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Abstracts

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Hämatologie

H01

ZUMA-23: A global, Phase 3, randomized controlled study of axicabtagene ciloleucel versus standard of care as first-line therapy in patients with high-risk large B-cell lymphoma

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Background: Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved to treat pts with relapsed/refractory (R/R) LBCL (Large B-cell lymphoma) after demonstrating significant clinical benefit as 2L (ZUMA-7) and ≥3L (ZUMA-1) therapy. In the Phase 2 ZUMA-12 study in pts with refractory 1L LBCL, axi-cel showed durable responses with an objective response rate of 89 % (complete response rate, 78 %) and an ongoing response rate of 73 % (median follow-up, 15.9 mo). ZUMA-23 is the first Phase 3, randomized controlled study to evaluate CAR T-cell therapy as a 1L treatment for any cancer and will assess axi-cel versus standard of care (SOC) in pts with high-risk LBCL (IPI 4–5).

Methods: ZUMA-23 will enroll ≈300 adult pts with high-risk, histologically confirmed LBCL (2016 WHO classification), including diffuse large B-cell lymphoma (DLBCL), HGBL, and transformed lymphoma. Eligible pts after 1 cycle of R-chemotherapy will be randomized 1:1 to receive axi-cel or continue with SOC. Pts in the axi-cel arm will undergo leukapheresis followed by R-CHOP or DA-EPOCH-R as bridging therapy, followed by lymphodepleting chemotherapy (fludarabine/cyclophosphamide), and a single axi-cel infusion (2×10^6 CAR T cells/kg). Prophylactic corticosteroids may be administered to reduce the incidence and severity of cytokine release syndrome at the investigator's discretion. Pts in the SOC arm will receive 5 additional cycles of R-CHOP or DA-EPOCH-R (investigator's choice).

The primary endpoint is EFS: Key secondary endpoints are OS and PFS. Key exclusion criteria include LBCL of the CNS. ZUMA-23 is open for enrollment (NCT05605899).

H02

Distinct chemokine receptor expression profiles in the development and early progression of follicular lymphoma

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Follicular lymphoma (FL) is one of the most frequent non-Hodgkin's lymphoma and represents a heterogeneous disease. Progression of disease within 24 months (POD24) is the most accurate predictor of worse clinical outcome but specific parameters useful for risk stratification before start of therapy are lacking. The role of chemokine receptors (CRs) in the development of various lymphoma entities has been identified as crucial. Thus, we aimed to comprehensively study CR expression profiles in FL.

We investigated of 17 well-characterized chemokine receptors (CCR1–CCR10, CXCR1–CXCR5, CX3CR1 and XCR1) in a cohort of FL patients with POD24 ($n=14$) and without POD24 ($n=57$) by RQ-PCR. Non-neoplastic tonsils ($n=5$) served as non-malignant controls.

The chemokine receptor expression profile of FL substantially differed from that of tonsils, with higher expression of CCR1, CCR6, CCR7, CXCR5 and CX3CR1 in this lymphoma entity. Furthermore, an at least 2.5-fold higher expression of CCR8, CCR10, CXCR1, CXCR2 and CX3CR1 was detected in grade 3a–b FLs compared to grade 1–2. Interestingly, CCR4 and XCR1 exhibited an at least four fold higher expression in POD24-FLs compared to non-POD24 FLs. Relating the CR expression levels to clinical data of our FL cohort, high levels of CCR3, CCR4 and CCR7 correlated with poor lymphoma-specific survival.

Overall, our results indicate that a distinct chemokine expression profile might be implicated in the development and early progression of FL. Thus, several receptors could serve as clinically useful prognostic markers for risk stratification and/or as potential novel therapeutic targets for lymphoma therapy.

Die mit Sternchen (*) markierten Autoren sind die korrespondierenden Autoren.

H03

Several blood-based parameters at time of diagnosis are associated with the occurrence of an aggressive clinical course of follicular lymphomas

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Follicular lymphoma (FL) is one of the most common lymphoma types in western countries. Typically, this hematologic malignancy is treated with chemo-immunotherapy in an advanced stage. Furthermore, the disease course is known to be very heterogeneous. Recently, it has been described that around 20 % of patients showed progression of disease under therapy within 24 months (POD24), which is associated with an aggressive clinical course. The aim of this project was to retrospectively study clinical, blood derived and histopathological features in a large clinically well-annotated FL patients' cohort from the Division of Hematology, Medical University of Graz.

Therefore, these parameters (four clinical, 16 blood derived and two histological features) were retrospectively collected from time of diagnosis and analysed in a cohort consisting of 269 FL patients treated at our center.

Four clinical, 10 blood derived and one histological parameters were significantly associated with poor overall survival in our FL cohort by performing univariate analyses. Interestingly, POD24 was the best predictor of worse clinical outcome. Comparing POD24 to nonPOD24 FL patients, higher monocytes counts and higher levels of c-reactive protein, lactate dehydrogenase and uric acid as blood derived parameters and a high risk FLIPI score as clinical factor at time of diagnosis were associated significantly with the occurrence of POD24.

In conclusion, we present variables available in clinical routine that were significantly associated with POD24, and which may serve as marker for risk stratification of FLs and could be used to develop novel prediction models.

H04

Daratumumab as a treatment option for acquired hemophilia a in a frail elderly patient

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Introduction and aims: Acquired hemophilia A (AHA) is a rare serious bleeding disorder caused by autoantibodies targeting coagulation factor VIII. The one-year survival rate is approximately 68 %, and even worse if the inhibitor cannot be eliminated. Complications mainly arise from the immunosuppressive therapy. Due to their increased susceptibility to complications it is especially challenging to find suitable treatment for frail elderly patients. We present here a case of AHA in a 83-year-old female patient with multiple health conditions who received subcutaneous daratumumab to treat AHA.

Material and methods: Recombinant coagulation factor VIIa (rFVIIa) was used for initial hemostatic therapy, followed by emicizumab to manage the bleeding tendency. However, the patient's frailty limited the immunosuppressive therapy, leading to the decision to treat the AHA off-label with daratumumab on an outpatient basis.

Results: The patient presented with spontaneous subcutaneous bleeds. Bleeding was controlled with rFVIIa and hemostasis was maintained with emicizumab. However, the inhibitor titer rose to 2653 Bethesda Units (BU)/ml after starting treatment with prednisolone and rituximab. As intensive outpatient immunosuppressive therapy was not feasible, rituximab and additional cyclophosphamide were discontinued. Instead, the patient received daratumumab weekly initially, followed by every 2nd week. Prednisolone was tapered off. After 23 weeks the inhibitor titer decreased to 3 BU/ml. No infusion-related reaction and no infection was observed.

Conclusion: The treatment with daratumumab and emicizumab was well-tolerated and effective for this elderly patient with AHA. However, clinical studies are needed to establish safe and effective treatment regimens using daratumumab for vulnerable AHA patients.

H05

NUP98::KDM5A directly regulates a core set of target genes to drive acute myeloid leukemia

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Introduction and aims: Oncogenic NUP98 fusion proteins are recurrently found in AML and are associated with poor prognosis. A better understanding of how NUP98 fusions alter gene expression programs is required for the development of tailored treatments. We aimed to decipher the epigenetic and transcriptional landscape of NUP98::KDM5A-driven AML to identify immediate critical effectors of the NUP98::KDM5A fusion protein.

Methods: We developed a murine leukemia model for dTAG-mediated degradation of the NUP98::KDM5A protein. We investigated global and direct effects of NUP98::KDM5A degradation on epigenetic and transcriptional regulation by CUT&Tag and nascent RNA-seq. In parallel, we conducted a genome-scale CRISPR/Cas9 loss-of-function screen in a NUP98::KDM5A-driven AML cell line to unravel functional genetic dependen-

cies. Primary patient samples were used to validate potential therapeutic targets.

Results: CUT&Tag revealed that NUP98::KDM5A directly mediates global changes in H3K27ac patterns. Our nascent RNA-seq analysis identified 45 immediate NUP98::KDM5A target genes. Analysis of a genome-wide CRISPR/Cas9 screen revealed that 12 were essential factors for leukemia cell growth. This subset of 12 direct essential NUP98::KDM5A target genes was characterized by strong NUP98::KDM5A binding and high levels of H3K27ac and H3K4me3. Among these, CDK12 represents a promising candidate revealing a dependency of NUP98::KDM5A-driven AML on the DNA-damage response, as murine and primary human NUP98::KDM5A AML cells were highly sensitive to genetic and pharmacological CDK12 perturbation.

Conclusion: We identified epigenetic patterns and direct transcriptional target genes of NUP98::KDM5A that are functionally essential in AML. Among these, we validated CDK12 as a promising therapeutic target in NUP98::KDM5A-driven AML cells.

H06

Ras mutations as potential therapeutic targets in Chronic Myelomonocytic Leukemia (CMML)

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Introduction and aims: CMML is a myeloid neoplasm characterized by sustained peripheral blood monocytosis ($>1 \times 10^9$/L). Twenty to 30 % of cases present with mutations in Ras oncogenes. Ras mutation-specific inhibitors, shRNAs and neoantigen-reactive Tcells are novel therapeutic options mainly explored with advanced solid tumors. Our aim is to apply these paradigms to Ras-mutated leukemia to investigate new treatment options.

Materials and methods: Bone marrow aspirates and peripheral blood samples were obtained with informed consent from four CMML patients. Mononuclear cells were isolated by Ficoll centrifugation and cryo-preserved or cultivated in-vitro. Immunophenotyping was performed by flow cytometry, and RNA and genomic DNA were isolated from PBMCs and MACS-purified CD14+ monocytes. Ras mutations were verified by PCR and Sanger sequencing. CFU assays and in-vitro cultures were performed using BM-derived CD34+ cells.

Results: NRasG12D and KRasG12D mutations were detected and verified in 2/4 CMML samples. Other CMML-typical mutations (eg TET2, SRFS2, ASXL1) could not be detected in the Ras mutants by panel sequencing. CFU assays showed strong skewing to GM-CFU colonies with strong reduction of erythroid colonies in samples with multiple CMML-typical mutations, but not on the putative „Ras-only" samples. Effects of Ras-targeted treatments on in-vitro cultures are compared between different patient samples.

Conclusions: We identified CMML patients where the neoplasm is driven by the KRas/NRas hotspot mutation G12D, enabling us to study the effect of novel, mutation-specific Ras-targeted approaches. Cultivated Ras-mutated cells from CMML patients display a flattened morphology reminiscent of senescent cells, but also long-term proliferation in-vitro, enabling testing novel Ras-targeted therapeutics.

H07

Next-generation sequencing in routine diagnostic workup of myelodysplastic syndromes: data from a tertiary care center

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Background: Next-generation sequencing (NGS) has enriched our knowledge about the molecular pathogenesis of myelodysplastic syndromes (MDS) and is nowadays part of routine workflows in MDS diagnosis. Most data about NGS feasibility and results are derived from controlled clinical intervention trials (CCIT).

Methods: This study retrospectively analyzed clinical and molecular data of 145 MDS patients treated between 2013 and 2022 at Medical University of Graz. NGS was locally available for the clinical routine during this time.

Results: NGS was ordered by the treating physician in 123/145 (85 %) patients and succeeded in all cases. Median processing time decreased from 18 days in 2013 to 11 days in 2022. 111/123 (90 %) of patients exhibited at least one mutation (median 2, range 1–9). The genes most frequently affected were TP53 (39/123, 32 %), TET2 (30/123, 24 %), ASXL1 (24/123, 18 %), DNMT3A (19/123, 15 %), SRSF2 (14/123, 11 %), and RUNX1 (14/123, 11 %). When focusing on IPSS-R risk stratification, 60/138 classifiable patients (43 %) were categorized as low-risk (≤ 3.5 points) and 78/138 (57 %) as high-risk (>3.5 points). High-risk patients had enrichment of mutations affecting TP53 ($p < 0.001$) and CEBPA ($p = 0.041$), whereas TET2 aberrations were more frequent in low-risk disease ($p = 0.002$). Older patients (>70) had an increased frequency of STAG2 mutations ($p = 0.046$). The number of mutations per patient and SF3B1 aberrations did not differ between age and risk groups.

Conclusion: This study demonstrates the feasibility of NGS profiling in the routine diagnostic work-up of MDS. Moreover, it reveals the molecular landscape of MDS in a real-world setting, thereby complementing CCIT data.

H08

Genome engineered TET2 loss-of-function mutations increase stem cell self-renewal in human hematopoietic stem and progenitor cells

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Introduction and aim: Ten–eleven translocation 2 (TET2) is an epigenetic regulator catalyzing DNA demethylation. Genomic studies have identified somatic TET2 loss-of-function (LOF) mutations across hematologic malignancies. Precise DNA Base editing (BE) is a new CRISPR-based application allowing for modification of single nucleotides without inducing double strand breaks (DDB) and DDB-induced apoptosis of fragile hematopoietic stem and progenitor cells (HSPCs). BE can be used to introduce in-frame STOP codons via C→T transitions, thereby leading to gene KO and mimicking (LOF) mutations. Here, we employ BE to mimic TET2 LOF and investigate its effect on HSPC function and engraftment into immune-compromised mice.

Material and methods: BE mRNA with sgRNAs were used to precisely introduce C→T transitions for the formation of premature in-frame STOP codons in TET2. Functional studies investigating differentiation and colony-forming potential were performed and engraftment of engineered cells into NSG mice was analyzed. Competitive advantage of TET2 LOF HSPCs was assessed over time in transplanted mice.

Results: TET2 LOF could be successfully engineered in HSPC. Mutated cells showed increased colony forming and self-renewal potential. In vivo experiments revealed TET2 mutations induced myeloid skewing and selective outgrowth of mutant over wild-type cells, resulting in shortened overall survival of transplanted mice.

Conclusion: CRISPR/Cas9-BE can be used to mimic LOF mutations such as TET2 in primary HSPCs. This low toxicity approach has negligible effects HSPC viability and should become the preferred method for leukemia disease modeling.

H09

GPR56 and C3AR1 expression patterns allow identification of leukemic stem cell activity in NPM1-mutated acute myeloid leukemia

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Introduction and aims: Although treatment modalities have improved over the last decade, prognosis in patients with acute myeloid leukemia (AML) is still poor due to high rates of relapse. Trace amounts of chemoresistant leukemic stem cells (LSCs) persisting beyond complete remission are responsible for difficult-to-treat, relapsed disease. Therefore, successful targeting of this LSC population is crucial to improve patient outcomes. In this study, we aimed for identification of putative LSC markers with a specific focus on NPM1-mutated AML.

Material and methods: Expression of surface markers was determined by flow cytometry in 104 diagnostic AML samples among them 39 with NPM1 mutation. Expression of genes comprising the LSC17 score was determined by RT-qPCR. Clinical data of patients were then correlated with surface protein expression and molecular data.

Results: We identified high expression of the complement C3a receptor 1 (C3AR1) in AML patients with NPM1 mutation. Mutual flow cytometry analysis with adhesion G-protein coupled receptor 56 (GPR56) allowed identification of distinct subpopulation patterns among the majority of NPM1-mutated AML samples. Intriguingly, in contrast to $GPR56^{neg}C3AR1^{hi}$ leukemic cells, the $GPR56^{pos}C3AR1^{dim}$ population displayed high expression of LSC17 genes, which are known to correlate with LSC activity in AML. Accordingly, NPM1-mutated AML patients with a higher fraction of $GPR56^{pos}C3AR1^{dim}$ than $GPR56^{neg}C3AR^{hi}$ cells showed worse overall survival after intensive chemotherapy.

Conclusion: These results indicate that LSC activity in NPM1-mutated AML may be found predominantly within the $GPR56^{+}C3AR1^{dim}$ subpopulation. Furthermore, distinct expression patterns of these two markers could be of prognostic significance in this AML subgroup.

H10

Derivatization of Caffeic Acid Phenethyl Ester identifies a potential new therapeutic molecule for aggressive T-cell lymphoma

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Introduction and aims: Anaplastic Large Cell Lymphoma (ALCL) is an aggressive CD30+ non-Hodgkin T-cell lymphoma, and about 30 % of patients relapse. The natural compound found in bee glue Caffeic Acid Phenethyl Ester (CAPE) was shown to have potential anti-cancer activity in preclinical studies. Our aim was to test CAPE efficacy in ALCL and to improve its pharmacological activity via chemical derivatization.

Materials and methods: CAPE and synthetic derivatives were tested for their effect on ALCL cell viability. Flow cytometry, cell cycle analysis, Western blot and RNA-Seq were used to elucidate the mechanism of cell death induction. Click chemistry allowed intracellular localization by spinning-disc fluorescence microscopy and identification of interacting proteins using mass-spectroscopy.

Results: Chemical derivatization of CAPE led to the identification of CM14, with considerably improved activity and systemic stability. Moreover, CM14 was able to overcome acquired ALK inhibitor resistance. Cell cycle analysis and RNA-seq after coincubation of ALCL cells with CM14 demonstrated arrest in the G2/M phase and altered expression of mitosis specific genes. Interestingly, fluorophore-labeled CM14 accumulated on a single spot per cell adjacent to the nucleus. Using ALCL cell lysates we pulled down CM14 interacting proteins using a biotin-labeled CM14 version. TUBGCP2, a centrosomal protein, was more than 20-fold enriched, suggesting CM14's interference in centrosome function.

Conclusions: We identified a synthetic derivative of CAPE which reduces ALCL viability and overcomes ALK inhibitor resistance inducing apoptosis via impediment of the cell division machinery. These results may open novel treatment avenues in this and other aggressive lymphoma types.

H11

Low NR4A2 is associated with poor clinical outcomes as well as an immune cell depleted phenotype of DLBCL

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Introduction and aims: Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid malignancy with increasing incidence and poor clinical outcome. We have shown that two members of the NR4A family, namely NR4A1 and NR4A3, have tumor suppressive function in DLBCL. The third member of the NR4A family, NR4A2, has not been investigated in DLBCL so far. Therefore, we aim to comprehensively study this member.

Material und methods: We used the gene expression dataset of 321 newly diagnosed, therapy-naive, de novo DLBCL patients from the research group of Prof. A. Novak, comprehensively investigated the NR4A2 expression and determined its association with clinical data.

Results: Low NR4A2 expression was associated with poor overall and event-free survival in the investigated DLBCL cohort. Remarkably, low NR4A2 was strongly associated with early progression of disease (EFS24). Differential gene expression analysis identified a deregulation of 779 genes, which were mainly associated with immune regulatory processes. When NR4A2 expression was comparted to new DLBCL classifiers (LME-, HRMN-, LymphGen- and Ecotype-classification), low NR4A2 was associated with the LME depleted phenotype. Furthermore, using the Cibersort-X algorithm, lower content of CD4-, CD8- and γT-cells, macrophages, follicular T helper cells, eosinophils, and dendritic cells were predicted in the NR4A2 low expressing subgroup. Finally, the main findings were confirmed in a second independent DLBCL cohort.

Conclusion: Our data suggest that NR4A2 possesses tumor suppressive function that may be mediated by its tumor microenvironment shaping properties in DLBCL. Thus, it might serve as a target for novel therapeutic approaches.

H12

TYK2 inhibition causes apoptosis but also a marked anti-tumor immune response in Anaplastic Large Cell Lymphoma

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Introduction and aims: Anaplastic Large Cell Lymphoma (ALCL) is an aggressive T-cell lymphoma. Half of the patients carry the t(2;5) translocation, resulting in the tumor-driving NPM-ALK gene product. Less is known about the driving factors in ALK negative patients. We demonstrated previously that TYK2 is a dependency factor in ALCL. On the other hand, TYK2 deletion has been shown to lead to reduced anti-tumor immune response in mice, questioning the benefit of systemic TYK2 inhibition. Thereby, elucidating the prevailing mechanism in ALCL is highly warranted.

Methods: To modify TYK activity in ALCL cells we created an inducible TYK2 shRNA knock-down system and used the allosteric inhibitor Deucravacitinib. Cocultures and transgenic reporter cells were employed to monitor effects of TYK2 ablation on both ALCL cell-induced macrophage polarization and PD-L1 dependent anti-tumor immune response.

Results: Deucravacitinib led to reduction of viability in ALCL cells. In ALK+ cell lines PD-L1 levels increased after TYK2 inhibition, while in ALK– cells it was decreased, resulting in enhanced T-cell receptor activation as measured by a GFP-reporter cell line. In coculture systems, Deucravacitinib completely blocked the IL-10-dependent ALCL-induced polarization of macrophages to a CD163+ pro-tumorigenic phenotype.

Conclusions: We show here that Deucravacitinib affects ALCL viability cells while reducing PD-L1 expression in ALCL, ALK– cells, resulting in a concomitant activation of antitumor immune response. Moreover, Deucravacitinib could abrogate ALCL-induced polarization of pro-tumorigenic macrophages. To sum up, TYK2 inhibition by Deucravacitinib couples apoptosis induction in ALCL with stimulation of antitumor immune cell function.

H13

Donor lymphocyte infusion as prophylactic, preemptive or salvage therapy in patients with acute myeloid leukemia or myelodysplastic syndrome after allogeneic hematopoietic stem-cell-transplantation: a single-institution experience

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Introduction and aim: Donor lymphocyte infusions (DLI) are used as immunotherapeutic intervention to restore graft-versus-leukemia effect after allogeneic hematopoietic stem cell transplantation (allo-HSCT). DLI can be used prophylactically in patients with high relapse risk, preemptively to convert mixed into complete chimerism or eradicate measurable residual disease (MRD), or therapeutically as salvage therapy. The aim of our study was to analyze DLI administrations in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) at our institution regarding response rates and side effects.

Material and methods: In this single-center study we retrospectively analyzed 14 patients with AML and 4 patients with MDS who received DLI after allo-HSCT from April 2016 to March 2023. DLI were applied prophylactically ($n=3$), preemptively ($n=10$) or therapeutically ($n=5$) with or without azacitidine. Median follow-up was 9 months.

Results: Estimated overall survival after two years was 72 % in the total cohort with all three prophylactically treated patients remaining in complete remission. Two patients experienced early death within 100 days of therapy and incidence of acute and chronic graft-versus-host disease (GvHD) post DLI was 22 % and 22 %, respectively. Nine out of 15 patients with preemptive ($n=7$) or therapeutic treatment ($n=2$) were still alive at last follow-up with 6 of them in complete remission.

Conclusion: Despite the limitations of the small number of patients and heterogeneity of their clinical characteristics, our study provides further evidence that DLI with or without azacitidine is a safe and promising therapeutic option in this difficult-to-treat patient population.

H14

Mutant STAT5B triggers NK-cell neoplasms

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Natural Killer (NK) cell leukemia are relatively rare but aggressive diseases with poor prognosis and limited treatment options, hence representing an unmet clinical need. They frequently feature gain-of-function (GOF) mutations of the JAK/STAT pathway. STAT5B^{N642H} is the most prevalent STAT5 mutation and has been detected in cases of NK-cell leukemia but its exact role in pathogenesis is unknown. Human NK cells transduced with STAT5B^{N642H} acquired cytokine-independency and the ability to induce leukemia in mice. To test whether STAT5B^{N642H} alone is an oncogenic driver, we generated a mouse model where STAT5B^{N642H} is restricted to the NK-cell lineage (N642H$^{NK/NK}$ mice). N642H$^{NK/NK}$ mice displayed an indolent chronic lymphoproliferative disorder of NK cells (CLPD-NK) that progresses to an aggressive leukemia with age.The analysis of samples derived from NK-cell leukemia patients revealed a distinctive transcriptional signature driven by mutant STAT5B which was consistent with the mouse NK cells carrying the STAT5B mutation.

We have generated the first STAT5B^{N642H}-driven pre-clinical mouse model that displays an indolent CLPD-NK progressing to aggressive NK-cell leukemia. This novel in vivo tool will enable us to explore the transition from an indolent to an aggressive disease and will thus permit the study of prevention and treatment options for NK-cell malignancies.

H15

Next-generation sequencing in routine diagnostic workup of acute myeloid leukemia: data from a tertiary care center

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Introduction: Next-generation sequencing (NGS) has recently entered routine acute myeloid leukemia (AML) diagnostics. It is paramount for AML risk stratification and identification of molecular therapeutic targets. Most data about NGS feasibility and results are derived from controlled clinical intervention trials (CCIT), lacking real-world validations.

Methods: This study retrospectively analyzed 284 AML patients treated between 2013 and 2023 at Medical University of Graz. NGS was locally available for the clinical routine during this time.

Results: NGS was ordered by the treating physician in 267/284 (94 %) patients, yielding evaluable results in all cases. It was performed from bone marrow aspirates or biopsies; we provide evidence that these approaches are comparable. The median time from bone marrow sampling until finished NGS results was 16 days (decreasing from 22 to 10 days from 2013/14 to 2022). ELN-2022 risk stratification was possible in 269/284 (95 %) patients, with NGS enabling categorization in ten cases where conventional karyotyping failed. Molecularly targeted therapy was added based on NGS results in 13 cases. Considering the genomic landscape, 257/267 (96 %) cases harbored mutation(s), most frequently in TET2, FLT3, DNMT3A, and NPM1. Older patients ≥70 years had a higher frequency of mutations in IDH2 ($p=0.011$), SRSF2 ($p=0.001$), and TET2 ($p=0.044$), whereas there was a trend for increased FLT3 aberrations in younger patients ($p=0.052$).

Conclusion: This study demonstrates the feasibility of NGS profiling in the routine diagnostic work-up of AML. Moreover, it reveals the molecular landscape of AML in a real-world setting and serves as a valuable tool for targeted treatment decisions.

H16

Loss of Nr4a1 results in bone marrow infiltration and deregulation of homing factors in the EμMyc lymphoma model

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Introduction and aims: Aggressive lymphomas, particularly diffuse large B cell lymphoma (DLBCL), exhibit poor survival rates. The tumor suppressive function of NR4A1 has been shown in human DLBCL as well as in murine lymphoma models. Interestingly, loss of Nr4a1 accelerates lymphoma development and increases tumor cell infiltration in the bone marrow and spleen in the EμMyc model. This study aims to comprehensively understand its impact on lymphoma dissemination.

Material and methods: We transplanted EμMyc Nr4a1−/− and EμMyc Nr4a1+/+ lymphoma cells into immunocompetent mice and determined lymphoma cell infiltration of the kidney, liver, brain, lung, spleen, thymus, and lymph nodes by histological examination. Furthermore, we determined the expression levels of chemokine receptors and integrins in EμMyc Nr4a1−/− and EμMyc Nr4a1+/+ lymphomas by RQ-PCR.

Results: Immunocompetent mice transplanted with EμMyc Nr4a1−/− lymphoma cells exhibited a significantly higher lymphoma cell infiltration rate in the bone marrow (62.5 % vs. 42 %, $p=0.045$) and a lower infiltration rate in the kidney (11.9 % vs 30.3 %, $p=0.002$). In contrast, no differences were observed in any other investigated organ. In the primary lymphoma, higher expression levels were observed in the chemokine receptor CXCR2 (5.5-fold. $p=0.04$), the integrin ITGA4 (3.43-fold, $p=0.006$), and the Cd44 Exon 5/16 transcript variant (6.48-fold, $p=0.05$) in EμMyc Nr4a1−/− lymphomas. Besides, there was even a decrease of chemokine receptor CXCR4 (0.62-fold, $p=0.05$) in EμMyc Nr4a1−/− lymphomas too.

Conclusion: Our data suggest that Nr4a1 may be involved in the process of bone marrow infiltration by regulating a specific pattern of chemokine receptors and integrins.

H17

Loss of Nr4a1 increases immune checkpoint expression, impairs T cell-mediated killing and maintains a suppressive tumor microenvironment in aggressive lymphomas

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Introduction and aim: Low NR4A1 expression in aggressive lymphomas correlates with poor cancer-specific survival, while its overexpression suppresses lymphoma cell growth in vivo, suggesting tumour suppressive properties. This study aims to investigate in detail the impact of Nr4a1 loss on lymphomagenesis.

Material and methods: Therefore, EμMyc Nr4a1+/+, EμMyc Nr4a1+/– and EμMyc Nr4a1–/– mice cohort was generated and monitored until disease onset. Lymphoma cells were transplanted into immunocompetent mice and immune cell populations were measured by flow cytometry. Finally, we performed co-culture cytotoxicity assays using OVA-targeting CD8+ T cells and OVA-peptide pulsed EμMyc Nr4a1+/+ and EμMyc Nr4a1–/– lymphoma cells and measured T cell-mediated lysis.

Results: Nr4a1 loss accelerated lymphomagenesis in vivo, accompanied by increased expression of Pd1-Pdl1-Pdl2 and Ctla4-Cd80-Cd86. Transplantation of Nr4a1-deficient lymphoma cells into immunocompetent mice resulted in rapid lymphomagenesis, reduced survival and increased immune checkpoint expression. Furthermore, CD3+ T cells content were decreased, while CD4+ and CD8+ effector T cells were increased, concomitant with a reduction in naive T cells, and an increased content of Tregs. Interestingly, a higher percentage of CD3+ T cells co-expressed multiple immune checkpoints, besides PD-1 in the Nr4a1–/– setting. We also observed reduced lysis of the EμMyc Nr4a1–/– lymphoma cell killing in our cytotoxicity assays. Low NR4A1 expression in our human diffuse large B-cell lymphoma (DLBCL) cohort aligns with elevated immune checkpoint components.

Conclusion: Our findings suggest that NR4A1 plays a central role in immune evasion in aggressive lymphomas by regulating immunoregulatory genes, creating an immunosuppressive microenvironment and increasing the expression of immunosuppressive molecules.

H18

Role of next-generation sequencing of non-driver mutations in routine diagnostic workup of primary myelofibrosis: a single center experience

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Background: Aside from the classical driver mutations in the JAK2, CALR or MPL genes, molecular alterations in other genes recurrently mutated in various myeloid neoplasms (MNs) can also be found in primary myelofibrosis (PMF). Although their pathophysiological role in PMF is less defined, some aberrations such as mutations in high molecular risk (HMR) genes, like ASXL1, EZH2, IDH1/2, SRSF2 and TP53 have been included in recent prognostic risk scores. Therefore, screening for such mutations by next generation sequencing (NGS) is increasingly recommended by current guidelines.

Methods: This study retrospectively analyzed clinical and NGS-derived molecular data of 120 patients with PMF diagnosed between 2015 and 2022 at the Medical University of Graz.

Results: Driver mutations in JAK2, CALR or MPL gene were identified in 66 (57 %), 33 (27 %) and 14 patients (12 %), respectively. Seven patients (6 %) were triple-negative. Full NGS data was available in 43 patients (36 %) with a median of one additional mutation identified per patient (range: 0–5). Twelve patients displayed at least one HMR mutation. NGS was performed predominantly in younger patients (median age 60 versus 68 years; $p < 0.05$), patients with overt myelofibrosis (56 % vs. 30 %; $p < 0.05$) and all patients undergoing allogeneic stem cell transplantation. Overall survival at 5 years was similar irrespective of whether NGS was performed or not (81 % vs. 79 %).

Conclusion: This study demonstrates the feasibility of NGS profiling in routine diagnostic work-up of PMF. In accordance to recent guidelines NGS was predominantly performed in younger patients and patients with overt PMF to support treatment decisions.

H19

Thrombosis rates in patients with cancer receiving immune checkpoint inhibitors: results from a prospective cohort study

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Cancer is associated with an increased venous thromboembolism (VTE) risk, which is partly attributable to systemic cancer therapies. The impact of immune checkpoint inhibitors (ICI) on VTE risk is still debated.

We assessed VTE risk in a single-center prospective cohort study including patients with cancer initiating systemic anti-cancer therapies. Competing risk analyses were performed.

In total, 880 patients (median age: 62 years [interquartile range, IQR:53–70], 47 % women) were included, 459 (52.2 %) with newly diagnosed and 421 (47.8 %) with recurrent/progressive disease. Of 831 patients with solid tumors, 551 (62.6 %) had metastatic disease at study inclusion. During a median follow-up time of 15.8 months (IQR:9.3–27.7), 68 (7.7 %) patients were diagnosed with VTE; 43 of 427 (10.1 %) receiving chemotherapy, 11 of 147 (7.5 %) receiving chemotherapy and ICI therapy, 6 of 138 (4.3 %) receiving ICI therapy, 7 of 109 (6.4 %) receiving targeted and chemotherapy, 1 of 44 (2.3 %) receiving targeted therapy, and none of 15 (0 %) receiving targeted and ICI therapy. The 6-month cumulative VTE incidences were 7.2 % (95 % confidence interval [CI]: 4.6–9.8) in patients with chemotherapy, 5.8 % (95 %CI: 1.8–9.6) with ICI and chemotherapy, 2.3 % (95 %CI: 0–4.8) with ICI, 5.2 % (95 %CI: 0.8–9.6) with targeted and chemotherapy, and 2.6 % (95 %CI: 0.0–7.7) with targeted therapy.

In our single-center prospective cohort, patients with cancer receiving systemic anti-cancer therapies had a substantial VTE risk. Patients with cancer receiving chemotherapy had the highest cumulative incidence, while the VTE incidence was lower in those treated with ICI therapy. In the future, further analyses considering other VTE risk factors are needed.

H20

Impact of early Cyclosporine A levels on acute GVHD in allogeneic hematopoietic stem cell transplantation: a retrospective analysis

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This study aimed to examine how trough levels of Cyclosporine A (CsA) across the first three weeks after allogeneic hematopoietic stem cell transplantation (HSCT) influence major outcomes.

Retrospectively, 307 matched related ($n=145$) and unrelated donor HSCT between January 2000 and April 2023 were examined. Consecutive peripheral blood stem cell (PBSC) and bone marrow (BM) transplantations for hematological diseases, except uncontrolled malignancies, were included. Anti-T-Lymhotyte Globulin (ATLG) was used in 200/307 HSCT (71.2 %). The initial three weeks‘ mean CsA trough levels were analyzed in landmark and multi-state models, using a cut-off of 200 ng/ml.

CsA levels above 200 ng/ml were associated with a reduced risk of acute GVHD grade 3–4 at the first-week landmark (SHR 0.59, $p=0.03$) and the second-week landmark (SHR 0.48, $p=0.004$), whereas there was no significant impact at the third-week landmark (SHR 0.93, $p=0.83$). This was supported by the multi-state model, in which week 1–2, but not week 3 CsA levels above 200 ng/ml were associated with a reduced aGVHD3-4 risk. Relapse incidence was not significantly affected by CsA levels. A significant overall survival benefit of a first-week CsA trough level above 200 ng/ml was revealed only after unrelated (sHR 0.51, $p=0.004$), but not matched sibling transplants.

Our findings emphasise the continuing importance of achieving sufficient CsA levels from the first week onward, even in an era of broad use of ATLG in related and unrelated HSCT.

H21

Genes associated with immune-cell function are deregulated in the pathogenesis of CLL

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Introduction: Chronic lymphocytic leukemia (CLL) is considered being a B-cell non-Hodgkin's lymphoma with leukemic progress and is known as the most common leukemia in the western world. Each year, 0.5–1 % of the CLL-patients develop Richter transformation (RT). Dysregulation of the immune system has been shown to play a crucial role in the pathogenesis of CLL. However, knowledge about this is limited. Thus, we aimed to comprehensively study the expression of genes associated with immune cell function in our CLL- and Richter- cohort.

Material and methods: We investigated a total of 31 genes (19 immune-checkpoints components, 9 immune-cell markers, 3 NR4As) in CLL- ($n=53$) and RT-lymph nodes ($n=14$) by RQ-PCR. Non-neoplastic tonsils ($n=3$) served as non-malignant controls.

Results: Comparing tonsils with CLL- and RT-lymph node samples we observed a lower PD-L2-expression in CLL and a lower GALECTIN9-expression in RT.

Furthermore, we detected a deregulation of six out of 19 immune-checkpoint components (CD86, HVEM, PTDSS1, PTDSS2 were higher and PDL2, CEACAM1 were lower expressed) and three out of nine immune-cell markers (IFNG, EOMES, GZMB were higher expressed) in CLL-lymph nodes of treated compared to untreated patients.

Remarkably, six out of 19 immune-checkpoint components (CD113, CD86, CEACAM1 and LSECTIN were higher and CD160, VISTA were lower expressed) were differentially expressed in RT- compared to CLL-lymph nodes.

Conclusion: Our data indicate that the immune system, especially the immune-checkpoint components, might be crucial for the development and the progression of CLL. Furthermore, it seems that current therapeutic interventions might significantly impact on immune-cell components.

H22

Simultaneous auto-transplant and CD19 CAR T-cell 2L therapy followed by a CD20 × CD3 bispecific antibody for a patient with refractory Burkitt lymphoma

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Introduction and aims: No standardized treatment regimen exists for relapsed/refractory Burkitt lymphoma (BL). We present a case of a 63y old female with BL with primary refractoriness to the intensive GMALL-chemotherapy protocol. The second line therapy consisted of a debulking therapy with Polatuzumab vedotin (Pola)-ICE followed by a sequential BEAM (BCNU, etoposide, AraC and melphalan)-based high-dose therapy plus autologous stem-cell-transplantation (autoSCT) and CD19-CAR T-cell therapy. The third line palliative therapy consisted of the CD20xCD3 bispecific antibody Glofitamab (Glo) with Obinutuzumab pretreatment plus Pola, which led to temporary disease stabilization for 2.5 months, until the patient relapsed again and died shortly after.

Materials and methods: Patient-derived peripheral blood mononuclear cells (PBMC, day+50) for functional T-cell analyses and CAR T-cell quantification by FACs and qPCR. Healthy-donor PBMC and human DLBCL cell lines.

Results: This combination and sequence of three distinct cell-based therapies was feasible and reasonably well tolerated. No neurological cytotoxicity, but a grade 2 cytokine release syndrome occurred after autoSCT/CAR T-cell application, and fully resolved upon tocilizumab and dexamethasone. The CD19-CAR T-cells peaked at day +17 after CAR-T infusion, followed by a decline into non-detectability on day+50 with a second proliferation upon treatment with Glo. In in vitro-experiments coculturing PBMC of the patient or of a healthy donor with 4 different DLBCL cell lines the patients T-cell-mediated killing was only unleashed, in combination of Glo and Atezolizumab, but not with each agent alone.

Conclusion: Triple-cell based therapy is a feasible treatment option in aggressive B-NHL. Potentially exhausted, DLBCL-primed T-cells can be reactivated by Glo in combination with immune checkpoint inhibition.

H23

Zurückgezogen

H24

Cell death in aggressive lymphomas in vitro and ex vivo caused by brusatol which synergizes with venetoclax

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Aggressive lymphomas represent the most common lymphoid malignancies in adults. Despite available therapies, one-third of patients experience treatment failure. The development of new therapies is therefore urgently needed. The aim of this study was to investigate the potential of brusatol, which has anti-tumour activity for the treatment of aggressive lymphomas.

We treated ten lymphoma cell lines with increasing concentrations of brusatol to determine IC50 values. Apoptosis induction and cell cycle distribution were assessed over 48 h of brusatol treatment, together with collecting samples for Western blot. Nascent protein synthesis was evaluated by click-chemistry after brusatol treatment (4 h). Co-treatment of brusatol with seven different inhibitors, including venetoclax, was performed and apoptosis induction was measured (24 h). Finally, potential of brusatol was investigated in lymphoma patient samples by immunofluorescence, automated microscopy.

Brusatol caused cell death in a concentration-dependent manner in patient samples and all tested cell lines which can be grouped into more and less brusatol-sensitive ones. In more sensitive cell lines, reduced protein levels of Bcl-2, Bcl-XL, Mcl-1, p53 and Myc were observed upon treatment. Interestingly, cell lines with higher Myc levels were more sensitive to brusatol. Click chemistry assay showed protein translation inhibition by brusatol. Moreover, the combination of brusatol and venetoclax synergistically increased lymphoma cell killing.

Our data indicate that brusatol induces cell death in aggressive lymphomas ex vivo. Additionally, the combination of brusatol with venetoclax results in enhanced induction of apoptosis. Thus, our study suggests that brusatol represents an interesting agent for the development of novel anti-lymphoma therapies.

H25

Stellar response, but fatal neurologic complication following teclistamab in a patient with extramedullary myeloma and CNS involvement

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Introduction: Bispecific antibodies have improved the treatment options for relapsed/refractory multiple myeloma (MM), but experience in patients with CNS involvement is limited. Here we report the case of a patient with CNS disease who showed fast response, but severe toxicity following teclistamab.

Case report: In July 2023, a 64 year-old female MM patient progressed on a carfilzomib-based third-line protocol. She had previously received local and whole-brain radiation as well as a daratumumab-containing regimen for treatment of CNS relapse in 2021. She now had triple-class refractory MM and presented with double vision and unsteady gait. Diagnostic workup revealed new intracranial lesions, clonal plasma cells in the CSF as well as hepatic and intramuscular manifestations.

During the first cycle of teclistamab she experienced CRS grade 1 as well as ICANS grade 3 that responded quickly to corticosteroids. CNS imaging showed complete resolution of intracranial lesions and paraprotein levels decreased rapidly.

Upon rechallenge, the patient developed a sepsis due to pseudomonas aeruginosa bacteremia and decreased levels of consciousness even after restoration of hemodynamic stability. Corticosteroids were started, without improvement of neurologic function. Cerebral edema was excluded, but electroencephalography revealed a non-convulsive status epilepticus, confirming recurrent grade 4 ICANS. No clinical improvement was seen despite treatment with anticonvulsants and high-dose methylprednisone as well as anakinra for concurrent macrophage-activation syndrome. The patient died 69 days after start of teclistamab.

Conclusion: Treatment with bispecific antibodies may lead to fulminant neurologic complication in MM with pre-existing CNS involvement. More detailed data and autopsy findings will be presented.

H26

Long lasting response to Belantamab mafodotin and successful rechallenge in a patient with high-risk multiple myeloma

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Introduction: The phase 2 DREAMM-2 study investigating the B-cell maturation antigen (BCMA) targeting antibody drug conjugate Belantamab mafodotin (Belamaf) has shown promising results in heavily pretreated relapsed/refractory multiple myeloma (rrMM) patients with an overall response rate of 31 %. However, the randomized phase 3 DREAMM-3 trial failed to show superiority in progression-free survival for Belamaf monotherapy versus pomaliomide and dexamethasone. As a result, the producing company has withdrawn the US marketing authorization for the compound while it is still available in Europe.

Case report: In June 2021 a 78 year-old MM patient with high-risk cytogenetics progressed on fifth-line treatment with elotuzumab, pomalidomide and dexamethason. Belamaf therapy was initiated for triple-class refractory disease. After two infusions at a dose of 2.5 mg/kg the patient developed grade 3 keratopathy and treatment was halted. A partial response (maximum reduction of serum M-protein of 80 %) was documented and ongoing for 12 months without further treatment. The keratopathy resolved within 4 months. Upon serologic relapse in July 2022, the patient was rechallenged with 2 infusions of dose reduced Belamaf (1.92 mg/kg) and a second partial response was achieved for another 12 months. Because of recurrent keratopathy treatment was once again interrupted. Massive clinical progression occurred in July 2023 that was unresponsive to Belamaf and subsequent salvage treatment. The patient died one month later. In total, treatment with Belamaf resulted in 24 months of progression-free survival.

Conclusion: Belantamab mafodotin can be considered a potent therapeutic option in rrMM patients but predictive biomarkers for patient selection are missing.

H27

Unraveling STAT1's role in Anaplastic Large Cell Lymphoma

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Introduction and aim: Anaplastic large cell lymphoma is an aggressive T-cell lymphoma with early onset. The JAK-STAT pathway has been shown to be activated in ALCL, however the role of the signal transducer and activator of transcription 1 (STAT1) is still unclear.

Material and methods: We used immunohistochemistry (IHC) in FFPE tissue of ALCL patients, transgenic mouse models and lentiviral transduction of GFP marked mutated forms of STAT1 in cell lines.

Results: It is known that pSTAT3 is a highly expressed tumor driver in ALCL. We show here that STAT1, which has been shown to heterodimerize with STAT3, is also highly expressed in ALCL. However its localization is more cytosolic in particular in the unphosphorylated state. Mutation of the Tyr701 site into phenylalanine creates a constitutively inactive STAT1 form. Interestingly overexpression of this STAT1 version led to cell death of ALCL cells suggesting a dominant negative effect. Moreover, in the established CD4 NPM-ALK mouse model we knocked-out STAT1 in a T-cell specific manner allowing us to study effects of STAT1 depletion on overall-survival but also on anti-tumor immunity.

Conclusions: STAT1 and its tyrosine 701 phosphorylated form is highly expressed in ALCL as assessed by IHC. In contrast to STAT3, STAT1 can be found also in the cytoplasmic compartment. T-cell specific knock-out of STAT1 in a ALCL mouse model will enable us to study its role in a systemic setting. Constitutive deactivation of tyrosine 701 phosphorylation led to cell death, suggesting possible therapeutic option with state of the art peptidomimetics.

H28

Senolytic capacity of obinutuzumab in t (14;18)—positive GCB DLBCL cell lines

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Introduction and aims: Diffuse large B-cell lymphoma (DLBCL) is a heterogenous disease that can be cured in about two thirds of the patients by Rituximab(R)-CHOP. The phase III GOYA-trial failed to show superiority of the CD20-antibody Obinutuzumab(O). Subgroup analyses revealed a patient subset with a particularly strong germinal center B-cell (GCB) gene expression profile, according to the lowest quartile of the RNA-based cell-of-origin linear predictor score, to significantly profit from O in terms of OS and PFS (Oestergraad et al., ASH 2017).

Upon CHOP Bcl2-overexpressing GCB lymphoma show a high senescence susceptibility (Jing-H et al., Genes Dev 2010). We hypothesized here, that O may exert superior efficacy in

bcl2-translocated t(14;18)-positive(t+) GCB-DLBCL-cell lines via its particular lysosomal killing activity.

Materials and methods: Human DLBCL cell lines were treated with adriamycin(ADR), followed by either R or O, in vitro. Further analyses comprised RNA-seq, flow cytometry, immunoblot, fluorescence microscopy using LysoSensor and RQ-PCR.

Results: T+ was enriched in the strong GCB-phenotype, therefore experiments were stratified as t+ vs. t– cell lines. Upon ADR, more cells of the t+ vs. t– cell lines entered senescence. Subsequent treatment with O, but not R, produced increased killing which included elimination of senescent cells in the t+ but not t- group. Mechanistically, R/O were similar regarding the classic apoptosis pathway, but a virtually O-exclusive pH-change of viable cells occurred in the t+-group, thus, indicating the O-mediated killing is via the caspase-independent, cathepsin-mediated lysosomal-pathway.

Conclusion: O exerts, at least in part, its superior „strong-GCB" efficacy through its senolytic activity in t+ chemo-senescent DLBCL via their enhanced susceptibility to lysosomal cell death.

H29

Functional precision medicine vs. genomics vs. clinical experience: feasibility results of the multicentric, prospective, randomized controlled EXALT-2 trial

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Introduction and aims: Relapsed/refractory (r/r) aggressive hematological malignancies represent an unmet medical need. Precision medicine (PM) promises to extend the number of treatment options. We launched a multicentric, prospective, randomized controlled trial to assess the benefit of PM in hematology (NCT04470947).

Material and methods: EXALT-2 is actively recruiting in five academic hospitals in Austria (Vienna, Graz, Innsbruck, Linz, Salzburg). Patients with r/r aggressive hematological malignancies and ECOG performance status ≤1 are eligible. Viably collected tumor cells are used for single-cell functional precision medicine (scFPM) and comprehensive genomic profiling (CGP) assays.

Depending on randomization study treatment is based on
i) scFPM or
ii) CGP results, or
iii) without PM support (Physicians' Choice).

Results: Feasibility results are available for the first 55 patients. Of these, 54 patients (98 %) underwent real-time biopsy and 42 patients (76 %) received a therapy suggestion. 39 patients (71 % total, 92 % with board recommendation) received treatment, of which 29 patients (53 % total, 69 % with board recommendation) continued for >1 cycle.

PM assays were technically feasible (flow cytometry-based scFPM: 80 % of tests; microscopy-based scFPM: 52 % of tests; CGP: 86 % of tests) and identified actionable hits in 100 %, 100 %, and 78 %, respectively. Median time to report was shorter for scFPM (7 vs. 19 days). CGP identified a median of 1 (0–5) druggable targets with a substantial overlap between genetic and functional results.

Conclusion: Our results provide further evidence that genetic-based and functional PM can be safely implemented in clinical routine. Treatment recommendations can be applied in the majority of cases.

H30

CDK9- dependent transcriptional regulation of BCMA in multiple myeloma: rationally derived combination regimens

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Introduction: Despite therapeutic advances, Multiple myeloma (MM), still remains incurable and majority of patients becomes refractory. Therefore, novel targets and therapeutic strategies are crucial for better patients' outcomes. B cell maturation antigen (BCMA), expressed on plasma cells and B lymphocytes, is the primary target for antibody drug conjugates, bispecific antibodies, and CAR T cells. BCMA-targeting agents are currently revolutionizing MM therapy but molecular mechanisms which regulate BCMA are elusive. Our data demonstrated the cyclin-dependent kinase 9 (CDK9) as a promising target in MM. However, the impact of CDK9- targeting agents on the efficacy of BCMA and related immunotherapies is unknown.

Methods: CDK9 and BCMA expression was profiled by genomic analysis, the impact of CDK9 on BCMA was outlined using 2D/3D MM models. CDK9-regulated effects on BCMA and treatment combinations were determined by gene arrays, qPCR, FACS; and western blot, and survival analyzes.

Results: CDK9 and BCMA correlated in 2D and 3D culture systems. Dependency of BCMA on CDK9 was demonstrated by siCDK9, Tet-on/shCDK-9 or selective degradation of CDK9 using proteolysis targeting chimera Thal-SNS-032. The requirement of CDK9 for BCMA expression was additionally verified by drug- induced inhibition of CDK9/T186 phosphorylation levels and the utilization of FLAG-CDK9 versus FLAG-CDK9/T186A in MM1.S cells. CDK9 inhibition alleviated anti-MM activity of BCMA- targeting agents belantamab and CD3xBCMA antibodies as evidenced by direct and T-cell mediated cytotoxicity.

Conclusions: In summary, although therapeutic inhibition of CDK9 is a promising option in MM, its impact on strategies involving BCMA- targeting agents warrant further consideration for clinical application.

H31

Prevalence of fungal DNAemia mediated by putatively non-pathogenic fungi in immunocompromised patients with febrile neutropenia: a prospective cohort study

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Introduction and aim: Invasive fungal diseases (IFDs) continue posing an important clinical challenge in the immunocompromised setting. The objective of the study was to gain insight on the expanding spectrum of fungal pathogens using diagnostic screening techniques with broad specificity.

Material and methods: We have employed serial panfungal PCR analyses with ensuing fungal genus identification to prospectively investigate >1000 peripheral blood (PB) specimens derived from 376 febrile neutropenic (FN) episodes in 215 high-risk patients, including 124 children and 91 adults.

Results: The findings in paediatric and adult patients revealed a concordantly low incidence of IFD. Across both cohorts, 12.7 % ($n=40$) of the evaluable FN episodes were classified as possible IFD, 1.6 % ($n=5$) as probable IFD and 0.6 % ($n=2$) as proven IFD. Accordingly, a rather small number of PB samples showed positivity by the broad-spectrum PCR screening techniques employed ($n=145$). They generally revealed only transient presence of fungal DNAemia, mostly attributable to environmental plant pathogens not regarded as clinically relevant in humans. Fungi representing common pathogens in the immunocompromised setting were only rarely observed ($n=12$), while Malassezia and Cladosporium spp. were the most frequently detected genera in PB specimens displaying fungal DNAemia ($n=44$).

Conclusions: Efficient antifungal prophylaxis may have contributed to the low overall detection rate of fungal DNAemia in the patient cohorts investigated. The findings indicate that identification of the fungal genus or species with subsequent verification by repeated testing are prerequisites for determining the potential clinical relevance of positive test results obtained by panfungal PCR screening approaches.

H32

Combinatorial treatment options for highly resistant compound mutations in the kinase domain of the BCR::ABL1 fusion gene in Ph-positive leukemias

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Introduction: In Ph-positive acute lymphoblastic leukemia (Ph+ALL) and in advanced phases of chronic myeloid leukemia (CML), patients frequently develop compound mutations (CMs), defined as the presence of more than one mutation on the same BCR::ABL1 molecule in a leukemic cell, which are often highly or even completely resistant to any individual tyrosine kinase inhibitor (TKI), including the 3rd generation compounds ponatinib and asciminib.

Materianl and methods: We have performed in vitro analyses using a common cell line model based on BaF3 cells expressing a variety of judiciously selected CMs in BCR::ABL1 constructs, which had been introduced into the cells by a transposon-mediated approach. The cells were exposed to different concentrations of ponatinib combined with a number of other agents including asciminib, hydroxyurea, palbociclib, venetoclax, ibrutinib, vodobatinib, and crizotinib. The concentrations of all drugs tested corresponded to the spectrum of respective dosing regimens used in the clinical setting.

Results: Compound mutations displaying high levels of resistance to all available TKIs applied as single agents mostly revealed adequate in vitro responses to drug combinations with ponatinib, most commonly including asciminib, hydroxyurea or crizotinib. Overall, combinatorial treatment of BCR::ABL1 CMs indicated that relatively low doses of the drugs used are capable of effectively inhibiting in vitro survival of mutant cells in nearly all instances.

Conclusions: Since our earlier data indicated a good correlation between in vitro test results and clinical responses, our observations may serve as a basis for novel treatment options in patients with CML or Ph+ALL displaying challenging BCR::ABL1 KD-mutations.

Onkologie

O01

Novel Immunomodulatory Partial Tumor Irradiation for Unresectable Recurrent Bulky Tumors

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Introduction and aims: A novel immunomodulatory approach for PArtial Tumor irradiation targeting HYpoxic segment (PATHY) sparing the Peritumoral Immune Microenvironment (PIM) was developed to add to direct radiation tumor cell killing also the component of immune-mediated killing. The hypothesis is that for effective immunomodulation, the entire tumor volume may not need to be irradiated but only a partial volume to initiate the immune cycle in radiation-spared PIM. The aim was to assess the impact of PATHY on QoL, tumor downsizing, tumor control and survival among patients affected by recurrent unresectable bulky tumors. Materials and methods: 130 patients were treated between 2018 and 2023. According to the Palliative Prognostic Index, majority of patients had a life expectancy of <3 months. All patients had unresectable bulky tumors unsuitable for conventional radio-chemotherapy. The prescription dose was 30, 36 or 45 Gy RBE in 3 fractions. Results: Median follow up was 12.9 months. Overall survival and progression-free survival at last follow up were 64 % and 46 %, respectively. Median patient survival was 12 months (estimated was < 3 months). Local tumor control at last follow up was 46 % following the single PATHY course. Local immunogenic effect was induced in 83 % of patients. Average tumor volume reduction was 0 %. In 40 % of patients an abscopal effect was reported.

Conclusions: PATHY was effective, safe and well tolerated treatment. It resulted in improvement in symptoms and quality of life of highly complex patients without associated treatment related toxicity. This approach showed high immunogenic and neoadjuvant potential.

O02

Treatment of stage IV colorectal cancer: Does failure of first-line treatment indicate failure of subsequent treatments? A retrospective cohort study

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Introduction and aims: Colorectal cancer belongs to the most frequent malignancies worldwide. Although current therapies for metastatic disease stratify for KRAS/NRAS/BRAF mutations, microsatellite instability, tumor location and comorbidities, the therapeutic mainstay is still 5-FU-based chemo-immunotherapy in first- as well as second-line.

The aim of this study was thus to investigate if response to first-line therapy can predict response to second-line therapy.

Materials and methods: This study evaluated responses of colorectal cancer patients treated at the University Hospital Krems from 01.01.2015 to 31.12.2021, who received at least two therapy lines ($n = 49$) for stage IV disease.

Response rates, PFS and OS were evaluated.

Results: All patients with first-line complete response (CR, $n = 6$) had at least stable disease in second-line treatment (ORR = 66.6 %). Conversly, all patients with progressive disease (PD) in first-line ($n = 7$) did not respond to second-line therapy (ORR = 0 %).

Moreover, patients with first-line CR had median OS of 80 months, whereas patients with PD had only median OS of 12 months ($p < 0.001$).

Conclusion: This study indicates that, with current treatment strategies applying 5-FU-based chemo-immunotherapy in first- and second-line treatment, response to first-line therapy is a strong predictor for response to second-line therapy and OS.

By merely exchanging the additive antibody and chemotherapeutic combination partner, the negative factor of non-response to first-line therapy could not be overcome, most likely caused by multi-drug resistance in our study population.

These findings have to be confirmed in larger studies, but raise the need for novel treatment options, especially for patients not responding to first-line 5-FU-based chemo-immunotherapy.

O03

Kombination von Radiotherapie und Systemtherapie beim Mammakarzinom

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Innerhalb der letzten Dekade haben nahezu in jedem Jahr neue Substanzklassen und Substanzen zur adjuvanten und palliativen Systemtherapie des Mammakarzinoms Eingang in den klinischen Alltag gefunden. So erfreulich diese Erweiterung der Therapieoptionen in Umfang und Geschwindigkeit auch ist, so groß ist auch die Herausforderung, die Wechselwirkungen dieser Substanzen bezüglich Tolerabilität und Effizienz mit der Radiotherapie abzuschätzen.

Dieser Umstand ist nicht nur auf die Behandlung des Mammakarzinoms beschränkt, allerdings ist dies erste Tumorentität, wo ein Konsensus herausgearbeitet und am 17. Juni in Florenz nach zweijähriger Vorarbeit präsentiert wurde. Daran wirkten Repräsentanten aus Epidemiologie, Statistik, medizinischer Onkologie, Radioonkologie und präklinischer Forschung mit. Von Seiten der medizinischen Onkologie waren dies unter anderem Nadia Harbeck, Javier Cortés, Giuseppe Curigliano und Hope Rugo. Was die Radioonkologie angeht, wurde das Resultat durch die ESTRO bereits offiziell angenommen.

Als Endpunkt wurden die Tolerabilität und Sicherheit einer kombinierten Anwendung von System- und Radiotherapie gewählt, wenn auch im Rahmen der Präsentationen immer wieder auf Wechselwirkungen bezüglich der Effizienz hingewiesen wurde. Vom klinischen Einsatz her wurde unterschieden zwischen adjuvanter und metastasierter Situation, ablativer und palliativer Bestrahlung sowie intra- und extrakranieller Indikation. Die Datenlage wurde in nahezu all diesen Szenarien als gering oder sehr gering mit klinischer Evidenz unterlegbar eingeschätzt.

Umso mehr sollten Patientinnen sorgsam über die bestehenden Unsicherheiten aufgeklärt werden und einer sequentiellen Anwendung von Systemtherapie und Radiotherapie gegenüber einer konkomitanten der Vorzug gegeben werden. Die Notwendigkeit, akute Toxizität und Langzeittoxizität im Rahmen der Zulassungsstudien prospektiv zu erheben, wurde betont.

O04

ctDNA as an unifiable biomarker to predict response to treatment after two weeks of chemotherapy at the same cut-off for GEC, PC and CRC

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Introduction and amis: ctDNA has emerged as promising biomarker in gastrointestinal cancer. However, definition for detectability and cut-offs are reported very heterogeneously.

We first in man evaluated response to treatment at an unifiable cut-off for dynamic changes during chemotherapy in 3 different major GI-cancer types ($n=924$ samples).

Material and methods: Liquid biopsy samples for $n=185$ stage IV patients with gastroesophageal (GEC, $n=37$), pancreatic (PC, $n=70$) and colorectal cancer (CRC, $n=78$) have been prospectively acquired pretherapeutically and every 2 weeks during chemotherapy until restaging, analyzed using ddPCR and correlated with response to treatment and outcome.

Results: Detection rates were 88.5 % (CRC), 77.8 % (GEC) and 64.3 % (PC).

ROC analysis (AUC >0.9) revealed a decline of under 58 % of the pretherapeutic MAF to predict response to treatment already after 2 weeks (CRC spec. 97.8 %, sens. 92.3 %, GEC spec. 100 %, sens. 66.7 %, PC spec. 100 %, sens. 91.7 %).

This was accompanied with a significant impact on OS and PFS for all tumor entities:

- GEC: 3.2 (95 %CI 1.9–4.5) vs. 9.5 (95 %CI 5.5–13.5) months, $p=0.001$
- PC: 2.5 (95 %CI 2.2–2.9) vs. 7.7 (95 %CI 4.0–11.3) months, $p<0.001$
- CRC: 2 (95 %CI 1.3–2.7) vs. 11 (95 %CI 9.0–13.0) months, $p<0.001$

Conclusion: ctDNA represents an already clinical applicable biomarker with remarkable sensitivity and specificity in displaying actual tumor burden, prediction of prognosis and response to treatment. This biomarker is superior to current gold standard markers CEA, CA19-9 and CA72-4 and predicts response to systemic treatment after 2 weeks (>80 % faster than computed tomography).

O05

Circulating tumor DNA (ctDNA) as precision medicine marker for neoadjuvant chemotherapy vs. upfront surgery in primary resectable localized pancreatic cancer

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Introduction and aims: Circulating tumor DNA (ctDNA) has emerged as a promising biomarker displaying systemic tumor burden in presumed localized pancreatic cancer (lPC). However, clinical applicability for neoadjuvant chemotherapy (NACT) guidance was flawed by low preoperative detection rates (10.2 %) without NGS until now. Recently, CA 19-9 > 500 U/ml has been implemented into the Austrian guidelines for administration of NACT.

Material and methods: Liquid Biopsy samples of $n=147$ patients with lPC were collected 1 day before, 1 day after and 10 days after curative intended surgery and have been analyzed by ddPCR for KRAS G12/13 and, if negative, KRAS Q61. Results have been correlated with tumor volume and outcome.

Results: Detection rates have improved by x3.6 to 36.8 % (preop.), 19.7 % (1d postop.) and 13.3 % (10d postop.).

ctDNA showed no correlation with primary tumor volume ($p=0.605$), but with nodal positivity ($p=0.029$).

Pretherapeutic ctDNA detectability was associated with worse OS (10.1 vs. 36 months, $p<0.001$) and DFS (6 vs. 23.1 months, $p<0.001$), whereas CA 19-9 > 500 U/ml was not.

Also, postoperative ctDNA detectability showed correlation to DFS (12.9 vs. 29.1 months, $p=0.027$) and OS (HR 3.120).

Conclusion: This study represents the currently largest prospective cohort on this topic (formerly $n=113$ by Guo et al., China, 2020).

ctDNA allows detection of actual systemic tumor burden and offers a cost effective and clinical applicable method to eventually guide NACT vs. upfront surgery as precision medicine approach in the future adding a biological criteria for high risk of relapse to the up to now radiological resectability.

O06

Anaemia is an independent risk factor for mortality in HCC patients

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Introduction and aims: Anaemia is frequent in patients with cancer and/or liver cirrhosis and is associated with impaired quality of life. Here, we investigated the clinical characteristics of anaemia and its impact on overall survival (OS) in patients with hepatocellular carcinoma (HCC).

Material and methods: HCC patients treated between 1992 and 2018 at the Medical University of Vienna were retrospectively analysed. Anaemia was defined as haemoglobin level <13 g/dL in men and <12 g/dL in women.

Results: Of 1262 evaluable patients, 555 (44.0 %) had anaemia. The main etiologies of HCC were alcohol-related liver disease ($n=502$; 39.8 %) and chronic hepatitis C ($n=375$; 29.7 %). Anaemia was significantly associated with impaired liver function (Child-Pugh class and Model for End-stage Liver Disease [MELD]), portal hypertension, more advanced Barcelona Clinic Liver Cancer (BCLC) stage and elevated C-reactive protein (CRP) level. On univariable analysis, anaemia was significantly associated with shorter median OS (9.5 months, 95 % confidence interval [95 % CI] 18.3–24.7 months) vs. patients without anaemia (21.5 months, 95 % CI 7.3–11.6 months) ($p<0.001$). On multivariable analysis adjusted for age, MELD, number of tumour nodules, size of the largest nodule, macrovascular invasion, extrahepatic spread, first treatment line, alpha-fetoprotein (AFP) and CRP, anaemia remained an independent predictor of mortality (adjusted hazard ratio [aHR] 1.23, 95 % CI 1.06–1.43, $p=0.006$).

Conclusion: Anaemia was significantly associated with mortality in HCC patients, independent from established liver- and tumour-related prognostic factors. If adequate management of anaemia can improve outcome of HCC patients needs further evaluation.

O07

Polypharmacy is a major and increasing challenge in patients with incurable cancer—Analysis of a single-center retrospective patient cohort with 3 years of follow-up

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Introduction and aim: Polypharmacy, i. e. taking at least 5 long-term medications, is a recognized problem in cancer patients. Even though pre-existing comorbidities, tumor therapy and side effects of tumor therapy requiring treatment are likely to be the three relevant risk factors, characteristics of polypharmacy and changes in medication during the course of metastatic disease have barely been studied to date.

Material and methods: A single-center cohort of 64 consecutive patients with syn- or metachronous metastatic cancer and an expected life expectancy between three months and three years (inclusion criteria) was evaluated and periodically followed up to a maximum of three years. Comorbidities, type and number of medications, including tumor therapy, and changes in pharmacotherapy were documented.

Results: At diagnosis of metastatic cancer, 34.4 % of patients had polypharmacy with a mean of 7.8 medications; at last follow-up visit, this proportion had doubled to 68.8 % (14.8 medications, mean). The longer the observation time was, the higher the proportion of patients with polypharmacy ($p<0.001$, $r=0.918$). With initiation of tumor therapy, the number of medications increased significantly, by a mean of 7 drugs from 4.1 to 11.2 drugs ($p<0.001$) in the overall cohort. Even shortly before death, no significant reduction in medication was observed; patients received a mean of 11.0 and 9.3 medications three to one months and less than one month before death, respectively ($p=0.34$).

Conclusion: Polypharmacy is a significant problem in patients with incurable cancer and methods to optimize pharmacotherapy and reduce polypharmacy in this patient population are urgently needed.

O08

An advanced CRISPR screening platform for exploring drug modifier interactions in vitro and in vivo

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Introduction: The efficiency of chemotherapeutic and targeted therapies varies greatly within patients suffering from acute myeloid leukemia (AML) and is rarely sufficient to induce long-term remissions, due to the rapid development of therapy resistance. Therefore, there is an urgent clinical need to identify rational combination therapies and predictive response biomarkers that enable effective precision medicine.

Methods: We took advantage of optimized sgRNA prediction algorithms (VBC-score) and a new dual-sgRNA design and constructed low-complexity genome-wide sgRNA libraries that transform the technical robustness and throughput of drug-modifier screens in culture and enable in vivo screens. With our platform, we performed genome-wide drug modifier screens for 18 clinically established and emerging therapeutics in human AML cell lines, including antimetabolites, anthracyclines, hypomethylating agents and various selective small-molecule inhibitors.

Results: We identified various established as well as previously unknown genes that selectively result in drug synergy or resistance to specific therapeutic interventions upon CRISPR-mediated knockout. In addition, few genes even had opposing effects that were dependent on the type of therapeutic intervention, which may predict new rational sequential treatment paradigms. We validated selected gene-drug interactions in multiple AML and solid cancer cell lines in vitro, suggesting that many of these interactions are conserved across tissues. High-confidence targets will be explored in syngeneic and xenotransplantation in vivo models of AML.

Conclusion: Pharmacological intervention of specific drug-gene interactions, as well as integration of selected genes within targeted exome sequencing panels, may pave the way for the development of novel combinatorial therapies and predictive response biomarkers.

O09

Liver metastases and their impact on liver function in high-grade neuroendocrine neoplasms

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Introduction: Liver metastases occur frequently in high-grade neuroendocrine neoplasms (hgNEN) and represent an important prognostic factor. Little is known about how this hepatic spread affects biochemical parameters of liver function.

Methods: This study included patients with extrapulmonary metastatic hgNEN, i. e., grade 3 neuroendocrine tumors (NET G3) and neuroendocrine carcinomas (NEC). Liver function parameters were retrospectively analyzed (median at baseline [mb], median at follow-up [mf]) and compared with the Wilcoxon signed-rank test in R version 4.3.1.

Results: Out of 50 patients with hgNEN, 40 had liver metastases and were included in this analysis (57.5 % female, median age at diagnosis 55.0 years, median overall survival for all 21.2 and for NEC 13.7 months). 25 patients had NEC, 15 NET G3; primarily pancreatic NEN ($n=15$) and CUP ($n=13$). In 29 patients, baseline and follow-up blood values (3–12 months apart) were available. There was a significant change over time in blood markers indicating cholestasis, i. e., alkaline phosphatase ($p=0.0099$, mb = 124.5, mf = 164) and gamma-GT ($p=0.0049$, mb = 102, mf = 313). Furthermore, albumin was significantly decreased ($p=0.0204$, mb = 43.6, mf = 39.9), and lactate dehydrogenase increased ($p=0.0098$, mb = 202, mf = 281). As expected, transaminases were not elevated. Bilirubin and cholinesterase remained relatively unchanged. Analyzed separately, these differences were present in the NEC subgroup but nonsignificant in the small NET G3 subgroup.

Conclusion: This is the first study to specifically report on biochemical parameters of liver function in the context of metastatic hgNEN, showing that this disease is associated with changes in liver function parameters. In a further step, this can be correlated with tumor volume.

O10

Palbociclib plus endocrine therapy in HR+/HER2– Advanced Breast Cancer patients: Interim results of the PERFORM study in Austria and Germany

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Introduction and aim: CDK4/6i+ET is the 1L standard for HR+/HER2– ABC patients. Clinical trial data showed high efficacy and good tolerability. Real World data provides important confirmation and closes knowledge gaps.

Methods: The prospective, non-interventional PERFORM study will enroll 1,900 patients across Austria and Germany to gain further insights on effectiveness, tolerability and longitudinal treatment. The interim analysis 2 (IA2) investigates response rates and dose modifications in the total population and age-related subgroups (≥75 vs <75 years).

Results: Between 10/2020–09/2022, 938 patients were enrolled. 624 patients were evaluable. Median age was 68 years, 39 % had de novo ABC and 11 % ECOG ≥2 at inclusion. 30 % were ≥75 years. Of these, 22 % had ECOG ≥2 at inclusion compared to 7 % <75 years. De novo ABC was more frequent in patients ≥75 (44 %) than <75 years (36 %). The number/distribution of metastases was comparable. PFS rate at 12 months was 71.7 %, ORR 33.2 % and CBR 57.4 %. Notably, these numbers were similar across age groups. Dose modifications occurred in 74.1 % of patients ≥75 vs 61.5 % <75 years. >70 % in both subgroups are still treated. Treatment discontinuation rates were comparable (28.6 % ≥75 vs 27.3 % <75 years). (S)AE as discontinuation reason was more frequent in the older subgroup (9.2 % vs 3.0 %).

Conclusion: The PERFORM IA2 shows comparable results regarding PFS, ORR and CBR of 1L treatment with palbociclib/ET in patients ≥ and <75 years. Patients ≥75 years required more dose modifications. This is in line with clinical trial data and supports age-independent use of palbociclib/ET.

O11

Demonstration of immunotherapy-induced alterations in cytokine release in a primary patient-derived microtumor-model (PMT)

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Background: Although the use of immunotherapy (IO) contributes to greater therapeutic success, the heterogeneity of patient's responses still poses a big challenge in oncology. Thus, a more tailored therapeutic approach is urgently needed! We established a functional 3D in vitro platform, generated from primary tumor tissue, to test personalized therapy options and improve outcome prediction in a clinically relevant manner.

Material and methods: To set up the model, freshly resected tumor material from 20 NSCLC patients was mechanically and enzymatically digested, to obtain single cell suspension, and subsequently seeded into ultra-low attachment plates. After six days of tissue maturation, the resulting PMTS were treated with CPIs and combinations with chemotherapies. Drug response was analyzed by monitoring size progression, using bright field imaging. Furthermore, supernatant was collected to perform an Elisa essay and thus monitor cytokine release.

Results: Regarding size regression of the PMTs under treatment (mimicking tumor shrinkage), the objective response rates in the model mirrored the clinical outcome distribution. However, to prove the effectiveness of IO, immune regulatory processes should also be observable. In this sense, Elisa DATA showed a remarkable change in the release of immune-dependent cytokines, depending on the different treatments and compared to control.

Conclusion: The highlighted PMT model is one of the first, to show a clinically relevant response to immunotherapy in terms of tumor cell death. Furthermore, a therapy-dependent release of cytokines, and thus an immunomodulatory effect of IO on the tumor and its microenvironment can be observed.

O12

Tucatinib in patients with locally advanced or metastatic HER2-positive breast cancer: Study design of the non-interventional study TRACE in Germany and Austria

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Introduction and aims: Tucatinib, a highly selective HER2 tyrosine kinase inhibitor, combined with trastuzumab+capecitabine, demonstrated a significant overall and progression-free survival benefit compared to placebo+trastuzumab+capecitabine [1, 2] in HER2CLIMB and was approved in the EU for HER2+ advanced breast cancer (ABC) patients after ≥ 2 prior anti-HER2 therapies. TRACE will collect real-world data of tucatinib+trastuzumab+capecitabine according to SmPC, including data after prior therapy with trastuzumab-deruxtecan and data for tucatinib in early ABC treatment lines.

Material and methods: 150 HER2+ ABC patients each (up to 30 Austrian patients each) will be enrolled into the 1st/2nd & 3rd/4th line cohorts scheduled to receive tucatinib+trastuzumab+capecitabine according to SmPC in 60 German and 10 Austrian sites. Primary endpoint is time to deterioration of patient-reported global quality of life (QoL), (EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BR23 questionnaires). Descriptive statistics will be used to analyze changes in the functional and symptom sub-scores compared to baseline, effectiveness, safety, physician decision making, and details on tucatinib treatment.

Conclusion: TRACE will provide real-world insights into treatment with tucatinib+trastuzumab+capecitabine for HER2+ ABC patients focusing on QoL, effectiveness and safety. Pre-planned subgroup analyses will fill knowledge gaps between the pivotal trial and routine clinical practice.

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O13

XPO1 expression in pancreatic cancer: a promising biomarker and therapeutic target

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Introduction and aim: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive disease associated with a very poor survival. Exportin-1 (XPO1) emerges as a potential novel therapeutic target. Overexpressed in various hematological and solid cancers, XPO1 mediates the nuclear export of tumor suppressor proteins (TSPs), leading to their inactivation. This study aims to assess the prognostic value and molecular landscape of XPO1 expression in PDAC.

Material and methods: XPO1 expression in PDAC samples was examined using immunohistochemistry. Additionally, 5488 PDAC specimens were centrally genetically profiled for XPO1 mRNA expression at Caris Life Sciences (Phoenix, AZ) via DNA

(WES) and RNA sequencing (WTS). Tumor microenvironment (TME) was analyzed using the QuantiSeq method.

Results: Immunohistochemical analyses revealed that XPO1 is overexpressed in PDACs vs adjacent healthy tissues. This overexpression was confirmed using the Caris cohort and was associated with a shorter overall survival. No differences in genetic alterations were observed between $XPO1^{high}$ and $XPO1^{low}$ tumors. Elevated XPO1 mRNA levels correlated significantly with increased infiltration of T-cells and M2 macrophages. Moreover, an activated MAPK pathway was observed within the $XPO1^{high}$ group.

Conclusion: This preliminary data reveals that while XPO1 is overexpressed in PDACs and correlates with poor patient outcome, its overexpression is not reflected in the tumors genetic profile. Moreover, we show that $XPO1^{high}$ tumors display an increased immune cell infiltration, particularly T-cells. Currently, single-cell RNA sequencing and in vitro experiments are ongoing to better delineate the TME according to the XPO1 status. These data will be presented at the FJT conference in 2024.

O14

Treatment patterns and outcome of advanced gastroesophageal adenocarcinoma over 15 years of follow up: a retrospective cohort study

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Introduction: We aimed to evaluate how treatment patterns in palliative first-, second- and third line of gastroesophageal adenocarcinoma have changed over the last 15 years before the introduction of immune checkpoint inhibitors (ICI) and how these treatment changes have impacted survival outcomes.

Material and methods: 382 patients with unresectable or metastatic esophageal, gastric, or gastroesophageal adenocarcinoma, who underwent palliative systemic treatment were included. Based on a cutoff date set at January 1st, 2013, patients were assigned to two treatment era groups: Cohort A (2006–2012) and Cohort B (2013–2020). The primary endpoint was overall survival from start of first-line therapy (OS1). Co secondary endpoints were the overall survival in second and third line (OS2, OS3).

Results: Patients in Cohort B ($n=207$) were treated more intensely, with a higher proportion of patients who received triplet therapies in first line (12.0 % vs. 23.7 %, $p=0.001$) and a higher rate of patients who underwent subsequent second- (43.4 % vs. 53.6 %, $p=0.005$) and third-line therapy. (13.1 % vs. 25.1 %, $p=0.004$) In terms of the endpoint analysis, only a non-significant improvement of OS1 could be observed for Cohort B. (median OS1 8.0 vs. 9.7 months, $p=0.055$), whereas a significantly superior OS2 (4.7 vs. 7.0 months, $p=0.006$) and OS3 (3.2 vs 5.0 months; $p=0.031$) were observed.

Conclusion: Although treatment patterns of palliative systematic therapy in advanced gastroesophageal adenocarcinoma have significantly changed over the last 15 years, our study indicates that these treatment changes did only translate into a marginal improvement of overall survival in the pre-ICI treatment era.

O15

Functional characterization of plasma membrane rupture mediator Ninjurin1 in lung adenocarcinoma

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Background/Aims: Lung cancer is the leading cause of cancer-related deaths. Introduction of immunotherapy improved patient outcomes, but it often fails to provide long-term remission. Triggering inflammatory cell death in cancer cells, thereby altering the tumor immune microenvironment (TIM) may be a strategy to boost immunotherapy response.

Plasma membrane rupture (PMR) is the final event of lytic forms of cell death which are associated with damage-associated molecular patterns (DAMPs) release, propagating inflammation and subsequently influencing the TIM. Recent studies identified Ninjurin 1 (NINJ1) as a key mediator of PMR. NINJ1 de-regulation was implicated in different cancers, but its role in lung cancer is not well-understood. Therefore, the aim of this study is to comprehensively characterize the role of NINJ1 in lung cancer.

Method/Results: Performing CRISPR/Cas9-mediated modulation of NINJ1 in lung cancer cells, we confirmed that changes in NINJ1 expression affects the release of DAMPs from tumor cells. Bioinformatic analysis of publicly available datasets revealed reduced immune cell infiltration in NINJ1-low tumors. Decreased NINJ1 levels also correlated with shorter patient survival.

For further functional characterization of NINJ1 in vivo, we used a unique murine lung cancer model which allows CRISPR-mediated somatic targeting of NINJ1 specifically in tumor cells. Preliminary analysis confirmed a tumor-suppressive role of NINJ1 in lung cancer development.

Conclusion: Our studies highlight an important role of NINJ1 in shaping the TIM in lung cancer and suggests that has tumor-inhibiting functions. This highlights the great potential of modulating regulators of lytic death to improve immune therapy in lung cancer patients.

O16

Pattern of venous thromboembolism (VTE) in patients with cancer treated with Immune Checkpoint Inhibitors (ICI)

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Background: Patients with cancer treated with ICI are at substantial VTE-risk, yet clinical risk profiles are unclear. Our aim was to identify risk factors for VTE during ICI-therapy to support the development of specific thromboprophylaxis strategies.

Methods: Consecutive adult patients treated with ICI at the Medical University of Graz were included in this retrospective cohort study and followed for the occurrence of VTE during ICI-therapy (AUTRICHE-register-based). Statistical analyses were conducted in competing risk analysis, accounting for all-cause mortality as competing event.

Results: Overall, 417 patients were included [non-small cell lung cancer (41 %), renal cell carcinoma (16 %) and melanoma (15 %)]. Over a median follow-up of 26.4 months, 37 VTE occurred [cumulative incidence: 12.2 % (95 % confidence interval [CI]: 8.7–16.4)]. VTE-risk was increased after ICI-initiation compared to the period from cancer-diagnosis to ICI-start (transition-hazard-ratio (HR): 3.30, 95 %CI: 1.95–5.57). Similar incidences and no significant differences in risk were observed according to demographics, comorbidity burden, cancer-type and -stage. The Khorana-score did not predict VTE-risk (subdistribution-HR [score ≥2]: 0.88, 95 %CI: 0.45–1.72). Baseline levels of routine laboratory parameters including C-reactive protein (CRP) did not predict VTE-risk, yet early increases in CRP (2-fold increase within 3 months of ICI-initiation) were associated with a significantly higher VTE-risk (adjusted subdistribution-HR: 2.31, 95 %CI: 1.06–5.02), with a cumulative incidence of 22.9 % in patients with an early CRP-flare.

Conclusion: A substantial burden of VTE among ICI-treated patients was observed, characterised by homogenously high risks according to patient- and cancer-characteristics. Longitudinal trajectories of inflammatory biomarkers might identify patients at very high VTE risk.

O17

Real-world treatment patterns and outcomes of patients with hormone-sensitive advanced prostate cancer

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Introduction: Androgen receptor pathway inhibitors (ARPI) have revolutionised treatment of patients with metastatic prostate cancer. The upfront use of ARPI in metastatic hormone-sensitive prostate cancer is known to improve overall survival.

Material und methods: Clinical data were derived from our prospective prostate cancer registry, including patients having received systemic treatment for castration-sensitive disease consisting of at least one course of chemotherapy, an ARPI or both from 2016 to 2023.

Results: Eighty-two patients with hormone-sensitive prostate cancer were evaluated. Median age was 68 years and median OS was 45.6 months. First line therapy consisted of an ARPI in 54 % of patients while 43 % received chemotherapy. Three patients were treated with a combination of both as first-line therapy. Docetaxel was predominantly used until 2019. In contrast, most patients diagnosed in 2020 and onwards received an ARPI.

Conclusion: Our retrospective study reveals treatment patterns in clinical routine showing a shift in first line therapy of metastatic hormone-sensitive prostate cancer from chemotherapy towards ARPI in recent years. Updated and more detailed data will be presented at the meeting.

O18

First description and biological profiling of a novel collagen score outperforming PSA, patient age and mpMRI for detection of clinically significant prostate cancer

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Introduction and aims: While the extracellular matrix (ECM) and collagen density have been implicated in poor prognoses in various cancers, it impact in prostate cancer (PCa) remains unclear.

Material and methods: We conducted a comprehensive analysis including mRNA and protein expression assessments from multiple databases. Additionally, 923 patients underwent urinary peptidomics analysis. The expression of collagen biosynthesis enzymes was confirmed using our scRNA-seq analyses of treatment-naïve PCa patients.

Results: We identified 51 differentially expressed collagen-related genes in significant PCa compared to benign prostate and ISUP 1 cancers. Analysis of the urinary peptidome revealed 352 collagen-related molecules, supporting the development of a urine-based collagen score capable of discerning significant from indolent PCa ($AUC_{ISUP\geq2}$: 0.82; $p<0.0001$). Integrating the urinary collagen score to PSA, age and mpMRI in a nomogram resulted in significant improvement in detecting significant PCa ($AUC_{ISUP\geq2}$: 0.87), compared to mpMRI ($AUC_{ISUP\geq2}$: 0.77; $p=0.0098$) or the urinary collagen score alone ($AUC_{ISUP\geq2}$: 0.79; $p=0.0158$). Bioinformatic segregation of the cellular TME composition of high in collagen PCa patients revealed elevated infiltration levels of cancer associated fibroblasts and endothelial cells. Cell-type-specific expression of collagen biosynthesis enzymes was validated using scRNA-seq, proving TME specific expression patterns.

Conclusion: Our non-invasive collagen-based score demonstrates superior diagnostic efficacy compared to PSA, age and mpMRI in detecting significant PCa. These findings emphasize the critical role of collagen in PCa progression and underscore the potential of urinary biomarkers in improving PCa diagnosis.

O19

Deciphering the role of IFN I signaling in tumor endothelium: a novel paradigm for vascular pathogenesis in Non-Small Cell Lung Cancer (NSCLC)

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The endothelium emerges as a pivotal factor in the microenvironment of NSCLC, functioning as a conduit for tumor propagation but also as crucial regulator of the anti-tumor immune response. This study investigates the intricate role of tumor-associated endothelium, offering insights into the mechanisms steering cancer progression.

Isolation and characterization of endothelial cells (ECs) from both healthy-adjacent and tumor tissues (TECs) of NSCLC patients formed the foundation of our investigation using functional and molecular analyses. Subsequent validation and broader experiments were carried out on HUVECs and EA. hy926. The identification of IFI27 as novel TEC marker was confirmed through immunohistochemical stainings on NSCLC tissue. Prognostic relevance, differential gene regulation, and pathway activation were explored using four bulk RNA datasets. Additionally, scRNAseq data from NSCLC patients and controls validated our findings on a single-cell level.

Our investigation revealed IFI27 as novel TEC marker, associated with IFN I upregulation within the NSCLC TME. IFN I activation significantly correlated with poorer survival and demonstrated the potential to induce a tumor-promoting endothelial phenotype. Our findings unveiled the tumor-endothelium as autocrine regulator of IFN I, emphasizing its role as a discerning organ responding to signals within the TME, thereby activating IFN I signaling.

This study positions IFN I signaling as a novel driver of vascular pathogenesis and ascribes a newfound role to the tumor-endothelium, casting it as discerning organ pivotal in tumor progression. These revelations furnish novel perspectives on the interactions between ECs and the TME, opening avenues for targeted interventions in the vascular pathogenesis of NSCLC.

O20

The role of lncRNAs in fusion-oncoprotein containing biomolecular condensates in Acute Myeloid Leukemia

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Biomolecular condensation of macromolecules in cells creates membraneless microenvironments that enable specific biological processes. Biomolecular condensates contain proteins and RNA, and various biochemical and biophysical parameters influence the propensity of these macromolecules to phase separate. In NUP98-fusion oncoproteins, which are found in aggressive forms of pediatric leukemia, the intrinsically disordered region in the NUP98 N-terminus is essential for their biomolecular condensation and for the induction of leukemia-associated transcriptional programs. Long noncoding RNAs (lncRNAs) are involved in the control of gene expression but how they affect biomolecular condensation of fusion oncoproteins is not known. While some lncRNAs were proposed to have direct roles in transcriptional regulation, others may exert structural roles that are important to establish and/or maintain interactions between proteins, RNA and chromatin. We aimed to investigate the contribution of cellular lncRNAs to biomolecular condensation of the NUP98::KDM5A fusion oncoprotein. We developed biotinylated isoxazole-mediated condensome RNA-sequencing (biCon-Seq) to identify lncRNAs that are enriched in biomolecular condensates in NUP98::KDM5A driven AML. We developed a solubility score based on RNA abundance ratios in biCon-Seq data and classified RNAs according to their differential propensity to localize to biomolecular condensates. NUP98::KDM5A expression strongly affected RNA solubility, as ligand-induced NUP98::KDM5A degradation revealed a global shift in RNA solubility. Thus, we propose that together with the oncogenic dysregulation of condensation driven by NUP98::KDM5A, the lncRNA composition of biomolecular condensates is essential to establish and maintain leukemia-associated gene expression.

O21

Case report of disseminated carcinomatosis of the bone marrow in newly diagnosed gastric cancer

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Background: Disseminated carcinomatosis of the bone marrow (DCBM) is a rare first manifestation of newly diagnosed solid tumours and often presents with a new onset pancytopenia as a first symptom. The etiologies for new onset cytopenia are various but most frequently connected to hematologic neoplasms. However, a range of other causes such as nonspecific changes due to systemic diseases, toxic etiologies and infections create a broad spectrum of differential diagnostics that have to be worked through.

Case report: Hereby we report a case of a 69-year-old man with newly diagnosed gastric cancer and coincident pancytopenia. Diagnostic work up showed a super scan in whole body scintigraphy finally leading to the diagnosis of disseminated carcinomatosis of the bone marrow without any other distant metastases. A systemic therapy with FOLFOX/Nivolumab was administered achieving a rapid response with hemotologic improvement. Ultimately therapy had to be interrupted due to tumor progression after six cycles of FOLFOX/Nivolumab and the patient died one month later after a second line therapy with ramucirumab plus paclitaxel.

More detailed data will be presented at the meeting.

O22

Alterations in the INK4a/ARF pathways allow the establishment of a preclinical NK cell leukemia mouse model

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The INK4a/ARF locus encodes two distinct tumor suppressors involved in two different pathways: p16INK4a blocks cell-cycle progression by inhibiting phosphorylation of the retinoblastoma protein, while p14ARF (murine orthologue p19Arf) promotes the functions of p53. Both pathways are important in the cell cycle regulation and involved in processes of senescence and apoptosis. Loss or epigenetic dysregulation of the INK4a/ARF locus or other players of these pathways is observed in several types of cancer, in particularly leukemias and lymphomas.

We observed that both INK4a and ARF are upregulated in senescent NK cells and that their concomitant loss allows NK cells to escape from senescence and to establish stable NK cell lines.

We further studied the role of the INK4a/ARF locus in the development and progression of NK cell malignancies in-vivo—rare but serious diseases with limited treatment options. NK cell leukemia is among the most aggressive lymphoid neoplasm. For a better understanding of the mechanisms of tumorigenesis and an exploration of possible new treatment options, an optimal mouse model is highly required.

Our data pinpoint a relationship between the loss of the INK4a/ARF gene within NK cells and their malignant transformation. By making use of this oncogenic potential of NK cells isolated from INK4a/ARF knockout mice, we established a transplantable NK cell leukemia mouse model. We now aim to use both, the leukemia mouse model, and the generated leukemic mouse NK cell lines, to further study the mechanism of transformation and to screen for novel therapeutic strategies.

O23

Advanced peritoneal carcinomatosis in metastatic gastric cancer treated with triple therapy including pembrolizumab/trastuzumab/FOLFOX

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Background: Peritoneal carcinomatosis is the second most common metastatic site in gastric cancer and results in significant morbidity and a high mortality rate. Primary treatment for metastatic gastric cancer is systemic chemotherapy with a combined fluoropyrimidine and platine regimen plus immunotherapy with checkpointinhibitors according to the PDL-1 status. The findings of the KEYNOTE-811 study showed more frequent and deeper remissions for the combination therapy with pembrolizumab/trastuzumab plus standard chemotherapy in HER-2 positive advanced gastric cancers.

Case: A 33-year-old woman was diagnosed with metastatic gastric cancer including advanced peritoneal carcinomatosis. The tumor was positive for high amplification of HER-2. Based on the decision of the tumor-board conference the patient was treated with pembrolizumab/trastuzumab/5-FU/oxaliplatine for 6 cycles. A significant partial remission was achieved with no sign of active peritoneal carcinomatosis in follow up positron emission tomograpy-computed tomograpy (PET-CT). Due to the positive clinical development, disapperence of metastasis in imaging und negative laparoscopy for peritoneal carcinomatosis, the decision for gastrectomy was made in the tumorboard conference. Finally gastrectomy with R0 resection could be performed.

At the time of this case report the patient is still receiving trastuzumab maintenance therapy.

More detailed data will be presented at the meeting.

O24

Zurückgezogen

O25

Phase II Study of daTopotamab derUXtecan (Dato-DXd; DS-1026a) in triple-negative brEast cancer patients with newly Diagnosed or prOgressing brain metastases (TUXEDO-2)

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Background: Breast cancer (BC) is the second most common cause of brain metastases (BM) among solid malignancies. Approximately 40 % of patients with metastatic triple-negative BC (TNBC) will develop BM, resulting in increased morbidity and mortality. In HER2-postive BC, systemic therapy has evolved as a standard approach to prevent or delay whole-brain radiotherapy. Currently, no systemic treatment option exists for TNBC BM. TUXEDO-2 investigates the activity and safety of the Trop2-directed antibody-drug conjugate datopotamab deruxtecan (Dato-DXd) in patients with active TNBC BM.

Methods: TUXEDO-2 is a prospective single-arm, single-centre phase II trial. The study includes adult patients with TNBC and newly diagnosed untreated BM or BM progressing after prior local therapy with or without extracranial metastases. Dato-DXd is administered at a dose of 6.0 mg/kg once every 3 weeks by intravenous infusion until progression, inacceptable toxicity or discontinuation for any other reason. Cranial MRIs are conducted after the second and fourth administration and once every three cycles thereafter.

The primary study endpoint is intracranial response rate (RR) centrally assessed by Response Assessment in Neuro-Oncology (RANO) BM criteria. Secondary endpoints consist of extracranial RR, progression-free survival, overall survival, safety, quality-of-life, and neurocognitive function. Based on a Simon's two-stage design (RR under alternative hypothesis >35 %; RR under null hypothesis ≤11 %), 8 patients will be accrued in the first stage. If ≥2 responses are observed, 12 additional patients will be included for a total of 20 patients. The null hypothesis will be rejected if ≥5 responses are observed.

O26

Effect of genetic manipulation of p53 on drug sensitivity in cancer cell lines

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Introduction and aims: Due to their inhibitory effect on tumor cell apoptosis, loss-of-function mutations in the p53 gene have long been considered to play a major role concerning drug resistance in many tumors. However, a paradox role of wildtype p53 has been described recently which mediates drug resistance in tumor cells by adopting a slow-cycling phenotype (Webster MR, Molecular Cell). The above-mentioned opposite effects make it necessary to thoroughly investigate the role of p53 on sensitivity towards various anti-cancer drugs in different tumors.

Material and methods: By genetically manipulating the p53 mutated colon cancer cell line SW620 we compared the effect of P53 function on sensitivities towards cytotoxic drugs including 5-Fluoruracil, Cytarabine and Azacitidine with sensitivities towards various Tyrosine Kinase Inhibitors (TKIs) including Ponatinib, Bosutinib and Imatinib. Cells were incubated with different concentrations of compounds and MTT assays were performed in order to gain data for subsequent calculation of IC50 values.

Results: Our results show that as compared to unmanipulated SW620 the substitution of wildtype p53 consistently decreased the IC50 values in the presence of cytotoxic drugs but increased IC50 in the presence of TKIs.

Conclusion: We conclude that the role of p53 on in vitro sensitivity towards various anti-cancer drugs may profoundly differ between classical cytotoxic compounds and TKIs. Our in vitro observation is compatible with the clinical in vivo experience that the chemotherapy resistance of chronic lymphocytic leukaemia patients with p53 mutations can be overcome by TKIs inhibiting the Bruton Tyrosine kinase.

O27

In vitro effect of targeted drugs in cancer cells with epithelial-mesenchymal transition

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Introduction and aims: Epithelial-mesenchymal transition (EMT) is a cellular process during which epithelial cells acquire mesenchymal phenotypes and behavior following downregulation of epithelial features. During the multistep progression of

cancer, epithelial cells acquire mesenchymal features that enable them to invade adjacent tissues, locally, and then to disseminate to distant tissues. Most importantly, EMT programs have been linked to resistance to anticancer drugs. The effect of novel cancer drugs such as Tyrosine Kinase Inhibitors (TKIs) in cancer cells showing EMT is poorly investigated. Therefore, the objective of this study is to examine how various TKIs and cytotoxic drugs effect the apoptosis/proliferation of cancer cells by performing cell viability assays.

Material and methods: Through immunohistochemistry it was shown that the colon cancer cell line SW620 strongly expresses Vimentin which acts as a marker of EMT. Consequently, we chose this model to determine the effects of anticancer drugs on cell growth through developing an approach using the MTT assay as a main technique. The assays provided the raw data to subsequently calculate the IC50 values for each compound and thus compare drug potency in EMT cells.

Results: The analysis and comparison of the IC50 values of different anti-tumor compounds revealed that some TKIs such as Ponatinib and Imatinib have inhibitory concentrations beneath 0.1 µM whereas certain cytotoxic drugs such as Cytarabine and Azacitidine only start to affect SW620 cells when added in concentrations above 1 µM.

Conclusions: This in vitro research emphasizes a potential therapeutic role of TKIs in cancer cells undergoing EMT.

O28

Treatment patterns of upper-GI adenocarcinoma: a single center, retrospective analysis

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Upper gastrointestinal adenocarcinoma are relevant cancerous diseases, whose outcome is still disadvantageous. The aim of this study is to investigate the treatment patterns of upper gastrointestinal adenocarcinoma, starting from the first line of palliative treatment and to analyze their effects on survival rates, regardless of curative treatment. The study is based on a real-life population of patients diagnosed with esophageal or gastric adenocarcinoma between 2007 and 2021. For that, retrospective data was collected for patients, diagnosed at the Ordensklinikum Linz. In total, 286 patients with advanced gastrointestinal adenocarcinoma were included in this study. 160 out of 286 patients received palliative therapy. The advantage of palliative chemotherapeutic treatment has been proven, as patients who underwent at least one palliative-line treatment had a median overall survival of 11.76 months, compared to 2.56 months without treatment ($p < 0.0001$). It has been demonstrated that overall survival enhanced. Clinical performance is important on decision making whether treatment is indicated or not. It could be demonstrated, that ECOG 0 was significantly less frequent, and ECOG ≥2 significantly more frequent in patients who received palliative chemotherapy ($p < 0.001$). It was shown that most patients did not have comorbidities according to the CCI, but scores raised regarding the age-adjusted CCI, as primary diagnosis appears more often at advanced age. Patients of higher age were significantly ($p < 0.001$) less likely to receive palliative therapy.

The result of this study provides insights into the current management of upper gastrointestinal adenocarcinoma and the effects of palliative treatment.

O29

Association of family history with patient characteristics and prognosis in a large European gastroesophageal cancer cohort

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Introduction: The role of family history in the development and prognosis of gastroesophageal cancer is a controversially discussed topic as appropriate data from Western cohorts are lacking. Therefore, we aimed to investigate its associations with other disease and outcome parameters in a large European cohort.

Methods: We retrospectively analyzed self-reported family history in patients with gastroesophageal cancer treated between 01/01/1990 and 31/12/2021 at the Medical University of Vienna. Association analyses with patient characteristics, tumor characteristics, symptoms and overall survival (OS) were performed.

Results: In our cohort of 1762 gastroesophageal cancer patients, 592 (34 %) reported positive family history for cancer (159 (9 %) gastroesophageal cancer). Positive family history was not associated with histopathological parameters or initial symptoms. However, there was an association with female gender (cancer in general: $p = 0.011$; gastroesophageal cancer: $p = 0.015$). Family history for cancer in general was associated with earlier cancer stages ($p = 0.04$), higher BMI ($p = 0.005$) and alcohol consumption ($p = 0.010$). While positive history for gastroesophageal cancer was associated with higher age at diagnosis ($p = 0.002$) and stomach cancer ($p = 0.002$). There was no statistically significant association of positive family history with OS ($p = 0.1$, $p = 0.45$), also not in subgroups for histology, number of family members and degree of relative.

Conclusion: Our results emphasize that positive family history is neither statistically significantly associated with worse prognosis nor with specific histopathological features in patients with gastroesophageal cancer. Yet, associations with distinct patient characteristics and positive family history indicate that these subgroups might profit from endoscopic surveillance. Prospective studies are warranted to further investigate these findings.

O30

Real-World Data on Trastuzumab-Deruxtecan (T-DXd) and pulmonary toxicity: a retrospective single-centre analysis

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Background: Trastuzumab-Deruxtecan (T-DXd) is a HER2-targeting antibody-drug conjugate (ADC). It is approved for HER2-positive and „HER2-low" metastatic breast cancer and HER2-positive metastatic gastric cancer. Drug-related interstitial lung disease (ILD)/pneumonitis is a common and sometimes serious adverse event associated with T-DXd. In the T-DXd clinical trials most cases of pneumonitis were low grade and detected early because of frequent screening measures. Real-life data on the toxicity of T-DXd is lacking.

Methods: We analysed all patients who were treated with T-DXd at our centre between June 2021 and November 2023. Data was collected retrospectively from electronic medical records.

Results: 24 patients were included in the analysis. Median age was 63 years (range: 43–82). 14 patients (58.3 %) were treated for „HER2-low" breast cancer, 7 (29.1 %) patients for HER2+ breast cancer, 2 (8.3 %) patients for HER2+ gastric cancer and 1 patient (4.2 %) for HER2+ extramammary Paget's disease. Median PFS and OS were 8 and 13.2 months, respectively. ILD/pneumonitis occurred in 4 (16.7 %) patients, with severe ILD/pneumonitis (≥ Grade 3) in 3 of those patients. Median onset of ILD/pneumonitis was 66 days after start of T-DXd (Range: 12–102 days).

Conclusion: The rate of ILD/pneumonitis was similar to that in the T-DXd clinical trials. However, some cases of ILD/pneumonitis in our study were of higher grade, highlighting the need for diligent early detection and treatment of ILD in a real-world setting. We aim to present a wider analysis of patients treated with T-Dxd at the congress.

O31

Kardiotoxizität durch die kurative Strahlenbehandlung thorakaler Tumore. Entwicklung und Maßnahmen im Rahmen der klinischen Routine anhand des Mamma- und Lungenkarzinoms

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Einleitung: Die kurative Strahlenbehandlung beim Mammakarzinom und Lungenkarzinom ist integraler Bestandteil einer tumorspezifischen Therapie. Pat*Innen mit einem Mammakarzinom werden nach brusterhaltender Operation nahezu ausnahmslos und nach modifizierter radikaler Mastektomie bei Vorliegen von Risikofaktoren postoperativ bestrahlt. Ein nicht unwesentlicher Anteil der Pat*Innen ist dabei unter 60 Jahren. Pat*Innen können akute und/oder chronische kardiale Nebenwirkungen auch durch andere erforderliche Therapiestrategien erfahren (Systemtherapie wie Chemotherapie oder Antikörpertherapie) bzw. diese können durch eine individuelle Vorschädigung/-erkrankung verstärkt werden. Vor allem bei linksseitigem Mammakarzinom ist eine potentielle Kardiotoxizität zu beachten und so gering wie nur möglich zu halten.

Methode: Es gibt mittlerweile eine Reihe von technischen Zugängen, die eine Dosisüberschreitung am Herzen vermeiden. Die Strahlenbehandlung im Falle eines Lungenkarzinoms wird je nach Stadium in der Kombination mit Systemtherapie (konkomitant/sequentiell) oder als alleinige Therapie durchgeführt und unterliegt aufgrund der sensiblen Strukturen in der Umgebung ebenso strengen Beschränkungen. Auch hier konnte technisch aber auch durch bessere Diagnostik und das individuelle Beachten der Zielvolumenkonzepte prä- und posttherapeutisch (Systemtherapie, Operation) eine deutliche Reduktion potentieller Nebenwirkungen erreicht werden.

Schlussfolgerung: Das Risiko für Strahlenfolgen am Herzen im Rahmen einer Behandlung thorakaler Tumore ist bekannt und wird mit geeigneten Bestrahlungstechniken minimiert. Der konsequente Einsatz von modernen Bestrahlungsmethoden wird individuell angepasst und hält die Strahlenbelastung des Herzens in einem akzeptablen Ausmass. Das Risiko für chronische Spätkomplikationen am Herzen wird dadurch so gering wie möglich gehalten, sodass es unter Berücksichtigung der individuellen Vorteile der kurativen Behandlung keine wesentliche Rolle spielt.

O32

Zurückgezogen

O33

Real-world data on pembrolizumab in advanced MSI-high colorectal cancer—a single center experience

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Introduction: First-line therapy for MSI-high/dMMR colorectal cancer (CRC) is pembrolizumab, according to the registrational KEYNOTE-177 study. Real-world data are needed.

Methods: In this retrospective, single center analysis, we report data from 10 patients with advanced (stage IV) MSI-high/dMMR CRC, who were treated with pembrolizumab (200 mg 3-weekly). Data cut-off is 10/2023 with a mean follow-up time of 1.6 years. Data were compared with results from KEYNOTE-177.

Results: Median line of therapy in our study was 1 (70 %, range 1–4). The overall response rate was 70 % (7/10 patients), compared to 43 % in KEYNOTE-177.

Partial responses (PR) could be attested in 70 % (7/10) of total cases in our study with no complete responses, compared to 32,7 % PR rate and 11,1 % complete response rate in KEYNOTE-177.

With a mean follow up time of 1.6 years, all 7 responding patients have not encountered progressive disease as of yet.

Concerning safety, 2/7 (29 %) of our responding patients discontinued treatment due to grade 3/4 immune-related toxicity (e. g., myocarditis and adrenal insufficiency). In comparison, grade 3/4 events were detected in 9 % in KEYNOTE-177.

3/10 (30 %) patients had progressive disease as their best response, compared to 29,4 % in KEYNOTE-177.

Conclusion: Real-world data confirm the efficacy of pembrolizumab monotherapy in advanced MSI-high/dMMR CRC. Safety issues however should not be underestimated.

O34

Therapeutic vulnerabilities in KRAS-mutant lung adenocarcinoma unmasked by afatinib

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>40 % of patients with lung adenocarcinoma (AC) harbor oncogenic KRAS mutations that are associated with poor prognosis. KRAS inhibitors have remained elusive; only recently covalent KRAS inhibitors targeting the G12C mutation have entered in clinics. However, a vast majority of patients fails to respond, emphasizing the unmet need for effective pharmaceuticals. We have recently demonstrated hypersensitivity of KRAS-driven lung AC to afatinib, a pan-ErbB (EGFR, HER2, HER4) inhibitor, in several preclinical models. Exposure to afatinib as single agent is expected to lead to resistance followed by tumor recurrence/relapse. Therefore, drug combinations will be required to achieve maximum response.

A high-throughput drug screen suggested inhibitors of AURORA A/B as preferred partners of afatinib. Pairwise drug combination viability assays in a panel of human lung AC cells with different KRAS mutations revealed a pronounced in vitro synergy in low nanomolar range. Dose-response experiments and colony formation assays verified the synergistic nature.

AURORA kinase A activation has been implicated in the development of resistance to third generation EGFR inhibitors in EGFR-mutant lung AC. Similarly, in response to afatinib monotherapy, KRAS-mutant lung AC cells demonstrated heightened phosphorylation of AURORA A. Simultaneous inhibition of both AURORA kinases and ErbB family suppressed this adaptive survival program, inducing apoptosis as revealed by a significant increase in annexin V staining. In line, cell cycle profiling revealed that concomitant treatment significantly increased the proportion of cells in sub-G1 compartment, which represents dead cells.

These findings provide an exciting ground for the best management of patients with KRAS-driven lung adenocarcinoma.

O35

DNA methylation profiling correlates with pathologic complete response in patients with early triple negative breast cancer treated with chemoimmunotherapy

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Introduction: Immune checkpoint inhibitors (ICI) are an important treatment pillar in solid cancers and standard components of systemic therapy in early triple negative breast cancer (eTNBC) independent of PD-L1 status. However, so far, no reliable biomarker exists to predict therapy response. We investigated immune cell DNA methylation as biomarker for pathologic complete response (pCR) at surgery after neoadjuvant chemoimmunotherapy.

Methods: eTNBC patients treated with chemoimmunotherapy at the Medical University of Vienna were included. Leukocyte DNA was isolated from blood samples collected at baseline before start of neoadjuvant systemic therapy. Methylation profiling was performed with Infinium Methylation EPIC microarrays and routine histologic work-up from surgery determined a pCR or non-pCR according to pathologic standard procedures.

Results: In this preliminary analysis 7 eTNBC patients (all female), with a median age of 63 years (40–83 years) were available and received neoadjuvant chemoimmunotherapy with pembrolizumab plus weekly paclitaxel/carboplatin followed by pembrolizumab plus epirubicin/cyclophosphamide. In 3/7 (42.9 %) of patients a pCR could be observed while in 4/7 (57.1 %) residual disease was present at surgery. DNA methylation profiling showed two distinct methylation clusters between patients with pCR and non-PCR based on the top 500 differentially methylated CpG sites.

Conclusion: In this analysis, we detected differentially methylated blood leukocyte DNA genes between eTNBC patients who achieved a pCR and patients with non-pCR after neoadjuvant chemoimmunotherapy. Therefore, circulating immune cell methylation profiling might reveal affected genes and might serve as predictive biomarker for immunotherapy response. Enlarging the patient cohort is currently ongoing and needed to validate our findings.

O36

Longitudinal analysis of PD-L1 expression in patients with relapsed NSCLC

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Background: The use and approval of checkpoint-inhibitors (CI) for the treatment of non-small-cell-lung-cancer (NSCLC) depends on PD-L1 expression. The purpose of this study was a longitudinal analysis of PD-L1 expression during the course of disease in patients with relapsed NSCLC.

Methods: We retrospectively compared PD-L1 expression of early stage NSCLC with subsequent relapse in preoperative samples, matched surgical specimens and biopsy samples of disease recurrence. Ventana PD-L1 (SP263) immunohistochemistry assay was used for all samples. PD-L1 expression was scored based on clinically relevant groups (0 %, 1–49 %, ≥50 %). Primary endpoint was the change of PD-L1 score-group between preoperative samples, matched surgical specimens and relapsed tumor tissue.

Results: 395 patients with stage I-III NSCLC were identified between 2015 and 2020 of whom 136 (34 %) patients experienced relapse. For 87 patients at least two specimens for comparison of PD-L1 expression between early stage and relapsed disease were available. In 72 cases analysis between preoperative biopsy, surgical specimen and rebiopsy of disease recurrence was possible. When comparing preoperative and matched surgical specimens, we found treatment relevant group change in 25 patients (34.7 %). Neoadjuvant treatment showed no significant effect on PD-L1 alteration ($p=0.39$). In 32 (36.8 %) out of 87 cases a change of PD-L1 group was observed when samples of disease relapse were compared to surgical tissue. Thirty-nine patients (54.2 %) showed at least one change into a different PD-L1 score group during the course of disease.

Conclusion: PD-L1 expression shows dynamic changes. Consensus guidelines on PD-L1 assessment are urgently needed.

Klinische Studie

S01

FRESCO-2: A global phase 3 multiregional clinical trial evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer (mCRC)

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Introduction and aim: Fruquintinib, a highly selective, oral inhibitor of all three VEGF receptors, was approved in China for 3L+ mCRC based on results from FRESCO (NCT02314819). FRESCO-2 (NCT04322539) evaluated fruquintinib in more heavily pretreated patients, reflecting current global practices.

Materials and methods: Patients were enrolled in the US, Europe, Japan, and Australia and randomised 2:1 to fruquintinib 5 mg or matching placebo PO daily, for 21 days every 28 days, plus best supportive care (BSC). Key criteria: prior chem-

otherapy, anti-VEGF therapy and, if RAS wildtype, anti-EGFR therapy; if BRAFV600E mutant or MSI-H, a targeted regimen; and prior trifluridine/tipiracil and/or regorafenib. Primary endpoint: overall survival (OS).

Results: From 14/08/2020–02/12/2021, 691 pts were randomised (fruquintinib+BSC:461 vs placebo+BSC:230; Europe $n=495$, fruquintinib+BSC:329 vs placebo+BSC:166; Austria $n=11$, fruquintinib+BSC:5 vs placebo+BSC:6). Baseline characteristics were balanced. Fruquintinib+BSC vs placebo+BSC significantly improved OS (median 7.4 vs 4.8 months; HR 0.66 [95 %CI 0.55–0.80]; $p<0.001$) and PFS (median 3.7 vs 1.8 months; HR 0.32 [95 %CI 0.27–0.39]; $p<0.001$); results were consistent in the European subgroup (median OS 7.6 vs 4.6 months; HR 0.69 [95 %CI 0.55–0.86]; median PFS 3.7 vs 1.9 months; HR 0.32 [95 %CI 0.26–0.40]). Grade ≥3 adverse events were reported in 62.7 % (fruquintinib+BSC) vs 50.4 % (placebo+BSC) of patients.

Conclusion: There was a clinically meaningful improvement in OS with fruquintinib+BSC v placebo+BSC in patients with refractory mCRC. The fruquintinib safety profile was consistent with the established profile for fruquintinib monotherapy. Fruquintinib was FDA-approved for previously treated mCRC, regardless of biomarker status, providing a new treatment option in refractory mCRC.

S02

Phase 3 study of tucatinib, trastuzumab, and modified FOLFOX6 as first-line treatment in HER2+ metastatic colorectal cancer (MOUNTAINEER-03, trial in progress)

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Introduction and aim: Standard of care (SOC) for treatment of metastatic colorectal cancer (mCRC) is multi-agent chemotherapy, +/– a VEGF or EGFR inhibitor. HER2 amplification occurs in 3 %–5 % of mCRC patients, and ~5 %–14 % of patients with RAS/BRAF wild-type (WT) mCRC tumors. Tucatinib (TUC), a highly selective, HER2-directed tyrosine kinase inhibitor, is approved in multiple regions for HER2+ metastatic breast cancer and mCRC. MOUNTAINEER (NCT03043313) demonstrated that TUC and trastuzumab had clinically meaningful activity (38.1 % confirmed objective response rate [ORR], 12.4 months median duration of response) and was well tolerated in patients with treatment-refractory RAS WT HER2+ mCRC. MOUNTAINEER-03 will investigate TUC plus modified FOLFOX6 (mFOLFOX6) + trastuzumab in patients with RAS WT, HER2+ mCRC.

Material and methods: MOUNTAINEER-03 (NCT05253651) is a global, open-label, randomized, phase 3 study for first-line treatment of HER2+ and RAS WT locally advanced/unresectable or mCRC. ~400 adult patients will be randomized 1:1 to TUC experimental arm (TUC [300 mg PO BID] + trastuzumab + mFOLFOX6) or the SOC arm (mFOLFOX6 +/– bevacizumab or cetuximab). Patients may have received maximum 2 doses of mFOLFOX6 in locally advanced/unresectable or metastatic setting before randomization, and/or adjuvant chemotherapy if completed >6 months before enrollment. Randomization is stratified by primary tumor location, liver metastases, and number of prior mFOLFOX6 chemotherapy doses. Primary endpoint is progression-free survival. Key secondary endpoints are overall survival and confirmed ORR. Enrollment is ongoing in all regions.

Abstract previously presented at ESMO 2022, Final Publication Number: 1037, by Thierry Andre (reused with permission)**:**

S03

Phase 3 study of tucatinib or placebo in combination with trastuzumab and pertuzumab as maintenance therapy for HER2+ metastatic breast cancer (HER2CLIMB-05, trial in progress)

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Introduction and aims: First-line (1L) standard of care (SOC) for human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (MBC) is trastuzumab (T) plus pertuzumab (P) and a taxane; most patients progress during maintenance therapy with T+P. Tucatinib is a tyrosine kinase inhibitor (TKI) approved in combination with T and capecitabine for HER2+ MBC with and without brain metastases (BM). In HER2CLIMB, tucatinib significantly improved outcomes in patients with HER2+ MBC, was well tolerated, and reduced the risk of disease progression or death in patients with untreated and/or active BM. HER2CLIMB-05 investigates tucatinib in 1L SOC maintenance therapy.

Material and methods: HER2CLIMB-05 (NCT05132582) is a phase 3, randomized, double-blind study evaluating whether adding tucatinib to 1L SOC maintenance therapy extends progression-free survival (PFS) while maintaining quality of life (QOL). Approximately 650 patients will be randomized 1:1 to either tucatinib or placebo twice daily, with T+P once every 21 days. Eligibility criteria include advanced HER2+ disease, no progression on prior 1L SOC, Eastern Cooperative Oncology Group performance status of 0 or 1, and no or asymptomatic BM. Exclusion criteria include prior treatment with anti-HER2 and/or anti-epidermal growth factor receptor TKI, or inability to undergo imaging of the brain.

Primary endpoint is investigator-assessed PFS. Secondary endpoints include overall survival, health-related QOL, central nervous system PFS, safety, and pharmacokinetic parameters.

Enrollment is ongoing in Europe (including Austria), North America, and several Asia-Pacific and Latin America countries.

Abstract previously presented at ESMO-BC 2022, Final Publication Number: 415, by Véronique Diéras (reused with permission).

S04

Acute Myeloid Leukemia monotherapy treatment: oral decitabine/cedazuridine vs intravenous decitabine—key results from a randomized, crossover pharmacokinetics study for registration approval

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Introduction: Parenteral hypomethylating agents (HMAs) decitabine and azacitidine, are approved in Europe (EU) for adult acute myeloid leukemia (AML) patients unfit for standard induction chemotherapy, alone or with venetoclax. DEC-C, an oral fixed-dose combination of decitabine (DEC) and cedazuridine (CED), a cytidine deaminase inhibitor, is now approved in the EU as monotherapy for AML patients not suitable for intensive induction therapy.

Aims: To present final AML clinical outcomes, including genetic and risk classification analyses.

Method: Patients were randomized 1:1 to 5 days of either intravenous DEC or oral DEC-C cycle 1 and the reverse in cycle 2. The primary endpoint was 5-day Area Under the Curve (AUC) pharmacokinetic exposure equivalence. From Cycle 3, all patients received Dec-C in 28-day cycles to evaluate safety and efficacy. Baseline molecular abnormalities were identified using a next-generation sequencing (NGS) panel. The study also examined the impact of DEC-C monotherapy on survival prognosis, referencing the latest ICC and ELN risk stratification.

Results: Of 69 PK-evaluable patients, systemic exposure was equivalent between formulations (5-day AUC ratio 99.64 % [90 % CI 91.23 %–108.80 %]). Demethylation rates were similar (≤1.1 % difference). Oral DEC-C showed median overall survival (8.9 months [CI: 6.0, 13.1 mos.]), clinical response (CR rate 21.8 %, CI 13.7, 32.0) and safety profile comparable to intravenous decitabine. In this older cohort (median age 78 years), neither the ELN nor ICC 2022 classification predicted survival. TP53 mutations correlated with poorer survival.

Conclusion: These findings support that Oral DEC-C monotherapy is an applicable treatment for AML patients ineligible for intensive chemotherapy.

S05

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 3000 (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.

S06

AGMT_CLL_Reg: Patient Registry

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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

AGMT_LungCA_Reg: Patient Registry

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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).

S08

AGMT_MBC_Reg: Metastatic breast cancer in Austria

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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

S09

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)

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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).

S10

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

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

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

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

S11

GMMG-HD8/DSMM XIX

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Full Title: „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" This is a prospective, multic enter, 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.

S12

Zanubrutinib in patients with Waldenström's macroglobulinemia, chronic lymphocytic leukemia, Marginal zone lymphoma and Follicular lymphoma (ARIADNE)

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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) Chronic lymphocytic leukemia (CLL), Marginal zone lymphoma (MZL) and Follicular lymphoma (FL) 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, where data is rare in all cohorts, patient's QoL and effectiveness of zanubrutinib treatment in adult patients with WM, CLL, MZL and FL in a real-world setting.

S13

Pola-R-ICE

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Full 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)" 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.

S14

R-Pola-Glo

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Full Title: „A prospective multicenter phase 2 study of the chemotherapy-light combination of intravenous rituximab with the antibody-drug conjugate polatuzumab vedotin and the bispecific antibody glofitamab in previously untreated aggressive B-cell lymphoma patients above 60 years of age ineligible for a fully dosed R-CHOP" 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: Previously not treated patients diagnosed with a histologically confirmed aggressive large B-cell lymphoma above >60 years of age not eligible for a fully dosed R-CHOP-like therapies will be included.

The primary objective of the trial is to evaluate an estimator of efficacy of the chemotherapy-light combination of glofitamab, polatuzumab vedotin and rituximab in patients with previously untreated aggressive large B-cell lymphoma. The results shall be used for initial effect estimation and planning of a subsequent phase III trial.

The secondary objectives of the trial are designed to

i.) further characterize the outcome and

ii.) to evaluate the safety and tolerability of the chemotherapy-light combination R-Pola-Glo in untreated patients with aggressive B-cell lymphoma.