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## Abstracts of the Swiss Oncology & Hematology Congress (SOHC)

Basel (Switzerland), November 16–18, 2022

**SOHC**

SWISS ONCOLOGY & HEMATOLOGY CONGRESS



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# 5<sup>TH</sup> SWISS ONCOLOGY AND HEMATOLOGY CONGRESS (SOHC)

BASEL, NOVEMBER 16–18, 2022

## TABLE OF CONTENTS

---

2 S	SSH best abstract & award session – hemostasis, transfusion medicine, vascular, laboratory medicine
3 S	SSH/SSMO best abstract & award session – experimental hematology / oncology
6 S	SSH/SSMO best abstract & award session – clinical hemato-oncology
7 S	SSH/SSMO best abstract & award session – clinical solid tumor oncology
8 S	Oncoreha / OPS / palliative.ch / SANS best abstract & award session – supportive & palliative care, rehabilitation & survivorship
9 S	SSH oral presentation – hemostasis, transfusion medicine, vascular, laboratory medicine
11 S	SSH/SSMO oral presentation – experimental hematology / oncology
14 S	SSH/SSMO oral presentation – clinical hemato-oncology
16 S	SSH/SSMO oral presentation – clinical solid tumor oncology
18 S	Oncoreha / OPS / palliative.ch / SANS oral presentation – supportive & palliative care, rehabilitation & survivorship
21 S	SSH poster presentation – hemostasis, transfusion medicine, vascular, laboratory medicine
29 S	SSH/SSMO poster presentation – experimental hematology / oncology
35 S	SSH/SSMO poster presentation – clinical hemato-oncology
43 S	SSMO poster presentation – clinical solid tumor oncology
49 S	Oncoreha / OPS / palliative.ch / SANS poster presentation – supportive & palliative care, rehabilitation & survivorship
52 S	ePoster – hemostasis, transfusion medicine, vascular, laboratory medicine
60 S	ePoster – experimental hematology / oncology
61 S	ePoster – clinical hemato-oncology
66 S	ePoster – clinical solid tumor oncology
68 S	Index of first authors



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Swiss Society of  
Pediatric Hematology  
and Oncology

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

Abstract ID: 65

**A GalNAc conjugated Small Interfering RNA Targeting Protein S Improves Hemostasis Potency in Hemophilia**R. Prince Eladnani<sup>1,2</sup>, U. Schaeper<sup>3</sup>, J. Aretz<sup>3</sup>, K. Vrotniakaitė-Bajercienė<sup>1</sup>, M. Reina Caró<sup>1,2</sup>, S. Dames<sup>3</sup>, M. Eisermann<sup>3</sup>, K. Löffner<sup>3</sup>, A. Martinez<sup>4</sup>, M. Laffan<sup>5</sup>, J. Ahnström<sup>5</sup>, A. Angelillo-Scherrer<sup>1,2</sup><sup>1</sup>Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, University of Bern, Switzerland, Inselspital, Bern, <sup>2</sup>Department for BioMedical Research, University of Bern, Switzerland, University of Bern, Bern, <sup>3</sup>Silence Therapeutics GmbH, Silence Therapeutics GmbH, Berlin, <sup>4</sup>Silence Therapeutics plc, Silence Therapeutics plc, London, <sup>5</sup>Centre for Haematology, Imperial College London, London

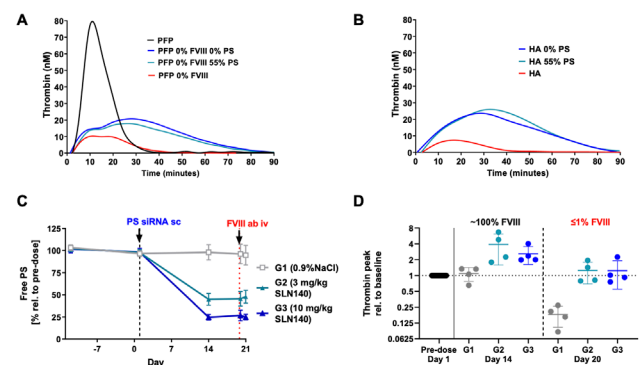
**Introduction:** Replacement factor therapy for hemophilia A (HA) has significant limitations. Patients may experience bleeding and develop antibodies against these therapeutic agents. We reported that genetic ablation of anticoagulant protein S (PS) improves hemostasis in HA mice and that partial reduction of PS by small interfering RNA conjugated to an N-acetylgalactosamine cluster (GalNAc-siRNA) protects HA mice against hemarthrosis.

**Methods:** Here, we studied hemostatic effects of partial PS reduction in human ex vivo HA models and characterized a novel PS siRNA drug candidate in a non-human primate (NHP) model of HA.

**Results:** We assessed the impact of PS lowering on thrombin generation (TG) in human platelet-free plasma (PFP). Addition of anti-FVIII antibody (FVIII-Ab) resulted in PFP with FVIII between 0 and 7%. PS reduction to 37% restored TG peak in PFP containing 0–7% FVIII indicating that partial PS depletion is sufficient to normalize TG in HA. FVIII-Ab lowered TG peak in normal PFP. Anti-PS antibody (0% or 55% residual PS) equally increased TG peak ( $21 \pm 0.1$  and  $27 \pm 13$  nM, respectively), endorsing that partial depletion of PS increases TG in PFP containing 0% FVIII (Fig 1A). These data were confirmed using severe HA patient derived-PFP. Anti-PS antibody increased TG peak ( $20 \pm 5$  nM and  $20 \pm 8$  nM at 0% and 55% free PS respectively, compared to  $8 \pm 1$  nM in untreated HA PFP), indicating suitability of 45% PS reduction in severe HA PFP (Fig 1B). We assessed the effect of partial PS reduction by PS siRNA in a NHP model of acquired HA (AHA). NHPs received either PS siRNA or NaCl

subcutaneously (SC). A single dose of 3 or 10 mg/kg PS siRNA reduced free PS level to 45% and 25% of baseline, respectively (Fig 1C). TG peak relative to baseline and endogenous thrombin potential were ~3-fold higher in the PS siRNA-treated groups than in the NaCl group. FVIII-Ab was injected into all NHPs and blood collected after 4 hours. In this AHA model, PS siRNA treatment restored TG to normal range (Fig 1D). The treatment was clinically well tolerated. Basic coagulation and safety parameters were not affected and comparable in both groups.

**Conclusions:** PS reduction enhanced TG in human models of HA ex vivo and a single SC administration of PS siRNA improved hemostasis in NHPs with AHA. These results are encouraging and support future clinical studies.



**Figure 1. Protein S (PS) reduction enhanced thrombin generation (TG) in human models of hemophilia A (HA) ex vivo and improved hemostasis in non human primates (NHPs) with severe HA.**

**A-B** Representative thrombograms at low tissue factor (1 pM TF) concentration: **A** in human normal pooled platelet free plasma (PFP) in presence of blocking anti-factor VIII (FVIII) and anti-PS antibodies, **B** in severe hemophilia A patient plasma in presence of blocking anti-PS antibodies. **C** Free PS level in NHPs (Cynomolgus monkeys) after SC injection with the small interfering PS siRNA (SLN140) on day 1. Free PS mean values relative to individual predose level. On day 20 AHA was induced with 20 000 BU of FVIII antibody (IV). **D** Blood samples of all animals were collected before (day 14) and after induction of AHA (day 20). TG was measured in the presence of 1 pM TF and 3.5 nM soluble thrombomodulin (TM) to enable protein C activation and full assessment of all PS anticoagulant functions and plotted relative to base line (day1). PS siRNA improved hemostasis in AHA model.

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

Abstract ID: 91

**Combination of PegIFN $\alpha$  and 5-azacytidine is Able to Overcome Resistance in JAK2 V617F Positive MPN with Loss of Dnmt3a**J. Stetka<sup>1</sup>, M. Lock<sup>1</sup>, D. Luque Paz<sup>1</sup>, N. Hansen<sup>1</sup>, T. Almeida Fonseca<sup>1</sup>, M. Usart<sup>1</sup>, S. Rai<sup>1</sup>, H. Hao-Shen<sup>1</sup>, G. Mild<sup>1</sup>, S. Dirnhofer<sup>2</sup>, R. C. Skoda<sup>1</sup><sup>1</sup>Department of Biomedicine, University Hospital Basel and University of Basel, Basel, <sup>2</sup>Institute of Medical Genetics and Pathology, University Hospital Basel, Basel

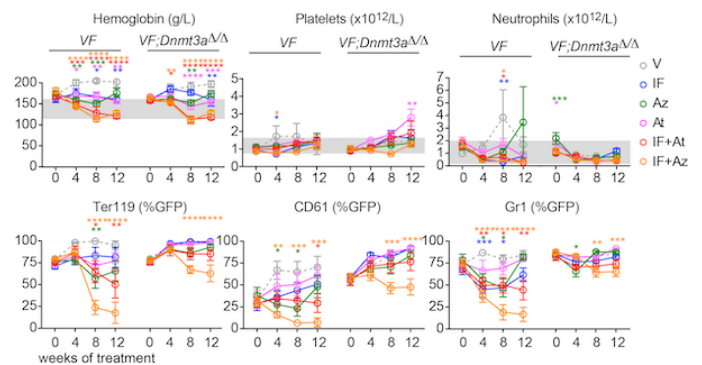
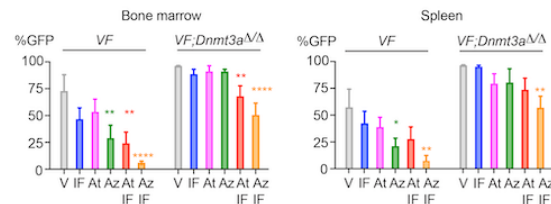
**Introduction:** Pegylated interferon alpha (IF) can induce molecular remissions in JAK2-V617F-positive MPN patients by targeting long-term hematopoietic stem cells (LT-HSCs). Patients with additional mutations in genes involved in LT-HSC self-renewal have been reported to have poorer responses to IF. We found that loss of Dnmt3a increases competitiveness and self-renewal of V617F-positive LT-HSCs and confers resistance to IF treatment in MPN mouse models and patient HSCs. We have now examined whether the resistance of double mutant JAK2-V617F;Dnmt3a $\Delta/\Delta$  hematopoietic cells to IF can be overcome by addition of arsenic trioxide (At), or 5-azacytidine (Az).

**Methods:** To test the effects of the combination treatments in vivo, we generated mice expressing JAK2-V617F (VF) alone, or in combination with a homozygous deletion of the Dnmt3a gene (Dnmt3a $\Delta/\Delta$ ). We used bone marrow cells from VF or VF;Dnmt3a $\Delta/\Delta$  mice that express a GFP reporter mixed with wildtype (WT) cells (1:10) to perform competitive transplantations. After 7 weeks, recipient mice were randomized into 6 treatment groups and a vehicle (V) group. Mice were then treated for 12 weeks with IF (25 $\mu$ g/kg; s.c. once per week), At (5mg/kg; i.p. every second day), or Az (2mg/kg; i.p. daily for 2 weeks followed by a break of 2 weeks), or combinations of IF+At and IF+Az (Figure 1).

**Results:** Peripheral blood parameters were normalized (Figure 1A) and spleen weight decreased in At and Az treatment arms in both genotypes. Expression of GFP allowed us to follow the contribution of mutant cells. In VF recipients, a pronounced decrease in GFP chimerism of peripheral blood was observed in the groups treated with a combination of IF+At, or IF+Az (Figure 1A). GFP chimerism in LT-HSCs showed reduction upon treatment with Az alone, compared to vehicle and further reduction below 10% was observed in combination of Az and IF (Figure 1B). Double-mutant VF;Dnmt3a $\Delta/\Delta$  recipient mice remained resistant to the single agent regimens, but showed a significant reduction of GFP chimerism in peripheral blood and in LT-HSC when treated with a combination of IF+Az (Figure 1B).

**Conclusions:** Thus, a combination of pegIFN $\alpha$  with 5-azacytidine is a promising approach to target MPN cells carrying mutations in JAK2 and Dnmt3a genes that could be also considered as a treatment option for therapy-resistant forms of MPN in patients carrying JAK2-V617F and loss-of-function DNMT3A mutations.

Figure 1

**A** Time course of blood counts and GFP chimerism**B** GFP chimerism in LT-HSCs

## Abstract ID: 125

**Anti-IL-1 $\beta$  antibody therapy reduces MPN disease initiation by limiting expansion of JAK2-V617F driven clonal hematopoiesis**S. Rai<sup>1,2</sup>, J. Sutter<sup>1,2</sup>, C. B. Stoll<sup>1,2</sup>, H. Hao-Shen<sup>1,2</sup>, C. J. Farady<sup>3</sup>, R. C. Skoda<sup>1,2</sup><sup>1</sup>Department of Biomedicine, University Hospital Basel, Basel, <sup>2</sup>Department of Biomedicine, University of Basel, Basel, <sup>3</sup>Novartis Institutes for BioMedical Research Forum<sup>1</sup>, Novartis, Basel

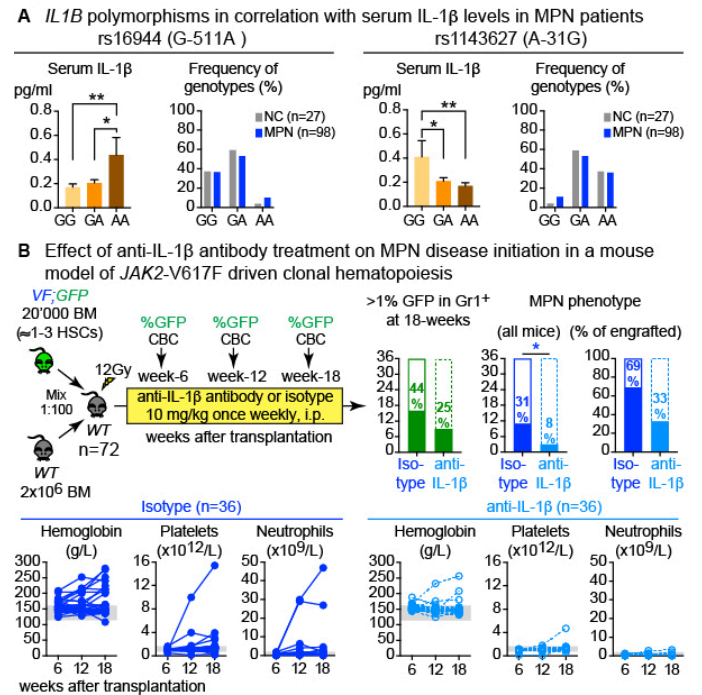
**Introduction:** JAK2-V617F, the most frequent myeloproliferative neoplasm (MPN) causing mutation, is also found in healthy individuals with clonal hematopoiesis of indeterminate potential (CHIP), with a frequency much higher than the prevalence of MPN. Previously, we reported that interleukin-1 beta (IL-1 $\beta$ ) promotes the transition of CHIP to MPN disease in a mouse model of JAK2-V617F driven clonal hematopoiesis. Here, we investigated the potential correlation of IL-1 $\beta$  mediated inflammation with disease initiation in MPN patients and examined the beneficial effects of anti-IL-1 $\beta$  antibody therapy on disease initiation in MPN mouse model.

**Methods:** We determined the genotypes of IL1B polymorphisms (rs1143627 and rs16944) in normal controls (NC) and MPN patients and correlated them with serum IL-1 $\beta$  levels. We tested the effects of anti-IL-1 $\beta$  antibody in our preclinical ScfCreER;JAK2-V617F (VF) mouse model. We crossed our VF mice with UBC-GFP reporter mice (GFP) to track donor cells in all hematopoietic lineages. We performed competitive transplantations of unfractionated bone marrow (BM) cells at high dilutions (1:100) between JAK2-mutant (VF;GFP) and wildtype (WT) BM cells that allowed us to assay MPN initiation from very few (1-3) hematopoietic stem cells (HSCs) per recipient, i.e., MPN of oligo- or monoclonal origin (Figure 1B, top left).

**Results:** We found that IL1B gene polymorphisms were associated with increased serum IL-1 $\beta$  levels in MPN patients and NC. Individuals with homozygous AA genotype (locus -511; rs16944) and homozygous GG genotype (locus -31; rs1143627) showed significantly higher serum IL-1 $\beta$  levels than individuals with other genotypes (Figure 1A). Interestingly, MPN patients showed higher frequencies of both AA (-511) and GG (-31) genotype compared to NC (Figure 1A). Mice treated with anti-IL-1 $\beta$  showed lower percentage of engraftment (defined as GFP-

chimerism >1% in peripheral blood Gr1+ granulocytes) versus isotype controls (25% vs 44%), and a lower percentage of mice with MPN phenotype (8%) than mice treated with isotype control (31%) (Figure 1B, top right and bottom panel).

**Conclusions:** Our results identify IL-1 $\beta$  driven inflammation as a risk factor for the development of MPN in individuals with JAK2-V617F CHIP. Moreover, our data convincingly show that anti-IL-1 $\beta$  antibody therapy can prevent clonal expansion of JAK2-V617F positive CHIP and reduce the transition to MPN disease in mice.



**Legend to Figure 1.** (A) Serum IL-1 $\beta$  levels (pg/ml) and frequency of the three genotypes of *IL1B* SNPs, rs16944 (G-511A) (left panel) and rs1143627 (A-31G) (right panel) is shown. (B) Schematic of the experimental setup for the anti-IL-1 $\beta$  treatment (top left) in a mouse model of JAK2-V617F driven clonal hematopoiesis. Frequency of engraftment (>1% GFP-positive cells in Gr1+ granulocytes) and percentage of mice with MPN phenotypes are shown after 18-weeks of drug treatment (top right). Blood counts in isotype (bottom left) and anti-IL-1 $\beta$  treated mice (bottom right) during 18-weeks of drug treatment is shown. Grey bar represents normal physiological range.

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

## Abstract ID: 108

**T Cell Receptor Sequencing Reveals Reduced Clonal Breadth of T Cell Responses against SARS-CoV-2 after Natural Infection and Vaccination in Allogeneic HSCT**

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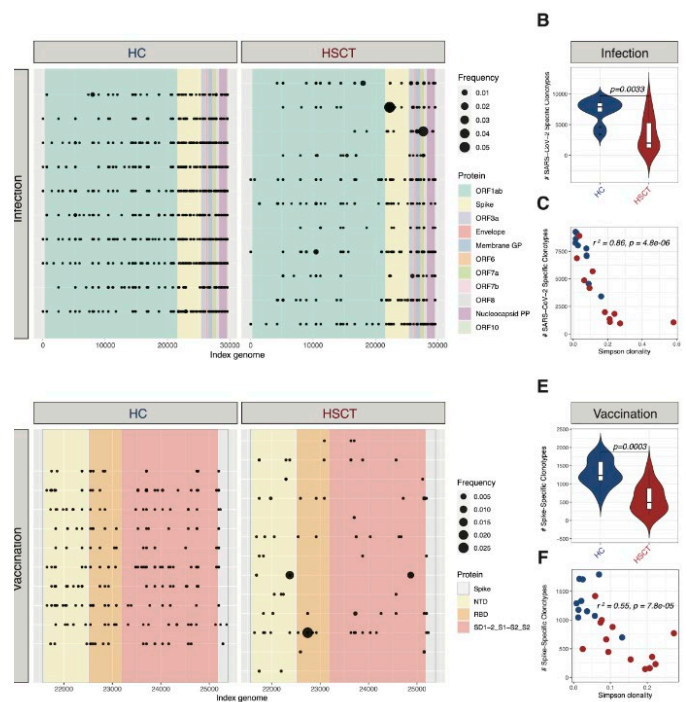
**Introduction:** Prevention of COVID by vaccination is important in allogeneic HSCT recipients but impaired humoral and cellular responses have been reported. To gain further insights into the immune defects leading to impaired immune, we performed a high-throughput T cell receptor (TCR) repertoire profiling of cells recovered from allogeneic HSCT recipients or healthy controls after SARS-CoV2 natural infection or mRNA-based vaccination.

**Methods:** Peripheral blood samples were obtained from allogeneic HSCT recipients after a median of 3 months after COVID-19 infection (n = 11) or 44 days after vaccination with 3 doses of mRNA-based SARS-CoV-2 vaccines (n = 13). Healthy controls at 1 to 3 months after SARS-CoV-2 infection (n = 10) or vaccination served as controls (n = 10). SARS-CoV-2-specific T cell clonotypes were identified by genomic DNA T-cell receptor (TCR) sequencing (immunoSEQ® T-MAP™ COVID, Adaptive). SARS-CoV-2-specific T cell responses were quantified based on IFN-γ release against a range of peptides from the SARS-CoV-2 proteins using an ELISpot assay.

**Results:** HSCT recipients displayed significantly reduced SARS-CoV-2-specific T cell clonotypes compared with HC (p = 0.0037; Figure 1 A-B) as well as a less diverse TCR repertoire as revealed by higher Simpson clonality (p = 0.0079). We also observed significantly lower numbers of IFN-γ spot forming units after stimulation of PBMCs from HSCT recipients with peptides from both the S protein (p = 0.0068) and the M plus N proteins (p = 0.0067) compared with HC. Performing the same analysis after SARS-CoV-2 mRNA vaccination, we observed a significant reduction in S-protein-specific T cell clonotypes in allogeneic HSCT recipient compared to HC (p = 0.0003; Figure 1D-E).

We detected a significantly negative correlation between the Simpson clonality and the number of different S-protein specific T cell clonotypes after vaccination (r<sup>2</sup> = 0.55, p = 7.8e-05; Figure 1F). ELISpot analysis of PBMCs recovered after vaccination and stimulated with S-protein peptides revealed significantly lower numbers of IFN-γ spot forming units in HSCT recipients compared with HC (p = 0.019), confirming the results obtained by TCR-seq.

**Conclusions:** Allogeneic HSCT recipients display a quantitative and qualitative defect in cellular SARS-CoV-2-specific responses associated with a reduced TCR repertoire after COVID-19 infection and vaccination.



## SSH/SSMO BEST ABSTRACT &amp; AWARD SESSION – CLINICAL SOLID TUMOR ONCOLOGY

## Abstract ID: 139

**SAKK 16/14: CD8 T cell positioning correlates with survival in stage IIIA(N2) NSCLC after neoadjuvant immunotherapy**

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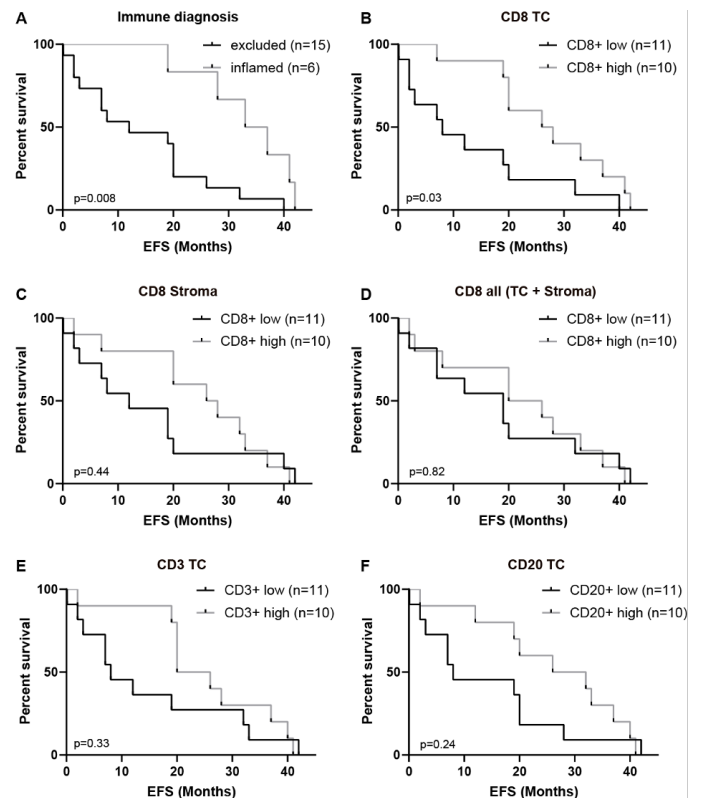
**Introduction:** Spatial distribution of immune cells within the tumor immune microenvironment (TIME) influences response to immunotherapy in many malignancies, but its role in neoadjuvant immunotherapy in non-small cell lung cancer (NSCLC) is not clearly established. To address this knowledge gap, we performed digital pathology analysis of tumor tissue obtained from patients with stage IIIA(N2) NSCLC undergoing neoadjuvant treatment including the PD-L1 antibody durvalumab in the single-arm phase II trial SAKK 16/14.

**Methods:** Formalin-fixed paraffin-embedded tissue specimens of 21 initial biopsies (IB) and 38 resection specimens (RES) were obtained from patients enrolled in the trial SAKK 16/14. Tissue was immunostained for CD3, CD8, CD20 and FoxP3. Digitalized slides were annotated for invasive cancer. A machine-learning classifier was trained to localize and quantify marker-positive immune cell densities within the epithelial and stromal compartments. Also, the TIME for each specimen was classified as excluded ('cold tumor') or inflamed ('hot tumor') by pathologist consensus. Event-free survival (EFS) was analyzed by Mann-Whitney-Wilcoxon test.

**Results:** The infiltration densities of CD3 T cells, CD8 T cells, CD20 B cells and Foxp3 T cells in IB (Fig. 1A) and RES (Fig. 1B) were comparable in hot and cold tumors. Stratification of tumors based on their immune cell positioning (excluded or inflamed phenotype) in the IB strongly correlated with EFS ( $p =$

0.008, Fig. 2A). This association was driven by CD8 T cell infiltration in the tumor (Fig. 2B), but not for the stromal compartment (Fig. 2C) or total T cell content (Fig. 2D) as assessed by digital pathology, with similar trends observed for CD3 T cells (Fig. 2E) and CD20 B cells (Fig. 2F).

**Conclusions:** Immune phenotyping of the tumor and spatial distribution of CD8 T cells correlates with EFS in the SAKK16/14 cohort.



**ONCOREHA / OPS / PALLIATIVE.CH / SANS BEST ABSTRACT & AWARD SESSION –  
SUPPORTIVE & PALLIATIVE CARE, REHABILITATION & SURVIVORSHIP**
**Abstract ID: 138**
**Complication Rates of Peripherally Inserted Central Catheters versus Implanted Ports in Patients Receiving Systemic Anticancer Therapy: a Retrospective Cohort Study**

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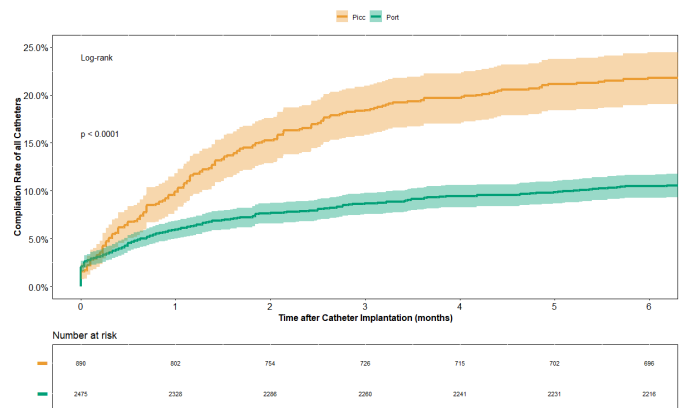
**Introduction:** Patients receiving intravenous systemic anticancer therapy (SACT) need safe central-venous access. While fully implanted port catheters ("PORTs") have historically been the standard device, the use of peripherally inserted central catheters (PICCs) has increased in recent years. However, with only limited data suggesting higher complication rates for PICCs, reliable guidelines for catheter selection are lacking.

**Methods:** Here we compare the complication rates of PORTs and PICCs in the administration of SACT over time from implantation in a retrospective cohort study of 3365 patients with both solid organ (n = 2612) and hematologic (n = 753) malignancies, between January 2001 and June 2021.

**Results:** 26.4% (n = 890) were treated via PICCs and 73.6% (2475) via PORTs. Overall, 20.7% (578) of all patients experienced a major catheter-related complication with a significantly

higher rate in PICCs than in PORTs (23.5% vs. 14.9%, p < 0.001). Among major complications, infections and mechanical complications were more common in PICCs than in PORTs (11.9% vs. 6.4%, p = 0.001, 7.3% vs. 4.2%, p = 0.002), whereas the rate of thrombosis was similar (3.4% vs. 3.0%, p = 0.9). While PORTs had a higher rate of periprocedural complications (2.7% vs. 1.1%, p < 0.05), PICCs overall complication rate exceeded PORTs within 3 days after implantation and continued to increase steeper over time. Median follow-up was 49 weeks (PICC) and 60 weeks (PORT).

**Conclusions:** This study suggests that PORTs are safer and therefore should be preferred in this setting regardless of catheter dwell time.





## SSH ORAL PRESENTATION – HEMOSTASIS, TRANSFUSION MEDICINE, VASCULAR, LABORATORY MEDICINE

### Abstract ID: 34

#### Obstetrical complications in hereditary fibrinogen disorders: the Fibrinogest Study

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**Introduction:** Women with hereditary fibrinogen disorders (HFD) seem to be at increased risk of adverse obstetrical outcomes, but epidemiologic data are limited

**Methods:** We conducted a retrospective and prospective international study to determine the prevalence of pregnancy complications, the modalities and management of delivery, and the post-partum events

**Results:** A total of 425 pregnancies were investigated from 159 patients (50 hypofibrinogenemia, 94 dysfibrinogenemia, 15 hypodysfibrinogenemia). Overall, 55 (12.9%) pregnancies resulted in an early miscarriage, 3 (0.7%) in a late miscarriage and 4 (0.9%) in an intrauterine fetal death, without difference between hypofibrinogenemia and dysfibrinogenemia ( $p = 0.989$ ). Obstetrical complications were observed in 54 (17.3%) of live birth pregnancies, including retroplacental hematoma (4.1%), vaginal bleeding (3.5%) and thromboses (1%). Most of women had a spontaneous labor (74.1%) with a vaginal non-instrumental delivery (63.3%). A loco-regional anesthesia was performed in 116 (40.4.9%) pregnancies, while 71 (16.6%) and 129 (44.9%) were under general or no anesthesia, respectively. A fibrinogen infusion was administered in a minority of deliveries (28, 8.9%). Post-partum hemorrhage were observed in 61 (19.9%) of pregnancies. Post-partum venous thrombotic events occurred in 5 (1.6%) pregnancies. Women with hypofibrinogenemia were more at risk of bleeding during the pregnancy ( $p = 0.016$ ).

**Conclusions:** Compared to the general population we did not observe a greater risk of miscarriage but found an increased risk of retroplacental hematoma as well as of post-partum hemorrhage and thrombosis. Most of women did not have analgesia due to the underlying fibrinogen disorders. Our findings highlight the urgent need for guidance on management of pregnancy in HFD

### Abstract ID: 96

#### In vivo and ex vivo thrombin generation parameters are associated with risk of venous thrombo-embolism in patients with liver cirrhosis

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**Introduction:** Venous thrombo-embolic events (VTE) and especially splanchnic vein thromboses are common complications in patients with liver cirrhosis. Splanchnic vein thromboses can, inter alia, worsen the portal hypertension and cause ascitic decompensation. Identification of high risk patients and consecutive targeted prophylactic anticoagulation could prevent these complications and improve patient quality of life and life expectancy. In this study, we aimed to investigate the role of in vivo and ex vivo thrombin generation (TG) parameter in the prediction of VTE in patients with liver cirrhosis.

**Methods:** We performed a prospective single-centre study at the Lausanne University Hospital (CHUV) including patients with liver cirrhosis. The main outcome was VTE including deep venous thrombosis, pulmonary embolism and splanchnic vein thrombosis. We analysed in vivo TG parameters [prothrombin fragments 1 and 2 (F1+2), thrombin-antithrombin complexes (TAT), D-dimers] and ex vivo TG. Ex vivo parameter were measured using the ST Genesis Thrombin Generation System (Stago). The analyses were performed without and with thrombomodulin (TM) as protein C/S system activator. We focused on the velocity index without TM, representing the TG velocity, the peak height, representing the maximal thrombin concentration, and the TM-mediated inhibition, representing the degree of diminution of TG after TM addition reflecting the activity of the protein C/S system. We also analysed routine hemostatic tests (activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, factor V activity). Comparisons between groups were analysed using Mann-Whitney tests.

**Results:** We included 294 unanticoagulated patients. Median age was 59 years (range 18–81) and 68 (23%) were female. Comparisons of the parameters between groups with and without VTE are presented in Table 1. The velocity index, TM-mediated inhibition, TAT, F1+2 and D-dimers were significantly associated with the risk of VTE. Of note, a prolonged aPTT and PT were significantly associated with this risk.

Table 1

	No thrombosis	Thrombosis	p-value
ETP [nM*min]	278 (94.6%)	16 (5.4%)	
Peak height [nM]	998 (241)	1261 (204)	0.15
Velocity index [nM/min]	222.9 (61.2)	246 (34.3)	0.19
ETP normalized [%]	140.8 (75.6)	180.8 (60.8)	<b>0.0198</b>
Peak height, normalized [%]	77.6 (15.6)	85.2 (13.3)	0.13
Velocity index, normalized [%]	77.6 (21.7)	85.7 (11.3)	0.06
TM-mediated inhibition [%]	84.6 (41.7)	124.6 (34.9)	<b>0.0027</b>
TAT [µg/l]	37.8 (21.5)	17.0 (19.2)	<b>0.0044</b>
F1+2 [pmol/l]	2.5 (3.2)	3.2 (1.5)	<b>0.0499</b>
D-dimers [ng/ml]	157.3 (127.6)	233.0 (166.0)	<b>0.0019</b>
aPTT [s]	459 (2513)	1323 (3046)	<b>&lt;0.0001</b>
Prothrombin time [%]	33 (6.7)	38.5 (5.5)	<b>0.0048</b>
Fibrinogen [g/l]	80 (17.8)	65 (12.5)	<b>0.0028</b>
Factor V [%]	2.6 (1.0)	2.4 (0.7)	0.11
Child-Pugh score	80 (30.2)	58.5 (21.8)	<b>0.0119</b>
	5 (1.4)	6 (1.6)	<b>0.0075</b>

Legend: Data are number (%), respectively median (standard deviation) and results of Mann-Whitney tests. ETP, endogenous thrombin potential; TM, thrombomodulin; aPTT, activated partial thromboplastin time

**Conclusions:** In vivo and ex vivo TG parameters are associated with the risk of VTE in patients with liver cirrhosis. Associating these parameters with clinical and other paraclinical parameter, especially parameters of portal hemodynamic like portal flow, is promising to identify high risk patients that could benefit from a primary prophylactic anticoagulation.

**Abstract ID: 126**

### Single-cell transcriptomics reveals age-related Mfsd2b expression in megakaryocyte progenitor cells that regulate thrombosis

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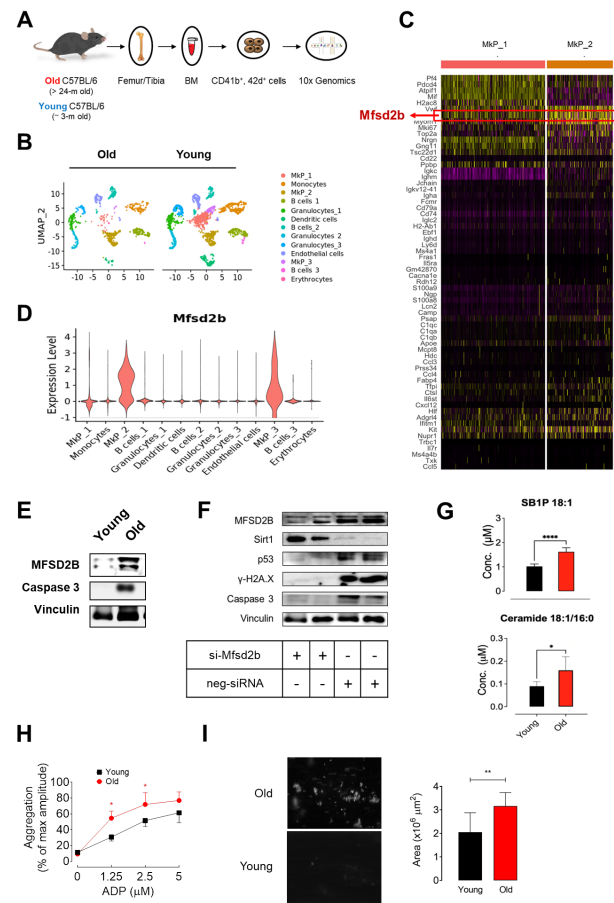
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**Introduction:** Aging is associated with a dramatic increase in thrombotic events, which represent a major cause of morbidity and mortality worldwide. The recent findings demonstrate that the sphingosine-1-phosphate (S1P) transporter, Mfsd2b, is critical for the platelet function and thrombosis. However, it is still uncovered whether and how aging affects the diversification and function of Mfsd2b in bone marrow-megakaryocyte progenitor cell (MkP) subpopulations, which thereby regulate platelet hyperreactivity and thrombus formation.

**Methods:** Here, we use single-cell RNA-sequencing (scRNA-seq) analysis in old (>24-months) and young (3-months) mice to characterize age-related bone-marrow MkP heterogeneity. We identify rare subpopulations of MkPs that increases in abundance of Mfsd2b, and we show that these subpopulations regulate plasma S1P and ceramides which thereby modulate platelet hyperreactivity and thrombosis.

**Results:** Our single-cell transcriptomics reveals that Mfsd2b-expressing cells of specific subpopulations are substantially enriched in bone marrow from old mice. These could explain higher concentrations of S1P 18:1 and ceramides 18:1/16:0 and 18:1/18:0, which are positively correlated with platelet hyperresponsiveness to multiple agonists and heightened thrombus formation in aged mice. Employing Mfsd2b-siRNA, we reveal that MkPs contribute reduced expression of cellular senescence markers  $\gamma$ -H2A.X (telomere shortening) and p53 (cell cycle arrest), and caspase-3 (apoptosis), and increased expression of Sirt1, which is known to delay cellular senescence and rejuvenate aged cells.

**Conclusions:** Our studies demonstrated that aging affects Mfsd2b expression in specific MkP subpopulations that regulate circulating S1P and ceramides. These findings indicate that modulation of sphingolipids and ceramides by deletion of Mfsd2b strongly regulates aging-related platelet hyperreactivity and thrombus formation, which suggest that targeting Mfsd2b in specific MkP subpopulations could contribute important clues to future personalized medicine for the prevention of thrombotic disorders in aging.



**Aging affects Mfsd2b-expressing subpopulations of bone marrow-MkPs which regulate plasma S1P and ceramides, and thereby increase platelet hyperreactivity and thrombosis.** (A) Schematic illustration of the experimental 10X Genomics scRNA-seq for CD41b<sup>+</sup>CD42b<sup>+</sup> MkP cells from tibial/femoral bone marrow; (B) BM clustering shown as UMAP plot; (C) Heat map of signature genes for each aged MkP subpopulation ( $n = >35,000$  cells); (D) Mfsd2b is differentially upregulated in MkPs from old (24-month-old) mice; (E) Violin & feature plots for Mfsd2b demonstrates its markedly higher expression in MkP subpopulations compared to other cell types; (F) Mfsd2b expression is remarkably increased in BM-MkPs obtained from old mice compared to young (3-month-old) mice. Consistent with age-dependent expression of Mfsd2b, the marker of apoptosis caspase-3 is upregulated in old mice; (G) Utilizing Mfsd2b-siRNA, replicative senescence represented by reduced  $\gamma$ -H2A.X (telomere shortening) and p53 (cell cycle arrest), and caspase-3 (apoptosis) was rescued, and Sirt1 was upregulated in MkPs; (H) A marked increase in plasma concentrations of S1P 18:1 and ceramide 18:1/16:0 in old versus young mice; (I) An increased platelet aggregation in young versus old mice in response to stimulation with specific doses of collagen (2.5, 5, and 10  $\mu\text{g}/\text{mL}$ ) for 4 min; (J) Enhanced thrombus formation over a vWF-coated microfluidic chamber under high-shear conditions (100 dyn/cm<sup>2</sup>) for 5 min in whole blood obtained from young compared to old mice. ( $n=6-9$ ) \* $P<0.05$ , \*\* $P<0.01$ , \*\*\*\* $P<0.0001$ .

**Abstract ID: 133**

### Characterization of the role of Gas6 protein in sepsis as a basis for novel therapies

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**Introduction:** Sepsis is a life-threatening organ dysfunction currently lacking effective therapeutic options. Evidence on the high plasma concentrations of growth-arrest specific gene 6 (Gas6), correlate this protein with disease severity and organ dysfunction in septic patients.

**Methods:** To study the role of Gas6 in sepsis, we injected lipopolysaccharide (LPS) to healthy volunteers and measured Gas6 levels in plasma. Next, we explored the role of endogenous Gas6 in experimental models of polymicrobial peritonitis and endotoxemia in Gas6<sup>+/+</sup>, Gas6<sup>+/-</sup> and Gas6<sup>-/-</sup> mice, with a focus on their survival and inflammatory phenotype.

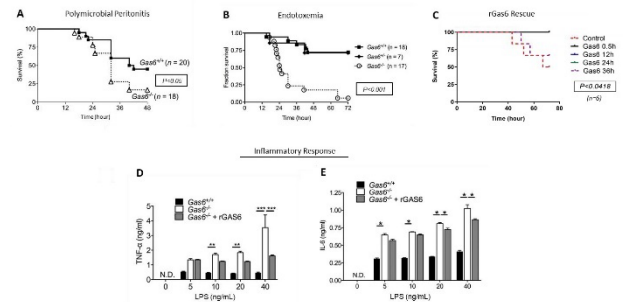
In parallel, we evaluated the role of exogenous Gas6 in bone marrow-derived macrophages (BMDMs) in vitro, stimulated with LPS, using recombinant Gas6 (rGas6). Its rescue activities were further assessed in endotoxemia model with Gas6<sup>+/+</sup> mice.

**Results:** Data from healthy volunteers receiving small dose LPS resulted in increased plasma levels of Gas6. In the polymicrobial peritonitis mouse model, Gas6<sup>-/-</sup> mice were more sensitive to cecal ligation and puncture (CLP). 48 hours after peritonitis-inducing surgery, only 17% of Gas6<sup>-/-</sup> survived compared to 45% of Gas6<sup>+/+</sup> mice (Fig.1 A). The results were validated in endotoxemia model where Gas6<sup>-/-</sup> mice showed increased vulnerability to 25mg/kg LPS i.p. injection with 25% survival in the first 48 hours compared to 73% survival of Gas6<sup>+/+</sup> mice (Fig.1 B). rGas6 was tested as a rescue compound in Gas6<sup>+/+</sup> mice injected with LPS. No death or septic symptoms were observed when rGas6 was given at 0.5h, 12h, and 24h after LPS (Fig.1 C).

Measurement of TNF- $\alpha$  (Fig.1 D) and IL-6 (Fig.1 E) release from Gas6<sup>+/+</sup> and Gas6<sup>-/-</sup> BMDMs, after in vitro LPS stimulation, demonstrated a tendency of Gas6<sup>-/-</sup> BMDMs to release more TNF- $\alpha$  and IL-6. Interestingly, the release of cytokines was dampened by the addition of rGas6, restoring the inflammatory phenotype of Gas6<sup>-/-</sup> to the baseline of Gas6<sup>+/+</sup>.

**Conclusions:** High Gas6 levels were released in the bloodstream during endotoxemia in the context of the systemic inflammation and Gas6 protected mice from experimental sepsis induced death. This is, at least in part, due to Gas6's ability to

reduce the production of inflammatory cytokines in macrophages. Future studies will explore the immunomodulatory effects of Gas6 in more detail and the potential of Gas6 agonists to treat sepsis.



**Figure 1. Lack of Gas6 enhances lethality in sepsis-induced mouse models and modulates their monocytic inflammatory response.** (A) Survival of Gas6<sup>+/+</sup> and Gas6<sup>-/-</sup> mice in polymicrobial peritonitis-induced sepsis by CLP. Pooled data from three independent experiments are shown (P < 0.05). (B) Survival of Gas6<sup>+/+</sup>, Gas6<sup>-/-</sup> and Gas6<sup>-/-</sup> mice upon endotoxemia-induced sepsis by 25mg/kg LPS injection i.p. Data are pooled from multiple independent experiments. (C) Survival of Gas6<sup>+/+</sup> mice upon rGas6 rescue treatment. Groups of mice were injected with 10mg/kg LPS i.p. (n=6). At 0.5h, 12h, 24h and 36 h after LPS injection, 10 $\mu$ g of rGas6 rescue was given per mouse. (D) Measurement of TNF- $\alpha$  release in BMDMs of Gas6<sup>+/+</sup>, Gas6<sup>-/-</sup> and Gas6<sup>-/-</sup> with rGAS6 (400 ng/ml), after 5-40 ng/ml LPS stimulation (\*\* P < 0.1, \*\*\* P < 0.001). (E) Measurement of IL-6 secretion in BMDMs of Gas6<sup>+/+</sup>, Gas6<sup>-/-</sup> and Gas6<sup>-/-</sup> with rGAS6 (400 ng/ml), after 5-40 ng/ml LPS stimulation (\* P < 0.05).

**SSH/SSMO ORAL PRESENTATION – EXPERIMENTAL HEMATOLOGY / ONCOLOGY**

**Abstract ID: 104**

**AXL tyrosine kinase mediates escape from type II JAK2 inhibition in myeloproliferative neoplasms**

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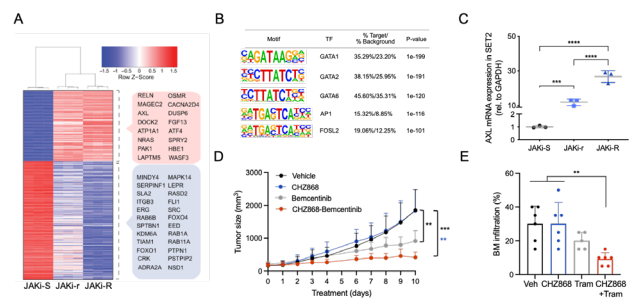
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**Introduction:** Myeloproliferative neoplasms (MPN) show dysregulated JAK2 signaling. JAK2 inhibitors as ruxolitinib are standard of care, but have modest disease-modifying effects and may lose efficacy. Type II JAK2 inhibitors in development stabilize inactive JAK2 with enhanced activity. We study whether MPN cells escape from type II JAK inhibition via alternative kinase signaling and assess therapeutic targeting.

**Methods:** MPN cells were exposed to type II JAK inhibitor CHZ868 and profiled by phosphoproteomic analysis and ATAC-/RNA-sequencing to characterize escape from type II JAK inhibition. We targeted candidate mediators in vitro and in vivo.

**Results:** Outgrowing MPN cells showed increased IC50 to CHZ868 and reduced susceptibility for apoptosis indicating resistance despite absence of JAK2 second-site mutations. Phosphoproteomic analysis identified >2500 differential phospho-sites with most prominent activation of MAPK signaling. Expression of MAPK components as RAS was increased as reflected by RNA-seq. In addition, expression of AXL, a tyrosine kinase signaling via MAPK pathway, was upregulated. Altered histone occupancy detected by ATAC-seq mediated increased binding site exposure for GATA and AP1 transcription factors promoting AXL expression. AXL knockdown sensitized resistant cells to JAK inhibition with reduced IC50. AXL inhibition by bemcentinib reduced proliferation and dual JAK2/AXL inhibition showed most pronounced effects with IC50 similar to sensitive cells. Resistant MPN cells engrafted subcutaneously into NSG

mice induced robust tumor growth despite JAK inhibitor treatment, but were significantly suppressed by combined JAK2/AXL inhibition. Since MAPK pathway inhibitors are in clinical use for other malignancies, we evaluated combined JAK2/MAPK inhibition to overcome AXL-MAPK driven resistance. JAK2/MAPK inhibition by CHZ868/trametinib reduced subcutaneous MPN cell growth in NSG mice similar to JAK2/AXL inhibition. Intravenous engraftment of resistant cells led to bone marrow infiltration shown by bioluminescence and hCD45 staining. Significant reduction was achieved by JAK2/MAPK inhibition.



**Figure 2. AXL kinase mediates escape of myeloproliferative neoplasms from type II JAK2 inhibition and is targetable in vitro and in vivo.** A. Type II JAK2 inhibitor resistant MPN cells (JAKi-r and JAKi-R) show upregulated AXL kinase and MAPK pathway components such as RAS as compared to sensitive MPN cells (JAKi-S). B. Chromatin remodeling mediates altered transcription factor binding motif exposure enriched for GATA and AP1 able to promote AXL expression. C. AXL expression is increased in JAK2 inhibitor resistant MPN cells vs. JAK2 inhibitor sensitive cells. D. AXL inhibitor treatment by bemcentinib sensitizes resistant MPN cells to JAK2 inhibition shown by significantly reduced MPN cell growth in NSG mice in vivo. E. Intravenous engraftment of NSG mice with luciferase-expressing JAK2 inhibitor resistant MPN cells showed significantly reduced bone marrow (BM) infiltration upon combined JAK2/ MAPK inhibition with trametinib.

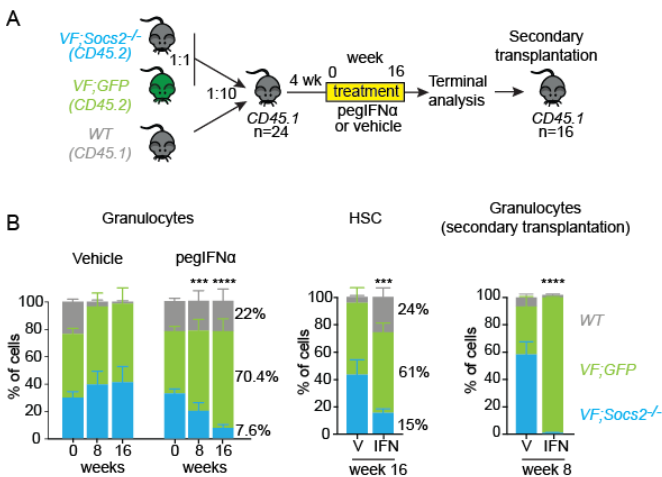
**Conclusions:** We report AXL-MAPK driven escape as mechanism of resistance to type II JAK inhibition which is targetable. This highlights the role of alternative tyrosine kinase signaling which should be addressed to restore sensitivity to JAK2 inhibition in MPN.

**Abstract ID: 112****Disrupting the Socs2-Mediated Negative Feedback to JAK-STAT Boosts Molecular Responses Induced By Interferon- $\alpha$  in a Mouse Model of Myeloproliferative Neoplasms**M. Usart<sup>1</sup>, C. Stoll<sup>1</sup>, R. Karjalainen<sup>1</sup>, H. Hao-Shen<sup>1</sup>, R. Skoda<sup>1</sup><sup>1</sup>Department of Biomedicine, University Hospital Basel, Basel

**Introduction:** Patients with myeloproliferative neoplasms (MPN) frequently carry a somatic mutation in the JAK2 gene (JAK2V617F) that is acquired in a hematopoietic stem cell (HSC). Therefore, in order to develop novel effective therapies, it is imperative to specifically target the mutant HSCs, as these cells are the reservoir that maintains MPN. To date, pegylated-interferon-alpha (pegIFN $\alpha$ ) is the only treatment known to induce molecular remission in some patients with MPN by pushing mutant HSCs into differentiation and exhaustion.

We hypothesized that disrupting components of the negative feedback loop to JAK-STAT signaling in HSCs would lead to JAK-STAT hyperactivation and thereby sensitize HSCs to the effects of pegIFN $\alpha$ . In scRNAseq experiments, we found that Socs2, a JAK-STAT negative regulator gene, was one of the top upregulated genes in MPN HSCs.

**Methods:** We examined the effects of loss of Socs2 by crossing our JAK2-V617F mice (VF) with a constitutional Socs2 knockout strain (Metcalf et al. Nature, 2000), to obtain VF;Socs2<sup>-/-</sup> mice. We performed competitive bone marrow transplantations by mixing bone marrow cells from VF mice that also express a GFP reporter gene (VF;GFP) at 1:1 ratio with bone marrow cells from VF;Socs2<sup>-/-</sup> mice, and added a 10-fold excess of bone marrow cells from wildtype CD45.1 mice. This mixture was transplanted into lethally irradiated wildtype CD45.1 recipient mice, which were then treated for 16 weeks with pegIFN $\alpha$  (25 ug/kg s.c. once weekly) or vehicle (Fig. 1A).



**Figure 1. A)** Experimental design to evaluate the effects of Socs2 knockout in mice with MPN upon treatment with pegIFN $\alpha$ . 12 mice were assigned to each treatment arm. **B)** Effects of the treatment (V: Vehicle, IFN: pegIFN $\alpha$  25ug/kg) on chimerism in Gr1<sup>+</sup> Cd11b<sup>+</sup> cells at different time points (left), lin<sup>+</sup> c-kit<sup>+</sup> Sca-1<sup>+</sup> CD150<sup>+</sup> CD48<sup>+</sup> hematopoietic stem cells (middle) and Gr1<sup>+</sup> Cd11b<sup>+</sup> granulocytes from secondary transplanted mice with BM cells from vehicle or IFN-treated mice (right).

**Results:** The ratio between VF;GFP and VF;Socs2<sup>-/-</sup> chimerism remained stable in the vehicle group during the course of the experiment (Fig.1B). However, pegIFN $\alpha$  selectively depleted the VF;Socs2<sup>-/-</sup> clone, as shown in peripheral blood granulocytes (7.6% compared to 70.4% chimerism of the VF;GFP clone) and in the bone marrow, where HSC chimerism of double mutant cells was 15%, much lower than the HSC chimerism of the VF;GFP clone, which was 61% (Fig.1B). In secondary transplan-

tation, the VF;Socs2<sup>-/-</sup> clone from IFN treated mice did not engraft after 8 weeks, further indicating that Socs2 deletion promotes HSC exhaustion upon pegIFN $\alpha$  treatment in JAK2-mutant cells (Fig.1B).

**Conclusions:** In conclusion, our data show that releasing the brake applied by Socs2 on Jak2 signaling magnifies the pegIFN $\alpha$ -induced effects on VF;Socs2<sup>-/-</sup> HSCs, leading to a better molecular response.

**Abstract ID: 123****The NFIA-ETO2 fusion blocks terminal erythroid maturation and induces pure erythroid leukemia in cooperation with mutant TP53**Z. Jevtic<sup>1</sup>, M. R. Piqué-Borràs<sup>1</sup>, F. Otzen Bagger<sup>2</sup>, J. Seguin<sup>1</sup>, M. Filgueira Bezerra<sup>1</sup>, A. Louwagie<sup>1</sup>, S. Juge<sup>1</sup>, I. Nellas<sup>1</sup>, R. Ivanek<sup>3</sup>, A. Tzankov<sup>4</sup>, U. M. Moll<sup>5</sup>, O. Cantillo<sup>1</sup>, R. Schulz-Heddergott<sup>6</sup>, A. Fagnan<sup>7</sup>, T. Mercher<sup>7</sup>, J. Schwaller<sup>1</sup>

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**Introduction:** Pure erythroleukemia (PEL) is a rare but aggressive human cancer characterized by the uncontrolled accumulation of blasts committed exclusively to the erythroid lineage. The NFIA-ETO2 fusion is the product of a t(1;16)(p31;q24) chromosomal translocation so far exclusively found in pediatric PEL patients. Sequencing studies revealed that tumor cells of almost all PEL patients carry mono- or bi-allelic TP53 mutations mostly affecting its DNA binding domain. Here we explored the in vitro and in vivo transforming activity of NFIA-ETO2 with or without the presence of PEL-associated TP53-R248Q mutation.

**Methods:** We expressed NFIA-ETO2 and inactive mutants in a murine erythroleukemia cell line (MEL) and primary fetal liver-derived erythroblasts and characterized the fusion's transforming activity in proliferation and colony-forming assays. To obtain insights into the molecular mechanism, we determined gene expression profiles, binding of the NFIA-ETO2 fusion to chromatin as well as chromatin conformation by ChIP- and ATAC-sequencing respectively. In addition, we explored the in vivo leukemogenic potential by transplantation of NFIA-ETO2-expressing cells in irradiated wildtype or TP53-R248Q/+ mutant mice.

**Results:** NFIA-ETO2 increased proliferation and impaired differentiation of murine erythroblasts depending on the NFIA DNA-binding, as well as the ETO2 neryv homology domains. Molecular studies indicated that NFIA-ETO2 bound and altered expression of genes related to erythroid differentiation that

contain NFI-binding sites and/or are decorated by ETO2, resulting in a shift from GATA- to ETS-motif-containing target genes. NFIA-ETO2-expressing erythroblasts acquired neither aberrant in vitro clonogenic activity nor disease-inducing potential upon transplantation into irradiated syngeneic mice. In contrast, in the presence of the TP53-R248Q mutation, expression of NFIA-ETO2 resulted in aberrant clonogenic activity and induction of a fully penetrant transplantable PEL-like disease in mice. Notably, TP53-R248Q per se did not affect erythroid differentiation but provided self-renewal and survival advantage to NFIA-ETO2-expressing cells by mostly downregulation of known tumor suppressive TP53 targets.

**Conclusions:** Our work indicates that NFIA-ETO2 blocks terminal erythroid differentiation by rewiring gene expression programs and cooperates with aberrant TP53 activity to induce PEL.

## SSH/SSMO ORAL PRESENTATION – CLINICAL HEMATO-ONCOLOGY

### Abstract ID: 29

#### Combining BeEAM with brentuximab vedotin for high-dose therapy in CD30 positive lymphomas before autologous transplantation – a phase I study

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**Introduction:** Standard treatment for CD30+ lymphomas includes high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT). Prognosis of patients relapsing after ASCT is poor. Therefore, achieving high rates of durable remissions following HDCT/ASCT is crucial. Brentuximab vedotin (BV) is an antibody drug conjugate combining a CD30-antibody with an antimetabolic agent. In HL, BV alone may be curative for some patients. In relapsed TCL, BV monotherapy induced CR in 57% of ALCL patients in a phase II trial. We studied safety and feasibility of combining BV and BeEAM HDCT before ASCT in CD30+ lymphomas.

**Methods:** This phase-I trial investigated 12 patients with CD30+ lymphoma (5 AITL; 7 relapsed Hodgkin lymphomas; median 2 previous treatment lines) undergoing ASCT. In a 3+3 dose escalation design, patients received a single BV dose at three levels (0.9/1.2/1.8 mg/kg) prior to HDCT/ASCT. Primary endpoint was the occurrence of predefined dose limiting toxicities (DLT) between day-8 and day+30. SAEs occurring until d+100 and AEs occurring until d+30 as well as overall survival (OS), progression free survival (PFS) and remission status at day+100 were secondary endpoints.

**Results:** The median age at diagnosis was 56 years (range, 19 to 63). Four patients had previously been exposed to BV. All patients were treated as planned; one DLT (paralytic ileus, fully resolving) occurred at 1.8 mg/kg BV. Grade-III febrile neutropenia occurred in one patient, two others had septic complications, all fully recovering. We saw no late non-infectious toxicities. No treatment-related death occurred. Median hospitalization was 23 days. Hematologic recovery was normal. CR rate was 75%. After median follow-up of 23 months, PFS rate was 8/12, and OS was 10/12 patients.

**Conclusions:** We evaluated whether combining standard HDCT with BV is safe and whether it adds efficacy in HDCT of CD30+ lymphomas. Toxicities were as expected for BeEAM alone, except an ileus potentially related to autonomic neuropathy. Infections occurred in two thirds of patients. Our study suggested

a CR rate of 75% after BV-BeEAM/ASCT, which seems promising considering the generally critical prognosis of patients with CD30+ lymphomas. PFS and OS at 1-year were 67% (n = 8/12) and 83% (n = 10/12). The efficacy of this novel HDCT combination with BV at 1.8 mg/kg should be explored in larger studies.

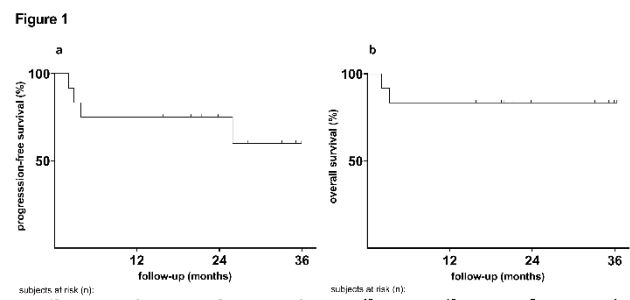


Figure 1. Kaplan-Meier estimator of cumulative survival rates of 12 patients with CD30 positive lymphoma after HDCT with BV-BeEAM followed by ASCT. (a) progression-free survival; (b) overall survival.

### Abstract ID: 30

#### Glofitamab treatment in relapsed or refractory DLBCL after CAR T-cell therapy

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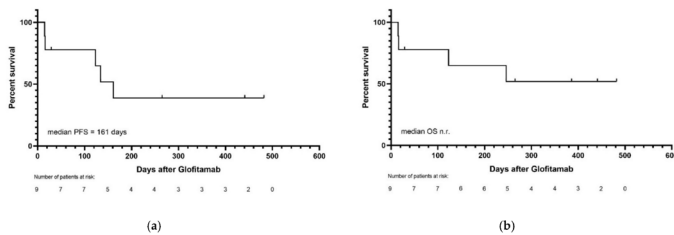
**Introduction:** Chimeric antigen receptor T-cells (CAR T) treatment has become a standard option for patients with diffuse large B-cell lymphomas (DLBCL), which are refractory or relapse after two prior lines of therapy. However, little evidence exists for treatment recommendations in patients who relapse after CAR T-cell treatment, while the outcome of such patients is poor. Treating DLBCL patients relapsing after CAR-T treatment with bispecific antibodies emerges as a novel therapeutic option, but data for such an approach are largely missing.

**Methods:** In this single-center study, we evaluated the safety and efficacy of a monotherapy with the bispecific CD20xCD3 antibody glofitamab in a series of consecutive patients who progressed or relapsed after CAR T treatment.

**Results:** We report nine consecutive patients with progressive or relapsing DLBCL after preceding CAR T-cell therapy. The patients received a maximum of 12 cycles of glofitamab after a single obinutuzumab pre-treatment in the first cycle at a single

academic institution. The treatment was generally well tolerated, and there were no discontinuations or dose reductions due to treatment-related adverse events. CRS was observed in two patients (grade 2 in both patients) during the study period, whereas no patient developed neurotoxicity. The overall response rate after glofitamab treatment was 67%, with four (45%) patients achieving a complete response and a partial remission was observed in two (22%) patients. Remarkably, we identified increased levels of persisting circulating CAR T-cells in the peripheral blood after initiation of glofitamab treatment in three of the five patients with measurable CAR T-cells.

**Conclusions:** Our data suggest that glofitamab treatment is well tolerated and effective in patients with DLBCL relapsing after CAR T-cell therapy. Additionally, we found evidence that Glofitamab administration may enhance circulating CAR T-cells in the peripheral blood in some patients, while the mechanisms involve await to be elucidated.



#### Abstract ID: 55

### Divergent incidence of CHIP after ASCT in patients with AML, myeloma and lymphoma

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**Introduction:** High-dose chemotherapy/autologous stem cell transplantation (ASCT) is a common consolidation option in patients with AML, lymphomas or myeloma. Whereas the incidence of CHIP in AML patients after ASCT is increasingly recognized, its incidence and impact on outcome after ASCT is hardly studied in lymphoma and myeloma.

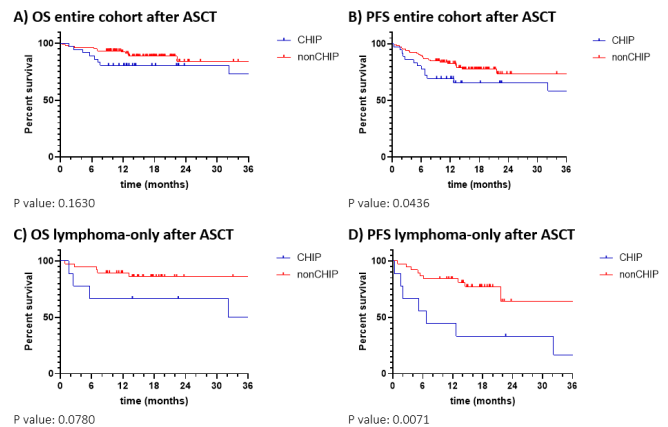
**Methods:** We retrospectively evaluated patients with AML, lymphoma and myeloma undergoing ASCT at a single academic center and with available data assessed after ASCT for the five common CHIP mutations ASXL1, DNMT3A, JAK2, TET2 and TP53. The incidence of CHIP in the three disease entities AML, lymphoma and myeloma was evaluated, and we compared outcome after ASCT between patients with and without CHIP (noCHIP).

**Results:** We identified 142 patients with CHIP data after ASCT. 64 (45%) had myeloma, 47 (33%) lymphoma, and 31 (22%) had AML. We observed CHIP after ASCT at a similar rate in (13; 20%) myeloma and in (9; 19%) lymphoma patients, but more often in (14; 45%) AML patients ( $p = .0162$ ). We found no differences in clinical characteristics, treatment modalities and response to treatment in patients with CHIP vs. noCHIP. Remarkably, strongly delayed or missing hematological regeneration was seen in four CHIP patients, but in none of the noCHIP patients ( $p = .0036$ ). After ASCT, more (13; 36%) CHIP patients relapsed so far compared to (17; 16%) noCHIP patients (PFS:  $p = .0436$ ) (Figure 1). This was predominantly seen in lymphoma patients with 6 (67%) of CHIP patients relapsing compared to only 6 (16%) of noCHIP patients ( $p = .0071$ ); in contrast, PFS between CHIP vs. noCHIP patients in AML or myeloma patients did not differ ( $p = .3869$ , and  $p = .1221$ , respectively). Similarly, overall survival (OS) tended to be shorter in CHIP vs. noCHIP patients ( $p = .0780$ ) for the lymphoma group, with deaths after ASCT seen in 4 CHIP (44%) and 5 noCHIP patients (13%;  $p = .0538$ ).

Again, OS was similar in AML and myeloma patients, and also for the entire cohort ( $p = .1630$ ).

**Conclusions:** Our analysis suggests that a panel of five markers identified CHIP after ASCT more often in AML than in lymphoma and myeloma patients. CHIP after ASCT resulted in similar survival outcomes in myeloma and AML patients, while lymphoma patients with CHIP had shorter survival rates than noCHIP lymphoma patients. Longer follow-up, larger cohorts and a prospective approach will be needed to ultimately validate our observations.

Figure 1



#### Abstract ID: 57

### Influence of comorbidities on outcome in 1153 patients with an allogeneic hematopoietic stem cell transplantation

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**Introduction:** The hematopoietic comorbidity risk index (HCT-CI) is a pre-transplant risk assessment tool used to qualify comorbidities and thus to predict non-relapse mortality (NRM) of patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). HSCT procedures continue to improve. Thus, the predictive value of HCT-CI needs to be re-evaluated.

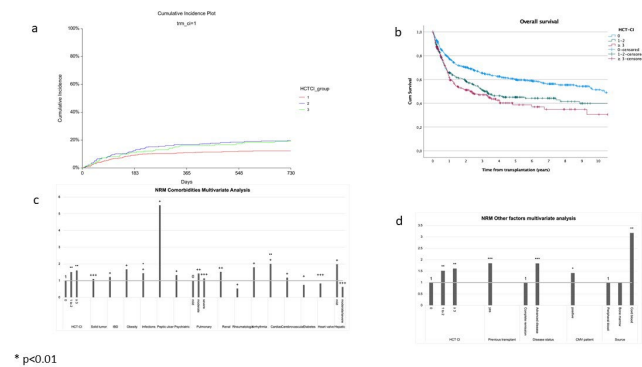
**Methods:** Our study is a retrospective analysis of pre-existing comorbidities assessing the relevance of the HCT-CI on the outcome of consecutive patients ( $n = 1153$ ) undergoing allo-HSCT from 2006-2021. HCT-CI was used to classify comorbidities, outcomes of interest are non-relapse mortality (NRM), overall survival (OS) and progression-free survival (PFS). HCT-CI was classified as low risk (HCT-CI 0), intermediate risk (HCT-CI 1-2) and high risk (HCT-CI  $\geq 3$ ).

**Results:** HSCT was done to treat AML ( $n = 435$ ), MDS/MPN ( $n = 188$ ), CML/CLL ( $n = 74$ ), ALL ( $n = 147$ ), Lymphoma/Myeloma ( $n = 188$ ), and others ( $n = 53$ ). Median age was 54 (0.6-75.8). MAC was used in 785 (68.1%), and RIC in 365 (31.7%). At 10 years, OS for low, intermediate and high risk HCT-CI group was 51.4%, 39.9% and 30.6%, respectively ( $p < 0.001$ ) (Figure 1b). NRM at 10 years differed significantly with 20.5%, 26.9% and 26.3%, respectively ( $p = 0.01$ ). NRM difference was significant between low to intermediate ( $p < 0.001$ ), but not between intermediate to high risk HCT-CI ( $p = 0.22$ ) (Figure 1a). The PFS at 10 years was 41.2%, 31.2% and 25.8% ( $p < 0.001$ ) and the relapse incidence 38.4%, 41.9%, 47.7% ( $p = 0.07$ ). There was no significant difference in acute and chronic GvHD regarding risk group. In multivariate analysis, we found significant differences in cardiac disease, infection comorbidities regarding NRM. Cardiac disease was most strongly associated with NRM (HR = 2.2,  $p = 0.002$ ) and OS (HR = 1.84,  $p < 0.001$ ) (Figure 1c). Further,

disease state (HR 1.8,  $p < 0.001$  for advanced disease), previous HSCT (HR 1.8;  $p < 0.001$ ) and HSCT source (HR 3.1;  $p < 0.001$  for cord blood) associated with NRM (Figure 1d).

**Conclusions:** We found no differences regarding NRM between intermediate and high-risk HCT-CI group. Therefore, the HCT-CI score may not be the only tool to decide towards an allo-HSCT. Cardiac comorbidities had the strongest association with NRM. All other comorbidities influenced NRM to a much lesser extent. Improvements in transplant techniques and supportive care may have improved outcome with respect to comorbidities in HSCT.

**Figure 1.** Association of outcome variables with HCT-CI a) Non-relapse mortality b) Overall survival c) comorbidities d) transplant variables



#### Abstract ID: 87

### Phase I trial of personalized multi-peptide vaccination combined with the TLR1/2 ligand XS15 in CLL patients receiving Bruton-Tyrosine-Kinase inhibitors (BTKi)

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**Introduction:** Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults. Despite the therapeutic success of novel small molecules, patients frequently experience early disease relapse due to the persistence of minimal residual disease (MRD). Targeting MRD by immunotherapy could improve CLL long-lasting remission. Here, we report on the preclinical development and clinical implementation of a phase I trial evaluating safety, immunogenicity and efficacy in terms of MRD response of a personalized multi-peptide vaccine adjuvanted with the novel toll-like receptor (TLR) 1/2 agonist XS15 emulsified in Montanide<sup>TM</sup> ISA51 VG in CLL patient receiving BTKi (NCT04688385).

**Methods:** Comparative mass spectrometry-based immunopeptidome analyses of 61 CLL patient samples and a dataset of benign tissues samples enabled the identification of high-frequency CLL-associated antigens for the most common HLA allotypes (HLA-A\*02, -A\*24, and -B\*07), recognized as T cell epitopes by pre-existing and de novo induced T cells in CLL patients and healthy volunteers. This enabled the selection of a 12-peptide panel comprising 9 HLA-class I and 3 HLA class II-restricted CLL-specific T cell epitopes as warehouse for the composition of study vaccine cocktails (SVC). Personalized SVC are selected from the warehouse based on patients' HLA allotype and immunopeptidome analysis. Three doses of personalized SVC are administered subcutaneously in a 4-weekly interval to 20 CLL patients after reduction of CLL-load by BTKi.

**Results:** So far, 17 CLL patients were included in the trial and 10 were vaccinated. The feasibility of warehouse-based peptide selection was confirmed, with more than one naturally presented warehouse peptide identified in 100% of analyzed patients. The expected local granuloma formation at vaccination site was observed in 100% of patients, which enables continuous local stimulation of CLL-specific T cells without systemic inflammation. Preliminary immunogenicity analysis revealed induction of peptide-restricted T cell response, mediated by multifunctional CD8+ and CD4+ T cells.

**Conclusions:** Personalized peptide-vaccination in CLL patients shows promising preliminary safety and immunogenicity results that warrants further evaluation in this phase I trial.

## SSH/SSMO ORAL PRESENTATION – CLINICAL SOLID TUMOR ONCOLOGY

#### Abstract ID: 24

### EV-301 Long-Term Outcomes: 24-Month Findings From Phase 3 Trial of Enfortumab Vedotin vs Chemotherapy in Previously Treated Advanced Urothelial Carcinoma

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**Introduction:** Enfortumab vedotin (EV) showed overall survival (OS) and progression-free survival (PFS) benefit in EV-301. We present efficacy/safety of EV vs chemotherapy over longer follow-up of ~2 yrs.

**Methods:** In phase 3 EV-301 (NCT03474107), patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC) who received prior platinum-containing chemotherapy and had disease progression during/after a PD-1/L1 inhibitor were randomized 1:1 to EV 1.25 mg/kg (days 1, 8, and 15 per 28-day cycle) or investigator-chosen chemotherapy with docetaxel, paclitaxel, or vinflunine (day 1 per 21-day cycle). Primary endpoint was OS; secondary endpoints were investigator-

assessed PFS per RECIST v1.1 and safety/tolerability. A pre-specified final OS analysis was planned (1-sided 0.02332 significance level) when 439 deaths occurred. Efficacy/safety ~1 yr after the interim analysis (IA; July 15, 2020) and when pre-specified number of deaths was reached are reported.

**Results:** Overall, 608 pts were randomized (EV, n = 301; chemotherapy, n = 307). As of the July 30, 2021 cutoff date, 444 deaths occurred (EV, n = 207; chemotherapy, n = 237). Median follow-up was 23.75 mo; median OS was prolonged by 3.97 mo with EV vs chemotherapy (12.91 vs 8.94 mo, respectively; HR = 0.704 [95% CI: 0.581-0.852], 1-sided P = 0.00015). OS benefit of EV was maintained in the majority of subgroups. PFS was improved with EV (median 5.55 mo) vs chemotherapy (median 3.71 mo) (HR = 0.632 [95% CI: 0.525-0.762]; 1-sided P <0.00001). Treatment-related adverse event (TRAE) rates (93.9% vs 91.8%), including serious TRAEs (22.6% vs 23.4%), were comparable between EV vs chemotherapy. Grade ≥3 TRAE rates were ~50% (EV, 52.4%; chemotherapy, 50.5%) in both arms; grade ≥3 decreased neutrophil count (14.1% vs 6.1%), decreased white blood cell count (7.2% vs 1.4%), and anemia (7.9% vs 2.7%) were more common with chemotherapy vs EV and maculopapular rash (7.4% vs 0%) was more common with EV. Of special interest AEs, all-grade treatment-related rash occurred in 44.9% of EV-treated pts vs 9.6% of chemotherapy-treated pts; peripheral neuropathy in 48.0% vs 31.6%; and hyperglycemia in 6.8% vs 0.3%.

**Conclusions:** After median follow-up of ~2 yrs, data showed continued survival benefit of EV, including sustained magnitude of benefit, over chemotherapy in pts with previously treated la/mUC and no new safety signals.

#### Abstract ID: 82

### Cutaneous angiosarcoma of head, neck, face or scalp is a distinct genomic subtype with potential sensitivity to immune checkpoint-inhibition

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**Introduction:** Angiosarcoma (AS) is a rare subtype of soft tissue sarcoma (STS), representing ~1-4% of STS. AS can arise in any tissue type, including skin (~5% of all cutaneous malignancies). AS arising from the head, neck, face or scalp (AS-HNFS) have been suggested to represent a distinct subtype induced by ultraviolet radiation (UV) and to carry a higher tumor mutational burden (TMB). Therefore, they are potentially sensitive to immune checkpoint inhibition (ICI). We aimed to test those hypotheses in a cohort of patients from our institution.

**Methods:** Patients with AS-HNFS or AS of a different location as controls were identified within the hospital's database. Archival tissue was analyzed by performing comprehensive genomic profiling (CGP; FoundationOne® Heme) to identify oncogenic driver alterations and to determine the TMB. In parallel, whole genome sequencing (WGS) was performed to define the mutational signatures. The genomic findings were correlated with an immuno-histochemical immuno-score, as well as clinical data.

**Results:** 57 patients were identified. Patients with radiation-induced AS and cases with insufficient tissue quality or quantity were excluded, narrowing the cohort to 25 patients. 11 cases were AS-HNFS, and 14 were control AS. In the samples, in which CGP was possible, 75% of AS-HNFS showed an elevated TMB versus none in the control group. In 19 samples (10 AS-

HNFS, 9 controls) WGS was possible. 7/10 (70%) AS-HNFS showed an UV-related mutational signature versus none in the control group. Of note, two of the three negative AS-HNFS were not cutaneous (mandible and thyroid), i.e. 7/8 cutaneous AS-HNFS were potentially UV-induced. Investigation of the immune infiltrate showed any type of immune reaction (inflamed, partially inflamed, or excluded immune phenotype) in 8/11 (72%) AS-HNFS, compared to 5/12 (41%) of control AS. 2/11 patients with metastatic AS-HNFS have received ICI so far.

**Conclusions:** Taken together, we identified a high TMB and / or an UV-mutational signature in a large fraction of cutaneous AS-HNFS, possibly justifying use of ICI. Of note, 4/7 cases (57%) with UV-mutational signature did not show a high TMB, meaning they would have been missed by CGP alone. This supports the use of WGS in selected cases. Moreover, our findings show that AS-HNFS should be considered a distinct AS subtype.

#### Abstract ID: 124

### Neoadjuvant treatment does not influence PD-L1 expression in stage III non-small cell lung cancer. Retrospective analysis of tumor samples from the trials SAKK 16/96, 16/00, 16/01 and 16/14.

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**Introduction:** Immune checkpoint inhibitors are expected to change treatment standards of operable stage III non-small cell lung cancer. PD-L1 protein expression on tumor cells has emerged as the most important biomarker for sensitivity to immune checkpoint inhibitors targeting the PD-1/PD-L1 axis. Little is known about the impact of neoadjuvant treatment on PD-L1 expression.

**Methods:** We assessed PD-L1 expression by immunohistochemistry (Ventana SP263 assay) on tumor cells in treatment-naïve diagnostic tumor samples and matched lung resections from patients with stage III NSCLC included in the Swiss Group for Clinical Cancer Research (SAKK) trials 16/96, 16/00, 16/01 and 16/14. All patients received neoadjuvant chemotherapy with cisplatin/docetaxel, either as single modality (CT), with sequential radiotherapy (CRT) or with the PD-L1 inhibitor durvalumab (CT+ICI).

**Results:** Overall, 132 paired tumor samples were analyzed from patients with neoadjuvant CT (n = 69), CRT (n = 33) and CT+ICI (n = 30). For CT and CRT, PD-L1 expression before and after neoadjuvant treatment did not differ significantly (Wilcoxon test, p = 0.94). Likewise, no statistically significant difference was observed between CT and CRT for PD-L1 expression after neoadjuvant treatment (p = 0.97). For CT+ICI, PD-L1 expression before and after neoadjuvant treatment did also not differ significantly (Wilcoxon test, p = 1.0). Event-free survival (EFS) and



overall survival (OS) for patients with down- or upregulation of PD-L1 expression after neoadjuvant treatment were similar.

**Conclusions:** Neoadjuvant treatment had no effect on PD-L1 expression, irrespective of the treatment modality (chemotherapy, chemoradiation, sequential immunochemotherapy). Potentially IO sensitizing effects of RT are unlikely to be caused by upregulation of PD-L1 expression. Dynamic change of PD-L1 expression did not correlate with EFS or OS.

#### Abstract ID: 130

### Comprehensive molecular tumor-testing of unresectable and metastatic biliary tract cancers identifies targetable molecular alterations in a large subgroup of patients

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**Introduction:** Biliary Tract Carcinomas (BTC) are difficult-to-treat tumors with limited therapeutic options and dismal prognosis. BTCs constitute a molecularly heterogeneous group of tumors arising at distinct anatomical locations within the biliary tract (intrahepatic cholangiocarcinoma (ICC); extrahepatic cholangiocarcinoma (ECC), gallbladder cancer (GBC)). Targetable molecular alterations can be identified in a subset of BTCs, yet a universally accepted molecular testing strategy for BTC patients has not been accepted.

**Methods:** At our institution, we implemented upfront comprehensive molecular profiling of advanced stage unresectable or metastatic BTCs in 2019. All test results undergo discussion at our institution's molecular tumor board (MTB). We here report molecular data and clinical outcome.

**Results:** 80 patients with locally unresectable (n = 14) or metastatic (n = 66) BTC underwent molecular testing. Testing was performed on cytology material (FNP, n = 6/80), tumor biopsies (n = 38/80) or resectates (n = 36/80). In 55/80 cases (68.8%) testing was performed prior to or at the beginning of first-line systemic therapy. In 44/80 (55%) cases, at least one targetable genomic alteration was identified. Most common molecular alterations across the population were detected in TP53 (27/80; 33.8%), KRAS (20/80; 25%), two of which were KRAS G12C, IDH1 (11/65; 13.4%) and FGFR2 (7/80; 8.8%). 16/80 (20%) BTCs showed alterations within HRR pathway genes, 3/80 BTCs were dMMR/MSI-H. FGFR2 alterations (3 genomic rearrangements, 4 activating mutations, 0 high focal amps) and IDH1 hotspot mutations were detected in ICC only, while KRAS and HER2 alterations and MSI-H were preferentially (13/24) detected in ECC and GBC, respectively. Genetic counselling and germline testing were recommended in 4/80 cases. 18/44 patients with a targetable alteration received targeted treatment during disease course (10/18 1st line, 8/18 later lines) and showed a numerically superior overall survival (HR = 0.50; 95% CI, 0.23–1.09; P = 0.0842). 1/9 patients with unresectable ICC converted to resectability during molecularly targeted treatment.

**Conclusions:** Comprehensive molecular testing for biliary tract cancer is clinically feasible and identifies targetable molecular alterations in a large subset of cases. We strongly recommend up-front molecular tumor testing for all stage IV BTC patients.

## ONCOREHA / OPS / PALLIATIVE.CH / SANS ORAL PRESENTATION – SUPPORTIVE & PALLIATIVE CARE, REHABILITATION & SURVIVORSHIP

#### Abstract ID: 27

### Context-specific adaption, implementation and evaluation of an eHealth-facilitated integrated care model in allogeneic stem cell transplantation – the Swiss SMILE project

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**Introduction:** Allogeneic stem cell transplant (alloSCT) patients could benefit from an eHealth-facilitated, integrated care model (eICM) to enhance health outcomes. By combining implementation, behavioural, and computer science methods, we developed an eICM for alloSCT (SMILE). For use in the Swiss setting, this version required various adaptations. However, little is known how to contextually adapt, implement and evaluate an eICM calling for sustainable implementation science-powered innovation.

We aim to describe 1) how to contextually adapt the SMILE-ICM for the Swiss setting and 2) its current evaluation for effectiveness and implementation outcomes at University Hospital X (anonymized).

**Methods:** 1) We used a mixed-methods design. Quantitative (n = 60 patients, n = 6 clinicians) and qualitative (10 patient interviews, focus groups with 15 clinicians) data were collected from 04/2019–06/2020 and analysed descriptively and thematically. Stakeholder involvement (n = 28), end-user tests (patients = 5, clinicians = 4) and theoretical frameworks (FRAME, ERIC) supported the adaption.

2) The adapted SMILE-ICM is currently under evaluation via a hybrid effectiveness-implementation RCT including a consecutive sample of 80 alloSCT patients, who were randomized into usual care or SMILE-ICM group. To gauge the SMILE-ICM's effectiveness (e.g., re-hospitalization rate, GvHD, survival) and implementation outcomes (e.g., acceptability, feasibility), we are using multi-method assessments (e.g., questionnaires, interviews).

**Results:** 1) Current clinical practice was mostly acute care driven. Patients and clinicians expressed high technology openness and valued eICMs for timely and integrated care (Table 1). Adaptions of SMILE-ICM were needed primarily at the organizational level (Fig. 1). Implementation strategies (e.g., visit first centre, create new clinical teams) were modified.

2) Recruitment for the RCT was completed 9 months ahead of time in June 2022, indicating successful implementation.

So far, patients express high satisfaction with the provided SMILE-ICM. Effectiveness and implementation outcomes will be available 09/2023.

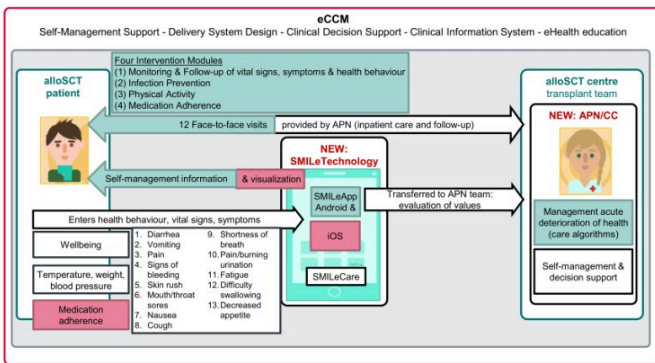
**Conclusions:** A theory-guided, context-driven adaption of an intervention is an important first step and should be applied in implementation projects. If effective, the applied methodology and its innovation can be a blueprint for future scaling-up and adaptations to further populations and settings.

Table 1. Patients' and clinicians' perspectives on practice patterns and self-management support in view of Chronic Illness Management

Patients' perspective		Results (N = 60)	
<b>Dimensions</b>	<b>Variables</b>		
Practice Patterns	Placement of follow-up care appointments		
	• Only at transplant center, n, %	35	58%
	• Also at external center, n, %	25	42%
	• Hospital X (anonymous), n, %	6	10%
	• Hospital Y (anonymous), n, %	16	27%
	• Other, n, %	3	5%
Patient's perspective of CIM implemented in follow-up program	Short version of the Patient Assessment of Chronic Illness Care (PACIC) instrument; mean, SD (range)	30.6	+5.8 (11 - 55)
Health opinions	Would you agree to input your wellbeing, your vital signs and symptoms?		
	• no, I wouldn't agree, n (%)	10	17%
	• yes, once a week, n (%)	23	38%
	• yes, every third day, n (%)	12	20%
	• yes, daily, n (%)	15	25%
<b>Clinicians' perspective</b>		<b>Results (N = 5)</b>	
<b>Dimensions</b>	<b>Variables</b>		
Level of CIM	BRIGHt Clinicians' Questionnaire; CMI-BRIGHt; mean, SD (range)	2.92	+ 0.58 (2.49 - 3.87)
Preparedness of the Tx team in view of CIM	BRIGHt clinician questionnaire; mean, SD (range)	3.14	+ 0.40 (2.89 - 3.70)
Completeness of the Tx team in view of CIM	BRIGHt clinician questionnaire; mean, SD (range)	3.00	+ 0.59 (2.42 - 3.67)

Note. Assessment of Chronic Illness Management (CIM) level from patients' and clinicians' perspectives by completing the adapted BRIGHt patient survey (N = 60), respectively the investigator-developed CMI-BRIGHt clinician questionnaire (N = 5). Abbreviations: mean = means, SD = standard deviation, Tx team = transplantation team.

Figure 1. The adapted SMILE-Integrated Care Model for the Swiss setting



Note. Elements of the original SMILE-Integrated Care Model highlighted in green have been adapted to the Swiss setting. Elements of SMILE-ICM highlighted in red has been added as new functions. Abbreviations: alloSCT = allogeneic stem cell transplantation; APN = Advanced Practice Nurse; CC = Care Coordinator; eCCM = eHealth-enhanced Chronic Care Model.

Abstract ID: 97

**SUNSHINE\_eHealth: continuous monitoring of vital signs for early detection of clinical deterioration in oncological patients with high risk for complications**

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**Introduction:** Timely recognition of clinical deterioration in oncological patients remains challenging. Remote monitoring of vital signs may provide support to current clinical practices but need to be extensively tested before routine implementation in the oncological environment. In our pilot project a telemedicine system was implemented for the early detection of vital signs deterioration in oncological patients with a high risk for complications, without need for hospitalization. Main objectives were the evaluation of the sense of safety and well-being of patients at home and feasibility of remote monitoring.

**Methods:** The used monitoring system is based on the IIa-class medical device VitalPatch (by VitalConnect) to monitor continuously in real-time 7 vital parameters for 7 days: respiratory frequency, heart rate, temperature, a single ECG lead, posture, number of steps and fall detection. An oximeter was integrated into the system and a smartphone was provided to each patient as gateway for data transmission. Eligible patients received the

medical devices at home and were instructed by a specialized nurse. Access to clinical information and remote monitoring was ensured to the patient's family doctor and medical oncologist through an online platform with the support of a professional 24/7 emergency call center (responsible for the management of alerts based on predefined thresholds). At the end of the monitoring period, a 14-item questionnaire was administered to patients exploring their sense of safety, satisfaction with monitoring and usability of the device.

**Results:** Thirty patients were monitored from October 2021 to July 2022. Median age at enrolment was 68.8 years (range 43 – 87). Most patients (78%) judged the devices very easy to use. The monitoring system increased the sense of safety of 96% of patients. The satisfaction with remote medical assistance was “very high” and “high” for 88% of patients. Remote monitoring information led to treatment change in 37% of patients. Five out of 30 patients had an acute event during the monitoring period, only 1 of them needed hospitalization.

**Conclusions:** Remote monitoring of vital signs of oncological patients with high risk for complications was feasible and well perceived by all patients. Future studies need to evaluate the impact of home monitoring on patient outcome as well as the cost-effectiveness of this new approach.

Abstract ID: 129

**Factors Impacting Advanced Practice Nurses' Cancer Service Implementation and Opportunities for Role Optimization: Preliminary Study Results**

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**Introduction:** Patients with complex cancer care needs and the interprofessional care team value Advanced Practice Nurses (APNs) services due to their autonomous and effective interventions resulting in i.e., timely cancer care coordination, and patients' better quality of life. However, APNs roles are still relatively new, and the extent to which they can fully implement their roles in cancer services has not been examined in Switzerland. It remains unclear how APNs cancer services are impacted by factors that influence the role implementation. Therefore, this study aims to explore APNs experiences in implementing their role and perceived opportunities for role optimization.

**Methods:** A qualitative research design with three focus group interviews was chosen, involving oncology APNs from Switzerland. APNs were recruited by a multi-variation sampling strategy. Semi-structured questions explored APNs' experiences in implementing their roles. Questions were based on a literature search identifying relevant themes to be further explored. Interviews were recorded, transcribed verbatim, and analysed thematically after Braun & Clarke (2006).

**Results:** APNs caring for different patient populations with cancer diagnoses in Switzerland participated. APNs described that their role implementation was successful when using a step-wise approach. Characteristics of APNs roles and their services illustrate that this new model of care is not yet fully and sustainably implemented in Switzerland. APNs explained that hindering and facilitating factors were experienced during role implementation. Barriers to APNs role implementation included missing structures in care organisations and the healthcare system and little knowledge about APNs by relevant decision-makers. However, factors that facilitated APNs role implementation were being supported by stakeholders and working in an

APN team. Furthermore, these factors were experienced to impact their job satisfaction and intention to stay or leave the job.

**Conclusions:** The results are highly relevant in the context of the creation of a sustainable APN cancer care workforce, due to identifying factors that can favor APNs intention to stay or leave their job in cancer care. Agreeing on a common agenda that addresses barriers might help to better implement APNs role and their cancer services in the Swiss healthcare system.

#### Abstract ID: 116

### Complications and supportive therapy of CAR T-cell therapies for lymphoma patients: A retrospective analysis in a single centre

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**Introduction:** With the approval of chimeric antigen receptor (CAR) T-cell therapy, a new promising and potentially curative treatment option for relapsed/refractory B-cell lymphoma is available. Patients face unique toxicities and complications that can persist long-term. Currently, there is no clear consensus in prophylaxis and treatment of both side effects and late events. We aim to provide real-world data on complications and the use of supportive therapies after CAR T-cell therapy.

**Methods:** In this single-centre and non-interventional study, we retrospectively analysed the data of complications of 56

lymphoma patients treated with the anti-CD19 CAR T-cell therapies Axi-cel, Tisa-cel or Liso-cel from 2019 to 2021. Patients not reaching the outpatient setting were excluded, and the follow-up was terminated in the event of lymphoma recurrence. We report the outpatient course, incident complications and used prophylactic therapies (i.a. fluconazole, valaciclovir, co-trimoxazole and prophylactic immunoglobulins (IVIg)) after CAR T-cell therapy until December 31, 2021 in comparison to currently available guidelines.

**Results:** Median follow up was 201 days (66–551). A complication density of 0.12 (0–0.55) complications per 100 days of follow-up and a cumulative infection incidence of 45% were observed. Most complications were infectious (77%) and caused by viral agents. One treatment- and three infection-related deaths were reported. Twenty-four per cent of complications occurred after more than one year post CAR T-cell therapy. All patients received co-trimoxazole and valaciclovir, and about half of the patients received fluconazole (52%) and IVIg (45%). In contrast to current guidelines, no clinical rationale for antifungal and PJP-prophylaxis for at least 6 months was found. However, we support evidence for one year of antiviral treatment. Furthermore, this study suggests that proactive IVIg substitution for IgG <5 g/L reduces infection density (0.18 vs. 0.31).

**Conclusions:** CAR T-cell patients have a long-lasting risk for infectious complications. Given the lack of evidence-based strategies for prevention and treatment, our descriptive real world data will help to further develop and establish appropriate guidelines for prophylactic therapies. Ideally, these interventions are validated in prospective and randomized studies, and should in addition identify potential and clinically useful biomarkers.

## SSH POSTER PRESENTATION – HEMOSTASIS, TRANSFUSION MEDICINE, VASCULAR, LABORATORY MEDICINE

#### Abstract ID: 37

### Proteomic profiling to identify new biomarkers for heparin-induced thrombocytopenia: an analysis of the TORADI-HIT study

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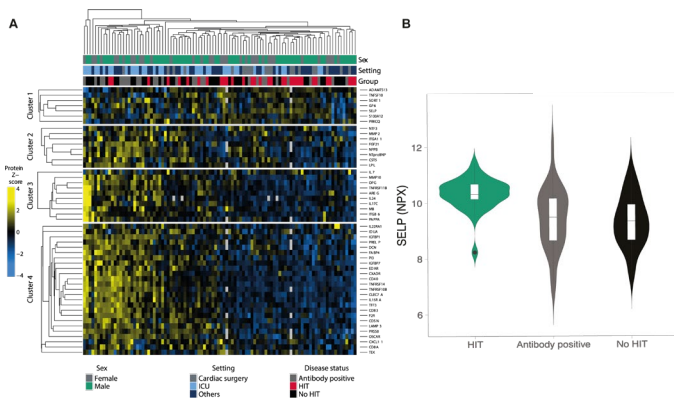
**Introduction:** New analytical techniques can assess hundreds of proteins with high sensitivity, facilitating the observation of their complex interplay and role in disease mechanisms. We hypothesized that proteomic profiling targeting proteins involved in thrombus formation, inflammation, and the immune response would identify potentially new biomarkers for the diagnosis, prognosis, and monitoring of heparin-induced thrombocytopenia (HIT).

**Methods:** Randomly selected patients with suspected HIT from the prospective TORADI-HIT study were included (confirmed HIT, n = 32; HIT ruled-out, n = 32; positive heparin/PF4 [H/PF4] antibodies but HIT ruled-out, n = 32). Four existing panels of the Olink proximity extension assay covering 362 proteins involved in thrombus formation, inflammation, and immune response were determined. Sources of variation between patients with and without HIT were explored by principal component analysis (PCA). The relative difference in protein concentration was analyzed using a linear regression model adjusted for sex and age. The Benjamini-Hochberg method with a false discovery rate of 5% was used to account for multiple testing. HIT was defined as a positive heparin-induced platelet aggregation test (HIPA). A heatmap of the 50 most significant proteins and the distribution of P-selectin is displayed in Figure 1.

**Results:** Among 96 patients analyzed, 34 were female (36.4%); the median age was 70.5 years (interquartile range [IQR]: 58.0, 79.8). The median OD of the IgG-specific H/PF4 ELISA was 3.00 (IQR: 1.51, 3.00), 0.28 (IQR: 0.08, 0.344), 0.90 (IQR: 0.72, 1.5), for patients with confirmed HIT, HIT ruled-out and positive H/PF4 antibodies respectively. Differences between HIPA positive and HIPA, negative patients were observed in PCA; overlapping clusters were interpreted as a consequence of low sample size. Protein abundance analysis revealed a statistically significant association of 31 proteins with HIT status (12 upregulated, 19 downregulated). Out of these proteins, P-selectin (SELP) remained statistically significant after multiple test adjustments (false discovery rate 5%;  $\beta = 1.04$ , 95% CI 0.63, 1.45).

**Conclusions:** Proteomic profiling is a promising new approach to identify new biomarkers for the diagnosis, prognosis, and

monitoring of heparin-induced thrombocytopenia (HIT). Future studies shall assess the diagnostic and prognostic value of P-selectin in the management of HIT.



#### Abstract ID: 39

### A machine-learning model for reducing misdiagnosis in heparin-induced thrombocytopenia: a prospective, multicenter, observational study

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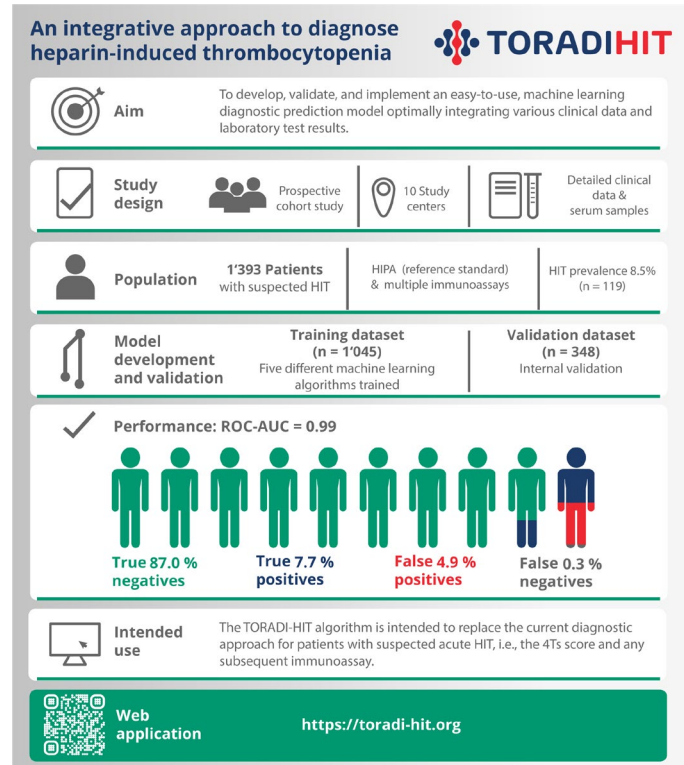
**Introduction:** Diagnosing the life-threatening disease heparin-induced thrombocytopenia (HIT) at the bedside remains challenging, exposing a significant number of patients at risk of delayed diagnosis or dangerous overtreatment. We hypothesized that machine-learning algorithms could be utilized to develop a more accurate and user-friendly diagnostic tool that integrates diverse clinical and laboratory information and accounts for complex interactions.

**Methods:** We conducted a prospective cohort study including 1'393 patients with suspected HIT from 10 study centers. Detailed clinical information and laboratory data were collected, and various immunoassays were conducted. The washed platelet heparin-induced platelet activation assay (HIPA) served as the reference standard.

**Results:** HIPA diagnosed HIT in 119 patients (prevalence 8.5%). The feature selection process in the training dataset (75% of patients) yielded the following predictor variables: (1) immunoassay test result, (2) platelet nadir, (3) unfractionated heparin use, (4) CRP, (5) timing of thrombocytopenia, and (6) other causes of thrombocytopenia. The best performing models were a support vector machine in case of the chemiluminescent immunoassay (CLIA) and the ELISA, as well as a gradient boosting machine in particle-gel immunoassay (PaGIA). In the validation

dataset (25% of patients), the AUROC of all models was 0.99 (95% CI: 0.97, 1.00). Compared to the currently recommended diagnostic algorithm (4Ts score, immunoassay), the numbers of false-negative patients were reduced from 12 to 6 (-50.0%; ELISA), 9 to 3 (-66.7%, PaGIA) and 14 to 5 (-64.3%; CLIA). The numbers of false-positive individuals were reduced from 87 to 61 (-29.8%; ELISA), 200 to 63 (-68.5%; PaGIA) and increased from 50 to 63 (+ 29.0%) for the CLIA.

**Conclusions:** Our user-friendly machine-learning algorithm for the diagnosis of HIT (<https://toradi-hit.org>) was substantially more accurate than the currently recommended diagnostic algorithm. It has the potential to reduce delayed diagnosis and overtreatment in clinical practice. Future studies shall validate this model in wider settings.



#### Abstract ID: 42

### Identification of key regulators of procoagulant COAT platelet generation by quantitative phosphoproteomic analysis

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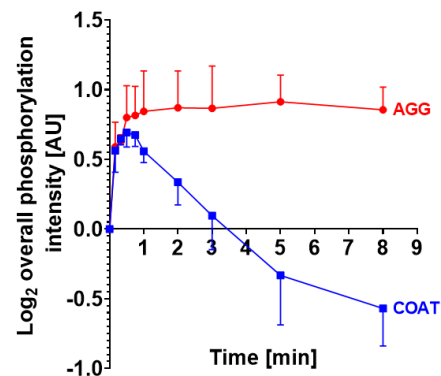
**Introduction:** At the site of vascular injury, upon combined activation by Collagen And Thrombin (COAT), a fraction of platelets loses their aggregating properties and becomes procoagulant. Procoagulant platelets enhance thrombin generation and fibrin deposition to consolidate the clot. Decreased or enhanced procoagulant platelet generation leads to bleeding or thrombotic events, respectively. The intracellular signalling underlying the dichotomous activation endpoint (either aggregating or procoagulant platelets) is only partially elucidated. Here, we investigated whether phosphoproteomic analysis could identify key regulators of the generation of procoagulant COAT platelets.

**Methods:** Platelets from healthy donors (n = 3) were activated at RT with convulxin and thrombin in presence or absence of

calcium, which generated procoagulant or aggregating phenotypes, respectively. Platelets were sampled at baseline and different time points up to 8 min after activation. The phosphoproteomes of unstimulated, aggregating, and procoagulant COAT platelets were analysed by Tandem Mass Tag and quantitative Mass Spectrometry.

**Results:** We identified over 7200 different phosphorylation sites (phosphosites) corresponding to 1886 unique proteins of which 1643 (87%) showed significant regulation upon stimulation. Our data indicate that proteins in procoagulant response are dephosphorylated (and hyper-phosphorylated during aggregation) compared to baseline. We identified 65 differentially regulated phosphosites in the two activation end-points: 29 phosphosites were down-regulated in procoagulant platelets (and up-regulated in aggregating ones); 36 phosphosites were down-regulated in aggregating platelets (and up-regulated in procoagulant ones). Among these, we observed an antithetical phosphorylation status of sodium-calcium-exchanger (NCX) at Serine382 and Serine381 in procoagulant COAT versus aggregating platelets. This observation is in line with our previous data showing a critical functional role of NCX for the dichotomous activation leading to procoagulant platelets.

**Conclusions:** The present study highlights and confirms the utility of phosphoproteomic analysis to detect critical molecular regulators of the dichotomous response leading to the generation of procoagulant platelets besides aggregating ones at the site of vascular injury.



#### Abstract ID: 46

### High incidence of intracranial haemorrhage in children with hereditary afibrinogenemia

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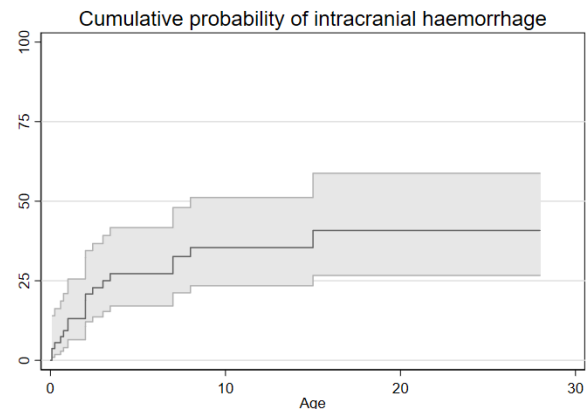
**Introduction:** Intracerebral bleeding (ICH) is associated with high morbidity and mortality in patients with afibrinogenemia. Details on type of cerebral haemorrhage, management, and neurological outcomes are lacking.

**Methods:** We performed a retrospective study on Egyptian children with afibrinogenemia who experienced ICH, in order to estimate the incidence and the neurological outcomes.

**Results:** Among 58 children with afibrinogenemia treated on demand, 18 (31%) had a history of ICH (28 episodes). ICH occurred in young patients, with a median age at first event of 1 year (Q1-Q3 1-7 years). The cumulative incidence of ICH at 10 years was 35% (95%CI 23-51) and at 20 years was of 40% (95%CI 26.7-58.8). Impaired consciousness level, vomiting and seizures were the most common presenting symptoms. Spontaneous bleedings were associated with a more severe clinical

presentation and worse neurological outcomes including hydrocephaly and impaired cognitive development. Only half of ICH events (n = 14, 50%) were treated in less than 24h from the onset of symptoms. Fibrinogen supplementation by FFP, cryoprecipitates or fibrinogen concentrates was administered in 7 (25%), 19 (68%) and 3 (10%) ICH events, respectively. Four (22%) patients underwent a surgical intervention. After the ICH, six patients started a secondary prophylaxis

**Conclusions:** Our results shows that ICH is frequent in children with afibrinogenemia. ICH was associated with adverse neurological outcomes and death. Prospective studies are required to determine whether a primary prophylaxis should be started early in childhood.



#### Abstract ID: 48

### The Contribution of Mitochondrial Calcium Homeostasis in ADP-Evoked Platelet Responses

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**Introduction:** Adenosine Diphosphate (ADP) is one of the important platelet agonists, which plays an essential role in platelet function. It is well known for inducing shape change, generation of thromboxane A<sub>2</sub>, and platelet aggregation. ADP rapidly triggers the cytosolic Ca<sup>2+</sup> rise and a part of this Ca<sup>2+</sup> is taken up by mitochondria. Mitochondrial Ca<sup>2+</sup> influx is tightly regulated by Mitochondrial Calcium Uniporter (MCU) and the extrusion is controlled via Sodium/Calcium/Lithium Exchanger (NCLX). While the cytosolic Ca<sup>2+</sup> elevation is a well-known signaling mechanism in ADP-stimulated platelets, the contribution of mitochondrial Ca<sup>2+</sup> transport in ADP-mediated platelet responses remains poorly explored. The present study aimed to explore the role of mitochondrial Ca<sup>2+</sup> fluxes in ADP-evoked platelet responses.

**Methods:** Expression of MCU and NCLX in platelets was confirmed at mRNA level using the conventional PCR. MCU was blocked by mitoxantrone (MTX) and NCLX with CGP-37157 (CGP). Lactate Dehydrogenase and Trypan blue assays were performed to check platelet membrane integrity. Platelet aggregation was determined by microplate-based spectrophotometric assay. Flow cytometry was employed for further testing markers of platelet activation (P-selectin expression and PAC-1 binding). Mitochondrial dehydrogenase activity was assessed by the MTT [3(4,5 dimethylthiazol2yl)2,5 diphenyltetrazolium bromide] assay.

**Results:** We optimized a time-lapse based spectrophotometric assay for determination of ADP-induced platelet aggregation and demonstrated that MTX did not alter the integrity of the

platelet membrane. Interestingly, our results revealed a decrease in ADP-mediated platelet aggregation by MTX. Likewise, MTX reduced the activation of platelets monitored with P-selectin and PAC-1. In line with these findings, MTX also reduced ADP-stimulated mitochondrial dehydrogenase activity. In addition to this, inhibition of NCLX with CGP resulted in enhanced platelet aggregation in response to ADP, which was in line with the increased positivity of P-selectin and PAC-1.

**Conclusions:** The findings of the present study reveal a so far uncharacterized role of mitochondrial calcium transport in ADP-induced platelet activation, which appears to be facilitated by the mitochondrial calcium content.

#### Abstract ID: 54

##### Use of global coagulation assays to monitor emicizumab pharmacodynamics

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**Introduction:** Emicizumab is a novel therapy to treat patients with hemophilia A (PwHA). Because of its mechanism of action, emicizumab over-corrects standard coagulation assays, precluding their use for treatment monitoring. The identification of biological markers reflecting the in vivo hemostatic competence of patients under emicizumab would have a great clinical value. Our aim was to investigate whether global coagulation assays are useful for monitoring the biological response to non-factor replacement therapy with emicizumab.

**Methods:** We investigated thrombin generation (TG), fibrin clot formation (FCF) and fibrin clot structure (FCS) over a period of two months in six adult PwHA treated with emicizumab (Hemlibra® F Hoffmann-La Roche, Basel, Switzerland). Patients received a weekly dose of emicizumab of 3 mg/kg during weeks (W) 1-4 and 1.5 mg/kg from W5 onwards. TG, FCF and FCS results were compared to patient baseline, peak FVIII replacement, and healthy donors. TG was measured by Calibrated Automated Thrombogram assay (Stago, France); FCF was investigated with Thrombodynamics analyzer (Hemacore, Russia) in a tissue-factor dependent and independent system and with turbidity assay (polymerization and lysis); FCS was investigated with scanning electron microscopy.

**Results:** i) TG and FCF significantly increased compared to patient baseline, reaching a plateau that lasted until the end of monitoring, but remained at the lower limits of reference values. ii) At emicizumab plateau and compared to baseline, fibrin clot network became denser and characterized by thinner fibrin fibers, similar to normal plasma. iii) Of note, PwHA achieved very different degrees of TG and FCF improvement despite similar emicizumab plasma concentrations.

**Conclusions:** Our data show that global coagulation assays measuring TG and in particular FCF capture emicizumab pharmacodynamics. Noteworthy, individual PwHA achieve variable levels of hemostatic correction despite similar emicizumab concentrations. This observation may open the path towards personalization of emicizumab treatment.

#### Abstract ID: 62

##### Von Willebrand factor (vWF) is involved in thrombophilia of severe COVID-19: in situ evidence from autopsies

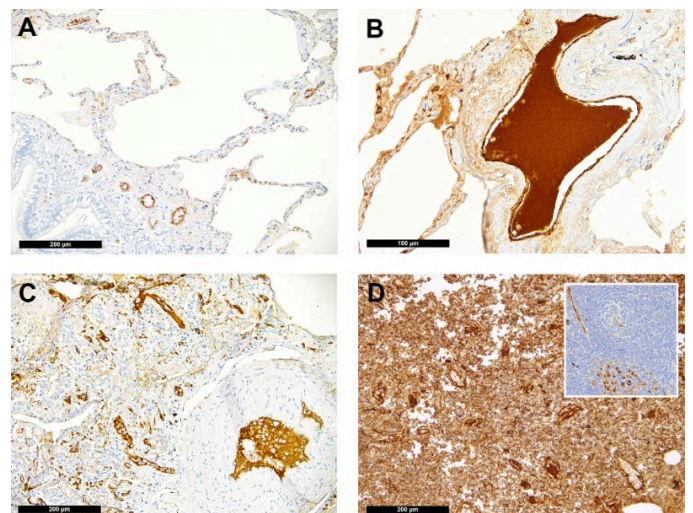
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**Introduction:** Coronavirus disease 2019 (COVID-19) is accompanied by a hypercoagulable state with micro- and macrovascular thrombotic complications. In plasma samples from COVID-19 patients, von Willebrand factor (vWF) levels were shown to be highly elevated and, like the relative lack of its counterpart, ADATMS13 (a disintegrin-like and metalloprotease with thrombospondin repeats 13), predictive of adverse outcomes, especially mortality. However, vWF is usually not included in routine coagulation analyses, and histologic evidence of its involvement in thrombus formation in COVID-19 is lacking. Moreover, since vWF is also an acute phase protein it needs to be determined whether it is a bystander, i.e. a biomarker reflective of endothelial dysfunction, or a causal factor in the pathogenesis of COVID-19.

**Methods:** We compared lung, lymph node and heart autopsy samples from 28 patients with lethal COVID-19 (B.1 virus-lineage) to controls, and systematically assessed for vWF and platelets (CD42b) by immunohistochemistry. Controls comprised of 24 lungs, 23 lymph nodes, and 9 hearts, and did not differ significantly from the COVID-19 group respecting age, sex, BMI, blood group, or anticoagulant use.

**Results:** Compact platelet-rich microthrombi were more frequent in patients, who died of COVID-19 (36% vs. 8%,  $p = 0.02$ ; staining for CD42b). This difference was more pronounced when lungs were analyzed for vWF: in normal lungs, vWF is physiologically present in vascular endothelial cells (Figure 1A).



A completely normal pattern of vWF was rare in both groups (controls vs. COVID-19: 25% vs. 7%;  $p = 0.081$ ), but vWF-rich thrombi were exclusive to COVID-19 (39% vs. 0%,  $p < 0.01$ ), as were NETosis thrombi enriched for vWF (25% vs. 0%,  $p < 0.01$ ). 46% of COVID-19 patients had either vWF-rich thrombi, NETosis thrombi, or both (Figures 1B&C). Such trends were also seen in pulmonary draining lymph nodes (35% vs. 17%,  $p = 0.147$ ), where the overall presence of vWF was very high (Figure 1C).

**Conclusions:** We bring in situ evidence of vWF-rich thrombi that we context as likely attributable to COVID-19. In line with the growing evidence that increased plasma vWF correlates with adverse outcomes, this supports the hypothesis that high levels of vWF and a dysregulation of the vWF/ADAMTS13 ratio contribute to COVID-19 morbidity and mortality. Hence, vWF may be a therapeutic target in severe COVID-19, warranting further studies.

#### Abstract ID: 98

### Analysis of cell types in apheresis material for CAR-T therapy: focus on patients with low CD3 counts

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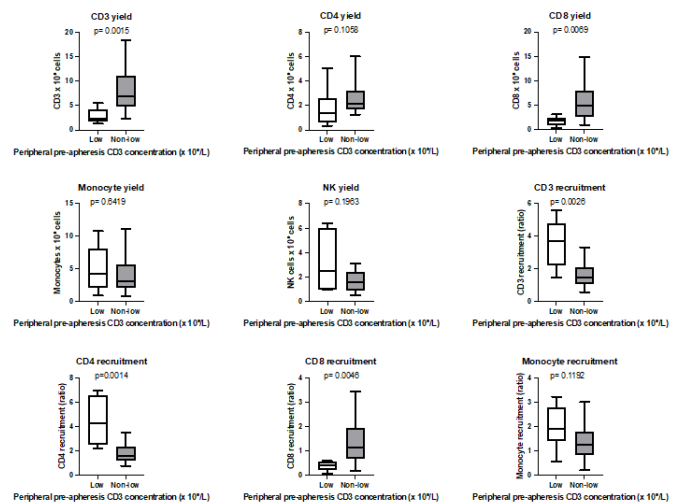
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**Introduction:** The manufacturing of CAR-T cells is a multi-step process starting with a lymphapheresis of peripheral CD3. The collection of a sufficient number of cells is critical for the successful manufacturing of CAR-T cells. Little is known about the cell composition of apheresis material, especially in patients with low peripheral pre-apheresis CD3 counts. We aimed to retrospectively analyse the PBC and FACS results of apheresis material in patients undergoing collections for Tisagenlecleucel (tisa-cel; Kymriah®).

**Methods:** We analysed 27 harvests conducted between October 2018 and November 2019. The peripheral blood count was tested using XP-300® Sysmex, immunophenotyping was performed using FACSCanto II. Recruitment of one specific cell type was assumed when the ratio of the yield to the absolute circulating prior to harvest was  $>1$ . The apheresis parameters and laboratory values, in low ( $<0.3 \times 10^9/L$ ) and non-low ( $\geq 0.3 \times 10^9/L$ ) peripheral pre-apheresis CD3 counts, were compared using the MWW test. **Results:** were assumed to be statistically significant if the p-value was  $<0.05$ .

**Results:** The median patients' age was 65 years (IQR 52 – 71 years). Diagnoses were B-ALL in 4% ( $n = 1$ ) and DLBCL in 96% ( $n = 26$ ) of all harvests. Low pre-apheresis peripheral CD3 counts were found in 22% ( $n = 6$ ), whereas non-low CD3 counts in 78% ( $n = 21$ ). The total yields and recruitment ratios are shown in Figure 1. In general, the total CD3 and CD8 yields were lower in patients with low pre-apheresis peripheral CD3 counts, whereas the yields for CD4, monocytes and NK-cells were not significantly different. In patients with low pre-apheresis peripheral CD3 counts the recruitment was significantly higher for CD3, CD4, and lower for CD8, but not significantly different for monocytes; data for NK recruitment was not available.

**Conclusions:** Patients with low pre-apheresis peripheral CD3 counts achieve sufficient yields of CD3 cells in apheresis material. Patients with low pre-apheresis peripheral CD3 counts recruit CD3 and CD4 cells better than the non-low group, whereas the recruitment of CD8 cells is better in the non-low group. Also, in the low group, CD8 yields are lower, whereas there is no difference in CD4 yields if compared to the non-low group. This fact may be of an importance for therapy outcomes. Deep immunophenotyping of cells in apheresis material would be advantageous for understanding the phenotype of recruited cells.



#### Abstract ID: 109

### Hemophagocytic Syndrome in Adults – Real-World data on Mortality from a tertiary reference center

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**Introduction:** Hemophagocytic Syndrome (HLH) is a rare, life-threatening disorder. Real-world data on HLH in adults are sparse. We analyzed the clinical characteristics and outcomes of HLH adult patients in our hospital.

**Methods:** The hospital database was searched to identify adult HLH patients diagnosed between January 2014- June 2021. We used the Saint Antoine score (HScore) (L. Fardet et al. Arthritis & Rheumatology 2014) to evaluate the data. Overall survival (OS) was estimated by Kaplan-Meier method and a logistic regression analysis to predict death including all variables with p value  $<0.10$  at univariate analysis.

**Results:** We analyzed medical reports of 591,136 patients. The diagnosis of HLH was mentioned in 79 patients. After the exclusion of 24 duplications, the remaining 55 patients were analyzed using the HScore and 54 patients were included (0.009% of all patients). The median age at HLH diagnosis was 61 years ( $r 22 - 83$ ) and 66.7% were female (Table 1). The most frequent observed diagnostic criteria were cytopenia (98.1%), hyperferitinemia (92.6%), hypertriglyceridemia (85.2%) and fever (81.5%). Underlying identified causes were hematological neoplasms in 18/54 (33.3%), infections in 14/37 (25.92%), rheumatic disorder in 7/54 (12.96%), and 31% were idiopathic. The OS at 180 days was 58%+6.85, all but one death occurred in the first 30 days after diagnosis. The clinical and laboratory data were compared between the survivors and dead patients. The statistically significant unfavorable predictive factors were: neurological symptoms, cardiovascular complications, requiring platelet transfusion, increased alkaline phosphatase and age  $>50$  years. In multivariate analysis, factors associated with

relative risk of death were older age (Relative Risk [RR] 1.175, 95%CI 1.0038-1.329;  $p = 0.01$ ); presence of cardiopulmonary complications (RR 254.9 (4.6-13979;  $p = 0.007$ ) and hypertriglycerides (RR 465 (3.4-62572;  $p = 0.014$ ).

**Conclusions:** These data confirm the rare occurrence and high risk of dying from HLH in adults patients. The number of diagnostic criteria and a high HScore were not related with higher death rates. Factors associated with overall mortality were advanced age, the presence of cardiovascular complications, and high triglycerides at diagnosis. Further awareness on this entity and multidisciplinary work are essential to improve outcome.

Patient's characteristics / comparison alive versus dead

Characteristics	total	alive	dead	P
All	54	32	22	
Male	18 (33%)	13 (72.2%)	5 (27.8%)	0.170
Female	36 (66.7%)	19 (52.8%)	17 (47.2%)	
Relapse	5 (9.3%)	4 (12.5%)	1 (4.5%)	0.322
Fever	44 (81.5%)	27 (84.4%)	17 (77.3%)	0.509
Cytopenia	53 (98.1%)	31 (96.9%)	22 (100%)	0.403
Neutropenia < 0.5	15 (27.8%)	11 (34.4%)	4 (18.2%)	0.192
Hyperferritinemia	50 (92.6%)	30 (93.8%)	20 (90.9%)	0.695
Splenomegaly	43 (79.6%)	23 (71.9%)	20 (90.9%)	0.088
Hypertriglyceridemia	46 (85.2%)	25 (78.1%)	21 (95.5%)	0.078
Hemophagocytosis in tissue biopsy	18 (33.3%)	10 (31.3%)	8 (36.4%)	0.695
Hypofibrinogenemia	16 (29.6%)	7 (21.9%)	9 (40.7%)	0.115
CD25	5 (9.3%)	3 (9.4%)	2 (9.1%)	0.972
Hepatomegaly	6 (11.1%)	5 (15.6%)	1 (4.5%)	0.203
Neurological symptoms	21 (38.9%)	8 (25.0%)	13 (59.1%)	0.012
Cardiopulmonary complications	30 (55.6%)	11 (34.4%)	19 (86.4%)	<0.001
Hepatitis	17 (31.5%)	7 (21.9%)	10 (45.5%)	0.067
Skin changes	12 (22.2%)	9 (29%)	3 (13.6%)	0.187
RBC transfusion	29 (53.7%)	14 (43.8%)	15 (68.2%)	0.077
Platelet transfusion	29 (53.7%)	12 (37.5%)	17 (77.3%)	0.004
Response to treatment	32 (59.3%)	31 (96.9%)	1 (4.5%)	< 0.001
Hematological malignancies (HM)	23 (42.6%)	10 (31.3%)	13 (59.1%)	0.042
Cancer (other than HM)	5 (9.3%)	4 (12.5%)	1 (4.5%)	0.332
Autoimmunity	9 (17.0%)	8 (25.0%)	1 (4.8%)	0.055
Age >50 years	40 (74.1%)	20 (62.5%)	20 (90.9%)	0.019
Ferritin >9999 µg/L	29 (54.7%)	15 (48.4%)	14 (63.6%)	0.272
Calendar year before 2018	22 (40.7%)	8 (25%)	14 (63.3%)	0.005
Calendar year since 2018	32 (59.3%)	24 (75%)	8 (36%)	

Characteristics	total	alive	dead	P
Age at HLH diagnosis	61 (22-83)	52.5 (24-79)	69.6 (22-83)	0.002
Diagnose criteria (HLH)	5 (3-7)	5 (3-7)	5 (3-7)	0.997
HScore %	96 (8.8-99.98)	95 (8.8-99.98)	98.07 (25-99.98)	0.246
WBC (3-10.5 G/L)	4.55 (0.06-53.1)	4.27 (0.53-26.1)	4.7 (0.6-53.1)	0.532
Hb (120-168, g/L)	84 (60-133)	84.5 (60-133)	82.5 (64-111)	0.245
Neutrophils (1.60-7.40, G/L)	1.93 (0.09-23.19)	1.97 (0.09-23.19)	1.87 (0.15-9.05)	0.295
Platelet count (150-450 G/L)	51.5 (1-408)	72.5 (7-408)	20.5 (1-236)	0.009
Triglycerides (<1.70, mmol/L)	3.24 (0.60-14)	2.74 (1.0-6.61)	3.57 (0.6-14)	0.274
Fibrinogen (1.75-3.75, gr/L)	2.07 (0.47-7.94)	2.12 (0.56-6.25)	1.51 (0.47-7.94)	0.567
ASAT (<50, UI/L)	181 (17-4860)	163.5 (17-1409)	181 (46-4860)	0.501
ALAT (<50, UI/L)	103 (17-1022)	107 (17-922)	63.5 (17-1022)	0.353
GGT (<60, UI/L)	251 (30-2477)	224 (30-973)	325 (57-2477)	0.213
Alkaline phosphatase (40-129, UI/L)	210 (36-1472)	162 (56-1472)	399.5 (36-1074)	0.017
Ferritin (20-250, µg/L)	11383 (1009-296420)	9349 (1009-103726)	15302 (2296-296420)	0.090

## Abstract ID: 110

### GAS6 and TAM receptors as biomarkers for disease severity in patients with COVID-19

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**Introduction:** COVID-19 patients often develop systemic inflammation and hypercoagulability, leading to an increased thromboembolism risk and a poor evolution. The D-dimer level at the time of hospitalization predicts the risk of acute respiratory distress syndrome development, intensive care admission and death. Identifying additional biomarkers to assist physicians in risk stratification and decision-making processes is of upmost importance. Growth arrest-specific gene 6 (GAS6) is a vitamin K-dependent protein that plays a role in thrombosis, hemostasis, and inflammation and is a ligand for tyrosine kinase

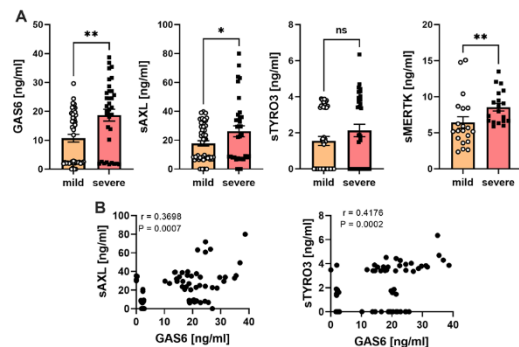
receptors AXL, MERTK & TYRO3 (TAM). AXL has been suggested to be a novel host receptor that promotes SARS-CoV-2 entry into human cells (Cell Research 2021, 31:126-140).

Our goal was to determine if GAS6 and TAM receptors plasma level may be used as biomarker of disease severity in patients with COVID-19 and to assess if there is a correlation between GAS6 and D-dimer levels.

**Methods:** We enrolled a prospective observational single-center study including 110 adult patients with PCR-confirmed SARS-CoV-2 infection from whom blood was collected at pre-specified time points. Plasma concentrations of GAS6 and TAM receptors were determined by ELISA. Furthermore, coagulation parameters were measured in plasma.

**Results:** The patient cohort was scored using the WHO Ordinal Scale for Clinical Improvement 2020 and divided into "mild COVID-19" ( $\leq 4$ ) and "severe COVID-19" ( $\geq 5$ ). Our data showed that plasma Gas6 level significantly increases with the severity of the COVID-19 disease (mild COVID-19:  $10.72 \pm 1.33$  ng/ml vs severe COVID-19:  $18.70 \pm 1.05$  ng/ml). Furthermore, we detected a significant increase in sAXL (mild COVID-19:  $17.80 \pm 1.85$  ng/ml vs severe COVID-19:  $26.14 \pm 3.81$  ng/ml) and sMERTK (mild COVID-19:  $6.42 \pm 0.8$  ng/ml vs severe COVID-19:  $8.55 \pm 0.53$  ng/ml) as well as an increase of sTyro3 by trend (mild COVID-19:  $1.55 \pm 0.25$  ng/ml vs severe COVID-19:  $2.13 \pm 0.35$  ng/ml) (Figure 1B). There was a positive correlation between increasing Gas6 levels and higher sAXL and sTYRO3 levels (Figure 1B). The WHO Ordinal Scale for Clinical Improvement 2020 positive correlated with sMERTK and D-Dimer levels.

**Conclusions:** Gas6, sAXL, sMERTK, sTYRO3 might constitute valid biomarkers to help the clinician to tailor therapy in the assessment of COVID-19 severity in individual patients.



**Figure 1** Increased GAS6 expression correlates with TAM receptors expression in COVID-19 patients. A: Plasma concentration of GAS6 (n=34-46), sAXL (n=34-46), sTYRO3 (n=33-43), sMERTK (n=19-20) in "mild COVID-19" ( $\leq 4$ ) compared to "severe COVID-19" ( $\geq 5$ ) patients. Mann-Whitney U-test. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ . Data are presented as mean  $\pm$  SEM. B: Relationship between sAXL vs. GAS6 and sTYRO3 vs. GAS6. Data analysis by nonparametric Spearman correlation.

## Abstract ID: 141

### Pre-operative anticoagulation management in patients with direct oral anticoagulation (DOAC) therapy

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**Introduction:** Each year countless patients receiving an anticoagulation therapy must undergo surgery. The management of peri-operative anticoagulation is a challenge, also with the use of DOACs. This management is crucial because an error can lead to haemorrhagic or thromboembolic complications as well as the postponing of surgical procedures. The study's primary goal is to assess the pre-operative anticoagulation management in a swiss university hospital according to internal guide-



lines based on the PAUSE study. The secondary aim is to determine the frequency of surgery postponements related to the anticoagulation management.

**Methods:** All patients receiving DOAC for venous thrombosis or atrial fibrillation (AF) that had an elective surgery between January 2019 and December 2020 were included in this study. The anticoagulation management was compared to the PAUSE study. The surgery bleeding-risk was assessed according to the BRIDGE study.

**Results:** A total of 1807 patients were screened and 337 included in the final analysis. The mean age was 73.8 years and most of patients were male (n = 214, 63.4%). The mean CHA2DS2VASC was 3.81 ( $\pm$ 1.60). Patients were receiving rivaroxaban (n = 189, 36.1%), apixaban (31.5%, n = 106), edoxaban (n = 31, 9.2%) and dabigatran (n = 12, 3.6%). Overall, 221 (65.6%) patients did not have a pre-operative anticoagulation management consistent with the PAUSE study. The causes of these non-observances were mostly due to premature (n = 89, 26.4%) or late interruptions (n = 27, 8.0%) or no interruptions at all (n = 20, 5.9%) of the anticoagulation therapy. We also observed non-indicated heparin bridges (n = 54, 16.0%) or indicated heparin (e.g. recent thrombosis) bridges not done (n = 3, 0.9%). The remaining 28 cases (8.3%) did not have enough data to determine the pre-operative anticoagulation management. In addition, 45 (13.4%) patients had their surgery postponed: 12 (3.6%) due to an incorrect preoperative anticoagulation management 15 (4.5%) due to medical or surgical reasons unrelated to anticoagulation and 18 (5.3%) for unknown reasons.

**Conclusions:** This study shows a suboptimal anticoagulation management of patients treated with DOACs undergoing an elective surgery. In addition, we report that a significant number of procedures are postponed due to a suboptimal pre-operative anticoagulation management. Institutional procedures are required to optimise the perioperative management of DOACs.

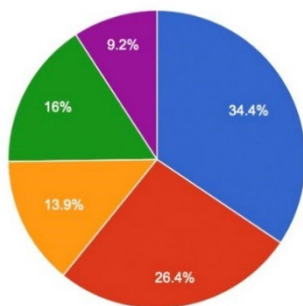


Figure 1 : percentage of the different pre-operative anticoagulation managements  
 Blue : Consistent with PAUSE study  
 Red : premature interruption  
 Yellow : Late interruptions tardives and no interruptions  
 Green : Non-indicated heparin bridging  
 Purple : Indicate heparin-bridging or unknown cause

## Abstract ID: 146

### Single-Center Experience with Emicizumab (Emi) in adult patients with severe Hemophilia A (PwHA): Thrombin generation, Emicizumab-levels and Interventions.

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**Introduction:** By the end of September nearly 100 PwHA are under treatment with Emi, which translates into ~25% of all PwHA (FVIII: <1%) in Switzerland. Emicizumab affects routine coagulation tests and its FVIII-equivalent level is under debate. We hypothesized that assessment of thrombin generation (TG) might be a useful alternative.

**Methods:** Since March 2018, we have switched 17 PwHA (15 adults, 2 children) to a prophylactic treatment with Emi in a standardized way. Plasma samples were withdrawn at baseline, before starting maintenance, at week 12 and then every 6 months.

We documented their annual bleeding rate (ABR) before and bleeding episodes after switching, side effects, assessed Emi plasma levels and TG (ST Genesia®).

Until the end of August 2022, 7 patients underwent 9 surgeries or interventions (3 major/ 3 minor and 3 gastro-/colonoscopies).

**Results:** PwHA switched to Emi treatment were aged 19–54y. While four, including the only high responder inhibitor PwHA in our cohort, had been treated on demand, 11 performed prophylaxis. Their ABR ranged from 0 – >35, and their cardiovascular risk factors from 0–5 (median 0). In the 291 patient months on Emi, we documented 1 spontaneous and 5 traumatic treated bleeds. For all six surgeries hemostatic treatment was given (recombinant activated FVII or factor VIII concentrates). Surgeons rated hemostatic efficacy as excellent and no transfusion of packed red cells was necessary. All patients received subcutaneous prophylactic low molecular heparin. There was one hemorrhage on postoperative day 11 following an ankle operation. Elective gastrocolonoscopies were done without factor replacement. One PwHA received after polypectomy one dose of an extended half-life FVIII concentrate. We have documented no serious adverse events.

A total of 57 blood samples (1–6 samples/ patient) were withdrawn. Emi plasma levels were stable during follow up (mean 52.53, median 51.35, Range 29.7– 75.4 ug/ml) and showed minimal fluctuation within individual patients. In TG/Bleed screen we documented normalized endogenous thrombin potential (ETP) between 23.5 to 115% and TG peak height of 20 – 75.77%. TG parameters were relatively stable within patients, but did not correlate with Emi plasma levels.

**Conclusions:** TG shows large inter-individual differences independently from Emi levels. Further research is necessary to understand inter-individual differences in PwHA on Emicizumab.

## SSH/SSMO POSTER PRESENTATION – EXPERIMENTAL HEMATOLOGY / ONCOLOGY

## Abstract ID: 45

### Single cell genotyping of matched stem/progenitor and mature blood cells in treatment naïve and AZA-treated MDS and CMML reveals significant contribution of mutated clones to blood production

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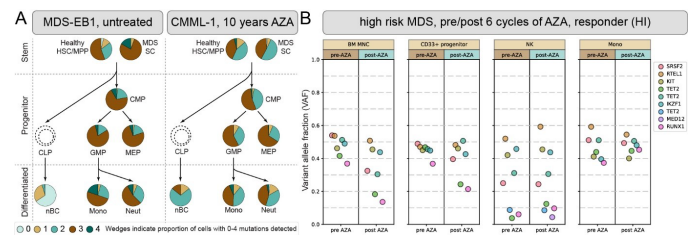
**Introduction:** Myelodysplastic Syndrome (MDS) and Chronic Myelomonocytic Leukemia (CMML) are clonal disorders driven by progressively acquired somatic mutations in hematopoietic stem cells (HSC) and characterized by the accumulation of blasts in the bone marrow and accompanying cytopenias. Hypomethylating agents such as azacitidine (AZA) are used as therapies for high-risk patients who are ineligible or for allogeneic bone marrow transplant. However, it is unclear whether in patients with established MDS; (a) hematopoietic stem and progenitor cells (HSPC) with multiple mutations progress through to mature cells with comparable robustness to their less mutated counterparts, or (b) the improvements in peripheral blood counts following AZA therapy is driven by residual wild-type HSPC.

**Methods:** We index sorted HSPC and mature blood cells (neutrophils (Neut), monocytes (Mono), and naïve B-cells (nBC)) from 3 MDS/CMML patients (1 treatment naïve, 2 treated >10 years with AZA) and performed targeted amplicon sequencing on thousands of single cells (n = 4248). In a second cohort (9 MDS patients; 6 responders, 3 non-responders) we sorted Mono, natural killer (NK) cells, and CD33+ progenitors and measured variant allele fraction (VAF) before and after 6 cycles of AZA.

**Results:** Single cell data showed the proportion of residual wild-type HSCs, and their contribution to mature myeloid cells, was minor (0 – 5.3% of HSCs, 0.3 – 4.5% of mature myeloid cells). Driver mutations were proportionately represented across multiple hematopoietic cell types including, in some cases, lymphoid cell types in vivo, irrespective of AZA treatment. In a second cohort, clonal composition differed slightly between cell types, most notably in NK cells which often harbored lower VAF

frequencies. We also observed treatment-associated reduction of a small subset of mutated alleles. However, in all patients, clonal composition was remarkably similar in pre- and post-AZA samples for all cell types, with highly mutated progenitors making a significant contribution to mature cell types even in patients showing clinical response with reduced blast and improved cell counts.

**Conclusions:** Highly mutated immature cells contribute significantly to mature blood production in MDS and CMML, before and after AZA treatment. AZA therefore is likely to promote output from these resident clones rather than simply eradicating them.



## Abstract ID: 68

### Large pharmacological screen to improve responses to dual PI3K/BCL2 inhibition in lymphomas

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**Introduction:** Copanlisib, a pan-PI3K inhibitor with stronger activity against the alpha and delta isoforms, is FDA approved for the treatment of patients with relapsed or refractory follicular lymphoma, and it has shown clinical activity in other indolent lymphomas including marginal zone lymphoma (MZL). Preclinical studies have demonstrated strong synergism of copanlisib and BCL2 inhibitor venetoclax in different lymphomas. A phase 1 study has explored this specific combination (NCT03886649 / SAKK 66/18), while others have explored similar schemes based on dual PI3K and BCL2 targeting. Here, we present the data from a large pharmacological screen with 1443 compounds in a MZL model with secondary resistance to the copanlisib/venetoclax (CO/VE) combination.

**Methods:** CO/VE-resistant cells were exposed to DMSO or a library of FDA-approved compounds at 5µM dose, as single or in combination with 1nM copanlisib + 50nM venetoclax for 72 hours (hr). Spatial and intra- and inter-plates effects were corrected. Values were then DMSO-normalized. Compounds giving cell viability <30% as single agent or improving combination (cell viability <50%, ratio combo/single <0.7) were selected. Synergy of combinations was evaluated according to the Chou-Talalay combination index (CI) and to the MuSyC algorithm.

**Results:** The screen identified 82 highly active compounds and 99 drugs improving the response to CO/VE. These inhibitors targeted WNT, CDK, HDAC, HSP, PLK, ALDH1, AURKA, proton pump and microtubule polymerization, among others. A selection underwent further validation experiments in parental and resistant upon CO/VE. Addition of the ALDH1 inhibitor disulfiram was beneficial in both parental and resistant cells, but espe-

cially in the latter condition with improved synergy and enhanced CO/VE efficacy, overcoming the resistance. Combinations with ganetespib (HSP90), rigosertib (PLK), panobinostat (HDAC), alisertib (AURKA) and AZ1602 (WNT) were beneficial either in parental and resistant cells and improved the sensitivity to copanlisib/venetoclax in resistant cells.

**Conclusions:** In conclusion, a large pharmacological screen has identified a series of compounds that could be added to CO/VE in a triple combination or used in patients developing CO/VE resistance. Further experiments are on-going to extend the findings to additional PI3K/BCL2 inhibitors.

#### Abstract ID: 81

### In-depth analysis of CD34pos hematopoietic stem and precursor cell (HSPC) subpopulations by flow cytometry using a single 20-color panel

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**Introduction:** Haematopoiesis was the first system for which a tissue-specific stem cell was identified, the haematopoietic stem cell (HSC). It was thought at the beginning that CD34pos cells corresponded to these HSC, but in recent years it became clear that the CD34pos cell population is heterogenous and contains subpopulations of different precursor cells (HSPC) with only <1% corresponding to real HSC, as evidenced by in vivo mouse transplantation assays.

Based on multicolor flow cytometry (MFC) with a 20-marker combination in a single tube we performed an in-depth study of the HSPC CD34pos cell compartment in normal bone marrow (BM) samples and in AML patients with the aim to develop an analysis pipeline for application in routine diagnostics.

**Methods:** BM samples were obtained from 7 normal donors, 10 AML patients at diagnosis, 17 follow-up samples after chemotherapy and/or BM transplantation (4 MRD pos; 13 MRD neg), and 13 samples from other diseases. Samples were stained with a 20-color antibody panel and were analyzed on a full spectrum flow cytometer (Northern Lights, Cytex). 1-1.5 x10<sup>6</sup> events were acquired. Files were analyzed using the Kaluza and Cytobank software (Beckman Coulter).

**Results:** 8 different CD34pos HSPC subpopulations were defined corresponding to HSC and multipotent progenitors, common myeloid progenitors (CMP), lymphoid, myeloid, monocytic, erythroid, megakaryocytic and pDC precursors, respectively. Reference values for these subpopulations in normal BM samples were determined. Analysis of AML samples at diagnosis revealed as yet unsuspected heterogeneity in the leukemic blast populations. Analysis of samples after chemotherapy or BM transplant allowed to analyze reconstitution of the HSPC compartment and the presence or absence of MRD, down to a sensitivity level of 0.01%. Unsupervised analysis of the data files based on dimensionality reduction (t-SNE) and clustering algorithms (FlowSOM) were used to establish a robust analysis pipeline.

**Conclusions:** Quantification of MRD after therapy is increasingly used for risk stratification, prognostication and evaluation of treatment efficiency in hematologic diseases. Using a single 20-color antibody panel and unsupervised clustering **Methods:** for the detection of HSPC subpopulations, we established an analysis pipeline for follow-up of AML patients which allows us to measure HSPC reconstitution and MRD after treatment.

#### Abstract ID: 101

### Identification of susceptibility to macrophage-based therapies in acute myeloid leukemia

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**Introduction:** CD47 is a "don't eat me" signal highly expressed on acute myeloid leukemia (AML) cells that binds SIRP $\alpha$ , a receptor expressed by macrophages, leading to phagocytic tolerance. Consequently, blocking the CD47-SIRP $\alpha$  interaction leads to the elimination of AML cells by macrophages, a concept currently evaluated in clinical trials. Studies have shown that upregulation of the pro-phagocytic signal calreticulin (CALR) can synergize with CD47 blockade. Therefore, we used the pharmacoscopy-based ex vivo drug screening approach, a high-throughput automated fluorescence microscopy platform, to identify compounds that can modulate innate immune checkpoint expression and act synergistically with CD47 blockade in AML cells.

**Methods:** For in vitro assessment, we performed a phagocytosis assay using human cord blood-derived monocyte differentiated macrophages and an AML cell line (NOMO-1). For in vivo validation, we transplanted NOMO-1 cells into MISTRG mice, and treatment with the compounds mentioned below was performed. Blood, bone marrow (BM), and spleen were analyzed using flow cytometry.

**Results:** Pharmacoscopy identified alisertib, an Aurora A kinase inhibitor, to increase the expression of CALR and CD47 on AML cells. To determine the synergy of alisertib with the clinically investigated anti-CD47 antibody magrolimab, we performed an in vitro phagocytosis assay. Alisertib, in combination with magrolimab, synergized to enhance the phagocytosis of AML cells. To validate our in vitro findings, we transplanted NOMO-1 cells into MISTRG mice to generate a human AML graft. Mice treated with alisertib were given 30 mg/kg daily with oral gavage for 21 days, while 100  $\mu$ g of magrolimab was injected intraperitoneally for 14 consecutive days. For the alisertib-magrolimab combination treatment, mice were first treated with alisertib and then both compounds for two weeks. The alisertib/magrolimab combination significantly reduced NOMO-1 engraftment in the BM, the peripheral blood, and the spleen compared to the single compounds.

**Conclusions:** Our in vitro and in vivo results show that alisertib is a promising candidate to further investigate in combination with CD47 blockade in AML. Importantly, alisertib, combined with intensive chemotherapy, showed promising activity in high-risk AML patients in a phase II clinical trial (Garcia-Manero, Lancet, 2022), supporting further investigation of this compound.

**Abstract ID: 103****Targeting PI3K signaling is a potential therapeutic strategy in Clear Cell Sarcoma**

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**Introduction:** Clear cell sarcoma (CCSA) is a rare and highly malignant soft tissue sarcoma, characterized by the expression of an oncogenic fusion proteins, either EWSR1-ATF1 or EWSR1-CREB1. CCSA is notoriously resistant to systemic therapy. We therefore aimed at identifying novel therapeutic approaches by performing an unbiased, high-throughput functional compound (cpd) screen.

**Methods:** We used a library of 960 candidate kinase modulators to screen two CCSA cell lines for reduction of viability, compared to a human fibroblast control cell line. Cell survival after drug exposure for 72 hrs was assessed using a resazurin read-out. The most promising cpds were validated extensively in vitro, by long-term proliferation assays, IC50 determination, apoptosis and autophagy assays. Additionally, in order to discover the potential target pathways of the two most promising cpds, we used ProteomeProfiler™ Human Phospho-Kinase Array membranes. To permit future in vivo validation, we have established xenograft models of CCSA in BALB/c nude mice.

**Results:** High-throughput screening identified 14 cpds with the desired effect pattern, of which we have validated 10 with the strongest effect using long-term proliferation assays. A more extensive in vitro validation was then performed on 4 cpds on multiple CCSA cell lines and other malignancies as controls, using IC50 determination, apoptosis and autophagy experiments. Those experiments robustly validated the results from the screen but showed that neither apoptosis nor autophagy are responsible for the observed reduction in CCSA cell survival. The phospho-kinase array showed multiple up- and down regulated kinases pointing at multiple involved signaling pathways with the most intriguing finding in PI3K-signaling. Further investigation showed that several PI3K/AKT/mTOR pathway inhibitors significantly impact on CCSA cell survival.

**Conclusions:** We have successfully performed and extensively validated an unbiased high-throughput cpd screen, which has identified several potential drug candidates. Investigation into the mode of action has pointed at a potential involvement of PI3K-signaling and CCSA cell lines are sensitive to pharmacologic inhibition of PI3K/AKT/mTOR signaling. Those observations will next be validated in in vivo experiments in our established CCSA xenograft models.

**Abstract ID: 113****Human pegivirus-1 replication is associated with impaired NK cell reconstitution after allogeneic haematopoietic stem cell transplantation**

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**Introduction:** Human pegivirus-1 (HPgV-1) is a commensal virus for which no known associated organ disease has been found to date. Yet, it displays an immunomodulatory role previously studied in the HIV population, in whom active co-infection with

HPgV-1 can modulate T and NK cell activation and differentiation leading to a protective effect against the evolution of the disease. Little is known on the immunomodulatory effect of HPgV-1 in allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients, a patient population in which high prevalence of HPgV-1 replication has been reported. The aim of this study was to compare the immune reconstitution after allo-HSCT among HPgV-1-viremic and HPgV-1-non-viremic patients.

**Methods:** 20 allo-HSCT recipients positive in plasma sample for HPgV-1 by rRT-PCR during the first year (1, 3, 6, 12 months) after transplantation were matched with 20 allo-HSCT recipients negative for HPgV-1. T and NK cell reconstitution was monitored by flow cytometry and IL7 was quantified in plasma samples using the LEGENDplex HSC assay

**Results:** We observed no significant difference in the absolute number and subsets proportions of CD4 and CD8 T cells between patient groups at any analysed timepoint. We observed a significantly higher absolute number of NK cells at 3 months among HPgV-1-viremic patients. Immunophenotypic analysis showed a significantly higher proportion of CD56bright NK cells mirrored by a reduced percentage of CD56dim NK cells in HPgV-1-positive patients during the first 6 months after allo-HSCT. At day 30, HPgV-1-viremic allo-HSCT recipients displayed higher IL-7 plasma levels compared to HPgV-1-non-viremic patients. At 6 months post-allo-HSCT, NK cell phenotype significantly differed depending on HPgV-1, HPgV-1-viremic patients displaying NK cells with lower CD16 and CD57 expression compared with HPgV-1-negative patients. In accordance with their less differentiated phenotype, we detected a reduced expression of granzyme B in NK cells in HPgV-1-viremic patients at 6 months.

**Conclusions:** Our study shows that HPgV-1-viremic allo-HSCT recipients displayed an impaired NK cell, but not T cell, immune-reconstitution compared with HPgV-1-non-viremic patients, revealing for the first time a potential association between replication of the non-pathogenic HPgV-1 virus and immunomodulation after allo-HSCT.

**Abstract ID: 114****anti-CD117 CAR T-cells in in vitro models of Advanced Forms of Systemic Mastocytosis**

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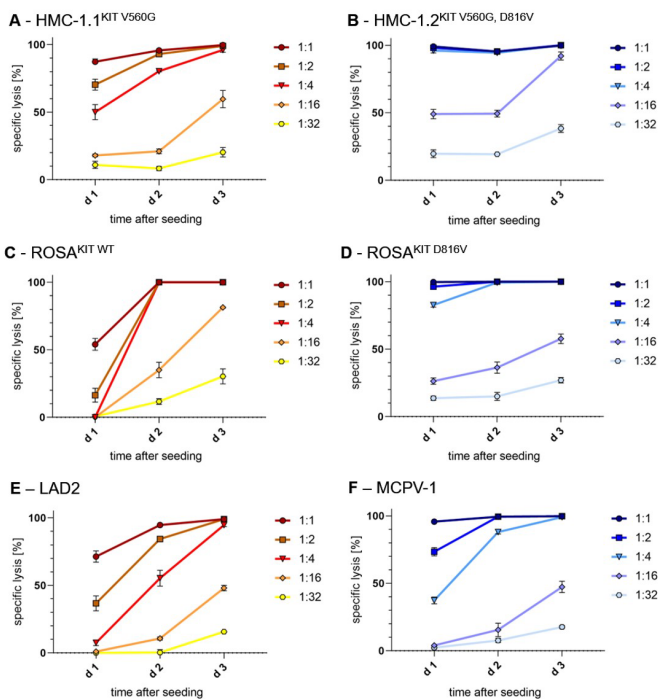
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**Introduction:** Mastocytosis is a malignant disease resulting from oncogenic transformed mast cells. More than 80% of malignant cells harbor a D816V mutation in the KIT-receptor (CD117), leading to constitutive kinase activation and proliferation and survival of mast cells. Advanced forms of mastocytosis (aggressive systemic mastocytosis: ASM, systemic mastocytosis with associated hematological disease: SM-AHN, mast cell leukemia: MCL) present as a therapeutic challenge. Although the recently approved poly tyrosine kinase inhibitors Midostaurin and Avapritinib lead to reduction of mast cell infiltration and consecutive organ failure, the only available curative approach so far is conditioning poly-chemotherapy followed by allogeneic stem cell transplantation (allo-HSCT). However, allo-HSCT is associated with substantial side-effects and, also due to high rates of relapse, only leads to an overall survival of 43% for ASM and 17% for MCL after three years. Thus, better therapeutic options are needed. Recently, we demonstrated that CD117 (KIT-receptor) positive human AML can be efficiently eradicated by anti-CD117 CAR T-cells in vitro and in vivo (Myburgh et al., Leukemia 2020). As mast cells, and also transformed mast cells, highly express CD117, we here tested if anti-CD117 CAR T-cells would equally efficiently eliminate this malignant cell population.

**Methods:** Established mast cell lines (partly harboring the oncogenic driver mutation KIT D816V) were co-cultured with anti-CD117-CAR T-cells in various effector to target ratios and up to 28 days of co-culture in vitro.

**Results:** After three days of co-culturing, the tumor cells were effectively killed up to an 1:4 effector to target ratio. Also, within 28 days of co-culture, the longest time followed in vitro, tumor cells were controlled and did not outgrow. Increased proliferation of anti-CD117-CAR T-cells in the presence of mast cells was observed and tracked throughout the 28-day experiment.

**Conclusions:** In conclusion, we demonstrate that the human mast cell lines HMC-1.1, HMC-1.2 KIT D816V, ROSA KIT WT, ROSA KIT D816V, LAD2 and MCPV-1 can be efficiently targeted and killed in vitro by allogeneic anti-CD117-CAR T-cells. Given that CD117 is expressed on healthy hematopoietic stem and progenitor cells (HSPCs) on a substantially lower level, there might be a therapeutic window for anti-CD117 immunotherapy in advanced forms of mastocytosis.



**Figure:** Specific lysis [in %] of given mast cell lines by anti-human CD117 CAR T-cells with differing effector to target ratios on three consecutive days. Data shows one experiment with CAR T-cells generated from one healthy donor. Experimental set up repeatedly performed with CAR T-cells independently generated with T-cells of three healthy donors each in triplicates.

## Abstract ID: 115

### Unraveling HRDness and therapeutic opportunities in sarcoma

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**Introduction:** Defects in homologous recombination repair (HRR) in tumours correlate with poor prognosis and metastases development. Determining HRR deficiency (HRDness) is of major clinical relevance as it is associated with therapeutic vulnerabilities and remains poorly investigated in sarcoma. Sarcomas are rare mesenchymal cancers, accounting for approximately

1% of all malignancies. Standard of care mostly relies on chemotherapy but sarcoma often show chemoresistance and metastatic disease is associated with a poor prognosis. There is an increasing emphasis on understanding the cancer biology of individual sarcoma subtypes to inform the development of personalized targeted treatment approaches.

**Methods:** We investigated genomic and transcriptomic features of HRDness in sarcoma and cross-validated our findings from different sarcoma subtypes among several datasets both publicly available and generated by us. We established and molecularly profiled eight patient-derived ex vivo sarcoma cell models. We functionally tested the sensitivity of our models to several targeted therapies including PARPi as gold standard treatment for HRDness and chemotherapies in six-point dose response curves either in monotherapy or in combination.

**Results:** We show that specific sarcoma entities exhibit high levels of genomic instability signatures and molecular alterations in HRR genes, while harbouring a complex pattern of chromosomal instability. Furthermore, sarcomas carrying HRDness traits exhibit a distinct SARC-HRD transcriptional signature that predicts PARPi sensitivity in patient-derived sarcoma cells. Concomitantly, HRDhigh sarcoma cells lack RAD51 nuclear foci formation upon DNA damage, further evidencing defects in HRR. We further identify the WEE1 kinase as a therapeutic vulnerability for sarcomas with HRDness and demonstrate the clinical benefit of combining DNA damaging agents and inhibitors of DNA repair pathways ex vivo and in the clinic.

**Conclusions:** We show that a subset of sarcoma entities exhibit features of HRDness at the genomic and transcriptomic level and highlight the need to characterize sarcoma patients with multiple parameters to better identify those with HRDness. In summary, we provide a personalized oncological approach to treat sarcoma patients successfully.

## Abstract ID: 120

### ULK1 inhibition preferentially targets Germinal Centre B-cell Lymphoma subtype by attenuating autophagy, C-MYC and inflammation

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**Introduction:** Two major subsets of Diffuse Large B-cell Lymphomas (DLBCL) are Germinal Centre B-cell (GCB) and Activated B-cell (ABC) lymphomas. Ibrutinib (Bcr Tyrosine Kinase inhibitor) demonstrated moderate activity in ABC tumours harbouring B-cell receptor mutations with concomitant MYD88 aberrations, unlike GCB. Differing molecular mechanisms promote PI3K-mTOR signalling leading to metabolic stress. Autophagy promotes nutritional adaptation and contributes to drug resistance using ULK1-dependent autophagy. We hypothesize autophagy facilitates cytoprotection and contributes to R-CHOP and Ibrutinib resistance in GCB DLBCL. Combination treatment with Ibrutinib and ULK1 inhibitor would be a strategic method to impair these oncogenic functions.

**Methods:** Gene set enrichment analysis (GSEA), Kaplan-Meier curves and X-Tile software enabled analysis of gene signatures and overall survival (OS) of transcriptomic data (NCT01324596). Colony formation, immunoblotting and RNA-sequencing characterized the effects of ULK1 inhibitor (MRT68921).

**Results:** Multiple autophagy-related-genes within the ULK1 complex (ULK1, RB1CC1 and ATG13) and VPS34 complex (AMBRA1, PI3K3C3, PIK3R4 and USO1) correlated with worse

OS in GCB patients treated with R-CHOP. Gene-overlapping analysis showed ULK1 complex was highly expressive ( $p = 0.0403$ ) and positively correlated with poor treatment outcome ( $p = 0.0030$ ). Multiple DLBCL cell lines were substantially autophagy dependent. Ibrutinib treatment enhanced autophagic flux in GCB cell lines. MRT68921 augmented the anti-tumour activity of Ibrutinib in several GCB cell lines. ULK1 inhibitors: MRT68921/ULK1-101 induced acute NF- $\kappa$ B activation in DLBCL lymphoma lines irrespective of their NF- $\kappa$ B mutational status. RNA-sequencing and GSEA of GCB and ABC cell lines treated with MRT68921, or vehicle reported diverse ULK1 inhibitory signalling pathways. Oci-Ly1 (GCB) treated cells significantly downregulated genes associated to PI3K-mTOR activity, metabolism, and cytokinesis. Immunoblotting data confirmed downregulation of c-MYC transcriptional activation/ pathway. In contrast, Oci-Ly3 (ABC) treated cells upregulated genes in JAK-STAT, inflammation, and apoptosis.

**Conclusions:** Our study provides a rationale to target ULK1 in GCB patients. Autophagy inhibition sensitised Ibrutinib *in vitro* by targeting metabolic pathways and inflammation. Early autophagy genes may provide prognostic value.

#### Abstract ID: 121

### Increased CIP2A-TOPBP1 interaction and filament formation in BRCA deficient mitotic breast- and ovarian cancer cells

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**Introduction:** Breast cancer (BC) is the most common (24.5%) and ovarian cancer (OC) the deadliest cancer in women. Germline mutation in BRCA1/2 gene predisposes individuals to develop BC and OC with a more aggressive tumor biology and a poor prognosis. Loss of function mutations in BRCA1/2 result in sensitivity to PARP inhibitors, but these drugs have a high non-response rate and drug resistance develops rapidly. Thus, combination strategies are urgently needed to improve patient outcome. Similar to PARP, CIP2A shows strong, albeit different, synthetic lethality in BRCA 1/2 deficient cells.

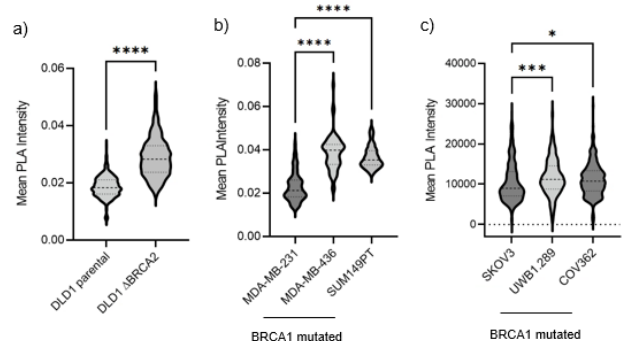
CIP2A forms a complex with the DNA damage response factor TOPBP1 and both proteins form filamentous structures of unknown functions in mitotic cells. CIP2A-TOPBP1 prevents lethal mis-segregation of acentric chromosomes, which is especially vital in the absence of homologous recombination. The expression level of CIP2A was shown to correlate with BC aggressiveness and CIP2A is essential for the induction of basal-like triple-negative BC in mice. Inhibition of both PARP and CIP2A might constitute a possibility for orthogonal therapy in BRCA 1/2 deficient cancers.

**Methods:** The CIP2A-TOPBP1 interaction and the prevalence of CIP2A-TOPBP1 filaments was quantitatively assessed in engineered parental and BRCA2 knock-out ( $\Delta$ BRCA2) colorectal adenocarcinoma (DLD1) as well as in BRCA1 deficient and BRCA1 proficient (wt) BC and OC cell lines using proximity ligation assay (PLA) and immunofluorescence, respectively. Microscopic images were analyzed with ImageJ.

**Results:** We show a significantly higher interaction of CIP2A-TOPBP1 in  $\Delta$ BRCA2 DLD1 cells (DLD1 parental mean PLA intensity 0.0186 a.u. vs. 0.0289 a.u.,  $p < 0.0001$ , in DLD1  $\Delta$ BRCA2). We also measured significantly increased PLA signals in BRCA1 deficient BC (mean PLA intensity of BRCA 1 wt BC MDA-MB231 0.0212 a.u. vs. 0.0398 a.u. and 0.0352 a.u.,  $p < 0.0001$  each, in BRCA mutated BC MDA-436 and SUM149PT, respectively), and OC cell lines (mean PLA intensity BRCA wt OC SK-OV3 10530 a.u. vs. 11780 a.u.,  $p = 0.0001$ , and 11156 a.u.,  $p = 0.0106$ , in BRCA mutated OC UWB1.289 and COV362, respectively).

CIP2A-TOPBP1 filaments are more prevalent in BRCA1 deficient BC and OC cells compared to BRCA1 wt cells.

**Conclusions:** Our results suggest that increased CIP2A-TOPBP1 interaction and filament formation in BRCA deficient mitotic cells may be used as a biomarker for BRCAness in BC and OC.



**Figure 1:** Proximity ligation assay (PLA) of engineered parental and  $\Delta$ BRCA2 colorectal adenocarcinoma (DLD1) (a), three BC- (b) and three OC cell lines (c), using primary antibodies against CIP2A and TOPBP1. MDA-MB-231 and SKOV3 are BRCA1 wild type, MDA-MB-436, SUM149PT, UWB1.289 and COV362 are BRCA1 mutated. Pooling of two independent experiments each and quantification of PLA intensity [a.u.].

#### Abstract ID: 127

### Significance of the Src homology 2 domain-containing phosphatase SHP2 in engaging MAPK pathway activation in myeloproliferative neoplasms

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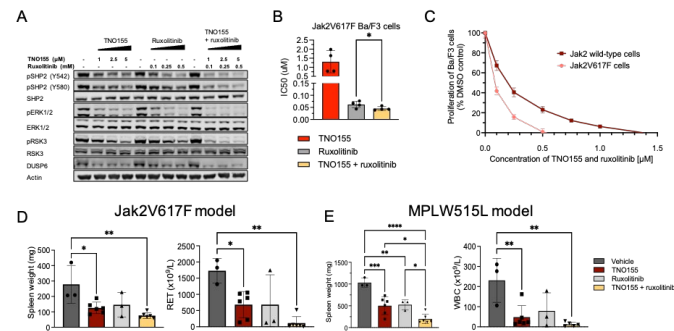
**Introduction:** Myeloproliferative neoplasms (MPN) are myeloid malignancies with somatic JAK2, CALR or MPL mutations and constitutive activation of JAK2 signaling. JAK2 inhibitors show limited efficacy due to residual MAPK pathway activation. The molecular connection of JAK2 and MAPK pathway in MPN is not fully clarified. We study the role of SHP2, a protein tyrosine phosphatase involved in MAPK activation in other tyrosine kinase-driven malignancies, and assess its therapeutic potential.

**Methods:** SHP2 was depleted by shRNA induced knockdown in Ba/F3 cells stably expressing Jak2V617F or wildtype Jak2. For SHP2 inhibition TNO155 and IACS13909 were used. Translational potential of JAK2/SHP2 inhibition was studied in Jak2V617F and MPLW515L mouse models.

**Results:** SHP2 was expressed at substantial levels in MPN cells including SET2, UKE-1 and Jak2V617F Ba/F3 cells. SHP2 knockdown reduced activation of MAPK pathway kinases including MEK, ERK and RSK as well as MAPK downstream effectors as DUSP6. SHP2 inhibition with TNO155 or IACS-13909 analogously interfered with MAPK activation and effector expression and effects were most pronounced when JAK2 inhibition by ruxolitinib and SHP2 inhibition were combined (A). MPN cell proliferation was inhibited at significantly lower IC50 when combining ruxolitinib with TNO155 or IACS-13909 compared to ruxolitinib as single agent (B). Since inhibition of wildtype haematopoiesis is a concern, anti-proliferative activity of JAK2/SHP2 inhibition was assessed in cells with wildtype Jak2, which showed more modest inhibition (C). In a Jak2V617F mouse model, the SHP2 inhibitor TNO155 mediated corrective effects on MPN phenotype including splenomegaly, erythrocytosis and leucocytosis within a week. Of note, TNO155 as single agent showed similar effects as ruxolitinib at tolerable doses, while combined JAK2/SHP2 inhibition enhanced efficacy. In a

MPLW515L mouse model with extensive leucocytosis, JAK2/SHP2 inhibitor treatment promptly normalized leukocyte counts which is not seen to this extent with ruxolitinib (D-E).

**Conclusions:** Our findings suggest a significant role of SHP2 function in MPN given enhanced MAPK suppression and corrective effects upon SHP2 targeting in MPN models. Further studies will delineate the involvement of phosphatase vs. non-phosphatase functions and address the potential of JAK2/SHP2 inhibition as therapeutic approach in MPN.



**Figure 1. Targeting SHP2 in vitro and in vivo suggests functional role in MPN.**  
A Cell signalling analysis of SHP2 and downstream effectors in the MAPK pathway with JAK2V617F BaF3 cells treated with TNO155 and ruxolitinib as single agents and in combination. B IC<sub>50</sub> overview for TNO155 and ruxolitinib as single agents and in combination in JAK2V617F BaF3 cells. C Proliferation curve for JAK2V617F vs JAK2 wild-type BaF3 cells using the combination of TNO155 and ruxolitinib. D Spleen weight and reticulocyte reduction in the JAK2V617F mutant mouse model after one week of treatment. E Spleen weight and white blood cell count reduction in the MPLW515L mutant mouse model after one week.

## Abstract ID: 136

### SMAD1 is a silenced tumor suppressor in AML with MLL rearrangement

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**Introduction:** Rearrangements, of the Mixed Lineage Leukemia 1 (MLL1) gene in hematopoietic stem and progenitor cells cause leukemias of myeloid and lymphoid origin. MLL1 is a histone lysine-methyltransferase, acts as an epigenetic gene expression

regulator and plays an important role in hematopoiesis. Due to aberrant function and protein complex formations of MLL fusion proteins (MLL-FPs) the expression of target genes is dysregulated. Upregulation of genes such as the leukemogenic HOX family members and MEIS1 was shown to be critical for initiation and sustainment of MLLr leukemias. SMAD1, which is part of the TGF- $\beta$  and BMP signaling axes, was previously described as a tumor suppressor in Diffuse Large B-cell Lymphoma (Stelling et al.). Here we aimed to unravel the role of MLL-FPs in SMAD1 downregulation and to identify the tumor suppressive potential of SMAD1 in MLLr AML.

**Methods:** In MV4-11 cells we used the CRISPR/Cas9 system to generate a MLL-FP knockdown (KD) and lentiviral transduction to introduce a SMAD1 overexpression cassette. Moreover, we used cord blood (CB) derived cells carrying a typical MLL fusion gene introduced by CRISPR/Cas9 technology (Secker et al.). We used RT-qPCR and Western Blot to analyze RNA and protein levels. For in vivo studies we used an orthotopic xenograft NSG mouse model.

**Results:** We observed that the expression of the transcription factor Mothers Against Decapentaplegic Homolog 1 (SMAD1) is markedly lower compared to other subtypes of AML in the bone marrow and blood of MLLr Acute Myeloid Leukemia (AML) patients. KD of the MLL-FP in SMAD1 negative MV4-11 cells led to a rescue of SMAD1 mRNA and protein levels. Vice versa, in MLL-FP carrying CB cells SMAD1 expression was nearly abolished compared to normal CB. Overexpression of SMAD1 caused a TGF- $\beta$  dependent growth disadvantage and cell cycle arrest in vitro. In the orthotopic model SMAD1 overexpressing cells displayed reduced engraftment in bone marrow and spleen compared to the control. Notably, the overexpression of SMAD1 decreased HOXA9 and MEIS1 mRNA levels, which was enhanced by TGF- $\beta$  treatment.

**Conclusions:** This data suggests that MLL-FPs are involved in the observed loss of SMAD1 expression and that SMAD1 has a tumor suppressive function in MLLr AML. Together this indicates that SMAD1 loss indirectly contributes to the leukemogenesis of MLLr AML.

## SSH/SSMO POSTER PRESENTATION – CLINICAL HEMATO-ONCOLOGY

### Abstract ID: 10

#### Multi-system Langerhans cell histiocytosis (MS-LCH): Clinical resistance associated with class 3 MAP2K1 (MEK1) Mutation in adult patients

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**Introduction:** Langerhans cell histiocytosis (LCH) in adults is rare (incidence of 1-2/1 million/per year). Data for clinical care is mainly limited to case studies. Understanding the key role of alterations of the MAPK signaling pathway as driver of LCH clonality lead to the successful use of BRAF/MEK inhibitors in LCH. However, certain alterations of the MAPK-Signaling pathway seem to be associated with a poorer clinical response. We

describe 3 cases of MS-LCH with a class 3 MAP2K1 (MEK1) mutation showing a poor response to multiple lines of systemic treatment.

**Methods:** We analyzed 8 patients (pts) with MS-LCH treated since 2014, with 3 showing a class 3 MAP2K1 (MEK1) mutation (p.E102\_I103del). Testing for somatic mutations included immunohistochemistry (IHC) for BRAF V600E (mutation specific antibody), phospho-ERK (indicative of pathway activation) and mutation analysis using Sanger Sequencing, allele-specific PCR and targeted next generation sequencing (NGS) using a custom lymphoma/histiocytosis panel (including ARAF, BRAF, HRAS, KRAS, MAP2K1, NRAS) and/or the OncoPrint Comprehensive Assay v3 (additionally including MAP2K2, MAP2K4, MAPK1).

**Results:** Characteristics of the 8 MS-LCH pts are shown in detail in Table 1. From 3 pts with class 3 MAP2K1 (MEK) mutation, 2 pts received 3 lines of systemic therapy (including cytotoxic and targeted therapy) with long-term treatment, 1 patient 2 lines plus local treatment for a single bone lesion. In comparison, in 5 pts with non class 3 MAP2K1 Mutation, 4 patients remain well controlled with 1st line therapy and only 1 patient received 2 lines.

**Conclusions:** Inhibition of the MAPK/ERK-signaling pathway is an effective treatment in LCH, but certain mutations are likely associated with poor clinical response. Class 3 MAP2K1 p.E102\_I103del mutation is located in exon 3, encoding the autoregulatory domain and the catalytic core of MAP2K1 (also called MEK1) and has been shown to be kinase-activating. Our cases demonstrate that cases with this mutation seem to respond worse to different lines of therapy, including targeted therapy (MEK-Inhibitors). All 3 cases were progressing following standard 1st therapy with cytotoxic regimens and targeted therapy, while in the internal reference group the disease was well controlled with 1st line therapy in 4/5 patients. A better understanding of the pathobiology and targeted therapy is highly needed in adult patients with MS-LCH.

**Table 1: Characteristics of MS-LCH-Patients with class 3 MAP2K1 (MEK1)-mutation vs non-class 3 MAP2K1 (MEK1)-mutation**

	class 3 MAP2K1 (MEK1)-mutation (p.E102_I103del)	non-class 3 MAP2K1 (MEK1)-mutation*
Patients	3	5
Sex		
male	3	3
female	-	2
Age at diagnosis	46 years (35-57)	45.6 years (26-76)
Affected Organ Systems		
Bones	3	4
Lung	2	2
LN	2	1
CNS	1	1
Skin	1	2
Liver	-	1
Bone Marrow	-	1
Treatment		
Cytarabine	3	2
Cladribine	2	-
Hydroxyurea	3	-
BRAF-inhibitor	-	1
MEK-inhibitor	3	1
Local Triamcinolon Injection	1	-
Radiotherapy	1	1
Watch&wait	-	1
Lines of systemic treatment		
1 Line	-	2
2 Lines	1	1
3 Lines	2	-

Abbreviations: LN: Lymphnodes, CNS: Central Nervous System  
 \* -Mutations of 5 patients with non-class 3 MEK mutation in detail: (BRAFV600E: 2/5, atypical BRAF mutation: 1/5, unknown or negative: 2/5)

**Abstract ID: 18**

**Effect of pharmacokinetics and pharmacogenomics in adults with Allogeneic Hematopoietic Cell Transplantation conditioned with Busulfan**

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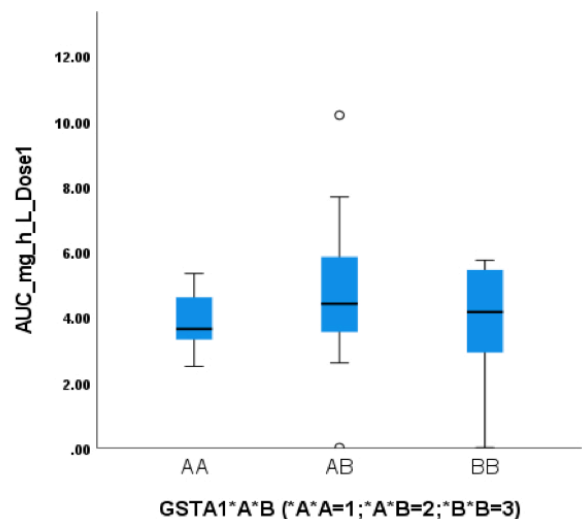
Zurich, <sup>6</sup>Division of Oncology, Hematology and Transfusion Medicine, Cantonal Hospital Aarau, Aarau

**Introduction:** Busulfan (Bu) and cyclophosphamide (Cy) is a commonly used myeloablative conditioning regimen for allogeneic hematopoietic cell transplantation (allo-HCT). There is inter-individual variability of Bu-pharmacokinetics (PK) and hence in toxicity and efficacy. The **Introduction** of therapeutic drug monitoring (TDM) of Bu has decreased toxicity of the regimen. Hepatic metabolism of Bu is mediated through Glutathione-S-Transferase (GST). Patients with GSTA1\*A haplotype are considered rapid metabolizers and GSTA1\*B corresponds to poor metabolism, though most studies have been done in pediatric population. Pharmacogenomic (PG) analysis may therefore be useful predicting the efficacy or toxicity of chemotherapy in the adult population.

**Methods:** The aim of the study was to explore the correlation between GSTA1 variants and Bu-PK in 60 adult patients receiving an allo-HCT from BuCyBu clinical study (ClinicalTrials.gov ID NCT01779882). DNA samples prior to conditioning were genotyped for variants in GSTA1.

**Results:** A total of 33% patients were GSTA1\*A\*A, 49% GSTA1\*A\*B and 18% GSTA1\*B\*B. In GSTA1\*A\*A patients, median Bu-AUC was 3.6 +/- 0.7 mg\*h/L, in GSTA1\*A\*B 4.5 +/- 1.6 and in GSTA1\*B\*B 4.9 +/- 1.4 (AUC 35% higher than GSTA1\*A\*A, p = 0.03, Figure 1), with a similar significant correlation with Bu-clearance (p = 0.04). This correlation remained significant in multivariate linear regression analysis. There was a trend for lower treatment-related mortality (TRM) in patients with low AUC. We could not demonstrate a correlation with TRM, acute graft-versus-host disease (aGvHD) and PG in this small cohort of adult patients, though there is a trend of higher aGvHD cumulative incidence in GSTA1\*A\*B patients.

**Conclusions:** PG adds to TDM in terms of safety and effectiveness in intensive chemotherapy regimens.





## Abstract ID: 31

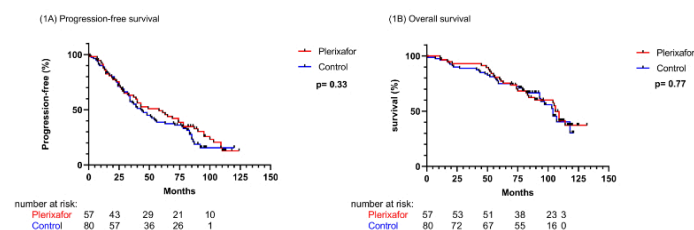
**Long-term safety of the stem cell releasing compound plerixafor for peripheral stem cell collection in myeloma patients**M. Maechler<sup>1</sup>, U. Bacher<sup>2</sup>, M. Daskalakis<sup>2</sup>, M. Nagler<sup>3</sup>, H. Nilius<sup>3</sup>, B. Jeker<sup>1</sup>, T. Pabst<sup>1</sup><sup>1</sup>Department of Oncology, Inselspital, Bern, <sup>2</sup>Department of Hematology, Inselspital, Bern, <sup>3</sup>Center for Laboratory Medicine, Inselspital, Bern

**Introduction:** Myeloma patients considered fit for autologous stem cell transplantation (ASCT) receive repetitive administration of granulocyte-colony stimulating factor (G-CSF), eventually together with chemotherapy, for peripheral stem cell (SC) mobilisation. For insufficiently mobilizing patients, the stem cell releasing compound plerixafor may enable successful stem cell collection. It triggers additional hematopoietic stem cell release from the bone marrow to the peripheral blood and, thereby, allows a substantial proportion of patients with imminent mobilization failure to collect sufficient stem cells. Given the steadily increasing survival rates of myeloma patients, however, the long-term safety of plerixafor is poorly reported.

**Methods:** We included all subsequent patients with multiple myeloma who received high dose chemotherapy (HDCT) with ASCT at a single academic center between 04/2010 and 01/2015, within an intention-to-collect analysis. We compared all myeloma patients with need of plerixafor for stem cell mobilisation to all myeloma patients without need of plerixafor support in this period. Primary endpoint of this study was to assess overall and progression-free survival in patients with versus without plerixafor.

**Results:** We identified 57 myeloma patients with administration of plerixafor and compared them to 80 myeloma patients without plerixafor. Patient characteristics at diagnosis and remission status after induction treatment were comparable. Hospitalization duration and number of febrile episodes after ASCT were similar. After a median follow-up of 86 months, we observed no differences for progression-free and overall survival rates ( $p = .33$  and  $p = .77$ , respectively), for rate of progression (71.9% vs. 73.7%;  $p = .81$ ), and of death (52.6% vs. 43.8%;  $p = .30$ ), as demonstrated in Figure 1.

**Conclusions:** In patients with insufficient stem cell mobilization, the use of the rescue compound plerixafor allows for timely peripheral stem cell collection also in poorly mobilising patients. Our data suggest that the use of plerixafor does not affect the long-term outcome of myeloma patients.



## Abstract ID: 32

**BeEAM with Polatuzumab (Pola-BeEAM) before ASCT in Patients with DLBCL**T. Stoffel<sup>1</sup>, U. Bacher<sup>2</sup>, Y. Banz<sup>3</sup>, M. Daskalakis<sup>2</sup>, U. Novak<sup>1</sup>, T. Pabst<sup>1</sup><sup>1</sup>Department of Oncology, Inselspital, Bern, <sup>2</sup>Department of Hematology, Inselspital, Bern, <sup>3</sup>Institute of Pathology, Inselspital, Bern

**Introduction:** BEAM is mostly applied as high-dose chemotherapy (HDCT) before autologous stem cell transplantation (ASCT) in diffuse large B-cell lymphoma (DLBCL). Bendamustine replacing BCNU (BeEAM) is similarly effective with fewer toxicities. However, relapse remains the major cause of death in DLBCL patients. In this study, we investigated for the first time the addition of polatuzumab vedotin (PV, targeting CD79b) together with standard BeEAM conditioning (Pola-BeEAM) in 12 DLBCL patients. The aim of this study was to evaluate feasibility and safety of this novel Pola-BeEAM regimen prior to ASCT.

**Methods:** This is a pilot single-center study investigating standard-dose BeEAM regimen with additional PV aiming to establish feasibility and safety of this procedure. PV was given once at the standard dose of 1.8 mg/kg at day -6, together with BeEAM-HDCT (from days -7 to -1) before ASCT in patients with DLBCL.

Table 1: Details of HDCT, engraftment, infections, toxicities

Parameter	Results	
Apheresis from peripheral blood, n (%)	12/12 (100%)	
Pola-BeEAM administered at full dose, n (%)	12/12 (100%)	
PV associated transfusion reactions, n (%)	0/12 (100%)	
Transplanted CD34 <sup>+</sup> cells, median, x10 <sup>6</sup> /kg b.w. (range)	4.1 (2.6-7.5)	
<b>Median time to engraftment, days (range)</b>		
Tc >20 G/L	13 (10-25)	
Neutrophils >0.5 G/L	11 (10-13)	
Lymphocytes >1.0 G/L	25 (16-51)	
Hospitalization, median, days (range)	23 (20-34)	
TPN given, n (%)	11 (92%)	
Units of erythrocyte transfusions, median, n (range)	3 (0-10)	
Units of platelet transfusions, median, n (range)	6 (2-15)	
Weight changes, median, kg (range)	-2 (-8;+3)	
<b>Infections</b>		
At least one febrile episode, n (%)	12/12 (100%)	
Median number of febrile episodes, n (range)	2 (1-3)	
Bacterial, n (%)	10/12 (83%)	
Viral, n (%)	2/12 (17%)	
Fungal, n (%)	1/12 (8%)	
<b>Non-hematological toxicities</b>		
Patients with >1 toxicity, all grades, n (%)	12/12 (100%)	
Patients with grade 3-4 toxicities, n (%)	10/12 (83%)	
<b>Grades of toxicities, n</b>	<b>Grade 1-2</b>	<b>Grade 3-4</b>
Mucositis	8	4
Diarrhea	7	4
Dysphagia	8	1
Neutropenic colitis	7	0
Acute kidney injury	0	2
Gastrointestinal bleeding	0	1
Thromboembolic events	0	1
Atrial fibrillation	1	0
<b>ICU admission, n</b>	1	0

HDCT: high-dose chemotherapy, Pola-BeEAM: polatuzumab vedotin, bendamustine, etoposide, cytarabine, melphalan, PV: polatuzumab vedotin, Tc: thrombocytes, TPN: total parenteral nutrition, ICU: intensive care unit.

**Results:** 8/12 patients (67%) received PV with BeEAM as a consolidation of first-line treatment due to high-risk initial presentation, and 4/12 patients (33%) received PV with BeEAM as second-line treatment after re-induction treatment. All patients experienced complete engraftment (neutrophils > 0.5 G/L: median 11 days; platelets > 20 G/L: 13 days). 10/12 patients (83%) had grade 3-4 toxicities. Gastrointestinal toxicities occurred in 7/12

patients (58%, grade 3). All patients developed infections during neutropenia with at least one identified pathogen (bacterial: 10/12 patients; viral: 2/12; and fungal: 1/12). The complete remission rate by PET-CT 100 days post-ASCT was 92%, and one patient (8%) died so far during follow-up due to early progression. Eleven out of twelve patients (92%) are alive so far and without progression after a median follow-up of 15 months.

**Conclusions:** Our data suggest that combining PV with BeEAM HDCT is feasible and safe, but the limited size of the cohort prevents definite conclusions regarding efficacy. Larger prospective trials will be needed to fully elucidate outcomes and toxicities after Pola-BeEAM treatment.

**Abstract ID: 35**

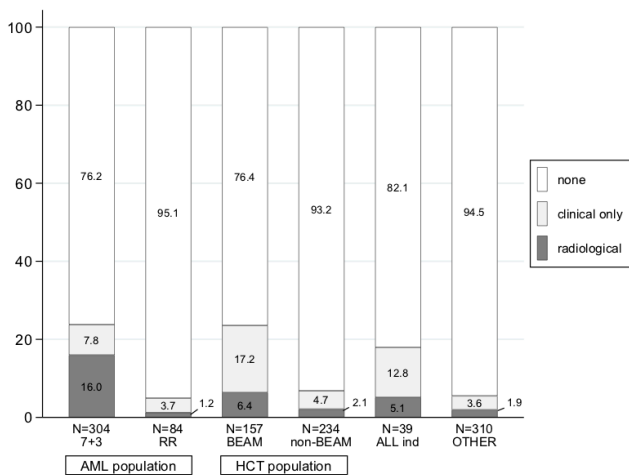
**Incidence and Risk Factors of Neutropenic Enterocolitis after Myelosuppressive Chemotherapy**

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**Introduction:** While neutropenic enterocolitis (NEC) is well known as a life-threatening complication after intensive chemotherapy, its incidence, impact and outcome in specific at-risk populations remain ill-defined.

**Methods:** We report the incidence, characteristics and outcome of NEC in a cohort of 670 hematological patients prospectively collected over 10 years. Risk factors were assessed by uni- and multivariate logistic regression models.



**Results:** Overall, NEC occurred in 156 out of 1128 chemotherapy courses (13.8%), including 73 “radiologically-proven” and 83 “clinical-only” NECs. NEC was independently associated with longer hospital courses (median 30 versus 26 days, P <0.001) but had no significant impact on survival. In acute myeloid leukemia (AML), NEC was more frequent during induction with a “standard” protocol (e.g. ARA-C with idarubicin, daunorubicin or amsacrine, 24.7%) than with a protocol for “relapsed or refractory” (RR) leukemia (ARA-C with fludarabine, cladribine or clofarabine +/- idarubicin, 4.8%, P <0.001). In autologous stem cell-transplant, NEC was more frequent after BEAM (carmustine, etoposide, cytarabine, melphalan, 23.6%) than non-BEAM (e.g. melphalan) conditioning (6.8%, P <0.001). In AML induction, independent risk factors for NEC included 2nd induction using amsacrine (Odds ratio [OR] = 2.41, 95% confidence interval [CI] 1.36-4.26, P = 0.003), initial blast count >50 G/L

(OR = 2.36, CI 1.09-5.08, P = 0.03), with a trend for a previous NEC (OR = 1.99, 95% CI 0.86-4.59, P = 0.09).

**Conclusions:** The incidence of NEC is highly dependent on the chemotherapeutic regimen, with particularly low occurrence in “RR” versus “standard” AML induction. While NEC was associated with extended hospital stays requiring specific management strategies, it did not affect patients’ short and long-term survival.

**Abstract ID: 38**

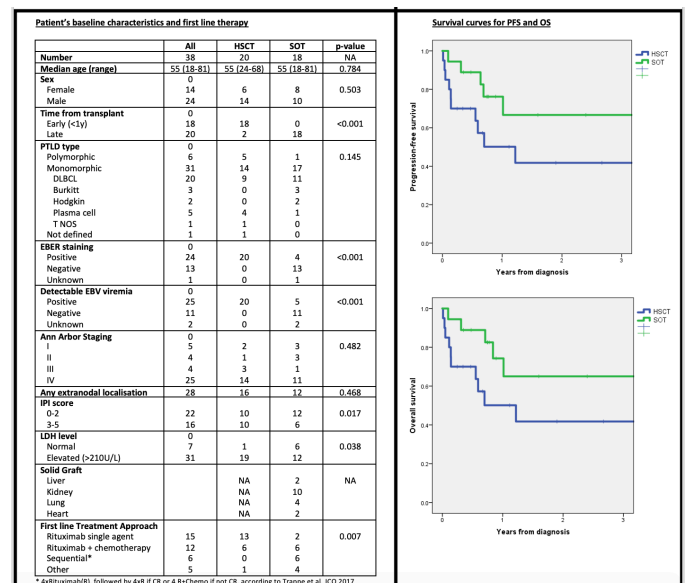
**Treatment and outcomes of patients with post-transplant lymphoproliferative disorder: a single centre experience**

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**Introduction:** Post-transplant lymphoproliferative disorder (PTLD) is a potentially severe complication that takes place after solid (SOT) or allogeneic hematopoietic stem cell transplant (HSCT). To date, its treatment is not standardised and choice of therapy depends on histology and clinical presentation.

**Methods:** Patients ≥18 yrs diagnosed with a PTLD between 2011 and 2020 were identified in our medical records database. Primary endpoints were 2 yrs progression-free survival (PFS), overall survival (OS), and relapse incidence (RI) estimated with Kaplan-Meier and comparison between HSCT and SOT group.



**Results:** A total of 38 patients were included. HSCT patients presented a significantly higher prevalence of early onset PTLD (90% in HSCT group vs 0% in SOT group), positive EBER immunostaining (100% vs 22%) and detectable Epstein Bar Virus (EBV) viremia (100% vs 28%), higher LDH (95% vs 66%), IPI score 3-5 (50% vs 33%), with a remarkable higher use of single agent Rituximab as first line therapy in HSCT patients (65% vs 11%). 2 yrs PFS was 54% (95%CI 36-73%) for the entire cohort, 42% (95%CI 16-67%) for HSCT and 67% (95%CI 41-92) for SOT; p-value 0.23. 2 yrs OS was 53% (95%CI 41-66%) for the entire cohort, 42% (95% CI 16-67%) for HSCT and 65% (95% CI 39-91) for SOT; p-value 0.22. 2 yrs RI was 9% (95% CI: 0-21%) for the entire cohort, 0% for HSCT and 14% (95% CI 0-33%) for SOT; p-value 0.26. ORR and CRR were similar with 82% (75% for HSCT, 89% for SOT, p-value 0.41) at the end of first line treatment. High IPI score (3-5) demonstrated worse outcome for PFS (HR: 2.5, 95%CI 0.95-6.65, p-value 0.063) and OS (HR: 2.4, 95%CI 0.92-6.48, p-value 0.07). A total of 17 patients died

during follow-up: 7 during first line treatment of PTLD complication and multiorgan failure (5 in the HSCT group, 2 in the SOT group; p-value 0.41); 2 following PTLD relapse after first CR (0 in the HSCT group, 2 in the SOT group; p-value 0.22).

**Conclusions:** This study highlights the clinical and therapeutic heterogeneity of PTLD. We observed a worse 2 yrs PFS and OS in patients with high IPI score. CRR after first line treatment is almost 90% in the SOT group, with a 2 yrs OS of 53% consistent with previous studies. The higher mortality observed in the HSCT group suggests that serious treatment-related toxicities remain main challenges in this fragile patient population. New tools to guide therapeutic approaches in PTLD patients are warranted.

#### Abstract ID: 59

### Mocravimod, a S1P receptor agonist, increases both T cell counts in bone marrow biopsies from patients undergoing allogeneic HCT and acute GvHD-freedom probability

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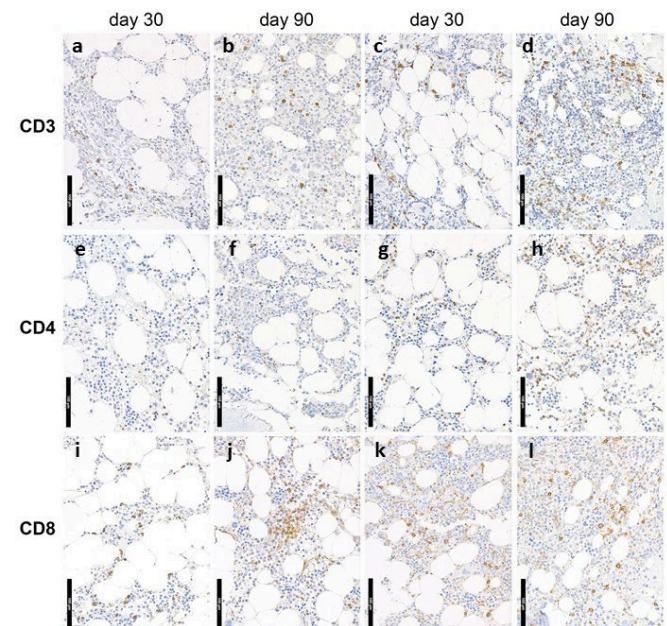
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**Introduction:** The graft-versus-leukemia (GvL) effect is critical to prevent relapses after allogeneic hematopoietic cell transplantation (allo-HCT). However, the success of allo-HCT is limited by graft-versus-host disease (GvHD). The sphingosine-1-phosphate receptor (S1PR) signalling plays a crucial role in lymphocyte trafficking. Mocravimod is an agonistic modulator of S1PRs and its administration leads to blocking lymphocyte egress from lymphoid organs, such as lymph nodes (LN), spleen and bone marrow (BM).

**Methods:** We analyzed BM biopsies from the clinical study with mocravimod (phase I trial in allo-HCT patients for GvHD prophylaxis) by immunohistochemical staining for CD3, CD4, CD8, TIA1, FoxP3, PD1, T-Bet, GATA3, and ROR- $\gamma$ t to identify T cell subsets. Allo-HCT patients without receiving mocravimod were used as controls.

**Results:** BM from 9 patients in the mocravimod group (1 AML, 2 MDS, 3 ALL, 1 myeloma, 1 lymphoma, 1 CML) and 10 patients in the control group were examined. Subsets expressing CD3, CD4, CD8, TIA1, FoxP3, PD1, T-Bet and GATA3 were observed at higher numbers per mm<sup>2</sup> BM in the mocravimod group (Figure 1). CD3+ T cells were found to accumulate in the BM of mocravimod-treated patients compared to controls, both on day 30 and 90 post-transplant (Figure 1a-d). The effect seemed to be stronger in CD4+ T cells, than CD8+ T cells, which is in line with data from murine studies showing that CD4+ T cells are more sensitive to mocravimod treatment than CD8+ T cells (Figure 1e-h). In accordance with CD8+ T cells being less sensitive to mocravimod treatment, no difference in numbers of activated cytotoxic T cells (TIA1+) was observed (Figure 1i-l). On day 30 post-transplant, both T-Bet+ Th1 and GATA3+ Th2 cells, but not ROR- $\gamma$ t+ Th17 cells, were enriched in BM biopsies from mocravimod-treated patients compared to controls. On day 90 post-transplant, Th1 cells were reduced in mocravimod-treated patients compared to controls while Th2 cells were comparable between the two groups. Grade 2 or higher acute GvHD-freedom probability was higher in mocravimod-treated patients compared to controls, indicating that clinically-relevant acute GvHD events were indeed limited when mocravimod was administered.

**Conclusions:** Taken together, the here presented data are supportive of mocravimod's mode of action and bring additional evidence of reduced GvHD severity for allo-HCT patients treated with S1PR modulators.



#### Abstract ID: 76

### Expansion of phenotypically senescent CD57+ CD8 T cells is associated with impaired immunocompetence after allogeneic hematopoietic stem cell transplantation

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**Introduction:** CD57 has been reported as a marker of human senescent CD8 T cells. Early studies have reported increased proportions of CD57-expressing CD8 T cells after autologous and allogeneic hematopoietic stem cell transplantation (allo-HSCT). Whether the expansion of CD57+ CD8 T cells is associated with impaired immunocompetence after allo-HSCT remains to be investigated.

**Methods:** Proportions and phenotype of CD57+ CD8 T cells were assessed by flow cytometry in peripheral blood mononuclear cells from healthy controls (HC, n = 21) and allo-HSCT recipients (n = 115). Non naïve CD57+ vs CD57- T cells were sorted and TCR $\beta$  sequencing was performed by immunoSEQ. Virus-specific CD8 T cells were identified by flow cytometry based on IFN $\gamma$  and/or TNF $\alpha$  expression after 6h stimulation with peptides derived from CMV, EBV, HHV6, BKV and Adenovirus. Torque Teno Virus (TTV) replication was quantified by quantitative PCR.

**Results:** CD8 T cells from allo-HSCT recipients displayed significantly higher proportions of CD57+ cells compared with HC ( $p = 8.1e-06$ ). Phenotypically, CD57+ CD8 T cells from allogeneic HSCT recipients displayed a senescent immunophenotype characterized by low expression of CD127. Functionally, CD57+ CD8 T cells from allo-HSCT recipients displayed a similar capacity to produce IFN- $\gamma$ , TNF- $\alpha$ , granzyme B and perforin when compared to cells from HC. TCR $\beta$ -sequencing revealed high

pathogen-specific clonotypes enrichment in CD57+ CD8 T cells from allo-HSCT recipients. Virus-specific CD8 T cells expressed higher levels of CD57 in HSCT recipients compared with HC for CMV ( $p = 0.0025$ ), EBV ( $p = 0.00041$ ), BKV ( $p = 0.043$ ) and adenovirus ( $p = 0.0012$ ). Using the TTV replication as a measure of impaired immunocompetence, we observed that the proportion of CD57-expressing cells among non-naïve CD8 T cells positively correlated with TTV titers in allo-HSCT recipients ( $R = 0.32$ ,  $p = 0.019$ ).

**Conclusions:** These results show that the proportion of phenotypically senescent CD57+ CD8 T cells increases after allo-HSCT as a result of an increased expression at the surface of memory CD8 T cells, including virus-specific cells. Moreover, CD57 expression at the surface of non-naïve CD8 T cells correlated with higher replication of TTV, reflecting a status of impaired immunocompetence after allo-HSCT.

#### Abstract ID: 95

### Outcomes of Matched Related Donor Hematopoietic Cell Transplantation with Reduced Intensity Conditioning in Hemoglobinopathies – a Single Center Experience

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**Introduction:** Hematopoietic cell transplantation (HCT) is an established method for curing Thalassemia major (TM) and Sickle Cell Disease (SCD). The latest American Society of Hematology guide-lines recommend myeloablative preparative regimen in patients under 18 years of age.

Our objective was to demonstrate safety and efficacy of a reduced intensity conditioning (RIC) regimen looking at overall and event-free survival, myeloid donor chimerism and immune reconstitution.

**Methods:** This RIC included fludarabine (30 mg/m<sup>2</sup> per day for 6 days), serotherapy with thymoglobuline (2.5 mg/kg per day for 3 days) and targeted busulfan (cumulative area under the curve 65 to 70 mg/L×h). Graft-versus-Host-Disease (GvHD) prophylaxis consisted of ciclosporin A or tacrolimus and mycophenolate mofetil.

Patients with hemoglobinopathies who received a matched related donor (MRD) HCT between 2012 and 2021 were enrolled in this retrospective cohort study.

**Results:** 10 patients with SCD and 6 patients with TM were enrolled. The median age at transplantation was 8.3 years (IQR 7.2 to 10.8). The median follow-up time was 5.2 years (IQR 3.0 to 6.0). Overall survival was 94.1% (95% CI 87.0 to 96.3%) in the total cohort. One patient with SCD died from complications of preexisting Moyamoya disease. There were four cases of mild acute GvHD grade I. Other events defined as higher than grade I acute GvHD or graft failure with need for retransplantation did not occur. Full myeloid chimerism was observed in all survived patients with a median follow-up time of 4.1 years (IQR 1.5 to 4.2). Immune reconstitution (defined as  $\geq 50$  CD4+ T cells/ $\mu$ L) was achieved at a median of 14.5 days (IQR 8.8 to 24.5 days). The corresponding 5th age percentile for recent thymic emigrants (CD31+CD4+CD45RA+ T cells) was reached at a median of 375 days.

**Conclusions:** In our experience, MRD HCT with RIC regimen was shown to be successful and safe in patients with hemoglobinopathies.

#### Abstract ID: 148

### A national Platform for allocation of CAR T-cell Therapy to Multiple Myeloma Patients

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**Introduction:** Idecabtagene vicleucel (ide-cel) CAR-T cell approval has improved treatment options for multiple myeloma (MM) in Switzerland. Bristol Myers Squibb (BMS) allocates a limited number (Switzerland: 4/month) therapy slots/country resulting in a mismatch between treatment availability and demand. The allocation of limited critical treatments to patients is established in transplantation and emergency medicine, while triage criteria for MM CART are lacking. Swiss Blood Stem Cell Transplantation and Cellular Therapy (SBST) successfully allocates ide-cel treatment to MM patients in a transparent, pre-specified, standardized, national process using evidence-based criteria.

**Methods:** Allocation process and triage criteria were developed by clinical experts in exchange with the ethical board of the swiss academy for medical sciences and health insurers December 2021 – February 2022 and approved by all clinical representatives and JACIE-accredited national centers. Patients are registered for the monthly national SBST MM-CART board in parallel with the approval of insurance coverage in one key document uploaded to insurances and the SBST online database.

Patient factors associated with not achieving CR by uni- and multivariate analysis from the KarMMa trial are complemented by prospectively confirmed factors associated with inferior overall survival under CART therapies. Tumor burden, inflammatory activity, ECOG patient status and comorbidities are combined to a score of 0-4 negative predictors. All registered patients are ranked by a score at monthly virtual meetings. Ranking is refined based on alternative therapy options resulting in a final national ranking of all MM patients registered for CART.

**Results:** Seven CART Myeloma boards (March-September 2022) lasted a median of 60 minutes (25-70) with median 8 participating centers (6-10), discussing total 35 patients (median 8/session, including re-presentations). All centers agreed to all final rankings. All therapy slots were successfully allocated, including short-notice changes in availability of slots or patients requiring immediate allocation of substituting patients. 74.2% of all patients registered with the SBST CART MM board received ide-cel.

**Conclusions:** The Swiss CART Myeloma Board is the first national allocation system for CART therapy to MM patients using a pre-specified, objective, transparent process

**Abstract ID: 149****Acquired aplastic anemia shows increased Nestin+ niches, upregulation of genes of the adaptive immune system and of CXCL12 in transformation**A. Beerlage<sup>1</sup>, J. R. Passweg<sup>1</sup>, C. Zinner<sup>2</sup>, A. Tzankov<sup>2</sup>, B. Drexler<sup>1</sup><sup>1</sup>Department of Hematology, University Hospital Basel, Basel, <sup>2</sup>Department of Pathology, University Hospital Basel, Basel

**Introduction:** Nestin+ niches play an important role in the healthy bone marrow (BM), dysregulation has been described in MPN, AML and GvHD. CXCL12 is involved in the maintenance and circadian rhythmicity of the healthy niche, but also facilitates adhesion and survival of malignant cells. To further understand the stem cell niche in AA we performed an immunohistochemical analysis of Nestin and CXCL12 staining quantities as well as high-scale gene expression profiling (GEP) of BM biopsies (BMB) from AA in comparison with controls.

**Methods:** Immunohistochemical stains for Nestin and CXCL12 were performed in 29 BMB. Normal BMB samples (n = 12) served as a control. To exclude the influence of cellularity, additional 7 BMB containing physiologically hypocellular subcortical BM spaces were also analyzed and served as controls for GEP. GEP was performed on 13 AA cases and 4 controls utilizing the HTG Transcriptome Panel<sup>®</sup> to identify dysregulated pathways in the BM environment of AA. Biomedical modelling was used to identify potentially enriched cell types.

**Results:** Nestin+ niches are increased in sAA (n = 17, mean 7.8 niches/mm<sup>2</sup>) compared to mAA (n = 10, mean 3.3 niches/mm<sup>2</sup>), normal BM (n = 12, mean 1.7 niches/mm<sup>2</sup>) and physiologically hypocellular subcortical BM spaces (n = 7, mean 4.4 niches/mm<sup>2</sup>). The density of CXCL12-expressing niche cells did not differ between mAA (n = 9, mean 1.3 niches/mm<sup>2</sup>), sAA (n = 15, mean 1.5 niches/mm<sup>2</sup>) and physiologically hypocellular BM spaces (n = 7, mean 1.1 niches/mm<sup>2</sup>). An increase was seen in samples of patients who transformed to myeloid malignancies (n = 2, mean 3.3 niches/mm<sup>2</sup>). GEP showed considerable upregulation of SLAMF1, CXCL12, ANGPTL8, CTNNA1, COL1A1 and PECAM1 in AA compared to controls. Biomedical modelling revealed a gene expression signature of increased presence of cells of the adaptive immune system.

**Conclusions:** In this study we show an increase of Nestin+ niches in AA, which is contrasting to other inflammatory conditions (GvHD, MPN), but similar to AML. These results indicate intact BM niches in AA and underline the understanding of AA as an autoimmune disease directly attacking HSC and not the microenvironment. Appropriately, GEP shows upregulation of the adaptive immune system. CXCL12 immunohistochemistry did not show significant differences between patients with AA and physiologically hypocellular subcortical BM spaces, although GEP indicated increased gene expression.

**Abstract ID: 150****Analysis of manufacturing failures and out-of-specification products of tisa-cel: focus on low pre-apheresis CD3+ count**I. Chanias<sup>1</sup>, E. Moutzouri Beifuss<sup>1</sup>, B. Lüscher<sup>2</sup>, T. Pabst<sup>3</sup>, U. Bacher<sup>1</sup>, B. Mansouri<sup>1</sup>, M. Daskalakis<sup>1</sup>, K. A. Jalowiec<sup>1</sup><sup>1</sup>Department of Haematology and Central Haematology Laboratory, Inselspital, Bern, <sup>2</sup>Department of Haematology and Central Haematology Laboratory, Ins, Bern, <sup>3</sup>Department of Medical Oncology, Ins, Bern

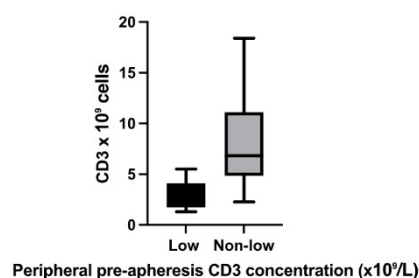
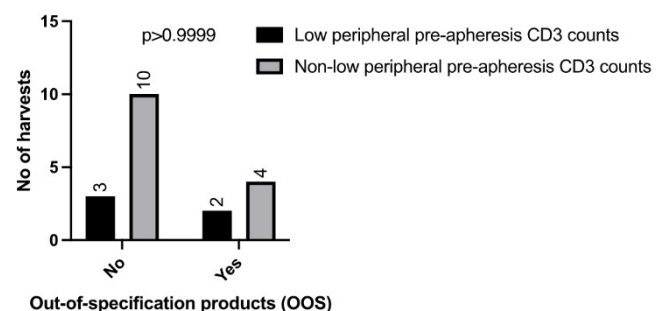
**Introduction:** Tisagenlecleucel (Kymriah<sup>®</sup>) CAR T-cells are approved for treatment of r/r B-ALL and r/r DLBCL in adults. Harvesting sufficient numbers of CD3+ cells via lymphapheresis is

critical for successful manufacturing of CAR-T cells. Absolute TNC  $\geq 2 \times 10^9$  and CD3+ of  $> 1.0 \times 10^9$  are requested by the manufacturer. Occasionally, despite of successful harvest, the CAR-T product fails to pass the pre-defined release criteria and is labelled as an out-of-specification (OOS) product. We aimed to investigate the frequency of OOS products in our center and to determine its correlation with low pre-apheresis peripheral CD3+ counts.

**Methods:** We analyzed 27 harvests of 20 patients with DLBCL or B-ALL between 10/2018 and 11/2019. Low count of peripheral blood CD3+ pre-apheresis was defined as  $< 0.3 \times 10^9/L$  (according to literature). Due to low patient numbers, non-parametric tests were used for our analysis. We compared patients with low ( $< 0.3 \times 10^9/L$ ) and non-low ( $\geq 0.3 \times 10^9/L$ ) peripheral pre-apheresis CD3+ count using the MWW test. The frequency of OOS products was compared by using Fisher's exact test. Total yield was defined as the absolute number of CD3 cells obtained at the end of apheresis (cells  $\times 10^9$ ).

**Results:** The median patients' age was 65 years (IQR, 52 – 71 years). Diagnoses were DLBCL in 96% (n = 26) and B-ALL in 4% (n = 1). 22% (n = 6) had low and 78% (n = 21) had non-low pre-apheresis peripheral CD3+ counts. In all collections, a total yield of  $> 1 \times 10^9$  CD3+ cells was achieved, being lower in the low than non-low group (2.32 vs. 6.82  $\times 10^9$ , p = 0.0015). Data on analysis of release criteria was available in 70% (n = 19) of all harvests and products were labelled as OOS in 6 of them (6/19, 31%). There was no difference in the frequency of OOS products in low vs. non-low groups (n = 2/5, 40% vs. n = 4/14, 29%; n.s.). Causes of OOS were low calculated cell dose (n = 4), low viability (n = 1) and failed IFN release (n = 1).

**Conclusions:** Our single-centre experience shows that successful CD3 cell harvest is feasible in patients with low peripheral pre-apheresis CD3+ counts  $< 0.3 \times 10^9/L$  as the minimum targeted of CD3+ count for manufacturing was achieved. Manufacturing failures were equally frequent in patients with low and non-low CD3+ counts, thus they do not seem to be related to quantitative but rather qualitative CD3+ cell issues. Other reasons for manufacturing failures, especially CD3+ fitness, need to be investigated.



## SSMO POSTER PRESENTATION – CLINICAL SOLID TUMOR ONCOLOGY

## Abstract ID: 9

**Phase Ib dose-escalation study of the hypoxia-modifier Myo-inositol trispyrophosphate in patients with hepatopancreatobiliary tumors**

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**Introduction:** Hypoxia is prominent in solid tumors and a recognized driver of malignancy. Thus far, targeting tumor hypoxia has remained unsuccessful. Myo-inositol trispyrophosphate (ITPP) is a re-oxygenating compound without apparent toxicity. In preclinical models, ITPP potentiates the efficacy of subsequent chemotherapy through vascular normalization.

**Methods:** The present study is a first in-human exploratory, prospective, open-labelled, mono-centric Phase IB study according to a classical 3+3 dose escalation design (ClinicalTrials.gov Identifier: NCT02528526) in patients with non-resectable primary and secondary tumors of the liver, pancreas, and biliary tract. The study intervention consists of 9 infusions of ITPP over 3 weeks, followed by administration of conventional cytotoxic chemotherapy. Primary endpoint is the determination of safety and tolerability of ITPP, secondary endpoint is assessment of efficacy/tumor response with FDG-PET/CT and MRI.

**Results:** Primary objectives are assessment of the safety and tolerability and establishment of the maximum tolerated dose, while secondary objectives include assessment of pharmacokinetics, antitumor activity via radiological evaluation and assessment of circulatory tumor-specific and angiogenic markers. The maximum tolerated dose is 12,390 mg/m<sup>2</sup>, and ITPP treatment results in 32 treatment-related toxicities (mostly hypercalcemia) that require little or no intervention. 52% of patients have morphological disease stabilization under ITPP monotherapy. Following subsequent chemotherapy, 10% show partial responses while 60% have stable disease.

**Conclusions:** Administration of ITPP before chemotherapy is safe and well tolerated with negligible side-effects. Decreases in angiogenic markers are noted in ~60% of patients after ITPP and tend to correlate with responses and survival after chemotherapy. Further exploration of its anti-tumor efficacy in Phase II/III trials is highly warranted.

## Abstract ID: 11

**21-Gene Oncotype DX® Recurrence-Score benefits and application in elderly breast cancer patients**

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**Introduction:** In early luminal HER2 negative breast cancer Oncotype DX® Recurrence-Score (RS) has been broadly validated in pre- and postmenopausal patients and can predict prognosis and benefit of chemotherapy. Its value in elderly breast cancer populations has not been deeply addressed. This study analyses clinical and pathologic factors, RS distribution and outcomes in an elderly vs. non-elderly breast cancer population

with the purpose of establishing RS added value to therapy decision-making in a geriatric cohort.

**Methods:** This is a retrospective analysis of clinico-pathologic data of patients with early luminal A breast cancer treated at the University Hospital Basel and the Cantonal Hospital Baselland between 2010 and 2022. In cohort A (A) all patients with the age below 70 years were included and in cohort B (B) all patients with the age above 69 were included. At moment of decision for adjuvant treatment all patients had known RS result.

**Results:** A and B included 60 (19%) respectively 266 (81%) patients. The median age in B was 74 years. The following clinico-pathologic factors were different in A vs. B: Comorbidities (56% vs. 35%, p = 0,005), BMI (overweight vs normal, p = 0.023) and tumor size (31.3 mm vs 23.6 mm p = 0.021). The RS distribution in A vs. B was low 23% vs 24% p = 0.79, intermediate 54% vs 57% p = 0.40 and high 23% vs 18% p = 0.068 Non-compliance rate for chemotherapy was higher in A vs. B (47% vs 23%, p <0.05). There was a trend for a higher mastectomy rate in A (40% vs. 29%, p = 0.065). Radiotherapy (61% vs 43%, p = 0.013) and osteo-oncologic treatment (64% vs 43%, p = 0.009) was applied more often in A. With a median Follow-up of 36 months the recurrence rate was higher in A (13% vs 6%) associated with higher RS (median 30 vs 18), higher death rate (25% vs 7%), but lower non-compliance (38% vs 47%) vs. B. The overall and disease-free survival was not statistically different.

**Conclusions:** Older breast cancer patients tend to have higher clinical risk status, more co-morbidities and higher BMI. RS distribution was not significantly different between the two cohorts, however higher RS did pose a higher relapse rate for older patients in our cohort. Although RS based guidelines still apply in therapy decision making, in the case of geriatric breast cancer patients clinical practice points to a rather individualized treatment in which all clinical and pathological factors are weighted.

## Abstract ID: 13

**The role of immunotherapies in real-world: an analysis of the treatment patterns, survival and toxicity of immune checkpoint inhibitors by sex**

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**Introduction:** Despite the increasing number of reports on real-world outcomes of immune checkpoint inhibitors (ICI) for specific cancer types, analyses defining the role of ICI in oncology practice are largely missing. The aim of our real-world analysis is to depict the role of ICI treatments at a tertiary center by assessing the percentage of ICI treatments among all systemic anticancer treatments prescribed, characterizing the patient population as well as tumor and treatment types and duration, and providing OS and toxicity rates by sex.

**Methods:** We used electronic health records to identify patients treated at the Cancer Center of the University Hospital Bern, Switzerland between January 1, 2017 and June 16, 2021. Descriptive statistics were used to describe patient, tumor, and treatment characteristics. Median OS was estimated for each subgroup using the Kaplan-Meier method.

**Results:** We identified 5109 patients, 689 of whom (13.5%) received at least one dose of ICI. The fraction of patients who

were prescribed ICI increased from 8.6% in 2017 to 22.9% in 2021. ICI represented 13.2% of the anticancer treatments in 2017 and increased to 28.2% in 2021. The majority of patients were male (68.7%), who were older than the female patients (median age 67 versus 61 years). We observed differences in age distribution by sex, with 23% the female patients being younger than 50 years and 63.6% younger than 65 years old as compared to 6.8% and 43.2% of male patients, respectively. The type of treatment setting (adjuvant versus metastatic) as well as the fraction of the different tumor types changed over time, with an increase in adjuvant and first line treatments for both sexes. Lung cancer and melanoma were the most common cancer types in males and females (Table 1A). The type of treatment and treatment duration was similar for both sexes. The incidence of irAEs was higher among females (38.4% vs 28.1%) and lead more often to treatment discontinuation in females than in males (21.1% vs 16.8%) (Table 1B). Independent of sex, the occurrence of irAEs was associated with greater median overall survival (OS, not reached vs 1.1 years). Female patients had a longer median OS than males (1.9 vs 1.5 years).

**Conclusions:** ICI play an increasingly important role in oncology. irAEs are more frequent in females and are associated with a longer OS. The sex related factors contributing to these differences need to be explored.

A		Men	Women
<b>Patients receiving ICI, n=689</b>			
Age (years) (median (range))		67 (21-88)	61 (21-87)
<b>Cancer type</b>			
NSCLC*	154 (22.0%)	66 (30.0%)	88 (41.9%)
Melanoma	80 (11.6%)	47 (21.8%)	33 (15.7%)
Urothelial carcinoma	50 (7.3%)	19 (7.4%)	31 (14.6%)
Hepatobiliary carcinoma	47 (6.8%)	6 (2.8%)	41 (19.4%)
Renal cell carcinoma	31 (4.5%)	13 (6.0%)	18 (8.5%)
HNSCC	30 (4.3%)	11 (5.1%)	19 (8.9%)
SCLC	20 (2.9%)	15 (6.9%)	5 (2.3%)
Colorectal carcinoma	18 (2.6%)	10 (4.6%)	8 (3.8%)
Triple negative breast cancer	12 (1.7%)	1 (0.5%)	11 (5.1%)
Other	25 (3.6%)	19 (8.7%)	6 (2.8%)
<b>Tumor stage</b>			
Adjuvant staging			
I	7 (1.0%)	0	7 (3.2%)
II	14 (2.0%)	8 (3.7%)	6 (2.8%)
III	79 (11.5%)	43 (19.9%)	36 (16.7%)
IV	307 (44.5%)	144 (66.7%)	163 (76.3%)
Metastatic disease			
HCC/BCLC staging			
BCLC A	9 (1.3%)	0	9 (4.1%)
BCLC B	15 (2.2%)	2 (0.9%)	13 (6.0%)
BCLC C	21 (3.0%)	4 (1.8%)	17 (7.8%)
BCLC D	1 (0.1%)	0	1 (0.5%)
<b>PD-L1 status</b>			
Known	207 (30.0%)	114 (52.8%)	93 (43.6%)
Unknown	286 (41.5%)	102 (47.2%)	184 (86.4%)

B		Men	Women
<b>Total number of treatments, n=798</b>			
<b>Treatments received</b>			
Anti-PD1	180 (22.6%)	83 (34.9%)	97 (45.1%)
Anti-CTLA4	138 (17.3%)	65 (27.8%)	73 (34.6%)
Anti-PD1 + Anti-CTLA4	112 (14.1%)	53 (22.6%)	59 (27.7%)
Chemotherapy	118 (14.8%)	58 (24.8%)	60 (28.1%)
Chemotherapy + Tyrosine kinase inhibitor	8 (1.0%)	4 (1.7%)	4 (1.9%)
Combination	9 (1.1%)	5 (2.1%)	4 (1.9%)
<b>Anti-PD1</b>			
Ipilimumab	17 (2.1%)	10 (4.3%)	7 (3.2%)
Atezolizumab	46 (5.8%)	22 (9.4%)	24 (11.2%)
Atezolizumab + Bevacizumab	42 (5.3%)	21 (9.0%)	21 (9.7%)
Durvalumab	42 (5.3%)	21 (9.0%)	21 (9.7%)
avelumab	6 (0.7%)	3 (1.3%)	3 (1.4%)
Ipilimumab + Atezolizumab	5 (0.6%)	3 (1.3%)	2 (0.9%)
Ipilimumab + Nivolumab	62 (7.9%)	37 (15.8%)	25 (11.6%)
<b>Number of cycles received (median, range), total</b>			
Anti-PD1	6 (1-10), 680	6 (1-10), 2078	6 (1-10), 2078
Anti-CTLA4	9 (1-10), 613	8 (1-10), 613	8 (1-10), 613
Anti-PD1 + Anti-CTLA4	10 (1-10), 49	4 (one treatment)	4 (one treatment)
Chemotherapy	4 (1-20), 7 (1-21)	4 (1-20), 7 (1-21)	4 (1-20), 7 (1-21)
Chemotherapy + Tyrosine kinase inhibitor	10 (1-10), 49	4 (one treatment)	4 (one treatment)
Combination	2 (2-4), 4	2 (2-4), 4	2 (2-4), 4
Ipilimumab + Nivolumab	3 (1-4), 3 (1-4)	3 (1-4), 3 (1-4)	3 (1-4), 3 (1-4)
Nivolumab maintenance	10 (1-10), 31 (14.6%)	10 (1-10), 31 (14.6%)	10 (1-10), 31 (14.6%)
<b>Treatment line</b>			
Neoadjuvant	6 (0.7%)	3 (1.3%)	3 (1.4%)
Adjuvant	7 (0.9%)	4 (1.7%)	3 (1.4%)
First line	252 (31.6%)	122 (52.8%)	130 (60.3%)
Second line	124 (15.6%)	64 (27.8%)	60 (28.1%)
Third and further line	37 (4.7%)	18 (7.8%)	19 (8.8%)
Maintenance	48 (6.0%)	22 (9.4%)	26 (12.1%)
<b>Treatment setting</b>			
Metastatic disease	41 (5.1%)	14 (6.0%)	27 (12.6%)
Partial response	14 (19.0%)	13 (57.0%)	13 (57.0%)
Complete response	11 (15.0%)	1 (4.3%)	10 (45.5%)
Progressive disease	5 (7.0%)	2 (8.7%)	3 (13.6%)
<b>Immune related adverse events (irAEs), n=216</b>			
Patients experiencing all grade irAEs	138 (28.1%)	83 (34.9%)	55 (25.5%)
Patients experiencing ≥1 irAE type	85 (10.8%)	54 (23.4%)	31 (14.4%)
Patients experiencing ≥2 irAE types	25 (3.1%)	21 (9.0%)	4 (1.8%)
Patients experiencing ≥3 irAE types	11 (1.4%)	8 (3.4%)	3 (1.4%)
Patients experiencing >3 irAE types	2 (0.3%)	0	2 (0.9%)
Dry/wet irAEs (median, range)	85 (11.2%)	41 (17.6%)	44 (20.3%)
Impairment of organ speciality (% of patients)	85 (10.8%)	45 (19.4%)	40 (18.4%)

**Abstract ID: 67**

**Taxane first or pegylated liposomal doxorubicin (PLD)? A retrospective analysis of PLD-taxane versus taxane-PLD in patients with metastatic breast cancer.**

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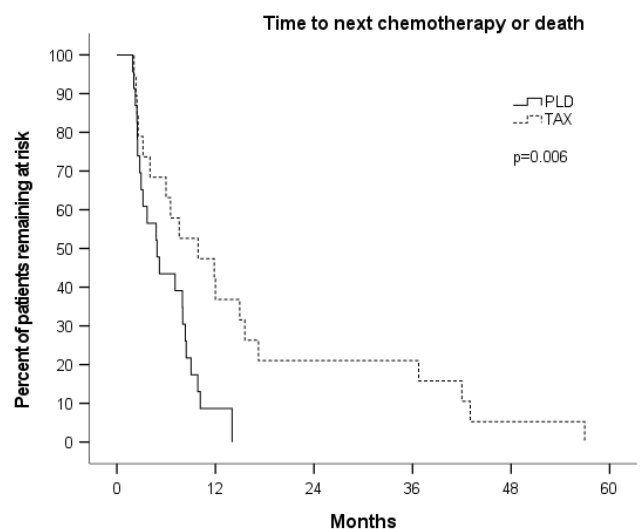
**Introduction:** Most patients with endocrine-resistant metastatic breast cancer (MBC) require multiple lines of cytostatic therapy. Single agent taxanes and/or anthracyclines are standard treatment options. Real world data about pegylated liposomal doxorubicin (PLD) and optimal sequencing of chemotherapy is limited. Our aim was to compare treatment sequence PLD-taxane to taxane-PLD retrospectively.

**Methods:** We analyzed electronic records of all patients with MBC treated with PLD and taxanes at a Swiss university hospital between 2003 and 2021. We included Her2-negative patients having received either 1st line single agent PLD or 1st line single age taxane, each with subsequent crossover. Primary endpoint was time to next chemotherapy or death (TTNC). Secondary endpoints were overall survival (OS), progression free survival (PFS) and objective response rate (ORR). We used

Kaplan Meyer method and logrank test to compare time to event endpoints and Fishers exact test to compare discrete variables.

**Results:** We retrospectively identified 42 patients with Her2-negative MBC having received either single agent PLD or taxane as 1st line chemotherapy with subsequent crossover between July 2003 and May 2021 at a university hospital in Switzerland. 23 patients have received 1st line PLD and later taxane and 19 patients have received 1st line taxane and later PLD. Baseline characteristics were retrospectively balanced between these two groups. Treatment sequence PLD-taxane was significantly inferior to taxane-PLD regarding all endpoints: TTNC 4.9 vs. 9.9 months (p = 0.006), OS 17.8 vs. 24.6 months (p = 0.05), PFS 4.4 vs. 9.0 months (p = 0.005), and ORR 13% vs. 65% (p = 0.002).

**Conclusions:** This is the first head-to-head comparison of treatment sequence PLD-taxane versus taxane-PLD in patients with MBC. Our study showed substantial advantages of using taxanes first, followed by PLD, compared to the opposite sequence. Given this significant and clinically highly relevant advantage regarding all endpoints, taxane treatment should not be postponed in patients with MBC, if feasible and likely to be given at a later time anyway. By the nature of this retrospective analysis, there might be a treatment bias, therefore a prospective validation is necessary.



**Abstract ID: 78**

**ASCENT-03: Phase 3 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in first-line (1L) metastatic triple-negative breast cancer (mTNBC)**

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**Introduction:** SG is a first-in-class antibody-drug conjugate composed of an anti-Trop-2 antibody coupled to a cytotoxic SN-38 payload via a proprietary, hydrolyzable linker. SG significantly improved outcomes over standard single-agent chemotherapy in patients (pts) with mTNBC who received ≥2 prior therapies (≥1 in the metastatic setting [Bardia et al. 2021]).

Chemotherapy is the mainstay treatment option for 1L programmed death-ligand 1 (PD-L1) negative mTNBC but is associated with poor outcomes. ASCENT-03 evaluates efficacy and safety of SG vs TPC in 1L locally advanced inoperable or mTNBC in pts with PD-L1 negative mTNBC irrespective of prior immune checkpoint inhibitors (ICI) in the early setting, or in PD-L1 positive mTNBC pts who received prior ICI in the early setting.

**Methods:** ASCENT-03 (EudraCT: 2021-005743-79) is a global, open-label, randomized, phase 3 study in 1L locally advanced inoperable or mTNBC. This study includes pts with either PD-L1 negative tumors (combined positive score [CPS]<10) or PD-L1 positive tumors (CPS ≥10) who received an anti-PD-(L)1 inhibitor in the curative setting. TNBC (human epidermal growth factor receptor 2 negative, estrogen/progesterone receptor <1%) and PD-L1 status will be centrally confirmed. Other eligibility criteria include measurable disease; ≥6 mo since completion of treatment with curative intent; ECOG performance status 0-1. Pts are randomized 1:1 to receive SG (10 mg/kg IV on D1 and 8) in 21-d cycles or TPC (gemcitabine/carboplatin, paclitaxel, or nab-paclitaxel) until blinded independent central review (BICR)-verified progressive disease/unacceptable toxicity. Pts randomized to TPC may be eligible to cross over and receive SG upon disease progression. Pts are stratified by de novo vs recurrent disease within 6-12 mo of all treatment vs recurrent disease after >12 mo from completion of all treatment in the (neo)adjuvant setting; geographic region. The primary endpoint is progression-free survival by BICR per RECIST v1.1. Secondary endpoints include overall survival, objective response rate, quality of life, and safety. ASCENT-03 will enroll ~540 patients and is open for recruitment, also in 5 centers in Switzerland.

#### Abstract ID: 80

### Which patients with advanced non-small cell lung cancer (NSCLC) benefit from combined immuno-chemotherapy? A single-center retrospective study.

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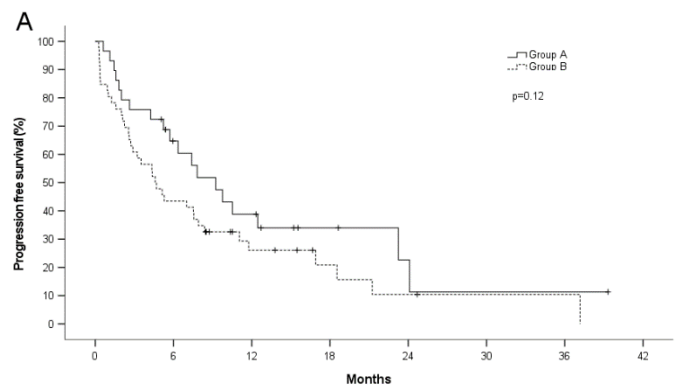
**Introduction:** Combined chemo-immunotherapy with platinum, pemetrexed and pembrolizumab (PPP) has become a standard treatment for many patients with metastatic non-small cell lung cancer (NSCLC) based on the results of the landmark trial KEYNOTE-189 (KN-189). Randomized clinical trials often lack external validity because eligibility criteria exclude patient subgroups commonly treated in real-world clinical practice. We have aimed to provide a real world treatment experience of PPP with retrospective consideration of trial eligibility.

**Methods:** We retrospectively collected data from all patients with metastatic non-squamous NSCLC without targetable mutation treated with PPP at the a Swiss university hospital until May 2021. We divided patients into two groups; (A) those who would retrospectively have met inclusion criteria of KN-189 and (B) those who did not. Our primary endpoint was progression free survival (PFS). Secondary endpoints were overall survival (OS) and objective response rate (ORR). Time to event endpoints were estimated by Kaplan Meyer method and compared by log-rank test. Multivariate subgroup analyzes were performed by Cox and logistic regression.

**Results:** We analyzed 75 patients with metastatic NSCLC treated with PPP a university hospital in Switzerland. 29 pa-

tients would have been eligible to KN-189 (Group A) and 46 patients (Group B) would have been ineligible (Figure 1, Table 1). Median PFS for patients in group A was 9.2 months compared to 4.6 months in group B (p = 0.12). Median OS for group A and B was 16.5 months and 6.5 months, respectively (p = 0.11). ORR differed significantly: 59% for group A and 33% for group B (p = 0.03). ECOG PS ≥2 and active infection predicted significantly shorter PFS and OS. Other trial exclusion criteria (e.g. instable brain metastases or steroid use) did not significantly affect any endpoints.

**Conclusions:** Real-world outcome for patients with advanced non-squamous NSCLC treated according to the KN-189 trial regimen differed considerably from published trial results, driven by patients not meeting the trial inclusion criteria but nevertheless receiving triple therapy. Patients with ECOG PS ≥2 and/or those with active infections had a significantly worse prognosis. Further evaluation of better therapeutic options for these patients and other special populations commonly seen in clinical practice is needed.



#### Abstract ID: 84

### Pegylated liposomal doxorubicin (PLD) in daily practice – A single center experience in elderly and co-morbid patients with metastatic breast cancer

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**Introduction:** Real world data about pegylated liposomal doxorubicin (PLD) in metastatic breast cancer (MBC) is limited. Current evidence is based on clinical phase II/III trials with restrictive inclusion criteria that cannot be met by all patients seen in daily practice. Here we highlight the role of PLD in daily practice by analyzing all patients ever treated with PLD at our hospital and focusing on elderly and co-morbid patients.

**Methods:** We analyzed electronic records of all patients with MBC treated with PLD at a Swiss university hospital between 2003-2021. Primary endpoint was time to next chemotherapy or death (TTNC). Secondary endpoints were overall survival (OS), progression free survival (PFS) and objective response rate (ORR). Time to event endpoints were calculated by Kaplan Meyer method. We performed univariate (logrank) and multivariate analysis (Cox/logistic regression) to determine the predictive impact of clinical factors such as age and co-morbidities.

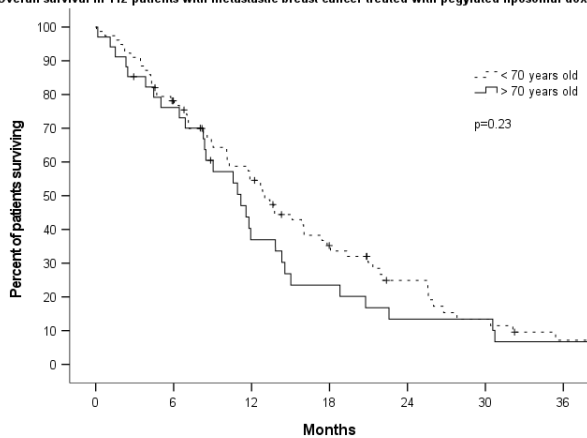
**Results:** 112 patients were analyzed, 34 of which were > 70 years and 61 of which had relevant co-morbidities, predominantly arterial hypertension (28%), heart disease (9%), and diabetes (7%). Median TTNC, OS and PFS were 3.8, 11.9, and 4.4



months, respectively. ORR was 13.6%. Age >70 years predicted shorter OS (median 11.2 months) in multivariate analysis (hazard ratio [HR] 1.83, 95% CI 1.07–3.11,  $p = 0.026$ ). Age and comorbidities did not significantly affect other endpoints. Disease characteristics and pretreatment did not significantly affect any endpoint. Unexpectedly, hypertension predicted longer TTNC (8.3 months,  $p = 0.04$ ) in univariate analysis, maintained in multivariate analysis as a trend for both TTNC (HR 0.62,  $p = 0.07$ ) and OS (HR 0.63,  $p = 0.1$ ). Results of PLD in 1st line vs. 2nd or later were comparable regarding all endpoints.

**Conclusions:** In patients with MBC treated with PLD, age predicted shorter OS significantly but not on a clinically relevant scale. However, real world results of PLD appear underwhelming compared to phase II/III trials through all age groups, pointing to an efficacy-effectiveness gap. PLD remains a treatment option in co-morbid and elderly patients, but expectations should be managed.

Overall survival in 112 patients with metastatic breast cancer treated with pegylated liposomal doxorubicin



#### Abstract ID: 85

### RIB-ELLE: Ribociclib + aromatase inhibitor/fulvestrant in HR+, HER2- advanced breast cancer in the real-world Swiss population: 1st interim analysis

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**Introduction:** Ribociclib (RIB) has demonstrated significant survival benefit in three Phase III trials of the MONALEESA (ML) programme. RIB-ELLE (CLEE011ACH01) is a non-interventional study documenting the safety and efficacy of RIB in combination with an aromatase inhibitor (AI) or fulvestrant (FUL) in the Swiss advanced breast cancer (ABC) population. This study is intended to verify the results of the ML trials in real-world, routine clinical practice in Switzerland. The results of the 1st interim analysis of the study are reported here.

**Methods:** RIB-ELLE is a prospective, multicentric, non-interventional study. Pre- and post-menopausal women with HR+,

HER2- ABC with either no or one prior endocrine treatment (ET) for ABC were enrolled. Patients (pts) were treated with RIB and either AI or FUL, as per investigator choice according to the Swiss RIB label and followed up as per investigator practice.

**Results:** At data cutoff (22 April 2022), out of 134 analyzed pts treated with RIB+ET, 79 pts (59%) continued treatment (tx) and 55 pts (41%) discontinued tx. The most common reasons for tx discontinuation were disease progression (40%,  $n = 22/55$ ) and adverse events (AEs, 33%,  $n = 18/55$ ). Median duration of follow-up was 11.2 months. Median age was 67.5 years. Visceral (lung, liver) metastases were reported in 44 pts (33%); bone-only metastases in 31 pts (23%). Prior adjuvant therapy was received by 76 pts (57%). RIB was prescribed in combination with an AI in 103 pts (77%) and with FUL in 31 pts (23%). The Kaplan Meier (KM) estimate for the median time to treatment failure was 18.4 months. Median progression-free survival was 24.7 months, and overall survival is still immature. In total 30% of pts had RIB dose reduction and 30% had RIB dose interruption. The majority of all AEs reported were grade 1 or 2; the KM estimate for the median time to first AE after tx start was 26 days. The most common AE reported was leukopenia (all grades:  $n = 51$ , 38%; grade 3:  $n = 12$ , 9%; includes 'white blood cell count decreased' and 'leukopenia'), followed by neutropenia ( $n = 41$ , 31%) and nausea ( $n = 29$ , 22%). Quality of life was maintained throughout the tx duration.

**Conclusions:** RIB + ET showed favourable efficacy and tolerable safety in routine clinical practice and the results were consistent with the ML trials.

#### Abstract ID: 86

### Durable Efficacy of Selpercatinib in Patients (pts) with Medullary Thyroid Cancer (MTC): Update of the LIBRETTO-001 Trial

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**Introduction:** Selpercatinib, a first-in-class highly selective and potent RET kinase inhibitor with CNS activity, is approved in multiple countries for the treatment of RET-mutant MTC and RET fusion-positive thyroid and lung cancers. In the previous report, duration of response (DoR) and progression-free survival (PFS) follow-up (f/u) was limited. Updated analysis of selpercatinib in pts with RET-mutant MTC in LIBRETTO-001 (NCT03157128) was conducted after an additional f/u of 15 months. Primary endpoint was objective response rate (ORR, RECIST 1.1) by independent review committee (IRC). Secondary endpoints included DoR, PFS, and safety.

**Methods:** Efficacy of selpercatinib was evaluated in cabozantinib/vandetanib (cab/van) naïve pts ( $N = 142$ ) and cab and/or van pre-treated pts ( $N = 151$ ) (Table).

**Results:** Naïve and pre-treated pts achieved an ORR of 81.0% and 73.5%, respectively. Despite a median f/u of ~2 yrs, DoR and PFS data are still immature, with response ongoing in most pts. At 2 yrs, 81.1% of naïve pts and 64.4% of pre-treated pts remained progression free. In the safety population (MTC pts with  $\geq 1$  dose,  $N = 319$ ), the most common  $\geq 3$  grade treatment-emergent adverse events (TEAEs) were: hypertension (21.6%),

increased aspartate (7.2%)/alanine (8.2%) aminotransferase, hyponatraemia (7.5%), lymphopenia (6.3%), and diarrhoea (6.3%). In total, 23 pts (7.2%) discontinued treatment due to TEAEs, including 13 pts (4.1%) due to treatment-related TEAEs.

**Conclusions:** With longer f/u and additional pts, selpercatinib continues to demonstrate very durable responses in MTC patients with or without prior cab/van therapy, suggesting first line use of selpercatinib appears to be highly effective in treatment of MTC. The safety profile is unchanged despite longer duration on treatment.

Disclosure: Funded by Eli Lilly and Company.

Previously presented at the ESMO Breast Cancer 2022, “FPN 1656P”, “Matthias Kroiss et al.” – Reused with permission.

**Table: Efficacy of Selpercatinib in RET-mutant MTC**

	Cab/van naïve (N=142)	Prior cab and/or van (N=151)
<b>ORR by IRC, % (95% CI)</b>	81.0 (73.6-87.1)	73.5 (65.7-80.4)
Complete response, n (%)	22 (15.5)	14 (9.3)
Partial response, n (%)	93 (65.5)	97 (64.2)
Stable Disease, n (%)	22 (15.5)	31 (20.5)
Progressive Disease, n (%)	2 (1.4)	2 (1.3)
Not Evaluable (NE), n (%)	3 (2.1)	7 (4.6)
<b>PFS by IRC</b>		
Median PFS, months (95% CI)	NE (NE-NE)	34 (25.7-NE)
Censored, %	83.1	62.3
PFS rate at 24 months, % (95% CI)	81.1 (72.4-87.3)	64.4 (55.4-72.0)
Median f/u, months	24.5	27.6
<b>DoR by IRC</b>		
Median DoR, months (95% CI)	NE (NE-NE)	NE (27.2-NE)
Censored, %	87.0	69.4
DoR rate at 24 months, % (95% CI)	83.7 (73.0-90.4)	64.5 (52.9-73.9)
Median f/u, mo	20.3	22.9

**Abstract ID: 92**

**SAKK 16/14 – Peripheral immune cell populations in response to neoadjuvant durvalumab in patients with stage IIIA(N2) NSCLC**

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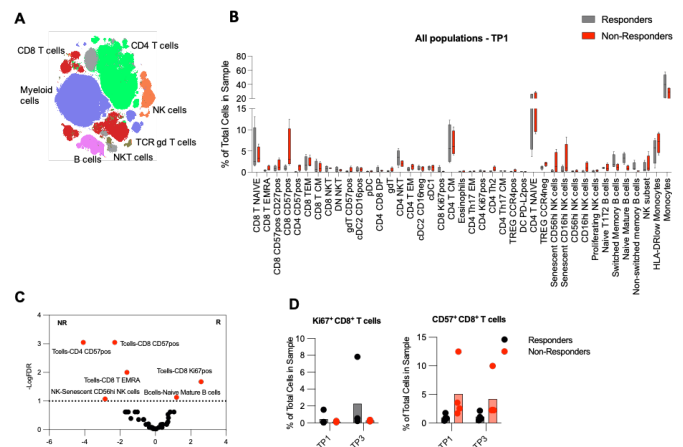
**Introduction:** Various peripheral immune cell populations have previously been implicated as potential biomarkers for response to immune checkpoint inhibition. The single-arm phase II trial SAKK 16/14 confirmed the efficacy of perioperative treatment with the anti-PD-L1 antibody durvalumab in patients with stage IIIA(N2) non-small cell lung cancer (NSCLC). To evaluate the impact of treatment on the immune system, we comprehensively profiled immune cell populations by mass cytometry.

**Methods:** PBMCs were obtained from 5 responder and 5 non-responder patients. For each patient, we analyzed PBMCs obtained before neoadjuvant treatment (TP1) and after sequential neoadjuvant chemotherapy and durvalumab (TP3). PBMCs were stained with a custom antibody panel designed to assess

the expression of 35 protein markers and analyzed with cytometry by time of flight (CyTOF).

**Results:** Four responders and four non-responders had sufficient cell events at both time points for analysis. Cells were displayed in twodimensional space with optSNE and clustered using the FlowSOM algorithm (Fig. 1A) to identify major immune cell populations. Differential enrichment between responders and non-responders was assessed with edgeR. No significant differences in frequencies of major immune populations were detected between the patients displaying different clinical outcomes (Fig. 1B). Senescent, CD57 T cells were enriched in non-responders whereas Ki67 proliferating CD8 T cells were enriched in responders (Fig. 1C). However, these differences were mainly driven by individual patients (Fig. 1D). There was also no on-treatment identified changes in peripheral immune cell populations in responding and non responding patients (TP1 vs TP3, Fig. 1D).

**Conclusions:** Although statistically significant enrichments of some immune populations were detected, the low number of samples prevented us to conclusively rule out changes in other peripheral immune populations. To increase confidence in the results, the analysis should be conducted in a larger patient cohort. Results obtained here will be put into context with other ongoing analyses of the trial SAKK 16/14.



**Abstract ID: 122**

**Real-world analysis of outcomes of first-line chemo-immunotherapy in patients with extensive disease small cell lung cancer (ED-SCLC)**

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**Introduction:** SCLC accounts for approximately 13% of lung cancer diagnoses. For the more than 70% of patients diagnosed with ED-SCLC the standard of care 1L-treatment is platinum and etoposide in combination with PD-L1 blockade, based on the 2-month improvement in median overall survival (OS) in two randomized phase III trials. Yet, the efficacy and safety of first line chemo-immunotherapy in patients with ED-SCLC in a real-world setting remains unclear.

**Methods:** Patients with ED-SCLC who received first-line ICI in combination with platinum-based chemotherapy at ten cancer centers in Switzerland were included in this retrospective analysis. Responses were assessed by the local investigators using standard RECIST v1.1 criteria. Progression-free survival (PFS) and OS were analyzed by the Kaplan-Meier method.

**Results:** 200 patients were included between October 2018 and October 2021. Mean age was 67 years, 117 (58.5%) were males, 125 patients (62.5%) were current and 68 (34.0%) former smokers. 39 patients (25.3%) had a performance status (PS)  $\geq 2$ . 185 patients (92.5%) were diagnosed with ED-SCLC, 15 patients (7.5%) had a relapse after initial limited disease stage treatment. The majority of patients was treated with atezolizumab (n = 190, 95.5%) in combination with chemotherapy, 4.5% received durvalumab. 69 patients (35.2%) had undergone radiotherapy (RT) prior to or during ICI. At the time of analysis, 132 patients (66.0%) have died. Median duration of response was 2.6 months. Median PFS and OS were 6.1 and 11.0 months, respectively. The overall response rate was 75.2%. Immune-related adverse events were seen in 25.0% of patients with no new safety signals. Most frequent sites of tumor progression were lung (21.5%), lymph nodes (19.5%) and brain (15.4%). 112 patients (56.6%) received another systemic therapy after combined chemo-immunotherapy.

**Conclusions:** This is one of the largest retrospective analysis of outcomes of 1L chemo-immunotherapy in patients with ED-SCLC in the real-world setting also including patients with ECOG PS  $\geq 2$ . Outcomes in this real-world cohort are comparable to data in the pivotal trials. It will be important to better characterize the patient population that benefits most from this treatment strategy.

#### Abstract ID: 128

### Contact x-ray radiotherapy (Papillon) to improve complete response and organ preservation in early rectal cancer

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**Introduction:** The paradigm of early stage rectal cancer treatment is rapidly changing with attempts to avoid unnecessary surgery. Radiotherapy (RT) with chemotherapy (RCT) play a major role in terms of local control and tumor sterilization. RT dose escalation would improve the rate of complete responses, but due to the toxicity of the surrounding tissues, this strategy remains limited even with modern external beam RT (EBRT) techniques. Papillon (CXB) is a unique treatment modality using low energy X-ray RT delivered directly to the tumor. We report the outcome of patients (pts) treated with CBX in order to achieve planned-organ preservation

**Methods:** In this intent, 23 patients between 2018 and 2022 were offered Papillon after EBRT or RCT. Pts with a FU <3 months (n = 4) were excluded. The outcome of 19 pts is reported. CXB was commonly delivered in 3 fractions to a dose of 90 Gy. Toxicities were systematically reported. All the pts included in the analysis were properly staged and treatment indications were discussed in multidisciplinary teams. Response to treatment was evaluated at 6 weeks (digital examination, DRE) and at 3 months (MRI, rectoscopy, DRE). FU with MRI, DRE, rectoscopy and endosonography was performed every 3 months for the first 2 years and every 6 months thereafter. A thoracic and abdominal CT scan was performed every 6 months

**Results:** Median FU was 27 months (range, 3–48). Median age was 70 years (range, 49–91). Nine patients had Stage I, 6 stage II, 3 stage III, 1 stage IV. All of our patients had a complete clinical response at their 3 months assessment. Biopsies were taken in 3 patients with dubious lesions, confirming no residual disease. So far, 7 patients achieved long term (>3 years) organ preservation. Acute toxicity was very mild with most patients experiencing erratic bowel movements within the first 3 months. G1 rectitis was the most common late effect (n = 4), except for one patient who needed argon cauterization (G2). There were no treatment related deaths.

**Conclusions:** Our experience with Papillon shows in our selected patients a complete local response achieving long-term organ preservation. Our results are in line with the recently proffered 3-year results of the OPERA randomized trial. This unique treatment modality may help future patients with early stage rectal cancer benefit from low toxicity RT dose escalation to achieve complete local response and avoid surgery.

#### Abstract ID: 83

### Efficacy and safety by menopausal status in monarchE: adjuvant abemaciclib combined with endocrine therapy in HR+, HER2- early breast cancer

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**Introduction:** Abemaciclib is the first and only approved CDK4 & 6 inhibitor in the adjuvant setting for certain types of HR+, HER2-, node-positive, high-risk early breast cancer (EBC). Patient with HR+, HER2- tumours who are premenopausal (preM) may have a different tumour biology and response to endocrine therapy (ET) than postmenopausal (postM) patients, warranting analysis of the prespecified subgroup within monarchE.

**Methods:** Randomized (1:1) patients received adjuvant ET +/- abemaciclib for 2 years+at least 3 years of ET as clinically indicated. Menopausal status (preM vs. postM) at diagnosis was a predefined stratification factor. Efficacy and safety results of abemaciclib+ET vs. ET-alone including invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) were assessed by menopausal status with a data cut-off date=1-April-2021 (median follow-up = 27 months).

**Results:** Among randomized patients, 2451 (43.5%) / 3181 (56.4%) were preM/postM. For preM patients, abemaciclib+ET resulted in clinically meaningful benefit in IDFS (HR=0.573, 95%CI=[0.437, 0.751]) and DRFS (HR=0.592, 95%CI=[0.441, 0.795]). Absolute improvement in IDFS/DRFS rates was 4.1%/3.4% at 2 years, and 5.7%/4.4% at 3 years. Consistent treatment benefit was observed in IDFS (HR=0.798, 95%CI=[0.644, 0.990]) and DRFS (HR=0.761, 95%CI=[0.600, 0.966]) for postM patients. The safety profile for preM patients was consistent with the safety population.

**Conclusions:** Abemaciclib+ET demonstrated a clinically meaningful treatment benefit in IDFS/DRFS vs. ET-alone regardless of menopausal status, with a numerically greater benefit in preM population.

## ONCOREHA / OPS / PALLIATIVE.CH / SANS POSTER PRESENTATION – SUPPORTIVE & PALLIATIVE CARE, REHABILITATION & SURVIVORSHIP

### Abstract ID: 21

#### Clinical symptoms, quality of life and treatment effects during oncological indoor rehabilitation

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**Introduction:** Modern, increasingly multimodal cancer therapy is becoming more and more efficient, but at the price of a large number of somatic side effects and toxicities. These somatic complaints and the cancer diagnosis can also lead to high psychological stress and a reduced quality of life. The aims of this prospective study were to record and evaluate these complaints at the beginning of oncological rehabilitation and to analyze the therapeutic effects of multimodal treatment in improving these complaints and symptoms until end of rehabilitation.

**Methods:** Between 10/2020 and 04/2022, 340 patients (178 female) were evaluated using standardized questionnaires (ESAS, SIF, HADS, PROMIS-10, EQ-5D) for the presence of somatic and psychological complaints and quality of life after admission to our hospitals. In addition, physical performance was recorded using 6-min walking test, time up and go test (TUG) and hand strength measurement (Jamar). To document the achieved rehabilitation effects, a second assessment (same tests) was carried out before discharge from the clinic.

**Results:** Mean age was 63,9 +/- 12,5 years. Most patients had colorectal cancer (n = 60; 18.6%), pancreas/bile ducts/liver (n = 48; 14.9%) and breast cancer (n = 38; 11.8). The ESAS showed a high burden of somatic impairments (27.3 ± 15.1), especially fatigue (n = 243; n = 158 ≥ score 5). This was also confirmed by SIF (20.8% ≥ 5). Other common complaints were loss of appetite / taste (n = 120 ≥ score 5) and a significantly reduced sense of well-being (n = 117 ≥ score 5). The subjective feeling of fatigue and lack of strength could also be verified based on significantly reduced results in the physical assessments using a 6-minute test, time up and go test and reduced hand strength.

Additionally, both the ESAS and the HADS showed significantly high values for anxiety (n = 65 ≥ score 5; HADS 37.8%) and depression (n = 62 ≥ score 5; HADS 28.6%) and the PROMIS-10 and EQ-5D a significant reduced quality of life (QoL; mean score 48,6±19,8)

In 288 cases (84.7%) a second assessment could be carried out before discharge. Almost all parameters showed a highly significant improvement. Both the PROMIS-10 and the ESAS showed a highly significant improvement (14.2±2.5 vs. 11.7±2.7, p <0.001; ESAS 27.3±15.1 vs. 19.7±15.1 vs. 19.7±13.1, p <0.001). In particular, fatigue improved significantly in the ESAS and SIF (4.7±5.4 vs. 2.5±1.7, p <0.001) as well as the functional independence (FIM: 103.9±20.9 vs. 111.2±19.5; p <0.001). These results were also confirmed by the physical function tests (6min walking test 373.1±151.0m vs. 467.4±143.2m; TUG 11.7±9.7s vs. 8.3±5.6s; Jamar reduced: 29.4 vs. 20.2%; respectively p <0.001). In addition, there was also a highly significant improvement in QoL, which was significantly reduced on admission (EQ-5D: 48.6±19.8 vs. 66.9.4±18.6; p <0.001), at the end of the rehabilitation.

**Conclusions:** The available data demonstrate the high rehabilitation needs of oncological patients and the great importance of routine screening for fatigue and psychological distress. Additionally, our data prove the high efficiency and effectiveness

of oncological rehabilitation both in the alleviation of somatic and psychological impairments and thus leads to a significant improvement in the mostly severely impaired quality of life of those affected. Therefore, multimodal oncological rehabilitation should be an integral part of interdisciplinary cancer treatment.

### Abstract ID: 25

#### A model of care using patient-reported outcomes for remotely managing symptoms of cancer patients treated with immune checkpoint inhibitors

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**Introduction:** Patients treated with immune checkpoint inhibitors (ICI) experience a complex range of symptomatic treatment toxicities. Close follow-up, timely intervention and self-management support are key to preventing and mitigating severe symptoms, yet intervals between treatments can be as long as three weeks. Interventions leveraging patient-reported outcomes (PRO) to monitor and manage symptoms remotely in patients treated with chemotherapy have shown promise by facilitating timely treatment, and improving symptom control, patient quality of life, and overall survival. Patients treated with ICI may thus benefit from similar interventions.

We report on the development of a PRO-based model of care to facilitate remote symptom monitoring, management and self-management support for patients treated with ICI, in two Swiss university hospitals.

**Methods:** A theoretical framework to guide the development of the model of care was identified through literature review. Communication flow, barriers, facilitators, clinical roles and resources involved in remote symptom monitoring, patient management and self-management support were defined through multiple internal discussions with the oncology team. A PRO measure was developed through an expert Delphi, and iteratively integrated within an electronic mobile platform. Telephone triage tools were identified in the literature to standardize patient management and define the workflow between triage nurses and physicians.

**Results:** The model of care is grounded on the eHealth-enhanced Chronic Care Model. Patients self-declare symptoms through a weekly PRO-CTCAE™-based questionnaire in the electronic application. Active symptoms are assessed daily. New or worsening symptoms are assessed over the phone by nurses using the United Kingdom Oncology Nursing Society 24 hour Triage Tool. Comprehensive triage reports are included in the electronic health record. Physicians are contacted via e-mail or telephone to address non-urgent or urgent symptoms respectively.

**Conclusions:** This PRO-based model adheres to recent guidelines for integrating PRO in routine practice, describing their use in the flow of care across patients, triage nurses and the broader oncology hospital team. By including standardized tools to assess and manage symptoms, it aims to facilitate the timely detection and prevention of severe symptoms, and enhance self-management support.

**Abstract ID: 26****Evaluation of the implementation of the Symptom Navi Programme, a nurse-led intervention supporting cancer outpatient self-management**M. Bana<sup>1,2</sup>, K. Ribi<sup>3,4</sup>, S. Zürcher<sup>5,6</sup>, M. Eicher<sup>3,6</sup>

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**Introduction:** The Symptom Navi Programme (SNP) is a standardised self-management support (SMS) intervention employing patient coaching and facilitating self-efficacy aiming at reducing patients' burden of symptoms. As part of an implementation study, we included the analysis of the nurses' behaviour before and after SNP implementation.

**Methods:** We conducted semi-structured focus group interviews with nurses at Swiss (German-speaking) outpatient cancer centres. Participants completed study-specific fidelity questionnaires after each SNP intervention and study team members conducted structured observations of the interventions. Thematic analysis and descriptive statistics were performed. The Howell et al. (2017) self-management education framework informed data interpretation.

**Results:** We conducted 4 focus group interviews with 14 oncology nurses before SNP training and 3 interviews with 9 nurses at study end. Before the training, nurses emphasised that they had established a solid partnership with their patients, and had informed them carefully about cancer therapy and its expected side-effects. Their SMS intervention was mainly based on Cancer League brochures and pharmaceutical information material complemented with inhouse leaflets. At study end, nurses referred mainly to SNP leaflets to guide patients, structure SMS interventions, and tailor information to patient needs. The nurses estimated that patients' communication regarding symptoms had improved and that patients showed more self-management behaviour than before the intervention. Employing SNP within daily nursing routine was considered feasible and nurses reported high fidelity rates to the SNP training with on average 92% of all items applied (95% CI: 87–95%). However, proactive coaching and facilitating patient self-efficacy did not appear in the focus groups nor in the observations. Nurses stated that they would require regularly updated SNP leaflets for long-term SNP implementation.

**Conclusions:** Although nurses self-reported high fidelity to the SNP training, their actual SMS behaviour was only partly in keeping with the intended intervention. In particular, coaching and the facilitation of patient self-efficacy was poorly reported and rarely observed. Nurse training would need to be enhanced to facilitate effective behaviour change to help improve SMS within daily routines.

**Abstract ID: 61****SwissCanOn – scientific patient registry for medicinal cannabis in oncology including ePROs – Trial in Progress**A. Trojan<sup>1</sup>, S. Breitkopf<sup>2</sup>, S. Pitti<sup>3</sup>, M. Heeren<sup>4</sup>

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**Introduction:** Worldwide, cannabis-based medicinal products (CBMP) are becoming an increasingly popular alternative to established supportive medicinal products in cancer related

symptoms including chemotherapy-induced nausea and vomiting, pain, anxiety, insomnia, anorexia, in acute and palliative care. Although there is clinical data supporting the hypothesis of cannabinoid analgesia and further positive influence in several indications, clinical evidence is limited leading to several uncertainties. The registry SwissCanOn is a multicenter, bi-national, prospective, patient registry that aims to collect comprehensive real-world data in Switzerland (CH) and Germany (DE) on prescription, usage, and effectiveness of CBMP in the treatment of refractory oncological indications, including patient reported outcomes (ePROs) via the "consilium care TM" app.

**Methods:** The first data assessment period is scheduled for two years and plans to include at least 100 patients. At patient's registry inclusion, physicians collect data such as diagnosis, medical treatment, etc. in a web-based application. Patients download the corresponding patient app and continuously enter their information on dosage, symptoms (ePROs), wellbeing, cognition, vital signs, etc. A CME certified medical education on CBMP is offered for participating medical doctors throughout the project and cooperation between all stakeholders is strongly supported.

**Results:** A first and purely descriptive data presentation with 6 patients in CH shows that 50% of patients stopped registry participation early due to either side effects or preference for non-medicinal cannabis.

**Conclusions:** This first data presentation shows that the SwissCanOn registry is an adequate method to (1) collect a sustainable data basis for a variety of different research questions, (2) serve as a solid basis leading to further clinical investigations, (3) create a growing network of patients, academic and industrial partners emphasizing science, (4) allow physicians to track efficacy and side effects of CBMP therapy with their patients, and (5) associate the project with an academic program on medicinal cannabis.

**Abstract ID: 100****Development of a reference model for Patient and Public Involvement in oncology research in French-speaking Switzerland**S. Colomer-Lahiguera<sup>1</sup>, T. Corbière<sup>1</sup>, K. Soukup<sup>1</sup>, F. Reeb-Landry<sup>1</sup>, A. Addeo<sup>2</sup>, M. Eicher<sup>1,3</sup>

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**Introduction:** Patient and public involvement (PPI) in research is increasingly encouraged as a means of improving its validity and relevance. Although gaining momentum, the implementation of PPI in research in Switzerland remains recent. Our aim was to establish a PPI model for cancer research adapted to the local context that will assist researchers to apply PPI approaches within their projects.

**Methods:** Two semi-directed focus groups were conducted with 10 local key informants including patient representatives (2), oncology healthcare professionals (3), PPI experts (2), experts in patient-reported measures (2), and health managers (1). A deductive thematic approach was used to identify the benefits, limitations and facilitators of establishing a PPI model in cancer research in the local context. In addition, we identified established frameworks in research and/or cancer research to analyse the main concepts and elements to be considered.

**Results:** Consensus was reached on the benefits of involving patients in research, allowing for more specific, relevant, and

comprehensive studies. Participants also identified limiting factors such as the lack of PPI culture in healthcare research or the need for a paradigm shift at different levels. Among facilitators for the success and long-term sustainability of PPI were awareness of the resources, capacities of the research organization and capabilities of the patients, the need for PPI training for both researchers and patients, and the recognition of patient's contributions. Nine different frameworks from seven countries were retained for further analysis. Main elements identified related to the goals to be achieved (why?), the types of patients to be involved (who?), the knowledge that patients can contribute (what?), and their degree of involvement (how?).

**Conclusions:** The resulting SCCL-PPI model is multidimensional, comprising the stages of research, different levels and types of involvement, capabilities required from patients and capacities of the research group/organization. It is important for researchers to make a careful assessment of each of these dimensions. We chose to depict it using the Rubik's cube to reflect the importance of adaptability of a PPI approach to each individual research project.

#### Abstract ID: 111

### Predictors of the adoption of guideline-based end-of-life and Bereavement Support for families in cancer care (BEST Care study)

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**Introduction:** Terminal cancer and the subsequent loss of a close other is a stressful, incisive experience that significantly affects the physical and mental health of family members. Yet, best practice recommendations for family support during end-of-life (EoL) and in bereavement (BER) are often not consistently adopted into routine care. This implementation research study identifies enablers and barriers of adoption in EoL cancer and BER care.

**Methods:** A sample of 81 nurses from seven acute and home care organisations providing care to cancer patients in German-speaking Switzerland completed an online survey on family support practices, organisational determinants (i. e., financial incentive, concept, culture, barriers) and individual characteristics, skills, resources, and experiences with family support. The two study outcomes are current adoption of guideline-based family support practices in EoL and BER care, each measured by a self-developed eleven-item quantitative assessment. Cross-sectional multiple fractional logistic regression and OLS identified the incremental effects of organisational and individual predictors.

**Results:** Working in a palliative care unit was the strongest predictor of adoption of family support practices in both EoL ( $p < 0.01$ ) and BER care ( $p < 0.01$ ). Age of nurses had a negative effect, even after controlling for work experience ( $p < 0.001$  in EoL;  $p < 0.05$  in BER), and a high score of a supportive organisational culture had a positive effect ( $p < 0.05$  in EoL;  $p < 0.01$  in

BER). Further positive predictors in EoL were the presence of a family support guideline ( $p < 0.05$ ), sufficient privacy with family members ( $p < 0.01$ ), high family nursing skills ( $p < 0.05$ ), and high self-perceived competence in family support ( $p < 0.05$ ). Further positive predictors in BER were reimbursement of conversations with family members after the patient's death ( $p < 0.05$ ), and sufficient nurse training ( $p < 0.05$ ).

**Conclusions:** A combination of organisational and individual context factors predict adoption. In the context of family support in EoL and BER care in cancer settings, some factors show much more pronounced statistical effects than others. As such, they provide an understanding of barriers and facilitators that need to be targeted with future implementation strategies, with the aim to promote adoption of guideline-based care delivery at the EoL and in BER.

#### Abstract ID: 143

### Patient, caregiver, and healthcare professional experience in adoptive cell therapies: An experienced-based co-design study

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**Introduction:** Adoptive cell therapy with tumor-infiltrating lymphocytes (ACT-TIL) is a rapidly growing strategy in the field of cancer therapies that relies on delivering specific autologous anti-tumor immune cells. While ACT-TIL entails a complex treatment procedure, the experience of care in this context remains understudied. Experience-Based Co-Design (EBCD) positions patients as active partners together with healthcare providers in services quality improvement. We herein present the approaches used to involve patients on a phase I clinical trial of ACT-TIL aiming to build consensus on priorities and solutions to improve care delivery.

**Methods:** EBCD relies on different stages articulating qualitative and co-design methods, from observation, interviews, and workshops.

**Results:** Patient and Public Involvement (PPI) strategies is applied on three dimensions. As participatory research method, EBCD involves patients as participants whose personal engagement contributes to validate qualitative results and to develop priorities for service improvement. In addition, we involve two patients representatives with experiences in similar contexts. The first patient was consulted to give advice on the content of the information provided to participants including the informed consent, and provided feedback on the relevance and comprehensibility of the interview guides; a second patient representative is member of the Advisory Board constituted to guide the study progress. This positions the patient as co-researcher participating on the protocol design, analysis and dissemination of the results, and to elaborate recommendations for implementation.

**Conclusions:** By applying different involvement approaches (stages, levels and types) we aim to assure the relevance, comprehensibility and to increase the acceptability of the study and results.

## EPOSTER – HEMOSTASIS, TRANSFUSION MEDICINE, VASCULAR, LABORATORY MEDICINE

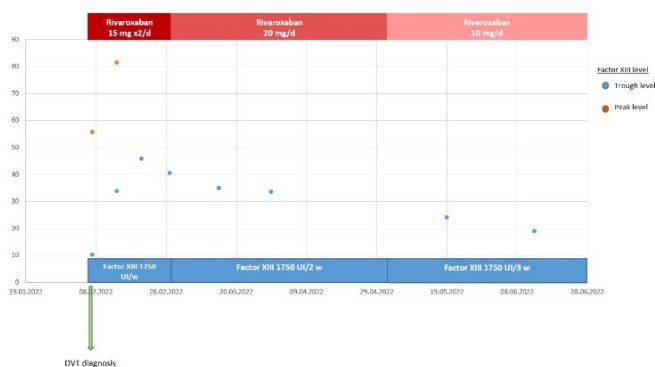
## Abstract ID: 22

**Recurrent venous thromboembolic disease in a patient with severe congenital factor XIII deficiency.**L. Bounaix<sup>1</sup>, P. Fontana<sup>1</sup>, A. Casini<sup>1</sup><sup>1</sup>Hemostasis, Geneva University Hospital, Geneva

**Introduction:** Congenital factor XIII (FXIII) deficiency is a very rare bleeding disorder. In patients with severe FXIII deficiency, bleeding complications are frequent, sometimes life-threatening, while thrombotic events seem to be rare. To our knowledge, we report the first case of congenital factor XIII deficiency associated with recurrent venous thrombotic events.

**Methods: Results:** Patient was diagnosed with severe FXIII deficiency when she was 5 years old as she was referred for cutaneous hematomas. At the age of 31, she presented a provoked left deep vein thrombosis (DVT; popliteal vein) with several risk factors (recent cryoprecipitate infusions, combined estrogen-progestin oral contraceptive, long haul travel). Thrombophilia testing showed heterozygous factor V Leiden mutation. At the age of 36, she had an uneventful pregnancy with a venous thromboprophylaxis by enoxaparin throughout the pregnancy and a concomitant factor XIII supplementation. When she was 48 years old, she had an unprovoked DVT (right femoral and popliteal veins), 6 days after factor XIII infusions (1750 IU, 25 UI/kg), treated by rivaroxaban 15 mg every 12h for 3 weeks then 20 mg/d for 6 months. It has been decided to maintain factor XIII trough level above 45% during anticoagulation. Finally at the age of 58, she presented an unprovoked pulmonary embolism associated to a DVT (left femoral vein) 2 weeks after factor XIII infusions (750 IU, 10 UI/kg). Day of thrombosis diagnosis, factor XIII level was 10.3%. We started rivaroxaban 15 mg twice a day for 3 weeks with a target FXIII trough level > 50% followed by 3 months of rivaroxaban 20 mg/d with a target FXIII trough level of > 30%. After the treatment of the acute phase, because of recurrence of thromboembolic events, we decided to continue long term anticoagulation with a reduced dose of rivaroxaban 10 mg/d together with FXIII infusion in order to maintain trough factor XIII level between 15–20%, corresponding to factor XIII substitution every 3 week (1750 IU, 20 UI/kg). Factor XIII activity was measured by a chromogenic test (Berichrom® F XIII, Siemens, Atellica Coag 360).

**Conclusions:** Rare bleeding disorders do not fully protect against occurrence of thrombosis. Management of thrombotic complications in such patients is challenging because physicians have to deal with both additional risk of bleeding related to antithrombotic therapy and the risk of recurrent thrombosis.



## Abstract ID: 60

**Pitfalls of measuring thrombination and chromogenic anti-Xa in presence of polybrene**K. Vrotniakaite-Bajerciene<sup>1,2</sup>, M. Pavicic<sup>1</sup>, M. Reusser<sup>1</sup>, J. Brodard<sup>1</sup>, O. Kocher<sup>1</sup>, A. Angelillo-Scherrer<sup>1,2</sup><sup>1</sup>Department of Hematology and Central Hematology Laboratory, Bern University Hospital, Bern, Inselspital, Bern, <sup>2</sup>Department of BioMedical Research, University of Bern, Bern

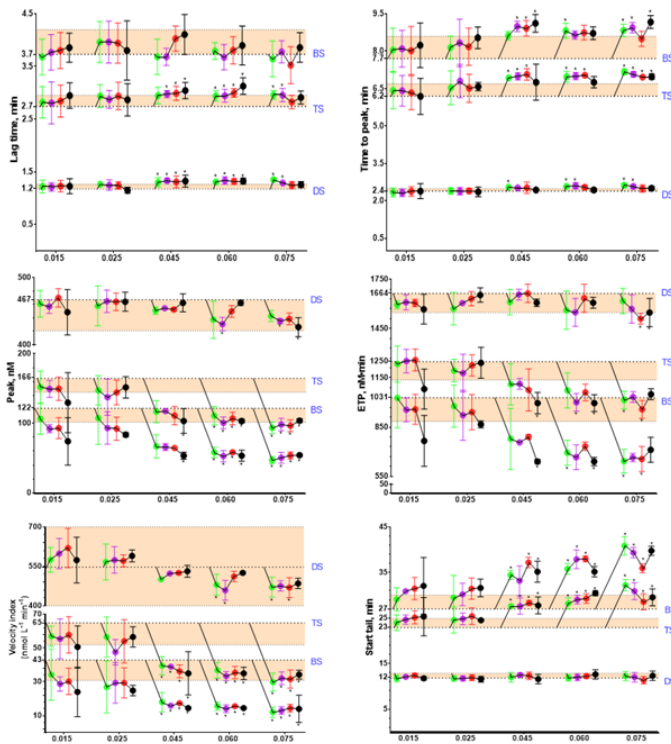
**Introduction:** Hexadimethrine bromide (Polybrene) is used in thrombination (TG) assay to antagonize the effect of unfractionated heparin (UFH). However, its usage lacks standardization and its effect on different chromogenic anti-Xa assay is unknown. We aimed to investigate the effect of polybrene on TG and chromogenic anti-Xa measurement in presence and absence of UFH and determine the best concentration of polybrene for TG measurement.

**Methods:** Polybrene was added at different concentrations (0.015mg/mL, 0.025 mg/mL, 0.045 mg/mL, 0.060 mg/mL, and 0.075 mg/mL) to commercial frozen normal plasma (VisuCon-F®, Affinity Biologicals Inc) treated with UFH (Liquemin®, Drossapharm AG) at concentrations of 0.3 IU/mL, 0.8 IU/mL and 1.5 IU/mL or alone. The aliquots were split and TG with ST-Genesis® (Stago) using STG-BleedScreen, ThromboScreen, DrugScreen and anti-Xa level measurement using Biophen® (Heparin LRT, Hyphen BioMed) and STA®-Liquid (Stago) assays were performed 3 times. The critical difference for each TG parameter and statistical difference between the groups were calculated with GraphPad Prism, V 9.1.2.

**Results:** Higher concentrations of polybrene (up to 0.045 mg/mL) showed a false, dose dependent anti-Xa activity despite the absence of UFH in STA®-Liquid assay, whereas the lower concentrations of polybrene (less than 0.060 mg/mL) failed to antagonize UFH in Biophen® assay despite the reversal of TG. Polybrene showed a statistically significant dose-dependent anticoagulatory effect in lag time, time to peak, start tail, and velocity index from 0.045 mg/mL, and peak, endogenous thrombin potential from 0.060 mg/mL (Figure 1). Triggering TG with higher concentration of tissue factor was less affected by polybrene with the exception of lag time. Both concentrations of polybrene 0.015 mg/mL and 0.025 mg/mL sufficiently antagonized UFH without a significant anticoagulatory effect, however the latter concentration performed within the critical difference better (Figure 1).

**Conclusions:** The polybrene concentration of 0.025 mg/mL shows the best TG profile when reversing a wide range of UFH. Due to the overestimation of anti-Xa with Biophen® assay when using lower concentrations of polybrene, the anti-Xa level should be monitored with STA®-Liquid assay.

**Figure 1.** All thrombogenesis parameters in BleedScreen®, ThromboScreen® and DrugScreen® assay using ST-Genesia® in presence of different concentrations of polybrene (mg/mL) shown in the x-axis in absence and presence of unfractionated heparin (IU/mL) represented in different colors. Green represents no unfractionated heparin; purple – 0.3 IU/mL; red – 0.8 IU/mL; black – 1.5 IU/mL. The mean value of each parameter in normal commercial plasma without polybrene and unfractionated heparin is displayed in dotted-line. The critical difference of each parameter of each assay is colored in orange. Values are presented as mean and standard deviation. Statistical difference between each group against normal plasma was calculated with Mann-Whitney test. \*p<0.05 versus thrombogenesis parameter of normal plasma. BS, BleedScreen; DS, DrugScreen; ETP, endogenous thrombin potential; TS, ThromboScreen



**Abstract ID: 69**

**Adherence to thrombophilia testing guidelines and its influence on anticoagulation therapy: a single-center cross-sectional study**

K. Vrotniakaite-Bajerciene<sup>1,2</sup>, T. Tritschler<sup>3,4</sup>, K. A. Jalowiec<sup>1</sup>, H. Broughton<sup>1</sup>, F. Schmidli<sup>1</sup>, J. S. Schneider<sup>1,2</sup>, A. Haynes<sup>5</sup>, A. Rovo<sup>1</sup>, J. A. Kremer Hovinga<sup>1,2</sup>, D. Aujesky<sup>3</sup>, A. Angelillo-Scherrer<sup>1,2</sup>

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**Introduction:** Guidelines on thrombophilia are based on expert recommendations since the collected evidence is scarce. Furthermore, evidence about their yield on clinical decisions is unknown. We aimed to investigate the adherence to thrombophilia testing guidelines and its therapeutic impact in patients with guideline-adherent and non-adherent testing.

**Methods:** We conducted a single-center cross-sectional study of patients referred for thrombophilia testing at the outpatient clinic of a tertiary hospital between 01/2010-10/2020. We systematically evaluated the adherence of thrombophilia testing to internal guidelines and the influence of test results on anticoagulation therapy. Using multivariable logistic regression, we evaluated the association between clinical characteristics and influence of thrombophilia tests on anticoagulation therapy in the entire cohort and by indication for referral.

**Results:** Of 3686 included patients, who were mostly referred for venous thromboembolism (2407, 65%) or arterial thrombosis (591, 16%), 3550 patients (96%) underwent thrombophilia testing. Indication for testing was in accordance with guidelines

in 1208 patients (33%). Test results influenced treatment decisions in 56 of 1102 work-ups (5.1%) that were adherent to guidelines, and in 237 of 2448 (9.7%) non-adherent work-ups (absolute difference, 4.3%; 95% confidence interval, 2.9–6.3%). Age <50 years, female sex, absence of risk factors and co-morbidities, weakly provoked venous thromboembolism and referral indication other than venous thromboembolism were associated with influence on anticoagulation therapy (Table 1).

**Conclusions:** Adherence to guidelines for thrombophilia testing was poor and did not have an impact on treatment decisions. Testing in age <50 years and weakly provoked VTE was independently associated with impact on treatment. Refinement of selection criteria is needed to increase the therapeutic impact of thrombophilia testing.

**Table 1.** Association between clinical characteristics and influence of thrombophilia testing on treatment decisions in the full study cohort and Patients with venous thromboembolism. Influence of clinical characteristics was calculated by logistic regression model. Models were adjusted for recurrent venous and arterial thromboembolism in the entire cohort; recurrent and unprovoked VTE in patients with VTE. Risk factors included smoking, immobilization > 4 hours, cancer, central intravenous catheter, infection, estrogen-based treatment, pregnancy, cancer, obesity, trauma, surgery, cancer, and its medication. Co-morbidities included diabetes, arterial hypertension, liver cirrhosis, kidney failure, rheumatic diseases, depression, dyslipidemia, lung diseases, neurological disorders, cardiovascular diseases, and chronic inflammatory diseases. Abbreviations: CI, confidence interval; OR, odds ratio; VTE, venous thromboembolism.

Clinical characteristic	Crude OR (95% CI)	Adjusted OR (95% CI)
<b>Full cohort (n=3686)</b>		
Age <50 years	2.20 (1.64-2.95)	2.20 (1.64-2.95)
Female	1.92 (1.47-2.51)	1.92 (1.47-2.51)
<b>Indication for consultation</b>		
VTE	1 (ref)	1 (ref)
Asymptomatic patients	7.09 (5.11-9.84)	7.12 (5.12-9.90)
Arterial thrombosis	6.60 (4.76-9.17)	6.60 (4.75-9.16)
Pregnancy-related morbidity	15.73 (9.95-24.86)	15.80 (9.98-24.99)
<b>Number of co-morbidities</b>		
≥2	1 (ref)	1 (ref)
1	1.33 (0.89-1.98)	1.32 (0.89-1.97)
0	1.61 (1.15-2.26)	1.61 (1.14-2.26)
<b>Number of risk factors for thromboembolism</b>		
≥2	1 (ref)	1 (ref)
1	2.10 (1.49-2.96)	2.10 (1.49-2.96)
0	2.42 (1.74-3.38)	2.42 (1.73-3.37)
<b>Patients with VTE (n=2407)</b>		
Age <50 years	1.93 (1.12-3.33)	1.73 (1.01-3.01)
Female	1.84 (1.08-3.12)	1.60 (0.93-2.76)
<b>Risk factors for VTE</b>		
Unprovoked	1 (ref)	1 (ref)
Minor risk factor	2.90 (1.46-5.75)	2.94 (1.48-5.84)
Major risk factor	0.97 (0.35-2.69)	0.97 (0.35-2.69)
Family history of VTE in first-degree relative	1.14 (0.67-1.92)	1.15 (0.68-1.94)
Recurrent VTE	0.45 (0.22-0.91)	0.49 (0.24-0.99)
<b>Number of co-morbidities</b>		
≥2	1 (ref)	1 (ref)
1	1.02 (0.43 – 2.43)	1.07 (0.45 – 2.54)
0	1.78 (0.89 – 3.56)	1.86 (0.93 – 3.72)

**Abstract ID: 70**

**Predictive factors for thrombophilia diagnosis: a single-center cross sectional study**

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**Introduction:** Clinical utility of thrombophilia testing has been proven to be limited. As only high-risk thrombophilia seems to influence a further treatment decision, more clear and homogeneous selection criteria for high-risk thrombophilia are needed. The aim of this study was to investigate the strongest predictive factors for hereditary low- and high-risk thrombophilia, and for antiphospholipid syndrome (APS).

**Methods:** We conducted a single-center cross sectional study of 3686 patients referred to the thrombophilia consultation at



tertiary university center from 01/2010 to 10/2020. Using logistic regression model, we investigated predictive factors of getting a positive result for hereditary and acquired thrombophilia in a cohort of patients selected for thrombophilia work-up.

**Results:** In 3550 patients (94%), a partial or full thrombophilia testing was performed and 1258 patients (28.9%) displayed at least one thrombophilia. Most of the included patients (2407, 65%) were referred because of venous thromboembolism (VTE) and arterial thromboembolism (591, 16%), followed by asymptomatic patients (567, 15%) and pregnancy morbidity (121 patients, 3%). Younger age (<50 years) and positive personal and first- and second-degree family history for VTE were associated with hereditary low-risk thrombophilia (defined in Table 1), whereas the presence of risk factors and co-morbidities reduced the likelihood of a hereditary low-risk thrombophilia diagnosis. Hereditary high-risk thrombophilia was more likely to be diagnosed in young female patients (<50 years) without co-morbidities, with a positive first-degree family history for VTE and with high D-dimer level (>500 µg/L) at time of the work-up, while the presence/absence of risk factors did not affect a positive hereditary high-risk thrombophilia finding. Meanwhile, APS was more likely to be diagnosed in patients with ≥2 co-morbidities (Table 1).

**Conclusions:** Several clinical and laboratory characteristics were associated with hereditary and acquired thrombophilia. A more personalized approach to improve hereditary high-risk thrombophilia diagnosis yield, including when risk factors are present, should be prospectively assessed.

**Table 1.** Characteristics of patients having a positive result for hereditary or acquired thrombophilia and associated odds ratios. Univariable logistic regression model were used to assess the predictors of thrombophilia. OR, odds ratio; CI, confident interval. \* No is used as a reference (1 (ref)) for this variable. **Low-risk hereditary thrombophilia** is defined by presence of heterozygous factor V Leiden and prothrombin G20210A mutation, plasminogen activator inhibitor type 1 mutation, methylenetetrahydrofolate reductase mutation or dysfibrinogenemia. **High-risk hereditary thrombophilia** comprises homozygous factor V Leiden or prothrombin G20210A mutation, protein C, S and antithrombin deficiency and compound heterozygous factor V Leiden and prothrombin G20210A mutation. Risk factors include smoking, immobilization, cancer, central intravenous catheter, infection, pregnancy, cancer, obesity, trauma, surgery, cancer and its medication. Co-morbidities include diabetes, arterial hypertension, liver cirrhosis, kidney failure, rheumatic diseases, depression, dyslipidemia, lung diseases, neurological disorders, cardiovascular diseases and chronic inflammatory diseases

Clinical characteristic	Hereditary low-risk thrombophilia		Hereditary high-risk thrombophilia		Antiphospholipid syndrome	
	Crude OR (95% CI)	P value	Crude OR (95% CI)	P value	Crude OR (95% CI)	P value
<b>Age &lt; 50 years*</b>						
Yes	1.46 (1.23-1.73)	<0.001	1.82 (1.34-2.46)	<0.001	0.95	0.784
<b>Gender</b>						
Male	1 (ref)		1 (ref)		1 (ref)	
Female	1.17 (0.99-1.37)	0.061	1.51 (1.14-1.99)	0.004	1.16 (0.79-1.69)	0.447
<b>Number of co-morbidities</b>						
0	1 (ref)		1 (ref)		1 (ref)	
1	0.72 (0.59-0.88)	0.001	0.60 (0.43-0.85)	0.004	1.33 (0.85-2.08)	0.218
≥2	0.51 (0.41-0.63)	<0.001	0.45 (0.30-0.67)	<0.001	1.63 (1.05-2.52)	0.03
<b>Number of risk factors</b>						
0	1 (ref)		1 (ref)		1 (ref)	
1	0.76 (0.61-0.91)	0.003	1.16 (0.85-1.59)	0.346	0.96 (0.62-1.49)	0.859
≥2	0.60 (0.49-0.73)	<0.001	1.06 (0.77-1.47)	0.710	0.91 (0.58-1.42)	0.668
<b>Positive personal history for venous thromboembolism*</b>						
Yes	1.31 (1.05-1.64)	0.016	1.12 (0.78-1.62)	0.545	1.04 (0.61-1.77)	0.878
<b>First degree family history for venous thromboembolism*</b>						
Yes	1.78 (1.51-2.09)	<0.001	1.39 (1.06-1.81)	0.016	0.64 (0.41-0.99)	0.046

**Abstract ID: 72**

**Physiological correction of hereditary hypofibrinogenemia during pregnancy**

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**Introduction:** Hereditary hypofibrinogenemia is a rare fibrinogen disorder characterized by decreased levels of fibrinogen. Pregnant women with hypofibrinogenemia are at risk of adverse obstetrical outcomes, depending on the fibrinogen level. We investigated how physiological changes of hemostasis throughout the pregnancy impacts the hemostatic balance in a woman with hereditary mild hypofibrinogenemia.

**Methods:** Fibrin clot properties were analyzed by turbidimetry and scanning electron microscopy; clot weight and red blood cells retention were measured by whole clot contraction; in-vitro thrombin generation was assessed by calibrated automated thrombogram and ex-vivo by TAT.

**Results:** Throughout the pregnancy, the fibrinogen levels increased reaching normal values in the third trimester (activity 3.1 g/L, antigen 3.2 g/L). In parallel, the fibrin polymerization increased, the fibrinolysis decreased, the fibrin clot network became denser with thicker fibrin fibers, and the fibrin clot weight and red blood cells retention increased, reaching control's value at the third trimester. Similarly, in-vitro and ex-vitro thrombin generation increased, reaching maximum values at the delivery.

**Conclusions:** In mild hereditary hypofibrinogenemia the physiological increase of fibrinogen and thrombin generation assures an efficient hemostasis. Extended studies are needed to establish whether global hemostasis assays can be useful in monitoring pregnancies and tailor the management of pregnant women with more severe hypofibrinogenemia.

**Abstract ID: 73**

**Software development to quantify fibrin clot images by laser scanning confocal microscopy (LSCM)**

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**Introduction:** Fibrin clot structure is associated with the thrombotic or bleeding risk. The fibrin clot structure characterisation from LSCM images are usually performed manually by quantifying 2D images. The aim of this work was to develop a new in-house software in order to quantify pore size, fibrin fibre diameter and fibrin density from LSCM from 3D images.

**Methods:** CRYOcheck pooled normal plasma (fibrinogen (fg): 2.5 g/L), fibrinogen calibrators (Siemens, fg: 0.7 – 10.4 g/L), and in-house purified fibrinogen (fg: 0.5, 1.0 and 1.5 g/L) were used in order to prepare clots of different structures varying thrombin concentration 0.1, 0.5 or 1.0 units/mL. Samples were clotted in the presence of Alexa Fluor™ 488 fibrinogen conjugate. Imaging was performed using a Nikon A1R spectral confocal microscope with a 60x oil NA1.4 CFI Plan Apo objective at a resolution of 0.08 µm/pixel laterally an 0.1 µm/pixel axially. The obtained 3D stacks were filtered with Denoise.ai (Nikon NIS-Elements) to increase the image signal-to-noise ratio. Then, the 3D stacks were resampled to have cubic voxels, and fibrin fibers were segmented automatically using Otsu's method followed by a skeletonization. Euclidean distance transformation inside and outside the fibers were computed. Fibrin density was expressed as the segmented fibrin fiber volume divided by the volume of acquisition; fibrin fiber diameter was expressed as

twice the average distance along the skeleton lines and pore size was expressed as the average of the distance transform outside the fibers.

**Results:** In our conditions, the distance distribution outside the fibers did not follow a Rayleigh distribution, both in plasma (CRYOcheck and fibrinogen calibrators), and purified fg, as has been previously described.

**Conclusions:** The software developed in-house could be used to measure pores size and fibers diameter for plasma samples with fg concentration of 0.7 to 3.9 g/L clotted with 0.1 – 0.5 units/mL thrombin, but not at higher fg concentrations, since the values were similar to those obtained at 3.9 g/L. With 1.0 units/mL of thrombin the fg cut off value was 2.6 g/L. With clots made with purified fg, pores size and fibres diameter can be measured with 0.1 – 0.5 units/mL thrombin, but not with 1 units/mL, since the values were similar to those obtained at 0.5 units/mL thrombin. The measurement of fibrin density is not reliable.

#### Abstract ID: 74

### Global coagulation assays capture the hemostatic status of Hemophilia A and B patients

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**Introduction:** Hemophilia A and B (HA and HB) are rare bleeding disorders caused by deficiency in coagulation factor VIII (FVIII) or IX (FIX), respectively. HA/HB patients are classified according to their baseline factor activity as severe (<1%), moderate (1–5%) or mild (>5–40%). Nevertheless, in patients with similar levels of FVIII or FIX, a wide heterogeneity of hemorrhagic manifestations is observed. This supports the concept that the activity of a single coagulation factor does not reflect the hemostatic status of the individual patient. Our aim was to evaluate whether global coagulation assays (GCA), measuring thrombin generation (TG) and fibrin clot formation (FCF), may have a clinical applicability for describing the hemostatic status of patients with HA and HB.

**Methods:** We measured TG and FCF in plasma from adult patients with HA (n = 44) or HB (n = 12) at baseline before receiving factor replacement. TG was measured by the Calibrated-Automated-Thrombogram assay (Stago, France). FCF was investigated with Thrombodynamics analyzer (Hemacore, Russia) in a TF-dependent and -independent coagulation system. **Results:** were compared within disease severity groups and to those of healthy controls (C). TG parameters were: peak height (PH, nM thrombin), velocity index (VI, nM/min), endogenous thrombin potential (ETP, nM thrombin\*min), and thrombin propagation rate (Vt um/min). For FCF stationary-rate of clot growth (V, um/min) describing the TF-independent velocity of clot growth and final clot size (CS, um) were measured.

#### Results:

- As expected, parameters of TG and FCF were significantly lower in HA/HB (proportionally to the degree of disease severity) compared to C.
- Surprisingly, FCF parameters discriminated the degree of disease severity (severe versus moderate; Fig.1A) while TG parameters did not (Fig.1B).
- FCF (evaluated in term of V and CS) overlapped across categories of disease severity, possibly capturing the individual baseline hemostatic state better than single factor activity.

**Conclusions:** GCA seem to capture inter-individual differences in the baseline coagulation potential of patient with hemophilia having similar levels of coagulation factor activity. FCF seems to be more sensitive in discriminating baseline phenotype compared to TG. This might be a useful tool for assessing individual baseline bleeding risk and pharmacodynamics monitoring of replacement therapy in patients with hemophilia.

Fig. 1A

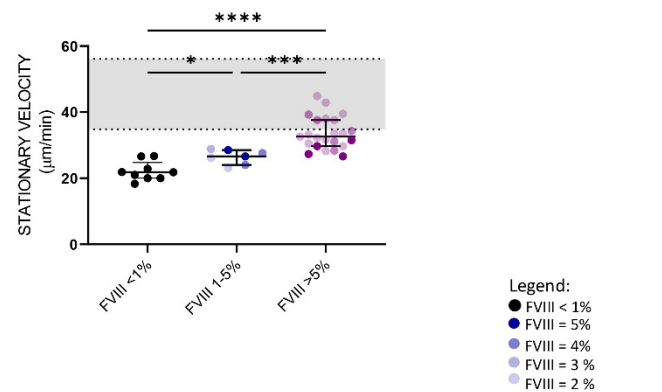
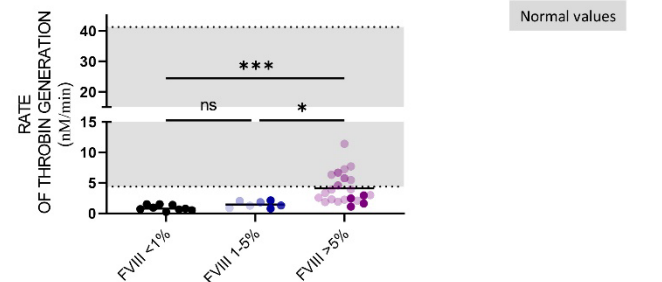


Fig. 1B



**Figure 1:** Rate of fibrin clot formation (Fig.1A) and rate of thrombin generation (Fig.1B) in plasma from patient having different degrees of hemophilia severity. Shaded grey area represents reference values in normal plasma. FVIII: coagulation factor VIII.

#### Abstract ID: 90

### A predictive model based on thrombin generation to manage postpartal bleeding in healthy women and those with inherited bleeding disorders

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**Introduction:** Hemostatic balance shifts toward a prothrombotic state during pregnancy and poses a significant risk of thromboembolic events in pregnant women. Paradoxically, postpartal hemorrhage (PPH) is still a leading cause of maternal morbidity and mortality worldwide. Thrombin generation (TG) parameters during pregnancy in healthy women and those with inherited bleeding disorders (IBD) are still largely lacking. We aimed to evaluate TG at three time points during pregnancy and at postpartal period in healthy pregnant women and those with IBD correlate to the PPH.

**Methods:** 180 healthy pregnant women and 60 pregnant women with IBD will be enrolled at Inselspital Bern and University hospital Zürich between 6 and 13 weeks of gestation. TG

was measured with the automated STGenesia® (Stago, France) at three different TF concentrations. Coagulation assays will be run on an Atellica COAG 360 (Siemens, Germany). Additionally, we will determine pregnancy outcomes including mode of delivery, gestational age, estimated blood loss, PPH and blood product usage. We will perform statistical analysis using GraphPad Prism 8.0.1 (San Diego, USA).

**Results:** Forty healthy pregnant women were collected at our center since ethic approval at four time point of pregnancy. TG was measured in 40 samples at both centres. Preliminary results of TG obtained from a healthy pregnant women followed at each time points (figure 2A) will showed. Besides, we showed an outpatient pregnant woman from our clinic diagnosed with an IBD, precisely with a Willenband Disease (VWD) 2A, which was managed with TG to prevent any possible PPH before and after delivery (figure 2B). TG, which was measured in the healthy pregnant women, increased very high at a very early stage on trimester (T1) (Peak: 140%, ETP: 150%) compared to the normal control. Interestingly, in trimester (T2) (Peak: 160%, ETP: 152%) is the stage which more TG was generated. In postpartal period, the TG behaves similar to the normal control. The TG in trimester (T3) (Peak: 78%, ETP: 105%) was similar to the normal control but higher than a female no pregnant with VWD 2A. Delivery went successful and the PPH was normal (500ml) in this case.

**Conclusions:** TG seems to be an excellent approach to monitor and prevent PHH in IBD. In addition, it will give a first insight into the potential of TG to manage pregnancies and in patients with IBD, exemplified prevent PPH.

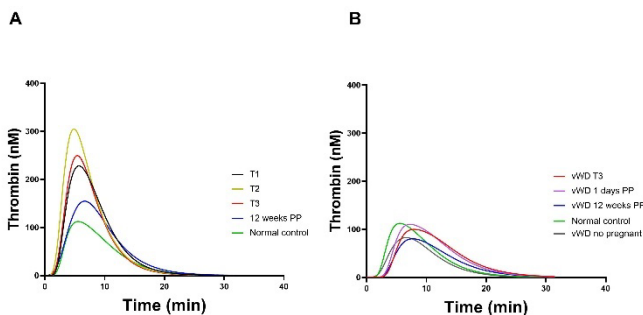


Figure 2: Thrombin generation measurement done by STGenesia®. TG was measured by BleedScreen (~1pM TF). Panel A. TG in one healthy women at all four pregnancy-related study time-points (T1 first trimester, T2 second trimester, T3 third trimester and 12 weeks postpartum) and a healthy female non-pregnant control (normal control). Panel B. TG measured in a female patient with VWD type 2A in T3, one-day and 12 weeks postpartal. Included are a healthy non-pregnant female (normal control) and female non-pregnant VWD patient (VWD non-pregnant) as controls.

**Abstract ID: 93**

**Fibrinogen replacement in hereditary dysfibrinogenemia: how much is enough?**

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**Introduction:** Fibrinogen is a key structural element in fibrin clots formed after vascular lesions to limit hemorrhaging. Hereditary fibrinogen disorders include several types of fibrinogen deficiencies. Patients with hereditary dysfibrinogenemia (HD) have normal levels of a dysfunctional fibrinogen molecule in circulation, increasing their hemorrhagic and thrombotic risk. Fibrinogen concentrates (FC) can be administered to treat or decrease the risk of bleeding, but the optimal fibrinogen concentration to target after FC infusion in HD patients has not yet been explored. The study aims to determine the fibrinogen supplementation value which allows HD plasma to achieve coagulation similar to that of a control plasma. The study endpoint is the change in structural clot properties such as fibre density

and diameter as plasma fibrinogen supplementation is incrementally increased.

**Methods:** The in-vitro clot structure and properties in both control (CC) and dysfibrinogenemic (DP) plasma were analyzed without supplementation, and then spiked with +0.5g/l, +1.0g/l, +2.0g/l and +4.0g/l of a FC (Haemocompletan®, CSL Behring). The DP used was from six patients with an FGA exon 2 Arg35His mutation. Turbidimetry was used to measure the rate of fibrin clot polymerization and fibrinolysis. Scanning electron microscopy (SEM) was used to assess clot density and fiber diameter.

**Results:** A results summary can be found in Figure 1. Fibrinolysis results showed a slower fibrin clot degradation as fibrinogen concentration increased. The SEM images showed increasingly dense and tightly-packed thin fibrin fibers. Despite the kinetics of clot formation being heterogeneous between patients, at a fibrinogen supplementation of +2.0g/l, the kinetics of DP start to resemble those of CC. For patients with a basal fibrinogen activity of <1g/l, the thrombin time was corrected at a supplementation of +4g/l. For patients with a higher basal fibrinogen activity (> 1g/l), a supplementation of +2g/l was sufficient for a corrected thrombin time.

**Conclusions:** Our results indicate that +2g/l might be the minimum value of plasma fibrinogen supplementation necessary for patient clot properties to resemble those of the control plasma. However, the somewhat unexpected results for the fibrin clot polymerization require further investigation to determine whether this was due to the interference of additional proteins in the fibrinogen concentrate.

Figure 1. Summary results for fibrin clot formation, fibrinolysis and scanning electron microscopy images

CryoCheck plasma (n)	Fibrinogen supplementation conditions (+ g/l)				
	CC + 0.0 (n = 6)	CC + 0.5 (n = 2)	CC + 1.0 (n = 2)	CC + 2.0 (n = 1)	CC + 4.0 (n = 5)
Lag time (min)	2.83 (0.35)	3.17 (0.34)	3.07 (0.13)	4.30 (0.00)	3.18 (0.79)
Slope (OD/sec)x10-4	9.02 (3.36)	6.27 (2.32)	7.21 (1.91)	7.30 (1.60)	9.17 (3.25)
Max Abs (mOD)	194 (27)	176 (48)	173 (42)	205 (11)	187 (23)
T50% (min)	10.40 (1.66)	10.96 (1.77)	14.00 (1.10)	12.00 (0.08)	21.56 (5.82)
Diameter (nm)	80 (0)	70 (3)	60 (2)	ND	55 (2)
<b>Dysfibrinogenemic plasma (n)</b>					
	DP + 0.0 (n = 6)	DP + 0.5 (n = 2)	DP + 1.0 (n = 2)	DP + 2.0 (n = 1)	DP + 4.0 (n = 5)
Lag time (min)	5.31 (1.11)	4.53 (0.35)	4.46 (0.21)	4.01 (0.04)	4.06 (0.44)
Slope (OD/sec)x10-4	8.37 (3.22)	5.49 (1.18)	4.85 (1.44)	9.32 (0.04)	7.61 (2.35)
Max Abs (mOD)	201 (72)	126 (11)	116 (0)	151 (0)	205 (64)
T50% (min)	11.27 (5.21)	11.34 (1.56)	11.30 (2.75)	22.39 (0.28)	20.98 (7.69)
Diameter (nm)	80 (4)	70 (3)	60 (3)	ND	63 (5)

ND : not done

**Abstract ID: 102**

**Congenital dysfibrinogenemia combined with antithrombin and factor V polymorphisms resulting in increased thrombin generation and abnormal fibrin clot structure**

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**Introduction:** Hereditary dysfibrinogenemia is a fibrinogen disorder characterised by heterogeneous clinical manifestations. The fibrinogen gene causative mutation is often not predictive

of the clinical phenotype. We investigated the impact of potential genetic modifiers on the fibrin clot properties in a 29-year-old asymptomatic woman with congenital dysfibrinogenemia due to a heterozygous hotspot mutation in FGA exon 2, p.Arg35His. She was also heterozygous for a rare polymorphism in SERPINC1 (p.Ser101Cys, rs199895690) and FV Leiden (rs6025). The fibrinogen activity (Clauss) was 0.49 g/L and antigenic was 2.8 g/L. The antithrombin activity was 95% (normal range >70%).

**Methods:** We compared our patient (DYS) to a control plasma (CC), a patient with FGA p.Arg35His heterozygous mutation (CDYS) and a heterozygous FV Leiden patient (FVL). The fibrin clot structure was assessed by turbidimetry, permeation, laser scanning confocal microscopy (LCSM) and scanning electron microscopy (SEM). We also performed thrombin generation (TG).

**Results:** The DYS patient had the longest lag time (444.7±8.1; CC:372.8±52.8; CDYS:272.0±0.0; FVL:216.0±19.8 s) and the highest maximal absorbance (0.223; CC:0.135; CDYS:0.118; FVL:0.118 OD). The polymerisation slopes were increased in DYS and FVL (9.77±0.00; 8.42±0.00; CC:5.18±1.8 OD/s x10<sup>-4</sup>). The CLT50 was increased in FVL compared to CC (26.2±0.73 vs 12.8±1.0 min; p <0.0001). The TG parameters of DYS showed a prolonged lag time (3.380 (3.378-3.383) min) and an increased ETP (2014.1±103.9; CC:1022.4±86.5 nmol/L min). The pore size was decreased in FVL (0.566±0.028; CC:0.769±0.032 μm). The fibrin diameter was the lowest in DYS and statistically lower compared to CDYS (0.398±0.017 vs 0.452±0.006, p <0.005; CC:0.484±0.066; FVL:0.404±0.011) based on the LCSM images. The fibrin fibers' diameter was higher in DYS compared to CC (97.96±6.07 vs 71.35±8.02 nm) based on SEM images. DYS had two times lower Ks value compared to CC and CDYS (1.44±0.12 vs 2.79±0.79 and 2.19±0.01 cm<sup>2</sup> x 10<sup>-8</sup>, respectively), and FVL had the lowest Ks value compared to others (0.84±0.01 cm<sup>2</sup> x 10<sup>-8</sup>).

**Conclusions:** Overall, the Leiden mutation leads to a thrombotic profile even when the resulting fibrin formation is already altered by the fibrinogen FGA p.Arg35His mutation. Additional studies are required to assess the impact, if any, of the antithrombin polymorphism on the TG.

#### Abstract ID: 105

### Sem and 3D reconstruction of ex-vivo arterial thrombi: A pilot study

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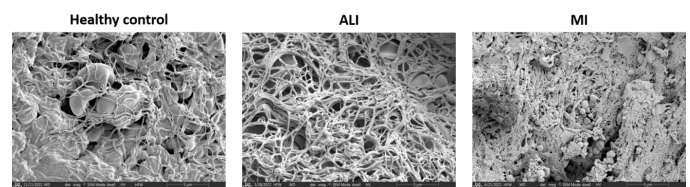
**Introduction:** Thromboembolism, including acute limb ischemia (ALI) and myocardial infarction (MI) is the leading cause of death and disability worldwide. On one side, arterial thrombosis can result from atherosclerotic plaque rupture that exposes sub-endothelial cells and procoagulant material, leading to platelet activation and aggregation in high shear rates and stress. On the other side, cardio-embolism can lead to an acute occlusion of the vessel. The primary aim of our study was to compare clot composition among ALI thrombi from plaque rupture, embolisms and MI thrombi. We present some preliminary results.

**Methods:** Ex-vivo thrombi were collected by thrombectomy (ALI n = 1; MI n = 1) and analysed by Scanning Electron Microscopy (SEM) and SEM 3D reconstruction and compared to whole blood thrombus obtained in vitro from a healthy subject (made with the addition of thrombin and calcium) (n = 1). The external

and internal surfaces of the thrombi were investigated after fixation and dehydration with SEM. SEM/FIB system was used to assess the ultrastructural organization of the clots. Thermo Scientific Amira, Imaris and ImageJ 2.3.0./1.51v software were used for the reconstruction.

**Results:** In MI thrombi we observed a biconcave shape of RBCs under the surface with a polyhedral shape of RBCs and abundant WBCs in the middle of the thrombi. Heterogenous networks of fibrin on the external and internal surfaces were identified compared to healthy controls. We found larger spaces between cells in the ALI thrombi and denser spaces in the MI thrombi.

**Conclusions:** In our pilot study the thrombi from ALI, MI and controls showed differences in the fibrin network. Future studies will include analysing the nature and number of different cells (WBCs, platelets and microparticles) found in the thrombi, categorising the types of fibrin fibers and the different shapes of RBCs, in order to define how specific cells are involved in the thrombus generation.



#### Abstract ID: 131

### Use of andexanet alfa for direct oral anticoagulant reversal: a retrospective study in a tertiary hospital

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**Introduction:** Until recently, no specific antidote was available for management of acute life-threatening bleeding secondary to direct oral anticoagulants. Andexanet alfa (AA) is a modified recombinant inactive form of factor X approved for reversal of factor Xa inhibitors rivaroxaban and apixaban. Our hospital edited internal guidelines for its use, in line with the approved labelling of Swissmedic but restricted for intracranial bleeding only.

**Methods:** We included all patients who received AA between May 2021 and September 2022. The primary endpoint was the proportion of patients who received AA according to the institutional protocol. Secondary endpoints include prescription of AA according to the inclusion criteria of the ANNEXA-4 trial, hemostatic efficacy at 12 hours after treatment, thrombotic events and mortality during hospital stay.

**Results:** Sixteen patients were identified; mean age was of 82±8 years with a slight male predominance (56%). Bleeding was exclusively intracranial and 62.5% of patients were on rivaroxaban, while the others were on apixaban. Fourteen patients were anticoagulated for atrial fibrillation, 1 for venous thromboembolism and 1 for unknown reason. Seven out of 16 patients (43.7%) did not received AA according to or institutional protocol. Protocol deviation occurred solely because of incorrect doses of AA prescription when timing of last dosing was unknown (prescription of the low dose regimen instead of the high dose as recommended) in 6 patients, and bolus administration not followed by the 2-hour infusion in 1 patient. Compared to the ANNEXA-4 trial inclusion criteria, only 1 patient would not have been included due to last intake of rivaroxaban beyond 18 hours. During the 30-day follow-up period, 3 patients out of 16

presented a thromboembolic complication and death occurred in 6 patients. Eleven patients had a follow-up CT-scan after AA administration (5 with low AA and 6 with full AA regimen). The follow-up CT-scan showed stability or regression of the bleeding in 8 patients (72.7%) and 2 patients out of 5 (40%) with low AA vs 1 out of 6 patients (17%) with full AA regimen showed intracranial bleeding extension.

**Conclusions:** Our study showed that AA was not prescribed as recommended in a significant number of patients. The impact on the clinical outcome is unclear but this study suggests that an effort should be made to promote institutional guidelines.

#### Abstract ID: 134

### G-CSF use in isolated severe neutropenia. A monocentric retrospective study.

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**Introduction:** Severe neutropenia ( $<0.5 \times 10^9/L$ ) may accompany a variety of diseases and is of great clinical relevance due to susceptibility to infections. Its management can however be challenging as no clear standards of treatment exist, especially since the use of granulocyte-colony stimulating factor (G-CSF) is not well defined. We analyzed the rate of G-CSF use, infections, hospitalization rate and fatality of patients with isolated severe neutropenia in our tertiary reference center.

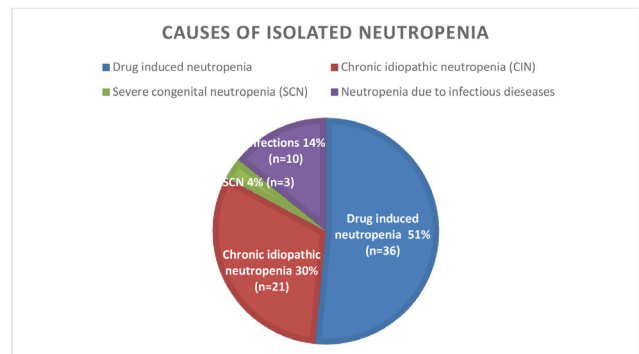
**Methods:** Data was collected retrospectively by chart review. Frequency of outcomes was assessed descriptively.

**Results:** During the period 2015 to 2020, we identified through our database management system patients with severe neutropenia. From 2249-screened patients with neutropenia, 1362 had isolated neutropenia  $<0.5 \times 10^9/L$ . Neutropenia due to chemotherapy, radiotherapy, neoplasia, additional cytopenia and benign ethnic neutropenia were excluded. We identified 70 patients with isolated neutropenia. 46 (65%) had an acute course and 24 (34%) had a chronic presentation, 3 of which were congenital and 21 were chronic idiopathic neutropenia (CIN).

There were 45 (65%) females and the median age was 34 years. Infections requiring hospitalization occurred in 25 patients (36%), none required intensive care. 18/70 (26%) patients received G-CSF. Drug-induced neutropenia was the main cause of acute neutropenia (51%, 36/70), 50% were hospitalized and 8/36 (22%) received G-CSF. Neutropenia caused by infectious diseases was observed in 14% of the patients (10/70), 2 were hospitalized, none received G-CSF. 13/24 (54%) of chronic neutropenia received G-CSF either permanently (9/13) or sporadically (4/13). 2 of the 3 patients with congenital neutropenia have required G-CSF permanently since infancy and have required hospitalisation due to infections. 2 patients with CIN (9.5%) have also required hospitalization during follow-up.

**Conclusions:** The presentation of isolated neutropenia is heterogeneous. The frequency of CIN cases was unexpectedly high, probably reflecting the patient population of a tertiary center. Treatment with G-CSF was observed mainly in patients with chronic neutropenia (CIN and SCN). Acute neutropenia rarely required G-CSF. Drug induced neutropenia associated with infections requiring hospitalisation seems to be a trigger to G-CSF prescription. Generally, a benign outcome was observed.

Neutropenia Cause	Nr	G-CSF use		Hospitalization-rate
		Nr	%	
Severe congenital neutropenia	3	2	66	66%
Chronic idiopathic neutropenia	21	11	52	9.5%
Drug induced neutropenia	36	8	22	50%
Neutropenia due to infections	10	0	0	20%



#### Abstract ID: 135

### Pregnancy in chronic idiopathic neutropenia. A monocentric retrospective study.

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**Introduction:** Chronic idiopathic neutropenia (CIN) is defined as isolated neutropenia lasting for at least for 3 months and not attributable to drugs or a specific genetic, infectious, inflammatory, autoimmune or malignant cause. These patients generally have a benign evolution; infections are generally infrequent. There is limited data on pregnancy outcomes in patients with this condition.

**Methods:** Data was collected retrospectively by chart review. Frequency of outcomes was assessed descriptively.

**Results:** During the period 2015 to 2020 we identified using our hospital database-management system 70 patients with isolated neutropenia ( $<0.5 G/l$ ). 31% of these patients (21/70) had chronic idiopathic neutropenia (CIN). There were 16 women with a median age of 28 at diagnosis (range 17- 67), 4 of them had a total of 8 pregnancies after CIN diagnosis. From these 4 patients, before pregnancy one was treated with G-CSF due to recurrent infections, this treatment was continued during pregnancy. This same patient had two miscarriages due to foetal malformation. There were 3 deliveries via C-Section, all due to breech presentation. The patients who were previously not on G-CSF, did not require G-CSF either during their pregnancies.

**Conclusions:** Pregnancy does not seem to affect the course of CIN and did not require additional treatment in those who did not have it before pregnancy. Delivery modality was explained by fetal factors and not by the disease itself. The influence of G-CSF could not be evaluated due to the low number of patients under treatment.

Patient	Number of pregnancies	Severe neutropenia during pregnancy yes/moderate/no	G-CSF During pregnancy	Length of pregnancy (weeks)	Delivery mode	Baby weight	Infections	Varia
1	1 (1996)	missing info	no	missing info	missing info	missing info	missing info	Baby alive, no maternal complications
2	2 (2015) (2019)	yes yes	no no	39 2/7 39 1/7	c-section (breech) vaginal	3365g 3180g	no no	
3	1 (1998)	yes	no	38	vaginal	3270g	no	Postpartal thrombosis
4	4 (2011) (2012) (2013) (2014)	- yes - yes (continues treatment under G-CSF)	yes yes yes yes	10 38 4/7 5 40 0/7	miscarriage c-section (breech) miscarriage c-section (breech)	- 3350g - 4370g	- no - no	

**Abstract ID: 137****Triple alloimmunization against leuco-platelet antigens and a successful allogenic hematopoietic stem cell transplantation**

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**Introduction:** Allogenic hematopoietic stem cell transplantation (alloHSCT) is a real challenge for physicians when it concerns patients with complex alloimmunization against human platelet antigen (HPA) and human leucocyte antigen (HLA).

We know that early diagnosis and selection of platelet donors is crucial to ensure a safe transfusion management for this procedure. Furthermore, the presence of antibodies directed against high frequency antigens (for example: anti-HPA-5a) adds a level of complexity regarding transfusions' logistic.

We report the case of a 54 years-old multiparous woman with both conditions such as multiple clinically significant anti-HLA (A11, A66, B76, A25) and anti-HPA-5a antibodies, associated with an anti-HPA-2a antibody related to an immune thrombocytopenic purpura (ITP) diagnosed years before. A haploidentical alloHSCT was planned for an acute lymphoblastic leukemia of B-cell type. The donor was her son. No donor specific antibody (anti-HLA) was identified but he was HPA incompatible (HPA-5ab). Moreover, the ABO incompatibility was major (donor AB, recipient A). The conditioning was myeloablative and consisted of ATG Graphalon® 10 mg/kg on day -8 and -7, Fludarabine 30 mg/m<sup>2</sup>/day from day -5 to -2, TBI 10 Gy given in 5 divided doses of 2 Gy from day-2 to day 0. Prevention of GvH disease was performed with cyclophosphamide post-transplantation, mycophenolate mofetil and tacrolimus. Reduction of circulating antibodies was attempted by two plasmapheresis on day -1 and day 0. She received a total amount of 18 compatible platelet concentrates (HPA-5bb, prevalence <1%) to maintain a level >20 G/L, that occurred 43 days after transplantation. No bleeding complication arose. However, the level of thrombocytes was under 50 G/L during the 6 months following transplantation. At year 5, the patient is in complete remission with a normal platelet count at the last follow-up.

**Conclusions:** This case report of a successful alloHSCT in a heavily allo-immunized patient, carried out in a setting of ITP and complex platelet alloimmunization, is another proof that HPA incompatible alloHSCT is possible and safe, but requires a rigorous planning and multidisciplinary approach. Thus, thinking of HPA alloimmunization weeks before alloSCT is essential.

**Abstract ID: 142****Decreased plasma protein S improves hemostasis in F12 deficient mice**

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**Introduction:** Complete protein S (PS) deficiency is lethal in utero, because of purpura fulminans and disseminated intravascular coagulation (DIC). Previous studies demonstrated that it is possible to rescue the lethal phenotype by targeting F8 or F9 gene in PS deficient (Pros1<sup>-/-</sup>) mice. Here, we investigated if we could obtain the same effect by targeting F12, whose absence is not associated with bleeding tendencies.

**Methods:** We assessed the viability of mice with combined Pros1 and F12 deficiencies. Coagulation parameters (DIC parameters, like TAT), global hemostasis assays (thrombin generation assay (TGA) and ROTEM) and clot contraction by electron microscopy (EM) were measured in Pros1<sup>+/+</sup>F12<sup>+/+</sup>, Pros1<sup>+/+</sup>F12<sup>-/-</sup> and Pros1<sup>+/-</sup>F12<sup>-/-</sup> mice.

**Results:** Pros1<sup>-/-</sup>F12<sup>-/-</sup> genotype mice died in utero at E18.5 indicating that F12 deficiency did not rescue the lethal phenotype of PS deficiency. These embryos showed haemorrhages subcutaneously, in blood vessels and lungs. Therefore, we focused our investigation on viable Pros1<sup>+/-</sup>F12<sup>-/-</sup> mice. There was no difference in DIC parameters between all groups except for a trend of higher TAT levels in Pros1<sup>+/+</sup>F12<sup>+/+</sup> than in Pros1<sup>+/+</sup>F12<sup>+/+</sup>, Pros1<sup>+/+</sup>F12<sup>-/-</sup> and Pros1<sup>+/+</sup>F12<sup>-/-</sup> (62±18 µg/L vs 46 µg/L vs 41±24 µg/L vs 47±27, respectively). TGA parameters were improved in Pros1<sup>+/+</sup>F12<sup>-/-</sup>, indicating an increased thrombin generation in F12<sup>-/-</sup> mice partially lacking PS. Endogenous thrombin potential (ETP) was 459 nM•min, 115 nM•min and 358.2 nM•min for Pros1<sup>+/+</sup>F12<sup>+/+</sup>, Pros1<sup>+/+</sup>F12<sup>-/-</sup> and Pros1<sup>+/-</sup>F12<sup>-/-</sup>, respectively. Thrombin generation peak was 62.8 nM, 15.1 nM and 36.0 nM for Pros1<sup>+/+</sup>F12<sup>+/+</sup>, Pros1<sup>+/+</sup>F12<sup>-/-</sup> and Pros1<sup>+/-</sup>F12<sup>-/-</sup>, respectively. ROTEM analysis revealed a trend towards a higher maximum clot elasticity (due to platelets) in Pros1<sup>+/+</sup>F12<sup>-/-</sup> compared to Pros1<sup>+/+</sup>F12<sup>-/-</sup> (325±140 vs 208±111), suggesting that the partial lack of PS might influence clot elasticity. Data collected from clot contraction analysis by EM showed thicker and firmer fibrin fibers in Pros1<sup>+/+</sup>F12<sup>-/-</sup> and Pros1<sup>+/+</sup>F12<sup>+/+</sup> compared to Pros1<sup>+/+</sup>F12<sup>-/-</sup>, suggesting a better clot contraction due to the partial lack of PS.

**Conclusions:** The lack of F12 did not restore the haemostasis imbalance caused by PS deficiency. F12<sup>-/-</sup>Pros1<sup>-/-</sup> mice died in utero. However, thrombin generation and clot contraction in F12<sup>-/-</sup>Pros1<sup>+/+</sup> can be ameliorated by concomitant PS heterozygosity.

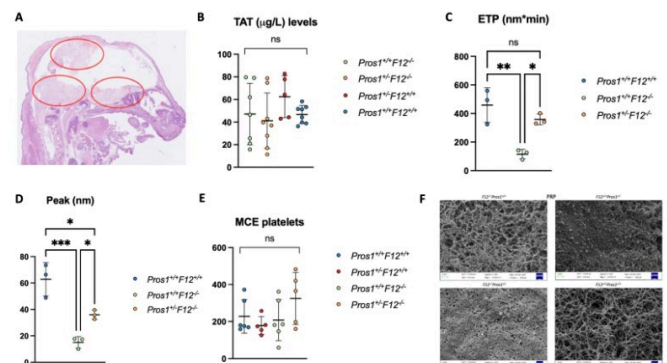


Figure 1 A) Dead pup's cranium with hemorrhagic zones indicated by the red circles. B) Thrombin-antithrombin complexes (TAT) levels. C) Endogenous thrombin potential (ETP) values. D) Thrombin peak values. E) Maximum clot elasticity (MCE) from platelets. F) External surface of clots from all four different genotypes in platelet rich plasma.

**Abstract ID: 145****Platelet concentrate without agitation prior to transfusion are effective in patients with acute myeloid leukemia or myelodysplastic syndrome**

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**Introduction:** Continuous agitation of platelet concentrate (PC) at room temperature leads to more stable pH values and correspondingly to improvement in viability and shelf life of PC. The interruption of agitation up to 24 h seems to be unproblematic on the basis of in vitro studies, however, only few studies exist today where this has been tested in vivo.

At the University Hospital of Zurich (main site: USZ Campus (CAM)), PC are agitated at room temperature in storage according to guidelines with the aim of obtaining an optimal viability prior to transfusion in the same building.

In October 2020, the site USZ Airport (CIR) was opened, where PC can be transfused electively. As distance between CAM and CIR is 11 km, time to transfusion (TTT) is significantly longer for these patients.

The aim of this prospective observational study is to compare the effectiveness of platelet transfusion by increment and corrected count increment (CCI) between our two sites in an outpatient setting. It will also compare bleeding complications, number of transfusions per month and transfusion reactions.

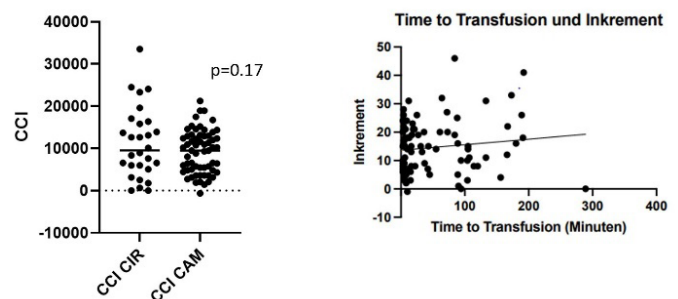
**Methods:** Patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) were treated at both sites de-

pending on the availability of day-clinic beds. Trigger for transfusion was set by the treating physician. Increment and CCI were calculated by determining platelet count before starting transfusion and 30 minutes +/- 15 minutes after transfusion.

**Results:** In this interim analysis, 7 patients were included; 6 patients were male at a median age of 65 years (range 50-80 years). 4 patients suffered from AML and 3 patients from MDS. All patients were treated with hypomethylating agents (Decitabine or Azacitidine), 4 patients additionally with Venetoclax.

From 01.01.2022 until 31.08.2022, 89 thrombocyte concentrates were transfused, 61 at CAM and 28 at CIR respectively. Mean time to transfusion (TTT) was 17 min (range 3 min – 120 min) at CAM and 123 min (range 36 min – 289 min) at CIR. Mean increment at CAM was 13.4 G/l and 17.2 G/l at CIR,  $p = 0.08$ ; mean CCI was 9192 at CAM and 11200 at CIR,  $p = 0.17$ , respectively.

**Conclusions:** Our limited preliminary data support the hypothesis that interrupting agitation for up to 5 hours has no impact on effectiveness of platelet transfusion. Safety issues and confounders are to be assessed.

**EPOSTER – EXPERIMENTAL HEMATOLOGY / ONCOLOGY****Abstract ID: 94****Exploring direct drug targets, drug-associated pathways and the tumor microenvironment using mass cytometry-based predictive biomarker analysis for precision oncology (a TumorProfiler sub analysis)**

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**Introduction:** Precision oncology has the goal to provide highly effective choices of individual therapeutic strategies for cancer patients. To this end, The Tumor Profiler Study has been designed as an observational study employing cutting edge analytical and functional assays to assess cancer biology and to support clinical decision. Moving beyond conventional genetic tumor profiling, the study utilized protein maker panels allowing for an unprecedented in-depth view of direct drug targets and associated signaling pathways and in both tumor and the tumor microenvironment (TME). The application of imaging mass cytometry (IMC) and cytometry by time of flight (CyTOF) enables the parallel assessment of up to 40 protein markers per sample, including phospho-proteins, on either formalin-fixed paraffin-embedded (FFPE) sections (IMC) or single cell suspensions (CyTOF).

**Objective:** To explore the expression and clinical significance of predictive biomarkers in tumors and the TME of patients with melanoma (MEL), ovarian cancer (OC) and AML assessed by IMC and CyTOF. To correlate molecular data with clinical data, including objective response, as a proof-of-concept for clinical utility.

**Methods:** We will mine predictive biomarker expression by IMC or CyTOF in MEL, OC and AML and clinical response to targeted therapies. Specifically, molecular markers will be correlated to the activation status of involved pathways, direct drug targets and key elements of the tumor microenvironment. DNA sequencing data will be correlated with protein level data. Treatment history and response to previous and current treatments will be correlated with the molecular profiles obtained as described.

**Results:** The Tumor Profiler study was active between 2018 and 2021 and 120 TB of data were generated (available on the ETH Zurich Leonhard-Med platform). The total of N = 216 patients were enrolled (N = 116 for MEL, N = 77 for OC and N = 23 for AML). The number of samples for these patient cohorts are N = 126, N = 82 and N = 34, respectively, including repeat samples (N = 10 for MEL, N = 5 for OC and N = 10 for AML). CyTOF was performed on N = 116 (99.2%) MEL (N = 40 markers), N = 34 AML (100%) (N = 41 markers) and N = 63 (81.8%) OC (N = 41 markers) patients. IMC was performed on N = 102 (87.9%) MEL (N = 40 markers), N = 30 AML (88.2%) (N = 41 markers) and N = 53 (68.8%) OC (N = 42 markers) patients. Data analysis is currently ongoing.

EPOSTER – CLINICAL HEMATO-ONCOLOGY

Abstract ID: 40

**Outcome of patients with multiple myeloma receiving allogeneic hematopoietic stem cell transplantation in the pre-CAR T cell era**

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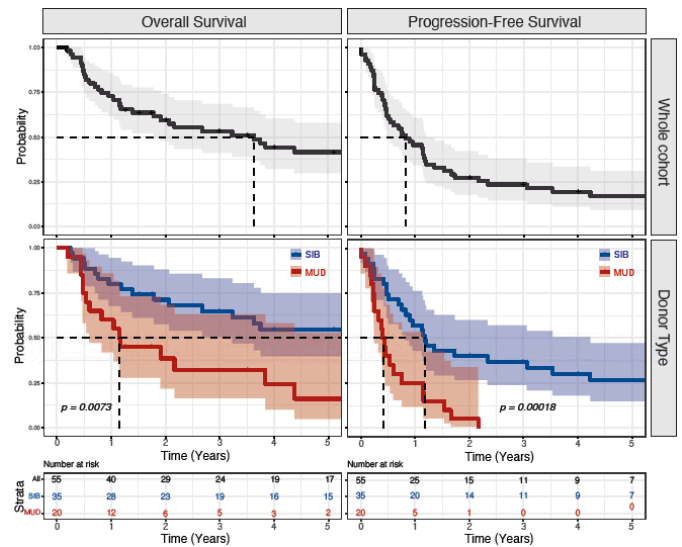
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**Introduction:** Before the approval of anti-BCMA chimeric antigen receptor (CAR) T cells, allogeneic hematopoietic stem cell transplantation (HSCT) was the only available cellular therapy thanks to the graft-versus-myeloma effect of adoptively transferred allogeneic T cells. However relapses after HSCT are frequent and its role in MM treatment remains unclear. The aim of this work was to evaluate the outcome of patients undergoing allogeneic HSCT for MM at our institution to generate a reference survival curve for new upcoming cellular therapies such as BCMA-CAR T cells.

**Methods:** We retrospectively analyzed the outcome of MM patients receiving allogeneic HSCT at our institution between 1990 and 2021.

**Results:** We included 55 patients in the analysis of which 14% received upfront allogeneic HSCT, while 42% and 38% had a single autologous HSCT and a tandem autologous autologous HSCT prior to allogeneic HSCT respectively. Among patients for which cytogenetics characteristics were available (n = 41), 14% displayed high risk cytogenetics. With a median follow-up for alive patients of 5.6 years(y), the median overall survival (OS) was 3.6y and the median progression-free survival (PFS) was 0.8y. The 5y OS and PFS were 41% (30%-58%) and 17% (9%-31%; Figure 1), respectively. The 5y cumulative incidence of disease progression/relapse was 64%±7% and of non-relapse mortality (NRM) was 22%±6%. We observed a trend not reaching statistical significance toward reduced PFS [2.1 (0.92-4.7); 0.078] in patients having received one or more previous autologous HSCT. Use of grafts from HLA-matched unrelated donors (MUD) was associated with a significantly reduced OS [2.6 (1.3-5.2); 0.0095] and PFS [3.1 (1.7-5.9); p = 0.00037] compared with grafts from HLA-identical siblings. The 5y OS for patient receiving grafts from SIB donors was 55% (40%-75%) and the 5y PFS was 26% (15%-47%) compared with a 16% (5%-53%) 5y OS and a 0% PFS for patients receiving grafts from MUD (Figure 1).

**Conclusions:** Our study identifies a subsets of MM patients, receiving grafts from SIB donors, displaying an improved long-term outcome after allogeneic HSCT, suggesting the curative potential of this treatment approach for a fraction of patients. Our results may help to evaluate the impact of new cellular therapies, including BCMA-CAR T cells, for relapsing/refractory MM.



Abstract ID: 41

**BeAM conditioning before autologous stem cell transplantation is safe and effective in patients with Waldenstrom's Macroglobulinemia**

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**Introduction:** High-dose chemotherapy (HDCT) conditioning with BCNU, etoposide, cytarabine and melphalan (BEAM) with autologous stem cell transplantation (ASCT) is commonly used as consolidation treatment in young fit patients with relapsed Waldenstrom Macroglobulinemia (WM). A number of inherent problems with BCNU including pneumotoxicity, neurologic tolerance, and availability of BCNU triggered the evaluation of alternative compounds and regimens. Consequently, bendamustine emerged as a promising candidate to replace BCNU within the novel BeAM conditioning regimen in patients with WM.

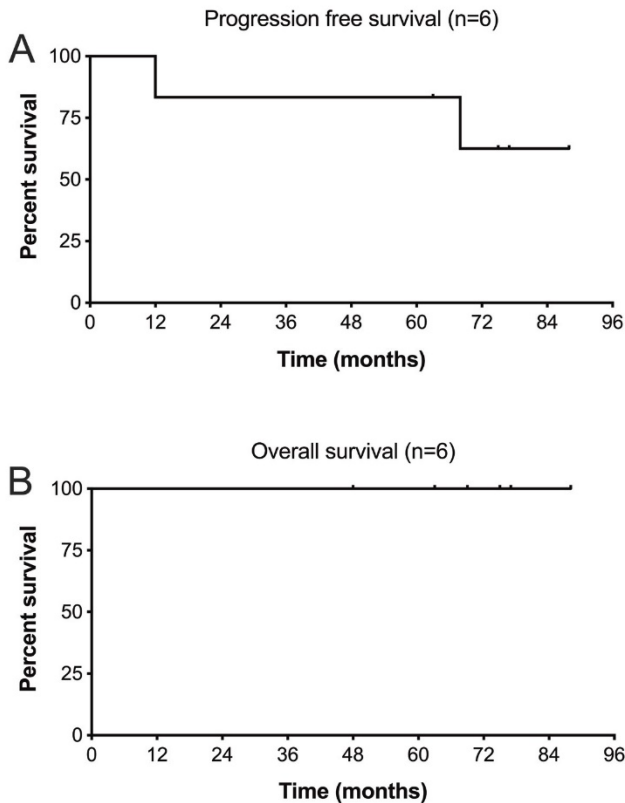
**Methods:** In this retrospective study, we investigated the safety and efficacy of BeAM HDCT before ASCT in consecutive patients with relapsed WM.

**Results:** We identified six patients with WM after preceding reinduction who received BeAM HDCT before ASCT between 2015 and 2022. The median age at HDCT was 58 years. Patients had between 1-4 (median 2) previous lines of therapy. Response to the last line of therapy before HDCT was stable disease (SD), minimal response (MR) and partial response (PR) in two patients each. All patients received the complete treatment as planned. Main toxicities were hematologic (CTCAE grade 3-4 in all 6 patients) and gastrointestinal (grade 3-4 anorexia in 5 patients, and grade 1-2 diarrhea in all 6 patients). Two patients had grade 3 acute kidney injury related to high-dose bendamustine, with one patient having had preceding chronic kidney disease, and both were completely reversible after conservative therapy with no hemodialysis needed. No unexpected toxicities were observed. Recovery of neutrophils >1.0 G/L occurred after a median of 11 days (range 11-12 days), lymphocyte recovery >0.5 G/L after 24 days (range 20-104 days), and platelet recovery >20 G/L after 13 days (range 11-15 days). 100 days after ASCT, four patients achieved a partial and two patients a very good partial remission. Best response to BeAM-HDCT was very good partial response (VGPR) in 4/6



and PR in 2/6 patients. After a median of 72 months of follow up, all 6 patients were alive, with so far only two relapses (34%), and no mortalities (0%) occurring until last follow-up.

**Conclusions:** Our data suggest that BeEAM HDCT before ASCT is effective in fit patients with WM. Responses so far seem to be promising and long lasting. The BeEAM conditioning regimen offers a manageable safety profile, without unexpected toxicities.



#### Abstract ID: 44

### HHV-8 positive Kaposi sarcoma and suspected coexistent multicentric Castleman disease following allogeneic hematopoietic stem cell transplantation: a case report

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**Introduction:** Iatrogenic Kaposi sarcoma (KS), though strongly associated with profound immunosuppression, is extremely rare after allo-HSCT (Cesaro et al, 2020). Infection with human herpes virus 8 (HHV-8) is identified as an underlying cause of KS and Castleman disease (CD).

**Methods:** A 61-year-old, HIV-negative, female, native of Portugal was diagnosed with de novo AML with overexpression of EVI-1. She was treated with induction chemotherapy leading to complete remission, followed by consolidation with reduced intensity conditioning regimen allo-HSCT from a haploidentical male sibling with peripheral blood stem cells. Serologic test for HHV8 was positive (IgG) for both donor and recipient. Immunosuppressive therapy included post-transplant cyclophosphamide, mycophenolate mofetil and tacrolimus. On day 70, she presented a grade 2 gastrointestinal tract acute Graft versus Host Disease (aGVHD), treated successfully with prednisone.

Four months after transplant, she developed erythematous macules on the upper extremities. Skin biopsy was aspecific with no sign of KS. Blood HHV-8 viremia (PCR) was detectable. PET-CT showed left subclavicular lymphadenopathy and small size subdiaphragmatic lymph nodes. A PET-CT performed 1 month later showed progression of lymphadenopathies (SUV max 9). The patient developed fever, fatigue, night sweats and severe thrombocytopenia. Bone marrow biopsy showed AML remission without any evidence of hemophagocytosis. HHV8 PCR was positive on blood (semi quantitative assay). Biopsy of the supraclavicular node was consistent with HHV-8 positive KS. Given the clinical inflammatory state, a co-existing CD was suspected even in the absence of histological confirmation. The patient received pegylated liposomal doxorubicin (20 mg/m<sup>2</sup> x4 cycles) associated with rituximab (375mg/m<sup>2</sup> x4 cycles) for the suspected CD. Clinical evolution was favorable and the PET-CT showed a complete remission. HHV8 viremia remains detectable but low.

**Results:** Regarding the positive serology of the donor and recipient before transplantation, we hypothesise that the mechanism underlying this KS is a viral reactivation during the post-transplant period while the patient received immunosuppressive drugs for GVHD.

**Conclusions:** Our experience suggests that due to their rarity and non-specific manifestations, diagnosis of KS and CD is a unique challenge for diagnosis and clinical care.

#### Abstract ID: 52

### Hepatic granulomatosis with regenerative nodular hyperplasia as a rare presentation of multiple myeloma – A case report

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**Introduction:** Multiple myeloma (MM) is a plasma cell neoplasm that usually presents with anemia, renal failure, hypercalcemia and/or bone lesions. It is commonly seen in patients in their 6th or 7th decade of life. Rarely cases are described with paraneoplastic syndromes as initial presentation, and even more rarely MM presents as hepatic disease.

**Methods:** We report a case of an 83 years old patient with few comorbidities, presenting with asthenia&weight loss. He had pancytopenia and inflammatory syndrome. Monoclonal IgG kappa was detected. Bone marrow biopsy showed monoclonal plasma cell infiltration 10% without amyloid deposits and a MM IgG kappa was diagnosed. However, his clinical status could not be explained by the MM at this stage. There was no drug or toxic exposure. An extensive microbiological, virological and autoimmune work-up was negative. A thoraco-abdominal CT showed many right hepatic hypervascular lesions without cirrhotic configuration. Spleen was not enlarged. Liver MRI confirmed multiples lesions compatible with hepatic angiomas. A PET CT was performed and showed a hypermetabolic infiltration of the right liver. Liver biopsy was performed and showed a non-necrotizing granulomatous and giganto-cellular lobular inflammation associated with non-necrotizing granulomas and regenerative nodular hyperplasia. After excluding causes of hepatic granulomatosis, the conclusion was that MM was the cause of hepatic disease. The patient started treatment with 1 cycle of Daratumumab-Lenalidomide (R) and dexamethasone (d) followed by 5 cycles of Rd with complete regression of hepatic hypermetabolic infiltration on PET CT after cycle 4. Blood count values normalized, the inflammatory syndrome disappeared and the general condition of the patient improved markedly.

**Results:** Our patient presented with weight loss, inflammatory state and pancytopenia. Work up showed MM and liver disease due to hepatic granulomatosis and nodular regenerative hyperplasia. An extensive microbiological and immune work up was performed and allowed us to exclude other etiologies than the MM. MM treatment led to total resolution of clinical, biological & radiological findings.

**Conclusions:** We conclude that a MM can rarely present with hepatic granulomatosis associated with hyperplastic nodular regeneration. An extensive work-up to exclude other etiologies is mandatory before concluding that MM is the cause of hepatic disease.

#### Abstract ID: 58

### B-NHL screening in patients with newly diagnosed monoclonal gammopathies

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**Introduction:** Newly diagnosed monoclonal gammopathies are associated either with plasma cell neoplasia (MGUS, multiple myeloma or amyloidosis) or mature lymphoproliferative B-cell disorders. The prevalence of MGUS is well documented and increasing with age (3 to 7% in individuals over 50y) whereas the underlying cause of the M-Protein is often unknown.

**Methods:** Retrospectively, we investigated the presence of mature B cell neoplasia / B-NHL in patients with newly diagnosed M-protein followed by immunophenotyping. M-Protein detection consisted of serum protein electrophoresis, immunofixation, and serum free light chain determination. Immunophenotyping of the lymphocytes was performed out of EDTA-blood samples, using a 10-colour immunophenotyping strategy. Where appropriate clonal B cell count was calculated based on the absolute lymphocyte number.

**Results:** From July 1, 2014, to July 31, 2021, we performed 98'690 immunofixations in 57'811 patients. Out of these patients 31.4% (n = 18'147: 51.1% females and 48.9% males) showed a M-Protein. In this population 3518 patients underwent immunophenotyping for the detection of B-NHL, 1206 patients upon recommendation of the lab and 2312 patients on the physicians' request. In 345 (9.8%) of 3518 patients we found B-NHL as follows: 50% (n = 173) chronic lymphocytic leukemia, 28% (n = 97) lymphoplasmacytic lymphoma/marginal zone lymphoma, 6.7% (n = 23) monoclonal B-lymphocytosis, 4.9% (n = 17) mantle cell lymphoma and 10.4% (n = 35) other B-NHL (follicular lymphoma (n = 7), hairy cell leukemia (n = 3), diffuse large B cell lymphoma (n = 1) and CD5+ B-NHL not otherwise specified (n = 24)).

Median age of patients with B-NHL was 72y, no difference was found between the recommendation by the lab or request by the physician. We found a higher proportion (11.1%) of B-NHL when immunophenotyping was requested by the physician when compared with the group diagnosed upon lab recommendation (7.4%). The diagnosis of B-NHL was not associated with lymphocytosis in peripheral blood. The size of clonal B-cell population was ten times higher (mean: 4.2 G/L vs 0.4G/L, p = 0.0072) when immunophenotyping was requested by the physician.

**Conclusions:** Peripheral blood B cell immunophenotyping in patients with newly diagnosed M-Protein revealed in 9.8% of the cases the presence of a B-NHL and was a powerful screening strategy for early diagnosis.

#### Abstract ID: 64

### Minimal residual disease monitoring by Ig/TCR rearrangement predicts post-transplant relapse and survival in adult patients with acute lymphoblastic leukemia

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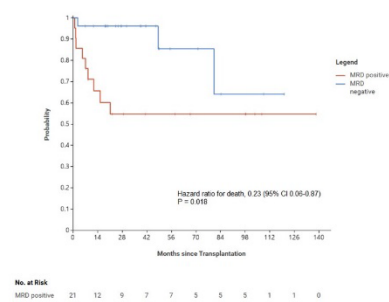
**Introduction:** Monitoring minimal residual disease (MRD) using Ig/TCR rearrangements has become standard in current treatment protocols for adult patients with acute lymphoblastic leukemia (ALL). While its prognostic significance after induction and consolidation therapy is well established, it has been less well studied in the pre- and post-transplant setting. In this retrospective study, we investigated the impact of MRD by Ig/TCR rearrangements on outcome in adult patients with ALL who underwent allogeneic stem cell transplantation.

**Methods:** 137 adult patients with ALL who received an allogeneic hematopoietic stem cell transplantation between 01.01.2006 and 01.12.2021 were included. In 47 patients, pre- and post-transplant MRD could be evaluated. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method, with the log rank test performed for comparison. Differences between categorical variables were assessed using Fisher's exact test. The Fine and Gray model was applied to evaluate for difference in non-relapse mortality.

**Results:** Patients with pre-transplant detectable MRD had significantly worse OS (P = 0.018, hazard ratio 0.23 [0.06, 0.87], Figure 1) and PFS (P = 0.028, hazard ratio 0.29 [0.09, 0.94]) than MRD negative individuals. Similarly, detection of MRD at three months post-transplant was associated with significantly worse OS (P < 0.001, hazard ratio 0.10 [0.02, 0.47]) compared with MRD negativity, even when the extent of MRD was below the quantifiable range. Patients with B-ALL were significantly more likely to achieve pre-transplant MRD negativity than those with T-ALL (P = 0.009, odds ratio 6.97 [1.59, 30.52]). No association was found between pre-transplant MRD negativity and abnormal karyotype or presence of a BCR:ABL1 fusion transcript. Non-relapse mortality did not differ dependent on pre-transplant detectable MRD (P = 0.170).

**Conclusions:** Pre-transplant detection of MRD based on Ig/TCR rearrangement is a strong predictor of survival and relapse in patients with ALL undergoing allogeneic hematopoietic stem cell transplantation. Post-transplant detection of MRD at three months identifies patients with particularly poor survival. The presence of a BCR:ABL1 fusion transcript has no impact on pre-transplant MRD state based on Ig/TCR rearrangement.

**Figure 1:** Overall survival after allogeneic hematopoietic stem cell transplantation, stratified by IgH/TCR rearrangement before transplantation



## Abstract ID: 71

### Single-center experience with CAR T-cell therapy with idecabtagene vicleucel (ide-cel) for triple-class exposed relapsed/refractory multiple myeloma

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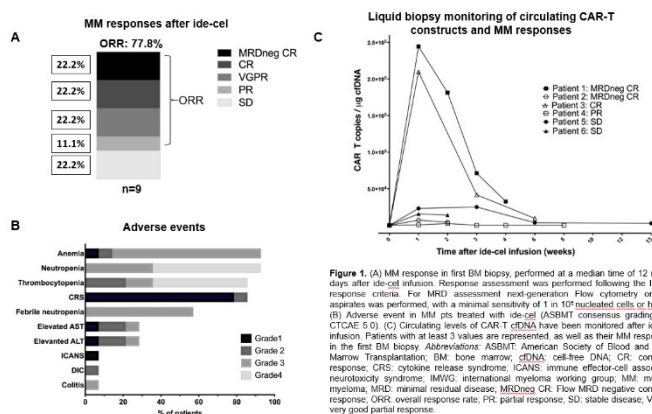
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**Introduction:** CAR-T treatment with Idecabtagenum vicleucel (ide-cel, Abecma®) showed an overall response rate (ORR) of 73% and a median overall survival of 24.8 months in heavily pretreated patients (pts) with multiple myeloma (MM) in the pivotal KarMMa (NCT03361748) study. The randomized phase 3 KarMMa-3 trial reported better progression-free survival for ide-cel compared to standard of care. In Switzerland, ide-cel is commercially available since April 2022. We report the first real-world experiences in MM patients treated with commercial ide-cel at our center.

**Methods:** This is a retrospective analysis of all consecutive patients with triple-class exposed relapsed/refractory (r/r) MM treated with commercial ide-cel. We assessed toxicities following ASBMT consensus grading and CTCAE 5.0, and MM response according to the IMWG criteria.

**Results:** We identified 14 consecutive patients with r/r MM treated with ide-cel between June and September 2022. Median age was 69 (57 – 83) years, 6 (43%) pts had high-risk cytogenetic alterations, and 3 pts (21%) had R-ISS stage III. Median number of previous treatment lines was 5 (4-11), and 3 pts (21%) had high tumor burden at CAR-T treatment. Production success rate was 86% (1 patient received an out-of-specification product, 1 patient required a second apheresis due to insufficient production quality issues). Median time from lymphapheresis to ide-cel infusion was 6 (6-10) weeks, and median duration of hospitalization was 18 (16-41) days. Preliminary response data were available from 9 pts, with an ORR of 78% in the first bone marrow biopsy after a median of 12 (9-35) days after ide-cel infusion (Figure 1A). 3 months response data are immature and updates will be reported at the meeting. CRS occurred in 11 (86%) pts (79% G1, 7% G2, no G3/4), ICANS occurred in 1 (7% G1, no G2/3/4), febrile neutropenia in 8 (57%), and infections with identification of a germ in 4 (29%). Other non-hematological toxicities were elevated ALT (29%, 7% G1, 15% G2, 7% G3, no G4), elevated AST (29%, 7% G1, 14% G2, 7% G3, no G4), colitis (7%, G3) and DIC (7%, G2) (Figure 1B). Finally, we report preliminary results of CAR-T ddPCR monitoring and correlation with tumor responses (Figure 1C).

**Conclusions:** Our preliminary data from the first cohort of Swiss MM patients treated with commercial ide-cel suggest that safety profile and response rates are comparable to published trial data.



**Figure 1.** (A) MM response in first BM biopsy, performed at a median time of 12 (9-35) days after ide-cel infusion. Response assessment was performed following the IMWG response criteria. For MRD assessment next-generation Flow cytometry on BM aspirates was performed, with a minimal sensitivity of 1 in 10<sup>5</sup> nucleated cells or higher. (B) Adverse event in MM pts treated with ide-cel (ASBMT consensus grading and CTCAE 5.0). (C) Circulating levels of CAR-T cDNA have been monitored after ide-cel infusion. Patients with at least 3 values are represented, as well as their MM responses in the first BM biopsy. Abbreviations: ASBMT: American Society of Blood and Bone Marrow Transplantation; BM: bone marrow; cDNA: cell-free DNA; CR: complete response; CRS: cytokine release syndrome; ICANS: immune effector-cell associated neurotoxicity syndrome; IMWG: international myeloma working group; MM: multiple myeloma; MRD: minimal residual disease; MRDneg CR: Flow MRD negative complete response; ORR: overall response rate; PR: partial response; SD: stable disease; VGPR: very good partial response.

## Abstract ID: 117

### Reimbursement of Car-T-Cell therapies in Switzerland – A single center experience

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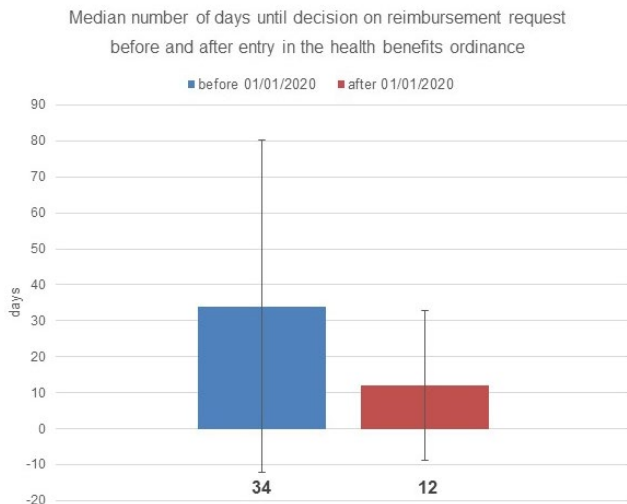
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**Introduction:** The costs of new cancer drugs have steadily increased, and their reimbursement is a major challenge for national health care systems. CARs are an effective, but time consuming therapy for a fragile patient population. After the authorization of CAR-T cell products since late 2018 in Switzerland, no criteria for the reimbursement existed. The off-label use led to delayed treatment and disputed rejection of reimbursement requests by health insurers. Only by January 1st 2020, CAR-T cell therapies were entered in the health care benefits ordinance ("Krankenpflege-Leistungsverordnung") resulting in a benefit obligation by the compulsory health insurance under certain, but in the case of CARs still poorly defined conditions. The goal of our study was to assess the duration of the reimbursement process, its development over time and displaying the reimbursement reality of approved CAR-T cell therapies in Switzerland.

**Methods:** All outgoing reimbursement requests issued for the for the approved CAR-T products Tisagenlecleucel and Axicabtagene-Ciloleucel from a University Hospital between October 18th 2020 and December 31st 2021 were included. We analyzed the duration in days between the issue date of the reimbursement request and the final decision of the insurer by year and before and after the entry in the health care benefits ordinance.

**Results:** In total, 88 reimbursement requests were issued. The processing time of a reimbursement request varied from one day to 167 days with a median processing time of 18 days for all requests (mean 31 days). The median processing time was 34, 13.5 and 10 days for the years 2019, 2020 and 2021, respectively. Before the entry in the health care benefits ordinance, the median processing time was 34 days and 12 days after this reference date. However, we also noticed a considerable variability between the insurance companies in the processing time, largely due to the poorly defined conditions and the perceived label.

**Conclusions:** Although progress has been made over the years by significantly reducing the processing time of a reimbursement request, especially after the inclusion of CAR-T therapies in the health care benefits ordinance, a clearly defined process and labels that allow a fair, universal and rapid reimbursement of CAR-T cell products is of utmost importance for the patients concerned.

**Abstract ID: 118****CAR-T cell therapy for a patient with active hepatitis B – a case report: practical aspects and review of literature**

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**Introduction:** Patients on immunosuppressive drugs and therapies may experience a reactivation of hepatitis B virus (HBV).

**Methods:** We here report on a patient with a HBV infection that needed a therapy with CAR-T cells.

**Results:** A 61y old male suffered from a 2nd relapse of an aggressive lymphoma, initially diagnosed in 1995. A first DLBCL relapse in 2005 was treated with salvage chemotherapy and high-dose consolidation. The 2nd relapse was classified as high-grade lymphoma with Burkitt features. At the time of referral, the patient was highly symptomatic and lymphapheresis for Kymriah® was planned as no prior approval by the insurance is needed. Serology revealed an unknown florid HBV, and a latent syphilis infection, rendered him ineligible for Kymriah®. The patient received five cycles of R-GEMOX with Tenovofir and two doses of Tardocillin. With the approval of the insurance, the patient was switched to Yescarta®. The initial HBV viral load was 26.1 Mio. IU/ml, and dropped to 819 IU/ml when the lymphodepletion for Yescarta® was started in April 2021. A grade 1 cytokine release syndrome was noted. PET-CT at months 3 and 6 revealed a gradual morphologic and metabolic reduction of the residual masses. CAR-T expansion was modest with maximal 902 copies/ug DNA, the peripheral B-cells were fully suppressed until the last test in March 2022. The maximum HBV viral load reached 1230 IU/ml. Radiotherapy was given for a localized biopsy proven relapse one year after CAR-infusion. Despite the immunosuppression by the CAR-T cell therapy, the HBV remained well controlled.

**Conclusions:** This case confirms the results of 17 CAR patients with active HBV infections were only one patient had a HBV reactivation after stopping Entecavir, and a series of 37 patients with immunologically controlled HBV that received Entecavir. Here we also report on a successful and safe CAR-T cell therapy with Yescarta® for this HBV+ lymphoma patient. Lymphocytes from HBsAG +, HBcAB +/-, HBsAB +/- or HBsAG -, HBcAB + and HBsAB +/- patients are ineligible for the production of

Kymriah®. In principle, Yescarta® can be produced also with lymphocytes from HIV, HCV and Syphilis positive patients. Certification for more than one CAR-T-cell product allows centers to provide the potentially curative CAR-T cell therapy for a broader patient population. However, its use as in this patient depends on the perceived label of this therapeutic option.

**Abstract ID: 132****Immune-reconstitution of GM-CSF-producing CD4 T cells after allogeneic hematopoietic stem-cell transplantation.**

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**Introduction:** Allogeneic hematopoietic stem-cell transplantation (HSCT) is a widely employed treatment for several hematological malignancies because of its graft-versus-leukemia (GvL) effect. Unfortunately, it is still associated with severe complications, namely graft-versus-host-disease (GvHD). Recent studies in murine models point to a pivotal role of GM-CSF in the GvHD pathogenesis. On the other side, preclinical and clinical data suggest a role of GM-CSF in the GvL effect. In humans, GM-CSF is mainly produced by a subset of CD4 T cells reported to be involved in autoimmune diseases. The objective of this study is to characterize the dynamics of immune-reconstitution of GM-CSF+ CD4 T cells after HSCT and analyze their association with clinical factors.

**Methods:** Peripheral blood mononuclear cells (PBMCs) have been obtained at 1, 3, 6 and 12 months from 25 patients undergoing HSCT and 13 healthy controls (HC). Cells were activated with PMA and ionomycin for 4 h and stained with antibodies targeting CD4, CD8, CD45RA, CD27, GM-CSF, IL-17, IFN $\gamma$  and TNF $\alpha$ . GM-CSF was quantified in plasma samples using the LEGENDplex™. Analyses were performed using an Attune Flow Cytometer.

**Results:** We observed a significant increase in GM-CSF+ CD4 T cells in HSCT recipients compared to HC mostly within the effector memory compartment. The percentage of GM-CSF+ CD4 T cells peaked at 3 (p = 0.031) and 6 months (p = 0.00017) after HSCT and normalized thereafter. Analyzing the relationship between GM-CSF+ CD4 T cells and transplant characteristics, we did not detect any associations with conditioning regimen (MAC, RIC), stem cell source (PBSC, BM), donor/recipient CMV serostatus. Conversely, we observed increased proportions of GM-CSF+ CD4 T cells in recipients of grafts from haploidentical donors compared with recipients of HLA-matched transplants (p = 0.0019). This was associated with increased GM-CSF levels in plasma of recipients of haploidentical grafts (p = 0.0019).

**Conclusions:** Our analysis provides the first characterization of the immune-reconstitution of human GM-CSF+ CD4 T cells after HSCT and reveals increased production of GM-CSF after HSCT in the HLA-haploidentical setting. Additional analyses are ongoing to assess the potential relationship between GM-CSF+ CD4 T cells and post-transplant complications, such as GvHD and disease relapse.

**Abstract ID: 144****Diffuse fibroblastic reticular cell tumor of the bone: a case report**

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**Introduction:** Fibroblastic reticular cell tumors (FRCT) derived from stroma- dendritic cells are part of the histiocytic neoplasms according to the WHO 2016 classification. They most frequently arise in lymph nodes and the spleen. FRCT are extremely rare malignant neoplasms and pose unique diagnostic and therapeutic challenges.

**Methods:** We report on a case of FRCT with diffuse bone involvement and on the diagnostic features and treatment strategies.

**Results:** The 41-year old patient initially presented with progressive fatigue and back pain. Imaging revealed an osteolytic and osteoblastic process with involvement of all osseous structures. Due to the pronounced sclerotic reaction of the affected

bones several lesions had to be biopsied to obtain representative tissue samples. The morphological spindle cell infiltrate with accompanying osteosclerosis and reticulin fibrosis expressed desmin, actin, calponin, CD14, CD68 and CD163 amongst others, with notable negative staining for S100, CD21, CD23 and CD35 as well as for pancytokeratin. With a delay of 4 months, the diagnosis of FRCT could finally be retained. Next generation sequencing revealed no targetable genetic alteration with tier I or II level of evidence. TMB was 7.1 mut/Mb.

Symptomatic progression of vertebral lesions resulted in myelopathy and required surgical decompression and local radiotherapy (RT). Systemic treatment was initiated with the MEK-inhibitor Cobimetinib based on the histiocytic origin of FRCT. Unfortunately, primary progression occurred, necessitating further palliative RT courses for symptomatic bone lesions, and leading to a rapid decline in performance status. In a discussion with an international panel of experts on histiocytic tumors, second line treatment with thalidomide was recommended. However, symptomatic progression could not be halted. The patient was transferred to hospice care and passed of complications of tumor-related progressive bone marrow failure associated with diffuse osseous involvement of FRCT.

**Conclusions:** To our knowledge, this is the first report on an FRCT diffusely affecting the bone.

**EPOSTER – CLINICAL SOLID TUMOR ONCOLOGY****Abstract ID: 51****PSMAddition: a phase 3 trial to compare treatment with 177Lu-PSMA-617 plus SOC versus SOC alone in patients with metastatic HSPC**

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**Introduction:** [177Lu]Lu-PSMA-617 (177Lu-PSMA-617) is a high-affinity prostate-specific membrane antigen (PSMA)-targeted radioligand therapy that delivers  $\beta$ -particle radiation to PSMA-expressing cells and the surrounding microenvironment. Androgen receptor pathway inhibitors (ARPI) may alter PSMA expression and radiosensitivity. PSMAddition will assess the efficacy and safety of 177Lu-PSMA-617 plus standard of care (SOC) versus SOC alone in adults with metastatic hormone-sensitive prostate cancer (mHSPC).

**Methods:** PSMAddition (NCT04720157) is an international prospective open-label, randomized, phase 3 trial in adults with mHSPC. Eligible patients are treatment-naïve or minimally treated candidates for hormonal therapy, with PSMA-positive disease (determined by [68Ga]Ga-PSMA-11 PET/CT), ECOG performance status of 0 to 2 and adequate major organ function. Patients are excluded if they have rapidly progressing tumours that require chemotherapy. Approximately 1126 patients will be randomized 1:1 to receive 177Lu-PSMA-617 (7.4 GBq i.v. every 6 weeks,  $\leq$  6 cycles) plus SOC or SOC alone (control arm). SOC is ARPI and androgen deprivation therapy. Stratification

factors are tumour volume (high/low), age ( $\geq$ 70/<70 years) and previous/planned prostatectomy or radiation treatment of the primary prostate tumour (yes/no).

**Results:** The primary endpoint is radiographic progression-free survival (rPFS), as assessed by blinded independent centralized review. Upon centrally confirmed radiographic progression, participants in the control arm can cross over to the 177Lu-PSMA-617 arm. The planned sample size provides 95% power to detect a hazard ratio of 0.7 for rPFS after 418 events with an overall one-sided significance level of 0.025. The key secondary endpoint is overall survival. Other secondary endpoints are the proportion of patients with a prostate-specific antigen (PSA) decline of  $\geq$ 90% from baseline, time to development of metastatic castration resistant prostate cancer, composite progression-free survival (radiographic, clinical or PSA progression), safety and tolerability, and health-related quality of life.

**Abstract ID: 77****ASCENT-04/KEYNOTE-D19: Phase 3 study of sacituzumab govitecan (SG) plus pembrolizumab (pembro) vs treatment of physician's choice (TPC) plus pembro in 1L programmed death-ligand 1-positive (PD-L1+) metastatic triple-negative breast cancer (mTNBC)**

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**Introduction:** A checkpoint inhibitor combined with chemotherapy is standard of care for patients (pts) with mTNBC whose tumors are PD-L1+. SG is an antibody-drug conjugate (ADC) comprising an anti-Trop-2 antibody coupled to a cytotoxic SN-38 payload, via a hydrolyzable linker. SG showed significant

clinical benefit (progression-free survival [PFS]; overall survival [OS]) over TPC chemotherapy in pts with mTNBC who received  $\geq 2$  prior therapies, with  $\geq 1$  in the metastatic setting (Bardia et al. NEJM. 2021). ASCENT-04 evaluates whether combining SG, a potent ADC, with pembro improves efficacy outcomes of 1L in PD-L1+ mTNBC.

**Methods:** ASCENT-04 (EudraCT: 2021-005742-14) is a global, open-label, randomized, phase 3 study in 1L locally advanced inoperable, or mTNBC in PD-L1+ (combined positive score  $\geq 10$ ) tumors; pts previously treated with/without anti-PD-L1 agent in the (neo)adjuvant setting may be included. TNBC (human epidermal growth factor receptor 2 negative, estrogen/progesterone receptor  $< 1\%$ ) and PD-L1 status will be centrally confirmed. Other inclusion criteria are pts  $\geq 6$  mo since completion of treatment with curative intent and ECOG performance status 0-1. Pts with prior treatment with topoisomerase inhibitors are excluded. Pts are randomized 1:1 to receive SG (10 mg/kg IV on D1 and 8) plus pembro (200 mg on D1) in 21-d cycles or TPC (gemcitabine and carboplatin, paclitaxel, or nab-paclitaxel) plus pembro until blinded independent central review (BICR)-verified progressive disease/unacceptable toxicity. Pts randomized to the control arm may be eligible to receive SG upon disease progression. Stratification is based on de novo vs recurrent disease within 6-12 mo of treatment vs recurrent disease occurring after  $> 12$  mo from completion of treatment in (neo)adjuvant setting, prior exposure to anti-PD-L1, and geographic region. The primary endpoint is PFS assessed by BICR review per RECIST v1.1. Secondary endpoints include OS, objective response rate, quality of life, and safety. ASCENT-04 will enroll  $\sim 440$  patients and is open for recruitment, also in 5 centers in Switzerland.

#### Abstract ID: 89

### PSMAfore: a phase 3 study comparing 177Lu-PSMA-617 treatment with change in androgen receptor pathway inhibitor in taxane-naïve patients with mCRPC

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**Introduction:** [177Lu]Lu-PSMA-617 (177Lu-PSMA-617) is a high-affinity prostate-specific membrane antigen (PSMA)-targeted radioligand therapy that delivers  $\beta$ -particle radiation to PSMA-expressing cells and their surrounding microenvironment. In the phase 3 VISION trial, 177Lu-PSMA-617 significantly improved radiographic progression-free survival (rPFS) and prolonged survival in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with  $\geq 1$  androgen receptor pathway inhibitor (ARPI) and 1–2 taxanes. PSMAfore is investigating the effect on rPFS in taxane-naïve patients with mCRPC treated with either 177Lu-PSMA-617 or a change in ARPI.

**Methods:** PSMAfore (NCT04689828) is a multicentre, open-label, randomized phase 3 trial in adults with progressive mCRPC and confirmed PSMA expression by [68Ga]Ga-PSMA-11 PET/CT. Eligible patients are taxane-naïve in the metastatic setting and have: received one prior ARPI and are candidates for a change in ARPI; an ECOG performance status of 0 or 1; a castrate level of serum/plasma testosterone ( $< 50$  ng/dL or  $< 1.7$  nmol/L); and recovered to grade  $\leq 2$  from toxicities related to prior therapies. Approximately 450 patients will be randomized 1:1 to receive 177Lu-PSMA-617 (7.4 GBq i.v. every 6 weeks for 6 cycles) or a change in ARPI to either abiraterone or enzalutamide. Best supportive care is allowed in both arms. Stratification factors are prior ARPI use in castration-resistant vs hormone-sensitive prostate cancer settings and pain symptomatology (score 0–3 vs 4–10 on the worst pain intensity item of the British Pain Inventory – Short Form).

**Results:** The primary endpoint is rPFS according to PCWG3-modified RECIST v1.1 criteria. Participants with radiographic progression in the ARPI arm can crossover to the 177Lu-PSMA-617 arm or receive another therapy. The planned sample size provides 95% power to detect a hazard ratio of 0.56 for rPFS after 156 events with an overall one-sided significance level of 0.025. The key secondary endpoint is overall survival; other secondary endpoints are safety and tolerability of 177Lu-PSMA-617 and health-related quality of life.

## INDEX OF FIRST AUTHORS

- Abdelwahab M 23S  
 Akhoundova Sanoyan D 64S  
 Arribas AJ 29S
- Bana M 50S  
 Baráth B 56S, 57S  
 Baur K 41S  
 Beck P 61S  
 Beerlage A 42S  
 Bernardi C 65S  
 Bertaglia Calderara D 24S, 55S  
 Berthold D 66S  
 Bertschinger M 66S  
 Bounaix L 52S  
 Brasier-Lutz P 34S  
 Britschgi C 17S  
 Brodard J 55S
- Caku S 10S  
 Casalino F 56S  
 Chanias I 42S  
 Chiru ED 43S  
 Codilupi T 11S  
 Colomer-Lahiguera A 50S
- da Silva Lopes A 49S  
 de Ramón Ortiz C 39S, 61S  
 Dietliker N 60S  
 Dietsche L 35S  
 Dufour A 30S
- Geese F 20S  
 Graber N 51S
- Hass HG 49S  
 Hugon-Rodin J 9S  
 Huober J 44S, 66S  
 Hussung S 18S
- Jevtic Z 12S
- Jungius S 34S
- Kaiser A 32S  
 Klink M 41S  
 König D 17S  
 Kroiss M 46S
- Laspa E 57S, 62S  
 Leuenberger LP 32S  
 Lorch A 67S  
 Lysenko V 30S
- Mach A 27S  
 Maechler M 38S  
 Mamez AC 6S  
 Mamot M 45S  
 Mandhair H 33S  
 Marchi R 54S  
 Marconato M 16S  
 Mayr K 63S  
 Medinger M 15S, 40S, 63S  
 Modesti M 20S  
 Monai N 21S  
 Morin S 40S  
 Moutzouri Beifuss E 26S
- Najaf Zadeh S 53S  
 Nilius H 21S, 22S  
 Njue L 58S
- Paluch-Shimon S 48S  
 Picardi C 48S  
 Planas-Paz L 33S  
 Popescu R 46S  
 Pradier A 32S  
 Prince Eladnani R 2S
- Rai S 4S  
 Rausch C 14S  
 Rentsch V 14S
- Rieger MJ 8S  
 Riguzzi M 51S  
 Ring A 60S  
 Rosenberg J 16S  
 Rösler W 35S  
 Royston E 59S
- Saeedi Saravi SS 10S  
 Saxer R 64S  
 Schmid C 15S  
 Schmid D 47S  
 Schnegg-Kaufmann A 29S  
 Schneider JS 27S, 28S  
 Schneider M 43S  
 Schöppenthau M 65S  
 Seydoux C 36S, 39S  
 Shehwar D 23S  
 Sobottka-Brillout B 7S  
 Stakia O 62S  
 Stetka J 3S  
 Stoffel T 38S
- Tripodo M 59S  
 Trojan A 50S
- Usart M 12S
- Valenta S 18S  
 van den Berg J 24S  
 Veuthey K 22S  
 Vrotniakaitė-Bajercienė K 52S, 53S
- Wahli MN 43S  
 Wallrabenstein T 44S, 45S  
 Wojtovicova T 26S
- Zellweger N 47S  
 Zermatten MG 9S

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