V683
Perioperative Chemotherapie mit Docetaxel, Oxaliplatin und Fluorouracil/Leucovorin (FLOT) versus Epirubicin, Cisplatin und Fluorouracil oder Capecitabine (ECF/ECX) bei resektablem Adenokarzinom des Magens oder ösophago-gastralen Überganges (FLOT4-AIO): Eine randomisierte, multizentrische Phase 3-Studie / Perioperative chemotherapy with docetaxel, oxaliplatin and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A randomized, multicenter phase 3 trial

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Introduction: The MAGIC trial established perioperative (periop) epirubicin, cisplatin, and 5-FU (ECF) as a standard treatment for patients (pts) with operable esophagogastric cancer,

but survival continues to remain poor. FLOT4 (NCT01216644) is a multicenter, randomized, investigator-initiated, phase 3 trial. It compares the docetaxel-based triplet FLOT with the anthracycline-based triplet ECF/ECX as a periop treatment for pts with resectable gastric or GEJ adenocarcinoma.

Methods: Eligible pts of stage ≥cT2 and/or cN+ were randomized to either 3 preoperative and 3 post-operative 3-week cycles of ECF/ECX (epirubicin 50 mg/m2, cisplatin 60 mg/m², both d1, and 5-FU 200 mg/m² as continuous infusion or capecitabine 1250 mg/m2 orally d1-21) or 4 pre-operative and 4 post-operative 2-week cycles of FLOT (docetaxel 50 mg/m2, oxaliplatin 85 mg/m², leucovorin 200 mg/m², and 5-FU 2600 mg/m² as 24-hour infusion, all d1). The primary endpoint was overall survival (OS; 80% power; HR of 0.76; 2-sided log-rank test at 5% type I error).

Results: Between Aug 2010 and Feb 2015, 716 pts (360 ECF/ECX; 356 FLOT) were randomly allocated. Baseline characteristics were similar between arms (overall, male 74%; median age 62; cT3/T4 81%; cN+ 80%; GEJ 56%). 91% and 37% of pts with ECF/ECX and 90% and 50% with FLOT completed planned pre-operative and post-operative cycles, respectively. Median follow-up was 43 mon. 369 pts died (203 ECF/ECX; 166 FLOT). FLOT improved OS (mOS, 35 mon with ECX/ECF vs. 50 mon with FLOT; HR 0.77 [0.63 - 0.94]; p=0.012). 3y OS rate was 48% with ECF/ECX and 57% with FLOT. FLOT also improved PFS (mPFS, 18 mon with ECX/ECF vs. 30 mon with FLOT; HR 0.75 [0.62 - 0.91]; p=0.004). Periop complications were 50% with ECF/ECX and 51% with FLOT. 30- and 90-day mortality was 3% and 8% with ECF/ECX and 2% and 5% with FLOT. There was more G3/4 nausea and vomiting with ECF/ECX and more G3/4 neutropenia with FLOT.

Conclusion: Periop FLOT improved outcome in patients with resectable gastric and GEJ cancer compared to periop ECF/ECX and is new standard therapy in this setting.

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V684
Therapiereduktion bei Patienten mit fortgeschrittenem Hodgkin Lymphom und negativem Interim-PET: Endauswertung der internationalen, randomisierten Phase III HD18 Studie der Deutschen Hodgkin Studien Gruppe / Treatment reduction in patients with advanced-stage-Hodgkin-lymphoma and negative interim PET: Final results of the international randomized phase 3 trial HD18 by the German Hodgkin Study Group

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Introduction: The HD18 trial of the German Hodgkin Study Group (GHSG) aimed to assess the feasibility of decreasing the number of eBEACOPP (dose escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) cycles in patients with a rapid response as determined by PET-2 negativity without loss of efficacy in terms of progression-free survival (PFS).

Methods: Patients aged 18-60 years were recruited between 05/2008 and 07/2014. PET-2 was centrally assessed with FDG uptake not higher than the mediastinal blood pool defined as negative. Patients with negative PET-2 were randomly assigned to receive 6 or 2 additional cycles until June 2011, and 4 or 2 additional cycles after the protocol amendment

in June 2011, respectively. PET-positive residues after chemotherapy were irradiated. The trial was designed to exclude inferiority of 6% or more of the experimental treatment (4 cycles of eBEACOPP) compared with the pooled standard treatment (8/6x cycles of eBEACOPP) at 5 years.

Results: We enrolled 2,101 patients. 1,005 patients with negative PET-2 were randomly assigned to either 8/6 cycles of eBEACOPP (n=504) or 4 cycles of eBEACOPP (n=501). With a median follow-up of 55 months, estimated 5-year PFS in the per-protocol set was 90.8% (87.9-93.7) with 8/6 cycles of eBEACOPP and 92.2% (89.4-95.0) with 4 cycles eBEACOPP (difference +1.4%, 95% CI 2.7-5.4, excluding the non-inferiority margin of -6%). In the standard arm, 95% of patients had at least one acute hematological toxicity of CTCAE grade 3-4 compared with 90% in the experimental arm, including severe infections in 75 (15%) and 40 (8%) patients, respectively. Acute severe organ toxicities were documented for 91 (18%) and 38 (8%), respectively. 25 patients (5%) in the standard group and 9 (2%) in the experimental group died; most frequent cause of death was second malignancy (11 and 1 patient, respectively). No patient in the experimental group died from treatment-related toxicities. Estimated 5-year overall survival (OS) in the per-protocol set was 95.4% (93.4-97.4) with standard eBEACOPP, and 97.7% (96.2-99.3) with 4 cycles of eBEACOPP (log-rank p=0.004).

Conclusion: Metabolic response assessment using FDG-PET after 2 cycles of eBEACOPP allows the reduction from therapy with 8/6 to only 4 cycles without loss of efficacy as determined by PFS. Furthermore, the improved tolerability of the abbreviated treatment leads to a significant OS benefit.

V685
Hämophagozytische Lymphohistiozytose (HLH): Sepsis-mimic und diagnostische Herausforderung / Hemophagocytic lymphohistiocytosis (HLH): A cytokine storm disorder mimicking sepsis and a diagnostic pitfall on intensive care units
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Introduction: Hemophagocytic lymphohistiocytosis (HLH) constitutes a severe hyper-inflammatory syndrome emerging from a deregulated immune system. If not recognized and treated effectively and early, patients (pts) develop cytokine storm disease with multiorgan failure. Due to the wide spectrum of triggering conditions (i.e. infections, malignancies), clinical presentation is highly diverse. Diagnostic vigilance on intensive care units (ICU) is a challenge, as patients with HLH and sepsis share main clinical features. Yet, in contrast to sepsis, HLH pts require immediate immunosuppression. Due to missing systematic data on adult HLH in Germany, a national multicenter registry (www.hlh-registry.org) was established.

Methods: 151 patients have been registered since 8/2010. To confirm diagnosis, HLH-2004 diagnostic criteria and the HScore (http://saintantoine.aphp.fr/score/) were used. Pts were eligible for analysis, if they either fulfilled HLH-2004 diagnostic criteria (5 required) or met at least 4 of these criteria and had a probability of more than 90 % for HLH according to the HScore.

Results: 132/151 pts (87 %) fulfilled the inclusion criteria, with 46 pts (36 %) being female. Median age at diagnosis was 50 years (range, 17 - 81). Triggering diseases were infections in 58 (44 %), malignancies in 47 (36 %), and autoimmune disorders in 13 pts (10 %). Besides fever, splenomegaly, and cytopenia, pts presented with liver or renal failure, bleeding, or pulmonary disease. 74 % of all pts showed peak ferritin values beyond 10,000 µg/l, highlighting the importance of this marker in diagnosing HLH. Pts with lymphoma-associated HLH had a significantly higher sIL2-R/ferritin ratio than pts with HLH due to other causes (2.38 vs 0.63; p=0.001), a finding which may give a hint towards a yet undetected lymphoma in pts harboring no obvious trigger. Treatment mostly included steroids (119/132 pts), etoposide (65 pts), or iv immunoglobulins (60 pts). Cyclosporine was given in 27 pts. In single cases, alemtuzumab or tocilizumab were used. Consolidating allogeneic stem cell transplantation was done in 4 pts, cytokine adsorption in 3 pts. With a median follow up of 154 days, 70/132 pts (53 %) are alive.

Conclusion: Adult HLH requires diagnostic vigilance throughout all medical subspecialties. Highly elevated ferritin values are strongly suggestive for potential HLH. Identifying the underlying disease is crucial, as trigger-directed therapy is pivotal for successful treatment.

V686
Positronen-Emissionstomographie-gesteuerte Therapie aggressiver Non-Hodgkin-Lymphome - Endergebnisse der PETAL-Studie / Positron-emission tomography-guided therapy of aggressive non-Hodgkin lymphomas - final results of the PETAL trial

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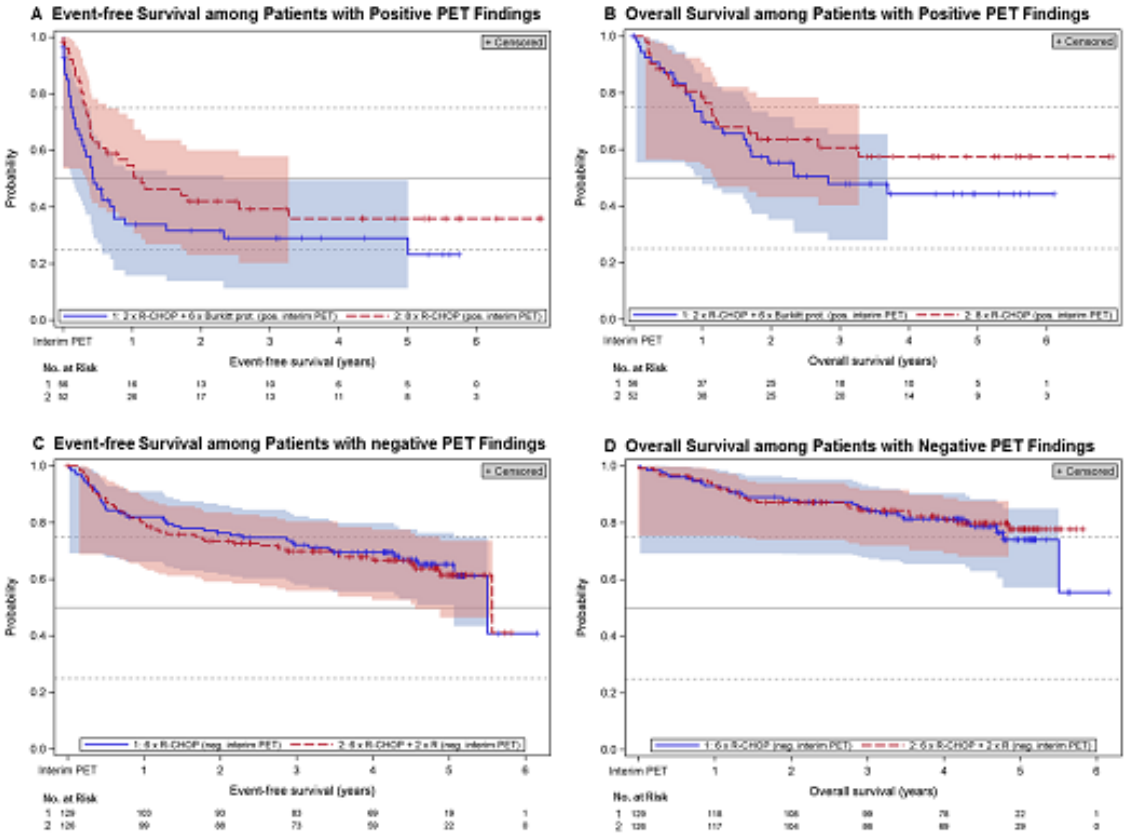
Introduction: We tested whether interim positron-emission tomography (PET) may be used to guide therapy in aggressive lymphomas treated with CHOP. Patients with CD20-positive lymphomas additionally received rituximab (R).

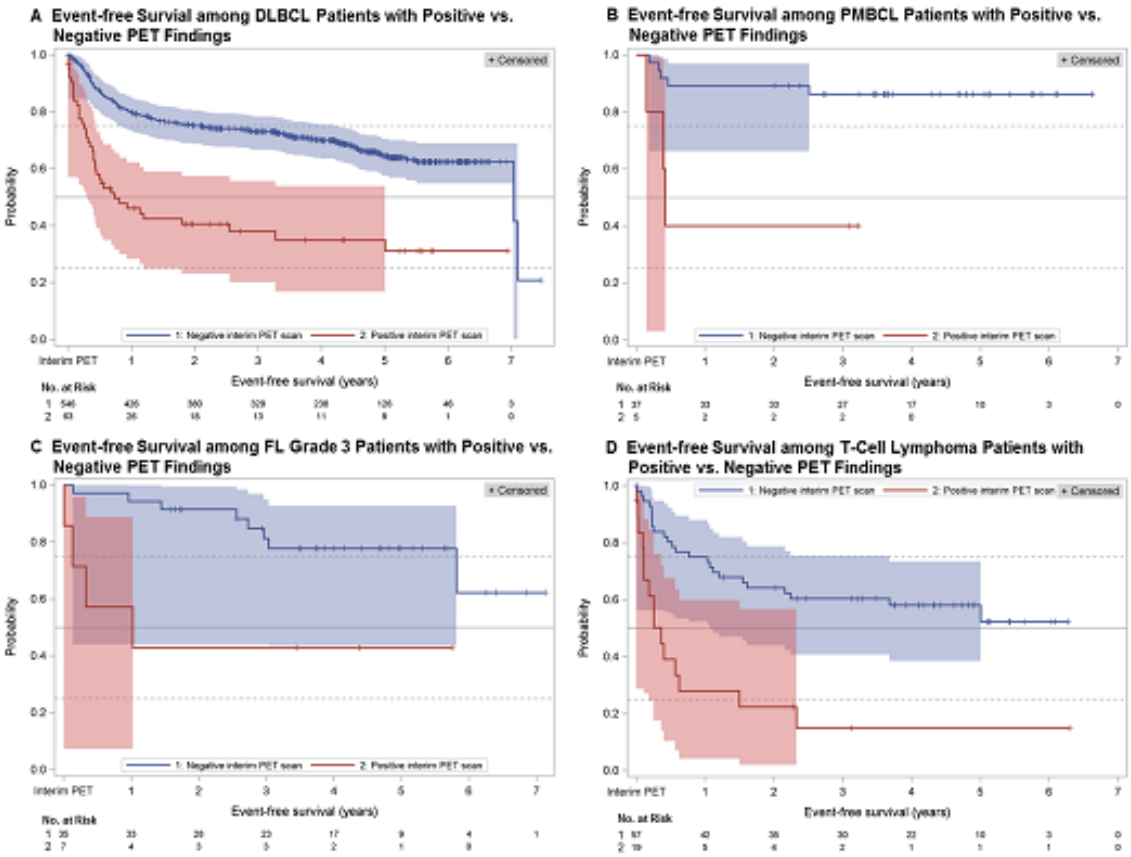
Methods: Newly diagnosed patients received 2 cycles (R-)CHOP followed by PET scanning. PET-positive patients were randomized to receive 6 additional cycles (R-)CHOP or 6 blocks of the German Burkitt's lymphoma protocol. PET-negative patients with CD20-positive lymphomas were randomized or allocated to receive 4 additional cycles R-CHOP or the same treatment with 2 extra doses rituximab. The primary end-point was event-free survival at 2 years.

Results: Interim PET was positive in 108 (12.5%) and negative in 754 (87.5%) of 862 patients treated, with statistically significant differences in event-free and overall survival between PET-positive and PET-negative patients. Among the former, 52 were randomized to (R-)CHOP and 56 to the Burkitt protocol. Two-year event-free survival rates were similar in both groups (42.0% [95% confidence interval [CI], 28.2 to 55.2] and 31.6% [95% CI, 19.3 to 44.6], respectively), but the Burkitt protocol produced significantly more toxicity. Among the PET-negative patients, 129 were randomized to R-CHOP and 126 to R-CHOP with additional rituximab. Event-free survival rates were 76.4% (95% CI, 68.0 to 82.8) and 73.5% (95% CI, 64.8 to 80.4), respectively (Fig. 1). The results were consistent in all age-, gender- or histology-related subgroups analyzed. Overall survival also remained unaffected by treatment changes.



[Fig. 1]

Outcome prediction by interim PET was equally effective in all major lymphoma subtypes (Fig. 2), and independent of the International Prognostic Index.



[Fig. 2]

Conclusions: Interim PET predicted outcome in patients with aggressive lymphomas treated with (R-)CHOP. PET-based treatment intensification did not improve survival.

V687
Alloreaktivität richtet sich gegen die Mikro-architektur des Knochenmarks nach allogener hämatopoietischer Zelltransplantation / Alloreactivity targets the bone marrow microenvironment following allogeneic hematopoietic cell transplantation
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Allogeneic hematopoietic cell transplantation (allo-HCT) represents the most powerful form of cellular therapy for hematological malignancies. Donor T-cell mediated immune reactions are critical for leukemia control, but can also target other tissues, causing graft-versus-host-disease. Little attention has been paid to alloreactivity against the bone marrow (BM) microenvironment and how its structural damage affects hematopoiesis.

Here, we studied in an MHC-matched, minor antigen mismatched mouse model (C3H.SWàB6) the effects of lethal radiation conditioning followed by infusion of pure hematopoietic stem cells (cKIT+Sca1+Lin-) +/- T-cell subsets. At 1, 2, 3, and 4w post-HCT bones and marrow were analyzed by FACS and 3D-confocal microscopy.

Post allo-HCT there was a transient weight loss in all groups (HSC and HSC+Tc), but no overt GVHD. Total BM cell counts dropped, but at 2w mice given HSC had significantly higher absolute BM counts compared with HSC+Tc recipients. Strikingly, B-cell recovery occurred promptly in HSC recipients but was severely impaired in the HSC+Tc group. Likewise, granulocyte recovery at 2, 3, and 4w was significantly better in HSC vs. HSC+Tc recipients. Alloreactive (but not congenic) T cells severely impaired not only hematopoiesis but also disrupted the non-hematopoietic compartment: at 2 wks post allo-HCT, B6 mice given pure C3H.SW-HSC showed prompt recovery of BM cellularity and numbers of endothelial cells (CD45-Ter119-CD31+), and CXCL12-abundant reticular ("CAR"; CD45-Ter119-CD31-CD140B+) cells. In contrast, recipients of HSC+T cell subsets had significantly lower absolute numbers of stromal subsets (arterial, sinusoidal and CAR cells) in the BM and their recovery was significantly delayed. 3D-confocal microscopy confirmed these observations and revealed rapid recovery of extracellular matrix and sinusoidal vascular structures, with simultaneous disappearance of adipocytes at 2w post-HCT in

the HSC group. In contrast, in recipients of HSC+Tc severe disruption of the structural integrity with impaired recovery of the BM microvessels but rather occupation of space by adipocytes at 2 wks post-HCT.

Our data shows the impact of alloreactivity on the non-hematopoietic BM compartments in terms of damage and reconstitution of the microenvironment, and ultimately hematopoietic recovery. Whether alloreactive T cells directly target these structures or act via an inflammatory milieu needs to be elucidated.

V688
Einfluss von Thrombozyten-exprimiertem RANKL auf die Metastasierung / The role of platelet-derived RANKL in metastasis
Stefanie Maurer, Tübingen, D

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The important role of platelets in tumor progression and metastasis has been recognized for more than 50 years, but the underlying molecular mechanisms are still a matter of research. Multiple mechanisms including supply of growth factors, facilitation of endothelial adhesion and transmigration supporting establishment of secondary lesions and also empowering immune evasion have been implicated to play a role. Recently, Labelle et al. demonstrated that platelets endorse a prometastatic phenotype of cancer cells that have entered the blood stream by providing TGF-β and a yet unknown membrane-bound factor (Labelle et al., Cancer Cell 2011). Here we identify the TNF family member RANKL as platelet-expressed factor that facilitates metastasis. We demonstrate by FACS and qPCR-analysis that megakaryocytes upregulate RANKL upon differentiation, and platelets activation dependently express RANKL (pRANKL) on the surface. Immunofluorescence staining and immuno-electron microscopy revealed that tumor cells (that express RANK, but not RANKL) rapidly get coated by platelets, which confers RANKL pseudo-expression due to transfer and integration of pRANKL in the tumor cell membrane. This in turn induced a prometastatic gene signature by altering expression of ZEB1, SNAIL, Slug, Fibronectin and Serpine1 in tumor cells and enhanced their migratory propensity as revealed by qPCR and transwell assays. The specific involvement of pRANKL in metastasis was further confirmed using mice with a platelet-specific RANKL knockout (RANKL fl/fl Pf4 cre/+ on a genetic C57BL/6 background) which, compared to control animals, displayed significantly reduced metastasis upon tail vein injection of B16-F10 melanoma cells. Notably, neutralization of pRANKL with RANK-Fc fusion-protein or denosumab, which is approved for the treatment of benign and malignant osteolysis, prevented the deleterious effects of pRANKL on prometastatic gene expression and tumor cell migration as well as metastasis in the B16-F10 lung metastasis model in vivo. Together, our data not only unravel the pathophysiological role of pRANKL in cancer metastasis; they also provide a functional explanation for unintended clinical findings that denosumab improved survival of patients with metastatic cancer (e.g., Gnant et al., 2015). Our findings thereby constitute a clear rationale to clinically evaluate adjuvant

treatment with denosumab in patients with solid tumors to prevent tumor progression and metastasis.