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The Circle at Zurich Airport, November 18–20, 2021

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SWISS ONCOLOGY & HEMATOLOGY CONGRESS (SOHC)

THE CIRCLE AT ZURICH AIRPORT, NOVEMBER 18–20, 2021

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SSH/SSMO BEST ABSTRACT & AWARD SESSION: HEMATOLOGY & ONCOLOGY

O01

Impact of thrombophilia testing on treatment decision and outcome of thromboembolism and pregnancy morbidity: a single center retrospective cohort study

K. Vrotniakaite-Bajerciene1,2, T. Tritschler3, K. Jalowiec1, H. Broughton4, J. Brodard1, A. Heynes5, A. Rovo1, J.A. Kremer Hovinga1,2, D. Aujesky3, A. Angelillo-Scherrer1,2

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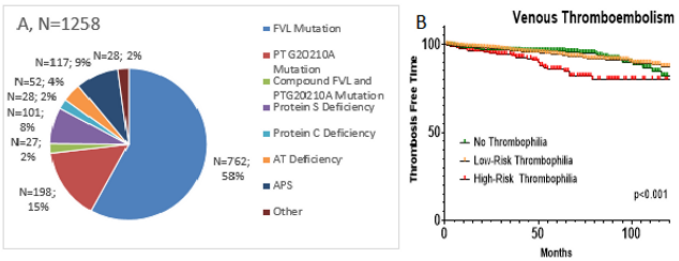
Introduction: Clinical utility of thrombophilia testing remains a topic of controversy since its introduction in clinical practice, because data showing its clinical usefulness and benefits for further clinical decision is still limited.

Methods: We conducted a single-center retrospective cohort study of 3686 patients referred to Thrombophilia Center at Bern University Hospital from 01.01.2010 to 31.10.2020. Results of thrombophilia work-up, and clinical and laboratory data were recorded. We systematically evaluated the impact of thrombophilia testing results on treatment decision according to guidelines and documented any new thromboembolic and pregnancy morbidity event after thrombophilia testing up to 01.03.2021.



A. Prevalence of Thrombophilia at Swiss Thrombophilia Center. FVL, Factor V Leiden; PT, prothrombin; AT, antithrombin; APS, antiphospholipid antibody syndrome. *Other – plasminogen activator inhibitor type 1 mutation, methyltetrahydrofolat reductase gene mutation, dysfibrinogenemia

B. Kaplan-Meier survival curve showing venous thromboembolism-free survival in patients with no thrombophilia, low-risk thrombophilia and high-risk thrombophilia

Table 1. Thrombophilia Influence on Treatment Decision

		No influence on therapy	Proper decision	Inappropriate decision			P-value
				Decision to undertreat	Decision to overtreat	Overlooked result	
	Total N=3550	N=3050 (85.9%)	N=211 (5.7%)	N=189 (5.1%)	N=11 (0.3%)	N=82 (2.2%)	<0.001
Negative thrombophilia work-up	N=2358 (66%)	2171 (71%)	0 (0.00%)	181 (98%)	1 (9.1%)	0 (0.00%)	
Low-risk Thrombophilia	N=822 (23%)	671 (22%)	112 (53%)	2 (1.1%)	7 (64%)	25 (30%)	
High-risk Thrombophilia	N=247 (6.3%)	144 (4.7%)	44 (21%)	0 (0.00%)	2 (18%)	33 (40%)	
Antiphospholipid Syndrome	N=119 (3.4%)	47 (1.5%)	50 (24%)	0 (0.00%)	1 (9.1%)	21 (26%)	

High-Risk Thrombophilia - Protein C, S, antithrombin deficiency, homozygous factor V Leiden mutation, homozygous prothrombin G20210A mutation, compound heterozygous factor V Leiden and prothrombin G20210A mutation. **Low-Risk Thrombophilia** – heterozygous factor V Leiden mutation, heterozygous prothrombin G20210A mutation, plasminogen activator inhibitor type 1 mutation, methylenetetrahydrofolate reductase mutation, dysfibrinogenemia

Results: In 3550 patients (94%), a partial or full thrombophilia testing was performed and 1258 patients (28.9%) displayed at least one thrombophilia (Figure1A). The majority of the patients were tested because of venous thromboembolism (2407, 65%), followed by patients with arterial thromboembolism (591, 16%) and with pregnancy morbidity (121, 3.3%). 341 asymptomatic subjects (30%), mainly patient family members, were also included.

Only 211 (5.7%) work-ups provided a further guidance to extend or initiate anticoagulation (Table 1).

2651 patients (72%) were followed-up more than 30 days with a median follow-up of 48 months (1 – 426 months). Patients with high-risk thrombophilia had significantly more new venous thromboembolic events compared to those without any thrombophilia or with low-risk thrombophilia (Figure 1B).

Conclusion: Our study confirms and quantifies the very low utility and potential harmful effect of thrombophilia work-up in all types of index thromboembolic events and pregnancy morbidity. Selection criteria to identify high-risk thrombophilia must be improved.

O02

Real-world experience with CAR-T therapy with Brexucabtagene Autoleucel for advanced relapsed mantle cell lymphoma

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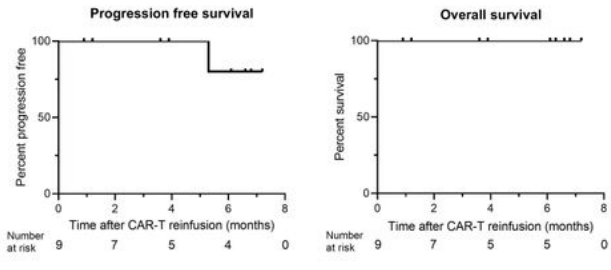
Background: MCL patients relapsing after BTK inhibitors have poor response rates and short duration to subsequent treatment. In contrast, CD19 directed CAR-T therapy with Brexucabtagene Autoleucel (Tecartus®) has shown unprecedented response rates of up to 93% and durable remission in 60% of responding MCL patients in trials. However, real-world outcome of CAR-T therapy in r/r MCL is limited.

Methods: We evaluated response rate, toxicities and survival of r/r MCL patients treated within the compassionate use program for Tecartus®.

Results: Nine patients were treated between February and August, 2021 at a single academic centre. Mean age was 71 years (57-81 years), and four (44%) pts were female. Patients had two to seven previous lines of treatment, all were refractory to BTK inhibitors, and three (33%) pts had previous ASCT. Despite heavy pre-treatment and predominantly advanced disease, therapy was well tolerated. Seven patients (77%) developed grade 1 or 2 CRS, no higher grade was observed. ICANS grades 1-4 were observed in four patients (44%; one at each grade), all of which also had CRS. ICANS was fully reversible in all patients following steroid therapy.



All seven patients with at least three months follow-up achieved metabolic CR by PET, and the two patients awaiting PET staging had PR by CT one month after CAR-T. So far, one patient relapsed with novel CNS manifestations five months after CAR-T.

Conclusion: CAR-T therapy with Tecartus® provides excellent response rate and a favourable safety profile in this small real-world cohort of heavily pre-treated r/r MCL patients.

O03

Single-dose carboplatin followed by involved-node radiotherapy in seminoma stage IIA/B: efficacy results from the international, phase II trial SAKK01/10

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Background: Standard treatment options for seminoma clinical stage (CS) IIA/B are either "dog-leg" para-aortic/pelvic radiotherapy (RT) or 3-4 cycles of cisplatin-based combination chemotherapy (ChT) with a 3-year PFS of ≥90%, but potential acute and late toxicities. SAKK01/10 aims at reducing therapy toxicity while preserving efficacy by combining deescalated ChT and RT.

Methods: SAKK01/10 is a multicenter, phase II study in CSIIA/B seminoma (de novo or relapse on active surveillance). Treatment included 1 cycle carboplatin AUC7 followed by involved-node RT (IIA: 30Gy; IIB: 36Gy). The primary endpoint is 3-year-PFS. Secondary endpoints include acute and late adverse events (AEs), including secondary malignancies.

Results: A total of 120 patients were included. 116 patients were eligible (IIA: 46, IIB: 70; de-novo: 76, relapsing: 40). Median age was 40 years (range 22-68). Minimal follow-up from inclusion of last patient is 3 years, median follow-up time is 4.5 years (range: 0.8 years-8.1 years). The 3-year PFS is 93.7% (90% CI [88.5%,96.6%]). All recurrences appeared outside the RT volumes and all were salvaged with conventional ChT. Treatment-related acute °III-°IV AEs occurred in 8.4% of all patients. No treatment-related late AEs were noted, 4 patients developed a second primary tumor not attributable to trial treatment.

Conclusions: SAKK 01/10 is the largest completed trial in seminoma CSIIA/B to date. A favorable 3-year-PFS using single dose carboplatin AUC7 and involved-node RT was achieved. At the same time, adverse event rates were very low. Based on our data, this regimen can be viewed as an attractive option in CSIIA/B seminoma.

Conflict of Interest statement: Personal & institutional financial interests:

Astellas, AstraZeneca, Bayer, Debiopharm, Janssen, Merck, Sanofi

O04

Ageing-Derived IL-1 Promotes *Tet2*$^{+/-}$ Clonal Expansion in Mouse Models of Clonal Hematopoiesis

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Clonal Hematopoiesis of Indeterminate Potential (CHIP) is defined as the presence of an expanded somatic blood cell clone carrying a mutation in hematologic malignancy driver genes (e.g *DNMT3A, TET2*) at a variant allele frequency of at least 2% in the absence of other hematological abnormalities. CHIP associates with increased risk of leukemia development, particularly in individuals carrying higher pre-malignant clonal sizes. While age is the best predictor of CHIP development in humans, the factors promoting CHIP clonal expansion during physiological aging are unclear. We hypothesized that ageing associated low-grade inflammation is a driver of CHIP clonal expansion. Using bone marrow chimeras and a irradiation-independent tamoxifen inducible genetic mosaicism mouse model of *Tet2*$^{+/-}$ driven CHIP (*HSC-Scl-Cre-ER*^{T}*; Tet2*$^{+/flox}$; R26$^{+/flox\text{-}stop\text{-}EGFP}$ triple transgenic mice) we observe that peripheral Tet2$^{+/-}$ clonal expansion rates increase with age and associate with higher bone marrow (BM) levels of inflammatory cytokine IL-1. Strikingly, continuous administration of IL-1 to young mice carrying CHIP leads to an IL-1R1-depedent expansion of *Tet2*$^{+/-}$ hematopoietic mature and stem/progenitors (HSPCs). Moreover, we observe that *Tet2*$^{+/-}$ clonal expansion under IL-1 exposure results from increased multilineage differentiation, associates with increased HSPC cell-cycle progression and repopulation capacity, without impacting on viability. Importantly, genetic (BM chimeras using donor BM from *Tet2*$^{+/-}$*; Il-1r1-/-* compound mutants) or pharmacological inhibition of IL-1 signaling (Anakinra, hIL-1ra) during ageing impairs *Tet2*$^{+/-}$ clonal expansion. Overall, our data provide proof-of-concept that IL-1 production derived from aged BM cells is a relevant and targetable driver of *Tet2*$^{+/-}$ clonal expansion in aged mice

SSH/SSMO ORAL PRESENTATIONS – CLINICAL HEMATO-ONCOLOGY

O05

Impact of Busulfan pharmacokinetics on outcome in adult patients receiving an allogeneic hematopoietic cell transplantation

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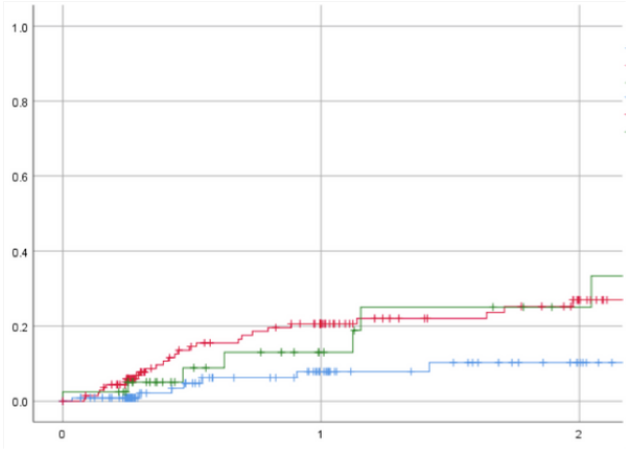
Busulfan (Bu) is widely used in conditioning regimens before allogeneic hematopoietic cell transplantation (allo-HCT). Its metabolism is variable due to inter-individual differences of pharmacokinetics, defined by Bu-AUC. We aimed to correlate administered dose, proportion of patients reaching target AUC and clinical outcome. Low-AUC, in range-AUC and high-AUC were defined as > and <25% of the targeted Bu-AUC. In 2019, we changed Bu dosing from 4x/day (Bu-4) to once daily (Bu-1) for ease of application. The target range was reached in 138 (46%) patients, 121 (40%) were in low-AUC and 41 (14%) in high-AUC. Bu dose adaptation was done in 60 (20%) patients, 102 were not in the target range but the dose was not modified because deviating <25% from the target AUC range. Regarding outcomes, viral and fungal infections were significantly more frequent in high-AUC compared with low-AUC (20% vs 8%; p = 0.01 and 37% vs 17%; p = 0.03), there was no statistical difference among groups in other organ toxicities (liver, mucositis, renal, neurological, cardiac, pulmonary, dermatologic).



With Bu-1, 66% were in low-AUC compared to 36% with Bu-4 (p<0.01); the only significant difference on toxicity was a higher incidence of mucositis when given once daily (p = 0.02). Outcomes at 2 years showed

a significantly higher non-relapse mortality (Figure 1, p<0.01), lower survival (p = 0.02), lower graft-versus-host-free-relapse-free-survival (p = 0.02) and lower progression-free-survival (p = 0.04) in the high AUC group. Incidences of relapse and aGVHD or cGvHD were not significantly different (p = 0.88, 0.64, 0.27, respectively). In conclusion, low-AUC BU-PK seems of benefit regarding NRM and GFRS.

O06

Real-world outcomes in elderly ALL patients with and without allogeneic hematopoietic stem cell transplantation: a single-centre evaluation over 10 years

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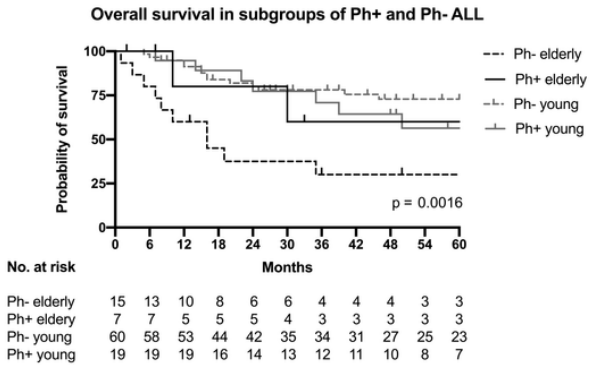
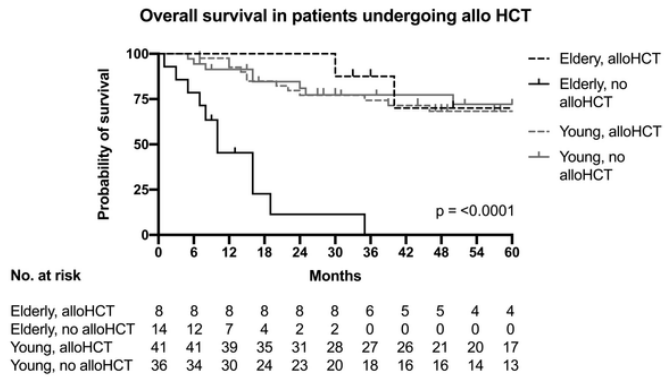
Elderly patients (EP) of 60 years and above with acute lymphoblastic leukemia (ALL) have a dismal prognosis, but paediatric-inspired chemotherapy and allogeneic stem cell transplantation (allo HCT) are used reluctantly due to limited data and historical reports of high treatment-related mortality in EP. We analysed 130 adult ALL patients treated at our centre between 2009 and 2019, of which 26 were EP (range 60-76 years). Induction with paediatric-inspired protocols was feasible in 65.2% of EP and resulted in complete remission in 86.7% compared to 88.0% in younger patients (YP) of less than 60 years. Early death occurred in 6.7% of EP. Five-year overall survival (OS) for Ph- B-ALL was significantly worse for EP than YP (72.8% vs 30.0%, p = 0.0016). Forty-nine patients received allo HCT including 8 EP, for which improved 5-year OS of 70.0% was observed, whereas EP without allo HCT died after a median of 9.5 months. In Ph+ B-ALL 5-year OS did not differ between EP (60%) and YP (56.3%). No transplant-related mortality and a low infection rate (12.5%) were reported in EP. Our data indicate that selected EP can be treated effectively and safely with pediatric regimens and might benefit from intensified therapy including allo HCT.





O07

Baseline creatinine predicts acute kidney injury during intensive therapy in transplant-eligible patients with acute myeloid leukaemia

S. Krieg[1], H. Seeger[2], P. Hofmann[3], C. Del Prete[1], M.G. Manz[1], A.M. Müller[1], A.P. Theocharides[1]

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Acute myeloid leukaemia (AML) is characterized by poor outcome and high treatment-related mortality. Despite the improvement in supportive care, acute kidney injury (AKI) is a common complication during intensive induction therapy and after allogeneic haematopoietic stem cell transplantation (allo-HSCT).

In this single-centre, retrospective study, 151 patients with AML, who underwent allo-HSCT between 2005 and 2016 were investigated for AKI development before and up to one year after allo-HSCT. We determined the incidence, patient characteristics, and predictive factors associated with AKI development.

According to the definition of the Kidney Disease Improving Global Outcome (KDIGO), 35.1% (53/151) of AML patients developed AKI during intensive chemotherapy with a male predominance (45% vs. 26.3%, p = 0.016). The baseline creatinine level was significantly higher in patients, who developed AKI (79 µmol/l vs. 66 µmol/l, p<0.001) and was an independent risk factor for AKI development during chemotherapy (p = 0.001). Most AKI were of KDIGO stage 1 (45.6%), stage 2 was observed in 38.6% and stage 3 in 15.8%. Patients suffering from AKI had a significantly higher risk of AKI recurrence after allo-HSCT (77.4% vs. 60.2%, p = 0.033). A high incidence of chronic kidney disease (CKD) was observed after allo-HSCT without a significant difference between the AKI and non-AKI group (35.8% AKI vs. 42.9% non-AKI patients, p = 0.67)

In conclusion, AKI occurred in one third of AML patients undergoing intensive chemotherapy before allo-HSCT with a male predominance. The serum baseline creatinine level was an independent predictor of AKI development.

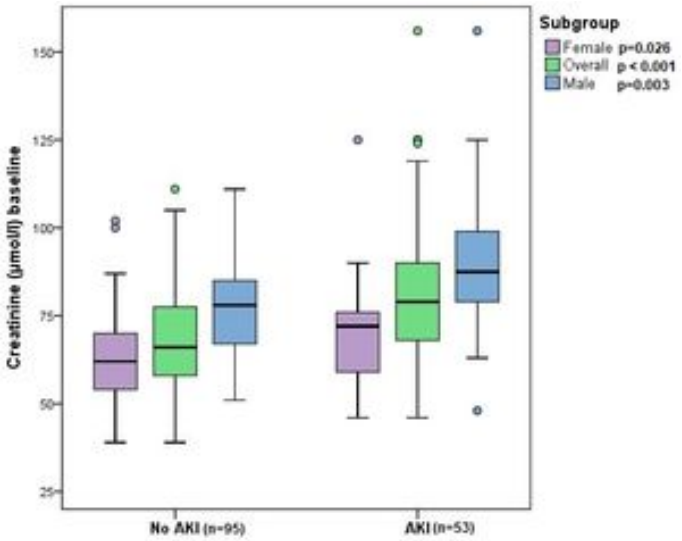

Fig. Correlation of baseline creatinine with AKI development stratified by gender.

Conflict of Interest statement: This paper was published online October 5, 2021. Br J Haematol. 2021 Oct 5. doi: 10.1111/bjh.17854. Please do not consider if against the SOHC abstract policy.

O08

Poor humoral responses to mRNA vaccines against SARS-CoV-2 in patients after CAR-T-cell therapy

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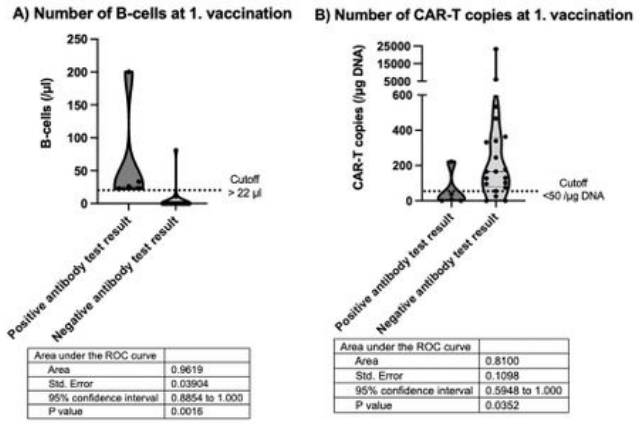
Introduction: Immunosuppressed patients are at risk of a severe SARS-CoV-2 course. Patients after CAR-T-cell therapy inevitably have B-cell aplasia and are particularly vulnerable. Data on efficacy and optimal sequence of SARS-CoV-2 vaccination in CAR-T-cell recipients are missing.

Methods: We analyzed all consecutive alive patients (predominantly DLBCL) undergoing CAR-T-cell therapy between 01/2019-08/2021. Patients received two Covid-19 mRNA vaccines between 01/2021-08/2021. We assessed the efficacy of the vaccines using IgG antibodies against SARS-CoV-2 spike protein (anti-S1/S2) (Clia Diasorin; cut-off >12 AU/ml) and separated patients into two groups: 1) CAR-T-cell infusion pre-vaccination; 2) CAR-T cell infusion post-vaccination.

Results: We identified 44 patients vaccinated with mRNA-1273 (Moderna) (33 pts; 75%) or BNT162b2 (Pfizer-BioNTech) (11 pts; 25%). In group 1 (28 pts), only 21% had positive antibodies after two vaccine doses while in group 2 (16 pts), 31% did so. In group 1, higher B-cell numbers (>22/µl B-cells; PPV 83,3%; NPV 100%) and lower CAR-T-cell copy numbers (<50/µg DNA CAR-T-cell copies; PPV 57.1%, NPV 94.4%) were predictive of positive humoral vaccine response. Patients without detectable B-cells when vaccinated produced negative antibody tests. In group 2, positive anti-spike protein IgG-antibodies after CAR-T-cell therapy declined by a median of 73.8 AU/ml at two consecutive assessments after a median of 74 days.

Figure 1 A-B



A) Violin plot depicting number of B-cells at time of 1. Vaccination in patients with positive anti-spike protein IgG antibody test result (>12AU/ml) compared to B-cell numbers of patients with a negative antibody test result. Optimal cut-off for positive test result at >22µl B-cells.

B) Violin plot depicting number of CAR-T-cell copies at time of 1. Vaccination in patients with positive anti-spike protein IgG antibody test result (>12AU/ml) compared to CAR-T cell numbers of patients with a negative antibody test result. Optimal cut-off for positive test result at <50µl CAR-T-cells.

Conclusion: Our results suggest poor humoral antibody responses in patients with prior CAR-T-cell therapy after mRNA Covid-19 vaccines. Low B-cell counts are associated with high CAR-T-cell copy numbers at vaccination and lacking antibody response. Anti-spike protein IgG values significantly declined in patients vaccinated before CAR-T-cell therapy.

O09

Mutational profiles by NGS in newly diagnosed and relapsed/refractory multiple myeloma

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Background: Due to complexity and costs, NGS has not yet been included into routine practice for myeloma patients. Here, we tried to analyze NGS data in correlation with treatment outcome in newly diagnosed (nMM) and relapsing (rMM) myeloma patients.

Patients and methods: 120 patients with MM, diagnosed at our center, were analyzed by NGS, including 8 genes - *CCND1*, *DIS3*, *EGR1*, *FAM46C* (*TENT5C*), *FGFR3*, *PRDM1*, *TP53*, *TRAF3*, - and 7 hotspots in *BRAF*, *IDH1*, *IDH2*, *IRF4*, *KRAS*, *NRAS*. Bone marrow investigation was performed in 83/120 (69%) cases of nMM and in 37/120 (31%) of rMM. If eligible, 67/83 (81%) of nMM patients received 1st line therapy with VRD followed by HDCT/auto-HSCT. 15/83 patients (18%) received other treatments.

Results: The most frequently mutated in nMM were *KRAS* 20/55 (36%), *NRAS* 16/55 (29%), *DIS3* 9/55 (16%), *FAM46C* 9/55 (16%) and in rMM - *KRAS* in 11/37 (30%) and *TP53* 9/37 (24%), *NRAS* in 6/37 (16%), *DIS3* 5/37 (14%).

1st line treatment in nMM resulted in CR in 50/67 (75%) and PR (or VGPR) in 14/67 (21%).

In both n/rMM *NRAS* Q61K (c.181C>A, p.(Gln61Lys)) was associated with PR (suboptimal outcome) in 7/9 cases (78%), and mutant *FAM46C* with CR in 9/13 (70%). 9 of 11 of mutant *TP53* carriers (81%) had rMM.

Conclusions: The most frequent mutations touched the MEPK pathway. *NRAS* Q61K could be associated with worse and mutant *FAM46C* with better treatment response. Mutations in *TP53* are more common for rMM. These associations should be investigated and confirmed in larger cohorts.

SSH ORAL PRESENTATIONS – HEMOSTASIS, TRANSFUSIONS MEDICINE & VASCULAR DISEASES

O10

Phosphoproteomic characterization of platelets highlights signalling proteins specific to the procoagulant function

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Background and Objectives: Upon combined activation with collagen-plus-thrombin, a fraction of platelets loses aggregatory properties and become procoagulant. The underlying dichotomous intracellular signalling is still not fully elucidated. Here, we investigated whether a phosphoproteomic approach could identify key pathways regulated differentially.

Methods: Human platelets from healthy donors (n = 3) were activated with convulxin (agonist of the collagen receptor GPVI) and thrombin in the presence or not of calcium, which generated either procoagulant or aggregating phenotypes, respectively. Flow cytometry (with fluorescently labelled Annexin-V and PAC-1) was used to characterize subpopulations. Using proteomics strategies (Tandem Mass Tag) and quantitative mass spectrometry, we analysed phosphorylation patterns to compare resting, aggregating, and procoagulant platelets.

Results: We quantified over 7200 different phosphorylation sites (phosphosites) corresponding to 1886 unique proteins of which 1643 (87%) showed significant regulation upon stimulation. Our data indicate that procoagulant platelets are prominently dephosphorylated (and aggregating hyper-phosphorylated) compared to baseline. At least 3645 phosphosites (51%) were significantly regulated in the procoagulant condition; among them, 65 were inversely regulated when compared to the aggregating endpoint: 36 phosphosites were down-regulated in aggregating platelets but up-regulated in procoagulant ones; 29 phosphosites were up-regulated in aggregating platelets but down-regulated in procoagulant ones. Noteworthy, we observed a significantly different regulation in the phosphorylation status of sodium-calcium-exchanger (NCX) protein, confirming our previous data showing a critical role of NCX for the dichotomous activation leading to procoagulant platelets (Thromb Haemost 2021;121:309).

Conclusion: The present study highlights the use of phosphoproteomics to understand better signalling pathways underlying platelet functional heterogeneity.

O11

Thrombin generation to predict the outcome of venous thromboembolism in the elderly: a prospective multicenter cohort study

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Introduction: The predictive ability of thrombin generation (TG) for recurrent VTE, major bleeding and mortality in the elderly is unknown. Therefore, we prospectively investigated the performance of the TG in predicting the risk of VTE recurrence, major bleeding and mortality in an elderly patient cohort.

Methods: TG was measured by the calibrated automated thrombogram assay 12 months after the index VTE in consecutive patients aged ≥65 years, and patients were followed-up for the next 2 years. Triggers were 1pM tissue factor with/without thrombomodulin (TM) and 13.6 pM tissue factor with/without activated protein C (APC). Primary outcomes were VTE recurrence, major bleeding and mortality.

Results: TG was assessed in 565 patients 12 months after index VTE. A this time, 59% of patients were anticoagulated.

Patients still anticoagulated 12 months after the index VTE were less likely to develop recurrent VTE in the next 2 years than patients without anticoagulation ($p<0.001$). However, the incidence of major bleeding and mortality was comparable in anticoagulated and non-anticoagulated patients ($p = 0.989$). TG was faster and lower in anticoagulated than in non-anticoagulated patients. Several TG parameters were discriminatory for primary outcomes in non-anticoagulated patients. Moreover, these parameters were more strongly associated with VTE recurrence than with other outcomes after adjustment for potential confounding factors. Notably, normalized peak ratio in presence/absence of TM was associated with VTE recurrence (Figure 1).

Conclusion: In elderly patients, TG was associated with VTE recurrence, major bleeding and/or mortality. These findings will set the basis for an external validation in another prospective study.

O12

Accuracy of a single, heparin-calibrated anti-Xa assay for the measurement of rivaroxaban, apixaban, and edoxaban drug concentrations: prospective cross-sectional study

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Background: Applying a single anti-Xa assay, calibrated to unfractionated heparin to measure rivaroxaban, apixaban, and edoxaban would simplify laboratory procedures and save healthcare costs.

Methods: We conducted a prospective multicenter cross-sectional study in clinical practice. Patients treated with rivaroxaban, apixaban, or edoxaban were included. Anti-Xa activity was measured using the Siemens INNOVANCE® heparin assay. Drug concentrations were determined using ultra-high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS). Cut-off levels regarding clinically relevant drug concentrations (30 mg L^{-1}; 50 µg L^{-1}; 100 µg L^{-1}) were determined in a derivation dataset (50% of patients) and sensitivities and specificities were calculated in a verification dataset (50% of patients).

Results: Out of 932 patients included, 845 were available for the present analysis. Correlation coefficients (r_s) between the heparin-calibrated anti-Xa assay and drug concentrations were 0.97 (95% CI 0.97-0.98) for rivaroxaban, 0.96 (0.95-0.97) for apixaban, and 0.95 (0.94-0.98) for edoxaban. In the derivation dataset, the area under the receiver operating characteristics curve (ROC) was 0.99 for all clinically relevant drug concentrations. In the verification dataset, the sensitivity was 94.2% (95% CI 90.8-96.6) for 30 µg L^{-1}, 95.8% (92.4-98.0) for 50 µg L^{-1}, and 98.7% (95.5-99.9) for 100 µg L^{-1}. Specificities were 86.3% (79.2-91.7), 89.8% (84.5-93.7), 88.7% (84.2-92.2) respectively.

Conclusions: In a large prospective study in clinical practice, a strong correlation of heparin-calibrated anti-Xa measurements with LC-MS/MS results was observed and clinically relevant drug concentrations were

predicted correctly. The implementation is likely to improve laboratory processes and potentially save healthcare costs.

Conflict of Interest statement: The study was supported by a research grant of the Research Fund Haematology Cantonal Hospital Lucerne. MN is supported by a research grant of the Swiss National Science Foundation (#179334). Implementation of the LC-MS/MS measurements was supported by the Gottfried & Julia Bangerter-Rhyner Stiftung. The study was supported by a research grant of Siemens healthineers. These funders had no role in study design, data collection and analysis, the decision to publish, or manuscript preparation. We thank the following companies for the provision of reagents and/ or pure substances: Bayer Healthcare AG, Bristol-Myers Squibb, and Daiichi Sankyo. These companies had no role in study design, data collection and analysis, the decision to publish, or manuscript preparation. MN reports research grants from Bayer Healthcare, outside of the submitted work, lecture honoraria from Bayer Healthcare, and Daiichi Sankyo. LA reports research grants from Bayer, CSL-Behring, Novartis, Novo Nordisk, Roche, Sobi, and Takeda. WAW reports research grants from Bayer Healthcare, BMS-Pfizer, Daiichi Sankyo and Sanofi, and honoraria for participating in scientific advisory boards from Bayer, Pfizer, and from Alexion Pharma GmbH, all outside the submitted. JDS reports lecture fees and advisory honoraria from Bayer Healthcare, Pfizer, Takeda, Siemens, and Sanofi.

O13

Pediatric patients with hereditary thrombotic thrombocytopenic purpura (hTTP): Opportunities and challenges in disease management, data from the international hTTP Registry (hTTPR)

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Hereditary TTP is a rare and life-threatening thrombotic microangiopathy, caused by bi-allelic *ADAMTS13* mutations leading to severe ADAMTS13 deficiency, and presents with a heterogeneous clinical course. We recently showed that children <10 years have an annual incidence of acute episodes of 1.46 (95%CI 1.09-1.93); whereas adults of 0.22 (95%CI 0.13-0.36)*.

At the end of August 2021, 47 pediatric hTTP patients were followed-up in the hTTPR. We analyzed the incidence and severity of acute episodes*.

Since birth, 39/47 patients experienced 297 episodes: 207 in females and 90 in males. Of the episodes, 90% were mild (score 1; characterized by fever, thrombocytopenia and mild gastrointestinal symptoms); and 5.3% and 4.2% classified as moderate (score 2) or severe (score 3) with acute renal failure and cerebrovascular/cardiovascular involvement with lasting sequelae*. No episode was fatal. Score 2 and 3 episodes happened mainly before enrolment into the hTTPR. Of 109 episodes occurring during prospective follow-up, 56 happened under regular plasma prophylaxis. Infections triggered 97% of episodes.

The annual incidence of prospectively observed episodes decreased from 1.11 (95%CI 0.89-1.36) in 80 patient-years in early childhood (≤6 years) to 0.29 (95%CI 0.12-0.60) in 24 patient-years in adolescence (>12-18 years), (Table).

Recognition of hTTP in pediatric patients is critical. Current prophylactic plasma treatment, every two-to-three weeks, is insufficient to prevent the occurrence of acute episodes. Pediatric hTTP patients seem to be particularly vulnerable during (mild) infections. The advent of recombinant ADAMTS13 with the possibility of home-treatment may ease prophylaxis, especially in children.

* Tarasco et al, 2021

Table: Annual incidence of acute episode during prospective follow-up

			Sex		Age at enrolment		Prophylaxis**	
	Overall	Male	Female	0-6	>6-12	>12-18	Yes**	No**
No. of patients with follow-up	47	22	25	20	12	15	29	34
No. of patients with any episodes	16	5	11	10	3	3	8	11
No. of prospective episodes	109	29	80	89	13	7	56	53
Person-years	142	65	77	80	37	24	95	47
Incidente rate (95%CI)	0.77 (0.63-0.93)	0.45 (0.30-0.64)	1.04 (0.82-1.29)	1.11 (0.89-1.36)	0.35 (0.19-0.59)	0.29 (0.12-0.60)	0.59 (0.44-0.76)	1.14 (0.85-1.49)

** 16 patients had follow-up time with and without prophylaxis (3 with episodes)

O14

Ravulizumab reduces thrombosis risk in adult PNH patients: 2-year data

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Background: Patients with paroxysmal nocturnal hemoglobinuria (PNH) are at an increased risk of thromboembolism (TE) which may be fatal.

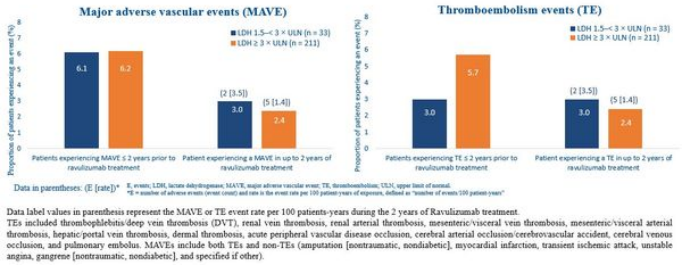
Objective: To evaluate the long-term effectiveness of ravulizumab at preventing TEs and major adverse vascular events (MAVEs) in patients with PNH and high disease activity (HDA) in a phase 3 study.

Methods: This ongoing phase 3, multicenter, randomized, open-label study (NCT02946463) enrolled complement-inhibitor-naïve adult patients with PNH and HDA. Patients received weight-based dosing of ravulizumab every 8 weeks or eculizumab during the randomized treatment period and continued or switched to ravulizumab during the extension period. In this post-hoc analysis, patients who received ravulizumab were stratified by baseline LDH levels into two groups: 1.5 – <3 × ULN (Group A) or ≥ 3 × ULN (Group B). Proportion of patients experiencing MAVE or TE in 2 years prior to enrolment and after receiving ravulizumab during 2 years of the study were compared for each group. MAVEs include both TEs and non-TEs.

Results: Patients were stratified to Group A (n = 33) or Group B (n = 211), respectively. Patient demographics were comparable between the two groups. Over the 2 years of study, patients in Group A and Group B underwent 56.7 and 361.2 patient-years of exposure to ravulizumab, respectively. Treatment with ravulizumab resulted in fewer reported MAVEs and TEs compared with the 2 years prior to enrolment in both groups.

Conclusions: Ravulizumab reduces the risk of thrombosis in patients with PNH and HDA, who are at an increased risk of TE.

Figure 1 Summary of MAVEs and TE events in patients with PNH and high disease activity



Data in parentheses: (E [rate])*

Data label values in parenthesis represent the MAVE or TE event rate per 100 patients-years during the 2 years of Ravulizumab treatment.
TEs included thrombophlebitis/deep vein thrombosis (DVT), renal vein thrombosis, renal arterial thrombosis, mesenteric/visceral arterial thrombosis, hepatic/portal vein thrombosis, dermal thrombosis, acute peripheral vascular disease occlusion, cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, and pulmonary embolus. MAVEs include both TEs and non-TEs (amputation [nontraumatic, nondiabetic], myocardial infarction, transient ischemic attack, unstable angina, gangrene [nontraumatic, nondiabetic], and specified if other).

Conflict of Interest statement: Novartis: Consultancy, Honoraria, Advisory Board, Research Funding; CSL Behring: Research Funding; Alexion: Research Funding; Advisory Board, Orphaswiss: Advisory Board. BMS: Advisory Board, Consultancy. AstraZeneca: advisory Board. Swedish Orphan Biovitrum AG: Advisory Board.

SSH/SSMO ORAL PRESENTATIONS – EXPERIMENTAL HEMATOLOGY / ONCOLOGY

O15

Inhibition of interleukin-1β reduces myelofibrosis and osteosclerosis in mice with *JAK2*-V617F driven myeloproliferative neoplasm

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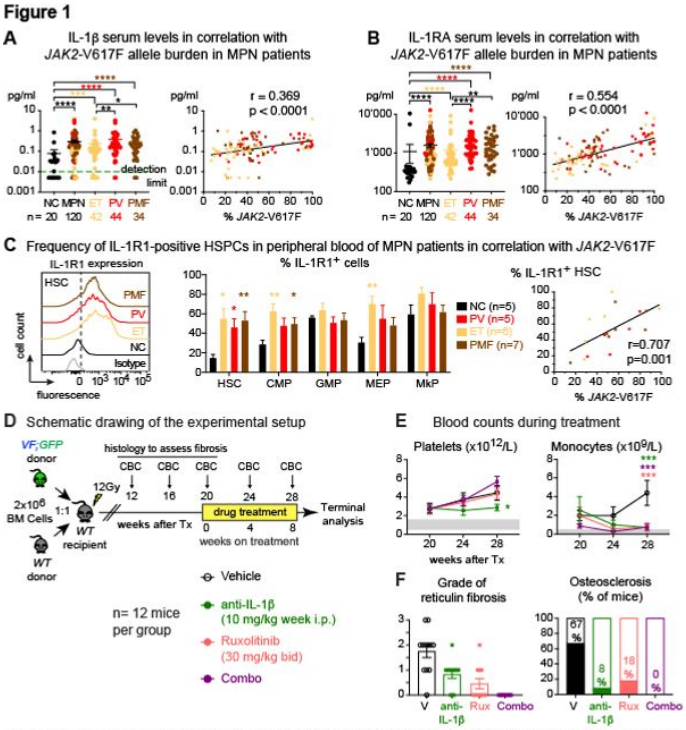
Interleukin-1β (IL-1β) is a master regulator of inflammation and its increased activity has been implicated in various pathological states. Here, we show that increased serum levels of IL-1β and IL-1 receptor antagonist (IL-1RA) and the expression of IL-1 receptors on hematopoietic stem and progenitor cells correlated with *JAK2*-V617F mutant allele fraction in peripheral blood of MPN patients (Figure 1A-C).

We found that the source of IL-1β overproduction in a mouse model of MPN were *JAK2*-mutant hematopoietic cells and the genetic ablation of *IL-1β* resulted in decrease of myelofibrosis and osteosclerosis. We next tested the effects of anti-IL-1β antibody on the course of MPN disease in mice transplanted with *JAK2*-V617F mutant bone marrow (Figure 1D). Grade of reticulin fibrosis was assessed in the bone marrow at 12-, 16-, and 20-weeks after transplantation and at 20-weeks, when all mice within the sacrificed group displayed myelofibrosis, remaining mice from cohort were randomized into four treatment groups. Anti-IL-1β antibody treatment alone reduced platelet and monocyte counts (Figure 1E). Anti-IL-1β antibody reduced reticulin fibrosis as well as the percentage of mice with osteosclerosis, and showed additive effects on both parameters with ruxolitinib (Figure 1F).

Figure 1



Legend to Figure 1. (A) Serum IL-1β levels (pg/ml) in normal controls (NC; n=20) and MPN patients (n=120); ET (n=42), PV (n=44), PMF (n=34). Correlation (r) and significance (p) between % *JAK2*-V617F in peripheral blood granulocytes and log transformed serum IL-1β levels. Dashed green line shows limit of detection at y=0.01 pg/ml. **(B)** Serum IL-1RA levels (pg/ml) and correlation (r) and significance (p) between % *JAK2*-V617F and log transformed serum IL-1RA. **(C)** Representative histogram showing the expression of interleukin-1 receptor type 1 (IL-1R1) in peripheral blood hematopoietic stem cells (HSCs) from isotype control, NC (n=5) and MPN patients (n=18); ET (n=6), PV (n=5) and PMF (n=7). Graph showig percentages of IL-1R1+ HSC and hematopoietic stem and progenitor cells (HSPCs) including common myeloid progenitors (CMP), granulocyte macrophage progenitor (GMP), megakaryocyte erythroid progenitor (MEP) and megakaryocyte progenitor (MkP). Graph showing correlation (r) and significance (p) between % *JAK2*-V617F and percentages of IL-1R1+ HSCs in peripheral blood. **(D)** Schematic of the experimental setup for the drug treatment. **(E)** Platelet and monocyte counts in peripheral blood during 8-weeks of drug treatment **(F)** Grade of reticulin fibrosis in bone marrow after 8-weeks of treatment. Stacking bar graph shows the percentage of mice with osteosclerosis in the bone marrow.

Using genetic and pharmacological approaches, we show that IL-1β inhibition reduced myelofibrosis in a preclinical *JAK2*-V617F MPN mouse model. Furthermore, the combination therapy with Jak1/2 inhibitor, ruxolitinib resulted in complete reversal of myelofibrosis and osteosclerosis. Our data highlight the role of IL-1β in MPN progression to myelofibrosis and provide a rationale for a clinical trial with anti-IL-1β antibody in MPN patients.

Conflict of Interest statement: R.C.S. has consulted for and received honoraria from Novartis and Celgene/BMS, he is a scientific advisor/SAB member and has equity in Ajax Therapeutics; N.H. owns stocks in the company Cantargia; C.J.F. is a full-time employee of Novartis Pharma AG. The inhibitor studies were carried out in the laboratory of R.C.S. with inhibitors provided by Novartis. The remaining authors declare no competing financial interests.

O16

Inflamm-ageing of hematopoietic stem cells is driven by microbiome via IL-1

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During ageing, hematopoietic stem cells (HSCs) increase in number, reduce self-renewal capacity, skew towards myeloid differentiation, and show mitigated bone marrow (BM)–homing ability. We here evaluated how and to what extend HSC-extrinsic factors determine HSC behaviour during aging.

Firstly, we observed that aged specific pathogen free (SPF) wild-type mice, in contrast to young SPF mice, produce more IL-1a/b in bone marrow (BM), with most of IL-1a/b being derived from myeloid BM cells. Secondly, blood of aged WT SPF mice contains higher levels of microbe associated molecular patterns (MAMPs), specifically TLR4 and TLR8 ligands. Thirdly, BM myeloid cells from aged mice produce more IL-1 in vitro, and aged mice show higher and more durable IL-1a/b responses upon LPS stimulation in vivo. Given these observations together, we hypothesized that HSC ageing is driven via microbiome/IL-1 axis, to test this we evaluated HSCs from IL-1R1KO and WT germ free (GF) mice. Indeed, aged HSCs from IL-1R1KO and WT GF mice show significantly mitigated ageing-associated inflammatory signatures and maintain unbiased lympho-myeloid hematopoietic differentiation upon transplantation, thus resembling the functionality of young HSCs. Finally, reducing the inflammatory burden by in vivo antibiotic suppression of microbiota or pharmacologic blockade of IL-1 signaling in aged WT mice was similarly sufficient to reverse myeloid biased output of their HSC populations.

Our data demonstrate that ageing associated phenotype and myeloid-biased differentiation of HSCs is a result of signals derived from the microbiome, that act through increased IL-1 signalling, locally in BM.

O17

Iron is a modifier of the phenotypes of *JAK2*-mutant myeloproliferative neoplasms

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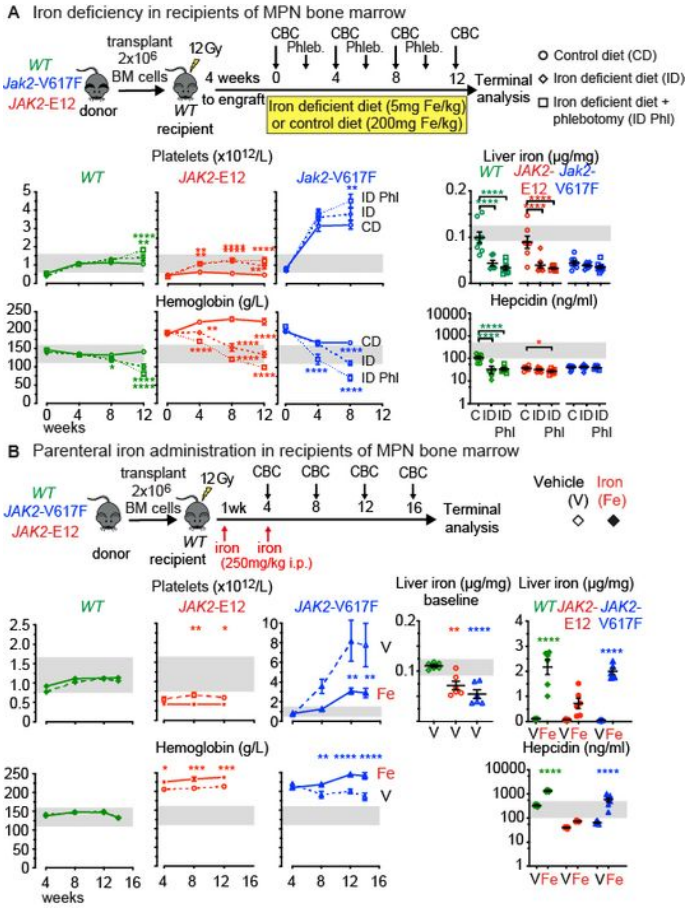
The majority of patients with myeloproliferative neoplasms (MPNs) carry a somatic *JAK2*-V617F mutation, that manifests as polycythemia vera (PV), essential thrombocythemia (ET) or primary myelofibrosis (PMF). The reasons why the same oncogenic *JAK2*-V617F mutation in some patients causes ET and in others PV remain unclear. We examined the influence of iron availability on MPN phenotype in mouse models expressing *JAK2*-V617F or *JAK2* exon 12. Iron deficient diet in MPN mouse models with PV phenotype resulted in a switch to ET phenotype (Figure 1A). PV models already displayed iron deficiency at baseline and these mice responded reciprocally to parenteral iron administration by decreasing platelet counts and further increasing red cell parameters (Figure 1B).



In contrast, the ET model had normal baseline iron stores and numbers of platelets and erythrocytes didn't change upon iron injections, consistent with the notion that iron overload in hereditary hemochromatosis, in the absence of mutant *JAK2*, is not associated with erythrocytosis. Alterations of iron availability did not impact hematopoietic stem cells (HSCs) or common myeloid progenitors (CMPs), but primarily affected the bi-potent megakaryocyte erythroid progenitors (MEPs), which constitute the iron-responsive stage of hematopoietic differentiation in *JAK2*-mutant mice. *JAK2*-V617F PV models were also able to stimulate platelet production through an iron-independent path originating in platelet-biased HSCs/CMPs. Thus, iron availability is one of the key factors influencing MPN phenotype manifestation, especially in regards to erythroid expansion and platelet production in PV. Exploring means of limiting erythropoiesis through iron restriction may therefore benefit PV patients requiring repeat therapeutic phlebotomy.

O18

Resistance to type II JAK2 inhibition in MPN is dependent on chromatin remodeling and MAPK activation and is targetable

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Myeloproliferative neoplasms (MPN) show constitutively activated JAK2 signaling. Clinical JAK2 inhibitors as ruxolitinib are hampered by occurrence of resistance. Novel type-II JAK2 inhibition as with CHZ868 inactivates JAK2, reduces the MPN clone and overcomes resistance to ruxolitinib. Here, we study whether type-II JAK2 inhibition may induce resistance and how it could be addressed.

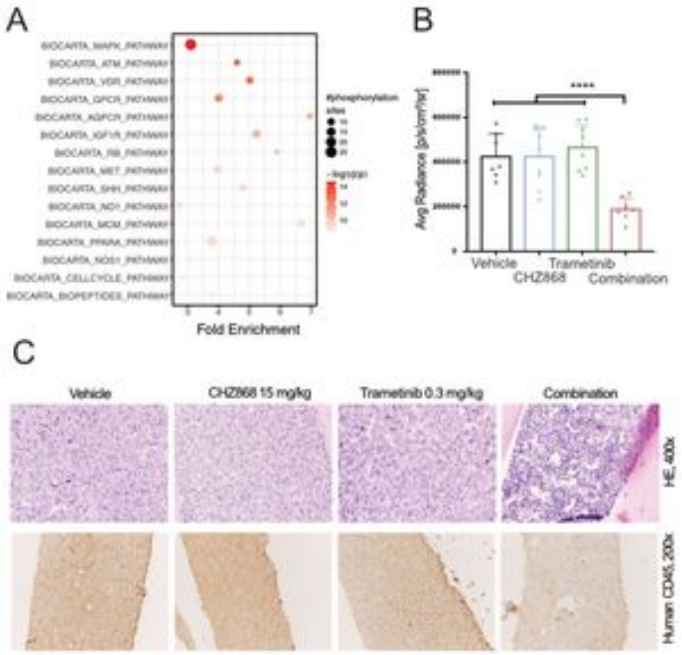

Fig. 1. MAPK pathway activation in type II JAK2 inhibitor resistance in MPN is targetable by combined JAK2 / MAPK inhibition. A. *Phospho-proteomic analysis shows most significant enrichment of MAPK pathway activation as compared to other pathways in type-II JAK2 inhibitor resistant JAK2 V617F MPN cells.* ***B.*** *Intravenous engraftment of NSG mice with luciferase-expressing JAK2 V617F cells resistant to type-II inhibitor CHZ868 induced extensive bone marrow infiltration as shown by bioluminescence imaging, and was significantly reduced by combined CHZ868 and MAPK inhibition with trametinib.* ***C.*** *H&E (upper panel) and human CD45 immunohistochemical staining (lower panel) of bone marrow illustrates significantly reduced infiltration upon combined CHZ868/ trametinib treatment of NSG mice.*

Long-term exposure to CHZ868 evoked resistance in *JAK2*V617F MPN cells with >10-fold increased IC_{50} and reduced CHZ868-induced apoptosis. Analysis of phospho-proteome by mass-spectrometry showed CHZ868 resistant cells maintain MAPK signaling (Fig.1A), which was confirmed by phospho-specific immunoblotting. Second-site JAK2 mutations were absent and resistance was reversible upon drug withdrawal. Paired ATAC-/RNA-sequencing revealed increased compaction of chromatin with enriched PRC2 and MAPK activation signatures in resistant cells. Exposure to the clinical MAPK inhibitor trametinib resensitized resistant cells to type-II JAK2 inhibition blocking proliferation and inducing apoptosis. NSG mice injected with CHZ868 resistant cells subcutaneously showed persistent tumors upon CHZ868 administration validating resistance in vivo, while additional MAPK inhibition reduced tumor growth and suppressed ERK phosphorylation in tumor tissue. In NSG mice engrafted with luciferase-expressing CHZ868 resistant cells intravenously, bioluminescence imaging and hCD45 immunohistochemistry demonstrated extensive bone marrow infiltration. Combined type-II JAK2 inhibition and MAPK pathway inhibition significantly reduced marrow infiltration (Fig.1B-C).

Our data show that resistance to type-II JAK2 inhibition in MPN relates to adaptive chromatin remodelling and MAPK pathway activation. We validate that CHZ868 resistant cells are dependent on MAPK signaling and are targetable by additional MAPK inhibition to restore therapeutic efficacy.

Higher Resolution Image: https://drive.google.com/file/d/1HZs-OY3fE_S8bo4RSn6s4tXoHPX3Owhy/view?usp=sharing

O19

Exploiting the CD47-SIRPα macrophage checkpoint to control polycythemia vera

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Polycythemia vera (PV) is a hematopoietic stem cell neoplasm characterized by increased red blood cells (RBCs) uncoupled from mechanisms that regulate erythropoiesis. The interaction between erythrocyte expressed CD47 and SIRPα, a receptor expressed on macrophages, protects RBCs from phagocytosis. To examine whether interfering with the CD47-SIRPα interaction affects PV erythropoiesis, we crossed tamoxifen (TMX)-inducible *SclCre*-recombinase *JAK2*-V617-transgenic mice (*JAK2*-mutant mice) with *Sirpα* mutant mice that lack intracellular signaling through SIRPα. In a second approach, *JAK2*-mutant mice with an established PV phenotype were treated with an anti-CD47 monoclonal antibody, inhibiting the CD47-SIRPα interaction. Hemoglobin (HGB) and RBC levels were consistently lower in *JAK2*-mutant mice on a *Sirpα* mutant background than *JAK2*-mutant mice on a *Sirpα* wild-type background with normalization of HGB/RBC levels five weeks after TMX induction. Mice on the *Sirpα* mutant background developed splenomegaly, and flow cytometry analysis showed an expansion of macrophages in the spleen of *Sirpα* mutant mice. Reduced HGB/RBC levels, more pronounced splenomegaly, and increased splenic macrophage fraction were also documented in *JAK2* mutant mice treated with an anti-CD47 antibody, consistent with the finding from the *JAK2* mutant mice on the *Sirpα* mutant background. Finally, we observed a reduction in the half-life of PV RBCs upon CD47 blockade, and preliminary data suggest that PV macrophages are more phagocytic than WT macrophages. This study demonstrates that genetic ablation and antibody-targeting of the CD47-SIRPα interaction markedly attenuates RBC levels in a PV mouse model.

SSMO ORAL PRESENTATIONS SOLID TUMOURS

O20

Outcome and prognostic factors of COVID-19 infection in cancer patients: final results of SAKK 80/20

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Background: These are the final results of a national registry on COVID-19 in cancer patients in Switzerland.

Methods: We collected data on 501 symptomatic COVID-19 infected cancer patients from 23 Swiss sites, starting March 1, 2020. The main objective of the study was to assess the outcome of COVID-19 infection in cancer patients, the main secondary objective was to define prognostic factors.

Results: With a cutoff date of March 15, 2021 and exclusion of 46 patients who refused consent, 455 patients were included into the final analysis. Most frequent malignancies were breast in 63 cases (14%) and lung in 47 (10%). Systemic treatment within 3 months prior to COVID-19 diagnosis included chemotherapy in 101 cases (23%), targeted therapy in 94 (21%), steroids in 78 (17%) and checkpoint inhibitors in 34 (8%). 285 patients (63%) were hospitalized for COVID-19, 213 (47%) required oxygen, 43 (9%) invasive ventilation, 62 (14%) were admitted to the ICU. Death from COVID-19 infection occurred in 98 patients, resulting in a mortality rate of 21.5%. Age ≥65 versus <65 (OR 3.35, p = 0.001), non-curative versus curative disease (OR 2.21, p = 0.021), ICU admission (OR 4.53, p <0.001) and oxygen requirement (OR 23.25, p <0.001) were independently associated with increased mortality.

Conclusions: We found a high COVID-19 mortality rate of 21.5% in real-world cancer patients for the first wave of the pandemic. The rate of hospitalization and ICU admission for COVID-19 in cancer patients is substantial.

O21

Darolutamide maintenance in mCRPC previously treated with novel hormonal agents and non-progressive on taxane: randomized phase II trial (SAKK 08/16)

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Background: We hypothesize that maintenance treatment with Darolutamide (Daro) for pts with disease stabilization under chemotherapy after pretreatment with a novel hormonal agent (NHA) can delay disease progression.

Methods: SAKK 08/16 is a randomized placebo-controlled double-blind phase 2 study. Pts with mCRPC and prior NHA therapy and non-progressive disease on taxane (docetaxel or cabazitaxel) were eligible. Pts received Daro 600mg bd or placebo bd. Primary endpoint: radiographic progression-free survival at 12 wks (rPFS12). Secondary endpoints: rPFS, EFS, OS, PSA 50% response (PSA50 RR), adverse events (AE). **Results:** 92 pts were accrued between 3/17 – 11/20. Median follow-up is 18 months (mo). rPFS12 was significantly improved with Daro 64.7% vs placebo 52.2% (p = 0.127, below significance level of 0.15). Median rPFS on Daro was 5.5 mo vs 4.5 mo on placebo (HR 0.54; 95% CI 0.32-0.91; p = 0.017) and median EFS 5.4 mo vs 2.9 mo (HR 0.46; 95% CI 0.29-0.73; p = 0.001). PSA50 RR was 22% on Daro vs 4% on placebo (p = 0.014). Median OS on Daro was 24 mo vs 21.3 mo on placebo (HR 0.62; 95% CI 0.3-1.26; p = 0.181). Treatment related AEs were mild and similar in both arms (Daro vs placebo): G1 26% vs 22%, G2 13% vs 15%, G3 2% vs 2%.

Conclusions: This proof of concept study met its primary endpoint and shows that switch maintenance with Darolutamide results in a statistically significant but clinically modest prolongation of rPFS and EFS with good tolerability. Median OS with Daro maintenance is promising and numerically superior to the control arm.

Conflict of Interest statement: Advisory role (institution): MSD, Astra Zeneca, BMS, Roche, Bayer, Astellas, Sanofi, Janssen (personal), Pfizer, Ipsen, Merck, Debiopharm; Speaker role (institution): Astellas, Janssen (personal); Travel support (institution): Astra Zeneca; Stock holding/Employment: none; Research support: none

O22

Long-term outcomes of operable stage III NSCLC in the pre-immunotherapy era

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Background: Chemoradiotherapy with durvalumab consolidation has yielded excellent results in stage III non-small cell lung cancer (NSCLC). Therefore, it is essential to identify patients who might benefit from a surgical approach.

Material and methods: Data from 437 patients with operable stage III NSCLC enrolled in four consecutive SAKK trials (16/96, 16/00, 16/01, 16/08) were pooled and outcomes analyzed in 431 eligible patients. All patients were treated with 3 cycles of induction chemotherapy (cisplatin/docetaxel), followed in some patients by neoadjuvant radiotherapy (44 Gy, 22 fractions) (16/00, 16/01, 16/08) and cetuximab (16/08).

Results: With a median follow-up time of 9.3 years (8.5-10.3), 5- and 10-year overall survival (OS) rates were 37% and 25%, respectively. Overall, 342 patients (79%) underwent tumor resection, with a complete resection (R0) rate of 80%. Patients (n = 272, 63%) with R0 had significant longer OS compared to patients who had surgery but incomplete resection (60.6 vs. 16.0 months, p <0.001). OS for patients who achieved pathological complete remission (pCR) (n = 66, 15%) was significantly better compared to patients without pCR (82.6 vs. 32.7 months; p = 0.003). For patients with pCR, the 5- and 10-year OS rates were 56% (95% CI: 43.2-67.5) and 42% (95% CI: 28.3-55.1), respectively.

Conclusion: We report favorable long-term outcomes in patients with operable stage III NSCLC treated with neoadjuvant chemotherapy with cisplatin and docetaxel plus/minus neoadjuvant sequential radiotherapy from four prospective SAKK trials. Almost two third of patients underwent complete resection after neoadjuvant therapy. We confirm R0 resection and pCR as important predictors of outcome.

O23

Association of tumour mutational burden with outcomes in patients with stage IIIA-NSCLC treated with neoadjuvant chemotherapy and durvalumab (SAKK16/14)

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Introduction: The utility of tumor mutation burden (TMB) as a predictive biomarker for the benefit of an immune checkpoint inhibitor therapy has been debated intensely. Here, we evaluate the association of tumor TMB with clinical outcome in resectable stage IIIA(N2) non-small cell lung cancer (NSCLC) patients undergoing neoadjuvant chemo-immunotherapy with three cycles of cisplatin/docetaxel followed by treatment with the PD-L1 antibody durvalumab.

Methods: Formalin-fixed paraffin-embedded (FFPE) tissue samples from 49 patients were processed. Total DNA was extracted and used for TMB. TMB-high was defined as >10 mutations/Mb. TMB was correlated with clinical endpoints using Log-rank (Mantel-Cox) test and Mann-Whitney-Wilcox test.

Results: 68 patients were enrolled and 55 were resected. TMB could be assessed in a total of 49 patients (10 pre- and 39 post-treatment tissue samples). Clinical parameters of these patients were not different from the overall population. TMB was not significantly different in patients with an EFS event after one year compared to patients with no EFS event observed (median TMB 7.5 mutations/Mb in both groups, p = .404). TMB-high patients showed no significant difference in EFS and OS (p = .696 and .824, respectively). No significant difference of TMB based on pCR (p = .057), MPR (p = .843), nodal clearance (p = .230) and nodal down-staging (p = .170) was observed. However, in patients with pCR there was a trend towards higher TMB (median TMB 13.9 versus 6.6 mutations/Mb).

Conclusions: Our results suggest that TMB is not associated with clinical outcome after neoadjuvant sequential chemo-immunotherapy with durvalumab in patients with resectable stage IIIA(N2) NSCLC.

O24

Selpercatinib efficacy and safety in patients with *RET*-altered thyroid cancer: a clinical trial update

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Background/Goals: Report an update of selpercatinib's efficacy and safety results in *RET*-altered thyroid cancer, with a longer follow up (30-Mar-2020 data cutoff vs 16-Dec-2019) and additional enrolment.

Methods: Patients with *RET*-mutant medullary thyroid cancer (MTC) and *RET*-fusion positive thyroid cancer (TC) were enrolled in global (16 countries, 89 sites) Phase-1/2 LIBRETTO-001. Primary endpoint: objective response rate (ORR). Secondary endpoints included DoR, PFS, clinical benefit rate (CBR; CR+PR+SD≥16 weeks), safety. The integrated analysis set (IAS, n = 143) includes efficacy evaluable MTC patients previously treated with cabozantinib and/or vandetanib (cabo/vande). The primary analysis set (PAS), a subset of IAS, is the first 55 enrolled patients. Cabo/vande-naïve MTC patients (N = 112) and TC patients with prior systemic treatment (N = 22) were also analysed. Safety population includes all patients who received ≥1 dose (MTC[N] = 315; TC[N] = 42) by data cutoff.

Results: For MTC patients, ORR%(95%CI) was 69.2(61.0,76.7) for IAS (n = 143), 69.1(55.2,80.9) for PAS (n = 55), 71.4(62.1,79.6) for cabo/vande-naïve MTC patients (n = 112). ORR%(95%CI) for TC patients (n = 22) was 77.3(54.6,92.2). Most TEAEs were low-grade; most common (≥25% MTC and/or TC patients treated with selpercatinib) were dry mouth, diarrhoea, hypertension, fatigue, constipation for both MTC/TC patients, increased ALT/AST, peripheral oedema and headache in MTC patients and nausea in TC patients. 4.8% MTC and TC patients discontinued selpercatinib due to TEAEs; 1.9% with MTC; none with TC discontinued due to treatment-related adverse events.

Conclusions: Selpercatinib continues to show marked and durable antitumor activity in patients with *RET*-altered thyroid cancers. It is well tolerated and no new safety concerns are identified.

Conflict of Interest statement: Daniela Weiler: Advisory Board: Lilly, MSD, Sanofi-Aventis

E-POSTER VIEWING

P01

Substantial differences in the immune response to ADAMTS13 in immune-mediated and in plasma-treated hereditary Thrombotic Thrombocytopenic Purpura (TTP)

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TTP results from a severe ADAMTS13 deficiency, caused by bi-allelic *ADAMTS13* mutations in hereditary TTP (hTTP), and by circulating ADAMTS13 autoantibodies, which are mainly of IgG_1 and IgG_4 subclass and recognize an epitope in the ADAMTS13 cys-rich-spacer domain in immune-mediated TTP (iTTP). Treatment with exogenous ADAMTS13 poses a risk of ADAMTS13 alloantibody formation present in ~10% of hTTP patients.

We characterized the anti-ADAMTS13 response in hTTP patients. We reassessed plasma samples with positive anti-ADAMTS13 titers, determined IgG subclass distributions and performed epitope mapping using recombinant ADAMTS13 fragments. In addition, we isolated peripheral blood mononuclear cells of three hTTP patients, treated on the demand (n = 1) or on regular plasma prophylaxis for >15 years (n = 2) to amplify the anti-ADAMTS13 IgG_4 Fab κ/λ repertoire by phage display technology.

Plasma anti-ADAMTS13 IgG antibody titers were confirmed in 9/12 hTTP patients with at least two different assays. The antibodies were non-inhibitory, predominantly of subclasses IgG_2 and IgG_3, and recognized epitopes in ADAMTS13 domains C-terminal of the spacer domain. The monoclonal anti-ADAMTS13 Fabs showed somatic hypermutation rates of 5.6 to 21.2% that correlated with the duration of plasma exposure. IGHV gene usage (V_H1-8, V_H1-46, V_H3-15, V_H3-30, V_H4-4, and V_H4-34) overlapped only minimally with that of iTTP ADAMTS13 Fabs.

These findings show substantial differences in functional properties, IGHV gene usage, IgG subclass distribution and epitope recognition of ADAMTS13 autoantibodies in iTTP and ADAMTS13 alloantibodies in hTTP. Somatic hypermutation in the latter correlated with the duration of plasma therapy, which remained possible and effective in all patients studied.

P02

Isolated severe neutropenia, evaluation of underlying causes and outcomes

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Background: Severe neutropenia, (neutrophil count <0.5 x 10(9)/L), may accompany many diseases and is of great clinical relevance due to susceptibility to infections. Primary care physicians and hematologists are frequently confronted with isolated neutropenia, its management can be challenging as no clear standards of treatment are defined.

Objective: We analyzed the incidence, causes, management and outcomes of patients with isolated severe neutropenia at a tertiary referral hospital.

Methods and results: The hospital database-management system was queried to find patients with severe isolated neutropenia. The search was restricted to the frame period 2015 to 2020 and was conducted across 2249 patients. We identified 1362 patients, chemotherapy, radiotherapy hematological neoplasia and additional cytopenias were excluded from this study. Thus 70 patients fulfilled the inclusion criteria. The mean age was 37 years and 65% (45/70) were females. Drug induced neutropenia was the main cause of acute neutropenia (51% (36/70), metamizol being the most common offending drug, followed by infectious diseases in 14% (10/70). 34% (24/70) patients had a chronic idiopathic neutropenia (CIN). Infections requiring hospitalization occurred in 25 patients (36%), none required intensive care and 18 received G-CSF. One patient died within this period, and there was no evolution to myeloid diseases.

Conclusion: Isolated acute neutropenia was observed in a young, otherwise healthy population, with the most important cause being drug-induced, particularly metamizol, suggesting the need to raise awareness on this potential complication. CNI cases were unexpectedly high, probably related to center characteristics offering hematological care. Generally, a benign outcome was observed.

P03

Monitoring haematocrit: Interim data on the accuracy of a handheld device (StatStrip Xpress® 2 Hb/Hct) for patient and professional use

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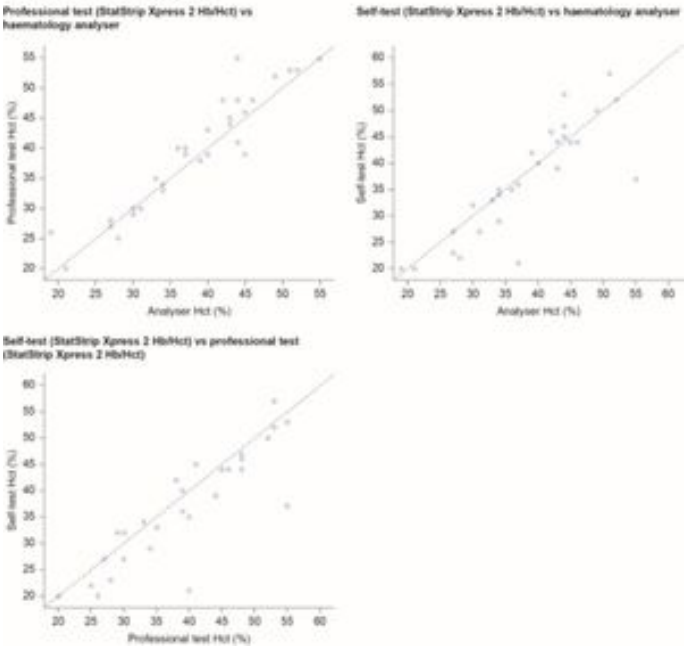
Patients with polycythemia vera (PV) are at high risk of morbidity and mortality. Maintaining haematocrit (Hct) levels below 45% can reduce this risk. Increasing the frequency of Hct monitoring could increase the time in Hct range below 45%, enable timely interventions, and improve quality of life. Increased monitoring frequency could be achieved by incorporating a self-testing device in patients' routine care. This observational study evaluated the accuracy of the StatStrip Xpress® 2 Hb/Hct meter (Hb/Hct meter; Nova Biomedical Corporation) for patient and professional use. Here we report interim data from 31 patients with PV, or other haematological conditions that require Hb/Hct monitoring. Blood samples were analysed using a laboratory analyser, and compared against values from measurements by healthcare professionals (HCPs; professional test) or patients (self-test) using the Hb/Hct meter at two Swiss centres. Accuracy was assessed as the mean difference in readings between two methods (*mdiff* [90% CI]).

Figure 1. Scatter plots showing interim data on the accuracy of Hct values collected via the StatStrip Xpress 2 Hb/Hct meter compared with the laboratory analyser.



Values were found to be aligned between the professional test and analyser (n = 30 measurements, *mdiff* = 1.2% [0.2, 2.2]), the self-test and analyser (n = 29 measurements, *mdiff* = -1.0% [-2.7, 0.7]), and the self-

test and professional test (n = 28 measurements, *mdiff* = -2.5 [-4.2, -0.8]). Patients had a positive opinion of the Hb/Hct meter, stating that it was easy to use, and patients with PV would feel safer using home monitoring than not. These findings support the accuracy of the Hb/Hct meter as a point-of-care device for HCPs and patients when measuring Hct in a real-world setting and demonstrate the potential of patient self-testing to monitor Hct levels at home.

Conflict of Interest statement: Alicia Rovo has worked at institutions that have received research funding from AG Alexion, CSL Behring, and Novartis. She has received honoraria from AG Alexion, BMS, and Novartis. She has received honoraria for attending advisory board meetings from AG Alexion, AstraZeneca, BMS, Novartis, OrPhaSwiss GmbH, and Swedish Orphan Biovitrum AG. She has received financial support for congresses and conference travel from Amgen, AstraZeneca, BMS, Sanofi, and Roche.

Claudia Baierlein-Leimbach, Therese Triemer and Daphne B. McCarthy-Pontier are employees of Novartis Pharma Schweiz AG. They were involved in the study protocol, data analysis, and the interpretation and writing of the publication.

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Cesare Medri, Ioannis Chanias, Loreen Errass, and Theresa Fehr declare no conflict of interest.

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P04

Thrombotic potential assessed by Thrombodynamics-Analyser during treatment of paediatric acute lymphoblastic leukaemia

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Introduction: Children with acute lymphoblastic leukaemia (ALL) are at highest risk for venous thromboembolism (VTE) during induction therapy (IT). Conventional laboratory coagulation assays do not enable to identify patients at risk for VTE. Unselective thromboprophylaxis in all patients is not justified.

Aim: We aimed to assess the utility of the Thrombodynamics-Analyzer (TD), an innovative thrombin generation (TG) and fibrin clot formation (FCF) assay enabling to monitor the dynamics of spatio-temporal blood coagulation, for assessing the haemostatic state in children with ALL before and during IT.

Methods: TG and FCF were assessed with TD (Hemacore, Russia) as Endogenous Thrombin Potential (ETP, AU/*min/L) and rate of clot-growth (V, mm/min) in 10 children with ALL treated according to the AIEOP-BFM protocol at day (d)0 (baseline), d8-12 (on steroids only), d22 (10d after PEG-Asparaginase) of IT. In addition, thrombin-antithrombin complexes (TAT) and prothrombin activation fragments (F1+2) were measured as *in-vivo* TG biomarkers.

Results: Children during IT showed a statistically significant higher pro-coagulant state compared to baseline: ETP [mean(±SD)] d0 = 1581(±358), d8-12 = 2334(±207) *p = 0.015*, d22 = 3012(±221) *p = 0.001*; and V d0 = 53(±6), d8-12 = 79(±20) *p = 0.02*, d22 = 84(±11) *p = 0.002*. In addition, TG tended to be higher at d8-12 and d22 in patients diagnosed with VTE (n = 3). Of note, TAT and F1+F2 were also increased but with a delay at around d30.

Conclusions: TD seems to be a promising assay to assess early *ex-vivo* pro-coagulant state and the potential thrombotic risk in children with ALL during IT. Additional research is needed to confirm these preliminary observations.

P05

Impact of a product-specific reference standard for the measurement of a PEGylated rFVIII activity: an *in-vivo* study

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Introduction: Monitoring activity of factor VIII (FVIII:C) for hemophiliac patients treated with extended half-life products remains challenging. We previously demonstrated that, using FVIII-deficient plasma spiked with PEGylated rFVIII (Adynovi®), product-specific reference standards (SS) with a chromogenic assay (CA) was the most reliable method to evaluate FVIII:C. The aim of this study was to compare different methods to evaluate FVIII:C in plasma samples of patients treated with PEGylated rFVIII (Adynovi®).

Material and Methods: We used 73 samples of 8 patients treated by Adynovi® at different time points. We compared FVIII:C measured with one-stage clotting assay (OSA) or CA with local reference standard (LS) or SS and compared the results with CA and SS, our reference assay.

Results: Compared to our reference assay, FVIII:C levels correlated well using OSA with LS (r2 = 0.96, p<0.001), OSA with SS (r2 = 0.96, p<0.001) or CA with LS (r2 = 0.98, p<0.001). When the results obtained with our reference assay was categorized into quartiles, there was only minimal differences between assays (Figure 1), with the largest mean difference in quartile #4 (-12%, p = 0,01 with OSA with LS).

Conclusion: Unlike our previous study, this *in-vivo* study shows a good correlation between the different FVIII:C assays. Although this study is based on a limited number of patients, it suggests that results of studies using spiked deficient plasma should be interpreted with caution.

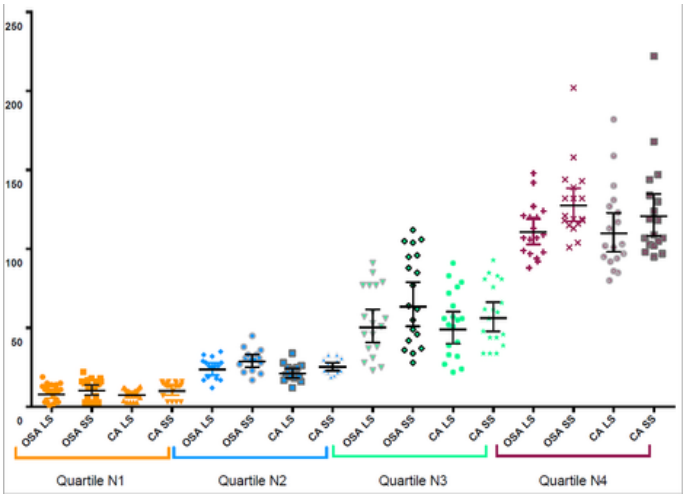

Figure 1: FVIII:C divided in quartiles. OSA: One-stage clotting assay, CA: chromogenic test, LS: local reference standard, SS: product-specific reference standard

P06

Anti-FY3 alloimmunisation: a threat to the management of sickle cell disease

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Sickle cell disease (SCD) has few curative treatments and red blood cell transfusion (RCT) remains essential for all therapeutic strategies. Hematopoietic stem cell transplantation and gene therapy are now promising opportunities, but both require transfusion support for prior exchange transfusion and the procedure.

Transfusion guidelines for SCD recommend to match RHDCEceK and if feasible FY1, FY2, JK1, JK2, MNS3 and MNS4. However 68% of Africans and only 2% of Caucasians are FY:-1,-2,-3. This genetic difference between recipients and donors is challenging for providing the best products. Consequently, as FY2 is expressed on other tissues in Africans, it is admitted that its prevention could be overlooked. But, matching only FY1 antigen prevents partly anti-FY3 alloimmunization, which has a serious impact in transfusion and obstetrics.

We report three patients with anti-FY3 alloimmunization diagnosed in Geneva (Table). Two of them ended with no more available donor in Switzerland because of poly-alloimmunization. In all three situations, all the transfusion releases where in accordance with above-mentioned recommendations. Moreover anti-FY3 was evanescent and not preceded by an anti-FY1 as classically described by experts.

Conclusion: Anti-FY3 is clinically significant and can lead to a transfusion deadlock, with obvious consequences on patient's outcomes. These cases illustrate that the risk of alloimmunization is concrete after almost all transfusions in Switzerland. Though we have access to highly specialized medical therapies in our country, our resources in rare blood is lacking. This report highlights that SCD and transfusion physicians should work closely to plan rigorously transfusions and curative treatments.

Year of birth and sex	Prior red cell concentrates N	FY1 positive red cell concentrates N	Transfusion reaction	Associated red cell antiobodies
1989 F	30	7	DHTR	Autoantibody
2001 F	32	12	DHTR	Anti-D, Anti-C, Anti-E, Anti-JK1, Anti-MNS3
2003 F	4	1	None	Anti-FY1, Anti-JK2, Anti-LE1, Anti-MNS1, Anti-MNS3, Anti-DO1, Anti-KN1

P07

Swiss Survey about current practices and opinions on clinical constellations that trigger the search for PNH clones

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This national survey investigates the current practice in Switzerland by collecting participants' opinions on clinical indications for the assessment of Paroxysmal Nocturnal Hemoglobinuria (PNH) clones. The participants' accessibility to flow-cytometry, and clinical attitudes for the follow-up (FU) of patients harboring PNH clones were examined. The survey includes 16 multiple-choice questions. The first 3 assess participants' demographics, using a triage question: those who answered not having access to investigate PNH clones were prevented from continuing the survey. Opinion on clinical management was collected using hypothetical clinical situations. Likewise, participants could select the option to be contacted to discuss the survey results. Alcimed powered the online survey and 264 doctors were contacted via email once a week for 5 weeks, from September 2020.

In total, 64 doctors (24.2%) from 23 institutions participated (81.3% hematologists, 67.2% from university hospitals). All reported having access to flow-cytometry for PNH clone testing, (76.6% in their own institution). The main reasons to search for PNH clones were unexplained thrombosis and/or hemolysis, and/or aplastic anemia(AA). Patients in FU with PNH clones are more likely to be AA and symptomatic PNH. 61% reported investigating again PNH clones during FU for AA /MDS patients even when at diagnosis were negative, and 75% test during FU at least once a year. Opinions related to clinical management were scattered. From the 37/64 participants reporting interest to participate in future discussions, 14 worked on the discussion of the results of this survey which represents the basis to understand unmet needs in the field.

Conflict of Interest statement: Alicia Rovo received research funding (to institution, not investigator) from Novartis, CSL Behring and AG Alexion. She has received speakers fee and honoraria from AG Alexion, BMS, and Novartis. She has received honoraria for attending advisory board meetings from AG Alexion, AstraZeneca, BMS, Novartis, OrPhaSwiss GmbH, and Swedish Orphan Biovitrum AG. Mathilde Gavillet made consulting for Alexion. Beatrice Drexler received honoraria from AG Alexion and Novartis. She has received honoraria for attending advisory board meetings from AG Alexion and Novartis. Yan, Beauverd received honoraria for attending advisory board meetings from AbbVie, BMS, Jazz Pharmaceuticals and Novartis. Thomas Lehmann received research funding (to institution) from Abbvie, Celgene and Novartis. He has received honoraria for attending advisory board meetings from BMS, Novartis, Abbvie, OrPhaSwiss GmbH. Sacha Zeerleder: received speakers fee and honoraria from Sanofi, Alexion, VIropharma and Jazz Pharma. All other authors declare no conflict of interest.

P08

Daratumumab for frequently relapsing and refractory immune thrombotic thrombocytopenic purpura

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Background: Immune thrombotic thrombocytopenic purpura (iTTP) is a life-threatening thrombotic microangiopathy. It is caused by severe ADAMTS13 deficiency due to circulating autoantibodies, and is associated with significant morbidity and mortality. Current treatment options include plasma exchange, immunosuppression, and caplacizumab. When remission is achieved, the risk of relapse is high, especially in patients with persistent ADAMTS13 deficiency.

Patients and methods: We administered daratumumab, a humanized antibody to CD38, a molecule expressed by plasma blasts and plasma cells, in two patients with iTTP. One patient had a frequently relapsing iTTP, and the other a treatment-refractory first episode. Daratumumab was given as 4 or 6 once-per-week intravenous infusions of 16 mg/kg body weight, respectively.

Results: Rapid and persistent clearance of ADAMTS13 inhibitory autoantibodies and restoration of normal ADAMTS13 activity was achieved by daratumumab. There were no relevant adverse drug reactions. We observe ongoing remission in both patients for 9 months now after the completion of daratumumab.

Conclusion: Targeting plasma cells with daratumumab is a new treatment option in relapsing and refractory iTTP.

P09

Acquired immune-mediated thrombotic thrombocytopenic purpura (iTTP) following mRNA-based COVID-19 vaccination (BNT162b2)

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Background: TTP is a rare and life-threatening thrombotic microangiopathy caused by auto-antibody induced severe deficiency of ADAMTS13, the specific von Willebrand-factor-cleaving protease. A few cases of iTTP after exposure to mRNA-based-COVID-19-vaccines have been described. The pathophysiology is unknown, but molecular mimicry and/or aberrant activation of the immune system are considered.

Goals: To describe the clinical context of the rare possible adverse effect acute iTTP following BNT162b2 vaccine administration, and its management.

Methods: We report the case of a 60-year-old man who suffered an ischemic stroke one week after the first exposure to BNT162b2. Ten days after his second exposure he was referred to our emergency department with retrosternal pain and confusion.

Results: Severe thrombocytopenia, anemia, signs of hemolysis, schistocytes on the blood smear, and slightly elevated high-sensitivity troponin were documented in the laboratory workup. ADAMTS13 activity was <5%, the functional ADAMTS13 inhibitor was negative, but non-inhibitory ADAMTS13 IgG-autoantibodies determined by ELISA were weakly positive, confirming the diagnosis of a first episode of iTTP. Antibodies to PF4-complex were negative, ruling out VIPIT/VITT. The patient was treated with three PEX sessions and steroids, achieving clinical and laboratory remission, including normalization of ADAMTS13 activity over the ensuing days.

Conclusions: We describe a first acute iTTP episode in the context of vaccination with BNT162b2. The close temporal association suggests a link between the vaccination and TTP, possibly through BNT162b2 induced formation of anti-ADAMTS13 antibodies. The patient is now in regular follow-up like other iTTP-survivors without an apparent trigger of their autoimmune reaction.

P10

Monitoring emicizumab pharmacodynamics with global coagulation assays

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Background: Emicizumab is a novel therapy approved for patients with hemophilia A. Differently from FVIII, emicizumab does not require activation by thrombin and it is immediately effective. Thus, even small concentrations of emicizumab shorten the activated thromboplastine time (aPTT) and affect aPTT-based factor assay, preventing monitoring of its efficacy.

Aim: To investigate whether global coagulation assays (GCA) are useful to monitor non-factor replacement therapy with emicizumab.

Method: We studied thrombin generation (TG) and fibrin clot formation (FCF) in two adult patients without inhibitors starting emicizumab treatment. Calibrated-Automated-Thrombogram and ST-Genesia assays (Stago, France) were used to measure TG. The innovative Thrombodynamics Analyzer (Hemacore, Russia), which monitors the spatio-temporal (tissue factor-dependent and -independent) dynamics of coagulation was used to measure FCF. Patients received emicizumab (Hemlibra®, F. Hoffmann-La Roche, Switzerland) weekly (3 mg/kg per body weight W1-4, 1.5 mg/kg from W5 onwards). Response to treatment was monitored weekly for two months.

Reault: We observed that:

i) Emicizumab improved TG and FCF compared to baseline;

ii) TG normalized after two weeks of treatment; FCF normalized already after one week;

iii) Both TG and FCF reached a plateau (starting at week 4) that lasted until the end of the monitoring;

iv) Despite same dose/kg patients had different coagulation potentials;

Conclusions: According to this preliminary and limited experience, emicizumab seems to improve the hemostatic potential in a patient-specific and "all-or-nothing" manner. GCA assays seem a useful method to judge the recovery of the hemostatic efficacy in presence of emicizumab and possibly to personalize patient treatment.

P11

Time to antibiotics in pediatric patients with fever in neutropenia during chemotherapy for cancer - SPOG 2015 FN definition study

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Background: Fever in neutropenia (FN) remains an unavoidable, potentially lethal complication of chemotherapy. Timely administration of empirical broad-spectrum intravenous antibiotics has become standard of care. But the impact of time to antibiotics (TTA), the lag period between recognition of fever or arrival at the hospital to start of antibiotics, remains unclear. Here we aimed to analyze the association between TTA and safety relevant events (SRE) in data from a prospective multicenter study.

Methods: We analyzed the association between time from recognition of fever to start of antibiotics (F-TTA) and SRE (death, admission to intensive care unit (ICU), severe sepsis and bacteremia) with three-level mixed logistic regression. We adjusted for possible triage bias using a propensity score and stratified the analysis by severity of disease at presentation.

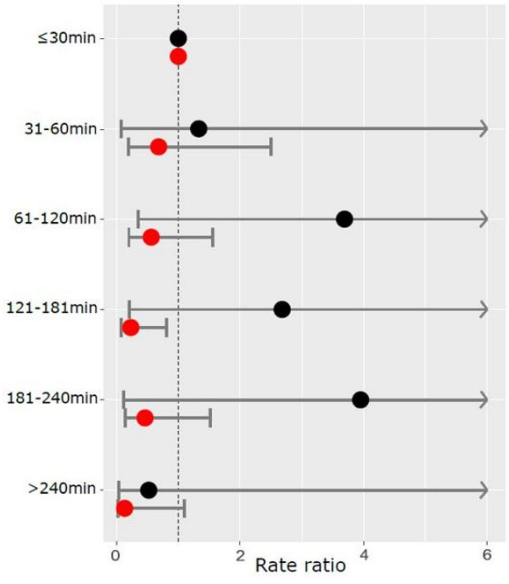

Figure 1: Rate ratios and 95% confidence intervals of F-TTA and safety relevant events, stratified by severity of the disease at presentation. Black circles: patients with severe disease at presentation; red circles: patients without severe disease at presentation.

Results: We analyzed 266 FN episodes, including 53 (20%) with SRE, reported in 140 of 269 patients recruited from April 2016 to August 2018. F-TTA (median, 120min; interquartile range, 49 to 180min) was not associated with SRE, with a trend for less SREs in episodes with longer F-TTA. Analyses applying the propensity score suggested a relevant triage bias. Only in patients with severe disease at presentation there was a trend for an association of longer TTA with more SRE (Figure 1).

Conclusion: We found little evidence that longer TTA leads to a higher risk of poor clinical outcome in pediatric patients with FN, except for those with severe disease at presentation. We saw strong evidence for triage bias which could only be partially adjusted.

P12

High-dose chemotherapy with treosulfan and melphalan before autologous transplantation in multiple myeloma

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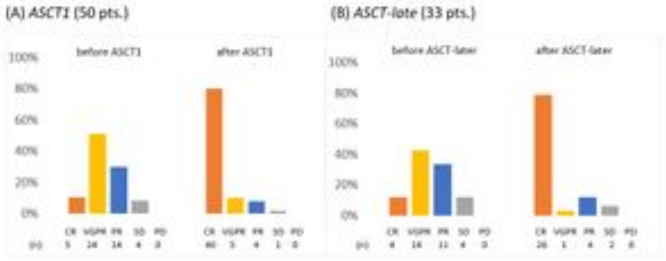
Introduction: Melphalan at 200mg/m^2 is the standard high-dose (HDCT) regimen before autologous transplantation (ASCT) in myeloma patients since decades. However, almost all myeloma patients will ultimately relapse, and progress in myeloma treatment may involve an improved HDCT strategy.

Methods: We evaluated consecutive myeloma patients treated with treosulfan 14 g/m^2 at days -4, -3 and -2 followed by melphalan 140 mg/m^2 at day -1. Serial treosulfan plasma levels were determined at day -3.

Results: The cohort comprised 83 patients undergoing ASCT as part of their first-line treatment (*ASCT1*; 50 pts) or second-/third-line treatment (*ASCT-late*; 33 pts). The median age was 63 years (range 32-75). Median duration of hospitalization was 21 days (range 16-33), and median duration of neutropenia was 8 days (range 4-16). Platelet transfusions were given in 95% and erythrocyte transfusions in 48%. Fully reversible acute renal impairment of any grade was observed in eight patients (10%). The CR rate in *ASCT1* patients improved to 80% after HDCT, and to 79% in *ASCT-late* patients (Figure 1). 44 of the 65 patients achieving CR had MRD <10-5 by highly sensitive MRD-flow (sCR). The median AUC of treosulfan was 861 mg/L*h (range 521-1582 mg/L*h), and the median peak level was 318 mg/L (range 210-538 mg/L), respectively. We observed no correlation between response rate and treosulfan AUC or peak values.

Conclusions: HDCT with treosulfan and melphalan is associated with promising response rates exceeding results traditionally seen with melphalan only. Our data serve as a rational for a prospective comparative trial.

Figure 1:



P13

Evaluating the prophylactic use of the IL-1 antagonist anakinra to prevent neurotoxicity after CAR-T cell infusion in DLBCL patients

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Introduction: Chimeric antigen receptor T-cell (CAR-T) therapy is increasingly used for relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). Severe side effects such as immune effector cell-associated neurotoxicity syndrome (ICANS) can occur in up to 64% of all patients, but pathogenesis and prophylaxis are still poorly understood. Recent studies suggested a role for IL-1, and, consequently, we investigated the use of anakinra, an IL-1 antagonist, to prevent ICANS following CAR-T cell infusion,

Methods: We compared the outcome of consecutive DLBCL patients receiving CAR-T cell infusion between 01/2019 and 03/2021 in two subsequent groups, comprising patients receiving (or not) fix 100 mg of anakinra s.c. at days 0 to +6.

Results: We analyzed 57 patients (tisagenlecleucel: n = 39; axicabtagene ciloleucel: n = 14, lisocabtagene maraleucel n = 4). Among them, the first 37 patients had no anakinra, and the later 20 patients received prophylactic anakinra for seven days following CAR-T cell infusion. PFS and OS did not differ between both groups. High-grade (3-4) ICANS was observed in 4/20 (20%) patients receiving anakinra compared to 9/37 (24%) patients without anakinra (p = 0.58). Intriguingly, hospitalization duration was shorter in patients with anakinra (24 versus 38 days; p = 0.113; Table 1). Administration of anakinra was well tolerated and no adverse effects were reported attributed to its use. **Conclusion**: Our data suggest that prophylactic administration of anakinra failed to modulate neurotoxicity following CAR-T cell infusion, whereas its use may be associated with shorter hospitalization duration. However, adequately powered prospective studies will be needed to ultimately clarify this prophylactic strategy in CAR-T cell recipients.

Table 1. Outcome of CAR-T cell recipients receiving (or not) prophylactic anakinra.

Parameter		all patients (n=57)		with anakinra (n=20)		no anakinra (n=37)		p-value
ICANS all grades	n (%)	18	(31)	9	(45)	9	(24)	**0.140**
ICANS grade 1 and 2	n (%)	6	(11)	5	(25)	1	(3)	0.017
ICANS grade 3 and 4	n (%)	12	(21)	4	(20)	8	(22)	0.585
Transfer to intensive care unit	n (%)	13	(23)	4	(20)	9	(24)	0.491
with ICANS	n (%)	10	(18)	3	(15)	7	(19)	0.507
w/o ICANS	n (%)	3	(5)	1	(5)	2	(6)	0.721
Median length of hospitalization	d (r)	24	(5-52)	22	(20-52)	21	(5-51)	0.481
with ICANS	d (r)	27	(20-52)	24	(21-52)	38	(20-51)	0.113
w/o ICANS	d (r)	21	(5-45)	21	(20-25)	20	(5-45)	0.435
Median follow-up	m (r)	6.6	(0.06-22.4)	2.6	(0.6-7.3)	8.8	(0.06-22.4)	0.001
Median PFS	m	6.9		n.r.		5.8		
PFSR within 6 months	(%)	51%		52%		50%		0.742
Median OS		n.r.		n.r.		n.r.		
OSR within 6 months	(%)	71%		66%		75%		0.751

ICANS: Immune effector cell-associated neurotoxicity syndrome; PFS: progression free survival; PFSR: Progression free survival rate; med: median; OS: overall survival, OSR: overall survival rate; n (%): total number and percentage; d: day; (r): range; m: months; n.r.: not reached; * ICANS grades 1+2 versus grades 3+4.

P14

Risk factors for cancer-related fatigue in adult childhood cancer survivors: a report from the CardioOnco study

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Cancer-related fatigue (CRF) is a distressing late effect in childhood cancer survivors (CCS) with prevalence between 10-85% and little evidence on its risk factors. We aimed to describe the prevalence of CRF in adult CCS and assess its risk factors.

As part of the CardioOnco study, we invited adult 5-year CCS treated at Inselspital Bern between 1976-2015 to a cardiooncological outpatient clinic and sent them questionnaires. We assessed fatigue with the Checklist Individual Strength subjective fatigue subscore (CIS, during last 2 weeks) and the Visual Analog Scale (VAS, at the current day). Increased fatigue was defined as CIS score 27-35 and VAS score ≥70. We collected information on previous cancer treatment and medical history and calculated mean CRF scores with ANCOVA adjusting for sex and age.

We included 158 CCS (participation rate 29%) with median age at study of 33 years (IQR: 26-38). We found that 19% of CCS had increased fatigue with CIS and 11% with VAS. Mean CIS fatigue score was higher in women (21, CI 20-22) than men (18, CI 16-19, p = 0.001), in those treated with radiotherapy (22, CI 20-23 vs. 18, CI 17-19, p<0.001), those with sleep disturbance (23, CI 21-24 vs. 18, CI 17-19, p<0.001), and those with an endocrine abnormality (24, CI 22-25 vs. 18, CI 17-19, p<0.001).

We found that one fifth of adult CCS experiences increased fatigue. Female CCS with history of radiotherapy and suffering from endocrine or sleep problems would profit from screening for CRF and further counselling with a specialist.

P15

Association of travel time to transplant centre and post-transplant care model with outcome parameters after allogenic transplantation

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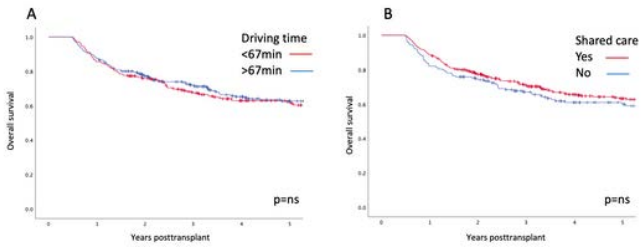
Allogenic stem cell transplantation is a complex intervention performed in specialized centres and necessitating regular follow-up visits, in turn leading to long travel times for patients. It is conceivable that travel burden might negatively impact outcomes, and previous studies conducted in North America analysing this question showed contrasting results

Due to the unique situation at our centre with long travel times but with established cooperations with other health care centres enabling a shared care model posttransplant, we were interested in analysing the influence of distance and posttransplant care model on outcome parameters.

We conducted a retrospective analysis of 678 patients with a median age of 53y who received an allogenic transplant at our centre between 2008 and 2017. The median follow-up of survivors was 1750 days while 57% of the patients were still alive after 3 years. The median travel time by car to the transplant centre was 67min (2-605). Of patients alive at day 180 (n = 553), 68% received shared care with another health care provider and also had significantly less visits at the transplant centre in the first year posttransplant.

In the landmark population alive at day 180, driving time being over or under the median or receiving shared care was not associated with overall survival. In summary we show that in the setting of shared care, distance to the transplant centre does not negatively impact outcome, and receiving shared care posttransplant reduced the travel burden.



P16

Antibody response to SARS-CoV-2 vaccination in patients following allogeneic hematopoietic cell transplantation

A. Huang[1], C. Cicin-Sain[1], C. Pasin[2,3], S. Epp[2], A. Audige[2], N.J. Mueller[3], J. Nilsson[4], A. Bankova[1], O. Vilinovszki[1], G. Nair[1], N. Wolfensberger[1], P. Hockl[1], U. Schanz[1], A. Trkola[2], R. Kouyos[2,3], B. Hasse[3], A. Zinkernagel[3], M.G. Manz[1], I.A. Abela[2,3], A.M. Müller[1]

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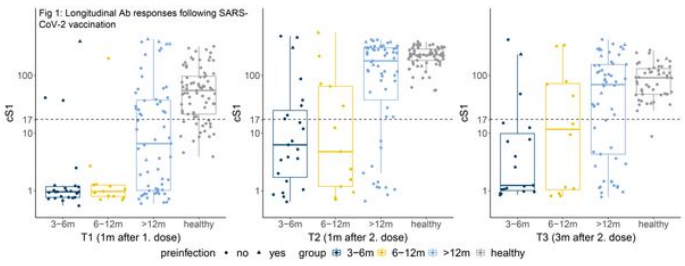
Background: Long-term data in allo-HCT patients after SARS-CoV-2 vaccination are lacking. We examined antibody (Ab) titers to the vaccination with BNT162b (BioNTech Pfizer) or mRNA-1273 (Moderna) Covid-19 vaccine in allo-HCT patients.

Methods: Serial Ab titers (prior to; 1m after 1. dose (T1); 1m (T2), 3m (T3) post 2. dose) against SARS-CoV-2 antigens (receptor binding domain (RBD), spike glycoprotein subunit S1/S2, nucleocapsid) were recorded with the **A**nti**B**ody **COR**onavirus **A**ssay (ABCORA) in allo-HCT patients and healthy controls.

Results: We enrolled 110 allo-HCT patients (median age 57y) and 86 healthy controls (median age 37y). Patients were grouped into: (A) 3-6m, (B) 6-12m and (C) >12m post-HCT. The sum of IgG, IgA and IgM S1 activities (cS1) >17 is considered to represent protective immunity. cS1 Ab levels were statistically different between the 4 groups both after the 1. and the 2. dose (ANOVA p-values<0.001, Fig.1) with the lowest antibody response in group A (S1 median value 0.959 at T1, 6.26 at T2, 1.24 at T3) and B (S1 median value 0.973 at T1, 4.76 at T2, 11.9 at T3) compared to group C (S1 median value 6.57 at T1, 179 at T2, 69.3 at T3) and healthy controls (S1 median value 54.9 at T1, 228 at T2, 91.1 at T3).

Conclusion: Allo-HCT patients early post-HCT displayed only low or no Ab formation to vaccination with a decline in AB response after T2. We conclude that Ab response in allo-HCT patients should be measured regularly to guide treatment decisions regarding re-vaccination and social behavior.



P17

Monitoring anti-BCMA CAR T-Cell Therapy with bb2121 in relapsed multiple myeloma

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Background: bb2121 represents a novel CAR T-cell therapy targeting BCMA (B-cell maturation antigen) for relapsed myeloma patients. However, the assays monitoring CAR-T cell expansion for this treatment await to be implemented in clinical routine

Methods: We monitored BCMA plasma levels and bb2121 CAR-T cell copy numbers in the blood following bb2121 CAR-T cell infusion. BCMA peptide concentration was determined in the plasma using a human BCMA/TNFRS17 ELISA kit. ddPCR was performed with probes targeting the intracellular signaling domains 4-1BB und CD3zeta of the bb2121 construct.

Results: We report the first five patients who received bb2121 at our department. Three patients developed CRS grade 1 or 2, and two patients had ICANS grade 1 or 2. All five patients achieved a complete remission in the bone marrow performed one month after CAR-T infusion, with 3 patients achieving stringent CR by flow techniques. bb2121 CAR-T was detectable in the peripheral blood for up to 180 days with copy numbers peaking 7 to 14 days post-infusion (Fig.1). BCMA plasma levels started dropping 1-10 days post infusion and reached normal levels 40 to 80 days post-infusion (Fig.2).

Conclusions: Our data confirm a favorable initial response to bb2121 in the first patients receiving bb2121 in Switzerland. bb2121 CAR-T cell expansion seems to peak in the peripheral blood in a similar pattern as compared to CAR-T cell products already approved for use in lymphomas. BCMA serum levels need to be further evaluated for their potential as biomarker for response to BCMA targeting therapies in myeloma patients.

Fig. 1

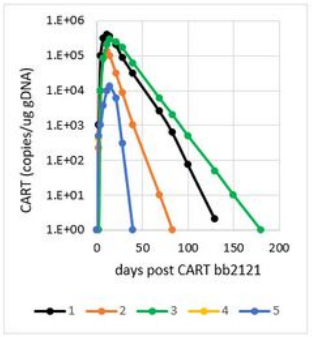
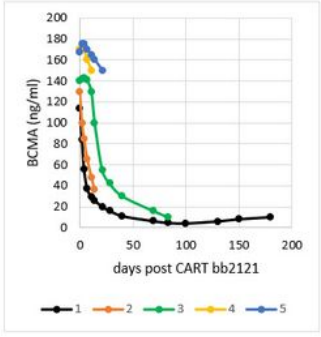


Fig. 2



P18

Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in patients with multiple myeloma three and six months after vaccination

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Background: Vaccination is considered essential for individual protection during the SARS-CoV-2-pandemic. The efficacy of the current vaccines in MM-patients is unknown.

Aim: To determine seroconversion rates and antibody levels in MM about 3 and 6 months after the second dose of the vaccine BNT162b2.

Methods: Patients with symptomatic MM without prior COVID19 were eligible. We measured levels of SARS-CoV-2-spike- and -nucleocapsid-antibodies (AB) by electro-chemiluminescence-immunoassay and extracted clinical data from hospital records.

Results: 101±14 (mean±SD) days after the second vacccination seroconversion (anti-spike-[S]-AB ≥0.8 U/l) was detectable in 54/59 (91.5%) MM-patients and 21/21 controls, with lower concentrations in MM-patients (median 166 U/l versus 929 U/l, p<0.001). The percentage of individuals with anti-S <250 U/l was 9% (1/11) for vaccination during "watch-and-wait", 39% (12/31) during maintenance and 82% (14/17) during (re-)induction. No patient developed COVID19. Details regarding the vaccination-response according to different clinical factors are shown in the table.

Parameter	Groups	n (%)	anti-Spike-IgG median (U/l)	anti-Spike-IgG range (U/l)	p
Sex	Female Male	20 (33.8) 39 (66.2)	279 153	0.7-1370 0-5670	0.51
Age	≥ 75 years <75 years	14 (23.7) 45 (76.3)	16 190	0-658 0-5670	**0.021**
R-ISS-Stage (missing n = 6)	R-ISS I R-ISS-II R-ISS III	14 (23.7) 32 (54.2) 7 (11.8)	250 172 14	0-5670 0-1740 0-3140	0.248
Remission status	at least VGPR PR or less	33 (55.9) 26 (44.1)	190 61	0-5670 0-1370	0.137
Treatment category	Watch and wait Maintenance (Re-)Induction Watch and wait vs. maintenance Watch and wait vs. (Re-)Induction (Re-)Induction vs. maintenance	11 (18.6) 31 (52.5) 17 (28.9)	641 179 27	0-3140 0-5670 0-658	**0.022** **0.001** **0.026**
Daratumumab-containing regimen	Yes No	16 (27.1) 32 (54.2)	124 57	11-1370 0-5670	0.168
Dexamethason >20mg/month (missing n = 2)	Yes No	39 (66.1) 18 (30.5)	13 309	0658 0-5670	**<0.001**
Lymphocytes <1x10^9/l	Yes No	26 (44) 33 (56)	20 385	0-1370 0-5670	**0.001**
IgG <4 g/l	Yes No	40 (67.7) 19 (32.3)	19 308	0-671 0-5670	**0.001**

The anti-S-concentration fell significantly (mean -45%, range -100% - +42%, p<0.001) at follow-up (mean 88±11 days after the first measurement; performed in MM-patients only).

Conclusions: Most MM-patients responded to the BNT162b2 vaccine, but often with lower concentrations of anti-S three months after the second vaccination, which additionally declined over time. Besides age and markers of immunosupression, treatment-modalities seem to affect the vaccination-response more than disease-related factors. Daratumumab did not influence the anti-S-concentration in our cohort. In order to determine the anti-S threshold for a third vaccination, regular assessment of the vaccination response in all MM patients, regardless of treatment, seems advisable.

P19

Engraftment dynamics are delayed in myelofibrosis after allogeneic haploidentical bone marrow transplantation with post-transplant cyclophosphamide

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Myelofibrosis is characterized by constitutional symptoms, splenomegaly and progression to bone marrow (BM) failure or blast phase. Allogeneic hematopoietic stem cell transplantation represents a potentially curative therapy, but is hampered in myelofibrosis by delayed engraftment promoting complications. Determinants of engraftment in myelofibrosis are incompletely characterized. Thus, we studied engraftment dynamics in myelofibrosis at our center.

We assessed 72 allo-transplants in 60 patients performed from 2000-2019. Median age was 59.5y (31–72y) and >50% were transplanted after 2015. Median time to neutrophil engraftment was 20d post-transplant (11-36d) with 3 engraftment failures and was significantly associated with infused stem cell number (p = 0.049). In univariate analysis, we observed a trend for delayed engraftment upon splenomegaly or higher grade fibrosis. Of note, neutrophil engraftment was significantly delayed in recipients of haploidentical BM transplants conditioned with Thiothepa-Busulfan-Fludarabine (TBF) plus post-transplant cyclophosphamide (PTCy), which was given in 11.3% and 17.6% of transplants performed 2000-2019 and after 2015, respectively (p = 0.038). Platelet engraftment >20G/l was analogously affected (p = 0.044). Engraftment was not altered by primary vs. secondary myelofibrosis, DIPSS-plus or MIPSS70 risk or driver mutation status. Use of ATG did not delay neutrophil engraftment but reduced engraftments >20d post-transplant (p = 0.015). By multivariate forward conditional Cox regression, stem cell source maintained a significant effect on neutrophil engraftment (p = 0.02).

Overall, our data show that engraftment dynamics in myelofibrosis, known to be slower than in most other myeloid malignancies, are further compromised by haploidentical BM transplants conditioned by TBF-PTCy. It needs to be clarified whether this affects graft function in longer term.

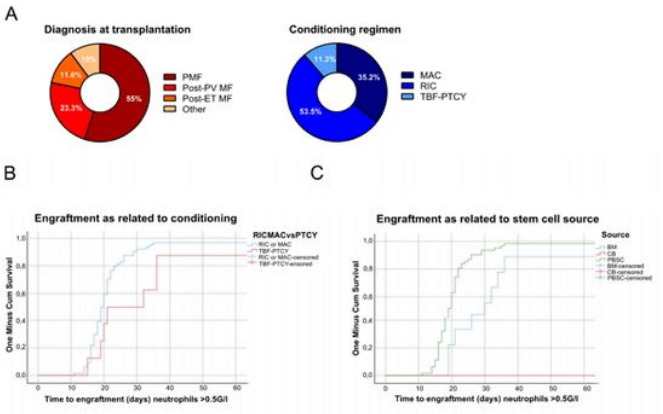

Figure 1. Delayed engraftment dynamics in myelofibrosis after haploidentical bone marrow transplants with TBF-PTCy conditioning. A. *Diagnosis and type of conditioning regimens in 72 transplants performed 2000-2019.* ***B.*** *Time to neutrophil engraftment (>0.5G/l) as related to conditioning regimen.* ***C.*** *Time to neutrophil engraftment (>0.5G/l) as related to stem cell source. PMF: primary myelofibrosis; post-PV MF: post-polycythemia vera myelofibrosis; post-ET MF: post-essential thrombocythemia myelofibrosis; other: transformation to AML or MDS, MPN-U; MAC: myeloablative conditioning; RIC: reduced-intensity conditioning; TBF-PTCY: thiothepa-busulfan-fludarabin plus post-transplant cyclophosphamide. BM: bone marrow; CB: cord-blood; PBSC: peripheral blood stem cells.*

P20

Co-occuring CSF3R W791X germline mutation and somatic T618I driver mutation in chronic neutrophilic leukemia with clonal progression to acute leukemia

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Chronic neutrophilic leukemia (CNL) is characterized by clonal neutrophilia with mutational CSF3R activation. Membrane proximal mutations as T618I are considered drivers, while significance of truncating mutations is not entirely clarified. Concomitant mutations may worsen prognosis, but insight into longitudinal acquisition is incomplete. We address the role of co-occurring CSF3R germline and driver mutations and clonal evolution in CNL for leukemic transformation.

We diagnosed a young (33y) patient with CNL presenting splenomegaly, neutrophilia, expanded granulopoiesis and CSF3R-T618I at 46% variant allele frequency (VAF). We detected a co-occurring CSF3R-W791X truncation mutation at 50%VAF. Analysis of hair follicle confirmed germline origin, which in contrast to CSF3R point mutations has not been reported. We evaluated a potential predisposing role of W791X for CNL development by assessing allelic localization via sequencing of patient-derived plasmid DNA clones and found T618I on the identical allele. We also detected concomitant ASXL1 mutation at 39%VAF. After treatment with ruxolitinib and subsequently interferon-alpha, transformation to mixed phenotype acute leukemia (MPAL) occurred. Underlying clonal evolution showed expansion of the CSF3R-double-mutant clone to 90%VAF due to CN-LOH on chromosome 1p and increased ASXL1 to 48%VAF. We also identified a RUNX1 co-mutated subclone (75%VAF), similar to CSF3R/RUNX1 co-mutant severe congenital neutropenia transforming to leukemia. The patient achieved remission after allogeneic transplantation.

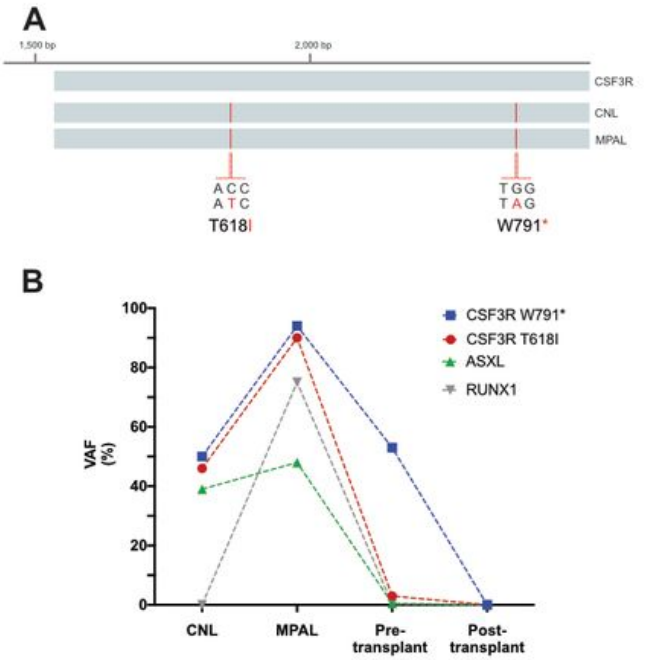

Figure 1. CSF3R mutation allelic co-localization in CNL and clonal progression to acute leukemia. A. *Patient CSF3R gene sequence was amplified from bone marrow DNA encompassing loci for T618I and W791X (indicated by red lines) and cloned into sequencing plasmid. Sanger sequencing of emergent colonies demonstrated co-localization of T618I and W791X in cis on the same allele at the stage of CNL (middle) and of mixed phenotype acute leukemia (MPAL, bottom) as compared to CSF3R reference sequence (top).* ***B.*** *At diagnosis of CNL, the germline CSF3R-W791X mutation was complemented by somatic CSF3R-T618I driver and an ASXL1 mutation. At transformation to MPAL, the CSF3R co-mutated clone expanded by copy neutral loss of heterozygosity (CN-LOH) of chromosome 1p and additionally acquired a RUNX1 mutation. The patient achieved remission as a result of induction therapy (pre-transplant) and allogeneic hematopoietic stem cell transplantation (post-transplant).*

In summary, this is a first report of CNL progression to acute leukemia of MPAL type. The finding of CSF3R- W791X as germline is remarkable and localization *in cis* with CSF3R-T618I may suggest increased susceptibility for mutation acquisition facilitating clonal progression.

Higher Resolution Figure:
https://drive.google.com/file/d/1OJgaY55cwnVyUSsIBcE_7GEFpmY-ERjJz/view?usp=sharing

P21

Antibody-response to mRNA SARS-CoV2 vaccination in patients after allogeneic stem cell transplantation

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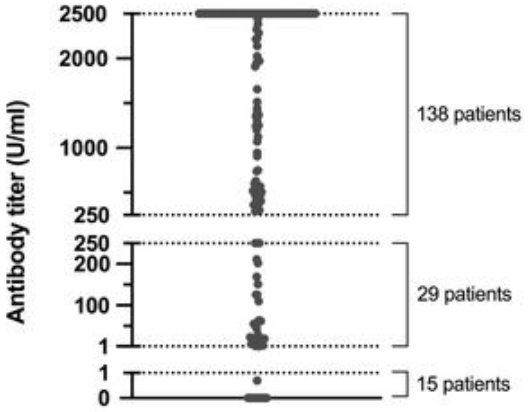
Introduction: Patients after allogeneic stem cell transplantation are at high risk for infection-related complications and vaccination efficacy might be impaired depending on the immune reconstitution. In this study we evaluate the response of 182 patients to mRNA vaccines against SARS-CoV2.

Methods: During routine follow up visits, patients were asked about their vaccination status and if they had a previous infection with SARS-CoV2. In fully vaccinated patients, the antibody titer was measured using the Roche Elecsys Anti-SARS-CoV2 S test. A titer of <1 U/l was considered as negative, titers of ≥250 U/ml as a high antibody titer and a titer of 50-249 U/ml as a low antibody titer. Patient characteristics were evaluated by chart review to identify risk factors for poor vaccination response.

Results: The majority of patients developed a high antibody titer (138 out 182 patients, 75.8%). Risk factors for a low antibody titer were immunosuppressive therapy, a lymphocyte count <0.9 G/l, ongoing treatment for the underlying malignancy and active GvHD. The vaccine (Moderna vs Pfizer), donor type, underlying disease, a previous SARS-CoV2 infection and sex did not significantly influence the response to the vaccination.

Discussion: While patients undergoing allogeneic stem cell transplantation have been excluded from the initial registration trials, our large patient cohort confirms the data of previous smaller studies, showing that most patients do have a good response to mRNA vaccines against SARS-CoV2. Nevertheless, a significant proportion of patients shows an inadequate vaccination response and thus qualifies for a third vaccination.



P22

A novel CSL-NICD inhibitor for the treatment of NOTCH-driven T-cell acute lymphoblastic leukemia: a case report

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[1]University Hospital Basel, Hematology, Basel, Switzerland, [2]University Hospital Basel, Institute of Medical Genetics and Pathology, Basel, Switzerland, [3]Cellestia Biotech AG, Basel, Switzerland

A 24-year-old patient diagnosed with high-risk T-ALL (PTEN gene deletion; NOTCH1 mutation), was treated with induction and consolidation chemotherapy (including nelarabine) achieving CR, MRD positive (<1.0E-4). After 6 months treatment, he relapsed and received salvage chemotherapy. Blasts were characterized by persistent BCL2 positivity, PTEN deletion, and NOTCH1 L1678P activating mutation. Multiple attempts to control disease progression failed . CB-103 selectively inhibits the CSL-NICD interaction leading to down-regulation of CSL-NICD mediated oncogenic pathway activation downstream of NOTCH signaling, and has shown potent anti-cancer activity as single agent and in combination with targeted/chemotherapies in preclinical models. In the phase 1 study, CB-103 was safe and showed clinical efficacy in solid tumor patients.

Under compassionate use the patient received CB-103. In a rapid dose escalation CB-103 was added to treatment with venetoclax and decitabine, which were phased out. There were only mild adverse events related to this combination. Within 1 week of starting CB-103, the bone marrow was free of T-ALL blast infiltration (MRD+) and underwent allo-HSCT. CB-103 was continued throughout the transplantation and post HSCT to control the NOTCH1-mutation carrying clone.

Sequential samples of ctDNA to monitor the disease after allo-HSCT showed a decrease of circulating variant allele frequency of the NOTCH1 and PTEN alterations reaching CRi, MRD negative, approximately 3 months after allo-HSCT. Downregulation of Notch target genes proved CB-103 target engagement.

This is the first T-ALL patient treated with CB-103. The observed clinical response encourages further exploration of CB-103 in this indication. A clinical trial is open (NCT03422679).

Conflict of Interest statement: The study was supported by Cellestia Biotech AG, Basel, Switzerland

P23

Antibody responses to SARS-CoV2 vaccination in a high proportion of allogeneic hematopoietic stem cell transplant recipients

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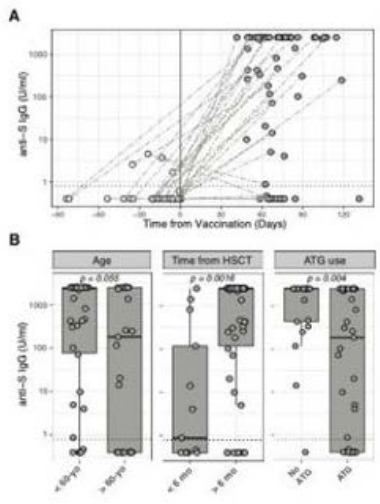
Allogeneic hematopoietic stem cell transplantation recipients have a higher risk of developing severe forms of COVID-19. Induction of protective immunity through prophylactic vaccination is therefore important. We analyzed humoral responses to two doses of mRNA-based SARS-Cov-2 vaccines in 63 patients transplanted at Geneva University Hospitals, following our institutional priority vaccination program whose inclusion criteria were: minimum 3 months and maximum 3 year since allogeneic HSCT; or at more than 3 years post-transplant with GvHD requiring immunosuppressive drugs; absence of Rituximab in the previous 3 months; absence of steroid treatment with Prednisone ≥ 10 mg/day. Vaccine-induced antibody responses against the SARS-CoV-2 spike protein (anti-S) were assessed in serum using the semi-quantitative Elecsys® Anti-SARS-CoV-2 immunoassay (Roche).Median age was 54 (18-78) years. The first vaccine dose was administered at a median of 14 (3-150) months after transplantation. Forty-six out of 63 (73%) patients received mRNA-1273 and 17/63 (27%) received BNT162b2 vaccines. Forty-eight out of 63 (76%) allogeneic HSCT recipients showed some degree of humoral response to vaccination based on anti-S IgG. Median levels of anti-S IgG were 815 U/ml. We observed significantly lower anti-S IgG responses in patients receiving the first vaccine dose within 6 months since transplantation (6/13, 46%; median 0.88 U/ml) compared with patients vaccinated after 6 months post-HSCT (42/50, 84%; median 2500 U/ml; p = 0.0016) and lower anti-S IgG responses in patients having received ATG as part of their conditioning (27/41, 66%; median 183 U/ml) compared with patients who did not receive ATG (21/22, 95%; median 2500 U/ml; p = 0.004).

FIGURE 1



1: Quantification of IgG against SARS-CoV-2 spike protein in response to vaccination in allogeneic HSCT

ts. (A) IgG against SARS-CoV-2 spike protein before and after mRNA-based SARS-CoV-2 vaccination (time 0). gray lines connect paired samples before and after mRNA-based SARS-CoV-2 vaccination in patients for oth samples were available. Dotted black line indicates the 0.8 U/ml positivity cutoff. (B) Levels of IgG SARS-CoV-2 spike protein in allogeneic HSCT recipient stratified by age, time post-HSCT and ATG use during oning. Groups were compared using the non-parametric Mann-Whitney U test.

P24

The efficacy of antibiotic prophylaxis in AML patients undergoing induction chemotherapy

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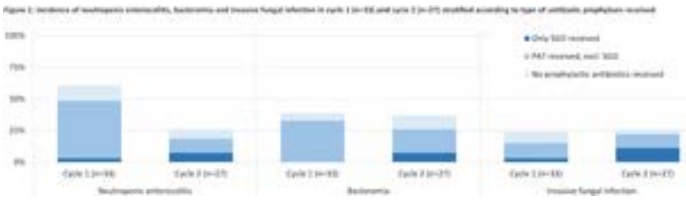
Introduction: Infections are a major cause of morbidity and mortality in acute myeloid leukemia (AML) patients (pts) receiving induction chemotherapy (CTx). The role of prophylactic antibiotic treatments (PAT) including selective gut decontamination (SGD) to lower the risk of infections (e.g., neutropenic enterocolitis (NE)) remains controversial. Therefore, we conducted a prospective, observational study on the efficacy of PAT in preventing infectious complications in AML pts during CTx.

Methods: AML pts admitted to our center from 03/2018 to 03/2021 who received cytarabine-based CTx were included in the ongoing study. Pts received SGD in the 1st cycle if relevant gastrointestinal disease (e.g., IBD) was present. In the 2nd cycle SGD was also given to those who had suffered from NE during cycle 1.

Results: So far, 33 pts with a median age of 57y (range, 18-71y) have been enrolled. 27 pts (81.8%) received PAT in cycle 1 (1 with SGD), 18 pts (69.2%) in cycle 2 (7 with SGD), respectively. 20 pts (60.6%) developed NE during CTx 1 and 7 (25.9%) during CTx 2. Yet, rates of bacteremia and invasive fungal infections were identical in both cycles, regardless of PAT and SGD (Figure 1).



Correlation analysis identified only male sex and lower age to be associated with an increased risk to develop bacteremia.

Conclusions: PAT including SGD had no significant effect on lowering the incidence of infectious complications during CTx in our study population. These results are limited by the as of yet low patient number and the non-interventional study design.

P25

Beliefs about medicines in patients with multiple myeloma in Switzerland

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Background: Medication beliefs have been found to be associated with medication adherence among various cancer patients. Despite its importance, medication beliefs have not been investigated in patients with multiple myeloma (MM). A study on quality of life in MM patients provided the opportunity to fill this gap.

Methods: Patients were recruited consecutively from three Swiss oncology/hematology centres. Inclusion criteria included confirmed histological MM diagnosis, age ≥18 years and informed consent. Exclusion criteria were participation in another clinical study, inability to communicate in German and more than one cancer diagnosis. Participants completed a survey including the Beliefs about Medicines Questionnaire (BMQ) and a sociodemographic questionnaire. Clinical data was extracted from medical records. The complete case dataset (N = 41) was analysed using descriptive statistical methods.

Results: Most participants were men (59%), married/partnered (80%), born in Switzerland (80%), economically inactive (85%) and completed at most upper secondary education (72%). Mean age at diagnosis was 61 years (range: 35-81 years). 48% of the participants were in a stable/plateau phase, 37% in a relapsed/progressive phase and 15% newly diagnosed; 96% had good ECOG performance status. Table 1 presents the results of the BMQ. The vast majority of the sample believed in the necessity of their medication for maintaining their health; however, 70% reported concerns about their long-term effects. The specific-necessity subscale and general-harm subscale showed the highest and lowest mean, respectively.

Conclusions: The results indicate higher necessity beliefs than concerns towards MM medication. Specific items point to topics to be raised by treating physicians.

Table 1	Agree / strongly agree (%)	Mean (SD)	Median
Specific-necessity			
My medication protects me from becoming worse	93.5		
My health at present depends on my medicines	89.1		
My health in the future will depend on my medication	87.0		
Without my medication I would be very ill	82.6		
My life would be impossible without my medication	80.4		
Specific-concerns			
I sometimes worry about the long-erm effects of my medication	69.6		
My medication is mystery to me	19.6		
I sometimes worry about becoming too dependent on my medication	30.4		
Having to take medication worries me	39.1		
My medication disrupts my life	30.4		
General-overuse			
Doctors use too many medicines	17.4		
If doctors had more time with patients, they would prescribe fewer medicines	17.4		
Doctors place too much trust on medicines	28.3		
Natural remedies are safer than medicines	34.8		
General-harm			
Most medicines are addictive	17.4		
People who take medicines should stop their treatment for a while every now and again	34.8		
Medicines do more harm than good	2.2		
All medicines are poisons	4.4		
BMQ Subscales			
Specific-necessity		21.43 (3.43)	22
Specific-concerns		13.98 (4.60)	14
General-overuse		10.37 (3.38)	10
General-harm		8.61 (3.27)	9
Data collected under the study NCT03537222. Financial support for the study was provided by Celgene.			

P26

Low Incidence of hepatic veno-occlusive disease in adults undergoing allogeneic hematopoietic stem cell transplantation

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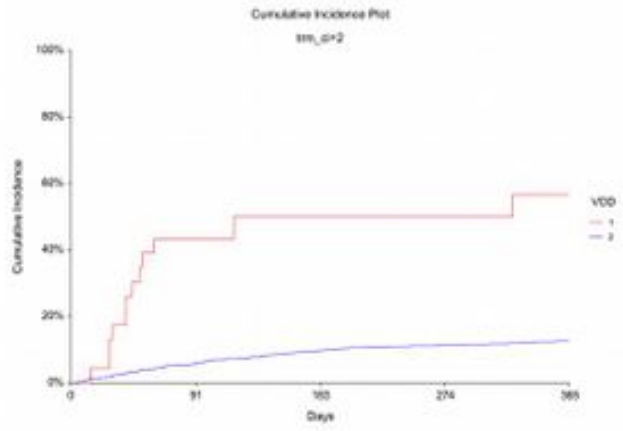
Hepatic veno-occlusive disease (VOD) is a complication after allo-HSCT with high mortality. The purpose of this study was to assess the incidence and outcome of VOD and the impact of ursodeoxycholic acid (UDCA) and low-dose heparin as VOD prophylaxis. We retrospective analysed 1'016 consecutive adult patients who underwent allo-HSCT between 2006 - 2020 at the University Hospital of Basel. We determined VOD incidence and factors associated with VOD occurrence by logistic regression analysis. Overall survival (OS) at day+100 and 1 year, progression-free survival (PFS) and non-relapse mortality (NRM) were compared. Cumulative incidence of VOD was 2.3% (95% CI 1.3 - 3.3) 6 months after HSCT. The day+100 survival of VOD patients was 39% (95% CI 18.7 - 59.5). Approximately one quarter of these patients (26.1%) had late-onset VOD. A high proportion were very severe VOD cases (74%), and 83% of the patients were treated with defibrotide. The median time to diagnosis was 14 days. In multivariate analysis, advanced disease (p = 0.003), previous HSCT (p = 0.025) and GvHD prophylaxis by PTCy (p = 0.055) were associated with the development of VOD. The 1-year OS was significantly lower in the VOD group compared to patients without VOD (13% versus 70%, p = 0.0001), as well as the PFS (13% versus 60%, p = 0.0001), NRM was significantly higher in the VOD group (57% versus 13%, p = 0.000001).



Non-relapse Mortality VOD vs. no VOD, 2006 – 2020 (p = 0.00001)

In conclusion, we found a low incidence of VOD in patients receiving low-dose heparin and UDCA prophylactically, but among VOD patients, a high mortality.

P27

Treosulfan-based reduced-intensity hematopoietic stem cell transplantation in adults with primary immunodeficiency

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We report three adult patients with primary immunodeficiency disease (PID) treated with reduced-intensity allogenic hematopoietic stem cell transplantation (HSCT) with fludarabine, treosulfan, and alemtuzumab GVHD-prophylaxis (Table 1).

The first patient is a 51-years old male with common variable immunodeficiency (CVID) with protein-losing enteropathy. After transplant, he developed neutropenic fever and colitis, which responded promptly to antibiotic therapy. He also developed a grade III mucositis, which resolved after engraftment. 8 months after transplant, he shows a 100% donor chimerism in the B-cell and granulocyte lineage and a stable mixed (64%) chimerism in the T-cell lineage. He developed mild steroid-responsive skin GvHD.

The second patient is a 29 years old woman with hyper-IgE Syndrome (HIES) with STAT-3 mutation. After transplant, she developed colitis with C. difficile and later severe colitis and duodenitis with Cryptosporidium parvum with poor response to antiprotozoal therapy. Possibly due to an increase in immunosuppression for possible intestinal GvHD, which has been treated with systemic steroids, vedolizumab, and alpha-1-antitrypsin. Because of the co-existent colitis, the diagnosis of GvHD is difficult to confirm definitively. Likewise, the efficacy of the GvHD therapy is difficult to assess. 1 month after transplant, the patient shows a 100% donor chimerism.

The third patient is a 25 years old male with XIAP syndrome with granulomatous enteropathy. He has not developed any relevant infectious or toxic complications so far. The patient engrafted on day+12. Until now, only mild toxicity and no GvHD occured. In conclusion, Treo-based conditioning seems to be feasible in PID patients.

	Patient 1	Patient 2	Patient 3
Diagnosis	CVID	Hyper-IgE Syndrome	XIAP syndrome, XLP2
Genetic mutation	RAG1/RAG2	STAT-3	XIAP
Complications prior to HSCT	Recidivating infections Protein losing enteropathy	Recidivating infections	Inflammatory bowel disease
Age at HSCT	51	29	25
Neutrophil engraftment	day+22	day +13	day+12
Chimerism	mixed	100%	not yet done
GvHD	Grade 2 skin GvHD	suspected grade 3 GI tract	none

P28

Lymphopenia is highly prevalent in MDS and provides prognostic information for IPSS-R (very)-low-risk patients. An analysis from the EU-MDS registry

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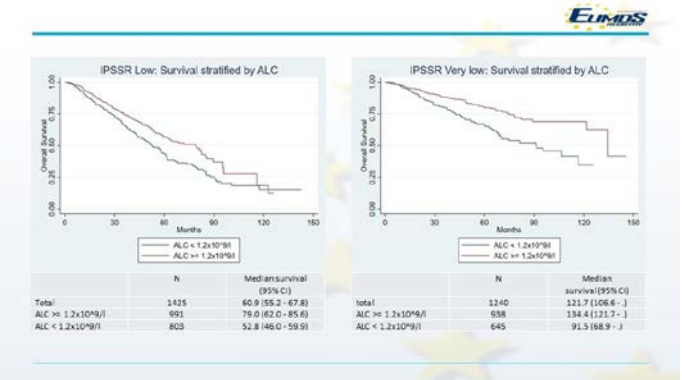
Background and aims: In MDS the clinical course is primarily determined by the extent of myeloid insufficiency and the risk of AML evolution. Data on the role of an impaired lymphoid homeostasis are emerging.

Methods: The database of the EUMDS registry was screened for patients with data on absolute lymphocyte count (ALC) at diagnosis and during follow-up. Lymphopenia was defined as an ALC <1.2x10^9/l. Cases with an ALC ≥5.0 x10^9/l were excluded.

Results: 2377 patients were identified (62% male, median age 74 years, median follow-up 44.2 months). 1469 were lymphopenic (970 at diagnosis, 499 during the observation period).

Lymphopenic patients had lower platelet and neutrophil counts (median 142 versus 198x10^9/l and 1.9 versus 2.7x10^9/l, p<0.001 each) and were more frequently transfusion-dependent (34 versus 26%, p<0.001). The median ALC at diagnosis differed between the IPSS-R-categories (very low [n = 848] 1.4x10^9/l, low [n = 976) 1.32x10^9/l, Intermediate [n = 280] 1.16x10^9/l, p<0.001).

Age-adjusted median survival was shorter for patients with an ALC <1.2x10^9/l (101.3 versus 53.8 months, p<0.001). No survival difference was noted for IPSS-R-very-high-, high- and intermediate-risk patients (n = 25, 85 and 347, respectively). For very-low (n = 1240) and low-risk patients (n = 1425), lymphopenia was associated with a shorter survival (91.5 versus 134.4 months, p<0.001, and 52.8 versus 79 months, p = 0.001, respectively).



Conclusions: Our data confirm the high prevalence of lymphopenia in MDS-patients. For IPSS-R-very low and low-risk patients, lymphopenia provides additional prognostic information. Further analyses will focus on the association of lymphopenia with the clinical course (development of transfusion-dependency, progression to higher-risk MDS, infection-risk).

P29

Immune reconstitution in patients with classical hairy cell leukemia during BRAF inhibitor treatment

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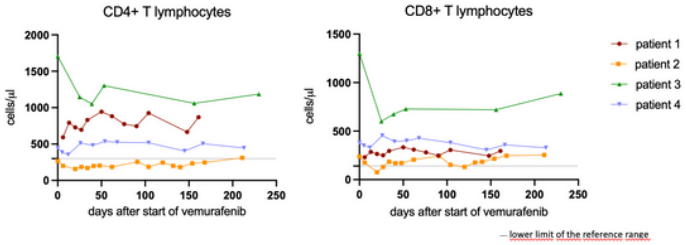
For patients with classical hairy cell leukemia (HCL) standard treatment options such as purine analogues (PA) achieve a durable response, but are associated with severe immunosuppression. In particular, PAs cause long-lasting depletion of CD4+-lymphocytes. The BRAF inhibitor vemurafenib is effective in HCL but its use in first line treatment is currently limited to select clinical situations such as active infection. There is a lack of clinical data on the impact of BRAF inhibitors on immune function or response to vaccines in HCL. Here, we report the use of vemurafenib in four patients with HCL during the coronavirus disease 2019 (COVID-19) pandemic with detailed immune monitoring during treatment. All patients responded to BRAFi with normalization of peripheral blood counts. None of the patients developed neutropenia or severe infection. We observed stable CD4+ and CD8+ T-lymphocyte counts while receiving vemurafenib (median treatment duration 131 days). Immunoglobulin levels were normal in all patients without decline. 3 out of 4 patients received the SARS-CoV-2 vaccination (Pfizer-BioNTech) during vemurafenib treatment. The IgG antibody levels against the spike-protein of SARS-CoV-2 were detectable in 3 out of 3 patients (2 - 12 weeks after the second vaccination).

Our findings suggest that BRAF inhibitors have limited effect on cellular and humoral immune function. The findings may support the use of BRAF inhibitors during the current pandemic to avoid the potentially detrimental effects of PA and thus minimize COVID-19 related morbidity and mortality in patients without SARS-CoV-2 vaccination.



P30

Safety profile of the adjuvanted recombinant zoster vaccine (RZV) in immunocompromised populations: an overview of 6 Trials

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Background: Immunocompromised (IC) populations are at increased risk of herpes zoster (HZ) and its complications. RZV demonstrated >68% efficacy against HZ in adult autologous hematopoietic stem cell transplant (HSCT) recipients. Here we present the safety data across 6 clinical trials in IC populations: HSCT recipients, HIV-infected adults, renal transplant recipients, patients with solid or with hematological malignancies.

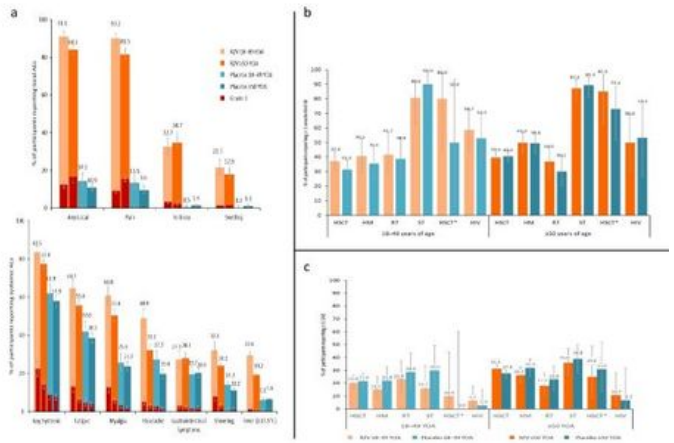
Methods: All 6 studies enrolled IC adults ≥ 18 YOA in RZV and Placebo groups. Solicited adverse events (AEs) were collected for 7 days and unsolicited AEs for 30 days after each dose. Serious AEs (SAEs) were collected from dose 1 until 1 year post-last dose or study end.

Results: In total, 1587 (RZV) and 1529 (Placebo) adults were included. Solicited AEs were more frequent in RZV than Placebo. Pain, fatigue, headache, myalgia, shivering and fever were more frequent in the RZV 18–49 YOA than in the RZV ≥50 YOA (Figure 1a). Solicited AEs were mostly mild/moderate and lasted ≤3 days and grade 3 solicited AEs lasted ≤2 days (median duration). Across studies, the percentage of adults reporting ≥1 unsolicited AE was similar between RZV and Placebo (Figure 1b). The percentage of adults with ≥1 SAE (Figure 1c) was similar between RZV and Placebo and between age groups. Overall, no safety concern was identified.

Conclusion: Reactogenicity symptoms were more frequent after RZV than placebo and in the younger age group, but no safety concern was identified. Overall, our data support a favorable benefit-risk profile for RZV in IC adults.

Encore of DOI:10.1093/ofid/ofaa439.082

Figure 1. a) Percentage of participants with solicited local and systemic AEs, reported across 6 pooled studies (7 days post-vaccination, overall/participant, pooled total vaccinated cohort). Grade 3 was defined as follows: pain that prevented normal activity; > 100 mm diameter for redness and swelling; symptoms that prevented normal activity for headache, myalgia, fatigue and gastrointestinal symptoms; fever >39.0°C (axillary/oral temperature). For the systemic AEs fatigue, headache (all, related), myalgia, shivering, and fever (all, related) were reported with higher incidences in the RZV 18–49 YOA group than in the RZV ≥50 YOA group; **b)** Percentage of participants reporting ≥ 1 unsolicited AE 30 days post-vaccination per study (total vaccinated cohort); **c)** Percentage of participants reporting ≥ 1 SAE from dose 1 until 1 year post-last dose per study (total vaccinated cohort)



AE, adverse event; **HIV,** human immunodeficiency virus; **HM,** hematological malignancies patients; **HSCT,** autologous hematopoietic stem cell transplant recipients; **HSCT*,** HSCT phase 1 study; **RT,** renal transplant recipients; **RZV,** adjuvanted recombinant zoster vaccine; **SAE,** serious adverse event; **ST,** solid tumors patients; **YOA,** years of age

Conflict of Interest statement: TOS, MC and FTdS are employed by the GSK group of companies. MLF, AB, PB, AFD, JJFG, AS were employed by the GSK group of companies during the conduct of this study. AB, AFD and FTdS hold shares in the GSK group of companies. All authors declare no other financial and non-financial relationships and activities.

P31

Lymphopenia is highly prevalent in overt myelofibrosis at diagnosis but lacks additional prognostic value

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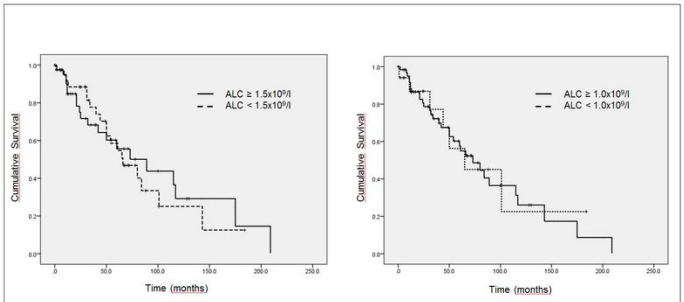
Background: Lymphopenia is prognostically relevant in several malignancies. Little is known about its role in myelofibrosis (MF).

Aim: To evaluate the prevalence of lymphopenia at diagnosis and its prognostic impact in MF.

Methods: Patients diagnosed between 2010-2020 at the Cantonal Hospitals St. Gallen and Muensterlingen with primary MF [PMF], MF secondary to essential thrombocytopenia or polycythemia vera [MF-post] and prefibrotic primary MF [pre-PMF] were evaluated for the absolute lymphocyte count (ALC) at diagnosis.

Results: 80 patients with overt MF (PMF n = 59, MF-post n = 21) and 28 with pre-PMF were included. The ALC was lower in overt MF compared to pre-PMF (median $1.5x10^9$/l versus $2.0x10^9$/l, p = 0.039). In MF-post (evaluable post-ET n = 8, post-PV n = 10), a drop of the ALC was documented at MF-diagnosis compared to the diagnosis of the preceeding disorder (median $1.35x10^9$/l versus $2.05x10^9$/l, p = 0.009). An ALC <$1.5x10^9$/l was associated with lower hemoglobin-concentration and

neutrophil-counts (median 100 vs. 115g/l and 5.5 vs. 8 G/l, p = 0.009 and p = 0.023). For cases with fibrosis grade 3 versus grade 2, a trend towards a lower ALC was noted (median 1.3x10^9/l versus 1.6x10^9/l, p = 0.07). The DIPSS-groups did not differ with regard to the ALC. Neither an ALC <1.0x10^9/l nor <1.5x1.0x10^9/l was associated with a survival difference (median 65 versus 73 months, p = 0.879 and 66 versus 89 months, p = 0.823).



Survival according to the absolute lymphocyte count at diagnosis
(six patients censored at the time of allogeneic stem cell transplantation)

Conclusions: Lymphopenia in MF is highly prevalent at diagnosis, but offers no additional prognostic information. Its association with lower hemoglobin values and the development of fibrosis in cases of MF-post points towards a possible relationship of lymphopenia with MF-pathophysiology.

P32

Epidemiological data on AL-amyloidosis from the amyloidosis registry of the comprehensive amyloidosis network Zurich

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Systemic amyloidosis is a generic term for a disease where the underlying pathomechanism is the misfolding of circulating proteins into a beta-sheet structure leading to extracellular deposition of amyloid and organ dysfunction. To date, more than thirty different proteins are known to be amyloidogenic.

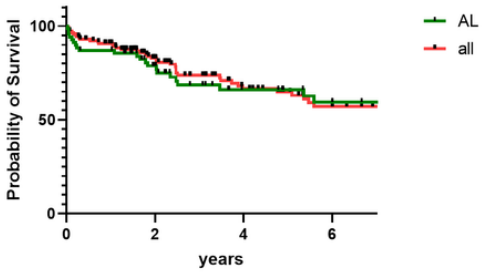
Light-chain (AL) amyloidosis is the most common form and is associated with an underlying plasma cell or a B-cell clone producing amyloidogenic light chains.

We here present data from the amyloidosis registry of the comprehensive amyloidosis network founded in 2013 at the university hospital Zurich on AL-amyloidosis. In this noninterventional, longintudinal, observational SecuTrial™ based registry patient data was collected (retrospective from 2005 – 2013, prospective from 2013 onwards) after given informed consent.

Up to date, we have included 155 patients in our registry. 77 patients (49.6%) suffer from AL-amyloidosis. Free light chains only were found in 57% (n = 44). Light-chain lambda was present in 70% (n = 54). Translocation t(11;14) was found in 27% (n = 21). Plasma cell myeloma (infiltration grade of plasma cells ≥ 10%) was diagnosed in 57% (n = 44), Waldenstroms macroglobulinemia in 5% (n = 4) and MGUS in 26% (n = 20).

In the AL cohort median survival was 12.1 years. There was a trend towards higher early mortality in the AL cohort than in the whole cohort (13% versus 8% at 6-months).

To our knowledge, this is the first registry collecting patient data with systemic amyloidosis in Switzerland. We consider this a valuable tool for epidemiological research and we will continue our effort to depict the landscape of amyloidosis in Switzerland.



Conflict of Interest statement: RS received financial support from Alnylam and Pfizer related to this article.

P33

Quality of life, functioning, and symptoms in patients with previously treated locally advanced or metastatic urothelial carcinoma from EV-301

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Background: In the phase 3 EV-301 trial (NCT03474107), enfortumab vedotin (EV) prolonged median OS by ~3.9 months and reduced death risk by 30% versus standard chemotherapy (SC) in patients with previously treated locally advanced/metastatic urothelial carcinoma. To contextualise EV benefits/risks, we report prespecified quality-of-life (QoL) endpoints from EV-301.

Methods: Patients completed the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) at baseline, weekly (first 12 weeks), and then every 12 weeks until discontinuation. Descriptive statistics summarised compliance rates/scores; mixed model repeated measures evaluated longitudinal changes from baseline. Logistic regressions assessed confirmed improvement rates (clinically meaningful improvement over two subsequent visits).

Results: Among 608 randomised patients (EV, n = 301; SC, n = 307), baseline questionnaire compliance rates were ~90% per group; average rates were 70.2% (EV) and 66.9% (SC). Baseline QLQ-C30 scores were similar between groups. At Week 12, global health status (GHS) scores were similar between groups; SC-treated patients had numerically greater deterioration/more variability in QoL (first 12 weeks). EV-treated patients had significant reduction in pain symptoms (difference: -5.73, P<0.05) but significant worsening of appetite loss (difference: 7.29, P<0.05) versus SC. Other symptom scores were no different between groups. Higher proportions of EV-treated versus SC-treated patients had significant confirmed improvements across functioning domains, GHS,

and several symptom scales. The greatest difference in improvement was for pain (EV: 51.6%, SC: 28.8%; OR = 2.76 [1.81-4.22]).

Conclusions: Versus SC, EV-treated patients had numerically less deterioration/variability in QoL during the first 12 weeks of treatment. Improvement in pain showed the largest benefit in the EV group over SC.

Conflict of Interest statement: **HG** Consulting BMS, Ipsen, Merck Sharp & Dohme, AstraZeneca, Janssen-Cilag, Pfizer, Roche, Merck Serono, Speakers' Bureau Merck Serono, Travel AstraZeneca; **RM** Honoraria Flatiron Health, Consulting Roche, Astellas/Seagen, Research Funding NIH, Merck; **JER** Consulting Lilly, Merck, Roche/Genentech, AstraZeneca/MedImmune, BMS, Seattle Genetics, Bayer, BioClin Therapeutics, QED Therapeutics, Adicet Bio, Fortress Biotech, Pharmacyclics, western oncolytics, GlaxoSmithKline, Janssen Oncology, Astellas Pharma, Boehringer Ingelheim, Pfizer/EMD Serono, Mirati Therapeutics, Immunomedics, Patents, Royalties, Other Intellectual Property Predictor of platinum sensitivity, Stock Illumina, Honoraria UpToDate, Medscape, Peerview, Research To Practice, Intellisphere, Clinical Care Options, ClinicalMind, Physicans' Education Resource, Research Funding Genentech/Roche, Seattle Genetics, Bayer, AstraZeneca, QED Therapeutics, Astellas Pharma; **TP** Consulting BMS, Merck, AstraZeneca, Ipsen, Pfizer, Novartis, Incyte, Seattle Genetics, Roche, Exelixis, MSD, Merck Serono, Astellas Pharma, Johnson & Johnson, Eisai, Travel Pfizer, MSD, AstraZeneca, Roche, Ipsen, Honoraria AstraZeneca, BMS, Exelixis, Incyte, Ipsen, Merck, MSD, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas Pharma, Johnson & Johnson, Eisai, Roche, Research Funding AstraZeneca, Roche, BMS, Exelixis, Ipsen, Merck, MSD, Novartis, Pfizer, Seattle Genetics, Merck, Serono, Astellas Pharma, Johnson & Johnson, Eisai; **GPS** Consulting Genentech, Merck, Eisai, AstraZeneca, Janssen, BMS, Exelixis, EMD Serono, Astellas Pharma, Bicycle Therapeutics, Pfizer, Seattle Genetics, Gilead Sciences, Scholar Rock, G1 Therapeutics, Speakers' Bureau Physicans' Education Resource, OncLive, Research to Practice, Medscape, Travel BMS, Honoraria UpToDate, Research Funding Institution Janssen, Sanofi, AstraZeneca, Gilead Sciences, QED Therapeutics, Other Relationship AstraZeneca, BMS, Astellas Pharma, Bavarian Nordic, Debiopharm Group, QED Therapeutics, Elsevier; **YL** Consulting Janssen, Janssen to Institution, Astellas Pharma, Roche, AstraZeneca, MSD Oncology, MSD Oncology to Institution, Seattle Genetics, BMS, Immunomedics, Taiho Pharmaceutical, Travel Astellas Pharma, Janssen Oncology, Roche, MSD Oncology, AstraZeneca, Seattle Genetics, Honoraria Sanofi, Pfizer, Research Funding Institution Sanofi, Janssen Oncology, MSD Oncology, AstraZeneca, Clovis Oncology, Exelixis, Boehringer Ingelheim, Incyte, Pfizer, Oncogenex, Medivation, CureVac, Nektar; **ID** Consulting Roche/Genentech, MSD Oncology, Bayer, BMS, Seattle Genetics, Pharmacyclics, Janssen Oncology, Novartis, Honoraria BMS, Ipsen, Roche/Genentech, Company: Janssen Oncology, MSD Oncology, Astellas Pharma, EUSA Pharma, Research Funding Institution Roche/Genentech, AstraZeneca Spain, Janssen Oncology, Astellas Pharma, Travel Roche/Genentech, AstraZeneca Spain, Ipsen; **JLL** Consulting Pfizer Korea, Sanofi Aventis Korea, BMS Korea, Alteogene, GI Innovation, MSD Korea, Merck, AstraZeneca, Research Funding Institution Pfizer, Janssen, Novartis, BMS, Roche/Genentech, AstraZeneca/MedImmune, MSD, Bayer Schering Pharma, Seattle Genetics, Honoraria BMS, Astellas Korea, Pfizer Korea, AstraZeneca, MSD Kerea, Stock Myovant Sciences, Johnson & Johnson/Janssen, Amgen, Merck, BeiGene, Innovent Biologics, Black Diamond Therapeutics, Karyopharm Therapeutics, Zymeworks; **NM** Consulting Sanofi, Janssen, AstraZeneca, Lilly, Honoraria Janssen, Chugai Pharma to Institution, MSD, Bayer, AstraZeneca, Research Funding Institution Janssen, MSD, Bayer Yakuhin, Chugai Pharma, AstraZeneca, Astellas Pharma, Bayer; **CV** Consulting Astrazeneca, GSK, Astellas, Ipsen, Roche, BMS, Merck, , Research Funding Institution Leo Pharma, Travel Roche; **DC** Consulting Janssen Oncology, Roche/Genentech, Astellas Pharma, AstraZeneca, Pfizer, Novartis, Ipsen, BMS, MSD Oncology, Bayer, Lilly, Sanofi, Sanofi, Pierre Fabre, Boehringer Ingelheim, Research Funding Institution Janssen Oncology, Travel Pfizer, Roche, BMS, AstraZeneca Spain; **SSS** Consulting to Institution Astellas Pharma, Janssen, Sanofi, Bayer, Roche/Genentech, BMS, AstraZeneca, Merck, Pfizer, Immunomedics, Research Funding Institution Bayer, Janssen, Pfizer; **HP** nothing to disclose; **JB** Consulting BMS, Eisai, EUSA Pharma, Ipsen, MSD Oncology, Novartis, Roche, Pfizer, Merck KGaA, Speakers' Bureau MSD Oncology, BMS, Merck KGaA, Pfizer, Ipsen, Research Funding Institution BMS, Astellas Pharma, Ipsen, MSD Oncology, Novartis, Roche, Roche, Exelixis, Pfizer; **MvdH** Consulting to Institution Roche/Genentech, Astellas Pharma, AstraZeneca/MedImmune, BMS, MSD Oncology, Seattle Genetics, Janssen, Research Funding Institution Astellas Pharma, BMS, Roche, AstraZeneca. Seagen, Travel Novartis, Astellas Pharma, MSD Oncology, Roche; **CW** Employment Astellas; **ZH** Employment and Stock Seagen Inc.; **CM** Employment Astellas, Janssen, Stock Merck, Janssen, Travel Janssen; **DPP** Consulting Bayer, Exelixis, Pfizer, Roche, Astellas Pharma, AstraZeneca, Lilly, Amgen, Boehringer Ingelheim, BMS, Clovis Oncology, Incyte, Janssen, Pharmacyclics, Seattle Genetics, Urogen pharma, Advanced Accelerator Applications, Ipsen, Bicycle Therapeutics, Mirati Therapeutics, Monopteros Therapeutics, Expert Testimony Celgene, Sanofi, Stock Bellicum Pharmaceuticals, Tyme, Research Funding Institution Progenics, Sanofi, Endocyte, Genentech, Merck, Astellas, Medivation, Novartis, AstraZeneca, Bayer, Lilly, Innocrin Pharma, MedImmune, Pfizer, Roche, Seattle Genetics, Clovis Oncology, BMS, Advanced Accelerator Applications, Agensys, BioXCel therapeutics, Eisai, Mirati Therapeutics, Replimune

P34

Updated overall efficacy and safety of selpercatinib in patients with RET fusion-positive non-small-cell lung cancer (NSCLC): LIBRETTO-001 study

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Background: Report updated efficacy and safety for selpercatinib in patients with *RET* fusion+ NSCLC.

Methods: Patients with *RET* fusion+ NSCLC enrolled in the global, multicentre, ongoing LIBRETTO-001 (16 countries, 89 sites) were included. The efficacy population includes all patients enrolled 6 months prior to data cutoff date. The primary analysis set (PAS) is a subset of the integrated analysis set (IAS, n = 218) and includes the first 105 consecutively enrolled patients with *RET* fusion+ NSCLC previously treated with platinum chemotherapy and is the more mature dataset. The treatment-naïve population includes 48 efficacy-evaluable patients. Primary endpoint: objective response rate (ORR) by independent review committee (IRC). . Secondary endpoints included DoR, PFS, safety. The safety population (N = 746) included all patients, regardless of histology, who received ≥1 dose by data cutoff (30Mar2020).

Results: ORR([95%CI]; n) by IRC was 64%(53.9,73.0; 67) for PAS, 57%(50.0,63.6; 124) for IAS, 85%(72.2,93.9; 41) for the treatment-naïve population. At median follow-up of 15.7 months, 58% responses in PAS are ongoing; thus a stable median DOR cannot yet be estimated. In treatment-naïve patients, at median follow-up of 9.8 months, 76% responses are ongoing. Most AEs were low-grade and included dry mouth, diarrhoea, hypertension, increased ALT/AST, fatigue, peripheral oedema. 2% pts discontinued due to a treatment related AE.

Conclusions: Selpercatinib continues to demonstrate durable antitumor activity in patients with *RET*-fusion+ NSCLC. It was well-tolerated with a safety profile consistent with previous reports. A global, randomized, phase-3 trial (LIBRETTO-431) evaluating selpercatinib vs with standard frontline platinum-based treatment is ongoing.

Conflict of Interest statement:

Oliver Gautschi: AMGEN, and Eli Lilly and Company; Advisory Board; Bayer, and Eli Lilly and Company

P35

Tepotinib in patients with *MET* exon 14 (*MET*ex14) skipping NSCLC

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Introduction: Tepotinib is a MET inhibitor approved in Switzerland for patients with *MET*ex14 skipping metastatic NSCLC, occurring in 3–4% of NSCLC. We report outcomes in patients with *MET*ex14 skipping NSCLC detected by tissue biopsy (TBx), used predominantly in Switzerland for biomarker testing.

Methods: In the Phase II VISION study, patients with advanced/metastatic *MET*ex14 skipping NSCLC, detected by liquid biopsy (LBx) and/or TBx, received 500 mg (450 mg active moiety) tepotinib once daily. Primary endpoint was objective response by independent review (RECIST 1.1). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Results: As of Feb 1, 2021, 174 patients enrolled via TBx (median age 73.0 years; range 41–94) were evaluated for efficacy (≥3 months' follow-up); 52.3% were male, 29.9%/69.5% had ECOG PS 0/1, and 45.4% had smoking history.

In treatment-naïve patients (n = 86), objective response rate (ORR) was 54.7% (95% CI: 43.5, 65.4), median (m) PFS was 15.3 months (9.6, not estimable [ne]), and mOS was 29.7 months (15.3,ne). In previously treated patients (n = 88), ORR was 47.7% (37.0, 58.6), mPFS was 11.1 months (8.2, 16.8), and mOS was 22.3 months (17.0, 27.2).

Of 291 patients (LBx and/or TBx) assessed for safety, Grade ≥3 treatment-related adverse events (TRAEs) were reported in 29.6%; 14.1% discontinued due to TRAEs. The most common TRAE, peripheral edema (60%), was mostly mild-to-moderate, rarely leading to discontinuation (4.5%).

Conclusion: Tepotinib demonstrated robust, durable clinical activity in TBx patients with *MET*ex14 skipping NSCLC. Overall, tepotinib TRAEs were manageable, with few discontinuations.

Efficacy	Treatment-naïve (n = 86)	Previously treated (n = 88)
Complete response, n (%)	0	0
Partial response, n (%)	47 (54.7)	42 (47.7)
Stable disease, n (%)	22 (25.6)	28 (31.8)
Progressive disease, n (%)	7 (8.1)	12 (13.6)
Not evaluable, n (%)	10 (11.6)	6 (6.8)
ORR, % (95% CI)	54.7 (43.5, 65.4)	47.7 (37.0, 58.6)
mDOR, months (95% CI)	32.7 (10.8, 32.7)	10.1 (8.3, 15.7)
mPFS, months (95% CI)	15.3 (9.6, ne)	11.1 (8.2, 16.8)
mOS, months (95% CI)	29.7 (15.3, ne)	22.3 (17.0, 27.2)

Conflict of Interest statement: Advisory/consultancy: AstraZeneca, Bristol-Myers Squibb, Takeda, MSD and Roche

P36

Identifying classes of the pain, fatigue and depression symptom cluster in long-term prostate cancer survivors - Results from the PROCAS study

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Purpose: Aside from urological and sexual problems, long-term (≥5 years after initial diagnosis) prostate cancer (PC) survivors might suffer from pain, fatigue, and depression. In this study, we aimed to investigate classes of this symptom cluster in long-term PC survivors, to classify PC survivors accordingly, and to explore associations between classes of this cluster and health-related quality of life (HRQoL).

Methods: The study sample included 653 stage T1-T3N0M0 long-term PC survivors, identified from the multiregional *Prostate Cancer Survivorship in Switzerland* study. Fatigue was assessed with the EORTC QLQ-FA12, mental health with the MHI-5, and pain with the EORTC QLQ-C30 questionnaire. Latent class analysis was used to derive cluster classes. Factors associated with the derived classes were determined with multinomial logistic regression analysis.

Results: Three classes were identified: class 1 (61.4%) – "low pain, low physical and emotional fatigue, moderate depressive symptoms"; class 2 (15.1%) – "low physical fatigue and pain, moderate emotional fatigue, high depressive symptoms"; class 3 (23.5%) – high scores for all symptoms. Survivors in classes 2 and 3 were more likely to be physically inactive, report a history of depression or some other specific comorbidity, be treated with radiation therapy, and have worse HRQoL outcomes compared to class 1.

Conclusions: Three distinct classes of the pain-fatigue-depression cluster were identified, which could be distinguished by treatment, comorbidities, lifestyle factors and HRQoL outcomes. Therefore, improving classification of PC survivors according to severity of multiple symptoms could assist in developing interventions tailored to survivors' needs.

P37

The effect of collaborative reviews of electronic patient-reported outcomes on congruence of patient- and clinician-reported toxicity

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Background: Electronic patient-reported outcomes (ePRO) are a relatively novel form of data and have the potential to improve clinical practice for cancer patients.

Objective: The primary objective of this study was to assess the level of agreement κ between symptom ratings by physicians and patients via a shared review process in order to determine the reliability and utility of self-reported electronic symptom monitoring.

Methods: Patients receiving systemic therapy captured ePRO for 52 symptoms over a period of 90 days. At 3-week intervals, randomly selected symptoms were reviewed between the patient and physician for

congruency on severity of the grading of adverse events according to CTCAE. The agreement for the symptom review was assessed via Cohen κ. Chi-square tests were used to determine whether the patient-reported outcome was different among symptoms, types of cancer, demographics, and physicians' experience.

Results: Among the 181 patients, there was a fair scoring agreement (κ = 0.24)) for symptoms that were entered 2 to 4 weeks before the intended review (first rating) and a moderate agreement (κ = 0.41) for symptoms that were entered within 1 week of the intended review (second rating). However, the level of agreement increased from moderate (first rating, κ = 0.43) to substantial (second rating, κ = 0.68) for common symptoms. Congruency seemed to be unrelated to the cancer type, demographics, and physicians' review experience.

Conclusions: The shared monitoring and review of symptoms has the potential to improve the understanding of patient self-reporting. The integration of ePRO into oncological research and continuous clinical practice provides reliable information for self-empowerment.

Conflict of Interest statement: Andreas Trojan is the founder and chief medical officer of Mobile Health AG, the company that operates the consilium care smartphone app with whom the study was conducted. He also owns stock in the company.

P38

Stratified two-stage molecular testing for patients with pancreatic adenocarcinoma: a single center real-life analysis

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Targetable molecular alterations can be identified in a subset of pancreatic ductal adenocarcinomas (PDAC), yet the routine use of molecular profiling for PDAC patients is still controversial. At our institution, we established a stratified two-stage PDAC molecular testing algorithm and retrospectively analyzed two years of real-life experience.

Within our algorithm, patients undergo tumor tissue immunohistochemistry for mismatch repair gene expression (MMR-IHC) and tumor NGS with a custom 37 gene panel ("HRD-Panel") covering common driver alteration of PDAC and additionally 20 genes implicated in DNA homology recombination repair (HRR) (stage 1). In case of pre-specified findings (*KRAS* wild type, dMMR), additional comprehensive molecular testing (FoundationOne CDx) is performed (stage 2). Testing results are discussed at our institution`s molecular tumor board (MTB).

67 PDAC patients underwent molecular testing. All tests were carried out on tumor tissue, no upfront germline testing was performed. In 45/67 cases, testing was performed according to the algorithm. Most common molecular alterations were detected in *KRAS* (63/67; 94%), *TP53* (44/67; 65.7%), *CDKN2/A* (23/67) and SMAD4 (11/67). In 29.9% cases, at least one targetable genomic alteration was identified, most frequently HRD. Of 3/67 *KRAS* WT PDACs, 2/5 had a targetable non-V600E *BRAF* mutation. MTB recommended platinum chemotherapy and PARP inhibition in cases with HRD, other targeted treatments in 2/67 cases.

Routine molecular testing for PDAC is feasible and identifies targetable molecular alterations in a subset of cases, most commonly alterations within HRR. We advocate stratified tumor tissue testing for all stage IV PDACs prior to 1st-line treatment.

P39

Impact of comprehensive genomic profiling and molecular tumor board decision on clinical outcome of patients with solid tumors

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Targeted therapies underlined by comprehensive genomic profiling (CGP) improved clinical outcome in patients with advanced tumours in numerous studies. An interdisciplinary team approach is crucial to rank and consent the most valuable therapy out of variable results of CGP. With this intent, the Molecular Tumour Board (MTB) at the Comprehensive Cancer Center Zurich (C3Z) was formed. We performed a single centre, retrospective analysis between 2018-2020 evaluating the impact of MTB and the personalized therapeutic approaches on clinical outcomes. Included patients with advanced or metastasized solid tumours received a CGP analysis (FoundationOneCDx®, Oncomine Focus or Comprehensive Assay™) followed by discussion at the MTB. We calculated the PFS2 (PFS of recommended therapy) to PFS1 (PFS of prior line) ratio for patients, in whom the recommended therapy was implemented plus at least one prior therapy line before CGP had been given. In total, 506 patients (55% male, median age 64 years, mean of one prior therapy line) underwent CGP. Entities highest represented were lung (40%), colorectal (11%), biliary tract (7%), sarcomas (6%), urogenital (6%), and head and neck (6%) cancers. A new therapy or trial option was recommended in n = 208 (41%) patients. In 73 patients, the suggested molecularly guided therapy was implemented, of whom 56 patients qualified for PFS2/PFS1 calculation. A PFS2/PFS1 ratio of ≥1.3 was observed in one third of patients, which finally underlined the relevance of CGP and MTB. Therefore, we recommend to perform CGP and discussion at a MTB in advanced solid tumours after standard of care therapy.

P40

Facilitators and barriers to centre- and home-based exercise training in breast cancer patients - A Swiss tertiary centre experience

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Background: Exercise is an effective therapy for breast cancer patients to reduce fatigue and to improve health-related quality of life and physical function. Yet, breast cancer patients often do not meet physical activity guidelines. To understand why recommendations are not met, this study aimed at identifying facilitators and barriers to supervised, centre-based exercise within a cardio-oncologic rehabilitation (CORE) programme and to unsupervised, home-based exercise both during and after the completion of the programme, as well as strategies used to manage these barriers.

Methods: Breast cancer patients who had previously completed a CORE programme at a Swiss tertiary centre were recruited. Semi-structured interviews were conducted with subsequent thematic analysis to identify common themes.

Results: Of 45 eligible breast cancer patients, 19 patients (42%, mean age 48.9±9.7 years) responded to our invitation. General facilitators for exercise were anticipated and experienced benefits for physical and mental health and enjoyment of exercise. Facilitators for centre-based exercise were social support, accountability and provision of structured exercise. Barriers towards centre-based exercise included physical and environmental barriers, whereby psychological barriers were reported predominantly in the context of home-based exercise. Strategies to manage barriers included the adaptation of training circumstances, behaviour change strategies and strategies to deal with side effects.

Conclusions: Findings from this first Swiss study on facilitators and barriers toward exercise in breast cancer patients support the importance of providing CORE programmes and suggest that a special focus should be directed at the transition from supervised to self-organized exercise to enhance long-term exercise participation.

Conflict of Interest statement: This study was partly supported by the Swiss cancer research and no potential conflict of interest relevant to this article is reported.

P41

Skeletal muscles involvement as a negative predictive factor for a metastatic cervix carcinoma

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Cervical cancer is a rare disease in Switzerland. Often patients are diagnosed in a locally advanced or metastatic stage. The usual sites of metastases are the lymph nodes followed by lungs, liver and bones. The 5 years' survival rate of metastatic disease is about 17%. Metastases into skeletal muscles are extremely rare and related with a worst prognosis.

A 44 years old woman presented some urinary discomfort and abdominal pain. The investigations showed a local tumour infiltration complicated with left urotero-hydronephrosis. The PET scan showed a large cervical tumour with diffuse lymph infiltration and two muscles lesions, one on the right hand, the other on the right leg. The performed primary and muscles biopsies confirmed the stage IV cervical cancer. Muscles lesions were asymptomatic. We started a combined treatment of 50 mg/m2 cisplatine, 175 mg/m2 paclitaxel and 15 mg/kg bevacizumab. The intermediate imaging results showed a dissociated evolution of the disease.

We present a rare case of cervical cancer patient with muscle metastasis. There are only 15 case reports described in the literature for the last 30 years. The clinical outcome of that patients has been reported to be poor and there is currently no standard recommendation for treatment.

P42

A Metastatic mucinous adenocarcinoma of gynecological origin: ovarian, uterine or cervical primary?

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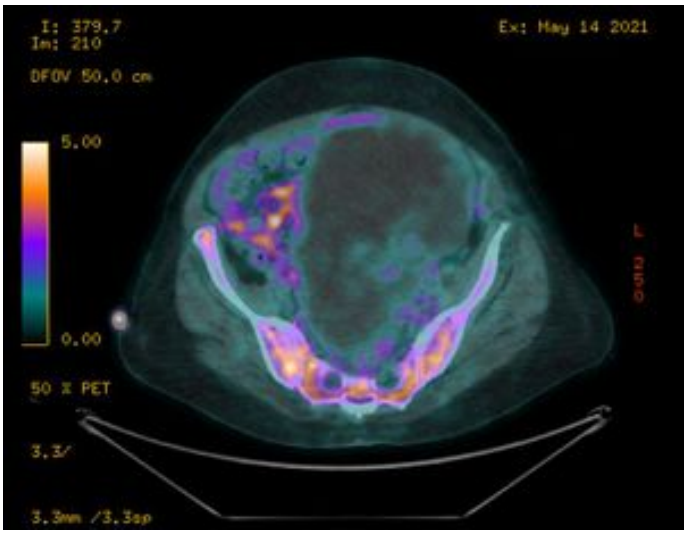
Mucinous adenocarcinoma of gynecological origin is a rare subtype of gynecological cancer. It can arise from the uterus, uterine cervix, peritoneum and ovary. These tumors, albeit been rare are often diagnosed at early stages. When metastatic, these tumors carry a grim prognosis, exhibit low response rate to standard of care platinum based chemotherapy, and their etiological diagnosis is challenging, mostly based on pathological and radiological features.We report the case of a 60-year-old woman initially diagnosed with metastatic gastric type mucinous endocervical adenocarcinomas of the uterine cervix (GAC) based on her initial imaging and vaginal pathology report. The subsequent radiological assessment was suggestive of a mucinous adenocarcinoma of the endometrium (MACE). Due to the diagnostic uncertainty and the lack of response to the first line platinum-based chemotherapy, a laparoscopy with tumor biopsies was performed. The pathological assessment with extensive immunohistochemistry panel and NGS concluded to a mucinous ovarian cancer (MOC). The tumor being ER, PR and vimentin negative but CK7, CK20, PAX8, p53 and CDX2 positive. Thus a second line fluorouracil based chemotherapy was initiated.The impact of the delayed diagnosis on the treatment initiation and the challenges encountered during the first line and second line treatment a discussed in our poster.



P44

The proteomic landscape of chronic lymphocytic leukemia

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Many functional consequences of mutations on tumor phenotypes in chronic lymphocytic leukemia (CLL) are poorly understood. This is in part due to missing information on global protein expression profiles in CLL. We determined the proteome of 117 CLL patient samples with data-independent acquisition mass spectrometry (DIA-MS). Proteomic results were integrated with genomic, transcriptomic, ex vivo drug response and clinical outcome data for the same patients. We identified trisomy 12 and IGHV mutational status as main disease drivers influencing protein expression in CLL (1055 and 542 differentially expressed proteins, FDR = 5%). Gene set enrichment analyses indicated BCR/PI3K/AKT signaling as tumor driver of CLL with trisomy 12. This finding was reinforced by analyses of protein complex formation and protein abundance buffering, which detected an upregulated protein complex involved in BCR, AKT, MAPK and PI3K signaling and limited protein abundance buffering in trisomy 12 CLL. The relative absence of protein abundance buffering seen in trisomy 12 CLL was in contrast to strong protein buffering effects observed in trisomy 19 CLL, highlighting the additional information gained by protein expression measurements compared to gene dosage or RNA expression. We examined proteins associated with drug response and identified STAT2 protein expression to be linked with response to BTK and MEK inhibitors. STAT2 was upregulated in IGHV-unmutated, trisomy 12 CLL and required for apoptosis-preventing interferon-α signaling in CLL. Our study highlights the importance of protein abundance data as non-redundant layer of information. It detects protein determinants of drug response and identifies STAT2 as key factor in CLL biology.

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The tumor profiler study for relapsed/refractory acute myeloid leukemia

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The Tumor profiler (TUPRO) consortium aims at integrating multiomics with clinical data in order to identify therapeutic vulnerabilities of patients with relapsed/refractory acute myeloid leukemia (rrAML). In this study, we investigated *ex vivo* drug responses of 18 rrAML patients by pharmacoscopy and established correlations with single cell RNA sequencing (ssRNA) and single cell proteomics (CyTOF) data. We first observed that AML patients clustered together according to the treatment received at sampling. In particular, we found that the *ex vivo* response to the BCL2-inhibitor venetoclax (ven) was significantly reduced in patients treated with the combination of a hypomethylating (HMA) and ven compared to patients pre-exposed to HMA only. In order to find compounds with activity in ven-refractory patients we explored drug-drug correlations. Interestingly, we detected a negative correlation between the response to ven and the ALK-inhibitor crizotinib (crizo, r = -047, $p<10^{-2}$). To identify predictive markers for a response to ven and crizo we used the lasso regression model trained to predict *ex vivo* responses to both drugs using all markers measured by CyTOF as predictors. In particular a high expression of CD36 was associated with poor response to ven and a good *ex vivo* drug-sensitivity to crizo. The predictive protein expression data was confirmed by ssRNA expression. In summary, using a comprehensive, integrative multiomics data analysis platform approach we identify compounds with activity in rrAML patients and identify predictive markers for *ex vivo* drug response.

P46

Ribosome associated protein RNH1 determines translation specificity for hematopoietic system

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Cell diversity in multicellular organisms is commonly attributed to the spatio-temporal gene expression regulated by cell/tissue specific transcription factors. However, existence of cell-type specific translation regulator and role of translation control to achieve cell diversity is largely unknown. Knowledge of such regulators is essential to understand ribosomopathies which are characterized by cell-type specific translation dysregulation. Here we report Ribonuclease inhibitor (RNH1) as a cell-type specific translation regulator that predominantly controls hematopoietic translation. RNH1 is ubiquitously present in human cells and tissues, however, RNH1 knockout (KO) significantly reduced polysome levels only in the hematopoietic but not in the non-hematopoietic cell-lines. Similarly, OP–Puro incorporation assay in RNH1 KO mice showed that RNH1-deficiency leads to translation loss in hematopoietic but not in the non-hematopoietic organ. How this higher vertebrate specific, ribosome associated protein is selective in regulating hematopoietic specific translation is still under investigation. Our results show that RNH1 KO decreases translation of mRNAs encoding ribosomal protein (RPs). This control of translation by RNH1 is independent of mTOR signalling. RNH1 neither binds to the 5`cap of mRNA nor regulates tiRNA production at steady state levels. Interestingly, it has been shown that RNH1 is translationally down-regulated in RPS19 knockdown primary human HSPCs, which is frequently mutated in Diamond-Blackfan anemia. Supporting RNH1 role in translation, overexpression of it rescues erythroid and translation defects in RPS19 knockdown cells. Collectively, our results unravel the existence of hematopoietic specific translation regulator and may partially explain cell-type specific defects caused by mutations in RPs genes.

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CAR T-cell killing of target cells depends on their TP53-status

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With current treatment regimens only <30% of all patients with newly diagnosed acute myeloid leukemia (AML) are alive 5 years after initial diagnosis, with TP53-mutated AML cases associated with a particularly poor prognosis. Thus, developing efficacious and safe CAR T cell therapies for AML is currently an active area of research.

We show in a series of in vitro and in vivo experiments that CAR T cells targeting three different surface antigens (CD33, CD123, CD371) co-incubated with TP53 knock-out or miss-sense but not wildtype MOLM-13 AML cells proliferated less, upregulated exhaustion markers and were not able to eradicate target AML cells in vitro. Fluorescence live-cell imaging showed a longer duration of the immunological synapse between CAR T cells and TP53 knockout than wildtype AML. Finally, NSG mice engrafted with MOLM-13 harboring wildtype but not TP53 knockout cells were cured by CAR T cell infusion.

Taken together, our results show a relative resistance of AML cells harboring a TP53 knockout or a miss-sense mutation to CAR T-cell killing leading to increased exhaustion and decreased proliferation of effector cells. As we could not observe antigen loss or increased immune checkpoint expression on target cells, we hypothesize that this relative resistance is due to an intrinsic apoptosis defect of TP53-deficient AML cells leading to prolonged antigen exposure, sustained activating intracellular signaling and ultimately exhaustion of CAR T-cells.

To challenge our working hypothesis and elucidate the mechanism behind the observed resistance we are currently further characterizing both the effector (CART) and target (MOLM-13) cells.

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Calreticulin mutations affect its chaperone function and perturb the glycoproteome

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CALR mutations occur in patients with *JAK2*-unmutated myeloproliferative neoplasms (MPNs). Calreticulin (CALR) is an endoplasmic reticulum (ER)-retained chaperone that assists glycoproteins (GPs) like myeloperoxidase (MPO) in obtaining their three-dimensional structure. CALR binds GPs using its holdase domain and simultaneously interacts with the foldase ERp57. Here, we investigated whether *CALR* mutations affect chaperone function. To detect the impact of *CALR* mutations on protein structure and expression levels in MPN, we subjected the proteomes of primary MPN granulocytes and *CALR* mutant cell lines to limited proteolysis-coupled mass spectrometry (LiP-MS). Hetero- and homozygous *CALR* mutations lead to structural perturbations of calcium-related proteins, whereas their protein expression levels remained unaffected. In contrast, homozygous *CALR* mutations and loss of CALR equally reduced GP expression levels and structural integrity suggesting that loss-of-function attributes of CALR MUT lead to GP maturation defects. To further investigate CALR chaperone function we expressed MPO in CALR knockout cells along with CALR wild-type or mutant constructs. Binding of CALR constructs to MPO was determined via proximity-ligation-assays and enzyme-linked immunoassay. We confirmed the CALR chaperone defect inferred by LiP-MS by demonstrating a decreased binding affinity of the CALR lectin domain to MPO. In addition to affecting the holdase function, the mutant C-terminus also prevented the foldase ERp57 from binding the CALR P-domain, which is consistent with previous data. In conclusion, by combining the *in situ* approach of LiP-MS with mechanistic data, we demonstrate that a complex amalgam of quantitative and qualitative chaperone defects of CALR mutants compromises GP maturation.

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SAKK 16/14 - T-cell receptor repertoire metrics predict response to neoadjuvant durvalumab in patients with stage IIIA(N2) NSCLC

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Introduction: T-cell receptor (TCR) repertoire assessment has emerged as a novel predictive marker for response to immune checkpoint inhibitor therapy. Here, we performed TCR sequencing in patients from the phase 2 trial SAKK 16/14 undergoing neoadjuvant chemotherapy with 3 cycles of cisplatin/docetaxel followed by treatment with durvalumab.

Methods: A total of 127 peripheral blood samples and 67 formalin-fixed paraffin-embedded (FFPE) tissue samples were processed from 67 patients before and after neoadjuvant treatment. Total RNA was extracted and used for TCR sequencing with the Oncomine TCR Beta-LR and SR Assays, respectively. TCR evenness, Shannon diversity, and TCR richness were calculated and correlated with clinical endpoints using Mann-Whitney-Wilcox test.

Results: TCR repertoire could be assessed in a total of 97 peripheral blood (47 pre- and 50 post-treatment) and 64 FFPE (15 pre- and 49 post-treatment) samples. In pre-treatment peripheral blood samples, TCR evenness ($p = 0.032$) was associated with 1 year EFS. In FFPE post-treatment samples, 1 year EFS as well as MPR were significantly associated with increased TCR richness ($p = 0.0168$ and 0.0134) and Shannon diversity ($p = 0.0278$ and $p = 0.0334$). Furthermore, nodal clearance was significantly associated with TCR richness and Shannon diversity in post-treatment tissue samples ($p = 0.0015$, $p = 0.0087$). In contrast, TMB was not associated with EFS, MPR or nodal clearance ($p = 0.91$, $p = 0.47$, $p = 0.52$).

Conclusions: Our results show that TCR repertoire measured in peripheral blood samples and tumor tissue may provide a useful tool for predicting risk of recurrence after neoadjuvant sequential chemo-immunotherapy with durvalumab in patients with resectable stage IIIA(N2) NSCLC.

P50

Updated results of pharmacoscopy on fluid samples from patients with solid tumors

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Background: In patients with metastatic malignancies there is an urgent need for predictive biomarkers. Fluids containing tumor cells, like pleural effusion or ascites, are easily accessible and could potentially provide information on drug sensitivities *ex vivo*.

Methods: Image-based single-cell drug response testing (pharmacoscopy) on fluid samples containing tumor cells is used to investigate drug response variability on an intra- and interpersonal level. A population of malignant and healthy cells is incubated with a drug panel (24 hours). After staining with fluorescent antibodies, cells are imaged using automated microscopy and then classified using convolutional neural networks. Multiplexed transcriptomic data is correlated with the *ex vivo* drug responses.

Results: The clinical cohort currently includes 178 samples. 66 are samples from lung adenocarcinoma (LUAD), comprising the largest subcohort. In 19 patients, pharmacoscopy was repeated on specimens taken within a short period of time, for which we observed a high intra-individual reproducibility of the drug response profiles. In a patient with LUAD harboring a BRAF p.V600E mutation pharmacoscopy was able to predict clinical response to targeted treatment with dabrafenib/trametinib. In this case multiplexed RNAseq under multiple drug conditions revealed MAPK pathway inhibition upon exposure to dabrafenib/trametinib when compared to other compounds and samples without BRAF aberration.

Conclusion: Pharmacoscopy on fluid samples is feasible to explore drug responses in solid tumors. Further integration of drug response profiles with molecular measurements including transcriptomic and genomic profiling will provide comprehensive insights into the molecular mechanisms underlying drug response variability and will help to develop clinical predictive relevance.

P51

Endogenous retroelements shaped *PBOV1* oncogene: immunological sequelae and immunotherapeutic implications

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Background: Endogenous retroelements are a main source of targetable tumor-specific antigens that have the potential to augment host adaptive antitumor responses.

PBOV1 is a human-specific oncogene that is overexpressed in several types of human tumors.

Goals: Herein we show that the human-specific *PBOV1* coding sequence (CDS) was evolutionarily shaped by endogenous retroelements and that it comprises an immunogenic peptide of retroelement origin.

Methods: PBOV1 protein expression data were downloaded from the Human Protein Atlas (HPA). Genome, mobilome and molecular evolutionarily analysis was performed through the corresponding tracks of UCSC Genome Browser Database. The Immune Epitope Database was used to investigate the presence of HLA class I epitopes in PBOV1 protein sequence.

Results: Data from HPA reveal expression of PBOV1 protein in cases of gliomas, hepatocellular and urothelial carcinomas as well as of squamous cell carcinomas of the skin. Previous studies have shown high PBOV1 protein expression in prostate cancer.

PBOV1 CDS comprises two endogenous retroelements, namely a L3/ LINE and a MIR/ SINE. The two key evolutionary events that allowed the generation of *PBOV1* CDS exclusively in human took place in these two retroelement sequences.

Previous HLA peptidome profiling of glioblastoma patient specimens revealed that the AILFTLTLQ peptide of PBOV1 protein represents an epitope of functional CD8+ T cell responses. The CDS of this immunogenic enneapeptide is comprised in the L3/ LINE retroelement.

Conclusions: PBOV1 protein represents an aberrant, retroelement-shaped molecule that is expressed in multiple cancers and could represent a potent candidate for T cell-based immunotherapy.

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Combination chemotherapy testing in patient-derived pancreatic cancer organoids – *ex vivo* modelling of clinical responses

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Clinical responses of pancreatic ductal adenocarcinoma (PDAC) to the available combination chemotherapy regimens are highly heterogenous. Molecular profiling uncovers predictive biomarkers in only a small fraction of cases. Patient-derived pancreatic cancer organoids (PDAC-PDOs) are therefore under investigation as functional precision oncology tool, allowing to test an individual tumor`s drug sensitivities in a co-clinical time-relevant setting.

For this study, we employed a fully characterized cohort of PDAC-PDOs (n = 20), derived from patients undergoing resection or surgical biopsy of PDAC at our institution. We studied *in vitro* drug sensitivity following rigorously standardized and quality-controlled protocols. We went on to assemble combination chemotherapy protocols form *in vitro* testing mimicking clinically applied regimens (FOLFIRINOX, gemcitabine/nab-paclitaxel). We assessed responses to single drugs versus combination regimens for correlation, cross-compared sensitivities between the distinct chemo-protocols and finally integrated *in vitro* testing results with clinically observed responses and molecular profiles of individual tumors (DNA and RNA sequencing data).

Ex vivo responses of PDAC-PDOs to individual chemotherapeutic drugs showed considerable variation (IC50, AUC), in line with previous reports. Notably, there was no correlation between responses to individual drugs and chemo-combinations observed. PDAC-PDOs showed highly heterogenous responses to FOLFIRINOX and gemcitabine/nab-paclitaxel *in vitro*. We will present further data regarding correlation of *in vitro* responses to clinical data and molecular profiles at the meeting.

Ex vivo chemotherapy sensitivity testing in PDAC-PDOs is technically feasible, generating robust results. Notably, single drug sensitivities show no correlation with response to clinically established chemotherapy combination regimens, which has significant implications for data interpretation and trial design.

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