

memo

magazine of european medical oncology

Official Journal of the Central European Cooperative Oncology Group (CECOG)
and Austrian Society for Haematology and Medical Oncology (OeGHO)

16. Jahrgang 2023 · Supplement 1

memo (2023) 16 :S1–S28

<https://doi.org/10.1007/s12254-023-00875-4>

Online publiziert: 10 March 2023

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Nature 2023

OeGHO

Österreichische Gesellschaft für
Hämatologie & Medizinische Onkologie

Abstracts

Proceedings of the Annual Meeting of the Austrian Society of Haematology and Medical Oncology

Frühjahrstagung 2023

der Österreichischen Gesellschaft für Hämatologie und Medizinische Onkologie
und der AHOP – Arbeitsgemeinschaft hämatologischer und onkologischer
Pflegepersonen in Österreich

Innsbruck, 30. März – 1. April 2023

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Poster Hämatologie

H01

Pancytopenia with transient increase of bone marrow blasts in a patient with COVID-19

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Introduction: Pancytopenia due to bone marrow (bm) suppression by viral infections is recurrently seen. Regarding Covid-19, recently a transient increase in myeloblasts has been reported.

Case: We report on a 55-year-old man that was admitted because of fever and oral-mucosal bleeding. He was diagnosed with Covid-19 pneumonia. Because of Morbus Ormond, therapy with methotrexate (MTX, 20 mg/week) was ongoing. At admission, pancytopenia (hemoglobin, 11.9 g/dL; leucocytes, 0.31 G/L; platelets, 5 G/L; reticulocytes, 7.5 G/L; MCV, 89.6fl), elevated CRP (30 mg/dL) and creatinine (3,27 mg/dL, known chronic kidney disease) were found, MTX serum levels were below the detection limit. Due to the severity of pancytopenia, a bm-puncture was done and revealed a slightly hypocellular bm with multilineage dysplasia and 15% myeloblasts. No mutations were found by next generation sequencing and the karyotype was normal (46,XY [20]). A treatment related myelodysplastic syndrome (MDS) with excess of blasts was discussed. Immediately after admission, treatment with MTX was stopped. After four days a spontaneous increase of leucocytes was observed, platelets (290 G/L) and hemoglobin (11.0 g/dL) recovered within two weeks. A second bm-puncture revealed a normo-cellular bm without signs of dysplasia. Myeloblasts were within the normal range (1%). Serum erythropoietin was within the normal range (8.0 mIU/mL). After discharge hemoglobin improved further (15.4 g/dL after 4 months), and a third bm-biopsy again showed a normo-cellular bm without dysplasia and <1% myeloblasts.

Conclusion: Transient increase of blasts mimicking MDS or acute leukemia should be considered as a differential diagnosis in COVID-19 patients with pancytopenia.

H02

Immune regulation in secondary hemophagocytic lymphohistiocytosis

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Introduction: Secondary hemophagocytic lymphohistiocytosis (sHLH) is a rare and life-threatening hyperinflammatory syndrome induced by excessive cytokine production, for which dysregulated cytotoxic NK- and CD8⁺ T-cells are hypothesized to be the main elicitors. However, the underlying mechanism why the breach of the immunological activation threshold occurs and immune checkpoints fail to limit sHLH disease development, are still unclear.

Methods: Thus, for an in-depth description of the immune status we determined the composition, activation and regulatory state of all major leukocyte populations in blood by seven multi-color flow cytometry panels including 10 sHLH patients and 35 healthy controls.

Patients were diagnosed according to the HLH-2004 criteria. Underlying diseases comprised malignancy ($n=4$), rheumatologic ($n=2$), infectious ($n=1$) and idiopathic conditions ($n=3$).

Results: Absolute numbers of all major leukocyte populations except neutrophils are decreased. Cytotoxic CD8⁺ T-cells display increased CD57 while maintaining mediocre CD69 levels and thus presenting a rather senescent than activated state. In line with current literature, NK-cells display an exhausted phenotype upregulating inhibitory NKG2A and KIR2DL receptors. Further, we identify a yet undescribed strong upregulation of CD57 and CD69 as well as perforin expression in CD4⁺ T-cells, introducing highly energized CD4⁺ T-cells as potential drivers of sHLH development.

Conclusion: In summary, our data show a profound alteration of the immune landscape and reveal yet unrecognized novel immune cellular contributors in sHLH disease. In order to better understand the induction mechanisms and subsequently improve sHLH disease treatment, we plan on further investigation using tissue-microarrays and single-cell RNA sequencing.

H03

Direct Effects of Ponatinib on Vascular Endothelial Cells: a Potential Explanation for Development of Vascular Adverse Events in Patients with CML

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Introduction and aims: BCR::ABL1-targeting ponatinib is used for treatment of multi-TKI resistant chronic myeloid leukemia (CML). However, increased cardiovascular events have been described in ponatinib-treated patients. To explain ponatinib-induced vascular events, we evaluated ponatinib effects using *in vitro*, *ex vivo* and *in vivo* models.

Methods and Results: In chemical proteomics, ponatinib bound several proteins relevant for angiogenesis, including TEK, PDGFRB and EPHB4 in the human microvascular endothelial cell line HMEC-1. In a phospho-receptor tyrosine kinase assay, ponatinib inhibited the activation of VEGF2 receptor, MER proto-oncogene, and insulin receptors in human coronary artery endothelial cells (HCAEC). Moreover, ponatinib induced apoptosis in HCAEC in a caspase-3/7 assay (relative apoptosis: 2.13 ± 0.42 , 100 nM) and inhibited the proliferation of HMEC-1 and human umbilical vein endothelial cells (HUVEC) in a thymidine-uptake assay (IC_{50} : 100–250 nM). In HUVEC, ponatinib (1 μ M) also increased adhesion to a plastic-surface (ponatinib: 85% adherent cells; DMSO-control: 10%). In a HUVEC network-formation assay, ponatinib demonstrated the strongest inhibitory effects compared to other TKI. In C57BL/6 mice, ponatinib (5 mg/kg/day, 35 days) inhibited blood flow recovery after femoral artery ligation (ratio of ischemic- vs. non-ischemic limb: 0.67 ± 0.07 control-group vs. 0.56 ± 0.1 ponatinib-group). As examined by wire myography in aortic rings from C57BL/6 mice, ponatinib (100 nM) enhanced norepinephrine-induced vasoconstriction (pEC_{50} : 7.76 ± 0.06 M ponatinib-free vs. 7.96 ± 0.05 M ponatinib-incubated) and attenuated acetylcholine-mediated vasodilatation (pIC_{50} : 7.45 ± 0.05 M ponatinib-free vs. 7.06 ± 0.1 M ponatinib-incubated).

Conclusion: Ponatinib is a potent inhibitor of multiple endothelial cell functions, which may contribute to the occurrence of vascular events in ponatinib-treated patients.

H04

Virus-induced senescence exerts a pro-coagulatory effect on human blood – a translational pilot study.

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Introduction and aims: The cellular status of senescence is associated with secretion of pro-coagulatory factors, as we confirmed by multiplex bead-based protein analysis of the supernatant (SN) of senescent cells.¹ Clinical conditions with premature senescence, like viral infections or hematologic malignancies, are associated with increased risk of thrombosis. The aim of our pilot study was to investigate the effect of senescence on hemostasis in a translational approach.

Material and Methods: In this monocentric pilot study we evaluated the influence of the elevated pro-coagulatory factors detected in SN of virus-induced senescent cells on clotting of human blood using modified rotational thromboelastometry assays. INTEM and EXTEM assays were performed using whole blood of adult healthy donors younger than 50 years. Inclusion criteria were normal platelet counts and absence of coagulation disorders. The assays were carried out spiking each blood sample with 15, 25 and 35 μ l SN of senescent cells. Simultaneously these assays were run with spiking of each blood sample with SN of non-senescent cells.

Results: Clotting times were significantly shorter in INTEM and EXTEM assays when whole blood was spiked with SN of senescent cells compared to spiking with SN of non-senescent cells.

Conclusion: Our data indicate a pro-coagulatory effect of the SN of senescent cells on human blood, as suspected based on the prior molecular findings. Further studies are planned to investigate the role of senescence in coagulopathies of patients with hematologic malignancies.

H05

Characterization of AML Patients with Recurrent Relapse who Achieved Repeated Complete Remission after Multiple Re-Induction and Consolidation Therapies

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Without transplantation, survival of patients (pts) with relapsed acute myeloid leukemia (AML) is poor. However, some pts may benefit from re-induction chemotherapy and enter a second or third complete remission (CR).

We identified 24 pts with *de-novo* AML who showed prolonged survival despite multiple relapses (multiCR). For com-

parison, matched pts with long-term leukemia-free survival (LT-LFS, $n=48$) or refractory disease (RD, $n=48$) were analyzed.

In pts with multiCR the median continuous CR (CCR) was 2.3 years (95% confidence-interval, CI: 1.5–3.1 years). The median duration of the second and third CCR were 1.2 (95% CI: 0.9–1.4) years and 0.8 (95% CI: 0.4–1.2) years, respectively and thus significantly shorter compared to the first CCR ($p<0.001$). Of all multiCR pts, 21% achieved a 4th CR and 12.5% a 5th CR. Significant differences in CCR were found between multiCR (median CCR: 2.3 years) and LT-LFS (median CCR: not reached; $p<0.001$). Median overall survival (OS) of multiCR pts was 6.3 (95% CI: 5.2–7.3) years and thus significantly shorter than OS in LT-LFS pts (15.5 years, 95% CI: 11.2–17.8 years) and RD pts (0.4 years, 95% CI: 0.3–0.5 years; $p<0.001$). The multiCR cohort differed markedly from the other groups regarding mutations in *BCORL1*, *BCOR*, *FLT3-ITD* and *IDH2*. Notably, in contrast to LT-LFS and RD pts, no multiCR patient had a *RUNX1* or *TET2* mutation.

Together, a small group of AML pts benefits from repeated re-inductions. In these pts a high prevalence of mutations in *BCORL1*, *BCOR*, *FLT3-ITD* and *IDH2*, but no mutations in *RUNX1* or *TET2* were found.

H06

Outcome of Adult Patients with Acute Lymphoblastic Leukemia Treated in Graz Between 2001 to 2021.

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Introduction and Aim: Acute lymphoblastic leukemia (ALL) is a rare disease in adults and patients' prognosis is still unsatisfying. The aim of this study is to evaluate whether the outcome of adult ALL patients treated in Graz from 2001 to 2021 has changed over time.

Material and Methods: Medical records of 95 patients (≥ 18 years; B-/T-ALL/LBL) were reviewed and statistically analyzed regarding overall survival (OS) and disease-free survival (DFS).

Results: Patients' median age at diagnosis was 40 (18–85) years and the median follow-up time 91.2 months (95% CI: 64.3–118.2). Seventy-one patients (75.8%) had B-ALL (43.7% *BCR::ABL* positive), 23 patients (24.2%) T-ALL/LBL. Thirty-five patients (36.8%) were classified as high-risk according to GMALL 08/2013 criteria. Ninety-three patients started induction treatment, two were treated palliatively and 42 received a transplant in first complete remission (CR1). The median OS of all patients was 30.8 months (95% CI: 18.4–72.9), with 1-, 3-, and 5-year OS rates of 75.5%, 46.6% and 41.3%, respectively. There was no OS difference between patients treated from 2001–2010 versus 2011–2021 ($p=0.680$). The median DFS of patients in CR1 was 16.4 months (95% CI: 10.4–29.7), with 1-, 3- and 5-year DFS rates of 57.6%, 34.8% and 31.9%. Age >30 years ($p=0.024$) and GMALL 08/2013 high-risk group ($p=0.028$) were significant adverse risk factors for worse OS in multivariate analysis.

Conclusion: These real-world outcome data are consistent with published reports from national cancer registries that continue to indicate a significant need for improvement in treatment of adult patients with ALL.

H07

An optimized comprehensive approach for detection of residual disease in acute myeloid leukemia

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Introduction: Acute myeloid leukemia (AML) is associated with poor prognosis due to high relapse rates caused by trace amounts of chemoresistant leukemic cells persisting in complete remission. Detection of these cells as measurable residual disease (MRD) is of prognostic relevance and important for improving disease outcomes. Since no uniform MRD detection method is available for all AML patients, novel approaches are clearly needed.

Material and Methods: We recently developed a two-step method of MRD detection consisting of flowcytometry-based leukemic cell enrichment using antibodies against surface markers highly expressed in AML followed by mutational analysis of recurrently mutated genes using next generation sequencing. We have now optimized this approach by using a combinatorial antibody panel against the surface markers CD117, CD123, CD312, CLL1 and TIM3 for leukemic cell enrichment.

Results: Results show a 70-fold enrichment of cells on average in $>95\%$ of AML patients with sufficient amounts of DNA for subsequent sequencing. Serial dilution experiments revealed a sensitivity of 10^{-3} to 10^{-5} meaning the unequivocal identification of one AML cell in up to 100.000 normal cells. Type (insertion/deletion versus substitution) and number of mutations in the diagnostic sample affected MRD sensitivity.

Conclusion: Based on these promising results we will run a prospective trial comparing this newly established approach to conventional MRD detection methods such as qPCR and flowcytometry. Our method is hypothesized to be non-inferior to conventional techniques in terms of sensitivity and specificity to predict relapse, but to allow a uniform approach in the vast majority of AML patients.

H08

Attrition rates in multiple myeloma treatment under real world conditions – an analysis from the Austrian myeloma registry (AMR)

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Multiple Myeloma (MM) is characterised by serial relapses, necessitating sequential lines of therapy (LoTs). Reports on attrition rates (ARs) across all lines of therapy (LoTs) vary widely in MM. The present study aimed at deriving for the first time ARs from the large Austrian Myeloma Registry.

ARs were defined as being either deceased, progressive without having received another LoT, or a lack of followed-up for ≥ 5 years.

571 MM patients diagnosed between January 2009 and August 2021 were included (median age: 72 yrs; follow-up: 50.8 mos). 507 patients received one LoT, with 43.6% undergoing stem cell transplantation (SCT). 26.5% of these patients received VRd as an induction, followed by maintenance in 55.7%. Transplant-ineligible patients were predominantly treated with Vd (21.6%) and VRd (16%), followed by maintenance in 27.1%. 37.5% of patients received a second LoT. ARs across one to five LoTs (16.7–27%) were low upon the achievement of a deep remission during frontline therapy ($p < 0.001$), and high in the elderly ($p = 0.002$). Frontline induction/SCT followed by maintenance reduced ARs associated with age. The presence of high-risk-cytogenetics (21.7%) affected follow-up (32.2mos vs 53.8mos; $p < 0.001$) and TTNT (3.1mos vs 4.2mos; $p = 0.033$), respectively.

In summary, our results demonstrate considerably lower ARs for MM patients within the Austrian versus other health care systems¹. Young age and deep remissions after frontline therapy resulted in particularly low ARs. The promising low attrition in our database additionally support a key role for the ease of drug access and reimbursement policies in governing long-term MM patient outcome.

H09

DNA methylation profiling allows to refine the prognostic classification of acute myeloid leukemia patients treated with intensive chemotherapy

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Introduction: Multiple studies described DNA methylation as frequently altered in acute myeloid leukemia (AML), yet its prognostic relevance remains unclear. We introduce DNA Methylation-based Risk Assessment (“DMRA”), a prognostic classifier on AML outcome after intensive cytarabine-based chemotherapy, trained and validated on 538 AML samples, comparing it to the ELN-2017 classification.

Methods: Patients were enrolled by the AMLCG study group ($n = 377$, training and cross-validation) or collected within BeatAML ($n = 161$, independent validation), DNA methylation profiles were generated using Illumina MethylationEPIC arrays. The DMRA classifier was trained on most variable CpG-sites genome wide, weighted upon their relevance to overall survival (OS) using ridge regression, resulting in three prognostic subgroups (“low”, “medium”, “high” risk).

Results: Overall, DMRA revealed more distinct risk groups with 3-year OS of 64%/39%/15% ($p=2e-08$ DMRA:low/DMRA:medium, $p=1e-05$ DMRA:medium/DMRA:high) as compared to ELN (64%/44%/31%, $p=4e-05$ ELN-favorable/ELN-intermediate, $p=0.02$ ELN-intermediate/ELN-adverse). Importantly, almost every second patient ($n=240/538, 45\%$) was assigned to a different risk group using DMRA. Within each ELN group, DMRA precisely defined subgroups with significant OS differences: (1) in ELN-favorable AML, $n=44/203$ (22%) were classified with increased risk (DMRA:medium, 3-year OS 70% vs. 44%, $p=0.003$); (2) in ELN-intermediate AML, $n=44/135$ (33%) were classified with reduced risk (DMRA:low, 3-year OS 58% vs. 38%, $p=0.03$); (3) in ELN-adverse AML, $n=142/200$ (71%) were classified with reduced risk ($n=27$ DMRA:low, $n=115$ DMRA:medium, 3-year OS 37% vs. 13%, $p=0.0002$). Multivariate testing confirmed DMRA risk groups as independent prognostic factors over (cyto-)genetically defined ELN subgroups.

Conclusion: In conclusion, DMRA allows to refine current standards in risk stratification and may thus serve as promising complement in prognostic classification of AML.

H10

Impact of additional chromosomal aberrations in multiple myeloma with t(11;14). Focus on gain or amplification 1q21

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Introduction: t(11;14) is one of the recurrent chromosomal translocations in multiple myeloma (MM), occurring in approximately 15% of patients. Gain or amplification of chromosome arm 1q21 (1q21+) is thought to occur as a secondary event and has been associated with worse prognosis. In this exploratory analysis we aimed to assess the frequency of 1q21+ in MM patients with t(11;14) and its impact on outcome.

Methods: We retrospectively identified 83 patients diagnosed with MM and t(11;14) with or without 1q21+ at our institution. We analysed overall survival (OS) and time to next treatment or death (TNT-D) stratified by treatment with or without autologous stem cell transplantation (ASCT).

Results: 1q21+ was detected in 14 of 61 (23%) MM patients with t(11;14) at primary diagnosis. Relapse samples were available in 30 of these patients, and presence of 1q21+ seen in 16 (53.3%). The frequency of 1q21+ was significantly increased later in disease ($p=0.005$). Presence of 1q21+ at primary diagnosis was associated with shorter TNT-D (37.2 vs. 43.0 months, $p=0.027$) and OS (51.2 months vs. not reached; $p=0.007$) for patients receiving ASCT. No significant differences in OS (51 vs. 44.3 months; $p=0.63$) and TNT-D (10.5 vs. 14.7 months; $p=0.75$) were observed in patients managed without ASCT.

Conclusion: 1q21+ is present in a significant fraction of t(11;14) MM patients already at diagnosis. Presence of 1q21+ is even more frequent later in disease. 1q21+ is an adverse prognostic factor in patients with t(11;14) receiving ASCT.

H11

Response to Interferon in early/prefibrotic primary myelofibrosis – retrospective single center study

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Introduction and Aim: Interferon is used in myeloproliferative diseases since decades due to its efficacy and potential disease modifying effect (Bewersdorf et al., Leukemia 2021). Prefibrotic myelofibrosis (prePMF) is recognized by the WHO only since 2008. Therefore, data on the efficacy of interferon in prePMF is scarce. We conducted a retrospective single center study to investigate hematological and molecular response rates and determine factors that influence response to interferon in a cohort of WHO classified prePMF patients.

Patients and Methods: For inclusion diagnosis according to WHO and a JAK2V617F or CALR mutation were requested. Clinical and molecular responses were calculated after 6 and 12 months. Pre-post-comparisons were performed by the paired t-test or the exact Wilcoxon test. The influence of several covariables on hematological and molecular response parameters was investigated by multiple linear regression analyses.

Results: 29 patients with a median time on interferon of 35.9 months were included. The study revealed a marked response in all laboratory and molecular outcome variables. Regarding molecular response after 6/12 months, 21%/40% and 10%/16% of patients showed a >25%/>50% reduction of the allele burden, respectively. Multivariate analysis did not reveal any substantial influence of the investigated variables including the type of driver mutation on hematological and molecular response.

Conclusion: Our study demonstrated a prompt hematological response in the majority of patients and a marked molecular response in up to 40% of patients irrespective of the type of underlying driver mutation. The results require confirmation in larger and prospective studies.

H12

Optimizing side effects management in patients with relapsed/refractory Multiple Myeloma (RRMM) using a Belantamab-Mafodotin (BM) specific weekly ePRO monitoring tool

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Introduction and aims: The existing web-based myeloma patient portal and ePRO (PRO: all reports by patients about their health status or treatment) monitoring system SymOn (SymOn: “Symptom monitoring online”) will be used to control for major BM related side effects, especially ocular toxicities, to monitor the need of individual interventions in case of relevant side effects. We hypothesize that SymOn (developed by ESD: [www.ches.pro] using CHES) can lower the need for high intensity on site controls (especially ophthalmologic visits) without threatening treatment outcomes.

Material and Methods: BM is a newly registered treatment with major treatment-limiting side effects such as blurred vision, diminished visual acuity and keratopathy. Patients report bi-weekly about their health status via SymOn using the validated ODSI questionnaire. In cases of ocular events the OncoNurse (which screens the outcomes) will contact the treating physician to initiate clinical action.

Besides OSDI, the following PRO measures will be used: EORTC QLQ-C30, EORTC QLQ-MY20 and a newly developed item list (from the EORTC item library) to measure side effects during BM Treatment.

Results: The project will be a proof-of-concept study showing that ePRO monitoring of BM-related side effects is possible, can reduce the amount of ophthalmologic site visits necessary, and will maintain high patient safety.

Conclusion: The goal of the study is the creation and feasibility testing of a BM-focused program as an extension of the ePRO monitoring system (used by the AMR: Austrian Myeloma Registry [www.myeloma.at]) to optimize side effects management in patients with RRMM.

H13

Tissue Factor Pathway Inhibitor is associated with risk of venous thromboembolism and all-cause mortality in patients with cancer

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Venous thromboembolism (VTE) is a common complication in patients with cancer. Tissue factor pathway inhibitor (TFPI) is a natural anticoagulant inhibiting complexes of tissue factor and factor VIIa/factor Xa. Conflicting results about its association with VTE risk in the general population and higher TFPI levels in cancer patients were reported. We investigated TFPI levels and their association with VTE risk and all-cause mortality in cancer patients.

Total TFPI antigen levels at study inclusion (Imunbind total TFPI ELISA kit, American Diagnostica Inc.) were measured in patients included in the Vienna Cancer and Thrombosis Study, a prospective observational cohort study with the primary out-

come VTE. Competing risk analysis and Cox regression analysis were performed.

TFPI was analyzed in 898 patients (median age 62 years, interquartile range [IQR]:53–68; 407 (45%) female). Sixty-seven patients were diagnosed with VTE and 387 patients died (24-month cumulative risk: 7.5%; 42.1%). Patients had median TFPI levels of 56.4 ng/mL (IQR: 45–70) and those with metastatic disease had higher levels (60 vs. 50.4 ng/mL, $p < 0.001$). In multi-variable analysis adjusting for age, sex, cancer type and stage, TFPI levels were associated with VTE risk (SHR per doubling: 2.01, 95%CI: 1.25–3.24; 12-month cumulative incidence $>75^{\text{th}}$ vs. $\leq 75^{\text{th}}$ percentile: 9.7 vs. 5.8, $p = 0.04$). Further, TFPI was associated with all-cause mortality (adjusted HR per doubling: 1.86, 95%CI: 1.47–2.35; 12-month cumulative incidence $>75^{\text{th}}$ vs. $\leq 75^{\text{th}}$ percentile: 47.2 vs 21.7, $p < 0.001$).

TFPI levels are independently associated with VTE risk and all-cause mortality in cancer patients and could be a biomarker for the prediction of VTE risk and mortality.

H14

T-PLL clotting immunohistochemistry for rapid TCL-1 diagnostic

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Introduction and aims: T prolymphocytic leukemia (T-PLL) is a rare, clinically aggressive clonal proliferation of prolymphocytes harboring a characteristic juxtaposition of the TCL1A or the MTCPI gene to a promoter sequence of the T-cell receptor gene locus. Detection of aberrant intracellular T-cell leukemia/lymphoma protein 1 (TCL1) expression is a key diagnostic criteria for T-PLL (Staber et al. Blood 2019) mostly requiring a bone marrow biopsy and immunohistochemistry, since intracellular TCL1 detection using flow cytometry of peripheral blood T-PLL cells is technically very challenging and not established in most diagnostic laboratories. This study aimed to assess if confirmed diagnosis for T-PLL is possible on peripheral blood with an easy to perform method on clotted blood with the use of immunohistochemistry.

Material und Methods: In two independent institutes in Clermont Ferrand, France, and Vienna, Austria, blood was sampled from patients with known diagnosis of T-PLL using a dry syringe and left vertical at room temperature for 30 minutes. The formed clot was transferred into a formalin based fixator and embedded in formalin. Immunohistochemistry was performed using antibodies directed against CD2, CD3, CD7, CD20, betaF1 and TCL1.

Results: Histology showed coagulated blood with diffusely scattered, small to medium sized, monomorphic lymphocytes. The T-PLL cells were easily identifiable by immunohistochemistry, showing positive staining for CD2, CD3, CD7, betaF1 and TCL1. The B cells were positive for CD20.

Conclusion: Immunohistochemistry in clotted blood of T-PLL offers a quick and easy way to diagnose TCL1 positive cases of T-PLL, referring to 95% of T-PLL cases.

H15**Functional precision medicine of T-cell prolymphocytic leukemia (T-PLL) subclones****Tea Pemovska^{1,2}, Alexander Pichler¹, Philipp Staber^{1,2}**¹Department of Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Wien, Österreich²Comprehensive Cancer Center Vienna, Medical University of Vienna and Vienna General Hospital, Wien, Österreich

Introduction & Aim: T-cell prolymphocytic leukemia (T-PLL) is a rare and aggressive mature T-lymphoid malignancy. T-PLL patients have a short survival time of approximately 12 months and are typically not responsive to alkylating agents or CHOP polychemotherapy. The only therapy that has been effective in a significant proportion of patients, albeit with short duration and considerable side effects, is the humanized CD52-antibody alemtuzumab. However, all patients eventually relapse with drastically limited treatment options. We here hypothesize that preexisting T-PLL subclones mediate treatment resistance and relapse.

Material and Methods: We performed single-cell RNA sequencing on 12 T-PLL patient samples from 6 different patients throughout the disease course to generate in-depth genetic characterization. Cell lineage and cell-cluster-specific markers were then used to measure responsiveness to clinical cancer drugs with a high-throughput flow cytometer.

Results: The single-cell dataset consisted of 62926 cancer and tumor microenvironment cells. Independent clustering of the transcriptional signature provided comprehensive knowledge of the T-PLL clonal composition and evolution as well as gene signatures that correlate with disease progression and response to therapy. Each cell cluster was annotated as T cells (~91%), B cells (1%), natural killer cells (~3%), monocytes (4%), and erythrocytes (1%) by using established marker genes. The malignant T-cells could be grouped in 3 different clusters, each with distinct gene expression and specific drug response signatures suggesting an effective combination rationale.

Conclusion: This study provides a novel basis for a rulebook for effective drug combinations to target all T-PLL subclones.

H16**Imatinib-induced sustained and complete long-term remission in therapy-resistant anaplastic large cell lymphoma****Alexander Pichler¹, Christoph Kornauth², Ines Garcés-de-los-Fayos-Alonso³, Lukas Kazianka¹, Arne Zibat⁴, Halima Alachram⁴, Tea Pemovska¹, Gerwin Heller⁵, Lukas Kenner³, Ulrich Jäger¹, Philipp Staber¹, Richard Greil⁶**¹Department of Medicine I, Medical University of Vienna, Division of Hematology & Hemostaseology, Vienna, Österreich²Department of Pathology, Medical University of Vienna, Vienna, Österreich³Clinical Institute of Pathology, Medical University of Vienna, Vienna, Österreich⁴Institute of Human Genetics, Georg August University of Göttingen, Göttingen, Deutschland⁵Department of Medicine I, Medical University of Vienna, Clinical Division of Oncology, Vienna, Österreich⁶SALK University Hospital Salzburg, Department of internal Medicine III, Salzburg, Österreich

Background: We have previously shown that platelet derived growth factor receptor (PDGFR) is expressed in nucleophosmin-anaplastic lymphoma kinase (NPM-ALK) -induced anaplastic large cell lymphomas (ALCL ALK+). We have also demonstrated that PDGFR blockade by the Abl/c-Kit/PDGFR kinase inhibitor imatinib is an effective treatment strategy for ALCL ALK+ in experimental mouse models. A young indicator patient whose ALCL cells expressed PDGFR and who failed three treatment lines (including ASCT) was successfully treated with imatinib.

Methods: We report imatinib treatment of 6 relapsed/refractory (r/r) ALK positive ALCL patients four of which were treated in a prospective clinical trial (EudraCT No.: 2013-003505-26). Additionally, we characterized these patients on genetic, epigenetic and immunological level.

Results: We observed that 4 out of 6 patients achieved a CR. At a median follow up of more than 5 years, all responding patients had an ongoing CR (range 3–8yrs). Lymphoma cells of the two non-responding patients did not express PDGFR. Cytoplasmic co-expression of both ALK and PDGFR in tumor cells of CR patients is a clear predictor for imatinib response in ALCL. We identified differentially methylated genes relevant to the PDGFR-axis between responders and non-responders and revealed enrichment for regulation of specific protein kinase activities. Moreover, non-responders showed significant upregulation of cytokines IL-5, IL-15, CXCL12, VEGFa, TNFa in comparison to responders in line with the methylation signatures.

Conclusion: We conclude that the assessment of PDGFR expression in ALCL tumour cells may have life-saving clinical implications for the treatment of patients with therapy-resistant ALK positive ALCL.

H17**High concordance of targeted next-generation sequencing from bone marrow and peripheral blood samples in patients with myelodysplastic neoplasms****Lorin Loacker¹, Verena Petzer², Sebastian Bachmann¹, Dominik Wolf², Reinhard Stauder²**¹University Hospital of Innsbruck, Central Institute for Medical and Chemical Laboratory Diagnosis, Innsbruck, Österreich²Medical University of Innsbruck, Department of Internal Medicine V (Haematology and Oncology), Innsbruck, Österreich

Introduction: Molecular monitoring forms the basis for clinical care in patients with myelodysplastic neoplasms (MDS). Whereas analysis of bone marrow (BM) samples actually represents the standard, peripheral blood (PB) may represent an alternative. We thus compared the concordance of mutation profiles based on next-generation sequencing (NGS) between these two sources.

Methods: BM and PB samples from 31 patients with confirmed MDS were analyzed in parallel. NGS was performed from total leukocytes using a targeted NGS myeloid 30-genes hotspot panel. Statistical analysis of variant allele frequencies (VAF) included descriptive statistics, correlation analysis and

calculation of sensitivity. The study was approved by the local Ethic Committee, all patients provided informed consent.

Results: NGS of all investigated samples revealed a total of 226 mutations (110 in BM and 116 in PB) in 14 affected genes. Based on both analyses at least one mutation was detected in 100% of patients, 84% had ≥ 2 mutations. There was a high correlation of VAF between BM and PB (Pearson correlation $r=0.91$, $p<0.01$), whereas VAF was significantly higher in BM (median 22.2% versus 10.3% in PB; $p=0.01$). Sensitivity based on the 2% threshold was 93.7% (BM) and 96.4% (PB).

Conclusion: MDS patients display a substantial mutational burden with a high degree of accordance of mutation profiles between BM and PB. Overall VAF were significantly higher in BM, whereas mutation counts did not significantly differ. Thus, NGS from PB might be a valuable and easily available diagnostic option for risk assessment and frequent monitoring in patients with MDS.

H18

Feasibility of self-reported electronic patient reported outcome measures (ePROMs) in patients with myelodysplastic neoplasms in daily clinical practice

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Introduction: This pilot study focuses on the feasibility of health-related quality of life (HRQoL) scoring in patients with Myelodysplastic Neoplasms (MDS).

Methods: 34 consecutive MDS-patients from our outpatient clinic were screened from June 2021 until November 2022. EORTC QLQ-C30, EORTC QLQ-FA12, EuroQol-5D-5L and G8 in German language were completed by patients using the computer-based Health Evaluation System (CHES). This study was approved by the local Ethic Committee and all patients provided informed consent.

Results: 17 patients (seven female and ten male) were finally enrolled in the study. Median age was 71 years (range 39 to 84 years). ECOG performance status was 0, 1 and 2 in nine, four and four patients, respectively. The exclusion of patients was to be attributed to personal reasons (47%), limited technical skills (29%), cognitive impairments (12%) and not being native in the German language (12%).

Six patients (35%) out of the cohort ($n=17$) were able to complete the questionnaire remotely, from whom four needed a reminder. Six patients (35%) were supported by given access to the questionnaires at our department and five (29%) needed a study nurse reading them the questions aloud and additionally filling out the questions according to patients' responses.

Conclusion: We were able to illustrate the successful integration of ePROMs in a relevant proportion of MDS-patients in daily clinical practice. To ensure a higher completion rate, it is important to provide different language versions and to improve

the accessibility particularly by providing audio-guided input assistance and a more elderly-friendly interface.

H19

Adverse impact of a high CD4/CD8 ratio in the allograft may be overcome by methotrexate- but not mycophenolate- or posttransplant cyclophosphamide-based graft versus host disease prophylaxis

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Introduction: Cellular graft composition may impact major outcomes of allogeneic hematopoietic stem cell transplantation (HSCT). A high CD4/CD8 T cell ratio in allografts was observed to predict graft-versus-host disease (GVHD) and non-relapse mortality (NRM).

Methods: This retrospective monocentric study included all consecutive HSCT performed with bone marrow (BM) or G-CSF mobilized peripheral blood stemcells (PBSC) between January 2000 and June 2021 ($n=641$). The impact of the graft CD4/CD8 ratio was analyzed in three cohorts defined by GVHD-prophylaxis: cyclosporin A/methotrexate (CSA/MTX; $n=195$), CSA/mycophenolate mofetil (CSA/MMF; $n=307$), and posttransplant cyclophosphamide (PTCy)/tacrolimus/MMF (PTCy/Tac/MMF; $n=139$).

Results: In the entire cohort, grafts with a high CD4/CD8 ratio (>2.38) had a significantly decreased overall survival in the multivariate analysis (Hazard ratio [HR] 1.43; $P=0.005$). Likewise, in the CSA/MMF subgroup, a high CD4/CD8 ratio was associated with decreased overall survival (HR 1.47; $P=0.02$), but not so in the CSA/MTX subgroup (HR 1.10; $P=0.71$), and in the PTCy/Tac/MMF subgroup (HR 1.72; $P=0.09$). Further, a high CD4/CD8 ratio was associated with a significantly higher risk of acuteGVHD-associated mortality in the overall cohort (sub-Hazard ratio [sHR] 1.83; $P=0.003$) and in the CSA/MMF subgroup (sHR 2.24; $P=0.002$). In the CSA/MTX and the PTCy/Tac/MMF subgroups, the CD4/CD8 ratio was not significantly associated with acute GVHD-associated mortality (sHR 1.62; $P=0.18$; and sHR 1.91; $P=0.25$).

Conclusion: A high CD4/CD8 ratio in the allograft may have an adverse impact on overall and GVHD-associated mortality, particularly in HSCT applying CSA/MMF as GVHD-prophylaxis. PTCy- or particularly MTX based prophylaxis may partly overcome the adverse impact of a high CD4/CD8 ratio.

H20

Delineating CDK9- regulated molecular events for the development of rationally derived multiple myeloma treatment strategies

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Despite advances in multiple myeloma (MM) therapy over the last 2 decades, most patients relapse and the novel targets are urgently needed. Aberrant expression of various cyclin-dependent kinases (CDKs) in MM results in the loss of proliferative control. CDK9, a subunit of pTEFb, is a regulator of numerous oncogenes and suggested as a therapeutic target in MM. This study proposes rationally derived anti-CDK9 treatments to improve MM patient outcome. The impact of CDK9 on downstreams was outlined in 2D/3D MM models. CDK9-regulated effects were determined by flow cytometry, and western blot, and survival analyses. A significant induction of CDK9 was determined in MM patients compared to normal cells. Loss-of-function screens in MM cell verified their dependency on CDK9. CDK9 silencing by siRNA decreased Mcl-1, cMyc, Mdm2, RNA Pol II, and tumor cell survival. Similarly, selective CDK9 degradation by Thal-sns-032 reduced CDK9, Mcl-1, cMyc, RNA Pol II, and Mdm2, and increased p53. CDK9 degradation inhibited the survival both in tumor cells and co-cultures. Notably, shCDK9 knockdown also showed a reduction in CDK9, Mcl-1, Mdm2 without affecting the Bcl-2. Combination of Thal-sns-032 with venetoclax and selinexor induced synergistic anti-MM effects. Moreover, selinexor and Thal-sns-032 enhanced the nuclear reduction of Mcl-1, CDK9, XPO1 compared to the treatment alone. Our study presents the delineating CDK9-regulated mechanism has a significant antitumor activity against MM and provides a combinational targetability of critical oncogenic proteins such as Bcl-2, Mcl-1 and XPO1. Taken together, the data strongly support the therapeutic role of CDK9 to improve MM patient outcomes.

H21

Clinicopathological characteristics of extranodal marginal zone lymphoma of the mucosa associated lymphoid tissue (MALT-lymphoma) of the intestine: A single center analysis

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Introduction: Extranodal marginal zone lymphoma of the mucosa associated lymphoid tissue (MALT-lymphoma) is most commonly diagnosed in the stomach (30–35%), but exceedingly rare in the intestinal tract (2%) and data on this subgroup are scarce.

Methods: Out of 484 patients with MALT lymphoma treated at our institution (1999–2020), 42 patients (9%) had intestinal involvement (24 primary, 18 secondary) who were retrospectively analyzed.

Results: Median age at diagnosis was 67 years (interquartile range (IQR) 53–72) and follow up time was 47 months (IQR 32–102). Symptoms at diagnosis were more common in primary vs secondary intestinal MALT lymphomas (52% vs 20%). Intestinal organs involved included the colon ($n=19$), duodenum ($n=11$), small intestine ($n=8$) and rectum ($n=5$). Treatment data were available in 41/42 patients. Eleven patients (27%) received local therapy (10 surgery, one radiotherapy; response rate 91%), 16 (39%) systemic treatment (ORR 87%) and 9 (22%) antibiotic treatment only (ORR 38%). In 4/41 patients watchful waiting was the initial treatment. Eighteen patients progressed during follow up; median progression free survival for first line therapy and overall survival were 50 and 301 months, respectively. No statistically significant difference in PFS or OS could be detected between primary intestinal and secondary intestinal MALT lymphomas. In addition, no significant differences could be found when compared to a cohort of 144 patients with gastric MALT-lymphoma from our registry.

Conclusion: Overall, patients with intestinal MALT-lymphoma seem to have a good prognosis which appears comparable to gastric MALT lymphoma.

H22

Peripheral T-Cell-Lymphoma (NOS) – long-term disease control with a dasatinib based therapy in relapse after high-dose chemotherapy and ASCT

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Peripheral T-Cell-Lymphomas, not otherwise specified (PTCL-NOS) are a heterogeneous group of non-Hodgkin-lymphomas accounting for approximately 35% of all T-Cell-Lymphomas in Europe. Standard first-line treatment consists of anthracycline-containing regimens (CHOP/CHOEP) and consolidation with autologous stem-cell transplantation (ASCT) and high-dose chemotherapy (HD-CHT) in patients with a satisfactory response. Durable remissions are uncommon even in patients with good response. Recurrence in patients with PTCL goes with a dismal prognosis and bad overall survival (mOS in relapsed PTCL-NOS <6 m).

We present a case of a 64-year-old female with PTCL-NOS. At initial diagnosis she presented with clinical stadium IVA (disseminated lymph node and lumbar vertebral body involvement), with an intermediate-low IPI and a good performance status (ECOG 0).

First line treatment consisted of 1 cycle CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) followed by 5 cycles CHOEP (Etoposide+CHOP). Before going to ASCT and HD-CHT, relapse was diagnosed with a subsequent line of ther-

apy with brentuximab-vedotin. Again, complete remission (CR) was diagnosed by PET-scan and the patient was able to proceed to HD-CHT and consolidation with brentuximab-vedotin. Two years after ASCT, another relapse is diagnosed. With next generation functional drug screening (ngFDS) through the EXALT-trial, another line of therapy with dasatinib, bendamustin and brentuximab-vedotin was established which led into continued therapy over 18 months with dasatinib as monotherapy, last given 40 months ago.

More than eight years after initial diagnosis the patient has an ongoing CR after a sequence of therapy lines. We hereby show a rather uncommon development for a patient with PTCL-NOS and multiple relapses.

Poster Onkologie

001

Prediction of response to palliative chemotherapy by circulating tumor DNA (ctDNA) kinetics in metastatic pancreatic cancer

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Introduction and aims: Circulating tumor DNA (ctDNA) represents a promising prognostic biomarker for predicting relapse and overall survival in patients with metastatic pancreatic cancer (PC). To test the clinical applicable prognostic value of ctDNA dynamics during treatment, we aimed to detect response to treatment ahead of radiological restaging.

Material and Methods: ctDNA detection using liquid biopsy (ddPCR utilizing *KRAS* G12/13 (and, if negative, Q61) commercial test kits) was prospectively performed on 70 patients with stage IV PC (i) prior to initiation of systemic chemotherapy and (ii) serially every two weeks until restaging.

Results: Detection rate at baseline was 64.3% (45/70). Reduction of ctDNA levels below 57.9% of its baseline value at week 2 after treatment initiation was significantly predictive for response to treatment (AUC = 0.918, sensitivity 91.67%, specificity 100%) and was associated with prolonged overall survival (OS) (5.7 vs. 11.4 months, $p=0.006$) and progression free survival (PFS) (2.5 vs. 7.7 months, $p<0.000$) regardless of treatment line. Pretherapeutic ctDNA detection was independently associated with worse OS in patients receiving first line regimen (7 vs. 11.3 months, $p=0.046$) and regardless of treatment line (11.4

vs. 15.9 months, $p=0.045$) and associated with worse PFS (3.4 vs. 10.8 months, $p=0.018$).

Conclusion: The dynamic change of ctDNA during systemic treatment allows the prediction of treatment response and is associated with OS and PFS. Progressive disease was correctly predicted in 100% of patients with preemptive detectable ctDNA after 2 weeks (ctDNA) compared to 12 weeks with current gold standard (CT), enabling change of treatment >80% earlier hereafter.

002

Feasibility and quality of life of dose-dense (neo)adjuvant chemotherapy with epirubicin/cyclophosphamide and paclitaxel in breast cancer patients in daily routine

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Background: Despite better disease-free and overall survival outcomes with dose-dense (neo)adjuvant anthracycline therapy, such as epirubicin/cyclophosphamide every 2 weeks (ECdd), many patients receive anthracycline every 3 weeks for reasons of tolerability and health-related quality of life (HRQOL). In this study, we evaluated the percentage of patients completing 4 cycles dose-dense ECdd plus 12 cycles of weekly paclitaxel and examined HRQOL during treatment.

Methods: For this single-arm study, we recruited patients at the Kufstein District Hospital qualifying for dose-dense EC plus paclitaxel. HRQOL was assessed at each chemotherapy cycle with the EORTC QLQ-C30 questionnaire. Study endpoints were the percentage of patients completing treatment per protocol and HRQOL while on treatment.

Results: Sixty patients were included in the analysis (mean age: 56.1 years). Therapy was completed per protocol by 37 patients (61.7%) while only 4 patients discontinued ECdd. Most discontinuations occurred under paclitaxel due to polyneuropathy. During ECdd HRQOL deteriorated on several domains including physical functioning ($p<0.001$), role functioning ($p<0.001$), global QOL ($p<0.001$) and fatigue ($p=0.007$). Patients discontinuing treatment showed stronger HRQOL deterioration than patients completing the treatment per protocol.

Conclusion: Our results indicate that ECdd is feasible in the majority of patients (93%), but with a significant impact on HRQOL during therapy. Premature treatment termination is mostly due to paclitaxel-induced polyneuropathy. Patients discontinuing treatment experienced HRQOL impairments on multiple domains, possibly reflecting treatment toxicity in these patients.

O03

Preoperative fibrinogen/CRP score predicts survival in upper urothelial tract carcinoma patients undergoing radical curative surgery

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Introduction and aims: Upper urothelial tract carcinoma (UTUC) is a rare and often aggressive malignancy associated with poor prognosis. Therefore, finding reliable prognostic biomarkers in patients undergoing curative surgery for improved risk stratification is crucial. For this reason, we evaluated the prognostic value of the Fibrinogen/C-reactive protein (FC)-score, in a cohort of surgically treated UTUC patients.

Material und Methods: 170 patients with radiologically and histologically verified UTUC, who underwent radical curative surgery between 1990 and 2020 were included. The FC-score was calculated for each patient, with patients receiving 1 point each if Fibrinogen and/or CRP levels were elevated. Patients were then divided into three subgroups according to their FC-score of 0, 1 or 2 point(s). Kaplan-Meier analysis, uni- and multivariable Cox proportional hazard models were implemented. We determined cancer-specific survival (CSS) as our primary endpoint, whereas overall survival (OS) and recurrence-free survival (RFS) were considered secondary endpoints.

Results: High FC-score (2 points) was significantly associated with adverse histological features such as vascular invasion (OR=4.08, 95%CI 1.18–14.15, $p=.0027$) and tumor necrosis (OR=6.67, 95%CI 1.35–32.96, $p=0.020$). Both, uni- and multivariable Cox proportional hazard models showed that the FC-score is a significant predictor for our primary endpoint CSS (univariable analysis: FC-score=1: HR=1.90, 95%CI 0.92–3.93, $p=0.085$ | FC-score=2: HR=2.86, 95%CI 1.22–6.72, $p=0.016$). Furthermore, in univariable analysis, patients with higher FC-score had significantly shorter OS (FC-score=1: HR=1.32, 95%CI 0.70–2.49, $p=0.387$ | FC-score=2: HR=2.19, 95%CI 1.02–4.67, $p=0.043$). However, this did not prevail in the multivariable analysis.

Conclusion: The FC-score represents a novel potential biomarker in patients with UTUC undergoing radical curative surgery.

O04

SBNO2 is a critical mediator of STAT3-driven hematological malignancies

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Introduction: Gain-of-function mutations in the SH2 domain of the STAT3 gene (eg. STAT3^{Y640F}) are recurrently identified in patients suffering from large granular lymphocytic leukemia (LGLL). Transcription factors are notoriously difficult to target, hence a better understanding of STAT3-dependent transcriptional co-factors and their molecular targets is critical to identify novel therapeutic approaches.

Methods: To unravel the molecular mechanisms behind STAT3^{Y640F}-induced malignancies, we developed a murine *in vitro* model that recapitulates common transcriptional features that are found in CD8⁺ transformed T-LGLL cells from patients harbouring STAT3 mutations. Gene expression analyses and chromatin occupancy profiling of mutated STAT3^{Y640F} identified a core set of direct transcriptional targets, which were interrogated for their functional relevance in genome-wide CRISPR/Cas9-based loss-of-function (LOF) screens.

Results: In contrast to wild-type STAT3, STAT3^{Y640F} resulted in a strong inflammatory gene expression signature that was characterized by over-activation of TNF alpha/Interferon gamma pathways, and is conserved in T-LGLL patients harbouring STAT3 mutations. Additionally, STAT3^{Y640F} transformed cells show accelerated proliferation and enhanced self-renewal potential. Through genome-wide LOF screens using CRISPR/Cas9 we identified that the transcriptional co-regulator strawberry notch homolog 2 (SBNO2) is an essential direct transcriptional target of STAT3^{Y640F} transformed cells. As seen with loss of STAT3^{Y640F} expression, loss of SBNO2 also impaired proliferation.

Conclusion: Strikingly, global analyses of gene dependency datasets revealed that various human T-cell malignancies that are driven by aberrant STAT3 signalling also depend on SBNO2 expression. In NPM-ALK T-ALCL patients, high SBNO2 expression correlates with shorter relapse-free- and overall survival.

Our findings identify SBNO2 as potential therapeutic intervention site for STAT3-driven hematopoietic malignancies.

O05

Application of genome-wide CRISPR/Cas9 screen to identify synthetic lethality with MCL-1 inhibition in lung cancer

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Introduction and aims: Lung cancer is among the most diagnosed cancers and the leading cause of cancer-related deaths. Histologically, it is divided into small cell lung cancer and more prevalent non-small cell lung cancer (NSCLC). Recent reports demonstrated frequent amplifications of anti-apoptotic gene myeloid cell leukemia 1 (MCL-1) in NSCLC. Pharmacologic inhibition of MCL-1 protein showed promising effects in pre-clinical models, but malignant cells frequently exhibit resistance to this mono-therapy. The aim of this study is to uncover synthetic lethal interactions between MCL-1 inhibition and specific genes and thereby identify potential new targets for combination treatment approaches.

Material und Methods: To reveal synthetic lethal relationships with MCL-1 inhibitors in NSCLC, we employed a genome-wide pooled CRISPR/Cas9 screen. MCL-1 inhibitor-resistant A549-Cas9 cells were lentivirally transduced with a whole-genome CRISPR knock-out guide-RNA library, and treated for 12 days with MCL-1 inhibitor. At the end of the treatment period, genomic-DNA was extracted and sequenced to identify differences in guide RNA expression.

Results: Bioinformatic analysis revealed that guide-RNAs against 26 genes were significantly downregulated upon MCL-1 inhibition. One of the obtained hits was *BCL2L1* gene that encodes for BCL-XL, a well-known resistance factor to a variety of therapies. Indeed, when we combined MCL-1 inhibitor with BCL-XL inhibitor, A549 cells were strongly sensitized and cell death induction was observed at very low concentrations of MCL-1 inhibitor. Notably, the cells were also not sensitive to BCL-XL inhibition alone.

Conclusion: Our data indicate the existence of synthetic lethal relationships between MCL-1 inhibitor and multiple genes in NSCLC.

O06

Localized Synovial Sarcoma in adolescents and young adults (AYA) versus adults – Is there a difference in outcome?

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Introduction and aims: Synovial sarcomas (SS) are a rare subgroup of soft tissue sarcomas arising both in adolescents and young adults (AYA) and in adult patients. The objective of our analysis was to investigate potential differences in outcome of AYAs versus adult patients with initially localized SS.

Materials and Methods: Fifty-one patients (25 AYAs and 26 adult) were identified and evaluated in this retrospective single center analysis. Baseline characteristics, treatments and survival outcomes were assessed.

Results: The predominant subtype in both groups was monophasic SS and the most common site was the extremities with mostly deep tumor location in both groups. Primary wide resection was performed in 15 AYAs and in 18 adults. Postoperative radiation therapy was more common in AYAs ($n=19$) than in adult patients ($n=12$; $p=0.029$). Nineteen and 17 patients, respectively, received adjuvant chemotherapy with no evidence of disease after 6 cycles. Nine and 11 patients relapsed after initial therapy and the most common metastatic site was the lung. Five-year overall survival rates were 85% and 75% ($p=0.899$). Female sex, tumor size ≤ 5 cm and absence of progressive disease showed a significant association with OS in AYA patients, whereas non-extremity tumors and progression after initial therapy were significant for worse OS in adult patients.

Conclusions: AYA and adult patients showed no significant difference in terms of overall OS. Male gender, tumor size >5 cm and progressive disease were predictive markers for worse outcome whereas tumor location and progression after initial therapy were markers for worse outcome in adult patients.

O07

Uncovering innovative molecular targets for lung cancer therapy on the highly recurrent chromosomal gain of 1q21

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Introduction and aims: Genotype directed/personalized therapies have revolutionized cancer treatment. Nevertheless, resistance development and treatment failure often limit its

effectiveness. Somatic copy-number amplifications strongly contribute to carcinogenesis and treatment resistance. One such example located on chromosome 1q21 is the pro-survival gene *MCL-1*, which is frequently amplified/overexpressed in lung adenocarcinoma (LUAD). Of note, *MCL-1* amplifications mostly co-occur with the amplification of a large genomic area on 1q21, resulting in the overexpression of *MCL-1* and 315 additional genes, with mostly unknown function in tumorigenesis. Thus, this study aims to identify the role of potential critical cancer drivers affected by the chromosomal gain of 1q21 in LUAD patients.

Material and Methods: Bioinformatic analysis evaluated the impact of increased expression of these amplified genes on lung cancer patient survival. Selected genes will be functionally studied in lung cancer cell lines using CRISPR/Cas9 genome-editing technologies to induce overexpression or knockouts. The most promising candidate genes will be studied in a unique clinically-relevant *Kras*- and *Tp53*-loss-driven lung cancer mouse model allowing the rapid CRISPR/Cas9-mediated somatic modification of certain genes.

Results: Elevated expression of individual 1q21 genes, such as *BCAN* or *NUF2*, in lung cancer patients is clearly associated with reduced survival. Increased expression of these genes was associated more strongly with survival than previously published *MCL-1*.

Conclusion: This proposed characterization will not only answer biological questions behind the functional role of the 1q21 amplicon genes, but also aid the urgently needed identification of innovative molecular targets for the development of new treatment strategies in lung cancer.

O08

Deciphering the role of E2F transcription factor-1 (E2F1) in glutamine metabolism of uterine carcinosarcoma and soft tissue sarcoma

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Introduction and aims: Metabolic reprogramming is considered as a hallmark of cancer and is clinically exploited as a target for therapy. E2F1 regulates several metabolic pathways and functions as an oncogene or tumor suppressor as evident by the observation that E2f1-knockout mice develop spontaneous tumors. This discrepancy warrants a detailed investigation how E2F1's metabolic functions control cellular proliferation and tumor growth.

Material und Methods: Taking advantage of mouse embryonic fibroblasts (MEFs), isolated from E2f1-wild-type (E2f1^{+/+}) and E2f1-knock-out (E2f1^{-/-}) mice as a genetic tool, as well as human sarcoma cell lines and patient-derived samples, we investigated the biological outcomes of altered E2F1 expression on glutamine metabolism.

Results: Our data indicate that E2F1 binds to the promoter of several glutamine metabolic genes. Interestingly, glutamine metabolic genes are strongly increased in E2f1^{-/-} compared to E2f1^{+/+} MEFs. In addition, we confirm that E2f1^{-/-} MEFs more

efficiently metabolize glutamine. Contrary, increased proliferation of E2f1^{-/-} MEFs can be strongly inhibited using specific glutamine pathway inhibitors. Mechanistically, we observe a co-occupancy of E2F1 and MYC on glutamine metabolic promoters and silencing of MYC decreases the expression of glutamine metabolic genes in E2f1^{-/-} MEFs, suggesting that MYC contributes to increased glutamine metabolic gene expression in E2f1^{-/-} MEFs. Observations from a screen of 21 different cancer types showed a high relevance of E2F1's glutamine metabolic function in uterine carcinosarcoma and soft tissue sarcomas.

Conclusion: Altogether, our results suggest that E2F1 is a novel transcriptional regulator of glutamine metabolism in sarcomas and highlights potentially new targets for cancer interventions.

O09

Influence of perioperative administration, transfusion volume and storage age of red blood cell concentrates on clinical outcomes in non-metastatic renal cell carcinoma patients

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Introduction and aims: Perioperative red blood cell transfusion (RCT) has been linked to poor oncological outcomes in renal cell carcinoma (RCC) patients undergoing curative surgical tumor resection. The aim is to validate previous findings and explore the potential impact of RCT volume and storage age on patients' survival.

Materials and Methods: Within this bi-center retrospective cohort study two cohorts of non-metastatic localized RCC patients, who underwent curative partial or radical nephrectomy, were pooled for analyses. Endpoints were cancer-specific survival (CSS; primary endpoint) and overall-, (OS) and metastasis-free survival (MFS)(secondary endpoints). The administration of perioperative allogenic RCT, the number of red blood cell concentrates, as well as their median storage time were analyzed for their potential impact on survival outcomes.

Results: 270 (15%) of 1797 patients received RCT. Administration of RCT was a significant predictor of CSS, OS and MFS in both uni- and multivariable Cox regression models (CSS: Hazard ratio [HR] = 1.405, $p=0.005$; OS: HR=1.290, $p=0.007$; MFS: HR=1.366, $p=0.008$). Patients who received more than 3 red blood cell concentrates had significantly shorter CSS and MFS (CSS: HR=1.786, $p=0.005$; MFS: HR=1.740, $p=0.006$). Patients

who received red blood cell concentrates with a median storage age of more than 28 days ('old conserves') showed significantly worse CSS (HR=1.920, $p=0.026$).

Conclusion: Perioperative RCTs, and a high number of red blood cell concentrates represented independent risk factors for poor oncological outcomes. In addition, the transfusion of older cell concentrates at the end of their storage time might be linked to shorter CSS.

O10

The long non-coding RNA NORAD and its role in triple negative breast cancer

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Introduction: Triple negative breast cancer (TNBC) represents the most aggressive breast cancer subtype with a poor prognosis. It is frequently associated with mutations in BRCA1/2 genes and patients harboring these mutations can be treated with approved PARP (Poly (ADP-ribose) polymerase) inhibitors. The long non-coding RNA Activated by DNA Damage (NORAD) is implicated in molecular mechanisms associated with carcinogenesis due to its function in maintaining genomic stability.

As our previous results revealed that NORAD silencing influences cellular growth of TNBC wild type cells, we investigated the impact of NORAD overexpression on PARP inhibitor sensitivity and its role in TNBC cells with BRCA mutated genetic background.

Methods: We used a NORAD overexpression plasmid in TNBC wild type (WT) cells to characterize its effects on features relevant for carcinogenesis. To analyze the consequences of NORAD silencing and overexpression in BRCA1/2-KO cell lines, we generated BRCA1/2 mutated cell lines by an inducible CRISPR/Cas9 based approach.

Results: High expression levels of NORAD were identified as a negative prognostic factor in TNBC patients. The overexpression of lncRNA NORAD has an influence on cellular growth and on PARP inhibitor sensitivity in BRCA-WT cells. The combination of NORAD silencing and PARP inhibition with olaparib influenced the expression pattern of several DNA repair proteins in BRCA-WT cells whereas this combinatorial approach did not influence the expression in BRCA-KO cell lines.

Conclusion: The primary data of this study indicate a relevance of NORAD in TNBC and may help to improve the understanding of resistance mechanisms against PARP inhibitors in TNBC.

O11

Upregulated expression of ACSL6 in colorectal cancer is linked to a specific molecular portrait and is associated with poor relapse-free survival

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Introduction and aim: Deregulation of long-chain acyl-coenzyme A synthases (*ACSLs*) has shown to be associated with cancerogenesis. *ACSL6* is believed to be a ferroptosis-associated gene, whose potential role in colorectal cancer (CRC) is scarcely investigated to date. Thus, we evaluated the prognostic impact, as well as the molecular and immunological profile of CRCs according to *ACSL6*-transcriptome expression.

Material and Methods: RNA-sequencing of 41 normal colon tissue samples and 285 CRC specimens of the TCGA Colon Adenocarcinoma cohort were analyzed. Samples were stratified into *ACSL6*^{low} and *ACSL6*^{high} mRNA expression by the optimal cutoffs, regarding relapse-free survival (RFS). Whole-genome differential genes expression was investigated by Benjamin-Hochberg-corrected two-tailed T test. Gene ontology term enrichment analysis was performed to investigate modulated biological processes.

Results: Analysis revealed that *ACSL6* is strongly upregulated in CRC compared to normal colon tissue ($p<0.001$). Differentially regulated transcriptomes of *ACSL6*^{high} expression referred to alterations in immune response (e.g., T cell activation), a differed genetic landscape (increased *APC* (85% vs. 63%) and *TP53* (70% vs 47%), and lower *BRAF* (4.1% vs. 26%) mutational rates) and clinical features (mucinous histology and primarily left-sided tumors). Moreover, *ACSL6*^{high} was significantly associated with poor RFS ($p=0.03$).

Conclusion: Our results delineate that the upregulation of *ACSL6* expression is associated with a significant higher risk of recurrence in CRC. *ACSL6*^{high} tumor related differences in gene regulation, leading to a distinct immunological, genetic and clinical profile, might qualify *ACSL6* as a future molecular target in CRC treatment. Currently, in-house validation studies are ongoing to confirm our first results.

O12

Multidisziplinäre Tumorkonferenzen in Österreich und Deutschland – Status quo und Perspektiven

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Einleitung und Fragestellung: In Österreich wie auch in Deutschland ist die Bedeutung multidisziplinärer Tumorkonferenzen (MTK) seit geraumer Zeit bekannt (Onkologie-Beirat

2017). Jedoch gibt es kaum Untersuchungen zu den strukturellen Rahmenbedingungen, der Funktionsweise und den Erfolgsfaktoren von MTK aus Sicht teilnehmender Ärztinnen/Ärzte. Ziel der vorliegenden Studie ist, aufzuzeigen, welche Rolle MTK in der Versorgung von Krebskranken einnehmen und welche Verbesserungspotenziale erkennbar sind.

Material und Methoden: Zunächst wurde ein orientatives Review zum Forschungsstand bzgl. MTK in Österreich durchgeführt. Der ermittelte Status quo wurde ergänzt um Erkenntnisse aus einem in Deutschland in 2021/2022 durchgeführten Online-Survey mit niedergelassenen Ärztinnen/Ärzten zu MTK.

Ergebnisse: In Österreich werden zahlreiche Forschungsanstrengungen unternommen, die MTK insbesondere unter Qualitätssicherungsgesichtspunkten betrachten. Beispielhaft dafür sind die All.Can-Austria-Initiative sowie verschiedene Projekte der Comprehensive Cancer Center der MedUni Wien/AKH Wien und des Tumorzentrums Oberösterreich. Im Rahmen der deutschen Studie wurden 612 Ärztinnen/Ärzte befragt. Mit 32 % war die Hämatologie und internistische Onkologie die stärkste Fachdisziplin. Bezogen auf die letzte MTK, an der sie teilgenommen hatten, bestätigten 47 % der Befragten, dass alle erforderlichen Befunde und Bildmaterialien für alle Patientinnen/Patienten vorlagen. 52 % gaben an, dies sei bei den meisten Patientinnen/Patienten der Fall gewesen. Lediglich 40 % der Befragten konstatierten, dass alle relevanten Entscheidungsfindungsfaktoren bei allen Patientinnen/Patienten bekannt waren.

Schlussfolgerung: Die Studienergebnisse lassen Verbesserungspotenziale hinsichtlich der Vollständigkeit relevanter Informationen in MTK erkennen. Informationen zu Komorbiditäten, Belastbarkeit, psychosozialen Faktoren und Präferenzen fehlen häufig. Es sollte evaluiert werden, welche Informationen unverzichtbar sind, damit fundierte individualisierte Behandlungsempfehlungen in MTK erstellt werden können, die die individuelle Situation der Patientinnen/Patienten angemessen berücksichtigen.

O13

In silico characterization of the immune landscape in luminal breast cancer

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Introduction: Breast cancer is the most common neoplasm in women worldwide and a heterogeneous disease at the molecular level. Molecular characteristics, such as hormone receptor (HR) and HER2/neu status, mark the classification of patients for different treatment strategies, e.g. luminal breast cancer being associated with HR positivity and HER2 negativity. Also, multi-gene signatures, like PAM50, give us trails for subtype assignment and also signatures of tumor-infiltrating leukocytes (TILs) may further allow to delineate breast cancer subtypes. While offering potential to guide immunotherapeutic approaches, the molecular background of different TIL patterns remains unclear.

Methods: Infiltration patterns of 14 different immune cell types were estimated across 778 primary luminal breast cancer patient samples using well-defined cell type specific marker

gene expression levels. TIL signatures were associated with intrinsic molecular PAM50 subtypes and clinical parameters, including tumor staging and overall survival (OS).

Results: The majority of immune cell types showed highly consistent infiltration patterns to each other. Three distinct clusters of patient samples based on TIL signatures were estimated (low TILs, $n = 420$; intermediate TILs, $n = 143$; high TILs, $n = 215$). TIL clusters were neither associated with PAM50 subtypes luminal A or B nor with tumor staging, yet substantial differences in OS between high and low TIL clusters were observed (3-year OS 96% vs. 87%, 5 year OS 87% vs. 80%, 7 year OS 78% vs. 66%, p -value = 0.022, log-rank test).

Conclusion: Our findings suggest that describing breast cancer patient samples based on immune cell infiltration signatures opens a new avenue to identify clinically meaningful breast cancer subtypes beyond known molecular determinants.

O14

IFN-I Signaling in Tumor Associated Endothelial Cells (TECs) in NSCLC

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Introduction: Endothelial cells (ECs) in the tumor microenvironment (TME) are not only essential for cancer growth by providing a required vascular supply-network but as well execute distinct pathological functions that promote tumor-progression and immune evasion. Therefore, unraveling the function of TECs in the setting of solid cancer, such as NSCLC, may help to understand underlying processes, which drive the referred pathogenesis.

Methods: Primary EC-culture from NSCLC patient-derived healthy and malignant tissues were generated and used for in-depth characterization of TEC-features by bulk RNA sequencing, molecular- and functional assays. Validation of target-expression in NSCLC vasculature was obtained using IHC stainings. Large-scale experiments were performed using commercially available ECs, such as HUVECs and EA.hy 926. Prognostic relevance, differential gene regulation and pathway activation were investigated using four different bulk RNA lung cancer datasets. In parallel, NSCLC single-cell data of 182 patients and 158 controls will be used to further confirm and elaborate obtained *in vitro* and *ex vivo* findings.

Results: Our analyses linked a pathological TEC-phenotype in NSCLC with extracellular nucleic acid-induced upregulation of IFN-I mediated innate immune response and identified a novel TEC-specific marker involved in this pathway, IFI27. TECs show enhanced migration as well as increased IFN-I induction-potential compared to normal lung ECs. In clinical data we could link IFN-I activation with worse patient survival. Further-

more, our data suggest that activation of IFN-I in ECs is directly involved in inducing a tumor-promoting phenotype.

Conclusion: Here, we propose for the first time an association of TEC-driven pathogenesis with the induction of IFN-I signaling in NSCLC.

O15

Clinical Characteristics, Treatment, and Outcomes of Patients with Large Cell Neuroendocrine Carcinoma of the Lung and Brain Metastases – Data from the Vienna Brain Metastasis Registry

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Introduction and aims: Large cell neuroendocrine carcinoma (LCNEC) of the lung is a highly aggressive malignancy, with brain metastases (BM) occurring in approximately 20% of cases. As data on patients with BM from LCNEC is very limited, we aim to better define the clinical presentation and treatment outcomes of this cohort.

Material and Methods: In our single center retrospective analysis, we analyzed data of patients with LCNEC and BM from the Vienna Brain Metastasis Registry, a comprehensive database managed by the Division of Oncology, Medical University of Vienna.

Results: 52/6083 patients (0.085%) in the Registry had LCNEC and verified BM. The median age at LCNEC diagnosis and BM diagnosis was 59.1 years (range 46–82) and 60.1 years (range 46–87), respectively. 22 patients (42.3%) had synchronous BM. $N=27$ presented with a single BM, while $n=12$ exhibited ≥ 3 BM initially. Neurologic manifestations included focal deficits ($n=24$), increased intracranial pressure ($n=18$), and seizures ($n=6$). BM were treated with resection ($n=13$), whole brain radiation ($n=19$), and/or gamma knife ($n=33$). The median overall survival (mOS) after LCNEC diagnosis was 16 months (range 1–192), and the mOS after BM diagnosis measured 7 months (range 1–63). Gamma knife treatment was associated with an increased mOS of 12 months (range 1–63), compared to 4 months (range 1–44) in the non-gamma knife group (p -value 0.018).

Conclusion: Patients with LCNEC and BM have a high symptom burden and a poor prognosis. Gamma knife may improve survival times; prospective trials are required for further investigation.

O16

Impact of Immune Checkpoint Inhibitors on Bone Turnover in Cancer Patients: in Vitro Studies and Clinical Correlate.

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Introduction and aim: Despite the widespread use of immune checkpoint inhibitors (ICIs), their effect on bone health is still poorly defined. Hence, we investigated the effects of ICIs on bone cell homeostasis in vitro and in patients with advanced cancer treated with single agent ICI.

Material and Methods: Dose-dependent effects of ICIs on osteoclast (OC) and osteoblast (OB) differentiation in vitro were evaluated by morphological and functional assays. C-terminal telopeptide (CTX), Osteocalcin (OCN) and procollagen type I N-propeptide (PINP) were measured before each ICI application in patients with advanced cancer and no bone metastases.

Results: In vitro studies show a strong dose-dependent impairment of OC differentiation and function in the presence of ICIs via inhibition of STAT3 phosphorylation and downregulation of cFOS expression. In contrast, no significant effect on osteoblastogenesis was evident. To confirm these data, we evaluated bone turnover markers in 10 patients treated with PD1 ($n=5$) and PD-L1 ($n=5$) inhibitors for a median of 15 weeks (range 7–31). We observed a significant decrease in CTX levels (mean CTX $0,51 \text{ ng/ml} \pm 0,42$ at baseline to $0,42 \pm 0,37$ at week 3; $p=0,017$) without significant changes in OCN and PINP. CTX at 3 weeks correlated with treatment response and a decrease above 20% was associated with a longer progression-free survival (PFS) (median PFS 68,7 months vs 15,8 months, $p < 0,003$).

Conclusions: Our study demonstrates that ICIs inhibit bone resorption in cancer patients by directly impairing osteoclastogenesis, ongoing analyses are elucidating the molecular mechanism involved.

O17

Response prediction by mutation- or methylation-specific detection of ctDNA dynamics in pretreated metastatic colorectal cancer

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Colorectal cancer (CRC) is a common cause of cancer-related death. Biomarker-based treatment strategies have increased the accuracy in first line treatment, but are lacking in patients treated beyond firstline. We aim to predict benefit from higher treatment lines by measuring the dynamics of circulating tumor DNA (ctDNA) during treatment.

CtDNA samples were collected from 42 patients treated in second- or higher lines at each treatment cycle. Treatments were based on local treatment guidelines. Mutations and methylation of NPY or WIF-1 in ctDNA were determined by digital droplet PCR. Dynamics of ctDNA was calculated by dividing ctDNA levels of each time point with ctDNA levels at the beginning of the treatment.

Detection rate of both, mutations and methylation of WIF-1/NPY in ctDNA was 83.7%. The most common mutations were found in RAS genes ((60.7%), WIF-1 detection was higher than NPY-methylation (73.0%). Median time from start of treatment to restaging was 93 days (95%CI 88.8–96). After a median of 19 days of treatment (95%CI 16.1–20.2) a decline of either mutation- or methylation-specific ctDNA levels of $\geq 58\%$ allowed the prediction of progressive disease at restaging with a sensitivity/specificity of 92.9/85.7% and 85.7/100%, respectively. Median time to restaging from this time point, was 66 days (95%CI 56.8–75.2) suggesting a potentially sparing of an insufficient treatment.

Lack of predictive biomarkers in higher treatment lines could be compensated by serial ctDNA analysis and prediction of clinical benefit from systemic treatment. This gains special interest in higher lines of therapy as quality of life gains higher importance.

O18

Modeling NF1 loss-of-function mutation in hormone receptor-positive breast cancer cells

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Introduction and aim: Acquired mutations during disease evolution are often associated with treatment resistance, disease progression, and consequently adverse outcomes in patients with advanced breast cancer. One such genetic alteration, that was detected by liquid biopsy in patients with metastatic disease, is a defect in Neurofibromin 1 (NF1). Its loss-of-function results in increased RAS activity, estradiol hypersensitivity, and tamoxifen agonism, resulting in endocrine resistance, a higher risk of recurrence and a worse prognosis. Our research aims to model mutations such as NF1-loss-of-function in-vitro, evaluate its functional implications and develop strategies to overcome treatment resistance.

Material and Methods: We introduced NF1 knock-out in MCF-7 cells by applying the CRISPR/Cas9 technology. The cells were then treated with CDK 4/6 inhibitors in combination with the selective estrogen receptor degrader Fulvestrant. Cell cycle alterations were measured with flow cytometry analysis and competitive assays were performed to evaluate a potential survival advantage in the genetically modified cells.

Results: Cell cycle analysis revealed that MCF-7 cells harboring the NF1 knock-out replicate faster. Also, the modified cells were able to outgrow wild-type cells in competition assay. Based on these experiments, in the next step, we will investigate how we can modulate this acquired resistance by using MEK inhibitors or other candidate drugs.

Conclusion: We have successfully established an in-vitro NF1 knock-out model for further evaluation of NF1-associated resistance and how to overcome it. NF1 deficiency leads to significant changes in cell proliferation, which is coherent with clinical findings, showing adverse outcomes in patients with NF1 alterations.

O19

Treatment patterns and oncological outcome of patients with advanced small intestinal neuroendocrine tumors: real-world data from the Medical University of Vienna

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Introduction and Aim: Different oncological therapies have been approved for small intestinal neuroendocrine tumors

(SI-NETs), but relatively little is known about efficacy and long-term outcome outside of phase III trials.

Material and Methods: This retrospective analysis assessed patients with well-differentiated, metastatic SI-NETs treated at the Medical University of Vienna. The primary objective was to assess progression-free survival (PFS) following approved therapies, i. e., octreotide, lanreotide, peptide receptor radionuclide therapy (PRRT), and everolimus.

Results: A total of 77 patients receiving systemic treatment for advanced SI-NETs between 2010 and 2021 were included, with a median follow-up time of 82.3 months. The estimated median PFS following first-line therapy was 32.0 months (95% CI, 23.5–40.5 months). Peritoneal carcinomatosis was significantly associated with worse PFS ($p=0.016$). As a first-line therapy, 59 patients received somatostatin analogs, and no significant difference in median PFS was observed between lanreotide and octreotide (29.3 versus 35.5 months, $p=0.768$). Across all treatment lines, 42 patients underwent PRRT (median PFS: 32.0 months), and a small subgroup of 7 patients received everolimus (median PFS: 9.2 months). For the total cohort, the median OS following first-line therapy was 100.6 months (95% CI, 82.3–118.8 months), but the high proportion of deaths attributed to NET (77.8%) underlines the lethal nature of the disease. No unexpected toxicities were observed.

Conclusion: While peritoneal carcinomatosis emerged as an adverse prognostic factor for PFS in this collective, the long-term outcome of patients treated at a specialized NET center using approved therapies appeared comparable to pivotal studies in SI-NET.

O20

Primary patient-derived microtissues (PMTs) for functional drug testing and prediction of immunotherapy efficacy

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Introduction and aims: Checkpoint immunotherapies (IO) have shown remarkable success in a subgroup of non-small cell lung cancer (NSCLC) patients. However, a significant patient population still don't benefit from IO.

Thus, we established a functional *in vitro* drug testing model to evaluate IO efficacy and to increase IO prediction.

Material and Methods: Fresh tumor tissues were collected immediately after surgery from NSCLC patients. These samples were then stepwise dissected and enzymatic digested in order to obtain a single cell suspension. Next, primary derived microtissues (PMTs) were generated from this single cell suspension in ultra-low attachment plates. Conditions were optimized to maintain the original cell composition including the different immune cell populations. After tissue maturation (six days) they were treated with chemotherapies, targeted agents, drug combinations and IO over 14-days. Treatment response was defined by growth inhibition or volume reduction of PMTs.

Results: We established a standardized protocol for the production and maintenance of PMTs by testing different conditions to optimize growth and reproducibility of the model.

PMTs were maintained in culture up to 14 days and initial cell compartments (cancer cells, stromal cells and immune cells) were preserved. Drug incubation led to a dose dependent decrease in tumor cell volume. Furthermore, IO alone or in combination with chemotherapy showed a significant decrease in volume of PMTs.

Conclusion: The present PMT model combined with a clinically relevant drug response analysis is one of the first to show checkpoint inhibitor-mediated cancer cell killing in a scalable long term *in vitro* assay.

O21

Immune-related adverse event (irAEs) and pathological complete response (pCR) rates in patients receiving chemotherapy (CHT) and pembrolizumab (PEM) for early triple-negative breast cancer (eTNBC)

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Background: The addition of the immune checkpoint-inhibitor PEM to CHT was shown to increase pCR rates and invasive event-free survival in the Keynote-522 (KN522) trial. We aimed to identify real-world occurrence rates of irAEs and pCR rates in women with eTNBC receiving neoadjuvant PEM and CHT.

Methods: Patients with eTNBC and receiving CHT + PEM were followed prospectively and monitored for occurrence of irAEs and neoadjuvant treatment outcome as defined by pCR from October 2020 until September 15th, 2022.

Results: 22 female patients with available pCR outcomes were included in this first analysis. Patients received a mean number of 6.1 (range 1–8) neoadjuvant cycles of PEM. Mean duration of CHT was 21 weeks (range 4–24). Neoadjuvant treatment with PEM was discontinued in 32% (7/22) of patients. Discontinuation of neoadjuvant CHT before week 18 occurred in 22,7% (5/22) of patients. IrAEs of any kind and all grades occurred in 50% (11/22) and of grade 3–4 in 9% of patients (2/22). IrAEs observed were hypothyroidism ($n=3$), arthritis ($n=3$), myocarditis ($n=2$), and single cases of hepatitis, nephritis and pneumonitis. Rates of pCR were 50% (11/22) in all patients and 59% (10/17) in patients who completed >18 weeks of neoadjuvant CHT.

Conclusion: In our real-world analysis, irAEs occurred in similar rates as observed in KN522, although numerically higher for irAEs of all grades. pCR rates were lower than those reported for KN522, most probably due to early treatment discontinuation of CHT in approximately one quarter of patients.

O22

Targeting Tumor-associated Neutrophils in Non-small Cell Lung Cancer

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Introduction and aims: By building a high-resolution single-cell reference atlas we recently uncovered the diversity and plasticity of tissue-resident neutrophils in non-small cell lung cancer (NSCLC; Salcher *et al.*, *Cancer Cell* 2022). Tumor-associated neutrophils (TAN) are associated with worse survival and drive anti-PD-L1 treatment failure in NSCLC. Hence, TANs represent an attractive therapeutic target.

Materials and Methods: A multi-omic approach combining single-cell RNA sequencing of low-mRNA content cells with multiparametric flow cytometry was designed to characterize TAN subtypes and validate putative novel drug targets in freshly resected NSCLC tumors. Bioinformatic cell-to-cell communication analysis demonstrated neutrophil crosstalk within the tumor microenvironment (TME). Functional analyses of tumor cell/neutrophil co-cultures were established to unravel mutual interactions and the impact on phenotypic properties.

Results: Neutrophils acquire new anti- and pro-tumor properties within the NSCLC TME. Tumor cells actively attract and sculpt neutrophils that evolve into distinctive TAN subtypes expressing putative drug targets, such as the oncogene lectin-like oxidized low-density lipoprotein (LDL) receptor-1 (LOX-1/*OLRI*). Functional analysis confirmed phenotypic plasticity of neutrophils *in vitro*. Remarkably, co-culture with lung cancer cells drives peripheral blood neutrophils towards the identified LOX-1⁺ TAN phenotype and affects neutrophil survival kinetics. Hence, the established model allows to modulate TAN properties *in vitro* (e.g. by the LOX-1 inhibitor BI-0115) and to study the potential impact of TANs on cancer cell migration, proliferation, and therapy-resistance.

Conclusion: In-depth characterization and functional analysis of TAN subtypes provides the basis for developing novel combination therapies for NSCLC patients who are not sufficiently responding to immune checkpoint blockers.

O23

Out-FOXOing Therapy-resistant Cancer Cells

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Introduction and aims: The transcription factor FOXO3 regulates a plethora of cellular functions and affects various pathological conditions, including cancer. Recent studies are pointing out putative oncogenic properties of FOXO3. Hence, modulating FOXO3 represents a novel therapeutic strategy in “FOXO3-resistant” cancers. By a drug repurposing approach, we identified the FDA-approved compound carbenoxolone (CBX) as the first FOXO3 inhibitor. The present project was designed to evaluate the therapeutic potential of FOXO3 modulation in non-small cell lung cancer (NSCLC) and prostate cancer (PCa).

Materials and Methods: Single-cell RNA sequencing (scRNAseq) was performed to investigate FOXO3 signaling in surgically resected NSCLC and PCa tissues. FOXO3 expression was validated by quantitative RT-PCR, immunoassays, immunofluorescence (IF), and immunohistochemistry experiments. The impact of FOXO3 modulation was assessed by cell viability/cytotoxicity assays using therapy-resistant tumor cell lines.

Results: scRNAseq revealed markedly elevated FOXO3 signaling in NSCLC and PCa tumor cell clusters. Chemotherapy induced subcellular shuttling of FOXO3 from the cell cytoplasm into the nucleus in NSCLC tumor tissues, indicating its transcriptional activation. Concordantly, therapy-pressure triggered FOXO3 activation and nuclear translocation *in vitro*. The expression of diverse direct transcriptional FOXO3 target genes associated with drug resistance was markedly elevated in chemotherapy-resistant tumor cell lines. Thus, we speculate that therapy-mediated FOXO3 activation drives tumor progression. Concordantly, FOXO3 silencing by CBX efficiently re-sensitized therapy-resistant NSCLC and PCa cells to chemotherapy.

Conclusion: FOXO3 silencing by dose-adjusted, temporary restricted treatment with the FDA-approved compound CBX could enable controlled modulation of FOXO3 to combat tumor progression, but also limit potential side effects.

O24

Delayed response to pembrolizumab therapy in a patient with choriocarcinoma

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Background: Checkpoint inhibition so far was unable to prove its efficacy in the treatment of germ cell tumors in large randomized trials. We report a patient with advanced chemotherapy refractory choriocarcinoma who showed a partial remission to pembrolizumab therapy.

Case: A 21-year old male patient was diagnosed with poor risk choriocarcinoma stage IIIC in January 2020. After firstline treatment with 4 cycles according to the PEB protocol, residual disease in the retroperitoneum and liver was resected. Eight months later, recurrent disease with liver metastasis and mesenteric lymph nodes was evident. After therapy according to the TICE protocol, residual tumor masses in the liver were again surgically removed. Hepatic recurrence two months later was treated with docetaxel/gemcitabine/oxaliplatin followed by radiotherapy of a single liver lesion. However, in May 2022, progressive disease with pulmonary and hepatic metastasis was evident. Taking into account the chemotherapy refractory dis-

ease and the positive PD-L1 status (PD-L1 TPS: 30%, CPS 40), therapy with pembrolizumab was initiated. After three months of treatment, β -HCG levels raised from 520 U/L to 16162 U/L corresponding to progressive disease revealed by CT. Therapy was continued and five weeks later, β -HCG unexpectedly dropped down to 2588 U/L. CT scan showed partial remission of the lungs and stable disease of the liver. Pembrolizumab was well tolerated and as of November 2022, the patient still receives treatment.

Conclusion: Despite overall dismal results of immunotherapy in germ cell tumors, selected patients may profit substantially. Our case is remarkable due to the delayed response achieved by pembrolizumab.

O25

Comprehensive Investigation of Non-coding Natural Antisense Transcripts in Human Cancers

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Introduction and Aim: Our understanding of long non-coding RNAs is still catching up to that of protein-coding transcripts, although the functional and regulatory roles of these transcripts are manifold. Especially, non-coding *cis* natural antisense transcripts (ncNATs) are intriguing, as these are transcribed from the same locus as their partner transcripts but originate from the opposite strand, and many could regulate their sense partners. To create a comprehensive view of ncNAT expression across cancer and healthy tissues, we analyzed more than 4000 publicly available RNA-seq samples using a strand-specific RNA-seq analysis pipeline.

Material and Methods: Our analysis approach followed strict quality control guidelines and involved the alignment of reads to a reference genome and the assembly of novel transcripts. Our workflow further evaluated novel transcripts using a custom filter and transcript selection process that incorporated merging novel transcripts with available lncRNA annotations. Subsequently, transcripts were classified according to their orientation and position in the genome. Following quantification of expression, known and novel assembled ncNATs were subjected to various downstream analyses.

Results: We assessed the expression of known and novel ncNATs in a high number of cancer and tissue types and provided a comprehensive view of their tissue- and cancer-specific expression. We further investigated the dysregulation of ncNATs in cancers, evaluated the correlation patterns of ncNATs and their partner genes and determined immune-related ncNATs.

Conclusion: Deepening the knowledge in the field of ncNATs aids our understanding of gene regulation and their role in cancer, and could identify new clinical marker candidates.

O26

Sustained response of a disseminated SMARCA4-deficient thoracic sarcomatoid tumor to maintenance immunotherapy following local radiotherapy after oligoprogression to firstline immunochemotherapy – an update

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Case presentation: A 68 year old male caucasian patient was diagnosed with a SMARCA4-deficient thoracic sarcomatoid tumor in July 2021. Programmed cell death ligand 1 expression presented negative as shown by a TPS less than 1%, IC <1% and a CPS of 0. A disseminated stage IV disease was detected by a FDG PET-CT scan. Carboplatin, paclitaxel and pembrolizumab as a systemic induction-immunochemotherapy were administered followed by pembrolizumab maintenance therapy. Local irradiation was used to achieve pain control in symptomatic osseous metastatic sites. After 6 months of systemic therapy a FDG PET-CT scan demonstrated complete metabolic remission of tumor formations in the lung and the liver as well as a significant reduction in PET-avidity of the adrenal gland tumor masses. Unfortunately after eight cycles of pembrolizumab maintenance therapy tumor progression occurred in the left adrenal gland and confirmed by biopsy.

Therapeutic approach to oligoprogression: To date no expert consensus exists on a specific firstline therapeutic approach let alone for management of progression to firstline therapy in this very rare entity. Our multidisciplinary tumorboard suggested a primary irradiation of the progressive adrenal gland metastasis and to continue maintenance therapy with pembrolizumab. After fourteen cycles of maintenance immunotherapy a partial remission of the metastatic adrenal gland and overall continuing stable systemic disease could be documented by a CT scan.

Conclusion: This updated patient report highlights the achieved clinically meaningful tumor control in an oligoprogressive setting in a multidisciplinary approach including radiotherapy and immunotherapy beyond progression in a highly aggressive SMARCA4-deficient sarcomatoid tumor.

Klinische Studien

S01

Rituximab Maintenance after Chemoimmunotherapy Induction in 1st and 2nd Line Improves Progression Free Survival: Long Term Follow up of the International Randomized AGMT-CLL8/a Maintenance Trial

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Introduction and aims: Primary analysis of the AGMT-CLL8/a Maintenance trial demonstrated positive PFS results of Rituximab maintenance after chemoimmunotherapy in 1st or 2nd line for 263 CLL patients (Greil, Lancet Haematology 2016). We present updated follow-up (FU) of 87.3 months (+53.9 months).

Results: The PFS benefit of maintenance remained stable over time, increasing median PFS from 35.6 to 47.5 months ($p=0.012$). Median time to next treatment (TTNT) also increased from 53.3 to 78.7 months in the maintenance arm ($p=0.01$). No significant OS difference (62.6% vs 68.4% in observation vs. maintenance at median FU ($p=0.24$)) was observed. MRD parameters (PB or BM) remained significant predictors of PFS and OS. Dynamic assessment of MRD during the first 6 months of observation predicted PFS independent of MRD strata. Analysis of 144 retreated patients showed that inclusion of novel drugs (i. e. BTKi, Venetoclax or PI3K) in retreatment at any time (in 59% of retreated patients) led to a highly significant and large increase in OS ($p<0.0001$). Maintenance patients had a higher percentage of novel drug treatment (66% vs 53% in the observation arm), likely due to a 25.4 months longer TTNT in a sensitive period for access to the novel drugs.

Conclusions: Longer FU shows stable and meaningful benefits for maintenance in PFS and TTNT. MRD endpoints for PFS and OS prediction and novel dynamic MRD endpoints are validated. Receiving novel drugs in any line of salvage derives large OS benefits, showing that effective salvage options may preclude the observation of OS benefits.

S02

AGMT_aMYELOIDr: AUSTRIAN MYELOID REGISTRY

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The Austrian Myeloid Registry (AMR) 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 AMR 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 (incl. patients of HMA Registry) documented patients.

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.

S03

R-Pola-Glo

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Title: A prospective multicenter phase 2 study of the chemotherapy-free combination of intravenous rituximab in combination with the antibody-drug conjugate polatuzumab vedotin and the bispecific antibody glofitamab in patients above 60 years of age with previously untreated DLBCL ineligible for R-CHOP chemotherapy and all patients above 80 years of age.

Design: Prospective, multicenter, bi-national (Germany and Austria) one arm phase-II-study with Rituximab (R) in combination with polatuzumab vedotin (Pola) and glofitamab (Glo) in patients with previously untreated DLBCL ineligible for R-CHOP chemotherapy (R-Pola-Glo).

Population: All previously not treated patients diagnosed with a histologically confirmed CD20 positive aggressive lymphoma above ≥ 80 years of age (cohort 1) and non-fit patients not eligible for full dosed R-CHOP-like therapies between 61–80 years of age (cohort 2).

Primary objective: The 1-year PFS of the chemotherapy-free combination of rituximab, glofitamab, polatuzumab in patients with previously untreated CD20 positive aggressive lymphoma ≥ 80 years of age (cohort 1), and; the 1-year PFS patients of unfit patients not eligible for R-CHOP-like therapies between 61–79 years of age (cohort 2).

Secondary objective: To evaluate feasibility, safety and efficacy, treatment compliance, and patient-reported symptoms of the chemotherapy free new combination therapy in the first line treatment of patients with CD20 positive aggressive lymphoma.

S04

Pola-R-ICE

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Title: An open-label, prospective Phase III clinical study to compare polatuzumab vedotin plus rituximab, ifosfamide, carboplatin and etoposide (Pola-R-ICE) with rituximab, ifosfamide, carboplatin and etoposide (R-ICE) alone as salvage therapy in patients with primary refractory or relapsed diffuse large B-cell lymphoma (DLBCL)

Design: International, multicenter, open-label, two-arm, randomized, prospective, phase III study with Polatuzumab vedotin plus rituximab, ifosfamide, carboplatin and etoposide (Pola-R-ICE) versus R-ICE alone in second line treatment of diffuse large B-cell lymphoma (DLBCL).

Population: Male and female subjects 18 years or older suffering from first relapse or primary refractory disease of DLBCL.

Primary objective: The primary objective of this study is to investigate the following question in patients with relapsed or primary refractory.

DLBCL: Does salvage therapy with Pola-R-ICE improve event-free survival (EFS) compared to R-ICE alone?

Primary endpoint: The primary endpoint is EFS of patients with DLBCL at first progression or relapse. EFS is defined as the time between the day of randomization and the occurrence of any of the following events:

- Failure to achieve sufficient response in PET-CT (Deauville score 3 or less) at end of study treatment (metabolic CR)
- Disease progression (PD)
- Start of additional unplanned anti-tumor treatment (radiation therapy allowed)
- Relapse after achieving CR
- Death due to any cause

Patients who have not experienced any of these events by the time of analysis will be censored at the most recent date of disease assessment.

S05

ARIADNE: Zanubrutinib (Brukinsa®) in patients with Waldenström's macroglobulinemia (WM) – a prospective multicenter observational cohort study

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Design: A non-interventional, open-label, prospective, single arm, multicenter, international study in Germany and Austria. The implementation of this non-interventional study (NIS) does not influence the physician's decision regarding therapeutic strategy, diagnostic methods, frequency of medical examinations and other procedures during and after the treatment. All data will be obtained in routine clinical practice.

Population: Adult patients (≥ 18 years) with Waldenström's macroglobulinemia (WM) in need of treatment with decision for treatment with zanubrutinib (Brukinsa®) according to the Summary of Product Characteristics (SmPC).

Objective: The objective of this NIS is to evaluate medical resource utilization, which had been never done before in WM patients, patient's QoL and effectiveness of zanubrutinib treatment in adult patients with WM in a real-world setting.

S06

AGMT CLL Registry

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

The goal of this registry is to build a disease-specific registry aimed at assessing the therapeutic landscape of patients with CLL in Austria. 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.

Primary objective:

- To describe general characteristics of CLL patients
- To describe genetic risk profiles
- To describe the proportion of CLL patients in Austria that require treatment
- To describe concomitant diseases at diagnosis of CLL
- To describe treatment and outcome of treatment
- To describe patient outcome (e. g. in patients with chemoimmunotherapy and patients with targeted therapy)
- To describe toxicity with a focus on infections, cardiotoxicity, nephrotoxicity bleeding, etc.

Recruitment: About 500 patients will be included in this registry. This number may be revised over time as interest and demand dictates.

S07

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 20Gy 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.

S08

GELTAMO18-HL: BRESELIBET – BREntuximab Vedotin in SEcond Line Therapy BEfore Transplant

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Study Title: A Randomized Phase IIb Study, Evaluating Efficacy of Salvage Therapy with Brentuximab Vedotin-ESHAP vs ESHAP in Patients with Relapsed/Refractory Classical Hodgkin's Lymphoma, Followed by Brentuximab Vedotin Consolidation (instead of Autologous Hematopoietic Stem Cell Transplantation) in Those who Attained a Metabolic Complete Remission after Salvage Therapy

Design: A phase IIb open label multi-center trial in patients with refractory/relapsed cHL. Patients. The first part of the study randomizes 3 cycles of ESHAP as a standard of care therapy for those patients with primary refractory cHL and those patients relapsing after first-line therapy versus 3 cycles ESHAP-BV with BV at a dose of 1.8 mg/kg IV. The rationale behind this first part is the lack of prospective randomized comparisons between conventional salvage chemotherapy protocols and its BV-containing counterpart in terms of rate of metabolic CRs and ORR.

In the second part of the trial, those patients that achieve a mCR will be consolidated with either 13 or 16 cycles of BV (depending on the prior treatment yes/no with BV together with the salvage second-line strategy) at the usual doses and time intervals (1.8 mg/kg iv in 30 min every 21 days). The objective of this second part is to try to avoid auto-HCT as well as early, mid and long-term toxicities associated to the procedure in a population of patients that have a better prognosis and substitute it by an anti-CD30 monoclonal-antibody drug conjugate that has demonstrated a beneficial effect as a consolidation strategy in the AETHERA Trial.

S09

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 confiden-

tiality, 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.

S10

GMMG-HD8/DSMM XIX

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Title: GMMG-HD8/DSMM XIX: A randomized phase III non-inferiority trial assessing lenalidomide, bortezomib and dexamethasone induction therapy with either intravenous or subcutaneous isatuximab in transplant-eligible patients with newly diagnosed multiple myeloma

Design: This is a prospective, multicenter, randomized, parallel group, open-label, phase III clinical trial. After completion of the screening phase patients will be randomly assigned in a 1:1 ratio stratified by R-ISS stages I/II versus III versus not classified, and body weight.

End of the interventional treatment will be at the end of induction therapy including mandatory response assessment and bone marrow aspirate for all participants.

Primary objective: Demonstration of non-inferiority of subcutaneous (SC) isatuximab compared to intravenous (IV) isatuximab, both in combination with RVd, with respect to rates of VGPR or better after induction therapy.

Population: Adult female or male patients up to the age of 70 years inclusive with previously untreated MM requiring systemic treatment.

S11

AGMT MBC Registry: 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: 2000-3000 patients

S12

AGMT LungCA 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)

S13

AGMT DISCOVER

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Title: Multicenter, randomized, double-blind, placebo-controlled, phase III clinical trial to investigate the efficacy and 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 (DISCOVER)

Design: This is a multicenter, randomized, double-blind, placebo-controlled clinical trial to investigate the efficacy and safety of dronabinol in the improvement of chemotherapy-induced and tumor-related symptoms in patients with advanced pancreatic cancer during first-line chemotherapy.

Population: Adult patients (≥ 18 years) with diagnosis of locally advanced or metastatic pancreatic cancer, assigned to first-line chemotherapy with FOLFIRINOX or gemcitabine + Abraxane®.

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 (scores at visits 1-9).

S14

AGMT_MM-4: Isatuximab in combination with Lenalidomide-Dexamethasone compared to Lenalidomide-Dexamethasone in elderly patients (aged ≥ 70 years) with newly diagnosed myeloma: a randomized phase II study (SGZ-2019-12650)

Heinz Ludwig¹

¹Wilhelminenkrebsforschungsinstitut, c/o 1. Medizinische Abteilung, Klinik Ottakring, Wien, Österreich

Design: This is a prospective, multicenter, multinational, randomized, open-label, parallel group, 2-arm study evaluating the clinical benefit of isatuximab in combination with lenalidomide and low-dose dexamethasone followed by isatuximab and lenalidomide maintenance therapy as compared to lenalidomide and low-dose dexamethasone followed by lenalidomide maintenance therapy for the treatment of patients with newly diagnosed multiple myeloma 70 years of age or older.

Patient population: A total of 198 patients with newly diagnosed multiple myeloma aged ≥ 70 years meeting the criteria for inclusion as outlined below will be included.

Primary Objective: To demonstrate the benefit of isatuximab in combination with lenalidomide and low-dose dexamethasone followed by isatuximab and lenalidomide maintenance therapy in increasing the proportion of patients with MRD negativity as compared to lenalidomide and low-dose dexamethasone followed by lenalidomide maintenance treatment in patients with newly diagnosed multiple myeloma (NDMM).

S15

Phase II Study of Neratinib and Trastuzumab +/- Vinorelbine p.o. in Pre-treated Metastatic HER2-positive Breast Cancer

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The treatment of HER2 positive disease has vastly improved over the last two decades. The introduction of trastuzumab deruxtecan (T-Dxd) and tucatinib in combination with trastuzumab and capecitabine in the treatment of advanced disease has widened the possibilities of treatment even in heavily pretreated patients. Nevertheless, the majority of patients will become eligible for further treatment after progressing on both treatments, and neratinib as a pan-HER tyrosine kinase inhibitor (TKI) is a potentially efficient therapeutic treatment in the later lines. So far there is no evidence on efficacy of neratinib after progression on tucatinib and/or T-Dxd, and NerHer will allow to close this knowledge gap. NerHer has been designed as a phase II clinical

study to evaluate the efficacy of neratinib and trastuzumab +/- oral vinorelbine in pretreated patients with metastatic HER2 positive breast cancer. Pretreatment will include trastuzumab emtansine and/or T-Dxd and/or tucatinib in combination with trastuzumab and capecitabine. Eligible patients will be evaluated by physician whether oral vinorelbine should be included in the combinational treatment. Regardless of the decision, it is a single-arm multicenter study and the evaluation of the primary endpoint will be performed in the whole group. The study was designed in an optimal Simon's two-stage design, and after inclusion of 65 patients in stage I efficacy will be evaluated. Implementation of the escalation dosing of neratinib over the first 3 weeks of therapy may diminish the rate of diarrhea. Cell-free DNA will be longitudinally collected at prespecified time points, and potential resistance mechanisms evaluated.

S16

Zur Rekrutierung offene klinische Studien der Austrian Breast & Colorectal Cancer Study Group

Marija Balic¹

¹Austrian Breast and Colorectal Cancer Study Group (ABCSCG), Wien, Österreich

ABCSCG 45: *A prospective, open, randomized, phase II study of carboplatin/olaparib in the pre-operative treatment of patients with triple-negative primary breast cancer which exhibit the features of positive homologous recombination deficiency (HRD) status.*

Hypothese: geringere *Residual Cancer Burden* (RCB) unter Zugabe von Olaparib im Vergleich zu konventioneller Taxan/Anthracyclin-Chemotherapie.

Studienpopulation: 90 PatientInnen mit frühem TNBC und positivem HRD-Status.

Einbringung: voraussichtlich bis Q3 2023.

ABCSCG 55N/AMBHER: *Description of patients with HER2 positive breast cancer undergoing neoadjuvant treatment and development of a dynamic composite risk score to predict the risk of distant recurrence.*

Hypothese: Entwicklung eines Modells zur Bewertung des Fernrezidiv-Risikos (Distant Recurrence).

Studienpopulation: Ca. 500 PatientInnen mit HER2+ frühem Brustkrebs (nach min. einer Dosis neoadjuvanter dualer HER2-Blockade), retrospektive PatientInnen können max. 5 Jahre nach Beginn der neoadjuvanter Therapie eingeschlossen werden.

Einbringung: voraussichtlich bis Q3 2025.

ABCSCG C08/Exercise II: *Randomized Trial of Endurance Exercise following adjuvant Chemotherapy for Colorectal Cancer.*

Hypothese: bessere Wirksamkeit von Ausdauertraining im Vergleich zu üblicher körperlicher Aktivität, bezogen auf erkrankungsfreies Überleben.

Studienpopulation: 100 PatientInnen mit lokal fortgeschrittenem Kolorektal-Karzinom nach adjuvanter Chemotherapie.

Einbringung: voraussichtlich bis Q3 2024 (*Bestätigung ausstehend*).

Weitere Informationen finden Sie unter <https://www.abscg.org/abscg-studien/>.

S17

Zur Rekrutierung offene klinische Studien mit Beteiligung der Austrian Breast & Colorectal Cancer Study Group

Marija Balic¹

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ABCSCG 49/POLAR: *A phase III open-label, multicenter, randomized trial of adjuvant palbociclib in combination with endocrine therapy versus endocrine therapy alone for patients with hormone receptor positive/HER2-negative resected isolated locoregional recurrence of breast cancer.*

Hypothese: besseres invasiv-krankheitsfreies Überleben (iDFS) unter Zugabe von Palbociclib.

Studienpopulation: 400 PatientInnen mit HR+, HER2-, isoliertem lokoregionären Brustkrebs-Rezidiv.

Einbringung: voraussichtlich bis Q4 2023 (6 Länder).

ABCSCG 50/BRCA-P: *A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, International Phase 3 Study to determine the Preventive Effect of Denosumab on Breast Cancer in Women carrying a BRCA1 Germline Mutation.*

Hypothese: Verringerung des Brustkrebs-Risikos durch präventives Denosumab.

Studienpopulation: 2.918 BRCA1-Keimbahnmutationsträgerinnen.

Einbringung: voraussichtlich bis Q4 2023 (7 Länder).

ABCSCG 56/SASCIA: *Phase III postneoadjuvant study evaluating Sacituzumab Govitecan, an Antibody Drug Conjugate in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment.*

Hypothese: besseres invasiv-krankheitsfreies Überleben (iDFS) bei Behandlung mit Sacituzumab Govitecan.

Studienpopulation: 1.200 PatientInnen mit HER2- Brustkrebs und Resttumor nach NACT.

Einbringung: voraussichtlich bis Q1 2024 (8 Länder).

ABCSCG 57/ALPHABET: *A randomized phase III trial of trastuzumab + Alpelisib +/- fulvestrant versus trastuzumab + chemotherapy in patients with PIK3CA mutated previously treated HER2+ Advanced BrEasT cancer.*

Hypothese: besseres progressions-freies Überleben (PFS) unter Zugabe von Alpelisib.

Studienpopulation: 300 PatientInnen mit PIK3CA-mutiertem HER2+ Brustkrebs im fortgeschrittenen/rezidierten Stadium (mit Trastuzumab und T-DM1 vorbehandelt).

Einbringung: voraussichtlich bis Q1 2025 (6 Länder).

Weitere Informationen finden Sie unter <https://www.abcs.org/abcsstudien/>.



► For latest news from international oncology congresses see: <http://www.springermedizin.at/memo-inoncology>