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Abstracts

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Poster Hämatologie

P01

Flow cytometry-based leukemic cell enrichment followed by mutational profiling for measurable disease detection in AML

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Background: Persistent measurable residual disease (MRD) is an independent and increasingly important prognostic marker in acute myeloid leukemia (AML). Currently, MRD is determined by multi-parameter flow cytometry (MFC) or PCR-based methods detecting leukemia-specific fusion transcripts and mutations. However, while MFC is highly operator-dependent, PCR-based methods are only available for a minority of AML patients.

Methods: We developed a sensitive and broadly applicable method for MRD detection by combining MFC-based leukemic cell enrichment using an optimized combinatorial antibody panel targeting CLL-1, TIM-3, CD123 and CD117 followed by mutational analysis using next generation sequencing (NGS) of recurrently mutated genes in AML.

Results: In dilution experiments this combined method showed a sensitivity of 10^−4 to 10^−5 for residual disease detection. In prospectively collected bone marrow remission samples this marker combination allowed for a median 67-fold cell enrichment with sufficient DNA quality for mutational analysis in 39 out of 41 patients. Twenty-one samples (53.8%) tested MRD positive, whereas 18 (46.2%) were negative. With a median follow-up of 559 days 71.4% of MRD positive (15/21) and 27.8% (5/18) of MRD negative patients relapsed ($p = 0.0065$). Accordingly, the cumulative incidence of relapse (CIR) was significantly higher for MRD positive patients than for MRD negative patients (5-year CIR: 90.5% vs 28%, $p < 0.001$). In multivariate analysis, MRD positivity was the most prominent factor for CIR.

Conclusions: MFC-based leukemic cell enrichment using antibodies against CLL-1, TIM-3, CD123 and CD117 followed by mutational analysis allows highly sensitive MRD detection and is informative on relapse risk in the majority of AML patients.

The authors marked with an asterisk (*) are the corresponding authors.

P02

Successful management of pregnancy in three women with advanced Ph-negative myeloproliferative diseases

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Background: Ph-negative myeloproliferative diseases (MPN) in patients with childbearing potential generate several therapeutic challenges. The most common complications during pregnancy in such patients are maternal thrombosis, hemorrhage and placental dysfunction leading to fetal growth restriction or loss. The live birth rate is about 70% (Maze et al., JAMA Network, 2019). Pregnancies are reported rarely in women with primary myelofibrosis (Griesshammer et al., Expert Rev Hematology, 2018).

Methods: We report 3 patients who were managed during pregnancy at our department; a 37 years old patient with advanced polycythemia vera (PV) and two women (30 and 28 years old) with overt primary myelofibrosis (PMF).

Results: Both patients with PMF were pretreated with pegylated interferon-alfa 2a (pegIFa) and could temporarily pause therapy during pregnancy. The patient with PV continued pegIFa successfully throughout pregnancy. All patients received antithrombotic prophylaxis. The live birth rate was 100%. No complications occurred during or after pregnancy.

Conclusions: We report the successful management of three pregnant patients with advanced MPN. There is very limited information on management of pregnancy in patients with advanced primary myelofibrosis with less than 20 reported cases (Griesshammer et al., Expert Rev Hematology, 2018). Our case reports confirm earlier data on the safe application of pegIFa prior and during pregnancy in patients with MPN (Kiladjian et al., Leukemia, 2008).

P03

Combined targeting of distinct c-Myc and JunB transcriptional programs for multiple myeloma therapy

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Background: c-Myc plays a pivotal role in multiple myeloma (MM) pathogenesis; the BET protein BRD4 is a key regulator of

c-Myc transcription. A pathophysiologic role in MM was also attributed to the AP-1-family member JunB. Despite promising results, approaches to target transcription factors (TFs), such as c-Myc and JunB, are challenged by redundancy phenomena.

Methods: The functional relevance of BRD4/c-Myc- and JunB-induced transcriptional programs were investigated using knockdown approaches followed by survival, proliferation assays, flow cytometry, WB and qPCR.

Results: MZ-1 is a novel proteolysis-targeting chimera (PROTAC) that combines the recognition sequence for the E3-ligase Von-Hippel-Lindau with JQ1, a moiety that targets BRD4. In MM cell lines and primary cells, MZ-1 significantly decreased BRD4 and c-Myc protein levels followed by inhibition of MM cell growth and survival. Patient-derived BMSC- or exogenous IL-6-induced BRD4/c-Myc upregulation in MM cells was inhibited by MZ-1, indicating that targeting BRD4 overcomes the protective effect of the microenvironment. Notably, MZ-1 did not have an impact on BMSCs/IL-6-induced upregulation of JunB RNA or protein levels. Conversely, knockdown of BMSC/IL-6-triggered JunB upregulation in TetshJunB/MM.1S cells did not decrease BRD4/c-Myc RNA or protein levels. These data support the co-existence of c-Myc- and JunB-mediated proliferative programs initiated by the same stimuli.

Indeed, MZ-1 in combination with knockdown of BMSC/IL-6-triggered JunB upregulation in TetshJunB/MM.1S cells synergistically inhibited tumor cell proliferation and survival.

Conclusions: Our data demonstrate for the first-time the existence of non-overlapping c-Myc- and JunB-regulated transcriptional programs; supporting the therapeutic benefit of combined targeting of these two TFs in MM.

P04

Overexpression of p53 is an independent adverse prognostic factor in primary testicular diffuse large B-cell lymphoma

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Background: Primary testicular diffuse large B-cell lymphoma (PT-DLBCL) is a rare and aggressive disease and displays a unique subtype within the heterogeneous group of DLBCL. Overexpression of the tumour protein 53 (TP53) has been reported as negative prognostic marker in a broad range of human tumours especially in haematological malignancies but its prognostic role in PT-DLBCL remains unclear. This study focuses on the role of p53 expression in PT-DLBCL and its prognostic significance.

Methods: In this study, we determined p53 expression status immunohistochemically in samples of 24 patients with newly diagnosed PCNSL and followed these patients for a median interval of 6.9 years. Overexpression of p53 was defined as at least 50% positive tumour cells on IHC analysis of the testicular specimen.

Results: Twenty-four males with a median age of 67 years were included in the study. Overexpression of p53 was observed in 10 (42%) patients and was more common in patients with higher clinical stage, a more unfavourable risk profile according to established prognosis scores (R-IPI, NCCN-IPI). P53 expression was associated with a significantly worse 10-year PFS (10 vs 66%) as well as 10-year OS (12 vs 70%). This finding prevailed after adjusting for the NCCN-IPI.

Conclusions: We could demonstrate that immunohistochemical overexpression of p53 was significantly associated with impaired PFS and OS independently of established risk scores. Therefore, p53 expression can be seen as a new biomarker for risk stratification in PT-DLBCL

P05

Changes in treatment options and survival in real life during the last 4 decades in patients with chronic myelomonocytic leukemia

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Background: Chronic myelomonocytic leukemia (CMML) is a hematopoietc malignancy in elderly patients. Changes in treatment options and survival over a long period of time are poorly investigated.

Methods: Using data from the Austrian Biodatabase for CMML (ABCMML) we analyzed the use of various treatment options and its impact on survival at different time periods during the last 4 decades.

Results: In 552 patients information regarding OS was available and in 168 of them data regarding treatment. The proportion of patients treated with hydroxyurea (HU), cytostatics and azacitidine (AZA), respectively was 0/0/0% before 1990, 67/22/0% 1990–2000, 50/25/32% 2000–2010, and 37/12/52% after 2010. During these 4 decades median OS increased from 13, to 19, 26 and 27 months, respectively (median OS before vs after 2000 16 vs 27 months, $p=0.047$). Collectively, AZA treated patients, but not patients treated with the other treatment options, had an improved survival as compared to CMML-patients without AZA-therapy (19 vs 25, $p=0.041$). When looking at subgroups the following patient cohorts had a significant survival benefit in association with AZA-therapy: patients with Hb >10 g/dL, patients with monocytosis >10 G/L and patients with mutations in RASopathy genes.

Conclusions: Our results demonstrate an improvement of survival in CMML patients in the new millenium which was associated with the use of AZA. Patients without significant anemia, with massive monocytosis and patients with hyperactive RAS signaling pathway seem to have the largest benefit from this treatment.

P06

The clinical significance of inflammation in patients with chronic myelomonocytic leukemia

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Background: Chronic myelomonocytic leukemia (CMML) is a rare hematopoietic malignancy which is mostly diagnosed

in elderly patients who frequently have one or more comorbidities. The clinical impact of infection and/or noninfection derived inflammation in CMML patients is poorly investigated.

Methods: Using data from the Austrian Biodatabase for CMML (ABCMML) we determined the frequency of positive (CRP) and negative (albumine) inflammation parameters in patients with CMML and their potential correlations with clinicolaboratory features.

Results: Data on inflammation parameters from charts were available in 156 patients. More than 10 fold elevated CRP levels were found in 37/151 (25%) patients. The median survival of these patients was 9 months as compared to 23 months of the remaining patients ($p=0.0005$). On the other hand reduced albumine levels were observed in 14/56 (25%) patients who had a median OS of 6 vs 23 months, $p=0.0165$). If only patients without documented infection were analyzed, both CRP and albumin levels lost their significant impact on survival.

Conclusions: Our findings show that laboratory parameters of infection associated inflammation can be found in a proportion of patients with CMML and predicts inferior survival.

P07

The clinical significance of blood coagulation in patients with chronic myelomonocytic leukemia

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Background: Chronic myelomonocytic leukemia (CMML) is a rare hematopoietc malignancy which is mostly diagnosed in elderly patients who frequently have one or more comorbidities. The clinical significance of abnormalities in blood coagulation in CMML is poorly investigated.

Methods: Using data from the Austrian Biodatabase for CMML (ABCMML) we analyzed the frequency of disturbances of blood coagulation and potential correlations with clinicolaboratory features in patients with CMML.

Results: Data on blood coagulation from charts were available in 172 patients, patients on Marcoumar or DOACs were excluded from analysis. Reduced PTZ values (< 70%) were found in 49/104 (43%) patients. Interestingly, the median survival of patients with reduced PTZ levels was significantly shorter than of patients without coagulation abnormalities (19 vs. 49 months, $p=0.0059$). Patients with reduced PTZ had higher WBC counts and lower platelet counts. The proportion of patients with hypofibrinogenemia was higher in patients with reduced PTZ (30% vs 6%, $p=0.0079$) but the proportion of patients with documented bleeding was not different (19% vs 16%, $p=0.8194$).

Conclusions: Our findings show a high prevalence of abnormalities of plasmatic coagulation, which is associated with laboratory features of advanced disease. Although CMML patients with disturbances of blood coagulation have an inferior survival, bleeding does not seem to have a major clinical impact.

P08

The significance of tumor comorbidity in patients with chronic myelomonocytic leukemia

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Background: CMML is a rare hematopoietc malignancy which is mostly diagnosed in elderly patients who frequently have one or more comorbidities and comedications. The clinical significance of an additional tumor comorbidity in CMML is poorly investigated.

Methods: Using data from the ABCMML we analyzed the prevalence of additional clonal diseases and potential correlations with clinicolaboratory features in patients with CMML.

Results: Data on tumor comorbidity from charts were available in 333 patients. Solid tumors, Non Hodgkin lymphomas and paraproteinemias were found in 60/333 (18%), 9/333 (2.7%) and 12/333 (3.6%) patients, respectively. The presence of additional solid tumors and of Non Hodgkin lymphomas had no significant influence on the overall survival of CMML patients, the presence of a paraprotein, however, was associated with an inferior survival (6 vs 25 months, $p=0.0076$). CMML patients with monoclonal paraprotein were comparable with other CMML patients regarding WBC counts, Hb levels and platelet counts.

Conclusions: Our findings show a prevalence of additional malignancies which is in the range of individuals without CMML. The detection of monoclonal paraproteinemia in CMML predicts a poor outcome.

P09

Clinicolaboratory characteristics of chronic myelomonocytic leukemia patients with CD56 expression

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Background: Chronic myelomonocytic leukemia (CMML) is a rare hematopoietc malignancy which is mostly diagnosed in elderly patients. CD56 expression can be found in a subgroup of patients but the clinicolaboratory characteristics of these patients are poorly investigated.

Methods: Using data from the Austrian Biodatabase for CMML (ABCMML) we analyzed the frequency of CD56 expression in CMML patients and compared clinical, hematologic and molecular features in patients with and without CD56 expression.

Results: Data on the immunopheotypic characterization including CD56 from charts were available in 98 patients. CD56 expression as defined as >20% of CD56 positive cells from nucleated blood and/or bone marrow cells was found in 19 (19%) CMML patients. The median survival of all CMML patients was 37 months and was not significantly different between the 2 cohorts ($p=0.465$). Median values for CD56 positive and CD56 negative patients were for WBC 17 vs 12 G/L ($p=0.6384$), for Hb 11.5 vs 11 g/dL ($p=0.3843$), and for platelets 138 vs 112

G/L ($p=0.1416$). The percentages of patients with circulating blast cells were 1/14 (7%) vs 18/67 (27%) ($p=0.1132$) and with RAS-pathway mutations 3/9 (33%) vs 19/49 (39%) ($p=0.7571$), respectively.

Conclusions: Our findings confirm a subgroup of CMML patients with CD56 expression. In our analysis CD56 positive as compared to CD56 negative patients were not significantly different regarding survival, blood cell levels and genotype.

P10

The clinical significance of cardiovascular comorbidity in patients with chronic myelomonocytic leukemia

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Background: Chronic myelomonocytic leukemia (CMML) is a rare hematopoietic malignancy which is mostly diagnosed in elderly patients who frequently have one or more comorbidities. The clinical significance of cardiovascular comorbidity in patients with CMML is poorly investigated.

Methods: Using data from the Austrian Biodatabase for CMML (ABCMML) we analyzed the prevalence cardiavascular comorbidity and potential correlations with clinicolaboratory features in patients with CMML.

Results: Data on cardiovascular comorbidity from charts were available in 117 patients. Coronary heart disease, atrial fibrillation and hypertension was documented in 41/112 (37%), 34/112 (30%) and 75/112 (67%) CMML patients. None of these conditions had a significant impact of survival. Patients with coronary heart disease (CHD) were not significantly different from patients without CHD regarding WBC counts, hemoglobin levels, platelet counts and the percentages of blood monocytes. Moreover, there was no significant differences regarding the proportion of patients with TET2 mutations.

Conclusions: Our findings show a high prevalence of cardiovascular abnormalities in patients with CMML. However, cardiovascular comorbidity does not seem to have a major impact on prognosis in these patients.

P11 Oral Best Submitted Abstract Hämatologie

Breakthrough hemolysis in adult patients with paroxysmal nocturnal hemoglobinuria treated with ravulizumab: Results of a 52-week extension from two phase 3 studies

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Background: In eculizumab-treated patients (pts) with paroxysmal nocturnal hemoglobinuria (PNH), ~11–27% may experience breakthrough hemolysis (BTH). In two phase-3 randomized, open-label trials, ALXN1210-PNH-301 (301; complement inhibitor-naïve pts) and ALXN1210-PNH-302 (302; pts stable on eculizumab), weight-based dosing of ravulizumab (q8w) was noninferior to eculizumab (900 mg; q2w) for the BTH endpoint at 26 wks. This analysis assessed causes and clinical parameters associated with BTH incidences for 1yr.

Methods: Pts received ravulizumab or eculizumab for 26wks. In the extension, pts continued (R-R) or switched to ravulizumab (E-R). BTH causation was categorized as related to suboptimal C5 inhibition, complement-amplifying conditions (CAC), or unrelated to either event.

Results: Study 301: Of the 243 pts entering the extension period (R-R: $n=124$; E-R: $n=119$), 99% of pts experienced no new BTH in 27–52 wks. In 27–52 wks, 2 BTH events (1 in each arm) were infection-associated and 5 BTH events (R-R=4; E-R=1) were unrelated to free C5 elevation or infection. Study 302: Of the 191 pts entering the extension period (R-R: $n=96$; E-R: $n=95$), majority of pts (R-R=97%; E-R=100%) had no new BTH incidents in 27–52wks. In 27–52 wks, infection-associated BTH events were 2 in R-R arm and 1 in the E-R arm, and 1 BTH event in the R-R arm was unrelated. In both studies, no BTH incidents were associated with free C5 of >0.5 µg/mL during 27–52 wks.

Conclusions: During 27–52 wks, in both studies, no BTH events were associated with free C5 elevations in ravulizumab-treated pts. Similar number of pts in both arms experienced infection-associated BTH events, possibly due to proximal complement activation.

P12

Effects of novel tyrosine kinase inhibitors (TKIs) on canine neoplastic mast cells (MCs)

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Background: Advanced canine mast cell tumors (MCTs) are characterized by uncontrolled growth of neoplastic mast cells (MCs), mediator related symptoms and poor prognosis. Despite the approval of two tyrosine kinase inhibitors (TKIs), namely masitinib and toceranib, which are directed against the KIT receptor, relapses are seen frequently. In order to treat recurrent or metastatic MCTs, more effective anti-neoplastic drugs are required.

Methods: We tested the effects of three novel TKIs, namely avapritinib (BLU-812), ripretinib (DCC-2618), and nintedanib (BIBF-1120) on two established canine MC lines, C2 and NI-1, and on primary MCs obtained from one canine MCT patient. As control agents the TKIs masitinib, toceranib and midostaurin were used in our experiments.

Results: All TKIs tested were found to suppress proliferation of C2 and NI-1 cells with IC_{50} values ranging between 0.01 and 0.25 µM (rank order of potency: toceranib>ripretinib>nintedanib>masitinib>avapritinib>midostaurin). Moreover, the TKIs reduced survival in C2 cells with ED_{50} values ranging between 0.05 and 1 µM (toceranib>nintedanib>ripretinib>masitinib>midostaurin>avapritinib), whereas in NI-1 cells the ED_{50} values ranged between 0.5 and 10 µM (toceranib>ripretinib>nintedanib>midostaurin>masitinib>avapritinib). Finally, the TKIs were found to decrease IgE-dependent histamine release in NI-1 cells and in primary MCT cells (nintedanib>midostaurin>ripretinib>avapritinib>toceranib>masitinib).

Conclusions: In summary, avapritinib, ripretinib and nintedanib suppress proliferation, survival and IgE-dependent histamine release in neoplastic canine MCs. The effects of these novel drugs were comparable to the effects of masitinib, toceranib and midostaurin. Whether these new TKIs are equally effective *in vivo* when compared to the established TKIs masitinib or toceranib remains to be elucidated in clinical trials.

P13

The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib blocks proliferation and histamine release in canine neoplastic mast cells (MCs)

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Background: The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib is a promising drug for the treatment of lymphoid neoplasms in humans. Recently, ibrutinib was found to block the IgE-dependent activation and histamine release in human basophils and mast cells (MCs). The aim of this study was to investigate whether ibrutinib could serve as a potential therapeutic drug in canine mast cell tumors (MCTs).

Methods: Here, we used two canine MC lines, C2 and NI-1, and primary MCs obtained from three MCTs. To study effects of ibrutinib on BTK activation, we examined the phosphorylation status by flow cytometry. Anti-proliferating effects of ibrutinib were examined by measuring ^{3}H-thymidine uptake. Apoptosis induction by ibrutinib was analyzed by morphological examination and flow cytometry. Additionally, the effects of ibrutinib on IgE-dependent histamine release were determined.

Results: Ibrutinib was found to suppress phosphorylation of BTK and of downstream STAT5 in both MC lines. In addition, ibrutinib decreased proliferation of primary MCT cells (IC_{50} range: 0.1–1 µM) and of MC lines (IC_{50} range: 1–3 µM). The drug-combination 'ibrutinib+midostaurin' produced synergistic growth-inhibitory effects in C2 cells. At higher concentrations, ibrutinib also induced apoptosis in MC lines. Finally, ibrutinib was found to inhibit IgE-dependent histamine release in NI-1 cells (IC_{50} range: 0.05–0.1 µM) and in primary MCT cells (IC_{50} range: 0.05–1 µM).

Conclusions: In summary, ibrutinib exerts anti-proliferative effects in canine neoplastic MCs and inhibits IgE-dependent histamine release in these cells. Whether ibrutinib may be considered as a novel therapeutic drug for the treatment of canine MCTs remains to be elucidated in clinical studies.

P14

Enteropathy-associated T-cell lymphoma – a case report

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Background: Enteropathy-associated T-cell lymphoma is a very rare type of non-Hodgkin lymphoma (NHL) arising from

the T-cell-line. The subtype of the EATL making less than 5% of all peripheral T-cell lymphomas (PTCL) which account for 7% of all NHL. The prognosis is poor with a median survival of less than 8 months.

Case description: We present a case of a 58-year-old male with enteropathy-associated T-cell lymphoma (EATL). The patient was admitted through our emergency unit with involuntary heavy weight-loss in the preceding few months, diarrhoea and abdominal pain. Coeliac disease was already known and diagnosed in his origin country. A gastroscopy realised in our hospital showed coeliac typical microscopical findings corresponding to Marsh 3c.

Following acute abdomen and exploratory surgery because of suspected perforation, EATL was diagnosed through histopathological workup. Due to surgical complications a re-operation was necessary and following recovery prolongated, postoperative weight amounting to 42 kg.

Treatment: After an initial cycle of Brentuximab/Vedotin mono (A), 7 cycles A-CHP were administered as therapy for this PTCL according to data that emerged from the ECHELON-2-trial. Since August 2019, a maintenance therapy with A-mono is being applied.

Conclusions: More than one year after diagnosis, the patient has gained weight (66 kg at last follow-up) and performs very well without relevant restrictions in daily activities (ECOG 0-1). With an ongoing CR and an impressive improvement of quality of life he hereby shows a rather unusual development for this pathological entity after therapy with a Brentuximab/Vedotin containing regimen.

P15 Oral Best Submitted Abstract Hämatologie

Increased expression of micro-RNA-23a causes resistance to azacitidine in acute myeloid leukemia

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Background: Chemoresistance is one of the major problems in the therapy of acute myeloid leukemia (AML). Aberrant expression of micro-RNA-23a (miR-23a) has been described in AML and is of functional relevance for leukemogenesis. In an ongoing project, we revealed that increased expression of miR-23a mediates resistance to cytarabine in AML. Here, we studied the role of miR-23a in chemoresistance to azacitidine, the most commonly employed non-intensive AML therapy.

Methods: Stable overexpression of miR-23a was performed by lentiviral transduction in THP-1 and U937 AML cells. miR-23a expression was assessed by quantitative-real-time PCR (qPCR). The effects of miR-23a overexpression were assessed by growth curves, BrdU proliferation, and Annexin V/7-AAD apoptosis assays. For chemosensitivity assays, cells were incubated with azacitidine for 48 h. Subsequently, we analyzed the effects on inducing apoptosis in Annexin V/7-AAD assays, and on cell viability in MTT assays.

Results: miR-23a expression was significantly higher in cells transduced with the lentiviral overexpression construct as compared to cells carrying the empty control vector. In functional assays, miR-23a overexpression increased the proliferation on the one hand, and decreased the apoptosis of leukemic cells on the other hand. Most importantly, however, miR-23a overexpression reduced the anti-leukemic effects of azacitidine. In more detail, the induction of azacitidine-induced apoptotic cell death was significantly reduced by the overexpression of miR-23a.

Conclusions: miR-23a mediates resistance to azacitidine in AML. As it has also been shown to mediate resistance to cytarabine, these data highlight the necessity of novel treatment approaches for AML patients with increased miR-23a expression.

P16

High expression of miR-15a-5p, miR-17-5p and miR-20a-5p is associated with poor cancer-specific survival of aggressive lymphomas

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Background: Aggressive lymphomas represent the most frequent type of lymphoid malignancies with a five-year survival rate of 60%. Despite effective initial treatment, one-third of patients will experience relapse, warranting more research to improve therapeutic strategies. Since an altered expression of miR-15a-5p, miR-15a-3p, miR-20a-5p, miR-17-5p, miR-124a-5p, miR-224-5p and miR-224-3p have been described in tumorigenesis, we aimed to investigate the expression of these miRNAs in aggressive lymphomas.

Methods: Therefore, we determined the expression levels of these seven miRNAs in 68 human aggressive B-cell lymphoma samples including germinal center B-cell (GCB)-DLBCL ($n=23$), non-GCB-DLBCL ($n=25$) and transformed DLCBL ($n=20$) as well as non-neoplastic GCB ($n=5$) as controls by semi-quantitative RQ-PCR.

Results: The miRNA expression of GCB cells significantly differed to that of aggressive lymphomas. We observed a higher expression of miR-15a-5p (6.2 fold), miR-15a-3p (30.7 fold), miR-17-5p (37.7 fold), miR-224-5p (147 fold) and miR-224-3p (169 fold) in DLBCL ($p<0.007$), whereas for miR-124a-5p no expression was detectable in lymphoma samples. Remarkably, high expression of miR-15a-5p ($p=0.002$), miR-17-5p ($p=0.013$) and miR-20a-5p ($p=0.004$) was associated with poor cancer-specific survival of DLBCL patients. Comparing the miRNA expression within the different DLBCL subgroups, miR-15a-3p was expressed lower in non-GCB-DLBCL compared to transformed DLBCL ($p=0.041$).

Conclusions: Our results suggest that higher expression of certain miRNAs is associated with a poor clinical course in DLBCL. Therefore, these miRNAs may serve as prognostic biomarker for aggressive lymphomas if confirmed in larger patient cohorts.

P17

Untreated remission after discontinuation of kinase inhibitor treatment in chronic lymphocytic leukemia: an observational cohort

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Background: Kinase inhibitors (KI) rapidly changed treatment in CLL Despite the "treat-until-progression" concept, real-life experiences show large proportions of discontinuations due to toxicity and patient decisions, rather than progression. These often happen in clinical remission, without achieving MRD negativity.

Methods: We here report a first real-world cohort of CLL patients from 7 academic centres, that had received ibrutinib or idelalisib in different lines of treatment, that had achieved measurable response, suffered toxicities or made decisions to stop therapy and remained in untreated observation after discontinuing the kinase inhibitor.

Results: We report on 54 patients, treated with ibrutinib or idelalisib (Median age 74 years; median number of treatments prior to KI was 1 (0–6)). After a median of 8 months on KI patients stopped due to toxicity ($n=49$) or patient's decision ($n=5$). Eleven patients stopped treatment in CR and 43 achieved PR. Median PFS after treatment cessation was 9.4 months, median TTNT was 12 months and OS was 62% at a median observation of 27 months. TTNT at 2a was 27%. No differences were observed between the two drugs in PFS and TTNT, but the idelalisib cohort showed better OS (median n. r. vs 20 mo, $p=.002$). Unmutated IgHV predicted earlier progression, but not OS. Achievement of CR showed better PFS, but not OS.

Conclusions: Treatment cessation in CR/PR after kinase inhibitor treatment is associated with limited PFS, but some patients experience prolonged treatment free intervals. OS from stop of kinase inhibitor was respectable for this elderly cohort, suggesting available salvage options.

P18

Modulation of the leukemic stem cell niche by PI3K inhibitors in CML

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Recent data suggest that the disease-related microenvironment (stem cell niche) is critically involved in drug resistance of leukemic stem cells (LSC) in chronic myeloid leukemia (CML). Attacking the stem cell niche in CML may thus be an effective approach to overcome LSC resistance. We have recently shown that osteoblasts induce substantial LSC resistance against TKI in CML. We also found that several BCR-ABL1 tyrosine kinase inhibitors (TKI), like ponatinib or nilotinib, exert growth-inhibitory effects on endothelial cells. However, so far little is known about the effects of other drugs on growth and survival of osteoblasts or endothelial cells. In the current study, we screened for drugs that are able to suppress the growth and viability of osteoblasts and endothelial cells in the CML context. Proliferation was analyzed by measuring 3H-thymidine uptake in niche-related cells and apoptosis was measured by AnnexinV/Dapi-staining. We found that the PI3-kinase/mTOR blocker BEZ235 suppresses growth and viability in primary osteoblasts (IC_{50}: 0.05 µM) and the osteoblastic cell line CAL-72 (IC_{50}: 0.05 µM) as well as in primary endothelial cells (IC_{50}:0.5 µM) and the endothelial cell line HMEC-1 (IC_{50}: 1 µM). Moreover, we found that BEZ235 cooperates with nilotinib and ponatinib in suppressing growth and viability of osteoblasts and endothelial cells. Finally, we were able to show that BEZ235 overcomes osteoblast-induced resistance of the CML cell lines K562 and KU812 against nilotinib and ponatinib. Together our data suggest that targeting niche cells by BEZ235 is an effective approach to overcome niche-induced TKI resistance in CML.

P19

Loss of Nr4a1 causes bone marrow infiltration accompanied by a distinct de-regulation of the chemokine receptor and integrin expression profile in aggressive lymphoma

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Background: In aggressive lymphomas, NR4A1 possesses tumor suppressive function. In the EµMyc transgenic lym-

phoma mouse model, we observed that loss of Nr4a1 causes an accelerated lymphomagenesis and a higher tumor cell infiltration of bone marrow and spleen. The aim of this study was to comprehensively study the impact of Nr4a1 loss on the lymphoma dissemination.

Methods: Therefore, we transplanted EμMyc Nr4a1-/- and EμMyc Nr4a1+/+ lymphoma cells into C57BL/6 mice and determined lymphoma cell infiltration of the bone marrow, spleen, kidney, lung, liver and brain by flow cytometric or histologic analysis. Finally, we determined the expression levels of the chemokine receptors and integrins in EμMyc Nr4a1-/- and EμMyc Nr4a1+/+ lymphomas by RQ-PCR.

Results: Transplanting EμMyc Nr4a1-/- and EμMyc Nr4a1+/+ lymphoma cells resulted in the engraftment of the lymphomas within 10 weeks. Mice transplanted with EμMyc Nr4a1+/+ lymphoma cells exhibited a higher percentage of lymphoma cell infiltration in the bone marrow (81.2% vs. 61.8%, $p=0.028$) and spleen (63.1% vs. 48.1%, $p=0.011$) and a lower lymphoma cell infiltration rate in the kidney (13.5% vs 49.5%, $p=0.049$). In contrast, no differences were observed for the other investigated organs. In the primary lymphoma, we observed a higher expression of the chemokine receptors CCR8 (4.8-fold) and CXCR2 (5.5-fold, $p<0.048$ for both) and the integrin VLA4 (3.4-fold), Intergin-αD (3.1-fold), Intergin-αE (15.4-fold) and Intergin-αL (3.5-fold, $p<0.09$ for all).

Conclusions: Our data suggest that the Nr4a1 might be implicated in the bone marrow infiltration process by regulating a certain pattern of chemokine receptors and integrins.

P20

Geriatric assessment in evaluation of eligibility and outcome prediction of hematopoietic stem cell transplantation in hematologic malignancies – a systematic review

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Background: Hematopoietic stem cell transplantation (HSCT) represents a cornerstone in the treatment of many hematologic malignancies. Assessment of eligibility of patients remains a challenge, namely at advanced age.

Methods: We performed a systematic literature search on the use and prognostic relevance of scores of the Geriatric Assessment (GA) in HSCT in hematologic malignancies.

Results: In 2326 studies, a minority of 59 used at least one score of the GA: performance status (PS) in 57, and comorbidity scores in three to determine eligibility for HSCT.

The prognostic impact of comorbidities was analysed in 128, of PS in 67, of functional activities in three, of nutritional status in ten and of health-related quality of life (HRQOL) in six studies. In univariate/multivariate analysis comorbidities were predictors of survival in allogeneic HSCT in 42/72 (58%) and in 39/58 (67%), PS in 20/33 (61%) and 30/37 (81%), nutritional status in 1/3 and 3/5, functional activities in 2/3 and 2/2 and in HRQOL in 2/3 and 2/2, respectively. Comorbidity scores were predictors of survival in 3/9 (33%) and 4/7 (57%) and performance status in 4/5 (80%) and 4/6 (67%) in univariate and multivariate analysis in autologous HSCT.

Conclusions: Domains of GA were so far rarely used to evaluate eligibility for HSCT. The prognostic impact of comorbidities and of PS was demonstrated in a relevant proportion of studies. Results for functional activities and HRQOL are promising. These results support the relevance and the further integration of GA in decision-making in HSCT.

P21

Targeting HDAC as a novel therapeutic approach in advanced systemic mastocytosis

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Systemic mastocytosis (SM) is a myeloid neoplasm characterized by abnormal growth and accumulation of neoplastic mast cells (MC) in diverse organs. Most SM patients exhibit a KIT D816V mutation which induces resistance against tyrosine kinase inhibitors, such as imatinib. By contrast, midostaurin is active against KIT D816V and has been approved for the treatment of patients with advanced SM. However, long-lasting hematologic remissions are rarely seen. Using a high-capacity screen and 8 human MC lines, we searched for novel drug-targets and effective targeted drugs. In this screen, histone deacetylase (HDAC) inhibitors were identified as most effective drugs in KIT D816V+ neoplastic MC. Panobinostat and quisinostat were among the most effective HDAC blockers and were used in subsequent experiments. Both drugs were found to inhibit the proliferation of HMC-1.1 (IC_{50}: 5–25 nM), HMC-1.2 (2.5–25 nM), ROSAKIT WT (2.5–25 nM), and ROSAKIT D816V cells (5–50 nM). In addition, both drugs suppressed the growth of primary neoplastic MC obtained from patients with SM (IC_{50}: <1–10 nM). Panobinostat and quisinostat also induced apoptosis in HMC-1 cells and both drugs were found to exert cooperative anti-neoplastic effects when combined with midostaurin in these cells. As assessed by immunocytochemistry, all cell lines tested expressed HDAC1 and HDAC2. In Western blot experiments, panobinostat and quisinostat were found to promote histone H3 and H4 acetylation in HMC-1 cells whereas no effects on KIT phosphorylation were seen. Whether HDAC inhibitors can produce anti-neoplastic effects in vivo in patients with advanced SM remains to be determined in clinical trials.

P22

Multiple myeloma possesses substantial differences in their chemokine receptor expression profile in comparison to non-neoplastic plasma cells

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Background: Multiple Myeloma (MM) is a hematologic malignancy characterized by proliferation of clonal plasma cells in the bone marrow (BM). It has been demonstrated that chemokine receptors (CCR) play an important role in B-cell differentiation and development of hematologic malignancies. Therefore, we aimed to investigate the CCR expression profile in patients' MM cells and non-neoplastic plasma cells.

Methods: We determined the CCR expression pattern of 19 well characterized chemokine receptors in non-neoplastic plasma cells ($n=4$) and macro-dissected BM samples containing more than 90% of MM cells ($n=20$) by semi-quantitative RQ-PCR.

Results: We observed that the CCR expression profile of MM cells differed significantly from those of plasma cells serving as non-neoplastic controls, with de-novo expression of CCR1, CCR2, CCR4, CXCR1, CXCR2, XCR1 and CX3CR1 and a higher expression of CXCR4 and a lower expression of CXCR5 in MM cells. In contrast, no differences for CCR7 expression between the two investigated groups and no expression of CCR3, CCR5, CCR8-CCR10, CXCR3, CXCR6 and CXCR7 was seen. High CCR7 expression and low CXCR1 expression were associated with poor survival in MM patients.

Conclusions: Our data suggest that the chemokine receptor expression profile of MM cells differs substantially from those of normal plasma cells and that the differentially expressed chemokine receptors might play an important role in the pathogenesis of MM. Hence, these multiple deregulated CCRs might serve as useful prognostic tools and might be of clinical importance if confirmed in a larger patient cohort.

P23

Asciminib and ponatinib exert synergistic anti-neoplastic effects on CML cells expressing BCR-ABL1 T315I-compound mutants

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Background: Ponatinib is the only available tyrosine kinase inhibitor (TKI) successfully applied in BCR-ABL1 T315I+ chronic myeloid leukemia (CML). However, T315I-including compound mutations may develop during ponatinib-treatment and lead to drug-resistance. Asciminib (ABL001) is a novel TKI targeting most BCR-ABL1 mutant-forms, including BCR-ABL1 T315I, but is ineffective against T315I+ compound mutants, at least when applied as single agent. We evaluated cooperative effects between ponatinib and asciminib in CML cells.

Methods: Primary cells obtained from 4 patients with chronic phase CML, human CML cell lines (K562, KU812, KCL22, KCL22-T315) and Ba/F3 cells expressing BCR-ABL1T315I or T315I-including compound mutations were used. Proliferation was evaluated by 3H-thymidine uptake, drug-induced apoptosis in cell lines and CD34+/CD38– CML stem cells by flow cytometry, and phosphorylation of CRKL by Western blotting.

Results: Ponatinib and asciminib were found to synergize in inhibiting proliferation and viability of all cell lines tested, including cells expressing T315I-including compound mutations of BCR-ABL1. These effects were accompanied by inhibition of CRKL-phosphorylation. Anti-proliferative effects of 'ponatinib+asciminib' were further enhanced by hydroxyurea, a drug that is often used in advanced CML and has recently been found to suppress the growth of CML cells exhibiting BCR-ABL1 T315I. Synergistic growth-inhibitory effects of 'ponatinib+asciminib' were also confirmed in primary CML cells. Finally, the combination 'ponatinib+asciminib' produced synergistic apoptosis-inducing effects in CD34+/CD38– CML stem cells.

Conclusions: Together, ponatinib and asciminib synergize in producing anti-leukemic effects in multi-resistant CML cells, including cells harboring T315I+ compound mutations of BCR-ABL1 and CML stem cells. The clinical efficacy of this TKI combination remains to be determined.

P24

Impact of HFE gene variants on iron overload, overall survival and leukemia-free survival in myelodysplastic syndromes

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Background: In myelodysplastic syndromes (MDS), little is known about genetic features contributing to disease evolution,

acute myeloid leukemia (AML) development, and survival. Accumulating data suggest that patients with MDS frequently display HFE gene variants. However, the clinical impact of HFE gene variants in MDS is unlcear.

Methods: In this study, we examined the HFE status in 168 patients with MDS (observation-period: 1992–2019) and 494 healthy Austrian controls. Furthermore, in 94 MDS patients a 'myeloid mutation' screen was performed by next-generation sequencing (NGS).

Results: Variant HFE species were detected in 65/168 MDS-patients (38.7%) and 170/494 controls (34.4%). At diagnosis, the median ferritin levels were higher in HFE-mutated (409 mg/dL; range: 23–7415) compared to non-mutated patients (346.5 mg/dL; range: 10–5450) ($p=0.62$) and HFE-mutated patients had a slightly faster increase in serum ferritin. Comparing MDS subgroups (according to French-American-British classification) the percentage of HFE variants was higher in refractory anemia (RA) (22/53 = 41.5%) or RA with ring sideroblasts (17/39 = 43.9%) than in RA with excess of blasts, RAEB (16/47 = 34.8%) or RAEB in transformation (5/17 = 29.4%). Clear differences were also observed between subgroups classified by World Health Organization criteria. There was no significant correlation between the expression of HFE variants and the NGS mutations status. Although not statistically significant, HFE-mutated MDS patients were found to have a slightly better AML-free survival ($p=0.089$).

Conclusions: HFE variants are frequently detected in Austrian MDS-patients but had no significant prognostic impact on survival or serum ferritin levels. Therefore, we currently do not recommend a routinely HFE screening in MDS.

P25

CDK4/CDK6-inhibition augments anti-neoplastic effects of midostaurin and avapritinib in KIT D816V+ neoplastic mast cells

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Aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL) are rare KIT-driven malignancies. Despite the use of KIT-targeting drugs, the prognosis remains unfavorable. Current efforts focus on the development of improved treatment strategies. Cyclin-dependent kinase-4 (CDK4) and CDK6 are oncogenic kinases that serve as therapeutic targets in various malignancies. However, CDK4/CDK6 has not been analyzed in the context of ASM/MCL so far. Primary samples ($n=14$) isolated from the bone marrow of patients with indolent SM (ISM, $n=4$), ASM ($n=1$), ASM with an associated hematologic neoplasm (ASM-AHN, $n=6$), MCL ($n=3$) and the mast cell lines HMC-1.1, ROSAKIT-WT, HMC-1.2, and ROSAKIT-D816V were exposed to the CDK4/CDK6-inhibitors palbociclib, ribociclib and abemaciclib. Proliferation was determined by ^{3}H-thymidine-uptake, cell cycle progression and apoptosis by flow cytometry, CDK4/CDK6 mRNA expression by qPCR, and phosphorylation of the retinoblastoma-protein (RB1) by Western Blotting. CDK4 and CDK6 mRNA were expressed in all primary samples, with higher levels detected in ASM/ASM-AHN/MCL than in ISM. Palbociclib, ribociclib, and abemaciclib suppressed proliferation of primary neoplastic MC, HMC-1 and ROSA cells expressing or lacking KIT D816V (IC_{50}: < 0.5 µM). In cell lines, anti-proliferative effects were accompanied by suppression of phospho-RB1, cell cycle arrest, and apoptosis. Furthermore, all 3 CDK4/CDK6-inhibitors were found to synergize with the KIT-targeting drugs midostaurin and avapritinib in inducing growth-arrest. Together, CDK4/CDK6-inhibition blocks proliferation and survival of neoplastic MC and potentiates the growth-inhibitory effects of KIT-targeting drugs. Whether CDK4/CDK6 inhibitors are effective in patients with ASM/MCL remains to be determined in clinical trials.

P26

CDK6 in hematopoietic stem cells: more than a cell cycle kinase

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Background: Several therapeutic options are available to eradicate malignant hematopoietic cells. However, leukemic stem/progenitor cells are unaffected by many therapeutic strategies and represent the major cause of relapse. We showed that the cell cycle kinase CDK6 plays not only a key role in the G1 cell cycle phase but also regulates transcription and stem cell activation especially under conditions of stress. The aim of the study is therefore to understand how CDK6 regulates stressed haematopoiesis.

Background: To investigate the effects of CDK6 in HSCs, in vivo serial transplants were performed to study HSCs re-population capacity. Stress-induced haematopoiesis was further induced by chemical treatments or oncogenic stress.

Results: We showed that transcriptional regulation by CDK6 plays a key role in (leukemic) stem/progenitor cells. Cdk6-/- HSCs lack the ability to re-populate in a serial transplant setting, whereas a kinase inactivated Cdk6K43M/K43M allele was capable to partially compensate the stem cell exhaustion phenotype in vivo. We also found that leukemic stem cells (LSCs) are able to initiate myeloid leukaemia in the presence of a kinase dead version of Cdk6. We established stem/progenitor cell lines (HPCLSK cells) as an in vitro tool to further delineate the importance of the transcriptional role of CDK6 in HSCs and LSCs.

Conclusions: Our study identifies a function of CDK6 in stress- induced hematopoiesis and stem cell activation that is largely kinase-independent.

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P27

Single center experience with Daratumumab monotherapy and Daratumumab combination therapy in heavily pretreated patients with relapsed/refractory multiple myeloma (rrMM)

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Background: The introduction of Daratumumab has significantly extended treatment options for patients with MM. Its efficacy as single agent or in combination with other drugs has clearly been documented in several trials. Here, we present our single center experience with Daratumumab in heavily pretreated patients.

Methods: 42 patients with rrMM (median age 65.8 yrs, range 36.4–86.5) have been enrolled (ISS Stage I 7.1%, Stage II 42.9%, Stage III 50.0%). Cytogenetics were available in 85.7% of patients (high-risk 27.8%, standard-risk 72.2%). Daratumumab was dosed according to international standards. Median number of prior therapies was 5 (range 1–11) and 3 (range 1–8), for patients treated with Daratumumab single agent (23 patients) and for patients receiving Daratumumab in combination with other drugs (19 patients), respectively. Progression free survival (PFS) and overall survival (OS) were estimated according to Kaplan-Meier.

Results: Median follow-up time was 6 months. Overall response rate (ORR) was 21.74% (PR 60%, CR 40%) for patients with Daratumumab monotherapy and markedly higher for patients receiving Daratumumab combination therapy: 57.9% ORR (36.4% PR, 9.1% VGPR, and 54.5% CR). PFS and OS rates were 2.5 and 12 months in single agent treated patients, and 17.5 months and not reached in those receiving combination protocols.

Conclusions: Our single center experience with Daratumumab as single agent or in combination with other drugs showed marked activity in heavily pretreated patients. These results are in line with previously reported data.

P28

How to detect the need for immunoglobulin substitution therapy in patients with hematologic malignancy

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Background: Clinically relevant antibody deficiency develops in a subset of patients secondary to treatment of B cell malignancy and is usually recognized as prolonged hypogammaglobulinemia. Diagnostic vaccination could be inappropriate or prohibitive in these patients when prompt decision on initiation of immunoglobulin replacement therapy is required.

Methods: We examined serum IgG antibodies against thirteen common pathogens in adult controls with normal antibody production ($n=1619$, median age [IQR] 42 [31–54] years), CVID patients with recurrent infection before long-term immunoglobulin substitution was started ($n=27$; age 38 [28.5–52.5] years), adults with hypogammaglobulinemia but without susceptibility to infections ($n=21$, age 48 [39–57] years), and adults with hypogammaglobulinemia and recurrent infections after treatment for hematologic malignancy ($n=13$, age 55 [45–68] years).

Results: An antibody score was calculated using a combined assessment of all 13 IgG antibody measurements and showed significantly reduced IgG responses in CVID patients (IgG-antibody score, mean ± SD, 0.12 ± 0.11) as compared to controls (0.70 ± 0.14, $p<0.00001$) and hypogammaglobulinemic patients without infections (0.55 ± 0.18, $p<0.00001$); antibody failure in CVID could be detected with a sensitivity of 96.3%, a positive predictive value of 92.9%, and a specificity and negative predictive value of 99.9%. Patients with secondary hypogammaglobulinemia had a reduction in IgG antibody score (0.15 ± 0.16) comparable to CVID patients ($p=0.5214$, n. s.), and their severe susceptibility to infections disappeared after initiation of immunoglobulin replacement therapy.

Conclusions: These findings could help to define those patients with secondary immunodeficiency after hematologic malignancy who benefit from long-term immunoglobulin replacement therapy.

P29

CDK4/CDK6-inhibitors suppress the proliferation and viability of CMML cells and synergize with ponatinib in producing growth arrest

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In chronic myelomonocytic leukemia (CMML), no targeted therapy has been established to date and therapeutic options are limited. Hydroxyurea (HU) which is used for cytoreduction in CMML, reduces CDK6-expression in various cell types. We analyzed the impact of HU and more specific CDK4/CDK6-inhibitors on CDK4/CDK6-expression, growth and survival in CMML cells. Primary neoplastic cells obtained from 6 patients (CMML I, $n=1$; CMML II, $n=2$; acute myelomonocytic leukemia, AML, $n=1$; secondary AML after CMML, $n=2$) as well as the monoblastic cell lines THP-1, Mono-Mac-6 and U937 were used. Proliferation was determined by ^{3}H-thymidine uptake, apoptosis and cell cycle-distribution by flow cytometry, and expression/phosphorylation of CDK4/CDK6 and the retinoblastoma protein (Rb) by qPCR and Western blot analysis. HU was found to inhibit proliferation in primary leukemic cells (IC_{50}: 50–250 μM) and all cell lines tested (IC_{50}: THP-1: 25–50 μM; Mono-Mac-6: 100–150 μM; U937: 500–750 μM). In THP-1 and Mono-Mac-6, HU induced cell cycle-arrest and apoptosis, and reduced CDK4/

CDK6-expression. The more specific CDK4/CDK6-inhibitors palbociclib, ribociclib and abemaciclib suppressed the phosphorylation of Rb and blocked cell proliferation in all cell lines examined (IC_{50}: 0.5–10 μM) and primary leukemic cells (IC_{50}: 0.01–0.5 μM). Finally, we found that the multikinase-inhibitor ponatinib synergizes with both HU and palbociclib in producing growth arrest in THP-1, Mono-Mac-6 and primary CMML cells. Together, our data suggest that inhibition of CDK4/CDK6, alone or in combination with ponatinib, may be an interesting therapeutic concept in CMML. The clinical value of these findings remains to be determined in forthcoming studies.

P30

Phenotypic characterization of disease-initiating neoplastic stem cells in BCR-ABL1-negative myeloproliferative neoplasms (MPN)

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The classical Ph-chromosome-negative myeloproliferative neoplasms (MPN) are characterized by over-production of differentiating myeloid cells, disease-related mutations in certain driver-genes (JAK2, CALR, MPL), and an increased risk of transformation into secondary acute myeloid leukemia (sAML). Despite being considered stem cell-derived neoplasms, little is known about the phenotype and functional properties of disease-initiating stem cells in classical MPN. Using a battery of monoclonal antibodies and flow cytometry, we established the immunological phenotype of putative CD34+/CD38– stem cells and CD34+/CD38+ progenitor cells in patients with polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). In almost all patients, the putative MPN stem cells expressed Siglec-3/CD33, Hermes/CD44, Campath-1/CD52, IAP/CD47, TM&LN1/CD97, MIC2/CD99, Endoglin/CD105, KIT/CD117, IL-3RA/CD123, AC133/CD133 and PD-L1/CD274. In subsets of patients, MPN stem cells also expressed MPL/CD110 and/or MDR-1/CD243, and in a very few cases with PMF, neoplastic stem cells expressed IL-2RA/CD25 and/or DPPIV/CD26. MPN stem cells did not express T44/CD28, Thy-1/CD90, Tactile/CD96, IL-1RAP or CD371/CLL-1. Almost identical stem cell phenotypes were detected in patients with sAML. The disease-initiating capacity of MPN stem- and progenitor cells (CD34+ cells) could be confirmed using primary PMF cells in xenotransplantation experiments in NSGS mice expressing human interleukin-3 (IL-3), granulocyte/macrophage colony-stimulating factor (GM-CSF) and stem cell factor (SCF). Together, MPN stem cells reside in a CD34+ fraction of the malignant clone and display a unique phenotype, including cytokine receptors, immune checkpoint molecules and other target antigens. The phenotypic characterization of neoplastic stem cells should facilitate their enrichment and the development of stem cell-eradicating therapies in MPN.

P31 Oral Best Submitted Abstract Hämatologie

CD19 CAR T-Zelltherapie bei r/r DLBCL – 4 Jahre Erfahrung an der Medizinischen Universität Wien

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Grundlagen: Seit 2016 werden an der Medizinischen Universität Wien (MUW) CD19 CAR T-Zellen bei Patienten mit r/r DLBCL eingesetzt. Dies ist eine Analyse der bisher gewonnenen Erfahrung an unserem Zentrum.

Methodik: Deskriptive Auswertung hinsichtlich Erkrankungscharakteristika, Therapieverläufe, Ansprechen und Nebenwirkungen aller DLBCL-Patienten, welche 04/2016–01/2020 an der MUW mit CD19 CAR T-Zellen behandelt wurden.

Ergebnisse: Im Beobachtungszeitraum erhielten 22 Patienten (medianes Alter: 61 [Range: 33–79] Jahre; f:m = 8.14) mit r/r DLBCL eine CD19 CAR T-Zelltherapie. Im Median waren die Patienten mit 4 (2–12) Linien vortherapiert. Einundzwanzig (95 %) Patienten hatten zum Zeitpunkt der Zellinfusion eine nachweisbare Erkrankung (CS III/IV: $n = 13$, 59 %). Es wurden Tisagenlecleucel ($n = 15$, 68 %), Lisocabtagen maraleucel ($n = 6$, 27 %) und Axicabtagen ciloleucel ($n = 1$, 5 %) in klinischen Studien ($n = 18$, 82 %) oder im Routineeinsatz ($n = 4$; 18 %) verabreicht. Zwei (9 %) Patienten entwickelten ein höhergradiges CRS (Grad ≥3). Es wurden keine höhergradigen Neurotoxizitäten (ICANs) beobachtet. Zwanzig Patienten konnten hinsichtlich des Gesamtansprechens 30 Tage nach Zellinfusion evaluiert werden. Die entsprechende Rate (ORR) betrug 60 % (CR: $n = 5$, 25 %; PR: $n = 7$, 35 %). Nach einem medianen individuellen Follow-up von 5 (1–42) Monaten waren alle erreichten CRs anhaltend. Alle Patienten mit einer PR als bestem Ansprechen waren im Verlauf progredient. Das geschätzte Kaplan-Meier-Überleben nach 12 Monaten lag bei 71 % (95 %CI: 52–84 %).

Schlussfolgerungen: Es liegt eine beinahe 4-jährige Erfahrung mit CD19 CAR T-Zellen an der MUW vor, die die Wirksamkeit der Behandlung belegt. Die Rate und Schwere an unmittelbaren Toxizitäten waren in unserer Kohorte gering. Die Überwindung der primären CAR T-Resistenz stellt beim DLBCL die größte Herausforderung für die Zukunft dar.

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Mutational status, but not cytoreductive treatment affects NETosis rates in Myeloproliferative Neoplasms (MPN)

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Background: Since their first description neutrophil extracellular traps (NETs) have been implicated in thromboembolic events occurring in broad variety of diseases such as cardiovascular disease, autoimmunity, inflammation and recently also in MPN. Although thrombosis as well as bleeding episodes are the major causes of morbidity and mortality in myeloproliferative neoplasms (MPN), data on NETosis and MPN are scarce and conflicting:

Methods: Primary neutrophils were isolated from peripheral blood samples of healthy donors ($n = 30$) and MPN patients ($n = 82$; essential thrombocythemia (ET, $n = 44$); polycythemia vera (PV, $n = 18$) primary myelofibrosis (PMF, $n = 20$)) using a consecutive 2-step density gradient separation method. Neutrophils were incubated for 4 h with 4 µM ionomycin to induce NETosis. Extracellular DNA and citrullinated histones as NETosis surrogates were quantified using by ELISA and microscopy.

Results: In-vitro induced NETosis rates were significantly increased in samples from MPN patients, particularly in ET and PMF, compared to neutrophils from healthy donors. However, no difference was found between MPN patients' subgroups. NETosis rates of JAK2-mutated ($n = 60$) and CalR-mutated ($n = 14$) patients compared to healthy donors were significantly increased. (JAK2-unmutated pVal = 0.0151 and CalR-mut-unmutated pVal = 0.0377)). Correlations of clinical parameters such as blood counts, LDH or age did not reveal significant associations neither did treatment have any effect on NETosis rates.

Conclusions: Susceptibility to induced NETosis is significantly increased in patients with ET and PMF. Mutational status shows the only significant correlation with NETosis rates and hints to intracellular signaling as one relevant determinant of NETosis in MPN. Cytoreductive treatment seems not to affect susceptibility to NETosis.

P33

Functional cooperation of CEBPA and TET2 mutations in acute myeloid leukemia

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Background: The gene encoding the transcription factor CEBPA is mutated in 9% of Acute Myeloid Leukemia (AML) patients. AML patients harbor either mono- or biallelic CEBPA mutations (CEBPAmo or CEBPAbi) and both genotypes are frequently associated with concurrent mutations in other genes. The most commonly co-occurring mutations in both groups are mutations in the methylcytosine dioxygenase TET2 (44.4% in CEBPAmo/34.8% in CEBPAbi). We hypothesize that combinatorial effects of CEBPA mutations together with TET2 mutations specifically rewire transcriptional and epigenetic circuitries in AML cells, thereby strongly influencing disease outcome.

Methods: We used CRISPR-Cas9 technology to establish novel cellular models harboring both mutations. To elucidate molecular mechanisms underlying changes dependent on these genetic alterations, we profiled the genomic landscapes of these cell lines using ATAC-Seq and RNA-Seq.

Results: Upon introduction of Tet2 mutations into Cebpa-mutated cell lines, we observed a strong selective advantage of Tet2-targeted cells, accompanied by a significant decrease of accessible chromatin regions. Detailed integrative analysis of the resulting differential gene expression in combination with RNA-Seq data from AML patients and in vivo models revealed specific sets of commonly de-regulated genes in patients, relevant mouse models and cell lines.

Conclusions: The datasets generated from these novel models enable deeper insights into the global epigenetic and transcriptomic changes dependent on CEBPA and TET2 mutations in a physiologically relevant mutational context. Together, our work will enhance our understanding of gene cooperativity in AML and could provide entry points for the development of novel patient management strategies.

P34

Unravelling the pre-clinical utility of MCL-1 inhibitors to optimize future clinical protocols in multiple myeloma

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Background: In order to obtain an advanced understanding about the prospects of MCL1 inhibitors in myeloma this study addressed the impact of the prior use of MCL1-targeting therapeutics (ProteasomeInhibitors), mechanisms of acquired drug resistance, and the definition of optimal combination partners.

Methods and Results: We first examined the impact of prior PI exposure and observed a complete loss of S63845 and A-1210477 activity in carfilzomib (CARF), but not ixazomib, resistant cell lines. Mass spectrometry based analysis of intracellular S63845 concentrations demonstrated significantly reduced S63845-levels in CARF resistant vs sensitive cells. Concurrent treatment with MDR-1 inhibitors or CRISPR/CAS9 mediated MDR-1-knockout restored intracellular concentrations and re-sensitized CARF resistant cells to S63845.

Next, we studied in-house generated cell lines with acquired S63845 resistance. This demonstrated alternative strategies of Bcl-2 family modulation. In OPM2-S63845, reduced levels of pro-apoptotic Bcl-2 family members were noted, whereas a striking upregulation of Bcl-2 and MCL1 was observed in KMS12BM-S63845. Co-immunoprecipitation experiments confirmed differential interaction patterns of pro- and anti-apoptotic proteins in both cell lines. Accordingly, venetoclax+S63845 demonstrated synergism in KMS12BM- but not OPM2-S63845.

Finally, high-throughput drug screenings ($n=528$) revealed different S63845 combination partners in S63845-resistant cells. Synergy scores designated varying BH3 mimetics as the optimal choice which was further confirmed in an independent panel of MM cell lines in mono- and co-culture.

Conclusions: Our findings suggest that different baseline BH3 profiles guide alternative routes to acquired drug resistance and reveal S63845 as a novel MDR-1 substrate. This underlines the importance of identifying optimal drug sequencing and combination strategies for future precision medicine approaches.

P35

Aberrant expression of micro-RNA-125a plays a role in the pathogenesis and treatment of chronic myelomonocytic leukemia

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Background: Chronic myelomonocytic leukemia (CMML) is an aggressive myeloid neoplasia, which is frequently treated with the hypomethylating agent azacitidine. Here, we studied the role of micro-RNAs (miRs) in CMML development and azacitidine efficacy.

Methods: miR expression profiling by miR-microarray and qPCR, respectively, was performed in purified hematopoietic stem and progenitor cells (HSPCs) of a KrasG12D-induced CMML mouse model, in 40 human CMML patient specimens, and in nine healthy human HSPC controls. For functional analyses, a series of myeloid/monocytic leukemia cell lines were transduced with a lentiviral miR-125a overexpression construct, with miR-125a shRNA knockdown reagents and/or treated with azacitidine. Subsequently, we performed bisulfite sequencing of the miR-125a promoter region, growth curves, BrdU/7-AAD proliferation assays, as well as Annexin-V/7AAD apoptosis assays.

Results: The expression of miR-125a is decreased in HSPCs of human and murine CMML. Functionally, overexpression of miR-125a in myeloid cells with decreased expression of endogenous miR-125a induced apoptosis while inhibiting cellular growth and proliferation. We further show that the decrease of miR-125a is caused by hypermethylation of its promoter region and can be reversed by the treatment with azacitidine. Indeed, analysis of serially obtained primary patient specimens revealed a higher miR-125a expression after azacitidine treatment than before. Importantly, miR-125a silencing by shRNA transfection prevented the azacitidine-induced miR-125a increase and hampered the cytotoxic effects of this drug.

Conclusions: Expression of miR-125a is decreased in CMML by hypermethylation of its promoter region. Azacitidine treatment increases miR-125a expression, which contributes to the anti-leukemic efficacy of this drug.

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Successful treatment of concomitant Polycythemia Vera and Multiple Myeloma with IFN-alpha

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Background: Cases of concomitant Polycythemia Vera (PV) and Multiple Myeloma (MM) are uncommon. We present a case of a 62-year old male patient initially diagnosed with PV and subsequently with IgA MM who was successfully treated with IFN-α.

Methods: The patient received hydroxyurea (HU) and acetylsalicylic acid (ASA) for PV and was treated with five cycles of a Bortezomib, Thalidomide and Dexamethasone (VTD) regimen followed by Thalidomide maintenance after the diagnosis of MM. We employed a Roche SeqCap custom panel and 2 × 100bp sequencing on the NovaSeq 6000 platform to analyze point mutations and copy number variations (CNV) in approximately 1500 cancer-associated genes.

Results: HU and thalidomide have been stopped due to intolerance and thalidomide-related polyneuropathy respectively, and IFN-α was introduced. The partial remission of MM was maintained and complete remission of PV was achieved and maintained after 33 months of IFN-α therapy. A JAK2 p.Val617Phe mutation was identified with an accompanying copy-neutral loss-of-heterozygosity event on the entire 9p chromosome or a majority of its length. No other genetic aberrations relevant were found.

Conclusions: The presence of concomitant PV and MM could be the result of two distinct malignancies originating from two separate abnormal clones or from a common hematopoietic stem cell. The lack of genetic aberrations except for the JAK2 mutation and response to IFN-α therapy might suggest a common origin of MM and PV in our patient. Further investigations are needed to elucidate the etiology and identify the optimal therapy in this unique patient population.

P37

A 53-year-old man with acute hepatic injury following induction for multiple myeloma

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Background: Acute liver failure is a rare event in the context of multiple myeloma (MM). We report a case of acute liver injury likely attributable to tumor lysis of previously unrecognised, diffuse myelomatous infiltration of the liver parenchyma.

Case report: A previously healthy man was diagnosed with MM presenting with IgG kappa paraproteinemia of 70 g/L and >90% bone marrow (BM) infiltration. Whole-body magnetic resonance imaging (MRI) was consistent with diffuse BM involvement but absence of extramedullary lesions. The patient received a short course of corticosteroids and was scheduled for lenalidomide/bortezomib/dexamethasone (VRd). Lenalidomide was initially withheld due to sepsis with E.coli bacteremia during cycle 1 and added in cycle 2. When he was readmitted on C2d7 for fever, a sharp decline in paraprotein levels was noted accompanied by a massive increase in GOT, GPT and LDH levels (>3.500 U/L each) without evidence of viral hepatitis, hyperbilirubinemia or encephalopathy. Liver MRI at this point showed diffuse parenchymal enhancement which prompted a biopsy. Histology confirmed diffuse intrasinusoidal infiltration by malignant plasma cells. Liver enzymes normalized within a few days with supportive care only. The patient went on to receive 4 cycles of VRd with daratumumab added after cycle 3, but only a transient partial response was achieved.

Conclusions: Disseminated hepatic involvement in MM may be missed even with contemporary imaging and heralds poor prognosis with insufficient response to a four-drug induction including an anti-CD38 monoclonal antibody. Outcome of high-dose melphalan and autologous stem cell transplantation will be reported.

Poster Onkologie

P38

Applicability of carboplatin containing neoadjuvant treatment regimen in triple negative early breast cancer patients

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Background: The role of carboplatin containing neoadjuvant treatment regimen for triple negative early breast cancer (eTNBC) is still controversial. In several clinical trials, carboplatin containing treatment regimen were associated with an increased pathologic complete response (pCR) rate and a higher toxicity rate. The aim of this retrospective analysis was to determine the applicability of neoadjuvant carboplatin in eTNBC in a real-world setting.

Methods: Patients with eTNBC (primary tumors, contralateral, or locoregional recurrences) diagnosed between 2009 and

2018 and treated with NAC at our tertiary cancer center who underwent breast surgery where included in this study.

Results: Overall, 175 eTNBC cases treated with NAC were identified. Out of them, 34 (19.4%) received a platin containing regimen (carboplatin group), most cases 21 (61.8%) in combination with paclitaxel followed by epirubicin and cyclophosphamide. Patients in the carboplatin group were significantly younger, but baseline tumor characteristics did not statistically differ between the treatment groups. The pCR rate (ypT0;ypN0/ypN0i+) was 38.3% ($N=67$), 47.1% ($N=16$) in the carboplatin and 36.2% ($N=51$) in non-carboplatin group. This was not statistically significant in univariate ($p=0.221$), nor in multivariate analysis ($p=0.204$). Comparing the rates of therapy discontinuation, no statistically relevant disparity became evident ($p=0.632$). Furthermore, applicated relative doses of cytotoxic drugs did not statistically differ between the treatment groups ($p=0.977$).

Conclusions: With a good patient selection, carboplatin-containing neoadjuvant regimens can be safely applicated without increasing patients risk of discontinuing therapy or reducing dose intensity.

P40

Neurological symptom burden impacts survival prognosis in patients with newly diagnosed non-small cell lung cancer brain metastases

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Background: Brain metastases (BM) are a frequent complication of advanced cancer and characterized by a variety of neurological symptoms. While the symptomatic burden is included in the response assessment in primary brain tumors, little is known on the prognostic impact of the symptomatic burden in BM patients.

Methods: Patients with newly diagnosed NSCLC BM were identified from the Vienna Brain Metastasis Registry and evaluated according to incidence, distribution and prognostic impact of neurological symptom burden at BM diagnosis.

Results: 1608 patients (male 57.3%, female 42.7%; median age 62 years) were available for further analyses. Neurological symptoms including neurological deficits (985/1608; 61.3%), signs of increased intracranial pressure (483/1608; 30.0%), epileptic seizures (224/1608; 13.9%) and neuropsychological symptoms (233/1608; 14.5%) were documented in 1186/1608 (73.8%) patients. Patients with oligo- to asymptomatic BM presented with a longer median overall survival after diagnosis of BM compared to patients with symptomatic BM (11 vs. 7 months; $p<0.001$). In multivariate analysis with DS-GPA (HR 1.41; 95% CI 1.33–1.50; $p<0.001$), the presence of neurological symptoms (HR 1.39; 95% CI 1.23–1.57; $p<0.001$) was independently associated with survival prognosis from diagnosis of BM.

Conclusions: Neurological symptom burden at BM diagnosis presented with a strong and independent association with survival prognosis. Our study highlights the need for integration of neurological symptom burden in the prognostic assessment of NSCLC BM patients.

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Prognostic assessment in patients with newly diagnosed small cell lung cancer brain metastases: results from a real-life cohort

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Background: Brain metastases (BM) are a frequent complication in small cell lung cancer (SCLC), resulting in a reduced survival prognosis. Precise prognostic assessment is an important foundation for treatment decisions and clinical trial planning.

Methods: Patients with newly diagnosed SCLC BM were identified from the Vienna Brain Metastasis Registry and evaluated concerning prognostic factors.

Results: 489 patients (male 62.2%, female 37.8%; median age 61 years) were included. Neurological symptoms were present in 297/489 (60.7%) patients. A- to oligosymptomatic patients (5 vs 9 months, $p=0.030$) as well as patients with synchronous diagnosis of BM and primary tumor (5 vs. 9 months, $p=0.008$) presented with improved overall survival (OS) prognosis. RPA (HR 1.66; 95% CI 1.44–1.91; $p<0.001$), GPA (HR 1.65; $p<0.001$), DS-GPA (HR 1.60; $p<0.001$) and LabBM score (HR 1.69; $p<0.001$) were statistically significantly associated with OS. In multivariate analysis, DS-GPA (HR 1.59; $p<0.001$), neurological deficits (HR 1.26; $p=0.021$) and LabBM score (HR 1.57; $p<0.001$) presented with statistical independent association with OS.

Conclusions: A- to oligosymptomatic BM as well as synchronous diagnosis of SCLC and BM were associated with improved OS. Established prognostic scores could be validated in this large SCLC BM real-life cohort.

P42

Alyref influences colorectal carcinogenesis via molecular interaction with the transcription factor E2F2

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The nuclear export factor Alyref has been implicated in human cancer, though the biological role and molecular mode of action in colorectal carcinogenesis have not been elucidated yet. We examined for the first time the clinical and biological relevance of Alyref as well as the molecular mode of action in colorectal cancer. High Alyref expression was significantly associated with poor survival in colorectal cancer patients (hazard ratio: 2.71, 95% CI 1.05–7.02; $p < 0.039$). Gain and loss of function experiments, clearly demonstrated that Alyref expression effects colorectal cancer cell growth, apoptosis and tumor growth in xenograft tumors. Gene expression profiling and correlation analysis in human tissue proposed a molecular link between Alyref and the oncogenic transcription factor E2F2. Consequently, we identified a direct physical interaction between Alyref and E2F2, thereby influencing the DNA-promoter binding-affinity of RNA polymerase II and transcriptional activity of E2F2-responsive genes that influence cell cycle regulation and cellular growth. In summary, Alyref is a novel cancer promoting factor in colorectal cancer, which can partly be explained by its interaction with E2F2 followed by functional consequences for the expression of important regulators of cellular growth.

P43

The long non-coding RNA POU3F3 as new player in clear-cell renal cell carcinogenesis

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Activated angiogenesis is a major pathophysiological driver and therapeutic target in clear cell renal cell carcinoma, though the complex underlying mechanisms have not been characterized yet. The long non-coding RNA POU3F3 (LINC01158) has been previously involved in angiogenesis in glioma. The aim of our study was to explore the role of POU3F3 in clear cell RCC. We analyzed the expression status of POU3F3 in different datasets between cancer and corresponding normal kidney tissue, as well as the impact on disease-free survival. Additionally, we evaluated the biological role of POU3F3 in RCC cell lines with regard to cancer cell proliferation, migration and tube formation, as well as the influence on angiogenesis-related gene expression. Independent datasets demonstrated that POU3F3 is significantly increased in kidney cancer tissue compared to normal kidney tissue. High expression levels of POU3F3 are significantly associated with poor disease-free survival of kidney cancer patients. In vitro experiments clearly demonstrate that changes in POU3F3 expression levels strongly impact cellular proliferation, migration and tube formation capacity. Furthermore, a decrease of POU3F3 expression results in down-regulation of pro-angiogenic genes. Therefore, we conclude that POU3F3 plays a role in the pathogenesis of clear cell RCC and could be a prognostic marker or even a future therapeutic target.

P44

Viennese risk prediction score for Advanced Gastroesophageal carcinoma based on Alarm Symptoms (VAGAS score) – Characterization of alarm symptoms and its correlation with outcome

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Background: The prognostic value of symptoms at disease presentation of advanced gastroesophageal cancer is unknown. Thus, the aim of this study was to characterize these symptoms and correlate them with the outcome, so new prognostic markers can be defined.

Methods: We analyzed clinical data including symptoms and survival of patients with stage IV gastroesophageal cancer treated between 2002 and 2018 at the Vienna General Hospital. Initial symptoms as well as stenosis in endoscopy and HER2 positivity were evaluated in a cross-validation model to ascertain the impact of each variable on patient survival.

Results: In total, 258 patients were evaluated. Five factors (stenosis in endoscopy, weight loss, HER2 positivity, dyspepsia, ulcer or active bleeding) have proven to be statistically relevant prognostic factors and were given a count of +1 and –1, if applicable. The resulting score ranges between –3 and +2. The survival probability for 180 days with a score of –3/–2, –1, 0, +1, +2 is 90%, 80%, 73%, 72%, 42%, whereas for 2 years it is 30%, 30%, 8%, 7%, 3%, respectively. The median overall survival of a score of –3/–2, –1, 0, +1, +2 was 579 (95% CI: 274-not measurable), 481 (95% CI: 358–637), 297 (95% CI: 240–346), 284 (95% CI: 205–371), 146 (95% CI: 120–229) days, respectively.

Conclusions: The data from this retrospective study indicate that the VAGAS score provides independent prognostic information that may support clinical decision making at diagnosis of advanced gastroesophageal cancer. Our findings should be evaluated in prospective studies.

P45 Oral Best Submitted Abstract Onkologie

Decreased activity of circulating butyrylcholinesterase in blood is an independent poor prognostic marker in pancreatic cancer patients

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Background: The activity of butyrylcholinesterase (BChE) plasma levels reflects liver function and has recently been associated with systemic inflammatory response and cachexia in cancer. As these conditions have been previously associated with pancreatic cancer, the purpose of the present study, is to evaluate the prognostic impact of plasma activity of BChE in a large cohort of pancreatic cancer patients.

Methods: Data from 574 consecutive patients with adenocarcinoma of the pancreas, treated between 2004 and 2018 at a single academic center, were evaluated retrospectively. The primary endpoint was cancer-specific survival (CSS), which was analyzed by Kaplan-Meier curve, and both univariate and multivariate Cox proportional models.

Results: BChE activity negatively correlated with other liver parameters (bilirubin, gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), C-reactive protein (CRP)), and positively correlated with albumin levels, respectively ($p<0.01$). In univariate analysis, we observed that a low BChE plasma activity was a consistent factor of poor CSS (HR = 1.41; 95%CI = 1.129–1.754, $p=0.002$). In multivariate analysis, tumour stage, grade, administration of chemotherapy, bilirubin levels and a low BChE activity (HR = 1.42, 95%CI = 1.10–1.82; $p=0.006$) were identified as independent prognostic factors in pancreatic cancer patients.

Conclusions: Decreased activity of BChE in blood is a poor prognostic factor in patients with pancreatic cancer, and this prognosticator might be helpful in stratification of patients into different prognostic risk groups.

P46

Tumor mutational burden and immune infiltrates in primary renal cell carcinoma and matched brain metastases

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Background: Tumor mutational burden (TMB) as well as density of tumor infiltrating lymphocytes (TIL) have been postulated as predictive response biomarkers for immune checkpoint inhibitor-based therapies. Therefore, we investigated the concordance of TMB and TIL of primary/extracranial renal cell carcinoma (RCC) specimens and matched brain metastases (BM).

Methods: 10 patients with RCC BM were retrieved from the Vienna Brain Metastasis Registry (6/10 primary renal cell tumor, 4/10 lung metastasis, 10/10 matched BM). TMB was assessed using the TruSight Oncology 500 gene panel with libraries sequenced on NextSeq instrument. TIL subsets (CD3, CD8, CD45RO, FOXP3, PD-L1) were investigated with Ventana Benchmark Ultra system for immunohistochemistry and automated tissue analysis (Definiens software). Spearman correlation coefficient (SCC) was used to correlate and compare scale variables.

Results: Higher TMB and TIL densities were observed in intracranial compared to extracranial specimens. In extracranial samples, low association between TMB and TIL subsets, and TMB and intracranial FOXP3+ and CD45RO+ TIL densities were observed (SCC:0.3–0.5). In intracranial samples, low correlation between TMB and CD8+ TIL densities, and TMB and extracranial CD45RO+ TIL densities were found (SCC:–0.31). Furthermore, moderate association between extra- and intracranial CD45RO+ TIL densities (SCC:–0.65) and between extracranial TMB and intracranial CD8+ TIL densities (SCC:–0.55) were observed.

Conclusions: TMB and TIL density were numerically higher in BM compared to matched extracranial samples in the present cohort. Although results have to be interpreted with caution due to limited sample size, our results support further exploration of immune checkpoints inhibitors in patients with RCC BM.

P47

Brustkrebs mit immunhistochemischer HER2 2+ Positivität: Subtypen, Therapie und Langzeitüberleben

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Grundlagen: Mammakarzinom stellt in Österreich bei Frauen die häufigste Tumorart und die häufigste Krebstodesursache dar. Der HER2 Status hat entscheidenden Einfluss auf die Therapiemöglichkeiten hinsichtlich HER2 gerichteter Therapien.

Methodik: Retrospektiv wurden PatientInnen, die zwischen 2006 und 2016 an der Klinischen Abteilung für Onkologie des LKH Graz behandelt wurden und eine histologisch bestätigte Diagnose eines Mammakarzinoms mit HER2 Status IHC 2+ haben, erfasst. Die Daten wurden hinsichtlich Verteilung der intrinsischen Subtypen, Erhalt von HER2 spezifischer Therapie und Überlebensparameter ausgewertet.

Ergebnisse: Von insgesamt 350 IHC 2+ PatientInnen (228 adjuvant, 82 neoadjuvant, 40 palliativ) waren nach In-Situ-Hybridisierung 35 (10,0 %) triple negativ, 224 (64,0 %) Hormonrezeptor positiv und 86 (24,6 %) HER2 positiv (5 unbekannt). Letztere unterteilen sich in 14 Hormonrezeptor negative und 70 Hormonrezeptor positive Fälle (2 unbekannt) mit einer medianen HER2/CEP17 Ratio von 3,16 (25.–75. Perzentile: 2,42–5,20) und 2,57 (25.–75. Perzentile: 2,37–3,52), respektive. 62 PatientInnen (20,0 %) erhielten eine HER2 gerichtete Therapie im (neo)adjuvanten Setting. Die mediane Nachbeobachtungszeit betrug 7,2 Jahre (25.–75. Perzentile: 5,0–9,2 Jahre). Adjuvante HER2 positive PatientInnen mit HER2 gerichteter Therapie hatten eine 5-Jahres-Überlebensrate von 93,2 %, jene ohne HER2 gerichtete Therapie 83,0 %. Adjuvante HER2 negative PatientInnen hatten eine 5-Jahres-Überlebensrate von 88,7 %.

Schlussfolgerungen: 24,6 % der IHC 2+ PatientInnen stellten sich im weiteren Verlauf als tatsächlich HER2 positiv heraus, 81,4 % davon hatten positive Hormonrezeptoren. 62 PatientInnen erhielten eine HER2 gerichtete Therapie. Die HER2/CEP17 Ratio bei HER2 ISH positiven PatientInnen war bei Hormonrezeptor negativen Fällen im Median größer als bei Hormonrezeptor positiven. Adjuvante HER2 positive PatientInnen mit HER2 gerichteter Therapie hatten die höchste 5-Jahres-Überlebensrate.

P48

Pembrolizumab in MSI-high pancreatic cancer

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Background: We report the outcome of a patient with MSI-high metastatic pancreatic sarcomatoid carcinoma refractory to multiple lines of chemotherapy treated with pembrolizumab successfully.

Case report: In Novembre 2015, our patient presented with epigastric pain leading to radiologic workup. A lesion in the pancreas as well as liver metastasis were diagnosed; liver biopsy revealed a poorly differentiated sarcomatoid carcinoma. He received chemotherapy with gemcitabine and nab-paclitaxel resulting in complete remission of the liver and partial remission of the pancreas. Consecutively, a whipple resection of the pancreatic tumor was performed. After receiving another two cycles of gemcitabine and nab-paclitaxel disease progression with appearance of new hepatic metastasis as well as retroperitoneal lymphadenopathy was evident in Octobre 2016. Second and third line therapy consisting of FOLFOX and FOL/nal-IRI failed to achieve a response and were poorly tolerated. Because of the tumor being MSI high, treatment with pembrolizumab was commenced in May 2017. Clinical response with better overall quality of life was soon reported and repeated CT scans showed an ongoing partial response leading to a near complete remission in the latest scan obtained. Adverse events during the course of therapy included immune mediated arthralgia grade 1, colitis grade 2 and pneumonitis grade 1 which were managed by administration of glucocorticoids without interruption of immunotherapy.

Conclusions: To our knowledge, this is the first case of a patient with MSI high metastatic sarcomatoid carcinoma of the pancreas successfully treated with immunotherapy for more than two and a half years.

P49

Impact of targeted therapies on the survival prognosis of patients with lung cancer brain metastases treated at a tertiary care center

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Background: Brain metastases (BM) are a frequent and devastating complication in patients with lung cancer. Targeted therapies (TT), including tyrosine kinase inhibitors for patients with oncogene addiction and immune checkpoint inhibitors (ICI) are well established therapies for the extracranial disease. However, patients with BM have been frequently excluded from clinical phase III trials, resulting in limited data on TT/ICI in brain metastasis patients, especially in a real-world setting. The aim of this study is to assess the effect of TT/ICI in patients with NSCLC BM in a real-life setting.

Methods: Patients with BM were identified from the Vienna Brain Metastasis Registry and clinical data on applied therapies as well as survival times were retrieved by retrospective chart review.

Results: 1626 (median age 61 years, female 693/1626 (42.6%)) patients were available for further analysis. 215/1626 (13.2%) patients received TT/ICI after diagnosis of BM. 134/215 (62.3%) were treated with EFGR inhibitors, 12/215 (5.6%) with

ALK/ROS1 inhibitors and 69/215 (32.1%) with ICI. Since 2001 the number of patients treated with TT/ICI increased reaching a proportion of 23,21% of patients (39/168) in 2017/2018. Overall survival from diagnosis of BM was 19 months in patients receiving a TT/ICI approach compared to 7 months in patients without TT/ICI. These differences were reflected in a *p*-value of <0.001 (Log Rank test).

Conclusions: TT/ICI significantly improved the overall survival of patients with NSCLC BM in the real-life setting. These changed survival times have to be taken into account in the treatment planning of newly diagnosed BM patients.

P50

Degradation of BRD4 – a novel approach for treatment of solid tumors

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Bromodomain and extra-terminal (BET) proteins are epigenetic readers that regulate gene expression and are involved in cancer pathogenesis. Therefore, pharmacological inactivation of these proteins has emerged as a promising anticancer approach. Among the BET proteins, BRD4 has recently been identified as potential drug target that upregulates MYC oncogene expression. Here, we compared the efficacy of the small-molecule BET inhibitor JQ1 with the recently developed BET protein degraders dBET1 and dBET6 in 3 colon, 3 breast, 3 melanoma, 3 multiple myeloma, 3 ovarian, 2 lung and 2 prostate cancer cell lines. As determined by qPCR, the BRD4-targeting drugs dose-dependently decreased MYC expression in all tested cell lines whereby dBET6 caused strongest MYC down-regulation. In addition, dBET6 revealed strongest anti-proliferative activity in most cell lines tested (IC50 0.001–0.5 μM) compared to JQ1 and dBET1 (IC50 0.5–5 μM). Next, we combined dBET6 with typical chemotherapeutics. Interestingly, we found a cooperative growth-inhibition in almost all cell lines when adding dBET6 to the chemotherapeutics. Furthermore, we examined the influence of BET inhibitors on the expression of the immune checkpoint molecule PD-L1, which negatively regulates the immune system. In fact, we were able to show that JQ1 and both BET degraders decreased the interferon-gamma-induced upregulation of PD-L1 expression in all tested cancer cell lines. In summary, our data demonstrated not only impressive effects of the novel BET degrader dBET6 on proliferation of various cancer cell lines but might also provide a new therapeutic strategy to improve the effect of immunotherapy in solid tumors.

P51

Real-world treatment patterns and outcomes of patients with advanced prostate cancer treated in a tertiary center in Austria

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Background: The aim of this study was to evaluate characteristics, treatment patterns and outcomes of patients with advanced prostate cancer treated at our institute. Our real world data were compared with outcomes of large randomized trials.

Methods: Clinical data were derived from our prospective prostate cancer registry, including patients having received systemic treatment consisting of at least one course of chemotherapy, novel antiandrogen agent or radionucleotide. All patients who presented at our clinic between 2013 and 2018 were included, data cut-off for follow up was November 28th, 2019.

Results: A total of 114 patients received systemic therapy beyond ADT of which 93 patients were castration resistant. Median age by the time of metastatic disease was 73 years (range 42–91), most patients presented with bone +/– lymph node metastasis only (66.7%). Overall, 71 patients (62.3%) received chemotherapy during the course of their disease. Median overall survival (OS) and time to subsequent therapy (TTST) after first-line intervention in castration resistant disease was 32.3 months and 11.1 months, respectively. Different treatment sequences in the overall population as well as outcomes of specific patient subgroups were analysed, detailed and updated data will be shown at the conference. Based on the data of long-term survivors, the benefit of multiple subsequent lines of therapy is demonstrated.

Conclusions: This retrospective study reveals treatment patterns in clinical routine. Median OS and TTST of our patient population compares favourably to outcomes of phase 3 trials of first line chemotherapy and novel antiandrogen agents.

P52

Austrian cohort analysis from a non-interventional long-term post authorization safety study of ruxolitinib in myelofibrosis

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Background: Lack of post-marketing exposure data of ruxolitinib led to an agreement with the European Medicines Agency to conduct a post-authorization safety study (PASS). Present subgroup analysis provided real-world safety data from Austrian patients with myelofibrosis exposed/non-exposed to ruxolitinib.

Methods: Primary objective: long-term safety (incidence of adverse drug reactions [ADRs]/serious adverse events [SAEs]) in patients with prescribed ruxolitinib. Secondary objectives: incidence/outcome of events of special interest (EoSI [bleeding events, serious/opportunistic infections, secondary malignancies, and deaths]).

Results: Present analysis was conducted in 115 Austrian patients (prevalent users = 72, new users = 8, non-exposed = 35, ruxolitinib-switch = 14) from overall PASS study cohort. ADRs were comparatively less frequent in prevalent users (55.6%) vs other cohorts (62.5% in new users; 78.6% in ruxolitinib-switch cohort). Thrombocytopenia and anemia were more frequent in ruxolitinib-switch cohort compared with the prevalent users/new users; higher ADR incidence rates in the ruxolitinib-switch cohort is likely due to the initial toxicity associated with ruxolitinib use and the shorter duration of exposure to ruxolitinib for the ruxolitinib-switch cohort. Frequency of treatment-emergent SAEs was higher in the prevalent users compared with other cohorts. Among the ruxolitinib-switch cohort, the incidence rate of treatment-emergent SAEs was slightly higher compared with the prevalent users/new users cohorts. Second primary malignancies were more frequent of patients in the prevalent users' cohort.

Conclusions: Long-term safety findings for ruxolitinib in this subgroup study were consistent with previous findings and no major safety differences were noted between the overall population and Austrian population. These data support long-term treatment with ruxolitinib in Austrian patients with myelofibrosis.

P53

External validation of the prognostic relevance of the Advanced Lung Cancer Inflammation Index (ALI) in pancreatic cancer patients

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Background: The Advanced Lung Cancer Inflammation Index (ALI) was originally established as a prognostic tool in lung cancer patients and consequently validated in various other cancer entities. To date, in pancreatic cancer (PC) patients, the prognostic potential of the ALI has only been assessed in a relatively small cohort of chemoradiotherapy-treated patients with locally-advanced PC.

Methods: In this large single-center cohort study ($n = 429$), patients with histologically-proven PC treated between 2003 and 2015 were included. The ALI was defined as body mass index (BMI; kg/m2)x serum albumin levels (g/dL)/neutrophil-lymphocyte ratio (NLR) and the optimal cut-off to differentiate between prognostic groups was identified using ROC-analysis. Kaplan-Meier method as well as uni- and multivariate Cox regression Hazard proportional models were applied to evaluate the predictive value of ALI in PC patients with regard to the primary endpoint of cancer-specific survival (CSS).

Results: The ALI was significantly negatively correlated with CA19-9 levels, CRP levels and associated with localized tumor stage and higher performance status ($p < 0.05$ for all mentioned variables). Low ALI was significantly associated with shorter CSS (HR = 0.606, 95%-CI: 0.471–0.779, $p = 0{,}001$) as compared to patients with a high ALI. Multivariate analysis revealed tumor grade, tumor stage, chemotherapy, CRP and CA19-9 levels as independent predictors of CSS (all p-values < 0.05), whereas the ALI did not independently predict for CSS in multivariate models (HR = 0.878, 95%-CI: 0.643–1.198, $p = 0.411$).

Conclusions: In this large cohort of PC patients, the ALI does not add additional prognostic value to the established clinico-pathological prognostic factors.

P54

Evaluation of blood-based biomarkers for prediction of response in carboplatin-treated metastatic castration-resistant prostate cancer patients

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Background: Carboplatin-containing treatment regimens have demonstrated moderate efficacy in metastatic castration-resistant prostate cancer (mCRPC) patients after failure of standard docetaxel chemotherapy. There are currently no markers available for selecting patients most likely to benefit from this potentially toxic agent. In this study, we retrospec-

tively analyzed the efficacy of carboplatin in relation to blood-based parameters to identify putative easily available predictive biomarkers.

Methods: A retrospective chart review was performed for 20 patients with mCRPC who received a carboplatin-containing regimen between 2009 to 2018 in a single center. We studied the predictive value of PSA, NSE, CgA, AP, AST, ALT, GGT, LDH, inflammatory markers such as CRP, absolute leukocytes, absolute neutrophils, absolute lymphocytes as well as GFR and albumin.

Results: Median OS was 3.8 months (95% CI 1.5–7.1) and median PFS was 1.7 months in our cohort. We observed two partial remissions (PR, 10%), four stable diseases (SD, 20%) and 14 disease progressions (PD, 70%), resulting in a clinical benefit rate (a composite of PR+SD as best response) of 30%. A doubling of NSE values was associated with a 19% absolute higher response rate (95%CI: 14–23, $p=0.027$). All other laboratory parameters, as well as age and Gleason score failed as predictive markers of response to carboplatin. In univariate Cox regression analysis, only NSE was significantly associated with impaired PFS (HR 0.7, 95% CI: 0.56–0.96, $p=0.030$).

Conclusions: Carboplatin showed moderate efficacy against mCRPC in this unselected population of patients and NSE levels may help to predict the success of this treatment.

P55

Analyse des Österreichischen Registers für Gastrointestinale Stromatumore

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Grundlagen: Das Österreichische GIST-Register hat sich zum Ziel gesetzt, von verschiedenen Krankenanstaltenabteilungen, die Patienten mit GIST operieren, medikamentöse Therapie verabreichen oder deren Gewebe untersuchen, Daten zu sammeln und in Statistiken aufzuarbeiten. Die medizinische Datenbank soll dazu beitragen, eine epidemiologische Datenbasis zu erstellen und wertvolle Informationen zu sammeln um künftig bessere Behandlungserfolge zu erzielen.

Methodik: Insgesamt wurden Stammdaten von 447 PatientInnen in 15 Zentren erfasst und ausgewertet. Zudem erfolgte eine Nachbeobachtung des Krankheits- und Therapieverlaufs. Der Zeitraum, in dem die aufgenommenen Patienten nachbeobachtet wurden und dem die vorliegende Auswertung zugrunde liegt, beträgt zwischen 2 und 6440 Tage.

Ergebnisse: Bei ausgeglichener Geschlechts- und Altersverteilung fand sich bei der Mehrzahl der PatientInnen histologisch ein spindelzelliger GIST (66 %), gefolgt von Mischtypen (17 %) und epitheloidzelligem GIST (8 %). Gemäß Risikostratifizierung nach Miettinen/Lasota wiesen die Mehrzahl der Fälle ein niedriges bis moderates Rezidivrisiko auf. Dagegen bestand bei 27 % des Kollektivs ein hohes Risiko. Bei 209 aller im Register aufgenommenen Patienten erfolgte ausschließlich eine chirurgische Intervention. Primär palliative Patienten wurden standardgemäß mit Imatinib behandelt. Obwohl Sunitinib als 2nd-line Therapie nach Imatinibversagen/Intoleranz als Therapie der Wahl angesehen wird, erhielten auch in dieser Therapielinie mehr als die Hälfte aller PatientInnen Imatinib, während in weiteren Therapielinien Sunitinib dominierte. Regorafenib war vor allem ab der vierten Linie eine weitere Therapieoption.

Schlussfolgerungen: Das österreichische GIST-Register stellt ein wertvolles Instrument dar, um Therapieentscheidungen und daraus resultierende Erfolge in der täglichen Praxis abzubilden. Es dient zudem als Basis, um innovative Substanzen im Rahmen von Studienprotokollen zu akquirieren.

P56

Preliminary results of therapeutic cooling of hands and feet during taxan infusion in patients treated for breast cancer in a tertiary center in Austria

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Background: Adjuvant treatment with taxanes in breast cancer patients is known to cause higher grade polyneuropathy and nail toxicity in a significant number of patients. The aim of this study was to evaluate whether these side effects could be reduced by using ice gloves during taxane infusion.

Methods: We introduced therapeutic cooling of hands and feet to –25 °C during infusion of (nab-)paclitaxel and docetaxel starting in May 2019 and prospectively analysed neuropathic and nail toxicities in these patients using a standardized questionnaire.

Results: Up to now, 18 patients used ice gloves during taxane treatment, and 16 completed therapy. Of these, 9 patients experienced grade 1, and only 2 patients developed grade 2 polyneuropathy. No grade 3/4 polyneuropathy was observed. Grade 1 and 2 nail toxicity was seen in 7 and 1 patients, respectively, with no higher grades noted. There was one treatment discontinuation due to combined neuropathic and nail toxicity caused by paclitaxel and one patient who had to be switched to docetaxel therapy because of painful polyneuropathy induced by nab-paclitaxel.

Conclusions: Since the implementation of therapeutic cooling at our clinic, no grade 3 polyneuropathy or nail toxicity were observed. Our results so far compare favourably to recent large phase 3 trials using taxane therapy in early breast cancer.

Therefore, therapeutic cooling of hands and feet during taxane infusion seems to be an inexpensive and feasible way to avoid polyneuropathy and nail toxicity in patients receiving chemotherapy for breast cancer. Updated results will be presented at the conference.

P57

Impact of PD-L1 scores and dynamics on clinical outcome in rectal cancer patients undergoing neoadjuvant chemoradiotherapy

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Background: Reports on the prognostic role of programmed death-ligand 1 (PD-L1) expression in rectal cancer are controversial. Our aim was to investigate the expression and dynamics of PD-L1 according to three established scores.

Methods: Analyses of this retrospective study were based on rectal cancer patients diagnosed and/or treated at the IIIrd Medical Department of the Paracelsus Medical University Salzburg (Austria). 72 patients with rectal cancer undergoing fluorouracil-based neoadjuvant chemoradiotheray were included.

Results: PD-L1 tumor proportion score (TPS) prior to neoadjuvant chemoradiotherapy had a statistically significant impact on survival (median: ≤1%: 95.4 months [95% CI: 51.8—not reached] versus >1%: not reached, $p=0.03$, log-rank). Patients with a PD-L1 TPS ≤1% prior to and after chemoradiotherapy showed an inferior survival compared to all other patients (median: 56.7 months [95% CI: 51.4—NR] versus not reached, $p=0.005$, log-rank). In multivariate analysis, PD-L1 TPS (HR: 0.29 [95%CI: 0.11–0.76], $p=0.01$) remained independently associated with survival. Combining PD-L1 TPS and the neoadjuvant rectal (NAR) score in a risk model separated patients with differing risk profiles for 10-year survival: PD-L1 TPS > 1% + NAR-score low: 100% versus PD-L1 > 1% + NAR-score intermediate/high: 78% (z-test: $p=0.002$); PD-L1 > 1% + neoadjuvant NAR-score intermediate/high: 78% versus PD-L1 ≤ 1% + any NAR-score: 49% (z-test: $p=0.04$).

Conclusions: Low PD-L1 TPS was associated with inferior survival. Combining PD-L1 TPS and the NAR-score may improve identification of patients with differing risk for survival.

P58

Pembrolizumab in advanced carinoma of the pancreaticobiliary tract

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Our patient first presented in our clinic in 2003 with Colon cancer (age 34), which was primarly operated (right sided hemicolectomy, lymphadenectomy, ileotransversostomy; second look operation with tumor debulking and metastasectomy) in a pT3 N2 M1 situation.

After that the patient received postoperative chemotherapy, where she achieved a complete remission which lasted for 12 years.

10/2015 the patient complained about abdominal discomfort and pain. The CT scan showed a thickened duodenum with an intraluminar stenosis—the histology showed a carcinoma of the pancreobiliary tract which is why we performed a duodenopancreaticotomie (Whipple operation). The histology showed a pT3, pN0(0/17), L0, V0, G3, RX stage (IIA). She received adj. CHT with Gemzar monotherapy for 6 cycles from 2/16 until 6/16.

11/16 CT staging showed a paracaval lymphadenopathy pararenal with a hydronephrosis II° where a biopsy was performed and revealed a poorly differentiated carcinoma. Primary radiation in VMAT-technique with 30 Gy (3Gy SD) was applied until 4/2017. For persisting hydronephrosis after radiation a DJ cath. was implanted.

9/2017 the patient had a disease progression with new liver mets with per continuitatem renal infiltration and progressive retroperitoneal lymphadenopathy. Biopsy revealed a poorly differentiated adenocarcinoma with BRAF/panRAS wildtype and high microsatellite instability.

Palliative FOLFIRI was started, the patient refused anti-EGFR therapy. Unfortunately the patient progressed during that therapy and still refused an anti-EGFR-treatment.

From 1/2018 we started Pembrolizumab monotherapy 200 mg every 3 week as Third-line-treatment where the patient is still in a partial remission until 1/2020 with a good tolerability.

P59

Molecular landscape of colorectal cancers harbouring RNF43 mutations

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Background: The transmembranous protein RNF43 is one of the major regulators of the Wnt/β-catenin pathway. Wnt-inhibitors, such as PORCN and LRP5/6 inhibitors, are currently under early clinical investigation for the treatment of colorectal

cancer (CRC). Herein, we evaluated the prevalence of RNF43 and its co-mutations in CRC.

Methods: Tumor DNA sequencing of 592 genes (NextSeq, Illumina), RNA sequencing of 53 gene fusions (ArcherDx, FusionPlex) and immunohistochemistry (PD-L1) were analyzed on CRC tissues at Caris Life Sciences, Phoenix, USA. Molecular profiles of RNF43 mutated (RNF43-mut) were compared with wildtype (RNF-wt) tumors.

Results: RNF43-mut were detected in 66 of 1,356 (4.9%) CRC specimens. Female gender and right-sided tumors were associated with RNF43-mut CRC. RNF43-mut were highly related to an immunogenic tumor-microenvironment (MSI-H: 59.1%, dMMR: 64.3%, TMB: 23.5% mut/Mb, PD-L1 positivity: 30.8%). Classical CRC mutations, such as APC (27.3 vs 78.2%), KRAS (28.2 vs 52.2%) and TP53 (48.6 vs 72.7%) occurred significantly less frequent than in RNF43-wt samples. ARID1A (63.8 vs 18.2%) was the most frequently detected co-mutation followed by KMT2D (38.2 vs 2.1%) and BRAF (34.5 vs 4.6%). A higher prevalence of NTRK1 fusion-protein was found in RNF43-mut cancers (7.6 vs 0.1%).

Conclusions: To the best of our knowledge, this is so far the largest analysis of co-mutations of RNF43-mut CRC patients. The unique molecular profile and the high prevalence of concomitant MSI-H status and high TMB might serve as a potential therapeutic rationale to combine immune-checkpoint inhibitors with therapies targeting the Wnt/β-catenin pathway in RNF43-mut CRC.

P60 Oral Best Submitted Abstract Onkologie

Immunoprofiling of non-small cell lung cancer patients (NSCLC) patient derived microtumors

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Background: In recent years, our knowledge of the immune landscape in solid malignancies has improved greatly. However, prediction of efficacy and failure of immune checkpoint inhibitor treatment remains a topic of intensive investigations. Furthermore, adequate in vitro tumor models to highlight these issues are limited. Therefore, we established a 3D patient derived microtumor (PMT) model from non-small cell lung cancer (NSCLC) patients.

Methods: Tumor samples were first dissected and then digested with enzymes immediately after surgery. The primary cells were profiled using flow cytometry and seeded into ultra-low binding plates. PMTs were harvested after 10 days of incubation and further analysed via flow cytometry using the same protocol.

Results: Different cell types (including immune cells, fibroblasts, epithelial and endothelial cells) were identified using distinct surface markers in the primary tumor and in the PMT sample. Besides innate immune cells, the diverse T cell subsets including naïve, CD4+ and CD8+ effector memory, stem cell memory and terminal effector cells, were identified. PD-1 expression followed the same pattern on higher levels in PMT compared with the primary tumor.

Conclusions: PMTs provide an auspicious approach to investigate the tumor immune microenvironment. Further investigations of immune cell activation and shifts, including therapeutic interventions, using NGS, TCR-repertoire measurements and analyses of supernatants are warranted to prove the relevance of this model.

P61 Oral Best Submitted Abstract Onkologie

Clinical outcome in patients with carcinoma of the esophagogastric junction treated with neoadjuvant radiochemotherapy or perioperative chemotherapy: a bicentric retrospective analysis

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Background: Adenocarcinoma of the esophagus or of the gastroesophageal junction (AEG) is a rare disease. Patients suffering from localized or locoregional disease are usually treated within different multimodal treatment concepts. Superiority of either treatment approach has not been shown to date.

Methods: Patients with AEG I-III treated at the Ordensklinikum Linz or the Kepler University Hospital were identified by either using a monitored tumor registry or chart review. Time-to-event data were analyzed by Kaplan-Meier product limit estimation. Kruskal-Wallis test and Fisher exact test were used for comparing continuous or categorical data, respectively. Software used was RStudio Version 01.02.5019.

Results: 85 patients, median age 63 years, median CCI 3, 1.2% ECOG 2, all others below, were analysed. 52 patients received neoadjuvant radiochemotherapy (NRCT; 81% CROSS), 33 neoadjuvant chemotherapy (NACT; 65% EOX, 35% FLOT). There was a significant higher pCR-rate in the NRCT group (30 vs 12%, p 0.010), distant relapses were higher in the NRCT group, local relapses were higher in the NACT group (both not significant). These differences, however, did not translate into a different DFS (20 months, CI 13; 34) or OS (44 months; CI 33; NA). Patients > 65 years had the same advantage of treatment as patients < 65 years.

Conclusions: Patients reached a median OS of 44 months, which is within the range of current clinical trials. NRCT and NACT seem to be of similar efficacy. However, the perioperative chemotherapy mainly used was EOX, which is meanwhile known to be inferior to FLOT.

P62

Clonal evolution selecting for gains of pro-survival genes secure tumor cell survival in non-small cell lung cancer

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Adenocarcinoma of the lung remains the leading cause of cancer mortality worldwide. Mutations in KRAS ranks amongst the most common driver mutations in lung cancer but current treatment regimens remain ineffective. Here, we explored the role of prosurvival genes in cancer cell integrity during clonal evolution in pulmonary adenocarcinoma. We found that highly recurrent clonal and subclonal copy number gains of MCL-1 in several independent patient cohorts. Copy number gains remained largely independent of the oncogenic driver suggesting a potent pro-survival mechanism in lung cancer evolution. Using gene-targeted mice, tumor cell survival relied on MCL-1 independent of the expression of BCL-2 family members. Pharmacological MCL-1 inhibition delayed tumor progression and maintenance even when p53 was co-deleted. In summary, MCL-1 copy number amplifications represent a common and functionally relevant event during pulmonary adenocarcincoma evolution, identifying MCL-1 as a rational therapeutic target.

P63

The influence of epithelial-mesenchymal transition – regulating microRNAs on immune checkpoint molecules

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Background: Epithelial-mesenchymal transition (EMT) is a process, which enables cancer cells to migrate and invade tissue. By changing the epithelial phenotype to a more migratory mesenchymal functional state, cancer cells not only acquire enhanced motility, but may also escape immune surveillance through upregulation of immunosuppressive immune checkpoint (IC) molecules. With its five members (miR-141, miR-200a, miR-200b, miR-200c, miR-429), the miR-200 family is involved in many fundamental processes of cancer development, above all in the regulation of EMT. However, although a strong link between the miR-200 family and EMT persists, its influence on the expression of IC molecules has not yet been studied. Our aim is to investigate (EMT-dependent and/or EMT-independent) effects of the miR-200 family on IC molecules in biliary tract cancer (BTC) with focus on underlying molecular interactions.

Results: Using a collection of BTC cell lines ($n=11$), endogenous expression levels of miR-200 family members, EMT markers, and IC molecules were evaluated via RT-qPCR to perform a correlative analysis. Based on these results, miR-141 and miR-200c were selected for further functional analyses. After transient upregulation of miR-200c (but not miR-141) using miRNA mimics, three out of 21 IC molecules (IDO1, LGALS9, and PD-L1) were upregulated across four independent cell lines.

Conclusions: So far, we identified three IC molecules, whose expression potentially is under the control of miR-200c. Since the concomitant upregulation of miR-200c and PD-L1, LGALS9, and IDO1 suggests an indirect miRNA action, further in-depth research is necessary to unravel the molecular relationship of miR-200c to the respective IC molecules.

P64

Generation of immortal murine hematopoietic stem/progenitor cell lines from mice to study the role of mutant STAT3 in the JAK-STAT Pathway

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Recently, gain-of-function mutations of STAT3 have been identified in patients suffering from various haematopoietic malignancies, particular T-cell large granular lymphocytic leukemia (T-LGLL) and are postulated to enhance the transcriptional activity of STAT3. As transcription factors are notoriously difficult to target, a better understanding of STAT3-dependent co-factors is essential to understand how mutant STAT3 drives malignancy and to find novel therapeutic approaches. Previously we found that the cell-cycle regulator cyclin-dependent kinase 6 (CDK6) co-activates transcription in transformed leukemic cells in concert with STAT3 (Kollmann et al., Cancer Cell 2013). The functional contribution of this interaction to oncogenic transformation remains to be determined.

To study mutant STAT3 and the role of its protein interactors in normal, non-malignant hematopoietic progenitor cells, we transduced high-purity sorted murine lin-, Sca-1+, c-Kit+ cells (LSKs) with Lhx2, a LIM-homeobox transcription factor, which facilitates ex vivo expansion of immature hematopoietic cells. These HPCLSK cells preserve LSK markers despite continuous proliferation and in vitro culture, and are able to repopulate lethally irradiated mice. HPCLSK cells, if transduced with mutant STAT3, proliferate faster, have an enhanced replating potential, increased pY705 signaling and drive cells to myeloid/lymphoid differentiation. Taking advantage of this system, we will investigate the consequences of mutant STAT3 on survival upon transplantation of transformed HPCLSK cells and study the gene expression, chromatin accessibility and protein interactors compared to wild-type STAT3.

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P65

Chemotherapy free treatment in estrogen receptor positive, Her2neu receptor positive metastatic breast cancer – a case report using triple targeted therapy in the 7th line

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Background: In metastatic Her2 positive breast cancer, several Her2-directed therapies are available. Similarly, CDk4/6 inhibitors have become available for ER+ metastatic breast cancer. We report the case of a 71-year old woman with metastatic, Her2neu positive, ER+ breast cancer, who responded to double-targeted therapy in the 7th line of treatment.

Case report: In 2011, a 64-year-old woman was diagnosed with pT3, pN3a (19/30) ER+ PR+ HER2 negative invasive ductal breast cancer. She received surgery, radiation, adjuvant chemotherapy (AC/docetaxel) and anastrozole for 5 years. In 2016, ER+ PR- and HER2 positive liver metastases were diagnosed. From 6/2016 to 6/2019 she received six different therapeutic lines, including trastuzumab/pertuzumab, trastuzumab-emtansin and lapatinib plus different chemotherapies. In 6/2019, the disease was progressing again, and the patient, with an ECOG performance status of 2–3, was worn down by the side effects of multiple previous treatments. Looking for a chemotherapy-free option, we found neoadjuvant data on the triple-targeted combination of trastuzumab, pertuzumab, fulvestrant and palbociclib. Our patient received a combination of exemestane, palbociclib (100 mg per day), trastuzumab and pertuzumab starting in July 2019. Encouragingly, improvement of quality of life and clinical benefit were noted soon, which was reflected in a clear response in the recent CT scan of January 2020. Treatment is still ongoing.

Conclusions: The combination of several targeted therapies might work synergistically in late lines of triple positive breast cancer. In addition, patients might benefit from the reduced side effects of this chemotherapy-free treatment option with respect to their quality of life.

P66

Dysregulated glutamate metabolism mediates therapy resistance via collagen modification in non-small cell lung cancer (NSCLC)

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Background: The tumor-microenvironment (TME) represents an attractive therapeutic target in NSCLC and metabolic rewiring plays an important role in mediating therapy resistance. In this study we investigated how metabolic alterations, especially in the glutamate pathway, lead to tumor stromal collagen accumulation and mediates therapy resistance in NSCLC.

Methods: Publicly available datasets (GSE19804, GSE30219) of NSCLC patients were used to evaluate the prognostic impact of key enzymes of glutamate to collagen synthesis. A three-dimensional co-culture model of A549 and SV80 cell lines was developed and incubation experiments to inhibit this pathway with RASi were performed. To investigate the influence of renin-angiotensin-inhibitor (RASi) intake on the TME and response to therapy we evaluated a cohort of metastatic NSCLC patients ($n=444$) and performed immunohistochemichal characterization of the TME ($n=20$).

Results: Analysis of datasets revealed that all genes involved in the glutamate to collagen synthesis pathway are upregulated in NSCLC compared to normal lung tissue. High expression of these metabolic enzymes (PYCR1, PLOD2 and P4HA1) was associated with reduced survival. In the 3-D co-culture RASi led to a dose dependent degradation of three-dimensional spheroids. IHC of RASi treated NSCLC patients showed increased CD31 staining intensity, CD4+ infiltration and improved ORR and OS in NSCLC patients.

Conclusions: Our results delineate that the glutamate to collagen pathway is upregulated in NSCLC and is associated with poor survival. We hypothesize that activation of tumor stromal collagen deposition may represent an important TME-mediated therapy resistance mechanism. Therefore targeting glutamate-detoxifying pathways may represent a novel anti-cancer therapeutic strategy.

P67

Patterns of venous and arterial thromboembolism in patients with advanced pancreatic cancer treated with palliative first line chemotherapy of Gemcitabine/nab-Paclitaxel or FOLFIRINOX

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Background: This multicenter retrospective cohort study aims to investigate the incidence, risk factors and disease out-

come of VTE (venous thromboembolism) and ATE (arterial thromboembolism) in advanced pancreatic cancer (aPC).

Methods: We retrospectively enrolled 338 aPC patients treated with palliative 1st-line chemotherapy of Gemcitabine/nab-Paclitaxel or FOLIRINOX at three academic centers in Austria (Graz, Salzburg, Innsbruck). The primary outcome was a composite of symptomatic or incidental VTE (deep vein thrombosis and/or pulmonary embolism) and/or ATE (myocardial infarction, stroke or systemic arterial embolism). As one center has not yet finished recruitment, updated results will be presented at the conference.

Results: During a median follow up of 28.1 months [IQR: 25–31] we observed 62 VTE [cumulative risk: 20.3%] and 10 ATE-events [cumulative risk: 3.2%]. Occurrence of VTE was associated with an immediate increase in the risk of death (transition hazard ratio (THR) for VTE occurrence = 1.45, 95%CI: 1.05–2.00, $p = 0.025$), while the impact of ATE on mortality was numerically but not statistically significant with the number of ATE events observed (THR for ATE = 1.83, 95%CI: 0.86–3.89, $p = 0.117$). The strongest predictors for VTE and ATE were history of VTE [sub-distribution HR (sHR) 4.64, 95%CI: 2,83–7,59; $p < 0{,}001$] and history of stroke or transient ischemic attack [sHR 31.15, 95%CI 9.08–106.89; $p < 0.001$], respectively. The Khorana-, CONKO, and PROTECHT-score failed to identify patients at high risk of VTE.

Conclusions: Risk of VTE and ATE is highly elevated in aPC and has a negative impact on prognosis. Clinical factors were mostly found to be ineffective for prediction of VTE/ATE in this patient cohort.

P68

Pembrolizumab monotherapy as a salvage treatment in sarcoma patients

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Background: Sarcoma is a rare and heterogenous entity. We investigated the clinical efficacy of pembrolizumab (P) in pre-treated sarcoma patients.

Methods: Sarcoma patients with PD after standard treatment received P as salvage treatment. Tumor mutational burden (TMB) was analyzed using NGS and microsatellite instability (MSI) using fluorescent multiplex PCR.

Results: Since May 2016, 30 patients (median age 46 (19–86) years; 15 females, 15 males; 21 (70%) soft tissue sarcomas; 9 (30%) osteosarcomas) were treated with P. Median number of prior systemic therapies was 2 (0–9). Median number of P applications was 6 (1–39). 25/30 patients had measurable tumors at P start and could be included in the response assessment. 2/25 (8%) patients achieved CR and 6/25 (24%) PR, resulting in an ORR of 32%. 4/25 (16%) had SD as best response, resulting in a CBR of 40%. 5/30 patients showed no measurable tumors at P start due to prior metastasectomies. 3/5 (60%) of these patients presented with longer PFS under P therapy compared to the PFS of the previous treatment. Median PFS and OS calculated from P start in the total cohort was 4.9 (0.4–30.1) and 17.8 (0.8–41.7) months, respectively. Twelve (40%) patients are still alive and one is still on P therapy. TMB and MSI assessed in 22/30 (73%) patients did not show significant correlations with treatment response or disease control ($p > 0.05$).

Conclusions: P showed promising clinical efficacy in this real-life cohort of advanced sarcoma patients. Further biomarker research is needed to identify patients who might benefit from P.

P69

Sequential treatment for non-resectable pancreatic cancer. A retrospective single centre analysis

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Background: Most patients with pancreatic ductal adenocarcinoma (PDAC) are diagnosed with non-resectable disease. Over the last years, novel combination regimens have significantly prolonged survival and allow for sequential treatment strategies in patients with advanced PDAC. The aim of this study was to provide real-world data on sequential treatment for non-resectable PDAC.

Methods: We identified 169 patients with locally advanced ($n = 52$), metastatic ($n = 94$) or recurrent PDAC ($n = 25$) treated at our centre between 2013 and 2019. We analysed therapy sequence, duration of each treatment line and overall survival (OS).

Results: The median age of our patients was 69 years and median OS was 10.2 months. Overall, 95 patients (56%) were eligible for sequential therapy, whereby 48 patients (28%) received two and 47 (27%) patients received ≥3 lines of therapy. Mean duration of first-line therapy was similar in these two groups with 4.8 and 5 months, respectively. However, in patients receiving only two treatment lines, mean duration of 2nd-line treatment (2.7 months) and median OS (11.7 months) were much shorter compared to patients getting ≥3 lines of therapy (mean duration of 2nd line: 5 months; median OS: 21 months). Patients who were not fit for 2nd-line treatment had a very short median OS of 3.9 months (P-value for OS between groups: < 0.001).

Conclusions: In a real-world setting, more than half of all patients with PDAC are nowadays eligible for sequential therapy and >25% receive >2 treatment lines. Encouragingly, OS is longer in those receiving more lines of treatment.

P70

Clinical features associated with long- and short-term survivorship in lower-grade glioma patients

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Background: Lower-grade gliomas (LGG) are heterogeneous tumors in terms of prognosis.

Methods: Patients treated for WHO grade II-III glioma at the Medical University of Vienna between 2000 and 2018 were identified. Short-term survivors (STS) were defined by a survival time ≤12 months, long-term survivors (LTS) by a survival ≥10 years after diagnosis.

Results: Among 812 LGG patients, 39 (4.8%) STS and 74 (9.1%) LTS with WHO grade II—III glioma were identified. LTS presented more frequently with WHO grade II (48/74, 64.9%), while STS presented more frequently with WHO grade III (30/39, 76.9%; $p<0.001$). Median age at diagnosis was higher in STS than in LTS (61 vs. 35 years; $p<0.001$). Median Karnofsky Performance Scale was higher in LTS than in STS (90% vs. 80%; $p<0.001$). Motoric deficits as presenting symptom were more common in STS (11/39, 28.2%) than in LTS (6/74, 8.1%, $p=0.004$). Epileptic seizures were more frequent in LTS (53/74, 71.6%) as compared to STS (19/39, 48.7%; $p=0.016$). Isocitrate dehydrogenase 1/2 mutations were found more frequently in LTS (30/36; 83.3%) than in STS (3/21; 14.3%; $p<0.001$). 1p/19q codeletions were more common in LTS (12/20, 60.0%) as compared to STS (1/11, 9.1%, $p=0.008$). Further molecular analysis is currently conducted to characterize the molecular diversity between STS and LTS.

Conclusions: Long-term survival over 10 years as well as short-term survival of less than one year were observed in the present real-life LGG cohort. Molecular markers and symptomatic presentation are correlated with long- and short-term survivorship.

P71

First-line treatment of extensive stage small cell lung cancer (SCLC) with carboplatin, etoposide and atezolizumab – a multicenter real-world cohort from Western Austria

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Background: With the results from the Impower 133 study atezolizumab alongside carboplatin and etoposide has been established as a new first line treatment standard for extensive stage SCLC. We aimed to collect real-world data from patients treated with this combination in Western Austria.

Methods: Patients with extensive stage SCLC, who received first line immuno-chemotherapy with atezolizumab from 10 hospitals were included in the study. Primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), response rate (RR), toxicity. All parameters were assessed retrospectively.

Results: In this interim-analysis 30 patients were analysed. Median age at diagnosis was 65.6 years (range 36.8–79.2) and most patients presented with performance status ECOG 1 (40%). 23.3% of patients initially had CNS metastasis, of which only one patient had neurological symptoms. The mean number of chemotherapy cycles was 3.5 (range 1–6). We observed a median PFS of 4.7 months. PR/CR was achieved in 86.7% of patients. Median OS reached 6.7 months. Main site of progression was the primary tumour, 13.3% of patients had CNS progressive disease (10% had received prophylactic cranial irradiation). No immune related toxicities were reported.

Conclusions: In this real-world cohort platinum-based chemotherapy combined with atezolizumab led to similar outcomes regarding PFS, RR and toxicity as reported in the literature. The OS-analysis is limited by a relatively short follow up. We will report an updated analysis with additional patients and longer follow up at the meeting.

P72

Efficacy of checkpoint inhibitors for urothelial carcinoma in a real-world setting: a single-center experience

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Background: In the past 3 years, checkpoint inhibitors have become the standard of care in the first- and second- line setting of urothelial carcinoma (UC). However, real-life data, especially in elderly, frail patients are lacking.

Methods: We retrospectively analyzed patients with metastatic urothelial carcinoma treated at our center with PD1 and PDL1 inhibitors outside of clinical trials between November 2015 and December 2019. We assessed progression-free (PFS) and overall survival (OS). Data on PDL1 status and toxicity were collected as well.

Results: Of the 32 patients (22 male, 10 female) with a median age of 73 years, 20 (62.5%) were treated with the PD1 inhibitor pembrolizumab and 11(34.4%) with the PDL1 inhibitor atezolizumab. One patient (3.1%) received nivolumab, the third approved checkpoint inhibitor for UC.

The most common indication for immunotherapy was after platin failure in the second + line setting ($n=23$, 71.9%). In addition, 9 (28.1%) platin ineligible patients were treated in the first line setting. Reasons for platin ineligibility were mainly renal insufficiency and an ECOG status >2. Patients received a median of 4 cycles. Grade 3–4 immune-related toxicities were rare, but one patient developed fatal I-O associated encephalitis.

Conclusion: Efficacy data according to PD-L1 status will be presented at the conference.

Our report provides real-life data of immune checkpoint inhibitors for UC. Although the observed toxicities were mostly moderate, one patient deceased due to I-O associated encephalitis. This underlines the necessity to carefully collect real-life clinical data of checkpoint inhibitors.

P73

Systemic inflammation and activation of haemostasis predict response to chemotherapy and poor prognosis in patients with advanced lung cancer

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Background: Systemic inflammation and activation of haemostasis are frequently observed in patients with lung cancer. Both conditions have been related to tumour growth and metastatic potential. Inflammatory and haemostatic biomarkers might be useful for synergistic prediction of therapy response and prognosis of disease.

Methods: Patients with metastatic/irresectable lung cancer initiating 1st-line chemotherapy ($n=277$, 83% NSCLC) were followed within a prospective, longitudinal observational study (Vienna Cancer and Thrombosis Study, CATS). Candidate haemostatic biomarkers (D-dimer, F1 + 2, sP-selectin, Fibrinogen, FVIII, Thrombin generation potential), blood count parameters and inflammatory markers (Hb, Leucocytes, Neutrophil-Lymphocyte-Ratio (NLR), Platelet-Lymphocyte-Ratio (PLR), CRP) were measured prior to initiation of chemotherapy. The association with outcomes was assessed per double increase of biomarkers by means of Cox regression (Mortality, Progression-free-survival [PFS]) and logistic regression (overall-response-rate [ORR]).

Results: D-dimer (HR for death 1.58 [95%CI: 1.38–1.81], Hb (0.19 [0.09–0.41]), NLR (1.25 [1.07–1.46]), PLR (1.28 [1.08–1.53]) and CRP (1.47 [1.31–1.65]) most efficiently predicted overall survival and therapy response and have been incorporated within a prognostic model. Within this model, patients with none of the markers above the median (and below the median for Hb) had a 2-year overall survival (OS) rate of 55%, compared to a median OS of only 7.4 months in patients within the highest risk group (log-rank $p<0.001$). Similarly, median PFS was 9.5 months in patients with the lowest-risk features compared to only 3.5 months in those with the highest risk score (log-rank $p=0.009$).

Conclusions: Systemic inflammation and hypercoagulability are synergistically prognostic and predict response to chemotherapy in advanced lung cancer.

P74

The role of Ca15-3 in the follow-up care of early breast cancer patients

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Background: Routine assessment of the tumor marker CA15-3 in the follow-up of asymptomatic early breast cancer (EBC) patients remains controversial. The aim of this retrospective study was to assess the prognostic impact of a routine Ca 15–3 assessment in the follow-up care of early breast cancer patients.

Methods: Patients with EBC diagnosed between 2009 and 2018 and treated at our tertiary cancer center, with a follow-up time of at least 6 months, a structured follow-up including Ca15-3 assessment, and no other active malignancies were included in this analysis.

Results: Overall, 2261 patients were identified for this analysis. In 162 patients (7.2%) a distant recurrence was diagnosed, 55 out of them (33.4%) due to an asymptomatic Ca15-3 increase. Distant recurrence free survival (DRFS) was not significantly shorter in patients, in whom distant recurrence was diagnosed due to an asymptomatic Ca15-3 increase, compared to recurrences diagnosed by other reasons (HR 0.93; 95%CI 0.64–1.36; $P=0.714$). Additionally, overall survival (OS) was not shown to be significantly longer (HR 0.68; 95%CI 0.38–1.21; $P=0.187$). However, an increase of Ca15-3 above the upper limit of normal was associated with a significantly shorter DRFS (HR 0.20; 95%CI 0.14–0.27; $P<0.001$).

Conclusions: While Ca15-3 was not shown to hold an advantage in terms of survival, it might hold prognostic value in the follow-up care of early breast cancer.

P75

Changes in the time to neoadjuvant chemotherapy start over the past 10 years and correlation with outcome in early breast cancer patients

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Background: In early breast cancer (EBC) patients scheduled for neoadjuvant chemotherapy (NAC), time window of treatment initiation to gain maximal survival benefit is not yet established. The aim of this retrospective study was to determine, if time to initiation of NAC has changed during the last decade and if this change alter outcome.

Methods: Breast cancer patients diagnosed with EBC (primary tumors, contralateral, or locoregional recurrences) between 2009 and 2018 and who were treated with NAC at our tertiary cancer center where included in this study. Time to neoadjuvant chemotherapy (TTNC) was defined as the number of days between histological diagnosis to initiation of NAC, with delayed TTNC determined as ≥ 28 days.

Results: Overall, 518 EBC cases treated with NAC were identified. Median TTNC was 24 (range 1–115) days. In 65% of cases TTNC was < 28 days. Mean differences in TTNC got significantly longer between 2009 and 2018 (i. e. delta 8.5 days between 2009/2010 and 2017/2018; $P=0.009$). TTNC < 28 vs ≥ 28 days was not statistically associated with worse disease-free survival (DFS), nor overall survival (OS). In a subgroup analysis according to subtype, longer TTNC was not significantly associated with worse DFS or OS in triple-negative breast cancer, nor in any other subtype.

Conclusions: Even though the time to treatment initiation got significantly longer in the past ten years, it did not correlate with worse prognosis of early breast cancer. Hence, postponed therapy start in favor of extensive diagnostic and a personalized treatment plan is justifiable.

P76

Changes in the time to adjuvant chemotherapy start over the past 10 years and correlation with outcome in early breast cancer patients

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Background: In early breast cancer (EBC) patients scheduled for adjuvant chemotherapy (AC), time window to treatment initiation to gain maximal survival benefit is not yet established. The aim of this retrospective study was to determine, if time to initiation of AC has changed during the last decade and if this change alter the outcome.

Methods: Breast cancer patients diagnosed with EBC (primary tumors, contralateral, or locoregional recurrences) between 2009 and 2018 and who were treated with AC at our tertiary cancer center where included in this study. Time to adjuvant chemotherapy (TTAC) was defined as the number of days between surgery to initiation of AC.

Results: Overall, 491 breast cancer cases treated with AC were identified. Median TTAC was 32 days (range 13 to 146) in the overall period, 19 days in the 2009–2019 period, and 36 days in the 2017–2018 period. In 43.6% and 50.7% of cases TTAC was < 30 and between 31–60 days, respectively. Mean TTAC difference got significantly longer from 2009 to 2018. No statistically significant association with disease free survival (DFS), or overall survival (OS) could be should between TTAC groups ≤ 30, 31–60, 60–90, or even 91 or more days. In a subgroup analysis according to breast cancer subtype no significant difference between TTAC could be shown.

Conclusions: Even though the time to initiation of adjuvant chemotherapy got significantly longer in the past ten years, it did not correlate with worse prognosis of early breast cancer. Hence, postponed therapy start in favor of extensive diagnostic and a personalized treatment plan is justifiable.

P77

Overall survival of hormone receptor positive/ HER2 negative metastatic breast cancer patients in Austria: results from the AGMT_MBC Registry

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Background: Hormone receptor (HR) positive/HER2 negative breast cancers can be divided in two biologically different subtypes, luminal A and luminal B. In early breast cancer luminal A tumors are associated with a better prognosis. The prognostic impact of luminal subtypes in metastatic breast cancer (MBC) is less clear.

Methods: The Austrian Study Group for Medical Tumor Therapy (AGMT) MBC Registry is an ongoing multicenter registry for MBC patients in Austria. Unadjusted survival probabilities were calculated by the Kaplan-Meier method. Multivariate hazard ratios were estimated using a Cox's proportional hazards model. Patients with HR+/HER2- disease, available Ki-67 and sufficient outcome data were included in this analysis.

Results: At data cut-off on 31/01/2019, 1,253 patients were enrolled into the AGMT MBC Registry. In HR+/HER2- patients median OS was 38.5 months (95% CI 34.9–41.5, $n=687$). According to subtype, median OS was 40.6 months (95% CI 34.9–44.3) for luminal A like (HR+/HER2-, G1-2 and Ki-67 ≤ 20%; $n=390$), and 35.5 months (95% CI 32.3–40.2) for luminal B like (HR+/HER2-, G3 or Ki-67 > 20%; $n=297$) tumors (log-rank $P=0.2$). In multivariate analysis a disease-free survival ≥ 24 months or de novo MBC, age < 60 years at diagnosis of MBC, metastatic spread at diagnosis to less than three organ sites, and non-visceral disease at diagnosis were significantly associated with longer survival.

Conclusions: Luminal subtypes had no statistically significant survival impact in HR+/HER- MBC. Therefore, a different biological behavior of the luminal subtypes between early and metastatic breast cancer can be suspected.

Klinische Studien

K78

Proton radiotherapy for mediastinal Hodgkin lymphoma: theoretical background and clinical experience

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Background: Radiotherapy (RT) plays important role in the treatment of Hodgkin lymphoma (HL). However, the results are suboptimal for a significant group of patients. Use of the most safe radiotherapy technique is crucial. Proton therapy (PT) is a modern radiation technique based on use of particles. Compared to conventional radiotherapy, PT allows higher protection of healthy tissues. This is associated with lower risk of severe acute (radiation pneumonitis, dysphagia) and late toxicity (cardiovascular, secondary malignancies).

Methods: Between May 2013 and December 2019, 129 patients received mediastinal PT via pencil beam scanning (PBS) technique. Seventy-three patients with a minimum follow up of 2 years, were analyzed for acute toxicity and treatment response. Median follow-up was 44.5 months (23.4–79.7 months), median age at the time of PT was 32.2 years (18.5–79.2 years). Median dose applied was 30 GyE (20–40 GyE). PT for PET positive disease was performed in 13 pts. Deep inspiration breath hold technique was used in 57 patients, other patients were treated under free breathing condition after 4D-CT control.

Results: Seventy-one patients (97%) achieved complete remission, two patients progressed outside of irradiated field. Acute toxicity was mild, mostly dysphagia, radiodermatitis, transient xerostomia, dysgeusia. No case of symptomatic pneumonitis was observed. No patient required growth factor application or blood supplementation. To date, no case of Lhermitt's syndrome or late pulmonary toxicity was reported.

Conclusions: PT offers safe possibility for mediastinal RT. PT via PBS in deep inspiration breath hold is the most normal tissue sparing radiotherapy approach for mediastinal lymphoma.

K79

AGMT_AIHA_Registry: Autoimmune Hemolytic Anemia (AIHA) with corresponding Biobank

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Design: This registry is a prospective and retrospective, multicentre collection of data on patients with AIHA in Austria. All disease characteristics, medical histories and also treatment sequences are documented in anonymised form. Additionally patients will be asked to complete the FACIT-Fatigue questionnaire. For documentation in the registry no further diagnostic or therapeutic measures are required than those already necessary in general. Participation in the project must not interfere with treatment routines.

Data will be collected from all sites in Austria willing to participate. An estimated 100 patients are expected to be included; this number may be revised over time as interest and demand dictates.

Within this project biomaterial of patients with AIHA in Austria will be collected in the AGMT biobank. This collection of biomaterial is optional.

Primary objective: The aim of the AIHA registry is to collect data regarding the following objectives of disease for all Austrian AIHA patients older than 18 years.

- Epidemiological evaluations
- Assessment of AIHA subtypes in Austria
- Assessment of specific characteristics and frequency of AIHA
- Patient care and treatment in Austria
- Treatments used, sequence of treatments
- Efficacy and toxicity
- Establishment of a central biobank to provide a basis for future AIHA related research (optional)

K80

AGMT_aMYELOIDr: Austrian Myeloid Registry

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Design: The Austrian Myeloid Registry (forthwith referred to as aMYELOIDr) is a non-interventional study. It collects data from patients with the myeloid diseases like myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML), primary myelofibrosis (PMF), chronic myeloid leukemia (CML), and other rarer disease subtypes. The aMYELOIDr is multi-center database and collects data at various sites in Austria and potentially also at other centers in other countries in future. The registry has an electronic case report form (eCRF), where all data is entered by clinical trial personnel and/or physicians. The registry also consists of patients previously documented in the Austrian Registry of Hypomethylating Agents.

The registry is intended as a long-term project. The initial medium-term goal regarding patient numbers will be 3.000 documented patients. It is planned as a long-term registry, and hence no upper limit to patient numbers has been defined.

The goal of the Austrian Myeloid Registry is to build a disease-specific registry aimed at assessing the therapeutic landscape of patients with myeloid diseases. Our intention is to advance our knowledge on the natural course of these diseases in untreated or best supportive care (BSC) treated patients, as well as the efficacy and toxicity and sequence of use of various treatments in a routine clinical setting.

Primary objective: To assess the treatment patterns (therapeutic landscape) of patients with myeloid diseases.

K81

AGMT_BV-NIS: Austrian Brentuximab Vedotin observational study

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Design: This non-intervenional clinical study (NIS) is a prospective and retrospective, observational, multi-center research initiative.

Brentuximab vedotin has been shown to offer a high overall response rate, including durable complete responses in both of its indications. This signifies an important advancement in the treatment of adult patients with these rare CD30 positive hematological cancers who are relapsed or refractory and previously had limited options.

This Brentuximab vedotin NIS is set up to collect real-world experience in the management of patients with Hodgkin's disease and PTCL (sub-entity sALCL) (according to the WHO 2008 classification) in Austria. The aim is to gain valuable insights on both efficacy and toxicity of this drug in a routine clinical setting in patients with various comorbidities.

Indication: Patients with Hodgkin's disease and PTCL (sub-entity sALCL) who are willing to participate and receive or qualify for BV therapy.

Primary objective: The objective of this study is to evaluate the use, efficacy and toxicity of Brentuximab vedotin (BV) in Hodgkin's disease (HD) and systemic anaplastic large cell lymphoma sALCL according to WHO 2008 in Austria and to identify the duration of therapy in these indications.

Further objectives are the evaluation of Progression free and Overall Survival (PFS and OS).

Recruitment: 100 patients.

K82

AGMT_DISCOVER: Multicenter, randomized, double-blind, placebo-controlled, phase-III clinical-trial to investigate efficacy + safety of dronabinol in the Improvement of ChemOthErapy-induced and tumor-related symptoms in patients with locally-advanced or metastatic pancreatic-cancer during first-line-chemotherapy

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Design: This is a multicenter, randomized, double-blind, placebo-controlled clinical trial. Aim of this phase III trial is to investigate the efficacy and safety of dronabinol (orally administered tetrahydrocannabinol (THC)) as adjuvant therapy to first-line standard chemotherapy in patients with metastatic pancreas cancer for improvement of chemotherapy and tumor-related symptoms applicated by individual titration up to the maximum tolerated dose.

In detail, we want to study whether dronabinol has a positive influence on quality of life and whether symptoms caused by the tumor or by the chemotherapy itself might be palliated by dronabinol. We want to document beneficial and potential harmful side effects and document the personal perception of advanced pancreatic cancer patients.

Population: Adult patients (≥ 18 years) with diagnosis of locally advanced or metastatic pancreatic cancer, eligible for first-line chemotherapy.

Primary endpoint: The primary endpoint variable is the standardized area under the curve of the EORTC QLQ-C30 symptom summary score over the on-treatment period.

K83

AGMT_HMA in myeloid neoplasms: Registry on hypomethylating agents in myeloid neoplasms, including Myelodysplastic Syndrome (MDS), CMML and AML

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Design: The VIDAZA® Patient Registry is set up to collect real-world experience in the management of patients with MDS, CMML or elderly patients with AML ineligible for high dose chemotherapy, treated with VIDAZA® (azacitidine) in Austria. This registry will collect data in a retrospective as well as in a prospective manner at various sites in Austria. The aim is to gain valuable insights on both efficacy and toxicity of this drug in a routine clinical setting in patients with various comorbidities.

No pre-defined visits, medical tests, laboratory tests, procedures, or interventions are required. Physicians who have already treated patients with VIDAZA® or are planning to initiate VIDAZA® treatment can include patient data in this registry. To help maintain patient confidentiality, each patient will be assigned a unique patient identifying number upon enrollment.

Additionally from some patients with ALL, AMS or CMML, blood or tissue samples will be stored for further analyses. These samples will also be obtained from patients, who are not treated with Vidaza®, to comprise a control.

Recently, EMA granted DACOGEN® (decitabine) approval for the treatment of Acute Myeloid Leukemia, irrespective of bone marrow blast count. Patients treated with DACOGEN® have been already enrolled in this registry.

Inclusion: Begin with or already have received treatment with a hypomethylating agent.

Objectives: Number of cycles and dosage of VIDAZA® therapy, response evaluation, toxicities, severe adverse reactions, overall survival

K84

AGMT_LungCA_Reg: Lung Cancer Registry

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Design: This registry is designed as multicenter observational cohort of patients with lung cancer.

It will be set up to collect real-world experience in the management of patients with this disease. This registry will collect data at various sites in Austria. The aim is to gain valuable insights on both efficacy and toxicity, as well as the sequence of use of various treatments in a routine clinical setting.

Indication: The registry will be made available for all disciplines and physicians caring for cancer patients and will include patients ≥ 18 years with locally advanced or metastatic lung cancer (advanced or metastatic stage patients in Austria (Stage III A-C and IV A-B NSCLC, limited disease (LD) and extensive disease (ED) SCLC)).

Primary objective:

- To describe the general characteristics of advanced or metastatic stage patients in Austria and molecular testing in patients with advanced or metastatic lung cancer
- To describe and characterize subgroups
- To describe treatment and outcome of treatment
- To describe patient outcome by means of overall survival and progression free survival
- To describe toxicity with a focus on immune related adverse events

Recruitment: 500 patients (this number may be revised over time as interest and demand dictates).

K85

AGMT_MBC_Reg: Metastatic breast cancer in Austria

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Design: This registry is a prospective and retrospective, multicenter collection of data on patients with metastatic breast cancer in Austria. All tumor characteristics, medical histories and also treatment sequences are documented in anonymized form. For documentation in the registry, no further diagnostic or therapeutic measures are required than those already necessary in general. Participation in the registry must not interfere with treatment routines. A written consent must be obtained prior to the input of data. No informed consent is required from deceased patients.

Indication:

- Histological evidence of breast cancer
- Histological and/or radiological evidence of metastases
- Metastasis within 10 years of registry initiation

Primary objective: Epidemiological evaluations (general characteristics of metastatic stage patients in Austria, assessment of metastatic stage breast cancer subtypes in Austria, assessment of the specific characteristics and frequency of metastatic breast cancer, data on survival of female patients with metastatic breast cancer in Austria) and therapy-specific evaluations

Recruitment: 1500–3000 patients

K86

AGMT_MBC-10: Ixazomib (MLN9708) in combination with carboplatin in pretreated women with advanced triple negative breast cancer (CARIXA)

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Design: This is an open-label phase I/II study. Subjects meeting all inclusion criteria will be enrolled receiving ixazomib on day 1,8 and 15 in combination with carboplatin on day 1,8 and 15. Cycles will be repeated every four weeks and safety measurements and analysis will be performed at each visit.

Phase I: The phase I part of this study uses an alternate dose escalation accelerated titration design. In the accelerated dose-escalation phase a single-patient cohort per dose level will be enrolled, until one dose limiting toxicity (DLT) or 3 moderate toxicities are observed during cycle 1, or until dose level 4 is reached. At this dose level the cohort is expanded to three patients and dose escalation reverts to a conventional 3 + 3 escalation design.

Phase II: After establishing MTD in phase I, accrual continues to evaluate the efficacy and safety of the combination. A total of 41 patients including patients enrolled in the phase I part within the conventional dose escalation phase at the dose level considered as the MTD will be included.

Primary endpoint:

Phase I: Determination of maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs)

Phase II: Overall response rate (ORR)

Patients:

Phase I: 9 to 24 patients

Phase II: 41 patients (incl. patients phase I)

K87

AGMT_MM2: Randomized phase II, 2-armed-study in transplant-ineligible patients with newly diagnosed multiple-myeloma (NDMM) comparing Carfilzomib + Thalidomide+dexamethasone (KTd) versus Carfilzomib + Lenalidomide + dexamethasone (KRd) induction-therapy with respect to response-rates and investigating Carfilzomib(K)-monotherapy maintenance-strategy

Heinz Ludwig*[1]

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Design: This is a randomized, 2-arm phase-II, multi-center-study to evaluate the overall response rates in newly diagnosed, transplant ineligible patients receiving 9cycles induction therapy with either KTd or KRd followed by randomization to either Carfilzomib maintenance treatment for 12 months or to observation only. Maintenance is given for 12cycles or until progression of disease or intolerance, whatever occurs first.

Therapy regime: Arm A) KTd: K: 56 mg/m^2 weekly = day 1, 8, 15 of each cycle; (Note: C1D1 + 2 start with 20 mg/m^2 K, D8 + 9 & 15 + 16 of C1: 27 mg/m^2; C2D1, 2, 8, 9, 15 + 16: 27 mg/m^2); Thalidomide 100 mg/day, day 1–28; dexamethasone: 40 mg/week, day 1, 8, 15, 22 or

Arm B) KRd: K: 56 mg/m^2 weekly = day 1, 8, 15 of each cycle (Note: C1 and C2 see Arm A); Lenalidomide: 25 mg/day, day 1–21; Dexamethasone: 40 mg/week-day 1, 8, 15, 22 for a maximum of 9 cycles as induction therapy. Each cycle has 28 days.

Primary endpoint is to show non-inferiority with respect to response rates between KTd and KRd.

Patients: A total of 146 adult patients (≥ 18 years) with newly diagnosed symptomatic MM will be enrolled in this study. Excluded are patients who are planned for an autologous-stem-cell-transplantation following induction, who are intolerable to IMiDs or Carfilzomib, are NYHA-class >II, present with PS ≥2, CrCl ≤ 30 ml/min, and/or neuropathy grade ≥ 2.

K88

AGMT_MM3: Denosumab for high-risk SMM and slim-CRAB-positive, early myeloma patient – a randomized, placebo-controlled, phase-II-trial „DEFENCE“ (DEnosumab For the rEductioN of the smoldering myeloma transformatioN inCidence ratE)

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Design: This is a randomized, placebo controlled, multicenter study of denosumab in patients with high risk SMM (Smoldering Multiple Myeloma) and “ultra-high risk” SMM (=now defined as “SLIM” CRAB defined early MM without symptoms).

Eligible patients will be randomized 1:1 in each of the two groups (stratification according to high risk SMM and “ultra-high risk” SMM):

- Arm A: treatment with denosumab 120 mg SC every 4 weeks (Q4 W) for 6 months, then every 3 months (Q3M) for a total of 3 years or until progression to active, symptomatic MM.
- Arm B: treatment with placebo SC every 4 weeks (Q4 W) for 6 months, then every 3 months (Q3M) for a total of 3 years or until progression to active, symptomatic MM.

Primary objective: Time until transformation from high-risk SMM and early ’slim CRAB’ positive MM to CRAB positive multiple myeloma and/or developing serological progression (as defined by IMWG criteria for MM).

Patients: A total of 164 high risk and “ultra-high risk” Smoldering Multiple Myeloma will be included.

K89

AGMT_NGS_Registry: The use of genomic testing and the resulting medical decisions according to target identification

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Design: This registry is designed as multicenter non-interventional (observational) cohort of oncology patients who received or plan to receive comprehensive genomic testing anytime on or after January 1, 2016. Patient medical, testing and treatment information will be obtained through extraction of data from existing patient medical charts. Longitudinal follow-up data, including survival and tumor progression, will also be extracted from patient medical charts. This patient follow-up data will be obtained until patient death or loss to follow-up.

For documentation in the registry, no further diagnostic or therapeutic measures are required than those already necessary in general. Participation in the registry must not interfere with treatment routines. Only routine data, which has already been recorded in the patient’s medical chart, is transferred to the electronic Case Report Forms. To maintain patient confidentiality, each patient will be assigned a unique patient identifying number upon enrolment; this number will accompany the patient’s medical and other registry information throughout the lifetime of the registry.

The goal of this registry is to landscape the clinical practice of molecular profiling in Austrian cancer patients with focus on identification of methods used, evaluation when the tests are performed in the course of the disease, and definition of the impact of the test result on the subsequent treatment decision.

It is expected, that the main data-bulk will be obtained from approximately 15 sites.

Recruitment: approx. 1000 patients.

K90

AGMT_NHL-15B: Phase II single-arm „window-of-opportunity“ study of a combination of obinutuzumab (GA-101) and venetoclax (ABT-199) in relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

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Design: This is an uncontrolled, open-label, single arm phase II pilot study. Obinutuzumab will be given i. v. at a dose of 1000 mg on days 1, 8, 15 in cycle 1 and on day 1 of each following cycles. Venetoclax will be given at 800 mg daily p. o. One cycle is 21 days.

This combination treatment will be repeated for up to 3 cycles.

Eligible patients will then proceed to stem cell transplantation. A 9 cycles (27 weeks) maintenance phase with obinutuzumab and venetoclax will be given in patients ineligible for transplant.

Primary endpoint is to evaluate clinical activity and tolerability of a combination of obinutuzumab plus venetoclax in patients with relapsed/refractory DLBCL.

Patients: 21 patients (Phase II Fleming design). After a run-in phase of 6 patients a safety analysis and after 10 patients a futility analysis was performed.

K91

AGMT_PTCL-Reg: Austrian Registry and Biobank of Peripheral T-cell Lymphomas

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Design: This Registry is a prospective as well as retrospective, observational, multi-center research initiative. Data will be collected from all sites in Austria willing to participate. Data and material of patients, that are enrolled prospectively, will be

considered for inclusion into the international "T-cell project" (NCT01142674).

The clinical data should provide more accurate information on the epidemiology of this rare disease in Austria, supplemented by information on type of therapy and response. Correlation of the clinical course with clinical variables or parameters assessed in primary tumor tissue samples will provide a deepened understanding of PTCL biology, as well as identify potential prognostic and predictive factors.

The integration of imaging studies into this registry will allow retrospective, centralized, independent, blinded response evaluation in certain patient subgroups, thereby achieving a quality of data comparable to current randomized phase 3 clinical trials.

Given the low incidence of PTCL, only the establishment of a substantial biobank can lay the foundations for scientifically meaningful and internationally competitive translational research. The incorporation of a biobank into a well characterized clinical registry will build the heart of this project, with the ultimate goal to enable research for the benefit of PTCL patients in Austria and around the world.

Within the registry biomaterial should be collected in the AGMT biobank, managed by the Medical University of Vienna and the Salzburg Cancer Research Institute.

K92

AGMT-ALL Reg: Registry and Biobank for the collection of clinical data and biomaterial from adult ALL patients

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Design: In Austria approximately 70 patients are diagnosed with adult ALL per year and are treated in up to 17 institutes. Obviously there is a need to collect all data possible in order to harmonize diagnosis and treatment and to make optimal therapy available for every Austrian patient. Therefore information on these patients should be prospectively collected, analysed and used for the generation of treatment protocols by a specialized study group.

As a first step a registry with a standardized data set including diagnosis, therapy and outcome should be implemented.

In order to achieve a maximum of data harmonisation it is recommended that patients are treated according to a standardized international protocol endorsed by the EWALL.

The use of molecular diagnosis in disease monitoring, risk stratification and the use of target orientated therapies are increasingly important in patient management of ALL. These diagnosis tools are currently not implemented in Austria. For that reason there are many open questions in adult ALL and the new prospects leave clinicians with uncertainty about how to optimally manage adult patients with ALL. A centralized and standardized diagnosis program is needed to assure quality.

Objectives: Data collection regarding diagnosis, therapy and progression of disease for Austian ALL patients older than 18 years

Biobank: Within the ALL registry biomaterial should be collected at diagnosis and once a year for 5 years and at relapse.

K93

DSMM_XVII: Elotuzumab (E) in combination with carfilzomib, lenalidomide + dexamethasone (E-KRd) versus KRd prior to and following autologous stem cell transplant in newly diagnosed multiple myeloma and subsequent maintenance with elotuzumab + lenalidomide versus single-agent lenalidomide

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Design: This is an interventional, multicentre, open-label, randomized phase III trial with two parallel arms to compare two different regimens. Quadruple elotuzumab in combination with carfilzomib, lenalidomide, and dexamethasone [E-KRd] versus triple carfilzomib, lenalidomide, and dexamethasone [KRd]) is given during induction treatment prior to ASCT and as consolidation treatment after ASCT in patients suffering from newly diagnosed multiple myeloma according to the updated IMWG criteria. Consolidation treatment is followed by maintenance treatment (elotuzumab in combination with lenalidomide versus lenalidomide monotherapy).

Patients are randomized in a 1:1 ratio to be administered 6 cycles induction treatment, either E-KRd (Arm A) or KRd (Arm B).

Primary objective: To compare the rate of patients who have VGPR or better response according to IMWG criteria and are MRD negative as assessed by flow cytometry following two different induction regimens (quadruple [E-KRd] vs. triple [KRd]) in newly diagnosed multiple myeloma patients and to determine progression-free survival (PFS) following maintenance treatment.

Patients: 576 patients will be randomized into this phase III trial. It is planned that the study will be performed in up to 45 German trial centres and 10 Austrian trial centres.

K94

GHSG_AERN: Abscopal effect of radiotherapy and nivolumab in relapsed Hodgkin lymphoma after anti-PD1 therapy

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Design: The trial is a prospective, international, non-randomized, multicenter phase II investigator-sponsored trial for patients with relapsed or refractory cHL progressing while on treatment with an anti-PD1 antibody. A Simon's optimal two-stage design has been chosen with 9 patients to be evaluated for the primary endpoint in stage 1. If there are 1 or more stage-1-patients with an abscopal response to localized RT and 6 applications of nivolumab (ARR-6), 20 additional patients will

be recruited into the second stage of the trial for a total of 29 patients to be evaluated for ARR-6.

Primary endpoint: Abscopal response rate (ARR-6) with abscopal response centrally confirmed as restaging result after RT to a single lesion and at least four but not more than six nivolumab infusions (RE-6 result).

The primary objective of the trial is to show efficacy of the experimental treatment strategy. Secondary objectives are to further evaluate efficacy, show safety and feasibility and perform correlative studies.

Treatment: Nivolumab 240 mg i.v. at 2-weekly intervals combined with 20 Gy radiotherapy (RT) to a preferably progressive and not pre-irradiated single lesion. Nivolumab will be continued for a maximum of 18 months or until disease progression or unacceptable toxicity.

K95

GHSG_HD21: Treatment optimization trial in the first-line treatment of advanced stage Hodgkin lymphoma; comparison of 4–6 cycles of escalated BEACOPP with 4–6 cycles of BrECADD

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Design: In this prospective, multicenter, randomized and open-label trial, patients in the standard group are treated with 4–6 cycles of escalated BEACOPP. Patients in the experimental group receive 4–6 cycles of the BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, adriamycin, dacarbazine, dexamethasone) chemotherapy regimen. After a recent amendment based on the results of the HD 18 trial, the GHSG defines 4 cycles of escalated BEACOPP as new standard of care for PET-2 negative patients, whereas PET-2 positive patients receive 6 cycles of escalated BEACOPP. In both groups patients with PET positive residual tumor masses ≥ 2.5 cm are subjected to local irradiation with 30 Gy.

It is planned to enter 1500 patients into this trial during a recruitment period of approximately 4 years. About 250 centers in Germany, Austria and other countries will participate in the trial.

Primary objective of the trial is to demonstrate non-inferior efficacy of six cycles of BrECADD compared to six cycles of escalated BEACOPP, each followed by radiotherapy to PET-positive residual lesions ≥2.5 cm, in terms of progression free survival (efficacy objective).

Primary endpoint is progression-free suvival.

K96

ImbruVeRCHOP: Ibrutinib (Imbruvica®), Bortezomib (Velcade®) s. c., Rituximab, CHOP for the treatment of elderly patients (age 61–80 years) with CD20+ diffuse-large B-cell lymphoma, IPI ≥ 2

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Design: This trial is designated as a single arm multi-center prospective open phase I/II trial with a safety run-in phase, i. e. the phase I part of the trial, which is followed by the phase II part of the trial to evaluate the efficacy of Ibrutinib and Bortezomib s. c. in the treatment of higher-risk elderly DLBCL patients of different molecular subtypes and to correlate outcome with clinical, molecular and imaging-guided response parameters.

Population: Target group of the study are patients with untreated CD20-positive DLBCL-like aggressive Non-Hodgkin's lymphoma, 61–80 years of age with unfavorable risk profile (IPI ≥ 2). The number of patients planned to be included is 60.

Primary objective: The main objective of this clinical trial is to assess the efficacy of the treatment determined as the 2-year PFS for patients with DLBCL.

Primary endpoint: Primary endpoint is the 2-year progression-free survival (PFS) for all patients.

K97

LYSARC_ORACLE: Randomized phase-3-study evaluating the efficacy and the safety of oral azacitidine(CC-486) compared to investigator's choice-therapy in patient with relapsed or refractory angioimmunoblastic T-cell lymphoma

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Design: This study evaluates the efficacy of Oral azacitidine versus single-agent Investigator's Choice Therapy in patients with Relapsed or Refractory Angioimmunoblastic T-cell Lymphoma.

Compared to B-cell Non-Hodgin Lymphoma (NHL), Angioimmunoblastic T-cell Lymphoma (AITL) is more resistant to conventional chemotherapy and is generally associated with an inferior outcome. In case of relapsed of refractory disease, survival durations are in the range of only a few months.

Several agents have been evaluated in this setting in recent years: romidepsin, bendamustine or belinostat. The response rate with these agents rarely exceeds 30% and responses are usually of limited duration.

Azacitidine is a nucleoside metabolic inhibitor indicated for the treatment of patients with various myelodysplastic syndrome (MDS) subtypes. In this case, azacitidine significantly increase the survival time compared to standard of care option. This response to azacitidine could be correlated to the existence of recurrent mutations and those mutations have also been described in AITL.

The present protocol will use Azacitidine according to the same schedule than in MDS that is continuous treatment until progression or unacceptable toxicity.

Population: Patients aged at least 18 years old with relapsed or refractory Angioimmunoblastic T cell lymphoma (AITL) or other subtypes of T-follicular helper (TFH) derived lymphoma histologically proven, with TFH phenotype as per the latest WHO classification, Ann Arbor clinical stage I to IV and a performance status from 0 to 3 will be enrolled to the trial.

Primary endpoint: Progression free survival (PFS) using local assessment of progressive disease according to Lugano Response Criteria (2014).

K98

DSHNHL_NIVEAU: Improvement of outcome in elderly patients or patients not eligible for high dose chemotherapy with aggressive Non-Hodgkin lymphoma in first relapse or progression by adding nivolumab to gemcitabine, oxaliplatin + rituximab in case of CD20+-disease

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Design: This trial is designed as an international, multicentre, randomised, open-label, treatment optimisation study, preceded by safety run-in phases conducted for B-cell and T-cell lymphoma separately. Aim of the phase-III trial is to test whether prognosis of patients with relapsed or refractory aggressive Non-Hodgkin Lymphoma not eligible for neither autologous nor allogeneic stem cell transplantation can be improved by combining nivolumab with (R)-GemOx.

Population: All patients with first relapse or progression of an aggressive Non-Hodgkin's lymphoma aged older than 65 years or older than 18 years with HCT-CI score > 2 are eligible for this study irrespective of their gender or stage of disease. There is no upper limit of age. Also patients not eligible for neither autologous nor allogeneic stem cell transplantation are eligible for this study.

Primary objective: Improvement of 1-yr PFS by nivolumab plus (R)-GemOx followed by nivolumab consolidation instead of (R)-GemOx alone.

Primary endpoint is 1-yrs progression-free survival.

K99

SAKK 41/14 ACTIVE-2: Physical activity program in patients with metastatic colorectal cancer who receive palliative first-line chemotherapy. A multicenter open label randomized controlled trial

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Design: This is a multicenter randomized open label trial.

Patient with histologically or cytologically confirmed colorectal carcinoma (CRC) required to start palliative first-line systemic therapy for inoperable or metastatic disease.

All patients will undergo standard systemic therapy for metastatic colorectal cancer. Patients in the care-as-usual group are not actively encouraged to change their physical activity level e. g. to start a fitness program during chemotherapy.

The physical exercise ACTIVE-program describes a 12-week exercise program consisting of a combination of a bi-weekly aerobic exercise (cycle ergometer) supervised by a physical therapist and a self-paced increase in physical activity during daily life using a pedometer with a daily step goal as a motivational tool. The program will be individually tailored to each patient based on the training protocol and is aimed at increasing physical activity levels and cardiorespiratory fitness.

Primary objective: To assess whether a structured physical activity program (PA) during palliative chemotherapy improves progression-free survival (PFS) and/or patient-reported outcomes (ESAS-r) in patients with metastatic colorectal cancer.

Primary Endpoint: The co-primary endpoints are PFS and patient-reported symptoms as measured by the ESAS-r (Edmonton Symptom Assessment System revised).

K100

Molecular-biological tumor profiling for drug treatment selection in patients with advanced and refractory carcinoma: a prospective phase II trial

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Background: Here we present the results of the ICT (individualized-cancer-treatment) trial investigating the efficacy of targeted cancer treatment based on molecular-biological-profiling in advanced and refractory cancer patients. To the best of our knowledge this is the first prospective phase II trial using circulating tumor DNA (ctDNA) based molecular profiling (MP) for individualized cancer treatment assignment.

Methods: Molecular profiles obtained by a mandatory blood draw for ctDNA analysis and an optional tissue biopsy were reviewed by a molecular tumor board in order to identify and match a MP-based treatment. The primary endpoint was the progression-free survival (PFS) ratio of the MP-based treatment compared to PFS of the last evidence-based drug treatment within the same patient.

Results: Due to slow patient accrual this study had to be prematurely closed after inclusion of 24 patients. Overall, a potential tumor specific drug based on MP could be matched in eleven out of 24 patients (46%). Eight patients (33%) received treatment according to MP results, of which none experienced a PFS ratio ≥ 1.2 compared to the PFS of the last evidence-based treatment line. Median PFS in the MP-based treatment group

was 61 days (IQR 49.8–71) compared to 78 days (IQR 61.5–144) of the last evidence-based treatment resulting in a median PFS ratio of 0.7 (IQR 0.6–0.9).

Conclusions: This trial although limited by the premature study termination does not support the routine use of ctDNA based molecular-biological-profiling for treatment selection in advanced cancer patients outside clinical trials.

Young Investigator Presentations

Y101

A pan-retinoic acid receptor antagonist reduces leukemic stemness and prolongs survival in an EVI1-positive mouse model of AML

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Background: Overexpression of ecotropic virus integration site 1 (EVI1) is associated with poor outcome of acute myeloid leukemia (AML). EVI1-related tumor suppressive effects of all-trans retinoic acid (atRA) have been reported in experimental model systems reflecting bulk leukemic cells, but do not correspond to clinical trial results. We therefore aimed to investigate the interactions between EVI1 and retinoids in leukemic stem cells (LSCs), the drivers of leukemogenesis, therapy resistance, and relapse.

Methods: The effects of EVI1 and retinoids on key properties of AML LSCs was investigated in an MLL-AF9-driven mouse model of AML and in human AML cell lines and primary samples. The impact of pan-RAR antagonist monotherapy on survival of mice with MLL-AF9-driven AML was determined.

Results: Evi1 promoted the abundance, quiescence, and activity of murine AML LSCs. atRA further augmented, and a pan-RAR antagonist counteracted, these effects in an Evi1-dependent manner. EVI1 also strongly enhanced atRA-regulated gene transcription in LSC enriched cells. In vivo treatment with pan-RAR antagonist delayed leukemogenesis and reduced stemness in Evi1-high AML. Results were confirmed in human myeloid cell lines retaining some LSC characteristics as well as in primary human AML samples.

Conclusions: We report for the first time the importance of EVI1 for key properties of AML LSCs. Furthermore, atRA enhanced, and a pan-RAR antagonist counteracted, the effects of EVI1 on AML stemness, raising the intriguing possibility of treating EVI1-high AML with RAR antagonists.

Y102

Deciphering transcriptional programs and dependencies evoked by EVI1/MECOM in acute myeloid leukemia

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Background: Chromosomal rearrangements involving EVI1/MECOM are associated with a two-year survival of <10% and represent the most adverse genetic event in acute myeloid leukemia (AML). As established treatment regiments commonly fail in these patients, there is an urgent need for rational therapeutic concepts that will require a better understanding of molecular and cellular functions of the EVI1 oncogene in AML.

Methods: We have developed a panel of murine and human models of EVI1-driven AML that recapitulate common phenotypic and transcriptional features of human EVI1-rearranged AML, enable conditional expression of EVI1 itself, as well as the RNAi- and CRISPR/Cas9-based genetic exploration of EVI1-associated candidate targets.

Results: We have characterized transcriptional programs evoked by EVI1 in cell culture models and in vivo, and systematically identified genetic dependencies through comparative CRISPR/Cas9-based screens. By integrating orthogonal data from transcriptome profiling, we identify factors that are both, aberrantly expressed and specifically required in EVI1-driven AML. Among these, we identify the deregulation of ERG, an ETS-related transcription factor that is overexpressed in subgroups of patients suffering from AML and T-ALL, as a selective dependency in EVI1-driven AML. Suppression of ERG in human and murine models triggers potent and selective anti-leukemic effects and terminal differentiation in EVI1-driven AML.

Conclusions: We find that a major oncogenic function of EVI1 is to drive aberrant expression of ERG and thereby maintain leukemia cells in an immature state. Interfering with this regulatory axis may provide new entry points for rational therapies that are urgently needed for this group of AML patients.

Y103

In situ proliferation of recipient tissue-resident T cells contributes to graft-versus-host disease after allogeneic hematopoietic stem cell transplantation

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Background: Graft-versus-host disease (GVHD) remains a major cause of mortality after allogeneic hematopoietic stem cell transplantation (HSCT). We have recently shown that a subset of skin-resident memory T cells (TRM) may survive myeloablative conditioning treatment preceding HSCT and coexists with donor T cells in healthy skin after HSCT.

Methods: To determine factors mediating long-term survival and pathogenic potential of TRM, we performed T cell receptor sequencing and TRM quantification of longitudinal skin and blood samples of patients undergoing HSCT. We furthermore assessed T cell proliferation and T cell origin (donor/host) by fluorescence-in-situ-hybridization in GVHD lesions.

Results: While peripheral blood T cell clonotypes were replaced by donor T cell clones upon HSCT, we found populations of top skin T cell clones to expand after transplantation. Interestingly, early expansion of TRM from baseline levels (>200%) was paralleled by development of acute GVHD of the skin after HSCT. Stable TRM numbers from baseline were found in patients without symptoms of cutaneous GVHD. Notably, acute and chronic GVHD skin lesions contained proliferating host-derived TRM that clustered with donor-derived cells in the upper dermis.

Conclusions: Our results point towards a new understanding of local tissue destruction through both host- and donor-derived TRM, challenging the paradigm of a one-directional graft-versus-host immunoreaction.

Y104

Ferroportin expression on erythrocytes – Implications to ineffective erythroid output in anemia of chronic disease

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Background: Iron uptake by developing red blood cells (RBC) is essential for sufficient hemoglobin production. As such, erythroblasts and mature RBC not only incorporate iron but can also effectively export iron via ferroportin.

Hepcidin, a hepatocyte-derived peptide, regulates ferroportin surface levels causing the internalization and degradation of this exporter. In anemia of chronic disease (ACD), hepcidin is constantly induced due to long-lasting inflammation. We herein investigate the effect of high hepcidin levels and its consequences on the erythroid compartment.

Methods: Chronic kidney disease (CKD) was induced in C57BL/6 mice via an adenine-diet. Bone marrows were harvested and further work-up performed using Western blot analysis and flow cytometry (FC). Mechanistic experiments were performed in iron-overloaded animals.

Results: In CKD mice, alongside microcytic anemia, reduced transferrin-saturation, increased hepcidin levels and splenic tissue iron overload, we found a ~38% increase in bone marrow tissue iron content associated with massively reduced ferroportin protein levels. Moreover, the individual iron-dependent erythroblast precursor populations (i. e. basophilic, polychromatic, orthochromatic erythroblasts and reticulocytes) showed higher levels of intracellular iron as measured by Calcein fluorescence via FC. Indeed, these higher erythroid intracellular iron pools correlated with higher levels of mitochondrial stress and lipid peroxidation (determined by FC using MitoSOX and Bodipy581/591).

Conclusions: Our data indicate that iron is a critical regulator of stress during erythroid development and can be regulated via the hepcidin-ferroportin axis in ACD. Moreover we herein present a novel mechanism contributing to ineffective erythroid output in ACD.

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t(8;21) leukemia hijacks T-cell antisense promoter

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The blood system serves as key model for cell differentiation and cancer formation. Its development is regulated by transcription factor PU.1. During myeloid differentiation PU.1 level increases to avoid leukemia; in contrast, for T-cell differentiation the activated gene locus of PU.1 needs to shut off completely. Here we demonstrate that PU.1 closing is a dynamic process involving an alternative promoter that is induced by RUNX transcription factors for noncoding antisense transcription. With our experiments including precision nuclear run-on sequencing for active polymerase mapping (PRO-seq) and the assay for transposase-accessible chromatin sequencing (ATAC-seq), we here demonstrated that RUNX1-ETO, the core binding factor leukemia (CBF) fusion in t(8;21) acute myeloid leukemia (AML), activates PU.1 antisense promoter thus shifting the antisense/sense transcription ratio and blocking myeloid differentiation. We found that elevated antisense/sense ratios represent a hallmark of CBF-AML patients compared to normal karyotype AML or healthy CD34+ cells. Using chromatin conformation capture at the genome-wide scale (hi-C) and at the PU.1 locus (3C), we showed competitive binding of PU.1 enhancer element to the proximal or the antisense promoter which forms two binary chromosome architectures states functioning as on/off switch during either myeloid or T-cell development. RUNX1-ETO utilizes this physiologic mechanism and induces a T-cell like state of increased antisense and blocked sense transcription. We conclude, that sense/antisense promoter pairs and their associated higher order chromatin states represent crucial functional switches that can be perturbed by leukemic oncogenes. As novel basic disease mechanism they exemplify a potential Achilles heel for precise therapeutic targeting.

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A comprehensive picture of antisense transcription across tissue and cancer types based on public data mining

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Background: Although antisense transcription is incredibly widespread, it has not been extensively studied to date. An antisense transcript refers to a long non-coding RNA, which is at least partially complementary to a corresponding, mostly protein-coding transcript and can exhibit diverse functional roles in gene regulation. Here, we investigated the transcriptional patterns of such transcripts, which are fundamental to comprehensively study molecular pathology and tissue/cancer-specific expression.

Methods: By exploiting the current wealth of transcriptomics data provided in public repositories, strand-specific RNA-seq data of healthy controls and cancer samples was selected and curated, comprising almost 2800 samples. A pipeline was implemented to analyze the data in a high-throughput manner including (i) pre-processing, (ii) alignment to the human genome with HISAT2, (iii) stringent quality control, (iv) assembly of novel antisense transcripts using StringTie and FEELnc, (v) generating the expression matrix with featureCounts, (vi) batch correction using ComBat as well as (vii) statistical analyses in R and visualizations.

Results: Using publicly available data, a comprehensive picture of antisense transcription across 28 normal tissues and 10 cancer types was constructed. The analysis revealed the expression of a large number of antisense transcripts–including many novel transcripts. Furthermore, numerous antisense transcripts show tissue-specific expression, potentially regulating their sense partner in a tissue-specific fashion. Interestingly, also antisense transcripts with cancer-specific expression could be identified.

Conclusion: Here, antisense transcription was investigated in a large-scale study, which can not only provide new insights into gene regulation but may also lead to novel marker and/or target candidates for clinical applications.