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Basel (Switzerland), November 20–22, 2024

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7TH SWISS ONCOLOGY AND HEMATOLOGY CONGRESS (SOHC)

BASEL, NOVEMBER 20–22, 2024

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SSH BEST ABSTRACT & AWARD SESSION – HEMOSTASIS, TRANSFUSION MEDICINE, VASCULAR, LABORATORY MEDICINE, BENIGN HEMATOLOGY

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Functional Platelet Generation from Engineered Megakaryocyte Cell Line Derived from Adult CD34+ Hematopoietic Cells Using a Modified Rotating Bed Bioreactor.

M. Humbert[1,2], Y. Grand[1], C. Rocca[1], P. Jeandet[1], V. Boand[1], V. Tâche[1], O. Naveiras[2,3], L. Burnier[1]

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Introduction: Platelet concentrates are crucial for managing severe thrombocytopenia, particularly prevalent in onco-haematology. Currently, platelets are sourced solely from blood donations, but their short shelf life (5-7 days) creates significant supply challenges, particularly during health crises or holiday periods. To address these limitations, we have developed a method to generate platelets from an engineered megakaryocytic cell line, derived from adult CD34+ hematopoietic cells, using a modified rotating bed bioreactor.

Methods: CD34+ hematopoietic cells were isolated from G-CSF-mobilized peripheral blood from adult donors. These cells were transduced with over 40 different gene combinations, controlled by doxycycline. Cells were cultured in serum-free media for expansion and differentiated into megakaryocytes (MKs) in the absence of doxycycline. Derived megakaryocytes were characterized by flow cytometry for key surface markers, including GPIIIa, GPIIb, GPIb, and GPVI. For platelet production, cells were transferred to HemostOD's modified rotating bed reactor containing microstructures in a 200 mL bioreactor, where they were spun at 900 RPM for two hours. The resulting platelet-like particles were analysed for surface marker expression (GPIIIa, GPIb), membrane integrity using CalceinAM, and functionality through convulxin and thrombin agonist-induced fibrinogen binding via flow cytometry.

Results: CD34+ cells transduced with specific homeobox gene family members exhibited long-term culture capability (up to 4 months) and megakaryocytic differentiation potential. The megakaryocytes generated from the cell bulk expressed GPIIIa+GPIb+ (16.6% ± 3) and GPVI+GPIIb+ (8.4% ± 3.3) markers and are polyploids. Platelet-like particles generated in HemostOD's bioreactor were intact and functional, showing GPIIIa+GPIb+CalceinAM+ expression and fibrinogen binding upon activation with convulxin and thrombin (39.35% ± 15.54), respectively.

Conclusions: In this study, we successfully established a megakaryocytic cell line derived from adult CD34+ haematopoietic cells that supports megakaryocytic differentiation in culture. Moreover, megakaryocytes produced from these transduced cells were able to generate functional platelets using a modified rotating bed bioreactor system.

SSH/SSMO BEST ABSTRACT & AWARD SESSION – EXPERIMENTAL HEMATOLOGY / ONCOLOGY

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POTENCY TUNED NOVEL CD70 CAR-T CELLS WITH A COMPUTATIONALLY DESIGNED CD27:CD70 BINDING INTERFACE FOR ACUTE MYELOID LEUKEMIA

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Introduction: The development of chimeric antigen receptor (CAR) T cell therapy for AML has met difficulties. Recently, CD70 emerged as an attractive target due to its differential expression on malignant versus normal hematopoiesis, evident role in AML biology, and compelling safety profile. Here, we adopted a rational approach to generate novel CD70 CARs with enhanced potency against AML.

Methods: To identify the optimal assembly of CAR structure, extracellular domain from natural ligand CD27 was paired with various hinge, transmembrane (TM), endodomains and encoded into a third-generation lentiviral vector. To optimize the CD27-CD70 binding interface, protein design calculations using physics and deep learning-based algorithms were applied. CAR-T cells produced with a good manufacturing practice-compatible protocol were evaluated for cytotoxicity in a sequential killing assay co-cultured with CD70+ MOLM-13.GFP-ffLuc AML cells. In vivo anti-leukemic activity was assessed in a MOLM-13.GFP-ffLuc xenograft or CD70low patient-derived xenograft model. Off-target screening of final candidate was performed by Retrogenix Cell Microarray technology.

Results: Among the four CAR assemblies tested, one displayed robust killing of AML cells ($p < 0.05$, n=3 donors) with significantly higher IFNγ and IL-2 production in vitro (IFNγ: $p < 0.001$, IL2: $p < 0.001$). At non-curative doses, the construct strongly suppressed leukemic growth and improved overall survival of mice in vivo (MOLM-13.GFP-ffLuc: BLI: $p < 0.01$, survival: $p < 0.05$, n=5 mice/group; PDX: complete leukemia clearance, n=4 mice/group). A total of 32 affinity-modulated variants with optimized binding interface were selected from computational designs and examined functionally. We identified two variants with better efficacy than the parental construct in vivo ($p < 0.05$, n=4-8 mice/group), accompanied with long-term persistence of functional CAR-T cells. Off-target screening of the most potent variant against 6500 human proteins showed no off-target interactions.

Conclusions: We demonstrated the enhanced potency of our CD70 CARs with an unique assembly and optimized binding interface, against AML. Our lead candidate has maintained specificity without off-target interactions. Together, our data showed the feasibility of integrating computational protein design in CAR development to identify potent candidates and instruct better molecule selection for clinical translation.

SSH/SSMO BEST ABSTRACT & AWARD SESSION – CLINICAL HEMATO-ONCOLOGY

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Comparing stem cell mobilization with chemotherapy and cytokine (G-CSF) versus cytokine alone in myeloma patients (MOCCCA): A randomized phase II, open-label, non-inferiority trial.

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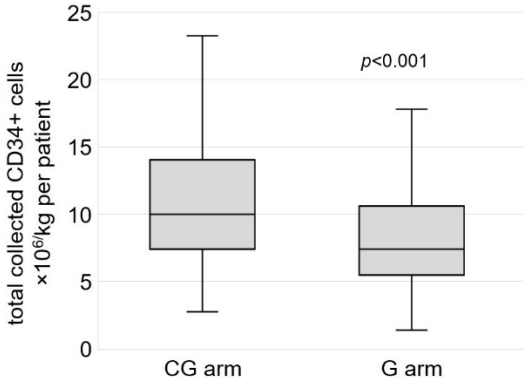
Introduction: In fit patients with newly diagnosed myeloma, high-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) is considered standard of care. For mobilization of CD34+ cells for ASCT, combined cytotoxic chemotherapy and G-CSF is commonly used. However, the importance of cytostatic chemotherapy for reliable mobilization remains unclear.

Methods: This prospective randomized phase II non-inferiority trial compared G-GSF only (G) compared to standard chemotherapy/G-CSF (CG) for CD34+ mobilization. The primary endpoint was a less than 15% difference in successful stem cell collection (≥5·0×106 CD34+ cells/kg b.w. in a single day collection procedure without additional stimulation with plerixafor) with the G regimen.

Results: 136 patients were 1:1 randomized. 94 (69%) of all patients had successful stem cell mobilization with total collected CD34+ cells >5·0×106 CD34+ cells/kg in a single day apheresis procedure without additional plerixafor, 53 (78%) patients in the CG arm and 41 (60%) in the G arm (p=0·04). With an 18% difference in favor of the CG therapy, the non-inferiority margin was not maintained (95% CI 1%, 34%, p=0·04). The median total CD34+ yield was 9·99×106/kg b.w. in CG patients and 7·42×106/kg b.w. in patients with G-CSF alone (p <0·001). There were no differences in adverse events, hematologic engraftment, quality of life, or pain perception between the groups, but more patients in the G arm needed additional plerixafor with 18 (26%) patients versus 9 (13%) patients in the CG arm, respectively (p=0·06). Ultimately, 130 (96%) patients proceeded to HDCT with ASCT. The median time until neutrophil engraftment (neutrophil count >0·5×109/l) after ASCT was 11 (median IQR 10-15) days in CG patients compared to 12 (median IQR 11-17) days in G patients (p=0·31), and the median time until platelet engraftment (platelet count ≥20×109/l) was 12 days in both groups (p=0.17).

Conclusions: Our data indicate that G-CSF only is inferior to chemotherapy with G-CSF for peripheral CD34+ stem cell mobilization.



SSMO BEST ABSTRACT & AWARD SESSION – CLINICAL SOLID TUMOR ONCOLOGY

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Adjuvant Aspirin Treatment in PIK3CA Mutated Colon Cancer Patients – The Phase III, Prospective-Randomized Placebo-Controlled Multicenter SAKK 41/13 Trial

U. Güller[1,2], S. Hayoz[3], D. Horber[4], W. Jochum[5], S. De Dosso[6], D. Koeberle[7], S. Schacher[8], R. Inauen[9], M. Stahl[10], T. Delaunoit[11], T. Ettrich[12], G. Bodoky[13], P. Michel[14], T. Koessler[15], K. Rothgiesser[3], S. Calmonte[3], M. Joerger[16,17]

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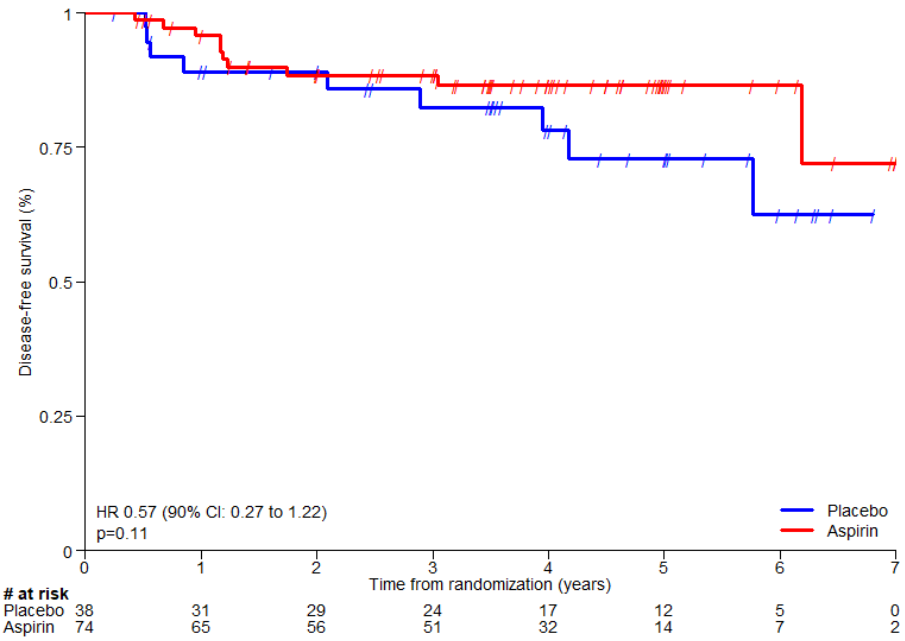
Introduction: Retrospective studies suggest adjuvant aspirin to be protective after colon cancer surgery, but this effect may be limited to patients with activating PIK3CA mutations. SAKK 41/13 assessed the benefit of adjuvant aspirin in PIK3CA-mutant colon cancer.

Methods: SAKK 41/13 is a randomized, placebo-controlled, double-blind international trial. Stage II and III colon cancer patients with a centrally-confirmed, activating PIK3CA mutation (exons 9, 20) were included. Patients were randomized 2:1 to daily aspirin 100mg or placebo for 3 years. The primary endpoint was disease-free survival (DFS), secondary endpoints included overall survival (OS), time-to relapse (TTR) and safety. One-sided type I error was 5% with a power of 80% to detect a hazard ratio (HR) of <0.456. The computed sample size was 185, with a number needed to screen of 1'088 patients. SAKK 41/13 was prematurely closed due to financial constraints.

Results: We screened 1'040 patients for PIK3CA mutations and randomized 112 patients to aspirin (N=74) and placebo (N=38),

respectively. Baseline patient characteristics were well-balanced between groups, with an overall median age of 66 years (range 29-89) and 42.9% of patients being female. After a median follow-up of 4 years, 19 DFS events occurred, including 10 in the aspirin group and 9 in the placebo group, respectively. The HR for DFS was 0.57 (90% CI 0.27-1.22) in favor of aspirin (p=0.11). Five-year DFS rates were 86.5% (90% CI: 77.7%-92.0%) in the aspirin group and 72.9% (90% CI 55.7%- 84.3%) in the placebo group, respectively. The HR for TTR was 0.49 (90% CI 0.21-1.19, p=0.089) in favor of aspirin. Both unstratified HR for OS (0.71, 90% CI 0.23-2.13, p=0.3) and stratified HR for OS (0.60 (0.15-2.43) were in favor of aspirin We did not documend any aspirin-related serious AEs.

Conclusions: SAKK 41/13 is the first prospective, randomized trial to provide clinical evidence of a protective effect of adjuvant aspirin in patients with resected, PIK3CA-mutant colon cancer, with a clinically relevant 43% DFS improvement and 51% TTR improvement. Even though the results are not statistically significant due to premature study closure, adjuvant aspirin warrants individual consideration in patients with resected, PIK3CA-mutant colon cancer stage II and III.



ONCOREHA/OPS/PALLIATIVE.CH/SOHC BEST ABSTRACT & AWARD SESSION – NURSING, SUPPORTIVE & PALLIATIVE CARE, REHABILITATION & SURVIVORSHIP

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Onco-hematology care through patients' eyes: findings from the 2023 Swiss Cancer Patient Experiences (SCAPE) survey

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Introduction: Patient-reported experiences of care measures (PREMs) are essential for understanding how well the care system is addressing both the medical and psychosocial needs of patients. To date, experiences of patients diagnosed with hematological cancer have rarely been investigated in Switzerland. Initiated by a patient association, this study aimed to evaluate patient-reported experiences among individuals with leukemia, lymphoma, or myeloma to identify areas for improvement in onco-hematology care.

Methods: We analyzed data from the third Swiss Cancer Patient Experiences (SCAPE) survey, a cross-sectional, multicenter study conducted in 2023. Patients from 23 cancer centers across Switzerland were asked to complete a survey on care experiences before diagnosis, at diagnosis, and during inpatient, outpatient and home care, as well as on survivorship care. Rates of positive experiences were compared between patients with hematological and other cancers.

Results: Of nearly 17,000 invited patients, 7,844 completed the questionnaire (49% response rate), including 1,126 with hematological cancer (14%). Overall, positive experiences were reported for most aspects of care, with some notable differences between onco-hematology and other cancer patients. The highest positive experiences included being treated with respect (95.8%), in regular contact with a reference person (98.3%), and access to diagnostic testing (91.5%). Lower-rated experiences included managing long-term symptoms (59.5%), receiving financial aid information (58.4%) and receiving information on late side effects (57.6%). Fewer onco-hematology patients reported timely access to a specialist (65.7% vs 73.3%) and adequate support for managing radiotherapy side effects (69.9% vs 78.5%) compared to other cancer patients. Despite this, onco-hematology patients rated their overall care slightly higher than patients with solid tumors (9.14 vs 9.01).

Conclusions: While overall experiences with cancer care were positive, onco-hematology patients face distinct challenges, especially in survivorship care. Strengthening collaboration between cancer centers and patient organizations could help address these issues. Theses challenges should be considered in future developments, in line with the national cancer plan currently being developed under the leadership of the Federal Office of Public Health.

SSH ORAL PRESENTATION – HEMOSTASIS, TRANSFUSION MEDICINE, VASCULAR, LABORATORY MEDICINE, BENIGN HEMATOLOGY

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Temporal flow cytometry analysis unravels the peculiar phosphorylation and proteolysis dynamics of Vasodilator-Stimulated Phosphoprotein during procoagulant COAT platelet generation

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Introduction: Abnormal procoagulant platelet (PLT) generation may lead to bleeding or thrombotic events. The role of the actin system in platelet activation is only partially described. In this study, we investigated the role of Vasodilator-Stimulated Phosphoprotein (VASP), a key player in actin filament formation, in the dichotomous generation of aggregating (AGG) and procoagulant (COAT) PLTs.

Methods: PLTs from healthy controls were activated in vitro with convulxin (CVX, collagen analogue) plus thrombin (THR) in 2.5 mM calcium while monitoring AGG and COAT PLT generation using PAC1-PE and Annexin V-Cy5. PLTs were fixed and permeabilized at baseline and at different timepoints up to 8 min after activation. VASP protein and phosphorylation levels at serine 239 (S239) were assessed by flow cytometry using FITC-coupled anti-(phospho-S239)-VASP antibodies. COAT

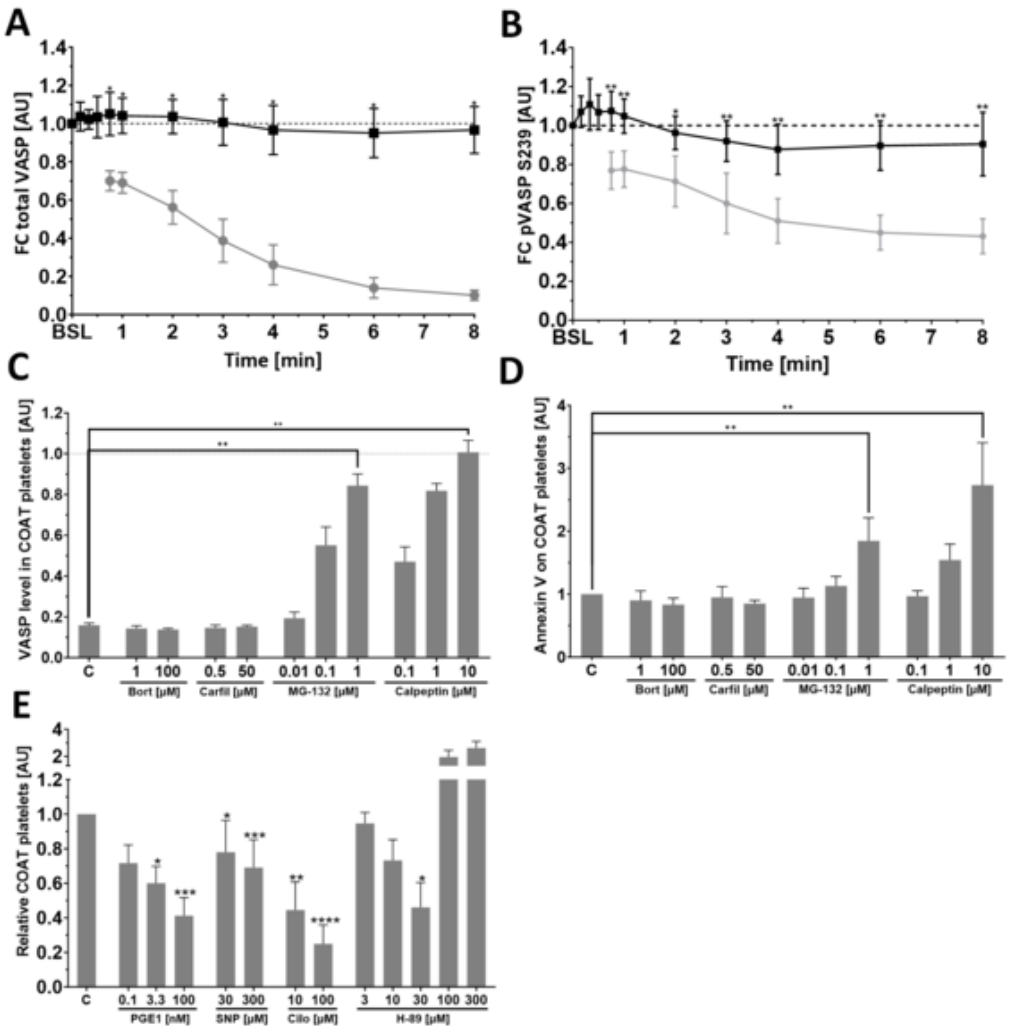

Figure: Monitoring and modulation of the phosphorylation at Serine 239 (S239) and protein level of Vasodilator Stimulated Phosphoprotein (VASP) and its impact on procoagulant COAT platelet phenotype. Temporal analysis by phosphoflow of (**A**) protein level (n=4) and (**B**) phosphorylation at S239 (n=5) of VASP in aggregatory (black line) versus procoagulant COAT platelets (grey line). Prior platelet stimulation with convulxin-plus-thrombin, platelet incubation with calpain inhibitors MG-132 and Calpeptin but not proteasome inhibitors Bortezomib and Carfilzomib prevents (**C**) VASP proteolysis in COAT platelets compared to baseline (dashed line) (n=4-5) and increases (**D**) Annexin V levels on the surface of COAT platelets compared to vehicle (C, DMSO control) (n=4-5). Platelet incubation with protein kinase A and G activators (Prostaglandin E1 [PGE1], Sodium Nitroprusside [SNP] and Cilostazol [Cilo]) resp. inhibitor H-89 (**E**) increase resp. decrease the procoagulant COAT platelet generation potential compared to vehicle (C, DMSO or ethanol as appropriate) (n=4-6). Data are shown as mean ± standard deviation. Mann-Whitney (panels **A** and **B**) or Kruskal-Wallis (panels **C** to **E**) statistical tests were performed. P-values, *≤0.05, **≤0.01, ***≤0.001, ****≤0.0001

PLT generation was monitored after addition of modulators of VASP protein level (proteasome/calpain inhibitors) and VASP phosphorylation (protein kinase A [PKA] and G activators/inhibitors).

Results: Upon CVX+THR stimulation, VASP protein level in COAT PLTs significantly decreased, reaching 10.9% ± 2.9% of the baseline level 8 min after activation. VASP S239 phosphorylation also decreased in COAT PLT down to 43.1% ± 8.9% of baseline. Calpain inhibitors (MG-132, calpeptin) but not proteasome inhibitors (bortezomib, carfilzomib) prevented the decrease in VASP protein level. Calpain-inhibited COAT PLTs retained 2.5-fold higher Annexin V levels at their surface and remained bigger than control (data not shown). PKA/G activators (sodium nitroprusside, cilostazol, prostaglandin E1) increased VASP S239 phosphorylation and reduced COAT PLT generation, while PKA/G inhibitor H89 decreased VASP S239 phosphorylation in resting PLTs and spontaneously generated high COAT PLT levels.

Conclusions: Calpain inhibition not only prevents the decrease in VASP protein levels in COAT PLTs, but it also maintains a higher level of Annexin V on COAT PLTs, by lowering microparticles generation. Moreover, while increased VASP S239 phosphorylation through PKA/G pathway inhibits COAT PLT generation, decreased phosphorylation spontaneously generates COAT PLTs, possibly by suppressing baseline platelet inhibition. Here, we propose that modulation of VASP phosphorylation and calpain activity could be promising strategies for fine-tuning platelet procoagulant phenotype.

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Zebrafish microRNA-150 controls thrombocyte function and clopidogrel response through the regulation of mastl protein

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Introduction: Thrombosis is a common underlying pathology of many cardiovascular diseases. Antiplatelet drugs are a primary treatment strategy to prevent its recurrence. However, the action of existing therapies is nonuniform, leading to the development of bleeding events or reoccurrence of thrombosis in some patients. This results from our poor understanding of factors regulating thrombocyte function. The microRNA-150 (miR-150) has been associated with platelet reactivity in multiple clinical studies, making it a promising candidate for biomarkers of cardiovascular events. However, the mechanism by which this miRNA regulates the thrombocyte function remains enigmatic.

Methods: To functionally validate miR-150 as a potential biomarker of platelet function, we developed a zebrafish model based on the real-time, in vivo monitoring of thrombus formation upon laser-induced venous injury in the presence or absence of an antiplatelet therapy. We also generated a zebrafish line overexpressing this miRNA specifically in thrombocytes.

Results: The miR-150 overexpression strategy in zebrafish resulted in a 30.84 +/- 2.77-fold increase in its miR-150 level in thrombocytes. This miRNA manipulation resulted in a decreased number of thrombocytes in the forming thrombus (39.7 +/- 7.8% lower) and reduced thrombus size (29.8 +/- 11.0%) after the venous laser injury, as compared to the control. Interestingly, overnight treatment of larvae with a P2Y12 inhibitor (clopidogrel) had no effect on thrombus formation in our assay, while treatment with a cyclooxygenase inhibitor (aspirin) resulted in a further decrease in thrombocyte aggregation at the injury site. To unravel the pathway involved in the observed phenotype, RNAseq of miR-150-overexpressing or control thrombocytes was performed. Among the effected transcripts, we identify one downregulated, predicted target of miR-150: microtubule associated serine/threonine kinase like (mastl), a protein involved in the regulation of the phosphorylation of the VASP protein.

Conclusions: The increased level of miR-150 in zebrafish thrombocytes resulted in their reduced aggregation at the injury site, and resistance to P2Y12 inhibitor treatment. We identified the downregulation of mastl transcript as a potential biological pathway responsible for these observations. We are currently investigating whether reduction in MASTL in human platelets can recapitulate the zebrafish phenotype.

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An observational biomarker study illustrates impaired elimination and toxicity of hemolysis products in Sickle Cell Disease patients

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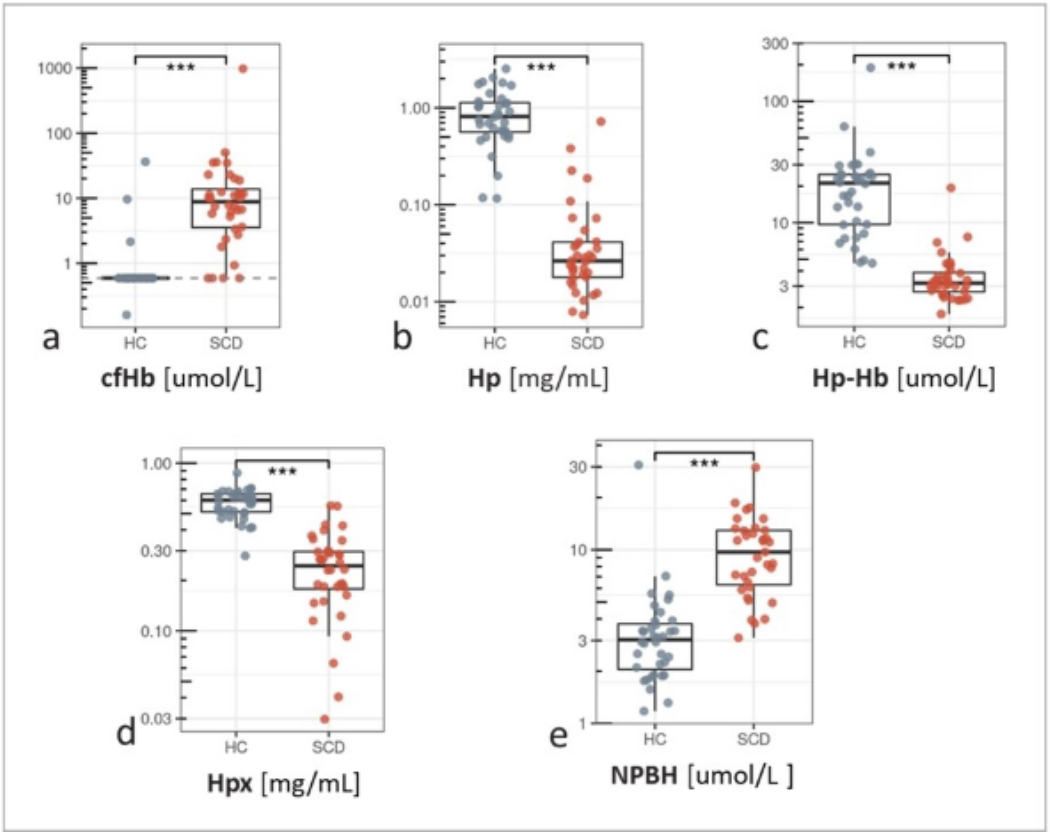
Introduction: Sickle Cell Disease (SCD) is the most common inherited haemoglobinopathy worldwide. To investigate the complex pathophysiology of SCD-related haemolysis, a comprehensive panel of biochemical parameters comparing SCD patients and healthy controls was investigated.

Methods: A cross-sectional observational study was conducted in two university hospitals, including adult SCD patients (HbSS and S/β-thalassemia) at baseline (routine visit) and controls matched for age (<30, ≥30 years), sex, and ethnicity. 105 biochemical parameters were investigated from blood and urine. Linear or logistic regression were used for comparing groups, adjusting for age, sex, and ethnicity.

Results: Between June 2020 and February 2023, 36 SCD patients and 36 controls with comparable demographic characteristics were included in the study. We found a strong elevation of reactive haeme compounds in SCD plasma. Cell-free haemoglobin (cfHb) was 20 times higher in SCD than in controls (Fig. 1a), and haptoglobin (Hp), the natural scavenger of cfHb, was decreased 13-fold (Fig. 1b). Hp-Hb complex – a novel biomarker introduced for the first time in this study – showed a 6-fold reduction in SCD compared to controls (Fig. 1c). The haeme scavenger haemopexin (Hpx) was also depleted in SCD (2.3-fold) compared to controls (Fig. 1d). We discovered significantly elevated spectroscopic haeme signatures on non-specific protein binders of haeme (e.g., albumin; Fig. 1e) and altered biomarkers of endothelial cell activation (VCAM-1, soluble E-selectin and P-selectin), inflammation (IL-8, uPAR, MCP1, TNFalpha and TNFR1), kidney damage (albuminuria, NGAL) and haemostatic dysregulation (D-Dimer, thrombin generation), indicating down-stream consequences of accumulated haemolysis products in SCD.

Conclusions: Hp-Hb complex arises as a promising biomarker to better illustrate cfHb elimination downstream of RBC lysis. We hypothesize that Hp-Hb complex depletion is related to chronic haemolysis in SCD, resulting in exhaustion of Hp and a decreased capacity to bind further cfHb. Hp and Hpx depletion results in increased non-specific binding and interaction of haeme with circulating and vascular cells, leading to toxicity, which is a major driver of SCD pathology. Together, these findings confirm a role for Hb and haeme as promising targets for future therapeutic interventions.

Figure 1. Impaired clearance of haemolysis products in Sickle Cell Disease (SCD) patients compared to healthy controls (HC).
(a) Significantly increased plasma concentrations of cell-free haemoglobin (cfHb) in SCD. A dashed horizontal line indicates the lower sensitivity limit of this assay. **(b)** Exhausted levels of haptoglobin (Hp) in SCD. **(c)** Haptoglobin-haemoglobin complex (Hp-Hb) is lower in SCD. **(d)** Haeme scavenger haemopexin (Hpx) is depleted in SCD compared to HC. **(e)** The concentration of non-specific protein binders of haeme (NPBH) is significantly increased in SCD. P-values for all comparisons (a to e) are < 0.001



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Hypercoagulability combined with routine laboratory parameters accurately predicts liver cirrhosis decompensation

M. G. Zermatten[1], M. Fraga[2], D. Bertaggia Calderara[1], A. Aliotta[1], C. Pereira Portela[1], E. Mdawar-Bailly[2], F. Artru[3], M. Marx[2], J. Wakim El-Khoury[2], M. Faouzi[4], D. Moradpour[2], L. Alberio[1]

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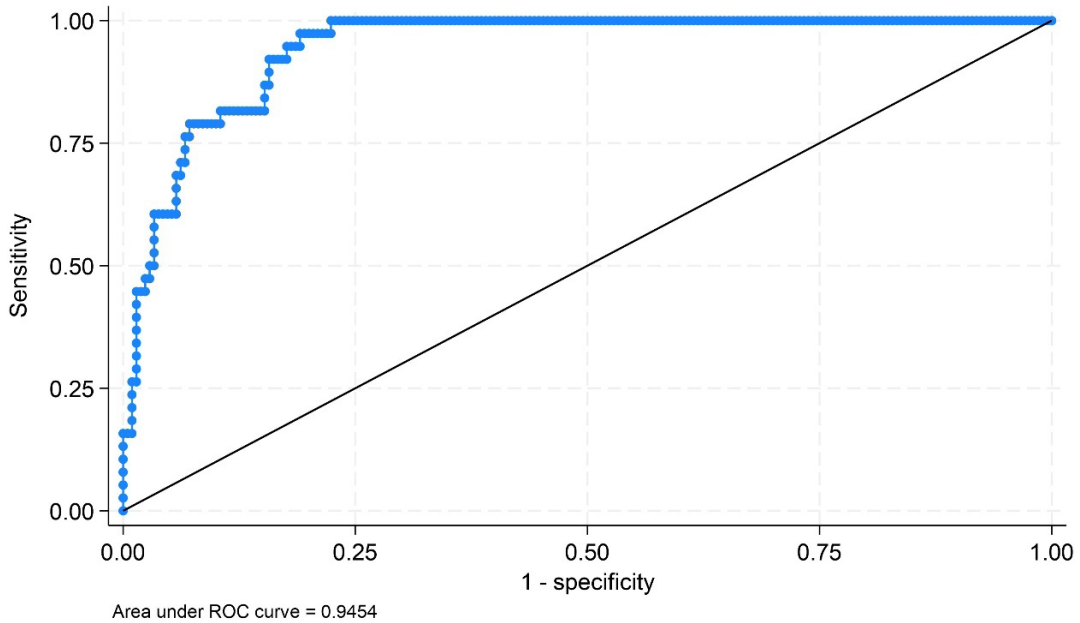
Introduction: Liver cirrhosis (LC) is a complex disease associated with hypercoagulability. Data suggest that hypercoagulability itself may drive LC progression/decompensation. Individual patients' coagulation profiles can be investigated using thrombin generation assays (TGA). Here, we aimed to explore the relation between hypercoagulability and the occurrence of LC decompensation, venous thromboembolic events (VTE), bleeding, and death. We also aimed to develop predictive models for these LC complications.

Methods: We performed a prospective single-centre study at the Lausanne University Hospital (CHUV), Switzerland. We included 303 non-anticoagulated adult patients with LC of all aetiologies and stages, with a planned one-year follow-up. The outcomes were LC decompensation, VTE, bleeding, and death. Ex vivo TGA (ST Genesia, Stago, France) and in vivo thrombin generation (TG) markers (prothrombin fragments 1+2, thrombin-antithrombin complexes, D-dimers) were assessed.

Results: Univariate analyses showed that hypercoagulability, assessed by ex vivo TGA and in vivo TG markers, was associated with an increased risk of LC decompensation (n=57/18.8%), VTE (n=15/5.0%), bleeding (n=32/10.6%), and death (n=23/7.6%). Based on the incidence of LC complications and the univariate analyses, we developed a multivariate model to predict LC decompensation, including thrombomodulin-mediated endogenous thrombin potential inhibition, D-dimers, alkaline phosphatase, and haemoglobin levels. This model reached an area under the receiver-operating characteristic (ROC) curve of 0.95 (Figure 1). The best cut-off identified by ROC analysis has a sensitivity of 92.1% and a specificity of 84.3% for predicting LC decompensation (positive predictive value 51.5%, negative predictive value 98.3%). Selecting a sensitivity of 100% to avoid false-negative results, the specificity was 77.6%.

Conclusions: Hypercoagulability, assessed by ex vivo TGA and in vivo TG markers, is associated with the risk of LC decompensation, VTE, bleeding, and death in a cohort of 303 non-anticoagulated LC patients. This data supports a possible pathophysiological role of hypercoagulability in LC progression/decompensation. Moreover, our 4-item TGA-based model accurately predicts LC decompensation. After external validation, our score may allow to investigate the utility of targeted anticoagulation for the prevention of progression and decompensation of LC.

Figure 1: Receiver-operating characteristic curve for the multivariate model for the prediction of the occurrence of hepatic decompensations



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Transfusing RhD negative patients with RhD positive red blood cell units: a single center observational study

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Introduction: Anti-D alloimmunisation is a serious concern for RhD-negative patients, especially those who need multiple blood transfusions. Because RhD-negative red blood cells (RBCs) are often in short supply, many RhD-negative elderly males end up receiving RhD-positive RBC in urgent situations. The pathogenesis of RhD alloimmunisation remains unclear. In this study, we describe our experiences with RhD-incompatible transfusions and explore potential risk factors for alloimmunisation.

Methods: We conducted a retrospective analysis of RhD-negative patients who received RhD-positive RBC units, using data from the blood donation center. Evaluated data included: age, sex, ABO blood type, alloantibody status before transfusion, reasons for needing a transfusion, types of blood products received, and the number of RBC transfusions within 48 hours of the RhD switch. Results from antibody screening tests were performed after the transfusions. Our statistical analysis included Wilcoxon rank-sum tests, Fisher's exact tests, and time-to-event analyses, focusing on incidence rates and median time to event with 95% confidence intervals, setting significance at $P < 0.05$.

Results: Between 2011 and 2024, we identified 105 RhD-negative patients who received RhD-positive RBC units. 56 patients were not tested due to death or loss to follow-up (53.3%). After receiving RhD-incompatible transfusions 19 (18.1%) tested positive, with 13 developing new anti-D (68.4%). There was no significant difference in overall mortality between those with positive and negative tests (p=0.953). The incidence rate of developing antibodies in type and screen patients (n=39) was 0.92 positive tests per person-year (PPY) (95% CI: 0.58-1.46), with a median time of 0.84 PPY (95% CI: 0.18-2.09). The highest incidence occurred in the first year after transfusion (1.38 PPY, 95% CI: 0.82-2.33). We found no significant differences regarding blood type, RBC product type or quantity, or sex. However, the median ages for negative and positive test results were 73.5 and 66.0 years (p=0.045).

Conclusions: Transfusing RhD-positive RBC units in carefully selected RhD-negative patients can help preserve vital blood supplies for those who are most vulnerable. Our findings did not identify significant factors associated with anti-D alloimmunisation. Further research and better follow-up are needed to gain more insights into this important issue.

Table 1: Details of Patient on the basis of alloimmunisation

		Alloimmunised Patients	Non-Alloimmunised Patients	Overall
Number of Patients		19	86	105
Sex	*m*	14	63	77
	w	5	23	28
Blood Group (RhDneg)	*A*	9	24	33
	B	1	11	12
	AB	0	4	4
	O	9	47	56
Diagnosis	*Cardiac/Thoracic/Vascular intervention*	8	32	40
	Polytrauma	2	9	11
	GI-Bleeding	3	21	24
	Bleeding any other location	6	14	20
	Other	0	8	8
	Not performend	0	2	2
Outcome	*Survival*	17	47	64
	Death due to Diagnosis	2	37	39
	lost of FU	0	2	2
Mean Number of Transfusion	*EC*	5,29 (range: 4 - 77)	3,25 (range: 1 - 83)	3,62 (range: 1 - 83)
	TC	0,68 (range: 0 - 16)	0,72 (range: 0 - 37)	0,77 (range: 0 - 37)
	FFP	8,05 (range: 0 - 89)	5,53 (range 0 - 238)	5,98 (range: 0 - 238)
Mean Number of Transfusion within 48h	*EC*	10,3 (range: 1 - 40)	9,02 (range: 1 - 55)	9,25 (range: 1 - 55)
of the Rhesus-Conversion	*TC*	1,42 (range: 0 - 12)	1,78 (range: 0 - 11)	1,71 (range: 0 - 12)
	FFP	11,89 (range: 0 - 55)	7,12 (range: 0 - 40)	7,98 (range: 0 - 55)
Antibody Screening Test after	*Positive*	19	-	
Rhesus-Conversion	*mean days after Rhesus-Conversion*	200,06 (range: 2 - 1200)		
	Negative	-	30	-
	mean days after Rhesus-Conversion		117,63 (range: 7 - 1401)	
	Not performed	-	56	-
Antibody formation	*Anti-D*	13	-	-
	Anti-C	7	-	-
	Anti-E	5	-	-
	Anti-Cw	1	-	-
	Anti-K	1	-	-
	Anti-Jka	1	-	-
	Anti-Lea	1	-	-
	Anti-Lua	1	-	-
	Anti-s	1	-	-
	no specifity	2	-	-

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Monitoring pharmacodynamics of recombinant FVIII concentrates in patients with hemophilia A

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Introduction: In hemophilia A (HA) bleeding tendency is inversely correlated to the residual factor VIII activity. However, phenotypic heterogeneity exists among patients with HA. Despite similar FVIII levels, individuals often display different bleeding phenotypes. This suggests that the use of FVIII monitoring as clinical indicator of replacement therapy may have limitations. Our aim is to investigate if global coagulation assays (GCA), assessing thrombin generation (TG) and fibrin clot formation (FCF) represent better tools to monitor individual coagulation potential at baseline and during replacement therapy.

Methods: We investigated 11 patients with severe (FVIII <1%), 9 with moderate (FVIII 1-5%) and 24 with mild HA (FVIII >5% and <40%). Samples were collected at baseline and post-infusion with standard recombinant FVIII (rFVIII) at 15 min, 24h, 48h, or extended half-life (EHL) rFVIII at 15 min, 24h, 48h, 72h, 96h. TG was measured using Calibrated-Automated-Thrombogram assay (Stago, France) and Thrombodynamics analyzer (Hemacore, Russia) and FCF using Thrombodynamics analyzer. TG parameters: peak height (PH, nM), velocity index (VI, nM/min), endogenous thrombin potential (ETP, nM thrombin*min). FCF parameters: initial and stationary rate of clot growth (Vi and V, µm/min), clot size (CS, µm).

Results:

1. Patients with severe and moderate HA had abnormal TG and FCF at baseline compared to healthy donors, while a partial overlap was observed for patient with mild HA. FCF discriminated the three degrees of HA severity while TG did not.

2. TG and FCF parameters of 334 measurements were plotted as a function of FVIII activity, which was regressed on the respective parameters of TG and FCF using a ordinary least squares regression model. A narrower spreading from the fitting model was observed for FCF compared to TG.

3. In addition, at similar levels of FVIII, a large variation of TG and FCF among individuals still exists. In some individuals, TG and FCF normalized before FVIII activity reached normal levels.

Conclusions: GCA measuring TG and FCF provide a global and functional assessment of hemostasis, offering more comprehensive information than FVIII alone. Both tests help in determining whether hemostasis is normalized, thus GCA might be useful for assessing individually the effectiveness or FVIII replacement therapy. Further research correlating TG and FCF to clinical outcome is needed.

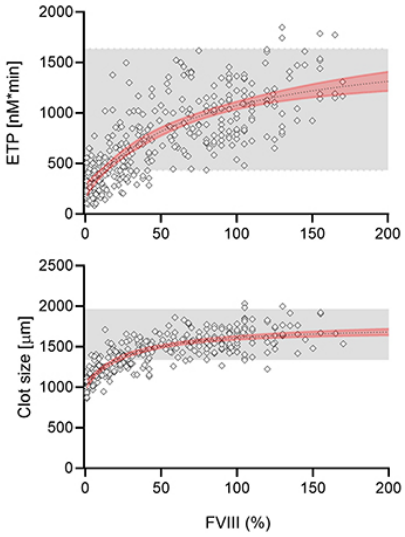

Figure: Thrombin generation and fibrin clot formation measured in plasma from patients with hemophilia A during factor replacement therapy. Values of endogenous thrombin potential (ETP) and the clot size (CS) measured in each individual are plotted as a function of FVIII activity in the studied cohort. The black dotted line represents the best fitted line, with 95% confidence interval (red area). Goodness of fit: ETP R^2, 0.62; CS R^2 0.67.

SSH/SSMO ORAL PRESENTATION – EXPERIMENTAL HEMATOLOGY / ONCOLOGY

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Combinatorial Adaptor-Mediated Targeting of AML with Bispecific T-cell engagers

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Introduction: Immunotherapy targeting B- and plasma cell surface antigens is successfully implemented in clinical practice, and collateral damage to healthy cells of origin (COO) well compensated by immunoglobulin infusion. Acute myeloid leukemia (AML) is a group of hematopoietic neoplasms due to malignant transformation of HSPCs (COO). If AML surface antigens are targeted, the collateral damage to COO causes long-term myeloablation, which is incompatible with patient survival unless therapy is terminated and depleted healthy HSPCs replaced by transplantation. We demonstrated efficient COO targeting with on-off tunable Adaptor CAR T-cells combined with adaptors with short half-lives (Volta et al., Leukemia 2024). As CAR T-cell generation is time- and resource-consuming, we designed a bispecific anti-fluorescein x anti-CD3 T-Cell Engager (AdFITC-TCE) and fluorescein-labeled diabody adaptors (Db-FM) against CD117 and CD33.

Methods: We engineered the AdFITC-TCE in a tandem single-chain variable fragment format analogous to blinatumomab. We investigated AML biocidal activity of healthy donor T-cells with AdFITC-TCE and different concentrations of Db-FM. As comparison, we used the same adaptors and AdFITC-CAR T-cells. We performed in vitro cytotoxicity assays using AML cell lines and patient-derived AML blasts. In vivo efficacy of the TCE was assessed in NSG mice engrafted with human AML cell lines.

Results: CD117 and CD33 Db-FM combined with AdFITC-TCE showed comparable efficacy to AdFITC-CAR T-cells against AML cell lines. AdFITC-TCE with both Db-FM exhibited higher efficacy than single Db-FM against heterogeneous tumor cell populations. This approach was efficient against primary AML patient blasts with different levels of CD33 and CD117. AdFITC-TCE and Db-FM promoted T-cell proliferation, activation and IL-2 and IFN-g secretion only in presence of antigen-positive target cells. Finally, the combination of AdFITC-TCE, CD117 Db-

FM and T-cells effectively inhibited AML cell growth in a low disease-burden therapeutic setting in vivo.

Conclusions: The combinatorial use of AdFITC-TCE with Db-adaptors represents a potent strategy to effectively target multiple antigens on heterogeneous AML cells. In contrast to CAR T-cell engineering, this approach allows for the off-the-shelf use of on-off tuneable designer immune molecules and builds on the immediately available endogenous reservoir of patient's T-cells.

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Inducible CXCL12/CXCR4-dependent extramedullary hematopoietic niches in the adrenal gland

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Introduction: Adult hematopoietic Stem and Progenitor Cells (HSPCs) reside in the bone marrow hematopoietic niche, which regulates HSPC quiescence, self-renewal, and commitment in a demand-adapted manner. While the complex bone marrow niche is responsible for adult haematopoiesis, evidence exists for simpler, albeit functional and more accessible, extramedullary hematopoietic niches. Inspired by the anecdotal description of retroperitoneal hematopoietic masses occurring at higher frequency upon hormonal dysregulation within the adrenal gland, we hypothesized that the adult adrenal gland could be induced into a hematopoietic supportive environment in a systematic manner, thus revealing mechanisms underlying de novo niche formation.

Methods: Using a strategy combining splenectomy and hormonal stimulation in mice (ACTH, testosterone and G-CSF), we induced blood cell recruitment in the adrenal gland and functionally tested haematopoiesis through colony forming assays, serial transplantation and immunostaining signs of in situ haematopoiesis as well as niche remodelling. We validated our findings in human myelolipoma, a benign tumour composed of adipose and hematopoietic tissue.

Results: We showed that the adult adrenal gland of mice can be induced to recruit and host functional HSPCs, capable of serial transplantation, and that this phenomenon is associated with de novo formation of platelet-derived growth factor receptor α (PDGFRα) expressing stromal nodules. We further showed that adrenal glands contain a stromal population reminiscent of the CXCL12-Abundant Reticular (CAR) cells, which are key in the bone marrow HSPC niche. Mechanistically, HSPC homing to hormonally-induced adrenal glands was found to be dependent on the CXCR4/CXCL12 axis. Mirroring our findings in mice, we found reticular CXCL12+ cells co-expressing FOXC1, a master regulator of the niche, in primary samples from human adrenal myelolipomas.

Conclusions: The adrenal gland can be hormonally induced to host HSPCs in adult mice. Furthermore, adrenal extramedullary haematopoiesis is associated to the formation of PDGFRα+LepR+/- foci in mice and CXCL12+FOXC1+ stroma in humans. Our findings reignite long-standing questions regarding hormonal regulation of haematopoiesis and provide a novel model to facilitate the study of adult-specific inducible hematopoietic niches which may pave the way to therapeutic applications.

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Oncogenic ASPP2kappa drives leukemic transformation and disease progression

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Introduction: Despite tremendous efforts and new therapeutics, acute myeloid leukemia (AML) remains difficult to treat and therapy outcome is far from satisfactory for many patients.

We have identified a novel, oncogenic isoform of the tumorsuppressor ASPP2, named ASPP2k, which is expressed in >50% of AMLs, and have demonstrated that deregulation of the ASPP2/ASPP2k – p53 axis associates with drug resistance and a more aggressive tumor biology. We now show that ASPP2k drives leukemic transformation and disease progression in vivo and proves to be a potent therapeutic target

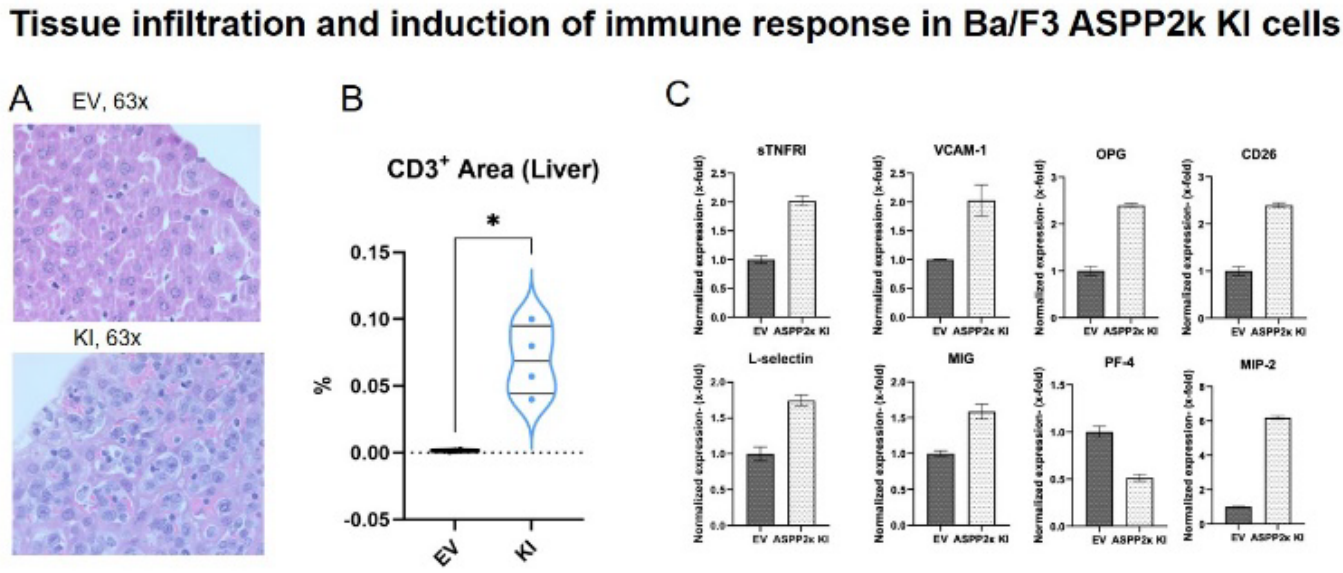
Methods: Isogenic AML ASPP2κ silenced (KD) (Molm14, HL60 and ex vivo patient blasts) were established and xenotransplanted into NSG mice. Ba/F3 interleukin-3 dependent pro-B cells, engineered to overexpress ASPP2k were transplanted into immunocompetent C3H mice to study the influence of ASPP2k on the tumor microenvironment. Disease development and progression were monitored using an IVIS Lumina imaging system. In addition, we designed and tested novel, fully chemically modified ASPP2k-specific siRNAs for in vivo application.

Results: All in vivo models demonstrate earlier leukemia development and engraftment as well as a more aggressive course of disease in dependency of ASPP2k expression (lifespan 30 vs 42 days pi for EV and KD, 22d for KI, p <0,001), underlined by higher WBC count (p <0,001), spleno- and hepatomegaly (p <0,0001) early weight loss (p <0,01) and dissemination into brain and lungs (p <0,001). Importantly, Ba/F3 cells lost their IL-3 dependency upon over-expression of ASPP2k, considered a first step of malignant transformation (proliferation +120 fold-change at 96h for KI vs EV). C3H mice transplanted with ASPP2k overexpressing Ba/F3 cells demonstrated higher organ infiltration (eg liver p <0,001) and a strong immuneresponse, as evidenced by significant T-cell infiltration (p <0,01) and secretion of pro-inflammatory cytokines (see figure).

Importantly, employing novel, fully chemically modified ASPP2k-specific siRNAs, we were able to silence ASPP2k in vivo (>60%) and again attenuated leukemia progression (p <0,01).

Conclusions: In summary, we here show that ASPP2k directly contributes to aggressiveness of the disease in vivo and provide a first rational to further develop ASPP2k specific siRNAs as a novel therapeutic approach to combat leukemia.

Future studies evaluating ASPP2k as a potential target for therapy are warranted.



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Oncogenic ASPP2kappa: a key regulator of classical hallmarks of cancer in triple negative breast cancer (TNBC)

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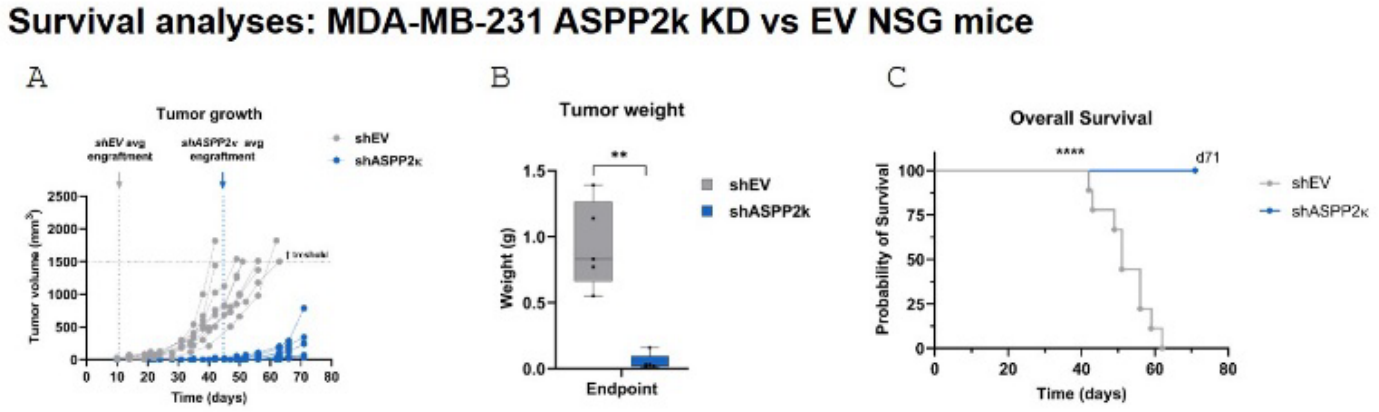
Introduction: ASPP2 is a tumour suppressor, directly interacting with p53, BCL-2 and NFkB, putting ASPP2 into a central position to orchestrate major cancer related pathways. In this context, we have identified a novel, oncogenic isoform of ASPP2, named ASPP2kappa (k), which is highly and frequently expressed in TNBC. As ASPP2k is characterized by loss of the p53- as well as partial loss of BCL-2 and NFkB-binding sites, its expression impairs major pathways controlling cellular fate, resulting in accelerated proliferation and drug resistance. We now show that expression of ASPP2k promotes all classical hallmarks of cancer – fueling a highly aggressive tumor biology in TNBC. Importantly we demonstrate for the first time, that silencing of ASPP2k, using specific siRNAs designed for in vivo use, slows down tumor growth and inhibits metastasis.

Methods: Employing our isogenic TNBC ASPP2κ interferenced (KD) cell models (MDA-MB-231 and HS-578T, n=18 per model) we studied the role of ASPP2κ in NSG models. Mice were xenotransplanted with EV or ASPP2k KD cells and tumor engraftment, progression, angiogenesis and metastasis were monitored using proteome profiler arrays and an IVIS Lumina imaging system.

Results: Tumor engraftment and growth were found to be significantly attenuated in the KD strains (representative data for MDA model: doubling times EV: 7.3d; KD: 12.8; p <0,0001). EV mice had to be sacrificed between day 40-60 after injection due to tumor size (median OS 51d) while ASPP2k KD only presented with small, localized tumors at day of termination (d72, OS<0,0001) (see Figure). Importantly, 100% of mice bearing ASPP2k expressing (EV) tumors, presented with distant metastasis in multiple different sites at time of sacrifice, while in ASPP2k KD mice, metastasis could only be detected in max. one site and 30% of mice. Regulation of pro-angiogenic and EMT markers as well as involvement of the NFkB pathway were confirmed to play a role in ASPP2k-mediated metastasis. Most importantly, we confirm potent inhibition of tumor growth in these models (p <0,01), employing novel, fully chemically modified ASPP2k-specific siRNAs generated for in vivo use.

Conclusions: In summary, we here provide absolutely novel insights into TNBC tumorbiology in dependency of ASPP2k expression and demonstrate first successful attempts to silence ASPP2κ employing highly specific, chemically modified siRNAs to target ASPP2k in vivo .



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IGLV3-21-G110R-directed bispecific antibodies activate T cells and induce killing in a high-risk subset of chronic lymphocytic leukaemia

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Introduction: The development of chimeric antigen receptor (CAR) T cells or bispecific antibodies represents significant progress towards more precise cellular therapies for cancer. Notable examples include anti-CD19 CAR T cells or the anti-CD3xCD19 T cell engager Blinatumomab. However, both therapies can lead to the complete eradication of the patient`s B cells. We previously provided proof of principle that an aggressive and treatment requiring subset of chronic lymphocytic leukaemia (CLL) carrying the highly oncogenic G110R mutation on its stereotyped immunoglobulin light chain variable 3-21 (IGLV3-21-G110R) can be treated with G110R-point mutation-specific CAR T cells. Here, we introduce an alternative strategy for targeting this CLL subset utilizing the bispecific antibody R110-bsAb.

Methods: We designed the heterodimeric, bispecific antibody targeting CD3 on T cells with a single-chain variable fragment (scFv) on the one arm and an anti-IGLV3-21-G110R antigen-binding fragment (Fab) targeting the CLL-specific IGLV3-21-G110R neoepitope on the other arm. For in vitro experiments, we engineered cell lines to express the B cell receptor (BCR) with the IGLV3-21 wild-type (G110) or mutated (R110) variant and performed co-culture assays with healthy donor or CLL-derived T cells. We further tested primary CLL, healthy B and hematopoietic stem cells (HSC) to assess the specificity of target cell killing and activation of T cells.

Results: In vitro experiments demonstrated the efficient and target-specific cell lysis of the engineered cell lines while sparing cells carrying a random BCR light chain or the IGLV3-21 wild-type light chain. Furthermore, T cell activation only occurred in the presence of the target mutation, and the anti-IGLV3-21-G110R antibody moiety alone did not induce apoptosis or activation. Cytolysis of primary CLL and T cell activation were lower as compared to cell lines. Polyclonal human B cells or HSCs are unaffected by the R110-bsAb. T cells derived from CLL patients were also activated and effectively lysed target cells in the presence of the R110-bsAb, while R110-negative cell lines remained unaffected.

Conclusions: Together, these data advocate for the continued exploration of bispecific antibodies for an off-the-shelf, tolerable immunotherapy that only targets relevant, high-risk mutations in a subset of CLL.

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A20 haploinsufficiency disturbs immune homeostasis and drives the malignant transformation of lymphocytes with permissive antigen receptors

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Introduction: Lymphocytes are indispensable for human health, but can turn “rogue” leading to malignant lymphoproliferations or autoimmunity. Non-Hodgkin lymphomas typically originate from self-reactive lymphocytes that acquired transforming genetic events. Since most biological data derive from established lymphomas, the sequence of mutational events and the relevance of single recurring mutations for transformation in synergy with microenvironmental stimuli remains elusive.

Methods: We use biomaterial from rare individuals with TNFAIP3 germline loss-of-function alterations (haploinsufficiency of A20, HA20) as model for early lymphomagenesis. We performed bulk immune repertoire sequencing and single-cell RNAseq to profile B and T cell repertoires of patients with HA20, lymphoma (ABC-DLBCL/Sézary syndrome) and healthy individuals, including longitudinal tracking of one patient under anti-TNF therapy. Immune repertoires and cytokine levels were profiled in murine models with conditional TNFAIP3 knock-out in B cells or the mononuclear phagocyte system. A20-dependent TNF secretion was analyzed in engineered cell models.

Results: Loss of A20 skews immune repertoires independent of antigen towards lymphocytes with classical self-reactive antigen receptors often found in B (IGHV4-23, IGHV3-23, IGHV3-7) and T (TRBV20-1) cell lymphomas. This skewing was mediated by a feed-forward TNF/A20/NF-kB loop that shaped pre-lymphoma transcriptome signatures in clonally expanded B (CD81, BACH2, NEAT1) or T (GATA3, TOX, PDCD1) cells. Skewing could be reversed by therapeutic TNF antagonism, but also progress to overt lymphoma when additional hits within the antigen receptor signaling axis were acquired. Notably, we also observed that healthy B cells with antigen receptor configurations common for neoplastic or autoreactive clones (e.g. IGHV4-34) exhibit lower TNFAIP3 levels.

Conclusions: Patients with HA20 provide an exceptional window into TNF/A20/NF-kB-mediated control of immune homeostasis and early steps of lymphomagenesis that remain clinically unrecognized. In addition, the link between a distinct receptor configuration and expression of a lymphoma driver suggests a gene dose model that can explain the antigen-independent enrichment of these receptors in lymphoma patients.

SSH/SSMO ORAL PRESENTATION – CLINICAL HEMATO-ONCOLOGY

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IL-10 Expressing CD19 CAR-T Cells Induce Complete Remission and Improve Long-term Protection in Relapsed or Refractory B-Cell Hematological Malignancies

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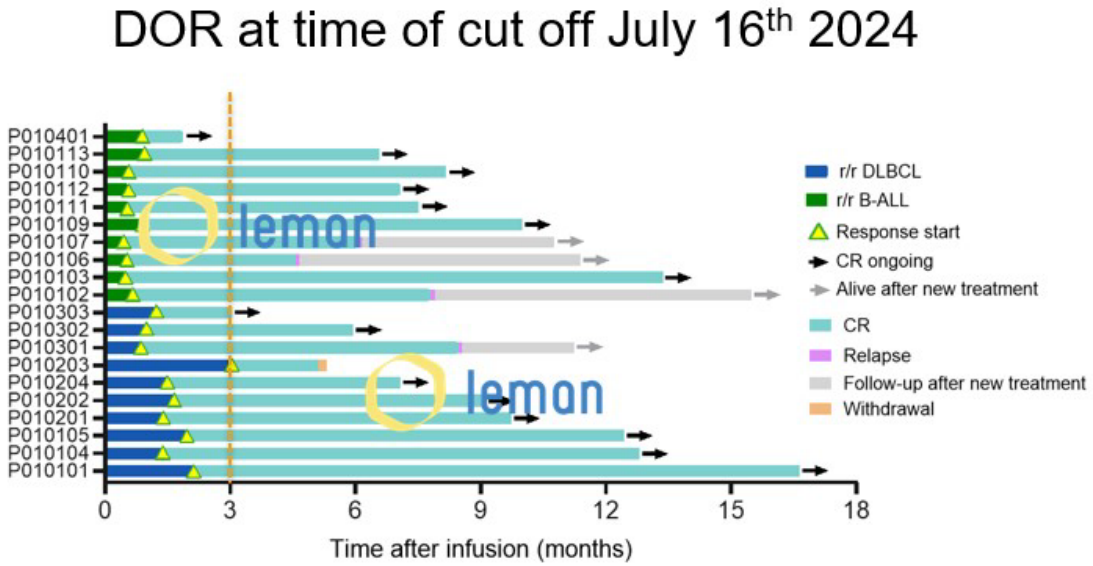
Introduction: CAR-T cell exhaustion and dysfunction often lead to reduced effectiveness and relapse in treating hematological malignancies. However, metabolically armored CAR-T cells expressing IL-10 show resistance to exhaustion and promote stem-like memory responses in animal models, resulting in effective tumor eradication and sustained in vivo protection. This phase I trial (NCT06277011) primarily aims to assess the safety and tolerability of Meta10-19 in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and B-cell acute lymphoblastic leukemia (B-ALL). Secondary objectives include investigating pharmacokinetics and evaluating initial efficacy outcomes.

Methods: From February 2023 to July 2024, 20 eligible patients with R/R B-cell hematological malignancies (10 with DLBCL and 10 with B-ALL) were enrolled and treated. Patients received a single infusion of Meta10-19 at varying dose levels (2.0×10^4 to 2.0×10^5 cells/kg) following a standard lymphodepletion regimen with fludarabine and cyclophosphamide. CRS and ICANS were graded using Lee 2014 and ASTCT 2019 guidelines, respectively, while adverse events were assessed as per CTCAE 5.0 criteria.

Results: As of July 16, 2024, Meta10-19 had been successfully infused into all 20 patients, who then underwent comprehensive safety and preliminary efficacy evaluations. The median age was 50 years (range 17-65). CAR-T cells reached peak expansion around day 12 for DLBCL and B-ALL patients. Remarkably, the complete response (CR) rate was 100% (20/20 patients) and sustained for 3 months (19/19), with a 94.11% CR rate at 6 months (16/17), significantly higher than commercial products (almost 50% at 6 months). Notably, 5 patients have been surviving beyond 12 months, with the longest remission lasting 17 months. Treatment-related AEs, primarily neutropenia, thrombocytopenia, and anemia, were manageable with standard supportive care.

Conclusions: This first-in-human trial of Meta10-19 has demonstrated encouraging preliminary efficacy and a manageable safety profile. Notably, Meta10-19 exhibited a significantly higher CR rate compared to commercial products. Additionally, it provided substantial long-term survival benefits for infused cancer patients, especially at 6 months post-treatment. Ongoing investigations with larger patient cohorts and extended follow-up periods aim to provide further insight into the efficacy and safety parameters.



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Challenging MDS and AML separation with covariate-aware unsupervised learning: introducing the MDS-AML Aggregative Risk Classification System (MARCS)

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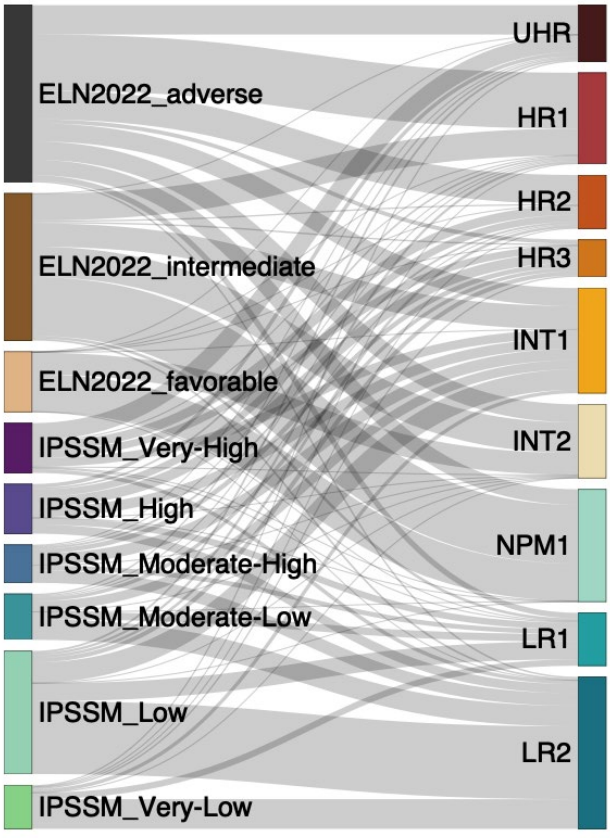
Introduction: Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) share clinical and genetic features. As understanding of genomic drivers increases, molecular criteria are partially replacing morphology-based definitions in MDS and AML classifications. Increasing evidence suggests that at least in some cases MDS and AML may represent a continuum of disease evolution, rather than distinct entities.

Methods: We analyzed 7,480 patients diagnosed with MDS (n=3,729) and AML (n=3,751) between 2008 and 2019, collecting data on blood parameters, mutations in 32 genes, and cytogenetic abnormalities. Using CANClust, a covariate-aware clustering method, we developed the MDS-AML Aggregative Risk Classification System (MARCS). This new system was validated on an independent cohort of 1,035 patients (MDS: n=489, AML: n=546), confirming the results.



Results: MARCS categorized patients into nine risk groups, accurately reflecting the genetic understanding of MDS and AML. It captured distinct groups like NPM1-mutated AML and identified an ultra-high-risk category with TP53 mutations. The system also aligned with favorable prognostic markers, such as SF3B1 mutations and del(5q). MARCS outperformed the 2022 European LeukemiaNet (ELN2022) and the Molecular International Prognostic Scoring System (IPSS-M) in predicting disease progression and outcomes, even when both scores were combined (likelihood ratio [LR] = 501.8; Wilks test p-value $<10^{-4}$, n = 7,480, df = 19). MARCS was particularly effective for patients in the new International Consensus Classification (ICC) MDS/AML subclass, outperforming IPSS-M (log-rank p-value <0.0001). When applying separate clustering processes for MDS and AML, predictive accuracy was inferior compared to the combined analysis (LR = 444.5 vs 502.6; Wilks test p-value $<10^{-4}$, df = 11 vs 10).

Conclusions: In conclusion, MARCS integrates genomic mutations and clinical data to predict outcomes in MDS and AML more accurately than current systems, effectively dissecting the MDS-AML continuum. It is particularly valuable in identifying high-risk patients and in guiding treatment decisions for aggressive disease. The classification is publicly accessible at https://marcs.ethz.ch.

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Efficacy of Idecabtagene vicleucel (ide-cel) in Patients with Relapsed/Refractory Multiple Myeloma and Prior Central Nervous System Manifestation: A Retrospective Real-World Analysis

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Introduction: Relapsed/refractory (r/r) multiple myeloma (MM) with central nervous system (CNS) manifestation is characterized by a poor prognosis. BCMA-directed chimeric antigen receptor (CAR)-T cell therapies represent a standard of care treatment in r/r MM. Yet, real-world evidence regarding the efficacy and safety of CAR-T cell therapy in MM patients (pts) with a history of CNS disease (MM-CNS) is limited.

Methods: We conducted a retrospective study including r/r MM pts undergoing idecabtagene vicleucel (ide-cel) treatment between March 2022/May 2024 at seven tertiary care centers. Only subjects with intradural and/or intraparenchymal lesions or detection of myeloma cells in the cerebrospinal fluid (CSF) were regarded as MM-CNS pts.

Results: We identified 153 r/r MM pts undergoing ide-cel therapy during the specified period. 17 (11%) pts met the criteria of CNS disease prior to CAR-T treatment. The median age for MM-CNS pts at CAR-T infusion and the median number of therapy lines prior to ide-cel was 62 years and 5, respectively. In terms of time of CNS manifestation prior to ide-cel, 2 (12%) pts presented with CNS manifestation at initial diagnosis, while the remaining cases (15/17; 88%) developed secondary CNS involvement later and after a median of 3 therapy lines. Median time from first CNS myeloma detection to CAR-T therapy was 10 mo. One pt experienced CNS manifestation after indication to ide-cel. CNS manifestations were parenchymal lesions (50%), leptomeningeal manifestation (44%) and/or central nerve lesions (31%).

Best radiologic response for CNS manifestation following ide-cel treatment was CR (69%) followed by PR (23%) and SD (8%) and PD in none of the cases. The best serologic response was documented as following: CR (47%), VGPR/PR in (35%) and PD in 18%. Overall, 7 (41%) pts experienced relapse post-CAR-T. Of these, 2 (12%) pts experienced relapse or progression of CNS disease after ide-cel, while the remaining 5 pts developed serologic progression. Notably, there were no high-grade (3-4) immune effector cell-associated neurotoxicity syndrome (ICANS) cases. With a median follow-up of 4.4 months, estimated median progression-free survival (mPFS) was 10.5 mo while mOS for MM-CNS pts was not reached; 1-year OS was 88%.

Conclusions: We here report for the first time that CAR-T cell therapy is an effective and feasible treatment option in MM-CNS pts.

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Effectiveness of emicizumab under real-world conditions in patients of all ages with hemophilia A with and without FVIII inhibitors: Third interim analysis of the non-interventional study EMIIL

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Introduction: Emicizumab is a monoclonal, humanized bispecific antibody bridging coagulation factors IXa and X and thereby replacing the coagulation function of activated factor VIII (FVIII) even in the presence of FVIII inhibitors. Emicizumab is approved for routine prophylaxis in adult and pediatric patients with hemophilia A (PwHA) with or without FVIII inhibitors. Subcutaneous administration of emicizumab has demonstrated a positive benefit/ risk profile in clinical trial settings. The non-interventional study (NIS) EMIIL was initiated to generate additional evidence for long-term effectiveness under real-world conditions.

Methods: EMIIL (ISRCTN58752772) is an ongoing single-arm, two cohorts, prospective, multicenter NIS in Germany and Switzerland collecting safety and effectiveness data in PwHA newly treated with emicizumab. The primary endpoint is the annualized bleeding rate (ABR) of treated bleeds, estimated using a negative binomial regression model. Here we report results from the third interim analysis of cohort A (PwHA without inhibitors).

Results: At data cut-off (May 15, 2023), a total of 112 patients with severe hemophilia A without inhibitors aged 0-75 years were available for evaluation of cohort A (Table 1). After a median treatment duration of 629 days (range 21-1244), the model-based ABR was 0.64 (95% CI 0.49-0.85). Zero treated spontaneous, joint, and target joint bleeds were recorded in 78.6%, 70.5%, and 95.5% of patients, respectively. Recorded in 12-week time windows, the majority of patients experienced zero treated bleeds across the study period (range 83.0-100.0%). At data cut-off, 66 (58.9%) patients experienced 218 adverse events, none of them leading to treatment discontinuation.

Conclusions: The results from the third interim analysis on the effectiveness of emicizumab in a real-world setting, particularly data on ABR and the proportion of patients with zero bleeds, appear to be consistent with results from previous clinical trials. The same applies to the safety results from this third interim analysis as none of the patients developed new FVIII inhibitors and no new safety signals were identified with emicizumab.

Table 1: Patient demographics and bleeding outcomes of cohort A

Parameter	N=112
Male, n (%)	112 (100.0)
Severity at baseline	
Severe (<1% FVIII activity)	112 (100.0)
Age (years), mean (SD)	26.2 (21.0)
Age group, n (%)	
Children (0-11 years)	40 (35.7)
Adolescents (12-17 years)	7 (6.3)
Adults (18-64 years)	62 (55.4)
Elderly (≥65 years)	3 (2.7)
Ethnicity, n (%)	
White	100 (89.3)
Black or African American	2 (1.8)
Asian	2 (1.8)
Not reported	8 (7.1)
FVIII inhibitors history[a], n (%)	
Yes	4 (3.6)
Unknown	108 (96.4)
Previous hemophilia A treatments, n (%)	
Yes	106 (94.6)
No	6 (5.4)
Calculated ABR[b], mean (SD)	
Treated spontaneous bleeds	0.25 (0.64)
Treated joint bleeds	0.44 (1.05)
Treated target joint bleeds	0.04 (0.21)
Location of treated bleeds, n patients (%) – n treated bleeds	
Joints	49 (43.8) – 62
Muscle	3 (2.7) – 3
Other	33 (29.5) – 43

[a]Highest measurement before start of treatment

[b]Bleeds due to surgery/procedure were included in the secondary endpoints. Calculated ABR = Number of treated bleeds for the whole study duration / study duration in years; with study duration defined as duration = (max. visit date with treated bleed assessment – date of first emicizumab administration)/365.25.

ABR, annualized bleeding rate; FVIII, factor VIII; SD, standard deviation

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Increasing Prevalence of Low-Frequency PPM1D Gene Mutations after Second HDCT in Multiple Myeloma

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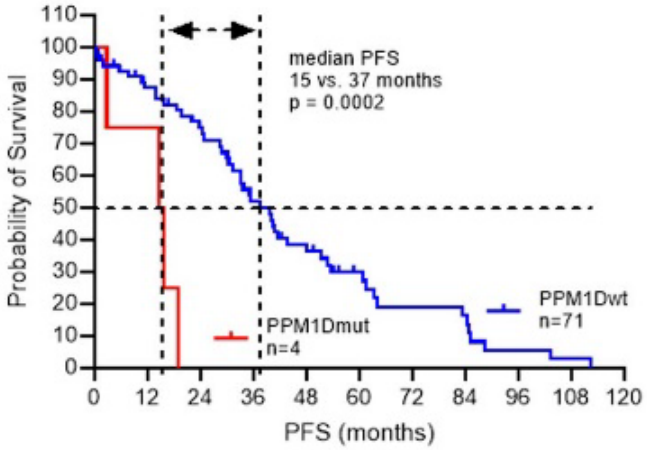
Introduction: Multiple myeloma (MM) first-line treatment algorithms include immuno-chemotherapy (ICT) induction, high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT) consolidation, followed by additional consolidation and subsequent maintenance therapy. After these initial therapies, most patients inevitably experience disease relapse and require subsequent treatment lines including ICT, additional HDCT and ASCT, or novel immunotherapies.

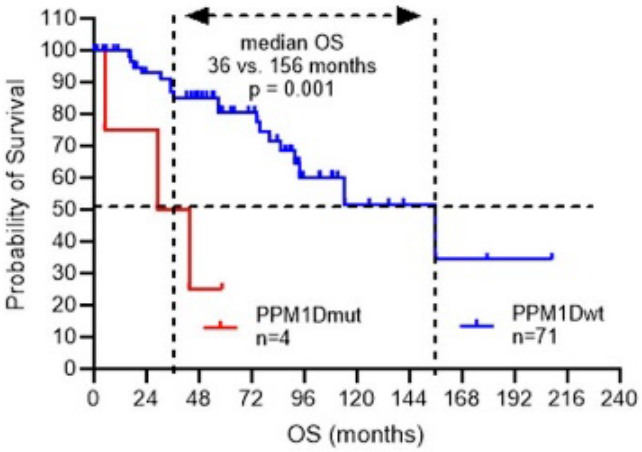
The presence of somatic mutations in peripheral blood cells has been associated with adverse outcomes in a variety of hematological malignancies. Nonsense and frameshift mutations in the PPM1D gene, a frequent driver alteration in clonal hematopoiesis (CH), lead to the gain-of-function of Wip1 phosphatase, which may impair the TP53-dependent G1 checkpoint and promote cell proliferation.

Methods: We determined the presence of PPM1D gene mutations in peripheral blood cells of 75 subsequent myeloma patients in remission after first or second HDCT/ASCT.

Results: We identified that the prevalence of truncating PPM1D gene mutations was 1.3% after first HDCT/ASCT, and 7.3% after second HDCT/ASCT, with variant allele frequencies (VAF) of 0.01 to 0.05. Clinical outcomes were inferior in the PPM1D-mutated (PPM1Dmut) subgroup with median progression-free survival (PFS) of 15 vs. 37 months (p = 0.0002) and median overall survival (OS) of 36 vs. 156 months (p = 0.001) for the PPM1Dmut and PPM1Dwt population, respectively.

Conclusions: Our data suggest that the occurrence of PPM1D gene mutations in peripheral blood cells correlates with inferior outcomes after ASCT in patients with multiple myeloma.





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Combination of post-transplant cyclophosphamide with antithymocyte globulin after haploidentical allogeneic hematopoietic stem-cell transplantation: a single center analysis

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Introduction: In haploidentical allogenic hematopoietic stem-cell transplantation (haplo-HSCT), post-transplant cyclophosphamide(PTCy) is widely used for in vivo T cell depletion with great efficacy in preventing GvHD. Some groups have tried to combine antithymocyte globulin(ATG) with PTCy with the aim of reducing the risk of GvHD without compromising outcomes. However, little is known about the impact of PTCy/ATG combination on immune reconstitution and risk of infection related mortality(IRM) after haplo-HSCT.

Methods: We conducted a retrospective analysis including 81 adult patients who underwent haplo-HSCT with PBSC with or without ATG at our institution between 2013 and 2023. We analyzed transplant outcomes (OS, PFS and GRFS) as well as the immune-reconstitution of major lymphocyte subsets at different timepoints post-HSCT.

Results: 50 patients received PTCy alone and 31 received PTCy/ATG (Neovii). Median follow-up among survivors was 26 (range 1-98) and 29 (16-64) months, respectively. No major differences were observed between the two groups. No significant differences were observed in OS and PFS at 2 years. Patients receiving PTCy/ATG displayed a significantly improved 2 years GRFS (48%, 95% CI 33-69%) compared to patients receiving PTCy alone (28%, 95% CI 17-46%, p-value = 0.029). Such difference was confirmed in a multivariable analysis (HR: 0.54, p=0.04). The 2 years cumulative incidence (CI) of relapse was not significant between the two groups while patients receiving PTCy/ATG displayed a significantly reduced NRM (6%, 95% CI 1-19%) compared to patients receiving PTCy alone (27%, 95% CI 15-41%). We found no differences in the CI of aGVHD II-IV, III-IV or moderate/severe cGvHD between the two groups. We observed a slower immune reconstitution of B cells and CD4 and CD8 T cells, when using the combination of PTCy/ATG with a significant reduction of the three subsets at day 30. Despite such differences in lymphocyte counts, the IRM was not significantly different between the two groups.

Conclusions: In our series, the prophylaxis based on combining PTCy/ATG appeared safe and was associated with an improved GRFS after haplo-HSCT using PBSC. Our results suggest that, despite a delayed immune reconstitution of major adaptive immune cell subsets, the addition of ATG was not associated to an increased risk of relapse or IRM after haplo-HSCT with PTCy.

SSMO ORAL PRESENTATION – CLINICAL SOLID TUMOR ONCOLOGY

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Osteonecrosis of the jaw (ONJ) in patients with bone metastases treated with denosumab every 4 vs. 12 weeks (randomized phase 3 trial; SAKK 96/12)

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Introduction: While reducing skeletal-related events in patients with bone metastases, bone-modifying agents such as bisphosphonates and denosumab have adverse events. One major adverse event of these agents is osteonecrosis of the jaw (ONJ), which often significantly impacts quality of life. The risk of ONJ increases with treatment duration and can reach cumulative rates of up to 10%. Here we report ONJ rates in a randomized phase III non-inferiority trial investigating the optimal dose schedule of denosumab (DN).

Methods: Patients with metastatic breast cancer (mBC) or metastatic castration resistant prostate cancer (mCRPC) were randomized 1:1 to receive DN q4w (Arm A) versus q12w (Arm B) after a 3-month induction phase with application q4w for both arms. Incidence of ONJ is a secondary endpoint of the study. An oral inspection at baseline as well as before each application of DN was mandatory. In patients with risk factors for ONJ, a prophylactic dentist visit was recommended. Data from patients who received at least one dose of DN and who were randomized at least one year before data cut-off (December 11, 2023) were included in this interim safety analysis. Since the differentiation between ONJ and tooth abscess (the term according to CTCAE v5.0 is tooth infection) can be difficult, we report these two outcomes separately as well as combined.

Results: 1271 patients with a median follow-up time of 3 years were analyzed. During the 3-month induction phase 2/1271 patients experienced an ONJ. In Arm A 48/575 (8.3%), in Arm B 32/561 (5.7%) patients experienced an ONJ. For tooth infections (tooth abscess) the numbers during the induction phase were 0.8%, then after induction 7.5% for arm A and 5.0% for arm B. Time to first ONJ and/or tooth infection differs remarkably with a clear advantage for the 3-months arm (HR 0.67; 95% CI 0.48-0.93).

Conclusions: The observed ONJ rate of 8.3% is in line with the literature for patients who received denosumab q4w for over two years (mBC: 6.0%, mCRPC: 8.2%). Administration of DN q12w reduces the risk of ONJ and/or tooth infections substantially. The numerical difference of events to the standard arm as well as the time to first ONJ and/or tooth infection is clinically relevant with a risk reduction by 33%. Efficacy data for the primary endpoint time to first symptomatic skeletal event is eagerly awaited.

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Perioperative Durvalumab in Addition to Neoadjuvant Chemotherapy in Patients With Stage IIIA(N2) Non–Small-Cell Lung Cancer – Final analysis of the multicenter single-arm phase II trial SAKK 16/14

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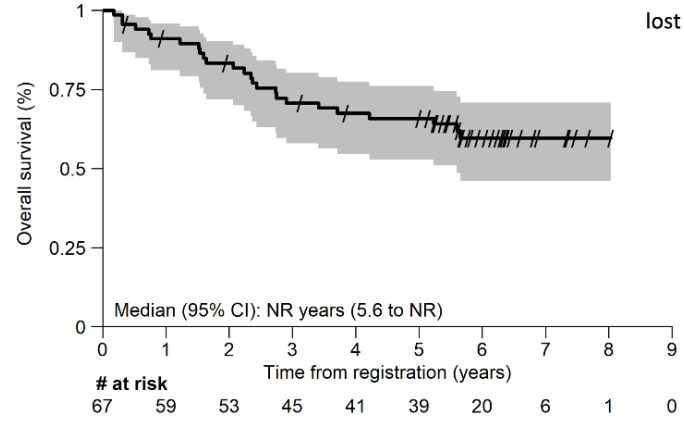
Introduction: In the trial SAKK 16/14 perioperative durvalumab showed favorable outcomes for patients with resectable stage IIIA(N2) non-small cell lung cancer (NSCLC). This has been confirmed in randomized trials. Here we present the final analysis with a median follow-up of 72 months.

Methods: This multicenter, single-arm phase II trial investigated the benefit of perioperative treatment with the anti-PD-L1 inhibitor durvalumab in addition to neoadjuvant chemotherapy with cisplatin and docetaxel, followed by surgery in patients with resectable stage IIIA (N2) NSCLC. Durvalumab was administered postoperatively for 1 year. The primary endpoint was event-free survival (EFS) at 1 year. The statistical hypothesis was based on an improvement in EFS at 1 year from 48% to 65%.

Results: The trial met its primary endpoint, achieving a 1-year EFS of 73%. Of the 68 patients enrolled, 55 (82%) patients underwent surgery, with 51 (93%) achieving a complete (R0) resection. As of September 2, 2024, 31 patients experienced an event (25 progressions, 3 second tumors and 3 deaths). The median EFS was 4.0 years [95% confidence interval (CI): 2.4 years-NR] and 5-year EFS rate was 45.9% [95% CI: 31.7 - 59.0%]. By the time of analysis, 25 deaths had occurred. The median OS was not reached and estimated 5-year OS rate was 65.8% [95% CI: 52.9-76.0%]. A major pathologic response (MPR; <10% viable tumor cells) was observed in 34 patients (62%), and 10 patients (18%) achieved a pathologic complete response (pCR). Postoperative nodal downstaging (ypN0-1) was reported in 37 patients (67%). Notably, patients who achieved a pCR had a 5-year OS rate of 100% [95% CI NR-NR], and those patients with a MPR had a 5-year survival rate of 97% [95% CI NR-NR].

Conclusions: To the best of our knowledge, this is the largest prospective trial to date investigating perioperative immunotherapy in patients with resectable NSCLC, with a follow-up period of 6 years. When compared to a pooled analysis of previous trials conducted by our working group on resectable stage IIIA(N2) NSCLC using the same chemotherapy regimen, the addition of immunotherapy nearly doubled the 5-year EFS and OS rate. It was particularly impressive in patients who achieved a major or complete pathological response. The currently recruiting trial SAKK 16/18 is further exploring the potential benefit of immune-modulatory radiotherapy targeting the primary tumor.



Until the time of this analysis, 25 deaths occurred, 25 patients were alive and 7 lost to follow-up. The median OS was not reached.

	OS rate
Years after registration	Estimator and 95% CI
1	91.0% [81.0%, 95.8%]
2	83.3% [71.8%, 90.4%]
3	70.7% [58.0%, 80.2%]
4	67.5% [54.6%, 77.5%]
5	65.8% [52.9%, 76.0%]

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Adoptive cell therapy with tumor-infiltrating lymphocytes and ANV419 in patients with advanced melanoma. Interim safety results of the phase I BaseTIL-03M trial.

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Introduction: Adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) is effective in patients (pts) with melanoma, but there is still substantial need to enhance the antitumor potential and treatment tolerability. TIL-ACT traditionally includes in vivo TIL expansion with interleukin-2 (IL-2), which has various limitations (efficacy, toxicity). Therefore, new approaches are needed.

Methods: BaseTIL-03M (NCT05869539) is an ongoing phase I study at the University Hospital Basel evaluating safety and tolerability of TIL-ACT with ANV419 in pts with advanced melanoma. ANV419 is a novel antibody-cytokine fusion protein consisting of IL-2 fused to an anti-IL-2 monoclonal antibody that sterically hinders binding of IL-2 to IL-2Rα but has selective affinity for the receptor β- and γ-subunits, thus limiting signaling through the α subunit on regulatory T cells. The study procedures include surgical collection of a tumor lesion, ex vivo TIL expansion, lymphodepletion with cyclophosphamide and fludarabine, followed by TIL transfer and subsequent in vivo TIL stimulation with two doses of ANV419 at 243 µg/kg two weeks apart. Here we present safety data on the first 3 pts who had TIL-ACT with ANV419.

Results: We have enrolled 4 pts, one was excluded, because TIL expansion was not feasible (insufficient TIL outgrowth). The remaining 3 pts received a TIL transfer with the intended study intervention: lymphodepletion, TIL transfer (median cell number in the TIL product: 56.5 x 109 TILs) and 2 doses of ANV419 (median dose: 19.2 mg). Serious adverse events occurred in all pts, including jejunal hemorrhage (Grade 3, relation: bleeding from a jejunal metastasis), and peripheral motor neuropathy (Grade 4, relation: TIL product and/or ANV419). All pts experienced lymphodepletion-related hematologic adverse events, including Grade 4 neutrophil, lymphocyte, and platelet count decrease. All pts experienced fever (in neutropenia) and received antibiotic treatment. The most important treatment-related non-hematologic adverse events of ≥ Grade 2 were cytokine release syndrome, rash, capillary leak syndrome, supraventricular tachycardia, and hypertension. The 30-day mortality (post-second ANV419 dose) was 0%.

Conclusions: TIL-ACT with ANV419 at the dose of 243 µg/kg was feasible and manageable in the first 3 pts in the BaseTIL-03M study. The trial continues enrolment to a planned total of 10 pts.

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Impact of cytostatic drug shortages and potential mortality in Switzerland: A 2018-2020 analysis

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Introduction: The rising incidence of cancer in Switzerland and the recent surge in cytostatic drug shortages, exacerbated by the COVID-19 pandemic, pose significant threats to effective cancer care. This study analyzes the impact of cytostatic drug shortages on oncology care in Switzerland, using data from Hôpitaux Universitaires de Genève (HUG) and the Swiss Federal Office of Public Health (OFSP) from 2018 to 2020. The focus is on the extent of these shortages and their potential impact on cancer-related mortality.

Methods: Data were collected from hospital records, national databases, and literature reviews. Statistical analyses assessed the correlation between drug shortages and cancer treatment outcomes, focusing on key cytostatic drugs and their unavailability periods.

Results: At HUG, doxorubicin was unavailable for 69 days and paclitaxel for 635 days. Nationally, capecitabine shortages spanned 70 days. Estimated additional deaths due to these shortages were 197 in 2018, 200 in 2019, and 214 in 2020 for breast cancer patients alone. Colorectal cancer saw 204, 197, and 221 estimated additional deaths for the same years. Non-small cell lung cancer (NSCLC) experienced 38, 38, and 41 additional deaths, while shortages of drugs like cisplatin and paclitaxel severely impacted treatment outcomes. For oesogastric, pancreatic, ovarian, and bladder cancers, shortages of key drugs led to significant reductions in survival rates as well.

Despite these shortages, alternative drugs produced by other pharmaceutical companies were utilized, often at higher costs.

Conclusions: Cytostatic drug shortages significantly impact cancer treatment outcomes and increase mortality. Urgent measures are needed to improve supply chain resilience and enhance global coordination to mitigate these shortages. Existing national stockpiles will become increasingly important in ensuring the continuous availability of critical drugs and safeguarding public health.

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From Trials to Approvals: The Evolution of Cancer Drug Approvals in Switzerland with the Rise of Biomarker-Driven Therapies, 2001-2020

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Introduction: Cancer treatment has advanced rapidly in recent decades. Pivotal clinical trials are the backbone of new cancer drug (CD) approvals. However, data on the long-term overview and trends in approvals and clinical trial characteristics is limited. This study aims to provide a 2-decade descriptive analysis in this regard in Switzerland.

Methods: Data on CD approvals and supporting clinical trials in Switzerland, between 2001 and 2020, were collected from Swissmedic's (SMC) database. Relevant information was extracted from clinical assessment reports. We performed descriptive and moving average (MA) analyses.

Results: SMC approved 362 cancer indications between 2001 and 2020, of which, 229 (63%) were attributed to solid cancers (SC) and 133 (37%) indications covered hematologic neoplasms (HN). The number of approved indications increased over time: 6 in 2001 to 34 in 2020. 11 (3%), 100 (27.6%), and 242 (66.9%) of approvals were based on phase I/II, II, and III trials, respectively. Remaining nine (2.5%), were approved based on submitted literature. Of phase III and randomized controlled trials (RCT), 61% had an open-label design and 38% had placebo-controlled arm. MA analysis revealed a clear upward trend in the use of single-arm trials (SAT) in SC approvals. For HN, the percentage of SAT use was in average higher compared to SC, but the increasing trend over time was less obvious.(Figure 1). Biomarker Driven Approvals (BDA) vs. non-BDA were 140 (38.7%) vs. 222 (61.3%) of indications. The proportion of BDA to all approvals steadily increased, 17% in 2001 to 56% in 2020. Among BDA, the leading cancers were breast cancer, lung cancer, and leukemia, with 32, 31, and 32 indications, respectively. Comparing BDA to non-BDA, over the 2 decades, 32% vs. 21% of indications were approved based on SAT. Within BDA, 24 (25.3%) and 70 (73.7%) in SC vs. 21 (46.7%) and 24 (53.3%) in HN were approved based on SAT and RCT, respectively.

Conclusions: The notable increase of SC and HN therapy approvals accompanied by an increased proportion of BDA in SC, has offered Swiss patients more diverse and tailored treatment options. While RCT served as the main basis for most approvals, use of SAT was more common for BDA compared to non-BDA. The growing reliance on SATs, particularly in SC, introduces uncertainties for regulatory agencies when assessing the benefit/risk profile of a new drug.

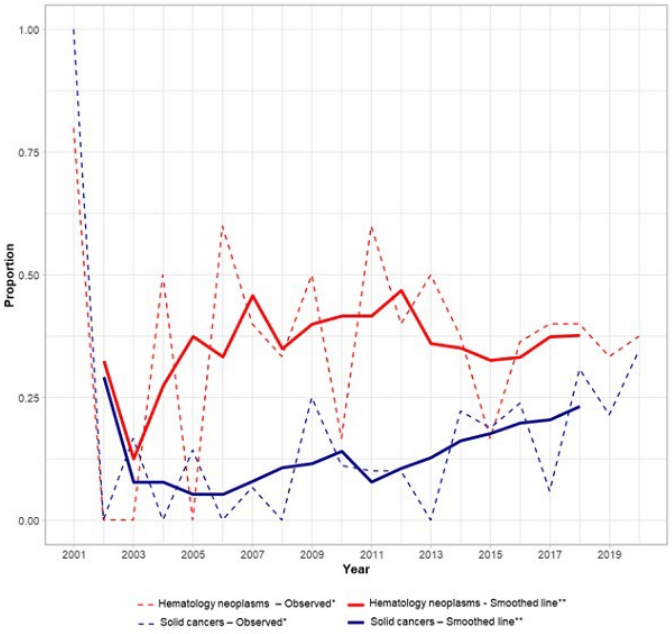

Figure 1. proportion of cancer indication approvals based on single arm clinical trials, 2001-2020 (The moving average analysis)
*Dashed lines depict the actual observed proportions
**Smoothed lines represent the 4-year moving average proportions

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Are we offering BRCA1/BRCA2 testing to the right women in Switzerland? Cost-effectiveness of the BRCA genetic testing threshold

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Introduction: Management options for women carrying a pathogenic/likely pathogenic (P/LP) variant of BRCA include intensive imaging and risk reducing surgeries. In Switzerland, costs are covered by mandatory health insurance after formal counselling and if national guideline (GL) criteria are filled. Our aims were to assess (i) current testing practices by determining the rate of P/LP variants among tested women with a personal history of breast cancer (BC) and examining compliance with Swiss GL and (ii) the cost-effectiveness (CE) of offering testing and risk-reducing surgeries to a larger group of patients with BC.

Methods: We obtained data from three Swiss hospitals (HUG, CHUV, USZ) on women with BC who underwent genetic testing in 2015-2020. We estimated the proportion of women tested positive and the compliance with the Swiss GL. We simulated the lifelong healthcare costs and health outcomes of a cohort of women with BC diagnosed up to age 70. We compared testing all women with BC to the current standard of care (10 % pretest probability). In addition, we explored testing of all women with triple negative breast cancer (TNBC). The main CE outcome was cost per quality-adjusted life year (QALY) gained, evaluated against a hypothetical threshold of CHF 100,000.

Results: Of 1,060 patients, 12% tested positive for any P/LP variant, while 9% tested positive for a BRCA variant. Among those tested after the introduction of the Swiss GL in 2017, 83% fulfilled the testing requirements; 15% tested positive for any P/LP variant and 9.8 % for a BRCA variant. We estimated that testing all women with BC up to 70 years resulted in an average lifetime cost of CHF 21,411, compared to CHF 18,740 per person with standard of care. The incremental CE ratio (ICER) was CHF 25,818 per QALY gained. The current strategy of care plus all addition women with TNBC yielded an ICER of CHF 3,948 per QALY gained, compared to standard of care.

Conclusions: Our analysis could show that major Swiss centres are selecting patients in accordance with the Swiss guidelines. With a simulated cohort, we estimated that widening the testing criteria would lead to better health outcomes, and still be cost-effective. The cost-effectiveness of extending the cascade testing of cancer-free relatives triggered needs yet to be explored.

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Potentially Inappropriate Medication in Geriatric Oncological Patients

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Introduction: Potentially inappropriate medicines (PIMs) are medications with an unfavourable risk-benefit ratio in geriatric patients. Avoiding PIMs can reduce the risk of adverse events, unplanned rehospitalisation or death. We assessed the risk of rehospitalisation and death associated with PIMs detected by any screening tool in geriatric and geriatric oncology patients in the literature and in real life. We also wanted to determine the prevalence of prescribing PIMs in geriatric cancer patients.

Methods: We conducted a meta-analysis investigating the association of at least one prescribed PIM with rehospitalisation and death within three months in patients aged ≥ 65 years detected by any screening tool. Additionally, an observational study assessed whether this association also applied to oncological patients aged ≥ 70 years at a Department of Medical Oncology and Hematology. We determined the PIM prevalences of the tools Beers (2023), STOPP (v3), and Priscus (2.0), and assessed all prescriptions for plausibility of dosages. The relationship between PIMs classified by these tools with the outcomes was assessed by logistic regression.

Results: In the meta-analysis, the association of prescribed PIMs and rehospitalisation in geriatric patients was statistically significant compared to no PIMs within 3 months (see Fig 1). There was no significant association between PIMs and mortality. In the observational study, 112 patients were screened and 87 included. Prevalence of PIMs in geriatric oncological patients was 45.98% (40/87) in total, while PIM prevalence between tools showed 28.74% (25/87, Beers (2023)), 13.79% (12/87, STOPP (v3)), and 33.33% (29/87, Priscus (2.0)), respectively (see Fig.2). PIM exposure was significantly associated with rehospitalization within three months [OR 5.18, CI 1.53 to 17.53, p = 0.008], but not with death [OR >1000, CI 0.00 to n.a., p = 0.997]. All dosages were plausible, according to the best of knowledge of a pharmacist.

Conclusions: Our results indicate that applying PIM tools in medication evaluation could reduce the risk of rehospitalization and potentially death in geriatric patients, regardless of cancer diagnosis. This is the first study to apply the latest versions of these tools in such a context. We suggest the implementation of PIM tools in the medication evaluation of all patients aged ≥ 70 years to rise awareness of PIMs and enable therapy optimisation.

Characteristics	Total n = 87 n(%) or mean ± SD	0 PIMs n = 47 n(%) or mean ± SD	≥1 PIMs n = 40 n(%) or mean ± SD	P-value
Age (years)	78.24±5.22	77.40±4.79	79.23±5.58	0.110
Male	60 (68.97%)	34 (72.34%)	26 (65.00%)	
Female	27 (31.03%)	13 (27.66%)	14 (35.00%)	0.614
Number of co-morbidities	6.21±3.25	6.09±3.26	6.35±3.27	0.710
Number of medications	6.97±4.30	5.26±3.51	8.98±4.31	<0.001*
Polypharmacy (≥5 medications)	63 (72.41%)	29 (61.70%)	34 (85.00%)	0.029*
PIM tools:				
Number of any PIMs	40 (45.98%)	n.a.	40 (100.00%)	
Number of Beers (2023) PIMs	25 (28.74%)	n.a.	25 (62.50%)	
Number of STOPP (v3) PIMs	12 (13.79%)	n.a.	12 (30.00%)	
Number of Priscus (2.0) PIMs	29 (33.33%)	n.a.	29 (72.50%)	
Outcomes:				
Rehospitalisation	17 (19.54%)	4 (8.51%)	13 (32.50%)	0.011*
Death	2 (2.30%)	0 (0.00%)	2 (5.00%)	0.405

Figure 1: Patient characteristics

Outcome	Unadjusted		Adjusted[a]	
≥1 PIMs of:	OR (95% CI)	P-value	OR (95% CI)	P-value
Rehospitalisation within 3 months:				
Any criteria	**5.18 (1.53-17.53)**	0.008*	1.09 (0.97-1.22)	0.153
Beers	2.77 (0.92-8.31)	0.688	1.01 (0.90-1.12)	0.907
STOPP	**3.75 (1.02-13.80)**	0.047*	1.26 (0.90-1.77)	0.174
Priscus	1.11 (0.37-3.39)	0.848	1.10 (0.97-1.25)	0.137
Death within 3 months:				
Any criteria	>1000 (0.00-n.a.)	0.997	1.03 (0.00-n.a.)	1.000
Beers	2.54 (0.15-42.29)	0.516	20.53 (0.00-n.a.)	0.998
STOPP	6.73 (0.39-115.58)	0.189	20.29 (0.00-n.a.)	0.997
Priscus	>1000 (0.00-n.a.)	0.996	1.03 (0.00-n.a.)	1.000

Abbreviations: CI = Confidence Interval, OR = Odds Ratio, PIM = Potentially Inappropriate Medication, STOPP = Screening Tool of Older People's Prescriptions.
[a]Adjusted OR for age and number of co-morbidities.
* Statistically significant on a 95% CI level.

Figure 2: Odds Ratio (OR) of outcomes rehospitalisation and death.

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Late effects of allogeneic stem cell transplantation for Non-Hodgkin lymphoma in Switzerland, 1997-2021, SBST register. Clinical analysis of ALLOHNS study cohort*.

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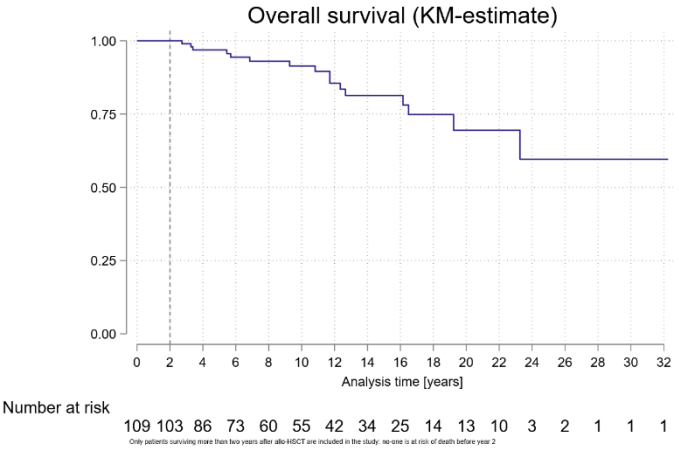
Introduction: Allogeneic stem cell transplantation (allo-HSCT) represents so far the only potentially curable treatment according to a longest follow in a setting of relapse/refractory NHL (rrNHL). However, it is performed in the majority of cases as a very last salvage ligne treatment and late effects in context of rrNHL are underexplored. We present here the first retrospective, multicentre, registry-based analysis (Swiss Blood Stem Cell Transplantation and Cellular Therapy, SBST) of late effects in patients underwent allo-HSCT for rrNHL in Switzerland. This is a clinical analysis of patient's cohort, analyzed for social and quality of life status (SQoL) in the ALLOHNS study.

* Krebsliga Swiss Cancer Research grant HSR-5223-11-2020, ALLOHNS SQoL, Abstract-ID 363.

Methods: We retrospectively analyzed data from 109 patients with all types of rrNHL who underwent allo-HSCT in 3 University Hospitals of Switzerland (Zurich, Basel and Geneva) between May 1997 and November 2021. The primary endpoint was the cumulative incidence (CI) of LE and secondary endpoint were overall survival (OS), relapse incidence (RI) and type of LE according to organ/systems involved. Final analysis is ongoing with more data possibly expected.

Results: Median of follow-up was 6.5 years. The mean age of patients at the time of allo-HSCT was 48 years. Patients who survived 2 years after allo-HSCT presented 5 and 10 years OS of 94% [95% CI 86.3 – 97.5] and 86% [95% CI 75 – 92.4] respectively (Figure). RI was 18.3% at 5 years and 34.4% at 10 years post allo-HSCT. Most frequent LE were secondary malignancies (21%), chronic kidney dysfunction (21%), osteoporosis (21%), cardiovascular disease (19%), and thyroid dysfunction (15%).



Conclusions: Our analysis of a mixed-type rrNHL cohort confirms the efficacy of allo-HSCT in heavily pretreated/refractory patients, showing excellent OS at 5 and 10 years for those who survived 2 years. Secondary malignancies, renal, bone and cardiovascular disease appear to be the most frequent types of LE, revealing accumulated toxicity in heavily pretreated patients with rrNHL. These results should be interpreted with caution due to the nature retrospective of the analysis, the long period analyzed, the heterogeneity of the conditioning regimen and the NHL cohort.

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Social quality of life experience after allogeneic stem cell transplantation for Swiss Non-Hodgkin Lymphoma long-term survivors (SQoL ALLOHNS study)

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Introduction: Non-Hodgkin Lymphoma (NHL) standardized relative survival 5-years after diagnosis is 74.9% (95% CI 73.7-76.1%). Allogeneic stem cell transplantation (alloHSCT) is the only potentially curative treatment for relapse/refractory NHL (rrNHL), a subgroup facing health and social problems. We explored rrNHL post alloHSCT psychosocial quality of life (SQoL) as part of the ALLOHNS study (Swiss Cancer Research grant HSR-5223-11-2020).

Methods: We invited 97 rrNHL survivors at least 2 years post alloHSCT treated in a Swiss University Hospital (Zurich, Basel, or Geneva) to an online survey. Participants completed the WHOQoL-BREF questionnaire in German or French. Survey data were descriptively analysed. Hypotheses testing was not possible due to the small cohort size. In-depths interviews on subjective health and psychosocial needs were added to complement survey results.

Results: 41 rrNHL, (42%) completed the survey between December 2023 and August 2024, with a median of 8 years (4-23) post alloHSCT. The median age was 64 (53-69) years and most participants were men (76%). The level of education in 22% was university, and 29% tertiary education level, 59% were married and 17% lived with a partner. Overall QoL satisfaction was mostly "very good" (46%) or "good" (39%). Most participants were very satisfied or satisfied with their work capacity (74%), social relationships (83%) and social support (90%). 39% of participants were retired and 12% self-employed. Sexuality concerns were frequently reported (67.5%). 11 patients participated in-depth interviews where they confirmed overall good SQoL but altered sexuality life, and reported furthermore fatigue affecting daily routines and work activities demanding modifications. Important support resources were the HSCT care team and a sustainable social network. Main issues reported were financial and insurance matters, reduced work capacity, dismissals, unemployment and the lack of support to solve them. Supportive peer meetings to facilitate after alloHSCT reintegration arised as a relevant unmet need.

Conclusions: Well-educated Swiss post alloHSCT rrNHL survivors report overall good SQoL and seem to be satisfied with their general situation, work capacity, and social network. In-depth interviews revealed support needs related to finances and professional integration post alloHSCT. The results should be interpreted with caution due to the small cohort size.

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Implementation of a structured geriatric assessment program in an academic setting: Results, perception and awareness by patients and treating physicians

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Introduction: Comprehensive Geriatric Assessment (CGA) for older cancer patients is recommended by major professional organizations. Nevertheless, CGA in clinical settings is still not standard for multiple reasons and treatment decisions are made based on age or overall performance status. Partnering with the Department of Geriatrics at our institution, we implemented CGA for patients with hematologic disorders age >65 years in 2019. We report the results of the implementation as well as perception of the program by physicians and patients.

Methods: This retrospective, single-center observational study was conducted at a University Hospital in Switzerland. Patients aged ≥65 years with hematological malignancies who underwent CGA within the last 5 years were included. All data were extracted from electronic medical records and later analyzed. Perception of the CGA by patients and physicians was assessed by a questionnaire.

Results: 46 patients who underwent CGA between April 2019 and July 2023 were included in this study. 89.1% showed at least one impaired domain in the CGA and in 84.8% of patients one or more interventions were suggested. Correlation between G8-Score and pathological CGA-Outcome was significant (p: 0.011). Of all patients, 19 were accessible for the questionnaire. 70% experienced CGA and the resulting recommendations as useful, stating that they had benefited from the process. 45 out of 67 physicians answered the questionnaire for professionals. 75% rated the CGA as helpful, especially in the fields of frailty assessment, cognition, nutritional status/optimization, physical function, and falls/risk of falls. 11.1% reported to have attended lectures during their studies specifically regarding geriatric oncology/hematology, 48.9% reported such lectures were not offered at all.

Conclusions: Our data support the use of a CGA in older patients with hematological cancers based on positive feedback, from both patients and physicians. The results emphasize the need for a dedicated geriatric assessment in an older cancer population as it contributes to a more comprehensive medical evaluation, supports treatment decisions and potentially improves overall patient care. The feedback from physicians indicates that geriatric oncology/hematology is underrepresented in medical curricula. This may contribute to the missing knowledge and low awareness of CGA, and should be addressed in the future.

Image 1: perception of CGA by patients

Response: 19/37 (51%) (as of September 2023: 53 CGA cases, 8 deceased, 8 lost-to-follow-up)

Question 1: The appointment at the Clinic for Geriatric Medicine was useful:
useful- very useful: 13/19 (68%)
not at all: 3/19 (15%)

Question 2: The recommendations made, e.g. on nutrition or physiotherapy (physiotherapy), were useful:
useful- very useful: 12/19 (63%)
not at all: 4/19 (21%)

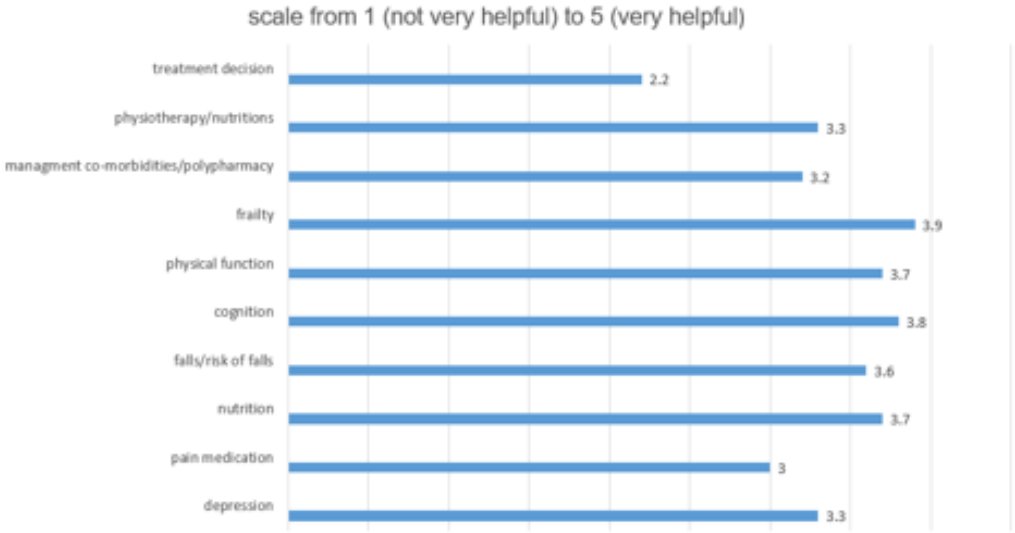
Question 3: I was able to implement the measures/recommendations well:
good-very good: 10/19 (52%)
not at all: 6/19 (32%)

Question 4: I have the impression that I benefited from the appointment:
good-very good: 13/19 (68%)
not at all: 3/19 (15%)

Question 5: I would have welcomed a further appointment at the clinic for geriatric medicine (e.g. after completion of the therapy):
good-very good: 4/19 (21%)
not (at all): 12/19 (63%)

Question 6: In principle, I consider such supplementary services as useful:
useful- very useful: 12/19 (63%)
not useful: 2/19 (10%)

Image 2: rating of CGA recommendations by treating physicians (n: 45)



SSH POSTER PRESENTATION – HEMOSTASIS, TRANSFUSION MEDICINE, VASCULAR, LABORATORY MEDICINE, BENIGN HEMATOLOGY

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Sequential combinations of rapid immunoassays for prompt recognition of heparin-induced thrombocytopenia: a prospective validation study

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Introduction: Early recognition and treatment of heparin-induced thrombocytopenia (HIT) are crucial to prevent severe complications. While qualitative immunoassays (IA) offer rapid diagnosis, their sensitivity and specificity are not optimal. Sequential combinations of quantitative IA results could improve the diagnostic accuracy. We aimed to validate our Bayesian approach and to compare it with other diagnostic algorithms ("Hamilton" based on two simultaneously performed IA and "TORADI-HIT" based on one IA and other laboratory values).

Methods: We included 1194 patients with suspected HIT (6.0% confirmed HIT). HemosIL Acustar HIT-IgG, a chemiluminescence-based IA (CLIA) and HemosIL HIT-Ab(PF4-H) (Instrumentation Laboratory, Munich, Germany), a latex immune-turbidimetric assay (LIA), were performed and used according to our algorithms (CLIA first/LIA for unsolved cases, resp. LIA first/CLIA for unsolved cases). Definite HIT confirmation or exclusion was made using heparin-induced platelet activation (HIPA) test and PF4-enhanced HIPA (PIPA). Performances of our approaches, the "Hamilton" and the "TORADI-HIT" algorithms were compared.

Results: Using CLIA first and LIA for unsolved cases correctly excluded HIT in 95.6% and predicted HIT in 95.8%; 3.3% of cases remained undetermined; there were 13 false positive and no false negative results. Using LIA first and CLIA for unsolved cases, correctly excluded HIT in 96.4% and predicted HIT in 96.4%; 2.3% of cases remained undetermined; there were 15 false positive and no false negative results. These sequential algorithms allowed to reach a diagnosis using only the first IA in 81.5%, resp. 85.4%. The "Hamilton algorithm" correctly excluded HIT in 92.1% and predicted HIT in 42.3%; 10.7% of cases remained undetermined; there were no false positive and two false negative results. The "TORADI-HIT algorithm" correctly excluded HIT in 97.9% and predicted HIT in 93.8%; there were 10 false positive and three false negative results.

Conclusions: A Bayesian approach sequentially employing two IA is accurate for HIT diagnosis. Performing IA simultaneously according to the "Hamilton algorithm" is less accurate and cost-effective. The "TORADI-HIT algorithm" offers better HIT exclusion at the cost of about 6% false negative results. Using our approaches, HIT exclusion or recognition can be achieved in >97% of cases within <1 hour with no false-negative results.

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Daratumumab for Refractory and Frequently Relapsing Immune Thrombotic Thrombocytopenic Purpura – a Case Series with Long-Term Follow-up

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Introduction: Immune thrombotic thrombocytopenic purpura (iTTP) is a life-threatening thrombotic microangiopathy (TMA) caused by inhibitory autoantibodies to ADAMTS13. Despite initial management of acute iTTP episodes with therapeutic plasma exchange (TPE), administration of anti-VWF nanobody caplacizumab, and immunosuppression with corticosteroids, relapse occurs in at least 30% of patients while some are refractory to treatment or show a frequently relapsing course (r/r iTTP). Management of these patients is challenging and no clear treatment recommendations exist. Daratumumab, an anti-CD38 antibody, has emerged as an efficacious and safe therapeutic option for a variety of autoimmune diseases, including iTTP. We present a series of patients with r/r iTTP which we have treated with daratumumab, with a median follow-up of 43 months.

Methods: Our retrospective analysis included 8 treatment episodes with daratumumab in 5 patients from 3 Swiss centres. Patient-level data from January 1st, 2014 through July 1st, 2024 included disease course, treatment with response and adverse reactions, ADAMTS13 activity and inhibitor. ADAMTS13 recovery following treatment was defined as partial (ADAMTS13 activity >20%) and complete (>50%).

Results: Prior to daratumumab, a median of 2 (range, 2-6) other immunosuppressive therapies were given. A median number of 6 (range, 4-8) daratumumab doses was administered per patient, either as an intravenous infusion (16 mg/kg bw) or subcutaneous injection (1800 mg). In all cases, daratumumab was initiated to reverse ADAMTS13 deficiency while the patients were in clinical remission. No severe adverse events were observed. ADAMTS13 response was seen in 87.5% (7/8 treatment episodes), including 7 complete responses. Mean ADAMTS13 activity at response was 70% (n=7, SD 23.1%), and median time to response was 2.5 weeks (range, 2-4). Median duration of response was 19 months (max. 37 months). After a median follow-up of 43 months, 85.7% of patients maintained their response at 12 months and 28.5% at 24 months. Eventually, ADAMTS13 relapse following daratumumab therapy was seen in 6/7 patients.

Conclusions: Our retrospective evaluation indicates that daratumumab is an efficacious and safe treatment option for r/r iTTP patients without response to rituximab. Prospective studies are warranted to confirm the long-term efficacy and safety of daratumumab treatment in such patients.

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Modification of fibrinolytic potential after cessation of combined hormonal contraceptives

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Introduction: Combined oral contraceptives (OCs) are known to contribute to a procoagulant state by increasing clotting factor production and decreasing levels of hemostatic inhibitors. Such effects can result in venous thromboembolism (VTE) and persist even after treatment discontinuation. To date, modification of fibrinolytic biomarkers has been observed in disease but specific data on fibrinolysis in OC users is limited. Therefore, we aimed to determine whether plasmin generation (PG) is elevated in OC users and assess the time needed for fibrinolytic biomarkers to normalise after OC cessation.

Methods: In a monocentric, observational study cohort of adult women, platelet-poor plasma was collected from an OC cessation group (n=66) and a control group (n=28) of women using progestin-only pills or an intrauterine device at T0 (the date of OC cessation) and T12 (12 weeks later). Twenty individuals with OC cessation presenting with the highest modifications of thrombin generation (TG) parameters between T0 and T12 were selected and compared to five controls. Fibrin clot degradation was evaluated using a) a PG assay recording endogenous plasmin potential (EPP; nM*min), Peak (nM), and time to peak (ttPeak; min) (Synapse Research Institute, Maastricht, Netherlands), and b) plasmin α2-antiplasmin complex concentration (PAP, ng/mL) by ELISA (Technozym®, Technoclone, Austria).

Results: At T0, Peak plasmin from OC cessation samples was significantly higher than in controls (p=0.002). However, at T12, OC cessation EPP and Peak were comparable to controls. Overall, we observed a statistically significant decrease in EPP (p=0.005) and Peak (p <0.001) between T0 and T12 in OC cessation samples. In comparison, no differences were noted in EPP and Peak

in control samples. TtPeak in OC cessation samples at T0 and T12 were similar and higher than controls at both time points (T0, p=0.005; T12, p=0.004). PAP complex concentrations decreased significantly with OC cessation between T0 and T12 (p <0.001, see Fig.1). This change was not observed in controls (p=0.761).

Conclusions: Compared to controls, women taking OCs exhibited enhanced fibrinolytic activity, reflected by high PG and PAP complex levels, linked to a procoagulant state during OC use. These levels decreased significantly 12 weeks after OC cessation.

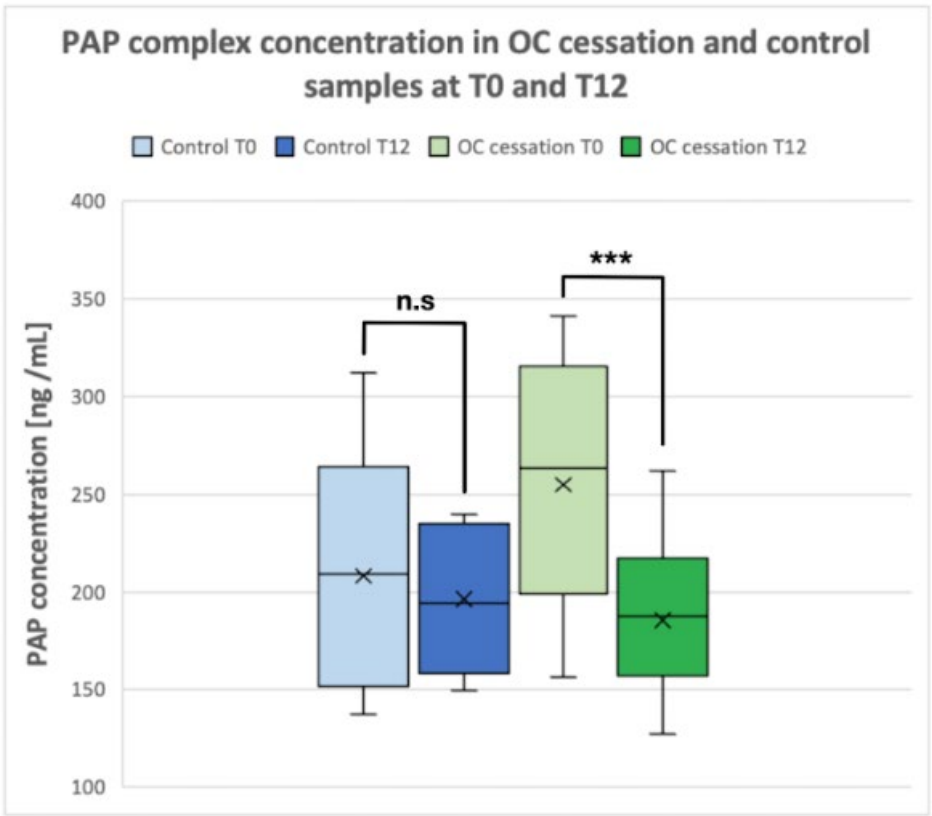

Figure 1 : PAP complex concentration in OC cessation and control samples at T0 and T12. Box plot showing PAP complex concentrations (ng/mL) in control and oral contraceptive (OC) cessation groups at baseline (T0) and 12 weeks later (T12). The boxes represent the interquartile range, with the median indicated by the horizontal line and the mean by the "x". Whiskers show standard deviation. The decrease in PAP complex concentration in the OC cessation group is statistically significant (***, p<0.001), while the difference in the control group is not significant (n.s).

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Appearance of isoagglutinins after minor ABO-incompatible allogeneic stem cell transplants

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Introduction: In 2022, we studied the time to disappearance or appearance of isoagglutinins A and B in patients undergoing ABO-incompatible allogeneic hematopoietic stem cell transplantation (HSCT). One year after HSCT, only 7 of 61 patients who underwent minor ABO-incompatible allogeneic HSCT showed de novo appearance of isoagglutinins according to transplanted blood type. We reviewed this cohort in 2024 with longer follow-up.

Methods: We included all patients who underwent allogeneic HSCT with minor ABO incompatibility at our institution between March 2015 and December 2019. For each patient, the occurrence and persistence of isoagglutinin A and B were monitored from the time of HSCT until September 20, 2024.

Results: We identified 61 patients. De novo production of isoagglutinin A and B was analyzed in 49 patients and 15 patients, respectively. Median follow-up was 46 months (range 1 month to 109 months). Appearance of isoagglutinin A was observed in 7/49 patients. In 6/7 patients, isoagglutinin A appeared between day+12 and day+20 after transplantation. The appearance of isoagglutinin was transient (detection persisted for 5 to 36 days) and was associated with positive DAT and mild hemolysis. In 3/7 patients, we later detected a one-time positivity for isoagglutinin A (on days 736, 1470 and 2534 after HSCT). We observed no occurrence of isoagglutinin B (0/15). The last analysis performed for each patient showed the absence of isoagglutinin A or B.

Conclusions: Shortly after HSCT, we observed the appearance of isoagglutinin A in 6/61 patients, associated with a positive DAT and mild hemolysis. The kinetics were compatible with a passenger lymphocyte syndrome.

We also observed isoagglutinins appearing more than one year after HSCT in 3/61 patients (4.91%), with no identified treatment that could explain this (e.g., immunoglobulin or transfusion). Due to the long intervals between analyses, the persistence of the isoagglutinin was difficult to assess. No hemolysis was detected in the three patients with late anti-A appearance.

In the case of minor ABO-incompatible HSCT, transfusion of red blood cells according to the donor blood group remains a necessity after HSCT if isoagglutinins are not carefully monitored.

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Parameters impacting fibrinolysis in patients with liver cirrhosis

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Introduction: Liver cirrhosis (LC) has a prevalence >1%, with an increase of over 80% in the last 30 years. LC is responsible for ca. 1% of deaths worldwide, notably due to thrombo-haemorrhagic complications. The mechanisms regulating fibrinolysis and its impact on LC complications remain to be investigated.

The aim of this work is to study fibrinolysis in patients with LC using (i) global fibrinolytic assay (GFA), (ii) calibrated plasmin generation (PG) assay, (iii) measurement of liver-produced proteins related to fibrinolysis, and to correlate the results with clinical events.

Methods: Plasma samples were obtained from 150 patients with Child-A, -B and -C LC. Fibrinolysis was assessed by a GFA (Lysis Timer, Hyphen Biomed, France), which measures the time required to lyse a plasma clot induced by thrombin in the presence of calcium, silica and tissue-type plasminogen activator (tPA). PG (Fluoroskan Ascent, Thrombinoscope, Netherlands) was induced by adding tPA to a plasma sample in which coagulation was triggered and assessed by a specific plasmin fluorogenic substrate. In addition, fibrinogen (fbg), factor XIII (FXIII), plasminogen (plg), α2-antiplasmin (α2-AP), and thrombin-activatable fibrinolysis inhibitor (TAFI) were measured.

Results: GFA lysis time, plasma concentrations of fibrinolysis proteins and PG were all significantly reduced as a function of increasing LC clinical severity ($p < 0.001$). GFA lysis time was strongly directly correlated ($p < 0.0001$) with α2-AP ($R2 = 0.47$) and fbg ($R2 = 0.41$) levels. GFA lysis time and α2-AP were significantly reduced in alcohol-induced LC compared to other aetiologies. Patients without portal hypertension (PHT) showed normal GFA lysis time, and all measured parameters (PG parameters – estimated potential, peak height and velocity index – TAFI, FXIII, α2-AP, plg, fbg) were significantly lower in patients with PHT than in those without ($p < 0.05$).

Conclusions: The concentrations of α2-AP and fbg, the stage of LC, and the presence of PHT seem to be crucial for the lysis time assessed by the GFA Lysis Timer in patients with LC. However, the lysis time was not able to predict the occurrence of thrombo-haemorrhagic events, which are mainly related to PHT. The development of other plasma lysis models focusing on either clot resistance or plasma lytic capacity is necessary to test their correlation with thrombo-haemorrhagic events in patients with LC.

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Dengue fever mimicking plasma cell leukemia – A case series of patients with recently diagnosed dengue fever

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Introduction: With the further spread of the tiger mosquito in Europe including to territories north of the alps, diseases transmitted by the tiger mosquito, such as dengue fever are expected to increase. While no direct transmission of dengue virus in Switzerland has been confirmed yet, the fast spread of the dengue virus around the globe alongside the tiger mosquito leads to increasing numbers of travelers that have conducted dengue Virus, seeking medical care after returning to Switzerland. Patients often present themselves with constitutional symptoms not very different from those accompanying malignancies. A peripheral blood smear frequently reveals plasmocytosis, a finding which, until recently, was most commonly associated with plasma cell leukemia or advanced stage multiple myeloma. Subsequent phenotypical investigations can help to discriminate a malignant from a reactive origin of the plasmocytosis. However, there are pitfalls as the plasma cells found in response to dengue virus can mimic those found in plasma cell leukemia.

Methods: Using flow cytometry, we investigated peripheral blood samples of patients with recently diagnosed infection with dengue virus to characterize their lymphocyte subsets, focusing on plasma cells. In total we investigated 5 patients, along with controls.

Results: We included 5 patients suffering from dengue virus infection showing plasmacytosis in peripheral blood. Flowcytometric analysis showed plasma cells expressing the following surface markers: CD138+ CD45+ CD19- CD56-. This phenotype is frequently shared by aggressive plasma cell leukemia. However, analysis of the light chains showed no monoclonal distribution of kappa/lambda light chains, indicating a reactive etiology rather than a malignant disease.

Conclusions: The increasing number of patients, who present themselves with the sometimes unspecific constitutional symptoms of dengue fever can be a challenge for diagnosis because the high amount of plasma cells in the peripheral blood can prompt hematological investigations, based on suspicion of a malignant disease. Subsequent flow cytometry analysis can show plasma cell phenotypes, that share similarities with the plasma cells found in plasma cell leukemia. However, the crucial difference which allows to rule out a malignant disease is the missing kappa or lambda restriction in case of dengue fever.

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Disease Phenotype in Northeastern Thailand Patients with JAK2V617F-Positive

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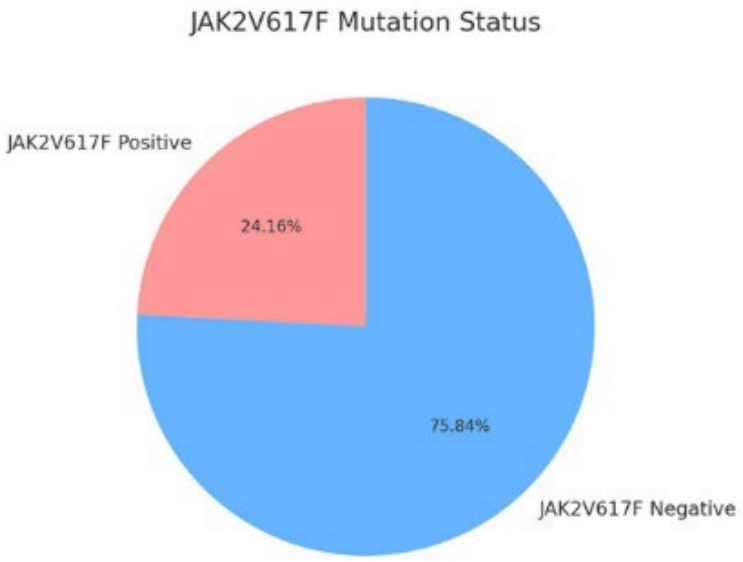
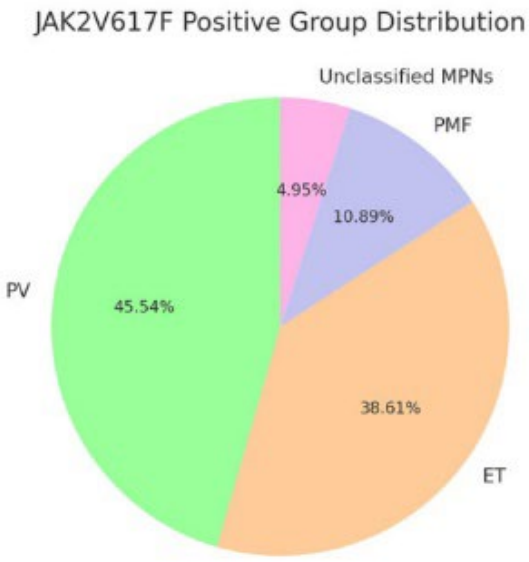
Introduction: Mutations in the genes JAK2V617F have been identified as drivers of Myeloproliferative Neoplasms (MPNs), including Polycythemia Vera (PV), Essential Thrombocytosis (ET), and Primary Myelofibrosis (PMF). JAK2V617F is included as major diagnostic criteria for MPN in the 2008 WHO diagnostic criteria. Therefore, we aimed to report the JAK2V617F mutation frequency and disease phenotype in northeast Thailand patients from January 2017 to January 2021.

Methods: A total of 418 peripheral blood and bone marrow samples were analyzed by qRT-PCR.

Results: In this group, 101 (24.17%) of the patients were positive for the JAK2V617F mutation, whereas 317 (75.83%) patients were negative for the JAK2V617F mutation. The JAK2V617F mutation-positive group (101 patients) included 46 (45.54%) patients with PV, 39 (38.61%) patients with ET, 11 (10.90%) patients with primary myelofibrosis (PMF), and 5 (4.95%) patients with unclassified MPNs. The mean age of JAK2V617F-positive male patients was 59.86 years (range: 21-88), which is higher than that of female patients, whose mean age was 57.14 years (range: 23-85). Laboratory findings showed that the mean hemoglobin level (17.8 g/dL, range 14.1-21.6 g/dL) and WBC level (10.2 x 10^9/L, range 5.8-43 x 10^9/L) in PV patients were higher than those in ET patients. PV patients had a mean platelet count of 512.5 x 10^9/L (range 151-1028 x 10^9/L), which was lower than the mean platelet count of 803 x 10^9/L (range 355-2571 x 10^9/L) in ET patients. The mean values of the JAK2V617F allele burden in patients with PV and ET were 62% and 31%, respectively.

Conclusions: The JAK2V617F mutation allele burden is higher in Thai patients with PV than in those with ET. The JAK2V617F mutation burden influences WBC counts and clinical characteristics of ET patients, such as WBC counts and hemoglobin levels. A higher JAK2V617F allele burden is associated with increased age, suggesting its potential role in prognostication and treatment protocol development.





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First real-world case report of danicopan as an add-on therapy in a patient with paroxysmal nocturnal haemoglobinuria in Switzerland

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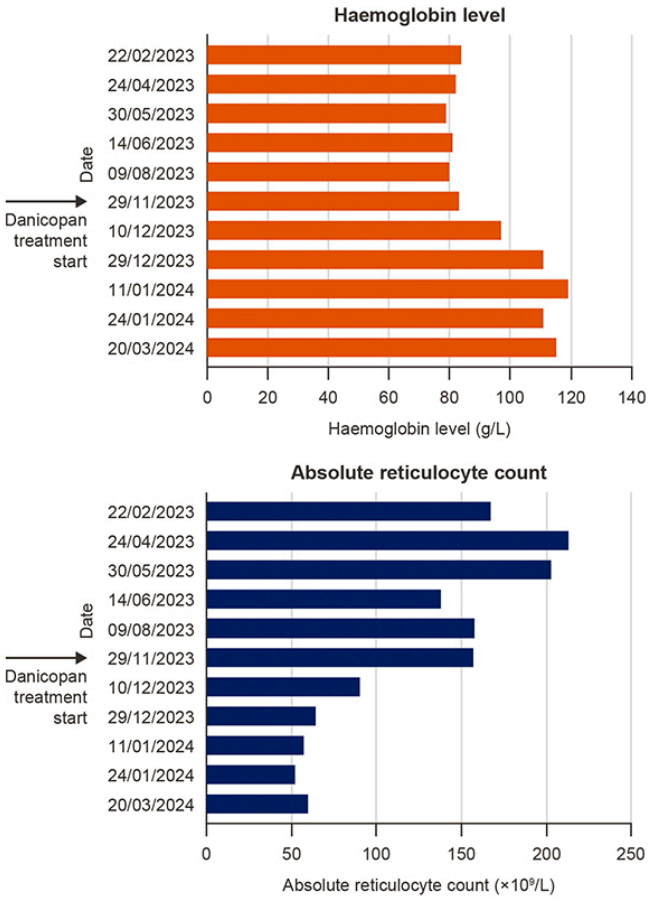
Introduction: In Switzerland, ravulizumab is the current standard of care for patients with paroxysmal nocturnal haemoglobinuria (PNH). However, 10–20% of patients receiving the C5 inhibitors (C5i) eculizumab or ravulizumab experience clinically significant extravascular haemolysis (csEVH: haemoglobin [Hb] <9.5 g/dL and absolute reticulocyte count [ARC] ≥ 120×109/L, as defined in clinical studies). Danicopan is an oral factor D inhibitor that has demonstrated benefit as an add-on therapy to C5i in patients with PNH and csEVH in clinical trials. We present the first real-world case report of a patient with PNH in Switzerland who received danicopan in addition to ravulizumab.

Methods: This case report uses available clinical data from the patient from 2012 to 2024.

Results: A 34-year-old female presenting with fatigue and abdominal pain was diagnosed with PNH in the USA in 2007 (baseline laboratory data unavailable). In 2012, the patient relocated to Switzerland (Hb: 87 g/L, ARC: 128×109/L, neutrophils: 4×109/L, platelets: 308×109/L; lactate dehydrogenase [LDH]: 1200 U/L). Eculizumab (900 mg every 2 weeks) was initiated, resulting in control of symptoms related to intravascular haemolysis. The patient remained anaemic and continued to experience fatigue (Hb: 80–90 g/L; LDH: normal). In 2020, the patient switched to ravulizumab for convenience (3300 mg every 8 weeks); after switch, symptoms related to intravascular haemolysis remained under control, but symptomatic anaemia was still present. In November 2023, owing to this symptomatic anaemia due to csEVH (Hb: 83 g/L), the patient began danicopan add-on therapy (150 mg three times daily). Following 3.5 months of danicopan, Hb and ARC were almost normalised (115 g/L and 60×109/L, respectively, Figure). The patient experienced improved quality of life with absence of anaemia-related fatigue. No adverse events (AEs) associated with danicopan were reported and the patient is continuing treatment.

Conclusions: This is the first report of a patient treated with danicopan add-on therapy in real-world clinical practice in Switzerland; treatment improved symptoms associated with csEVH and quality of life, with no AEs reported. This case will inform clinical practice in Switzerland and provide support for danicopan use in patients with csEVH. Long-term response remains to be determined.



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An interesting case of concomitant anemia secondary to prolonged PARP inhibitor toxicity, and a hemolytic anemia with non-specific warm autoantibodies

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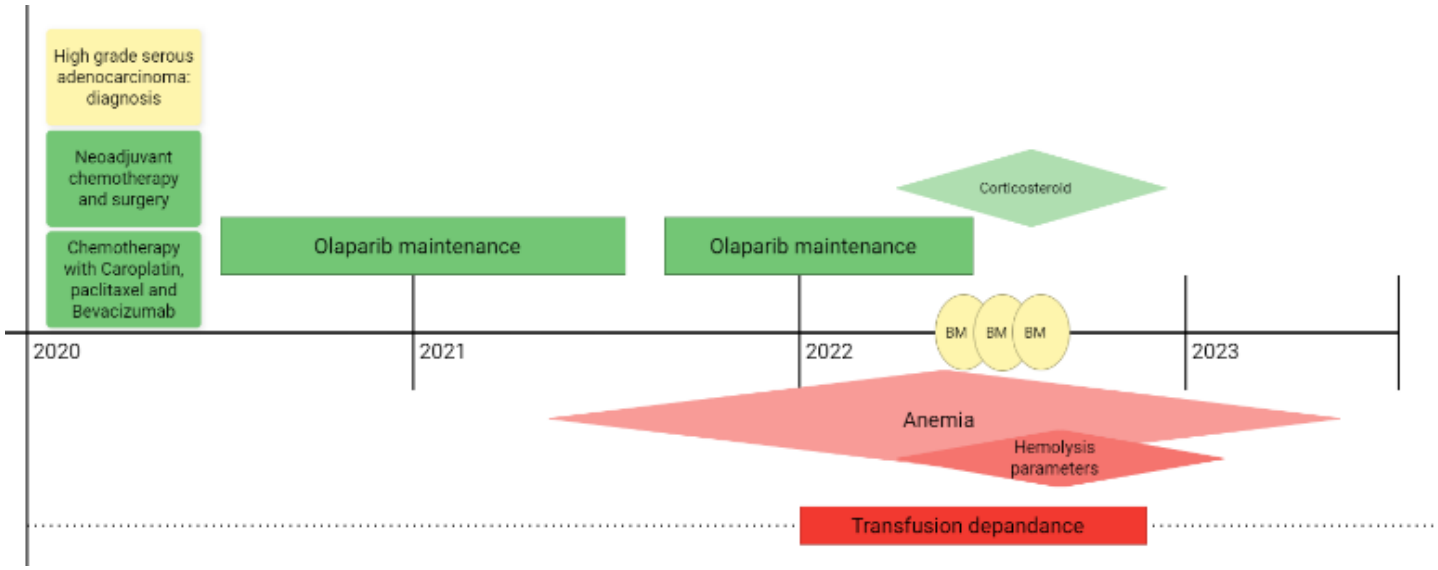
Introduction: This case report discusses a 71-year-old female patient with a history of high-grade serous ovarian adenocarcinoma. After receiving neoadjuvant chemotherapy, surgery, and subsequent adjuvant therapy, she was placed on olaparib maintenance. The patient developed severe progressive anemia starting in March 2022, culminating in a hemoglobin level as low as 55 g/L, which presented significant clinical challenges.

Methods: NA

Results: Initial investigations ruled out common causes of anemia, including iron and vitamin deficiencies, autoimmune disorders, and infections. Bone marrow biopsies were conducted, revealing a clonal cytotoxic T-LGL population and a DNMT3A mutation, but no signs of myelodysplasia or metastatic infiltration. A mixed anemia profile was observed, characterized by declining reticulocyte counts and the presence of warm autoantibodies (IgG). Despite discontinuing olaparib, the patient remained transfusion-dependent, with no initial improvement in her condition. The identification of warm autoantibodies and a progressive drop in reticulocyte counts suggested a complex anemia with both central hyporegenerative components from prolonged PARP inhibitor toxicity and an extravascular hemolytic mechanism. High-dose corticosteroids were administered in July 2022 to address the hemolytic part of the anemia. Following corticosteroid treatment, the patient experienced rapid hematological improvement, achieving transfusion independence and reduced hemolysis markers.

Conclusions: This case illustrates a severe mixed anemia stemming from prolonged olaparib toxicity combined with warm autoantibody-mediated hemolysis. The coexistence of these mechanisms emphasizes the need for meticulous hematologic monitoring in patients receiving PARP inhibitors. The prolonged toxicity observed in this patient, along with the identified DNMT3A mutation, suggests potential interactions that warrant further investigation. Regular follow-ups and comprehensive assessments are crucial for managing complex hematological conditions in oncologic patients.



SSH/SSMO POSTER PRESENTATION – EXPERIMENTAL HEMATOLOGY / ONCOLOGY

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Differential MAPK Pathway Targeting for Improved Therapeutic Efficacy in Myeloproliferative Neoplasms

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Introduction: Myeloproliferative neoplasms (MPN) are hematopoietic malignancies with constitutive JAK2 signalling activation. JAK2 activates the STAT3/5, PI3K/Akt and mitogen-activated protein kinase (MAPK) pathways. Clinical JAK2 inhibitors show limited disease-modifying potential due to maintained MAPK pathway activation. JAK2 interacts with the MAPK pathway via Src homology 2 domain-containing phosphatase 2 (SHP2), but the further molecular link to MAPK components and the most beneficial component to target are not clarified. We investigate the potential of MAPK pathway targeting at the level of SHP2 or MEK1/2 when combined with ruxolitinib and whether targeting both levels enhances efficacy.

Methods: We performed shRNA-mediated knockdown of SHP2, MEK and dual SHP2/MEK in Ba/F3 cells stably expressing JAK2V617F or JAK2WT (wildtype). Effects of SHP2, MEK or SHP2/MEK depletion combined with JAK2 inhibition by ruxolitinib on cell proliferation and signalling were tested. Pharmacological SHP2 and MEK inhibition by TNO155 and trametinib, respectively, was assessed and combined with ruxolitinib. As translational approach, a Jak2V617F mutant mouse model was evaluated for corrective effects of dual SHP2/MEK inhibition combined with JAK2 inhibition.

Results: SHP2 depletion sensitized Ba/F3 mutant cells to ruxolitinib by lowering IC50 and enhancing MAPK inhibition without affecting the JAK/STAT pathway. MEK knockdown impaired MPN cell proliferation, further sensitized cell growth to ruxolitinib, and concentration-dependently suppressed MEK-ERK downstream targets. Pharmacological inhibition of JAK2/SHP2 and JAK2/MEK significantly reduced proliferation and suppressed pERK1/2 and downstream targets in mutant cells. In vivo, dual SHP2/MEK inhibition with ruxolitinib led to more extensive MPN phenotype correction, reflected by reduced myeloid (MP), erythroid (PreCFU-E) and megakaryocytic (PreMegE) progenitor cells (Fig.1).

Conclusions: Targeting the MAPK pathway at one or multiple levels enhances therapeutic efficacy in MPN cells and preclinical models by increasing sensitivity to ruxolitinib, as highlighted by suppressed MAPK downstream targets and reduced proliferative capacity. Our data emphasize the interplay among the JAK2, SHP2, and MAPK pathways in MPN, revealing the therapeutic benefits of targeting multiple intersections in this signalling cascade.

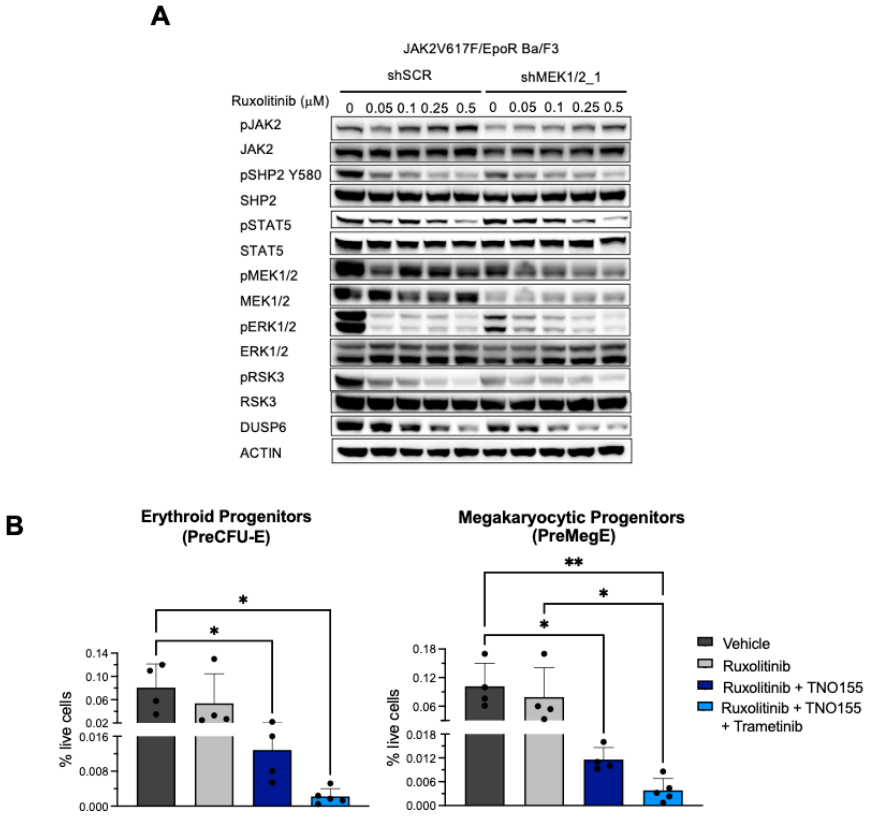

Fig.1 **(A)** Effect of increasing concentration of ruxolitinib on cell signalling of Jak2 V617F EpoR Ba/F3 cells expressing shSCR (control cells) and shMEK1/2 constructs analysed via western blot. Results are normalized to those of the DMSO control in cells expressing shSCR. **(B)** Triple pharmacological inhibition of JAK2/SHP2/MEK for 1 week showed highest suppression of hematopoietic progenitor cells, as myeloid progenitors (MP), pre-colony forming unit-erythroids (PreCFU-E), and pre-megakaryocyte-erythrocyte progenitors (PreMegE).

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Expression of KITD814V in murine hematopoietic stem cells results in an advanced systemic mastocytosis phenotype with associated myeloid neoplasm

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Introduction: Mastocytosis is characterized by an abnormal expansion of mast cells (MC) in one or various organs such as bone marrow (BM), skin and/or intestine, driven in >90% of patients by the KITD816V mutation. KITD816V-specific inhibitors reduce symptoms and prolong survival in systemic mastocytosis, but not all patients benefit from this therapy; therefore, there is an urgent need for novel treatment options.

Methods: To advance treatment development, we generated by CRISPR/Cas9 technology a novel pre-clinical mastocytosis mouse model carrying the KITD814V mutation (homologous to human KITD816V). KITD814V expression in hematopoietic stem cells (HSC) was obtained by tamoxifen-induced Scl-Cre-mediated recombination. Mice were monitored for peripheral blood count, survival and MC number. Transplanted mice receiving WT or KITD814V BM cells were analyzed for malignant clone chimerism in blood, BM and spleen. Moreoever, they were monitored for disease progression upon treatment with a specific KIT inhibitor.

Results: Expression of KITD814V in the hematopoietic compartment led to development of a myeloid neoplasia, with spleno-hepatomegaly, leukocytosis, erythrocytosis and reduced survival. MC in BM, skin and spleen were expanded, and correlated with elevated serum levels of MC protease 1 (Mcpt1); besides, they had a constitutively active KIT, Stat5 and MAPK. The HSC compartment showed reduced stem cells in the BM, but expanded committed erythroid and MC progenitors. In competitive BM transplantation, the mutant clone expanded over WT cells, indicating a proliferative advantage. Transplanted mice recapitulated the phenotype of the donor mice, with enlarged spleen, leukocytosis, erythrocytosis, MC expansion and elevated serum Mcpt1. Treatment with the specific KIT inhibitor avapritinib for 16 days reversed this phenotype as shown by correction of splenomegaly and normalized WBC values, and significantly reduced the mutant clone in BM, PB and spleen.

Conclusions: In the present study, we show that expression of KITD814V in the HSC compartment leads to a phenotype closely resembling human advanced systemic mastocytosis with myeloid neoplasia. We also demonstrate that this phenotype can be corrected by treatment with the KIT inhibitor avapritinib. Thus, this novel mouse line represents an invaluable tool for elucidating molecular pathogenetic mechanisms and testing novel therapeutic targets in mastocytosis.

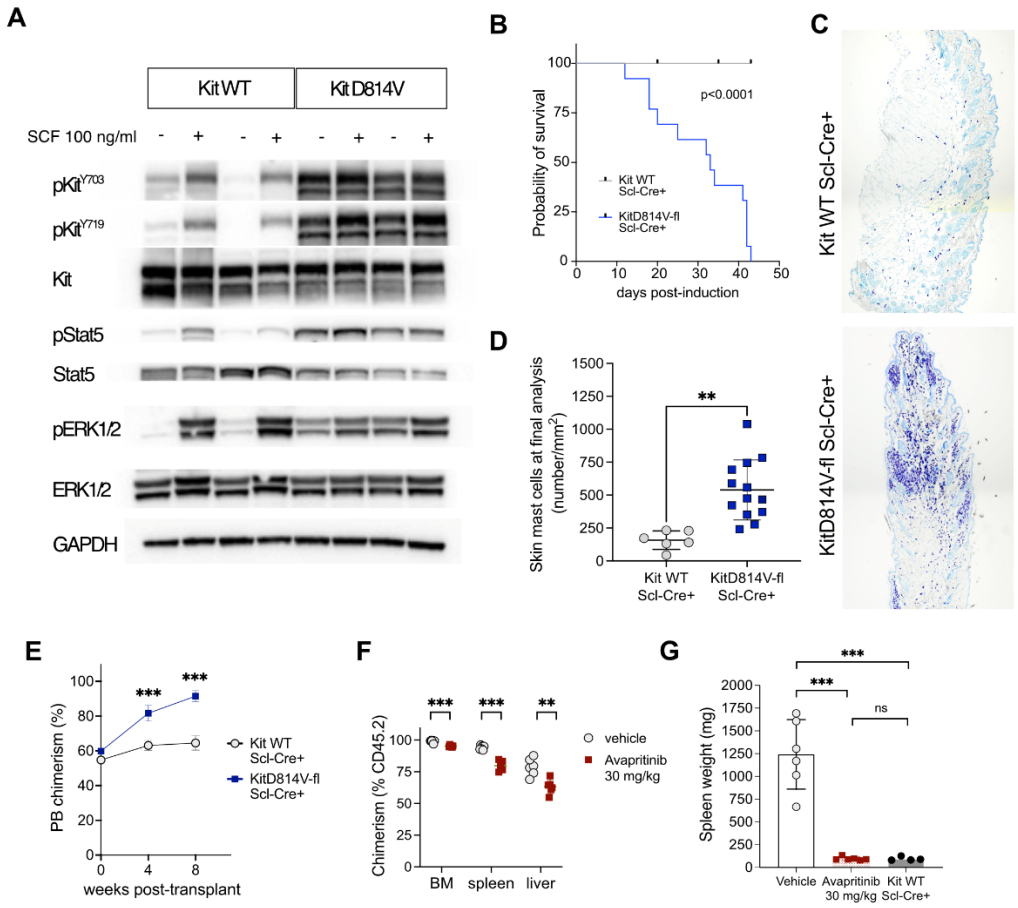

Fig. 1 Expression of KIT D814V in HSC leads to advanced systemic mastocytosis. Mice expressing the mutant KIT show constitutively phosphorylated KIT and active downstream JAK/STAT and MAPK pathways (**A**), reduced survival (**B**), and expansion of mast cells in the skin (**C, D**). Malignant BM cells show a proliferative advantage in competitive transplantation (**E**). Treatment with 30 mg/kg avapritinib reduced the mutant clone and normalized spleen size (**F, G**).

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Targeting the SHP2 phosphatase enhances therapeutic effects of the JAK2 inhibitor ruxolitinib in myeloproliferative neoplasms by inhibiting the MAPK pathway

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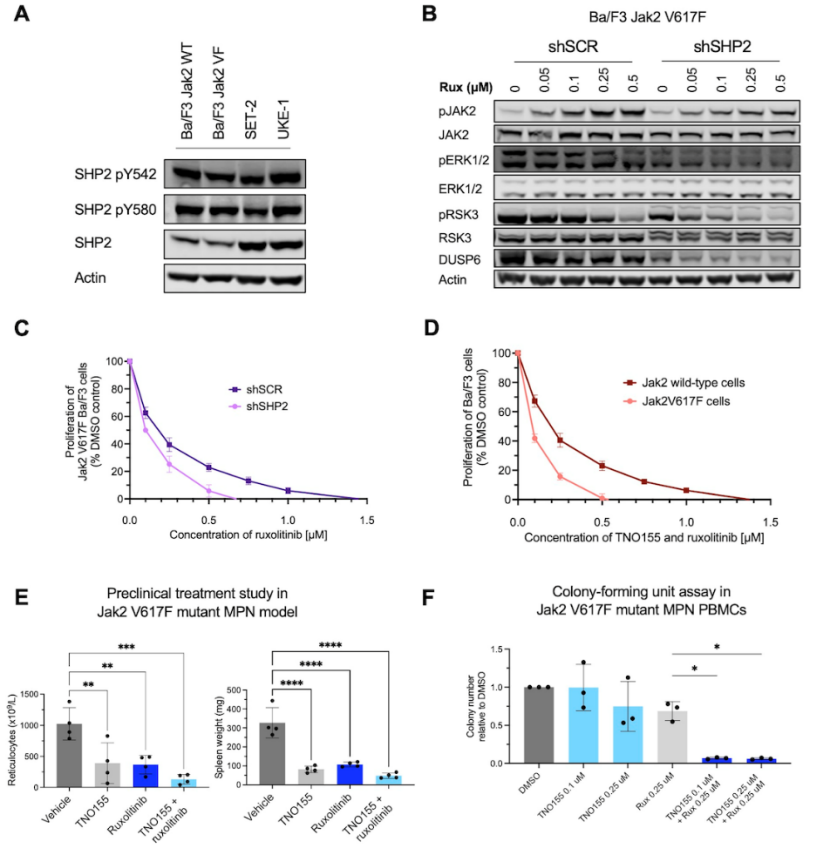
Introduction: Myeloproliferative neoplasms (MPN) are haematologic malignancies with constitutive JAK2 kinase signalling, resulting in activation of STAT3/5, PI3K/Akt and MAPK pathways. Sustained MAPK pathway activation limits therapeutic potential of JAK2 inhibitors like ruxolitinib (Rux). We assess SHP2 as proximal mediator of MAPK activation and as a novel therapeutic target in MPN.

Methods: We targeted SHP2 by shRNA-mediated knock-down and using pharmacologic SHP2 inhibitors TNO155 and IACS-13909 in MPN cells. Translational potential was evaluated in Jak2V617F (Jak2VF) or MPLW515L mutant MPN mouse models. Findings were validated in a bioreactor platform modelling bone marrow ex vivo and in primary haematopoietic cells of MPN patients.

Results: SHP2 was expressed and phosphorylated in Jak2VF human MPN cell lines and in Jak2VF or wild-type (WT) Jak2 Ba/F3 cells (A). Targeting of SHP2 reduced MAPK pathway activation (B) and sensitized Jak2VF cells to Rux (C). Importantly, Jak2VF cells were more vulnerable to SHP2/JAK2 inhibition than Jak2 WT cells (D). Jak2VF mice showed reduced erythrocytosis and splenomegaly upon TNO155 treatment (7.5 mg/kg BID), and most pronounced effects in combination with Rux (60 mg/kg BID) (E). In the MPLW515L mouse model, SHP2/JAK2 inhibition corrected splenomegaly and leucocytosis, while partial effects were seen with single agents. Notably, comparable effects were observed upon SHP2/JAK2 inhibitor treatment at a lower Rux dose (30 mg/kg BID). TNO155 was well tolerated in both mouse models as single agent and in combination with Rux. To validate our results, we engrafted Jak2VF CD117+ haematopoietic cells in a bioreactor system. Proliferation and differentiation into all haematopoietic lineages were observed and most effectively reduced with combined JAK2/SHP2 inhibition. Similarly, myelo-erythroid colony formation in primary MPN patient PBMCs was most efficiently suppressed with combined JAK2/SHP2 inhibition (F).

Conclusions: Our results suggest a relevant role of SHP2 in MPN. SHP2 inhibition enhanced JAK2 inhibitor efficacy in vitro and in vivo. Notably, Jak2VF cells were preferentially inhibited. Confirmation of the translational potential in a bioreactor system and in primary MPN patient cells encourage further evaluation of combined SHP2/JAK2 inhibition as a therapeutic approach in MPN.



A SHP2 is expressed and phosphorylated at two tyrosine phosphorylation sites (Y542/Y580) in isogenic (Ba/F3 Jak2 EpoR) and Jak2 V617F mutant human (SET-2, UKE-1) MPN cell lines. **B** shRNA-mediated knock-down of SHP2 enhances suppression of MAPK pathway effectors including pERK1/2, pRSK3, and DUSP6 by ruxolitinib compared to ruxolitinib as single agent in Jak2 V617F Ba/F3 cells. **C** shRNA-mediated knock-down of SHP2 sensitizes Jak2 V617F Ba/F3 cells to ruxolitinib. **D** Proliferation is more strongly inhibited by combined JAK2/SHP2 inhibition in Jak2 V617F mutant vs Jak2 wild-type Ba/F3 cells. **E** Combined treatment with TNO155 and ruxolitinib enhances corrective effects in a Jak2 V617F mutant competitive transplantation mouse model compared to either drug. **F** Ex vivo exposure of primary MPN patient PBMCs to TNO155 and ruxolitinib shows significantly reduced colony formation after 14 days.

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CD19 CAR T Cells drive a remodeling of the Immune Microenvironment associated with T-cell dysfunction in B-Cell Acute Lymphoblastic Leukemia

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Introduction: In patients with B-cell Acute Lymphoblastic Leukemia (B-ALL), Chimeric Antigen Receptor (CAR) T cells targeting CD19 have achieved durable responses. However, a substantial fraction of patients remains refractory or relapses with suboptimal CAR T-cell activity. In this context, the contribution of the tumor microenvironment on CAR T-cell fate and endogenous immunity remains incompletely understood. We hypothesized that bone marrow (BM) immunological niche reacts to CAR T cell-mediated inflammation by activation of inhibitory pathways and molecules.

Methods: We performed single-cell RNA sequencing and spectral flow cytometry on BM resident immune cells of patients undergoing CAR T-cell infusion. Data in this study were generated from patients enrolled in the FT01CARCIK Phase I/IIb clinical trial (NCT03389035), in the FT03CARCIK Phase II study (NCT05252403) or autologous CAR T cells in the context of either phase I/II trial or commercial cell therapy.

Results: Unbiased clustering of BM cells and infusion products was performed. Extensive integration of the dataset coming from the individual patients was observed. The more representative clusters were classified into infusion product, CD4 and CD8 endogenous population, B cells, myeloid cells, pDC, NK, and NK-T cells. We observed profound changes in the composition of BM after CAR T-cell infusion compared to pre-treatment samples, with an increase in the myeloid cells, and exhausted CD8 T cells. After CAR T-cell infusion, myeloid cells displayed a higher resemblance to myeloid-derived suppressor cells (MDSCs). Significant enrichment in Interferon response, Hypoxia, and TGF-β signaling was associated with the expansion of MDSC, and exhausted T cells, detected by performing spectral flow cytometry of additional 20 matched BM samples pre and post CAR T-cell treatment. By modeling intercellular communications, we revealed that HIF1-α, VEGF and TGFβR2 are key players in the crosstalk between CAR T cells and the immune niche, leading to general immune suppression. These data were also validated in n-hu-PDX-NSG mice. PD1 expression in endogenous T cells post CAR-T treatment was associated with a lack of durable response.

Conclusions: CAR T cells-mediated myeloid activation is associated with pathways of immune dysregulation that may dampen CAR T cell expansion and antagonize the effects of the therapy.

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Enhancing CD117 directed bispecific T-cell engagers and activators by CD33 target-selective co-stimulation

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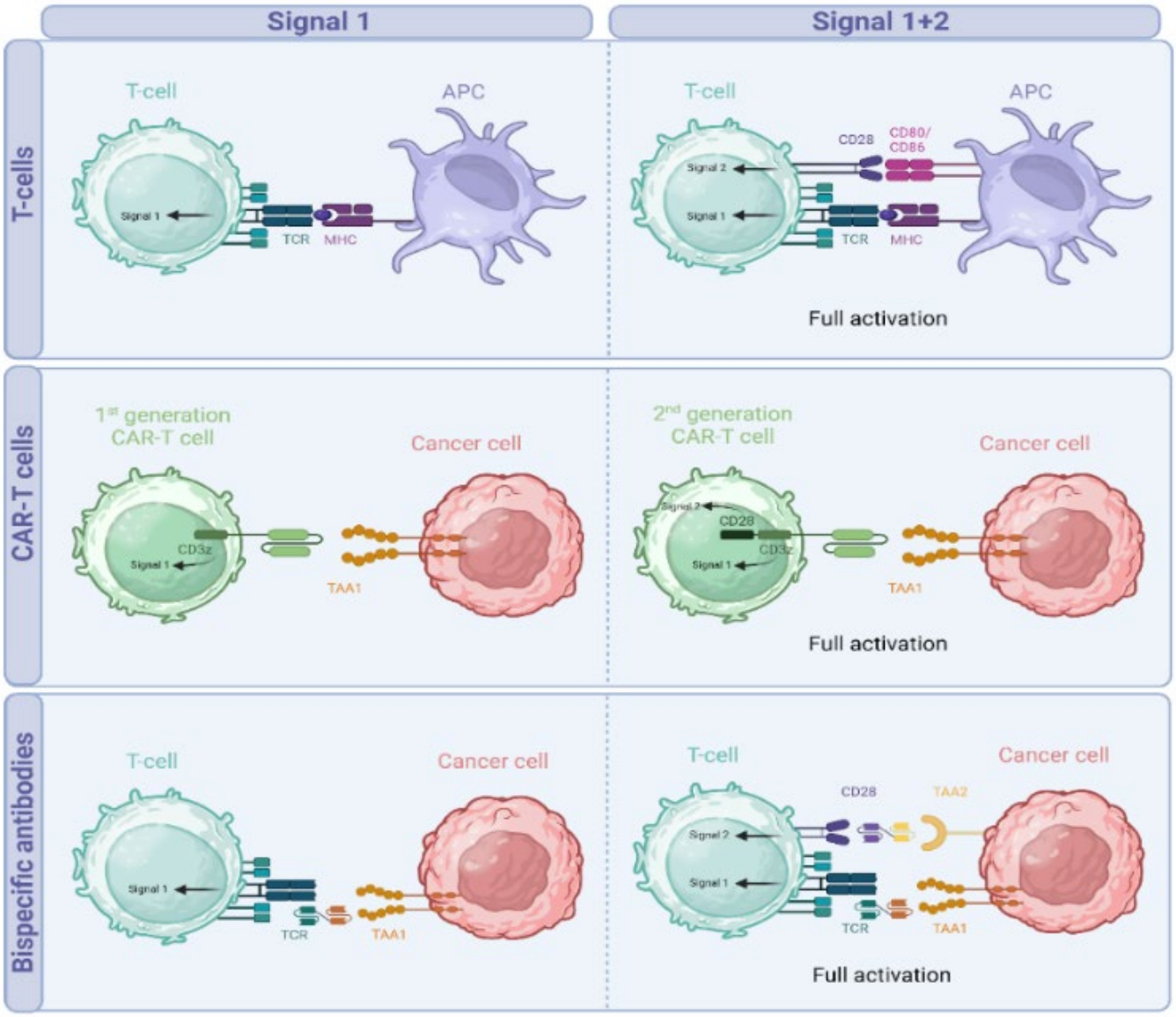
Introduction: Acute Myeloid Leukemia (AML) is an aggressive hematologic malignancy with overall poor clinical outcome. T-cell engaging bispecific antibodies (TCEs) are a new class of antibody-based therapies, which redirect T-cells to the target-antigen expressing cells in an MHC/TCR-independent fashion. However, their development for clinical application face several challenges. Firstly, in the setting of hematopoietic stem and progenitor cell (HSPC) diseases like AML, the overlapping expression of tumor-associated antigens on healthy HSPCs poses a major challenge for immunotherapies, as loss of these cells results in permanent aplasia, requiring hematopoietic stem cell transplantation for compensation. Secondly, CD3-directed TCEs lack a second T-cell activation signal (e.g. CD28 or 41BB), limiting their effectiveness compared to second-generation CAR T-cells. To address these issues, we propose combining a CD28 binding bispecific antibody with a CD117xCD3 TCE to enhance T-cell activation and improve specificity by targeting a second antigen (CD33) in AML.

Methods: We produced a tandem scFv TCE targeting CD117 and two T-cell engager and enhancers: a tandem scFv (CD33xCD28 1+1) and an IgG-HC-scFv (CD33xCD28 2+2 IgG4). The benefits of the combination therapy was evaluated in vitro against an AML cell line with varying degrees of CD117 expression (low, mid and high) and primary AML patient samples. We measured specific lysis, T-cell activation and proliferation, and cytokine release. Furthermore, we performed in vitro safety studies to assure that the CD33xCD28 2+2 IgG4 has no superagonistic properties. Lastly, we performed pharmacokinetic studies of the CD33xCD28 2+2 in NSG mice.

Results: The addition of a CD33xCD28 2+2 IgG4 resulted in improved T-cell activation, proliferation and specific lysis compared to CD117xCD3 monotherapy in all our in vitro models. In the absence of CD117xCD3, neither specific lysis nor T-cell activation nor proliferation occurred, indicating that CD28 does not exhibit superagonistic properties.

Conclusions: Co-stimulatory signals like CD28 and 41BB are crucial in CAR-T cell therapy and have been highlighted in various studies on bispecific antibodies. We here show, to our knowledge for the first time in AML, that combining a CD117xCD3 TCE with a CD28 activating bispecific antibody targeting a second tumor antigen (CD33) enhances specific lysis of AML target cells.



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Ribonuclease Inhibitor (RNH1) is a Novel Regulator in Myelopoiesis and Resolves Differentiation Blockade in Acute Myeloid Leukaemia

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Introduction: Ribonuclease Inhibitor (RNH1), traditionally known for inhibiting pancreatic ribonucleases, has emerged as a key regulator of haematopoiesis, crucial in embryonic development and erythropoiesis. In-vivo mouse studies highlighted this role, whereby Rnh1 deletion in haematopoietic cells caused an anaemic phenotype but increased myelopoiesis. Despite the increase, there was no leukaemogenesis and the myeloid cells were functional, the phenotype likened to a subtle emergency myelopoiesis. Acute myeloid leukaemia (AML) treatment is challenging due to it's heterogeneity, uncontrolled proliferation and differentiation blockage in myeloid progenitors. Leveraging these insights, we hypothesized that targeting RNH1 could alleviate myeloid differentiation arrest in AML, offering a novel therapeutic avenue.

Methods: RNH1 KO AML cell lines (THP1, Molm13, HL60, OCI-AML3) were generated using CRISPR-Cas9 method. RNA sequencing, mass spectrometry and biochemical/functional assays were done to uncover mechanisms of myelopoiesis regulation by RNH1. Lentivirus mediated RNH1 knockdown (KD) was performed in AML patient derived mononuclear cells and differentiation/proliferating potential was measured.

Results: Loss of RNH1 increased myeloid differentiation (MD), which was observed both in AML cell lines and in patient derived blast cells. Transcriptomic analysis in THP1 cells revealed that MD related genes were upregulated in the KO cells. Although transcription levels of key myeloid transcription factors (TF) remained unchanged, their protein levels increased, suggesting post-transcriptional or translational regulation by RNH1. Absence of RNH1 also resulted in reduced global protein synthesis rates, observed in all the AML cell lines. Mass spectrometry analysis identified interaction of RNH1 with histone

deacetylases (HDAC1/2) and the master myeloid TF C/EBP alpha, indicating possibility of RNH1 mediated epigenetic regulation of myelopoiesis. Further, expression of acetylated histones was altered in RNH1 KO cells. Whether the RNH1 mediated enhancement of myeloid differentiation is attributed to defective translation or due to differences in epigenetic regulation of myeloid TFs, is currently under investigation.

Conclusions: Our findings highlight RNH1 as a novel regulator of myeloid differentiation, offering a promising therapeutic target for resolving the differentiation block in AML.

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Proteomic characterization of the blood-tissue interface of pre-metastatic lung and liver

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Introduction: Metastasis is the primary cause of death in cancer. It has been shown that tumours generate a favourable environment in secondary organs, termed the premetastatic niche, which facilitates the seeding of circulating tumour cells and the formation of metastatic colonies in these new locations. In this study, we employed a chemical proteomics strategy within an orthotopic mouse model of breast cancer, utilising in vivo biotinylation of the vasculature, to identify proteins specifically expressed at the blood-tissue interface in premetastatic organs.

Methods: The vasculature of 4T1 tumour-bearing BALB/c mice in the premetastatic phase was perfused with sulfo-NHS-LC-biotin, to covalently label proteins at the blood-tissue border. Matched mice bearing the related but non-metastatic 67NR tumour model and healthy mice served as controls (all n=4). Perfused livers and lungs were harvested, biotinylated proteins purified on streptavidin-resin, and subjected to LC-MS/MS mass spectrometry after tryptic digestion. Resulting spectra were analysed with MaxQuant and protein regulation assessed with Perseus. Targets were validated using immunostaining of murine and human tissue samples. A proteomic dataset on target expression in human normal organs was generated to assess potential on-target side effects of future therapeutics. An in vivo biodistribution analysis was performed in mice to assess the specificity of a pharmaceutical drug against the most promising target.

Results: In total, 2322 proteins were identified in the liver and 1199 in the lung. The proteins were mainly related to cellular component gene sets of the cell surface, plasma membrane, extracellular matrix and secretory vesicles. Proteins upregulated in the 4T1 group were mainly related to various inflammatory processes. Interestingly, one protein was identified as a specific biomarker in pre-metastatic lungs. Biodistribution analyses with a fluorophore-tagged clinical-grade inhibitor confirmed it as a potential target of the lung pre-metastatic niche in vivo.

Conclusions: In conclusion, this comparative spatial analysis of the targetable proteome in the pre-metastatic niche provides a valuable dataset as a basis for the development of pharmaceutical agents targeting tissue remodelling in the pre-metastatic phase of solid tumours.

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Role of ERK1/2 kinases for thrombopoiesis and platelet function in myeloproliferative neoplasms

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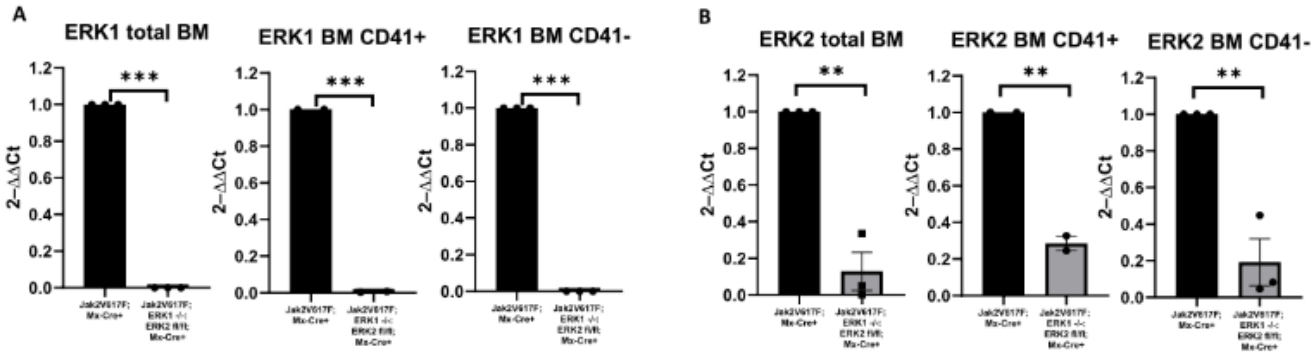
Introduction: Myeloproliferative neoplasms (MPN) are myeloid malignancies driven by constitutive activation of JAK2 signaling. They are characterized by excessive production of myeloid blood cells including megakaryocytes and platelets. Thromboembolic events and bleeding complications, which relate to cytoses, relevantly contribute to morbidity and mortality. Therefore, platelet production and function are of high interest. Given that ERK1/2, which are distal kinases of the MAPK pathway, are essential for hematopoiesis and remain activated in MPN despite JAK2 inhibitor therapy, we assess the role of ERK1/2 kinases in thrombopoiesis and platelet function in MPN.

Methods: We generated murine models of constitutive Jak2 activation with ERK1/2 deficiency in hematopoiesis or specifically in thrombopoiesis by crossing Jak2V617F knock-in with ERK1-/-ERK2f/f mice and Cre-recombinase under the control of Mx-1 or PF4 promoters. Aspects of megakaryopoiesis, thrombopoiesis, platelet function and thrombosis as part of MPN phenotypes were studied in these models with ERK1/2 deficiency including characterization of megakaryocyte ploidy and ex vivo differentiation dynamics.

Results: Jak2 V617F ERK1-/-ERK2f/f Mx-1 Cre mice developed ERK1/2 deficiency of 0-20% within 4 weeks of transgene induction in total bone marrow and CD41+ cells. Cytoses in peripheral blood and splenomegaly were reduced suggesting improvement of MPN phenotype by ERK deficiency. Formation of mature megakaryocytes in ex vivo culture was reduced in ERK-deficient Jak2V617F mice. Mutant allele burden as reflected by CD45.2/CD45 ratio in competitively transplanted mice, was significantly lowered suggesting a reduction of the MPN clone in all hematopoietic cell types. For specific characterization of ERK1/2 kinases in megakaryo- and thrombopoiesis, Jak2V617F ERK1-/-ERK2f/f Pf4-Cre mice were also generated. While Jak2 activation in megakaryocytes resulted in subtle but significant thrombocytosis along with increased ploidy of megakaryocytes and prolonged tail vein bleeding times, the impact of ERK deficiency in this model is currently in evaluation.

Conclusions: Our preliminary data suggest a relevant role of ERK1/2 kinases for megakaryo- and thrombopoiesis as well as platelet function in Jak2V617F-driven MPN models.



qPCR experiments showing ERK1 (A) and ERK2 (B) mRNA expressions (fold change) 4 weeks after polyI:C induction (n=2-3)

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Single Cell Multi-Omic Correlation of Single Nucleotide Variants, Copy Number Variation and Surface Epitopes for Clonal Profiling of Myeloma

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Introduction: Myeloma develops from clonal expansions, such as monoclonal gammopathy of uncertain significance (MGUS) or smoldering multiple myeloma (SMM), although not all progress to full myeloma. Nearly all patients relapse due to genetic differences in myeloma cells, highlighting the need for regular, long-term surveillance. Identifying subclones linked to disease progression or resistance could enhance precision therapies. We present proof of concept using Mission Bio's Tapestri platform, showcasing single-cell, multi-omic data that identifies clonal populations driving myeloma or resistance.

Methods: Cryopreserved, CD138-enriched, matched SMM/MM patient samples were multiplexed in groups of 3 on the Mission Bio Tapestri platform. Samples were thawed and stained with a 20-plex antibody-oligo cocktail to label myeloma-specific surface markers for sequencing analysis and processed with an 846-plex DNA amplicon panel that combined whole-genome CNV coverage with MM gene hotspots. Single cell quantification of subclones by single nucleotide variants (SNV), copy number variants (CNV), IgH/IgK/IgL clonotyping, and surface protein expression analysis was performed. From an average of 3,500 cells recovered per multiplexed specimen, raw sequencing data was analyzed using Mission Bio proprietary algorithms.

Results: We analyzed SMM subclones to identify rare driver mutations leading to MM. These mutations correlated with changes in point mutations, Ig chains, copy number gains/losses, and protein expression. At MM diagnosis, clonal differences, including sequential copy gains/losses, aligned with changes in MM markers like BCMA and GPRC5D, as well as drug resistance mutations. Protein expression progression was mapped on a single plot, showing higher MM-marker levels as subclonal genetic variants accumulated, though occasional reversals occurred. The proportion of T-cells and low-viability cells decreased as mutational burden increased.

Conclusions: As precision therapies for myeloma grow, correlating multiple clonal features improves prognostics, treatment of pre-myeloma conditions, and identifies resistant subclones at diagnosis or relapse, guiding treatment adjustments. The Tapestri platform enables high-resolution analysis of SNVs, CNVs, Ig clonotyping, and protein expression from thousands of cells, even from cryopreserved MM specimens, surpassing bulk sequencing and flow cytometry in clinical relevance.

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Ribosome profiling defines the translational sequelae of proteasome inhibition in multiple myeloma

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Introduction: Multiple myeloma (MM) cells rely heavily on the ubiquitin-proteasome system to maintain proteostasis. As a result, proteasome inhibitors (PIs) form the backbone of MM therapies. PIs induce cytotoxicity mainly through proteotoxic mechanisms such as misfolded protein accumulation and disruption of amino acid (AA) recycling, yet the mechanisms of PIs resistance are poorly understood. Here, we use ribosome profiling to investigate the proteostatic responses that allow MM cells to overcome PI-induced stress.

Methods: MM cells were treated with a 1h pulse of carfilzomib (CFZ) to mimic patient pharmacokinetics. RNA sequencing (RNA-seq) and ribosome profiling (Ribo-seq) were conducted at 4h, 48h and 6 days post-treatment. Protein synthesis was measured via puromycin incorporation, and AA levels were quantified using targeted metabolomics (LC-MS/MS). qRT-PCR and immunoblotting were used to evaluate changes in gene and protein expression.

Results: Ribosome profiling revealed extensive, kinetically complex changes in the translatome of MM cells after PI treatment. During acute stress (4h), cells exhibited increased transcription and translation of proteasome subunits, indicative of a proteasome bounce-back response, along with reduced translation efficiency (TE) of protein synthesis-related genes, global translational repression and suppression of MTOR signalling. LC-MS/MS showed reduced intracellular AAs concentration and ribosome collisions (RCs), evidenced by increased RPS10 ubiquitination and p38 phosphorylation.

During early recovery (48h), AAs remained low, but RCs had resolved. RNA- and Ribo-seq showed increased TE of protein synthesis-related genes, accompanied by enhanced global

protein synthesis and a significantly higher MTOR activity in PI-treated cells. 6 days after CFZ treatment (late recovery), resistant cells retained high TE of protein synthesis related genes, though global protein synthesis was no longer increased. Finally, MTOR inhibition by rapamycin impeded MM cell recovery from CFZ treatment.

Conclusions: Our study reveals that proteasome inhibition rapidly triggers RCs and a suppression of protein translation, which is followed by upregulated translational activity linked to MTOR activation in surviving MM cells. The findings suggest new avenues to overcome PI resistance.

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Patient-derived lymphomoids preserve the tumor architecture and allow testing response to therapies in lymphoma

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Introduction: The efficacy of anti-cancer therapies depends on the genomic composition of the tumor, its microenvironment, spatial organization, and intra-tumor heterogeneity. B-cell lymphomas are a heterogeneous group of tumors emerging from B-cells at different stages of differentiation and exhibiting tumor-specific interactions with the tumor microenvironment. Thus, the effect of drug treatments can be influenced by the tumor composition and functional interactions among immune cells.

Methods: Here, we developed a platform to maintain small fragments of human lymphoma tissue in culture for several days, and use them to test response to small molecules. We collected 27 patient samples representative of different lymphoma subtypes, and established ex vivo tissue fragments, here referred to as lymphomoids.

Results: Analysis of the lymphomoids using multiplex fluorescent staining showed that they retain histological, cellular, and molecular characteristics of the original tissue. Using lymphomoids, we tested sensitivity to several clinically approved drugs in parallel and examined tissue remodeling upon treatment using spatial transcriptomics. Moreover, when this information was available, we showed that the effect of the inhibitors observed in lymphomoids was consistent with the patients' response in the clinic.

Conclusions: In conclusion , lymphomoids represent an innovative ex vivo model to assess the effect of anti-cancer therapies while preserving the tissue structure and its components.

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Molecular mechanisms of regulation of apoptosis and autophagy in pediatric Immune Thrombocytopenia

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Introduction: Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder characterized by low platelets counts. Most treatments are effective in a limited number of patients only. Previous studies, also from our group, have demonstrated a role of platelet apoptosis in the pathogenesis of pediatric ITP, while the role of the autophagic machinery is far less characterized. We aimed to investigate the gene expression and activation mechanisms of apoptosis and autophagy as well as ER-phagy signaling in megakaryocytes (MKs), the precursors of platelets.

Methods: We used the MEG-01 cell line and MKs differentiated from PMBCs derived from healthy controls (HC) or ITP patients, which were treated with plasma isolated either from HCs or ITP. We investigated the expression of specific regulatory genes both at mRNA level by qRT-PCR and at protein level by Western blot and immunofluorescence. We further performed transmission electron microscopy (TEM) on primary MKs derived from PBMCs of ITP patients and HC.

Results: We could demonstrate a significant upregulation of the apoptosis markers (CASP3, BAX and BCL2) in ITP plasma treated MKs compared to all other groups ($p < 0.05$). Similarly, both autophagy (ULK1, BECN1 and LC3II) and ER-phagy (FAM134B and ATL1-3) were significantly induced in the ITP plasma treated group compared to all other conditions ($p < 0.05$). The increased mRNA expression of the investigated markers could be reversed upon ITP plasma heat inactivation ($p < 0.05$). We further confirmed the increased expression levels of autophagy (ATG5, LC3-II, LAMP-1) and ER-phagy markers (FAM134B, ATL2) by Western blotting at 3, 12 and 24 h and by immunofluorescence. By TEM, ITP-derived-MKs showed a marked vacuolization of the cytoplasm, nuclear condensation and fragmentation compared to healthy MKs.

Conclusions: Our results revealed alterations in the apoptosis and autophagy as well as in ER-phagy signaling mechanisms in healthy MKs treated with plasma isolated from ITP patients indicating that these pathways may be involved in the disease pathophysiology. These findings could be further used to identify promising molecular targets with therapeutic potential in ITP and other hematological or autoimmune disorders.

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A novel single-cell measurable residual disease (SCMRD) assay for simultaneous DNA mutation and surface immunophenotype profiling

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Introduction: MRD testing is now standard in AML to detect residual leukemic cells after therapy, which may predict relapse. MRD typically reflects an evolved disease with high biological heterogeneity, making it difficult to monitor. Current methods like multiparameter flow cytometry (MFC) and bulk next-generation sequencing (NGS) are limited by false positives/negatives. Additionally, concordant MRD data from single-analyte approaches can lead to discordant patient outcomes, underscoring the incomplete insights each method provides. We present a new single-cell MRD (scMRD) multiomic assay that assesses genotype and immunophenotype with a 0.01% detection limit. The assay detects rare cells on a standard Tapestri run by incorporating (i) a bead-based protocol to enrich blast cells, (ii) a DNA and protein panel for AML MRD diagnosis and treatment, and (iii) an automated analysis pipeline for single-cell multi-omics output.

Methods: We used cryopreserved bone marrow samples from AML patients in complete remission. The assay detects rare cells by incorporating (i) a bead-based protocol to enrich blast cells, (ii) a DNA and protein panel for AML MRD diagnosis per ICC and ELN guidelines, and (iii) an automated analysis pipeline for single-cell multi-omics. Multiplexing up to three patient

samples in one run through germline identification reduces costs and increases throughput.

Results: Five pathogenic mutations (DNMT3A, FLT3-ITD, FLT3-TKD, RUNX1, SF3B1) were detected in one patient sample, forming four pathogenic sub-clones based on zygosity and co-occurrence. The largest clone (wild-type, 4,059 cells) was non-neoplastic, followed by two triple-mutant clones (DNMT3A/FLT3-TKD/SF3B1, 1,487 cells and DNMT3A/FLT3-ITD/SF3B1, 315 cells), a double-mutant clone (DNMT3A/SF3B1, 159 cells), and a single-mutant clone (RUNX1, 12 cells), which was undetected by bulk NGS. Immunophenotyping confirmed a CD34+ signature linked to the largest sub-clones. Phylogeny reconstruction revealed a branched evolution.

Conclusions: Using this single-cell approach, we distinguished true MRD from pre-leukemic clones and identified multiple leukemic clones with co-occurring driver mutations. Integrating genotype and immunophenotype improved MRD detection by linking specific mutations to protein expression patterns. This high-sensitivity, multi-omic assay offers a scalable solution for comprehensive MRD detection to guide therapy decisions.

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The effects of released exosomes from stimulated NK-Cells with IL15 on the apoptosis of human acute myeloid leukemia cell line (HL-60)

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Introduction: Most cancers are treated with conventional methods such as chemotherapy and radiotherapy. However, the limitations associated with cytotoxic therapies have led researchers to explore alternative solutions. Immunotherapy is a promising avenue due to its safety and effectiveness. Nevertheless, cancer cells have devised tactics to escape detection, making the immune system inadequate. Researchers have introduced certain modifications to immunotherapy methods, offering hope for a potential cancer treatment breakthrough. NK cells, the forefront of the immune system's defense against cancerous cells, exhibit enhanced activation and improved functionality when exposed to stimulating interleukins such as IL-2 and IL-15. Exosomes, small intracellular nanoparticles, mirror their parent cells' characteristics. As a result, exosomes derived from NK cells possess NK cell components like perforin, granzyme, and Fas-L. The small size, proximity to the tumor microenvironment, and stability of these exosomes allow cancer cells to readily internalize them. Using exosomes derived from activated NK cells may be more cytotoxic and effective compared to the ones extracted from non-activated cells and may lead to more apoptosis in target cells.

Methods: By adding 100 nanograms per milliliter of IL-15 to NK-92 cell culture, the cells are incubated for 48h. Then, the exosomes are isolated from treated and non-treated NK-92 cell lines by the ultracentrifuge method. After isolation, different concentrations of both groups are added to HL-60 cells for treatment. After 24h, the apoptosis rate is assessed by the Annexin-V method.

Results: Increased light absorption in the BCA test,along with thicker bands of CD63 and CD81 in the Western blotting test,indicate a higher exosome yield in post-treated NK-92 cells.The low p-value from the t-test demonstrates that the exosomes derived from treated NK cells are more cytotoxic than those from the control group.The results of the two-way ANOVA confirm differences between the control and treatment groups at each concentration,and the results of Welch’s t-test prove that all differences in the ANOVA test are significant.

Conclusions: This article presents evidence that exosomes obtained from IL-15-induced NK cells not only increase in quantity of exosome but also demonstrate significant cytotoxicity against leukemia cells compared to exosomes obtained from non-stimulated NK cells.

SSH/SSMO POSTER PRESENTATION – CLINICAL HEMATO-ONCOLOGY

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High iASPP (PPP1R13L) expression is an independent predictor for adverse clinical outcome in acute myeloid leukemia (AML)

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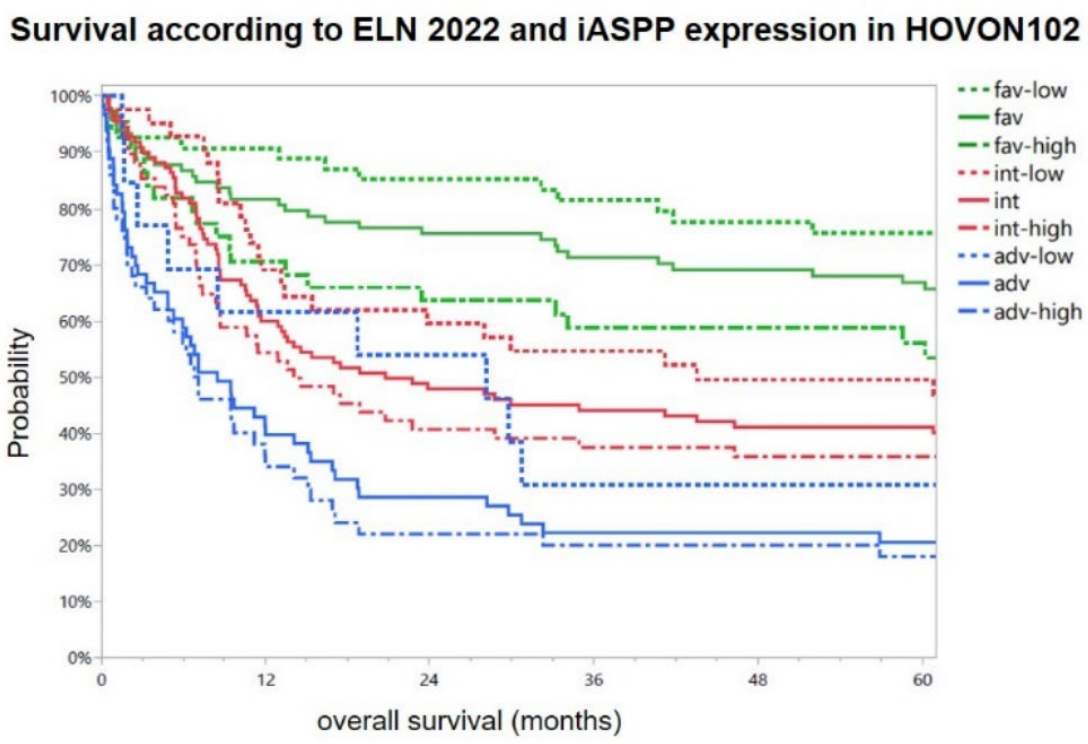
Introduction: Despite remarkable progress in the last decades, the majority of patients diagnosed with AML face a poor prognosis. Predictive scores have been established to guide therapy, nevertheless, rates of refractory or relapsing (R/R) disease remain high and even in the favorable risk situation patients face a considerable risk of relapse. Additional or better markers are needed to predict therapy outcome and guide treatment decisions. Oncogenic iASPP is an evolutionarily conserved inhibitor of p53-mediated apoptosis and has been shown to have pro-proliferative and antiapoptotic properties. We studied iASPP expression, function and its predictive value in AML – and confirm that high levels of iASPP predict for a poor prognosis.

Methods: A large RNAseq leukemia cohort and myeloid tissue deriving from three repositories (TCGA, TARGET and GTEx, n>50.000) were assessed for iASPP expression in AML. In addition, an independent random validation cohort of newly diagnosed patients with AML (n=99), a bone marrow donor cohort (n=31) and two clinical trial cohorts of intensively treated patients (SAKK/HOVON study group cohorts) with follow-up data were studied to confirm iASSP expression and correlate with survival data. iASPP AML KD models were established to study iASPP function in vitro and in vivo.

Results: We demonstrate that iASPP is frequently overexpressed in AML in all tested patient cohorts ($p \leq 0.001$) – and high iASPP expression levels associate with poorer survival rates in all clinical cohorts ($p < 0.0001$). In line, higher expression levels are found in secondary AML ($p=0.015$) and R/R compared to de novo AML ($p=0.04$). Notably, the predictive role of iASPP is independent of, and adds information to, the European LeukemiaNET (ELN) risk classification (fig 1). Functional analyses in iASPP-interference (KD) AML models (MOLM14 / HL60) reveal reduced proliferation rates ($p=0.028$ / $p=0.001$) and sensitization of cells to cytotoxic therapy (e.g. apoptosis after daunorubicin 5nM/48h: 40% in EV vs. 65% in MOLM14 KD cells). Consequently, xenograft mouse experiments confirm a significant delay in leukemia onset in iASPPi strains ($p < 0.001$).

Conclusions: Together, we confirm a functional and predictive role of iASPP in AML. This is of specific importance, e.g. in favorable risk patients, to help to identify individuals at risk for early therapy failure that might benefit from early treatment intensification (HSCT)



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Idecabtagene vicleucel (ide-cel) shows similar efficacy and toxicity in patients with multiple myeloma aged 70 and older compared to younger patients: A multicenter cohort study

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Introduction: The introduction of B-cell maturation antigen (BCMA) directed chimeric antigen receptor T (CAR-T) cell therapies have revolutionized the treatment landscape of relapsed/refractory (r/r) multiple myeloma (MM). Yet, data on the efficacy and safety of these therapies in older patients (pts) remain limited.

Methods: We conducted a multicenter retrospective analysis including 136 r/r MM pts without CNS manifestation undergoing idecabtagene vicleucel between March 2022/May 2024 at 7 tertiary centers. Pts were grouped by age at CAR-T infusion (<70 vs. ≥70 years).

Results: We identified 91 pts aged <70 and 45 pts aged ≥70 years. The median age for both groups was 61 years (range: 36-69) and 72 years (range: 70-82) at CAR-T infusion, respectively. Both groups had similar proportions for ECOG score 0-2, R-ISS stage III at diagnosis, high-risk cytogenetics, median time from the first diagnosis to CAR-Ts, penta-refractory status, prior BCMA-directed therapy and prior autologous transplantation (p≥0.12 for all). Both groups had a median of 5 treatment lines (p=0.49). There were no significant differences in disease status at CAR-T infusion. Both groups had a median of one bridging therapy line (p=0.65). Extramedullary disease at CAR-T was more frequent in pts <70 years compared to those ≥70 years (37.6% vs. 14.0%, p=0.007). Cytokine-release syndrome (CRS) grade >2 occurred in 7.7% of the younger and 4.4% of the older group (p=0.71). For all grades of ICANS, there was a higher proportion in pts ≥70 years (24.4% vs. 6.6%, p=0.005), but no difference for ICANS grade >2 (0% vs. 2.2%, p=1.0).

Overall response rates (CR/VGPR/PR) were comparable for both age groups (87.8% vs. 92.7%; p=0.274). With a median follow-up of 8.1 months (mo), median progression-free survival (PFS) was 9.2 mo for the younger group and 9.6 mo for the older group (p=0.39), with 1-year PFS rates of 42.9% and 48.7%, respectively. Median overall survival (OS) was not reached; 1-year OS was 67.1% and 66.8% (p=0.95). No significant differences were noted in the cumulative incidence of 1-year non-relapse mortality (p=0.17) and cumulative relapse incidence (p=0.08) between both groups.

Conclusions: Our data provide additional support that CAR-T cell therapy is feasible and effective in pts with r/r MM aged 70 years or older, demonstrating outcomes comparable to those observed in younger pts.

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Reducing autophagy potentiates the restoration of MHC-I genes in Germinal B-cell Diffuse Large B-cell lymphomas

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Introduction: Diffuse Large B-cell Lymphoma (DLBCL) is an aggressive mature B-cell malignancy, characterised by significant clinical and biological heterogeneity. The two major DLBCL subtypes: germinal B-cell (GCB) and activated B-cell (ABC) lymphomas. Immune evasion is a major obstacle for DLBCL treatment. Major histocompatibility complex class I (MHC-I) is largely compromised in GCB tumours. Genetic aberrations in the antigen presentation machinery HLA and β2M genes contributes to MHC-I deficiency reducing the tumour immunogenicity. The exact mechanisms underlying the loss of MHC-I remains elusive. Macroautophagy (herein autophagy) is a major lysosome-dependent degrading pathway. Autophagy initiation activates the ULK1 complex. Deregulated autophagy rewires metabolism and confers resistance by regulating immune cells recruitment in the tumour microenvironment, decreasing the tumour immunosurveillance. In solid cancer, autophagy is reported to degrade MHC-I to promote immune evasion. We speculate that autophagy inhibition will restore surface MHC-I.

Methods: LS-MS/MS was conducted on several ABC and GCB lines to identify metabolic pathways and MHC expression. Primary DLBCL gene expression profiles was used to correlate autophagic genes with antigen presenting genes.

Results: Gene expression of the ULK1 complex was markedly increased in GCB gene expression profiles compared to VPS34. Positive correlation was determined between the ULK1 complex and pro-autophagy cargo receptors CALCOCO2, OPTN, NBR1 and TAX1BP1. Autophagy proteins were enriched in DLBCL subtypes. ABC lines significantly upregulated proteins relating to lipid and mitochondrial metabolism unlike GCB. GCB cells showed reduced expression of MHC-I molecules. Autophagic genes of ULK1 complex ATG13, cargo receptor NBR1 and autophagosome-lysosome scaffold WDR45 genes negatively correlated with HLA-A/B in GCB tumours. ULK1 complex genes ULK1, RB1CC1 and its substrate ATG14 negatively correlated with MHC-I transactivator NLRC5. Reduced tumour infiltrating lymphocytes is associated with downregulation of NLRC5 expression. This provides us with a rationale to target ULK1-mediated autophagy in GCB DLBCL.

Conclusions: Our data provides a rationale to target ULK1-mediated autophagy in GCB DLBCL. Autophagy inhibition potentiates the restoration of MHC-I surface levels and elevate tumour immunogenicity to enhance the antigen presentation to T-cells.

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The cost-effectiveness of Axicabtagene Ciloleucel versus standard of care as second-line therapy in patients with large B-cell lymphoma in Switzerland

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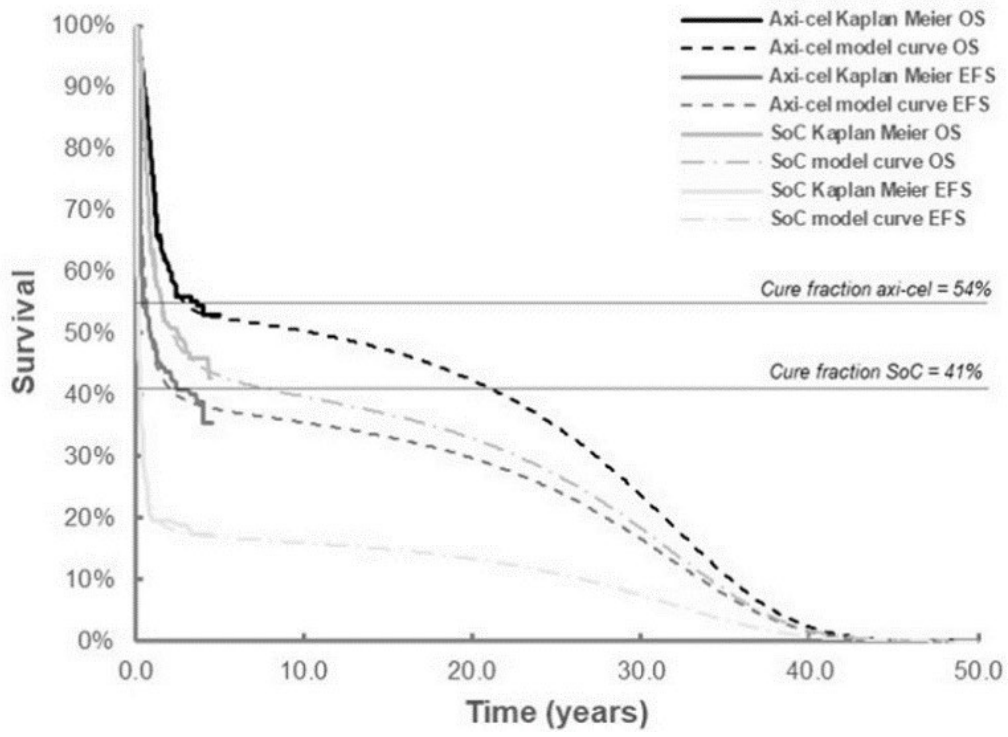
Introduction: Axicabtagene ciloleucel (axi-cel) demonstrated superior overall survival versus standard of care (SOC; salvage chemoimmunotherapy followed by high-dose chemotherapy with autologous stem-cell transplantation for responders) in the treatment of relapsed or refractory large B-cell lymphoma (2L LBCL) in adults in the ZUMA-7 trial (NCT03391466). This study aimed to estimate the cost-effectiveness of axi-cel versus SOC in 2L LBCL from the Swiss compulsory health insurance system perspective.

Methods: Using a 3-health state partitioned survival model, we estimated costs, life-years (LYs), and quality-adjusted life-years (QALYs) over a lifetime horizon of 50 years. The model was populated with efficacy and safety inputs based on patient level data from ZUMA-7. Event-free survival (EFS), time-to-next therapy (TTNT) and overall survival (OS, Primary OS dataset median follow-up 47.2 months) were extrapolated beyond the trial period using mixture cure models with Swiss population mortality (Figure 1). Health-state utility values were estimated from EuroQoL five-dimensions five-levels (EQ-5D-5L) collected in ZUMA-7 for the pre-event health states and from ZUMA-1 for the progression state. Medical resource use data and unit costs in Swiss Francs (CHF) were derived from the Swiss analysis & specialty lists (AL & SL), TARMED and Swiss DRG tariffs. Outcomes and costs were discounted at 3% annually. Deterministic and probabilistic sensitivity analyses were conducted to assess robustness of the results.

Results: 2L axi-cel treatment resulted in LY and QALY gains of 1.95 and 1.57, respectively, and incremental costs of CHF 71,084 compared to SOC, resulting in an incremental cost-effectiveness ratio (ICER) of CHF 45,228 per QALY. The results were driven by better long-term survival of patients and more time spent in the event-free state in the axi-cel arm, despite substantial utilization of CAR T in third line in the SOC arm. Model results were robust in sensitivity analyses. Key drivers included the CAR T therapy costs, the mean age at which patients enter the model and the utility post-progression.

Conclusions: Axi-cel treatment results in meaningful increases in LYs and QALYs compared to SOC in adult patients with 2L LBCL. Axi-cel is cost-effective vs SOC in 2L LBCL from a Swiss compulsory health insurance system perspective.

Figure 1: Survival in the economic model



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Utility of the 2024 best practice recommendations from the EBMT Cellular Therapy and Immunobiology Working Party for use of donor lymphocyte infusions after allogeneic haematopoietic stem cell transplantation

A.-C. Mamez[1], A. Pradier[2], S. Morin[1], F. Giannotti[1], S. Masouridi-Levrat[1], C. Bernardi[1], Y. Chalandon[1], F. Simonetta[1]

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Introduction: Donor lymphocyte infusions (DLI) are a widely employed strategy to increase the graft-versus-tumor (GvT) effect but can increase non-relapse mortality (NRM) risk mainly secondary to the induction of graft-versus-host disease (GvHD).

In recent recommendations(Pagliuca et al, Lancet Haematol. 2024) , the EBMT CTIWP proposes the use of T cell doses adapted to the DLI indication (prophylactic, pre-emptive and therapeutic), the donor type and the time of infusion.

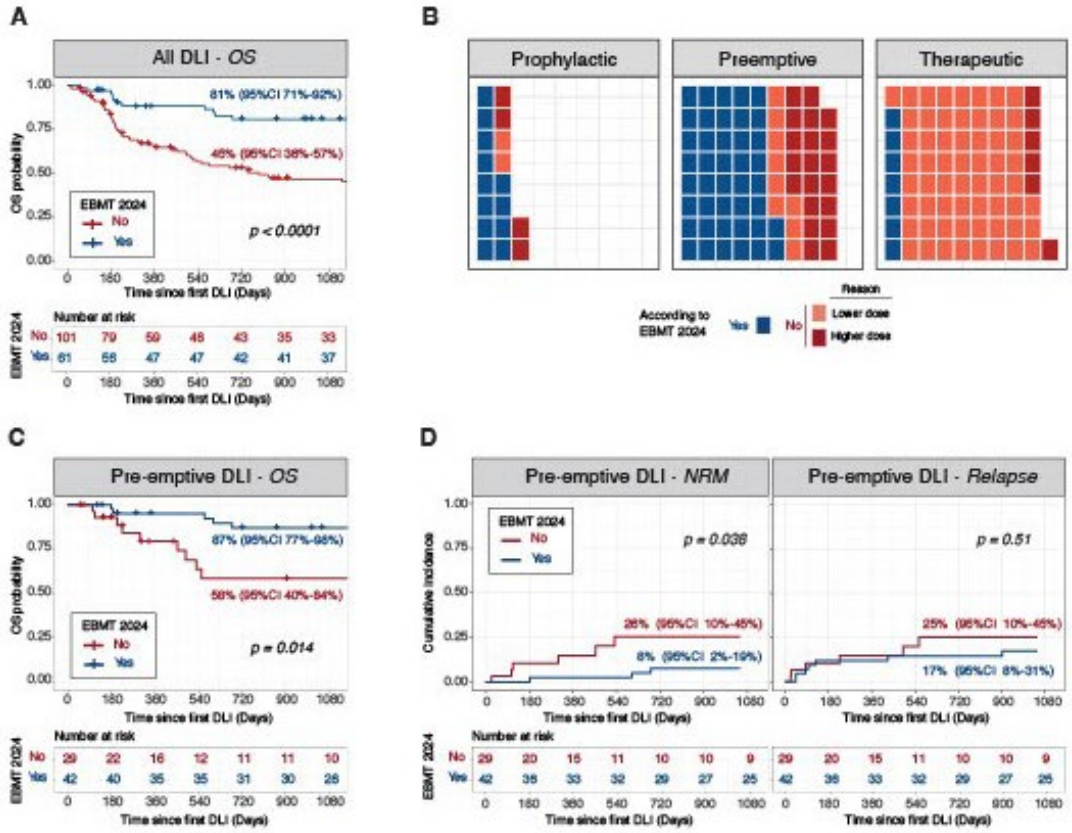
Methods: To evaluate the utility of these recommendations on real-world data, we retrospectively analysed a cohort of 162 patients receiving DLI after allogeneic HSCT at our centre between January 2010 and December 2023 and they outcomes considering if the first dose of DLI was administered in accordance or not with the EBMT 2024 recommendations.

Results: Median age at allogeneic HSCT was 51 years (range 15-74). First dose of DLI was infused in a median time of 214 days (range 60-3753 days) after allogeneic HSCT. No patient received immunosuppressive drugs at time of DLI. Thirty-seven percent of patients had a history of GvHD (acute GvHD, n=60 and/or chronic GvHD, n=8). Median number of DLI infusions was 2 (range 1-7).

We observed a significantly improved overall survival (OS) of patients receiving DLI according to the EBMT recommendations (81%, 95%CI 71%-92%) compared to patients receiving different doses (45%, 95%CI 36%-57%; p <0.0001).

In the subgroup receiving pre-emptive DLI, the 42 patients who received doses in accordance with the EBMT 2024 recommendations showed a significantly improved OS (p=0.014) and lower NRM (p=0.038), respectively 87%(95% CI 77%-98%) and 8%(95% CI 2%-19%), compared to patients receiving different doses (respectively 58% (95% CI 40%-84%); and 26% (95% CI 10%-45%)). Patients receiving pre-emptive DLI at doses higher than the ones recommended by EBMT displayed a higher cumulative incidence of grade 2-4 acute GvHD within 100 days since DLI infusion (35%, 95% CI 15.1%-55.8%) compared to patients receiving DLI doses according to EBMT recommendations (11.9%, 95%CI 4.3%-23.7%; p=0.023). We observed no difference in terms of relapse incidence between the two groups (p=0.51).

Conclusions: Despite several limitations, our data support the utility of the new EBMT 2024 recommendations on DLI administration after allogeneic HSCT .



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Comparative effectiveness of tyrosine kinase inhibitors (TKI) and blinatumomab versus TKI and chemotherapy in Philadelphia-positive acute B-lymphoblastic leukemia

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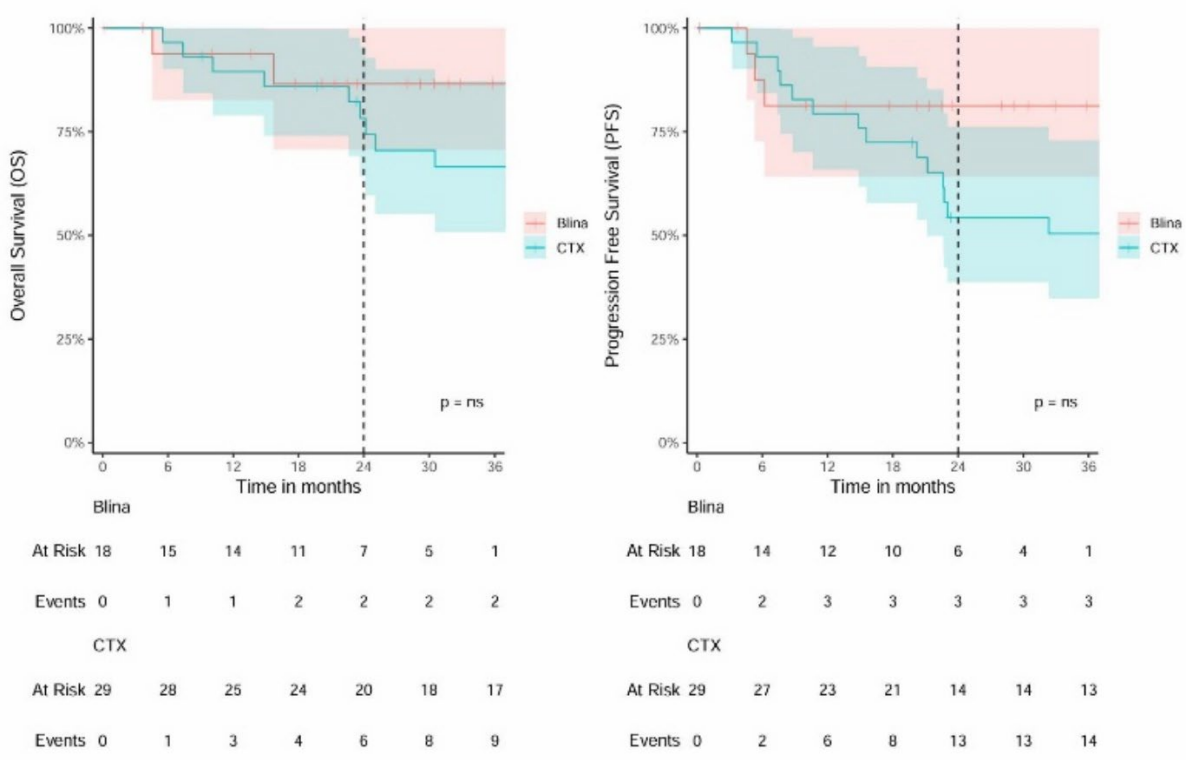
Introduction: The subsequent introduction of tyrosine kinase inhibitors (TKIs) and blinatumomab has improved outcomes in patients with Philadelphia chromosome-positive (Ph+) B-lymphoblastic leukemia (B-ALL). However, in the absence of a randomized controlled trial, it remains unclear whether the upfront treatment with TKI and blinatumomab alone is equally effective or possibly superior to standard chemotherapy and TKI protocols.

Methods: Here we report our single-center retrospective results of 18 patients with de novo (N=13) and relapsed (N=5) Ph+ B-ALL treated with TKI and blinatumomab compared to 29 patients with de novo Ph+ B-ALL treated with conventional chemotherapy and TKI.

Results: While the blinatumomab patients were significantly older (median age 65 years vs 48 years), more likely to have active central nervous system disease (27.7% vs 0%) and less likely to be consolidated with an allogeneic stem cell transplantation (33% vs 79%, p <0.05), overall survival, progression-free survival and non-relapse mortality were not statistically different between the groups (2-year OS 87% vs 78%, PFS 81% vs 54%, NRM 6.3% vs 14%). While treatment-related severe adverse events were significantly more frequent in patients treated with conventional chemotherapy and TKI, no significant difference was observed in the achievement of molecular complete response within the first 6 months of therapy.

Conclusions: With our results being comparable to those of published prospective trials, we conclude that the combination of TKIs and blinatumomab is safe and effective in the treatment of elderly patients with Ph+ B-ALL. Its role in the treatment of younger patients warrants further investigation.



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Early and long-lasting alteration of naive CD45RA(+) Foxp3(low) regulatory T-cell reconstitution after allogeneic hematopoietic stem cell transplantation

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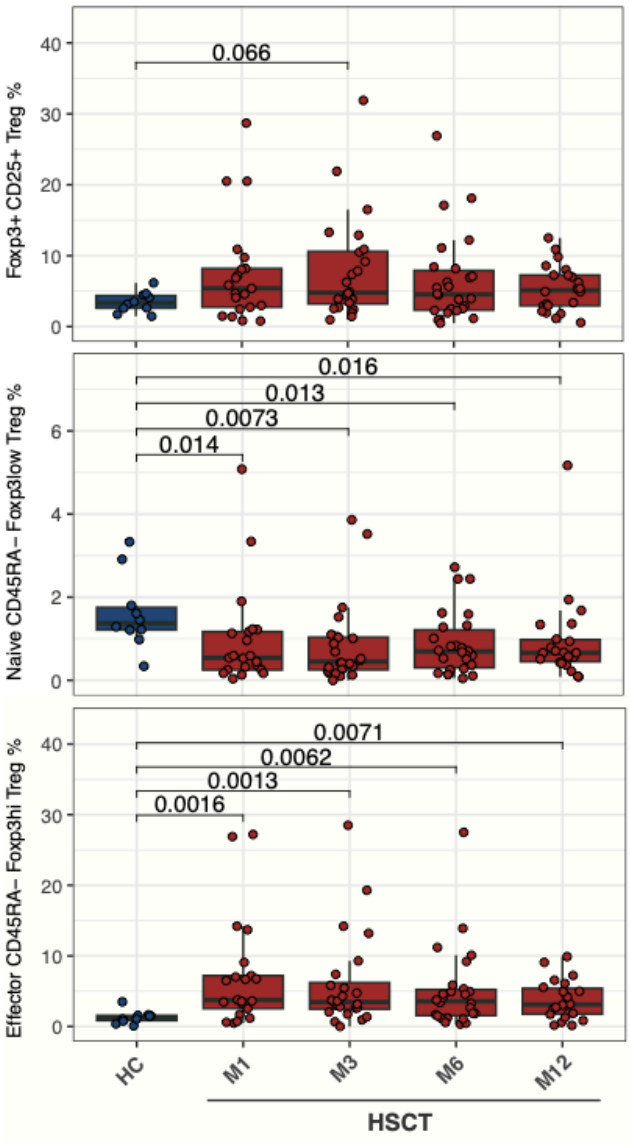
Introduction: CD4+CD25+Foxp3+ regulatory T cells (Tregs) play a crucial role in the generation and maintenance of immunological tolerance after allogeneic hematopoietic stem cell transplantation (HSCT). Extensive evidence suggests that impaired immune-reconstitution of Treg cells can lead to an increase risk of graft-versus-host-disease (GvHD). Despite the small proportion of Tregs among CD4 T cells, several Treg subsets can be further distinguished on the basis of makers defining their differentiation stage. In particular, a classical definition based on CD45RA and Foxp3 expression allows the identification of naïve and effector Treg subsets. The aim of this work was to assess immune-reconstitution of Treg subsets after allogeneic HSCT.

Methods: We obtained peripheral blood mononuclear cells at 1, 3, 6 and 12 months from 34 allogeneic HSCT recipients and 10 healthy controls (HC). Cells were analyzed by flow cytometry and percentages of total (CD25+ Foxp3+), naive (CD45RA+Foxp3(low)), and effector (CD45RA(-)Foxp3(high)) Tregs among CD4 T cells were quantified.

Results: We observed that total Treg percentages were similar in HC and in allogeneic HSCT recipients at all time point studied (Figure 1, upper panel). Conversely, when Treg heterogeneity was taken into account, we noticed a significant reduction in percentages of naive CD45RA+Foxp3(low) Tregs in allogeneic HSCT recipients at 1 (p= 0.014), 3 (p=0.0073), 6 (p=0.013) and 12 (p=0.016) months post transplant compared to HC (Figure 1, middle panel). This was mirrored by a relative increase in the proportion of effector CD45RA(-)Foxp3(high) Tregs at the same time points (Figure 1, lower panel). Analyzing the relationship between Treg subsets and clinical characteristics, we did not detect any impact of donor type (SIB, MUD, Haploidentical), conditioning regimen (MAC, RIC), or stem cell source (PBSC, BM), on percentages of total, naïve or effector Tregs.

Conclusions: Our analysis provides a detailed characterization of the immune-reconstitution of Treg subsets after allogeneic HSCT and reveals an early and long lasting impairment in naïve Treg reconstitution. We are now extending the patient cohort to have sufficient statistical power to assess the potential relationship between reconstitution of Treg subsets and post-transplant complications, namely acute and chronic GvHD.



333

Are there non-hematological causes of hyperleukocytosis? Hyperleucocytosis cases in a tertiary university hospital over 10 years

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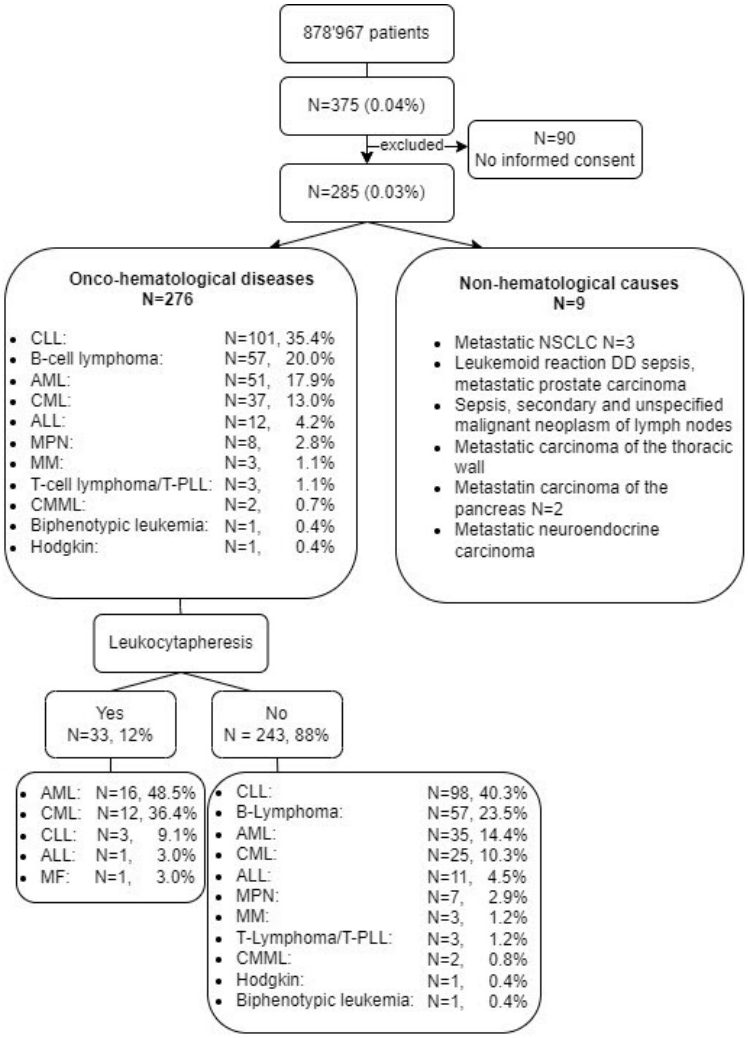
Introduction: Hyperleukocytosis (HL) is defined by an increase in leukocytes >100×10^9 /L. Symptomatic HL is often associated with increased morbidity and mortality and is considered a medical emergency. In this study, we aimed to assess the causes of HL, the use of leukocytapheresis (LCAP) and associated outcomes.

Methods: We searched the hospital database for adult patients with HL between 2013-2023. Patients with at least one episode of HL and written agreement to general consent were further evaluated. We collected data for age, sex, leukocyte count, underlying cause of HL, use of LCAP and early mortality (death within 1 month since HL) and analyzed them descriptively. We assessed possible predictors for LCAP by means of logistic regression models. Calculated odds ratio (OR) were adjusted for sex, age and maximal leucocytes.

Results: We retrospectively analyzed 878'967 adult patients and identified 375 (0.04%) with HL. Of those, 285 did not object to general consent and comprised the population evaluated. 276/285 (97%) patients had an underlying onco-hematological disease with frequencies as indicated in Figure 1, median age 66.8 years (range 18.4-93.6), 32% female. 9 HL patients had a non-hematological underlying cause, median age 61.7 years (range 53-81), 22% female, (figure 1): 7/9 paraneoplastic (N=4 lung, N=2 pancreas , N=1 neuroendocrine tumor); 2/9 sepsis. The median leucocyte count observed in the last group was 103.3×10^9/L (range 100-161). The median leucocyte count observed in the onco-hematological group was 161×10^9/L (range 100-1210). LCAP was performed in 33/285 (11.6%) patients, and the main indication was respiratory symptoms in 21/33 (63.6%), followed by ophthalmological and neurological symptoms. No patient with a non-hematological cause underwent LCAP. Female sex was significantly associated with LCAP (adjOR 2.6, 95%CI 1.23-5.62) for the whole population and for AML (adjOR 4.25, 95%CI 1.04-17.3). Early mortality was similar in AML patients with HL treated with LCAP 7/16 (44%) versus no LCAP 15/35 (43%).

Conclusions: Even in a tertiary hospital the presence of HL is an unusual event. The causes, as expected, are mainly hematological, but non-hematological causes exist and should not be neglected, most were paraneoplastic. The management of HL is not well standardized. The relatively high number of LCAP observed may be biased by the availability of this method at our institution.



395

Older patients with non-Hodgkin Lymphoma receive as much treatment lines as younger ones through adjustment, in a real life setting

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Introduction: As patients are living longer, the aging phenomenon is a major challenge in the management of cancer. This is particularly true for patients with non-Hodgkin lymphoma (NHL), where the median age at diagnosis is around 70 years. In our study, we aim to investigate outcomes of older patients treated for NHL in a real-world setting.

Methods: 172 patients with NHL treated between 2016 and 2021 at the Fribourg Oncology Department at HFR Hospital have been included in this analysis. Clinical data collected included: gender, age, comorbidities (standardized using the Cumulative Illness Rating Scale for Geriatrics, CIRS-G score), tumor histology and stage, treatment types (including number of lines and treatment intensity) as well as outcomes, including response to treatment, toxicities as Grade >2 according to CTCAE V5.0 and survival. Clinical data were analyzed using generalized linear models and Kruskal Wallis test.

Results: From the entire cohort of patients, 70 patients were younger than 70 years (Group 1) and 102 were 70 years or older (Group 2). The most common NHL subtype was diffuse large B cell lymphoma (35%). A statistical difference of the CIRS-G score between the two groups was observed, with higher CIRS-G scores in patients older than 70 years (p value <0.05). A decrease in absolute number of toxicities with increasing age was detected (p value 0.01), with a stable number of toxicity events per treatment lines. Even if the number of treatment lines received was equal between the two groups, treatments were less intensive in group 2 (p value 0.007). While age did not affect the number of treatment lines, an increasing CIRS-G score lead to a reduced number of treatment lines and intensity (p value 0.001 and 0.0002 respectively).

Conclusions: This analysis shows that the favorable toxicity profile in older patients treated for NHL is possible through adaptation of treatment intensity. Such adaptation allows multiple treatment lines independently of age but based on CIRS-G score. Response to treatment and survival will be presented at the conference.

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10-year retrospective study on 5-azacitidine, 5-day 100mg/m2 schedule, as monotherapy for MDS and MDS/MPN (AZA-CHUV study)

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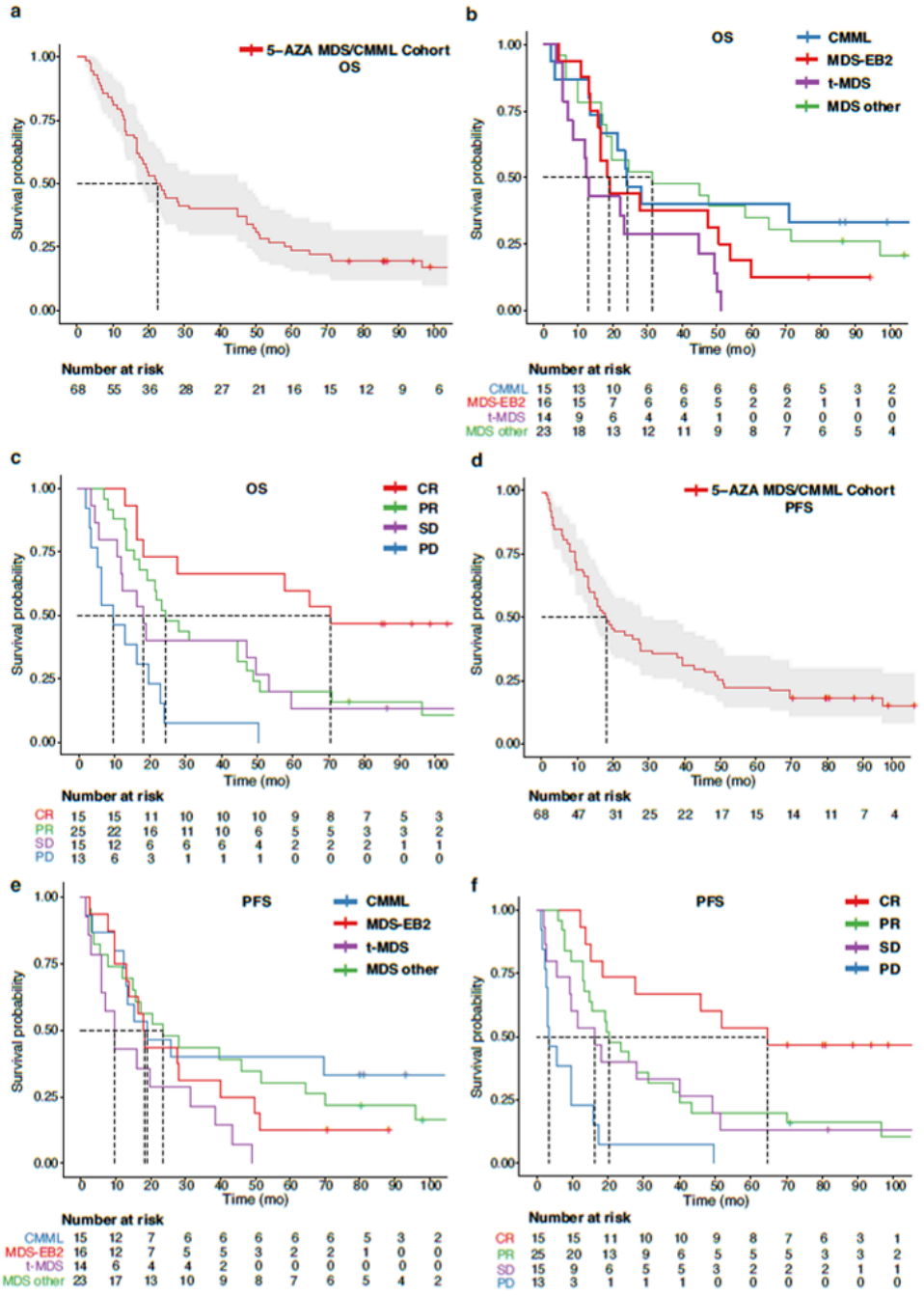
Introduction: Azacitidine (AZA), a hypomethylating agent used for the treatment of myelodysplastic neoplasms (MDS) and sometimes myelodysplastic/myeloproliferative (MDS/MPN) neoplasms. Validated dosage is 75 mg/m2, subcutaneously over 7 days every 28 days. Other schedules have been tested, but none showed superiority. We conducted a retrospective analysis of an alternative AZA dosing of 100 mg/m2 administered over 5 consecutive days every 28 days in patients with high-risk MDS and MDS/MPN. Primary endpoint was efficacy and secondary endpoints were median overall survival (OS), progression-free survival (PFS), and toxicities.

Methods: Patients who received AZA monotherapy as a first or subsequent line of treatment for MDS or MDS/MPN between 2008 and 2018, were screened. Statistics were performed with R (v 4.2.0; CRAN project). The package 'survival' for analysis and the package 'survminer' for the drawing of survival curves was used. Kaplan–Meier estimator to report the survival probability and a Cox regression to calculate hazard ratios (HR) was used. Median follow-up was calculated using the reverse Kaplan–Meier method. A Log-rank statistical test was applied to assess significance when comparing KM estimates. Univariate Cox regression analysis was performed to assess the predictive value of best response on OS. A Wald statistical test was applied to assess significance.

Results: Among 68 patients, 51 had MDS and 17 from MDS/MPN. Five patients were re-exposed to AZA after allogeneic stem cell transplantation (HSCT), accounting for 74 responses. AZA as first-line was used in 50 patients. Sixteen patients presented complete responses (CR) (16/74, 22%) and 30 partial responses (PR) (30/74, 41%). Best response was significantly linked to OS, with patients without CR presenting an HR of 2.86 (95%CI: [1.21–6.76]), 3.36(95%CI: [1.33–8.5]), and 8.31(95%CI: [3.2–21.7]) for PR, stable disease, and progressive disease, respectively. Median OS was 22.5 months and PFS 18.2 months. HSCT was significantly associated with better OS and PFS. Grade 3/4 hematotoxicity, mostly neutropenias, was present in 41% of patients.

Conclusions: Five-day 100 mg/m2 AZA schedule seems to be as efficacious as the standard schedule. CR and PR rates as well as OS were similar to historic AZA-001 results. It is more suitable for ambulatory settings, avoiding weekends, and enhances quality of life by reducing the number of treatment days.

Figure 1



Legend. a. Kaplan-Meier curve showing the overall survival (OS) of the 68 patients treated with 5-AZA from 2007 to 2018 in our clinic. The mOS of the entire cohort was 22.5 months (95% CI: 17.2-47.3). b. OS comparison between the groups diagnosed with CMML, MDS-EB2, t-MDS, and remaining MDS categories (i.e. MDS other) according to 2016 WHO classification. The mOS of CMML, MDS-EB2, t-MDS, and MDS other was 24.0 (95% CI: 16.6-NA), 18.8 (95% CI: 15.8-59.7), 12.8 (95% CI: 8.4-49.7) and 31.2 months (95% CI: 18.1-96.5), respectively. c. OS comparison between the patient groups who achieved either a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) under 5-AZA treatment according to IWG 2006 MDS response criteria. The mOS of CR, PR, SD, and PD other was 70.6 (95% CI: 27.7-NA), 24.4 (95% CI: 19.5-49.0), 18.1 (95% CI: 12.1-59.7) and 9.9 months (95% CI: 5.4-NA), respectively. d. Kaplan-Meier curve showing the progression-free survival (PFS) of the 68 patients treated with 5-AZA from 2007 to 2018 in our clinic. The mPFS of the entire cohort was 18.2 months (95% CI: 13.7-31.5). e. Progression-free survival (PFS) comparison between the groups diagnosed with CMML, MDS-EB2, t-MDS, and remaining MDS categories (i.e. MDS other) according to 2016 WHO classification. The mPFS of CMML, MDS-EB2, t-MDS, and MDS other was 19.1 (95% CI: 13.0-NA), 18.3 (95% CI: 13.0-51.4), 9.6 (95% CI: 5.9-43.4) and 23.6 months (95% CI: 15.0-70.2), respectively. f. PFS comparison between the patient groups who achieved either a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) under 5-AZA treatment according to IWG 2006 MDS response criteria. The mPFS of CR, PR, SD, and PD other was 64.7 (95% CI: 27.7-NA), 20.5 (95% CI: 15.0-40.0), 16.4 (95% CI: 9.5-51.4) and 3.5 months (95% CI: 2.7-NA), respectively.

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Prognostic value of the new AML60+ score for elderly patients with acute myeloid leukemia (AML) treated with hypomethylating agents

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Introduction: The AML60+ score combines clinical and genetic parameters (age, sex and leukocyte count; monosomal karyotype, TP53-, DNMT3A-, ASXL1-, RUNX1- and FLT3-ITD-mutations) and has recently been proposed for risk assessment in intensively treated elderly patients (pts) with AML or high-risk Myelodysplastic Syndrome (MDS) (doi: 10.1200/JCO.23.02631). Its prognostic significance in elderly pts treated with hypomethylating agents (HMAs) is currently unknown. We therefore aimed to evaluate the prognostic impact of the AML60+ score in this frequent population in comparison to the ELN2022 classification.

Methods: We performed a retrospective chart review of pts diagnosed with AML or MDS/AML between 2017 and 2023. Pts were evaluable, if they had received an HMA-based therapy for at least one cycle. The AML60+ was calculated as suggested (https://hovon-aml.shinyapps.io/AML60_score/).

Results: 53 pts were evaluable (female n=23; median age 77 years, range 61-91; AML/MDS n=7, AML n=46). 29 pts received an HMA and Venetoclax, 5 pts an HMA and Ibrutinib and 19 pts an HMA alone. During follow-up (median 6 months [mo], range 0-44) 45 pts (85%) died.

According to the AML60+ score, 14/53 (26%) pts were assigned to the intermediate (int)-risk group, 22/53 (42%) to the poor- and 17/53 (32%) to the very-poor-risk group. No pts were allocated to the favorable risk group due to the low number of pts <65 years of age (n=2). Stratification of pts classified according to ELN2022 by the AML60+ was as follows:

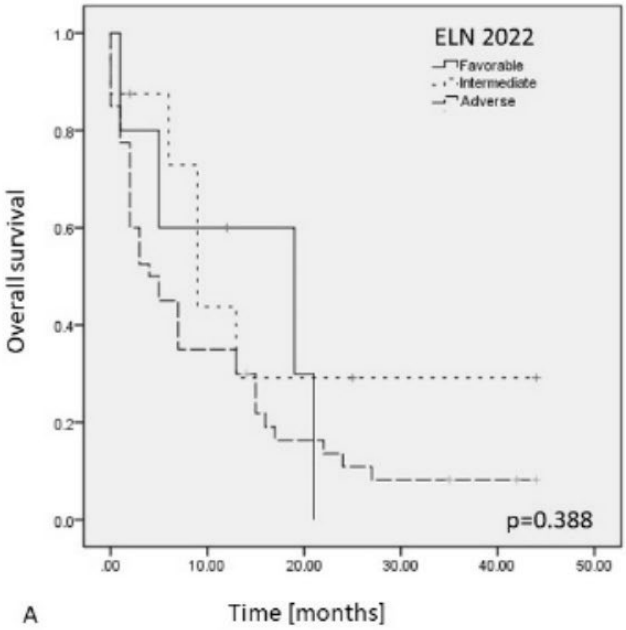
ELN favorable (n= 5): AML60+ int: n=4, poor n=1;

ELN int (n=8): AML60+ int n=4, poor n=3, very poor n=1;

ELN adverse (n=40): AML60+: int n=6, poor n=18 and very poor n=16.

No significant overall survival (OS) differences were noted between the ELN2022 risk groups (Figure 1A), whereas int-risk pts according to AML60+ had a significantly longer median OS (16 mo [95% CI 9-23]) compared to pts with poor- or very poor-risk (5 mo [95% CI 2-8] and 2 mo [95% CI 1-7], respectively), p=0.004 (Figure 1B).

Conclusions: According to this retrospective analysis of a small cohort, the AML60+ score may be a useful prognostic tool for elderly AML patients treated with HMAs. In particular, it may help to identify a group with a relatively favourable prognosis that is not clearly identified by the ELN 2022 risk classification. However, analyses of larger cohorts are needed to provide more evidence for this obervation.



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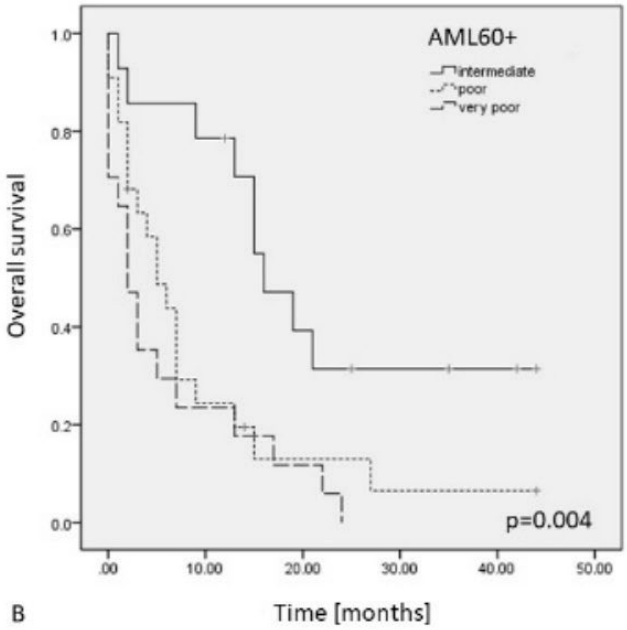

B

SSMO POSTER PRESENTATION – CLINICAL SOLID TUMOR ONCOLOGY

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Olaparib not cost-effective as maintenance therapy for platinum-sensitive, BRCA1/2 germline-mutated metastatic pancreatic cancer

T. Mehra[1], J. Lupatsch[2], T. Kössler[3], K. Dedes[4], A. Siebenhüner[5], R. von Moos[6], A. Wicki[1], M. Schwenkglenks[7]

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Introduction: To assess the cost-effectiveness and budget impact of olaparib as a maintenance therapy in platinum-responsive, metastatic pancreatic cancer patients harboring a germline BRCA1/2 mutation, using the Swiss context as a model.

Methods: Based on data from the POLO trial, published literature and local cost data, we developed a partitioned survival model of olaparib maintenance including full costs for BRCA1/2 germline testing compared to FOLFIRI maintenance chemotherapy and watch-and-wait. We calculated the incremental cost-effectiveness ratio (ICER) for the base case and several scenario analyses and estimated 5-year budget impact.

Results: Comparing olaparib with watch-and wait and maintenance chemotherapy resulted in incremental cost-effectiveness ratios of CHF 2,711,716 and CHF 2,217,083 per QALY gained, respectively. The 5-year costs for the olaparib strategy in Switzerland would be CHF 22.4 million, of which CHF 11.4 million would be accounted for by germline BRCA1/2 screening of the potentially eligible population. This would amount to a budget impact of CHF 15.4 million (USD 16.9 million) versus watch-and-wait.

Conclusions: Olaparib is not a cost-effective maintenance treatment option. Companion diagnostics are an equally important cost driver as the drug itself.

Table 1 Results from cost-effectivess analysis

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER[3]	ICER without BRCA cohort testing
Base Case						
Observation	110,445	141,212	1.43	0.05	2,711,716	814,167
Maintenance	136,252	115,405	1.43	0.05	2,217,083	318,732
Olaparib	251,657		1.48			
Scenarios						
1 Olaparib - 25%	231,330	120,884	1.48	0.05	2,322,345	432,815
2 Olaparib OS curve	279,133	168,688	1.79	0.36	468,605	195,491
3 Different PD QALY[1]						
Observation	110,445		1.22			
Olaparib	251,657	141,212	1.37	0.15	943,604	283,188
4 Different PD QALY[1] + Olap OS curve						
Olaparib	279,133	168,688	1.61	0.39	429,973	195,492
5 Disutility for Adverse Events[2]						
Observation	110,445		1.08			
Olaparib	251,657	141,212	1.16	0.07	1,916,845	575,514
6 BRCA test USD 200 (180 CHF)						
Olaparib	153,043	42,598	1.48	0.05	818,007	

gBRCA1/2: germline BRCA1 and BRCA2. All costs in CHF.

[1] Progressive disease utility: 0.58 [15], instead of 0.73 [29]
[2] Disutility of – 0.2
[3] Considering g*BRCA1/2* testing costs of all eligible patients
The olaparib maintenance strategy included costs for *gBRCA1/2* testing of all pancreatic cancer patients evaluated for eligibility.

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Integrating AI into Swiss Primary Care to strength Medical Excellence

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Introduction: Artificial intelligence (AI) chatbots for primary care have yet to gain traction in Switzerland despite high-performing large language models (LLM) being preferred for accessing and retrieving complex information. "In a Nutshell ", an online educational program for physicians, organises clinical information in a NUTE manner (near-real time, understandable, time-saving, and efficient) using "Ask Dr. Nuts", a purpose-built chatbot for retrieving curated medical information. This tool can be a co-pilot for navigating medical literature in daily care practice. We assessed the UTuCo (Utility, Trustworthiness and Correctness) of the chatbot´s information and its acceptance by physicians.

Methods: The chatbot was trained using Azure´s pre-processed model. Medical literature was stored in segmented units, converted into semantic embeddings, and used to generate the responses. We analysed 1015 interactions for the date and time of interaction, the message type (user or chatbot), the document context, and response correctness. A survey captured user experiences and expert confidence in the answers—the first analysed "Therapy" and "Diagnosis" classes with a battery of non-case-sensitive strings. The experts evaluated high-rated responses across five medical fields.

Results: Physicians use chatbots during practice hours (Fig1 a) to support diagnosing and treating (b) the most common diseases aligned with general practitioners' roles (c). Users rated the "In a Nutshell" answers (d, e, f) trustworthy and recommendable: 78.6% trusted the answers (g), 57.1 % would consult the chatbot again (h), and 53.6% would recommend it to colleagues (i). Medical experts confirmed the chatbot´s accuracy (71%) (j), completeness (46%) (k), and applicability (81%) (l).

Conclusions: The potential of medical AI chatbots in primary care highlights challenges that must be addressed before broader implementation. Responses require greater transparency, traceability, accuracy, and rate. The chatbot must provide reliable information in all official Swiss languages. Establishing agreements on training data, evaluation criteria, accuracy, and risk factors is crucial for quality assurance. Ensuring high medical content standards, comprehensively training AI, and benchmarking against other AI healthcare tools are necessary for improving patient care.

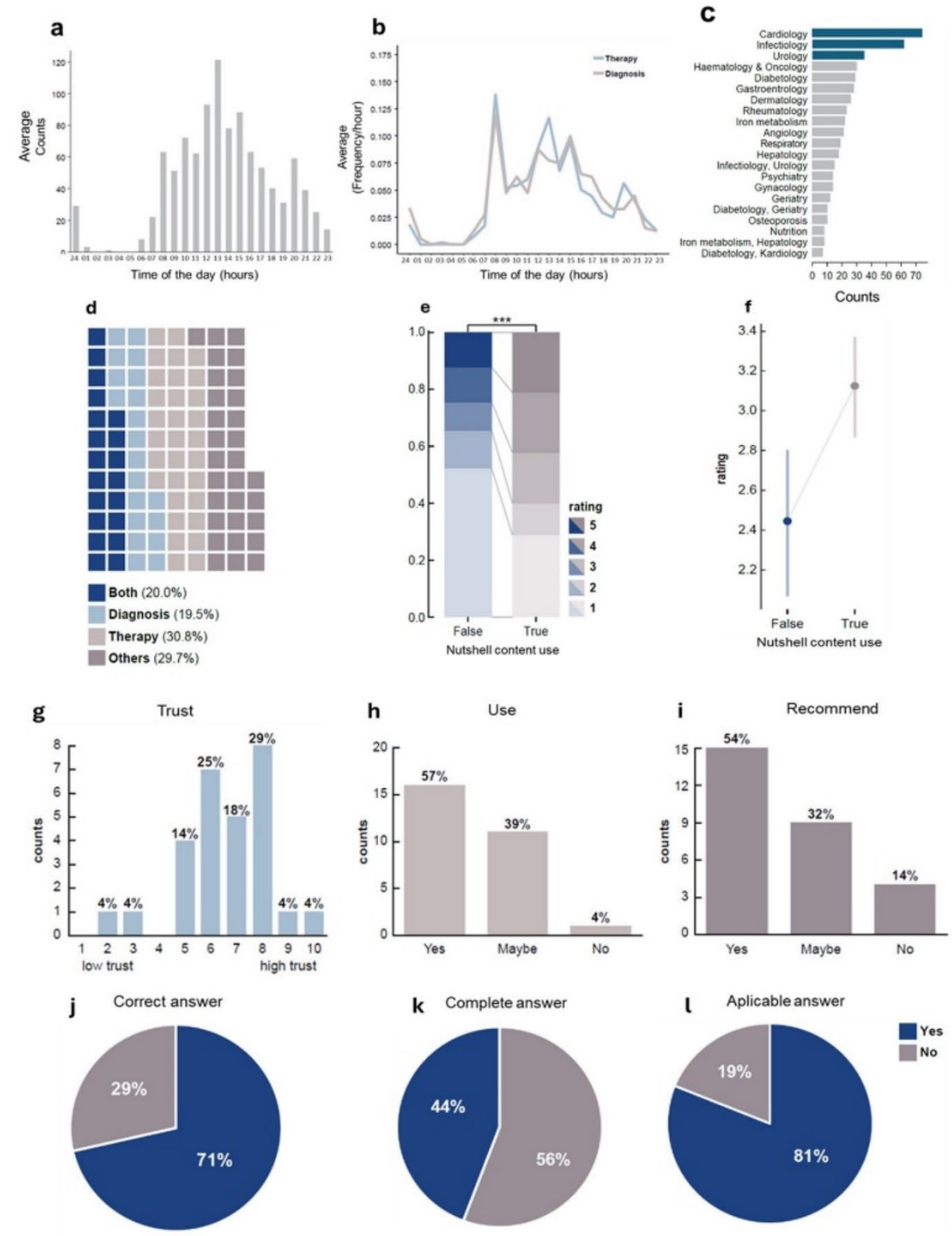

Figure 1. Histograms (a) and (b) show user-chatbot interactions over a day filtered by "Therapy" and "Diagnosis" classes, and bar chart (c) shows the medical topics accessed. (d) The waffle chart highlights the fraction of user-chatbot interactions by class. (e) The studded bar chart evidences the significant differences ($p < 0.001$ Chi-square test) in responses rated (rating from 1 to 5) using or not chatbot content. (f) "In a Nutshell" content use rates the answers—survey results. Bar graphs contain the counts per category and the fractional equivalent in percentages above each bar for chatbot (g) trust, (h) re-use, and (i) recommendation to a colleague. The pie chart graphs present the percentage of (j) correct, (k) complete and (l) applicable chatbot answers to daily medical practice.

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Co-alterations impacting first-line treatment in PD-L1 high KRAS G12C mutated lung adenocarcinoma in Real World Data within the Precision-Oncology-Program

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Introduction: Advanced PD-L1 high KRAS G12C mutated lung adenocarcinoma (LUAD) are currently treated with chemo-immunotherapy (C-ICI) or immunotherapy (ICI) in the first treatment line (1L), without genomic biomarkers to support treatment choice. Co-occurring alterations in STK11 and KEAP1 are known to affect treatment response in LUAD (Ricciuti et al., 2022); CDKN2A/B alterations were reported to impact the effectiveness of ICI in solid tumors (Adib et al., 2021, Balli et al., 2017, Liu et al., 2022). Here, we present insights from the Precision Oncology Program (POP) on the impact of STK11, KEAP1 and CDKN2A/B on the mean duration of treatment (DOT) of 1L C-ICI or ICI in PD-L1 high LUAD depending on KRAS G12C status based on patient-matched Real World Data (RWD) obtained from a large-scale clinicogenomic database.

Methods: This study matched individual patients treated at the University Hospital Zurich (USZ) to the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine advanced NSCLC CGDB (FH-FMI CGDB) based on disease characteristics patients (stage, oncogenic mutations, PD-L1). The de-identified FH-FMI data originated from approximately 280 US cancer clinics (~800 sites of care). Using the POP framework to extract a FH-FMI RWD matched cohort, we assessed DOT in 1L for LUAD with PD-L1 ≥ 50% and with or without KRAS G12C. This assessment included a comparison of cases with and without co-alterations in STK11, KEAP1, or CDKN2A/B, using a t-test for analysis.

Results: In FH-FMI CGDB, we found 468 KRAS G12C mutant (m) LUAD, 183 of which were PD-L1 high. In KRAS G12C wildtype (wt) and KRAS G12C m LUAD without co-alterations DOT on ICI and C-ICI is comparable. In KRAS G12C wt LUAD, CDKN2A/B and KEAP1 alterations are associated with a significantly shorter DOT on ICI while in KRAS G12C m LUAD co-alterations in CDKN2A/B, STK11 and KEAP1 were associated with a shorter DOT on C-ICI. (Table 1.)

Conclusions: In this large PD-L1 high LUAD RWD cohort, we identified CDKN2A/B and KEAP1 status with or without KRAS G12C as biomarkers associated with altered DOT in 1L ICI or C-ICI. These molecular insights suggest a need for escalation / de-escalation of the treatment choice for PD-L1 high LUAD based on the molecular tumor profile.

PD-L1 ≥ 50%	C-ICI DOT	ICI DOT	p-value	n C-ICI	n ICI
No oncogenic driver*	13.5	14.7	0.5	116	208
• CDKN2A/B	20.1	8.8	0.02	28	42
• STK11	10.4	8.9	0.62	28	32
• KEAP1	15.3	6.7	0.04	21	44
KRAS G12C	15.5	17.2	0.57	55	81
• CDKN2A/B	9.5	16.8	0.24	9	18
• STK11	4.7	11.1	0.13	9	6
• KEAP1	3.1	6.6	0.35	5	8

Table 1.: **DOT of C-ICI, ICI in stage IV CGDB LUAD with PD-L1 ≥ 50% depending on co-alterations.**
C-ICI, carboplatin, pemetrexed, pembrolizumab. ICI, pembrolizumab.
*No oncogenic driver was defined as lack of the following molecular alterations: EGFR exon 19 deletion, EGFR L858R, EGFR T790M, EGFR exon 20 insertion, ALK fusion, ROS1 fusion, RET rearrangement, MET exon 14 skipping, MET amplification, KRAS G12C, BRAF V600E, HER2 alteration.

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KEAP1/STK1/KRAS co-Alterations promote central nervous system (CNS) metastasis in Lung Adenocarcinoma and are associated with primary therapy resistance

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Introduction: S T K 1 1 / K E A P 1 / K R A S co-alterations are associated with an immunological cold and biologically aggressive lung adenocarcinoma (LUAD) subtype. There is limited data on the impact of these hard-to-treat alterations on the incidence of central nervous system (CNS) metastases.

Methods: Between November 1st, 2021, and October 1st, 2023, patients with LUAD carrying mutations in any of the genes K E A P 1 , S T K 1 1 , or K R A S , detected by FoundationOneCDx, were enrolled in the study. Multiple clinical endpoints, including overall survival (OS), duration of response to different treatment lines (DOR), and real-world progression-free survival (rwPFS) according to the treatment lines, were retrospectively assessed.

Results: A total of 104 patients with LUAD and mutations in any of the genes K E A P 1 , S T K 1 1 , or K R A S were analyzed. 32 (31%) patients (pts.) showed measurable CNS metastases at initial diagnosis, 19 (59%) of whom were males with a median age of 67 years. Further subgroups were classified based on their genomic co-alteration profile: 14 (44%) pts. with S T K 1 1 / K R A S mutations, 7 (22%) pts. With K E A P 1 / L O H , 6 (19%) pts. with K E A P 1 / K R A S and 5 (15%) pts. with S T K 1 1 / K E A P 1 / K R A S mutations. In the S T K 1 1 / K E A P 1 / K R A S mutated subgroup, median real-world progression-free survival 1 (rwPFS1) to the first treatment line was the shortest with 1 month (ms), followed by the K E A P 1 / L O H subgroup of 1.5 ms. The median OS was 7 ms in the S T K 1 1 / K E A P 1 / K R A S subgroup. Additionally, rwPFS for further treatment lines were analyzed according to PD-L1 and TMB status, number of CNS metastases as well as further treatment lines.

Conclusions: The incidence of CNS metastases at initial diagnosis of patients carrying concurrent mutations of interest was much higher than previously described for non-oncogenic NSCLC emphasizing an aggressive phenotype. Our findings based on real-world data indicate that S T K 1 1 / K E A P 1 / K R A S mutations are hard-to-treat alterations that coincide with primary CNS metastases, especially in the S T K 1 1 / K E A P 1 / K R A S-mutated or K E A P 1 /LOH-mutated subgroups. The short rwPFS1 associated with primary therapy resistance underline the unmet need for new therapeutic strategies.

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AI Driven Application in Digital Pathology for Breast Cancer Risk Prediction: A Swiss Retrospective Cohort Study

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Introduction: The integration of artificial intelligence (AI) in digital pathology holds great promise for improving breast cancer recurrence risk prediction and treatment decisions. This study assesses the Ataraxis AI model, which previously demonstrated superior accuracy in a cohort of 377 breast cancer patients from NYU Langone Health, achieving a C-index of 0.79 compared to Oncotype DX's 0.63. The current project evaluates the Ataraxis model's predictive performance against Oncotype DX and real-world clinical data in HR+/HER2- breast cancer patients treated at Basel University Hospital and Cantonal Hospital from 2010 to 2021.

Methods: A retrospective cohort of 326 BC patients was analyzed, with 317 patients having pathology slides available for digital analysis. The slides were digitized and processed using Ataraxis' AI-based algorithm to predict recurrence risk and guide adjuvant therapy decisions. The AI model's predictions, incorporating clinical data, will be compared to recurrence risk categories from Oncotype DX scores, with both models being evaluated against real-world clinical data.

Results: The cohort consists of 317 evaluable patients, with a median age of 58 years. Of the total cohort, 66.25% (210 patients) are postmenopausal. The median tumor size was 20 mm, with 39.43% (125 patients) presenting with node-positive disease. Most patients has stage II disease (57.41%), followed by stage I (33.44%) and III (6.62%). Estrogen receptor (ER) expression had a median value of 1.0, and the median Ki-67 index was 20%. Oncotype DX scores are available for all patients, categorizing 68 (22%) of patients into low, 195 (62%) into intermediate, and 53 (17%) into high recurrence risk groups. At a median follow up of 62 months, there were 33 (10%) cases of relapse of which 13 (40%) distal relapse and 6 (2%) BC related deaths.

Conclusions: The analysis is currently ongoing, focusing on the concordance between AI-based digital pathology predictions, Oncotype DX scores and real world data. The final results will include hazard ratios (HR), concordance index (C-index), and recurrence outcomes, which will be submitted at a later date. This study seeks to demonstrate whether AI-based digital pathology can provide a scalable and cost-effective alternative for breast cancer risk stratification in real-world settings.

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Dynamic electronic reporting of treatment related symptoms (ePROs) can reversely identify the type of underlying cancer

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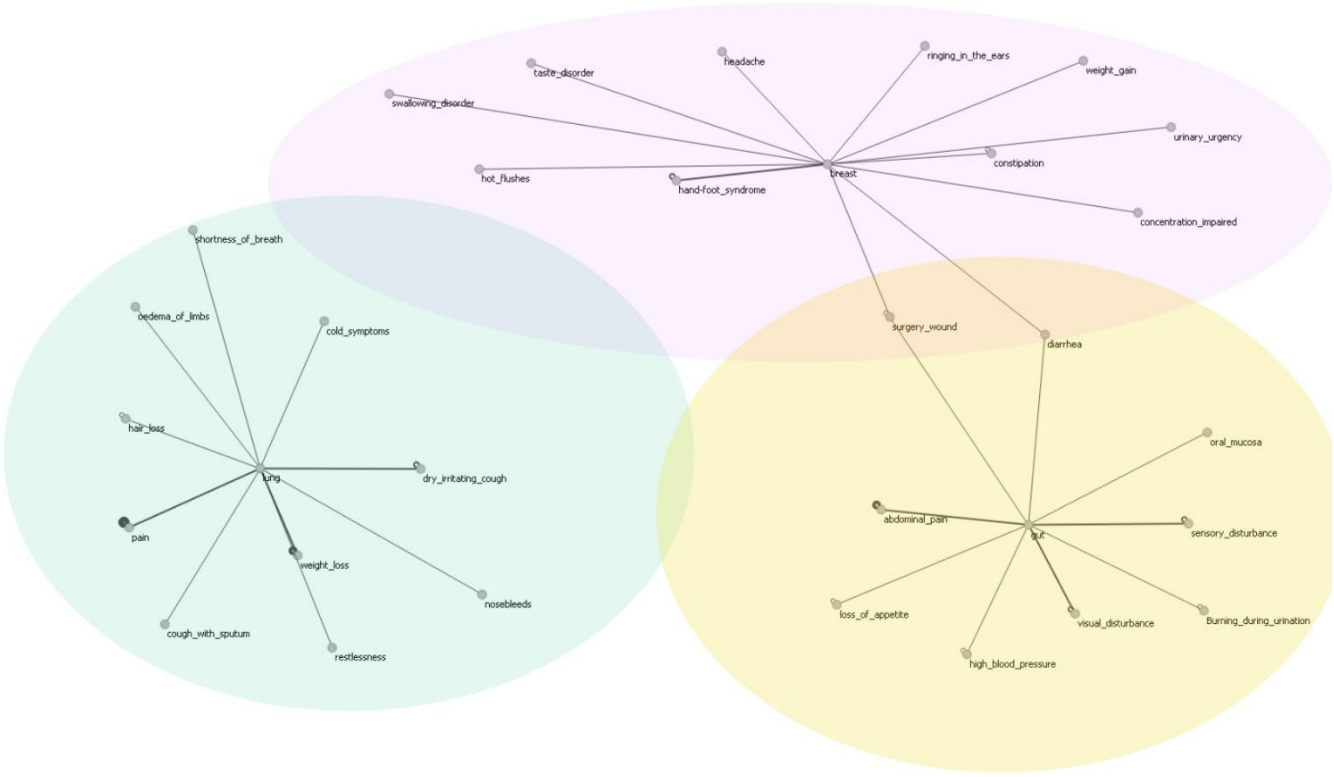
Introduction: Digital symptom reporting of patients undergoing systemic treatment demonstrated early detection of symptoms, reduction of unplanned admissions, and may support Machine learning (ML) to predict when patients will require emergency treatments. We examined whether dynamic reporting of treatment related symptoms and high quality ePROs can reversely identify the type of underlying cancer and treatment.

Methods: 226 patients on treatment had self-reported on presence and severity (according to CTCAE) of more than 90 available symptoms via a medical device App. For a balanced analysis we used data from 25 patients treated for breast cancer, 19 for cancer of lung, 16 for colon, 12 for lymphoma and 7 for prostate cancer, respectively. Patients` symptoms over the entire study period were aggregated by counting the days on which a particular symptom was reported. Thus, each patient was represented by a vector of symptoms indicating how often the given symptom occurred. A human-interpretable ML logistic regression model was applied to predict the primary tumor of the patient from his/her respective symptom vector. All

symptoms with positive coefficient above a certain threshold (0.1) were collected and then graphically displayed for association between symptoms and cancer type.

Results: The ML model was not able to recognize the prostate and blood-lymph patients in retrospect since their number was too small. Analysis for three remaining cancer types revealed a mean area under the curve (AUC) score of 0.72 (breast cancer AUC 0.74, CI: 0.62–0.85; gut cancer AUC 0.78, CI: 0.66–0.89; lung cancer AUC 0.63, CI: 0.50–0.77). Results indicate that ML performs "fair" and significantly better than random guessing (which would result in AUC = 0.5) for the reverse identification of the underlying cancer upon ePRO reporting from patients.

Conclusions: Cloud aggregation of patient reported symptoms and ML harbor the potential in identifying the type of cancer for which patients receive systemic treatment. Whether associations can be made from dynamic changes of reported symptoms, regarding the underlying cancer and adherence to oral medication shall be explored in prospective studies. Finally, ML and the anticipation of specific side effects might be a cost-effective tool in decentralized clinical trials and registries, enabling a more nuanced understanding of symptom associations with different cancer types.



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Interim results from the AVENUE study: real-world patient characteristics and safety with avelumab maintenance treatment for locally advanced/metastatic urothelial carcinoma

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Introduction: Avelumab first-line maintenance (1LM) is a standard of care for locally advanced or metastatic urothelial carcinoma (la/mUC) that has not progressed after 1L platinum-based chemotherapy (PBC). The AVENUE study is evaluating the effectiveness and safety of avelumab 1LM treatment in routine clinical practice in Germany, Spain, Switzerland, and Russia.

Methods: AVENUE is a prospective, noninterventional study in patients with la/mUC without disease progression after 1L PBC. Initiation of avelumab 1LM is decided by the treating physician prior to enrollment per local approval. The primary objective is to evaluate the overall survival rate. Updated baseline data and initial safety data are reported.

Results: By data cutoff (15 Sep 2023), 173 patients had received avelumab 1LM; 84 (48.6%) remained on treatment. Median age was 70 years (range, 43-89); 77.5% were male. ECOG PS was 0 in 36.4%, 1 in 52.0%, ≥2 in 5.2%, and not reported in 6.4%. 37.6% had visceral metastases. 1L PBC regimen was gemcitabine + cisplatin in 61.8% (split dose in 8.7%), gemcitabine + carboplatin in 35.3%, and other/switch in 3.5%. The number of PBC cycles was <4, 4-6, and >6 in 11.6%, 85.5%, and 2.9%, respectively. Median duration of avelumab 1LM was 16 weeks (IQR, 8-28). Treatment-related adverse events (AE) occurred in 54.3%, were serious in 14.5%, and led to discontinuation in 7.5%. Grade ≥3 immune-related AEs and infusion-related reactions occurred in 4.6% and 3.5%, respectively. 3 pts died following an AE classed as treatment related (2 had an unknown relationship to avelumab, per investigator).

Conclusions: Interim data from the AVENUE study show the acceptable safety profile of avelumab 1LM, consistent with previous studies, in a representative population of patients with la/mUC treated in clinical practice. Enrollment is ongoing.

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General Practitioners' and Urologists' Perspectives on Organised Prostate Cancer Screening in Switzerland: A Cross-Sectional Online Survey

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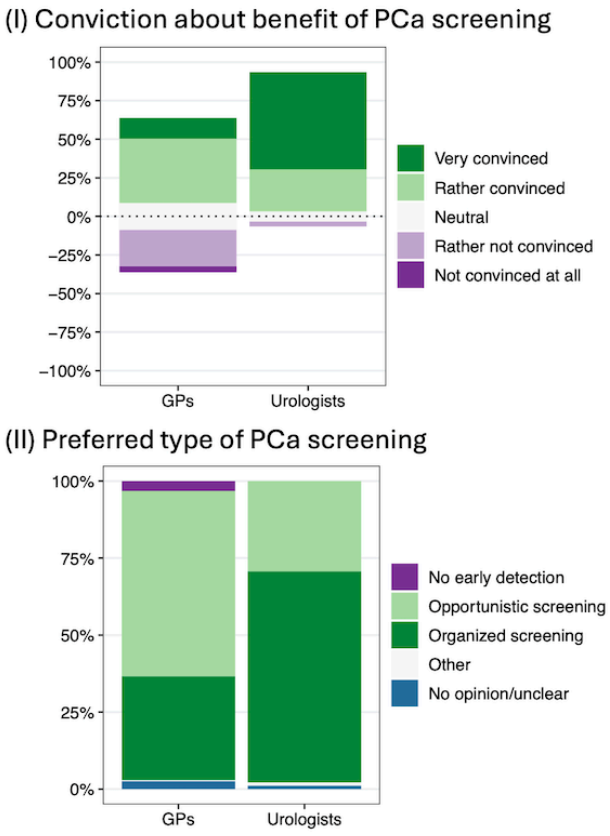
Introduction: Early detection of prostate cancer (PCa) using prostate-specific antigen (PSA) testing in an opportunistic setting is widespread in Switzerland, but bears the risk of overdiagnosis with resulting harms and poor cost-effectiveness. Efforts in the European Union are ongoing to evaluate the introduction of organised PCa screening programmes. As part of a similar initiative, this study aimed to evaluate the perspectives of general practitioners (GPs) and urologists with respect to implementing organised PCa screening in Switzerland.

Methods: A cross-sectional online survey was conducted among Swiss GPs and urologists from 15 Mar 2024 until 30 Sep 2024. The survey was co-developed with clinical experts and a patient representative and available in German, French and Italian. It was disseminated through mailing lists from mediX Schweiz, SGAIM, Argomed, Réseau Delta and Swiss Urology. The survey entailed questions related to perceptions on PCa screening (Likert scale) and screening implementation (multiple choice), diagnostic algorithms, shared decision making and participant characteristics, in two versions tailored to GPs and urologists. Descriptive statistical analyses were performed for all outcomes.

Results: 276 GPs and 92 urologists completed the survey, with a median age of 51 years and median clinical experience of 23 years. While 90% of urologists reported to be convinced that PCa screening can provide a benefit to men in general, this proportion was 55% among GPs. Among urologists, 69% were in favour of implementing organised PCa screening in Switzerland. In contrast, only 34% of GPs supported organised screening, with 60% preferring the current opportunistic screening approach (vs. 29% of urologists). Both groups broadly agreed on the importance of MRI in the diagnostic algorithm after a positive PSA test, while differences were observed for digital rectal examination, risk calculators, biomarker testing, and PSA density. The importance of shared decision making was rated as high by 89% of GPs and 83% of urologists.

Conclusions: The perspectives of Swiss GPs and urologists differ with respect to the value and optimal implementation of PCa screening in Switzerland. The potential introduction of a PCa screening programme in Switzerland will need to consider the perspectives of both important stakeholder groups and incorporate sound shared decision making processes.



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Outcomes and Disparities in Lung Cancer: Insights from a Real- World Registry before, during and a@er the COVID-19 pandemic

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Introduction: Lung cancer remains the leading cause of cancer-related death globally, driven by a complex interplay of gene:c, environmental, and socioeconomic factors. Despite advances in personalized medicine, comprehensive real-world data on lung cancer treatment outcomes remain limited.

Methods: This single-center, retrospective study evaluated a registry of 744 lung cancer patients between 01.01.2018 and 30.07.2024 to assess molecular and outcome parameters affected by the COVID-19 pandemic.

Results: Of the 744 patients, 83% (n = 618) had Non-small Cell Lung Cancer (NSCLC), 11.5% (n = 86) had Small Cell Lung Cancer (SCLC), and 5.5% had other histology. The median age was 69 years (IQR: 62-75). For NSCLC, median overall survival (mOS) ranged from 74 months (stage I) to 17 months (stage IV). In the adenocarcinoma (AdNSCLC) cohort (n = 417), molecular analysis was performed in 281 cases; gene:c altera:ons were found in 71% of patients, including EGFR (16.4%, n = 46), ALK (6.7%, n = 19), KRAS (56.2%, n = 158), and TP53 (51.9%, n = 146). Stage IV AdNSCLC patients with ac:onable EGFR muta:ons had significantly improved mOS (37 vs. 13 months, p <0.05). Co-mutational analysis revealed non-associated/associated clusters (e.g., EGFR-KRAS, MET-BRCA1). Univariate analysis showed improved outcomes for early versus late-

stage AdNSCLC (HR 5.28 [95% CI: 3.62, 7.71], p <0.001), never-smokers (HR 0.46 [95% CI: 0.29, 0.73], p <0.001), and younger patients (HR 1.04 [95% CI: 1.03, 1.06], p <0.001). For SCLC, 66.3% (n = 57) were diagnosed with extensive disease, and 33.7% (n = 29) with limited disease. Median overall survival was 10 months for extensive and 20 months for limited disease. Patients under 65 years showed better outcomes (HR 1.08 [95% CI: 1.03, 1.13], p = 0.002). No significant survival difference was observed across cohorts before, during, or after COVID-19. Patients were area-coded and assigned to the Swiss Socioeconomic Index evaluating Socioeconomic impact.

Conclusions: This study highlights comprehensive real-world data in lung cancer patients. It also integrates ongoing disparities in socioeconomic groups, which might influence patient outcomes. These data might become crucial for future prevention strategies and therapeutic interventions in a real-world setting.

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Cost-Effectiveness of Biomarker Testing Among Early-Stage Breast Cancer Patients in Switzerland

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Introduction: In Switzerland, early-stage HR+/HER2- breast cancer (BC) patients (pts) may receive adjuvant chemotherapy (CT) followed by endocrine treatment to reduce the risk of recurrence. However, CT does not improve survival for all pts and can result in treatment-related toxicities. CT is associated with significant direct (healthcare) and indirect (work productivity) costs. The Oncotype DX Breast Recurrence Score® test (Exact Sciences) can predict the clinical benefit of adding CT to endocrine therapy alone, helping to minimise over- and undertreatment with ca. 80% of patients not benefitting from chemo versus 20% benefitting. This analysis aims to provide a cost-effectiveness evaluation of the Oncotype DX® test and biomarker testing in general in Switzerland.

Methods: A cost-effectiveness Markov model was developed utilising a decision tree based on pts Recurrence Score® result to track adjuvant CT and subsequent outcomes. Pts' distributions and distant recurrence probabilities for the Oncotype DX® test were derived from the TAILORx (N0) and RxPONDER (N1) trials. CT allocation reflected Swiss clinical practice, informed by expert opinion, and incorporated Swiss drug costs. The model included a Swiss payer and societal perspective. The analysis included testing, CT, administration, management of adverse events, and terminal care.

Results: The numerical differences observed in total cost, QALYs, and life years demonstrate clinically meaningful trends that support the utility of genomic testing, such as Oncotype DX® test by reducing chemotherapy-indication by approx. 50% of patients compared to no testing. These benefits are observed as early as ten years for both N0 and N1 pts and continue to improve over a lifetime.

Conclusions: The numerical differences observed in total cost, QALYs, and life years demonstrate clinically meaningful trends that support the utility of genomic testing, such as the Oncotype DX® test in early-stage HR+/HER2- breast cancer (BC) patients. The results of this study are in line with health economic assessments in other countries.

		10 years		Lifetime	
		No testing	Oncotype	No testing	Oncotype
N0 pts	Total cost (CHF)	24'834	23'850	49'979	46'160
	QALYs	6.51	6.56	13.19	13.44
	Life years	8.32	8.36	17.36	17.68
N1 pts	Total cost (CHF)	31'661	29'327	57'776	55'442
	QALYs	6.50	6.52	13.06	13.21
	Life years	8.31	8.33	17.11	17.37

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Neoadjuvant immunotherapy for stage III melanoma – the cohort study of a large swiss hospital

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Introduction: The OpACIN-neo and PRADO trials showed excellent outcomes for stage III melanoma treated with neoadjuvant immunotherapy. The superiority of the neoadjuvant approach was confirmed later on in the phase III NADINA trial. The results of the OpACIN-neo and PRADO trials led us to adopt the neoadjuvant immunotherapy for stage III melanoma since summer 2022.

Methods: All patients showing macroscopic lymph nodes metastases clinically or on staging PET-CT were treated with two neoadjuvant cycles of ipilimumab 1mg/kg and nivolumab 3mg/kg followed by either the resection of the involved node(s) only or a complete lymph node dissection. Patients showing a major pathological response (MPR, ≤ 10% vital tumour cells) on histology didn't receive any further adjuvant treatment. Patients lacking a MPR received an adjuvant treatment, either dabrafenib and trametinib for BRAF mutated melanoma or nivolumab for BRAF wildtype tumors for the duration of one year. Patients who had only the involved lymph node resected and were lacking a major pathological response were strongly recommended to proceed to a complete lymph node dissection.

Results: Our cohort encompasses 8 patients so far with a median age of 66.5 years (range 56-86). On pathological examination of the resected node 4 patients showed a complete response (CR), 1 patient a near complete response nearCR), 1 patient a partial response and 2 patients no response. 4 CR and 1

nearCR account for a MPR rate of 5/8 = 62.5%. None of the patients with MPR relapsed so far (median time to follow-up 24.2 months, range 4.6 -33.6). Two out of three patients lacking an adequate response (MPR) on neoadjuvant immunotherapy relapsed, one of the two with distant metastases at restaging between neoadjuvant treatment and lymph node dissection. Immune-related adverse events seem to correlate with an optimal response on neoadjuvant immunotherapy.

Conclusions: Our results are in line with the published data on neoadjuvant immunotherapy for stage III melanoma. This approach is more effective and ressource-sparing than the adjuvant treatment, thus has to be adopted as a standard of care. More effective salvage strategies are needed for patients failing neoadjuvant immunotherapy.

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Transforming Precision Diagnostics of Switzerland: Applying Whole Genome and Transcriptome Data for Improved Patient Outcomes in Cancer Care

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Introduction: In recent years, the landscape of cancer molecular diagnostics has rapidly evolved. For decades, hotspot analyses were the standard, later giving way to gene panel sequencing in the late 2010s, which are currently and slowly being replaced by whole genome sequencing (WGS). Tumor-normal WGS is now validated for molecular profiling in cancer diagnostics. Further applications of WGS include low-coverage WGS for the detection of cancer in cell-free DNA and shotgun metagenomics to identify bacterial, fungal, or viral pathogens in molecular pathology. Bulk RNA sequencing, a whole transcriptome analysis method, also enables unbiased detection of oncogenic gene fusions.

Methods: In our study, technical and clinical validation of WGS has been achieved by comparing its performance to established pan-cancer and entity-specific gene panels. In total, three analyses—WGS, FoundationOne CDx (324 genes), and an in-house melanoma panel (190 genes)—were performed from the same DNA aliquot. WGS demonstrated analytical validity, detecting up to 98% of short variants, and up to 96% CNVs identified by gene panels. In addition, WGS also identified complex biomarkers such as UV-associated mutational signatures, HLA types, and genome-wide copy number alterations, broadening its clinical utility.

Results: Additionally, recent innovations in metagenomic WGS pipelines have shown promise in molecular pathology. For instance, in 2022, Swiss pathologists developed a metagenomics-based WGS pipeline that successfully identified an infectious pathogen as the underlying cause of a suspected lung tumor. This pipeline has since been refined and identified only the second known case of a recently discovered virus. The completeness of WGS data further enables its use in reporting pharmacogenomic mutations, chimerism, and tissue typing. Furthermore, WGS offers long-term utility of the data as compared to evolving gene panels. However, implementing WGS in routine diagnostics requires a more complex infrastructure and an interdisciplinary analysis.

Conclusions: WGS will improve patient care by delivering an interdisciplinary wholistic molecular view on the patient with a single analysis. If properly set up, this one-stop-shop type of analysis will save time and may dramatically alter the frequency of unexpected, but actionable feedback. And this transformation has already begun.

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Targeted Therapies in ROS1-Mutated NSCLC: Long-Term Efficacy and Renal Cyst Formation with Crizotinib and Entrectinib

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Introduction: Managing advanced lung adenocarcinoma remains challenging, but new treatments like immunotherapy and targeted therapies have improved long-term outcomes. The ROS1 mutation, seen in 1-2% of cases, is a key target for these therapies. While Crizotinib has been effective as the first ROS1-directed treatment, it can cause significant side effects, notably renal impairment, which requires careful clinical assessment and management.

Methods: We report the case of a 73-year-old patient with a central lung tumour harbouring a ROS1 mutation. The patient developed progressive renal cysts during Crizotinib therapy. Suspected malignancy prompted two biopsies, both of which were negative, indicating a drug-related effect. The treatment was subsequently switched to Entrectinib, resulting in resolution of most cysts, though one persistent lesion remained. Renal function declined with both therapies, necessitating dose adjustments. The patient's long-term response was monitored, and possible co-mutations contributing to sustained efficacy were explored.

Results: Crizotinib-associated renal cysts (CARCs) exhibited radiological features mimicking malignancy and abscess formation, underscoring the importance of pathological confirmation to prevent misdiagnosis. The cysts appeared linked to the MET pathway, as Crizotinib targets both ROS1 and c-MET proto-oncogenes. Switching to Entrectinib is advised when cysts form and malignancy is excluded, given its different mechanism of action. The patient's response to Crizotinib significantly exceeded the median duration of 17.6 months, lasting over 55 months and persisting after the switch to Entrectinib. Co-mutations are hypothesised to contribute to this prolonged response, though further molecular studies are needed.

Conclusions: The formation of renal and hepatic cysts during Crizotinib therapy represents a significant adverse event, likely driven by MET pathway activity. Histological evaluation is crucial before transitioning to Entrectinib. This case highlights the potential impact of co-mutations on prolonged treatment response, warranting further research into the molecular mechanisms that influence therapeutic outcomes.

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Cancer-related fatigue (CrF) – Incidence, predictive factors and treatment effects during oncological indoor rehabilitation

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Introduction: Cancer-related fatigue (CrF) is one of the most common acute and chronic sequelae after cancer and is therefore of great importance for QoL and professional participation of the affected patients. According to current studies, 40 – 70% of all patients are affected.

The aim of this prospective data collection was to evaluate the incidence of fatigue in oncological rehabilitation, to demonstrate possible predictive factors and the therapeutic effects of multimodal fatigue therapy.

Methods: In total, this prospective study evaluated data from 1220 patients during oncological inpatient rehabilitation. The incidence of CrF was systematically recorded at the beginning and at the end of rehabilitation using standardized screening forms (SIF, ESAS). In addition, the performance and muscle strength were evaluated using a 6-min walk test, TUG and hand strength measurement (Jamar) and the clinical and sociodemographic data in relation to predictive factors for CrF.

Results: Overall results from 925 patients (52.8% women, average age 64.5 years) were able to evaluate all data on fatigue as well as the predictive evaluations at the beginning and at the end of rehabilitation. In n = 363 (43.4%), SIF (≥4) could be detected at the start of rehabilitation. Increased SIF values correlated significantly in up to 94.8% with significantly increased values in the ESAS (3). Furthermore, the increased SIF values correlated with gender (51.0% women vs. 37.8% men; P <0.001) and patient age (51.7% (<60 years) vs. 38% (≥60 years)) . As a result, women with breast cancer had the highest incidence (60.2%) and SIF values (4.58 ± 2.0) compared to with other tumor entities. Furthermore, increased SIF values correlated significantly with worse patient reported outcomes measures (PROMIS) in the mental and physical areas (P <0.01) as well as with a subjectively significantly worse QoL (43.1 ± 19.1 vs. 54.4 ± 20.1 ; P <0.001). After rehabilitation there was a significantly reduced incidence of CrF (15.7% vs. 43.4%; p <0.001). In addition, there was a significant improvement in PROMIS and QoL (43.1±19.1 vs. 58.5±19.7; p <0.001).

Conclusions: The data presented confirm the frequent incidence of CrF and typical predictive factors as well as the positive, significant effects on its course during inpatient rehabilitation or multimodal therapeutic approaches.

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Enhancing Cancer Care: Implementation of Nurse-Led Consultations (NLC) in Oncology for Improved Patient experience"

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Introduction: The growing incidence of cancer, along with advances in treatment and demographic shifts, has increased demand for oncological care. This has led to staffing shortages and longer patient wait times, threatening care quality. NLC present a solution to alleviate pressure on physician-led services and improve patients' experience.

Methods: Single institution study at the KSGR in collaboration with the Lucerne University of Applied Sciences and Arts. It implemented a nurse-led consultation model for ambulatory oncology patients, with therapies selected based on suitability for nurse-led care. Oncology nurses received specialized training to conduct these consultations. Surveys based on standardized questionnaires, were conducted with medical oncologists (at intervals of 0, 6, and 12 months, n=11), nurses (at intervals of 0, 6 and 12 months, n=15), and patients (at intervals of 0 (n=77) follow up after 3 to 6 months (n=51)). The surveys assessed satisfaction, workflow, efficiency and overall experience. The project followed a pre-post design over 18 months incooperating regular evaluations and adjustments based on ongoing feedback from all steakholders.

Results: The implementation of a NLC model demonstrated improvements in patient flow and satisfaction. Over 90% of patients included in the study expressed a preference to continue with nurse-led consultations, citing better time management and more streamlined visits. Nurses reported greater job satisfaction, with over 70% indicating that the new consultation model fully utilized their skills and enhanced their professional responsibilities. Physicians, while supportive of the model, observed only a modest reduction in workload due to increasing patient numbers and occasional staffing challenges.

Conclusions: Nurse-led clinic represents a promising approach to addressing several of the current challenges in oncology care and leading to reduced patient waiting times reflected by increased patients' satisfaction. In addition, nurses reported enhanced job satisfaction due to the more comprehensive use of their skills and increased professional responsibilities. Although the direct reduction in physician workload was modest, the model showed potential for improving care efficiency and quality. Additional refinements to nurse responsibilities, resource allocation and care processes could yield even greater benefits.

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PROMs, quality of life and treatment effects during oncological indoor rehabilitation – analysis of 1230 cases

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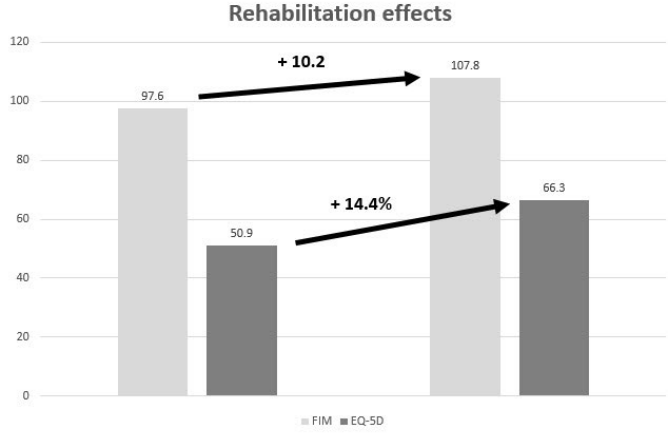
Introduction: Modern multimodal cancer therapy is becoming more and more efficient, but at the price of a variety of somatic side effects and toxicities. These complaints can lead to high psychological stress and a reduced QoL. Aim of this prospective study was to record treatment side effects at the beginning of oncological rehabilitation and to analyze the therapeutic effects of multimodal treatment.

Methods: Between 10/2020 and 04/2024, 1230 patients (51.4% female) were examined for the presence of somatic and psychological complaints and QoL after admission using ESAS, SIF, PROMIS-10, and EQ-5D. In addition, physical performance was recorded using a 6-minute walk test (6-min-WT), time-up-and-go test (TUG), hand strength (JAMAR) and FIM measurement. To evaluate the rehabilitation effects, a second assessment was carried out before discharge.

Results: Mean age was 64.2 +/- 12.7 years. Most patients had colorectal cancer (n=219; 17.7%), breast cancer (n=140; 11.3), and pancreas/biliary tract/liver (n=130; 10.5%). The mean ESAS showed a high burden of somatic impairments (2.4 ± 1.3), especially fatigue (n=395 ≥ score 4). This was also confirmed by SIF (n=380 ≥ 4). Furthermore, PROMIS-10 and EQ-5D showed significantly reduced quality of life (QoL; mean score 50.9 ± 20.3). In 925 cases (75,2%) a second assessment could be carried out. PROMIS-10 score showed a significant improvement (14.3±2.6 vs. 11.9±2.6, p <0.001). In particular, fatigue improved significantly in the ESAS and SIF (3.6±1.9 vs. 2.1±1.7, p <0.001) as well as the functional independence (FIM: 97.6±19.2 vs. 107.8±19.4; p <0.001). These results were also confirmed by physical function tests (6min-WT 322.3±185.2m vs. 407.1±207.2m; TUG 13.0±12.4s vs. 8.7±6.2s; Jamar 26.3±10,9 vs. 24,5±11,3; p <0.001). In addition, there was also a highly significant improvement in QoL compared to the values before rehabilitation (EQ-5D: 50.9±20.3 vs. 66.3±19.8; p <0.001).

Conclusions: The available data demonstrate the high rehabilitation needs and the great importance of routine screening for fatigue and psychological distress. Additionally, our data prove the high efficiency and effectiveness of oncological rehabilitation both in the alleviation of somatic and psychological impairments and thus leads to a significant improvement in QoL. Therefore, multimodal oncological rehabilitation should be an integral part of interdisciplinary cancer treatment.



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Nurse-Led Consultations (NLC) in Oncology: Financial Impact and Productivity Gains

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Introduction: The increasing demand for oncology services and staffing shortages have led to a need for more efficient care models. NLC offer a potential solution to improve productivity, patient satisfaction, and cost management. This study evaluates the financial impact of NLC using Tarmed with a tax point value of CHF 0.83.

Methods: A financial analysis was conducted at KSGR using a simplified model focusing solely on salary costs. Salaries for an advanced nursing practitioner (HöFa) and a senior physician were used, excluding infrastructure costs, as the same rooms were used in both models. Assistant physicians could not delegate their patients to NLC to ensure proper training. The conventional physician-led model was the baseline (100%) for revenues and costs, and productivity gains were assessed based on the reallocation of physician time with 50% and 100% utilization of freed-up hours.

Results: NLC generated 57.5% of the revenue compared to the conventional model (100%). Salary costs were reduced to 56.2% of the conventional model. Consequently, profitability under the nurse-led model was 63.5% of the conventional model. However, considering productivity gains from reallocating physician time:

At 50% utilization, profitability increased to 96% of the conventional model.

At 100% utilization, profitability rose to 129%.

Conclusions: NLC offer a financially viable solution, improving cost efficiency and productivity, while addressing staff shortages. However, the model's productivity gains rely on excess demand for services. In a fully utilized or overcapacity setting, the benefits are maximized. In contrast, in an underutilized system, the model may lead to reductions in physician staff. To ensure sustainability, structured nurse training and tariff adjustments are essential.

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Influence of HCP Supervision on Quality-of-Life Questionnaire (QLQ) Scoring by Cancer Patients (Pts): A Prospective, Randomized, Cross-over Study (IMSUP).

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Introduction: Structured implementation of patient reported outcomes can improve the quality of care, e.g. by the identification of adverse events or areas that need attention, and thus patients' quality of life (QoL). QoL is also an endpoint in many clinical trials. QoL is routinely assessed by questionnaires (QLQs) that are increasingly provided digitally for self-completion at home. Advantages over HCP-supervised completion on paper include low costs, patient convenience, less HCP time, and automated analysis/reporting; however, response rates are typically lower. Older pts also often lack digital skills and access to devices. Since HCP supervision may influence the scoring and completion of QLQs by cancer pts, particularly in sensitive

domains, we have set up a study to investigate the impact of HCP supervision on the scoring of financially- and sexuality-related domains of QLQs, compared to digital completion at home.

Methods: The IMSUP study is an investigator-initiated multicentre study, enrolling adult cancer pts who have completed ≥2 cycles of systemic antineoplastic therapy and are planned to receive ≥2 additional cycles, can complete QLQs in German, and have the skills and tools to complete web-based QLQs at home. The financially- and sexuality-related domains of the EORTC QLQ-C30 and SH22, and a specific financial-consequences-questionnaire are used. For each of the 3 QLQs, the hypothesis is tested that the method of completion influences the scoring. A sample size of 200 subjects will be recruited yielding 90% power to detect an effect size as small as 0.11 points on the QLQ-SH22 scale (IQR=60 points; α=0.0166, corrected for multiple testing). Participants are randomized 1:1 to complete the QLQs under HCP supervision first, followed by digital completion at home before the next cycle, or in the opposite order. ClinicalTrials.gov: NCT06490393.

Results: At submission, 52 pts were enrolled. Recruitment started April 2024 and is planned to last 2 years. Pt demographics and descriptive interim results will be presented.

Conclusions: HCP supervision may improve QLQ completion rates, but might also influence scoring by pts, potentially impacting the clinical utility for the individual pt and external validity. In the present IMSUP study, the impact of HCP supervision on scoring of sensitive domains in QLQs by cancer pts is studied. Results will guide future studies and QLQ administration strategies.

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Exercise interventions for cancer patients. A Systematic Review.

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Introduction: Exercise is safe and beneficial for cancer patients and survivors before, during and after cancer treatment. An international consensus roundtable convened in 2018, advanced the pre-existing exercise recommendations for cancer patients and survivors published by the American College of Sports Medicine in 2010. The latest guidelines refer to prescriptive programs specific for cancer type, treatment and/or health related outcome. However, there is lack of evidence to support specific exercise prescription for a number of health related outcomes in various cancer types. A systematic review conducted by Sturgeon et al in 2023 updated the Exercise Guidelines for cancer patients and survivors. The body of literature published in the time span 2018-2023 was not adequate to cover the evidence gaps in this field. Therefore, we sought to cover these evidence gaps by conducting a Delphi study. The purpose of this systematic review is to inform the panelists of this Delphi study in regards with the available evidence in the field of exercise for cancer patients. This review investigates the efficacy of exercise interventions in patients with various cancer types for different health related outcomes.

Methods: In this systematic review we included randomized controlled trials, investigating the effects of exercise interventions for adult cancer patients for any possible outcome.

Results: We retrieved 12722 titles. After title and abstract screening 1736 were full-text reviewed. Finally, we included 363 studies.

A total of N=4645 measurements were extracted. We grouped these measurements in N=26 outcome categories: Anxiety, depressive symptoms, chemotherapy induced peripheral neuropathy, cardiovascular disorders, cancer treatment related symptom burden, pulmonary dysfunction, metabolic disorders, cognitive impairment, fatigue, impaired bone health, impaired arm and shoulder function, impaired balance and risk of falling, impaired body constitution, impaired physical function, impaired psychosocial adjustment, pain, sleep disorders, reduced strength and reduced endurance were among the most frequently studied outcomes.

Conclusions: A number of problems faced by cancer patients and survivors can be mitigated by exercise interventions. Current evidence is adequate to inform expert consensus roundtables seeking to generalize exercise prescriptions for understudied populations.

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Project Cancer Move Continuum Schweiz

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Introduction: The oncological treatment spectrum has developed considerably in recent years at a multidisciplinary level. Due to its diverse biopsychosocial effects, exercise has a significant positive effect on quality of life, course of treatment and prognosis of the underlying disease in cancer patients. Despite the available evidence favoring exercise as supportive treatment for cancer patients and survivors, access to specialized exercise programs is currently hampered by the lack of organized facilities and patient-pathways across Switzerland. This leads to a lack of treatment among Swiss cancer patients and survivors. The Cancer Move Continuum Schweiz (CMCS) project aims to enable cancer patients and survivors to participate in specialized exercise programs in their convenient proximity.

Methods: In order to allow convenient access for cancer patients and survivors, the CMCS project seeks to achieve high geographical coverance in terms of specialized exercise programs. This should be achieved in three steps:

The first step is to develop an evidence-based therapeutic concept that allows the systematic, structured, personalized and interdisciplinary consideration and treatment of the various problems of cancer patients.

The second step is to develop a treatment pathway based on a structured and evidence-based list of treatment-indications.

The third step is to build up a network of facilities whose geographical distribution ensure convenient access for all cancer patients and survivors residing in Switzerland.

Results: So far a total of nine renowned Swiss Institutions have formed the core of the CMCS network: University Hospital Zurich, Inselspital Bern, University Hospital Basel, Cantonal Hospital Winterthur, Cantonal Hospital St. Gallen, Lucerne Cantonal Hospital and Balgrist University Hospital, University of Applied Sciences of Eastern Switzerland, Department of Health (physiotherapy and nursing sciences) and Cancer League of the Canton of Zurich. The first steps for the definition of the common therapeutic concept have been completed after the conduction of a systematic review.

Conclusions: Disparities among cancer patients and survivors referring to their access to specialized health-services can be effectively addressed by coordinated holistic approaches which engage all crucial stakeholders and exploit available ressources and scientific potential.

POSTER – CLINICAL HEMATO-ONCOLOGY

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Plasma cells with Auer-rod-like inclusions in a patient with MGUS and acute myeloid leukaemia with NPM1 mutation

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Introduction: A 76-year-old man with asymptomatic monoclonal gammopathy of undetermined significance (MGUS) type IgM kappa, presented with fever, joint pain, leukocytosis and monocytosis. On admission the blood count showed anaemia (haemoglobin concentration 102 g/L), leukocytosis with monoblasts (leukocytes 86.5 × 109 /L; monoblasts 48.5 × 109 /L) and thrombocytopenia (platelets 111 × 109 /L). A non-progressive paraprotein level of 3.5 g/L (IgM kappa) was confirmed.

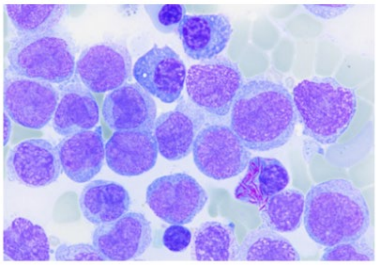
Methods: Bone marrow aspirate showed hypercellularity with 85% blasts, and acute monocytic leukaemia was diagnosed (Figure 1.A). The other diagnostic procedures, including trephine biopsy, immunophenotyping, genetic studies and next-generation sequencing allowed classification according to WHO criteria as acute myeloid leukaemia (AML) with NPM1-Type A mutation, FLT3-ITD negative, with additional DNMT3A- and PTPN11-mutations, but no chromosomal anomalies. The patient was treated with azacitidine 75 mg/m2 day 1-5, day 8-9 and venetoclax 400 mg day 1-14, achieving a complete remission after one cycle of chemotherapy. Bone marrow examination after two cycles therapy showed significant reduction of blasts (<2%).

Results: Interestingly, plasma cells containing numerous intracellular Auer-rod-like, needle-shaped cytoplasmatic inclusions were observed (Figure 1:B: plasma cells with and without intracytoplasmic inclusions, May-Grünwald-Giemsa stain, x 100 objective, total magnification ×1000). Retrospectively, the presence of rare plasma cells with the same cytoplasmatic inclusions were detected in the first bone marrow slide prepared at diagnosis of AML before chemotherapy (Figure 1.A: hypercellular bone marrow showing blasts and a single plasma cell with cytoplasmatic inclusions, May-Grünwald-Giemsa stain, x 60 objective, total magnification × 600). No Auer rods were detected in the myeloid blasts in either bone marrow smears.

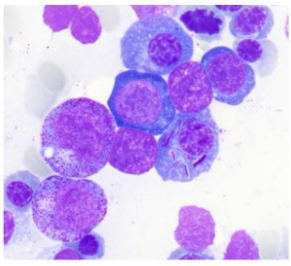
Conclusions: Cytoplasmatic inclusions that are sometimes indistinguishable from Auer rods have been described in B-cell, myeloid or plasma cells malignancies. This case of MGUS and AML with NPM1 mutation where "bundled" Auer-rod-like structures were present in abnormal plasma cells of MGUS but not in blast cells, emphasises the surprises that morphology can sometimes present [1].

Figure 1:

1. A



1. B



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Influence of occupational exposure to pesticides on the development of MDS: a systematic review

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Introduction: Myelodysplastic neoplasms (MDS) are a heterogeneous group of diseases. The origin of MDS most likely be related to a number of conditions and not to a single factor. Among them, the role of occupational exposure to pesticides remains unclear. The aim of this study is to assess the state of the evidence in the literature on the effect of pesticide exposure on the risk of MDS.

Methods: A systematic review was conducted with a pre-specified study protocol registered on PROSPERO (CRD42023400851). A literature search was performed in MEDLINE ALL, Embase, Web of Science on September 27, 2024 using controlled vocabulary and free terms related to "Myelodysplastic Syndromes", "Preleukemia", "Leukaemia, Myeloid", "Myelodysplastic-Myeloproliferative Diseases", "Occupational Diseases", "Occupational Exposure", "Pesticide", "Herbicide". The inclusion criteria were defined as retrospective, randomized, or non-randomized cohort studies and case-controlled studies published in English that include adult patients with MDS and the analysis of their exposure to pesticides.

Results: After meeting the inclusion criteria, eighteen studies were included. Ten were conducted in Europe, six in North-America, two in Asia. The oldest study dates from 1989, the most recent from 2018. During this time the MDS classification has changed: three used the WHO 2008 classification, one the WHO 2001, two the ICD-O-3, the others the FAB criteria. Regarding pesticide exposure, 8 case-control studies reported statistically significant association with the risk of developing MDS, while the others showed no differences. Regarding herbicides exposure, 3 studies showed a significant association while 3 did not. Only five studies used an exposure index, all others were based on data extracted with a simple questionnaire or interviews. No correlation was found either from the year of publication, the continent or the method used to measure exposure.

Conclusions: Although Jin's meta-analysis in 2014 demonstrated an association between pesticide exposure and the development of MDS, the articles found in our review have conflicting results, which are difficult to compare given the heterogeneity of the studies and differences in exposure assessment methods. Further prospective studies with a standardised assessment methods are needed to clarify a possible association.

Study	Study type	Country	MDS number	Controls number	MDS classification system	Exposure assessment	Association pesticide exposure and MDS	Association herbicides exposure and MDS
Poynter 2017	case-control study	USA	265	698	WHO 2008 classification	self-administered questionnaire	No	No
Avgerinou 2017	case-control study	Greece	126	102	FAB criteria	Interview and questionnaire	Yes	Yes
Copley 2017	case-control study	China	604	1193	WHO 2008 classification	self-administered questionnaire	-	No
Kokouva 2011	case-control study	Greece	78	455	FAB criteria	self-administered questionnaire	Yes	No
Lv 2010	case-control study	China	403	806	WHO 2008 classification	Face to face interview with questionnaire	Yes	Yes
Pekmezovic 2006	case-control study	Serbia	80	160	FAB criteria	Interview and questionnaire	Yes	Yes
Strom 2005	case-control study	USA	354	452	WHO 2001 Classification	self-administered questionnaire Exposure index	Yes	Yes
Albin 2003	case-control study	Sweden	330	177	FAB criteria	Telephone interviewed	No	-
Nisse 2001	case-control study	France	204	204	FAB criteria	Interview and questionnaire Exposure index	Yes	-
Rigolin 1998	case-control study	Italy	178	178	FAB criteria	Interview and questionnaire Exposure index	Yes	-
West 1994	case-control study	UK	400	400	FAB criteria	Interview and questionnaire Exposure index	No	-
Ciccone 1993	case-control study	Italy	19	246	FAB criteria	Interview and questionnaire	No	-
Pasqualetti 1991	case-control study	Italy	48	1240	FAB criteria	Interviewed	Yes	-
Goldberg 1990	case-control study	USA	52	52	FAB criteria	Interview Exposure index	No	-
Brown 1990	case-control study	USA	63	1245	-	Interview and questionnaire	No	-
Narod 1989	case-control study	Canada	17	38	FAB criteria	Telephone interviewed	No	-
Lerro 2018	cohort study	USA	48	-	ICD-O-3	Self-administered questionnaires	No	-
Lemarchand 2017	cohort study	France	219	-	ICD-O-3	self-administered questionnaire	No	-

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Reversible transverse myelitis after CAR T-cell therapy in a patient with primary CNS lymphoma

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Introduction: Chimeric antigen receptor (CAR) T-cell therapy has greatly improved outcomes for patients with B-cell malignancies but can be associated with significant and life-threatening adverse events. For concerns about neurotoxicity, most CAR T- trials excluded patients with cerebral disease manifestations such as primary CNS lymphoma (PCNSL), a rare disease with a poor prognosis.

Methods: We present a case of reversible transverse myelitis in a patient with relapsed PCNSL following anti-CD19 CAR T-cell therapy. Spinal MRI revealed transverse myelitis and CAR T-cells were detected in the cerebrospinal fluid (CSF) by flow cytometry.

Results: A 51-year-old male with relapsed PCNSL was previously refractory to chemotherapy but achieved good partial remission with whole-brain radiotherapy. He then received off-label CD19-directed CAR T-cells (tisa-cel). Between days +1 to +3 he developed cytokine release syndrome (CRS), max. ASTCT grade 2, which resolved after a single dose of tocilizumab. On day +12, correlating with peak CAR T-cell expansion in the blood, the patient developed plegia of the left leg, sensory loss in the right leg, and allodynia of the lower torso. MRI of the spinal cord revealed contrast enhancement from T1 to T7, indicating transverse myelitis. Analysis of CSF showed an inflammatory infiltrate and ruled out bacterial or viral infection. CAR T cells were detected in the CSF by flow cytometry while excluding lymphoma. Therapy with high-dose dexamethasone and IL-1-R-antagonist Anakinra led to a rapid reversal of neurological deficits, with near complete resolution of MRI-abnormalities 1 week later (day+21). Early withdrawal of steroids on day +25 led to an increase in myelitis-related symptoms, but an iterative pulse of steroids with slow taper led to a final resolution by day +47. Unfortunately, while earlier brain MRIs showed a response, lymphoma progression was noted on day +70. After a brief course of Ibrutinib, the treatment transitioned to palliative care.

Conclusions: Transverse myelitis, so far only described in case reports, is a rare complication of CAR T-cell therapy, and this is the first reported case in a PCNSL patient. Early and sufficiently long anti-inflammatory treatment may reverse spinal cord inflammation and lead to favorable outcomes. Reports on CAR T cell-associated myelitis can help improve the treatment of this rare complication.

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True donor cell leukemia after allogeneic hematopoietic stem cell transplantation: Diagnostic and therapeutic considerations.

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Introduction: Donor-cell leukemia (DCL) is a rare complication after allogeneic hematopoietic stem cell transplantation (HSCT) accounting for 0.1% of relapses and presenting as secondary leukemia of donor origin. Distinct in phenotype and cytogenetics from the original leukemia, DCL's clinical challenge lies in its late onset. Its origin is affected by donor cell anomalies, transplant environment, and additional mutations.

Methods: A 43-year-old woman, treated for early-stage triple-negative breast cancer, developed mixed-phenotype acute leukemia (MPAL), 12 years later. Following induction chemotherapy, myeloablative conditioning, and allo-HSCT from her fully HLA-matched brother, she exhibited multiple cutaneous relapses of the MPAL, evolving into DCL. Cytogenetic analysis revealed a complex male karyotype in 20/21 metaphases, however still showing MPAL phenotype. DCL diagnosis was confirmed by 90.5% XY in FISH analysis and the male karyotype. Declining further intensive chemotherapy including a second allo-HSCT, she was treated with radiotherapy, palliative systemic therapies, and finally venetoclax and navitoclax but died seven months post-DCL diagnosis.

Results: Mutations in donor or post-transplant cells due to factors like bone marrow injury, reduced immune monitoring, and replicative stress contribute to leukemia onset. Donor age does not appear to impact DCL development. This case suggests that either the recipient's immune deficiency contributed to hematopoietic alterations in recipient and donor cells or the donor had low-level clonal changes that increased under the recipient's immunosuppression. The extent to which post-transplant therapy influenced this remains speculative. A combination of venetoclax and navitoclax, guided by pharmacoscopy represented a personalized approach.

Conclusions: Our data empasize the complexity of DCL, characterized by unique genetics. It highlights the need for advanced diagnostic techniques for DCL identification and underscores the urgency for early detection, better prevention and treatment strategies.

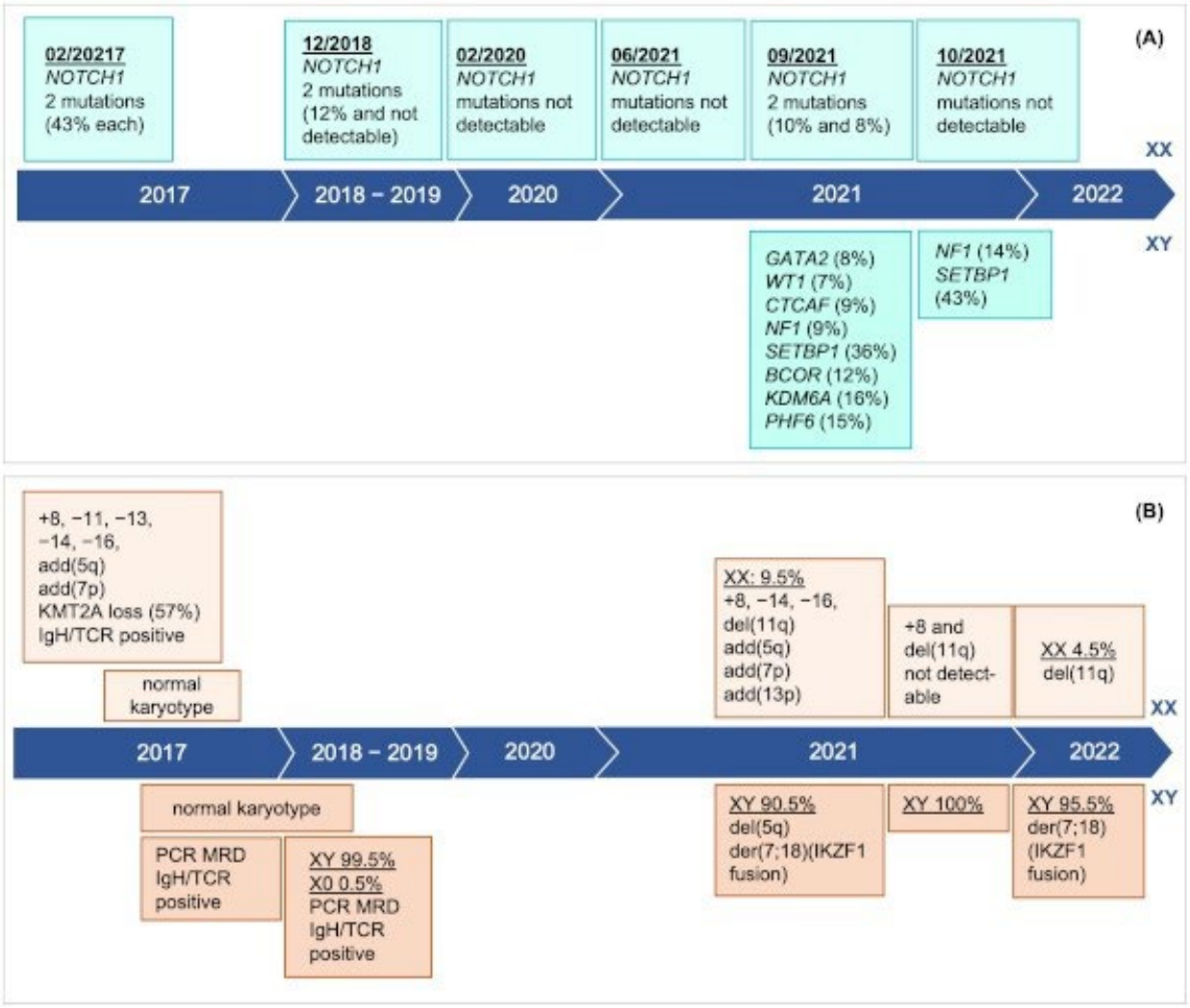

Figure 1. Timeline composite figure indicating the molecular diagnostics **(A)** and cytogenetics and FISH analysis **(B)**.

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The challenges of sequential CD19 directed therapies in relapsed/refractory DLBCL: a case report

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Introduction: The development of CD-19 directed chimeric antigen receptor T (CAR-T) cells offers new options in the treatment of relapsed/refractory (r/r) B-cell lymphomas with high response rates and long-term survival. Nevertheless around 40-50% of patients with diffuse large B-cell lymphoma (DLBCL) relapse or do not respond to initial treatment. Currently bispecific anti-CD20/anti-CD3 antibodies and monoclonal anti-CD19 antibodies provide additional options in the treatment of B-cell lymphomas.

Anti-CD19 CAR T-cells and the anti-CD19 monoclonal antibody tafasitamab share the same target. Questions about the sequence of these different anti-CD19 treatments arise. With this case we aim to improve understanding of the possible sequence of these two treatment options.

Methods: Tafasitamab was administered at a dose of 12 mg/kg body weight as IV infusion on day 1, 8, 15, and 22 for two cycles. Lenalidomide was added from day 1 to 21. CAR T-cell (tisagenlecleucel) therapy was administered after 3 days of lymphodepletion with fludarabine and cyclophosphamide. CAR T-cell expansion was measured by flowcytometry.

Results: We present a 78-year-old female patient with a transformed diffuse large B-cell lymphoma from a follicular lymphoma. The patient was already treated with several lines of chemo-immunotherapy. Unfortunately, progression occurred early after the end of the treatment. Treatment was changed to tafasitamab with lenalidomide and the patient was scheduled for CAR T-cell therapy.

FDG PET-CT after two cycles of tafasitamab showed lymphoma progression with new hypermetabolic findings in the right distal femur (Deauville 5). Biopsy of this femoral lesion revealed the known transformed DLBCL with persistent homogeneous CD19 expression on the cell surface.

Two months after receiving the last tafasitamab infusion, the patient underwent CAR T-cell therapy. Rapid CAR T-cell expansion was observed in vivo. One month after receiving CAR T-cell therapy FDG PET-CT showed a complete metabolic response.

Conclusions: In our experience treatment with Anti-CD19 CAR T-cell remains an effective option even after pretreatment with Anti-CD19 monoclonal antibodies. In our case, CD19 expression was documented before CAR T-cell therapy. This was not an inclusion criteria in all major CAR T-cell trials.

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Therapy-related acute myeloid leukemia after CAR-T cell therapy with brexu-cel for relapsed mantle cell lymphoma

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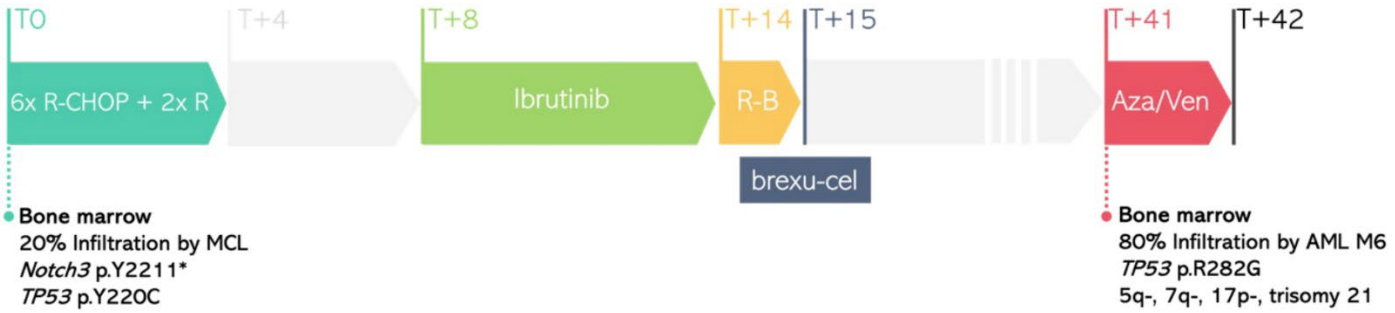
Introduction: Mantle cell lymphoma (MCL) treatment has seen significant progress by introducing Bruton Tyrosine Kinase (BTK) inhibitors and CAR-T cell therapies such as brexucabtagene autoleucel (brexu-cel). In particular, the ZUMA-2 trial reported a 91% response rate with brexu-cel in relapsed/refractory (r/r) MCL, which was confirmed in real-world reports. However, secondary malignancies, such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), have emerged as late complications after ,CAR-T therapy. AML has been reported in up to 3.1% of lymphoma patients after CAR-T but has not been reported after brexu-cel for MCL so far.

Methods: This report describes a 74-year-old male diagnosed with stage IVB MCL who developed acute erythroid leukemia (AML-M6) 26 months after brexu-cel CAR-T therapy.

Results: After initial treatment with R-CHOP and Ibrutinib for progressive MCL, the patient underwent CAR-T therapy with brexu-cel, achieving normalized blood counts and a CR according to PET staging. However, 25 months later, he developed anemia and thrombocytopenia, and bone marrow biopsy revealed MDS. This rapidly progressed to overt AML, with complex cytogenetic abnormalities, including biallelic TP53 inactivation. Retrospective analysis indicated that the TP53 mutation in AML cells differed from the TP53 mutation identified in the MCL cells, suggesting a therapy-related origin. Despite treatment with azacytidine and venetoclax, the patient succumbed to progressive AML

Conclusions: This is the first report of acute erythroid leukemia following brexu-cel therapy in patient with r/r MCL. It highlights the potential leukemogenic effects of prior chemotherapy treatments, as well as CAR-T-related immunosuppression. The occurrence of distinct TP53 mutations in separate hematologic malignancies in the same patient is particularly interesting. This case underscores the potential risk of secondary malignancies like AML after CAR-T therapy, likely due to prior chemotherapies and immunosuppression. Comprehensive genetic screening in patients with unexplained cytopenia before CAR-T therapy may be crucial to identify patients at higher risk for therapy-related malignancies.



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The Glasgow Prognostic Score provides additional prognostic information for elderly patients with adverse-risk acute myeloid leukemia (AML)

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Introduction: Prognosis in AML is currently determined by genetic aberrations as defined by the European Leukaemia Net (ELN) classification of 2022. According to ELN2022, the vast majority of elderly patients (pts) are at an unfavourable risk, which limits its clinical value for this frequent population. In this context, the Glasgow Prognostic Score (GPS), which combines levels of CRP and albumin may add prognostic information. Thus, we aimed to evaluate the prognostic impact of the GPS in elderly AML pts ineligible for intensive treatment.

Methods: We performed a retrospective chart review of pts diagnosed with AML or Myelodysplastic Syndrome (MDS)/AML between 2016 and 2023, treated with hypomethylating agents (HMAs) or best supportive care (BSC). The GPS was determined using values obtained at diagnosis: GPS-0 (albumin ≥ 35 g/L and CRP ≤ 10 mg/L), GPS-1 (either albumin <35 g/L or CRP >10 mg/L) and GPS-2 (both albumin <35 g/L and CRP >10 mg/L).

Results: 85 pts (female n=39; median age 77 years, range 63-91; AML n=69; MDS/AML n=16) were analysed. 17 pts (20%) received BSC and 68 pts an HMA +/- venetoclax. During follow-up (median 4 months [mo], range 0-56) 75 pts (88.2%) died. There were significant differences in overall survival (OS) between patients with a GPS-0 (n=27; median OS 15 mo [95% CI 7-23]) and those with GPS-1 (n=33; median OS 2 mo [95% CI 0-4]) or GPS-2 (n=25; median OS 1 mo [95% CI 0-5]), p <0.001.

To avoid bias, patients with known infections (n=20) or missing data (n=6) were excluded from the analysis with similar results for the remaining 59 pts: GPS-0 (n=27) median OS 15 mo [95% CI 7-23], GPS-1 (n=22) median 3 mo [95% CI 1.5-4.5] and GPS-2 (n=10) median 4 mo [95% CI 1-7], p=0.001. The ELN2022 stratification was available for 49/59 pts (83%): adverse: 40/49 (82%), intermediate: 7/49 (14%) and favourable 2/49 (4%).

Within the adverse risk group, median OS according to GPS was as follows: 13 mo (GPS-0 [n=18], 95% CI 7-20), 3 mo (GPS-1 [n=14], 95% CI 1-5) and 4 mo (GPS-2 [n=8], 95% CI 1-7), p=0.014, see Figure 1.

Conclusions: The results of this retrospective study indicate that the GPS provides additional prognostic information for elderly patients with adverse-risk AML according to ELN2022, taking into account systemic inflammation and/or catabolism. However, further analyses of larger cohorts are required to provide more robust evidence for this observation.

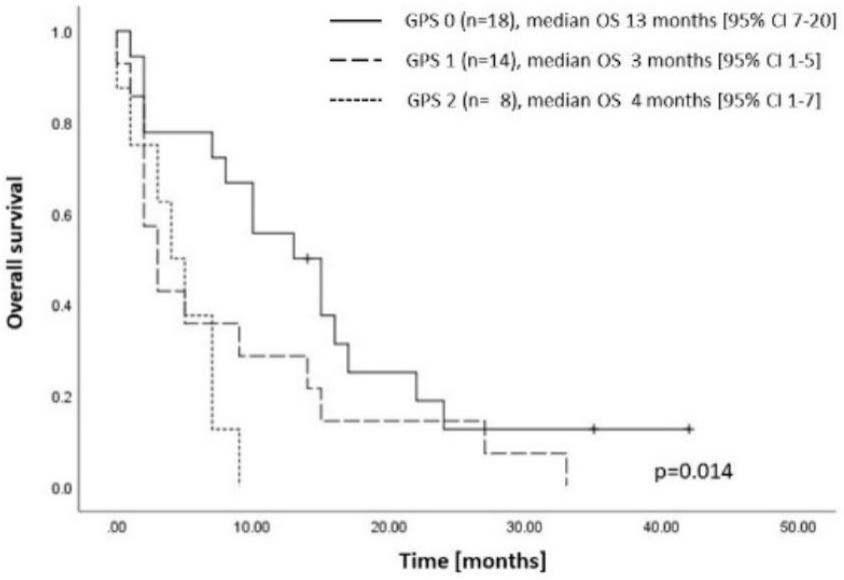

Fig 1: Survival of 40 patients with adverse risk AML (ELN2022), free of infection at the timepoint of diagnosis according to the GPS

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Venetoclax combined with FLAG-based chemotherapy induces rapid and deep responses in early T-cell precursor lymphoblastic leukemia/lymphoma. Report of two cases

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Introduction: Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL) is a rare and aggressive subtype of acute lymphoblastic leukemia (ALL), comprising 17% of adult T-ALL cases. It arises from hematopoietic stem cells and exhibits multipotent characteristics, leading to poor responses to induction chemotherapy and higher levels of measurable residual disease (MRD). This report examines the efficacy of combining Venetoclax with the FLAG regimen in treating two ETP-ALL patients.

Methods: Two male patients, aged 36 and 30, presented with ETP-ALL diagnosis. Both patients underwent induction therapy with a FLAG- (fludarabine, cytarabine, G-CSF)-idarubicin and venetoclax protocol. Both patients' MRD statuses were assessed using flow cytometry (FC) and next-generation sequencing (NGS) throughout their treatment courses, with follow-ups for potential hematopoietic stem cell transplantation (HSCT).

Results: After induction the first patient achieved CR (complete remission) with negative MRD (MRD-) by FC. At this point, mutations were undetectable with NGS, and IgH/TCR was detected at a level of 10-6 by qPCR. The patient then received an additional cycle by decitabine and venetoclax, achieving undetectable disease on MRD2 as confirmed by qPCR, NGS, and FC. Because patient's refusal to undergo HSCT, treatment was followed by consolidation and maintenance according to the GRAALL-T study regimen. Maintenance therapy was interrupted after 5 months due to liver toxicity and was switched to decitabine and venetoclax for a total of 2 years of maintenance with persistent CR from MRD2 to present. Following initial induction therapy with FLAG-Idarubicin-Venetoclax, the second patient achieved CR with MRD- by FC, but some mutations were persistent in NGS (FLT3, RUNX1, and WT1). A second induction was initiated with FLAG-Venetoclax and midostaurin, followed by HSCT, achieving MRD- by both FC and oncogenomic analysis. One-year post-HSCT, the patient remains in CR and continues a maintenance therapy with midostaurin.

Conclusions: These cases highlight the potential of Venetoclax in enhancing treatment outcomes for ETP-ALL. While HSCT remains the standard of care, early deep responses indicated by MRD- are critical for improved prognosis. The findings suggest a need for further prospective studies to evaluate the efficacy of Venetoclax in ETP-ALL and optimize treatment protocols.

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Persistent & complete B-cell depletion more than 4 years after anti-CD19 CAR-T-cell therapy enables prolonged Cryptosporidium infection emphasizing the pivotal role of B-cells immunity in the resolution of Cryptosporidium infection

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Introduction: CAR-T cell therapies directed against CD19+ lymphoma represent a milestone in the treatment of such. As a side effect of complete long term depletion of the B-cell lineage, patients become vulnerable to infectious diseases, which are primarily controlled by humoral immune response. While regular replacement of immunoglobulins may prevent certain infections, its efficacy depends on the exposure of the donor collective providing the serum for immune globulin collection, towards infectious diseases. Patients with specific depletion of the B-cell lineage can provide unique insights of the contribution of humoral immunity to resolution of infectious diseases.

Methods: We describe the case of a 73-year-old patient, currently 4 years and 4 months after CAR-T cell therapy directed against CD19+ lymphoma, who is in continuous complete remission and B-cell aplasia. The patient presented himself with Cryptosporidium infection in our outpatient department. Lymphocyte subsets and CAR-T cells were assessed by flow cytometry and Cryptosporidium was measured by PCR and direct microscopy.

Results: The patients flow cytometry analysis show a persistence of CAR-T cells and in parallel a complete lack of B-cells with a consecutive demand for substitution with immune globulins. Other lymphocyte subsets were not markedly decreased. After onset of watery diarrhea abroad, the patient sought medical attention after he returned and infection with Cryptosporidium was confirmed 10 days after initial onset of the symptoms, both by PCR and microscopy. After an initial amelioration of the symptoms our patient opted for an expectative approach and therapy with nitazoxanide was only established 19 days after persistence of symptoms. Upon initiation of treatment symptoms stopped within days and microscopic stool investigation turned negative.

Conclusions: The present case shows how a patient with a selective depletion of the B-cell lineage and an otherwise numerically and presumably functionally intact immune system was unable to clear cryptosporidium infection without antibiotic therapy. In summary this independently supports the previously described pivotal role of B-cells in the elimination of cryptosporidium infection.

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Newly established flow-cytometry panel helps to prove infiltration of a NK-large granular lymphocytic leukemia (NK-LGLL) at previously undescribed sites.

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Introduction: Natural killer large granular lymphocytic leukemia (NK-LGLL) is a very rare neoplasm defined by a persistently increased NK cell count in the peripheral blood, usually showing a chronic and indolent course of disease. NK-LGLL are normally found in peripheral blood and secondary lymphoid tissues, while organ infiltration is a rarity. As opposed to NK-LGLL, patients suffering from aggressive NK-cell leukemia often present themselves with strong constitutional symptoms and also organ infiltration is well described. We recently treated a patient at our clinic, who presented himself with neurological symptoms but without any further or constitutional symptoms. Laboratory analysis indicated a clearly increased NK-cell count. Based on the otherwise rather indolent course of disease NK-LGLL was suspected, possibly accompanied by a paraneoplastic phenomenon causing the neurological disorders.

Methods: We studied the case of a 92-year-old patient suffering from a NK-LGLL and neurological symptoms. Critically involved in diagnosis and disease monitoring was our newly developed NK-cell panel offering flow cytometry based analysis of NK-cell phenotype including clonality.

Results: Initial findings included a lymphocytosis in peripheral blood and a massively increased number of mononuclear cells in the liquor. Immunophenotypic analysis from both peripheral blood and the liquor of the above described patient showed that more than 98% of CD3-CD56+ NK-cells expressed the following surface marker profile: CD16+, KIR2DL1+, KIR3DL1+, KIR3DL2/3+, NKG2A+, confirming a monoclonal NK-cell expansion/infiltration in the peripheral blood and liquor. In addition, further analysis showed that the neoplastic NK-cells were negative for EBV, confirming the entity of NK-LGLL, which are usually EBV negative in contrast to aggressive NK cell leukemia.

Conclusions: Peripheral blood and liquor samples showed infiltration with the same NK-LGLL cells. This confirms the suspected infiltration of the central nervous system by the NK-LGLL of our patient. While central nervous system infiltration by more aggressive NK-cell neoplasms were shown before, this is new for NK-LGLL.

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