im Mittel bei 23.9 (range 0.1-229; SD+/-49.6). pTNM zeigte kein understaging, alle Pat. hatten einen pT4 Tumor. PSM lagen in 53.5% und positive Lymphknoten in 50% vor. Der mittlere Gleason score betrug 7 (range 5-10). 43.2% der Pat. wurden mit einer neoadjuvanten HT behandelt. 17.7% und 62.3% erhielten eine adjuvante RT oder HT. Nach einem mittleren Follow-up von 59.9 Mon. (SD+/-68.5) wiesen 60.7% einen klinischen Progress auf (18% lokal, 57.4% Metastasen). Das 5- und 10-Jahres tumorspezifische Überleben betrug 44.5% und 35.7%. Cox multivariate Regressionsanalysen konnten zeigen dass PSM und adj.HT unabhängige Prädiktoren des tumorspezifischen Überleben waren (p = 0.05; 95% CI:0.25-0.99 und 0.05; 95%CI:1-4.2)
Conclusio: Einige Männer mit T4 Prostatakarzinom haben die Chance durch die Radikale Zystektomie geheilt zu werden. Die Mehrzahl der Patienten entwickelt ein Rezidiv das überwiegend in Form von Fernmetastasen auftreten.

Translational Oncology

ID 0126

Network of epigenetically silenced tumor suppressor microRNAs and targeted oncogenes S100A4 and MACC1 in colorectal cancer

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MicroRNAs (miR) are posttranscriptional regulators of gene expression. Altered expression patterns of tumor suppressor miRs by epigenetic silencing could be involved in colorectal cancer (CRC) tumorigenesis. In our study we are focusing on a panel of miRs (miR-200, -218, -505, -520 and -548) targeting the oncogenes S100A4 and MACC1.
The methylation status of miRs was analyzed *in silico* and *in vitro* by methylation specific PCR in CRC cell lines. Subsequently, a panel of 59 CRC and 5 normal colon samples was examined and correlated with clinical parameters. Quantitative RT-PCR was used to determine the expression of miRs, their putative host and target genes endogenously and in cell lines also after treatment with the demethylating drug 5-Azacitidine (5-AZA).
Methylated miRs were found in almost all cell lines and tumor samples at low expression levels. Further we observed a positive correlation of both, miR-218 and -505, and their corresponding host genes. We also confirmed inverse correlation of miR expression and their target genes. In cell lines 5-AZA treatment led to upregulation of all analyzed miRs. Within the tumor samples miR-218, -520 and -548 were significantly lower expressed than in the normal controls. Especially high expression of miR-218 was beneficial for patients.
We showed that most of the analyzed miRs are epigenetically silenced in CRC cell lines and in tumor samples. In ongoing studies we evaluate the underlying mechanism analyzing the promoter region of selected miRs by bisulfite-sequencing considering putative transcription factor binding sites. Our study emphasizes that activation of tumor suppressive miRs, e.g. through demethylating drugs, could serve as a novel therapeutic option in CRC.

ID 0265

Cathepsin D characterizes human osteosarcoma and pulmonal metastasis

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Background: Cancer proteomics provide a powerful approach to identify biomarkers in screening for alterations in protein levels and posttranslational modifications that are associated with tumors. Particularly, biomarkers for early detection, prognosis and therapeutic intervention of bone cancers, especially osteosarcomas, are missing.
Material and Methods: Protein expression patterns between cell lines of fetal osteoblasts, osteosarcoma and pulmonal metastasis derived from osteosarcoma were compared using two-dimensional gel electrophoresis (2-DE). Mass spectrometry served for identification of differential expressed protein spots. Target validation was performed by Western Blot on cell lines and by immunohistochemistry using tissue microarrays (TMA) on clinical samples, respectively.
Results: Comparison of gel-electrophoresis protein patterns revealed 34 differentially expressed protein spots ($p < 0.05$). 17 (50%) Proteins were identified by mass spectrometry that interact in pathways of *Gene Expression, Cell Death and Cell-To-Cell Signaling and Interaction.* Ran/TC4-binding protein (RANBP1) and Cathepsin D (CTSD) were validated by Western Blot in cell lines while the latter one showed higher expression differences also in clinical samples using tissue microarrays.
Conclusion: This study showed significant differences in protein expression between fetal osteoblasts, osteosarcomas, and pulmonal metastasis. Particularly, CTSD distinguished pulmonal metastasis from ostoesarcomas in clinical material and could thus trigger malignant transformation in bones.

ID 0280

Telomerase activation by genomic rearrangements in high-risk neuroblastoma

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Background: Neuroblastoma is a pediatric tumor of the sympathetic nervous system with a broad range of clinical behavior, ranging from spontaneous regression to fatal progression. The molecular mechanisms underlying these different phenotypes have remained largely elusive.
Methods: We applied an integrated genomics approach combining whole genome sequencing, RNA sequencing, targeted sequencing, FISH analysis, and chromatin immunoprecipitation coupled to sequencing.
Results: We discovered genomic rearreangements affecting a chromosomal region at 5p15.33 proximal of the *telomerase reverse transcriptase* (*TERT*) gene in 28/217 neuroblastomas (13%). These rearrangements occurred almost exclusively in high risk tumors lacking *MYCN* amplification (22/65 cases), and were strongly associated with poor patient outcome. Despite a large structural diversity of the rearrangements, they consistently induced massive upregulation of *TERT* expression accompanied by elevated enzymatic telomerase activity. We found that 5p15.33 rearrangements juxtapose the *TERT* locus to strong enhancer elements, resulting in massive epigenetic remodeling of the affected region. In the remaining high risk tumors, *TERT* expression was also upregulated in *MYCN*-amplified cases, while alternative lengthening of telomeres was present in high risk tumors without *TERT* or *MYCN* alterations. By contrast, telomere maintenance mechanisms were lacking in low risk tumors.
Conclusion: We show that remodeling of the genomic context abrogates transcriptional *TERT* silencing in high risk neuroblastoma. Our data suggest that activation of telomere maintenance mechanisms is the central molecular event distinguishing high risk from low risk neuroblastoma.

ID 0388

Mathematical Modelling of Cellular Systems for Personalized Medicine

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Identification of successful therapies for complex disease such as cancer is difficult due to the high level of genetic heterogeneity extant even within single tumour types. Pathway analysis of omics data using, e.g. gene enrichment analysis, can provide crucial insights, however, mathematical modelling of related cellular processes can enhance understanding of the underlying disease mechanisms. Building on current knowledge, we have developed a large mathematical model of cellular processes using the modelling software PyBioS. Development of such detailed mathematical models is hampered by limited availability of data on reaction kinetics and their respective kinetic parameters. To overcome this bottleneck we use a Monte Carlo strategy in tandem with parameter estimation, the latter using publically available cancer-related drug response data. Simulation permutations (e.g. modelling of a specific mutation or drug treatment) allows prediction of individual perturbation effects. The model is optimised in an iterative fashion using omics and drug response data from experimental cell lines and animals, permitting the validation of pathway and parameter information. The established resources, tools, algorithms and models have been integrated into the modelling platform ModCell™, establishing the foundation for the application of systems biology strategies in medical and pharmaceutical research and, based on omics data, enabling the development of personalised medicine.

ID 0464

Selective tumor eradication of claudin-3 and -4 overexpressing pancreatic cancer by suicidal gene therapy

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Selective cancer therapies act on specific molecular targets. Such targets are the tight junction proteins claudin-3 and -4, which are highly upregulated in several human epithelial cancers such as colon, ovarian and pancreatic cancer. Claudins are known receptors for *Clostridium perfringes* Enterotoxin (CPE), a pore forming toxin with a receptor-dependent cytotoxicity. CPE binding to its receptor triggers membrane pore complex formation, which leads to rapid cell death.
Here we aimed at *in vitro* evaluation of an efficient tumor-targeted eradication of claudin-3 and / or claudin-4 overexpressing pancreatic cancer by using a non-viral translation optimized CPE expressing vector (optCPE). Therefore we investigated the sensitivity of selected human pancreatic cancer cells and cells of patient derived pancreatic cancer xenograft (PDX) for treatment with recombinant CPE (recCPE) and more importantly by optCPE gene transfer. To demonstrate the specificity of the toxin action we also used a CPE mutant construct, lacking claudin-3 and -4 -binding (YALA-CPE). Claudin-3 and / or -4 overexpressing cells showed high sensitivity towards both, recCPE and optCPE gene transfer, but remained unaffected after YALA-CPE treatment. We demonstrated a positive correlation between cytotoxic activity of CPE and level of claudin-3 and / or -4 expression. The optCPE gene transfer led to rapid cytotoxic effects such as massive membrane disruption, cell and nuclear disintegration in claudin overexpressing cells, whereas the YALA-CPE gene transfer did not permit any cytotoxicity.
This study emphazies the great potential of a selective, tumor-targeted CPE gene therapy of claudin-3 and / or -4 overexpressing pancreatic tumors.

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Posters

Breast Cancer

ID 0034

Moderate Level of HER2 Expression and its Prognostic Significance in Breast Cancer with Intermediate Grade

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Purpose. Overexpression of human epidermal growth factor receptor 2 (HER2) is an important prognostic and predictive marker of response to anti-HER2 therapy in breast cancer. Our goal was to analyze the prognostic significance of moderate expression of HER2 in breast cancer with intermediate differentiation grade.
Patients and methods. We performed a multicentre retrospective register study of 8494 patients with primary non-metastatic breast cancer admitted between 2000 and 2011 to 8 Clinics in Saxony-Anhalt, federal state of Germany. Patients were divided into three groups according to their HER2 score: 4073 were classified as HER2 negative (HER2 0 and 1+), 822 HER2 moderate (HER2 2+/*HER2*), and 1238 HER2 positive (HER2 3+ or HER2 2+/*HER2*+). HER2 positive cases were excluded from analysis.
Results. Tumors with moderate HER2 (HER2 2+) expression demonstrated an aggressive behavior and worse patient survival compared with HER2 0 and 1+ status. HER2 2+ status was associated with shorter median overall survival (OS) (P<0.0001) in breast cancer patients with an intermediate grade of differentiation. Comparing low-grade and high-grade tumors, HER2 moderate expression did not significantly influence patient survival. In multivariate analysis after adjustment for other prognostic factors HER2 2+ status remained an unfavorable prognostic factor for OS (HR=1.224, 95% CI=1.059-1.415, P=0.006) in breast cancer patients with an intermediate grade of differentiation.
Conclusion. HER2 2+ status is an unfavorable prognostic factor regarding the OS of breast cancer patients with intermediate grade of differentiation and could be used to identify patients, who may benefit from adjuvant therapy.

ID 0040

Prognosis of breast cancer subtypes in routine clinical care

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Background / Aim: Analysis of up-to-date oncological outcome of breast cancer (BC) subtypes in routine clinical care of a specialized breast cancer unit (BCU).
Patients and Methods: A prospectively followed monocenter cohort of 4102 female cases with primary, unilateral, non-metastatic BC treated between 01.01.2003 and 31.12.2012 has been analyzed for the five routinely used subtypes (i.e. Luminal A-like, Luminal B/HER2 negative-like, Luminal B/HER2 positive-like, HER2-type, triple negative). The median follow-up time of the cohort was 52 months. We calculated estimates for local control rate (LCR), disease-free survival (DFS), distant disease-free survival (DDFS), overall survival (OS) and relative overall survival (ROS).
Results: LCR, DFS, DDFS, OS and ROS over 5 years for the cohort of invasive cases (n = 3603) were 96.1%, 83.7%, 85.7%, 90.5% and 94.7%, respectively. Luminal A-like tumors were the most frequent (44.7%) and showed the best outcome with LCR, OS and ROS over 5 years at 99.1%, 95.1% and 100.0%, respectively; while triple negative tumors (12.3%) presented the poorest outcome with LCR, OS and ROS over 5 years at 89.6%, 78.5% and 80.1%, respectively.
Conclusions: This outcome analysis of a large cohort of patients with primary BC, diagnosed, treated and prospectively followed on a routine basis at a specialized BCU confirmed subtype outcome data presented in clinical trials.

ID 0065

Real-time long-term detection of circulating breast cancer cells induced by medical interventions

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Background: The purpose of this research was to study the long-term impact of medical interventions on the circulating tumor cell (CTC) dynamics. We have investigated whether tumor compression, punch biopsy or tumor resection cause dissemination of CTCs into peripheral blood circulation using *in vivo* fluorescent flow cytometry.
Methods: For this purpose we used a breast cancer-bearing mouse model inoculated with MDA-MB-231-Luc2-GFP cells in the mammary gland. Two weeks after tumor inoculation, three groups of mice received the following intervention: (1) tumor compression for 15 minutes using 400 g weight to approximate the pressure during mammography; (2) punch biopsy; or (3) surgery. The CTC dynamics were determined before, during and six weeks after the procedure. An additional group of six tumor-bearing mice was used as control and did not receive an intervention. The CTC dynamics in all mice were monitored weekly for eight weeks after tumor inoculation.
Results: We found that tumor compression did not significantly affect CTC dynamics, either during the compression procedure itself ($P = 0.28$), or during the 6-week follow-up afterward. In the punch biopsy group we detected a significant increase in CTC immediately after the biopsy ($P = 0.02$) and the rate stayed elevated up to six weeks after the procedure in comparison to the tumor control group. The CTCs in the last group of mice, which received a complete tumor resection, disappeared immediately after the surgery ($P = 0.03$). However, CTC recurrence in small numbers was detected during six weeks after the surgery.
Conclusion: In the future, to prevent these side effects of medical interventions, the defined dynamics of intervention-induced CTCs may be used as a basis for initiation of aggressive anti-CTC therapy at time-points of increasing CTC number

ID 0083

Recurrence and survival of breast cancer patients depending on intrinsic subtypes defined by surrogate parameters – A population-based analysis

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Background: The aim of this study was to evaluate recurrence and survival for intrinsic subtypes defined by surrogate parameters in a population-based cohort of breast cancer patients.
Methods: 8828 patients diagnosed with invasive breast cancer between 2010 and 2014 in the catchment area of the Munich Cancer Registry were included in this analysis. Intrinsic subtypes were classified according to surrogate parameters oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67. Survival was investigated using the Kaplan-Meier method and multivariate Cox regression analysis.
Results: 5-year cumulative incidence of local recurrences and distant metastases was highest in triple negative tumours (11% and 16.7%), followed by HER2-like tumours (8.4% and 13.8%). In triple negative tumours, besides the common localizations lung (28%), skeleton (18%) and liver (15%), metastases were also frequently found in distant lymph nodes (12%) and in the central nervous system (11%). 5-year overall survival (OAS) was about 74% and 5-year relative survival (RS) was about 80% in both, triple negative and HER2-like cases. Luminal A-like cases, however, had an excellent prognosis (5-year OAS 94%, 5-year RS 102%). In the multivariate Cox regression analysis, tumour size, nodal status, and subtype were the most important factors for the prediction of survival. Compared with luminal A-like cases, patients with triple negative tumours have a 4.9-fold higher risk of dying (HER2-like 3-fold, luminal B-like 2.2-fold).
Conclusions: Patients with luminal A-like disease have an excellent prognosis, triple negative tumours have the worst outcome and a different metastasation pattern.

ID 0084

Probability of metastatic disease at primary diagnosis according to different intrinsic subtypes defined by surrogate parameters – A population-based analysis of breast cancer patients

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Background: The aim of this study was to evaluate the probability of primary distant metastasis (M1) for different intrinsic subtypes of breast cancer by surrogate parameters.
Methods: 8828 patients diagnosed with invasive breast cancer between 2010 and 2014 in the catchment area of the Munich Cancer Registry were included in this analysis. Intrinsic subtypes were classified according to surrogate parameters oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67. To estimate the probability of M1, multiple logistic regression models were calculated.
Results: 510 patients (6.2%) had distant metastasis at primary diagnosis. Proportion of M1 was highest in pT4 tumours (27.3%), HER2-like tumours (13.2%), luminal B-like (HER2+) tumours (10.1%), and in G3-tumours (9.4%). In node negative cases, only 0.6% of the patients were M1. In the multiple logistic regression tumour size and nodal status were identified as the most important parameters for the prediction of M1; age, grading and subtype were also significant in the model. Compared with pT1 tumours, pT4 tumours had a 33-fold higher risk of M1; luminal B-like and HER2-like tumours had a 1.7-fold higher risk compared to luminal A-like tumours.
Conclusions: Tumour size and nodal status are more important predictors for metastatic disease at diagnosis than biological factors like subtype classification. In node negative cases, the probability of distant metastases is very low.

ID 0091

Prognostic impact of interferon regulating factor 4 (IRF4) in node-negative breast cancer

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Background: The transcription factor IRF4 regulates immunoglobulin class switch recombination as well as plasma cell differentiation. We examined the prognostic significance of IRF4 expression in node-negative breast cancer.
Methods: IRF4 expression was evaluated by using immunostaining in a cohort of 200 node-negative breast cancer patients not treated in adjuvant setting. The prognostic significance of immunohistochemically determined IRF4 expression on metastasis-free survival (MFS) was examined by Kaplan-Meier survival analysis as well as univariate and multivariate Cox analysis. Additionally, IRF4 mRNA expression was evaluated using microarray-based gene expression profiling in four previously published cohorts consisting of 824 node-negative breast cancer patients in total, which were not treated with adjuvant therapy. The prognostic significance of IRF4 mRNA expression was examined in the whole cohort and in different molecular subtypes. The IRF4 mRNA expression was compared with immunohistochemically determined IRF4 expression using Spearman correlation.
Results: Univariate Cox analysis showed that immunohistochemically determined IRF4 expression correlates significantly with higher MFS (HR=0.183, $p < 0.001$). IRF4 retained its significance independently of etablished clinical factors for MFS (HR=0.133, $p < 0.001$). Immunohistochemically determined IRF4 expression correlated with mRNA expression (r=0,504). Higher mRNA expression of IRF4 was associated with better MFS in a meta-analysis of the whole cohort (HR=0.49, P<0.0001). Prognostic significance was more pronounced in the $HER2^+$ positive molecular subtype (HR=0.18, P=0.0008) as compared to the luminal A, luminal B and basal-like subtypes.
Conclusion: IRF4 expression showed independent prognostic significance (HR=0.394, P<0.0001) in node negative breast cancer.

ID 0097

Topotecan-induced ABCG2 expression in MCF-7 cells is associated with decreased CD24 and EpCAM expression and a loss of tumorigenicity

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Human breast cancer shows a considerable heterogeneity regarding the expression of CD24, CD44, EpCAM and HER2. These markers are involved in cell adhesion, migration and proliferation and thus affect metastasis and in turn patients outcome. The ATP-driven efflux pump (ABC transporter) breast cancer resistance protein (BCRP, ABCG2) is known to confer resistance to a wide variety of structurally unrelated cytostatics and defines subpopulations with enhanced tumor initiating capacity. The expression of ABCG2 can be induced by treatment with different cytostatic drugs. Concurrent effects of such treatments on the expression of the

aforementioned marker proteins and cellular properties related to cancer initiating cells have not been examined thoroughly.
Here we investigated the effect of the ABCG2 substrate topotecan on the MCF-7 breast cancer cell line and analyzed CD24, CD44, EpCAM and HER2 expression by flow cytometry. Moreover, we examined the impact of topotecan treatment on the sphere forming ability *in-vitro* and the tumorigenicity in immunodeficient NMRI-*nu/nu* and NSG mice.
We found an elevated ABCG2 expression in MCF-7 cells in the presence of 500 nM topotecan. Compared to untreated MCF-7 cells, the application of topotecan induced a subpopulation with decreased CD24/EpCAM expression, whereas CD44 expression remained largely unchanged. Topotecan-treated cells showed an impaired mammosphere formation capacity *in-vitro* and reduced tumorigenicity in immunodeficient mice. The data indicate that ABCG2 induction is not necessarily linked to increased tumorigenicity and suggest a major role of CD24 and EpCAM for the preservation of self-renewal capacity in MCF-7 cells and tumor outgrowth *in-vivo*.

ID 0118

Breast cancer and therapy in migrating and native women in Germany: Is there a difference?

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Background: Aim of the study was to identify differences between breast cancer patients with and without migrant background in Germany concerning patient-, tumor- and therapy characteristics.
Patients and Methods: Information on 99 breast cancer patients (50 native Germans and 49 Turkish immigrants) who were operated due to breast cancer between the years 2009–2012 at the University Women's Hospital Heidelberg was retrospectively reviewed.
Results: Patients with migrant background were significantly younger at the time of receiving the diagnosis of breast cancer than native Germans with an average age difference of 9 years. Immigrants needed a second operation for re-excision significantly more often than native Germans (44 vs. 20%). Medication used for hormone therapy was significantly different between the two collectives. Premenopausal status, estrogen-receptor-positive tumors, multifocal or bilateral tumors, BRCA-mutations and an accompanying carcinoma in situ tended to be more common in immigrants. In all other reviewed factors, no differences could be found between the two groups.
Conclusion: Breast cancer patients with migrant background were significantly younger at diagnosis. The different medication used for hormonal therapy could be explained by that difference in age. Migrant patients more frequently needed a second operation for re-excision. This could be explained by several observed risk factors like a young age, premenopausal status, multifocal tumors and an accompanying carcinoma in situ. Since no other differences between the two collectives could be found, we conclude that the German health care system includes migrant women well.

ID 0129

Evaluation of Option Grids to support shared decision-making in breast cancer treatment

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Background: Shared decision-making (SDM) is important in oncology, where many preference-sensitive treatment options exist. Many cancer patients wish active engagement in treatment decision-making. Despite evidence, SDM is not widely implemented in routine practice. Option Grids are short decision aids that help patients and physicians to compare treatment options. So far Option Grids are not available in German. The aims of this study are to translate and adapt two Grids on breast cancer treatment, to evaluate their acceptance and feasibility in routine care, and to assess needs for further Grids.
Method: We have designed a two-phased study: 1) Translation of both Option Grids into German, comparison to German clinical standards, testing of patients' understanding via cognitive interviews. 2) Pilot testing including focus groups with patients and clinicians to assess acceptability, followed by real world testing in routine breast cancer care using participant observation.
Results: First results show that physicians and patients valued the idea of Option Grids. However, several cycles of adaptation were found to be necessary in order to reach adequate acceptance. In addition, the feasibility of using Option Grids in Germany was questioned by several physicians. They expressed doubt if Option Grids can be used in current health care structures and if the options in the translated Option Grids are relevant in Germany. Final results, including pilot testing data, will be presented during the conference.
Discussion: This study provided a German version of two Option Grids for breast cancer treatment to be used in Germany for the first time as well as an assessment of their acceptability and feasibility in routine clinical settings.

ID 0130

The DETECT Study Concept – Metastatic breast cancer and circulating tumor cells

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Circulating tumor cells (CTCs) are detectable in early as well as metastatic setting. They have prognostic relevance and their impact on therapy decisions should be evaluated within the DETECT study program.
Within a combined **Screening program**, women with HER2-negative metastatic breast cancer (MBC) are screened for circulating tumor cells.

Patients with HER2-positive CTCS are randomized in **DETECT III** to standard endocrine or standard chemotherapy with or without lapatinib to evaluate the benefit of an anti-HER2 targeted therapy.
Patients with only HER2-negative CTCs are included in **DETECT IV**. Postmenopausal patients with Hormone-receptor positive MBC and no indication of chemotherapy are treated with everolimus + endocrine therapy (**DETECT IVa**), and patients with Hormone-receptor positive MBC and indication for chemotherapy or triple-negative tumors receive eribulin monotherapy (**DETECT IVb**).
DETECT V/CHEVENDO is focused on CTCs and treatment strategies in patients with Hormone-receptor positive, HER2-positive MBC. Women are randomized to either endocrine treatment or chemotherapy, both in combination with dual, anti-HER2 targeted therapy with trastuzumab and pertuzumab. Effectiveness as well as quality of life (assessed by presence of adverse events in both cohorts) are study endpoints in this phase III trial.
Several translational research projects embedded in the DETECT study program aim to identify further markers for CTC characterization and to analyze relevance of CTC detection and monitoring for treatment decisions in patients with MBC.
Individualized therapy concepts based on presence and phenotype of CTCs should optimize anti-cancer treatment with improved patients´ outcome.

ID 0131

Factors Predicting Discordance in HER2 Phenotype between Primary Tumor and Circulating Tumor Cells in Women with Metastatic Breast Cancer

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Background: Discordance of HER2-status between primary tumor and circulating tumor cells (CTCs) might have important implications for treatment response and therapy decisions. The aim of this study was to evaluate whether primary tumor and/or patient characteristics can predict discordance in HER2-phenotype between primary tumor and CTCs in patients with HER2-negative metastatic breast cancer (MBC) that are screened within the DETECT study program.
Methods: The number of CTCs (using the FDA-cleared CellSearch® System; Janssen Diagnostics, LLC) and their HER2 status were evaluated in 1123 women with HER2-negative MBC. Patients were defined as having HER2-positive CTCs if at least 1 CTC with a strong (+++) immunocytochemical HER2 staining intensity was found. Factors predicting discordance of HER2 phenotype were assessed using a multivariate logistic regression model with discordance in HER2 phenotype (yes/no) as binary response variable.
Results: At least one HER2-positive CTC was found in 134 of 711 HER2-negative MBC patients with one or more CTCs (median 2 HER2-positive CTCs, range 1–80); thus, 18.8% of patients showed discordance of HER2 phenotype between primary tumor and CTCs. Multivariate analyses revealed that the discordance in HER2 phenotype was significantly predicted by histological tumor type (lobular vs. ductal, odds ratio OR 2.66, $p < 0.001$), hormone receptor status (HRS, positive vs. negative, OR 2.89, $p = 0.022$) and number of CTCs detected (5 or more CTCs vs. 1–4 CTCs, OR 7.57, $p < 0.001$).
Conclusion: Discordance in HER2 status between primary tumor and CTCs was found in 19% of patients with HER2 negative MBC and can be predicted by histological type and HRS of the primary tumor as well as by the number of CTCs detected.

ID 0135

Komplementärmedizin in der niedergelassenen Praxis

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In Deutschland erkranken derzeit ca. eine halbe Million Menschen an Krebs, mehr als 200.000 Menschen sterben jährlich daran.
An Mamma Carcinom sind ca. 75.000 Neuerkrankungen pro Jahr zu verzeichnen.
Verlässliche Untersuchungen zeigen, dass sich eine erkrankte Person als erstes die frage stellt: Was kann ich für mich selbst tun?
Onkologen müssen sich die Frage stellen: Was erwartet die Patientin von uns?!
Genau in dieser Lücke entstand bereits schon seit Jahren die „CAM“ (Complementary alternative medicin)
Die Mehrzahl der Betroffenen wenden sich an kompl. medizinische Maßnahmen und wünscht sich diese auch.
Dies wird in akt. studienbasierten Ergebnissen aufgezeigt. Leider ignorieren viele klinisch tätige Onkologen diese Bewegung häufig. Dies führt dazu, dass sich Pat. zum Teil unseriös und nicht evidenzbasierten Maßnahmen zuwenden. Der wirtschaftliche Faktor in diesem Gebiet ist sehr hoch. Vor 2 Jahren wurde die AGO IMED auf dem DKK gegründet.
Seitdem werden an unterschiedlichen univ. Hotspots in Deutschland integrative Therapieverfahren klinisch untersucht und angewendet. Mehr als 15 Studien über CAM laufen in der BRD.
Der Vortrag soll auch einen spannenden Einblick in die CAM Anwendungen in der gynäkoonkologischen Schwerpunktpraxis gewähren.
Zielsetzung für die teilnehmenden Onkologen ist die Sensibilisierung für die Wünsche, Befürchtungen und Gefühle der Betroffenen, um Krebspatienten empathisch und aufmerksam begegnen zu können.

ID 0154

Disseminated tumor cells in luminal breast cancer: Prognosis and treatment

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Introduction: Disseminated tumor cells (DTCs) in the bone marrow (BM) of primary breast cancer (BC) patients are a surrogate marker of micrometastatic spread and an independent predictor of poor prognosis for disease-free survival (DFS) and overall survival (OS). The present study aims to analyze DTCs as an independent prognostic factor for DFS/OS in regard to tumor biology and bisphosphonate treatment.
Methods: We included 504 patients with operable primary BC and medium observation time of 72 months. DTCs were detected via immunohistochemistry in the BM of 59.13% (298/504) of the patients.
Results: For Luminal A and Luminal B groups, we observed a significant benefit of BM DTC negative patients with respect to DFS (Luminal A, $p = 0.0498$; Luminal B, $p = 0.0224$). In triple negative patients, DTC negative BM was associated with a longer OS ($p = 0.0326$).
Our multivariate Cox survival analysis in regard to DFS and OS with BM DTC status and luminal immunophenotypes as adjusted covariates implied DTC status (p
A further multivariate Cox survival analysis in regard to DFS and OS exclusively among the DTC positive patients with luminal phenotypes and Clodronate application as adjusted covariates has shown Clodronate ap-

plication (p = 0.0326) and Luminal A/B Phenotype (p = 0.0023) as independent prognostic factors for DFS.
Conclusions: The findings of our multivariate analysis point out BM DTC positivity as an independent risk factor for DFS particularly in Luminal A/B BC patients. This might possibly offer luminal phenotype and DTC positive status as an additional criterion to select candidates most likely to benefit from adjuvant therapy including bisphosphonates.

ID 0173

Young breast cancer survivors- reproductive concerns, life satisfaction and cancer-specific distress

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Introduction: The number of young patients with breast cancer is increasing and it is known that they are at risk to have a higher grade of the disease and therefore more aggressive treatment. This study serves for an evaluation of reproductive concerns, life satisfaction and cancer-specific distress in order to improve our support strategies.
Materials and Methods: Those patients having been treated at Breast Center, CCC of LMU (Munich/Germany) between 2006 and 2013 and with
Results: Of those patients who evaluated their decision about fertility preservation, 76.4% were satisfied with their choice. Most of the patients with current desire to have children refrained from childbearing because of fear of negative impact on prognosis, shortened life expectancy and treatment-related infertility.In the domains of health and sexuality, a significantly lower satisfaction was shown, but not in other domains or overall life satisfaction. The most pronounced cancer-specific problems were fear of cancer recurrence, diminished sexual activity, and psychosomatic problems.
Conclusion: Our data show that there is a need for counselling regarding childbearing after BC treatment. In contrast, fertility preservation seems to be well established in medical consultations.Also, cancer-related fears stress young patients and need to be addressed by supportive care programs.

ID 0189

Detection of EpCAM-negative circulating tumor cells in metastatic breast cancer patients by using VyCAP filters technology

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Circulating tumor cells (CTCs) are epithelial cells identified in the peripheral blood stream of epithelial cancer and are believed to be their metastatic precursors. Their exact composition is unknown. It has been discovered that they possess similar characteristics as their primary tumor but also show different phenotypes ranging from epithelial to mesenchymal. Detection of CTCs in peripheral blood provides prognostic information and might also represent an alternative to the invasive biopsies.
Nowadays CTCs are mostly detected and enriched by EpCAM-based systems. However, they cannot detect CTCs that have downregulated epithelial markers e.g. in the process called 'epithelial-mesenchymal transition'.
In a project funded by the EU ('CTCtrap: Circulating Tumor Cells TheRapeutic APheresis: a novel biotechnology enabling personalized therapy for all cancer patients " Grant agreement no: 305341) a protocol was established to detect EpCAM-negative CTCs by filtration using the VyCap-Filters technology. Samples are filtered through 5µm pore sized silicon nitride filters with a constant pressure of 100mbar. After enrichment, cells are stained for cytokeratins and CD45 to identify their epithelial origin. Filters are automatically scanned with a fluorescence microscope integrated in the CellCelector™ micromanipulator.
We processed a cohort of 19 samples: 26% of them were found positive for EpCAM+ CTCs, 37% were found positive for EpCAM- CTCs and 16% were found positive for both EpCAM+ and EpCAM- CTCs. We detected 36 EpCAM- CTCs and at our best knowledge there are no studies yet about correlation of both EpCAM+ and EpCAM- CTCs numbers in same blood samples in breast cancer. Further molecular analysis are needed to prove EpCAM- CTCs malignant origin.

ID 0202

Provision of breast cancer care and survival in Germany – results from a population-based high resolution study from Saarland

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Background: Studies on the implementation of Clinical Practice Guidelines (CPG) and its effect on breast cancer (BRC) survival on a population-level are scant. This study provides data on the usage of BRC treatment, the extent of adherence to CPG and, as novelty, survival of BRC patients according to major recommended treatment options.
Methods: Data from the Saarland Cancer Registry including women diagnosed with invasive BRC without distant metastasis and follow up in 2000-2009 were used. Provision of treatment according to CPG is presented by age, BRC type, and over time. Period analysis was used to derive estimates of 5-year relative survival (RS) and the effect of non-adherence to CPG on relative excess risk of death (RER).
Results: The study revealed increasing guideline adherence, with high levels already seen for local treatment (e.g. 67% of the patients in 2008/09 received breast conserving surgery), and substantial progress over time with regard to sentinel node dissection (SND) and adjuvant systemic treatment (e.g. SND and chemotherapy was provided to 62% of all patients and 79% of the patients with N+ or hormone receptor negative BRC in 2008/09, respectively). It further demonstrated increased cancer related mortality among patients without guideline compliant cancer treatment (e.g. patients with N+ and hormone receptor negative BRC without chemotherapy had a 5-year RS of 29% compared to 54% for patients receiving chemotherapy (RER: 2.89, 95% CI: 1.46-5.71)).
Conclusions: This study provides data on the implementation of CPG in Germany, extends available survival data of BRC patients and may provide evidence of increased cancer related excess mortality, if BRC patients do not receive guideline compatible treatment.
Reference: *BMC Cancer* 2014, 14:757.

ID 0225

WSG BCIST study: Prosigna® results impact on adjuvant decision making in early breast cancer (EBC)

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Background: Prosigna is a standardized test measuring expression levels of 50 classifier genes (PAM50) in breast tumor tissue using nCounter® Technology (Nanostring Technologies Inc., Seattle, WA). It provides intrinsic subtype and risk of recurrence (ROR) score predicting 10-year recurrence probability. WSG BCIST prospectively evaluated its impact on therapy decisions in EBC and the quality assurance at its implementation in clinical routine.
Methods: The study recruited 201 consecutive postmenopausal patients in 11 centers with ER+ HER- N0 EBC (10/2013 to 10/2014). Its primary objective was to assess the effect of the Breast Cancer Intrinsic Subtype Test (BCIST) on the oncologist's treatment recommendations regarding adjuvant chemotherapy (CT) and actual treatments received for EBC patients and confidence in this treatment decision from physician and patient at a 6-month follow up. As a secondary endpoint for quality assurance, we repeated Prosigna in a second de-central pathology lab in Germany for inter-observer-control.
Results: In the total evaluable cohort (n = 198), median ROR score was 45 (0-94). There was a 29.3% discordance in intrinsic subtyping between Prosigna and IHC. Concordance between central pathology and the second lab regarding molecular subtype was 95.5%. Overall, there was a change of treatment choice (change in CT-indication and change in regimens) in 18.2% compared to the pre-Prosigna decision.
Conclusion: Substantial discordance between PAM50 and local IHC underlines the importance of molecular subtyping prior to adjuvant treatment decisions and may thus help to improve understanding of treatment decision making and adherence in EBC.

ID 0230

Analysis of prognostication and treatment benefit tools for women with early breast cancer as a prerequisite for informed shared decision making

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Background: Shared decision making (SDM) is strongly recommended in the German treatment guideline for breast cancer. Following evidence-based criteria informed SDM requires decision aids that are based on individualized risk information rather than mere cancer prognosis such as 5-year relative survival. Treatment decisions should be based on individual prognostic data that include comorbidities and age-dependent risk of death from causes other than breast cancer.
Methods: Systematic literature search in Pubmed and EMBASE and free internet search. Prognostication tools for women with early, ER-positive breast cancer were analyzed for incorporated variables, information on the prognosis without adjuvant therapy, underlying data base, model validation and being up-to-date.
Results: We identified 3 relevant prognostication tools on survival: Adjuvant!, PREDICT and CancerMath. All tools consider age and tumor characteristics; 2 tools differentiate between cancer death and death from other causes but use US data and are outdated. Adjuvant! has shown to improve SDM and to change treatment decisions in a randomized controlled trial.
Limitations of the identified tools include lack of variables as comorbidity, Her2 status or mode of cancer detection. No tools using German data could be identified; PREDICT uses European data.
Conclusion: All tools have relevant limitations. A prognostication tool for individualized risk communication is not available for women with early breast cancer in Germany but is urgently needed. Otherwise informed shared decision making as recommended in guidelines cannot be realized.
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ID 0234

Phototheranostics immunoconjugates to detect eliminate triple negative breast cancer cells

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Triple-negative breast cancer (TNBC) is a very heterogeneous disease with a comparably poor prognosis. TNBC are classified as tumors that lack expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Consequently, TNBC patients do not benefit from currently available receptor-targeted therapies.
Photoimmuno-theranostics (PIT) approach holds great promise for improving cancer prognosis and management. It combines a minimally invasive approach with a targeted therapy: Specific antibodies are linked to nontoxic photosensitizers that can be activated at the target cell using light producing cytotoxic reactive oxygen species that kill malignant cells by inducing cell apoptosis and/or necrosis.
Due to TNBC heterogeneity, it is unlikely that any single targeted therapy will be efficacious in all TNBC patients. To overcome this limitation, we have investigated the use of three PIT agents targeting the most common cell receptors found in TNBC. Using SNAP-tag technology specific antibody fragments that target epidermal growth factor receptor (EGFR), epithelial cell adhesion molecule (EpCam) and chondroitin sulfate proteoglycan 4 (CSPG4) were conjugated with the highly potent photosensitizer, IRDye®700DX phthalocyanine dye. These PIT agents show powerful imaging properties and highly potent phototherapeutic activity, individually and in combination. In four different TNBC cell lines that express different levels of EGFR, EpCAM and CSPG4 receptors, combination of PIT-agents lead to reduced cell viability and increased apoptosis rates in our in-vitro model. Furthermore, this method has an excellent safety profile due to the non-toxic effect of free IR700 dye, even after irradiation.

ID 0236

Brain Metastases in Breast Cancer Network Germany (BMBC, GBG 79): The introduction of the multicenter register and analysis of patient data

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Background: The incidence of breast cancer brain metastases is rising. The evidence for the treatment strategies is rare and only a few data about the genesis and tumorbiology of the brain metastases exists. The project "Brain Metastases in Breast Cancer Network Germany " was started to analyse the clinical data of the patients in a multicenter setting. The translational investigation projects are planned with the biobank tissue material of the registered patients.
Methods: 91 centers in Germany are participating in the project. Data of 1047 patients is available for evaluation, the biobanking has been initiated. The intended number of included patients is n = 2000, the intended number of the tissue samples from brain metastases is n= 400. As one of the aspects, evaluation of patients diagnosed with asymptomatic brain metastases of breast cancer is in progress.
Results: The characteristics of the asymptomatic patients with brain metastases of breast cancer will be presented: tumobiology, presence of extracranial metastases, nodal status, time from the primary diagnosis to extracranial metastases etc. as this patients might be a cohort for the brain metastases screening.
The survival data of this cohort will be compared with the patients with symptomatic brain metastases to evaluate a possible benefit of the early brain metastases detection strategy.
Conclusion: The evidence-based approach for the treatment strategies of the brain metastases of breast cancer is insufficient. The aim of BMBC Registry is to improve the treatment strategies of the patients on the basis of the analysed clinical data and translational research.
The analysis of the cohort with the asymptomatic brain metastases will be presented to circumscribe the patients who might have benefit of the early detection of the brain metastases using the brain metastases screening strategy.

ID 0248

β-hydroxybutyrate inhibits growth of breast cancer cell lines

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Despite constant improvements in the treatment, breast cancer is one of the major causes of cancer death among females worldwide. In newer times the specific cancer metabolism as a "hallmark of cancer" pops up into focus as promising target for cancer therapies. According to the literature, there is preliminary evidence for the inhibitory influence of the metabolites acetoacetate and β-hydroxybutyrate on tumour growth.
In our study, we examined the effect of β-hydroxybutyrate (3-OHB) on the growth of six different breast cancer cell lines. In a 5 day cell culture, the proliferation of the luminal cell lines ZR75, MCF7, T47D and the triple negative basal A breast cancer cell line BT20 was significantly reduced in a dose dependent manner. In contrast, the growth of the triple negative basal B breast cancer cell lines MDA231 and MDA468 and of the HUVEC cells as benignant control was not changed by the influence of 3-OHB. This effect on cell growth was found independent of the expression of the key enzymes of ketolysis in the tumour cell lines, indicating an effect of beyond the energy production.
In summary, 3-OHB seems to be a very interesting physiological metabolite being beneficial for the control of tumour growth. However, this advantage seems to be depending on the cancer characteristics and subtype. So, after further research, a personalized therapy is conceivable.

ID 0271

Prototypical implementation of an expert system supporting medical documentation and clinical decision

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According to the results of the BRENDA study only 52% of the patients were treated in concordance with the recommendations of the Interdisciplinary S3 Guideline for the Diagnosis, Treatment and follow-up Care of Breast Cancer of the German Cancer Society (DKG). However, information about the reasons for physicians' deviation from the rules is limited. We designed an expert system based on the analysis of the decisions rules represented by the S3-Guideline, supported by structured expert interviews in order to improve transparency of physicians' decisions and to increase the integrity of clinical documentation. The rule basis of this prototype was challenged with 100 anonymized data sets from the Brandenburg´s Tumor Registry. This challenge resulted in a 61% concordance of the systems treatment proposals in relation to the tumor boards' de facto decisions. However, the mean age of the patients in the non-conforming group was 73 years (with age being a potential decision node against a systemic chemotherapy according to the results of the BRENDA II study) and in 31 out of 39 cases comorbidities were documented. Since the probable influence of the documented comorbidities on physicians' decisions remains intransparent, we will analyze a larger number of data sets, paying special attention to the respective comorbidities documented. The results of our study are not fully satisfactory and require a re-design of the system supported by data mining methods thus detecting further decision nodes.

ID 0279

EpCAM-independent enrichment of circulating tumor cells (CTCs) in metastatic breast cancer

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Most assays established to detect CTCs rely on the expression of the Epithelial cell adhesion molecule (EpCAM). Here we present an EpCAM-independent enrichment strategy combining different antibodies specific for surface proteins (e.g. Trop2, CD49f) and ECM components (e.g. hyaluronic acid (HA)) to capture $EpCAM^{neg}$ CTCs from blood samples of breast cancer patients (bc pts) depleted for $EpCAM^{pos}$ cells. The expression of respective proteins was verified by IF on $EpCAM^{pos}$ and $EpCAM^{neg}$ bc cell lines. To isolate $EpCAM^{neg}$ cells, the capture molecules were first spotted in a single-/multi-array format onto glass slides and cell adhesion of $EpCAM^{pos/neg}$ cell lines was visualized by Coomassie/MitoTracker staining. As expected marginal binding of $EpCAM^{neg}$ cells to EpCAM-antibodies could be observed. However, efficient adhesion/capturing of $EpCAM^{neg}$ cells could be achieved via HA and antibodies against CD49f and Trop2. Optimal capture conditions were then applied to magnetic beads to detect $EpCAM^{neg}$ CTCs from clinical samples. Captured CTCs were verified/quantified by IF for anti-CK-FITC/anti-CD45 AF647/DAPI. In total, in 20 of 29 EpCAM-depleted fractions (69%) from 25 met bc pts additional $EpCAM^{neg}$ CTCs could be identified increasing the CTC-positivity rate from 38% ($EpCAM^{pos}$ only) to 55% ($EpCAM^{pos}$ and/or $EpCAM^{neg}$) for samples with ≥5 CTCs. $EpCAM^{neg}/CK^{pos}/CD45^{pos}$ cells could be traced in 28 out of 29 samples. In conclusion, we established a novel enhanced CTC enrichment strategy for $EpCAM^{neg}$ CTCs from clinical blood samples by targeting various cell surface antigens with antibody mixtures and ECM components. Comparison of $EpCAM^{pos}/EpCAM^{neg}$ CTCs regarding genomic aberrations with array comparative genomic hybridization is underway.

ID 0294

Life satisfaction and life quality in the elderly patient with breast cancer

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Introduction: Due to increasing life expectancy and demographic trends, elderly patients and their specific needs are shifting into the spotlight. The aim of this study was to determine the impact of adjuvant chemotherapy on health-related quality of life (HRQOL) and life satisfaction in elderly breast cancer patients.
Methods: All breast cancer patients who had been treated at the Breast Center of the University Hospital of Munich, Germany between 2010 and 2013 and with>60 years at primary diagnosis were eligible for participation. Several validated questionnaires to assess life satisfaction and health-related quality of life (HRQOL) were used.
Results: This analysis includes data of 279 patients. Compared to a published normative data, our cohort reported significantly higher overall as well as domain-specific life satisfaction regardless of receipt of chemotherapy. Regarding HRQOL, patients who had received chemotherapy (n = 88, 31.5%) demonstrated more distress due to *fatigue, dyspnea, hair loss, breast and arm symptoms, mobility, body image, social and emotional functioning* and *financial difficulties* compared to patients without chemotherapy (n = 188, 67.4%). Obesity and the presence of comorbidities were associated with both a reduced health-related quality of life and life satisfaction, regardless of the type of the treatment.
Conclusion: In our cohort, chemotherapy affected several domains of HRQOL, but did not impact on life satisfaction. Comorbidities and obesity are independent factors influencing HRQOL and life satisfaction.

ID 0295

Possible role of estrogen receptor-alpha in the signaling mechanism of progesterone receptor membrane component-1 in human breast cancer

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In the present work, the influence of different inactivated PGRMC1 phosphorylation sites together with various preparations of estrogens and progestogens on the proliferation of breast cancer cell lines was determined. Moreover, the potential estrogen receptor (ER)-regulated kinase, CK2 (casein kinase 2), that may participate in the phosphorylation of PGRMC1 was investigated. Furthermore, the transcription of the ER dependent gene, Trefoil factors 1 (TFF1), in these two breast cancer cell models, was evaluated, to investigate the possibility of a cross-talk between PGRMC1 and ER in estrogen/progestogen-regulated breast cancers.
Different progestogens as well as estrogens can induce the proliferation of PGRMC1 over-expressing breast cancer cells. Breast cancer cells containing PGRMC1 with mutated putative interaction sites responde differently to stimulations. Both, ER and CK2 inhibitors can significantly reverse the proliferative effect of progestogens and estrogens on PGRMC1 over-expressing breast cancer cells. Transcription of TFF1 is significantly amplified in these cells by various progestogens and estrogens. Finally, a significant suppression of TFF1 transcription was observed applying either PGRMC1, CK2 or ER inhibitors.
Our results suggest that in terms of breast cancer risk in women overexpressing PGRMC1 kind and dosage of the estrogen and progestogen used should be considered.

ID 0296

Isolation and characterization of tumor infiltrating lymphocytes in primary human breast cancer

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Introduction: Priming the immune system against tumor cells in breast cancer (BC) has recently become a major issue in developing personalized therapeutic strategies. Although the immunogenicity of BC has previously not been strongly considered, recent advances emphasize the importance of tumor-infiltrating lymphocytes (TIL). Previous studies provide evidence that TILs have prognostic value in BC, particularly in aggressive or metastatic forms. However, the therapeutic significance of TIL´s in BC is still poorly investigated.
Methods: We have successfully established a method generating cell suspensions of living TIL´s and single cancer cells out of primary human tumor tissues isolated under sterile conditions after surgical intervention. We studied the tumor infiltrating immunocytes (TII) isolated from therapy naïve primary human BC tissues using a multicolor FACS analysis, antigen dependent cell isolation and cultures.
Results: We identified two different tumor modalities: 1) high TIL count and 2) low / very low TIL infiltration infiltration (>15% vs. <5% [% of TIL´s per 100 BC cells]). The distribution of TII´s showed a predominant infiltration through $CD3^{high}$ T-lymphocytes (65 ± 16% [% of $CD45^{high}$ TII]) with an mean CD4/DC8 ratio of 2,4, along with $CD19^{high}$ B-lymphocytes (11 ± 5%) and $CD33^{high}$ myeloid cells (21 ± 8%). Concerning the analyzed TII distribution no significant difference was found between high vs. low TIL count samples. Subsequently $CD3^{high}$ TIL´s and primary tumor cells were isolated and cultivated for *ex vivo* analyses.
Conclusions: Generation of single cell suspension of primary human tumor tissue enables a detailed characterization, antigen specific isolation and cultivation of BC TIL´s along with primary tumor cells to study the biological behavior and *ex vivo* response of tumor cells to TIL´s.

ID 0303

Frequent expression of PDL-1 on circulating epithelial tumor cells (CETCs) could be a new therapeutic target in breast cancer patients

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Background: Analysis of CETCs is a promising diagnostic field for estimating the risk for metastatic relapse and progression. The phenotypic characterization of CETCs may provide real time information and can be of great value in therapy monitoring. Programmed cell death ligand 1 (PDL-1) is an important protein frequently upregulated in a number of different cancers. Cancer cells expressing PDL-1 inhibit immune-modulatory T-cell activation allowing disease progression. Therefore this immune checkpoint has emerged as important target for immune therapy. The purpose of the current study was to identify potential patients who may benefit from PDL-1 targeted immunotherapies.
Methods: CETCs were determined from blood of 22 (69%) non-metastatic and 10 (31%) metastatic breast cancer patients. The number of vital CETCs and the expression of PDL-1 were investigated using the maintrac® method.
Results: PDL-1 expressing CETCs were detected in 94% of breast cancer patients; however the fraction varied between 0 to 100% in individual patients. There was no association between the number of PDL-1 positive CETCs and obtaining chemotherapy. Interestingly, we found a relationship between the numbers of PDL-1 positive CETCs and progression of cancer disease. Patients with metastatic disease had more PDL-1 positive CETCs as compared to patients without metastasis.

Conclusion: Breast cancer patients harbour PDL-1 positive CETCs that have the capacity to block the immune system and therefore may be a promising target for anticancer therapies. Monitoring the number of PDL-1 positive CETCs could reflect individual patient's response for an anti-PDL-1 therapy.

ID 0351

In Vitro Cultivation of Circulating Tumor Cells of Metastatic Breast Cancer Patients

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Solid tumors are constantly releasing cells into the circulatory system. They are genotypically and phenotypically different from the primary tumor. These circulating tumor cells (CTCs) are extremely rare events, with less than 50 CTCs per 7.5 ml blood. Therefore, it would be of high importance to expand this cell population for further characterization of CTCs. Our aim is to cultivate isolated breast cancer CTCs. This offers the opportunity to increase the CTC number available for analysis, allows to restrict analysis to viable CTCs that might have had the potential to form metastasis and enables to perform chemosensitivity assays in order to predict the success of considered treatments.
Fresh blood was obtained from patients with metastasized breast cancer. CTCs from fresh blood were enriched by Ficoll density gradient centrifugation and resulting cells were cultured with stem cell medium. Growing cells were harvested and checked for epithelial and hematopoietic markers by immune fluorescence microscopy. Further, cultured CTCs are analyzed and compared to CTCs isolated from patient blood samples on genomic, transcriptomic and proteomic level.
Growing cells were *bona fide* CTCs (CK+/CD45-). Their tumorigenic origin was confirmed by STR analysis and array CGH, respectively. RT-PCR analysis at various points during culture revealed expression of epithelial, mesenchymal and stemcell markers.
So far, we were able to culture CTCs from some patients. They show similarities but also differences to patient CTCs regarding the expression pattern of transcripts related to epithelial, mesenchymal and stemcell markers. The similarities as well as the differences will be part of further analysis to find the optimal culture conditions.

ID 0358

TruRisk® based next-generation sequencing reveals a high prevalence of deleterious *ATM* mutations in *BRCA1/2*-negative breast and ovarian cancer families

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Approximately 24% of familial breast cancer (BC) and/or ovarian cancer (OC) cases analyzed within the framework of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) are due to pathogenic *BRCA1/2* mutations. However, the mutation frequencies of non-*BRCA1/2* genes associated with familial BC and/or BC/OC are largely unknown. Here, we present the first NGS data generated by using the GC-HBOC-designed gene panel TruRisk®. In this study a cohort of 574 *BRCA1/2*-negative index cases were analyzed which comprises 256 unselected patients with triple negative breast cancer (TNBC) and 318 cases from high-risk BC and BC/OC families. By focusing on 21 BC/OC associated genes (*ATM, BARD1, BRIP1, CDH1, CHEK2, FANCM, MLH1, MSH2, MSH6, MRE11A, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMARCA4, STK11, TP53, XRCC2*), we identified 40 different pathogenic variants in 38 unrelated mutation carriers derived from 318 high risk BC and BC/OC families (12%). In contrast, only 9 mutation carriers (3.5%) were discovered among the unselected TNBC cases. Interestingly, we identified a high frequency of pathogenic *ATM* mutations *(n = 10, 3.1%)* in the familial cases whereas no *ATM* mutations were found in the TNBC cohort. Additionally, we found a high frequency of mutations in *CHEK2, PALB2, RAD50* and confirm *FANCM* and *SMARCA4* as novel BC/OC predisposing genes. Due to the unexpectedly high mutation frequencies in familial cases, our study highlights the importance of these genes to be included in BC/OC routine diagnostics. Furthermore this approach confirms the TruRisk® gene panel as a reliable tool for this comprehensive analysis.

ID 0359

Ten years of mammography screening in North Rhine-Westphalia: Analysis of impact indicators

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Background: The European Guidelines (EG) have defined indicators for the evaluation of mammography screening programs (MSP) that may serve as surrogate markers of an expected reduction of BC mortality. We investigated the course of these indicators for the MSP in NRW, the most populous federal German state.
Methods: The MSP was introduced since 2005 in a step-wise manner and fully implemented by 2009 for the target group of women aged 50 to 69 years. Data from all screening units that had completed prevalence screening (PS), first (SR1) and second subsequent screening (SR2) round by the end of 2012 were linked with data from the population based cancer registry. In total, 703.569 (PS), 484.440 (SR1) und 363.789 (SR2) screening examinations were available for this study.
Results: The detection rates were 83.0 (PS), 57.2 (SR1) and 61.9 (SR2) /10.000 women screened, corresponding to the 3.0-, 2.1- and 2.3-fold of the background incidence (BI) (EG: ^{3}3.0 (PS)/ ^{3}1.5 (SR)). The interval cancer rates were 24.1 (PS) and 21.4 (SR1) /10.000 among negatively screened MSP-participants, corresponding to 0.84 BI and 0.74 BI, respectively (EG: ≤0.8). Tumor characteristics of screen-detected cancers were: UICC II+-tumors: 31.6% (PS) to 26.5% (SR2) (EG:70/75%); proportion invasive cancer: 83.5% (PS) to 81.5% (SR2) (EG: 80-90%). Overall, three out of four BC cases among MSP-participants were detected at screening.
Conclusions: Evaluation indicators of the MSP in NRW closely comply with the ranges defined by the EG, indicating that the MSP meets expectations in terms of quality and has the potential to decrease BC mortality.

ID 0360

eHealth acceptance in breast cancer care

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Introduction: Lack of compliance and adherence in oral and s.c. treatment of breast cancer (BC) are huge problems leading to significant impacts in mortality. Where conventional mailing systems failed eHealth could be a possible solution to increase adherence among patients and to ameliorate the communication between patients, oncologist and nurses. The objective of this study is to investigate the actual internet usage habits and property of new media among BC patients, their oncologists and the nursing stuff to find new possible ways to improve compliance and adherence in long term treatment.
Methods: By using 3 different questionnaires (33 items), the actual usage of internet and modern media among BC patients and their healthcare professionals is surveyed.

Results: 631 patients, 120 oncologists and 96 nurses completed the questionnaire. The internet usage in general and for health related issues is very high among all three. Among patients, even above age 60, 51% report to use the internet every day. Medical professionals as well as the majority of patients can imagine getting additional support during long term therapy using eHealth technologies.
Discussion: This survey, which is the first BC specific study representing internet usage habits among BC patients and their medical professionals, shows high acceptance of new interactive ways of communication between patients, doctors and nurses who are all taking part in treatment of BC. Introducing eHealth may help increase compliance and improve the doctor-patient-relationship which will possibly lead to decreased mortality and higher patient satisfaction.

ID 0370

Cognitive Function in Relation to Aromatase Inhibitors among Breast Cancer Survivors

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Background: The use of aromatase inhibitor (AI) therapy has been increasing over the years due to efficacy of reduction of breast cancer (BC) recurrence. In a pilot prospective study we sought to assess the cognitive function of BC survivors who had been exposed to AI agents.
Material and Methods: Participants were recruited from our breast center and a neurophysiological test was administered bevor starting the AI-therapy. After 12 and 24 months the same tests were repeated. Of 38 participants 26 had been treated with AI and 12 had no AI exposure (Tamoxifen). No patients had received chemotherapy.
Results: the AI group did not differ significantly from the non AI group at the beginning. However over the time (>24 months) a trend for toward worse cognitive function among the AI subjects were evaluating. Verbal episodic memory was mainly impaired in elderly patients (>65 years).
Conclusion: There are reasons for concern about the effects of AI's on cognition. If the results are confirmed patients with early cognitive decrements might be good candidates for participation on a larger trial with MRI in screening.

ID 0379

Comparison of 12 weeks neoadjuvant Nab-Paclitaxel combined with Carboplatinum vs. Gemcitabine in triple negative breast cancer: WSG-ADAPT TN randomized phase II trial

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Background: Pathological complete response (pCR) is associated with improved prognosis in TNBC. However, optimal chemotherapy regimens to achieve this remain to be defined. Both use of nab-paclitaxel (Nab-Pac) q1w vs. paclitaxel and addition of carboplatinum (Carbo) to anthracycline-taxane (A/T) containing chemotherapy results in significantly higher pCR rates in TNBC, however, with unclear impact on survival and increased toxicity.
Methods: ADAPT TN compared two 12-week neoadjuvant regimens (Nab-Pac/Carbo vs. Nab-Pac/Gem) and aimed to identify early-response markers for pCR (yPN0 and ypT0/is). TNBC patients (centrally confirmed ER/PR cN0/+ were randomized to arm A (Nab-Pac 125/Gem 1000 d1,8 q3w) vs. B (Nab-Pac 125/Carbo AUC2 d1,8 q3w). The trial was powered for pCR comparison by therapy arm and by presence vs. absence of early response markers. Pre-planned interim analysis aimed to identify a dynamic biomarker, e.g. drop of 3-week Ki67, and to validate trial assumptions.
Results: Overall, 336 patients were enrolled from 47 centers from 06/13-02/15. Interim analysis was performed among the first 130 randomized patients: 69 in arm A, 61 in arm B; 84% vs. 93% completed therapy ($p = 0.1$), respectively. Median age was 50y. At baseline, 93% had G3 tumors, median Ki67 was 65%; 64% had cT2-4c tumors, 23% cN+. Overall pCR rate was 36%: A: 25%, B: 49.2% ($p = 0.006$). Final pCR data and correlation with early response will be presented at the meeting.
Conclusions: Our first large randomized study comparing two short 12 week A-free regimens suggests superior efficacy and favorable toxicity of Nab-Pac/Carbo vs. Nab-Pac/Gem in unselected TNBC. Patients with pCR might be potentially overtreated by anthracyclines due to quite comparable pCR rates to longer A/T-Carbo containing regimens.

ID 0383

Validation of a BRCAness test to select for targeted therapies in triple-negative breast cancer

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Background: Triple-negative breast cancer (TNBC) accounts for 15-20% of all breast cancer cases and is still characterized by unfavorable prognosis. Therefore, strategies to improve treatment efficiency towards targeted therapy approaches are highly demanded. Recent studies suggest that TNBCs defective in homologous recombination repair respond with high sensitivity to DNA damaging therapeutics (i.e. carboplatin) and possibly to PARP inhibitors. These molecular characteristics are often summarized as "BRCAness". Currently, platinum therapy is available for TNBC patients with germline BRCA1/2 mutations. However, including tumors with a "BRCAness" signature beyond BRCA1/2 mutations might enhance the number of TNBC patients which could benefit from targeted therapies.
Methods: We used the MLPA-based "BRCA1-like" test and classification by a nearest shrunken centroids classifier to discriminate between BRCA1-like vs. non-BRCA1-like samples. Data were subsequently compared with the BRCA1-mutation/methylation status of the samples to assess the sensitivity of the test. Association of BRCAness with clinicopathological data was performed by the chi-square test.
Results: 155 TNBC specimens were analyzed and more than 40% of the samples were classified as BRCA1-like. Among these, the MLPA test correctly predicted 83% of the samples with a pathogenic BRCA1-mutation and 91% exhibiting BRCA1-promoter methylation. BRCA1-like tumors were particularly frequent in G3 cancers (p = 0.0004).
Conclusion: Our results speak in favor of a broad applicability of the MLPA-based assay in clinical routines. It may thus serve as a valuable tool to select TNBC patients for platinum-based chemotherapy regimens.

ID 0396

Compelling evidence for *FANCM* as a breast cancer susceptibility gene

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Recently, Kiiski et al. reported an association between a single truncating *FANCM* mutation (p.Gln1701Ter) and BC risk in the Finnish population (OR 1.86, 95% CI = 1.26-2.75; *P* =0.0018). Mutational analysis of *FANCM* by NGS in 1,697 familial BC and/or OC index-cases from Germany identified four distinct truncating *FANCM* alterations, p.R658Ter (2×), p.Val1095TyrfsTer16 (1×), p.Gln1701Ter (10×) and p.R1931Ter (3×), resulting in a mutation load of 0.94% (16/1,697). In 907 geographically-matched controls, 5 mutation carriers have been identified (p.R658Ter [1×], p.Gln1327ValfsTer16 [1×], p.Gln1701Ter [2×], p.R1931Ter [1×]), resulting in a mutation load of 0.5% (5/907). This mutation frequency in controls was similar to that observed in the EVS EA control database (21/4,300; c.1581+1G>A [1×] p.R573Ter [1×], p.R627Ter [1×], p.R658Ter [1×], p.E869KfsTer2 [3×], p.D1440N [1×], p.Q1701Ter [5×], p.R1931Ter [8×]). Statistical evaluation of mutation frequencies in cases (n = 1,697) versus controls (n = 5,207) showed a significant association of *FANCM* mutations with the BC and/or OC phenotype (OR: 1.89; 95% 0.96-3.66; p = 0.049). An extended analysis of the most prevalent *FANCM* mutation, p.Gln1701Ter, in 4,598 index cases and 9,633 controls clearly confirmed these results (16/4,598, CF=0.308% in cases versus 13/9,633, CF = 0.135%; OR 2.51, 95%CI = 1.15-5.54; p = 0.016). The mean age at first BC diagnosis of individuals carrying truncating *FANCM* alterations was 49 years with predominantly ER+, PR+, HER2- tumours of grade 2. Due to the apparently low *FANCM* mutation frequency, however, large collaborative studies are required to quantify the risk for BC and possibly other cancer entities associated with deleterious *FANCM* alterations.

ID 0416

TREAT CTC: An innovative therapy approach to eliminate circulating tumor cells (CTCs)

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Circulating tumor cells (CTCS) in peripheral blood are associated with an unfavorable prognosis in both early and metastatic breast cancer. Therefore patients with persisting CTCs after (neo-) adjuvant chemotherapy could benefit from an additional systemic therapy (Rack 2014).
Current data support the hypothesis that trastuzumab fights tumor cells with antibody-dependent cell-mediated cytotoxicity and that its therapeutic benefit is associated with an impact on tumor stem cells (Ithimakin 2013). Trastuzumab was able to eliminate CTCs irrespective of their HER2-status or that of the primary tumor and to reduce the risk of relapse (Georgoulias 2012).
TREAT CTC is an European phaseII study sponsored by the EORTC under the BIG umbrella. It is designed to investigate the efficacy of trastuzumab in the elimination of CTCs after (neo-) adjuvant chemotherapy and surgery in HER2-negative early breast cancer.
Enrolled patients are randomized to either receive 6 cycles of trastuzumab or observation. In 100 centers in 6 European countries about 2175 patients will be screened to randomize 174 participants.
Main inclusion criteria are adequately surgically excised HER2-negative early breast cancer, detection of CTCs after (neo-) adjuvant chemotherapy with CellSearch® and completed (neo-) adjuvant chemotherapy with invasive tumor residue in breast or lymph nodes.
Given the prognostic relevance of CTC in BC, the Treat CTC trial will be the first multicenter, randomized trial in which CTC are used to guide treatment decisions in EBC. The results of this trial will help to clarify the clinical utility of CTCs in early disease.

ID 0441

Characterization of Circulating Tumor Cells regarding Mutational Status of *PIK3CA* and Expression of Androgen Receptor

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Enumeration of circulating tumor cells (CTCs) in metastatic breast cancer is of prognostic relevance. However, the predictive value of these cells still remains unclear. The DETECT study concept evaluates the impact of CTCs on therapy decisions. The study program currently comprises DETECT III, IV and DETECT V/Chevendo. Associated with this study program is a variety of translational research projects aiming to characterize CTCs and to identify prognostic and predictive markers of these cells.
Phosphatidylinositol 3-phosphate kinase/Akt signal transduction pathway is frequently altered in breast cancer patients. These hotspot mutations are associated with therapy resistance against HER2-directed therapy and endocrine therapy. Analyzing the mutational status of CTCs using sequencing strategies on single cell level and for bulk analysis is one of the translational projects run in the DETECT studies. 872 CTCs out of 55 samples have been isolated using micromanipulation and have been banked for subsequent single cell analysis. Whole genome amplification (WGA) has been performed for 86 single CTCs of 8 samples. 92 samples of 84 patients have been isolated and amplified (WGA) for subsequent bulk analysis.
Androgen receptor (AR) is one of the most frequently expressed hormone receptors. In triple negative breast cancers which lack the expression of estrogen and progesterone receptor, AR is expressed in up to 75% of all primary tumors. In this DETECT associated project, the expression of AR on CTCs is analyzed using immunofluorescence. After establishment of enrichment and staining, 77 CTCs in 5 samples have been analyzed so far. Validation results and latest numbers of both projects will be shown.

ID 0469

Estrogen receptor β selective agonists reduce invasiveness and CXCR4 expression of mesenchymal transformed breast cancer cells.

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Objectives: Recently we have shown that breast cancer cell invasion was dramatically increased when co-cultured with osteoblast-like cells. In addition, we have generated mesenchymal transformed MCF-7 breast cancer cells (MCF-7-EMT), showing mesenchymal characteristics and significantly increased invasion in contrast to wild type MCF-7 cells. Using these models we have analyzed the role of estrogen receptor β (ERβ) in epithelial-mesenchymal transition (EMT) and invasiveness of breast cancer cells.
Methods: Mammosphere culture was used to induce EMT in MCF-7 cells. Induction of EMT was verified by analysis of expression of epithelial and mesenchymal markers. Invasion was quantified by assessment of cancer cell migration rate through an artificial basement membrane in a modified Boyden chamber. The effects of ERβ agonist treatment on CXC motive chemokine receptor 4 (CXCR4) expression was quantified using western blot. Proliferation was measured using Alamar blue assay.
Results: Induction of EMT in MCF-7 resulted in a significant increase of expression of ERβ and CXCR4. In addition, after EMT invasion of MCF-7 cells was significantly increased. The increased invasion was reduced after treatment with ERβ selective estrogen agonists. In addition, ERβ agonist treatment resulted in a significant decrease of expression of CXCR4, an important pro-metastatic factor. Furthermore, expression of mesenchymal markers N-cadherin and Vimentin was clearly decreased. Both ERβ agonists showed no effects on cell proliferation.
Conclusions: Our findings suggest that ERβ plays a major role in breast cancer invasion and EMT. Invasion of mesenchymal transformed breast cancer cells can be inhibited by ERβ selective agonists.

ID 0496

HEr2 testing in neoadjuvant breast cancer trials – improved concordance of HER2 status in different pathology laboratories

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Background: Breast cancer will still be the most diagnosed cancer in females. About 15% of invasive human breast cancers show an HER2 overexpression which leads to a more aggressive behavior. Several agents targeting HER2-positive breast cancer were developed. We evaluated the discordance rate comparing central and local pathology in five large neoadjuvant clinical trials in a total of 1597 tumor samples over a time of 12 years.
Methods: All patients for whom both the local and central Her2 measurements were available, were included in this analysis. Due to the central pathology in GeparSixto and GeparSepto, patients with locally or centrally diagnosed HER2 positive tumor were included, too.
Results: The discordance rate in the whole cohort decreased from 52.4% in GeparTrio to 8.4% in the GeparSepto trial (GeparQuattro: 25.4%, GeparQuinto: 22.7%, GeparSixto: 7.0%). Therefrom, 999 patients (62.6%) exhibited hormonreceptor positive, HER2 positive tumors. Here, the discordance rates were higher comparing with the whole cohort: GeparTrio 58.8%, GeparQuattro: 30.8%, GeparQuinto: 29.2%, GeparSepto: 9.2%.
The remaining 598 patients (37.4%) had hormonreceptor negative, HER2 positive tumors. Here, the discordance rate was less comparing with the hormonreceptor positive group or the whole cohort, except for GeparSixto: GeparTrio 37.9%, GeparQuattro: 18.9%, GeparQuinto: 13.9%, GeparSixto: 16.3%, GeparSepto 6.1%.
Conclusions: As a conclusion, our results show that the discordant HER2 rate in breast cancer is at this time in Germany obviously decreased comparing to published rates in the past. This could be due to the different approaches which include e.g. standardized procedures and interlaboratory tests.

ID 0511

Comparison of tumor cell dissemination into the blood and bone marrow in patients with primary breast cancer

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Background: Disseminated tumor cells (DTC), detected in the bone marrow of patients with primary breast cancer (PBC) are associated with an impaired prognosis. Bone marrow aspiration, however, is an invasive procedure. A promising alternative are circulating tumor cells (CTC) that can be isolated from venous blood. We therefore aimed to compare the detection and prognostic significance of simultaneous DTC and CTC detection.
Methods: DTC were isolated during primary surgery and detected using immunocytochemistry (pan-cytokeratin antibody A45-B/B3). CTC were determined using an RT-PCR based (AdnaTest Breast Cancer) or an immunocytochemistry based assay (CellSearch).
Results: DTC were detected in 131 of 585 patients (22%). CTC were detected in 19/202 (9%) and 18/383 (5%) using AdnaTest and CellSearch, respectively. There was no significant association between DTC and CTC detection ($p = 0.248$ for AdnaTest and $p = 0.146$ for CellSearch, chi-squared test). The detection of DTC ($p = 0.046$) and the detection of CTC as determined by CellSearch ($p = 0.007$) predictive of an impaired disease-free survival.
Conclusion: Our results confirm the prognostic relevance of DTC and CTC determination in EBC. There was, however, no association between CTC and DTC detection. These results emphasize molecular studies to evaluate whether DTC and CTC are independent subpopulations of malignant cell clones.

ID 0520

Eribulin 1,23 mg/m² an d1/8 q3w als Therapieoption beim fortgeschrittenen metastasierten Mammakarzinom in der Klinischen Anwendung

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Fragestellung: Beim fortgeschrittenen metastasierten Mammakarzinom sind nach mehreren Vortherapien die Therapieoptionen zum Teil begrenzt. Seit der Zulassung von Eribulin als Chemotherapeutikum beim metastasierten Mammakarzinom besteht eine neue Therapieoption.
Die klinischen Erfahrungen mit Eribulin sind jedoch noch unzureichend. Daher werteten wir unser Patientenkollektiv bezüglich Einsatz und Verträglichkeit von Eribulin aus. Weiterhin wird eine Auswertung in Hinsicht auf den Einsatz in der 2. und 3. Linie gegenüber den Einsatz in der fortgeschrittenen Therapie erfolgen.
Methode: Retrospektive Untersuchung aller fortgeschrittenen metastasierten Mammakarzinom- Patientinnen an der UFK Homburg die bis heute Eribulin 1,23 mg/m² an d1/8 q3w als Kurzinfusion über 2-5 min in der Therapie des metastasierten Mammakarzinoms erhalten haben.
Ergebnisse: Insgesamt n = 31 Patientinnen erhielten im Beobachtungszeitraum Eribulin 1,23 mg/m² an d1/8 q3w.
Eribulin wurde durchschnittlich im metastasierten Stadium als 4,0 Therapielinie (Range 1-8) sowie in der Gesamttherapie als 5,5 Therapielinie eingesetzt (Range 3-10). Die durchschnittliche Therapiedauer beträgt zum aktuellen Beobachtungszeitpunkt 6,7 Zyklen (Range 2-31 Zyklen) bzw. 6,2 Monate (Range 2-22 Monate).
Schlussfolgerung: Eribulin ist beim fortgeschrittenen metastasierten Mammakarzinom eine effektive und gut verträgliche Therapieoption.
Selbst in der fortgeschrittenen Therapielinie kann der Progress über mehrere Monate bis > als 1,5 Jahr vermieden werden.

ID 0531

Treatment with eribulin mesylate influences expression of genes known to induce malignant transformation in triple negative breast cancer cell lines in vitro

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Diagnosis of triple negative breast cancer (TNBC) is associated with adverse prognosis particularly in case of chemotherapy resistance in its distinct molecular subtypes. The goal was to compare TNBC vs. non-TNBC and cell lines of distinct TNBC subtypes with regard to eribulin sensitivity. 17 established breast cancer cell lines comprising both TNBC of distinct molecular subtypes and non-TNBC phenotypes were subjected to cell viability assay, migration experiment, apoptosis analysis and quantitative

RT-PCR analysis of GABRP, MMP7, ELF5, YBX1, RARRES1, PRNP, SOX 10 and EGFR after exposure to eribulin or control.
The effect of eribulin on the cell viability varied to a lesser extent among the TNBC compared to the non-TNBC cell lines though no significant difference could be observed. Mentionable the TNBC cell line DU 4475 representing the interleukin phenotype displayed a significant stronger resistance to eribulin compared to all other phenotypes. A decelerated migration could be observed in the TNBC cell line MDA-MB 231 after exposure to eribulin. Induction of apoptosis by eribulin was verified by PARP cleavage in various TNBC cell lines. GABRP known to be overexpressed especially in basal like TNBC showed a slight decrease in gene expression after exposure to eribulin. Additionally, downregulation of ELF5 and upregulation of YBX1 and PRNP, MMP7 and SOX 10 gene expression could be investigated after eribulin treatment.
We did not observe a significant association with regard to eribulin sensitivity between TNBC and non-TNBC. Eribulin inhibits cell proliferation and migration, induces apoptosis in TNBC, and influences gene expression of overexpressed genes in TNBC known to participate in and induce malignant transformation.

ID 0536

Use of BSP II and Her2 as markers of breast cancer metastasis

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Breast cancer is the most common carcinoma of females and the main cause of death of women aged 35-55 in Western countries. Bone Sialoprotein II (BSP II) is a heavily glycosylated protein which is physiologically located in the extracellular matrix of bone; it has been linked to breast cancer skeletal metastasis. Human epidermal growth factor 2 (Her2) is a glycoprotein, which is physiologically located in various human tissues. It is highly expressed during the embryonal period and in different cancers, as in ca. 17-25% of breast cancers.
Methods: Serum and plasma samples were collected from 199 women suffering from breast cancer. The levels of Her2 were measured by an established enzyme-linked immunosorbent assay (ELISA) in all patients and those of BSP II were determined in 35 patients with an experimental ELISA for BSP II. The sera of 30 blood donors without malignant disease served as controls.
Results: A significant relation between Her2 serum levels and distant metastases of breast cancer patients was observed. BSP II levels in plasma and serum were not significantly related to distant metastasis for two reasons: the number of patients with skeletal metastasis was too low (n = 2) within the number of all patients investigated for BSP II, and the BSP II ELISA needs further technical validation. Nevertheless, there were significantly increased BSP II levels in the sera of breast cancer patients as compared to those from blood donors.
Conclusions: A significant correlation was found between Her2 serums levels and distant metastases of breast cancer patients. A significant correlation was also found for BSP II levels of patients with breast cancer as compared to those of blood donors without malignant disease. Future studies will show whether determining BSP II levels will be more beneficial if done in a larger number of breast cancer patients.

ID 0548

5-year survival of young mothers with breast cancer

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Background and objective: A considerable proportion of women with breast cancer is of young age at diagnosis. The mother-child-rehabilitation-program „gemeinsam gesund werden“ is open to young women with breast cancer, who have a child younger than 12 years. These women often have more aggressive and advanced tumors and their treatment regime is often more aggressive as compared to the overall population of women with breast cancer [Banz-Jansen et al. 2012, 2013]. Thus, we aim to describe the survival of young mothers with breast cancer.
Materials and Methods: A total of 535 young mothers who were first diagnosed between 2002 and 2008 with primary breast cancer and who participated in the mother-child-rehab-program were followed up for 7-13 years. The vital status was checked regularly at the respective registry offices (most recent follow up: August 2015). Absolute and relative 5-year survival and Cox Proportional Hazard Regression Models were computed.
Results: The median age of the young cohort was 40 years at diagnosis. The mean time under observation was 95 months and a total of 64 women had passed away by the time of the most recent follow up (as of September 4th, information was pending for 68 women). The absolute 5-year survival was 92% and the 7-year survival was 89%. Only type of surgery (breast preservation HR=0.5 [95% CI 0.2-0.8] as compared to mastectomy) and lymphangiosis (HR=2 [95% CI 1.1-3.6]) were determinants of death during follow up.
Conclusion: Absolute 5-year survival of German breast cancer patients (mean age at diagnosis 64 years) is approximately 79% [RKI und GEKID 2012]. Compared to this, young women with breast cancer have an increased survival.

ID 0560

GAIN2: Adjuvant phase III trial comparing an intensified dose-dense (idd) adjuvant therapy with EnPC compared to a dose-dense (dd), dose-adapted therapy with dtEC-dtD in patients with primary high risk breast cancer: Results of the second safety interim analysis

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Introduction: Combined chemotherapy requires compromises in terms of dosage and treatment interval due to toxicities. Sequential administration of monotherapies, allows higher doses of single substances and shorter intervals.
Methods: The GAIN2 study compares toxicity and efficacy of a pre-defined iddregimen (EnPC; E:150mg/m², nP:330mg/m², C:2000mg/m²) with a dd regimen, where single doses are adjusted depending on individual hematological and non-hematological toxicities (tailored dtEC-dtD; E:38-120mg/m², C:450-1200mg/m², D: 60-100mg/m²).
Primary endpoint is invasive disease-free survival in patients with primary node-positive or high-risk node-negative breast cancer
The second safety interim analysis after 900 treated patients will be presented.
Results: The rates of febrile neutropenia grade 3-4 (12% vs. 8%) and thrombopenia grade 3-4 (12% vs. 5%) was significantly higher in the EnPC arm. As for the non-hematological side effects grade 1-4, the rate of increased AP (59% vs. 40%), increased ALAT (69% vs. 59%), peripheral neuropathy (83% vs. 68%), arthralgia (63% vs. 49%), myalgia (48% vs. 41%), and bone pain (25% vs. 17%) was significantly higher in the EnPC

arm whereas epistaxis (10% vs. 25%), edema (13% vs. 26%), and hand-foot-syndrome (12% vs. 28%) were significantly higher in the dtEC-dtD arm. No differences for the toxicities of special interest (cranial nerves affections, macula degenerations, anaphylactic reactions) were seen. Overall 30% in EnPC vs 10% in dtEC-dtD required dose-reductions due to hematological toxicities (p
Conclusion: Due to toxicity profiles as expected, the study will be continued without changes.

ID 0561

nab-Paclitaxel at a dose of 125 mg/m² weekly is more efficacious but less toxic than at 150 mg/m². Results from the neoadjuvant randomized GeparSepto study (GBG 69)

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Background: nab-paclitaxel (nP) increases the pathological complete response (pCR) rate compared to solvent-based paclitaxel (P) as part of anthracycline/taxane based neoadjuvant chemotherapy in early breast cancer (BC) patients (pts). We report efficacy and safety of pts treated with 150 mg/m² nP (nP150) or 125 mg/m² nP (nP125) compared to P at 80 mg/m² (P80).
Methods: GeparSepto (NCT01583426) randomized 1207 pts to nP150 or P80 q1w for 12 wks followed by 4 cycles EC q3w. The primary objective was pCR (ypT0 ypN0). Pts with HER2+ tumors received trastuzumab plus pertuzumab q3w concomitantly to all cycles. After a safety analysis showed higher rates of dose reductions and treatment discontinuations with nP150 compared to P80, nP dose was reduced to 125 mg/m².
Results: For most cycles nP150 was given to 179 pts and nP125 to 426 pts. Treatment characteristics were balanced between the two sequential cohorts and the 601 pts receiving P80 except for HER2 status (HER2+: nP150 22%, nP125 37%, P80 33%) and Ki67 (<20%: nP150 60%, nP125 73%, P80 69%). Taxane was discontinued in 16% (nP150), 11% (nP125) and 6% (P80), respectively. Median dose per cycle (based on relative total dose intensity (RTDI)) was 129 mg/m² (nP150), 119 mg/m² (nP125) and 78 mg/m² (P80). Peripheral sensory neuropathy (PNP) grade 3/4 (NCI-CTCAE v4.0) was seen in 15% (nP150), 8% (nP125) and 3% (P80). pCR was 32% (nP150), 41% (nP125) and 29% (P80) in all pts and 46% (nP150), 49% (nP125) and 26% (P80) in 277 pts with triple-negative BC.
Conclusions: Risk-benefit ratio of nP125 was improved over nP150 with better drug adherence and RTDI, lower frequency of PNP but a higher pCR rate. It should thus be considered as the preferred schedule when nP is used as neoadjuvant therapy for primary BC.

ID 0562

Higher Rate of Severe Toxicities in Obese Patients Receiving dose-dense (dd) Chemotherapy according to Unadjusted Body Mass Index – Results of the Prospectively Randomized GAIN study.

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Background: In routine clinical practice chemotherapy doses are frequently capped at a body surface area (BSA) of 2.0 m² or adjusted to an ideal weight for obese patients due to safety reasons.
Methods: Between August 2004 and July 2008 a total of 3023 patients were enrolled in the GAIN study, a randomized phase III adjuvant trial, comparing two types of dd regimen (ETC vs EC followed by T plus capecitabine). We retrospectively evaluated a total of 543 patients with a BMI>30 for safety and outcome
Results: 18.0% of all patients were obese: 30.9% of those received chemotherapy according to an unadjusted BSA. For the remaining (69.1%). BSA was adjusted to ideal weight or was capped at 2.0 m².14.5% of obese patients receiving full dose of chemotherapy vs 6.4% of obese patients with an adjusted BSA experienced febrile neutropenia (p = 0.005) and 9.6% vs 2.9% high grade thrombopenia (p = 0.002). 16.7% vs 10.1% had a thromboembolic event (p = 0.034), which was high grade in 12.5% vs 6.4%, respectively (p = 0.027) and 3.0% vs 0.3% high grade hot flushes (p = 0.012). Dizziness (4.2% vs 10.7%; p = 0.013), diarrhea (18.5% vs 26.9%; p = 0.039) and an increase in serum creatinine (6.8% vs 14.0%; p = 0.019) were higher in the non-adjusted group. However, no differences in DFS and OS were observed between the two groups (5year DFS 81.9% [CI 74.9%-87.2%] vs 80.8% [76.3%-84.6%]; p = 0.850; 5year OS 86.4% [79.9%-90.9%] vs 88.3% [84.4%-91.3%]; p = 0.491).
Conclusion: Obese patients who received dd chemotherapy according to their real BSA have a higher risk of developing severe toxicities without influencing survival. Therefore, a dose adjustment of intense dd chemotherapy should be performed to avoid life-threatening complications.

ID 0565

Mammakarzinom des Mannes – Erste Ergebnisse aus einer prospektiven Registerstudie

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Das männliche Mammakarzinom ist eine seltene Erkrankung mit einer daraus folgenden schlechten Datenlage zur Diagnostik und Therapie. Die Registerstudie hat das Ziel mehr Informationen zur Diagnostik und Therapie zu gewinnen, die Grundlage für eventuelle Therapiestudien sein kann.
Seit 2009 bis September 2015 wurden 300 Patienten in die Registerstudie prospektiv eingeschlossen.
Auf dem Krebskongress werden erste Daten der Studie zur Diagnostik und endokrinen Therapie des männlichen Mammakarzinoms präsentiert.

Cancer Prevention

ID 0309

Be smart against cancer – a school-based program promoting cancer awareness

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Background The World Health Organization estimates that one third of all newly diagnosed cancers could be prevented if behavioral factors such as smoking, limited physical activity, unbalanced diet, alcohol consumption and excessive exposure to sunlight were changed. Cancer-related risk factors emerge during childhood and adolescence and once established, they can contribute to cancer occurring later in life. Based on the successful school project 'Be smart against cancer' for secondary schools, the University Cancer Center Dresden (UCC) developed a media-based interactive version in 2014.
Methods First students watch the interactive film covering the cancer-related risk behaviors. While watching, they are encouraged to perform experiments on class level. Following the film, an online-questionnaire assesses the students' health behavior and recommends a 4-week-class-project targeting the health-behavior most in need of improvement. Pilot-testing evaluated health-behavior intentions as well as project acceptance in 164 seventh-grade students.
Results 98,5% of the students stated that they liked the „BSAC"-Workshop. Immediately after the workshop 93,3% were convinced to being able to reduce their cancer-related risk beahavior in the future. A significantly higher intention ($p = .002$) to drink less softdrinks and eat less sweets within the next three months (77,4% to 93,6%) could be observed. Additionally, the intention to use sun-lotion in the summer increased substantially (71% to 93,5%).
Discussion „BSAC" was appraised as attractive and well applicable prevention-project increasing the intention to reduce cancer-related risk behavior. The use of multimedia-components as well as taking seventh-grade curricula into account, the project shows a high dissemination character and is a promising approach for cancer awareness.

ID 0364

Feasibility assessment on a lifestyle intervention in healthy and diseased BRCA 1/2 mutation carriers

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Objective: The aim of this multicenter, interdisciplinary, prospective, randomized pilot study was to assess the feasibility and efficacy of a lifestyle intervention in women with BRCA 1/2 mutations.
Methods: In LIBRE-Pilot 69 women (age 24-72) that were tested positive for a pathogenetic BRCA 1/2 gene mutation were randomized to either control or intervention group. The control group received general information about a healthy lifestyle and cancer risk at the beginning of the study. The intervention group took part in a 12 month intervention program including structured physical exercise and the adoption of Mediterranean diet.
All patients underwent a regular clinical examination .
Feasibility was measured by a successful organization of an intervention system, a recruiting of at least 60 patients and a drop out rate less than 30% in the first 3 months. Patients were supposed to fulfill at least 70% of all exercise units and at least 50% of the nutrition courses.
Results: The intervention program was successfully conducted in a clinical context.
6 patients took back their declaration of consent (drop out rate: 16%).
27 of 33 participants of the intervention group attended at least 70% of the intervention units (compliance rate: 82%).
First data analysis showed a significant improvement of attitude towards exercise and nutrition and adherence to Mediterranean diet in the intervention group and a significant improvement of BMI in both groups.
Conclusion: The study indicates that the implementation of an interdisciplinary lifestyle intervention concept is feasible, save and well accepted by the subject group and that a structured exercise and nutrition training for BRCA 1/2 mutation carriers appears promising as a method of primary prevention.

ID 0434

Benchmarking of the DKG check list for inclusion criteria of *BRCA* testing

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Introduction: The inclusion criteria of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) allow the identification of breast and ovarian cancer patients with an at least 10% risk to carry a *BRCA1* or *BRCA 2* mutation (check list risk score ≥3). These inclusion criteria are summarized in an "easy to use" check list for certified breast and gynaecological cancer centers (www.krebsgesellschaft.de/) firstly to ease the identification of persons at risk and secondly to implement the structured compilation of these patients. Here, we present results from the evaluation of the check lists with regard to the empirical mutation frequency per individual check lists risk score sent by our co-operating partners*.
Method: Doctors from the co-operating certified cancer centers sent more than 3000 check lists (2014-2015). A total of 350 patients were counseled in our center by now and decided to undertake a *BRCA* mutation analysis. We evaluated the empirical mutation frequency (EMF) in the *BRCA1/2* genes within this group in correlation to the risk score of the individual check list.
Results: The EMF increases with a rising risk score. The EMF in patients with risk score 3 (n = 140) was 12%. The EMF in patients with risk score 4 (n = 87) was 16%, in patients with risk score 5 (n = 52) was 17%, in patients with risk score 6 (n = 33) was 18%, and with risk score 7 (n = 15) was 40%. Patients with a risk score >/= 7 to 15 (n = 26) showed an EMF of 73%.
Conclusion: This project is an excellent example for the active improvement of genetic literacy. The counselors in the certified cancer centers can now improve their risk communication by relating the EMH to the individual risk score.

*62 certified breast cancer centers: *www.konsortium-familiaerer-brustkrebs.de/das-konsortium/kooperationspartner/*

ID 0506

DNA repair in the defense against alkylation-induced colorectal carcinogenesis

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Alkylating agents, notably N-nitroso compounds (NOC) are tightly linked to the etiology of colorectal cancer (CRC). The agents induce a variety of DNA adducts, including O^6-methylguanine (O^6-MeG) and N-methylated purines. O^6-MeG adducts are removed by the suicide enzyme O^6-methylguanine-DNA methyltransferase (MGMT), whereas the latter undergo N-alkylpurine-DNA glycosylase (AAG) dependent excision repair. Using knockout mouse models, we set out to determine the impact of DNA repair on alkylation-induced CRC. DNA repair proficient (wildtype, WT) mice and mice lacking MGMT (*Mgmt*$^{-/-}$) or AAG (*Aag*$^{-/-}$) or both (*Mgmt*$^{-/-}$, *Aag*$^{-/-}$) were treated with a single dose of azoxymethane (AOM) followed by the tumor promoter dextran sodium sulfate (AOM/DSS protocol of colorectal carcinogenesis). Non-invasive mini-endoscopy revealed a non-linear increase in CRC formation in WT and *Aag* deficient individuals, whereas a linear dose-dependent increase in tumor frequency was shown for *Mgmt*$^{-/-}$ and *Mgmt*$^{-/-}$/*Aag*$^{-/-}$ mice. Modeling of the data yielded similar carcinogenic threshold doses for WT and *Aag*$^{-/-}$ mice, while *Mgmt*$^{-/-}$ and *Mgmt*$^{-/-}$/*Aag*$^{-/-}$ did not display a non-carcinogenic threshold. The amount of the mutagenic DNA adduct O^6-MeG and depletion of MGMT activity correlated well with the observed dose-response in CRC formation. AOM triggered robust activation of the ATR-Chk1-p53 axis in all mouse strains and dose-dependently induced the DSB marker γ-H2AX in basal colon crypts including Lgr5-positive colon stem cells. Intriguingly, *Mgmt*-deficient mice displayed significantly enhanced levels of γ-H2AX, suggesting the usefulness of γ-H2AX as an early marker of genotoxic stress in the large intestine. The study demonstrates a non-linear dose-response for alkylation-induced colorectal cancer and reveals at low alkylation levels MGMT as the key player in the defense against colorectal carcinogenesis.

Central Nervous System Tumors

ID 0178

Temozolomide resistance in human glioblastoma cell line U251 is caused by mismatch repair deficiency and can be overcome by lomustine

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Background: Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. While the alkylating agent temozolomide (TMZ) has prolonged overall survival, resistance evolution is almost inevitable. Although lomustine (CCNU) in combination with TMZ has scored impressive clinical results for MGMT-methylated GBM, the underlying mechanisms remain unclear.
Methods: We studied the GBM cell line U251 and its *in vitro* derived TMZ-resistant subline, U251/TMZ-R. Cytotoxicity of TMZ, CCNU and their combination were tested with regard to apoptosis, necrosis, cell cycle progression and growth inhibition. Both cell lines were analyzed for MGMT promotor status and expression of several mismatch repair genes (MMR). The influence of the inhibition of MMR proteins mediated by Cadmiumchloride (CdCl2) on the effects of both drugs was evaluated.
Results: During the resistance evolution process *in vitro*, U251/TMZ-R developed MMR deficiency but MGMT status did not change. U251/TMZ-R cells were more resistant to TMZ than parental U251 cells (cell viability: 92.0% in U251/TMZ-R / 69.2% in U251; P = 0.032) yet more sensitive to CCNU (56.4% / 80.8%; P = 0.023). Combination of CCNU and TMZ showed promising results for both cell lines and overcame resistance. CdCl2-induced MMR deficiency increased cytotoxicity of CCNU.
Conclusions: Our results suggest MMR deficiency as a crucial process for resistance evolution to TMZ *in vitro*. Most importantly, MMR-deficient GBM cells were particularly sensitive to CCNU. As a consequence, CCNU in combination with TMZ might be preferentially considered as a treatment option for recurrent GBM and may be even suitable for prevention of MMR deficiency mediated resistance evolution in primary treatment.

ID 0218

Robo1-Expression decreases the motility of irradiated glioma cells *in vitro*

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Glioblastoma is a primary brain tumor with a poor prognosis despite of the application of many treatment modalities. This tumor is highly invasive and often multifocal. Slit2 and Robo1 are evolutionarily conserved proteins which are involved in the axon guidance, migration and branching of neuron cells. New studies have shown that Slit2 and Robo1 play an important role in leukocyte chemotaxis and that they are less expressed in glioblastoma than in the normal brain. Therefore, we investigated whether the Slit2/Robo1-complex has an impact on the motility of glioblastoma cells and whether irradiation with therapeutic doses may modulate this effect. Our studies revealed that radiotherapy, which is the standard treatment of glioblastoma patients, might enhance the migration of glioblastoma cells *in vitro*. qRT-PCR and western blot of two glioblastoma cell lines with different malignity (in terms of motility) revealed that both Slit2 and Robo1 are extremely less expressed in the cell line with higher motility. Irradiation with photons reduced this expression even more. An overexpression of Robo1 decreased significantly the motility of the cells and also suppressed the increase in motility observed after irradiation in the wild type. In contrast siRNA-mediated knockdown of Robo1 increased the cellular motility. A western blot analysis of focal adhesion kinase (pFAK), a key protein in cellular migration, showed a decreased expression in Robo1-overexpressing cells compared to the wild typ. Our findings confirm a role for Robo1 in the motility of glioblastoma cells and suggest that an expression of this protein may reduce migration as well as the irradiation induced increase in motility of glioblastoma cells.

ID 0240

Long-term outcome and prognostic factors of radiation therapy for low grade gliomas

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Purpose: To analyse outcome in patients with low grade gliomas (LGG) following radiotherapy (RT)
Patients: 206 patients were included (median age: 39 years). Histology was astrocytoma (79%), oligoastrocytoma (14%), and oligodendroglioma (7%). Median latency until first line treatment (surgery or RT) was 1.5 months. 50 patients (24%) received their initial therapy after intervals of >6 months. 115 patients received primary RT and 35 patients were irradiated postoperatively. 56 patients underwent RT for tumor progression. Median dose was 54 Gy. In 71 patients, dose escalation > 54 Gy was performed.
Results: Treatment was tolerated well. One secondary malignancy was noted during follow-up.
OS following RT at 5 and 10, was 91% and 78%. Oligodendroglial differentiation was associated with significantly improved OS (p = 0.008), whereas local control remained unchanged. Patients receiving total RT doses > 54 Gy showed inferior OS despite unaltered local control.

Local control rates following RT were 58% and 24% after 5 and 10 years. Histological confirmation prior to RT significantly improved local control (0.023). However, radical surgery did not further improve local control. Patient age at RT (≤ vs. > 18 years and < vs. ≥ 40 years) and tumor location affected neither local control nor OS.
The predominate pattern of tumor recurrence was local within prior RT fields. ReRT was performed in 44 patients, while 113 patients were treated with chemotherapy.
Conclusions: Patients with LGG show high survival rates with low toxicity. Histological confirmation is mandatory in all patients, as biopsy and even more neurosurgical resection will improve local control and enable identification of patients with oligodendroglial differentiation, in whom improved prognosis can be anticipated. Doses ≤ 54 are sufficient, and further dose escalation should not be performed outside of clinical trials.

ID 0270

Assessment of the use of complementary therapy in a cohort of Swiss glioma patients

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During the course of the disease, glioma patients learn that there is no cure for their tumor. It is therefore not uncommon that the patients seek for complementary and alternative treatments (CT). For Swiss glioma patients, the extent of CT use, the reasons for it, the patient characteristics and the costs are not known.
A questionnaire published by the German Glioma Network was adapted for Swiss conditions and distributed to more than 200 patients suffering from gliomas of WHO grades II to IV. Here, we describe the final evaluation of complementary therapy use in this patient cohort treated at the neuro-oncology centers in Zurich, Aarau and Basel (Switzerland). Half of the patients reported the use of CT. One of the main motivations for the use of CT was to contribute actively to the treatment of the disease. However, CT use was commonly not supervised by a physician. CT usage in glioma patients is more frequent in this Swiss cohort compared to a cohort from the German Glioma Network and seems to be frequent in glioma patients in general. Physicians caring for glioma patients should be aware of complementary self-treatments outside neuro-oncology centers and outside medical competence.

ID 0319

Role of valproic acid or levetiracetam in survival of glioblastoma patients

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Purpose: Symptomatic epilepsy is a common complication of brain tumors, such as glioblastoma, that most often requires antiepileptic drug therapy. In newly diagnosed glioblastoma, several retrospective case series and a post-hoc analysis of the registration trial for temozolomide suggested an association between valproic acid (VPA) use and improved survival outcomes.
Methods: To confirm the above-mentioned hypothesis, a combined analysis of survival association of anti-epileptic drug (AED) use at the start of chemoradiotherapy with temozolomide was performed in the pooled patient cohort (n = 1869) of four contemporary randomized clinical trials in newly diagnosed glioblastoma: AVAGlio (NCT00943826), CENTRIC (NCT00689221), CORE (NCT00813943) and RTOG-0825 (NCT00884741). Progression-free (PFS) and overall survival (OS) were compared between VPA versus: (i) no AED, (ii) enzyme-inducing (EI)-AED, or (iii) other non-EI-AED (without VPA). Results of Cox regression models stratified by trial and adjusted for baseline prognostic factors were performed. The same analyses were performed with levetiracetam (LEV).
Results: VPA use at start of chemoradiotherapy was not associated with improved PFS or OS compared with patients receiving no AED (PFS: hazard ratio (HR) =0.92, 95% confidence interval (CI) 0.75-1.13, p = 0.41; OS: HR=1.00, 95% CI 0.80-1.25, p = 0.95), EI-AED (PFS: HR=0.95, 95% CI 0.74-1.21, p = 0.62; OS: HR=1.02, 95% CI 0.0.77-1.33, p = 0.93) or non-EI-AED (PFS: HR=1.02, 95% CI 0.80-1.3, p = 0.92; OS: HR=1.06, 95% CI 0.83-1.35, p = 0.67). No association with improved outcomes was observed for LEV use, either.
Conclusion: This pooled analysis did not validate an association of VPA or LEV use with improved survival or progression-free survival.

ID 0395

Is a Modification of the Radiotherapeutic Target Volume Necessary after Resection of Glioblastomas with Opening of the Ventricles?

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Background: Extensive surgical resection of centrally localized, newly diagnosed glioblastoma can lead to opening ventricles and therefore carries a potential risk of spreading tumor cells into the cebrospinal fluid. However, whether ventricle opening consequently implies a greater frequency of distant tumor recurrence after radiation therapy – and, therefore, reduced survival – remains unknown. Therefore, is an adaption of target volumes in radiation therapy necessary to account for a potential tumor cell spread into the ventricle system?
Materials and Methods: The present study assessed the resection statuses of 311 primary-glioblastoma patients who underwent radiation therapy. Overall, in 78 cases (25.1%) the ventricle system was opened during surgical resection. This study assessed the connection between ventricle opening and *progression-free survival* (PFS), *overall survival* (OS), and distant and multifocal recurrence.
Results: PFS (p = 0.53) and OS (p = 0.18) did not differ due to ventricle opening during surgical resection. However, in a subsample of subtotal resected cases increased survival was observed when the ventricle system was opened (16.8 vs. 14.3 months; p = 0.03). The occurrence of distant (OR: 0.75; p = 0.75) and contralateral recurrence (OR: 1.02; p = 0.87) was not influenced by ventricle opening.
Conclusions: In short, patients profit from surgical resections that are as extensive as reasonably possible, even if this entails ventricle opening. Thus, additional inclusion of the ventricles in the radiation therapy target volume after ventricle opening does not seem to be indicated.

ID 0401

Are there correlations between clinical patient data and molecular expression profiles of the key RTK/MAP kinase & AKT/mTOR signaling pathways in human meningiomas?

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Objective: PI3K/Akt/mTOR and RTK/MAPK pathways propagate tumor proliferation and are constantly over-/activated in numerous tumors. In meningiomas gene expression analysis of those pathways revealed intriguing differences in individual expression profiles independent of the WHO-grade. To assess the potential use of targeted RTK-/mTOR-inhibitors this study analyzed correlations between clinical patient data and individual molecular expression profiles of their tumors
Method: In 75 meningiomas (WHO I-III) expression of PDGFRbeta, VEGFR-2, pan-Ras, B-Raf, ERK1, ERK2, Akt1 and mTOR was determined by qPCR and analysed by the dd ct method in comparison to leptomeningeal tissue and correlated with the individual tumor WHO-grade, edema, size and location as well as clinical patient data like age, sex, co-morbidities, and co-medication. Mixed linear model was used for statistical analysis
Result: Individual differences in expression profiles of all target genes were found. Surprisingly there were no significant variations of these expressions in correlation with the WHO-grade or the tumor properties like size, location, and degree of peritumoral edema. Looking at the individual patient data, this study reveals correlations between gene expression profiles of both pathways and a female sex as well as an age dependency
Conclusion: Analyzing a larger group of meningiomas for gene expression of the PI3K/Akt/mTor & RTK signaling cascades revealed differences to non-pathological leptomeningeal tissue, but no WHO grade dependency. Correlations between a subgroup of clinical patient data, like sex and age and the individual molecular expression pattern may lead the way to a more targeted tumor therapy stratified according to WHO-grade independent parameters

ID 0406

FGFR1 seems to be a key regulator of pluripotency and/or differentiation in meningiomas

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Objective: Fibroblast growth factor receptor (FGFR) regulates not only numerous processes such as proliferation, survival, migration and differentiation but is also involved in regulation of pluripotency. Aim of this study was to correlate FGFR1-mRNA expression levels in meningiomas with genes maintaining pluripotency, and with selected genes encoding for key proteins of the RTK/MAPK pathway.
Method: In 34 meningioma samples (WHO I°-III°) mRNA expression of key RTK/MAKPK pathway genes (FGFR1, AKT1, MAPK3) as well as of genes maintaining pluripotency (NANOG, Oct4, Sox2, Sall4B, Klf4) was determined by qPCR. Analysis was performed by the efficiency based ΔΔCt method against non-pathological leptomeningeal tissue.
Result: In meningiomas mRNA expression of all tested genes was found. FGFR1 as well as NANOG, Sall4B and MAPK3 showed a clear over-expression in meningiomas. Expression of Oct4, Sox2, Klf4 and AKT1 revealed no differences compared to normal tissue, but in comparison FGFR1 expression was significantly positively correlated with the key transcription factors not of genesis of pluripotency, but of its maintenance (NANOG, Oct4, Sox2, Klf4, Sall4B). In contrast AKT1 and MAPK3 showed no expression correlation with genes for pluripotency, but to each other.
Conclusion: Analyzing transcription levels of meningiomas with regard to FGFR1 compared to other genes of proteins of the RTK-MAPK pathway and the key factors for maintenance of pluripotency revealed high expression levels of lots of tested genes of both developmental states. In the end, correlation data indicate, that both processes are executed independently of each other, confirming the hypothesis, that in tumours in general and specifically in meningiomas pluripotent cells are only a subpopulation.

ID 0442

Congenital deafness leading to the diagnosis of "atypical teratoid/rhabdoid tumor (AT/RT)"

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Typical symptoms of brain tumors are signs of intracranial pressure and focal neurological deficits. We report about on an atypical case of a one year old male patient with deafness since birth, diagnosed by screening, and no other neurological abnormalities. Treatment with hearing devices until the age of 12 months allowed adequate sensory and motor development. Family and patient history were without further abnormalities. At 12 months, by a routine cranial MRI performed in order to plan cochlea implant, an infratentorial brain tumor incidentally was discovered, which was not yet obstructing the cerebrospinal fluid drainage. Subtotal resection was possible, and histological examination showed the rare diagnosis of an "atypical teratoid/rhabdoid tumor (AT/RT)". Genetic analysis showed sporadic mutation without any germ line mutation. The patient is receiving polychemotherapy according to the EuRhab protocol, including intraventricular methotrexate, and proton beam irradiation initiated at the age of 18 months. Clinical hints indicate an improvement of hearing under therapy – objective measuring will follow after termination of treatment. To our best knowledge, the combination of congenital deafness and AR/RT has not yet been described in the literature. The combination seems to be incidental. For the patient, however, the constellation enabled early diagnosis and might thus have been beneficial for the treatment course.

ID 0445

Anaplastic meningiomas WHO grade III lack of somatic AKT1-mutations and show an overexpression of EGF-receptor

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Background: The AKT1 mutation was newly described in a subset of meningiomas and inhibitors of this mutation have shown promise in clinical trials in multiple cancer types. We sought to determine the frequency of the AKT1 mutation as well as the expression level of multiple growth factor receptors in a patients with Anaplastic meningiomas (AM) WHO °III.
Methods: Patients with AM °III were tested for the AKT1 (E17K) mutation using PCR technique. Additionally, the expression level of the epidermal growth factor receptor (EGFR), the platelet derived growth factor receptor 1alpha (PDGFR) and the vascular endothelial growth factor receptor (VEGFR) was detected by immunohistochemistry (IHC) on tissue multi arrays (TMA) of paraffin-embedded specimens. Staining was evaluated using a semi-quantitative scoring system.
Results: We identified 22 AM °III patients with 45 tumors (median follow-up of 8 years). None of the examined 45 tumor samples in this cohort showed an AKT1 mutation (0%). Regarding the IHC, recurrent AM showed increasing proliferation with each recurrence. Overexpression of EGFR was associated with malignancy (p Somatic AKT1 mutations are absent in anaplastic meningiomas WHO grade III. Additionally, our data demonstrate that the overexpression of EGFR in AM might make this receptor valuable as a therapeutic target for their treatment.

Developmental Therapeutics: Cytotoxic Chemotherapy

ID 0020

Chemosaturation With Percutaneous Hepatic Perfusion Of Melphalan For Hepatic Metastases From Uveal Melanoma: Multiinstitutional Evaluation

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Purpose: This multiinstitutional evaluation intends to retrospectively evaluate the results of the treatment of non-resectable hepatic metastases of uveal melanoma using percutaneous hepatic perfusion (PHP; Hepatic CHEMOSAT® Delivery System; Delcath Systems Inc., USA).
Materials and Methods: Between 2012 and 2014 fourteen patients with hepatic metastases of uveal melanoma received one to three sessions of Chemosaturation-PHP. Eleven patients were evaluated by means of RECIST criteria. Survival time analysis was performed. Adverse events and complications were registered.
Results: Chemosaturation is well tolerated by the majority of all fourteen patients. After therapy seven patients developed leukopenia, six patients had thrombopenia and two patients showed neutropenia, infection and fever each. Out of the eleven patients evaluated by means of RECIST criteria, four patients (36%) showed PR, SD was observed in five patients (46%) and two patients (18%) had PD. Two patients underwent two further sessions. After the first session tumour response of one patient turned from SD to PR and returned to SD. The other patient's treatment response showed PR in all three sessions. Survival time of all patients ranged from 1.5 to 23 months (median OS 6.5 months) following first Chemosaturation. Time to progression of the two patients with PD was 6.2 months in one patient. The other patient died 1.6 months after evaluation.
Conclusion: Chemosaturation-PHP has been manifested as a potential treatment for patients with non-resectable hepatic metastases of uveal melanoma.

ID 0371

Investigation of erufosine and solarmagine for anticancer effects and their targets in pancreatic adenocarcinoma cells

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The poor response of current regimens in pancreatic adenocarcinoma (PDAC) necessitates evaluation and development of novel drugs. To this end we have evaluated the alkylphosphocholine erufosine (ErPC3) and the glycoalkaloid beta2- solamargine (β2-SM) for anticancer effects in two PDAC cell lines. Although ErPC3 and β2-SM have been extensively evaluated in leukemic and non-melanoma skin cancer cells, respectively, their cellular targets remain largely unknown.
ErPC3 was synthesized as per the published procedures and β2-SM purified from fruits of *Solanum incanum*. Their effects in Asml (rat) and Suit2-007 (human) PDAC cells were assessed by MTT assay. To identify drug targets, cultured cells were harvested at 80% confluence and tumor nodules from liver were harvested at 21days after intraportal implantation in BDX (Asml) or nude (Suit2-007) rats. Membrane fractions were purified by resin affinity HPLC and identified by mass spectrometry analysis. Assessment of drug-protein interaction was performed by mixing known concentrations of drugs, with protein fractions and analyzed by affinity HPLC and microscopy.
The IC50 values for ErPC3 at 48h were 3.75 and 7.5μM for Asml and Suit2-007 cells respectively. Those of β2-SM were 12-15 μM in both cell lines. Protein purification by affinity HPLC resulted in 2 fractions, with or without column binding. For in vitro samples, 215 non-binding and 284 binding proteins were identified. For ex vivo samples, 228 non-binding and 114 binding proteins were identified. Unlike the non-binding protein fraction, some proteins in the binding fraction formed aggregates with these agents and were not able to bind to the column. These proteins could therefore be the potential targets of ErPC3 and β2-SM in PDAC.

ID 0508

Cell death induced by the antioxidant alpha-lipoic acid in colorectal cancer cells

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Alpha-lipoic acid (LA) is a naturally occurring dithiol compound that plays an important role in the mitochondrial energy metabolism as co-factor of multi-enzyme complexes including pyruvate dehydrogenase. Because of its antioxidative functions it is used as dietary supplement. It has been reported that LA displays growth-inhibitory effects. In the present study, we analyzed cell death induced by LA in colorectal cancer (CRC) cells with different p53 status (HT-29, CaCO-2 and HCT116). Cancer cells were challenged with LA for 72 h and cell death was measured by flow cytometry. In all cell lines, Annexin-V/PI staining revealed strong induction of apoptosis. In HT-29 and CaCO-2 cells, LA induced dose-dependent cleavage of caspase-9 associated with an increase in its activity, whereas caspase-8 cleavage was not observed. LA treatment resulted in downstream activation of caspases-3/7, as demonstrated by activity assays and cleavage of their substrate PARP-1, a hallmark of apoptosis. In contrast, HCT116 cells underwent cell demise without cleavage and/or activation of caspases-3/7 and caspases-8/9 after treatment with LA (250 μM - 1000 μM) for 72 h. In line with this, PARP-1 cleavage was not detectable by immunoblot analysis. However, LA treatment resulted in apoptotic DNA fragmentation after 72 h as monitored by agarose DNA laddering and subG1 measurements. Additional analysis revealed a LA-induced loss of mitochondrial membrane potential (MMP) in HCT-116 cells after 72 h, which can promote the release of toxic proteins such

as AIF from mitochondria. Collectively, our findings demonstrate that the dietary supplement LA induces apoptosis in colorectal cancer cells. The synergistic action of LA with anticancer drugs is currently under study.

ID 0532

Identification of anticancer activity in *Caesalpinia pulcherrima, Bauhinia variegate* and *Cassia fistula* aqueous extracts.

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In recent years, fruits and vegetables receive considerable interest of the different components, so called as "phytochemicals", for their presumed role in the prevention of various chronic diseases including cancers diseases.
Plants are rich sources of functional dietary micronutrients, fibers and phytochemicals, such as phenolic compounds, that individually, or in combination, may be beneficial for health since they demonstrate antioxidative activity in vitro
The aerial parts of each plant (1.5 kg) were collected and individually extracted with double distilled water (8 L). The aqueous extracts were evaporated in vacuo at low temperature till dryness yielding 160 g of *Caesalpinia pulcherrima*, 190 g of *Cassia fistula and 150 g of Bauhinia variegata*. The dried aqueous extract of plants were dissolved in ethanol to extract the highest percentage of phenolics followed by evaporation of the filtrate to obtain crude phenolic content of 90, 110 and 85 mg from each plant, respectively.
The antineoplastic efficacy of the extracts was evaluated in 5 human and two rat, pancreatic and colorectal cancer cell lines. MTT and cell cycle arrest assays were used for detection cell proliferation after 24 h, 48 h and 72 h following exposure. In addition Apoptosis related genes were investigated in the treated cells by Western blot analysis.
The phenolic abstracts were tested at concentrations between 10 and 2000 µg /ml. No cytotoxic activity could be observed at concentrations below 100 µg /ml. Concentrations between 200 and 2000 µg /ml reduced the ratio of surviving cells in all 7 cell lines to 26-87%.
In addition, a moderate effect of the cell cycle arrest assay was observed, mainly at the G1 phase.
The resulting apoptotic effect was slightly shown by cleavage of caspases 3, and 9.

Developmental Therapeutics: Immunotherapy/Cellular Theraphy

ID 0049

Immunomodulatory impacts of the novel HDAC inhibitor Resminostat

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Background: The anti-cancer effects of HDAC inhibitors were shown to require the immune system. Further, synergistic effects of HDAC inhibitors and different cancer immunotherapy approaches were demonstrated indicating that HDAC inhibition itself may mediate an anti-tumoral immune response during cancer therapy.
Aim: Evaluating possible immunomodulating properties of resminostat which potentially contribute to its overall anti-tumoral effect.
Method: Resminostat-induced effects on mechanisms affecting the anti-tumoral immune response such as immunosuppression, immunogenicity, immunogenic cell death (ICD) and natural killer (NK) cell recognition were analyzed in several cancer cells.
Results: Resminostat has the potency to affect the immune response at different levels on tumor as well as immune cells. Resminostat strongly reduced the expression of immunosuppressive enzymes, IDO1 and ARG1 which deplete the tumor microenvironment of amino acids essential for T cell activity. Further, resminostat considerably enhanced the expression of various cancer testis antigens and MHC class I molecules leading to enhanced tumor immunogenicity. Immunogenicity was further enhanced by upregulation of the ICD marker and dendritic cell engulfment signal Calreticulin. Additionally, resminostat was also able to up-regulate the expression of MHC class II and co-stimulatory molecules converting tumor cells into unprofessional antigen-presenting cells. Furthermore, by up-regulating NK cell activating ligands on tumor cells, resminostat increased NK cell-mediated tumor cell cytotoxicity.
Conclusions: Resminostat displayed promising immunomodulatory effects and immune priming capacity. Thus, this novel HDAC inhibitor demonstrates potential synergistic effects with immunotherapeutics such as opsonizing antibodies (e.g. rituximab), immunostimulating agents (e.g. cytokines and TLR ligands) and immune checkpoint blockers (such as PD1/PDL1 and CTLA-4 inhibitors) which will be analyzed on functional assays and *in vivo* models.

ID 0069

CD40L: A new decisive antitumor effector function of CD8$^+$ T cells

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T cell therapy is emerging as one of the most effective treatment options to combat malignancies. However, it is still a matter of debate and investigation which subset and functional quality of CD8$^+$ T cells is more suitable for achieving effective and durable responses in the strong immunosuppressive context of cancer. We detected recently that in average 25% of human memory CD8$^+$ T cells express CD40L, a strong immunostimulatory molecule of activated CD4$^+$ T helper cells that is even able to overcome cancer-induced immunosuppression. Therefore, we analyzed the role of this distinct CD8$^+$ T cell population in antitumor responses.
We observed that CD40L expressed on activated CD8$^+$ T cells has a critical role in tumor rejection. In syngeneic tumor models, up to 50% of tumor-specific CD8$^+$ T cells express CD40L, and conditional gene ablation of CD40L in these cells results in decreased tumor rejection. As well isolated CD40L$^{-/-}$ CD8$^+$ T cells transferred into RAG1$^{-/-}$ mice cannot control tumor growth in contrast to wt CD8$^+$ T cells. Further we elucidated that the CD40L-mediated tumor rejection by CD8$^+$ T cells in humans and mice is based on interaction via CD40 on cancer cells, thereby inducing programmed cell death via caspase 8 activation or other cell death pathways.
Taken together, our data reveal that so far CD40L expression on CD8$^+$ T cells is an unrecognized antitumor effector function of these cells and represents a crucial element in control and rejection of tumors. Therefore, the capability of CD8$^+$ T cells to express CD40L should be considered and implemented in immunotherapies and in particular by adoptive T cell therapies against CD40$^+$ expressing cancers, which is a common feature among many human cancer types.

This work was supported by the SFB TR36 and Th806/5-1.

ID 0212

Improvement in efficacy of Cetuximab, Panitumumab, Trastuzumab and Rituximab by dianthin conjugation and co-application of SO1861

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The therapeutic effect of immunotoxins is based on the conjugation of antibodies or their fragments to toxins. Immunotoxins do not only bind to tumor-associated antigens and mediate the elimination of tumor cells through the innate immune system or apoptosis pathways, but also increase target cytotoxicity by the intrinsic toxin activity. In the present study, the therapeutic antibodies Cetuximab (anti-EGFR, Erbitux®), Panitumumab (anti-EGFR, Vectibix®), Trastuzumab (anti-HER2, Herceptin®) and Rituximab (anti CD20, MabThera®) were chemically conjugated to the protein toxin dianthin. Initially, recombinant dianthin was characterized by mass spectrometry and its stability was analyzed by circular dichroism. Dianthin showed increased cytotoxicity on MCF-7 cells when applied in combination with a glycosylated triterpenoid (SO1861). Live cell imaging revealed that SO1861 specifically mediates the endo/lysosomal escape of dianthin without disrupting the plasma membrane. The cytotoxicity of the conjugates was evaluated in the presence of SO1861. Dianthin-Cetuximab presented a GI50 (50% growth inhibition) of 5.3 pM, dianthin-Panitumumab of 1.5 pM, and dianthin-Trastuzumab of 23 pM whereas the three immunotoxins do not cause any cytotoxic effects at concentrations below 10 nM in the absence of SO1861. Finally, the specificity of these immunotoxins was validated in an impedance-based real-time assay, where their binding to target cells was prevented by pre-incubation with an excess of label-free unconjugated antibody. Based on these data, we propose the use of dianthin and SO1861 as a new enhancer technology to improve the efficacy of therapeutic antibodies.

ID 0331

Generation of new DNA- and protein vaccines for active immunotherapy against *MYCN*-expressing neuroblastoma

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Introduction: MYCN oncogene is overexpressed in high-risk neuroblastoma (NB) and MYCN-specific T-cells were found in NB patients. Therefore, we developed MYCN DNA- and protein vaccines for active immunotherapy.
Methods: First, a bicistronic DNA plasmid encoding for MYCN epitopes and interleukin-21 (IL-21) was generated and characterized. Next, a fusion protein consisting of human IgG1 constant heavy chain and MYCN epitopes was developed. Minigenes encoding for MYCN epitopes with high affinity to MHC-I combined with an ubiquitin sequence were designed and inserted in a bicistronic plasmid using standard molecular biology techniques. Additionally, DNA sequences encoding for IL-21 stimulating cytotoxic but not regulatory T cells were inserted into this plasmid. For generation of the fusion protein, MYCN minigenes combined with a leader sequence for protein secretion were integrated into a plasmid encoding for human IgG1 constant heavy chain
Results: MYCN and IL-21 protein expression were shown in CHO cells transfected with respective plasmid by ELISA and western blot analysis and IL-21 bioactivity was confirmed by flow cytometry. Finally, MYCN-specific immune response will be induced using attenuated *Salmonella typhimurium* and aluminum hydroxide as adjuvants for DNA- and protein vaccines, respectively.
Conclusion: We generated and partly characterized new DNA- and protein vaccines against MYCN-expressing tumors.

ID 0335

Generation and characterization of a new chimeric human/mouse anti-Idiotype antibody ganglidiximab for active immunotherapy against neuroblastoma

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Introduction: Vaccination with proteins mimicking glycolipid GD2 is a promising strategy to induce a long lasting GD2-specific humoral immune response against neuroblastoma (NB). We showed *in vivo* efficacy of a murine anti-Idiotype antibody (anti-Id Ab) ganglidiomab that mimics GD2. To tailor immune response to Ab paratopes in humans, we generated a human/mouse chimeric anti-Id Ab ganglidiximab and report here its GD2-mimicking properties.
Methods: Murine variable regions (VL and VH) of ganglidiomab were inserted into mammalian expression vectors encoding for human IgG1 constant regions (CL and CH), respectively. Next, CHO cells were stably co-transfected with both vectors allowing permanent Ab production.
Results: Binding of purified ganglidiximab to anti-GD2 Abs of the 14.18 family was shown by ELISA and similar binding affinities were determined using Biacore technique. Importantly, GD2-specific NB cell lysis mediated by ch14.18 as well as binding of anti-GD2 Abs to GD2 was competitively inhibited by ganglidiximab confirming its anti-idiotypic characteristics. Finally, ganglidiximab was successfully used as a protein vaccine *in vivo* for induction of a GD2-specific humoral immune response.
Conclusion: We generated and characterized a new chimeric human/mouse anti-Id Ab and demonstrate induction of GD2-specific humoral immunity in mice providing a baseline for protein vaccine development.

ID 0437

Colitis as an immune-mediated side effect of ipilimumab treatment?!

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In this case report we describe the case of a 54-year-old woman with a diagnose of malignant melanoma at first without metastazation. An ipilimumab treatment was initiated after low-dose-interferon therapy and discovery of lymphatic and pulmonary metastases. Five days after the second cycle of ipilimumab she developed severe diarrhoea with high fever. Under the suspicion of an immune-mediated side effect a methylprednisolone therapy was started. Because of missing improvement we initiated a colonoscopy, which showed an oedematous-ulcerative colitis. Microbial test were negative. With continuation of the high dose methylprednisolone therapy and there was an amelioration of symtoms after eight days. Three days after discharge the patient had to be readmitted with acute watery diarrhea and gastrointestinal bleeding. A bleeding source could not be discovered in the repeat colonoscopy. The patient continued to bleed nightly, especially between 2 an 4 a.m. In the microbiological re-examination Rotavirus was positive. We changed time of application of methylprednisolone and the medical condition stabilized.
In summary we have to assume that is was a case of an immune-mediated side effect of ipilimumab intensified by rotavirus infection. The rotavirus infection was exacerbated because of the immunosuppressive therapy with methylprednisolone.

ID 0440

"Small potpourri" of an immune-mediated side effect of ipilimumab treatment of metastatic melanoma with difficult diagnostic challenge

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We report the case of a 74-year-old man with primary acral lentiginous melanoma with lymphatic metastazitation and adjuvant interferon therapy as well as 50 cycles of DTIC-chemotherapy after discovery of metastases. We initiated ipilimimab therapy after discovering an increase in size of the mediastinal lymphatic metastases and finding no BRAF-V600 mutation. After 4 cycles of ipilimumab treatment with significant tumor mass reduction the patient developed psychological personality changes with introvert behavior and depression. His wife reported complete social isolation. The laboratory results were unremarkable. Under the assumption of a Fatique syndrome with and further exacerbation of the psychological symptoms the patient underwent a psychiatric examination. Because of increasing fatique, somnolence and loss of appetite we examined levels of cortisol, testosterone and ACTH in serum and found reduced concentrations of all three substances. The MRI showed signs of hypophysitis. In conclusion assumed a iatrogenic hypophysitis. With substitution of prednisolone, testosterone and levothyroxine the symptoms could be alleviated. The insufficiency of the pituary gland however could not be reversed.

Developmental Therapeutics: Molecular Therapeutics

ID 0031

Novel SMO-Independent Hedgehog Inhibitor 4SC-208 for Treatment of SHH Medulloblastoma

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Medulloblastoma is the most common malignant pediatric brain tumour, and a leading cause of cancer-related morbidity and mortality in children. The survival rate has reached ~70%, but aggressive combination of surgery, radio- and chemotherapy leads to developmental, neurological, endocrine, and psycosocial deficits. An alternative therapy that improves survival and reduces side effects is highly in need. About 30% of medulloblastoma cases – SHH MB – display a distinct Hedgehog (HH) signature and overexpression of HH signaling target gene and transcription factor GLI1 suggesting its importance for tumor development and growth. Hedgehog inhibitors – vismodegib and sonidegib – targeting the pathway at the level of an upstream HH regulator SMO have demonstrated efficacy in SHH subtype of medulloblastoma. Unfortunately, a remarkably rapid development of resistance becomes apparent. Additionally, a significant proportion of SHH MB patients do not response to SMO antagonists due to activating pathway mutations downstream of SMO. We have identified two novel kinases crucially regulating HH/GLI signalling downstream of SMO and have developed new small molecules targeting both kinases and specifically inhibiting GLI expression *in vitro* and *in vivo*. The selected clinical candidate 4SC-208 inhibits HH/GLI signalling in medulloblastoma cells with an IC50 of 80 nM. 4SC-208 has demonstrated favourable pharmacokinetics and was well tolerated in rodents. We are now conducting preclinical evaluation program with the aim to be ready for FIM in the end of 2017.

ID 0123

Targeting fibroblast growth factor receptors (FGFR) with BGJ398 impairs tumor growth and angiogenesis in a gastric cancer model

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Background: The FGF/FGFR system is involved in various oncogenic processes, including tumor growth and angiogenesis. In gastric cancer, FGFR overexpression has been associated with poor prognosis. Therefore, we assessed the efficacy of targeting FGFRs with the pan-FGFR inhibitor BGJ398 (Novartis Oncology, Basel) in a gastric cancer model.
Material and Methods: Expression of FGFR1-4 was determined in 3 human gastric cancer cell lines (KKLS, MKN-45, TMK-1) by PCR. MTT and migration assays were used to evaluate effects of BGJ398 on cancer cell growth and motility. Modulation of transcription factors and signaling intermediates upon FGFR inhibition was assessed by Western blotting, while VEGF-A secretion was quantified by ELISA. Results were subsequently confirmed in subcutaneous tumor models.
Results: *In vitro*, significant inhibitory effects of FGFR blockade on growth, motility, signaling and VEGF-A secretion were observed in KKLS (high FGFR1, FGFR2IIIc, no FGFR2IIIb expression). In contrast, MKN-45 (intermediate FGFR1, high FGFR2IIIb, low FGFR2IIIc expression) showed mild response, while TMK-1 (low FGFR1, no FGFR2IIIb and FGFR2IIIc expression) were almost unaffected by BGJ398. *In vivo*, significant growth inhibition of xenografts was found in all 3 cell lines. However, FGFR inhibition was more effective in KKLS than in MKN-45 and TMK-1. Finally, significant reduction of CD31 vessel area was detected in KKLS tumors *in vivo*, whereas no impairment of angiogenesis was found in MKN-45 and TMK-1.
Conclusion: Targeting FGFRs with BGJ398 inhibits tumor growth of gastric cancer cells by effects on angiogenesis *in vitro* and *in vivo*. However, efficacy of FGFR inhibition seems to depend on expression of FGFR1 and FGFR2IIIc in cancer cells.

ID 0180

Tailoring an activatable peptide-metal prodrug to successfully fight breast cancer

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Despite the widespread use of platinum drugs, the only cure to date is resecting and subsequently treating testicular cancer with cisplatin. However, a recurrence is usually platinum resistant, and many primary tumors remain untreatable. Recently, stable gold (III) compounds have been reported to treat even cisplatin resistant tumor cells via a differing mode of action, though still lacking tumor specificity. Peptides are a convenient tool to design tailored drugs due to their versatile utility within the human body. Using an activatable cell penetrating peptide system comprising a specific enzyme recognition site conjugated to a gold (III) complex, we designed, produced, and tested a cyclometalated, inert prodrug to specifically target cancers secreting the corresponding enzyme, namely matrix metalloproteinase-2 (MMP-2), to be activated on site. Notably, the in breast cancer highly overly secreted MMP- 2 was successfully targeted and utilized *in vitro* to subsequently target and destroy the secreting tumor cells. The peptide-metal prodrug dependency was proven by MMP-2 inhibition on breast cancer cell lines derived from primary and metastatic sites known to be highly aggressive and tough to treat due to being estrogen receptor negative or even triple negative. In summary, this work

culminates to presenting the first highly specific anticancer peptide-metal targeting prodrug with the most interesting feature of being activated by the cancer cell itself.

ID 0238

Resveratrol: A novel anti-lymphangiogenic compound?

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Question: There is growing evidence that lymphatic vessels provide a route for tumor cells to metastasize. Therefore, influencing lymphangiogenesis is an interesting target for cancer therapy. Signaling via the vascular endothelial growth factor receptor-2/-3 (VEGFR-2/3) and Tie-2 pathways is critical for lymphangiogenic responses. Recent studies suggest that Resveratrol, a natural phenol and phytoalexin found in the skin of red grapes, may mediate part of their antitumor effects by interfering with angiogenesis. Therefore, we explored whether the known anti-tumorigenic properties of Resveratrol might be additionally mediated in part by anti-lymphangiogenic effects through the reduction in VEGFR-2/3 and Tie-2 expressions in primary human lymphatic endothelial cells.
Methods: Human lymphatic endothelial cells (LEC) were cultured in vitro and treated with or without Resveratrol. Effects of HDACi on proliferation, apoptosis and expression of the important endothelial receptors VEGFR-2/3 and Tie-2 were analyzed mainly by BrdU-Assay, cell death assay, caspase-3/7 activity assay and immunoblotting. *In vitro* angiogenesis was investigated using the Matrigel tube formation assay.
Results: Reveratrol inhibited cell proliferation in a concentration-dependent manner. In our study we found that Resveratrol induced apoptosis by activating Caspase-3/-7 in LEC. In addition, we could demonstrate an inhibition of the formation of lymphatic capillary like structures by Resveratrol treatment. Furthermore, we demonstrated that Resveratrol-significantly inhibited VEGFR-2 and -3 protein expression whereas Tie-2 expression was unaffected after treatment with Resveratrol.
Conclusion: In conclusion, our results provide for the first time clear evidence, that Resveratrol has distinct anti-lymphangiogenic effects mainly by inhibition of the endothelial VEGFR-2/-3 as well as apoptosis.

ID 0312

Induktion einer Tumorzellmigration durch zelluläre Mikropartikel aus malignen Ergüssen: Hemmung des Effekts durch das niedermolekulare Heparin „Tinzaparin“

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Hintergrund: S.c. Applikation von *Tinzaparin* hat bei Mäusen die Bildung von Lungenmetastasen nach der i.v.-Injektion von Tumorzellen gehemmt. Weitere Untersuchungen zeigten, dass eine Hemmung der Tumorzellmigration vermittelt durch TFPI für den antimetastatischen Effekt verantwortlich ist, der genaue molekulare Mechanismus ist noch nicht geklärt; die Wirkung von Tinzaparin im Vergleich zu anderen LMWH könnte durch die hohe Potenz der TFPI-Ausschüttung erklärt werden.
Material und Methoden: Gerinnungsaktive Mikropartikel/Mikrovesikel (MPs) wurden nach einem ISTH-empfohlenen Protokoll aus Ergüssen von Krebspatienten angereichert und charakterisiert. Tumorzellmigration wurde mittels RTCA mit dem „xCELLigence-System analysiert.
Ergebnisse: Ergüsse enthielten große Mengen MPs, die TF, FVIIa und FXa präsentieren. Akkumulierte MPs induzierten eine Tumorzellmigration (Colo357), die durch eine Prä-Inkubation mit Tinzaparin blockiert werden konnte. Tinzaparin induzierte eine TFPI Freisetzung aus Tumorzellen, rTFPI, wie auch Par2- und ERK-Inhibitoren blockierten die MP-induzierte Tumorzellmigration.
Schlussfolgerung: Wir verwendeten Colo357 Zellen, weil sie konstant Par1 und Par2 exprimieren. Unser Modell ist, dass die Tinzaparin induzierte TFPI-Ausschüttung die Induktion der Migration durch Tissue Factor und FXa exprimierende MPs blockiert. Die Hemmung durch spezifische Par2 und ERG-Blockade legt nahe, dass die MPs aus den malignen Ergüssen die Tumorzellmigration durch eine Aktivierung des Par2/G-Protein-Signalweges induziert. Anderer Mechanismen, wie z.B. P-Selektine können nicht komplett ausgeschlossen werden. Die klinische Relevanz dieser Ergebnisse wird diskutiert.

ID 0389

The bromodomain BRD4 regulates heat-shock induced co-transcriptional splicing

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Cellular mechanisms under heat stress closely resemble the proteotoxic stress response during tumor development. During heat stress post-transcriptional splicing is inhibited whereas co-transcriptional mRNA-splicing is maintained. How the different splicing events are regulated is unknown.
The bromodomain protein BRD4 has been identified as an integral member of the oxidative stress as well as of the inflammatory response and functions as a therapeutic target in many tumour entities. Using RNA-Seq analyses we found a significant increase in splicing inhibition, in particular intron retentions, during heat treatment in BRD4-deficient cells, but not under normal conditions. Subsequent experiments revealed that heat stress leads to the recruitment of BRD4 to nuclear stress bodies, to the interaction with the heat shock factor 1 (HSF1) and to the transcriptional up-regulation of non-coding Sat III RNA transcripts. In addition, we find a large overlap between introns retained and lung adenocarcinomas. The overlap contains eight oncogenes including *EZH2* and *BCR*.
These findings not only implicate BRD4 as a central regulator of splicing during heat stress but also again highlight the splicing machinery as potent target for anticancer therapies.

ID 0461

Regulation of Raf-kinase with consequences on therapies

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The Raf kinase was discovered 30 years ago as a retroviral oncogene (1). It is a activated in several human cancers and a major target of recent drug design. However, the Raf kinase can also induce differentiation instead of proliferation, depending on the cell-type and growth factor stimuli. Thus an inhibitor of the Raf kinase in cells where it is normally inducing Differentiation, anti-cancer drugs may induce prolieration and cause an undesired opposite effect, increasing or inducing proliferation This has been observed repeatedly in patients treated with one of the novel drugs against the Raf kinase. We also described previously negative feedback loops inducing upstream signalling to the EGF receptor. Again, inhibition of this loop by drugs against Raf may induce the opposite effect. This was observed in patients and therefore recently a dual therapy was applied in order to compensate for the loss of the negative feedback, with some therapeutic success. Another feedback loop has been described (4) which involves a phosphatase and has also been recently described in tumors. Considering the unexpected counterintuitive effects of Raf kinase inhibitors and novel therapeutics it is woth discussing the known regulatory mechanisms we have described, and avoid side-effects.

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ID 0483

LBPS03, a novel apoptosis inducer, overcomes a XIAP-mediated resistance by reactivation of caspases in the multidrug-resistant RCC cell line ClearCa-2

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Background: Dysregulation of apoptosis plays an important role in tumour progression, carcinogenesis, and resistance to chemotherapy. The most potent caspase inhibitor of all known IAP members is the anti-apoptotic protein XIAP. Own observations exhibit that the multidrug resistance of ClearCa-2 cells is associated with an increased basal expression levels of XIAP, whereas a downregulation sensitizes the cells against recombinant TRAIL treatment. With a ligand-based virtual screening method we identified a set of novel small-molecules, which possibly bind to the BIR3 pocket of IAPs. In this study, we focus on the promising molecule LBPS03 to overcome the XIAP-mediated resistance in RCC cell lines such as in ClearCa-2.
Methods: We used proliferation assays to determine cell survival (IC50-values), and western blot analysis to detect possible variation in expression patterns of BIR3-IAPs and PARP. Additionally, examination of PI-stained nuclei and caspase activity to determine apoptosis was performed by flow cytometry.
Results: (1) The novel small-molecule LBPS03 causes significant cell death at IC50-values at 1.5 µM. **(2)** LBPS03 shows a concentration-dependent degradation of XIAP, however controversy results were obtained exhibiting an upregulation of cIAP-1 and cIAP-2. **(3)** Different caspases were activated by LBPS03 and apoptosis was induced in a time-dependent manner. **(4)** The novel apoptosis inducer LBPS03 shows only marginal toxicity on normal renal tubulus epithelial cells.
Conclusions: The novel small-molecule LBPS03 can specifically induce apoptosis in the multidrug-resistant renal cell carcinoma cell line ClearCa-2. The findings contribute to new therapeutic options for the treatment of renal cell cancer.
Key words: Apoptosis, small-molecules, XIAP

ID 0489

LBPS01, a novel small-molecule, acts as a tumor specific apoptosis inducer in the ALL cell line Jurkat

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Background: In the hematopoietic system as well as in other tissues with a high cellular turnover and an intrinsic proliferation capability, the strict regulation of programmed cell death is of vital importance. However, the ability of malignant degenerated cells to evade apoptosis is a frequently observed problem, often connected with an aberrant expression of cell death regulators, such as Inhibitor of Apoptosis Proteins (IAPs). IAPs block apoptosis in response to diverse stimuli through interactions with inducers and effectors of apoptosis; - making them promising targets for therapeutic intervention. Here, we report the characterization of the cell death inducer profile of the novel small-molecule LBPS01.
Methods: Proliferation assays were used to determine cell survival (IC50-values) of the ALL cell line Jurkat (JM) and normal T-cells, which have been propagated from PBMCs. Mode of cell death was analyzed via flow cytometry of hypodiploid DNA-content peak in PI-nuclei, isolated from Jurkat cells, as well as by measuring intracellular caspase activity.
Result: (1) LBPS01 showed a cytotoxic effect in micromolar concentrations on the lymphoblastic cell line Jurkat, however no toxic effects were observed on normal T-cells. **(2)** Acceleration of cell death by LBPS01-pretreatment combined with death receptor ligand TRAIL was not detected. **(3)** Cell death analysis of PI-stained nuclei (hypodiploid DNA-content peak) revealed an induction of apoptosis. **(4)** Flow cytometric analysis of intracellular caspase -8 and -9 activity showed a dose-dependent activation of initiator caspases.
Conclusion: The novel compound LBPS01 induces tumor specific, apoptotic cell death with no effects on normal T-cells.
Key words: apoptosis, cell death inducer, tumor specifity

ID 0523

Resource for personalized tumor therapy

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Currently, cancer is one of the most frequent causes of human death. During the development of methods for cancer diagnosis and treatment, a continuous stream of information is generated. Here, we present a resource to improve personalized tumor therapy.
Novel cancer target proteins have been identified and many compounds that activate or inhibit cancer-relevant target genes have been developed. With upcoming information on target expression and mutations in patients' tumors, the need for systems supporting decisions on individual therapy is growing. This knowledge is based on numerous of experimentally validated drug-target interactions as well as supporting analyses such as measuring changes in gene expression using microarrays and HTS-efforts on cell lines. To enable an easy overview about similar drug-target data and supporting information, a series of novel information connections are established and made available as described in the following. We integrate drug-target relationships with cancer-relevant information on genes, mutations and cellular effects. This resource contains about 50,000 drug-target relations, more than 2.000 cell lines as well as drug sensitivity data for more than 50.000 (experimental) validated drugs.
Features like an integrated cellular fingerprints comprising of mutation, expression and drug-sensitivity can promote the understanding of genotype to drug sensitivity associations. This fingerprint can also be used to determine the most effective drug treatment for a cancer cell line. To get a better overview how drug-target interactions play a role in the treatment of cancer, target genes and compounds are projected onto cancer-related (signaling) pathways from the KEGG database.

Epidemiology

ID 0088

Subsequent malignancies among survivors of multiple myeloma in Germany: Cancer registry data-based analysis (1990–2011)

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Although new multiple myeloma (MM) therapies have improved the survival rates, some types of these new therapies have been associated with increased incidence of subsequent primary malignancies (SPM). We therefore calculated the standardized incidence ratio (SIR) as a relative risk for developing SPM in adult patients diagnosed with first MM from 1990 to 2011 in 14 German population-based cancer registries. Results were compared with the US data (1992-2011) obtained from 13 cancer registries of the SEER program. The SIRs were compared across different groups of age, sex, latency, and calendar periods (1990-2000 vs. 2001-2011). Over-

all SIR of SPM following MM was significantly increased in Germany (**1.11**) and in the US (**1.09**) compared with the general population. The SIRs were slightly higher in patients first diagnosed at a young age (<60 years). Increased risk of acute myeloid leukaemia (AML), non-Hodgkin lymphoma, and kidney cancer were observed. Risks for Hodgkin lymphoma, melanoma and lip/oral cavity cancers were elevated among German patients only. In Germany, the overall risk was limited to the first year of follow-up, whereas in the US the risk was significantly increased 10 years after diagnosis. This increase was mainly due to increased SIR for AML after 10 years. We found no statistically significant differences in the overall SIRs (and of AML) over the two calendar periods in both data. However, SIRs for AML were notably decreased after 2000 in younger patients, and remained unchanged in older patients (≥60 years). The current study shows no trend of increase in the risk of SPM overall or of AML over the recent years, however, the unchanged risk of AML in older patients may indicate persistent toxic effects of some MM therapeutic agents.

ID 0165

Objections to be registered at the Cancer Registry of Baden-Württemberg

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Since October 2011 physicians and dentists located in Baden-Württemberg (BW) are required to inform patients diagnosed with or treated for cancer about the compulsory registration at the Cancer Registry (CR) of BW, as well as about their right to object to the registration. In case of objection cancer cases are not reported to the CR and any information already sent must be deleted. The objection must be submitted in writing and signed by the physician and patient. Since the beginning of registration the number of objections have increased to peak in 2013 (1.386 objections) and then dropped to 851 objections in 2014. The regional distribution of objections submitted varied to a great extend: more than 45% coming from two of the 14 zip-code areas in BW. Analyzing the data according to the type of reporting institution (tumour centre, hospital, registered physician) shows that 82% of the objections originate from registered physicians, 6% and 3% come from hospitals and tumour centres, respectively. The origin of a further 9% cannot be determined, since the institution submitting the objection initially was not recorded. The number of deleted reports is higher than the number of objections. This is caused by the fact, that the CR of BW can receive information concerning diagnosis, therapy andcourseofdiseasefrom one or more than one institution. On average, every objection leads to the deletion of 2 registered reports (3.438 objections, 6.916 deleted reports). This shows that extensive information about the individual cancer patient has been reported prior to the objection. This can either be due to insufficient information about the right to object, or the patient changing their mind about the registration in view of a later physician-patient contact.

ID 0182

German and American lymphoma study and cancer registry data – comparison of subtypes

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In 2009, the cancer registry Baden-Württemberg (BW) established a state wide cancer registry, being the last federal state in Germany to do so. Since then the degree of reporting all cancers has steadily risen, but in 2012 was still less than 70% for lymphoma overall.
We compared the lymphoma prevalence of the cancer registry BW for 2012 with the German lymphoma study (Becker et al 2005) and the United States SEER cancer registries (Morton et al 2006). Lymphoma entities were classified according to the WHO (Jaffe et al 2001), missing morphologies were converted from the ICD-10 diagnoses to the ICD-O-3 (Fritz et al 2000). Only malignant /3 lymphoma entities were included.
The 2012 lymphoma sample from the cancer registry BW (n = 2.851) agrees very well with the relative frequency data of the German lymphoma study (n = 700) and the SEER data (n = 87.420), e.g. for CLL/SLL 15,4%, 14,9%, 17,3%, respectively. We found that the rate of lymphoma entities not being immunophenotyped for B-, T-, U-cells was lower in the German lymphoma study than in the registry data (9,6%, 0,1%, 10,3%). Conspicuous was an extremely low frequency of precursor B-cell in the German lymphoma study compared to the other studies (acute lymphoblastic leukaemia/lymphoma 2,4%, 0,3%, 2,8%, respectively), which was explained by the study design (participants > 18 years).
Lymphoma data of the year 2012 in BW coincide well with the data of the German lymphoma study and SEER data from the US. Thus, further evaluations of lymphoma data from the cancer registry BW can be performed with confidence.

ID 0330

Reporting of colorectal cancer (ICD-10 C18-C21): Decline in colorectal cancer incidence does not apply to temporal anal cancer trends in Germany

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Objectives: Colorectal cancer is one of the most common malignancies in men and women in Germany. Temporal development over the past 20years indicates a decline in incidence and mortality rates. While anal cancer can be regarded as a distinct entity, is it commonly grouped among colorectal cancers, also in our regular reports on cancer in Germany. However, sharp increases in anal squamous cell carcinoma are reported in several Western societies, female rates have increased at a faster pace than male rates over this period. We aim to provide an overview on recent developments of anal cancer in Germany, using population-based cancer registry data.
Methods: We analyzed anal cancer incidence using data from ten population-based German cancer registries for the period 1999-2012. ICD-10 codes and ICD-O-3 morphology codes were used to select site and histologic types. The annual percentage change was calculated on age-adjusted incidence rates with a joinpoint regression model.
Results: A total of 5,524 histologically verified cases of invasive carcinoma of the anus were included in the analyses, hereof were 83.5% of squamous cell origin (SCC). Age-standardized incidence rates of anal cancer annually increased by 4.3% (95% confidence limits: 3.5-5.1) among women and by 3.8% (95% confidence limits: 2.3-5.4) among men, though not exceeding 2 per 100 000 population. Women below the median age of 65 years were most heavily affected by a 6.5% annual increase.
Conclusion: An annual increase in anal cancer incidence rates in Germany is observable over the past decade, however not as steep as described in other Western societies. An increasing predominance of women affected by the disease cannot be confirmed. In consideration of the observed temporal developments, separate reporting of the entity from other colorectal cancer seems reasonable.

ID 0334

„Cancer in Germany" 2015 – Current Epidemiological Cancer Statistics

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We present here the latest statistics from the tenth Edition of the report "Cancer in Germany", published in 2015 by the German Centre for Cancer Registry Data (ZfKD) at the Robert Koch Institute (RKI) and the Association of Population-based Cancer Registries in Germany (GEKID). This report includes nationwide analyses of more than twenty-seven cancer en-

tities through the year 2012. The data for this report were regularly transferred to the ZfKD in anonymised form by all German population-based cancer registries. As in previous years, cancer incidence and mortality are presented by age and sex. Current trends are analysed and put into international context. Additional focus is placed on prevalence, five- and ten-year survival and tumour extent (T-stage) at diagnosis.
For the year 2012, the RKI estimates that up to **478,000** cases of invasive cancer were newly diagnosed. As with previous estimates, the most common cancer sites were the prostate among men, with **63,700** cases, and the breast among women, with **69,600** cases. Increasing incidence rates since 1999 are observed for cancer of the lung and vulva in females and thyroid cancer in both sexes. Incidence rates of lung cancer in males and cancer of colon and rectum in both sexes were declining.
The ZfKD may provide, upon application, the verified dataset from the population-based cancer registries to third parties for scientific use. Furthermore, an interactive database at the Homepage of the ZfKD provides data for public use.

ID 0338

Trends of advanced breast cancer incidence rates after implementation of the mammography screening program in the Regierungsbezirk (RB) Münster

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Background: Mammography screening programs (MSP) aim to detect early-stage breast cancers and to decrease the incidence of advanced stages in order to reduce breast cancer mortality. We investigated whether the incidence of advanced stage breast cancers changed in the MSP target population of women aged 50-69 years since implementation of the MSP in 2005.
Methods: In the RB Münster, 12,713 women were newly diagnosed in the target population with invasive breast cancer (BC) between 2000 and 2012. Data from the population-based epidemiological cancer registry (EKR) were used to stage cancers; missing values (9.7%) were imputed. The incidence rates for early stage (UICC I) and advanced stage (UICC II+) BC were determined and a join-point analysis was performed using 3-years moving averages.
Results: The incidence of UICC I BC increased rapidly after the introduction of the MSP in 2005 and declined modestly after 2010. The incidence rates of UICC II+ BC rose after the start of the MSP and decreased markedly after 2009 to levels lower than in the pre-MSP phase 2000-2004. Decreases in UICC II+ BC incidences were observed only in the age groups 55 to 74 years corresponding to annual percent changes (APC) ranging from -4.4% to -8.5%. No changes in the incidence rate of UICC II+ BC were found for the age groups 50-54 and 75+ years, respectively.
Discussion: The incidence rate of advanced stage breast cancers decreased in the MSP target group below pre-screening levels. Such changes were not seen in age groups newly entering the program and those at least five years above the eligible age range. Our results indicate that the MSP meets expectations and holds potential of reducing BC mortality.

ID 0347

Papillary type mostly accounts for rise in incidence rates of thyroid cancer in Germany

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Objectives: In recent years, the age-standardized incidence rates for thyroid cancer have increased considerably for both sexes in many industrialised countries, predominantly in younger adults. However, mortality rates are staying relatively stable or are even decreasing. We aim to provide an overview on recent developments of thyroid cancer in Germany, using population-based cancer registry data.
Methods: We analysed thyroid cancer incidence using data from 14 population-based German cancer registries (13 of 16 federal states and one district) from 2003 to 2012 stratified by sex, age group and histologic subtype. Rates were age-standardised using European standard population.
Results: In Germany, 4,119 women and 1,753 men have been diagnosed with thyroid cancer in 2012 (preliminary results). In the period from 2003 to 2012, age-standardised incidence rates have been steadily rising. The increase was predominantly observed at a younger age (15 to 39 years) and only for papillary adenocarcinomas. Within Germany, the highest incidence rates by far are to be observed in Bavaria, however there was no clear geographical pattern to be found.
Discussion: Papillary carcinomas are predominantly responsible for the increase in thyroid cancer incidence in Germany, this subtype affects mostly young adults. The reasons for the rising numbers still remain unclear, improvements in imaging techniqes might play a role. However, the rather favourable prognosis of the papillary subtype is reflected in a slight decline in mortality rates for thyroid cancer. The high incidence rates in Bavaria correspond to similar rates reported from Austria.

ID 0409

How plausible is the cause of death statistics in cancers?

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Question: Incidence, mortality and lethality rates show the effectiveness of the health service. There originate the questions: How reliable are these statistics, also in the international comparison? How often misdiagnoses are made? How often autopsies are carried out which serve the validity of the clinical cause of death diagnostics?
Methods: Results from summarized studies of the German Federal Medical Association, from obligatory registration upraised statistics from the publications of the health ministry in Russia and from the department for health service of the government of Moscow were compared.
Results: The diagnostically (d.) autopsy rate (AR) 35 years ago was in the GDR at 30% (1979) and in the FRG at 10% (1980). In comparison in 2012 it was less than 1% of all deaths. Legal-medical (lm.) AR in 2012 was only 2.3% of all deaths.
In Russia, apart from Moscow, where the d. AR from 2002 till 2009 was between 22 and 27% and rose to 37.8% in 2013, the d. AR was halved from 2000 to 2010 to 11% of all deaths. In Moscow the lm. AR was 23.9% (2013) from all deaths.
According to old studies misdiagnosis rates (MR) was between 35 and 42% in Germany with deaths in the hospital (1978–1987) and 45% with deaths in hospitals, homes and urban institutions (1978–1987).
The MR in Russia (11. 9%) are lower, however, point to big differences in the quality of the cause of death diagnostics with deaths in the hospital (12. 1% in Moscow, in 2013) and at home (23. 8% in Moscow, in 2013).
Conclusions: A quality control of the clinical diagnostics in Germany is not possible with the today's AR and the non-investigation of statistics. For the inquiry of reliable cause of death statistics and lethality rates a reform becomes urgently necessary.

Gastrointestinal (Colorectal) Cancer

ID 0015

Characteristics and outcomes of patients enrolled in the CORRECT and CONCUR phase 3 trials of regorafenib for metastatic colorectal cancer (mCRC)

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Introduction: The international CORRECT trial (NCT01103323) showed that regorafenib improves overall survival (OS) *vs* placebo in patients with previously treated mCRC. The CONCUR trial (NCT01584830) confirmed the survival benefit for regorafenib in Asian patients. We examined the characteristics of patients in the two trials.
Methods: The designs of both phase 3 trials were similar, except that CONCUR included only Asian patients and prior use of biologic targeted therapy was not mandatory. Patients were randomly assigned 2:1 to regorafenib 160 mg or placebo for the first 3 weeks of every 4-week cycle. The primary endpoint was OS.
Results: CORRECT involved 760 patients from North America, Europe, Australia, and Asia (n = 4 Chinese; n = 100 Japanese), whereas CONCUR included 204 patients from Asian countries (n = 172 Chinese; n = 0 Japanese). In CONCUR, patients had fewer treatment lines for metastatic disease, a higher proportion of patients were PS1, and overall 40% had no prior biologic targeted therapy. The most frequent drug-related grade ≥3 adverse events in CORRECT were hand-foot skin reaction (HFSR, 17%), fatigue (10%), diarrhea and hypertension (7% each). In CONCUR, the most frequent drug-related grade ≥3 adverse events were HFSR (16%), hypertension (11%), hyperbilirubinemia, hypophosphatemia, and alanine aminotransferase increase (7%, each).
Conclusion: CONCUR and CORRECT confirm the clinical benefit of regorafenib in patients with previously treated mCRC and a statistically significant improvement in OS in Asian and non-Asian patients. Adverse events were mostly similar across both trials and consistent with the known safety profile of regorafenib.

ID 0044

Langzeitoutcome bei KRK- Patienten des Darmkrebszentrums Lichtenfels im Zeitraum 2003–2013

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Zielsetzung: Trotz politischer Vorgaben bis 1999 verpflichtend Krebsregister in allen Bundesländern einzurichten ist die epidemiologische Datenlage zum Langzeitoutcome bei KRK-Patienten national unzureichend. Ziel war die Evaluierung der stadienbezogenen Mortalität mit strukturierten Follow-Up Daten des Darmkrebszentrums Lichtenfels bezüglich der 5 Jahres Überlebensrate und der Vergleich mit Daten anderer klinischer und epidemiologischer Register des Bundeslandes Bayern.
Methodik: Die im Rahmen des Qualitätsmanagements generierten Follow-Up Daten der Jahre 2003–2013 wurden hinsichtlich des Gesamtüberlebens (OAS) statistisch analysiert und mit Daten der bayernweiten Registers.
Ergebnis: Bei konstant hohen Follow Up Quoten> 98% liegt die stadienabhängige 5 Jahres- Überlebensrate bei KRK Patienten des Darmzentrums LIF im Zeitraum 2003–2013 zwischen 78% (UICC I) und 19% (UICC IV). Sie sind damit stadienübergreifend erwartungsgemäß deutlich höher als in den 90er Jahren. Im Vergleich mit aktuellen bayernweiten Daten sowie Erhebungen des Tumorzentrums Oberfranken zeigen sich tendenziell bessere OAS- Raten, insbesondere im UICC Stadium IV (19 vs 8%).
Schlussfolgerung: Die vorliegenden Daten zeigen ein überdurchschnittliches Outcome hinsichtlich des Gesamtüberlebens für die im Darmzentrum LIF behandelten Patienten, insbesondere im weit fortgeschrittenen Stadium. Hierfür relevante Faktoren müssen in weiteren Untersuchungen identifiziert werden. Patienten sollte die Anbindung an Darmkrebszentren empfohlen werden, dabei scheint eine größere Fallzahl der Zentren nicht mit einem verbessertem Qutcome assoziiert zu sein. Weitere Studien sind notwendig um geeignete Indikatoren zur Verbesserung des zentrumsinternen QM zu identifizieren.

ID 0068

Proposal for a new M1 subclassification in colorectal carcinoma

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Objectives: In 2010, the seventh edition of the TNM cancer staging system of the UICC and the AJCC introduced a subdivision of M1 in the TNM classification of colorectal carcinomas. For the eighth TNM edition which will be released in 2016 new proposals are appreciated. The aim of our study was to define a new optimized proposal for M1 subclassification for colorectal carcinomas based on data of a large single-center cohort of patients.
Methods: In a total of 814 consecutive patients with stage IV colorectal carcinoma treated between 1995 and 2013 prognostic factors were analyzed in univariate and multivariate analyses. Treatment was planned individually in a multidisciplinary tumor board. The patients were followed up until 01 January 2015.
Results: Advanced age, treatment in the earlier period 1995-2003, involvement of multiple metastatic sites, missing CEA, and non-curative resection were found to be independent prognostic factors. In patients with only one metastatic site, survival was superior in patients with liver or lung metastasis, moderate in patients with metastasis of the peritoneum or non-regional lymph nodes and poor in patients with other rarely metastatic involved organs. The new proposal defines M1a, Metastasis confined to one organ: liver or lung (2-year survival 51.6%); M1b, Metastasis confined to one organ: peritoneum or non-regional lymph nodes, or Metastasis confined to liver plus lung (2-year survival 39.4%); and M1c Metastasis confined to one organ: all other sites, or Metastasis in more than one organ, but not liver plus lung (2-year survival 21.6%).
Conclusions: The new proposal can identify three prognostic groups in stage IV colorectal carcinomas with significant differences in survival.

ID 0070

Prevalence and influence on outcome of *Neuregulin- (NRG1), HER2/neu- and HER3- expression* in patients with metastatic colorectal cancer (mCRC) treated with irinotecan-based first-line regimens (FUFIRI vs. mIROX) in the FIRE 1-trial.

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Aim: Little is known about the role of *HER2/neu*- and *HER3*-receptor as part of the epidermal growth factor receptor (*EGFR*) family in metastatic colorectal cancer (mCRC). Hence, we explored the impact of *HER2/neu*, *HER3*- receptor as well as their ligand's neuregulin (*NRG1)* expression in patients with mCRC.
Methods: *NRG1*, *HER2/neu* and *HER3* expression was detected by immunohistochemistry in 208 patients with mCRC receiving 5-FU/LV plus irinotecan (FUFIRI) or irinotecan plus oxaliplatin (mIROX) as first-line treatment within a randomized trial (FIRE1). For evaluation, Rüschoff-score for *HER2* expression in gastric cancer (i.e. +++ and ++ vs. + and 0) was used. Biomarker expression was correlated with response, median progression-free survival (PFS) and median overall survival (OS).
Results: *NRG1* (low: 192 vs high: 16), *HER2/neu* (low: 178 vs high: 30) and *HER3* (low: 69 vs high: 139) expression was assessed in 208 patients. Neither high versus low *HER3* expression (PFS: 7.1 vs 8.8 months, HR: 1.11 [95% CI: 0.82–1.50], p = 0.50; OS: 19.8 vs 21.1 months, HR: 0.95 [95% CI: 0.70–1.30], p = 0.75) nor high compared to low *HER2/neu* expression (PFS: 7.7 vs 8.0 months, HR: 1.07 [95% CI: 0.71–1.60], p = 0.75; OS: 16.6 vs 21.1 months, HR: 1.13 [95% CI: 0.75–1.71], p = 0.57) did influence outcome. High versus low *NRG1* expression affected PFS (4.7 vs 8.2 months, HR: 2.45 [95% CI: 1.45–4.13], p = 0.001), but not OS (15.5 vs 20.7 months, HR: 1.33 [95% CI: 0.76–2.35], p = 0.32).
Conclusion: High IHC-expression of *NRG1*, *HER2/neu* and *HER3* was detected in 8%, 14% and 67% of tumors, but only high *NRG1*-expression was associated with inferior PFS in the FIRE1-trial. Further research is warranted to explore if *HER2/neu*- and *HER3*-receptors represent potential targets in the treatment of mCRC.

ID 0094

MALDI-imaging reveals TYB4 to classify diploid from aneuploid colon cancer

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Background: DNA aneuploidy has been identified as a prognostic factor for epithelial malignancies. In this study, we compared diploid and aneuploid colon cancer tissues against normal mucosa of the colon by means of matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry (IMS).
Material and Methods: DNA image cytometry determined the ploidy status of tissue samples that were subsequently subjected to MALDI-IMS. After obtaining protein profiles through direct analysis of tissue sections, a discovery and a validation set were used to predict ploidy and disease status by applying proteomic classification algorithms [Supervised Neural Network (SNN) and Receiver Operating Characteristic (ROC)]. Clinical target validation was performed by immunohistochemistry using tissue microarrays (TMA) comprising healthy controls as well as diploid and aneuploid colorectal carcinomas.
Results: SNN algorithm categorized 99% of normal mucosa and 90% of colon carcinoma as well as 99% of diploid and 94% of aneuploid colon cancers correctly. Validation of both comparisons showed a correct classification of normal mucosa in 92%, tumors in 96%, and diploid and aneuploid colon cancers in 92% and 78%, respectively. Five peaks (m/z 2,396 and 4,977 for the *diploid vs. aneuploid comparison* and m/z 3,375, 6,663, 8,581 for the *normal mucosa vs. carcinoma comparison*) reached significance in both SNN and ROC analysis. Among these, m/z 4,977 was identified as thymosin beta 4 (TYB4). TYB4 showed expression differences also in clinical samples using a tissue microarray of normal mucosa, diploid and aneuploid colorectal carcinomas and could serve to predict overall survival.
Conclusion: Our data underscore the potential of MALDI-IMS proteomic algorithms to reveal significant molecular details from distinct tumor subtypes such as different ploidy types.

ID 0145

Targeted therapies of two different *Braf* mutated colorectal carcinoma cell lines and the establishment of a 3D tumor model on the basis of a decellularized intestinal matrix

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Vemurafenib is a potent inhibitor of BRAF in *braf* mutant melanomas but shows response rates of just about 5% in *Braf* mutant colorectal carcinomas (CRCs) (Corcoran et al. 2012). It has been reported that the inhibition of BRAF increases the phosphorylation of the epidermal growth factor receptor (EGFR) via a feedback loop in CRC cell lines (Prahallad et al. 2012). Thus, we tested combination therapies with vemurafenib and the EGFR inhibitor gefitinib as well as the effect of the PI3K inhibitor LY294002 to block the PI3K/Akt/mTOR pathway. We used different combinations of all three inhibitors in two cell lines (HROC24, HROC87) carrying a *Braf* mutation (V600E) but differing in other mutations (Maletzki et al. 2012).
In conventional 2D cell culture, vemurafenib mono-treatment increased apoptosis rate in HROC24 but not in HROC87 cells, whereas gefitinib or LY294002 alone did not show an effect. The combination of two or three drugs was more efficient than the respective mono-therapy in HROC87 but not in HROC24 cells. In 3D cell culture, the combination of drugs does not show an increase in apoptosis rate compared to the mono-treatment. This leads to the conclusion that the determination of a single genetic lesion is not always sufficient to choose the most effective therapy. In general, it is reported that 3D tumor models are more resistant to chemotherapies than 2D cell culture models and that they show more reliable results in drug testing (Stratmann et al. 2013). For this reason, we established a 3D model on a decellularized intestinal scaffold to compare the effect of drugs on apoptosis, proliferation and pathway signaling with common 2D cell culture. We conclude that our 3D test system is a reliable model to test new therapies for the treatment of cancer.

ID 0159

A first community-based, observational study on panitumumab as 1st and 2nd line combination therapy of metastatic colorectal cancer (mCRC) in *RAS* wildtype patients

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Background: This study evaluated the use of panitumumab (pmab) in routine clinical practice in Germany, as adjunct to either FOLFOX as 1st line therapy (FLT) or to FOLFIRI as 2nd line therapy (SLT) of mCRC patients (pts) with wild-type (WT) *RAS*.
Methods: Data on use and outcomes of pmab in adult mCRC pts with WT *KRAS* (until Aug 2013) or WT *RAS* were collected at baseline, after treatment had started, and once it was stopped or the 12-month observation period had ended.
Results: From Dec 2012 until 15 Jan 2015, 102 pts had received combination treatment with pmab in this ongoing study, 80 as FLT with FOLFOX and 22 as SLT with FOLFIRI. The majority of pts were men ≥65 years with synchronous mCRC and liver metastases; 89 pts had *RAS* WT and 13 *KRAS* WT (without testing for *RAS* WT). Overall, 81% of pts had undergone surgery beforehand, most of them with palliative intent. The most commonly specified treatment goal was tumour shrinkage (25% of FLT pts). On average, pts had received 9 pmab doses (range 1-27) for up to 17 months. Differences in exposure between patient groups were minor, but FLT pts required dose reductions or delays more frequently, particularly due to adverse events (AEs): 25% vs. 9.1%. At the end of the observation period, disease had progressed in 15 FLT (19%) and 4 SLT (18%) pts, of whom 6 and 2 had died, respectively. Overall, 57 FLT (71%) and 12 SLT pts (55%) had AEs, which led to discontinuation in 6 FLT (7.5%) and 3 SLT (14%) pts. In 15 FLT (19%) and 2 SLT (9.1%) pts, AEs were of grade ≥3; 4 FLT pts had serious AEs.
Conclusions: Pmab is used more frequently in 1st than in 2nd line combination therapy of mCRC. Good tolerability in general and rate of non-response so far appear to be consistent with data from controlled clinical trials.

ID 0161

Tumor cell mediated expression and stimulation of CD137/CD137L causes reduced proliferation in human colorectal cancer

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Background: The presence of costimulatory CD137/CD137L signaling in the tissue microenvironment has been shown to vary between healthy and cancerous organs and is suspected to weaken the endogenous anti-tumor T-cell response by creating evasion mechanisms. In this study, the expression of CD137 and its ligand CD137L as well as the effects of tumor cell related reverse signaling of CD137L were analyzed in human colorectal cancer (CRC).
Methods: Expression of CD137 and CD137L was examined in human colorectal cancer cell lines HT29, SW480 and SW620 using RT-qPCR, Western blot and FACS analysis. Its differentiated expression was further analyzed in human CRCs and HT29 BALBc mouse xenografts by RT-qPCR and immunohistochemistry. To dissect the effects of CD137L activation on cancer cells, MTS proliferation assays were additionally performed.
Results: All three human colon cancer cell lines demonstrated high cellular (FACS) and protein (Western Blot) CD137L expression. CD137 was found only in SW480 cells at weak expression. RT-qPCR analysis of primary CRCs showed an UICC stage-dependent increase of CD137L expression, while CD137 was less expressed in late stages compared to early stages. Interestingly, activation of CD137L by immobilized CD137-Fc resulted in reduced cancer cell proliferation compared to IgG1-Fc controls.
Conclusion: Our results demonstrate tumor cell mediated expression of the costimulatory molecule CD137 and its ligand CD137L in both colon cancer cell lines and human colorectal cancer. Moreover, CD137L reverse signaling was found to reduce cancer cell proliferation *in vitro*. Based on these data, the CD137/CD137L signaling pathway seems to present a promising target for cancer therapy in CRC.

ID 0175

Tumor response as important parameter during first-line treatment of metastatic colorectal carcinoma (mCRC) with panitumumab + FOLFIRI

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Background: Efficacy of adjunctive panitumumab (pmab) treatment for mCRC has been shown to depend on the *RAS* genotype. In a single-arm, exploratory, phase 2 study, we compared tumour responses to pmab along with FOLFIRI as first-line treatment in patients (pts) with wild-type (WT) and mutant (MT) *RAS* mCRC.
Patients and Methods: Pts with mCRC were treated with pmab (6 mg/kg) + FOLFIRI q2w and compared by *RAS* status regarding objective response rate (ORR), progression-free survival (PFS), relative tumour shrinkage (TS), and median duration (first response to progression or death) and depth (%TS at nadir or progression) of response (DoR and DpR, respectively). TS ≥30% or ≥20% by week 8 were defined as early TS (ETS).
Results: Of 143 pts with available *RAS* data (69 WT, 74 MT), 141 were included in the ORR analysis and 135 had TS data available at baseline and week 8. Pts of both genotypes showed comparable baseline characteristics. WT pts had greater ORR (59% vs 41%), PFS (median: 11.2 vs 7.3 months), and DpR (59.3% vs 35.7%) and more often an ETS (≥20%: 74% vs 50% of pts; ≥30%: 49% vs 37% of pts) than MT patients. Median DoR was also greater in *RAS* WT (13.0 vs 5.8 months). ETS was generally associated with significantly longer PFS (≥30% vs <30%: median 10.9 vs 7.2 months, HR: 0.45, p = 0.0003; ≥20% vs <20%: 9.1 vs 6.9 months, HR: 0.48, p = 0.0005), and particularly in the *RAS* WT population (≥30% vs <30%: median 14.3 vs 7.8 months, HR: 0.29; ≥20% vs <20%: 13.3 vs 7.3 months, HR: 0.34).
Conclusions: These exploratory analyses support the anti-tumour efficacy of Pmab in combination with FOLFIRI in *RAS* WT pts. Accordingly, the European label for pmab was recently extended to include first-line combination with FOLFIRI for pts with *RAS* WT mCRC.

ID 0244

Establishment and characterization of early colorectal cancer patient-derived xenografts (PDX) as platform for drug screen, molecular- and biomarker analysis

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Newly developed targeted therapies against colorectal cancer (CRC) can improve the therapeutic outcome of patients. However, to optimize their antitumoral activity, predictive biomarkers are needed. Therefore, *in vivo* CRC models are required for evaluation of drug treatments in the context of mutation status or signaling pathways. In this study a cohort of CRC patient-derived xenografts (PDX) was established, which can be used for preclinical biomarker exploration and drug screening.
Tumor tissues from 87 CRC patients were transplanted into immunodeficient mice, of which 56% engrafted as passageable PDX. 53% of the engrafted PDX derived from primary tumors and 47% from liver and lung metastases. Histopathology and histochemistry staining for human nuclei confirmed resemblance of the PDX to the original patient tumor. Sequencing of patient tumors, normal tissues and the corresponding PDX confirmed maintenance of the genetic profile.
Drug responsiveness of PDX was assessed towards classical and targeted therapies and reflected the heterogeneity regarding sensitivity. Mutational profiling by the Illumina Cancer Panel, gene expression and copy number analysis of selected genes was correlated to therapy outcome. Mutations and expression of tumor biomarkers EpCAM, EGFR, p53, etc. are maintained in the PDX. The ratio of key mutations, e.g. KRAS, and expression of EGFR ligands showed involvement in resistance mechanisms towards targeted therapies.
Thus, PDX models are well suited for preclinical studies, as they reflect the heterogeneity and dynamics of CRC and can be used for validating hypothesis for personalized medicine, search for biomarkers, as well as for testing of new compounds.

ID 0264

Neoadjuvant radiochemotherapy for rectal cancer: Comparison of different therapy regime

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Background: Preoperative radiochemotherapy (RCT) for locally advanced rectal cancer (LARC) is associated with acute toxicities like abdominal pain or diarrhea. Aim of this study was to analyze the acute toxicities of different chemotherapy regime and intensity-modulated radiation therapy (IMRT) vs. 3D-conformal radiation therapy (3DCRT) during RCT for LARC.
Methods: 185 patients with LARC preoperatively treated with 3DCRT or IMRT concurrent with either a mono-RCT (5-FU or Capecitabine) or a combined-RCT (Capecitabine + Oxaliplatin or + Irinotecan or + Irinotecan and Cetuximab) were retrospectively evaluated. Chi-square or Fisher's exact test were applied to detect statistical differences in incidences and severity of diarrhea, pain and frequency of treatment breaks between mono-RCT and combined-RCT, 3DCRT vs. IMRT and the 4 subgroups (mono-CT + 3DCRT or IMRT vs. combined-CT + 3DCRT or IMRT). Survival estimates were generated using the Kaplan Meier method.
Results: There was no significant difference in the incidence respectively severity of diarrhea and number of treatment breaks in any therapy arm. Abdominal pain requiring treatment was significantly more often seen in the IMRT compared to the 3DCRT group (72.5% vs 52.4%; p = 0.023). Overall Survival (OS) and disease free survival (DFS) were higher among patients receiving IMRT compared to patients receiving 3 DCRT. The 5-year OS rate was 89.9% in the IMRT group and 69.5% in the 3DCRT group (p = 0.023). The 5-year DFS rate was 80.9% in the IMRT group and 60.7% in the 3DCRT group (p = 0.031).
Conclusion: IMRT compared to 3DCRT significantly improve OS and DFS of patients receiving neoadjuvant RCT for LARC under the acceptance of significantly more abdominal pain.

ID 0288

Intravenous ferric carboxymaltose vs. oral iron substitution in patients with metastatic colorectal cancer (mCRC) and iron deficiency anemia: A randomized multicenter treatment optimization study (A Study in Progress Report)

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Introduction: Iron deficiency has a high prevalence (60%) in colorectal cancer patients (pts). About 70% of these pts suffer from iron deficiency anemia (IDA). Iron substitution is usually administered orally. Due to low resorption rates, side effects and thus poor pts compliance parenteral substitution seems to be a better option in terms of efficacy. In a randomized explorative multicenter phase II trial (FerInject) a comparison of efficacy parameters of parenteral vs. oral iron substitution will now be conducted in order to identify the best treatment for clinical practice. Quality of life-data (QoL) will be collected in the treatment arms for effect comparison.
Methods: MCRC pts with IDA and concomitant palliative chemotherapy are randomly assigned to one of the treatment arms (parenteral vs. oral). Parenteral pts receive up to 1.000 mg ferric carboxymaltose i.v. per week for a maximum of 2 weeks. Oral pts take 200 mg iron per day for a total of 12 weeks. Course of therapy and QoL-data will be collected. Primary endpoint is the increase or normalization of hemoglobin. Secondary endpoints are (selection): fatigue; QoL; tolerance and toxicity; dropout rate and overall survival. 64 pts shall be enrolled. Data will be evaluated exploratively due to lacking reference data. The development of hemoglobin status will serve as an indicator for a trend towards a better treatment option if a level of significance p = 0.2 (Fisher's exact test) can be detected.
Results: Recruitment started in 04/2015.
Conclusions: FerInject is a trial in progress with high relevance for the clinical management of mCRC pts with IDA and a concomitant palliative chemotherapy. It will return additional information to both efficacy and QoL issues of these pts.

ID 0304

Heterogeneity of KRAS Mutation Status in Rectal Cancer

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Introduction Anti-EGFR targeted therapy is of increasing importance in advanced cancer and prior *KRAS* mutation testing is mandatory for therapy. In rectal cancer patients the impact of preoperative chemoradiotherapy (CRT) on *KRAS* status as well as the applicability of *KRAS* testing in small pre-therapeutic biopsies is still under debate.
Materials and Methods *KRAS* mutation status analyses were performed in 199 tumor samples from 47 patients with rectal cancer. To evaluate the heterogeneity between different tumor areas within the same tumor prior to preoperative CRT 34 patients were analyzed. For the assessment of heterogeneity after CRT residual tumor tissue from 12 patients were analyzed (intratumoral heterogeneity) and assessment of heterogeneity before and after CRT was evaluated in corresponding patient samples (intertumoral heterogeneity). Primer extension method was used for initial *KRAS* mutation status testing. Discordant results in the primary test were reevaluated by using the *KRAS* RGQ PCR Kit.
Results Heterogeneity of *KRAS* mutation status within preoperative biopsies was only found in a single patient (2.9%). The comparison of pre- and postoperative *KRAS* mutation status revealed a discrepancy in 6 out of 47 patients (12.8%), after reevaluation with the therascreen® *KRAS* test 4 cases turned out to be concordant. For 2 cases no DNA was available for reevaluation. In the tissue of resected tumors a mosaic of wild-type and mutations of the *KRAS* gene was initially found in six patients (50%), after reevaluation by the therascreen® *KRAS* test no intratumoral heterogeneity was detected by confirming the KRAS mutation status in all discordant samples.
Conclusions We did not find significant differences of the *KRAS* mutation status within tumor samples obtained from different biopsies or determined before preoperative treatment and after tumor resection in rectal cancer patients.

ID 0307

Effects of CXCR4 blockage/knockdown and its newly identified ligand ubiquitin in colorectal cancer cells

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The C-X-C chemokine receptor type 4 (*CXCR4 or CD184*) higher expression level has been correlated to the poor prognosis and metastasis of colorectal cancer (CRC). In this study, we studied the outcomes of blocking this receptor by an antagonist (AMD3100) and siRNA mediated knockdown to study the possible alterations in biological properties of CRC cells (SW480, SW620). In addition, we investigated the effects of ubiquitin, a newly identified ligand for CXCR4, in the selected cell lines.
Methods included functional effects of CXCR4 blockade/knockdown on SW480 and SW620 cells by proliferation, colony formation, migration and scratch assays. Apoptosis induction was studied by Hoechst 33342 staining and annexin-V assays. Additionally, ubiquitin mediated effects on migration and proliferation of CRC cells were investigated.
Blockage and knockdown of CXCR4 induced significant reduction in proliferation, colony formation and migration of CRC cells. Substantial apoptotic effects were noticed by Hoechst 33342 nuclear staining and annexin-V based labeling of the cells by microscopic and flow cytometry analysis, respectively. Both CRC cell lines demonstrated significant migration towards ubiquitin, while no significant proliferative effects were observed upon ubiquitin exposure.
In conclusion, expression of CXCR4 contributes to enhanced proliferation of CRC cells and its blockage/inhibition induces anti-clonogenic, anti-migratory and apoptotic effects in CRC cell. Furthermore, ubiquitin turned out to be a significant ligand, which could favor CXCR4 mediated migration of CRC cells. Thus, targeting the CXCR4-ubiquitin axis could be an important addition to the treatment options for CRC and will need further validations in future.

ID 0322

Lynch Syndrome Expert Opinion Questionnaire – What Would You Do?

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Purpose: In Lynch syndrome patients screening recommendations differ internationally. We were interested to investigate the opinion of experts towards the management of mutation carriers regarding, among others, extended or prophylactic surgery, predictive testing and chemoprevention.
Methodology: A online questionnaire was designed and broadly distributed on behalf of InSiGHT to any potentially interested professionals.
Results: Of the 147 responses, 27.7% were gastroenterologists, 32.5% surgeons, 28.9% geneticists, 1.2% pathologists, and 9.6% had another speciality. 57.3% suggest a yearly colonoscopy which should start at the age of 25 (47.9%). At the age of 35 and without diagnosis of colorectal cancer 40.9% would consider a purely prophylactic surgery. In case of a colon cancer at the age of 35 only 20.2% would opt for the standard oncological resection. 48.2% would opt for a subtotal colectomy and 28.9% for a total colectomy and ileorectal anastomosis. At diagnosis of rectal cancer 41.2% would opt for a standard oncological resection, 43.9% for a restaurative proctocolectomy. Chemoprevention with aspirin was attractive for 80.7% of the participants. 41.3% opting for 100mg, the rest for a higher dosage.
Conclusion: 40.9% of the participants interestingly would request a purely prophylactic surgery and in case of a colon cancer 80% would opt for prophylactically extended colorectal surgery. Thus experts prefer a more aggressive preventive approach than discussed in any guidelines worldwide. In the event of a rectal cancer almost half of the participants would request a restorative proctocolectomy. The rationale for more aggressive disease management in the light of these results from experts in the field should be recognized.

ID 0355

HIF1A is a versatile regulator of colon cancer pathogenesis

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Chronic inflammation is a key factor in the pathogenesis of colon cancer with largely elusive molecular nature. HIF-1a controls central pro-tumorigenic pathways such as glycolysis and angiogenesis. Furthermore, HIF-1a constitutes a pivotal regulator of myeloid cell function and is activated strongly by pro-inflammatory cytokines. We have analyzed inflamma-

tion-associated colon cancer growth in mice lacking HIF-1a specifically in intestinal epithelial or myeloid cells, respectively. Enterocyte-specific deletion of HIF-1a led to decreased tumor size, while tumor number was not affected. Inflammatory activity was strongly diminished in KO mice. In addition, loss of HIF1A in enterocytes inhibited full activation of the wnt/b-catenin pathway as well as the emergence of tumor-specific metabolic reprogramming. Deletion of HIF-1a in myeloid cells resulted in a significant decrease of both tumor size and tumor number. Remarkably, inflammatory activity in the colon was not affected by the loss of HIF1A in myeloid cells. Adenoma-associated matrix formation and the emergence of tumor-associated fibroblasts were strongly inhibited in myeloid cell-specific HIF1A KO mice. Expression of TGF-b, a central pro-fibrogenic factor, in macrophages was found to be under transcriptional control of HIF1A. In summary, our results identify HIF1A as a versatile regulator of colitis-associated cancer and point towards a crucial role of enterocytic HIF1A in the control of intestinal inflammation. Furthermore, HIF1A in myeloid cells is pivotal for fibroblast activation and matrix synthesis during intestinal adenoma formation. This multilevel importance of HIF1A argues for HIF-1a-inactivating substances as promising agents for the treatment of colon cancer.

ID 0419

Perfusion kinetic analyses using high resolution contrast enhanced ultrasound can reliably predict therapy effects of metronomic topotecan in preclinical models of colorectal liver metastases

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Background: Aim of the present study was to transfer high resolution contrast enhanced ultrasound "from bedsite to bench" and to investigate the diagnostic potential of contrast-enhanced ultrasound and perfusion kinetics during the preclinical development of novel anticancer therapies.
Materials and Methods: The human colon cancer cell line HT29, transfected with luciferase cDNA for in vivo bioluminescence monitoring, was injected intrasplenically or orthotopically into CB17.SCID mice. Mice were monitored weekly by bioluminescence imaging and high resolution ultrasound and contrast enhanced ultrasound. Digital cine loops from the arterial phase, portal venous phase up to the late phase of individual liver metastases and the whole liver were analyzed.
Results: Control animals showed a significantly higher peak intensity compared to animals receiving metronomic topotecan therapy. Furthermore, other than treated animals, a significant decrease of "time to peak" and transit-time over time was observed in control animals. Metronomic topotecan therapy significantly reduced hepatic metastatic spread. Ultrasound analyses correlated with histologic analyses of necrotic tumor area and vessel density.
Conclusion: CEUS combined with perfusion kinetics can reliably monitor therapy effects in preclinical colorectal liver metastases. This novel technology may in the future serve as positive predictive marker for therapy response in cancer patients treated with chemotherapy.

ID 0429

Rising incidence of CRC (colorectal cancer) in the Young (<50): are we missing something?

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The Incidence of colorectal cancer (CRC) in the United States in individuals aged 50 and older is rapidly decreasing, dropping 3.9% per year for the decade 2001-2010. In marked contrast, recent literature details significant increases in the incidence of CRC among young adults (YA) aged 50 and younger for the same decade.

Effective strategies to reverse this trend require an improved understanding of its causes. Progress in reversing YA (young age) CRC incidence and mortality will require significant redesign of and investment in epidemiologic tools as well as the deployment of considerable intellectual resources. We were interested in identifying parallel developments in Europe and at this staged analysed the publicly available data from the population-based registry of Saarland and of NRW (Northrhine Westphalia.
Interestingly, the analysis demonstrated discrepant **Results:** whereas the data over the past 10 years in NRW confirmed the US-American observation, the data from Saarland did not.
We present and analyze the intriguing observation of the CRC incidence in Germany, confirming a decrease of incidence in the population aged >50 versus a markedly increasing incidence in the population of NRW versus a stable incidence in Saarland.

ID 0474

Functional interference screens targeting signaling components in colorectal cancer cells

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Numerous oncogenic mutations can be found at high frequencies across different tumor entities. Two of these alterations occur within the *KRAS* (e.g. pancreas, colorectal and lung cancer) and the *BRAF* oncogene (e.g. thyroid cancer, melanoma and colorectal cancer), mutations that result in a deregulation of the MAPK pathway. Development of targeted therapies specifically inhibiting this pathway hold the promise to improve treatment outcome of some cancer types. However, recently developed drugs targeting the BRAFV600E mutant protein showed high initial response in melanoma yet not in colorectal cancer patients harboring this mutation. Feed-back activation as well as intrinsic and acquired mechanisms of resistance became a huge hurdle on the way to a successful targeted therapy. Our knowledge about inter- and intra-pathway crosstalk as well as specific oncogene dependencies has to improve to develop efficient combinatorial therapies.
We used CRC cell lines harboring conditionally activated $KRAS^{G12V}$ and $BRAF^{V600E}$ oncogenes and challenged them with shRNA libraries targeting about 12000 genes involved in signaling, transcription, splicing and cell cycle regulation. A proliferation-based screen was performed in $BRAF^{V600E}$-mutant cells to identify genes essential only in an oncogene-induced state, yet being indolent in a 'normal' setting. The screen revealed a small number of targets that upon inhibition by shRNA or siRNA showed a strong suppression of BRAF-transformed CRC cell lines. The gene products are involved in processes such as signaling, DNA repair or splicing and are currently investigated as potential novel drug targets for BRAF-transformed colorectal cancers.

ID 0492

Identification of metabolic changes in Pancreatic Ductal Adenocarcinoma

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Introduction: One of the hallmarks of pancreatic ductal adenocarcinoma thatcontributes to its dismal prognosis and high therapeutic resistance is its altered metabolism.
Methods: We used Genetically Engineered Mouse Models (GEMMs) with pancreas specific activation of oncogenic Kras and concomitant deletion of p53 ($Ptf1a^{+/Cre}$, $Kras^{+/LSL\text{-}G12D}$, $p53^{loxP/loxP}$; *CKP*). Animals develop moderately differentiated PDAC with strong stromal reaction thus resembling the human situation. Multicenter matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) was used to anal-

yse metabolic variations in blood and tissue samples from CKP animals. Upon initial identification of metabolic changes with MALDI-IMS, confirmation studies with semi-quantitative RT-PCR and Western Blot were performed.
Results: Dramatically decreased blood glucose levels in *CKP* mice indicated an elevated consumption of glucose, potentially by the cancer. With MALDI-MSI, we detected 1350 significantly different masses in PDAC tissue compared to wild type pancreas. The identified metabolites indicated to changes in 2 prominent metabolic pathways the Pentose Phosphate Pathway (PPP) and the glutamine and glutamate. Western blot analysis verified an increased expression of the glucose transporter 1 (GLUT1), glutamine fructose-6- phosphate transaminase 1 (Gfpt1) and glucose dehydrogenase-1 (Glud1) in pancreatic tumours. RT-PCRs showed a transcriptional up-regulation of mRNA coding for proteins and enzymes involved in glucose uptake and glycolysis, the pentose phosphate pathway and in the non-canonical glutamine synthesis.
Conclusion: This study provides an *in vivo* insights into metabolic reprogramming of PDAC and illuminates potential metabolic biomarkers and therapeutic targets.

ID 0533

Digital chromoendoscopy with i-scan for in-vivo prediction of advanced colorectal neoplasia – a multicenter study

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Fragestellung: Recent studies have analyzed the potential of advanced endoscopic imaging techniques for differentiating hyperplastic and adenomatous colorectal lesions. Latest endoscopic resection techniques now also allow for treatment of more advanced staged lesions including treatment of early cancerous lesions. To assess the potential of the i-scan technology to differentiate between adenomatous polyps and advanced staged neoplasia.
Methoden: Consecutive patients undergoing colonoscopy at a tertiary referral center were included. After a dedicated training, participating endoscopists underwent a review of 298 unknown images of colonic lesions to assess colorectal lesion histology.
Ergebnisse: Overall accuracy for prediction of advanced staged neoplasia was 92.2% (sensitivity: 94.2%, specificity 90.9%). The positive and negative predictive values were calculated with 87.5% and 95.9%. The κ-value for differentiating adenomatous polyps and advanced staged neoplasia was: 0.8193 (0.7894–0.8492). Intraobserver agreement was calculated with a kappa value of 0.9301 (0.8875–0.9727).
Schlussfolgerung: Accurate interpretation of i-scan images for prediction of advanced colorectal neoplasia can successfully be performed even by non-expert endoscopists with a high overall accuracy and excellent interobserver agreements.

ID 0554

Evaluation of prognostic markers in patients (pts) with metastatic colorectal cancer (mCRC) treated with a bevacizumab (bev) based chemotherapy (ctx) at the West German Cancer Center

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Introduction: Predictive and prognostic markers for antiangiogenic therapy are still lacking in pts with mCRC. We evaluated routinely assessed markers for the efficacy of bev based ctx in patients treated at one of the 12 Oncology Centers of Excellence in Germany.
Methods: We retrospectively evaluated 159 mCRC pts treated with bev in combination with ctx from 2007–2013. Clinical parameters at onset of palliative treatment as anemia, tumor localization (right vs left), primary tumor in situ and an adjuvant therapy were correlated with response rate (ORR) to ctx, progression free (PFS) and overall survival (OS) using Kaplan-Meier curves and Cox proportional hazard models.
Results: Median age was 59y (24–81), 39% of pts had KRAS Exon 2 mutations. Sixty-six % received bev and 60.4% an oxaliplatin based first line regimen. Median OS was 30.4 mo (95% CI 25.3–35.5). All analyzed prognostic markers were significantly associated with reduced OS in univariate analysis, but only localization and primary in situ were significantly associated with reduced OS in multivariate analysis. For pts with at least one of these factors ORR and PFS upon first line therapy, as well as OS were significantly reduced. Interestingly for pts with KRAS mutations who received FOLFOX/bev OS was dramatically reduced (21.6 vs 39.8 mo) compared to pts absent KRAS mutations. In contrast for pts treated with other ctx regimens no differences in OS were observed between pts with and without KRAS mutations.
Conclusion: Routinely assessed clinical parameters can be easily used as prognostic markers in mCRC. In our cohort pts with KRAS mutations had dramatically reduced OS upon FOLFOX/bev compared to other CTX regimes. These finding must be evaluated prospectively in a larger cohort.

Gastrointestinal (Noncolorectal) Cancer

ID 0009

Patients' treatment goals and preferences for palliative chemotherapy (CT) of locally advanced or metastatic gastric cancer (mGC) or adenocarcinoma of the gastroesophageal junction (mGEJ-Ca): a choice-based conjoint analysis (CBC) study from Germany

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Objectives: When trading off potential risks and benefits of palliative CT for mGC, patients' treatment goals and preferences are considered in consultations between oncologists and patients before any CT is given. We

explored these goals and preferences in patients who had already received ≥2 CT cycles and thus had gained initial experience regarding tumor response and side effect intensity.
Methods: Patients' treatment goals for palliative CT of mGC or mGEJ-Ca were evaluated by direct questioning and patient preferences were quantified by CBC analysis. The CBC matrix spanned the 3 attributes of ability to self-care (measure for performance status and quality of life), treatment toxicity, and survival benefit (3-4 factor levels, 15 iterations). A minimum of 50 participants was needed. CBC models were estimated by multinomial logistic regression (MLR) and hierarchical Bayes analysis (HB).
Results: If asked directly, the 55 participants (78% male, median age 63yrs, 82% on current CT, 65% each with marked weight loss and poor performance) most frequently reported survival (prolonged survival, full recovery or gaining time: 54.6%) as their most important treatment goal, followed by avoiding progression/achieving tumor shrinkage (34.6%) and symptom improvement (improved overall performance, no limitations in daily routine or pain-free living: 25.5%). In the CBC analysis, low treatment toxicity was ranked highest (44.6% relative importance, MLR), followed by ability to self-care (32.3%) and an additional survival benefit of up to 3 months (3mo 23.1%, 2mo 18.3%, 1mo 11.2%). MLR and HB analyses yielded similar results.
Conclusions: In this population of patients with mGC or mGEJ-Ca and previous experience with CT, patients' spontaneous answers on treatment goals differed from their well-considered preferences explored by CBC analysis. Although patients' varied experiences with CT will have affected the specific responses, these data indicate that patients' preferences might be captured more precisely after discussing detailed examples illustrating the risks and benefits of the different treatment options.

ID 0042

The pancreatic carcinoma – treatment research and treatment reality in oncology practices

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Approach: Gemcitabine, gemcitabine/erlotinib, FOLFIRINOX are recommended as adjuvant or palliative 1st-line therapy, 5-FU/oxaliplatin as 2nd-line therapy. Gemcitabine/albumin-bound paclitaxel has been approved for 1st-line treatment since March 2014.
Methods: Data related to the treatment of pancreatic cancer have been analysed within the national scientific register ONCOReg since March 2009. The register contains the records of a total of 31,000 patients from 364 practices in 16 federal states, including 1,791 pancreatic carcinomas from 66 practices. 1,612 disease histories with 2,722 therapies are available for evaluation so far.
Results:
Patient characteristics**:**
Gender: 867 (53.8%) male, 745 (46.2%) female
Age at initial diagnosis: 69 (35-95) year; 22% older than 75 years
UICC stages: 45 (2.8%) I; 570 (35.4%) II; 158 (9.8%) III; 747 (46.3%) IV, 92 (5.7%) n.s.
667 (41.4%) patients were operated. An R0 resection was achieved in 518 cases (78.7%), an R1 resection in 114 (17.3%) patients.
Adjuvant therapies:444 (66.6%) patients, R1-additive therapies: 94 (14.1%); 538 (96.3%) gemcitabine monotherapy. Duration of treatment at 5.1 resp. 5.0 months.
Survival rates of the adjuvant resp. R1-additive therapy: DFS 14.4 resp. 9.1 months; OS 33.6 resp. 20.8 months.
Palliative therapies:
1,346 patients received 2,122 palliative therapies: 752 (55.9%) gemcitabine; 379 (29.2%) gemcitabine/erlotinib; 156 (11.6%) FOLFIRINOX; 137 (10.2%) OFF; 116 (8.6%) gemcitabine/albumin-bound paclitaxel; 90 (6.7%) FUFOX, 57 (4.2%) gemcitabine/oxaliplatin. The median duration of treatment was at 79 days.
1,346 patients received a 1st-line therapy; 562 (41.8%) a 2nd-line; 158 (11.7%) a 3rd-line therapy.
The responses were assessed in 1,988 therapies, and the objective response (CR/PR) was at 10.3%. In 34.1% of the cases NC was achieved.
Survival data:
PFS: 1st-line 5.0 mths.; 2nd-line 3.3 mths.
OS: 1st-line 9.3 mths.; 2nd-line 6.4 mths.
Conclusion: Data collection and analysis is an integral part of the routine in oncology practices.
Data on the duration of therapy, the response and survival of selected first- and second-line therapies will be presented.

ID 0062

Circulating tumor cells detection in hepatocellular carcinoma

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Background: Circulating tumor cell (CTC) is unique biomarker of deadly metastasis, recurrence, and the main participants in all steps of metastatic progression. The aim of this work is to isolate, detect and enumerate CTCs in hepatocellular carcinoma (HCC) using different methods.
Methods: Blood samples were collected from 1) healthy volunteers and spiked with HepG2 cells (human-HCC cell line); 2) healthy volunteers as control; and 3) HCC patients. Following methods were used: Magnetic-activated cell sorting (MACS); flow cytometry (FC) and quantitative polymerase chain reaction (qPCR). For MACS, blood was completely lysed, labeled with anti-ASGPR- FITC antibody and anti-FITC microbeads. Isolated HCC cells were identified by immunofluorescence staining using a combination of anti-ASGPR-FITC, EpCAM-PE, and CD45-APC. For FC cells were labeled with anti-ASGPR-FITC, EpCAM-PE and CD45-APC, detected and counted by Axio observer Z1. For qPCR, RNA was isolated from the enriched fraction, transcribed to cDNA and subjected to SYBR green-based qPCR using AFP, ASGPR1 and EpCam as gene specific primers.
Results: CTCs were successfully detected in spiked samples. The average recovery of CTCs enriched was 61% (MACS); 66% (FC) and 69% (qPCR). However, FC and qPCR were not able to detect rare CTCs.
Conclusion: Taken together, these approaches may provide novel biological insights into the process of metastasis and may elucidate signaling pathways involved in cell invasiveness and metastatic competence. In clinical approach, liquid biopsy may emerge to be powerful predictive, non-invasive in analyzing tumor genotypes and could therefore may become an essential tool in cancer decision making that needs absolute precision in establishing personalized medicine.

ID 0105

Towards new protocols and guidelines for diagnosis and treatment of Gastrointestinal stromal tumour (GIST)

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GIST (Gastrointestinal stromal tumour) is a rare disease with a high potential for metastases and an average life expectancy of less then 3 years. The MITIGATE project that is co-funded by an EC grant (FP7 602306) will develop and validate an integrated closed-loop molecular environment for minimally invasive treatment of patients with metastatic GIST resistant to the current medication class (tyrosine kinase inhibitors, TKI). This personalised treatment concept combines novel strategies for biopsy, inline tissue analysis, molecular tumour characterisation, theranostics by PET & MRI technologies and companion radiopharmaceuticals followed by assessment of biodistribution, dose calculation and measurement of therapeutic effectiveness. In its 2nd year of operation the project has al-

ready achieved several promising results. A novel endoscopic biopsy system coupled to a tissue dissociation device and a new robotic assistance device for minimally invasive treatments was developed. GIST subtype classification based on mass spectrometry could show that TKI-resistant & -responsive cells were separable with a high accuracy. Immunocompromised GIST animal models were established to evaluate potential radiotracers. Small molecule and peptide derived precursors targeting GIST biomarkers (e.g. KIT, GLP-2, NT-1, DOG-1) for the visualisation of lesions and therapy response were synthesized and are currently being tested. Standard procedures to radiolabel peptides with ^{68}Ga were developed for the synthesis of radiopharmaceuticals. A concept clinical study combining MITIGATE's developments is set to start in 2016.

ID 0109

Anti-tumor effects of Bromelain and Papain on human cholangiocarcinoma cells

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Introduction: Cholangiocarcinoma (CCC) worldwide is the most common biliary malignancy with poor prognostic value and limited treatment options. Plant extracts are gradually evolving as potential therapeutic options with potent anti-cancerous activities. Bromelain and Papain, cysteine-protease inhibitors, obtained commercially from the fruit or stem of pineapple and papaya respectively are known to have anti-cancerous effect. It is already identified that NF-κB signaling plays an important part in various types of cancers. Moreover, studies have also demonstrated that AMPK activation down-regulates NF-kB signalling. Therefore, in this study for the first time we investigated the anti-cancerous effect of both of these plant extracts (Bromelain and Papain) in CCC via inhibition of NF-kB AMPK pathway in intra- and extrahepatic human CCC cell lines (SZ-1 and TFK-1).
Methods: The effect of Bromelain and Papain on CCC cell growth, migration, invasion and epithelial plasticity was analyzed using WST-1, wound healing and invasion assay, as well as western blot.
Results: Bromelain and Papain lead to a decrease in the proliferation, invasion and migration abilities of CCC cells. We were also able to inhibit NF-kB AMPK signalling via Bromeain and Papain treatment in CCC cells. Common downstream signalling effector proteins like p-AKT, p-ERK, RAC1 etc. and notably, MMP9 expression associated with epithelial-mesenchymal transition (EMT) was also found to be effectively down-regulated upon Bromelain and Papain treatment. Interestingly, Bromelain shows an overall more effective inhibition of CCC as compared to Papain.
Conclusion: Our study demonstrates that Bromelain and Papain can effectively inihibit CCC carcinogenesis and furthermore, can evolve as promising, potential therapeutic options that might open new insights for the treatment of this deadly disease.

ID 0111

Notch and wnt-beta catenin pathways are inhibited in CD44+ gastric cancer (GC) tumor intiating cells by γ-secretase IX inhibitor

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Introduction: Gastric cancer (GC) is the second most common cause of cancer related death worldwide and new advances in GC treatment are of utmost importance. Cancer stem cells (CSCs) which might be responsible for recurrance, tumor metastasis, resistance to cancer therapy are identified and characterized in different type of GCs. Recent studies have indicated that Notch signaling is crucial for GC carcinogenesis. In this study, we focussed on inactivation of Notch in CD44+ gastric tumor initating cells using the γ-secretase inhibitor IX (GSI IX) and also higlighted on wnt/beta-catenin pathway activation, which can act as a potential feedback loop in relation to Notch activation in GC.
Methods: We have used GC cell line MKN45 in our experiments. For *in vitro* experiments proliferation, wound healing, invasion and tumorsphere assays were performed to analyse the migration, invasive and tumorogenic potential of CD44+ sorted GC initaiting cells after GSI IX treatment. Western blot analysis of downstream signaling targets of Notch and beta catenin were tested after GSI IX treatment. For *in vivo* analysis sorted CD44+ cells were subcutaneously injected into *NMRI-nu/nu* mice and were treated with vehicle or GSI IX.
Results: GSI IX treatment effectively inhibits cell growth, migration, invasion and tumor sphere formation of CD44+ tumor initiating cells. Interestingly, Notch1 was also found to be important in co-activation of Notch and wnt/beta-catenin signaling cascades in CD44+ GC cells. Therefore, GSI IX treatment effectively inhibits the concomitant activation and downstream signaling of Notch wnt/beta-catenin pathways in GC.
Conclusion: Our study highlights the correlation of Notch and wnt/beta-catenin in gastric tumor initiating CD44+ cells and its and its effective inhibition by GSI IX treatment. Therefore, GSI IX could be an excellent, alternative treatment option for human GC.

ID 0140

Taurolidine, substance 2250 and not gemcitabine display anti-neoplastic activity on pancreatic stem-cell like multicellular spheroid-cultures

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Taurolidine (TRD) is an anti-neoplastic agent showing a high anti-proliferative and death inducing effect on many tumor-cells *in vitro* and *in vivo*. Its antitumoral capacity is caused by its metabolites a.o. Taurultam (TRLT). In this study, we show for the first time that TRD and substance 2250, a new derivative of TRLT, show an anti-neoplastic effect on multicellular stem-cell like spheroid-cultures of pancreatic tumor-cell-lines. Although still an *in vitro* tumor model system, these 3-dimensional multicellular spheroids simulate the growth, micro-environmental conditions and stem-cell like characteristics of real tumors, therefore being an innovative model of intermediate complexity between the standard monolayer and tumors *in vivo*. The effect on stem cell like cancer cells within spheroid populations were monitored by the reduction of the stem cell maker CD133, by FACS. Both substances, TRD and substance 2250, were able to significantly reduce the amount of stem cell like entities in spheroid cultures. In contrast the standard therapeutical agent gemcitabine, which clearly showed anti-neoplastic activity against the bulk population of cancer cells, was not able to reduce CD133+ cells within all treated spheroid cultures. Based on the latest tumor development theories, where a tumor always consists of differentiated and non-differentiated cell types, our results point towards a new option of pancreatic cancer therapy by targeting the stem cell like population within heterogeneous pancreatic tumors. TRD and new substance 2250 could display a promising therapeutic potential against pancreatic tumor stem cells, combined with the standard agent gemcitabine, which evidently is not able to target pancreatic cancer stem cells.

ID 0148

Metabolic disorders and pancreatic cancer: High glucose promotes cancer stemness and epithelial-mesenchymal-transition via TGF-β signalling in premalignant pancreatic ductal epithelial cells

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most fatal tumor diseases with an overall 5-year survival rate of less than 5%. Diabetes mellitus, being one of the risk factors, is associated with elevated blood glucose levels. However, the mechanisms by which glucose might promote PDAC initiation are still unknown. Thus, we investigated the impact of high (25 mM) versus low (5 mM) glucose on cancer stemness, being indispensable for tumor initiation and maintenance, and epithelial-mesenchymal-transition (EMT), as a central step in dissemination, in premalignant (H6c7-kras) and malignant (Panc1) human pancreatic ductal epithelial cells.
Panc1 cells already exhibited a mesenchymal phenotype along with stem cell characteristics, being moderately affected by differing glucose levels. More pronounced effects were seen in H6c7-kras cells. Herein, high glucose clearly increased the expression of stem cell markers Nestin, ALDH1A1 as well as ABCG2 and elevated the colony formation ability. Moreover, high glucose promoted EMT indicated by elevated TGF-β1 protein level, activated Smad signalling, enhanced nuclear Slug expression, downregulation of E-cadherin and increased cell migration. Preliminary data indicate that suppression of TGF-β signalling by siRNA mediated knockdown of Smad2 reversed EMT associated alterations, decreased Nestin expression and the colony formation ability under glucose enriched conditions.
Overall, our results demonstrate that high glucose promotes EMT and cancer stemness in premalignant pancreatic ductal epithelial cells by activating TGF-β signalling. Moreover, our data reveal a mechanism by which glucose directly mediates malignancy associated alterations already in precursor cells.

ID 0162

Activation of cancer cell mediated TLR 2, 4, and 9 expression inhibits tumor proliferation and negatively influences apoptosis in pancreatic cancer

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Background: Toll like receptor (TLR) ligands are in use for cancer therapy. They are supposed to induce an inflammatory anti-tumor immune response. Several studies showed that TLRs are expressed by cancer cells themselves and that their activation can support an inflammatory microenvironment. For pancreatic cancer, TLR expression and its impact in tumor cells is only poorly understood. This study analyzed the impact of TLR2, 4, and 9 expression and activation in pancreatic cancer.
Methods: Expression of TLR 2, 4, and 9 was analyzed in pancreatic cancer cell lines BxPC-3, MIAPaca2 und PacaDD135 (qRT-PCR, Western Blot). TLR stimulation was performed using oligodeoxyribonucleotide2006 (ODN2006), lipoteichonic acid of *Staphylococcus aureus* (LTA-SA) and High-Mobility Group Box 1 (HMGB1). Activation of TLR signaling was detected by analysis for MyD88. Proliferation was investigated using MTS assay.
Results: Expression of TLR2, 4 and/or 9 was demonstrated in all analyzed human pancreatic cancer cell lines. Receptor activation by single or combined use of TLR ligands resulted in increased MyD88 expression. Additionally, up-regulated anti-apoptotic protein Bcl-2 expression was found in stimulated cells, but not in unstimulated tumor cells. Interestingly, TLR activation showed inhibitory effects on tumor cell proliferation.
Conclusion: Our results demonstrate TLR2, 4 and/or 9 expression in all human pancreatic cancer cell lines. Interestingly, our *in vitro* findings suggest chronic inflammation-mediated TLR signaling to negatively influence tumor cell apoptosis. These data emphasize the particular role of TLR2, 4 and 9 and their activation in pancreatic cancer, outlining their relevance as potential targets for cancer therapy.

ID 0170

Synergistic anti-tumor effects after combined inhibition of c-met and HER family receptors in gastric cancer cells

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Background: Medical treatment has shown limited efficacy in gastric cancer thus far. Therefore, an urgent need exists for more active drugs targeting critical oncogenic pathways. However, the effects of single molecule inhibitors are often hampered by upregulation of compensatory signaling pathways. To address this issue, our study aims at exploring synergistic anti-tumor effects by combined inhibition of c-MET and HER family receptors.
Methods: We investigated a panel of human gastric cancer cell lines exhibiting different expression levels of HER1, HER2, HER3 and c-MET, as determined by RT-qPCR. We employed receptor-specific RNAi-based knockdown as well as pharmacological inhibitors.
Results: Markedly different patterns of sensitivity against c-MET and HER family inhibition were observed between the cell lines, being largely independent of expression levels. While HER3 knockdown showed a significant growth reduction in all cell lines, HER1 and HER2 inhibition had minor effects on proliferation. Two cell lines were resistant against c-MET blockade. Interestingly, the combination of HER2 and c-MET inhibition produced a pronounced antiproliferative effect in two cell lines. Likewise, combined inhibition of HER3 + HER1 or HER2 resulted in synergistic growth reduction. In contrast, in another cell line profound growth reduction upon c-MET inhibition was observed that could be partially rescued by treatment with heregulin. Of note, in this c-MET-addicted cell line, but not in other cell lines, a profound induction of HER3 expression upon c-Met inhibition was found.
Conclusion: Gastric cancer cell lines show cell-specific redundant functions of different oncogenes. Biology-adapted combination of inhibitors may be needed to achieve optimal growth reduction in gastric cancer.

ID 0226

Development of a robust and useable readout of cytotoxic treatment effects in human gastrointestinal cancer-derived slice cultures

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Introduction: Human tumor-derived slice cultures of gastrointestinal cancers offer the potential to study treatment response and drug resistance. They can serve as a platform to gain new insights into cancer biology. Due to the underlying tumor heterogeneity and intra- as well as inter-observer variability, the reliable assessment of changes in tumor cellularity during drug exposure remains difficult. This research project seeks to define a robust readout to discriminate responders from non-responders

Methods: By comparing analysis strategies, including different pixel-based software approaches in combination with different stains for assessing tumor cellularity, proliferation, and apoptosis, we aim to find the best readout. We intend to minimize inter- and intra-observer variability by limiting the possibilities to make individual read-out adjustments. Enzyme-linked immunosorbent assays of caspase cleaved cytokeratin 18 (M30/M65 ELISA) and fluorometric assays for LDH assessment in culture supernatants are conducted to obtain additional information about cell death and the applicability in slice cultures of gastrointestinal cancers.
Results: Our pixel-based readout approach which correlates with manual cell counting and analytic assays of products of different cell processes in culture supernatants both represent promising options to analyze tissue slices.
Conclusions: We report first results of this combined-modality approach based on histological and biochemical parameters to assess the response to chemotherapy in human tumor-derived slice cultures and present this technology as a novel tool to study tumor biology. This is a first step to enable high-throughput and continuous analysis of slice cultures.

ID 0242

GPC-1 positive exosomes are ultrasensitive serum biomarkers for the non-invasive detection of early pancreatic cancer

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Introduction: Exosomes are nanovesicles of endocytic origin with a size of 50–120 nm. Their cargo includes RNA, DNA and proteins that reflect the RNA signature and mutation status of the parental cell. Exosome-bound proteins have been suggested as non-invasive biomarkers for the detection of gastrointestinal cancer.
Material and Methods: Exosomes were isolated from cancer cell cultures and analysed by mass spectroscopy. Circulating GPC1-positve exosomes were identified and isolated using FACS from cancer patients and mice with cancer. Statistical evaluation included survival analysis and ROC curve analysis.
Results: We show that GPC-1 is up regulated on tumor-derived exosomes. The fraction of GPC-1-positive exosomes correlates strongly with tumor burden and growth in several pancreatic cancer mouse models (PKT-mice und KPC-mice). In two independent cohorts, ROC curve analysis reveals that GPC-1 positive exosomes have a sensitivity and specificity of 100% to distinguish between patients with pancreatic cancer and control (healthy donors and patients with a benign pancreatic disease). This high sensitivity and specificity can be already observed in patients with early stage pancreatic cancer (carcinoma-in-situ, stage I). Moreover, GPC-1-positive exosomes tracked disease burden in post-surgically resected patients and a strong decrease of GPC-1-positive exosomes in a longitudinal cohort was associated with improved disease-specific and disease-free survival.
Conclusion: GPC-1-positive exosomes are ultrasensitive serum biomarkers for the non-invasive detection of early pancreatic cancer.

ID 0284

Intratumor heterogeneity in hepatocellular carcinoma: Impact on tumor classifications and targeted therapies

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Purpose: Intratumor heterogeneity is an emerging challenge for diagnostic and therapeutic decisions in many solid cancers. In hepatocellular carcinoma (HCC), the 2nd most common cause of cancer-related death worldwide, morphological tumor heterogeneity is well-known to surgical pathologists, but has not been systematically analyzed. This study aimed to investigate phenotypic intratumor heterogeneity (i.e. morphology, immunohistochemistry) in conjunction with clonal (genetic) diversification of the tumor cells.
Methods: In a comprehensive analysis of 23 treatment-naïve HCC, a total of 120 tumor areas were defined. Analyzed were tumor morphology (growth patterns, cytology) and the expression of the liver cell markers CK7, CD44, AFP, EpCAM and glutamine synthetase. Genetic heterogeneity was determined by multiregional sequencing of the two most important HCC driver genes (*TP53* and *CTNNB1*), using Sanger and next generation sequencing.
Results: Overall, intratumor heterogeneity was detectable in the majority of HCC cases (20/23, 87%). Heterogeneity solely on the level of morphology was found in 6/23 cases (26%), morphological heterogeneity combined with immunohistochemical heterogeneity in 9/23 cases (39%). Heterogeneity of morphology, immunohistochemistry in conjunction with differing mutational status of *TP53* or *CTNNB1* was detected in 5/23 cases (22%).
Conclusions: Our findings demonstrate that intratumor heterogeneity is frequently found in hepatocellular carcinoma. As a consequence for daily practice, single tumor biopsies might not sufficiently represent molecular characteristics of the whole tumor. Intratumor heterogeneity challenges HCC classifications based on *TP53/CTNNB1* mutational status and might contribute to drug resistance and treatment failure.

ID 0286

Intrahepatic and Extrahepatic Cholangiocarcinoma Cell Lines Differ in Proportion of Tumor Stem Cells and Response to Notch-Inhibitors

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Introduction: Intrahepatic (IH-CC) and extrahepatic (EH-CC) cholangiocarcinomas show an unfavorable diagnosis and a markedly poor response against conventional therapies. Cells with stem cell properties are crucial for the malignant potential of the tumor. Targeted therapies against embryologic signaling pathways could therefore offer new therapeutic options. As the Notch signaling pathway plays a pivotal role in tumor formation in CC, we studied the therapeutic effect of Notch inhibitors in IH-CC and EH-CC with focus on the tumor stem cell fraction.
Material and Methods: The side population (SP) of EH-CC (TFK1, EGI1) and IH-CC (HuCCT1, RBE) cell lines was determined using Hoechst 33342 and CD44 staining . The therapeutic effect of gemcitabine and GSI (mono-/or combination therapy) was determined via XTT Assay.
Results: EH-CC cell lines displayed and significantly lager proportion of SP cells (3.58% vs. 1.10%, $p < 0.0001$) and showed significantly less CD 44 positive cells (45.38% vs. 99.85%, $p < 0.0001$). Gemcitabine and GSI showed a significant therapeutic effect on TKF1, EGI1 and RBE ($p < 0.03$) whilst HuCCT1 showed no response to therapy. The SP fraction of EH-CC cell lines decreased significantly when treated with gemcitabine and GSI simultaneously ($p < 0.006$) whilst IH-CC SP cells showed no response. SP

cells did not respond to monotherapy with GSI. None of the therapeutic agents had an effect on the expression of CD44.
Conclusion: EH-CC and IH-CC differ remarkably regarding their proportion of tumor stem cells, phenotype and response to Notch-Inhibitors. Due to the role of stem cells in chemotherapy resistance, a differential treatment of these tumor entities may be required.

ID 0290

Metastatic Pancreatic Carcinoma: Observational Registry Study on Quality of Life and Molecular Biology of Patients Receiving Nab-paclitaxel/Gemcitabine First Line Therapy – A Study in Progress Report

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Introduction: Current studies resulted in a superiority of a combination of nab-paclitaxel/gemcitabine vs. gemcitabine mono therapy. There is no sufficient data available yet on the quality of life (QoL) of patients (pts) under this combination therapy and there is high need to identify predictive and prognostic markers. In the framework of a multicenter registry study (QoliXane), detailed QoL-data are now being collected and compared to existing data on gemcitabine mono therapy. Moreover, paraffin embedded tissues are collected for molecular analysis.
Methods: QoL will be assessed by the EORTC-QLQ-C30 and an additional questionnaire focusing on pts worries regarding risk of progression and side effects. Primary endpoint is the proportion of pts with maintained Global Health Status/QoL at 3 months. Secondary endpoints are QoL at different time points, efficacy (also in special subgroups of pts with high bilirubin levels), safety and the identification of predictive and prognostic factors. 600 pts shall be enrolled at 80 sites.
Pts with metastatic pancreatic cancer are enrolled if they had no prior treatment in the metastatic stage and a combined treatment with nab-paclitaxel/gemcitabine is planned. QoL and observational data will be collected once a month over a 6-month period. Paraffin embedded tissues are collected.
Results: Recruitment started in late 2014. 150 pts were enrolled by 08/2015. A descriptive interim analysis of all pts with at least 3 cycles will be conducted regarding pts characteristics and the additional questionnaire by December 2015.
Conclusions: QoliXane is a trial in progress with limited effort for the local investigators and large potential to close an information gap within a highly important setting.

ID 0320

Correlation between abdominal wall desmoids and protective ileostomies: Should a routine-ileostomy be avoided in FAP patients?

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Purpose: Desmoid tumours are typically triggered by surgical intervention and cause significant morbidity and mortality. Considering this well-established correlation between surgical trauma and desmoid growth, we investigated the impact of loop-ileostomy construction and closure and abdominal wall desmoids.
Methodology: All patients with classical FAP that were treated with a prophylactic proctocolectomy and ileoanal pouch anastomosis in the time period 10/2005 to 10/2011 were included in this study. A minimal follow-up of 12 months after a loop-ileostomy closure was required.
Results: A total of 115 patients were included (52 males). 97 patients received a loop-ileostomy. Of these 21 developed an abdominal wall desmoid at the ileostomy site (mean interval 16±4 months) - 11 patients additionally developed mesenteric desmoid disease. None of the remaining 18 patients without an ileostomy developed an abdominal wall desmoid tumour, but 5 developed mesenteric desmoid tumour.
All 21 patients with an abdominal wall desmoid after ileostomy closure received conservative therapy with high-dose tamoxifen (120mg daily) and sulindac (300mg daily) following diagnosis. Despite immediate treatment 18 patients showed rapid progression and 3 patients suffered serious desmoids-related complications; two cases of bowel obstructions and one enteric fistula.
Conclusion: We have demonstrated, that there is a correlation between construction of a protective loop-ileostomy at the time of pouch surgery and the occurrence of abdominal wall desmoids. Taking the morbidity of the condition into account in this young patient group, we suggest that when technically feasible, construction of a protective loop ileostomy should be avoided.

ID 0333

Nab®-paclitaxel plus gemcitabine in subjects with advanced pancreatic cancer who have cholestatic hyperbilirubenemia secondary to bile duct obstruction

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Introduction: The combination nab-paclitaxel/gemcitabine is one standard of care for palliative first-line therapy in patients (pts) with advanced pancreatic adenocarcinoma (APC). The aim of this investigation was to evaluate the safety, feasibility and efficacy of this combination in pts with elevated bilirubin (bil) levels treated in a compassionate use setting.
Methods: Pts with APC treated at our institution with nab-paclitaxel (100mg/m² or 125mg/m²) and gemcitabine (1g/m²) between June 2012 and June 2015 were analysed with regard to several parameters like bil levels, stents, primary cancer resection, gender, treatment, (non)-haematological toxicities and overall survival. Pts were primary divided into 5 groups (gr.) according the bil level (gr.1: bil 1.2-1.5xULN, n = 7; gr.2: bil >1.5-2xULN, n = 7; gr.3: bil >2-3xULN, n = 3; gr.4: bil >3-5xULN, n = 3; gr.5: bil >5xULN, n = 10).
Results: 30 pts with median age of 62 [42-78] years were retrospectively analysed. 3 pts (10%) underwent primary surgical resection, 13 (43%) had stent implantation. 26 pts (87%) had metastases at the time of diagnosis. Median treatment duration was 20 [1-442] days. Nab-paclitaxel was 1st/2nd line therapy for 10 pts (33%) respectively, 3rd line for 6 (20%) and 4th line for 4 pts (13%). 27 pts (90%) were treated in last line therapy. Median OS (mOS) was 11.2 [95%CI: 6.5-16.7] months (m). According the subgroups the mOS was for gr.1: 8.8m, gr.2: 21.9m, gr.3: 12.1m, gr.4: 13.0m and gr.5: 6.5m. MOS from the last application of nab-paclitaxel for groups 1-5 was: 1.3m, 1.0m, 0.7m, 0.9m, and 0.9 months respectively.
Conclusions: Adapted nab-paclitaxel/gemcitabine dosage treatments in those pts seem to be feasible but should be given with caution on an individual basis.

ID 0367

Fendiline reduces caveolin1 concentrations and inhibits proliferation of pancreatic ductal adenocarcinoma cells.

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Caveolin1 (CAV1) is a 22 kda protein present in caveolae, its role in tumor development has been controversial as it may act as a tumor suppressor gene in some cancers while in pancreatic ductal adenocarcinoma (PDAC) it increases tumor progression. Fendiline, a Ca^{2+} channel blocker, has shown antitumor activity. Here, we studied the level of expression of CAV1 in BXPC3 PDAC cells and the effect of its knockdown by siRNA to identify its function among cellular properties. The influence of fendiline on CAV1 was also examined. Methods included gel electrophoresis to show the level of expression of CAV1 in human BXPC3 cells. Downregulation of CAV1 was done by gene specific siRNA and the effect on mRNA was confirmed by real time PCR. Functional effects of inhibiting the CAV1 gene were examined by MTT and scratch assays. The effect of fendiline on CAV1 expression was tested by western blot using IC25, IC50 and IC75 concentrations. At mRNA and protein levels, CAV1 was highly expressed in BXPC3 cells. Knockdown of CAV1 caused about 80% reduction in CAV1 expression as determined by real time PCR for 24, 48 & 72 hours. A by >15% decreased proliferation and no change in migration were observed following the knockdown of CAV1. Fendiline decreased the proliferation of BXPC3 cells concentration dependently. The respective IC50 was 7 µM. Concentrations of fendiline ranging from IC25-IC75 caused a significant decrease in the CAV1 protein concentration. In conclusion, the high expression of CAV1 is a new feature in pancreatic cancer cell lines which may contribute to progression of pancreatic cancer and CAV1 inhibition causes reduced proliferative activity. Fendiline causes also reduced expression of cav1 and this might be a reason for its antiproliferative effect.

ID 0384

CRS and HIPEC for patients with peritoneal metastases of gastric cancer

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Introduction: Patients with peritoneal metastases of gastric cancer have poor prognosis with a median survival time of 7 months. Cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) showed major improvement in survival in a selected group of patients. The aim of this study was to investigate the impact of CRS and HIPEC on morbidity and survival.
Material and Methods: This retrospective analysis of prospectively collected data includes all patients with peritoneal metastases of gastric cancer treated with CRS followed by HIPEC (60min, mean temperature 41°C) at our center between 01/2008 and 03/2015 (n = 41). The mean age was 55.1 (SD 10.2) years with a mean BMI of 25.5 (SD 5.1). 40 (97%) patients received preoperative systemic chemotherapy.
Results: Overall morbidity was 29% and one patient died within the hospital stay (mortality: 2%). 7 patients (17%) developed surgical complications as anastomotic leakage (n = 2), burst abdomen (n = 2), wound healing deficit (n = 5), fistula of the pancreas (n = 2) intraabdominal abscess (n = 2) and postoperative hemorrhage (n = 1). The mean operation time was 371 (SD 138) minutes with a mean blood loss of 679 (SD 488) ml. Mean follow up was 12 months, median survival of the patients was 11 months. Our study confirmed PCI <13 (13 vs. 7 months; p = 0.03) and CCR0 (16 vs. 7 months; p = 0.04) as relevant predictive factors of higher patient survival.
Conclusions: CRS and HIPEC showed positive results in selected patients with peritoneal metastases of gastric cancer. The rate of severe complications and in hospital mortality was acceptable. The impact of HIPEC in addition to cytoreductive surgery will be evaluated by the ongoing GASTRIPEC study.

ID 0428

Elevated interferon-induced protein with tetratricopeptide repeats 3 (IFIT3) is a poor prognostic marker in pancreatic ductal adenocarcinoma

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Aims: Pancreatic cancer, characterized by a high mortality, rapid progression, and resistance to chemo and radiation therapy with only around 5% survival rate beyond five years after initial diagnosis. Interferon-induced protein with tetratricopeptide repeats 3 (IFIT3) gene is among hundreds of IFN-stimulated genes. We have found that overexpression of IFIT3 enhances tumor biology of the PDAC cells. However, the clinical relevance of IFIT3 is not yet known in pancreatic cancer. We will analyze the prognostic significance of this gene in this tumor entity.
Methods: To evaluate the clinical relevance, we applied tissue microarray (TMA) analysis by performing an immunohistochemical assessment of IFIT3 in surgical samples from total 274 consecutive patients affected by pancreatic adenocarcinoma. The prognostic significance of IFIT3 staining intensity for was evaluated.
Results: In PDAC tissues, 20.8% was IFIT3 negative expression while 46.4% case displayed weak expression and 32.9% of patients showed middle or high expression. The PDAC patients with high expression of IFIT3 statistically linked to higher staging and with shorter survival (p = 0.042) Multivariate analysis showed that pathological stage and grading and IFIT3 over-expression were statistically associated with poor prognosis. Particularly, in pN1 patients, we found a same incidence of IFIT3 expression with survival (p = 0.035) but not in pN0 patients (p = 0.323). In PDAC patients with chemotherapy, survival analysis data displaying a better prognosis in low expression of IFIT3 indicated a positive therapy response (p = 0.020). Therefore, high expression of IFIT3 was independently correlated to shorter patient survival and could serve as a prognostic marker.

ID 0430

Evolution of laparoscopic liver surgery as standard procedure for HCC in cirrhosis

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Patients with HCC in cirrhosis have an increased risk for postoperative complications including liver failure. However, there is some evidence, that the use of laparoscopy markedly decreases this risk.
Patients: Between 2010-2015 a total of 21 laparoscopic liver resections were performed for HCC in Child A cirrhosis at our center. Mean MELD-score was 9 (6–12), mean LiMAx 278 µg/h/kg (101-489). All resections were performed by conventional laparoscopy using 4-5 trocars. Liver parenchyma was transected using ultrasonic shears. Hilar occlusion was used on demand. In the earlier years laparoscopic resections were per-

formed occasionally and mainly if tumors were easily accessible. With an increasing experience, currently most HCC in cirrhosis are resected laparoscopically. Likewise 12 out of the 21 resections were performed within the last 12 months including two anatomic left hemihepatectomies.
Results: Conversion rate, postoperative mortality and operative revision rate were all 0%. Four patients (19%) developed mild complications Clavien-Dindo grade 1 or 2 (ascites, transfusion, pneumonia, renal impairment). One patient (4,8%) developed a grade 3 event (bile leak, percutaneous drainage). All but one early patient underwent R0 resection (95%). The mean duration of hospital stay was 10,5 days (5-21), the mean duration of ICU-stay 1,8 days (1-7). No case of decompensation of liver cirrhosis was observed.
Conclusion: Even in patients with severely impaired liver function no severe complications and especially no decompensation of cirrhosis was observed. Therefore, in accordance with other single center experiences liver resection for HCC in cirrhosis should be performed preferentially by laparoscopy.

ID 0435

Identification of pancreatic cancer related genes and miRNAS during the metastasis process in the rat liver

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Introduction: Pancreatic ductal adeno carcinoma (PDAC) invasion and metastasis are the most life-threatening aspects of this disease. Local invasion, cancer growth crossing the organ boundaries and along the nerve sheaths, as well as lymphatic and hematogenic spread, make liver the most affected organs in PDAC.
We hypnotized that identifying new genes and miRNAs that are modulated at the different colonization stages can be useful for better understanding of the metastasis process, as well as instrumental for new diagnostic approaches.
Material and Methods: To establish suitable metastasis model, PDAC rat ASML cells were injected into the liver of BDX rats.
The growing cells were then re-isolated after different time points of liver colonization.
The total mRNA and miRNA of these samples was used to evaluate expression profiles of more whole known genes and miRNA during this process
Results: Depending on the colonization time in the rat liver, 7 to 15% of all known genes were deregulated.
The analyzed miRNAs exhibited differential modulation pattern at different colonization period. During day 3, 6, 15 and 21, it was evident that 23, 14, 11 and 19 miRNAs respectively, were differentially modulated.
At day three, 10 miRNAs were down regulated and 13 up regulated. At day six, 6 miRNAs were down regulated and with 9 being up regulated. At day fifteen, 3 miRNAs were down regulated and 7 up regulated. And at day 21, 16 miRNAs were up regulated and only 2 of them up regulated.
Conclusion: We hypothesize that targeting the modulated genes and miRNAs could improve the survival of PDAC patients.
Further investigations are needed to evaluate this possibility and analyze the relation between the modulated genes and miRNA.

ID 0525

Sorafenib and Oleanolic Acid – a promising approach to overcome chemotherapy resistance in Hepatocellular Carcinoma (HCC)

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Background: Hepatocellular carcinoma (HCC) is the most common liver tumor. The chemotherapy resistance of HCC and the dose-dependent liver toxicity of the only routinely used palliative chemotherapy with Sorafenib are still an unsolved problem highlighting the need to develop novel therapeutic strategies.
Methods: Human HCC cell lines were treated with sub-toxic concentrations of Sorafenib and the triterpenoid Oleanolic acid (OA). Cell viability and cell death were evaluated by MTT test and DNA fragmentation (flow cytometry). For mechanistic studies we performed a caspase activity assay, ROS staining and we used different inhibitors of cell death target proteins and ROS-scavengers.
Results: Here, we identify a novel synergistic induction of cell death by the combination of Sorafenib and OA. Importantly, Sorafenib and OA cooperate to suppress short-term as well as long-term clonogenic survival. Mechanistic studies show that Sorafenib/OA cotreatment leads to DNA fragmentation and caspase-3/7 activation, suggesting apoptosis as the dominating mechanism of cell death. The pan-caspase inhibitor zVAD.fmk revealed a cell type-dependent requirement of caspases for Sorafenib/OA-induced cell death. Notably, the significant ROS production caused by the cotreatment and the complete rescue from Sorafenib/OA-triggered cell death by the addition of ROS scavengers indicating that ROS production contributes to Sorafenib/OA-induced cell death. In further studies the Sorafenib/OA cotreatment does not primarily engage necroptotic cell death or ferroptosis.
Conclusion: In conclusion, cotreatment of Sorafenib and OA represents a novel approach to induce cell death in HCC and may allow a significant reduction of the concentration of Sorafenib. These promising results require further studies.

Genitourinary Cancer including Prostate Cancer

ID 0019

HYAL-1 hyaluronidase inhibitor sHA8k – a potent inhibitor of bladder cancer

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Objectives: HYAL-1, a tumor cell-derived hyaluronidase, degrades hyaluronic acid (HA) into angiogenic fragments and promotes tumor growth and metastasis. Small molecular mass sulfated HA derivatives (sHA8k) inhibit HYAL-1. We evaluated antitumor activity of sHA8k and mechanism of action in BCa models.
Methods: Cell counting, Cell Death ELISA kit, Matrigel invasion and Boyden chamber assays were used to examine the effect of sHA8k on cell proliferation, apoptosis and invasive activity in BCa cells (253J-Lung, HT1376, UMUC-3, T24, RT4). Effect of sHA on signaling, apoptosis cascade, HA receptor (CD44, RHAMM) and EMT markers (b-catenin, E-cadherin, Snail, Twist) was evaluated by qPCR and immunoblotting. Mechanism of action was analyzed by adding angiogenic fragments and

performing mAkt transfection. Athymic mice bearing 253J-Lung xenografts were treated with sHA by i.p. injection.
Results: Proliferation, motility and invasion of BCa cells that expressed HYAL-1 was inhibited by sHA8k. At IC50 for HAase activity inhibition (~20µg/ml), sHA induced >3-fold apoptosis and inhibited invasive activity of BCa cells. Caspase-3,-8,-9 activation and up-regulation of Fas, Fas-L, FADD, DR4, DR5 and E-cadherin was induced by sHA8k. It downregulated CD44, RHAMM, bcl-2, phospho(p)-Akt, pGSK3β, pβcatenin(ser552), Snail and Twist expression. Angiogenic HA fragments or overexpression of mAkt attenuated sHA8k effects. CD44 and RHAMM downregulation mimicked sHA8k effects. Xenograft growth was significantly inhibited by sHA. Majority of animals did not form palpable tumors at 50mg/kg dose. No weight loss or serum/organ toxicity was observed.
Conclusion: This study shows that sHA8k is a potent inhibitor of BCa.
Support**:** R01CA72821-14(VBL)

ID 0024

Ansprechen von Patienten mit fortgeschrittenem Urothelkarzinom auf eine Behandlung mit Vinflunin nach vorhergehender platinbasierter Chemotherapie: Welchen Einfluss hat die Tumorlokalisation ?

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Fragestellung: Das Ergebnis einer Chemotherapie bei Patienten mit metastasierendem Urothelkarzinom (UC) des oberen Harntrakts (UT) gilt allgemein als schlechter im Vergleich zur Blase. Es liegen nur wenige prospektive Daten zum Ansprechen auf ein Zytostatikum bei UTUC vor. In diesem Artikel werden Daten aus einer nicht-interventionellen Studie bei Patienten mit UTUC und UC des unteren Harntrakts (LTUC) vorgestellt, die nach Versagen einer platinbasierten Chemotherapie mit Vinflunin behandelt wurden.
Methoden: Bei mit Platin vorbehandelten Patienten mit UC (39 Zentren) mit Vinflunin behandelt wurden, wurden prospektiv Daten erhoben. Dosierung von Vinflunin, Tumorbeurteilung und Begleitmedikation erfolgten nach der üblichen ärztlichen Praxis.
Ergebnisse: Von den 77 an der Studie teilnehmenden Patienten war das Urothelkarzinom bei 18 (23%) im oberen Harntrakt und bei 59 (77%) im unteren Harntrakt lokalisiert. Der Performance Status war in beiden Gruppen vergleichbar (Karnofsky Index 83.9% gegenüber 83.7%). Die Patienten mit UTUC waren im Durchschnitt vier Jahre älter (68.2 gegenüber 64.4 Jahre) Die Haupttoxizitäten Grad 3/4 in der Gesamtpopulation von UTUC- und LTUC-Patienten waren Leukopenie 16.9/27.8/13.6%, Anämie 6.5/5.6/6.8%, erhöhte Leberenzyme 6.5/5.6/6.8% und Obstipation 5.2/0/6.8%. In Bezug auf die Gesamtansprechrate (22.2% vs. 23.7%), Disease Control Rate (50.0% vs. 54.2%) und progressionsfreie Überlebenszeit (2.76 [KI 1.38-8.28] Monate vs. 2.76 [KI 2.27-3.38] Monate) war die Wirksamkeit in der UTUC- und der LTUC-Gruppe vergleichbar.
Schlussfolgerungen: Diese prospektive Studie bestätigt, dass Vinflunin in der Routinepraxis einen bedeutenden Nutzen mit gutem Sicherheitsprofil bei Patienten mit fortgeschrittenem/ metastasierendem Urothelkarzinom sowohl des oberen wie des unteren Harntrakts bietet, die zuvor eine platinbasierte Behandlung erhalten hatten. Diese Ergebnisse sprechen für die weitere Anwendung von Vinflunin bei Patienten mit Urothelkarzinom des oberen Harntrakts.

ID 0071

Decision making in metastatic renal cell cancer. A retrospective analysis of predictive factors for application of 2nd line therapy

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Background: Targeted therapies are the mainstay of medical treatment in metastatic renal cell carcinoma (mRCC) and achieve an overall survival (OS) of 30 months in contemporary series. Because less than 50% of patients receive 2nd line therapies, the choice at each line of treatment remains an important issue in mRCC. We therefore sought to determine clinical predictive factors for the application of 2nd line therapy.
Methods: A random sample of 161 patients treated for RCC between 2005 and 2012 at our institution was identified by retrospective chart review and included. Treatment and therapy monitoring was applied according to institutional standards. Clinicopathologic data was evaluated Chi-square or Fisher's exact tests. Continuous parameters were compared applying the Mann-Whitney test. Survival analysis was conducted using Kaplan-Meier analysis, univariate and multivariate cox regression analysis.
Results: 105 (65%) patients received 2nd line therapies, whereas 56 (35%) did not. There was no significant difference between clinical baseline parameters between patients who either did or did not receive 2nd line therapies. Patients with early progression were numerically higher in patients without 2nd line therapy (27% vs. 22%, respectively, p = 0.063), while more patients who received 2nd line were treated for more than 6 mo. in first line (44 vs. 21%; p = 0.063). 3-year OS was superior in patients with 2nd line treatment (71% vs. 47,6%; p = 0.007). In univariate analysis ability to receive 2nd line therapy was associated with a significantly better outcome (HR 1,75; p = 0,008).
Conclusion: The major limitations of our analysis are it's retrospective nature, small sample size and missing values. Predictive baseline characteristics for use of 2nd line therapy could not be identified. 2nd line therapy was given irrespective of MSKCC risk category, but early progression was seen more frequently among patients without 2nd line treatment. Improvement for 3-year-OS was detected in patients who were eligible for a 2nd line therapy, underscoring the relevance of continuous treatment in RCC.

ID 0081

The Treatment Reality of Octogenarians with Bladder Cancer in a Maximum Care Hospital

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Introduction: The incidence of urothelial carcinoma of the bladder (UCB) increases with age and reaches its maximum in patients aged ≥80 years. With the increasing life expectancy of western societies, the curative treatment of this patient population therefore becomes more important. In our study we present the treatment situation of octogenarians with UCB at a maximum care hospital.
Materials and Methods: 276 octogenarians with UCB treated at the University Hospital of Erlangen between 1982 and 2011 have been retrospectively analyzed regarding their treatment.
Results: 146 patients (52.9%) had superficial tumors (pTa, pT1, CIS), 71 patients (25.7%) had muscle-invasive bladder cancer (MIBC) (pT2-T4). There was no data on tumor-stage for 59 patients (21.4%).
Most of the patients with superficial bladder cancer were treated with transurethral resection of the bladder (TURBT) followed by regular follow-up in 58.2% of the cases (85 of 146 patients). 26% of the patients (38 of 146 patients) obtained an intravesical therapy with either Mitomycin or BCG, 13 patients (8.9%) were treated with radiochemotherapy, 6 patients (4.1%) were treated with radiotherapy, 2 patients (1.4%) received systemic chemotherapy and 2 patients (1.4%) received a cystectomy.

Patients with MIBC received TURBT alone in 54.9% (39 of 71 patients), one patient obtained systemic chemotherapy only. 43.7% of the patients with MIBC (31 of 71 patients) received a potentially curative therapy. Out of these, 51.6% (16 of 31 patients) received radiochemotherapy, 29.0% (9 of 31 patients) received radiotherapy and 19.4% (6 of 31 patients) received a cystectomy. In Kaplan-Meier analysis patients with MIBC showed a better outcome at curative treatment compared to TURBT alone (median overall survival 28 months vs. 9 months; $p < 0.001$, Log Rank test).
Conclusion: By offering a wide range of treatment options, 43.7% of octogenarians with MIBC can be treated with a curative therapy at a maximum care hospital.

ID 0099

3-Year Follow-up of Chemotherapy Following Radium-223 Dichloride (Ra-223) in Castration-Resistant Prostate Cancer (CRPC) Patients (Pts) With Symptomatic Bone Metastases (Mets) From ALSYMPCA

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Background: Ra-223 prolongs overall survival (OS), whether administered with prior or no prior docetaxel treatment (tx). Chemotherapy (chemo) after Ra-223 tx was safe and well tolerated. These current post hoc analyses evaluated chemo after ALSYMPCA study tx, including an additional 62 pts and a more extensive analysis of 3-year follow-up data.
Materials and Methods: The analysis includes ALSYMPCA pts who had chemo following study tx (Ra-223 or placebo [pbo]). Chemo agents were identified, and time from last study tx to start of chemo and its duration were calculated. OS was analyzed, and hematologic (heme) safety based on lab values reviewed.
Results: 142/614 (23%) Ra-223 and 64/307 (21%) pbo pts had chemo following study tx, including an additional 52 Ra-223 and 10 pbo pts from time of preliminary analysis in 2012. Most common chemo agents were docetaxel (100 [69%] Ra-223, 46 [72%] pbo) and mitoxantrone (23 [16%] Ra-223, 13 [20%] pbo). Median time to chemo was 35 days longer after Ra-223 (115 d) vs pbo (80 d). Median chemo duration was longer with Ra-223 (141 d) than with pbo (127 d). Median total daily docetaxel dose was lower with Ra-223 (93 mg) than with pbo (120 mg). Percentages of Ra-223 vs pbo pts with grade 3/4 heme values were 9/116 (8%) vs 2/49 (4%) for hemoglobin; 11/114 (10%) vs 1/48 (2%) for neutrophils; and 1/116 (1%) vs 0/49 (0%) for platelets. Heme lab measurements over time are quite similar. Median OS from start of chemo was 16 months following Ra-223 and 15.8 months following pbo. Similar proportions of Ra-223 pts (41/142 [29%]) and pbo pts (21/64 [33%]) died during and 30 days after chemo; most common cause was prostate cancer-related death, in 37/41(90%) Ra-223 and 20/21(95%) pbo pts.
Conclusions: In this post hoc analysis with up to 3 yr follow-up, pts receiving chemo following Ra-223 have OS and heme safety profiles similar to those of pts receiving chemo after pbo.

ID 0100

Phenotype plasticity may contribute to cisplatin resistance of urothelial carcinoma cell lines

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Objective: Although initial responses of urothelial carcinoma (UC) to standard cisplatin-based chemotherapy are frequently observed, most patients will recur with cisplatin-resistant relapses. In this study, it was investigated whether phenotypic plasticity, especially as epithelial-mesenchymal transition (EMT), may contribute to cisplatin-resistance.
Methods: Seven cisplatin-resistant UCC sublines were selected by long-term drug treatment (LTT) with escalating doses. Sensitivity towards cisplatin and cell cycle distribution were evaluated by MTT assay and FACS analysis, respectively. Phenotypical changes were molecularly followed by expression analysis (qRT-PCR, immunofluorescence, reporter assay) of EMT markers and WNT-target genes.
Results: LTT-UCCs grew generally more slowly, but with a similar cell cycle distribution as their parental cell lines. They displayed significant phenotypic plasticity indicated by increases in mesenchymal (Vimentin) and decreases in epithelial markers (E-Cadherin). In addition to EMT markers (Zeb1, Twist), WNT-pathway target genes (ß-catenin, Axin-2, Cyclin-D1, c-myc, Pitx2) were induced. However, a reporter assay (TOPflash/FOPflash assay) revealed only moderate activation of nuclear WNT signaling and the WNT signaling inhibitor niclosamide did not revert resistance.
Conclusion: Morphological changes indicative of EMT were observed in cisplatin-resistant UCCs selected by escalating doses of cisplatin. Although overexpression of some WNT-target genes was observed, EMT is likely not WNT-dependent. Our findings indicate that UCCs cells are capable of substantial phenotypic plasticity that may significantly contribute to the emergence of cisplatin resistance.

ID 0119

Effects of concomitant use of abiraterone and/or enzalutamide with radium-223 on safety and overall survival in metastatic castration resistant prostate cancer (mCRCP) patients treated in an international early access program (EAP)

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Background: Here we present data on Ra-223 with concomitant abiraterone (Abi) and/or enzalutamide (Enza) from EAP pts recruited in 14 countries (Europe, Canada and Israel).
Methods: The EAP was a prospective phase IIIb study of mCRPC pts with symptomatic or asymptomatic bone metastases (no visceral disease). Pts received Ra-223 50 kBq/kg (iv injection) every 4 weeks for 6 cycles. Concomitant treatment was defined as any agent given after the first Ra-223 injection or prior to Ra-223 initiation and continued during Ra-223 treatment. Effects of concomitant Abi or Enza on OS and safety were investigated.
Results: Of 696 pts treated with Ra-223, 154 (22%) received concomitant Abi, 50 (7%) Enza and 15 both Abi and Enza; a total of 189 pts (27%) received Abi and/or Enza (Abi/Enza). 277 (40%) and 56 (8%) pts had

received Abi or Enza prior to Ra-223, respectively. 75% of pts receiving concomitant Abi/Enza and 54% receiving Ra-223 alone had received prior docetaxel. From the first Ra223 injection, median time on concomitant Abi or Enza was 24.9 and 15.5 weeks, respectively. . Median OS was not reached in the concomitant groups vs 13 mos in the Ra-223 alone group. In the concomitant treatment groups AE rates were comparable with the Ra-223 alone group. Grade ≥3 hematological AEs in the concomitant Abi/Enza vs Ra-223 alone group included anemia, (12% each), thrombocytopenia (1% vs 3%), leukopenia (1% vs <1%), and neutropenia (1% each). Grade 3/4 diarrhea was reported in <1% of pts in the concomitant Abi/Enza and Ra-223 alone groups.
Conclusions: Pts receiving Abi/Enza with Ra-223 had a longer OS compared with Ra-223 alone, suggesting that this combination may be more effective than Ra-223 alone. The safety profile was comparable between pts with or without concomitant Abi/Enza with no new toxicities reported. These findings require further confirmation and are currently being assessed in a randomized, phase III clinical trial.

ID 0121

Stage adapted indications for and complications of nephron-sparing surgery in renal cell carcinoma patients. A single-center analysis over a 13-year period in the context of changing guidelines.

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Over the past years the guidelines for localized RCC have changed; the indication for partial nephrectomy(PN) has been extended considerably. There is still a lack of information whether the use of PN has increased accordingly. In this monocentric analysis the indications for nephron sparing surgery and the complications of PN and radical nephrectomy (RN) over a 13 year period were evaluated.
The retrospective database analysis assessed all patients (185 PN, 533 RN) operated on for a renal mass from 2001 to 2013. We collected relevant demographic and histopathological data, risk factors (smoking, diabetes, cardiovascular disease, hypertension and body mass index), length of stay, duration of surgery and complications.
From 2001 to 2013 the percentage of nephron-sparing surgery has increased from below 20% to over 35%. Among the patients with T1a tumor-stages nephron sparing surgery increased from almost 50% to over 90%. Risk factors were comparable in both groups. The most common histological subtype of RCC in our patients was clear cell carcinoma (73,4%). The median length of hospital stay showed no significant difference (10 days in both groups). Transfusion rate (RN 29,3% vs. PN 11,4%; p = 0,001) and the incidence of pleura lesions (RN 4,7% vs. NSS 0,5%; p = 0,009) were significantly higher in the nephrectomy cohort. Every tenth patient (10,2%) undergoing PN experienced urinary leakage (UL). The incidence of UL is significantly higher in advanced tumors (T1a 5,7% vs. T1b-T2 25%; p = 0,002).
In the last years partial nephrectomy has become the method of choice for localized renal tumors. Comparing PN and RN, we found a higher transfusion rate and more pleura lesions in the RN cohort. However, UL is a specific complication of PN and its incidence increases with tumor size. Our results support the guidelines for localized renal cell carcinoma.

ID 0210

Trials in progress: SCOPE – an international, prospective, non-interventional trial to evaluate the influence of the therapy sequence in patients with metastatic castration resistant prostate cancer (mCRPC) treated with Cabazitaxel

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Introduction: Although different systemic treatment options are available for men with mCRPC, only limited data exist regarding optimal sequencing of these drugs. Retrospective studies suggest that post-Docetaxel, the sequence of Cabazitaxel followed by an androgen receptor (AR) targeted agent may be associated with a longer survival than the inverse sequence. SCOPE, an international, prospective, non-interventional trial, will evaluate the influence of treatment sequences in which Cabazitaxel is applied on the therapeutic outcome in clinical routine.
Methods: The SCOPE trial will be conducted in 300 centers in Germany, Austria and Switzerland with a total of 900 planned patients, starting in summer 2015. Patients with mCRPC who are intended for Cabazitaxel treatment and are pretreated with Docetaxel will be observed. The primary objective is to evaluate the impact of treatment sequence on progression free survival (PFS) with Cabazitaxel, as assessed by the investigator. The analysis will focus mainly on the following two sequences: 1. Docetaxel pre-treatment followed directly by Cabazitaxel (continuous taxane-therapy sequence), 2. Docetaxel followed by an AR-targeted or other therapy prior to Cabazitaxel (intermittent taxane-therapy sequence). Secondary endpoints include PSA response, time to PSA progression with each therapy, number of Cabazitaxel cycles received, overall survival and safety.
Conclusion: SCOPE aims to analyze and compare outcomes for different sequences in which Cabazitaxel is used in daily clinical practice to gather insight into the best treatment sequence according to patient and tumor characteristics.
This study is funded by Sanofi

ID 0254

The current value of radical prostatectomy (RP) – data from the urological early rehabilitation (n = 3574)

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Introduction: We analysed the current oncological and functional outcome as well as the psychological distress of patients after RP.
Material and Methods: 3574 inpatients underwent an early rehabilitation (3-4 weeks) after RP between 3/2013 and 8/2014: at the start (T1) and at the end (T2) of rehabilitation urinary loss (24-h-pad-test) and psychological distress (FBK-R10) was measured. The patients were compared and divided in age groups.
Results:
<60 years:
pT3 in 30.0%, R1 in 20.3%, GS>7 in 13.8%, 166g urinary loss (T1), FBK-R10 (T1):14.6
60 to 69 years:
pT3 in 35.3%, R1 in 20.9%, GS>7 in 16.5%, 274g urinary loss (T1), FBK-R10 (T1): 12.0
>69 years:
pT3 in 43.8%, R1 in 25.1%, GS>7 in 25.1%, 379g urinary loss (T1), FBK-R10 (T1): 11.1
In the time of rehabilitation urinary loss decreases on an average of 44.4% as well as psychological distress decreased significantly ($p < 0.001$).

Conclusions: In aging tumor biology und postoperative urinary loss are considerably getting worse, but psychological distress in younger patients is stronger than in elder patients ("Simpsons paradox"). In early urological rehabilitation functional impairments and psychological distress are significantly diminished.

ID 0340

Distribution of curative treatment strategies for localized prostate cancer

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Introduction: According to recommendation of the 2014 S3 guideline "Early detection, diagnosis and treatment of different stages of prostate cancer" patients should be informed about the curative local therapy options radical prostatectomy (RP), percutaneous radiotherapy (RT) and active surveillance (AS) equally.
Methods: The study is based on data from the Health Services Research HAROW study. The recruitment of patients took place 2008-2013. The study included men with clinically localized prostate cancer without evidence of lymph node or distant metastases (N0 M0 ≤cT2). Total 3169 men were included by 259 investigators in the study.
Results: Of these patients 1722 (59.9%) received an RP, 511 (16.1%) were curative irradiated and 489 (15.4%) actively monitored. In 397 (12.6%) patients palliative concepts (hormone therapy, watchful waiting) were elected. While the AS-group increased from 12.8% to 19.8% in 2011, the proportion of RP went down from 60% to 47.8%. The proportion of RT was relatively constant. Tumor category cT2 was found in only 16,4% with AS, the proportion with 47.7% and 40.9% in the RT and the RP was higher. The age distribution of RP, RT and AS was 64.9; 70.4 and 67.9 years. The distribution of comorbidities was comparable for the RP and the AS. Patients who opted for radiation therapy, more often suffering from secondary diseases.
Conclusion: The age distribution and the proportion of comorbidities are comparable between the local treatment options. Nevertheless, there is a remarkable asymmetry in the choice of treatment strategy is, although the options should be informed equivalent to each other. This discrepancy is not explained only by the higher proportion of cT2b/c of the patients recieved surgery, since almost 70% of them have a suitable tumor category for AS.

ID 0349

Survival of non-muscle-invasive bladder cancer in Germany by tumor stage and grade

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Background: According to the guidelines of the European Association of Urology (EAU), non-muscle-invasive bladder cancer (NMIBC) includes T1, in situ (Tis) and non-invasive papillary tumors (Ta). Treatment recommendations are based on the assessment of recurrence risk, which is presumed to be high for T1, Tis and large recurrent Ta tumors and low for low-grade Ta tumors. We studied survival of NMIBC patients in Germany up to ten years after initial diagnosis according to tumor stage and grading.
Method: Using the population-based cancer registry data pooled from nine German federal states and one administrative district, we included 66,387 patients (aged 15 years or older) who were first diagnosed with NMIBC between 1998 and 2012 and derived period survival estimates for 2008-2012 to calculate relative survival rates for up to ten years by tumor stage, grading and gender.
Results: Relative survival of NMIBC differed by stage and grade of tumor. The 5-year relative survival rates ranged from 73% (T1, high grade) to 97% (Ta, low grade). Ten year relative survival rates varied between 62% and 94%, respectively. Male patients had a poorer relative survival compared to female patients except for T1 tumors.
Conclusions: NMIBC patients presumed to have a high risk of recurrence had considerably lower survival rates compared to low-risk patients. These results probably reflect their higher recurrence risk although they are treated more intensively according to EAU guidelines.

ID 0404

Multiparametric MRI and MRI-TRUS fusion-biopsy in patients with prior negative prostate biopsy

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Background: Multiparametric MRI (mpMRI) plays an increasingly important role in prostate cancer (PCa) diagnostics and is recommended in men with previously negative biopsy. However, the consecutive diagnostic pathway after mpMRI is still under discussion.
Objective: PIRADS- and START-confom analysis of the relevance of mpMRI and MRI/TRUS-fusion guided biopsy in patients with prior negative prostate biopsy.
Patients and **Methods:** Between 10/2012 and 08/2015 278 patients with prior negative biopsy and persistent suspicion of PCa underwent mpMRI and a software-assisted, rigid MRI/TRUS-fusion-biopsy. In addition to and strictly separated from systematic perineal saturation biopsy (sB; median cores n = 24), MRI-targeted biopsies (tB; median cores n = 4 per patient) were performed in case of suspicious MRI-lesions (PIRADS≥2). Both biopsy methods were compared using McNemar-tests.
Results: Out of the 278 patients 148 (52%) had positive biopsies. Of these 107 (37%) had significant PCa (Gleason score (GS)=3+3 and PSA≥10ng/ml or GS≥3+4) and 43 (15%) had a GS≥4+3 PCa. SB failed to diagnose 8/148 PCa (5.4%) and 6/107 significant PCa (5.6%) whereas tB failed to diagnose 48 (32.4%) PCa (p≤0.0001) and 22 (20.5%) significant PCa (p = 0.0046). 11 of the PCa missed by tB had a GS≥3+4 and 5 of these a GS=4+3. 17 of the significant PCa were missed due to targeting-errors while using only 2 tB-cores per lesion.
MRI with PIRADS≥2 lesions failed to diagnose 5 significant PCa (4.7%) while PIRADS≥3 lesions missed 10 significant PCa (9.3%).
Conclusions: In men with unsuspicious MRI, there is only a small risk of significant PCa. In case of suspicious MRI-lesions, the combination of both biopsy approaches offers most accurate detection of significant PCa.

ID 0479

Multiparametric Magnetic resonance imaging and MRI/TRUS-fusion-biopsy for index tumor detection: Correlation with radical prostatectomy specimen

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Background: Multiparametric MRI (mpMRI) and MRI-targeted fusion-biopsy (TB) detect significant prostate cancer (PC) more accurately than conventional biopsies alone.
Objective: To evaluate the detection accuracy of mpMRI and TB on radical prostatectomy (RP) specimen.
Material and Methods: Out of a cohort of 755 men who underwent transperineal MRI/TRUS-fusion-biopsy under general anesthesia between 2012 and 2014, we retrospectively analysed 120 consecutive patients who had a subsequent RP. All received saturation biopsy (SB) in addition to TB of lesions with PIRADS≥2. Index lesion was defined as the lesion with extraprostatic extension, highest Gleason Score (GS), or largest tumor volume (TV) if GS were the same, in order of priority. GS=3+3 and TV>1.2ml or GS≥3+4 and TV≥0.55ml were considered significant PC (sPC). We assessed the detection accuracy by mpMRI and different biopsy approaches and analyzed lesion agreement between mpMRI and RP specimen.
Results: Overall, 120 index lesions and 71 non-index lesions were detected. 107(89%) index and 51(72%) non-index lesions harbored sPC. MpMRI detected 110/120(92%), TB (two cores per lesion) alone diagnosed 96/120(80%) and SB alone 110/120(92%) index lesions. Combined SB and TB detected 115/120(96%) index foci. Calculating rate differences in paired samples and McNemar`s tests, TB performed significantly inferior compared to mpMRI ($p = 0.003$), SB alone ($p = 0.007$) and the combination for index tumor detection ($p$pp
Conclusions: MpMRI identified 92% index lesions compared to RP histopathology. The combination of TB and SB was superior to both approaches alone, reliably detecting 97% of sPC lesions.

ID 0490

Cold atmospheric plasma affects prostate cancer cells by alteration of intracellular redox signaling

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Introduction: Cold atmospheric plasma (CAP) is a low-temperature ionized gas, which already offered antiproliferative potency. CAP could increase patients outcome by tumor-free surgical margins and the increase of recurrens-free survival of prostate cancer (PC).
Methods: In vitro proliferation after CAP treatment with kINPen MED (Neoplas) was measured by Casy Cell Counter and Analyzer Model TT (Roche). Apoptotic activity was determined by quantitative RT-PCR and Western blot analysis as well as TUNEL and cellular morphology assay. Cellular redox levels were determined by oxidation status conservation with N-ethylmaleimide and prx redox blot. Intracellular gluthation (GSH) levels after N-acetylcystein (NAC) incubation were measured by 5,5'-Dithio-bis-(2-Nitrobenzoic acid)-assay (Carl Roth).
Results: CAP significantly attenuated PC cell proliferation within 120 h compared to argon treated control cells. The cytostatic potency of CAP thereby was comparable to docetaxel. CAP treated cells showed a significantly increased apoptotic activity due to induction of p53 protein, Bax, caspase-3 and p21 mRNA, the reduction of surviving mRNA as well as increased nuclear fragmentation and morphological changes. Notably, NAC incubation completely neutralized the anti-proliferative CAP effects by a rapid NAC uptake and conversion to GSH, in contrast to GSH independent vitamin C. Prx redox blot revealed an immediate increase of Prx 1, 2 and 3 oxidation indicating high intracellular peroxide levels following CAP treatment.
Conclusion: The potent inhibition of PC proliferation by CAP probably occurs due to peroxide increase and altered redox signaling. Thus, CAP may represent a powerful tool for future oncological surgery.

ID 0500

Template-based salvage extended lymph node dissection in prostate cancer recurrence with lymph node metastases

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Introduction: Salvage extended pelvine lymph node dissection (ePLND) is a treatment option for patients with biochemical recurrence (BCR) of prostate cancer (PCa). We believe that optimal salvage ePLND results can be achieved by means of a template-based surgical technique.
Methods: Over the period of the last 11 years, we performed 67 template-based salvage ePLNDs in PCa patients with BCR. Out of these, 13 (19.4%) had received radiation as the primary therapy and thus also underwent prostatectomy during salvage surgery. We described the surgical topography of the Kiel template procedure by defining 9 anatomical areas. The strategic principles of the Kiel Salvage ePLND are as follows: exclusive selection of a transperitoneal access; definition of landmarks such as the iliacal vessels prior to LND; careful separation of the ureter from the surrounding tissue; systematic top-to-bottom performance of LND, utilization of small or medium clips to prevent extensive ligature. In addition, we use the *Harmonic scalpel* to seal lymphatic vessels and to reduce surgical time.
Results: We dissected a total of 1450 LK in 67 patients, i. e. 21.6 LN per patient on average. Overall, we found LN metastases in 37 (55.2%) patients, resp. 292 (20.1%) positive LNs out of 1450 LK. Postoperatively, 4 (6.0%) patients developed lymphoceles that required laparoscopic fenestration. There was no case of urinary incontinence or *de novo* erectile dysfunction after salvage ePLND.
Conclusions: Salvage ePLND can be useful in patients with LN metastases, especially in CRPC patients. Standardization of a step-by-step surgical technique is also useful for achieving comparability of results in a multi-center analysis.

ID 0504

The Relevance of Reference Pathology of Prostate Biopsy Diagnostics in the PREFERE Trial

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Background: The PREFERE-trial is a nation-wide study prostate cancer study that aims to evaluate the outcomes of different treatment modalities (surgery, external beam radiation, brachytherapy and active surveillance) in low to early-intermediate risk prostate cancer patients. The inclusion criteria depend significantly on histological parameters, hence a mandatory reference pathology was implemented in the study protocol. We aim to

report on the procedure, the progress and pitfalls of reference pathology in the PREFERE trial and to provide first results.
Methods: Study cases sent in for re-evaluation (September 2015) to the five reference centers were considered. The histo-pathological results of the reference pathology was compared to the primary histology reports.
Results: Biopsies of 262 patients were re-analysed, the median reporting time was five calendary days. The diagnosis of cancer could be confirmed in the vast majority of cases. Marked differences, however, were found in the correct identification of the number of positive cores, the tumor extent or the Gleason scores, which in consequence led to the study exclusion of 55 patients (21%).
Conclusions: Although it is too early to estimate the full value of the central reference pathology in the PREFERE trial, this preliminary data already indicates its importance for therapy planning in low to early intermediate risk prostate cancer patients.

ID 0510

Marine compound rhizochalinin shows high anticancer activity in castration resistant and AR-V7 positive prostate cancer cell lines

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Introduction: We examined the efficacy of rhizochalinin (Rhiz) - a marine sphingolipid-like compound – in a human prostate cancer model.
Methods: Anticancer activity of Rhiz was investigated using the CRPC cell lines PC3, DU145 and the AR-V7 positive cell lines 22Rv1 and VCaP. Effects on cell viability and cell cycle were investigated by MTT, trypan blue staining and flow cytometry. Mode of action of Rhiz was analysed by fluorescence microscopy, Western blotting and a global proteome screening. Electrophysiological experiments were performed in a *Xenopus* oocytes expression system. *In vivo* experiments were performed using PC3 and 22Rv1 tumor xenografts in NOD/SCID mice.
Results: *In vitro* Rhiz significantly decreased viability of PC3, DU145, 22Rv1 and VCaP cells at low micromolar concentrations with 22Rv1 and VCaP showing the highest drug sensitivity
Rhiz induced caspase-3-dependent apoptosis, down-regulation of the anti-apoptotic protein survivin, up-regulation of the pro-apoptotic factors p53, PTEN and p21, and a G2/M cell cycle arrest. Up-regulation of the autophagy marker LC3B-II was detected.
The global proteome analysis revealed regulation of several proteins associated with metastasis formation and tumor cell invasion. Current inhibition of voltage dependent potassium channels were observed in a *Xenopus* oocytes expression system. *In vivo* Rhiz significantly reduced the growth of PC3 and 22Rv1 tumor xenografts in NOD/SCID mice.
Conclusion: Rhiz is a promising novel substance for the treatment of CRPC, showing high *in vitro* and *in vivo* efficacy in castration resistant and AR-V7 positive prostate cancer cell lines. Regulation of pro-apoptotic and autophagy-associated pathways are supposed modes of action of the drug.

ID 0564

Exosomes are characterized by a specific miRNA pattern depending on invasiveness of originating bladder tumor cells

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Introduction: Small microvesicles (exosomes (EV)), which contain different molecules including miRNAs, affect the communication between tumor cells and the tumor microenvironment. The aim of this study is the definition of a specific miRNA expression pattern in EV obtained from different UBC cell lines. Furthermore, the possible transfer of miRNAs between tumor cells and tumor-associated fibroblasts (TAFs) will be investigated.
Methods: EV were isolated from UBC cell lines (non-invasive: RT-112, 5637, invasive: T-24, J82, 253J-BV) by differential centrifugation. The number and size of vesicles were measured by nanoparticle tracking analysis. MiRNA expression pattern was analyzed using miRNA microarrays followed by qPCR. EV-mediated miRNA transfer was verified by transfection of UBC cells with cel-miR-39, EV isolation and RNase treatment, EV incubation of TAFs, miRNA-specific qPCR in recipient TAFs.
Results: EV secreted by invasive UBC cells are characterized by a specific miRNA signature of 25 miRNAs compared to EV from non-invasive UBC cells. Similar profiles were detected in the originating tumor cells. After successful transfection of RT-112 and T-24 with cel-miR-39 this miRNA was detected in the related EV as well as in recipient TAFs cultivated with these EV.
Conclusion: EV secreted by UBC cells exhibit a specific miRNA signature depending on the invasive potential of the originating cells. For the first time we proofed the EV-mediated transfer of miRNAs between tumor cells and TAFs in bladder cancer. These results emphasize the role of exosomal miRNAs for the interaction between tumor cells and the tumor microenvironment. Further studies have to show the functional relevance of selected exosomal miRNAs.

Geriatric Oncology

ID 0075

The Geriatric Cancer Patient – Therapy and Quality of Life Preliminary Results of a Bicenter Study to Develop, Modulate and Pilot-test a Patient-centered Interdisciplinary Care Concept for Geriatric Oncology Patients (PIVOG)

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Introduction: Prior to cancer specific therapy the identification of relevant risk factors by comprehensive geriatric assessment (CGA) is recommended for elderly cancer patients.
Objective: This study and pilot test a complex intervention including a patient-centered interdisciplinary care concept for geriatric oncology patients based on comprehensive geriatric assessment (CGA including PHQ9) and patient-reported health related quality of life (HRQOL).

Methods: The complex intervention was developed comprising treatment pathways with tailored supportive measures and nurse-led telephone based counselling during aftercare. It is now pilot-tested (recruitment ongoing until Dec. 2015) in the participating centres in order to test feasibility, acceptance and potential benefit. Inclusion criteria: Oncologic patients ≥70 years with at least one comorbidity and/or one functional impairment regarding ADL with written informed consent. Aspired sample size: n = 100. Primary endpoint: HRQOL (EORTC QLQ-C30, ELD14), measured at admission and 6 month-follow-up. Secondary endpoints: cancer specific therapy, side effects (CTCAE), applied supportive measures, causes for counselling, number and reasons of readmissions, overall and disease specific survival and patient satisfaction.
Results: Out of n = 158 eligible patients so far n= 65 participated (palliative intention: n = 17), age mean = 75.7 (SD=4.5), max. n = 12 comorbidities (high blood pressure: n = 40). Individual assessments show large inter-individual differences regarding HRQOL, functional status, symptom intensity and supportive needs. Supportive care is triggered by summarized individual results (e.g. malnutrition, reduced HRQOL, low functioning, high symptom-intensity).
Conclusion: Preliminary analyses indicate feasibility and benefit of CGA and HRQoL assessments to facilitate supportive therapy. The nurse-led after care is well accepted.

ID 0274

Interdisciplinary screening and assessment for establishing age-adapted therapy concepts in elderly cancer patients

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Objectives: The aim of this study is to improve therapy decisions in elderly cancer patients by implementing an onco-geriatric assessment which is able to predict chemotherapy-associated toxicity in this patient group.
Methods: Two possible tools are published for toxicity prediction in elderly cancer patients: the CARG score (Cancer and Ageing Research Group) and the CRASH score (Chemotherapy Risk Assessment Scale for High-Age Patients). They combine different geriatric and oncological parameters and stratify patients into different risk categories of chemotherapy-related toxicity. In a pilot study we tested the feasibility of both scores by evaluating the necessary time for patient interviews, as well as physicians' therapy decisions and patient-reported symptoms (PRO-CTCAE).
Results: In the pilot study we recruited n = 20 elderly cancer patients (≥ 70 years). The results indicate that the interview of the CARG score can be performed much faster than the one of the CRASH score (mean 3.3 min vs. 27.1 min). Besides, the results of both scores differ from the physician's assessment by predicting a higher chemotherapy-associated toxicity (CRASH Combined Score 10% vs. CARG 15% vs. Physicians 90%). The correlation between patient-reported toxicity and the scores' or physicians' predictions remains to be further analyzed.
Conclusion: The pilot study indicates the potential of an oncogeriatric assessment to improve therapeutic decisions for cancer therapy in the elderly. However, it is essential to further evaluate which of the two scores predicts chemotherapy-associated toxicity best.

All institutions contributed equally to this study.

ID 0376

Treatment of Elderly Breast Cancer (BC) Patients

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Background: The management of elderly patients with breast cancer is influenced by factors that can vary widely among individuals. A study intend to determine whether treatment of and screening for BC in the elderly in a community hospital is appropriate.
Material and Methods: For this study a search in our tumor registry was performed. In the period 2002-2014 from 2071 patients (pts) with BC about 42% have been identified diagnosed as elderly women. A comparison between 3 different subgroups 65-70, 71-80 and 80 years and older were made using the chi square test.
Results: Lumpectomy was performed in 74% of all patients while mastectomy was done in 26% of pts. The majority of the patients (78%) were ER and PR receptor positive and hormonal therapy was done. Adjuvant chemotherapy and radiation was done in 25% and 56% respectively. The overall five years survival was worse in patients' elderly than 75 years and when the adjuvant treatments were excluded.
Conclusion: The highly individual aging process must be considered in determining optimal treatment for elderly patients

Gynecologic Cancer

ID 0033

Survival Advantage of Lymphadenectomy in Endometrial Cancer- Data from Sachsen-Anhalt Registry on 1502 Patients with median Follow-up of 78 Months

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Background. The lymphadenectomy in the treatment of endometrial cancer is topic of ongoing debate. The direct comparison between no-lymphadenectomy, pelvic, and pelvic/para-aortic lymphadenectomy regarding overall survival of patients with endometrial cancer is missing.
Methods. We performed a multicenter, retrospective registry-based study of 1502 patients with endometrial cancer treated with no lymphadenectomy (n = 697), systemic pelvic lymphadenectomy (n = 543) and systemic pelvic/para-aortic lymphadenectomy (n = 262). The patients were divided into three groups of recurrence risk: low, intermediate, and high. The outcome measure was overall survival.
Results. Lymphadenectomy did not improve overall survival of patients with low risk of recurrence. The survival effect of systemic lymphadenectomy was significant in patients with intermediate and high risk of recurrence. Multivariate analysis showed that both pelvic(HR 0.63, CI 0.38-0.82, P=0.001)and combination of pelvic/para-aortic lymphadenectomy(HR 0.50, CI 0.43-0.81, P<0.0001) significantly reduced the mortality risk in patients with intermediate riskcompared to the patients who underwent no lymphadenectomy. In patients with high risk only combined pelvic/para-aortic lymphadenectomy (HR 0.62, CI 0.48-0.82, P=0.005) was associated with decreased mortality rate compared with no-lymphadenectomy. Among patients with intermediate and high risk of recurrence who did not receive any adjuvant therapy, pelvic/para-aorticlymphadenectomysignificantly reduced the mortality risk (HR 0.52, CI 0.37-0.73, P<0.0001) in comparison to no lymphadenectomy. This management was superior to pelvic lymphadenectomy alone. In patients with low risk of recurrence lymphadenectomy had no effect on overall survival.
Conclusions. Pelvic/para-aortic lymphadenectomy should be performed in all patients with endometrial cancer at intermediate and high risk of recurrence.

ID 0041

Fertility-sparing surgery (FSS) in patients with borderline ovarian tumors (BOT)

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Background: Fertility-sparing surgery (FSS) is an option in patients with BOT. However, data regarding long-term safety are sparse. Completion of surgery after childbearing is discussed as a recommendation. We analyzed our data regarding this issue.
Methods: Exploratory analysis of all consecutive patients treated for BOT 1/2000-4/2015. All patients had central histopathological validation. Fertility sparing surgery was performed after individual discussion. Complete surgical staging in our centre was defined according to FIGO but without lymphadenectomy and with a waiver for preservation of uterus and one ovary in case of FFS.
Results: We treated 247 patients with a median age of 46 years (13-83). 78.8% had FIGO stage I, 5.7% stage II, 15.8% stage III, and 0.4% stage IV. The rate of complete surgical staging by laparotomy (88.3%) or laparoscopy (10.7%) was 88.3%. FSS was performed in 63 patients, 50% had FIGO stage I and 14% stage II/III. After a median follow up of 49 months the relapse rate was 4% in all patients, 2.7% in patients with complete surgery and 7.8% in FSS. The relapse rate of patients with FSS in stage I was 2% and 28.6% in stage II/III. All relapses in FSS were seen within 36 months after surgery. So far, none of the patients with endoscopic staging relapsed.
Conclusion: FSS in stage I is a safe procedure. In all other stages it has to be discussed individually. Our data do not support the hypothesis that completion of surgery after childbearing is necessary because we did not observe any relapse later than after 3 years.

ID 0076

Prognostic impact of conventional tumor grade in surgically treated FIGO stage IB to IIB squamous cell cervical cancer

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Introduction: Tumor differentiation is a prognostic factor and a morphologic feature for decision making for adjuvant treatment in several cancers. The prognostic knowledge for surgical treated squamous cell cancer of the uterine cervix (CX) is limited.
Methods: A total of 467 cases of CX FIGO stage IB to IIB who received upfront surgery were re-examined for conventional tumor grade according to the WHO-classification of 2014 regarding its prognostic impact for recurrence free and overall survival.
Results: The grading distribution for the whole cohort was 46.0% G1, 30.6% G2 and 23.3% presented poorly differentiated tumors (G3). There was a prognostic impact for recurrence free but not for overall survival using a 3-tired grading system (see table). After creating a 2-tired grading system (merging G1- and G2-tumors) there was a statistic significant impact on both, recurrence free and overall survival.
Prognostic impact of conventional tumor grade

	3-tired grading system			**2-tired grading system**		
	G1	G2	G3	p-value	G1/2	G3	p-value
RFS-rate	81.4%	70.6%	64.2%	0.008	77.1%	64.2%	0.008
OS-rate	78.7%	72.2%	65.1%	0.089	76.0%	65.1%	0.031

Conclusions: The results indicate that conventional tumor grading in squamous cell CX is of prognostic impact. But, a 2-tired system fits better that the most commonly used 3-tired WHO-grading system.

ID 0077

Prognostic impact of tumor size using a cut-off value of 2 cm in surgically treated FIGO stage IB cervical cancer

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Introduction: A cut-off value of tumor size of 2 cm has been discussed within the tailoring of surgical treatment of cervical carcinoma (CX) in cases without trachelectomy.
Methods: A total of 366 cases of CX FIGO stage IB who received upfront surgery were evaluated regarding tumor size, the prediction of pelvic lymph node involvement, and recurrence-free and overall survival during a median follow-up time of 94 months. Tumors ≤2.0 cm were defined as small, tumors 2.1-4.0 cm as medium sized and those larger than 4 cm as bulky disease.
Results: Small tumors were seen in 28.7%, medium sized in 52.5% and bulky tumors in 18.9%. There was a significant higher frequency of pelvic lymph node involvement with increasing tumor size (13.3% vs. 23.4% vs. 43.5%, respectively; $p < 0.001$) and an increase of recurrent disease (6.7% vs. 18.8% vs. 29.4%, respectively; $p < 0.001$). The 5-year overall survival rate was significantly reduced with increasing tumor size (94.0% vs. 85.1% vs. 69.9%, respectively; $p < 0.001$). Pelvic lymph node involvement and maximal tumor size were independent prognostic factors for both recurrence-free and overall survival in multivariate analysis.
Conclusions: The results support that tumor size is of prognostic impact in FIGO stage IB cervical carcinomas. A further substaging is suggested for tumors up to 4.0 cm maximum dimension using a cut-off value of 2.0 cm as discriminator. Patients with tumors ≤2.0 cm may represent low risk disease.

ID 0078

Peritumoralen Entzündung beim Zervixkarzinom – prognoserelevant ??

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Fragestellung: Die peritumorale Entzündung stellt eine Reaktion auf das Tumorwachstum dar und steht zunehmend im Fokus der sog. Checkpoint-Therapie.
Methodik: 716 operativ therapierte CX pT1b1 bis pT2b wurden retrospektiv bezüglich des Grades der peritumoralen Entzündung (PER) evaluiert. Die Graduierung erfolgte semiquantitativ (Eggen et al. 2007): 0 = keine PER, 1 = geringe PER (einzelne peritumorale Entzündungszellen, ohne Clusterbildung), 2 = mäßiggradige PER (peritumorales Clustering von Entzündungszellen), 3 = hochgradige PER (kontinuierliches peritumorales Band aus Entzündungszellen). Die PER wurde zu kliniko-pathologischen Parametern korreliert.
Ergebnisse: Bei 104 Patientinnen (14,5%) fehlte die PER vollständig, 35,9% zeigten eine geringgradige, 24,3% eine mittel- und in 25,3% eine hochgradige PER. Zwischen der PER und dem Grading der CX bestand keine signifikante Korrelation. Patientinnen mit pelvinen Lymphknotenmetastasen zeigten signifikant seltener eine mittel- bzw. hochgradige PER im Vergleich zu nodalnegativen Patientinnen (38,6 versus 54,9%; $p < 0.0001$). Der Grad der PER korrelierte signifikant mit dem rezidivfreien Überleben (PER 0: 90,1 Monate, PER 1: 113,2 Monate und PER 3: 144,6 Monate; $p < 0.001$).
Schlussfolgerung: Die peritumorale Entzündung korreliert beim CX mit dem Auftreten von Lymphgefäßeinbrüchen und dem pelvinen Lymphknotenstatus sowie dem rezidivfreien Überleben. Eine Steigerung der Immunantwort wäre ein Therapieansatz auch beim Zervixkarzinom.

ID 0080

KRAS and BRAF mutational analyses indicate monoclonal origin of peritoneal implants and lymph node deposits in serous borderline ovarian tumors (s-BOT)

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Introduction: Molecular studies have shown that the most prevalent mutations in serous ovarian borderline tumors (s-BOT) are BRAF and/or KRAS alterations. About one third of s-BOT represent peritoneal implants and/or lymph node involvement. These extraovarian deposits may be monoclonal or polyclonal in origin.
Methods: To test both the hypotheses, mutational analyses using pyrosequencing for BRAF codon 600 and KRAS codon 12/13 and 61 of microdissected tissue was performed in 15 s-BOT and their invasive and non-invasive peritoneal implants. Two to 6 implants from different peritoneal sites were examined in 13 cases. Lymph node deposits were available for the analysis in 3 cases. Six s-BOT showed mutation in exon 2 codon 12 of the KRAS proto-oncogen.
Results: Five additional cases showed BRAF p.V600E mutation representing an overall mutation rate of 73.3%. Multiple (2-6) peritoneal implants were analyzed after microdissection in 13 of 15 cases. All showed identical mutational results when compared with the ovarian site of the disease. All lymph node deposits, including those with multiple deposits in different nodes, showed identical results, suggesting high intratumoral mutational homogeneity.
Conclusions: The evidence presented in this study and the majority of data reported in the literature support the hypothesis that s-BOT with their peritoneal implants and lymph node deposits show identical mutational status of BRAF and KRAS suggesting a monoclonal rather than a polyclonal disease regarding these both tested genetic loci. In addition, a high intratumoral genetic homogeneity can be suggested. In conclusion, the results of the present study support the monoclonal origin of s-BOT and their peritoneal implants and lymph node deposits.

ID 0106

Trends in surgery of squamous cell vulvar cancer patients over a 16-year-period (1998–2013): A population-based analysis

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Objective: The objective of this study was to identify population-based long-term trends in prognostic factors and treatment of invasive squamous cell vulvar cancer over a 16-year period from 1998 to 2013 in the area of the Munich Cancer Registry (MCR).
Methods: 1,113 patients with an invasive squamous cell vulvar cancer diagnosed between 1998 and 2013 in the catchment area of the Munich Cancer Registry (MCR) (population meanwhile 4.6 million) were analysed. Trends in prognostic factors and treatment were analysed by comparing patients diagnosed 1998-2008 (n = 629) with patients diagnosed 2009-2013 (n = 484).
Results: The high median age at diagnosis did not change significantly (p = 0.306) between patients diagnosed 1998-2008 (75.4 years) compared to patients diagnosed 2009-2013 (74.1 years). There are no significant changes in subsite of tumour and grading. In total, 94.8% of the patients underwent surgery. The proportion of patients with adjuvant radiotherapy did not alter significantly. In surgery there is a trend towards less radical locoregional procedures, with a decrease in the number of patients who underwent complete vulvectomy from 27.7 to 17.8% (p
Conclusions: Guideline recommendations towards a less radical locoregional surgery approach in vulvar cancer seem largely implemented in the area of Munich Cancer Registry (MCR).

ID 0127

Prognostic and predictive values of primary vs secondary platinum resistance for bevacizumab treatment in platinum-resistant ovarian cancer in the AURELIA trial

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Background: Progression-free survival (PFS) and patient-reported outcomes (PRO) were significantly improved with the addition of bevacizumab (BEV) to standard chemotherapy (CT) for platinum-resistant ovarian cancer (OC) in the randomized phase III AURELIA trial. We examined the relevance of primary (PPR) vs secondary platinum resistance (SPR) on treatment efficacy.
Methods: Platinum resistance was categorized as PPR if progression was <6 months after completing first platinum therapy or SPR if not. We performed exploratory Cox and log regression analyses to correlate platinum resistance with PFS, OS, and PRO from the time of randomization to CT ± BEV.
Results: Of the 361 randomized pts, 262 (72.6%) had PPR and 99 (27.4%) had SPR. In the BEV+CT arm (n = 179), SPR was associated with more favorable PFS (median 10.2 vs 5.6 months [mo] in the PPR subgroup; P < 0.001) and OS (median 22.2 vs 13.7 mo, respectively; P < 0.001) but not PRO (22.0% vs 21.9% with ≥15% improvement in abdominal/GI symptoms at week 8/9; P = 0.99). In two separate multivariate analyses, SPR remained an independent prognostic factor for better PFS (HR 0.41, 95% CI 0.25–0.67, P < 0.001) and OS (HR 0.49, 95% CI 0.30–0.80, P = 0.005) in the BEV+CT arm. The magnitude of benefit from adding BEV to CT appeared greater in the SPR than the PPR subgroup for PFS (SPR: HR 0.30, 95% CI 0.18–0.48, P < 0.001; PPR: HR 0.55, 95% CI 0.42–0.71, P < 0.001; interaction P = 0.07) with a similar direction of effect for OS (SPR: HR 0.62, 95% CI 0.37–1.02, P = 0.06; PPR: HR 0.94, 95% CI 0.71–1.24, P = 0.65; interaction P = 0.18).
Conclusions: Median PFS and OS were more favorable in SPR than PPR pts treated with BEV+CT but BEV effect on PRO was similar. The PFS and OS benefit of BEV+CT over CT alone was more pronounced in the SPR than the PPR subgroup. PPR vs SPR should be a stratification factor in future trials of anti-angiogenic therapy for OC.

ID 0167

Human Papillomavirus (HPV) vaccinated and still dysplasia

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Aim: It should be the aim to protect women from a carcinoma of the cervix and its preliminary stages with a type specific vaccination. Half of all women form barely to no antibodies against HPV. On the basis of this observation the HPV vaccination was introduced, to support the process of raising antibodies against HPV.
Method: During microscopic inspection of gynocological cell images of the cervix of vaccinated women using the known malignancy criteria, mild, moderate and severe dysplasia as classified in the Münchner Nomenklatur III in German-speaking areas, can be detected.

Result: From January 2015 to June 2015 twenty cases of dysplasia of the cervix in PAP smears of vaccinated women were diagnosed. The dysplasias show the following distribution: 65% of cases show a mild dysplasia (low SIL). In 35% a high SILesion can be verified. Thereof 30% have a moderate dysplasia and 5% a severe dysplasia. In 10% of cases a dysplasia shows after 1 year, in 5% after 4 years and in 10% after 5 years of HPV vaccination. There are 65% of cases in dysplasia follow-up examinations, 20% of these are healed up within 2 years. In 15% of high SIL cases a histological clarification followed, which confirmed the high SILesion 100%.
Conclusion: At this particular time there is no valid specific marginal limit for a HPV-antibodytiter-identification and also a subtype determination of HPV antibodies isn't possible, that's why a reliable statement about the length of immunity and of the actual raising of specific antibodies against HPV isn't possible. The HPV test doesn't indicate dormant HPV infections reliably. The effect of the HPV vaccination into a dormant HPV infection to the actual effect on the formation of a dysplasia is therefore unclear. Thus the importance of gynocological screening with morphological diagnostics becomes apparent.

ID 0172

Retrospective analysis of compliance, compatibility and quality of life of gynecological cancer patients under complementary treatment

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Introduction: 50–70% of all gynecological cancer patients use complementary therapies and up to 80% require to be advised regarding the application of complementary treatments.
Material & Methods: 107 gynecological cancer patients who were seen in our integrative clinic between 2009 and 2014 were investigated retrospectively regarding the administration of complementary medicine as well as the compliance, compatibility and quality of life under complementary treatment. The median age of the group numbers 56 years (27–83).
Results: Initial presentation: 41/107 (38%) of the patients presented to the integrative clinic shortly after receiving their cancer diagnosis. 25% (27/107) presented to the consultation during their first relapse, 26% (28/107) at further progression of their cancer. Compliance: 21% (23/107) only presented to the clinic once. 22% (24/107) of the patients presented to the clinic repeatedly, yet did not conduct the recommended therapy. 51% (55/107) visited the consultation hours regularly and conducted the therapy as it was recommended. Quality of life: 90% (96/107) of our patients tolerated the complementary therapy without showing any side effects under the integrative treatment. 72% of the compliant patients reported about a better quality of life through CAM treatment. 10% (11/107) of the patients showed minor local side effects under the complementary treatment. One patient had an allergic reaction to helleborus niger e planta tota D3.
Conclusion: Mainly younger patients are interested in additional complementary treatments during cancer therapy. 38% (41/107) of our patients started complementary treatment shortly after receiving their cancer diagnosis. 69% (55/79) of the patients who decide for an integrative treatment are compliant under the therapy. 72% (41/55) of these compliant patients reported about a better quality of life under complementary treatment.

ID 0184

Biomarker results from PENELOPE, A randomised phase III trial evaluating chemotherapy (CT) ± pertuzumab (P) for platinum-resistant ovarian cancer (PROC) with low tumor HER3 mRNA expression

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Background: Retrospective analyses in PROC suggested improved progression-free survival (PFS) by adding P to gemcitabine in patients (pts) with low tumor HER3 mRNA expression. PENELOPE aimed to confirm this signal in pts with centrally tested low tumor HER3 mRNA expression. Adding P to CT improved independent review committee (IRC)-assessed PFS without reaching statistical significance (HR=0.74; p = 0.14).
Patients and Methods: To explore prognostic and predictive effects of HER2/HER3 mRNA/membrane H-score, pts were dichotomised using each median as the cut-off. HER2 and HER3 H-score were scored analogous to the current HER2 ASCO CAP guidelines.
Results: Within this prespecified HER3 mRNA low expressing patient population P treatment effect was similar in pts with HER3 mRNA expression below and above the median (HR 0.79; 95% CI 0.48-1.33 vs HR 0.68; 95% CI 0.42-1.12). Further, quartile analysis showed no consistent linear trend: P effect was greatest in the lowest and highest quartiles, whereas no benefit could be detected within the two intermediate groups. There was a signal for an improved IRC-assessed PFS in pts with low HER2 expression on IHC (HR 0.52; 95% CI 0.31–0.87), however, this was not confirmed by HER2 mRNA analysis. HER3-H-score did not predict improved P benefit.
Conclusions: Within the pre-selected 'low HER3 mRNA' population, no further consistent HER3- and HER2-related differential benefit was discernible, preventing refinement of the HER3 cut-off. For the quartile-analysis that subgroups are considerably small (n= 10–19), which precludes firm conclusions. Further analyses, including prognostic effects and the screened population (N=324), will be presented.
Sponsor of the study is F. Hoffmann-La Roche Ltd.

ID 0192

The risk of contralateral non-sentinel metastasis in patients with primary vulvar cancer and unilaterally positive sentinel node

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Background: In patients with primary vulvar cancer and bilateral sentinel lymph node (SLN) biopsy, bilateral complete inguino-femoral lymphadenectomy (LAE) is recommended even in cases with only unilaterally positive SLN by most guidelines. The risk of contralateral non-SLN metastasis is unclear.
Methods: All patients with primary vulvar cancer receiving a SLN dissection with radioactive tracer +/– blue dye at the University Medical Center Hamburg-Eppendorf between 2001 and 2013 were retrospectively evaluated. Median follow-up was 33 months.
Results: 140 patients were included; 124 with bilateral and 16 with unilateral SLN dissection. A median number of 2 SLN (range 1-7) per groin were dissected. 53 (53/140, 37.9%) patients received a complete inguino-femoral LAE. 41 of 53 patients (77.4%) had presented with a positive SLN before (33 unilaterally, 8 bilaterally). Of the 33 patients with unilateral positive SLN, 28 (84.9%) underwent complete bilateral inguino-femoral LAE despite a contralateral negative SLN. Of these patients, none presented a contralateral non-SLN metastasis (0/28, 0%) in full dissection. However, one developed groin recurrence in the initially SLN negative fully dissected groin after 19 months (1/28; 3.6%).
Conclusion In case of bilateral SLN biopsy for clinically node-negative disease and only unilateral positive SLN the risk for contralateral non-SLN metastases appears to be low. These data support the omission of contralateral LAE to reduce surgical morbidity

ID 0193

Analytical validation of a CE marked companion diagnostic tumor test to detect *BRCA1* and *BRCA2* mutations in ovarian cancer for clinical use

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Background: Somatic and germline mutations in the *BRCA1* and *BRCA2* genes may predict outcomes to ovarian cancer therapies such as platinum and PARP inhibitors. To identify patients that may benefit from these therapies, a companion diagnostic test has been developed to analyze tumor specimens for *BRCA1/2* mutations. The aim of this study is to validate the test's analytical performance.
Methods: Genomic DNA isolated from 42 anonymized ovarian tumor samples underwent full sequence and large rearrangement analysis using next generation sequencing (NGS). The criteria for calls required 99% of bases to have ≥ 100 reads. The reproducibility of this test was evaluated by sequencing 10 samples in triplicate across 6 batches. All samples underwent analysis by an independent laboratory to verify results.
Results: The analytical sensitivity was estimated to be >99.07% (lower bound of 0.95 C.I.), with an analytical specificity >99%. The average read depth was approximately 425X per base, with a minimum inclusion criterion of 50X per base. All samples that were previously identified by alternative methods as positive for deletions/duplications were correctly identified using NGS dosage analysis. This study also showed that the results were 100% concordant with independent laboratory analysis – both finding 319 sequence variants – and had 100% intra- and inter-run reproducibility.
Conclusions: Ovarian tumor testing for *BRCA1/2* mutations including sequence and large rearrangement variants using NGS has been validated with high sensitivity and specificity for companion diagnostic use. It may be used for identifying patients with somatic or germline mutations to help guide therapy decisions.
*This abstract was presented at ESHG 2015

ID 0194

C-met is overexpressed in type I ovarian cancer – results of an explorative analysis in a cohort of consecutive ovarian cancer patients

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Fragestellung: The tyrosine kinase c-met alters signaling cascades like BRAF-MAPK and PI3K-PKB pathways. These alterations are involved in the carcinogenesis of type I but not type II ovarian cancer (OC). Therefore, we explored the patterns of c-met expression in a cohort of consecutive OC patients.
Methoden: Expression of c-met was determined by immunohistochemistry. Differences in c-met overexpression among subgroups of established clinico-pathological features like age, histological subtype, tumor stage, histological grading, postoperative tumor burden and completeness of chemotherapy were determined by chi-square test. Cox regression analyses were performed to determine the prognostic influence of c-met. Survival rates were estimated using the Kaplan-Meier method.
Ergebnisse: 106 patients entered this study. C-met was overexpressed in 20.8% of the entire cohort. Patients with type I OC showed overexpression of c-met in 35.7%, whereas patients with type II OC overexpressed c-met in 8.6% ($p = 0.001$). However, c-met overexpression was not associated with any other established clinico-pathological features (all p-values >0.05). Univariable Cox regression analysis showed that overexpression of c-met was associated neither with progression free survival (PFS) nor with disease specific survival (DSS) ($p = 0.835$ and $p = 0.414$, respectively). Kaplan-Meier plots failed to demonstrate an influence of c-met on five years PFS and DSS rates, too ($p = 0.938$ and $p = 0.412$, respectively).
Schlussfolgerungen: These findings support the hypotheses that overexpression of c-met is associated with type I but not type II OC and that overexpression of c-met does not influence the prognosis of OC.

ID 0198

Circulating U2 small nuclear RNA fragments as a novel diagnostic tool for patients with epithelial ovarian cancer

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Background: Ovarian Cancer is the leading cause of death among female malignancies. Despite advances in treatment, more than 50% of patients relapse. For disease-monitoring, the identification of a blood-based biomarker would be of prior interest. In this regard, non-coding RNA, such as microRNA (miRNA) or small nuclear RNA (snRNA), were suggested as biomarkers for non-invasive cancer diagnosis. In the present study, we aimed at identifying differentially expressed miRNA/snRNA in sera of ovarian cancer patients and investigated their potential to aid therapy monitoring.
Methods: MiRNA/snRNA abundance was investigated in serum (n = 10) by microarray analysis and was validated in an extended serum set (n = 119) by RT-qPCR.

Results: Abundance of U2-1 snRNA fragments (RNU2-1f) was significantly elevated in sera of ovarian cancer patients ($p < 0.0001$) and paralleled FIGO-stage as well as residual tumor burden, left after surgery ($p < 0.0001$; $p = 0.011$, respectively). Moreover, for patients with suboptimally debulking, pre-operative RNU2-1f level associated with the patient's radiographic response after chemotherapy and platinum-resistance ($p = 0.0088$, $p = 0.0015$, respectively). Interestingly, according to the RNU2-1f abundance dynamics, persistent RNU2-1f positivity before surgery and after chemotherapy identified a subgroup of patients with high risk of recurrence and poor prognosis.
Conclusions: This is the first report, suggesting that a circulating snRNA can serve as an auxiliary diagnostic tool for monitoring tumor-dynamics in ovarian cancer. Notably, our results provide the rationale to further investigate, whether this "high-risk" patient group may benefit from an additional therapeutical concept.

ID 0200

Trends in prognostic factors and treatment of invasive cervical cancer patients over a 16-year-period (1998–2013): a population-based analysis

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Objective: The objective of this study was to identify trends in prognostic factors and treatment of invasive cervical cancer in a population-based setting.
Methods: 3,246 patients with an invasive cervical cancer diagnosed between 1998 and 2013 in the catchment area of the Munich Cancer Registry (MCR) (population meanwhile 4.6 million) were analysed. Trends in prognostic factors and treatment were examined by comparing patients diagnosed within the years 1998–2008 (n = 2,108) and 2009–2013 (n = 1,138).
Results: The median age at diagnosis of 50.0 years ($p = 0.918$) and grading with 46.5% G3-tumours ($p = 0.396$) did not change significantly over time. Furthermore, treatment approaches did not alter ($p = 0.951$), with 7.1% of the patients having conisation, 64.9% treated by surgery, 21.9% having radiochemotherapy alone.
Nevertheless, in pT/cT2 the number of patients who underwent surgery alone decreased, while surgery supplemented by adjuvant radiochemotherapy increased. The percentage of radiochemotherapy in patients with positive lymph node status increased from 23.6 to 29.6% ($p = 0.035$).
In lymph node surgery there was a slight increase in the use of sentinel lymph node biopsy from 2.4 to 10.1% ($p < 0.001$). For patients with lymph node dissection the median number of examined lymph nodes increased from 28 to 33 ($p < 0.001$). In surgery of the primary tumour, the percentage of patients with no residual tumour (R0) increased from 85.7 to 91.7% ($p < 0.001$), and was 98.5% in pT/cT1a and 97.6% in pT/cT1b patients diagnosed 2009-2013.
Conclusions: There is a trend towards increased use of radiochemotherapy, especially in advanced stages. In surgery there is a slight increase in the use of sentinel lymph node biopsy and an increase in R0-resections

ID 0224

Distribution pattern of node metastases in advanced ovarian cancer

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Background and Aim: The importance of systematic lymphadenectomy in primary advanced ovarian cancer and its prognostic impact is still unclear. Known is an increasing node affection in advanced ovarian cancer with a rate of about 50% of node metastases. Objective was to delineate the distribution pattern of pelvic and para-aortic node metastases in advanced ovarian cancer.
Methods: 161 consecutive patients with advanced ovarian cancer (FIGO IIIC/IV) were enrolled. All patients got stage related surgery according to FIGO stage. Clinicopathological parameters and the distribution pattern of node metastases influenced by the clinicopathological parameters were evaluated.
Results: Most often serous cancers were detected in advanced ovarian cancer. Node metastases were detected in 62.2% in FIGO IIIC and in 52.9% in FIGO IV. Negative nodes were seen in 22.8% in FIGO IIIC and in 11.8% in FIGO IV. 15% in FIGO IIIC and 38.2% in FIGO IV got no lymphadenectomy. Most often a combined affection of pelvic and para-aortic nodes was seen in both groups. In FIGO IIIC a sole affection of the pelvic and even the para-aortic region was shown in 13.5% vs. 12.7%. Histologic grade 3 and serous histology were associated with node metastases in FIGO IIIC. Node metastases in the pelvic and para-aortic region were most often detected in serous cancers (28%), followed by a sole affection of the pelvic region (15.0% and the sole affection of the para-aortic region (11.2%).
Conclusion: In advanced ovarian cancer node metastases were detected in about 55% of the patients. A systematic lymphadenectomy might detect occult node metastases due to sole affection of para-aortic region in 12.7%. The prognostic impact has to be evaluated in prospective studies.

ID 0239

Influence of educational videos or information sheets on the levels of knowledge and anxiety of patients consulting for cervical dysplasia

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Introduction: Suspicious findings in gynecologic cytodiagnosis causes incertainty and anxiety in patients. We investigated if this anxiety of patients consulting for cervical dysplasia can be influenced by presenting previously different types of information material.
Methods: We included 90 patients between 20 and 77 years of age. Previously, we compiled an educational video and an information sheet. Before their consultation for cervical dysplasia patients were randomized to either receive the information sheet, watch the educational video or stay without any previous information. Anxiety was assessed using the State-Trait Anxiety Inventory (STAI), measuring the state- (STAI-X1) as well as the trait anxiety (STAI-X2). After Intervention a short knowledge test was completed.
Results: In both intervention groups a significant reduction of the anxiety level was achieved ("sheet" $p = 0{,}009$; "video" $p = 0{,}001$), however, fear was reduced more in patients receiving the educational video compared to those who read the information sheet (reduction by 5,704 points versus 3,250 points on the STAI-scale). Regarding the total score achieved in the knowledge test, a significant difference between the intervention groups and the group who did not receive previous information material was found ($p = 0{,}000$), without a significant difference between the two intervention groups ($p = 0{,}968$).
Conclusion: Our data shows that the offer of information materials, either by videos or hand-outs, reduces the anxiety level of patients consulting for cervical dysplasia significantly. Their use should be considered in patients with abnormal cervical cancer screening-test results and should be implemented in the clinical routine.

ID 0241

Salvage chemotherapy for heavily pretreated ovarian carcinoma or related malignancies: High activity of oral treosulfan combined with prolonged low-dose infusional gemcitabine is equal in both platinum-resistant and potentially platinum-sensitive disease

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Background: Treosulfan combined with prolonged low-dose gemcitabine (GeT) has shown promising activity in platinum-resistant EOC. This non-interventional study sought to obtain detailed informations regarding the clinical value of GeT given under routine conditions.
Methods: 59 pts with recurrent EOC (n = 54), fallopian tube cancer (FTC; n = 2), peritoneal papillary-serous carcinoma (PPSC; n = 2), and type II endometrial carcinoma (EC-II; n = 1) were included. Pts had failed a median of 3 prior Ctx, 37 were platinum-resistant (group R) and 22 were sensitive (group S). GeT comprised treosulfan at 1 g/m² PO on d 1-4 and gemcitabine at 450 mg/m² IV (3 h infusion) on d 1 for a q2w schedule. Adverse effects were scored according to CTCAE 4.02. Responses were classified according to the integrated GCIG criteria. PFS and OS were calculated from the start of GeT until progression, death or loss to follow up.
Results: GeT was well tolerated. Hematological side-effects were manageable with G3-4 neutropenia seen in 6, G3-4 anemia in 8, G3 fever in 3, and G4 infection in 1 pt. Non-hematological toxicities exceeded G2 in only 4 pts. A total of 8 CR and 19 PR accounted for an ORR of 45.8%. Adding 16 pts with SD, the clinical benefit rate (CBR) was 72.9%. PFS was 17.3 weeks (wks) and OS was 67.6 wks. No significant differences between groups R and S were found in regard to ORR (40.5 vs 54.5%), CBR (70.3% vs 77.3%), PFS (17.0 vs 18.4 wks), and OS (63.0 vs 72.6 wks). Moreover, prior Ctx with one of the single agents did not lower the likelihood to benefit from GeT.
Conclusions: GeT given under routine conditions is well-tolerated and efficacious in heavily pretreated EOC, FTC, PPSC, and EC-II. Its particularly promising activity in platinum-resistant diseaseshould be further explored in large-scaled prospective clinical trials.

ID 0256

Lifestyle changes in patients following the diagnosis of breast- and/or gynecologic carcinoma

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Introduction: In the past few years the influence of lifestyle factors on the occurrence and development of cancer has increasingly become a subject of discussion. Especially the effects of physical activity, body weight and diet have been researched. This study examines if and which lifestyle changes are being made by women after being diagnosed with breast or gynecological cancer.
Material and Method: 291 patients with gynecologic cancers that underwent surgery in the Klinikum rechts der Isar during 2011-2013 and 285 patients with breast cancer (year 2012) were chosen to participate in this study. A telephone survey was conducted with 333 participants using a questionnaire with detailed questions about the patients' lifestyles before and after receiving the diagnosis.
Results: 90% (299/333) of the surveyed patients changed their lifestyle after the cancer diagnosis. 74% of patients that smoked before their diagnosis (31/42) reduced their cigarette consumption, 36% (107/294) reduced the alcohol intake, 59% (197/333) improved their diet and 33% (110/333) increased their physical activity. 74% (246/333) of the patients stated that they are now less stressed than before their cancer diagnosis, whereof 75% (185/246) stated that they achieved the lower stress levels by actively changing their lifestyle.
Conclusion: 90% of the interviewed patients changed their lifestyle subsequently to being diagnosed with cancer. The impact of lifestyle changes on the quality of life and the course of oncological diseases should increasingly be taken into consideration regarding prevention and therapy of gynecological and breast tumors. For further evaluation, prospective studies in this field are required.

ID 0306

Chemotherapy (CT) ± pertuzumab (P) for platinum-resistant ovarian cancer (PROC): AGO-OVAR 2.20/ENGOT-ov14/ PENELOPE double-blind placebo-controlled randomized phase 3 trial

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Background: Adding P to gemcitabine (GEM) for PROC improved progression-free survival (PFS) in a subset of patients (pts) with low tumor HER3 mRNA expression [Makhija 2010].
Methods: Eligible pts had recurrent PROC (progression [PD] during/within 6 mo of completing ≥4 platinum cycles) with centrally tested low tumor HER3 mRNA expression and ≤2 prior CT lines. Investigators (INVs) chose CT (topotecan [TOP], paclitaxel [PAC] or GEM); recruitment was capped to ensure similarly sized CT cohorts. Pts were stratified by chosen CT, prior anti-angiogenic therapy and platinum-free interval (<3 vs 3-6 mo) and randomized 1:1 to CT with either placebo or P 840®420 mg q3w until PD/unacceptable toxicity. The primary objective was to determine if independent review committee (IRC)-assessed PFS was superior with P + CT vs placebo + CT. Other endpoints include overall survival, INV-assessed PFS, objective response rate, safety and translational research.
Results: Adding P to CT improved clinical benefit rate (CBR; response/stable disease for ≥42 days). Improvements in objective response rate and PFS did not reach statistical significance. Efficacy was inconsistent between chemotherapy cohorts: a more pronounced P effect was seen for PFS in the GEM cohort and for PFS and CBR with PAC, but not with TOP. Tolerability was consistent with the known safety profiles of P and each chemotherapy.
Conclusion: Although the primary objective was not met, subgroup analyses showed trends favouring P in the GEM and PAC cohorts. Imbalances in baseline characteristics may contribute to apparent differences. Further evaluation of these combinations may be warranted.
Sponsor of the study is F. Hoffmann-La Roche Ltd.

ID 0343

Identification of differentially activated signal transduction pathways in platinum-resistant ovarian cancer

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In Ovarian cancer (OC) up to 75% of patients develop recurrent disease due to increasing resistance to *platinum*-based chemotherapy. The molecular mechanisms of resistance development still remain unknown. The goal of this study was to find differences in underlying signaling pathways in resistant and sensitive OC, resulting in a different protein pattern.
24 fresh frozen serous OC tissues were selected and assessed by a pathologist. Out of these samples 12 were classified as resistant and 12 as sensitive to platinum-based therapy according to their clinical response data. Samples were then cut and solubilized in a protein lysis buffer. Lysates were analyzed by DIGI-West, a new antibody-based technique enabling comprehensive protein profiling by using 500 antibodies on one sample.
In between the two groups, three proteins were found differentially expressed and 10 differentially phosphorylated. The proteins were associated with growth promoting signaling pathways, regulators of central epigenetic pathways and the cell cycle. Some of these findings were verified in *in-vitro* studies using the cell lines A2780, A2780cis and OVCAR-3. Cells were classified as sensitive, highly or medium resistant according to their responsiveness to normally used chemotherapeutics (Carboplatin, Paclitaxel) measured by ATP-Assays. Interestingly, protein modification dynamics of two key players in diverse signaling pathways were altered after treatment in sensitive and resistant cell lines.
Consequently, not only the differential protein expression but rather protein modifications may be important in developing platinum resistant ovarian cancer.

ID 0447

Robot-assisted surgery in morbidly obese patients with endometrial cancer

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Objectives: To evaluate feasibility and perioperative morbidity of robot-assisted surgery for morbidly obese endometrial cancer patients
Material and Methods: Data from all endometrial cancer patients with a body mass index (BMI) of ≥40 kg/m^2 planned for robot-assisted surgery between December 2008 and March 2014 at two tertiary referral centers was retrospectively reviewed. Patients' demographics, surgical approach, intraoperative complications, and perioperative morbidity for at least 1 year post surgery were analyzed.
Results: Fifty one morbidly obese endometrial cancer patients were included. The median BMI was 43 kg/m2 (range 40-69 kg/m2). In 46 patients simple hysterectomy was carried out, five patients received radical hysterectomy. Pelvic- or pelvic- and paraaortic lymph node dissection was added in 18 patients. Intraoperatively two patients (3.9%) required repair of visceral organ- or vessel damage, one patient (2.0%) required conversion to laparotomy due to inadequate exposure of paraaortic lymph nodes. A postoperative complication mandating secondary surgery was found in 3 patients (5.9%), including one patient with vaginal cuff dehiscence, and two patients with bowel herniation. Readmission for conservative management of complications was observed in three further patients (5.9%).
Conclusions: Robot assisted hysterectomy in morbidly obese women with endometrial cancer can be performed with a low conversion rate and acceptable morbidity.

ID 0452

Management of recurrent and metastatic endometrial cancer in Germany: Results of the nationwide AGO pattern of care studies from the years 2013, 2009 and 2006

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Fragestellung: The available literature on the treatment options for recurrent and metastatic endometrial cancer (EC) is full of controversies. Therefore, we explore the results of the AGO pattern of care studies from the years 2013, 2009 and 2006.
Methoden: A questionnaire was developed and sent to all 682 German gynecological departments in 2013 (775 in 2009, 500 in 2006, respectively). The results of the questionnaires were compared with each other using Fisher's exact test.
Ergebnisse: Responses were available in 40.0% in 2013, 33.3% in 2009 and 35.8% in 2006. In 2013 the most preferred endocrine drug was progestin (79.8), followed by tamoxifen (42.8%), aromatase inhibitor (19.8%), fulvestrant (16.3%) and a combination (3.9%) ($p < 0.001$). 65.3%, 59.8%, 51.7% and 38.2% of the participants used platinum, taxane, a combination of cytostatic drugs, anthracycline in metastatic EC, respectively ($p = 0.215$). 96.2%, 92.7%, 49.8% and 60.9% of the participants performed an operation, radiotherapy, endocrine therapy and chemotherapy in 2013 because of a local recurrence, respectively ($p < 0.001$). Compared to 2009 and 2006 these rates remained stable (no p-value <0.05). Because of a distant metastasis 50.4%, 64.2%, 78.5% and 90.8% of the participants performed an operation, radiotherapy, endocrine therapy and chemotherapy in 2013, respectively ($p < 0.001$). Compared to 2009 and 2006 more participants performed an operation or radiotherapy and less an endocrine treatment.
Schlussfolgerungen: Whereas progestin was the favorite drug, the participants of this study did not prefer a specific cytostatic drug for metastatic EC. This might reflect the available literature, which did not provide a real standard of care.

ID 0455

Comparison of delphi screener and evalyn brush self-samplers for HPV screening in low resource settings (accessing*)

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Objective: To compare the feasibility of using the self-sampling devices Delphi Screener or Evalyn Brush with HPV genotyping and the low-complexity Arbor Vita OncoE6™ test for cervical cancer screening in low resource settings.
Methods: During 2 pilot studies 400 women (200 HIV+, 200 HR-HPV) were recruited at Catholic Hospital Battor. 250 women (100 HIV+, 150 HR-HPV) collected samples with the Delphi Screener and 150 women (100 HIV+, 50 HR-HPV) with the Evalyn Brush. Cytobrush and swab samples were reference samples. Samples were tested with the Arbor Vita OncoE6™ Cervical test in Ghana and HPV genotyped with GP5+/6+ PCR followed by Luminex-MPG readout at the Charité Universitätsmedizin Berlin.

Results: HPV genotyping for 27 HPV types performed on Delphi Screener samples showed 50% Sensitivity and 99% Specificity compared to the cytobrush sample. Evalyn brush samples revealed 86% Sensitivity and 98% Specificity.
The Arbor Vita OncoE6 cervical test was positive for the respective HPV type for all patients with CIN3+ sampled with the Delphi Screener. The Evalyn brush revealed less positive results but histological confirmation of these results is still ongoing.
Conclusions: These pilot studies show that the sensitivity of HPV genotyping is higher when using the Evalyn Brush for self-sampling compared to the Delphi Screener. Furthermore, Delphi Screener sample is not inferior to the swab sample for the OncoE6 cervical test.
We conclude that Delphi Screener and Evalyn brush is feasible for cervical cancer screening by HPV testing in low resource settings and could allow screening women "on the doorstep" in their rural communities.

*ACCESSING (Adequate Cervical cancer Capacity building, Education and Screening by new Scientific INstruments in Ghana): GIZ/ESTHER funded trial

ID 0457

SPECT/CT for preoperative SLN detection in vuvlar cancer: Improved detection and anatomical localization of SLN by threedimensional visualization

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Objective: We evaluated the feasibility and clinical advantages of single photon emission computed tomography with CT (SPECT/CT) for sentinel lymph node (SLN) detection in vulvar cancer.
Methods: During this unicentric trial vulvar cancer patients underwent preoperative SLN marking (10 MBq Technetium(TC)-99m-nanocolloid) and subsequent planar lymphoscintigraphy (LSG) and SPECT/CT for SLN visualization. Directly before surgery, patent blue dye was injected. We analysed the sensitivity, negative predictive value and false negative rate.
Results: At Hannover Medical School, 40 patients suffering from vulvar cancer underwent SLN dissection after preoperative LSG and SPECT/CT. The mean diameter of all tumours in final histology was 2.23 (0.1-10.5) cm with a mean tissue infiltration of 3.93 (0.25-11) mm.
SPECT/CT identified significantly more SLNs (mean 8.7 (1-35) LNs per patient) compared to LSG (mean 5.9 (0-22) LNs, $p < 0.01$). Additionally, due to its high spatial resolution SPECT/CT allowed for the detection of aberrant lymphatic drainage. In detail, aberrant lymphatic drainage was detected in 7/40 (17.5%) patients. Regarding inguino-femoral LNs, for all patients who underwent complete groin dissection, sensitivity was 100%, NPV 100% and false negative rate 0%.
Conclusion: Due to its higher detection rates compared to planar LSG, its spatial resolution and three-dimensional anatomical localisation of SLNs, SPECT/CT provides the surgeon with important additional information, facilitates intraoperative SLN detection and predicts aberrant lymphatic drainage. The clinical impact of aberrant lymphatic drainage has to be further evaluated.

ID 0471

Primary diffuse large B-cell lymphoma with manifestation in uterus: Cases duplicity in gynecological oncology 2015

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Objective: Primary lymphomas in the female genital tract are very rare. More cases are non-Hodgkin lymphomas of which diffuse large B-cell lymphomas (DLBCL) are most commonly seen. The presented symptoms are non-specific and associated with common disorders in gynecology: abdominal pain, abnormal bleeding ex uterus, hydronephrosis.
Methods: We present two cases of primary DLBCL of uterus, which are diagnosed and treated 2015 in our hospital. Both patients had an extensive infiltration of the uterine corpus and were primarily inoperable.
Results: Histological diagnosis was confirmed by biopsy in surgery setting: the first one (52 year old) by laparotomy and the second one (80 year old) by laparoscopy. Immunhistological examination revealed for both patients the typical findings for DLBCL with CD 20 positive B-Blasts and high proliferation fraction (Ki-67) of 70%. Case 1 was staged Ann Arbor IV A IPI low risk, case 2 was staged Ann Arbor IVA, IPI high risk. Both patients received R-CHOP regimen, the elder one with a prephase of Vincristine and Prednisone. Follow-up is ongoing.
Conclusion: Due to similar symptoms of DLBCL of uterus and more common gynecologic disease, including leiomyoma or sarcoma, this differential diagnosis should be considered until the correct diagnosis is confirmed by immunhistochemical analysis. In case of malignant lymphoma hysterectomy is not recommended for primary treatment with curative intention and systemic polychemotherapy should be initiated as soon as possible.

ID 0481

Experiences with off-lable use of bevacizumab in patients with first-diagnosed locally advanced and metastatic cervical cancer

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Introduction: Invasive cervical cancer is the fourth most cancer of women in western civilization. Complete recurrence rates after neoadjuvant therapy in bulky disease remain poor and new strategies are needed. Here, we present our clinical experiences with platinum- and taxane based cytotoxic therapy in combination with bevacizumab in patients with cervical cancer.
Methods: All patients from 2008–2015 with locally advanced and metastatic cervical cancer who have been treated with radiochemotherapy or platinumbased chemotherapy in combination with or without bevacizumab were included in this retrospective study.
Results: We identified 32 patients, who have been treated with neoadjuvant chemotherapy or radiochemotherapy. 23 patients received cisplatin and docetaxel, four of these patients underwent a combined radiochemotherapy in FIGO stage III and IV. Four patients received platinum-based chemotherapy in combination with bevacizumab, whereas one patient had FIGO stage IIb and two patients had FIGO stage IVa. The fourth patient had a FIGO stage IVb cervical cancer due to liver metastasis. Complete pathologic recurrence could be achieved in patients with FIGO stage I or II cervical cancer. In FIGO stage III and IV no complete pathologic recurrence was noted. In combination with bevacizumab two complete pathologic recurrences, one complete clinical recurrence and one partial pathologic recurrence was observed.
Conclusion: Our results show that a complete pathologic recurrence with conventional neoadjuvant chemotherapy is possible in early stage (FIGO I) cervical cancer. Moreover, patients with advanced and/or metastatic cervical cancer can benefit from bevacizumab in combination with conventional neoadjuvant chemotherapy.

ID 0505

A new tool for detection of HPV E7 proteins in cervical samples

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Background: Persistent infection with high-risk human papillomavirus (hrHPV) types is a prerequisite for development of cervical dysplasia and cancer. During progression, deregulation and overexpression of viral proteins E6 and E7 occur, leading to loss of cell cycle control and neoplastic transformation. Current cervical cancer screening methods rely on cytological analyses compromised by frequent false-negative results and thus low sensitivity. HPV DNA-based tests pick up frequently infections without underlying disease leading to a low specificity. A more effective and reliable screening approach may involve exploitation of the oncoproteins E6 and E7 for specific detection of cervical dysplasia.
Method: RabMabs with high specificity and sensitivity against the E7 protein of different hrHPV types were generated and a hrHVP E7 ELISA was developed.
Results: The ELISA was validated with recombinant proteins of all HPV types included and with cell lysates of cervical cancer cell lines CaSki (HPV16+), HeLa (HPV18+), and MS751 (HPV45+). The proof of concept was also shown by measurement of well characterized clinical samples. Furthermore, sensitivity, specificity, and positive and negative predictive value (PPV/NPV) of the ELISA is being calculated by several clinical studies: (i) feasibility of the ELISA in a routine screening setting, (ii) triage tests in patients with HPV infection or equivocal cytology results (ASCUS and LSIL), and (iii) a test of cure to monitor successful therapy in CIN2/CIN3/AIS.
Discussion: As E7 expression is upregulated in high grade dysplasia the hrHPV E7 ELISA has a high potential for detection of dysplasia with a higher specificity for disease than HPV DNA-based tests.

ID 0507

Her2-neu score as a prognostic factor for outcome in patients with triple-negative breast cancer

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Purpose: Triple-negative breast cancer (TNBC) is characterized by a strong heterogeneity as well in the tumour biology as in the clinical course of disease. This study has the aim to analyse if there are any prognostic factors which are able to predict the individual outcome of patients with TNBC. Main goal of this analysis is to find out if there are any differences with regard to the chances of survival between patients with TNBC and a Her2-neu score 0 versus 1+2.
Experimental Design: Retrospectively, we studied a cohort of 1014 patients with TNBC, diagnosed at the Saarland University Medical Center, Medical Center – University of Freiburg, University Hospital Düsseldorf, University Hospital Schleswig-Holstein/Campus Luebeck, Medical Faculty and University Hospital Carl Gustav Carus/Dresden, Hospital St. Wendel and Hospital Idar-Oberstein between May 2002 and February 2015. We compared the disease-free survival (DFS) and overall survival (OS) in those women on the basis of the different Her2-neu scores (0 versus 1 or 2 with negative FISH).
Results: 1014 patients were included in this study. 44.08% of them had a T2-4 tumour.
31.07% were nodal positive and 70.51% had high grade tumours. The Her2-neu score of all participating patients was determined. 57.99% of them had a Her2-neu score 0. We found out that in addition to tumour size and nodal status the Her2-neu score is an important prognostic factor. This study shows that TNBC patients with a Her2-neu score 0 had a significantly poorer outcome regarding DFS ($p = 0.0002$) and OS ($p = 0.0068$). In contrast grading does not seem to have any prognostic value in TNBC.
Conclusion: The Her2-neu score 0 is able to function as a prognostic factor in patients with TNBC.

ID 0509

A unique Assay for Verification of cervical Cancer tests targeting specific cytoskeletal Biomarkers

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Background: Cervical cancer is one of the leading causes of cancer morbidity and mortality in women, with more than 98% related to a human papillomavirus (HPV) infection. HPV is known to infect basal keratinocytes. The stratified squamous epithelium of the cervix consists of multiple layers of cells. By cervical sampling, only the most superficial layers are scraped away for analysis. Incorrect sampling of superficial layers only could easily lead to false results. To ascertain that a proper sampling has been taken, validity testing of cervical samples is required.
Method: For this purpose, a unique ELISA was developed for detection of basal keratinocytes by specific cytoskeletal protein in cervical cell lines and smear samples. Cervical samples were analyzed for presence of HPV and carefully characterized by microscopy for presence or absence of basal cells.
Results: The ELISA was validated with cell lysates of different cell lines of cervical origin and the proof of concept was shown by measurement of well characterized clinical samples. Linearity between number of cells and signal strength was demonstrated by measurement of dilution series of cell lysates. Samples of healthy donors as well as from patients with different progression stages resulted in signals if basal cells were present in the sample (confirmed by microscopy); whereas samples which contained only superficial cells did not result in any signals at all. Hence, differentiation between valid and invalid sampling was shown.
Discussion: Usage of a biomarker for testing of cervical samples may be important for valid interpretation of negative results obtained in cervical cancer tests.

ID 0519

Langzeitanwendung von Eribulin 1,23 mg/m² an d1/8 q3w beim stark vorbehandelten und fortgeschritten metastasierten Mammakarzinom – ein Fallbericht

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Fragestellung: Beim fortgeschrittenen metastasierten Mammakarzinom sind nach mehreren Vortherapien die Therapieoptionen zum Teil begrenzt. Mit Eribulin steht seit der Zulassung eine weitere Therapieoption zur Verfügung.

Methoden: Wir berichten über den Fall einer 60 jährigen Frau mit metastasiertem Mammakarzinom die als Sechstlinien Therapie mit Eribulin behandelt wurde. Insgesamt erhielt die Patientin 49 Zyklen Eribulin ohne nennenswerte Nebenwirkungen und dem enormen Benefit eines stabilen Erkrankungsstadiums über 34 Monate bis zur Progression.
Ergebnisse: Unsere Patientin ist eine 60-jährige Patientin mit Erstdiagnose eines invasiv ductalen Brustkrebs (pT1c, pN1b (3/6), cM0, G2) im Jahr 1991 im Alter von 38 Jahren.
Nach entsprechender Stadiengerechter Therapie mit Brusterhaltender Therapie sowie Axilladissektion, adjuvanter Radiatio sowie Chemotherapie mit 6 Zyklen CMF kam es im Jahr 2007 zur Erstdiagnose von Metastasen bei nun Pulmonal und ossär metastasiertem, axillär rezidivierten invasiv ductalen Mammakarzinom. Nach weiteren endokrinen und palliativen Chemotherapien entschieden wir uns bei erneuten Progress zur Anwendung von Eribulin in der Sechsten Linie. Bei insgesamt guter Verträglichkeit konnten insgesamt 49 Zyklen Eribulin in der Langzeittherapie durchgeführt werden.
Zusammenfassung: Unser Fall verdeutlicht, dass Eribulin eine angemessene therapeutische Option für ein metastasiertes Mammakarzinom, auch in stark vorbehandelten Patienten, darstellt und eine Langzeittherapie ohne nennenswerte Nebenwirkungen möglich ist.

ID 0522

Functionality of the tumor suppressor microRNA-1 in ovarian cancer progression

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Backround: Even though ovarian cancer (OC) represents the most lethal cancer in gynecologic oncology, an unsatisfactory characterization of the underlying molecular and cellular mechanisms primarily prevents the development of promising future approaches for diagnosis, prognosis and treatment benefit. In this study we examined the role of the tumor suppressor microRNA-1 (miR-1) in OC cells and OC tumor samples to evaluate miR-1 as a putative biomarker.
Materials and Methods: miR-1 levels were detected by quantitative RT-PCR applying total RNA preparations from OC cell lines and tumor samples. For in vitro modulation of miR-1 expression, a miR-1 encoding overexpression vector was cloned and applied in subsequent transfection experiments. miR-1 functionality in OC cell lines was assessed by cell growth kinetics.
Results: In OC cell lines, surprinsingly, higher miR-1 levels were linked to higher cell growth rates. Subsequently, experimental upregulation of miR-1 failed to significantly alter cellular growth compared to control cells. Further analysis of OC patients samples (1) revealed no significant differences between healthy and malignant ovary tissue samples, and (2) showed increased miR-1 levels in relapsed tumors compared to primary tumor tissue.
Conclusion: miR-1 has been characterized as an anti-proliferative, and anti-metastatic tumor suppressor in several solid cancer entities. This study exhibited that OC cell growth was not affected by high levels of miR-1, which points to a so far unknown dysregulation of miR-1 dependent signaling and/or effector cascades. Despite the disordered functionality of miR-1 in OC cells, however, increased expression of miR-1 during OC progression may serve as biomarker for tumor relapse.

ID 0539

The impact of age on comorbidity, toxicity of chemotherapy and survival in recurrent ovarian cancer patients

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Background: Elderly patients are the fastest growing patient group in ovarian cancer. However, they frequently receive suboptimal treatment and enrollment in clinical trials is less frequent. Aim of this study was to assess the impact of age on comorbidity, toxicity of chemotherapy and survival in recurrent ovarian cancer.
Methods: This individual participant data meta-analysis of three phase II/III trials of the North-Eastern German Society of Gynecological Oncology (NOGGO) includes 1213 patients with recurrent ovarian cancer and was conducted using multivariate logistic and cox regression analyses.
Results: Median age at randomization was 62 years. Patients were divided into two patients' groups: < 65 years (n = 864) and ≥ 65 years (n = 349). Comorbidities such as diabetes (p = 0.001) and cardiovascular disease (p < 0.001) were more frequent in the elder age group. Elderly patients developed hematological grade III/IV toxicity more often (p = 0.03 OR 1.35). Regarding non-hematological grade III/IV toxicity there was a difference seen in cardiovascular toxicity (p = 0.04 OR 1.83). Dose reductions were not more frequent in patients ≥ 65 years (p = 0.96). Median progression free survival was 8.2 months in the younger age group and 6.7 months in patients ≥65 years (p = 0.053 HR 1.14).
Conclusion: Comorbidities and hematological toxicity are more frequent in elderly patients and should be closely monitored. Elderly patients should not be excluded from clinical trials just because of their age.

ID 0545

Laparoskopische Corpus-und Cervixcarcinom-OPs: Erfahrungen eines universitären Zentrums

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Fragestellung: Endoskopische OP-Verfahren bei Patientinnen mit frühen Stadien eines Corpus- und Cervixcarcinoms gelten seit Jahren als onkologisch sicher. Dennoch stellt die Laparoskopie viele Kliniken vor einer Herausforderung. Ziel unserer Arbeit war es den EInfluss durch die steigende Erfahrung des Operateurs und weitere Qualitätsmerkmale, die sich auf das Outcome dieser Patientinnen auswirken, anhand unseres Kollektivs zu ermitteln.
Material/Methoden: 225 Patientinnen mit einem frühen Stadium eines Corpus- und Cervixcarcinoms wurden zwischen 01/10 und 09/14 in unserer Klinik laparoskopisch operiert. Von den 95 Patientinnen mit einem Cervixcarcinom erhielten eine radikale Trachelektomie und 85 eine radikale Hysterektomie und LNE pelvin und paraaortal. Von den 130 Patientinnen mit einem Corpuscarcinom erhielten alle eine TLH mit Adnexektomie bds. und pelviner und paraaortaler LNE. Die demographischen Daten, intraoperative Verläufe und das postoperative Outcome wurden retrospektiv ausgewertet.
Ergebnisse: Die durchschnittliche Cervixcarcinompatientin war 51J alt. Die mittlere OP-Zeit betrug 247+/-82min; es wurden im Mittel 18 Lkn entnommen. Ein Rezidiv trat in 9 Fällen auf (11%). Die durchschnittliche Corpuscarcinompatientin war 67J alt u. Die mittlere OP-Zeit betrug 205+/-77min; es wurden im Mittel 15 Lkn entnommen. Ein Rezidiv trat in 7 Fällen auf (5%). Ein Abfall der OP Zeiten konnten bei allen Verfahren innerhalb von 1Jahr festgestellt werden, die entnommene Lkn Anzahl blieb im Verlauf gleich, die restlichen Parameter (Konversionsrate, Komplikationen, Transfusionsrate etc) waren bei beiden Carcinomen ähnlich gering.
Schlussfolgerung: Man kann einen Lerneffekt innerhalb von 20 Operationen im Durchschnitt erzielen.

ID 0551

A simple and precice Test towards Prevention of HPV induced Cancers via direct Detection of the viral E6 Oncoprotein

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Background: Unlike for many cancers, the causing molecular agents for cervical and anal cancer have been identified in nearly 100% as the up-regulated expression of HPV encoded oncoproteins. While prevalence of anogenital HPV infection in general populations is high (10-20%), most infections are without relevant clinical consequences. Few infections undergo genomic changes causing elevated expression of the viral oncoproteins (E6 and E7), thus increasing the risk of oncogenic transformation. This prompted development of a test for HPV induced cancers based on detection of elevated E6 oncoprotein (Onco*E6*™ Cervical Test; Arbor Vita Corp, Fremont, USA).
Method: The Onco*E6*™ Cervical Test format is lateral flow, based on E6-specific antibodies, with visual readout. The test is simple to perform and void of any complex machinery or cold chain requirements.
Results: The test format and the high specificity for detection of disease or the future risk thereof, make the Onco*E6*™ Cervical Test a diagnostic option for cancer prevention in developing countries, where scarce resources call for highly efficient yet simple to implement tests. In the developed world, the specificity of ~ 99% (CIN3+) and the high positive predictive value (for CIN3 > 40% vs <10% for HPV testing in a typical developed country setting) suggest use in triage of subjects who are positive for HPV, or for subjects with otherwise undetermined pathology. In several instances, pathology negative subjects by cytology with positive Onco*E6*™ Cervical Test were found to have high grade disease upon histology examination.
Discussion: The test format, its suitability for a variety of use scenarios and results from clinical studies in China and Ghana (ACCESSING study) will be presented.

Head and Neck Cancer

ID 0023

Improvement in survival in patients with oral squamous cell carcinoma

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Background: An association between the survival of patients with oral squamous cell carcinoma (OSCC) and advancements in diagnosis and therapy has not been established.
Methods: This was a retrospective, longitudinal, international, population-based study of 2738 patients who underwent resection of OSCC during 2 different decades. Characteristics of patients from 7 international cancer centers who received treatment between 1990 and 2000 (group A; n = 735) were compared with patients who received treatment between 2001 and 2011 (group B; n = 2003).
Results: Patients in group B had more advanced tumors and tended to develop distant metastases more frequently than patients in group A ($p = 0.005$). More group B patients underwent selective neck dissection and received adjuvant radiotherapy ($p < 0.001$). Outcome analysis revealed a significant improvement in 5-year overall survival, from 59% for group A to 70% for group B ($p < 0.001$). There was also a significant improvement in disease-specific survival associated with operations performed before and after 2000 (from 69% to 81%, respectively; $p < 0.001$). Surgery after 2000, negative margins, adjuvant treatment, and early stage disease were independent predictors of a better outcome in multivariate analysis. The decade of treatment was an independent prognostic factor for cancer-specific mortality (hazard ratio, 0.42; 95% confidence interval, 0.3-0.6).
Conclusions: The survival rate of patients with OSCC improved significantly during the past 2 decades despite older age, more advanced disease stage, and a higher rate of distant metastases. The current results suggest that the prognosis for patients with OSCC has improved over time, presumably because of advances in imaging and therapy.

ID 0058

The value of the HPV status and its detection methods in oral and oropharyngeal squamous cell carcinomas- a meta-analysis

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The current controversial study about the disease-specific survival of patients with HPV positive and negative squamous cell carcinoma of the head neck region (HNSCC) was crucial for the implementation of this meta-analysis.
Different detection methods for HPV are available, often with lacking sensitivity. As a consequence, this leads to a false interpretation of survival rates and the HPV status is playing a non-durable relevance.
170 studies were evaluated from 2007 to 2014 in this meta-analysis. The HPV detection methods, patient characteristics, tumor localisations and stages; as well as (neo-) adjuvant therapies and survival times were analysed.
The evaluation of these studies showed that the survival rates in many studies were not multifactorial evaluated and important confounders were excluded in the statistics. The used HPV detection methods were often not sufficient in representing HPV positivity. In addition, oropharyngeal and oral squamous cell carcinomas were assessed together in the localization in a variety of studies, which is not sustainable in terms of the survival of these patients. The widely differing number of HPV positive patients in the various studies (range 7% - 62%) could be explained by insufficient detection methods and by a lack of localization distinctions. Our meta analysis confirmed the results of our experimental study. The discussion about different therapies according to the HPV status should be rejected based on present knowledge. Previously published studies should be read very critical and do not represent a basis for therapeutic decisions.

ID 0063

The oral cancer awareness campaign in Schleswig-Holstein: Conceptual background and design to increase early detection of oral cancer

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Background: About 13,000 people are annually diagnosed with oral and pharyngeal caner in Germany. The majority of these cases are still diagnosed at advanced stages. International studies and also own results have shown a substantial lack of knowledge about the existence, symptoms, risk factors and early detection among the public, especially in groups affected by certain socio-economic factors. The aim was to implement and to evaluate an oral cancer campaign based on the conceptual steps of health communication strategies.
Methods: The conceptual background, based on preliminary comprehensive studies, was developed. The design of the layout and slogan, the communication channels, media carrier, were identified by a qualitative exploration. A flowchart was developed to schedule content and time flow of the campaign, and the use of each medium was documented. For the evaluation, a comprehensive survey was carried out by telephone interview.
Results: The state-wide awareness campaign was launched with the focus on the target group ≥50 years in urban areas in April 2012. The campaign process combined the recommended mediamix divided in mass media, interpersonal communication, PR and medical journalistic network, and local events. In order to reach the high-risk group, a regional network including e.g. health authorities and charities was established. Evaluations were carried out in March 2012 (baseline) and in November 2012, 2013 and 2014.
Conclusion: Typical lifestyles including media usage as well as known risk factors were taken into account to address the target group. The flowchart was successfully realised and the first results confirmed the selected conceptual strategy.

ID 0064

In vivo detection of circulating tumor cells during tumor manipulation

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Background: Melanoma of the head and neck and its treatment are complex issues. The behavior of head and neck melanoma is aggressive, and it has an overall poorer prognosis than of other skin sites. The goal of this research was to determine if melanoma manipulation could enhance penetration of cancer cells from the primary tumor into the circulatory system.
Methods: Nude mice were inoculated with melanoma cells in the mouse ear. Blood vessels were monitored for the presence of circulating tumor cells (CTCs) using *in vivo* photoacoustic (PA) flow cytometry (PAFC). The implanted tumor underwent compression, incisional biopsy, or surgical excision, and the release of CTCs was monitored using *in vivo* PAFC in real time.
Results: We discovered that some medical procedures, like compression of an implanted tumor of a mouse model or an incisional biopsy, may either initiate CTC release in the blood which previously contained no CTCs or dramatically increased (10-30-fold) CTC counts above the initially recorded level.
Conclusion: These findings indicate that some intervention (such as palpation during physical exam, or incisional biopsy) can potentially enhance penetration of cancer cells from a primary tumor into the blood circulation, which may increase the risk of metastases.

ID 0095

Ibuprofen and diclofenac restrict migration and proliferation of human glioma cell lines *in vitro*

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Non-steroidal anti-inflammatory drugs (NSAIDs) have been related to anti-tumorigenic effects in different tumor entities. For glioma, research focus concentrates on diclofenac. Data on other NSAIDs, such as ibuprofen, is limited. We therefore performed a comprehensive investigation of the cellular, molecular and metabolic effects of ibuprofen in comparison to diclofenac on human glioblastoma cells.
Ibuprofen treatment led to a stronger inhibition of cell growth and migration of glioma cell lines than treatment with diclofenac. Proliferation was affected by cell cycle arrest at different checkpoints by both agents. In addition, diclofenac, but not ibuprofen, decreased lactate levels in all concentrations used. Both decreased phosphorylation of the signal transducer and activator of transcription 3 (STAT-3), but whereas diclofenac led to decreased c-myc expression, and lactate dehydrogenase-A (LDH-A) activity, treatment with ibuprofen had no impact on c-myc and less on LDH-A expression. The specific effects of diclofenac and ibuprofen on STAT-3 were investigated by comparison with those of the specific STAT-3 inhibitor STATTIC.
This study indicates that, both ibuprofen and diclofenac strongly inhibit glioma cells, but the subsequent metabolic responses of both agents are varying. We postulate that ibuprofen may inhibit tumor cells also by COX- and lactate-independent mechanisms on long-term treatment in physiological dosages, whereas diclofenac mainly acts by inhibition of STAT-3 signaling and downstream modulation of glycolysis. Further comparative studies will affirm the effects of ibuprofen and diclofenac on glioma cells *in vitro* and *in vivo* and compare their molecular mechanisms of action in more detail.

ID 0096

Isolation and characterization of human brain tumour initiating cells leading invasion in an *in situ* migration model

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Glioblastoma multiforme (GBM) is one of the most aggressive cancers. Fast and widespread invasion of the brain parenchyma by a subpopulation of progenitor tumour cells is a main pathophysiological feature of glioblastoma, which renders localized therapies ineffective. In consequence, the tumour cell fraction of invasive progenitors is a strategic prime target for early and sustained anti-invasion therapies.
Invasion of GBM cells was induced and investigated in an *in situ* model of organotypic brain slice cultures (OBSC), a valuable tool to analyse migration and invasion in conditions simulating normal brain tissue.

Invasion of GBM cells is induced by inoculation of fluorescence tagged human brain tumour initiating cells (BTIC) in the hippocampal region of OBSCs and monitored for three weeks. During this analysis, invasive (leader) cells emerge from the initial cell population, thus driving invasion into the surrounding tissue. Those invasive cells differ in morphology and behaviour from stationary cells that remain at the implantation site. To assess the leader cell expression profile, a micromanipulator adapter was developed to isolate the different cell subpopulations from the OBSCs. After cDNA library generation and subsequent microarray analysis, a detailed comparison revealed a markedly distinct expression pattern of invasive cells. This led to the identification of a leader cell-specific expression signature. This molecular signature is currently verified in fresh patient tumour biopsies and other BTICs analysed in the OBSC model. Overall expressed genes specific for leader cells will shed light on the chronology of one of the gliomagenesis milestones and tumorigenicity of BTICs.

ID 0102

Invasive Head and Neck Cancer – Data of a population-based Clinical Cancer Registry

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Introduction: Head and neck cancers represent 3.7% of all male and 1.5% of all female malignant tumours in Germany.
Objective: The aim of this analysis was to examine frequency and outcome of patients with cancer of the oral cavity, pharynx or larynx in a population-based setting.
Methods: 9373 patients with an invasive carcinoma of oral cavity, pharynx, and larynx diagnosed between 1998 and 2013 in the catchment area of the Munich Cancer Registry (MCR) (Upper Bavaria and in part Lower Bavaria, population meanwhile 4.6 million) were analysed stratified by tumour site. Cumulative incidence (CI) was used to calculate time to locoregional recurrence (LRR) and time to distant metastasis (dMET). Survival was examined by Kaplan-Meier method, calculation of relative survival and Cox proportional hazard model.
Results: The most frequent cancer sites are oropharynx (31.3%) and oral cavity (29.5%), larynx (22%) and hypopharynx (14.8%) were less frequent; nasopharynx (2.4%) was rare. All sites were more frequent in male than in female. Together the most favourable stage distribution is in oral cavity (UICC stage I 32%, IV 37%), advanced tumour stage is most in hypopharynx with 83% UICC IV, thereunder 12% primary M1.
10-year CI of LRR is 16% to 23% (nasopharynx and oral cavity). 10-year CI of dMET in primary M0 is 11% in larynx and oral cavity and 30% in hypopharynx. 10-year relative survival is the best in laryngeal and nasopharyngeal cancer with 52% and the worst in hypopharyngeal cancer with 22%. Cox regression shows the best prognosis for nasopharynx, followed by larynx, oropharynx, oral cavity and the worst prognosis for hypopharynx.
Conclusion: Given the moderate prognosis of head and neck cancer the only chance for cure is a diagnosis in early tumour stage.

ID 0124

Deeskalationsstrategie beim Oropharynxkarzinom – Risikostratifikation an einer prospektiv erfassten, primär chirurgisch therapierten Kohorte

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Fragestellung: Für das Oropharynxkarzinom (OSCC) wird aktuelll die Deeskalation der Therapie in klinischen Studien geprüft. Die Risikostratifizierung wurde dabei auf Grundlage klinischer Studien ohne chirurgische Therapie ermittelt. In Deutschland werden jedoch über 50% der Patienten primär chirurgisch behandelt. Ziel war es, an einer prospektiv erfassten Kohorte bekannte Risikomodelle zu überprüfen und ein alternatives Modell vorzuschlagen.
Methoden: 396 Patienten mit neu aufgetretenem OSCC wurden von 2000–2009 erfasst und biometrische, klinische und histologische Risikoparameter wurden ausgewertet. Der HPV-Status wurde bei allen Patienten mittels DNA- und p16-Test bestimmt. Die Nachbeobachtungszeit lag im Mittel bei 5,9 Jahren. Rezidivfreies- und Gesamtüberleben (OS) wurden mittels uni- und multivariater Analysen und Rekursiver Partitionierung (Recursive Partitioning (RP) Analysis) ausgewertet.
Ergebnisse: 75/380 (19,7%) der Patienten waren HPV-positiv. Nach Anwendung des Modells von Ang et al. (NEJM 2010) ergab sich ein 5-Jahres OS von 84% (n = 52) für low-risk-, 53% (n = 37) für intermediate-risk- und 35% (n = 248) für high-risk-Patienten. Die Verteilung der Gruppenstärken und die Konfidenzintervalle zeigten jedoch keine ausreichende Diskrimination. Mittels RP-Analysen wurde ein Modell für die Risikostratifizierung von primär chirurgisch therapierten OSCC entwickelt. Anstatt Niktinabusus wurde der Performance Status als wichtiger Einflussfaktor für das Überleben herausgearbeitet.
Schlussfolgerung: Die nach Radiochemotherapie entwickelte Risikostratifizierung für OSCC ist für primär chirurgisch behandelte OSCC in Deutschland möglicherweise nicht valide. Alternative Algorithmen zur Risikoeinschätzung müssen daher entwickelt werden.

ID 0139

Changes in macrophage polarization between diagnostic biopsy and tumor resection in oral squamous cell carcinomas

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Background and objectives: The prognosis of solid malignancies was shown to be associated with immunologic parameters, such as macrophage polarization (M1/M2). Recently, it was reported that preoperative oral surgery leads to a worsening of prognosis in oral squamous cell carcinomas (oscc). Diagnostic incision biopsies can be considered as oral surgery procedures that might lead to healing-associated M2 macrophage polarization with a potential negative influence on tumor biology. It is not known if biopsies of oscc induce a M2 polarization of macrophages in the tumor microenvironment.
Methods: Diagnostic biopsies (n = 25) and tumor resection specimens (n = 34) of T1 and T2 oral squamous cell carcinomas (oscc) were investigated by immunohistochemistry. Automated staining with an LSAB kit was used to detect CD68, CD11c, CD163 and MRC1 positive cells. Complete digitalization of all samples using "whole slide imaging" and quantitative assessment of the number of stained cells per area was performed.
Results: Tumor resection specimens showed a significantly ($p < 0,05$) increased infiltration of CD163 positive M2 macrophages compared to diagnostic biopsies. Additionally, the CD163/CD68 ratio as indicator of M2 polarization was significantly ($p < 0,05$) higher in tumor resections compared to biopsy specimens.
Conclusion: In the time interval between the diagnostic biopsy and the definitive tumor resection a shift towards M2 polarization in seen in tumor associated macrophages. M2 macrophages are shown to have tumor promoting capabilities and are associated with tumor progression and increased malignancy. The prognostic relevance of a biopsy derived shift towards M2 polarized macrophages should be investigated in clinical trails.

ID 0146

Association of macrophage polarization with tumor outcome in early stage oral squamous cell carcinomas

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Background and objectives: Macrophage polarization correlates with the prognosis of solid malignancies and is associated with the occurrence of lymph node metastases in oral squamous cell carcinomas (oscc). Early stage (T1/T2, N0) oscc are characterized by a good prognosis and can be cured by surgery. The postoperative regime usually contains no adjuvant radio-/chemotherapy. The current pilot study should elucidate if macrophage polarization in tumor resection specimens and diagnostic biopsies of early stage oscc is associated with tumor outcome.
Methods: Patients with T1/T2, N0, R0>5mm oscc without adjuvant therapy and 3 year follow-up after tumor resection were retrospectively selected. Tissue microarrays (TMA) containing diagnostic biopsies (n = 17) and tumor resection specimens (n = 17) were processed for immunohistochemistry in this pilot study to detect CD68-, CD11c-, CD163- and MRC1-positive cells. Samples were digitized and the expression of macrophage markers was quantitatively analyzed.
Results: Infiltration of M2 polarized macrophages correlated significantly ($p < 0.05$) with tumor outcome in early stage (T1/T2, N0) oscc. This correlation could be seen in tumor resection specimens but also in diagnostic biopsies. Macrophage polarization in biopsies – but not in tumor resection samples – correlated significantly ($p < 0.05$) with tumor grading.
Conclusion: Macrophage polarization in early stage oscc could be a prognostic marker for tumor outcome. The correlation of M2 polarized macrophages with tumor outcome can already be detected in the initial biopsies. Furthermore, M2 polarization of macrophages in biopsies is associated with an increased malignancy. Patients with high infiltration of M2 macrophages in diagnostic biopsies could benefit from neoadjuvant radiotherapy protocols or macrophage modulating therapies.

ID 0185

Glukosestoffwechsel und Aggressivität des Mundhöhlenkarzinoms

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Malignome benötigen eine erhöhte Glukoseaufnahme zwecks Aufrechterhaltung ihres Energiestoffwechsels, wie bereits durch Otto Warburg Ende der 20er Jahre des vergangenen Jahrhunderts beschrieben. Das Ziel der Untersuchung war, diesen gesteigerten Glukosestoffwechsel anhand immunhistochemischer Untersuchungen zu verifizieren und mit der Prognose zu korrelieren.
In einer prospektiven Studie (100 Patienten mit einem Mundhöhlenkarzinom) erfolgten am Paraffinschnitt immunhistochemische Untersuchungen GLUT-1 (Antikörper Acris Polyclonal Antibody to GLUT1 / SLC2A1 (C-term)). Nach lichtmikroskopischer Auswertung unabhängiger Untersucher (DB und CW) und Zusammenfassung der Färbeintensitäten und -anteile zu einem immunhistochemischen Score wurde dieser mit den klinischen Daten korreliert.
Negativ bzw. schwach GLUT-1-exprimierende Tumoren zeigten ein Überleben von 67%, wohingegen im Falle einer mäßigen und starken GLUT-1-Expression das Überleben nur noch 27% betrug. Die multivariate Cox-Regressionsanalyse (adjustiert nach Tumorgröße und histologischer Differenzierung und Ausmaß der Lymphknotenmetastasierung) bestätige ein 3,8 ($p = 0,027$)-fach erhöhtes Risiko des tumorassoziierten Versterbens im Falle einer GLUT-1-Überexpression.
Das Glukosetransportmolekül GLUT-1 kann als unabhängiger additiver Prognoseparameter beim Plattenepithelkarzinom der Mundhöhle herangezogen werden. Nach unserem Kenntnisstand ist dies die erste prospektive Untersuchung zum Zusammenhang einer GLUT-1-Expression und dem Überleben der Tumorpatienten. Das Ziel weiterführender Analysen ist, am Tumornativgewebe den Proteingehalt an GLUT-1 zu erfassen und mit den immunhistochemischen Resultaten hinsichtlich deren Validität zu korrelieren.

ID 0186

Adenoid-zystisches Karzinom des Oberkiefers

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Adenoid-zystische Karzinome sind die häufigsten bösartigen Tumoren der Speicheldrüsen. In der Literatur finden sich nur wenige Studien mit größeren Fallzahlen. Es war das Ziel der Untersuchung, alle adenoid-zystischen Karzinome der Oberkieferregion über einen 45-jährigen Zeitraum im Rahmen einer monozentrischen Analyse zu erfassen.
Es wurden seit 1969 bis dato sämtliche Malignome der Oberkieferregion erfasst. Neben dem Alter, dem Geschlecht und der Lokalisation wurden vor allem die histologischen Subtypen (cribriform, tubulär und solid-basaloid) zu einer Datenbank im SPSS-Format zusammengefasst. Die Überlebensanalysen erfolgten mit Hilfe der KAPLAN-MEIER-Statistik.
Im Bobachtungszeitraum konnten 199 Mailgnome der Oberkieferregion erfasst werden. Davon entfielen 26 auf die Diagnose adenoid-zystisches Karzinom (13%). Frauen waren deutlich häufiger betroffen (15 Frauen und 11 Männer). Hinsichtlich des Überlebens konnte festgestellt werden, dass nach 5 Jahren noch 16/21 der betrachteten Patienten am Leben waren.
Die Vorzugslokalisation adenoid-zystischer Karzinome sind die kleinen Speicheldrüsen, wie sie an der Schleimhaut des Hartgaumens vorkommen. Unter der Sammeldiagnose „Oberkiefermalignom" werden in der Regel Plattenepithelkarzinome verstanden. An zweiter Stelle der Häufigkeitsverteilung finden sich adenoid-zystische Karzinome. Diese sind – verglichen mit den Plattenepithelkarzinomen – bezogen auf den klassischen 5-Jahres-Zeitraum – mit 76% lebender Patienten deutlich besser hinsichtlich der Überlebensprognose. Problematisch ist allerdings die Ausbreitung entlang von Gefäß- und Nervenscheiden, so dass das Rezidiv und damit das Schicksal der jeweiligen Patienten besiegelt ist.

ID 0206

Molekulare Parameter zur Rezidivkalkulation beim Plattenepithelkarzinom der Mundhöhle

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Ein Kernproblem in der Therapie des Mundhöhlenkarzinoms ist die Entwicklung von Rezidiven nach einer Primärtherapie. Ziel dieser Untersuchung war es, anhand molekularer Parameter das Rezidivrisiko zu kalkulieren. Im Rahmen einer prospektiven Analyse erfolgte an Tumor-Nativgewebe von 99 Patienten mit einem Plattenepithelkarzinom der Mundhöhle die Bestimmung folgender Parameter: miRNA 486, mRNA für Osteopontin, Survivin und GLUT-1 und EGFR. Der klinisch wichtigste Faktor der Entwicklung von Rezidiven und Metastasen war das Alter der Patienten. So waren Patienten die ein Rezidiv entwickelten 63 Jahre alt versus 59 Jahre (ohne Rezidiventwicklung) ($p = 0,089$). Jüngere Patienten (Altersdurchschnitt 55 Jahre) hingegen entwickelten mindestens eine lokale Metastase (p

ID 0214

Effect of sorafenib on cisplatin-based radiochemotherapy in head and neck cancer cells

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Background: Despite of aggressive chemoradiation (CRT) protocols in the primary treatment of patients with head and neck squamous cell carcinomas (HNSCC), the outcome is still limited. To improve therapy efficacy we had already successfully tested sorafenib in combination with irradiation (IR) in previous studies on HNSCC cell lines. In this study, sorafenib was used to investigate the effect on combined CRT treatment using cisplatin.
Material and Methods: In HNSCC cell lines and normal fibroblasts (NF) radio- and chemosensitivity with and without sorafenib was measured by colony formation assay. Apoptosis and cell cycle analysis were performed by flow cytometry.
Results: In HNSCC cells, sorafenib increased the antiproliferative effect of cisplatin without affecting apoptosis induction. Sorafenib added prior to irradiation resulted in an increased cellular radiosensitivity in several HNSCC cell lines which was not influenced when cisplatin was added, resulting in a massive overall cell inactivation. In contrast, sorafenib did not radiosensitize NF and reduced cell inactivation due to cisplatin treatment.
Conclusions: In HNSCC, cell inactivation by IR and cisplatin is further increased by the addition of sorafenib in contrast to NF cells. Therefore, sorafenib seems to be suitable to improve therapy efficacy for HNSCC.

ID 0216

Identification of functional proteomic signatures in HPV positive head and neck cancer

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Background: Head and Neck Squamous Cell Carcinoma (HNSCC) can be divided into two distinct groups according to their etiology- HPV (human papilloma virus) negative and HPV positive HNSCC patients. These two groups are not only different in terms of etiology and clinical parameters, they are also diverse on the basis of tumorigenesis. Therefore the aim of this study was, to identify distinct protein profiles by mass spectrometric analysis of HPV positive and HPV negative HNSCC, which could be able to further characterize prognostic groups of HNSCC by a distinct protein profile.
Materials/Methods: HPV positive oropharyngeal tumors (OPSCC) were compared to a HPV negative OPSCC. Formalin-fixed paraffin- embedded tumors were prepared for mass spectrometric analysis by tandem-MS technique with a Q-TOF mass spectrometer. Identification and quantification of mass spectrometric signals were performed by OpenMS/TOPP Software.
Results: Many proteins could be identified and quantified by MS technique and further analysis. Over 20 proteins showed significant differences in expression in between the HPV positive and HPV negative tumor group. Besides structural proteins, proteins involved in the cell cycle and replication process were differentially expressed in both groups.
Conclusions: The identification and quantification of proteins has the potential to differentiate between the two distinct groups of HNSCC despite already established biomarkers and clinical features. Especially the identification of proteins involved in cell cycle process and replication, being a delicate step for tumor survival, reveals the potential advantages of a mass spectrometric proteomics approach.

ID 0217

Treatment of recurrent or metastatic Head and Neck squamous cell carcinomas (HNSCC) acoording to the EXTREME protocol in daily routine. Survival outcomes compared to the EXTREME study results and conventional chemotherapy.

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Introduction: In the therapy of recurrent/metastatic HNSCC not eligible for surgery or radiation therapy the EXTREME (cisplatin, 5FU, Erbitux) protocol (Vermorken et al., N Engl J Med 2008) has been established rapidly. Our retrospective study analyzed the survival results in clincal routine of a tertiary university center compared to the study results and to platinum based chemothrapies.
Methods: Retrospective analysis of 160 patients with recurrent and/or metastatic disease diagnosed after at least 6 months of complete remission following curative treatment. Patients were recruited either from our own population or out of admissions from other Head and Neck departments. Survival was analyzed from the beginning of the first line therapy either due to the EXTREME protocol or individual mono / poly- chemotherapies (cisplatin, carboplatin, 5-FU, taxane, MTX). Study endpoints are progression free survival (PFS), median survival and overall survival (OS) after start of first line therapy.
Results: With a median follow up of two years, the median survival was 28.2 months (EXTREME) vs. 19.2 months (individual CT). The median progression free survival was 7.3 months (EXTREME) vs 6.9 months (individual CT). The survival function by Kaplan Meier analysis reveal no statistical significant differences regarding OS ($p < 0,692$) and PFS ($p < 0,948$) Further details will be presented.
Conclusion: The median survival seems better, the progression free survival comparable to the EXTREME study results. The overall survival after 2 years seems to be better in our cohort compared to the reference study. Individual regimes show no significant worse results in daily practice.

ID 0219

Importance of nodal yield in neck dissection: Indicator of surgical and oncological quality

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Background: In head and neck cancer patients, the locoregional control and survival are affected by the N status of the neck. The pathological staging of the neck is therefore of great importance to secure the (clinical) N0 situation, especially when renunciation of an adjuvant radiation (pN0 or pN1 without ECS) is defined.
Materials and Methods: We prospectively compared two different surgical methods of neck dissection. As a result, the so called "Nodal Yield" values were collected and statistically analyzed.
Results: The data of 150 patients (223 Neck Dissections) were statistically evaluated. Between the two operation techniques a significant difference in Nodal yield was statistically demonstrated. With the so-called "Fascia unwrapping" technique, 23 lymph nodes could be harvested from a neck dissection on average, whereas by the conventional surgical method only an average of 16 lymph nodes were found in the surgical specimens.
Conclusions: The "Fascia unwrapping" technique succeeds to remove consistently more lymph nodes from the neck as the other surgical technique. Accurate staging of cervical lymph nodes is therapeutically and prognostically essential. Especially in a clinical N0 situation the question

emerges, if enough lymph nodes were removed and examined to substantiate a pN0 status, on which a renunciation of adjuvant therapy is decided.

ID 0235

Feasibility and Results of Radiotherapy (RT) or Chemoradiation (RCT) for unselected elderly patients with squamous cell carcinoma of the head and neck (SCCHN) – a retrospective monoinstitutional study

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Introduction: SCCHN belong to the frequent malignancies worldwide. In an aging society, also the incidence of SCCHN in elderly patients will rise. Nevertheless, elderly patients are underrepresented in clinical trials. The aim of this study was to evaluate the feasibility of a RT/RCT and the treatment results in an unselected collective of elderly patients with SCCHN.
Methods: All patients older than 70 years, which received RT or RCT at the University Hospital Regensburg from 2004 to 2012 were included.
97 patients achieving these criteria could be identified with a median age of 75 years. Most patients suffered from a SCCHN UICC stadium IVa. For 75 patients a curative intended treatment was performed. Of those, 43 patients received definitive and 32 adjuvant RT/RCT. 33 patients got a simultaneous RCT. The median follow up was 19 months (range 1 to 90 months).
Results: The feasibility of radiotherapy was good. For 25 patients radiotherapy had to be interrupted for more than one day.
18/33 patients could receive at least 75% of the planned dose of the chemotherapy. 69% of all patients suffered from any acute toxicity of CTC grade III or IV. The overall survival was 70% after 12, 41% after 24 and 29% after 60 months. There was no significant difference between definitive RT/RCT and resection followed by adjuvant RT/RCT for overall survival. For those patients with curative intended treatment, the progression free survival was 69% after 12, 53% after 24 and 46% after 60 months.
Discussion: The feasibility of a RT or RCT for elderly patients with SCCHN is good. There is no obvious difference in overall survival in comparison with collectives of younger patients. Because of our results a deintensification of treatment just because of age seems not to be justified.

ID 0245

Vitamin D3 serum level influences lymphogenic metastasization as well as natural killer cell-mediated cytotoxicity in patients with head and neck squamous cell carcinoma

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Background: Recent studies showed subnormal vitamin D3 (VitD3) serum levels in the majority of patients with head and neck squamous cell carcinoma (HNSCC) and an association of VitD3 deficiency with an adverse prognosis in these patients. In our study, we investigated the prevalence of hypovitaminosis D3 in HNSCC patients and analyzed the patients' natural killer (NK) cell mediated cytotoxicity directed against HNSCC cells before and after VitD3 substitution.
Methods: Blood samples of 100 HNSCC patients and 48 healthy controls were collected to measure the VitD3 serum level. For a subset of patients and controls, NK cell mediated cytotoxicity directed against FaDu-cells was evaluated by a lactate dehydrogenase release assay with and without addition of cetuximab. The same patients then received 2000 IE VitD3 per day for 12 weeks, followed by another blood collection to control the VitD3 serum level and perform a second NK cell cytotoxicity assay.
Results: We observed a highly significant hypovitaminosis D3 in HNSCC patients as opposed to healthy controls ($p < 0{,}0001$), a trend towards higher VitD3 serum levels in HPV-positive compared to HPV-negative cases and significantly lower VitD3 serum levels in patients with lymph node metastases (N+) compared to patients without lymph node metastases (N0; $p = 0{,}045$). In the cytotoxicity assays, VitD3 substitution led to a significant increase of NK cell mediated cytotoxicity in all healthy controls and 50% of HNSCC patients.
Conclusions: The VitD3 serum level needs careful attention in HNSCC patients as this study indicates frequent hypovitaminosis D3, which we found to be associated with a higher rate of lymphogenic metastasization and a decreased NK cell mediated cytotoxicity.

ID 0259

Two-Year survival analysis of fifty consecutive Head and Neck sqamous Cell Carcinoma Patients treated primarily with transoral robotic Surgery (TORS) in a single European Academic Centre

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Purpose: To report 2-year survival outcomes for head and neck squamous cell carcinoma treated primarily with transoral robotic-assisted resection.
Methods: This is a single-institution, prospective study from an academic care center, to date the largest of its kind with two-year follow-up from Europe. Fifty consecutive, appropriately staged head and neck cancer patients were enrolled prospectively, and underwent transoral robotic surgery (TORS) between September 2001 and August 2013.
Results: Twenty-four patients had T1, twenty-three T2, two T3 and one had a T4a primary tumour. There were 18 patients with overall Stage I-II and 32 patients with Stage III-IV disease. Following transoral robotic resection of their primaries and appropriate neck dissection(s) as indicated, adjuvant treatment could be spared for 20 patients. Another 5 patients refused the recommended adjuvant treatment. Seventeen patients received 60 Gy adjuvant radiotherapy and 8 patients underwent 66 Gy adjuvant chemo-radiotherapy. At the time of the last follow-up visit (median, 27 months), the disease specific survival rate was 96%, while the overall survival was 94%. The two-year disease free survival rate was 88%, and the two-year recurrence-free survival was 80%. However, local recurrence rate was only 10%.
Conclusion: Using TORS as their primary modality, 40% of the patients did not need adjuvant treatment and showed similar survival rates to that of conventional surgery or primary chemoradiotherapy. In another 34% of the patients, adjuvant chemotherapy could be spared and adjuvant radiotherapy could be reduced by 10 Gy, compared to standard primary chemoradiotherapy of 70 Gy. Regarding long-term survival, further studies are warranted.

ID 0362

Erufosine causes cell cycle downregulation in Head and Neck Cancer

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Cell cycle progression is a highly ordered and tightly-regulated process that involves multiple checkpoints, which assess extracellular growth signals, cell size, and DNA integrity. Cyclin-dependent kinases (CDKs) and their cyclin partners are positive accelerators that induce cell cycle progression. Oral squamous cell carcinoma (OSCC), which is the most com-

mon cancer of the oral cavity, is one of the leading causes of cancer-related death. Erufosine is a novel chemotherapeutic agent belonging to the third generation of alkylphosphocholines. It simultaneously induces apoptosis and autophagy in OSCC. Here we evaluated the effect of erufosine on cell cycle progression in OSCC cell lines, HN5 and SCC-61.
The anti-proliferative effect of erufosine in OSCC cells was determined by MTT assay after 24h, 48h and 72h exposure. HN-5 cells were exposed to erufosine at concentrations effecting IC25, IC50 and IC75, for 16, 24 and 48h and differential gene expression analysis was performed for the treated and untreated groups. Gene set enrichment analysis was performed to identify core KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways and GO (Gene Ontology) terms that were significantly enriched in our analysis. Interestingly, we observed that cell cycle and related processes were strongly enriched among the down regulated genes (cell cycle, $p < 0.001$). The downregulated cyclins (Cyclin A, cyclin D) and CDKs (CDK2, CDK4 & CDK6) were verified through qRT-PCR and Western blot in both cell lines. We carried out cell cycle analysis through PI staining and observed a significant G2 block with erufosine treatment. These findings show that erufosine has a central downregulating role in cell cycle progression through targeting CDKs in cancer cells.

ID 0378

Chemosensitivity of HPV-positive and HPV-negative HNSCC cell lines

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Patients with HPV-positive HNSCC show remarkably better survival rates than patients with HPV-negative. The favorable survival is described to be independent of treatment but since data from single modality regimes are rare, so far only an enhanced radiosensitivity is truly established. In contrast, an enhanced chemosensitivity and a favorable survival after surgery alone – though often stated – remain speculative. Standard radiochemotherapy for HNSCC is performed with cisplatin, which is associated with high-grade toxicities. In addition to its cytotoxic effects, cisplatin is generally referred to as a potent radiosensitizer. Here we compared the cytotoxic and radiosensitizing effects of cisplatin in a panel of HPV-positive and HPV-negative HNSCC cell lines previously described to show pronounced differences in radiosensitivity with HPV-positive strains being far more radiosensitive.
While HPV-positive cell lines showed a slightly more pronounced response on the level of cell proliferation, there was no difference with regard to colony formation, which represents a more robust readout for cytotoxicity. As cellular responses to the drug, we assessed cell cycle distribution, apoptosis and γH2AX-induction and found no principal differences between the two entities. Combining cisplatin with radiation, we generally observed an additive effect on colony formation but only one out of five HPV-negative and two out of six HPV-positive strains demonstrated a clear radiosensitization. In summary, HPV-positive and HPV-negative HNSCC cell lines demonstrate varying, but comparable sensitivity toward cisplatin suggesting that the favorable response of HPV-positive tumors is largely driven by an enhanced radiosensitivity.

ID 0381

Radiosensitization of HPV-positive HNSCC cells through the inhibition of Chk1 and Wee1

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Patients with HPV-positive HNSCC show remarkably better survival rates than patients with HPV-negative. The treatment of locally advanced disease nearly always includes radiotherapy and we have previously shown that for HPV-positive HNSCC an enhanced radiosensitivity, which is due to a defect in DNA double-strand break repair, is evident already on the cellular level. The repair defect is associated with an unusually profound and sustained radiation-induced G2-arrest. The normal function of this arrest is to provide time for the repair of the radiation induced DNA double-strand breaks (DSB) to ensure genomic integrity before the critical passing of mitosis. Therefore, inhibition of the arrest may be a proper way to radiosensitize HPV-positive HNSCC cells while exerting only little effect on the G1-arrest competent and mostly non-dividing normal tissue.
Radiation-induced G2-arrest depends on two kinases, Chk1 and Wee1. Molecular targeting of both of these kinases by specific inhibitors is currently being explored in clinical trials. We show here that the inhibition of both Chk1 and Wee1 by the specific and clinically relevant inhibitors LY2603618, SCH-900776 (Chk1) and MK-1775 (Wee1) results in a reduction of radiation-induced G2-arrest and subsequent radiosensitization of HPV-positive HNSCC cell lines. The radiosensitization conferred by the specific Chk1-inhibitors was equivalent to that conferred by the less specific Chk1/2-inhibitors UCN01 and AZD7762. Our data suggest that the specific molecular targeting of Chk1 and Wee1 is a viable approach for the radiosensitization of HPV-positive HNSCC and should be further explored for it`s potential to act in deintensified regimes.

ID 0382

Characterization of Tumor-associated B lymphocytes in head and neck squamous cell carcinoma

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Introduction: The immune system plays a role in both the promotion and prevention of tumor development. To date, little is known about the role that B cells play in cancer pathophysiology. Recent evidence suggests that B lymphocytes can both promote and inhibit the development of tumors which seems to depend on factors like timing and composition of the B cell subsets. Tumor-infiltrating B cells have been described in solid tumors including head and neck squamous cell carcinoma (HNSCC). The aim of this study was to provide a detailed phenotypic characterization of the B cell subsets as a first step to elucidate the impact of B lymphocytes in HNSCC.
Methods: We obtained tumor samples, healthy mucosa and peripheral blood from patients with treatment-naive HNSCC and healthy donors. Analysis of B cell subsets was performed by flow cytometry and immunohistochemistry.
Results: Flowcytometric analyses revealed lymphocytic infiltration in all analyzed HNSCC tumors (n = 31) and B cell infiltration in the majority of tumors. Immunohistochemical analysis showed similar results. Subclassification of tumor-infiltrating B cell subsets showed high numbers of activated B cells, antigen-presenting B cells, plasma blasts and memory B

cells. The number of certain regulatory B cell subsets also seemed to be increased in HNSCC.
Conclusion: In accordance with previous results we found that there is a marked B cell infiltration in the majority of HNSCC. Our results are indicative of an antigen recognizing B cell phenotype in HNSCC and provide a first comprehensive analysis of the subsets of tumor-infiltrating B cells in HNSCC so far. In murine carcinogenesis models of squamous cell carcinoma a crucial role for B cells has been proposed. If this holds true for human HNSCC as well remains to be evaluated in further studies.

ID 0432

Laboratory values as prognostic factors for the Outcome of concurrent radiochemotherapy in the treatment of locally advanced head and neck cancers: Secondary results of two European randomized phase III trials (ARO 95-06, SAKK 10/94)

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Background: To determine the influence of baseline laboratory values on treatment outcome in patients with locally advanced head and neck cancer.
Methods: Data of the randomized trials ARO 95-06 (n = 384) and SAKK 10/94 (n = 224) were pooled and the total sample size of 608 patients were analyzed.
Hemoglobin and creatinine were available at baseline and their association with locoregional failure-free survival (LRRFS), distant metastasis-free survival (DMFS), cancer specific-survival (CSS) and overall survival (OS), was analyzed using univariable and multivariable Cox regression models.
Results: A total of 580 and 564 patients were available with baseline hemoglobin and creatinine values. Univariable analyses revealed that lower baseline hemoglobin values were significantly associated with decreased LRRFS, DMFS, CSS and OS. This effect remained significant for OS when the treatment arms (RT alone vs. chemoradiation) were analyzed separately.
Higher baseline creatinine was associated with improved OS. Interestingly, the predictive value of baseline creatinine appeared to be limited to the subgroup of 284 patients who were treated with chemoradiation. In the multivariable Cox regression model lower baseline hemoglobin remained to be associated with decreased OS both in the patients who received chemoradiation HR 0.79 (95% CI 0.66, 0.94, $p = 0.009$) and in those patients who underwent RT alone HR 0.67 (95% CI 0.58, 0.78, $p < 0.001$). However, increased baseline creatinine remained significantly associated with improved OS in patients who underwent chemoradiation HR 0.79 (95% CI 0.69, 0.92, $p = 0.002$) but not in patients who underwent RT alone.
Conclusions: Besides a strong association between lower baseline hemoglobin and inferior treatment outcome increased creatinine appeared to predict improved outcome in patients undergoing chemoradiation.

ID 0449

Evaluation of Hyperspectral Imaging in early recognition of precancerous and cancerous lesions in mouth and oropharynx

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Background: Early detection of precancerous or cancerous lesions is pivotal for the prognosis of head and neck cancer patients. The Incidence remains high even though diagnostic access to the oral cavity and oropharynx is comparably easy. This is due to the fact, that the lesions are being recognized too late on a purely visual basis. Therefore we evaluated the application of Hyperspectral Imaging for early detection of cancer in the oral cavity and oropharynx.
Material and Methods: In patients -being scheduled for Panendoscopy or Oro-/Laryngopharyngoscopy for diagnostic reasons- hyperspectral imaging of the lesion was performed using a rigid 0° endoscope, a light-adjustable monochromator and a hyperspectral camera. Training sites from physiological, precancerous and cancerous tissues were marked and a classifier was trained by using the acquired hyperspectral data. Afterwards it was applied for an automatic detection of precancerous and cancerous lesions of a third patient.
Results: Application of Hyperspectral Imaging was sufficient and easy. The accurrancy was 78%-85%, the sensitivity was calculated 61%-86%, specificity 84%-100%.
Conclusion: Hyperspectral Imaging for early detection of precancerous of cancerous lesions of the oral cavity and the oropharynx is a non-invasive and innovative concept which could shorten delays, open the field of optical biopsies and therefore could lead to a better prognosis and a cost-reduction in diagnosing malignancies in head and neck cancer patients.

ID 0494

Influence of microRNA profiles and immune signatures on the efficacy of radiochemotherapy in locally advanced head and neck squamous cell carcinoma

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The treatment of locally advanced HNSCC is still challenging with a high frequency of recurrence. Hence, identification of predictive markers which improve patient selection for optimized treatment are of high clinical relevance. In this study the predictive value of miRNAs and the role of infiltrating immune cells for the efficacy of radiochemotherapy were evaluated.
FFPE material was collected from patients with locally advanced HNSCC, who had been treated with hyperfractionated accelerated radiotherapy in combination with either 5-fluorouracil/cisplatin (CDDP-based) or 5-fluorouracil/mitomycin C (MMC-based) within the ARO0401 phase III trial. The miRNA and immune profiles of tumor tissues were established by Affymetrix miRNA microarrays and the NanoString PanCancer Immune Profiling Panel, respectively. Results were validated by qRT-PCR.
The expression levels of 15 miRNAs (e.g. miR-200b) were identified to correlate with overall survival of patients treated with MMC-based chemoradiation, whereas the level of 10 other miRNAs (e.g. miR-146a) were correlated with overall survival within the CDDP-based arm. Interestingly, the expression of miR-146a correlated with local recurrence, whereas miR-200b was associated with the occurrence of distant metastases. Since miR-146a has immune regulatory function, we analyzed the immune signature of these tumors. First data indicate that miR-146a represents a surrogate marker of immune cell infiltration.

Expression levels of miR-146a and miR-200b were established as predictive markers for the efficacy of two commonly used regimens of chemoradiation. The interference between the immune signature and outcome after CDDP-based chemoradiation warrants further investigation

ID 0538

Multimodale Therapie bei immunsupprimierten Patienten nach Organtransplantation mit fortgeschrittenem HNSCC des UICC Stadiums IV – was ist möglich? Eine Fallbeschreibung

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Die met-CT ist eine Therapieform, die zunehmende Bedeutung, insbesondere bei fortgeschrittenen Tumoren und palliativem Intent, gewinnt. MTD-Regime wurden in der Vergangenheit in verschiedenen Setups geprüft. Sequentielle und konkomitante RCT-Protokolle wurden in den letzten 25 Jahren mit wechselndem Erfolg und teils hohen Nebenwirkungsraten bei HNSCC eingesetzt. Neuere Erfahrungen zeigten, dass nicht nur die Akut-, sondern gerade auch die Langzeittoxizität der derzeit favorisierten simultanen RCT-Regime Anlass zur kritischen Prüfung der Therapieempfehlungen geben. Es besteht begründete Hoffnung, dass die in fast allen Fällen problemlos tolerierte metronomische CT (met-CT), in den Signalweg von Tumor- und Endothelzellen eingreift und ein für diese Anwendung „neues Therapieprinzip" Anwendung findet. Berichtet wird über eine Kombination aus MTD und met-CT („metronomisiertes Kelsen-Regime"), das im Zeitraum von 1987 bis 1996 an der Universitätsklinik des Saarlandes praktiziert wurde und danach bis heute an unserer Praxisklinik in Ramstein. Die Nebenwirkungsrate dieser Therapie wurde in 2 Dissertationen in Zusammenarbeit mit der Abteilung für Strahlentherapie überprüft. Die Grundidee dieser Therapieform ist die Überlegung, dass gerade größere, fortgeschrittene Tumore einer länger dauernden Exposition eines therapeutischen Agens bedürfen, das im Falle des Intents der Organerhaltung, möglichst redifferenzierende Eigenschaften haben sollte.Im vorliegenden Fall besteht ein Zustand nach Lebertransplantation 9 Jahre vor ED eines Hypopharynxkarzinoms des Stadiums T4, N3, M0, (UICC IV) das trotz 9 jähriger Alkohol- und Nikotinkarenz, möglicherweise auf Grund langjähriger Kortikoid- und Immunsuppressivagabe, auftrat. Es wird das Vorgehen im Rahmen einer erfolgreichen multimodalen Therapie in diesem komplizierten Fall dargestellt.

ID 0567

TCF-21-Hypermethylierung in Plattenepithelkarzinomen des Nasenvestibulums

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Einleitung: Plattenepithelkarzinome des Nasenvestibulums sind rar und machen weniger als 1% aller Kopf-Hals-Tumoren aus. Epigenetische Alterationen des Transkriptionsfaktor-21 (TCF-21) wurden in Lungenkarzinomen und Plattenepithelkarzinomen der Kopf- Hals- Region beschrieben, wobei Untersuchungen zum Nasenvestibulum fehlen.
Methoden: In einer retrospektiven Studie untersuchten wir die formalin-fixierten Schnitte von 35 Patienten mit Naseneingangskarzinomen. Die Promotorregion des TCF-21 wurde mittels methylierungsspezifischer-PCR analysiert und mit den klinisch-pathologischen Parametern verglichen. Zusätzlich wurde sämtliche Proben auf ihren HPV-Status (GP5+/6+ und E6/E7) untersucht.
Ergebnisse: Das Durchschnittsalter der Patienten bei Erstdiagnose betrug 59,9 ± 11,8 Jahre bei einem Geschlechterverhältnis von 1:1,7 (f:m). Die mediane Nachbeobachtungszeit betrug 47,4 ± 29,5 Monate. Eine Hypermethylierung des TCF-21 wurde in 10 Tumorproben (28,6%) nachgewiesen. Ein HPV-Nachweis gelang in 11/35 Tumoren. In den Tumorenproben mit TCF-21-Hypermethylierung fanden sich tendenziell häufiger HPV-negative Tumoren (8/2; p = 0,248). Der Methylierungs-Status hatte weder signifikanten Einfluss auf die Prognose, noch auf klinisch-pathologische Parameter.
Schlußfolgerungen: Wir konnten epigenetische Veränderungen des TCF-21 bei Plattenepithelkarzinomen des Nasenvestibulums detektieren. Zusätzlich scheint ein Zusammenhang mit dem HPV-Status der Tumoren zu bestehen. Weitere Untersuchungen an einem größeren Kollektiv sollten die genauen Zusammenhänge evaluieren.

ID 0568

Die Bedeutung von Nodal Yield bei der Neck Dissection: Chirurgischer und onkologischer Qualitätsindikator

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Einleitung: Bei Kopf-Hals-Tumorpatienten werden die lokoregionäre Kontrolle und das Überleben durch den N-Status des Halses beeinflusst. Das pathologische Staging des Halses ist somit von großer Bedeutung zur Sicherung der (klinischen) N0 Situation. Besonders beim Verzicht auf eine adjuvante Bestrahlung (pN0 oder pN1 ohne ECS) ist es wichtig, dass die Lymphknotenanzahl in einem Neck Dissection-Präparat möglichst groß ist.
Methode: Wenn eine pN0-Situation festgestellt wird, und weitere Entscheidungen auf diesem N-Status basieren, ist die Aussagekraft des pathologischen Befundes von höchster Priorität. Aus diesem Grund verglichen wir zwei verschiedene OP-Methoden zur Neck Dissection prospektiv miteinander. Als Ergebnis wurden die sogenannten „Nodal Yield"-Werte gesammelt und statistisch ausgewertet.
Ergebnisse: Die Daten von 150 Patienten (223 Neck Dissections) wurden statistisch evaluiert. Zwischen den zwei OP-Methoden wurde ein signifikanter Unterschied statistisch nachgewiesen. Mit der sogenannten "Fascia unwrapping"-Technik konnte man im Durchschnitt 23 Lymphknoten aus einer Neck Dissection gewinnen, wohingegen bei der herkömmlichen OP-Methode durchschnittlich 16 Lymphknoten im Präparat zu finden waren.
Schlussfolgerungen: Mit der Technik des "Fascia unwrapping" gelingt es, konsequent mehr Lymphknoten aus einem Halsbereich zu entfernen, als mit anderen chirurgischen Techniken. Ein exaktes Staging der Halslymphknoten ist sowohl therapeutisch als auch prognostisch unerlässlich. Insbesondere bei einer klinischen N0-Situation ergibt sich die Frage, inwieweit genügend Lymphknoten entnommen und untersucht worden sind, um einen pN0-Status so zu erhärten, dass auf eine adjuvante Therapie verzichtet werden kann.

Health Economy/Public Health

ID 0025

Regional Quality Discussion Board and Benchmarking of Cancer Treatment in Baden-Wuerttemberg (BW), Germany

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Introduction: In 2013 Germany passed a law named KFRG assigning clinical cancer registries (CCR) to assure quality of cancer therapy. In BW the ministry for social affairs defined KLR and VS (Vertrauensstelle, "trust agency ") of the Cancer Registry („Krebsregister") BW (KRBW) as central CCR of BW. The CCR assigned QualiKo to set up regional quality discussion boards (RQDB). Here we will report our experiences with the first set of RQDB regarding colorectal and pancreatic cancer.
Objectives: Quality assurance of regional cancer treatment is the goal, respecting in- and outpatients. We look at BW in five regions each covering about 2 Million residents. Tasks of QualiKo are: analyzing registered

KRBW data, benchmarking of quality indicators (following S3 guideline) and sharing the results during RQDB. The participants, local expert medics, discuss the results and – if needed – develop procedures to enhance the quality of cancer therapy. QualiKo offers support when performing the procedures. The results of RQDB are then reported in the Statewide Quality Board ("Landesqualitätskonferenz").

Results and Conclusions: Benchmarking of quality indicators concerning quality of therapeutic units as well as population based quality of cancer therapy is possible using the registered KRBW data.

Currently, data completeness is not satisfactory both regarding quantity of registered patients as well as treatment and course of the disease to assess oncological therapy. Therefore efforts to enhance completeness of data are initial priority in the RQDB. Experiences in other states show that the discussion in RQDB is helping to improve data quality.

Despite the primary need for data quality discussion, participants to date considered the RQDB as rewarding for the future quality enhancement.

ID 0045

Cancer Survivorship in Germany: Education of General Practitioners – Why and How

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General Practitioners (GP) play a pivotal role in caring for patients with malignant diseases in screening and detection of cancer, additional supporting care whilst treatment, and (long-term) follow-up. They often do not feel to be qualified enough for this task, and as well claim to lack support by specialists.

As an increasing number of patients will be diagnosed with cancer – and will survive for many years, following curatively intended treatment or with a chronic cancer disease, Cancer Survivorship was identified as the area of utmost importance.

Together with the State Chamber of Medicine of Südbaden, we started an education program for GPs to improve this critical interface.

During a 6 hours training, we provided a training program covering the most relevant topics in Cancer Survivorship: physical sequelae and late complications after multimodal treatment, their prevention and treatment; fatigue and self management, reasonable complementary medicine; management of chronic pain syndromes, recommendations for tertiary prevention, physical activities, nutrition and a guideline conform follow-up. Training was completed by a knowledge test and an overall evaluation.

All participants welcomed this newly implemented training program and considered it as very useful for their daily practice. Further support was urgently requested by the GPs, preferably in the format of (defined) Survivorship Care plans and follow-up schedules.

GPs need more support and information in Cancer Survivorship. Widespread trainings programs should be developed and offered, in close collaboration with the respective State Chambers of Medicine and cancer specialists, and GPs, and further improve the outpatient care of cancer survivors.

ID 0158

Individual blister packaging and interdisciplinary patient care to achieve a cost-effective use of oral oncologic medications

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The packaging sizes of many high-priced oral cytotoxic therapies are often not in line with the treatment protocol and dosage modifications and lead to high costs because of unused doses. Furthermore, tyrosine kinase inhibitors and other drugs often interact with other drugs leading to a loss of efficacy or an increase of side effects.

One objective of this project was to lower the costs of therapies with oral drugs (capecitabine, erlotinib, everolimus, lapatinib, pazopanib, regorafenib, sorafenib, sunitinib) by 5-15% by reducing the number of discarded doses. Another aim was to increase safety and lower drug interactions by establishing an efficient management of oral drug application. These aims were to be achieved by individual blister packaging and medical attendance by an interdisciplinary team of oncologists and pharmacists. The project was performed with 45 patients for 27 months and was a collaborative project of the health insurance company DAK-Gesundheit, six oncologic practices and the antares-pharmacy. Medication related problems and the patients' satisfaction were evaluated by self assessment questionnaires and regular telephone questioning.

Overall, costs with the different oral cytostatic drugs could be lowered by 10%. The patients' satisfaction regarding the applied therapy based on individual blister packaging was very high. Drug interactions were identified for 34 of the 45 patients: 16 of them were classified as contraindication, 1 would have lead to an increased and 13 to a decreased effectiveness of the applied oral cytostatic drugs.

In conclusion this project reveals that costs of oral therapy can be markedly reduced by individual blister packaging. Interdisciplinary patient care was shown to be an effective way to significantly increase safety, efficacy and quality of drug supply.

ID 0199

Patient derived criteria for oncological treatment benefit

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Introduction: Benefit criteria for oncological treatment are almost exclusively developed based on physicians' perspective. Clinical trials need to consider patient-derived criteria for benefit preferences.

Methods: A questionnaire was developed using user-benefit evaluation. The design enabled open items, but weighed answers regarding references (treatment benefit, general decisions in life). SF12 (4-weeks) measured QoL at time of questionnaire. 786 consecutive oncological patients were included (< 3 mo. after treatment). ICD10 diagnosis was grouped according to RKI. Gender, age, diagnoses were compared for responders/nonresponders (Chi^2, F-test). Factorial analysis (principal component analysis) and cluster analysis were used in stepwise evaluation process.

Results: 374 patients responded to questionnaire (48% response rate). Diagnoses and age slightly differed between responder/non-responders, whereas gender distribution was comparable. 1480 items for treatment preferences were provided (grouped into 25 variables). 86% of preferences related to treatment efficacy, 8% to employability/normal life and 6% to soft factors of care. For preferences in life 1311 items were grouped into 21 variables (28% social relationships, 22% social secureness, 26% physi-

cal needs, 24% self-realization). Factorial data reduction and hierarchical clustering enabled definition of patient groups with comparable benefit preferences for oncological treatment.
Conclusion: Patient-derived user-benefit evaluation and clustering of preferences provides a basis for future definition of patient-derived end point in clinical trials. Dynamic changes of preferences during oncological treatment need to be further evaluated.

ID 0215
National Cancer Plan (NCP) Survey

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The NCP is a public health program launched in 2008 by the Federal Ministry of Health. It was developed as collaboration of German Cancer Society, German Cancer Aid and Association of German Tumor Centers.
The NCP focuses on four main goals:
Further development of cancer screening
Further improvement in structural aspects of oncology care and quality assurance
Ensuring effective oncological treatment
Strengthening patient orientation in cancer care
While initiatives for three goals have already been implemented, the fourth field hasn´t received greater attention yet. As first step a holistic understanding of the respective attitudes and expectations of citizens and patients is needed.
A quantitative research was conducted during summer 2014 with 1.233 respondents (859 citizens representative of the German population, 128 cancer patients, 246 family members of patients). The questionnaire was developed through a multistage process with experts and parliamentarians.
Main Results:
Awareness of the NCP is low at 14% (citizens) / 49% (patients).
Increasing patient orientation is commonly seen as important goal.
To achieve this goal, comprehensive information, addressing patients' needs and shared decision making are critical factors.
For gathering information patients primarily rely on physician's guidance, while citizens mainly refer to public media. The greatest need concerning quality of information is independence and reliability.
Patients expect information to be provided at hospitals or physicians' offices, by sick funds, public health authorities and advocacy groups. Most relevant topics are therapy, prevention, quality of life related aspects and info about contact persons.

ID 0220
Training Courses for Oral and Subcutaneous Tumor Therapy for specialized Nurses – A Survey of the Impact on the Improvement of Professional Patient Care in Oncology

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Oral and subcutaneous tumor therapy becomes more important. Benefits are e.g. no infusions, marginal waiting time and less visits in oncology units. Possible problems are: complex and false drug intake, serve side effects, limited control of therapy. A partial delegation of control of therapy to specialized personnel (special assistant for oral and subcutaneous tumor therapy) is a possible solution.
4 training courses (each 40 hours) were performed with a total of 165 participants in 2013–2015. Key aspects were: pharmacokinetics and -dynamics, side effects and -management and communication. Now a survey evaluating the implementation reality was performed. Structured questionnaires of person-based data, benefits of the new knowledge for everyday work and possibilities of implementing the acquired knowledge were sent to all participants. The survey used open questions and rating scales. Of 165 questionnaires 45 were answered. Participants were 50% physician assistants and nurses, respectively. The courses were perceived as very helpful (55%) or helpful (39%). The expertise has been perceived as majorly improved (62%) or improved (38%). 66% were able to implement the new knowledge either very efficiently or efficiently. 66% of the participants evaluated the delegation of tasks in the oral/subcutaneous tumor therapy as satisfactory. 75% were able to conduct a consultation with a patient.
Further education of specialized personnel in the field of oral and subcutaneous tumor therapy becomes increasingly important in clinical practice. A large benefit for their daily work is perceived by the participants. The delegation of medical subtasks to specialized personnel is of benefit to all participants in professional patient care.

ID 0499
Economic burden in lung cancer trials: Experience in a Comprehensive Cancer Center in Germany

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Background: Conducting clinical trials is an organizational and economic challenge for health-care institutions. One of the major tasks of Comprehensive Cancer Centers (CCC) is to adopt innovative treatment methods within clinical trials. This analysis focuses on the economic burden of early phase clinical trials for advanced lung cancer patients in a German CCC.
Patients and Methods: 154 advanced lung cancer patients treated in 5 Investigator-Initiated Trials (IIT) and 22 Pharma-Sponsored Trials (PhST) were analyzed. We have evaluated medical and economic data based on a profit center perspective including all trial-related services and efforts in IITs compared to PhSTs.
Results: In 161 study patients enrolled in 27 clinical trials (7 patients participated in several clinical trials) we have identified `study visit` as a key economic parameter. Due to the number of study visits per patient there is a significant difference between IITs and PhSTs ($p = 0.009$). Regarding the duration of treatment per patient both types of trials were indifferent. Clinical trials with <5 patients enrolled are not cost covering, neither in IITs nor in PhSTs. Pharma-independent clinical trials seem to be hardly feasible in academic centers.
Conclusion: Personalized lung cancer trials are characterized by increasing number of early phase I/II trials and rare genetic subgroups with low patient recruitments. Future challenge for German CCCs will be the balance between independent research and cost covering conducting of clinical trials.

ID 0524
Lessons learned: Using Clinical Cancer Registry data for adherence-testing of interdisciplinary tumor board recommendations

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Introduction: The Center for Integrated Oncology (CIO) Cologne Bonn has developed its quality-oriented auditing system to investigate adherence to interdisciplinary tumor board (ITB) recommendations by using data of its Clinical Cancer Registry (CCR) instead of studying electronic patient files only.
Aim: The aim was to investigate the suitability of CCR data for adherence testing (including investigation of implementation of ITB recommendations to patient care and identification of causes of non-adherence) in lung cancer patients with initial diagnosis in 2013.

Methods: ITB records were retrospectively analyzed. Recommendations were compared with actually implemented therapies/diagnostics, documented in the database of CCR.
Results: 185 ITB recommendations of 112 LC patients with initial diagnosis in 2013 were analyzed. Regarding overall adherence, 167 of 185 (90%) recommendations were completely implemented. Data of CCR were suitable to test adherence. However, it was not possible to identify causes of non-adherence. For this purpose, electronic files had to be additionally consulted. Causes of non-adherence: course of disease made treatment-/diagnostic-change necessary (50%), patient refused the recommendation (22%), non-adherence due to physician´s decision (11%), cause of treatment-change unknown (11%), patient's condition was worse/different than described in ITB (6%).
Conclusion: Data of CCR are suitable for evaluation of adherence to clinical decisions made in multidisciplinary teams. This strategy helps to simplify adherence analysis compared to individual random sample analysis based on patient records. However, detailed analyses, such as identification of causes of non-adherence, are not completely realizable.

Imaging

ID 0108

In vivo analysis of formation and endocytosis of the Wnt/β-Catenin signaling complex in zebrafish embryos

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Wnt/β-Catenin signaling is an essential, evolutionarily conserved pathway in embryonic development, stem cell biology and human disease, including cancer. In the Wnt-off state, β-Catenin is constantly targeted for degradation by a destruction complex. After activation by Wnt/β-Catenin ligands, a multi-protein complex assembles at the plasma membrane as membrane-bound receptors and intracellular signal transducers are clustered into the so-called Lrp6-signalosome. However, the mechanism of signalosome formation and dissolution is yet not clear. Our imaging studies of live zebrafish embryos show that the signalosome is a highly dynamic structure. It is continuously assembled by Dvl2-mediated recruitment of the transducer complex to the activated receptors and partially disassembled by endocytosis. We find that, after internalization, the ligand-receptor complex and the transducer complex take separate routes. The Wnt-Fz-Lrp6 complex follows a Rab-positive endocytic path. However, when still bound to the transducer complex, Dvl2 forms intracellular aggregates. We show that this endocytic process is not only essential for ligand-receptor internalization but also for signaling. The μ2-subunit of the endocytic Clathrin adaptor Ap2 interacts with Dvl2 to maintain its stability during endocytosis. Blockage of Ap2μ2 function leads to Dvl2 degradation, inhibition of signalosome formation at the plasma membrane and, consequently, reduction of signaling. We conclude that Ap2μ2-mediated endocytosis is important to maintain Wnt/β-catenin signaling in vertebrates.

ID 0482

Optical and nuclear in vivo imaging of tumor xenografts using novel receptor-targeted peptide tracers

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Targeted multimodal imaging is an emerging approach in personalized cancer diagnostics. Altered expression of certain molecules enables targeted imaging and tumor selective treatment of cancer cells. One of these challenging targets is the chemokine-like receptor 1, with its peptide ligand chemerin being an encouraging molecular entity for tracer development. Aim of this study was utilization of our chemerin probes for optical and nuclear in vivo imaging with near-infrared imaging, positron emission tomography, magnetic resonance imaging and complementary biodistribution studies.
We developed highly specific and affine CMKLR1 peptide ligands by substitution of wild type chemerin-9 and structure-activity relationship analysis. Combination of these peptides linked to either near-infrared dye- (ITCC) or radiolabeled (^{68}Ga) chelator DOTA and target positive cancer mouse model enabled tumor-specific imaging in vivo.
We found CMKLR1 to be overexpressed in different tumor entities such as breast cancer and pancreatic adenocarcinoma. Optical near-infrared and PET/MR imaging of our target positive cancer model revealed strong CMKLR1 specific tumor uptake of the targeted tracers within 24 hours (ITCC) respectively two hours (^{68}Ga), which could be blocked by excess of unlabeled peptide. Furthermore, uptake, organ distribution and corresponding kinetics correlated strongly with chemical and physical properties of different tracers and molecular expression analysis of ex vivo tissue confirmed target selectivity.
Eventually, we demonstrated applicability of our novel tracers by visualizing CMKLR1 positive tumors in optical and PET/MR imaging and thus developed promising candidates for potential clinical translation.

ID 0484

Use of Diffusion-weighted magnetic resonance imaging for therapy response evaluation in pancreatic cancer

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Introduction: With new therapeutic regimens emerging for otherwise lethal pancreatic ductal adenocarcinoma (PDAC), there is great need for imaging-based biomarkers that would allow early assessment of therapy response.
Methods: We designed a preclinical approach and used *Ptf1a*$^{wt/cre}$;*Kras*$^{wt/LSL\text{-}KrasG12D}$;*p53*$^{fl/fl}$ (*CKP*) genetically engineered mouse model (GEMM) that develops moderately differentiated PDAC with strong stromal reaction faithfully recapitulating locally advanced human PDAC. Animals were subjected to 2 different therapy regimens, gemcitabine and refametinib, a novel MEK kinase inhibitor, and response to therapy was monitored with

T2-weighted (T2w-) and diffusion weighted-magnetic resonance imaging (DW-MRI).
Results: Targeted MEK inhibition by refametinib induced a prolongation of animal life and strong reduction in tumor volume, as estimated by T2w-MRI, as early as 5 days upon therapy onset. Gemcitabine treatment did not induce dramatic changes both in survival or tumor volume. Changes in tissue composition were monitored with DW-MRI derived apparent diffusion coefficient (ADC) parameter. Refametinib treatment induced an increase in ADC values as early as 24h after therapy onset while ADC did not change in the gemcitabine treated group. In limited number of patients with stage IV PDAC that received first line chemotherapy, we observed similar concomitant changes in tumor volume and ADC.
Conclusions: ADC merits further evaluation as therapy response marker in PDAC.

Leukemia, Myelodysplasia, and Transplantation

ID 0047

Vorstellung des Konzepts einer Pflegeberatungsstelle für KMT-Patient/innen an der MHH

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Eine Stammzelltransplantation ist nicht nur mit Hoffnung und Heilung verbunden, sondern auch mit vielen Ängsten und Zweifeln. Deshalb ist es wichtig, dass eine lückenlose Aufklärung, Information und Beratung sowie eine kontinuierliche Begleitung dieser Patienten stattfindet. Seit März 2015 berät eine onkologisch fachweitergebildete Pflegekraft in der KMT-Ambulanz alle Patienten, die eine allogene Knochenmarktransplantation vor oder hinter sich haben. Die Patienten werden vor der Transplantation ärztlicherseits aufgeklärt. Arzthelferinnen übernehmen administrative Aufgaben auf Anweisung des Arztes. Nach der Transplantation finden engmaschige Kontrollen statt. Vor der Implementierung der Pflegeberatung in dieser Abteilung fehlten jedoch pflegerische Informations- und Beratungsgespräche, die die nachstehenden Probleme beseitigen oder mildern: „Schockmoment" bei Erstkontakt mit der Station durch mangelnde Vorbereitung. Ressourcen, mögliche Risiken und Probleme wurden bislang nicht ermittelt. Viele Patienten sind durch die Fülle an verfügbarem Informationsmaterial verunsichert und können deren Qualität nicht beurteilen. Unsicherheiten nach der Entlassung (z.B. Medikamenteneinnahme; Verhaltensweisen im Alltag; keimfreie Ernährung; Körperpflege, Verhalten in Notfallsituationen). Sog. Drehtüreffekte aufgrund fehlender oder nicht ausreichender häuslicher Versorgung, unzureichender Information oder mangelnder Adhärenz. Schwere Folgeschäden, wenn Patienten „kleine Beschwerden" wegen der großen Angst vor einem erneuten Krankenhausaufenthalt ignorieren. Bereits nach einem halben Jahr ist der Benefit für die Patienten und alle an der Versorgung Beteiligten beeindruckend.

ID 0067

Launch of an hematology e-learning tool

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Objectives: Medical education should combine theoretical sessions, practical exercises and individual elaborations of the learning matter. Hematology is complex and a lot of clinical experience is needed, especially with regard to diagnosis based on cytological results. For this purpose an hematology e-learning tool was launched in 2015.
Methods: Personal experiences in dealing with the online tool zytologieseminar.de should be reported.
Results: 247 case histories which cover entire hematology are presented. The tool can be used as a reference at the microscope, for exam preparation and for lesson planning. The user can switch between an interactive development of case histories and a lecturer mode. For each case medical history, laboratory parameters and 40-60 high-quality pictures of blood, bone marrow and lymph nodes as well as MRI or CT imaging are available. A search function allows a targeted search for disease patterns and a convenient download of the corresponding images. Numerous renowned hematologists enriched the collection by their own case reports. A scientific advisory board and an English translation will be available in the future. Experienced consultants have been using the tool for years to conduct hematology trainings for medical students.
Conclusion: Zytologieseminar.de is a free software available to everyone who is interested in hematology and especially in cytology. It can be used as a lecturer, as a self-study tool or for reference purposes.

ID 0079

CLL – Patient registries confirm bendamustine-containing regimen (BR) as an effective first-line therapy

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Introduction: CLL is the most common leukemic disease in Central Europe. The median age of onset is between 70 and 75 years. The combination of bendamustine and rituximab has proven effective for the treatment of this disease in clinical trials and everyday use.
Methods: Since 2008, 61 hemato-oncological practices from 16 federal states within the project team of internal oncology (PIO) have been documenting disease histories of patients with chronic lymphocytic leukaemia in the registry ONCOReg. 782 patients received a bendamustine-containing therapy, 539 (68.9%) as first-line therapy, 126 (23.4%) of which bendamustine mono and 413
(76.6%) bendamustine/rituximab (BR).
Results: This analysis presents the results of the use of bendamustine/rituximab in the first-line treatment of CLL patients in clinical practice.
Patient characteristics:
Gender: 62% m / 38% f
Median age: 72 years
Without B-symptoms: 61%
ECOG 0/1/2: 24% / 58% / 17%
BINET A/B/C: 10% / 55% / 35%
Period from initial diagnosis until first therapy: 24,8 months
Comorbidities: 39% hypertension, 20% diabetes; 11% *CHD*; 6% AIHA; 3% ITP
Therapy:
A median of 6 (1-8) cycles were administered. The median total dose of bendamustine was
840 mg/m².
Response:
The objective remission rate is at 88%, 42% of which CR (haematologically tested) and 46% PR.
Survival:
The median follow up is 26,2 months.
The median progression-free survival is at 40,6 months.
The median overall survival has not been reached yet. The 3-year survival rate is at 80%.
Conclusion: The analysis of the registry reflects the treatment routine and reveals the treatment of mostly older comorbid patients.
The therapy with bendamustine in combination with rituximab proves to be highly effective and safe. The remission rates and PFS of ONCOReg are comparable to those of other patients registries (TLN) or to clinical studies such as CLL2M or CLL10. Recent studies in which older and comorbid ("not fit") patients were treated with newer substances do not show better results with regard to CR and PFS than the combination BR.

The results emphasize the high quality of the treatment of patients in the everyday routine and in specialized oncology practices.

ID 0082

Two rare cases of pleural effusion in hematologic-oncologic patients: A connection between two cavities and mycobacteria

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Background: Pleural effusion is a common complication in hematologic/oncologic patients. Due to the multimorbidity and immunosuppression of these patients also considerably rare reasons can occur.
Material and Methods: We report two striking cases of pleural effusion from a rural hematologic/oncologic practice in Bavaria.
Results: Case 1: In a 64 year old male initially resected for intrahepatic cholangiocellular carcinoma a bilioma of 14×7×7 cm was detected a few months after surgery and drained by CT-guided puncture. Meanwhile, pleural carcinosis causing pleural effusion and peritoneal carcinosis were confirmed. To remediate the persisting bilioma, an internal and external drainage was placed and was later replaced by an internal metal-stent. Pleural effusion increasingly showed a yellowish colour and a bilirubin level of 21.3 mg/dl was detected, probably caused by a biliary-pleural fistula.
Case 2: A 69 year old male patient with myelodysplastic syndrome with refractory anemia (MDS) increasingly showed left-sided pleural effusion. As the pleural effusion rapidly and repeatedly reappeared after relief, pleural biopsies were gained by thoracoscopy. Pathologic examination revealed an exsudative pleurisy with caseating granuloma, highly suspicious for tuberculous pleurisy. An immediate quadruple-therapy was initiated. The patient´s performance status stabilized and pleural effusion was significantly regressive.
Conclusion: In case 1, the drainage of the bilioma was upfront technically demanding due to multiple pretreatments. In case 2, the patient did not obviously have risk for tuberculosis but this putatively rare reason for pleural effusion had to be considered due to immunosuppression.

ID 0113

Results of the non-interventional TARGET study – Efficacy and safety of nilotinib in routine healthcare: Management of CML patients failing prior therapy

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Introduction: Nilotinib (NI) is approved for the treatment of Ph+ CML patients (pts) in CP and AP with failure of prior therapy including imatinib (IM) as well as for de novo Ph+ CML in CP.
Methods: Follow-up analysis of an observational study of NI in 449 pts with Ph+ CML resistant to or intolerant of prior treatment within routine clinical management in 149 centres in Germany (01/2008-04/2015).
Results: 59.2% of the pts were older than 60 years and predominantly in CP (99.1%). 93.1% of all pts were pretreated with IM (any dose). Further medical pretreatment were chemotherapy (23.6%), IFN (16.7%), dasatinib (18.9%) and other unspecified drugs (12.7%). Treatment with NI was mostly due to resistance/intolerance against IM (48.1%/39.6%). Initial NI dose was 800 mg/d in 53.2%. More than half of the pts were treated in 2nd line. At study entry remission status was 61.7% in CHR, 42.6% in MCyR/22.9% in CCyR (missing data in 19.8%), 30.1%/10.5% in MMR/CMR. These responses improved significantly under NI reaching cumulative incidences of CHR, MMR and CMR of 90%, 62.6% and 34.3%, respectively. Cytogenetic response improved as well but is not conclusive enough due to missing examinations. Dose reduction/therapy interruption occurred in 29.4%/15.8%. 75.9% experienced at least one AE which was considered serious in 14.7%. Hematologic toxicity was observed in 13.1%, non-hematologic toxicities occurred in 38.5% of pts. The most frequently reported AEs were pruritus (11.8%), rash (10%), and alopecia (6.7%), fatigue (10.2%), thrombocytopenia (6.7%), arthralgia (5.6%), nausea (6.7%), and upper abdominal pain (5.4%) as well as headache (10.2%).
Conclusions: In this broad population of CML pts with poor response or intolerance to a prior therapy these data support the use of NI as an efficacious and safe drug.

ID 0114

Efficacy and safety of Nilotinib in routine clinical management of newly diagnosed Ph+ CML patients in chronic phase - 3rd interim analysis of the non-interventional MOMENT II-study

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Introduction: As a potent and highly selective BCR-ABL inhibitor Nilotinib (NI) is approved for treatment of newly diagnosed Ph+ CML patients (pts) in CP as well as for pts with Ph+ CML in CP and AP with failure to prior therapy including imatinib.
Methods: 3rd interim analysis of a non-interventional study of NI in 279 pts with de novo Ph+ CML in CP within routine clinical management in 110 centres in Germany (08/2011–03/2015).
Results: All pts were newly diagnosed with a median age of 57.5 years (range 17-88) and 54% were male. The median observation period was 388.5 days (range 4-818) with a median daily dose of 600 mg NI (range 150-800 mg). There were 13.6% of pts with one, 3.2% with more than one interruption of therapy with a median of 14 days (range 1-319) for the duration of each interruption. At last visit 80.2% (of 266 pts with a hematologic examination) had a CHR, 81.5% (of 27 pts with a cytogenetic examination) had a CCyR, 52.3% (of 199 pts with a molecular examination) had an MMR. In the subgroup of pts with molecular response (n = 178) the median time to MMR or better was 183 days (range 56-740). A premature study discontinuation took place in 16.1% of pts mostly due to AEs/non-hematologic toxicity, in 4 cases due to disease progression. Altogether, 76.7% of pts experienced AEs. Hematologic toxicity was observed in 9% of pts, non-hematologic toxicities in 35.5% of pts. The most frequently reported AEs were skin reactions, gastrointestinal symptoms, dyspnoea as well as headache. No cardiac/vascular disorders occurred in ≥ 2% of pts. The most frequent biochemical abnormalities were increases in blood bilirubin and GGT.

Conclusions: These data from routine clinical management support the use of NI as an effective and safe drug for treatment of newly diagnosed Ph+ CML pts in CP.

ID 0301

Synergistic effects of ABT-199 with conventional chemotherapeutic agents and the CDK inhibitor Dinaciclib in childhood B-cell precursor acute lymphoblastic leukemia

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Treatment failure and relapse in B cell precursor (BCP) ALL are associated with defective apoptosis signaling. ABT-199 is a potent and highly specific BCL-2 inhibitor and currently evaluated pre-clinically and in first clinical trials. However the intrinsic or acquired resistance indicates the need for predictive markers and for effective combination treatment strategies.
In this study, we estimated the effectivity of ABT-199 in BCP-ALL cell lines (n = 5) and a set of patient-derived xenograft (pdx) samples (n = 10) and investigated combinations of ABT-199 with conventional drugs and the CDK inhibitor dinaciclib. Apoptosis regulating molecules were investigated by western blot analysis or flow cytometry.
We found sensitivity in all tested cell lines with half maximal inhibitory concentration (IC50) values in the nanomolar range (mean 212 nM), except for Nalm-6, showing resistance (IC50 >10 µM). High sensitivity (IC50 from 3 to 156 nM) was also found in 9 / 10 pdx samples, with one insensitive sample with an IC50 value of > 1 µM, similar to PBMCs from healthy donors. Resistance to ABT-199 was associated with low BCL-2 and increased MCL-1 expression compared to ABT-199 sensitive leukemias. Co-exposure of Nalm-6 cells to ABT-199 and vincristine, dexamethasone and asparaginase and their combination (VDA) revealed synergism (CI's 0.4, 0.14, 0.002 and 0.03). Strikingly, dinaciclib treatment resulted in down-regulation of MCL-1 showing strong synergism with ABT-199 in Nalm-6 and resistant primary ALL (CI's 0.03, 0.04).
Taken together, these data indicate effective cell death sensitization by ABT-199 and potential strategies to overcome ABT-199 resistance in BCP-ALL.

ID 0311

Establishment and characterization of patient-derived xenograft models of acute leukemias

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The hematological malignancies Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) are characterized by a rapid increase of immature blood cells. They are distinguished by their cells of origin. If untreated, AML and ALL are life-threatening and patients show different responses to current standards of care (SoC) therapy. The majority of acute leukemias are genetically heterogeneous and therefore a challenge for the development of new targeted therapies. There is a need to develop robust animal models to investigate leukemia in vivo. Patient-derived xenograft (PDX) mouse models recapitulate many clinical features of the original cancer. They have proven to be useful tools for the evaluation of novel therapeutic strategies and biomarkers, and for the study of cancer biology.
The aim of our work was to establish PDX models of AML and ALL and to characterize their sensitivity to different therapeutic agents.
Bone marrow aspirates were obtained from primary and relapsed AML/ALL patients and were intravenously (i.v.) and/or subcutaneously (s.c.) inoculated into immunodeficient mice. Mice were sacrificed when signs of disease were obvious and single cell suspensions of spleens (i.v.) or tumor fragments (s.c.) were transferred to new recipient mice. Chemosensitivity to SoC treatments was tested.
In our study several AML-PDX and ALL-PDX were established. These models show different sensitivity to SoC treatment. The models will be used for further investigations like gene expression or mutation analysis or biomarker identification.
The established PDX models of AML and ALL are suitable tools for preclinical drug development. In order to cover the complex heterogeneity of acute leukemias, the establishment of further PDX models is currently in progress.

ID 0327

CONIFER – Non-interventional study to evaluate therapy monitoring during Exjade®(Deferasirox) treatment of iron toxicity in MDS patients with transfusional iron overload in the course of treatment

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Introduction: Myelodysplastic syndromes (MDS), a diverse group of hematological disorders, are characterized by ineffective hematopoesis. Long-term blood transfusions are an important therapeutic regime and many MDS patients show increased iron levels. Exjade® (Deferasirox) is a once-daily, oral iron chelating agent that binds and removes toxic iron from the body. The effectiveness and safety of Exjade® treatment for patients with transfusional iron overload is approved by clinical trials.
Methods: Analysis of a non-interventional, post-marketing surveillance study of Exjade® in MDS patients with transfusional iron overload.
Results: 99 pts with mainly IPSS low (23%) or intermediate 1 (36%) MDS were evaluated (57 m., 42 f., age 72.5y (42-88y)). The mean time from the initial diagnosis to start of the Exjade® therapy was ≤0.5 years (27%). The most frequent initial dose of Exjade® was 5 to <10 mg/kg (40% of pts) with a mean daily dose of 11.8 ± 7.0 mg/kg at baseline (range 3-38 mg/kg). Pts were treated for a mean duration of 16 months. Iron overload was assessed by serum ferritin level (2080 ± 1244 µg/L at baseline). Stratification of serum ferritin levels by Exjade® dosage showed a serum ferritin reduction at higher and no reduction at the lower dose (Exjade® <15mg/kg vs. ≥15mg/kg). This result was confirmed by a second stratification by Exjade® dosage (<20mg/kg vs. ≥ 20mg/kg). Dosage was adjusted in 59% of pts mainly due to insufficient chelation (27%) and AEs (12%). AEs occurred in 81% of pts (21% drug-related, 54% sAEs) with decreased renal creatinine clearance being the most frequent.
Conclusion: Higher doses of Exjade® effectively and safely reduce serum ferritin levels in MDS patients with transfusional iron overload.

ID 0374

APR-246 targets pediatric acute lymphoblastic leukemia carrying mutant P53

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Mutations of the tumor suppressor gene *TP53* have been described to be associated with poor prognosis in different cancer types. *TP53* alterations are rarely present in acute lymphoblastic leukemia (ALL), however associations of mutated *TP53* with therapy resistance and relapse have been described. APR-246 (initially PRIMA-1^{MET}), a small molecule compound reported to restore p53 function has shown activity in malignancies with mutated *TP53* (*TP53*mut). In ALL, mutant *TP53* was so far not addressed as therapeutic target.
In this study, we analyzed a cohort of 62 B-cell precursor (BCP) ALL primograft samples and identified 4 cases with *TP53*mut, at a frequency also reported in patient cohorts. In addition, 2 of 6 BCP-ALL cell lines analyzed were *TP53*mut. Next, we investigated the activity of APR-246 (kindly provided by Aprea, Stockholm, Sweden) on *TP53*mut or wild type (wt) BCP-ALL cells lines and observed high sensitivity to APR-246 in *TP53*mut ALL (IC50: 5 µM) with increased induction of apoptosis. Interestingly, upon APR-246 exposure increased p53 phosphorylation and induction of the transcriptional targets NOXA and PUMA were detected in *TP53*mut but not *TP53*wt BCP-ALL cells, indicating restoration of p53 function. Moreover, we investigated the effective range of APR-246 on primografts and also identified a clear responsiveness of *TP53*mut patient-derived ALL samples with induction of significantly higher cell death rates.
In conclusion, *TP53*mut BCP-ALL can be targeted by APR-246 leading to p53 re-activation, NOXA and PUMA mediated apoptosis and effective leukemia cell killing. Thus, targeting and re-activation of mutated p53 provides a promising novel therapeutic strategy in this high-risk subtype of BCP-ALL.

ID 0438

Making CAR T-cells for AML Safer

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A high percentage of children with acute myeloid leukemia (AML) will ultimately fail standard AML-BFM 2012 therapy, including allogeneic stem cell transplantation. Therefore, it is paramount to develop 2nd line treatment options. Adoptive T-cell therapy (ACT) with autologous T-cells genetically engineered with chimeric antigen receptors (CARs) to specifically recognize tumor-expressed antigens has recently been established as a potent treatment strategy that can induce regression and even cure of human leukemias. CD33 or CD123 CARs efficiently kill both, human AML cells and normal human myelopoiesis, *in vitro* and *in vivo* in mice in a non-MHC restricted manner. Therefore, for ACT of poor-prognosis and relapsed AML, we are developing three distinct approaches to make the CAR T-cell treatment safer and more feasible: 1. Co-expression of a novel human suicide gene together with the CAR. This allows to eliminate the genetically modified T-cells *in vivo* by infusion of a prodrug. 2. *In vivo* inducible expression of the CAR on transduced T-cells. This enables us to adjust the CAR expression on transduced T-cells according to the clinical needs and if unwanted side effects occur. 3. Increasing the specificity of CAR therapies by separating recognition and co-stimulatory signals on two CARs, thus allowing to restrict the cytotoxicity of the redirected T-cells to the blasts with pathological antigen expression profiles. As even a single dose of re-infused genetically modified CAR T-cells can survive and expand for extended periods of time in the recipient, these 'safer' CAR strategies might allow to increase the percentage of AML patients that is cured, e.g. by inducing remission in patients with persistent blasts prior to transplantation or by treating (molecular) relapses after transplantation.

ID 0448

Prognostic Significance of Aneuploidy in Children with Relapsed Acute Lymphoblastic Leukemia

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Aneuploidy is a cytogenetic hallmark of pediatric acute lymphoblastic leukemia (ALL). High hyperdiploidy (HeH) with >50 chromosomes (or a DNA Index ≥1.16) occurs in 30% of B cell precursor (BCP) ALL and is associated with favourable prognosis after frontline treatment. In contrast, hypodiploidy with
By DNA Index, we identified eight patients (8/316; 2.5%) with hypodiploid cells and very poor outcome after relapse (pEFS±SE .13±.12). Forty-eight patients (48/316; 21.5%) had a DI≥1.16, but their outcome was only slightly better than that of other patients (pEFS±SE .63±.08 vs. .48±.03; p = 0.029). To better classify HeH ALL, we used K-means to cluster hyperdiploid patients by their patterns of chromosomal gains and losses detected by multiplex-ligation dependent probe amplification. Two clusters showed a high number of chromosomal gains (6-14) of which one cluster (n = 24) presented with the classical HeH pattern and most favourable outcome (pEFS±SE .71±.10), whereas the other (n = 8) showed multiple non-classical gains and much inferior outcome (pEFS±SE .25±.15). SNP genotyping indicates reduplicated hypodiploid genomes in the latter group, a phenomenon known as "masked" hypodiploidy.
We conclude that hypodiploidy can aid in identifying poor prognosis ALL relapse patients eligible for alternative treatment strategies. To avoid misclassification of "masked" hypodiploidy SNP genotyping should be used to detect aneuploidies.

ID 0498

CLL2-BIG – a Novel Treatment Regimen of Bendamustine Followed By GA101 and Ibrutinib Followed By Ibrutinib and GA101 Maintenance in Patients with Chronic Lymphocytic Leukemia (CLL): Interim Results of a Phase II-Trial

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Introduction: With the CLL2-BIG trial, the German CLL Study Group (GCLLSG) designed a novel combination regimen composed of bendamustine, obinutuzumab and ibrutinib according to the "sequential triple-T" concept [Hallek, ASH 2013] of a **t**ailored and **t**argeted treatment aiming at **t**otal eradication of minimal residual disease (MRD).
Methods: 62 patients with chronic lymphocytic leukemia (CLL) are to be recruited, irrespective of treatment line or fitness. Patients with initial high tumor burden receive two cycles of bendamustine debulking before start of six cycles of induction treatment with obinutuzumab and ibruti-

nib. Maintenance therapy with ibrutinib and obinutuzumab follows until achievement of MRD-negative complete remission or up to 24 months.
Primary endpoint is overall response rate (ORR) at the end of induction; secondary endpoints include MRD evaluations as well as safety and survival parameters.
Results: As of July 2015, 62 patients were included; 29 were treatment-naïve and 33 relapsed/refractory.
Obinutuzumab was administered to 41 patients of whom 22 received prior debulking. 14 infusion related reactions (IRR) CTC AE v4.0 grade I-III were reported in 13 patients. Only 4 IRRs occurred after two cycles of debulking (18%). 2 IRRs were reported as SAEs, one after prior debulking and one without. No grade IV IRR and no IRR after the first two infusions of obinutuzumab occured so far.
Baseline characteristics, occurrence of IRRs as well as first safety and efficacy data will be available for presentation at the meeting.
Conclusion: The data suggest that debulking prior to obinutuzumab might reduce the occurrence of severe IRRs compared to historical data and to patients who did not receive debulking.

ID 0547

DasPAQT: Treating Patients with Chronic Myeloid Leukemia (CML) in Chronic Phase (CP) with Dasatinib – PCR-Monitoring, Adherence, Quality of Life, Therapy Satisfaction (OMC 2014-I; BMS CA180-565)

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Introduction: Although tyrosine kinase inhibitors (TKI) have shown remarkable efficacy in clinical trials, there is a lack of published data on CML management in the real-life clinical practice setting. DasPAQT is a non-interventional, multi-center study designed to document the response to Dasatinib (DAS) treatment of patients with CML in chronic phase including PCR monitoring, adherence, quality of life and therapy satisfaction in clinical routine – outside of clinical studies.
Methods: Patients with newly diagnosed Ph+ CP-CML and patients in chronic phase resistant or intolerant to prior CML therapy are treated with DAS according to the common clinical routine. 300 patients in 75 centers (hematological and oncological hospitals or practices) will be documented to answer the following questions: What is the real-life treatment pattern of DAS including treatment strategies in first-line chronic CML or in a switch setting? What is the efficacy and outcome of DAS treatment and which prognostic clinical and scientific factors determine treatment strategy? What is the patient-reported benefit and the impact of first-line DAS treatment on patients' quality of life? What are the rates of adherence/compliance, how satisfied are patients with their treatment? Which factors determine treatment discontinuation? Can long-term treatment response be predicted in a "real-world" setting?
Results: Diagnostic monitoring and treatment strategy with DAS of the initial study phase as well as baseline characteristics, treatment duration and safety data of the first 100 patients will be presented.
Conclusion: DasPAQT intends to provide insight into the routine health care management of CML-patients. The factors that CML patients and treating physicians may encounter in a real-life setting will reflect the benefits and efficacy of DAS treatment.

Lung Cancer

ID 0048

Outcome and prognostic factors of postoperative radiation therapy (PORT) after incomplete resection of non-small cell lung cancer (NSCLC)

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Purpose: Current guidelines recommend postoperative radiation therapy (PORT) for incompletely resected non-small cell lung cancer (NSCLC). However, there is still a paucity of evidence for this approach. Hence, we analyzed survival in 78 patients following radiotherapy for incompletely resected NSCLC (R1) and investigated prognostic factors.
Patients and Methods: All 78 patients with incompletely resected NSCLC (R1) were treated at the University Hospital of Heidelberg and received PORT between December 2001 and September 2014. The median total dose for PORT was 60.0 Gy (range 44–68 Gy). The majority of patients had locally advanced tumor stages (stage IIA (2.6%) stage IIB (19.2%), stage IIIA (57.7%) and stage IIIB (20.5%)). 21 patients (25%) received adjuvant chemotherapy.
Results: Median follow-up after radiotherapy was 17.7 months. Three-year overall (OS), progression-free (PFS), local (LPFS) and distant progression-free survival (DPFS) rates were 34.1%, 29.1%, 44.9% and 51.9%, respectively. OS was significantly prolonged at lower nodal status (pN0/1) and following dose-escalated PORT with total radiation doses > 54 Gy ($p = 0.012$, $p = 0.013$). Furthermore, radiation doses > 54 Gy significantly improved PFS, LPFS and DPFS ($p = 0.005$; $p = 0.050$, $p = 0.022$). Interestingly, survival was neither significantly influenced by R1 localization nor by dimension (localized vs. diffuse). Multivariate analyses revealed lower nodal status and radiation doses > 54.0 Gy as the only independent prognostic factors for OS ($p = 0.021$, $p = 0.036$).
Conclusion: For incompletely resected NSCLC, PORT is used for improving local tumor control. As local progression is still the major pattern of failure, a radiation dose > 54 Gy should be recommended for improving local control and overall survival.

ID 0190

Exposure-response relationship for ramucirumab (RAM) from the randomized, double-blind, phase 3 REVEL trial (docetaxel [DOC] plus placebo [PL] vs DOC plus RAM) in second-line treatment of metastatic non-small cell lung cancer (NSCLC)

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Background: An exploratory exposure-response analysis for RAM was performed using data from the REVEL trial (NCT01168973).
Methods: Patients (pts) received RAM (10 mg/kg) or PL + DOC (75 mg/m^2) every 3 weeks (q3w). Population PK (PopPK) analysis provided model-predicted RAM exposure parameters (Cmin,1, Cmin,ss, Cmax,ss, and Cave,ss; expressed in µg/ml) to explore the relationship between RAM exposure and measures of efficacy and safety. For efficacy, RAM+DOC pts were separated into 4 quartiles by Cmin,1 (Q1-4; n = 94 each): Q1≤15.7; Q2>15.7-≤20.7; Q3 >20.7-≤27.9; Q4 >27.9. For safety RAM+DOC pts were separated into Q1-4 by Cave,ss (n = 94 each): Q1≤79.3; Q2>79.3-≤97.4; Q3 >97.4-≤118; Q4 >118. Kaplan-Meier, Cox regression, and ordered categorical analyses evaluated these relationships.
Results: Analyses included 376 RAM+DOC and 366 DOC+PL pts. As RAM exposure increased (Q1-4), greater improvements (smaller HRs) were seen in OS (adjusted HR range 1.19-0.67 and median OS 11.1-17.1 months) and PFS (adjusted HR range 0.71-0.92 and median PFS 5.6-7.0 months). Similar trends were seen for all exposure parameters. Median OS and PFS in DOC+PL pts were 13.3 and 5.5 months, respectively. A correlation was observed for RAM exposure (Q1-4) and grade ≥3 febrile neutropenia (7.5-22.3%) and hypertension (4.3-13.8%). In DOC+PL pts, incidence of grade ≥3 febrile neutropenia and hypertension were 11.8% and 2.8%, respectively.
Conclusions: Results from exposure-response analyses suggest improvements in efficacy and increased toxicity may occur with increasing RAM exposure. RAM (10 mg/kg q3w) in combination with DOC is appropriate for the NSCLC indication.

ID 0237

Reirradiation in Locally Recurrent Lung Cancer Patients

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Purpose: Lung cancer remains one of the most lethal tumors, and innovations have yielded only modest survival improvements . There is no consent on how to treat local relapse in patients after first line treatments. Radiotherapy is commonly administered in this situation; however, data supporting its effectiveness are rare. The purpose of this retrospective analysis was to evaluate overall survival (OS), local progression free survival (LPFS), and toxicity in patients re-irradiated for thoracic tumours.
Patients: 56 patients were included . Median follow-up was 7 months. Patients with target volumes both in lung and mediastinum were re-irradiated with conventional 3-dimensional or IMRT techniques. Median overall dose of re-irradiation was 38.5 Gy (range 20-56 Gy) using single fraction dose of median 2 Gy (1.8-3 Gy). Mean total lung dose was 6 Gy (range 1-15.7 Gy). Clinical documents were collected and evaluated. Dose-volume parameters were derived from treatment plans. Statistical analysis was performed using a software tool.
Results: Both OS and LPFS following re-irradiation was 9 months. OS and LPFS were not affected by histology, dose or patient age and gender. OS, however, was improved in patients, in whom re-irradiation volumes included less mediastinal lymph node regions (p = 0.97). 14 patients suffered from pneumonitis °II. 1 patient presumably died from pneumonitis °IV. There were no bronchial bleedings or fistula, and no significant decline in FEV1 was detected.
Conclusion: Re-irradiation in recurrent lung cancer patients is safe and does not impose indecent risks of bronchial injury. Oncological outcome is still dismal and appears to be affected by mediastinal target volumes. Prospective clinical trials are warranted to substantiate the role of re-irradiation in recurrent lung cancer.

ID 0289

Development of a 3D organotypic lung tumor model in combination with FDG-PET to monitor treatment response

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Tumor models in 2D cell culture neglect several aspects concerning the microenvironment, which might influence tumor-biology and alter drug response. We therefore aimed to build a tumor model based on acellular rat lung scaffolds which can be combined with a bioreactor and monitored non-invasively by positron-emission-tomography (PET).
Lung adenocarcinoma cell lines were cultured on acellular rat scaffolds for 14 days. A bioreactor was developed to induce ventilation and enable perfusion of the vascular system. Statically cultured tumor models treated with gefitinib, an EGFR-inhibitor were examined histologically and by FDG-PET-scans
Tumor cells formed distinct clusters on the scaffold, exhibited up-regulation of carcinoma-associated marker and a reduced proliferation-rate, compared to 2D culture. FDG-PET allowed detecting and tracking of individual tumor lesions over time. Correlation of autoradiography with DAPI staining verified specific FDG uptake by tumor cells. Treatment with gefitinib reduced FDG uptake in EGFR-mutated but not in -wildtype tumor cells. Interestingly, EGFR-mutant tumor clusters varied in their response to gefitinib.
This organotypic tumor model provides tumor nodules with a tumor relevant gene expression and proliferation rate. This reflects the *in vivo* situation better, compared to 2D culture models. Assessment of single tumor lesions and their response to treatment is possible using µPET imaging. The different responses of distinct tumor nodules indicate heterogeneity in our models. This might allow longitudinal studies regarding tumor growth and metabolism as well as preclinical testing and development of strategies against resistant sub-clones.

ID 0341

Clinical Outcome of Targeted Therapy with Gefitinib in Metastatic NSCLC Depending on the Type of EGFR Mutation: A REASON Subgroup Analysis by Exon

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Introduction: In NSCLC, therapy response to TKI depends on the presence of EGFR mutations (EGFR-Ms) known to be TKI-sensitive. REASON provides the largest database with details on EGFR-M patterns in Caucasians with stage IIIB/IV NSCLC including further clinico-pathological features, systemic therapies and clinical outcome.
Methods: REASON (NCT00997230) is a national, multicenter, prospective, non-interventional study. 4,243 patients (pts) were enrolled in 149 sites from 09/2009 to 03/2011. EGFR-M+ rate in 4,200 pts was 10.3%. EGFR-M+ pts were followed for course of treatment / clinical outcome until 10/2012.
Results: EGFR-Ms were mostly found on exon 19 / 21 (48.1% / 35.2%) and less frequent on exon 18 / 20 (7.2% / 9.3%). TKI-sensitivity was shown for 76.9% of mutations on exon 19 and 51.6% / 7.5% on exon 18 / 20. 1st line gefitinib therapy of pts with exon 19 mutations improved progression free survival (PFS) (11.3 vs. 6.5 months (CHX) HR: 0.5; $p < 0.002$). Gefitinib at 1st / later line significantly prolonged overall survival (OS) (21.8 vs. 10.6 months HR: 0.27; $p < 0.0001$). Gefitinib therapy of pts with EGFR-Ms on Exon 18 and/or 20 showed not only an effect on PFS (6.8 vs. 4.3 months), but also prolonged the OS (20.4 vs. 8.3 months HR: 0.47; $p < 0.1$).
Gefitinib was generally well tolerated with grade 1 diarrhoea (14%) and grade 1 rash (14%) as the majority of adverse drug reactions (ADRs). Severe ADRs were recorded for 7.7% of pts.
Conclusion: REASON confirms known EGFR-M patterns with the majority of mutations identified on exons 19 and 21. While generally well tolerated targeting mutations on exon 19 and exons 18 / 20 with gefitinib achieved an improved clinical outcome with respect to PFS as well as OS.
The study is sponsored by AstraZeneca Germany.

ID 0345

REASON: Factors influencing outcome in patients (pts) with NSCLC stage IIIB/IV and mutated EGF receptor (EGFR-M+) treated with gefitinib

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Introduction: REASON provides the largest database of EGFR mutations in Caucasians with stage IIIB/IV NSCLC describing clinico-pathological features, systemic therapies and clinical outcome.
Methods: REASON (NCT00997230) is a national, multicenter, prospective, non-interventional study. 4,243 pts were enrolled in 149 centres from 09/2009 to 03/2011. 4,200 pts displayed an EGFR-M+ rate of 10.3%. EGFR-M+ pts were followed to capture treatment algorithm / clinical outcome until 10/2012.
Results: Gefitinib was applied 1st line to 206 (64%) out of 320 EGFR-M+ pts. Among these, 63% were male, 92% had an adenocarcinoma, 57% were ≥65 years old and 52% were non-smokers. Median PFS was 10.0 months (95% CI 8.8–5.1) and for subgroups: female pts 10.3 / male pts 7.0, ever smoker 8.2 / never smoker 10.3, adenocarcinoma 10.1 / non-adenocarcinoma 6.7, <65 years 9.0 / ≥65 years 10.1 months. Multivariate Cox Regression (MCR) showed a significant difference in PFS for gender (male vs female HR 1.7, $p = 0.0016$), but no significant difference was detected for age, smoking habit and histology.
The 213 (66%) pts receiving gefitinib at any time during their course of therapy reached a median OS of 18.1 months (95% CI 15.5–21.3), for female pts 21.8 / male pts 12.4, ever smoker 16.3 / never smoker 20.4, adenocarcinoma 18.1 / non-adenocarcinoma 18.4, <65 years 20.5 / ≥65 years 16.3 months. Like for PFS, MCR showed a difference in OS for gender (male vs female HR 2.0, $p = 0.0009$), but not for smoking habit, histology or age.
Conclusion: In REASON, gefitinib was the most common first- and later-line treatment of EGFR-M+ pts leading to an overall benefit on clinical outcome. Of all subgroups, this positive effect proved to be most prominent in females and non-smokers.
The study is sponsored by AstraZeneca Germany.

ID 0394

Discovery of a novel *EGFR* resistance mutation by capture based NGS following AZD9291 treatment.

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Question: Understanding oncogenic drivers and molecular resistance mechanisms paves the way to personalized medicine in oncology. For example, AZD9291 was developed as irreversible TKI to inhibit EGFR with a T790M resistance mutation in lung cancer. Here, we describe a patient diagnosed with lung adenocarcinoma in 9/2011. Due to an activating EGFR exon19 deletion, patient was treated with erlotinib but progressed. At this time the patient was treated within a study with an HSP90 inhibitor, followed by irradiation, chemotherapy and afatinib within a compassionate use program . After detecting T790M, the patient was included in the AURA1 study to receive AZD9291 in 6/14. In 7/15, the patient progressed with a pleural effusion, which was sent for molecular testing using NEO technology.
Method: With limited cellular material, NEOliquid analysis was performed on available effusion supernatant. NEOliquid is a hybrid-capture based NGS assay to detect point mutations, InDels, copy number alterations and gene fusions in more than 30 clinically relevant genes from circulating tumor DNA.
Results: NEOliquid confirmed the EGFR exon19 deletion and T790M mutation, and detected a previously undescribed EGFR C797G mutation. The mutated cystein is pivotal for covalent and potent binding of AZD9291 to EGFR. Tissue biopsy confirmed the EGFR C797G mutation. The patient's condition then deteriorated and the patient died in 7/2015.
Conclusion: Hybrid-capture based NGS is able to detect genomic alterations in circulating tumor DNA extracted from pleural effusions. A new resistance mutation to AZD9291 involving C797G essential in covalent binding of 2nd and 3rd generation EGFR TKIs was detected.

ID 0443

Efficacy of Rociletinib (CO-1686) in Centrally Confirmed T790M-positive and T790M-negative Non-small Cell Lung Cancer (NSCLC) Patients (Pts)

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Background: Rociletinib is an oral inhibitor of mutant epidermal growth factor receptor (EGFR), including the T790M resistance mutation. The phase 1/2 TIGER-X study (NCT01526928) is evaluating rociletinib in mutant EGFR NSCLC pts who have received prior treatment with EGFR-directed therapy.
Methods: Pts are required to have advanced or recurrent NSCLC with a documented activating EGFR mutation. Central nervous system metastases are allowed if stable. Pts were treated with 500mg, 625mg, 750mg, or 1000mg BID rociletinib. In the phase 2 portion, T790M+ tumor status by central tissue genotyping (QIAGEN *therascreen*® assay) is required.
Results: As of April 27, 2015, 456 pts were enrolled and received ≥1 dose of rociletinib; 119 pts received rociletinib at the 500mg BID dosing level. Median age was 63 yrs; 66% of pts were female, and 20% were of Asian ethnicity. Pts received a median of two prior therapies. The RECIST (v1.1) objective response rate (ORR) across all dosing levels was 53%. At the 500mg BID dosing level, the ORR was 60% in 48 centrally confirmed tissue T790M+ pts. Across all doses, the ORR was 37% in 35 centrally confirmed T790M– pts. Across all doses, the most common all-grade treatment-related adverse events (TRAEs) included hyperglycemia (46%), diarrhea (36%), and nausea (31%); the rate of grade ≥3 hyperglycemia was 25%. At the 500mg BID dose, the three most common all-grade TRAEs included hyperglycemia (35%), diarrhea (33%), and nausea (19%). Across all doses, the drug discontinuation rate due to AEs was 4% .
Conclusions: In the ongoing TIGER-X study, rociletinib has efficacy and is tolerated at the recommended dose (500mg BID) in pts with EGFR-mutant T790M+ NSCLC.

ID 0497

An effective *in vivo* Liquid Biopsy tool for the isolation of circulating tumor cells in non-small cell lung cancer

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Background: Circulating tumor cells (CTCs) are a possible prognostic biomarker in the analysis of tumors. Evaluation of CTCs and tumor tissue before and after therapy, at disease progression or before new treatment initiation would be informative for the selection of appropriate prognosis, treatment efficacy and therapy options. Common CTC technologies have limits particularly in detecting low frequency CTCs. The GILUPI CellCollector®, screens a large volume of blood directly in the vein. Here, we demonstrate the application of the GILUPI CellCollector® in the assessment of CTCs in non-small cell lung cancer (NSCLC) patients at different tumor stages.
Patients and Methods: 59 NSCLC patients, stage IA to IIIB, were recruited for CTC isolation before (n = 59) and after surgery (n = 25). CTC enumeration was conducted by immunofluorescence (IF) microscopy followed by analysis for KRAS mutations using the PointMan DNA mutation enrichment assay. Primary tumor tissue was analyzed for the same mutations to investigate concordance. For (n = 21) CTC samples a direct comparison with CELLSEARCH® was performed.
Results: A significantly higher isolation efficiency compared to CELLSEARCH® is shown. No CTCs could be found in controls. The overall sensitivity of the GILUPI CellCollector® is 89%. A pre-surgical isolation rate of 84% compared to 62.5% post-operative was observed.
Conclusions: The GILUPI CellCollector® overcomes blood volume limitations of other CTC extraction approaches and thereby increases the diagnostic sensitivity of CTC isolation. It allows CTC enumeration, molecular characterization, and biomarker expression analysis, which could help guide treatment strategies and monitoring therapy efficacy.

ID 0502

The Network Genomic Medicine first joint cost-effectiveness and outcome evaluation based on multiplex lung cancer genotyping

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Background The Network Genomic Medicine (NGM) Lung Cancer is one of the biggest European networks for personalized medicine offering comprehensive next generation sequencing (NGS)-based multiplex genotyping for all inoperable lung cancer patients (pts) in Germany. In 2014 NGM and the AOK Rheinland/Hamburg have successfully contracted and established the first "flat rate" cost reimbursement model for NGS-based comprehensive genotyping in Europe.
Methods The AOK Rheinland/Hamburg cooperates with NGM within the integrated care contract (ICC). Other nationwide German public and private health insurances has joined the ICC in 2015. We elaborated a model to analyze cost-effectiveness and cost-utility of NGS including diagnostic results, treatment strategies and outcome.
Results In 2014 about 4500 lung cancer NGM patients were centrally genotyped on the central NGS platform in Cologne. In 2015 NGS-based genotyping for over 35% of all German annually newly diagnosed inoperable lung cancer pts is covered by the ICC. All ICC pts were stratified according to their diagnostic results and molecular guided therapy options (targeted drugs including off-label use, participating in clinical trials or standard chemotherapy). Clinical outcome data are collected within NGM (by over 220 partners) and reimbursement data will be provided by health insurances.
Conclusions NGM stands for the implementation of personalized cancer therapy into clinical routine in Germany. Now we systematically evaluate NGS-based molecular results and clinical outcome besides of clinical trials. First-time in Europe data evaluation is provided in a close cooperation between health care providers and health insurance companies and even matching pts' data.

ID 0526

Immunophenotyping in Non-Small Cell Lung Cancer as an indicator for prognostic Information and treatment Decisions

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Lung cancer is generally divided in non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with most patients suffering from NSCLC. Therapeutic strategy is determined by the functional / performance status, comorbidity, histopathological evaluation, molecular analyses and the TNM stage. Despite of comparable histopathology and TNM of patients within the same tumor stage clinical outcome as well as the course of the disease can vary significantly, indicating the need for additional prognosticators helping to choose appropriate therapeutic procedures.
It was shown that in NSCLC high frequencies of $CD8^+$ memory- and regulatory T-cells are correlated with better survival.
Aim of our retrospective study is to perform a broad characterization of lymphocytic infiltrates, macrophages and cytokines and thus to identify possible prognostic markers, which may be suited for prediction of the clinical course. For implementation a patient cohort covering Stage I – Stage IV NSCLC with known clinical outcome and existing PET/CT imaging follow-up was chosen and formalin fixed paraffin embedded (FFPE) tissue was used for tissue micro array generation. Using multispectral imaging up to 7 markers can be screened in a single section. Markers for CD3, CD8, FoxP3, CD163, and PD-L1 are also included in our study; additional markers are yet to be evaluated.
Information on immune infiltrates in the tumor tissue and the tumor margin can be obtained and correlated with overall / progression-free survival, metastases or relapse. This may help to generate a patient "classification" for clinical trials. We expect that some biomarkers are surrogates for suppressive pathways and might be connected to a short progression-free survival. This might result in the identification and evaluation of determinants helping to improve prognostic / predictive assessment and thus enhancing therapeutic approaches in lung cancer.

Lymphoma and Plasma Cell Disorders

ID 0125

Impact of centralized diagnostic review on quality of initial staging in Hodgkin lymphoma: Experience of the German Hodgkin Study Group (GHSG)

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Introduction: Accurate clinical staging is crucial for adequate risk-adapted treatment in Hodgkin lymphoma to prevent patients from under- or over-treatment and achieve optimal outcomes.
Methods: Within the latest GHSG trial generation including 5965 HL patients enrolled between 2003 and 2009, diagnostic findings such as histopathology, CT-imaging and clinical risk factors were re-evaluated by expert panels. Here we retrospectively analyzed patients in whom major discordant findings changed allocation to first-line treatment.
Results: In 87 patients, histopathology review did not confirm the initial diagnosis of HL. Treatment allocation was revised in 312 of the remaining 5878 patients: 176 were assigned to a higher and 128 to a lower risk group, respectively. Correct treatment group remained unclear in 8 patients. Cases of revised treatment allocation accounted for 9.8%, 6.0%, 0.8%, and 14.8% of patients initially assigned to HD13, HD14, HD15, and NLPHL-IA, respectively. Most revisions were due to wrong application of clinical stage (20.5% of 312 patients with revised treatment group), histological subtype (9.0%) or the risk factors ≥3 involved areas (46.8%) or large mediastinal mass (9.3%). We additionally describe critical regions and potential risk factors for inadequate treatment allocation.
Conclusion: Quality control measures including centralized review of diagnostic findings by experienced experts changed risk-adapted first-line treatment in a relevant proportion of HL patients. Since exact initial staging of HL is crucial for risk-adapted treatment, multidisciplinary expert review and more sensitive modalities such as PET should be implemented in initial staging for all HL patients to ensure high quality of care.

ID 0420

ELOQUENT-2 Update: A Phase 3, Randomized, Open-Label Study of Elotuzumab in Combination with Lenalidomide/ Dexamethasone (ELd) vs Lenalidomide/Dexamethasone (Ld) in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM) - 3-Year Safety and Efficacy Follow-up

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Question: We present 3-year follow-up data for the ELOQUENT-2 study (NCT01239797) comparing ELd with Ld.
Methods: Pts were randomized 1:1 to ELd or Ld in 28-day cycles until disease progression/unacceptable toxicity. Primary endpoints: PFS and ORR. Secondary/other endpoints: OS, and health-related quality of life. *Post hoc* analyses assessed Worst Pain (Brief Pain Inventory-Short Form); sustained improvement in pain defined as ≥3-point decrease for ≥2 consecutive cycles.
Results: 646 RRMM pts were randomized (ELd 321, Ld 325). Baseline demographics: median age 66 yrs (20% ≥75 yrs); del17p, 32% of pts; t(4;14),10% of pts; median prior therapies, 2; refractory to last therapy, 35% of pts. At data cut-off (16 May 2015), 29% (ELd) vs 15% (Ld) of pts

remained on study therapy; discontinuation was mainly due to disease progression (ELd 46%, Ld 51%). Grade 3-4 adverse events in ≥15% of pts: lymphopenia (ELd 78%, Ld 49%), neutropenia (ELd 35%, Ld 44%), anemia (ELd 20%, Ld 21%), thrombocytopenia (ELd 21%, Ld 20%). Infections in 83% (ELd) vs 75% (Ld) of pts. Exposure-adjusted infection rates (incidence/100 person-yrs of exposure): 196 (ELd) vs 193 (Ld). Infusion reactions (ELd arm; mostly Grade 1-2), 11% of pts. Deaths during follow-up: 263 (ELd 123 [47%], Ld 140 [53%]); 62% of required 427 deaths for final OS analysis. Sustained improvement in Worst Pain was seen in pts with ORR, with more pts showing sustained improvement with ELd (n = 74) vs Ld (n = 56). Updated data will be shown.
Conclusions: Safety/tolerability data are consistent with previous findings, confirming minimal incremental toxicity with elotuzumab. More ELd vs Ld pts with an ORR had improvement in Worst Pain. Updated data will be shown.
Prior submission: ASH 2015

Molecular Pathology

ID 0313

Identification of prognostic and predictive biomarkers in malignant pleural mesothelioma in 134 patients from two research sites (Berlin and Essen)

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Background: Malignant pleural mesothelioma (MPM) is a highly aggressive tumor that is mainly linked to asbestos exposure. E3 ubiquitin ligase (MDM2) overexpression was found in approximately 20% of MPM, and this was significantly associated with decreased overall survival and poor response to treatment. MDM2 is a negative regulator of P53 leading to strongly decreased P53 activity and stability. Nutlin-3A (a *cis*-imidazoline analogue) is a potent and selective MDM2 inhibitor preventing MDM2-P53-interaction.
Material and Methods: 134 MPM patients from two German locations (Berlin and Essen) were selected for IHC- and/or qPCR-based analysis of the expression of P53, MDM2 and P14/ARF. The effect of MDM2 inhibition via Nutlin-3A and standard first line therapy were comparatively tested in three MPM cell lines (NCI-H2052, MSTO-211H, NCI-H2452) representing the expression profiles of P53 and MDM2 as identified in the patient collectives.
Results: In both MPM collectives, MDM2 expression was identified as prognostic marker. For the patients from Essen data for response to treatment were available and MDM2 was identified as predictive marker. In *in vitro* experiments, Nutlin-3A plus cisplatin showed an up to 9.75 times higher reduction of cell viability and up to 5 times higher induction of apoptosis compared to the first line therapy.
Conclusion: Our study demonstrates that Nutlin-3A is associated with a significant induction of apoptosis and reduction of cell viability in MPM cell lines and is more potent than the conventional regimens. Thus, Nutlin-3A may be proposed as a promising substance for a targeted therapy in a subgroup of MPM patients with MDM2 overexpression.

ID 0460

Ioncopy: A novel method for calling copy number alterations in amplicon sequencing data including significance assessment

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Recently, it has been demonstrated that calling of copy number alterations (CNAs) from amplicon sequencing (AS) data is feasible. Most approaches, however, require non-tumor (germline) DNA from for data normalization. Here, we present the novel method Ioncopy for CNA detection which does not need normal controls and includes a significance assessment for each detected alteration.
Ioncopy was evaluated in a cohort of 184 clinically annotated breast carcinomas. A total number of 254 amplifications were detected, whereof 183 (72.0%) could be validated by a call of a second amplicon interrogating the same gene. Further, a total number of 33 deletions were found, whereof 27 (81.8%) could be validated. Analyzing the 16 most frequently amplified genes, validation rates were higher than 89% for 11 of these genes. Further, Ioncopy CNA calls correlated significantly with RNA expression for 11 of the top 16 genes. 89.5% of the HER2-amplified tumors were also GRB7 and STARD3 co-amplified, whereas 68.4% of the HER2-amplified tumors had additional MED1 amplifications, both in good agreement with the co-amplification rates described elsewhere. Finally, AS based detection of HER2 amplifications had a sensitivity of 89.5% and a specificity of 98.2% compared to the gold standard of HER2 immunohistochemistry combined with in situ hybridization.
In summary, we developed and validated the novel method Ioncopy for detection and significance assessment of CNAs in AS data. Using Ioncopy, AS offers an easy and straightforward opportunity to simultaneously analyze gene amplifications and gene deletions together with simple somatic mutations in a single assay.

ID 0468

Linking tumor evolution and therapy response using diagnostic targeted next generation sequencing in colorectal cancer

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Complex sets of driver mutations critically control clinical course and treatment response in colorectal cancer (CRC). It is expected that multiple mutations in different signaling pathways interact to establish an individual cancer cell phenotype. Mutational patterns can evolve under selective pressure during tumor metastasis or targeted therapy. Yet only few mutations, such *KRAS, NRAS* and *BRAF* are routinely assessed in the clinic today. With the introduction of next generation sequencing (NGS) many more genes can be simultaneously analyzed, allowing detailed analyses of mutational patterns.
We have assembled the CRC5.2 NGS panel for application with Ion Torrent PGM covering 100 frequently mutated genes in colorectal cancer with 799 amplicons, going well beyond the scope of commercially avail-

able cancer panels. In particular, exon coverage was optimized to embrace all genomic information related to drug sensitivity, using several drug and signaling network databases. Furthermore, known oncogenic drivers activated via amplification in colorectal cancer where included in the panel. In retrospective and prospective clinical studies we addressed several key questions relevant for current diagnostics and treatment in colorectal cancer including mutational heterogeneity in primary tumors, synchronous and metachronous metastases of individual patients, treatment response, novel mechanisms of secondary resistance and genomic profiles within histologically heterogenic CRC tumors. In-depth (>1000×) NGS mutational and CNV analyses identified (epi-)genetic alterations occurring as a consequence of selective pressure during tumor evolution e.g. during metastasis, chemotherapy or targeted tumor therapy.

ID 0558

Molecular Genetic Analysis of Primary CNS Lymphoma (PCNSL)

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Primary CNS lymphomas (PCNSL) are extranodal malignant B-cell lymphomas confined to the CNS in the absence of systemic lymphoma at the time of diagnosis. Their pathogenesis is largely unknown. To gain more insight into the genetic landscape and pathogenesis of PCNSL, we assembled a unique collection of primary CNS lymphoma samples, totalling 17 matched pairs of tumor and peripheral blood. We utilized whole genome sequencing (WGS), RNA sequencing (RNAseq) and single nucleotide polymorphism (SNP) arrays to obtain a comprehensive view of the molecular alterations of these tumors. We identified a mean of 140 (range: 6-464) somatic single nucleotide variants (SNV) and 21 small indels (range: 2-50). The mutations affected genes involved in the Jak-STAT, B-cell receptor, and toll-like receptor signaling pathways, in antigen processing and presentation as well as in cell cycle regulation. The results were validated by Sanger sequencing in 25 additional PCNSL. Beside mutations in genes known to be functionally relevant in PCNSL, including e.g. *PIM1*, *MYD88*, *PAX5*, we also detected mutations that have not been recognized previously. In 5 of 17 (30%) PCNSL samples we found deletions in a not yet in PCNSL recognized tumor suppressor gene suggesting that genomic deletions of this tumor suppressor gene are involved in the pathogenesis of PCNSL.

Novel Agents/Early Clinical Trials

ID 0039

Platelet receptors are involved in regulation of cell growth and can be pharmacologically targeted.

H.-A. Fabricius

Berlin

Growing cells require the presence of growth factors; mostly platelet derived growth factors, PDGF. Depletion of PDGF in vitro terminates cell growth and leads to apoptosis. PDGF are under normal circumstances not dissolved in blood plasma or other physiological liquids. Their presence in blood is confined to platelets, where they are stored in alpha granules.
A daily co-incubation of permanently growing cells in vitro with platelets for 30 minutes only, enables these cells to escape apoptosis and to proliferate even in the complete absence of serum supplement.
Proliferating normal and malignant cells do have a common property, missing in resting cells: They bind platelets to their outer membrane. Platelets, bound to the cell membrane are thus able to provide PDGF specifically to the binding cell.
PDGF is also in vivo known to be of great importance for cell growth. The ubiquitous binding of platelets to proliferating cells in vitro, leads to the conclusion, that this must be a key mechanism also in vivo, by which cells are getting access to PDGF and thus to sustain proliferation and avoid apoptosis. The permanent expression of platelet receptors on malignant cells is obviously related to uncontrolled proliferation.
Basing hereupon, a group of substances is presented, which in vitro are able to interfere with the binding of platelets to proliferating cells, therefore being able to interfere with cell growth and probably to provide a therapeutic effect on cell growth in vivo.
The author has received no funding and has no financial conflict of interest. The findings presented above have been submitted as an application to the European Patent Authority.

ID 0422

Evaluation of the outcome of long-term conservative treatment with sulindac and high-dose selective estrogen receptor modulators (SERMs) for sporadic and FAP-associated Desmoid tumors.

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Summary Background Data: Desmoids are very rare tumors in the general population but occur frequently in FAP patients, being encountered in 23–38%. Treatment of desmoids is still most controversial since response cannot be predicted and they are prone to develop recurrence.
Methods: This study included all desmoid patients that were treated and followed at our institution and had completed at least one year of treatment. Response was defined as stable size or regression of desmoid size between two CT or MRI scans.
Results: A total of 134 patients were included. 64 (47.8%) patients had a confirmed diagnosis of FAP, 69 (51.5%) patients were sporadic. Overall 114 (85.1%) patients showed regressive or stable desmoid size. Patients with previous history of multiple desmoid-related surgeries showed less-favorable response.. The mean time to reach at least stable size was 14.9 (± 9.1) months. After regression or stabilization, medication was tapered in 69 (60.5%) of the treated patients with only one long-term recurrence after > 10 years.
Conclusions: The results of this study fortify the role of sulindac and high-dose SERMs as an effective and safe treatment for both, sporadic and FAP-associated desmoid tumors. While invasive treatment frequently results in high recurrence rates, high morbidity and high mortality, this conservative treatment is successful in most patients. The recurrence rate is negligible with no desmoid-related mortality in this large series. There-

fore surgical resection, especially for mesenteric desmoids, should be deferred favoring this convincingly effective, well tolerated regimen.

Paediatric Cancer

ID 0179

Transgenic antigen-specific, allogeneic HLA-A*0201-restricted cytotoxic T cells recognize tumor-associated target antigen STEAP1 with high specificity

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Background: Ewing Sarcoma (ES) patients with disseminated disease into lung and bone have an approximate long-term survival rate of 10 to 30%, compelling the search for new therapeutic treatment modalities including engineered T cell therapy. Here, the specific recognition and lytic potential of transgenic allo-restricted $CD8^+$ T cells directed against the ES-associated antigen STEAP1 was examined.
Methods: Following repetitive $STEAP1^{130}$ peptide-driven stimulations with HLA-A*0201$^+$ dendritic cells, allo-restricted HLA-A*0201$^-$ $CD8^+$ T cells were sorted with HLA-A*0201/peptide multimers and expanded by limiting dilution. After functional analysis of suitable T cell clones via ELISpot, flow cytometry and xCelligence assay, TCR α and β chains were identified, cloned into retroviral vectors, codon optimized, transfected into HLA-A*0201$^-$ primary T cell populations and tested again for specificity and lytic capacity *in vitro* and in a $Rag2^{-/-}\gamma c^{-/-}$ mouse model.
Results: Initially generated as well as transgenic T cells specifically recognized $STEAP1^{130}$ pulsed or transfected cells in the context of HLA-A*0201 with minimal cross-reactivity as determined by specific IFN-γ release, lysed cells and inhibited growth of HLA-A*0201$^+$ ES lines more effectively than HLA-A*0201$^-$ ES lines. Additionally *in vivo* tumor growth was decelerated more effective with transgenic $STEAP1^{130}$ specific T cells than with unspecific T cells.
Conclusion: Our results identify TCRs capable of recognizing and inhibiting growth of STEAP1 expressing HLA-A*0201$^+$ ES cells *in vitro* as well as *in vivo* in a highly restricted manner. Such STEAP1 specific TCRs are potentially useful for immunotherapy of other STEAP1 expressing tumors.

ID 0229

Therapieentscheidungen am Lebensende in pädiatrischer Onkologie und Intensivmedizin inDeutschland

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Hintergrund und Fragestellung: Entscheidungen am Lebensende sind immer eine ethische Herausforderung für das medizinische Team, besonders wenn es um Kinder und Jugendliche geht. Wir untersuchten, wie an deutschen Kliniken die Entscheidungsfindungsprozesse ablaufen und wie sich diese auf das Team auswirken, unter anderem wie sehr diese Entscheidungen die Teilnehmer belasten und ob es dabei zu Konflikten kommt.
Studienteilnehmer und Methodik: Ein eigens entwickelter anonymisierter Fragebogen wurde an 297 Personen (Ärzte, Pflegepersonal, Therapeuten und Psychologen) versendet, an Kliniken, die sich zur Teilnahme an der Untersuchung bereit erklärt hatten. Die Daten wurden mit IBM SPSS Statistics 20 deskriptiv ausgewertet.
Ergebnisse: Von den 297 versendeten Fragebögen erhielten wir 77 zurück (*25.92%* Rücklaufquote), davon 53 aus der Onkologie. Der mit Abstand häufigste Ablauf (*80.52%)* ist der, dass sich das Klinikteam erst intern eine Haltung bildet und dann mit dieser an die Eltern und den/die Patienten/-in heran tritt. Bei *35,6%* kam eine Zusammenarbeit mit einem Klinischen Ethikkommittee gelegentlich oder oft vor. Wenn im Entscheidungsfindungsgespräch keine eindeutige Entscheidung getroffen werden konnte, empfanden es *92.8%* der Teilnehmer als belastend. Auf die Frage wie häufig Konflikte bei der Entscheidungsfindung das Team belasten, antworteten 22,37% mit oft und 11,84% mit immer. Kommt es zu Konflikten, spielen sich diese häufig auf allen Ebenen ab: zwischen Berufsgruppen, zwischen Hierarchieebenen und zwischen Einzelpersonen.
Zusammenfassung: Therapieentscheidungen am Lebensende in der Pädiatrie sind belastend für alle daran Beteiligten und können auch zu Konflikten im medizinischen Team führen.

ID 0276

Personalized peptide-vaccination for pediatric acute lymphoblastic leukemia patients based on patient-individual tumor-specific variants (iVacALL)

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Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy and primary disease has a favourable prognosis. However, relapsed disease has a poorer outcome and additional therapeutic options are needed. Accumulation of somatic mutations is a characteristic feature of malignant cells. These single nucleotide variants can lead to altered amino acid sequences of the translated proteins, which can be presented as antigenic peptides on HLA molecules. Mutated peptides represent ideal T cell targets being true specific neoantigens, and should not interfere with central tolerance selection mechanisms.
For this purpose we detect nonsynonymous mutations by whole exome and transcriptome sequencing of patient leukemic blasts and normal tissue. HLA binding peptides harboring the altered amino acids are subsequently predicted by algorithms SYFPEITHI, NetMHC and NetMHCpan. Whole exome sequencing was performed for 20 sample pairs. ALL-specific SNVs and InDels were identified using a comparative bioinformatics pipeline. The determined variants were further validated by deep sequencing with an average of 12 (+/-8) validated mutations per patient. For all patients, MHC I & II epitopes could be predicted successfully. Up to now, 3 patients received individual peptide vaccines (16 injections over 33 weeks using GM-CSF and Imiquimod as adjuvant). Response to the vaccination was monitored by detection of peptide-specific T cells occurring over time in patient peripheral blood. In all patients we could detect a CD4+ T cell response against vaccinated mutated MHC II binding peptides.
A peptide vaccination composed of mutated T cell epitopes specific for individual patient tumors is therefore a promising approach to prevent relapse.

ID 0310

Development of motor performance in pediatric cancer patients within one year after treatment: Improvements are shown, but impairments persist

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Introduction: Impairments in motor performance could negatively affect physical activity and participation in sports. Therefore this study aimed at analyzing the development of motor performance skills in pediatric cancer patients within the first year after cessation of acute cancer treatment.
Methods: Motor performance was assessed in children with different tumor entities with the MOON-test specifically developed for pediatric cancer patients that provides age- and gender-matched reference values of healthy children (Götte/Kesting *et al.* 2013).
Results: Motor performance was assessed in 40 patients (m=24) aged 12.5±4.0 years at baseline (end of acute treatment, 6.9±2.3 months post-diagnosis), the retest was conducted 11.7±2.2 months later. At baseline, patients showed reduced performance in 7 out of 8 tested dimensions compared to the reference population. Distinct improvements ($P<0.001$) between reduced skills at baseline and retest were identified for eye-hand coordination, flexibility, static balance, muscular endurance of the legs and bilateral hand grip strength. Speed ($P=0.701$) and explosive strength ($P=0.179$) did not change significantly. In the retest, patients still scored lower than the reference population except for static balance and leg strength.
Discussion: Even though intra-individual improvements in several dimensions of motor performance were seen, impairments persisted up to one year after the end of acute treatment. These results highlight the need for interventions during all stages of cancer treatment. Furthermore, individually tailored support should be provided after treatment to improve motor performance and help to find feasible and appropriate sports activities.

ID 0315

Sarkoma on Ski: Concepts of integration in winter sports activities after multimodal paediatric anticancer therapy and surgery

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Introduction: Paediatric sarcomas require intensive combined therapy. Survivors suffer from chemotherapy associated late often leading to relevant changes in body image and movement patterns. Physical activity levels therefore are dramatically reduced and such limitations persist throughout adulthood.
Patients: In the years from 2011–2015, 28 sarcoma-patients participated in 59 courses. 11 soft tissue sarcoma (RMS 11), Ewing-S (ES 9), Osteosarcoma (OS 8). Examples: RMS, 10 y, femoral amputation / ES, 12 y, lower leg amputation, kidney disorder, osteoporosis / OS, 17 y, endoprothetic prox. Tibia / metastatic ES, 18 y, endoprothetic prox. Femur / undiff. sarcoma, 17 y, internal hemi-pelvectomy, hemi-sacrectomy, spinal decompression, peronaeus paresis, complete loss of sensitivity in the foot and partly in the leg.
Methods: Statistical overview and descriptive analysis of individual solutions and general decision making strategies including resources, tools and techniques to optimize risk-benefit-ratio.
Results: Discussion: All of them were able to learn autonomous skiing, some were even integrated into school ski trips. Skiing did support their physical recovery in general and especially according to their restrictions after surgery. Up to now, we did not see any no-go situation. Recognition of the need and addressing the individual challenges has a high chance of success.

ID 0380

Translation of exercise research into practice models in children and adolescents with cancer

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Introduction: Cancer disease and treatment lead to exclusion from physical education at school and sport clubs. Therefore, compensatory exercise programs should be implemented during treatment, but heterogenic characteristics regarding age, motivations, tumor entity, performance limitations and specific barriers require individual solutions. Translating scientific findings into practice is essential to adapt exercise programs to individual conditions.
Methods: Current scientific data showed reduced levels of physical exercise during hospital stays (-91%) as well as at home (-74%), motor performance limitations during and after cancer treatment and revealed positive attitudes as well as individual barriers regarding exercise during treatment. Bone and brain tumors were associated with an increased risk of inactivity, reduced motor skills and problems in reintegration into sport structures after treatment.
Results: Based on these results, we are currently evaluating a two-part model that consists of 1) a supervised exercise intervention during hospital stays and 2) a personal training plan comprising individual step goals and exercises for home stays that are based on motor performance testing. An activity tracker and regular contact ensures individual support and safety and helps to motivate children and adolescents with physical and psychosocial barriers to exercise.
Conclusion: The current program seems to be feasible and is well accepted. However, future research should focus on the impact of exercise on clinical parameters like peripheral neuropathy and cardiotoxicity to develop effective and safe exercise recommendations. Secondly, existing best practice models should be transferred to other departments of pediatric oncology.

ID 0387

The feasibility and effectiveness of whole-body vibration (WBV) for inpatient childhood cancer patients undergoing chemotherapy: The KiVi study protocol

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Childhood Cancer, medical treatment and associated immobility can cause various late effects. Specifically, limited ankle dorsiflexion has lately been posited as a potential explanation for the restrictions in gait, mobility, and activity levels seen in young cancer patients. Recently, WBV has been used for the treatment of adult cancer patients and children with disabling conditions. First encouraging results indicate feasibility and effects on e.g. muscle strength promoting functional and physical performance. To date, the influence of WBV remains unknown in young cancer patients.
The primary objective of the KiVi study will be to determine feasibility of implementing WVB during in-patient care. The secondary objective will be to explore effects of the intervention on ankle dorsiflexion, gait, mobility and physical activity levels.
This single-site randomized controlled trial will investigate the influence of WBV for pediatric cancer patients undergoing chemotherapy on different physical parameters by comparing patients receiving standard care

(can include clinical exercises) and patients receiving WBV in addition to standard care. During hospitalization, the intervention group will participate in supervised WBV-sessions 2-3 times/week for 9-14 minutes (Frequency 18-30Hz; p-t-p-amplitude 2mm). One follow-up assessment is arranged 3 month after the intervention.
WBV has demonstrated utility treating functional and physical limitations in other clinical populations. This study will add to previous research by exploring the effectiveness of WBV for inpatient childhood cancer patients. Further, it will provide the foundation to continue investigating WBV as a potential addition to current pediatric oncology care.

ID 0390

Preliminary self-reported physical activity and accelerometer data from childhood cancer patients.

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Background: Physical activity (PA) is an important component of healthy development for children. Current data suggests childhood cancer patients and survivors do not achieve the recommended levels of PA. However, these findings are based on reports of young cancer patients using measures designed for the general populations. To date, no specific PA questionnaire for pediatric cancer patients exists. Thus, a cancer-specific tool is necessary to better assess PA behaviors in this population and to provide a better understanding of PA among young cancer patients.
Methods: The PA questionnaire AktiveO for childhood cancer patients and survivors is based on the PA questionnaire used in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) and has been adapted to the specific needs of children with cancer. To compare the questionnaires' results about self-reported PA with objectively measured accelerometer data, 19 outpatient pediatric cancer patients (various entities, between 4 and 17 years) wore the ActiGraph GT3X+ for two weeks and subsequently completed the ActiveO questionnaire. The analysis includes 7 consecutive days considering overall activity in minutes per week. In addition, results of a visual analogue scale, as well as number of days with at least 60 minutes of PA were analyzed.
Results: Data is currently being analyzed and results will be presented at the congress.
Conclusions: Specific PA questionnaires are necessary in pediatric oncology due to the specific needs in this population. The results from this study are part of the validation process of the AktiveO questionnaire and provide implications for future investigative efforts seeking to measure PA in young cancer patients.

ID 0393

Transcriptome Based Individualized Therapy Of Refractory Pediatric Bone and Soft Tissue Sarcomas: Feasibility, Tolerability and Efficacy

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Background: The rapid increase in molecularly targeted therapies (TT) and methods of genetic profiling have enabled patient stratification and new therapy options especially in refractory setting.
Methods: Tumor samples in patients with refractory pediatric solid tumors underwent transcriptome analysis with Affymetrix arrays. We focused on genes with > 1.5 fold expression vs. normal tissue. Targets ranked between 1-100 by TARGETgene were considered for therapy. Drug selection criteria: delivery, no previous use in the patient, citations related to disease, citations related to other cancers, side effects, drug interactions, oral application, approval by German authorities.
Results: During 30 months biopsies of 19 patients between the ages of 4-22 years were assessed for TT. Primary diagnosis was 8 Ewing sarcomas, 5 soft tissue sarcomas, 4 osteosarcomas, 2 embryonal tumors. Addressable targets were identified in 18 patients. Due to patient compliance and bad performance status, TT was only administered in 9 patients. An average of 3 drugs per patient was administered; this included PKIs, TKIs, TOP2Is, and cytotoxic agents. Dosing was adjusted according to possible drug interactions and cumulative side effects. In this small patient population no significance in overall survival was determined (Log-rank P value= 0.1195). However a trend towards an increased survival in the TT group was observed (median survival TT= 294 d, noTT= 184 d).
Conclusion: Although TT shows promising results, its exact survival benefit, feasibility and tolerability is yet to be determined. Further prospective studies with appropriate sample size could determine the exact benefit of molecularly targeted therapies in a refractory patient population.

ID 0407

AutoFLOW: Towards automation of flow cytometric analysis for quality-assured MRD assessment in childhood acute lymphoblastic leukemia

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In childhood acute lymphoblastic leukemia (ALL), quantification of minimal residual disease (MRD) is essential for risk stratification. Flow cytometry (FCM) is a sensitive and fast method for MRD assessment, however, the FCM-MRD analysis is complex and largely relies on operator skills and experience requiring intensive training and quality control. In this European Union-funded project we aim to develop an automated FCM-MRD analysis tool by machine-learning technology to support quality-assured MRD assessment. We collected FCM-MRD data obtained at treatment days 15, 33 and 78 (AIEOP-BFM 2009 protocol) from 196 B cell precursor ALL patients. All FCM read-outs were quality controlled and annotated with class labels for relevant cell populations. This data set of 524 FCM-MRD samples was used to test different machine-learning methods for their applicability and accuracy in automated MRD quantification. Most promising results were obtained by a probabilistic model, where each new sample is reconstructed by artificial reference samples

represented by Gaussian Mixture Models. The artificial samples were calculated from a training set by non-negative matrix factorization leading to a lower dimensional feature space. A Bayes decision was done to assign each observation to one of the specified sub-populations in the training set. Using this approach the majority of samples (91%) were correctly risk-classified (low, medium or high). Misclassified samples were mostly those with low MRD (<100 leukemic cells) with many of them having an atypical phenotype. The systematic expansion of the learning data set and improvements in the methodology are expected to continuously reduce the current limitations of our analysis approach.

ID 0436

A more precise sensitive response monitoring using genomic breakpoint of *ETV6-RUNX1* gene fusion in *ETV6-RUNX1* positive ALL

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ETV6-RUNX1 fusion resulting from the translocation t(12;21) is the most common structural genomic alteration in childhood B-cell precursor acute lymphoblastic leukemia (ALL) with a frequency of 25%. There is evidence that this fusion is the initiating event in ALL development and stable throughout the disease and at relapse. We investigated whether the individual ETV6-RUNX1 genomic breakpoint is a suitable marker for sensitive response monitoring. We compared the ETV6-RUNX1 fusion as minimal residual disease (MRD) marker to T-cell receptor (TCR)/Immunoglobulin(Ig)-gene rearrangements which have been applied as gold standard MRD marker in ALL. In our study, 57 ETV6-RUNX1 positive first ALL-relapses were quantified by their individual breakpoint sequence. A reproducible sensitivity of at least 10-4 could be reached in 93% (53/57) by optimizing patient specific real-time PCR assays. Comparing MRD results obtained from every single TCR/Ig marker to the genomic ETV6-RUNX1 breakpoint (401 follow-up samples; 1038 comparisons) a good correlation between the quantitative data obtained by the two methods was observed (Spearman's correlation coefficient =0.841, $p < 0.01$). Differences > 0.5 log steps only occurred in 72/1038 cases (6.94%), explained mainly by a loss of the corresponding TCR/Ig marker. Comparing to the highest available TCR/Ig marker for each time-point most of those discrepancies are lost. MRD kinetics of single patients during treatment and over different disease stages reveal ETV6-RUNX1 as a dominant stable clonal marker. In summary, we could proof in a large cohort of ETV6-RUNX1 positive first ALL relapses that the genomic breakpoint of the fusion allows a more precise MRD response monitoring.

ID 0559

Online expert survey on Fear of Progression in parents of children with cancer

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Background: Fear of Progression (FoP), the fear of further disease progression, is one of the most common psychological strains of cancer patients, and parents of children with cancer are also at risk of developing distinct FoP. A previous study assessed FoP in parents whose child was diagnosed with cancer and identified relationships between parental FoP and disease- and treatment-related issues of the child, e.g. current medical condition, time since diagnosis, etc. (Schepper et al., 2015). The adapted parent version of the FoP-Questionnaire (Herschbach et al., 2005) is currently being validated in a sample of parents of children with cancer. The present expert survey aims to investigate how professionals in paediatric oncology handle parental FoP and to scientifically and practically integrate the adapted FoP-Questionnaire for parents into existing care structures.
Participants: Professionals in pediatric oncology who have contact with parents of children with cancer were defined as experts in terms of study participation.
Method: An online-survey was designed to investigate how FoP is perceived, diagnosed and dealt with by professionals in paediatric oncology. A first draft of the survey was piloted in a small group of experts who gave feedback on survey content and usability. Invitations to participate in the survey were sent out via e-mail by the Psychosoziale Arbeitsgemeinschaft in der Gesellschaft für Pädiatrische Onkologie und Hämatologie (PSAPOH) and the study team.
Results: To date, 64 psychosocial and medical professionals have taken part in the ongoing online-survey. Results of the expert survey will provide insight into current diagnostics and treatment of FoP in parents of children with cancer.

Palliative Care

ID 0022

Symptom control and quality of life as primary outcome parameters in clinical studies – a systematic review

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Introduction: Even in incurable ("palliative") stages of cancer, clinical studies focus on time dependent parameters, although both, the remaining length of life as well as the quality of life are found to be main objectives when undergoing anticancer therapy and in general.
Methods: We therefore performed a systematic review analyzing randomized controlled or observational clinical studies that were designed and performed in order to investigate a possible benefit of systemic anticancer therapies on symptom burden and quality of life. Analyses of tolerability and toxicity data as well as clinical trials for symptom relieving substances that are not used for anticancer purposes were excluded.
Results: The search string revealed 2229 abstracts that were categorized into five sub-categories, depending on study design and primary outcome parameters. 39 abstracts fulfilled the above named criteria and were included for detailed full text analysis that will be accomplished by December 2015.
Conclusions: Preliminary analysis reveals that, to date, secondary publications of QoL and toxicity data denote one of the major sources of information about the impact of anticancer therapies on QoL. Clinical studies investigating primarily the possible benefits of anticancer therapies on symptom burden and QoL are very rare. With respect to what we know about our patients´ wishes when entering incurable stages of their disease, symptom and QoL based outcome parameters should deserve much more explicit attention in clinical study design.

ID 0029

Music therapy in palliative care: Results of a randomized, controlled trial on psychophysiological indicators of relaxation and well-being

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Music therapy treatments have been applied to terminally ill patients in palliative care settings for more than 30 years. Despite promising clinical experience regarding the support of symptom management, emotion regulation, communication, and spirituality, little is known about the effectiveness and underlying mechanisms. Therefore, the aim of the present study was to investigate, whether a standardized, live music therapy relax-

ation intervention could be used to promote relaxation and well-being in terminally ill patients.
84 patients from a palliative care unit were randomly assigned to either two sessions of live music therapy using monochord music and vocal improvisation or two sessions of listening to a prerecorded verbal relaxation exercise. The primary outcomes were patients' self-reported levels of relaxation, well-being, and acute pain. Heart rate variability (HRV) and quality of life were assessed as secondary outcomes.
The music therapy group showed significantly greater improvements than the control group regarding relaxation ($p < .001$) and well-being ($p = .01$), with medium to large effect sizes. No significant differences were observed for acute pain ($p = .53$). Examination of HRV data revealed a significant increase in high-frequent (HF) variations of heart rate ($p = .01$). In addition, the music therapy intervention showed to be superior concerning the reduction of fatigue ($p = .03$).
Results from both self-reported and objective data indicate that music therapy is an effective treatment to promote relaxation and well-being in palliative care patients. Low baseline values on acute pain may explain the lack of significant effects on pain reduction. Future research may address the promising effect on fatigue symptoms.

ID 0035

Palliative Care at Comprehensive Cancer Center: A comparative look at integration in Germany

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Issue: Holistic cancer treatment also means to enable a view at specialized palliative care (SPC). But how extensively is SPC integrated in Comprehensive Cancer Centers (CCCs) funded by the German Cancer Aid?
Method: In 2014 structured interviews with open and closed questions with 14 leaders of departments for SPC and 12 stakeholders of CCCs from upper management, teaching and physicians of other disciplines in cancer care took place. Data were analyzed by SPSS and content analysis of Mayring using MAXQDA.
Results: Of 14 institutions, 12 sites (86%) had a palliative care unit. Physicians of 11 sites could provide a SPC consultation service (79%). Participation of SPC in tumor consultation of other departments was not designated in half of the CCC (50%), in tumor boards it was not explicitly provided in 3 sites (21%). On average, heads of SPC estimate that SPC is involved in the treatment of 10% [range: 5-40%] of cancer patients. Chairs in palliative care were available in 4 sites (29%). Mostly the acceptance and establishment of SPM is described as "good", although there were still barriers. Integration often depends on department and "personal academic interests of chairs". 10 heads (71%) of SPC still not received an invitation of another department for a joint research project.
Conclusion: Integration of SPC is poorly to well developed with respect to clinic, research and training of the CCCs.

ID 0147

End-of-life decision making on patients dying from cancer – an empirical-ethical analysis of decision making about treatment limitation amongst German physicians

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Background: Treatment limitation is a frequent and challenging part of cancer care. In Germany, there is scarcity of empirical data on frequency and characteristics of decisions to limit treatment in patients with cancer.
Methods: Cross-sectional study among a random sample of physicians working in the area of five German Chambers of Physicians. Data on end-of-life practices was gathered by means of a questionnaire developed by the EURELD (European end of life)-Consortium. Statistical analysis was performed in order to analyse factors associated with treatment limitation.
Results: The response rate was 36.9% (734 of 1.988). 438 respondents (59.7%) had cared for a dying patient in the last 12 months. In 174 cases the patient died of cancer. Treatment limitation (withholding / withdrawing) was performed in 105 of these cases (60.3%). In 50 of these cases (28.7%) there was a possible shortening of life and in 26 cases (14.9%) limitation of treatment was performed with the intention to shorten life. In six of the cases (25%) with intended life shortening the estimated time of shortening life was between one to six months. Statistical analysis shows that withholding of treatment was significantly associated with the patients' age ≥ 65 years ($p = 0.021$). There was no significant association between the patients' gender and treatment limitation.
Conclusions: Treatment limitation is a common practice in the care of cancer patients. The empirical findings can serve as a starting point for further examination of ethical and clinical aspects of limiting treatment.

ID 0228

Thromboprophylaxis at the end of life – A comparison before and after the introduction of a new qualtity asssurance programme that should help avoiding the oversupply at the end of life

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Background: Palliative Care Medicine increasingly is being integrated earlier into oncologic care than was hitherto the case. As a result, not only dying patients but also those with progressive diseases in earlier stages are taken care of on the palliative wards with the aim of stabilization and building up the patient's strength. In cases of deterioration the goal of the palliative care intervention must be changed from "stabilization" to "terminal care".
According to the S3-Guidelines medication during the dying phase should only be continued or started if they are conducive to enhance the quality of life, and medication for primary and secondary prevention should be stopped. The main focus of interest in our study is thromboprophylaxis. We want to examine the effects of a "choosing wiseliy quality assurance program" that was introduced in June 2015. The aim is avoiding the oversupply at the end of life and especially the reduced use of unnecessary medication.
Procedure: By means of retrospective analysis of the patients' files and records we determined: age, diseases, medication at admission, medication during the last week of life, symptoms just before the death and symptoms that could possibly point to a thrombotic event.

We compared two periods: from 1.6.2014 to 28 2.2015, and from 1.6.2015 to 28.2.2016.
In both time periods a total of 477 patients were treated on the palliative care ward in the Würzburg University Hospital. Assuming a death rate of 40% we have a predicted number of 192 patients in our study who died on the ward.
Results: Until 31.8.2015 we have analyzed ten files. In the lecture in February 2016 we will present the results of approximately 50 patients in each period studied.
Conclusion: – We will see –

ID 0275

Fears associated with the idea of advance directives amongst cancer patients and healthy controls. An empirical study.

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Introduction: The number of cancer patients (CP) who have fulfilled an advance directive (AD) remains low despite their binding nature being regulated by laws in may countries. Barriers that may hinder patients from writing an AD have been identified (J Med Ethics 2005, 437-40), yet not been researched after the respective law has come into effect in Germany.
Methods: Cancer patients (CP) and healthy controls (HC) were interviewed using an established questionnaire. Attitudes towards AD and apprehensions about negative effects related to the idea of ADs were inquired. In particular interviewees were asked whether they think three types of barriers be realistic to them (answer yes/no): coercion to fulfill an AD (Coercion); fear of dictatorial reading of what had been laid down by attending physicians (Dictatorial reading); fear of abuse of ADs by surrogates (Abuse).
Results: 100 CPs and 100 HCs were interviewed. The frequency of barriers amongst the groups wereCoercion: 51% vs. 44% for CP and HC, respectively;Dictatorial reading: 31% vs. 29%;Abuse: 40% vs. 39%. There were no differences between the groups and no associations found with demographic data.
Conclusion: After a law regulating the binding nature of ADs has come into effect in Germany apprehensions about potential negative effects of ADs are widely spread amongst CPs. There is no difference to HCs. This finding has not changed compared to the time before the law has been enacted. Oncologists should be aware of hidden barriers that may keep patients from fulfilling an AD when discussing CPs` wishes for treatment at the end of life.

ID 0298

Shared Decision Making and Patients' Control Preferences in different palliative care settings

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Background: Advancing treatment in palliative care challenges patients and physicians when facing therapeutic decisions. This study reports first findings on how Shared Decision Making (SDM) and Patients Control Preference (PCP) influence the decision for different care settings such as a palliative care unit (PCU), a hemato-oncological ward (HOW) or a specialized ambulatory palliative care (SAPV)-team.
Methods: Patients with advanced disease receiving palliative treatment at a PCU, a HOW or from a SAPV team were included in this cross-sectional, non-interventional questionnaire study. Primary outcomes included amount of SDM during decision for different care settings, measured with the Shared Decision Making Questionnaire (SDM-Q) and PCP, measured with the Control Preference Scale (CPS).
Results: 52 patients (36,5% female; median age: 68,5 years, SD: 11.5 years) were included, of whom 14 (26.9%) were treated at PCU, 16 (30.8%) at HOW and 22 (42.3%) from SAPV. 40 patients reported on their control preferences, of whom 9 (17.3%) prefer an own active role, 23 (44.2%) favor SDM and 8 (15.4%) prefer an passive role in decision making. 43 Patients reported on their SDM and indicate a moderate amount (mean: 26.6, SD: 13.0; range 0-45) during the decision for a specific palliative care pathway. There are no significant differences concerning the amount of SDM in decision for SAPV, HOW or PCU. Furthermore, patients in SAPV, HOW or PCU do not differ in their PCP.
Conclusion: This trial adds descriptive data to the scarce knowledge about decision making in palliative care. Further trials could focus on significant differences in SDM and PCP between patients in palliative care settings as well as possible longitudinal changes.

ID 0470

The Role of End-of-Life Issues in the Design and Reporting of Cancer Clinical Trials: A Structured Literature Review

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Background: The aim of this structured literature review [1] was to explore how the end-of-life (EoL) situation of patients with advanced cancer is considered in the design and reporting of RCTs investigating anti-cancer treatments.
Methods: A journal pool of 19 core clinical journals was searched (MEDLINE via Ovid) for RCTs investigating anticancer treatments for four cancer types (glioblastoma, lung cancer stage ≥IIIb, malignant melanoma stage IV, pancreatic cancer).The 25 most recent publications for each cancer were included. EoL was defined as a life expectancy of less than two years. Extracted information included (1) descriptions of the terminal stage of the disease, (2) endpoints, (3) authors' appraisal of the intervention's effects, and (4) terminology referring to the patients' EoL situation.
Results: Median survival was less than one year, but descriptions of the terminal stage of the disease were ambiguous or lacking in most publications. Primary endpoints focused on survival (50%), surrogates (44%), and safety (3%). Patient-reported outcomes (PROs) were assessed in 36/100 RCTs. The implications of treatment-related harms for the patients were discussed in 22/100 studies. Terminology referring to the patients' EoL situation (e.g. "terminal") was scarce, whereas terms suggesting control of the disease (e.g. "cancer control") were common.
Conclusions: Patients studied in the RCTs were in the last phase of life. For these patients, quality of life (QoL) and symptom control are the main goals of care. Yet, these outcomes were inadequately reported and discussed. Most publications avoided to refer to the patients´ EoL situation. Suggestions for improving standards for study design and reporting are presented.

Reference

1 Gaertner et al PLoSONE 2015.

ID 0473

Palliative Care in Rural Areas: A Pilot Project for Accomplishing Sufficient Care in the Future

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Background: To provide palliative-care patients, in particular those living in rural areas, with sufficient care will become more problematic in the future.Germany faces an increasing demand of palliative care specialists due to demographic and health care changes. Thisis in particular problematic for rural Bavaria. The impending lack of specialists due to concentration in urbanized areas and retirement is highly contrary tothe stated demands of professional societies, health insurance companies and politics regarding this topic. New approaches are needed.
Methods: The "Oncological- and Palliative- Care Network of Landshut" is an unique and innovative approach in collaboration with the oncology department of the University Hospital of Großhadern. Goal is optimizing oncological and palliative care for cancer patients in rural areas. As one part of this pilot project, yearly rotations of young resident doctors to the rural area of Landshut in lower Bavaria has been established for working and education in palliative care.
Results: The goal of this undertaking is to counteract the future lack of palliative care specialists and to generate a incentive for young doctors to permanently work in rural areas after completing their specialization. This Project, dubbed the "Taking Care Project" has been implemented 2013 and recently granted financial and political support by the BavarianMinistry of Health and may be a model project for other areas facing similar problems.

ID 0475

Stellenwert der Palliativen Sedierung in der Spezialisierten Ambulanten Palliativversorgung – Vollerhebung im Sinne empirischer Sozialforschung bei Palliativmedizinern in allen SAPV-Teams im Saarland und Hessen sowie Kinder-SAPV-Teams in Deutschland

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Einen besonders hohen Stellenwert als effiziente Behandlungsoption nimmt als ultima ratio unter Palliativmedizinern in der spezialisierten ambulanten Palliativversorgung bei bestehendem Behandlungswunsch auch gegen schwerstes Leiden die palliative Sedierung ein. Obgleich palliative Sedierung nach deren Einschätzung nicht häufig zum Einsatz kommen muss, ist sie unisono die Methode der Wahl, die immer angeboten werden kann, wenn ein Patient andere Behandlungen nicht mehr akzeptiert und/ oder erleben will. Hinterfragt werden sollte, dass bei einer hohen Selbsteinschätzung der Leitlinienkenntnis zur palliativen Sedierung (*79% trifft zu oder trifft voll zu*) und insbesondere auch der Leitlinieneinhaltung (*66% trifft voll zu oder trifft zu*) eine überraschend geringe Entkoppelung von Sedierungsbeginn und Fortführung lebenserhaltender Maßnahmen wie Nahrung, Flüssigkeit, Beatmung stattfindet (*15% trifft voll zu oder trifft zu*). In der Leitlinie zur palliativen Sedierung wird eindeutig vorgegeben, dass die Entscheidung zur Flüssigkeits- und Nahrungszufuhr unabhängig von der Entscheidung zur Sedierung ist und nur gut die Hälfte erachtet für wichtig, Vitalparameter wie die Atemfrequenz und auch die Sedierungstiefe angemessen zu kontrollieren und zu dokumentieren (*trifft voll zu oder trifft zu*), was eine palliative Sedierung leicht in die Nähe der terminalen Sedierung rücken kann.

Pflegerische Beiträge

ID 0136

Therapiebegleitendes Patientenhandbuch

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Das Nationale Centrum für Tumorerkrankungen (NCT) in Heidelberg ist eine ambulante und teilstationäre Einrichtung in der pro Woche um die 400 Patienten mit verschiedensten Tumorerkrankungen behandelt werden. Nach der Diagnose Krebs erhalten die Patienten eine Vielzahl an Informationen durch Aufklärungs- und Beratungsgespräche. Durch Studien und Umfragen ist bekannt dass nur ca. 30% dieser Informationen langfristig in Erinnerung bleiben. Zudem ändert sich im laufe einer Erkrankung und der dazu gehörigen Therapie auch der Informations- und Beratungsbedarf. Aus dieser Erkenntnis heraus entstand im Januar 2014 die Idee zum Projekt „Therapiebegleitendes Patientenhandbuch". Die Idee und Gestaltung stammen von einer Fachkrankenschwester für Onkologie und einer angehenden Palliativ Care Nurse. Ein inhaltlicher Schwerpunkt im Handbuch sind die ganz allgemein auftretenden Nebenwirkungen unter der Therapie. Diese werden einzeln aufgezählt, gleichzeitig wird auf Empfehlungen und auf das passende Beratungsangebot mit Kontaktdaten hingewiesen. Ein weiterer Schwerpunkt war die Auflistung von Symptomen, die Patienten wann und wo melden müssen. Das Patientenhandbuch soll in einer dazugehörigen Mappe ausgehändigt werden, in der die Möglichkeit besteht die Empfehlungen der Beratungsteams abzuheften. Das soll unter anderem die Zusammenarbeit mit ambulanten Pflegediensten und Hausärzten erleichtern. Der Druck der Erstauflage ist für November 2015 geplant und wird durch Spenden finanziert. Ziel ist jeden Patienten Sicherheit zugeben, durch optimale Information, ab Beginn der Therapie. Daher sollte das Patientenhandbuch als Art Wegbegleiter zur Therapie gesehen werden.

ID 0187

Staff retention and job satisfaction of non-medical personnel in oncology practices

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Introduction: While cancer incidence rates increase, oncology practices witness a shortage and high fluctuation of qualified non-medical personnel. In order to gain insights into needs of non-medical staff, the Scientific Institute of Office-based Hematologists and Oncologists (WINHO) conducted a survey in oncology practices focusing on aspects associated with job satisfaction such as workload and educational training of staff, commitment and support from their management.
Methods: Two surveys were conducted in 2011 and 2013 following the questionnaire "Mitarbeiterkennzahlenbogen (MIKE)" developed by the Institute for Medical Sociology, Health Services Research and Rehabilitation Science (IMVR) of the University of Cologne. For both surveys, all 210 WINHO partner practices were invited to participate.
Results: Altogether, 1,214 employees from 39 (2011) and 53 (2013) practices participated in the surveys. The majority of the non-medical staff was female (mean age: 39.65). Most of them work in reception, laboratory and therapy assistance. Overall satisfaction and good work equipment were rated the most positive. By contrast, work intensity and burning oneself out reached high sores on the negative side. Social support from the management was rated better in the second survey.
Conclusion: Based on the study results, participating practices received the recommendation to improve social relations within the team by optimizing communication and personnel management. Comparing the results of both surveys, it seems that the management has improved its behavior towards non-medical staff especially regarding praise and appreciation for work effort.

ID 0344

Individualisierte Onkologie durch Digitalisierung – Smart and Safe !

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Jeder Mensch hat eine persönliche genetische Struktur. Daher sollten Krankheitsursachen so individuell wie möglich diagnostiziert und die Behandlung daran ausgerichtet werden. Da der Mensch ein Recht auf moderne Behandlungsmethoden hat, wird ein Gesundheitssystem benötigt, das sich mit steigenden Anforderungen effizient und dynamisch weiterentwickelt. Individualisierte Medizin braucht Digitalisierung und durch technische Innovationen könnten tausende Menschenleben jährlich gerettet werden. Der Einsatz von IT-Systemen zur Unterstützung einer maßgeschneiderten Behandlungsstrategie hilft, die Qualität und auch die Wirtschaftlichkeit der Patientenversorgung zu verbessern. Aber um die Digitalisierung des deutschen Gesundheitswesens voranzutreiben, ist eine Verflechtung von Experten aus den unterschiedlichsten medizinischen, IT-elektronischen, wirtschaftlichen und politischen Bereichen notwendig. Denn nicht nur technische und infrastrukturelle, gerade auch rechtliche sowie ethische Aspekte müssen miteinander vereinbart und neue, smarte Ideen in bewährte, evidenzbasierte Prozesse eingebunden werden. Durch interdisziplinäre Zusammenarbeit kann die elektronisch basierte, personalisierte Medizin im Bereich der Onkologie verbessert und künftig viele Tumorarten mittels einer zielgerichteten Therapie geheilt werden.

ID 0451

Parastomale Hautveränderungen unter zielgerichteter Antikörpertherapie in der Onkologie – eine neue Ursache für parastomale Komplikationen und deren pflegerischen Versorgungsschwierigkeiten?

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Hintergrund: Bei Betroffenen mit der Grunderkrankung Darmkarzinom und einem Kolostoma können Metastasen auftreten. Um diese zu behandeln, werden in der Onkologischen Therapie zielgerichtete Therapien – „Targeted Therapies" – eingesetzt, um das Tumorwachstum oder eine Metastasierung zu beeinflussen.
Unter der Anwendung kommt es zu Nebenwirkungen, die die Pflege und Ärzte vor neue Herausforderungen stellen, auch bei Patienten nach Stoma-Anlage. So treten polyzyklische Hautveränderungen in 50 bis zu 90% der Fälle auf, da die Medikamente in die Wirkweise zentraler Prozesse im Hautorgan eingreifen. Die Nebenwirkungen der Haut, besonders das akneiforme Exanthem, können auch im parastomalen Bereich auftreten.
Methode: Zur Darstellung der Gesamtproblematik wurde eine Literaturanalyse durchgeführt.
Die spezielle Pflege und Versorgung der Betroffenen mit Stoma und einem parastomalen akneiformen Exanthem, wurde bisher noch nicht in der deutschen Literatur beschrieben.
Ergebnis: Parastomale Komplikationen zeigen ein anderes Erscheinungsbild als für die Haut beschrieben. Mit diesem Beitrag werden Ergebnisse, Zusammenhänge, das parastomale Erscheinungsbild und nötige pflegerische Optionen aufgezeigt, um für die Betroffenen mit Stoma eine adäquate Beratung, Schulung und Versorgung, auch mit Hilfsmitteln, sicher zu stellen.
Schlussfolgerung: Da für die auftretenden Nebenwirkungen im parastomalen Bereich noch keine Untersuchungen oder Studien vorhanden sind, werden pflegerische Studien gefordert.

ID 0517

Onkologische Pflegeberatung in der Rehabilitationsphase an der Klinik Bavaria Kreischa in Sachsen: Ein Beratungskonzept für Patienten der Station 6/7

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Beratung in der Pflege gewinnt immer mehr an Bedeutung. Sie ist nicht nur Teil der Ausbildung in den Gesundheitsfachberufen, sondern steht den Patienten laut dem Pflegeweiterentwicklungsgesetz zu.
Die onkologischen Patienten haben nach Beendigung der Tumortherapie einen gesetzlichen Anspruch auf eine Rehabilitation.
Die Sicherung bzw. Wiederherstellung der körperlichen, geistigen und seelischen Leistungsfähigkeit aufgrund der Erkrankungsfolgen kann man nur gemeinsam mit dem Patienten durch den Einsatz der Patientenedukation erreichen.
Bis auf das Pflegekräfteteam sind das ärztliche, therapeutische und psychologische Team sowie die Sozialdienstmitarbeiter fester Bestandteil des Rehabilitationsangebotes in Form der Anwendung von Patientenedukation.
In der Zeit der Rehabilitation ist es besonders wichtig, dem Patienten auch gezieltes pflegerisches Wissen zukommen zulassen, damit eine optimale Vorbereitung für den Alltag stattfinden kann. Denn erst durch die Rehabilitation wird ersichtlich, inwiefern die Patienten noch pflegerische Tipps in Form von Beratung für das Leben in ihrer gewohnten Umgebung brauchen.
Im Zusammenhang mit diesem Aspekt stellte sich für mich die Frage: Wie kann man die onkologische Pflegeberatung in der Rehabilitationsphase für die Patienten der Station 6/7, auf der ich tätig bin, an der Klinik Bavaria Kreischa in Sachsen ausbauen?
Die Antwort darauf ist ein von mir entwickeltes Kontaktformular.
Den Patienten soll somit die Möglichkeit gegeben sein, einen individuellen Beratungsbedarf anzuzeigen und ein beratendes Gespräch in geschützter Atmosphäre zu erhalten.

ID 0544

„Die Übelkeit hat mir meine Grenzen aufgezeigt" – Erfahrung, Umgang und Auswirkungen von Übelkeit bei Erwachsenen, die sich zuhause nach ambulant verabreichten emetogenen Chemotherapien selbst versorgen: Eine qualitative Studie

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Zielsetzung: Bei ambulant verabreichten Chemotherapien müssen Patienten zuhause alleine entscheiden, wie sie mit Übelkeit umgehen. Bisher ist kaum bekannt, was Übelkeit für Betroffene im Alltag bedeutet. Ziel dieser Studie war es herauszufinden, wie Patienten mit Übelkeit zuhause umgehen und welche Probleme und Ansatzpunkte es zur Unterstützung gibt.
Methode: Es wurden neun leitfadengestützte Interviews mittels der qualitativen Methode der Interpretativen Beschreibung analysiert. Die Studienteilnehmer wurden in der onkologischen und der gynäkologisch-onkologischen Ambulanz des Universitätsspitals Basel rekrutiert.
Ergebnisse: Die Analyse ergab folgende Hauptthemen: Das Erleben der Übelkeit wurde als sehr eindrückliche Empfindung beschrieben, die sich extrem auf das physische und psychische Befinden auswirkte. Die Betroffenen erfuhren massive Einschränkungen in ihrem Alltag, der letztlich durch die Übelkeit bestimmt und begrenzt wurde. Es war ihren wichtig, im Alltag wieder Normalität herzustellen, hierfür haben sie verschiedene Maßnahmen ergriffen.
Schlussfolgerungen: Der Einfluss der Übelkeit war sehr unterschiedlich. Einige traf sie so massiv, dass die Grenzen des Ertragbaren, insbesondere auf psychischer Ebene, erreicht wurden. Dennoch war Übelkeit nur eines von mehreren Symptomen, die in ähnlicher Weise einschränkten. Um wieder etwas Normalität herzustellen war es von Bedeutung, die Übelkeit

nicht isoliert zu behandeln, sondern alle Symptome zu berücksichtigen. Bereits entwickelte Strategien im Umgang mit anderen Krankheiten erwiesen sich als besonders hilfreich.

Psychooncology

ID 0006

Comparison between online and face-to-face support groups for prostate cancer

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Background: In addition to traditional face-to-face support groups (FtF) online services (OS) are becoming increasingly important for patients diagnosed with prostate cancer. To date it is unknown how these two forms of peer-to-peer support compare.
Methods: We performed a cross-sectional comparison study of the largest German prostate cancer OS and the national association of FtF in 2013/14. Applying validated instruments the survey covered socio-demographic and disease-related information, decision-making habits, psychological aspects, and quality of life.
Results: 686 Patients using OS were younger (65/72y), had higher education levels (47/21%), higher income, and a larger share of metastatic disease (17/12%) than 955 patients visiting FtF. Patients using OS reported higher distress scores, but their depression and anxiety scores were lower. Global quality of life did not differ. In FtF patients' ratings were better for exchanging information, gaining recognition, and caring for others. Patients using OS demanded a more active role in the treatment decision-making process (58/33%) and changed their initial treatment decision more frequently (29/25%). In this group, more patients opted for radiotherapy (39/28%).
Conclusions: There are significant differences that cannot be explained solely from the age distribution. OS offers low-threshold advice for acute problems and distress while FtF provide continuous social backing for long-term mental stress. Both forms of self-help have significant impact on treatment decision-making. Therefore, peer-to-peer support should be touched upon during patient counseling.

ID 0028

Patientinnenteilnahme an Tumorboards in NRW-Brustzentren – die Sicht teilnehmender Patientinnen

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Fragestellung: Die Patientinnenbefragung in den nordrhein-westfälischen Brustzentren ergab in 2013, dass Patientinnen in einigen Zentren und abhängig von Patientinnenmerkmalen zur Teilnahme am Tumorboard eingeladen werden (Ansmann et al. 2014). Bisher ist unerforscht, wie Tumorboards mit Patientinnenteilnahme ablaufen und welche Vor- und Nachteile die Teilnahme für die Patientinnen selbst und für die Versorger hat. Dieser Beitrag erforscht die Sicht der teilnehmenden Patientinnen.
Methoden: Die jährliche poststationäre Patientinnenbefragung in den nordrhein-westfälischen Brustzentren wurde in 2014 um eine Definition des Tumorboards und weitere Fragen zur Information über und zur Teilnahme am Tumorboard ergänzt. Es wurden n = 4194 Patientinnen (Rücklauf 87%) mit primärem Mammakarzinom zwischen Februar und Juli 2014 befragt. Die Ergebnisse werden deskriptiv dargestellt.
Ergebnisse: Es berichten 8,4% der Patientinnen über das Angebot der Teilnahme am Tumorboard und 4,2% (n = 165) über die tatsächliche Teilnahme. Die meisten teilnehmenden Patientinnen berichteten über eine Dauer ihrer Teilnahme von bis zu 20 Min. (70,1%) und über die Teilnahme von bis zu 4 weiteren Personen (52,6%). Dauer und Teilnehmerzahl variieren jedoch stark. Zudem konnten etwa 95% der Patientinnen ihre Meinung zur weiteren Behandlung äußern und etwa 90% wurden im Tumorboard in die Entscheidung einbezogen. Etwa 92% der Patientinnen antworteten auf die Frage, ob sie die Teilnahme bereuten, mit „überhaupt nicht" oder „eher nicht".
Schlussfolgerungen: Die Patientinnenteilnahme ist in den Häusern unterschiedlich organisiert. Die Einschätzung der Patientinnen bzgl. ihrer Partizipation und das seltene Bereuen der Teilnahme deuten auf eine hohe Zufriedenheit der Patientinnen hin. Weitere Forschung zur Evaluation der Patientinnenteilnahme und der Machbarkeit aus Versorgersicht erscheinen notwendig, bevor Empfehlungen für die Praxis ausgesprochen werden können.

ID 0055

Evaluation of psychosocial stress in patients with penile cancer

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Background: The penile cancer is a rare highly aggressive tumor entity. The psychological stress of patients with penis carcinoma arises from the cancer diagnosis per se and the correlating with tumor suffering side effects (loss of body integrity and sexual function). In addition there is cancer-specific distress e.g. fear of metastasis, progress, recurrence or death. Studies on the psychosocial stress of penile carcinoma patents are rare. This study investigated the stress situation of patients with penile malignancies using screening questionnaires and integration with inpatient mental health care programs.
Material and Methods: Prospective analysis of patients with penile carcinoma (n = 25) who underwent a surgical treatment (n = 17) or chemotherapy (n = 8) in the period between 06/2014 and 06/2015. Assessment of stress in patients with penile cancer using standardized screening questionnaires (Distress Thermometer and Hornheider FB) and integration with inpatient mental health care programs.
Results: The average stress level was 4, 4. 48% of the patients showed an elevation care needs. All affected patients received inpatient psychosocial care. The main stressors were sorrow (44%), micturition (40%), fear (36%) and exhaustion (32%).
Conclusions: Patients with penile cancer have, due to the often mutilating surgery, increased psychological stress and consequently increased psychosocial care needs. Therefore emotional stress should be recognized and support provided. This illustrates the importance of interdisciplinary collaboration in cancer treatment.

ID 0056

The psychosocial stress of patients with bladder cancer according to gender-specific aspects in inpatient care

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Background: 25,000 people/year are diagnosed for an urothelial bladder cancer (BC). Despite improved diagnostics and therapy, BC is characterized by its aggressiveness with a high recurrence and progression rate. The side effects of therapy and the poor prognosis in advanced stage, a psycho-oncology co-supervision is essential. Studies on the psychosocial care needs of patients with BC are rare. This study investigated the stress situation of patients with BC by means of screening questionnaires according to gender and invasiveness of surgical therapy.
Material und Methods: Analysis of patients (n =237; m =189, f =48) who underwent a surgical treatment (n =220) or chemotherapy (n =17) during the period from 06/2014 to 06/2015. Evaluated by using standardized questionnaires to stress screening and identification of need for care (Dis-

tress Thermometer and Hornheider FB) and utilization of psychosocial support.
Results: 28% of the patients showed a need of psychosocial support (m = 24%, f = 38%). The average stress level was 4,6, regardless of the surgical procedure and sex. 50% of female cystectomy patients communicated a support request, none of the male. All cystectomy patients were integrated into a psychosocial support program. Main stressors were pain (33%), diarrhoea (32%), fear (29%) and sleep (28%).
Conclusion: There is an evident number of BC patients with elevated psychological stress and a consecutive need of psychosocial care. Female BC patients and patients with advanced disease show significantly higher distress levels and higher care needs and are therefore frequently integrated into psychosocial care programs. Patients with muscle-invasive BC are more often supervised by a psycho-oncological therapist.

ID 0066

Auf dem Weg in die Personalisierte Psychoonkologie?

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Die Fortschritte der Medizin führen zu einer am individuellen Patienten ausgerichteten bio-medizinischen Therapie. Diese Entwicklung führt in der Onkologie zu einer erheblichen Steigerung der Wirksamkeit der Behandlung bei deutlich verbesserter Lebensqualität. Die Entwicklung führt auch zu einer Debatte im Gesundheitswesen, die nicht allein fragt, wie evidenzbasiert eine Therapie ist, sondern wie sie individuell, personalisiert oder zielgerichtet, zum Nutzen einer konkreten Person, „zurechtgeschnitten" werden kann. Dieser „Trend" stellt auch an die Psychologie die Frage nach dem individuellen Nutzen einer Therapie.
Die Definition des Begriffes der „Personalisierung in der Medizin" ist noch nicht konsentiert. Ziel der „Personalisierung" ist es, die optimale Therapie für einen individuellen Patienten zu finden, um den therapeutischen Nutzen zu maximieren und unerwünschte Nebenwirkungen zu minimieren. Dieser Maxime kann sich die Psychologie ohne weiteres anschließen. Bezüglich der eingesetzten Mittel in der „Personalisierten Medizin", der Identifikation relevanter Biomarker und der Stratifikation der Patienten, kommt es zu deutlichen Unterschieden zwischen Medizin und Psychologie. Im psychologischen Bereich sind die Mittel eher die „Beziehung" zwischen dem Therapeuten und dem Patienten, von welcher eine therapeutische Wirkung ausgeht, als ein spezifisches Behandlungspaket, und es ist eher ein begleitender Prozess der Risikoabwägung mit wiederholten Adaptationen einer Intervention, als eine definitive Zuweisung zu einer risikoangepassten Behandlungsgruppe.
In der öffentlichen Diskussion kommen diese Unterschiede darin zum Ausdruck, dass die Psychologie von „Individualisierung" und die Medizin von „Personalisierung" spricht.
Der Vortrag befasst sich mit den Gemeinsamkeiten und Unterschieden einer auf den einzelnen Krebspatienten zugeschnittenen Therapie in der Onkologie und Psychoonkologie und stellt zur Diskussion inwiefern „Individualisierung" und „Personalisierung" verwandte oder gar deckungsgleiche Konzepte beschreiben.

ID 0093

Implementierung der S3-Leilinie Psychoonkologie in die klinische Routineversorgung: Empfehlung 12.3. Sicherstellung der Prozessqualität der psychoonkologischen Tätigkeit

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In der neuen S3-Leitlinie zur „Psychoonkologischen Diagnostik, Beratung und Behandlung von erwachsenen Krebspatienten" ist definiert, dass die psychoonkologische Versorgung sich vor allem an den krankheits- und therapiebedingten Belastungen und den daraus resultierenden individuellen Bedürfnissen der Patienten und ihrer Angehörigen orientiert. Die psychoonkologische Unterstützung sollte über ein standardisiertes Belastungsscreening oder andere geeignete Assessmentverfahren ermittelt werden.
Seit dem Jahre 2012 ist am Centrum für Integrierte Onkologie eine „standard operating procedure (SOP)" zur Psychoonkologischen Früherkennung und Frühintervention durch den Vorstand des CIO verabschiedet worden. Die SOP-Psychoonkologie konnte nunmehr sukzessive in den Krebszentren des CIO eingeführt werden. Der Prozess der Implementierung wurde seitens des CIO durch das SOP-Management, seitens der Zentren durch die Qualitätsbeauftragten und seitens der Psychoonkologie durch den Verein LebensWert begleitet. Im Verlauf des Implementierungsprozesses sind vielfältige Maßnahmen geplant und durchgeführt worden, um den Implementierungserfolg sicherzustellen. Hierzu zählen Verfahrensanweisungen, Schulungen sowie konzeptuelle, organisatorische oder technische Maßnahmen und die Bereitstellung personeller Ressourcen.
Der Vortrag stellt exemplarisch den Prozess der Entwicklung der SOP-Psychoonkologie sowie deren Implementierung im Centrum für Integrierte Onkologie Köln Bonn, am Standort Köln dar.

ID 0103

Causal attributions and illness perception of patients with prostate cancer in consideration of cancer family history, sociodemographic and clinical factors

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Introduction: The growing number of cancer patients requires a better knowledge and understanding of illness representations in order to offer individualized therapy options and to optimize compliance. This information can also help to influence knowledge and preventive behavior in the general population as well as in the patients themselves.
Materials: 4054 of 9047 (44.8%) patients of the national database "Familial Prostate Cancer in Germany" answered a question about the perceived cause of their prostate cancer. This question was taken from the Brief Illness Perception Questionnaire. Patients' answers were classified into 17 categories, and compared in subgroups considering family history, second primary cancer and age at diagnosis using the Chi-Square-Test.
Results: Most frequently answers were: *Don't know* (1287; 31.8%), *Genetics* (30.1%; familial vs. sporadic $p < 0.001$; other cancers: yes vs. no $p < 0.001$), *Stress* (18.5%), *Lifestyle* (14.7%), *Environment* (12.0%). Patients with a second primary tumour more frequently mentioned *Other diseases* ($p < 0.001$), *Environment* ($p = 0.001$) and *Immune system* ($p = 0.038$). Patients diagnosed at a younger age (≤65 years) answered more often at all and in particular mentioned *Stress* ($p < 0.001$), *Lifestyle* ($p < 0.001$), *Environment* ($p = 0.014$) more often than older patients. They significantly mentioned *Don't know* less frequently ($p < 0.001$). Patients diagnosed less recent (≤5 years) gave a specific answer more often (other than *Don't know*), in particular *Lifestyle* ($p < 0.001$), *Genetics* ($p = 0.001$), *Age* ($p = 0.001$), *Environment* ($p = 0.001$).
Conclusion: Patients with a positive family history according to prostate cancer/other cancer types mentioned more often genetics, alike younger patients and those diagnosed more recently. Younger patients seem to have a stronger necessity to find reasons causing their cancer.

ID 0138

Risk perception and worry of developing prostate cancer among 45-year old men in Germany – data from the PROBASE trial

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Objectives: Aims of this study were to investigate the risk perception and worry of developing prostate cancer as a function of education and family history, as this may affect the use of screening tests.
Methods: Data of 45-year old men were gathered within the PROBASE study since March 2014. 3503 men received a questionnaire containing 4 questions about risk perception and concern. These questions were correlated with education, a previous cancer disease, familial cancer [FC], familial prostate cancer [FPC], and International Prostate Symptom Score [IPSS].
Results: 3.0% estimated their risk of developing prostate cancer to be high, 8.6% higher than the average man. Both was higher in men with high school education (3.6%, 10.4%), IPSS> 7 (4.1%, 13.0%), a previous cancer disease (7.2%, 18.0%), FC (3.6%, 10.4%) and FPC (11.5%, 30.3%) (all $p < 0.01$). 7.3% of the men reported frequently being worried about developing prostate cancer. This was more common in men with low education (12.1%), IPSS> 7 (18.6%), FPC (12.7%) (all $p < 0.01$), FC (7.7%, $p = 0.31$) and a previous cancer disease (11.7%, $p = 0.14$). 48.5% agreed that developing prostate cancer would be one of the worst life events. This was higher in men with low education (60.4%), IPSS> 7 (54.7%), without a previous cancer disease (48.9%), without FC (51.2%) and without FPC (50.0%) (all $p < 0.05$).
Conclusion: Education, a previous cancer disease, FC and FPC have a different impact on risk perception and concern. The risk is higher rated in men with high school education, a previous cancer disease, FC and FPC. The assessment that developing prostate cancer would be one of the worst life events in contrary was higher in men with low education, without a previous cancer disease and without FC or FPC.

ID 0223

Development of psychooncological stress in breast cancer patients – a longitudinal study

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Background: Breast cancer is frequently associated with psychooncological burden for the affected women. So far, little is known about the long-term development of this burden and the major factors of influence. Therefore, the aim of this study was to monitor the psychooncological burden of breast cancer patients in the long-term and to analyse the effect of treatment intention.
Materials and Methods: Quantity and quality of the patients' burden were assessed by two surveys at an interval of 30 weeks (median) using the standardised self-rating *Questionnaire on Stress in Cancer Patients – short form* (QSC-R10). Data were collected from 232 patients (curative: 160, palliative: 72) at 17 German study centres from May 2011 until August 2015.
Results: At the time of the 1st survey, 37.5% of the entire study population needed psychooncological support. This proportion was comparable among palliatively (40.3%) and curatively treated patients (36.3%). The 2nd survey revealed that the percentage of these patients remaining burdened over a longer period was much higher in the palliative (89.7%) than in the curative group (56.9%, $p = 0.003$, Fisher's exact t-test). Accordingly, the proportion of previously unburdened patients having turned burdened accounted for 27.9% in the palliative and 15.7% in the curative group.
Conclusions: Our results show that the psychooncological burden of breast cancer patients changes substantially over time. Treatment intention was found to be one of the major factors influencing this development. We conclude that long-term monitoring is required to identify breast cancer patients in need of psychooncological support and to timely initiate adequate measures.

ID 0231

Patients with breast-, prostate- and colorectal cancer talk about their experiences on *www.krankheitserfahrungen.de*

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Purpose: For cancer patients the personal experiences of other patients can be helpful. By sharing people's real-life experiences, the website www.krankheitserfahrungen.de provides reliable information about health issues, based on an approved qualitative methodology. Patients' stories are

systematically collected and published to supply a low-threshold and scientifically controlled resource for patients, families and healthcare professionals. In 2015 the Universities of Freiburg and Berlin published modules for breast-, prostate- and colorectal cancer patients, funded by the Federal Ministry of Health.
Sampling and Methods: By maximum variation sampling, 131 narrative interviews with 42 colorectal-, 45 prostate-, and 44 breast cancer patients were collected, transcribed, coded with maxqda and presented on the website in topic summaries. Video, audio or written clips from the interviews illustrate the range of views and experiences.
Results: On the website, the head themes "diagnosis", "living with cancer", "treatment options" and "messages" subsume about 35 topic summaries for each cancer, as well as participants' personal stories and further information, presenting highly informative insights into living with the condition. The websites are evaluated with qualitative and quantitative methods.
Conclusions: The modules can empower cancer patients, families and health professionals by providing other peoples' experiences. The website can also enrich medical teaching and further education regarding a personalized medicine. We show how the website can be used in oncological rehabilitation.

ID 0253

Functional and psychological outcome after radical cystectomy and ileal neobladder (n = 325) – data from urological inpatient rehabilitation

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Introduction: We questioned whether after radical cystectomy and ileal neobladder the extent of postoperative urinary loss and psychological distress correlate.
Material and Methods: 325 male patients underwent an early rehabilitation after radical cystectomy and ileal neobladder between 3/2013 and 8/2014. At the start (T1) and at the end (T2) of rehabilitation urinary loss (24-h-pad-test) and psychological distress (FBK-R10) was measured. The patients were compared and divided in age groups.
Results:
<60 years: urinary loss 516g (T1)/ 201g (T2), FBK-R10: 14.7 (T1)/ 9.6 (T2)
60 to 69 years: urinary loss 599g (T1)/ 277g (T2), FBK-R10: 13.3 (T1)/ 7.2 (T2)
>69 years: urinary loss 783g (T1)/ 391g (T2), FBK-R10: 11.6 (T1)/ 8.0 (T2)
In higher age urinary loss is increasing. Younger patients were more psychologically compromised than older patients. Urinary loss as well as psychological distress decreased significantly in the course of rehabilitation ($p < 0.05$).
Conclusions: Analysis shows an inverse correlation of functional outcome and psychological distress in relation to the age of the patients.

ID 0527

Psychooncological counseling and treatment as part of the Comprehensive Cancer Center (CCC): Multicenter study to detect the psycho-oncological needs, indications and using

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Introduction: The multicenter CCC study is developed, because despite many advances in psycho-oncological research and care a structured psycho-oncological care by psycho-oncology services (POD) in the Comprehensive Cancer Center's (CCC) is currently not sufficient enough.
Methods: The study was conducted in cooperation with 13 CCC's of the cancer network and should include four measurement times (T0-T3). As core tools were used standardized questionnaire on psychosocial stress, psychological well-being, quality of life and social support (DT, PHQ-D, GAD, HADS, SF-12, SSUK) and self-developed tools (expectations and wishes regarding psycho-oncological care, satisfaction with the provided information and the available psycho-oncological support, information strategies and barriers for non-user). Furthermore, the course of the subsequent use of psychosocial and medical offers; the use of self-help groups and the socio-demographic and medical characteristics were detected.
Results: The aim was to include a total number of 1,320 patients (102 patients per CCC). Overall, 1,635 patients could be included for T0 & T1, still 1,589 for T2 and only 1,359 for T3. 56.6% of study participants were female, 43.4% male; with an mean age of 59.2 ± 12.3 years; a total number of 362 patients died during the investigation period. In T1 22.2% of cancer patients used the psycho-oncological support; in T2 24.2% and in T3 20.7%.
Summary: Overall, it can be stated that the psycho-oncological support during the investigation period remains relatively constant (between 1/5 to 1/4 of the participants).

ID 0540

Rostock´s breakthrough in the improvement of psycho-social care of adolescents and young adults with cancer

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The diagnosis of a malignant disease means a big challenge – and a breakdown of life, especially for AYA (adolescents and young adults) patients. Adolescents and young adults are in a vulnerable phase of life, full of decisions for the achievement of a meaningful life.
Our intention was to assess the feelings and perceptions of care from AYA cancer patients, using a set of questionnaires. Therefore, we contacted all AYAs and a control group of older patients who were listed in Rostock´s cancer registry in 2012. In a questionnaire, the categories "quality of life" (SF-36), "personality" (NEO-FFI), "anxiety/depression" (HADS), "compliance" (published from Kondryn et al. 2010, with friendly consent), "fertility" (Leipzig´s study group) and the "doctor-patient relationship" (Rostock´s study group) were covered.

36.0% (88/243) of AYAs and 33.0% (33/100) of the control group responded. Most interesting were the following Results: In case of uncertainty in medical questions, AYAs used the internet significantly more often than the control group. 25.9% of AYAs and 3.6% of the older patients did not agree with the statement: "I decide about my own therapy; the doctors are my advisers." In comparison to older patients, AYAs think more often about breaking off therapy (12.1% vs. 0%) and about pursuing alternative medical methods (19.5% vs. 10.3%).
All in all, AYAs are a heterogeneous group of cancer patients, expressing a stronger need for information and thinking more often about breaking off the therapy as compared to older adults.To fulfil the special requirements of AYAs, it would be necessary to improve and better focus their care. The use of new media and technology (the development of new apps e.g.) might represent an important chance.

Quality-of-Life

ID 0043

Cancer-related fatigue in breast cancer patients: Investigation of cortisol dysregulations as potential underlying pathway

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Fatigue is a major burden for breast cancer patients undergoing adjuvant therapy. Yet, its pathophysiology is still not well understood. Dysregulations in the hypothalamic-pituitary-adrenal (HPA) axis, reflected in alterations in the diurnal cortisol pattern, are frequently hypothesized but still unproven pathways.
Therefore, we assessed diurnal salivary cortisol (awakening, +0.5 h, noon, 5 pm, 10 pm) in 265 breast cancer patients undergoing adjuvant chemo- or radiotherapy at three timepoints. Cancer-related fatigue was assessed with the validated multi-dimensional Fatigue Assessment Questionnaire (FAQ). Multiple adjusted linear regression analyses performed cross-sectionally at the three timepoints as well as longitudinally considering changes in cortisol and fatigue over time yielded consistent significant associations of the physical dimension of cancer-related fatigue with increased evening cortisol levels and higher overall cortisol secretion. These associations were independent of depressive symptoms. In contrast, physical fatigue was not associated with morning cortisol levels. Affective and cognitive fatigue showed no clear association with any of the cortisol parameters.
In conclusion, our results suggest that physical fatigue and mental (affective/cognitive) fatigue might differ in their pathophysiology, thus are possibly separate phenomena. Physical fatigue appears to be associated with cortisol dysregulations characterized by an unaffected cortisol level in the morning but blunted decline to the evening level. Research focusing on disturbances of the cortisol rhythm and HPA dysregulations during and after breast cancer treatment may open new strategies to reduce cancer-related fatigue.

ID 0059

Implementing a clinical pathway with quality of life diagnosis and therapy of patients with primary colorectal cancer: A randomised controlled trial

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Background: The effectiveness of a clinical pathway with quality of life (QoL) diagnosis and therapy is tested in a randomised controlled trial (RCT) for colorectal cancer patients. An essential part of the implementation process is to motivate physicians to participate in the trial. This requires a multifaceted strategy.
Methods: In a 2-arm RCT 220 primary colorectal cancer patients are recruited in 4 certified colorectal cancer centres. In intervention group QoL of patients is measured at 0, 3, 6, 12, 18 months postoperative (EORTC QLQ-C30, QLQ-CR29). The coordinating practitioner (CP: physician, responsible for outpatient treatment) is informed about the results of QoL measurement (QoL profile) and receives recommendations for QoL therapy (expert report). Control group patients` QoL is also measured but the CP neither receives a QoL profile nor an expert report (routine follow-up care according to S3 guideline). Methods to motivate CPs to participate in the trial include telephonic information about the study by the clinical surgeon, followed by educational outreach visits (2 study group members meet in person with the CP and explain the QoL concept and the details of the RCT).
Results: To date (31 July, 2015), 196 patients have been included in the RCT and 186 CPs (n = 20 clinicians, n = 166 resident doctors) have been implemented. Most of the resident doctors could be implemented by outreach visits, and only 7 CPs wished to be informed via phone call. Two physicians refused to participate in the RCT.
Conclusion: The multifaceted implementation strategy (outreach visit, information by surgeon) is very effective and can serve as a model for implementation of quality of life diagnosis and therapy into routine health care.

ID 0087

Patient-reported outcome (PRO) results from the AGO-OVAR 2.20/ENGOT-ov14/PENELOPE double-blind placebo-controlled randomised phase III trial evaluating chemotherapy ± pertuzumab for platinum-resistant ovarian cancer (PROC)

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Background: The placebo-controlled randomised phase III PENELOPE trial evaluated pertuzumab plus chemotherapy in low tumour HER3 mRNA-expressing PROC. Adding pertuzumab to chemotherapy improved progression-free survival (median 4.3 vs 2.6 months for placebo-chemotherapy), although not significant for the primary endpoint analysis. PROs were a secondary endpoint.
Methods: PROs included EORTC QLQ-C30 and QLQ-OV28, the Hospital Anxiety Depression Scale, FACT/NCCN Ovarian Symptom Index and a 'three worst symptoms' questionnaire (baseline only). Questionnaires were completed before tumour assessment and treatment administration at baseline and every 9 weeks until disease progression. The predefined primary PRO endpoint was mixed-model repeated measures analysis of the QLQ-OV28 abdominal/gastrointestinal symptoms scale. Secondary PRO endpoints focused on QLQ-C30 functional and symptomatic scales most relevant to pertuzumab and PROC.
Results: Baseline questionnaires were available from 92% (pertuzumab-chemotherapy) and 97% (placebo-chemotherapy) of 156 randomised patients. Week 9 compliance was 91% versus 83%, respectively. The most common reason for missing questionnaires was missed site administration. There was no significant difference over time between treatments in abdominal/gastrointestinal symptoms (profile difference: 3.9, 95% CI −3.3 to 11.2; Table 1). Diarrhoea symptoms (QLQ-C30) worsened significantly more with pertuzumab-chemotherapy than placebo-chemotherapy (profile difference: 21.2, 95% CI 10.1–32.3; p = 0.0003). No other prespecified QLQ-C30 scale differed significantly between arms.
Conclusions: Pertuzumab-chemotherapy demonstrated neither beneficial nor detrimental effects on PROs compared with placebo-chemotherapy in PROC, except for increased diarrhoea symptoms, consistent with the recognised pertuzumab safety profile.

ID 0133

Efficacy of a holistic rehabilitation program on quality of life and mental power after radical prostatectomy

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Introduction: Aim of this prospective study was an evaluation of the efficacy of a holistic rehabilitation program focusing on mental parameters, psychooncolocical situation and quality of life after prostate cancer therpay.
Methods: 184 patients (Ø 64.1 years) after prostate surgery were evaluated. All patients completed a 3-week-rehabilitation program including evaluation of quality of life using different questionnaires (FACT-G, FACT-P, and FACIT-Fatigue).
Results: The following results (pre-post-comparison) were obtained:
significant improvement of quality of life (physical wellbeing: 23,1 to 24,9; efficiency: 17,7 to 19,7; mental wellbeing 19,8 to 20,8 points)
significant increase of FACT-P parameters (30,5 to 33,1 points)
significant improvement of fatigue syndrome (42,1 to 44,7 points).
Conclusion: A holistic rehabilitation program after prostate cancer surgery allows a significant improvement of quality of life and mental health. Therefore a rehabilitation program should be offered to all prostate cancer patients.

ID 0155

Symptom burden and outcomes in patients with platinum resistant/refractory (PRR) and potentially platinum sensitive ROC receiving ≥ 3 lines of chemotherapy (PPS ≥3) – GCIG Symptom Benefit Study (AGO PRO1).

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Background. The primary endpoint for clinical trials in PRR/PPS≥3 ROC is progression free survival (PFS) and symptom benefit is not typically measured or reported. The primary aim of GCIG SBS is to validate a patient-reported outcome measure (PROM), the MOST (Measure of Ovarian Symptoms and Treatment concerns), to assess symptom benefit from palliative chemotherapy (PC). The SBS recruited 949 patients; the secondary aims provide insights into symptom burden, patients' and clinician's expectations of treatment and outcomes.
Methods. Patients with PRR/PPS≥3ROC completed 4 PROMs before each cycle of chemotherapy. They reported expectation of symptom improvement. Clinicians documented the indications for PC, symptoms at baseline, adverse events and estimated the number of cycles patients would receive.
Results. Palliation was the major indication for chemotherapy. 60% of patients had PRR and 40% had PPS>3 ROC. At baseline, most patients were symptomatic; 75% rated at least one symptom as moderate (≥5 on a 0-10 scale) and 30% rated >5 symptoms as moderate or worse. The symptoms included pain, fatigue, anorexia, abdominal distension, dyspnea, and constipation. Many had symptoms related to prior chemotherapy. Most pa-

tients had high expectations of symptom benefit from chemotherapy. 36% of patients received the predicted number of cycles. 25% of patients with PRR-ROC stopped treatment in < 8 weeks mainly due to progression/ death. The median number of cycles and median PFS were 4 and 5.6m in PPS≥ 3ROC, and 3 and 3.7m in PRR ROC respectively.
Conclusions. Patients with PRR/PPS≥3ROC reported a number of significant baseline symptoms. They had high expectations of symptom improvement and this should be measured. The results underscore the importance of incorporating PROMs and including symptom benefit as primary endpoints in trials in patients with PRR/PPS≥3 ROC.

ID 0213

Individual Risk Stratification – Individual Decision Making. First findings from an empirical-ethics study in oncology

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Purposes: Individualised decision making is increasingly advocated in oncology. This empirical-ethics project aims to reconstruct the process of decision making between patients and oncologists and explores ethical challenges associated with prognostic uncertainty.
Methods: Non-participant observation of the decision making in patients with gastrointestinal cancers for whom adjuvant chemotherapy is optional. In addition we conducted semi-structured interviews subsequent to the observation. Observation notes and interview transcripts were analyzed according to principles of grounded theory.
Results: The preliminary analysis of 9 observations and 5 interviews suggests that in cases of uncertainty oncologists seek access to biographical and value related information first, to be able to individualise the process of medical information giving. In contrast patients seek mainly information on prognosis, treatment options and consequences.
Oncologists' strategies to cope with this informational imbalance vary between two different types of approaches. Type one is rather focusing on a relation of care with empathic understanding of the patient's needs. Type two by contrast, is focusing on the rational consideration of pros and contras of available treatment options, whereby the physician is taking the role of an expert advisor.
Conclusion: The interdisciplinary clinical-ethics analysis suggest that in particular in situations of prognostic and therapeutic uncertainty oncologists may benefit from a systematic approach to eliciting patients' preferences and value related information to be able to individualise information and decision making.

ID 0251

Recovery after bladder cancer surgery – Results of a neobladder rehabilitation program

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Introduction: After radical cystectomy and neobladder surgery patients are faced with a lot of changes in anatomy, physiology and metabolism as well as side effects of cancer disease and treatment. Aim of this study was an evaluation of the efficacy of a neobladder rehabilitation program on functional, physical parameters and urinary continence.
Methods: 125 patients after radical cystectomy and neobladder surgery were evaluated. All patients completed a standardized spezialiced rehabilitation program including daily neobladder continence training. At the beginning/ end a 24-h-pad-test, evaluating urinary continence, and a standardized six-minutes-walking test, evaluating physical condition, were performed. The FBK-R23 questionaire was used for psychooncological screening.
Results: The following results were obtained:
- Significant improvement (p
- Significant increase (p
- Successful psycho-oncological intervention in 24% of all patients

Conclusion: A specialized rehabilitation of bladder cancer patients allows a significant improvement of disease and treatment associated deficits and side effects. Early recovery of quality of life, social participation and timely return to work are feasible.

ID 0285

Quality of Life in Germany – First Results of the LinDe-Study

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Research Question: Quality of life (QoL) has become increasingly important in the assessment of short- and long-term outcomes after cancer diagnosis. To identify detriments in QoL in survivors, up-to-date reference data of the general population (GP) is needed. Also, knowledge on differential effects of potential determinants of QoL in the GP and survivors is important. LinDe was initiated to collect up-to-date reference data on QoL (EORTC-QLQ-C30) as well as data on possible determinants of QoL.
Methods: 10580 men and women of the German GP (18+ years) were selected randomly by registration offices (Recruitment: Kantar Health). As the mean age in survivors is higher than in the GP, participants were selected stratified by age-group, not based on the age distribution of the GP. A sufficient number of participants in the oldest age-groups permits meaningful analyses in these subgroups. A questionnaire, including EORTC-QLQ-C30, GDS (depression), mMOS-SS, LSNS-6 (social support/ networks), FFKA (physical activity) as well as questions on diseases, demographics, and lifestyle was sent to participants.
Results: 2849 men and women participated (response: 29%). Mean age was 59 years. Global QoL was 66.6 (of 100; higher score=better QoL). 21.6% of the GP were socially isolated, 4.9% had a score on the GDS suggesting manifest depression. First results on non-cancer related determinants and comparisons with long-term cancer survivors will be presented.
Conclusion: The LinDe-study provides up-to-date reference data for the EORTC-QLQ-C30 as well as data on important potential determinants of QoL in the GP. Results can help to identify detriments in QoL in survivors and can help optimize QoL. Particularly data of the oldest age-groups are important.

ID 0314

Patient reported symptoms of cancer treatment and patient satisfaction in BNGO practices – a survey among 1509 patients with gynaecologic tumors

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Physicians who are BNGO members document all patients in an online registry in order to control, maintain and improve the treatment quality and measure outcome and also to control patients` (pts) quality of life during their cancer treatment in the practices.
From Jan.to Mar. 2015, 1,509 pts with gynaecological cancers treated in 31 BNGO practices answered a questionnaire about their satisfaction with the practice and tumor- and therapy-related symptoms. Chemotherapy (ctx) pts reported side effects rated the most distressing in a scale of 1 (least) to 10 (most).
94% of all pts regarded the practice equipment, organisation and staff and their treating physician as very good or good. 99% said their physician´s attentiveness was very good or good and almost 100% rated their physi-

cian´s competence as good or very good. 99% would seek treatment in the same practice again. The most frequent symptom in all patients was fatigue. Most distressing were hot flushes. 73% of patients received ctx. 66% rated the burden of chemotherapy high or extremely high. Alopecia was most frequently reported, followed by fatigue. Nausea (N) and Vomiting (V), which was one of the most frequently was less frequent in the current survey. 70% of patients had no V on the day of ctx and 66% on the days after. Less than 8% reported frequent/repeated V-episodes. Alopecia was regarded the most distressing side effect, followed by fatigue, tiredness, and delayed N.

ID 0356

Restorative Proctocolectomy in FAP patients – Outcome of smaller pouches in a single surgeon series – any benefit?

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Purpose: Traditionally, the ileal J pouch is created by doubling 15cm of the terminal ileum with a stapler anastomosis, suturing the pouch apex to the anal canal. In this series the functional outcome and QoL following construction of a shorter J-pouch limb of 8-9cm length were analyzed.
Methodology: All patients of a single-surgeon series with FAP who underwent proctocolectomy and small ileal pouch-anal anastomosis between 11/2005 and 01/2009 were retrospectively analyzed. All FAP patients with a minimal postoperative period of 6 months were requested to fill out the SF36 questionnaire. Additionally the Wexner score was assessed and the stool frequency in addition to the regular medication and diet were interrogated.
Results: In 46/51 (90.2%) patients a pouch was conducted as a primary procedure (21 males, 25 females) and included in the study. The mean age at the time of surgery was 27.14±1.78 years.
After a mean follow-up of 38.1±3.0 months 43/46 (93.5%) did not have incontinence, 3 patients (6.5%) reported incontinence during the night only. The mean stool frequency per day was 6.25±0.36. 32/46 patients (69.6%) quoted not to use any medication for stool regulation. Loperamide was used by 9/46 patients (19.6%) and expanding agents like Mucofalk were taken by 3/46 patients (6.5%). Both medications were used by 2/46 patients (4.3%). The Wexner score for incontinence was as follows: solid 0.663±0.18, liquid 0.893±0.19, gas 0.800±0.18, wear pad 0.310±0.14, lifestyle altered 0.667±0.15, total 3.158±0.68.
Conclusion: Smaller pouches perform equally when compared to larger pouches – both regarding functional results and QoL. Interestingly in this series a good functional result was achieved in a short time-period after ileostomy closure.

ID 0566

Wirksamkeit einer Yogatherapie bei Patienten mit einer Tumorerkrankung

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Hintergrund: Eine Tumorerkrankung geht mit vielfältigen Belastungen einher. Je nach Tumorentität, Schwere, Dauer, Tumortherapie erleben Menschen psychische und physische Belastungen individuell unterschiedlich.
Deshalb kann es für Tumorpatienten neben der Standardtherapie der Krebsbehandlung hilfreich sein, ergänzend komplementäronkologische Verfahren wie zum Beispiel eine Yogatherapie durchzuführen.
Es besteht noch großer Forschungsbedarf hinsichtlich wirksamkeitsgeprüfter Studien über Yoga als Komplementärmaßnahme gerade im deutschsprachigen Raum. Im Rahmen der Studie sollten folgende Fragen beantwortet werden:
Wie wirksam ist Yogatherapie für die Krankheitsbewältigung?
Kann die Durchführung einer Yogatherapie Patienten mit einer Tumorerkrankung helfen, Symptome wie Angst, Depression und Fatigue verbessern?
Welche Verarbeitungsstrategien nutzen Menschen mit einer Tumorerkrankung?
Methode: Die Tumorpatienten wurden konsekutiv in die Studie aufgenommen und individuell randomisiert der Yogatherapie oder der Wartekontrollgruppe zugewiesen.
Eingeschlossen wurden erwachsene Patienten mit einer Tumorerkrankung, die sich für die Studienteilnahme freiwillig melden. Die Follow-up-Untersuchung diente der Bestimmung der Nachhaltigkeit von möglichen Effekten.
Ergebnisse: Für die Studie liegen bislang von 70 Patienten vollständige Datensätze vor. In dem Kongressbeitrag werden erste evidenzbasierte Ergebnisse einer Yogatherapie vorgestellt
Schlussfolgerungen: Yogatherapie ermöglicht Patienten einen besseren Umgang mit einer Tumorerkrankung.

Radiation

ID 0051

Establishing high precision radiotherapy with flattening-filter-free techniques in clinical routine – Initial experiences in a single institution

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Purpose: Duration of radiotherapy in hypofractionated high precision radiation techniques has been a worry for many patients who are commonly positioned within rigid and uncomfortable masks or even full body casts. Using flattening-filter-free (FFF) techniques, delivery of radiotherapy doses has been tremendously accelerated. In Heidelberg, this method has been clinically available for one year.
Patients and Methods: In total, 63 pulmonary lesions in 58 patients were treated. Treatment planning was performed usng 4-D-CT scans and the internal target volume (ITV) concept. Central lesions were treated with 8 x 7.5 Gy delivered to the conformally enclosing 80%-isodose with desired dose maxima of up to 75 Gy. Peripheral lesions were planned to receive 3 x 15 Gy, prescibed to the 65%-isodose with desired maximum doses of up to 69 Gy.
Results: In all patients, treatment was tolerated well without radiation- or positioning-related interruptions.
NSCLC patients presented with central locations in 26 cases and with peripheral lesions in 37 cases. Delivery techniques comprised 3D-conventional (n = 31), step-and-shoot IMRT (n = 1) and VMAT (n = 31) radiotherapy. Mean PTVs were 30.7 ml (range: 6.1–436.2 ml). Mean maximum dose was 112%. At the time of this analysis, all patients treated were still alive, and only one local relapse has been detected. On the contrary, 7 patients were diagnosed with metastastic disease during follow-up. Acute toxicities comprised fatigue (n = 7), dysphagia (n = 3), cough (n = 15), chest wall pain (n = 2), and pneumonitis requiring oral steroids (n = 4). Pretreatment mean FEV1 was 1.70l (range: 0.84–4.38l).
Conclusions: Patient treatment with hypofractionated precision radiotherapy using FFF techniques is safe and provides promising clinical results with only modest toxicity. Even though follow up in this analysis is very short, only one progression within prior radiations targets has been diagnosed until today.

ID 0297

Effective long-term local results and prognostic factors after fractionated stereotactic radiotherapy of 257 intracranial meningeoma

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Background: The aim of this study was to evaluate the local tumour control and safety of patients with meningioma after fractionated stereotactic radiotherapy. Moreover, we have analysed the overall survival and identified prognostic factors after SRT.
Methods: 233 patients with 257 meningeoma of the skull base (71.2%), falx (12.1%), convexity (14.4%) and meningeomatosis (2.3%) were treated between 01/2002 and 01/2015 at the Erlangen University Hospital. 81.7% (210) of patients received SRT postoperatively and 18.3% (47) as primary treatment. 119 (46.3%) had a WHO grade I, 64 (24.9%) grade II, 16 (6.2%) grade III meningioma. In 58 cases no histology was obtained, whereas 47 (18.3%) of which received SRT alone. SRT was given in 28 or 30 fractions. The lesion (PTV) received a median reference dose of 54.0 (range: 35.50-66.60) Gy in single fraction of 1.80 Gy.
Results: The median follow-up at the time of overall survival (OS) analysis was 38.10 (range: 0.46-130.03) months.
Local control rate was 97% at 5- and 83% at 10 years. OS rate was 92% at 5- and 90% at 10 years. No radiation associated acute toxicity occurred. In one patient considerable worsening of vision in left eye was observed (opticus left dose: 56.16 Gy). The most common chronic symptoms were headache.
The skull base meningioma (vs. other location), female sex and irradiation of primary tumour (vs. reccurence) were a high significant ($p = 0.000$) prognostic factor for progression-free-survival.
Conclusions: The SRT was associated with excellent local control of 97% after 5- and 83% after 10 years. It has been shown that local control was significantly associated with the tumour location, irradiation of primary tumour or recurrence and the gender.

ID 0372

The radiotherapy of glioblastoma might be enhanced by the addition of chloroquine prior to irradiation.

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Objective: In 2006 a small clinical study, published by Sotelo et al., revealed that the addition of the malaria drug chloroquine (chq) to radiotherapy of glioblastoma extended the overall survival of the patients. In the present study we examined whether chloroquine interferes with proliferation and motility of human glioblastoma cells in vitro.
Methods: U343 glioblastoma cells were incubated with 0 or 10 µM chq for 24 h prior to irradiation with 0–8 Gy photons from a linac (5 Gy/min). The viability of the cells was analyzed by colony formation assays. Migration and motility were observed by time-laps videography. The data obtained were analyzed as to velocity, accumulated, and Euclidean distance. DNA double-strand breaks were analyzed by IF of γH2AX-foci.
Results: The addition of chq reduced significantly the number of colonies. To reduce the colonies by 50% 2.6 Gy were required without and only 1.5 Gy in the presence of chq. A reduction by 90% was obtained at 5.3 Gy without and at 3.7 Gy in the presence of chq. The motility of the cells was considerably reduced in the presence of chq. After 24h the Euclidean distance of travelling cells was: untreated, 0 Gy, 15.0 µm; untreated, 2 Gy, 16.9 µm; chq, 0 Gy, 5.4 µm; chq, 2 Gy, 7.7 µm. Velocity and accumulated distance yielded similar results. Staining of γH2AX revealed an increase in double-strand breaks by about 20% after chq.
Conclusions: Our data demonstrate that the addition of chloroquine to radiotherapy of glioblastoma multiforme may enhance the efficiency of the treatment. In the presence of chq the viability of the cells is impaired at lower doses and the migratory potential of the cells is reduced. This might probably result in less or later recurrences, the main reason for the unfavorable prognosis for glioblastoma patients.

ID 0377

Motility as well as clonogenic survival of breast cancer and glioblastoma cells is reduced by hyperthermia alone or in combination with irradiation.

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Reliable experimental data on the efficacy of hyperthermia in cancer therapy are scarce and inconsistent. We have therefore examined the effects of hyperthermia alone and in combination with photon irradiation on the clonogenic survival and motility of cultured cells. In the light of the cancer stem cell hypothesis both parameters together are expected to give a good estimation of the probability of local as well as distant recurrences.
The experiments were performed on MDA-MB 231 and U251 cells. For hyperthermia the cells were incubated for 1 h at 39-42 °C. The clonogenic survival was tested in a colony formation assay. The expression of HSP70 was analyzed by Western blotting. The cells were irradiated with photons from a linac at 5 Gy/min. The motility of the cells was examined by time-laps videography.
After hyperthermia the clonogenic survival was increasingly reduced with increasing temperature. A maximal reduction of 26% was obtained for MDA 231 and of 41% for U251. The motility of U251 cells was increased significantly after irradiation with 2 Gy. This increase could by totally impeded by hyperthermic treatment following irradiation. After irradiation the accumulated distance was enhanced by 17%, The Euclidean distance by 24%. Additional hyperthermia reduced the values by 13% and by 35% relative to the untreated baseline. With respect to the enhanced value after irradiation the reduction was 48%. The directness was also reduced significantly indicating that hyperthermia leads to more detours or erratic "back-and-forths" of the cells.
Hyperthermia might counteract recurrences since the hyperthermic treatment decreases the clonogenic survival as well as the motility of malignant cells and is able to suppress the irradiation-induced increase of the cellular migration.

ID 0466

Radiotherapy, Bisphosphonates and Surgical Stabilization of complete or impending pathologic fractures in patients with metastatic bone disease

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Purpose: To report the treatment outcomes of patients with metastatic bone disease with complete or impending pathologic fractures, who were treated with postoperative radiotherapy (RT), bisphosphonates or both after orthopedic stabilization.
Material and Methods: We retrospectively evaluated the results of RT, bisphosphonates or both after orthopedic stabilization for complete or impending pathologic fractures in 72 patients with skeletal metastases. After surgery, 32 patients (44%) were treated with RT alone (group 1), 31

patients (43%) were treated with RT and bisphosphonates (group 2) and 9 (13%) patients were treated with bisphosphnates (group 3), respectively. Patients were treated with a median dose of 30Gy (30-40 Gy/2-3Gy per fraction).The local tumor progression, pain progression and need for re-operation or re-radiotherapy were assessed from patients' medical records. Median follow-up time was 9 months.
Results: Median overall survival time was 14 months (95% CI: 12-17). Secondary surgical intervention at the same location was necessary in 1 patient of group 1 (2%), 2 patients of group 2(5%) and 2 patients of group 3 (15%), respectively (p = 0.097). Local tumor progress was observed in 3 patients of group 1 (9%), 2 patients of group 2 (7%) and 4 patients in group 3 (44%), respectively (p = 0.021). Local pain progress was observed in 19%, 16% and 67% of the same groups (p = 0.011).
Conclusion: Our data confirm the efficacy and necessity of postoperative RT after orthopedic stabilization for metastatic bone disease to control the local disease. Bisphosphonates do not obviate the need for RT in the management of bone metastases after surgical stabilization. The combined treatment might lead to a better local tumor and pain control.

ID 0467

Genital sparing with vaginal dilator for pelvic radiotherapy for female patients

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Purpose: Acute vaginitis, acute urethritis, and permanent sexual dysfunction are common among patients treated with radiotherapy in pelvic region. A vaginal dilator may help delineate and displace the vulva and lower vagina away from the PTV. The goal of this study is to evaluate the influence of the diameter of the dilator on sparing of organs at risk.
Methods: The study protocol was approved by the Ruhr-University Bochum Ethical Committee at the Medical Faculty. Five healthy female volunteers aged 55-65 will participate in this study. Each participant will receive 4 pelvic MRI´s: one without dilator and 3 with 2.6, 3.0 and 3.5 cm in diameter. Different tumor localisations will be defined to compare the sparing effect of the dilators. Till now, three female volunteers have participated in the study. The whole anal canal was defined as gross tumor volume (GTV). Clinical target volume 1 (CTV1) encompassed the elective nodal volumes and GTV and the internal and external anal sphincters + 20 mm. PTV1 was created with an isotropic 5 mm expansion to CTV1. PTV2 (Boost volume) was created with an isotropic 15 mm expansion to GTV.
Results: Without a dilator, more than 99% of the vagina and urethra were inside the planning target volume. With the 2.6 cm dilator, 100% of the urethra and 30% of the vaginal tissue, with the 3.0 dilator 100% of the urethra and 33% of the vagina and with the 3.5 cm dilator 100% of the urethra and 35% of the vagina could be shifted out of the PTV1. The 2.6, 3.0 and 3.5 cm dilator provided a 14 cm^3, 22 cm^3 and 24 cm^3 space between PTV1 and vagina. 81%, 83% and 87% of the vaginal volume were out of the boost volume using the 2.6, 3.0 and 3.5 cm dilator, respectively.
Conclusions: Vaginal dilator help displace the vagina away from the planning target volume. Detailed results will be presented on DKG 2016

ID 0491

The Therapeutic Effect of Photon Irradiation on Viable Glioblastoma Cells Is Reinforced by Hyperbaric Oxygen.

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Background: Hyperbaric oxygen (HBO) seems to intensify the effect of ionising radiation. We investigated whether HBO combined with irradiation decreases the capability of U251 glioblastoma cells for relapse and metastasis.
Methods: Cells were treated with O2 at 1.3 bar and then irradiated with 2 Gy photons. Clonogenic survival was tested with colony formation. Motility is an important feature of metastasis and was measured with time-lapse videography.
Results: The clonogenic survival diminished by 22% through HBO, by 49% through irradiation, and by 70% through the combination of both. The accumulated distance travelled by cells fell by 3% with HBO, rose by 17% with irradiation, but was reduced by 11% with their combination. The respective values for the Euclidean distance travelled were +8%, +47% and −14%. Compared to normoxic irradiation, additional HBO lowered travel by 41%.
Conclusion: HBO strengthens the effect of irradiation on clonogenic survival and reverses radiation-induced increase in the mobility of cells.

ID 0543

Proton beam irradiation for uveal melanoma

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Introduction: Uveal melanoma have been treated with proton beam therapy at the Helmholtz-Institute Berlin since 1998. This study outlines all treatment procedures and their outcomes over the past 17 years.
Methods: All patients treated with proton beam therapy between1998-2013 were included. Minimum follow-up was 24 months. Endpoints were local tumor control, survival, and eye retention.
Results: Over the past 17 years >2500 patients were irradiated with proton beam therapy of whom 95% were treated for uveal melanoma. Other diagnoses comprised choroidal hemangioma and conjunctival melanoma. Patients treated for choroidal melanoma presented with tumors graded T1 in 30.4%, T2 in 36.3%, T3 in 25.4%,T4 in 3.8%, and Tx in 4.1% while patients treated for choroidal ciliary body melanoma presented with tumors graded T1 in 3.9%, T2 in 3.5%, T3 in 51.7%, T4 in 39.4%, and Tx in 1.5%. Additional tumor resections were performed in 19.2% of choroidal melanomas consisting of endoresections in 17.8% and transscleral resections in1.4%. Of ciliary body melanoma 42.9% underwent transscleral resection.
Local tumor control was 96% with an eye retention rate of 95%. Metastasis-free-survical 5 years after primary proton beam treatment was 85%.
Conclusion: Proton beam therapy is a safe and convincing first line treatment for uveal melanoma. Interdisciplinary irradiation planning including multimodal imaging ensures local tumor control and preservation of the globe.

Rehabilitation and long term burden in social medicine (survivor)

ID 0030

Influence of arm crank ergometry on development of lymphedema in breast cancer patients after axillary dissektion

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Background/Aim: Breast cancer-related lymphedema of the arm can be a long-term sequela of medical treatment and is associated with reduced physical functioning and quality of life. In the past physical activity has been proscribed for women with breast-cancer-related lymphedema. The purpose of this study was to assess the safety and efficacy of an arm crank ergometer (ACE) in breast cancer patients with axillary dissection.
Method: In a randomized, controlled clinical intervention trial twice-weekly supervised ACE-training was compared with usual care (UC) in 49 breast cancer patients after medical treatment over 12 weeks. Endpoints were change in body composition of the upper extremity measured by bioelectrical impedance analysis (BIA), arm volume (arm circumference), muscular strength (NM), quality of live (QL) (EORTC QLQ C30+BR23) and fatigue (MFI 20) before and after 12 weeks.
Patients in the ACE improved significantly in lean body mass (LBM) (OP-arm p: 0.017; control-arm p: 0.004), skeletal muscle mass (ACE p: 0.049; UC p: 0.385) and in a significant decrease in body fat (ACE p: 0.009; UC p: 0.393). Both in the ACE and in the UC an increase of circumference of the armpit over 5% was detected, although the severity was in the UC higher. In all further measuring ranges a significant decrease were seen. In both groups a significant increase in muscular strength was observed. Compared with the control group, the ACE-group had a greater improvement in muscular strength of the upper extremity. In both groups a non-significant trend for improvement of QL was seen (ACE p: 0.101; UC p: 0.202). The ACE improved significant in general fatigue (ACE p: 0.032.; UC p: 0.483), physical functioning (ACE p: 0.038; UC p: 0.428) and physical fatigue (ACE p: 0.002; UC p: 0.42).
Conclusion: The results confirm the safe execution of the training with an ACE and highlight improvements in strength, QL and reduced symptoms.

ID 0085

Optimization of Patient Transition from Acute Care to Rehabilitation – First results of the OPTIREHA Study

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Background: Rehabilitation for cancer patients aims to achieve improvement of reintegration, participation and quality of life. To reach these objectives patient transition from primary care to rehabilitation should be based on comprehensive trans-sectoral flow of information regarding patients' individual condition and needs.
Objective: The multi-centre pilot-study aims to develop and pilot-test a modular assessment tool based on standard nursing assessments and ICF criteria in order to optimize patient transition between acute care and rehabilitation.
Method: Analysis of exemplary patient records and structured survey of health care professionals (HCP) with respect to care transition resulted in suggested optimization measures that were consented (Delphi-survey) and pilot-tested in 4 centers in order to obtain first results regarding feasibility and acceptance.
Results: Analysis of patient records (n = 12), and HCP questionnaires (n = 13) in 3 centres showed insufficient assessment, documentation and communication of functional impairments and partly insufficient patient information. Standardized patient-information and an assessment tool based on nurse routine documentation and ICF criteria were developed. This OPTIREHA-Assessment comprises documentation of psychosocial aspects including information about patient related barriers and resources, assessment of functional impairments, special nursing needs and "red flags" indicating critical medical conditions demanding direct communication with the rehabilitation clinic. The pilot-testing showed reasonable time frames for completing the OPTIREHA-Assessment: Max. 5 min. were needed for summarizing existing data; max. 10 min. were needed if the assessment was completed in more than one go. Rehabilitation experts valued the information summarized in the OPTIRTEHA-Assessment.
Conclusion: First results indicate feasibility and possible benefit of the OPTIREHA-Assessment.

ID 0134

Efficacy of a specialized rehabilitation program in prostate cancer patients – improving urinary continence and physical strength

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Introduction: Specialized rehabilitation programs allow an early social and occupational reintegration of patients after prostate cancer surgery. Aim of this prospective study was an evaluation of the efficacy of a complex training program on functional, physical parameters and urinary incontinence.
Methods: 184 patients (Ø 64.1 years) after prostate surgery were evaluated. All patients completed a functionally oriented, specialized 3-week-rehabilitation program including an 1- and 24-hour pad-test, a 6-minutes-walk-test and uroflowmetry.
Results: The following results (pre-post-comparison) were obtained:
significant reduction of urinary incontinence (22,8g to 13,1g / 1-hour pad test and 240,2g to 153,6g / 24-hour pad test)
significant increase of 6-minute walk distance – Ø 59,1m
significant increase of uroflowmetry parameters (max. uroflow: 14,6ml/s to 18,5ml/s; micturition volume: 134,8ml to 168,9ml).
Conclusion: A specialized rehabilitation program after prostate cancer surgery allows a significant improvement of functional deficits and physical health. Therefore a rehabilitation program should be offered to all prostate cancer patients.

ID 0157

Effect of an 8-months-exercise program on cytokine levels in breast cancer patients

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It has been shown that mortality and risk of tumor recurrence can be reduced by physical activity in breast cancer patients. The mechanisms responsible for these effects are still not well understood. The purpose of

this prospective study was to determine the effects of an aerobic training program on circulating cytokine levels.
66 patients with breast cancer (mean age of 54,1 years) underwent an individualized training program as inpatient rehabilitation program over 3 weeks followed by outpatient training recommendations on an autonomous basis. At the beginning of the rehabilitation (t0), after 3 weeks of rehabilitation (t1) and after a follow-up of 8 months (t2) physical activity was determined by the BodyMedia Sensewear System and the Freiburger Questionnaire for physical activity. Serum levels of TNF-alpha, IGF-1, MIF and BDNF were measured by ELISA.
Physical activity comprised more than >7-9 hours/week (15-20 MET/week) during inpatient rehabilitation gradually declining to 2,83 hours/week after a follow up of 8 months. TNF-alpha levels significantly decreased between t0 and t1, but increased again to t2. The serum level of MIF fell from 26,46ng/ml at t0 to 16,32ng/ml at t1 and rose to 28,14ng/ml 8 months later ($p < 0,0005$). BDNF was 135,62 ng/ml at t0, decreased to 26,87ng/ml at t1 and rose to 149,8ng/ml at t2 ($p < 0,0005$). No significant changes could be observed for IGF-1.
In summary, intensive physical activity decreased serum levels of TNF-alpha, MIF and BDNF in the short term. Long-term effects on cytokine profiles could not be observed although patients remained physically active which might reflect a dose-dependent effect of physical activity. The pathophysiological relevance of these changes has to be elucidated in further studies.

ID 0250

Does it make a difference for inpatient or outpatient early rehabilitation after radical prostatectomy (RP) of working patients?

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Introduction: Are there differences of inpatient and outpatient treatment in rehabilitation after RP with regard to objective micturition patterns?
Material and Methods: 837 patients underwent an early rehabilitation treatment (3-4 weeks) after RP between 10/2010 and 6/2012 in 4 centers (inpatient n = 718, outpatient n = 119). At the start (T1) and at the end (T2) of rehabilitation urinary loss (24-h-pad-test), bladder capacity and voiding function (uroflowmetry) was measured.
Results: The average age of the patients was 57 years identically in both branches.
At T1 the urinary loss differs significantly between the two groups: inpatients 181g versus outpatients 72g ($p < 0.001$). At T2 continence rate is significantly higher in inpatients than in outpatients (51.7% versus 33.9%; $p < 0.001$).
Only the inpatients at the UKR were trained evidence based and diagnostically guided at a specific regime of therapy. Those UKR-patients reached the highest rate of urinary continence at 54.6%.
Conclusions: The significant best results in early urinary continence after RP were achieved by urological inpatient treatment and following the guidelines of a multimodal, differentiated therapeutic concept.

ID 0252

Does the autonomic nervous activity change after prostate cancer surgery?

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Background: Several chronic diseases are accompanied by changes of the autonomic nervous system (ANS). Since the lower urinary tract is primarily controlled by the ANS, the question emerges, whether the ANS plays a role in the occurrence and severity of temporary urinary incontinence after prostate cancer surgery (PCS).
Methods: The heart rate variability (HRV) is a well-established marker for ANS activity. We investigated 31 patients after PCS without comorbidities (no medication, no psychological disorders) and 31 healthy, age matched men. A 15-minutes heart rate recording in a lying position was performed. All patients completed 1-hour and 24-hour pad test to quantify urinary incontinence.
Results: The patient group showed significant lower values for HRV (T-3,07; $p = 0,004$). Also ANCOVA´s showed significant differences between both groups considering age ($p = 0,003$) and heart rate ($p < 0,001$) as covariates. Furthermore there was a significant inverse correlation between HRV and 24-hour pad test ($r=-0,428$; $p = 0,047$). No correlation was found between "rmssd" and 1-hour pad test.
Discussion: Patients following PCS have a lower HRV compared to healthy men. The HRV significantly decreases with an increased urinary leakage (24 hours pad test). In conclusion there is a close interaction of lower urinary tract dysfunction and the ANS. This is of major importance for treatment and rehabilitation of post prostatectomy urinary incontinence.

Sarcoma

ID 0017

Exploratory analysis of tumor growth rate in patients (pts) with advanced gastrointestinal stromal tumors (GIST) treated with regorafenib (REG) in the GRID phase 3 trial

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Introduction: In the randomized double-blind (DB) phase 3 GRID trial, REG significantly improved the primary endpoint of progression-free survival (PFS) vs placebo (PBO) in pts with advanced GIST who progressed on imatinib and sunitinib (HR 0.27; one-sided $p < 0.0001$). After progression on DB PBO, randomized pts were allowed to crossover to open-label (OL) REG, while pts initially randomized to REG were allowed to continue as OL REG. This exploratory analysis evaluated the growth rate of target lesions during DB and OL treatment.
Methods: Target lesions were assessed at baseline, q4 weeks for the first 3 months, q6 weeks for the next 3 months, and then q8 weeks until the end of treatment. Changes in target lesion diameters over time were approximated by a parabola-like 3-parametric model separately for the DB and OL periods. Tumor growth rate (TGR), defined as the percent change from baseline per month in the sum of target lesion diameters, are given by the slope at the earliest and latest time points of the model curve.
Results: Of the 133 pts randomized to DB REG, 41 continued OL REG; 129 and 37 were evaluable for TGR analysis, respectively. Of 66 pts randomized to DB PBO, 56 (85%) crossed over to OL REG and 65 and 53 were evaluable, respectively. During the DB period, TGR for REG pts was typically close to zero early reflecting target lesion stabilization and then positive from nadir to progression reflecting tumor growth. TGR remained low (5.2 and 4.6) in REG pts who continued OL REG after progression. In contrast, pts treated with PBO during the DB period had early and late tumor growth. In the subgroup of PBO pts who crossed over to OL REG at progression, TGR decreased from 13.6 with PBO to below zero (-2.6) after starting OL REG, which was similar to early TGR in pts treated with REG during the DB period.

Conclusion: REG reversed or stabilized tumor growth during the DB period with a similar benefit in DB-PBO pts who switched to REG at progression. TGR for REG-treated pts before and after progression was less than that of pts treated with PBO, suggesting that despite evidence of tumor growth or prior RECIST progression, REG continued to slow tumor growth relative to that observed in the absence of REG.

ID 0205

Incidence of sarcomas and histological subtypes in Germany

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Introduction: The population-based incidence of sarcoma and its histological subtypes in Germany is unknown. The aim was to determine this incidence with data from the German epidemiological cancer registries.
Material and Methods: Pooled data from the German Centre for Cancer Registry Data for the year of primary diagnosis (data call: December 2014) were used. All German cancer registries with sufficient completeness and with no objection because of reasons of data protection were included. Temporarily, these were all except for Hesse and Baden-Wuerttemberg. All malignant sarcomas according to the RARECARE Project[1] and to the WHO classification[2] were considered for analysis and, above all, gastrointestinal stromal tumours of uncertain behaviour. Sensitivity analyses were performed excluding certain histologies.
Results: The analysis included 2.822 cases in men and 3.126 cases in women diagnosed in 2012. The age adjusted incidence of sarcomas (European standard) was 6.9 (men) and 6.5 (women) per 100.000 inhabitants. More than 90% of sarcomas were soft tissue sarcomas, about 10% (men) and 7% (women) bone sarcomas. The most common histology subtypes were gastrointestinal stromal tumours (GIST) (24%), fibrosarcomas (14%) and liposarcomas (11%) in men and complex neoplasia (21%), GIST (20%) and fibrosarcomas (9%) in women.
Discussion: This study is the first detailed analysis of a German wide population-based incidence of sarcomas being comparable to the incidence detected in the RARECARE Project (1).

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ID 0232

Role of thyroid receptor interacting protein 6 (TRIP6) in migration and invasion of Ewing' sarcoma cells

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Ewing's sarcoma (ES) is the second most common bone-associated malignancy in children that is driven by the fusion oncogene EWS/FLI1. Despite the great propensity of ES toward early metastasis, recent evidence showed that EWS/FLI1 expression reduces migration and invasiveness of ES cells. However, we strived for exploring the underlying mechanisms of how ES maintains its basal migratory and invasive properties ultimately contributing to metastasis.
We focused on the Zyxin-protein family comprising key players in actin remodeling, migration, and invasion. By interrogation of published microarray data, we observed that of all seven Zyxin-proteins only TRIP6 (thyroid receptor interacting protein 6) is highly overexpressed in ES. Besides its effects on cytoskeletal organization, TRIP6 is a nucleocytoplasmic shuttling protein involved in telomere protection, apoptosis, chemo-resistance, and transcriptional control. Initial experiments indicate that TRIP6 expression is independent of EWS/FLI1 and that EWS/FI1 is unable to bind to a conserved ETS-binding-site within the TRIP6 promoter. However, RNAi-mediated knockdown of TRIP6 in ES cells significantly reduced clonogenicity, migration, and invasion *in vitro* as well as tumorigenicity *in vivo*, whereas proliferation, cell cycle progression, and resistance to chemotherapy were only mildly affected. DNA microarrays revealed that TRIP6 knockdown is accompanied by the downreguation of important pro-migratory and pro-invasive genes such as Radixin, CD164, and crystalline zeta, whose differential regulation was confirmed on the transcriptional and protein level.
Taken together, these data indicate that TRIP6 might partially account for the EWS/FLI1-autonomous migratory and invasive properties of ES. Further investigations are ongoing to explore the mechanisms involved in TRIP6-signaling.

ID 0247

Evaluation of mono- and combined therapeutic effect of TIMP-1-GPI with doxorubicin in a HT1080-based human fibrosarcoma model

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Introduction: Adult-type fibrosarcoma is a highly aggressive subtype of soft tissue sarcomas. It has been reported that tumor progression of fibrosarcoma is supported by a high concentration of tissue degrading, growth-enhancing matrix metalloproteinases (MMPs). Our current focus lies on the re-establishment of tissue homeostasis within the tumor by locally enriching the concentration of tissue inhibitors of MMPs (TIMPs). In this context, the combination of the recently developed TIMP-1-GPI protein and doxorubicin is subject of our current research.
Methods: The experimental design of *in vitro* and *in vivo* experiments consisted of six different treatment groups. *In vitro*, human fibrosarcoma cells (HT1080) were either treated with PBS as a control/vehicle (V), doxorubicin (D), recombinant TIMP-1 (rh), recombinant TIMP-1 plus doxorubicin (rh+D), TIMP-1-GPI (T), or TIMP-1-GPI plus doxorubicin (T+D). For the *in vivo* part of our studies, HT1080 cells were implanted s.c. into 27 Balb/c-Nude mice. The animals were randomized into six treatment groups (V, D, rh, rh+D, T, T+D) and therapy was initiated. TIMP-1-GPI and rh-TIMP-1 protein or vehicle were applied locally, whereas doxorubicin was applied i.v. The total duration of treatment was 14 days.
Results: Compared to TIMP-1-GPI monotherapy, the combination with doxorubicin shows an additive cytotoxic effect in cell proliferation, migration and clone formation assays. While both, monotherapy of doxorubicin as well as the combination treatment with TIMP-1-GPI resulted in an overall antitumoral effect *in vitro*, doxorubicin treatment astonishingly acted vice versa *in vivo* by even increasing the tumor growth.
Conclusion: While drug combinations with doxorubicin have proven efficient in many tumors, we show that the combination of TIMP-1-GPI and doxorubicin is not suitable for treating this type of human fibrosarcoma.

ID 0261

Hepatobiliary Toxicity during Regorafenib Treatment in Metastatic GIST Patients? – A Real World Experience from 3 German Centers -

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Background: Grade 3/4 hepatobiliary toxicity (HBT) has been reported for regorafenib (REG) in colorectal cancer. Therefore, we addressed the question for incidence and clinical course of REG associated HBT in a real world setting in gastrointestinal stromal tumor (GIST) patients.
Material and Methods: GIST patients treated with REG during 09/2012–5/2014 were retrospectively analyzed. HBT was defined by serum-value alterations (CTC ≥3 AE: AST, ALT, GGT, AP, Bilirubin) and/or corresponding clinical signs. PFS and OS were calculated by Kaplan-Meier curves.
Results: 21 patients were followed at median for 11.3 (range [r]: 2-25) months. REG was given at median as 4th line (r: 3-8). HBT occurred in 5 patients (25%) (CTC ≥3 AE hepatobiliary lab value alteration: n = 4, clinical sign: n = 1) after a median treatment of 60 (r: 43-335) days. Median maximum serum-values in patients with HBT were: ALT: 200 (r: 12-992) U/L, AST: 118 (r: 39-1104) U/L, AP: 397 (r: 208-571) U/L, GGT: 498 (r: 205-771) U/L, Bilirubin: 79 (r: 36-127) µmol/L. Increase of bilirubin and AP were significant ($p < 0.05$). In 3 patients no other causes for hepatobiliary toxicity than REG were identified, while 1 patient had potential hepatotoxic co-medication, and 1 patient had liver progression. In 3 patients REG was continued, without HBT recurrence. Clinical PFS was 6.7 [95%-CI: 0-14.8] months (Log rank: patients with vs. without HBT: $p = 0.58$). At last follow up OS was 22.3 [95%-CI: 19.1-25.4] months.
Conclusion: 24% of GIST patients suffered from severe HBT during REG treatment. Thereof, in 60% of the patients REG could be continued. Clinical monitoring and adequate therapy management ensures treatment continuation of REG in order to maintain optimal clinical outcome.

ID 0300

Sites of primary and metastatic Tumor vary with Age in Patients with Ewing Sarcoma

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Background: The incidence of Ewing sarcoma (ES) varies by age with a peak around 14–15 years. ES potentially arises in any bone, but differences in primary and metastatic tumor site are well known. The impact of age at diagnosis on sites of disease involvement has not been fully described.
Objective: The goal of this study was to describe differences in sites of primary tumor and metastatic tumor involvement according to age groups.
Design/Method: Ewing sarcoma data from the central database of the Cooperative Ewing's Sarcoma Studies CESS 81, CESS 85/86 and the subsequent European Intergroup Cooperative Ewing's Sarcoma Studies EICESS 91/92 and 99 were reviewed. Age group differences were compared with the chi square test.
Results: Our study population included 2635 patients with bone ES. Site of primary and metastatic tumor are shown in the table according to the age groups of young children (0–9 years), early adolescence (10–14), late adolescence (15 -19 years), young adults (20–24), and adults (more than 24 years). Young children demonstrated the most striking differences in site of disease involvement compared to their older counterparts. Compared with older patients, young children had a lower proportion of pelvic primaries and axial tumors. Young children presented less often with metastatic disease. They were more likely to present with lung metastases instead of extrapulmonic or bone metastases compared to older patients.
Conclusions: Site of primary and metastatic tumor involvement in ES differs according to age. The biologic and developmental etiology for these differences requires further investigations.

ID 0342

Molecular Precision Chemotherapy: Adressing Tumor Heterogenity as a Challenge of Genomic Cancer Therapy

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Genomics engendered the promise of targeted therapies. They failed in childhood cancer, priming for resistance instead.
The cancer stem cell model promised efficacious targeted therapies, but may not represent intratumoral diversity. Pediatric cancers display under selective pressure genomic and epigenomic plasticity, yielding subclones, non-dominant at one point and dominant at another: In longitudinal biopsies, we observed activation of oncogenic pathways during individualized expression-based targeted therapy in advanced Ewing Sarcoma (ES). Simultaneous targeting of both the EWS/FLI1 dependent catalytic subunit polycomb repressor complex 2 enhancer of zeste homologue 2 (EZH2) as well as reactive oxygen species (ROS) independent pathways yielded loss of EWS/FLI1 target genes expression and up regulation of ROS signature. Cytotoxic drugs can have specific effects on oncogene signaling. Increase of sensitivity due to repression of oncogene targets widens the sensitivity of the tumor as compared to normal cells. In ES, trabectedin interferes with EWS-FLI1 driven Werner (WRN) protein (Grohar 2014). Since WRN-deficient cells are hypersensitive to irinotecan, we performed a pilot trial using trabectedin to block EWS-FLI1 activity, and selectively sensitizing ES cells to the DNA damaging effects of irinotecan. We controlled about half of advanced pediatric sarcomas refractory to any including targeted therapy, with persistent quality of life (Herzog 2015).
In conclusion, intratumoral diversity requires strategies of molecular precision chemotherapy with synergy but also collateral damage. Such oncogene addiction directed precision chemotherapy may overcome resistance to targeted therapies.

ID 0391

Uterine sarcoma: A retrospective analysis and review of the literature

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Background: Uterine sarcomas (US) are rare malignant tumors with several distinct histological subtypes. Local recurrences and distant metastasis can differ and in some cases it can occur even 20 years after initial diagnosis.
Material and Methods: For this study a search in our tumor registry was performed. In the period 2002-2014 116 patients (pts) with US were identified. The clinical characteristics and the follow-up are reported.
Results: In the most cases the women had lack symptoms and present only a rapidly enlarging leiomyomas. 8 Patients had at first only an abdominal hysterectomy without bilateral salpingo-oophorectomy and in 4 cases a laparoscopical hysterectomy with morcellation was performed. After a median follow-up of 60 months 12 patients died. Tumor morcellation and higher stage of uterine leiomyosarcoma were associated with poorer overall survival.
Conclusion: Tumor morcellation during surgery increased the rate of abdominal pelvic dissemination and has adversely affected OS in patients with apparently US.

ID 0413

Trabectedin Followed By Irinotecan Can Stabilize Disease in Advanced Translocation-Positive Sarcomas

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Purpose: Preclinical data indicate that trabectedin followed by irinotecan has strong synergistic effects in Ewing sarcoma. This is presumably due to hypersensitization of the tumor cells to the camptothecin as an effect of trabectedin. A strong synergistic effect was also reported in a human rhabdomyosarcoma xenograft. Twelve patients with end-stage, refractory translocation-positive sarcomas were treated with trabectedin followed by irinotecan within a compassionate use program.
Design:Twelve patients with refractory sarcomas, all heavily pretreated with chemotherapy were treated with trabectedin followed by irinotecan. Diagnosis was Ewing sarcoma in eight and soft tissue sarcoma in four patients.
Results: As of February 1, 2015, stable disease according to RECIST criteria was achieved in six patients, progressive disease was seen in six patients. Median survival was 0.75 at three months after start of this therapy. In the majority of patients significant hematological toxicity (grade 3 and 4) was observed. Reversible liver toxicity and diarrhea also occurred. Only one patient suffered from dose limiting diarrhea and severe prolonged neutropenia, so that irinotecan had to be omitted in subsequent courses.
Conclusion: Our experience with the combination of trabectedin followed by irinotecan in patients with advanced sarcomas showed promising results in controlling refractory solid tumors. While the hematological toxicity was significant, it was reversible. Quality of life during therapy was maintained. These observations encourage a larger clinical trial.

ID 0417

Human T Cell Receptor transgenic CD8$^+$T cells specifically kill HLA-A*0201/CHM1$^+$ Ewing Sarcoma Lines in vitro and in a preclinical Mouse Model

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Advanced Ewing sarcomas are associated with poor prognosis. Despite multimodal therapeutic approaches including surgery, irradiation, high-dose chemotherapy and autologous or allogeneic stem cell transplantation, overall survival is still unsatisfactory in particular in patients with bone marrow involvement. adverse effects may be severe. We previously generated clonal ES-specific allo-restricted T cells for adoptive transfer to enhance efficacy and to decrease toxicity of donor lymphocyte infusions (DLI) after allo-SCT. However, inclusion of these cells in current therapy protocols is limited due to high complexity in production, relatively low cell numbers, and rapid T cell exhaustion. In order to overcome these obstacles and to facilitate off-the-shelf products in the future, we generated HLA-A*0201-restricted T cell receptor (TCR) transgenic T cells directed against ES selective antigen CHM1^{319} by retroviral transduction. Expansion protocols revealed sufficient cell numbers and a purified TCR-transgenic T cell population could be engineered to express a partial CD62L$^+$/CD45RO$^+$ central memory (CM) phenotype after short-term expansion. These cells maintained specific in vitro recognition and lysis of HLA-A*0201$^+$ ES cell lines expressing the antigen. When co-injected with ES cells in Rag2$^{-/-}\gamma c^{-/-}$ mice, CHM1-specific TCR-transgenic T cells significantly inhibit the formation of lung and liver metastases. Here, we present the first successful generation of ES-specific TCR-transgenic T cells causing anti-tumor response in vitro and in vivo. In the future, the infusion of ES specific TCR transgenic donor lymphocytes may serve to render DLI after allo-SCT more efficacious and less toxic.

ID 0493

Sarcoma research by 3D-Cell culture

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Introduction: Soft tissue sarcomas display a rare and heterogeneous group of tumors derived from connective tissue. A main difficulty in cell research is the lack of according culture models. Since, *in vitro* 2D cell culture model show lack in comparability to *in vivo* situation, the aim of this study was to generate a 3D spheroid model for HT1080 human fibrosarcoma cells to analyze the effect of 3D-co-cultivation with stromal cells like human fibroblasts and/or endothelial cells.
Materials and Methods: The ATCC listed cell line HT1080 was cultivated by „liquid overlay technique" to generate a 3D form. Human fibroblasts (HFB) and endothelial cells (HEC) were isolated from human adipose tissue by ferromagnetic antibody purification and were co-cultivated with HT1080 cells. The Growth of the spheroids, histological morphology, proliferation, expression of different markers and angiogenesis were analyzed and compared between HT1080 mono-culture and co-culture spheroids.
Results: During 14 days of monitoring, co-culture spheroids consisting of HT1080 and HEC showed a significantly increased volume, than HT1080 monoculture spheroids. Histological analyses revealed decreased central necrosis and showed first indications for rudimentary vascular networks in HT1080-HEC co-culture spheroids, than in HT1080 monoculture spheroids. Additionally, compared to monoculture spheroids, co-culture spheroids exposed an improved proliferation, angiogenesis and differences in expression profile.
Conclusion and outlook: The co-culture with HEC cells provides a positive effect on spheroid formation, due to autonomous assembly of vascular networks, which may intensify the diffusion driven support of the spheroid core with nutrients.

ID 0555

DEFEKTDECKUNGEN AM CAPILLITIUM: Therapieoptionen und perioperatives Management

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Hintergrund: Das Weichgewebe am Kopf weist nur eine geringe Dehnbar- und Verschieblichkeit auf und ist verhältnismäßig dünn. Hinzu kommt eine starke Exponiertheit, was den ästhetischen Aspekt im Vergleich zu anderen Körperregionen mehr in den Vordergrund rücken lässt. Technisch ist die postoperative Lagerung problematisch, da auf Grund der verhältnismäßig kleinen Auflagefläche die Weichteildeckung einem starken Druck standhalten muss, der die Perfusion kompromittiert.
Patienten: Ursachen der präsentierten Defekte sind Plattenepithelkarzinome, Sarkome, Meningeome und unterschiedliche Traumata. Die Deckung erfolgte durch konservative Maßnahmen, Hautverpflanzungen mit und ohne Dermisersatz, lokale Lappenplastiken bis hin zu einfachen und kombinierten freien Lappenplastiken.
Ergebnisse: Vor Herausforderungen stellt neben dem intra- insbesondere das postoperative Management der Patienten. Neben Halofixateuren sind teilweise Nachbeatmungen und spezielle Lagerungen – sitzend oder auf dem Bauch – notwendig. Gerade bei sehr ausgedehnten Defekten, die eine Doppellappenplastik erzwingen, erfordern die Anastomosen auf Grund stark unterschiedlicher Lumendurchmesser eine differenzierte Herangehensweise, die die Auswahl der Anschlussgefäße mit einschließt.

Zusammenfassung: Ein gutes perioperatives und interdisziplinäres Management erlaubt die Versorgung auch ausgedehnter Defekte des Capillitium und ermöglicht damit häufig eine kurative oder zumindest adäquate palliative Versorgung. Anhand von Beispielen werden verschiedene Deckungsvarianten dargestellt und kritisch diskutiert.

ID 0556

Freie Lappenplastiken nach Sarkomresektion – Überleben, Funktion, Lebensqualität

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Hintergrund: Sarkome sind seltene mesenchymale Tumoren, die einen Anteil von 1% an allen Malignomen haben und häufig an den Extremitäten lokalisiert sind. Gerade hier entstehen durch ihre Resektion häufig Defekte die ohne eine adäquate Rekonstruktion nicht mit dem Extremitätenerhalt vereinbar sind. Ziel dieser Studie war es daher, die Möglichkeiten des Extremitätenerhaltes durch freie Lappenplastiken nach Sarkomresektion zu untersuchen.
Methode: Es wurde eine Nachuntersuchung der Patienten die zwischen 2001 und 2013 eine freie Lappenplastik nach Sarkomresektion in unserer Klinik erhalten haben durchgeführt. Neben Patienten- und Behandlungsbasierten Daten wurden u.a. die Rezidivraten sowie das Überleben erfasst. Außerdem wurden Extremitätenfunktion und Lebensqualität mittels TESS und SF-36 erfasst.
Ergebnis: Insgesamt konnten 78 Patienten identifiziert werden. Das mittlere follow-up lag bei 5,7 Jahren. Das mittels Kaplan-Meier-Analyse geschätzte Überleben nach 5 Jahren lag bei 70%, das disease-free survival nach 5 Jahren bei knapp 60%. 28% der Patienten entwickelten Rezidive. 86% der Extremitäten konnten über die Dauer der Nachuntersuchung erhalten werden. Die TESS und SF-36 Ergebnisse zeigten gute Extremitätenfunktion bzw. eine Annäherung an die Normstichproben mit malignen Erkrankungen.
Diskussion: Freie Lappen ermöglichen die Resektion ausgedehnter Tumoren, insbesondere an den Extremitäten. So ist u.a. ein langfristiger Erhalt der Extremität ohne Kompromittierung der onkologischen Sicherheit möglich. Die erreichten Überlebensraten sowie die postoperative Extremitätenfunktion sowie Lebensqualität sind im Kontext der Erkrankung als gut zu werten.

ID 0557

Knapp oder Weit? Welcher Sicherheitsabstand sollte bei Weichgewebssarkomen erzielt werden

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Fragestellung: Insbesonders an den Extremitäten ist ein weiter Resektionsabstand oft nur unter Resektion funktioneller Strukturen oder Amputationen erzielbar, weshalb die Beantwortung der Frage nach dem notwendigen Sicherheitsabstand von herausragender Bedeutung für die Betroffenen ist.
Methode: Von 1994 bis 2007 wurden etwa 600 Patienten mit unterschiedlichen Sarkom-Entitäten (Liposarkome, NOS, Leiomyo-, Rhabdomyo- und Dermatofibrosarkome in der eigenen Klinik operiert und die Daten in einer prospektiven Datenbank gespeichert. Der Nachuntersuchungszeitraum betrug im Median knapp 50 Monate. Analysiert wurden bekannte prognostische Faktoren sowie insbesondere der Resektionsabstand. Dieser wurde innerhalb der R0-Gruppe in drei Untergruppen unterteilt: unter 1mm, 1-10mm und über 10mm.
Ergebnisse: Die unterschiedlichen Resektionsabstände innerhalb der R0-Gruppe zeigten keine signifikanten Unterschiede bezüglich Rezidivneigung, Metastasierung und Überleben. Entscheidende Faktoren waren vielmehr die Tumorgröße und Lokalisation sowie das Grading und Geschlecht.
Schlussfolgerung: Für die Lokalrezidiv-, Metastasierungs- und Überlebenswahrscheinlichkeit bei Patienten mit Weichteilsarkomen ist die R0-Resektion der entscheidende Faktor. Weite Resektionsabstände bringen keinen Vorteil für das Gesamtüberleben, verschlechtern aber die Funktion. Die Tendenz zu geringen Sicherheitsabständen und damit weniger mutilierenden Eingriffen scheint auch in der Literatur durch Daten immer stärker belegt, auch wenn es hierzu keine prospektiv randomisierten Studien gibt.

Skin Cancer including Melanoma

ID 0054

Comparison of intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) in total scalp irradiation (TSI) of extensive skin maligancies of the scalp

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Background: Total scalp irradiation offers effective local treatment for extensive scalp malignancies such as angiosarcoma or cutaneous lymphoma. The complex geometry of the head which is often significantly altered by the multifocal tumor lesions complicates adequate superficial target dose delivery, uniform dose distribution and critical organ sparing (brain, optical structures). This treatment planning study compared intensity-modulated radiotherapy (IMRT) with volumetric modulated arc therapy (VMAT).
Methods: 5 consecutive patients previously treated with whole brain RT at the Martin Luther University Halle-Wittenberg were selected. For each patient, we retrospectively created 3 treatment plans: a coplanar IMRT, a non-coplanar IMRT and a VMAT plan with 50 Gy in fractions of 2 Gy to the planning target volume (PTV) usually applied in the radical RT of scalp angiosarcoma. Plan conformity (CI), homogeneity (HI), dose-volume relation and organ-at-risk protection was comparatively evaluated.
Results: Mean dose gradient was 1.6, 1.1 and 1.3 Gy/mm in VMAT, coplanar and non-coplanar IMRT. PTV coverage was .94 for coplanar/non-coplanar IMRT and .95 for VMAT plans (mean). Mean HI was .119 for IMRT and .118 for VMAT plans; mean CI was .45 (CI98) in non-coplanar, .4 in coplanar IMRT and .43 in VMAT plans. Min. PTV dose was 43.7 Gy (VMAT), 41.4 Gy (non-coplanar IMRT) and 41.3 Gy (coplanar IMRT); max. PTV dose was 54.7 Gy (VMAT, non-coplanar IMRT) and 54.8 Gy (coplanar IMRT). Mean brain dose was 18.6 in VMAT plans, 21.9 in non-coplanar IMRT and 22.8 in coplanar IMRT plans. Mean dose at optical structures was 9.1 Gy in VMAT, 14.5 Gy in non-coplanar and 11.5 Gy in coplanar IMRT.
Conclusion: Target volume coverage and organ-at-risk protection was superior in VMAT plans which also produced the sharpest dose gradient. Homogeneity was comparable between plans but non-coplanar IMRT plans were most conformal.

ID 0117

Pembrolizumab in an advanced melanoma and immune suppressed patient with a Churg-Strauss syndrome following ipilimumab-induced colitis

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Background: Pembrolizumab, an anti-programmed death-1 (PD-1) monoclonal antibody, has been approved by the European Medicines Agency in July 2015 based on improved progression-free and overall survival in metastatic melanoma.

Case report: A 69-year-old immune suppressed patient with a Churg-Strauss syndrome, diagnosed with a 2.9 mm nodular melanoma of his right temple in 2007, was referred to our skin cancer unit in 2012. At that time, it was classified as AJCC stage IV (M1a) melanoma harbouring no relevant oncogenic mutation (BRAF, NRAS and C-Kit wild-type). Due to tumor progression after treatment with dacarbazine and carboplatin plus paclitaxel, ipilimumab was initiated. An immune-related colitis occurred after three ipilimumab infusions and resolved after high-dose steroids. After intensive discussion in the interdisciplinary tumor board considering the risk of potential excaberation of autoimmune colitis and Churg-Strauss syndrome, he was treated with pembrolizumab due to further progression in December 2014. Until today, no exacerbation of the underlying autoimmune disorders is detected. Adverse events were mild fatigue, itching and dry skin. The latest imaging demonstrated a remarkable partial response after eight infusions. The treatment is currently continued with the 11th infusion.
Conclusions: This case report suggests that pembrolizumab can be administered with caution in patients with pre-existing autoimmune disease. As the use of checkpoint inhibitors currently expands, knowledge about safety in patients with underlying autoimmune diseases will become increasingly important, in particular since these patients were typically excluded from clinical trials with immune checkpoint inhibitors.

ID 0350

Metastatic melanoma in pregnancy – a diagnostic and therapeutic challenge

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A 33-year-old pregnant woman presented in the 17th week of pregnancy. During a routine ultrasound examination a tumor mass with a maximum diameter of 5cm in the iliac right abdomen had been detected. Eight years ago, a melanoma (nodular type, tumor thickness 1.7mm) had been removed from the right thigh, a sentinel-node biopsy from the right inguinal had showed two positive sentinel nodes. A complete lymph node dissection and a complete CT staging were without pathologic findings. An adjuvant immunotherapy with interferon-alpha was stopped after a few weeks due to poor tolerance. In 2009 the patient gave birth to a healthy baby girl after a pregnancy without complications. Dermatologic follow-up examinations had been inconspicuous.
A whole-body MRI in the 18th week of the second pregnancy showed intraabdominal tumor masses adjacent to the iliacal vessels and the aorta. An operation to remove all tumor masses was performed during pregnany, but a R0-resection was not possible. Examination of the tumor tissue showed wild types for gene mutations of the BRAF-, NRAS or c-KIT gene. Generally, performance of chemotherapy during pregnancy is possible but limited in case of melanoma by low response rates. There are no data for the use of ipilimumab, PD1-inhibitors or BRAF-/MEK inhibitors during pregnancy. The use of these substances is not recommended as in animal assays these drugs led to injury of the embryo or fetus in all phases of pregnancy.
A termination of pregnancy was performed. Another attempt to remove all tumor masses by operation failed again. A therapy with ipilimumab was initiated that would have not been possible during pregnancy. This treatment had to be stopped due to hypophysitis and myositis. Now, the patient is treated with nivolumab.

ID 0398

Difficult treatment of cutaneous T-Cell Lymphoma with a haematological malignancy in medical history

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Primary cutaneous Lymphomas are the second most common type of extra-nodal non-Hodgkin Lymphomas, Mycosis fungoides (MF) being the most frequent subtype of disease.
Herein we describe a case series of two female patients presenting to our institution with intensely itching, erythematous macules and infiltrated patches concentrated on the extremities. Another common denominator was an underlying haematological malignancy, one being a B-CLL (B-NHL) and the other being a follicular Lymphoma (B-NHL). Both had undergone extensive therapy for their haematological disease including radiation, chemotherapy and antibody-therapy. Based on the clinical presentation, histological features and imaging studies the diagnosis of MF Stage IB was established. Hereafter, according to newest guidelines, a combined therapeutic approach with skin-directed therapy, photochemotherapy as well as chemotherapy with Bexaroten in one patient and immunmodulatory therapy with Interferon α in the other patient was first successfully employed. Under these therapeutic measures the cutaneous T-cell Lymphoma showed a regression but both patients developed, based on the haematological background, a therapy-induced pancytopenia which limited the therapeutic options. One patient further progressed to a lethal CML.
As increasing age and advancement in chemotherapeutical treatment possibilities, patients with an underlying malignancy pose an increasingly common challenge for dermatologists, hence not only caution should be exercised in treating these patients but also an interdisciplinary approach should be adapted, to best these patients as good as possible.

ID 0399

Atypical Fibroxanthoma (AFX) – a Sarcoma or a Spindel Cell Carcinoma (SpCC)?

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The Atypical Fibroxanthoma (AFX) applies with an incidence of 2,5: 100.000 as a rare diagnose and was classified as one of the intermediate-malignant tumors of the skin. Originally it was ranked among soft tissue sarcomas. Recent histological findings that were also presented within the 32nd "Aachener Dermatologenabend" (Dezember 5th 2014) suggest that the AFX could be a variant of undifferentiated Spindle cell carcinoma. We present four cases that also sustain this hypothesis. The common features shown by these causes are the increased incidence of these tumors in sun-exposed areas, an old age as well as preexisting field-cancerisation or the occurrence of epithelial tumors in prehistory.
The clinical courses show up, despite the described benign clinical course, very different cases. With aggravated and delayed wound healing partly by resection to the skullcap or its partial resection and its consequent complications such as bleeding or wound infection. That implies extended wound conditioning and wound closure by use of skin graft..
In summary, however it shows the currentness of this diagnosis, and suggests a clinical as well as a histological affinity between squamous cell carcinoma and Atypical Fibroxanthoma, with a, sometimes conditioned by localization, complex process.

ID 0433

Challenges in treating in transit melanoma metastases and development of new approaches

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Melanoma is responsible for 90% of all skin cancer related deaths by high metastatic potential. The incidence of in transit metastases is 4-11% of all Melanoma recurrences.
The current treatments of in transit disease vary to total surgical excision, local techniques, intralesional and systemic therapies.
A 70-year-old woman presented with an AJCC Stage III B Melanoma at left Hallux, harboring BRAF positive mutation in 2009. After a radical left inguinal lymphadenectomy by histologically confirmed metastases at sentinel lymph node, she was treated with an adjuvant IFN-a therapy for a period of 18 months. In 2012 she developed in transit metastases at the left thigh. Though a variety of long term therapeutic approaches such as electrochemotherapy, radiotherapy, cryosurgery and surgical excision of large metastases, the patient showed local progression of in transit filiae. After multidisciplinary consultation, the patient received a systemic therapy with Vemurafenib for a period of 4 months, which was discontinued due to side effects. Hereafter an intralesional IL-2 therapy and a therapy with Dabrafenib combined with Imiquimod and Fluorouracil for 7 months were performed, which only showed a partial regression of filiae. Althouth there was no evidence of metastasis to internal organs, the 3-year long term treatment failed to control the extended cutaneous lesions, which adversely impact the quality of the patient's life and are related to an unfavorable prognosis. By the necessity of development of alternatives, anti PD-1 therapy was followed with an initial stable disease.
The use of anti PD-1 could be valuable to in transit metastases, but further studies are required.

ID 0472

HDAC1/HDAC2/HDAC3 mediated RAD51 and FANCD2 expression contribute to the resistance of melanoma cells to alkylating chemotherapeutics

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Alkylating therapeutics remain part of the standard therapeutic choice for metastatic melanoma. Epigenetic reprogramming, caused by increased histone deacetylase (HDAC) activity arising during tumor formation may contribute to the resistance of melanomas to therapeutics such as temozolomide, dacarbazine, fotemustine and ionizing radiation. Here we report on a mechanism of resistance mediated by class I histone deacetylases (HDACs). We show that melanomas *in situ* contain HDAC1 and HDAC2 and melanoma cell lines overexpress HDAC1, HDAC2 and HDAC3 compared to primary melanocytes, fibroblasts and blood lymphocytes. We further show that inhibition of class I HDACs sensitizes melanoma cells to ionizing radiation, the chloroethylating agent fotemustine and the methylating agent temozolomide, while not sensitizing primary melanocytes. For temozolomide, the sensitization caused by HDAC1, HDAC2 and HDAC3 inhibition was observed in melanoma cells *in vitro* and in a melanoma xenograft model *in vivo*. We provide evidence that class I HDACs protect melanoma cells by stimulating DNA double-strand break (DSB) repair by homologous recombination. Upon HDAC1, HDAC2 and HDAC3 inhibition, the homologous recombination proteins RAD51 and FANCD2 become downregulated, which consequently leads to increased levels of residual DSBs that trigger cell death by apoptosis. Collectively, HDAC1, HDAC2 and HDAC3 contribute to the resistance of melanoma cells to genotoxic therapeutics by stimulating RAD51 and FANCD2 mediated homologous recombination.

ID 0495

The nerve growth factor receptor CD271 is crucial for stem-like properties of melanoma cells and determines drug response

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Drug resistance in systemic and targeted melanoma therapy continues to be a major clinical challenge. Several factors such as oncogenic mutations, the activation of anti-apoptotic signaling or acquisition of a stem-like state which is associated with increased DNA-repair capacity, are involved in acquired drug resistance. Here we demonstrate that nerve growth factor receptor CD271 is a crucial determinant of drug response in melanoma cells. We found CD271 highly expressed in drug-resistant cell lines. We observed that CD271 but not ABCB5 or CD133 expression was increased by drug-induced DNA-damage after 24 hours at low dose (300 nM) and immediately (2 hours) after etoposide treatment. Conversely, drug-resistant cells showed no response to DNA-damaging agents as monitored by levels of phosphorylated H2AX (S139) and p53 (S15).
To assess whether increased expression of CD271 is potentially associated with altered DNA-repair capacity and drug resistance, we performed genome-wide expression analysis of CD271 knock-down and overexpressing cell lines. Comparative analysis of data sets and gene-set enrichment analysis (GSEA) identified several genes regulated in a CD271-dependent manner associated with DNA-repair (e.g. DDB2, RAD51AP1, XPC) melanoma relapse (e.g. RRM2, PTTG1) and drug resistance (e.g. HMMR, AKT3). The functional role of CD271 in melanoma cells was further investigated by knock-down of the gene. CD271 knock-down cells were incapable to respond to DNA-damaging drugs, suggesting a bimodal role of CD271. Although the mechanism of drug-dependent regulation of CD271 is not yet understood, we observed a decreased effect of cisplatin in the presence of sorafenib, suggesting MAPK signaling as a potential regulator of CD271.

ID 0537

PD-1 blockade in nonmelanoma skin cancer

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Introduction: Cancer immunotherapy has become a therapeutic option in various malignancies. Immune checkpoint inhibitors targeting immune escape mechanisms have been approved for the treatment of metastasized melanoma. However, little is known about PD-1 blockade in nonmelanoma skin cancer.
Case Report: We report on a 62-year-old patient with pulmonary metastasized basal cell carcinoma. After 22 months of therapy with Vismodegib disease progression occurred and individual treatment with the anti-PD-1 antibody Pembrolizumab was initiated in 11/2014. Restaging revealed that size of the mediastinal lymph nodes and lung metastases had increased after 4 cycles of Pembrolizumab. However, ACE was elevated and sarcoid-like reaction of the mediastinal lymph nodes was confirmed histologically. Follow-up imaging in 04/2015 and 07/2015 revealed disease stabilization without any further therapy.
The next patient to report on is a 74-year-old woman who was diagnosed with squamous cell carcinoma of the left ear in 02/2014. Despite several operative approaches and radiation therapy, disease progression occurred with ulcerated tumor infiltrating large parts of the facial cutis, pterygoid muscle and scalp. Imaging revealed further progression under first-line systemic treatment with Cetuximab and Celecoxib. In 07/2015 therapy with Pembrolizumab was initiated and after 3 cycles significant reduction of tumor extension already becomes evident.
Conclusion: Our cases provide first evidence for the efficacy of anti-PD-1 antibody therapy in metastasized basal cell carcinoma and advanced squamous cell carcinoma. Further studies are needed to investigate which patients may benefit from treatment with immune checkpoint inhibitors.

ID 0550

LDC-3 and PTPIP51 a winning team!

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Protein tyrosine phosphorylase interacting protein 51 (PTPIP51) is an important protein for proliferation, differentiation, migration, motility, elongation, vascular remodeling, inflammation. PTPIP51 regulates these relevant processes by interacting with proteins at the signal transduction (e.g. EGFR, Erk, Raf), transcription factors (RelA), enzymes (PTP1B, cSrc, Lyn), proteins involved in calcium hemostasis (VAPB), lipid signaling proteins (DAGK) and proteins regulating migration (Rac1). Many tumors have an altered PTPIP51 protein expression as seen in Acute Myeloid Leucemia (AML), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), in glioblastoma, cervical cancer, colorectal cancer, endometrial cancer, head and neck squamous cell carcinoma, melanoma, ovarian cancer, pancreatic cancer, stomach cancer, testis cancer, thyroid, and urothelial cancer.
The development of small molecular effectors presents a highly specific intervention in diseases as new therapy strategies. LDC-3 is a newly developed small molecule, which specifically binds to PTPIP51. We investigated the effects of LDC-3 on the interactome of PTPIP51 in human keratinocytes.LDC-3 can profoundly affect the interactome of PTPIP51. By DPLA (Duolink II proximity ligation assay) we analyzed the PTPIP51 interactome in dependence from LDC3. Changes depended on time and concentrations.This offers the possibility to selectively promote or reduce the interaction profile and affect selectively signal transduction.
Thus, the interaction between PTPIP51 and the small molecule LDC3 probably gives the possibility for therapeutic intervention in many diseases.

Supportive Care

ID 0046

The relevance of nutritional treatment in cancer therapy

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In a pilot study the relevance of nutritional therapy was inquired in a group of specialists and general practitioners via an online survey. Data were collected aboutnutritional topics discussed during physician-patient conversations as well as about the intervention by nutritional counseling and oral nutritional supplements and the experience gained from it. Indicators and thresholds for detecting a malnutrition as well as the time intervals for data collection were also inquired.
The results of the survey demonstrated that nutritional and eating habits are usually subject of physician-patient conversations.The weight development is the most frequently recorded value to detect a malnutrition and defined screening tools are used by half of the participating physicians. Nutritional counseling and medical nutrition are integrated on average very often or often in the therapy by the physicians. Generally it can be statedthat a plurality of therapeutically interventions are used after detection of an occurring weight loss in order to stop the unintentional loss of body weight.
This shows the awareness for the importance of a stable weight trend for prevention of an imminent or treatment of an already existing malnutrition in the course of the therapy ofoncological patients.This pilot study was carried out as part of a bachelor thesis at the university of Weihenstephan-Triesdorf kindly supported by Nutricia GmbH.

ID 0107

Patient Satisfaction during Treatment With Sancuso For CINV

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Introduction: Sancuso transdermal Granisetron has demonstrated efficacy for prevention of CINV in patients receiving multi-day moderately (MEC) to highly emetogenic (HEC) chemotherapy.
Objectives: The objective of this study is to examine patient satisfaction with Sancuso in clinical practice. Final results are presented.
Methods: The study was conducted in 19 oncology units in Germany. Patients scheduled to receive Sancuso for prevention of CINV in MEC or HEC chemotherapy were observed. Patients were asked to record on a visual analogue scale (VAS [0-100]) their 'general satisfaction' with Sancuso treatment. Basic demographic and clinical information was also collected about each patient.
Results: In this study 250 treatment episodes with Sancuso in 169 (55.4% female, 44.6% male) patients have been observed. The median age of the observed population was 66 (range: 31-87) years. The most common diagnoses were colorectal cancer (N=74), breast cancer (N=57), gastric cancer (N=25) and NSCLC (N=24) in more than 70% of the observed cycles. Overall, moderate and high emetogenic therapy was applied in 51.6 and 48.4% of the observed episodes. Complete control was achieved in 84.8%, complete response was seen in 9.2% and in 15 episodes (6.0%) patients had an emetic event. The distribution of response was independent of age groups, tumour diagnoses and chemotherapy applied. The reported satisfaction scores (N=193) showed a median of 92.6 with 83.4% of the values showing a VAS score of ≥80. The patient reported satisfaction in the HEC treated group was significantly lower than in the MEC treated group with a median value of 80.6 vs. 94.9 [$p < 0.001$, Mann-Whitney's U-test].
Conclusions: This is the first analysis of Sancuso based CINV prophylaxis in a daily life setting confirming the pivotal trial's results. The overall patient satisfaction was high, probably due to good control rates for nausea and vomiting.

ID 0171

Evaluation of a Multiprofessional Cancer Care Model as Contribution to Patient Safety

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Objectives: Due to the high toxicity of anti-cancer drugs and the complexity of the medication, patients are at high risk of experiencing adverse events. Patient safety may be enhanced by providing a structured multiprofessional medication management for cancer patients.
Methods: The medication management consists of four multiprofessional care modules composed of a basic module (medication review, interaction check) and specific modules for the management of three common adverse events (nausea and emesis, mucositis, fatigue). All care modules contain a care algorithm, evidence-based recommendations for supportive care and patient information brochures. In a single-arm pilot study the medication management was evaluated by measuring patient-reported symptom load, quality of life and patient satisfaction with information.
Results: For the pilot study 21 cancer patients with any solid tumor were recruited. At time of recruitment the mean age of 14 women and 7 men was 57.6 years. The most frequently applied adverse event module was nausea and emesis (100%) followed by mucositis (91%) and fatigue (62%). Mainly patients with head and neck cancer receiving concomitant radiochemotherapy showed early toxic symptoms of high severity.

Outlook: Our pilot study confirmed the feasibility of the medication management and acceptance by the patients and the multiprofessional care team. Assuming that patients with head and neck cancer may particularly benefit from the care model, a randomized two-arm study will be conducted by focusing on this patient cohort. Primary endpoint of the study will be the frequency and severity of treatment-associated toxicity.

ID 0174

OncoBOS: Biosimilar epoetin alfa in patients with chemotherapy induced anaemia – first analysis from a non-interventional German cohort study

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Introduction: Anaemic cancer patients treated with chemotherapy (CT) may receive epoetin for reducing transfusion requirements and to improve quality of life (QoL). The non-interventional study OncoBOS describes anaemia management in up to 400 cancer pts receiving CT.
Methods: Pts are treated with Epoetin alfa HEXAL® for up to 6 CT cycles. Parameters include anaemia treatment indication, epoetin dose and schedule, other medication, Hb and QoL. For details see DRKS00005282 atwww.germanctr.de. We here report the first planned interim analysis of 196 pts.
Results: Median age was 66 yrs, 66% of pts were female. The most frequent tumour types were breast (35%), lung (13%) or ovarian cancer (9%) and multiple myeloma (7%). CT was palliative in 70%. Investigators stated adherence to CT (70%), QoL (67%) and the reduction of transfusions (59%) as their top-tier indications for treating anaemia. 74% of sites followed German and/or international guidelines on anaemia management. The most frequent epoetin dose was 40,000 I.U. (24% at the 1st injection), followed by 30,000 (18%) and 20,000 I.U. (14%) once per week. 8% of pts received i.v. iron, 3% oral iron and 25% had additional erythrocyte transfusions. Median Hb value at start was 9.7 g/dL and reached 10.6 at week 6. Five thromboembolic events were recorded (2× thrombosis; 3× pulmonary embolism, one possibly epoetin related). Three QoL scales improved by ≥1 (0-10 scales), i.e. to a clinically relevant extent. 98% of pts assessed the use of epoetin alfa prefilled syringes as easy or very easy, 96% the handling of the needle protection system.
Conclusions: QoL improvement was a main indication for anemia treatment. The use of epoetin resulted in the expected increase of Hb and a clinically relevant rise in QoL.

ID 0243

Primary prophylaxis of febrile neutropenia in female patients receiving dose-dense biweekly chemotherapy in the clinical routine using long-acting granulocyte colony-stimulating factors is safe and effective

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Background: Dose-dense q2w chemotherapy (ddCtx) requires primary prophylaxis of febrile neutropenia (FNPP) using granulocyte colony-stimulating factors (G-CSFs). This observational study sought to yield detailed information on the use of long-acting (LA) G-CSFs as FNPP in patients (pts) with breast (BC) or other gynecologic cancers (GC) in the clinical routine.
Methods: 54 pts were included with either 27 receiving pegfilgrastim (P), or lipegfilgrastim (L). In all pts, 1-4 ddCtx cycles (C) were evaluated. G-CSF-related toxicities were scored according to CTCAE 4.03. Hematological efficacy was determined by calculating the mean values for white blood cells (WBC), absolute neutrophil count (ANC), and absolute lymphocyte count (ALC) at baseline and for C 1-4. Additionally, the incidence of FN and G3-4 hematological toxicities during all ddCtx cycles was recorded.
Results: Mean baseline values for WBC, ANC, and ALC were equal in both cohorts. Mean values for WBC, ANC, and ALC [10^9/L] for cohort P vs L were: C 1, 5.88 vs 12.67, 4.06 vs 12.57, 1.06 vs 1.70; C 2, 6.49 vs 12.34, 3.60 vs 10.03, 1.03 vs 1.37; C 3, 4.88 vs 17.10, 3.41 vs 12.37, 0.92 vs 1.55; C 4, 4.99 vs 8.65, 3.18 vs 6.91, 1.11 vs 1.15 with most these differences being statistically significant. The incidence of FN, G3-4 neutropenia, and G3-4 lymphocytopenia was: cohort P, 2.2%, 5.6%, 5.6%; cohort L, 0%, 3.2%, 9.5% with none of these differences reaching statistical significance. C-CSF-related toxicities were generally manageable and did not significantly differ between both cohorts with: fever, 2 (7.4%) vs 1 (3.8%) pts; chills 2 (7.4%) vs 0 (0%) pts; bone pain, 2 (7.4%) vs 4 (15.4%) pts.
Conclusions: LA G-CSFs were safe and effective as FNPP and other severe forms of ddCtx-related leukopenia. The higher hematological efficacy of lipegfilgrastim vs pegfilgrastim did not translate into a higher incidence of side-effects.

ID 0255

The effect of a chemotherapy accompanying 4-week aerobic endurance exercise intervention on incidence and severity of cancer related cognitive impairments in leukemia patients. A randomized controlled trial.

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Cancer related cognitive impairments (CRCI) are frequently observed among cancer patients during and after medical therapy. It is well known that physical exercise reduces cancer treatment specific side effects, such as fatigue and general physical decline, resulting in an improved quality of life. Results from animal studies suggest that physical exercise might be a promising supportive therapy to counteract CRCI as well. Initial results in cancer patients support this presumption. However, existing studies in the context of CRCI and physical exercise have severe methodological limitations regarding control groups, assessments and measurement time points.
In the present randomized controlled trial, patients suffering from myelodysplastic syndrome or acute myeloid leukemia (n = 66) will be allocated to an aerobic exercise group (3×/week aerobic exercise), a placebo control group (3×/week stretching) and a passive control group (usual care). Study participants will be tested before starting their four week induction chemotherapy (including Anthracycline and Cytarbin), after completing chemotherapy as well as four weeks after completing chemotherapy. As recommended by the international cancer and cognition task force, a battery of objective neuropsychological assessments will be executed to determine cognitive alterations. Furthermore, electro encephalographic recordings (EEG), serum levels of neurotrophic factors, self-perceived cognitive performance and potential confounders (IQ, fatigue, depressions, post-traumatic stress) will be evaluated.
This RCT is the first to study the effect of an aerobic endurance exercise intervention on CRCI at current methodological state of the art. We hope that this study will contribute to a better understanding of CRCI and will give first solid hints if aerobic exercise should be recommended to counteract CRCI.

ID 0268

Internet as an appropriate medium for training support in cancer patients – a systematic review of the literature

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The use of the Internet as source of information is getting more and more important with studies already showing effective educational transfer via computer-based programs. Positive effects of training before, during and after treatment of cancer are well described in the literature, while suitability of Internet-based approaches with this regard is still matter of debate. This review reflects upon computer-based exercise intervention studies with cancer patients.
A systematic literature search was conducted using MEDLINE and Web of Science. Studies were applicable, if they had performed an Internet-based physical training with cancer patients. Information was extracted regarding participant characteristics, type of exercise, form of Internet application used, and primary outcomes.
A total of 12 studies met the requirements. These studies involved the use of common online pages, workshops and online diaries using pedometers. The intervention periods varied from 6 to 24 weeks. Amongst others, primary endpoints were fatigue, Quality of Life, and minutes per week of vigorous exercise.
Online platforms enable patients to realize supported training sessions in their familiar domestic environment, enabling a higher level of independence. Staff members can easily spread relevant material to the patients. Besides training support, community access plays a crucial role. Forum and chat function could improve motivation and may therefore help to achieve a higher level of compliance.
So far the few studies conducted are to heterogeneous with regard to outcome measures, methodology, and can only provide an orientation for future studies aiming at improving primary endpoints in cancer patients.

ID 0323

Influence of a single exercise session on natural killer cell cytotoxicity and tumor infiltration in preoperative esophageal carcinoma patients – a study protocol

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Natural killer cells (NK-cells), which represent an essential part of the endogenous tumor defense, have previously been described to be strongly influenced by exercise. However, studies in that field are limited to blood analysis, which may not reflect the NK-cell-tumor interaction in vivo.
For this purpose, the present monocentric randomized controlled trial investigates the impact of a single bout of endurance exercise prior to surgery on NK-cell function as well as NK-cell tumor infiltration in 24 esophageal carcinoma patients. The primary outcome is NK-cell-cytotoxicity. Secondary endpoints are the NK-cell distribution in respect to their subgroups and the number of intratumoral NK-cells. Patients of the intervention group (n = 12) perform a single bout of endurance exercise, whereas participants of the control group (n = 12) receive a low intensive stretching program. Before (t0), after (t1) and 12 hours after (t2) the intervention blood samples are collected. Tumor tissue is extracted by surgery immediately after t2. NK-cells are isolated from blood samples and are further analyzed for cytotoxicity against the tumor cell line K562. Additionally, flow cytometry analysis is conducted to determine NK-cell distribution as well as NK-cell subsets. Furthermore, tumor tissue will be stained for CD56 and CD57 to count intratumoral NK-cells.
This study is the first trial which focusses on the influence of a single bout of exercise on NK-cell-cytotoxicity in cancer patients. Further on, this is the first study which investigates intratumoral immune cells in respect to exercise. We assume that the results of this study will expand the mechanistic knowledge of how exercise may interact with the immune system to counteract cancer diseases.

ID 0402

Comparing different supportive measures – how cancer patients profit from exercise and stress management

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There are various supportive measures helping cancer patients to cope with their disease. The goal of our research was to compare the effects of an exercise intervention to a stress management intervention on physical activity (PA), perceived stress and subjective health.
Cancer patients [N=72; 54% female; M=56 years, SD=12.34; most with breast or colon cancer (34%, 15%)] treated in an outpatient setting were enrolled in the MOTIVACTION study, a 4-week randomized intervention (1hr counseling followed by weekly phone calls), with pre-test (T1), post-test (T2), and a 10-week follow-up (T3). The exercise intervention emphasized self-regulatory strategies; the stress management intervention consisted of coping and relaxation techniques. Sixty-seven patients remained in the study and completed the SQUASH assessment of PA, perceived stress (Distress-Thermometer) and self-ratings of global health. PA was validated by Actigraph accelerometry.
At T2, 46% of the patients in the exercise group, and 19% of stress management patients met the PA guidelines (>150min/week; $\chi^2(1)=5.51$, $p = .019$). At T3, participants in the exercise intervention maintained their exercise level (46%), but also 31% of the stress management patients met the guidelines, rendering the group difference at T3 insignificant. Patients of both intervention groups reported similar and significant reductions in perceived stress from T1 to T3. With regard to ratings of global health, the stress management intervention had a positive and persisting effect.
In sum, both supportive measured turned out to be effective. Interestingly, the stress management intervention not only reduced stress and increased subjective health, but also helped to increase physical activity.

ID 0513

Thromboembolic events in hematological/oncological patients: Diagnosis, treatment patterns and adherence to treatment guidelines in clinical practice

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Research Question: Cancer is a well known risk factor for venous thromboembolism (VTE). According to guidelines, patients (pts) with cancer and VTE have to be treated differently compared to VTE patients without cancer. Our objective was to compare clinical reality patterns with treatment guidelines.
Methods: Single center retrospective database analysis using the university hospitals electronic data capturing system and patient charts. Observation period was one year (2013). Inclusion criteria: ICD corresponding to VTE (I.26, I.80, I.81, I.82, I.67.6). Age >18 years, inpatient stay, VTE diagnosed and treated at the university hospital of Munich, department of oncology/haematology.
Results: 85 patients could be identified. Mean age was 65,7 years, 50% were male. 74% of pts suffered from a solid tumor, 26% from a hematological disease. In 7% of patients VTE diagnosis occurred before tumor diagnosis. 14% of VTEs have been diagnosed coincidently during staging. VTE prophylaxis has been documented for 32% of pts. 28% of pts were treated with UFH, 70% with low molecular weight heparin (LMWH), 1%

with phenprocoumon, 1% of pts received no drug treatment because of contraindications, 94% received physiotherapy and for 67% compression stocking were prescribed. Adherence to guidelines 77%-91%.
Conclusion: Results show that in clinical routine LMWH is mostly used as standard of care as recommended in clinical guidelines. The high number of VTE events, the number of coincidently diagnosed events and the low number of pts on primary prophylaxis support the notion that patients with cancer should be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter.

ID 0515

Analysis concerning responsibility for rehabilitation sports in oncology throughout Germany on federal state level

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Background: Due to numerous studies that prove the positive effects of exercise therapy especially on side effects of cancer treatments and therefore quality of life in cancer patients, appropriate physical activity programs should be available for each person concerned. To assure this, lots of sports clubs in Germany provide cancer sport groups. Given that organisation is assumed by different institutions in doing so, it should be figured out who is the contact for the individual states.
Methods: By the use of an e-mail- and telephone- survey with 33 different associations, most of them regional sports associations and disabled sports federations, information on the responsibilities, the number of listed cancer sport groups at land level and lastly the currentness of data had been compiled.
Results: The estimated value of listed cancer sport groups nationwide is at 1.631. There are considerable differences shown in the responsibility of exercising and the number of participating organizations of cancer rehabilitation in each state. Also the refresh period of the published offers is considerable varying.
Discussion: A lack of cooperation among the individual organizations leads to imprecise data concerning the number of cancer sports offers. In addition to that differences in each state regarding responsibility shape the search for offers confusing. Therefore it is absolutely essential to seek for an explicit competence at state level and a consistent provided search function for the appropriate groups.

ID 0516

The effects of sensorimotor training and whole body vibration on patients suffering from chemotherapy-induced peripheral neuropathy

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Chemotherapy-induced peripheral neuropathy (CIPN) is a highly prevalent and clinically relevant side-effect of chemotherapy. Depending on the agent, 60-90% of patients are affected. The motor and sensory symptoms, not only severely diminish patients' quality of life, but represent a decisive limiting factor for medical therapy, consequently affecting the clinical outcome. To date approved and effective treatment options are lacking. Promising results have now been achieved with specific exercise interventions. Our objective was therefore, to analyze the effects of sensorimotor training (SMT) as well as whole body vibration (WBV) on the relevant side-effects of CIPN.
We conducted a three-armed randomized, controlled trial, to evaluate the feasibility and effects of SMT and WBV on patients with a neurologically diagnosed CIPN. Patients (N=39) were randomized either into one of the intervention groups or a control group and matched by gender and age with a healthy control. The supervised exercises had to be performed twice a week for 6 weeks. Primary objective was the subjective improvement of CIPN related symptoms. Secondary endpoints were balance control, nerve conduction velocity and amplitude, peripheral deep sensitivity, Achilles- and Patellar tendon reflex, proprioception, quality of life, CIPN-related pain and the level of activity.
Both the SMT and WBV group profited. They were able to reduce symptoms and regain functions comparable to healthy controls. Both groups showed improved reflexes, peripheral deep sensitivity and quality of life. The interventions targeted slightly different symptoms. SMT induced higher performance in balance control while WBV was more efficient regarding peripheral deep sensitivity and the reduction of pain.
We conclude that SMT and WBV are not only feasible in patients with CIPN but also effective to reduce CIPN related Symptoms.

ID 0521

MeMa pilot study – Effects of an exercise program for patients with metastatic breast cancer

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Background: The improvement of medical treatments for advanced cancer patients can prolong a patient's life time. This legitimizes the need of measures to maintain or improve their quality of life. It can be reached by reducing tumor- and treatment-related side effects and by increasing the physical fitness level. However a lack of knowledge still exists.
Methods: This single armed trial was examining the feasibility of an exercise program for women with metastatic breast cancer. Within a supervised intervention of twelve weeks 11 women (age: 38-70 yrs.) participated in a 45-minute combined resistance and endurance training on medical exercise machines twice a week. Physical performance (spiroergometry), muscle strength (h1RM), fatigue (MFI 20), anxiety and depression (HADS) and quality of life (EORTC QLQ-C30, BR 23) were evaluated.
Results: The results showed that the exercise-intervention was feasible and could significantly reduce fatigue, side effects from systemic therapy and furthermore significantly improved physical fitness. Quality of life was improved, but did not show a statistic significance. There were no influences on anxiety and depression. Three women did not complete the intervention.
Discussion: The feasibility of the MeMa-Pilot-study was confirmed, furthermore the study showed positive effects on physical and psychological level. Limitations have been observed in the missing control group, the small number of patients and the realization and determination of the parameters. Based on the positive influence of exercising in this study, further studies must be developed.

ID 0529

Routine nutritional evaluation and subsequent initiation of a case and finding adapted nutritional therapy in the clinical-surgical daily - "Standard Operating Procedure" (SOP) -

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Initiation: The aim is, with increased nutritional / metabolic risk as early as possible, as such, to recognize and adequately treat nutritional medical patients, since the metabolic risk of inpatient treatment has a significant impact on morbidity, hospital stay and mortality. For this purpose a standard operating procedure ("SOP") on the topic "Nutrition evaluation and therapy" developed.

Materials and Methods: SOP-Flow-chart
Results: The early detection of undernourishment and malnutrition with their timely treatment has undoubtedly Budget relevance. The costs for the treatment of malnutrition, included also complications, are annually at 9 billion euros in Germany, which the published in 2007 CEPTON study calculated based on the available scientific literature. The introduction of the DRG system, it is important for the nutritional medicine to illuminate next to the medical and the economic point of view. Undernourishment and malnutrition are associated with an increased resource requirements for a doctor (hospital).
Summary: Undernourishment and malnutrition are relevant risk factors in hospitals and clinics, which affect essential clinical parameters, especially the mortality, morbidity, length of hospital stay, complications, the treatment benefit and – not to be underestimated – the quality of life of patients.
In order to achieve a successful treatment, early, selective detection of nutritional status is necessary to enforce the guideline-based implementation of the developed concepts based on the nutritional levels regimen. Success guaranteed only the consistent implementation of established nutritional concepts, which aim to preserve the energy and protein balance of the patient and to improve.
What can be achieved with the nutritional medicine, causes no single drug.

ID 0534

Corneale confokale Mikroskopie in der Frühdiagnostik Chemotherapie induzierter Neuropathie (CIN) – eine Pilotstudie

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Hintergrund Die corneale confokale Mikroskopie (CCM) erlaubt beim Diabetes mellitus und der Sarkoidose sensitiver als andere Methoden (wie z.B. die quantitative sensorische Testung (QST) oder Elektroneurographie die Frühdiagnostik einer Polyneuropathie (PNP). Da nach Gabe platinhaltiger Chemotherapeutika eine Chemotherapie-induzierte PNP (CIN) häufig ist und eine Früherkennung einer CIN sinnvoll wäre, untersuchten wir die Häufigkeit abnormaler Befunde bei der CCM in einer Pilotstudie mit Patienten mit und ohne klinisch manifeste PNP nach Chemotherapie.
Methodik Eingeschlossen wurden 18 Patienten zwischen 50 bis 79 Jahren überwiegend mit Lungenkarzinom und gastrointestinalen Tumoren, meist 3 bis 24 Monate nach einer Chemotherapie mit platinhaltigen Chemotherapeutika. Erfaßt wurden klinisch der Neuropathiescore, die Detektionsschwellen für Kälte, Wärme und mechanische Reize an Fuß und Hand mittels QST nach DFNS-Protokoll sowie die Länge, Dichte und Verzweigungsdichte der cornealen Nerven mittels unilateraler CCM. Der Pearsons-Korrelations-Koeffizient wurde für die Korrelation linearer Beziehungen berechnet.
Ergebnis Bei 12 von 18 Patienten (15 Männer) mit PNP (5 schmerzhaft) zeigte sich im QST ein Large-Fiber-Funktionsverlust. 77% der CCM waren pathologisch, darunter auch bei 5 der 6 Patienten ohne PNP. Die Vibrationsschwelle korrelierte enger mit allen CCM-Parametern (r: 0,43) als die thermischen Schwellen.
Diskussion Obgleich bei der CIN der Funktionsverlust der Aβ-Fasern dominiert (Geber 2013), rarefizieren offenbar, wie bislang nur für Small-fiber Neuropathien beschrieben, auch hier frühzeitig die Nerven in der Cornea. Daher könnte die risikoarme, nicht-invasive CCM für die Früh- und Verlaufsdokumentation einer Neuropathie auch in der Onkologie Bedeutung erlangen.

Surgical Oncology

ID 0037

Comparing proliferation, apoptosis and angiogenesis in "one-stage liver resection" (OSLR) vs. "in-situ split" (ISS) in colorectal liver metastases (CRLM)

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Background: ISS-liver resection (a.k.a. ALPPS) is a two-stage procedure to convert irresectable liver malignancies into a resectable stage. Promising hypertrophy rates of the liver remnant were reported within a few days. The aim of this study was to assess the impact of ISS on tumor proliferation, apoptosis and angiogenesis.
Methods: 6 patients with CRLM undergoing ISS procedure were matched with 11 patients undergoing OSLR regarding size, number of metastases, preoperative chemotherapy, time of appearance, localization and TNM-stage of the primary tumor and patients' characteristics (age, gender). Tumor specimens were immunohistochemically examined for vascularization (CD31), apoptosis (TUNEL, Casp-3), proliferation (Mib-1) and αSMA-expression at x40 magnification at the tumor invasion front.
Results: Matching criteria were not different between patients undergoing ISS and OSLR. Vascularization (CD31 vessel area; $p = 0.1485$), proliferation (Mib-1; $p = 0.2442$) and αSMA-expression ($p = 0.2054$) did not significantly differ between the two groups, although a trend towards less proliferation and αSMA-expression upon ISS was observed. Concerning apoptosis, Casp-3 staining showed significantly less apoptotic cells in the ISS group ($p < 0.0001$) but this was not confirmed by TUNEL staining ($p = 0.7344$).
Conclusion: No significant difference between ISS and OSLR were found regarding vascularization, proliferation and αSMA-expression. The difference in Casp-3 was not confirmed in TUNEL staining. Although results should be interpreted carefully due to low patient numbers and potential differences in tumor biology between both groups, this study does not support the concern that ISS stimulates tumor progression.

ID 0122

Surgery in recurrent cholangiocarcinoma (CCA) – single centre experience

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Background: Even after curative resection, recurrence (intra- and/or extrahepatic) is the major problem in patients with cholangiocarcinoma (CCA). Due to diffuse recurrence, chemotherapy is usually the only therapeutic option. However, in localized disease, the role of surgery is unclear so far.
Material & Methods: We retrospectively analysed patients that underwent surgery for recurrent CCA between 2005 and 2015 in our centre. Prior to the operation, all patients were discussed in an interdisciplinary tumour board.
Results: 27 (11 female, 16 male) patients with median age of 65 years (range 37-71) underwent surgery. Median time from the first operation to recurrent surgery was 15.5 months (3.5-87). In 10 patients, R0-resection of recurrent CCA was possible and an R1-situation was achieved in 8 patients. 2 patients underwent R2-resection and in 7 patients no resection was possible (exploration). Postoperative complications >°IIIa occurred in 4 patients (14.8%). Median postoperative overall survival (OS) after re-

current resection was 20.7 months (2.1-68.1). Upon R0-resection, median disease free survival was 11 months (2.7-30.5). Median OS was 29.8, 20.7, 10.5, 6.4 months for R0-, R1-, R2-resection and exploration, respectively.
Conclusion: Since R0/R1-resection provides acceptable OS, patients with localized recurrence of CCA might be considered for re-resection upon discussion in an interdisciplinary tumour board.

ID 0152

Prospektive nicht-interventionelle Studie zur Untersuchung der Auswirkung der radikalen Prostatektomie auf Lebensqualität (QoL) und Überleben von Männern mit ossär oligometastasiertem Prostatakarzinom (ProMPT-Studie). Erste Ergebnisse.

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Einleitung: Die Rolle der radikalen Prostatektomie (rP) bei Patienten mit einem primär ossär metastasiertem Prostatakarzinom (PCa) bleibt unklar. Ziel dieser nicht-interventionellen, prospektiven Studie ist es, den Verlauf sowie die Lebensqualität von Patienten zu untersuchen, die sich aufgrund eines ossär metastasierten Prostatakarzinoms einer rP unterzogen.
Material und Methoden: Zwischen 02/2014 und 01/2015 wurden 32 Männer im Rahmen der ProMPT Studie operiert. Eingeschlossen wurden Patienten mit max. 3 Knochenmetastasen (Kmets), PSA <150 ng/ml, klinisch resektablem Lokalbefund. Präoperativ, 3 Wochen nach rP sowie alle 6 Monate erfolgt die Dokumentation von Krankheitsstadium, QoL und Bestimmung von Biomarkern.
Ergebnisse: Das mediane Alter der Patienten betrug 66 (IQR 63–72) Jahre, mittlerer PSA Wert 32 (IQR 10–56) ng/ml, mediane Anzahl von Kmets: 1 (IQR 1-2). Die Komplikationsrate (Clavien) war in 25% Grad II, 19% IIIa, 16% IIIb. Histopathologisch fanden sich ein pT2c, pT3a, pT3b und pT4 Tumor in 9%, 25%, 53% und 13%. Die R1 Rate lag bei 75%, 72% waren pN+. Nach einem mittleren Follow-up von 3 Monaten entwickelte sich bei 2 Patienten eine Kastrationsresistenz mit metastatischem Progress.
Schlussfolgerung: Die rP bei ossär metastasierten PCa Patienten mit limitierter Tumorlast bleibt eine individuelle Therapieoption. Ca. 1/5 der Patienten zeigten ein organbegrenztes, nodal negatives Stadium, was möglicherweise auf eine nicht unerhebliche Rate an Fehldiagnose der Kmets durch bildgebende Verfahren hinweist. Ein-Jahres QoL Bestimmungen sowie Langzeit-Follow-up Daten sind abzuwarten, um diesen Therapieansatz abschließend bewerten zu können.

ID 0153

Prävalenz von zirkulierenden Tumorzellen bei Patienten mit hormonnaivem, ossär metastasiertem Prostatakarzinom (PCa). Erste Ergebnisse der Biomarkeranalyse aus der ProMPT-Studie.

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Einleitung: Die Präsenz (<5 vs. >5 Zellen) und dynamische Veränderungen von zirkulierenden Tumorzellen (CTC, CellSearch®-System, Veridex, Janssen Diagnostics, LLC, Raritan, NJ, USA) sind etablierte Biomarker zur Therapieüberwachung vom Patienten mit kastrationsresistentem, metastasiertem PCa unter Systemtherapie. Ziel dieser Studie war es, die Rolle der CTC beim hormonnaiven, ossär metastasierten PCa zu untersuchen.
Material und Methoden: Zwischen 02/2014 und 01/2015 wurden 32 Männer im Rahmen der ProMPT Studie mit einem ossär oligometastatischem PCa durch radikale Prostatektomie behandelt. Präoperativ, 3 Wochen nach rP sowie alle 6 Monate erfolgt die Dokumentation von Krankheitsstadium, QoL sowie eine Bestimmung von Biomarkern, einschließlich der Bestimmung der der CTC im Vollblut gemäß CellSearch®-Assay.
Ergebnisse: Das mediane Alter der Patienten beträgt 66 (IQR 63–72) Jahre. Der mittlere PSA Wert beträgt 32 (IQR 10–56) ng/ml. Die mediane Anzahl von Kmets beträgt 1 (IQR 1-2). Präoperativ waren 48,4% der Patienten CTC positiv, mit einer medianen Anzahl von 1 CTC (1-4). Drei Wochen postoperativ war die Rate der CTC leicht angestiegen (57% positiv, median 1, 1-9). Nach einem mittleren Follow-up von 3 Monaten entwickelte sich bei zwei Patienten eine Kastrationsresistenz. Bei diesen Patienten konnte eine Konversion von 0 auf 3 bzw. 1 auf 17 CTC beobachtet werden, begleitet von einem PSA – Anstieg auf 16,3 bzw. 102 ng/ml.
Schlussfolgerung: 48,4% der Patienten mit hormonnaivem, primär ossär metastasiertem PCa weisen CTC im Blut auf, allesamt < 5 Zellen mit einem diskreten Anstieg postoperativ auf 57%. Auch beim hormonnaiven PCa scheint eine Progression durch Anstieg der CTC begleitet zu sein. Langzeitanalysen müssen abgewartet werden, um die Rolle der CTC bei der weiteren Tumorprogression abschliessend bewerten zu können.

ID 0415

ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy) Technique in Our Group of Patients

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Introduction: Increasingly, we see patients with extensive metastatic liver disease and we are trying to find an effective therapy for them. The limiting factor of major surgical liver resection is to maintain an adequate function of the liver parenchyma. Therefore, multi-stage interventions were created One of these techniques applying consecutive steps is ALPPS.
Material and Methodology: Since August 2013 we have operated 9 patients by ALPPS technique based on the recommended criteria for this operation. 5 patients were indicated for metastases of colorectal cancer, 2 patients of gallbladder carcinoma, one patient for metastasis of leiomyosarcoma, and one for cholangiocellular carcinoma. 7 patients underwent a complete two-stage ALPPS surgery, 2 patients underwent only the first stage. The indication for ALPPS was evaluated, operation technique, complications, survival, and recurrence. Our results were compared with the results of international ALPPS register (NCT01924741).
Results: The 30-day mortality was 44.4%, 55.5% morbidity according to Clavien Dildo. Currently 4 patients are still alive. One patient died of other cause (suiciduum). In the group of surviving patients, one patient had recurrence in the liver and also three new metastases occurred in the lungs at an interval of three months from the OP. Three patients are without recurrence with DFI 18, 16, and 11 months.
Conclusion: The results of our group correspond with the data of the international register. For the last three years there has been an effort to define indication criteria, pre-operative monitoring, timing of both stages, and modification of the technical aspects that would contribute to the improvement of the operation results. The findings of the first consensus conference ALPPS from February 2015 will be summarized as well. The technique of ALPPS is suitable for a highly selected group of patients.

Translational Oncology

ID 0090

Targeting MYC in colorectal cancer by inhibition of translation initiation

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Deregulated expression of MYC is a driver of colorectal carcinogenesis, suggesting that inhibiting MYC may have significant therapeutic value. The PI3-kinase and mTOR pathways control MYC turnover and translation, respectively, providing a rationale to target both pathways to inhibit MYC. Surprisingly, inhibition of PI3-kinase does not promote MYC turnover in colon carcinoma cells, but enhances MYC expression since it promotes FOXO-dependent expression of growth factor receptors and MAPkinase-dependent transcription of *MYC*. Expression of a active 4E-BP1(4A) is sufficient to reduce MYC levels. But inhibition of mTOR fails to inhibit translation of MYC, since levels of 4E-BPs are insufficient to fully sequester eIF4E and since an IRES-element in the 5'-UTR of the MYC permits translation independent of eIF4E. A small molecule inhibitor of the translation factor, eIF4A, silvestrol, bypasses the signaling feedbacks, reduces MYC translation. Silvestrol significant reduce the amount of ribosomes bound to MYC mRNA but not to control mRNAs as Beta Actin. Additionally Silvestrol inhibits tumor growth in a mouse model of colorectal tumorigenesis, reduces MYC protein levels but leaves MYC mRNA unchanged. Suggesting a specific inhibition of MYC translation by Silvestrol. We propose that targeting translation initiation is a promising strategy to limit MYC expression in colorectal tumors.

ID 0092

The impact of radical radiotherapy on circulating levels of heat shock protein 70 (HSP70) and its correlation with the hypoxia-related proteins osteopontin (OPN), vascular-endothelial growth factor (VEGF) and carbonic anhydrase IX (CAIX) in patients with non-small-cell lung cancer (NCSCLC)

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Introduction: Elevated circulating levels of stress-inducible heat shock protein 70 (HSP70) and the hypoxia-related proteins osteopontin (OPN), vascular endothelial growth factor (VEGF) and carbonic anhydrase (CA) IX were reported for many cancer entities. A relation with radioresistance and potential role as a tumor biomarker has been suggested for HSP70. We previously demonstrated an additive prognostic effect of OPN-VEGF-CAIX co-detection in radical radiotherapy (RT) of NSCLC and showed that OPN level changes after RT predict prognosis. In this study, we evaluated the impact of RT on HSP70 levels and their correlation with OPN, VEGF and CAIX.
Methods: Blood samples were prospectively collected of 98 consecutive patients with inoperable NSCLC and indication for radical RT (n = 55, University Halle-Wittenberg; n = 43, Technical University Munich). A HSP70 control group of 126 healthy donors was used. Plasma/serum concentration of HSP70, OPN, CAIX and VEGF was determined by ELISA before and 4 weeks after RT (OPN, HSP70).
Results: Basal HSP70 was higher in NSCLC patients compared to controls ($p < .001$). HSP70 levels before and after RT correlated ($p < .0001$) and declined during RT ($p = .01$). Basal HSP70 correlated with OPN ($r=.3$, $p = .01$), VEGF ($r=.4$, $p = .002$) and we found high basal HSP70 in patients with high baseline OPN ($p = .009$) and VEGF ($p = .02$). Basal HSP70 correlated with gross tumor volume ($r=.3$, $p = .03$) which was higher in patients with elevated HSP70. HSP70 levels after RT were associated with therapy response in M0 patients ($p = .01$; AUC .76, $p = .01$).
Conclusion: This data suggests an impact of RT on HSP70 levels which may serve as a potential biomarker in NSCLC, indicating viable tumor mass after RT which influences therapy response. The correlation with hypoxia-related proteins supports further prognostic evaluation of HSP70 in conjunction with OPN, VEGF and CAIX.

ID 0128

Characterization of infiltrating B cells in human colorectal and kidney cancer

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Introduction: It is now recognized that B lymphocytes are phenotypically and functionally heterogeneous. In addition to their essential role as antibody producing B cells, they serve as antigen-presenting cells, contribute to immunoregulation and represent an important source of cytokines and chemokines. Although several subpopulations have been identified, to date there is a lack of a phenotypically well-defined antigen-presenting B-cell subset. With the help of the CD40-system was possible to identify the phenotypic characteristics of the highly immunostimulatory CD40-activated B cells. After prolonged stimulation with CD40 and pro-inflammatory cytokines, B cells up-regulate the co-stimulatory molecules CD80 and CD86 and down-regulate the complement receptor CD21. Searching for a similar phenotype in the peripheral blood of healthy donors was possible to identify a small population of $CD21^{low}$ $CD86^{pos}$ B cells with an activated, class-switched-memory phenotype and potent immunostimulatory capacity.
Methods and Results: Flow cytometric analysis of 22 tumor specimens from patients with colorectal cancer revealed that $CD21^{low}$ $CD86^{pos}$ B cells were enriched within the tumor tissue compared to the peripheral blood of colorectal cancer patients and healthy controls. Preliminary data on kidney tumors showed that more than 60% of the infiltrating-B cells are of the $CD21^{low}$ $CD86^{pos}$ phenotype.
Conclusions: The role of this novel B-cell subset in peripheral blood from healthy donors seems to be of antigen presentation. Specially, in the tumor microenvironment of kidney tumors the majority of the B cells were of the $CD21^{low}$ $CD86^{pos}$ phenotype. This suggests that this subset might be playing a role in the tumor biology.

ID 0132

MACC1 interacts with growth factor associated receptor tyrosine kinase signalosomes

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Colon cancer is the third most common cancer worldwide. Overall survival severely drops with the development of distant metastases. Our group identified the novel gene MACC1 as metastasis inducer and prognostic biomarker for colorectal cancer. MACC1 acts as a key regulator of HGF (hepatocyte growth factor)/Met signaling engaging cell proliferation, migration, invasion and metastasis. Recently, we also reported that tyrosine phosphorylation of MACC1 increases the metastatic capability of colorectal cancer *in vitro* and *vivo*. Based on these findings, we want to identify the role of MACC1 and its phosphorylation in signaling pathways. A mass spectrometry-based approach identified promising interactions of MACC1 with important signaling proteins, *e.g.* GRB2 and SHP2. All the suggested pTyr-dependent bindings have been confirmed by co-immunoprecipitation. We performed site-directed mutagenesis at the respective

tyrosine sites to test the functional abilities of these cell clones in proliferation, migration, invasion and colony formation assays. First results indicate a role of MACC1 in important receptor tyrosine kinase signalosomes, which contributes to further understanding of its molecular features and, therefore, emphasizes its importance in CRC signaling. It might also reveal possible drug intervention points for future cancer treatment.

ID 0150

Platelet proteins Clusterin, Cofilin-1 and Glutathione synthetase as biomarker for early detection of colorectal cancer

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Introduction: Colorectal cancer (CRC) is one of the most frequent malignancies in the western world. Early tumor detection and intervention are important determinants on CRC patient survival. During tumor proliferation, platelets store and segregate proteins, which therefore could potentially serve as screening markers for early malignancy.
Material and Methods: Protein profiles of platelets between healthy volunteers (n = 12) and patients with early- (n = 7) and late-stage (n = 5) CRCs were compared using multiplex-fluorescence two-dimensional gel electrophoresis. Differences in protein levels between these groups were analyzed with SameSpots® software followed by Principle Component Analysis. Proteins of interest were identified by mass spectrometry. Target proteins were validated by multiplex-fluorescence-based Western blot analyses using an independent cohort of platelet protein samples [healthy controls (n = 15), early CRCs (n = 15), late CRCs (n = 15)].
Results: By inter-group comparison, 39 differentially expressed protein spots were detected ($p < 0.05$) between healthy controls and patients with early- and late-stage CRCs. Of those, Clusterin was lower expressed especially in early-stage CRCs, whereas Cofilin-1 and Glutathione synthetase (GSH-S) were present at higher levels in platelets from early-stage CRC patients compared to control individuals. These expression characteristics were confirmed by Western blot analyses in an independent cohort.
Conclusion: Different protein levels within platelets distinguishing healthy controls from patients with early- and late-stage CRCs were identified. The potential of Clusterin, Cofilin-1 and GSH-S as platelet biomarkers, in particular for early detection of CRC, should be confirmed in a prospective multicenter trial.

ID 0151

Molecular profiling of single circulating tumor cells (CTCs) in ovarian cancer patients using multi-marker gene panel analysis

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CTCs are present in approx. 20% of ovarian cancer patients (oc pts.) at primary diagnosis and were shown to correlate with decreased overall survival. Considering that CTCs with epithelial-mesenchymal-transition (EMT)- or stem-cell like (sc) traits are supposed to be involved in metastatic progression/recurrence, we established a multi-marker panel including epithelial, EMT- and sc associated transcripts for molecular characterization of single CTCs.

Dual priming oligonucleotide primers for three independent multiplex RT-PCR panels were designed for transcripts, associated with epithelial- (EpCAM, Muc1, CK5, CK7), EMT (N-Cadherin, Vimentin, Slug, CD117, CD146, CD49f, Snai1) and sc traits (CD44, ALDH1A1, Nanog, SOX2, Notch1, Notch4, Oct4, Lin28). For single cell analysis OvCar-3 cells were spiked into blood of a healthy donor and enriched by ficoll based density gradient centrifugation. Enriched cells were labeled with directly conjugated antibodies specific for cytokeratin (CK/EpCAM(FITC) /CD45 (Cy5) and stained with DAPI. CK^{pos} and/or $EpCAM^{pos}$, $CD45^{neg}$ single cells were isolated (CellCelector, ALS), RNA was extracted, reversely transcribed and examined with our multi marker gene panel. PCR-products were assessed by capillary electrophoresis.
We have established a multi-marker panel for the detection (epithelial markers) and characterization (sc and EMT markers) of single CTCs. As proof of principle we analyzed single CTCs from 3 oc pts. and found a distinct heterogeneity between these single cells regarding expression of all tested transcripts, except for Muc-1. CTCs were sc^{pos} in 27% & $EMT^{pos.}$ in 87%. Our goal is to investigate single CTCs with these panels *before, during and after* therapy of OC patients.

ID 0164

Inhibition of microparticle-induced PAR-activation by Rivaroxaban

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Introduction: Epithelial and tumor cells upon activation, e.g. under inflammatory stress, actively release microparticles/microvesicles (MPs).
Our previous work indicates that the molecular structure of MPs, especially TF associated complexes formed on their surface, might be decisive for the biological pathways activated by MPs.
Systemically released MPs seem to be responsible for the cancer associated pro-thrombotic state of patients. Also, they are able to activate tumor cells through the PAR/ERK-signaling pathway.
Methods: Human ovarian carcinoma OvCar3 cells were stimulated (TNFα and TGFβ) to induce active formation of MPs. MPs were isolated from the cell culture supernatant using a recently published method (Gieseler et al., Cell Bio Int, 2014), counted (FACS) and characterized (ELISA). Tumor cell stimulation (ERKphos, migration, proliferation) was determined after formation of different TF complexes, especially after supplementation with FXa.
Results:

4. Tumor cells release high amounts of MPs under inflammatory stress as can be found in the tumor micro environment
5. MPs from tumor cells without contact to the plasma coagulation system present TF on their surface, but no association with FV, FVII, FX
6. PAR/ERK activation by MPs from tumor cells is significantly increased by adding the coagulation factors FXa and FVa
7. The importance of active FX association is shown by inhibitory experiments with rivaroxaban

Conclusion: Possible clinical relevance is shown by supplementary characterization of MPs isolated from ascites of ovarian carcinoma patients, which also contain high amounts of TF-presenting MPs that show a divergent co-expression of FXa. MP diversity could be a factor for clinical phenomena such as thrombosis or tumor progress. The inhibitory effect of rivaroxaban in vitro should be explored regarding its clinical relevance

ID 0169

D,L-Methadone: A sensitizer for conventional anticancer therapies?

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Introduction: Drug resistance is a major limitation for successful treatment of cancer. Therefore, novel strategies are needed to improve therapeutic success. Cancer cells overexpress opioid receptors. Opioid receptors are the target of the therapeutic opioid D,L-methadone. In this study, we analyzed different solid tumors *in vitro*, in mouse models and in cancer patients *in vivo* after D,L-methadone treatment in addition to conventional therapies.
Methods: Different cancer cells of breast, ovary, pancreas, prostate, liver, lung, brain were treated with D,L-methadone alone or in combination with conventional therapies. *In vitro,* cell death and molecular cell death mechanisms were analyzed after D,L-methadone and/or anticancer drug treatment. Different cancer patients were treated with D,L-methadone in combination with conventional therapies. In patients, tumor markers were measured and tumor growth was analyzed by computer tomography and magnetic resonance imaging.
Results: *In vitro,* a strong induction of cell death was observed after combination therapy with D,L-methadone and anticancer drugs. Blocking of μ-opioid receptor signaling pathway inhibited the sensitizing effect of D,L-methadone. *In vivo* in patient, strong inhibition of tumor growth, reduction of tumor size, reduction of metastases and reduction of tumor markers were observed after treatment with D,L-methadone in addition to conventional therapies in patients with breast, pancreatic, lung, prostate, liver and brain cancer. The tumors were progressive and/or refractory to conventional therapies.
Conclusions: Our studies suggest that D,L-methadone is a promising strategy for improvement of conventional therapies, resulting in a higher clinical outcome.

ID 0201

Comprehensive Analysis of Disease-Related Genes in Chronic Lymphocytic Leukemia by Multiplex PCR-Based Next Generation Sequencing

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Background: High resolution molecular studies have demonstrated that the clonal acquisition of gene mutations is an important mechanism that may promote rapid disease progression and drug resistance in chronic lymphocytic leukemia (CLL). Therefore, the early and sensitive detection of such mutations is indispensable for future predictive CLL diagnostics in the clinical setting.
Methods: For the present study we established a novel, target-specific next generation sequencing (NGS) approach, which combines multiplex PCR-based target enrichment and library generation with high-throughput parallel sequencing using a MiSeq platform. We designed a CLL specific target panel, covering hotspots or complete coding regions of 15 genes known to be recurrently mutated and/or related to B-cell receptor signaling.
Results: Sequencing was performed using as little as 40 ng of peripheral blood B-cell DNA from 136 CLL patients and a dilution series of two *ATM*- or *TP53*-mutated cell lines, which demonstrated a limit of mutation detection below 5%. Using a stringent functional assessment algorithm, 102 mutations in 8 genes were identified, including hotspot regions of *TP53*, *SF3B1*, *NOTCH1*, *ATM*, *XPO1*, *MYD88*, *DDX3X* and the B-cell receptor signaling regulator *PTPN6*. The presence of mutations was significantly associated with an advanced disease status und molecular markers of an inferior prognosis, such as an unmutated IGHV status or positivity for ZAP70 by flow cytometry.
Conclusion: In summary, targeted sequencing using an amplicon based library technology allows a resource-efficient and sensitive mutation analysis for diagnostic or exploratory purposes and facilitates molecular subtyping of patient sets with adverse prognosis.

ID 0222

Prediction of therapy resistance in preclinical PDX models of soft tissue sarcomas

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Soft tissue sarcomas belong to the rare form of cancer and arise from different origin. In the past, cell line studies contributed to the understanding of sarcomas, but they lack in vivo conditions for tumour biology. The main objective of the present study was to establish and characterise patient-derived xenografts (PDX) of soft tissue sarcomas (STS) in mice in order to use the PDX for the evaluation of therapeutic options in a clinically-related way.
Tissue from 29 primary human STS was directly transferred to the laboratory. Fragments from representative areas of the original tumour were transplanted subcutaneously into immunodeficient mice. A pharmacological study was initiated after successful and stable growth of the tumor in early passages. The sensitivity of the PDX to several cytostatics (ifosfamide, docetaxel, gemcitabine, doxorubicin, dacarbazin) was evaluated and compared the corresponding outcome of the patient in the clinic.
In this regard 11 PDX could be recently established, complementing a total panel of 22 PDX available. Identical morphology of the PDX compared to the original tumour was shown by histological staining. Mutations were detected in *KDR*, *MET*, *RB1* and *TP53* and showed individual profiles in the PDX. Most of the PDX responded to docetaxel and gemcitabine followed by doxorubicin and ifosfamide. The comparison of the chemosensitivity profile of the PDX and the patients outcome revealed that the prediction for a therapy resistance was correct in 10 out of 13 cases.
The newly established PDX closely resemble the patient malignancy particularly concerning response prediction. The patient-derived sarcoma xenografts allow comprehensive investigation of therapy-related markers.

ID 0246

XPA – A biomarker with potential prognostic value in patients with oropharyngeal squamous cell carcinoma

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Purpose: Platinum based chemotherapy resistance has been under investigation for a long time looking at the nucleotide excision repair (NER) pathway which is responsible for DNA adduct repair. One of the participating proteins in that pathway is XPA. Due to little information on the prognostic value of XPA expression, we investigated patients with head and neck squamous cell carcinoma (HNSCC) looking at overall survival (OS) and time to recurrence (TTR).
Material and Methods: Tissue microarrays were constructed from 453 cases of HNSCC. 293tumor blocks were evaluable for XPA via immunohistochemistry. Expression levels were dichotomized into a high and low XPA expressing group. Outcomes for OS and TTR were analyzed by using the Kaplan-Meier method and performed for different subsites of the head and neck.

Results: Analysis of OS and TTR showed no difference between both XPA expression levels in the overall patient cohort. Subsite analysis, however, revealed a superior OS in patients with oropharyngeal SCC and a high XPA expression (p = 0.0386). Looking at SCCs of the oral cavity a slight trend towards an inferior OS in patients with a high XPA expression could be shown. Investigations in the hypopharynx and larynx showed no differences between high and low XPA expressing tumors.
Conclusions: Gained results suggest that XPA might be a novel predictive marker for OS in patients with oropharyngeal SCC with a superior survival in tumors with high XPA expression. Further, this study shows that subsites in the head and neck will have to be looked at separately in the future to determine the predictive value of biomarkers for therapy outcome and to allow pretherapeutic risk stratification of patients.

ID 0260

Restriction of metastasis formation by inhibition of MEK1 dependent MACC1 tyrosine phosphorylation

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MACC1 is a decisive driver of metastasis formation and prognostic biomarker in colorectal cancer (CRC) and other solid tumor entities, but its molecular function and regulation remains to be elucidated.
Here we show the impact of MACC1 tyrosine phosphorylation on its function as a metastasis inducer. As the connection of HGF/Met and MAP kinase signaling with MACC1 function points to the involvement of kinases and phosphorylation steps in MACC1 regulation, we were able to show MACC1 tyrosine phosphorylation (pY) at predicted sites using targeted proteomics. Effects of pY-MACC1 mutants were assessed *in vitro* using proliferation, cell migration, colony formation and scratch assays. Mutation of the tyrosine phosphorylation sites prevented MACC1 enhanced proliferation and motility. In addition, only wild type MACC1 is able to induce MET expression. In concordance, cells overexpressing mutant MACC1 are not able to show scattering when treated with HGF. MACC1 overexpression of cells xenografted in mice leads to metastasis formation to the liver, whereas the phosphorylation mutant MACC1 does not show metastasis inducing abilities. Using mass-spectrometry based interactomics we characterized the MACC1 interactome and identified in particular MEK1 as interaction partner. This was validated by immunoprecipitation. Impact of MEK1 inhibitors was assessed in human CRC-xenografted mice by *in vivo* imaging.
We report, that motility and proliferation *in vitro*, tumor growth and metastasis formation *in vivo* is essentially driven by the hierarchical tyrosine phosphorylation of MACC1. Targeting MEK1 using inhibitors employed in clinical trials restricts MACC1-induced tumor growth and metastasis in mice.

ID 0267

Therapeutic response to chemotherapeutic drugs of glioma-PDX and correlation to common mutations identified by panel sequencing

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The most common malignant brain tumor in adults is glioblastoma multiforme (GBM) showing a very heterogeneous, diffuse infiltrative and aggressive growth with a mean survival time between 8 and 18 months. Because efficient standard therapies for glioma are limited, translational research is focusing on the molecular mechanisms of glioma formation and development of resistance to identify new therapeutic targets.
We transplanted more than 50 glioma tissue samples to immunodeficient mice and were able to establish and characterize 13 patient-derived xenotransplant (PDX) models (engraftment rate 25%). Glioma PDX models were screened for sensitivity towards selected drugs (everolimus, sorafenib, bevacicumab, irinotecan, salinomycin, temozolomide). A strong treatment response was observed for bevacicumab (7/13), irinotecan (7/13) and temozolomide (10/13), while the other drugs investigated mostly had no activity. The frequency of common "onco-mutations" was analyzed using the Illumina TrueSeq Cancer panel sequencing. Although some frequent mutations were detected, i.e. in KDR, FGFR3, PIK3CA, PTEN, P53 and NOTCH1, no correlation with drug sensitivity was identified. Extended correlation between drug sensitivity, gene expression profiles, and further mutations are still under evaluation.
The available histopathological and molecular biological data demonstrate that our glioma PDX model panel has retained the original tumor biology and reflects the heterogeneity of the disease, ensuring a high similarity to the clinical situation. Our approach can not only be used for testing of established and new drugs, but also offers a screening platform for individualized treatment of patients.

ID 0293

Response Prediction by whole Transcriptome Sequencing in Gastric Cancer

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Introduction: Response to chemotherapy is a prognostic factor for patients with gastric cancer (GaCa). No biomarkers exist to predict response to chemotherapy. We analyzed early response to chemotherapy by sequential RNA sequencing
Method: 9 patients with local advanced GaCa were included. Tumor and benign tissues were endoscopically biopsied before and after the first cycle of chemotherapy. After 3 cycles, the response was evaluated after resection (Response (R)=3, Non-Response (NR)=7). RNA sequencing was performed and ANOVA was calculated including response and treatment. We focused our analysis on the hallmarks of cancer genes to reduce the impact of transcriptional passenger signatures and compared benign, R and NR profiles using principal component analysis (PCA).
Results Pre-therapeutic profiles of R were clustered but similar to profiles of NR which confirms the difficulty of pre-therapeutic classification and explains the current lack of biomarkers. Analyzing the early response to therapy however, we observed a common shift of R towards a center as opposed to centrifugal PCA profiles of NR.

Regarding gene expression we saw a significant enrichment of hallmarks genes that were downregulated in R and upregulated in NR (OR 2.0). These results could reproduced for the subgroups metastasis/Invasion (OR 1.9), proliferation (OR 4.0), promotion of inflammation (OR 2.2).
Discussion: Sequential expression screening of endoscopic biopsies results in differential overall response in R versus NR. Initial heterogeneous tumors could be identified as R by their homogeneous reaction to chemotherapy. Additional insight in molecular mechanisms provided tumor hallmarks as key structures disturbed in differential therapy responses.

ID 0305

Preclinical biomarker discovery for stratified clinical trials with novel compounds in head and neck cancer: Patient derived xenografts

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Novel treatments in head and neck cancer are urgently needed. In order to take molecular subtypes into account for preclinical drug screening and biomarker development, we established and characterized a large series of patient derived xenografts (PDX) from patients with head and neck cancer (HNC).
Methods: Fresh tumor tissue was transplanted within 24 hours subcutaneously to NSG mice. Drug screening was done for compounds as used in clinical routine such as 5FU, cis- or carboplatin, docetaxel, methotrexate and cetuximab. Further, novel compounds not previously evaluated in HNC such as everolimus and regorafenib were screened for efficacy. Dosing was adjusted to MTD.
Results: Median time from transplantation to first passage was 69 days. From 109 patients we observed an engraftment in 36%. Currently 39 models characterized for drug response, gene expression and mutational profile. Best response was observed for docetaxel with a response rate (RR) of 84% followed by cetuximab with a RR of 61%. Everolimus (23%) and platinum (28%) had an intermediate response whereas regorafenib (13%), MTX (4%) and 5FU (17%) resulted in poor response. For biomarker evaluation biological profiles were compared between responders and non-responders. For the mTOR inhibitor everolimus response to treatment was associated to high RPS6KB1 mRNA expression ($p = 0.0784$) by trend. Regorafenib response was associated to the occurrence of mutation within the RET gene.
Conclusion: We established the largest platform of HNC PDX for drug screening. Through the number of models established, we are able to mimic phase II trials and vigorous tumor profiling enables to associate response to biological profiles for biomarker discovery and subsequent validation.

ID 0325

Isolation and characterization of circulating tumor cells using a new workflow combining CellSearch and CellCelector

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Background: Circulating tumor cells (CTC) are rare cells dissociated successfully from the primary tumor into the blood stream. The presence of CTCs is associated with increased risk to develop metastases and a short survival. Detection and isolation of CTCs is necessary. Here we show a workflow to isolate single CTCs for molecular characterization by combining the CellSearch and CellCelector.
Material and Methods: Single cells were classified as CTCs if nucleus (DAPI) and cytokeratin (FITC and/or TRITC) positive while CD45 (Cy5) negative. Detection and quantification of single cells from control samples and patient samples were performed using CellSearch- and CellCelector. CTCs were isolated from CellSearch-Cartridge using the CellCelector and transferred into PCR-tubes for whole genome amplification (WGA).
Results: After standard CellSearch analysis 97% of spiked SKBR3 cells and 95% of patient CTCs were detected by rescanning using the CellCelector system. Isolation/Deposit-ratio was tested using different cell lines and a recovery rate of >95% was determined. After transfer of the CellSearch cartridge content to chamber slides on a special magnet adapter 87% of CellSearch classified CTCs could be detected and isolated using the CellCelector following transfer to PCR tubes. Next, CTCs were processed for WGA. Quality of WGA products was checked by the Ampli1 - QC protocol and genomic analyses (Panel-Sequencing) were performed successfully.
Conclusion: The established work-flow for enrichment of CTCs by CellSearch analysis followed by the isolation of single CTCs using the CellCelector enables the enumeration and molecular characterization of single CTCs to investigate the heterogeneity of CTCs in patient samples.

ID 0329

Effects of progestins used for hormone therapy in contraception and post-menopause on PGRMC1 overexpressing breast cancer cells

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The progesterone receptor membrane component 1 (PGRMC1) potentially offers a new pathway to explain the observed effect of increased risk of breast cancer development of patients receiving progesterone based hormone replacement therapies, used in contraception and post menopause. In preliminary studies we could show that various progestins significantly increased proliferation of PGRMC1 overexpressing MCF-7 cells, revealing a potential role of PGRMC1 in forwarding membrane-initiated progestin signals into the cell. To further study the downstream signaling of PGRMC1 and to identify potential interaction partners of the receptor after progestin binding, co-immunoprecipitation experiments were performed with MCF-7/PGRMC1 cells, followed by western blot and mass spectrometry analysis. Further, to study the influence of PGRMC1 on tumor progression in breast cancer, proliferation and apoptosis of MCF-7/PGRMC1 cells after progestin treatment was investigated.
Our results after co-immunoprecipitation confirmed our former hypothesis that phosphorylation of the CK2 binding sites and interaction with the SH2 target sequence of PGRMC1 may be participated in recruitment of signaling proteins after progestin binding. Further, additional potential interaction partners after binding of progestins could be identified. Apoptosis studies showed that the progestin NET might be able to rescue MCF-7/PGRMC1 cells from apoptosis. These results again demonstrate the role of PGRMC1 in breast cancer development and suggest that screening for PGRMC1 expression might enable identification of women with a higher susceptibility to breast cancer under hormone therapy.

ID 0373

Using cell-free DNA (cfDNA) to monitor the course of disease in head and neck squamous cell carcinoma and peritoneal carcinomatosis.

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Very recently, cell free tumor DNA analysis was developed as a non-invasive tool to monitor cancer progression and recurrence. Implementing next-generation sequencing in cancer diagnostics it is now feasible to observe changes in the genetic composition of a tumor by so-called "liquid-biopsy". Merging quantitative information, genetic profile and clinical data, this "liquid-biopsy" promises to be an innovative tool for guiding therapeutic decision making in oncology. Here we report about our approach to isolate and quantify cfDNA applied in two different clinical settings; peritoneal carcinomatosis (PER) and head and neck cancer (HNSCC). The amount of cfDNA in plasma ranged from 1.6 to 34.01 ng/ml before treatment. In patients with PER we observed increased cfDNA values after surgery and HIPEC (hyperthermic intraperitoneal chemotherapy) followed by a decrease at the first follow-up. HNSCC patients showed an overall increase in cfDNA concentration followed by a decline. Besides mere quantification, the genetic composition of the tumor and its respective reflection in cfDNA was of great interest. Sequencing results in four HNSCC patients revealed alterations of the cell cycle (*TP53, CDKN2B*), PI3K; AKT; RAS signaling cascades (*ERBB3, HRAS, VHL, MTOR*), chromatin regulation (*TET2, ARID1A, KMT2A, EZH2, MEN1*), Notch signaling (*FBWX7, NOTCH1*) and DNA damage response (*BRCA1/2, MLH1*). Currently we are verifying these mutations in ctDNA from plasma with the SafeSeqS (safe-sequencing system) and Nextera^{XT} technologies. In conclusion monitoring the disease burden by quantifying cfDNA and multi gene panel sequencing is feasible and can yield individual tumor signatures that might provide a rationale for targeted therapies.

ID 0386

Detection of DNA double strand breaks by means of the yH2AX-Assay in peripheral lymphocytes treated with Bendamustin and R-CHOP in vitro

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DNA double strand breaks are the most severe form of DNA damage in eukaryotic cells treated with ionizing radiation or chemotherapeutic drugs. In order to investigate the individual response to chemotherapeutic agents, peripheral lymphocytes of healthy donors were incubated in vitro with either bendamustine (n = 10) or with the R-CHOP protocol (n = 4). The drug dosage per cell number was calculated to resemble standard therapeutic dosage by body surface area and standardized throughout the subjects. DNA double strand breaks were quantified by a yH2AX assay applying the AKLIDES NUK® system (MEDIPAN GmbH, Dahlewitz).
With bendamustine, we detected 0.24 to 1.12 yH2AX foci /cell (negative control 0,049 ± 0,158 foci/cell), where the number of foci quantitatively represents DNA double strand breaks. Fully dosed R-CHOP proved too toxic in vitro, hence we used a 10 fold dilution. This resulted in the detection of 1.44 to 5.39 yH2AX foci/cell. With both cytostatic settings, there was no inter-individual correlation between drug dose and number of foci, whereas dose titrations on the cells of each individual donor demonstrated a clear correlation between dose and yH2AX assay result.
The lack of correlation across individuals between yH2AX foci and drug dosage based on standard calculation by body surface area suggests that standardized dosing of chemotherapeutic drugs based on gross physical determinants such as body surface area does not correspond to the individual's biological response and clinical effect. Adjusting the dose individually based on biological response such as DNA double strand breaks could therefore offer a way of personalized medicine with "classical" substances, reducing toxicity while increasing the therapeutic efficacy.

ID 0427

Patient-derived organoids to model intra- and intertumoral heterogeneity of pancreatic cancer in high-throughput drug screens

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Introduction: For the year 2020, it is estimated that the number of cancer deaths caused by pancreatic ductal adenocarcinoma (PDAC) will surpass colorectal and breast cancer. In contrast to many other tumor types, there are no effective targeted therapies available. One reason for the poor outcome is a high degree of tumor heterogeneity in PDAC.
Materials and Methods: Utilizing a novel human PDAC model system – three dimensional (3D) organoid culture – derived from surgical specimen and endoscopic fine needle aspirations, we aim to address inter- and intratumoral heterogeneity in order to develop personalized treatment strategies.
Results: To date, we have established several patient-derived organoid lines. In parallel, we have generated 2-dimensional (2D) lines from the same patients. Both, 2D and 3D culture systems allow expansion of PDAC biopsies including repetitive freeze-thaw cycles, depletion of stromal cells and enrichment of cancer cells. Drug-screens are performed using conventional chemotherapeutic drugs as well as targeted therapeutics directed against PDAC core pathways. Besides addressing patient-to-patient differences (inter-tumoral heterogeneity), we are in the process of developing single-cell organoid lines from individual patients to investigate treatment response of different tumor subclones (intra-tumoral heterogeneity).
Conclusion: Taken together, the organoid culture system allows us to measure drug responses of a growing panel cell lines of individual PDAC patients. The predictive value of these lines remains to be proven, however, having the opportunity to generate, expand and assay cells lines in real-time harbors great potential for individualized medicine.

ID 0439

Dendritic Cell vaccination to treat checkpoint-blockade resistant tumors by induction of mutation-specific T cells

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Checkpoint-blockade responsive cancers (such as *cutaneous* melanoma) harbor many mutations resulting in spontaneous neoantigen-specific T cells which are suppressed but can become clinically highly effective upon checkpoint blockade. In contrast, tumors displaying few mutations (such as *uveal* melanoma) are a priori largely resistant to checkpoint blockade probably as spontaneous neoantigen-specific antitumor T cells are scarce. We hypothesized that employing mature, monocyted-derived RNA-trans-

fected dendritic cells (DC) can induce the required T cell responses against passenger and driver mutations. We have designed a randomized adjuvant phase III (NCT01983748) trial in high risk (monosomy 3) uveal melanoma using total RNA-transfected DC to vaccinate against the total antigenic repertoire of patient´s individual tumors to retard or prevent metastases after resection or destruction of the primary tumor in the eye. The trial is currently performed in cooperation with Departments of Ophthalmology at 8 University Hospitals in Germany (Erlangen, Essen, Hamburg Eppendorf, Homburg/Saar, Köln, Lübeck, Tübingen, and Würzburg). In metastatic patients we have also vaccinated to specific passenger and driver (such as GNAQ) mutations identified by exome and RNA sequencing with restriction to those predicted to form high affinity epitopes. Neoantigen-specific T cells were induced and clinical regressions occurred, notably in combination with checkpoint blockade. One major advantage of our mRNA-DC vaccine approach is that (useless) vaccination to epitopes that are not naturally presented (about half of the neoantigens predicted by current algorithms) is avoided.

ID 0456

The Impact of Free Fatty Acids on MDSC Function and Phenotype

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Myeloid-derived suppressor cells (MDSCs) represent a heterogeneous group of cells that expand during cancer and inflammation, have been reported to modulate cytokine production of macrophages, suppress T-cell response, and promote tumor angiogenesis, tumor cell invasion as well as metastasis. An accumulation of MDSC in peripheral blood can be observed both in cancer and chronic inflammation, including Inflammatory Bowel Disease and Colon Cancer, while the mechanism, which modulates the functional phenotype of MDSC inhibition is still unclear.
Here we use the MDSCs cell line MSC-2 to describe a possible cellular mechanism for functional regulation of MDSCs. We found that not only IL-4, but also oleate, an unsaturated fatty acid, can induce a regulatory phenotype in these cells, paralleled by an increase in intracellular lipid droplet accumulation. Furthermore, this inhibitory effect can be reversed by treatment with TOFA, an inhibitor of droplet formation. We compared the ability of oleate (C18:1) and stearate (C18:0) to induce the regulatory phenotype of MDSCs. Our results demonstrate that both fatty acids can induce droplet formation while only oleate treated MSC-2 cells exhibit a suppressive ability. Analysis of nitric oxide (NO) production indicates that the oleate induced regulatory phenotype is mediated by NO and that the effect of oleate can be neutralized by L-NMMA, a non-selective inhibitor of NO synthetase. Thus we suggest a novel unsaturated fatty acid-dependent pathway to regulate formation of MDSCs, a mechanism which demonstrates the impact of metabolic processes on the control of inflammation and tumor progression.

ID 0488

Challenges and opportunities for molecular driven care in prostate cancer: The EORTC SPECTApros program

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Newly developed targeted drugs are tested on restricted patient groups exhibiting specific biomarkers in many cancers. When the prevalence of those biomarkers is low, a high number of patients need to be screened. Recruitment of patients in a biomarker-led clinical trial requires significant effort due to the number of patients screened, the complexity and cost. Moreover, when various clinical trials are targeting the same patient population, the availability of samples may be restricted and patients may lose the opportunity to enter a potential clinical trial. To guarantee efficient patient access to clinical trials, the EORTC is building a program of collaborative molecular screening platforms for various tumor entities. One of the platforms is dedicated to prostate cancer.
SPECTApros is the first European initiative intended to accelerate clinical trial access by ensuring robust imaging and screening of markers that can potentially allow patients to be enrolled in clinical trials. Patients will be proposed to have their material centrally processed for imaging, pathological examination and screening of cancer gene alterations. By matching clinical, imaging, pathological and molecular profiles to eligibility criteria of available biomarker-led clinical trials, SPECTApros achieves an identification of eligible patients and patient-oriented parallel screening for multiple trials. In this presentation, we will describe SPECTApros as a new model which is based on an active network of clinical centers, a central imaging/biobanking/pathology facility, qualified assays laboratories, software to collect, trace and secure the data and algorithms to match the patients with trials.

ID 0501

An innovative teaching model: Summer Academy for high school students in translational cancer research at the Center for Integrated Oncology Cologne

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As a comprehensive cancer center, The Center for Integrated Oncology Cologne (CIO) wants to provide an excellent teaching infrastructure for oncology training. Inspired by the Summer Academies of US-American cancer centers, in particular from our partner cancer center in Pittsburgh (USA), we launched the first "CIO Summer Academy" in 2014 with 5 local students. Our goal was to give talented and motivated high school students the opportunity to get a deep insight into translational cancer research in order to encourage them to pursue careers in the field of cancer research and clinical management. While we aim to instill theoretical knowledge of cancer biology and clinical care, we also want to provide hands-on research experience as well as develop presentation and communication skills. Since the 2014 pilot program was assessed as an extremely positive experience by the students as well as the participating laboratories, we expanded our program to ten students in 2015, including one student from Pittsburgh. Students experienced four weeks of research-focused didactic and experiential learning in nine different laboratories as well as one clinical trial office location. There, the scholars worked on their own research projects in a dedicated laboratory and attended a series of cancer biology lectures presented by graduate students and post docs of the CIO. At the end of the program, scholars were asked to present their projects orally, as well as during a poster session. On feedback surveys the students were highly enthusiastic about this opportunity of having such a deep and application-oriented insight into translational cancer research. We believe that it represents a model for inspiring students to focus on translational cancer research. Accordingly,4 of the students of our Summer Academy already started to work as student helpers in research groups of our cancer center.

ID 0549

Metastasis formation in human colorectal cancer and the intervention with new therapeutic strategies, using the biomarkers S100A4 and RAGE

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Metastasis formation in colorectal cancer (CRC) has the worst effect on CRC patient survival. S100A4 is an inducer of metastasis in many cancer types, including CRC, and is used as a prognostic biomarker for aggressive tumor progression. In CRC, metastasis formation and decreased patient survival correlated with higher S100A4 expression in the primary tumor. Patients might benefit from a reduction of S100A4 early in the disease, leading to lower metastatic burden and prolonged survival.

Here we demonstrate that knock-down of S100A4 in CRC cell lines rendered the cells less motile *in vitro*, and resulted in fewer liver metastases in an intrasplenic xenograft mouse model. When transplanted mice were systemically treated with S100A4-specific shRNA expression plasmids via repeated hydrodynamics-based tail vein injection, the levels of tumor progression markers S100A4 and MMP9 were significantly decreased in the primary tumor, and significantly fewer metastases were observed in the liver.

S100A4 in the tumor interstitial fluid can interact with extracellular partners, like the receptor for advanced glycation end products (RAGE). Extracellular S100A4 hyperactivated MAPK/ERK and hypoxia signaling in CRC cells overexpressing RAGE, and induced cell migration and invasion. Soluble RAGE and RAGE-specific antibodies interfered with the higher motility of the treated cells.

The expression level of S100A4 and RAGE in primary tumors of stage I-III CRC patients correlated with metachronous metastasis and lower patient survival.

In summary, S100A4 and RAGE are prognostic biomarkers for CRC and intratumoral target gene knock-down, as well as blocking of specific interactions, can be used to interfere with their metastatic potential.

Late-Breaking-Abstracts (Freie Beiträge)

Breast Cancer

ID0586

Detection of disseminated tumor cells from the bone marrow of patients with early breast cancer is associated with high 21-gene recurrence score

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Background: High 21-gene recurrence score (RS) is associated with an impaired prognosis in patients with HR-positive / HER2-negative early breast cancer and predictive of response to adjuvant chemotherapy. Detection of disseminated tumor cells (DTCs) in the bone marrow is a surrogate of minimal residual disease and also of prognostic value. The aim of this study was to compare DTC detection with the 21 gene RS.
Methods: DTCs were identified in bone marrow aspirates of HR-positive / HER2-negative EBC patients by immunocytochemistry (pancytokeratin antibody A45-B/B3) and cytomorphology at primary surgery. The 21-gene RS was assessed in paraffin-embedded tumor tissue samples using OncotypeDX (Genomic Health).
Results: A total of 114 patients were included into the study. DTCs were detected in 13 of these (11%). Of the women with a low RS (<18) 5/75 (7%) were DTC positive. Of the women with a intermediate/high RS (≥18) 8/39 (21%) were DTC positive (p = 0.027, Chi-squared Test). The median RS in DTC-negative patients was significantly lower as compared to DTC-positive patients (15 versus 20, p = 0.040, Mann-Whitney-U Test).
Conclusion: Detection of DTCs in patients with early breast cancer is associated with high 21-gene recurrence score. These findings are meaningful for further basic research that aim to investigate the biological mechanism of tumor cell spread and cancer progression and may have prognostic and / or predictive clinical implications that should be evaluated in future clinical trials.

Developmental Therapeutics: Immunotherapy/Cellular Theraphy

ID0575

Activation of the cytosolic RNA receptor RIG-I in tumor and immune cells triggers efficient anti-tumor immunity and synergizes with checkpoint blockade.

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Introduction: Targeting inhibitory T-cell receptors such as CTLA-4 has shown great promise in cancer therapy but its success is limited to a minority of patients. We address the potential to target the nucleic acid receptor RIG-I in combination with checkpoint blockade. RIG-I has been shown to induce both potent type I IFN release and an immunogenic variant of cancer cell death.
Methods: Mice bearing bilateral B16 melanomas were treated by intratumoral injections with the specific RIG-I ligand 3pRNA in combination with anti-CTLA-4. Using CRISPR/Cas9 to generate RIG-I-deficient B16 cells, we address the importance of tumor-intrinsic versus host immune cell RIG-I signaling.
Results: We show that activation of RIG-I synergizes with CTLA-4 checkpoint blockade. Selective RIG-I ligation in the tumor microenvironment induced strong *in situ* vaccination with expansion of tumor-specific CD8+ T cells that resulted in regression of local and distant tumors that are poorly susceptible to anti-CTLA-4 mono-therapy. Fully efficient anti-tumor immunity was dependent on RIG-I activation in both malignant and host immune cells. Furthermore, protein vaccination together with RIG-I ligation and anti-CTLA-4 induced expansion of antigen-specific CD8+ T cells that translated into potent anti-tumor immunity. Cross-priming of cytotoxic T cells as well as anti-tumor immunity were dependent on the adapter protein MAVS and host type I IFN signaling and were mediated by dendritic cells.
Conclusion: RIG-I activation either in combination with a cancer vaccine or selectively engaged in the tumor microenvironment strongly synergizes with CTLA-4 blockade. These data may serve as the basis for new combinatorial approaches in the immunotherapy of cancer.

Gastrointestinal (Noncolorectal) Cancer

ID0581

Stereotactic body radiotherapy in hepatocellular and cholangiocellular carcinoma (HCC, CCC): First results of the German Society of Radiation Oncology (DEGRO) working group "stereotactic therapy" cohort.

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Aims: To analyse the pattern of care of SBRT for HCC/CCC in a pooled cohort of the German Society for Radiation Oncology (DEGRO).
Material and Methods: From 9 German radiotherapy centres, data after SBRT was collected and entered into a centralised database as an effort of the task group stereotactic radiotherapy of the DEGRO. Patient characteristics, treatment specifics and follow-up (FU) data were collected. Analysis focused on local control and on overall survival.
Results: Overall, 76 patients with 87 lesions (median 1 lesion/patient; range 1–3) were entered into the data base, treated between 1999 and January 2015. Histologies were HCC in 43 (72% male) and CCC in 33 (55% male) with 49 and 38 lesions (50% intrahepatic and 50% Klatskin tumours), respectively. Treatment was performed with a SBRT-specific setup in all participating centres with high precision positioning and image guided radiotherapy (IGRT) including motion management. Median fraction number was 5 (3–15) with a predominance of 3 (24%), 5 (26%), 10 (11%) and 12 (22%) fractions per lesion in single doses of 4–12.5 Gy. Median biological equivalent dose (BED) was 67.2 Gy (36 – 116 BED Gy; SD ±15.4 BED Gy). Patients alive at analysis had a median FU of 27 months (5–50 m; SD ±19 m). Local control rate of target lesions at 1 year (y) was 95% and comparable for HCC and CCC. Median overall survival (OS) from SBRT was 14 m for all patients and not statistically different for

HCC and CCC. Median OS from diagnosis was 69 m for HCC and 21 m for CCC ($p < 0.001$).
Conclusion: SBRT is highly effective for local control for both, HCC and CCC. Stage dependent overall survival agrees with the current literature. Based on these encouraging data prospective trials for HCC and CCC are in preparation.

Head and Neck Cancer

ID0583

Assessing the need for psychooncological support in patients with primary and secondary/recurrent oral cancer: A study based on an electronic psychooncological screening instrument (ePOS) for head and neck cancer centre demand planning.

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Cancer patients suffer from severe distress, and oral cancer patients report some of the highest distress levels of all cancer patients. The German S3-Guidline and the certified Head and Neck Cancer Centres recommend psychooncological support for patients. This study analysed the need for psychooncological support with an electronic screening instrument (ePOS). This instrument included the DISTRESS questionnaire (DT), the Hornheider Screening Instrument (HSI) and enquires for personal support need.
A total of 139 patients were screened including 115 patients with primary cancers (PC) and 24 with secondary/recurrent cancers (SRC). The mean age was 64.2 years and 60% were male. Results from the DT (cut-off 6) revealed that 44% of PC patients and 33% of SRC patients indicated a treatment need. Similar results were noted with the HSI (cut-off 0.3) with 42% in both patient groups (PC and SRC). Patients had one of both tests in 62% (PC) and 58% (SCR) positive. However, only 35% (PC) and 33% (SRC) of patients opted for psychooncological support.
The electronic ePOS instrument was widely accepted and demonstrated a psychooncological support need in up to 60% in test results, but only 35% of patients opted for psychooncological support. Both patients groups (PC and SRC) showed similar test values and subjective needs. At present, the combination of assessment instruments and patients` subjective need is good practice for identifying patients with psychooncological need. Head and neck cancer centres should be prepared for psychooncological treatment in a minimum of 35% of all head and neck cancer patients.

Lung Cancer

ID0571

Exploratory analysis of efficacy by histology and frontline therapies in a nonsquamous (NSQ) non-small cell lung cancer (NSCLC) subgroup in REVEL: A randomized phase III study of ramucirumab (RAM) plus docetaxel (DOC) vs DOC plus placebo (PL) for second-line treatment of stage IV NSCLC

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Background: The phase III trial REVEL (NCT01168973) led to FDA approval of RAM + DOC for metastatic NSCLC patients (pts) with disease progression on/after standard platinum-based frontline chemotherapy (pbFCT). Pemetrexed (PEM) is standard of care in NSQ NSCLC within pbFCT. An exploratory efficacy analysis of RAM + DOC for NSQ NSCLC, including adenocarcinoma (ADC), is reported.
Methods: Pts received DOC (75 mg/m^2) + RAM (10 mg/kg; N = 465) or DOC + PL (N = 447) after disease progression on pbFCT. Frontline therapy for NSQ pts was defined as PEM induction therapy (IT) ± any maintenance therapy (MT) (PEM) and non PEM IT ± MT (non PEM). Endpoints [median overall and progression-free survival (OS, PFS), objective response rate (ORR)] were analyzed using Kaplan-Meier, Cox Proportional Hazard model and Cochran Mantel Haenszel methods.
Results: Of 912 NSQ tumors, the majority was ADC (79%; N = 725). Baseline characteristics and post-study therapy use in NSQ pts were balanced between PEM and non PEM subgroups. MT use was higher for PEM (37.9%) than non PEM (13.7%). Results for RAM + DOC vs DOC + PL were: PEM OS = 11.8 months (m) vs 9.0 m, HR (95% CI): 0.779 (0.62–0.98); non PEM OS = 11.0 m vs 9.9 m, HR (95% CI): 0.855 (0.68–1.07); PEM PFS = 5.1 m vs 3.7 m, HR (95% CI): 0.691 (0.56–0.85); non PEM PFS = 4.5 m vs 3.5 m, HR (95% CI): 0.772 (0.63–0.94); PEM ORR = 20.0% vs 14.9%; non PEM ORR: 24.0% vs 14.3%. RAM + DOC efficacy for ADC [OS = 11.2 m (HR, 95% CI: 0.83, 0.69–0.99); PFS = 4.5 m (HR, 95% CI: 0.75, 0.64–0.88); ORR = 19%] was consistent with NSQ [OS = 11.1 m (HR, 95% CI: 0.83, 0.71–0.97); PFS = 4.6 m (HR, 95% CI: 0.77, 0.67–0.88); ORR = 22%].
Conclusions: In NSQ NSCLC, RAM improved OS, PFS and ORR regardless of PEM or non PEM. Favorable efficacy was seen for NSCLC histological subtypes, including ADC.

ID0585

High prevalence of concomitant oncogene mutations in prospectively identified patients with ROS1-positive metastatic lung cancer

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Purpose: We report clinical outcomes and genomic findings of patients with ROS1-positive lung cancer that were prospectively identified within a multiplex biomarker profiling program at the West German Cancer Center.
Patients and Methods: Standardized immunohistochemistry, FISH and mutation analyses were prospectively conducted in 665 patients with metastatic lung adenocarcinoma. Clinical and epidemiological data were retrieved from the institutional database.
Results: ROS1-positivity by immunohistochemistry was detected in 22 lung cancer patients (5.6%), including 12 patients (3.1%) with FISH-positivity using ≥15% events as cut-off. 32% of ROS1-positive cases presented with concomitant oncogenic driver mutations involving *EGFR* (4 cases), *KRAS* (2 cases), *PIK3CA* and *BRAF*. Five patients had sustained responses to crizotinib. Three cases which were initially classified as ROS1 FISH-negative passed the threshold of 15% positive events when tumor rebiopsies were analyzed at progression. Median overall survival of 22 ROS1-positive lung cancer patients (not reached) was significantly superior to 261 patients with EGFR/ALK -negative lung adenocarcinoma (24.4 months, p = 0.039). Overall survival of 12 ROS1-positive lung cancer patients from initiation of pemetrexed-based chemotherapy was significantly prolonged compared to 169 pemetrexed-treated patients with EGFR/ALK -negative adenocarcinoma (p = 0.011).
Conclusion: ROS1-positive metastatic lung adenocarcinomas frequently harbor concomitant oncogenic driver mutations. Levels of *ROS1* FISH-positive events are variable over time. This heterogeneity provides additional therapeutic options if discovered by multiplex biomarker testing and repeat biopsies.

Molecular Pathology

ID0597

Viral-cellular DNA junctions are ideal molecular markers for assessing intra-tumor heterogeneity and for the detection of cell-free tumor DNA in serum

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Aim: Integration of HPV DNA into the host genome is frequently observed during cervical carcinogenesis and can confer a selective growth advantage to the affected cell. The resulting viral-cellular junction sequences are highly tumor specific. By using viral-cellular junctions as tumor cell markers we addressed the question of intra-tumor heterogeneity and their use for the detection of circulating tumor DNA (ctDNA) in the serum of cervical cancer patients.
Methods: For intra-tumor heterogeneity analyses tumors of 8 patients displaying up to 5 viral-cellular junctions per tumor were included. From cryosections of tumor sub-blocks representing different tumor regions, tumor islands were micro-dissected and directly analyzed in junction-specific PCR assays. For the detection of circulating tumor DNA junction-specific PCR assays were applied to sera of 21 patients. Sera were collected preoperatively and during follow up.
Results: Intra-tumor heterogeneity was evident in only one tumor. Seven of 8 tumors showed remarkable homogeneity. In five of 21 analyzed preoperative serum samples junction fragments could be specifically amplified. No correlation was found between the detection of viral-cellular junction fragments and TNM-stage. However, Kaplan Meier analyses of the patients with primary tumors revealed a significant association between the detection of junction fragments in pre-operative sera and a reduced recurrence free survival ($p = 0.003$)
Conclusions: Viral-cellular junction fragments are representative tumor cell markers and thus comprise highly specific novel biomarkers which may proof to be of value for disease monitoring and prognostication.

Palliative Care

ID0580

Metamizole/dipyrone for the relief of cancer pain -A systematic review and evidence based recommendationsfor clinical practice of the German Guideline Program in Oncology

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Background: Dipyrone (metamizole) is one of the most widely used non-opioid analgesics for the treatment of cancer pain in the world. Because evidence based recommendations are not yet available, a systematic review was conducted for the German Guideline Program in Oncology to provide recommendations for the use of dipyrone in cancer pain.
Methods: First, a systematic review for clinical trials assessing dipyrone in adult patients with cancer pain was conducted. Endpoints were pain intensity, opioid sparing effects, safety and quality of life. The search was performed in MedLine, Embase (via Ovid), and the Cochrane Library (1948–2013) and additional hand search was conducted. Then, recommendations were developed and agreed in a formal structured consensus process by 53 representatives of scientific medical societies and 49 experts.
Results: Of 177 retrieved studies, four could be included (three randomized control trials (RCTs), one cohort study, n = 252 patients): Dipyrone significantly decreased pain intensity compared to placebo, even if low doses (1.5–2g/d) were used. Higher doses (3×2g/d) were more effective than low doses (3×1g/d), but equally effective as 60mg oral morphine/d. Pain reduction of dipyrone and NSAIDs did not differ significantly. Com-

pared to placebo, NSAIDs and morphine, the incidence of adverse effects (AEs) was not increased.
Conclusion: Dipyrone can be recommended for the treatment of cancer pain as an alternative to other non-opioids either alone or in combination with opioids. It can be preferred over NSAIDs due to the presumably favorable side effect profile in long-term use, but comparative studies are not available for long-term use.

Poster

Breast Cancer

ID0577

Can a pathological complete response after neoadjuvant chemotherapy in breast cancer patients be diagnosed by minimal invasive biopsy?

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Background: Neoadjuvant chemotherapy (NACT) is increasingly used and pathological complete response (pCR = ypT0) in the breast is a achievable result. As breast imaging does not accurately predict a pCR, this study aimed to systematically explore the ability of a minimal invasive biopsy to diagnose pCR after NACT.
Methods: 50 patients were included in this review-board approved prospective, monocenter cohort study between Aug. 2014 and Feb. 2015. Ultrasound guided, vacuum-assisted, minimal-invasive biopsy (VAB) was performed after NACT and before surgery. To assess the possible sampling error, representativeness the sample was evaluated during the VAB by the performing physician, and afterwards by radiography and histopathology. Breast conserving surgery or mastectomy was performed in every case after VAB. Residual cancer in VAB and surgical specimen was defined a positive result. Negative predictive values (NPV) and false negative rates (FNR) to predict a pCR (= ypT0) in surgical specimen were calculated for the whole study cohort and different subgroups defined by the evaluation of the representativeness.
Findings: Differentiating VAB specimen with and without vital tumor cells (ignoring the evaluation of representativeness) yielded a NPV of 76,7% and an FNR of 25,9%. Given the pathologically diagnosed representativeness of the VAB specimen (n = 38), the NPV was 94,4% (95% CI 87,1–100,0) and the FNR 4,8% (95% CI 0,0–11,6). Non-representative VABs were mainly due to a bad visibility of the target lesion in ultrasound.
Interpretation: Given a representative (according to the pathologist´s evaluation) VAB minimal invasive biopsy can accurately diagnose a pCR. A confirmative, multi-center, diagnostic trial to validate the results is warranted.

ID0584

Families and breast cancer: Needs and coping in the final phase of life

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To date, there are only very few research findings dealing with the families of patients with advanced breast cancer. Not only do the women themselves suffer but also the members of their families. In order to widen the knowledge on this phenomenon, we examined how the families experienced the palliative phase of breast cancer, how they coped with it and what their own needs were.

Questions:
a) What influence does advanced breast cancer disease have on family life?
b) What needs arise in families?
c) What resources do these families fall back on?
Method: The Grounded Theory qualitative research approach was used for this study. Data was collected by means of guideline-supported interviews. The 29 interviews were transcribed and systematically analysed in order to develop the concepts. The application to the Ethics Committee was approved.
Results: Not only the individual family members are influenced by the approaching decease of the wife/mother and the end of existence as a family, but also the complete family system. The emotional strain on the family members is high. The importance of the disease and the approach to it differ for each individual person. The existential threat to family life, the specific approach to the woman's last phase of life in the present and the outlook on the future situation are important themes for all of the family members.
Summary: The results of this study give an indication of how specially trained care experts could provide continuous support for the family members in their approach to the illness and death of the wife/mother.

ID0598

Excercise induced changes in muscle metabolism in BRCA mutation carriers (BIJOU study)

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Objectives: BRCA mutation carriers (BRCA-MCs) have a high lifetime risk of developing cancer compared to normal population. In the ongoing BIJOU study the effects of exercise on the improved integrity of DNA repair complexes and the reduction of DNA-damaging molecules are examined for the first time. Subjects at elevated risk may be interested in less aggressive approaches to risk reduction.
Design: In this two-arm, controlled trial BRCA-MCs (m/f; 18 to 69 years) are enrolled in a 6-week supervised high-intensity training intervention group (IG) versus a supervised low-intensity training control group (CG), each with a frequency of three times a week and a duration of 60 min per session. Muscle biopsies and blood samples evaluate the changes in energy metabolism before and after interventions. Secondary endpoints include gene regulation of the lipid metabolism, markers of inflammation, QoL (SF-36), Life-Orientation-Test (LOT-R), anthropometric data and physical performance.
Results: Preliminary results with 11 male and female participants to date show a significant median increase of strength in the IG (n = 7) of 40% and no changes in the CG (n = 4). We observed improvements in maximal aerobic power by 16% in the IG versus no changes (<1%) in the CG (n = 4). As by the time of writing participants highly recommend the study participation. With continued recruitment like this first preliminary results can be expected by the end of February.
Conclusion: By improving the cellular metabolome the tumor initiation and proliferation in BRCA gene defects in this high risk group may be actively influenced and the improvement of positive effects on the quality of life should be expected.
Key-Words: BRCA, High Intensity training, DNA-repair, metabolome

Developmental Therapeutics: Immunotherapy/Cellular Theraphy

ID0587

Generation of a new bicistronic DNA vaccine encoding for tyrosine hydroxylase and IL-15 to induce an active immune response against neuroblastoma

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Introduction: Tyrosine hydroxylase (TH) is a promising target for active immunity approaches against neuroblastoma (NB) and Interleukin-15 (IL-15) is an attractive adjuvant for DNA vaccination due to its ability to induce cytotoxic but not regulatory T cells. Here, we report generation and characterization of a new bicistronic DNA vaccine encoding for TH and IL-15 for active immunotherapy against NB.
Methods and Results: A previously described DNA-sequence encoding for TH combined with upstream Ubiquitin (Ub) was cloned into the first multiple cloning site of the bicistronic expression vector pIRES using standard molecular biology techniques. Ub ensures proteasomal degradation of TH in antigen-presenting cells and its MHC class I presentation to cytotoxic T lymphocytes. After synthesis and insertion of murine splenocyte IL-15 cDNA-sequence into the second multiple cloning site of pIRES, CHO cells were transfected in order to prove cytokine secretion *in vitro* using ELISA. Correct insertion of the gene sequences was verified by gene-specific PCR, restriction- and sequence analysis. To evaluate anti-tumour immunity *in vivo*, A/J mice will be vaccinated with the new vaccine by oral application of plasmid-bearing attenuated *Salmonella typhimurium* SL7207.
Conclusion: We generated and partly characterized a new bicistronic DNA vaccine encoding for TH and IL-15 to induce a long lasting immunity against NB.

Epidemiology

ID0590

Pharmacogenetics of BRCA variants: Vulnerability to longterm adverse effects of chemotherapy or radiation in cancer patients

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BRCA variants lead to a high lifetime risk of breast and ovarian cancer. However, relevant improved overall survival has been reported in *BRCA* mutation carriers compared to *BRCA* mutant negative patients. This has been assumed to be due to increased chemosensitivity towards DNA damaging substances. On the other side, BRCA mutations may leave patients more vulnerable to adverse effects of chemotherapy and radiation.
In a prospective cohort study of patients with platin-sensitive relapse of ovarian cancer undergoing *BRCA* gene diagnostics we will assess associations between *BRCA* mutations and t-MDS or t-AML as a sign of vulnerability to longterm adverse effects of DNA damaging substances. In addition, we will collect cases of unexpected adverse effects of radiochemotherapy. Matching these cases to disease related controls, we will genotype patients for *BRCA* to analyze associations to therapy-related vulnerability.
Literature and review of the clinical trial reports point to an incidence rate of t-AML or t-MDS that is higher in patients with deleterious germline BRCA mutations than in BRCA negative patients. For example, the rate of AML was 1–2% in the drug development studies of the first PARP-inhibitor for patients with *BRCA* mutations and relapsed ovarian cancer.
BRCA mutations may lead to less effective DNA repair with higher error tolerance. Thus, there may be a greater probability to develop new genetic mutations resulting in t-AML or t-MDS. For breast cancer, higher rates of t-AML samples than of primary AML samples with a reduced expression of the BRCA 1 gene has been reported in the literature.

Gastrointestinal (Colorectal) Cancer

ID0576

Overexpressing endogenous retroviral elements in chemorefractory colorectal adenocarcinoma cells are repressed by antiviral drugs

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Background: Endoretroviruses account for circa 8% of all transposable elements found in the genome of humans and other animals. Traces of human endogenous retroviruses are physiologically expressed in ovarial, testicular and placental tissues as well as in stem cells. In addition, a number of these fossil viral elements have also been related to carcinogenesis. However, a relation between endoretroviruses expression and chemoresistance has not been reported yet.
Methods: Twenty colorectal carcinoma patient samples were scrutinized for HERV-WE1 and HERV-FRD1 endoretroviruses using immunohistochemical approaches. In order to search for differential expression of these elements in chemotherapy refractory cells, a resistant HCT8 colon carcinoma subline was developed by serial etoposide exposure. Endoretroviral elements were detected by immunocytochemical staining, qPCR and ELISA. IC50-values of antiviral and cytostatic drugs in HCT8 cells were determined by MTT proliferation assay. The antivirals-cytostatics interaction was evaluated by the isobologram method.
Results: In this work, we show for the first time that HERV-WE1, HERV-FRD1, HERV-31, and HERV-V1 are a) simultaneouslyexpressed in treatment-naïve colon carcinoma cells and b) upregulated after cytostatic exposure, suggesting that these retroviral elements are intimately related to chemotherapy resistance. We found a number of antiviral drugs to have cytotoxic activity and the ability to force the downregulation of HERV proteins in vitro. We also demonstrate that the use of different antiviral compounds alone or in combination with anticancer agents results in a synergistic antiproliferative effect and downregulation of different endoretroviral elements in highly chemotherapy-resistant colorectal tumor cells.

ID0596

Expanded analyses of NAPOLI-1: Phase 3 study of nal-IRI (MM-398), with or without 5-fluorouracil (5FU) and leucovorin (LV), versus 5-fluorouracil and leucovorin (5FU/LV), in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy

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Question: Nal-IRI is a nanoliposomal encapsulated formulation of irinotecan. OS in the ITT population was significantly longer with nal-IRI+-5FU/LV (n = 117) vs 5FU/LV (n = 119) (median OS was 6.1 m vs 4.2 m; unstratified HR = 0.67, log-rank test p = 0.012). Most frequent grade 3+ AEs included neutropenia, fatigue and GI-effects. These expanded, pre-specified analyses have been presented.
Methods: Patients with mPAC (n = 417) previously treated with gemcitabine-based therapy, were randomized 1:1:1 to receive: Nal-IRI (120 mg/m^2; IV 90 min) q3w; 5FU (2,000 mg/m^2; 24 h) + LV (200 mg/m^2; 30 min) ×4w followed by 2w rest; or combination of nal-IRI (80 mg/m^2; IV 90 min) prior to 5FU (2,400 mg/m^2; 46h) + LV (400 mg/m^2; 30min) q2w. Primary endpoint was OS. The ITT population included all randomized patients; the Per Protocol (PP) population included patients who received ≥80% of the target dose in the first 6 weeks and did not violate any in/exclusion criteria.
Results: Analysis of the PP populations confirmed the favorable OS of the combination nal-IRI+5FU/LV, which was also reflected by the PFS, ORR and CA19-9 levels. Median OS in the PP population for nal-IRI+5FU/LV-arm was 8.9 m (n = 66) vs 5.1 m (n = 71) for 5FU/LV (unstratified HR = 0.57, log-rank test p = 0.011). The nal-IRI monotherapy arm did not show a statistically significant OS improvement over 5FU/LV. Analysis of subgroups, based on pretreatment characteristics including stage at diagnosis, time since initial histological diagnosis, prior lines of therapy, time since last prior therapy, and CA19-9, favored OS for the nal-IRI+5FU/LV arm.
Conclusions: Expanded analysis of the PP population and sensitivity analyses support the favorability of nal-IRI+5FU/LV over 5FU/LV, with amanageable safety profile.

Gastrointestinal (Noncolorectal) Cancer

ID0592

A tumor protective role of Hemeoxygenase-1 in the Barrett's sequence?

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The esophageal adenocarcinoma (EAC) is characterized by an increasing incidence in the western population. An improvement in early diagnoses and advanced treatment options is needed because the overall survival is still poor due to early lymphatic metastasis. The redox status mediated by the hemeoxygenase-1 (HO-1) could play a potential therapeutic target in EAC.
To span the Barrett's sequence resulting in EAC, we used the epithelial (EPC1, EPC2), metaplastic (CP-A), dysplastic (CP-B) and adenocarcinoma (OE19, OE33) cell lines to investigate the redox status enzymes by RT- and qRT-PCR and the influence of 5-fluorouracil (5-FU) in OE33 and OE19 cells.
The detoxifying enzymes glyoxalase 1 (GLO1) and 2 (GLO2), HO-1 as well as their inductive transcription factor Nrf2 are increased with the Barrett's sequence from squamous epithelium to EAC. The EAC cell line OE33 is highly receptive for 5-FU with an IC50 of 0.74µM, however 5-FU has no significant proliferation inhibitory effect in the EAC cell line OE19. GLO1 is only slightly increased in 5-FU treated OE33 and OE19 cells (1.5fold) after 48h. Whereas HO-1 is increased in 1µM and 10µM 5-FU treated OE33 after 24h, 48h and 72h with a maximal induction by 5.4fold after 72h. 5-FU had no effect on HO-1 expression in OE19 cells. The transcription factor Nrf2 is only increased in 5-FU treated OE33 cell after 24h. Showing different expression levels in the cellular detoxifying enzymes GLO1, GLO2 and HO-1 in the EAC cell lines OE33 and OE19 as well as the defences in the responsiveness to 5-FU in OE33 and OE19 cells reflect a recently described heterogeneity in esophageal adenocarcinoma. Inhibition or reduction in GLO1/2, Nrf2 and HO-1 expression in 5-FU resistant tumor cells could represent a potentially therapeutically target in EAC treatment.

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ID0593

Aberrant expression levels of Wnt-signalling molecules in the Barrett's esophagus

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Lately the incidence of the esophageal adenocarcinoma (EAC) is increasing in the western population. Despite the currently available treatment options and the overall survival remains poor, due to late diagnosis and early lymphatic metastasis. The Wnt-signalling pathway has been studied in various malignancies, but its role in carcinogenesis of EAC remains illusive.
The epithelial (EPC1, EPC2), metaplastic (CP-A), dysplastic (CP-B) and adenocarcinoma (OE19, OE33) cell lines were utilized to cover the Barrett's sequence from squamous epithelium to EAC. Expression pattern of Wnt-signalling molecules were analysed by RT- and qRT-PCR.
While EPC1 and EPC2 cells show a high expression for Wnt3a and Wnt5a, whose expression is decreasing with the Barrett's sequence resulting in loss of expression in the EAC cells (OE33/OE19). We discovered an altered expression profile of all frizzled receptors (FZD 1–10) and the co-receptors LRP5 and LRP6 between the different cell lines. In OE33 cells the Wnt-inhibitory molecule Dkk1 is overexpressed consequently, while the Wnt-signalling target gene Axin2 is increasing within the Bar-

rett's sequence. Dkk1-silenced OE33 cells showed a reduced motility and proliferation rate as well as an increased receptivity for Wnt3a-mediated by β-catenin stabilization and a reduced GSK3β-(Ser9)-phosphorylation. For the first time we analysed the expression levels of a brought range of Wnt-signalling molecules including ligands, antagonists, receptors, co-receptors and downstream targets in Barrett's sequence and demonstrated altered gene expression profiles in the different stages of Barrett's progression from squamous epithelium to EAC. These findings indicate a strong contribution for of the Wnt-axis in the tumorigenesis of the esophageal adenocarcinoma.

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Genitourinary Cancer including Prostate Cancer

ID0600

Interleukin-22, a T cell secreted cytokine, contributes to renal cell carcinoma progression and is associated with poor outcome in RCC patients

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Immunotherapy holds promise in RCC therapy. However, tumor-induced immune mechanisms add to resistance in RCC and little is known about how immunotherapy affects this. Interleukin-22 (IL-22) directly stimulates tumor cells, hence we examined the effect of IL-22 and its receptor (IL22R) on both RCC overall survival (OS) and progression free survival (PFS) and characterized the biological effect of IL-22 on RCC cells.
Methods: RNA-seq data on 413 RCC cases from TCGA were analyzed by cbioportal. Intratumoral IL-22 and IL22R expression-stratified OS and PFS were calculated with Kaplan-Meier. Results were validated in an independent cohort of 40 RCC patients. FFPE-tissues were stained for IL-22 and IL22R. An array of eleven RCC cell lines was screened for IL22R expression and their biological behavior was characterized.
Results: IL22R expression in RCC patients inversely correlates with median OS (46.12 vs. 85.45 mo; p
Conclusion: We show an effect of IL-22 on RCC outcomes in two independent patient cohorts. Both intratumoral IL-22 and IL22R are associated with worse prognosis and these findings are linked to RCC biology in vitro. We suggest IL22R as a prognostic marker and for the first time provide evidence for potential negative effects of immunotherapy by inducing T cell-derived IL-22 in RCC.

Leukemia, Myelodysplasia, and Transplantation

ID0572

Cytogenetic classification according to IPSS/-R is possible from peripheral blood in patients with Myelodysplastic Syndromes

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Introduction: In myelodysplastic syndromes (MDS) International Prognostic Scoring Systems (IPSS/-R) are used to predict the individual risk for overall and AML-free survival (OS, AFS) based on the number of peripheral cytopenias, the percentage of bone marrow (BM) blasts and the cytogenetic risk by conventional chromosome banding analyses (CBA) of BM metaphases. For MDS patients (pts) with inaspirable BM (5–20%), a risk classification according to IPSS/-R is impossible due to missing cytogenetic data. Here, we ask whether IPSS/-R classification is also feasible using peripheral blood (PB).
Methods: Immunomagnetically enriched circulating myeloid CD34+ progenitor PB cells were used for Fluorescence-in-situ-hybridization (FISH) analyses with probe panels of 19 probes detecting the most common aberrations in MDS. In a multicentre German prospective diagnostic study (clinicaltrials:NCT01355913) MDS pts were analysed by FISH of CD34+ PB cells. Here, we compared cytogenetic data of 328 pts with primary MDS of our study analysed by CD34+PB-FISH with 2902 previously published MDS pts analysed by CBA.
Results: For the 2 groups (CD34+PB-FISH versus CBA) OS and AFS curves separated significantly for cytogenetic and prognostic risk groups and the IPSS/-R allowed a valid discrimination of the cytogenetic risk groups. Multivariate analyses showed that neither treatment (BSC vs. any other) nor the diagnostic tool (CD34+PB-FISH versus CBA) significantly influenced the predictive power of the scoring systems.
Conclusions: FISH cannot replace CBA as the gold standard of cytogenetic diagnostics in MDS. But for MDS pts with dry BM, a reliable valid risk stratification to IPSS/-R is now possible from PB by using comprehensive probe panels for FISH analyses of CD34+ PB cells.

Lymphoma and Plasma Cell Disorders

ID0601

Primary Cutaneous Follicle Center Lymphoma: Prognostic Impact of the ISCL/EORTC Classification for Non-MF Cutaneous -lymphomas

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Background: Primary cutaneous follicle center lymphomas (pcFCL) belong to a group of indolent non-Hodgkin B cell lymphomas. Their clinical appearance as well as their prognosis favorably differs from nodal disease and is mostly treated by local means only resulting in a long term complete remission in most of the cases. However, a proportion of patients will present with relapsing cutaneous disease. The International Society of Cutaneous Lympoma (ISCL)/European Organization for Research and Treatment of Cancer (EORTC) have published a proposal for TNM stages in primary cutaneous lymphomas other than Mycosis fungoides/Sézary syndrome.
Methods: In an attempt to validate the prognostic value of the ISCL/EORTC stage classification, a single center cohort of 29 patients (11 females, 18 males) where classified accordingly with 16 cases belonging to T1a (single lesion <5cm), 9 cases T2a (regional dissemination <15cm), 2 cases T2b (regional dissemination 15–30 cm), and one case each T3a (generalized, 2 body regions) and T3b (generalized, >2 body regions). All cases were N0 M0 B0, as by definition of primary cutaneous B cell lymphomas.
Results: After a mean follow-up of 5.7 years relapses occurred in 13 (44.8%) patients. All relapses were limited to the skin. There were no systemic progressions or lymphoma related deaths. Cases with initial T1a lesions were significantly less likely to relapse than cases with T2 or T3 disease (25.0% vs. 69.2%). Among those with limited disease, all relapse occurred in patients treated by initial surgery only.
Conclusion: The ISCL/EORTC proposal for the classification of non-MF cutaneous lymphomas showed significant prognostic value on relapse free survival in a single center cohort of pcFCL.

ID0569

Gene expression profiling in patients with plasma cell myeloma treated with novel agents

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Introduction: Novel agents like thalidomide, lenalidomide or bortezomib have in part anti-angiogenic properties. Angiogenesis plays a role in the pathogenesis and in progression of plasma cell myeloma (PCM). In this study we examined gene expression of angiogenic molecules in patients with PCM and correlated these markers to treatment response to novel agents.
Methods: We included 93 PCM patients treated with novel agents IMiDs (thalidomide or lenalidomide)-based regimens, (bortezomib (V)-based regimens or a combination of IMiD and bortezomib-based regimen (IMiD/V). The mRNA levels of angiogenic molecules were measured using the Human Angiogenesis RT2 Profiler PCR Array. The response evaluation was performed after 3 cycles.
Results: Regarding all 93 patients, gene expression of 15 from 84 genes tested (pre and post-treatment and changes in levels pre-treatment/post-treatment) were significantly different in responders compared to non-responders. Responders had a decreased expression of pro-angiogenic factors (e.g. *CCL2, HGF, MDK, PGF, IL-6, VEGFA, ANGPT2, NRP1, FGFR, MMP-9*) and increased expression of antiangiogenic factors (e.g., *TIMP3, TGF-β, PF4, JAG1 and CXCL10*). In the different treatment groups, the angiogenic gene levels (14/84) were significantly different in responders compared to non-responders in the IMiD-based group and the combination group after 3 cycles of therapy but not in the V-based group.
Conclusion: In the IMiD-containing therapy groups we found significant changes of angiogenic gene expression in responders compared to non-responders, whereas in the bortezomib-based group the difference in angiogenic gene expression was not significant. Possibly, anti-angiogenic properties play a higher role in IMID-based treatment as compared to proteasome inhibitor based treatment.

Other Topics

ID0589

A rare late side effect after curative treatment of a testicular and colorectal cancer in a now 67-year old man. A case report.

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Our patient suffered 1982 at age of 34 years from a right-sided testicular cancer (pT3 N1) and was treated with resection of the testis + RLA + 4 courses PEB. After that as documented by regular tumour control exams he remained in remission till 1/2010. Then a rectal cancer (pT3 pN0 V0 L0 R0, A-Ca) was detected and resected (TME, rectum resection + protective ileostomy).
After that an adjuvant combined CRTX was administered according to Sauer-protocol leading to a tumor-free remission.
Since 1/2015 the patient suffered from repeated haematuria and repeated episodes of urosepsis without detected cause. A renal exploration surgery of the left kidney with a uretero-cutaneo-stomy was performed. On the right site a partial proximal ureter fissure was detected. But haematuria continued. In 9/2015 a fistula between a.iliaca and the left ureter was detected and a substitution of the ureter (Ileum interponat) with ureteroanastomosis both sites with urine bladder anastomosis followed.
In summary the interaction of prior irradiation and performed abdominal surgery was estimated to be the cause of this late side effect (fistula between a.iliaca and left ureter).
Now the patient is recovered without haematuria and tumor-activity.

ID0591

Clincal trials do not often reflect patient reality in an oncology department of an academic hospital

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Introduction: In the treatment of tumor patients comorbidities, functional parameters and psychosocial factors play a decisive role,
Methods: We investigated our patients collective with NSCLC, gastric cancer and NHL with regard to the eligibility for clinical trials inclusion between 6/2014 till 6/2015. (ABC-Studies for NSCLC stage iV, neoadjuvant treatment of gastric cancer and DSHNHL-1999-1 Ricover 60-study).
Results: From our 87 new detected NSCLC patients stage IV only 7 could be included in clinical trials. 80 patients did not fulfill including criterias for the following reasons: brain metastasis, paraplegia, reduced Karnofsky-Index <50.
From 19 patients with gastric cancer only 5 patients could be treated according to S3-rules, while 14 patients had to be treated by an individual decision due to comorbidities, age, stage IV at detection.
From 23 patients considered to be eligible for the Ricover 60-study only 10 patients performed the including criterias (exclusion reasons were NYHA IV, renal insufficiency, age over 80 years and reduced KI).
Conclusion: Many clinical trials excluded the majority of patients in our oncology department of academic hospital.

Pflegerische Beiträge

ID0582

Establishing a central consultation service for oncology nursing to ensure knowledge transfer

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Background: Requirements of the DKG for Oncology Centers ask for a minimum of nurses specialized in oncology nursing in order to assure high nursing care quality. However, the required number of trained nurses is not available on a regular basis on all wards of the Center for Integrated Oncology (CIO) at the University Hospital Cologne.
Methods: We establish a central consultation service for oncology nursing for the CIO. The first two years of institutional development are financed by the *Deutsche Krebshilfe*. Two specialized oncology nurses (one with a bachelor degree) work part time for the consultation service and on a ward as well. They supply nursing teams with new evidence based information by nursing care visits, short teaching lessons during shift reports and individual training on the job with new team members.
In addition they offer special education and training for patients and their significant others if necessary. They also support care and discharge planning for patients with complex needs. The consultation service can be requested by all members of the team and by all wards and outpatient departments of the CIO.
In order to enhance professional exchange between the oncology nurses of the different departments, they plan to create a network with regular meetings. A central aim will be to continually develop the oncology nursing manual.
Results: In October 2015 we started the central consultation service; the first ward was included in December following a request of the head nurse. All wards will be included by September 2016.
Conclusion: The first steps are promising: There is a high demand of information on new treatments and special issues in oncological nursing.

Psychooncology

ID0570

Cancer and treatment specific distress and its impact on post-traumatic stress in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT)

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We investigated cancer and treatment specific distress and its impact on symptoms of post-traumatic stress disorder (PTSD) in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Patients were consulted before (T0, N = 239), three (T1, N = 150) and twelve months after HSCT (T2, N = 102). Medical (e.g., cancer entity) and demographic information, cancer and treatment specific distress (CTXD) and PTSD (PCL-C) were assessed. Random intercept models revealed that the sum score of CTXD was highest pre-HSCT (T0), and decreased until T1 (γ = –0.18, 95%CI [–0.26/–0.09]), and again until T2 (γ = –0.10, 95%CI [–0.20/–0.00]). Uncertainty, family strain and health burden were rated most distressing during HSCT. Uncertainty and family strain decreased from T0 to T1 (γ = –0.30, 95%CI [–0.42/–0.17]; γ = –0.10, 95%CI [–0.20/–0.00]) and health burden from T1 to T2 (γ=–0.21, 95%CI –0.36/0.05]). Women were more likely to report uncertainty (γ = 0.38, 95%CI [0.19/0.58]), family strain (γ = 0.38, 95%CI [0.19/0.58]) and concerns regarding appearance and sexuality (γ = 0.31, 95%CI [0.14/0.47]). Cancer entity, time since diagnosis and education did not predict CTXD. Uncertainty (γ = 0.18, 95%CI [0.12/0.24]), appearance and sexuality (γ = 0.09, 95%CI [0.01/0.16]) and health burden (γ = 0.21, 95%CI [0.14/0.27]) emerged as predictors of PTSD symptomatology across the three assessment points. Our data provide first evidence regarding the course of six dimensions of cancer and treatment specific distress during HSCT and their impact on PTSD symptomatology.

ID0573

Posttraumatic stress disorder in the course of allogeneic HSCT: a prospective study among patients with hemato-oncological diseases

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Background: Allogeneic HSCT is a life-threatening procedure often leading to psychological stress responses and even Posttraumatic Stress Disorder (PTSD). The present study provides longitudinal data investigating PTSD in patients undergoing allogeneic HSCT. We aimed to validate and expand previous results about prevalence, temporal course and predictors of PTSD among this population.
Methods: Patients were assessed before HSCT (T0), 100 ± 20 days after HSCT (T1) and 12 ± 1 months after HSCT (T2). We measured PTSD via the Posttraumatic Stress Disorder Checklist - Civilian Version (PCL-C). Additionally, sociodemographic and medical information were collected. We conducted multilevel modeling and multiple regression analyses.
Results: 239 patients participated at baseline, 150 at T1 and 102 at T2. Up to 31% met the criteria for PTSD at least once during the course of treatment. 75% of all patients showed clinically relevant levels of intrusion, 53% in avoidance, and 84% in arousal at least once. Apart from arousal, whose severity increased between T0 and T1 ($t = -2.13$, $p = 0.03$), neither the prevalence rates nor the severity scores significantly differed between time points. Impairment by pain ($t = -3.30$, $p < 0.01$), pain level ($t = 2.36$, $p = 0.02$) and being female ($t = -3.39$, $p < 0.01$) predicted PTSD across time points. Having both types of GvHD and hospital stay predicted PTSD at T2 ($t = 2.09$, $p = 0.04$; $t = 2.21$, $p = 0.03$).
Conclusions: Our results indicate that a considerable number of patients undergoing allogeneic HSCT meet the criteria for PTSD. However, the data provides no statistical evidence that allogeneic HSCT directly leads to PTSD. Psycho-oncological intervention programs should focus on pain management.

Sarcoma

ID0574

A randomized phase 1b/2 study evaluating the safety and efficacy of doxorubicin (dox) with or without olaratumab (imc3g3), a human anti-platelet-derived growth factor α (pdgfrα) monoclonal antibody, in advanced soft tissue sarcoma (sts)

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Objective: Olaratumab (IMC-3G3), a human monoclonal antibody, selectively binds PDGFRα, blocks ligand binding and enhances Dox activity.
Methods: In a phase 1b, openlabel, randomized, phase 2 study of Dox-±olaratumab in unresectable/metastatic STS, patients received Dox (75 mg/m^2 Day 1) with (Arm A) or without (Arm B) olaratumab (15 mg/kg Days 1 and 8, every 21 days), for up to 8 cycles. In Arm A, olaratumab monotherapy continued after Dox until disease progression; in Arm B, patients at progression could receive subsequent olaratumab. Primary endpoint was progressionfree survival (PFS); OS was a secondary endpoint.
Results: Of 133 patients randomized, 129 (97%) were treated (64 Arm A; 65 Arm B). Demographics were balanced. Final PFS analysis (103 events) revealed medians of 6.6 months (Arm A) and 4.1 months (Arm B) (stratified HR; 95% CI: 0.672 [0.4421.021]; p = 0.0615). Interim OS analysis (83 deaths) revealed medians of 25.0 months (Arm A) and 14.7 months (Arm B) (HR = 0.44; p = 0.0005). Objective response rates were 18.8% (Arm A) and 12.3% (Arm B) (p = 0.3407). The following Grade ≥3 adverse events occurred in ≥5% of the population: Arm A>Arm B: neutropenia (51.5% vs 33.8%); anemia (12.5% vs 7.7%); fatigue (9.4% vs 3.1%); thrombocytopenia (9.4% vs 7.7%); Arm A
Conclusions: This study of olaratumab in combination with Dox met its primary PFS endpoint and achieved an improvement of 10.3 months in median OS. Olaratumab is the first agent added to Dox to improve OS in advanced/metastatic STS in a randomized trial.

ID0578

Limb sparing procedures in sarcoma of the hand and wrist. Long term results.

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Sarcoma of the hand and wrist frequently receive the recommendation for amputation.
Method: 169 consecutive patients with 122 high grade sarcoma were analyzed after oncological surgical treatment at Frankfurt, München r.d. Isar, Bochum and Essen CC between 1981 and 2015. Ages ranged from 5 to 85 years, mean: 42,5 years. 123 patients were suffering from local recurrence or R1/R2 sarcoma remnants. Reference pathology uncovered discordant diagnosis in 17 cases. Employing multimodality treatment including major reconstructive procedures 71 upper distal limbs could be salvaged, in 22 patients extended ray-amputation were deemed necessary to achieve R0-resection, 10 external local recurrences and 4 in domo cases received major forearm or transhumeral amputation due to extended tumor growth.
Results: During the period 13 Patients died of other causes (DOC), 26 of distant metastases (DOD), not available (NA): N = 11, alive with disease (AWD): N = 9. Kaplan Meyer Analysis demonstrated subgroup cumulative survival: while chondrosarcoma (N = 16) reached 93,8% within 11 years, only 47,5% epitheloid sarcoma (N = 19) were alive at the same point. Synovial sarcoma resulted in 70,8% (N = 22), USTS in 82,2% (N = 18), myofib/fibroblastic sarcoma (N = 14) in 84,4% and all other 8 minor subgroups (N = 37) in 71,5%. After more than 11 years p.o. none of the patients died from sarcoma disease. Employing the Michigan Hand Questionnaire the rehabilitated hands reached an average of 72,3 points compared to 92,3 points of the contralateral side.
Sarcoma of the hand and wrist should be referred to specialized centers presenting the whole conservative and operative spectrum.

Skin Cancer including Melanoma

ID0595

Eine 4-Gensignatur, Teil einer prognostischen 8-Gensignatur, ist differentiell exprimiert in tumorfreier Haut von Melanompatienten

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Wir haben kürzlich eine prognostische Gensignatur in Primärmelanomen der Haut (n = 336) identifiziert. Ein Signatur-basierter Risikoscore präzisiert die Prognose des Gesamtüberlebens unabhängig vom AJCC-Staging (ROC-Analyse: AUC-Wert 0.91).
Der Risikoscore ändert die Therapiebedürftigkeit von:
(i) Patienten im AJCC-Stadium II mit niedrigem Score (60%), die zurzeit behandelt werden, denen aber adjuvante Therapie erspart werden könnte
(ii) Patienten im AJCC-Stadium I mit hohem Score (ca. 9.3%), die zurzeit nicht behandelt werden, aber adjuvante Therapie benötigen
Der Risikoscore kann auch zur Risikostratifizierung im AJCC-Stadium III eingesetzt werden, um adjuvante Therapiestudien auf Hochrisiko-Patienten zu fokussieren.
Da die Signaturgene eher im Stroma als in den Tumorzellen selbst exprimiert zu sein scheinen, haben wir die Signaturexpression in der Haut von Melanompatienten (Nachexzisionen; n = 23) mit der in Kontrollhaut (n = 24) verglichen. RNA wurde aus FFPE-Melanomen isoliert, revers transkribiert, die cDNA präamplifiziert, und die Gensignaturexpression quantifiziert.
Während 4 der 8 Signaturgene nicht differentiell exprimiert waren (0.9–1.3-fach; 3 Housekeeping-Gene: 0.8–1.2-fach), waren die 4 übrigen Gene stark erhöht exprimiert (10.1–23.4-fach) in tumorfreier Haut von Melanompatienten (Expressionsprofil homogen) im Vergleich zu Kontrollhaut (Expressionsprofil heterogen). Diese 4-Gensignatur könnte daher die Grundlage bilden für einen Genscore spezifisch für die Haut von Melanompatienten.
Ob die differentielle Expression der 4-Gensignatur eine systemische Reaktion auf die Tumorregion ist oder individuelle Risikoprofile in der Haut widerspiegelt ist gegenwärtig noch unbekannt.

Supportive Care

ID0599

Quality of life, fatigue and health behaviour aspects in cancer survivors participating in a open group-based exercise program - an explorative survey in a real-life setting

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Aims: Despite the evidence on the beneficial impact of regular physical activity (PA) during and after cancer treatment, fewer than 10% to 30% of cancer patients are active during and after treatment, respectively. Data on cancer patients and survivors taking up programs aimed at increasing PA offered outside the medical setting is scarce. This study aimed at providing insight on the characteristics of cancer patients and survivors participating in open exercise groups by means of data collected under real-life circumstances.
Methods: Cancer patients and survivors attending open group-based exercise programs in urban as well as rural areas in Tyrol, Austria, are subjected to patient-reported outcome assessment with the EORTC QLQ-C30/+HDC29, FACT-G/+BMT/+F and the GPAQ as well as a rating of their self-perceived physical capacity and history of PA behaviour at three time points in course of the offered program.
Results: The exercise program is still ongoing. Preliminary results (n = 120) suggest participants to be mainly retired female (83%) breast cancer survivors in aftercare having been physically active prior to diagnosis.
Conclusion: Results imply the uptake of this program to be limited to a certain group of cancer survivors, thereby missing those who would potentially benefit from increased PA. Further analysis will allow for the development of improved counselling strategies to encourage participation in exercise programs also in a wider range of cancer survivors.

Translational Oncology

ID0579

Translational oncology: Identification of candidate biomarkers for chemotherapy, using DigiWest multiplex protein profiling

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The analysis of cellular signaling cascades is essential for understanding the processes that underlie drug response and drug resistance. Profiling of such cell signalling cascades requires more than RNA profiling, namely the detection of protein expression and activation. Our novel DigiWest protein profiling technology enables the parallel analysis of up to 600 total and phospho proteins, from <50µg of protein sample.
Applying DigiWest, we analysed 24 fresh frozen tumor specimens from relapsed vs cured ovarian cancer patients. With 466 antibodies per sample, we compared activation states of signaling cascades and tumor marker proteins. The results allowed us to cluster relapsed vs cured patients via differential activation states of several signal transduction pathways. Based on this, we extracted a signature of 8 proteins and phosphoproteins whose differential expression was sufficient to distinguish relapsed from cured patients, thus representing promising biomarker candidates.
The results demonstrate the power of multiplex protein profiling for identification of prognostic markers for chemotherapy, and for the development of precision therapies.
Conflict of interest: NMI TT Pharmaservices offers DigiWest as a service (for research use only).

ID0594

Co-clinical assessment of tumor cellularity in pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) is a fatal malignant disease. Pretherapeutic detection of relevant prognostic marker would greatly facilitate patient care. Given recently reported protective role of tumor stroma, non-invasive detection of tumor composition is relevant for personalized approaches. In this proof-of-concept study we aimed to evaluate and image tumor cellularity as a prognostic marker in PDAC.
We stratified PDAC developed in genetically engineered mouse models (GEMM) and patients that underwent curative resection based on tumor cellularity in three subgroups: low, medium and high. We applied diffusion weighted- (DW-) MRI and thereof derived apparent diffusion coefficient (ADC) for their detection and correlated ADC with the overall survival of patients.
Histopathological analysis showed an inverse relationship of tumor cellularity and stroma content in both murine and human PDAC. Patients exhibiting low tumor cellularity revealed a significantly prolonged mean survival time (PDAClow = 21.93 versus PDACmed = 12.7 months, Log rank, $p < 0.0004$, Hazard ratio 2.23). Multivariate analysis using Cox regression method confirmed this observation ($p = 0.049$, HR = 1.69). Tumor cellularity showed a strong negative correlation with the ADC in murine ($r = -0.84$, CI=–0.90 – –0.75) and human ($r = -0.66$, CI=–0.84 – –0.36) PDAC. Examination of the lowest ADC value, found in pre-operative DW-MRI revealed prolonged survival for PDAC patients with high values (ADChigh = 41.7 months; ADClow = 14.77 months, Log rank, $P = 0.040$).
In conclusion, this study identifies high tumor cellularity as a negative prognostic factor in PDAC and supports ADC parameter as a candidate marker for the non-invasive stratification of PDAC.

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