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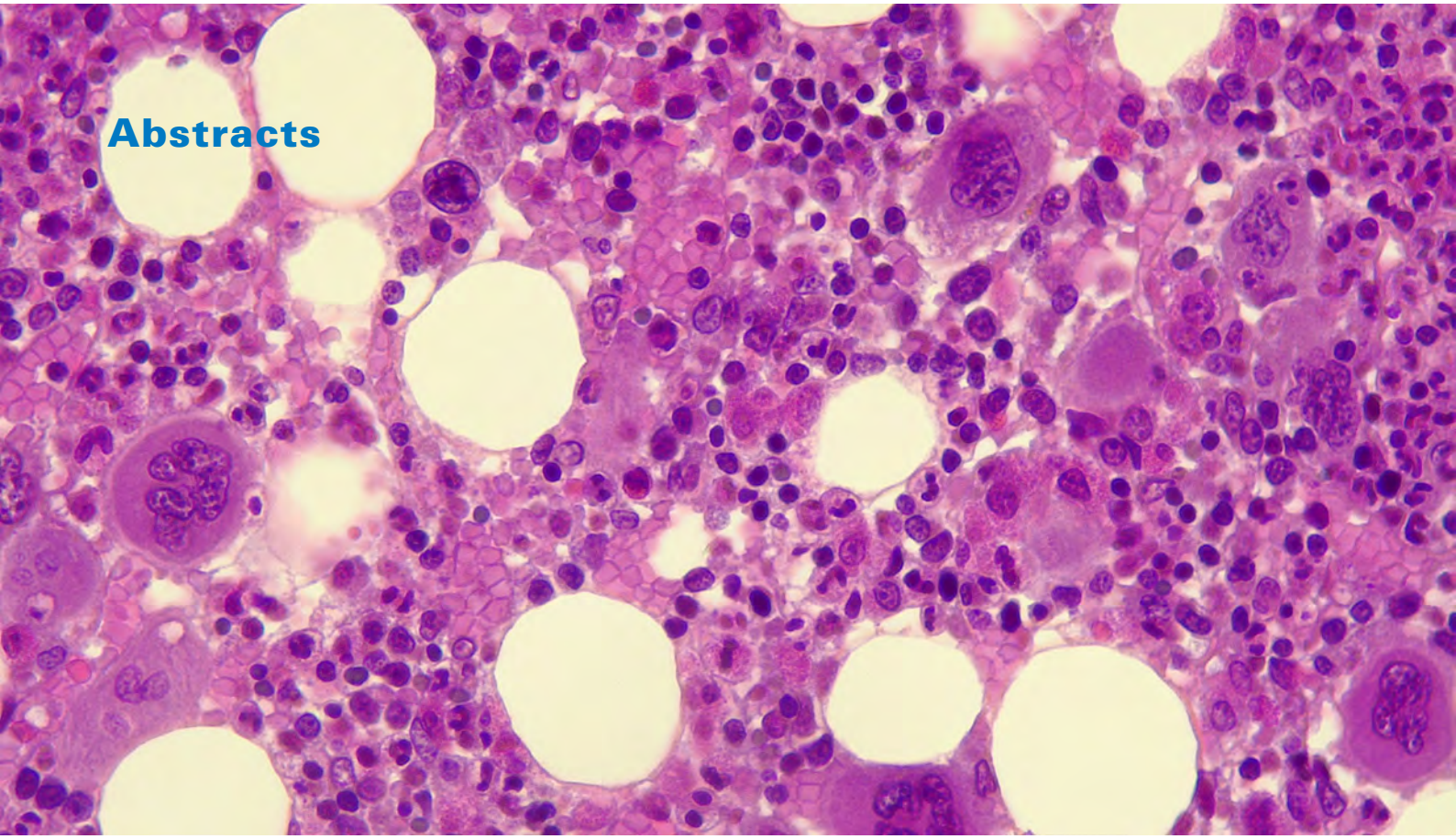
Virtual congress, November 18–21, 2020

SOHC
SWISS ONCOLOGY & HEMATOLOGY CONGRESS



Abstracts

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SWISS HEMATOLOGY & ONCOLOGY CONGRESS (SOHC)

VIRTUAL CONGRESS, NOVEMBER 18–21, 2020

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ORAL PRESENTATIONS

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

Topic: Hemostasis, transfusion medicine, vascular, laboratory medicine (SSH award for hemostasis)

O1

Targeting protein S using small interfering RNA is well tolerated and protects mice with hemophilia A from acute hemarthrosis

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Introduction and aim: Hemophilia A patients (HA) often suffer from spontaneous bleeding into *joint* spaces affecting the synovium, cartilage and bone tissues. Current prophylactic treatments are not always effective and patients with HA can experience breakthrough bleeds. We demonstrated that inhibition of protein S (PS), a natural anticoagulant, controls coagulation and constitutes a potential therapeutic target in hemophilia.

Here we aim to translate our findings using small interfering RNA conjugated to an N-acetylgalactosamine (GalNAc) to target *Pros1* gene expression (GalNAc-siRNA-PS) in vivo.

Results: 42 days after subcutaneous injection of GalNAc-siRNA-PS, *WT* mice were alive with no overt disseminated intravascular coagulation (DIC) supporting safety of GalNAc- -siRNA-PS treatment. Mice treated with GalNAc-siRNA-PS displayed lower plasma PS compared to vehicle treated mice (52±12 vs 100±11 %). In the liver, PS mRNA levels were reduced compared to vehicle treated mice (31±10 vs 100±24 %).

In hemophilic A mice (*F8*$^{-/-}$), clot formation (assessed by rotative thromboelastometry) and thrombin generation were partially restored after treatment with GalNAc-siRNA-PS.

Acute hemarthrosis (AH) was applied to *F8*$^{-/-}$ mice treated with GalNAc-siRNA-PS. Vehicle treated *F8*$^{-/-}$ mice developed extensive bleeding in injured knees as compared to GalNAc-siRNA-PS treated mice. Intra-articular bleeding and synovial hyperplasia were higher in *F8*$^{-/-}$ mice treated by vehicle than in those treated by GalNAc-siRNA-PS. Knee joint swelling was reduced in GalNAc-siRNA-PS treated mice.

Conclusion: GalNAc-siRNA conjugate for *Pros1* gene expression modulation is well tolerated, improves hemostasis and protects *F8*$^{-/-}$ mice from AH pointing to PS targeting using GalNAc-siRNA-PS as a new valuable therapeutic approach for hemophilia.

Disclosure: Nothing to disclose

Topic: Clinical hemato-oncology (lymphoma, myeloma, leukemia, transplantation for SSH and SSMO) (SSH/SSMO award for clinical hemato-oncology)

O2

Busulfan-cyclophosphamide versus cyclophosphamide-busulfan before allogeneic hematopoietic transplantation: a prospective randomized trial

C. Seydoux[1], M. Medinger[1], S. Gerull[1], J. Halter[1], D. Heim[1], Y. Chalandon[2], S. Masouridi Levrat[2], U. Schanz[3], G. Nair[3], M. Ansari[4], P. Simon[5], J.R. Passweg[1], N. Cantoni[6]

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Busulfan and cyclophosphamide (BuCy) is a frequent conditioning regimen for allogeneic hematopoietic cell transplantation (allo-HCT). As prior application of Bu may trigger liver toxicity of subsequent Cy, reversing the order to cyclophosphamide-busulfan (CyBu) might be preferable. Our aim was to test the impact of the order of application of Bu and Cy before allo-HCT.

We performed a prospective multicenter randomized trial 2012 to 2017 exploring BuCy vs CyBu. Endpoints were liver toxicity at day 30 after HCT and long-term follow-up with relapse, non-relapse mortality (NRM) and survival.

We analyzed 70 patients, median age of 47 years, receiving HCT from HLA-matched siblings (49%) or unrelated donors (51%) after conditioning with BuCy or CyBu (33 vs 37 patients). Patient baseline characteristics showed no significant differences between the groups.

We showed a higher liver toxicity in the BuCy vs. CyBu group, with higher levels of ASAT on day 30 (p=0.03), higher frequency of VOD criteria (p=0.05) and slightly more patients fulfilling CTCAE criteria for liver toxicity. Overall survival at 4 years tended to be lower (43% vs. 63%; p=0.06) and TRM to be higher (28% vs. 6 %; p=0.049) with BuCy compared to CyBu. Other outcomes (causes of death, engraftment, relapse and GvHD) were similar in both groups.

This prospective RCT found some evidence of superiority of CyBu over BuCy as conditioning in allo-HCT patients. We showed lower liver toxicity at day 30, lower NRM and a tendency of better overall survival in patients receiving CyBu instead of BuCy.

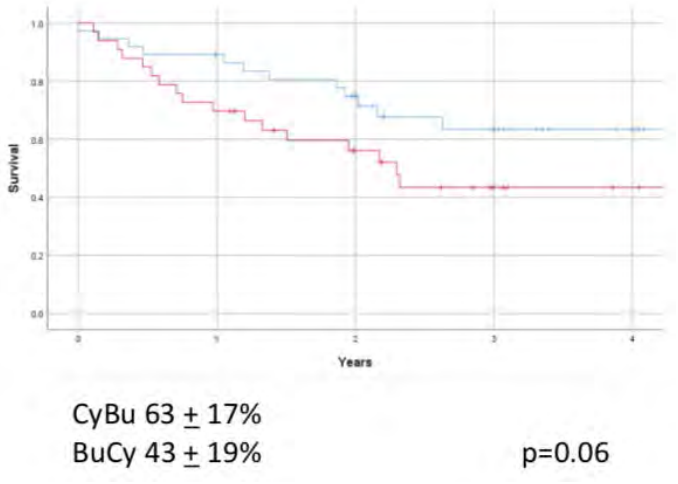

Figure 1: Survival at 4 years

Disclosure: Conflict of interest: none Fundings: Baxter SA and Robapharm / Pierre Fabre SA

Topic: Clinical solid tumor oncology (SSMO award for clinical solid tumor oncology)

O3

SAKK 16/14: Anti-PD-L1 antibody durvalumab in addition to neoadjuvant chemotherapy in patients with stage IIIA(N2) non-small cell lung cancer (NSCLC)

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Background: For patients with resectable stage IIIA(N2) non-small cell lung cancer (NSCLC) neoadjuvant chemotherapy with 3 cycles cisplatin (cis)/docetaxel (doce) followed by surgery is an accepted standard of care. PD-(L)1 inhibitors have recently shown high response rates in resectable NSCLC.

Methods: Neoadjuvant treatment consisted of 3 cycles of cis 100 mg/m^2 and doce 85 mg/m^2 q3w followed by 2 cycles of durvalumab 750 mg q2w. Durvalumab was continued after surgery for 1 year. The primary objective of the study is to improve the EFS after 1 year from 48% to 65%.

Results: Sixty-eight patients were included. Radiographic response rate was 44.8% (95%CI: 32.6-57.4) after neoadjuvant chemotherapy (CR: 4.5%, PR: 40.3%, SD: 44.8%) and 58.1% (95%CI: 44.8-70.5) after additional neoadjuvant immunotherapy (CR: 6.5%, PR: 51.6%, SD: 25.8%). Of 55 resected patients, 10 patients (18.2%) had a pathological complete response and 33 patients (60.0%) a major pathological response defined as ≤10% viable tumor cells by central pathology review. Postoperative nodal down-staging was observed in 37 patients (67.3%). 1-year EFS was 73.3% (90%CI: 60.1-82.7). At the time of the analysis, median EFS was not reached. After a median follow up of 28 months, median OS was not reached. 59 patients (88.1%) had an AE grade ≥3 including two fatal cases (one postoperative bleeding complication and one respiratory failure).

Conclusions: The addition of perioperative durvalumab to standard of care cis/doce is safe and results in a encouraging 1-year EFS rate exceeding historical data of chemotherapy alone and achieves a high major pathological response rate.

Disclosure: The study was supported by AstraZeneca and research agreements with the following institutions: State Secretary for Education, Research and Innovation (SERI), Swiss Cancer Research Foundation (SCS) and the Swiss Cancer League (SCL).

Topic: Experimental Hematology / Oncology (SSH/SSMO award for experimental hematology / oncology)

O4

Loss of Dnmt3a confers resistance to pegIFNα in JAK2-V617F mouse model

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Pegylated interferon alpha (pegIFNα) is the only therapy for myeloproliferative neoplasms (MPN) that can induce molecular remission of the *JAK2*-V617F$^+$ clone. Clinical studies suggested, that patients with additional mutations in *DNMT3A* have poorer responses to pegIFNα. We compared the effects of pegIFNα on hematopoiesis in a MPN mouse model expressing *JAK2*-V617F (*VF*) and in *VF* mice crossed with a *Dnmt3a* knockout (*VF;Dnmt3a*$^{-/-}$). To follow the *JAK2*-mutant cells, the *VF* and *VF;Dnmt3a*$^{-/-}$ mice were further crossed with a *GFP*-reporter strain and used for competitive bone marrow (BM) transplantations in a 1:20 ratio with wildtype BM cells (Figure 1A). After reconstitution, the recipient mice were treated for 16 weeks with pegIFNα or saline. PegIFNα normalized blood counts, and the percentages of GFP-positive cells in peripheral blood (Figure 1B). However, pegIFNα did not reduce spleen size and had no significant effect on GFP-chimerism in BM of *VF;Dnmt3a*$^{-/-}$ recipients. Platelets remained higher in *VF;Dnmt3a*$^{-/-}$ recipients and bone marrow histology showed higher degree of myelofibrosis (not shown). Long-term hematopoietic stem cells (LT-HSCs) in *VF;Dnmt3a*$^{-/-}$ mice accumulated less reactive oxygen species (ROS), less DNA damage (Figure 1B) and remained dormant under pegIFNα, compared to *VF*. BM from pegIFNα treated *VF;Dnmt3a*$^{-/-}$ double mutant mice transplanted into secondary and tertiary recipients induced more aggressive disease than vehicle and BM from *VF* mice (not shown). Our results demonstrate that loss of *Dnmt3a* protects LT-HSCs from pegIFNα-induced damage and suggest that pegIFNα therapy in patients carrying *JAK2*-V617F and *DNMT3A* mutations has possible detrimental effects.

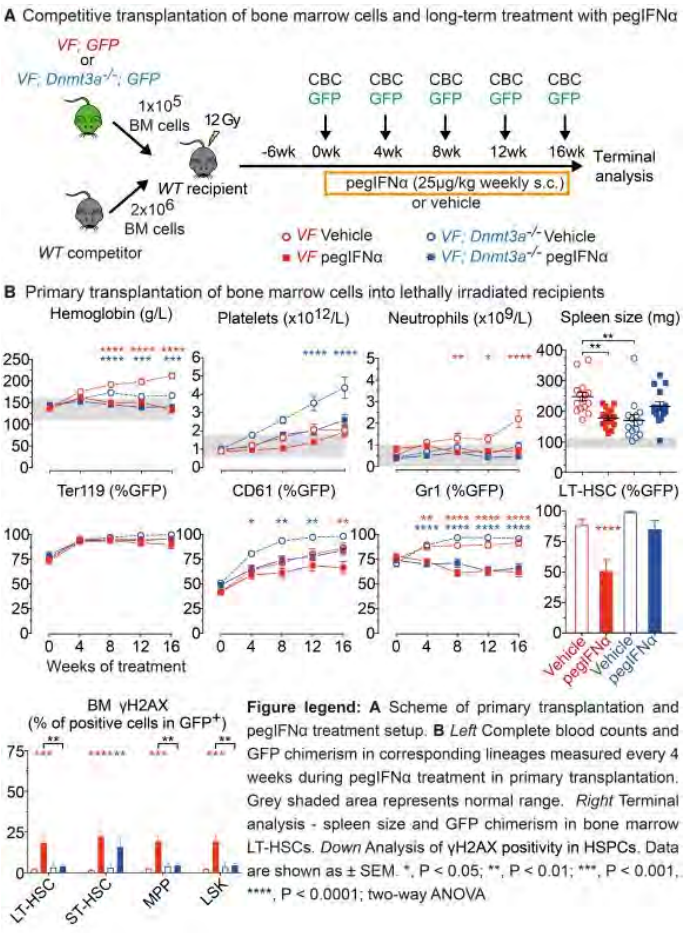

Figure legend: **A** Scheme of primary transplantation and pegIFNα treatment setup. **B** *Left* Complete blood counts and GFP chimerism in corresponding lineages measured every 4 weeks during pegIFNα treatment in primary transplantation. Grey shaded area represents normal range. *Right* Terminal analysis - spleen size and GFP chimerism in bone marrow LT-HSCs. *Down* Analysis of γH2AX positivity in HSPCs. Data are shown as ± SEM. *, P < 0.05; **, P < 0.01; ***, P < 0.001, ****, P < 0.0001; two-way ANOVA

Disclosure: Nothing to disclose

SSH/SSMO ORAL PRESENTATIONS CLINICAL HEMATO-ONCOLOGY, HEMOSTASIS, TRANSFUSION & VASCULAR DISEASES

Topic: Hemostasis, transfusion medicine, vascular, laboratory medicine (SSH award for hemostasis)

O5

MiR-204-5p regulates platelet adhesion to fibrinogen

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Background: Circulating miRNA profile is a biomarker of platelet reactivity and cardiovascular outcome. Recent studies functionally validated miRNA as regulator of platelet function but the exact mechanism is largely unknown.

Aims: To investigate the impact of miR-204-5p on platelets and to address the mechanistic issues mediating its functional effect using a model of human hematopoietic stem cells.

Methods: Human hematopoietic stem cells were differentiated into megakaryocytes, allowing transfection of miR-204-5p and recovery of subsequent platelet like structures (PLS). Surface receptors of PLS were characterized by FACS. The impact of miR-204-5p overexpression on fibrinogen binding was assessed by measuring inactive and active form of GPIIbIIIa by FACS, spreading on immobilized fibrinogen and binding of soluble labeled fibrinogen.

QPCR and western blot were used to assess the impact of miR-204-5p on Cdc42 a target of miR-204-5p. The impact of the Cdc42 modulation was investigated using silencing strategy.

Results: FACS analysis revealed that miR-204-5p was associated with an overexpression of the two subunits of the GPIIbIIIa at the surface of PLS. Moreover, miR-204-5p increased the expression of the activated form of GPIIbIIIa and binding of PLS to both immobilized and soluble fibrinogen.

MiR-204-5p transfection decreased both Cdc42 mRNA and protein level in human-derived cells. Silencing of Cdc42 induced similar results than miR-204-5p transfection.

Conclusions: We functionally validated miR-204-5p as a regulator of platelet reactivity that occurs through the regulation of the fibrinogen receptor expression and activation. These data support a potential role of miR-204-5p as a biomarker of platelet reactivity and cardiovascular outcome.

Disclosure: Nothing to disclose

O6

Spatio-temporal fibrin clot formation is increased in patients with liver cirrhosis

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Introduction: Liver cirrhosis (LC) is a prothrombotic condition. However, it remains difficult to assess the individual haemostatic imbalance and to individualise the prevention of thrombotic and bleeding complications in LC-patients. Thrombodynamics (Hemacore, Moscow, Russia) is a novel global assay assessing the spatio-temporal propagation of fibrin clot formation. This could be of particular interest in LC-patients.

Method: This is a study including LC-patients (n=132) from all aetiologies and severities at the Lausanne University Hospital. Thrombodynamics was performed using PLS-reagents (Hemacore) according to manufacturer instructions. Analyses were done with and without thrombomodulin (4 nM), which activates the protein C-pathway. Parameters of interest were: initial clot formation velocity (Vi), stationary clot formation velocity (V) and clot size (CS). Results were compared to healthy donors using T-/Mann-Whitney test.

Results: Vi did not differ between LC-patients and controls. V was significantly higher than in controls already without thrombomodulin, while CS did not differ. With thrombomodulin, both V and CS were significantly higher in LC-patients compared to controls

Conclusion: Using a novel test assessing the spatio-temporal fibrin clot formation, we observed a prothrombotic state in LC-patients. Indeed, the stationary velocity (V) was higher in LC-patients, possibly indicating a hyperactive amplification loop of coagulation compared to controls. This prothrombotic profile tended to increase with thrombomodulin. In sum, the spatio-temporal analysis of clot formation confirmed a prothrombotic state in LC-patients. Thrombodynamics seems to be a promising tool for identifying LC-patients at increased thrombotic risk. Further studies are needed to confirm this observation and to elucidate the underlying mechanisms.

Disclosure: Nothing to disclose

Topic: Clinical hemato-oncology (lymphoma, myeloma, leukemia, transplantation for SSH and SSMO) (SSH/SSMO award for clinical hemato-oncology)

O7

A randomized evaluation of vinorelbine versus gemcitabine chemotherapy mobilization of stem cells in myeloma patients

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Background: In myeloma patients, a non-myelosuppressive regimen combining a single dose of vinorelbine chemotherapy together with G-CSF is effective to harvest peripheral blood progenitor and stem cells (PBSC) before ASCT. Considering its neurotoxic potential, vinorelbine may aggravate pre-existing bortezomib-induced polyneuropathy, and gemcitabine represents an alternative mobilization regimen.

Methods: In this prospective phase-II study (ViGeM Trial; NCT# 02791373), we compared in a 1:1 randomization vinorelbine or gemcitabine with G-CSF in 130 evaluable myeloma patients in first remission. The primary endpoint is mobilization success defined as apheresis product comprising at least 6.0×106 CD34+ cells/kg b.w. at day 8 after chemotherapy.

Results: We observed successful CD34+ mobilization in 75% [95% CI: 63%-85%] of patients in the vinorelbine group versus 49% [95% CI: 36%-62%] with gemcitabine; the pre-specified non-inferiority margin -15% was not reached. More vinorelbine recipients achieved the collection goal in a single-day procedure (78% vs 60%). The median CD34+ yield was 11.4×106/kg b.w. in vinorelbine versus 8.7×106/kg in gemcitabine (P=0.001). At apheresis and day +100 following ASCT, polyneuropathy occurred more frequently in vinorelbine recipients. Special attention should be given to the fact that no patients with gemcitabine was observed with grade ≥ 3 polyneuropathy. Finally, less patients in the vinorelbine group (1%) needed two apheresis days as compared to 14% in the gemcitabine group(P=0.007).

Conclusion: This comparison indicated that non-inferiority of gemcitabine and vinorelbine chemotherapy regarding CD34+ mobilization was not reached. Polyneuropathy was aggravated in vinorelbine, but not in gemcitabine recipients. Our study allows individualization of CD34+ mobilization regimens in myeloma patients.

Table 1. Mobilization and Apheresis with vinorelbine and gemcitabine combined with G-CSF. Successful mobilization was defined by a harvest of at least 6.0×10^6 CD34+ cells/kg b.w. at day 8, in a single-day procedure without the use of plerixafor.

Parameter	Vinorelbine n=67		Gemcitabine n=63		*P*-value
	n (%)	95% CI	n (%)	95% CI	
Mobilization successful at day +8	52* (78%)	[66%-87%]	31 (49%)	[36%-62%]	0.947†
≥6x10^6 cells in single day apheresis‡	52 (78%)	[66%-87%]	38 (60%)	[47%-72%]	0.038
≥6x10^6 cells in 2 apheresis days	1 (1%)	[0%-8%]	9 (14%)	[7%-25%]	0.007
≥6x10^6 cells in >2 apheresis days	1 (1%)	[0%-8%]	1 (2%)	[0%-9%]	1.0
≥2.0x10^6, but <6.0x10^6 cells	13 (20%)	[11%-34%]	15 (24%)	[13%-39%]	0.745
not achieving 2.0x10^6 cells	0 (0%)		0 (0%)		1.0
Plerixafor use	11 (16%)	[9%-28%]	6 (10%)	[4%-20%]	0.303
	Median	**Range**	**Median**	**Range**	
Peripheral leukocytes, day +8, G/L	16.7	(2.08-51.6)	35	(2.5–79.3)	<0.0001
CD34+ collection					
CD34+ cells in PB at day +8 (×10^6/L)	68.0	(1.7-223.3)	39.1	(0.9-400.6)	0.050
Total collected CD34+ cells (×10^6/kg b.w.)	11.4	(3.7–27.9)	8.7	(1.3–26.3)	0.001

Disclosure: Nothing to disclose

O8

Prophylactic corticosteroid use prevents engraftment syndrome in patients after autologous stem cell transplantation

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Introduction: Engraftment syndrome (ES) following autologous stem cell transplantation (ASCT) at the time of neutrophil recovery may comprise fever, rash, pulmonary edema or diarrhea. Usually, ES is easily manageable using corticosteroids but it may prolong hospitalization and lead to additional diagnostic/therapeutic procedures with increased costs.

Methods: In two consecutive cohorts of patients with myeloma, lymphoma types, and testicular/germ cell cancer, we assessed the benefit of corticosteroid use to prevent incidence and severity of ES following ASCT. Whereas cohort A (82 patients) received no prophylactic corticosteroids, 4 mg dexamethasone p.o. was given in a subsequent cohort B (60 patients) at day +9 until day +13 following ASCT. The diagnosis of ES was following criteria proposed by Maiolino (fever over 38.0°C and skin rash, pulmonary infiltrates or diarrhea) and by Spitzer (fever over 38.3°C, rash, pulmonary infiltrates, hepatic dysfunction, renal failure, weight gain and encephalopathy).

Results: Steroid prophylaxis significantly reduced the incidence of ES following Maiolino criteria (33/82; 40.0% vs 6/60; 10.0%; p< 0.001) and ES following Spitzer criteria (10/82; 12.2% vs 1/60; 1.7%; p=0.025). Hospitalization duration was longer in patients with ES than in patients without ES in both cohorts (cohort A: p=0.007; and B: p=0.011), but did not differ significantly between cohorts A and B. Finally, overall survival tended to be better for cohort A in patients without ES compared to patients with ES (p=0.066).

Conclusion: Our results suggest that corticosteroid prophylaxis from days +9 to +13 following ASCT significantly reduces the risk of engraftment syndrome and shortens hospitalization duration.

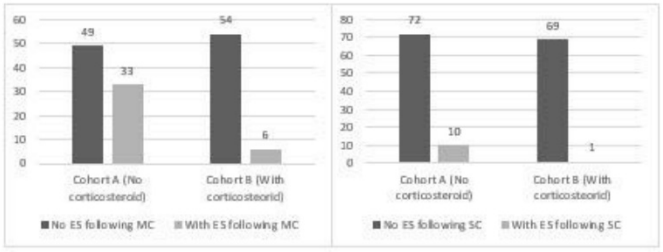

Figure: Incidence of Engraftment syndrome in both cohorts (Cohort A without prophylactic corticosteroids; cohort B with prophylactic corticosteroids), following Maiolino criteria (MC) and Spitzer criteria (SC), respectively.

Disclosure: Nothing to disclose

O9

Clonal hematopoiesis of indeterminate potential after autologous stem cell transplantation does not confer adverse prognosis in patients with AML

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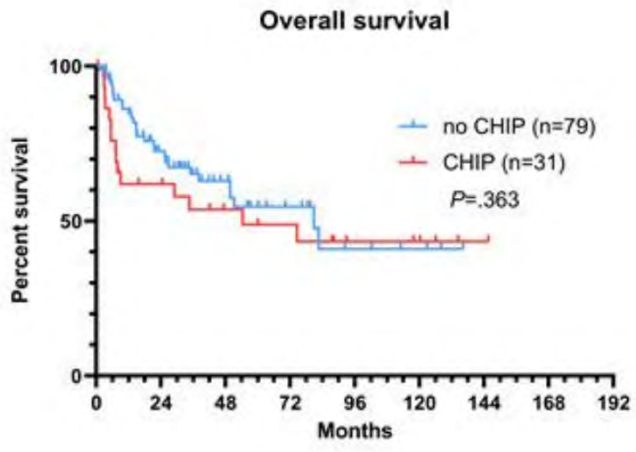
Introduction: Relapse remains the main cause of death in AML patients consolidated with autologous stem cell transplantation (ASCT) in first remission. Clonal hematopoiesis of indeterminate potential (CHIP) defines expansion of myeloid precursor cells in individuals without established hematological disease. CHIP can be part of the normal aging process, but increases the risk for hematological and cardiovascular disorders and death. The impact of CHIP persisting after ASCT in AML patients is unclear.

Materials/Methods: We retrospectively investigated the prognostic value of persisting *DNMT3A*, *TET2* or *ASXL1* (DTA) mutations after ASCT. Patients were stratified depending on the presence or absence of DTA mutations and survival rates were compared.

Results: We identified 110 consecutive patients with AML receiving ASCT in first remission after two cycles of intensive chemotherapy induction at our center between 2007 and 2020. Baseline characteristics including ELN risk groups were equally distributed between patients with or without persisting DTA mutations after ASCT. CHIP-related mutations were present in 31 patients (28.2%) after ASCT. We found no significant differences in survival rates between the two groups (median PFS 26.9 vs. 7.1 months, *P*=.155; median OS 80.9 vs. 54.4 months, *P*=.363, Fig. 1). HR for PFS were 0.68 (0.39-1.22) and for OS 0.75 (0.39-1.45).

Conclusion: Our data suggest that CHIP after ASCT is not associated with increased risk for relapse or death. Persistence of DTA mutations after induction treatment should not prevent appropriate AML patients in first remission from ASCT consolidation. However, longer follow-up and larger cohorts are needed to ultimately clarify this issue.



Disclosure: Nothing to disclose

O10

The AML EBMT Cytogenetic Risk Score for acute myeloid leukaemia (AML) is prognostic for outcomes of allogeneic stem cell (HSCT)

Y. Beauverd, S. Morin, M. Nabergoj, C. Stephan, C. De Ramon Ortiz, A.-C. Mamez, E. Mahne, A. Petropoulou, F. Giannotti, F. Simonetta, C. Ayer, B. Bruno, L. Bounaix, M. Anastasiou, M. Mappoura, T.-A. Tran, S. Masouridi-Levrat, Y. Chalandon

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Background: The AML EBMT Cytogenetic Risk score is a new prognostic model recently published (Canaani et al. Leukemia. 2019 Aug;33(8):1944-1952; Nagler el al. Am J Hematol. 2020 Jun 12) combining cytogenetics and *FLT3*ITD status for AML patients in complete remission (CR) at transplant time. The AML EBMT Cytogenetic Risk score is prognostic for leukemia-free survival (LFS), overall survival (OS), GVHD-free/relapse-free survival (GRFS) and cumulative incidence of relapse (CIR). In our centre, we frequently offer *in-vitro* partial T-cell de-

pleted graft (pTDEP) for patient in CR to decrease morbidity and mortality associated with graft-versus-host disease (GvHD). Currently, The AML EBMT Cytogenetic Risk score has not been evaluated in this population.

Aims: We investigate the impact of the AML EBMT Cytogenetic Risk score for 3 years OS, LFS, GRFS, CIR and NRM in a cohort with patients allografted with pTDEP graft.

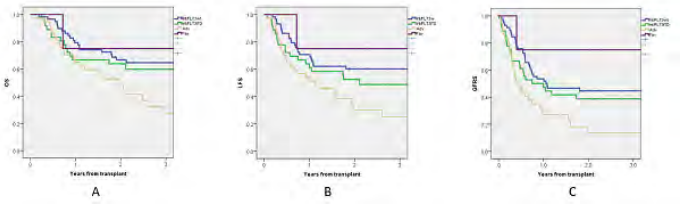
Methods: All consecutive ≥18 years patients who received a first allograft for AML between 2008 and 2018 with data available to determine The AML EBMT Cytogenetic Risk score in CR at transplant time were included. OS and LFS were investigated with the Kaplan-Meier method and we used the cumulative incidence estimator as defined by Fine and Gray to calculate CIR (with NRM as competing event), NRM (with relapse as competing event) and GvHD (with relapse as competing event).

Results: 135 patients were included, median age at transplant time was 56 years (range: 19-74), 44% were female, median Karnofsky index was 90 (80-100). 21% of graft were from HLA identical, 57% from matched unrelated donor, 10% from mismatched unrelated donor and 12% from haploidentical donor. Stem cell source was peripheral blood in 89% and bone marrow in 11%. Partial *in-vitro* T-cell depletion (pTDEP) was performed in 40% of HSCT. Reduced-intensity (RIC) was performed in 62%. Median follow-up was 3.1 year (range 1.3-10 years) for living patients.

Among the 135 patients, 4 (3%) were assigned in the favourable (Fav), 58 (43%) in the intermediate/FLT3wt (Int/*FLT3*wt), 36 (27%) in the intermediate/*FLT3*ITD (Int/*FLT3*ITD), and 37 (27%) in the adverse (adv) risk group.

3-years OS for Fav, Int/*FLT3*wt, Int/*FLT3*ITD and Adv was 75% (32-100%), 65% (52-77%), 60% (43-77%) and 28% (10-45%), respectively (p=0.033) (Fig 1A). 3-years LFS for Fav, Int/*FLT3*wt, Int/*FLT3*ITD and Adv was 75% (95%CI: 32-100%), 60% (47-73%), 49% (32-66%) and 25% (8-42%), respectively (p=0.028) (Fig 1B). 3-years GRFS for Fav, Int/*FLT3*wt, Int/*FLT3*ITD and Adv was 75% (32-100%), 45% (31-58%), 39% (22-55%) and 14% (0-27%), respectively (p=0.008) (Fig 1C). 3-years CIR for Fav, Int/*FLT3*wt, Int/*FLT3*ITD and Adv was 0%, 22% (11-33%), 31% (15-47%) and 56% (37-75%), respectively (p=0.02). 3-years NRM for Fav, Int/*FLT3*wt, Int/*FLT3*ITD and Adv was 25% (95%CI: 0-75%), 17% (7-28%), 21% (6-35%) and 17% (2-32%), respectively (p=0.92). 3-years grade 2-4 aGVHD for Fav, Int/*FLT3*wt, Int/*FLT3*ITD and Adv was 0%, 35% (22-47%), 19% (2-36%) and 42% (25-58%), respectively (p=0.46). 3-years cGVHD for Fav, Int/*FLT3*wt, Int/*FLT3*ITD and Adv was 25% (95%CI: 0-75%), 17% (6-27%), 22% (7-38%) and 21% (6-35%), respectively (p=0.9). In addition to The AML EBMT Cytogenetic Risk score, variables with a significance in univariate for OS with a p-value ≤0.1 (Karnofsky index [< 90 vs. ≥90]; stem cell source [PBSC vs. BM] and donor type [matched vs mismatched donor]) and pTDEP were included in the multivariable model. In multivariable analysis, only the Cytogenetic Risk Score (Fav + Int/FLT3wt: ref; Int/FLT3ITD + Adv: HR: 1.8 [95%CI: 1.1-3.1], p-value 0.03) and Karnofsky index (< 90: ref; ≥90: HR 1.8 [95%CI: 1.0-3.2], p-value 0.049] remain significant. Because of the low number of patients in pTDEP (53) and non-pTDEP (82), statistical analysis couldn't be performed specifically in these subgroups but pTDEP had no impact in multivariable analysis for OS.

Conclusion: In the analysis of our retrospective cohort including 40% of pTDEP patients, we confirm that the AML EBMT cytogenetic risk is prognostic for relevant outcomes (OS, LFS, GRFS, CIR) of HSCT. Similarly with recently published data, we confirm this prognostic model can help physicians and patients in transplant choice and remains valid for patients undergoing HSCT with in-vitro graft manipulation.



Disclosure: Nothing to disclose

SSH/SSMO ORAL PRESENTATIONS EXPERIMENTAL HEMATOLOGY / ONCOLOGY & CLINICAL SOLID TUMOR ONCOLOGY

Topic: Clinical solid tumor oncology (SSMO award for clinical solid tumor oncology)

O11

Selpercatinib (LOXO-292) in patients with RET-fusion+ non-small-cell lung cancer

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Background: Selpercatinib (LOXO-292) is a highly selective and potent small-molecule RET kinase inhibitor. We report an update on selpercatinib's efficacy and safety in RET-fusion+ non-small-cell lung cancer (NSCLC).

Methods: Patients with RET-fusion+ NSCLC were enrolled to global, multicentre, Phase 1/2 LIBRETTO-001 trial. Following Phase 1 dose escalation, patients received the recommended dose (160mg orally BID). Primary endpoint: objective response rate (ORR). Secondary endpoints included duration of response (DoR) and safety. Primary analysis set was defined as the first 105 enrolled patients previously treated with platinum-based chemotherapy. Treatment-naïve patients were analyzed separately. Cutoff date for all analyses:16-Dec-2019.

Results: In the primary analysis set (platinum-treated patients, median 3 prior systemic regimens; range 1-15), investigator-assessed ORR: 70%(95%CI=59.8-78.1, n=73/105). Responses did not differ by fusion partner or number/type of prior therapies, including anti-PD-1/PD-L1 agents and off-label multikinase inhibitors. Median DoR:20.3 months (95%CI=15.6-24.0) (45/73[62%] responders censored at median follow-up of 14.8 months). Among 39 treatment-naïve patients, investigator-assessed ORR: 90%(95%CI=75.8-97.1, n=35/39 [2 responses pending confirmation]). Median DoR was not reached (27/33[82%] confirmed responses ongoing at median follow-up of 7.4 months). Safety analysis set comprised all selpercatinib dosed patients (N=702), most common treatment-related adverse events (TRAEs) occurring in ≥15% patients: dry mouth(33.3%), increased AST(24.5%), increased ALT(23.8%), hypertension(23.2%), diarrhea(19.7%), fatigue(16.8%). Only 2% (n=14/702) patients discontinued selpercatinib for TRAEs.

Conclusions: Selpercatinib achieved marked and durable antitumor activity in patients with RET-fusion+ NSCLC. Selpercatinib was well tolerated. Efficacy data assessed by independent review committee based on the cutoff date will be presented.

Disclosure: Goto:grants:Xcoo, Inc, grants and personal fees:Lilly, Technologies Japan, Janssen Pharmaceutical, Kyowa Hakko Kirin, DAIICHI SANKYO, Astellas Pharma, Thermo Fisher Scientific, MSD, AstraZeneca, Novartis, Pfizer, Merck Serono, TAIHO PHARMACEUTICAL, CHUGAI PHARMACEUTICAL, Nippon Boehringer Ingelheim, Takeda Pharmaceutical Company, personal fees:AbbVie GK, NIPPON KAYAKU, IQVIA Services Japan, Otsuka Pharmaceutical, Guardant Health, grants:Eisai, Sumitomo Dainippon Pharma, RIKEN GENESIS, Ignyta, Inc., Loxo Oncology, Inc., Sysmex Corporation, MEDICAL & BIOLOGICAL LABORA-TORIES, Amgen, outside the submitted work; G Oxnard reports consulting fees:AstraZeneca, Abbvie, Illumina, Inivata, Janssen, Sysmex, and honoraria:Foundation Medicine; Dr. Loong reports personal fees:Boehringer-Ingelheim, Celgene, Pfizer, Eli-Lilly, grants and personal fees:Novartis, Merck, Sharp & Dohme, personal fees:Bayer, Guardant Health, Eisai, grants:Mundipharma, outside the submitted work; Dr. Bauer reports grants from XXX, during the conduct of the study; grants:Daiichi Sankyo, Medpacto, Incyte, Mirati Therapeutics, MedImmune, Abbvie, AstraZeneca, MabVax, Stemline Therapeutics, Merck, Lilly, GlaxoSmithKline, Novartis, Genentech, Deciphera, Merrimack, Immunogen, Millennium, Phosplatin Therapeutics, Calithera Biosciences, Kolltan Pharmaceuticals, Principa Biopharma, Peleton, Immunocore, Roche, Aileron Therapeutics, Bristol-Myers Squibb, Amgen, Onyx, Sanofi, Boehringer-Ingelheim, Astellas Pharma, Five Prime Therapeutics, Jacobio, Top Alliance BioScience, Janssen, Clovis Oncology, Takeda, Karyopharm Therapeutics, Foundation Medicine, ARMO Biosciences, grants and other from Leap Therapeutics, grants, non-financial support and other from Ignyta, grants, non-financial support and other from Moderna Therapeutics, grants, personal fees and other from Pfizer, grants, personal fees and non-financial support from Loxo, grants, personal fees and non-financial support from Bayer, Guardant Health, personal fees from Exelesis, outside the submitted work; Dr. Drilon reports other from AstraZeneca, other from Loxo/Bayer/Lilly, other from Pfizer , other from Roche/Genentech, Exelixis , Takeda/Ariad/Millenium, TP Therapeutics, Blueprint Medicines, Helsinn, Beigene, BergenBio, Hengrui Therapeutics, Tyra Biosciences, Verastem, MORE Health, Abbvie, outside the submitted work

O12

Selpercatinib (LOXO-292) in patients with RET-mutant medullary thyroid cancer (MTC)

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Background: Selpercatinib (LOXO-292) is a highly selective and potent small-molecule RET kinase inhibitor. We report selpercatinib's efficacy and safety in RET-mutant MTC.

Methods: Patients with RET-mutant MTC were enrolled to the global, multicentre Phase 1/2 LIBRETTO-001 trial. Following Phase-1 dose escalation, patients received the recommended dose (160mg orally BID). Primary endpoint: objective response rate (ORR). Secondary endpoints included duration of response (DoR) and safety. Primary analysis set was defined as the first 55 enrolled patients previously treated with cabozantinib and/or vandetanib. Patients naïve to cabozantinib and vandetanib were analysed separately. Cut-off date for all analyses:16-Dec-2019.

Results: In the primary analysis set (prior cabozantinib and/or vandetanib-treated patients [n=55]), investigator-assessed ORR was 62%(95%CI=47.7-74.6, n=34/55) and median DoR was not reached (95%CI=18.4 months-not estimable) despite median follow-up of 14.8 months. In treatment-naïve patients (n=88), investigator-assessed ORR was 69%(95%CI=58.6-78.7, n=61/88 [2 responses pending confirmation]). Of 59 confirmed responding patients (median follow-up:8 months), responses were ongoing for 57 responders at time of analysis. Safety analysis comprised all selpercatinib-dosed patients (N=702); most common treatment-related adverse events (TRAEs) occurring in ≥15%patients: dry mouth(33.3%), increased AST(24.5%), increased ALT(23.8%), hypertension(23.2%), diarrhoea(19.7%), fatigue(16.8%). 2% (n=14/702) of patients discontinued selpercatinib for TRAEs.

Conclusions: Selpercatinib achieved marked and durable antitumor activity in prior cabozantinib and/or vandetanib-treated patients and in

cabozantinib/vandetanib-naïve patients with RET-mutant MTC. Selpercatinib was well tolerated. Efficacy data assessed by independent review committee based on the cut-off date will be presented.

Disclosure: BR:Personal fees:Eisai,LOXO, outside the submitted work; BS:personal fees:Loxo Oncology, during the conduct of the study; personal fees:AstraZeneca,Novartis, grants and personal fees:Pfizer, Roche/Genentech,Bristol Myers Squibb,Merck,Gritstone Oncology, outside the submitted work; MB:grants:University of Pennsylvania School of Medicine, during the conduct of the study; personal fees:Loxo Oncology,Lilly Oncology,Exelixis,Blueprint Medicines, outside the submitted work.

O13

MONARCH 2: subgroup analysis of patients receiving abemaciclib+fulvestrant as first- and second-line therapy for HR+, HER2- advanced breast cancer (ABC)

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Background: In MONARCH 2 (M2), abemaciclib+fulvestrant demonstrated statistically significant improvements in PFS and OS versus placebo+fulvestrant in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) ABC. Numerically more pronounced PFS and OS improvement was noted in subgroups with visceral disease and primary endocrine resistance. We report efficacy data for M2 with respect to 1L and 2L subgroups (last line of endocrine therapy [ET] in (neo)adjuvant and metastatic setting, respectively).

Methods: In M2 (global, randomised, double-blind Phase3 trial of abemaciclib+fulvestrant [N=446]/placebo+fulvestrant [N=223]), women with ET-resistant (ETR), HR+, HER2- ABC regardless of menopausal status were stratified by site of metastasis (visceral, bone-only, other) and resistance to prior ET (primary versus secondary). Exploratory subgroup analyses of PFS and OS were conducted in ITT patients with 1L versus 2L. Hazard ratios (HR) were estimated using Cox models.

Results: At data cut-off (June-20-2019), effect of abemaciclib+fulvestrant versus placebo+fulvestrant was consistent across 1L (N=265/133) and 2L (N=170/86) subgroups (no statistically significant interaction for PFS[p=0.341] or OS[p=0.265]). For 1L patients, PFS(HR=0.57; 95%CI=0.45,0.73) and OS(HR=0.85; 95%CI=0.64, 1.14) improved. Similar efficacy results were observed for 2L patients (PFS: HR=0.48[95%CI=0.36,0.64]; OS: HR=0.66[95%CI=0.46,0.94]). Numerically largest effects in 1L population were noted in patients with less favourable prognostic factors like primary ETR (PFS: HR=0.40[95%CI=0.26,0.63]; OS: HR=0.58[95%CI=0.35, 0.97]) and visceral disease (PFS: HR=0.54[95% CI=0.39,0.73]; OS: HR=0.82[95%CI=0.57, 1.17]).

Conclusion: Statistically significant benefit observed in M2 was consistent across 1L and 2L patients. In 1L patients (abemaciclib+fulvestrant), PFS and OS improved (most pronounced effects noted in patients with less favourable prognostic factors).

O14

Treatment compliance and early toxicity in SAKK 01/10: single-dose carboplatin and involved-node radiotherapy for treatment of stage IIA/B seminoma

A. Papachristofilou[1], J. Bedke[2], S. Hayoz[3], N. Fischer[4], X. Schiel[5], U. Schratzenstaller[1], S. Krege[6], A. Lorch[7], D.M. Aebersold[8], P.M. Putora[9], D.R. Berthold[10], D. Zihler[11], N.C. Azinwi[12], F. Zengerling[13], A. Dieing[14], A.C. Mueller[2], R. Cathomas[15], SAKK, GTCSG

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Background: Standard treatment options for stage IIA/B seminoma include extensive paraaortal/pelvic radiotherapy or intensive chemotherapy with 3x BEP/4x EP. Both treatment modalities are highly efficient but can lead to acute and late toxicities. De-escalation strategies aim to minimize toxicities while maintaining efficacy.

Methods: Patients with stage IIA/B seminoma (de novo or relapse on active surveillance) were included in this single arm phase II trial. Treatment consisted of one cycle carboplatin AUC7 followed by involved-node radiotherapy (30 Gy stage IIA; 36 Gy stage IIB). The primary endpoint of the trial is 3-year progression free survival. We report on treatment compliance and early toxicity.

Results: 120 patients with stage IIA/B seminoma were recruited from 10/12 until 06/18 in 20 study centers. 116 patients were eligible. Median applied dose of carboplatin was 984 mg. Median planning target volume for radiotherapy was 297 cm³. Radiotherapy was delayed/interrupted in two patients due to adverse events. During chemotherapy, grade 2 and grade 3 adverse events were seen in 21% and 2% of all patients respectively (most common grade 2 events: neutropenia 6%, nausea 5%). During RT, grade 2 and grade 3 adverse events were seen in 26% and 6% of all patients respectively (most common grade 2 events: neutropenia 15%, nausea 6%). One case of transient creatinine increase was reported as a severe adverse event, resolving without sequelae.

Conclusions: Treatment with one cycle carboplatin AUC7 and 30-36 Gy involved-node radiotherapy for stage IIA/B seminoma is feasible and demonstrates a very favorable early toxicity profile.

Disclosure: Nothing to disclose

EXPERIMENTAL HEMATOLOGY / ONCOLOGY (SSH/SSMO AWARD FOR EXPERIMENTAL HEMATOLOGY / ONCOLOGY)

O15

JAK2-V617F mutant clone requires IL-1β for its expansion and optimal MPN disease initiation

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Myeloproliferative neoplasm (MPN) are clonal disorders of the hematopoietic stem cell (HSC). *JAK2*-V617F is the most frequent driver gene mutation in MPN, but *JAK2*-V617F can also be found in healthy individuals with clonal hematopoiesis of indeterminate potential (CHIP). We therefore examined factors that might favor transition from CHIP to MPN and hypothesized that inflammation mediated by IL-1β promotes early expansion of the *JAK2*-V617F clone to reach a critical clone size capable of initiating MPN. To test our hypothesis, we used a *JAK2*-V617F mouse model and performed competitive transplantations at high dilution into lethally irradiated wildtype recipients (Figure 1A). 36 weeks after transplantation, 14/29 (48%) mice transplanted with *VF;GFP* bone marrow (BM) cells developed MPN phenotype as compared to only 4/29 (14%) mice transplanted with *VF;IL16$^{-/-}$;GFP* cells, suggesting that indeed the loss of IL1β in donor BM reduced MPN initiation. GFP chimerism in the peripheral blood was significantly reduced in mice transplanted with *VF;IL16$^{-/-}$;GFP*, suggesting that IL-1β protein was required for promoting the expansion of the MPN clone (Figure 1A). IL-1β levels were elevated in BM and plasma of mice that developed MPN phenotype and originated from *VF;GFP* cells (Figure 1B). Interestingly, IL-1β levels were very low in all wildtype recipients transplanted with *VF;IL16$^{-/-}$;GFP* cells, indicating that the non-hematopoietic wildtype cells of recipient mice cannot increase IL1β levels. Overall, our results show that IL-1β secreted by *JAK2*-mutant cells is required for optimal MPN disease initiation and suggests that inflammation is a factor favoring the transition from CHIP to MPN.

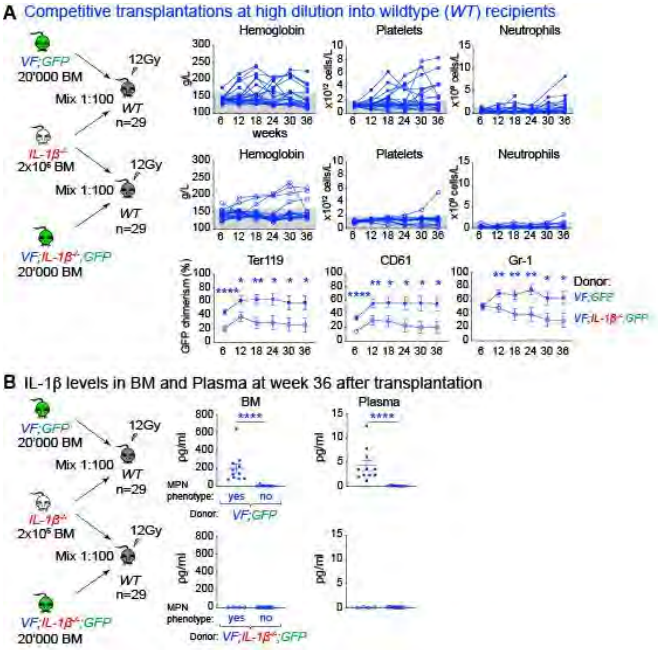

Figure 1 Legend:

1A) Competitive transplantation at high dilution into WT recipients:

Bone marrow (BM) cells co-expressing *JAK2*-V617F and a GFP reporter (*VF;GFP*) mixed with an excess of *IL1β$^{-/-}$* BM competitor cells at a 1:100 ratio and transplanted into lethally irradiated *WT* recipients. In comparison, to test the effects of IL1β deficiency, BM cells from *VF;IL1β$^{-/-}$;GFP* donor mice were used. Complete blood counts measured every 6 weeks after transplantation.

Grey shaded area represents normal range (upper panel). GFP chimerism in erythroid (Ter119+), megakaryocytic (CD61+) and granulocytic lineages (Gr-1+) are shown (bottom panel). All data are presented as mean ± SEM.

Multiple t tests analyses were used for multiple group comparisons. *P < .05; **P < .01; ***P < .001, ****P < .0001.

1B) IL-1β protein levels in BM and Plasma at week 36 after transplanation:

ELISA result showing levels of IL-1β in BM and plasma in mice transplanted with *VF;GFP* BM cells (upper panel) and *VF;IL1β$^{-/-}$;GFP* BM cells (bottom panel). Green dashed line at y-axis represents Lower Limit of Detection (LLOD) of IL-1β.

All data are presented as mean ± SEM. Non-parametric t tests were performed for statistical comparison.

*P < .05; **P < .01; ***P < .001, ****P < .0001.

Disclosure: Nothing to disclose

O16

Dual genetic targeting of ERK1 and ERK2 reduces the fitness of the malignant clone in myeloproliferative neoplasm mice

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Introduction: Myeloproliferative neoplasms (MPN) are chronic leukemias with dysregulated Jak2 signaling. We hypothesized that genetic targeting of ERK1/2 could enhance control of the MPN clone by preventing MAPK pathway activation.

Methods: We genetically targeted ERK1/2 in MPN by introducing ERK1/2 knockout alleles and hematopoiesis-specific Mx-Cre in Jak2V617F mice. To assess engraftment and competitive fitness of the MPN clone, CD45.2 Jak2V617F bone marrow (BM) +/- ERK1$^{-/-}$ ERK2$^{fl/fl}$ was competitively transplanted with CD45.1 Jak2 WT BM.

Results: Loss of ERK1/2 in Jak2V617F Ba/F3 cells reduced cells growth by 60% and potentiated Jak2 inhibition by ruxolitinib. In MPN mice, it moderated splenomegaly and excessive erythropoiesis including red cells, reticulocytes and erythroid progenitors. Hematopoietic stem/progenitor compartments were reduced and myeloid colony formation diminished in Jak2V617F ERK1$^{-/-}$ ERK2$^{fl/fl}$ mice, suggesting reduced disease-initiating cells. In competitive transplants, ERK1/2 loss significantly reduced the Jak2V617F MPN clone in peripheral blood, BM, myeloid and erythroid progenitors. Myeloid colonies emerging from Jak2V617F ERK1$^{-/-}$ ERK2$^{fl/fl}$:WT competitively transplanted mice were predominantly Jak2 WT as compared to settings with intact ERK. Polyglobulia was normalized and BM fibrosis prevented in recipients of Jak2V617F ERK1$^{-/-}$ ERK2$^{fl/fl}$ BM. ERK1/2 deletion combined with Jak2 inhibition with ruxolitinib enhanced therapeutic efficacy with extensive reduction of the MPN clone and correction of the MPN phenotype.

Conclusions: ERK1/2 loss abrogates the competitive fitness of the MPN clone by restricting stem/progenitor compartments and cooperates with JAK2 inhibition resulting in correction of MPN features. Our data suggest targeting of ERK1/ERK2 in combination with JAK2 inhibition as an enhanced therapeutic strategy in MPN.

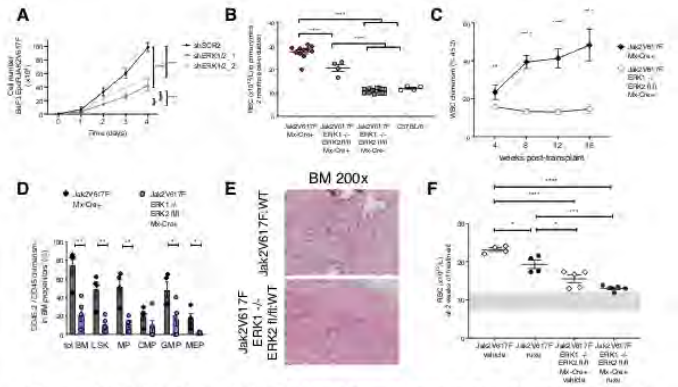

Fig. 1 Genetic deletion of ERK1 and ERK2 kinases impairs the JAK2V617F clone in myeloproliferative neoplasms (MPN). **A** ERK1 and ERK2 knock-down by shRNA in JAK2VF Ba/F3 cells reduced cells growth by 60%. **B** Ablation of ERK1 and ERK2 in MPN primary mice reduces red blood cell counts. **C** Competitive bone marrow (BM) transplantation 1:1 with wild-type BM shows a smaller JAK2V617F clone by CD45.2 chimerism in peripheral blood of mice where ERK1 and ERK2 were targeted. **D** The malignant clone was significantly reduced in BM and stem/progenitor cells 16-weeks after transplantation, and BM fibrosis was prevented **(E). F** Combined ERK deletion and JAK2 inhibition by ruxolitinib was more effective in correcting erythrocytosis than ruxolitinib alone.

Disclosure: Nothing to disclose

O17

Combined JAK2 and ERK1/2 kinase inhibition as a potent therapeutic approach in myeloproliferative neoplasms

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Background: Myeloproliferative neoplasms show dysregulated JAK2 signaling, but clinical JAK2 inhibitors have limited benefits. We demonstrated that compensatory MAPK pathway activation limits JAK2 inhibitor efficacy in vivo and combined JAK2/MEK inhibition improved therapeutic efficacy. We hypothesized that inhibition of ERK1/2 kinases, which are distal in the MAPK pathway and essential for hematopoiesis, could be more potent and less prone to compensatory feedback.

Methods: We assessed ERK inhibitors interfering with ATP binding (LTT462, MK-8353) or ERK dimerization (DEL-22379) as single agents and in combination with the JAK2 inhibitor ruxolitinib. Effects were studied in CD34+ cells from blood and bone marrow of *JAK2*V617F-mutant patients including PV, ET and PMF as well as MPN cell lines and a *Jak2*V617F-mutant MPN mouse model. *MPL*W515L-mutant mice were particularly assessed for myelofibrosis.

Results: Combined JAK/ERK inhibition suppressed colony formation from CD34+ blood and BM cells from MPN patients and proliferation of *Jak2*V617F-mutant cells more potently than ruxolitinib alone and suggested higher susceptibility of *Jak2*V617F vs. wild-type cells. In *Jak2*V617F mice, ruxolitinib monotherapy was unable to inhibit ERK activation, whereas combined LTT462/ruxolitinib suppressed ERK signaling. LTT462/ruxolitinib was superior in reduction of splenomegaly, hematocrit and erythroid progenitor compartments. BM fibrosis in *MPL*W515L mice was reduced to an extent not seen with JAK2 inhibitor monotherapy. There was moderate, but consistent reduction of the MPN clone in both mouse models.

Conclusion: Our data demonstrate that ERK kinase activation should be targeted to enhance the corrective potential in MPN and that dual inhibition of JAK2 and ERK1/2 increases therapeutic efficacy.

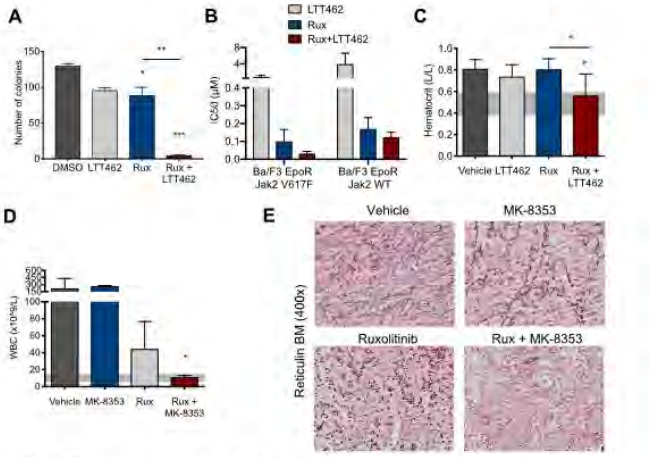

Figure 1. Pharmacologic targeting of ERK1/2 in patient samples, MPN cells and *JAK2*V617F and MPLW5151L mutant mouse models. Combined ERK (LTT462) and JAK2 (ruxolitinib) inhibition suppressed growth of the colonies derived from CD34+ peripheral blood mononuclear cells (PBMCs) from MF patient more potently then JAK inhibitor alone (**A**). Combination of JAK and ERK inhibitor further suppressed proliferation of EpoR *Jak2*V617F mutant Ba/F3 cells as compared to ruxolitinib alone, as seen by a stronger decrease of the IC50 value. A potential preferential inhibition of *Jak2*V617F mutant cells over wild-type cells is also evident (**B**). Combined JAK2 and ERK inhibition resulted in superior reduction of hematocrit in *Jak2*V617F mice (**C**) and leukocytosis (**D**) and BM fibrosis (**E**) in *MPL*W515L mice.

Disclosure: Nothing to disclose

O18

Therapeutic resistance to the novel JAK2 inhibitor CHZ868 in MPN is dependent on MEK-ERK activation and is targetable

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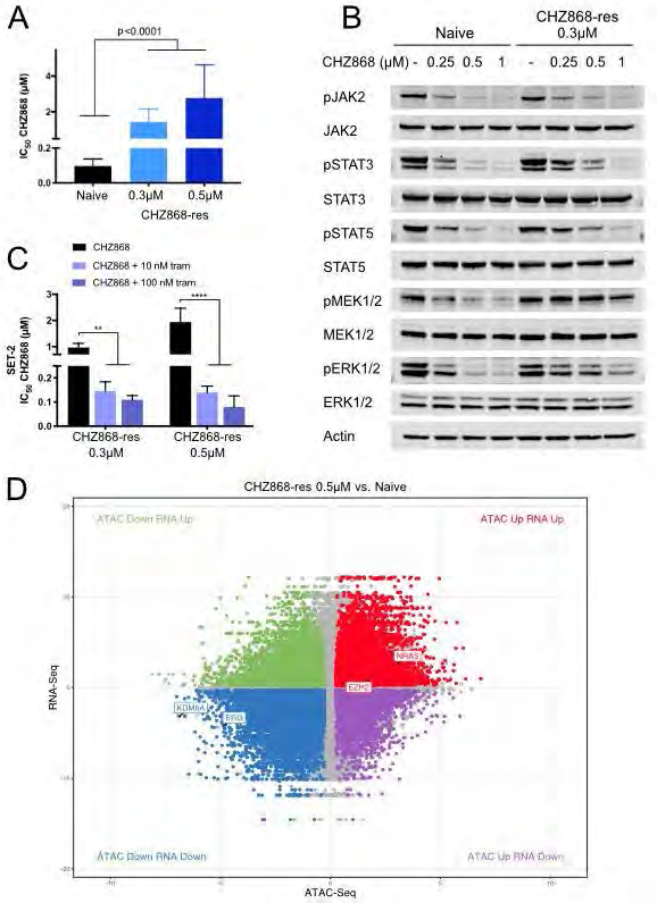
Myeloproliferative neoplasms (MPN) show constitutively activated JAK2 signaling. Clinically available JAK2 inhibitors as ruxolitinib are hampered by occurrence of resistance. The novel type II JAK2 inhibitor CHZ868 effectively inactivates JAK2, reduces the MPN clone and overcomes resistance to ruxolitinib. Here, we study whether type II JAK2 inhibition also elicits resistance and how it could be overcome.

Long-term exposure to CHZ868 evoked resistance in several *JAK2*V617F MPN cell lines (SET2, UKE-1) with >10-fold increased IC_{50} and absence of CHZ868-induced apoptosis (Figure 1A). CHZ868-resistant cells-maintained MAPK signalling reflected by MEK/ERK activation, while pSTAT3/5-axis remained responsive to CHZ868 (Figure 1B). Second-site JAK2 mutations were absent and resistance was reversible upon drug withdrawal suggesting adaptive processes mediating resistance. Paired ATAC-seq/RNA-seq revealed increased compaction of chromatin with enriched PRC2-complex signatures in the resistant cells (Figure 1D). Combined treatment with CHZ868 and trametinib, a clinical MEK inhibitor, abrogated CHZ868 resistance by blocking proliferation and inducing apoptosis (Figure 1C).

Our data show that resistance to type II JAK2 inhibition in MPN relates to adaptive chromatin remodelling and is dependent on MEK/ERK activation responsive to trametinib. These findings indicate combined JAK2 and MEK inhibition as a therapeutic approach for MPN, particularly in resistance settings.



Disclosure: Nothing to disclose

O19

Targeting the microenvironment in acute myeloid leukemia: benefits of "protumoral" macrophage reprogramming

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Acute myeloid leukemia (AML) is a poor prognosis hematological malignancy, with overall survival of < 50%. Relapse and resistance to therapy remain critical issues related to acquired gene mutations and malignant cell interactions with their microenvironment. Many studies indicate that

malignant cells can instruct surrounding cell populations to adopt immunosuppressive functions. Tumor-associated macrophages (MΦs) can be polarized on a spectrum from an anti-tumoral ("M1-like") to a protumoral ("M2-like") phenotype. We observe that MΦs with a protumoral "M2"-like orientation are predominant in the bone marrow of AML patients at diagnosis. Little information is yet available, in AMLs, on the role of macrophages in resistance to chemo and/or immunotherapies, which play a crucial role in the achievement of long-term complete remission. Our data indicate that myeloblasts can polarize macrophages to adopt a "protumoral" phenotype, which promotes in turn blast survival. Moreover, we show that reprogramming the protumoral, "M2-like" MΦs towards the anti-tumoral "M1" phenotype by targeting the CSF1 Receptor and MIF, reduces survival of primary patient AML cells and leukemia cell lines. Importantly, the re-orientation of macrophages reverses AML blast resistance to drugs used in the clinic (FLT3-ITD and Bcl-2 targeting inhibitors). Our initial in vivo experiments confirm our in vitro observations, that macrophages reprogramming, reduces leukemia cell proliferation, and has a dramatic effect on tumor vascularization, as evidenced by intravital multiphoton imaging. Deciphering the mechanisms controlling macrophage polarization and interactions with myeloblasts offers novel promising translational approaches in the treatment of AMLs.

Disclosure: Nothing to disclose

SOHC 2020 – POSTERS

Topic: Hemostasis, transfusion medicine, vascular, laboratory medicine (SSH award for hemostasis)

P1

Breakthrough haemolysis in ravulizumb-treated adult patients with paroxysmal nocturnal haemoglobinuria: results of a 52-week extension from two phase 3 studies

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Introduction: Approximately 11-27% of patients with paroxysmal nocturnal haemoglobinuria (PNH) treated with eculizumab may experience breakthrough haemolysis (BTH). Two phase-3 randomized, open-label trials [ALXN1210-PNH-301 (NCT02946463); 301; complement inhibitor-naïve patients and ALXN1210-PNH-302 NCT03056040; 302; patients stable on eculizumab], demonstrated that ravulizumab (q8w) was non-inferior to eculizumab (900mg q2w) across key efficacy endpoints, including BTH, after 26 weeks. This analysis assessed causes and clinical parameters associated with BTH in a 52-week extension.

Methods: Patients received ravulizumab or eculizumab for 26wks in both trials. In the extension, after 26wks, patients continued (R-R) or switched (E-R) to ravulizumab. BTH causation was categorized as related to suboptimal C5 inhibition, complement-amplifying conditions, or unrelated to either event.

Results: Study 301: Of the 243 patients entering the extension (R-R: n=124; E-R: n=119), 99% experienced no new BTH in 27-52wks. In 27-52wks, two BTH events (1 per group) were infection-associated and five (R-R=4; E-R=1) were unrelated to free C5 elevation or infection.

Study 302: Of the 191 patients entering the extension (R-R: n=96; E-R: n=95), majority of patients (R-R=97%; E-R=100%) experienced no new BTH incidents in 27-52wks. In 27-52wks, infection-associated BTH events included two in R-R group and one in E-R group; one BTH event in the R-R group was unrelated. No BTH incidents were associated with free C5 of >0.5 µg/mL during 27-52wks.

Conclusions: During 27-52wks, in both studies, no BTH events were associated with free C5 elevations in ravulizumab-treated patients. Of BTH events associated with infections was similar between groups, possibly due to proximal complement activation.

Disclosure: *Disclosures of presenting author PD. Dr. med. Alicia Rovó: Novartis: Consultancy, Honoraria, Advisory Board, Research Funding; CSL Behring: Research Funding; Alexion: Research Funding; Orphaswiss: Advisory Board. Celgene: Advisory Board Consultancy. AstraZeneca: advisory Board.

P2

Haemostatic alterations in a large Swiss cohort of patients with liver cirrhosis: a descriptive study

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Introduction: Patients with liver cirrhosis (LC) undergo deep and complex haemostatic changes and exhibit both haemorrhagic and thrombotic complications. The prevalence of these changes and the number and type of complications remain uncertain. Here, we present the data observed in a large Swiss cohort.

Method: This is an observational study at the Lausanne University Hospital, including patients with LC of various aetiologies and severities. Here, we focus on the prevalence of haemostatic complications, thrombocytopenia, and hypofibrinogenemia.

Results: Thus far, we included 336 LC-patients. Of these, 256 (76.2%) are classified Child-Pugh A, 62 (18.5%) B and 18 (5.4%) C. One hundred and twenty-nine (50.4%) A-patients, 51 (82.3%) B-patients and 15 (83.3%) C-patients developed thrombocytopenia [severity repartition: A) 10 (8%) severe, 51 (39%) moderate, 68 (53%) mild; B) 4 (8%), 30 (59%), 17 (33%) respectively; C) 4 (27%), 8 (53%), 3 (20%) respectively]. Moreover, 7.4% of the A-patients, 27.6% of the B-patients, and 72.2% of the C-patients presented a hypofibrinogenemia (< 2 g/l). Twenty-three (9.0%) A-patients, 10 (16.1%) B-patients and 3 (16.7%) C-patients developed splanchnic thromboses (36/336, 10.7%). Sixteen (6.3%) A-patients, 4 (6.5%) B-patients and 0 C-patients developed another venous thromboembolism (20/336, 6.0%). Forty-two (16.4%), 24 (38.7%), and 11 (61.1%) developed bleeding complications (77/336, 22.9%).

Conclusion: The prevalence of haemostatic alterations and frequency of haemostatic complications increase markedly with LC-severity, indicating more important and profound alterations in patients with more severe LC. A better understanding of prevalence and underlying mechanisms of these complications is needed to improve the management of these patients.

Disclosure: Nothing to disclose

P3

One-year efficacy and safety of the long acting C5 inhibitor ravulizumab for treatment of atypical haemolytic uraemic syndrome in adults

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Introduction: Ravulizumab is a long-acting C5 inhibitor that is dosed q8w. Ravulizumab was approved in the US and EU for patients with atypical haemolytic uraemic syndrome (aHUS) based on the phase 3 trial (NCT02949128) results at 26 weeks. The aim of the study was to evaluate longer-term efficacy and safety of ravulizumab obtained from the ongoing extension period.

Methods: This phase 3 trial was a single-arm, open label study in adults (≥18 years of age) with aHUS naïve to complement-inhibitor therapy. Ravulizumab was administered i.v. q8w.

Patients that completed the 26-week initial evaluation period could enter the extension period. The primary endpoint was complete TMA response (normalisation of platelet count, LDH, and ≥ 25% improvement in SCr from baseline; measured at 2 separate assessments, ≥28 days apart). Treatment-emergent AEs were evaluated. Here, interim cumulative data through at least 52 weeks are reported.

Results: Forty-seven of 56 patients received at least one dose of ravulizumab in the extension period. The proportion of patients achieving the individual components of complete TMA response improved during the extension period. At last follow-up, the number of patients achieving complete TMA response increased from 30/56 (53.6%) in the initial evaluation period to 34/56 (60.7%).

Although 3 new SAEs were reported during the extension period, there were no further fatal AEs. No meningococcal infections occurred through the last patient follow-up.

Conclusions: These results suggest that with ravulizumab further improvement in efficacy is possible with longer treatment, no compromise in safety and better convenience of 8-week dosing intervals.

Disclosure: Disclosure of presenting author PD. Dr. med. Hirt-Minkowski: Advisory boards from Alexion Pharmaceuticals, Inc. Boston MA

P4

Epinephrine enhances platelet aggregation at the expense of procoagulant activity

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Background: Platelet activation is characterized by shape change, granule secretion, activation of fibrinogen receptor (glycoprotein [GP] IIb/IIIa) sustaining platelet aggregation, and externalization of negatively-charged aminophospholipids contributing to platelet procoagulant activity. Epinephrine alone is a weak platelet activator. However, it is able to potentiate platelet activation initiated by other agonists. Here, we investigated the role of epinephrine in the generation of procoagulant platelets.

Methods: Human platelets were activated with convulxin (CVX, agonist of the collagen receptor GPVI), thrombin (THR), epinephrine (EPI), and combination thereof. Platelet aggregation was assessed by light transmission aggregometry or with PAC-1 binding by flow cytometry. Procoagulant COAT platelets, induced by combined activation with CVX-plus-THR, were visualized by flow cytometry as Annexin-V-positive and PAC-1-negative platelets. Cytosolic calcium fluxes were monitored by flow cytometry using Fluo-3 indicator.

Results: EPI increased platelet aggregation induced by low doses of CVX alone, THR alone, and combined CVX+THR. On the other hand, EPI dose-dependently reduced the formation of procoagulant COAT platelets generated by combined CVX+THR activation. We observed a decrease (relative -10%) of Annexin-V positivity and an increase (relative +10%) binding of PAC-1 with the triple activation (CVX+THR+EPI) compared with CVX+THR. Calcium mobilization with triple activation was decreased with the higher dose (1000 µM) compared with calcium kinetics from CVX+THR.

Conclusions: While CVX+THR induced the formation of procoagulant COAT platelets (express negatively charged phospholipids at their surface, and lose aggregatory properties), the addition of EPI (triple stimulation) modulated platelet activation reducing cytosolic calcium mobilization, decreasing the procoagulant response and enhancing platelet aggregation.

Disclosure: Nothing to disclose

P5

Evaluation of thrombin generation in patients with sickle cell disease in stable disease and sickle cell crises

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Introduction: Sickle cell disease (SCD) is complicated by repetitive pain crises and coagulation activation. In this study we looked for a possible way to monitor coagulation activation by using thrombin generation assay (Calibrated automated thrombogram CAT) as a global coagulation assay. After specifying preanalytical conditions we compared 11 patients suffering from SCD or sickle cell/b thalassemia in stable disease and pain crises to 6 patients suffering from transfusion dependent thalassemia.

Methods: Blood probes were drawn using corn trypsin inhibitor (CTI) or citrate as anticoagulants and fresh probes were compared to frozen. The tests were performed on a CAT Thrombinoscope system using platelet poor plasma (PPP), phospholipids with high/low tissue factor (TF) concentrations.

Results: Citrated blood showed higher peak heights with similar lag-times and endogenous thrombin potential (ETP) compared to CTI anticoagulant in 18 normal controls. There was no difference in fresh or frozen samples. In SCD patients and controls PPP with low TF resulted in a more prolonged lag-phase and lower peak while ETP differed only marginally to PPP high TF. SDC patients showed a higher peak and ETP values compared to controls, but ranges were overlapping. ETP was reduced during sickle cell crises. Patients suffering from crises showed higher ETP and peak heights even outside crises compared to patients with stable disease. TGA values were not related to D-dimers.

Conclusions: Hypercoagulable states in SCD patients can be monitored by CAT. ETP is lowered during crises reflecting prolonged coagulation activation or factor consumption. Combination with cellular components might improve sensitivity.

Disclosure: Nothing to disclose

P6

Abdominal thrombosis in polycythemia vera patients

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Introduction: Thromboembolic events (TE) are the most prevalent complications in patients with polycythemia vera (PV). Deep vein thrombosis (TVT), pulmonary thrombosis (PE), abdominal thrombosis (AbdThr), and cerebral venous thrombosis are particularly feared. We aimed to evaluate the frequency and associated risk factors of AbdThr in PV patients followed in our outpatient clinic.

Methods: We retrospectively reviewed medical data of adult PV patients followed in our clinic during 2019. Patients who were misfiled and therefore presenting a polyglobulia from another etiology were excluded.

Results: We evaluated 83 PV patients (pts). 38 (46%) were female, the median age at diagnosis of PV was 58 years (18-86), the median follow-up was 118 months (10-323). 44 (53%) pts had a first TE (20pts (45%) venous/24pts (55%) arterial). 19/44 pts developed a second TE. 10 pts had an AbdThr (23% of all thrombosis) being the 3rd most frequent localization after cerebral and TVT / PE. 90% of AbdThr occurred at time of PV diagnosis. Patients with AbdThr were significantly younger (P=0.021) and showed lower prevalence of arterial hypertension and smoking than those without AbdThr (Table 1). Splenomegaly was a constant finding in all patients with AbdThr.

Conclusion: 53% of PV pts presented a TE, AbdThr was the 3rd most frequent localization and affected younger patients mostly at disease presentation. Blood values and cardiovascular risk factors did not show any influence. Splenomegaly is more likely associated with splenic vein thrombosis than with the PV itself.

Variable	With Abdominal thrombosis	No Abdominal thrombosis	p-value
Number of patients	10	73	-
Female gender	5/10 (50%)	33/40 (55%)	0.775
Median Age at PV - years (range)	42.5 (26-78)	59 (18-86)	0.021
Median follow-up - months (range)	118 (11-323)	114 (10-319)	0.520
Timing of abdominal thrombosis			
At diagnosis of PV	9/10 (90%)		
After diagnosis of PV	1/10 (10%)		
Cell Blood Counts			
Median Hb (range)	161.5 g/L (146-188	173 g/L (125-215)	0.199
Median Hct (range)	50 % (45-58)	53 % (40-67)	0.302
Median WBC (range)	13.8 G/L (10.3-17.7)	11.2 G/L (5.10-22.9)	0.104
Median platelet count (range)	581 G/L (384-873)	546.5 G/L (192-2271)	0.789
Nr patients with platelet >550 G/L	4/6 (67%)	30/60 (50%)	0.436
Nr patients with platelet >450 G/L	5/6 (83%)	40/60 (67%)	0.403
Nr of patients with Hb >170 g/L	2/6 (33%)	33/60 (55%)	0.311
Nr of patients with Hct >49 %	3/6 (50%)	37/55 (67)	0.398
Clinical information			
Splenomegaly	10/10 (100%)	38/73 (52%)	0.016
Diabetes	0/10 (0%)	9/72 (13%)	0.236
Arterial Hypertension	3/10 (30%)	53/73 (73%)	0.007
Overweight/Obesity	5/5 (50%)	17/56 (30%)	0.225
Dyslipidemia	3/10 (30%)	29/70 (41%)	0.490
Smoking	1/8 (13%)	21/39 (54%)	0.033
Nr patients with ≥ 3 risk factors	1 (10%)	23 (31%)	0.159
Alive at last contact	67/73 (92%)	9/10 (90%)	0.849

[Table 1. Comparison of PV patients with and without abdominal thrombosis]

Disclosure: NN: nothing to disclose; KJ: nothing to disclose; AT: nothing to disclose; LNM: nothing to disclose; TW: nothing to disclose; AAS: Silence Therapeutics: Research Funding AR: Novartis: Consultancy, Honoraria, Advisory Board, Research Funding; CSL Behring: Research Funding; Alexion: Research Funding; Orphaswiss: Advisory Board. Celgene: Advisory Board Consultancy. AstraZeneca: advisory Board.

P7

The measure of tissue factor-independent coagulation parameters is useful for monitoring FXI-concentrate replacement in patients with FXI-deficiency

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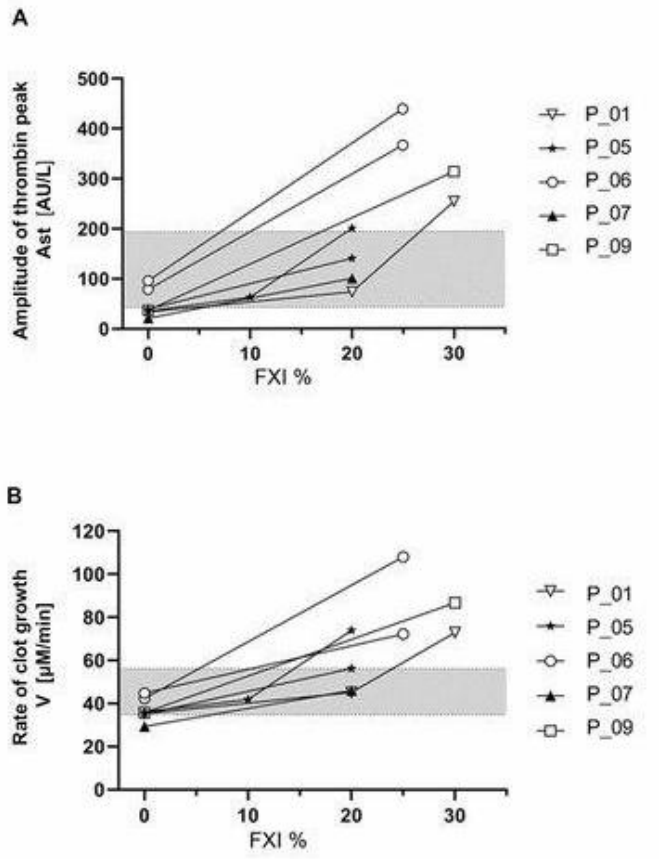
Background: Clinical management of FXI-deficient patients is challenging due to the heterogeneity of bleeding symptoms and to the lack of tools able to predict bleeding risk. Replacement therapy with FXI-concentrates is associated with an increased thrombotic risk. Assays able to monitor the hemostatic potential of FXI-replacement therapy would have a high clinical value.

Aim: To evaluate the utility of a new global coagulation assay, Thrombodynamics (TD), for monitoring the hemostatic potential of FXI-deficient patients after FXI-replacement with a commercial FXI concentrate (Hemoleven®, LFB-Biomedicaments, Les Ulis, France).

Methods: TD measures the tissue-factor (TF) dependent and independent coagulation. First, we established reference ranges for thrombin generation (TG) and fibrin clot formation (FCF) parameters analyzing plasma from healthy donors. Subsequently, we studied the effect on coagulation parameters of increasing doses of Hemoleven® spiked to FXI-deficient plasma. Finally, we measured the hemostatic potential in patients treated with Hemoleven® prior planned interventions (n=7).

Results: During the TF-independent phase of coagulation, TG and FCF increased dose dependently after in vitro FXI spiking. Similarly, TG (reflected by amplitude of thrombin peak) and FCF (reflected by rate of clot growth) were strongly increased in patients receiving Hemoleven® already at FXI-concentrations of 20% and shifted towards hypercoagulation at FXI-levels of about 30%.

Conclusions: TD seems useful for assessing patient's hemostatic potential after administration of Hemoleven®, thus representing the first laboratory tool allowing patient-tailored management in FXI-deficiency. Our study supports the use of low doses of Hemoleven®, aiming to FXI plasma levels ≤20%, which is lower than currently recommended (30-40%).



[TG and FCF at baseline and after replacement with Hemoleven®. Shaded zone = normal values.]

Disclosure: Nothing to disclose

P8

Platelet function analysis: a comparison between conventional PRP-Aggregation and FACS before and after activation with TRAP (thrombin receptor activating peptide)

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Introduction: Some platelet function alterations are not easily recognized with platelet aggregation (AG) from platelet rich plasma (PRP). Flow cytometry (FACS) can be a challenging method to study platelet function.

Aim: To describe and compare platelet function analysis performed with PRP-AG (Born) and FACS before and after TRAP activation.

Methods: We studied platelet function in 71 patients referred for investigation of bleeding diathesis. PRP-AG was assessed with standardized platelet activators. FACS before and after TRAP activation (11mM), was done using PRP. We used specific monoclonal antibodies against platelet antigens to measure receptor density semi-quantitatively on platelet surface.

Results: From 71 patients (56 females, 15 males), 33 patients (47%) had pathological and 38 (53%) had normal PRP-AG. Using FACS analysis before and after TRAP activation, we compared the patients with normal (N-group) and pathological PRP-AG (P-group).24 (63%) patients in N-group had normal and in the P-group 20 patients (61%) had abnormal FACS. In addition, in the P-group we identified 10 patients (31%) with not further classified PRP-AG but with reduced release reaction, signal transduction or storage pool defect with FACS.

Conclusion: FACS analysis of platelet function before and after activation with TRAP mainly follows the pattern of PRP-AG. However, in some cases PRP-AG masks the existing defects in platelet receptor activation or release reaction. In the case that PLT function alterations are not identified with PRP-AG, those could be revealed in a semi-quantitative way using FACS analysis. Reproducibility and sensitivity of FACS analysis on platelets still need careful attention.

Disclosure: Nothing to disclose

Topic: Clinical hemato-oncology (lymphoma, myeloma, leukemia, transplantation for SSH and SSMO) (SSH/SSMO award for clinical hemato-oncology)

P9

Relationship between patient-reported outcomes and clinical outcomes in patients with FLT3-mutated relapsed/refractory acute myeloid leukemia: results from the ADMIRAL study

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Introduction: The relationship between patient-reported outcomes (PROs) and clinical outcomes in AML is unclear. We therefore examined this relationship in *FLT3*-mutated relapsed/refractory (R/R) AML patients who received gilteritinib or salvage chemotherapy (SC) in the phase 3 ADMIRAL trial.

Methods: The following PRO measures were implemented: Brief Fatigue Inventory (BFI), Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu), EuroQol Five-Dimension Five-Level (EQ-5D-5L), Functional Assessment of Chronic Illness Therapy-Dyspnea, and leukemia-specific symptom (dizziness, mouth sores) evaluation. Associations between longitudinal PRO changes and clinical outcomes were evaluated using a time-dependent Cox regression model. Median time-until-definitive-deterioration (TUDD: duration between randomization date and death or first deterioration of ≥1 minimum clinically important difference unit) was compared between gilteritinib-treated patients who achieved CR/CRh and those who did not.

Results: Across 371 enrolled patients (gilteritinib, n=247; SC, n=124), reductions in overall survival were significantly associated with clinically meaningful worsening of all BFI and EQ-5D-5L scores, and nearly all FACT-Leu scores (P< 0.001). Decreased event-free survival was significantly associated with clinically meaningful worsening of all BFI (P< 0.05) and EQ-5D-5L scores

(P< 0.005). In gilteritinib-treated patients, median TUDD was significantly longer with achievement of CR/CRh than without achievement of CR/CRh (P< 0.001) for BFI Global (14.1 months versus 3.6 months, respectively), FACT-Leu total (14.6 versus 3.8 months, respectively), and EQ-5D-5L visual analog scale scores (14.3 versus 4.8 months, respectively).

Conclusions: The observed relationship between improved PROs and better clinical outcomes in *FLT3*-mutated R/R AML show that PROs related to FLT3-targeted therapy may inform therapy selection and demonstrate treatment value.

Disclosure: D Cella: Personal Fees - Astellas; President - FACIT.org E Ritche: Grants - Jazz Pharmaceuticals; Advisory Board - Celgene, Pfizer, Agios, Tolero, Incyte, Genentech F Fabbiano: A Pigneux: Grants and Personal Fees - Astellas Y Kanda: Grants and Personal Fees - Astellas C Ivanescu: Employment - IQVIA B Pandya: Employment - Astellas M Shah: Employment - Astellas

P10

No evidence of excess mortality in the winter season in hematopoietic stem cell transplant recipients - a Swiss multi-center study

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Introduction: In winter, mortality in the elderly population is increased partly due to infections from seasonal respiratory viruses and pneumonia. Patients after hematopoietic stem cell transplantation (HSCT) frequently experience such infections. We therefore hypothesized that HSCT recipients experience excess winter mortality.

Methods: This is a retrospective cohort study using the SBST database assessing the proportion of HSCT-patients who died during winter (October to March) compared to summer. Univariate analyses for death after allogeneic and autologous HSCT of factors potentially associated with higher risks of winter deaths (age, disease, disease stage, GvHD, treatment center) were done by chi-squared tests. Multivariable logistic regression was done for all patients and those surviving less and more than 100 days and more than one year to separately evaluate early and late deaths.

Results: Between 1997 and 2019 12´412 patients received HSCT (8107 autologous, 4305 allogeneic). 4904 patients died (3218 autologous, 1686 allogeneic). Overall, 2517 patients (51.3%) died in winter, 2387 (48.7%) in summer (figure 1). The proportion of patients with deaths in winter did not differ by type of HSCT, age, disease, disease stage at the time of transplant or GvHD. Excluding patients dying in the first 100 days and in the first year after transplant or those dying without relapsed disease did not change these results.

Conclusion: Contrary to our assumption, no higher mortality in winter was found in HSCT patients pointing to no increased death rate due to respiratory viruses.

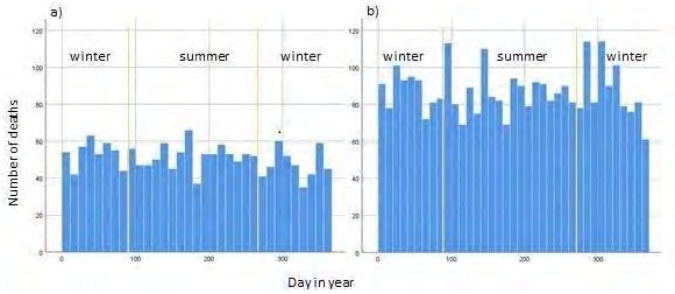

Figure 1: Distribution of deaths in allogeneic (a) and autologous (b) HSCT patients during the year

Disclosure: Nothing to disclose

P11

JAK2- negative polyglobulia - real life data of 10 years from a tertiary reference centre

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Background: Real life data of underlying causes of JAK2-negative polyglobulia is sparse. We aimed to analyse clinical and laboratory data of patients with JAK2-negative polyglobulia at our tertiary referral hospital.

Methods: The hospital database was queried to find patients ≥15 years of age with polyglobulia (hospitalized and outpatients) between 01.10.2008 and 31.07.2019. Using a stepwise process, we concentrated on patients in whom JAK2 result was available.

Results: Files of 727'731 patients were evaluated and in 4'391 polyglobulia was mentioned as diagnosis; from them in 1'483 we confirmed polyglobulia on laboratory values. 391 patients were tested for JAK2 and 294 were negative (our study cohort). The main reason for polyglobulia was sleep apnoea confirmed on polysomnography (n=61, 20.7%), followed by nicotine use (n=40, 13.6%), pulmonary diseases (n=15, 5.1%), androgen use (n=10, 3.4%), renal transplantation (n=7, 2.38%) and renal cysts (n=5, 1.7%). Cancers known for an association with polyglobulia were found in 3 patients (1.02%) being renal cell carcinoma (n=2) and HCC (n=1). 19 patients had an underlying neoplasia with not known association with polyglobulia. Mutations for congenital erythrocytosis were found in 2 patients (0.68%). In 95 (32.3%) patients, polyglobulia was considered as idiopathic, in 33% of them it was persistent during the follow-up. All patients with persistent idiopathic polyglobulia were males and 25 were < 40 years old.

Conclusion: One third of JAK2-negative patients had an idiopathic polyglobulia form. Patients with persistent idiopathic polyglobulia were exclusively males. NGS testing evaluating congenital forms might contribute to clarify the diagnosis of such patients.

Disclosure: KAJ, NF, AC, TW, RJ, AT, NAP: nothing to disclose; AR: Novartis: Consultancy, Honoraria, Advisory Board, Research Funding; CSL Behring: Research Funding; Alexion: Research Funding; Orphaswiss: Advisory Board. Celgene: Advisory Board Consultancy. AstraZeneca: advisory Board.

P12

Molecular determinants of ZAP70 and CD38 expression in CLL

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Background: ZAP70 and CD38 have emerged as strong predictors of poor prognosis in CLL, yet little is known regarding the molecular features underlying varying ZAP70/CD38 expression beyond IGHV. While marker assessment is primarily based on FACS, RNA sequencing may lead to more complete marker measurements.

Aims: To understand the molecular basis for variable ZAP70 and CD38 expression in CLL.

Methods: We performed multi-omics analysis in 217 CLL tumors using correlation and LASSO regression analysis to understand ZAP70/CD38 expression variability and underlying biological processes.

Results: We found positive correlations of RNA levels and protein abundance (R^2 0.12 - 0.75) for common B-cell tumor markers. Gene expression of theses markers accurately separated B-cell tumors including major subgroups (e.g. IGHV mutated and unmutated CLL).

ZAP70 expression strongly correlated with IGHV associated genes (AGPAT4, PLD1, ZNF667). Blocking for IGHV mutational status identified different gene sets correlated with ZAP70 (n=4762 w/o blocking, n=2764 w/ blocking) and CD38 (n=3067 w/o blocking, n=3972 w/ blocking) (FDR 10%) expression and identified novel markers strongly correlated with ZAP70 (ICOS, TMEMT173, MAF) and CD38 (RHBDF2, ITGAL, SIRPB1).

Genomic features influenced the expression of CD38 (del11q (*p*=4.31E-3) and trisomy 12 (*p*=4.41E-6) in M-CLL) and ZAP70 (U1 mutations in U-CLL (*p*=0.0279), IP programming in U-CLL).

Conclusion: RNA Sequencing uncovers major molecular disease subtypes in B-cell lymphoma and gene networks associated with ZAP70/CD38 expression in CLL. Combined with genomic features our approach leads to a more comprehensive characterization of CLL based on ZAP70 and CD38 expression.

Disclosure: Nothing to disclose

P13

Comparison of melphalan together with busulfan or treosulfan before autologous stem cell transplantation in AML in first remission

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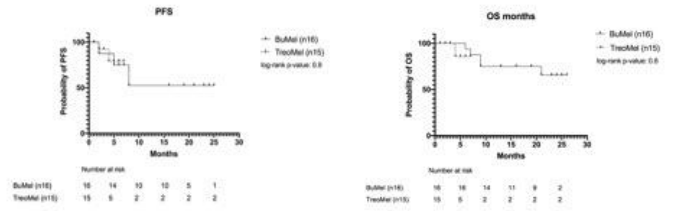
Background: Treosulfan compares favourably to busulfan regarding its lower interindividual bioavailability and attractive toxicity profile. Comparisons between treosulfan and melphalan (TreoMel) conditioning before ASCT in AML patients in CR1 to busulfan and melphalan (BuMel) are lacking.

Methods / design: We studied AML patients undergoing ASCT in CR1. A first cohort (16 patients) received busulfan 16 mg/kg b.w. days -5 to -2 and melphalan 140 mg/m^2 day -1 (BuMel). In a subsequent (TreoMel) cohort, 15 patients were treated with treosulfan 14 g/m^2 days -4 to -2 and melphalan 140 mg/m^2 day -1. Plasma concentrations of busulfan and treosulfan were prospectively determined.

Results: BuMel patients had more CNS toxicities (seizures 6.25% vs 0%; encephalopathy 12.5% vs 0%; p=0.15). Definite alopecia was exclusively reported in the BuMel cohort (18.75%; p=0.0068). Median neutrophil engraftment in BuMel patients occurred at day +14 compared to +12 days (p=0.40). Platelet recovery >20 G/L occurred at day +43 and +26, respectively (p=0.02). The PFS (p=0.1) and OS (p=0.3) at 12 months for BuMel were 56 % and 74%, respectively, and 86% and 93% for TreoMel. The mean AUC for busulfan was 1471.32 ± 161.97 µmoL/min, and for treosulfan 840.98 ± 162.74 mg/h. Median peak values for busulfan were 1351 ± 108.2 µg/L and for treosulfan 312.43 ± 51 mg/L.

Conclusion: TreoMel for pre-ASCT treatment in AML patients has a favourable safety profile. Considerable interindividual differences in plasma levels were observed for both busulfan and treosulfan, suggesting that pharmacologic monitoring may also be warranted for treosulfan.

Figure 1: Progression free survival and overall survival of the BuMel and the TreoMel cohorts.



Disclosure: Nothing to disclose

P14

Impact of donor-recipient sex mismatch in patients receiving partial t-cell depleted allogeneic stem cell transplantation for hematological malignancy: a retrospective monocentric study

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Background: The donor-recipient sex mismatch is a recognized risk factor for GVHD and increased non-relapse mortality. Conversely, partial T-depletion (pTCD) permits to lower risk of both these parameters without a negative impact on the overall outcome. The purpose of our study is to analyse whether the outcomes of pTCD were influenced by the donor-recipient sex mismatch.

Methods: A single-center retrospective analysis was conducted at our clinic in all adult patients (18 =years) that received their first partial T-cell depleted allogenic stem cell transplantation for a hematological malignancy from 2005 to 2018. pTCD was performed *ex vivo* using alemtuzumab, and it is offered to low-risk patients in CR, 1st, or beyond. Only matched donors were considered.

Results: Overall, 192 patients were identified. 111 had sex-matched and 81 had sex-mismatched donor. Median age for both groups was 51 years with a median follow up of 74 and 78 months, respectively. 68% of subjects in sex-matched and 67% mismatched cohort underwent myeloablative conditioning (MAC), and the most frequent indication for transplant was AML (51% and 40%, respectively). Globally, the groups were well balanced for the other characteristics, except for donor type which was an HLA-identical sibling in 36 and 65 % of cases in sex-matched and mismatched groups, respectively (p< 0.01), and in vivo T-cell depletion: ATG was used in 68 and 52% of patients, respectively (p=0.04). Peripheral blood was the primary source of stem cells in both groups. Median time to neutrophil engraftment did not differ between cohorts (16 and 17 days). No difference in 3-year probabilities was noted for overall survival (OS, 67.3% in sex-matched and 67.0% in sex-mismatched, p=0.63) and disease-free survival (DFS, 59.3%, and 52.7%, respectively). Cumulative incidence of non-relapse mortality (NRM) and relapse incidence (RI) at 3 years did not differ between sex-matched or mismatched donor (NRM: 12.7% vs. 11.6%, p=0.89; RI: 31.7% vs 37.6, p=0.50). Rates of grade II to IV acute GVHD were significantly lower in sex-matched cohort (11.3 vs. 20.0, p=0.03). No differences were noted for both all grade and extensive chronic GVHD 2-year rates (12.6 and 8.1% for matched patients; 11.1 and 7.4% for mismatched, p=0.89 and 0.73, respectively). Regarding the composite endpoint of GVHD-free/relapse-free survival (GRFS), the 1-year estimate GRFS was 59.4% in the sex-matched and 61.0% in the sex-mismatched group (P=0.67). In multivariable analysis for OS, having a matched unrelated donor (MUD) and a Karnofsky Performance Status (KPS) of 90 or less were associated with worse prognosis (HR= 2.0 for MUD, p< 0.01 and HR=2.46 for KPS, p< 0.01) while having a sex donor-recipient mismatch didn´t retain significance.

Conclusions: In conclusion, *ex-vivo* pTCD offers similar overall results in the presence of sex-matched or mismatched donor, albeit a higher aGVHD rate was observed in the latter group without an impact on non-relapse mortality. Thus, in a context of partial T-depletion, the gender-

mismatch seems not to impact the OS and NRM anymore which allow to have more choices in the presence of matched donors. A more large and homogeneous cohort should be exanimated to validate this approach.

Disclosure: Nothing to disclose

P15

Reduced survival after autologous stem cell transplantation in myeloma and lymphoma patients with low vitamin D serum levels

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Introduction: High-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) is applied for consolidation in myeloma and relapsing lymphoma patients. Vitamin D (VitD) exerts effects during hematopoietic stem cell proliferation, differentiation and interactions with the immune system. VitD deficiency is common in patients with hematological malignancies, but its prognostic relevance after HDCT/ASCT is unclear.

Methods: We analysed the prognostic effect of VitD serum levels in all adult patients (≥18 years) with myeloma or lymphoma types undergoing HDCT/ASCT between 03/2012 and 07/2018 at a single institution. Patients were included in this study if the serum VitD status was available within one week before the start or one week after the end of HDCT. We collected data on clinical characteristics at diagnosis, previous treatments, parameters related to HDCT/ASCT and clinical outcomes.

Results: The cohort (n=183) was divided in two groups: 81 (44%) patients had VitD levels >52 nmol/L and 102 (56%) ≤52 nmol/L at ASCT. VitD levels >52 nmol/L were associated with better PFS (p=0.0194) and OS (p=0.011). Similarly, when evaluating myeloma patients alone, patients with lower VitD levels (≤52 nmol/L) had inferior PFS (p=0.0412) and OS (p=0.049). The multivariate analysis indicated that varying VitD levels were the only parameter significantly associated with OS (p=0.0167), also when stratifying patients in groups with VitD levels above versus below 52 nmol/L (p=0.0421).

Conclusions: Our data suggest that reduced serum VitD levels in myeloma and lymphoma patients undergoing HDCT/ASCT are associated with inferior outcome. Optimizing VitD levels before HDCT/ASCT should be prospectively evaluated.

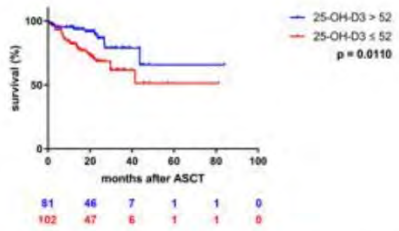

Figure 1: Kaplan Meier curve depicting overall survival of patients after HDCT/ASCT with 25-OH-D3 serum levels above (blue curve) versus below (red curve) 52 nmol/L.

Disclosure: Nothing to disclose

P16

Real-world outcome of myeloma patients qualifying for CAR-T treatment in the pre-CAR-T era

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Background: CAR-T treatment is likely to be introduced 2021 for patients with relapsed/refractory myeloma (r/r MM) in Switzerland. To qualify for commercial CAR-T treatment, r/r MM patients will have to be exposed to at least three lines of treatment including lenalidomide, bortezomib and anti-CD38 treatment.

Methods: We analyzed all subsequent r/r MM patients between 01/2016 (when anti-CD38 treatment was introduced in Switzerland) and 04/2020 at our institution. Patients were eligible if they had at least three lines of treatment including one proteasome inhibitor (PI), one immunomodulatory drug (IMID) and one anti-CD38 antibody, and if they were in need and effectively received further treatment.

Results: Among 56 patients fulfilling the criteria of at least three such lines of treatment, only 34 (60%) effectively received further therapy. For patients fulfilling all criteria, the median number of previous lines was 4.5 (range 2-12), with 13 (37%) patients being penta-refractory. 21 (62%) patients received two or more additional lines. The median PFS was 6.6 months, TTNT 7.5 months, and OS 13.5 months for the first subsequent treatment. The overall response rate to the first subsequent treatment was 41%, with a median duration of response of 5 months.

Conclusion: Myeloma patients in need of treatment after at least three lines of anti-CD38/PI/IMID treatment have a poor prognosis with a PFS of 6.6 months and OS of 13.5 months. This data may serve as reference to compare the potential benefit of CAR-T treatment in this group of myeloma patients when available in the near future.

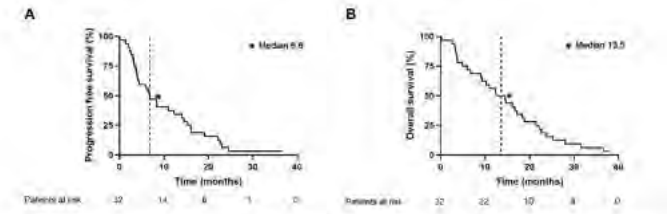

Figure 1: Kaplan-Meyer curves depicting (**A**) progression free survival and (**B**) overall survival of MM patients refractory after at least three lines of anti-CD38/PI/IMID treatment, from the start of the first subsequent treatment.

Disclosure: Nothing to disclose

P17

Efficacy of hypomethylating agents and Venetoclax in unfit patients with acute myeloid leukemia

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Treatment options for patients with acute myeloid leukemia (AML) who do not qualify for intensive therapy are limited. Recently, a phase 3 study showed that the addition of the BCL-2-Inhibitor venetoclax (VEN) leads to a survival benefit in this vulnerable patient group. Here we report the outcome of patients treated with hypomethylating agents (HMA) + VEN at our centre from 1.1.2019 - 1.1.2020. VEN is not an approved AML therapy in Switzerland yet.

We retrospectively analysed an AML patient cohort unfit for intensive therapy. The primary endpoint was overall survival (OS); secondary outcome was time to VEN-addition and source of VEN supply.

79 patients with AML treated with HMA were assessed for eligibility. VEN was applied for in 47 patients and obtained in 31 patients of which 10 patient received the combination as first line treatment. Overall, we could not find a significant difference in OS. Median OS was 7.9 months in the HMA+ VEN group and 6.2 moths in the HMA group. In first line patients, there was no significant difference either, median OS was even lower with 6 months in the HMA+VEN and 5 months in the HMA group respectively. Median time to VEN was 23 days (range 0 - 75 days).

Despite promising results from the randomized controlled trial (RCT) our data failed to show a benefit from VEN addition. The delay in start of VEN might be a factor that explains the lack of efficacy of HMA-VEN in contrast to published data.

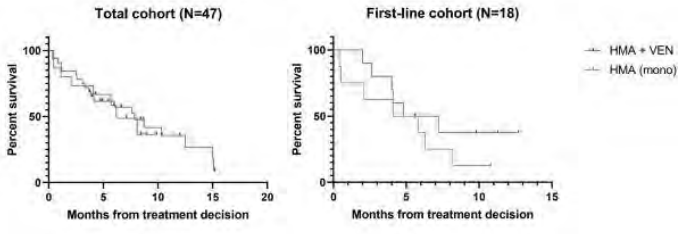

Figure 1: Overall survival

Disclosure: Nothing to disclose

P18

Role of diagnostic lumbar puncture in treatment of grade 3 ICANS in an elderly patient with anti-CD-19 CAR-T cell therapy

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Introduction: Chimeric antigen receptor T cells (CART) are a very promising innovative treatment approach in relapsed/refractory lymphoma. However, their immunologically mediated side effects, such as immune effector cell-associated neurotoxicity syndrome (ICANS), require distinctive monitoring and treatments that continue to pose a challenge.

Here, we report on a 76 year old patient treated with anti-CD19-directed CART (axicabtagen-ciloleucel) for relapsed aggressive B-cell lymphoma.

Results: On day +5 after CART infusion, his neurological condition changed rapidly with an impairment in temporo-spatial orientation and handwriting (ICANS grade 3). At this time he had no signs of cytokine release syndrome. Cerebrospinal fluid (CSF) analysis showed 7 cells/ml with no evidence of lymphoma cells or infection. In addition, CSF was examined for CART by flow cytometry. The majority of lymphocytes were CART (58%), and this percentage was higher in CSF than in blood (44%) at that time. Steroids were administered according to guidelines for 10 days overall. The patient completely recovered from these neurological symptoms and was discharged on day +17. Follow-up revealed no further complications, PET-CT imaging showed complete metabolic remission of his lymphoma 5 weeks after CART infusion.

Conclusion: Neurotoxicity is commonly observed following CART treatment. Predisposing conditions may be prior neurological diseases, CNS involvement of underlying lymphoma, and age, although clear predictive parameters do not exist. Once severe ICANS is manifested, imaging is done rather to exclude other underlying factors than to confirm ICANS. Here, we demonstrate that detection of CART in CSF can provide valuable information for diagnosis and treatment of ICANS.

Disclosure: Nothing to disclose

P19

Anticancer activities of novel nicotinamide phosphoribosyltransferase inhibitor in haematological malignancies

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Background: One of the hallmarks of cancer is a high energy demand to sustain constant cell proliferation. Nicotinamide adenine dinucleotide (NAD) is the main co-factor involved in cellular energy pathways that are crucial for cancer cell survival. Inhibiting NAD synthesis is a therapeutic strategy to selectively eliminate malignant cells. Nicotinamide phopshoribosyltransferase (NAMPT) is the rate-limiting enzyme catalysing the NAD synthesis. Several NAMPT inhibitors, such as APO866, demonstrated their high efficacy in preclinical studies. Unfortunately, their clinical activity proved limited. There is still a strong need to synthesize more efficient NAMPT inhibitors. We now tested the anti-leukemic/myeloma activities of FEI-199, a new highly specific NAMPT inhibitor and analogue of APO866.

Methods: Enzymatic approaches were used to confirm the NAMPT specific activity of FEI 199 and that it profoundly depletes intracellular NAD and ATP. The types of cell death were assessed using flow cytometry. Various precursors of NAD synthesis were added extracellularly to confirm their ability to protect from FEI 199-induced cell death.

Results: FEI 199 suppressed the growth of different leukemic/myeloma cells. It was more potent to kill cancer cells; with IC_{50} 2-times lower than that of APO866. Moreover, it fully depleted intracellular NAD and ATP contents at 24 and 48 hours respectively. The supplementation with NAD precursors fully blunted the anti-tumor activities of FEI 199 with a complete cell death reversion (from ~95% to 0%) at 96 hours.

Conclusion: The results support the potential interest of FEI 199 to be further evaluated *in vivo* in pre-clinical models of haematological malignancies.

Disclosure: Nothing to disclose

P20

Real-life experience of sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for FLT3-ITD AML reveals high rates of toxicity-related treatment interruption

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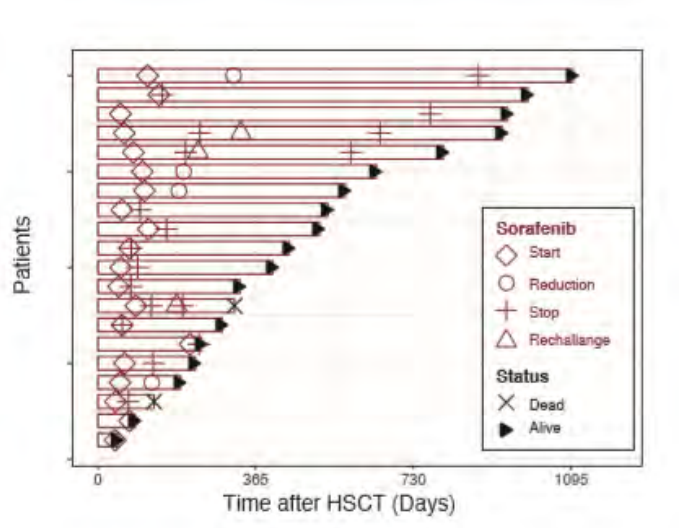
Introduction: Post-HSCT maintenance with sorafenib - a broad-spectrum TKI with strong activity against FLT3 - was shown to reduce the risk of relapse and improve survival in the phase II SORMAIN trial (Burchert, JCO 2020) in patients with FLT3-ITD AML.The aim of our single-center retrospective analysis was to evaluate the real-life experience in patients treated with post-allogeneic HSCT sorafenib maintenance therapy for FLT3-ITD AML

Methods: We conducted a single-center retrospective study on 33 FLT3-ITD AML patients undergoing allogeneic HSCT in complete remission between 2013 and 2020, including 20 patients who received sorafenib maintenance and 13 who did not.

Results: Overall, 16 patients (80%) experienced toxicities leading to dose reduction (4 patients, 20%) or interruption (12 patients, 60%). In these patients, the average time on sorafenib before toxicity occurrence was 98 days (range 1-717). Most common toxicities were skin (7, grade II), gastrointestinal (5, grade II), and hematologic (5, grade II and III). One patient experienced uveitis (grade III) and pneumonia (grade IV), both resolutive after sorafenib interruption. One patient experienced severe hypertension (grade III), 1 had hepatitis (grade III) and another one a PRESS syndrome (grade IV) possibly related to sorafenib (Figure 1). Importantly, the analysis of patients' outcome confirmed the previously reported positive impact of sorafenib maintenance on overall survival (2-year overall survival: Sorafenib 88%±9% vs No maintenance 45%±14%; logrank test: p=0.021) despite high rates of treatment interruption.

Conclusion: Our real-life analysis reveals higher rates of toxicity-related interruption of sorafenib maintenance after allogeneic HSCT than those previously reported in clinical trials.



Disclosure: Nothing to disclose

P21

Analysis of clinical and laboratory parameters associated with outcome after CAR-T treatment in DLBCL patients

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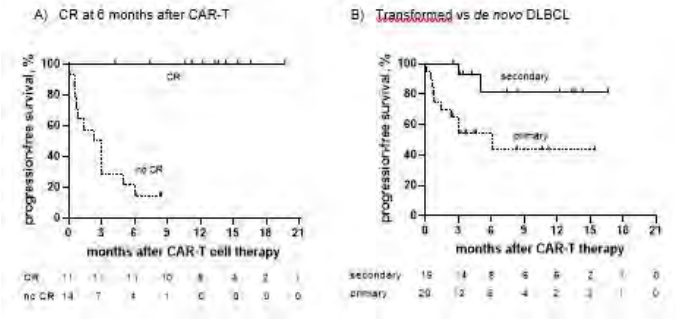
Introduction: CAR-T cell therapy is a novel treatment option for patients with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). However, parameters associated with favorable outcome in this patient population are poorly identified.

Methods: We investigated the following parameters in consecutive r/r DLBCL patients undergoing CAR-T treatment: age; transformed disease; previous treatment lines; remission status and LDH level at CAR-

T treatment; development of CRS or neurotoxicity; CAR-T DNA peak concentration and persistence in the peripheral blood; remission status 6 months after CAR-T; and need of bridging therapy.

Results: 26 patients received Kymriah® (Novartis; tisagenlecleucel), 8 patients had Yescarta® (Gilead; axicabtagene ciloleucel), and 2 patients received JCAR017® (Celgene; lisocabtagene maraleucel). CRS was observed in 24 (67%) patients, and neurotoxicity in 14 (39%) patients. Bridging therapy was given in 17 (47%) patients. CR at CAR-T treatment was seen in 2 (6%) patients, PR in 9 (25%) patients, SD in 8 (22%) patients, and PD in 17 (47%) patients. Best response 6 months after CAR-T treatment was CR in 44%, PR in 28%, SD in 16%, and PD in 12%. Parameters associated with better outcome were transformed versus *de novo* disease (PFS; *P*=.0340), LDH (OS; *P* =.0577), and achievement of CR after 6 months (PFS; *P* < 0.0001) in the univariate analysis.

Conclusion: Our single-center real-world results suggest that lymphoma load at CAR-T treatment represented by LDH levels, presence of transformed disease, and response to treatment 6 months after CAR-T therapy are the relevant parameters indicating favorable outcome after CAR-T in r/r DLBCL patients.



Disclosure: Nothing to disclose

P22

Outcome of patients with mantle cell lymphoma relapsing after autologous stem cell transplantation before availability of CAR-T treatment

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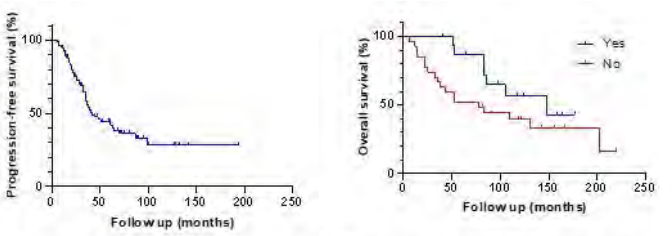
Introduction: Fit mantle cell lymphoma (MCL) patients are consistently treated with aggressive induction therapy, followed by autologous stem cell transplantation (ASCT) and subsequent CD20 targeting maintenance treatment. Relapsing MCL patients increasingly receive bruton's tyrosine kinase (BTK) inhibitors. For patients relapsing after BTK inhibitors, CAR-T-cell therapy will likely become available during 2021 in Switzerland. Therefore, detailed knowledge on the course of the disease of this patient population is of increasing interest.

Methods: We retrospectively analyzed the outcome of MCL patients receiving ASCT at a single academic center between 2000 and 2020. Their outcome in the pre-CAR-T era was analyzed.

Results: We identified 87 MCL patients undergoing ASCT in the study period with a median follow-up of 54 months. 43 (48%) of the patients ultimately relapsed, and 28 (32%) patients died so far. The median overall survival (OS) for the entire population was 148 months, and the median progression free survival (PFS) was 42 months. The median OS of relapsing patients with BTK inhibitors post-transplant was 148 months compared to 78 months in relapsing patients who never received BTK inhibitors (P=0.1235). MCL patients relapsing after ASCT had one (26 pts; 60%), two (10 pts; 23%), or more than two lines (2 pts; 5%) of additional treatment.

Conclusion: Despite receiving intensive first-line treatment with ASCT, a substantial proportion of MCL patients is ultimately relapsing. However, BTK inhibitor treatment is decisively prolonging the long-term outcome of such patients, with CAR-T treatment representing a promising upcoming option in r/r MCL patients following BTK inhibitor treatment.



(A). Progression free survival of all patients with mantle cell lymphoma after diagnosis

(B) Overall survival of patients relapsing after ASCT according to subsequent treatment with/without BTK inhibitors (P=0.1235)

Disclosure: Nothing to disclose

P23

Incidence and impact of Epstein-Barr virus events in the early phase after allogeneic hematopoietic cell transplantation

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Background: Epstein-Barr virus (EBV) reactivation may evolve to a life-threatening complication after allogeneic haematopoietic cell transplantation (allo-HCT).

Methods: In a retrospective analysis of patients receiving an allo-HCT between 2010 and 2016 we determined the incidence rates of EBV-events.

Results: We assessed 382 patients (166 female; 43.5%) suffering from AML n=137, lymphoma/myeloma n=77, MDS/MPN n=68, ALL n=48, CLL n=26, CML n=12, or others n=13, who had undergone myeloablative (278, 72,8%) and non-myeloablative (103; 27,0 %) allo-HCT between 2010 and 2016 (Table 1). Of 382 patients, 216 (56.5%) had EBV-events with a median value was 11935.50 GEq/mL (range 1000 - 4440000 GEq/mL). The median time interval from allo-HCT to EBV-events was 35 days (range 4 to 1879 days). The median time interval from allo-HCT to the maximum EBV-events was 62 days (range 8 to 543 days). EBV-events were significantly correlated with EBV IgG donor serology (p=0.012), but not with EBV IgG recipient serology (p=0.285). EBV-events were associated with HLA mismatched HCT (p=0.035), donor type (p=0.001), GvHD prophylaxis (p=0.0001) and ATG use for GvHD prophylaxis (p=0.0001). OS was significantly shorter among patients with EBV-events (562 ± 468 days) compared to those without (640 ± 594 days; p< 0.0001). Twenty-six patients received pre-emptive rituximab therapy at a median EBV load of 36.000 GEq/mL (range 3000 - 900000). Five patients developed PTLD.

Conclusions: Despite better approaches with weekly surveillance, monitoring and pre-emptive therapy for EBV, EBV-events are associated with reduced overall survival.

	No EBV event (n=166; 43.5 %)	**EBV events (n=216; 56.5 %)**	**p-value**
acute GvHD ≥ grade 2	37	73	0.201
chronic GvHD	33	57	0.733
EBV IgG serostatus donor positive	137	191	0.012
EBV IgG serostatus donor negative	18	9	
Stem cell source bone marrow	16	20	0.231
Stem cell source peripheral blood	149	195	
Stem cell source cord blood	2	0	
Conditioning myeloablative	112	166	0.071
Conditioning reduced intensity	54	49	

[Table 1. Comparison of patients with and without EBV reactivation]

Disclosure: Nothing to disclose

P24

Outcome of patients with DLBCL relapsing after autologous stem cell transplantation in the pre-CAR-T era

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Introduction: HDCT with ASCT is standard of care for patients with DLBCL who relapse or progress after first line immuno-chemotherapy. However, DLBCL patients relapsing after ASCT have a dismal outcome, whereas CAR-T treatment offers a promising treatment option in such patients. Consequently, knowledge on outcome of this patient population in the pre-CAR-T era is crucial.

Methods: We analyzed 125 r/r DLBCL patients who underwent HDCT (BeEAM 59%, BEAM 34%) with ASCT between 2005 and 2019.

Results: After a median follow up of 26 months, OS and PFS for the entire population were 65% and 55%. Refractory disease (n=21) or relapse (n=32) after ASCT after a median interval of 3 months were observed in 53 patients (42%). 81% of relapses occurred within the first year after ASCT and were associated with inferior OS in contrast to patients relapsing after 12 months (19% versus 40%; p=0.0022). 41 (77%) of relasping patients had died after ASCT, 35 due to lymphoma progression and 6 for other reasons. Patients without further anti-lymphoma treatment for relapse after ASCT (n=22) had worse OS compared to patients with one or up to four treatment lines (n=31), with OS rates of 0% and 39%, and median OS of 3 versus 25 months, respectively

(p< 0.0001).

Conclusions: Further therapies are able to extend overall survival, but in most cases cannot prevent death due to lymphoma in DLBCL patients relapsing or refractory after HDCT/ASCT. This study may serve as a reference to emerging results after CAR-T treatment in this patient population.

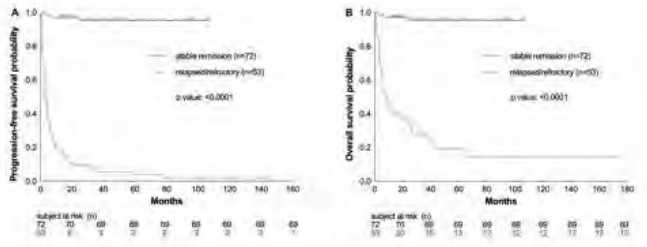

Figure 1: Progression-free survival (PFS; Figure A) and overall survival (OS; Figure B) of patients with DLBCL after autologous stem cell transplantation according to Kaplan Meier method. The red curves represent the patients with relapsed or refractory disease. The black curves depict the patients in stable remission.

Disclosure: Nothing to disclose

P25

Fludarabine pharmacokinetics: a new tool for reduction of conditioning regimen toxicity?

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Background: In allogeneic hematopoietic cell transplantation (HCT), fludarabine is a frequently used agent mainly in reduced conditioning regimes. For the fludarabine dose calculation in adults, only the body surface area is used, which might result in interindividually variable fludarabine exposure. This might result in higher exposition (AUC) and increased toxicity resulting in more transplant related mortality (TRM) or with lower exposition in an increase of the relapse incidence (RI). To optimize TRM and RI we established pharmacokinetics in fludarabine.

Methods: Fludarabine was measured with a validated LC-MS/MS method. The exposure as AUC was calculated for each patient using a three-compartmental model (adapted from *Langenhorst* et al.). n=8 consecutive patients received a conditioning regime with fludarabine. 30mg/m^2 of fludarabine was given on days -7 to -2 i.v. over 30 minutes. The time points of analysis were 30 minutes, 4h, 6h, and 7h after the end of infusion.

Results/**Conclusion:** In contrast to the published data of *Langenhorst et al.*, we observed significant differences in our patients pharmacokinetics without any acute toxicity. In the analysis of *Langenhorst et al.* the optimal AUC was postulated to be 20 mg*h/l. In our (n=8) patients the median range of the AUC was 30.13 (+/- 4.98) mg*h/. In our analyzed population, there was no major toxicity seen at day 100, even though the AUC was 50% higher than the suggested optimal levels.

Disclosure: Nothing to disclose

P26

Improving T cell lymphoma diagnosis using the TRBC1 antibody

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Background: Diagnosis of T-cell lymphomas is often challenging due to overlapping features with reactive T-cells, and the limitations of currently available T-cell clonality assays based on flow cytometry or oncogenomic methods. The recent commercialization of an antibody specific for one of two mutually exclusive T-cell receptor (TCR) β-chain constant regions (TRBC1) provides the possibility for cytometric detection of clonal TCRαβ T-cell populations based on TRBC-restriction. We report here our experience with this antibody.

Methods: 100 patients with a suspected hematologic malignancy were studied. Peripheral blood (83), bone marrow (7) and other samples (10) were evaluated by 10-color flow cytometry including the TRBC1 antibody (CD2/CD3/CD4/CD5/CD7/CD8/CD26/CD45/TCRγδ/TRBC1). Restricted TRBC1 expression on any immunophenotypically distinct and aberrant TCRγδ-negative T-cell population was considered indicative of T cell clonality.

Results: All immunophenotypically distinct CD4- or CD8-positive/TCRγδ-negative T-cell subsets from 80 patients without T-cell malignancies showed the expected distribution of TRBC1-positive and TRBC-1-negative subpopulations. Restricted (clonal) TRBC1 expression was identified on immunophenotypically abnormal T-cells from all 10 patients with T-cell malignancies, including 5 cases with a Sezary phenotype (CD26neg CD7neg). Interestingly, 10 cases diagnosed previously as malignant based on standard antibody panels could be reclassified as reactive T-cell populations. In situations of viral infections or other diseases with T-cell activation, as well as after bone marrow transplant minor clonal T-cell populations could be detected in several cases, in particular in CD8-positive T-cell subsets.

Conclusion: Inclusion of the anti-TRBC1 antibody into a standard diagnostic T-cell flow cytometry panel greatly improves the rapid identification of clonal αβ-positive T-cell malignancies.

Disclosure: Nothing to disclose

P27

Lymphopenia is highly prevalent in myelofibrosis at diagnosis and associated with lower peripheral blood values. A retrospective, single center analysis

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Background: Lymphopenia is common in a variety of malignancies, including lymphoma and MDS. Little is known about its prevalence in BCR-ABL1-negative MPN.

Methods: Patients diagnosed with a BCR-ABL1-negative MPN between 2012 and 2020 were evaluated for the absolute lymphocyte count (ALC) at diagnosis. MPN were classified according to WHO2016, especially with regard to the distinction between ET and prefibrotic PMF by systematic correlation of BM cytology and histology.

Results: 130 patients were included into this preliminary analysis. Patients with overt myelofibrosis had a significantly lower median ALC compared to ET, PV and prefibrotic PMF (1.5x10^9/L versus 2.0x10^9/L, 1.9x10^9/L and 1.8x10^9/L, respectively; p=0.024).

An ALC< 1x10^9/L was rare in ET (2/44; 4.5%), PV (1/31; 3.2%) and prefibrotic PMF (1/24; 4.2%), but more common in overt MF (9/31; 29%; including 24 cases of PMF and 7 cases of post-ET or post-PV MF).

For overt MF, an ALC below the median (1.5x10^9/L) was associated with a lower hb concentration (93 vs. 119 g/l, p=0.02) and lower counts of

neutrophils and platelets (4.6 vs. 8.1x10^9/L, p=0.021 and 269x10^9/L vs. 545x10^9/L; p=0.02).

Conclusions: The relatively high prevalence of lymphopenia in overt myelofibrosis compared to other BCR-ABL1-negative MPN and its association with lower peripheral blood values point towards a causal relationship of lymphopenia and the pathobiology of the MF-associated bone marrow failure. Further work will focus on the association of lymphopenia with clinical disease characteristics, markers of systemic inflammation and the mutational profile in order to identify its prognostic impact.

Disclosure: Nothing to disclose

P28

Polatuzumab vedotin in relapsed/refractory diffuse large B-cell lymphoma

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Background: In DLBCL first line treatment with R-CHOP induces sustained remission in a majority of patients (pts), but 30-40% will relapse or are refractory (R/R). For pts not eligible for high-dose chemotherapy and ASCT treatment options are limited. Polatuzumab vedotin (Pola) is an antibody-drug conjugate targeting the B-cell receptor component CD79b. Combination of Pola with Rituximab and Bendamustin (Pola-BR) recently showed promising results.

Methods: We evaluated 7 pts with R/R aggressive lymphoma treated with Pola-BR that were not eligible or relapsed after ASCT or CAR T-cell therapy.

Results: From 07/2019 to 06/2020, 6 pts with R/R DLBCL and 1 with DLBCL leg-type were treated with Pola-BR. Median age was 73 years (25-86). 6 pts had biopsy confirmed relapse, 1 refractory DLBCL, all samples expressed CD79b. Median number of prior treatment lines was 4 (2-6) including CAR T-cell therapy (3) and allogenic stem cell transplantation (1). 3 pts achieved a CR, 1 relapsing 8.3 months after end of therapy. 2 pts achieved a PR, 2 progressed on therapy. Median PFS was 3 months (median follow-up 4 months). Treatment with Pola-BR was well tolerated. Grade 3-4 cytopenia occurred in 4 pts, 2 had severe cytopenia before therapy due to prior stem cell transplantation/CAR T-cell therapy. In comparison, median PFS in a historic cohort was 2 months, which is comparable to published outcomes.

Conclusions: Despite the limitations of the small number of pts and the short FU, preliminary results are promising. Therapy was well tolerated and safe in elderly, heavily pretreated pts.

Disclosure: Nothing to disclose

P29

FlowSOM, an unsupervised clustering method, improves flow cytometric MRD detection in AML patients

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Introduction: Minimal residual disease (MRD) measurement by flow cytometry has become an essential element for prognostication and therapeutic management of haematological malignancies. Recently, mathematical approaches have been developed to allow unsupervised and automated presentation and analysis of multidimensional flow cytometric data. We compared one of these approaches, FlowSOM, with our routine flow cytometric MRD analysis in AML patients.

Methods: Data were collected from 10 AML adult patients, followed for periods up to 45 months after diagnosis. 40 MRD data files, obtained with a standard 10 color antibody panel, were analysed using the FlowSOM algorithm and compared to data files from diagnosis and from a merged data file from 16 normal bone marrows. Results were further compared to MRD results from the routine flow cytometric analysis and the results from oncogenomics.

Results: At diagnosis FlowSom analysis was found to be 100% concordant with conventional analysis. In MRD analysis positive values were found in 19/40 cases with a sensitivity down to 1 x 10^{-3}. Concordance with results from routine analyses was obtained in 29/40 cases (73%) and with results from oncogenomics in 22/29 cases (76%). Discordant results could be explained by absence of aberrant markers on leukemic blasts, absence of available sensitive markers in oncogenomics and, in cases of positive MRD by oncogenomics but negative results by FlowSOM, use of highly sensitive PCR probes.

Discussion: This study shows the potential of performing MRD analyses with fully automated approaches for routine applications in the near future.

Disclosure: Nothing to disclose

P30

Lenalidomide effects on the bone marrow microenvironment in acute myeloid leukemia: translational analysis of the HOVON103 AML/SAKK30/10 Swiss trial cohort

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Background: This translational study aimed at gaining insights on the effects of lenalidomide in AML.

Methods: Forty-one AML patients aged 66 or older of the Swiss cohort of the HOVON-103 AML/SAKK30/10 study were included. After randomization, they received standard induction chemotherapy with or without lenalidomide. Bone marrow biopsies at diagnosis and before the 2nd induction were obtained to assess the therapeutic impact on leukemic blasts and microenvironment.

Results: In patients with AML with myelodysplasia-related changes (AML-MRC) the median PFS differed between the patients who received standard treatment (0.4 months) and the remaining patients receiving additional lenalidomide (2.6 months). Fittingly, morphological analysis revealed a higher initial microvessel density in AML-MRC and a more substantial decrease of microvascularization after lenalidomide exposure. A slight increase of T-bet-positive TH1-equivalents was identifiable under lenalidomide (Figure 1: A: Morphology at diagnosis B: Morphology before the 2nd induction cycle C: CD34 staining revealing higher microvessel density D: CD34 staining of the post-treatment biopsy illustrating a significant decrease of the microvessels E and F: Increasing amount of CD8-positive T-cell at initial diagnosis (E) and at follow-up (F) G and H: Increasing amount of T-bet-positive T-helper cells at initial diagnosis (G) and at follow-up (H). Cereblon (the target of lenalidomide) genotyping did not have an impact on the treatment effect or the prognosis, irrespective of the therapy applied.

Conclusions: Addition of lenalidomide may be beneficial to elderly patients suffering from AML-MRC, where it leads to a reduction of microvascularization and, probably, to an intensified T-cell-driven anti-leukemic response.

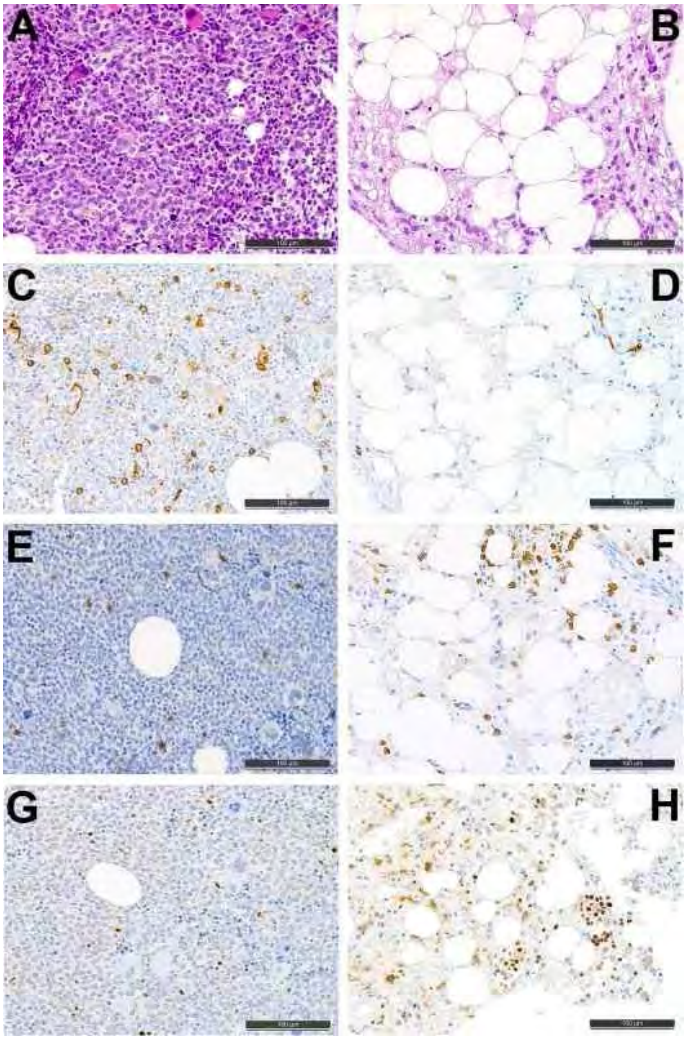

Figure 1: Pre- (left) and post-treatment (right) BM biopsies of a patient with AML

Disclosure: Nothing to disclose

P31

Feasibility of electronic patient-reported outcome monitoring with self-instructions and symptom-based warnings in aplastic anaemia and paroxysmal nocturnal haemoglobinuria

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Introduction: Electronic patient-reported outcome (ePRO) systems have the potential to improve patient safety and outcomes in cancer care, but have not yet been evaluated for aplastic anaemia (AA) and paroxysmal nocturnal haemoglobinuria (PNH). This pilot study evaluated the feasibility of an adapted and tested ePRO monitoring (Kaiku®), self-instruction and symptom-based warning system for patients with AA and PNH.

Methods: AA and PNH patients were asked to report symptoms by answering a weekly questionnaire within the ePRO system for six months. Based on a predefined algorithm the patients received self-management advice and prompts to contact clinicians in case of severe symptoms. The medical team could view patient-reported symptoms and received alerts of severe symptoms electronically.

Results: Nine patients completed the study. Compliance to weekly symptom-reporting was high (72%), whereby it decreased from 91 % to 53 % over the six month study duration. Satisfaction was high: ePRO was found easy to use, to understand and to integrate into daily life. Most patients (78%) would continue to use the platform and all would recommend the application to other AA/PNH patients. Of 331 symptoms reported, 82 (25%) were graded as severe with subsequent 36 clinician alerts. Clinicians saw the system as a useful supplement, but recommended to incorporate the system into the hospital information system (HIS).

Conclusion: Adherence was high and usability rated as very good, while the strongest benefit was indicated for newly diagnosed patients. To ensure compliance and improve patient care the incorporation into clinical workflows and the HIS is crucial.

Disclosure: Grants from Kaiku Health Ltd., University of Basel, ProPatient foundation and Novartis.

P32

Severe peripartum thrombocytopenia: a case of TTP with possible overlapping HELLP syndrom

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A 31-year-old patient was referred with macrohematuria in her 38th week of a previously uncomplicated second pregnancy. Her initial blood count revealed severe thrombocytopenia of 5 G/l, hemoglobin of 108 g/l with signs of hemolysis as well as discretely elevated liver enzymes (ASAT 52 U/l, ALAT normal) and nephrotic range proteinuria (5 g/l). Only a small number of schistocytes were present in the blood smear. The main differential diagnosis included (Pre-)eclampsia and HELLP syndrome, as well as the more rare causes of thrombotic microangiopathy (TMA) during pregnancy, thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome.

Since it is the only effective treatment of HELLP, cesarean section was opted for, requiring platelet transfusion support, which is controversial in the setting of TTP due to potential thrombotic complications and to be avoided except for life-threatening bleeding. Post cesarian section, microangiopathy worsened and our patient was ultimately diagnosed with pregnancy-associated TTP by evidence of severe deficiency in ADAMTS13 (1% in the reference laboratory) and presence of inhibitory antibodies. However, this diagnostic test is not readily available and results cannot be awaited before initiation of treatment. Fortunately, complications were minimal (splenic and small, asymptomatic cerebral infarctions).

Soon after delivery, specific TTP therapy, consisting of steroids and plasma exchange, was initiated. However, after an initial platelet increase, normalization was not achieved until the addition of Caplacizumab.

Our case illustrates the differential diagnoses, diagnostic and therapeutic challenges of severe thrombocytopenia during pregnancy.

Disclosure: Nothing to disclose

P33

Impact of different T cell depletion protocols on immune reconstitution following allogeneic hematopoietic stem cell transplantation

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a well-established therapeutic modality for a variety of hematological diseases unfortunately often complicated by graft-versus-host-disease (GVHD). Removal of T cells from the graft is a strategy to prevent GVHD. In this work, we analysed the impact of different T cell depletion strategies on immune reconstitution after HSCT.

We retrospectively analysed data from 168 patients transplanted between 2015 and 2019 at Geneva University Hospitals where several methods of TCD are being used: 1) *In vivo* T cell depletion using antithymocyte globulin (ATG); 2) partial T cell depletion (pTCD) using

alemtuzumab in the bag followed by an add-back of unmanipulated grafts; 3) Post transplant Cyclophosphamide (PTCy).

ATG was administered to 77 patients, 15 patients received a pTCD graft and 26 patients received ATG and pTCD graft. 24 patients were treated with PTCy and 26 patients received a T replete graft. TCD protocols had no significant impact on CD3 or CD8 T cell reconstitution during the first year post-HSCT (Figure 1). Conversely, CD4 T cells recovery was affected by the ATG/pTCD combination when compared to the T cell replete group (Figure 1). Interestingly, pTCD alone or in combination with ATG resulted in a better reconstitution of NK cells and B cells compared to T replete group.

All TCD protocols with the exception of PTCy are associated with a delayed recovery of CD4 T cells whereas pTCD of the graft significantly improves NK and B cell reconstitution.

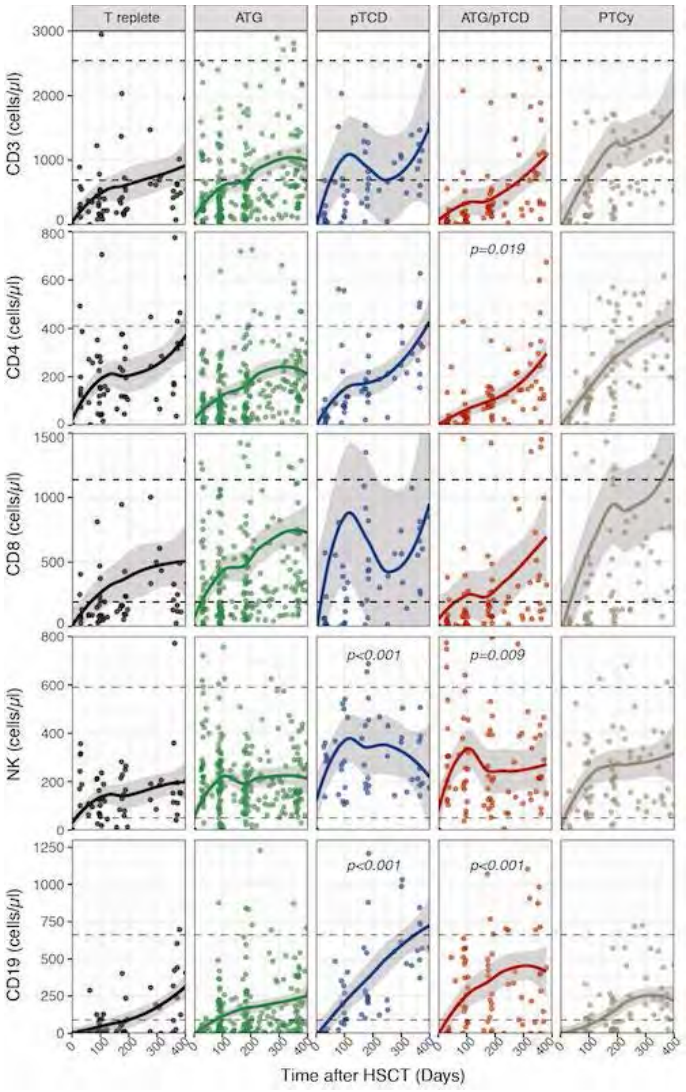

FIGURE 1 - Influence of T cell depletion on immune cells number in HSCT patients.

Disclosure: Nothing to disclose

P34

Continuous monitoring of health data with a wearable device in paediatric patients undergoing chemotherapy for cancer: a feasibility pilot study

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Background: During chemotherapy, delayed diagnosis and treatment of infections can increase mortality. Infections can trigger changes of vital signs, long before further clinical symptoms. Continuous monitoring with a non-invasive wearable device (WD), may detect such changes earlier than discrete measurements. We aimed to assess feasibility of continuous monitoring of health data in paediatric oncology patients.

Methods: In this single-centre pilot study a WD (Everion®, by Biovotion) was worn on the upper arm, for 14 days. The primary outcome was acceptable quality of monitored heart rate, during ≥18/24h per day on ≥7 consecutive days. Secondary outcomes included other vital signs, side effects, effort for the investigators and acceptability.

Results: Twenty patients were included (median age 6years; 3 to 16y). Six patients (age 3 to 16 years) fulfilled the primary outcome. Heart rate was monitored with acceptable quality for ≥18/24h in 142 (52%) of 274 study days. Side effects reported were sweating, local skin irritation and one superficial skin lesion. The effort for the investigators was high due to a time-consuming inclusion process, daily data availability checks and 52 contacts, mostly for data problems. Eighteen of 20 patients or parents indicated that the Everion® is suitable to measure health data in children.

Conclusion: This study shows that continuous monitoring of health data by a WD is feasible across the entire age range of paediatric oncology patients, although the predefined feasibility criterion (15/20 patients) was not reached. These results will influence future WD-studies, which aim to identify patterns predicting imminent fever or infection.

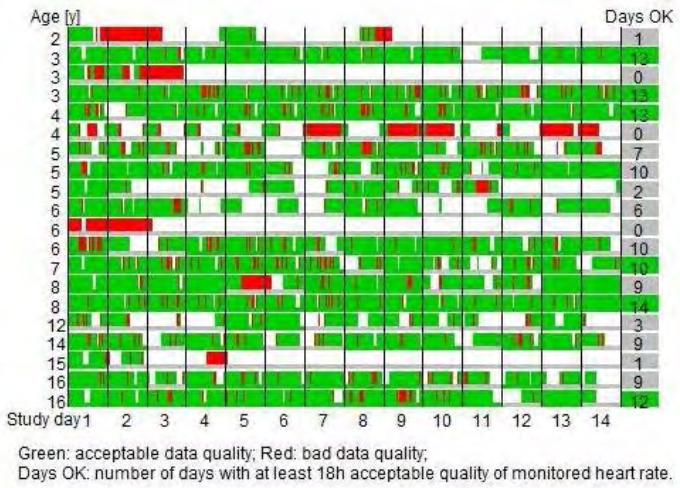

Figure 1: Primary outcome (heart rate) of all 20 patients ordered by age, per study day.

Disclosure: Nothing to disclose

P35

CARTcell infusion following checkpoint inhibition can induce remission in chemorefractory post-transplant lymphoproliferative disease (PTLD) of the central nervous system (CNS)

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Background: CD19-CARTcells are a potent treatment in relapsed/refractory lymphomas. Patients with CNS lymphoma were excluded from most CART trials due to concerns of neurotoxicity. Case series revealed activity of CART in the CNS with no excess neurotoxicity. For PTLD the use of checkpoint-inhibitors (CI) and CART requires thorough consideration as it puts the allograft at risk.

Methods: We present a 19 y/o patient who received CART (Tisagenlecleucel) following CI for PTLD manifesting as EBV-associated DLBCL of the intestines with secondary CNS involvement.

Results: 1st-line therapy with R-CHOP achieved a CR after 3 cycles. After cycle 5 our patient presented with seizures. Multiple CNS lymphoma lesions were found (90% PD-L1-Expression), with no other manifestations outside the CNS. Salvage MATRIX chemotherapy resulted in a PR. Due to the poor condition (ECOG 2-3), treatment with Pembrolizumab was initiated, and tolerated well with no signs of autoimmunity, but stable kidney parameters, and shrinking CNS lesions. 4 weeks later, the patient received $0.9x10^8$ CART. CRS°1 and neurotoxicity (ICANS) °1 resolved without specific interventions. Imaging confirms an ongoing remission. With no signs of allograft dysfunction, the patient is in good condition 10 months after treatment.

Discussion: Pembrolizumab resulted in a PR. Consolidation with CART deepened the response with only mild side effects. The role of CART for suppression of humoral immunity against the allograft remains unclear. But CI followed by CART therapy can be safe and efficient in selected patients with PTLD, even with CNS involvement. Strongest precautions are needed regarding possible complications and allograft loss.

Disclosure: Supervisory board MagForce, Berlin Shares MagForce, Berlin Travel support/reimbursement Janssen, Amgen

P36

Case report: complexity of CRS/ ICANS management in clinical practice

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A 69 year old male, diagnosed with DLBCL stage IVA involving bone in 2018 had achieved a CR after R-CHOP x6. In May 2020 the disease relapsed with marrow involvement and leukemic manifestations and loss of CD 20. The salvage therapy with DHAP did not result in a remission.

He received CAR-T cells in June 2020 after lymphodepleting chemotherapy with fludarabine and cyclophosphamide.

On day +1 he developed immediately a high temperature > 40°C and within 3 days vasopessor demanding hypotension (CRS grade III). In spite of treatment with tocilizumab (4 doses) and steroids (up to 80mg dexamethasone qd) the inflammatory state could not be controlled. He went on to devlop CIRS IV and ICANS IV with coma, epilepsy, intubation, vasopressor use, hemodialysis and use of the cytosorb filter. In addition he was treated with Siltuximab to block IL-6 (single dose) and by Dasatinib for seven days.

The patient recovered to a large degree from all these inflammatory complications is in CR from the DLBCL to this date but is suffering from prolonged pancytopenia. As a consequence he suffered from infectious complications.

We use this to illustrate graphically the course of IL-6, CRP, Ferritin, and cytopenia in particular illustrating the duration of suppression of inflammation when measured through CRP and IL-6 after the combined use of tocilizumab and siltuximab. The CAR-T cells went through manifold expansion and continue to persist in the patient circulation along with absent B-cells and hypogammaglobulinemia.

Disclosure: Nothing to disclose

P37

Achieving complete remission of primary effusion lymphoma with daratumumab and chemotherapy, a case report

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Primary effusion lymphoma (PEL) is a rare disease with dismal prognosis and no well-established treatment standards. Overall survival of the patients rarely exceeds three to four months. Here we report the case of a 55-years old man with newly diagnosed HIV infection that presented initially with histologically confirmed Kaposi sarcoma of the stomach and colon as well as multicentric Castleman's disease. After initiating HAART, clinical improvement and shrinkage of the generalized lymphadenopathies were achieved. Six months after initiation of HAART, the patient developed symptomatic ascites, with presence of monoclonal lymphoblastic cells expressing HHV-8, CD38, CD43, CD45, CD138dim and CD3dim, leading to the diagnosis of PEL. The HHV-8 positivity was also demonstrated by immunohistochemistry in Kaposi sarcoma and in Castleman's disease. Given the poor prognosis of PEL, the lack of treatment standards, and the expression of CD38, we decided to combine Daratumumab, a monocolonal antibody targeting CD38, to a classical CHOP regimen. After 4 cycles of full dose chemotherapy and 11 weekly doses of daratumumab, the patient achieved a morphologic and metabolic complete remission of the PEL as well as of Kaposi and Castleman's disease, as documented by negative FDG-PET/CT. Remission of Kaposi was histologically confirmed. Unfortunately, about a month later, PEL recurred, leading to paralytic ileus and to the death of the patient within four weeks. In conclusion, daratumumab combined to CHOP was well tolerated and led to a complete remission of PEL as well as Kaposi sarcoma and Castleman's disease.

Disclosure: Nothing to disclose

P38

Combination of Cobimetinib and Cladribine can lead to complete remission in heavily pre-treated adult patients with multi-system langerhans cell histiocytosis

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Background: Langerhans cell histiocytosis (LCH) is a rare disease in adults with limited data to clinical care. Clinical presentations is heterogeneous, treatment varies from observational strategies to chemotherapy. Current data suggests first-line treatment with cytarabine or cladribine. Data for BRAF and MEK inhibitors are promising as alterations of the MAPK-signaling pathway (BRAFV600E and MAP2K1-Mutations) occur in up to 70% of LCH-Patients. We report a case of a heavily pretreated patient with MS-LCH, achieving complete remission with the combination of MEK-Inhibitor cobimetinib and chemotherapy.

Case report: Our patient (62 yrs) was diagnosed with multi-systemic LCH and treated with cytarabine, achieving only a partial remission after 12 cycles. As MAP2K1 mutation was detected, we treated him with the MEK-Inhibitor cobimetinib for 12 months, later combined with hydroxyurea as maintenance therapy, achieving a complete remission for the first time. After nearly 1.5 years of maintenance therapy with hydroxyurea, LCH progressed. We stopped hydroxyurea and re-installed cobimetinib, achieving a stable disease after 6 month. We combined the treatment with cladribine for 6 cycles in total. A PET-CT-Scan showed again a CR. We continue cobimetinib as maintenance, without clinical signs of progression so far. Side effects were rosacea and CK elevation and the dosage of cobimetinib was reduced to 20 mg daily.

Conclusions: Treatment of MS-LCH in adults is a challenge. Optimal treatment is unclear. Approaches with monotherapy seem to be not sufficient in MS-LCH. In case of BRAF/MAP2K1-mutations a combination of chemotherapy and BRAF/MEK-Inhibition as well as maintenance therapy might be a reasonable combination.

Disclosure: supervisory board magforce ag, berlin, travel support/reimbursement janssen, amgen shares: magforce ag, berlin,

P39

Severe pulmonary emphysema associated with systemic AL-amyloidosis

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Introduction: Diffuse parenchymal pulmonary amyloidosis, also known as diffuse alveolar septal amyloidosis, is characterised by the presence of amyloid deposits in the alveolar septa and vascular walls.

Here we report on a 52-year-old patient with a history of plasma cell myeloma (PCM) type IgD lambda and consecutive AL amyloidosis, who was treated with immunochemotherapy containing a proteasome inhibitor, lenalidomide and dexamethasone for ten cycles in 2018, resulting in a stringent complete response. Due to chronic obstructive pulmonary disease (COPD) with severe, heterogeneous pulmonary emphysema, he was treated with lung volume reduction surgery (LVRS) recently. No measurable PCM activity was detected at the time of LVRS.

Results: Histopathologic analysis of the lung tissue revealed extensive diffuse parenchymatous pulmonary amyloidosis with abundant evidence of free light chain lambda amyloid perivascular and in the alveolar septa (Figure 1). The intervention led only to short-term success due to rapid progression of emphysema and hyperinflation.

Conclusion: Only a few cases of diffuse parenchymal pulmonary amyloidosis have been described so far and none of them led to emphysema. Therefore, the pathogenesis of severe emphysematous changes due to amyloid deposition remains unclear. In our case, the distribution of the amorphous material in the small bronchial walls suggests a check valve mechanism that favours emphysematous changes and inflammation. In summary, diffuse parenchymal pulmonary amyloidosis despite its rarity, might be added to the differential diagnosis of a rapidly worsening emphysema.

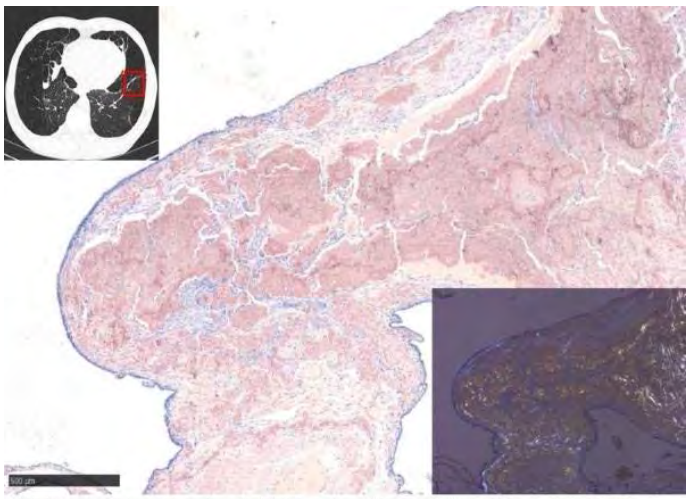

Figure 1. Histology of emphysematous lung tissue with septal and perivascular amyloid deposits with apple-green birefringence under polarised light.

Disclosure: Nothing to disclose

Topic: Clinical solid tumor oncology (SSMO award for clinical solid tumor oncology)

P40

Trastuzumab deruxtecan (T-DXd, DS-8201) in HER2-positive metastatic breast cancer previously treated with T-DM1: DESTINY-Breast01 Study

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Background: Trastuzumab deruxtecan (T-DXd; DS-8201) is an ADC with a HER2-antibody, tetrapeptide-based-cleavable linker and novel topoisomerase I inhibitor payload. In a phase 1 study the ORR was 59.5% and median PFS 22.1 months in patients with HER2-positive metastatic breast cancer (mBC) previously treated with T-DM1 (Tamura, Lancet Oncol, 2019).

Methods: DESTINY-Breast01 (NCT03248492) is an open-label, international, phase 2 registration study of T-DXd in patients with centrally-confirmed HER2-positive mBC.

Patients were required to have mBC that progressed on or after T-DM1. The primary endpoint was ORR (CR+PR) per independent central review (ICR). Additional endpoints included Disease Control Rate, Duration of Response and Progression Free Survival.

Results: At data cutoff (01 August 2019), 184 patients received the RP2D (5.4mg/kg). The confirmed ORR was 60.9 % (112/184 [95% CI, 53.4%-68.0%]). ORRs were consistent across subgroups. DCR, 97.3% (95% CI, 93.8%-99.1%). Median DOR, 14.8 months (95% CI, 13.8-16.9); median PFS 16.4 months (95% CI, 12.7-not reached).

TEAEs grade ≥3 occurred in 57.1% of patients; the most common were decreased neutrophil count (20.7%), anemia (8.7%), nausea (7.6%), decreased white cell count (6.5%), decreased lymphocyte count (6.5%), and fatigue (6.0%). 25 patients (13.6%) had interstitial lung disease (ILD); ILD was primarily grade 1/2 (10.9%; one grade 3, no grade 4; 2.2% grade 5).

Conclusion: Overall, T-DXd treatment demonstrated clinically meaningful and durable activity in heavily-pretreated patients with HER2-positive mBC. T-DXd had a generally manageable safety profile with ILD identified as a risk warranting proactive awareness and management.

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P41

Impact of baseline disease volume and prior docetaxel therapy on PSA-related outcomes in patients with mHSPC receiving enzalutamide plus ADT

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Background: Enzalutamide plus androgen deprivation therapy (ADT) significantly reduced the risk of radiographic progression or death in men with metastatic hormone-sensitive prostate cancer (mHSPC), regardless of baseline prostate-specific antigen (PSA) levels (ARCHES; NCT02677896). Here, we further assess PSA-related outcomes in patients enrolled in ARCHES by disease volume and prior docetaxel therapy at study entry.

Methods: Patients with mHSPC (n=1150) were randomised 1:1 to enzalutamide (160 mg/day) plus ADT or placebo plus ADT. Primary endpoint was radiographic progression-free survival. Secondary endpoints included time to PSA progression and PSA undetectable rate. *Post hoc* analyses were based on disease volume and prior docetaxel at study entry, which were stratification factors, as well as time to 50% PSA reduction and time to undetectable (< 0.2 ng/mL) PSA.

Results: Overall, 423 (36.8%) patients had low-volume disease and 205 (17.8%) patients reported prior docetaxel use. Enzalutamide plus ADT significantly improved PSA-related outcomes versus placebo plus ADT, regardless of disease volume or prior docetaxel use at study entry (Table). The proportion of patients with ≥50% PSA reduction from baseline was 85-95% for enzalutamide plus ADT and 18-66% for placebo plus ADT across subgroups.

Conclusions: Enzalutamide plus ADT improved all assessed PSA-related outcomes versus placebo plus ADT in patients with mHSPC, irrespective of disease volume or prior docetaxel therapy. True baseline PSA is unknown for some patients due to prior ADT use in this population.

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Editorial: Complete HealthVizion.

Endpoint	Overall population	Disease volume		Prior docetaxel therapy	
	(n=1150)	Low (n=423)	High (n=727)	No (n=945)	Yes[a] (n=205)
Time to PSA progression[b]					
HR (95% CI)[c]	0.19 (0.13, 0.26)	0.08 (0.03, 0.20)	0.22 (0.16, 0.32)	0.18 (0.13, 0.26)	0.22 (0.11, 0.45)
Time to 50% PSA reduction					
HR (95% CI)[d]	3.76 (3.20, 4.41)	3.59 (2.77, 4.65)	3.89 (3.17, 4.77)	3.31 (2.79, 3.94)	11.54 (6.88, 19.35)
Time to undetectable PSA					
(n)[e]	(n=1017)	(n=356)	(n=661)	(n=875)	(n=142)
HR (95% CI)[d]	5.88 (4.64, 7.45)	4.71 (3.40, 6.53)	7.82 (5.49, 11.14)	5.50 (4.30, 7.03)	12.66 (5.00, 32.08)

Table. PSA-related outcomes for enzalutamide plus ADT versus placebo plus ADT

All p<0.0001. [a]1–6 cycles; [b]PSA progression was defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir, confirmed by a second consecutive value ≥3 weeks later; [c]HR <1 favours enzalutamide plus ADT, as it reduces the risk of PSA progression; [d]HR >1 favours enzalutamide plus ADT, as it increases the chance of PSA reduction; [e]Only includes patients with detectable (≥0.2 ng/mL) PSA at baseline. CI=confidence interval; HR=hazard ratio.

PSA-related outcomes for enzalutamide plus ADT versus placebo plus ADT

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P42

First-line (1L) enfortumab vedotin plus pembrolizumab demonstrates durable antitumour activity in cisplatin-ineligible patients with locally advanced/metastatic urothelial carcinoma (la/mUC)

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Background: For patients with la/mUC and high PD-L1 expression, PD-1/PD-L1 inhibitors show promising durability with 1L platinum chemotherapy. Enfortumab vedotin (EV) is an antibody-drug conjugate delivering MMAE to cells expressing Nectin-4. EV received FDA accelerated approval based on tumour response rates for adults with la/mUC who have previously received a PD-1/PD-L1 inhibitor and a platinum-containing chemotherapy. EV is investigational in the 1L setting. We describe the safety and ORR/durability of EV+pembrolizumab in 1L cisplatin-ineligible patients.

Methods: The multicohort study (NCT03288545) evaluates safety/activity of EV with other therapies. This report highlights 1L cisplatin-ineligible patients treated with EV 1.25 mg/kg (Days 1, 8) and pembrolizumab (Day 1) in 21-day cycles. Endpoints included safety/tolerability, investigator-assessed response per RECIST v1.1, and OS.

Results: As of October 2019, 45 1L la/mUC patients (median age 69 years) received a median of nine EV+pembrolizumab cycles (range 1-22). Common treatment-emergent AEs included fatigue (58%; 11% ≥G3), alopecia (53%), and peripheral sensory neuropathy (53%; 4% ≥G3). One patient died from treatment-related AE (multiple organ dysfunction syndrome). During the 11.5-month median follow-up, confirmed ORR was 73.3% (95% CI: 58.1-85.4%); DCR was 93.3%. Encouraging ORR was observed in important subgroups (Table). Of 33 responders, 18 had ongoing response (11 responses >10 months). Median DoR and OS were not reached; median PFS was 12.3 months. The 12-month DoR, PFS, and OS rates were 53.7%, 50.1%, and 81.6%, respectively.

Conclusions: In 1L cisplatin-ineligible patients with la/mUC, EV+pembrolizumab is an investigational platinum-free option demonstrating activity and durability, with a manageable safety profile.

Table. Best Overall Response per Response Evaluation Criteria in Solid Tumors v1.1 by Investigator (N=45)

Response Parameter	% (n)
Confirmed ORR	73.3 (33)
Complete response	15.6 (7)
Partial response	57.8 (26)
Stable disease	20.0 (9)
Progressive disease	2.2 (1)
Not evaluable	4.4 (2)
ORR by subgroup	
ORR in patients with liver metastasis	53.3 (8/15)
ORR by PD-L1 expression	
High expression	78.6 (11/14)
Low expression	63.2 (12/19)

Abbreviation: ORR, objective response rate.

Table. Best Overall Response per Response Evaluation Criteria in Solid Tumours v1.1 by Investigato

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P43

Quality of life in patients with aflibercept and FOLFIRI for metastatic colorectal cancer: final analysis of the non-interventional study QoLiTrap

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Background: Aflibercept is approved in combination with FOLFIRI for treatment of metastatic colorectal cancer that is resistant to or has progressed after oxaliplatin-containing therapy.

Methods: QoLiTrap was a non-interventional study conducted in Germany, Austria and Switzerland to evaluate quality of life, treatment outcomes and safety in mCRC patients treated with aflibercept + FOLFIRI under routine conditions.

Results: From September 2013 to September 2019, 1293 patients were enrolled. Hereof, 1277 patients (mean age: 65.5±9.8 years; 64.8% male, 50.7% with documented RAS mutation, ECOG 0-1: 84.7%) were considered for final analysis, the primary endpoint set comprised 872 patients.

For 55.7% of the patients, a decrease of ≥5% of EORTC QLQ-C30 global health score was documented whereas 40.3% of patients showed a decrease of < 5% or an improvement during the first 12 weeks of treatment (mean change: -4.6%).

23.1% of patients pretreated with anti-VEGF/R and/or anti-EGFR exhibited CR+PR and 48.3% had SD as best response to 2nd line aflibercept (RAS-wt patients: 25.7% CR+PR, 50.5% SD; RAS-mut patients: 21.8% CR+PR, 46.0% SD). Median PFS of patients pretreated with anti-VEGF/R and/or anti-EGFR was 7.4 months (95% CI 6.4-9.4) for RAS-wt and 7.1 months (95% CI 6.1-7.8) for RAS-mut patients. Overall survival was 23.6 months (95% CI 14.2-31.6) for RAS-wt and 18.1 months (95% CI 13.2-21.0) for RAS-mut patients.

No new safety signals were observed for aflibercept.

Conclusions: Final results indicate partially better outcomes in the routine population than in the Phase 3 VELOUR registration trial, especially regarding OS.

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P44

Ramucirumab for patients with advanced HCC and elevated alpha-fetoprotein following non-sorafenib-based therapy: interim results from phase 3 REACH-2 expansion cohort

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Introduction: Similar to other contemporary trials, REACH (NCT01140347) and REACH-2 (NCT02435433) did not include patients who received first-line therapy other than sorafenib, which was the only treatment with demonstrated OS when the trials were designed. This global open-label expansion (OLE), single-arm REACH-2 cohort studies ramucirumab in patients with advanced HCC and baseline alpha-fetoprotein (AFP)≥400ng/mL following a non-sorafenib-based therapy.

Methods: Eligible patients have advanced HCC, Child-Pugh-A, ECOG PS 0/1, baseline AFP≥400ng/mL and 1-2 prior systemic regimens for HCC, excluding sorafenib or chemotherapy. Liver transplant patients are eligible. ~44 patients will receive ramucirumab 8mg/kg IV Q2W. Primary endpoint: safety; secondary endpoints include OS, PFS, objective response rate (ORR), and patient-reported outcomes. Final analysis will occur after all patients have completed ≥3 cycles of ramucirumab or discontinued.

Results: As of interim data cut-off (31-January-2020), 24 patients were enrolled: 96% male, median baseline AFP=2094ng/mL (IQR:854, 7981), 50% ECOG PS 0, 96% Child-Pugh-A, 67% ALBI grade1, and 92% BCLC stage C. Most common prior systemic therapies were lenvatinib (n=8), monotherapy PD-1/PD-L1 inhibitor (n=9), PD-1 inhibitor+lenvatinib (n=3), and atezolizumab+bevacizumab (n=3). Grade≥3 TEAEs (≥10%) were hypertension (n=4), proteinuria (n=3), and pneumonia (n=3). No deaths due to AEs occurred. With median follow-up=6.5 months, median PFS was 5.5 months (18 events; 95%CI=1.3-7.5). ORR was 16.7% (95%CI=1.8-31.6). Median OS was immature (10 events).

Conclusions: Safety and efficacy of ramucirumab following a non-sorafenib-based systemic therapy was consistent with that observed in patients who received prior sorafenib in ITT REACH-2 population.

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P45

Patient-reported outcomes in patients with metastatic bone disease from solid tumors treated with bone-targeted agents: a real-world study (SAKK 95/16)

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Background: Bone-targeted agents (BTAs) are widely used in the management of patients with bone metastases from solid tumors. Knowledge

of the impact of their routine care use on patient-reported pain and bone pain-related quality of life (QoL) is limited.

Patients and **Methods:** This real world, cross-sectional study enrolled patients over a 3-month period. Patients were ≥18 years, had solid tumors and at least one bone metastasis, and received routine care for bone metastases. Physicians provided data on BTA-related practices, risk of bone complications and BTA regimen. Patients completed questionnaires about pain, general and bone pain-related QoL and treatment satisfaction.

Results: Eighteen sites recruited 417 patients. Patients not treated with a BTA had better overall QoL (FACT-G: p=0.031) and bone pain-related QoL (FACT-BP, p=0.007) than those treated with a BTA. All pain and other QoL scales did not differ between groups. Patients perceived at 'low risk of bone complications' by their physician not receiving a BTA reported less pain and better QoL than those considered at 'low risk' but receiving BTA treatment or those considered at 'high risk' regardless of BTA treatment. Overall satisfaction with the treatment was good; almost 50% of patients reporting that they were completely satisfied.

Conclusions: Overall, pain and QoL did not differ according to BTA treatment or physicians' risk perception. Patient with low risks not receiving BTA treatment reported least pain and highest QoL scores. These results indicate that treating physicians assess bone complication risk appropriately and treat patients accordingly.

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P46

Oncological outcomes at a medium sized Cantonal Hospital: 2008 to 2017

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Background: Retrospective data from the Swiss National Institute for Cancer Epidemiology and Registration (NICER) showed regional differences in the management and outcome of breast and lung cancer. Until 2019 patients treated in the Canton of Solothurn were not included in a cancer registry. Olten Cantonal Hospital (OCH) is a medium sized general hospital with 225 beds serving a population of ~100`000. Since 2008 OCH has its own in-house medical oncology service (MOS).

Material and Methods: We performed a retrospective chart review of all patients with Hodgkin lymphoma, DLBCL, NSCLC, breast, testicular and colon cancer from 2008 to 2017 with at least one outpatient visit in the MOS. Progression free survival and overall survival (OS) were clinical outcomes of interest. In addition, correlations between these results and the stage of illness, the performance status, the comorbidity index and compliance with guidelines were investigated.

Results: Until September 8th 2020, 843 patients with a median follow-up of 70 months were analysed. 31.0% had stage 1 (of which 71,3% are breast cancer patients) and 33.7% had stage 4 disease. In the potentially curative setting, 89.9% achieved a complete remission. In the palliative setting, 55.7% achieved at least stable disease to first line treatment. The results of OS stratified by tumor type are presented in Table 1.

Conclusion: OS for oncological patients at OCH seems to be comparable to national data. In order to obtain comparable data for national health policy beyond OS, a standardised prospective collection of clinical data is necessary.

Table 1 Outcome summary

TUMOR TYPE			OS PROBABILITY AT 12 MONTHS		OS PROBABILITY AT 60 MONTHS	
OCH	NICER	NR (%)	OCH(95%CI)	NICER	OCH(95%CI)	NICER
		N=843				
BREAST CANCER	BREAST CANCER	344 (40.8)	96.12 (94.08,98.21)	95.20	78.62 (73.94,83.61)	78.70
COLON CANCER	LARGE BOWEL CANCER	143 (17.0)	86.44 (80.95,92.30)	84.20	50.36 (42.25,60.04)	58.50
DLBCL	NON-HODGKIN LYMPHOMA	46 (5.5)	91.16 (83.24,99.82)	83.20	72.16 (59.87,86.98)	64.50
HODGKIN LYMPHOMA	HODGKIN LYMPHOMA	26 (3.1)	84.62 (71.82,99.69)	93.60	72.53 (57.08,92.15)	86.40
NSCLC	LUNG+TRACHEA /BRONCHUS	234 (27.8)	55.44 (49.35,62.29)	52.50	24.09 (18.80,30.87)	21.10
TESTICULAR CANCER	TESTICULAR CANCER	50 (5.9)	100 (100,100)	98.10	97.30 (92.21,100)	93.70

OS (overall survival), OCH (Olten Cantonal Hospital), NR (number), CI (confidence interval), NICER (National Institute for Cancer Epidemiology and Registration, 2012-2016)

Disclosure: Nothing to disclose

P47

SAKK 19/17-safety analysis of first-lLine durvalumab in patients with PD-L1 positive, advanced NSCLC and a performance status of 2

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Data from 21 patients were available at this interim safety analysis. Among these, 13 deaths (13/21; 62%) were reported, including one treatment-related fatal colonic perforation at 9 months after treatment initiation (1/13; 8%). Twelve deaths were not treatment-related (12/13; 92%), and mostly attributed to tumor progression (10/13; 77%). Of note, seven deaths (7/13; 54%) occurred during the first 5 weeks (range: 0.6-4.7 weeks) after treatment initiation. Four (4/7; 57%) were respiratory failures attributed to tumor progression. One of these patients (25%) had pre-existing COPD, and three (75%) had baseline dyspnea grade 2-3 related to the tumor. Grade ≥3 treatment-related AEs (TRAEs) included colonic perforation (grade 5), abdominal pain, and colitis (grade 3 each) in one patient and fatigue (grade 3) in another. Other Grade ≥3 AEs unrelated to treatment were all of pulmonary origin: lung infections (19%), dyspnea (24%), cough (5%), and bronchial obstruction (5%).

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A phase 3, multicenter, randomized, open-label trial of trastuzumab deruxtecan (T-DXd; DS-8201) vs investigator's choice in HER2-low breast cancer (DESTINY-Breast04)

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Introduction: HER2-targeted therapies have greatly improved survival in patients (pts) with HER2-positive breast cancer (BC). However, for pts with HER2-low BC (IHC1+ or IHC2+/ISH negative), no HER2-targeted therapies is approved. Trastuzumab deruxtecan (T-DXd; formerly DS-8201) is an antibody-drug-conjugate comprised of a humanized anti-HER2 antibody attached to a membrane-permeable topoisomerase I inhibitor payload via a cleavable, tetrapeptide-based linker with a drug-to-antibody ratio of ≈8. In a recent phase 1b study, T-DXd showed activity in pts with HER2-low (IHC2+/ISH−, IHC1+/ISH−, or IHC1+/ISH untested), advanced BC, demonstrating a confirmed ORR by independent central review (ICR) of 37.0% (20/54) (Modi et al. *JCO*, 2020). This phase 3 trial evaluates T-DXd in pts with HER2-low BC.

Methods: DESTINY-Breast04 is a randomized, phase 3, 2-arm, open-label, multicenter trial comparing the efficacy and safety of T-DXd with investigator's choice of treatment in HER2-low (IHC1+ or IHC2+/ISH−), unresectable and/or metastatic BC. The trial is recruiting pts from 223 sites in North America, Europe, and Asia. Approximately 540 pts (480 HR+ and 60 HR-) will be randomized (2:1) to T-DXd (5.4 mg/kg intravenously q3w) or investigator's choice (capecitabine, eribulin, gemcitabine, paclitaxel, or *nab*-paclitaxel) and stratified by HER2 IHC status, number of prior treatments, and prior CDK4/6 inhibitor therapy/HR status. The primary efficacy endpoint is PFS (by blinded ICR). Secondary efficacy endpoints include investigator-assessed PFS, OS, ORR, and duration of response. Safety endpoints include TEAEs SAEs, and AEs of special interest (including interstitial lung disease/pneumonitis, cardiotoxicity, and infusion-related reactions). For further information about this trial, visit ClinicalTrials.gov (NCT03734029).

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A blood based targeted proteomics biomarkers signature for malignant pleural mesothelioma

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The clinical use of blood tests for the detection of malignant pleural mesothelioma (MPM) or patient's stratification is currently hampered by the lack of sensitive blood biomarkers. In a previous work, we have identified a targeted proteomics candidate biomarkers signature for MPM from the blood and composed of seven N-linked glycopeptides (N-glycopeptides). Here, we have verified a reduced version of the original proteomics signature (now composed of six N-glycopeptides) within a multicenter cohort of more than 400 serum samples collected in the USA, Australia and Europe from MPM patients and cancer-free asbestos exposed donors. The AUC of the proteomics signature was 0.738 for discriminating MPM patients and asbestos exposed donors. For early stage MPM (stage I/II) AUC was 0.765. These results were in line with what we observed by using an FDA approved ELISA test for the best investigated MPM blood biomarker SMRP (soluble mesothelin-related peptides). This highlighted the potential of our academically developed MPM proteomics signature once further optimized for routine clinical use. The negative likelihood ratio of the proteomics signature was 0.11 for early stage MPM, reflecting its higher sensitivity also if compared to SMRP. This will be relevant in the context of early disease detection and screenings for thoracic malignancies. Further, the proteomics signature demonstrated prognostic capacity, separating high-risk and low-risk groups of MPM patients with a hazard ratio of 1.659 and which may support clinical treatment decisions. In summary, targeted proteomics permitted to establish a blood based biomarkers signature with diagnostic and prognostic ability for MPM.

Disclosure: No potential conflicts of interest

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Intravesical recombinant BCG followed by perioperative chemo-immunotherapy for muscle-invasive bladder cancer (MIBC). A single arm phase 2 trial (SAKK 06/19)

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Background: Neoadjuvant chemo-immunotherapy is currently investigated in MIBC demonstrating somewhat higher response rates but further improvement is needed.

Intravesical BCG has been successfully used for non-muscle invasive bladder cancer (NMIBC) for decades in patients (pts) with CIS and as adjuvant treatment for high risk papillary tumors. It induces a local inflammation leading to induction of the innate immune system, probably followed by a tumor-specific adaptive immune response. Recently, a novel recombinant BCG vaccine (VPM1002BC) has been developed and has proven low local toxicity, good safety and efficacy in a single arm clinical study in NMIBC (SAKK 06/14).

We hypothesize that intravesical VPM1002BC improves the efficacy of perioperative chemo-immunotherapy in pts with operable MIBC.

Methods: SAKK 06/19 is an open-label single arm phase II trial for pts with operable MIBC pT2 or cT2-T4a cN0-1 without contraindication for cisplatin. Prior intravesical BCG is excluded as are pts unable to keep BCG instillation for less than 1 hour.

Intravesical VPM1002BC is applied weekly for 3 instillations followed by 4 cycles of neoadjuvant cisplatin/gemcitabine (cis/gem) q3w in combination with 4 cycles atezolizumab (atezo) 1200mg q3w followed by radical cystectomy. Atezo is continued after surgery q3w for 13 cycles.

pCR (ypT0) at cystectomy is the primary endpoint. Using A´Hern Fleming design and null hypothesis of ≤35% with an alternative hypothesis of ≥55% pCR a total of 62 pts is needed.

Secondary endpoints include pathological response rate (< ypT2N0), event-free survival, recurrence-free survival, overall survival, feasibility and toxicity.

Accrual to the trial starts in January 2021.

Disclosure: Advisory Board: Astra Zeneca, Bayer, BMS, Astellas, Janssen, MSD, Roche, Sanofi, Ipsen, Pfizer Honoraria: Debiopharm, Roche, Janssen, Astellas Travel support: Astra Zeneca

P51

Co-clinical modelling and therapeutic targeting of BRAF-R506_K507ins_VLR in a patient with KRAS wild type pancreatic cancer

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Precision treatment for pancreatic ductal adenocarcinoma (PDAC) is extremely challenging due to the high prevalence of undruggable mutations in KRAS. 5-7% of PDACs harbor unmutated, wild type KRAS and for these, a variety of potentially targetable oncogenic driver alterations have been described.

Comprehensive molecular profiling of a *KRAS* wild type PDAC diagnosed in a 74-year-old patient identified BRAF-R506_K507ins VLR as potential driver oncogene. Structure modelling predicted this mutation to increase BRAF activity through enhanced homo- and heterodimerization. The patient received MEK inhibitor trametinib as 4th line treatment. Best achieved response was prolonged stable (6 months) disease together with a significant drop in CA19-9 levels.

Patient-derived tumor organoids (PDOs) were generated as part of a living biobanking project. *Ex vivo* drug testing confirmed enhanced sensitivity to MEK inhibition compared to *KRAS*-mutated PDAC-PDOs assayed in parallel. None of several tested approved and experimental

BRAF- and pan-RAF inhibitors showed efficacy. Combination drug testing showed weak synergy for trametinib in combination with CDK4/6 inhibitor abemaciclib.

This is the first reported case of BRAF-R506_K507ins_VLR in PDAC. This exemplary case illustrates the importance of comprehensive genomic profiling in *KRAS* wild type PDACs. It also highlights the potential of co-clinical organoid modelling for translational research.

Disclosure: Nothing to disclose

P52

An extra-osseous Ewing sarcoma mimicking ovarian carcinoma: a case presentation

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Ewing´s sarcoma is an aggressive form of malignancy affecting mostly children, rarely diagnosed in patients over 40 years of age.

The specter of Ewing sarcoma encompass a vast variety of subtypes including classical Ewing tumors, atypical Ewing tumors and peripheral primitive neuroectodermal tumors (pPNET). Extra-osseous Ewing sarcoma of the ovary is extremely rare, posing great diagnostic challenges.

In this report, we describe the case of a 37 years old woman admitted to the gynaecological oncology department for a symptomatic right ovarian mass discovered on pelvic ultrasound. Laboratory findings revealed an elevated CA 125 tumor marker at 356 kU/l (UNL 35kU/L) with normal values for CA 19-9, CA 15-3, CEA, AFP and β-HCG. ^{18}F-FDG PET/CT revealed a metastatic spreading of the pelvic mass to the peritoneum, the mediastinum and the bones. Although the diagnostic workout suggested primary ovarian malignancy, the histological assessment unveiled Ewing sarcoma. This prompted a first line VDC/IE chemotherapy treatment. After 2 cycles a surgical debulking was performed. All surgical specimens exhibited extensive necrosis (99%). In total, 13 cycles were administered. Disease relapse occurred one moth from her last chemotherapy with diffuse leptomeningeal carcinomatosis. The relapse extension precluded radiotherapy therefore a palliative treatment based on the TEMIRI regiment was initiated. The patient died after two months.

Our case illustrates an extremely rare presentation of an extra-osseous Ewing sarcoma that clinical, radiological and tumour markers were all misleading initially, suggesting an epithelial or a non-epithelial ovarian cancer.

Disclosure: Nothing to disclose

Topic: Experimental Hematology / Oncology (SSH/SSMO award for experimental hematology / oncology)

P54

An injectable, scalable, 3D tissue-engineered model of bone marrow adipogenesis and hematopoiesis

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Current methods to recapitulate the bone marrow (BM) microenvironment primarily rely on heterotopic ossicle formation to establish a vascularized niche. 3D in vitro cultures or bioengineered niches typically require cell recovery from scaffolds or bulky implantation in vivo. Modelling the interaction of hematopoietic stem/progenitor cells (HSPCs) with the supportive BM stroma is of high interest in regeneration of the niche in blood disorders. For this purpose, we present an injectable co-culture system in a transferable in vitro microcarrier suspension to an in vivo transplantation model.

We assemble a 3D hematopoietic niche *in vitro* by co-culture of supportive BM-derived OP9 stromal cells and HSPCs in a porous collagen-coated carboxymethylcellulose microscaffold (CCM). Flow cytometry and hematopoietic colony forming assays demonstrate the stromal supportive capacity for *in vitro* hematopoiesis in the absence of exogenous cytokines. We are able to recover the paste-like living niche biomaterial from CCM co-cultures by controlled, partial dehydration while preserving cell viability and the association between OP9 stromal cells and HSPCs. Following subcutaneous injection of the living artificial niche *in vivo*, we find maintenance of stromal and hematopoietic populations over 12 weeks in immunodeficient mice. Indeed, vascularization is enhanced in the presence of HSPCs. Moreover, we find that the OP9 stromal cells are able to efficiently differentiate to adipocytes *in vitro* and are also observed *in vivo*. Our approach provides a minimalistic biomimetic *in vitro* BM model in a microcarrier format that preserves HSPC function, while being injectable *in vivo* without disrupting the cell-cell interactions established *in vitro*.

Disclosure: Nothing to disclose

P55

BMI1-inhibitor PTC596 in combination with MCL1 inhibitor S63845 or MEK inhibitor trametinib in the treatment of acute myeloid leukemia

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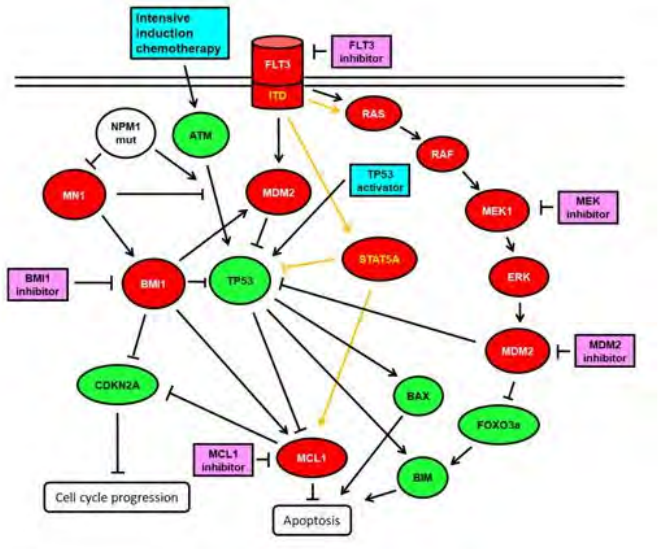
Background: Prognosis for AML patients is poor, particularly in p53 mutated AML, secondary, relapsed, and refractory AML and in patients unfit for intensive treatment, thus highlighting an unmet need for novel therapeutic approaches. The combined use of compounds targeting the stem cell oncogene BMI1 and activating the tumor suppressor TP53 may be a promising treatment option for this poor risk AML subset.

Methods / Design: BMI1 inhibitor PTC596, MCL1 inhibitor S63845 and MEK inhibitor trametinib, as well as the p53 activator APR-246 were assessed as single agents and in combination for their ability to induce apoptosis and cell death in leukemic cells. AML cells represented all major morphologic and molecular subtypes with normal karyotype, including *FLT3*-ITD and *FLT3* wild-type, *NPM1* mutant and wild-type, as well as *TP53* mutant and wild-type cell lines.

Results: *TP53*wt AML cells were susceptible to PTC596 and to combination treatments with PTC596 and MCL1 inhibitor S63845 or MEK inhibitor trametinib. *TP53*mut AML cells were susceptible to PTC596 and to combination treatments with PTC596 and MEK inhibitor trametinib or p53 activator APR-246.

Conclusions: The combination of PTC596 with S63845 or trametinib may be an effective treatment in *TP53* wild-type and *TP53*mut AML, respectively.



Disclosure: Nothing to disclose

P56

Randomized, double-blind, phase II study of tiragolumab plus atezolizumab versus placebo plus atezolizumab as first-line treatment for PD-L1-selected NSCLC (CITYSCAPE)

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Background: In the phase I study GO30103, co-inhibition of the immunomodulatory receptor TIGIT and PD-L1 signaling with tiragolumab plus atezolizumab (TA) in CIT-naïve PD-L1+ NSCLC potentially improved overall response rates (ORR) versus historical ORR with PD-L1/PD-1 inhibitors. We conducted a phase II study (GO40290, NCT03563716) to confirm efficacy and safety of TA versus placebo plus atezolizumab (PA) in first-line NSCLC.

Methods: This prospective, randomized, double-blind, placebo-controlled trial enrolled patients with chemotherapy-naïve PD-L1+ (TPS ≥1%) locally advanced or metastatic NSCLC with measurable disease, ECOG PS 0-1, and without *EGFR* or *ALK* alterations. Patients were randomized 1:1 to TA (600+1200 mg IV) or PA (atezolizumab 1200 mg IV) on day 1 of every 3-week cycle. Stratification factors were PD-L1 status, histology, and tobacco history. Co-primary endpoints were investigator-assessed ORR and PFS; additional endpoints were duration of response (DOR), OS, and safety.

Results: 135 patients were randomized. At primary analysis (median follow-up 5.9 months), TA improved ORR and median PFS compared to PA (Table). In the safety population (n=135), treatment-related AEs occurred in 72% (PA) and 80.6% (TA) (Grade ≥3: 19.1% [PA] and 14.9% [TA]). AEs leading to treatment withdrawal occurred in 10.3% (PA) and 7.5% (TA).

Improvement in ORR and median PFS for TA versus PA was maintained with an additional six months of follow-up since the primary analysis (median follow-up 10.9 months). The safety profile remained tolerable.

	PA	TA
n (ITT and safety populations)	68	67
Primary analysis (30 Jun 2019)		
ORR % (95% CI)	16.2 (6.7, 25.7)	31.3 (19.5, 43.2)
Stratified odds ratio (95% CI)	2.57 (1.07, 6.14)	
Median PFS, months (95% CI)	3.6 (2.7, 4.4)	5.4 (4.2, NE)
HR (95% CI)	0.57 (0.37, 0.90)*	
Six month follow-up (2 Dec 2019)		
ORR % (95% CI)	20.6 (10.2, 30.9)	37.7 (25.0, 49.6)
Median PFS, months (95% CI)	3.9 (2.7, 4.5)	5.6 (4.2, 10.4)

Conclusions: Treatment with TA compared to PA showed clinically meaningful improvement in ORR and PFS in the ITT population, with a similar safety profile.

Disclosure: https://coi.asco.org/Report/ViewAbstractCOI?id=307273

P57

Performance of PD-L1 immunohistochemistry (IHC) assays in unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC): post-hoc analysis of IMpassion130

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Background: IMpassion130 is a phase 3 study evaluating atezolizumab (A) + *nab*-paclitaxel (nP) vs placebo (P) + nP as 1L treatment for patients with mTNBC. A+nP significantly improved PFS in PD-L1+ patients. This exploratory post-hoc analysis evaluated the analytical concordance of SP142 with 2 other PD-L1 IHC assays, and their ability to predict clinical activity.

Methods: Available samples were evaluated for PD-L1 status using VENTANA SP142 or SP263 IHC assays (immune cells [IC] ≥1%, SP142+ or SP263+) or Dako PD-L1 IHC 22C3 assay (combined proportion score [CPS] ≥1, 22C3+) by central laboratory in a biomarker-evaluable population (BEP).

Results: The BEP consisted of 614 patients (68% of ITT). PD-L1+ prevalence was 46% for SP142+, 81% for 22C3+, and 75% for SP263+. The overall percentage agreement (OPA) of SP142 with 22C3 and SP263 was 69% and 63%, respectively. PPAs of 98% for both assays suggests SP142+ patients are captured by the other two tests, while negative percentage agreements were < 45%. The PFS and OS HR (95% CI) in SP142+ patients were 0.60 (0.47, 0.78) and 0.74 (0.54, 1.01) respectively; 0.68 (0.56, 0.82) and 0.78 (0.62, 0.99) in 22C3+ patients, respectively; and 0.64 (0.53, 0.79) and 0.75 (0.59, 0.96) in SP263+ patients, respectively. Subgroup outcomes indicate the PFS and OS benefit with A+nP in SP263+/SP142- or 22C3+/SP142- was smaller than in double-positive subgroups (table).

Conclusions: At the evaluated cutoffs, 22C3 and SP263 assays identified more patients with PD-L1+ tumours. The patients in the SP142 PD-L1+, derived the greatest clinical benefit with A+nP.

HR (95% CI)		SP142		
		IC < 1%	IC ≥ 1%	
22C3	CPS < 1	n = 111 (18%)	n = 6 (1%)	PPA 98% NPA 45% OPA 69%
		PFS 1.00 (0.66, 1.51)	–	
		OS 1.08 (0.67, 1.76)	–	
	CPS ≥ 1	n = 218 (36%)	n = 279 (45%)	
		PFS 0.81 (0.61, 1.09)	PFS 0.60 (0.46, 0.78)	
		OS 0.92 (0.64, 1.31)	OS 0.71 (0.52, 0.98)	
SP263	IC < 1%	n = 147 (24%)	n = 7 (1%)	PPA 98% NPA 34% OPA 64%
		PFS 1.13 (0.79, 1.61)	–	
		OS 1.1 (0.72, 1.68)	–	
	IC ≥ 1%	n = 182 (30%)	n = 278 (45%)	
		PFS 0.68 (0.49, 0.94)	PFS 0.61 (0.47, 0.79)	
		OS 0.87 (0.58, 1.29)	OS 0.71 (0.52, 0.97)	

NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agre

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P58

Clinical efficacy of atezolizumab (atezo) in biomarker subgroups by PD-L1 immunohistochemistry (IHC) assays and blood tumour mutational burden (bTMB): IMpower110

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Background: IMpower110 is a Phase III study (NCT02409342) evaluating atezo (anti-PD-L1) monotherapy as 1L treatment in PD-L1-selected patients with NSCLC independent of tumour histology. Efficacy analyses in prespecified biomarker subgroups by the SP263 and 22C3 PD-L1 IHC assays and bTMB are reported.

Methods: Chemotherapy-naive patients with stage IV NSCLC, PD-L1 ≥1% tumour cell (TC) or immune cell (IC)(TC1/2/3 or IC1/2/3; VENTANA SP142 IHC assay), were randomised 1:1 to atezo 1200 mg IV q3w or platinum-based chemotherapy (4 or 6 21-day cycles). OS was tested hierarchically in wild-type (WT, *EGFR/ALK*-negative) patients; OS and PFS were tested in the SP263 and 22C3 PD-L1 IHC and bTMB populations. PD-L1 cutoffs of ≥1% and ≥50% were evaluated for tumour proportion score (TPS) and TC in 22C3 and SP263, respectively; bTMB cutoffs were ≥10, ≥16 and ≥20.

Results: Biomarker-evaluable populations (BEP) in the TC1/2/3 or IC1/2/3 WT population (SP142; 554) included 534 (22C3), 546 (SP263) and 389 (bTMB) patients. Baseline characteristics in the IHC and bTMB BEP subgroups were generally balanced. OS and PFS in the PD-L1-high (TC3 or IC3; ≥50% TPS; ≥50% TC) subgroups favoured atezo (OS data shown in table). Stepwise OS and PFS improvement, favouring atezo, was seen up to bTMB ≥16; no further benefit was seen at ≥20.

Conclusions: Patient subgroups had similar OS and PFS benefit with atezo. Clinical benefit, favouring atezo, was also seen in bTMB positive subgroups. Atezo monotherapy is a potential new 1L treatment option for patients with PD-L1-high NSCLC.

Subgroup	Median OS				HR* (95% CI)
	Atezo		Chemo		
	n	mo	n	mo	
VENTANA SP142 (n = 554)					
TC1/2/3 or IC1/2/3 WT	277	17.5	277	14.1	0.83 (0.65, 1.07)
TC3 or IC3 WT	107	20.2	98	13.1	0.59 (0.40, 0.89)
Dako 22C3 (n = 534)					
22C3 BEP	268	17.5	266	14.1	0.82 (0.64, 1.06)
≥ 50% TPS	134	20.2	126	11.0	0.60 (0.42, 0.86)
≥ 1% TPS	213	17.8	201	14.0	0.73 (0.55, 0.97)
VENTANA SP263 (n = 546)					
SP263 BEP	271	17.2	275	14.9	0.85 (0.66, 1.09)
≥ 50% TC	150	19.5	143	16.1	0.71 (0.50, 1.00)
≥ 1% TC	212	17.8	210	14.0	0.77 (0.58, 1.02)
Foundation Medicine bTMB (n = 389)					
bTMB BEP	196	13.3	193	15.3	0.98 (0.74, 1.30)
≥ 10	92	11.2	83	10.3	0.87 (0.58, 1.30)
≥ 16	42	13.9	45	8.5	0.75 (0.41, 1.35)
≥ 20	27	17.2	29	10.5	0.77 (0.36, 1.64)

*Stratified OS HRs for SP142 only.

Tab. 1

Disclosure: Funding: F. Hoffmann-La Roche, Ltd.

P60

Linking lysosomes with chemotherapy resistance in acute myeloid leukemia

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Acute myeloid leukemia (AML) patients frequently experience relapse or refractory AML due to the survival of chemotherapy-resistant leukemic cells (CRLC). Therefore, further knowledge of AML cell and CRLC biology can improve chemotherapy effectiveness. Interestingly, AML cells have a higher lysosomal mass than normal hematopoietic cells and disrupting lysosomes agents target AML cells and progenitors sparing healthy hematopoietic cells. Although lysosomes are the recycling center of cells, recent evidence suggest that disruption of lysosomal function can contribute to chemotherapy resistance in solid cancer. We hypothesized that perturbation of lysosomes and lysosomal degradation mechanism, mainly autophagy, influence resistance development in AML cells to first-line therapy, Cytarabine (Ara-C).

We screened our AML cell line panel for lysosomal mass ($LAMP1^+$ vesicles) and autophagy activity (Macroautophagy: $LC3B^+$ vesicles, Chaperone-mediated autophagy (CMA): $HSPA8^+LAMP2A^+$ vesicles) by immunofluorescence microscopy. Our data indicated that lysosomal content correlates inversely to Ara-C treatment sensitivity. To understand the importance of lysosomes in therapy response, we generated Ara-C resistant cell lines (NB4 and MOML13) via pulsed treatment method. Interestingly, Ara-C resistant cells had increased $LAMP1^+$ vesicles compared to parentals. Furthermore, we found consistently higher CMA positive vesicles but not macroautophagy. For better insight of CMA activity upon treatment, we have developed a split-Venus fluorescent protein tagged HSPA8 and LAMP2A to assess real time change in LAMP2A/HSPA8 co-localization upon Ara-C treatment.

Understanding CLRC biology is a prerequisite to develop novel therapies. Our data suggest that CMA positive lysosomes play a role in the development of Ara-C resistance, opening up new therapeutic options.

Disclosure: Nothing to disclose

P61

Tissue-scale spatial analysis of hematopoietic stem cells and stromal niche subtypes in the fetal liver microenvironment

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During embryonic development, hematopoiesis migrates through different tissues in a sequential and finely timed manner. Hematopoietic stem cells (HSCs) are generated from endothelial walls of large blood vessels, subsequently colonize the fetal liver (FL), where they undergo proliferative expansion, before definitely settling in the bone marrow (BM). While adult BM niches have been extensively studied, the cellular and molecular makeup of FL niches that promote continuous self-renewing proliferation of embryonic HSCs, remain less characterized.

We employed a customized pipeline for 3-dimensional quantitative microscopy to visualize distribution patterns of HSCs in the FL, reveal the identity of putative stromal niche components, and investigate their spatial relationships.

Unexpectedly, organ-wide mapping of HSCs in reporter mice (*Hlf*-tdTomato/*Ctnnal1*-GFP) revealed no significant spatial association of HSCs or progenitor cells with liver sinusoids or portal vessels. Instead, HSCs displayed a widespread distribution throughout entire FL lobes. We next employed *Cxcl12*-GFP and *Scf*-GFP reporter mice to identify and visualize potential niche cell types. Abundant expression of CXCL12 and SCF was detected in two non-hematopoietic cell types, which were unequivocally characterized as DLK1+ hepatoblasts and CD140b+CD51+ mesenchymal cells. At E13.5, both densely populate the entire FL, restricting available space, and closely associate with HSCs. Interestingly, by E17.5 the strong downregulation of pro-hematopoietic gene expression in hepatoblasts and their differentiation into mature hepatocytes lead to a rapid decrease in SCF levels, which temporally coincide with declining liver hematopoiesis.

Our results are therefore consistent with a model in which hepatoblasts and mesenchymal cells create a developmentally restricted hematopoietic-supporting FL niche.

Disclosure: Nothing to disclose

P62

Distinct roles of hexokinase 2 and 3 in energy metabolism, myeloid differentiation and cancer development

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Background: Control of metabolic processes is crucial for normal hematopoietic cell development, proliferation and cancer cell expansion. These processes require variable bioenergetic supply, which is partly met by regulation of glycolytic metabolism. Hexokinases (HK1-4) catalyze the first and irreversible step of glycolysis. Recent evidence implicates a tumor promoting role for HK2 in certain solid tumors. In contrast

to the ubiquitously expressed HK1 and 2, HK3 is predominantly expressed in hematopoietic cells. We have identified HK3 as a transcriptional target of the hematopoietic-specific transcription factor PU.1.

Methods and Results: In primary human CD34^{+} HSPCs, we found HK1-3 to be present at similar levels. During myeloid differentiation, HK3 mRNA increased significantly while HK1 and HK2 mRNA levels remained unchanged. Using Crispr/CAS9, we generated HK2 and HK3 knockouts (KO) in HL60 and NB4 AML cell lines. Analysis of energy metabolism in HK altered cells showed that loss of HK3 had no effect on steady state glycolytic activity. Loss of HK2, however, drastically reduced steady state glycolysis. In contrast, KO of HK3 resulted in massive cell death during all-trans retinoic acid (ATRA) induced differentiation. HK3 KO cells show increased levels of DNA damage (measured by the presence of yH2AX foci within the nucleus) both at steady state and upon ATRA.

Our findings implicate HK2 as the major glycolytically active isoform in myeloid cell lines, whereas HK3 potentially exerts non-canonical regulatory functions. Studies are underway to assess DNA integrity and repair mechanisms during myeloid differentiation in HK3 gene edited HSPCs.

Disclosure: Nothing to disclose

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Homozygous calreticulin muations affect chaperone function and perturb the glycoproteome

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Introduction: Myeloproliferative Neoplasms (MPN) patients frequently carry mutations in the chaperone Calreticulin (CALR). CALRMUT is secreted since it lacks the ER retention signal “KDEL”. Patients with a homozygous CALR mutation develop an acquired MPO deficiency due to premature MPO degradation in the proteasome. We investigated whether MPO (or GP) misfolding arises due to low intracellular CALR levels, or whether CALRMUT exhibits holdase (GP-binding) or foldase defects. Additionally, we assessed whether further GPs are misfolded in context of (homozygous) CALR mutations.

Methods: MPO expression in murine CALR^{KO} (KO) fibroblasts or human CALR^{KO} HL-60 cells served as a readout for chaperone function. Binding of CALR to MPO was determined via coimmunoprecipitation (co-IP) assays or proximity-ligation-assays (PLA). As protein function is tightly linked to structural integrity, we profiled the *in situ* conformational landscape of primary *CALR*-mutated, *JAK2*-mutated and healthy donor-derived granulocytes using limited proteolysis-coupled mass spectrometry (LiP-MS).

Results/discussion: Restoring intracellular levels of CALR^{MUT} by either blocking its secretion or by expression of “secretion-resistant” KDEL-positive CALR^{MUT} did not rescue MPO expression, suggesting that low CALR^{MUT} levels do not cause MPO misfolding. Furthermore, binding of CALR^{MUT} to MPO was still possible indicating an intact holdase function. We observed in homo- but not heterozygous *CALR*-mutated proteomes, that further GPs apart from MPO exhibited reduced expression levels and structural perturbations which is indicative of protein misfolding. We conclude that a reduced foldase function of CALR^{MUT} affects the folding of MPO and other GPs. Future studies will show how increased protein misfolding/degradation can be clinically exploited.

Disclosure: Nothing to disclose

P64

Platelet apoptosis and autophagy in pediatric immune thrombocytopenia: new mechanistic insights

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Immune thrombocytopenia (ITP) is an autoimmune disease that can cause severe bleeding symptoms and it can occur in pediatric and adult patients. T-cell mediated destruction of platelets, antiplatelets antibodies and impaired megakaryopoiesis leading to a reduced platelet formation by loss of autophagy have been described as possible etiologies of the low platelet counts that hallmark this disorder. We have previously reported an increased phosphatidylserine exposure in chronic ITP, suggesting that platelet apoptosis is involved into the ITP pathogenesis.

In our present study, we aimed to identify ITP platelets' clearance mechanisms that control activation of apoptotic and autophagic machinery. We could demonstrate significantly increased protein expression levels of some apoptotic genes such as clusterin, pro-caspase 3, catalase and Bcl-2 compared to healthy controls, by proteomic profiling (Figure 1) in platelet-rich plasma (PRP) from 10 ITP patients. We could validate by both, qRT-PCR and Western blotting that clusterin, a stress-activated chaperone, is significantly increased in both acute and chronic ITP. Additionally, we investigated specific autophagy and apoptosis markers by Western blot and RT-qPCR. We could observe that mRNA expression of autophagy-initiation (Beclin-1), -autophagosome (p62) and -lysosome (LAMP1) markers were up to 3-fold significantly increased, whereas the expression levels of intrinsic apoptosis genes Bad, Bax and Bid were significantly decreased in in acute and chronic ITP patients. We assume that by targeting apoptosis and/or autophagy pathway genes, the onset of symptoms and the duration of the disease could be altered and thereby, could provide an augmented quality of life of ITP patients.

Disclosure: Nothing to disclose

P65

Nicotinaldehyde solution supplementation antagonizes the anti-leukemic/lymphoma effect of APO866, an inhibitor of NAD biosynthesis, through an NAPRT-dependent pathway

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Background: Nicotinamide adenine dinucleotide (NAD) is an essential cofactor playing a central role in cellular fundamental processes. Inhibiting NAD biosynthesis represents a promising strategy for cancer treatment, given the high demand in NAD for sustaining cancer cell rapid proliferation and energy production. APO866 is an inhibitor of nicotinamide phosphoribosyltransferase (NAMPT), involved in the major NAD biosynthetic pathway. Elucidating the implications of different intermediates and pathways in the NAD metabolome is essential for dissecting and enhancing APO866 anti-tumour effects. Here, we focused on nicotinaldehyde, the aldehyde form of nicotinamide, and aimed to assess its impact on APO866 cytotoxicity in hematological cancer cells.

Methods: Jurkat and ML2 cells were treated with APO866 in presence or absence of nicotinaldehyde to assess cell viability by flow cytometry with annexin-V/7AAD staining. Functional analyses included time-course evaluation of cellular NAD, ATP, ROS and mitochondrial membrane potential (MMP).

Results: Co-treatment with nicotinaldehyde fully reversed APO866-mediated cell death. It allowed the partial and significant maintenance of intracellular NAD at 13% of basal level, contrasting with the complete depletion under APO866 treatment alone. Although APO866 increased mitochondrial and cytosolic ROS and MMP depolarization by 19, 13 and 7 fold, respectively, nicotinaldehyde supplementation fully prevented these events. Interestingly, this protection by nicotinaldehyde was absent in cells lacking nicotinate phosphoribosyltransferase (NAPRT), the rate-limiting enzyme of an alternative NAD biosynthetic pathway.

Conclusion: The results report an undescribed effect of nicotinaldehyde supplementation, highlighting the complexity of the NAD metabolome and the importance of the biosynthetic pathways in the optimization of NAD-based cancer therapy.

Disclosure: Nothing to disclose

P66

Predicting patient-reported symptoms for patients undergoing immune checkpoint inhibitor (ICI) therapies using different measurement system than in prediction model training

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Background: ICIs have introduced novel immune related toxicities, arising from various organ systems without strong timely dependency on initiation and discontinuation of the therapy. Electronic patient-reported outcomes (ePROs) data can be used to train machine learning (ML)

models for symptom onset and continuity prediction to enable earlier detection of these toxicities, which could result in an improved safety profile of the treatments and better quality-of-life for the patients.

Methods: ML models were trained for 16 monitored symptoms with a dataset, collected using Kaiku Health digital platform, consisting of over 3300 ePRO reports from 160 ICI patients. In this study the prediction performance of these models is evaluated with a new dataset from Tumor Zentrum Aarau collected with a slightly different measurement system PRO-CTCAE (training data used Kaiku Health's self-developed symptom library). With the training data and the new dataset eight symptoms overlapped closely and were selected for model testing. The test data consisted of 21 ICI treated patients and 291 PRO-CTCAE based symptom reports.

Results: The prediction models had a good performance with seven out of the eight predicted symptoms. The more detailed metrics are presented in Table 1.

Predicted symptom	Accuracy	AUC	F1 score	MCC
shortness of breath	86.03	0.90	0.87	0.72
itching	90.39	0.86	0.77	0.71
cough	77.73	0.85	0.77	0.55
diarrhea	86.46	0.81	0.61	0.53
nausea	73.36	0.70	0.34	0.20
fatigue	86.90	0.90	0.90	0.72
rash	87.77	0.81	0.61	0.54
decreased appetite	80.35	0.83	0.69	0.55

Conclusion: This study shows that the symptom prediction models trained with ePRO data perform well when evaluated with ePRO data using a different measurement system. This implies that the models generalise well to different geographical areas with variations in the data collection. However, the results should be validated with a larger dataset.

Disclosure: J. Ekström, H. Virtanen and V. Kataja are employed by Kaiku Health Ltd.

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Drug and genomic profiling in patients with soft tissue sarcoma

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Background: Soft tissue sarcomas comprise a heterogeneous group of more than 70 tumor subentities. In the relapsed and metastatic setting response to systemic treatment is often limited leading to a poor prognosis and new approaches in precision medicine are needed to improve patient outcome.

Methods: First we explored optimal culture conditions for short-term culture of cells from fresh tissue of patients with soft tissue sarcoma. We performed high throughput drug screening and used metabolic viability and image based single-cell viability by automated microscopy as readout.

Results: At this early stage of the study we want to highlight a case of a 27-year-old patient with metastatic epitheloid sarcoma. During routine work-up, a FGFR2 copy number gain (6 copies) was detected. The patient received targeted therapy as second line therapy with the multikinase inhibitor pazopanib, a multikinase inhibitor also inhibiting FGFR. This resulted in disease stabilization for seven months.

A tumoroid model from a fresh tissue sample was generated. Drug testing revealed strong sensitivity to several FGFR inhibitors in line with the genetic findings.

As a later line of therapy, treatment with the specific FGFR-inhibitor erdafitinib was introduced, but unfortunately did not show a response.

Conclusion: We present a drug response profiling platform suitable for ex vivo testing of soft tissue sarcoma patient specimens. This platform has the potential to help to identify targeted treatment options beyond routine genomic findings currently not implemented in conventional treatment regimes and might help to dissect this heterogenous group of tumors into new, biologically defined subgroups.

Disclosure: Nothing to disclose

P68

Early results of a single-cell ex vivo drug response testing platform 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 responses 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. A convolutional neural network infers cell types directly from single-cell images based. Eventually, data is correlated with clinical response.

Results: So far, the clinical cohort includes 67 samples. 73% of included samples had a sufficient viability and cancer cell content to be analyzed. In multiple patients, pharmacoscopy was repeated on specimens taken within a short period of time. We observed a high intra-individual reproducibility of the obtained drug response profiles.

At this early stage of this study, we want to highlight one case of a patient with *BRAF*p.V600E mutated lung adenocarcinoma. Combined tyrosine kinase inhibition with dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) was started and resulting in a partial response. In parallel, pharmacoscopy predicted an *ex vivo* response to dabrafenib.

Conclusion: Pharmacoscopy on fluid samples is a feasible diagnostic tool to test drug responses. Integration of drug response profiles and morphological profiles with molecular measurements including genomic profiling and transcriptomics will provide further insights into the molecular mechanisms underlying drug response variability.

Disclosure: Nothing to disclose

P69

Role of PαS cells for proliferation and expansion of hematopoietic stem cells in bone marrow during early postnatal development

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Bone marrow (BM) cavities are the primary sites of life-long blood cell production, termed hematopoiesis. Hematopoiesis is sustained by rare population of self-renewing and multipotent hematopoietic stem cells (HSCs) under the systematic regulation of a specialized, highly complex and multicellular BM stromal compartment. Studies have shown that during embryonic and early postnatal development, the HSC pool undergoes exponential growth, which is essential to meet the increasing demand in hematopoietic output. With acquisition of final body size and stabilization of BM cavities, at 2-4 weeks post birth, the majority of HSCs switch to a homeostatic quiescent state, in which they will reside for the majority of adult life. The cellular and molecular mechanisms enforcing this crucial, developmentally-timed transition of HSCs, remain to be defined. Our previous work suggests that PDGFR-α+Sca-1+ (PαS) perivarterial mesenchymal stromal cells, whose function remains unknown, potentially contribute to postnatal HSC control. PαSc are abundant in early postnatal, but not adult BM, and express genomically imprinted genes, such as Igf2, with known mitogenic activity, which get abruptly downregulated with entry into adulthood. Our working model is that PαSc promote the expansion of the HSC pool in specific BM niches during postnatal life. In this project we will test this hypothesis by combining the analysis of mouse models in which PαSc can be genetically target in an inducible and specific manner, with single cell technologies to dissect changes in stromal cell composition and function, as well as advanced 3D-imaging techniques to visualize dynamics of HSC niches in postnatal stages.

Disclosure: Nothing to disclose

P70

Unraveling the role of a novel subtype of bone marrow mesenchymal stromal cell in healthy and pathological hematopoiesis

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The orchestration of hematopoiesis is highly dependent on local cues derived from the bone marrow (BM) stromal microenvironment. Among BM stromal components, mesenchymal cells, termed CXCL12-abundant reticular cells, have been best characterized for their role in hematopoietic stem cell (HSC) maintenance and progenitor differentiation. Once regarded as a homogenous pool of cells, recent single-cell sequencing data suggest that CARc include a number of distinct subsets with potentially distinct functional properties. However, the identity, spatial distribution, and roles in the control of hematopoietic development of different subpopulations of these cytokine-producing cells remain poorly understood. Preliminary results demonstrate that a defined fraction (10-15%) of CARc, is stably labeled in CXCL13-Cre/ROSA26YFP mice (designated hereon as CXCL13-YFP$^+$). CXCL13-YFP$^+$ CARc are found distributed throughout the entire BM parenchyma, displaying a subtle tendency to accumulate in periendosteal and metaphyseal BM regions, and increase in numbers during the ageing process, as visualized via 3D microscopy. In this project, we aim to study this novel subtype in detail, assess its frequencies, localization, and interactions with other cell types using 3D quantitative microscopy and describe their transcriptomic landscape via scRNA-seq. To evaluate their functional relevance for the hematopoietic compartment, we will use genetic models to specifically delete the expression of key supportive cytokines in CXCL13-YFP$^+$cells and assess the potential effects on HSC fitness and hematopoietic regulation during homeostasis and inflammation-induced hematopoiesis. Altogether, these studies will provide new nuanced insights on the faceted regulatory activities of BM mesenchymal stroma in healthy and pathological BM function.

Disclosure: Nothing to disclose

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MarrowQuant in human trephine biopsies: a digital pathology tool for interrogating bone marrow architecture in acute myeloid leukemia

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Bone marrow (BM) mesenchymal stromal cells are rare elements known to contribute to the hematopoietic stem cell niche. Underlying the importance of the stroma in hematological malignancies, diseased BM stroma in animal models can solely induce a pre-leukemic state, then drive progression into leukemia. Due to technical challenges, the human BM stroma has not been thoroughly characterized. In fact, no studies have yet correlated architectural characteristics of the BM stroma to clinical outcomes in leukemia. In this study, we aimed to develop a plugin for the quantification of the main architectural components of BM stroma and track stromal modifications in acute myeloid leukemia (AML) patients. MarrowQuant is a semi-automated image analysis tool acting by identifying four mutually exclusive architectural compartments, the bone, hematopoietic cells, adipocytes and interstitium/microvasculature fractions. Recognition is based on the difference in color and texture after hematoxylin/eosin staining. We also applied MarrowQuant to clinical samples of human trephine biopsies from AML patients at different timepoints of chemotherapy. It offers a semi-automatic quantification of BM fractions in human sections in an unbiased manner. It successfully recognizes the four compartments of the marrow leading to a more reproducible discrimination than gold-standard pathologist evaluation. In our dataset, we have been able to quantitatively validate the reciprocal relationship between the hematopoietic and adipocytic marrow compartments. This semi-automatic tool for the quantification of BM components will be used in combination with a locally developed stromal panel to study BM modifications in AML in the context of an HOVON/SAKK European collaboration.

Disclosure: Nothing to disclose

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