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Abstracts of the Swiss Oncology & Hematology Congress (SOHC)

Basel (Switzerland), November 19–21, 2025

SOHC
SWISS ONCOLOGY & HEMATOLOGY CONGRESS

SSMO SSOM SGMO SGHOSSH SWISS CANCER INSTITUTE

8TH SWISS ONCOLOGY AND HEMATOLOGY CONGRESS (SOHC)

BASEL, NOVEMBER 19–21, 2025

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

3966

Enhancing hemostasis in Glanzmann thrombasthenia via protein S inhibition

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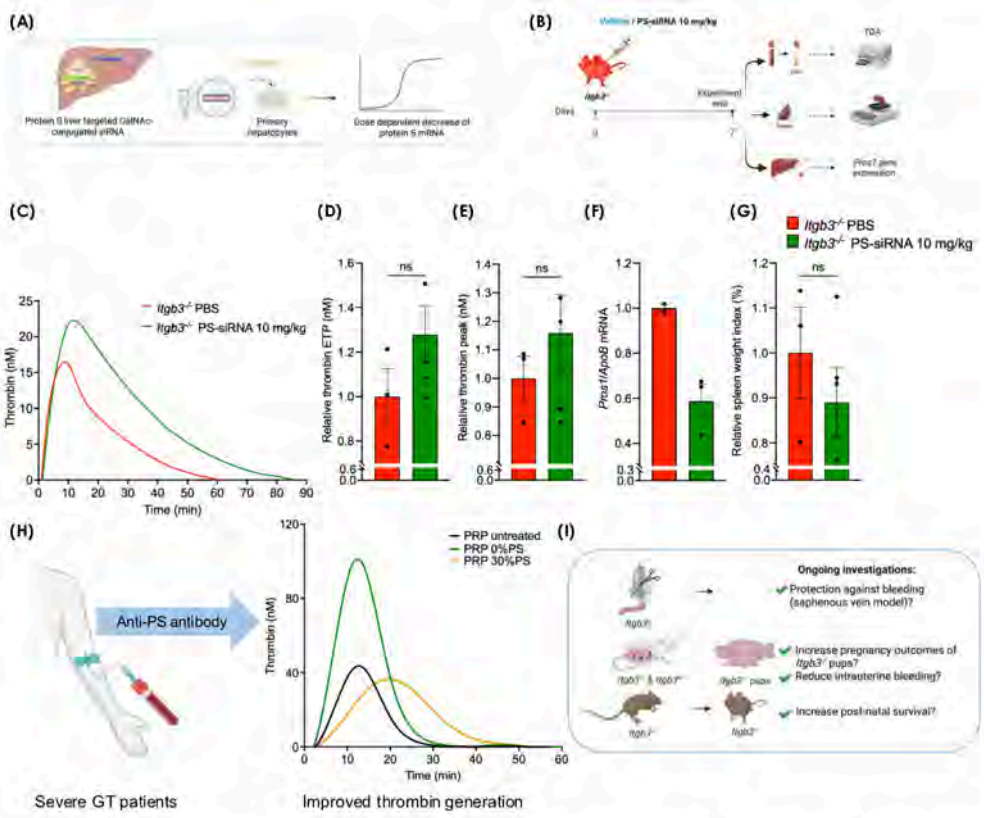
Background and objective: Glanzmann thrombasthenia (GT) is a rare inherited bleeding disorder caused by deficiency of platelet integrin αIIbβ3, impairing platelet aggregation and clot formation. Patients present with mucocutaneous bleeding, while severe cases develop gastrointestinal (GI) and life-threatening hemorrhages. Management relies on platelet transfusions for acute episodes and recombinant factor VIIa for refractory or perioperative cases. Protein S (PS), a natural anticoagulant in blood, acts as a cofactor for activated protein C and tissue factor pathway inhibitor, and directly regulates prothrombinase and tenase complexes, thereby increasing thrombin generation (TG). We previously showed hepatic PS silencing with small interfering RNA (PS-siRNA) (Fig.A) rebalanced hemostasis in hemophilia models. This strategy may also therapeutically benefit GT. Here, we evaluated whether PS-siRNA improves TG and provides prophylactic protection against bleeding in GT.

Methods: GT mice (Itgb3$^{-/-}$) received a single subcutaneous dose of PS-siRNA or vehicle (Fig.B). After seven days, TG was assessed in platelet-rich plasma (PRP). Spleens weight; an index of splenomegaly and indirect marker of chronic bleeding was measured. In parallel, PRP from GT patients was spiked with an anti-PS antibody to reduce free PS to 0% or 30%, or left untreated, and TG was measured in the presence of 1 pM tissue factor and 2 nM thrombomodulin.

Results: A single PS-siRNA injection in Itgb3$^{-/-}$ mice prevented overt mucocutaneous and GI bleeding observed in control mice. This hemostatic benefit correlated with a marked rise in endogenous thrombin potential (ETP) (Fig.C-E), indicating that ~50% PS silencing enhances TG (Fig.F). Spleen weights were lower in treated Itgb3$^{-/-}$ mice, consistent with reduced bleeding (Fig.G). In GT patient PRP, antibody-mediated PS reduction to 0% or 30% increased ETP versus untreated samples (40% ± 12.6 and 21% ± 14.6, respectively) (Fig.H).

Conclusions: PS modulation enhances hemostasis in GT. Partial PS inhibition increased TG and reduced splenomegaly in GT mice, while antibody-mediated PS blockade boosted TG in patient PRP. Ongoing studies include saphenous vein bleeding in PS-siRNA–treated Itgb3$^{-/-}$ mice and administration to pregnant GT females to assess intrauterine bleeding and pregnancy outcomes (Fig.I).



PS–small interfering RNA (PS-siRNA) enhances global hemostasis in Glanzmann's thrombastenia (*Itgb3*$^{-/-}$) mice and severe GT patients *ex vivo*. (A) Illustration showing the mode of action of protein S (PS) siRNA in the liver and primary hepatocytes to reduce PS mRNA levels. **(B)** Schematic experimental design: *Itgb3*$^{-/-}$ mice received a single dose of 10 mg/kg PS-siRNA or vehicle (phosphate-buffered saline) on day 1. On day 7, blood was collected for thrombin generation assay **(C-E). (C)** Representative thrombograms and **(D)** relative endogenous thrombin potential (ETP) and **(E)** relative peak thrombin in treated and control *Itgb3*$^{-/-}$ mice. Thrombin generation (TG) in platelet-rich plasma (PRP) was measured with the calibrated automated thrombography assay in presence of 0.5 pM tissue factor. **(F)** Liver tissue sections were isolated for quantitative real-time PCR analysis to measure *Pros1* mRNA expression normalized to *ApoB*. **(G)** Spleens were harvested and weighed to evaluate the effect of PS-siRNA on splenomegaly *Itgb3*$^{-/-}$ mice. Spleen weight was normalized relative to mouse total body weight. *P* values: ns: unpaired *t* test. **(H)** Representative thrombogram of ETP in severe GT patient PRP spiked with anti-PS antibody to achieve 0% and 30% free PS, or left untreated. TG was measured with the calibrated automated thrombography assay in presence of 1 pM tissue factor and 2 nM human recombinant thrombomodulin (TM). **(I)** Graphical illustration summarizing ongoing investigations in GT mouse model.

SSH/SSMO BEST ABSTRACT AWARD – EXPERIMENTAL HEMATOLOGY / ONCOLOGY

7656

Loss of SHP2 reduces JAK2V617F hematopoietic stem cell clone size and corrects MPN phenotype in preclinical models and patient cells

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Introduction: Myeloproliferative neoplasms (MPN) are driven by constitutive JAK2 signaling with persistent MAPK activity that limits the disease-modifying effects of JAK2 inhibitors (JAK2i). SHP2, a proximal MAPK mediator, may sustain this resistance. We tested whether SHP2 depletion reduces Jak2V617F stem/progenitor clones and ameliorates MPN.

Methods: We depleted Shp2 by shRNA in Jak2V617F Ba/F3 cells and profiled signaling, proliferation, RNA-sequencing, and phosphoproteomics ± JAK2i. We generated conditional Shp2 deletion in Jak2V617 Shp2f/f Mx-Cre transgenic mice and used competitive bone marrow transplants to track Jak2V617F clone dynamics. SHP2 inhibition (SHP2i) by TNO155 was evaluated as monotherapy and combined with ruxolitinib in Jak2V617F and MPLW515L mouse models. Primary patient PBMCs were tested for SHP2/MAPK and JAK2 activation and colony formation under SHP2i/JAK2i.

Results: Genetic SHP2 loss suppressed ERK phosphorylation and MAPK target expression including Bcl-xL and sensitized Jak2V617F cells to ruxolitinib. In Jak2V617FShp2f/f mice, Shp2 deficiency reduced erythrocytosis, leukocytosis and splenomegaly. Notably, Shp2 depletion substantially reduced Jak2V617F clone size in recipients of 1:1 competitive transplants. Specifically, Jak2V617F clones in the Lin-Sca-Kit+ (LSK) stem/progenitor compartment were decreased to 31% suggesting disease-modifying potential of SHP2 abrogation. Similar to genetic SHP2 depletion, SHP2 inhibition by TNO155 decreased activation of MAPK targets incl. MEK, ERK, RSK and Bcl-xL and enhanced effects of JAK2 inhibition by ruxolitinib. Jak2V617F and MPLW515L mice showed most complete correction of cytosis and splenomegaly as well as reduction of LSK, megakaryocytic and erythroid progenitors upon combined SHP2/JAK2 inhibition by TNO155/ruxolitinib. The effects of SHP2/JAK2 inhibition was recapitulated in Jak2V617F and MPLW515L MPN patient PBMCs, which showed suppressed SHP2, ERK and RSK phosphorylation as well as significantly reduced myelo-erythroid colony formation.

Conclusions: SHP2 is required for persistence of MPN clones under JAK2 inhibition. Genetic or pharmacologic SHP2 loss suppresses MAPK outputs, reduces Jak2 V617F clone burden, and corrects MPN features in vitro, in MPN mouse models and in primary MPN patient cells. Combined SHP2/JAK2 inhibition emerges as a rational disease-modifying strategy for MPN.

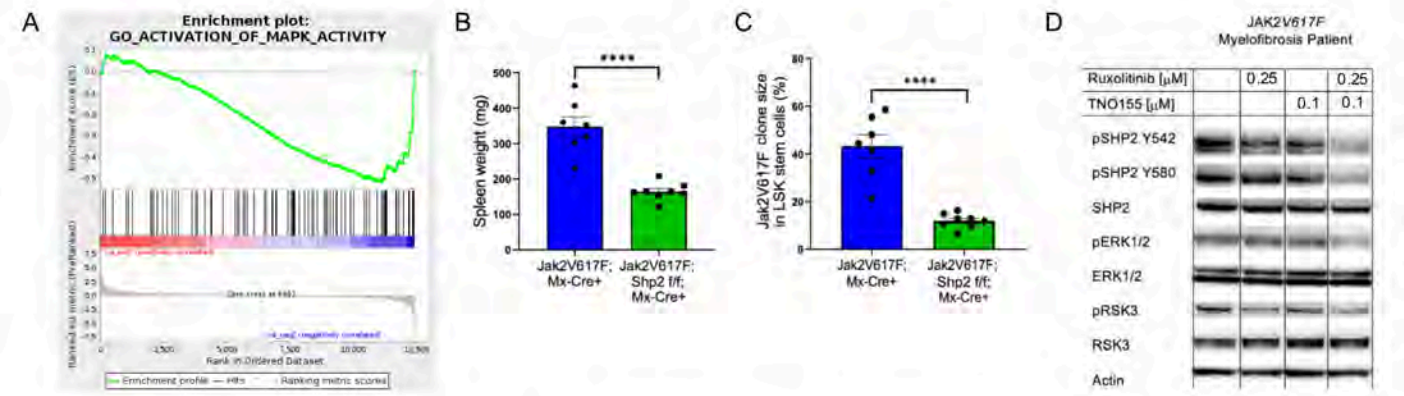

Figure 1. Loss of SHP2 reduces JAK2^{V617F} hematopoietic stem cell clone size and corrects MPN phenotype in preclinical models and patient cells. A: SHP2 loss suppresses MAPK pathway target gene expression as shown by RNA-sequencing and gene set enrichment analysis in Jak2^{V617F} Ba/F3 cells depleted of SHP2. **B:** SHP2 loss in Jak2^{V617} Shp2$^{f/f}$ Mx-Cre transgenic mice significantly reduced splenomegaly 4 weeks after plpC induction. **C.** SHP2 loss in Jak2^{V617} Shp2$^{f/f}$ Mx-Cre transgenic mice significantly reduced Jak2^{V617F} MPN clones in the Lin-Sca1+c-Kit+ (LSK) compartment in competitive bone marrow transplantation settings. **D:** In primary peripheral blood mononuclear cells (PBMCs) of a Jak2^{V617F} myelofibrosis patient, SHP2 inhibitor exposure by TNO155 and JAK2 inhibition by ruxolitinib effectively suppressed activation of SHP2 and MAPK downstream targets incl. ERK1/2 and RSK3.

SSH/SSMO BEST ABSTRACT AWARD – CLINICAL HEMATO-ONCOLOGY

1422

Feasibility of ctDNA and PET guided therapy in untreated DLBCL. preliminary results of the SAKK 38/19 phase II trial

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is an aggressive yet potentially curable lymphoma. Despite extensive research, no regimen has improved overall survival (OS) over R-CHOP. Molecular profiling identified genetic subtypes, notably MCD, which responds poorly to R-CHOP but may benefit from BTK inhibition. Combining circulating tumor DNA (ctDNA) with PET imaging could refine treatment strategies. We report early results of the ctDNA/PET-guided SAKK 38/19 trial.

Methods: SAKK 38/19 (NCT04604067) is a phase II trial enrolling untreated, CD20-positive DLBCL patients (pts) eligible for 6 R-CHOP cycles. A liquid biopsy at baseline determines the genetic subtype. Treatment plan: MCD subtype (Cohort A): 6 cycles of R-CHOP + acalabrutinib; Non-MCD patients: PET/ctDNA response after 2 cycles of R-CHOP guides cohort allocation: Cohort B: 4 more R-CHOP + acalabrutinib, followed by 2 months of acalabrutinib. Cohort C: 2 more R-CHOP + 2 rituximab doses. Cohort D: 4 more R-CHOP cycles. Primary endpoint: Progression-free survival (PFS) (Cohorts A, C, D), complete remission rate (Cohort B). Here we present baseline characteristics, trial feasibility and PET/ctDNA responses after 2 cycles.

Results: Of 230 screened, 134 were registered and 124 evaluable. Median age 65 years (24–91); F:M = 59:65; stages I–II:III–IV = 34:90; IPI 0–1:2:3:4–5 = 33:31:40:20. ctDNA was analyzable in 220 pts, undetectable in 26 (11.8%). Median turnaround time for ctDNA analysis was 9 days; median time from consent to first R-CHOP, 15 days. Twenty-seven pts (21.8%) had MCD subtype (Cohort A). Among 97 non-MCD pts with available ctDNA, the median baseline value was 307 hGE/mL (13–13,167), increasing with higher IPI (p = 0.0003). After 2 cycles, non-MCD pts were allocated B:C:D = 8:38:44. Molecular response was achieved in 84/97 (86.6%); PET2 Deauville 1–3:4:5 = 38:35:11.

Conclusions: Preliminary findings from the SAKK 38/19 trial demonstrate the feasibility of integrating a combined PET and ctDNA assessments for treatment allocation in DLBCL. Baseline ctDNA correlated with IPI score, while a low concordance has been so far observed between molecular response and PET2 after 2× R-CHOP in the non-MCD pts. Future analyses will assess the impact on PFS and OS of this approach and the usefulness of BTK inhibition in pts with MCD DLBCL.

SSMO BEST ABSTRACT AWARD – CLINICAL SOLID TUMOR ONCOLOGY

0645

Single-dose carboplatin and involved-node radiotherapy for seminoma stage IIA/B: long-term follow-up from the international multicenter phase II trial SAKK 01/10

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Introduction: The SAKK 01/10 trial (NCT01593241) tested de-escalated treatment with single-dose carboplatin followed by involved-node radiotherapy (RT) for seminoma stage IIA or IIB. The primary analysis of the trial in 2021 showed favorable progression-free survival (PFS) and minimal toxicity (Lancet Oncol. 2022;23:1441-1450). The current National Cancer Center Network (NCCN) guidelines endorse this regimen as a treatment alternative to standard of care. We report extended follow-up addressing efficacy and safety.

Methods: SAKK 01/10 is a multicenter, single arm, phase II trial of the Swiss Group for Clinical Cancer Research (SAKK) and the German Testicular Cancer Study Group (GTCSG) in patients with seminoma stage IIA/B (de novo or relapse on active surveillance). Treatment consisted of one cycle carboplatin AUC7 followed by involved-node RT (IIA: 30 Gy; IIB: 36 Gy). The primary endpoint was 3-year progression-free survival (PFS). Key secondary endpoints included late renal, thromboembolic and gastrointestinal events as well as secondary malignancies (SM) at least possibly related to treatment.

Results: A total of 120 pts were included and 116 pts were eligible. 46 pts had stage IIA and 70 pts IIB seminoma. Current median follow-up is 8 years (minimal 5.9, maximal 12) for 85 patients still on follow-up. PFS at 10 years is 92.8% (IIA: 95.2%; IIB: 91.3%) and no further events have been recorded since the primary analysis in 2021. OS at 10 years is 99.1% (1 death due to SM). One late thromboembolic event was reported, possibly

related to treatment. A total of 9 cases of SM, including 4 contralateral germ cell tumors, were recorded, none of which were deemed related to treatment.

Conclusions: Extended follow-up of SAKK 01/10 confirms favorable efficacy with no further events in the past 5 years and a 10-year PFS of 92.8%. Furthermore, this novel treatment causes minimal toxicity also in the long-term. Our findings oppose concerns about higher incidence of SM or late toxicities due to the combined treatment. Single-dose carboplatin and involved-node radiotherapy for seminoma stage IIA/B should be considered as a new standard of care given its efficacy, minimal acute toxicity, and long-term safety.

ONCOREHA/OPS/PALLIATIVE.CH/SNIO/SOHC BEST ABSTRACT AWARD – NURSING, SUPPORTIVE & PALLIATIVE CARE, REHABILITATION & SURVIVORSHIP AND INTEGRATIVE ONCOLOGY

3364

Young Survivors Registry – Prospective and Longitudinal Assessment of Health in Survivors of Childhood and Adolescent Cancer

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Introduction: Many survivors of childhood and adolescent cancer experience late effects. Most cohort studies on late effects are retrospective or questionnaire-based, with unavoidable limitations (e.g., different definition/ grading of late effects). The "Young Survivors Registry" overcomes these limitations.

Methods: The "Young Survivors Registry" is multicenter, prospective, and longitudinal and collects data in a standardised way. Survivors already in follow-up care and those just completing cancer treatment are eligible. We excluded survivors with surgery only (outside CNS) and not at risk for late effects according to long-term follow-up care guidelines (COG or IGHG). Data about diagnosis and treatment are collected once. Data about current health, organ systems at risk, and socioeconomic aspects are entered annually and coded according to the modified CTCAE criteria.

Results: To date, 145 survivors are included. Leukemia (47%) was the most frequent diagnosis. The median age at diagnosis was 7.6 years (IQR 3.8 – 12.6). The median follow-up was 14.2 years (IQR 8.8 – 18.5). The annual entries per survivor range up to 20. The endocrine system was affected most frequently at first entry (28%), followed by cardiovascular (22%) and musculoskeletal (18%). The largest increase in prevalence was observed in the cardiovascular (40%), endocrine (27%), and musculoskeletal (16%) system. It took less than 60 minutes for the first data entry including retrospective data collection. The prospective (annual follow-up visits) takes up to 5 minutes, which is feasible directly after the visit.

Conclusions: Our results confirm that late effects are frequent in survivors of childhood cancer with increasing prevalence over time. The prospective data collection is feasible during clinical care. Due to the benefit of the prospective design, such registries should be implements widely. Using the same approach in different registries allows to pool the data and build a rich source for future research in survivorship care.

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

7845

Is dual targeting of FXII and Gas6 a good strategy to prevent thrombosis with no risks of bleeding?

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Introduction: Preventing thrombosis without increasing bleeding remains a key challenge. Safer anticoagulants are being explored by targeting early coagulation factors like FXII. Gas6, a ligand for Tyro3, Axl and Mertk receptors, supports hemostasis, and its inhibition prevents thrombosis in mice without bleeding. Since FXII and Gas6 act via distinct pathways, combined targeting may enhance thrombosis prevention without raising bleeding risk. This study assessed whether dual targeting of FXII/Gas6 offers a bleeding-free antithrombotic approach and explored interplay between both pathways.

Methods: Double knockout mice lacking FXII and Gas6 (F12-/-Gas6-/-) were generated (Fig.1A), with F12-/-, Gas6-/- and wild-type (WT) as controls. Haemostasis was tested by tail bleeding. Thrombosis was assessed by platelet-dependent thromboembolism (VTE), ultrahigh-frequency ultrasound (UHFUS) of vena cava, and intravital microscopy (IVM) of mesenteric arterioles. Ex vivo assays included platelet aggregation, clot retraction, scanning electron microscopy (SEM), plasmin generation (PG), and neutrophil extracellular trap (NET) formation.

Results: F12-/-Gas6-/- mice were viable, phenotypically normal and showed shorter bleeding times than WT (Fig.1B). After VTE induction, all knockout groups survived better than WT. (Fig.1C). Lung histology of survivors revealed less thrombi in WT vs. knockouts (Fig.1D), suggesting reduced thrombus stability and embolization in knockouts. UHFUS showed less vena cava occlusion (Fig.1E), and IVM demonstrated prolonged occlusion times in knockouts (Fig. 1F). Volume reconstruction showed higher fibrin and platelet content in WT thrombi (Fig.1G). SEM revealed similar fibrin coverage and fiber diameter across groups, but Gas6-/- and F12-/-Gas6-/- clots displayed disorganized fiber networks lacking string-like structures (Fig.1H). Platelet aggregation was comparable among groups. PG was accelerated in knockouts (Fig1I). NET formation was reduced in F12-/-Gas6-/- mice (Fig.1J).

Conclusions: Dual targeting of FXII and Gas6 prevented bleeding but increased thrombus instability and embolism risk, likely via accelerated fibrinolysis and reduced NET formation. These data highlight challenges of combined inhibition. Gas6 inhibition alone appears safer for thrombosis prevention and warrants further study as a bleeding-free antithrombotic strategy.

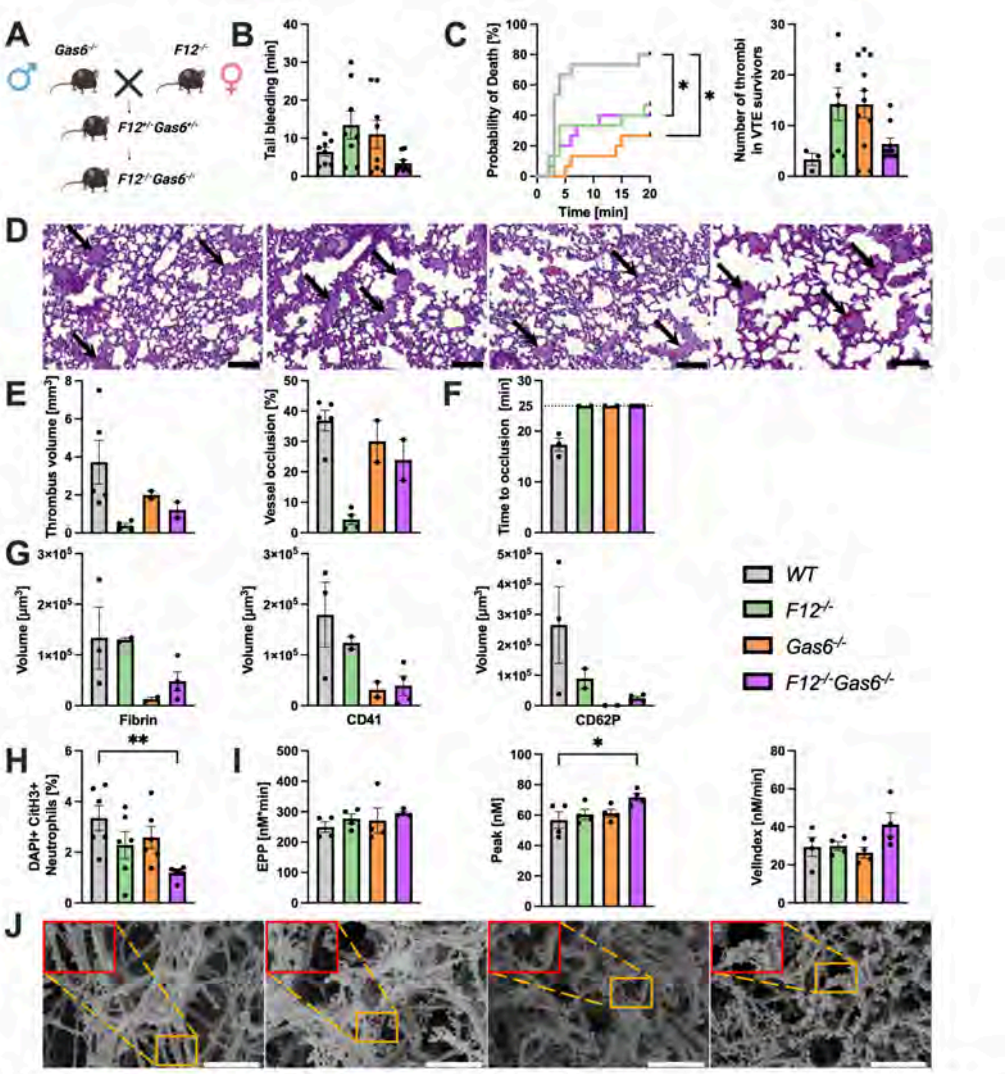

Figure 1: Dual targeting of FXII and Gas6 reduced bleeding but unexpectedly increased thrombus instability and embolism risk. A: Breeding scheme to obtain *F12*$^{-/-}$*Gas6*$^{-/-}$ mice. **B:** Bleeding time recorded in tail bleeding assay. **C, left:** Survival after venous thromboembolism (VTE) induction through collagen/epinephrine injection in the vena cava, n=15, log-rank Mantel-Cox test with Bonferroni's correction for multiple comparisons, Bonferroni's corrected p value = 0.017; **C, right:** Number of thrombi counted in the lungs of survivors of VTE challenge, from histologic sections. **D:** Representative histology of lungs of succumbed mice from VTE challenge. Genotypes from left to right: *WT*, *F12*$^{-/-}$, *Gas6*$^{-/-}$, *F12*$^{-/-}$*Gas6*$^{-/-}$. Scalebar: 100µm. **E, left:** Results of thrombus volume reconstructed from ultrahigh frequency ultrasound (UHFUS) of ferric chloride induced thrombus in the vena cava; **E, right:** Percentage of occluded vessel after UHFUS monitoring. **F:** Results of time for complete occlusion of mesenteric arteriole vessel after ferric chloride thrombus induction, monitored with intravital microscopy. **G:** Volume quantification of fibrin, CD41 and CD62P deposition in mesenteric arteriole vessels at 17 minutes after thrombus induction monitored with IVM. **H:** Percentage of neutrophil extracellular trap forming neutrophils after PMA stimulation, n=6, ordinary one-way ANOVA, p<.05. **I, left:** endogenous plasmin potential measured in platelet poor plasma samples, in a plasmin generation assay. **I, middle:** peak of plasmin produced in a plasmin generation assay, n=4, ordinary one-way Anova, p<.05. **I, right**: concentration (nM) of plasmin generated per minute in a plasmin generation assay. **J:** representative image of the internal structure of clots generated with thrombin in platelet rich plasma (PRP). Genotypes from left to right: *WT*, *F12*$^{-/-}$, *Gas6*$^{-/-}$, *F12*$^{-/-}$*Gas6*$^{-/-}$. Scalebar: 3µm.

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

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Introduction: Emicizumab is approved for routine prophylaxis in adult and pediatric patients with hemophilia A (PwHA) with or without Factor VIII (FVIII) inhibitors The ongoing non-interventional study (NIS) EMIIL is collecting primary observational data in PwHA newly treated with emicizumab in Germany and Switzerland. To better understand the long-term effectiveness of emicizumab prophylaxis in PwHA with and without FVIII inhibitors under real-world conditions.

Methods: EMIIL (ISRCTN58752772) is a single-arm, two-cohort, prospective, multicenter NIS 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. Cohort A includes patients with severe Hemophilia A without FVIII inhibitors; Cohort B PwHA with FVIII inhibitors. Here we report results from the fourth interim analysis.

Results: As of the data cut-off (13 May 2024), 125 patients in Cohort A and 7 in Cohort B were available for evaluation (Table 1). In Cohort A, after a median treatment duration of 918 days (range 190-1608), the model-based ABR for treated bleeds was 0.656 (95% CI 0.516-0.832). Zero treated bleeds were recorded in 44.8% of patients, and zero treated spontaneous, joint, and target joint bleeds were recorded in 76.0%, 66.4%, and 95.2% of patients, respectively. Recorded in 12-week time windows, most patients in Cohort A experienced zero treated bleeds across the study period (range 87.8%-94.2%). In Cohort B, all patients had zero treated bleeds after a median treatment duration of 378 days (77-1260). Overall, 87 of 132 safety-evaluable patients reported 313 adverse events (AEs). In Cohort A (N = 125), 82 patients (65.6%) reported 308 AEs. This included 60 serious AEs in 30 patients (24.0%), 55 adverse drug reactions (ADRs) in 26 patients (20.8%), and 9 serious ADRs in 5 patients (4.0%). One patient discontinued treatment due to an AE, and two patients experienced three fatal AEs. In Cohort B (N = 7), five patients (71.4%) reported five AEs; no serious AEs or ADRs were recorded.

Conclusions: The results from the fourth interim analysis support the effectiveness and safety of emicizumab in a real-world setting. Particularly data on ABR and the proportion of patients with zero bleeds are consistent with results from previous clinical trials. No new safety concerns emerged.

Table 1: Patient demographics and bleeding outcomes of cohort A

Patient demographics	Cohort A N=125	Cohort B N=7
Male, n (%)	125 (100.0)	7 (100.0)
Severity at baseline		
Mild (>5-40% FVIII activity)	0	1 (14.3)
Moderate (1-≤5% FVIII activity)	0	1 (14.3)
Severe (<1% FVIII activity)	125 (100.0)	5 (71.4)
Age (years), mean (SD)	26.34 (21.07)	23.57 (22.62)
Age group, n (%)		
Children (0-11 years)	45 (36.0)	2 (28.6)
Adolescents (12-17 years)	7 (5.6)	2 (28.6)
Adults (18-64 years)	69 (55.2)	2 (28.6)
Elderly (≥65 years)	4 (3.2)	1 (14.3)
Ethnicity, n (%)		
White	113 (90.4)	6 (85.7)
Black or African American	2 (1.6)	0
Asian	2 (1.6)	0
Not reported	8 (6.4)	1 (14.3)
FVIII inhibitor history[a], n (%)		
Yes	5 (4.0)	6 (85.7)
Missing	120 (92.3)	1 (14.3)[c]
Previous hemophilia A treatments, n (%)	117 (93.6)	7 (100.0)
Bleeding outcomes		
Calculated ABR[b], mean (SD)		Not assessed
All treated bleeds	0.67 (0.93)	
Treated spontaneous bleeds	0.27 (0.66)	
Treated joint bleeds	0.37 (0.70)	
Treated target joint bleeds	0.03 (0.14)	
Location of treated bleeds, n patients (%) – n treated bleeds	69 (55.2%) - 159	Not assessed
Joints, n treated bleeds	85	
Muscle, n treated bleeds	8	
Other, n treated bleeds	66	
New FVIII inhibitors, n (%)	3 (2.4)	Not applicable

[a]Highest measurement before start of treatment

[b]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.

[c]For this patient, it was documented that Factor VIII inhibitors occurred before and at start of treatment but no value for Bethesda units was listed.

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

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Temporal phosphoproteomics reveals key regulators of procoagulant COAT platelet generation

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Introduction: Abnormal procoagulant platelet generation leads to bleeding or thrombotic events. Procoagulant (COAT) platelets develop from aggregating (AGG) ones upon stimulation with collagen-plus-thrombin. The mechanisms driving this dichotomous activation are only partially described. We employed temporal phosphoproteomics to identify proteins regulating the procoagulant differentiation.

Methods: Washed platelets from healthy donors (n = 5) were activated by convulxin-plus-thrombin with (COAT-generating condition) or without calcium (AGG-generating condition). Platelets were sampled at different timepoints up to 8min post-activation. Phosphoproteomes of AGG and COAT platelets were analysed by Liquid-Chromatography-Mass-Spectrometry (LC-MS). Phosphosites significantly differentially regulated among AGG versus COAT conditions were identified by Mann-Whitney test.

Results: Temporal phosphoproteomics analysis identified 1404 consistently quantified phosphosites. During the first minute post-activation, prior to the development of the procoagulant response, some phosphosites were already differentially phosphorylated in COAT versus AGG conditions (five hyper- and 38 hypo-phosphorylated). These were ion channels (calcium, sodium, hydrogen, chloride), negative feedback loops, cyclic nucleotide-dependent inhibitory pathways, and cytoskeleton interactors. During the phenotypic development of the procoagulant response (1-3 min post-activation), additional calcium channels, phosphatidylinositol-transfer proteins and regulators of fibrinogen receptor activation were differentially phosphorylated (out of 18 hyper- and 457 hypo-phosphorylated).

Conclusions: Temporal phosphoproteomics identified several proteins differentially phosphorylated early upon platelet activation by convulxin-plus-thrombin. In particular, the 43 phosphorylation events preceding the development of procoagulant platelets from aggregating ones, most likely orchestrate this dichotomous activation pathway. For instance, they may regulate the reverse sodium-calcium exchanger (NCX) functional mode, which is required for the procoagulant response (Thromb Haemost 2021;121:309-321). This work highlights the utility of temporal phosphoproteome analysis to capture timely-regulated processes driving the procoagulant response.

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Modulation of protein S benefits joint integrity and bone health in hemophilia A

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Background and objective: Therapies for hemophilia A (HA) have extended life expectancy to near-normal but do not fully prevent spontaneous or subclinical bleeds, leading to progressive arthropathy. We identified protein S (PS) as a therapeutic target to rebalance hemostasis and developed a liver-targeted PS-siRNA that restored hemostasis and prevented joint bleeding in HA mice. In HA patient synovium, PS levels were lower in those on prophylaxis vs. on-demand therapy. This study aimed to determine how PS reduction protects joints from blood-induced inflammation and supports bone health in HA.

Methods: We used models of recurrent hemarthrosis (RH), autologous intra-articular knee blood injection, macrophage phagocytosis assay, synovial RNA-seq, whole-body dual energy X-ray absorptiometry (DXA), and knee µCT (Fig.1).

Results: In injured synovium, F8−/−Pros1−/− mice upregulated phagocytosis and efferocytosis pathways compared to F8−/− controls (Fig.1A-B). Bone-marrow–derived macrophages from F8−/−Pros1−/− exhibited higher uptake of senescent RBC than F8−/−, though less than WT (Fig.1C). Seven days after intra-articular blood injection, F8−/− knees displayed swelling and persistent RBC deposition, unlike WT or F8−/−Pros1−/−, indicating improved clearance and reduced inflammation with PS deficiency. After RH, genes linked to inflammation resolution were upregulated in WT and F8−/−Pros1−/−, but not in F8−/− synovium. At baseline, F8−/− synovium showed increased expression of bone remodeling and osteoclast differentiation markers, indicating imbalanced osteogenesis (Fig1. B). At 16 weeks, F8−/−Pros1−/− mice had higher whole-body bone mineral density (BMD) and bone mineral content (BMC) than F8−/− (Fig.1D). µCT of knees revealed increased trabecular connectivity density (TCD) and reduced trabecular spacing (TS); TCD remained higher at 22 and 24 weeks (Fig.1E-F). F8−/−Pros1+/− mice showed improved BMD and BMC. µCT in F8−/−Pros1+/− and F8−/− mice treated with PS-siRNA showed trends toward increased TCD and reduced TS, supporting the role inhibition of PS inhibition in preserving bone microarchitecture.

Conclusions: Partial PS reduction (~50%) enhances phagocytosis, promotes inflammation resolution, and preserves joint and bone health in HA mice. Ongoing studies are evaluating PS-siRNA to improve skeletal outcomes and advance clinical translation.

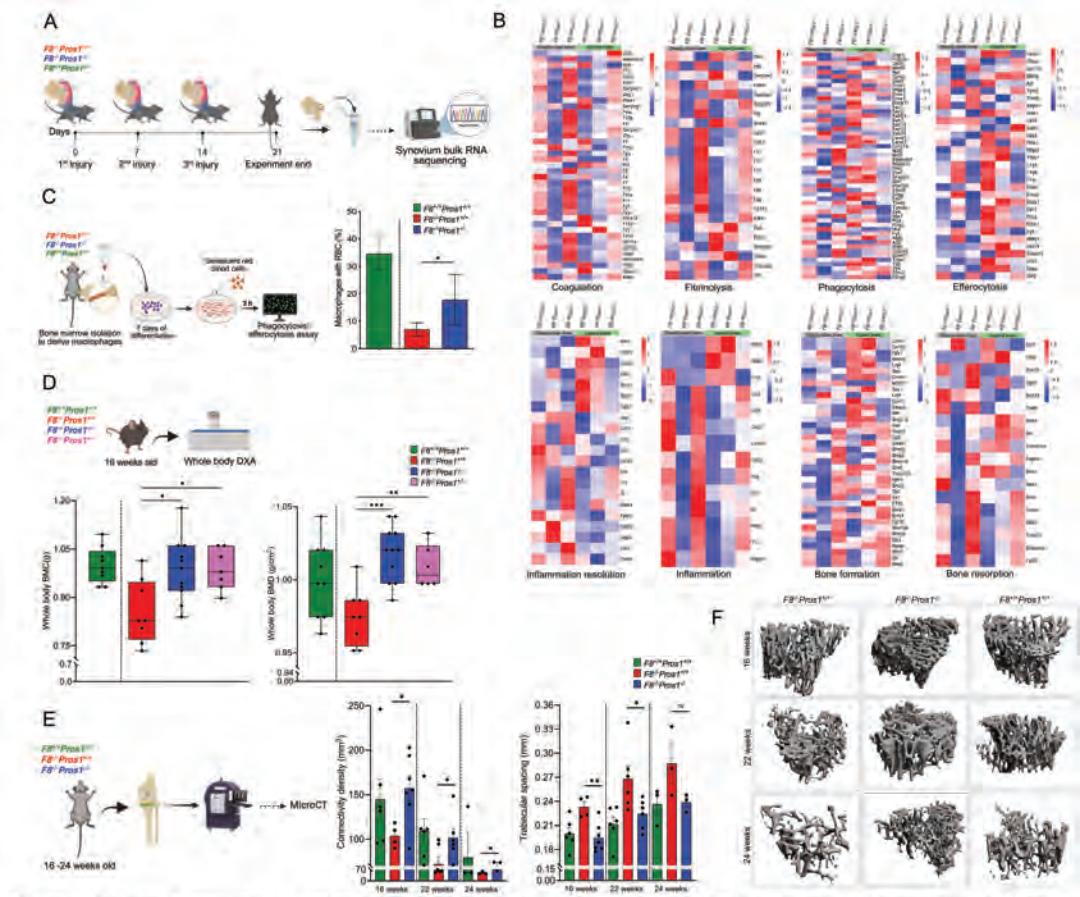

Figure 1: Protein S complete or partial inhibition ameliorates joint and bone health outcome in hemophilia A (A) *F8*$^{+/+}$ *Pros1*$^{+/+}$, *F8*$^{-/-}$*Pros1*$^{+/+}$, *F8*$^{-/-}$*Pros1*$^{-/-}$ mice underwent recurrent hemarthrosis. Right knees were injured using a 30 gauge-needle at 0, 7 and 14 days. Knees were collected at the end of the experiment for synovial tissues bulk RNA sequencing (n=5-6/genotype and condition). Left knee and steady state knee joints were used as controls. (B) Heatmaps for differential expression of mRNAs encoding proteins related to coagulation, fibrinolysis, phagocytosis, efferocytosis, inflammation, inflammation resolution, bone formation and bone resorption. (C) Quantification of phagocytosis of erythrocytes exposing phosphatidylserine by primary bone marrow-derived macrophages. Data are expressed mean±SD, *p<0.05. (D) Relative whole body bone mineral content (BMC) and relative whole body bone mineral density (BMD) were measured using dual energy X-ray absorptiometry in 16 weeks old *F8*$^{+/+}$ *Pros1*$^{+/+}$, *F8*$^{-/-}$ *Pros1*$^{+/+}$, *F8*$^{-/-}$*Pros1*$^{-/-}$, *F8*$^{-/-}$*Pros1*$^{+/-}$. Data are expressed mean±SD, *p<0.05, **p<0.01,***p<0.001, (E) trabecular connectivity denstity and trabecular spacing assessed by microcomputed tomography (µCT) in *F8*$^{+/+}$ *Pros1*$^{+/+}$, *F8*$^{-/-}$*Pros1*$^{+/+}$, *F8*$^{-/-}$*Pros1*$^{-/-}$ mice at 16, 22 and 24 weeks. (F) Representative rendered µCT images of trabecular structure in mice at 16, 22 and 24 weeks. Data are expressed mean ± SD. ns, not significant, *p<0.05.

4090

NET formation contributes to clinical relapses but not ADAMTS13 biomarker relapses in immune-mediated thrombotic thrombocytopenic purpura (iTTP)

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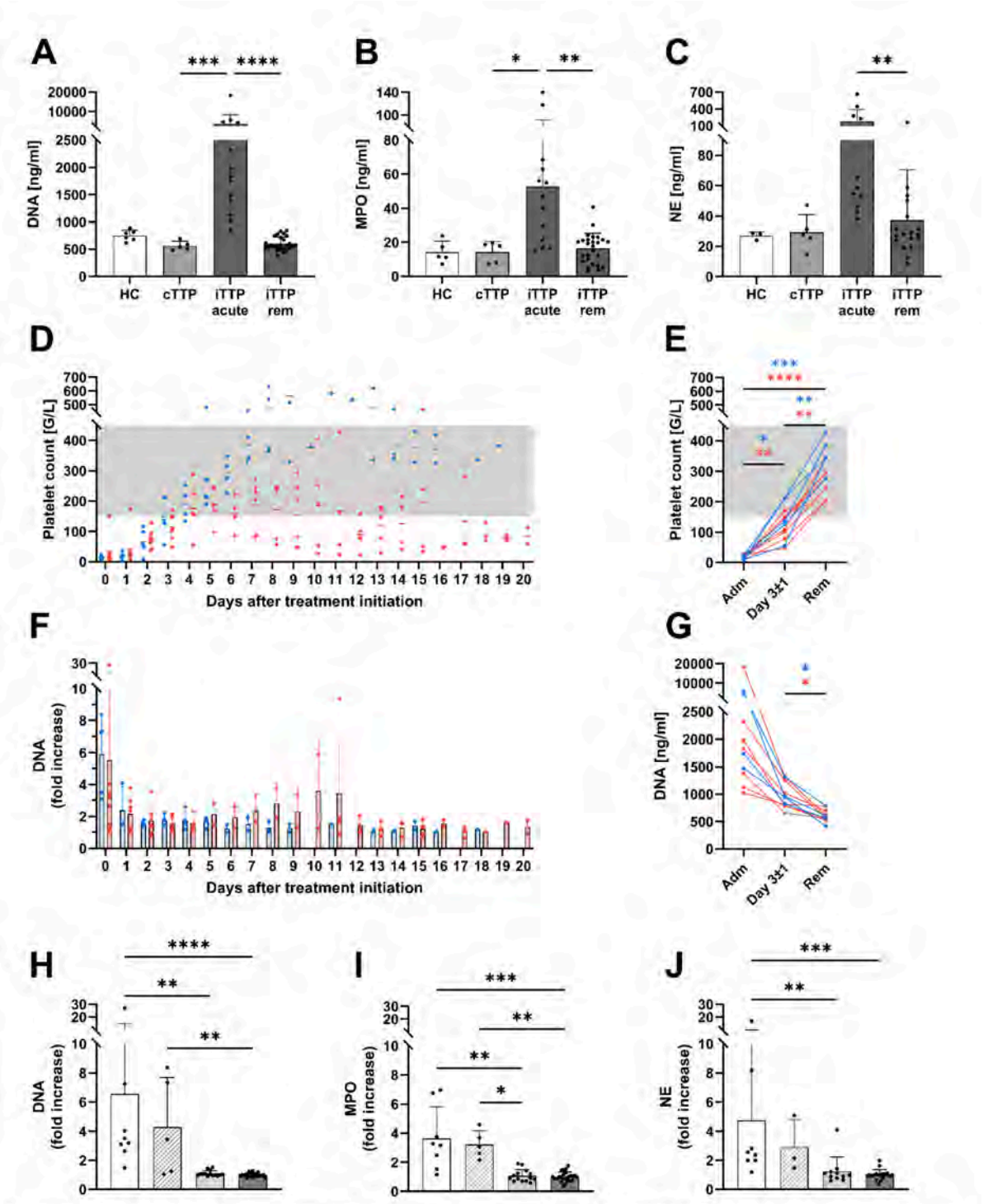
Introduction: Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a thrombotic microangiopathy (TMA) caused by a severe acquired ADAMTS13 deficiency, resulting in persistence of ultra-large von Willebrand Factor (VWF) in circulation. Treatment rests on three pillars, therapeutic plasma exchange (TPE), immunosuppression, and caplacizumab, a nanobody that prevents platelet binding to VWF. Neutrophil extracellular traps (NETs) contribute to thrombus formation in TMAs, yet their role in association with various clinical stages of iTTP and under different treatment modalities remains to be investigated.

Methods: We conducted a retrospective, observational study in 8 patients with confirmed iTTP who were followed for 7.4 (range 0.4-15.2) years. We studied their first acute episodes (3/8 treated with, 5/8 without caplaci-zumab), 14 ADAMTS13 relapses, and 6 clinical relapses (2 treated with, 4 without caplacizumab). Remission samples were used as patient baselines and controls. Besides clinical and ADAMTS13 parameters, we measured circulating NET markers, DNA, myeloperoxidase (MPO), neutrophil elastase (NE), and citrullinated histone H3 (CitH3).

Results: All NET markers were significantly elevated at presentation with acute iTTP episodes and declined during treatment. The rate of NET marker reduction at 3 days post-treatment initiation was similar in patients treat-ed with and without caplacizumab (DNA -61% ± 21% vs. -49% ± 23%; MPO -15% ± 49% vs. -46% ± 33%; NE -55% ± 36% vs. -49% ± 31%). During ADAMTS13 relapses NET markers remained at baseline (DNA 1.1-fold; MPO 1.1-fold) while at time of overt clinical relapse increases were documented (DNA 4.3-fold; MPO 3.2-fold). Longitudinal analysis of platelet counts over a 20-day period following treatment initiation revealed a more sustained platelet count recovery in the caplacizumab-treated group. Without caplacizumab platelet counts dropped below the normal range (<150 G/L) after the first week of treatment, which was reciprocally paralleled by an increase in plasma DNA and MPO levels (days 5-11).

Conclusions: Our findings demonstrate that NET formation is a prominent feature of acute iTTP episodes but is not solely driven by ADAMTS13 deficiency. This study provides pathophysiological support for the use of caplacizumab in acute iTTP episodes, for regular follow-up of iTTP patients, and pre-emptive immunosuppressive treatment to prevent clinical relapses.



Comparable decrease of NET markers, but different platelet recovery patterns across treatment regimens in acute iTTP. Plasma levels of NET markers, DNA (A), MPO (B) and NE (C), were elevated during acute iTTP episodes (DNA, MPO: n = 13; NE: n = 11) compared to remission (DNA, MPO: n = 26; NE: n = 18). Severe thrombocytopenia (E) recovered and circulating DNA (G) decreased by day 3 ± 1 and normalized at remission in both treatment groups. In patients treated without caplacizumab, a trend towards a secondary increase in plasma DNA (F) was observed between days 5 to 11, coinciding with a decline in platelet count (D). DNA (H), MPO (I), and NE (J) were not elevated during ADAMTS13 biomarker relapse (n = 14) but remained at concentrations comparable to those measured during remission (DNA, MPO: n = 26; NE: n = 18). n: number of events/samples; HC: healthy controls; cTTP: congenital TTP; iTTP acute: first acute episodes and clinical relapses; iTTP rem: iTTP remission; Adm: admission; Rem: remission; Grey: platelet count reference range 150-450 G/L. Data is reported as mean ± SD. (F,H-J) are presented as fold change over the patients' respective remission samples and statistics were performed on log2-transformed values. (A-C,H-J) Kruskal-Wallis test; (D,F) Multiple Mann-Whitney tests; (E,G) Repeated measures two-way ANOVA; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$.

6079

Clinical impact of pathogen-reduced platelet concentrates stored for up to 7 days in routine use in patients receiving allogeneic haematopoietic stem cell transplantation in Switzerland

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Introduction: In 2011, pathogen inactivation (PI) of platelet components (PC) using amotosalen and UVA light was introduced in Switzerland, resulting in a longer shelf life (7 vs. 5 days) for PI PC in comparison to conventional gamma irradiated PC. The clinical efficacy of PI PC was debated. We aimed to retrospectively assess the clinical impact of this measure in the first 100 days after allogeneic HSCT, the time of most intensive need of PC and red blood cell (RBC) transfusion.

Methods: A retrospective two period comparative study to assess the transfusion requirements and standard allogeneic HSCT outcomes (survival, therapy related mortality and development of GvHD) of all consecutive patients from d+100 after first allogeneic stem cell transplantation at the 3 adult allo -centres in Switzerland 5 years before (2006-2010, period 1, P1) and 5 years after (2011- 2016, period 2, P2) the introduction of pathogen inactivation of PC.

Results: A total of 1930 patients were analyzed (635 in P1, and 1295 in P2). Diagnoses were distributed equally in the two periods. In P2, patients were older ($p < 0.01$, more donors were unrelated $p < 0.01$). In all, in P2 EBMT Risk score was higher $p < 0.01$). PLT usage was 10,3 platelet components in P1 in the first 100 days vs 11,3 ($p < 0.01$) in P2, showing a considerable inter centre difference. RBC usage was 8,16 vs 8,15 ($p = 0.681$) in both periods. There was a statistically significant difference between the 2 periods on survival and cumulative incidences of therapy-related mortality (TRM) and acute and chronic GvHD at d100 and after 5 years ($p < 0.01$).

Conclusions: The use of amotosolen- UVA pathogen inactivated PC with storage up to 7 days yielded in more PLT transfusions, but did not result in an increased need of RBC usage and did not have a negative impact on transplant related mortality, survival or GvHD at day 100- or 5-year post allo HSCT as compared to conventional gamma irradiated PC stored for 5 days in this two period retrospective study.

SSH/SSMO ORAL PRESENTATION – EXPERIMENTAL HEMATOLOGY / ONCOLOGY

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Clinical transcriptomics reveal therapeutically highly relevant alterations in adult Ph- B-ALL

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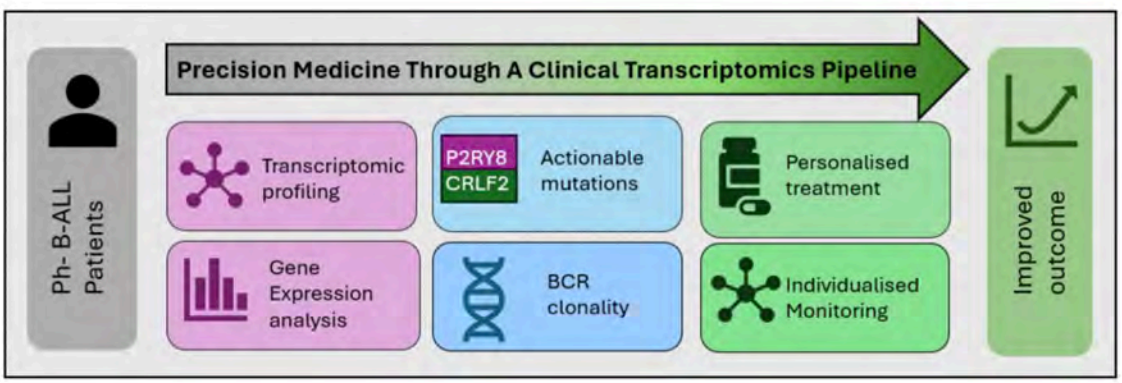
Introduction: Curative-intended treatment of B-acute lymphoblastic leukemia (B-ALL) often relies on intensive chemotherapy regiments and frequently allogeneic stem cell transplantation. The translocation causing the Philadelphia-Chromosome (Ph+, BCR::ABL1) occurs in 20-30% of adults and historically conferred poor outcomes, but ABL1-directed tyrosine kinase inhibitors (TKI) have greatly improved survival and enabled chemotherapy-free regimens. "Philadelphia-like" (Ph-like) driver alterations are functionally similar and targetable, yet heterogeneous and often missed by conventional diagnostics.

Methods: We implemented a clinical transcriptomic pipeline and analyzed whole-RNA from 28 consecutive patients with Ph-negative B-ALL treated at our center (2020-2025). RNA was extracted from bulk samples with >50% tumor cells using a strand-preserving kit. A short-read sequencing library was synthetized and sequenced on an Illumina NovaSeq X Plus sequencer. Target sequencing depth was >20 million 150bp PE read pairs. After aligning to the GRCh38 reference genome using the STAR aligner, fusion transcripts were called using Arriba. The transcriptional profile was inferred using the AI tool ALLCatchR.

Results: Ph-like defining alterations were detected in 8/28 (29%) cases; among these activating PDGFRB transcripts (n = 2), , activating ABL2 Fusions (n = 2), an enhancer-capture translocation of CRLF2 (n = 1), an activating JAK2 fusion transcript (n = 1), an activating LYN fusion transcript (n = 1), and an activating ERBB4 fusion (n = 1). All were potentially actionable by available TKIs, which could have been incorporated into frontline regimens. As none of those alterations had been previously detected by conventional cytogenetics, they were all unknown at the time of diagnosis and only 2/8 patients received such genomically guided therapies.

Conclusions: Clinical transcriptomics proved reliable and clinically highly relevant as it revealed actionable alterations in nearly a fourth of patients with Ph- B-ALL, previously undetected by conventional cytogenetics. These data support adoption of transcriptome-based profiling as a diagnostic standard in the work-up of Ph- B-ALL.



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Dual inhibition of JAK2 and Gas6/TAM signaling mitigates disease progression and vascular complications in polycythemia vera

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Introduction: Polycythemia vera (PV) is a JAK2-driven myeloproliferative neoplasm with excessive red cell production. Current therapies (phlebotomy, cytoreduction, ruxolitinib/RUX) often provide incomplete control, leaving risks of progression, thrombosis, and bleeding. Growth arrest–specific gene 6 (Gas6), a TAM receptor ligand (Tyro3, Axl, Mertk), regulates erythropoiesis and hemostasis and becomes essential under pathological stress. We examined the role of Gas6 in PV and whether its inhibition by batiraxcept (BAT) enhances RUX efficacy.

Methods: A tamoxifen-inducible JAK2 exon 12 mouse model (Jak2Ex12), with or without Gas6 (Gas6-/-Jak2Ex12), was used (Fig.1A). Disease was assessed at 4–6 weeks by blood counts and spleen weight. Splenic erythropoiesis was analyzed by flow cytometry. Bleeding was tested via saphenous vein puncture (SVP), and thrombosis by $FeCl_3$-induced vena cava injury with ultrasound. For therapy, mice received RUX or RUX+BAT.

Results: Six weeks after PV induction, Jak2Ex12 mice showed pronounced erythrocytosis and splenomegaly compared to Gas6-/-Jak2Ex12 mice, which had ~26% smaller spleens, indicating a milder phenotype (Fig.1B-D). Histology confirmed reduced extramedullary hematopoiesis and better-preserved splenic architecture in Gas6-/-Jak2Ex12 mice. RUX+BAT led to no significant change in hematocrit but yielded a substantial improvement in the reticulocyte count (Fig.1E-F). RUX reduced spleen weight by 46%, while RUX+BAT achieved a 72% reduction (Fig.1G-H) and corrected abnormal erythroid differentiation (Fig.1I). In Jak2Ex12 mice, plasma Gas6 levels were lower than in WT but increased with RUX, suggesting that RUX may upregulate Gas6 expression or stability, potentially sustaining erythropoiesis (Fig.1J). As assessed by SVP, the average bleeding episode (ABE) was prolonged in both Jak2Ex12 and Gas6-/-Jak2Ex12 mice compared to WT, accompanied by fewer hemostatic events. RUX normalized both parameters (Fig.1K-L). Thrombus volume was reduced in RUX-treated mice (Fig.1M).

Conclusions: Gas6 deletion mitigates PV, supporting its role in disease proliferation. RUX+BAT improved splenomegaly and erythroid differentiation, though high hematocrit persisted, indicating longer therapy is needed. Preliminary data also implicate Gas6 in clotting abnormalities. Ongoing Jak2V617F studies are evaluating combined therapy's effects on erythropoiesis, thrombosis, and hemostasis.

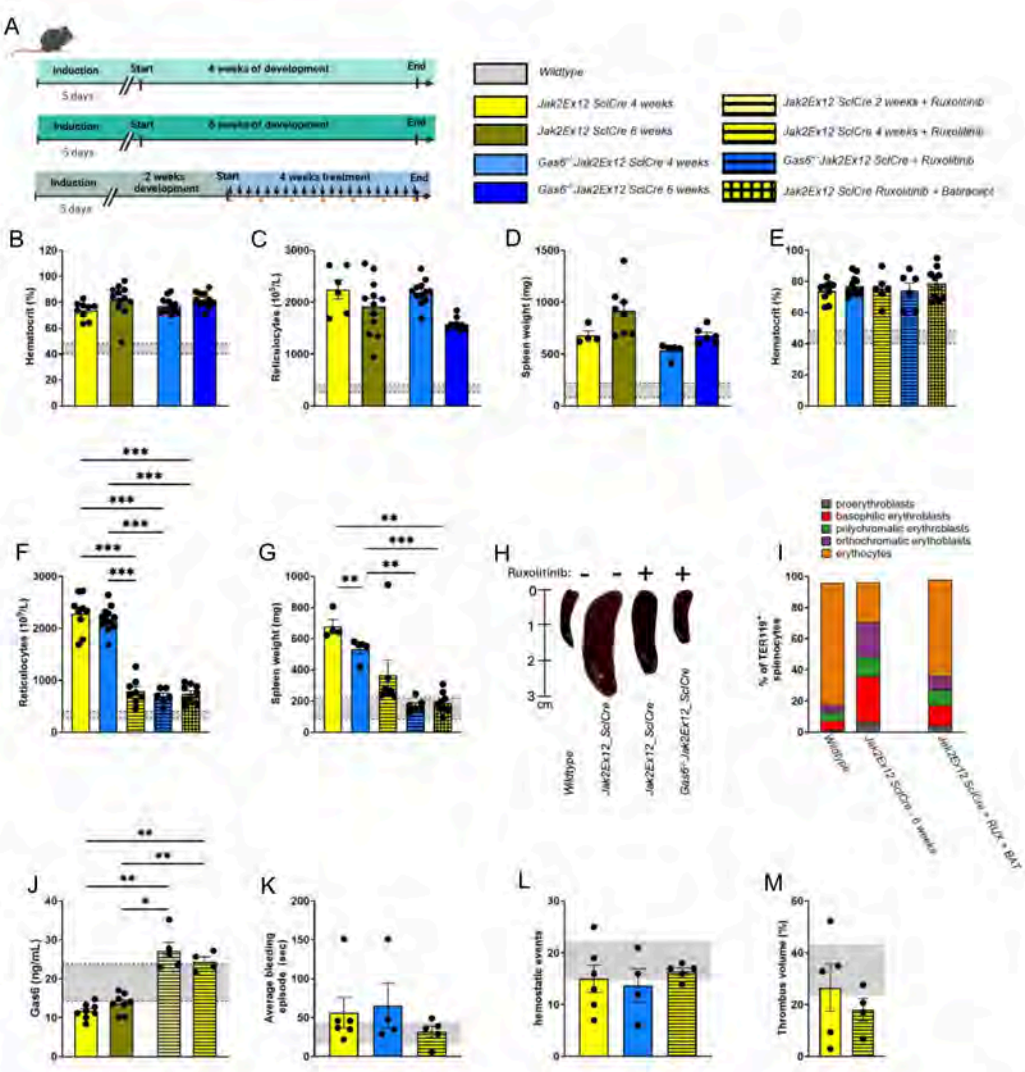

Figure 1: Gas6 deletion mitigates the PV phenotype, while the combination of Batiraxcept and Ruxolitinib significantly improves disease control. A: Schematic representation of the experimental design using tamoxifen-induced *JAK2exon12* (*E12*)knock-in mouse models. Tamoxifen was administered for 5 consecutive days, after which mice were analyzed at 4 or 6 weeks of disease development. Starting 2 weeks after induction, mice were treated for 4 weeks with ruxolitinib (60 mg/kg twice daily; black arrows) or with ruxolitinib plus the Gas6/Axlinhibitor batiraxcept (5 mg/kg subcutaneously every 3 days; orange arrows). B: hematocrit levels, reticulocyte counts (C), spleen weight (D) at different time points. The grey shaded area indicates the wildtype reference range, n=4-12.E: hematocrit levels, reticulocyte counts (F), spleen weight (G)after treatment. H: Representative pictures of spleen from different mice treated with ruxolitinib or vehicle. I: Flow cytometry analysis of splenic erythroid progenitors using TER119/CD71staining to quantify proerythroblasts, basophilic, polychromatic, and orthochromatic erythroblasts, as well as mature erythrocytes, n=4-5. J: Gas6 antigen levels in plasma. The grey zone represents the wild-type range, n=5-8. K: Saphenous vein bleeding assay, including averagebleeding episode and number of hemostatic events (L). Greyshaded area indicates wild-type reference range, n=3-6. M: *In vivo* thrombus volume in the vena cava was evaluated 30 minutes after $FeCl_3$injury. Using an ultra-high-frequency ultrasound system, 3D reconstructions of the inferior venacava and thrombus were generated to calculate the percentage of thrombus volume relative to the total vessel volume, n=4-5* P<0.05,**P<0.01,***P<0.001

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JAK2 signalling to HNRNPA1 represses retrotransposon activity in haematopoietic stem cells and protects the genome.

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Introduction: Retrotransposon expression must be tightly controlled, particularly in long-lived multipotent stem cells, to prevent deleterious consequences including insertional mutations. Integration of retrotransposable elements into host genomes has provided a major source of genetic variation across evolution but has also generated many sequences that have acquired advantageous host functions. Little is known about retrotransposon expression and mobility in adult stem cells or about how these processes might be dynamically regulated. Here we describe the landscape of somatic retrotransposition in haematopoietic stem cells and identify a previously unrecognised pathway which links cytokine signalling, RNA-modulating HNRNP complexes and repression of retrotransposon activity.

Methods: To detect rare somatic retrotranspositions amidst the plethora of preexisting repetitive elements littering the genome we developed a highly specific and sensitive method that was applied to whole genome sequencing data of single-cell derived samples of haematopoietic stem cells (HSCs).

Results: Somatic retrotransposon integrations do contribute to the mutational landscape of HSCs with a much higher rate of insertions per HSC-year in mice than in humans. HSCs in both species accrue many fewer insertional mutations than colorectal epithelium indicating that HSCs are relatively well-protected from retrotransposition. We found that thrombopoietin and activated JAK2 reduced retrotransposon expression in mouse and human HSCs. A phosphoproteomic screen revealed that thrombopoietin signalling causes direct phosphorylation of HNRNPA1 by JAK2. We generated several phosphomutant mouse- and cell-lines to show that HNRNPA1 phosphorylation is required for the repression of retrotransposons and prevents insertional mutagenesis.

Conclusions: Repression of retrotransposon activity is essential to protect eukaryotic genomes from insertional mutagenesis, a hazard that is particularly perilous in long-lived stem cells. Here we demonstrate a direct link in HSCs between cytokine signalling, HNRNP function and retrotransposon activity. The MPL/JAK2/NHRNPA1 pathway described here provides a mechanism for integrating retrotransposon activity with cellular context or state and also for coordinating cytokine-induced proliferation with protection against the increased risk of retrotransposition during cell division.

0147

Divergent Effects of Tet2- and Dnmt3a-mutant Clonal Hematopoiesis on Breast Cancer Progression Upon Aging

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Introduction: Clonal hematopoiesis of indeterminate potential (CHIP) is defined by the expansion of a somatic blood cell clone carrying mutations in leukemia driver genes, commonly in DNMT3A or TET2, at a variant allele frequency >2% without other hematological abnormalities. CHIP incidence increases with age and is associated with elevated risks of hematologic malignancies and all-cause mortality, which is associated with pro-inflammatory immune responses. Recent studies report higher CHIP prevalence in solid tumor patients, including elevated breast cancer risk in CHIP carriers. However, whether and how CHIP-mutant hematopoietic cells influence solid tumor manifestation and progression remains poorly understood. We hypothesize that Tet2- or Dnmt3a-driven CHIP contributes to breast cancer incidence, growth, and/or metastasis by modulating the tumor immune microenvironment.

Methods: To test this, we developed transgenic mouse models of CHIP, where floxed Tet2 or Dnmt3aflR878H alleles alongside a reporter gene are controlled by inducible CreER. These were combined with a syngeneic, orthotopic, and traceable breast cancer model using E0771 cells, in both young (3–4 months) and middle-aged (12–14 months) mouse cohorts, achieving ~70% mutant leukocyte chimerism. Tumor growth and metastasis were monitored longitudinally, supported by histology, flow cytometry, and scRNA-seq to elucidate molecular mechanisms.

Results: Young Tet2+/- CHIP mice exhibited similar primary tumor growth, but increased lung metastasis compared to WT animals. In middle-aged mice, Tet2+/- CHIP led to significantly enhanced tumor growth and metastasis, accompanied by reduced tumor-infiltrating Tet2+/- CD8+ and NKT cells. In contrast, both young and middle-aged Dnmt3aflR878H CHIP mice showed slower tumor growth with no change in metastasis. Preliminary scRNA-seq revealed suppressed T-cell responses in middle-aged Tet2+/- CHIP mice, while Dnmt3aflR878H CHIP animals showed enriched type I interferon signatures.

Conclusions: These findings suggest age and CHIP mutations synergistically influence breast cancer progression by reshaping tumor-infiltrating immune populations. Further investigation is needed to define the molecular mechanisms and therapeutic implications of CHIP in solid tumor contexts.+

4236

Drivers of Therapy-Related Clonal Hematopoiesis and Its Progression to Myeloid Neoplasms

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Introduction: Myeloid neoplasms post cytotoxic therapy (MN-pCT) frequently arise from clonal hematopoiesis (CH). While age-related CH is dominated by DTA mutations (DNMT3A, TET2, ASXL1) therapy-related CH (t-CH) is associated with DNA-damage-response pathway (DDR) mutations (PPM1D, CHEK2, TP53). How the interplay of CH and cytotoxic therapies

governs clonal expansion and transition to MN-pCT remains unclear.

Methods: We compared mutational landscapes of 72 MN-pCT and 399 de novo MN cases from our institution. To define DTA- and DDR-mutation frequencies across healthy individuals and how these change throughout cancer diagnosis, cytotoxic therapy and leukemic transformation, we meta-analyzed 21 studies (>760.000 subjects) and assessed carrier frequencies in all cohorts. We generated hematopoietic stem and progenitor cell (HSPC) lines with Dnmt3a, Tet2, Asxl1, Ppm1d, Chek2 or Trp53 mutations and assessed responses to genotoxic stress, i.e. cell cycle control, apoptosis, p21 activation, DNA repair, drug resistance, clonal competition and malignant transformation across major cytotoxic drug classes. Transplantation-based bone marrow chimeras with 5% DDR-mutant cells were used to monitor clonal expansion and MN-pCT development under irradiation. Obtained MN-pCT were characterized by immunophenotyping, whole-genome sequencing, karyotyping and immunohistochemistry.

Results: PPM1D and TP53 mutations were enriched in MN-pCT versus de novo cases. Across >760.000 subjects, both DTA and DDR mutations were more prevalent in cancer patients versus healthy individuals, but only DDR mutations were enriched post-therapy, with TP53 mutations uniquely enriched in MN-pCT compared to post-therapy patients. Functionally, Trp53 deficiency led to strongest defects, broad resistance, and clonal dominance in response to cytotoxic stress, while Ppm1d and Chek2 mutations conferred modest, drug-specific resistance. Malignant transformation occurred exclusively in Trp53-mutant HSPCs, with complex karyotypes emerging after platinum, etoposide, and melphalan treatment. In vivo, DDR-mutant cells expanded after irradiation, but only Trp53-mutant chimeras developed lethal MN-pCT.

Conclusions: DDR but not DTA mutations promote t-CH, while only TP53-mutant CH drives near-universal transition to MN-pCT. CH screening prior to cytotoxic therapy may guide treatment decisions in cancer patients with less leukemogenic therapeutic alternatives.

3868

A Human CRISPR-Engineered MLLr Leukemia Model Enables Functional Analysis Across MLL Fusion Variants

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Introduction: Acute leukaemias with MLL (KMT2A) rearrangements (MLLr) are an aggressive malignancy subtype associated with poor outcomes, particularly in infants. Most fusions occur within MLL exons 8-14, with AF4 (AFF1) and AF9 (MLLT3) being frequent partners. We established a CRISPR/Cas9-based model for MLL-AF4 and MLL-AF9 leukaemias with breakpoints in intron (i.) 9 or 11 of MLL. This model allows for the detailed characterisation of the influence of the MLL breakpoint and fusion partner on leukaemogenesis in vitro and in vivo.

Methods: MLL rearrangements were induced in human cord blood-derived CD34+ cells and kept in liquid culture. Pure MLLr cells were characterised by flow cytometry (FACS), RNA sequencing (RNA-seq), and colony-forming assays (CFUs). To assess their behaviour in vivo, cells were transplanted into NOD scid gamma mice. At signs of illness or after one year, mice were sacrificed and engrafted cells from the bone marrow were analysed by FACS and RNA-seq.

Results: Compared with healthy controls, MLLr cells showed increased proliferation, upregulation of AML-associated markers (CD32, CD9, CD123), and downregulation of the differentiation marker CD14. Transcriptomic profiling revealed that both fusion partner and breakpoint influenced gene expression and correlated with functional traits such as self-renewal in CFUs. Notably, while MLL-AF4 and MLL-AF9 cells with breakpoint in i.9 displayed high self-renewal in vitro, only MLL(i.9)-AF9 cells robustly engrafted in vivo. By FACS, we detected higher CD52 expression and a population of tumour-supportive M2 macrophages, both of which may have supported engraftment of MLL(i.9)-AF9 cells. Despite >90 days of myeloid in vitro culture, MLL(i.9)-AF9 cells maintained lineage plasticity, switching in vivo from myeloid (CD33+ CD19-) to B lymphoid (CD33- CD19+) identity. RNA-seq revealed transcription factor networks that primed the cells for lineage switching. Moreover, individual mice represented distinct stages of B-cell differentiation, reflected in immunophenotype and stage-specific transcriptional programs.

Conclusions: We show that not only the MLL fusion partner but also the breakpoint contribute to different leukaemic properties. Our model can be further utilized to explore in detail how MLL fusion partners and breakpoints influence leukaemia biology and offers a platform to uncover therapeutic vulnerabilities for personalised treatment.

7670

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

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Introduction: Acute Myeloid Leukemia (AML) is an aggressive hematologic malignancy, originating in the hematopoietic stem and progenitor cell compartment, with overall poor clinical outcome. T-cell engaging bispecific antibodies (TCEs) redirect T-cells to antigen expressing cells independently of MHC/TCR but face two challenges in AML. Many TCEs target cell of origin antigens rather than tumor specific antigens, and overlapping expression on healthy HSPCs risks irreversible aplasia that requires hematopoietic stem cell transplantation, so hematopoietic stem cells directed therapies need controllable effector activity. CD3 directed TCEs also lack a co stimulatory signal (e.g., CD28 or 4 1BB) present in second generation chimeric antigen receptor (CAR) T-cells, limiting T-cell efficacy. We evaluated whether adding a CD33xCD28 IgG4 scFv2 bispecific engager to a CD117xCD3 TCE enhances T-cell activation and AML cytotoxicity.

Methods: We generated a tandem single chain variable fragment (scFv) TCE targeting CD117 and CD3 (CD117xCD3) and an IgG-Heavy Chain-scFv TCE targeting CD33 and CD28 (CD33xCD28 IgG4-scFv2). In vitro safety studies assessed potential CD28 superagonism. The combination was evaluated against two AML cell lines with low, intermediate and high CD117 expression and against primary AML samples. Real-time imaging quantified target-effector dynamics and specificity assays assessed selective activity.

Results: The antibody bound its intended target. CD33xCD28 IgG4-scFv2 alone did not induce antigen-specific target lysis,

T-cell activation or proliferation, indicating absence of CD28 superagonism. Combining CD33xCD28 IgG4-scFv2 and CD117xCD3 improved T-cell activation, proliferation and specific lysis versus CD117xCD3 monotherapy across all models. The CD33xCD28 IgG4-scFv2 reduced effector-target attachment times and increased attachment and killing rates. Combination treatment preferentially eliminated dual positive population (CD117+CD33+) cells.

Conclusions: Adding a CD28 targeted bispecific engager to a CD117×CD3 TCE augments T cell responses against AML targets in vitro without evidence of CD28 superagonism. This strategy improves cytotoxicity, kinetics and selectivity and warrants further preclinical development.

SSH/SSMO ORAL PRESENTATION – CLINICAL HEMATO-ONCOLOGY

7753

Immune Effector Cell–Associated Hemophagocytic Lymphohistiocytosis Following CAR T-Cell Therapy: A Real-World Analysis from a Single Center

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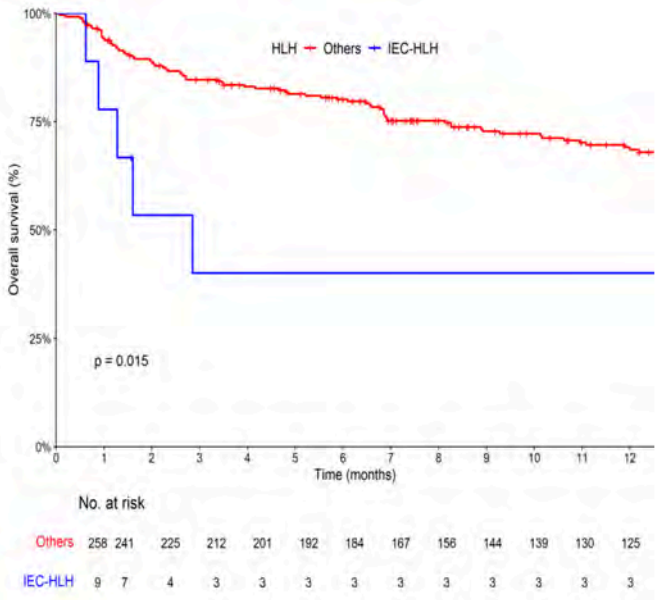
Introduction: Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HLH) is a rare, life-threatening toxicity following CAR T-cell therapy. Its diagnosis is challenging due to overlap with cytokine release syndrome (CRS) and lack of standardized criteria. The American Society for Transplantation and Cellular Therapy (ASTCT) recently defined IEC-HLH to better characterize this entity, though data on clinical characteristics, optimal management, incidence and outcome remain limited.

Methods: We performed a retrospective single-center analysis to assess incidence, diagnostic features, clinical presentation, and management of IEC-HLH in patients with hematologic malignancies treated with CAR T cells at an academic institution.

Results: We reviewed 267 patients treated with CAR T-cell therapy between January 2019 and July 2025. IEC-HLH was identified in 9 patients (pts) (3%) with underlying diseases including DLBCL (3 pts), MM (4 pts), MCL (1 pt), and B-ALL (1 pt). Risk factors included high tumor burden, elevated ferritin (median 1372 µg/l), cytopenias, and increased LDH (median 316 U/l). All patients developed CRS prior to onset of IEC-HLH, which occurred at a median of 10 days post-infusion. Clinical features included hyperferritinemia, pancytopenia, and hepatic dysfunction. All patients showed a marked expansion of CAR T cells (median 53,542 copies/ml). Treatments included corticosteroids (7/9) and anakinra (8/9); in addition, siltuximab, etoposide, or tocilizumab were given in selected cases. Infectious complications occurred in 7 patients, primarily bacteremias; 2 patients had mixed infections (bacteremia with CMV viremia; bacteremia with mucormycosis). IEC-HLH resolved in 5 patients (56%) after a median of 8 days, while 4 (44%) patients died due to active HLH with or without concurrent infection. At last follow-up, 3/9 (33%) were alive, all with MM treated with BCMA-directed CAR T cells.



Conclusions: IEC-HLH occurred in 3% of CAR T-cell recipients and was associated with high morbidity and mortality. Early identification and timely immunosuppressive therapy are critical. Ferritin, LDH, and early CAR T-cell expansion may help identify patients at risk. Further multicenter studies are needed to refine diagnostic criteria, validate predictive biomarkers and standardize treatment strategies.

3954

Real world experience with maintenance treatment after allogeneic hematopoetic cell transplantation for myeloid neoplasia

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Introduction: Maintenance therapies after allogeneic hematopoietic cell transplantation (HCT), such as hypomethylating agents, FLT3 inhibitors and donor lymphocyte infusion are increasingly explored to reduce relapse risk and improve outcomes in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).

Methods: In this observational study, we analyzed 216 patients diagnosed with AML, or MDS, who underwent HCT at our institution. Our primary objective was to assess the impact of maintenance strategies on overall survival, leukemia-free survival (LFS), and relapse rates. We further investigated how measurable residual disease (MRD) status at HCT, the presence of molecular alterations, and patient age modulate outcomes following these maintenance approaches.

Results: Of eligible patients, 61 (28.2%) received hypomethylating agents (HMA), 7 (3.2%) received DLI alone, 46 (21.3%) received DLI and HMI, 36 (16.7%) received FLT3 inhibitors, and 66 (30.6%) received no maintenance treatment in spite of being eligible for various reasons. Maintenance treatment was started at a median of 74 days after HSCT. The two-year survival rates for patients receiving no treatment, HMA, DLI, HMA and DLI, and FLT3 inhibitors were 58% (+/- 12%), 60% (+/- 13%), 100%, 56% (+/- 16%), and 68% (+/- 16%), respectively (p = 0.24). The two-year survival rates by age was 89% (+/-10%) survival rate for age under 40 years, 58% (+/-11%) for 40-60 years of age

and 51% (+/-11%) for patients older than 60 years (p <0.001). Patients with TP53 mutation had a two-years survival rate of 25% (+/-19%) compared to no mutation at 65 (+/-7%) (p <0.001). In a time dependent covariate analysis correcting for time to starting maintenance therapy the relative risk (RR) of death for patients treated with HMA was 1.25 (95% CI: 0.64-2.30, p = 0.51) and for patients treated with DLI 0.50 (95% CI: 0.07-3.86, p = 0.51). The combination of HMA and DLI resulted in a relative risk of 1.44 (95% CI: 0.71-2.90, p = 0.31). Treatment with FLT3 inhibitors yielded an RR of 0.94 (95% CI: 0.41-2.12, p = 0.87).

Conclusions: While several trials have suggested that maintenance strategies, particularly with FLT3 inhibitors and HMAs may confer a relapse-preventive benefit post-HCT, our findings did not align with these outcomes.

6618

AL-amyloidosis patients continue to benefit from HDCT with ASCT compared to chemoimmunotherapy only in the daratumumab era.

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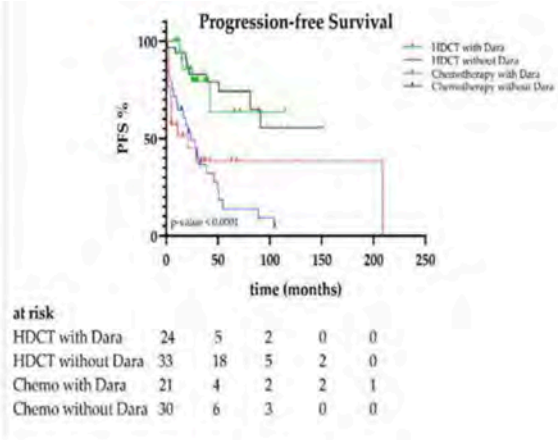
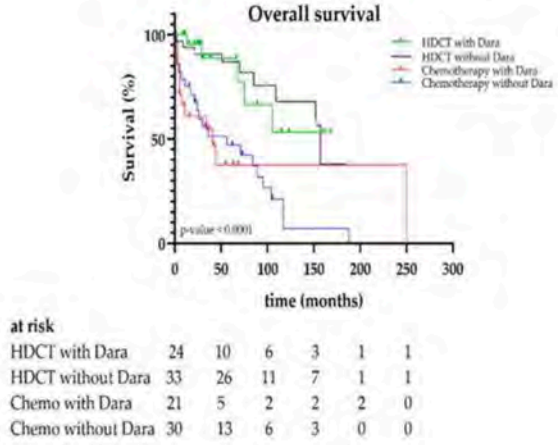
Introduction: AL amyloidosis patients eligible for high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) have superior outcomes compared to patients without HDCT/ASCT. However, available data are limited due to disease rarity, differing patient selection, and evolving treatment algorithms. The introduction of daratumumab has improved outcomes; however, it is unclear whether HDCT/ASCT still confers additional benefit in the context of current antibody-containing regimens.

Methods: This retrospective, single-center study aimed to compare patients diagnosed 01/2003–12/2024 and consolidated in first remission with HDCT/ASCT vs. without HDCT/ASCT both before and within the era of CD38-targeting regimen. Diagnosis was confirmed via biopsy/Congo red staining and amyloid subtype analysis.The primary aim was to assess overall survival (OS), and progression-free survival (PFS) and impact of FISH abnormalities were secondary objectives.

Results: We identified 108 AL amyloidosis patients. 57 patients underwent HDCT/ASCT after induction therapy, while 51 had conventional chemoimmunotherapy alone. The two groups differed at initial diagnosis in age (p = 0.0028), renal function (eGFR, p = 0.0052); troponin T levels (p <0.0001) and NT-proBNP (p = 0.0379). Patients treated with HDCT/ASCT had better outcome than patients without HDCT/ASCT. The median OS was 157 vs. 36 months (p <0.0001), median PFS was 81 vs. 24 months (p <0.0001). Daratumumab was given in 45 patients (41.7%). during first-line treatment, and patients were divided into additional subgroups: HDCT/ASCT ± daratumumab and chemotherapy ± daratumumab. OS and PFS were longer in patients treated with HDCT, regardless of whether daratumumab was added. Median PFS has not been reached in both groups with HDCT. PFS at 2 years were 85.4% for HDCT/ASCT + daratumumab versus 82.9% for HDCT/ASCT without daratumumab (p = 0.822; Figure 1). The median OS tended to be longer in patients treated with HDCT, with the median OS not yet reached for HDCT/ASCT + daratumumab patients, compared to 157 months in HDCT/ASCT patients without daratumumab (p = 0.915).

Conclusions: Independently of whether daratumumab was given (or not) during induction treatment, our study suggests that patients with AL amyloidosis undergoing HDCT/ASCT have better PFS and OS compared to patients treated with chemo-immunotherapy only.





3514

Cyclophosphamide-ATG Compared to BEAM-ATG as Conditioning for Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis

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Introduction: High-dose chemotherapy followed by antithymocyte globulin (ATG) and autologous hematopoietic stem cell transplantation (ASCT) is a treatment option for therapy-refractory multiple sclerosis (MS). Unlike in malignant diseases, the rationale in MS is long-term immunomodulation with minimal toxicity. BEAM-ATG and cyclophosphamide-ATG (Cy-ATG) are both commonly used conditioning regimens, yet the most suitable of them remains uncertain. To address this, we conducted a single-center retrospective analysis comparing BEAM-ATG and Cy-ATG in 50 MS patients undergoing ASCT. We focused on safety, engraftment kinetics, transfusion burden, infectious complications, lymphocyte recovery, and neurological outcomes.

Methods: We retrospectively analyzed 50 patients with MS who underwent ASCT at our center between 2016 and 2025 following BEAM-ATG (n = 41) or Cy-ATG (n = 9). The primary

endpoint was safety, defined as the incidence of grade ≥3 adverse events. Secondary endpoints included overall survival, hematologic toxicity, transfusion burden, hospitalization, weight loss, immune reconstitution, infectious complications, and neurological outcomes.

Results: Cy-ATG was associated with fewer severe adverse events, faster engraftment (including faster T- and B-cell recovery), shorter duration of hospitalization, and less weight loss compared to BEAM-ATG. Infectious complications, including neutropenic fever and bacterial infections, were markedly reduced in the Cy-ATG group. Neurological function and disability remained stable in both groups at 12 months.

Conclusions: Our single-center comparison demonstrates that BEAM-ATG is associated with stronger myelotoxicity, delayed immune recovery and higher gastrointestinal and infection-driven non-fatal toxicity, while Cy-ATG offers a more favorable safety profile. Neurological efficacy at 12 months was preserved in both regimens, underscoring the therapeutic value of high-dose chemotherapy with ATG and ASCT in MS.

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Performance of ELN Risk Stratifications in a Real-World Setting: A 20-year Analysis of Patients with Acute Myeloid Leukaemia

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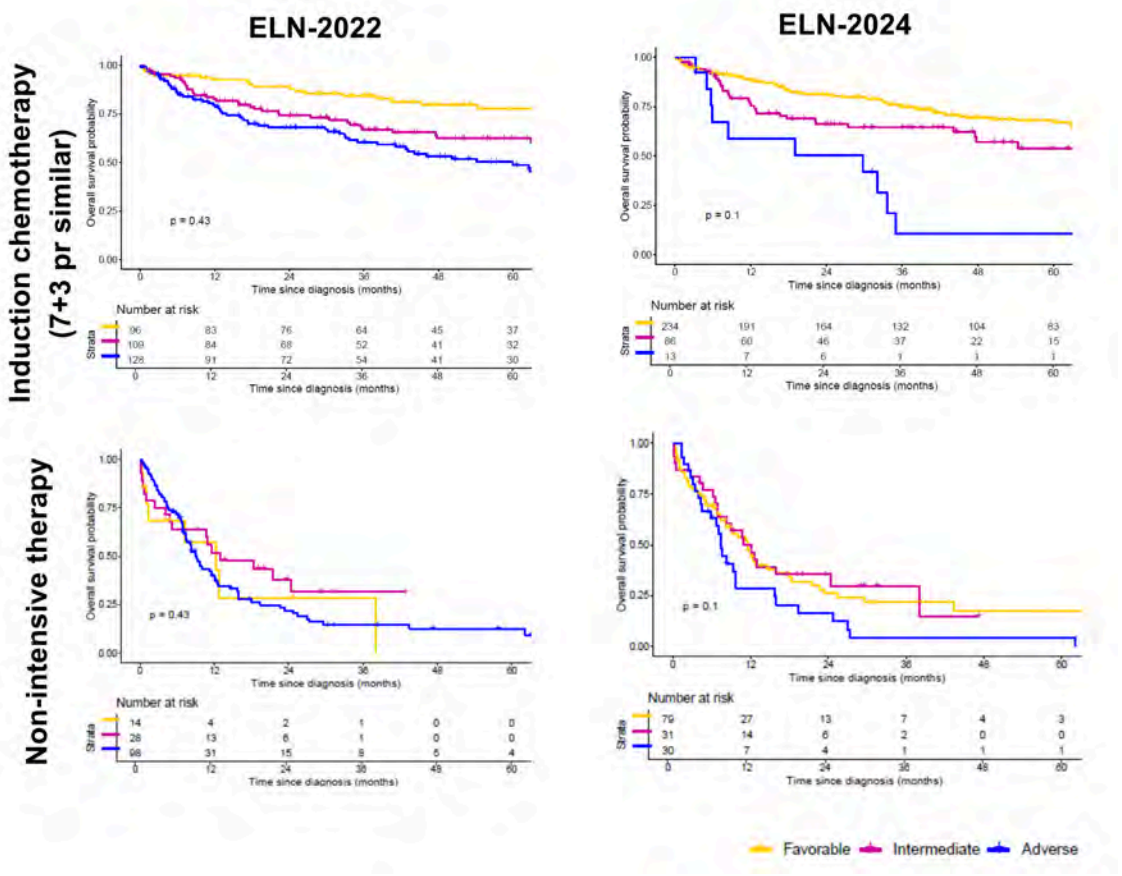
Introduction: The European LeukemiaNet (ELN) risk stratification is a cornerstone of AML management, classifying patients based on genetic factors to guide treatment decisions. The application of these guidelines to real-world data (RWD) is crucial for assessing patient care in routine clinical practice. Data from institutions like ours reflects the complexities of real patients, including comorbidities and personalised treatments. By comparing the predictions by the ELN systems to observed local results can be compared to global benchmarks, which is essential for quality management and real-world validation of classification systems.

Methods: We retrospectively analysed 558 AML patients treated at the University Hospital of Zurich from September 2004 to November 2024. We systematically collected clinical data, genetic characteristics, treatments and outcomes using a custom electronic data recording system (Cinderella). Using Kaplan-Meier and Cox models, we assessed survival across risk and treatment groups. For each patient, we applied both the ELN-2022 and ELN-2024 risk stratifications and compared their performance across patient subgroups.

Results: In our cohort with a median age of 58.1 years, 67% received intensive chemotherapy while 30% were treated with hypomethylating agents with or without Venetoclax. The ELN 2022 and ELN 2024 systems stratified patients by overall survival in the intensively treated group, although without statistical significance. Both systems performed poorly in patients not receiving intensive chemotherapy. The ELN 2024 adverse risk group provided the most useful survival separation in this group but included less than 10% of these patients.

Conclusions: Applying ELN risk stratifications to real-world data reveals challenges in their predictive power, especially in patients unable to receive intensive chemotherapy. While the ELN 2022 and 2024 systems both trended toward predicting overall survival in intensively treated patients, real-world factors such as patient heterogeneity and comorbidities not reflected in clinical trials may have diluted their prognostic value. For patients on less intensive therapeutic settings, both systems performed remarkably poorly. The limited utility of the ELN 2024 system designed for this group highlights the need for better risk tools that accurately reflect outcomes in diverse AML populations not receiving intensive treatment.



8819

Longterm-outcome of myeloma patients after high-dose chemotherapy with melphalan alone versus melphalan with bendamustine.

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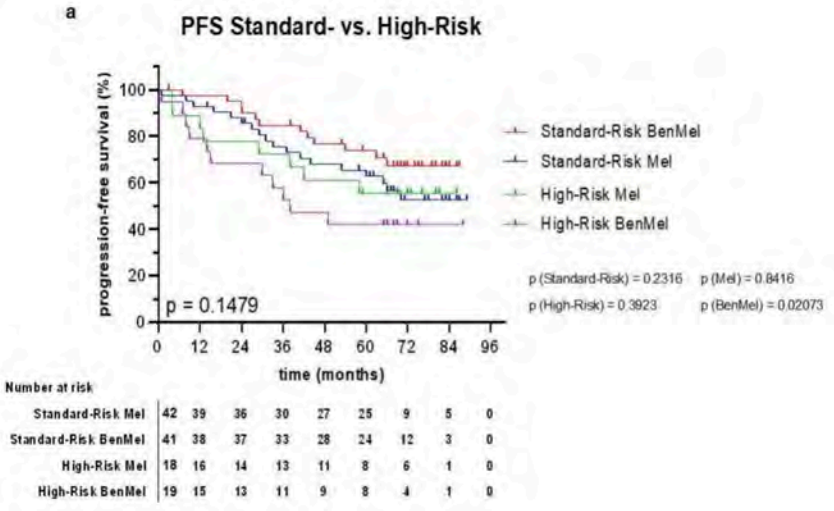
Introduction: Melphalan-based high-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) remains a cornerstone in the treatment of myeloma patients. Enhancing the efficacy of HDCT in myeloma is an unmet clinical need. Whether the combination of bendamustine and melphalan (BenMel) improves progression-free (PFS) and overall survival (OS) compared to melphalan alone (Mel), and whether eventual survival benefits are limited to cytogenetic subgroups remains unclear.

Methods: With extended follow-up, we analysed a randomised trial including 120 patients treated with HDCT and ASCT between 2017–2020. 60 patients received Mel, and 60 pts had BenMel HDCT. Subgroup analyses were conducted for standard-risk (SR; Mel: 42 pts; BenMel: 41 pts) and high-risk (HR) patients (Mel: 18 pts; BenMel: 19 pts) according to FISH abnormalities at first diagnosis.

Results: After a median follow-up of 69 months, the PFS was 56.7% for Mel and 61.7% for BenMel pts (p = 0.68). OS rates were 82.7% for Mel and 70% for BenMel (p = 0.20; Mel: 11 deaths; BenMel: 18 deaths), with causes of death including secondary malignancies in no patient in the Mel and 3 pts in the BenMel group, respectively. SR patients in the entire cohort tended to have better PFS, with relapses observed in 30/83 (36.1%) SR versus 19/37 (51.4%) HR pts, respectively (p = 0.16). BenMel patients with SR abnormalities tended to have better PFS than Mel treated SR patients, with relapses seen in 12/41 (29.3%) SR BenMel compared to 18/42 (42.9%) SR Mel patients, respectively (p = 0.23). In contrast, in the HR group, there was no difference in the outcomes of BenMel treated patients versus Mel pts (relapses in 11/19 (57.9%) versus 8/18 (44.4%) patients; p = 0.39), as shown in Figure 1. Since lenalidomide alone was given as maintenance after HDCT, we hypothesize that lenalidomide may have been sufficient to maintain remission in SR, but not in HR patients thereby selectively abolishing the eventual benefit of HDCT intensification in HR patients.

Conclusions: Although no differences were observed for PFS and OS in the overall cohort, our results suggest that BenMel intensification of HDCT before ASCT may be favorable in SR patients. Independent confirmation of these results in a larger cohort are warranted.



9229

Swiss Real-World Experience with Tafasitamab and Lenalidomide in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The SWISS-MIND Study

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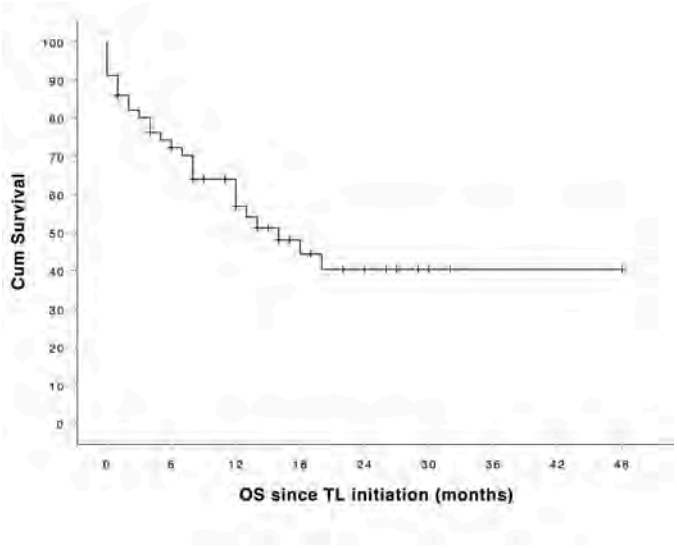
Introduction: Tafasitamab plus lenalidomide (TL) has been approved for use in patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) who are ineligible for autologous stem cell transplantation (ASCT). The phase II L-MIND trial included 81 patients and reported promising outcomes, however, real-world data (RWD) from broader, less-selected patient groups have produced conflicting results. Data from Switzerland are lacking, and TL's benefit-risk profile in routine practice remains unclear.

Methods: SWISS-MIND is a multicenter, retrospective, real-world study of 57 patients with R/R DLBCL treated with TL at 12 Swiss institutions between 2021 and 2025. The primary endpoint is overall survival (OS). Secondary endpoints include progression-free survival (PFS), overall response rate (ORR), hematotoxicity, hospitalizations, and characterization of subsequent therapy.

Results: The median age was 79 years (range 48-94); 65% were male; 28% had transformed indolent lymphoma. Most patients had comorbidities and poor performance status. High-risk features included 75% extranodal disease, 55% high/high-intermediate IPI, 35% ABC-subtype, 35% double-expressor, 11% double/triple hit. The first-line was R-CHOP in 60% and R-mini-CHOP in 30% of cases. Refractory disease (within 6 months) was seen in 70% of patients. 56% had ≥2 prior DLBCL therapies, 35% had ASCT, 28% CAR-T. The median OS from TL initiation was 16 months (95% CI: 8.9-23.1 months; 27 events; median follow-up: 14 months). The median PFS was 9 months (95% CI: 1.8-16.2 months; 45 events; median follow up: 12 months). The ORR was 46% (18% CR, 28% PR). Discontinuation due to toxicity occurred in 5%. Grade ≥3 hematotoxicity was reported in 16%, and 26% required hospitalization for any reason during TL. 44% received subsequent therapy, including 5% each with ASCT or CAR-T and 23% with bispecific antibodies.

Conclusions: SWISS-MIND provides real-world insight into TL use in Switzerland in patients with R/R DLBCL. Most patients had high-risk disease and were heavily pretreated. Yet, OS, PFS and ORR compared favorably to prior RWD and even L-MIND. TL remains a viable option, especially for those ineligible for ASCT or CAR-T.



SSMO ORAL PRESENTATION – CLINICAL SOLID TUMOR ONCOLOGY

8269

Perioperative chemo-immunotherapy with Durvalumab for operable muscle-invasive urothelial carcinoma: final analysis of the single arm phase II trial SAKK 06/17

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Introduction: The primary analysis of SAKK 06/17 investigating the addition of perioperative immunotherapy with Durvalumab (Durva) to neoadjuvant chemotherapy in resectable muscle-invasive urothelial carcinoma (MIUC) has been published previously and met its primary endpoint of event-free survival (EFS) at 2 years (J Clin Oncol 2023, 41:5131-39). We report on the final analysis with a median follow up of 64 months.

Methods: SAKK 06/17 was an open label single arm phase II study for cisplatin-fit patients (pts) with stage cT2-T4a cN0-1 operable MIUC. Pts received 4 cycles of neoadjuvant chemo with Cis/Gem q3w in combination with 4 cycles Durva 1500mg q3w (Durva started on day 22) followed by surgery. Adjuvant Durva 1500mg q4w was given for 10 cycles or a maximum of 40 weeks. The primary endpoint was EFS at 2 yrs after neoadjuvant treatment (NAT) start. An event was defined as progression during NAT, appearance of metastases, locoregional recurrence after surgery or death from any cause. We report the final analysis of the full analysis set (FAS, received at least one dose of Durva). NCT03406650

Results: 61 pts were included between 7/2018 and 9/2019. Median follow up is 64 months (95%CI 64 – 65). FAS consisted of 57 pts (79% male, median age 68 yrs) with bladder cancer (95%) or upper urinary tract/urethral cancer (5%). Baseline staging cT2, cT3, cT4 was 70%, 20%, 11%, respectively, and 16% had cN1. Resection was performed in 53 pts (91%; 4 refused, 1 unresectable). 47 (90%) of resected pts started adjuvant Durva and 31 (66%) completed it. Overall, 14 pts experienced an event and only one event occurred after 3 years. EFS at 2 years was 75.7% and at 5 years 73.6%, median EFS was not reached. Median OS was also not reached, OS at 2 years was 85.1% and at 5 years 75.4%, respectively. Three deaths occurred after 3 years. No new safety signals were observed.

Conclusions: The addition of perioperative Durvalumab to neoadjuvant cisplatin/gemcitabine chemotherapy in pts with resectable MIUC results in a high and sustained EFS and OS after a median follow-up of 64 months. Only very few events were noted more than 3 years after treatment start.

6568

Intravesical recombinant BCG followed by perioperative chemo-immunotherapy for patients with muscle-invasive bladder cancer: interim analysis of SAKK 06/19 study

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Introduction: Perioperative chemo-immunotherapy (chemo-IO) improves outcome in operable muscle-invasive bladder cancer (MIBC). Intravesical BCG is effective in high-risk non-MIBC by induction of the innate immune system and an adaptive immune response. We previously investigated a recombinant BCG vaccine (rBCG, VPM1002BC) demonstrating good safety and efficacy (SAKK 06/14). We hypothesize that induction therapy with intravesical rBCG improves the efficacy of perioperative chemo-IO.

Methods: SAKK 06/19 is an open-label single arm phase II trial for cisplatin-eligible patients (pts) with cT2-T4a cN0-1 MIBC.

rBCG is instillated weekly 3 times (day 1, 8, 15). Atezolizumab (Atezo) 1200 mg is administered on day 1 and then 4 times every 3 weeks (q3w). Cisplatin and gemcitabine start on day 22 and are given for 4 cycles q3w followed by radical cystectomy (RC). In case of ≥ ypT2 or ypN+, Atezo is continued after surgery for 13 cycles. pCR assessed by central review is the primary endpoint defined as ypT0 ypN0. H0 is pCR ≤35% and H1 is pCR ≥55%. 46 pts are planned to be included based on Simon's minimax 2-stage design. We report the pre-specified interim analysis after 21 pts have undergone RC. Nine or more patients with pCR were required to continue to stage 2. NCT04630730

Results: 24 pts were accrued between 06/22 and 10/24 and 21 had RC (3 pts refused). Median age was 67 years (range 24-78) and 3 (14%) were female. Staging was cT2 in 14 (67%), cT3 in 5 (24%) and cT4 in 2 (10%) pts. 3 pts (14%) had cN1. 20 pts (95%) had at least one rBCG and 15 pts (72%) had all 3 instillations. All pts had 4 cycles of Atezo and 4 cycles of platinum. Surgery was laparoscopic in 16 pts (76%) and diversion was with neobladder in 12 (57%) and ileum conduit in 9 (43%) pts. Adverse events (AE) attributed to rBCG was grade 1 (G1) in 9%, G2 in 13% and G3 in 9%. G3 and G4 adverse events related to Atezo were 17% and 0%, related to chemo 38% and 17%, respectively. No G5 events occurred. Among 21 evaluable patients, ≥9 achieved a pCR.

Conclusions: The combination of intravesical rBCG with perioperative chemo-IO was feasible and well-tolerated, without unexpected toxicities. The interim analysis met predefined efficacy and safety criteria and the trial continues enrollment into stage 2.

0435

Efficacy and Safety Evidence Supporting Cancer Drug Approvals in Switzerland (2001–2020): A Meta-Analysis of Pivotal Randomized Controlled Trials

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Introduction: Randomized controlled trials (RCTs) are considered the gold standard for primarily establishing efficacy and safety of new cancer drugs. However, the robustness and completeness of evidence available at the time of approval are often debated, and systematic evaluations remain limited. To address this gap, we evaluated the evidence supporting cancer drug approvals in Switzerland between 2001 and 2020.

Methods: Pivotal RCTs supporting Swissmedic (SMC) cancer drug approvals were identified and their hazard ratios (HRs) for Overall Survival (OS) and Progression Free Survival (PFS), Risk Ratios (RRs) for Serious Adverse Events (SAE) and Odds Ratios (ORs) for Objective Response Rate (ORR) were pooled using random-effects model under the framework of meta-analysis.

Results: A total of 241 RCTs supported SMC cancer drug approvals, mostly for solid tumors (71%), with PFS as the primary endpoint in 62.3%. At approval, 140 solid tumor trials reported OS, PFS, and SAE outcomes. By pooling them, HRs were 0.76 (95%CI, 0.74-0.78, I2 = 23.8%) for OS and 0.57 (0.54-0.60, I2 = 86.8%) for PFS, while RR for SAE was 1.28 (1.21-1.36, I2 = 83.2%). Median OS gain was 2.24 months (1.92-2.57) across 70 trials where median OS was reached and reported in both arms. The OR for ORR (n = 121) was 2.45 (2.18-2.76, I2 = 80.9%). The difference between OS and PFS varied across solid tumor types in the palliative setting (Figure 1). The HRs for OS and PFS in molecular targeting agents (n = 57) were 0.74 (0.71-0.77) and 0.48 (0.44-0.52), respectively, while for immune checkpoint inhibitors (n = 31), they were 0.71 (0.68-0.74) and 0.72 (0.68-0.74).

Conclusions: At the time of SMC approval, cancer drugs demonstrated a favorable benefit-risk profile, with significant reduction in disease progression and death, alongside manageable increase in SAEs. The benefit in OS was usually smaller than that of PFS and strongly dependent on cancer type. Limited availability of median OS at the time of approval indicates a limitation in the submitted evidence. These findings highlight the importance of submitting mature OS and safety data after initial approval, along with additional clinically relevant endpoints, such as quality of life to fully assess long-term benefits and risks.

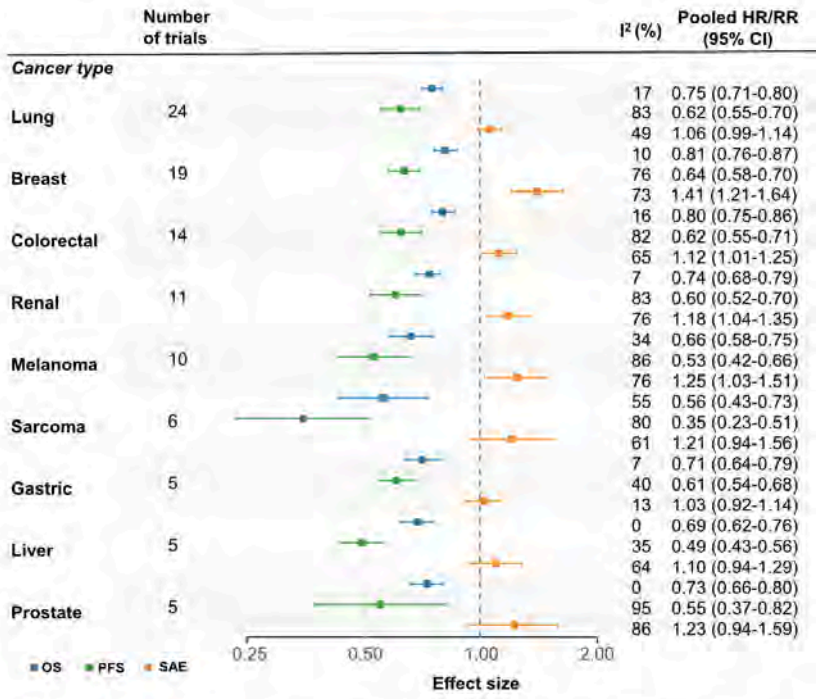

Figure 1. Subgroup meta-analysis of randomized controlled trials supporting solid tumor drug approvals in the palliative setting in Switzerland (2001–2020).

The plot shows pooled hazard ratios (HRs) with 95% confidence intervals (CIs) for Overall Survival (OS) and Progression-Free Survival (PFS), and Risk Ratio (RR) for Serious Adverse Events (SAEs). PFS includes progression-free survival, time to progression, and metastasis-free survival. Only cancer types with ≥5 randomized controlled trials (RCTs) were included in the analysis.
I^2, the degree of heterogeneity across studies

1217

Co-Alterations Associated with Resistance to EGFR-Inhibitors in EGFR+ NSCLC: Insights from the Precision Oncology Program in Two International Real-World Cohorts

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Introduction: EGFR inhibitors (EGFRi) are standard first-line therapy for advanced EGFR+ NSCLC, but their effectiveness can be limited by resistance. Understanding co-alterations associated with resistance is critical for guiding personalized treatment recommendations, especially in this patient group, where emerging treatment options require careful consideration. We assess the impact of co-alterations in the EGFR signaling pathway on first-line EGFRi in two complementary real-world data (RWD) cohorts within the Precision Oncology Program (POP; NCT06680726) (1) focusing on TP53.

Methods: We assembled patients with NSCLCs with EGFR exon 19 deletion / L858R mutation at University Hospital Zurich (USZ) (n = 43) and a matched patient cohort in the Flatiron Health-Foundation Medicine NSCLC Clinicogenomic Database (FH-FMI-CGDB) (n = 1,927). Duration of treatment (DOT) with EGFRi in the first treatment line was assessed per co-alteration. TP53 alterations were further stratified based on the specific functional domains (zinc-binding (amino acids 176 – 239), DNA-binding (amino acids 102 – 292), tetramerization (amino acids 323 – 356)).

Results: DOT on osimertinib was shorter in FH-FMI-CGDB cases with co-alterations in MET, KRAS, BRAF, CCNE1, with significance for ERBB2 ($p < 0.01$), PIK3CA ($p = 0.04$) and TP53 ($p < 0.01$). A similar trend was observed in the USZ cohort for TP53. DOT on erlotinib/afatinib was shorter in cases with co-alterations in MET, KRAS, PIK3CA, CCNE1, MDM2, with significance for ERBB2 ($p = 0.027$) and TP53 ($p < 0.01$). TP53 mutations were the most common co-alteration, and residue-level analysis showed zinc-binding and dimerisation variants conferred shorter DOT compared to other or none TP53 alterations.

Conclusions: Key resistance-associated co-alterations in advanced EGFR+ NSCLC were identified across two RWD cohorts. Our study demonstrates the clinical utility of upfront, residue-based TP53 analysis, offering a novel layer of molecular insight that could support treatment decisions already in the first-line setting. Beyond TP53, we identified additional co-alterations linked to variation in DOT with EGFRi, pointing to their potential role in guiding escalation/de-escalation strategies. Furthermore, these findings emphasize the power of RWD in addressing precision oncology questions and molecularly detailed cohorts through collaborative approaches that enable comprehensive assessment.

0172

Inflammation and limited adaptive immunity predict worse outcomes on immunotherapy in head and neck cancer

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Introduction: Over half of patients with head and neck squamous cell carcinoma develop recurrent or metastatic disease (rmHNSCC), often ineligible for local therapy. Pembrolizumab is standard for PD-L1-positive patients, but most show limited or short-lived responses even in combination with vaccine-induced neoantigen-directed T cell responses as recently shown in the FOCUS trial (NCT05075122). PD-L1 tissue expression is the most commonly applied response marker, but remains an insufficient predictor of treatment outcome.

Methods: We used biomaterial from the baseline and follow-up of the FOCUS trial to quantify 28 plasma cytokines and soluble immune checkpoint molecules, cell-free (cf)DNA, and the neutrophil-to-lymphocyte (NLR) ratios and performed bulk immune repertoire sequencing to profile T cell receptor architectures. The PD-L1 combined positive score was assessed in the primary tumor. Data were correlated with survival, and significant factors underwent unsupervised cluster analysis to define candidate compound biomarkers ("Immunotypes"). Multivariate Cox regression with Lasso regularization and cross-validation was applied to derive a predictive model.

Results: In 75 evaluable patients, median PFS was 3.4 months and median OS 13.1 months, comparable to historical pembrolizumab data. PD-L1 levels in the tumor or tumor microenvironment were not associated with treatment benefit. In contrast, TCR repertoire restriction and high IL-6, soluble (s)CD25, sTIM-3, NLRs, and cfDNA were associated with worse outcomes. Patients lacking these high-risk markers performed remarkably well on pembrolizumab. Multivariate Cox modeling with Lasso regularization selected sCD25, IL-6, and TCR clonality as independent predictors, yielding a final model with C-index = 0.774 and time-dependent AUCs up to 0.95 at 6 months.

Conclusions: Biomarker-guided patient selection for pembrolizumab monotherapy or novel combinatorial approaches (e.g. including anti-inflammatory agents) for HNSCC patients with immune-impaired, inflammatory profiles may be the next step in personalizing immunotherapy for these hard-to-treat cases.

6591

Prognostic role of exosome in patients with stage IIIA(N2) non-small cell lung cancer treated with perioperative durvalumab in addition to neoadjuvant chemotherapy (SAKK 16/14)

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Introduction: In the trial SAKK 16/14 perioperative durvalumab showed favorable outcomes for patients (pts) with resectable stage IIIA(N2) non-small cell lung cancer (NSCLC). Exosomes are extracellular vesicles (EV) released by cancer cells, holding promise as prognostic biomarkers and for therapeutic monitoring.

Methods: In this phase II trial 68 pts with stage IIIA(N2) NSCLC were treated with perioperative durvalumab in addition to neoadjuvant chemotherapy (chemo) with cisplatin/docetaxel, followed by surgery. For each patient, blood serum samples were acquired at baseline (timepoint 1, TP1), post neoadjuvant chemo (TP2), post neoadjuvant durvalumab (TP3) and after four cycles of adjuvant durvalumab (TP4) and at the end of adjuvant durvalumab (TP5). This study examines exosomal dynamics in 20 serum samples from this trial. A recently developed galectin-based exosome isolation bead technique was used. Bead-based flow cytometry was used to assess five exosomal markers (PD-L1, PanEV, PanCK, EpCAM, and CD45) at five defined time points. Successful exosome isolation was confirmed by nanoparticle tracking analysis and electron microscopy.

Results: There was a trend toward decreasing extracellular vesicle (EV) mean fluorescence intensity (MFI) values at TP2. Notably, smoking status influenced exosomal profiles, with current smokers exhibiting significantly lower PanEV levels. The area under the receiver operating characteristic curve (AUC) for PD-L1$^+$ PanEV$^+$ EV-bead complexes at TP4 was 0.875. Prognostic analysis and AUC evaluation revealed a significant negative correlation between post-therapy (TP4) PanEV$^+$ PanCK$^+$ EV-bead complexes and both overall survival (OS) and event-free survival (EFS) ($p = 0.0067$, AUC = 0.838; $p = 0.0003$, AUC = 0.789, respectively). A similar trend was observed for PanEV$^+$/PanCK$^+$ levels at TP1 and for EpCAM$^+$/PanEV$^+$ exosomes at TP4.

Conclusions: These findings emphasize the feasibility of assessing exosomes in NSCLC and highlight their prognostic potential. Elevated post-treatment PanEV/PanCK levels were associated with significant shorter EFS and OS, highlighting the potential of exosome-based liquid biopsies.

ONCOREHA/OPS/PALLIATIVE.CH/SNIO/SOHC ORAL PRESENTATION – NURSING, SUPPORTIVE & PALLIATIVE CARE, REHABILITATION & SURVIVORSHIP AND INTEGRATIVE ONCOLOGY

4016

Cancer surveillance in HBOC and LS: The international CASCADE study

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Introduction: Individuals with pathogenic/likely pathogenic (P/LP) variants associated with Hereditary Breast and Ovarian Cancer (HBOC) and Lynch syndrome (LS) are at increased risk for various types of cancer. Cancer risk management options include regular cancer surveillance from age 25 and risk-reducing surgeries. The purpose of the study is to examine risk management in individuals with P/LP variants associated with HBOC or LS, and identify predictors of surveillance and risk-reducing surgeries for different types of cancer associated with these syndromes. Comparisons include data from three countries with similar healthcare systems.

Methods: CASCADE is an international, open-ended, family-based cohort initiated in Switzerland, and replicated in Korea (2019), and Israel (2022). The cohorts include individuals with a P/LP variant, untested relatives, and true negatives. Information about cancer surveillance and risk reducing surgeries is collected through self-administered questionnaires at the time of entering the cohort. Cancer risk management is evaluated according to gene and age cut-offs, based on the National Comprehensive Cancer Network guidelines, as implemented in each country.

Results: The Swiss and Korean cohorts include n = 910 carriers of P/LP variants associated with HBOC and LS. Among females in Switzerland without double mastectomy and without a prior cancer diagnosis, 10.8% of BRCA1 and 8.9% of BRCA2 carriers did not have a breast MRI in the past 12 months. In Korea, these proportions were 40.1% and 24.3%, respectively. Among females older than 35 with a P/LP variant in BRCA1, 6.5% in Switzerland and 10.3% in Korea did not have risk-reducing salpingo-

oophorectomy; for BRCA2 carriers older than 45, these percentages were 3.4% in Switzerland and 6.4% in Korea. Annual PSA above the age of 40 was reported by 50% of Swiss male BRCA2 carriers. Among Swiss carriers with P/LP variants associated with LS without colorectal cancer, 20.3% did not have a colonoscopy the past 12 months. Receiving care from non-specialists and being tested more than 5 years were predictors of non-optimal cancer risk management. Anxiety and depression were positively associated with risk-reducing double mastectomy.

Conclusions: There is need for sustained follow-up and psychosocial support to improve cancer outcomes and promote effective cancer risk management.

4386

The experience of women with breast or gynecological cancer after participation in an online Mindfulness-Based Cancer Recovery (e-MBCR) program: secondary outcomes analysis of a pilot mixed methods randomized controlled trial

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Introduction: Mindfulness-Based Interventions (MBIs) are recognized as beneficial in oncology supportive care. While qualitative analyses of mindfulness program experiences exist, this is the first mixed methods study to examine patients' experiences after participating in the online Mindfulness-Based Cancer Recovery (e-MBCR) program.

Methods: The SERENITY study was a pilot randomized controlled trial evaluating the early implementation, and effects of the e-MBCR program for women with breast or gynecological cancer in a French-speaking context. This article reports on secondary outcomes from a mixed methods analysis, exploring psychosocial aspects through questionnaires and participants' experiences through interviews. Sixty-two patients were randomized in a 2:1 ratio. Quantitative assessments were carried out at three timepoints; qualitative interviews only post-intervention. Both datasets were analyzed separately, then merged for interpretation.

Results: The intervention group showed a significant reduction in depression compared to the control group, with a medium effect size post-intervention. While other psychological measures did not show significant differences, this exploratory analysis revealed favorable trends, particularly in anxiety, spiritual well-being, and post-traumatic growth. At 3-month follow-up, most scales showed a diminished effect compared to post-intervention. Qualitative interviews revealed four themes: a safe and validating environment, acquiring skills and taking action, enhanced well-being, and exposure to memories of cancer. This last dimension was a source of beneficial inner work for most participants, although it was a deeply challenging experience for four women.

Conclusions: In line with previous research findings, our study revealed a favorable and beneficial experience following regular mindfulness practice. Among the interesting themes that emerged from the qualitative analysis, we note the importance of the group as a support for self-exploration and change, the notion of improved empowerment through the program, but also the fact that mindfulness practice and this program can lead to difficult experiences, linked to a context reminiscent of cancer, that are important to recognize and reflect on in order to protect patients from these potentially deleterious effects.

4948

Evaluation of an Oncological Rehabilitation Program as part of the Promotion of Therapeutic Physical Activity in Adults Cancer Patients

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Introduction: Novel cancer therapies have extended survival but often leave patients with motor, neurological, and psychological impairments such as fatigue and depression. While rehabilitation is well established in cardiovascular and neurological care, its role in oncology remains less defined. Evidence supports physical activity as effective supportive care, improving function, independence, fatigue, and survival. However, most data come from randomized controlled trials involving highly selected participants. Real-world studies are needed to assess feasibility and outcomes in broader cancer populations. Since 2023, Luzerner Kantonsspital (LUKS) has offered a 12-week, supervised outpatient rehabilitation program for patients before, during, or after chemotherapy. This study evaluates its feasibility, acceptability, and effectiveness regarding quality of life, physical, psychological, and social functioning.

Methods: This is a monocentric, prospective before–after study without a control group. Recruitment began in July 2024. Assessments are conducted at baseline (T0) and after 12 weeks (T1). Primary outcomes include quality of life (FACT-G), anxiety and depression (HADS), fatigue (MFI), and nutritional status (PG-SGA). Secondary outcomes assess functional performance (sit-to-stand test, handgrip strength, and body composition) as well as program feasibility (attendance rates) and patient satisfaction. Follow-up data are collected six months after program completion.

Results: Fifty-eight patients completed the program and were included in the analysis. Since program initiation, 81% attended at least 80% of sessions. Functional performance improved by 43% in the sit-to-stand test and 10% in handgrip strength, with a 5% mean gain in muscle mass. Quality of life (FACT-G) remained stable immediately post-intervention and at six months. In contrast, fatigue and disease burden (MFIS and FBK-R10) improved significantly and continued to improve at follow-up. Six months post-program, 63% of participants maintained physical activity at least twice weekly.

Conclusions: This outpatient cancer rehabilitation program was feasible and effective in improving physical performance, fatigue, and disease burden. Although quality of life remained stable, sustained physical activity suggests lasting behavioral benefits. Future subgroup analyses may identify patients who benefit most from extended or intensified interventions

9720

Non-pharmacological Interventions for Distress Management for Patients with Cancer and their Family Caregivers: A Systematic Review and Meta-Analysis

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Introduction: With cancer treatments taking place mostly in outpatient settings, family caregivers provide critical care and psychosocial support for extended periods of time. However, unaddressed patient and caregiver psychological distress can lead to diminished quality of care provided at home and worse outcomes.

Methods: This systematic review and meta-analysis evaluated the efficacy of non-pharmacological interventions (NPIs) on patient and family caregiver distress, anxiety, and depression. We identified randomized trials (RCTs) published until 01.27.2025, targeting both adult patients with solid tumors and their family caregivers. We calculated random effects using Hedge's g. Meta-regression analyses focused on patient and caregiver characteristics, along with NPI type, delivery format, dose, and duration. Risk of Bias (RoB) was assessed using Cochrane RoB tool (v.1).

Results: We included n = 56 RCTs with a total sample of 11,989 participants. NPIs were categorized as psychoeducation, therapeutic counseling, skills training or behavior modification. Effect sizes showed significant reduction in patient distress at 0-3 months (g = 0.16) and 3.1-6 months (g = 0.26), but had non-significant effects on caregiver distress. They also showed significant short-term reduction (0-3 months) in patient and caregiver anxiety and depression. NPIs delivered jointly to the dyad and those using both remote and in-person delivery yielded higher effects.

Conclusions: Findings show that NPIs offer psychological benefits for patients with cancer and family caregivers. They support the integration of caregiver-inclusive programs into cancer care, further enabling the active participation of caregivers in the oncology care team. However, lack of long-term assessments limit applicability for patients and/or caregivers with prolonged or delayed-onset distress, anxiety, or depression.

3890

The (underestimated) importance of oncological rehabilitation for multimodal breast cancer therapy – Analysis of rehabilitation needs and rehab effects.

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Introduction: Breast cancer is the most common cancer in women in Switzerland, with an incidence of approximately 6,600 cases per year. Through increasingly individualized, multimodal therapy approaches as well as standardized preventive screenings, the 5-year survival rate has been improved to over 80%. However, these intensified therapy concepts have also led to longer treatment durations and the occurrence of a variety of, sometimes chronic, somatic and psychological sequelae. Compared to Germany, where about 50% of affected women take advantage of rehabilitation services, breast cancer patients in Switzerland are offered oncological rehabilitation to a much lesser extent (< 20%).

Methods: To evaluate the need for rehabilitation and therapy-induced side effects, as well as the effects of the treatment strategies used in rehabilitation, a large retrospective data collection (n = 10.900) was conducted at a german oncological rehabilitation hospital, alongside a prospective study (n = 1.230, BC n = 140) at 2 swiss rehabilitation centers.

Results: The most common somatic side effects were fatigue (60.2%), polyneuropathies (CIPN; 36.8%), arthralgia-like complaints (31.4%), and lymphedema (14.8%). High psychological burden (distress ≥ 4/10), sleep disturbances and depressive symptoms were observed in 66%, 52.8% and 18.2%. Especially patients with TNBC showed significantly higher values compared with other breast cancer patients. At the end of rehabilitation, there was a significant reduction in fatigue scores (ESAS, SIF; p <0.001) as well as in the incidence of fatigue (28.9% vs. 56.5%; p <0.001), along with a highly significant improvement in physical performance, including 6 minutes walking test(6-MWT), stand-up-and-go-test (TUG) and handgrip strength (p <0.001). Additionally, improvements in physical complaints (PROMIS-10, FIM; p <0.001) and in quality of life was documented (EQ-5D 50.9±20.3 vs. 66.3±19.8; p <0.001).

Conclusions: The present data confirm the high incidence of therapy-induced side effects following multimodal breast cancer therapy, as well as the partly highly significant improvements during rehabilitation. The current data on the improvement of 5-year survival rates, as well as the significant risk reduction and secondary prevention resulting from exercise interventions, also emphasize the importance of oncological rehabilitation in the context of modern breast cancer treatment and prevention.

6198

A prospective cross-sectional study of cancer survivors' self-reported long-term experiences in Canton Fribourg over a ten-year post-diagnosis period.

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Introduction: Cancer survivors may experience long-term effects alongside with chronic conditions. This study explores the long-term effects of cancer and its treatments, including the impact on work, and self-reported comorbidities.

Methods: We conducted a retrospective cross-sectional survey based on the NCCN survivorship questionnaire for patients and the Self-Administered Comorbidity Questionnaire, next to questions related to sick leave and time until return to work. Initial cancer treatment related factors potentially causing long-term effects were gathered from medical records. We included individuals diagnosed 1 to 5 and 5 to 10 years ago with breast, colorectal, lung, prostate cancer, or diagnosed with a lymphoma or myeloma and excluded those not treated at the Hôpital fribourgeois, or not understanding German or French. Used variables were Likert-like scales (from never to always), numeric scales (0 = none to 10 = extreme), and dichotomous yes/no answers. All scales were dichotomized for group comparisons. Regression analyses predicted the different symptoms by the time since diagnosis, adjusted for confounders.

Results: 335 participants (41.55% return rate) completed the survey online or on paper between February and June 2024. The mean age was 61.5 years (SD 11.75), 56% were female, and 14% German speaking. All participants had undergone multiple therapies (mean 2.52, SD 0.94): systemic therapy (85%), surgery (73%), radiotherapy (54%), and/or anti-hormonal therapy

(39%). The prevalence of long-term effects did not differ between the two groups except for hormone-related symptoms, sexual health, and concerns about weight, which were more prevalent in the group 5 to 10 years post-diagnosis (p = 0.0212, 0.0148, and 0.0325 respectively). The most frequently reported comorbidities were high blood pressure and back pain (40% & 42% respectively). 37% of participants reduced their working hours by 56% (SD 29.68) for about 27.21 months (SD 43.81); 23% did so due to symptoms. Having multiple comorbidities and being of younger age were significantly associated with long-term effects such as depression/anxiety, impaired cognitive function, lymphedema, pain, hormone-related symptoms, sexual health, or sleep disturbances.

Conclusions: Cancer survivors in Canton Fribourg experience multiple long-term effects up to ten years after their diagnosis. Our results could inform tailored cancer survivorship care.

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

9470

Long-term outcomes in patients with antiphospholipid antibody monopositivity and initial venous thrombosis: a retrospective cohort study

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Introduction: Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by arterial and/or venous thrombosis and/or obstetric morbidity, with persistent antiphospholipid antibodies (aPL). Vitamin K antagonists (VKAs) are the standard of care for secondary thromboprophylaxis in thrombotic APS, but direct oral anticoagulants (DOACs) have raised interest, particularly in low-risk APS defined by single antibody positivity. Current evidence suggests that in patients with thrombotic APS, DOAC therapy is associated with an increased risk of arterial thrombotic events compared with VKAs, while the risks of venous thromboembolism (VTE) recurrence and major bleeding do not differ significantly between the two groups, regardless of APS phenotype. Our objective was to evaluate the safety and efficacy of DOACs in venous thrombotic APS with single aPL positivity, compared with VKAs.

Methods: We conducted a retrospective study (2010–2025) of patients ≥18 years with a first VTE and APS defined according to the 2006 Sydney criteria and single aPL positivity (aCL, aβ2GP1, or LA confirmed ≥12 weeks apart). Initial anticoagulation included acenocoumarol (n = 21), rivaroxaban (n = 15), apixaban (n = 6), dabigatran (n = 2), edoxaban (n = 1), and others (n = 4). The primary efficacy endpoint was thrombotic recurrence, stratified according to VKAs vs. DOACs. The primary safety endpoint was major bleeding or clinically relevant non-major bleeding. All patients were followed for at least 12 months after their first recurrent thrombotic event.

Results: We included 49 patients (20 men and 29 women; mean age 49 ± 13.5 years), with the first VTE occurring at a mean age of 40 ± 13.5 years (Table 1). The mean follow-up was 41 months. Single positivity was most often for aCL (n = 42), less for aβ2GP1 (n = 4) and LA (n = 3). During follow-up, ten patients became aPL-negative. Eighteen patients (36.7%) experienced 23 recurrences: 6 while on therapy (2 rivaroxaban, 2 apixaban, 2 acenocoumarol), mainly arterial (5/6), and 12 after anticoagulant discontinuation (mean 55 months), mostly venous.

Conclusions: Although limited by its retrospective, single-center design, this study suggests a high rate of recurrence in single aPL-positive APS, regardless of the type of anticoagulation. Recurrence was particularly observed in patients who had undergone inappropriate thrombophilia testing, leading to premature discontinuation of therapy.

6097

Correlation between the level of hemoglobin variants (HbS, C and E) and alpha-thalassaemia

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Introduction: Heterozygous hemoglobin (Hb) variants HbS, HbC and HbE, are often associated with α-thalassemia. The combination of these abnormalities leads to a reduction in abnormal Hb levels from 50% to less than 20%. The aim of the study was to determine at what level of HbS, C and E an additional α-thalassemia is present, and which pathogenic variants of the alpha genes (HBA1, HBA2) are associated with these three abnormal hemoglobins.

Methods: Retrospective study of samples sent to our institution for hemoglobinopathy assessment. Abnormal Hb were identified by capillary electrophoresis. α-thalassemia testing was performed using DNA extracted from EDTA whole blood. PCR-amplified products were hybridized on a nitrocellulose.

Results: From 8943 hemoglobin electrophoreses performed between 09-2013 and 10-2024, 224 samples with HbS, C, or E and a α-thalassemia test were included in the study. Exclusion criteria were (1) cancellations (n = 408), (2) absence of abnormal Hb or elevated HbA2, i.e. β-thalassemia (n = 7102), (3) absence of α-thalassemia testing, because of abnormal Hb level >40% (according to institutional criteria) or <40% when the prescriber did not follow the recommendation to perform the test (n = 1188), and (4) the presence of Hb variants other than HbS, C, or E (n = 21). Among samples with HbS <40% (n = 131), a very strong predominance of the -3.7 α-globin single gene deletion was detected (n = 76) while two samples had a poly A-2 mutation and 52 samples had no pathogenic α-globin variant. There was a strong correlation between lower percentages of HbS, hemoglobin, Ec count and MCV and the number of α-globin genes (αα/αα vs. -α/αα vs. -α/-α). In HbC and E samples a similar trend was observed for lower percentages of variant Hb, increased Ec count and decreased MCV depending on the number of α-globin genes.

Conclusions: Our results confirm the relationship between abnormal Hb percentages, α-thalassemia, and hematological indices. Specifically, HbS, C and E are almost exclusively associated with the α-thalassemia -3.7 single gene deletion, suggesting an interaction between genetic and selective factors. Based on these results, we will modify the criteria for recommending α-thalassemia test-ing by lowering thresholds from 40% to 36% for HbS, 33% for HbC, and 30% for HbE. This revision will reduce the number of negative test results while maintaining sensitivity to detect cases.

3873

Use of Pegcetacoplan in Swiss Patients with Paroxysmal Nocturnal Hemoglobinuria – Retrospective Case Series Analysis

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Introduction: Pegcetacoplan (PEG), a C3 inhibitor, offers a novel treatment for Paroxysmal Nocturnal Hemoglobinuria (PNH) by preventing both intravascular (IVH) and extravascular hemolysis (EVH), improving outcomes beyond C5 inhibitors. We aimed to report real-world experience with PEG in PNH patients from Switzerland.

Methods: We retrospectively reviewed clinical and laboratory data from all identified Swiss PNH patients treated with PEG via an expert physician network.

Results: Seven patients treated at five Swiss centers were analyzed: five female and two male; two with aplastic anemia; one with myelodysplastic syndrome. At diagnosis, all patients presented with symptomatic hemolysis and 3 had suffered thrombosis. Previously all patients received C5 inhibitors (either eculizumab and/or ravulizumab). The main indications for initiating PEG were ongoing IVH and EVH (in 6/7 and 5/7 patients, respectively) and persistent transfusion dependency (3/7 patients). At PEG initiation, the median hemoglobin (Hb) level was 84.5 g/L (range 68 – 100) and LDH was 308 U/L (range 201-600). PEG was administered at a baseline dose of 1080 mg twice weekly. After 12 months of therapy, the median Hb level had increased to 116 g/L (range 89 -128) and LDH had normalized to 196 U/L (range 158 – 324). One episode of breakthrough hemolysis occurred, associated with infection and was managed by intensifying PEG therapy. Two patients died during PEG treatment, one due to a new neoplasm, another due to acute sepsis; this last patient was admitted in a coma and PEG was discontinued due to lack of information of the attending team about the underlying disease. Death was due to PNH-related complications.

Conclusions: In line with data reported in clinical trials, pegcetacoplan significantly improved anemia and hemolysis in Swiss PNH patients with a favorable safety profile and minimal breakthrough hemolysis. Awareness of therapy discontinuation in critical acute clinical situations should be raised.

9630

BlastenBlaster – An interactive learning program for blood and bone marrow cell differentiation

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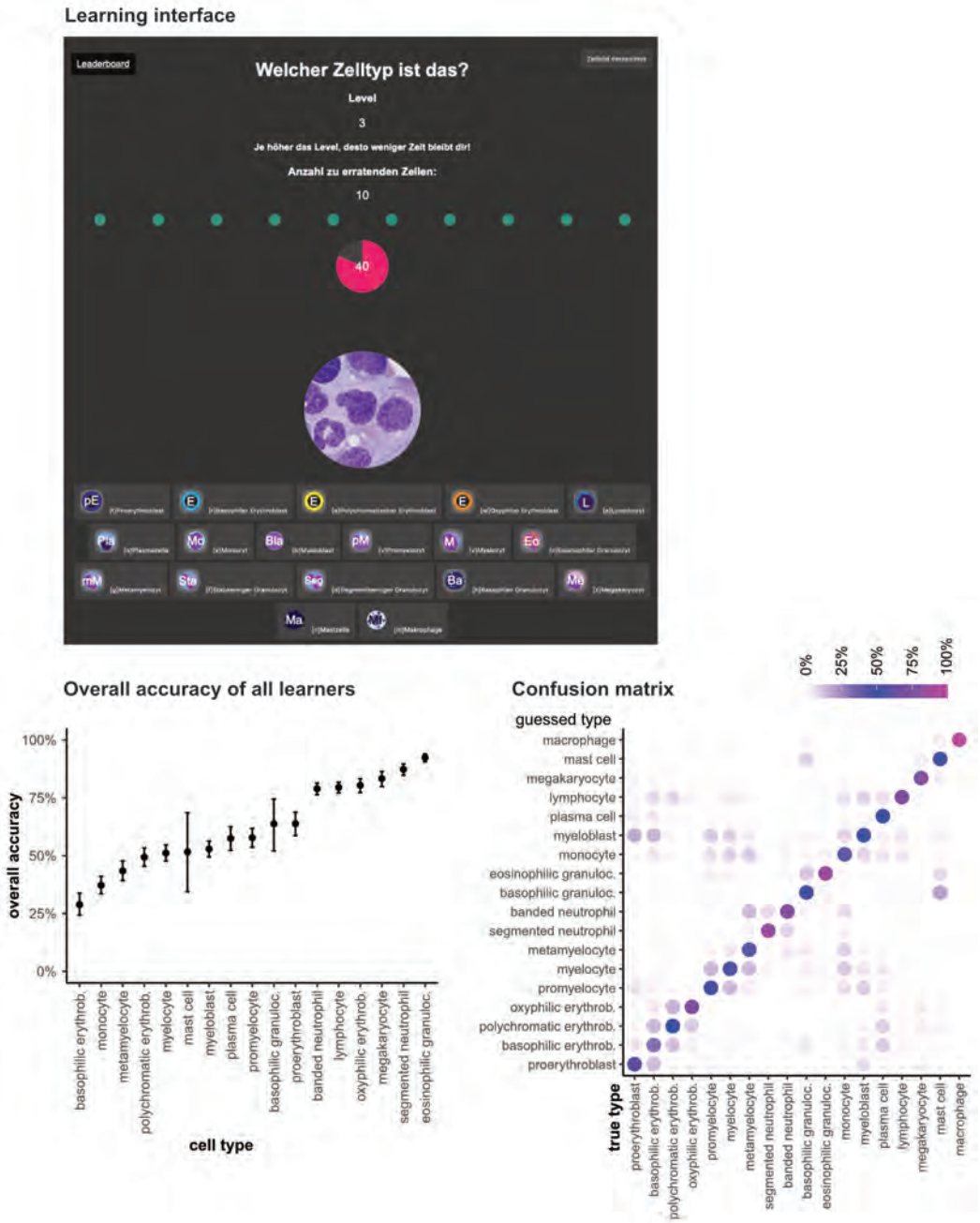
Introduction: Accurate identification of blood and bone marrow cell types in smears is an essential skill of hematologists. Traditional learning tools often use idealized textbook images, which do not reflect real-world ambiguity, limiting real-world applicability. We developed a gamified web-based learning tool to improve cell differentiation skills in an engaging, interactive way.

Methods: The web-based application offers two modes: an open practice mode with randomised cell images at three difficulty levels without time constraints or login, and a competitive "BlastenBlaster" mode requiring login, where users identify 10 cells under a decreasing time limit across levels of growing difficulty. Immediate feedback and a leaderboard enhance motivation. Available time declines logarithmically with level increases. The dataset contains anonymised cell images and metadata provided by haematology experts, with ethical clearance.

Results: Post-launch, the tool was presented to hematologists and biomedical analysts at University Hospital Zurich and is available free of charge at https://www.blastenblaster.uzh.ch to anyone. We then analysed 19,172 cell typing attempts at proficiency ≥3, covering 2,503 cells with a median of 7 guesses per cell; every individual users typed a median of 916 cells. Binomial modelling was used to estimate typing accuracy per cell type; some cell types – basophilic erythroblasts, monocytes, metamyelocytes – appeared especially demanding to differentiate. Confusion clusters were revealed by plotting guessed versus true cell types. To assess the efficacy of training with BlastenBlaster, we measured the increase in accuracy as user progress through the levels and found an odds ratio (OR) of 1.42 (95% CI 1.37–1.47, $p < 0.0001$) per 10 levels of learning progression. User survey feedback revealed high satisfaction ratings (4.6–4.7/5) and perceived skill improvements (4.3/5), underscoring the application's educational benefit.

Conclusions: BlastenBlaster provides an innovative, interactive platform combining practice and competition to enhance hematology education through gamification. Individual training with BlastenBlaster substantially improves accuracy, particularly for difficult-to-recognize blood cell types. Positive user feedback supports its use for exam preparation and professional development. Wider adoption could broaden its impact across health disciplines.



3134

Defining indications for thrombophilia testing– a modified Delphi consensus study in Switzerland

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Introduction: Thrombophilia is a hereditary or acquired condition associated with an increased risk of venous thromboembolic events (VTE) and VTE-recurrence. The clinical relevance of thrombophilia testing remains uncertain, and existing recommendations regarding patient selection for testing are inconsistent. This has resulted in considerable variability of thrombophilia testing in clinical practice nationally and internationally.

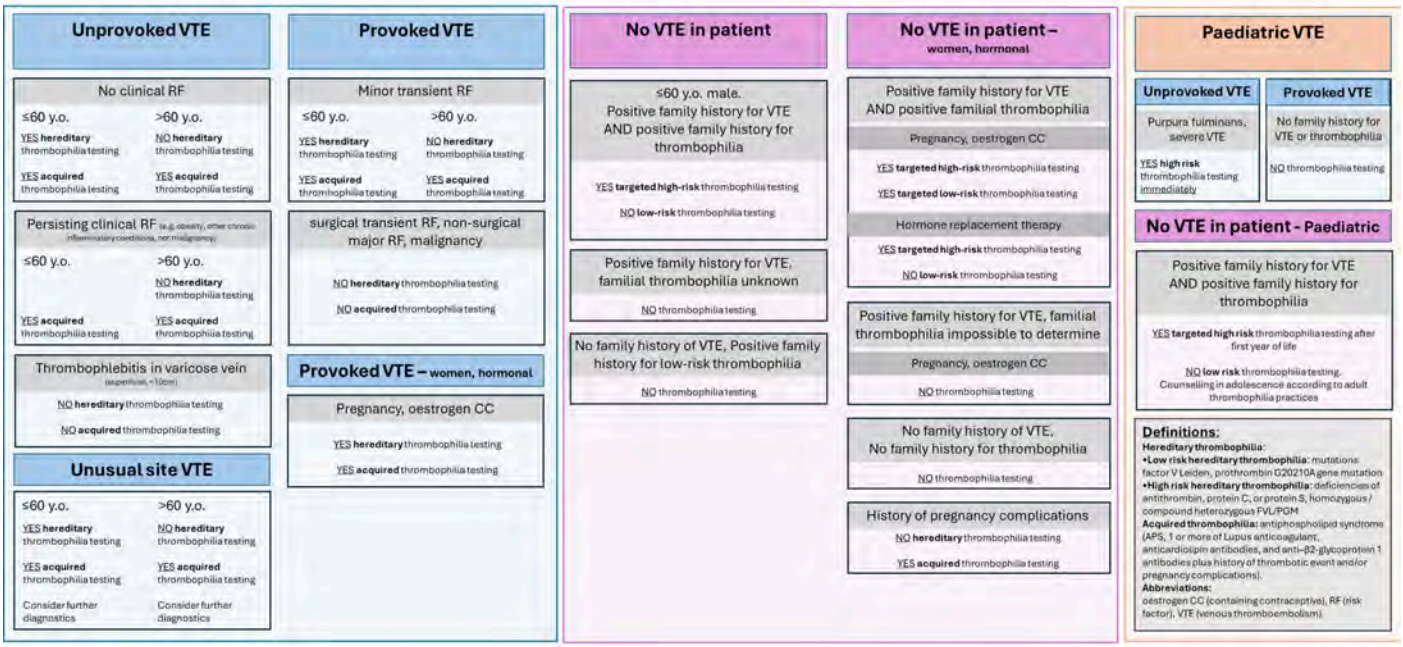
This Delphi survey was conducted to establish expert consensus on thrombophilia testing in Switzerland.

Methods: A modified Delphi study was performed with clinical experts managing VTE-patients in Switzerland. A steering committee developed clinical scenarios and statements on thrombophilia testing. These were distributed to the expert panel who rated their agreement and provided written feedback. Consensus was defined as ≥70% of experts rating a statement ≥5 on a 7-point Likert scale.

Results: Forty-two clinical experts completed the survey. Consensus was reached after two rounds on 32 statements covering indications such as unprovoked VTE, provoked VTE (incl. hormonal risk factors), unusual site VTE, paediatric VTE, and

patients without VTE. Strong consensus supported thrombophilia testing in patients <60 y.o. with unprovoked VTE, women with hormone-associated VTE, or unusual-site VTE. Consensus discouraged testing in patients with VTE and major transient risk factors and in asymptomatic individuals with VTE in family history where familial thrombophilia is unknown. No consensus was reached on testing patients <60 y.o. with unprovoked VTE and an additional persistent VTE-risk factor. Figure 1 shows statements where consensus was reached.

Conclusions: In this modified Delphi process, an expert panel achieved consensus on 32 practical recommendation statements defining indications for thrombophilia testing. The consensus statements align with most existing recommendations, though some diverge (e.g., thrombophilia testing in unprovoked VTE). The consensus provides clear guidance for physicians on thrombophilia testing in specific clinical scenarios. Dissemination of this study to front-line clinicians will contribute to harmonised testing across Switzerland. By standardising strategies, these statements may reduce variability in care, support consistent clinical decision-making, and ultimately improve patient counselling, management, outcomes and healthcare resource use.



4995

Clinical utility of thrombin generation using ST-Genesia® instrument in patients with hereditary and acquired thrombophilia

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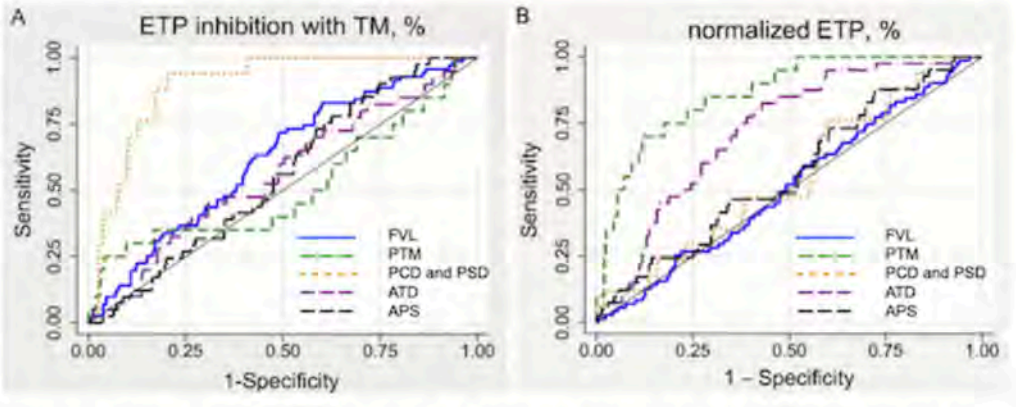
Introduction: The diagnostic utility of thrombin generation (TG) in patients with thrombophilia is unknown. We investigated the ability of TG to discriminate between patients with and without hereditary or acquired thrombophilia, to complement thrombophilia testing as a rule-out diagnostic tool in patients at high risk of arterial thrombosis or venous thromboembolism (VTE).

Methods: TG was measured in all non-anticoagulated patients who underwent thrombophilia testing for factor V Leiden (FVL), prothrombin gene G20210A mutation (PTM), protein C, S and antithrombin deficiency (PCD, PSD, ATD), and antiphospholipid antibody syndrome (APS) because of previous VTE, unexplained arterial thrombosis or a positive family history for VTE over the period of 3 years using ST-Genesia® instrument/STG-Thromboscreen® assay. To assess the screening utility of TG, we calculated the area under the receiver operating curve (AUC), and thresholds for 85%, 95% and 99% sensitivity, followed by associated positive and negative predictive values and likelihood ratios of each TG parameter for all investigated thrombophilias. To assess the clinical utility, cohort-related diagnostic failure rates (% of false negative) and the diagnostic yield (% in whom thrombophilia could be ruled out) were also calculated.

Results: Out of 804 screened patients, 467 (median age 43, interquartile range 32 – 56; 59% female) could be included in the analysis. Most patients were referred because of previous VTE (n = 283, 61%). Thrombophilia testing was positive in 161 patients (35%). Normalized endogenous thrombin potential (ETP) effectively discriminated for ATD (AUC = 79 [95%CI 72–87]) and PTM (AUC 86 [95%CI 79–93]) while ETP inhibition with thrombomodulin discriminated for PCD/PSD (AUC 90 [95%CI 85–95]) (Figure 1B, A). Using the established best-performing TG parameter cut-offs (Table 1), PCD/PSD, PTM, ATD, and low-risk APS could be safely (<3% failure rate) excluded in 62%, 58%, 27%, and 29% of cohort patients, respectively.

Conclusions: TG assessment using ST-Genesia® system shows promise as a supportive screening tool in the thrombophilia work-up, safely avoiding further testing in at least a quarter of patients and reducing testing-related costs. Incorporating TG into the thrombophilia testing framework could enable a more individualised approach to the diagnostic and clinical management of patients with high thrombotic risk.

Figure 1. Diagnostic accuracy of ETP inhibition with TM (A), normalized ETP (B) for all investigated thrombophilias.



Abbreviations: APS, antiphospholipid antibody syndrome; ATD, antithrombin deficiency; ETP, endogenous thrombin potential; FVL, factor V Leiden; PCD, protein C deficiency; PSD, protein S deficiency; PTM, prothrombin gene G20210A mutation; TM, thrombomodulin.

Table 1. Overall diagnostic performance of clinical utility of selected thrombin generation parameter to exclude all types of investigated thrombophilias.

	TG parameter	Cutoff	Sensitivity (95 % CI)	NPV (95 % CI)	Negative LHR (95 % CI)	Post-test probability, % (failure rate)	Proportion of patients below the cutoff (yield, %)
Protein C and S deficiency	ETP + TM, nM/min	734.0	88.2 (65.7-97.7)	99.5 (98.1-99.9)	0.17 (0.05-0.62)	0.6	62.1
Antithrombin deficiency	Normalized ETP, %	87.3	97.5 (87.1-99.6)	98.9 (94.3-99.8)	0.09 (0.01-0.64)	0.8	26.8
Factor V Leiden mutation	ETP + TM, nM/min	470.0	85.9 (76.0-92.2)	92.1 (86.1-95.7)	0.48 (0.26-0.86)	7.8	27.2
Prothrombin gene G20210A mutation	Normalized ETP, %	102.0	90.0 (69.9-97.2)	99.3 (97.3-99.8)	0.17 (0.05-0.63)	0.8	57.8
Antiphospholipid antibody syndrome	Start tail ratio	0.98	95.1 (83.9-98.7)	98.3 (94.2-99.5)	0.17 (0.04-0.67)	1.6	29.1

Abbreviations: CI, confidence interval; ETP, endogenous thrombin potential; TM, thrombomodulin; TG, thrombin generation; PPV, positive predictive value, NPP, negative predictive value, LHR, likelihood ratio.

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What is the best way for a blood bank to manage immune-hematological interference related to Daratumumab treatment?

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Introduction: Daratumumab (Dara) treatment can produce artefacts in pre-transfusion tests, which makes difficult to identify anti-erythrocyte antibodies that are relevant for transfusion. Its use is increasing, primarily in the treatment of multiple myeloma. There are two options for avoiding immune hemolytic transfusion reactions. Either select red cell concentrates (RCC) that are at the least incompatible with common antigens known to be harmless, or use pre-analytical techniques to eliminate artefacts, such as treating the test red blood cells or the patient's serum. According to a previous evaluation in our laboratory, treating test red blood cells with trypsin and dithiothreitol (DTT) enables the search for common antibodies to be completed in 97% of cases. However, this method needs about three hours of work. The aim of this study is to evaluate whether this approach is justified for a proper management of a blood bank.

Methods: We examined transfusion records of all patients having received Dara treatment at our hospital. All of them received transfusions after undergoing complete pre-transfusion testing to exclude all current and dangerous antibodies. We examined the immunization rate, the average number of transfusions and the number of immunohematological workup after the start of Dara treatment.

Results: Between January 2016 and September 2025, we detected four cases (2%) of new alloimmunization among 194 patients treated with Dara. Ten patients were alloimmunized, six of whom were already carriers of an alloantibody prior to commencing Dara treatment. The average number of immune-hematological workup after the start of treatment and the average number of transfusions per patient were 4.7% and 5.65 respectively. The number of pre-transfusion testing was 920 and 1074 red cell concentrates could be transfused without selecting the less incompatible product.

Conclusions: Only 2% of patients experienced alloimmunization after starting dara treatment This rate is notably much lower than that of sickle cell patients. Efforts to perform complete pretransfusion testing, allows selection of RCC according to the "type&screen" concept instead of choosing the less incompatible product (RH, KEL, FY, JK, MNS). This allows the preservation of precious blood resources for patients at high risk of alloimmunization, such as sickle cell patients, or already alloimmunized patients.

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Biopsy-based KIT D816V digital droplet PCR improves detection of residual disease after allogeneic hematopoietic cell transplantation in systemic mastocytosis

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Introduction: Background: Systemic mastocytosis (SM) is a rare myeloid neoplasm, most frequently driven by the somatic KIT D816V mutation. Allogeneic hematopoietic cell transplantation (allo-HCT) is the only curative option in advanced SM. Measurable residual disease (MRD) remains challenging, as mast cells are tissue resident and often not aspirable, potentially limiting the sensitivity of molecular testing from bone marrow smears or peripheral blood. Objective: To assess the concordance of KIT D816V digital droplet PCR (ddPCR) performed on formalin-fixed and EDTA-decalcified bone marrow biopsies versus aspirates in SM patients after allo-HCT and to evaluate the potential role of biopsy-based ddPCR result for MRD monitoring.

Methods: We retrospectively analyzed 17 bone marrow samples from 8 patients with advanced systemic mastocytosis who underwent allo-HCT at our institution between 2019 and 2025. Mast cell infiltration was assessed on bone marrow biopsies applying immunohistochemistry for mast cell tryptase and CD117. KIT D816V was quantified by ddPCR from aspirates and from DNA extracted from histological bone marrow biopsy sections.

Results: A clear discrepancy was observed between biopsy-based and aspirate-based KIT D816V detection. In seven paired analyses, the biopsy result remained positive while the corresponding aspirate was negative. No sample demonstrated the opposite pattern. This discordance between biopsy and aspirate results was statistically significant (exact McNemar's test, P = 0.016).

Conclusions: KIT D816V ddPCR testing on bone marrow biopsies appears more sensitive for MRD detection in SM after allo-HCT than analysis of aspirates, likely reflecting the poor aspirability of mast cells. Biopsy-based molecular monitoring may therefore represent a valuable tool for post-transplant disease assessment and warrants prospective validation.

Results of digital droplet PCR for *KIT* D816V

		Bone marrow biopsy	
		negative	*positive*
Bone marrow aspirate	*negative*	**5**	**7**
	positive	**0**	**5**

Exact McNemar's test: $P = 0.016$

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Mitochondrial DNA Enhances Adrenaline-Induced Platelet Activation in Type-II Diabetes Mellitus

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Introduction: This study is designed to explore the priming effect of mtDNA on Adr-induced activation of platelets.

Methods: Platelets were obtained from healthy donors (HD) and diabetic patients (DP). Time-lapsed based spectrophotometric assay was employed to measure Adr-induced platelet aggregation. mtDNA was isolated from platelets for assessing the priming effect on healthy platelets. To elucidate mitochondrial function, mtDNA primed platelets were treated by the anti-diabetic drug metformin, which is also and inhibitor of complex I of electron transport chain (ETC).

Results: Our results showed that Adr-induced platelet aggregation is significantly increased in DP compared to HD. We observed that mtDNA primes platelets in HD and enhances their Adr-induced aggregation. Interestingly, application of metformin significantly decreased the Adr-induced platelet aggregation in HD. with a similar tendency to reduce the priming effect of mtDNA on Adr-induced platelet aggregation.

Conclusions: The present study revealed that (1) Adrenaline-induced platelet activation was accelerated in diabetic patients compared to healthy donors and (2) In vitro priming of healthy platelets with mtDNA augmented adrenaline-induced aggregation, which could reflect the pathophysiological condition in diabetic patients. These data suggest that cell-free mtDNA enhances platelet reactivity and that this may be hampered by metformin

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Evaluation of Sebia Free Light Chain ELISA Tests in a routine diagnostic laboratory

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Introduction: Serum free light chain (FLC) Kappa/Lambda (K/L) ratio is used for diagnosis and monitoring of clonal B-cell or plasma cell disorders. This study compares the concordance of FLC measured with Freelite on the Optilite (The Binding Site) and SEBIA FLC (Sebia) on the Dynex Agility platform.

Methods: Non-interventional study analyzing consecutive, unselected samples in routine diagnostic laboratory settings using both methods. Patients were classified as normal, high-risk smoldering multiple myeloma (HRSMM) or multiple myeloma (MM) based on FLC results obtained with Freelite and Sebia according to IMWG criteria, i.e. K/L ratio >20 for HRSMM and K/L ratio >100 for MM, respectively. Comparation and agreement were assessed with appropriate nonparametric tests.

Results: Between January 28, and June 3, 2025, a total of 2995 samples were analyzed; 36 (1.2%) samples were excluded and 2959 (98.2%) included in the statistical analysis. Concentration of FLC and the K/L ratio were significantly different between both methods (p <0.0001), especially for samples with high levels of FLC (>150 mg/L; p <0.0001). Methods agreement was high (96.3%) for cohorts with normal K/L ratio but low for cohort with abnormal ratio (47.2%). Overall, the agreement classification with IMWG criteria reached 77.8% [95% CI: 76.2% – 79.2%]

for the total cohort, 57.4% [95%CI: 48.0% – 66.3%] for the HRSMM group and 45.5% [95% CI: 33.0% – 58.5%] for the MM group. 1609 samples out of 2959 (54% of the cohort) were negative for monoclonality at both protein electrophoresis and immunofixation. Of these, 294 samples (18.3%) fell outside the normal range (0.26 – 1.65) with the Freelite test, mostly just above the upper limit, while with Sebia they were within normal limits (0.27 – 1.67). 81% of these outliers had Freelite ratios between 1.65 and 2.14. Only 2.1% of samples with normal Freelite ratios exceeded the Sebia reference values.

Conclusions: Quantitative agreement between both methods was low, probably explained by Freelite limitations such as Kappa drift, as already known in the literature. Despite limited quantitative agreement, IMWG risk classification was good, supporting commutability of the "20" and "100" cut-offs with Sebia FLC assays. Because this study does not include clinical data, further studies are needed to confirm this observation.

8459

Case report: a novel approach to prevent chronic histiocytic intervillositis and recurrent pregnancy loss by targeting maternal alloimmunity

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Introduction: Recurrent pregnancy loss (RPL) is a distressing condition with limited therapeutic options. Chronic histiocytic intervillositis of unknown etiology (CIUE) is an inflammatory placental disorder characterized by maternal immune cell infiltration of the intervillous space, fibrin deposition, and ischemic tissue damage, leading to RPL. The condition likely reflects an immune response against paternal alloantigens, with histopathological features resembling antibody-mediated rejection in solid organ transplantation.

Methods: We investigated two women with CIUE-related RPL. Detailed immunological profiling included anti-human leukocyte antigen (HLA) antibody characterization, compatibility testing, and histopathological examination of previous placentas, as well as screening for other causes of recurrent pregnancy losses. Based on evidence of antibody-mediated alloimmune injury, we implemented a targeted immunosuppressive regimen derived from transplantation medicine, combining intravenous immunoglobulins (IVIG), tacrolimus, corticosteroids, and hydroxychloroquine, with close pregnancy monitoring.

Results: The first patient, after six consecutive CIUE-related pregnancy losses, underwent preconception desensitization and continued treatment throughout pregnancy. Early signs of placental dysfunction prompted therapy intensification, leading to delivery of a viable infant at 33+2 weeks. Placental histology showed only minor residual CIUE lesions. The second patient, with two pregnancy losses miscarriages and a fetal demise from CIUE, began treatment at 6 weeks' gestation and delivered a healthy infant at 36 weeks. In both cases, therapy was generally well tolerated, with gestational diabetes as the main complication, and no major maternal or neonatal adverse events.

Conclusions: These cases support the concept that CIUE represents a breakdown of maternal immune tolerance toward paternal antigens, mediated by fetal-specific anti-HLA antibodies – akin to solid organ graft rejection. An immunosuppressive protocol adapted from transplantation medicine achieved two successful live births after multiple CIUE-related pregnancy losses. Targeting antibody-mediated alloimmunity may represent a promising therapeutic strategy for selected patients with recurrent miscarriage due to CIUE. Further studies are warranted to define optimal regimens and identify predictors of response.

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Impact of recalcification on procoagulant COAT platelet generation in PRP samples with low platelet counts

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Introduction: Assessment of platelet procoagulant function by flow cytometry is increasingly recognized for diagnosing platelet disorders. Induction and accurate detection of phosphatidylserine exposure on platelets' surface requires proper recalcification of citrated blood samples, particularly in thrombocytopenic patients, where residual citrate can limit extracellular calcium availability. The objective is to define optimal recalcification conditions for reliable measurement of procoagulant COAT platelets in platelet-rich plasma (PRP) samples with low platelet counts.

Methods: Fresh PRP from healthy donors was diluted with autologous platelet-poor plasma to simulate platelet counts from 160 G/L down to 15 G/L. Undiluted PRP (control) and diluted samples were spiked with varying calcium concentrations and stimulated with convulxin and thrombin. Flow cytometry was used to measure annexin V and PAC1 binding to assess procoagulant platelet generation.

Results: For platelet counts ≥100 G/L, no additional calcium beyond buffer levels was required. For platelet counts between 30–80 G/L, supplementation with 3 mM calcium restored procoagulant platelet generation within 85–115% of undiluted PRP control levels. Counts of 20–30 G/L required 5 mM calcium. Of note, higher calcium concentrations (>5 mM) impaired platelet function, highlighting the need to avoid excessive recalcification.

Conclusions: Optimized recalcification prevents underestimation of procoagulant platelet potential in thrombocytopenic samples. This practical approach addresses a key gap identified by the ISTH SSC and helps laboratories to ensure reliable platelet function testing in PRP samples from thrombocytopenic patients.

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Spontaneous post-orthopedic HIT-like syndrome: a case report and literature review with diagnostic / therapeutic recommendations for a rare life-threatening complication

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Introduction: Spontaneous heparin-induced thrombocytopenia-like syndrome (spHIT), a subtype of autoimmune HIT, is a rare but severe thromboembolic complication typically occurring after orthopedic surgery, particularly total knee arthroplasty (TKA). Given the limited number of reported cases, guidelines are lacking. We aim to describe a new case of spHIT after TKA and suggest diagnostic and therapeutic approaches.

Methods: We report an unpublished case and a review of published cases (n = 22).

Results: A 57-year-old man was admitted to a peripheral hospital with epigastric pain on postoperative day (POD) 7 after TKA. He was receiving thromboprophylaxis with rivaroxaban and had not been exposed to heparin. Platelet count was 473 G/l. CT-scan revealed pneumonia, which was treated with antibiotics. From POD 8, the patient experienced a rapid decline of the platelet count (38 G/l at POD 11). On POD 11, hemodynamic instability prompted imaging and demonstrated pulmonary embolism, hepatic and renal vein thromboses, as well as bilateral adrenal hemorrhages. Therapeutic anticoagulation with unfractionated heparin was initiated. At POD 12, spHIT was suspected, and anti-PF4/heparin antibodies were tested. Heparin was continued, and intravenous immunoglobulins (IVIG; 0.4 g/kg) were administered. On POD 13, the patient suffered an ischemic stroke. Anti-PF4/heparin antibodies returned positive. Heparin was discontinued, IVIG (1 g/kg) were given, and the patient was transferred to a tertiary center for argatroban treatment. Clinical evolution was favorable, with full platelet recovery by POD 14. A positive heparin-induced platelet aggregation (HIPA) assay confirmed the suspicion of spHIT. A summary of this case and previously reported cases is presented in Table 1.

Conclusions: SpHIT is a prothrombotic condition that is likely underdiagnosed, as recognized only after thromboembolic complications. In particular, adrenal infarctions or hemorrhages (secondary to adrenal vein thrombosis) should prompt consideration of spHIT in post-orthopedic surgery patients. Considering the surgery day as day 0, the 4T score appears adequate to assess pretest probability, with high scores reported in all cases. Prompt initiation of non-heparin anticoagulation is warranted. Early administration of IVIG is key for a successful treatment, given the frequent argatroban resistance.

Study (reference)	Report year	Age (years)	Sex	Surgery	Venous thromboembolic prophylaxis	Platelet count at spHIT diagnosis (G/l)	Timing of thrombocytopenia (POD)	Alternative causes of thrombocytopenia	4T score at spHIT diagnosis	Thrombo-embolic events	Timing of events (POD)	Diagnosis mode	Acute treatment	Further treatment	Outcome
Illustrative case	2025	57	Male	Total knee arthroplasty	Rivaroxaban	38	8	Infection, antibiotics	7	Renal vein, hepatic vein thromboses, PE, bilateral adrenal hemorrhage, CVI under heparin	11, 13	EIA positive HIPA positive	Argatroban IVIG 0.4 and 1 g/kg at two following days	Acenocoumarol for three months	Rapid complete platelet count recovery under argatroban and IVIG
Olevsky and Rosove	2021	57	Female	Total knee arthroplasty	Aspirin	70	10	Possible (infection)	7	Acute segmental PE, acute left popliteal DVT	10	ELISA IgG strongly positive SRA strongly positive	Therapeutic argatroban	Rivaroxaban for six months	Rapid platelet count recovery and D-dimers decrease
Olevsky and Rosove	2021	70	Female	Total knee arthroplasty	Aspirin	27	NR	No	6		NR	ELISA IgG strongly positive SRA strongly positive	Therapeutic argatroban	Apixaban for an unclear duration	Progressive platelet count recovery over two weeks
Warkentin and Greinacher	2021	70	Female	Total knee arthroplasty	Aspirin	50	20	No	7	Popliteal DVT, iliac artery thrombosis, recurrence at day 36, Rethrombosis at day 36 and 38, amputation of the lower limb, PE and popliteal DVT, PICC DVT at day 38 under argatroban	20, 36, 38	EIA positive SRA positive	Therapeutic argatroban with thrombolysis, rivaroxaban 2x 15mg IVIG	Rivaroxaban 2x 15 mg for an unclear duration	Thromboses under UFH and under argatroban, partial recovery of platelet count at day 54 under rivaroxaban and IVIG
Saengbon et al.	2021	68	Female	Bilateral total knee arthroplasty	NR	52	12	Antibiotics	6	Lower extremity arterial occlusion, progression under UFH, adrenal hemorrhage	12, 16, 18	HIPA positive	Fondaparinux IVIG (1 g/kg on two following days)	Apixaban for three months	Rapid complete platelet count recovery after fondaparinux and IVIG
Hwang et al.	2020	58	Female	Total knee arthroplasty	Aspirin	43	11	No	7	Cerebral venous sinus thrombosis, DVT of the left internal jugular vein	11	EIA moderately to strongly positive SRA strongly positive	Bivalirudin IVIG (1 g/kg on two following days)	Long-term warfarin	Progressive platelet count recovery until post-operative day 25
Swan et al.	2020	32	Male	Left femoral and tibial curettage, bone grafting with nailing for monostotic fibrous dysplasia	-	49	10	No	6	PE in main and descending pulmonary arteries, extensive proximal and distal DVT	10	ELISA IgG strongly positive SRA positive	Therapeutic argatroban	Warfarin for two years	Platelet count recovery in one week
Hornick and Aydin	2020	51	Male	Bilateral total knee arthroplasty	Aspirin	111	11	No	6	Bilateral subsegmental PE, bilateral femoral and popliteal DVT	16	ELISA positive HIPA positive	Rivaroxaban	Rivaroxaban for three months	Complete platelet count recovery at one month
Van der Veer et al.	2019	66	Male	Total knee arthroplasty	Rivaroxaban	71	8	No	6	Bilateral adrenal infarction		EIA strongly positive SRA strongly positive	Prophylactic rivaroxaban until day 26	Prophylactic rivaroxaban for one month	Complete platelet count recovery
Alidoost et al.	2019	66	Female	Total knee arthroplasty	Rivaroxaban	35	12	No	7	Bilateral adrenal hemorrhage occurring after IVC filter placement, DVT in the IVC in the right lower extremity	3	SRA positive	Therapeutic argatroban	Warfarin for an unclear duration	Complete platelet count recovery
Mohanty et al.	2019	52	Female	Total knee arthroplasty	Aspirin	63	13	No	6	Ischemic colitis/ mesenteric ischemia	12	EIA strongly positive SRA positive	Therapeutic argatroban, fondaparinux IVIG (1 g/kg on two following days)	Fondaparinux for an unclear duration	Persistence and worsening of thrombocytopenia under argatroban and fondaparinux, rapid recovery after IVIG
Poudel et al.	2017	53	Female	Total knee arthroplasty	Aspirin	18	15	No	6	Acute PE	14	ELISA strongly positive SRA strongly positive	Fondaparinux, argatroban with new DVT	Rivaroxaban	No improvement under fondaparinux, DVT under argatroban at day 39, progressive platelet count recovery under rivaroxaban (day 79); SRA negative at day 151, EIA further positive
Baker and Lim	2017	72	Female	Total knee arthroplasty	Aspirin	25	12	No	7	Bilateral PE, left cephalic, left common femoral, left popliteal, right posterior tibial vein DVT	12	EIA strongly positive SRA strongly positive	Therapeutic argatroban, IVC filter placement, platelet transfusion	Apixaban for three months	Complete platelet count recovery at day 28
Elshoury et al.	2015	46	Female	Total knee arthroplasty	Aspirin	57	8	No	6	Bilateral adrenal hemorrhage, bilateral PE	8, 10	EIA strongly positive SRA strongly positive	Therapeutic argatroban with recurrent PE, IVC filter placement	Warfarin	Thromboses under argatroban, complete platelet count recovery
Warkentin et al.	2015	71	Female	Total knee arthroplasty	Apixaban	37	12	No	7	Bilateral adrenal hemorrhage, PE, inferior vena cava and popliteal DVT	12, 13	EIA strongly positive SRA strongly positive	Therapeutic argatroban	Fondaparinux for three months	Complete platelet count recovery
Warkentin et al.	2014	34	Female	Shoulder hemiarthroplasty	NR	85	15	No	7	Upper-extremity DVT, acute CVI of the left posterior inferior cerebellar artery territory	15	EIA strongly positive SRA strongly positive	Therapeutic argatroban	Fondaparinux for three months	Progressive complete platelet count recovery
Ketha et al.	2013	90	Female	Total knee arthroplasty	NR	NR	NR	NR	5	Adrenal hemorrhage	NR	EIA positive SRA positive	NR	NR	NR
Ketha et al.	2013	65	Male	Total knee arthroplasty	NR	NR	NR	NR	5	Adrenal hemorrhage	NR	EIA positive	NR	NR	NR
Ketha et al.	2013	71	Female	Total knee arthroplasty	NR	NR	NR	NR	6	Adrenal hemorrhage	NR	EIA positive	NR	NR	NR
Ketha et al.	2013	81	Female	Total knee arthroplasty	NR	NR	NR	NR	6	Adrenal hemorrhage	NR	EIA positive SRA positive	NR	NR	NR
Mallik et al.	2011	90	Male	Bilateral total knee arthroplasty	Warfarin	20	10	DD ITP	7	Left popliteal DVT, bilateral lower extremity DVT under argatroban	11	EIA positive SRA positive	Therapeutic argatroban, IVIG (1 g/kg on two following days) after rethrombosis	Warfarin for 10 months	Complete recovery at day 53
Pruthi et al.	2009	61	Female	Total knee arthroplasty	Warfarin	29	8	NR	6	Bilateral adrenal hemorrhage, saphenous DVT, non-occlusive popliteal and femoral DVT	7	EIA positive SRA positive	IVC placement, argatroban with PE and progression of DVT, lepirudin	Warfarin for an unclear duration	Progressive complete platelet count recovery
Jay and Warkentin	2008	69	Female	Total knee arthroplasty	Warfarin	51	9	No	6	Lower extremity DVT, digital infarcts, bilateral adrenal hemorrhage, DIC [illegible]	9, 11	EIA positive SRA strongly positive	Danaparoid	NA	Progressive complete platelet count recovery at day 23, death from complications of anoxic brain damage

SSH/SSMO POSTER PRESENTATION – EXPERIMENTAL HEMATOLOGY / ONCOLOGY

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Dissecting MLL–ENL and MLL–ELL Fusions in Infant AML: a CRISPR Human HSPC Model for Biology and Therapy

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Introduction: MLL (KMT2A) rearrangements (MLLr) account for >50% of infant acute myeloid leukaemia (AML), drive chemoresistance and poor outcomes, and can initiate malignancy with few cooperating mutations, yet faithful human models remain scarce. We built a human, patient-relevant platform to define MLL–ENL and MLL–ELL biology and therapeutic vulnerabilities in AML.

Methods: Patient-informed sgRNAs targeting recurrent MLL introns 9/11 and ENL/ELL intron 1 were delivered as Cas9 ribonucleoprotein complexes into $CD34^+$ haematopoietic stem and progenitor cells from cord blood and cultured in myeloid-inductive medium. Fusion junctions were confirmed by PCR and Sanger sequencing; fluorescence in situ hybridisation (FISH) quantified fusion-positive fractions. Leukemic transformation was measured by colony-forming assays, long-term growth and flow-cytometric immunophenotyping. Bulk RNA-seq profiled transcriptional programmes; whole-cell liquid chromatography–mass spectrometry (LC–MS) proteomics and immunohistochemistry (IHC) are ongoing.

Results: Within 8 weeks, our system generated fifteen fusion-positive cultures from independent donors, showing >90% MLLr purity by FISH and faithfully reproducing key patient-like AML phenotypes. All cultures showed sustained proliferation versus controls, robust colony formation, and enrichment of $CD34^+CD38^-$ and $CD34^+CD90^+$ stem-like compartments with

high CD33, CD56, CD64 and CD117 and reduced/stable CD14 expression, mirroring primary MLLr AML. Transcriptomics revealed canonical MLLr signatures (HOXA cluster, MEIS1, SKIDA1↑; CEBPE, ETS1, CD1A/C↓). Several features varied between fusions, consistent with fusion-driven molecular differences. Differential expression nominated repurposable/novel targets upregulated in our cells and patient cohorts: MEIS1, HOXA9, RET, CRNDE, PRLR, RNF220, GPC3, PLXNA4 and STS. LC–MS is validating signatures and targets to guide drug screens and test pharmacological validity. IHC is confirming immunophenotypes.

Conclusions: Our CRISPR-engineered human HSPC system faithfully recapitulates infant MLLr AML, delineates fusion-specific biology and reveals actionable vulnerabilities. Planned in vivo xenografts will test leukemogenicity and benchmark menin inhibitors alongside agents against the nominated targets, supporting a predictive platform for mechanistic and pre-clinical studies.

5002

CAR T Cells Secreting Synthetic Proteins to Target Solid Tumors

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Introduction: CAR T cell therapy is highly effective for treating hematological malignancies; however, challenges remain in applying this treatment option to solid tumors. One such challenge is the immunosuppressive tumor microenvironment (TME). To target the TME more effectively, Wehrli et al. previously developed large CAR T cell constructs that secrete bispecific T cell engagers (TCEs) composed of single-chain variable fragments (scFvs). Based on these so-called CARTEAM cells, we hypothesized that using the smaller, synthetic Designed Ankyrin Repeat Proteins (DARPins) as alternative protein structures might allow the integration of multiple TCEs into a single CAR T cell. This could further enhance the efficacy of CAR T cells in treating solid tumors.

Methods: We generated anti-mesothelin CAR T cells secreting DARPins by lentiviral transduction of T cells from healthy donors. Their functionality was evaluated through various in vitro cell cytotoxicity assays, including a Luciferase-based killing assay and a real-time cytotoxicity assay, and compared to CAR T cells secreting scFvs.

Results: We observed successful secretion of DARPins into the supernatant and lysis of target cells after exposure to DARPin-secreting CAR T cells or their supernatant, combined with untransduced T cells. Their performance was similar to CAR T cells secreting scFvs, except when the supernatant containing TCEs was diluted. Moreover, CAR T cells secreting DARPins exhibited higher transduction efficiencies compared to those secreting scFvs.

Conclusions: We hypothesize that DARPins can be released from CAR T cells to promote the killing of target cells. When diluted, DARPins exhibited lower cytotoxicity than scFvs, suggesting that DARPins are most effective at high concentrations, such as at the secretion site. Additionally, DARPins may incorporate into T cells more efficiently.

3817

Machine learning approach identifies targeting strategy for selective AML dependency

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Introduction: Acute myeloid leukaemia (AML) remains difficult to treat, with limited targeted therapies and poor outcomes. We previously identified Interferon Regulatory Factor 2 Binding Protein 2 (IRF2BP2) as a selective AML dependency, demonstrating that its loss induces cell death in AML patient cells, while sparing colony-forming capacity in healthy donor-derived $CD34^+$ bone marrow cells, thus suggesting a therapeutic window for targeting IRF2BP2. Still, no IRF2BP2-specific molecules are currently available for clinical testing.

Methods: To address this limitation, we developed a computational pipeline integrating machine learning with transcriptomic data to identify upstream druggable regulators of IRF2BP2. We trained over 90 neural network architectures on publicly available AML bulk RNA sequencing data to predict IRF2BP2 expression levels. We then evaluated their performance using the coefficient of determination (R^2). Gene-level attribution scores were applied to ranked candidate regulators, distinguishing positive and negative influences. In parallel, a closed-form linear regression model predicted IRF2BP2 expression as a weighted sum of other genes, providing interpretable coefficients. An integrative analysis across both approaches prioritised genes consistently highlighted as regulators, thereby refining the candidate list and strengthening confidence.

Results: Among the top candidates, insulin receptor substrate 2 (IRS2) emerged as a robust positive regulator of IRF2BP2, thus predicting that reduced expression of IRS2 should lead to decreased IRF2BP2 expression. To test our model, we treated AML cell lines and patients derived AML cells with NT157, a selective IRS1/2 inhibitor, known to decrease IRS2 expression. Upon treatment with low NT157 concentrations, we found decreased IRF2BP2 protein expression after a few hours, phenotypically followed by a reduction in cell viability and an increase in Annexin/PI positive cells as a surrogate marker of apoptosis.

Conclusions: Our study presents a machine learning framework to identify transcriptional regulators of cancer dependencies. Experimental validation of one predicted regulator underlines the biological relevance of our strategy. This approach may facilitate the discovery of therapeutic entry points for biologically hard-to-characterize or otherwise intractable targets across diverse biological contexts.

3274

Overall survival in patients with Recurrent/Metastatic Head and Neck cancer after systemic therapy treated with an encapsulation-based cellular immunotherapy

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Introduction: Over the past two decades, most cancer vaccines have failed to translate into clinical benefit. This may be due to inefficient priming with tumor-relevant antigens and/or insufficient immunostimulation. A novel encapsulation-based cell immunotherapy has been developed, combining inactivated autologous tumor cells with encapsulated allogeneic human cells genetically engineered to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF). This platform enables sustained local delivery of a potent adjuvant at the vaccination site. By addressing both key immunological barriers, tumor antigen presentation and effective immune activation, this approach aims to induce a coordinated antitumor response. The objective of the study was to assess overall survival in patients treated with this investigational therapy.

Methods: A multicenter, open-label, Phase IIa clinical trial was conducted in patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC) who had progressed after at least one prior systemic therapy. The primary endpoint was overall survival (OS), with a predefined objective of at least 50% OS at 6 months following treatment initiation.

Results: In this heavily pretreated population, the primary endpoint was met, with 68.8% of patients alive at 6 months. Median OS was 11.4 months, and 32% of patients were still alive at 18 months. Both complete and partial responses were observed with monotherapy. All patients who developed a positive delayed-type hypersensitivity (DTH) response to their tumor cells following vaccination survived at 12 months. Patients living beyond 12 months also showed higher antibody titers against tumor-associated antigens. Exploratory analysis indicated a median OS of 21.7 months from the initiation of prior anti-PD-1 therapy. No treatment-related systemic adverse events or new safety concerns were reported. Manufacturing was successfully achieved at all participating centers.

Conclusions: These results suggest that this encapsulation-based cell immunotherapy can elicit a coordinated immune response with clinical activity and survival benefit as a standalone treatment. Prior exposure to immune checkpoint blockade may further enhance this effect.

4951

PD-L1: a novel therapeutic target in mastocytosis

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Introduction: Mastocytosis is a rare disease characterized by abnormal mast cell (MC) accumulation, mainly driven by the KitD816V mutation. Current Kit-targeting tyrosine kinase inhibitors often fail to achieve adequate responses in advanced systemic mastocytosis (advSM), highlighting the need for more effective therapies. PD-L1, an emerging immune checkpoint target also in mastocytosis, may play a role in MC function. Since Kit and PD-L1 activate separate pathways, PD-L1 blockade could offer a novel alternative or additional treatment strategy.

Methods: To explore this, we use a recently generated knock-in mouse model with inducible KitD814V expression (homologue to human KitD816V) in the hematopoietic stem cell compartment (Scl-CreERT;KitD814Vfl).

Results: Tamoxifen-induced expression in these mice caused rapid advSM-like disease with MC infiltration in skin, bone marrow (BM), spleen, and an associated myeloid neoplasm. These mice also exhibited increased serum PD-L1 levels as well as PD-L1 overexpression on MCs. Furthermore, we detected increased expression of its receptor (PD-1) on various immune cell populations, particularly T cells. Experiments using BM-derived MCs (BMMCs) from these mice revealed that PD-L1 upregulation is driven by Kit signaling, with PI3K acting as a downstream contributor. In vivo administration of a PD-L1-blocking antibody reduced MC counts in tissues and peripheral blood relative to controls.

Conclusions: Together, these results highlight a functional role for PD-L1 in disease development/progression and support further investigation of anti–PD-L1 therapies in mastocytosis.

8578

Modeling Advanced Systemic Mastocytosis: An Inducible Kit D814V Mouse as a Preclinical In Vivo Platform for Therapeutic Development

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Introduction: Systemic mastocytosis (SM) is a heterogeneous disease characterized by clonal mast cell (MC) expansion, mainly driven by the KIT D816V mutation. SM is divided into cutaneous and systemic subtypes, including chronic and advanced forms like SM-AHN (SM with associated hematopoietic neoplasia). Although treatments have improved, therapy development remains slow due to lacking preclinical models. We previously generated an inducible transgenic mouse line, Mx1-Cre;KitD814V, that develops marked MC hyperplasia and B-cell malignancy (Gerbaulet 2011). SM-AHN occurs in 20–40% of advSM patients but is mostly myeloid. To better model human advSM, we created a novel line (Scl-CreERT;KitD814V) expressing KitD814V in hematopoietic stem cells (HSC).

Methods: Disease progression was monitored by skin biopsies, blood analyses, histology, and flow cytometry. IgE- and MRGPRX2-mediated anaphylaxis were performed as described. Additionally, diseased mice received oral avapritinib, a tyrosine kinase inhibitor (TKI) approved for human SM, and were observed for its impact on disease progression and anaphylaxis susceptibility.

Results: Tamoxifen-induced Kit D814V expression caused a symptomatic disease after a median of 139 days, with MC accumulation in skin and stomach, splenomegaly and elevated serum protease levels in all animals. Mutant mice furthermore experienced greater temperature drops following MRGPRX2-mediated anaphylaxis , while IgE-mediated responses were similar to controls. 75% of the mutant mice displayed hematological changes, with immature blast-like cells in blood and hematopoietic organs, reduced MC progenitors (MCP), expanded Lin-Sca1+Kit+ (LSK) and long-term HSC in the bone

marrow (BM) and increased mature BM MCs. Conversely, peripheral blood (PB) analysis showed an increased number of MCP. These changes were however not attributed to different copy numbers in individual mice. Importantly, avapritinib significantly improved several disease parameters, including reduced skin MC numbers and protease levels, along with normalization of PB counts, spleen weight and stomach MC. Furthermore, avapritinib normalized LSKs and mature MC levels in the BM and improved MRGPRX2-mediated anaphylaxis.

Conclusions: This novel inducible transgenic mouse line reproduces key features of advSM including SM-AHN of myeloid origin and might serve as a pre-clinical in vivo platform for testing novel therapies.

5737

B-cell receptor repertoire profiling reveals distinct clonal architectures and early lymphoma-associated patterns in PPBL

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Introduction: Persistent polyclonal B-cell lymphocytosis (PPBL) is a rare and understudied immune dysregulation, almost exclusively affecting women, characterised by expansion of marginal-zone-like B cells and elevated serum IgM. Despite its generally benign classification, up to 20% of patients develop B-cell lymphoma, yet molecular predictors of malignant progression remain undefined. Recent analyses have also identified individuals with PPBL-like immune phenotypes who share many immunological features but do not meet full diagnostic criteria. This study aimed to characterise B-cell receptor (BCR) repertoires in PPBL and PPBL-like patients to identify immunogenetic features linked to disease heterogeneity and lymphoma risk.

Methods: Bulk immunoglobulin heavy-chain (IGH) repertoires were sequenced from peripheral blood mononuclear cells of seven PPBL and four PPBL-like patients and compared with age- and sex-matched healthy donors. Reads were processed using standardised pipelines (MiXCR, tcR, immunarch) to quantify repertoire richness, diversity, somatic hypermutation (SHM), clonal space distribution, and V-gene usage.

Results: IGH sequencing revealed that PPBL repertoires are broadly polyclonal, dominated by numerous medium-sized clones, exhibiting lower overall clonality and significantly lower levels of SHM compared with healthy donors. PPBL patients who later developed lymphoma, however, already displayed early signs of clonal selection, with enrichment of large and hyperexpanded clones years before clinical diagnosis. V-gene usage analysis via principal-component analysis separated PPBL patients from healthy donors, while PPBL-like cases occupied an intermediate position, reflecting partial repertoire remodeling. Specifically, the use of IGHV1-2 was favoured in PPBL patients in contrast to PPBL-like and healthy donors. These findings highlight distinct immunogenetic alterations in PPBL subsets that may influence disease trajectory.

Conclusions: B-cell receptor repertoire profiling identifies immunogenetic signatures that distinguish PPBL and PPBL-like patients from healthy individuals. Early detection of clonal enrichment in patients progressing toward lymphoma indicates the value of repertoire-based monitoring. Together, these insights refine understanding of PPBL pathogenesis and may help guide risk-adapted patient management.

6062

Unraveling apoptosis and autophagy mediated mechanisms contributing to the pathogenesis of pediatric Immune Thrombocytopenia

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Introduction: Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder with poor response treatment in some pediatric patients. Abnormalities in platelets, produced by megakaryocytes (MKs) in the bone marrow (BM), are implicated in ITP pathophysiology. Previous studies, including those from our group, have demonstrated a role of platelet apoptosis while the contribution of autophagy remains elusive. Therefore, we aim to investigate: 1) the autophagy flux and the autophagy mediated effects and 2) the mechanistic interplay between apoptosis and autophagy in pediatric ITP.

Methods: We used the MEG-01 cell line and MKs from peripheral blood mononuclear cells (PBMCs) of healthy controls (HCs) and age-matched pediatric ITP patients. Differentiation of CD34+ selected PBMCs into platelet-producing-MKs was assessed by flow cytometry using antibodies against CD61, CD41, CD42a and CD42b. We investigated the expression of apoptosis and autophagy at mRNA level by qRT-PCR and at protein level by Western blot and confocal microscopy. Autophagic flux was assessed with chloroquine treatment for 6h. Furthermore, both MEG-01 and $CD34^+$ derived MKs were nucleofected with the LC3B-GFP-mCherry reporter and incubated either with control or pediatric ITP-derived plasma. We performed siRNA CASP3 silencing to study upstream effects of apoptosis and autophagy pathway.

Results: MEG-01 cells treated with ITP plasma revealed a significant upregulation at mRNA and protein level of specific apoptosis (BCL2, CASP3, CASP8) and autophagy markers (BECN1, ATG5) compared to the control plasma treated and untreated cells. Both MEG-01 cells and CD34+ MKs nucleofected with the LC3B-GFP-mCherry reporter treated with ITP plasma showed increased LC3B puncta compared to control plasma treated cells by confocal, and downregulation of P62 at protein level, suggesting an enhanced autophagy flux in megakaryocytic treated cells.

CASP3 siRNA transfected cells showed a downregulation in autophagy markers (ULK1, ATG7) in ITP derived MKs at protein level but had no effect on BAX and BCL2 at mRNA level.

Conclusions: Our results suggest impaired apoptosis and autophagy-induced mechanisms in ITP at MK level. Understanding these pathomechanisms might enable developing more effective and targeted treatment approaches. We further aim to reproduce all the experiments in HC and ITP derived MKs in an ex vivo 3D BM model.

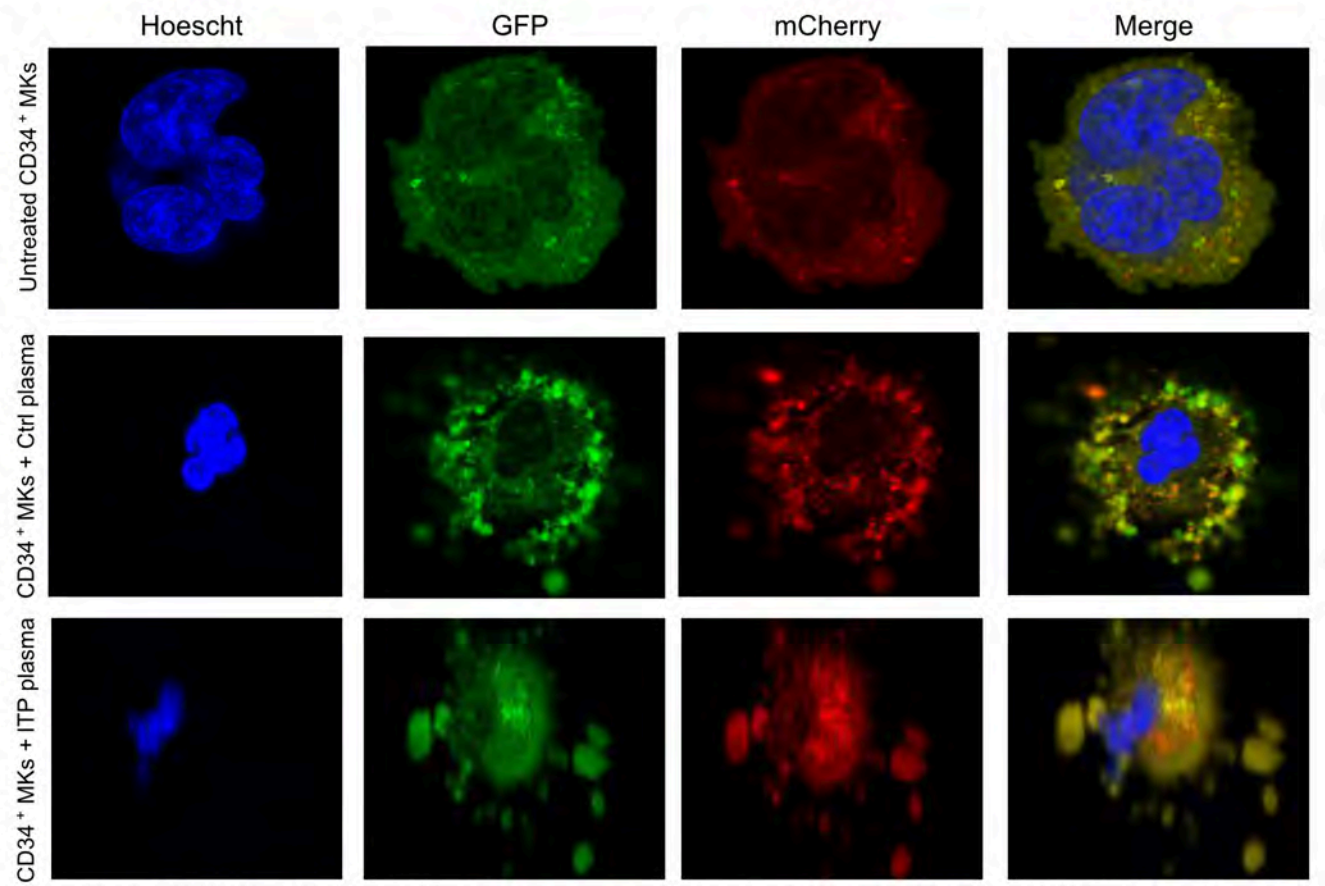

Figure 1. Assessment of the autophagy flux in mature megakaryocytes isolated from CD34+ selected PBMCs derived from adult healthy donors. MKs were nucleofected with the LC3B-GFP-mCherry reporter on Day 11 of differentiation and seeded on fibrinogen coated coverslips 24 h post transfection prior to treatment with healthy control or pediatric ITP derived plasma for 3h. Cell nuclei were visualized with Hoechst staining (blue), early autophagosomes (yellow) and autolysosomes (red). Representative confocal images were acquired by the Leica SP8 microscope at 63X magnification.

8540

TGFβ driven metabolic reprogramming of PDL1+ macrophages defines a targetable axis of immune evasion in diffuse large B cell lymphoma

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Introduction: Diffuse large B cell lymphoma (DLBCL) remains a heterogeneous and refractory malignancy. Although immune checkpoint blockade benefits selected subtypes, most DLBCLs show limited clinical benefit, highlighting the need to identify alternative therapeutic intervention. We previously showed that macrophage PDL1 correlates with aggressive DLBCL and promotes lymphoma progression in EμMyc models, suggesting its role in shaping treatment response. However, the mechanisms maintaining PDL1+ TAMs and their role in immunotherapy resistance remain unclear. Here, we investigated the cytokine and metabolic signals driving PDL1+ macrophage function, aiming to uncover targetable mechanisms that could enhance immune and antibody based therapies in DLBCL.

Methods: We used immunocompetent EμMyc lymphoma models that recapitulate aggressive human DLBCL. Mice with macrophage specific PDL1 deletion (Mrc1^CreERT2×Cd274^fl/fl) were analyzed. Spleen or lymph node tumours were collected for single cell RNA sequencing, high dimensional spectral flow cytometry, and phagocytosis assays. Cytokine blockade were performed to assess how TGFβ regulate PDL1 expression and macrophage phagocytic capacity.

Results: PDL1+ TAMs represented a metabolically adapted, immunosuppressive subset enriched for oxidative phosphorylation and lipid metabolism, with increased expression of Ace, Eno3, Pparg, Hfe, Fabp4, Cyp2ab1, Wnt6, IL10, and Marco, and a marked loss of FcγR1 and FcγR3. This transcriptional program integrates metabolic reprogramming with immunosuppressive signalling. Pparg expression inversely correlated with FcγR1, linking lipid metabolic activation to reduced antibody dependent effector function. Deletion of macrophage PDL1 enhanced the expansion of cytotoxic CD8+ T cells enriched for Cep55, Nek2, Ska3, Gzmb, and Ifng, indicating increased proliferative and effector capacity. Mechanistically, TGFβ induced macrophage PDL1, whereas the blockade downregulated PDL1 and restored BMDM phagocytosis.

Conclusions: Our findings define a cytokine–metabolic checkpoint that maintains PDL1+ macrophages and limits both T cell and antibody mediated immunity. Targeting TGFβ signalling or restoring FcγR function may overcome macrophage driven resistance and improve the efficacy of PDL1 or anti-CD20 based therapies in DLBCL. These results provide a mechanistic basis for macrophage directed combination immunotherapy in B cell lymphomas.

2474

Oncogenic splicing of the p53-related tumorsuppressor ASPP2 drives tumor aggressiveness and therapy resistance in pancreatic cancer

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Introduction: The average patient diagnosed with late-stage pancreatic cancer (PC) will live for about one year – and the five-year survival rate drops down to 1%. Improving the understanding of PC oncogenesis and drug resistance as well as developing novel treatment options is urgently needed. We have identified a novel, oncogenic dominant-negative isoform of the tumor suppressor ASPP2 (ASPP2kappa (k)) with high prevalence in cancer. Physiologically, ASPP2 wt orchestrates cellular homeostasis via directly interacting with key proteins such as p53, RAS, BCL-2 and NFkB. In contrast, ASPP2k is characterized by loss of important p53-, BCL-2 and NFkB-binding sites, thus impairing major pathways controlling cellular fate.

We here show that ASPP2k is highly expressed and functionally active in pancreatic cancer.

Methods: The role of ASPP2kappa in PC was studied in patient tumor tissue and isogenic PC cell models (PSN-1, DAN-G, HUP T4). Proteome arrays, RNA sequencing and Incucyte live cell imaging analyses were performed on ASPP2k-silenced and -overexpressing cells and a PC NSG mouse model was established. In addition, we tested novel, ASPP2k-specific siRNAs designed for in vivo application.

Results: We unravel a functional role of ASPP2k in PC tumor growth, invasion, metastasis and drug resistance: Silencing of ASPP2k (KD) resulted in attenuated cell proliferation (doubling times decreased on av. by 55%) and increased susceptibility towards CX (av +25% apoptosis for cisplatin and paclitaxel). Additionally, migration was inhibited on av. by 45%, hinting towards a role of ASPP2k in early metastasis. Vice versa, ASPP2k-overexpressing cells presented with accelerated proliferation (+35%) and migration (+30%, PSN-1) and displayed an even higher apoptotic threshold. Ongoing mouse xenotransplant models confirm significantly longer OS rates and inhibition of metastasis for mice bearing ASPP2k KD tumors. Most importantly, employing novel, fully chemically modified ASPP2k-specific siRNAs, we were able to silence ASPP2k in vivo and again attenuate tumor progression.

Conclusions: We confirm that ASPP2k is highly expressed in PC and associates with a more aggressive tumor biology and drug resistance. Importantly, we provide proof of concept that ASPP2k is targetable by isoform-specific siRNAs in vivo.

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

6428

Cytokine-induced hexokinase 3 (HK3) supports macrophage cell survival

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Introduction: Hexokinases (HKs) catalyze the first step of glycolysis, but in cancer important non-glycolytic functions are emerging. The three isoforms – HK1, HK2, and HK3 – share high similarity, complicating isoform-specific antibody development and raising concerns of cross-reactivity. This is particularly relevant for HK3, whose functions remain poorly defined. We aimed to find a HK3-specific antibody and characterize HK3 regulation and function in myeloid cells.

Methods: We analyzed public transcriptomic datasets to assess HK3 expression patterns. Human myeloid cell lines (HL60, THP1) were engineered for HK3 overexpression or knockout to validate commercially available HK3-specific antibodies. RNA-seq and immunohistochemistry (IHC) data from healthy and cancerous human tissues were used to study HK3 tissue distribution. Cytokine and growth factor stimulation of murine RAW264.7 macrophage cells, with or without JAK/STAT inhibitors, were used to analyze signaling pathways. Caspase-3/7 apoptosis assay was performed to assess Hk3 functional roles in survival.

Results: Transcriptomic analyses revealed that HK3 expression is largely restricted to the myeloid lineage in normal and malignant contexts. Using engineered myeloid cell lines, we identified the first HK3-specific antibody and confirmed correlation between HK3 mRNA and protein levels. Analysis of RNA-seq and IHC data in colon, lung and skin showed HK3 enrichment in macrophage subsets, including TAMs and granulomatous macrophages. To model different macrophage subsets, we stimulated RAW264.7 macrophage cells with various cytokines. This treatment resulted in rapidly induced Hk3 mRNA levels. This induction was blocked by JAK/STAT inhibitors linking Hk3 regulation to this pathway. Knocking down Hk3 in RAW264.7 macrophages did not affect caspase-3/7 activity under basal conditions or after cytokine treatment. However, combined cytokine stimulation and JAK/STAT inhibition increased caspase-3/7 activity 1.5-fold compared to controls, suggesting a conditional pro-survival role for Hk3.

Conclusions: We report the first HK3-specific antibody and demonstrate that HK3 is a cytokine-responsive gene regulated by JAK/STAT signaling. HK3 expression is confined to subsets of macrophages and contributes to survival under specific signaling contexts. These findings underscore the importance of isoform-specific tools to elucidate HK3's role in macrophage biology.

0120

Identifying Novel Vulnerabilities in Clear Cell Sarcoma Through Functional and Genomic Screening

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Introduction: Clear Cell Sarcoma (CCSA) is a rare soft tissue sarcoma characterized by specific gene fusions EWSR1::ATF1 or EWSR1::CREB1, leading to the expression of an oncogenic fusion protein. Metastasized CCSA is resistant to conventional chemotherapy, targeted therapy or immunotherapy. This study aims to uncover new therapeutic strategies for CCSA by utilizing a whole-genome CRISPR/Cas9 knock-out screen combined with functional drug screening.

Methods: We performed a genome-wide knock-out screen in the CCSA cell line model KAS using the pooled Brunello sgRNA library (Addgene # 73178, ~4 guides/gene, 19'114 genes). In parallel, two CCSA patient samples and CCSA cell lines SU-CCS-1, DTC-1 and KAS were screened with a library of 82 pan-cancer drugs, and a custom drug library tailored to the hits of

the CRISPR screen (70 compounds). Genes identified as critical vulnerabilities in CCSA were validated through single-gene knockouts, and promising therapeutic targets were further mechanistically interrogated and evaluated in a CCSA xenograft model.

Results: Results revealed 1'552 significantly depleted genes (log fold change <-1 and FDR < 0.01) after 21 days, with enriched pathways in proteasome activity, mismatch repair, DNA replication, and, mTORC1 signaling, revealing critical vulnerabilities. Notable highly ranked depleted genes include the transcription factor and CCSA marker SOX10, as well as MDM2, MCL1, CHEK1, HSPA5, PSMA5 and mTOR. Through integration of genetic knock-out and pharmacological inhibition data identified in our dual screening, we were able to identify several overlapping vulnerabilities. Drug screening confirmed strong sensitivity to proteasome inhibitors, DNA damage response inhibitors, PI3K-pathway inhibitors and targeted compounds against MCL1 and MDM2. Pharmacological inhibition of MCL1 significantly reduced viability in CCSA cell lines and patient-derived models and synergized with the BCL2 inhibitor venetoclax to enhance apoptosis and suppress xenograft tumor growth.

Conclusions: Together, these findings establish MCL1 as a previously unrecognized vulnerability in CCSA and provide preclinical rationale for combined MCL1 and BCL2 inhibition as a therapeutic strategy in sarcoma. Future studies will investigate this synergistic combination further to optimize treatment efficacy and validate further vulnerabilities identified by our dual screening approach.

9232

Targeting the thyroid-stimulating hormone receptor in poorly-differentiated thyroid cancer with CD3-engaging bispecific antibodies or CAR T cells

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Introduction: Poorly differentiated thyroid cancer (PDTC) is associated with poor prognosis and limited response to available therapies. With thyroid cancer incidence rising over the past decade, novel and specific treatment options are highly desirable. PDTC shows expression of the thyroid-stimulating hormone receptor (TSHR). In addition, Graves` and Hashimoto`s disease have provided well-characterized, patient-derived, TSHR-specific autoantibodies. We hypothesized that this TSHR-specific immune response could be redirected to therapeutically eliminate TSHR-expressing thyroid cancers with bispecific antibodies (bsAbs) or chimeric antigen receptor (CAR) T cells – two treatment strategies advancing precision cellular therapy.

Methods: TSHR expression in differentiated thyroid cancer (DTC), PDTC and anaplastic thyroid cancer was analyzed by immunohistochemistry. Anti-TSHR CAR T cells were generated using single chain variable fragment (scFv) sequences derived from stimulating, neutral or blocking antibodies. Heterodimeric bsAbs were designed with antigen-binding fragments (Fab) based on the same antibodies on the one arm and anti-CD3 scFvs on the other arm. For in vitro co-culture experiments, we combined TSHR-expressing target cells with either unmodified T cells and bsAb or with modified anti-TSHR CAR T cells. The most effective candidates from both approaches were selected for in depth validation.

Results: In DTC and PDTC, TSHR expression was comparable to normal thyroid tissue, confirming TSHR as a viable antigenic target for immune therapy. Co-culture experiments demonstrated the efficient and TSHR-dependent cell lysis of target cells by both, a selection of bsAbs or CAR T cells. Analysis of activation markers revealed that T cells were only activated above baseline in the presence of the target receptor. Interestingly, the performance of anti-TSHR CAR T cells did not fully match that of their bsAb counterparts. The orientation of the light and heavy chains in the CAR design played a significant role for their efficacy.

Conclusions: These findings provide proof-of-principle that thyroid cancer can be targeted through TSHR-engaging bsAbs and CAR T cells, highlighting a promising avenue for future thyroid cancer therapies.

2385

Inflammation-mediated Resistance to FLT3 Inhibition in Acute Myeloid Leukemia

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Introduction: FMS-like receptor tyrosine kinase 3 (FLT3) is the most frequently mutated gene in acute myeloid leukemia (AML). FLT3 inhibitors have improved patient outcomes but resistance limits durable disease control. Chronic inflammation is linked to cancer drug resistance, and studies on cell line models suggest that inflammatory signaling is activated during resistance to FLT3 inhibition. However, longitudinal studies at single-cell resolution tracking the rewiring of inflammatory pathways in matched diagnostic and relapsed samples from AML patients are limited. Here, we used orthogonal models to map the dynamics of inflammatory signaling under the selective pressure from FLT3 inhibition.

Methods: Gilteritinib-resistant AML cell lines were generated by continuous exposure of parental cells to stepwise dose-escalating drug concentrations, followed by mutation profiling and bulk RNA sequencing. In parallel, we performed single-cell RNA sequencing on bone marrow and peripheral blood mononuclear cells from FLT3 mutated AML patients, analyzing matched samples obtained at primary diagnosis and at relapsed/refractory disease post FLT3 inhibition.

Results: We established gilteritinib-resistant AML cell lines that were also cross-resistant to midostaurin, suggesting a common resistance mechanism among FLT3 inhibitors. Gene set enrichment analysis revealed altered inflammatory signaling in the resistant cell line models, with TNFα-NFκB signaling as the most prominently altered pathway. Consistently, in a matched diagnostic-relapse pair from a FLT3 mutated patient treated with a FLT3 inhibitor, the relapse sample showed enrichment of TNFα-NFκB signaling, driven by monocyte-like cells. Notably, altering the timing or nature of the treatment affected resistance dynamics and led to distinct changes in inflammatory signaling, underscoring heterogeneous resistance trajectories.

Conclusions: Resistance to FLT3 inhibition is associated with transcriptional rewiring of inflammatory signaling pathways. Drug-resistant AML cell line models reflect gene expression changes observed in sequential patient samples and are thus valuable models to study resistant disease states. Future work will determine whether altered inflammation provides a clonal advantage in drug resistance and identify the leukemic clones driving resistance. This knowledge will be crucial in developing strategies to prevent and overcome resistant states.

2323

Targeting Long-Chain Fatty Acid Elongation Disrupts Cancer Membranes Organization and Triggers Anti-Cancer Immunity

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Introduction: Modern cancer immunotherapies aim to stimulate anti-tumor immunity, but their efficacy is often limited by tumor immune evasion and suboptimal immune activation. Cancer cells can escape recognition by reprogramming spatial receptor-ligand interactions at the cell membrane. This study aimed to identify the molecular dependencies driving these interactions and reveal therapeutic vulnerabilities that could restore effective immune surveillance.

Methods: We conducted a large-scale small-molecule co-culture screen combining photo-affinity labeling, quantitative proteomics, and lipidomics to uncover mechanisms regulating cancer-immune cell communication. Integrative multi-omics analyses and functional validation in both cancer and immune cells were used to pinpoint critical pathways shaping cell-cell interactions.

Results: We found that inhibiting long-chain fatty acid elongation disrupted membrane organization selectively in cancer cells, without affecting immune cells. Pharmacological and genetic targeting of the key enzyme HSD17B12 reduced very-long-chain fatty acid synthesis, leading to altered membrane architecture and receptor redistribution, including immune checkpoints and lipid transporters. Conversely, HSD17B12 inhibition enhanced glycolytic metabolism and cytotoxic activity in macrophages, T cells, and NK cells. These opposing effects reduced tumor growth and increased immune activation in preclinical models.

Conclusions: Our findings reveal a cancer-specific dependency on very-long-chain fatty acids as a mechanism of immune evasion. Targeting HSD17B12 reprograms membrane organization to restore immune recognition and boost anti-tumor immunity.

1400

Regulation of cancer cell metabolism and proteostasis by mechanical tissue cues

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Introduction: The integrated stress response (ISR) is an evolutionarily conserved signalling pathway that modulates protein synthesis in response to diverse stressors such as amino acid scarcity and is implicated in cancer progression and treatment resistance. Tissue stiffness, a mechanical property of the tumor microenvironment, influences cell behavior through mechanotransduction, thereby also modulating cancer cell aggressiveness and treatment responses. Given the importance of both mechanotransduction and the ISR in cancer biology, we hypothesise that stiffness may modulate ISR activation, thereby linking mechanical cues to stress adaptation in tumor cells.

Methods: Solid cancer cell lines were cultured on fibronectin-coated polyacrylamide hydrogels with tunable stiffness ranging from 0.5 to 40 kPa. ISR activation was induced by glutamine starvation, and pathway activation was assessed by qRT-PCR, RNA sequencing, and immunofluorescence to evaluate global gene expression and regulation of selected ISR and proteostasis networks.

Results: As predicted, stiffer substrates led to increased cell spreading, reduced cell circularity, and upregulated activity of the transcriptional coactivators, Yes-associated protein (YAP) and Transcriptional co-activator with PDZ-binding motif (TAZ). Gene set enrichment analysis revealed that, under nutrient-replete homeostatic conditions, cells on softer substrates exhibited downregulated protein turnover pathways including tRNA charging, ribosome-associated protein synthesis, translation initiation, and proteasomal degradation. Glutamine starvation-induced ISR activation was substantially enhanced on stiffer matrices, as shown by increased nuclear localisation of activating transcription factor 4 (ATF4). Moreover, RNA sequencing highlighted a globally more pronounced response to glutamine depletion on stiff substrates which included canonical ISR signalling and ATF4 targets as well as anabolic and catabolic protein metabolism that was partly mediated by YAP/TAZ.

Conclusions: These findings demonstrate that tissue stiffness modulates key cellular proteostasis pathways such as the ISR, highlighting a mechanosensitive dimension to stress adaptation that may help explain treatment resistance and guide the development of more effective therapeutic strategies.

SSH/SSMO POSTER PRESENTATION – CLINICAL HEMATO-ONCOLOGY

3988

Association of CAR T-Cell Area Under the Curve with Clinical Outcomes in Patients Treated with Tisagenlecleucel: A Real-World Study

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Introduction: Chimeric antigen receptor (CAR) T-cell therapy has reshaped treatment for relapsed or refractory B-cell malignancies, offering curative potential where conventional therapies have failed. Since approval, tisagenlecleucel (Kymriah®) has achieved durable remissions in diffuse large B-cell lymphoma (DLBCL), though outcomes remain heterogeneous. Cellular pharmacokinetics of CAR T-cell expansion are increasingly recognised as relevant. The area under the curve (AUC) may serve as a composite marker of in vivo expansion and persistence, potentially linking exposure with efficacy and toxicity.

Methods: In this single-centre retrospective study, CAR T-cell kinetics were assessed using digital droplet PCR (ddPCR) in patients treated with Kymriah® at the University Hospital of Bern (2018–2023). CAR transgene copy numbers were quantified by ddPCR, and AUC calculated by linear interpolation at fixed cut points (day 100, "3 months," and day 280, "9 months"). Variables were compared using Fisher's exact test, ANOVA, or Kruskal–Wallis tests. Associations between continuous variables were analysed with Spearman correlation.

Results: Seventy-one patients were included (DLBCL 82%, FL 10%, ALL 9%). At 3 months, 31% achieved CR and 27% PR; at 9 months, 40% were in CR, while 40% had died (missing data ≤1 per timepoint). Median AUC values were right-skewed and did not differ significantly across remission categories at either 3 or 9 months. Survivors had higher AUC at the last measurement than non-survivors (median 160 vs. 102), but this did not reach statistical significance ($p = 0.06$); follow-up was longer among survivors. Transduction efficiency correlated weakly with AUC at 9 months ($\rho = 0.41$, $p = 0.03$), but not at 3 months ($\rho = 0.26$, $p = 0.08$) or the last measurement ($\rho = 0.18$, $p = 0.14$).

Conclusions: In this real-world cohort, AUC of CAR T-cell copy number quantification alone did not differentiate remission categories or predict survival. Its association with transduction efficiency was modest and time-dependent. Findings support the need for multidimensional models integrating AUC with factors such as immune context, disease burden, and product characteristics, and highlight the importance of rigorous sampling schedules in cellular pharmacokinetic studies.

1455

Causes of death in 5- and 10-year survivors after allogeneic hematopoietic cell transplantation.

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Introduction: Allogeneic haematopoietic cell transplantation (allo-HCT) can be curative for malignant and benign haematological diseases, but data on long-term outcomes of long-term survivors are limited. With a growing population of survivors, there is a need to better define prognosis and late risk factors. We aimed to identify predictors of mortality among survivors at ≥5 and ≥10 years after allo-HCT.

Methods: We analysed 757 patients who survived ≥5 years after first allo-HCT (1979–2019); 464 also survived ≥10 years. Patients with syngeneic or cord blood transplants were excluded. Overall survival (OS) was estimated using Kaplan–Meier methods, and predictors of mortality tested by multivariable Cox regression including age, conditioning, donor type, stem cell source, and chronic graft-versus-host disease (cGvHD). Causes of death were classified as relapse, cGvHD, infection, cardiovascular disease, secondary malignancy, organ failure or unknown.

Results: Median follow-up was 11.9 years. Twenty-year OS was 74% in ≥5-year survivors and 83% in ≥10-year survivors; relapse-free survival exceeded 75% in both. Age at transplant strongly stratified outcomes: at 20 years OS was 85–91% for ≥18 and <40 years vs 63-73% for 40-60 years vs. 41–46% for >60 ($p < 0.001$). Severe/extensive cGvHD reduced OS at both landmarks. In multivariable models, older age remained the dominant predictor (vs ≥18 and <40: HR 2.5 [40–60] and HR 2.1 [>60] at 5 years; HR 3.3 and HR 6.9 at 10 years; all $p < 0.001$). Severe/extensive cGvHD independently increased late mortality (HR 1.9, 95% CI 1.2–2.8 at 5 years; HR 1.8, 1.0–3.1 at 10 years). Conditioning affected only ≥5-year survivors (RIC/NMA vs MAC HR 1.7, 1.1–2.5). Causes of death shifted: in ≥5-year survivors relapse was still the leading cause of death (23.6%), while in ≥10-year survivors non-relapse causes predominated, especially secondary malignancies (29.8%), cardiovascular disease (13.8%) and cGvHD (14.9%).

Conclusions: Long-term survival after allo-HCT is favourable, but advanced age and severe cGvHD remain consistent predictors of late mortality, even decades post-transplant. In long-term survivors, non-relapse causes, particularly secondary malignancy and cardiovascular disease, surpass relapse as the leading contributors. These findings emphasise the need for lifelong survivorship programmes that extend survival while preserving long-term health and quality of life.

2821

Comprehensive Screening & Monitoring for systemic Light Chain Amyloidosis in Patients with Monoclonal Gammopathy of clinical significance (COSMO-AL)

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Introduction: Systemic AL amyloidosis is underdiagnosed, and optimal strategies and timing for screening remain unclear. The peripheral nervous system (PNS) is a common yet frequently overlooked site of affection. There is a clear need for earlier, minimally invasive screening approaches.

Methods: We propose a minimally invasive screening approach that integrates random skin biopsies to detect amyloid, transmission electron microscopy to precisely type deposits, and intraepidermal nerve fiber density measurements to quantify small-fiber loss as a marker of amyloid neurotoxicity (IENFD). We intend to apply this to all patients with monoclonal gammopathy and unexplained organ malfunction ("clinical significance", MGCS). Primary outcomes are diagnostic yield (sensitivity & specificity) relative to current practice; secondary outcomes include concordance between amyloid presence/type and IENFD, and associations with serum neurofilament light chain (sNFL) levels.

Results: Among 29 patients undergoing skin biopsy screen in the ongoing study, AL amyloid was detected in 5 (17%) patients; 3/5, concurrent standard fad pad aspiration and bone marrow biopsy were negative. In 67 patients with sNFL measured, levels trended higher in patients with MGCS with biopsy-proven proven AL amyloidosis than in those without (not statistically significant after age and sex adjustment). sNFL was higher in cases with clinically objectified peripheral neuropathy than in those without. To date, no clear correlation is seen between sNFL levels and IENFD.

Conclusions: Random skin biopsies and sNFL may improve screening for AL amyloidosis in MGCS, enabling earlier diagnosis and thereby lead to improved outcome.

5771

The Glasgow Prognostic Score adds Prognostic Information in Elderly AML Patients Ineligible for Intensive Treatment Independently from the Molecular Risk Profile – a Retrospective Multicentre Analysis

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Introduction: The Glasgow Prognostic Score (GPS) combines C-reactive protein (CRP) and albumin as biomarkers of inflammation and catabolism. It has demonstrated prognostic value in various solid tumors and several hematologic malignancies. Its prognostic impact in elderly patients (pts) with acute myeloid leukemia (AML) or high-risk myelodysplastic neoplasms (MDS) treated with hypomethylating agents (HMA)± Venetoclax (Ven) remains less well characterized. Therefore, we investigated the prognostic significance of the GPS in this patient population.

Methods: We conducted a multicentre, retrospective chart review of newly diagnosed elderly patients with AML- or MDS/AML who were ineligible for intensive treatment. Levels of CRP and albumin were recorded at time of diagnosis (+/- 30 days). Patients were stratified according to treatment modality, presence of infection at time of diagnosis, and the molecular prognostic risk score (mPRS).

Results: 153 pts were included (female n = 65 [43%]; median age 78 years, range 61-91; AML n = 131 [86%], AML/MDS n = 22 [14%]). 91 pts (60%) received HMA+Ven, 34 pts (22%) HMA alone or in combination with other agents including Hydroxyurea or Ibrutinib (HOVON135/SAKK-30/15 trial). 28 pts (18%) received best supportive care. An active infection at diagnosis was documented in 31 pts (20%). During follow-up (median 6 months [mo], range 0-69) 128 (84%) pts died. A GPS of 0 (CRP <10 mg/l and albumin ≥35g/l, n = 62) was associated with a significantly longer median OS of 13.2 mo [95% CI 7.2-17.1) compared with 3.9 mo [95% CI 2.1-5.4] for pts with a GPS of 1 or 2 (CRP >10 mg/l and/or albumin <35 g/l, n = 91), p = 0.0006. Comparable results were obtained in the subgroup of pts without infection at diagnosis who were treated with HMA+Ven (n = 75): median OS 16.8 months (95% CI, 7.8–24) for GPS 0 vs. 6.5 months (95% CI, 2.9–13) for GPS 1/2 (p = 0.015). The GPS retained its independent prognostic value in bivariate Cox regression models including the mPRS, as shown in the table.

Conclusions: In this retrospective analysis, the GPS, a parameter easily accessible in daily clinical practice, provided prognostic information in elderly AML-patients independent of the molecular risk profile. Considering CRP and albumin may help to identify a particularly vulnerable subgroup of AML pts, even in the context of treatment with HMA+Ven. However, validation of these findings in larger cohorts is warranted.

Bivariable Cox Regression model for OS by GPS and mPRS (whole population, n=153)

Characteristic	HR	95% CI	p-value
GPS			
0*	—	—	
1	1.71	1.15, 2.56	0.008
mPRS			
higher benefit*	—	—	
intermediate benefit	1.43	0.82, 2.49	0.2
lower benefit	2.42	1.55, 3.77	<0.001

Bivariable Cox Regression model for OS by GPS and mPRS for patients without infection at diagnosis treated with HMA+Ven (n=75)

Characteristic	HR	95% CI	p-value
GPS			
0*	—	—	
1	2.35	1.27, 4.36	0.007
mPRS			
higher benefit*	—	—	
intermediate benefit	1.59	0.72, 3.49	0.3
lower benefit	3.28	1.63, 6.64	<0.001

*Reference category; Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

7628

Impact of body mass index (BMI) on response and tolerance to azacitidine (AZA) in myeloid neoplasms (MN)

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Introduction: The impact of BMI on AZA outcomes in myeloid neoplasms is debated : some studies suggest that obesity may influence survival or toxicities, while others do not. In addition, BMI is also a risk factor for MN. We assessed the effect of BMI

on efficacy, survival and tolerance to AZA in a single-centre haematology-oncology cohort.

Methods: Retrospective study of 168 adults treated with AZA (2008-2024). Patients categorised by BMI: <18.5 kg/m² (UW), 18.5-24.9 kg/m² (NO), 25-29.9 kg/m² (OW) and ≥30 kg/m² (OB). Primary endpoints were overall response rate (ORR), overall survival (OS), progression-free survival (PFS), transfusion dependence and ≥ grade 3 haematologic toxicities. Comparisons were performed using χ^2 tests, Kaplan-Meier curves with log-rank test, and multivariable Cox regression models.

Results: The AML cohort comprised 100 patients (54 men, median age 66 y), 6% UW, 47% NO, 36% OW and 10% OB. Most had de novo AML (87%) and 58% had unfavourable ELN risk. Global ORR was 37.8%, varying across BMI groups: 43.1% in NO, 43.4% in OW and 10% in OB; without statistical significance. Complete responses were more frequent in NO (35%) and OW (38%), while none were achieved in OB. Median time to best response was 2.1 months, shortest in NO (1.7 months). No significant association was found between BMI and OS or PFS. Grade ≥3 toxicities occurred in 30% of patients, mostly neutropenia (20.2%), thrombocytopenia (11.5%) and anaemia (4.8%), with no BMI association. Dose reductions (DR) were required in 35.6% of AML patients, without clear BMI association. The MDS/CMML cohort included 68 patients. ORR was 62.4%, with no significant variation between BMI groups. However, median OS was significantly longer in patients with BMI above a post-hoc threshold of 27.5 kg/m² (21.8 vs 12.8 months; p = 0.012), but this benefit disappeared after adjustment in multivariable analysis. Grade ≥ 3 thrombocytopenia was more frequent in OB patients (p = 0.0238). Half of the patients (50%) required DR, not related to BMI.

Conclusions: BMI showed no independent impact on response, survival or tolerance to AZA. Although longer survival was seen in high-BMI MDS/CMML patients and better AML response in NO/OW groups, these associations disappeared after multivariable adjustment. BMI alone should not guide AZA dosing. Standard dosing remains appropriate, and prospective studies including body-composition metrics are warranted.

8565

Outcome, quality of life and patient expectations of the first 55 CAR-T patients at our hospital

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Introduction: CAR-T cell therapy is a major breakthrough for treating relapsed or refractory blood cancers, offering durable remissions and improved survival. While evidence supports its efficacy and safety, less is known about its impact on patient-reported outcomes, quality of life, and how patients' expectations compare to their real experiences after treatment.

Methods: The study was a retrospective observational analysis including all patients who received CAR-T cell therapy at our hospital before the end of August for lymphoma, multiple myeloma, or B-cell acute lymphoblastic leukemia (B-ALL). Quality of life was assessed using the EORTC QLQ-C30 instrument, supplemented by a structured questionnaire evaluating patient expectations. Data were analyzed using descriptive statistics. Only patients with general consent will be included; a declaration of consent will be obtained for current quality of life surveys.

Results: The cohort included 55 patients in total; in 3 cases, cells were collected but not retransfused, resulting in an evaluable cohort of 52 patients. Of these, 22 were female and 30 male, with a mean age of 66.6 ± 11.6 years. At a median follow-up of 466d +/-444d, 11 patients were deceased and 41 were alive (78.8%). CAR-T cell products used were Abecma in 4 patients, Breyanzi in 5, Carvykti in 11, Tecartus in 8, and Yescarta in 24 patients. On September 30, 2025, 17 evaluable questionnaires were available. Patient questionnaire results (scale 1–10) showed the following: patients felt well informed before therapy (9.1 ± 1.1), were confident that the treatment was the right decision (9.4 ± 0.8), reported side effects as expected (6.5 ± 3.0), were satisfied with the overall result (8.1 ± 3.0), and would choose the treatment again (8.8 ± 2.0). In the EORTC QLQ-C30 questionnaire (scale 1–7), patients rated their health status during the past week at 5.1 ± 1.5 and their overall quality of life at 5.4 ± 1.6.

Conclusions: This retrospective observational study analyzed all patients who received CAR-T cell therapy for lymphoma, multiple myeloma, or B-ALL at our hospital before the end of September 2025. Patients reported high satisfaction and confidence in their treatment decision, felt well informed, and most would choose CAR-T therapy again. Health and quality-of-life scores on the EORTC QLQ-C30 were favorable, indicating overall positive patient perception and outcome.

0375

Therapy refractory ICANS after CAR T cell therapy with Brexucabtagene-Autoleucel (Tecartus) for Relapsed Mantle Cell Lymphoma: Successful Management with Intrathecal Triple Chemotherapy

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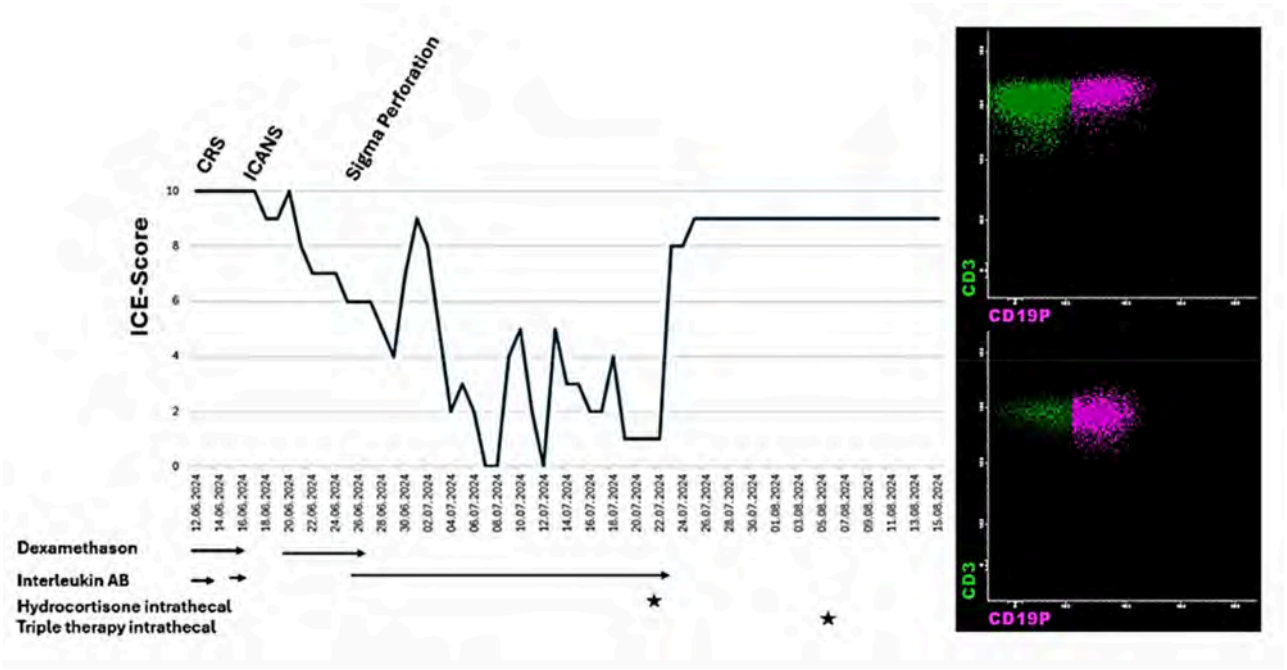
Introduction: Immune effector cell-associated neurotoxicity syndrome (ICANS) is a common complication of CAR T cell therapy, often linked to inflammatory cytokines disrupting the blood-brain barrier and causing neuroinflammation. The "on-target, off-tumor" effect is suggested by CD19 expression on brain mural cells and higher ICANS rates in CD19-directed CAR T therapies compared to BCMA or EGFRvIII targets. ICANS typically occurs 5 days to 3 weeks post-infusion, with symptoms ranging from mild confusion to coma, assessed by the ICE score. First-line treatment includes corticosteroids and interleukin receptor inhibitors like tocilizumab and anakinra.

Results: A 67-year-old male with relapsed mantle cell lymphoma (MCL) was treated with CD19-directed CAR T cells. He developed Grade III cytokine release syndrome (CRS) on day 1, successfully managed with dexamethasone and tocilizumab. On day 5, he developed immune effector cell-associated hemophagocytic syndrome, followed by ICANS symptoms (somnolence, speech hesitancy, disorientation, ICE score 6). MRI was unremarkable, and lumbar puncture revealed no pathogens or infiltration of MCL but the presence of CAR T cells in the cerebrospinal fluid. Treatment included dexamethasone, tocilizumab and anakinra. Dexamethasone had to be discontinued after the patient suffered a sigmoid colon perforation and subsequent partial colon resection and stoma placement, likely due to significant reduction of intra-abdominal tumor mass. Despite prolonged anakinra therapy, ICANS persisted for over a month. A second lumbar puncture confirmed CAR T cell presence, and to avoid systemic steroid therapy following abdominal surgery, intrathecal hydrocortisone was administered. The patient showed a rapid improvement of ICANS symptoms, which lasted for about 2 weeks, at which point he showed a discreet worsening of neurological symptoms that resolved completely after

administration of intrathecal triple chemotherapy (methotrexate, cytarabine, dexamethasone).

Conclusions: This therapy-refractory ICANS case suggests intrathecal hydrocortisone and chemotherapy as promising second-line treatments. While small series show benefit, larger studies are needed. Identifying biomarkers and prophylactic strategies remain vital to improve outcomes.



6045

Pseudo-Richter Transformation in a patient with chronic lymphatic leukemia after cessation of therapy with Venetoclax/Ibrutinib

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Introduction: Pseudo-Richter transformation (Pseudo-RT) in chronic lymphocytic leukemia (CLL) refers to rapid clinical progression resembling Richter transformation (RT) but lacking histological evidence of high-grade lymphoma. It presents with systemic symptoms and lymphadenopathy, often complicating diagnosis. Distinguishing Pseudo-Richter from true Richter transformation is essential due to differences in prognosis and treatment approaches.

Methods: In addition to the description of the case, we conducted a PubMed search using the term Pseudo-Richter Transformation

Results: A 69-year-old previously healthy Caucasian man was diagnosed with CLL, with unmutated IGHV and no TP53 mutation. Treatment was initiated per the GLOW trial with ibrutinib (cycles 1–15) and venetoclax (cycles 4–15). The patient responded well, with clinical and hematological complete response. One week after the last cycle was completed, the patient developed fever, abdominal pain, and recurrent lymphadenopathy. Imaging revealed partial regression and new progression of lymph nodes, splenic infarction, and an eventual splenic rupture requiring emergency splenectomy. Histology showed paraimmunoblasts with high proliferation index (~50%), raising suspicion of RT. However, molecular testing was negative for typical findings of high-grade lymphoma and PET-CT did not support it as well. Suspecting pseudo-RT ibrutinib was reintroduced 14 days after cessation, leading to rapid normalization of leukocyte counts and clinical improvement

Conclusions: We report a case of pseudo-RT in a CLL patient treated with ibrutinib/venetoclax combination therapy, contrasting prior reports involving Bruton tyrosine kinase inhibitor (BTKi) monotherapy alone. The impressive and rapid onset of transformation-like symptoms following recent BTKi interruption should raise suspicion for pseudo-RT, though true RT must be excluded. As BTKi use in CLL increases, this phenomenon may become more common. Prompt interdisciplinary collaboration is essential for accurate diagnosis and appropriate management. Further research is needed to develop fast diagnostic tools to distinguish pseudo-RT from true RT.

1897

Systemic AL-amyloidosis diagnosed via histopathological screening in patients undergoing carpal tunnel surgery: A case report.

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Introduction: Amyloidosis, particularly transthyretin (ATTR) but also immunoglobulin light chain (AL) amyloidosis, is a recognised but often underdiagnosed cause of carpal tunnel syndrome (CTS). A recent study identified amyloid deposits by tenosynovial biopsies in 10% of elderly men and women. Patients with detection of ATTR-amyloid are at an increased risk of de-

veloping cardiac amyloidosis within 10 years, whereas the association between cardiac amyloidosis and CTS-related AL-amyloidosis is relatively uncommon.

Methods: As of 2025, we routinely perform histopathological examination for amyloidosis after CTS surgery. We here report a case of a patient suffering from lambda light chain multiple myeloma with systemic AL-amyloidosis, identified through screening after CTS surgery.

Results: The 83-year man presented to the haematology department following CTS surgery with detected AL-amyloid deposits. Laboratory testing revealed mild hyporegenerative anemia (hemoglobin 115 g/l), markedly elevated lambda light chains (1010 mg/l), proteinuria (505 mg/d) and the presence of lambda Bence-Jones protein. Cardiac biomarkers (NT-proBNP 6664 ng/l, troponin-T hs 45 ng/l) were elevated. Renal impairment (kreatinin 135 µmol/l) was pre-existing, while hypercalcemia was absent. FDG-PET/CT showed a metabolically active lesion in the L5 vertebral body. Bone marrow biopsy revealed 40% plasma cells with a monoclonal aberrant phenotype (K/L-Ratio 0.15, CD38+, CD138dim, CD56+, CD19-, CD81+, CD117+, CD27+, CD28+). Cardiac evaluation demonstrated reduced global longitudinal strain with an apical sparing pattern, and cardiac MRI was suggestive of cardiac amyloidosis. Based on the findings, a diagnosis of systemic AL amyloidosis with soft tissue, neurological, cardiac and renal involvement secondary to light chain multiple myeloma was established. Systemic treatment with daratumumab, cyclophosphamide, bortezomib and dexamethasone (per ANDROMEDA protocol) resulted in a rapid decrease in lambda light chains. Bisphosphonate therapy was administered for bone protection.

Conclusions: Screening for amyloid after CTS surgery offers an opportunity for the early detection of amyloidosis. Immunohistochemical subtyping enables precise amyloid differentiation, which has an important therapeutic implication. Furthermore, the detection of amyloidosis and assessment of systemic involvement is crucial, especially in cases of AL-amyloidosis.

2241

Elranatamab for relapsed/refractory multiple myeloma with severe renal impairment requiring hemodialysis

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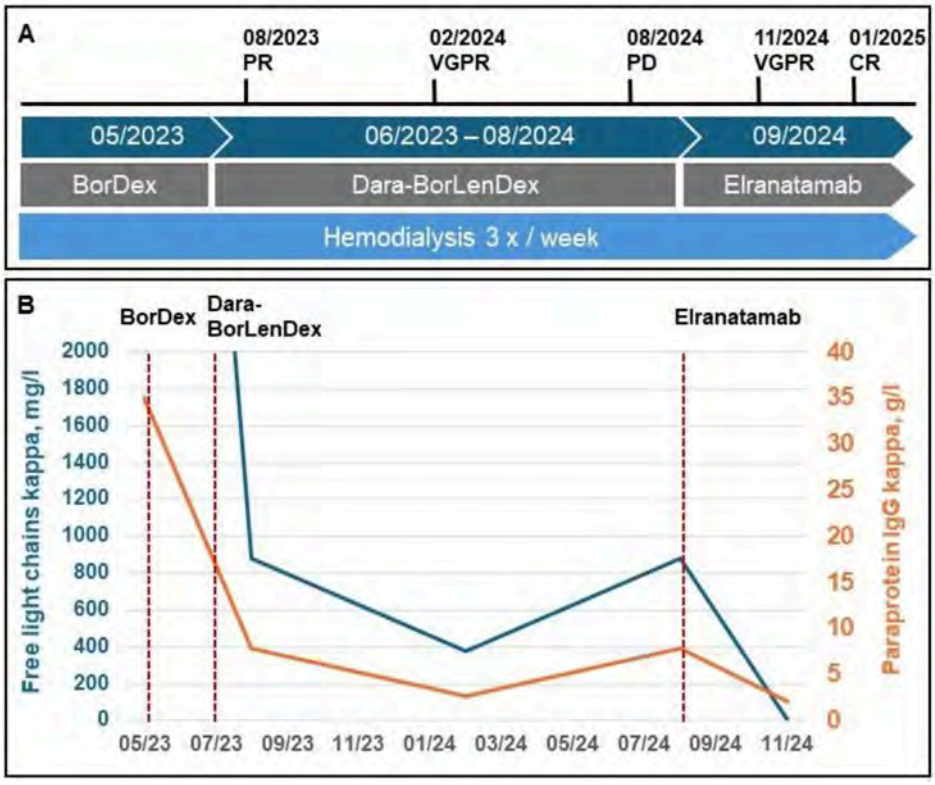
Introduction: Relapsed/refractory multiple myeloma (RRMM) patients with dialysis-dependent renal impairment face limited therapeutic options due to exclusion from clinical trials, a lack of evidence-based guidelines, and inferior outcomes. Bispecific antibodies targeting B-cell maturation antigen (BCMA) have shown promise in RRMM treatment but remain understudied in this vulnerable population.

Methods: A 68-year-old female with triple-class RRMM and end-stage renal disease requiring hemodialysis, was treated with elranatamab as a second line treatment following progression after therapy with daratumumab, bortezomib, lenalidomide, and dexamethasone. Grade I cytokine release syndrome during the initial administrations was managed effectively with tocilizumab and dexamethasone, allowing treatment continuation. A secondary immunoglobulin deficiency with increased infection susceptibility was treated by supplementation with polyvalent immunoglobulins. The patient achieved a very good partial remission within seven weeks although hemodialysis dependence persisted.

Results: BCMA-directed immunotherapies, including teclistamab, belantamab mafodotin, and idecabtagene vicleucel, have shown efficacy in dialysis-dependent RRMM patients, though data remain limited. Pharmacokinetic analyses indicate that mild or moderate renal impairment does not have a significant impact on the pharmacokinetics of elranatamab. Although no retrospective studies or case series have investigated the use of elranatamab in dialysis-dependent patients, a single case report suggests that its administration is both feasible and well-tolerated in this population despite the absence of comprehensive pharmacokinetic data. This review highlights feasibility, safety, and encouraging efficacy of elranatamab in managing RRMM in a dialysis-dependent patient, representing the second case report in the literature.

Conclusions: By providing real-world evidence for the use of bispecific antibodies in end stage renal disease patients, our data emphasize the potential for expanding therapeutic options to this vulnerable population while highlighting the need for vigilant monitoring of infection prevention and management. Prospective studies are warranted to validate these findings and optimize therapeutic strategies for patients with RRMM and severe renal impairment.



1411

Follicular T-Helper cell lymphoma of the Angioimmunoblastic type with associated Marginal zone lymphoma – a diagnostic and therapeutic challenge

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Introduction: Follicular T-Helper cell lymphoma (FTHL) of the Angioimmunoblastic type resembling a plasma cell leukemia at hospital admission presents a rare and potentially misleading primary diagnostic constellation, even more rare together with an EBV-associated marginal zone lymphoma.

Methods: We present a very rare case of a 78-year-old patient with an FTHL with an associated EBV-positive marginal zone lymphoma focusing on the difficult path leading to the diagnosis and the therapeutic challenges.

Results: The patient was admitted to our emergency department with progressive generalized weakness and unintentional weight loss within a period of three months. The initial peripheral blood smear showed a leukocytosis with 11% of plasma cells and a normochromic normocytic anaemia pointing towards the diagnosis of a plasma cell myeloma and/or leukemia. There were bone marrow alterations in the MRI indicating changes due to myeloma and the bone marrow histology showed an increased amount of plasma cells, supporting the possible diagnosis of myeloma. However, the bone marrow flowcytometry demonstrated the presence of a kappa restricted B-lymphocyte population without any evidence of clonality within the plasma cells. A hypergammoglobulinaemia was also found to be of polyclonal nature. After a PET-CT scan demonstrated a diffuse FDG-avid lymphadenopathy, a lymph node excision was performed and showed the presence of a rare combination of an EBV-associated marginal zone lymphoma with an underlying FTHL, while the initially present plasma cell population in the peripheral blood showed a fluctuating pattern. After taking in account all the diagnostic findings as well as the patient performance status, an unusual therapy combination of rituximab, bendamustin and daratumumab was initiated, and a follow-up CT scan showed a significant regression of the lymphadenopathy. The patient showed a protracted clinical improvement with a cessation of the B symptoms within the first month of treatment.

Conclusions: This case highlights the importance of integrative diagnostics in complex cases, such as EBV-associated marginal zone lymphoma arising on the background of FTHL, where misleading initial findings may obscure the diagnosis. Effective treatment can be achieved once the correct diagnosis is established and appropriate therapy selected.

SSMO POSTER PRESENTATION – CLINICAL SOLID TUMOR ONCOLOGY

6708

Sacituzumab govitecan (SG) + pembrolizumab (pembro) vs chemotherapy (chemo) + pembro in previously untreated PD-L1–positive advanced triple-negative breast cancer (TNBC): primary results from the randomized phase 3 ASCENT-04/KEYNOTE-D19 study

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Introduction: PD-1/PD-L1 inhibitors plus chemo have expanded options for previously untreated PD-L1–positive advanced TNBC, but an unmet need remains. SG has shown benefit in pretreated mTNBC. We report results from ASCENT-04/KEYNOTE-D19 in untreated, PD-L1–positive locally advanced unresectable or mTNBC. The study was also open for recruitment in 5 centers in Switzerland.

Methods: Patients were randomized 1:1 to SG (10 mg/kg IV, day 1 & 8) + pembro (200 mg, day 1, max 35 cycles) in 21-day cycles or chemo (gemcitabine + carboplatin, paclitaxel, nab-paclitaxel) + pembro until disease progression or unacceptable toxicity. Stratification was by treatment-free interval, geography, and prior PD-(L)1 exposure. Primary endpoint: progression-free survival (PFS) by Blinded Independent Central Review (BICR); key secondary endpoints: overall survival (OS), objective response rate (ORR), DOR by BICR, safety.

Results: 443 patients were randomized (221 SG + pembro, 222 chemo + pembro). Median follow-up was 14 months. SG + pembro significantly improved PFS by BICR vs chemo + pembro (median PFS: 11.2 vs 7.8 months; HR 0.65, 95% CI 0.51–0.84; P = .0009). ORR: 59.7% for SG + pembro vs 53.2% for chemo + pembro. Median DOR: 16.5 months vs 9.2 months, respectively. Although OS data were immature, a positive early trend in OS improvement was noted. Any grade/ grade ≥3 treatment-emergent adverse events (TEAEs) in >99%/71% of SG + pembro and >99%/70% of chemo + pembro patients. TEAEs led to dose reductions in 35% vs 44%, and treatment discontinuations in 12% vs 31%, respectively. The most frequent (≥ 10% of patients) grade ≥ 3 TEAEs with SG + pembro were neutropenia (43%) and diarrhea (10%); and with chemo + pembro neutropenia (45%), anemia (16%), and thrombocytopenia (14%).

Conclusions: SG + pembro led to a statistically significant and clinically meaningful improvement in PFS with durable responses, no new safety concerns for SG or pembro, and a lower rate of treatment discontinuation due to TEAEs in patients with previously untreated PD-L1–positive advanced TNBC, supporting its potential as a new standard of care.

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1433

Adjuvant Therapy in Early Breast Cancer: Meta-Analysis

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Introduction: Adjuvant endocrine therapy (ET) for hormone receptor-positive early breast cancer reduces recurrence risk, but optimal duration and type remain debated. This meta-analysis synthesises recent evidence (2015–2025) to evaluate disease-free survival (DFS) benefits of extended ET (>5 years) versus standard 5-year ET, focusing on aromatase inhibitors (AIs) and ovarian function suppression (OFS) in pre- and postmenopausal women, to inform de-escalation strategies.

Methods: PubMed, Scopus, and Web of Science were systematically searched (January 2015–September 2025) for randomised controlled trials (RCTs) or cohort studies with ≥100 participants, comparing extended versus standard ET in early-stage, ER-positive/HER2-negative breast cancer. Inclusion required quantitative endpoints (e.g., hazard ratios [HRs] for DFS, overall survival [OS]) and minimum 2-year follow-up. Quality was assessed using Cochrane Risk of Bias tool. Data were pooled using RevMan 5.4 with random-effects model; heterogeneity via I^2 statistic. Subgroup analyses examined menopausal status and nodal involvement. Novelty ensured by incorporating 2023–2025 data (e.g., NATALEE updates on CDK4/6 integration) not covered in prior EBCTCG overviews.

Results: Twelve RCTs (n = 28,450 patients; median age 52 years) met criteria, including TEXT/SOFT (OFS), NSABP B-42 (extended AI), and monarchE (abemaciclib+ET). Extended ET improved 10-year DFS (HR 0.68, 95% CI 0.62–0.75; p <0.001) versus standard ET, with low heterogeneity (I^2 = 28%). OS benefit was modest (HR 0.82, 95% CI 0.71–0.95; p = 0.009; I^2 = 42%). Subgroups showed greater DFS gains in node-positive disease (HR 0.64, 95% CI 0.57–0.72) and premenopausal women with OFS (HR 0.71, 95% CI 0.60–0.84). Adverse events increased (e.g., osteoporosis odds ratio 1.45, 95% CI 1.22–1.72), but quality-of-life impacts were minimal in recent trials.

Conclusions: Extended adjuvant ET significantly enhances DFS in early breast cancer, particularly for high-risk subgroups, with new 2024–2025 data supporting AI extension by 2–3 years post-5-year tamoxifen. These insights advocate personalised durations to balance efficacy and toxicity, potentially reducing overtreatment in low-risk cases.

Subgroup	Studies (n)	Patients (n)	HR (95% CI)	I^2 (%)
Overall Extended ET	12	28,450	0.68 (0.62–0.75)	28
Node-Positive	8	15,230	0.64 (0.57–0.72)	35
Premenopausal + OFS	5	7,890	0.71 (0.60–0.84)	22
Postmenopausal AI Extension	7	20,560	0.70 (0.63–0.78)	30

4927

Methylthioadenosine Phosphorylase (MTAP)-loss and KRAS Mutations in patients with advanced non-small cell lung cancer (NSCLC)

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Introduction: Homozygous deletion of S-methyl-5'-thioadenosine phosphorylase (MTAP) is observed in 13–15% of NSCLC, conferring sensitivity to PRMT5 inhibitors currently being tested in early phase trials. MTAP loss has been associated with an inferior outcome, but evidence on the prognostic relevance of MTAP loss and its associations with other established molecular biomarkers remains scarce. We evaluated the association of MTAP loss with established predictive biomarkers and its prognostic relevance in advanced NSCLC.

Methods: We included all patients with advanced NSCLC treated at a Swiss Hospital (2022–2025) from a prospective clinical registry. Endpoints included overall survival (OS) stratified by MTAP status (intact expression vs. loss of expression, assessed by immunohistochemistry (IHC)) and associations between MTAP loss and established relevant biomarkers (next-generation sequencing (NGS)-assessed: KRAS, BRAF, ERBB2, MET, EGFR; IHC-assessed PD-L1). The study was approved by the research ethics committee. Survival analyses used the Kaplan-Meier method with log-rank tests; biomarker associations were analyzed using Fisher's exact test with Benjamini-Hochberg correction. We did not apply imputational techniques for missing values.

Results: 178 advanced NSCLC patients were included: 113 (63.5%) had intact MTAP expression, 29 (16.3%) had MTAP loss, and 36 (20.2%) had unknown MTAP status. Tissue-based NGS information was available in 146 patients. MTAP status was unknown in 30 of 146 patients (20.5%). For the 146 patients with available NGS, KRAS mutation was significantly associated with MTAP loss (adjusted p = 0.038, OR = 4.65 [95% CI: 1.41–20.09]). Among the 58 KRAS mutant tumors, KRAS G12C was the predominant variant (20 of 58). Among patients with known MTAP status, OS did not differ between patients with intact MTAP expression (N = 113) and those with MTAP loss (N = 29) (12-month OS rate both 78.6%, log-rank p = 0.73). Restricting analysis to patients who received immunotherapy with or without chemotherapy (N = 59 intact versus N = 13 loss) also showed no relevant difference (12-month OS rate both 75%, log-rank p = 0.41).

Conclusions: MTAP loss was significantly associated with the presence of KRAS mutation, but it was not associated with worse OS prognosis. Further detailed analyses, including multivariable and cluster analyses, will be presented at the meeting.

9840

Single-Cell Co-Expression Networks reveal Actionable Resistance Mechanisms to Targeted and Immunotherapy treatments in Melanoma.

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Introduction: Therapeutic resistance is the major challenge in advanced melanoma, particularly in patients with BRAF mutations under targeted treatments (BRAF/MEKi, TT) or immune checkpoint inhibitors (ICI). While single-cell RNA sequencing (scRNA-seq) accurately captures the cellular heterogeneity and gene expression per cell, it fails to resolve the connectivity dynamics driving treatment escape.

Methods: We applied Single-Cell Co-Expression Network (SCENE) analysis to scRNA-seq profiles from tumor and T cells of BRAF-mutated skin melanoma patients (n = 25) within the Tumour Profiler cohort, who progressed upon therapy with TT and ICI and compared them to a treatment-naïve group. Moreover, we assessed the gene network dynamics of the two resistance mechanisms (TT–ICI) and cases with long (>6 months) versus short (≤6 months) progression-free survival (PFS)

treated with ICI as adjuvant therapy. The top 20 pathways differentially co-expressed for each group and clinical question were filtered. From then, the 50 most frequently occurring genes were selected to assess connectivity of those connected with five or more other genes.

Results: The mutational profiles and single-cell transcriptome analysis confirmed a heterogeneous tumour microenvironment, primarily consisting of tumour cells and T cells. SCENE identified treatment-dependent rewiring of hub gene connectivity across both cell types. PI3K–AKT–mTOR regulators dominated the networks in tumour cells in response to TT, while T cells were anchored by cytoskeletal signalling hubs (VAV1, MAPK). However, the different activation of stress-response hubs characterised the difference between TT and ICI. Moreover, metabolic rewiring (GSK3B-centred) in tumour cells and memory T cell signatures (NFATC1–STAT5B) were identified in prolonged PFS of cases under ICI treatment as adjuvant, in contrast to early progressors.

Conclusions: SCENE identified key resistance-associated gene co-expression dynamics in tumours and T cells across the clinical scenarios of the BRAF-mutated skin melanoma cohort. Thereby, highlighting the importance of gene connectivity associated with the resistance to the treatment-specific hidden in scRNA-seq. Our study demonstrates that SCENE distinctly reveals biological mechanisms of resistance, identifying actionable vulnerabilities and potential biomarkers for guiding personalised treatment based on the mechanisms of patient resistance.

9241

Impact of Platinum Dosing Intensity in Patients with Advanced Lung Cancer Treated with Palliative Chemotherapy or Chemo-Immunotherapy

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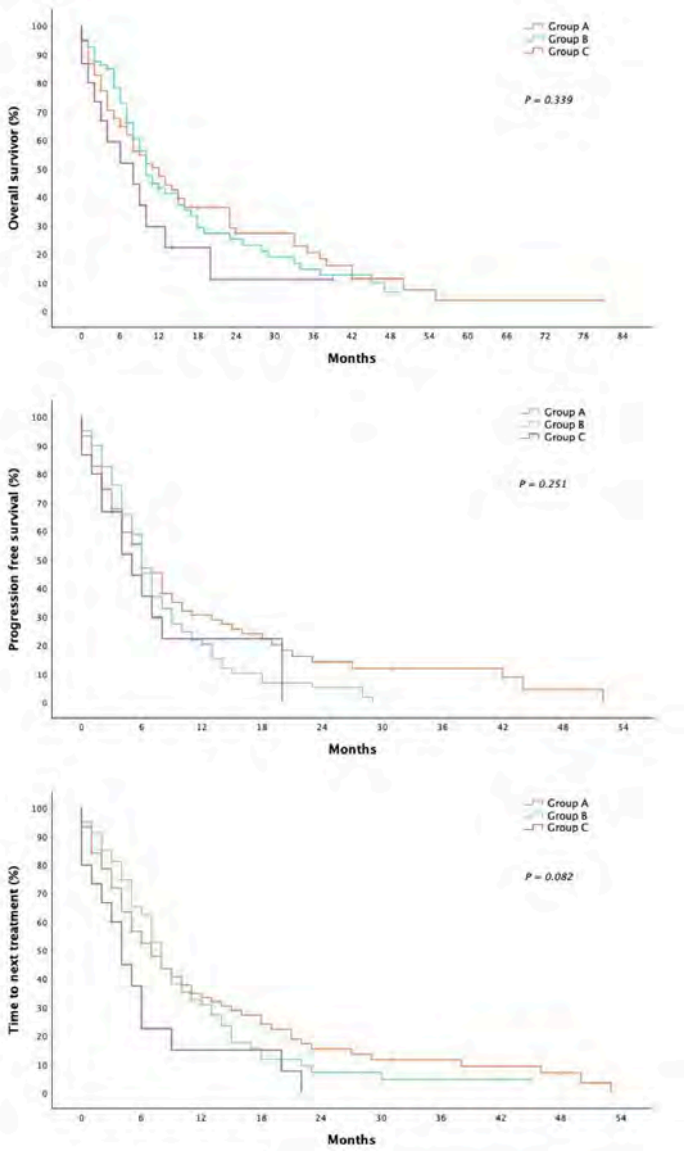
Introduction: Lung cancer is a leading cause of cancer death worldwide, especially among elderly patients. Platinum-based chemotherapy with or without immunotherapy is a standard treatment for advanced/metastatic lung cancer. Most clinical trials exclude frail and geriatric patients with comorbidities and/or poor performance status, limiting evidence for this group. Preemptive dose reductions of chemotherapy are common in clinical practice despite the lack of any evidence regarding optimal dosing in these populations.

Methods: We retrospectively analyzed patients with advanced/metastatic lung cancer aged ≥60 years treated with platinum based palliative chemotherapy with or without checkpoint inhibitor from 2016-2025 at our institution. Patients were grouped by platinum dosing intensity, AUC >5 being defined as 100%: A) 90-100%, B) 70-89%, C) <70%. Primary endpoint was OS. Secondary endpoints included PFS, time to next treatment (TTNT), ORR and toxicity.

Results: 170 patients were included, 75 belonging to group A, 80 to group B, and 15 to group C. Median age was 72 years across all groups. 47% of patients had adenocarcinoma, 29% SCLC, 19% squamous and 5% other histology. 32% of patients had ECOG PS ≥2. Only 2 of 170 patients received cisplatin-based therapy, the rest receiving carboplatin. Median follow-up for OS was 42 months. No significant differences in median OS (Group A: 12 months (95% CI 7.1-16.9); group B: 10 months (95% CI 8-12), group C: 8 months (95% CI 1-15), p = 0.34), PFS (median 6/6/5 months, respectively, p = 0.25), or TTNT (median 7/8/4 months, respectively, p = 0.08) were observed. ORR was comparable across groups with no significant dose-dependency detectible (group A 48%, group B 56%, group C 40%, p = 0.41). Treatment discontinuation rates were similar across groups (p >0.05). Subgroup analyses and multivariate regression showed that factors such as ECOG PS, histology, cardiovascular comorbidity, brain metastases and treatment kind (with or without immunotherapy) significantly influenced outcomes regardless of dosing.

Conclusions: Reduced platinum dosing intensity in patients with advanced lung cancer did not significantly impact survival or response in this real-world cohort. These data support individualized dosing and argue for broader clinical trial inclusion criteria to improve representation of frail populations.



6358

Gender-specific effects of tumour infiltrating clonal haematopoiesis in NSCLC.

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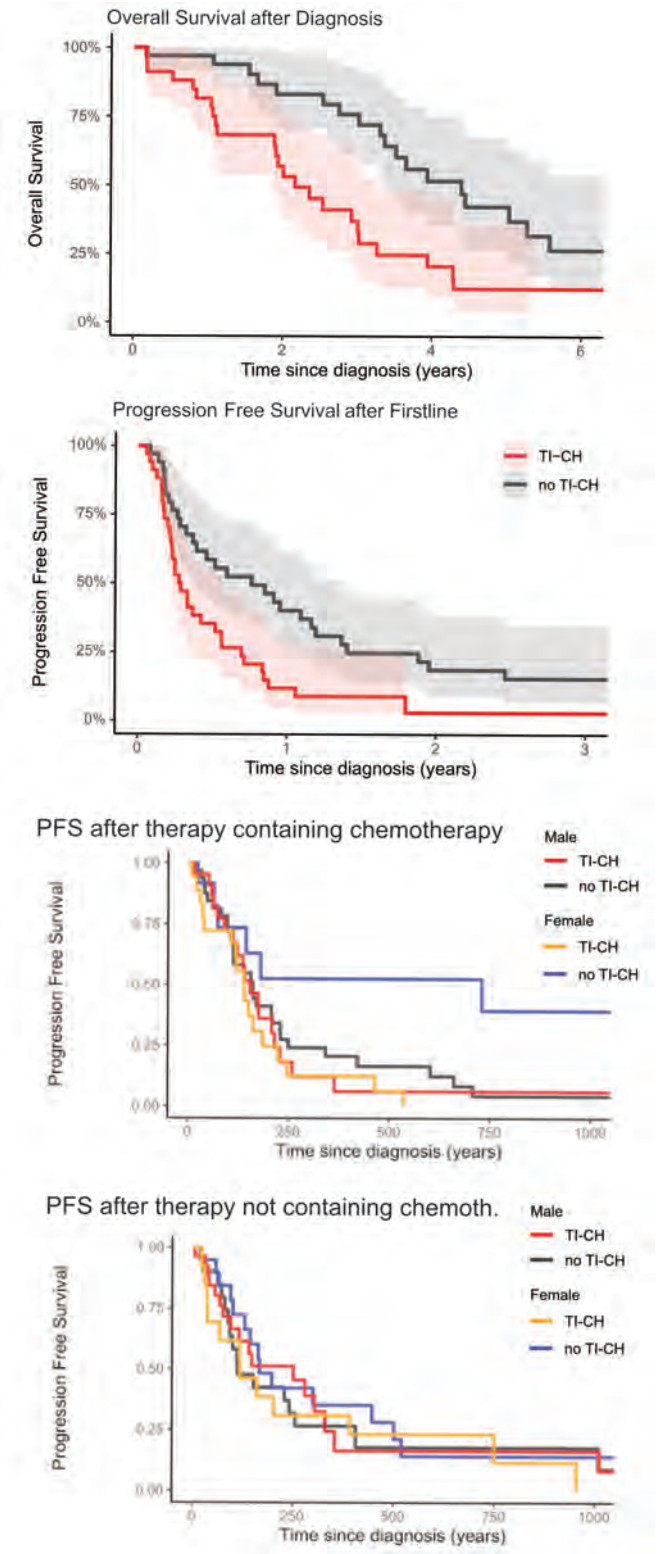
Introduction: Clonal hematopoiesis (CH), a common age-associated phenomenon, has been shown to be associated with adverse cancer outcomes, including progression-free and overall survival in non–small-cell lung cancer (NSCLC). Emerging evidence suggests that tumor-infiltrating CH (TI-CH) may affect the anti-tumor immune response; however, the clinical relevance, particularly in the context of first or second line-line ICI therapy remains to be confirmed. To our knowledge, gender-specific differences in the adverse effect of TI-CH have not been reported so far.

Methods: In this retrospective analysis we analyzed 114 patients with all stage adeno-NSCLC diagnosed and treated at our institution, including 35 patients with confirmed CH mutations. TI-CH was detected by searching for subclonal pathogenic mutations in the genes TET2, DNMT3A, ASXL1, JAK2, SF3B1 and U2AF1 associated with CH in the mutational profile of tumour samples as obtained by the FoundationOne testing. We used propensity score matching to balance known confounders between the groups. Kaplan-Meier analyses were performed to evaluate the impact of CH status on progression-free (PFS) and overall survival (OS) across different therapies (TKI, ICI and Chemotherapy) and between male and female patients and Cox Proportional Hazards models were used to calculate hazard ratios.

Results: In our cohort, patients with TI-CH had a significantly increased risk of all-cause death (HR = 2.26, 95% CI 1.25-4.07, p = 0.007) and decreased progression free survival after first-line therapy (HR = 2.11, 95% CI 1.26-3.50, p = 0.004), confirming findings of previous studies. Interestingly, we observed a gender-based difference in the influence of TI-CH on outcomes in chemotherapy including regiments: While males showed no significant difference in PFS with TI-CH (HR = 1.08, 95%CI = 0.60-1.95, p = 0.78) females showed a severely decreased PFS with TI-CH (HR = 4.12, 95% CI 1.55-10.94, p = 0.004).

Conclusions: Our findings highlight the role of TI-CH as an important risk factor on outcomes in NSCLC and to our knowledge for the first time suggest gender-specific effects of TI-CH. Although we cannot exclude that our results are spurious given the small single-center cohort, gender-differences in the adverse effect of TI-CH in the context of treatment might explain our findings, and further studies including larger cohorts are necessary to confirm our results.



8201

IKF/AIO-PHERFLOT: Perioperative Chemoimmunotherapy with Translational Biomarker Analyses in Localized HER2-Positive Esophagogastric Adenocarcinoma

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Introduction: Perioperative treatment of localized HER2-positive esophagogastric adenocarcinoma (EGA) is rapidly evolving. Building on the success of HER2- and PD-1–directed therapies in metastatic disease, the phase II IKF/AIO-PHERFLOT trial evaluates their integration with the established FLOT chemotherapy backbone. Alongside clinical efficacy, a translational research program was embedded to explore immune repertoire dynamics and circulating tumor DNA (cfDNA) as biomarkers of treatment response.

Methods: Thirty-one patients with localized HER2-positive EGA received perioperative chemoimmunotherapy. Serial blood samples for translational research were collected in 27 patients, with 23 providing paired samples at baseline and after one treatment cycle (day 15). T cell receptor β-chain variable region (TRBV) repertoires were profiled, assessing diversity and clonality by metrics including D50 and Shannon index. In parallel, cfDNA was quantified as a surrogate of tumor burden.

Results: The clinical regimen demonstrated feasibility and induced high rates of pathological complete response (pCR). Serial immune profiling revealed that patients achieving pCR had higher TRBV diversity and richness both at baseline and after cycle 1 compared to non-pCR cases. Similarly, patients with lower tumor stage (T1/T2) exhibited higher repertoire diversity than those with T3/T4 tumors. These findings suggest that preserved T cell repertoire diversity may support more effective tumor clearance under chemoimmunotherapy. CfDNA monitoring was feasible in nearly all patients, with dynamic changes under treatment consistent with tumor response; detailed results will be presented.

Conclusions: The IKF/AIO-PHERFLOT regimen achieved a high pCR rate in localized HER2-positive EGA and represents the most active perioperative strategy tested to date in this population. Translational analyses indicate that immune repertoire diversity and cfDNA dynamics may serve as early biomarkers of response. As biomarkers mature, they may guide treatment de-escalation and help identify patients in whom surgery could potentially be spared after achieving pCR. While repertoire diversity alone is not a perfect discriminator, its combination with cfDNA kinetics and serial biopsy assessment may provide clinically meaningful decision support in future trials.

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Patient Characteristics and Treatment Patterns in Patients with Head and Neck Squamous Cell Carcinoma Undergoing Chemoradiotherapy

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Introduction: Chemoradiotherapy (CRT) represents an important treatment option for patients with locally advanced head and neck squamous cell carcinoma (HNSCC), either as definite treatment or in the adjuvant setting. Cisplatin is most frequently used in this context. For patients who are not candidates for cisplatin, alternative agents such as docetaxel may be considered. Our study aims to identify factors influencing chemotherapy choice and compare side effect profiles between cisplatin and docetaxel in a representative real-world HNSCC population.

Methods: We included adult patients with HNSCC who had their first visit at the Department of Medical Oncology between November 1, 2022, and May 31, 2025. Eligible patients received either definitive or adjuvant CRT with weekly cisplatin (40 mg/m²) or docetaxel (15 mg/m²). All data originate from routine clinical workflows within the University Hospital. We used data and infrastructure from an ongoing registry (AO_2023-00091). Diagnoses of all patients are prospectively documented and coded within routine clinical workflows in a validated RedCap database. Laboratory data were pulled from the existing clinical data warehouse. Statistical analyses were performed using R software.

Results: We included 70 patients with HNSCC; 52 patients were treated with cisplatin, 18 patients received docetaxel (Table 1). Patients treated with docetaxel were older, had poorer performance status according to the ECOG scale, and a higher Charlson Comorbidity Index compared to those receiving cisplatin. Baseline estimated GFR values were similar between the two groups. The incidence of grade 3 or higher toxicities according to CTCAE varied by treatment regimen. While cisplatin was associated with greater hematologic toxicity, patients in the docetaxel group experienced more adverse events related to elevated CRP levels and decreased albumin.

Conclusions: Our findings indicate that the decision to withhold cisplatin was not influenced by baseline kidney function, but by other factors such as patient age, performance status, and comorbidities. In the frailer docetaxel-treated patient population, adverse events more frequently affected albumin and CRP levels, potentially due to docetaxel's higher risk of causing mucositis. Further in-depth analyses will be presented at the meeting.

Table 1. Baseline characteristics and adverse events in cisplatin and docetaxel treated patients

Baseline variable	RT plus cisplatin (n=52)	RT plus docetaxel (n=18)	Total (n=70)
Age, years			
Median	63	71	64
Q1,Q3	58.00, 67.00	64.25, 75.75	58.25, 70.00
Sex, No. (%)			
Male	39 (75.0)	14 (77.8)	53 (75.7)
Female	13 (25.0)	4 (22.2)	17 (24.3)
Clinical situation, No. (%)			
First diagnosis	50 (98.0)	16 (88.9)	66 (95.7)
Relapse/Progression	1 (2.0)	2 (11.1)	3 (4.3)
Treatment, No. (%)			
Definitive RCT	48 (92.3)	14 (77.8)	62 (88.6)
Adjuvant RCT	4 (7.7)	4 (22.2)	8 (11.4)
ECOG, No. (%)			
ECOG 0	33 (63.5)	8 (44.4)	41 (58.6)
ECOG 1	17 (32.7)	6 (33.3)	23 (32.9)
ECOG 2	1 (1.9)	4 (22.2)	5 (7.1)
Missing	1 (1.9)	0	1 (1.4)
Charlsen Comorbidity Index			
Median	2.0	3.5	3.0
Q1,Q3	2.00, 4.00	3.00, 6.25	2.00, 4.00
missing	15	4	19
Polyneuropathy, No. (%)			
Yes	2 (3.8)	0	2 (2.9)
No	35 (67.3)	14 (77.8)	49 (70.0)
Missing	15 (28.8)	4 (22.2)	19 (27.1)
Hearing impairment, No. (%)			
Yes	6 (11.5)	8 (44.4)	14 (20.0)
No	31 (59.6)	6 (33.3)	37 (52.9)
Missing	15 (28.8)	4 (22.2)	19 (27.1)
Treatment duration, weeks			
Median (range)	5.10 (0.90-7.10)	4.25 (1.00-6.10)	5.00
Cumulative chemotherapy dose (mg)			
Median (range)	443.50 (160.40-966.50)	141.75 (45.60-225.90)	-
Creatinine (µmol/L) at baseline			
Median (range)	66.0 (31.0-119.0)	64.5 (40.0-99.0)	66.0 (31.0-119.0)
Estimated GFR (ml/min/1.73m^2) at baseline			
Median (range)	96.5 (52.0-134.0)	92.5 (61.0-113.0)	(96.0 52.0-134.0)
Adverse events, grade 3 or higher, No. (%)			
Albumin	4 (7.7)	3 (16.7)	7 (10.0)
C-reactive protein	36 (69.2)	16 (88.9)	52 (74.3)
Estimated GFR	2 (3.8)	1 (5.6)	3 (4.3)
Creatinine	1 (1.9)	0	1 (1.4)
Hemoglobin	14 (26.9)	4 (22.3)	18 (25.7)
Absolute Neutrophils	13 (25.0)	0	13 (18.6)
Platelets	1 (1.9)	0	1 (1.4)

RT, radiotherapy; RCT, radiochemotherapy; ECOG, Eastern Cooperative Oncology Group scale; GFR, Glomerular Filtration Rate

8257

Molecular subtypes and their correlation with clinical outcomes in a real-world study of patients with extensive stage small cell lung cancer (ES-SCLC) undergoing combined chemo-immunotherapy

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Introduction: For patients (pts) with ED-SCLC, combined chemo-immunotherapy (Chemo-IO) is the standard 1st-line therapy. The most commonly used molecular subtyping of SCLC is based on the expression levels of mammalian achaete scute homolog-1 (MASH1), neurogenic differentiation factor 1 (NEUROD1), and POU class 2 homeobox 3 (POU2F3). Additionally, lower expression of Schlafen 11 (SLFN11) has been reported to correlate with worse prognosis and emerged as a predictive marker for several drugs, but its predictive role for Chemo-IO remains to be clarified. In this study we investigate the outcome to Chemo-IO based on immunohistochemical SCLC subgroups, SLFN11 expression and RNA-based T cell receptor (TCR) analyses.

Methods: Pts with ED-SCLC who received 1st-line Chemo-IO were included in this retrospective analysis. Initial tumor biopsies were centrally collected.

Immunohistochemical analysis for MASH1, NEUROD1, POU2F3 and SLFN11 was performed using standard protocols. Total RNA was extracted and used for TCR sequencing with the Oncomine TCR SR Assays. Molecular subtypes, TCR evenness, Shannon diversity, and number of clones were analyzed and their association with clinical endpoints (progression-free survival (PFS), overall survival (OS) and overall response rate (ORR)) was investigated using Cox regression models and Kruskal-Wallis tests.

Results: 201 pts were included between 2018 and 2021. Tumor tissue is available for 60 pts. So far, we have analyzed the tumor tissue of 20 pts. Patient characteristics of pts included in this analysis look comparable to the overall population. Expression of MASH1 (p = 0.110), lack of expression of NEUROD1 (p = 0.121) and TCR eveness (p = 0.186) show a trend towards longer OS with Chemo-IO. A lower number of TCR clones (p = 0.31) and Shannon diversity (p = 0.14) show a trend to a higher ORR. SLFN11 is expressed in 55% of samples and the subgroup of pts with SLFN11 expression shows higher ORR (40% vs. 69%, p = 0.33).

Conclusions: Immunohistochemical subgroups and T cell repertoire diversity are possible factors influencing outcome under chemo-IO. Analyses of further tissue samples from the cohort will be shown at the meeting.

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Survival in Prostate Cancer with Novel Therapies: A Meta-Analysis

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Introduction: Novel therapies, including PARP inhibitors (PARPi) and androgen receptor signaling inhibitors (ARSIs), have transformed metastatic castration-resistant prostate cancer (mCRPC) management. This meta-analysis synthesises evidence from 2015–2025 to evaluate overall survival (OS) and progression-free survival (PFS) benefits of PARPi (e.g., olaparib, talazoparib) and ARSIs (e.g., abiraterone, enzalutamide) versus standard androgen deprivation therapy (ADT) or placebo, with subgroup focus on homologous recombination repair (HRR)-deficient tumours, to guide precision de-escalation.

Methods: PubMed, Scopus, and Web of Science were systematically searched (January 2015–September 2025) for randomised controlled trials (RCTs) with ≥100 participants comparing PARPi or ARSIs to ADT/placebo in mCRPC. Inclusion required quantitative endpoints (e.g., hazard ratios [HRs] for OS/PFS) and ≥12-month follow-up. Quality assessed via Cochrane Risk of Bias tool. Data pooled in RevMan 5.4 using random-effects model; heterogeneity via I^2. Subgroups analysed by HRR status and therapy line. Novelty achieved by integrating 2023–2025 data (e.g., TALAPRO-2, PROpel updates) beyond prior EBCTCG meta-analyses, emphasising combination efficacy in non-HRR cohorts.

Results: Fourteen RCTs (n = 12,340 patients; median age 71 years) met criteria, including PROfound (olaparib), TALAPRO-2 (talazoparib+enzalutamide), PROpel (olaparib+abiraterone), and LATITUDE (abiraterone). PARPi+ARSI combinations improved OS (HR 0.72, 95% CI 0.65–0.80; p <0.001) versus ARSI monotherapy, with moderate heterogeneity (I^2 = 45%). PFS benefit was significant (HR 0.61, 95% CI 0.54–0.69; p <0.001; I^2 = 52%). In HRR-deficient subgroups (n = 2,150), OS gains were greater (HR 0.67, 95% CI 0.58–0.77; I^2 = 32%), but benefits extended to HRR-proficient patients (HR 0.76, 95% CI 0.68–0.85). Adverse events rose (grade ≥3: odds ratio 1.58, 95% CI 1.32–1.89), mainly anaemia (PARPi) and hypertension (ARSIs), though quality-of-life remained stable in recent trials.

Conclusions: Novel PARPi+ARSI combinations significantly enhance OS and PFS in mCRPC, with robust benefits in HRR-deficient cases and emerging value in broader populations per 2024–2025 updates. These findings support biomarker-driven upfront use, balancing efficacy against toxicity to optimise sequencing and reduce resistance in high-risk subgroups.

Supporting Table: Pooled OS Outcomes by Subgroup

Subgroup	Studies (n)	Patients (n)	HR (95% CI)	I^2 (%)
Overall PARPi+ARSI	14	12,340	0.72 (0.65–0.80)	45
HRR-Deficient	7	2,150	0.67 (0.58–0.77)	32
HRR-Proficient	9	10,190	0.76 (0.68–0.85)	48
First-Line mCRPC	6	5,620	0.70 (0.62–0.79)	40

1466

Implementation of liquid biopsies in routine clinical care in patients with advanced solid cancer (LIQPLAT) – a single arm trial enabling randomized comparisons

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Introduction: Circulating tumor DNA (ctDNA) is a promising tool for the non-invasive monitoring, detection of targetable alterations, and stratification of cancer. Yet, evidence for routine clinical use remains limited. LIQPLAT seeks to optimize cancer care by investigating the integration of repeated ctDNA measurements into clinical routine.

Methods: LIQPLAT is a random invitation single arm trial being conducted at the University Hospital Basel. We assess feasibility and impact of routine ctDNA analysis (Oncomine Pan-Cancer Cell-Free Assay, Thermo Fisher) in patients (pts) with advanced solid cancers with an indication for systemic first-line therapy, excluding primary brain tumors (NCT06367751). 200 randomly selected pts will be invited for ctDNA testing alongside standard care. ctDNA samples will be collected before treatment, at 2-3 and 6-7 months, and at disease progression or treatment change. ctDNA results are reviewed at a molecular tumor board and shared with the treating team. Random selection aims for a representative sample, enabling unbiased comparisons with pts receiving standard care.

Results: As of October 01, 2025, 162 pts were randomly selected, participation was offered to 140, of whom 133 (82%) accepted. 43 (27%) were female, median age was 71 years (IQR, 35-89 years), 111 (69%) had an ECOG performance status 0-1. Most common cancers were lung (40, 25%), head and neck (23, 14%), and colorectal cancer (22, 14%). Median turnaround time for ctDNA analysis was 17 days. At least one pathogenic mutation was found in 85 of 133 (64%) baseline samples. The most frequent mutations were TP53 (48, 36%), KRAS (22, 17%), and PIK3CA (12, 9%). Molecular data from tumor tissue were available for most patients, allowing comparison with ctDNA profiling.

Conclusions: LIQPLAT demonstrates that routine ctDNA measurement is feasible in a real-world cancer population and will further elucidate its utility in supporting clinical decision-making. Recruitment is expected to be complete in spring 2026. Preliminary findings on ctDNA profiles, their tumor board reviews, and their impact on clinical management will be presented at the meeting.

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The SAKK OvCaR Registry: First Interim Analysis of a Multicenter Swiss Ovarian Cancer Registry (OvCaR)

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Introduction: Ovarian cancer remains one of the most lethal gynecologic malignancies, with over 700 new diagnoses and 300–400 deaths annually in Switzerland. The SAKK OvCaR registry was established to systematically collect retrospective and prospective data on patients with FIGO stage I–IV ovarian, fallopian tube, and primary peritoneal cancers to inform treatment patterns and outcomes. Any histologic subtype was allowed to be included.

Methods: SAKK OvCaR is a national, multicenter, exploratory registry including retrospective patients (Cohort A, diagnosed after January 2018) and prospectively enrolled patients (Cohort B). Data were extracted from secuTrial® on data cutoff May 5, 2025. Inclusion required age ≥18 years, histologically confirmed ovarian cancer, and comprehensive clinical data including molecular data and treatment outcomes. Key endpoints are overall survival (OS) and progression-free survival (PFS).

Results: As of May 2025, 347 patients were enrolled across 15 Swiss sites (Cohort A: 128 [37%]; Cohort B: 219 [63%]). Median age at diagnosis was 68 years (range 25–95). Most patients presented with high-grade serous carcinoma (68%) and advanced disease (FIGO stage III–IV in 84%). Median follow up from diagnosis was 2.8 years. Primary debulking surgery was performed in 61% of patients (n = 212). BRCA status was mutated in 18%, wild type in 63% and unknown in 19%.

A total of 303/347 patients (87%) received at least one line of systemic treatment. Platinum based chemotherapy was the most common prescribed regimen (N = 290 patients, 96%). Maintenance therapy was given in 146 patients (48%) including PARPi (N = 52, 17%), PARPi plus VEGFi (N = 30, 10%) and VEGFi (N = 64, 21%). Median duration of first-line treatment including maintenance phase was 13 months.

Conclusions: This first interim analysis highlights the successful accrual and feasibility of the SAKK OvCaR registry in a retrospective and prospective cohort, capturing real world treatment patterns in Swiss ovarian cancer patients. Most patients were diagnosed with advanced high grade serous carcinoma and treated with platinum-based regimens, with increasing integration of targeted therapies such as PARP and VEGFi inhibitors in 1st line. Ongoing inclusion of patients and follow-up will provide comprehensive insights into survival outcomes and evolving standards of care.

ONCOREHA/OPS/PALLIATIVE.CH/SNIO/SOHC POSTER PRESENTATION – NURSING, SUPPORTIVE & PALLIATIVE CARE, REHABILITATION & SURVIVORSHIP AND INTEGRATIVE ONCOLOGY

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Cancer Survivorship Fatigue: Characteristics, Multimodal Fatigue Interventions (MMFI) and Time Course of 108 Cancer Fatigue Clinic (CFC) patients

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Introduction: Cancer survivors (CS) experience fatigue as life-disrupting condition after curative anticancer treatment, and require structured diagnosis identifying treatable cofactors and capabilities relevant for tailoring evidence-rooted MMFI. Symptomatic, behavioural, functional and vocational outcomes may therewith improve or stabilize, our objective is to investigate them.

Methods: A CFC applies an outpatient diagnostic workup (anticancer treatment history, ESAS, Single-Item-Fatigue, BFI, DICRFS, Distress-T, WHODAS, HADS, BAI, BDI, Self-Efficacy-Expectation, Coherence, Screening-PTBS, Five-Time-Sit-To-Stand; Cofactors incl. Labs; NeuroPSychological Examination), advice on MMFI and insurance-medicine aspects. Protocol-based (EKOS 2024-02085) data extracted from anonymized medical letters was analyzed (descriptive statistics, Pearson, Anova, paired T-Test [SPSS]).

Results: Of 184 CS, 41 were excluded for preexisting psychiatric disease, 35 for <2 full consultations. Of 108 CS (Age 54 [range 21-79], 79% female; 52% Breast, 14% Hem, 11% GI, 23% other cancer) time between first (5.2020-12.2024) and second CFC was 70 days [median, mean 93], and last CFC 245 days [326 days], respectively. Anticancer treatment included Chemo- (84), Immun- (35), Radio- (68), and Surgical Therapy (95), 53 had Combined (C/I & R & S) Therapy (CT). Cofactors for Fatigue included emotional burden (94), pain (62), CINP (32), Insomnia (72), Malnutrition (35), Covid-history (43) and other (108). NPS (88) revealed impairments in all CS (mild 15, mild-moderate 27, moderate 46). CT correlated with ESAS-Fatigue (p = .029), SIF-cognitive (p = .001), and BFI (p = .004). All outcomes (NPS not assessed) improved from first to last CFC significantly (p <.001; SWE p = .043, DT p = .030), except ESAS wellbeing, fatigue, and anxiety, SkPTBS, Coherence, and WHODAS. Optimal MMFI (all MMFI elements done) was at first CFC in 2%, at last CFC in 62%; recommendation for ≥3 MMFI occurred in 43% and 9%, respectively. Optimal MMFI at last CFC correlated with less depressive symptoms (BDI-II p = .045, ESAS Depression p = .066), and some characteristics at first CFC (SIF physical p = .037, BFI p = .028, Distress p = .040). 1/3 of CS reported Insurance problems.

Conclusions: CS can succesfully implement MMFI in their lifes based on CFC-advice when not burdened with depressive symptoms. Implementation is associated with improved symptomatic but less with functional outcomes.

6030

Towards the Integration of Complementary Approaches within Oncology and Palliative Care Services: A Mixed-Methods Study at Geneva University Hospitals

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Introduction: The integration of complementary approaches within conventional medicine is rapidly expanding, giving rise to integrative medicine (IM). The prevalence of complementary medicine (CM) use among oncology and palliative care patients is increasing worldwide. At Geneva University Hospitals, the most recent study on this population dates back to 2008. This study provides an update in 2025, in the context of the creation of an in-hospital IM center.

Methods: A mixed-method study combined a quantitative questionnaire with semi-structured interviews. The questionnaire assessed the prevalence, type, and reasons for CM use, while interviews explored patients' motivations, facilitators, and barriers. Quantitative and qualitative data were analyzed separately, then combined into a final analysis.

Results: The questionnaire was distributed to 373 eligible patients. Among the 107 completed questionnaires, 83 were retained for analysis as they included data on CM use, which was the main focus of the study. Overall, 65% of respondents reported using CM alongside conventional treatment. The most frequently used practices were acupuncture (74.1%), homeopathy (40.7%), and hypnosis (40.7%), mainly to improve physical well-being (61.4%), mental well-being (52.3%), and to relieve symptoms (45.5%). In the interviews, CM use was perceived as a means of empowerment in coping with illness, fostering active participation in care (11/14) and a sense of self-reappropriation (11/14). Facilitators of CM use included recognition by conventional medicine (7/14), as well as information provided by HUG (12/14) or by peers (7/14). Reported barriers included reimbursement issues (12/14), lack of information (7/14), and limited integration into conventional care (6/14).

Conclusions: CM use is increasing among oncology and palliative care patients, motivated by the pursuit of well-being, autonomy, and medical recognition. However, it is hindered by cost, lack of information, and insufficient integration within conventional medicine. Patients express a clear need for a coordinated and accessible IM service. The planned IM center at HUG could adress these expectations, provided that information sharing and care coordination are strengthened.

7661

Dermatological reactions during antitumor therapies: Introduction of a skin assessment

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Introduction: Dermatological reactions affect 75–90% of patients undergoing certain anticancer therapies (Dermatological reactions in oncological therapies, 2023). These skin changes can cause psychosocial burdens and functional impairments, potentially leading to therapy interruptions. Collaboration within the multi-professional oncology team is essential. Besides patient education and symptom management, qualified nursing staff are responsible for assessing and documenting skin conditions. However, at a cantonal hospital in Switzerland, skin conditions were not standardly recorded. This study examined whether introducing a basic dermatological assessment would ensure consistent documentation of skin findings, evaluation of personal hygiene habits, and provision of appropriate skin care kits.

Methods: As part of an MAS thesis, a basic dermatological assessment was developed based on the "Dermatotoxicity in Oncology" course by Oncology Nursing Switzerland. It was finalised by a multi-professional team at the oncology outpatient clinic of a cantonal hospital and introduced in November 2021. A retrospective data analysis in the hospital information system (KISIM) recorded all patients who received the substances: Erbitux, Taxotere, or Vectibix between December 2021 and December 2024. The study assessed documentation of the dermatological assessment, provision of skin care kits, and recording of skin findings.

Results: Among 139 patients, seven received Erbitux, 14 Vectibix, and 118 Taxotere. The dermatological assessment was performed in 87 cases (63%), and 76 patients (55%) received appropriate skin care kits.

Conclusions: The introduction of the basic dermatological assessment led to standardised documentation, discussion of personal hygiene, and provision of suitable care kits. Patients thus receive targeted skin care advice. Literature shows early detection and systematic documentation improve symptom control and reduce therapy interruption (Dermatological Reactions in Oncology Treatments, 2023).

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A Delphi Consensus in Integrative Oncology: Towards Shared Principles and Criteria for Integration

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Introduction: The Swiss Network for Integrative Oncology (SNIO), founded in 2024, unites cancer centres in Switzerland that, alongside conventional oncology, offer a structured complementary and integrative medicine (CIM) service with regular consultations by physicians with CIM training. Its mission is to foster quality, education, and research in integrative oncology. Although CIM use is increasing, there is no agreed position or coordinated approach for integrative oncology in Switzerland. A national consensus paper defining shared principles and integration criteria is therefore being developed to strengthen professional identity and provide orientation for patients and colleagues.

Methods: Consensus development follows a two-phase Delphi process, coordinated by a steering committee and supported by a multidisciplinary scientific committee. Preparatory input came from literature, committee members, and SNIO delegates, complemented by a session at SOHC 2024. Two steering committee members (a nurse and a physician) drafted statements, which were merged and refined into the first set for Delphi voting. In Phase 1, CIM physicians and nurses of SNIO centres vote on principles and standards until ≥80% consensus is reached, followed by endorsement from oncologists, nurses, and patient representatives. In Phase 2, all stakeholder groups define integration criteria, also requiring ≥80% consensus. Voting is online using Likert scales; subgroup perspectives are analysed from demographic data.

Results: By September 2025, drafts for both phases were consolidated. Preparatory work for Phase 1 produced nine topics, addressing, among others, the view of human nature (Menschenbild), salutogenesis, patient self-efficacy, and self-care of professionals. These form the starting point for the Delphi process. The first voting round is scheduled for autumn 2025.

Conclusions: This project is the first nationwide effort to formulate a shared position on integrative oncology in Switzerland. Using a sound methodology and broad stakeholder involvement, it aims to foster integration of CIM services, strengthen interprofessional collaboration, and provide a framework for practice, education, and research. The consensus paper will articulate a shared professional stance and establish clear criteria for meaningful integration into oncology care, making this position visible to patients, colleagues, and institutions.

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

1907

Achieving remission with the second generation BTK-inhibitor zanubrutinib in a male patient with steroid-refractory recurrence of immune-mediated thrombotic thrombocytopenic purpura

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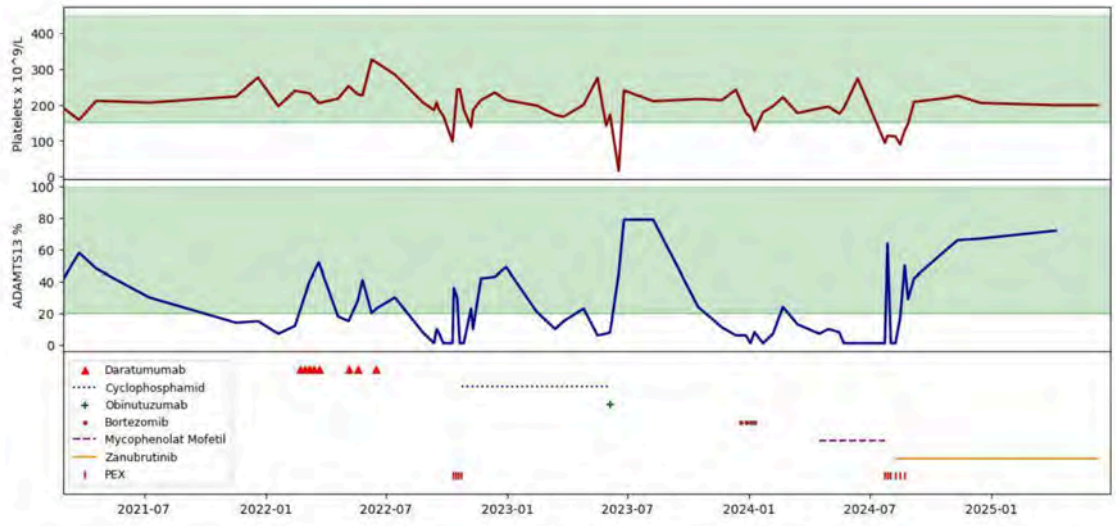
Introduction: Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a life-threatening thrombotic microangiopathy characterized by severe ADAMTS13 deficiency, with relapses occurring in up to 30% within two years. Standard treatment includes plasma exchange, corticosteroids, rituximab, and caplacizumab, yet management of relapsed or refractory cases remains challenging. Bruton's tyrosine kinase (BTK) has emerged as a therapeutic target in autoimmune diseases. We report the first successful use of the second-generation BTK inhibitor zanubrutinib in a patient with multiply relapsed, treatment-refractory iTTP.

Methods: We describe the clinical course of a 43-year-old male with iTTP who experienced seven relapses over 14 years. Multiple immunosuppressive agents (rituximab, obinutuzumab, daratumumab, cyclophosphamide, mycophenolate mofetil, bortezomib) were either ineffective or discontinued due to allergic reactions or intolerance. Plasma exchange and corticosteroids failed to restore ADAMTS13 activity during the latest relapse. In order to avoid complications related to the splenectomy, it was deferred in favor of off-label zanubrutinib.

Results: Zanubrutinib was initiated at 320 mg daily. Within four days, ADAMTS13 activity became detectable and the inhibitor disappeared, allowing cessation of plasma exchange within two weeks. Platelet counts normalized after three weeks and ADAMTS13 activity after eleven weeks. Corticosteroids were tapered and discontinued by week seven. The patient remains in complete remission after 11 months of continuous zanubrutinib. During this time, the patient noticed increasing levels of blood sugar and blood pressure in the context of a preexisting metabolic syndrome, both requiring medical treatment. Otherwise zanabrutinib was well tolerated.

Conclusions: This case highlights the potential of BTK inhibition as a therapeutic strategy in refractory iTTP. The rapid and sustained hematologic and biochemical response to zanubrutinib, together with its favorable safety profile compared to first-generation BTKis, supports further evaluation of BTK inhibitors in autoimmune thrombotic microangiopathies. Systematic investigation in clinical trials is warranted to determine efficacy, safety, and optimal positioning of BTKi in the treatment algorithm of relapsed or refractory iTTP.



0865

HbF-inducing gene therapies for β-hemoglobinopathies: materno-fetal implications in future pregnancies and a framework for antenatal surveillance

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Introduction: The most recent somatic gene therapies strategies for β-haemoglobinopathies – sickle cell disease and β-thalassemia – aiming at stable rexpression of high level of fetal hemoglobin (HbF) are transforming the contemporary therapeutic landscape. HbF, expressed during in utero life and physiologically silenced after birth, has a higher affinity for oxygen allowing for transplacental exchange of oxygen. Its persistence at significant levels in the maternal circulation could impair fetal oxygenation during subsequent pregnancies.

Methods: To anticipate the obstetric challenges in this emerging population, we synthesize existing evidence on pregnancy outcomes in women with hereditary persistence of fetal hemoglobin (HPFH) – a naturally occurring model of elevated HbF – to apprehend potential maternal and fetal impacts in individuals having undergone gene therapy for β-haemoglobinopathies.

Results: Evidence is very limited. It strongly suggests that moderate HbF levels (10–30%) reduce both maternal and fetal complications in sickle cell disease. However, levels exceeding 50%, as observed after gene editing in β-thalassemia, might blunt the maternal-fetal oxygen affinity gradient and contribute

to placental insufficiency and fetal growth restriction. Based on these elements this viewpoint outlines pragmatic adaptation of the current recommendations for antenatal monitoring in pregnancies with supraphysiological level of maternal HbF.

Conclusions: As gene-therapies are offered to teenagers and young adults and includes fertility preservation prior to conditioning, obstetricians and hematologists will be requested to manage post-therapy pregnancies in this population. Multidisciplinary guidelines and dedicated registries will be essential to ensure maternal safety and optimize perinatal outcomes within this evolving therapeutic landscape.

0095

Platelets phagocytosis in acute Dengue infection

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Introduction: A 55-year-old woman presented with malaise, fever, myalgias and arthralgias 3-day after a trip to Martinique in Caribbean Sea. Laboratory investigations showed bicytopenia (leukocytes 1.9 G/l; platelets 121 G/l). A screening test for Dengue detecting NS1 Antigen was performed and resulted positive. Dengue antibodies IgM and IgG were negative. Molecular testing via polymerase chain reaction revealed a Dengue viral load of 10 million copies/ml, confirming a primary acute Dengue infection.

Methods: The peripheral blood film on the Digital Imaging System CellaVision® DC-1 showed platelets satellitism around granulocytes. At the same time, platelets merging with neutrophil granulocytes and attracting other granulocytes were observed. Granulocytes with internalised and phagocytosed platelets showing multiple vacuoles are also seen. The patient received a supportive therapy and recovered after one-week.

Results: Platelets satellitism is a phenomenon in which platelet arrange themselves on the surface of other cells. It is generally observed in peripheral blood smears of normal subjects prepared from blood samples anticoagulated with EDTA, in which platelets rosette around polymorphonuclear neutrophils. This phenomenon is frequently triggered in-vitro by EDTA in the presence of cryptic antibodies forming bridges between the glycoprotein IIb/IIIa complex of the platelet membrane and the neutrophil Fc gamma (FcgRIII) receptor. Commonly seen in EDTA, but not in samples treated with heparin or sodium citrate, platelets satellitism represents an in-vitro cause of thrombocytopenia, i.e. pseudothrombocytopenia, without clinical consequences.

Conclusions: In Dengue infection platelets satellitism represents the first step in platelets clearance through phagocytosis. It is also an in-vivo and not only an in-vitro phenomenon. Dengue virus binds on the receptor dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin, which is present on the primary target represented by dendritic cells and by platelets. The binding between Dengue virus and platelets lead to apoptosis and to phagocytosis by macrophages. This case shows that the sequentially binding of infected platelets around granulocytes, the internalisation and the phagocytosis process happens in vivo in the absence of antibodies

1057

Compound HFE/PIGA Mutation as cause of hemochromatosis and neurological dysfunction: case report of a Swiss patient

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Introduction: Phosphatidylinositol glycan anchor biosynthesis class A (PIGA) mutations disrupt glycosylphosphatidylinositol (GPI) anchor synthesis, leading to a spectrum of congenital disorders characterized by neurological impairment, multisystem involvement, and, in select cases, systemic iron overload.

Methods: We describe the case report of a swiss patient affected by compound het. HFE/PIGA deficiency presenting since childhood with symptoms affecting the nervous system (autism, epilepsy and psychomotoric retardation); the cardiovascular system (dilatative cardiomyopathy); and the iron homeostasis (with overload in both liver and heart).

Results: The patient was referred to the Hematology department when he turned 22 y/o due to a hyperferritinemia (4592 ug/l). The MRI T2* performed showed a severe iron overload of the heart (4.2ms) and a moderate one of the liver (2.9 ms). Genetic test for the HFE locus showed only a heterozygous C282Y mutation, HJV and HAMP mutation were negative. Bloodletting was initiated; although a rapid normalization of the ferritin values was observed, the patient presented with repeated epilepctic events after the bloodletting. After multidisciplinary discussion and the new literature findings, a genetic investigation of the PIGA gene was performed, leading to the diagnosis of X-chromosomal inherited PIGA-Deficiency, Mutation c.242G>A. Iron chelation therapy was suggested; sue to the numerous interactions with the antiepileptics of both deferoxamine and deferasirox, deferiprone was chosen as best therapy, leading to no neurological complication. Regardless of the optimal plasmatic iron values, the cardiac status of the patient turned for the worse. The patient developed various serious complications, including a thrombotic stroke with senso-motoric hemisyndrome. He expired after an infectiuos complication.

Conclusions: PIGA catalyzes the first step of GPI anchor biosynthesis, a process that is important for the dynamics and cell membrane attachment of approximately 150 human proteins. As postulated before, iron overload in PIGA deficiencies could be caused by a failure to attach GPI anchors to HJV and a subsequent inability to appropriately induce hepcidin expression by hepatocytes. How this interacts with the heterozygous HFE C282Y mutation needs to be further investigated.

8582

Utility of screening for aberrant T-cell marker expression in diagnostic evaluation of plasmablastic myeloma: A case report.

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Introduction: The diagnosis of multiple myeloma is usually straightforward, based on characteristic clinical features, bone marrow plasma cell infiltration, and demonstration of clonality. However, the morphology of neoplastic plasma cells can vary considerably, posing a diagnostic challenge – particularly when immature cells with plasmablastic features are present. We report the case of a 78-year-old female patient, referred to our centre with severe anaemia and osteolytic bone lesions ultimately leading to the diagnosis of plasmablastic myeloma (PBM). The case illustrates how comprehensive immunophenotyping can guide early suspicion and diagnostic work-up in this morphologically challenging entity.

Methods: Standard blood smear and serum protein electrophoresis were performed according to institutional protocols. Bone marrow cytology and histopathology were used to assess plasma cell morphology and the degree of infiltration. Immunophenotyping was conducted primarily by multiparameter flow cytometry using panels of B-cell, T-cell, plasma cell and lineage markers. Immunohistochemistry was applied for morphological correlation of antigen expression patterns.

Results: The peripheral blood smear demonstrated marked rouleaux formation and a clearly visible protein film. Serum protein electrophoresis confirmed the presence of a monoclonal protein type IgA lambda. Bone marrow cytology revealed an infiltration of >80% plasma cells, predominantly exhibiting atypical morphology with additional plasmablastic forms, as confirmed by histopathological examination. Flow cytometric analysis identified a population of clonal, light chain lambda–restricted plasma cells with loss of CD19 and aberrant expression of CD56. Notably, aberrant expression of T-cell markers, specifically sCD3 and CD5, was observed in approximately 50% of the clonal plasma cells, along with CD10 expression.

Conclusions: Consistent with previous reports, our observations contribute additional descriptive information and indicate that expression of T-cell markers may support the diagnosis of PBM – therefore carrying prognostic significance. In cases lacking myeloma-typical clinical features and detectable monoclonal paraproteinaemia, plasmablastic lymphoma should be considered. Our results highlight the importance of including T-cell markers in flow cytometry panels to improve diagnostic accuracy and prevent misclassification of PBM.

4980

Operational performance evaluation of two Tests for Free Light Chain in Serum

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Introduction: Good laboratory quality and performance are critical in managing analysis costs. Performance assessment is an important tool to evaluate all steps and components of the analysis – i.e. handling, reagents, run, rerun and maintenance – and concurrently allow to improve performance too. Performance of free light chain (FLC) assays is unknown. To compare the performance of FCL assays in serum we performed an operational evaluation of two different tests.

Methods: Analysis of Kappa and Lambda FLC of non-selected samples were performed in parallel using Freelite on the Optilite (The Binding Site) and SEBIA FLC (Sebia) on the Dynex Agility platform. Performance was assessed measuring all steps of the analysis in the routine diagnostic. Activities were defined at refill (reagent, wash solution, diluent, consumables), call and quality controls (handling, testing, validation), daily maintenance (waste, wash, refill bulk solutions, cleaning), sample (handling, loading, unloading, storage) and resulting (not included in the analysis). Hands-on time (HT) was defined for preparation before starting. Total lead time (TLT) was defined as run preparation, run testing and end-phase.

Results: HT for all activities on Optilite and on Dynex Agility platform was similar (HT: 29 min. for both essays). For a similar number of samples analyzed pro run (n = 50 on Dynex Agility and n = 54 on Optilite), the TLT was significantly shorter for FLC on Optilite than on Dynex Agility (TLT: 136 min and 150 min, respectively; difference 24 min). Based on 2959 samples that have been tested in parallel on each method, re-run and dilution were significantly lower for Sebia (6.8% and 16.2% respectively).

Conclusions: Sebia ELISA assay needs longer TLT but requires fewer dilutions, i.e. lower lab workload and reagent costs. Sebia platform may have lower costs per test and offer better workflow integration in routine labs. Microplate format for batch testing may perfectly fit to handle large volume testing needs.

7673

JAK2V617F mutation in northeast Thailand patients with Myeloproliferative neoplasms.

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Introduction: The activating JAK2 mutation resulting from a G>T transversion at codon 617 (JAK2-V617F) is associated with myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The JAK2-V617F mutation is included as a major diagnostic criterion for MPNs in the 2008 WHO classification. Its frequency varies among populations, but data from northeastern Thailand have been lacking. Therefore, we aimed to determine the frequency of the JAK2-V617F mutation and its laboratory correlations in patients from northeastern Thailand.

Methods: We retrospectively reviewed all patients from hospitals in northeastern Thailand who were referred by hematologists for JAK2-V617F testing between January 2019 and January 2024. A total of 418 peripheral blood and bone marrow samples were analyzed using quantitative allele-specific amplification (QUASA) real-time PCR.

Results: Of the 418 patients, 101 (24.2%) were positive and 317 (75.8%) were negative for the JAK2-V617F mutation. Among the 101 mutation-positive patients, 46 (45.5%) had PV, 39 (38.6%) had ET, 11 (10.9%) had PMF, and 5 (5.0%) had unclassified MPNs. The frequency observed in this cohort is consistent with previous reports from other regions. Incorporating JAK2-V617F mutation screening into the initial evaluation of patients suspected of having MPNs is valuable.

Conclusions: The frequency of the JAK2-V617F mutation in our study is compatible with previous reports. JAK2-V617F mutation screening can be incorporated in the initial evaluation of patients suspected of having MPNs. Detection of JAK2-V617F is of diagnostic significance and quantification of this mutation is also useful in monitoring patients as a residual disease marker.

Table 1. Characteristics of patients.

Parameter	JAK2 V617F Positive patients	JAK2V617F Negative patients
Patients N (%)	101 (24.17%)	317 (75.87%)
Male mean age (range)	59.86 (21–88)	43.29 (4–91)
Female mean age (range)	57.14 (23–85)	48.12 (6–82)

Table 2. Characteristics of patients with the JAK2 V617F mutation.

Disease	Number of patients (%)	Male/ Female	Male mean age (range)	Female mean age (range)
PV	46 (45.54)	28/18	59.80 (29–88)	56.28 (22-78)
ET	39 (38.61)	24/15	60.93 (22-85)	57.28 (22-79)
MF	11 (10.90)	5/6	60.39 (39-86)	55.22 (25-80)
Unclassified MPNs	5 (4.95)	5/0	50.17 (25-84)	-

POSTER – EXPERIMENTAL HEMATOLOGY / ONCOLOGY

5442

The BTK-degrader BGB-16673 and the BCL2-inhibitor sonrotoclax are active as single agents and in combination in marginal zone lymphoma models

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Introduction: Targeting the B cell receptor signaling with BTK and PI3K inhibitors (i) is efficacious in treating patients with lymphoid tumors, including marginal zone lymphoma (MZL). Unfortunately, resistance occurs, indicating the need for combinations and novel approaches. BGB-16673 (BTK-d) is a first-in-class cereblon-mediated BTK degrader currently in phase 1 in refractory/relapsed B-cell lymphoma. Here, we assessed BTK-d in MZL models as a single agent and in combination with clinically relevant compounds to provide the rationale for future trials.

Methods: Cell viability was assessed by MTT assay after 5 days of exposure to increasing concentrations of drugs or DMSO (control) in six MZL models and in resistant derivatives to PI3K-i, BTK-i and BCL2-i (n. = 7). Analyses included apoptosis and cell cycle analyses, immunoblotting, and RNA-Seq.

Results: BTK-d was very active in 2 models (SSK41, IC50 = 0.27 nM; Karpas1718 – K1718, 1.89 nM). VL51 achieved a maximal reduction in proliferation of 25% at 10 nM. Less than 20% of the reduction was observed in HC1, HAIRM and ESKOL. The activity did not differ from the BTK-i zanubrutinib (Zanu) and, accordingly, was limited in cells resistant to BTK-i (n. = 2), PI3K-i (n. = 3), and BCL2-i (n. = 2). BTK-d induced apoptosis and cell cycle arrest in K1718 and SSK41. It downregulated p-BTK(Tyr223) and total BTK levels in all six models. RNA-Seq was performed on K1718 exposed to BTK-d, Zanu or DMSO. Both molecules down-regulated the BCR-NF-κB pathways, MYC targets, and upregulated DNA-damage genes. Oxidative phosphorylation was repressed by BTK-d but upregulated by Zanu. BTK-d was combined with conventional and targeted agents. Combination with BTK-d improved the activity of single agents, with synergism with BCL2-i (venetoclax, sonrotoclax), lenalidomide, and rituximab. BTK-d exposure was associated with down-regulation of BCL-XL and MCL1. Notably, the new BCL2-i sonrotoclax was over ten times more active than venetoclax in HC1 and K1718 and equally active in the remaining two SSK41 and VL51.

Conclusions: Its ability to degrade BTK, combined with its synergy with other targeted therapies, positions BTK-d as a promising candidate for further development in MZL patients. The 2nd generation BCL2-i sonrotoclax appears as another drug to be explored in the same patient populations, possibly combining the two molecules.

6003

Locus specific proteomics identify potential regulators of the MYC super enhancer in NOTCH-driven T-ALL

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Introduction: T-ALL is an aggressive hematologic malignancy resulting from the transformation of immature T cell progenitor

cells. Activating mutations in NOTCH1 are found in over 60% of human T-ALLs and in about 80% of paediatric T-ALL cases. In the context of T-ALL, NOTCH regulates the expression of MYC through a downstream super-enhancer region, which is an essential hub for transmitting growth promoting signals for disease progression. The complete composition of the NOTCH transcription complex (NTC) is still unknown. Moreover, it is currently unknown if the NOTCH regulated transcription factor compositions differ between disease driving super-enhancers and canonical promoter regulated Notch target genes e.g. HES1 and pT-alpha. The aim of this project is to identify, in a locus specific manner, the proteins regulating NICD dependent promoters and (super)enhancers.

Methods: The method of choice is based on the CRISPR technology and is termed CAPTURE (CRISPR Affinity Purification In Situ of Regulatory Elements). Briefly, sgRNA design ensures the specificity of the chromatin purification while overexpressed Cas9 protein enables its purification. Namely, Cas9 is engineered to be enzymatically inactive and to be in vivo biotinylated. Hence, the chromatin region of interest is purified by Streptavidine affinity chromatography and the DNA bound proteins are identified by LC-MS/MS.

Results: We have identified the proteins regulating two MYC super enhancer regions crucial for leukemic cell survival, NMe (NOTCH dependent MYC enhancer) and TMe (TCF1 dependent MYC enhancer). The ongoing efforts are focused on two transcription factors: BCL11B and SIX6. These analyses aim at gaining new insights into molecular mechanisms of NOTCH and disease driving loci-specific transcriptional regulation. The ultimate goal will be to identify novel druggable therapeutic targets.

Conclusions: These analyses aim at gaining new insights into molecular mechanisms of NOTCH and disease driving loci-specific transcriptional regulation. The ultimate goal will be to identify novel druggable therapeutic targets.

0184

Analysis of Published Case Reports on Lymphoma Using Large Language Models

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Introduction: Lymphoma's heterogeneous presentations complicate treatment decisions. While randomized trials are foundational, they often exclude unique patient situations that are captured in case reports. Evidence from case reports remains underutilized due to the labor-intensive manual classification process. We developed and validated a large-scale, automated analysis of lymphoma case reports using generative AI.

Methods: PubMed was searched using MeSH terms for lymphoma case reports. A 51-item questionnaire covering demographics, type of lymphoma, diagnostics, disease location, treatments, and outcomes was created. The LLM Rombos-LLM-V2.6-Qwen-14b, combined with the data-element-extractor Python package, systematically extracted information from titles and abstracts. Performance was benchmarked against 298 manually labeled reports.

Results: We identified 10,681 publications. On the validation dataset, the model achieved an overall accuracy of 96.1% and an F1-score of 80.1%, with an F1 score greater than 90% in 13 questions. The LLM analysis identified 3,347 of the 10,681 publications as case reports on individual patients with lymphoma. Of these patients, sex was identified as male in 40.8% (n = 1364) and female in 59.2% (n = 1016). Patient age was identified in 2,898 cases (86.6%), with a median age of 52 years (range, 0-100 years), and 17.2% of patients were younger than 18 years. Hodgkin lymphoma was identified in 224 cases (11.1%). A PET-CT scan was reported in 117 patients (3.5%), and a bone marrow biopsy was performed in 113 patients (6.7%). Identified organs most frequently involved by lymphoma included skin (n = 272, 8.1%), gastrointestinal tract (n = 264, 7.9%), central nervous system (n = 222, 6.6%), eye (n = 100, 4.1%), liver (n = 77, 2.3%), oral cavity (n = 73, 2.2%), and spleen (n = 66, 2.0%). Mentions of therapies included chemotherapy in 668 cases (20.0%), radiotherapy in 297 cases (8.9%), and surgery in 119 cases (3.6%). The patient's death was mentioned in 541 cases (16.2%).

Conclusions: This is the first systematic analysis of all PubMed lymphoma case reports using generative AI. LLMs can accurately extract diverse clinical data at a massive scale, enabling living case report registries to enhance understanding of lymphoma's complex landscape.

2338

Transcriptional regulation of cell fate plasticity in hematopoiesis

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Introduction: Hematopoietic stem cells possess high plasticity, giving rise to all blood lineages, but this potential must be precisely regulated to maintain balanced output. Disruptions in these processes contribute to hematological disorders, including anemia and leukemia. While master TFs such as GATA1 and TAL1 activate lineage programs, less is known about TFs that repress alternative fates and stabilize differentiation. Our objective is to systematically uncover transcriptional regulators of erythropoiesis using integrative single-cell approaches and human genetics.

Methods: We analyzed publicly available single-cell multiome data spanning erythroid, myeloid, and lymphoid trajectories. Gene regulatory networks were reconstructed using state-of-the-art methods such as scGRaNIE and SCENIC+, capturing both dynamic and more stable TF–target interactions. TFs were ranked with GRaNPA, which measures how well each TF regulon explains transcriptional variation across successive steps of differentiation. Functional roles were inferred from GO enrichment of TF target sets and connected to GWAS signals for red blood cell traits using LDSC enrichment of TF target peaks.

Results: Our framework recovered established TFs in erythropoiesis, including GATA1 and TAL1, validating the approach. We also identified factors with less defined roles. Among these, ZNF385D emerged as a strong candidate: its regulon predicted transcriptional variation along the erythroid trajectory and was enriched for genes in heme biosynthesis and hemoglobin expression. ZNF385D targets were strongly expressed in early erythropoiesis and enriched for pathways regulating heme biosynthesis and hemoglobin, consistent with a potential repressor role during erythroid maturation. Integration with genome-wide association studies supported this candidate, as ZNF385D targets overlapped red blood cell traits. Together, these findings nominate ZNF385D as a novel TF regulator of erythropoiesis alongside canonical factors.

Conclusions: This integrative strategy identifies both known and previously uncharacterized TFs in erythropoiesis, with ZNF385D emerging as a promising candidate that connects regulatory networks to human genetic variation in red blood cell traits. Ongoing CRISPR-based perturbations in primary hematopoietic cells will provide causal validation and clarify how such TFs contribute to lineage control and hematological disease.

5798

Evaluation of translational potential of research focused on hematological neoplastic diseases – results of a large-scale analysis of PubMed and iCite databases

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Introduction: Evaluating biomedical databases identifies trends in clinical research and emerging therapeutic areas. We examined how advanced AI and ML methods can support these traditionally labor-intensive activities.

Methods: We systematically identified scientific publications on hematological neoplastic diseases (HND). We extracted terms from the WHO classification of hematopoietic and lymphoid tumors, expanded them with OncoTree and MONDO disease ontology data, and supplemented the list with non-standard terms based on expert input. We used a combination of regular expressions and BERT-based large language models to identify abstracts in PubMed (January 1950–April 2025; 38,644,614 abstracts) that mentioned HND. This process was repeated multiple times with manual expert oversight to reduce false positives and negatives. Results were combined with the iCite database for translational potential assessment, using composite scores that integrated clinical relevance (60%) and research impact (40%).

Results: Analysis of 632,471 publications revealed that HND research is dominated by leukemia (39.8%), lymphoma (31.2%), and myeloma (10.3%), accounting for more than 80% of the literature. The remaining research focused on myelodysplastic syndromes (3.6%), myeloproliferative neoplasms including myelofibrosis and polycythemia vera (2.2%), histiocytic disorders (3.1%), lymphoproliferative disorders (2.1%), and mature T-cell neoplasms such as mycosis fungoides (1.2%). Historically, Hodgkin Lymphomas showed the highest translational potential (score: 710,219) with 80.2% of studies involving humans, followed by myelodysplastic syndromes (667,226; 74.2% human studies) and myeloproliferative neoplasms (599,926; 71.3% human studies). A recent 10-year analysis revealed that myeloid neoplasms have the highest translational potential (712,343), with myelodysplastic syndromes leading the way (832,439). All major categories showed increasing potential (+16.4% to +22.1%) except histiocytic disorders (-25.8%).

Conclusions: While leukemia, lymphoma, and myeloma dominate the literature, myelodysplastic syndromes exhibit the highest translational potential, indicating a shift in paradigm toward myeloid disorder research. A validated framework for research prioritization requires input from the broader medical community.

0163

Primary and Acquired Resistance to Targeted Treatment in BRAF V600E-mutated Metastatic Colorectal Cancer – PARTACER-Suisse (SAKK 41-23, Trial in Progress)

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Introduction: BRAF V600E–mutated metastatic colorectal cancer (mCRC) is characterized by an aggressive disease course and poor prognosis. The current standard of care involves molecularly targeted combination therapy using the anti-EGFR antibody cetuximab and the BRAF inhibitor encorafenib (CE), with or without chemotherapy. However, durable responses are rare and acquired resistance limits long-term patient benefit. The molecular mechanisms driving resistance to CE remain incompletely understood, and strategies to prevent, delay, or overcome resistance are urgently needed.

Methods: PARTACER-Suisse is an investigator-initiated, prospective, HRO Chapter 2 multicenter study enrolling patients undergoing molecularly targeted treatment with CE with or without chemotherapy, for BRAF V600E-mutated mCRC. The study is organized through Swiss Cancer Institute (SCI), formerly known as Group for Clinical Cancer Research (SAKK; trial number 41-23), with 13 study sites across Switzerland actively engaged in patient recruitment. In the clinical part of the study, pre-treatment and on-progression tissue, stool, and liquid biopsies are collected from patients undergoing treatment at participating sites. NGS-based DNA profiling is performed upon sample receipt, and results are reported back to the recruiting centers. The translational part of PARTACER-Suisse focuses on multi-omics molecular analyses of paired patient samples, as well as on the generation and characterization of patient-derived 3D organoids (PDOs) established from pre- and post-treatment biopsies. These PDOs are employed for in vitro treatment and resistance modeling, aiming to preclinically establish novel therapeutic strategies to overcome relevant resistance mechanisms.

Results: Patient enrollment and sample collection are ongoing across participating centers. Preliminary quality assessments confirm feasibility of coordinated multi-site sampling and data integration.

Conclusions: By integrating genomics, transcriptomics, immune tumor microenvironment, and microbiome analyses in a prospectively assembled patient cohort, PARTACER-Suisse aims to deliver the first comprehensive molecular characterization of acquired resistance in BRAF V600E mCRC. Through the exploitation of PDOs, the study seeks to preclinically define novel therapeutic approaches that could be rapidly translated into interventional clinical trials.

5786

Synergistic Effects of Immunotherapy and Chemotherapy in Reducing Drug Resistance in Leukemia Cells

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Introduction: Drug resistance in leukemia cells remains a major challenge in effective treatment. Combining immunotherapy with conventional chemotherapy has emerged as a promising strategy to enhance therapeutic efficacy and overcome cellular resistance, potentially improving patient outcomes.

Methods: A comprehensive review of recent literature was conducted, focusing on the combined effects of immunotherapy agents and chemotherapy drugs in leukemia. Additionally, a computational simulation model was developed to predict the interaction of these therapies on resistant leukemia cell populations and assess their impact on treatment outcomes.

Results: Preliminary analyses suggest that the combination therapy may significantly reduce drug resistance in leukemia cells, increasing chemotherapy efficacy while minimizing toxicity to healthy cells. The simulation supports the potential of this strategy to optimize treatment protocols and guide future experimental studies.

Conclusions: Integrating immunotherapy with chemotherapy represents an innovative approach to combat drug resistance in leukemia. This study highlights its potential clinical implications and provides a foundation for subsequent in vitro and in vivo research, paving the way for improved patient management and treatment strategies

POSTER – CLINICAL SOLID TUMOR ONCOLOGY

7619

Neoadjuvant Immunotherapy in Stage III Colon Cancer with Deficient Mismatch Repair: A Single-centre Experience

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Introduction: High microsatellite instability (MSI-H) or deficient mismatch repair (dMMR) colon cancer occurs in approximately 10% to 15% of all colorectal cancer cases.

Recent trials, including NICHE and NICHE-2, have demonstrated remarkable efficacy of neoadjuvant immunotherapy in dMMR colon cancer, reporting high pathological complete response (pCR) rates.

This case series presents real-world, single-centre data on neoadjuvant treatment with nivolumab and ipilimumab in patients with locally advanced, resectable stage III dMMR colon cancer, focusing on safety and pathological response outcomes.

Methods: Between December 2022 and August 2025 eight patients with dMMR colon carcinoma (clinical stage cT2-cT4, cN+) received neoadjuvant immunotherapy following the NICHE-2 protocol:

- Ipilimumab 1 mg/kg (single dose) and
- Nivolumab 3 mg/kg (two doses, two weeks apart).

All patients underwent surgery within six weeks after the last nivolumab infusion. Immune-related adverse events (IRAEs) were monitored throughout treatment and follow-up.

Results: All eight patients completed treatment and surgery as scheduled. A pathological response was observed in seven of eight patients (87.5%), including four (50%) who achieved complete pathological remission. One pCR case was confirmed to have Lynch syndrome, while another is undergoing genetic evaluation for hereditary predisposition.

Three patients showed major pathological response, while one patient demonstrated no pathological regression. Overall, therapy was well-tolerated. One patient developed immune-related diarrhoea requiring steroids and subsequent biological therapy with a monoclonal antibody. No other patient experienced >grade 1 IRAEs, and no ongoing adverse events were reported at last follow-up.

Conclusions: Neoadjuvant combination immunotherapy with nivolumab and ipilimumab is highly effective, safe and feasible in patients with locally advanced dMMR colon cancer, yielding high complete and major pathological response rates consistent with those reported in the NICHE-2 trial. No new safety concerns were identified.

Table 1: Patient and diseasecharacteristics and pathological response

Patient		(years)	Primary tumour location				
all - no. (%) 8 (100)	m/f - 4/4 (50/50)	) 67 (34 – 88)	right/left - 6/2 (75/25)	- no. (%) 1/5/2 (12.5/62.5/25)	cN1/cN2 - 5/3 (62.5/37.5)		/ - no. (%) 4/4 (50/50)
1	m		right		cN2	ypT0 ypN0 (0/36),	
2	f	8	left		cN1	ypT0 ypN0 (0/42),	4:
	m	34	left		cN1	ypT3 ypN0 (0/35),	
	f	80	right	cT4	cN1	ypT4a ypN0 (0/26), L0 V0 Pn0	
	f		right	cT2	cN1	ypT0 ypN0 (0/18	
	m		right	cT3	cN2	pT4a pN1b (2/32),	
	f		right	cT3	cN2	ypT2 ypN0 (0/32),	
	m	74	right	cT4	cN1	ypT0 ypN0 (0/32),	

Note: m: male; f: female; TRG:Tumour Regression Grade; CR:Complete Response; PR:Partial Response; NCR:Near Complete Response; MR: Minimal Response

4902

Analysis of the clinical and tumor biological differences of pre- vs. postmenopausal ER-positive breast cancer based on 2029 patient cases

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Introduction: The significance of hormone status (pre- vs. postmenopausal) in the largest subgroup of breast cancer, the so-called estrogen receptor (ER)-positive tumors, continues to be controversially discussed. However, clinical experience increasingly indicates that ER-positive tumors may also be different subgroups. Previous studies have shown that younger, premenopausal patients often have a more aggressive course of the disease not only in the presence of estrogen receptor-negative tumors (e.g. TNBC), but also in the presence of an ER-positive tumor disease.

Methods: In this study, the significance of menopausal status in the subgroup of ER+ breast cancer in relation to tumor biological and clinical parameters (>40 parameters) was investigated. For this purpose, the statistical analysis (SPSS 22) of the "Scheidegger Breast Cancer Registry" (BreCaReg) of the Paracelsus Clinic in Scheidegg was carried out after written consent by the patients.

Results: Of 8000 patients, 5788 women had ER+ breast cancer. Due to a lack of data and exclusion criteria, 2029 patient cases (1228 postmenopausal, 801 premenopausal) could be evaluated. There were no significant differences in terms of tumor stage (p = 0.3), but positive lymph node status was significantly more common in the premenopausal, ER+-MCA group (34.19% vs. 28.74%; p = 0.008). In terms of biological factors, more aggressive tumor biology was also significantly more frequently detected in premenopausal women (G3 in 34 vs. 26%; p <0.001; Ki67 >30% in 26.9 vs. 18.6%; p <0.001). With regard to the estrogen and Her2 receptor, postmenopausal breast cancer showed significantly stronger estrogen receptor expression (93 vs. 85%; p <0.001), whereas premenopausal patients were significantly more likely to overexpress the Her2 receptor (21.5 vs. 13.5%; p <0.001). As a result of the different tumor biological parameters, a "luminal B-like" ER+ MCA could be detected, especially in the group of premenopausal women (44.3 vs. 34.7%; p <0.001).

Conclusions: In summary, these data show that premenopausal women with an ER+ MCA are significantly more likely to have lymphogenic metastasis and a significantly more aggressive tumor biology at diagnosis than the older, postmenopausal subgroup.

9258

Rare Lung Cancer with a Non-Functional NTRK Fusion: "A Cautionary Tale"

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Introduction: The NTRK1-3 genes encode the TRK family of receptor tyrosine kinases. Oncogenic fusions involving these genes represent actionable targets for tumor-agnostic therapies, which have demonstrated efficacy across diverse histologies. However, due to the heterogeneity of fusion partners and breakpoint locations, comprehensive functional characterization of NTRK1-3 fusions is essential. It is particularly important to distinguish between functional and non-functional fusions to optimize patient selection for targeted therapy, as illustrated in this case report.

Methods: A 60-year-old female presented with dyspnea. CT revealed an 11 cm right lower lobe mass with enlarged hilar lymph nodes. Transthoracic biopsy morphology was challenging, prompting broad NGS, which detected an HP1BP3::NTRK1 fusion. A high-grade NTRK-rearranged spindle cell neoplasm was initially favored, and the patient was started on larotrectinib. Due to unusual morphology and intrinsic resistance, a second pathological opinion was sought. Pancytokeratin-positive small nests supported a diagnosis of sarcomatoid carcinoma of the lung, and the patient subsequently underwent neoadjuvant chemotherapy followed by surgical resection.

Results: Based on the morphology of the resection specimen, a diagnosis of pulmonary blastoma was made and subsequently confirmed by the detection of a pathogenic DICER1 mutation. Analysis of the NTRK fusion: The fusion breakpoints are located in intron 8 of HP1BP3 and exon 12 of NTRK1, preserving the kinase domain of NTRK1. HP1BP3 lacks a known dimerization domain, unlike some common NTRK1 partners (e.g., TPM3, LMNA), which can limit constitutive activation of the kinase. Immunhistochemical analysis demonstrated no detectable pan-Trk protein expression (clone EPR17341).

Conclusions: No pan-Trk protein expression was detected by immunohistochemistry, indicating that the fusion is unlikely to be transcriptionally active. Furthermore, the identification of a potent driver mutation in DICER1 suggests that the NTRK fusion, is more likely a passenger event. Given the heterogeneity of fusion partners and breakpoint locations, comprehensive functional characterization of NTRK fusions is essential to determine their oncogenic potential and therapeutic relevance.

7687

Clinical Benefit of PIK3CA Inhibition in Therapy-Refractory Endometrial Cancer: A Single-Case Report

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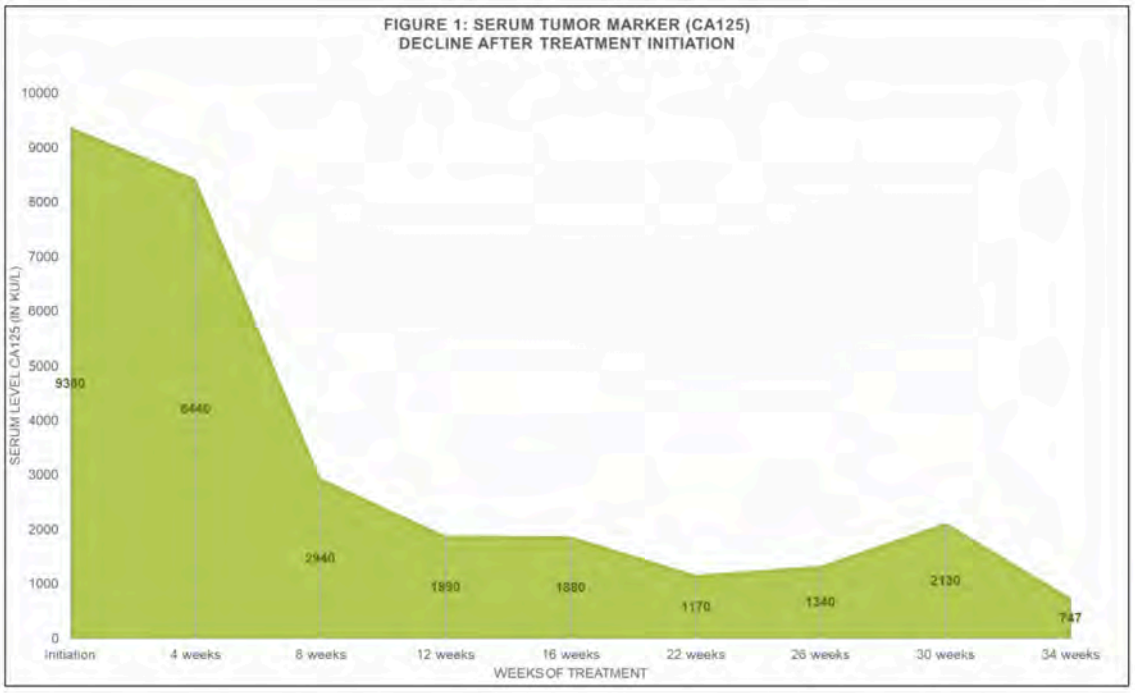
Introduction: PIK3CA mutations are frequenly seen in solid tumours, including endometrial cancer, driving resistance to therapy. We report a patient with metastatic, therapy-refractory PIK3CA-mutant endometrial cancer with a durable response to Fulvestrant combined with the PIK3CA inhibitor Capivasertib.

Methods: A 64-year-old woman with FIGO IB endometrial cancer (diagnosed July 2021) underwent hysterectomy with bilateral salpingo-oophorectomy. Disease recurred in December 2022 with inguinal lymph node and pelvic bone metastases. Prior therapies included carboplatin/paclitaxel, palliative radiotherapy, pembrolizumab/lenvatinib, letrozole/palbociclib, and a carboplatin/paclitaxel rechallenge. Molecular profiling (12/2024) revealed ESR1 p.(D538G), KRAS p.(G12C), and PIK3CA p.(N345K) mutations. Fourth-line therapy with Fulvestrant/Capivasertib commenced in March 2025. Therapy response was closely monitored through serial serum tumour markers, regular CT scans, clinical examinations, and histological evaluation of resected tissue for residual malignancy.

Results: CA125 levels declined rapidly, and imaging confirmed tumour regression. Histology from Girdlestone resection arthroplasty revealed fat necrosis with macrophage infiltration and maturing bone marrow, with no evidence of malignancy. Clinically, the patient improved quickly with reduced analgesic

use. Treatment was associated with hyperglycaemia grade II but no unexpected safety signals.

Conclusions: Fulvestrant combined with Capivasertib resulted in substantial antitumour activity in therapy-refractory PIK3CA-mutant endometrial cancer. Although not generalisable, this case highlights the importance of early molecular profiling, including PIK3CA testing, and close, multimodal monitoring to guide personalised therapy in advanced disease.



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Unlikely five-year survival after R1 resection and metachronous oligometastasis in pancreatic ductal adenocarcinoma

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Background: Despite continuous advances in oncological therapy, the outcome of pancreatic ductal adenocarcinoma (PDAC) remains dismal. Prognosis is further influenced by factors such as R1 resection, adherence to adjuvant therapy, and the presence of metastases. Nevertheless, some patients defy expectations and achieve long-term survival.

Case presentation: We report the case of a woman in her fifties with metabolic syndrome and type 2 diabetes mellitus diagnosed with borderline resectable PDAC. After one cycle of mFOLFIRINOX, induction chemotherapy was switched to gemcitabine and nab-paclitaxel due to intolerable diarrhoea, cholangitis, and dehydration. Following four dose-reduced cycles, she underwent capecitabine-based radiochemotherapy, after which the tumour was deemed resectable. Despite a marked rise in CA 19-9, PET-CT revealed no metastases. A partial pancreaticoduodenectomy (Kausch-Whipple technique) was performed. While intraoperative frozen sections suggested negative margins, final histopathology revealed extensive perineural invasion reaching the medial margin, confirming R1 resection. Adjuvant chemotherapy was discontinued after one cycle of gemcitabine/nab-paclitaxel due to severe fatigue. On surveillance, a pulmonary metastasis was histologically confirmed as PDAC harbouring KRAS p.G12V and TP53 mutations and treated with cryoablation two years postoperatively. She remains disease-free three years later, corresponding to five years after initial surgery.

Conclusions: This case demonstrates that long-term survival is possible in PDAC despite R1 resection, metastatic relapse, and unfavourable molecular alterations, underscoring the value of individualised multimodal therapy.

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