LBA6500 **Oral Abstract Session**

ASC4FIRST, a pivotal phase 3 study of asciminib (ASC) vs investigator-selected tyrosine kinase inhibitors (IS TKIs) in newly diagnosed patients (pts) with chronic myeloid leukemia (CML): Primary results.

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Ponatinib (PON) in patients (pts) with chronic-phase chronic myeloid leukemia (CP-CML) and the T315I mutation (mut): 4-year results from OPTIC.

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Background: PON, an approved BCR::ABL1 TKI, potently inhibits native BCR::ABL1 and all reported single-resistance muts, including T315I. In the primary analysis of the phase 2 OPTIC study (NCT02467270) at 12 mo, pts with CP-CML and the T315I mut had robust responses to PON. We present 4-year results from the OPTIC trial in pts with the T315I mut. **Methods:** Pts with CP-CML resistant to ≥2 TKIs or with the *BCR::ABL1*T315I mut were randomized 1:1:1 to PON starting doses of 45, 30, or 15 mg QD, with dose reduction to 15 mg upon achievement of ≤1% *BCR::ABL1*^{IS} in the 45-mg and 30-mg cohorts. This subgroup analysis evaluated 48-mo ≤1% *BCR::ABL1*^{IS}, PFS and OS rates and safety outcomes in pts with the T315I mut. **Results:** Overall, 283 pts received PON (45 mg/30 mg/15 mg: n=94/95/94); 23.8% had the T315I mut (n=25/21/21). At the data cutoff for the 4-year analysis (May 8, 2023), median follow-up in the 45-, 30-, and 15-mg cohorts was 60.6, 63.5, and 60.7 mo, respectively. The proportion of pts with the T315I mut achieving ≤1% *BCR::ABL1*^{IS} by 48 mo was highest in the 45-mg cohort (64%; Table). Median time to response (mo) and estimated median duration of response (mo) were 6.0 and 16.7 in the 45-mg cohort, 3.1 and 12.0 in the 30-mg cohort, and 6.0 and not reached (NR) in the 15-mg cohort. In the 45- and 30-mg cohorts, 15 and 5 pts had dose reduction to 15 mg after achieving ≤1% *BCR::ABL1*^{IS}, of which 7 and 2 maintained response; of pts not maintaining response, 6 and 1 regained response after dose re-escalation. Median PFS was NR, 28.4 mo, and 45.6 mo in the 45-, 30-, and 15-mg cohorts, respectively, and median OS was NR in all groups. The 45-mg cohort had the highest 4-year survival rates (OS: T315I 86%; overall 88%; Table). Grade ≥3 TEAE rates in the 45-, 30-, and 15-mg cohorts were 60%, 38%, and 38%, with TEAEs leading to discontinuation in 8%, 14%, and 5%, respectively. Arterial occlusive events (AOEs) occurred in 8%, 14%, and 5% of pts in the 45-, 30-, and 15-mg cohorts; exposure-adjusted AOE rates were 2.4%, 7.3%, and 2.8%, respectively. **Conclusions:** PON demonstrated robust long-term efficacy and manageable safety in this 4-year update in pts with the T315I mut. A PON starting dose of 45 mg with reduction to 15 mg upon achievement of ≤1% *BCR::ABL1*^{IS} provided the optimal benefit:risk ratio. Clinical trial information: NCT02467270. Research Sponsor: Takeda Development Center Americas, Inc.

	PON 45 mg → 15 mg		PON 30 mg → 15 mg		PON 15 mg	
Outcome at 48 mo[a]	T315I (n=25)	Overall (n=94)	T315I (n=21)	Overall (n=95)	T315I (n=21)	Overall (n=94)
No. of pts evaluated	25	93	20	93	19	91
Pts who achieved response, n (%)						
≤1% *BCR::ABL1*^{IS}	16 (64)	56 (60)	5 (25)	38 (41)	3 (16)	36 (40)
≤0.1% *BCR::ABL1*^{IS}	12 (48)	42 (45)	3 (15)	27 (29)	2 (11)	22 (24)
≤0.01% *BCR::ABL1*^{IS}	7 (28)	19 (20)	2 (10)	15 (16)	2 (11)	17 (19)
≤0.0032% *BCR::ABL1*^{IS}	6 (24)	11 (12)	1 (5)	10 (11)	2 (11)	14 (15)
PFS						
Events, n	6	23	12	28	10	27
PFS rate, %	75	73	40	63	41	64
OS						
Events, n	3	15	7	14	5	12
OS rate, %	86	88	70	86	75	88

[a]ITT population; includes all pts who were randomized and had measurable *BCR::ABL1*^{IS} at baseline.

Updated safety and efficacy data from the phase 3 MANIFEST-2 study of pelabresib in combination with ruxolitinib for JAK inhibitor treatment-naïve patients with myelofibrosis.

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Background: Pelabresib (PELA) is an oral, small-molecule, investigational BET inhibitor that aims to decrease expression of genes involved in MF. MANIFEST-2 (NCT04603495), a global, randomized, double-blind, Phase 3 study, investigated the efficacy and safety of PELA + ruxolitinib (PELA+RUX) vs placebo + RUX (PBO+RUX) in JAKi treatment-naïve patients (pts) with MF. **Methods:** Eligible pts had DIPSS score ≥ INT-1, platelet count ≥100 × 10^9/L, spleen volume ≥450 cm^3, ≥2 symptoms with an average score ≥3 or total symptom score (TSS) ≥10 (MFSAF v4.0), peripheral blast count <5%, and ECOG PS ≤2. Pts were randomized 1:1. PELA or PBO was administered (QD for 14 consecutive days of 21) with RUX (BID for 21 days [1 cycle]). Primary endpoint was ≥35% spleen volume reduction from baseline (BL) (SVR35) at Week (Wk) 24. Secondary endpoints included absolute change in TSS and ≥50% reduction in TSS from BL (TSS50) at Wk 24, and safety. Other endpoints included hemoglobin (Hb) response (≥1.5 g/dL mean increase from BL without transfusions in the prior 12 wks), RBC transfusion number and bone marrow fibrosis (BMF). **Results:** As of Aug 31, 2023, 430 pts were randomized. At Wk 24, 65.9% (141/214) vs 35.2% (76/216) (p<0.001) of pts had an SVR35 response in the PELA+RUX vs PBO+RUX arms, respectively. SVR35 responders at any time were 80.4% (172/214) vs 50.0% (108/216); 80% (137/172) vs 63% (68/108) of responders reached SVR35 at Wk 12 scan; 83.7% (144/172) vs 79.6% (86/108) maintained response at cutoff. Mean change in absolute TSS was -15.99 (SE 1.028) vs -14.05 (SE 0.986) (p=0.0545), and TSS50 was 52.3% (112/214) vs 46.3% (100/216) (p=0.216) at Wk 24. There was a 2-fold difference in pts with both SVR35 and TSS50 with PELA+RUX (40.2% [86/214]) vs PBO+RUX (18.5% [40/216]). Hb response occurred in 10.7% (23/214) vs 6.0% (13/216) of pts, with differences in mean Hb levels maintained at 48 wks. In pts with anemia (Hb BL <10 g/dL), Hb response occurred in 16.4% (11/67) vs 14.1% (10/71). A total of 30.8% (66/214) vs 39.8% (86/216) of required RBC transfusion during the first 24 wks. BMF improvement ≥1 grade occurred in 38.5% (40/104) vs 24.2% (24/99) of pts (odds ratio 2.09; p=0.019). Of 426 pts evaluated for safety, the most common treatment-emergent AEs (≥20%) in the PELA+RUX vs PBO+RUX arms were anemia (43.9% vs 55.6% [Grade ≥3, 23.1% vs 36.4%]), thrombocytopenia (32.1% vs 23.4% [9% vs 5.6%]), platelet count decreased (20.8% vs 15.9% [4.2% vs 0.9%]), and diarrhea (23.1% vs 18.7% [0.5% vs 1.4%]). Updated results will be presented at the congress. **Conclusions:** PELA+RUX significantly and durably reduced splenomegaly, with a trend toward reduced TSS, and improved anemia and BMF at Wk 24 compared with PBO+RUX in JAKi treatment-naïve pts with MF, addressing key hallmarks of MF. Resultssupport a potential paradigm shift to combination therapy for MF. CH and JM contributed equally. Clinical trial information: NCT04603495. Research Sponsor: Constellation Pharmaceuticals, Inc., a MorphoSys Company; The development of pelabresib was funded in part by Leukemia and Lymphoma Society.

6503 Oral Abstract Session

Post-transplant cyclophosphamide-based graft-*versus*-host disease prophylaxis following mismatched unrelated donor peripheral blood stem cell (PBSC) transplantation.

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Background: Our prior prospective multi-center clinical trial (15-MMUD; NCT02793544) estimated 79% overall survival (OS) at one year in adult patients with hematological malignancies undergoing reduced intensity conditioning (RIC), receiving bone marrow (BM) grafts from HLA-mismatched unrelated donors (MMUD), and post-transplant cyclophosphamide (PTCy)-based graft-*versus*-host disease (GVHD) prophylaxis (Shaw et al, J Clin Oncol 2021). We sought to determine whether OS in adults receiving mobilized PBSC from MMUD would be comparable. **Methods:** We conducted a prospective, multi-center Phase II study (ACCESS; NCT04904588) to assess the impact of PTCy-based GVHD prophylaxis on OS following MMUD transplantation in adults and children with advanced hematological malignancies. The study included three strata: two for adults based on conditioning regimen intensity [myeloablative (MAC) or RIC] using PBSC, and one pediatric cohort using MAC and BM. Eligible donors were matched at 4-7/8 HLA-loci (HLA -A, -B, -C, and -DRB1) and < 35 years. The primary endpoint was OS at one year following transplantation. We report the results of a planned interim analysis of the first 70 adult patients enrolled on the RIC PBSC stratum. **Results:** Thirteen sites enrolled 70 patients with the following demographics: median age of 65 years (range 24-77); 50% male; diagnoses: AML (53%), MDS (26%), ALL (7%), other heme malignancies (14%); and patient race/ethnicity: non-Hispanic white (48%). Donor characteristics included: median age 25y (range 18-35); male (44%); and HLA match level: 7/8: 67%; 6/8: 27%; 5/8: 6%. Conditioning regimens included fludarabine (flu) and melphalan (63%), flu/busulfan (20%), other (17%). OS at one year post HCT was 79% (95% confidence interval (CI): 68-87%). Secondary endpoints are provided in the table. **Conclusions:** Encouraging OS was observed at one year following MMUD PBSC in patients receiving RIC and PTCy. Notably, half of enrolled patients were people of color. OS was similar to our prior study using BM grafts. Rates of GVHD and other complications appear comparable to those in HLA-matched donor recipients, suggesting MMUD HCT could expand access to a potentially life-saving therapy. Accrual to both adult strata of ACCESS is complete, with over 200 patients in follow-up. Accrual to the pediatric stratum continues. Clinical trial information: NCT04904588. Research Sponsor: NIH/National Cancer Institute; U24CA076518; NIH/National Heart, Lung and Blood Institute (NHLBI); U24CA076518; NIH/National Institute of Allergy and Infectious Diseases (NIAID); U24CA076518; Health Resources and Services Administration (HRSA); HHSH250201700006C; Office of Naval Research; N00014-20-1-2705; Office of Naval Research; N00014-20-1-2832; Biomedical Advanced Research and Development Authority (BARDA); R01AI128775; Biomedical Advanced Research and Development Authority (BARDA); R01HL130388.

Clinical Endpoint	One Year Estimate (%) (95% CI)[#]
GVHD-free, relapse free survival (GRFS)	47% (36-59%)
Primary graft failure by Day 28	6% (2-14%)
Non-relapse mortality (NRM)	13% (6-22%)
Relapse	21% (13-32%)
Acute GVHD grade II-IV	43% (31-55%)*
Acute GVHD grade III-IV	9% (3-16%)*
NIH moderate/severe chronic GVHD	9% (3-17%)

*6-month estimate [#] OS and GRFS using Kaplan-Meier method; NRM, relapse, and GVHD using cumulative incidence method.

Obecabtagene autoleucel (obe-cel, AUTO1) in adults with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL): Overall survival (OS), event-free survival (EFS) and the potential impact of chimeric antigen receptor (CAR)-T cell persistency and consolidative stem cell transplantation (SCT) in the open-label, single-arm FELIX phase Ib/II study.

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Background: Obe-cel is an autologous CAR-T cell product with a fast off-rate CD19 binder designed to mitigate immunotoxicity and improve expansion/persistence. Pooled results from the pivotal FELIX phase Ib/II study (NCT04404660) of obe-cel in adults with R/R B-ALL were recently presented (Roddie C et al. Blood 2023;142[Suppl 1]:222). Here, OS and EFS in all patients (pts) treated with obe-cel are reported, alongside the impact of CAR-T cell persistency and consolidative SCT for pts in remission. **Methods:** Pts aged ≥18 yrs with R/R B-ALL were enrolled. CAR-T products were generated via an automated process (Roddie C et al. Blood 2023;142[Suppl 1]:222). Pts received bridging therapy as appropriate and underwent lymphodepletion (fludarabine, $4\times30mg/m^2$; cyclophosphamide, $2\times500mg/m^2$), followed by obe-cel split dose infusions on Days 1 and 10 based on pre-lymphodepletion leukemic burden at a target dose of 410×10^6 CAR-T cells. **Results:** A total of 127/153 (83%) enrolled pts were infused. At screening, pts' median age was 47 yrs; 42%/31%/44% had received prior blinatumomab/inotuzumab ozogamicin/allogeneic SCT; median bone marrow blast burden was 36% (range: 0–100). At data cut-off (13 September 2023), median follow-up was 16.6 mos (range 3.7–36.6 mos). The overall complete remission or complete remission with incomplete count recovery rate among infused pts was 78%. Among responding pts, 17/99 (17%) proceeded to consolidative SCT while in remission; all 17 (100%) were in measurable residual disease (MRD)-negative remission ($\leq10^{-4}$ leukemic blasts) and 10/17 (59%) showed CAR-T cell persistency prior to SCT. Loss of CAR-T cell persistency was associated with a hazard risk of relapse or death 2.9 times compared with pts who had ongoing CAR-T cell persistency. Pts who experienced B-cell recovery had a hazard risk of relapse or death 1.7 times compared with pts without B-cell recovery. At 12 mos, the EFS rate was 50% and 43% with or without censoring for consolidative SCT or new therapies, respectively; the OS rate was 61% and 59% with or without censoring for SCT, respectively. **Conclusions:** Ongoing CAR-T cell persistency and B-cell aplasia were associated with improved EFS without further consolidation post-obe-cel. At the current follow-up, consolidative SCT for pts in MRD-negative remission post-obe-cel did not improve EFS or OS. Clinical trial information: NCT04404660. Research Sponsor: This study was funded by Autolus Therapeutics.

6505 Oral Abstract Session

Phase I study of CN201, a novel CD3xCD19 IgG4 bispecific antibody, in adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia.

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Background: Patients with relapsed or refractory B-cell acute lymphoblastic leukaemia (B-ALL) still need more and better treatment options. CN201 is a novel CD19-targeting T-cell-engaging IgG4 bispecific antibody. This phase I study is to investigate the safety, tolerability and preliminary efficacy of CN201 in B-ALL (ClinicalTrials.gov identifier: NCT05579132). The data from the dose escalation and expansion of the ongoing study is presented. **Methods:** The study is enrolling patients with B-ALL who are refractory to primary induction therapy or to salvage therapy, or relapse. Patients with Philadelphia chromosome-positive after two or more tyrosine kinase inhibitors (TKIs) were eligible. Single-agent CN201 was administered intravenously once per week with a step-up dose approach during cycle 1, a priming dose on Day 1 followed by an intermediate dose on Day 8 and the target dose administered on Day 15 and thereafter. The patients will receive 2 cycles of CN201 for induction. Responders will continue to receive a further 3 cycles for consolidation, and up to an additional 7 cycles for maintenance treatment or until PD or unacceptable toxicity. **Results:** As of January 31, 2024, 42 adult patients received CN201 with full dose from 600 μg to 40mg. 37 patients were evaluable for efficacy (Table1). Maximum tolerated dose has not reached. The most common adverse events (≥20%) of grade 3 or higher were leukopenia (47.6%), lymphopenia (42.9%), neutropenia (38%), thrombopenia (33.3%) , anaemia (26.2%). 6 patients (14.3%) had infections of grade 3 or higher. Cytokine release syndrome occurred in 13 (30.9%) patients, mainly occurred following the first dose, most were low-grade, except for one patient with grade 3. No immune effector cell-associated neurotoxicity syndrome was observed. Overall, 11 (30%) of 37 patients had complete remission (CR) , 1 (2.7%) patient had complete remission with incomplete haematological recovery (CRi), 75% of responders had MRD negativity. The CR rate significantly increased with dose descalation, reached 50% (4 of 8 patients) with 10mg target dose, two of those occurred within the first two weeks following CN201 treatment. Among those responders, 100% were MRD negative. The CR rate in patients with higher dose levels are under investigation. **Conclusions:** Preliminary data show CN201 has a well tolerable safety profile and promising activity in adult patients with relapsed or refractory ALL. Clinical trial information: NCT05579132. Research Sponsor: None.

Summary of dose escalation and expansion.

DL	C1D1	C1D8	C1D15	C1D22 and Thereafter	Number of Patients	CR (%)
1	150 μg	300 μg	600 μg	600 μg	4	1 (25)
2	300 μg	600 μg	1.2 mg	1.2 mg	3	0 (0)
3	500 μg	1 mg	2.5 mg	2.5 mg	6	1 (16.7)
4	500 μg	1.5 mg	5 mg	5 mg	11	3 (27.3)
5	1mg	5mg	10mg	10mg	8	4 (50)
6	1.5mg	10mg	20mg	20mg	3	1 (33.3)
7	2.5mg	20mg	40mg	40mg	2	1 (50)

*Only show efficacy evaluable patients. DL: dose level. C: Cycle. D: Day. CR: complete remission.

Frailty risk assessment and impact on acute myeloid leukemia outcomes (FRAIL-AML): A population-based study from Ontario, Canada.

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Background: In acute myeloid leukemia (AML), treatment decisions, specifically intensive versus non-intensive approaches, depend on the clinician's assessment of patient fitness. Frailty as a measure of fitness is a broader concept than commodities and is associated with worse outcomes in many cancers. Frailty assessment is incorporated to provide the precision to oncology treatment selections in addition to disease-related factors. The impact of frailty on outcomes in AML is not well studied. **Methods:** This retrospective cohort study from population-based health administrative databases in Ontario, Canada (ICES) included all patients (pts) ≥18 years diagnosed with AML between 2006 and 2021, treated within 90 days after diagnosis. Frailty was measured using McIsaacs's frailty index (MFI)- a validated tool. Progressively increasing tertiles of MFI were categorized as fit (FT), pre-frail (PFR), or frail (FR). Treatment intensity was classified as intensive (IT) or non-intensive (NIT) based on standard practices. The primary outcome was overall survival (OS). Association of frailty with OS was measured using Cox regression separately for IT and NIT AML. **Results:** Out of 5450 pts, with a median age of 65 (IQR 54-74), 55.8% were males and 44.2% were females. 65% (n=3543) received IT, out of which 29.4% and 35.5% pts were FR and PFR respectively. Remaining 35% (n=1907) received NIT, with 41.1% and 32.3% pts being FR and PFR. Median overall survival in months (OS, 95% CI) for the entire group, IT, and NIT were 12.5 (12.0-13.2), 16.7 (15.7-18.2), and 7.6 (7.0-8.2), respectively. OS (table) was notably lower in FR pts compared to fit pts ($p<0.0001$) in both IT and NIT. Univariate and multivariate analyses identified frailty, advanced age, and previous non-AML malignancy as risk factors associated with worse OS in both IT and NIT groups (table). **Conclusions:** Higher frailty is independently associated with worse OS in AML pts after adjusting for advanced age. A substantial proportion of AML pts in both IT and NIT groups exhibit a mismatch in treatment intensity assignments based on their frailty status, with about 30 % FR pts receiving IT and over 25 % FT pts receiving NIT. This study sheds light on the need for frailty evaluations using standardized tools to optimize treatment decisions in AML pts. Research Sponsor: Princess Margaret Early Career Investigator Grant.

Median OS (95% CI) (months)				
Frailty	**IT**	**p value**	**NIT**	**p value**
FT	22.9 (19.7-27.4)	<0.0001	11.4 (10.0-12.7)	<0.0001
PFR	18.0 (15.5-20.6)		8.3 (7.5-9.3)	
FR	11.8 (10.6- 12.8)		4.4 (3.9-5.4)	
Multivariable analysis for OS*: Hazard ratio (95% CI)				
Frailty				
FT	1.00 (Ref)		1.00 (Ref)	
PFR	1.07 (0.97-1.18)	0.14	1.02 (0.89-1.16)	0.73
FR	1.25 (1.12-1.39)	<0.0001	1.39(1.22-1.58)	<0.0001
Age (per year)	1.021 (1.024-1.028)	<0.0001	1.021 (1.016-1.025)	<0.0001
Non-AML malignancy	1.32 (1.20-1.46)	<0.0001	1.23 (1.12-1.36)	<0.0001

*Adjusted for sex, income, Ontario marginalization index, ethnicity and rurality.

6507 Oral Abstract Session

A retrospective comparison of abbreviated course "7+7" vs standard hypomethylating agent plus venetoclax doublets in older/unfit patients with newly diagnosed acute myeloid leukemia.

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Background: Hypomethylating agent (HMA) plus venetoclax (VEN) regimens are standard of care in older/chemotherapy ineligible patients with acute myeloid leukemia (AML). While the VEN label recommends continuous 28-day cycles, shortened VEN durations may mitigate cytopenias and improve tolerability. It is unknown how shorter VEN cycles compare to standard HMA+VEN in terms of efficacy/safety. **Methods:** We performed a retrospective comparison of patients with newly diagnosed (ND) AML treated with azacitidine (AZA) x 7 days plus VEN x 7 days ("7+7" regimen) at 7 French centers (n=82, Willekens, ASH 2022) vs patients treated with standard dose HMA+VEN (s-HMA/VEN) at a US center (n=173), generally consisting of 21-28 days of VEN. We compared composite complete remission rate (CRc, consisting of CR + CRi), overall survival (OS), event-free survival (EFS), and myelosuppression between regimens. **Results:** Baseline characteristics are shown in the table. The s-HMA-VEN group consisted of 10-day decitabine (DAC) in 59% with the remaining patients receiving 5-day DAC or 7-day AZA. The CRc rate was similar; 72% with "7+7" vs 71% with s-HMA/VEN (p=0.89). The CR rate was 57% with "7+7" vs 55% with s-HMA/VEN (p=0.72). Median cycles to first response was 1 in both groups, however 42% of responders on "7+7" required more than 1 cycle for first response whereas almost all responders on s-HMA-VEN (99%) had a first response after cycle 1. Median cycles to best response was 2 with "7+7" vs 1 with s-HMA-VEN (p=0.02). 4-week mortality was similar (2% with "7+7", 6% with s-HMA-VEN; p=0.24). 8-week mortality was higher with s-HMA-VEN (17%) compared to "7+7" (6%) (p=0.02). The median OS was 11.2 months (2-year 28%) with "7+7" vs 10.1 months (2-year 33%) with s-HMA/VEN (p=0.93). Outcomes stratified by molecular groups will be updated at the meeting. Fewer patients required platelet transfusions during cycle 1 with "7+7" compared to s-HMA/VEN (62% vs 77%, p=0.01). The cycle 1 rates of neutropenic fever and red cell transfusion requirements were similar. **Conclusions:** Acknowledging the limitations of a retrospective comparison across multiple centers, we did not observe a signal for a difference in efficacy between "7+7" vs standard VEN-based HMA doublets in ND-AML. The "7+7" regimen was associated with lower platelet transfusion requirements and lower 8-week mortality. Research Sponsor: None.

Baseline patient characteristics.

Parameter	"7+7", n=82	Standard HMA + VEN, n=173
Age	75 [50-89]	74 [61-89]
ECOG		
0-1	52 (63)	104/156 (67)
2-4	30 (37)	52/156 (33)
Prognostic risk signature		
Higher benefit: all others	46/80 (58)	58/139 (42)
Intermediate benefit: *FLT3*-ITD and or *N/KRAS*-mutated	18/80 (23)	29/139 (21)
Lower benefit: *TP53*-mutated	16/80 (20)	52/139 (37)
Prior MDS/MPN	26 (32)	31 (18)
Therapy-related AML	28 (34)	38 (22)

Data displayed as n(%) or median [range].

LBA6508 **Oral Abstract Session**

Multi-site randomized trial of a collaborative palliative and oncology care model for patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) receiving non-intensive therapy.

Areej El-Jawahri, Alison Kavanaugh, Joseph A. Greer, Vicki Jackson, Jillian Gustin, Alice S. Mims, Albert Cook, Thomas William LeBlanc, Joanna Choe, Mathew Reynolds, Amir Tahmasb Fathi, Gabriela Hobbs, Andrew Mark Brunner, Jennifer S. Temel; Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital, Harvard Medical School, Boston, MA; The Ohio State University Wexner Medical Center, Columbus, OH; The Ohio State University, Columbus, OH; Duke University School of Medicine, Durham, NC; Massachusetts General Hospital Cancer Center, Boston, MA

6509 Rapid Oral Abstract Session

Preliminary safety and efficacy of oral azacitidine (Oral-AZA) in patients (pts) with low-/Intermediate (Int)-risk myelodysplastic syndromes (MDS): Phase 2 results from the ASTREON trial.

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Background: There is an unmet need for new treatment (tx) options in lower-risk MDS (LR-MDS) to address cytopenias and prevent progression to higher-risk MDS and acute myeloid leukemia. Here, we report safety and preliminary efficacy data from phase 2 of the ASTREON study, which evaluated 14-day Oral-AZA regimens in pts with Low-/Int-risk MDS. **Methods:** ASTREON is a phase 2/3, multicenter study evaluating safety and efficacy of Oral-AZA plus best supportive care (BSC) in pts with Low-/Int-risk MDS (NCT05469737). Phase 2 is an open-label, dose optimization study to determine the recommended phase 3 Oral-AZA dose. Eligible pts (≥ 18 years of age with Revised International Prognostic Scoring System [IPSS-R] Low-/Int-risk MDS and ≥ 1 cytopenia) were randomized 1:1 to receive Oral-AZA 200 mg or 300 mg QD for 14 d per 28-d cycle plus BSC. Primary endpoints are rates of adverse events (AEs) and complete remission (CR) within 6 cycles per International Working Group (IWG) 2006 criteria. Secondary endpoints include achievement of overall response (OR) (including CR, partial remission, marrow CR, hematologic improvement-erythroid response [HI-E], HI-platelet response, and HI-neutrophil response per IWG 2006 criteria); best OR; and OR duration. HI rates within 6 cycles were calculated by investigator assessment per IWG 2006 criteria for pts who received ≥ 75% of the cycle 1 dose and had ≥ 1 post-baseline (BL) efficacy assessment (modified intent-to-treat [mITT] population). **Results:** As of December 4, 2023, 47 pts were randomized and received ≥ 1 Oral-AZA dose (200 mg, n = 24; 300 mg, n = 23); 6 and 5 pts discontinued tx in the 200 mg and 300 mg arms. The median (range) tx durations were 24.1 (12.1–34.1) and 24.7 (7.7–39.1) wk for the 200 mg and 300 mg arms, respectively. IPSS-R scores and RBC transfusion burden at BL were balanced between tx arms. Most pts (42/47 [89.4%]) had prior MDS tx, including but not limited to erythropoiesis-stimulating agents, lenalidomide, luspatercept, and imetelstat. AE rates were similar between arms: 11/24 (45.8%) vs 12/23 (52.2%) pts in the 200 mg vs 300 mg arms reported ≥ 1 tx-related grade 3 or 4 tx-emergent AE. The most common tx-related AEs in both arms were hematologic and gastrointestinal. Tx-related serious AEs occurred in 1/24 and 3/23 pts in the 200 mg and 300 mg arms, respectively. One death occurred in the 300 mg arm and was considered tx-related. In the mITT population, 8/22 and 7/21 pts achieved any HI in the 200 mg and 300 mg arms, respectively. Six pts in each dose group achieved HI-E. Among mITT pts with anemia at BL, 6/19 (31.6%) pts in the 200 mg and 5/18 (27.8%) pts in the 300 mg arm achieved HI-E. Updated results will be presented. **Conclusions:** The safety of Oral-AZA 200 mg and 300 mg was consistent with the known Oral-AZA safety profile. Preliminary efficacy data support continued evaluation of Oral-AZA in LR-MDS. Clinical trial information: NCT05469737. Research Sponsor: Bristol Myers Squibb.

Latest results of a phase 2 study of IMM01 combined with azacitidine (AZA) as the first-line treatment in adults with higher risk myelodysplastic syndromes (MDS).

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Background: Patients diagnosed with higher-risk myelodysplastic syndrome (MDS) have poor prognosis. Azacitidine (Aza) has been shown to prolong survival in patients with treatment-naive, higher-risk MDS compared to a menu of standard of care options. IMM01 is a fusion protein comprising a recombinant signal regulatory protein α (SIRPα) and IgG1, exerting anti-tumor effects by inhibiting the "Don't eat me" signal and activating the "Eat me" signal, leading to robust antibody-dependent cellular phagocytosis (ADCP). **Methods:** This is an open-label, multi-center, phase 2 study (NCT05140811) that evaluated safety and efficacy of IMM01 in combination with AZA as the first-line treatment for patients with untreated higher-risk MDS. Enrolled patients were aged ≥18 years with intermediate to very high risk MDS, as defined by the Revised International Prognostic Scoring System (IPSS-R) score >3.5, and were not eligible for stem cell transplant or intensive chemotherapy. Patients were received intravenous IMM01 at a dosage of 2.0mg/kg/week and subcutaneous AZA at a dosage of 75 mg/m^2 on days1-7 per 28-day cycle. **Results:** By the cutoff-day of Dec 22, 2023, 57 patients were enrolled in the study. The median age was 64 (30-83) years, with 41 (71.9%) being male, and 55 (96.5%) having an ECOG of ≥1. Based on risk classification per IPSS-R, 43.9% were high risk (HR) and 31.6% were very high risk (vHR). At baseline, the median levels of blood counts were 69 (35-136)g/L for hemoglobin, 43 (2-409)×10^9/L for platelets and 0.8 (0.1-8.6)×10^9/L for neutrophils. The median duration of follow-up was 12.8 months (95%CI:9.7-15.3). Among the 51 efficacy evaluable patients, overall response rate (ORR) was 64.7%, including 29.4% complete response (CR) rate, 15.7% marrow CR (mCR) with hematologic improvement (HI), 5.9% HI and 13.7% mCR alone. The median time to response (TTR) was 1.9 months (95%CI:1.8-2.8) and the median duration of response (DoR) was not reached(NR). The median of progression-free survival (PFS) was not reached, with an estimated 12-month PFS of 54.4% (95% CI, 31.4-72.6). NGS analysis identified common mutations in DNMT3A, ASXL1, U2AF1 and RUNX1. Notably, NPM1 mutations significantly correlate with treatment response, particularly achieving CR. The most common ≥G3 treatment related adverse events (TRAEs) (≥10%) included leukopenia (78.9%), thrombocytopenia (66.7%), neutropenia (66.7%), lymphopenia (56.1%), anemia (43.9%), infection (15.8%) and pneumonia (10.5%). Without using of a low priming dose, the Grade ≥3 hemolysis was rare (only 1.8%). **Conclusions:** IMM01 (without low-dose priming) combined with AZA were well tolerated and showed exciting efficacy results in patients with treatment-naive higher-risk MDS. Clinical trial information: NCT05140811. Research Sponsor: None.

6511 Rapid Oral Abstract Session

Interim safety and efficacy of BP1001 in a phase II acute myeloid leukemia (AML) study.

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Background: Oncogenic tyrosine kinases induce AML progression via the growth factor receptor bound protein-2 (Grb2). BP1001, a liposome-incorporated Grb2 antisense oligonucleotide,enhanced cancer cell sensitivity to chemotherapy, such as decitabine (DEC) and venetoclax (VEN). A multi-center open-label Phase II study was initiated to assess whether the BP1001 + DEC + VEN combination provides higher response rates than historically reported responses of DEC + VEN in newly diagnosed AML (including secondary AML) (cohort 1) or refractory/relapsed (R/R; cohort 2) AML patients (pts) considered unsuitable for intensive chemotherapy. Per protocol, when 19 evaluable pts are enrolled in each cohort, interim analysis will be performed to determine which cohort has ≥5 complete responses and will continue with enrollment. **Methods:** BP1001 was given, beginning on Day 4, at 60 mg/m^2 IV, 2x weekly for a total of 8 doses over a 28-day cycle. DEC was given IV on days 1 to 5 at 20 mg/m^2. VEN was given PO at 100 mg on day 1, 200 mg on day 2, and 400 mg from day 3 to day 14 or 21. Eligible pts were considered unsuitable for or refused intensive chemotherapy and had ECOG performance status of 0-2. Interim analysis was performed on Jan 24, 2024 on pts enrolled between July 28, 2020 and December 26, 2023. Evaluability for efficacy was defined as: completion of at least 4 cycles of combination therapy, documented Progressive Disease (PD) or any drug toxicity at any time, or CR/CRi/CRh prior to 4 cycles. **Results:** In Cohort 1, 31 newly diagnosed pts were enrolled; 20 evaluable pts (9 male: 45%) with a median age of 75 years (range, 69 - 84), treated with at least 1 cycle of BP1001 + DEC + VEN, had adverse-risk (n=12, ELN 2017 classification) or secondary AML (sAML; n=7) evolved from MDS (n=4), CMML (n=1) or treatment-related AML (n=2). Fifteen pts (75% of evaluable; 54% of enrolled) achieved CR/CRi/CRh; 2 pts achieved partial remission (PR) and 2 achieved stable disease (SD). In Cohort 2, 38 R/R pts were enrolled; 23 evaluable pts (13 male: 57%) with a median age of 63 years (range, 24 - 89), treated with at least 1 cycle of BP1001 + DEC + VEN, had adverse-risk (n=13) or sAML (n=5). Twelve pts (55% of evaluable; 32% of enrolled) achieved CR/CRi/CRh; 1 pt achieved PR, 8 achieved SD and 1 had treatment failure. Among the evaluable pts of both cohorts, adverse events were consistent with those expected with DEC, VEN and/or AML, including fatigue (72%), anemia (60%) and neutropenia (49%), while the most frequent serious adverse events were febrile neutropenia (26%) and sepsis (5%). **Conclusions:** BP1001 + DEC + VEN has been safely administered to pts without drug-related toxicity. Since >5 responses are observed in both cohorts, the study will continue with enrollment up to 98 and 54 evaluable pts in cohorts 1 and 2, respectively. Efficacy data are encouraging in a challenging population of frontline adverse-risk, sAML and R/R pts. Clinical trial information: NCT02781883. Research Sponsor: None.

Long-term efficacy of high-dose imatinib in Hispanic patients without access to second-generation tyrosine kinase inhibitors treated in LATAM centers.

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Background: Treatment for patients with chronic myeloid leukemia (CML) had a benchmark with the introduction of imatinib, a tyrosine kinase inhibitor (TKI). Nevertheless, resistance due to genetic mutations in the BCR::ABL1 kinase receptor remains relatively common for many patients, leading to failure, lack of response, or suboptimal response. Ideally, to bypass genetic resistance, guidelines recommend switching to a second-generation TKI, but for many developing countries, socioeconomic barriers hinder the possibility of switching medication. Despite this scenario, scarce information is available to evaluate the clinical prognosis of these patients. **Methods:** We conducted a retrospective cohort analysis to compare the overall mortality of patients with CML who developed a suboptimal response to standard-dose imatinib and were treated with either high-dose imatinib or a second-generation TKI. We created a marginal structural model with inverse probability weighting and stabilized weights and depicted the survival curves and median using the Kaplan-Meier estimator. Our primary outcome was overall survival (OS) at 150 months, defined as the number of deaths once patients had reached treatment response based on parameters of the European Leukemia Net Guidelines for CML. Our secondary outcomes were disease-free survival (DFS) at 150 months, defined as the number of months after patients achieved either major molecular response or deep molecular response, and adverse events that included gastrointestinal, dermatologic, hematologic, and others. **Results:** The cohort included 148 patients, of which 32 received high-dose imatinib and 116 a second-generation TKI. While we found no difference in the 150-month risk in both OS and DFS (Table), patients receiving second-generation TKI had an increase in median survival of OS (p-value = 0.009). No difference was found in the median survival of DFS (p-value = 0.55). No difference was found in either hematologic, gastrointestinal, dermatologic, or other adverse events (p-values of 0.39, 0.94, 0.24, and 0.33, respectively). **Conclusions:** Ideally, patients who develop a suboptimal response to imatinib should be switched to a second-generation TKI. However, If impossible, our findings suggest that patients treated with high-dose imatinib have a similar OS and DFS prognosis to those receiving a second-generation TKI. Research Sponsor: None.

Estimates for primary and secondary outcomes.

	Overall Survival		Free-Disease Survival	
Type of Estimate	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Risk Ratio	0.91	0.55 – 1.95	1.02	0.53 – 2.71
Risk Difference	0.77	-0.3 – 0.21	0.01	-0.26 – 0.22

6513 Rapid Oral Abstract Session

PTPN11 variants in chronic myelomonocytic leukemia: Phenotypic and prognostic correlates.

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Background: *PTPN11* (Ch12q24) is a proto-oncogene that codes for SHP2, a regulatory protein tyrosine phosphatase that impacts RAS/MAPK signaling. Germline variants have been described in juvenile myelomonocytic leukemia, while somatic variants have been associated with inferior survival in acute myeloid leukemia. *PTPN11* variants are infrequent in chronic myelomonocytic leukemia (CMML), and their impact on disease phenotype and survival remains unclear. **Methods:** After IRB approval, 396 molecularly annotated CMML patients at Mayo Clinic were screened for somatic *PTPN11* variants within 12 months of diagnosis while still in chronic phase disease. Overall (OS), acute myeloid leukemia (AML)-free survival (LFS), and predictors of survival were estimated using standard statistical measures. **Results:** 396 patients (median age 71 years; males 67%) with CMML were considered; pathogenic *PTPN11* variants were seen in 12 (3%) with a median VAF of 20.5% (range: 4-50): A72T (n = 2), F285S (n = 2), and A72S (n = 2). Variants were most likely to be seen in the N-terminal SH2 domain (n = 7), followed by the PTP domain (n = 6), and the C-terminal SH2 domain (n = 1). *PTPN11* variants clustered with CMML-2 ($p = 0.02$), higher absolute neutrophil count ($p = 0.04$), peripheral blood ($p = 0.06$) and bone marrow ($p = 0.02$) blast %, older age ($p < 0.01$), and were less likely to have *SRSF2* comutations ($p = 0.02$). After a median follow-up of 18 months (range 0-193), 253 (64%) deaths and 68 (17%) AML transformations were recorded. *PTPN11* variants negatively and independently impacted both OS (median 13 vs. 31 months; $p < 0.01$) and LFS (AML events: 42% (5/12) vs. 16% (63/384); $p < 0.01$). In age-adjusted multivariate analysis restricted to genetic risk factors, survival was negatively affected by abnormal karyotype and mutations involving *PTPN11*, *DNMT3A*, and *SETBP1*, and positively by *TET2* mutations. All but *SETBP1* retained significance in the presence of additional independent risk factors, namely male sex ($p < 0.01$) and leukocyte count ($p < 0.01$); HR in the latter analysis was 4.3 for *PTPN11*, 2.8 for *DNMT3A*, and 1.6 for abnormal karyotype. A similar analysis for LFS identified, as risk factors, *PTPN11* ($p = 0.01$), *DNMT3A* ($p < 0.01$), and *ASXL1* ($p = 0.03$) mutations, as well as bone marrow blast % ($p < 0.01$), absolute monocyte count ≥ 10 ($p = 0.02$), and immature circulating myeloid cells ($p < 0.01$). **Conclusions:** The current study identifies *PTPN11* and *DNMT3A* mutations as independent risk factors for both OS and LFS in CMML. In regard to additional genetic risk factors, OS was positively affected by *TET2* mutations and negatively by abnormal karyotype, while LFS was negatively affected by *ASXL1* mutations. Research Sponsor: None.

Impact of JAK2 allele burden on MF outcome in the era of ruxolitinib.

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Background: Myelodepleted myelofibrosis (MF), characterized bycytopenias, lower JAK2V617F allele burden (JAK2%) and shorter benefit from JAKi ruxolitinib (RUX), has worse survival (OS) compared to myeloproliferative MF. Lower JAK2% and inferior OS is more typical for primary MF (PMF) vs MF from essential thrombocythemia or polycythemia vera (PPV/PET-MF). We sought to investigate the impact of JAK2% (</≥ 50%), cytopenias and the use of RUX in outcome of PMF/PPV-PET-MF patients from our center. **Methods:** 601 medical charts of JAK2 mutated patients with MF (known JAK2%) were retrospectively reviewed. We divided patients based on the absence (-) or presence (+) of cytopenias (hemoglobin < 10 g/dL or platelets < 100 x10^9/L) and leukocytosis (WBC ≥ 25 x10^9/L) into: Gr1 = (-)/(-) [absence of both]; Gr2 = (-)/(+) [proliferative]; Gr3 = (+)/(-) [cytopenic]; Gr4 = (+)/(+) [cytopenic and proliferative]) and evaluated OS per JAK2 </≥ 50% and PMF vs PPV/PET-MF. We assessed the tolerance of RUX ≥3 years. We used descriptive statistics, Kaplan-Meier curve with log-rank test and regression analysis for demographics, estimation of OS and its comparison. OS was censored at the time of stem cell transplantation. **Results:** Median age of the entire cohort was 75 years (64% males). Patients with JAK2 <50%, more likely PMF, had more anemia and thrombocytopenia, higher blasts, less leukocytosis, and smaller splenomegaly. JAK2 </≥ 50% did not discriminate OS of the entire group, PMF or PPV/PET-MF (median OS of ~ 45 months for each; only PPV/PET-MF with 64 months). OS of Gr1-4 according to JAK2 </≥ 50% and PMF/ PPV/ PET-MF and combined OS of patients with comparable outcome (A-D) are shown in the table. The final groups with distinct outcomes included: A+B) non-cytopenic PET/PPV-MF and PMF irrespectively of proliferation and JAK2% - with one exception of non-cytopenic, proliferative PMF with JAK2 ≥50% - had median OS of 70 months (range, 54-86); D) cytopenic and proliferative PMF with any JAK2% and PPV/PET-MF with JAK2 < 50% of median OS 19 months (range, 13-25), and C) the rest of the cytopenic patients and non-cytopenic, proliferative PMF with JAK2 ≥50% with a median OS of 36 months (range, 32-42). Among the 3 final groups, similar proportion of patients were exposed to RUX during their follow-up: 36% (A+B), 31% (B) and 28% (C), respectively (p =0.13). The most patients in (A+B) group were able to tolerate RUX for ≥3 years (p =0.036). All patients had improved OS with RUX (data to be presented). **Conclusions:** Cytopenias and/or proliferation, rather than JAK2 </≥50%, define the outcome of PMF and PPV/PET-MF patients. Research Sponsor: None.

Median OS, months	Gr1	Gr2	Gr3	Gr4
PMF JAK2 < 50%	85 (A)	48 (B)	35 (C)	14 (D)
PMF JAK2 ≥ 50%	53 (B)	37 (C)	34 (C)	21 (D)
PPV/PET-MF JAK2 < 50%	102 (A)	91 (A)	28 (C)	3 (D)
PPV/PET-MF JAK2 ≥ 50%	80 (A)	72 (A)	36 (C)	30 (C)

Comparable outcome and combined median OS = months: (A) = 84; (B) = 51; (C) = 36; (D) = 19. OS of (A) and (B) groups was not statistically different, p 0.193.

6515 Rapid Oral Abstract Session

Safety and efficacy of CD7-CAR-T cell in patients with relapsed/refractory T-lymphoblastic leukemia/lymphoma: Phase I dose-escalation/dose-expansion study.

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Background: Patients with relapsed/refractory T-lymphoblastic leukemia/lymphoma (r/r T-ALL/LBL) are clinically manifested by rapid disease progression, poor prognosis and lack of therapeutic options. There is an urgent need to develop other effective modalities. Apart from its expression in normal T and NK cells and no expression in other tissue cells, CD7 is highly expressed in T-ALL/LBL cells. Therefore, CD7 is considered a potential target for the development of CAR-T therapy for T-ALL/LBL. The challenge, however, is to avoid fratricide caused by the expression of CD7 in T cells. We developed a CAR-T cell injection based on CD7 nano antibodies, named PA3-17 injection, by blocking the expression of CD7 molecule on the surface of T cells through anti-CD7 protein expression blocker (PEBL) and evaluate the safety, efficacy and Recommended Phase II Dose (RP2D) of PA3-17 Injection in patients with r/r T-ALL/LBL in a phase I clinical study. **Methods:** The clinical study (NCT05170568) adopted a "3+3" dose escalation schema and proceed cohort expansion. T-ALL/LBL patients who met the inclusion/exclusion criteria were deployed by entering three dose groups (DL: 0.5×10^6, 2×10^6, 4×10^6 CAR-T/kg) to evaluate the initial safety, efficacy and dose-limited toxicities (DLTs). All patients were treated with lymphodepleting chemotherapy pre-treatment before CAR-T cell infusion. The primary endpoints were DLTs and maximum tolerable dose (MTD). **Results:** As of Nov 28th, 2023, a total of 12 patients were enrolled (3 patients in dose 1, 2, 3 group, 3 patients in RP2D group), all of whom received a single infusion of PA3-17 injection and completed a 28- day DLTs assessment. The median age of enrolled patients was 33.5 years (range 20-64), and 25.0% (3/12) of patients had previously received hematopoietic stem cell transplantation. No DLTs occurred. The RP2D was 2×10^6 CAR-T/kg. The safety analysis showed that 83.3% (10/12) of patients developed cytokine release syndrome (CRS), of which 25% (3/12) had grade 3, and no grade 4 CRS occurred, 16.7% (2/12) of patients experienced 1-2 grade of immune effector cell-associated neurotoxicity syndrome (ICANS), and no grade 3 or higher ICANS occurred. The efficacy data showed that the best ORR was 83.3% (10/12) and the CR rate was 75% (9/12). The median follow-up time was 213.5 days. Five patients (Pt 1/5/6/7/9) maintained CR for more than 6 months. One patient (Pt6) had a tumor mass with a diameter greater than 7cm at baseline prior CAR-T infusion but achieved CR 28 days after infusion, then she underwent transplantation at sixth month but died at eighth month because of heart problems, which is unrelated with PA3-17 infusion. **Conclusions:** PA3-17 injection has shown a good safety profile and encouraging efficacy in r/r T-ALL/LBL patients. RP2D has been determined and the key Phase II clinical study is about to begin. Clinical trial information: NCT05170568. Research Sponsor: None.

Safety outcomes in patients with acute myeloid leukemia receiving gemtuzumab ozogamicin and proceeding to allogeneic hematopoietic stem cell transplantation.

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Background: Gemtuzumab ozogamicin (GO) is a CD33-directed antibody-drug conjugate approved by the FDA in 2017 for the treatment of newly diagnosed and relapsed/refractory (R/R) CD33-positive acute myeloid leukemia (AML) in adults and pediatric patients of 1 month and older and 2 years and older, respectively. Previous data have associated GO with adverse events (AEs) including hepatotoxicity and hepatic veno-occlusive disease (VOD). Patients receiving allogeneic hematopoietic stem cell transplantation (HSCT) may be at greater risk of VOD with GO. This study aimed to characterize AEs after HSCT in adult patients with AML who were treated with GO. **Methods:** This non-interventional post-authorization safety study used de-identified healthcare data from the Center for International Blood and Marrow Transplant Research (CIBMTR) database. Data were collected from 01 September 2017. Safety outcomes post-HSCT were evaluated in adult patients with newly diagnosed or R/R AML who received GO prior to first HSCT. Data cutoff was 04 July 2023. **Results:** We present the interim data of 157 patients from 24 centers with a median follow-up of 12.9 months (range, 3.0-49.7). At the time of HSCT, 84 patients were in first complete remission (CR1), 48 patients were in second CR (CR2) and 25 patients were in third or greater CR, relapse or primary induction failure (CR3, n=5; Rel, n=12; PIF, n=8). Most patients (n=105; 67%) received GO as first line therapy. Median lines of therapy prior to HSCT were 2, 3.5 and 5 in CR1, CR2 and CR3/Rel/PIF groups, respectively. Median age was 52.5 y (range, 18.7-74.9); 53% male. Time from diagnosis to first GO dose was $<$3 months for most patients (n=120; 76%). Total cumulative GO dose was 1-3 mg/m2 in 25 (16%), 4-6 mg/m2 in 28 (18%), 7-9 mg/m2 in 45 (29%) and $\geq$10 mg/m2 in 14 (9%) patients. The most common HSCT donor type was unrelated (n=93; 59%), and 55% of patients received myeloablative conditioning regimens. Non-fatal VOD was reported in 7 (4%) patients. Median time from HSCT to VOD was 0.9 months (range, 0.4-2.2). No VOD-related deaths occurred. Outcome probabilities for 6-month transplant-related mortality (TRM) were 8% (95% CI, 4-13) and 5% (95% CI, 2-8) for 100-day VOD. **Conclusions:** The use of GO appears to be safe prior to HSCT in adults with AML. Rates for 100-day VOD and TRM were comparable to those previously reported for patients with AML who received HSCT with or without prior GO. Clinical trial information: B1767034. Research Sponsor: Pfizer.

6517 Rapid Oral Abstract Session

Hematopoietic stem cell transplant for adults with mixed phenotypic acute leukemia.

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Background: Mixed phenotype acute leukemia (MPAL) is a rare acute leukemia subtype characterized by expression of lymphoid and myeloid lineage markers on blasts. Consequently, the role of hematopoietic stem cell transplant (HCT) consolidation is unclear. We conducted a retrospective study of MPAL patients treated at our institution integrating the impact of transplant status, chemotherapy, and initial response on survival. **Methods:** We evaluated patients with MPAL at Fred Hutchinson Cancer Center from 1/2005 – 9/2022, some of whom were previously reported (Huang et al, ASH 2023). Independent pathology review using 2022 WHO criteria verified MPAL diagnosis. Potentially transplant eligible patients were defined as those <75 years of age, diagnosed at least 6 months prior to data retrieval date, and alive 100 days after diagnosis with an evaluable induction response. Log-rank and Cox proportional hazard models were used to compare survival and adjust for baseline covariates. Survival was landmarked at 100 days. **Results:** Of 55 total patients, 42 were potentially HCT eligible and 30 received HCT (71.4%; 20/30 myeloablative). Patients who did not complete HCT were similar in age (median 46.2, range 18-70 vs median 50.3, range 24 – 74, p = ns) and had similar ECOG (ECOG 0-1 86.6% vs 75.0%, p = ns) at diagnosis. Nine of 12 non-transplanted patients had age-adjusted HCT-CI score ≤ 3. Patients receiving a HCT had better progression free survival (PFS) (p = 0.025) and were more likely to be alive at 48 months (61.6% vs. 32.4%, p = 0.011) with a median overall survival (mOS) of not reached (NR) (95% CI, 43 months – NR) compared to a mOS of 13 months (95% CI, 9 months – NR) for those not transplanted. Given that our prior work showed that the type of induction chemotherapy did not influence OS (p = 0.40) or remission status (p = 0.16) (Huang et al. ASH 2023), we investigated impact of remission status at the time of transplant. Differences in PFS and OS persisted when stratifying patients by induction response status with HCT status (PFS p = 0.0048; OS p < 0.0001). Patients who had a complete response (CR) followed by HCT had the longest mOS = NR (17 of 24 patients alive after 48 mo). Patients who had resistant disease (RD) and completed HCT had mOS = 43 months (95% CI, 43 months– NR). Patients who achieved CR but did not undergo HCT had mOS = 19 months (95% CI, 11 months – NR). Patients who had RD and did not undergo HCT had median OS of 6 months (95% CI, 6 – NR). The hazard ratio for death among patients who underwent HCT was 0.28 (95% CI 0.077 – 0.99, p = 0.049). **Conclusions:** HCT consolidation was significantly correlated with improved survival (p = 0.011). While potentially biased by selection and limited by small sample size, patients benefitted from undergoing a HCT regardless of response to prior therapy (p < 0.0001). This study suggests that patients with MPAL in CR after induction chemotherapy as well as those with less than complete responses should be considered for HCT consolidation. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; 5T32CA951539; American Society of Hematology; National Cancer Institute/U.S. National Institutes of Health; P30 CA015704-48.

Phase I study of functionally enhanced CD33 CAR T cells in patients with relapsed or refractory acute myeloid leukemia.

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Background: Chimeric antigen receptor (CAR) T-cell therapy has shown promising efficacy in B-cell malignancies (Majzner RG, et al. Nat Med. 2019 Sep;25(9):1341-1355). However, its feasibility in acute myeloid leukemia (AML) is not fully established. CD33 CAR T-cell therapy in relapsed or refractory (r/r) AML have reported limited or no significant anti-leukemic effects (Tambaro FP, et al. Leukemia. 2021 Nov;35(11):3282-3286; Wang QS, et al. Mol Ther. 2015 Jan; 23(1):184-91). CD123 CAR T-cell therapy has weak proliferation and low CR rates (Wermke M, et al. Blood. 2021 Jun 3;137(22):3145-3148; Cummins, Katherine D. et al. Blood. 2017; 130: 1359), while CLL1 CAR T-cell therapy has induced anti-leukemic responses in a small subset of patients without sustained expansion (Pei K, et al. Cancer Med. 2023 Apr;12(8):9655-9661; Jin X, et al. J Hematol Oncol. 2022 Jul 7;15(1):88). Here, we present early safety and efficacy of functionally enhanced CD33 CAR T cells in AML. **Methods:** We improved the performance of CD33 CAR T cells by adding a potentiating molecule linked to human CD33 scFv by P2A. The study was registered with ClinicalTrials.gov (NCT04835519). The trial used the "3+3" approach, starting with an initial dose of 5×10^5 ($\pm$20%)/kg. The primary endpoint was safety with efficacy secondary. **Results:** Four relapsed patients, including three who underwent stem cell transplantation, were enrolled and received initial dose of CAR T cells between April 13, and July 28, 2021. The Data and Safety Monitoring Committee approved the preliminary report. Three patients (75%) experienced grade 1–2 cytokine release syndrome (CRS), while one (25%) had grade 4 CRS. One developed grade 2 CRS after the second infusion. One patient had dose-limiting toxicity. Two patients (50%) had grade 1 neurotoxicity, and two (50%) developed grade 1–2 graft-versus-host disease. All patients experienced grade 2–4 neutropenia, monocytopenia, and thrombocytopenia. One patient developed sepsis. Two patients achieved CR with incomplete hematologic recovery (CRi) and were MRD-negative at day 30, while two had no response. Of these, one patient received a second infusion and achieved MRD^+ CRi. Two patients have remained disease free for over two years. One patient remained disease free for one year before $CD33^+$ relapse. The two patients with CRi had peak CAR T cell counts of 192 and 23.5 cells/μl, while the two without CRi had lower peak counts of 2.12 and 10.3 cells/μl. One patient peaked at 1.73 cells/μl after the second infusion. The two patients with CRi also had a higher proportion of CAR T cells among the lymphocytes (46.8% and 53.0%). As expected, peripheral blood $CD33^+$ cells decreased. **Conclusions:** We report the safety and efficacy of functionally enhanced CD33 CAR T cells. While some patients had CRi, there was also depletion of CD33-positive normal cells. Thus, further research is needed to address the issue of normal cell depletion. Clinical trial information: NCT04835519. Research Sponsor: the National Key R&D Program of China.

6519 Poster Session

FLAG-IDA + venetoclax in newly diagnosed (ND) or relapsed/refractory (RR) AML.

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Background: We report the outcomes of a phase 2 study of FLAG-IDA+VEN in AML. **Methods:** Pts ≥18 with ND or RR AML / MDS-EB2 fit for intensive chemotherapy were eligible. Induction comprised fludarabine 30mg/m^2 D2–6, cytarabine 1.5g/m^2 D2–6, idarubicin 8 (6 if RR) mg/m^2 D4–6 & filgrastim 5mcg/kg D1–7. VEN 400mg was administered D1–14 with CYP3A inhibitor dose adjustment until Jul 2023; following a protocol modification, VEN is now administered D1–7. The primary outcome was ORR (CR + CRh + CRi + MLFS + PR). Secondary outcomes were CRc (CR + CRh + CRi), overall survival (OS), event-free survival (EFS) & duration of response (DOR). Measurable residual disease (MRD) was assessed by flow cytometry. **Results:** As of Jan 2024, 134 pts have enrolled, 127 (68 ND & 59 RR) evaluable at data cut. Median age was 45 (18 – 73); 19 (15%) age ≥60. 13 (19%), 22 (32%) & 33 (49%) ND pts were ELN22 favorable, intermediate & adverse respectively. There were 7 (10%) secondary (s), including 4 hypomethylating agent failure, & 7 (10%) therapy-related (t) AML. In RR pts, 40 (68%) were in salvage 1 (S1), of whom 32 (54%) were *TP53*^{WT}. 20 (34%) had prior stem cell transplant (SCT). Median of 2 cycles were given. In ND pts, ORR was 99%, (96% CRc, of whom 89% MRD negative [Table]). Similar responses were seen across ELN groups & s/tAML. At median follow-up (mFU) of 30 months (mo), the mOS, mEFS & mDOR were not reached. The 2yr OS, EFS & DOR were 75% (64 – 88), 68% (56 – 81) & 71% (59 – 85) respectively, with no differences among ELN groups. 57% went to SCT in CR1. 4/4 pts with *TP53*^{mut} became CRc MRD–, but mDOR was only 8.2 mo (95% CI, 2.2 – NE), resulting in poor mOS (13.5 mo, 95% CI, 8.6 – NE). In RR pts, ORR was 70% (66% CRc, of whom 79% MRD negative [Table]). At mFU 27 mo, the mOS, mEFS & mDOR were 12 (7 – 33), 7 (4 – 23) & 21 (8 – NE) mo respectively. The 2yr OS, EFS & DOR were 40% (28 – 55), 34% (23 – 49) & 49% (35 – 68) respectively. 58% went to SCT. S1+*TP53*^{WT} pts had mOS of 34 mo (12 – NE), with 72% going to SCT. 30d & 60d mortality were 0% & 3%. Of the 4 deaths within 60d, 1 was sepsis-related in CR in a ND pt while 3 were disease-related in NR RR pts. The most frequent adverse event was infection. Grade ≥3 infections, gastrointestinal toxicities & bleeding occurred in 102 (80%), 20 (16%) & 9 (7%) pts respectively. The median time to neutrophil >1x10^9/L & platelet >50x10^9/L were 27d & 28d for C1, 39d & 67d for C2 & 35d & 50d for C3 respectively. **Conclusions:** FLAG-IDA+VEN results in high MRD negative response rates, leading to impressive survival outcomes across ELN risk groups in ND AML. It is an effective salvage regimen for RR AML, especially for S1+*TP53*^{WT} pts. Clinical trial information: NCT03214562. Research Sponsor: None.

	ND All n = 68 (%)	Fav n = 13 (%)	Int n = 22 (%)	Adv n = 33 (%)	RR All n = 59 (%)	S1 + TP53^{WT} n = 32 (%)
ORR	67 (99)	13 (100)	21 (96)	33 (100)	41 (70)	26 (81)
CRc	65 (96)	13 (100)	20 (91)	32 (97)	39 (66)	24 (75)
CR	56 (82)	13 (100)	19 (86)	24 (73)	24 (41)	18 (56)
CRh	3 (4)	0 (0)	1 (4)	2 (6)	8 (14)	4 (13)
CRi	6 (9)	0 (0)	0 (0)	6 (18)	7 (12)	2 (6)
MLFS	2 (3)	0 (0)	1 (4)	1 (3)	2 (3)	2 (6)
NR	1 (2)	0 (0)	1 (4)	0 (0)	18 (31)	6 (19)
MRD Neg	58 (89)	12 (92)	18 (90)	28 (88)	31 (79)	20 (83)

A real-world picture of patients with a new diagnosis of acute myeloid leukemia in Italy.

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Background: Acute myeloid leukemia (AML) is a blood malignancy with poor prognosis. Antineoplastic strategies are still mostly restricted to fit patients. This analysis of administrative healthcare data identified and described newly AML diagnosed patients, their antineoplastic treatment and survival from the perspective of the Italian National Health Service (SSN). **Methods:** From the Fondazione ReS (Ricerca e Salute) database (~5 million inhabitants/year), among adults with primary/secondary in-hospital diagnosis of AML in 2018 (index date) and analysable look-back period until 2013, patients newly AML diagnosed were selected. They were characterized by age, sex and comorbidities (cardiometabolic, thyroid and cerebrovascular disorders, chronic kidney and liver disease, and inflammatory bowel diseases). During 1 year following index date, antineoplastic treatment and allogeneic stem cell transplantation (alloSCT) were assessed. Among patients undergoing antineoplastic therapy, those fit and unfit for intensive chemotherapy (ICHT) were categorized according to proxies based on the setting of chemotherapy administration (i.e., overnight hospitalization=fit, while daily hospitalization or local outpatient ambulatory=unfit). The 2-year overall survival (OS) of treated patients was assessed through a Kaplan Meyer analysis. **Results:** In 2018, 228 newly AML diagnosed patients (incidence: 5.7x100,000 adult inhabitants) were identified. Males were 56.6%. Mean age was 69±16 years, and 61% patients had ≥2 comorbidities. During 1 year following index date, 75% of newly AML diagnosed patients received antineoplastic treatment (males were 57%, mean age was 66±15 years, and 49% had ≥2 comorbidities). Of them, 19% underwent alloSCT (mean age was 50±14 years). On average, remaining untreated patients (57/228; 25%) were older (77±14 years) and affected by more comorbidities (79% with ≥2 comorbidities) than treated patients. At 2 years following index date, 97% of treated patients survived (vs 65% of untreated patients; $p<0.01$). Among treated patients, 51% (mean age was 64±15 years) were considered fit for ICHT, and 24% were considered unfit for ICHT (mean age was 71±15 years). At 2 years following index date, 38% of patients fit for ICHT survived (vs 29% of patients unfit for ICHT; $p<0.01$). **Conclusions:** This real-word analysis suggests that patients receiving antineoplastic treatments, regardless of a following alloSCT, were younger and affected by less comorbidities than untreated patients. Also, older patients are likely to be excluded from the ICHT option, as recommended by most of guidelines. However, these findings suggest that being treated with chemotherapy and/or alloSCT can increase survival probabilities. Research Sponsor: None.

Recombinant *Erwinia* asparaginase (JZP458) in acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL): Post hoc analysis of adverse events of interest from AALL1931.

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Background: The pivotal Children's Oncology Group Study AALL1931 (NCT04145531) evaluated JZP458, a recombinant *Erwinia* asparaginase (ASP), in patients with ALL/LBL who developed hypersensitivity/silent inactivation to *E. coli*-derived ASPs, leading to approval of JZP458 by the FDA and EMA. Primary efficacy and safety data have been reported; here, we report on adverse events of interest (AEIs: allergic reaction, pancreatitis, thrombosis, hepatotoxicity) and nausea/vomiting, and summarize post hoc descriptive analyses of AEIs by timing and known risk factors (eg, age and ethnicity). **Methods:** Each pegylated *E. coli* ASP remaining on treatment was replaced by 6 doses of JZP458 administered Monday/Wednesday/Friday (MWF). Three intramuscular (IM) cohorts (1a [25 mg/m^2 MWF], n=33; 1b [37.5 mg/m^2 MWF], n=83; and 1c [25/25/50 mg/m^2 MWF], n=51) and 1 intravenous (IV) cohort (25/25/50 mg/m^2 MWF, n=61) were evaluated. **Results:** Rates of any-grade treatment-related allergic reactions, pancreatitis, thrombosis, increased ALT/AST, and increased bilirubin were 11%, 7%, 1%, 16%, and 7% in the total IM cohort and 26%, 5%, 2%, 18%, and 5% in the IV cohort, respectively. Rates of treatment-related grade ≥2 nausea/vomiting (N/V) were 32% and 64% in the total IM and IV cohorts. Table shows the median number of JZP458 doses on or before the first AEI. Notably, rates of grade ≥2 N/V events were similar after 25 and 50 mg/m^2 dosing. Subgroup analyses showed no consistent trends in the rates of any-grade AEIs by age except for pancreatitis where rates were numerically higher in patients aged 12 to <18 (9/62 [15%]) and ≥18 years (4/31 [13%]) than in those aged 6 to <12 (1/71 [1%]) or <6 years (1/64 [2%]). Overall, incidences of any-grade treatment-related allergic reactions, pancreatitis, thrombosis, increased ALT/AST, and increased bilirubin among Hispanic patients (n=74) were 12%, 5% 1%, 19%, and 7% respectively, similar to non-Hispanic patients (n=140). **Conclusions:** The safety profile of JZP458 is consistent with other ASPs in patients with ALL/LBL and generally similar across age and ethnicity subgroups. Clinical trial information: NCT04145531. Research Sponsor: Jazz Pharmaceuticals.

Timing and dose information of treatment-related adverse events.

	25/25/50 mg/m^2 MWF IM (n=51)	25/25/50 mg/m^2 MWF IV (n=61)
Median (range) doses on/before first event		
Allergic reactions[a]	28 (9-64)	6 (1-25)
Pancreatitis	12 (6-18)	18 (12-18)
Thrombosis	-	21 (21-21)
ALT/AST/bilirubin increased	7 (4-18)	8 (2-30)
Number of grade ≥2 nausea/vomiting events, n (%)	n=29	n=104
After 25 mg/m^2 dose	11 (38)	44 (42)
After 50 mg/m^2 dose	11 (38)	52 (50)
No dose within 7 days	7 (24)	8 (8)

[a]Includes anaphylactic reaction, (drug) hypersensitivity, infusion-related reaction, rash, rash erythematous, rash maculopapular, and urticaria. ALT, alanine aminotransferase; AST, aspartate aminotransferase; IM, intramuscular; IV, intravenous; MWF, Monday/Wednesday/Friday.

A post-hoc analysis of outcomes of patients with acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) who received oral azacitidine (Oral-AZA) maintenance therapy in the QUAZAR AML-001 study.

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Background: AML-MRC represents 25%–34% of all AML cases, and patients with this AML subtype generally have poor outcomes. In this subanalysis of the QUAZAR AML-001study, we report outcomes of patients with AML-MRC who received Oral-AZA vs placebo (PBO). **Methods:** QUAZAR AML-001 was a phase 3 study of Oral-AZA maintenance therapy in patients with AML in first remission after intensive chemotherapy who were not eligible for hematopoietic stem cell transplantation (HSCT). Patients ≥ 55 years of age with AML and intermediate- or poor-risk cytogenetics received Oral-AZA 300 mg or PBO QD for 14 d per 28-d cycles. In this analysis, WHO 2008 criteria were used to identify patients with secondary AML and/or patients with AML-MRC (both groups are referred to as AML-MRC in this analysis). Data on mutational profiles at diagnosis were not available. Overall survival (OS) from time of randomization to time of death from any cause after censoring for HSCT, and relapse-free survival (RFS) from time of randomization, were calculated using the Kaplan–Meier method. Duration of measurable residual disease (MRD) negativity achieved on treatment was calculated from the first MRD-negative assessment. **Results:** Overall, 101/472 patients had AML-MRC; 56/238 (23.5%) patients in the Oral-AZA arm and 45/234 (19.2%) patients in the PBO arm. Karyotype/cytogenetics data at diagnosis were available for 87/101 (86.1%) patients with AML-MRC and 331/371 (89.2%) patients with non-AML-MRC. A greater proportion of AML-MRC than non-AML-MRC patients had poor-risk cytogenetics (20/101 [19.8%] vs 46/371 [12.4%]), del(5q) (10/87 [11.5%] vs 9/331 [2.7%]), and monosomy 7/del(7q) (9/87 [10.3%] vs 14/331 [4.2%]). Median OS did not significantly differ in patients with AML-MRC vs non-AML-MRC in either treatment arm (Oral-AZA: 19.9 mo vs 25.1 mo, $P = 0.2694$; PBO: 14.8 mo vs 14.9 mo, $P = 0.2099$). In both treatment arms, the median RFS was inferior for patients with AML-MRC vs non-AML-MRC (Oral-AZA 7.5 mo vs 10.5 mo, $P = 0.0430$; PBO: 3.7 mo vs 4.9 mo, $P = 0.0109$). Oral-AZA significantly prolonged median OS and RFS, and the duration of MRD negativity for patients with AML-MRC compared with PBO (Table). **Conclusions:** Oral-AZA significantly improved OS and RFS compared with PBO for patients with AML-MRC indicating that Oral-AZA maintenance is an effective treatment option for these patients with particularly poor prognosis. Clinical trial information: NCT01757535. Research Sponsor: Bristol Myers Squibb.

Summary of outcomes of patients with AML-MRC in each treatment arm.

Outcome	Oral-AZA (n = 56)	PBO (n = 45)	*P* value
OS, median (95% CI), mo	19.9 (14.59–31.97)	14.8 (10.05–19.65)	–
HR (95% CI)	0.59 (0.36–0.94)		0.0261
RFS, median (95% CI), mo	7.5 (3.75–14.29)	3.7 (1.94–6.34)	–
HR (95% CI)	0.57 (0.36–0.88)		0.0111
Duration of MRD negativity, median, mo	8.1	0	0.0032

HR, hazard ratio.

6523 Poster Session

Evaluation of the toxicity and outcomes of the combination of midostaurin and CLAG-M in patients with FLT3-mutated acute myeloid leukemia (AML): A multi-center retrospective analysis.

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Background: FLT3-mutated AML is associated with poor outcomes. Addition of midostaurin (multi-targeted kinase inhibitor) to standard "7+3" with cytarabine and daunorubicin significantly prolongs overall and event-free survival for these patients (Stone 2017). At the University of Washington/Fred Hutchinson Cancer Center (UW/FHCC), the standard regimen for newly diagnosed (ND) and relapsed/refractory (r/r) AML is cladribine, high-dose cytarabine, GCSF, and mitoxantrone (CLAG-M); midostaurin is added if FLT3-mutated (Halpern 2018). There is currently no peer-reviewed literature to support this combination for these patients. The purpose of this study is to evaluate the safety and efficacy of the combination of midostaurin with CLAG-M in FLT3-mutated AML patients and compare the toxicity profile to midostaurin plus 7+3. **Methods:** This is a retrospective multi-center review conducted at three major cancer centers. Through pharmacy records and/or an institutional AML database, we identified adults with FLT3-mutated AML undergoing (re)induction chemotherapy who received either CLAG-M (UW/FHCC, Swedish) or 7+3 (OHSU, Swedish). The primary outcome was toxicity profile of the combination as measured by rate of adverse events ([AE], CTCAE Version 5.0). Secondary outcomes included disease response per ELN2017 AML working group criteria and 28-day mortality (TRM) (Döhner 2017). Patients treated on a clinical trial and in whom midostaurin was started $>$ 30 days after day 1 of chemotherapy were excluded. Rates of AEs were compared using Fisher's exact test. **Results:** Eighty patients treated between 10/2022-12/2023 were included; 35 patients received CLAG-M, and 44 patients 7+3. Baseline characteristics were similar across all institutions, with most patients having adverse or intermediate risk disease. AE rates were similar between the two cohorts, (Table 1) except diarrhea and bleeding events were more common in the 7+3 vs. CLAG-M cohort (p = 0.004 and p = 0.037, respectively). The rate of complete remission (CR) plus CR with incomplete blood count recovery (CRi) did not significantly differ between the two cohorts: CLAG-M, 86% versus 7+3, 70% for 7+3 (p =0.11). No TRM occurred. **Conclusions:** The toxicity profile of CLAG-M combined with midostaurin is comparable to the combination of 7+3 with midostaurin, and induces high remissions rates in adults with FLT3-mutated AML. Research Sponsor: None.

	All Grade			*Grade 3-4*		
N (%)	**CLAG-M N = 36**	**7+3 N = 44**	***p-value***	**CLAG-M**	**7+3**	***p-value***
Rash	6 (17%)	5 (11%)	0.53	-	-	
Nausea	6 (17%)	4 (9%)	0.33	2 (6%)	1 (2%)	0.59
Hepatotoxicity	2 (6%)	9 (20%)	0.10	-	3 (7%)	0.25
Electrolyte Abnormalities	7 (20%)	5 (11%)	0.36	-	-	
Delayed Counts	4 (11%)	1 (2%)	0.17	-	-	
Diarrhea	3 (8.6%)	16 (36%)	0.004	-	1 (2%)	1
Bleeding events	1 (3%)	8 (18%)	0.037		3 (7%)	0.25
QTc prolongation	3 (9%)	-	0.09	3 (9%)	-	0.09

6524 Poster Session

Molecular characterization and biomarker identification in pediatric B-cell acute lymphoblastic leukemia.

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Background: B-cell acute lymphoblastic leukemia (B-ALL) is the most prevalent hematologic malignancy in children and a leading cause of mortality. Despite high cure rates, the management of B-ALL remains challenging due to its high heterogeneity and propensity for relapse. This study aimed to delineate molecular features of pediatric B-ALL and explore the clinical utility of circulating tumor DNA (ctDNA) as a biomarker in B-ALL. **Methods:** The study analyzed 146 primary pediatric B-ALL patients who were diagnosed from August 2020 to April 2023 and received systemic chemotherapy in Wuhan Children's Hospital. Baseline bone marrow (BM) and plasma samples were collected for next-generation sequencing (NGS) to profile the mutational landscape. BM samples collected on day 19 of the treatment were utilized for minimal residual disease (MRD) testing to assess treatment efficacy. Transcriptomic profiling of baseline BM samples was performed via bulk RNA sequencing. Fisher's exact test and the Wilcoxon rank sum test were utilized to compare categorical and continuous variables between groups, respectively. A two-tailed P-value<0.05 was considered statistically significant unless indicated otherwise. **Results:** Transcriptomic analysis revealed that 86.3% of patients (126 out of 146) could be categorized into 13 distinct molecular subtypes, with hyperdiploidy emerging as the predominant subtype. Baseline BM NGS identified gene fusions in 61% of patients, including 37 novel fusions previously unreported in B-ALL. Specifically, the KMT2A-TRIM29 novel fusion was detected and validated in a male child diagnosed with the KMT2A-rearranged subtype. Despite initially responding well to therapy, the patient experienced disease progression after a year, indicating a poor prognosis. We also found that elevated mutant counts and maximum-variant-allele-frequency (maxVAF) in baseline BM were associated with significantly poorer response to chemotherapy (P=0.0012 and 0.028, respectively). Additionally, MRD-negative patients exhibited upregulated expression of immune-related pathways ($P<0.01$) and increased CD8+ T cell infiltration (P=0.047), indicating a more active immune microenvironment in better responding tumors. Baseline plasma ctDNA, which exhibited high mutational concordance with paired baseline BM samples, also demonstrated significant associations with chemotherapy efficacy, highlighting its potential as a non-invasive tool for disease monitoring and treatment outcome prediction. **Conclusions:** This study elucidated novel gene fusions and potential biomarkers for treatment response in pediatric B-ALL. Importantly, both baseline plasma ctDNA and BM samples offer promising prognostic insights into chemotherapy responses, paving the way for non-invasive monitoring strategies in the management of pediatric B-ALL. Research Sponsor: None.

6525 Poster Session

Multi-drug algorithm to accurately predict best first-line treatments in newly-diagnosed acute myeloid leukemia (AML).

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Background: AML is a heterogeneous hematological malignancy with poor prognosis. Several treatments are approved for AML, but clinical trials have shown that current stratification approaches to determine patients' eligibility produce false positives (treated patients that fail to respond) and negatives (patients not treated but could have responded). Venetoclax + azacitidine (VA) treatment is currently reserved for unfit patients, with younger patients stratified based on their *FLT3*status, and treated with either intensive chemotherapy (IC), or IC plus midostaurin (MIC). Here, we used phosphoproteomics to build a signature and algorithm that accurately predict which of these approved therapies may be more efficacious for a given patient. **Methods:** Routine bone marrow and peripheral blood diagnosis samples (s, n=182) were collected across the UK, Austria, Canada and the USA from 138 patients (p) subsequently treated with MIC (n=44/64 p/s), VA (n=40/48 p/s) or IC (n=54/70 p/s). Patients were grouped into Good Responders (GR) and Poor Responders (PR) based on treatment response. For VA, patients that achieved complete remission (CR) were considered GR, while refractory patients were considered PR. For MIC and IC, we considered patients that achieved CR without relapse within 6 months as GR, and those refractory or relapsed within 6 months as PR. Samples were processed for mass spectrometry-based phosphoproteomics. Phosphopeptide abundance data, generated with in-house PiQuant software, was used to identify phosphopeptides that distinguish GR and PR groups in each cohort. Statistical models based on these features were assessed via cross-validation. **Results:** We compared phosphoproteomes of 182 diagnosis samples from 138 AML patients, from three treatment cohorts (treated with IC, MIC or VA), with each cohort stratified by patients' response to their respective treatment. Enrichment analysis in each cohort identified several phosphopeptides specific to one of the responder groups, mapping both to proteins with known roles in AML biology (e.g. DNMT3A or RUNX1) and proteins not yet implicated. Next, using machine learning, we identified phosphopeptides that could distinguish between PR and GR, and trained drug response prediction models based on the abundance of these phosphopeptides. In cross-validation, each model stratified patients with log rank $p<0.001$, $HR<0.1$ and more than 90% accuracy, greatly outperforming all currently-used stratification methods for first-line AML therapies. **Conclusions:** We built a suite of predictive models that accurately predict patient response to first-line AML treatment using phosphoproteomic data from routine diagnosis samples. Following validation in independent patient cohorts, this tool will be developed into a single test that predicts treatment response for AML patients, thus addressing an unmet clinical need in this disease. Research Sponsor: Innovate UK; 22217; Innovate UK; 10054602.

Outcomes of blast-phase MPN and *JAK2*, *MPL*, and *CALR*mutated de novo AML: A propensity score-adjusted cohort study.

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Background: Progression to blast phase (BP) occurs in about 10% of patients with BCR-ABL-negative myeloproliferative neoplasms (MPN) and is associated with an extremely poor prognosis with no defined standard of care. The VIALE-A trial, which showed that venetoclax (VEN) improves overall survival (OS) in patients with acute myeloid leukemia (AML) when combined with azacitidine, excluded patients with MPN-BP. Rarely, patients develop de novo AML with a genetic profile like an MPN, harboring *JAK2*, *MPL*, or *CALR* mutations. However, there are a lack of data on the outcomes of these patients. **Methods:** We conducted a single-center retrospective cohort study to compare composite complete response (CCR), OS and event-free survival (EFS) of patients with MPN-BP or de novo AML with underlying *JAK2*, *MPL*, or *CALR* mutations (AML-D-MPN). CCR was defined as complete response (CR) or CR with incomplete count recovery. Propensity score (PS) modeling was used to adjust for baseline characteristics at AML diagnosis: age, sex, race, comorbidities, ECOG status, cytogenetics, and underlying mutations. **Results:** Of 750 patients treated from 2015 to 2023, 61 had MPN-BP and 12 had AML-D-MPN. The table describes baseline characteristics. The median time for MPN to BP transformation was 8 years (IQR: 2.8-13.6). With a median follow-up of 8.2 months (mo) (95CI: 1.6-59.6), the median OS for MPN-BP was 4.8 mo (95CI: 2.7-8) and for AML-D-MPN was 6.1 mo (95CI: 1.6-NC). In the MPN-BP, 40 received therapy, which included: intensive regimen [7+3 (n=13); CPX-351 (n=1)], hypomethylating agents (HMA) (n=11), HMA+VEN (n=11) and others (n=4). All AML-D-MPN received therapy, which included 7+3 (n=4), HMA (n=1), HMA+VEN (n=2), and others (n=5). In the whole treated population (n=52), the unadjusted CCR was 60% in intensive regimen, 20% in HMA, 20% in HMA+VEN and 0% in others (p=0.3). The PS-adjusted median (m) OS in mo (95%CI) was: 2.6 (1.4-NC) in intensive regimen, 6.2 (1.2-NC) in HMA, 15 (10-15) in HMA+VEN and 1.7 (0.46-NC) in others (p=0.1). The adjusted m-EFS in the same treatment groups was 1.5 (0.43-NC), 6.2 (1.2-NC), 15 (4.3-15) and 0.92 (0.46-NC) (p=0.16), respectively. In MPN-BP group, the adjusted m-EFS in mo (95%CI) was: 0.62 (0.43-NC) in the intensive regimen, 6.2 (1.2-NC) in HMA, 15 (4.2-15) in HMA+VEN and 0.92 (0.92-NC) in others (p=0.25). **Conclusions:** Patients with MPN-BP and AML-D-MPN have poor survival with similar responses to therapy. These patients have variable outcomes with different treatments; however, there is a trend toward improved survival with the use of HMA+VEN. Research Sponsor: None.

	MPN-BP (n=61)	De Novo AML with MPN Mutations (n=12)
Median age (IQR), years	73 (66, 78)	74 (68, 82)
Sex (female)	24 (39%)	2 (17%)
Cytogenetics: normal/ low-risk	16 (26%)	3 (25.3%)
Cytogenetics: interme-diate/high-risk	26 (42.8%)	8 (66%)
Mutations:		
JAK2	51 (84%)	12 (100%)
MPL & *CALR*	10 (16)	0 (0%)
TP53	6 (23%)	0 (0%)
FLT3	5 (8.2%)	2 (17%)

Safety and efficacy of olutasidenib treatment in elderly patients with relapsed/refractory m*IDH1* acute myeloid leukemia.

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Background: Elderly patients with relapsed/refractory (R/R AML) are a special population that may elevate safety concerns, which must be balanced with clinical benefit. Olutasidenib (OLU), a targeted therapy for m*IDH1* AML, was well tolerated in a registrational, Ph2, open-label, multicenter trial and, in the pivotal cohort, demonstrated complete remission (CR) or CR with partial hematologic recovery (CRh) in 35% of patients (age 32-87 years, y) for a median duration of 25.9 months. We evaluated safety and efficacy of OLU in the elderly subgroup (≥75y) with m*IDH1* AML. **Methods:** In the Phase 2 trial, the pivotal cohort enrolled adults with R/R m*IDH1*AML. OLU was administered at 150 mg BID. Adverse events (AE) and lab values were collected at least monthly and graded based on the NCI CTCAE Version 4.03. Efficacy was based on response criteria of the International Working Group in AML (2003). **Results:** 153 patients received OLU monotherapy, 147 had centrally-confirmed mIDH1 AML, , and 45 were ≥75y (range 75-87) at study entry. Of the 45 elderly patients, 27 (60%) were male, 51% had ECOG=1, 16% had ECOG =2, 71% were relapsed, 29% had refractory AML, 58% had prior HMA, 11% received prior venetoclax, and none had prior stem cell transplant. Median bone marrow blasts were 43% (5-93). Genetic co-mutations included FLT3 in 9%, NPM1 in 20%, and TP53 in 2%. Grade 3 or 4 adverse events were reported in 45.8% of elderly patients; the most common were decreases in red blood cells (31%), platelets (13%) and neutrophils (10%) as well as febrile neutropenia (15%). AEs were consistent with published pivotal Phase 2 results, with no new safety signals. Deaths occurred in 19 patients due to disease progression (9), pneumonia (2), sepsis (2), GI haemorrhage (1), aortic stenosis (1), atrioventricular block (1), cardiac failure congestive (1), acute kidney injury (1) and other (1). The response to OLU therapy is summarized in the table. 31% of patients ≥75 y achieved CR/CRh; median time to CR/CRh was 1.5 mos (0.9-5.6) and median duration of CR/CRh was 25.9 mos (95%CI 7.4, not reached). **Conclusions:** Olutasidenib was generally well tolerated in elderly patients with R/R m*IDH1*AML and induced durable remissions. Despite the challenges of treating elderly patients who had already failed prior AML treatment, the results suggest that elderly patients can benefit from therapy with olutasidenib. Clinical trial information: NCT02719574. Research Sponsor: Rigel Pharmaceuticals, Inc. (Contact person: Leslie Todd).

Best Response, n (%)	Age ≥75 years (n=45)
Overall Response Rate	21 (47) [95% CI: 31.7, 62.1]
Complete Remission (CR)	13 (29)
CRh	1 (2)
CRi	6 (13)
Composite CR (CRc)	20 (44)
MLFS/Partial Remission	1 (2)
Stable disease/Clinical Benefit/Resistant Disease	15 (33)
Disease Progression (PD)	4 (9)
Not Evaluable/Not Done	5 (11)

Olutasidenib for mutated IDH1 acute myeloid leukemia: Final five-year results from the phase 2 pivotal cohort.

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Background: Olutasidenib is a potent, selective, oral inhibitor of mIDH1 and is FDA-approved for relapsed/refractory (R/R) acute myeloid leukemia (AML) based on a registrational, Phase 2, open-label, multicenter trial (NCT02719574). We report final five-year results from the pivotal cohort. **Methods:** In the pivotal cohort of the Phase 2 trial, patients with mIDH1 AML received olutasidenib 150mg BID. Primary endpoint was complete remission (CR) + CR with partial hematologic recovery (CRh) by modified IWG Criteria 2003. Data cutoff: May 15, 2023. **Results:** Baseline characteristics of 153 enrolled patients are shown in Table. Of 147 efficacy evaluable patients, CR was achieved in 32% (95% CI: 24.5, 40.2) and CR/CRh in 35% (95% CI: 27, 43; $P<0.0001$). Median time to CR/CRh was 1.9 mo (range: 0.9, 5.6). The median duration of CR/CRh was 25.3 mo (95% CI: 13.5, not reached), with maximum duration 54.6 mo. Overall response rate was 48% (95% CI: 40, 56.7), with median duration 15.5 mo (95% CI: 7.4, 26.2) and maximum duration 54.6 mo. Median overall survival was 11.6 mo (95%CI: 8.9, 15.5). In the 12 patients R/R to prior venetoclax, 33% achieved a CR/CRh; median duration of CR/CRh is not reached (ongoing at 54.3 months), and median overall survival is 16.2 months (95%CI: 2.6, not reached). Transfusion independence from red blood cells and platelets was achieved in 34 of 87 (39%) patients and 28 of 69 (41%) patients, respectively, who were dependent at baseline. 16 (11%) patients proceeded to stem cell transplant. The 5-year safety profile was consistent with what was previously reported. The most common AEs (% reported over 3 years and over the full 5 years) were: febrile neutropenia (22% and 22%), constipation (26% and 27%), diarrhea (20% and 21%), nausea (38% and 39%), fatigue (23% and 23%), pyrexia (24% and 24%), hypokalaemia (20% and 22%), red blood cell count decreased (26% and 26%), white blood cell count increased (25% and 25%). Differentiation syndrome was reported in 14% by Year 3, with no new events by Year 5. The safety profile was stable with long-term follow up. **Conclusions:** This analysis provides an additional 2 years of data beyond the results that led to FDA approval of olutasidenib. This first report of the five-year data further demonstrates the rapid and durable responses observed with olutasidenib in heavily pretreated patients with mIDH1 AML, including those R/R to prior venetoclax. Clinical trial information: NCT02719574. Research Sponsor: Rigel Pharmaceuticals, Inc. (Contact person: Leslie Todd).

Baseline Patient Characteristics	Safety Population (N=153)
Median age	71 y (range: 32, 89)
ECOG performance status score 0-1	126 (82%)
Primary AML	65%
Median time from diagnosis	12.7 mo (range: 0.7, 151.5)
Cytogenetic risk	intermediate in 73%; poor in 17%
Median number of prior regimens	2 (range: 1, 7)
Refractory to prior regimen	35%
Prior cytarabine	71%
Prior hematopoietic stem cell transplant	11%

Treatment discontinuation due to toxicity for patients with acute myeloid leukemia (AML) treated on SWOG S1203.

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Background: Curative-intent therapy for patients with newly diagnosed AML centers on the use of cytarabine as part of an intensive multi-drug induction regimen. Treatment-related toxicity may lead to patients stopping treatment, despite the considerable risk of inadequately treated AML. We compared rates of protocol therapy discontinuation due to adverse events (AEs) in either of two standard induction regimens (7+3 or high dose cytarabine + idarubicin, IA) on the S1203 study (Garcia-Manero; Leukemia 2023). **Methods:** S1203 was a randomized study of patients <60 years old with newly diagnosed AML. Patients were required to have performance status (PS) <3, ejection fraction >45%, and no prolonged QTc interval or known cardiac disease. There were no exclusion criteria for kidney or liver function. On the 7+3 induction arm, subjects received daunorubicin 90 mg/m^2 IV daily days 1-3 with continuous infusion cytarabine 100 mg/m^2 daily days 1-7. On the IA arm, subjects received idarubicin 12 mg/m^2 daily days 1-3 with continuous infusion cytarabine 1.5 g/m^2 daily days 1-4. Toxicities were assessed per the Common Terminology Criteria for Adverse Events version 4.0. Rates of discontinuation were compared using Fisher's exact test. **Results:** From 4/2013-11/2015, 522 subjects were randomized (261 to each arm). Treatment discontinuation due to either death or toxicity occurred in 8 vs 22 patients on 7+3 vs IA respectively (p=0.014). During induction, 0 patients on the 7+3 arm discontinued treatment due to toxicity versus 4 patients on the IA arm (0% vs 2%; p=0.12). Toxicities leading to treatment discontinuation on the IA arm included congestive heart failure (n=2, one with concurrent arrhythmia), acute kidney injury (n=1), and hypotension complicated by stroke and cardiac arrest (n=1). Two of the 4 patients who discontinued treatment due to toxicity on IA achieved a complete remission after their first cycle. For patients with PS 2-3 (n=40 on 7+3, n=27 on IA), rates of grade 3-5 AEs were 85% vs 86% and rates of grade 5 AEs were 0% vs 11% (p=0.065). **Conclusions:** 7+3 was well tolerated. Excluding patients from S1203 with PS 2-3 or decreased hepatic/renal function would not have prevented treatment-related toxicity. The low rate of protocol therapy discontinuation due to toxicity suggests that eligibility criteria for clinical trials could be further broadened to improve patient access. Clinical trial information: NCT0180233. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; CA180819, CA180888; NIH/NHLBI; T32HL007093; National Cancer Institute; NCI 5 P30 CA015704-48.

Reasons for Discontinuation of Therapy	7+3 (n=261)	IA (n=261)
Completed induction as planned	215 (82%)	207 (79%)
Progressive disease	1 (<1%)	3 (1%)
Patient refusal unrelated to toxicity	6 (2%)	6 (2%)
Toxicity	0 (0%)	4 (2%)
Death	8 (3%)	18 (7%)
Other	31 (12%)	23 (9%)

Achievement of therapeutic levels using dose-reduced peg-asparaginase in adult patients with acute lymphoblastic leukemia.

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Background: Peg-asparaginase (PEG) doses range from 2000-2500 IU/m^2 in pediatric-inspired regimens for acute lymphoblastic leukemia (ALL). Pediatric PEG dosing in adolescents and young adults (AYAs) has resulted in improved outcomes, but PEG-associated toxicities increase with age and often limit its use. Therapeutic dosing is determined by asparagine (ASP) depletion for 14 days after dose; L-asparaginase levels can act as a surrogate marker of ASP depletion. We previously showed dose reduced PEG (defined as <2000 IU/m^2) results in high rates of therapeutic L-asparaginase 7 days post PEG (Derman et al, Leuk Lymphoma 2020). Here we describe prolonged duration of ASP depletion and comparable toxicities after dose reduced PEG in adults with ALL. **Methods:** Patients ≥18 years with ALL or lymphoblastic lymphoma (LBL) who received PEG from 1/1/2008 to 9/28/2023 were identified for retrospective chart review. Those with ≥1 PEG trough level (defined as 10-20 days after dose) were included. The primary endpoint was therapeutic PEG levels (≥0.1IU/mL L-asparaginase) at 7 and 14 days post administration, with secondary endpoint being induction grade 3+ toxicities (CTCAE v.5.0). **Results:** 49 patients met inclusion criteria, of which 48 received PEG during induction. Median age was 34.7 (range 18-66), 67% were male and 53% had B-cell ALL. 17 (35%) received an induction dose ≤ 500 IU/m^2, 22 (46%) received 501 to ≤1000 IU/m^2 and 9 (19%) received >1000 IU/m^2. Induction median dose was 1000 IU/m^2. Among those with PEG trough levels, 79% were therapeutic after induction; of note, 4 patients were transitioned from PEG to Erwinia asparaginase due to silent inactivation. During induction, 23 (48%) patients had ≥1 grade 3+toxicity, including 5 (10%) with hepatotoxicity, 1 (2%) with pancreatitis, and 2 (4%) with a thrombotic event. There was no statistical relationship between dose level and toxicities (p=.8). **Conclusions:** This study demonstrates durability of therapeutic L-asparaginase levels and ASP depletion that persists 14 days despite dose reduction. There were decreased rates of hepatotoxicity and comparable rates of pancreatitis and thrombotic events compared to rates reported in CALBG 10403 (C10403) (Stock et al, Blood 2019), which utilized standard pediatric dosing. In addition, our cohort's median age was significantly older than those treated on C10403. This suggests PEG dose reduction may offer similar therapeutic ASP depletion with comparable or reduced toxicities. Dose reduction should be studied prospectively in AYAs with ALL. Research Sponsor: None.

Achievement of therapeutic levels and toxicities during induction.

	PEG Dose (IU/m^2)		
	≤500	501-≤1000	>1000
PEG 14 day activity IU/mL, median (range)	0.077 (0-0.12)	0.1655 (0-0.31)	0.2925 (0.168-0.417)
Peak (7 day) level at goal, N=39, n(%)	11 (79)	19 (90)	9 (100)
Trough (14 day) level at goal, N= 18, n(%)	4 (31)	11 (79)	3 (100)
Any Grade 3+ toxicity, n(%)	7 (41)	11 (50)	5 (56)

6531 Poster Session

Long-term survival outcomes of patients (pts) with relapsed or refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) treated with brexucabtagene autoleucel (brexu-cel) in ZUMA-3.

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Background: Brexu-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for pts ≥18 y with R/R B-ALL in the US (≥26 y in the EU). In the 3-y follow-up of ZUMA-3, median overall survival (OS) was 25.6 mo (N=78). Survival benefit was seen regardless of age, prior treatment, or subsequent allogeneic stem cell transplant (sub alloSCT) status (Shah et al. ASCO 2023. #7023). Here we report 4-y survival outcomes for ZUMA-3. **Methods:** Eligible pts (≥18 y) had R/R B-ALL and received brexu-cel (1×10^6 CAR T cells/kg) after leukapheresis and lymphodepleting chemotherapy. The primary endpoint was overall complete remission (CR)/CR with incomplete hematologic recovery (CRi) rate per independent review with OS as a key secondary endpoint. Descriptive statistics are reported for post hoc exploratory subgroup analyses. **Results:** As of July 23, 2023, median follow-up time in Phase 1 and 2 pts who received the pivotal dose of brexu-cel (N=78) was 53.6 mo (range 44.7-82.3). Median OS (95% CI) was 25.6 mo (16.2-60.4) in all treated pts and 47.0 mo (23.2-not estimable [NE]) in pts with CR/CRi (n=57). In pts <26 y (n=15), median OS (95% CI) was 23.2 mo (9.0-NE) and was 26.0 mo (15.9-NE) in pts ≥26 y (n=63). Median OS (95% CI) in pts with 1 prior therapy (n=15) was 60.4 mo (7.6-NE) and was 25.4 mo (15.9-47.0) in pts with ≥2 prior therapies (n=63). Medians for OS (95% CI) in pts with (n=38) and without (n=40) prior blinatumomab (blina) were 15.9 (8.3-26.0) and 60.4 mo (18.6-NE), respectively. Median OS (95% CI) was 36.3 mo (10.2-NE) in responders who went on to sub alloSCT (n=14) and 60.4 mo (23.2-NE) in those who did not (n=43). The 48-mo OS rate was 40% (95% CI, 28-52) in all pts but appeared lower in pts with prior blina (24%; Table). No new adverse events or deaths occurred since the prior analysis. Grade ≥3 infection rates since the start of study appeared higher in pts <26 y and in pts with prior blina (Table). Rates of non-relapse mortality (NRM) and relapse-related mortality (95% CI) at 48 mo were 25% (15-37) and 34% (24-45; N=78), respectively. Of note, 6/17 NRM events (35%) occurred in pts with sub alloSCT. **Conclusions:** After >4 y follow-up, pts in ZUMA-3 continued to experience OS benefit regardless of age, prior therapy, or sub alloSCT status, though pts with prior blina had a numerically lower 48-mo OS rate. Small subgroups and unbalanced pt characteristics limit interpretation of these results. No new safety signals were observed. Further studies are needed to fully assess the impact of age, prior therapies, and sub alloSCT on outcomes after brexu-cel. Clinical trial information: NCT02614066. Research Sponsor: Kite, a Gilead Company.

		Age		Prior Blina		Prior Therapies	
	All Pts (N=78)	<26 y (n=15)	≥26 y (n=63)	No (n=40)	Yes (n=38)	1 (n=15)	≥2 (n=63)
48-mo OS rate, % (95% CI)	40 (28-52)	32 (9-58)	42 (29-55)	55 (35-70)	24 (11-40)	57 (29-78)	36 (23-49)
Grade ≥3 infection, n (%)	23 (29)	6 (40)	17 (27)	8 (20)	15 (39)	3 (20)	20 (32)

Efficacy of GCN2 inhibition by a novel small molecule AP030 in acute leukemia.

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Background: GCN2 is an evolutionarily conserved kinase and a pivotal regulator of the Integrated Stress Response (ISR) that is activated in response to amino acid scarcity. Active GCN2 phosphorylates translation initiation factor eIF2α resulting in the attenuation of global protein synthesis. ISR signaling primarily promotes cell survival but may trigger cell death, dependent on the cellular context. In hematological tumors GCN2 promotes tumor cell survival under conditions of nutrient scarcity. Several GCN2 inhibitors are in clinical development for treatment of both solid and hematological tumors. Here, we describe the preclinical results of a novel, selective ATP-competitive inhibitor of GCN2. **Methods:** GCN2 inhibition by AP030 was determined using a biochemical Lanthascreen assay and a cell based HTRF assay measuring eIF2a phosphorylation following stimulation with Borrelidin. Kinase selectivity was determined using KinomeScan, and bespoke biochemical and cell-based assays. Interaction of AP030 with GCN2 was determined using X-ray crystallography. AP030 activity in disease-relevant tumor cell lines was determined using cell viability, caspase activation, protein expression and qPCR gene expression endpoints. Inhibition of hematological tumor growth and induction of cell death was investigated in patient samples, and ALL and AML in vivo animal models. **Results:** Potent inhibition of GCN2 in the Lanthascreen assay was demonstrated with AP030 (Ki of 4.4nM). Following stimulation with Borrelidin, AP030 inhibited eIF2a phosphorylation with an IC_{50} of 50.8nM and inhibited downstream targets CHAC1 and DDIT3 measured by qPCR. X-ray crystallography confirmed that AP030 binds to the ATP-binding site of GCN2. The KinomeScan confirmed that AP030 was highly selective against the human kinome. AP030 led to partial or complete reduction of AML cell line viability as a single agent and acted synergistically with asparaginase in ALL cell lines. Caspase 3/7 induction was observed in the AML and ALL cell lines evaluated and AP030 increased the proportion of cells undergoing apoptosis in AML patient primary samples. In the CCRF-CEM ALL systemic in vivo tumor model AP030 inhibited tumor growth in combination with asparaginase (TGI 79.33%). Treatment with 0.5-5mg/kg (q.d.) of AP030 resulted in dose-dependent tumor growth inhibition and regression of the MOLM-16 AML in vivo model (TGI 97.37% 5mg/kg). RNA sequencing of residual tumor cells revealed disruption of amino acid and protein metabolism, consistent with GCN2 inhibition. **Conclusions:** Targeting hematological tumor reliance on the GCN2 arm of the ISR during nutrient scarcity is a novel approach to preventing tumor cell survival. AP030 a novel, potent, selective, ATP-competitive kinase inhibitor has been shown to lead to impressive efficacy in acute leukemia. Based on these preclinical results, a phase 1/2 study has been initiated in AML. Research Sponsor: None.

6533 Poster Session

In-depth analysis of responders in the phase 3 PhALLCON trial of ponatinib vs imatinib in newly diagnosed Ph+ ALL.

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Background: Ponatinib, a third-generation BCR::ABL TKI, has potent activity against all clinically relevant BCR::ABL1 variants, including T315I. PhALLCON (NCT03589326), a phase 3 trial comparing frontline TKIs in adults with Ph+ ALL, met its primary endpoint with a higher rate of minimum residual disease–negative (MRD-neg) complete remission (CR) at end of induction (EOI) with ponatinib vs imatinib (34.4%/16.7%; P=0.002). Here, we report response rates of MRD-neg at any time and PFS by age and *BCR::ABL1* variant subgroups. **Methods:** Adults with newly diagnosed Ph+ ALL were randomized 2:1 to ponatinib (30 mg QD reduced to 15 mg QD upon MRD-neg CR at or after EOI) or imatinib (600 mg QD) plus 20 cycles of reduced-intensity chemotherapy (induction: 3 cycles; consolidation: 6 cycles; maintenance: 11 cycles), followed by single-agent ponatinib or imatinib until disease progression or unacceptable toxicity. Hematopoietic stem cell transplant (HSCT) was per investigator's discretion. Post hoc analyses compared MRD-neg (*BCR*::*ABL1*$^{IS}\leq$0.01%; MR4) at any time and PFS (any-cause death, failure to achieve CR by EOI, relapse from CR, or failure to achieve/loss of MRD-neg) by age (</≥65 y) and *BCR*::*ABL1* variant (p190/p210). Data cutoff: Aug 12, 2022. **Results:** In the population of randomized patients (pts) with p190/p210 confirmed by central lab (n=232; 154/78 ponatinib/imatinib; median follow-up 20.1 mo), 68% vs 50% in the ponatinib vs imatinib arms were MRD-neg at any time, with similar benefit of ponatinib across age and variant subgroups (Table). Median PFS was more than twice as long with ponatinib vs imatinib across subgroups (Table). Pts achieving MRD-neg at any time were less likely to have HSCT with ponatinib vs imatinib (32%/56%). Among 107/42 pts without HSCT, exposure was >2-fold longer in the ponatinib vs imatinib arms (median 12.8/5.1 mo) with comparable rates of arterial occlusive (3%/2%) and venous thromboembolic events (11%/12%), and discontinuations due to TEAEs (13%/14%). **Conclusions:** Ponatinib was superior to imatinib in combination with reduced-intensity chemotherapy for frontline treatment of Ph+ ALL, with higher rates of MRD-neg at any time, substantially longer PFS across age and *BCR::ABL1* variant subgroups, and a safety profile comparable to imatinib. Clinical trial information: NCT03589326. Research Sponsor: Takeda Development Center Americas, Inc.

Outcome	Subgroup	Ponatinib (n=154)	Imatinib (n=78)	Relative risk (95% CI)
MRD-neg at any time, n/N (%)	Overall	104/154 (68)	39/78 (50)	1.35 (1.05, 1.73)*
	Age <65 y/ ≥65 y	83/120 (69)/ 21/34 (62)	31/63 (49)/ 8/15 (53)	1.41 (1.06, 1.86)*/ 1.16 (0.67, 1.99)
	p190/ p210	80/114 (70)/ 24/40 (60)	30/53 (57)/ 9/25 (36)	1.24 (0.95, 1.62)/ 1.67 (0.93, 2.98)
				Hazard ratio (95% CI)
Median PFS, mo	Overall	20.0	7.9	0.58 (0.41, 0.83)*
	Age <65y/ ≥65 y	18.7/ 22.5	7.3/ 7.5	0.50 (0.34, 0.74)*/ 0.65 (0.28, 1.49)
	p190/ p210	22.5/ 9.0	9.3/ 4.1	0.52 (0.34, 0.81)*/ 0.48 (0.26, 0.90)*

*95% CI did not include 1.00.

PMB-CT01 (BAFFR-CAR T cell) therapy to examine preliminary safety and clinical responses in patients with B-cell malignancies who are ineligible for or failed CD19-directed therapy, including CD19-negative disease.

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Background: CD19-targeted therapies have shown remarkable efficacy in patients with B-cell malignancies. However, relapse with CD19 loss as a mechanism of tumor escape is common and represents a serious challenge. Patients who are ineligible for or have failed prior CD19-directed therapy have limited salvage options and a very poor prognosis. The B-cell activating factor receptor (BAFF-R) is functionally expressed in B-cell acute lymphoblastic leukemia (B-ALL) and non-Hodgkin lymphomas (NHL), including in patients with CD19-negative relapse (Qin et al., Sci Transl Med. 2019). As a critical regulator of B-cell function and survival, BAFF-R may be less prone to downregulation by tumors as a mechanism of antigen escape. **Methods:** We are conducting two phase 1 clinical trials of BAFFR-CAR T cells in patients with relapsed/refractory (r/r) B-ALL (NCT04690595) and NHL (NCT05370430). Primary endpoints are dose limiting toxicities (DLTs) and all other toxicities. Secondary endpoints include response rate, minimal residual disease (MRD) negative rate, PFS and OS. Response is evaluated using European LeukemiaNet criteria for B-ALL and Lugano 2014 for NHL. **Results:** As of Feb. 1st, 2024, 1 B-ALL and 3 NHL patients have completed treatment and post-treatment evaluations. Each received 50M BAFFR CAR T cells (starting dose level in both trials). The B-ALL patient had CD19/CD20/CD22-negative disease, and had received prior blinatumomab. NHL patients #1 and #2 both had CD19-expressing mantle cell lymphoma (MCL) and had received prior CD19 CAR T cells. Patient #2 had also received a CD3/CD20 bispecific antibody. NHL patient #3 had CD19/CD20-negative T cell/histiocyte-rich large B-cell lymphoma (THRBCL) and had not received prior CD19 CAR T cells. There were no DLTs, all patients had Gr. 1 cytokine release syndrome, and 2/3 NHL patients had Gr. 1 immune effector cell-associated neurotoxicity syndrome. Robust CAR T cell expansion was seen in all patients with a peak on days 12-14 post-infusion. The B-ALL and the 2 MCL patients reached MRD-negative complete response (CR) at 1 month post-treatment. The THRBCL patient had partial response (PR) at 1 month that converted to CR at 3 months. The B-ALL patient successfully transitioned to allogeneic HCT while in CR at 3 months post-infusion. Responses are ongoing in all NHL patients at 14, 10, and 8 months for patients #1, #2 and #3, respectively. Additional patients have been enrolled at the next dose level (200M CAR T cells). Results for these patients will be presented at the meeting. **Conclusions:** With a 100% CR rate at 3 months in the first 4 patients and durable responses at dose level 1, BAFFR-CAR T cells are a promising therapeutic option for patients with r/r B-cell malignancies who are ineligible or failed prior CD19-targeted therapy, including with CD19 antigen loss. Clinical trial information: NCT04690595, NCT05370430. Research Sponsor: PeproMene Bio, Inc.; Leukemia & Lymphoma Society; MCL–RI 7000-18; National Cancer Institute; 2P50CA107399; National Cancer Institute; CA269569.

6535 Poster Session

Trends in hematopoietic cell transplantation (HCT) in acute myeloid leukemia (AML) from 2004-2019.

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Background: Many patients with AML achieve remission after induction chemotherapy, but the relapse rates remain high. For patients with intermediate and adverse-risk AML that have achieved complete remission, HCT often presents the best option for cure. HCT, usually reserved for fit patients with good disease control, comes with different operational, financial, and technical challenges, even in eligible patients. Our study analyzed HCT use in patients with AML from 2004 to 2019 to determine whether the use of HCT has improved in more recent years and identify study subpopulations with an increase in the use of HCT. **Methods:** Patients with AML from the National Cancer Database were divided into two primary cohorts: patients diagnosed from 2004-2010 and 2011-2019. Logistic regression was used to estimate the effect of patient and disease characteristics on the odds of receiving HCT and evaluate differences between the constructed patient cohorts. **Results:** Of 78,092 patients with AML, 7204 (9.2%) received HCT. HCT use increased continuously over the years: 6.5% in 2004, 8.4% in 2010, and 10.6% in 2015. There was a slight decrease in HCT from 13.1% in 2018 to 12.2% in 2019. The receipt of HCT declined with increasing age with higher use of HCT in all groups in 2011-2019 compared to 2004-2010: 71-80 years= 2 vs. 0.4 %, 60-70 years= 13 vs 6%, 41-59 years= 18 vs 15%, and 18-40 years = 19 vs 16%. HCT use declined with higher Charlson Deyo Comorbidity Index (CCI) with higher use of HCT in all groups in 2011-2019 compared to 2004-2010: CCI: 2-3= 4 vs 2%, CCI 1= 7% vs 5%, CCI 0= 12% vs 9%. HCT use was higher in patients who traveled longer distances to hospitals with higher HCT use in 2011-2019 compared to 2004-2010: travel distance ≥38.4 miles= 15 vs. 13%, 12-34.7 miles= 12 vs 9%, 5-11.9 miles= 8 vs 5%, and 0-4.9 miles= 5 vs 3%. On multivariable analysis, the odds of receiving HCT increased significantly in 2011-2019 compared to 2004-2010, particularly in older patients, patients with higher CCI, and patients who traveled longer distances for treatment. Black race, lower income, no insurance, and lower educational attainment were associated with a lower likelihood of receiving HCT; however, the odds of receiving HCT did not improve over the two time periods based on these variables. **Conclusions:** To our knowledge, this is the largest-scale analysis of HCT utilization in patients with AML in the United States. The increase in HCT utilization from 2004-2010 to 2011-2019, particularly in older adults and those with more comorbidities, may reflect improvement in risk-stratification models, better supportive care, and better management of treatment-related toxicity. However, despite a modest increase in HCT use over the years, significant disparities exist based on race, insurance type, income, and education. Innovative strategies are necessary to increase HCT and make it accessible to all patients regardless of socioeconomic and demographic factors. Research Sponsor: None.

6536 Poster Session

Mutation profiles and outcomes of patients with acute myeloid leukemia with autoimmune disease.

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Background: Therapy-related acute myeloid leukemia (t-AML) defines a group of patients who develop AML after being treated with chemotherapy or radiation therapy. Most of these patients have a history of malignancy, but some have exposure to cytotoxic therapy for non-cancerous conditions such as autoimmune diseases (AD). This study looked at the characteristics, genetics, and outcomes of patients with AD and AML. **Methods:** This study included patients diagnosed with AML from 1999 - 2019. AML was divided into 4 groups: de novo AML, AD- AML (AML after AD diagnosis), t-AML (excluding AD-AML), secondary AML (s-AML) (AML arising out of myelodysplastic syndrome or myeloproliferative neoplasm). All molecular data were obtained via next generation sequencing (NGS) of genes frequently observed to be mutated in AML and analyzed using Chi-square test. BUM method was used to control false-discovery rate (FDR) at 8%. Overall survival (OS) and progression free survival (PFS) were estimated by Kaplan-Meier method and compared using log rank test. **Results:** A total of 1587 pts were included: 10.1% (n=160) with AD-AML, 71.3% (n=1131) de novo AML, 13.1% sAML (n=208) and 5.6% t-AML (n=88). The median age at diagnosis was 54.5 years; 54% were male; 67.3% received intensive induction therapy (Intensive defined as a 7+3 regimen). Cytogenetic (CG) data were available for 97.3% pts. According to MRC 2010 classification, CG were favorable in 14%, intermediate in 57%, and poor in 28% of the pts. The most prevalent AD were Crohn's/ ulcerative colitis (n=30, 17%) and rheumatoid arthritis (n=23, 13%); 10.6% of pts had 2 disorders. In AD-AML group, the median age at diagnosis of first AD was 53 years; the median interval from AD diagnosis to AML was 82.5 months (mo); the majority of pts (56.25%) did not receive treatment (not including steroids) for their AD; 23.8% of pts were treated with immunomodulating agents, 23.1% with cytotoxic agents and 15% with anti-inflammatory agents; 20.1% received $\geq$ 2 drug classes. Poor risk CG were more common in AD-AML than in de novo AML (30% vs. 12.2%, $p<.0001$). Mutations in NF1 were more common in AD-AML (9.7%) than in de novo (2.7%), sAML (1.0%), and t-AML (2.7%, $p=0.024$). FLT3 mutations were less common in AD-AML (9.5%) than in de novo (36.1%) and t-AML (33.3%, p=0.004). Mutations in *SRSF2* were more common in AD-AML (20.3%) than in de novo (12.3%) and sAML (8.8%, $p=0.119$). Median PFS varied among de novo (8 mo), AD-AML (6 mo) and t-AML (5 mo) groups. For the AD-AML grp, the median OS was 9 months; less than the de novo AML (11 mo), and greater than t-AML (6 mo) and sAML (6 mo, $p<0.0001$). **Conclusions:** Patients with AML and a prior history of AD have CG profile and outcomes similar to those with t-AML but with distinct molecular features (i.e. NF1 and *SRSF2)*. These findings need to be validated in large series; however, they suggest that the MAPK signaling pathway as well as spliceosome inhibitors might be a future focus of investigation in pts with AD-AML. Research Sponsor: None.

6537 Poster Session

7+3 versus decitabine + venetoclax: A global, propensity-matched study comparing outcomes for both regimens in AML.

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Background: In the treatment of AML, 7+3 (seven days of standard-dose cytarabine and three days of anthracycline therapy) has long been the standard for attempted remission induction. Recently published studies have explored the efficacy and tolerability of decitabine and venetoclax as a favorable alternative regimen in older adults with AML. However, there has not yet been a head-to-head study in the literature comparing real world outcomes for both regimens. Here we present a retrospective database analysis comparing remission status and mortality among elderly patients treated with 7+3 versus decitabine and venetoclax. **Methods:** The TriNetX research network was used for this study. Two patient cohorts were created by utilizing International Classification of Disease 10 (ICD-10) codes and medication codes in the TriNetX platform. Both cohorts had patients age 65 and up with a diagnosis of AML (C92.0) and who started treatment within six weeks of diagnosis. The 7+3 cohort received cytarabine and either idarubicin or daunorubicin, while the other cohort received decitabine and venetoclax. Each cohort was excluded from the other treatment to remove crossover as a confounding factor. The cohorts were balanced for age, race, gender, and ethnicity by propensity score matching and the greedy nearest neighbor algorithm. This resulted in 519 patients in each arm. They were then evaluated for the outcome of AML in remission (C92.01) and for death within 12 months. **Results:** Patients treated with 7+3 were more likely to obtain remission status (54.5% vs 34.7%, RR 1.57, 95% CI (1.36,1.81), P value < 0.0001). The 7+3 cohort also had a lower rate of mortality at 12 months (37% vs 54%, RR 0.69, 95% CI (0.60,0.79), P value < 0.0001). **Conclusions:** These results show that among elderly patients with AML, treatment with 7+3 is associated with statistically higher remission rates and lower mortality when compared with decitabine and venetoclax therapy. One limitation of our study was that we were not able to determine the cytogenetics in either arm. These results should be taken into consideration when choosing an induction regimen in this population. Research Sponsor: None.

Outcomes of patients with bone marrow fibrosis in de novo and secondary acute myeloid leukemia.

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Background: The outcomes of patients with *de novo* acute myeloid leukemia (AML) with bone marrow fibrosis (MF) have not been systematically studied. Our objective was to define the prognosis of patients with AML and multiple degrees of bone marrow fibrosis, efficacy of therapy, and survival outcomes. **Methods:** We retrospectively evaluated 2302 patients diagnosed with AML at a single center from 2007 to 2023 and annotated clinicopathologic characteristics and outcomes. **Results:** We identified 492 (21%) with AML and MF. We found 344 (69.9%) had MF 0-1 and 148 (30.1%) had MF 2-3. Median age was 67 (IQR: 57-73). Fifty-five (11.1%) had a history of myeloproliferative neoplasm (MPN). Patients with MF 2-3 were associated with complex cytogenetics (39.2%), *JAK2* mutations (25.7%), and lower incidence of *IDH2*(16.9%) or *CEBPA*(15.5%) mutations (Table). For patients with MF 0-1, median overall survival (mOS) was 14.2 months compared to 7.5 months for those with MF 2-3 ($p<0.005$). Survival in patients with MPN history was 9.4 months compared to 12.4 months in patients with *de novo* AML. In a multivariate analysis, MF 2-3 (HR 2.00 95%CI 1.59-2.51), non-diploid cytogenetics (HR 1.29, 95%CI 1.33-1.69), and number of co-morbidities (HR 1.26 95%CI 1.10-1.43) were prognostic for shorter mOS. Sixty-four percent were treated with low-intensity chemotherapy (LIC), 36.1% with intensive chemotherapy (IC). Complete remission (CR)/CR with incomplete count recovery (CRi) rates were 63.5% for IC vs 37.9% for LIC ($p=0.007$). Four-week mortality after induction was 5.8% with IC, 8.4% with LIC ($p = 0.809$). In patients aged 60 and older, with MF 2-3, intensive therapy did not result in improved survival (6.5 months vs 7.0 months, $p = 0.19$). **Conclusions:** Patients with AML and MF 2-3 have worse outcomes irrespective of MPN history. For patients aged 60 and above, intensive chemotherapy does not result in improved survival. Research Sponsor: None.

Patient characteristics by degree of marrow fibrosis mild (0-1), advanced (2-3).

No. (%) / median [IQR]	Overall (n=492)	MF 0-1 (n=344)	MF 2-3 (n=148)	*p*
Female, n (%)	224 (45.5)	162 (47.1)	62 (41.9)	0.335
Age	67.0 [57.0, 73.0]	67.0 [57.0,74.0]	66.0 [56.8,72.0]	0.508
ANC x10^9/L	0.7 [0.2, 2.0]	0.6 [0.2,1.7]	1.1 [0.4,3.0]	<0.001
Hemoglobin g/dL	9.2 [8.6, 9.7]	9.3 [8.6,9.8]	9.1 [8.5,9.6]	0.07
Platelet count x10^3/L	34.0 [19.0, 71.5]	37.0 [20.0,69.0]	31.0 [17.0,75.5]	0.289
Bone marrow blast %	41.0 [24.0, 65.0]	47.0 [26.0,69.0]	30.0 [22.0,52.5]	<0.001
Diploid CG	143 (29.1)	109 (31.7)	34 (23.0)	0.065
Complex CG	143 (29.1)	85 (24.7)	58 (39.2)	0.002
History of MPN	145 (29.5)	90 (26.2)	55 (37.2)	0.019
TET2	194 (39.4)	141 (41.0)	53 (35.8)	0.328
JAK2	100 (20.3)	62 (18.0)	38 (25.7)	0.07
RAS	130 (26.4)	93 (27.0)	37 (25.0)	0.72
CEBPA	118 (24.0)	95 (27.6)	23 (15.5)	0.006
IDH2	114 (23.2)	89 (25.9)	25 (16.9)	0.04
OS (months), median	11.3	14.2	7.5	<0.001

OS: overall survival.

6539 Poster Session

Preliminary safety, efficacy and molecular characterization of emavusertib (CA-4948) in patients with relapsed/refractory (R/R) acute myeloid leukemia (AML) with FLT3 mutation (FLT3m).

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Background: AML is a heterogenous disease and exhibits a dynamic mutational landscape as the disease progresses. Internal tandem duplication (ITD) of FLT3 is considered an acquired late-event mutation and is associated with a poor prognosis in AML. Emavusertib is a potent oral inhibitor of both IRAK4 and FLT3, conferring potential dual efficacy advantages compared to other IRAK4 or FLT3 inhibitors as single agents. IRAK4 is upregulated during anti-FLT3- or other cytotoxic therapies, which drives a resistance pathway of early relapse and progression. **Methods:** The safety, clinical activity, and potential biomarkers of emavusertib in R/R AML and higher-risk myelodysplastic syndrome are being investigated in the ongoing open-label, Phase 1/2a TakeAim Leukemia trial (NCT04278768). Next generation sequencing (NGS) of 68 genes was performed on genomic DNA from bone marrow or peripheral blood mononuclear cells at baseline and on treatment. Here, we present preliminary safety, efficacy data and molecular characterization in a subset of enrolled AML patients who carried FLT3m at baseline and were treated with emavusertib monotherapy. **Results:** In this study, we treated 11 R/R AML patients with FLT3m at dose levels of 200-400 mg BID. The median number of prior anti-cancer therapies was 2 (range 1-6). 8 of 11 patients had prior exposure to FLT3 inhibitors. Treatment-related adverse events (TRAEs) Grade $\geq$ 3 were reported in 2 of 11 (18%) patients. All responders were dosed at the Recommended Phase 2 Dose (RP2D) of 300 mg BID and with $<$ 3 lines of prior therapy. In addition, responders demonstrated more than 90% bone marrow blast reduction compared to baseline. The most common co-mutations in this subset of patients included RUNX1, NRAS, and TET2. Emavusertib treatment significantly decreased the variant allele frequency of these mutations. FLT3-ITD levels were decreased or became undetectable in responders. Additional corelative analysis between bone marrow blast counts and mutation status indicates that AML patients with FLT3m demonstrated increased bone marrow blast reductions ($P \leq 0.05$) on emavusertib treatment, when compared to FLT3 WT AML patients. **Conclusions:** Emavusertib has a favorable safety and tolerability profile in pretreated AML patients with FLT3m and demonstrated monotherapy anti-cancer activity in patients with FLT3m, including patients who have progressed on prior FLT3 inhibitors. Mutational profiles are suggestive of disease-modifying activity of emavusertib. We will present updated safety and efficacy data, including data for patients who proceeded to stem cell transplant. Enrollment in this ongoing trial is continuing at RP2D in patients with $<$ 3 lines of prior anti-cancer therapies. Clinical trial information: NCT04278768. Research Sponsor: Curis.

Evaluation of treatment outcomes with CPX-351 in adults with AML: A meta-analysis.

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Background: CPX-351 is a liposomal formulation of cytarabine and daunorubicin which has shown survival benefit when compared to 7+3 in older adults with myelodysplasia-related (AML-MRC) and therapy-related AML (t-AML). Aiming to investigate the clinical efficacy of CPX-351 against 7+3 in adults with AML, we performed a meta-analysis. **Methods:** A systematic search with controlled vocabulary encompassing AML, CPX-351 and 7+3 was conducted in PubMed, Embase, Scopus, and Cochrane on November 1, 2023 with no search restrictions. 3461 were found; 2581 were left after duplicates were removed using Mendeley 1.19.8. Remaining records were imported into Rayyan and independently screened by 2 reviewers. 8 studies were included in the analysis as they provided data for both CPX-351 and 7+3. 17 studies only including CPX-351 were identified. RevMan was used to analyze the Odds Ratio (OR) with 95% Confidence Interval (CI), derived from random effects (RE) model with Mantel-Haenszel (MH) method. **Results:** We identified 8 studies comparing CPX-351 to 7+3, encompassing a total of 1368 total patients: 44% (604/1368) received CPX-351, 56% (764/1368) received 7+3. Most patients had AML-MRC or t-AML. The median age in the CPX-351 group was 66 (range 58-67) and in the 7+3 group was 67 (range 58-67). The median overall survival grossly favored CPX-351 with 10.3 months (range 8.8-22 months) compared to 6.2 months (range 4.6-12 months) in 7+3. The OR of complete remission (CR) for CPX-351 versus 7+3 using the RE model was 1.66 (CI=1.15-2.39, p=0.006, I^2=55%). Similarly, the OR of patients undergoing hematopoietic stem cell transplantation (HSCT) for CPX-351 versus 7+3 was 1.52 (CI=1.01-2.30, p=0.05, I^2=47%). Including the additional 17 studies with CPX-351, the overall CR rate for all patients was 49%. Average 30-day mortality with CPX-351 was 4.9%. **Conclusions:** From our analysis, the OR of attaining CR and HSCT were shown to be significantly improved with CPX-351 when compared to conventional 7+3 chemotherapy in adult patients with AML. Both groups had similar median age, and patients in the CPX-351 arm had longer median overall survival. Our meta-analysis highlights that while CPX-351 achieves CR/HSCT at a higher rate than 7+3, data in younger populations (<60 years old) and patients with de novo AML are sparse. Heterogeneity between studies and lack of mutational analysis are limitations of our study. Research Sponsor: None.

	CPX-351		7+3		CR	CPX-351		7+3		HSCT
STUDY	Events	Total	Events	Total	OR	Events	Total	Events	Total	OR
Andrews	38	76	69	136	0.97 (0.55, 1.170)	26	38	40	69	1.57 (0.68, 3.62)
Cortes	64	139	42	141	2.01 (1.23, 3.29)	46	139	38	141	1.34 (0.80, 2.24)
Guolo	28	35	55	101	3.35 (1.34, 8.36)					
Kingler	11	28	27	54	0.65 (0.26, 1.64)	53	153	39	156	1.59 (0.97, 2.60)
Lancet	73	153	52	156	1.82 (1.15, 2.89)					
Madarang	10	28	12	33	0.97 (0.34, 2.78)	12	28	20	33	0.49 (0.18, 1.36)
Medeiros	15	22	5	20	6.43 (1.66, 24.86)	10	22	2	20	7.50 (1.39, 40.43)
Ryan	59	123	40	123	1.91 (1.14, 3.21)	31	123	17	123	2.10 (1.09, 4.04)

6541 Poster Session

Safety and efficacy of lisaftoclax, a novel BCL-2 inhibitor, in combination with azacitidine in patients with treatment-naïve or relapsed or refractory acute myeloid leukemia.

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Background: Investigational agent lisaftoclax (Lisa) was shown in preclinical findings to synergistically induce apoptosis in acute myeloid leukemia (AML). Here, we present follow up safety and efficacy data from a phase 1b/2 study evaluating Lisa + azacitidine (AZA) in adults with AML. **Methods:** Elderly (≥ 75 years)/unfit treatment-naïve (TN) and relapsed or refractory (R/R) AML (≥ 18 years) patients (pts) were enrolled. Lisa (400/600/800 mg) was administered orally once daily in 28-day cycles (a daily ramp up schedule was used for Lisa to prevent tumor lysis syndrome, TLS) combined with AZA (75 mg/m^2/day on D1-7). **Results:** As of January 25, 2024, 76 AML pts were enrolled (R/R [n = 37]; elderly/unfit TN [n = 39]). The median (range) age was 66 (20-81) years and 61.8% of pts were male. All pts treated with Lisa + AZA reported TEAEs, with 89.5% Grade 3/4 AEs; and 43.4% SAEs. Common TEAEs (≥ 30%) included neutropenia (60.5%), thrombocytopenia (60.5%), diarrhea (42.1%), hypokalemia (40.8%), pyrexia (35.5%), and vomiting (30.3%). Grade ≥ 3 TEAEs reported in ≥ 10% of pts were neutropenia (57.9%), thrombocytopenia (50.0%), anemia (27.6%), pneumonia (17.1%), and febrile neutropenia (10.5%). No TLS was reported, and the 30-/60-day mortality rates were 1.3% and 3.9%, respectively. In pts with R/R AML treated with Lisa + AZA, the overall response ([ORR] = CR + CRi + morphologic leukemia-free state [MLFS] + PR) and composite complete remission (CRc = CR + CRi) rates were 72.7% and 45.5%, respectively. In the 600 mg cohort (n = 30), ORR and CRc were 76.7% and 50.0%; the median (range) duration of treatment (mDoT), 3.8 (0.8–15.4) month (mo); median time to CRc (mTTCRc), 2.5 (95% CI, 1.5-6.1) mo; median PFS was 10.2 (95% CI, 6.5-NR) mo; and median OS was 14.7 (95% CI, 7.8-NR) mo. Among 39 pts with TN AML treated with Lisa + AZA, ORR and CRc were 64.1% and 51.3%, respectively (Table). In the 600 mg cohort (n = 29), mDoT was 3.3 (1.0- 9.9) mo; mTTCRc was 1.9 (95% CI, 1.2-3.3) mo; median PFS was not reached (3.5, NR). 600 mg of Lisa + AZA was established as the recommended phase 2 dose. **Conclusions:** Our data support an emerging role for this new BCL-2 inhibitor Lisa combined with AZA for the treatment of elderly/unfit TN and R/R AML pts, especially with low early mortality and promising mPFS. A phase 3, randomized, double-blind clinical study is in progress to determine whether Lisa + AZA improves OS in elderly/unfit pts with AML. *HW, XW, and YL are co-first authors. Clinical trial information: NCT04501120. Research Sponsor: Ascentage Pharma Group Corp. Ltd. (Hong Kong).

Overall response of Lisa plus AZA in evaluable AML patients.

	R/R AML, n = 33	Elderly/unfit AML, n = 39
Best response, n (%)		
CR	7 (21.2)	13 (33.3)
CRi	8 (24.2)	7 (17.9)
MLFS	6 (16.2)	3 (7.7)
PR	3 (9.1)	2 (5.1)
SD	8 (24.2)	13 (33.3)
PD	1 (3.0)	1 (2.6)
ORR, n (%)/	24 (72.7)/	25 (64.1)/
95% CI	(54.5-86.7)	(47.2-78.8)
CRc, n (%)/	15 (45.5)/	20 (51.3)/
95% CI	(28.1-63.6)	(34.8-67.6)

Domain-based analysis of *RUNX1*somatic mutations in myeloid neoplasms.

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Background: *RUNX1*is a master regulator of hematopoiesis. ELN2022 risk stratification categorizes *RUNX1* as an AML/MDS gene associated with poor prognosis. Functional domains in *RUNX1*are the Runt homology domain (RHD) and a transactivation domain (TAD), with DNA binding and co-activator recruitment functions, respectively. Domain-based analysis can elucidate the functional and biological impact of somatic *RUNX1*mutations, which have not yet been reported in the literature. **Methods:** Sequencing data from Karmanos Cancer Institute and a publicly available meta-analytic cohort [Awada et al., Blood 2021, Kewan et al., Nature Communications 2023, cBioPortal (Cerami et al., 2012) and AACR GENIE (v 13.1)] were used to construct a larger dataset of 16,565 patients with myeloid neoplasms. Baseline clinical and molecular characteristics were noted. The chi-square test was used to study various parameters described, and Kaplan-Meier curves were used to estimate survival. **Results:** *RUNX1*was mutated in 10.8% (1804/16,565) of patients. Median OS (mOS) for $RUNX1^{MT}$ vs. $RUNX1^{WT}$ was significantly worse at 16.4 vs 23.4 mos. ($p < 0.0001$). 990 patients with somatic mutations were studied; germline variants were screened and excluded if VAF was between 40-60%. Among somatic $RUNX1^{MT}$ patients, primary AML was the most frequent at 52.8%, followed by secondary AML-35.7% and MDS-9%. Most patients had mutations in the RHD (53.8%), followed by TAD (22%), and the remaining in non-RHD, non-TAD zones (NRNT). There was no statistically significant difference in OS by domain stratification; TAD had the numerically least mOS at 13.6 mos, RHD at 16.1 mos, and NRNT at 20.4 mos. The median age of patients was 70.9 (62-76) years, similar across domains. TAD patients were less likely to be male when compared to RHD (47% vs. 56%, p=0.04). No specific enrichment of disease type or abnormal karyotype was observed across domains. Co-mutational profiles across RHD and TAD domains among all diseases showed spliceosome co-signature enriched in RHD vs. TAD (59% vs. 46%, p=0.01). *NPM1*was noted to be inversely correlated with *RUNX1* in general, with 1% and 3.5% in RHD and TAD. *ASXL1*was the most frequently distributed co-mutation in both groups, but not statistically different (41% vs. 33%, p=0.11). TAD patients with spliceosome co-mutation had worse mOS (11.4 mos) than those without spliceosome mutation (16.2 mos, p=0.02) or RHD patients with spliceosome co-mutation (16 mos, p=0.001). Missense mutations were strongly associated with RHD (55.3% vs. 7.9%); $p < 0.00001$, while frameshift mutations were enriched in TAD (24.1% vs. 69.8%); $p < 0.0001$. **Conclusions:** Domain-based analysis of somatic $RUNX1^{MT}$ myeloid neoplasms reveals TAD mutation to be common in females, frequently a frameshift mutation, and numerically has the worst survival. There appears to be a unique spliceosome signature enrichment in RHD compared to TAD, with worse OS in TAD patients with spliceosome co-mutations overall. Research Sponsor: None.

6543 Poster Session

Improved overall survival in acute myeloid leukemia over the last 15 years.

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Background: Overall survival (OS) for acute myeloid leukemia (AML) has remained dismal over the past decades. In the last five years, 11 drugs have been approved for newly diagnosed and relapsed/refractory AML. We, therefore, hypothesized that OS has increased significantly in recent years. **Methods:** We identified 78,092 pts diagnosed with AML between 2004 and 2019 from the National Cancer Database and divided them into 2 cohorts based on year of diagnosis, 2004-2010 and 2011-2019. The Kaplan-Meier method was used to estimate OS probabilities. Cox regression was used to evaluate the association of patient and disease characteristics with OS and differences in these associations between the two cohorts. **Results:** Sixty-one percent of patients were ≥60 years old, 46% were female, 85% were white, and 90% had Charlson comorbidity index of 0-1. Forty-five percent were diagnosed in 2004-2010, and the rest were diagnosed in 2011-2019. Chemotherapy use increased over the years, with 81% of patients receiving chemotherapy in 2019 compared to 73% in 2004. Similarly, 12.2% of patients in 2012 received hematopoietic cell transplant (HCT) compared to 6.5% in 2004. One-year, 3-year, and 5-year OS for patients diagnosed in 2011-2019 were 48%, 31%, and 28% compared to 42%, 25%, and 22%, respectively, for patients diagnosed in 2004-2010. On multivariable analysis, OS differed significantly over the years based on race, AML subtype, receipt of chemotherapy, and HCT use. OS for white people was better compared to black in 2004-2010 but similar in 2011-2019. Both white and black people had worse OS compared to other race types in 2004-2010 and 2011-2019. Acute promyelocytic leukemia had the best OS compared to core-binding factor, therapy-related, and other AML types; OS improved the most in acute promyelocytic leukemia and core-binding factor AML over the years. Compared to 2004-2010, OS increased significantly in 2011- 2019 with the receipt of chemotherapy and HCT. Older age, male sex, lower income, no insurance, higher Charlson comorbidity index, and lower educational attainment were associated with worse OS with no significant change in recent years. **Conclusions:** In one of the largest studies, we identified improved OS in patients with AML in recent years. Improvement in OS is likely multifactorial, including recent drug approvals, increased use of chemotherapy and HCT, and better supportive care. Despite a meaningful improvement in OS, only one out of four patients with AML were alive after five years, highlighting a continued need for further drug development and the importance of HCT. Research Sponsor: University of Iowa, Department of Internal Medicine, Division of Hematology, Oncology, Blood and Marrow Transplantation.

Outpatient blinatumomab with digital monitoring in patients with measurable residual disease positive (MRD+) B-ALL in a phase 4 study.

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Background: Blinatumomab, a CD3/CD19-directed BiTE® (bispecific T-cell engager) molecule, is an effective therapy for patients (pts) with MRD+ B-ALL. Hospitalization is recommended for days (D) 1–3 of cycle (C) 1 and D1–2 of C2 for these pts receiving blinatumomab to monitor for serious adverse events (SAEs). This phase 4 study evaluated the safety and feasibility of outpatient (outpt) digital monitoring to replace hospitalization in pts with MRD+ B-ALL (NCT04506086). **Methods:** Enrolled adults with MRD+ B-ALL in complete remission received continuous intravenous (cIV) blinatumomab at 28 μg/day. Current Health Wearable Monitoring System (CHWMS) was worn by pts at home for D1–3 (C1) and D1–2 (C2), in the presence of a caregiver, and provided heart rate, respiratory rate, and oxygen saturation; a separate patch monitored temperature. Manual blood pressure measurements were taken every 3-6 hrs. Vital signs (VS) were streamed to a provider smartphone/laptop; changes outside a predetermined threshold generated audible alarms. The primary endpoint was incidence of grade (G) ≥3 cytokine release syndrome (CRS), neurotoxicity, or any adverse event (AE) requiring hospitalization during the monitoring period. **Results:** As of 12/15/2023, 9 pts (median age 43 [20-73] years) received outpt blinatumomab for (completed C1, n=7; C2, n=6). During outpt monitoring, dose interruption was reported in 5 of 9 pts (1 pt had 2 dose interruptions: AE, n=2; dose administration error, n=2; other, n=2). CRS was reported in 2 pts (SAE, n=1; G≥3, n=0; led to interruption, n=1) and neurologic events in 4 pts (SAE, n=0; G≥3, n=0; led to interruption, n=0). Two pts experienced AEs requiring hospitalization (CRS, n=1; fever, n=1). Most VS changes were physiological or from routine pt activity. Median (range) number of alarms triggered/pt was 79 (12-135); among 3 pts, 1.2%, 5.1% and 8.9% of alarms led to therapeutic intervention (Table). **Conclusions:** To date, outpt administration of cIV blinatumomab in pts with MRD+ B-ALL was feasible and safe with appropriate outpt digital monitoring. Study enrollment is ongoing. Clinical trial information: NCT04506086. Research Sponsor: Amgen Inc.

Safety and alarm findings during monitoring period.

n (%)	n=9
All TEAE	8 (89)
SAE	2 (22)
Treatment-related	5 (56)
TEAE in >20% of pts	Pyrexia, 4 (44.4)
	CRS, 2 (22.2)
	Headache, 2 (22.2)
	Tremor, 2 (22.2)
Pts with ≥1 alarm triggered	9 (100)
Reasons for alarm trigger	Technical, 9 (100)
	Spo2, 6 (67)
	Respiratory rate, 7 (78)
	Axillary temperature, 4 (44)
	Systolic blood pressure, 4 (44)
	Pulse rate, 3 (33)
	Patient messages, 2 (22)
Mean time to intervention, min (SD)	14.9 (26.8)
Therapeutic intervention*	Antipyretic, 2 (22)
	Other medication, 2 (22)
	Suspend dose, 1 (11)
	Dexamethasone, 1 (11)
	Suspend dose and take antipyretic, 1 (11)
	Suspend dose and take dexamethasone, 1 (11)

*Among 3 pts. Spo2, continuous oxygen saturation; TEAE, treatment emergent adverse event.

6545 Poster Session

A prospective study of all-trans retinoic acid plus venetoclax and azacitidine in newly diagnosed acute myeloid leukemia.

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Background: Over the decade, anthracycline and cytarabine-based intensive chemotherapy remains the standard of care for acute myeloid leukemia (AML) but is hampered by serious toxicities like myelosuppression, increased transfusion requirement and disappointing clinical outcomes among the so-called poor-prognosis AML subsets. BCL-2 inhibitor plus azacitidine (AZA) has become a preferred treatment for AML, but the remission rate and overall survival (OS) are suboptimal. Apart from hematologic toxicities, 70.0% of patients were RBC transfusion dependent and 58.6% were platelet transfusion dependent. At present, all-trans retinoic acid (ATRA) is used as a differentiation drug, and there is no combination regimen with BCL-2 inhibitor. This study aimed to assess the efficacy and safety of ATRA plus venetoclax and AZA for newly diagnosed AML. **Methods:** This study enrolled 35 patients (≥18 years) with newly diagnosed AML between 2022 and 2023. For induction, patients received AZA (75 mg/m^2) from Day 1 to 7, venetoclax at a target dose of 400 mg/d from Day 2 to 10, and ATRA (45 mg/m^2/d) from Day 12 to 28 of each 28-day cycle for up to 2 cycles or until disease progression. Patients who achieved complete remission (CR) after two cycles of induction therapy received bone marrow transplantation or consolidation at their own discretion. For consolidation, patients received ATRA (45 mg/m^2/d) from Day 1 to 21 and AZA (75 mg/m^2) from Day 1 to 7 of each 28-day cycle for up to 4 cycles or until disease progression. For maintenance, patients received ATRA (45 mg/m^2/d) for 21 days per cycle plus AZA (75 mg/m^2). Maintenance therapy was given every 3 months until disease progression and ATRA was provided during intermissions. The primary endpoint was the composite CR rate (CR and CR with incomplete hematologic recovery) at the end of cycle 1 of inductive therapy. **Results:** As of now, the composite CR rate reached 74% (26/35) and the objective response rate reached 91% (32/35). The composite CR was 73% (11/15) in the adverse risk group and 75% (15/20) in the favorable-intermediate risk group at the end of cycle 1. Thirty-three patients entered cycle 2. The cumulative composite CR rate reached 91%(30/33) after 2 cycles of induction therapy. The median event-free survival was 390 days, and the median OS was 573 days. Platelet transfusion independence occurred in 17% (6/35) patients in cycle 1 and 73% (24/33) in cycle 2. Furthermore, 20% (7/35) and 73% (24/33) patients were RBC transfusion independent in cycle 1 and 2, respectively. Any-grade infections occurred in 74% (26/35) patients, including 12 before admission. **Conclusions:** The treatment regimen achieved a high composite CR rate and was well tolerated, with reduced hematologic toxicities in cycle 2 of induction therapy. Both adverse risk and favorable-intermediate risk patients benefited from the regimen, which holds promise for treating AML in adult patients. Clinical trial information: NCT05654194. Research Sponsor: None.

6546 Poster Session

TP53 mutation screening for patients at risk of myeloid malignancy.

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Background: Cellular therapy is a promising approach for many diseases but is associated with a risk of subsequent myelodysplastic syndrome and/or acute myeloid leukemia, also known as therapy-related myeloid neoplasms (tMN). This phenomenon has recently been described with allogeneic hematopoietic cell transplantation (HCT) and gene therapy for sickle cell disease (SCD). Mutation(s) in functional domains of *TP53* are often associated with the development of tMN but currently no prospective screening or monitoring technology is available. **Methods:** A next-generation sequencing (NGS) assay with unique molecular identifiers (UMI) and bio-informatic noise-suppression was designed to discover somatic mutations at a variant allele frequency (VAF) 1% throughout the *TP53*gene. The background error profile at each base position was calculated using blood genomic DNA from healthy donors. The minimal detectable allele fraction with 95% confidence (MDAF) was calculated for all reported known AML/tMN *TP53* hotspots. Orthogonal validation was performed using droplet digital PCR (ddPCR). **Results:** The median error corrected sequencing depth at 62 known *TP53* hotspot regions was 14,512 (95% CI: 14,769 – 15,430) with a theoretical median *de novo* NGS variant discovery limit of 0.058% (range: 0.037% - 0.13%). Experimental evidence of assay performance characteristics was produced using serial dilutions of 4 missense, 2 splicing, and 1 frameshift *TP53* variants with 100% discovery specificity observed (lowest detected VAF range: 0.05 – 0.12%). High correlation was observed in quantification using NGS discovery and ddPCR validation ($r = 0.958$, $p<0.0001$). Pre- and post-HCT clinical samples from 19 patients with SCD, 11 of which had graft failure including 4 who developed tMN, were screened for *TP53* mutations. In all tMN cases, the AML-associated *TP53* variant was detectable at least 6 months and up to 2.5 years prior to clinical diagnosis of myeloid malignancy. In contrast, no pathogenic *TP53* variants were detected in 15 SCD patients who underwent HCT but did not develop tMN. **Conclusions:** This study provides generalizable evidence that ultra-sensitive discovery of *TP53* mutations prior to cellular therapy is possible and could be a potentially valuable clinical tool to screen for tMN risk. Research Sponsor: This work was funded by the Intramural Research Program of the National Heart, Lung, and Blood Institute of the National Institutes of Health.

6547 Poster Session

Mutation patterns and prognostic implications in acute myeloid leukemia with chromosomal 7 deletions.

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Background: Chromosomal 7 deletions (del7/7q) are the most common adverse cytogenetic event in acute myeloid leukemia and are associated with high rate of relapse. We analyzed gene mutation profiles in del7/7q AML patients who relapsed after initial remission to identify molecular patterns associated with clinical outcomes. **Methods:** Out of 351 newly diagnosed AML patients with del7/7q, 115 (32%) achieved complete remission after first-line treatment between 2012-2023. Of the 115 patients, 77 (67%) patients relapsed during the study follow-up. Kaplan-Meier and Cox regression were used to analyze survival outcomes. Next-generation sequencing was performed on a targeted panel of 81 genes for 59 patients who relapsed on bone marrow samples at diagnosis and relapse for paired analysis. **Results:** The median age of the 115 patients at diagnosis was 74 (41-93). Thirty-four patients (30%) received intensive treatment. With 30.8-month median follow-up, the median overall survival (OS) was 10.4 months, with improved survival in patients without *TP53* mutation (13.04 vs. 8.6 months, p=0.005) or complex karyotype (12.4 vs. 8.6 months, p=0.03). The median duration of response for the 77 patients who relapsed was 5 months (2-7). Allo-HSCT significantly improved median OS (not reached vs. 8.5 months, P=6e-06), and was identified as the key variable impacting survival in multivariate analysis. *TP53* was the most commonly mutated gene at diagnosis (67%) and relapse (71%). Mutations in *CBLC* and *KDM6A* were cleared after induction therapy, while *BCOR* and *BCORL1* were commonly acquired at relapse (Table). At diagnosis, a lower co-mutation burden was observed in *TP53* mutant patients as compared with wild type (average 1.84 vs. 3.65 respectively, p=0.0001). Patients with mutated *TP53* and coexisting mutations in *GATA2*, *NF1*, *BCORL1*, or *RUNX1* at diagnosis had shorter relapse free survival (RFS, 2 vs. 5 months, p=0.01) and OS (7.2 vs. 10.4 months, p=0.01) compared to patients with solely mutated *TP53* (HR 2.2; 95% CI 1.2-4; P = 0.004). Allo-HSCT significantly improved the OS in patients with mutated *TP53* (13 vs. 8 months, p=0.01). **Conclusions:** Mutated *TP53* clones persist from diagnosis to relapse in patients with del7/7q AML. In patients with mutated *TP53*, co-occurring mutations in *GATA2*, *NF1*, *BCORL1*or *RUNX1* at diagnosis were linked to a shorter RFS and indicate a particularly high-risk subgroup that require proceeding to allo-HSCT in CR1 without delay. Research Sponsor: None.

Gene	Status	Rate (%, No. of patients)
CBLC	Diagnosis	Clearance rate - 100%, 12/12
KDM6A	Diagnosis	Clearance rate - 100%, 6/6
EZH2	Diagnosis	Clearance rate - 86.6%, 13/15
BCOR	Relapse	Emergence rate - 75%, 3/4
BCORL1	Relapse	Emergence rate - 30%, 3/10
TP53	Persistent	Persistence rate - 95.2%, 40/42
DNMT3A	Persistent	Persistence rate - 68%, 13/19
RUNX1	Persistent	Persistence rate - 62.5%, 5/8
NRAS	Persistent	Persistence rate - 57.1%, 4/7
PTPN11	Persistent	Persistence rate - 50%, 3/6

Impact of protein energy malnutrition on hospitalized patients with acute myeloid and lymphoid leukemia: A United States population-based cohort study.

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Background: Acute leukemia poses a significant burden to the society and the healthcare system. Advances in chemotherapeutics and hematopoietic stem cell transplantation (HSCT) have increased survival in these patients. Protein energy malnutrition (PEM) frequently complicates the clinical picture in patients with cancer, however data on the impact of PEM in patients with acute myeloid and lymphoid leukemia is limited. **Methods:** We utilized the 2020 National Inpatient Sample (NIS) Database in conducting this retrospective cohort study. We identified patients with acute leukemia (myeloid and lymphoid) and PEM using appropriate ICD-10 diagnostic codes. We stratified patients with acute leukemia based on the presence or absence of PEM. A survey multivariable logistic and linear regression analysis was used to calculate adjusted odds ratios (ORs) for the primary and secondary outcomes. A p value of <0.05 was considered statistically significant. The aim of this study was to investigate the impact of PEM on in-hospital mortality, hospital length of stay (LOS), and total hospitalization charge among patients with acute leukemia. **Results:** We identified a total of 30995 hospitalized patients with acute leukemia, of which 13.06% (4050/30995) had comorbid PEM. The overall in-hospital mortality among patients with acute leukemia was 8.95% (2775/30995). Among those with co-morbid PEM, the mortality rate was significantly higher at 12.47% (505/4050, $p<0.001$). Utilizing a stepwise survey multivariable logistic regression model that adjusted for patient and hospital level confounders, PEM was found to be an independent predictor of increased in-hospital mortality (adjusted OR 1.50; 95% (confidence interval [CI], 1.18 -1.91); p=0.001), longer LOS (coefficient 10.50; CI 8.59 -12.41; $p<0.001$), and higher total hospitalization charge ($208,308; CI $147,516- $269,100; $p<0.001$). **Conclusions:** Our analysis demonstrated that PEM was widely prevalent in hospitalized patients with acute leukemia and significantly worsened outcomes including increased in-hospital mortality, LOS, and cost of healthcare utilization. A proactive approach for prevention and early management of cancer associated malnutrition is required. Further prospective multicentric studies are needed to better describe these associations. Research Sponsor: None.

A phase II study of venetoclax (VEN) in combination with 10-day decitabine (DEC) in older/unfit pts with newly diagnosed (ND) or pts with relapsed/refractory (R/R) acute myeloid leukemia (AML), or high-risk myelodysplastic syndrome (HR-MDS).

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Background: We report long-term results of phase 2 study of 10-day DEC and VEN (DEC10-VEN) in AML/HR-MDS. **Methods:** This single-institution study (NCT03404193) included intensive chemotherapy-ineligible pts >60y with ND de novo AML or secondary AML (sAML), or R/R AML, or HR-MDS. Induction therapy: DAC 20 mg/m^2 IV x 10d + VEN days 1-28. VEN was stopped on day 21 if bone marrow blasts ≤5%. Consolidation included DEC IV x 5 days + VEN days 1-21, every 4-8 weeks as previously described (DiNardo et al. Lancet Haem. 2020). Primary endpoint was ORR. Secondary endpoints are duration of response, OS, RFS, and safety. Here, we report an update with 232 pts and results of HR-MDS/CMML cohort. **Results:** 232 pts were enrolled thus far (ND AML-86; sAML-49; R/R AML-76; HR-MDS/CMML-21). Median follow up is 39 mo (36-46 mo). Median age was 73y in ND AML and 64y in R/R AML (Table). Three-fourths of pts inAML cohort were adverse risk by ELN 2022 risk. CR/CRi rates in ND AML, sAML, and R/R AML were 92%, 53%, and 40% and ORR was 88%, 69%, 58%, respectively. Median OS was 12.3 mo in frontline (FL, ND (16.7 mo) and sAML (10.4 mo)) and 7.6 mo in R/R. Similarly, median RFS was 9.1 (ND-10 mo and sAML-6.4 mo) and 7.5 mo, respectively. Median time to ANC ≥500 x 10^9/L in cycle 1 was 41 days and Plt ≥50 x 10^9/L was 31 days in FL pts. 30-day mortality was 2% in FL and 5% in R/R cohort. 18% in FL and 22% in R/R cohort proceeded to SCT. In HR-MDS cohort, the median age was 71y; 18/21 pts had prior treatment. ASXL1 was the most frequent mutation. ORR was 52% (CR+CRi-33%). Median OS-12.1, RFS-7.3 mo. Median time to ANC ≥500 x 10^9/L was 55 and plt ≥50 x 10^9/L was 51 days. Most common grade 3/4 AEs were infection with neutropenia (38%), febrile neutropenia (32%), thrombocytopenia (17%), and neutropenia (15%), consistent with HMA + VEN experience. **Conclusions:** DEC10-VEN demonstrated expected safety and efficacy in a particularly high-risk cohort of ND and R/R pts, with no evidence that 10-days of DEC provides improved responses over standard 5-days DEC. Clinical trial information: NCT03404193. Research Sponsor: None.

		Secondary AML		Relapsed/ Refractory	
Baseline Characteristics	**Newly Diagnosed AML (n=86)**	**Untreated (n=18)**	**Treated (n=31)**	**AML (n=76)**	**High-risk MDS (n=21)**
N, % or [range]					
ORR	76 (88)	14 (78)	20 (65)	44 (58)	11 (52)
CR	57 (66)	9 (50)	8 (26)	16 (21)	5 (24)
CRi	13 (15)	3 (17)	6 (19)	14 (18)	2 (10)
CR + CRi	70 (92)	12 (67)	14 (45)	30 (40)	7 (33)
MLFS	6 (7)	2 (11)	6 (19)	13 (17)	0
PR	0	0	0	1 (1)	0
MRD† negative	47/73 (64)	6/13 (46)	10/20 (50)	13/30 (43)	NA
No response	8 (9)	4 (22)	9 (29)	26 (34)	10 (48)
Unevaluable	1* (1)	0	0	2‖ (3)	0
MRD† negative	47/73 (64)	6/13 (46)	10/20 (50)	13/30 (43)	NA

†MRD assessed by multicolor flow-cytometry in BM.
*Treatment was stopped after day 1 due to AKI and TLS
‖One pt refused treatment after day 10 and another patient received only 2 doses of DEC and stopped treatment due to pneumonia of unknown pathogen, liver mass and hemorrhage.

Predictive biomarkers of response to the IRAK4/FLT3 inhibitor emavusertib in hematological malignancies.

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Background: Myelodysplastic neoplasms (MDS) and acute myeloid leukemia (AML) display a dynamic and diverse mutational landscape. Various mutations can induce the overexpression of a highly active long isoform of interleukin-1 receptor-associated kinase 4 (IRAK4), leading to downstream activation of transcription factors such as NFκB. This activation triggers inflammation, oncogenesis, and the survival of cancer cells. Emavusertib, a potent oral inhibitor of IRAK4 and FLT3, has demonstrated efficacy in pre-clinical leukemia models and in patients. In this abstract, we present data suggesting potential biomarkers of response to emavusertib based on clinical samples from the ongoing TakeAim Leukemia trial. **Methods:** In Phase I/IIa of the TakeAim Leukemia trial (NCT04278768), patients with relapsed/refractory (R/R) AML or high-risk MDS (hrMDS) received treatment with emavusertib monotherapy. Baseline and on treatment patient samples underwent RNA sequencing and proteomic analyses. RNA-seq was conducted on mononuclear cells from bone marrow or peripheral blood (n=42). Plasma proteins were quantified by the Luminex platform (n=51). **Results:** hrMDS patients responding to emavusertib monotherapy exhibited decreased gene expression levels of the NFκB target gene *IL1β* ($P \leq 0.05$) compared to non-responders. Protein analyses revealed that hrMDS responders had lower baseline levels of proliferation and migration-related factors, like Vascular Endothelial Growth Factor (VEGF-A) and CXCL12, in plasma compared to non-responders ($P \leq 0.05$). In AML samples, baseline VEGF-A levels were significantly higher in responders. The concentration of soluble PD1 (sPD1) increased in on-treatment samples in hrMDS patients ($P \leq 0.05$), but not in AML patient samples. Additionally, hrMDS samples presented lower IL2 and higher sCD47 levels compared to AML ($P \leq 0.05$). **Conclusions:** In this work, several baseline biomarkers indicative of a response to emavusertib were identified in patients with hematological malignancies. Responders in hrMDS showed lower baseline expression of the NFκB-associated pro-inflammatory gene, *IL1β*, and lower protein levels in plasma of the angiogenic factor VEGF-A and the chemokine CXCL12. In AML samples, responders have higher baseline levels of VEGF-A, indicating distinct predictive biomarkers for both pathologies. Other molecules of clinical interest, such as sPD1, showed increased concentrations in on-treatment plasma samples of hrMDS patients regardless of their response to emavusertib. Our findings highlight distinct baseline biomarkers for AML and hrMDS related to the pathophysiology of hematological malignancies. These results suggest that inflammatory and migration mediators, along with angiogenesis factors, hold potential as predictive biomarkers for assessing responses to emavusertib monotherapy treatment in hematological malignancies. Clinical trial information: NCT04278768. Research Sponsor: None.

Impact of body mass index and karyotype on clinical outcomes in adolescents and young adults (AYA) with acute myeloid leukemia.

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Background: Acute myelogenous leukemia (AML) represents 15%–20% of leukemias in children and approximately 33% in adolescents and young adults (AYA) (1). Obesity has been associated with worse outcome in acute lymphoblastic leukemia in AYA patients (pts). To date, however, the relationship between weight and clinical outcomes in AYA pts diagnosed with AML has not been established. We investigated the impact of body mass index (BMI) along with other prognostic factors on outcomes of AYA AML pts receiving intensive chemotherapy and/or allogeneic stem cell transplant (SCT). **Methods:** This retrospective chart review included pts 18-39 yrs newly diagnosed with AML between 01/2006-12/2023. All pts received intensive chemotherapy with cytarabine- and anthracycline-based induction followed by consolidation chemotherapy +/- SCT. BMI was calculated using height and weight at AML diagnosis. Pts were classified by BMI into under, normal, overweight, or obese categories. AML risk classification (ELN 2022) and HCT co-morbidity index (HCT-CI) were performed. Outcomes included complete response (CR), CR with incomplete counts (CRi), overall response rates (CR+CRi), event free survival (EFS), and overall survival (OS). **Results:** Eighty-seven pts (median age 25 yrs, range 18-38) were identified. 44 (51%) were male; 85% were Caucasian. Per ELN 2022, 27 (31%) had favorable, 40 (46%) intermediate, and 20 (23%) adverse risk. Overall response rate to chemotherapy was 92% (CR 80%, CRi 12%). CR rate by ELN was 96%, 72% and 58%, respectively. Median OS for all pts was 788 days and per ELN risk was 1379, 569, and 595 days, respectively. Co-morbidity indices (HCT-CI) ranged from 0-5. Sixty-two percent underwent SCT. 29% relapsed. The percentage of pts alive at 2 and 5 years was 54% and 29%. Pts were categorized by BMI: underweight (BMI $<$ 18.5, 6%), normal weight (NW) (BMI 18.5-24.9) (37%), overweight (OW)(BMI 25-29, 26%), and obese (OB) (BMI $>$ 30, 31%) pts. Overall, there was a trend to improved outcomes in NW vs OW and OB pts. Median OS was 1006 (NW) vs 748 (OW) vs 678 (OB) days (p=0.0036 for NW vs OW/OB). Two-year OS was 63%, 52%, and 48%; 5-year OS was 38%, 26%, and 19%. The impact of BMI was dependent on AML karyotype. In favorable risk AML AYA pts, the relapse rate was 4%, 4% and 12%. Median OS was 1982 (NW), 1169 (OW), and 1256 (OB) days (p=0.0525 NW vs OW/OB). Five-year OS was 50%, 25% and 18%. The most common causes of death were GVHD-induced multi-organ failure and respiratory failure which did not correlate with HCT-CI. In intermediate and adverse risk AML, there was no difference in outcomes by BMI. **Conclusions:** Outcomes of favorable risk AYA AML pts following intensive chemotherapy +/- SCT was influenced by BMI with increased mortality and shorter OS in pts with high BMI (overweight and obese) as compared to normal BMI. Additional studies to confirm this finding and elucidate the underlying reasons are warranted. Research Sponsor: None.

Treatment of acute myeloid leukemia with Orca-T.

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Background: Allogeneic hematopoietic stem cell transplants (alloHSCT) offer a potential curative treatment for many hematological cancers, however, traditional alloHSCT is associated with high mortality from complications including infection, graft versus host disease (GvHD) and relapse. Orca-T is an investigational allogeneic T-cell immunotherapy that includes stem and immune cells, derived from allogeneic donors, that leverages highly purified, polyclonal donor regulatory T cells to control alloreactive immune responses. In this sub-group analysis, we evaluated the safety and efficacy of patients with acute myeloid leukemia who were treated with Orca-T. **Methods:** Data from 37 patients with the diagnosis of acute myeloid leukemia (AML) in CR/CRi who received myeloablative conditioning with busulfan, fludarabine, and thiotepa (BFT) followed by Orca-T by 6/30/22 as part of a multicenter phase 1b single-arm trial (NCT04013685) are reported here. Patients enrolled in the phase 1b trial who did not meet these criteria were not included in this analysis. Patients received BFT prior to Orca-T, followed by single-agent GvHD prophylaxis with tacrolimus, and had an 8/8 related or unrelated matched donor. Donors were matched via DNA-based high-resolution typing of HLA-A, -B, -C, and -DRB1. **Results:** Orca-T was successfully manufactured at a centralized GMP facility, distributed, and infused at study sites throughout the U.S. Vein-to-vein time (i.e. time between end of donor apheresis to start of recipient's Orca-T infusion) was < 72 hours for all patients, with the majority < 60 hours. Median age was 51 years, 49% were female and 16% were of Hispanic or Latino ethnicity. Twenty-three (62%) had matched related donors and 14 (38%) had matched unrelated donors. Baseline HCT-CI score was 3 and 4 in 27% and 8% of the patients, respectively. The majority had intermediate DRI scores (89%) and 41% were MRD positive at baseline. The median duration of follow-up was 14 months. Relapse-free survival at 12 months was 81.4% (95% CI: 62.9, 91.2). Non-relapse mortality and overall survival were 0% and 100% at 12 months, respectively. **Conclusions:** These encouraging results suggest that investigational Orca-T could represent a reduced toxicity alternative to conventional alloHSCT. This combination of Orca-T with myeloablative BFT led to $> 80\%$ RFS without treatment related mortality, and 100% overall survival in this AML patient population. These outcomes were accomplished with consistent and reliable cell manufacturing and distribution of Orca-T at a national scale. A multi-center randomized controlled phase 3 trial comparing Orca-T to SOC, utilizing BFT or TBI-based conditioning, will complete enrollment during the first half of 2024. (NCT05316701). Clinical trial information: NCT04013685. Research Sponsor: Orca Bio.

Trajectories of patient-reported outcomes after prolonged stays for hematopoietic cell transplant.

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Background: Patients hospitalized for hematopoietic cell transplantation (HCT) may have prolonged length of stay (PLOS). The longitudinal effect of PLOS in this population on quality of life (QOL) and psychological distress is unknown. **Methods:** We conducted secondary analyses of data from three prospective studies of patients undergoing HCT (2011-2022) at three academic centers. We defined PLOS as ≥30 days for allogeneic and ≥21 days for autologous HCT from date of admission. We collected patient-reported outcomes (PROs) for QOL, anxiety, depression, and posttraumatic stress disorder (PTSD) symptoms at baseline, 2 weeks, 3 and 6 months post-HCT. We used multivariate logistic regression to assess the effect of change in PROs from baseline to week 2 on PLOS adjusting for age, transplant type, donor, and diagnosis. We then fit linear mixed effects models to characterize the trajectory of PROs by PLOS over time. **Results:** 593 patients (mean age 56 years) were included, the majority of whom were male (57%), white (82%), and underwent allogeneic HCT (52%). The most common diagnosis was acute leukemia (28%). Patients with PLOS (26%) were younger (57 [range 18-78 yrs], 53 [19-75 yrs], p = 0.002), had acute leukemia (26%, 34%, p = 0.001), received myeloablative conditioning (21%, 41%, $p < 0.001$), and underwent allogeneic HCT (50%, 60%, $p < 0.001$). At baseline, patients with PLOS had lower QOL (108, 102, p = 0.001) and more depression symptoms (4.4, 5.3, p = 0.02). There was no difference in baseline anxiety or PTSD symptoms. An increase in depression symptoms from baseline to week 2 was associated with greater odds of PLOS (adjusted OR = 1.08, p = 0.04). The table depicts longitudinal differences in PROs by PLOS. Compared to those without PLOS, patients with PLOS reported lower QOL (time*PLOS interaction, $\Delta = -6.6$, SE = 2.1, p = 0.001) and greater increase in depression symptoms (time*PLOS interaction, $\Delta = 1.9$, SE = 0.6, $p < 0.001$) at week 2. Lower QOL in those with PLOS persisted through 6 months (Table). PLOS was associated with more re-admissions (0.8, 1.1, p = 0.02) and mortality (9%, 19%, p = 0.001) within 1 year of HCT. No difference was seen in rate of relapse and severe acute or chronic graft-*versus*-host disease. **Conclusions:** Patients with PLOS experienced worse QOL and increased psychological distress. Increase in depression symptoms from admission to week 2 may be an early indicator of PLOS and supports mental health screening during the index HCT hospitalization. Patients with PLOS may benefit from enhanced supportive care during and after HCT. Research Sponsor: National Cancer Institute; R01CA222014.

Absolute difference in patient-reported outcomes by length of stay.

	ΔBaseline	p val	Δ2 weeks	p val	Δ3 months	p val	Δ6 months	p val
Quality of Life	-5.1 (2.4)	0.03	-11.6 (2.5)	<0.001	-5.9 (2.6)	0.03	-5.9 (2.8)	0.04
Depression	0.6 (0.5)	0.23	2.5 (0.6)	<0.001	1.0 (0.6)	0.09	1.2 (0.6)	0.05

Δ: difference in estimated mean (standard error) quality of life and depression between those with and without PLOS

Biomarkers in a phase 1b study of investigational microbiome therapeutic SER-155 in adults undergoing allogeneic hematopoietic cell transplantation (allo-HCT).

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Background: Acute graft-*versus*-host disease (aGvHD) is a life-threatening complication following allo-HCT. Microbiome dysfunction and associated GI barrier disruption may contribute to aGvHD via activation of inflammatory immune responses. Circulating biomarkers in the peri-transplant period are correlated with risk of severe aGvHD, including suppression of tumorigenicity 2 (ST2), regenerating islet-derived 3-alpha (Reg3a) and inflammatory cytokines (IL6, IFNϒγ & TNFα). SER-155 is an investigational cultivated oral microbiome therapeutic designed to restructure the GI microbiome, improve GI barrier integrity and reduce GI inflammation and is being assessed in a 2-part Phase 1b study in adults undergoing allo-HCT. We present preliminary safety, GvHD, PK, and exploratory biomarker data from the completed open-label Cohort 1 through Day 100 post-HCT. **Methods:** Adult recipients of allo-HCT were eligible. HCT conditioning and aGvHD prophylaxis were per investigator discretion. Patients received 2 courses of SER-155 (pre-HCT and post-neutrophil engraftment, each comprised of 4 days of microbiome conditioning with oral vancomycin followed by 10 days oral SER-155. The primary endpoint was safety. Strain engraftment (PK) and biomarkers were assessed in stool and plasma samples. **Results:** Fifteen adults enrolled; 13 received at least 1 course of study drug (median age 67; 54% male), and 11 underwent allo-HCT. Following each course, the majority of the 16 SER-155 strains were detected in stool. Treatment-emergent adverse events (AEs) were reported in all patients with GI AEs the most common. No serious AEs (SAEs) were deemed related to SER-155. Most SAEs and AEs of special interest (ie, BSIs, invasive or GI infections) occurred between HCT and the 2nd SER-155 course. There were no deaths before Day 100. No BSIs were attributable to SER-155 strains. The rate of grade 2-4 aGvHD based on MAGIC criteria through Day 100 was 45.5%; no severe grade 3-4 aGvHD was observed. Median levels of plasma biomarkers REG3α, ST2 and inflammatory cytokines were not elevated relative to a reference range (Table). **Conclusions:** In this small open-label cohort, SER-155 was generally well-tolerated through Day 100 without drug-related SAEs and no severe aGvHD. Plasma biomarkers were not elevated at HCT Day 0 or neutrophil recovery. These preliminary observations align with the design and preclinical evaluation of SER-155. Clinical trial information: NCT04995653. Research Sponsor: Seres Therapeutics.

Biomarker	HCT Day 0 # (N=11)	Neutrophil Recovery # (N=10)	Published Literature and Laboratory Healthy Reference Range #
Reg3α	7889 (4866 – 17183)	7950 (1141 – 25967) *	2680 – 11274
sST2	34804 (8365 – 395014)	26618 (369 – 118110) *	1000 – 50000
IL6	1.61 (0.94 – 5.92)	3.25 (0.94 – 9.72)	19.1 (8.7 – 36.6)
TNFα	1.47 (0.6 – 23.92)	1.585 (0.79 – 15.09)	20.7 (4.8 – 37.4)
IFNγ	3.13 (2.86 – 16.83)	5.9 (2.86 – 14.19)	10.2 ± 3.4

#pg/mL; median (range); *N=8.

Improved survival for myeloid malignancy patients receiving thiotepa/cyclophosphamide (TT/Cy) versus total body irradiation/cyclophosphamide (TBI/Cy) conditioning and allogeneic stem cell transplantation.

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Background: TBI/Cy is a commonly used conditioning regimen prior to allogeneic stem cell transplant (SCT). Chemotherapy only regimens, mostly containing busulfan, have been shown to be effective and less toxic in patients with myeloid malignancies. Here, we present the largest reported experience with a non-busulfan myeloablative chemotherapy regimen of TT/Cy in myeloid malignancy patients undergoing allogeneic SCT and compare outcomes with TBI/Cy. **Methods:** Patients with myeloid malignancies receiving allogeneic SCT at Indiana University from 2007-2020 were included. TT/Cy consisted of TT 15 mg/kg and Cy 120 mg/kg. TBI/Cy consisted of 13.2 Gy in 8 fractions and Cy 3600 mg/m^2. The primary endpoint was overall survival (OS). Secondary endpoints included relapse-free survival (RFS), engraftment, and toxicities within the first 100 days. Median follow up for surviving patients is 2,046 (range 816-5,572) days. **Results:** 225 patients with AML (n=160), CML (n=45), and MDS (n=30) of median age 44 (range 19-59 years) received conditioning with TT/Cy (n=159) or TBI/Cy (n=66). Baseline characteristics were similar. For TT/Cy patients, the median OS was not reached, and 4-year OS was 57.2% (95% confidence interval [CI], 49.2-65.2%), which was significantly better than with TBI/Cy, with median OS 373 days and 4-year OS 33.9% (95% CI, 22.3-45.5%; p<.001). Similarly, for TT/Cy patients, the median RFS was not reached and 4-year RFS was 59.2% (95% CI, 52-67.2%), significantly better than median RFS of 341 days and 4-year RFS 35.2% (95% CI, 23.7-46.9%; p<.001) for recipients of TBI/Cy. On multivariable analysis adjusting for age, sex, diagnosis, disease risk, comorbidity index (HCI), and degree of stem cell source, TT/Cy had significantly lower risk of death (HR 0.44, 95% CI, 0.30-0.65; p<.001) together with female sex (p=.03) and lower HCI (p=.046). As shown in the Table summarizing secondary endpoints, TBI/Cy was associated with significantly higher rates of mucositis, sinusoidal obstruction syndrome (SOS), TPN usage, multiorgan failure, and length of stay of primary admission. **Conclusions:** TT/Cy is an efficacious regimen for patients with myeloid malignancies undergoing myeloablative allogeneic SCT with less toxicity and improved RFS and OS compared with TBI/Cy. TT/Cy should be compared to other non-TBI containing busulfan-based regimens. Research Sponsor: None.

Secondary Endpoints	TT/Cy (n = 159)	TBI/Cy (n = 66)	p-value
Length of stay, median days (range)	17 (6-209)	21 (3-121)	.012
Toxicities within first 100 days of SCT, n			.010
TPN usage	51	9	.003
Mucositis	127	52	.003
SOS	1	13	<.001
Respiratory failure with intubation	14	17	.001
Multiorgan failure	6	10	.004
Days to platelet engraftment, median (range)	16 (4-97)	20 (6-226)	<.001
Days to neutrophil engraftment, median (range)	13 (9-41)	11 (9-22)	<.001

Thiotepa/cyclophosphamide (TT/Cy) preparative regimen for patients with acute lymphoblastic leukemia (ALL) undergoing allogeneic stem cell transplantation.

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Background: Total body irradiation (TBI)-based preparative regimens have been standard for patients with ALL undergoing allogeneic stem cell transplant (SCT). It is unclear if chemotherapy-only regimens are equally efficacious. Here, we present the largest reported experience with myeloablative TT/Cy in patients with ALL undergoing allogeneic SCT and compare outcomes with TBI-based regimens. **Methods:** Patients with ALL receiving myeloablative allogeneic SCT at Indiana University from 2007-2020 were included. TT/Cy consisted of TT 15 mg/kg and Cy 120 mg/kg. TBI/Cy consisted of 13.2 Gy in 8 fractions and Cy 3600 mg/m^2 or etoposide 60 mg/kg. The primary endpoint was overall survival (OS). Secondary endpoints included relapse-free survival (RFS), engraftment, and toxicities within the first 100 days. Median follow up for surviving patients is 2,532 (range 599-4,762) days. **Results:** 80 patients with ALL of median age 40 (range 22-59 years) received conditioning with TT/Cy (n=25) versus TBI/Cy or TBI/etoposide (n=55). Baseline characteristics were similar. For patients receiving TT/Cy, the median OS was not reached, and the 4-year OS was 54.5% (95% confidence interval [CI], 34.3-74.7%), compared with a median OS of 1,491 days and a 4-year OS of 50.9% (95% CI, 37.8-64.2%) for those receiving TBI-based conditioning (p=.75). Similarly, for TT/Cy patients, the median RFS was 847 days and 4-year RFS was 43.2% (95% CI, 23.4-63%), not significantly different from median RFS of 1491 days and 4-year RFS 50.2% (95% CI 36.9-63.5; p=.232) for recipients of TBI regimens. On multivariable analysis, only a higher disease risk index was associated with significantly worse OS (p<.001), while conditioning regimen was not predictive of OS. Similarly, there was no significant difference in RFS between TT/Cy and TBI-based regimens on either univariable or multivariable analysis. Secondary endpoints are summarized in the table. As shown, TT/Cy was associated with significantly lower incidence of mucositis, TPN usage, bacterial infection, sinusoidal obstruction syndrome (SOS), and longer length of stay of primary transplant admission. **Conclusions:** While there was no significant difference in OS or RFS for patients receiving either TT/Cy or TBI-based conditioning, TBI was associated with greater toxicity. Our data suggests that TT/Cy is an acceptable alternative to TBI-based conditioning for ALL patients undergoing myeloablative allogeneic SCT. Research Sponsor: None.

Secondary Endpoints	TT/Cy (n = 25)	TBI/Cy (n = 55)	p-value
Length of stay, median days (range)	16 (7-175)	21 (7-80)	.005
Toxicities within first 100 days of SCT, n			
TPN use	7	38	<.001
Mucositis	23	54	.013
SOS	0	6	.03
Cardiac toxicity	6	4	.044
Bacterial infection	3	27	<.001
Days to platelet engraftment, median (range)	15 (6-34)	12 (6-40)	.013
Days to neutrophil engraftment, median (range)	13 (10-20)	13 (10-20)	.494

6557 Poster Session

Symptom burden in adult survivors of allogeneic hematopoietic stem cell transplantation.

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Background: Progress in allogeneic hematopoietic cell transplantation (HCT) and supportive care has significantly improved transplant outcomes and expanded the number of HCT survivors. A growing responsibility exists to address long-term morbidity and symptom burden. We sought to investigate symptom burden in adult survivors of HCT using a set of validated tools. **Methods:** We analyzed adults aged 19 years or older with hematologic malignancies who were treated with allogenic HCT at our institution from June 2018 to November 2022. Patients required at least one visit to our survivorship clinic for inclusion. We assessed symptom burden using the National Comprehensive Cancer Network (NCCN) Survivorship Assessment Questionnaire, which is a 25-question survey designed to assesses symptoms related to the following domains: cardiac, mood, cognition, fatigue, lymphedema, hormonal, pain, sexual dysfunction, and sleep. The short physical performance battery (SPPB) and short blessed test were used to assess physical function and conduct cognitive screen, respectively. Finally, we compared scores between patients <60 and ≥ 60 years old to examine an association between age and post-transplant symptoms. **Results:** A total of 152 patients have a median age of 61 years (range 21-76); 59.2% were males, and 28.5% had a BMI ≥ 30. Median Hematopoietic Cell Transplantation-specific Comorbidity Index was 3. The most common indication for transplant was acute myeloid leukemia (48.0%), and the most common donor type was matched unrelated (57.2%). The median time from transplant to the first survivorship clinic visit was 99 days. The most common symptom domains affected, according to the NCCN questionnaire results, were fatigue (50.7%), sleep (45.3%), and cognition (42.0%) whereas the least affected domains were pain (29.5%), cardiac (26.2%), and sexual (19.4%). When we stratified patients by <60 years old and ≥ 60 years old, we saw similar rates of reported symptoms, particularly regarding sleep disorder (44.3% vs. 45.7%, respectively), mood disturbance (31.4% vs. 34.1%, respectively), and sexual dysfunction (17.9% vs. 20.5%, respectively). Older patients, however, had higher rates of physical impairment according to SPPB scores (50.0% vs. 15.7%, OR = 5.4 [95% CI = 2.2-14.3]). Blessed test showed impaired cognitive screen in 7.2% without a significant difference based on age. **Conclusions:** Adult survivors of allogeneic HCT at 3-month post-transplant commonly suffer from symptoms across a variety of domains, especially pertaining to fatigue, sleep, and cognition. These symptoms affect both younger and older patients, although older patients are more likely to have physical impairment. The NCCN Survivorship Assessment Questionnaire captures a number of symptoms related to quality of life and can be more widely utilized as a tool to evaluate survivorship symptoms in patients who undergo HCT. Research Sponsor: None.

Impact of spleen volume on post-allogenic hematopoietic transplant outcomes in myelofibrosis: Utility of 3D volumetrics in splenomegaly.

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Background: Splenomegaly is a hallmark of myelofibrosis, thought to be correlated with graft failure and worsened overall survival in transplant patients. Past studies have utilized manual spleen measurement, potentially affecting accuracy. Using 3D volume can more precisely measure spleen size. Hence, the true impact of splenomegaly on transplant outcomes remains unclear. In this retrospective study, we examined myelofibrosis patients who underwent HCT and, using 3D volumetrics, analyzed the impact of splenomegaly and volume reduction over time on post HCT outcomes. **Methods:** This retrospective study included 130 City of Hope myelofibrosis patients with pre HCT imaging (2004–2023). Patients were divided into pre HCT spleen volume of >3000 cc and <3000 cc, with >3000 cc considered massive splenomegaly. Spleen volume was measured using Vitrea 3D volumetric software. For each patient, depending on imaging available, volume was measured 0-3 months pre HCT, 3-6 months, 6-9 months, and 9-12 months post HCT with corresponding volume reduction calculations. Pre HCT spleen volume was also temporally correlated with several post HCT outcomes. **Results:** Median age at HCT was 60 (17-75), and 95% of patients received the Fludarabine/Melphalan conditioning regimen. Median spleen volume pre HCT was 1150 cc (41-6695 cc). Sixteen patients measured >3000cc, and 114 patients measured <3000cc. Median spleen volume 3-6 months post HCT was 661 cc (80-1731 cc) with a median 48% volume reduction. The data suggests that majority of volume reduction occurred during this time (table). Five-year overall survival (OS) was 72.8%. Relapse was 11.0% at 1 year and 14.7% at 5 years. NRM at 5 years was 17.3%. ANC engraftment peaked at 28 days at 92.3%. Pre HCT spleen volume (<1000 cc, 1000-2000 cc, >2000 cc) did not have a significant impact on OS (P = 0.992), disease free survival (P = 0.783), relapse (P = 0.187), NRM (P = 0.627), or ANC Engraftment (P = 0.526). There was a statistically insignificant downward trend for platelet engraftment (P = 0.162). For patients with or without massive splenomegaly (>3000cc), there was no significant effect with any of the analyzed post HCT outcomes. **Conclusions:** This retrospective study includes an analysis of spleen volume by 3D volumetrics, a more accurate measurement of spleen size, and whether it significantly impacts post HCT outcomes. Our data analysis demonstrates that splenomegaly, massive or not, does not significantly impact transplant outcomes for patients receiving a reduced intensity conditioning regimen. Research Sponsor: None.

	Spleen Volume (cc)			Spleen Volume % Reduction		
	Median	Low	High	Median	Low	High
Pre HCT (N=130)	1150	41	6695	X	X	X
Post HCT (3-6 months) (N=25)	661	80	1731	47.87	23.76	154.79
Post HCT (6-9 months) (N=10)	620	252	1116	47.05	18.57	75.64
Post HCT (9-12 months) (N=11)	604	91	962	33.79	18.27	112.32

6559 Poster Session

Outcomes of older adults undergoing allogeneic stem cell transplant with post-transplant cyclophosphamide.

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Background: The two most common disease indications for stem cell transplants (SCTs) are AML and MDS, with average age of diagnoses of 71 and 68, respectively. However, SCTs historically were not offered to older adults because of the associated risks, such as graft-vs-host disease (GVHD). The use of post-transplant cyclophosphamide as an immunosuppressant has been shown to help prevent GVHD. We aimed to compare the effectiveness of GVHD prophylaxis regimens with (post-Cy) and without (non-Cy) cyclophosphamide and to identify characteristics that make patients more likely to be long-term survivors. To our knowledge, studies focusing specifically on patients aged 70+ remain very limited. **Methods:** This was a retrospective, single-institution study assessing all patients aged 70+ who received an allogeneic SCT between 2009-2023. Our main outcome was GVHD-free, relapse-free survival (GRFS) at endpoints of 1 and 5 years. We also assessed risks of developing clinically significant acute (grade III-IV) and chronic (extensive) GVHD, relapse rate, overall survival (OS), and non-relapse mortality (NRM) at one and five-year endpoints. **Results:** We evaluated 61 patients aged 70+ (median 75, IQR 5), 23 of whom were female (38%). 42 patients received GVHD prophylaxis with post-Cy and 19 patients received non-Cy regimens (18 ATG-based). Myeloid malignancies were the primary indication for transplant (85%). We stratified patients based on Disease Risk Index, with 64% of patients as intermediate risk and 33% high risk. Unrelated donors contributed 80% of allografts, and 100% of non-Cy patients had a 10/10 HLA-matched donor compared to post-Cy patients having 64% 10/10, 29% haploidentical, and 7% mismatched unrelated donors. Acute GVHD developed in 19% of post-Cy patients, compared to 26% in non-Cy (p = ns). At one year, the probability of having chronic GVHD was 12% vs 26% in post-Cy vs non-Cy patients (p = ns). Post-Cy patients had a one-year relapse rate, NRM, and OS of 2%, 52%, and 45%, respectively, whereas non-Cy patients had 5%, 26%, and 68% (p = ns). Notably, patients treated with both regimens had a similar one-year GRFS (33% post-Cy, 37% non-Cy; p = ns). At five years, OS was 19% vs 32% and GRFS was 14% vs 16% for post-Cy and non-Cy patients, respectively (p = ns). **Conclusions:** We observed similar outcomes among patients aged 70+ receiving GVHD prophylaxis with post-Cy compared to non-Cy regimens. Importantly, non-Cy patients had HLA-matched donors, whereas mismatched donors were possible for the post-Cy group. In this way, post-Cy seems to have equalized the outcomes for fully matched and non-matched SCTs by yielding a similar one and five-year GRFS. Patients without a full match would otherwise have a poor outcome. We also found no significant difference in relapse rate, NRM, OS, and five-year GRFS between patients aged 70-74 and ages 75+, showing that numerical age should not be a contraindication to SCT with post-Cy. Research Sponsor: Clinical and Translational Research Scholars Program at UMass Chan Medical School.

Effect of pre-transplant functional status on length of hospital stay in patients undergoing allogeneic hematopoietic stem cell transplant in an outpatient transplant program.

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Background: The use of reduced intensity conditioning regimens including non-myeloablative regimens in allogeneic hematopoietic stem cell transplant (allo SCT), has expanded the pool of transplant candidates in the United States. Nonetheless, allo SCT, is associated with significant morbidity and mortality especially in patients 65 and older. In our outpatient transplant program, allo SCT patients undergo a comprehensive physical and occupational therapy (PT/OT) evaluation pre-transplant. **Methods:** We retrospectively reviewed all patients undergoing an allo SCT between January 2019 and December 2022 who had a PT/OT evaluation pre-transplant. We analyzed lower extremity functional scale (LEFS) and fatigue score (FACIT). The FACIT score is a patient reported outcome tool where the lower the score, the less fatigue impacts a patient's performance. **Results:** We identified 218 patients who had at least one variable reported. Eighty-one patients were 65 years of age or older. All patients in the 65 and older group had a RIC or NMA conditioning regimen. In the 65 and older group, 72.8% had an HCTCI score of 3 or more compared to 59.1% in the group younger than 65. In patients younger than 65, those who had a lower LEFS (ie less lower extremity strength), had a statistically significant longer hospital stay of 15.5 days compared to 9 days (p=0.003). In patients 65 and older, lower FACIT scores (ie less patient reported fatigue), resulted in a statistically significant shorter hospital stay of 7.5 days compared to 13 days (p=0.019). In addition, there was a trend towards shorter hospital stays in patient 65 and older who had a higher LEFS of 5 days compared to 12.5 days (p=0.07). There was no difference in survival outcomes but there was a trend towards better overall survival in patients 65 and older with high LEFS (p=0.08) and a trend towards better NRM in this group (p=0.11). **Conclusions:** Our study highlights the need for comprehensive assessments in patients undergoing allo SCT. Geriatric functional status assessments are necessary to determine patients at risk for complications and to optimize such patients with exercise and cognitive rehabilitation programs prior to allo SCT. Research Sponsor: None.

Patient characteristics in age<65 and age≥65 groups (N=218).

	Age<65 (N=137)	Age≥65 (N=81)
Age, median (min, max)	47 (18, 64)	69 (65, 80)
Male sex	69 (50.4%)	48 (59.3%)
Diagnosis		
AML	45 (32.9%)	32 (39.5%)
ALL	40 (29.2%)	3 (3.7%)
MDS/MPS	31 (22.6%)	37 (45.7%)
Other	21 (15.3%)	9 (11.1%)
Donor type		
MRD	42 (30.7%)	18 (22.2%)
MUD	28 (20.4%)	30 (37.0%)
HAPLO	67 (48.9%)	33 (40.8%)
Cell source		
PBSC	128 (93.4%)	80 (98.8%)
BM	9 (6.6%)	1 (1.2%)
DF DRI		
Low	15 (10.9%)	3 (3.7%)
Intermediate	92 (67.2%)	59 (72.8%)
High/very high	25 (18.3%)	16 (19.8%)
N/A	5 (3.6%)	3 (3.7%)
HCT-CI		
0-2	56 (40.9%)	22 (27.2%)
≥3	81 (59.1%)	59 (72.8%)
Regimen intensity		
Myelo	89 (65.0%)	0 (0%)
Non-Myelo/RIC	48 (35.0%)	81 (100%)

Frequency of comedication of proton pump inhibitors with crystalline dasatinib in chronic myeloid leukemia and effects on TKI-bioavailability.

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Background: Tyrosine kinase inhibitors (TKI), including dasatinib, have profoundly improved clinical outcome in chronic myeloid leukemia (CML). However, solubility, bioavailability and systematic exposure of the crystalline formulation of dasatinib (Sprycel) is reduced at higher gastric pH levels. This is problematic for comedication with acid reducing agents as lower bioavailability may reduce clinical response. **Methods:** We investigated proton pump inhibitor (PPI) and TKI comedication, including dasatinib, in a large real world CML cohort. Furthermore, we assessed the influence of timing of PPI comedication on the absorption and bioavailability of dasatinib. **Results:** Using the Swedish CML- and Prescribed Drug-Registries, we identified 1,328 chronic phase CML patients, diagnosed 2002-2018. 1,261 (95%) had received specified/known TKI treatment and 685 of those (54%) were prescribed a PPI (ATC-code: "A02BC") at some point after CML diagnosis. TKIs and PPIs prescribed within 12 months of CML diagnosis were prescribed by different HCPs in 66% of cases (284/432). Of the 388 patients treated with dasatinib, 91 (23.5%) received a concomitant PPI. The PPI prescription rate increased to 53% (204/388) in the dasatinib cohort after dasatinib treatment had ended. Further, we assessed the drug-drug interaction (DDI) in 18 healthy volunteers given crystalline dasatinib (100mg) alone or together with omeprazole (40mg, at steady state) administered 9 hours apart; a time point when a high effect on bioavailability is expected. Compared to dosing with crystalline dasatinib alone, C_{max} and AUC_{0-24} were reduced by 96% and 88% by omeprazole comedication (Table). **Conclusions:** Despite warnings, comedication with PPI is common among dasatinib treated CML patients. Further, an even larger proportion of patients need PPI co-treatment, which however, cannot fully be administered due to its negative impact on dasatinib pharmacokinetics. Moreover, with an optimized study design, we observed a higher than previously reported negative interaction of PPI comedication on crystalline dasatinib bioavailability. This may compromise clinical efficacy and risk CML disease progression. For patients in need of PPI, selection of a non-crystalline, less pH-sensitive formulation of dasatinib therefore appears more appropriate. Clinical trial information: NCT06145217. Research Sponsor: Xspray; Nordic CML Study Group.

Pharmacokinetic (PK) parameters of dasatinib following crystalline dasatinib alone or with concomitant omeprazole.

PK Parameter (unit)	Least Square Geometric Means		Ratio test/ control (%)	90% Confidence Interval (%)	p (ANOVA)
	Crystalline Dasatinib	Crystalline Dasatinib + Omeprazole			
C_{max} (ng/mL)	195.02	7.17	3.7%	2.73-4.96%	0.0001
AUC_{0-24} (h*ng/mL)	734.63	84.79	11.5%	9.13-14.59%	0.0001

ANOVA: Analysis of variance, Cmax: Maximal plasma Concentration, AUC: Area Under the plasma Concentration curve.

Pharmacokinetics and safety of asciminib (ASC) in pediatric patients (pts) with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP): Interim results from the ASC4KIDS study.

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Background: For pediatric pts with Ph+ CML-CP, treatment options with improved efficacy and long-term safety are needed. ASC is a first-in-class tyrosine kinase inhibitor (TKI) Specifically Targeting the ABL Myristoyl Pocket (STAMP), approved for adults with Ph+ CML-CP treated with ≥2 prior TKIs. The phase Ib/II ASC4KIDS study (NCT04925479) aims to characterize the pharmacokinetics (PK) and long-term safety profile of ASC in pediatric pts. **Methods:** This multi-center, open-label study included pts aged 1–<18 years (yrs) with Ph+ CML-CP, without T315I mutation, treated with ≥1 prior TKIs. The primary endpoint is to characterize the PK of ASC in pediatric pts and identify a dose using the pediatric formulation (PF, taken with food) leading to an ASC exposure comparable to the adult dose and formulation (AF, 40 mg tablet twice daily [BID] fasted). Secondary endpoints include safety, molecular responses and acceptability/palatability of the pediatric formulation. In an exploratory group, pts 14–<18 yrs old were treated with the AF (fasted). In study Part 1 (dose-determining cohort), pts received PF at an initial dose of 1.3 mg/kg BID (with food) to assess ASC exposure (measured by area under the curve from dosing to the time of the last measured concentration [AUC_{last}] and maximum plasma concentration [C_{max}]) and safety. In Part 2 (dose expansion cohort), additional pts will be treated with the dose confirmed in Part 1 (across Part 1 + Part 2; 10 pts per age group: 1–<12 yrs and 12–<18 yrs, for a total of 20 pts). In Part 3, another 10 pts will be enrolled (5 pts per age group), who will receive the same total ASC dose as a once daily regimen. **Results:** 4 and 9 pts were enrolled in the Part 1 AF and PF groups, respectively. At interim data cutoff (03-Aug-2023), all pts were receiving ongoing treatment. Age ranges were 15–16 yrs (AF group) and 2–16 yrs (PF group). Averaged ASC exposure in the AF group was comparable to that observed in adults. 3/4 (75.0%) pts on ASC AF experienced adverse events (AEs); none were Grade ≥3. There were no new safety signals as compared to the known safety profile of ASC in adults. Averaged ASC exposure in the PF group was comparable to that observed in adults (median AUC_{last}: 5051 vs 5130 hr*ng/mL; median C_{max}: 711 vs 939 ng/mL, respectively). Based on these data, the PF dose of 1.3 mg/kg BID (with food) was confirmed as the pediatric dose. All pts on ASC PF experienced AEs; Grade ≥3 AEs were reported for 2/9 pts (22.2%). No predefined dose-limiting toxicities, serious AEs, or AEs leading to discontinuation were reported in either group. **Conclusions:** ASC exposure with the PF (with food) in pediatric pts was comparable to that of adult pts treated with ASC 40 mg BID (fasted); the confirmed PF dose of 1.3 mg/kg BID will continue to be tested in Part 2 of the study. ASC was safe and well tolerated in pediatric pts. Clinical trial information: NCT04925479. Research Sponsor: Novartis Pharmaceuticals Corporation; N/A.

6563 Poster Session

Cardiovascular complications associated with asciminib use: A retrospective analysis.

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Background: Asciminib, a newly developed drug, has shown promising results in the treatment of several diseases. It is a cellular tyrosine kinase inhibitor (TKI) that specifically targets ABL myristoyl pocket (STAMP) inhibitor, responsible for the malignant growth and proliferation of leukemia cells in chronic myeloid leukemia (CML) patients, assuring a positive treatment of CML. However, as with all medications, there are possible side effects that must be carefully monitored. In comparison to Ponatinib (tyrosine kinase inhibitor) which is extensively used to treat CML and exhibits a cardiovascular risk profile, cardiovascular side effects with the use of Asciminib are rarely reported in literature, prompting its use in patients at a higher risk of these events. Through this study, we aim to highlight the cardiovascular complications associated with the use of Asciminib by integrating patient experience and clinical research. **Methods:** A publicly available FDA Adverse Events Reporting System (FAERS) database was utilized to review cardiovascular events associated with the use of Asciminib in patients with Chronic Myeloid leukemia (CML) between 2018-2023. Cardiovascular events such as coronary artery disease (CAD), peripheral arterial disease (PAD), and cerebrovascular accidents (CVA) were reviewed. The study focused only on adverse events reported by healthcare providers and observed in adults (above 18 years old). **Results:** We identified a total of 563 adverse events pertaining to the use of Asciminib in patients with CML. Of which, 63 were cardiovascular events, contributing to 11.2% of the total adverse events. Out of the reported cardiovascular side effects, 29 (46%) were due to CAD, 6 (9.5%) were due to PAD, and 28 (44.45%) were due to CVA. The mortality rate amongst patients who experienced cardiovascular side effects was 11%. Moreover, cardiovascular events contributed to 7% of all mortality associated with the use of Asciminib, with CAD contributing to most of the deaths. **Conclusions:** It is imperative to consider the potential of cardiovascular events in patients initiated on Asciminib. This study emphasizes the importance of using patient records and medical research to obtain complete information. Patients with underlying risk factors for the development of cardiovascular diseases should be thoroughly evaluated before drug initiation. The minimum threshold for drug discontinuation should be considered in patients with suspected heart disease. Research Sponsor: None.

6565 Poster Session

Clinical benefit of luspatercept treatment (tx) in transfusion-dependent (TD), erythropoiesis-stimulating agent (ESA)–naive patients (pts) with very low-, low- or intermediate-risk myelodysplastic syndromes (MDS) in the COMMANDS trial.

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Background: There is an unmet need for effective tx that provides durable benefit for pts with anemia due to lower-risk MDS (LR-MDS). Here we report clinically meaningful responses to luspatercept tx in TD, ESA-naive pts with LR-MDS in the COMMANDS trial. **Methods:** Eligible pts were ≥ 18 years of age, had LR-MDS with or without ring sideroblasts and < 5% bone marrow blasts, endogenous serum erythropoietin < 500 U/L, required red blood cell (RBC) transfusions (defined as 2–6 RBC units/8 weeks [wk] for ≥ 8 wk prior to randomization), and were ESA-naive. Pts were randomized 1:1 to subcutaneous administration of luspatercept (1.0–1.75 mg/kg) once every 3 wk or epoetin alfa (EA; 450–1050 IU/kg) once weekly for ≥ 24 wk. New assessments of clinical benefit reported here include achievement and duration of ≥ 50% reduction in RBC units transfused over ≥ 12 wk (wk 1–end of tx [EOT]), transfusion burden (TB) on tx (wk 1–24), time to first transfusion, achievement and cumulative duration of all separate RBC transfusion independence (RBC-TI) ≥ 12 wk response episodes, and mean hemoglobin (Hb) increase ≥ 1.5 g/dL over wk 1–24. **Results:** As of March 31, 2023, 151/182 (83.0%) luspatercept- and 121/181 (66.9%) EA-treated pts achieved ≥ 50% reduction in RBC units transfused over ≥ 12 wk (wk 1–EOT; *P*= 0.0002), with median (95% confidence interval [CI]) durations of 130.0 (120.6–not evaluable [NE]) and 77.0 (54.9–123.1) wk, respectively (*P* = 0.0004). A greater proportion of luspatercept vs EA pts achieved ≥ 50% reduction in RBC units transfused over ≥ 12 wk (wk 1–EOT), regardless of baseline (BL) TB: 105/118 (89.0%) luspatercept vs 82/111 (73.9%) EA pts with BL TB < 4 RBC units/8 wk and 46/64 (71.9%) luspatercept vs 39/70 (55.7%) EA pts with TB ≥ 4 RBC units/8 wk. The median (interquartile range) number of RBC units transfused during wk 1–24 of tx was 1.0 (0–5.0) in the luspatercept arm and 3.0 (0–8.0) in the EA arm. The median (95% CI) time to first transfusion was 155.0 (80.0–266.0) days for luspatercept vs 42.0 (23.0–55.0) days for EA pts (*P* < 0.0001). Among pts who achieved RBC-TI ≥ 12 wk (wk 1–24), 22/124 (17.7%) luspatercept pts vs 12/88 (13.6%) EA pts achieved ≥ 2 separate RBC-TI ≥ 12 wk response episodes and cumulative median (95% CI) duration of all response episodes was 147.9 (122.0–NE) wk in the luspatercept arm and 95.1 (73.1–NE) wk in the EA arm (*P* = 0.0067). Mean Hb increase ≥ 1.5 g/dL over wk 1–24 was achieved by 135/182 (74.2%) luspatercept pts and 95/181 (52.5%) EA pts (*P* < 0.0001). **Conclusions:** Significantly greater proportions of luspatercept vs EA pts achieved improvements in Hb levels, reduction in TB and RBC units transfused, and had durable RBC-TI responses. Luspatercept provided clinically meaningful outcomes, supporting its use as the preferred tx for ESA-naive pts with LR-MDS-associated anemia. Clinical trial information: NCT03682536. Research Sponsor: Celgene, a Bristol-Myers Squibb Company, in collaboration with Acceleron Pharma, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Efficacy of imetelstat on red blood cell (RBC)-transfusion independence (TI) in the absence of platelet transfusions or myeloid growth factors in IMerge.

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Background: In the IMerge trial (NCT02598661) of RBC transfusion-dependent (TD) patients (pts) with lower-risk myelodysplastic syndromes (LR-MDS) relapsed/refractory to or ineligible for erythropoiesis stimulating agents, imetelstat showed significant efficacy vs placebo (PBO) for 8-wk, 24-wk, and 1-y TI endpoints, with neutropenia and thrombocytopenia as the most common adverse events (Platzbecker. *Lancet* 2024). Supportive care was given to all pts as needed, per investigator discretion. Here we report RBC-TI rates in the absence of platelet transfusions or myeloid growth factor use. Separately, RBC-TI with mean central hemoglobin (Hb) rise of ≥1.5 g/d was assessed in all pts. **Methods:** Pts were randomized 2:1 to receive imetelstat (n=118) 7.5 mg/kg or PBO (n=60) Q4W IV until disease progression. Primary endpoint was 8-wk RBC-TI; 24-wk RBC-TI was a key secondary endpoint. Primary analysis cutoff was Oct 2022, with Oct 2023 cutoff for 1-y RBC-TI analyses. **Results:** Overall, 21/118 (18%) pts in the imetelstat group and 1/60 (2%) pts in the PBO group needed platelet transfusions; 41/118 (35%) and 2/60 (3%) pts received myeloid growth factors, respectively. Significantly higher percentages of pts achieved 8-wk, 24-wk, and 1-y RBC-TI with imetelstat vs PBO in the absence of either platelet transfusions or growth factor support (Table). In a separate analysis, 8-wk, 24-wk, and 1-y RBC-TI and concurrent Hb rise of ≥1.5 g/dL with imetelstat vs PBO occurred in 28% vs 2%, 23% vs 0%, and 17% vs 0% of pts, respectively (Table). Among responders, imetelstat increased median central Hb levels compared with PBO: 3.6 g/dL vs 0.8 g/dL for 8-wk, 4.2 g/dL vs 1.1 g/dL for 24-wk, and 5.2 g/dL vs 1.7 g/dL for 1-y RBC-TI. **Conclusions:** Results from this subanalysis confirm that pts who achieve RBC-TI with imetelstat do so without developing severe neutropenia and thrombocytopenia (functionally defined as needing myeloid growth factors or platelet transfusions, respectively), therefore not negating the clinical benefit of the drug. Imetelstat also led to significant rise in Hb levels in RBC-TI responders, particularly long-term responders. These data further support the efficacy of imetelstat in TD pts with LR-MDS. Clinical trial information: NCT02598661. Research Sponsor: Geron Corporation.

IMerge phase 3 RBC-TI.

Pts, n (%)	8-wk TI Imetelstat	8-wk TI PBO	8-wk TI *P* value	24-wk TI Imetelstat	24-wk TI PBO	24-wk TI *P* value	1-y TI Imetelstat	1-y TI PBO	1-y TI *P* value
RBC-TI in ITT*	47 (40)	9 (15)	<.001	33 (28)	2 (3)	<.001	21 (18)	1 (2)	.002
RBC-TI + Mean Central Hb Increase ≥1.5 g/dL	33 (28)	1 (2)	<.001	27 (23)	0	<.001	20 (17)	0	<.001
RBC-TI + Platelet TI	46 (39)	9 (15)	.001	32 (27)	2 (3)	<.001	19 (16)	1 (2)	.004
RBC-TI + No Myeloid Growth Factors	46 (39)	9 (15)	.001	32 (27)	2 (3)	<.001	21 (18)	1 (2)	.002

*ITT, intent-to-treat; includes pts receiving platelet transfusions and myeloid growth factors.

6567 Poster Session

Impact of complete cytogenetic response on survival in patients with myelodysplastic syndromes.

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Background: Response to therapy prolongs survival in patients with myelodysplastic syndromes (MDS). The aim of this study is to evaluate the impact of complete cytogenetic response (CCyR) on survival in patients with MDS and abnormal cytogenetics. **Methods:** We reviewed 2311 consecutive patients with MDS and cytogenetic abnormalities who were treated at our institution from 2006 to 2023. **Results:** CCyR was observed in 330 patients (14%), complete response (CR) in 208 (9%), CR with bilineage recovery (CRbi) in 255 (11%), CR with unilineage recovery (CRuni) in 151 (7%), CR with incomplete hematologic recovery (CRh) in 4 (0.2%), and non-CR in 1363 (59%). With a median follow-up of 59 months, the median overall survival (mOS) was 14 months. Ten months for non-CR, 19 months for CRh/CRbi/CRuni, 21 months for CR, and 26 months for patients with CCyR ($p < 0.001$). With stem cell transplant (SCT) censoring, mOS was 15 months. Eleven months in non-CR, 19 months in CRh/CRbi/CRuni, 19 months in CR, and 27 months for patients with CCyR ($p < 0.001$). In low-risk MDS by the International Prognostic Scoring System (IPSS), mOS with SCT censoring was 87 months for CCyR, compared to 40 months for non-CR, 38 months for CRh/CRbi/CRuni, and 36 months for CR ($p < 0.001$). In intermediate/high-risk MDS mOS with SCT censoring mOS was 25 months in CCyR, compared to 9 months in non-CR, 15 months in CRh/CRbi/CRuni, and 17 months in CR ($p < 0.001$). In a multivariate regression analysis, age > 75 years (HR 3.1, $p < 0.001$), complex karyotype (HR 2.15, $p < 0.001$) performance status 3-4 (HR 1.48, $p < 0.001$), hemoglobin < 8 g/dL (HR 1.48, p=0.003), creatinine > 1.3 g/dL (HR 1.44, $p < 0.001$), therapy-related AML (HR 1.41, $p < 0.001$), infection at diagnosis (HR 1.34, p =0.003), white blood cells > 50 $x10^9$/L (HR 1.31, $p <0.001$), cardiac comorbidities (HR 1.26, $p < 0.001$), platelets < 20 $x10^9$/L (HR 1.26, p=0.001), pneumonia at diagnosis (1.22, p =0.006), and core-binding factor cytogenetics (HR 0.48, $p < 0.001$) were independently prognostic for survival in this select group. **Conclusions:** Achievement of CCyR in patients with MDS and abnormal cytogenetic abnormalities leads to improved survival. Given poor outcomes in older patients with MDS, CCyR can be used as a valid surrogate for long-term outcomes. Research Sponsor: Charif Souki Cancer Resarch Grant.

Time toxicity for patients receiving oral versus parenteral hypomethylating agents for myelodysplastic syndromes/neoplasms (MDS).

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Background: Patients spend substantial time receiving cancer care. Patients with higher-risk MDS treated with hypomethylating agents (HMAs) are generally older and have a median life expectancy of 11–17 months. Patients receiving parenteral treatment for MDS spend significant time in clinics receiving HMA treatment; as such, information on the time burden of treatments ("time toxicity") is needed to help clinicians guide patients and caregivers with alternative routes of administration. The development of oral HMA therapies offers a strategy that mitigates the time toxicity associated with MDS treatment by increasing the number of "home days" for patients. This study details the time burden among patients with MDS receiving oral HMA therapy versus those receiving intravenous and subcutaneous (IV/SC) HMAs. **Methods:** This was a retrospective analysis of adult patients with MDS initiating HMA therapy (oral or IV/SC HMA), using the US Cerner Enviza claims database (08/2020–08/2022). Propensity score matching (1:1) was performed on the treatment groups to balance confounding factors; matched cohorts were analyzed (N=158 each). The total direct healthcare encounter days for oral and IV/SC HMA administered patients were evaluated based on the number of healthcare encounter days spent on parenteral HMA administration (0 days for oral HMAs), outpatient, inpatient, and emergency room (ER) visits, and infusion days. Only distinct encounter days were included in the total count; multiple visits in a day were de-duplicated. Mean (SD) healthcare days for oral versus IV/SC HMA groups were calculated for each type of healthcare encounter and summarized. **Results:** Patients receiving oral HMA incurred a mean total of 15.2 healthcare encounter days compared with 32.8 days for those receiving IV/SC HMAs (Table). Most encounter days for the oral HMA cohort were in the outpatient setting (34.9%) while most encounters for the IV/SC HMA cohort were attributed to receiving parenteral HMA administration (55.5%), followed by inpatient (16.2%) and outpatient visits (14.9%). **Conclusions:** This study, which is the first report to date of time toxicity in MDS among patients treated with HMA therapy, revealed that patients receiving oral HMA incurred half the time burden of those receiving IV/SC HMAs. Further research is warranted to validate these results in a larger patient cohort and compare these findings with other cancer therapies. Research Sponsor: Taiho Oncology, Inc.

Healthcare encounters among patients receiving HMAs.

Healthcare encounters – mean (SD) days	Oral HMA (N=158)	IV/SC HMAs (N=158)
Parenteral administration of HMA	0	18.2 (11.4)
Outpatient visits	5.3 (8.1)	4.9 (8.1)
ER visits	0.3 (0.8)	0.2 (0.8)
Hospital overnight stays	4.3 (9.3)	5.3 (11.9)
Red blood cell transfusions	3.5 (4.4)	3.0 (4.7)
Platelet transfusions	1.7 (4.6)	1.1 (3.0)
Other infusions	0.1 (0.8)	0.1 (0.7)
Combined encounters	15.2 (16.3)	32.8 (22.2)

Impact of frailty on patients hospitalized with myelodysplastic syndrome: A nationwide analysis.

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Background: Myelodysplastic Syndrome (MDS) is a complex group of neoplasms that arises from abnormalities in the bone marrow's hematopoietic stem cells, leading to ineffective blood cell production. Frailty signifies increased vulnerability to internal and external stressors, with its impact on survival in MDS gaining recognition. We conducted a retrospective analysis to explore the impact of frailty on hospitalized MDS patients and its association with unfavorable hospital outcomes. **Methods:** National Inpatient Sample (NIS) 2019 and 2020 was utilized to identify the patients admitted with a primary diagnosis of MDS and had a concurrent diagnosis of Frailty. The Primary outcome was Mortality, and secondary outcomes included length of stay, total cost of hospitalization, and other adverse in-hospital outcomes. Multivariate logistic regression analysis was used to calculate the outcomes after adjusting for baseline sociodemographic characteristics. **Results:** A total of 17,000 patients were admitted with a primary diagnosis of MDS, among whom 4,285 (25.20%) patients had a concurrent diagnosis of Frailty. The mean age of patients with and without Frailty was 75.75 (+/-14.01) and 71.54 (+/-14.68), respectively, $p<0.001$. After adjusting for confounding variables, Frailty was considered an independent predictor of mortality in MDS patients (OR=1.80 (1.22-2.64); p=0.003). Patients with Frailty had a prolonged length of stay in the hospital (8.62 days(3.2-9.6) without and 11.56 days (4.6-12.1) with Frailty, $P<0.001$), as well as an increased total cost of hospitalization ($ 132159 (3256-23651) without and $173898 (5317-389146) with Frailty, $p<0.001$). Additionally, Frailty was associated with an increased likelihood of sepsis (OR=2.02 (1.33-3.06); p=0.001), acute kidney injury (OR=1.22 (1.02-1.50); p=0.04), major depressive disorder (OR=1.51 (1.19-1.91); p=0.001), and a higher association with chemotherapy (OR=3.46 (1.21-9.91); p=0.021) and palliative care (OR=2.23 (1.72-2.90); $p<0.001$). However, frail patients were less likely to receive blood transfusions (OR=0.73 (0.61-0.88); p=0.001), and no difference was noted in the risk of platelet transfusions (OR=0.95 (0.73-1.25); p=0.763). **Conclusions:** Frailty is considered an independent predictor of mortality and is associated with increased healthcare resource utilization along with other adverse in-hospital outcomes. Careful and thorough identification of frailty and its effective management is crucial for improving outcomes, reducing mortality, and enhancing the quality of life for patients with debilitating MDS. Research Sponsor: None.

Outcomes	MDS with and without Frailty
Length of stay without Frailty	8.62 days (3.2-9.6), $p<0.001$
LOS with Frailty	11.56 days (4.6-12.1), $p<0.001$
Total charges without Frailty	$ 132159 (3256-23651), $p<0.001$
Total charges with Frailty	$173898 (5317-389146), $p<0.001$
	OR (95% CI)
Mortality	1.80 (1.22-2.64); p=0.003

A phase I study of the myeloid cell leukemia 1 (MCL1) inhibitor tapotoclax (AMG 176) in patients with myelodysplastic syndromes after hypomethylating agent failure.

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Background: Though hypomethylating agent (HMA) therapy is standard for patients (pts) with myelodysplastic syndromes (MDS), once pts are refractory to or no longer respond to HMA therapy (i.e. HMA failure), survival remains dismal and treatment options non-existent. Tapotoclax directly induces apoptosis in cells dependent on MCL1 for survival. Given preclinical data establishing MCL1 as a promising target in MDS, we hypothesized that tapotoclax may be safe and clinically active in pts with HMA failure MDS. **Methods:** We designed a phase I study evaluating the safety and tolerability of tapotoclax (NCT05209152). Adult pts with HMA failure MDS (no response after ≥4 HMA cycles or progression/relapse at any time on HMAs) were eligible. Using a standard modified Toxicity Probability Interval design, all pts received intravenous tapotoclax every 7 days with each cycle lasting 28 days in the exploratory dose-finding portion. **Results:** Between 10/2022-12/2023, 4 pts received tapotoclax 120 mg/m^2 and 3 pts 240 mg/m^2. Pts were overall very high risk and heavily pre-treated with a median of 4 lines of therapy. The median number of cycles of tapotoclax received was 3. No dose-limiting toxicities (DLTs) were observed. The most common treatment-related adverse events (AEs) were nausea (85%), fatigue (43%), diarrhea (29%), and palpitations (14%). Regarding cardiac AEs, 1 pt experienced arrhythmias that were possibly related to tapotoclax but self-resolved. One pt had prolonged QTc intervals but had similar prolongation prior to tapotoclax exposure. No clinically-significant troponin elevations were observed. No pts responded, and this trial was terminated due to lack of clinical activity. Three pts (43%) were taken off study due to no response, 1 (14%) to proceed to stem cell transplantation, 1 (14%) from recurrent peritoneal cancer, 1 (14%) due to transformation to acute myeloid leukemia, and 1 (14%) from an unrelated death due to infection. However, 2 of 3 pts (67%) who started the clinical trial with BM blasts ≥ 5% underwent transient but unsustained blast reduction after cycle 3. All pts were transfusion-dependent with red blood cells (RBCs) at the time of clinical trial enrollment, but 5 pts (71%) decreased RBC transfusions by ≥2 units between cycle 1-2 and 1 individual (14%) attained transfusion independence for 7 weeks. **Conclusions:** This phase 1 study demonstrated that tapotoclax was safe and tolerated in a high-risk cohort of pts with MDS after HMA failure. No DLTs were observed, and cardiac AEs self-resolved without dose reductions. Though no pts responded, some pts experienced transient blast reduction and decreased RBC transfusion burden. Given its manageable toxicity profile and transitory anti-leukemic and transfusion-independent effects, the use of tapotoclax in combination with HMA or other therapies may warrant further consideration. Clinical trial information: NCT05209152. Research Sponsor: Amgen.

Long-term survival adjusted for treatment crossover in patients (pts) with myelofibrosis (MF) treated with momelotinib (MMB) vs danazol (DAN) in the MOMENTUM trial.

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Background: Anemia and transfusion dependence affect nearly all pts with MF and are associated with poor prognosis.The phase 3 MOMENTUM trial (NCT04173494) evaluatedMMB—a JAK1, JAK2, and ACVR1 inhibitor—vs DAN (2:1 randomization) in JAK inhibitor (JAKi)–experienced pts with MF and anemia who had symptoms and splenomegaly. While MMB showed spleen, symptom, and anemia benefits vs DAN at wk 24, comparative estimates of long-term overall and leukemia-free survival (OS and LFS) are confounded and may underestimate the MMB effect, as all pts in the DAN arm who entered the open-label phase of the trial crossed over to receive MMB at wk 24. We used a rank-preserving structural failure time (RPSFT) model to estimate the OS and LFS that might have been observed without crossover. **Methods:** This exploratory analysis evaluated survival over the entire MOMENTUM trial period; most pts entered an extended access study (NCT03441113) after wk 48. The RPSFT model assumes that treatment slows the speed of disease progression and death proportionally regardless of time of crossover. Analyses were conducted with and without recensoring, and CIs were constructed to appropriately account for additional model fitting uncertainty. **Results:** As of December 29, 2022, 38 (29%) and 20 (31%) deaths had occurred in the MMB and DAN arms, respectively. Risk of death was reduced with MMB vs DAN by 11% (HR, 0.89) with no crossover adjustment, and by 22% (HR, 0.78) and 13% (HR, 0.87) using the RPSFT model with and without recensoring, respectively. Similarly, 40 (31%) and 22 (34%) LFS events had occurred at data cutoff in the MMB and DAN arms, respectively. Risk of an LFS event was reduced with MMB vs DAN by 20% (HR, 0.80) with no crossover adjustment, and by 36% (HR, 0.64) and 23% (HR, 0.77) using the RPSFT model with and without recensoring, respectively (Table). **Conclusions:** Consistent with the original unadjusted survival analysis, RPSFT models adjusting for the effects of treatment crossover showed prolonged OS and LFS in pts initially randomized to MMB vs those initially randomized to DAN; HRs in favor of MMB were lower after crossover adjustment. While these RPSFT analyses maintain the significance level of the original unadjusted analysis ($P>.05$), these results support the trend of long-term survival benefits with MMB vs DAN in JAKi–experienced pts with MF and anemia. Clinical trial information: NCT04173494. Clinical trial information: NCT03441113. Research Sponsor: GlaxoSmithKline.

Survival	HR (95% CI)[a]
OS	
Original (unadjusted)[b]	0.890 (0.504-1.572) (P=.688)
RPSFT	0.870 (0.442-1.713)
RPSFT (recensored)	0.780 (0.232-2.620)
LFS	
Original (unadjusted)[b]	0.804 (0.466-1.386) (P=.432)
RPSFT	0.769 (0.400-1.480)
RPSFT (recensored)	0.636 (0.206-1.965)

[a]95% CI derived for RPSFT models via the ITT method (standard error inflated to match the P value of the original unadjusted result).
[b]HR from a stratified Cox proportional hazards model with a single factor of treatment group by study stratification factors.

Long term follow-up results of phase II clinical trial evaluating ruxolitinib (RUX) and azacitidine (AZA) combination therapy in patients (pts) with myelofibrosis (MF).

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Background: Monotherapy with JAK inhibitors improve spleen and symptom burden in MF, but their disease modifying effect is less clear. We conducted a phase 2 clinical trial evaluating the combination of RUX with hypomethylating agent AZA in MF. The interim analyses (Masarova *et al.*Blood, 2018) showed objective responses in 72% pts. We report the long-term follow-up of the full cohort of pts treated on this trial. **Methods:** The trial was conducted at MD Anderson Cancer Center, Houston including adult pts (≥ 18 years) with MF intermediate (Int) 1-2 or high-risk disease by Dynamic International Prognostic Scoring System (DIPSS). Responses were assessed per the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria. **Results:** From 3/2013-10/2021, 61 pts with a median age of 66 yrs (46-87) were treated (Table). Median Hb was 10.1 g/dl (6.8-16.2), and bone marrow blasts (BM) 2% (0-14%); 14 (23%) had BM blasts ≥ 5%. *JAK* 2 was mutated in 35 (57%); 38 pts (62%) had Int-2 or high risk DIPSS disease. IWG-MRT responses occurred in 44 pts (72%): clinical improvement (CI) in 37 (61%), including IWG-MRT CI spleen reduction >50% in 28/46 pts (61%) with baseline length ≥5 cm below left costal margin, and 31/51 pts (61%) with baseline TSS>12 having a >50% improvement in total symptom score (TSS 50). Partial response was seen in 4 pts and cytogenetic complete remission in 3 pts. With a median follow up of 93 mos, median overall survival (OS) was 46 mos (95% CI: 25-66), median event free survival was 33 mos (95% CI: 24-43) and median duration of any objective response was 43 mos (95% CI: 24-62). Transformation to AML occurred in 14 pts (23%) with median time to transformation of 19 mos (1-46). 20 pts (33%) received a stem cell transplant (SCT), 11 (55%) with Int-2/high risk DIPPS disease. Pts in the Int-2/high risk DIPPS group who got SCT had a trend towards improved median OS vs. those who did not (38 vs 27 mos, p=0.2). Grade ≥ 3 adverse events (AE) regardless of treatment attribution occurred in 30 pts (49%), most common were pneumonia (10,16%), anemia (7,12%), and sepsis (5, 8%). 3 pts had grade 5 AEs, and 4 pts were taken off study due to toxicity. **Conclusions:** Long term follow up data from this phase 2 clinical trial shows good efficacy of the AZA-RUX combination in MF, with durable responses and promising survival outcomes. Clinical trial information: NCT01787487. Research Sponsor: Incyte pharmaceuticals; MD Anderson Cancer Center; CA016672, CA100632; Charif Souki Cancer Research Fund; MD Anderson Moon Shots Program.

Baseline characteristics.

Parameters		N (%), median [range]
Age (years)	Age	66 [46-87]
	> 65	32 (53)
Males		38 (62)
Performance Status	ECOG<2	59 (97)
Clinical Splenomegaly ≥ 5 cm		46 (75)
Baseline blood and BM	Hb (g/dl)	10.1 [7-16]
	WBC (10^9/L)	12.1 [2-61]
	Platelet (10^9/L)	271 [63-1070]
	BM blasts (%)	2 [0-14]
EUMNET fibrosis grade	MF-1	5 (8)
	MF-2	27 (44)
	MF-3	28 (46)
	NA	1 (2)
Cytogenetics	Diploid	32 (53)
	Complex	7 (12)
	Others	20 (33)
	NA	2 (3)
Driver mutational profile	*JAK2*	35 (57)
	CALR	8/27 (30)
	MPL	6/45 (13)
DIPSS	Int-1	23 (38)
	Int-2	25 (41)
	High	13 (21)

6573 Poster Session

Efficacy and safety of ruxolitinib in patients with lower risk myelofibrosis: A single-arm, exploratory and prospective study.

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Background: The COMFORT studies assessed the efficacy and safety of ruxolitinib in patients with intermediate-2 and high risk myelofibrosis (MF), and JUMP study has broadened the investigation including patients with intermediate-1 MF in the classification of DIPSS. However, there have been limited prospective studies evaluating the efficacy and safety of patients with low risk MF in the classification of more comprehensive scoring system. Here we present a single-arm, exploratory and prospective study to assess the efficacy and safety of ruxolitinib in patients with lower risk MF in China. **Methods:** Lower risk was defined as MIPSS-70 $\leq$ 3, MIPSS+V2.0 $\leq$ 3, DIPSS-Plus $\leq$ 1, DIPSS $\leq$ 2 or MYSEC-PM $<$ 14 according to the expert guidelines. Patients aged $\geq$ 18 with overt primary myelofibrosis (overt-PMF), prefibrotic primary myelofibrosis (pre-PMF), post-polycythemia vera myelofibrosis (post-PV MF) or post-essential thrombocythemia myelofibrosis (post-ET MF), classified as lower risk were enrolled. The primary endpoint was the proportion of patients with a spleen length reduction of $\geq$ 50% from baseline at week 48. Secondary endpoints included the best spleen response, the proportion of patients with a $\geq$ 50% reduction in Total Symptom Score (TSS50) and safety. **Results:** A total of 40 patients were enrolled in the lower risk group, including 7 pre-PMF, 17 overt-PMF, 8 PPV-MF, and 8 PET-MF patients. The median age was 62.0 years. 32 (80%) were JAK2V617F positive. 16 patients had next generation sequencing (NGS), the most frequent non-driver mutation was in TET2 (43.8%), followed by BCOR (12.5%). By week 48, 26 (65.0%) patients achieved a $\geq$ 50% decrease in palpable spleen length. 32 (80.0%) patients achieved a $\geq$ 50% reduction from baseline at any time. The median time to a spleen response was 4.3 weeks. The TSS50 rates at week 48 was 25%. No patients required red blood cell transfusion at baseline. And only 1 patient had a baseline hemoglobin (HB) $<$ 100 g/L, which remained stable during the follow-up process. The most common grade $\geq$ 3 hematological treatment emergent adverse events (TEAEs) were anemia (10.0%) and thrombocytopenia (2.5%). 6 (15.0%) and 15 (37.5%) patients experienced grade 1 or 2 anemia and thrombocytopenia, respectively. The mostly common non-hematological TEAEs was infection (12.5), including upper respiratory tract infection (7.5%), urinary infection (2.5%), fever (2.5%), predominantly of grade 1 or 2. Of note, 1 patient developed staphylococcal sepsis and 1 patient experienced acute renal failure. No one discontinued ruxolitinib treatment due to TEAEs. **Conclusions:** Ruxolitinib is an effective treatment for patients with intermediate-1 and low risk MF, resulting in improved spleen and symptom responses, along with fewer hematological and non-hematological TEAEs. This trial was registered as ChiCTR2200064250 at ClinicalTrials.gov. Clinical trial information: ChiCTR2200064250. Research Sponsor: Key R&D Program of Zhejiang; No. 2022C03137; Public Technology Application Research Program of Zhejiang, China; No. LGF21H080003; Zhejiang Medical Association Clinical Medical Research special fund project; No. 2022ZYC-D09.

Association between hemoglobin (Hb) improvement and patient-reported outcomes (PROs) in patients (pts) with myelofibrosis (MF) and anemia: Post hoc pooled analysis of momelotinib (MMB) phase 3 trials.

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Background: Pts with MF experience debilitating symptoms that negatively impact health-related quality of life (HRQOL), a burden compounded in those with anemia. Prior analysis of the phase 3 SIMPLIFY-1 (S1) and SIMPLIFY-2 (S2) trials found that achieving transfusion independence at wk 24 was associated with improved PROs, but the association of anemia severity by Hb level with PROs was inconclusive (Mesa, ASCO 2023, Poster 7066). This new post hoc analysis explored the impact of Hb improvement on PROs in pts with MF and anemia. **Methods:** The pooled treatment-agnostic analysis set included pts with anemia (baseline [BL] Hb <10 g/dL) from 3 phase 3 trials: S1 (JAK inhibitor [JAKi] naive; MMB vs ruxolitinib), S2 (JAKi experienced; MMB vs best available therapy), and MOMENTUM (JAKi experienced; MMB vs danazol). The EQ-5D-5L was administered, and health state index (UK value set) and visual analog scale (VAS) scores derived, in all 3 trials. Patient Global Impression of Change (PGIC) was administered in S1/S2. Hb improvement was defined as an increase of ≥1, ≥1.5, or ≥2 g/dL from BL at wk 24. Multivariate (MV) analyses included change in EQ-5D-5L scores from BL as the dependent variable, with wk 24 Hb improvement and key BL characteristics as independent variables. **Results:** Mean age of the anemic subpopulation (N=480) was 68.8 y; 62% were male, 81% were White, and 64% had primary MF.436 pts were evaluable for Hb improvement at wk 24; 298 and 297 were evaluable for EQ-5D-5L index and VAS scores, respectively. Mean improvements from BL in index and VAS scores were greater in pts who achieved Hb improvement at any threshold than in those who did not (Table). 241 pts were evaluable for Hb improvement at wk 24 in S1/S2; 215 were evaluable for PGIC. Hb improvement was associated with a higher percentage of pts with any symptom improvement and lower percentage with symptom worsening based on PGIC (Table). In MV analyses, Hb improvement at any threshold was significantly associated with positive change in EQ-5D-5L VAS scores at wk 24 (mean change estimates of 5.5 to 7.3); similar trends were observed in MV analyses for EQ-5D-5L index scores. **Conclusions:** In these trial populations, Hb improvement at wk 24 was associated with improved HRQOL and symptoms in pts with MF and anemia. These results highlight the value of treatments with anemia-related benefits in improving the pt experience in MF. Clinical trial information: NCT04173494; NCT02101268; NCT01969838. Research Sponsor: GlaxoSmithKline.

Hb improvement, g/dL	≥1		≥1.5		≥2	
	Yes	No	Yes	No	Yes	No
Change from BL in EQ-5D-5L score at wk 24, mean (SD)[a]	(n=193)	(n=243)	(n=134)	(n=302)	(n=89)	(n=347)
Index	0.06 (0.2)	0.02 (0.2)	0.06 (0.3)	0.03 (0.2)	0.07 (0.3)	0.03 (0.2)
VAS	9.9 (18.9)	4.3 (21.2)	11.2 (19.7)	5.0 (20.3)	11.8 (20.8)	5.7 (20.0)
PGIC in MF symptoms at wk 24, %	(n=102)	(n=139)	(n=67)	(n=174)	(n=38)	(n=203)
Improvement	89	71	90	75	91	77
No change	6	15	8	12	6	12
Worsening	4	14	2	13	3	11

[a]Positive change = improvement.

Association of elevated pulmonary artery systolic pressure with hematologic progression in myeloproliferative neoplasms.

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Background: Pulmonary hypertension (PH) is associated with myeloproliferative neoplasms (MPN), including essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF). Prior studies have suggested that patients with MPN and cardiovascular disease (CVD) with PH are at increased risk of progression of MPN to secondary MF or acute leukemia. Further characterization of risk of hematologic progression among all-comers with MPN is lacking. **Methods:** In this single-center, retrospective cohort study, patients with MPN and ≥ 1 transthoracic echocardiogram (TTE) after diagnosis were identified. PH was defined as an estimated pulmonary artery systolic pressure (PASP) ≥ 40 mmHg on first TTE after MPN diagnosis. Primary outcome was hematologic end-point, composite of progression of MPN to secondary MF, acute leukemia, death related to MPN, or bone marrow transplantation (BMT). Secondary endpoint was major adverse cardiovascular events (MACE), composite of arterial thrombosis, venous thromboembolism, heart failure (HF) and CV death. Multivariable Fine-Gray competing-risk regression (with non-hematologic death and non-CV death as competing-risks for hematologic endpoint and MACE, respectively) were used to estimate risk of outcomes. **Results:** Of 272 patients with MPN identified, 69 (25.4%) had PH on first TTE. Patients with PH were older at MPN diagnosis, had more MF (27.5% vs 11.8%, p = 0.004), and prior HF (18.8% vs 6.4%, p = 0.004). Patients with PH had higher rates of secondary mutations (24.6% vs 13.3%, p = 0.024), particularly in *ASXL1* (8.7% vs 2.5%, p = 0.034) and *RUNX1*(4.3% vs 0, p = 0.016). After a median follow-up of 46.2 months (IQR 29.3, 69.1), hematologic endpoint (30.4% vs 8.4%, $p < 0.001$ and MACE (53.6% vs 23.6%, $p < 0.001$) were higher in PH group. Rates of secondary MF (13.0% vs 4.9%, p = 0.030), acute leukemia (13.0% vs 0.5%, $p < 0.001$), and death related to MPN (8.7% vs 1.5%, p = 0.01) but not BMT (2.9% vs 3.4%, p = 1.00) were higher in PH. After adjusting for age, sex, MPN type, mutation, and time from MPN to first TTE, PH was associated with higher risk of hematologic endpoint (aSHR 3.70, 95% CI 1.55 – 8.82). After adjusting for the same variables as well as LVEF, left atrial size, prior CVD, PH was associated with increased risk of MACE (aSHR 2.38, 95% CI 1.42 – 3.97). **Conclusions:** Among patients with MPN, PH on TTE was associated with increased risk of hematologic progression and MACE. Prospective studies are needed to confirm our findings. Further investigation into the underlying mechanisms of PH in MPN should be conducted. Research Sponsor: None.

	No PH by PASP N = 203	PH by PASP N = 69	P value
Age at MPN, median (IQR)	67 (56, 76)	73 (66, 82)	< 0.001
Female	110 (54.2)	32 (46.4)	0.27
Non-White Race, N (%)	30 (14.8)	15 (21.7)	0.19
MPN Type			0.007
PV	89 (43.8)	27 (39.1)	
ET	90 (44.3)	23 (33.3)	
MF	24 (11.8)	19 (27.5)	
***JAK2*Mutation**	149 (73.4)	56 (81.2)	0.35
Prior CVD	98 (48.3)	45 (65.2)	0.018

Bromodomain and extra-terminal (BET) inhibitor INCB057643 in patients with relapsed or refractory myelofibrosis (MF) and other advanced myeloid neoplasms: A phase 1 study.

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Background: In a previous phase 1/2 clinical trial, the small-molecule oral BET inhibitor INCB057643, as monotherapy and with ruxolitinib (RUX), had favorable tolerability and encouraging clinical activity in patients (pts) with advanced malignancies. **Methods:** This ongoing phase 1, 3+3 dose-escalation/expansion study (NCT04279847) evaluates INCB057643 (4 mg → 12 mg once daily [qd]) in adults as (1) monotherapy (part 1) in relapsed/refractory (R/R) MF, myelodysplastic syndromes (MDS), or MDS/myeloproliferative neoplasm (MPN) overlap syndromes (MDS/MPN) or (2) added to RUX (part 2) in pts with MF and suboptimal response to RUX. Primary endpoints are safety/tolerability. Secondary endpoints in pts with MF include spleen volume response (SVR35; ≥35% reduction from baseline [BL] at Wk 24), symptom response (TSS50; ≥50% reduction from BL at Wk 24 in MPN-Symptom Assessment Form Total Symptom Score), and anemia response (hemoglobin increase ≥1.5 g/dL from baseline [if transfusion independent at BL] or achieving transfusion independence [if dependent at BL] for ≥12 wk). **Results:** As of 6NOV2023 data cutoff, 18 pts were treated in part 1 (4 mg, n=6; 6 mg, n=1; 8 mg, n=4; 10 mg, n=5; 12 mg, n=2), and 11 in part 2 (4 mg, n=5, 6 mg, n=6). In part 1, median (range) age was 70 (50–79) years and study treatment duration was 175 (15–504) d; in part 2, pt age and treatment duration were 70 (50–76) y and 127 (23–369) d, respectively. 24 pts overall had MF. 5 pts discontinued treatment due to treatment emergent adverse events (TEAEs; 4 with monotherapy). Thrombocytopenia was the most common TEAE (n=15) and most common leading to discontinuation (n=4). Grade ≥3 TEAEs occurred in 19 pts, most commonly thrombocytopenia (n=8) and anemia (n=6). Serious AEs occurred in 6 pts; all but 1 (pneumonia) was considered unrelated to study treatment. There were 2 dose-limiting toxicities with 12 mg monotherapy and 1 with 6 mg combination therapy (hyperbilirubinemia, n=1; thrombocytopenia, n=2). No treatment-related fatal TEAEs have occurred. At Wk 24, SVR35 was achieved by all 3 evaluable pts receiving ≥10 mg monotherapy, and 3/12 achieved a best response of SVR35. In the combination group, 1/5 evaluable pts achieved Wk 24 SVR35 and 1/7 achieved best response of SVR35. Best response of TSS50 was achieved by 6/10 evaluable monotherapy pts (3/4 receiving doses ≥10 mg) and 6/11 combination therapy pts. Anemia response occurred in 2/15 monotherapy pts. **Conclusions:** INCB057643 monotherapy (4–10 mg qd) and combined (4 and 6 mg qd) with RUX was generally well tolerated, with no treatment-related fatal events. Improvements in spleen size and symptom burden were observed in both the monotherapy and combination therapy groups. Dose finding is complete for monotherapy and dose escalation is ongoing in the combination therapy group. Clinical trial information: NCT04279847. Research Sponsor: Incyte Corporation.

Impact of pacritinib on symptoms in with thrombocytopenia and myelofibrosis who require red blood cell transfusion.

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Background: Patients (pts) with myelofibrosis (MF) and anemia experience negative impact on both quality of life and prognosis. Pacritinib (PAC), a JAK2/IRAK1/ACVR1 inhibitor, has demonstrated clinically and statistically significant improvement in transfusion requirements in pts with MF who required red blood cell (RBC) transfusion at baseline in the phase 3 study, PERSIST-2. Here, we evaluate the impact of PAC versus best available therapy (BAT), including ruxolitinib (RUX), on symptom burden in pts with baseline RBC transfusions. **Methods:** This analysis focused on PERSIST-2 pts who randomized ≥12 weeks (for efficacy analyses ≥22 weeks) prior to study termination on PAC 200 mg twice daily or BAT (including RUX) and required RBC transfusions. The proportion of pts who achieved transfusion independence response (TI-R, any 12-week interval with no RBC transfusions) by week 24 was determined for each group. Symptom improvement was measured by Total Symptom Score (TSS; version 2.0, excluding tiredness) and Patient Global Impression of Change (PGIC) at week 24. Statistical testing using Fisher Exact test was performed for PAC vs BAT. **Results:** The analysis included 3 groups: 35 pts on PAC, 34 on BAT, and 13 of whom were on RUX. Baseline characteristics were similar amongst these groups, including median platelet count (45 vs 45 vs 43 x 10^9/L) and hemoglobin (8.5 vs 8.7 vs 8.6 g/dL) respectively. More than 50% of pts in each group had prior JAK inhibitor exposure. The median total daily RUX dose was 10 mg at week 24. A significantly greater proportion of pts treated with PAC vs BAT achieved ≥50% TSS response (31% vs 9%, *P*=0.034), with only 15% of pts achieving TSS response on RUX. Of the 11 PAC pts with TSS response, 6 (54.5%) also achieved TI-R. By contrast, none of the TSS responders on BAT achieved TI-R. A similar trend for ≥50% TSS response was observed in pts with baseline platelets <50 x 10^9/L with PAC (24%) vs BAT (10%) or RUX (11%). TSS reduction on PAC was primarily due to reductions in both spleen- and cytokine-related symptoms. Physical function-related symptoms (not included in the total score) also showed a higher median % reduction on the PAC arm compared to BAT (tiredness: 37% vs 13%; inactivity: 30% vs 4%). In addition, a higher proportion of pts reported symptoms at week 24 as "very much" or "much" improved (PGIC) with PAC (37%) compared to BAT (9%, *P*=0.009), including RUX (8%). Pts experiencing ≥1 treatment emergent grade 3 anemia was similar in the PAC (17.1%) and BAT (16.3) groups. No pts in the PAC group reported ≥1 treatment emergent grade 3 fatigue compared to 5% in BAT. **Conclusions:** PAC has previously demonstrated improvement in symptoms in pts with MF. These findings are consistent in showing that PAC compared to BAT or low dose RUX provides substantial symptom benefit in those pts who require RBC transfusions. PAC could therefore be a potential option to address an unmet need for this patient population. Clinical trial information: NCT02055781. Research Sponsor: Sobi Inc.

Efficacy of pacritinib in patients with myelofibrosis who have both thrombocytopenia and anemia.

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Background: Both thrombocytopenia and anemia pose treatment challenges in myelofibrosis (MF). When these two cytopenias co-occur ("bicytopenia"), management becomes particularly challenging, and appropriate treatment selection is critical to optimize efficacy while minimizing myelosuppressive side effects. Pacritinib (PAC) is a JAK1-sparing inhibitor of JAK2/IRAK1/ACVR1 that has been studied at full dose in patients (pts) with MF regardless of baseline thrombocytopenia or anemia. Here, we present data on spleen and symptom benefit in PAC-treated pts with moderate or severe bicytopenia. **Methods:** Pts treated with PAC 200 mg twice daily or best available therapy (BAT) on PERSIST-2 with bicytopenia at baseline (platelet count <100 x10^9/L and hemoglobin <10 g/dL) were included. This group was retrospectively analyzed for spleen volume reduction (SVR) $\geq$35%, total symptom score (TSS; version 2.0, excluding tiredness) reduction of $\geq$50%, Patient Global Impression of Change (PGIC), median dose intensity, and transfusion independence response (TI-R). TI-R was assessed among pts who required red blood cell (RBC) transfusion at baseline (within 90 days) and defined as the absence of RBC transfusions over any 12-week period through 24 weeks (Gale criteria). Baseline characteristics are presented in the safety population (pts randomized $\geq$12 weeks prior to study end and treated); efficacy is presented in the intention-to-treat efficacy population (pts randomized $\geq$22 weeks prior to end of study). Statistical testing was performed using Fishers Exact Test for efficacy endpoints. **Results:** Among 46 pts on PAC and 47 on BAT, baseline characteristics were generally similar between groups respectively: median age (65 vs 68 years), platelet count (46 vs 46 x10^9/L), and hemoglobin (8.4 vs 8.6 g/dL). A lower percentage of pts in PAC than BAT were receiving RBC transfusions (59% vs. 77%) and had prior JAK inhibitor exposure (43% vs 55%). Most pts treated with PAC were able to maintain full doses over time, with median actual dose intensity for PAC being 400 mg/day. A total of 45% of pts in the BAT group received ruxolitinib (median last total daily dose: 10 mg). In the PAC group, 20% (8/40) had SVR $\geq$35% compared to 0% (0/38) in the BAT group (P=0.0054). Similarly, 32.5% of the pts in the PAC group had $\geq$50% reduction of TSS compared to 10.5% of pts in the BAT group (P=0.0274). PGIC response (patient-reported symptoms "very much" or "much" improved) at week 24 was greater in the PAC group (30%) compared to BAT (13.2%; P=NS). Among the 27 pts on PAC and 36 on BAT who received RBC transfusions at baseline, 26% of pts on PAC and 8% of pts on BAT achieved TI-R (P=0.0838). **Conclusions:** PAC at full dose demonstrates efficacy for spleen, symptoms, and transfusion response in pts with MF and both thrombocytopenia and anemia. These findings suggest PAC may be an effective option to address the unmet need for pts with MF and bicytopenias. Clinical trial information: NCT02055781. Research Sponsor: None.

Real-world treatment patterns and outcomes in patients with myelofibrosis treated with pacritinib in the United States.

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Background: Pacritinib (PAC), a JAK1 sparing JAK2/IRAK1/ACVR1 inhibitor, has shown clinically significant activity in spleen volume and symptom reduction in patients (pts) with thrombocytopenic myelofibrosis (MF). Thrombocytopenic MF is challenging to manage and pts with platelets (PLT) <50 x10^9/L have limited median overall survival (OS) of 15 months (mo) (Masarova 2018). Since approval as the only agent for thrombocytopenic MF, real-world evidence of PAC use is limited. This study aims to assess treatment patterns, hematological outcomes, and survival in pts with MF treated with PAC in the US. **Methods:** For this retrospective study, Integra-PrecisionQ de-identified database was used to locate pts with MF (ICD-10: 75.81, D47.4) treated with PAC from 6/1/2022 to 8/31/2023. Treatment-related outcomes include PLT and hemoglobin (Hb) levels from PAC initiation (index) and 30-day intervals post-index. OS was assessed from index through the end of the study period. Data are presented as medians and interquartile ranges (IQR). **Results:** 142 pts with MF were treated with PAC, the majority being male (60%) or White (66%), with a median age at MF diagnosis of 72 years and median of 13.4 mo from diagnosis to index. In pts receiving $\geq 2^{nd}$ line (2L) PAC (65.5%), the median time from the end of prior MF therapy to PAC initiation was 1 day. Median follow up from index was 6 mo and median exposure to PAC during the observation period was 5.3 mo. In pts with PLT and Hb levels at index and follow up, 28.5% (34/119) had severe thrombocytopenia (PLT<50 x10^9/L) at index and 29% (35/119) had severe anemia (Hb <8.0 g/dL). Median PLT count was 81 x10^9/L (47.5,179) at index (n=119) and 96 x10^9/L (68.5,125) at post-index day 360 (n=15). Median Hb level was 8.8 g/dL (7.9,10.3) at index (n=119) and 10.4g/dL (9.2,11.6) at post-index day 360 (n=15). Increases in PLT and Hb were observed across index PLT and Hb groups over follow up (Table 1). 1-year OS probability was 69.4% (95% CI=56.8-79.0) overall, 77.3% (95% CI=61.5-87.3) in pts treated with 1L PAC, and 75.2% (95% CI=46.3-90.0) for pts treated with 1L PAC with PLT <50 x10^9/L. **Conclusions:** In addition to spleen and symptom benefits, real-world outcomes demonstrate stability or improvement in thrombocytopenia and anemia in MF pts treated with PAC, with OS in the 1L setting comparing favorably with other JAK inhibitor historical controls. Research Sponsor: Sobi Inc.

	N	PLT <50	N	PLT 50-100	N	PLT >100	N	Hb <8	N	Hb ≥8
Index	34	26 (21, 40.5)	40	72.5 (63.5, 87)	45	246 (158, 418)	35	7.2 (6.9,7.7)	84	9.6 (8.8, 10.8)
Day 30	30	33 (21, 54)	36	79.2 (59.5, 103.5)	36	201.5 (121.5, 344)	31	8 (7.2,8.9)	71	9.9 (8.5, 10.7)
Day 90	22	35.5 (18.3, 54.5)	24	93.5 (74, 108.5)	32	249.5 (140.5, 372)	23	8 (7.3, 8.8)	56	10 (8.5, 11.1)
Day 180	19	47 (23, 64)	24	94 (57.8, 122.5)	25	201 (123, 308)	22	7.9 (7, 8.7)	58	9.8 (8.5, 11.1)
Day 360	6	76 (59.3, 84.5)	4	113 (105, 121.5)	5	142 (68, 258)	4	8.7 (8.3, 9)	11	11.2 (10.1, 11.9)

A phase Ib, open-label study of add-on therapy with CK0804 in participants with myelofibrosis and suboptimal response to ruxolitinib.

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Background: Suboptimal response to JAK2 inhibitor ruxolitinib in patients with myelofibrosis (MF) remains a major unmet medical need. Deregulated inflammatory pathways including CXCR4/CXCR12 axis might limit the therapeutic efficacy of ruxolitinib and contribute to disease progression. In preclinical studies, cord blood-derived, CXCR4 enriched T regulatory cells [CK0804; T-regs] showed ability to suppress inflammatory cytokines playing major role in MF (Huang et al., Cytotherapy, 2023). **Methods:** This phase Ib study evaluates the safety and activity of up to 6 doses of CK0804 (non-HLA matched, Cryopreserved) T-regs therapy, fixed dose of 100 million cells, added every 28 days to ruxolitinib. Patients with MF on ruxolitinib for ≥12 weeks and stable dose for ≥8 weeks, who have palpable splenomegaly, symptoms, or grade 2 cytopenia are eligible. Primary objective is safety, secondary objective is overall response per IWG-MRT criteria at 24 weeks. Present analysis includes cohort of initial run-in safety phase. **Results:** Nine patients of median age 68 years (range, 55-84) were enrolled, 44% were males. Median blood counts [range] showed while blood cells 10.6 [3.1-70.4] x10^9/L, hemoglobin 8.8 [7.8-11.5] g/dL, platelets 177 [148-311] x10^9/L. Three patients were transfusion dependent. Median spleen volume was 1449 cubic centimeters (176-5609), 7 patients (78%) had clinically worsening splenomegaly. Median symptoms score (MPN-SAF TSS) was 23 (20-40). Six (67%) had diploid karyotype, 5 (56%) had JAK2 mutation and 8 (89%) had additional no-driver mutations. Median duration of prior ruxolitinib was 35 months (range, 10-132), all patients were on ≥ 10 mg twice daily dose with no dose change throughout the study. Four patients received all six doses of CK0804, three patients have ongoing treatments. One patient experienced infusion reaction to second dose of CK0804 likely due to the excipient dimethylsulfoxide and withdrew consent. One patient died of unrelated cause prior to the infusion 6. There were no nonhematologic or hematologic adverse events. Two transfusion dependent patients who were evaluable for response had decreased monthly need for transfusions by the end of the sixth cycle: 4 to 2.8 units and 1.2 to 0.8 units, respectively. All patients noticed symptoms improvement; median best decline in MPN-SAF TSS was -38% (range, -20% to -71%); with ≥ 50% reduction in 3 patients. One patient achieved ≥ 35% spleen volume reduction at week 12. Longitudinal analysis of markers of inflammation is in progress and will be presented at the conference. **Conclusions:** This preliminary analysis of run-in phase of study evaluating CXCR4 enriched T regs cell therapy as addition to ruxolitinib shows initial safety with no myelosuppressive adverse events and promising clinical activity. Active enrollment of participants to the expansion cohort is ongoing. Clinical trial information: NCT05423691. Research Sponsor: National Cancer Institute; P30 CA016672.

6581 Poster Session

Trends in the thrombotic complications of myeloproliferative neoplasms: A nationwide analysis.

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Background: Thrombotic complications are a well known cause of morbidity and mortality in Philadelphia-negative Myeloproliferative Neoplasms[Polycythemia Vera, Essential thrombocythemia, Primary Myelofibrosis]. Current study evaluated thrombotic events incidence and outcome trends in Myeloproliferative Neoplasms[MPN] from 2012 to 2020. **Methods:** This is a longitudinal study of thrombotic events in MPN using the Nationwide Inpatient Sample. All patients with a diagnosis of MPN admitted with any thrombotic event including arterial or venous thrombosis were included in the study. Arterial thrombotic events included Myocardial infarction[MI], Ischemic stroke[IS], Transient Ischemic Attack[TIA] while venous thrombotic events included Deep Vein Thrombosis[DVT], Pulmonary Embolism[PE], Budd-Chiari Syndrome[BCS], Portal Vein Thrombosis[PVT]. Thrombosis related inpatient mortality rate, incidence, length of hospital stay, and total hospital charges were calculated. **Results:** Mortality rate from any thrombotic event overall[arterial plus venous] increased from 2.3% to 2.6% from 2012 to 2020. There was an increase in mortality rates from 2.8% to 3.8% among arterial thrombosis while there was a decrease in venous thrombosis related mortality from 1.7 to 0.4%. Specifically MI and IS related mortality increased from 3.7% to 4.3% and 3% to 4% respectively over the same period. The incidence of any thrombotic event declined from 2 to 1.3 cases/100,000 persons from 2012 to 2020. A similar decline in incidence of arterial, venous events, MI, IS were observed. The mean length of stay decreased from 5.8 days in 2012 to 5.2 days in 2020 among MPN patients with venous thrombosis which was statistically significant. Similar decline was noted in MI patients as well. Though the mean length of stay increased from 7.9 to 9.5 days among MPN patients with IS, this increase was not statistically significant. The mean hospitalization charges for thrombotic events increased from $53,421 in 2012 to $101,598 in 2020 after adjusting for inflation. Similar trends were noted in all types of thrombotic admissions which were all statistically significant. Upon age based stratification of MPN, mortality for those less than 60 years reduced from 2% to 0.3%, while it increased from 4.1 to 5.6% in those more than 60 years from 2012 to 2020. **Conclusions:** Inpatient mortality from thrombotic events in MPN has shown an increasing trend from 2012 to 2020 though there was a decline in overall incidence of thrombosis during the same period. Despite the decreasing trend in length of stay, the total economic burden of thrombotic complications in MPN is increasing in the US. Specifically the effects were more pronounced in those greater than 60 years. This points to the need for revisiting guidelines regarding thromboprophylaxis in MPN. Research Sponsor: None.

Predictors of symptom scores in myeloproliferative neoplasms: A real-world retrospective cohort study.

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Background: Although high symptom burden indicates poor survival and informs treatment decisions, little is known about the impact of demographic, clinical, and laboratory features on total symptom score (TSS) in patients with myeloproliferative neoplasms (MPN). **Methods:** Patients with MPN (polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF)) were identified from the retrospective chart review. TSS, individual symptom scores (fatigue, early satiety, abdominal discomfort, inactivity, concentration problems, fever, night sweats, itching, bone pain, weight loss), demographic characteristics (race, ethnicity, age, gender), clinical features (time since diagnosis, depression status, obesity status, spleen size), laboratory results and season at the time of visit were recorded from the clinical encounter when index assessment of TSS was performed for each patient. Normality was assessed using visual inspection of data distribution, whereas multicollinearity was assessed using various inflation factors. A univariable regression followed by a multivariable regression analysis was conducted using a backward selection approach. A p-value <0.05 indicated a statistically significant association of a given feature with TSS. **Results:** The chart review identified 252 patients (PV: 78; ET: 81; MF: 93). Mean age was 59 (SD: 17.7), 67 (SD: 13.0), and 68 (SD: 10.9) years for ET, PV, and MF respectively. Most patients were white (PV, MF: 92%; ET: 83%) and females (ET: 75%; PV: 60%; MF: 53%). The TSS of patients was highest with PV (mean: 18.5; SD: 16.9) followed by MF (mean: 18.1; SD: 15.4) and ET (mean: 14.3; SD: 15.9). Fatigue was the most reported symptom whereas the least reported symptoms were fever and weight loss. Univariable regression analyses showed depression (B: 17.7; p=0.02), female gender (B: 10.6; p=0.01), platelet count (B: 0.03; p=0.03), and hemoglobin (Hb) (B: -2.6; p=0.01) in PV patients, depression (B: 19.8, $p=2x10^{-5}$) in ET patients and depression (B: 11.0, p=0.03), white blood cell (WBC) count (B: 0.2; p=0.01), neutrophil count (B: 0.3, p=0.01), and non-neutrophil WBC count (B: 0.6; p=0.02) in MF patients to have significant association with TSS. Multivariable regression analyses (*Table*) showed Hb (B: -2.5; p=0.01) and platelet count (B: 0.02; p=0.03) in PV patients, depression (B: 19.7; $p=2x10^{-5}$) in ET patients and depression (B: 12.3, p=0.01) and WBC count (B: 0.3; p=0.002) in MF patients to have a significant association with TSS. **Conclusions:** Depression in ET and MF and low Hb in PV were identified as significant drivers of symptom burden. Identifying and managing patients with these comorbidities could improve their quality of life with a potential survival benefit. Research Sponsor: None.

MPN	Variable	Coefficient (B)	p-value
PV	Hemoglobin	-2.5	0.01
	Platelet count	0.02	0.03
ET	Depression (vs no depression)	19.7	$2x10^{-5}$
MF	Depression (vs no depression)	12.3	0.01
	WBC count	0.3	0.01

6583 Poster Session

Meta-analysis of mutational site-specificity and concordance/discordance characteristics of myeloid sarcoma.

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Background: Myeloid sarcoma (MS) is an atypical, extramedullary manifestation of acute myeloid leukemia. Next-generation sequencing (NGS) studies have explored mutational profiles of MS tumor sites and bone marrow (BM) samples. However, site-specific molecular patterns and mutational concordance/discordance between MS sites and BM remain unclear. **Methods:** Relevant studies about MS retrieved from a Pubmed search (1999-2023) with information about MS site involvement and NGS data were included. With R software, a meta-analysis (MA) of descriptive data, MS tumor site, mutations, and mutational concordance/discordance was performed to obtain pooled prevalence estimates using the Freeman-Tukey double arcsine transformation, inverse variance, and random effects model. MA of median age was pooled using the methods of McGrath et al. (2023). Meta-regression (MR) was performed with mixed-effects model. Chi-square test was used for statistical analysis of categorical variables. **Results:** 87 patients with MS from 10 studies were identified. Median age was 53 years (95% confidence interval [CI]: 48-56), and MS was more common in males (pooled estimate of 67%, 95% CI: 54.8-78.5). Skin was the most common site involved in MS with random effects pooled estimate of prevalence of 39.4% (95% CI: 20.8-59.3), followed by lymph node (10.1%, 95% CI: 1.8-21.8), bone (5%, 95% CI: 0.2-13.3), and soft tissue (2.4%, 95% CI: 0-9.5). Pooled estimates of most common mutated genes were *NPM1* (20.3%, 95% CI: 6.2-38), *FLT3* (18.3%, 95% CI: 5.5-34.6), *TP53* (8.4%, 95% CI: 1.8-17.7), *NRAS*(6.6%, 95% CI: 0.9-15.4), and *IDH2* (4.3% 95% CI: 0-13.4). *NPM1* (13/34), *FLT3* (7/34), and *IDH2* (6/28) were enriched in cutaneous MS. *KIT* was exclusively enriched in non-cutaneous MS (8/53) compared to cutaneous MS (0/34) ($p = 0.017$). Although the prevalence of small bowel MS was low ($n = 3$), *FLT3* was mutated in all cases ($p < 0.01$). Comparing MS tumor site to BM, pooled prevalence of mutation concordance was similar to discordance (49.8% [95% CI: 34.4-65.1] and 50.2% [95% CI: 34.9-65.6], respectively). Most common concordant mutations were *FLT3* (5/28) and *NRAS* (5/28). *NPM1* and *FLT3* were most common discordant mutations and enriched in MS tumor sites ($p < 0.01$ and $p < 0.05$, respectively). *NPM1* was a discordant mutation in MS tumor site only. Univariate MR of cutaneous MS found no significant influence from male sex and mutational concordance/discordance. Multivariate MR showed significant interaction with males and mutational discordance toward cutaneous MS ($p < 0.01$). **Conclusions:** Our meta-analysis highlights potential site-specific and mutational disparities in MS. Knowledge about such differences may allow the use of targeted therapies against different molecular aberrations, emphasizing the need to sequence both BM and MS sites. Findings suggesting interaction of male sex and mutational discordance in cutaneous MS needs further validation. Research Sponsor: None.

6584 Poster Session

Genomic evolution of patients with myeloid neoplasms and known antecedent clonal hematopoiesis.

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Background: Clonal hematopoiesis (CH) refers to the clonal expansion of hematopoietic stem cells (HSCs) with one or more somatic mutations in the absence of a hematologic malignancy. Although it is associated with normal aging, CH confers an increased risk of several comorbidities and hematologic malignancies, including myeloid neoplasms (MNs). However, the outcomes of patients with CH that transformed to MN are unknown. Here, we aim to evaluate the clinicopathologic characteristics and survival outcomes of patients with MN with known antecedent CH. **Methods:** We retrospectively evaluated patients seen at a tertiary cancer center from May 2016 to July 2023 with myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML), or acute myeloid leukemia (AML) and identified those who had CH prior to MN diagnosis. At the time of MN transformation, genomic data was extracted from whole bone marrow aspirate samples and subject to 81-gene target PCR-based sequencing using a next-generation sequencing platform. **Results:** A total of 36 patients were identified; at the time of CH diagnosis, 79% had known cardiovascular comorbidities and 81% had a prior diagnosis of non-myeloid malignancies for which 72% received prior chemotherapy and 25% radiation. According to the Clonal Hematopoiesis Risk Score (CHRS), 22% were low, 56% deemed intermediate, and 22% at high risk of transformation to MNs. The most frequently observed CH-associated mutations were TET2 (41%), TP53 (38%), IDH2 (16%), EZH2 (16%), ASXL1 (13%), and DNMT3A (13%); 69% had more than one somatic mutation, and 61% had normal cytogenetics. The median time to transformation to MN was 15 months, 26 months, and 24 months for MDS (n=28), CMML (n=2), and AML (n=6) patients, respectively (p=0.72). The median overall survival from MN diagnosis was 54 months, not reached, and 2 months for MDS, CMML, and AML, respectively (p=0.0015). We further delved into the genomic evolution from CH to MN. In the 6 pts who transformed to AML, 4 had a TP53 mutation at CH with expansion of the clone at MN transformation, 2 acquired NPM1 mutations and 1 acquired FLT3 mutations. Both pts who progressed to CMML had expansion of their underlying CH clones (KRAS and ZRSR2). In those who developed MDS, 22 pts had expansion of their CH-mutated clone at the time of MN, most frequently in TET2 (36%), IDH2 (18%), and TP53 (14%); 5 pts acquired new driver mutations outside of their CH clone; and 1 pt lost their CH clone with no new somatic mutations detected. **Conclusions:** Individuals with CH are at risk of progressing to MN, especially with external selective pressures like antineoplastic therapy that are not accounted for in prognostic systems like CHRS. Patients often have underlying high-risk clones at the time of CH diagnosis that expand at the time of MN, though some patients acquired new driver mutations. Research Sponsor: None.

TPS6585 Poster Session

A phase 1b/2 study of pivekimab sunirine (PVEK, IMGN632) in combination with venetoclax/azacitidine for patients with newly diagnosed CD123-positive acute myeloid leukemia.

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Background: Despite improved outcomes with azacitidine (AZA) and venetoclax (VEN) in newly diagnosed (ND) unfit acute myeloid leukemia (AML), only a subset of patients (pts) respond (CR 37%; CR/CRi 66%) and long-term survival remains inadequate (mOS <15m, DiNardo NEJM 2020). The measurable residual disease (MRD)-negative rate was 41% in AZA-VEN treated pts in VIALE-A which was associated with improved survival (Pratz JCO 2022). CD123 is expressed on the majority of AML blasts and leukemic stem cells while minimally expressed on normal hematopoietic stem cells (Kovtun Blood Adv 2018). Pivekimab sunirine (PVEK, IMGN632) is an antibody-drug conjugate comprising a high-affinity CD123 antibody, cleavable linker, and an indolinobenzodiazepine pseudodimer (IGN) payload. The IGN payload alkylates DNA and causes single strand breaks without crosslinking. IGNs are designed to have high potency against tumor cells, while demonstrating less toxicity to normal marrow progenitors than other DNA-targeting payloads. Clinical data from the first 50 pts in the dose expansion cohorts 1 and 2 with ND AML demonstrated a 76% (22/29) MRD negativity rate (by flow cytometry, negativity threshold <0.1%) (Daver ASH 2023), supporting the continued enrollment of the PVEK+AZA+VEN triplet and further evaluation of the regimen's antileukemia activity and safety in consideration of potential registration-enabling trials. **Methods:** This is an open-label, multicenter, phase 1b/2 study of PVEK administered in a combination with AZA+VEN in pts with ND CD123-positive (CD123+ by flow cytometry or IHC) AML, with no prior treatment with hypomethylating agents (HMA). Pts will receive the recommended phase 2 dose of PVEK 0.045 mg/kg IV as a < 30-minute outpatient infusion on day 7, AZA 75 mg/m^2 SC or IV daily on days 1 to 7, and VEN 400 mg PO daily for up to 28 days in a 28-day cycle. During cycle 1, a bone marrow evaluation at or around day 21 is required to inform VEN dose duration. Current eligibility criteria for continued enrollment of AML patients unfit for intensive chemotherapy include age ≥ 75 years old, or age < 75 years old with ECOG 2-3, or at least one defined comorbidity. The primary study objectives are to assess antileukemia clinical activity (composite CR [complete remission] rate, overall response rate, duration of remission) and MRD-negativity rates. Key secondary objectives are safety and tolerability, pharmacokinetics and immunogenicity. The PVEK+AZA+VEN triplet in pts with ND unfit AML is currently enrolling across sites in France, Germany, Italy, Spain, UK and USA. Clinical trial information: NCT04086264. Research Sponsor: ImmunoGen, Inc.

TPS6586 **Poster Session**

A first-in-human phase 1, multicenter, open-label study of CB-012, a next-generation CRISPR-edited allogeneic anti-CLL-1 CAR-T cell therapy for adults with relapsed/refractory acute myeloid leukemia (AMpLify).

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Background: CAR-T cell therapies have shown significant clinical benefit in treating adults with many hematologic malignancies. In acute myeloid leukemia (AML), a challenge in the development of CAR-T cell therapies has been the limitation of suitable target antigens since many are also expressed on hematopoietic stem cells (HSCs). The target antigen C-type lectin-like molecule-1 (CLL-1) has emerged as an attractive therapeutic target due to its expression on AML mature blasts and leukemic stem cells and its absence on HSCs. CB-012 is an allogeneic CAR-T cell therapy that targets CLL-1. CB-012 is derived from healthy donor T cells by using Cas12a CRISPR hybrid RNA-DNA (chRDNA) technology to introduce 5 genome edits: (1) *TRAC* gene knockout (KO), which eliminates T cell receptor expression to reduce the risk of graft-versus-host disease, (2) site-directed insertion of a fully human anti-CLL-1 CAR into the *TRAC* locus, (3) KO of PD-1 to enhance antitumor activity by reducing T cell exhaustion, (4) β2-microgobulin (*B2M*) gene KO, which eliminates HLA class I presentation to mitigate host T cell-mediated rejection, and (5) site-directed insertion of a B2M–HLA-E-peptide fusion into the *B2M* locus to reduce NK cell-mediated rejection. In murine xenograft models of AML, CB-012 significantly reduced the tumor burden and increased the survival of mice bearing CLL-1^{+}PD-L1^{+} tumors. **Methods:** CB-012 is being evaluated in a multicenter, Phase 1 clinical trial in patients with relapsed/refractory (r/r) AML. A 3+3 dose escalation design is being utilized with the primary objectives to determine the safety and tolerability of CB-012 and the recommended Phase 2 dose (RP2D). An expansion phase will follow dose escalation at the recommended dose(s) for expansion. Additional objectives include preliminary antitumor activity and pharmacokinetics. Key inclusion criteria include nonproliferative disease defined as ≤25% blasts in the bone marrow and peripheral blood, ECOG performance status ≤1, and adequate organ function. After receiving lymphodepletion therapy with cyclophosphamide (750 mg/m^2/d) and fludarabine (30 mg/m^2/d) administered concurrently for 3 days followed by a 2-day break, patients receive a single-dose infusion of CB-012 and are followed for safety and efficacy. The dose escalation portion of the study is actively enrolling patients. The AMpLify trial is registered at clinicaltrials.gov (NCT06128044). Clinical trial information: NCT06128044. Research Sponsor: Caribou Biosciences, Inc.

TPS6587 Poster Session

A phase 1 single-arm, open-label study of emavusertib (CA-4948) in combination with azacitidine and venetoclax in patients (pts) with acute myeloid leukemia (AML) in complete response (CR) with measurable residual disease (MRD).

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Background: Emavusertib is a novel potent oral inhibitor of interleukin-1 receptor-associated kinase 4 (IRAK4) with additional inhibitory activity against FMS-like tyrosine kinase 3 (FLT3) and CDC-like kinases (CLK1/2/4). Inhibition of these 3 onco-proteins by emavusertib may address the unmet need for novel therapies in AML. Clinical studies with emavusertib monotherapy have demonstrated a significant reduction in AML blasts with clinical and molecular responses in pts with relapsed or refractory AML (Metzeler 2022). Azacitidine + venetoclax (aza+ven) is an approved therapy for newly diagnosed pts with AML, unfit for intensive chemotherapy. Pre-clinical studies have demonstrated that emavusertib in combination with aza+ven has synergistic and antileukemic effects. In the VIALE-A study, composite CR (CRc) (CR, CRh, or CRi) in the absence of MRD of <1 residual blast/1000 leukocytes (MRD negative [MRD−]) resulted in longer duration of response (DOR), event-free survival, and overall survival (OS) compared with AML pts who achieved CRc but were MRD+ (Pratz, 2022). Therefore, adding emavusertib to aza+ven in CR or CRh, MRD+ pts may convert MRD status without significant toxicity and become a potential new regimen in front-line therapy. **Methods:** This is a single-arm, open-label Phase 1 study of emavusertib in combination with first line aza+ven in AML pts $\geq$60 years of age who achieved CR or CRh with MRD+ status based on local testing. The primary objective is to determine a safe and tolerable dosing schedule for the triple combination. Secondary objectives include determining the MRD conversion rate, pharmacokinetics, DOR, and OS. The study will enroll approximately 24 pts at 5 to 10 sites globally. Pts will have received aza+ven as first line therapy and achieved CR or CRh after 1-6 cycles of aza+ven. If MRD status remains positive, emavusertib will be added to the existing aza+ven regimen. Key exclusion criteria include residual toxicities and significant comorbidities. In the first cohort, the starting emavusertib dose is 200 mg BID for 7 days per cycle of 28 days. The duration of emavusertib treatment will extend to 14 and 21 days, in subsequent cohorts. The pts will continue triple treatment (emavusertib+aza+ven) until consent withdrawal, disease progression, intolerable toxicity, or not achieving MRD- after 6 cycles of treatment. Enrollment to cohort 1 began in December 2023. (EU CT Number 2023-505828-58). Clinical trial information: 2023-505828-58. Research Sponsor: None.

TPS6589 **Poster Session**

Covalent-103: A phase 1, open-label, dose-escalation and expansion study of BMF-500, an oral covalent FLT3 inhibitor, in adults with acute leukemia (AL).

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Background: FLT3 mutations occur in 25-35% of AML and result from an internal tandem duplication (ITD) of amino acids in the juxtamembrane domain of FLT3 kinase or point mutations in the tyrosine kinase domain (TKD). FLT3-ITD mutations are associated with increased relapse, shorter remission, and decreased disease-free and overall survival. BMF-500 is a novel oral, highly potent and selective covalent inhibitor of FLT3 including wild-type (WT), ITD, TKD, and resistance mutations (e.g., gatekeeper F691). BMF-500 has high affinity for FLT3, lack of cKIT inhibition, and sustained cell-killing despite drug washout (Law et al., ASH 2022 Abst 2756). BMF-500 shows sustained tumor regression and improved survival in subcutaneous and disseminated xenografts of FLT3-m AML. **Methods:** COVALENT-103 (NCT05918692) is a multicenter, first-in-human study evaluating the safety, tolerability, and antileukemic activity of escalating doses of daily BMF-500 in patients with relapsed or refractory (R/R) AL, including AML, ALL, or MPAL, with or without FLT3-m. The trial has 2 arms that dose escalate in parallel: Arm A (without) and Arm B (with) concomitant use of a CYP3A4 inhibitor. Using an accelerated titration design (ATD), doses of BMF-500 are escalated in single-subject cohorts until one subject experiences ≥Grade 2 related adverse event or dose-limiting toxicity (DLT). At that point, the cohort will switch to a classical "3 +3" design. Patients with WT FLT3 AL may enroll up to 33% per arm. Treatment continues in 28-day cycles until progression or intolerability. Expansion cohorts will enroll additional patients to obtain further safety and efficacy data. Patients must be refractory, relapsed or have progressed on or following discontinuation of the most recent anti-cancer therapy or be ineligible for any approved standard of care, including hematopoietic stem cell transplant (HSCT). FLT3-positive AML patients must have received a FLT3 inhibitor approved for R/R FLT3-m AML. Additional inclusion criteria include ECOG PS ≤2, adequate organ function, and documented FLT3 mutation status. Key exclusion criteria include known CNS disease, clinically significant cardiovascular disease, and WBC >50,000/μL (uncontrollable with cytoreductive therapy). The primary objective is to evaluate safety and tolerability and determine the optimal biological dose (OBD)/ recommended Phase 2 dose (RP2D) of BMF-500 monotherapy based on available pharmacokinetic/pharmacodynamic (PK/PD), safety and efficacy data. Secondary objectives include characterization of the PK/PD of BMF-500, and assessment of its antitumor activity per modified Cheson (2003) criteria or NCCN Clinical Practice Guidelines (ALL Version 1.2022) as determined by the investigator. The study was initiated in July 2023, is currently in dose escalation, and we plan to enroll approximately 110 patients total. Clinical trial information: NCT05918692. Research Sponsor: None.

TPS6590 **Poster Session**

A first-in-human, phase 1, dose escalation study of SGR-2921 as monotherapy in patients with relapsed/refractory acute myeloid leukemia or myelodysplastic syndrome.

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Background: Cell division cycle 7-related protein kinase (CDC7) is a cell cycle kinase that maintains DNA replication by phosphorylation and activation of the minichromosome maintenance protein 2 and 4 (MCMs), components of the replicative DNA helicase. Due to the CDC7's central role in maintaining replication fork integrity, chemical inhibition of CDC7 can ultimately lead to cancer cell death. SGR-2921 is an oral, small molecule inhibitor of CDC7. Preclinical studies demonstrate that SGR-2921 has potent anti-proliferative activity in AML cell lines representative of difficult to treat patient populations, agnostic of serious mutations (including those with p53 mutations), BTK resistance, and multiple prior lines of treatment. This anti-tumor activity has also been demonstrated in cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) AML models. **Methods:** This is a phase 1, FIH, open-label, single-agent, two-arm, dose escalation study (NCT#05961839) designed to evaluate safety and tolerability and identify the recommended phase 2 dose (RP2D) of SGR-2921 as monotherapy in subjects with relapsed or refractory (R/R) AML, high risk (HR) MDS, or very high risk (VHR) MDS. The study utilizes an accelerated titration design with single patient cohorts that transitions to a 3+3 design once a single Grade 2 event is observed. This is a multicenter global study (US, Spain and France). SGR-2921 will be administered orally, once daily, utilizing a 5-day on and 9-day off dosing schedule over a 28-day cycle. A maximum of 144 patients will be enrolled into dose escalation and exploratory cohorts. To evaluate the effect of CYP3A4 inhibition on SGR-2921 exposure, subjects will be enrolled into one of two staggered, parallel study treatment arms, according to concomitant administration with (Arm B) or without (Arm A) azole antifungals that are strong CYP3A4 inhibitors. A single dose PK run-in will be required for subjects enrolled into the first 3 cohorts of each treatment arm. Subjects will be treated at increasing doses of SGR-2921 until the maximum tolerated dose (MTD) is exceeded. A RP2D will be selected from one of the tolerable dose levels. Key study inclusion criteria include: Age $\geq$ 18 years of age; Life expectancy $\geq$ 8 weeks; Confirmed diagnosis of R/R AML or HR and VHR MDS; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2. Key study exclusion criteria include: Active malignancies not related to AML or MDS within two years prior to the first dose or requiring ongoing treatment; active CNS leukemia; QTcF $\geq$470 msec. The primary objectives are to evaluate the safety and tolerability of SGR-2921 as monotherapy and to identify the RP2D. Secondary objectives include evaluating SGR-2921 pharmacokinetics and investigating preliminary antitumor activity. Clinical trial information: NCT05961839. Research Sponsor: Schrodinger.

TPS6591 Poster Session

Phase 1b trial of IRAK 1/4 inhibition for low-risk myelodysplastic syndrome refractory/resistant to prior therapies.

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Background: Chronic stimulation of both the interleukin-1 receptor (IL-1R) and toll-like receptors (TLRs) in myeloid progenitors is thought to promote a proinflammatory environment in the bone marrow that causes persistent cytopenia in patients with low-risk myelodysplastic syndrome (LR-MDS). The serine/threonine kinases IRAK1 and IRAK4 are critical for the signaling downstream of IL-1R and most TLRs promote production of proinflammatory cytokines and NLRP3 inflammasome-driven pyroptosis, leading to bone marrow inflammation and cell death. IRAK1/4 is a potential target for inhibition for the treatment of LR-MDS by decreasing inflammation and cell death within the bone marrow, allowing for restoration of hematopoiesis. R289 is a prodrug for R835, a potent and selective inhibitor of IRAK1 and IRAK4 kinases. The safety and pharmacokinetic properties of R289/R835 were evaluated in a phase 1 study in healthy volunteers (Study C-906289-001). R289 was well tolerated with no serious or severe adverse events (AEs) reported. Most AEs were mild and transient; the most common AEs (mild/moderate) were headache and GI disturbance. Overall, the study supported the further evaluation of R289. An open-label, phase 1b study to determine the tolerability and preliminary efficacy of R289 for patients with LR-MDS refractory to prior therapies is currently enrolling patients. **Methods:** The R289 phase 1b open label, single arm, multi-center study (NCT05308264) includes a dose escalation phase (up to 24 patients) and a dose expansion phase (up to 10 patients). Inclusion criteria for both phases: patients ≥18 years with a definitive diagnosis of LR-MDS. Exclusion criteria include prior MDS treatment(s) within 4 weeks of study treatment. Dose Escalation Phase: A 3+3 dose escalation design will be used to determine the maximum tolerated dose (MTD). An initial R289 dose of 250 mg qd, will be given orally, with or without food, progressing to 1 g qd with dose limiting toxicity (DLT) assessed at each dose level. The DLT evaluation period will be 28 days. After completion, patients without DLTs may remain at their respective dose levels if clinical benefit continues without toxicity. Dose Expansion Phase: R289 will be administered to up to 10 additional patients with LR-MDS at a dose not exceeding the MTD in the dose escalation phase. The primary endpoint is safety and tolerability of R289. Secondary endpoints include preliminary efficacy and pharmacokinetics of R289. Statistical analyses will be primarily descriptive. The trial is currently ongoing at 9 US sites. Clinical trial information: NCT05308264. Research Sponsor: Rigel Pharmaceuticals, Inc. (Contact person: Leslie Todd).

TPS6592 **Poster Session**

VERIFY: A randomized controlled phase 3 study of the hepcidin mimetic rusfertide (PTG-300) in patients with polycythemia vera (PV).

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Background: PV is a myeloproliferative neoplasm characterized by overproduction of red blood cells and increased risk of thrombosis. Patients may require frequent therapeutic phlebotomies (TP) alone or in combination with cytoreductive therapy to maintain hematocrit (HCT) <45%. Hepcidin regulates iron homeostasis but is downregulated in PV, increasing iron availability for erythropoiesis, which complicates TP optimization. In a phase 2 study (REVIVE, NCT04057040), rusfertide led to rapid, sustained, and durable HCT control with over 90% of patients achieving TP independence in part 2.[1] It was well tolerated; majority (77.1%) of treatment-emergent adverse events (TEAEs) had a maximum grade of 2. There were no Grade 4 or 5 TEAEs. The phase 3 study VERIFY (NCT05210790) aims to confirm efficacy and safety of rusfertide in patients with PV. **Methods:** VERIFY is a multicenter, global, randomized trial comparing efficacy and safety of rusfertide (starting dose: 20 mg subcutaneously once weekly) vs. placebo when added to ongoing therapy for PV. Patients with PV who require frequent TP with or without concurrent cytoreductive therapy to control HCT are included in this 3-part study: Part 1a: 1:1 randomized, double-blind, placebo-controlled, add-on parallel-group period lasting 32 weeks (Week 0-32); Part 1b: open-label treatment phase with cross-over for previous placebo-treated patients. During this phase, all patients who completed Part 1a successfully will receive rusfertide for 20 weeks (Week 32-52); and Part 2: long term extension phase where all patients who complete Part 1b will continue to receive rusfertide for 104 weeks (Week 52-156). **Results:** Major inclusion criteria prior to randomization include PV diagnosis by 2016 WHO criteria; ≥3 TP in the previous 28 weeks or ≥5 in the previous 12 months due to inadequate HCT control; HCT <45%, white blood cells 4-20 $\times 10^9$/L and platelets 100-1000 $\times 10^9$/L at Week 0; stable PV therapy regimen in patients receiving cytoreduction at randomization; and cessation of cytoreductive therapy 2-6 months before screening in patients treated with TP alone. Major exclusion criteria are thrombosis or bleeding (active and/or chronic) within 2 months before randomization and a history of invasive malignancy within the previous 5 years. Primary endpoint is the proportion of patients achieving a response in Part 1a from Week 20-32. A response is defined as absence of TP eligibility. TP eligibility: HCT ≥45% and ≥3% higher than baseline HCT or HCT ≥48%. Secondary endpoints are mean number of TPs from Week 0-32; proportion of patients with HCT <45% from Week 0-32; mean change from baseline to Week 32 in total fatigue score measured by PROMIS Short Form and in total symptom score measured by MFSAF v4.0. **Conclusions:** VERIFY opened in January 2022 and aims to enroll approximately 250 patients globally. Reference: 1. Ritchie EK, et al. *Blood.*2023; 142(Suppl 1):745. Clinical trial information: NCT05210790. Research Sponsor: Protagonist Therapeutics, Inc. [Contact person: Katharina Modelska].

TPS6593 Poster Session

Phase 2 study evaluating selinexor monotherapy in patients with JAKi-naïve myelofibrosis and moderate thrombocytopenia.

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Background: While multiple JAKi therapies are approved in myelofibrosis, thrombocytopenia, which commonly occurs in myelofibrosis and is associated with poor outcomes, is an on-target side effect; use of suboptimal ruxolitinib doses used to manage adverse effects leads to reduced efficacy. In a Phase 1 study (NCT04562389) of selinexor, an investigational XPO1 inhibitor, plus the JAKi ruxolitinib in JAKi-naïve myelofibrosis the most common AEs in the 60 mg cohort were nausea (79%), anemia (64%), thrombocytopenia (64%), and fatigue (57%). Nausea events were predominantly Grade 1 and transient in nature. Among patients who received at least one prophylactic antiemetic (64% of 60 mg cohort), nausea (Grade 1 only) was experienced by 67% of patients compared with 100% of those who did not receive prophylactic antiemetics (Grades 1-3). In the selinexor 60 mg cohort, 79% of the intent-to-treat population achieved SVR35 and 58% achieved TSS50 at Week 24. Response rates were consistent across subgroups, including sex and regardless of ruxolitinib dose. In a Phase 2 study, selinexor monotherapy in patients with myelofibrosis refractory or intolerant to JAKi therapy (NCT03627403; ESSENTIAL) was generally tolerable and preliminary signs of efficacy were observed with single-agent selinexor. These results provide rationale to explore selinexor monotherapy in myelofibrosis subpopulations with high unmet need such as those with thrombocytopenia. **Methods:** XPORT-MF-044 (NCT05980806) is a two arm, sequential, multicenter, open-label, Phase 2 study evaluating the efficacy of selinexor (40 mg or 60 mg QW; N=29 per arm) in patients with JAKi-naïve MF and moderate thrombocytopenia (platelet count: 50-100x10^9/L) with optional expansion arms (n=30 per arm). Optional ruxolitinib or pacritinib, or momelotinib treatment (based on platelet count) may be added for patients whose SVR from baseline is <10% at week 12 or <35% at week 24. Inclusion criteria include ≥18 years of age, spleen volume ≥450 cm^3 by MRI or CT scan, DIPSS intermediate-1 with symptoms, intermediate-2, or high-risk, ECOG ≤2, platelet counts of 50-100x10^9 /L, and not eligible for stem cell transplantation. Select exclusion criteria include >10% blast in peripheral blood or bone marrow and previous treatment with JAKi for myelofibrosis. Primary endpoint is SVR35 at week 24. Key secondary endpoints are safety, TSS50 at week 24, anemia response at week 24, overall survival, and overall response rate. Clinical trial information: NCT05980806. Research Sponsor: Karyopharm Therapeutics.

TPS6594 **Poster Session**

Phase 3 randomized double-blind study evaluating selinexor, an XPO1 inhibitor, plus ruxolitinib in JAKi-naïve myelofibrosis.

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Background: Myelofibrosis (MF) is a myeloproliferative neoplasm with common somatic gene driver mutations in *JAK2*, *CALR*, and *MPL*. Selinexor, an investigational oral XPO1 inhibitor, may inhibit MF-relevant JAK/STAT and non-JAK/STAT pathways. Preclinical studies have shown potential synergy with ruxolitinib treatment. In the phase 1 portion of XPORT-MF-034 evaluating selinexor plus ruxolitinib in JAKi-naïve patients with MF, the most common AEs in the 60 mg cohort were nausea (79%), anemia (64%), thrombocytopenia (64%), and fatigue (57%). Nausea was predominantly Grade 1 and transient in nature. Treatment-related AEs leading to treatment discontinuation were thrombocytopenia (n=1) and neuropathy (n=1). SVR35 and TSS50 was achieved by 79% and 58% of the 60 mg cohort intent-to-treat population at Week 24, respectively. Response rates were consistent across subgroups, including sex and regardless of ruxolitinib starting dose. These data provide strong support to further evaluate selinexor (60 mg) and ruxolitinib in patients with JAKi-naïve MF. **Methods:** The XPORT-MF-034 (NCT04562389) trial includes a global, Phase 3 randomized, double-blind, placebo-controlled study designed to evaluate selinexor and ruxolitinib. JAKi-naïve patients with MF will be randomized 2:1 to receive oral selinexor 60 mg or placebo once weekly (28-day cycle) and twice daily ruxolitinib. Randomization will be stratified by DIPSS risk category (int-1 vs int-2 or high-risk), spleen volume (<1800 cm^3 vs >1800 cm^3 by MRI/CT scan), and baseline platelet counts ($100\text{-}200 \times 10^9$/L vs $>200 \times 10^9$/L). Dual anti-emetics for nausea prophylaxis will be required for the first two cycles. Select eligibility criteria include ≥18 years of age, spleen volume ≥450 cm^3 by MRI or CT, DIPSS intermediate-1, intermediate-2, or high-risk, active symptoms of MF (MFSAF v4.0), currently not eligible for stem cell transplantation, ECOG≤2, and platelet count $\geq 100 \times 10^9$/L. Select exclusion criteria include >10% blasts in peripheral blood or bone marrow; previous treatment with JAKi for MF, or previous treatment with selinexor or other XPO1 inhibitors. The co-primary study endpoints are SVR35 and TSS50 at Week 24 and will be tested hierarchically. The key secondary endpoint is anemia response at Week 24 per the IWG-MRT and ELN criteria. The XPORT-MF-034 Phase 3 trial is currently open for enrollment; a total of 306 JAKi-naïve MF patients will be enrolled and the study was initiated on June 28, 2023. Clinical trial information: NCT04562389. Research Sponsor: Karyopharm Therapeutics.

TPS6595 Poster Session

Phase 2 study of the lysine-specific demethylase 1 (LSD1) inhibitor bomedemstat in patients with polycythemia vera (PV).

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Background: PV is a myeloproliferative neoplasm (MPN) characterized by clonal erythrocytosis that is driven by mutations in *JAK2*. Currently available treatments reduce thrombotic risk and symptom burden but have little impact on disease course or risk of progression to post-PV myelofibrosis (PPV-MF) or acute myeloid leukemia (AML). There remains a need for novel treatments that can alter the natural history of PV. LSD1 is an enzyme that regulates megakaryocytes and erythrocyte maturation. Bomedemstat is an irreversible inhibitor of LSD1 that has been shown to have manageable safety and clinically relevant activity in other *JAK2*-mutation–prevalent MPNs (essential thrombocythemia and myelofibrosis). Here, we describe the methods for an open-label phase 2 study (NCT05558696) that has been designed to evaluate the efficacy and safety of bomedemstat in patients with PV who are resistant to or intolerant of standard cytoreductive therapy. **Methods:** Eligible patients are ≥18 years, have a confirmed diagnosis of PV per World Health Organization 2016 diagnostic criteria, a bone marrow fibrosis score of grade 0 or 1, an ECOG performance status of 0-2, a platelet count of $\geq 250 \times 10^9$/L, an absolute neutrophil count of $\geq 1.5 \times 10^9$/L, and resistance to or intolerance of ≥1 standard cytoreductive therapy. All patients will receive bomedemstat at a starting dose of 40 mg/d by mouth for 36 weeks, with dose titration to a hematocrit target of <45% with no grade ≥1 thrombocytopenia. Treatment with bomedemstat can continue beyond week 36 in patients deriving clinical benefit. Clinic visits will occur every 2 weeks until week 12 and monthly thereafter. Adverse events will be graded per NCI CTCAE version 5.0 criteria and will be monitored for up to 30 days after treatment end. Transfusions or phlebotomy can be administered during treatment as needed. The primary end points are safety and the proportion of patients who achieve a reduction in hematocrit to <45% without phlebotomy by week 36. Secondary end points will be the durability of reduction in hematocrit <45% without phlebotomy; the incidence and durability of reduction in platelet count to $\leq 450 \times 10^9$/L and white blood cell count to $< 10 \times 10^9$/L; the incidence of new thrombotic or major hemorrhagic events; reduction in spleen volume by week 36 in patients with an enlarged spleen at baseline; progression to PPV-MF or myelodysplastic syndrome or transformation to AML; pharmacokinetics; and change in patient-reported symptom burden assessed using the MSAF v4.0 and PGIC. Exploratory end points include change in the concentration of circulating inflammatory cytokines and growth factors, change in mutant allele frequency of *JAK2*and other mutations, and change in bone marrow fibrosis grade. Approximately 20 patients will be enrolled. Recruitment for this study is currently underway in Australia, the United Kingdom, and the United States. Clinical trial information: NCT05558696. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS6596 **Poster Session**

Phase 3 study of the lysine-specific demethylase 1 (LSD1) inhibitor bomedemstat in patients with essential thrombocythemia (ET).

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Background: ET is a myeloproliferative neoplasm (MPN) driven by mutations in *JAK2*, *CALR*, and *MPL* that is characterized by thrombocytosis and megakaryocyte hyperplasia. Currently available treatments can prevent thrombotic complications but do not substantially alter the natural history of ET. LSD1 is an enzyme that regulates hematopoietic stem and progenitor cell proliferation and is overexpressed in MPNs. In a phase 2 study, the LSD1 inhibitor bomedemstat was generally well tolerated and improved symptoms, durably reduced platelet and white blood cell counts, and reduced mutation burden in patients with ET. Here, we describe the methods for a randomized, open-label, phase 3 study (NCT06079879) that has been designed to evaluate bomedemstat versus best available therapy in patients with ET who had an inadequate response to or were intolerant of hydroxyurea. **Methods:** Key eligibility criteria include age ≥18 years, a diagnosis of ET per World Health Organization 2016 diagnostic criteria, a bone marrow fibrosis score of grade 0 or 1, a platelet count of >450 x 10^9/L, and an absolute neutrophil count of ≥0.75 x 10^9/L. All patients must have a history of inadequate response to or intolerance of hydroxyurea per modified European LeukemiaNet (ELN) criteria. Patients will be randomly assigned 1:1 to bomedemstat 50 mg/day by mouth (starting dose) or investigator's choice of best available therapy (anagrelide, busulfan, interferon alfa/pegylated interferon alpha, or ruxolitinib). Bomedemstat dose will be titrated to a target platelet count of ≥150 to ≤350 x 10^9/L. After 52 weeks, patients receiving best available therapy can cross over to bomedemstat at the investigator's discretion and patients in the bomedemstat arm can continue on treatment (maximum of 156 weeks on study). Randomization will be stratified by hydroxyurea history (inadequate response vs intolerance) and MFSAF v4.0 baseline score (≥4 vs <4). Clinic visits will occur every 2 weeks until week 12 and monthly thereafter. Adverse events will be graded per NCI CTCAE v5.0 criteria and monitored for up to 30 days after last dose of study drug. The primary end point is durable clinicohematologic response rate per modified ELN criteria. Secondary end points are duration of clinicohematologic response, duration of hematologic remission, change from baseline in total symptom and fatigue score per MFSAF v4.0 criteria, change from baseline in total fatigue score per the PROMIS Fatigue SF-7a scale, incidence of thrombotic or major hemorrhagic events, transformation to post-ET myelofibrosis or myelodysplastic syndrome/acute myeloid leukemia, event-free survival, and safety. Exploratory end points include pharmacokinetics, the proportion of patients reporting stability or improvement versus decline on the MSAF v4.0 and PROMIS Fatigue SF-7a domains, and molecular biomarkers. Approximately 300 patients will be enrolled. Clinical trial information: NCT06079879. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.