Ropeginterferon alfa-2b versus anagrelide for the treatment of essential thrombocythemia: Topline results of the phase 3 SURPASS-ET trial.

Ruben A. Mesa, Harinder Gill, Zhijian Xiao, Norio Komatsu, Albert Qin, Tsewang Tashi, Lei Zhang, Jie Jin, Keita Kirito, Kohshi Ohishi, Shuichi Shirane, Lee-Yung Shih, Sung-Eun Lee, Winnie Z.Y. Teo, Dawn Maze, Stephen Oh, Toshiaki Sato, Weichung (Joe) Shih, John Mascarenhas, Lucia Masarova, SURPASS-ET Study Group; Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC; Department of Medicine, School of Clinical Medicine, LKS Faculty of Medicine, the University of Hong Kong, Hong Kong, China; Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; Department of Hematology, Juntendo University School of Medicine, Tokyo, Japan; PharmaEssentia Corp., Taipei, Taiwan; University of Utah, Huntsman Cancer Institute, Salt Lake City, UT; Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, Japan; The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Hematology and Oncology, University of Yamanashi Hospital, Yamanashi, Japan; Department of Transfusion Medicine and Cell Therapy, Mie University Hospital, Mie, Japan; Division of Hematology-Oncology, Chang Gung Memorial Hospital, Chang Gung University, Taipei, Taiwan; Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; Department of Hematology-Oncology, National University Cancer Institute, Singapore (NCIS), National University Health System, Singapore, Singapore; Princess Margaret Cancer Centre, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada; Division of Hematology, Department of Medicine, Washington University School of Medicine, St. Louis, MO; PharmaEssentia Japan KK, Tokyo, Japan; Rutgers University School of Public Health, Piscataway, NJ; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: *BCR::ABL1*-negative myeloproliferative neoplasms (MPNs), including essential thrombocythemia (ET), polycythemia vera (PV) and myelofibrosis (MF). No new treatments have been approved for ET in the US since anagrelide in 1997. Ropeginterferon alfa-2b (ropeg) is an anti-clonal interferon-based therapy approved by the FDA and globally for PV, providing the rationale for evaluation in ET and other MPNs. **Methods:** SURPASS ET is an open-label, multicenter, Phase III trial comparing ropeg with anagrelide over 12 months in patients with ET who were hydroxyurea-resistant or-intolerant. A total of 174 patients were randomized in a 1:1 ratio to receive ropeg or anagrelide. Ropeg was administered at 250 mcg at Week 0 titrating to 350 mcg at Week 2 and 500 mcg from Week 4 if tolerated. The primary endpoint was the rate of response, as defined by the Modified European LeukemiaNet response criteria, at both Months 9 and 12. Secondary endpoint assessments included *JAK2*V617F allele burden, MPN-associated symptoms, thromboembolic events, spleen size, and safety. **Results:** Baseline patient characteristics were balanced across treatment arms (Table 1). The primary endpoint was achieved in 42.9% of patients in the ropeg arm versus 6.0% in the anagrelide arm (p=0.0001). Ropeg showed response improvements by each parameter: 1) Platelets $\leq 400 \times 10^9$/L and white blood cells $<9.5 \times 10^9$/L: 56.0% vs. 6.0%. 2) Improvement or stabilization of splenomegaly: 87.9% vs. 54.2%. 3) Symptom improvement or stabilization: 71.4% vs. 33.7%. 4) Absence of hemorrhagic/thrombotic events: 84.6% vs. 51.8%. ET-related major thrombotic and cardiovascular events occurred in 1 (1.1%), and 0 patients in the ropeg arm vs. 7 (8.8%) and 6 (7.5%) patients, respectively, in the anagrelide arm. Mean *JAK2*V617F allelic burden decreased from 33.7% at baseline to 25.3% at 12 months (ropeg arm) vs. 39.7% to 37.3% (anagrelide arm). Ropeg showed lower rate of adverse event (AE)-related discontinuation (5.5% vs.18.8%) and treatment-related serious AEs (2.2% vs. 10.0%). **Conclusions:** Ropeg showed superior efficacy and safety compared to anagrelide as second-line therapy for ET. It represents a potential new therapeutic option for ET. Clinical trial information: NCT04285086. Research Sponsor: PharmaEssentia Corporation.

Patient demographics and baseline characteristics.

	Ropeg (n*=91)	Anagrelide (n=83)	Total (N=174)
Age, y	61 (21-80)	64 (20-83)	63 (20-83)
Race, x (%)			
Caucasian	5	2	7
Asian	86	81	167
Gender, x (%)			
Female	47 (52)	44 (53)	91 (52)
Male	44 (48)	39 (47)	83 (48)
Total symptom score at baseline (MPN-SAF)	9 (0, 71)	9 (0, 74)	9 (0. 74)
Spleen length by ultrasound, cm	13.1 (5.2-16.3)	15.2 (9.2-23.4)	13.9 (5.2-23.4)
Leukocytes, $x10^9$/L	11.4 (7.2-47.7)	11.6 (7.2-75.9)	11.5 (7.2-75.9)
Platelets, $x10^9$/L	942 (384-2132)	870 (406-4199)	925 (397-4199)
***JAK2*V617F, x (%)**	72 (79)	70 (84)	142 (82)
***CALR* exon 9, x (%)**	11 (12)	10 (12)	21 (12)

*n (%) presented for categorical variables. Median (range) for continuous variables.

6501 Oral Abstract Session

Primary endpoint results of the phase 3b ASC4START trial of asciminib (ASC) vs nilotinib (NIL) in newly diagnosed chronic phase chronic myeloid leukemia (CML-CP): Time to treatment discontinuation due to adverse events (TTDAE).

Andreas Hochhaus, François-Xavier Mahon, Tim H. Brümmendorf, Phillipp D. Le Coutre, David Jacob Andorsky, Susanne Saussele, Stephen Strickland, Thomas Cluzeau, Françoise Huguet, Jiří Mayer, Viviane Dubruille, Dong-Wook Kim, Ilina Micheva, Gabrielle Roth Guepin, Virginia Pilipovic, Jacqueline Ryan, Nabil Amirouchene Angelozzi, Nithya Agrawal, Ennan Gu, Delphine Réa; Klinik für Innere Medizin II, Universitätsklinikum Jena, Jena, Germany; Institut Bergonié, Bordeaux, France; Uniklinik RWTH Aachen, Medizinische Klinik IV, Center for Integrated Oncology (CIO), Aachen, Germany; Department of Oncology and Hematology, Charité-Universitätsmedizin Berlin, Berlin, Germany; Rocky Mountain Cancer Centers, Boulder, CO; Universitätsmedizin Mannheim, III. Medizinische Klinik, Mannheim, Germany; Sarah Cannon Research Institute, Nashville, TN; Université Cote d'Azur, CHU de Nice, Service d'hématologie, Nice, France; Institut Universitaire du Cancer de Toulouse-Oncopole, Centre Hospitalier Universitaire, Toulouse, France; University Hospital Brno, Brno, Czech Republic; CHU de Nantes, Nates, France; Uijeongbu Eulji Medical Center, Geumo-dong, Uijeongbu-Si, South Korea; Medical University of Varna, Varna, Bulgaria; CHRU Nancy, Nancy, France; Novartis Pharma AG, Basel, Switzerland; Novartis Pharmaceuticals UK Ltd, London, United Kingdom; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Pharmaceuticals Corporation, Cambridge, MA; Hôpital Saint-Louis, Paris, France

Background: ASC, the first BCR::ABL1 inhibitor to Specifically Target the ABL Myristoyl Pocket, recently received FDA Accelerated Approval for newly diagnosed CML-CP based on major molecular response (MMR) rates in the ASC4FIRST trial (NCT04971226). We present results from ASC4START (NCT05456191), with the primary objective of assessing the tolerability of ASC vs second-generation tyrosine kinase inhibitor NIL in patients (pts) with newly diagnosed CML-CP. **Methods:** Adults were randomized 1:1 to receive ASC 80 mg once daily or NIL 300 mg twice daily, stratified by ELTS risk category. The primary endpoint is TTDAE. Events included AEs leading to treatment (tx) discontinuation and deaths due to AEs. Secondary endpoints include molecular response and safety. **Results:** Pts were recruited by 120 participating sites across 24 countries and randomized to ASC (n=284) or NIL (n=284). Two pts who did not receive NIL were excluded from safety analyses. Median follow-up was 9.7 mo. At cutoff (Sep 3, 2024), 10.9% and 17.3% of pts discontinued ASC and NIL, respectively, most commonly due AEs (4.9% vs 11.6%) and unsatisfactory therapeutic effect (2.5% vs 2.8%). The study met its primary endpoint, showing statistically significant difference in TTDAE in favor of ASC with a cause-specific hazard ratio of 0.45 (95% CI, 0.25-0.81; *P*=.004). Fewer pts discontinued due to AEs with ASC (16/284 [5.6%]) vs NIL (34/282 [12.1%]). There were 3 deaths on study due to AEs (ASC: cardiac arrest and suicide, n=1 each; NIL: cardiac arrest, n=1). Median duration of exposure was 39.1 wk with ASC vs 38.0 wk with NIL. Mean relative dose intensity was 94.8% vs 92.6%, respectively. Any-grade AEs occurred in 80.3% of pts with ASC vs 86.5% with NIL. Grade ≥3 AEs occurred in 25.0% and 31.9% of pts, respectively. AEs leading to dose adjustment/interruption occurred in 24.3% of pts with ASC vs 30.1% with NIL. Most frequent any-grade AEs (≥10%) with ASC vs NIL were thrombocytopenia (15.1% vs 13.8%), headache (10.2% vs 13.1%), myalgia (10.2% vs 8.2%), rash (8.5% vs 16.3%) and increased alanine aminotransferase (3.2% vs 12.4%). AEs of special interest included arterial occlusive events (0.7% vs 2.1%), acute pancreatitis (clinical events; 0.4% vs 2.5%), and hepatotoxicity (including laboratory terms; 8.1% vs 24.8%). *BCR::ABL1*^{IS} ≤10% (89.8% vs 82.0%), *BCR::ABL1*^{IS} ≤1% (69.0% vs 52.5%), MMR (22.9% vs 10.2%), MR^4 (4.6% vs 1.1%), and MR$^{4.5}$ (2.5% vs 0.4%) rates by wk 12 were higher with ASC vs NIL. **Conclusions:** The study met the primary endpoint with ASC showing significantly superior tolerability vs NIL based on TTDAE. The study is ongoing with additional analyses planned for tolerability and efficacy. The findings further support the potential for ASC to be a preferred therapy for newly diagnosed CML-CP, allowing more pts to meet tx goals without requiring tx switch. Clinical trial information: NCT05456191. Research Sponsor: Novartis Pharma AG.

6502 Oral Abstract Session

Efficacy and safety of pivekimab sunirine (PVEK) in patients (pts) with blastic plasmacytoid dendritic cell neoplasm (BPDCN) in the CADENZA study.

Naveen Pemmaraju, Giovanni Marconi, Pau Montesinos, Andrew A. Lane, Luca Mazzarella, David Andrew Sallman, Matthew Ulrickson, Gary J. Schiller, Harry Paul Erba, Eunice S. Wang, Roland B. Walter, Eric Deconinck, Ahmed M. Aribi, Ollivier Legrand, Delphine Lebon, Giovanni Martinelli, Daniel J. DeAngelo, Yining Du, Jalaja Potluri, Naval Guastad Daver; The University of Texas MD Anderson Cancer Center, Houston, TX; Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori "Dino Amadori" (IRST) IRCCS, Gatteo, Italy; Hospital Universitari i Politècnic La Fe, Valencia, Spain; Dana-Farber Cancer Institute, Boston, MA; IEO, European Institute of Oncology IRCCS, Milan, Italy; Moffitt Cancer Center and Research Institute, Tampa, FL; Banner MD Anderson Cancer Center, Gilbert, AZ; UCLA, Los Angeles, CA; Duke University, Durham, NC; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Fred Hutchinson Cancer Center, Seattle, WA; CHU Besançon-Hématologie, Besançon, France; City of Hope, Duarte, CA; Hospital St. Antoine, Paris, France; CHU Picardie, Amiens, France; AbbVie, Inc., North Chicago, IL

Background: BPDCN is a rare, clinically aggressive hematological malignancy primarily involving the skin, bone marrow, and lymph nodes. CD123 (IL-3Rα) is highly overexpressed on the surface of all BPDCN blasts making it an ideal target for novel immunochemotherapy. PVEK is a first-in-class antibody-drug conjugate comprising a high-affinity CD123 antibody, cleavable linker, and an indolinobenzodiazepine pseudodimer payload. Here, we present the primary analysis of efficacy and safety from CADENZA. **Methods:** In the open-label, multicenter, phase 1/2 CADENZA study, adults with BPDCN received PVEK monotherapy intravenously on day 1 of a 21-day cycle, as a <30-min outpatient infusion. Primary endpoint was the rate of composite complete response, defined as complete response (CR) + clinical CR (CR with minimal skin abnormality [CRc]) in frontline (1L) pts. Key secondary endpoints were duration of CR + CRc, median overall survival (OS), overall response rate (ORR), % of pts who were bridged to stem cell transplantation (SCT) after PVEK, and safety and tolerability. **Results:** At primary analysis (data cutoff: October 2, 2024), CADENZA enrolled 84 pts with CD123-positive BPDCN who received PVEK at the recommended phase 2 dose (RP2D) of 0.045 mg/kg every 21 days, including 33 pts with 1L BPDCN (median age, 73.0 [range, 48-84]; ≥65 years, 91%; male, 82%) and 51 pts with relapsed/refractory (R/R) BPDCN (median age, 69.0 [range, 19-85]; ≥65 years, 59%; male, 82%). Pts with R/R BPDCN had received 1-3 prior systemic therapies; 57% had prior tagraxofusp. Median follow-up was 21.5 mo for 1L pts and 24.1 mo for the R/R group. Among 1L pts, CR + CRc was 70% (95% CI, 51.3-84.4) and median duration of CR + CRc was 9.8 months (mo) (95% CI, 4.6-Not Reached [NR]); ORR was 85%. Median OS was 16.6 mo (95% CI, 11.4-NR). Among 13 (39%) 1L pts bridged to SCT, CR + CRc was 92% (95% CI, 64.0-99.8) and median OS was NR. In the R/R group, CR + CRc was 14% and median duration of CR + CRc was 9.2 mo (95% CI, 2.4-NR); ORR was 35%. Median OS was 5.8 mo (95% CI, 3.9-8.4) and 12% of pts bridged to SCT. Median (IQR) PVEK treatment exposure was 5 (4-9) cycles for the 1L group and 3 (2-5) cycles for the R/R group. Safety was assessed in all 84 pts. The most common treatment-emergent adverse event (TEAE) was peripheral edema (any grade, 54%; grade ≥3, 12%). TEAEs led to discontinuation in 9% and 7% of pts with 1L and R/R BPDCN, respectively. No capillary leak syndrome (CLS) events or treatment-related deaths were reported, and 2 (2%) pts experienced veno-occlusive disease of grades 2 and 3 after cycles 4 and 8, respectively, which resolved. **Conclusions:** PVEK treatment demonstrated promising efficacy, with high and durable CR + CRc responses. PVEK was tolerable at the RP2D. The safety profile was manageable, with no CLS events. These results support PVEK as a potential new treatment option for adult pts with BPDCN. Clinical trial information: NCT03386513. Research Sponsor: AbbVie.

6503 Oral Abstract Session

Phase II study of cladribine, low-dose cytarabine, and venetoclax, alternating with azacitidine and venetoclax, in higher-risk chronic myelomonocytic leukemia and myelodysplastic syndromes.

Guillermo Montalban-Bravo, Nicholas James Short, Naval Guastad Daver, Yesid Alvarado, Kelly Sharon Chien, Elias Jabbour, Gautam Borthakur, Mahesh Swaminathan, Abhishek Maiti, Danielle Hammond, Ghayas C. Issa, Lucia Masarova, Prithviraj Bose, Xuelin Huang, Heather Schneider, Kristy Bodden, Lizabeth Romero, Tapan M. Kadia, Hagop M. Kantarjian, Guillermo Garcia-Manero; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX

Background: Responses to hypomethylating agents (HMAs) in patients (pts) with higher-risk myelodysplastic syndromes (HR-MDS) and chronic myelomonocytic leukemia (CMML) are short-lived, with a high risk of transformation to acute myeloid leukemia (AML). Cladribine (CDA) induces monocyte apoptosis and is active in AML when combined with low dose cytarabine (LDAC) and venetoclax (VEN). We aimed to evaluate the safety and activity of CDA, LDAC and VEN in HR-MDS and CMML. **Methods:** We designed a phase II clinical trial (NCT05365035) for pts with newly diagnosed (ND) or relapsed/refractory (R/R) HR-MDS or CMML. Induction consisted of CDA 5 mg/m^2 daily IV on days 1-3, LDAC 20 mg s.c bid days 1-5 and VEN 400 mg daily days 1-5 followed by azacitidine 75 mg/m^2 daily days 1-7 with VEN 400 mg daily days 1-7 or CDA 5 mg/m^2 days 1-3, LDAC 20 mg s.c bid days 1-5 and VEN 400 mg days 1-5 alternating every 2 cycles. The primary end point was to evaluate safety and efficacy of the combination. **Results:** Between 10/2022 and 01/2025, 50 pts have been treated (19 [38%] ND and 31 [62%] R/R). Thirty pts (60%) had MDS, and 20 (40%) had CMML. Thirty-seven (74%) pts had high/very high IPSS-Molecular risk and 5 (10%, 4 R/R, 1 ND) pts had biallelic *TP53* (*biTP53*) loss. The median age was 75 years (range 52-83). Among R/R pts, the median number of prior therapies was 1 (range 1-4) with 6 (19%) having received prior VEN treatment and 2 (4%) having undergone allogeneic stem cell transplant (SCT). The median number of cycles received was 2 (range 1-15). The 4- and 8-week mortality was 2% and 4%, respectively. Overall, the combination was well tolerated with thrombocytopenia (n=17, 35%), febrile neutropenia (n=6, 13%) and neutropenia (n=5, 10%) being the most common grade ≥3 adverse events. Among the 48 pts with evaluable responses, the overall response rate (ORR) based on the IWG 2006 response criteria was 43% (complete response [CR] rate of 13% [n=4]) in R/R pts and 72% (CR rate of 39% [n=7]) in ND pts. Based on the IWG 2023 response criteria, the ORR was 40% (n=12, CR: 5 [17%]) and 72% (n=13, CR: 10 [56%]) in R/R and ND pts, respectively. Median number of cycles to best response was 1 (range 1-5). Among responders, 85% and 73% of pts demonstrated neutrophil (>1x10^9/L) and platelet (>100x10^9/L) recovery after cycle 1 after a median of 27 and 21 days, respectively. Eight (16%) pts required dose reductions due to cytopenias. Fifteen (30%) pts underwent subsequent SCT. After a median follow up of 15.1 months, the median overall survival (OS) was 5.8 months and not reached in R/R and ND pts, respectively. The median leukemia-free survival was 4.1 months and not reached in R/R and ND pts, respectively. Among R/R pts, *biTP53* was associated with shorter OS (3.1 vs 12.3 months, p=0.0344). **Conclusions:** CDA, LDAC and VEN is safe in pts with HR-MDS and CMML, demonstrating promising results in ND pts. Clinical trial information: NCT05365035. Research Sponsor: None.

6504 Oral Abstract Session

An all-oral regimen of decitabine-cedazuridine (DEC-C) plus venetoclax (VEN) in patients (pts) with newly diagnosed acute myeloid leukemia (AML) ineligible for intensive induction chemotherapy: Results from a phase 2 cohort of 101 pts.

Amer Methqal Zeidan, Elizabeth A. Griffiths, Courtney Denton Dinardo, Gabriel N. Mannis, Pau Montesinos, Montserrat Arnan, Michael R. Savona, Olatoyosi Odenike, James K. McCloskey, Harsh V. Amin, Amir Tahmasb Fathi, Teresa Bernal del Castillo, Gabriela Rodriguez-Macias, Jane Liesveld, Annie P. Im, Aram Oganesian, Qing Xu, Margit Dijkstra, Harold N. Keer, Gail J. Roboz; Yale University School of Medicine, New Haven, CT; Roswell Park Comprehensive Cancer Center, Buffalo, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; Stanford University School of Medicine, Stanford, CA; Hospital Universitari i Politècnic La Fe, Valencia, Spain; Institut Catala d'Oncologia (ICO) - Hospital Duran i Reynals, Barcelona, Spain; Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN; The University of Chicago Medicine and Comprehensive Cancer Center, Chicago, IL; John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; Boca Raton Clinical Research, Boca Raton, FL; Massachusetts General Hospital Cancer Center, Boston, MA; Hospital Universitario Central de Asturias/Instituto Universitario del Principado de Asturias (ISPA)/Instituo Universitario de Oncología del Principado de Asturias (IUOPA), Oviedo, Spain; Hospital General Universitario Gregorio Marañon, Madrid, Spain; University of Rochester Medical Center, Rochester, NY; University of Pittsburgh/UPMC Hillman Cancer Center, Pittsburgh, PA; Taiho Oncology, Inc., Pleasanton, CA; Weill Cornell Medicine, NewYork-Presbyterian Hospital, New York, NY

Background: In pts with AML aged ≥75 years and ineligible for induction chemotherapy, the combination of the Bcl-2 inhibitor VEN plus azacitidine (AZA) was approved based on the Phase 3 VIALE-A trial (complete remission [CR] rate, 36.7%; median CR duration, 17.5 months; median overall survival [OS], 14.7 months). However, monthly seven-day clinic injections of parenteral AZA until progression impose a significant burden on pts. Further, multiple adjusted comparisons have demonstrated similar clinical efficacy between AZA and decitabine. Oral DEC-C (decitabine 35 mg and cedazuridine 100 mg) has equivalent pharmacokinetic (PK) area under the curve exposure to intravenous decitabine. This Phase 1/2 trial was designed to evaluate the all-oral regimen of DEC-C plus VEN in pts with AML aged ≥75 years or with comorbidities precluding first-line intensive induction chemotherapy (NCT04657081). Here, we report results from the pivotal Phase 2 part of the trial. **Methods:** Eligible pts received oral DEC-C on Days 1–5 plus VEN 400 mg daily in 28-day cycles after Cycle 1 VEN ramp up (100 mg Day 1, 200 mg Day 2, 400 mg Day ≥3). Bone marrow examination during Cycle 1 was optional, with VEN and/or DEC-C dose adjustments based on response and count recovery. The primary endpoint was CR rate, based on European LeukemiaNet (ELN) 2017 response criteria. The sample size was calculated based on the lower limit of the 95% confidence interval (CI) of the target CR rate exceeding the clinically meaningful historical rate of 17.9%, with a one-sided α of 0.025, which required ~100 pts to ensure ≥95% power. **Results:** As of September 30, 2024, 101 pts were enrolled and had completed a median of 4 (range, 1–15) cycles. Median age was 78 years. ELN 2017 classification was favorable, intermediate, and adverse in 31.7%, 33.7%, and 29.7% of pts, respectively. Median follow-up was 11.2 months. The CR and CR/CR with incomplete hematologic recovery rates were 46.5% (95% CI, 36.5%–56.7%) and 63.4% (95% CI, 53.2%–72.7%), respectively. Median time to CR was 2.4 months. Median CR duration was not reached; among pts who achieved CR, 80.0% remained so at 6 months and 75.3% at 12 months. Median OS was 15.5 (95% CI, 7.6–not estimable) months. Grade ≥3 treatment-emergent adverse events were reported in 98.0% of pts, most commonly febrile neutropenia (49.5%), anemia (38.6%), and neutropenia (35.6%). The 30- and 60-day mortality rates were 3.0% and 9.9%, respectively. PK data confirmed no drug-drug interactions between oral DEC-C and VEN. **Conclusions:** The all-oral regimen of DEC-C plus VEN resulted in comparable safety, response, and survival rates to parenteral AZA plus VEN in pts with newly diagnosed AML ineligible for intensive induction chemotherapy. These data support the potential use of DEC-C plus VEN as a treatment option for these pts. Clinical trial information: NCT04657081. Research Sponsor: Taiho Oncology, Inc.

6505 Oral Abstract Session

Phase 1b/2 study of lisaftoclax (APG-2575) combined with azacitidine (AZA) in patients (pts) with treatment-naïve (TN) or prior venetoclax (VEN)-exposed myeloid malignancies.

Michael Francis Leahy, Shaun Fleming, Patricia Kropf, Chong Chua, Tapan M. Kadia, Caspian Oliai, John Kwan, Chun Yew Fong, Joshua Richmond, Paul Cannell, James Dugan, Maria R. Baer, Stephen Ting, Daniel Egan, Zi Chen, Qian Niu, Mingyu Li, Mohammad Ahmad, Hengbang Wang, Yifan Zhai; Royal Perth Hospital, Perth, Western Australia, Australia; The Alfred Hospital & Australian Centre for Blood Diseases, Monash University, Melbourne, Australia; Novant Health Cancer Institute, Charlotte, NC; Northern Health, Epping, Australia; The University of Texas MD Anderson Cancer Center, Houston, TX; UCLA Health, Los Angeles, CA; Westmead Hospital, Westmead, Australia; Austin Health, Heidelberg, Australia, and University of Melbourne, Melbourne, Australia; Sunshine Coast Hospital, Birtinya, Australia; Fiona Stanley Hospital, Murdoch, Australia; Novant Health Cancer Institute, Winston-Salem, NC; University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD; Eastern Health, Box Hill & Monash University, Melbourne, Australia; Swedish Medical Center, Seattle, WA; Ascentage Pharma (Suzhou) Co., Ltd., Suzhou, China; Ascentage Pharma Group Inc., Rockville, MD; Ascentage Pharma (Suzhou) Co., Ltd., Suzhou, China, and Ascentage Pharma Group Inc., Rockville, MD

Background: Lisaftoclax (LISA), an investigational, orally active small molecule BCL-2 inhibitor, has shown enhanced treatment responses when combined with AZA in preclinical and clinical studies. We evaluated the safety and efficacy of LISA plus AZA in pts with myeloid malignancies. **Methods:** This open-label, multicenter study enrolled pts with TN or relapsed/refractory (R/R) AML/MPAL or high-risk (HR) MDS/CMML. Prior VEN treatment was permitted. In Part 1, LISA was administered at escalating doses (200, 400, 600, or 800 mg once daily [QD]) and combined with AZA to assess DLTs and determine the MTD. Part 2 evaluated the safety and efficacy of LISA 200, 400, or 600 mg QD over 28 or 14 days of 28-day cycles, combined with AZA at the standard dose (75 mg/m^2 on days 1-7 or 1-5 and 8-9 of each cycle). Safety and efficacy assessments were conducted for all pts receiving at least one dose of LISA. **Results:** As of January 6, 2025, 97 pts were enrolled, with a median treatment duration of 2 (0-16) cycles. Pt distribution included: 49 R/R AML; 20 R/R HR-MDS; 14 TN HR-MDS; 7 TN AML; 4 R/R CMML; 2 R/R MPAL; and 1 TN CMML. The median (range) age was 71 (23-89) years, with 59.8% of pts being male and 73.2% having an ECOG PS $\geq$ 1. Pts with R/R AML/MPAL D1-28, D1-14, and MDS/CMML had median prior therapies of 2.0 (1.0-8.0), 1.0 (1.0-3.0), and 1.0 (1.0-2.0), respectively, with prior VEN exposure in 46.2% (12/26), 50.0% (5/10), and 14.3% (2/14), respectively. There were no DLTs, and the MTD was not reached. The RP2D for TN HR-MDS was AZA (standard dose) + LISA 600 mg on days 1-14; for TN AML, it was AZA (standard dose) + LISA 600 mg on days 1-28. Common grade 3/4 TEAEs included neutropenia (40%), febrile neutropenia (31%), and thrombocytopenia (22%). Others included sepsis (9%), pneumonia (7%), and lower-respiratory-tract infections (3%). Febrile neutropenia was the most frequently reported SAE (26.8%). Only 3% of pts had neutropenia leading to a dose reduction of LISA, with no 60-day mortality reported. In 14 efficacy-evaluable pts with TN-MDS/CMML, the ORR was 64%, with CR and marrow CR achieved by 29% and 36% of pts, respectively; no PRs were observed. In pts with R/R AML treated with LISA for either 28 (n = 18) or 14 days (n = 8) of repeated 28-day cycles, the ORRs were 39% and 50%, respectively, including CR rates of 28% and 37.5%, respectively. In 20 pts refractory to VEN, the ORR was 17% (3/18) in pts with AML/MPAL and 50% (1/2) in pts with HR-MDS; 11% of pts with AML/MPAL and 50% with MDS had bone marrow blasts $<$ 5%. **Conclusions:** LISA at different dose regimens combined with AZA provides promising treatment options for pts with HR-MDS or AML. No DLTs occurred. The MTD was not reached. The combination was efficacious and well tolerated, with few dose modifications and low infection rates, supporting further clinical development of this regimen in these populations (APG2575AU101; NCT04964518). Clinical trial information: NCT04964518. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

Ziftomenib in relapsed/refractory (R/R) *NPM1*-mutant acute myeloid leukemia (AML): Phase 1b/2 clinical activity and safety results from the pivotal KOMET-001 study.

Eunice S. Wang, Pau Montesinos, Ghayas C. Issa, James M. Foran, Harry Paul Erba, Eduardo Rodríguez-Arbolí, Kateryna Fedorov, Mael Heiblig, Florian Heidel, Jessica K. Altman, Maria R. Baer, Lionel Adès, Kristen M. Pettit, Pierre Peterlin, Cristina Papayannidis, Zijing Zhang, Marcie Riches, Daniel Corum, Mollie Leoni, Amir Tahmasb Fathi; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Hospital Universitari i Politècnic La Fe, Valencia, Spain; The University of Texas MD Anderson Cancer Center, Houston, TX; Mayo Clinic Comprehensive Cancer Center, Mayo Clinic, Jacksonville, FL; Duke Cancer Institute, Durham, NC; Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBiS/CSIC), University of Seville, Seville, Spain; Vanderbilt-Ingram Cancer Center, Nashville, TN; Centre Hospitalier Lyon Sud, Lyon, France; Hannover Medical School, Hannover, Germany; Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD; Hôpital Saint-Louis, Paris, France; University of Michigan, Ann Arbor, MI; CHU de Nantes - Hôtel Dieu, Nantes, France; IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; Kura Oncology, Inc., San Diego, CA; Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: *NPM1*-m drives leukemogenesis in ~30% of AML. Despite current risk stratification, nearly half will have R/R disease within a year, after which outcomes are poor with <10% complete response following chemotherapy. Ziftomenib – a potent, highly selective, oral, investigational menin inhibitor – has shown clinical activity as monotherapy and in combination for adults with R/R *NPM1*-m and *KMT2A*-r AML, with 600 mg once-daily (QD) as the recommended phase 2 monotherapy dose for *NPM1*-m. Here we present the primary analysis for *NPM1*-m patients (pts) treated with ziftomenib 600 mg QD in the pivotal KOMET-001 study. **Methods:** KOMET-001 (NCT04067336) is a multicenter, open-label phase 1/2 study of ziftomenib in adults with R/R AML. In phase 2, pts with *NPM1*-m R/R AML received ziftomenib 600 mg QD. Phase 2 primary endpoint: complete remission with full/partial hematologic recovery (CR/CRh); key secondary endpoints: composite complete remission (CRc), durations of CR/CRh and CRc, and safety. The analyses below include *NPM1*-m pts pooled from phase 1b/2. **Results:** The phase 2 primary endpoint was met (p=0.0058). As of 20 Dec 2024, 112 pts were enrolled (51% US/Canada, 49% Europe/UK) in phase 1b/2 and treated with ziftomenib 600 mg QD, with a median follow-up of 4.2 months. Median age was 69 yrs (range 22–86), 56% female, 83% ECOG PS 0–1, median of 2 prior therapies (range 1–7), including 60% prior venetoclax (VEN) and 23% prior transplant. CR/CRh rate in all phase 1b/2 pts was 25% (28/112; 95% CI 17–34) and overall response rate was 35% (39/112; 95% CI 26–44). In phase 2 pts, 23% (21/92; 95% CI 15–33) achieved CR/CRh (Table), with 67% (10/15) MRD negativity among CR/CRh responders tested (local). Comparable CR/CRh rates were observed in both VEN-naïve and exposed pts (21% vs. 24%). Ziftomenib was well tolerated with 3% (3/112) discontinuing due to treatment-related adverse events (TRAEs). 40% (45/112) of pts had Grade (Gr) ≥3 TRAEs, including 13% differentiation syndrome (all Gr3), ≤5% each anemia, febrile neutropenia and thrombocytopenia, and 2% QTc prolongation (Gr3). Updated clinical activity and safety data will be presented. **Conclusions:** In the pivotal KOMET-001, the phase 2 primary endpoint was met: Ziftomenib achieved deep and durable responses in R/R *NPM1*-m AML, regardless of prior VEN. Ziftomenib was well tolerated with limited myelosuppression and only 3% ziftomenib-related discontinuations. Taken together, these data support the potential use of ziftomenib monotherapy as a new treatment option for R/R *NPM1*-m AML. Clinical trial information: NCT04067336. Research Sponsor: Kura Oncology, Inc.

Response, n (%)	Phase 2 600 mg QD N=92	Phase 1b/2 600 mg QD N=112
CR	13 (14)	20 (18)
CR/CRh	21 (23)	28 (25)
CRc	24 (26)	32 (29)
Median duration, months (95% CI)		
CR/CRh	3.7 (1.9–NE)	3.7 (1.9–7.7)
CRc	4.6 (2.8–11.4)	5.1 (2.8–8.1)
Restricted mean duration, months (95% CI)		
CR/CRh	4.3 (3.1–5.6)	5.2 (3.6–6.7)
CRc	5.9 (4.0–7.7)	6.4 (4.6–8.1)

6507 Oral Abstract Session

γ9δ2 T-cell activation (γδTCA) with ICT01 combined with azacitidine-venetoclax (AV) for older/unfit adults with newly diagnosed (ND) AML: Preliminary efficacy and dose selection in phase 1/2 study EVICTION.

Pierre Yves Dumas, Abhishek Maiti, Pierre Peterlin, Daniel Morillo, Jose Miguel Torregrosa-Diaz, Matthew Ulrickson, Agustin Penedo, Aude De Gassart, Emmanuel Valentin, Maelle Mairesse, Patrick Brune, Katrien Lemmens, Daniel Olive, Stephan Braun, Naval Guastad Daver, Sylvain Garciaz; CHU, Bordeaux, France; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; CHU de Nantes, Service d'hématologie Clinique, Nantes, France; START Madrid - Fundacion Jimenez Diaz, Madrid, Spain; Hopital La Miletrie, Poitiers, France; Banner MD Anderson Cancer Center, Gilbert, AZ; START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; Imcheck Therapeutics SAS, Marseille, France; Cancer Research of Marseille (CRCM), Institut Paoli-Calmettes, INSERM U1068, CNRS U7258, Aix-Marseille Université, Marseille, France; ImCheck Theapeutics, Marseille, France; Institut Paoli-Calmettes, Aix-Marseille University, Marseille, France

Background: AML impairs immunosurveillance bypassing target recognition and subsequent cytotoxic T cell responses. Immunomodulatory and cytotoxic effects of AV and γδTCA with ICT01 have shown synergistic efficacy in an in-vivo AML model with adoptive γδTC transfer. ICT01 is a first-in-class humanized, Fc-disabled anti-butyrophilin 3A mAb selectively inducing γδTCA for direct anti-leukemic cytotoxicity and IFNγ/TNFα release. γδTC are known to drive anti-leukemic efficacy in the post-transplant setting and intratumor presence of γδTCs is prognostic. γδTCA by ICT01 was dose dependent, safe, and tolerable. Here, ICT01-mediated γδTCA added to AV has been investigated in a dose-optimization Phase 1/2 study. **Methods:** ND-AML pts ≥ 75 years old or unfit to receive intensive chemotherapy were randomized 1:1 to AV plus either 10 mg ($ICT01^{LOW}$) or 75 mg ICT01 ($ICT01^{HIGH}$) Q4W. We assessed cytogenetics, NGS, pharmacodynamics (PD) in peripheral blood (PB) and bone marrow (BM), safety, and anti-tumor efficacy. **Results:** Of 45 pts randomized, 33 had conclusive disease assessments as of 20-Jan-2025, median age was 75 yrs (range 51–87), the minority (30%) had favorable risk (ELN 2024) and 55% had abnormalities of uncertain risk, some of which are suggestive of a poor response to AV. Median number of BM blasts at diagnosis was 38% (range 5–98%). No DLT was reported, and all pts had at least one adverse event; 30-day mortality was 3%. Grade 3/4 febrile neutropenia was seen in 19 (42%) and neutropenia in 32 pts (71%). ICT01 reproducibly induced rapid γδTCA in PB and BM, followed by increased serum IFNγ/TNFα reflective of downstream immune-cell effects. γδTC counts rapidly dropped in both PB and BM upon first ICT01 dosing and returned to near baseline values during $ICT01^{LOW}$ dosing but became almost undetectable during continued $ICT01^{HIGH}$ dosing. $ICT01^{LOW}$ exhibited a favorable benefit–risk profile with 90% CR/CRi (71% CR, 19% CRi) and lower rates of neutropenia/febrile neutropenia than both $ICT01^{HIGH}$ and published data, while PD effects seen with $ICT01^{HIGH}$ suggestive of activation-induced γδTC death upon repeated dosing were associated with less efficacy (75% CR/CRi [42% CR, 33% CRi]). Notably, response rates were high (particularly with $ICT01^{LOW}$) both in pts with adverse (CR 40% / CR/CRi 60% for *TP53/CK*; N=10), intermediate/uncertain (CR 47% / CR/CRi 95% for *MECOMr, NRAS, ASXL1*, *JAK2*, *DNMT3A*, *SF3B1*, *U2AF1*, *SRSF2*, *RUNX1*, *STAG2*; N=19) and favorable (CR 80% / CR/CRi 90% for *NPM1*, *IDH1/2*; N=10) risk mutations per ELN 2024. **Conclusions:** For AV combination, the recommended Phase 2 dose is 10 mg ICT01 Q4W. Both ICT01 regimens were safe and very well tolerated and generated very high CR and CR/CRi rates in older/unfit ND-AML pts. The high response rates seen in adverse risk pts warrant further clinical investigation. Clinical trial information: NCT04243499. Research Sponsor: ImCheck Therapeutics.

Long-term outcomes of patients surviving beyond 2 years post–allogeneic stem cell transplantation.

Nihar Desai, Tommy Alfaro-Moya, Eshrak Al-Shaibani, Igor Novitzky-Basso, Ivan Pasic, Fotios Michelis, Dennis Dong Hwan Kim, Auro Viswabandya, Rajat Kumar, Jonas Mattsson, Arjun Datt Law; Princess Margaret Hospital, Toronto, ON, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; Princess Margaret Cancer Centre,, Toronto, ON, Canada; University Health Network, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Advances in hematopoietic stem cell transplantation (HSCT) have been driven by progress in supportive care, conditioning regimens, and graft-versus-host disease (GvHD) prophylaxis. Post-transplant morbidity and mortality are most pronounced in the first two years after HCT. Long-term outcomes have been previously described in a CIBMTR study, which reported a 10-year survival of 85% for those who survived the first two years. Post-transplant cyclophosphamide (PTCy) has revolutionized transplant outcomes. However, its impact on long-term survival remains unclear. **Methods:** We included patients undergoing HSCT from Jan 2015 to Dec 2023 who were alive and without relapse two years after HSCT. We aimed to compare long-term outcomes in patients receiving PTCy-based GvHD prophylaxis to previous conventional GvHD prophylaxis strategies. Overall survival (OS) was calculated using the Kaplan–Meier method. The incidence of non-relapse mortality (NRM) and relapse were estimated using Fine & Gray's competing risk analysis. **Results:** Of the 1,401 patients, we included 571 patients alive and relapse-free two years after HCT (Table 1). The median follow-up post-HSCT was 4.8 years (3-5.9). The 5-year OS was 91% (95% CI: 88 – 94). The causes of death were: disease recurrence (17, 3%), infection (8, 1.4%), GvHD (4, 0.7%), second primary malignancies (3, 0.5%), and cardiac complications (3, 0.5%). The use of PTCy was associated with improved OS, 91.7% (95% CI: 88 – 95) vs. 88.7% (95% CI: 81 – 93), p=0.05. NRM at 5 years was 4.9% (95% CI: 3 – 7) and was significantly lower in patients receiving PTCy (2.9 % vs. 10.4%, p<0.001). Relapse risk at 5 years was 9.2% (7 – 13) and was not significantly different between the groups, 10.6% in recipients of PTCy vs. 5.6%, p=0.06. On MVA accounting for confounding variables, PTCy was independently associated with improved OS [HR: 0.46 (0.2 – 0.8), p=0.01], and NRM [HR: 0.23 (0.1 – 0.5), p<0.001]. Age >60 years at HSCT was associated with increased mortality [HR: 2.8 (1.5 – 5.3), p=0.001]. The development of chronic GvHD was protective against relapse [HR: 0.5 (0.3 – 0.9), p=0.04] (Table 1). **Conclusions:** The long-term outcomes for patients alive and relapse-free 2 years after HSCT are excellent. Relapse remained the most common cause of death even after 2 years. PTCy-based GvHD prophylaxis was associated with improved NRM and OS without an impact on disease relapse. Research Sponsor: None.

Baseline characteristics and multivariable analysis.

	PTCy	Others	p
Age, years, median (IQR)	57 (40 – 64)	52 (37 – 62)	0.04
Diagnosis, n (%)			
AML	231 (54)	60 (43)	
MDS	57 (13)	19 (14)	0.78
MF	46 (11)	5 (4)	
Donors, n (%)			
HLA-matched sibling	90 (21)	69 (49)	<0.01
HLA-matched unrelated	220 (51)	60 (43)	
HLA-mismatched unrelated	38 (9)	8 (7)	
Haploidentical	84 (19)	2 (1)	
GVHD prophylaxis, n (%)			
CnI + MTX	-	43 (31)	
ATG + CnI + MTX	-	73 (52)	-
Alemtuzumab + CnI	-	24 (17)	
PTCy-ATG-CnI	383 (89)	-	
PTCy- CnI – MMF	48 (11)	-	
Cryopreservation, n (%)	100 (23)	52 (36)	0.004
CD34$^+$ x 10^6/kg, median (IQR)	7.2 (6 – 8.1)	7.3 (5.9 – 7.6)	0.76
MVA			
OS	**HR**	**95% CI**	**p**
Age >60 years (vs <60 years)	2.84	1.5 – 5.3	0.001
PTCy (vs non-PTCy)	0.45	0.2 – 0.8	0.01
NRM			
Age more than 60 years (vs <60 years)	2.50	1 – 6.2	0.04
PTCy (vs non-PTCy)	0.23	0.1 – 0.5	<0.01
Relapse			
Age >60 years (vs <60 years)	1.47	0.7 – 3.0	0.29
PTCy (vs non-PTCy)	1.54	0.4 – 5.4	0.49

AML: Acute myeloid leukemia; ATG: anti thymocyte globulin; BM: bone marrow; CnI: calcineurin inhibitor; MDS: Myelodysplastic syndrome; MF: myelofibrosis; MTX: methotrexate; MMF: mycophenolate mofetil; PTCy: post-transplantation cyclophosphamide; RIC: Reduced-intensity conditioning; IQR: interquartile range (25% - 75%); TBI: total body irradiation.

6509 Rapid Oral Abstract Session

A phase I study of asciminib in combination with dasatinib, prednisone, and blinatumomab for Ph-positive acute leukemia in adults.

Marlise R. Luskin, Mark Alan Murakami, Julia H. Keating, Eunice S. Wang, Malgorzata McMasters, Yael Flamand, Eric S. Winer, Maximilian Stahl, Hunter Smith, Stella L. Jaeckle, Chase Weizer, Joseph Daniel Fleming, Caner Saygin, Wendy Stock, Daniel J. DeAngelo; Dana-Farber Cancer Institute, Boston, MA; Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY; Beth Israel Deaconess Medical Center, Boston, MA; University of Chicago, Chicago, IL

Background: Treatment of Ph+ acute lymphoblastic leukemia (ALL) requires potent BCR:ABL1 inhibition. Acquired resistance to the ATP-competitive ABL1 inhibitor dasatinib (DAS) justifies combination with the allosteric inhibitor asciminib (ASC) to deepen responses and prevent mutational resistance. Our phase 1 study (NCT03595917) confirmed the safety and preliminary efficacy of DAS 140 mg/day(d) and ASC 80 mg/d (Luskin *Blood* 2024). Blinatumomab (blin), a bispecific CD19-CD3 T-cell engager, is effective consolidation for Ph+ ALL. Here we report a 15-patient (pt) expansion cohort testing the safety of DAS, ASC and blin. **Methods:** Pts ≥18 years (yrs) with Ph+ ALL or chronic myeloid leukemia (CML) blast crisis, no prior DAS or ASC treatment or ABL1 T315I were eligible. Induction: DAS 140 mg/day (d), ASC 80 mg/d and prednisone 60 mg/m^2/d (max 120) 1-24 (tapered d 25-32). Consolidation: DAS 140 mg/d, ASC 80 mg/d, and blin (28 mcg/d d1-28 of a 42-d cycle) for 5 cycles. DAS and ASC are administered indefinitely. Dose-limiting toxicity (DLT) was CTCAEv5 non-heme toxicity grade (gr) 3+ during the first DAS, ASC, and blin combination cycle. **Results:** The 15-pt (9 male, 6 female) cohort accrued 08/2023-09/2024 (data cut 11/15/24). Median age was 62 yrs (range 25 – 83; 87% [13] ≥60). All pts were newly diagnosed: median WBC 11.1x10^3/μL (20% [3] ≥50), transcript type p190 (11, 73%) vs p210 (4, 27%), *IKZF1*^{plus} in 36% (5/14). Most (87%, 13/15) were trackable by clonoSEQ. Median time to blin was 33 days (range 28 – 77). There were no DLTs during the 6-pt safety run-in so 9 additional pts enrolled with all completing at least 1 cycle of ASC, DAS, plus blin. DAS dose reductions were common (n=7) for pleural effusion (n=3), transaminitis (n=1), and other (n=3). ASC dose reduction to 40 mg/d was required in 1 pt (asymptomatic gr3 lipase increase). One pt (age 81) discontinued protocol after 1 blin cycle due to general health decline. Five pts were transplanted per physician discretion after 2 (n=2), 3 (n=2), or 4 (n=1) blin cycles (suspected CML n=2; high-risk genetics n=2; persistent *BCR::ABL1* n=1). All others (n=9) have completed 4 or 5 blin cycles, or blin is ongoing. Responses deepened after the first cycle of blin (Table). No pt has progressed (median follow-up 238 days, 95% CI 112-420). **Conclusions:** Dual ABL1 inhibition with ASC and DAS can be safely combined with blin in Ph+ acute leukemia. An additional 25-pt cohort is planned with blin in combination with DAS and ASC at optimized doses. Clinical trial information: NCT03595917. Research Sponsor: Novartis.

Response kinetics.

	Induction (ASC, DAS, prednisone)	Consolidation Cycle 1 (ASC, DAS, blin)
Hematologic CR	**100%** (15/15)	**100%** (14/14)
Cytogenetic CR	**86%** (12/14)	**100%** (14/14)
Flow Negative (<10^{-4})	**79%** (11/14)	**100%** (14/14)
***BCR::ABL1* Molecular Response**		
(MR)	**87%**(13/15)	**100%**(14/14)
MR1	**60%**(9/15)	**100%**(14/14)
MR2	**20%**(3/15)	**57%** (8/14)
MR3	**7%**(1/15)	**43%**(6/14)
MR4		
clonoSEQ Response		
<10^{-4}	**67%**(6/9)	**67%**(6/9)
<10^{-6} (0 transcripts)	**11%**(1/9)	**11%**(1/9)

MRD negativity after end of induction in the phase 3 PhALLCON trial: A post hoc analysis.

Ibrahim Aldoss, Pankit Vachhani, Hagop M. Kantarjian, Pau Montesinos, Jessica Taft Leonard, David Gomez-Almaguer, Maria R. Baer, Carlo Gambacorti-Passerini, James K. McCloskey, Yosuke Minami, Cristina Papayannidis, Vanderson Geraldo Rocha, Philippe Rousselot, Eunice S. Wang, Lin Yang, Meliessa Hennessy, Alexander Vorog, Niti Patel, Jose-Maria Ribera-Santasusana, Elias Jabbour; City of Hope – Duarte, Duarte, CA; University of Alabama at Birmingham, Birmingham, AL; The University of Texas MD Anderson Cancer Center, Houston, TX; Hospital Universitari i Politecnic La Fe de Valencia, Valencia, Spain; Oregon Health and Science University, Portland, OR; Hospital Universitario, UANL; Dr. José Eleuterio Gonzalez, Monterrey, Mexico; University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD; University of Milano-Bicocca, Monza, Italy; Hackensack University Medical Center, Hackensack, NJ; National Cancer Center Hospital East, Kashiwa, Japan; IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli", Bologna, Italy; Instituto do Câncer do Estado de São Paulo, University of São Paulo, São Paulo, Brazil; Hospital Mignot University de Versailles Saint-Quentin-en-Yvelines, Paris, France; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Takeda Development Center Americas, Inc., Cambridge, MA; ICO-Hospital Germans Trias i Pujol, Badalona, Spain

Background: The phase 3 PhALLCON trial (NCT03589326) in adults with newly diagnosed Ph+ ALL met its primary endpoint, showing a significantly higher rate of minimal residual disease negativity (MRDneg; *BCR::ABL1*^{IS} ≤0.01%) with complete remission (CR) at end of induction (EOI) with ponatinib (PON) vs imatinib (IMA; 34.4% vs 16.7%; *P*=0.002) and safety comparable to IMA. We report post hoc analyses of patients (pts) who did not reach MRDneg by EOI. **Methods:** Pts were randomized 2:1 to PON (30 mg QD reduced to 15 mg upon MRDneg CR at EOI) or IMA (600 mg QD) plus 20 cycles (C) of reduced-intensity chemotherapy (induction C1–3; consolidation C4–9; maintenance combination C10–20) then PON/IMA monotherapy until disease progression or unacceptable toxicity. Cumulative molecular response rates, event-free survival (EFS; defined as any-cause death, no CR by EOI, or relapse from CR), and safety were evaluated in pts with *BCR::ABL1* p190/p210 confirmed by central lab at baseline who did not reach MRDneg by EOI and those achieving MRDneg post-cycle 4 day 1 (C4D1). Data cutoff: Aug 12, 2022. **Results:** Of 232 pts (PON/IMA: n=154/78) with p190/p210, 140 (86 [56%]/54 [69%]) did not have MRDneg by EOI (median age: 54 y; ≥60 y: 37%; female: 55%; ECOG 0/1: 44%/49%; p190/p210: 66%/34%). Of these, 113 pts (PON/IMA: 73/40) continued treatment after EOI, 48 of whom (35 [48%]/13 [33%]) reached MRDneg (MR4 or better) post-C4D1 (Table). Of those 48 pts (median age: 54 y; ≥60 y: 33%; female: 60%; ECOG 0/1: 46%/54%; p190/p210: 71%/29%), median duration of MRDneg (95% CI) was not reached (NR; 13.0 mo–NR) with PON and 3.8 mo (2.3–NR) with IMA; 16 pts (PON/IMA: 10/6) had HSCT. In the 140 pts without MRDneg by EOI, median EFS (mEFS; 95% CI) was NR (NR–NR) with PON and 24.8 mo (21.3–NR) with IMA; 2-y EFS (95% CI) was 82% (69–90) and 62% (41–77), respectively. In the 48 pts with MRDneg post-C4D1, mEFS was NR (NR–NR) and NR (21.3 mo–NR); 2-y EFS was 88% (68–96) and 80% (20–97), respectively. In the 140 pts without MRDneg by EOI, treatment-emergent adverse event (TEAE) rates with PON/IMA were 100%/98% (gr ≥3: 91%/94%); dose modification due to TEAEs: 71%/54% (discontinuation: 15%/9%; reduction: 16%/28%; interruption: 66%/41%). In the 48 pts with MRDneg post-C4D1, TEAE rates with PON/IMA were 100%/100% (gr ≥3: 91%/100%); dose modification due to TEAEs: 69%/62% (discontinuation: 6%/0%; reduction: 11%/46%; interruption: 69%/38%). **Conclusions:** Among pts without MRDneg by EOI, more pts who continued the study achieved deep and durable molecular response after C4D1, and 2-y EFS appeared to be better with PON than IMA. These data support the clinical benefit and tolerability of continuing PON in pts without MRDneg by EOI. Clinical trial information: NCT03589326. Research Sponsor: Takeda Development Center Americas, Inc.

Response in pts without MRDneg by EOI who continued treatment post-C4D1, n (%)	PON (n=73)	IMA (n=40)
MRDneg	35 (48)	13 (33)
By end of C9	28 (38)	11 (28)
By end of C20	30 (41)	12 (30)
MR4.5 (*BCR::ABL1*^{IS} ≤0.0032%)	27 (37)	4 (10)
By end of C9	17 (23)	2 (5)
By end of C20	23 (32)	3 (8)

6511 Rapid Oral Abstract Session

Reduced dose PTCy in patients with acute myeloid leukemia receiving matched unrelated donor allogeneic hematopoietic stem cell transplantation.

Nihar Desai, Mohammed Althobaiti, Tommy Alfaro-Moya, Eshrak Al-Shaibani, Igor Novitzky-Basso, Ivan Pasic, Fotios Michelis, Dennis Dong Hwan Kim, Rajat Kumar, Jonas Mattsson, Arjun Datt Law; Princess Margaret Hospital, Toronto, ON, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; Princess Margaret Cancer Centre,, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Post-transplant cyclophosphamide (PTCy) at 50 mg/kg on D+3 & +4 after allogeneic hematopoietic cell transplantation (HCT) is established for graft-versus-host disease (GvHD) prophylaxis. PTCy causes significant toxicities, including bloodstream infections (BSI), delayed engraftment, viral reactivations, hemorrhagic cystitis (HC), cardiotoxicity, and fluid overload (FO), contributing to increased non-relapse mortality (NRM). **Methods:** In July 2024, we initiated a pilot to evaluate reduced (35 mg/kg on D+3 & +4) PTCy dosing (PTCy70). We included patients with AML receiving 10/10 matched unrelated donor peripheral blood grafts. All patients received fludarabine and busulfan conditioning. GvHD prophylaxis included anti-thymocyte globulin (ATG 2 mg/kg), a calcineurin inhibitor, & PTCy70. Outcomes were compared with a contemporary cohort receiving PTCy 100. **Results:** From July-Dec 2024, 30 patients received PTCy70. Baseline characteristics were comparable except for conditioning intensity (Table 1). Median follow up was 497 days (316 – 733) & 80 days (56 – 119) for PTCy100 & PTCy70, respectively. No graft failure occurred in PTCy70 group vs one in PTCy100 group. Median time to neutrophil engraftment was comparable, 20 days (19–21). Median time to platelet engraftment was shorter in the PTCy70 group (14 vs. 16 days, p=0.01). At D+30, the incidence of platelet engraftment was significantly higher in the PTCy70 group (87% vs. 81%, p=0.01).D+30 incidence of BSI was much lower in the PTCy70 group (30% vs. 59%, p=0.005). Most BSIs in both groups were caused by gram-positive organisms (71% vs. 77%, p=0.7). CMV at D+100 was 7.2% (95% CI: 1.2 – 21) in PTCy70 and 18.7% (95% CI: 12 – 27) in the PTCy100 group (p=0.14). None of the patients receiving PTCy70 developed HC vs. 11 in the PTCy100 group. FO occurred in 16 (53%) patients (grade 1: 12; grade 2: 4) receiving PTCy70, with none developing >grade 2 FO. There was no difference in the median duration of admission (31 days, p=0.9).Six patients receiving PTCy70 developed grade II-IV aGvHD. Four had grade II skin GvHD & responded to topical steroids. At D+100, there was no significant difference in grade II-IV (18.7% vs. 29%, p=0.29), grade III-IV acute GvHD (4.8% vs. 3.3%, p=0.80), and NRM (5.3% vs 1.8%, p=0.62). **Conclusions:** PTCy70 is associated with faster platelet engraftment & lower BSI, with no increase in aGVHD. PTCy70 also seems to reduce HC and viral reactivation. Extended follow-up is necessary to examine longer term outcomes. Research Sponsor: None.

Baseline characteristics.

	PTCy 100	PTCy 70	p
Age, years, median (IQR)			
Recipient	59 (49 – 66)	63.5 (57 – 67)	0.07
Myeloablative conditioning, n (%)	46 (41)	5 (17)	0.01
CMV serostatus, n (%)			
D+/R+	57 (51)	14 (47)	
D+/R-	35 (31)	6 (20)	0.13
D-/R+	4 (4)	4 (13)	
D-/R-	16 (14)	6 (20)	
CD34+ cell dose x 10^6/kg, median (IQR)	7.5 (6.3 – 8.1)	6.7 (5.3 – 8)	0.07

Overall survival (OS) and duration of response for transfusion independence (TI) in erythropoiesis stimulating agent (ESA)–naive patients (pts) with very low-, low-, or intermediate-risk myelodysplastic syndromes (MDS) treated with luspatercept (LUSPA) vs epoetin alfa (EA) in the COMMANDS trial.

Guillermo Garcia-Manero, Matteo Giovanni Della Porta, Amer Methqal Zeidan, Rami S. Komrokji, Veronika Pozharskaya, Shelonitda Rose, Karen Keeperman, Yinzhi Lai, Sameer Kalsekar, Barkha Aggarwal, Dimana Miteva, David Valcárcel, Pierre Fenaux, Jake Shortt, Uwe Platzbecker, Valeria Santini; University of Texas MD Anderson Cancer Center, Houston, TX; IRCCS Humanitas Research Hospital, Milan, Italy; Yale University School of Medicine, New Haven, CT; Moffitt Cancer Center, Tampa, FL; Bristol Myers Squibb, Princeton, NJ; Bristol Myers Squibb, Hyderabad, Telangana, India; Bristol Myers Squibb, Boudry, Switzerland; Hospital Universitari Vall d'Hebron, Barcelona, Spain; Hôpital Saint-Louis, Université de Paris 7, Paris, France; Monash University and Monash Health, Melbourne, VIC, Australia; University Hospital Leipzig, Leipzig, Germany; University of Florence, DMSC, AOUC, Florence, Italy

Background: In the phase 3 COMMANDS trial (NCT03682536), LUSPA was superior in improving red blood cell (RBC)-TI ≥12 wks with concurrent hemoglobin increase ≥1.5 g/dL in Wks 1 to 24 vs EA and had durable clinical benefit in pts with ESA-naive transfusion-dependent (TD) lower-risk MDS (LR-MDS; Della Porta MG, et al. *Lancet Haematol*. 2024; Garcia-Manero G, et al. *ASH*. 2024). Here, we report updated results including OS and duration of response. **Methods:** Eligible pts (≥18 yrs; ESA-naive; RBC TD; very low/low/intermediate-risk MDS) were randomized 1:1 (stratified by baseline [BL] RBC transfusion burden [TB], serum erythropoietin [EPO] level, and ring sideroblast [RS] status) to receive LUSPA (1.0-1.75 mg/kg) SC Q3W or EA (450-1050 IU/kg; max dose 80,000 IU) SC QW for ≥24 wks. Secondary endpoints included OS, duration of RBC-TI ≥12 wks, and safety. **Results:** As of Nov 4, 2024, median follow up (FU) was 29.0 and 27.1 mos for the LUSPA (n=182) and EA (n=181) groups, respectively. Median OS for LUSPA was not reached (NR) and was 46.7 mos for EA (HR, 0.86; 95% CI, 0.60-1.24); 3-yr OS rates were 63.8% and 62.2%, respectively, and 5-yr OS rates were 54.0% and 41.8%. In subgroups, similar OS trends were observed (Table). Overall, RBC-TI ≥12 wks (Wk 1 to end of treatment [EOT]) was reached by 76.4% (139/182) of pts in the LUSPA group and 55.8% (101/181) in the EA group. Median cumulative duration (95% CI) of RBC-TI ≥12 wks (sum of all durations of RBC-TI ≥12 wks episodes from Wk 1 to EOT) was 187.3 (119.6-NE) wks for LUSPA vs 94.9 (73.1-179.0) wks for EA (HR, 0.51; 95% CI, 0.34-0.77). Median duration (95% CI) of longest RBC-TI ≥12 wks period (from Wk 1 to EOT) was 126.6 (81.0-184.4) vs 86.7 (55.9-111.1) wks (HR, 0.64; 95% CI, 0.44-0.93). At cutoff, 24.7% of LUSPA pts and 11.2% of EA pts were on treatment; 84.6% and 82.7%, respectively, had ≥1 dose escalation. With longer FU, no new safety concerns emerged. Deaths occurred in both groups on- (10.4% vs 9.5%) and post-treatment (20.9% vs 26.3%). Progression to acute myeloid leukemia was comparable between groups (3.8% vs 4.4%). **Conclusions:** LUSPA led to improvements in response rate and duration, with a positive OS trend requiring further evaluation through more extended follow up. LUSPA signifies a new standard of care for anemia in first-line LR-MDS. Clinical trial information: NCT03682536. Research Sponsor: Bristol Myers Squibb.

Median OS, mos	LUSPA	EA	HR (95% CI)
Overall (ITT)	(n=182)	(n=181)	0.86
	NR	46.7	(0.60-1.24)
Stratification subgroup			
BL TB <4 U	(n=118)	(n=111)	0.87
	NR	46.7	(0.55-1.38)
BL TB ≥4 U	(n=64)	(n=70)	0.74
	NR	48.2	(0.42-1.31)
RS+	(n=133)	(n=130)	0.77
	NR	48.2	(0.50-1.19)
RS−	(n=49)	(n=50)	0.93
	NR	46.2	(0.50-1.75)
BL EPO ≤200 U/L	(n=145)	(n=144)	0.84
	NR	51.4	(0.55-1.27)
BL EPO >200 U/L	(n=37)	(n=37)	0.81
	NR	35.4	(0.40-1.64)

ITT, intention-to-treat; U, units.

6513 Rapid Oral Abstract Session

Efficacy of macrophage checkpoint Clever-1 inhibition with bexmarilimab plus azacitidine in myelodysplastic syndrome: Results from the ph1/2 BEXMAB study.

Naval Guastad Daver, Mika Kontro, Johanna Rimpiläinen, Marja Pyörälä, Timo Siitonen, Mikko Myllymäki, Joshua F. Zeidner, Ruth Witherall, Emma Searle, Petri Bono, Dr Birge Berns, Sofia Aakko, Maija Hollmen, Amer Methqal Zeidan, Anthony Selwyn Stein; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; Helsinki University Hospital and University of Helsinki, and Finnish Cancer Institute, Helsinki, Finland; Department of Internal Medicine, Tampere University Hospital, Tampere, Finland; Kuopio University Hospital, Kuopio, Finland; Cancer Center, Oulu University Hospital, Oulu, Finland; Helsinki University Hospital and University of Helsinki, Helsinki, Finland; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Royal Cornwall Hospitals NHS Trust, Truro, United Kingdom; The Christie Hospital NHS Foundation Trust; University of Manchester, Manchester, United Kingdom; Faron Pharmaceuticals, Turku, Finland; Faron Pharmaceuticals Oy, Turku, Finland; University of Turku, Turku, Finland; Department of Internal Medicine, Yale Cancer Center and Smilow Cancer Hospital, New Haven, CT; City of Hope Cancer Center, Duarte, CA

Background: Treatment of higher-risk (HR) myelodysplastic syndrome (MDS) represents an unmet medical need. Hypomethylating (HMA) agents, including azacitidine, are used in the frontline setting for HR MDS patients with complete remission rate reported as 16% (Hasegawa et al., 2023) After HMA-failure, including primary refractory disease or relapse after frontline treatment (r/r MDS), the reported median overall survival (mOS) is <6 months (Prébet et al., 2011). Bexmarilimab, a first-in-class macrophage checkpoint inhibitor, blocks Common lymphatic and vascular endothelial receptor-1 (Clever-1) to enhance macrophage antigen presentation and T cell activation. In the MDS bone marrow (BM), Clever-1 is also abundant on malignant blasts. Translational data suggest that by inhibiting blast Clever-1, bexmarilimab hampers the energy production of the malignant cells. Thus, bexmarilimab may alter the BM immune microenvironment and make the blasts susceptible to other cytotoxic agents, such as HMAs, thereby enhancing their effectiveness in patients with HR MDS, both in frontline and r/r setting. **Methods:** The Phase 1/2 (Ph1/2) BEXMAB study investigates safety, tolerability and preliminary efficacy of bexmarilimab in combination with standard-of-care, azacitidine, in HR MDS. Key inclusion criteria include indication for azacitidine treatment with a risk score of >3 based on the revised International Prognostic Scoring System (IPSS-R) and for r/r MDS, failure to achieve response to or disease progression during treatment with HMA or HMA containing regimen. In Ph1, Bayesian optimal interval (BOIN) design was used for dose escalation to identify recommended dose for expansion (RDE). Ph1 studied 1, 3 and 6mg/kg bexmarilimab, administrated weekly in 28-day cycles, in combination with a standard regimen of azacitidine (75 mg/m^2 D1-7 each cycle). r/r MDS was selected as the first population for Ph2 dose optimization and expansion following a Simon's 2-stage design, with subjects randomized to RDE (6mg/kg) and RDE-1 (3mg/kg). After dose escalation, Ph1 expansion cohorts were used to enrich frontline MDS population at RDE and RDE-1. **Results:** Safety and efficacy data from 20 frontline HR MDS and 35 r/r MDS patients, comparing bexmarilimab dose levels, will be reported. Previous analysis per IWG2006 criteria indicated an overall response rate (ORR) of 100% in 5 frontline MDS patients and 80% in 20 r/r MDS patients (65% per IWG2023). Simultaneously, a median overall survival estimate of 13.4 months, was reported for the r/r MDS population. During dose escalation, no dose limiting toxicities (DLT) were reported during the 28-day DLT period. Ongoing safety follow-up indicates a total of 277 treatment-emergent adverse events, of which 38 (13.7%) are considered bexmarilimab-related. **Conclusions:** Enrolment for both dose finding and randomized dose optimization parts (n=55) of the BEXMAB Phase 1/2 study has been completed. Safety and efficacy results for both populations will be reported for the first time. Clinical trial information: NCT05428969. Research Sponsor: Faron Pharmaceuticals.

6514 Rapid Oral Abstract Session

Dosing decitabine and venetoclax for terminal differentiation to improve outcomes in TP53 mutant MDS and AML.

Bradley Rockwell, Ioannis Mantzaris, Aditi Shastri, Brian Andrew Jonas, Yogen Saunthararajah, David Levitz, Jhannine Verceles, Dennis Cooper, Anne Munoz, Aradhika Dhawan, Kith Pradhan, Noah Kornblum, Alejandro R. Sica, Stephen Peeke, Ridhi Gupta, Kira Gritsman, Marina Konopleva, Eric J. Feldman, Amit Verma, Mendel Goldfinger; Montefiore Einstein Comprehensive Cancer Center, Bronx, NY; UC Davis Comprehensive Cancer Center, Sacramento, CA; Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH

Background: Mutations in the tumor suppressor TP53 gene are common in elderly patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) and confer resistance to conventional chemotherapeutic DNA damaging agents. Venetoclax (Ven) added to the hypomethylating agents (HMA) of Decitabine or Azacitidine is the current standard of care for elderly patients with AML and is frequently used in high-risk MDS (HR-MDS). Currently approved dosing schedules of HMA/Ven rely on cytotoxicity and have not improved outcomes in the TP53 mutant population. The efficacy and tolerability of metronomic weekly dosing of Decitabine and Ven in HR-MDS and AML were previously described (Goldfinger et al, Blood 2024). Mechanistically, metronomic dosing relies on terminal differentiation, rather than cytotoxicity making it an attractive regimen for TP53 mutant MDS/AML. **Methods:** Patients with histologically confirmed AML or MDS and a TP53 mutation received a once-weekly dose of decitabine 0.2 mg/kg subcutaneously and one dose of Ven 400 mg on days 1, 8, 15 and 22 of a 28-day cycle. **Results:** Between April 2020 and January 2025, 40 patients with TP53 mutated myeloid malignancies were treated with metronomic weekly low-dose Decitabine/Ven (14 AML, 26 MDS). Twenty-four patients were followed prospectively as part of a clinical trial (NCT05184842), and 16 were treated off-trial and had data collected retrospectively. Median age at diagnosis was 76.5 years, 13 (32%) were from minority backgrounds, 28 (70%) had complex cytogenetics and 31 (82%) had biallelic TP53 mutations (median VAF 36%). All AML patients were ELN-poor risk, 21 MDS patients (82%) were R-IPSS high or very high risk. The median time on therapy was 5.8 months, with 10 (25%) patients still on therapy at time of data cut-off. Four patients in the AML and five in the MDS cohorts were not evaluable (2 withdrew consent, 1 lost to follow-up and 6 did not have a BM biopsy for evaluation). Of the evaluable AML patients, 7 (70%) achieved a complete remission (CR), 3 (30%) did not respond. In the evaluable MDS patients, 9 (43%) achieved a CR and 3 (15%) a marrow CR, 4 (19%) with stable disease, 5 (24%) with no response. Of the 26 patients who were transfusion-dependent at the start of therapy, 15 (58%) became transfusion-independent. For the entire cohort (n=40), the median overall survival (OS) was 11.3 months. For the AML and MDS cohorts, the OS was 11.6 and 9.9 months, respectively. In patients who underwent allogeneic stem cell transplant (n=6), OS was 16 months. Non-heme therapy-related adverse events of $\geq$ grade 3 was seen in 13 (54%) of patients. **Conclusions:** In this cohort, of elderly patients with poor risk TP53 mutated MDS and AML the use of a non-cytotoxic dosing schedule of Decitabine and Ven resulted in over half the patients achieving a CR and transfusion independence. The median OS of 11.3 months compares favorably to currently approved cytotoxic dosing of HMA/Ven. Clinical trial information: NCT05184842. Research Sponsor: None.

6515 Rapid Oral Abstract Session

IMproveMF update: Phase 1/1B trial of imetelstat (IME)+ruxolitinib (RUX) in patients (pts) with intermediate (INT)-1, INT-2, or high-risk (HR) myelofibrosis (MF).

John Mascarenhas, Terrence J. Bradley, Bart L. Scott, Habte Aragaw Yimer, Souria Dougherty, Lixian Peng, Fei Huang, Ying Wan, Faye Feller, Vivian Rodolf, Judy Ho, Tymara Berry, Andrew Tucker Kuykendall, Salman Otoukesh; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL; Fred Hutchinson Cancer Center, Seattle, WA; Texas Oncology/US Oncology Research, Tyler, TX; Geron Corporation, Foster City, CA; Moffitt Cancer Center, Tampa, FL; City of Hope Comprehensive Cancer Center, Duarte, CA

Background: IME, a first-in-class, direct, and competitive inhibitor of telomerase activity, showed potential survival improvements and disease-modifying activity in the phase 2 IMbark MF trial (NCT02426086). Preclinical evidence demonstrated IME+RUX reduced disease burden better than either agent alone. IMproveMF (NCT05371964) aims to evaluate IME+RUX in pts with INT-1/INT-2/HR MF. **Methods:** IMproveMF is an open-label, single-arm, phase 1/1b trial (part 1: dose escalation; part 2: dose confirmation and expansion) of IME+RUX in adults with DIPSS INT-1, INT-2, or HR MF. In part 1 (up to 21 pts), RUX was required for ≥12 wk with a stable dose for ≥4 wk immediately before adding IME; pts received IME via intravenous infusion at each dose level cohort (4.7, 6.0, 7.5, and 9.4 mg/kg IME sodium; equivalent to 4.4, 5.6, 7.1, and 8.9 mg/kg active dose, respectively) every 28 d based on Bayesian Optimal Interval design to identify the recommended part 2 dose (RP2D). Pts in part 1 were dose adjusted to the RP2D as needed in part 2, with 2 dose reductions allowed. Part 2 of the trial will enroll pts who are RUX naive. Primary endpoints are adverse events (AE), including dose-limiting toxicity (DLT), in part 1 and AEs and 24-wk response rate (≥50% reduction in MF total symptom score [TSS]) in part 2. Secondary endpoints include pharmacokinetics (PK) and clinical activity. Total planned enrollment is ≈41 pts. **Results:** As of 11/04/2024, 17 pts were enrolled in part 1 with a median age of 67 y (71% aged ≥65 y); 7 had INT-1, 9 INT-2, and 1 HR MF. Respective to the dose levels in the Methods, 3, 3, 4, and 7 pts received the corresponding IME dose level. No DLTs were reported for IME; 2 pts had dose reductions due to neutropenia. Five pts discontinued IME (none due to AEs). Four pts had RUX dose reductions (due to AEs and other, n=2 each). AEs were experienced by 15 pts; 8 experienced grade 3 events of anemia (n=4), neutropenia (n=3), leukopenia (n=2), abdominal pain, fatigue, epistaxis, and pneumonia (n=1 each; the latter 2 and 1 anemia event were considered serious AEs). There were no grade 4/5 AEs. There was an overall reduction in TSS from baseline (median, −5 points in maximum absolute reduction up to wk 24) with IME regardless of dosing, and a trend of dose-dependent spleen volume decrease. A reduction in variant allele frequency of several driver mutations was also observed. Hematologic, PK, and additional mutational data will be included in the presentation, as available. **Conclusions:** In part 1 of IMproveMF, no DLTs were observed and the RP2D dose of 9.4 mg/kg IME was determined. AEs were consistent with those observed in other IME clinical trials, and preliminary efficacy was positive, demonstrating the potential of IME+RUX in this pt population with high unmet needs. Part 2 of this trial is ongoing across the US at 6 sites. Clinical trial information: NCT05371964. Research Sponsor: This study was funded by the Geron Corporation. All authors contributed to and approved the abstract; writing and editorial support were provided by Jeremy J. Henriques, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by the Geron Corporation.

Efficacy and safety of asciminib (ASC) in patients (pts) with chronic-phase chronic myeloid leukemia (CML-CP) after 1 tyrosine kinase inhibitor (TKI): Interim analysis (IA) of the phase 2 ASC2ESCALATE trial.

David Jacob Andorsky, Marlise R. Luskin, Srinivas Kiran Tantravahi, Koji Sasaki, James Dugan, Celeste A. Bremer, Vivian G. Oehler, Joshua F. Zeidner, Moshe Yair Levy, Camille N. Abboud, Ehab L. Atallah, Paul B. Koller, Bonnie Kiner-Strachan, Habte Aragaw Yimer, Daisy Yang, J. Randy Sabo, Bridget Cooper, Dheeraj Gianchandani, Jorge E. Cortes, Michael J. Mauro; Rocky Mountain Cancer Centers, US Oncology Research, Boulder, CO; Dana-Farber Cancer Institute, Boston, MA; Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; Novant Health Cancer Institute, Winston-Salem, NC; Virginia Oncology Associates, Virginia Beach, VA; Fred Hutchinson Cancer Center Hematology Clinic, Seattle, WA; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Baylor Scott and White Research Institute, Dallas, TX; Washington University School of Medicine, St. Louis, MO; Medical College of Wisconsin, Milwaukee, WI; City of Hope National Medical Center, Duarte, CA; Perlmutter Cancer Center, NYU, Long Island, NY; Christus Trinity Mother Frances Hospital Texas Oncology, Tyler, TX; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Healthcare Private Limited, Hyderabad, India; Georgia Cancer Center, Augusta, GA; Memorial Sloan Kettering Cancer Center, New York, NY

Background: ASC2ESCALATE (NCT05384587) is the first prospective trial of ASC in CML-CP after 1 TKI (2L) with dose escalation for pts with suboptimal response; ASC is also being assessed in a separate newly diagnosed (1L) cohort. A previous IA of the 2L cohort reported ASC's safety (n=71) and wk 24 efficacy (n=28; *BCR::ABL1*^{IS} ≤1%, 85.7%; major molecular response [MMR], 42.9%). We report updated safety (n=101) and wk 24 efficacy (n=63) results. **Methods:** ASC2ESCALATE is a phase 2, single-arm, open-label US study of ASC in adults with 1L or 2L CML-CP without the T315I mutation. In the 2L cohort, eligible pts had discontinued their prior TKI due to warning or failure per ELN2020 or intolerance with *BCR::ABL1*^{IS} >0.1% at screening. Pts received ASC 80 mg once daily (QD). If *BCR::ABL1*^{IS} >1% at wk 24, dose was increased to 200 mg QD. If *BCR::ABL1*^{IS} >0.1% at wk 48, dose was increased from 80 to 200 mg QD or from 200 mg QD to 200 mg twice daily, or pts could be taken off study. If pts had any grade 3/4 or persistent grade 2 toxicity refractory to optimal management, they were ineligible for dose escalation at wk 24 and/or 48 and continued the same dose. **Results:** This IA included all 101 pts enrolled with 2L CML-CP; all pts had received ≥1 ASC dose by the cutoff (Nov 15, 2024). Prior treatment (Tx) included dasatinib (44.6%), imatinib (42.6%), nilotinib (9.9%), or bosutinib (5.0%); 66.3% of pts had received prior Tx for ≥12 mo. Pts discontinued prior Tx due to lack of efficacy (56.4%) or intolerance (43.6%). By the cutoff, 92 pts (91.1%) remained on ASC; 9 pts (8.9%) discontinued ASC, mostly due to adverse events (AEs; n=4) and pt decision (n=3). Median duration of ASC exposure was 26.1 (range, 6-100) wk. Pts evaluable for all efficacy analyses completed assessments for the respective timepoint or discontinued earlier (wk 4, n=94; wk 12, n=86; wk 24, n= 63). At wk 4, 12, and 24, 46.8%, 84.9%, and 82.5% pts, respectively, had *BCR::ABL1*^{IS} ≤1%. Deeper responses were also achieved at wk 12 (MMR, 39.5%; MR^4, 11.6%; MR$^{4.5}$, 2.3%) and 24 (MMR, 44.4%; MR^4, 25.4%; MR$^{4.5}$, 9.5%). Seven pts had dose escalation from 80 to 200 mg QD per their response level at wk 24 (n=3) and 48 (n=4). All-grade AEs ≥20% were headache (22.8%) and nausea (20.8%). Grade ≥3 AEs ≥5% were hypertension (8.9 %), thrombocytopenia (6.9%), and neutropenia (5.9%). AEs led to dose adjustment/interruption in 27 pts (26.7%). AEs led to discontinuation in 4 pts; 1 of these AEs occurred >30 d after last ASC dose. No arterial-occlusive events or on-Tx deaths occurred. **Conclusions:** 2L ASC demonstrated high molecular response rates at wk 24 and safety consistent with previously established ASC data across Tx lines; no new or worsening safety signals arose. ASC was tolerable with few AEs leading to discontinuation. These IA results support ASC as a Tx option in 2L CML-CP. The impact of dose escalation continues to be explored. Clinical trial information: NCT05384587. Research Sponsor: Novartis Pharmaceuticals Corporation.

6517 Rapid Oral Abstract Session

Age-related macular degeneration in individuals with clonal hematopoiesis.

Keishla Marie Arce-Ruiz, Lachelle D. Weeks, Caitlyn Vlasschaert, Shai Shimony, Yating Wang, Md Mesbah Uddin, Pradeep Natarajan, Alexander G. Bick, Benjamin Levine Ebert, Demetrios Vavvas; McGraw/Patterson Center for Population Sciences, Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Queen's University, Kingston, ON, Canada; Dana-Farber Cancer Institute, Boston, MA; Program in Medical and Population Genetics and Cardiovascular Disease Initiative, Broad Institute of Harvard and MIT, Cambridge, MA; Program in Medical and Population Genetics and Cardiovascular Disease Initiative, Broad Institute of Harvard and MIT, Boston, MA; Vanderbilt University Medical Center, Nashville, TN; Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA

Background: Clonal hematopoiesis (CH), an age-related condition involving somatic mutations in blood stem cells, increases the risk of myelodysplastic syndrome (MDS), blood cancers and cardiovascular disease through inflammatory pathways. Age-related macular degeneration (AMD), the leading cause of blindness in the developed world, is also characterized by chronic inflammation. An increased prevalence of AMD has been observed in older adults with MDS, but the association between CH and AMD remains unexplored. Understanding this relationship could reveal shared inflammatory mechanisms in age-related diseases and guide prevention strategies. **Methods:** This retrospective cohort study used exome sequencing and electronic medical records (EMRs) from 467,200 adults ≥40 years of age in the UK Biobank (UKB), recruited between 2006–2010 and followed until 2020. Participants with prevalent blood cancer, AMD, or with missing AMD diagnosis dates were excluded. CH was defined as pathogenic somatic mutations with a variant allele fraction (VAF) ≥0.02. Incident AMD was identified using ICD-10 codes (H35.3). Kaplan-Meier estimates and log-rank tests assessed cumulative incidence, while Cox regression models calculated hazard ratios (HRs), adjusted for age, sex, smoking and hypertension. A separate cohort of 4,079 patients from Dana-Farber Cancer Institute (DFCI) validated findings and enabled granular clinical data abstraction from EMRs. **Results:** CH was detected in 29,550 (6.8%) individuals of the UKB. The 12-year cumulative incidence (C.I.) of AMD was higher in individuals with CH (n=671, C.I. 2.45%) compared to those without (n=6,728, 1.61%; p<2x10-16). In unadjusted Cox models, individuals with CH had a 51% higher risk of AMD compared to those without (HR =1.51 (95% CI: 1.39–1.63; $p < 2\times10^{-16}$), remaining significant after adjusting for covariates (p=0.023). CH genotypes most associated with AMD risk included *ASXL1* (HR: 1.32; p = 0.0146) and splicing factors (HR: 1.54; p = 0.0345). Individuals with CH and AMD had a 33% higher risk of progressing to blindness compared to those without CH, though this was not statistically significant (p = 0.242). In the DFCI cohort (n= 4,079), CH was present in 1,028 (25.2%) individuals. 86 (8.37%) individuals with CH had AMD diagnoses compared to those without CH (n= 86, 3.21%; $p = 2.53\times10^{-10}$), with exudative AMD, a more severe subtype, being more prevalent in CH patients (n=11; $p = 1.1\times10^{-5}$). **Conclusions:** There is a significant association between CH and AMD, suggesting that AMD prevalent in individuals with MDS is related to presence of CH in the pre-MDS state. Real world data support these findings, highlighting a trend towards severe AMD subtypes in individuals with CH. The identification of specific genes linked to AMD incidence suggests that certain CH genotypes may confer a higher risk for AMD, highlighting the role of AMD screening in individuals with myeloid malignancy precursor conditions. Research Sponsor: Conquer Cancer - The ASCO Foundation.

6518 Poster Session

Outcomes in patients (pts) younger than 50 years old (yo) with treatment-naïve blastic plasmacytoid dendritic cell neoplasm (BPDCN) treated with tagraxofusp (TAG): Subanalysis of a phase 1/2 trial.

Anthony Selwyn Stein, Andrew A. Lane, Kendra Lynn Sweet, Sumithira Vasu, Alessandra Tosolini, John Katsetos, Marina Konopleva, Naveen Pemmaraju; City of Hope, Duarte, CA; Dana-Farber Cancer Institute, Boston, MA; Moffitt Cancer Center, Tampa, FL; The Ohio State University Comprehensive Cancer Center, Columbus, OH; Menarini Group, New York, NY; Montefiore Medical Center, Albert Einstein Comprehensive Cancer Center, Bronx, NY; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: BPDCN is an aggressive, orphan hematologic malignancy characterized by cells expressing CD123 and other markers. In BPDCN pts <50 yo, including in the adolescent and young adult (AYA) population (ie, pts 15-39 yo), data are limited. TAG, a first-in-class CD123-targeted therapy, is the only drug approved for adults (US/EU) and pediatric pts aged ≥2 yo (US only) with BPDCN. TAG has a well-characterized and manageable safety profile, with transient adverse events (AEs) occurring mostly in cycle 1, no cumulative long-term toxicity, and no myelosuppression. While not approved, multi-agent chemotherapy is used in AYAs, resulting in short- and long-term toxicity, including myelosuppression. Here we report the safety and efficacy of 1L TAG treatment, with prespecified/multi-system response criteria, for BPDCN pts <50 yo from a subgroup analysis of the phase 1/2 TAG monotherapy study (NCT02113982). **Methods:** We analyzed outcomes in treatment-naïve pts <50 yo who received 1L TAG 12 μg/kg intravenously on days 1-5 of a 21-day cycle. Assessed outcomes included best response, time to best response, duration of response (DOR), overall survival (OS), treatment-related adverse events (TRAEs), and capillary leak syndrome (CLS). **Results:** Ten pts (median age of 31.5 yo [range 22-45]) were included in this analysis, including 6 AYA pts. All pts had ECOG PS of 0-1, 20% had bone marrow involvement, and 60% had ≥2 sites of BPDCN disease. Pts received a median of 4 cycles (range 2-7) of TAG. In cycle 1, pts received a median of 5 TAG doses (range 3-5) in line with the USPI dosing. At a median follow-up of 34 months, the CR/CRc rate was 70%, with a 41-day median time to CR/CRc. DOR was not reached (range 8.4-51.8 months); median OS was 38.4 months. All pts were bridged to stem cell transplantation (SCT), including 2 autologous SCTs: 7 pts with CR/CRc following TAG treatment (median time from last TAG dose to SCT, 38 days) and 3 pts with PR or SD were bridged to SCT following subsequent multi-agent chemotherapy. Most common Grade 3-4 TRAEs were thrombocytopenia and ALT/AST elevation; the majority of TRAEs resolved with resolution in the same cycle; no grade 5 TRAEs occurred. No pts had a dose reduction or discontinuation due to a TRAE. No investigator-assessed CLS was reported, although some pts required dose interruption due to weight gain or hypoalbuminemia. **Conclusions:** In treatment-naïve BPDCN pts <50 yo, including AYAs, TAG, a chemotherapy-free option, induced high rates of CR/CRc (70%) and allowed all pts who achieved CR/CRc to bridge to SCT. TAG was well tolerated with no cumulative AEs or cumulative myelosuppression. No investigator-assessed CLS was observed in these younger pts. Overall, TAG is an effective front-line therapy, including in pts <50, with durable (median not reached) responses and prolonged survival. Clinical trial information: NCT02113982. Research Sponsor: Menarini Group.

6519 Poster Session

Decoding immune dysregulation in AML: Insights from integrated genomic and transcriptomic analysis.

Harsh Goel, Pranay Tanwar; All India Institute of Medical Science (AIIMS), New Delhi, India

Background: Acute Myeloid Leukemia (AML) is an aggressive hematologic malignancy marked by abnormal proliferation of myeloid progenitor cells, often leading to poor outcomes and high relapse rates. While the genetic underpinnings of AML are well-documented, the role of immune dysregulation in its progression remains underexplored. This study integrates whole exome sequencing (WES) and transcriptome analysis to identify genetic mutations, transcriptional alterations, and immune regulatory disruptions, with a focus on their contributions to hematopoiesis and immune dysfunction. **Methods:** WES and RNA sequencing were performed on 10 AML patient samples to investigate somatic mutations, differential gene expression, and immune-related pathways. WES data were analyzed to detect mutations in AML-associated genes, while transcriptomic analysis compared gene expression profiles between AML cells and normal hematopoietic stem cells (HSCs). Bioinformatic tools, including differential expression analysis, Gene Set Enrichment Analysis (GSEA), and pathway mapping, were employed to identify key regulatory networks. Single-cell RNA sequencing (scRNA-seq) was conducted to assess cellular heterogeneity and differentiation dynamics, with a focus on immune cell subsets and pathways involved in immune evasion. **Results:** Analysis revealed recurrent mutations and dysregulation in genes critical to hematopoiesis, apoptosis, and immune regulation, including *RUNX1, FLT3, CEBPA, TP53, WT1, GATA2,* and *TET2*. Transcriptomic profiling highlighted distinct gene expression patterns in AML cells, with significant disruption in cell cycle control, differentiation, and apoptosis. Dysregulated immune pathways, such as IL-7R and PD-1, were identified as key contributors to immune cell activation impairment and immune tolerance. scRNA-seq data provided insights into the cellular heterogeneity of AML, uncovering altered lineage differentiation and immune subset composition, which may facilitate immune evasion and disease progression. **Conclusions:** This integrative analysis illuminates the interplay between genetic mutations, transcriptional dysregulation, and immune dysfunction in AML. The findings underscore the pivotal role of immune pathways, such as IL-7R and PD-1, in AML pathogenesis, presenting them as potential therapeutic targets. By linking genetic and immune alterations, this study advances our understanding of AML biology and highlights the need for therapies addressing both genetic and immune dysfunctions to improve clinical outcomes. Research Sponsor: None.

V-RULES: Real-world effectiveness and safety of CPX-351 in patients with secondary acute myeloid leukemia (AML).

Thomas William LeBlanc, Catherine Lai, Amir Ali, Onyee Chan, Doria Cole, Jesus David Gonzalez Lugo, Kristin Lynn Koenig, Mimi Ming Lo, Matthew Newman, Saemi Park, Giuseppe Piccoli, Charlotte Burton Wagner, Amanda Lopez, George Yaghmour, Eunice S. Wang; Department of Medicine, Duke University School of Medicine, Durham, NC; Division of Hematology and Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Department of Pharmacy, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA; Department of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Jazz Pharmaceuticals Inc., Philadelphia, PA; Division of Hematologic Malignancies and Cellular Therapeutics, The University of Kansas Medical Center, Kansas City, KS; Division of Hematology, Department of Medicine, The Ohio State University, Columbus, OH; Department of Clinical Pharmacy, University of California San Francisco, San Francisco, CA; Department of Pharmacy, The Johns Hopkins Hospital, Baltimore, MD; Department of Pharmacy, University of Utah Hospitals and Clinics, Huntsman Cancer Institute, Salt Lake City, UT; Abramson Cancer Center, Perelman Center for Advanced Medicine, University of Pennsylvania, Philadelphia, PA; Jane Anne Nohl Division of Hematology, Keck School of Medicine, University of Southern California, Los Angeles, CA; Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: CPX-351 was approved for newly diagnosed (ND) therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC) following the pivotal phase 3 trial, which demonstrated improved CR/CRi (47.7% vs 33.3%) and median OS (9.56 vs 5.95 months [mo]), and comparable safety vs conventional 7+3 in adults aged 60-75 years. The Vyxeos Real-world US Long-term Effectiveness and Safety Study (V-RULES) evaluated real-world (RW) clinical outcomes and safety of CPX-351 in US patients with ND t-AML or AML-MRC. **Methods:** V-RULES is a retrospective, multicenter, single-arm study based on medical records of patients with ND t-AML or AML-MRC who were treated with CPX-351 since its FDA approval in August 2017. Primary endpoints were CR/CRi/CRh and OS. **Results:** Overall, 161 patients (t-AML, n=47; AML-MRC, n=114) received ≥ 1 induction of CPX-351 (1 cycle, n=142; 2 cycles, n=19) and 50 patients received consolidation (1 cycle, n=40; 2 cycles, n=10). Median age at AML diagnosis was 60 years (range: 21-78); 78 (48%) patients were aged <60 years. Of patients with available cytogenetic data, 88/154 (57%) were classified as adverse-risk per Grimwade 2010 and 49/155 (32%) had complex karyotype. Notably, 33/134 patients (25%) had *TP53* mutations (*TP53*m) and 57/91 patients (63%) had myelodysplasia-related gene mutations (MRm). Median follow-up time (IQR) was 9.7 mo (4.1, 27.8). CR (including minimal residual disease negativity)/CRi/CRh at any time was 63% in 149 evaluable patients (t-AML, 85%; AML-MRC, 53%). Median OS was 12.9 mo (95% CI: 8.9, 19.7) and estimated 4-year OS was 29% (95% CI: 21%, 38%). Survival was longer in patients aged <60 vs ≥ 60 years: median OS was 17.8 (95% CI: 9.6, 45.4) vs 10.6 mo (95% CI: 6.7, 13.8) and estimated 4-year OS was 37% (95% CI: 24%, 49%) vs 22% (95% CI: 12%, 34%). Compared with the overall population, median OS was shorter in patients with *TP53*m (5.3 mo [95% CI: 2.3, 7.4]) and longer in patients with MRm (17.8 mo [95% CI: 11.4, 38]). Patients who underwent hematopoietic cell transplantation (HCT) after CPX-351 treatment (38%) had a median OS post-HCT of 45.6 mo (95% CI: 24.9, not estimated). In patients with CR/CRh/CRi, median time to neutrophil (≥ 500/μL) and platelet (≥ 50,000/μL) recovery in induction 1 was 35 days (n=76) and 36 days (n=72), respectively. Infection (52%) and febrile neutropenia (42%) were the most common grade ≥ 3 adverse events (AEs); 2 patients had a serious AE of cardiac events. **Conclusions:** These results highlight the effectiveness and safety of CPX-351 for the treatment of t-AML and AML-MRC in the US RW setting, consistent with the pivotal trial and published RW data. Notably, this study demonstrated favorable outcomes for younger patients (<60 years) who were not included in the pivotal trial. Patients who received HCT also had improved outcomes, as did those with MRm. These results support the continued use of CPX-351 as the standard of care for ND t-AML or AML-MRC. Research Sponsor: Jazz Pharmaceuticals; N/A.

Venetoclax as cytoreductive therapy in high-risk acute promyelocytic leukemia: A potential alternative to anthracyclines.

Ravi Teja Banda, Attili Venkata Satya Suresh, Pradeep Reddy; Continental Hospitals, Hyderabad, India

Background: High-risk acute promyelocytic leukemia (APL) presents a significant mortality risk during induction therapy, primarily due to complications like disseminated intravascular coagulation (DIC) and treatment-related toxicities. Anthracyclines, traditionally used for cytoreduction, can cause cardiotoxicity, increase DIC risk, and induce severe neutropenia. Venetoclax has demonstrated efficacy in relapsed/refractory APL. This study explored the feasibility of using venetoclax for cytoreduction in high-risk APL patients, particularly those contraindicated for anthracyclines (cardiac issues, advanced age and in select patients based on physician discretion). **Methods:** We evaluated the safety and efficacy of venetoclax in high-risk APL patients unsuitable for anthracycline-based induction therapy. Venetoclax was initiated at 100 mg and gradually increased to 400 mg over a week. Treatment duration was determined by the patient's leukocyte count, with the goal of achieving a count below 4000/mm^3. All patients received standard ATRA (All-Trans Retinoic Acid) + ATO (Arsenic Trioxide) induction. **Results:** Ten patients received venetoclax for cytoreduction. The median age was 45 years (range: 26-70). The median duration of venetoclax therapy was 8 days (range:6-12). All patients achieved complete hematological remission within 31 days of induction and molecular remission by 28 days of the first consolidation cycle. Two patients experienced laboratory tumor lysis syndrome, and one developed differentiation syndrome which was effectively managed with continued venetoclax therapy. No patients required interruption of ATRA or ATO. Notably, no patients experienced prolonged neutropenia (> 28 days), severe mucositis (Grade 3 or 4), cardiotoxicity, or DIC. **Conclusions:** This study demonstrates the feasibility of using venetoclax for cytoreduction in high-risk APL patients. Venetoclax effectively reduced tumor burden while minimizing the risks associated with anthracyclines. These encouraging results warrant further investigation into the potential role of venetoclax in high-risk APL to improve patient outcomes and mitigate treatment-related toxicities. Research Sponsor: None.

Patient characteristics.

Patient Age/ Sex	WBC(10^3/ μL)	Platelet(10^3/ μL)	Hb (g/ L)	BM blast (%)	WBC max (10^3/ μL)	No of days venetoclax used	Cardiac comorbidity	Time to achieve HCR (days)
45/M	15000	30000	9	30	25000	9	CAD	26
40/F	13000	25000	8.8	55	19000	7	NIL	24
33/M	12000	35000	8.1	45	18000	7	NIL	28
31/F	25000	45000	9.6	40	25000	9	NIL	30
65/M	17000	10000	7.5	33	19000	9	NIL	30
45/F	15000	10000	8.5	25	16000	8	RHD	28
66/M	22000	20000	9.7	60	24000	7	CAD	29
70/F	38000	25000	7.8	34	45000	10	CAD	31
46/M	16000	10000	7	33	18000	8	CAD	30
26/F	13000	45000	9.7	30	17000	8	NIL	28

BM -Bone Marrow; WBC max- Maximum WBC before starting venetoclax; CAD-Coronary Artery Disease; RHD- Rheumatic Heart Disease; HCR-Hematological Complete Response.

6523 Poster Session

Use of BAFFR CAR-T to treat B cell leukemia/lymphoma and auto-immune diseases.

Min Luo, Guangchao Li, Wen Ding, Yongwei Zheng, Lisen Luo, Jingsong Liu, Kaikai Zeng, Donghui Ma; Guangzhou Bio-gene Technology Co., Ltd., Guangzhou, China; Department of Hematology, The Affiliated Guangdong Second Provincial General Hospital of Jinan University, Guangzhou, China; School of Life Sciences, Guangzhou Medical University, Guangzhou, China; DIMA Biotechnology, LTD., Wuhan, China

Background: BAFFR (B-cell Activating Factor Receptor) is a member of the tumor necrosis factor (TNF) receptor superfamily and is almost exclusively expressed on B cells. Meanwhile, BAFFR is found to be highly expressed on the surface of lymphoma cells. In addition, blocking the BAFF/BAFFR interaction can inhibit the maturation of B cells, which is beneficial for alleviating autoimmune diseases, such as psoriasis, inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis. These characteristics make BAFFR a promising target for B-cell malignancies and auto-immune diseases. It has been reported that BAFFR CAR-T (PMB-CT01) treated six non-Hodgkin lymphoma (NHL) patients, and all of these patients achieved CR and showed tolerable safety profile. **Methods:** In the current study, we screened out three different BAFFR antibodies (1312, 1313, and 1315) and constructed them into second-generation CARs, consisting of BAFFR scFv, 4-1BB co-stimulatory domain and CD3ζ. The preclinical efficacy of BAFFR CAR-T cells was evaluated *in vitro* and *in vivo.* **Results:** *In vitro* experiments showed that all three CAR-T cells effectively killed Raji tumor cells, with 1312-CAR-T demonstrating the strongest cytokine release and cytotoxicity. *In vivo* tumor-bearing mouse experiments using Raji cells showed that 1312-CAR-T could effectively clear tumor cells in the mice. While the control group all mice died by day 33, and the experimental group remained fully alive. In addition, SLE model using MRL/MpJ-Fas^{lpr} mice showed that BAFFR CAR-T cells could decrease the dsDNA-IgG levels in the serum. **Conclusions:** The results of this study suggest that BAFFR is an active and promising immunotherapeutic target for B-cell malignancies and auto-immune diseases. In the future, BAFFR CAR-T clinical trials will be conducted to treat B-ALL, lymphoma, and autoimmune diseases. It would be interesting to see whether BAFFR CAR-T can achieve similar or even better results than CD19 CAR-T in treating these diseases. Research Sponsor: National Natural Science Foundation of China; No. 82202034.

The IRAK4 long isoform as widely upregulated in non-splicesome mutated acute myeloid leukemia and as altered by hypomethylating agent therapy.

Eric J. Vick, Sean Walulik, Avery Sampson, Aishlin Hassan, Mark Wunderlich, Andrew Volk, Daniel Starczynowski; University of Cincinnati, Cincinnati, OH; Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background: IRAK4, a kinase effector of MyD88 signaling downstream of Toll-Like Receptor and IL-1 receptor pathways, has recently been shown to function independently of MyD88 in Myelodysplastic Syndrome (MDS) and AML leukemic cells. Our previous research demonstrated that AML leukemic stem and progenitor cells (LSPC) rely on signaling through IRAK4. Notably, AML LSPCs express a hypermorphic long splice isoform of IRAK4 (IRAK4-L) resulting from the inclusion of exon 4. IRAK4 inhibitors, currently in clinical trials for the treatment of MDS and AML, show improved efficacy in spliceosome mutants, which preferentially express IRAK4-L. However, in patients without known spliceosome mutations, the extent of IRAK4-L expression remains unclear. Additionally, the impact of IRAK4-L levels in Venetoclax and Azacitidine treatment is unknown in refractory or unfit AML. **Methods:** Umbilical cord vein blood stem cells expressing MLL-AF9 and $NRAS^{G12D}$ (CD34+MA9.NRAS) were maintained in vitro using supplemented media. Venetoclax and Azacitidine doses were incrementally increased in combination until cells tolerated co-treatment with up to 1 μM of each compound with minimal cell death. Patient-derived xenograft (PDX) samples were obtained from the Cincinnati Children's Biobank and included AML samples from diverse genetic backgrounds, relapsed/refractory cases, and pediatric populations (ages 1-20). Cell lysates were normalized to total protein and analyzed using a chemiluminescent capillary-based immunoblotting system, which requires minimal lysate quantities. An IRAK4 C-terminus antibody was used to detect both the shorter and longer IRAK4 protein isoform. RNA sequencing was performed, and transcripts were normalized per million counts. IRAK4 transcript ratios were calculated by dividing the total long isoform transcripts by the short isoform transcript for each condition in duplicate. **Results:** Analysis of PDX and human AML cell lines revealed that 8/9 PDX preferentially expressed the IRAK4-L isoform (>70% of IRAK4-L), with 4/9 PDX samples and 5/6 previously uncharacterized cell lines producing it almost exclusively (>95% IRAK4-L). MA9.NRAS cells predominantly express IRAK4-L, but transiently shifted to IRAK4-S during treatment with AZA/VEN (27% IRAK4-S), an effect reversed upon recovery from treatment. **Conclusions:** IRAK4-L is widely expressed in AML patient-derived samples, including those with complex karyotypes and TP53 mutations, suggesting that IRAK4 inhibitors may be useful beyond splicing factor-mutant MDS/AML. Our models demonstrate that changes in IRAK4-L expression during treatment with hypomethylating agents may be useful as a biomarker to guide therapy strategies. Further research is needed to understand how prolonged treatment and other standard of care therapies affect IRAK4-L expression and sensitivity to IRAK4 inhibitors. Research Sponsor: Conquer Cancer, the ASCO Foundation; Leukemia and Lymphoma Society; Harris Scholar Award.

6525 Poster Session

A phase I study of allogeneic anti-CD19 CAR-T therapy for patients with CD19+ relapsed/refractory acute B-lymphoblastic leukemia.

Sun Guangyu, Heng Mei, Zhou Yali, Wang Anyou, Pan Tianzhong, Lu Han, Jiangtao Ren, Xiaoyu Zhu; The First Affiliated Hospital of University of Science and Technology of China, Hefei, China; Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Bioheng Therapeutics, Nanjing, China

Background: Acute B-lymphoblastic leukemia (B-ALL), characterized by CD19 expression, responds well to CD19-targeted CAR-T therapy. However, autologous CAR-T is limited by cost and accessibility. We've developed RD06-03, an allogeneic CAR-T product engineered with TCR/Gene-X knockout and NK inhibitory molecule overexpression, exhibiting resistance to allogeneic rejection and enhanced anti-tumor effects without inducing graft-versus-host disease (GvHD). Our phase 1 trial (NCT06307600) aims to assess the safety and efficacy of RD06-03 in R/R B-ALL patients, offering a novel "off-the-shelf" solution. **Methods:** Patients aged 3-70 years with CD19+ R/R B-ALL were eligible and enrolled in a dose escalation study with dosing groups (CAR+ T cells/kg) of DL1: 1×10^5, DL2: 3×10^5, DL3: 5×10^5 and EDL (exploratory dose level): 6.5×10^5. All patients received lymphodepletion with fludarabine (30mg/m^2/day) and cyclophosphamide (500mg/m^2/day) for 3 days before CAR-T infusion. Dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) were evaluated using accelerated titration and "3+3" escalation, followed by case expansion at the appropriate dose. **Results:** As of December 15, 2024, six R/R B-ALL patients were enrolled (DL1: 1, DL2: 3, DL3: 1 and EDL: 1) with a median age of 37.5 years (range, 18-63) and a median of 3 prior therapies (range, 2-8+). One patient relapsed after unrelated umbilical cord blood transplantation. Baseline median bone marrow blasts were 41.9% (range, 10%-88.5%). RD06-03 was well tolerated with no DLT, neurotoxicity or GvHD observed. CRS occurred in 4 of 6 patients (66.7%, all Grade 1) with a median duration of 2.5 days (range, 1-4). For doses above DL2, all 5 patients achieved CR/CRi (100%) with undetectable MRD, indicating a deep remission. The majority of responders remain in remission, with the longest remission duration reaching 147 days and a median follow-up of 128 days (range, 60-175). Robust expansion was observed in all patients receiving doses above DL2, with rapid expansion occurring at a median of 4 days post-infusion. The median peak expansion exceeded 1 million copies/μg DNA, with a median persistence of 28 days and the longest persistence surpassing 3 months. **Conclusions:** The phase I trial of RD06-03 confirms its safety and efficacy in patients with R/R B-ALL. Notably, RD06-03's engineered TCR/Gene-X and NK inhibitory molecules enhance its resistance to rejection and antileukemic activity without GvHD. RD06-03 demonstrates robust persistence, achieving a 100% CR/CRi rate in medium- to high-dose groups, which is even lower than that of autologous CAR-T, while maintaining a manageable safety profile under standard lymphodepletion. This aligns with its genetic modifications designed for optimal immune rejection resistance. Further studies are essential to solidify these findings and explore RD06-03's therapeutic potential. Clinical trial information: NCT06307600. Research Sponsor: None.

TLR9 agonists as a potential therapeutic option for B-ALL patients with low P53 expression.

Ling Bai, Fei Chen, Jianting Xu, Jiuwei Cui; First Affiliated Hospital of Jilin University, Changchun, China; First Hospital of Jilin University, Changchun, Jilin, China; The First Hospital of Jilin University, Changchun, China

Background: B-cell acute lymphoblastic leukemia (B-ALL) is a highly malignant hematologic cancer with poor prognosis, especially in relapsed or refractory cases. Abnormal P53 expression is more prevalent in relapsed/refractory B-ALL and is associated with increased drug resistance. B-ALL cells in the bone marrow (BM) promote the survival of malignant cells by suppressing P53 accumulation. Therefore, identifying drugs that can reactivate P53 signaling may provide novel therapeutic strategies for patients with low P53 expression, particularly by targeting BM-resident B-ALL cells. **Methods:** Building on our previous findings that TLR9 agonists can activate the P53 signaling pathway and preferentially eliminate BM-resident B-ALL cells over peripheral B-ALL cells, we investigated the mechanisms by which TLR9 agonists regulate glucose metabolism through P53 to induce B-ALL apoptosis. We constructed P53 knockdown cell lines, conducted seahorse assays to analyze glucose metabolism, and performed RNA sequencing to identify key molecules. Mechanistic studies focused on the regulation of glucose metabolism and its P53-dependent pathways. Furthermore, we elucidated the role of glucose metabolism in TLR9 agonist-induced reactive oxygen species (ROS) production and mitochondrial apoptosis. **Results:** TLR9 agonists preferentially eliminate BM-resident B-ALL cells via P53-dependent pathways. Specifically, TLR9 agonists suppress glycolysis while enhancing oxidative phosphorylation and ROS generation through the P38-P53-TIGAR signaling axis. Elevated ROS levels further facilitate the formation of the BAX/BAK/TOM20 complex, promote TOM20 oxidation and accumulation, and activate BAX. The P53-TIGAR-ROS-MOMP axis was identified as the critical mechanism underlying TLR9 agonist-induced apoptosis in B-ALL. Additionally, patient-derived xenograft models confirmed that ROS generation is key to the efficient clearance of BM-resident B-ALL cells by TLR9 agonists. **Conclusions:** As P53-reactivating agents, TLR9 agonists selectively eliminate B-ALL cells while preserving immune cell anti-tumor function. This study highlights the role of glucose metabolism in the TLR9 agonist-mediated clearance of BM-residual B-ALL cells, providing a potential maintenance or combination therapy strategy for relapsed/refractory B-ALL patients, particularly those with low P53 expression. Research Sponsor: Science and Technology Department Science and Technology Development Plan Project in Jilin Province; YDZJ202301-ZYTS425; National Natural Science Foundation of China; 82303732; the First Hospital of Jilin University; JDYYCB-2023003.

6527 Poster Session

Real-world patient management practices in responders to venetoclax for newly diagnosed acute myeloid leukemia.

Ofir Wolach, Pinkal Desai, Evan Chris Chen, Joshua F. Zeidner, Thomas William LeBlanc, Sameem M. Abedin, Pankit Vachhani, Kendra Lynn Sweet, Yakir Moshe, Daniel A. Pollyea, Catherine Lai, Marina Konopleva, Boaz Nachmias, Lee Mozessohn, Marin Feldman Xavier, Tsila Zuckerman, Yanqing Xu, Chia-Wei Lin, Rebecca Burne, Aaron David Goldberg; Rabin Medical Center, Petach Tikva, Israel; Weill Cornell Medicine, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Department of Medicine, Duke University School of Medicine, Durham, NC; Medical College of Wisconsin, Milwaukee, WI; O'Neal Comprehensive Cancer Center at University of Alabama, Birmingham, AL; Moffitt Cancer Center, Tampa, FL; Tel Aviv (Sourasky) Medical Center, Tel Aviv, Israel; University of Colorado School of Medicine, Aurora, CO; University of Pennsylvania, Philadelphia, PA; Montefiore Einstein Comprehensive Cancer Center, Bronx, NY; Department of Hematology, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel; Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; Scripps Cancer Center, San Diego, CA; Rambam Health Care Campus, Haifa, Israel; AbbVie, Inc., North Chicago, IL; Genentech, South San Francisco, CA; Analysis Group Inc., Montreal, QC, Canada; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Venetoclax (VEN) is approved for adult patients (pts) with newly diagnosed (ND) acute myeloid leukemia (AML) in combination with hypomethylating agents (HMAs) or low dose cytarabine. This abstract describes real-world pt management practices among pts with ND AML who respond to VEN+HMA. **Methods:** The AML Real world evidenCe (ARC) Initiative is a multicenter chart review study of adults with ND AML treated with VEN at 17 academic sites in the US, Israel, and Canada. Pts ineligible for intensive chemotherapy (IC; ie, aged ≥75 years or ≥1 Ferrara criteria comorbidity) who initiated VEN+HMA on or after April 2016 were included (ie, before and after release of product label). Pt management practices in first-line VEN treatment and related impact on duration of response (DoR; assessed with Kaplan-Meier analyses) were examined among pts achieving composite complete remission (CRc; ie, CR or CR with partial hematologic recovery or incomplete count recovery). **Results:** Among IC-ineligible VEN-treated pts, 116 (60.4%) achieved CRc (median age 73.0 years, 37.9% female, 53.4% European LeukemiaNet 2017 adverse risk, 24.2% Eastern Cooperative Oncology Group grade ≥2). Median DoR was 11.0 months (95% confidence interval: 8.8; 15.2). Most pts (75.9%) received VEN + azacitidine. Median observed VEN treatment duration was 5.8 months and 31.9% remained on VEN as of data entry; 12.1% received hematopoietic stem cell transplant post-VEN. Almost all pts (93.6%) had ≥1 marrow assessment post-VEN initiation, usually in cycle 1 (68.0%) or 2 (19.4%). During VEN treatment, 44.8% received granulocyte colony stimulating factor. Antifungals were used in cycle 1 by 68.1% (83.5% prophylactic; 63.3% strong CYP3A4 inhibitor); DoR did not differ by antifungal use. Most pts (68.1%) had VEN dose ramp-up, from a median of 100 mg to 400 mg daily over 3 days. In cycle 1, 59.5% started with 28 VEN dosing days; this proportion declined in subsequent cycles. Among pts still treated, 48.6% and 54.8% had ≤21 dosing days in cycles 2 and 3, respectively. Most pts achieved CRc in cycle 1 (58.6%) or 2 (21.6%); median DoR did not differ significantly between these pts vs later responders. Among 93 pts treated for ≥1 cycle post-response, most (87.1%) had a dose hold before initiating the next cycle; 51.6% of these 93 pts had a dose hold up to 14 days. Of 50 pts remaining on 28 dosing days until CRc, 26.0% reduced to ≤21 dosing days in the next cycle. Neither postremission dosing days modifications nor between-cycle dose holds significantly impacted DoR. **Conclusions:** Among VEN-treated ND pts with AML achieving CRc in real-world academic settings, most achieved CRc by the end of cycle 2, consistent with clinical trial results. Nevertheless, timing of response did not appear to affect DoR. Postremission dosing days modifications and between-cycle dose holds were common in clinical practice and did not appear to impact DoR. Research Sponsor: AbbVie; Genentech.

Nucleophosmin (*NPM1*) genomic alterations (GA) in acute myeloid leukemia (AML): A genomic landscape study.

Osama Batayneh, Alexandra Goodman, Devashish Desai, Dean Pavlick, Chelsea Marcus, Caleb Ho, Jeffrey S. Ross, Teresa Gentile, Zheng Zhou, Krishna Bilas Ghimire; SUNY Upstate Medical University, Syracuse, NY; Foundation Medicine, Inc., Cambridge, MA; Foundation Medicine, Inc., Boston, MA; Department of Pathology, SUNY Upstate Medical University, Syracuse, NY; SUNY Upstate Medical Center, Syracuse, NY; Suny upstate medical university, Syracuse, NY

Background: *NPM1* GA characterize a clinically important subset of AML cases which relapse in more than 50% of treated patients despite being generally sensitive to conventional chemotherapy regimens. In AML, the interactions between GA in *NPM1*, *KMT2A* and menin protein have been linked to leukemogenesis and represent new potential targets for anti-tumor therapies. **Methods:** 4,206 cases of AML underwent comprehensive genomic profiling from 2019 through 2024, using the FoundationOne Heme combined hybrid capture based DNA and RNA sequencing assay. All classes of relevant GA were evaluated. The tumor mutation burden (TMB), homologous recombination deficiency signature (HRDsig) and microsatellite Stability (MSS) status were determined from the sequenced data. **Results:** 633 (15.1%) of the 4,206 AML featured *NPM1* GA (NPM1mut). Short variant mutations were found in >99% of the NPM1mut AML with the W288fs*12 frameshift base substitution accounting for 92.4% of cases. An *NPM1* - *MLF1* fusion was identified in 1.3% of NPM1mut cases. The NPM1mut+ were more frequently associated with female patients (53.4% vs 41.5%; p<.0001) and had a slightly higher median age compared to the NPM1 wild type (NPM1wt) AML patients (62yrs vs 60yrs; p<.0001). Majority of patients (>60%) were from European decent. There were greater NPM1 GA in patients with European (77.1% vs 68.5%; p<.0001) and lower with African ancestry (9.2% vs 10.2%; p<.0001). MSI High (0% in both groups) status, HRDsig+ (0—0.1%) and elevated TMB (median < 1 mutation/Mb) were extremely uncommon in both groups. GA more frequent in NPM1mut AML compared to the NPM1wt AML cohort included *DNMT3A* (39.2% vs 12.6%; p<.0001), *FLT3* (54.5% vs 14.7%; p<.0001), *IDH1* (16.1% vs 5.6%; p<.0001), *IDH2* (19.0% vs 9.0%; p<.0001), *TET2* (23.4% vs 13.5%; p<.0001) and *WT1* (12.5% vs 9.4% p=.02). GA more frequent in NPM1wt AML included *ASXL1* (17.1% vs 3.6%; p,.0001), *BCOR* (7.5% vs 1.6%; p<.0001), *KMT2A* (14.7% vs 0.2%; p<.0001), *RUNX1* (22.5% vs 1.9%; p-,.0001), *STAG2* (6.9% vs 1.6%; p<.0001) and *TP53* (19.1% vs 4.1%; p<.0001). **Conclusions:** The development of menin inhibitors has recently identified GA in *NPM1* as a promising target of therapy for AML patients. Other therapy targets in AML such as *FLT3* and *IDH1/2* are more frequently identified in NPM1mut than NPM1wt AML, while *KMT2A* is more frequently identified in NPM1wt AML. This genomic landscape study reveals significant differences in important GA associated with AML in NPM1mut and NPM1wt cases which may enrich our understanding of the molecular profile in AML and identify additional targets for therapy. Research Sponsor: None.

Pathogenic genomic alterations in NPM1mut and NPM1wt AML.

	NPM1wt AML (n=3573)	NPM1mut AML (n=633)	P-value
ASXL1	17.1%	3.6%	<.0001
CEBPA	6.4%	8.2%	NS
DNMT3A	12.6%	39.2%	<.0001
FLT3	14.7%	54.5%	<.0001
IDH1	5.6%	16.1%	<.0001
IDH2	9.4%	19.0%	<.0001
KMT2A	14.7%	0.2%	<.0001
RUNX1	22.5%	1.9%	<.0001
TET2	13.5%	23.4%	<.0001
TP53	19.1%	4.1%	<.0001

6529 Poster Session

Real-world outcomes of inaticabtagene autoleucel in Chinese patients with B-ALL.

Hongsheng Zhou, Yuhua Li, Jin Wang, Erlie Jiang, Jie Jin, Baohong Ping, Lei Fan, Suning Chen, Li Wang, Mingzhi Zhang, Zengjun Li, Xiaobing Huang, Guangxun Gao, Xinsheng Xie, Meng Lv, Xi Zhang, Heng Mei, Jian Li, Aibin Liang, Ying Wang; Southern Medical University Southern Hospital, Guangzhou, China; Zhujiang Hospital of Southern Medical University, Guangzhou, China; Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, VA, China; Institute of Hematology and Blood Diseases Hospital, Tianjin, China; The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Jiangsu Province Hospital, Nanjing, China; The Affiliated First Hospital of Soochow University, Suzhou, China; The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China; Sichuan Provincial People's Hospital, Sichuan, China; Department of Hematology, The First Affiliated Hospital, the Air Force Medical University, Xian, Shanxi, China; The First Affiliated Hospital of Zhengzhou University, Henan, China; Peking University People's Hospital, Beijing, China; Xinqiao Hospital of Army Medical University, Chongqing, China; Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Peking Union Medical College Hospital, Beijing, China; Tongji Hospital of Tongji University, Shanghai, China; Institute of Hematology and Blood Disease Hospital, Tianjin, China

Background: Inaticabtagene autoleucel (Inati-cel) is a CD19-specific chimeric antigen receptor (CAR) T-cell product, featuring a CD19 scFv derived from the clone HI19α and a 4-1BB/CD3-ζ costimulatory domain, which was approved in China for adult patients with relapsed or refractory B-acute lymphoblastic leukemia (r/r B-ALL) in November 2023. **Methods:** We conducted the multi-center, non-interventional real-world study (NCT06450067) to evaluate Inati-cel for adult B-ALL patients. Between November 20, 2023, and November 13, 2024, 62 patients received Inati-cel and were evaluable. The median age was 37.5 (range, 14-76) years, with 13 patients aged≥60 years. At screening, 16 cases relapsed after hematopoietic stem cell transplantation (HSCT), 4 cases were primary refractory, and over 70% of patients carried high-risk genetic abnormity. The median infusion dose was 0.60 (range: 0.46-0.9) $\times 10^8$CAR-T live cells. **Results:** The data as of December 30, 2024, with a median follow-up of 3.8 months (range: 0.5–12.4 months), 89.5% achieved MRD-negative ORR after Inati-cel in r/r patients, including 31 with CR and 3 with CRi (table1). Nine patients with MRD-positive at screening, the MRD-negativity rate reached 100% after Inati-cel. After Inati-cel, 26 patients had MRD results detected by q-PCR, and 92.3% obtained negative results. After achieving CR/CRi, 4 patients subsequently underwent allo-HSCT in remission. The median DOR, OS and RFS have not been reached with and without censoring patients at subsequent allo-HSCT. Among the evaluable patients, the 1-year RFS and DOR rates were 76.2% and 74.1%, respectively. Seven patients experienced relapses, including 3 CD19+ relapses, 2 CD19- relapses, and 2 with unclear CD19 status. It is worth noting that in 6 cases of extramedullary disease, 4 cases were effective, but 2 cases relapsed within 3 months after Inati-cel. All patients who received the Inati-cel infusion were alive, except for one death from disease progression. The most common adverse events (AEs) of special interest were cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Fifty-one percent of patients developed CRS, but grade 3 or higher CRS and ICANS only occurred in 3.2% and 1.6% of patients, respectively; all patients recovering without sequelae, no AE-related deaths. **Conclusions:** The real-world use of Inati-cel demonstrates a high MRD-negative ORR in adult B-ALL. The safety profile was manageable, with a low incidence of grade ≥3 CRS and ICANS in the real-world setting. Longer follow-up data will be presented. Clinical trial information: NCT06450067. Research Sponsor: None.

Efficacy profiles treated with Inati-cel.

Response	r/r B-ALL at enrollment , n=32	isolated extramedullary disease, n=6	MRD-pos, n=4	MRD-neg, n=20
CR or CRi (No. of patients)	30	4	-	-
Rate	93.7%	66.7%	-	-
CR, No. (%)	27(84.3%)	4(66.7%)	-	-
CRi, No. (%)	3 (9.4%)	-	-	-
MRD-neg rate, No. (%)	30/30 (100%)	-	4/4 (100%)	-
1-year DOR rate	67.4%		93.3%	
1-year RFS rate	68.2%		93.8%	

Comparable efficacy of venetoclax 50mg with posaconazole versus venetoclax 400mg in newly diagnosed AML patients: A prospective study of pharmacokinetics, toxicity, and clinical outcomes.

Gaurav Prakash, Rudra Narayan Swain, Anu Kumari, Smita Pattanaik, Charanpreet Singh, Arihant Jain, Alka Khadwal, Pankaj Malhotra; PGIMER, Chandigarh, Nehru Hospital, Chandigarh, India; Department of Clinical Hematology and Medical Oncology, PGIMER, Chandigarh, India; PGIMER CHANDIGARH, Chandigarh, India; Post Graduate Institute of Medical Education and Research, Chandigarh, India; PGIMER, Chandigarh, India

Background: Metabolism of Venetoclax(VEN) by CYP3A enzymes gives a unique opportunity to administer it at a lower dose with a CYP3A inhibitor. Azoles are strong CYP3A inhibitors & they are commonly used for antifungal prophylaxis during AML induction. Current data suggest that VEN 100mg with posaconazole achieves comparable clinical efficacy but is associated with higher myelotoxicity. We prospectively explored further dose reduction of VEN to 50 mg with posaconazole & compared it with VEN 400 mg with respect to pharmacokinetics, response rates & toxicity. **Methods:** We conducted an open-label, prospective study & enrolled 31 AML patients unfit for intensive chemotherapy. Patients received either VEN 50 mg with posaconazole (VEN50 cohort, n=20) or VEN 400 mg without posaconazole (VEN400 cohort, n=11). Pharmacokinetic parameters, including C0, Cmax, & AUC(0–24), were assessed using high-performance liquid chromatography. Clinical outcomes: overall response rate (ORR), composite complete response (CRc), measurable residual disease (MRD), & hematological recovery time-were analysed. **Results:** The median age of patients was 50 years (IQR: 35.5–60). Under the ELN2024 model, 74% of VEN50 patients & 63.6% of VEN400 patients were favourable-risk, while 26% & 36.4% were intermediate-risk, respectively. The ORR was 80% in the VEN50 cohort & 81.8% in the VEN400 cohort. CRc rates were comparable between the VEN50 (60%) & VEN400 (63.6%) cohorts, with similar MRD negativity rates (30% vs. 36.3%). Pharmacokinetic analysis revealed significantly lower systemic drug exposure in the VEN50 cohort [AUC(0–24): 17.88 μg·h/mL vs. 48.05 μg·h/mL, p=0.002] with C0 levels of 0.42 μg/mL vs. 1.08 μg/mL (p=0.004) & Cmax levels of 1.435 μg/mL vs. 3.63 μg/mL (p=0.002). Patients in VEN50 cohort experienced shorter neutropenic phase (17.5 vs. 24 days). Adverse events, including febrile neutropenia (60% vs. 72.7%, p=0.501) & culture-positive infections (20% vs. 27.2%, p=0.569), were comparable between the two cohorts. No treatment-related death occurred in either of the group. **Conclusions:** Our findings suggest that lower plasma levels achieved with VEN50 can lead to comparable CR rate & MRD negative rate in comparison with VEN400 with lesser myelotoxicity. Research Sponsor: None.

Comparison of baseline characteristics and outcomes.

Category	VEN 50mg + Posaconazole)	VEN 400 mg	P-Value
Median Age (IQR)	50 (35–59)	39 (35–52)	0.32
ECOG (0–2) (%)	90	91	0.29
C0 (μg/mL, Median)	0.42 (0.17–1.57)	1.08 (0.4–2.78)	0.004
Cmax (μg/mL, Median)	1.435 (0.54–5.51)	3.63 (1.27–6.92)	0.002
AUC0-24 (μg·h/mL, Median)	17.88 (8.09–81.47)	48.05 (19.96–94.79)	0.002
Overall Response Rate (ORR) (%)	80	81.8	1.0
CRc (CR + CRi) (%)	60	63.6	1.0
MRD Negativity (%)	30	36.3	0.98
Febrile Neutropenia (%)	60	72.7	0.501
Neutropenia Recovery (days, Median)	17.5	24	0.4
Culture-Positive Infections (%)	20	27.2	0.569

6531 Poster Session

Subgroup analysis by fitness criteria of patients (pts) with blastic plasmacytoid dendritic cell neoplasm (BPDCN) treated with first-line (1L) tagraxofusp (TAG).

Naveen Pemmaraju, Marco Herling, Kendra Lynn Sweet, Anthony Selwyn Stein, Sumithira Vasu, Todd Louis Rosenblat, David Rizzieri, Cristina Papayannidis, Eunice S. Wang, Marina Konopleva, Michael Zuurman, Alessandra Tosolini, Muzaffar H. Qazilbash, Andrew A. Lane; The University of Texas MD Anderson Cancer Center, Houston, TX; University Hospital Leipzig and Cancer Center Central Germany (CCCG), Leipzig-Jena, Germany; Moffitt Cancer Center, Tampa, FL; City of Hope, Duarte, CA; The Ohio State University Comprehensive Cancer Center, Columbus, OH; Columbia University Medical Center Herbert Irving Comprehensive Cancer Center, New York, NY; Novant Health Cancer Institute, Charlotte, NC; IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY; Montefiore Medical Center, Albert Einstein Comprehensive Cancer Center, Bronx, NY; Menarini Group, Machelen, Belgium; Menarini Group, New York, NY; Dana-Farber Cancer Institute, Boston, MA

Background: BPDCN, an aggressive orphan hematologic neoplasm, expresses CD123 and presents in skin, bone marrow, blood, and viscera. For pts eligible to undergo hematopoietic cell transplantation (HCT), the 1L treatment goal is to rapidly induce a durable complete response (CR) before HCT. TAG is a first-in-class CD123-targeted therapy with a well-characterized and manageable safety profile without cumulative myelosuppression and the only drug approved to treat BPDCN. In 1L pts with a median age of 68 yrs, TAG has demonstrated, in a phase 1/2 pivotal trial with prespecified/multisystem response criteria, a 75% overall response rate, 24.9-month (mo) median duration of CR/clinical CR (CRc), and the ability to bridge 51% of pts with CR/CRc to HCT (Pemmaraju, JCO 2022). Notably, multi-agent intensive chemotherapy (IC) prior to HCT is still used, particularly in young fit pts, despite short- and long-term toxicity/myelosuppression and despite short durations of response (DOR). Also, many pts with BPDCN are ineligible for IC before HCT. We assess outcomes, based on pretreatment comorbidity burden, across HCT-specific comorbidity index (HCT-CI; Sorror, JCO 2007) fitness groups for pts who received 1L TAG for BPDCN in the pivotal trial (NCT02113982). **Methods:** Pts who received 1L TAG 12 μg/kg IV on days 1-5 of a 21-day cycle (C) were retrospectively assigned to categories by HCT-CI score (0 [low], 1-2 [intermediate; int] and 3+ [high]) per baseline medical history, concomitant medications, and labs. Outcomes included best response, time to response (TTR), DOR, overall survival (OS), HCT rate, treatment-related adverse events (TRAEs), and capillary leak syndrome (CLS). **Results:** 65 pts were scored as HCT-CI low (n=15), int (n=22), or high (n=28). Median age was 61, 67.5, and 70 yrs, respectively; disease was more extensive in high-risk pts. Objective responses (80%, 68%, 79%) were high regardless of HCT-CI group, with CR/CRc rates of 73%, 59%, and 46%. Median TTR was similar; median DOR was longer in low and int (24.9 mo/not reached [NR]) vs high (3.9 mo). HCT rates were 33%, 45%, and 21%; pre-transplant CR/CRc rates were 100%, 90%, and 83% with median DOR NR. Median OS in HCT pts was 38.4 mo, NR, and NR. In each group, most common Grade 3-4 TRAEs were thrombocytopenia and increased ALT/AST; most were in C1 and transient. Two deaths due to CLS occurred in int pts. Grade 3-4 CLS occurred in 0%, 9%, and 4% of pts; all CLS events were in C1 and all grade 1-4 CLS events resolved. **Conclusions:** 1L TAG BPDCN treatment yielded high response rates regardless of HCT-CI fitness, with a similar safety profile across HCT-CI groups. TAG enabled bridge to HCT across all fitness groups, including pts with high risk possibly ineligible for IC, as TAG is not associated with prolonged myelosuppression seen with IC. These results affirm TAG as the SOC in 1L treatment for the majority of pts with BPDCN. Clinical trial information: NCT02113982. Research Sponsor: Menarini Group.

6532 Poster Session

Detection of KMT2A partial tandem duplication (PTD) in AML by whole genome sequencing (WGS): Addressing limitations of traditional techniques in the era of revumenib approval.

Robert Huether, Derick Hoskinson, Pavana Anur, Raul Torres, Karl Beutner, Kristiyana Kaneva, Yan Yang, Kelly Potts, Andrew Frazier, Iris Braunstein, Brett Mahon, Michael A. Thompson, Kate Sasser, Halla Nimeiri, Lewis J. Kraft, Francisco M. De La Vega, Alejandro Marinos Velarde; Tempus AI, Inc., Chicago, IL; UT Southwestern Medical Center, Dallas, TX

Background: The menin inhibitor revumenib was recently FDA approved for treating patients with relapsed or refractory KMT2A-rearranged (rKMT2A) acute leukemias. Cytogenetics, FISH, and targeted next-generation sequencing (NGS) frequently miss KMT2A 11q23 partial tandem duplications (KMT2A-PTD)). Although KMT2A-PTDs have expression signatures similar to rKMT2A, they were excluded from revumenib's registration trial. Preclinical models have shown that menin inhibitors may also be effective for KMT2A-PTD, highlighting the need for precise breakpoint and KMT2A fusion product detection. Here, we evaluated the effectiveness of high-resolution WGS to identify a diverse array of KMT2A-PTD. **Methods:** Using a WGS assay (Tempus xH) optimized for comprehensive profiling of myeloid neoplasms, we capture the entire KMT2A locus at base pair resolution. DNA was extracted from blood or bone marrow aspirates and was used to construct paired-end libraries via tagmentation. Sequencing was performed on the Illumina NovaSeq-X platform, achieving a mean coverage of 80X. Data were analyzed using the DRAGEN Platform with custom post-processing filters. Exon copy number calls from a targeted NGS assay and exon capture RNAseq NGS assay (Tempus xT and xR, respectively) were used for verification. **Results:** WGS from 230 hematopoietic neoplasms (68% AML, 18% MDS, 12% CML, and 2% others) identified 13 specimens (5.6%) containing a KTM2A-PTD, with variant allele frequencies (VAFs) between 9-66%. All PTDs contained breakpoints within known intron boundaries: one breakpoint in intron 1 (13/13) with terminal breakpoints located in intron 8 (6/13) or intron 10 (7/13). RNA data was available for 11 of 13 specimens and contained direct support for the presence of all the KMT2A-PTDs (100%). Using an NGS-targeted panel, exon-level copy calls were assessed for all 13 specimens with PTDs. Although unvalidated, we observed exon level gains in 9 of the 13 specimens (69%). As shown in prior studies, KMT2A-PTDs were mutually exclusive to other translocations, including rKMT2A. However, other high-frequency mutations for myeloid disease were present in select samples including mutations in IDH1, DNTM3A, WT1, and RUNX1. **Conclusions:** WGS is an effective tool for detecting KMT2A alterations that may be missed by traditional techniques such as NGS targeted capture, FISH or cytogenetics. 100% concordance was observed between WGS and RNAseq for KMT2A-PTDs, supporting the reliability of WGS. The FDA approval of menin inhibitors for KMT2A-rearranged AML/ALL suggests potential clinical opportunities for broad tests (WGS) to identify other rearrangements, including KMT2A-PTDs, highlighting the need for further research into targeted anti-leukemia therapies. Research Sponsor: Tempus AI, Inc.

6533 Poster Session

Mitoxantrone hydrochloride liposome combined with cytarabine (MA) for patients with newly diagnosed secondary acute myeloid leukemia.

Stephen Yang Liang, Yun Wang, Weida Wang, Jingbo Xu, Ji Ma, Hua Wang, Binyi Wu, Yuanbin Song, Weiran Lv, Le-zong Chen; Department of Hematologic Oncology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou, China; Department of Hematologic Oncology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Gaungzhou, China; Department of Hematology, The Fifth Affiliated Hospital, Sun Yat-Sen University, Zhuhai, China; Department of Medical Oncology, Shandong Cancer Hospital and Institute, Jinan, China

Background: Secondary acute myeloid leukemia (sAML) is an aggressive subset typically characterized by unfavorable biological features. CPX-351, a dual-drug liposomal formulation of cytarabine and daunorubicin, has demonstrated improved remission rates and overall survival (OS) in sAML; however, its use remains limited in China. Mitoxantrone hydrochloride liposome (Lipo-MIT), a pegylated liposomal formulation of mitoxantrone, provides enhanced anti-tumor efficacy and reduced toxicity. Here we report the outcomes of a novel regimen combining Lipo-MIT and cytarabine (MA) for patients (pts) with newly diagnosed sAML. **Methods:** This is a single-arm, prospective, exploratory study. Eligible pts were aged 18 to 75 years and had newly diagnosed therapy-related AML, AML with antecedent myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML), or de novo AML with MDS-related cytogenetic abnormalities. Patients received MA regimen consisting of Lipo-MIT ($24mg/m^2$ on day 1) and cytarabine ($100mg/m^2$/d from days 1 to 7) every four weeks for up to 2 cycles. The primary endpoint was CRc (complete remission (CR)+CR with incomplete neutrophil or platelet recovery (CRi)). The secondary endpoints included the rate of CRc with negative minimal residual disease (MRD), overall response rate (ORR), overall survival (OS) and safety. **Results:** As of January 20, 2025, a total of 13 pts were enrolled with a median age of 53 years (range, 24.0-65.0), including 8 with therapy-related AML and 5 with AML arising from antecedent MDS. According to the 2022 edition of the European Leukemia Network recommendations, 2 (15.4%) pts were classified as a favorable prognosis, 2 (15.4%) as intermediate, 8 (61.5%) as adverse, and 1 (7.7%) as unknown. The most commonly mutated gene and abnormality karyotype was TP53 and del(7q), respectively, both occurring in 23.1% (3/13). Of 13 pts, 5 were assessed as CR, 3 as CRi and 1 as PR. The CRc rate was 61.5% (8/13) and the ORR was 69.2% (9/13). Among 8 pts who achieved CRc, the rate of negative MRD was 75% (6/8). With a median follow-up of 3.4 months, the 1-year OS rate was 88.9% (95% CI, 43.3-98.4) while the median OS was not reached. The median duration of absolute neutrophil count <500 cells/μL was 21.0 days (range, 7.0-29.0) and platelet count <50000 platelets/μL was 20.0 days (range, 14.0-61.0) in pts who achieved CRc after initial induction. The non-hematological treatment-emergent adverse events (TEAEs) graded at 3 were febrile neutropenia (46.2%), fever (7.7%), sepsis (7.7%), pulmonary infection (7.7%), oral mucositis (7.7%), anaphylaxis (7.7%) and pruritus (7.7%). No non-hematological TEAEs of grade 4 or worse were observed and the 60-day mortality rate was 0%. **Conclusions:** The MA regimen demonstrated encouraging remission rates and a superior safety profile, indicating its potential as a treatment option for newly diagnosed sAML. Clinical trial information: ChiCTR2300076618. Research Sponsor: None.

Co-mutational landscape of Indian core binding AML: An answer to the unfavorable outcome in a favorable AML?

Rahul Bhargava, Shrinidhi Nathany, Dinesh Bhurani, Nikhil Kumar, Anusha Swaminathan, Neha Rastogi, Chitresh Yadav, Swati Bhayana, Dr. Sunisha Arora, Sohini Chakraborty, Aastha Gupta, Arun Danewa, Vikas Dua; Fortis Memorial Research Institute, Gurugram, India; Rajiv Gandhi Cancer Institute and Research Center, New Delhi, India

Background: Core binding factor AML, which encompasses RUNX1/RUNX1T1 and CBFB/MYH11, comprise 10-15% of all AML, currently classified as favorable risk in the 2022 European LeukemiaNet Risk Stratification. The Indian CBF AML cohort as reported in earlier studies tends to be younger, with extramedullary disease and with higher number of co-mutations. Also due to unavailability of the anti CD33 gemtuzumab ozogamicin in India, the outcomes to standard therapies tend to be dismal when compared to the West. This raises a dilemma for the ELN risk stratification of this entity as a favorable risk. **Methods:** 165 patients of CBF AML were accrued, from two different centers. Non-disclosure consents from the participating centers were obtained. Patients with documented CBF AML who have undergone NGS based testing were included. Descriptive statistical analysis was done for continuous and ordinal data. The analysis was done using SPSS version 24. A two tailed p value of $<5\%$ was considered significant. The data from TCGA studies was compared which was accessed through www.cbioportal.org and all studies of AML were included. **Results:** A total of 165 patients of CBF AML were included in the study. Median age was 33.4 years (range 16-45) with a clear male predilection (male to female ratio of 3.1:1).RUNX1/RUNX1T1 rearrangement was detected in 70% (116) cases and 49 (30%) cases harbored the CBFB/MYH11 gene rearrangement. At least one additional mutation was detected in 70% cases with RUNX1/RUNX1T1 rearrangement and 80% cases of CBFB/MYH11.The most frequent co-occurring alteration was NRAS (32% cases across both subtypes, more common in CBFB/MYH11). Another statistically significant finding was patients with inv(16) manifested a significantly higher frequency of Spliceosome mutations ($p = 0.028$) and WT1 mutations ($p = 0.021$) compared to t(8;21). Two patients harbored concomitant TP53 mutations predicted to be pathogenic based on ClinVar database as well as IARC TP53 database. Both these patients also had a complex karyotype along with RUNX1/RUNX1T1 fusion. Mutation in DNA methylation genes occurred more in CBFB/MYH11 vs RUNX1/RUNX1T1 cases ($p<0.06$). The patients with CBFB/MYH11 also depicted a higher prevalence of mutations in the polycomb repressor genes ASXL1 and ASXL2 when compared to RUNX1/RUNX1T1($p<0.06$).Another feature was higher prevalence of cohesin complex gene mutations involving SMC1A and SMC3 which were seen in 20% cases overall. The inv(16) group showed a lower predilection compared to the t(8;21) group ($p<0.061$). **Conclusions:** The presence of higher number of additional mutations in the Indian cohort underscores the need of larger studies/controlled trials of this subset, which otherwise has been stratified as favorable. The access to standard of care like GO is a necessity and there is a need to formulate national/regional guidelines for the Indian subset.
Research Sponsor: None.

6535 Poster Session

Outcomes of Ph-like B-lineage acute lymphoblastic leukemia in the era of novel therapies.

Hamed Rahmani Youshanlouei, Syed Abdul Mannan Shah, Francisca Anazco, Sinan Cetin, Anand Ashwin Patel, Adam DuVall, Michael William Drazer, Mariam Nawas, Angela Lager, Carrie Fitzpatrick, Peng Wang, Melissa Tjota, Sandeep Gurbuxani, Girish Venkataraman, Jason X. Cheng, Jeremy Segal, Olatoyosi Odenike, Wendy Stock, Caner Saygin; University of Chicago, Chicago, IL; FMH college of Medicine and dentistry, Lahore, Pakistan; Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL; University of Chicago, Chicago; University of Chicago Medical Center, Chicago, IL; University of Chicago Bucksbaum Institute for Clinical Excellence, Chicago, IL

Background: Ph-likeALL) is a high-risk subset of B-ALL with poor treatment response and high relapse rates. We examined outcomes of Ph-like B-ALL pts (pts) treated at a large academic center in the current era of novel therapies. **Methods:** We retrospectively analyzed 68 adults with Ph-like B-ALL treated at the University of Chicago (2014-2023). Ph-like status was classified per WHO 2022 criteria using FISH, DNA and RNA sequencing. **Results:** Median age at diagnosis was 34 years (range, 18-74), 68% were male. We found CRLF2 rearrangements (CRLF2-r) in 75%, JAK2-r in 10%, ABL1-r in 6%, FGFR-r in 3%, and rearrangements in ABL2, CSF1R, PDGFR and ROS1 at 1.5% each. Most common co-occurring somatic gene mutations involved IKZF1 (41%), CDKN2A (37%), JAK2 (37%), KRAS (16%), PAX5 (12%) and NRAS (10%). First-line therapy was chemo alone in 80% of pts with the following distribution: CALGB 10403 in 43%, hyper-CVAD in 28% and other chemo in 9%. The remaining 20% of pts received novel therapies in first-line setting, including C10403 + inotuzumab (InO) in 7%, ino + blinatumomab (blin) in 6%, hyperCVD + venetoclax in 4% and C10403 + imatinib in 3%. Post-induction flow cytometry-based measurable residual disease (MRD) negativity rate was significantly higher in pts who received novel therapies upfront vs pts who received standard chemo (55% vs 20%, p= 0.02). This is lower than our non-Ph-like B-ALL pts, for whom the MRD-negative CR rate after chemo induction was 62% (p< 0.01). We also observed higher 5-year relapse-free survival (RFS) rate for pts who received novel therapies upfront vs standard chemo alone (65% vs 20%, p< 0.01). We did not detect a significant difference in overall survival (OS) for pts treated with novel therapies vs standard of care (p= 0.52), which is likely due to the utilization of novel therapies as salvage regimens after relapse. Of note, 5 pts received kinase inhibitors (ruxolutinib, dasatinib, imatinib) in salvage setting, but did not achieve remission. There were no differences in OS or RFS outcomes when pts were stratified based on CRLF2-r vs non-CRLF2-r. Among co-occurring gene alterations, we observed higher risk for relapse in cases with KRAS mutations (HR= 4.29, 95% CI= 1.3-13.4), which was independent from the type of first-line therapy. 7% received anti-CD19 CAR-T cell therapy. 32% had allogeneic transplant (HCT), which was done in CR1 in 31%, while 69% received HCT after salvage (CR2 or CR3). 64% received myeloablative conditioning (TBI-based regimens) with the following distribution of donors: 46% matched unrelated, 27% mismatched unrelated, 18% matched related, 9% haplo-cord. Median OS after HCT was 10 months. **Conclusions:** Ph-like B-ALL pts treated with standard chemo have lower CR and RFS rates. Adding novel agents (InO, blin, venetoclax) to upfront regimens may improve outcomes. Future studies should focus on optimal first-line combinations and higher-risk groups such as KRAS-mutated Ph-like B-ALL. Research Sponsor: None.

Potential benefits of using a different donor for transplantation consolidation after donor-derived CD7 CAR T.

Jing Pan, Liping Zhao, Fan Wu; State Key Laboratory of Experimental Hematology, Boren Clinical Translational Center, Department of Hematology, Beijing Gobroad Boren Hospital, Beijing, Beijing, China; State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Tianjin, Tianjin, China

Background: Stem cell transplantation (SCT) is often used in patients with relapsed or refractory T-cell acute lymphoblastic leukemia (r/r T-ALL) after CD7 CAR T therapy, in order to consolidate efficacy or promote immune reconstitution to reduce the risk of infection. Previous studies have shown that consolidatory SCT may be able to prolong the survival of patients after CD7 CAR T. However, infections after SCT raise concerns. Here, we explored optimization strategies for SCT consolidation after newly HLA-matched donor-derived CD7 CAR T therapy in r/r T-ALL patients. **Methods:** This is a retrospective analysis of SCT consolidation following donor-derived CD7 CAR T therapy, based on a phase 1 trial (ChiCTR2000034762) and a phase 2 trial (NCT04689659) approved by the Institutional Review Board (IRB) of Beijing Goboard Boren Hospital, and a phase 1/2 trial (NCT06316427) approved by the IRB of Beijing Goboard Hospital. The analysis was aimed to evaluate the impact of using different donors for CAR T therapy and the subsequent SCT, compared to using the same donor. **Results:** A total of 19 patients were included in this analysis, including four from the phase 1/2 trial who used different donors for CAR T therapy and SCT consolidation (Group A), and 15 patients who used the same donor for CAR T therapy and SCT consolidation (Group B, 7 from the phase 1 trial and 8 from the phase 2 trial). The median age of the 19 patients was 11 (range 2-43). 16 patients (84%) were male, and three (16%) were female. The median interval from CAR T cell infusion to stem cell infusion was 32 days (range, 26-34) for group A, and 39 days (range 32-48) for group B. After stem cell infusion, all patients in group A had no detectable CAR T cells in the peripheral blood. However, in group B, six of the 13 patients evaluated had detectable CAR T cells in the peripheral blood, whereas the other seven did not. Within three months after stem-cell infusion, no patients in group A had CMV or EBV activation, while nine patients (60%) in group B had CMV or EBV activation. Two patients (50%) in group A and 10 patients (67%) in group B had any type of viral activation. Compared to group B, patients in group A tended to have a higher chimerism rate in the peripheral blood at two months and in the bone marrow at three months after stem cell infusion. **Conclusions:** In post-CD7-CAR patients, the risk of viral activation (especially CMV/EBV activation) after SCT using the same donor as CAR T was high. This may be partly related to the persistence of CAR T cells after SCT. The results showed that using a different donor from CD7 CAR T for subsequent SCT may contribute to the timely clearance of CAR T cells from patients and simultaneously reduce the rate of CMV/EBV activation after stem cell infusion. In addition, the chimerism rate was slightly increased at some time points. These results will be further evaluated in an ongoing phase 1/2 study at our center. Clinical trial information: NCT04689659, NCT06316427, ChiCTR2000034762. Research Sponsor: None.

6537 Poster Session

Overcoming acquired venetoclax resistance in acute myeloid leukemia through cell metabolism targeting.

João Agostinho Machado-Neto, Gustavo Nery de Queiroz, Marcella Cipelli, Victoria Tomaz, Luiz Gustavo Ferreira Cortes, Marina de Franca Basto Silva, Rafael Lucas Muniz Guedes, Paulo V. Campregher, Eduardo Rego, Niels Olsen Saraiva Câmara, Leticia Costa-Lotufo, Keli Lima; Department of Pharmacology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil; Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil; Hospital Israelita Albert Einstein, São Paulo, Brazil; Center for Cell Therapy, Foundation for Research Support of the State of São Paulo, São Paulo, Brazil; Laboratory of Medical Research in Pathogenesis and Target Therapy in Onco-Immuno-Hematology, University of São Paulo, São Paulo, Brazil

Background: Venetoclax is a selective inhibitor of the anti-apoptotic protein BCL2, often overexpressed in acute myeloid leukemia (AML), contributing to cell survival and resistance to standard therapies. It has expanded treatment options, especially for elderly or chemotherapy-ineligible patients. However, acquired resistance to venetoclax is a significant challenge, limiting long-term effectiveness. Understanding the mechanisms of resistance is crucial for improving therapeutic strategies and identifying biomarkers for personalized treatment. This study investigates these mechanisms by analyzing cellular phenotype, metabolic changes, BCL2 family gene/protein expression, and signaling pathways in venetoclax-resistant AML cell lines. **Methods:** Venetoclax-sensitive AML cell lines, MOLM-13 and MV4-11, were exposed intermittently to increasing concentrations of the drug to induce resistance. Cell viability was assessed using MTT assays, clonogenicity by colony formation, and apoptosis, mitochondrial damage, and DNA content by flow cytometry. Metabolic profiles were analyzed with Seahorse XF96, and signaling pathways were studied by Western blotting, qPCR, and global proteomics. Synergy assays were conducted with metformin (mitochondrial complex I inhibitor) and KPT-9274 (NAMPT inhibitor). **Results:** Intermittent exposure to venetoclax selected for resistant clones, MV4-11VR (IC_{50} > 1000 nM; parental cells IC_{50} = 2.5 nM) and MOLM-13VR (IC_{50} = 723 nM; parental cells IC_{50} = 3.3 nM). Venetoclax-induced apoptosis, mitochondrial damage, and DNA fragmentation were absent in resistant cells. Metabolic analysis showed increased mitochondrial metabolism in MOLM-13VR cells and enhanced glycolysis in MV4-11VR cells. Molecularly, MV4-11VR cells exhibited downregulation of BCL2L10, BAX, BCL2L11, BBC3, BIK, and BNIP3, while MOLM-13VR cells showed reduced BID, PMAIP1, BAD, BMF, and BECN1, along with increased MCL1. MOLM-13VR cells displayed enhanced MAPK signaling, and both resistant models had activation of the PI3K/AKT/mTOR pathway and upregulation of BCL-XL. Proteomic analysis revealed enhanced metabolic activity, with MV4-11VR cells enriched in fatty acid biosynthesis and carbohydrate metabolism pathways, while MOLM-13VR cells showed upregulation of aerobic respiration and ATP metabolism. Both parental and resistant cells exhibited comparable sensitivity to metformin and KPT-9274. The combination of these inhibitors with venetoclax resulted in synergistic effects, with KPT-9472 and venetoclax eliminating over 95% of resistant cells. **Conclusions:** This study provides key insights into the mechanisms of venetoclax resistance in AML. Targeting cellular metabolism with metformin or KPT-9274, combined with venetoclax, offers promising synergistic effects and potential strategies to overcome resistance, improving treatment outcomes in resistant AML cases. Research Sponsor: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP); 2023/12246-6.

6538 Poster Session

Should we treat TP53-mutated high-risk myeloid neoplasms in older patients?

Talha Badar, Mobachir E.I. Kettani, Kashish Shah, Omer Hassan Jamy, Rory Shallis, Kendall Diebold, Alexander Coltoff, Aaron David Goldberg, Anand Ashwin Patel, Jan Philipp Bewersdorf, Charles Foucar, Yasmin Abaza, Neil Palmisiano, Adam DuVall, Vamsi Kota, Amer Methqal Zeidan, Ehab L. Atallah, Mark Robert Litzow; Mayo Clinic, Jacksonville, FL; Division of Hematology-Oncology and Blood and Marrow Transplantation and Cellular Therapy Program, Mayo Clinic, Jacksonville, FL; University of Alabama at Birmingham, Department of Psychiatry and Behavioral Neurobiology, Birmingham, AL; Yale Cancer Center, New Haven, CT; University of Alabama at Birmingham, Birmingham, AL; Medical University of South Carolina, Charleston, SC; Memorial Sloan Kettering Cancer Center, New York, NY; University of Chicago Medical Center, Chicago, IL; Yale University School of Medicine and Yale Cancer Center, New York, NY; University of Michigan Health Management Research Center, Albuquerque, NM; Northwestern Memorial Hospital, Chicago, IL; Rutgers Cancer Institute, New Brunsvick, NJ; Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL; Augusta University, Augusta, GA; Department of Internal Medicine, Section of Hematology, Yale School of Medicine, New Haven, CT; Medical College of Wisconsin, Milwaukee, WI; Mayo Clinic, Rochester, MN

Background: *TP53* mutated ($TP53^{mt}$) high-risk myeloid neoplasm (HR-MN) confers a dismal prognosis in the contemporary era with only a subset of eligible patients (pts) able to achieve long-term remission with allogeneic stem cell transplantation (allo-HCT). Owing to poor outcomes, many physicians believe it is futile to treat older pts with disease-directed therapy, since curative intent allo-HCT cannot be offered. We sought to describe the outcomes of older pts with $TP53^{mt}$ HR-MN receiving disease directed treatment. **Methods:** We conducted a multicenter observational study in collaboration with 11 U.S. academic centers under the COMMAND consortium. We reviewed the data of 451 older (≥ 60 years [yrs]) $TP53^{mt}$ HR-MN (n= 282 acute myeloid leukemia [AML], n= 91 MDS transformed AML, n= 50 myeloproliferative neoplasm blast phase (MPN-BP) and n= 28 high-risk myelodysplastic syndromes [HR-MDS]) pts to analyze their outcome with disease directed treatment. **Results:** The median age was 70 yrs (range [R],60-90) and 58% were male. Proportions of pts with age ≥ 70 yrs were 47.5%. Eastern Cooperative Oncology Group Performance Status (ECOG-PS) was available in 68% (n= 306) of pts; 10.5%, 49%, 32% and 8.5% had ECOG-PS 0-3, respectively. The median bone marrow (BM) blast % was 32 (R, 5-99) and *TP53* variant allele frequency (VAF) was 45% (R, 2-97). The proportion of pts with multi-hit (MH) $TP53^{mt}$ and complex cytogenetics (CG) was 83% and 82%, respectively. 43 %, 31%, 20% and 6% received hypomethylating agent (HMA) + venetoclax, intensive chemotherapy, HMA and other low-intensity therapy, respectively. The complete remission rate with or without count recovery (CR/CRi) amongst evaluable patients (n= 356) was 37%. The median duration of response was 6.7 months (mo) (R, 5.9-7.5). Amongst 56 (12%) pts who underwent allo-HCT, the median overall survival (mOS) from time of allo-HCT was 21.9 mo. The mOS among pts ≥ 70 yrs was 6.5 mo. The mOS in mo was better in HR-MDS (16.4), compared to *de novo* AML (6.5), MDS transformed AML (7.1) and MPN-BP (5.27), p= 0.003. We conducted multivariable analysis for OS using baseline variables that were significant/ showed trend towards significance, on univariate analysis ($p<0.1$). HR-MDS (HR; 0.43, 95% CI: 0.23-0.82, p= 0.01), CR/CRi (HR; 0.55, 95% CI: 0.39-0.77, p= <0.001) and allo-HCT (HR; 0.28, 95% CI: 0.16-0.47, p= <0.001) positively impacted OS. Whereas age ≥ 70 yrs showed trends towards inferior OS (HR; 1.31, 95% CI: 0.95-1.80, p=0.09). Complex CG (HR; 1.63, 95% CI: 0.83-3.21, p=0.15) and MH$TP53^{mut}$ (HR; 1.30, 95% CI: 0.67-2.52, p= 0.42) did not retain significance for OS. **Conclusions:** Our multi-center study suggests that disease directed treatment in older $TP53^{mt}$ HR-MN leads to modest response rates with short durations of response in the absence of allo-HCT. 12% of pts were able to receive allo-HCT with improvement in OS close to 2 yrs. The decision to treat this poor risk gp of pts should be based on individual pt characteristics and desires. Research Sponsor: None.

6539 Poster Session

Cytomolecular mechanisms of relapse after frontline FLT3 inhibitor (FLT3i)-based therapy in FLT3-mutated (mut) acute myeloid leukemia (AML).

Sankalp Arora, Hagop M. Kantarjian, Naval Guastad Daver, Sanam Loghavi, Tapan M. Kadia, Courtney Denton Dinardo, Musa Yilmaz, Ghayas C. Issa, Sherry Pierce, Katie M. Gaw, Farhad Ravandi-Kashani, Nicholas James Short; Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Data regarding the mechanisms of relapse and outcomes with salvage therapies in patients (pts) with *FLT3* mut AML after frontline FLT3i-based therapy are limited. **Methods:** This is a retrospective study of pts with *FLT3* mut AML who received frontline FLT3i-based therapy at our institution. Molecular and cytogenetic (CG) testing was compared between diagnosis and relapse. **Results:** 272 pts received frontline treatment with FLT3i from 9/2013-7/2024: 214 $FLT3^{ITD}$, 27 $FLT3^{ITD+TKD}$ and 31 $FLT3^{TKD}$. Induction therapy was intensive chemotherapy (IC) in 107 pts and low intensity therapy (LIT) in 165 pts [including HMA+venetoclax(VEN)+FLT3i in 93 pts]. FLT3i's used were gilteritinib (n=105), sorafenib (n=96), quizartinib (n=54), midostaurin (n=16), and crenolanib (n=1). Composite complete remission (CRc = CR + CRi) was attained in 203 pts (75%). 97 pts (36%) underwent allogenic stem cell transplant (ASCT) in 1st remission. After a median (med) follow-up of 46 months (mos), 80 pts (35% of responders) relapsed. Post-ASCT relapses occurred in 22/97 pts (23%). Relapse rates in pts receiving IC+FLT3i, HMA+VEN+FLT3i, and LIT+FLT3i (no VEN) were 23% ($p<0.01$), 31% ($p<0.01$), and 65% (ref), respectively. At relapse, loss of a *FLT3* mut (ITD and/or TKD) was noted in 34/72 tested pts (47%), with similar rates among transplanted and non-transplanted pts. *FLT3* loss at relapse was more common in pts who received IC+FLT3i or HMA+VEN+FLT3i *vs* LIT+FLT3i (no VEN): 57% vs 32% (p=0.05). Among 55 pts with comprehensive molecular testing at relapse, 24 (44%) had a newly detectable non-*FLT3* mut, most commonly *RAS* pathway (8, 15%), *WT1* (7, 13%), *TET2* (4, 7%), and *IDH1/2* (4, 7%). New mutations at relapse were less common in post-ASCT pts (19% vs 59%; $p<0.01$). Among $FLT3^{ITD}$ pts, new $FLT3^{TKD}$ mut at relapse occurred in 8/58 tested pts (14%): 7 had received frontline type 2 FLT3i. New CG abnormalities at relapse occurred in 27/65 tested pts (42%), most commonly trisomy in 11 pts (17%). No *BCR::ABL1* was observed at relapse. 51 pts received 1st salvage therapy after relapse (22 $FLT3^{wt}$ and 29 $FLT3^{mut}$ relapses). $FLT3^{wt}$ relapses had higher CRc rates (41% vs 10%, p=0.02), and a trend to higher med OS (8.6 mos vs 5.7 mos, p=0.13) with salvage therapy compared with $FLT3^{mut}$ relapses. **Conclusions:** Loss of *FLT3* mut at relapse occurred in almost 50% of pts receiving frontline FLT3i and was more common in pts receiving IC+FLT3i or HMA+VEN+FLT3i. Common mechanisms of clonal evolution included emergent mutations in *RAS* pathway, *WT1*, and DNA methylation genes (*TET2*, *IDH1/2*). Mutational clonal evolution was less frequent in post-ASCT relapses. Persistent *FLT3* mut at relapse was associated with a worse prognosis. Research Sponsor: MD Anderson Cancer Center Leukemia Specialized Programs of Research Excellence (SPORE) Grant CA1100632.

Initial results from a phase II study of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) ± rituximab (R) + tafasitamab (tafa) for adults with newly-diagnosed (ND) Philadelphia chromosome negative (Ph-) B lymphoblastic leukemia (B-ALL).

Noam Edward Kopmar, Jonathan R. Fromm, Noah Pinke, Christen Martino, Ashtyn Sherrow, Cristina Maria Ghiuzeli, Raya Mawad, Ted Gooley, Jason Phillip Cooper, Erik Lesley Kimble, Bart L. Scott, Paul Hendrie, Johnnie J. Orozco, Joshua Veatch, Mary-Elizabeth M. Percival, Ryan Daniel Cassaday; Fred Hutchinson Cancer Center, Seattle, WA; Division of Hematopathology, University of Washington, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; University of Washington, Seattle, WA; University of Washington/Fred Hutchinson Cancer Center, Seattle, WA; University of Washington Medical Center, Seattle, WA; University of Washington, Fred Hutchinson Cancer Center, Seattle, WA

Background: For adults with ND Ph- B-ALL, treatment consists of intense multiagent chemotherapy, with outcomes linked to early measurable residual disease negativity (MRD-). The addition of blinatumomab to frontline chemotherapy improves survival, but regimens used are limited by toxicity and complexity. DA-EPOCH ± R is well-tolerated, effective (32% MRD- after cycle [C]1), and relatively simple to administer for ND B-ALL. Tafa is a CD19 monoclonal antibody with activity in B-cell lymphomas. We hypothesized that adding tafa to DA-EPOCH ± R in adults with ND Ph- B-ALL would improve rates of early MRD- without an increase in toxicity. **Methods:** This is a phase II investigator-initiated trial of DA-EPOCH ± R + tafa in adults with ND CD19+ Ph- B-ALL who are not candidates for pediatric-inspired therapy: age >40, unable to receive all care in specialized center, etc. (NCT05453500). The primary endpoint is MRD- (<0.01%) by multiparameter flow cytometry (MFC) after C1; secondary endpoints include rates of MRD- by C4, incidence of grade 3+ non-hematologic adverse events (AEs) by CTCAE v5, and event-free (EFS) and overall survival (OS). Exploratory endpoints include high-throughput sequencing (HTS)-based MRD detection in marrow and cerebrospinal fluid (CSF) by clonoSEQ. DA-EPOCH (+ R if CD20+) with intrathecal chemo given on days (D) 1-5 every 21 D for up to C8 (Cassaday, et al. *Leuk Lymphoma*, 2023). Tafa is given at 12 mg/kg IV on D 1, 8, and 15 in each C. Risk and response are assigned per NCCN. We used a Simon 2-stage design based on results with DA-EPOCH alone: if ≥5/15 pts (33%) achieved MRD- after C1, we would enroll up to 30 pts. **Results:** From 3/2023 to 1/2025, 17 pts have enrolled: 15 are evaluable (2 on treatment without sufficient time to categorize response), with 1 pt removed during C1 for AE (grade 4 AST elevation). Median age was 67 (range: 44-84), and 67% (12/16) had poor-risk cytogenetics. Six pts (38%) received R. In those with sufficient follow-up (f/u), complete response rate was 80% (12/15); MRD- by MFC after C1 was 40% (6/15) and 71% (10/14) by C4. In pts MRD- by MFC, 56% (5/9) were MRD- by HTS. Initial CSF evaluation demonstrated disease by MFC in 3 pts; HTS on CSF was positive in those pts, plus 3 more (6 total). There were 2 grade 4 AEs (reported as serious AEs): sepsis and intracranial hemorrhage. Grade 3 AEs seen in > 1 pt were fibrinogen decreased (5), infections (5), febrile neutropenia (4), hypotension (3), and syncope (2). With the longest f/u at 21 mo (range 0.6-21), 0 pts have relapsed. Four pts have died: 3 from non-relapse mortality unrelated to study treatment (2 following allogeneic transplantation) and 1 from refractory ALL. **Conclusions:** In a cohort of ND Ph- B-ALL, the addition of tafa to DA-EPOCH ± R led to rates of MRD- that are higher than historical rates, with similar toxicity. Since the target C1 MRD- rate was reached in part 1 of the 2-stage design, the trial is proceeding to part 2 and accrual will be completed. While f/u is short, no relapses have been seen. HTS is feasible on CSF and extends the level of detection beyond MFC. Clinical trial information: NCT05453500. Research Sponsor: Incyte.

6541 Poster Session

Outcomes in patients with B-cell precursor acute lymphoblastic leukemia receiving inotuzumab ozogamicin stratified by body mass index.

Wendy Stock, Ryan Daniel Cassaday, Daniel J. DeAngelo, Anjali S. Advani, Nicola Gökbuget, Jose-Maria Ribera-Santasusana, Wei Jiang, Susana Pulido, Erik Vandendries, Elias Jabbour, Hagop M. Kantarjian; University of Chicago, Chicago, IL; University of Washington and Fred Hutchinson Cancer Center, Seattle, WA; Dana-Farber Cancer Institute, Boston, MA; Cleveland Clinic, Cleveland, OH; Goethe University Hospital, Frankfurt, Germany; Catalan Institute of Oncology, Barcelona, Spain; Pfizer Inc, New York, NY; Pfizer Spain, Madrid, Spain; Pfizer Inc., Cambridge, MA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Inotuzumab ozogamicin (InO) is approved for the treatment of adults for relapsed/refractory B-cell precursor acute lymphoblastic leukemia (R/R B-ALL). In previous studies, elevated body mass index (BMI) has been associated with worse outcomes in adult patients treated for ALL. We report the efficacy and safety of InO in adult patients with R/R B-ALL, stratified by BMI. **Methods:** Data from three previous studies, NCT01363297/B1931010 (InO: 0.8–1.8 mg/m^2/cycle [Ph1], 1.6–1.8 mg/m^2/cycle [Ph2]) NCT01564784/B1931022 (InO: 1.5–1.8 mg/m^2/cycle) and, NCT03677596/B1931030 (InO: 0.9–1.2mg/m^2 or 1.5–1.8mg/m^2 per cycle) were pooled, participants (pts) were grouped by formal BMI definitions: <25 kg/m^2 (healthy), 25–30 kg/m^2 (overweight) and >30 kg/m^2 (obese). Data presented as descriptive statistics only. A genAI tool was used with author review to develop the first draft (8 Jan 2025; Pfizer; GPT-4o); authors take full responsibility for the content. **Results:** Data from 338 pts (18–79 years; median age 44, 41% female) were analyzed, with 155 pts in the <25 kg/m^2 group, 116 pts in the 25–30 kg/m^2 group and 67 pts in the >30 kg/m^2 group. Across the <25, 25–30 and >30 kg/m^2 BMI groups, CR/CRi was achieved in 108 (70%), 88 (76%) and 46 (69%) of pts, and MRD negativity observed in 87 (56%), 73 (63%) and 35 (52%) of pts, respectively. At 24 months, the probability of progression-free survival (95% CI) was 19.9% (13.2, 27.5), 12.8% (7.2, 20.1) and 10.9% (4.2, 21.1), and the probability of survival (95% CI) was 28.1% (21.0, 35.6), 22.1% (14.8, 30.3) and 17.5% (9.2, 27.8) in the <25, 25–30 and >30 kg/m^2 BMI groups, respectively. Most pts experienced TEAEs, and incidence was similar across BMI groups (97%–99%). Common hepatic Grade ≥3 TEAEs were sinusoidal obstruction syndrome (SOS) (10 %, <25 kg/m^2; 6%, 25–30 kg/m^2; 9%, >30 kg/m^2) and GGT increase (7 %, <25 kg/m^2; 5%, 25–30 kg/m^2; 5%, >30 kg/m^2). Overall, 143 pts (42%) proceeded to hematopoietic stem cell transplantation (HSCT) after InO treatment, sixty-seven (43%) in the <25 kg/m^2 group, 49 (42%) in the 25–30 kg/m^2 group, and 27 (40%) in the >30 kg/m^2 group. Post-HSCT, non-relapse mortality within 100 days was estimated to be 22% in the <25 kg/m^2 group, 22% in the 25–30 kg/m^2 group and 19% in the >30 kg/m^2 group. Post-HSCT SOS was observed in 18 pts (27%) in the <25 kg/m^2 group, 7 pts (14%) in the 25–30 kg/m^2 group and 6 pts (22%) in the >30 kg/m^2 group, with grade 3–4 SOS observed in 10 (15%), 7 (14%) and 5 pts (19%), respectively. **Conclusions:** In this pooled analysis of pts treated with InO for R/R B-ALL, efficacy and safety outcomes were broadly consistent across BMI groups. However, lower PFS and OS rates at 24 months were noted in pts with higher BMI. Research Sponsor: Pfizer.

Summary of outcomes.

%	<25 kg/m^2 (N=155)	25–30 kg/m^2 (N=116)	>30 kg/m^2 (N=67)
CR/CRi	70	76	69
CR	33	36	40
CRi	37	40	28
MRD-negativity	56	63	52
PFS (24 months)	20	13	11
OS (24 months)	28	22	18

Novel potent and selective inhibitors targeting FLT3 for AML therapy.

Gauthier Errasti, Thomas Delacroix, Kalpana Ghoshal, Robert Lee, Anisha Ghosh, Raj Chakrabarti; PMC Isochem, Paris, France; CCM Biosciences, Mount Laurel, NJ; McGill University, Montreal, QC, Canada

Background: Acute Myeloid Leukemia (AML) is a malignancy frequently driven by mutations in the FMS-like tyrosine kinase 3 (FLT3) gene. The FLT3 internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations, particularly D835 and F691, appear in approximately 30% of AML patients, often leading to poor prognosis and resistance to existing therapies. Gilteritinib and Quizartinib are two FDA-approved FLT3 inhibitors, with the former approved only for relapsed/refractory AML and the latter approved only for newly diagnosed AML. Quizartinib does not target TKD resistance mutations, whereas Gilteritinib's efficacy on FLT3-ITD-D835Y is limited and it is not effective against FLT3-ITD-F691L. Consequently, there is a critical need for next-generation FLT3 inhibitors that can address all of these mutations. **Methods:** We have characterized efficacy of two novel FLT3 inhibitors, CCM-405 and CCM-445. *In vitro* enzymatic binding affinities were determined by the KdELECT assay, and cellular IC_{50}s were determined by the Cell-Titer Glo assay. *In vivo* antitumor activity of CCM-405 / 445 was evaluated in mutant cell line-derived xenograft (CDX) models of AML. Tumor growth inhibition (TGI) was measured in the FLT3-ITD luciferase-expressing MV4-11 (MV4-11-luc) systemic xenograft model as well as subcutaneous xenograft models of FLT3-ITD F691L and D835Y mutants. Efficacy of novel inhibitors was compared with Gilteritinib. *In vitro* efficacy was compared with experimental FLT3 TKD mutant inhibitor Luxeptinib. **Results:** Enzymatically, CCM-405 / 445 inhibit FLT3-ITD, FLT3-ITD-D835V and FLT3-ITD-F691L with K_ds of 12 nM / 4.1 nM, 1.9 nM / 0.39 nM and 1.6 nM / 0.4 nM, respectively (Luxeptinib K_ds: ITD-D835V: 550 nM; ITD-F691L: 97 nM). CCM-405 / 445 inhibit the proliferation of Ba/F3 FLT3-ITD and FLT3-ITD D835Y cell lines with potency comparable to Gilteritinib, and FLT3-ITD F691L with potency superior to Gilteritinib, and are significantly less toxic to Ba/F3 FLT3 WT than to the mutants (Luxeptinib: negligible cellular mutant/WT selectivity). CCM-405 / 445 are also potent against human AML cell lines MV4-11 and MOLM-13. *In vivo*, in the systemic FLT3-ITD model, CCM-405 induced ~90% tumor regression (> 100% TGI) and was significantly more effective than Gilteritinib ($p < 0.001$), which did not regress the tumor, when these agents were administered orally at doses corresponding to equal fractions of their maximum tolerated doses (MTDs). In both FLT3-ITD-F691L and FLT3-ITD-D835Y CDX models, CCM-405 induced almost complete tumor regression (>100% TGI). Both novel inhibitors were significantly more efficacious than Gilteritinib (45% and 4% TGI, respectively). **Conclusions:** Novel FLT3 inhibitors have been developed that can both target FLT3-ITD and potentially overcome mutational resistance to FDA-approved FLT3 inhibitors. These agents are significantly more effective than Gilteritinib and have potential clinical applications. Research Sponsor: CCM Biosciences.

6543 Poster Session

Brexucabtagene autoleucel (Brexu-cel) as consolidation treatment in adults with B-cell acute lymphoblastic leukemia.

Niranjan Khaire, Elias Jabbour, Nicholas James Short, Shilpa Paul, Alexandra Lovell, Jayastu Senapati, Fadi Haddad, Tapan M. Kadia, Naveen Pemmaraju, Naval Guastad Daver, Rabiul Islam, Sa A Wang, Partow Kebriaei, Bouthaina Shbib Dabaja, Elizabeth J. Shpall, Sattva Swarup Neelapu, William G. Wierda, Farhad Ravandi-Kashani, Hagop M. Kantarjian, Nitin Jain; University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Brexu-cel is a CD19 CAR T cell approved for adult patients with R/R B-cell ALL. We aimed to evaluate toxicity/efficacy in adult pts with marrow blasts <5%. **Methods:** We retrospectively analyzed pts (≥18y) with B-ALL who received brexu-cel (not on clinical trials) at MDACC, Houston. Pts were included if they had marrow blasts <5% and without any clinical (and imaging) evidence of extra-medullary disease (EMD) at the time of LD. CAR T levels were monitored post infusion in PB using flow cytometry. **Results:** 46 pts received Brexu-cel from Feb 2022 to Dec 2024. Baseline characteristics are as in table 1. 36/46 pts were NGS MRD negative (30 had undetectable disease at 10^{-6} sensitivity and 6 had disease detectable < LLOD of the assay; clonoSEQ). 10/36 pts were positive at values ranging from 3-3283 cells/million. Post infusion peak CAR T expansion was noted at a median of 8 days from infusion and the median peak expansion was 13.5 cells/μL [range <1-2222]. A peak CAR T expansion threshold of 15 cells/μL was identified as an optimal predictor for RFS with a neg predictive value of 97%. 23/46 (50%) pts of the whole cohort had a peak CAR T expansion of ≥15 cells/μL. Amongst the 10 pts who were NGS MRD positive at the time of CAR T infusion, the median peak CAR T expansion was 77.5 cells/μL [range 3-573] and 7/10 (70%) had a peak expansion of ≥15 cells/μL. Amongst those (n=36) who were NGS MRD negative at the time of CAR T infusion, the median peak CAR T expansion was 10 cells/μL [range <1-2222] and 16/36 (44%) had a peak expansion of ≥15 cells/μL.Among the 23 pts who had a peak expansion of ≥15 cells/μL, 1 had a relapse, 1 died while in MRD negative remission and the remaining 21 (91%) are alive in remission. In contrast, among the 23 pts with a peak expansion of <15 cells/μL, 8 pts had a molecular/clinical relapse while 15/23 (65%) were alive in remission. With a median follow-up of 12.8 mos (range 1-27), the 12-mo RFS is 71% for the whole cohort (86% in the CAR T expansion ≥15 cells/μL; 58% in the peak CART expansion <15 cells/μL). The 12-mo OS is 94% for all pts. 6 pts had a subsequent allo-SCT after the CAR T infusion at the treating physician's discretion at a median of 3.6 mos (range 2.8-8.8) from the cell infusion. Among the 3 pts with G3-4 CRS/ICANS, (table1) the peak CAR T expansion was 102, 1270 and 2222 cells/μL. **Conclusions:** Brexu-cel CAR T expansion was observed even in pts with no morphologic disease. CAR T expansion threshold of ≥15 cells/μL could identify pts with durable RFS. Rates of G3-4 CRS/ICANS were low when brexu-cel was used as consolidation. Research Sponsor: None.

Parameters		N (%), median [range] N=46
Age		38 [20-84]
	≥60 years	9 (20)
Gender	Male	29 (63)
Disease / Prior Therapy	Median lines of therapy	2 [1-4]
	CART infusion in CR1	12 (26)
	Prior blinatumomab	44 (94)
	Prior inotuzumab	35 (76)
	Prior allo-SCT	7 (15)
	Ph positive ALL	15 (33)
	Ph like ALL	10 (28)
Post CAR T complications	G3 CRS	3 (7)
	G4 CRS	0
	G3 ICANS	1 (2)
	G4 ICANS	1(2)

Impact of *TP53* mutations and variant allelic frequency on survival in adults with newly diagnosed acute lymphoblastic leukemia.

Roberta Santos Azevedo, Hagop M. Kantarjian, Sravanthi Lavu, Sanam Loghavi, Nitin Jain, Fadi Haddad, Jayastu Senapati, Eitan Kugler, Rebecca Garris, Koichi Takahashi, Farhad Ravandi-Kashani, Elias Jabbour, Nicholas James Short; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: *TP53* mutations are associated with poor outcomes in acute lymphoblastic leukemia (ALL); however, a variant allele frequency (VAF) cutoff (mutation burden) which may more accurately predict overall survival (OS) has not been identified. **Methods:** We retrospectively analyzed adult patients (pts) with newly diagnosed ALL with *TP53* mutation status tested at diagnosis. The maximum log-rank test was used to evaluate the impact of *TP53* VAF. **Results:** Among 654 pts, 115 (18%) harbored *TP53* mutations. *TP53* mutations were more common in B-cell ALL (19% vs. 6% in T-cell ALL, p=0.003), older age (61 vs. 45 years, p<0.001), low hypodiploid/near-triploid (Ho-Tr) karyotype (98% vs. 10%, p<0.001), and therapy-related ALL (20% vs. 9%, p<0.001). 11 pts (10%) harbored ≥2 *TP53* mutations. The median *TP53* VAF was 42% (range, 1-94%) and was higher in pts with Ho-Tr karyotype (54%) compared to diploid karyotype (41%, p=0.02). *TP53*-mutated ALL was associated with significantly inferior OS in pts ≥60 years of age (2-year OS 55% vs. 69%; p=0.03). In the older pts, *TP53* VAF was associated with worse OS and the optimal cutoff was 45%. Among pts ≥60 years, *TP53* VAF ≥45% had a 2-year OS of 37% compared to 71% for those with VAF <45% (p=0.01), which was driven by higher rates of both relapse and non-relapse mortality. In older pts who received frontline inotuzumab ozogamicin (InO) and/or blinatumumab (Blina), *TP53* VAF ≥45% remained a strong predictor of OS (2-year OS 37% vs. 75% for VAF <45%; p=0.04). By multivariate analysis (MVA) in pts aged ≥60 years, *TP53* VAF ≥45% (HR 1.8, 95% CI 1.0-3.2, p=0.03) and complex karyotype (HR 2.9, 95% CI 1.2-7.3, p=0.02) were associated with inferior OS, while frontline InO and/or Blina trended toward improved OS (HR 0.6, 95% CI 0.3-1.0, p=0.07). *TP53*-mutated ALL was associated with a trend towards inferior OS in pts <60 years of age (2-year OS 66% vs. 88%; p=0.06), despite higher rates of allo-SCT in pts with *TP53*-mutated ALL (47% vs. 22% for *TP53* wild type; p<0.001). In these younger pts, *TP53* VAF was not prognostic (2-year OS 72% vs. 61% for VAF ≥45% vs. <45%; p=0.6). Outcomes were similar in younger pts with *TP53* VAF≥45%, irrespective of allo-SCT status (2-year OS of 68% vs. 74% for those with VAF≥45% who underwent allo-SCT vs. those who did not; p=1.0). By MVA in younger pts, Ph-like was associated with worse OS (HR 2.1, 95% CI 1.3–3.1, p=0.002), while frontline InO and/or Blina significantly improved outcomes (HR 0.5, 95% CI 0.3–0.7, p<0.001). Neither *TP53* mutation status nor VAF impacted OS on MVA. **Conclusions:** *TP53* mutations were associated with worse outcomes in both younger and older adults with ALL. VAF ≥45% can risk stratify pts aged ≥60 years but did not impact OS in younger pts. Incorporating frontline InO and/or Blina into therapy might improve outcomes of *TP53*-mutated ALL. Research Sponsor: None.

6545 Poster Session

A phase 2 study of olutasidenib in relapsed/refractory acute myeloid leukemia: Outcomes by number of prior treatment regimens.

Eunice S. Wang, Jorge E. Cortes, Andrew H. Wei, Stéphane De Botton, Antonio Curti, Pau Montesinos, Karen W.L. Yee, Joseph G. Jurcic, William Bruce Donnellan, Jay Yang, Brian Andrew Jonas, Aaron Sheppard, Hua Tian, Justin M. Watts; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Georgia Cancer Center, Augusta, GA; Peter MacCallum Cancer Centre, Royal Melbourne Hospital and Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; Institut Gustave Roussy, Villejuif, France; IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; Hospital Universitari i Politecnic La Fe de Valencia, Valencia, Spain; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Columbia University Irving Medical Center and New York-Presbyterian Hospital, New York, NY; Sarah Cannon Research Institute, Nashville, TN; Wayne State University School of Medicine and Karmanos Cancer Institute, Detroit, MI; University of California Davis School of Medicine, Sacramento, CA; Rigel Pharmaceuticals, Inc., South San Francisco, CA; University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL

Background: A subset of patients (7-14%) with acute myeloid leukemia (AML) have mutations in the isocitrate dehydrogenase 1 gene (m*IDH1*). Olutasidenib (OLU), a selective, potent, oral inhibitor of mIDH1, is approved for treatment of relapsed/refractory (R/R) m*IDH1* AML. Results from the phase 2 pivotal cohort (NCT02719574) demonstrated clinical efficacy and tolerability of OLU, with a complete remission/complete remission with partial hematological recovery (CR/CRh) rate of 35% for a median duration of 25.9 months. Here we evaluated the efficacy and safety of OLU in patients with R/R AML grouped by the number of prior regimens. **Methods:** The pivotal cohort of the phase 2 study assessed OLU 150 mg BID in adult patients and included efficacy endpoints of CR/CRh, overall response rate (ORR), duration of response (DOR), and overall survival (OS). This post hoc analysis evaluated outcomes based on when patients received OLU: after 1-2 or ≥3 prior lines of therapy. **Results:** There were 147 patients in the efficacy evaluable analysis set (1-2 prior regimens, n=93; ≥3 prior regimens, n=54). Median age was 72 years in patients with 1-2 prior regimens and 66.5 years in those with ≥3 prior regimens. Forty-three percent and 33% of patients had prior treatment with a hypomethylating agent, and 11% and 4% received prior venetoclax therapy (1-2 and ≥3 prior regimens groups, respectively). In patients with ≥3 prior regimens, 31% had prior hematopoietic stem cell transplantation vs none in those with 1-2 prior regimens. Those in the 1-2 prior regimens group had a higher ORR and CR/CRh rate and longer median OS, with a larger percentage of patients achieving CR, than those in the ≥3 prior regimens group (Table 1). All patients experienced ≥1 treatment-emergent adverse event (TEAE). Serious TEAEs were reported in 73% (68/93) and 77.8% (42/54) of patients in the 1-2 and ≥3 prior regimens groups, respectively, and TEAEs ≥grade 3 occurred in 89.2% (83/93) and 90.7% (49/54). The most common TEAEs included nausea, decreased red blood cell count, and fatigue. No new safety signals were identified. **Conclusions:** Higher response rates (including CR and CRh) and greater survival were observed in patients receiving OLU following 1-2 versus ≥3 prior treatment regimens, providing rationale for initiating OLU earlier in the R/R treatment paradigm. Clinical trial information: NCT02719574. Research Sponsor: Forma Therapeutics, Inc; Rigel Pharmaceuticals, Inc.

Efficacy of OLU stratified by number of prior regimens.

	1-2 Prior Regimens n=93	≥3 Prior Regimens n=54
ORR, n (%); 95% CI	50 (54); 43.1, 64.2	21 (39); 25.9, 53.1
DOR, median months (95% CI)	14.8 (7.4, 25.9)	16.6 (5.8, NR)
CR rate, n (%); 95% CI	35 (38); (27.8, 48.3)	12 (22); (12.0, 35.6)
DOR, median months (95% CI)	21.3 (12.0, NR)	NR (8.7, NR)
CR/CRh rate, n (%); 95% CI	38 (41); 30.8, 51.5	13 (24); 13.5, 37.6
DOR, median months (95% CI)	25.3 (12.0, NR)	NR (8.7, NR)
OS, median months (95% CI)	13.0 (9.3, 18.9)	8.9 (5.8, 14.9)

NR, not reached.

Matching-adjusted indirect comparison (MAIC) of olutasidenib (OLU) and ivosidenib (IVO) in isocitrate dehydrogenase 1 (IDH1)-mutated relapsed/refractory (R/R) acute myeloid leukemia (AML).

Justin M. Watts, Brian Andrew Jonas, Eunice S. Wang, Florence R. Wilson, Julie Park, Shannon Cope, Aaron Sheppard, Stéphane De Botton, Jorge E. Cortes; University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL; University of California Davis School of Medicine, Sacramento, CA; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Precision AQ, Vancouver, BC, Canada; Rigel Pharmaceuticals, Inc., South San Francisco, CA; Institut Gustave Roussy, Villejuif, France; Georgia Cancer Center, Augusta University, Augusta, GA

Background: OLU and IVO are allosteric type II IDH1 inhibitors approved by the FDA and recommended by NCCN for *IDH1*^{mut} R/R AML patients based on single-arm trials. In the absence of a head-to-head trial, a MAIC was performed to estimate relative treatment effects of OLU vs. IVO in *IDH1*^{mut} R/R AML. **Methods:** Analyses used registrational data for OLU (Study 2102-HEM-101; N=147; individual-level data) and IVO (AG120-C-001; N=174; study-level data). A logistic propensity score model was used to estimate weights based on the first moment for Study 2102-HEM-101 patients to match AG120-C-001, including the following characteristics identified from a literature review, validated by clinical experts: number of prior systemic therapies, age, prior stem cell transplant, AML type, relapse type, cytogenetic risk, ECOG PS, and *IDH1* mutation. Complete remission (CR) and CR + CR with partial hematological recovery (CRh) were summarized as odds ratios (ORs) and 95% confidence intervals (CIs). Duration of CR (DoCR), duration of CR+CRh, and OS were summarized in terms of difference in medians and 95% CIs. OS was also summarized in terms of hazard ratios (HRs) and restricted mean survival time (RMST). A simulated treatment comparison (STC) was performed as a sensitivity analysis. **Results:** Table 1 summarizes MAIC-adjusted estimates. Naïve and adjusted rates of CR and CR+CRh for OLU vs. IVO were comparable, but point estimates favored OLU for CR. Differences in median DoCR were not statistically significant but favored OLU over IVO. OLU had a significantly longer duration of CR+CRh than IVO. For OS, the naïve comparison suggested OLU was better than IVO (HR=0.72; 95% CI 0.55, 0.92), whereas the MAIC was uncertain but favored OLU. STC results were consistent with the MAIC. **Conclusions:** Naïve and adjusted rates of response for OLU vs. IVO were comparable (adjusted point estimate favored OLU for CR and IVO for CR+CRh), while a longer duration of CR+CRh was observed with OLU. Adjusted OS was similar between the two groups, although the HR favored OLU, and could not be estimated by response category given lack of patient characteristics and reduction in effective sample size (ESS). Results rely on the assumption of no unmeasured confounders which reflects a limitation of the methodology. Research Sponsor: Rigel Pharmaceuticals, Inc.

MAIC results.

Outcome	OLU – adjusted (95% CI)	IVO – observed (95% CI)	MAIC OLU vs. IVO (95% CI)	N	ESS
CR	27%	25%	OR=1.12 (0.61, 2.08)	147	73.03
CR + CRh	29%	33%	OR=0.83 (0.46, 1.50)	147	73.03
DoCR, median mos	21.3 (12.0, NE)	10.1 (6.5, 22.2)	Diff=11.18 (-4.30, 22.72)	47	17.76
Duration of CR+CRh, median mos	17.5 (12.0, 29.1)	8.2 (5.6, 12.0)	Diff=9.84 (3.24, 22.28)	51	21.06
OS, median mos	9.7 (5.6, 16.4)	9.0 (7.4, 10.2)	HR=0.75 (0.53, 1.07)	147	73.03
OS, RMST mos	15.6 (12.1, 19.2)	12.2 (10.6, 13.9)	Diff=3.39 (-0.51, 7.29)	147	73.03

N, sample size; NE, not estimable.

6547 Poster Session

Investigating age of onset and prognosis of p53 mutant myeloid malignancies in African Americans.

Brendon Fusco, Madeline D'Agostino, Kith Pradhan, Lauren Shapiro, Stephen Peeke, Ridhi Gupta, Noah Kornblum, David Levitz, Aditi Shastri, Eric J. Feldman, Alejandro R. Sica, Marina Konopleva, Dennis Cooper, Ioannis Mantzaris, Amit Verma, Mendel Goldfinger; Montefiore Einstein Comprehensive Cancer Center, Bronx, NY; Department of Internal Medicine, Albert Einstein College of Medicine, Bronx, NY

Background: TP53 mutations drive poor outcomes in Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML), aggressive hematologic malignancies characterized by clonal abnormalities in myeloid hematopoiesis. Prognostic scoring systems incorporate cytogenetic and molecular abnormalities based on data from majority White populations and have limited applicability to minorities. Racial disparities in survival are well-known, with Black patients experiencing worse outcomes. While TP53 mutations are associated with poor outcomes, there is limited data about their implications in minority populations. Objective: To study TP53 mutation status, variant allele frequency (VAF), and co-mutations on outcomes in MDS and AML between White and minority populations in the Bronx, a racially diverse region. **Methods:** This retrospective cohort study analyzed 84 patients diagnosed with TP53 mutated AML and MDS between 2014 and 2024 at Montefiore Medical Center. Data included race/ethnicity (Black, White, Hispanic), age, age at diagnosis, gender, diagnosis, first-line chemotherapy, and bone marrow blast percentage. Molecular data included TP53 mutation status (bi- vs. mono-allelic), variant allele frequency (VAF), and co-mutations. Co-mutation patterns will be presented at the meeting. Comparisons were made using descriptive statistics, and survival outcomes were analyzed using Cox proportional hazards models adjusted for age and gender. **Results:** Black patients were diagnosed at a younger age than White or Hispanic patients (mean: 63.7 vs. 72.6 vs. 65.9 years, p = 0.029) and had shorter median overall survival (3.9 vs. 16.4 vs. 10 months, p = 0.014). Black patients had higher mean VAF (48.1 vs. 31.9 vs. 38.2, p = 0.047) and were more likely to have co-mutations than isolated TP53 mutations, though this was not significant (OR 4.21, p = 0.06). Patients with VAF above the median had a threefold increased risk of death (aOR 3.14, p = 0.019), independent of age or gender. **Conclusions:** Black patients with TP53 mutant MDS and AML present younger and have worse outcomes than White patients, associated with a higher TP53 VAF and more frequent co-mutations. This is to our knowledge the largest dataset of TP53 in minorities with MDS and AML; highlighting the need for personalized prognostic models that incorporate minorities to overcome racial disparities in myeloid malignancies. Research Sponsor: None.

Socioeconomic and clinical predictors of 30-day readmissions in AML patients undergoing allogeneic stem cell transplantation.

Aditi Sharma, Vijendra Singh; Barbara Ann Karmanos Cancer Institute, Detroit, MI; Wayne State University, Karmanos Cancer Institute, Detroit, MI

Background: 30-day readmissions among acute myeloid leukemia (AML) undergoing allogeneic hematopoietic stem cell transplantation (allo-HCT) are a key quality metric, contributing to morbidity, mortality, and healthcare costs. We analyzed age-specific characteristics and factors associated with readmissions. **Methods:** Using the 2016–2021 National Readmissions Database, we identified adult AML hospitalizations for allo-HCT, stratified into <45, 45–65, and >65 years. Patient demographics, hospital factors, comorbidities, complications and outcomes were analyzed. Multivariable Cox regression determined adjusted hazard ratios for 30-day readmissions. **Results:** Of 15,757 admissions, 3,743 were <45, 8,169 were 45–65, and 3,844 were >65 years. The younger cohort had a higher proportion of females (53% vs. 47% vs. 39%, p<0.001). Overall infection rates, acute graft-versus-host disease, and use of total body irradiation were similar across groups (p>0.05). Mean LOS was 29 vs. 32 days for >65 and <45 years (p<0.001). Inpatient mortality was 4%, 5% and 6% in young, middle-aged and older group (p=0.02), while readmission rates (27% vs. 27% vs. 30%, p=0.16) and mortality during readmission (5% vs. 7% vs. 7%, p=0.42) were comparable. Mean time to readmission was 12 days, primarily driven by infections (34%), GI/hepatobiliary complications (10%), active AML (5%), & kidney dysfunction (5%). Lower-income quartiles vs. wealthiest and Medicare vs. private insurance were linked to higher readmission risk. Depression further elevated risk, whereas home-health care lowered it. Among clinical variables, GVHD, chronic kidney disease, and acute respiratory failure each predicted higher readmission (see Table). **Conclusions:** Our findings highlight disparities in 30-day readmissions after allo-HCT for AML, driven by socioeconomic, clinical, and mental health factors. Targeted interventions, such as optimizing post-discharge care and providing psychosocial support, may help reduce the readmission burden in high-risk patients. Research Sponsor: None.

Factors associated with 30-day readmissions	Adjusted Hazard Ratio	95% Confidence Interval	p value
Year of Admission (2021 vs. 2016)	0.71	0.53-0.95	0.02
Median household income			
Quartile 1 (poorest)		Reference	
Quartile 2	0.84	0.74-0.96	0.011
Quartile 3	0.83	0.72-0.95	0.006
Quartile 4 (wealthiest)	0.74	0.65-0.85	<0.001
Private Insurance vs. Medicare	0.86	0.76-0.97	0.018
Large Metro Hospital vs. Others	1.25	1.03-1.52	0.023
Home-health care vs. Routine discharge	0.88	0.78-0.99	0.027
Acute Respiratory Failure	1.32	1.06-1.65	0.013
Fluid-electrolyte imbalance	1.11	1.01-1.22	0.034
Cardiac arrhythmia	1.17	1.02-1.33	0.021
Acute graft-versus-host disease	1.21	1.05-1.39	0.007
Chronic kidney disease	1.45	1.18-1.78	0.001
Depression	1.16	1.02-1.32	0.021
Length of Stay			
≤30 days		Reference	
31-40 days	1.28	1.13-1.46	<0.001
>40 days	1.29	1.11-1.51	0.001

6549 Poster Session

Outcomes of therapy-related AML (T-AML) with venetoclax-based therapies.

Jennifer Croden, Courtney Denton Dinardo, Koichi Takahashi, Naval Guastad Daver, Tapan M. Kadia, Guillermo Garcia-Manero, Gautam Borthakur, Nicholas James Short, Elias Jabbour, Fadi Haddad, Hussein Abbas, Patrick Kevin Reville, Guilin Tang, Sanam Loghavi, Elizabeth J. Shpall, Uday R. Popat, Richard E. Champlin, Farhad Ravandi-Kashani, Hagop M. Kantarjian, Jayastu Senapati; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Stem Cell Transplantation & Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: T-AML refers to AML in patients (pts) with prior exposure to cytotoxic chemotherapy (CT) and/or radiotherapy (RT) and is often associated with adverse risk (AR) genomics. Evaluation of outcomes of T-AML with respect to type of prior therapy exposure, AML genomics, and contemporary AML therapy, especially with venetoclax (VEN), is warranted. **Methods:** We retrospectively analyzed pts aged ≥18 years with newly diagnosed T-AML. Pts with an antecedent myeloid disorder (MDS/CMML) prior to AML diagnosis were excluded; thus, including only pure T-AML. Composite complete response (CRc) included CR and CRi and overall response (OR) included CRc + morphologic leukemia free state. **Results:** From 1/2012 to 12/2023, 317 pts were included; median (med) age was 69 years (range 21-92). Overall, 120 (38%) received prior CT alone, 77 (24%) received prior RT alone (RT), and 114 (36%) received both (CRT). The most common prior malignancy was non-Hodgkin lymphoma (37%) in the CT group, prostate cancer (60%) in the RT group, and breast cancer (45%) in the CRT group.- Among 286 pts with complete cytogenetic data, 180 (63%) were adverse, of whom 132 (46%) had complex karyotype (CK; 42% of CT, 48% of RT, and 61% of CRT groups). *TP53* was mutated in 113/286 patients (40%) tested (36% of CT, 35% of RT, and 47% of CRT groups). Stratified by type of CT received, CK and *TP53* mutation were seen in 5/5 (100%) and 3/5 (60%) of PARP inhibitor-exposed, 98/184 (53%) and 78/183 (43%) of alkylator-exposed, and 21/36 (58%) and 16/37 (43%) of topoisomerase inhibitor-exposed. Overall, 217/304 (71%) were ELN 2017 AR. In total, 251 pts (79%) received low-intensity AML therapy (LIT). CRc and OR was achieved in 122 (49%) and 146 (58%) pts treated with LIT (vs 58% and 65% with LIT+VEN). In pts treated with intensive chemotherapy (IC), the CRc and OR rate was 64% and 68% (vs 68% and 73% with IC+VEN). Overall, med RFS was 7.2 months (mos; 95% CI 5.6-8.9), and med OS was 11.8 mos (10.0-13.7). Med OS was 5.7 vs 9.0 mos (p=0.02) with LIT and LIT+VEN, respectively (resp), and med OS was 10.9 vs 48.9 mos (p=0.03) for IC vs IC+VEN, resp. Among pts treated with LIT+VEN, med OS was 14.0, 12.4, and 9.6 mos in those who had received prior CT, RT and CRT, resp; when stratified by ELN 2017 criteria, med OS was 24.6, 9.4 and 4.8 mos in the favorable, intermediate and AR groups, resp. Sixty-seven (21%) pts underwent HSCT with a landmarked comparison showing improved OS with HSCT (28.5 months vs 9.4, $p<0.001$). On multivariate Cox analysis in the LIT+VEN group, with forward model selection, using variables age </≥ 60, adverse cytogenetics, *ASXL1, IDH1/2, FLT3-ITD, RAS, RUNX1, TP53* status, HSCT, and prior therapy group, HSCT was favorable (HR=0.19, 95% CI 0.01-0.37), along with *IDH2* and *NPM1* mut, while *RAS* and *TP53* mut was associated with higher hazards of death. Other factors were not significant. **Conclusions:** Venetoclax improves outcomes in T-AML. In LIT+VEN treated patients, ELN 2024 risk stratification is prognostic. Research Sponsor: None.

Impact of clinical trial treatment and area deprivation index in the outcomes of adolescent and young adult patients with acute myeloid leukemia.

James Wesley Hill, Koji Sasaki, Hussein Abbas, Michael Roth, Naval Guastad Daver, Tapan M. Kadia, Courtney Denton Dinardo, Gautam Borthakur, Elias Jabbour, Naveen Pemmaraju, Yesid Alvarado, Maro Ohanian, Nitin Jain, Nicholas James Short, Prithviraj Bose, Koichi Takahashi, Sherry Pierce, Paul Edelkamp Jr., Farhad Ravandi-Kashani, Mahesh Swaminathan; Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth Houston), Houston, TX; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Bellaire, TX; University of Texas MD Anderson Cancer Center, Houston, TX

Background: Socioeconomic status (SES) is an independent prognostic factor in patients (pts) with acute myeloid leukemia (AML). Adolescent and young adult (AYA, age 15-39) pts with AML traditionally have better outcomes than older adult pts. Prior studies have shown that SES adversely impacts outcomes in AYA pts. Area Deprivation Index (ADI) is one of the most advanced SE tools, incorporating 17 SE factors to rank neighborhoods based on disadvantaged status. Higher ADI score corresponds to more disadvantaged neighborhoods. Here, we report the largest cohort of AYA pts with AML treated at a single institution with molecular, cytogenetic (CG) and ADI data. **Methods:** AYA pts with AML treated at MD Anderson Cancer Center from 3/2013 to 3/2023 were included. ADI data was downloaded from https://www.neighborhoodatlas.medicine.wisc.edu. Backward elimination was applied to the multivariable model, removing variables sequentially until only variables with $p<0.1$ remained. **Results:** 190 AYA pts were included (non-Hispanic White, NHW-139, non-Hispanic Black-24, Hispanic-16, Asian-11). Median age was 31 years (17-39). 81 pts (43%) had adverse risk by ELN 2022 and 135 (71%) were treated in clinical trials. Both median overall survival (OS) and relapse-free survival (RFS, not censored for transplant (SCT)) was 85.4 months, respectively. ADI national rank 61-100 (HR 1.906, 1.069-3.396, p=0.029), complex CG (HR 2.854, 1.530-5.324, p=0.001), intermediate risk (HR 2.514, 1.160-5.449, p=0.020), and adverse risk (HR 4.257, 1.975-9.177, $p<0.001$) adversely affected OS. Notably, treatment in clinical trials (HR 0.499, 0.309-0.806, p=0.005) and SCT (HR 0.499, 0.288-0.862, p=0.013) led to longer OS. Only complex CG and adverse risk negatively impacted RFS. **Conclusions:** AYA pts from disadvantaged neighborhoods (ADI national rank 61-100) had an inferior OS. Our data showed that treatment in clinical trials and SCT led to longer OS. These results underscore the importance of treatment in clinical trials and SCT for improving OS in AYA, particularly for AYA pts from disadvantaged neighborhoods. Efforts to improve access to clinical trials and SCT, especially for AYA pts from disadvantaged neighborhoods are needed. Research Sponsor: None.

Results of Cox regression analysis for overall survival (p value cutoff 0.100 for MVA).

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
ADI state 1-6	ref	ref	ref	ref	ref	ref
7-10	1.558	0.964-2.517	0.070	1.178	0.625-2.221	0.612
ADI national 1-60	ref	ref	ref	ref	ref	ref
61-100	1.918	1.232-2.986	0.004	**1.906**	**1.069-3.396**	**0.029**
CG: Complex	5.046	3.021-9.428	<0.001	**2.854**	**1.530-5.324**	**0.001**
Favorable	ref	ref	ref	ref	ref	ref
Intermediate	2.162	1.005-4.650	0.049	**2.514**	**1.160-5.449**	**0.020**
Adverse	4.640	2.347-9.175	<0.001	**4.257**	**1.975-9.177**	**<0.001**
Clinical trial	0.495	0.315-0.779	0.002	**0.499**	**0.309-0.806**	**0.005**
SCT (time-dependent)	0.643	0.389-1.062	0.085	**0.499**	**0.288-0.862**	**0.013**

6551 Poster Session

Phase II trial of 10-day ASTX727 (decitabine/cedazuridine) in combination with venetoclax for relapsed or refractory acute myeloid leukemia.

Mehmet Uyanik, Courtney Denton Dinardo, Maro Ohanian, Kelly Sharon Chien, Yesid Alvarado Valero, Gautam Borthakur, Naval Guastad Daver, Ghayas C. Issa, Elias Jabbour, Lucia Masarova, Koichi Takahashi, William G. Wierda, Corey Alexander Bradley, Allison Pike, Duyen H Nguyen, Farhad Ravandi-Kashani, Guillermo Garcia-Manero, Marina Konopleva, Abhishek Maiti; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; Montefiore Medical Center, Albert Einstein Comprehensive Cancer Center, Bronx, NY

Background: The disease outcomes in relapsed refractory acute myeloblastic leukemia (R/R AML) remain dismal. We previously demonstrated safety and encouraging activity of 10-day regimen of IV decitabine with venetoclax (VEN) in R/R AML. In this prospective clinical trial, we investigate the efficacy of a novel 10-day induction regimen with fully oral combination therapy for pts with R/R AML. **Methods:** We conducted a phase II trial in pts with R/R aged ≥18 y with ECOG performance status ≤2 was eligible for enrollment. Exclusion criteria included GI conditions affecting absorption of the drugs, active GvHD, and APL. For induction, pts received oral ASTX727 (100mg/35mg) D1-10 and VEN 400mg D1-28. In subsequent cycles, ASTX727 was reduced to D1-5 in pts achieving CR/Cri (NCT04975919). **Results:** Between December 2021 and March 2024, 20 were enrolled on this trial. The median age was 65 (39-76), 25% of pts (n=5) had therapy-related AML. 60% pts (n= 12) had prior VEN exposure. Eighty-five percent of the pts were either and/or harbored complex karyotype. Median duration of the treatment was 1.7 m (0.5-9.5) and median no of cycles was 1 (range 1-6). The composite CR/CRi/MLFS rate was 40% (n=8), with best response achieved at median 1.3 m. Duration of response in responders was 8.5 m (2.9-30.8). MRD was negative in 25% (2/8) of responding pts, and 3 pts (15%) proceeded to stem cell transplantation (SCT). Two transplanted patients (67%) were in CR before SCT, while 1 patient (33%) was in MLFS. The median OS was 8.6 m. VEN-naive pts showed longer OS (10.5m vs 4.4m with prior VEN, p=0.12). Responding pts who could be bridged to SCT had better OS benefit (not reached vs 6.6m, p=0.01). The median OS of pts with $TP53^{mut}$ was 3.1 m vs 8.6 m in pts who were $TP53^{WT}$ (p=0.60). The 4-week mortality rate was 6%, and the 8-week mortality rate was 17%. Treatment-emergent adverse events of Gr 3/4 were observed in 81% of pts (17), with infections and febrile neutropenia being the most frequent complications (35% each). After a median follow up of 8.7 m (0.5-30.8), 80% of pts (16) died. Among the deaths, 40% were attributed to disease progression, and 25% to bacterial infections. None of the deaths were associated with bacterial infections occurred in patients with CR. **Conclusions:** The 10-day ASTX727-VEN combination showed safety profile comparable to other HMA-VEN regimens in salvage setting. TP53 wild type, VEN-naïve pts and those who could be bridged to SCT had better outcomes. Novel therapies are needed to improve outcomes in R/R AML. Clinical trial information: NCT04975919. Research Sponsor: MD Anderson Cancer Center.

Factors associated with frailty in vulnerable hematopoietic cell transplantation candidates.

Hyunhae Lee, Alexi Vasbinder, Mohamed Lotfy Sorror; University of Washington, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Allogenic hematopoietic cell transplantation (allo-HCT) is increasingly offered to older patients and those with comorbidities. Frailty, characterized by reduced muscle strength and functional decline, is associated with lower quality of life, increased mortality, and higher hospitalization after allo-HCT. However, frailty prior to allo-HCT remains understudied. The study investigated factors associated with frailty in allo-HCT candidates prior to transplant. **Methods:** This cross-sectional analysis utilized data from the ACE-BMT study, an ongoing longitudinal, unblinded, randomized seamless phase II/III trial, that enrolled adult patients allo-HCT candidates either age of ≥65 years, with HCT comorbidity index (HCI-CI) score of ≥3, or 4-meter walk speed test <0.8 m/s. We classified frailty in participants at baseline using the Fried frailty phenotype: 1) unintentional weight loss, 2) low energy (Patient Health Questionnaire 9-item [PHQ-9]), 3) grip strength or stand-up time below standard, 4) 4-meter walk test < 0.8m/s, and 5) the lowest 20% of physical functioning (Medical Outcomes Study Physical Health). Participants were classified as frail (≥3), pre-frail (1-2), or not frail (0). We assessed pre-HCT variables including demographics, comorbidities, and self-reported social support (ENRICHED Social Support Instrument), symptom severity and interference with daily life (MD Anderson Symptom Inventory), depression (PHQ-9), cognitive impairment (Bless Orientation Memory Concentration), quality of life (Euro Quality of Life 5-Dimensions), and functional status (Karnofsky Performance Status). We compared baseline characteristics based on frailty status and conducted a multivariable logistic regression to identify the factors associated with frailty. **Results:** Among 381 patients (mean age 65.49, 38.32% female) included in the analysis, 81.7% were pre-frail and frail at baseline. Compared to non-frail, participants as frail were younger (mean age 66.49 vs 61.49), more likely to be female (35.7% vs. 48.7%), to have cardiovascular disease (1.3% vs. 9.2%) and diabetes (9.8% vs. 23.7%), and a HCT-CI score ≥3 (39.3% vs. 61.8%). They also self-reported greater depression, symptom severity and interference, cognitive impairment, and poorer quality of life. In a multivariable logistic regression model, older age (OR: 0.98, 95% CI: 0.95, 1.00), higher symptom interference (OR: 1.04, 95% CI: 1.01-1.08), and depression (OR: 1.14, 95% CI: 1.03-1.27) were significantly associated with frailty. **Conclusions:** Frailty prior to allo-HCT is associated with symptom burden and depression, underscoring the importance of addressing these factors pre-HCT. These findings provide preliminary support for psychological screening and symptom-focused interventions. Future analyses will examine the incidence and risk factors of post-HCT frailty and its association with clinical outcomes. Research Sponsor: NIH, NCI; R01CA227092.

6553 Poster Session

Allogeneic hematopoietic cell transplantation for acute leukemia patients not in complete remission.

Shlomo Elias, Samantha Brown, Ogechukwu Egini, Moneeza Walji, Sylvester Homsy, Arash Velayati, Sean Devlin, Doris Ponce, Vanessa Elaine Kennedy, Sushma Bharadwaj, Parveen Shiraz, Ann A. Jakubowski, Esperanza Bouza Papadopoulos, Lori S. Muffly, Miguel-Angel Perales, Sergio Giralt, Melody Smith, Boglarka Gyurkocza; Hadassah University Hospital Jerusalem Israel, Jerusalem, Israel; Memorial Sloan Kettering Cancer Center, New York, NY; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Adult Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Division of Blood and Marrow Transplantation and Cellular Therapy, Department of Medicine, Stanford University School of Medicine, Stanford, CA; Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; Stanford University, Palo Alto, CA; Stanford University, Stanford, CA; Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University School of Medicine, Stanford, CA; Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA

Background: Current guidelines support allogeneic hematopoietic cell transplantation (allo-HCT) in patients with acute leukemia who achieve complete remission (CR) and are at high risk for relapse. Patients with primary refractory disease or those refractory to re-induction therapy after relapse have a poor prognosis without allo-HCT. While several studies have explored the role of allo-HCT in this setting, most have focused on patients receiving myeloablative conditioning (MAC) and have not included contemporary transplant patients or accounted for the impact of molecular genetic risk factors. Consequently, the benefit of allo-HCT in this patient population remains unclear. **Methods:** This study evaluated the outcomes of patients with acute leukemia from two centers who underwent allo-HCT between 2009 and 2020 while not in CR at the time of transplant, receiving either myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) regimens. **Results:** Our cohort included 196 patients who underwent transplantation between 2009 and 2020, with the majority (86%) diagnosed with acute myeloid leukemia (AML). At 36 months post-transplant, the probability of overall survival (OS) was 24% (95% CI: 19-31). In multivariable analysis, the presence of circulating blasts, recipient CMV seropositivity, and low pre-transplant albumin levels were associated with reduced OS. The cumulative incidence of relapse was 54% (95% CI: 47-61) at 36 months, with the presence of circulating blasts being significantly associated with an increased incidence of relapse. Among AML patients, the presence of at least one high-risk mutation (TP53, RUNX1, ASXL1, or FLT3-ITD, historically considered high-risk per National Comprehensive Cancer Network [NCCN] criteria version 3.2021) was also associated with an increased incidence of relapse. **Conclusions:** Allo-HCT provides a durable remission in a select group of patients with relapsed or refractory acute leukemia, with an overall survival of 24% at 36 months. The presence of circulating blasts, CMV seropositivity, and low albumin levels at the time of allo-HCT were associated with increased relapse and inferior OS in this retrospective analysis. The impact of these factors should be further investigated in larger, prospective cohorts to better identify patients with acute leukemia not in CR who would benefit from allo-HSCT. Research Sponsor: None.

Exploratory analyses of immune reconstitution biomarkers from a Ph1b study of an investigational, oral, live biotherapeutic, SER-155, in adult allo-HCT.

Emily Walsh, Jonathan U. Peled, Doris Ponce, Satyajit Kosuri, Nandita Khera, David I. Lichter, Kelly Brady, Brooke R. Hasson, Swarna Pandian, Nathan D. Hicks, Meghan Chafee, Elizabeth M. Halvorsen, Mary-Jane Lombardo, Christopher B. Ford, Bina Tejura, Matthew R. Henn, Lisa von Moltke, Marcel R.M. van den Brink, Zachariah Michael DeFilipp, Seres Therapeutics SER-155 Team; Seres Therapeutics, Cambridge, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL; Division of Hematology/Oncology, Mayo Clinic, Phoenix, AZ; Seres Therapeutics, Quincy; Division of Hematology and Oncology, Department of Medicine, Massachusetts General Hospital; Harvard Medical School, Boston, MA

Background: SER-155 is an investigational, oral, live biotherapeutic product (LBP) comprised of 16 bacterial strains designed to decolonize gastrointestinal (GI) pathogens, improve epithelial barrier integrity, and modulate immune responses to prevent bloodstream infections (BSI). In the placebo-controlled cohort 2 of the phase 1b study, SER-155-001 (NCT04995653), SER-155 was generally well tolerated with a safety profile similar to placebo and the incidence of BSIs, a secondary endpoint, was significantly lower after treatment with SER-155 when compared to placebo. We report exploratory analyses of biomarkers of T cell expansion relevant for immune reconstitution after HCT. **Methods:** Participants were randomized 1:1 to receive 4 days of oral vancomycin (for microbiome conditioning) and 10 days of SER-155 or placebo/placebo administered pre-HCT (course 1) and post-neutrophil engraftment (course 2). Primary endpoints were safety and SER-155 strain engraftment (PK). Exploratory endpoints included plasma cytokine concentrations measured by ELISA and analysis of peripheral blood mononuclear cells (PBMCs) by flow cytometry. **Results:** Demographics were comparable across treatment arms. 34 of 45 randomized participants were treated and received allo-HCT (SER-155, 20; placebo, 14); 28 received course 2 (SER-155, 19; placebo, 9). SER-155 strain engraftment was observed in the peri-transplant period (median 11.5 strains after course 1) and post-HCT (median 11 strains after course 2 and HCT Day 100). Significant differences and trends in cytokines of systemic inflammation and immune homeostasis were observed relative to placebo prior to HCT Day 0 and post-HCT. On HCT Day 0, both arms had similar concentrations of IL7 and IL15 (Table 1). However, after course 2, and at HCT Day 100, significantly higher concentrations of IL7 were observed in the SER-155 arm relative to placebo ($p=0.02$, and $p=0.003$, respectively). In a preliminary analysis of PBMCs from a subset of participants, a high frequency of CD4+ T cells were observed in the SER-155 arm at the same timepoints. For homeostatic cytokine IL15, no significant differences were observed between arms. **Conclusions:** The significantly higher concentrations of IL7 with SER-155 treatment and observed frequency of CD4+ T cells support the potential role of the GI microbiome in promoting homeostatic expansion of peripheral T cells and immune reconstitution important for successful HCT. Clinical trial information: NCT04995653. Research Sponsor: Seres Therapeutics.

Median plasma IL7 and IL15 (pg/mL), SER-155 vs. placebo (generalized linear model).

HCT Day or event	SER-155 IL7	Placebo IL7	SER-155 IL15	Placebo IL15
D0	13.8	13.0	31.9	30.4
D7	15.1	14.6	50.9	62.6
D14	12.8	15.5	56.6	69.8
Post-neutrophil engraftment	13.4	9.0	16.3	15.4
Post-course 2	7.4*	3.9	6.2	9.1
D100	7.1**	3.5	6.2	6.2

*$p<0.05$, **$p<0.01$.

Peripheral blood cell-free DNA testing as a predictor for relapse post-allogeneic stem cell transplant for AML.

Vanisha Patel, Maciej Kabat, Andrew Ip, Hyung C. Suh, Maher Albitar, Sukhdeep Kaur, David H. Vesole, Michele Donato, Christina Cho, Scott D. Rowley; Hackensack University Medical Center, Hackensack, NJ; John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; Genomic Testing Cooperative, Lake Forest, CA; John Theurer Cancer Center, Hackensack University Medical Center, Livingston, NJ

Background: Allogeneic stem cell transplantation (allo-SCT) is a curative option for acute myelogenous leukemia (AML), but relapse is a challenge. Monitoring minimal residual disease post-transplant through tumor-derived circulating cell-free DNA (cfDNA) in peripheral blood (PB) and bone marrow is an emerging strategy. Persistent mutations in cfDNA may be prognostic indicators of relapse. **Methods:** This single-center retrospective study included 120 AML patients who received allo-SCT from 2018 to 2022, with PB cfDNA collected between Days 30-200. Samples were analyzed by commercial assays (Liquid Trace or Hematology Profile Plus), that use next generation sequencing, Sanger Sequencing, and fragment length analysis to identify molecular abnormalities in DNA of 179 genes associated with hematologic neoplasms. cfDNA positivity was determined by identifying gene amplifications, deletions, single nucleotide variations and indels, including reported variant allele frequency (VAF) above 0. cfDNA negativity was defined by absence of genomic alterations. The primary endpoints were the association of cfDNA presence with overall survival (OS) and relapse-free survival (RFS). A secondary endpoint was the association of mutation risk (adverse/intermediate) with OS and RFS. **Results:** Patients were grouped by cfDNA presence at Day 45±15 (n=30, median survival time 1.173 years) and Day 150±50 (n=90, median survival time 1.4822 years). Kaplan-Meier analysis revealed that patients positive for PB cfDNA at Day 150±50 had significantly worse OS ($p<0.0001$) and RFS ($p<0.0001$) compared to cfDNA negative. Similarly, cfDNA positivity at Day 45±15 also correlated with worse OS ($p<0.01$) and RFS ($p<0.0007$). Regarding mutation risk, adverse mutations at Day 150±50 were linked to worse OS ($p<0.0001$) and RFS ($p<0.0001$). Multivariate analysis revealed that adverse-risk mutations were significantly associated with relapse (odds ratio [OR] 29.48, 95% CI 4.306-350.4, $p<0.002$), RFS (hazard ratio [HR] 12.62, 95% CI 3.541-44.35, $p<0.0001$), and OS (HR 19.24, 95% CI 5.242-75.73, $p<0.0001$). Intermediate-risk mutations also correlated with relapse (OR 13.27, 95% CI 2.818-89.91, $p<0.002$), RFS (HR 9.325, 95% CI 2.748-35.25, $p<0.0005$), and OS (HR 11.48, 95% CI 3.279-45.61, $p<0.0002$). Transplant age, donor type, CMV status, and GvHD regimen were not statistically significant. **Conclusions:** This study demonstrates that cfDNA detection in PB post-allo-HSCT is strongly associated with increased relapse and mortality in AML patients. Persistent high-risk mutations correlate with increased risk of relapse and poor survival outcomes. These findings highlight the potential of PB cfDNA as a predictive marker, potentially enabling earlier intervention to alter post-transplant treatment strategies. Research Sponsor: None.

The impact of the use of hypomethylating agents prior to reduced intensity conditioning allogeneic bone marrow transplant among patients with MDS.

Yanal Mufeed Alnimer, Reinhold Munker, Ayman Qasrawi, Chait Iragavarapu, Zena Chahine, Gregory P. Monohan, Fevzi Firat Yalniz; University of Kentucky, Lexington, KY; Markey Cancer Center, Lexington, KY; University of Kentucky Department of Biostatistics, Lexington, KY

Background: Allogeneic transplantation is the only potential cure for patients with myelodysplastic syndrome (MDS). It is unclear whether cytoreduction with hypomethylating agents (HMAs) prior to reduced intensity conditioning (RIC) transplantation in patients with 5–10% bone marrow blasts impact transplant outcomes. **Methods:** We utilized the publicly available CIBMTR dataset from the publication *"Alternative Donor Transplantation for Myelodysplastic Syndrome: Haploidentical Relative and Matched Unrelated Donor"* to evaluate the differences in relapse-free survival (RFS), transplant-related mortality (TRM), and overall survival (OS) between recipients and non-recipients of pretransplant HMAs among MDS patients undergoing RIC Allo-SCT. The two groups were matched on confounding variables, including donor type, blast percentage at diagnosis and at the time of transplant, age, sex, race, IPSS-R score, CMV donor status, conditioning regimen, time to transplant, and year of diagnosis. Matching was performed using the inverse probability of treatment weights (IPTW) method. Weighted Kaplan-Meier curves were used to evaluate OS, RFS, and TRM between the two groups. Additionally, a doubly robust Cox regression model was constructed to estimate hazard ratios (HR) for the effect of pretransplant HMA use on OS and RFS. **Results:** A total of 603 patients were included in our analysis. The median age was 67.1 years (IQR 63.1–70.5), and the median follow-up was 21.8 months (0.95 CI 13.1–NR). In the weighted data. The 0.75 quantile for RFS was 7.57 months (0.95 CI 6-NR months) for the non-HMA group versus 5.79 months (0.95 CI 4.14–6 months) for the HMA group (P = 0.027). Similarly, the 0.75 quantile for OS was 9.54 months (0.95 CI 7.96–NR) for the non-HMA group versus 5.79 months (0.95 CI 4.38–7.43 months) for the HMA group (P = 0.005). There was no significant difference in the incidence of acute or chronic GVHD or TRM. In doubly robust Cox regression model. Pretransplant HMA was associated with worse RFS and OS with a HR of 0.66 (0.95 CI 0.44-0.97, P value =0.035) and HR of 0.60 (0.95 CI 0.42-0.90, P value< 0.01) respectively. **Conclusions:** Pretransplant use of HMA in MDS patients with less than 10% bone marrow blasts is associated with worse RFS and OS following allogeneic SCT with RIC. Notably, this detrimental impact is most pronounced in patients with less than 5% blasts, raising critical questions about the role of pretransplant HMA in this low-risk subgroup and emphasizing the need for refined treatment strategies. Research Sponsor: None.

Doubly robust (weighted) Cox-regression model on RFS.

Variable	Estimate	Lower .95 CI	Upper .95 CI	P-Value
No-Hypomethylating agents before Transplant (Reference=HMA pretransplant)	0.66	0.44	0.97	**0.035**
Sex (Reference=Male)	1.27	0.89	1.80	0.186
MUD VS Haploidentical	0.92	0.42	2.02	0.84
Poor cytogenetics (Reference=very good and good)	3.9	2.66	5.82	**<0.01**

Allogeneic stem cell transplantation in chronic myelomonocytic leukemia: Analysis of post-transplant survival and risk factors in 138 Mayo Clinic patients.

Ali Alsugair, Estefania Gauto Mariotti, Mohammad M. Alhousani, Saubia Fathima, Abiola Bolarinwa, James M. Foran, Abhishek A. Mangaonkar, Mark Robert Litzow, Hemant S. Murthy, Lisa Sproat, Jeanne M. Palmer, William J. Hogan, Mithun Vinod Shah, Hassan B. Alkhateeb, Naseema Gangat, Mrinal Patnaik, Ayalew Tefferi; Mayo Clinic, Rochester, MN; Mayo Clinic Comprehensive Cancer Center, Mayo Clinic, Jacksonville, FL; Mayo Clinic Florida, Jacksonville, FL; Mayo Clinic, Phoenix, AZ; Mayo Clinic Arizona, Phoenix, AZ; Division of Hematology, Mayo Clinic, Rochester, MN

Background: Allogeneic stem cell transplantation (ASCT) is currently the only curative therapy in chronic myelomonocytic leukemia (CMML). **Methods:** A Mayo Clinic enterprise-wide database search identified 138 CMML cases who underwent ASCT. Conventional statistical methods were used for analyses. **Results:** 138 CMML patients (transplanted between 1995-2024) were included (median age 63 years; males 62%);104 (group A) received ASCT before and 34 (group B) after blast transformation (BT). At initial diagnosis, CMML-1/CMML-2 and dysplastic/proliferative representations were 78%/22% and 54%/46%; 31% displayed abnormal karyotype and most frequent mutations were *ASXL1* (56%), *TET2* (44%) and *SRSF2* (38%). At time of initial diagnosis, CPSS-Mol risk categories were low (17%), intermediate-1 (11%), intermediate-2 (40%), and high (32%). Median time from diagnosis to ASCT was 11 months (range 0-201). Median overall survival (OS) from the time of initial diagnosis was 67 months (range 4-239) and from the time of ASCT 54 (range 0-212) months. Occurrence of BT before ASCT was associated lower post-transplant survival (PTS; 16 vs 95 months, P=0.01, HR 1.9, 95% CI 1.2-3.2). Bone marrow (BM) blasts, at the time of ASCT, $<5\%$, 5-9%, and 10-19% correlated with median OS of 171, 81, and 18 months in group A (p=0.01) and 50, 25, and 13 months in group B (P=0.07), respectively. Pre-ASCT hypomethylating agent exposure was associated with lower PTS in group A (P=0.02). PTS was also adversely affected by *DNMT3A* and *SETBP1* mutations. In group A, PTS was the longest with myeloablative busulfan-based (median not reached) and the shortest (median 22 months) with Cy-TBI-based conditioning (p=0.1). Donor type did not impact PTS: matched unrelated (63%), matched sibling (23%), mismatched unrelated (7%), or haplo-identical (7%). Post-transplant cyclophosphamide was associated with a numerically lower median PTS (22 months), compared to other forms of GVHD prophylaxis (107 months; p=0.1) and significantly higher non-relapse mortality (p=0.02). Documentation of morphologic CR at day 100 was associated with significantly longer PTS in both groups A (92%,164 vs. 18 months; p=0.01) and B (84%, 42 vs. 11 months; p=0.01). The presence of abnormal karyotype at day 100 was associated with shorter PTS in group A (p=0.01). Grade ≥ 3 acute and moderate to severe chronic GVHD occurred in 20% and 34%, respectively, in group A patients and in 26% and 44% in group B. GRFS at 1/3 years were 42/21% in group A and 31/16% in group B. At last follow up, 44% in group A and 65% in group B were dead. Causes of death were relapse/non-relapse related in 36/64% in group A and 39/61% in group B. **Conclusions:** ASCT is effective in securing long-term survival in CMML, especially when the procedure is performed prior to BT and in the setting of $<5\%$ BM blasts/promonocytes. Response assessment at day 100 was highly informative of outcome. Research Sponsor: None.

6559 Poster Session

Allogeneic hematopoietic stem cell transplantation in T-cell acute lymphoblastic leukemia adults in complete remission: A systematic review and meta-analysis.

Muhammad Umair Mushtaq, Pramod Singh, Asad Zaman, Muhammad Abdullah Humayun, Abdul Rafae Faisal, Ali Shan, Hameer Ali, Muhammad Faizan, Waseh Ahsan, Arfa Ahmed, Rameesha Mehreen, Muhammad Ahmad Sadiq, Saba Sattar, Muhammad Kashif Amin, Joseph McGuirk, Moazzam Shahzad; Division of Hematologic Malignancies & Cellular Therapies, University of Kansas Medical Center, Kansas City, KS; University of Kansas Medical Center, Kansas City, KS; Division of Hematologic Malignancies & Cellular Therapeutics, University of Kansas Medical Center, Kansas City, KS; Tufts Medical Center, Boston, MA; H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, FL

Background: There is limited data on the outcomes of allogeneic hematopoietic stem cell transplantation (allo-HCT) in T-cell acute Lymphoblastic Leukemia (T-ALL) patients. This study aims to assess complications, recurrence rates, and survival outcomes in T-ALL patients in clinical remission receiving allo-HCT. **Methods:** Following PRISMA guidelines, a comprehensive literature search was conducted across PubMed, Embase, Cochrane, and the clinicaltrials.gov registry from inception to December 2024 using keywords related to T-ALL and allo-HCT. Out of 1161 identified search results, 8 studies were included in this meta-analysis. Data was analyzed for outcomes including overall survival (OS), leukemia-free survival (LFS), relapse rates, non-relapse mortality (NRM), and graft-versus-host disease (GVHD) of Allo-HSCT in adult T-ALL patients in clinical remission. R version 4.4.2 was used to conduct a proportional meta-analysis using an inverse variance, random effects model. **Results:** This study included eight retrospective studies involving 3,280 T-ALL patients undergoing allo-HCT, with a median age of 32 years (range: 17–49) and a median follow-up of 37 months (range: 28–44). Seventy-one percent of the patients were male. Donor types included matched sibling (48.3%), matched unrelated (33.7%), haploidentical (10.2%), and mismatched unrelated (7%). Most grafts were from peripheral blood (75.8%), with the remainder from bone marrow. A myeloablative conditioning regimen was used in 86% of patients. At the time of HSCT, 92.16% of patients were in clinical remission. The pooled 2-year overall survival (OS) for patients in clinical remission was 63.2% (95% CI: 47.2–79.2; $p<0.0001$; $I^2 = 89.4\%$), and 53.5% at 5 years (95% CI: 25.9–81.1; $p<0.0001$; $I^2 = 93.7\%$). Similarly, the pooled leukemia-free survival (LFS) was 64.5% at 2 years (95% CI: 51.9–77.1; $p<0.0213$; $I^2 = 74\%$) and 62.7% at 5 years (95% CI: 26.9–99.4; $p<0.0003$; $I^2 = 92.5\%$). The pooled relapse rate was 23.4% at 2 years (95% CI: 9.6–37.2; $p<0.0001$; $I^2 = 89.4\%$) and 53.3% at 4 years (95% CI: 0.0–100; $p<0.0001$; $I^2 = 98.5\%$). The pooled non-relapse mortality (NRM) rate was 14.5% at 1 year (95% CI: 9.1–19.6; $p = 0.0695$; $I^2 = 69.6\%$), 20.8% at 4 years (95% CI: 17.9–23.8; $p = 0.4907$; $I^2 = 0\%$), and 26% at 5 years (95% CI: 18.6–29.9; $I^2 = 0\%$). The pooled incidence of chronic graft-versus-host disease (cGVHD) was 34.3% (95% CI: 27.0–41.5; $p = 0.6564$; $I^2 = 75.8\%$). **Conclusions:** T-ALL patients in clinical remission at allo-HCT showed favorable survival outcomes, though relapse remains a significant concern, particularly over time. Non-relapse mortality stabilizes after the first year but continues to pose a challenge. Chronic graft-versus-host disease prevalence remains high, underscoring the importance of long-term management strategies. Research Sponsor: None.

Factors associated with outcomes following reduced intensity conditioning haploidentical hematopoietic cell transplantation in acute myeloid leukemia.

Muhammad Umair Mushtaq, Muhammad Kashif Amin, Amir Kasaeian, Iman Oskouie, Hediyeh Alemi, Naghmeh Khavandgar, Sibgha Gull Chaudhary, Iqra Anwar, Joseph McGuirk, Moazzam Shahzad; Division of Hematologic Malignancies & Cellular Therapies, University of Kansas Medical Center, Kansas City, KS; Division of Hematologic Malignancies & Cellular Therapeutics, University of Kansas Medical Center, Kansas City, KS; Liver and Pancreatobiliary Diseases Research Center, Digestive Diseases Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran; Urology Research Center, Tehran University of Medical Sciences, Tehran, Iran; H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, FL

Background: Allogeneic hematopoietic cell transplantation (HCT) is a curative therapy for high-risk acute myeloid leukemia (AML). Elderly patients can undergo HCT using a reduced-intensity conditioning (RIC) regimen. When HLA-matched donors are unavailable, haploidentical (Haplo) family donors can be used, offering outcomes similar to those with matched donors. This study investigates factors influencing outcomes following RIC haplo HCT with posttransplant cyclophosphamide (PT-Cy)-based GVHD prophylaxis. **Methods:** A retrospective multicenter study was conducted using the CIBMTR registry (2012-2017, P-5737 dataset, Ustun et al.) to assess AML patients undergoing first RIC haplo-HCT. Outcomes included overall survival (OS), disease-free survival (DFS), relapse, non-relapse mortality (NRM), acute and chronic GVHD, GVHD-free relapse-free survival (GRFS), and engraftment. Patient- and transplant-related factors were analyzed with Chi-square and Wilcoxon tests. Kaplan-Meier and univariate and multivariate Cox regression analyses were conducted. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Statistical significance was defined as $p<0.05$. **Results:** We included 185 AML patients undergoing the first RIC haplo-HCT with PT-Cy-based GVHD prophylaxis. The median age was 63.8 years, 58% were male, and 70% were Caucasians. Graft sources were peripheral blood (55%) and bone marrow (45%), with a graft cell dose of>2 million CD34 cells/kg in 82% of patients. HCT-Comorbidity index (CI) was three or higher in 45% of patients, and Karnofsky's performance status was <90% in 53% of patients. The median follow-up was 4 years, and 36% were alive at the last follow-up. The median OS, DFS, and GRFS were 1.59, 0.76, and 0.31 years, respectively. Primary disease (33.5%), organ failure (9%), and infection (8%) were the leading causes of death. Relapse, acute (grade II-IV), chronic GVHD, and NRM occurred in 52%, 36%, 30%, and 20.5% of patients, respectively. Neutrophil engraftment occurred over a median of 17 days. In multivariate analyses, high disease risk independently predicted inferior OS (HR 1.72, p=0.012), inferior DFS (HR 1.49, p=0.136), higher relapse (HR 1.88, p=0.028), and higher NRM (HR 2.12, p=0.011). Higher HCT-CI predicted inferior OS (HR 1.88, p=0.041), higher NRM (HR 5.21, p=0.043), and delayed neutrophil engraftment (HR 0.37, $p<0.001$). Asians, compared to Caucasians, had superior GRFS (HR 0.46, p=0.040). **Conclusions:** In AML patients undergoing RIC haploidentical HCT, favorable outcomes were observed, and key determinants were high disease risk and comorbidities. Relapse remains the leading cause of treatment failure. These findings suggest pre-transplant assessments and post-transplant strategies to mitigate relapse risk for optimizing outcomes in this patient population. Research Sponsor: None.

Myeloablative fractionated busulfan conditioning regimen with sorafenib for allogeneic stem cell transplant in AML: Results of a phase 1/2 study.

Uday R. Popat, Roland L Bassett Jr., Peter F. Thall, Amin Majid Alousi, Gheath Alatrash, Qaiser Bashir, Chitra M. Hosing, Jin Seon Im, Partow Kebriaei, David Marin, Rohtesh S. Mehta, Yago Nieto, Amanda Leigh Olson, Betul Oran, Benigno Valdez, Muzaffar H. Qazilbash, Richard E. Champlin, Elizabeth J. Shpall, Borje S. Andersson; Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Myeloablative conditioning for allogeneic stem cell transplant (allo-SCT) can be given safely to older patients by extending the duration of busulfan (Bu) administration. This allows the addition of agents like sorafenib for a 3-week period to synergize with the conditioning. Here, we studied 4 doses of sorafenib with myeloablative fludarabine and fractionated Bu (f-Bu) in a phase 1/2 study (NCT03247088). **Methods:** From 3/2018-9/2023, 59 AML patients 18-70 years old with 8/8-HLA matched donors were enrolled prospectively. Sorafenib dose finding was done in phase 1 with a Bayesian Model Averaging Continual Reassessment Method with target toxicity probability .30 and cohort size 3, with DLT defined as grade >3 regimen-related toxicity occurring on days -24 to 30. Subsample sizes were 3 patients at 200, 400, and 600mg, and 50 patients at the highest tolerated dose of 800mg (400mg bid), given daily on days -24 to -5. The f-Bu dose targeted an area under the concentration vs time curve of 20,000 ± 12% μmol.min, given over 3 weeks. The first 2 doses (80 mg/m2 each) were given outpatient on days -20 and -13. The last 4 pharmacokinetically guided doses were given inpatient after Flu 40mg/m2 on days -6 to -3. GVHD prophylaxis was cyclophosphamide 50mg/kg on days 3-4 and tacrolimus. Unrelated donor graft recipients also received MMF. All patients were eligible for sorafenib maintenance for 1 year post-transplant. 30 (51%) patients began this maintenance and 13 (21%) completed 1 year. **Results:** Median age was 53 years (range, 24-70). Disease status at SCT was CR1 in 42 (71%) patients, CRi in 6 (10%), and advanced disease in 11 (19%). 34 (58%) had ELN22 adverse risk disease, 31 (53%) were MRD+, 17 (29%) had FLT3 ITD, donor was unrelated in 37 (63%), and peripheral blood was the graft source in 53 (90%). The cohort's 2-year overall survival (OS) was 74.9% (95% credible interval (CrI) 61.8-84.8%), with a median follow-up in 43 surviving patients of 2.2 years. A fitted Bayesian Weibull regression model for OS showed a higher risk of death with MRD+ disease (posterior mean HR = 3.13, 95% CrI 1.01–12.03) and age > 60 (posterior mean HR = 2.22, 95% CrI 0.76–6.91). No association was seen with OS or PFS and comorbidity score, remission status, or ELN22 risk group. Outcomes were similar in FLT3 ITD and wild type patients. **Conclusions:** The f-Bu regimen with sorafenib results in promising outcomes for AML patients. Clinical trial information: NCT03247088. Research Sponsor: National Cancer Institute.

Outcomes (n=59).

	1 year	2 years
OS	86%	75%
PFS	83%	69%
Relapse	12%	22%
NRM	10%	10%
		Percent
Acute GVHD II-IV, day 100		36%
Acute GVHD III-IV, day 100		3%
Chronic GVHD, 2 years		14%
Mod/Severe Chronic GVHD		9%
		Median (range) days
Neutrophil Engraftment		15 (12-28)
Platelet Engraftment		23 (14-164)
T Cell Chimerism, day 30		100 (33-100)
Myeloid Chimerism, day 30		100 (91-100)
Grade 3-5 toxicity, day 100 (>10%)	**Events**	**Percent**
Febrile Neutropenia	24	41%
Bacterial infection	21	36%
Pneumonitis/IPS	8	14%
Rash	6	10%

Association between pre-transplant biological aging markers and clinical outcomes in allogeneic hematopoietic cell transplant recipients.

Kelly E. Rentscher, Paul Auer, Steve W Cole, J. Douglas Rizzo, Tao Wang, Naya He, Brent Logan, Stephen Spellman, Stephanie Lee, Michael Verneris, Jesusa Arevalo, Jennifer Knight; Medical College of Wisconsin, Milwaukee, WI; University of California, Los Angeles, Los Angeles, CA; Froedtert & the Medical College of Wisconsin, Milwaukee, WI; CIBMTR (Center for International Blood and Marrow Transplant Research), NMDP, Minneapolis, MN; Fred Hutchinson Cancer Center, Clinical Research Division, Seattle, WA; CU Anschutz, Denver, CO

Background: Cancer and its treatments can accelerate the aging process, placing survivors at increased risk for poor outcomes. Hematopoietic cell transplant (HCT) recipients may show variations in biological aging before HCT due to previous treatment exposures; however, pre-transplant transcriptomic markers of biological aging have not yet been investigated as predictors of clinical outcomes. We used data from the Center for International Blood and Marrow Transplant Research (CIBMTR) to examine the hypothesis that recipients with greater pre-transplant expression of molecular processes in the cellular senescence pathway—a fundamental mechanism of aging—would have worse clinical outcomes. **Methods:** Participants included 261 adults (M_{age}=41.3 years) that received an HLA-matched unrelated donor myeloablative HCT between 1995–2005 for acute myelogenous leukemia (AML) in complete remission and had pre-transplant blood samples available in the CIBMTR Repository. Whole-genome RNA sequencing of recipient peripheral blood mononuclear cells (PBMCs) was used to derive molecular senescence markers, including the DNA damage response (DDR; 29-gene composite), cellular senescence signals $p16^{INK4a}$ and p21 (*CDKN2A* and *CDKN1A*, respectively), the pro-inflammatory senescence-associated secretory phenotype (SASP; 60-gene composite) and the SenMayo senescence gene set (125-gene composite). We examined acute and chronic graft-versus-host disease (GVHD), transplant-related mortality (TRM), relapse, leukemia-free survival (LFS), and overall survival (OS) as clinical outcomes. **Results:** Transcriptomic composites were examined as continuous variables. Cox proportional hazard models adjusting for patient, disease, and transplant characteristics and major cell subsets in the PBMC pool revealed that elevated SASP and SenMayo expression were associated with increased risk of TRM (*HR*=3.56, *p*=.005 and *HR*=6.88, *p*=.002, respectively) and OS (*HR*=2.31, *p*=.03 and *HR*=4.50, *p*=.004, respectively). However, enhanced expression of senescence signal p21 was associated with decreased risk of relapse (*HR*=0.52, *p*=.01) and LFS (*HR*=0.70, *p*=.03). The DDR and senescence signal $p16^{INK4a}$ did not significantly relate to clinical outcomes. **Conclusions:** Transcriptomic markers of biological aging assessed in allogeneic HCT recipients before transplant are predictive of relapse and survival outcomes. Specifically, findings suggest that enhanced expression of pro-inflammatory SASP and SenMayo genes may represent a pre-transplant molecular risk profile, whereas elevated expression of p21 may serve as a protective prognostic indicator in the HCT setting. Given the heterogeneous nature of senescent cells, research that examines these transcriptomic markers following HCT as well as how recipient and donor profiles may interact to influence outcomes is warranted. Research Sponsor: NIH National Institute on Aging.

6563 Poster Session

Pre-transplant measures of geriatric assessment domains and outcomes of allogeneic hematopoietic cell transplantation in adults aged 75 and older.

Amar Harry Kelkar, Haesook T. Kim, Nichoals Groblewski, Joseph Harry Antin, Corey S. Cutler, Mahasweta Gooptu, Vincent Ho, John Koreth, Ansh Mehta, Prashant K. Nageshwar, Sarah Nikiforow, Rizwan Romee, Roman M. Shapiro, Robert Soiffer, Catherine J Wu, Clark DuMontier, Gregory A. Abel; Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital, Roxbury Crossing, MA

Background: The upper age limit for allogeneic hematopoietic cell transplantation (HCT) has risen over time, yet prior studies indicate worse outcomes—particularly non-relapse mortality (NRM)—in patients over 70 compared to younger patients (Shahzad, *Transplant Cell Ther* 2025). As the population ages, we expect the transplant-eligible age range to extend, underscoring the need to identify reliable predictors of outcomes in older adults. **Methods:** We conducted a retrospective study of all adults aged ≥75 who underwent HCT at Dana-Farber Cancer Institute from January 2008 to August 2024. We evaluated overall survival (OS), progression-free survival (PFS), NRM, and cumulative incidence of relapse (CIR). Guided by geriatric assessment (GA) domains, clinical health data were collected from pre-HCT consent session notes. Log-rank (OS, PFS) and Gray's tests (NRM, relapse) were used for group comparison; Cox (OS, PFS) and Fine-Gray (NRM, relapse) models were used for multivariable analysis. **Results:** Sixty-seven patients (median age 76 years, range 75-80) were analyzed; 73.1% were male and 86.6% were White. Acute myeloid leukemia (46.3%) and myelodysplastic syndromes (35.8%) were the most common HCT indications. Neutrophil engraftment occurred in 94% of patients by a median of 15 days (range 3-40). Median follow-up for survivors was 21 months (range 11-125), and median OS was 33 months (95% CI: 18-55). At 18 months, OS was 61% (95% CI: 48-72%), PFS 54% (95% CI: 41-66%), NRM 11% (95% CI: 4.9-21%), and CIR 34% (95% CI: 23-46%). In univariable analysis, age ≥77 (p=0.0095), number of medications ≥15 at HCT consent (p=0.0078), and post-HCT bacterial or fungal infection (p=0.039) were associated with worse OS; similar factors affected PFS (e.g., for patients with bacterial or fungal infection, p=0.049). Diabetes (p=0.0001) and ≥15 medications at time of HCT consent (p=0.001) correlated with higher NRM. On multivariable analysis, age ≥77 (HR 2.44; p=0.028) and ≥15 medications (HR 2.68; p=0.019) significantly predicted worse OS; both factors also predicted inferior PFS. **Conclusions:** In this relatively large cohort of the oldest HCT recipients, older age, polypharmacy, and comorbidities emerged as likely predictors of worse clinical outcomes. Interestingly, relapse—rather than NRM—was the primary cause of treatment failure, aligning with established links between advanced age and the biology of myeloid malignancies. While the expanding upper age limit for HCT is a promising development for patients ≥75, our data are vital to facilitate informed consent discussions. These findings also underscore the need for robust pre-HCT evaluations, such as assessment of other GA domains via dedicated functional assessments (e.g., IADLs and gait speed) to improve risk stratification. Investigation in a larger cohort (≥70 years) is underway to further explore these results. Research Sponsor: None.

Assessment of long-term toxicities of imatinib in CML: Experience from a tertiary care cancer centre in south India.

Akhil Santhosh, Prasanth V. Parameswaran, Sreedharan P.S., Sajeevan K.V., Narayanankutty Edavalath Warrier; MVR Cancer Centre & Research Institute, Calicut, India; MVR Cancer Centre & Research Institute, Kozhikkode, India; MVR Cancer Centre & Research Institute, Kozhikode, India

Background: Imatinib has been the standard 1st line drug for chronic myeloid leukemia (CML) in chronic phase for decades. Literature is replete with data regarding acute toxicities of imatinib, but chronic long-term effects of the drug on cardiac, renal, endocrine, skin and bone health are less explored. In rare cases, imatinib has been postulated to cause left ventricular dysfunction, impairment in bone mineral density, thyroid hormone abnormalities and sensorineural hearing loss. **Methods:** We conducted a prospective study on CML patients aged 18 and above who had taken Imatinib for a minimum duration of 10 years. All patients were subjected to a detailed skin examination, laboratory tests including complete blood count, liver/renal function tests, thyroid profile, 2D echo, bone densitometry and pure tone audiometry. All tests were organized in accordance with a camp conducted for CML patients in our center. Children, pregnant women, patients who had not achieved major molecular remission and patients in accelerated phase/blast crisis were excluded. **Results:** 100 patients (males n=60, females, n=40) participated in the study. Median age was 45years (IQR 30-60). All patients were in major molecular remission with excellent drug compliance. Regarding the rarer side effects, 2D echo revealed left ventricular dysfunction in 4 patients (4%, n=1 moderate, n=3 mild). After interruption of drug, ejection fraction improved in all 3 patients with mild LV dysfunction (repeat 2d echo after 3 months). Pure tone audiometry revealed bilateral sensorineural hearing loss in 5 patients (5%, moderate n=3, severe n=2). Repeat testing done after 3 months post drug discontinuation showed improvement for 2 out of 3 patients with moderate sensorineural hearing loss (conversion to mild degree). 10 patients had osteopenia and 2 patients had osteoporosis in bone densitometry scans. Drug was not discontinued for the same. Patients were started on calcium+ vitamin D supplementation for osteopenia and 6 monthly zoledronic acid injections for osteoporosis. Cutaneous side effects were reported in 43%(N=43). Hyperpigmentation was the most common, seen in 30%(n=30) followed by hypopigmentation in 11% and chronic malar flush in 2%. Menstrual irregularities were reported in 10 females (n=10, 25%), most common being oligomenorrhea(n=7). 4 males (6.66%) had gynecomastia on examination. Anemia was seen in 25% (n=25,10 males and 15 females). Hypophosphatemia and elevated TSH were seen in 12 (12%) and 7 patients (7%) respectively. **Conclusions:** CML is now equated to a chronic disease with patients attaining a near normal life expectancy which makes it very important for clinicians to be well versed with both acute and chronic toxicities of imatinib. Through our study, we were able to highlight certain rare toxicities like ejection fraction abnormalities, hearing loss and bone mineral density changes that may be seen with imatinib. Research Sponsor: None.

6565 Poster Session

Early predictors of treatment-free remission in chronic myeloid leukemia.

Aziz Farhat, Georgina El Hajjar, Hagop M. Kantarjian, Fadi Haddad, Fadi Haddad, Nicholas James Short, Guillermo Montalban-Bravo, Danielle Hammond, Elias Jabbour, Guillermo Garcia-Manero, Koji Sasaki, Ghayas C. Issa; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX

Background: Tyrosine kinase inhibitors (TKIs) have significantly improved outcomes for chronic myeloid leukemia (CML), allowing most patients to achieve near-normal life expectancy. This has shifted treatment goals toward achieving treatment-free remission (TFR), particularly important for younger patients. Current criteria for TFR rely on sustained deep molecular remission after years of therapy, but early predictors are lacking. We aimed to identify factors predictive of TFR eligibility. **Methods:** We screened 780 patients with newly diagnosed chronic phase CML treated at The University of Texas MD Anderson Cancer Center from January 2012 to December 2023. Among them, 412 patients (53%) met the NCCN criteria for TFR (sustained MR4.5 for 2 years following 3 years of therapy). Thirty patients (4%) were excluded due to insufficient treatment duration. The remaining 338 patients (43%) formed the control cohort. We compared these cohorts and evaluated predictive factors for TFR eligibility using univariate and multivariate logistic regression, including factors with $P < 0.1$ in the multivariate model. **Results:** Patients in the TFR cohort were older (median age 51 vs. 46 years, $P = 0.007$) and had a different distribution of Sokal risk categories ($P = 0.037$): 67% low risk, 27% intermediate, and 6% high risk, compared to 64%, 25%, and 11% in the control group. TKI usage also differed ($P = 0.01$), with 32% vs. 41% receiving imatinib, 43% vs. 33% dasatinib, 19% receiving nilotinib in both groups, and 6% vs. 8% receiving ponatinib. *BCR::ABL* transcript distribution was significantly different ($P < 0.001$). The e13a2 transcript was more common in the control group (51% vs. 33%), while the e14a2 transcript predominated in the TFR group (46% vs. 32%). Co-occurrence of both transcripts was similar (21% vs. 16%), but other variants were rare and only observed in the control group (1% vs. 0%). Resistance mutations in the ABL gene were exclusively detected in the control group (13%, 44 patients). Univariate analysis identified older age (OR: 1.02; $P = 0.001$), BCR::ABL halving-time <30 days (OR: 4; $P < 0.001$), and achieving molecular milestones—transcript levels <10% IS at 3 months (OR: 11.4; $P < 0.001$), <1% IS at 6 months (OR: 10.5; $P < 0.001$), and <0.1% IS (MMR) at 1 year (OR: 6.5; $P < 0.001$)—as predictive factors for TFR eligibility. The e14a2 transcript (OR: 2.2; $P < 0.001$), co-occurrence of both transcripts (OR: 1.9; $P = 0.001$), and treatment with newer-generation TKIs vs. imatinib (OR: 1.5; $P = 0.008$) were also significant predictors. Multivariate analysis confirmed that older age (OR: 1.2; $P = 0.045$), halving-time <30 days (OR: 2; $P = 0.041$), achieving MMR at 1 year (OR: 5.6; $P < 0.001$), and the e14a2 transcript (OR: 1.6; $P = 0.049$) were independent predictors. **Conclusions:** Early predictors of TFR eligibility include older age, halving-time <30 days, MMR at 1 year, and the e14a2 transcript. These factors could guide prospective trial designs as early surrogates for TFR. Research Sponsor: None.

Long-term follow-up of treatment-free remission in chronic myeloid leukemia after discontinuation of tyrosine kinase inhibitor therapy.

Mehmet Uyanik, Fadi Haddad, Koji Sasaki, Ghayas C. Issa, Jayastu Senapati, Nicholas James Short, Nitin Jain, Lucia Masarova, Courtney Denton Dinardo, Tapan M. Kadia, Elias Jabbour, Hagop M. Kantarjian; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Treatment-free remission (TFR) is an important goal of therapy in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP). Here, we report our TFR experience in pts with CML-CP after a longer follow-up. **Methods:** Pts with CML-CP who were treated with tyrosine kinase inhibitors (TKIs) and subsequently discontinued therapy between October 2011 and January 2024 were included in this analysis. Molecular responses were assessed by qPCR (MMR, MR4, and MR4.5 defined as *BCR::ABL1* transcripts ≤0.1%, ≤0.01%, and ≤0.0032% on the international scale, respectively). The Kaplan Meier method was used to estimate the probability of TFR. **Results:** A total of 351 pts with CML-CP discontinued TKI therapy after a median treatment duration of 118.5 mo (range, 15.8-303.2). Most of the pts opted for elective discontinuation (70.2%) or discontinued therapy due to adverse events (24.3%). The median duration of sustained MR4.5 before TKI discontinuation was 61.8. mo (range, 1.0-206.8), and the median duration of sustained MR4 before TKI discontinuation was 76.5 mo (range, 1.37-215.1). With a median follow-up of 66.8 mo (range, 4.7-211.4) after TKI discontinuation, 93 pts (26.5%) lost MMR after a median of 7.2 mo (range, 1.2-124.9) from stopping therapy. 88 (93%) pts regained MMR after resuming therapy after a median of 3.6 mo (range, 0.4-36.5). The median TFR duration was not reached, with a 5-year TFR rate of 72.2%. The 5-year TFR rates were 63.0% and 79.2% in pts with a MR4.5 duration of <5 years, and ≥5 years before cessation of the TKI, respectively. The 5-year TFR rates were 54.5%, and 80.4% in pts with a MR4 duration of <5 years, and ≥5 years before cessation of the TKI, respectively. There was no significant difference in the rates of 5-year TFR between pts who received frontline first- or second-generation TKIs (P=0.79). Five-year TFR rates were similar between pts who were treated at standard TKI dose and those treated with TKIs at reducing dosing (p=0.52). There was no significant difference in the TFR rates according to the *BCR::ABL1* transcripts subtypes (p=0.1). **Conclusions:** The long-term follow-up results continue to demonstrate improved TFR rates of approximately 80% in patients who achieve a deep molecular response (MR4 or deeper response) sustained for 5 years or more. Research Sponsor: None.

6567 Poster Session

Allogeneic stem cell transplantation-related outcomes in myelodysplastic syndromes.

Alexandre Bazinet, Guillermo Garcia-Manero, Alex Bataller, Samuel Urrutia, Tapan M. Kadia, Kelly Sharon Chien, Koji Sasaki, Guillermo Montalban-Bravo, Rashmi Kanagal-Shamanna, Danielle Hammond, Mahesh Swaminathan, Wei Ying Jen, Georgina Gener-Ricos, Ian Michael Bouligny, Julie Braish, Eitan Kugler, Richard E. Champlin, Elizabeth J. Shpall, Hagop M. Kantarjian, Uday R. Popat; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; Washington University in St. Louis, St. Louis, MO; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Stem Cell Transplantation & Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Allogeneic stem cell transplantation (SCT) is the only known curative modality in myelodysplastic syndromes (MDS). Its use has historically been limited due to older patient age and comorbidity burden. Recent advances in reduced-intensity conditioning (RIC) have expanded the use of SCT in MDS. **Methods:** This was a retrospective single center database review study to evaluate contemporary outcomes in SCT-treated MDS. We identified all patients with newly diagnosed MDS presenting to our center between Jan 2000 and Mar 2023 and stratified them by receipt of SCT. Biallelic *TP53*-mutated status was defined as 2 *TP53* mutations, VAF $\geq$ 50%, or concomitant del(17p). Landmark analyses were performed to compare outcomes with or without SCT (median time from diagnosis to SCT as landmark). **Results:** 3649 patients with newly-diagnosed MDS were included. 573 (16%) underwent SCT. 4-week, 8-week, and 100-day mortality were 3%, 6%, and 14%, respectively. Acute GVHD occurred in 64% of patients (14% grade 3/4). Chronic GVHD occurred in 33%. Patients undergoing SCT (ages 18-77) had a median OS of 25 m from SCT day 0. The 5-year cumulative incidences of death and relapse were 21% and 31% with myeloablative conditioning (MAC) and 27% and 36% with reduced-intensity conditioning (RIC). Stratified by IPSS-R, the median OS post-SCT was 136, 40, 92, 103, and 8 m in Very Low, Low, Intermediate, High, and Very High risk. Patients with *TP53*wt, *TP53*mut monoallelic, and *TP53*mut biallelic had a median OS of not reached (NR), 9 m, and 7 m. Patients with non-complex, complex (3 abn), and very complex ($>$ 3 abn) CG had a median OS of 96 m, 14 m, and 7 m. Transplanted patients without *TP53* mutations had 5-year OS of 59% and those without complex CG had 5-year OS of 54%. Immediate pre-SCT blasts $<$5% and 5-9% were associated with similar post SCT OS (median 29 and 30 m) whereas patients with 10-19% (8 m) and $>$ 20% (12 m) had inferior survival. Multivariate analysis identified bone marrow ring sideroblast %, *TP53* mutations, haplo donor, pre-SCT transformation to AML, and increasing donor age as associated with worse post-SCT OS while receipt of venetoclax pre-SCT and higher Karnofsky score were favorable. By landmark analyses, SCT was associated with improved OS across IPSS-R risk categories. Median OS was 185 m with SCT vs 82 m without SCT in Very Low risk ($p<0.01$), 107 vs 58 m in Low risk ($p<0.01$), 103 vs 31 m in Intermediate risk ($p<0.01$), 108 vs 18 m in High risk ($p<0.01$), and 16 vs 13 m in Very High risk ($p<0.01$). No significant benefit of SCT was noted in patients with *TP53* mutations. The median OS was 27 m with SCT vs 17 m without SCT in *TP53*mut monoallelic ($p=0.10$) and 14 vs 13 m in *TP53*mut biallelic ($p=0.16$). **Conclusions:** SCT is curative in 50-60% of patients with MDS without *TP53* mutations or complex CG. Efforts should be made to improve accessibility of SCT in this population. Alternative therapies are urgently needed in patients with *TP53* mutations or complex CG. Research Sponsor: University of Texas MD Anderson Cancer Center Support Grant; CA016672.

Impact of static and dynamic risk assessment in HMA-treated MDS patients undergoing stem cell transplantation.

Luis E. Aguirre, Haesook T. Kim, Hany Elmariah, Stacey M. Frumm, Amar Harry Kelkar, Vincent Ho, Mahasweta Gooptu, Joseph Harry Antin, Robert Soiffer, Shai Shimony, Marlise R Luskin, Jacqueline Suen Garcia, Evan Chris Chen, Eric S. Winer, Richard M. Stone, Daniel J. DeAngelo, Najla Al Ali, Corey S. Cutler, Rami S. Komrokji, Maximilian Stahl; Dana-Farber Cancer Institute, Boston, MA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: MDS risk assessed by the IPSS-R and IPSS-M at diagnosis impacts outcomes post-hematopoietic stem cell transplant (HSCT). Recent EBMT data showed no post-HSCT survival benefit from downstaging IPSS-R scores with hypomethylating agent (HMA) therapy. However, the lack of mutational data precluded evaluating dynamic IPSS-M changes. This study aimed to determine whether evaluating IPSS-M at diagnosis or pre-HSCT more accurately predicts post-HSCT outcomes in pts treated with HMA. Additionally, in the absence of consensus on the role of cytoreductive therapy in the pre-HSCT setting for pts with higher-risk MDS, we investigated whether the dynamic application of IPSS-M offers any advantages for such therapy. **Methods:** We analyzed 176 paired samples from higher-risk MDS pts treated with HMA followed by HSCT at Dana-Farber (n=91) and Moffitt (n=85). Disease risk was assessed by IPSS-M at diagnosis and after HMA therapy pre-HCT. Dynamic assessment was categorized as decrease (improvement), no change, or increase (progression) in IPSS-M risk category from diagnosis to HSCT. The primary outcome was post-HSCT progression-free survival (PFS). **Results:** In the cohort, 60% were male, with a median age of 66 yrs (range 26-79). At diagnosis, 87.5% had MDS with increased blasts and 9.7% had MDS with low blasts. Pts received a median of 4 cycles of HMA prior to HSCT, with 63.1% having MUD donors and 84.1% receiving RIC. At diagnosis, 80% were higher-risk (MH/H/VH) per IPSS-M. Post-HMA, 61.4% improved in IPSS-M, while 24.4% had no change and 14.2% progressed. The 4y PFS for the cohort was 47%, with no significant differences between centers (48% vs 47%, p=0.75). In MVA, there was no difference in prognostic accuracy between IPSS-M estimated at diagnosis and pre-HSCT (c-index: 0.635 vs. 0.645). Dynamic assessment showed a 4y PFS of 50% for both improved/unchanged IPSS-M vs 31% for progressive IPSS-M (c-index: 0.647, p=0.09). Substantial improvement in IPSS-M (≥2.5 score change) yielded a 4y PFS of 38%, comparable to those with progression (23%) and much worse than those with discreet/evident improvement (53%/56%). Pts with substantial improvement in IPSS-M had a higher proportion of VH risk MDS at diagnosis than those with discreet/evident improvement (77% vs. 28%), indicating that adverse disease biology at diagnosis negatively affected outcomes despite favorable response to HMA. **Conclusions:** Pre-HSCT IPSS-M assessment did not enhance post-HSCT outcome predictions compared to evaluation at diagnosis. Worsening IPSS-M correlated with worse outcomes, while improvement did not yield better results than unchanged risk. For those with high-risk disease, improvement in IPSS-M achieved through HMA does not appear to mitigate the adverse risk established at diagnosis. Thus, in HMA-treated pts, downstaging of IPSS-M pre-HSCT should not be a therapeutic goal or an endpoint for response evaluation in MDS trials.
Research Sponsor: None.

6569 Poster Session

Effect of prior treatment (tx) on the clinical activity of imetelstat (IME) in transfusion-dependent (TD) patients (pts) with erythropoiesis-stimulating agent (ESA), relapsed or refractory (R/R)/ineligible lower-risk myelodysplastic syndromes (LR-MDS).

Rami S. Komrokji, Valeria Santini, Amer Methqal Zeidan, Mikkael A. Sekeres, Pierre Fenaux, Azra Raza, Moshe Mittelman, Sylvain Thepot, Rena Buckstein, Ulrich Germing, Yazan F. Madanat, Maria Diez-Campelo, David Valcárcel, Anna Jonasova, Sheetal Shah, Qi Xia, Libo Sun, Shyamala Chendeal Navada, Michael R. Savona, Uwe Platzbecker; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; University of Florence, AOUC, Florence, Italy; Yale University School of Medicine and Yale Cancer Center, New Haven, CT; Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; Hôpital Saint-Louis, Université de Paris 7, Paris, France; Columbia University Medical Center, New York, NY; Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel; Centre Hospitalier Universitaire d'Angers, Angers, France; Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Clinic for Haematology, Oncology and Clinical Immunology, Düsseldorf University Hospital, Heinrich Heine University, Düsseldorf, Germany; Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; Department of Hematology. Salamanca-IBSAL University Hospital, Salamanca, Spain; Hospital Universitari Vall d'Hebron, Barcelona, Spain; 1st Medical Department - Hematology, General Hospital, Prague, Czech Republic; Geron Corporation, Foster City, CA; Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN; Leipzig University Hospital, Leipzig, Germany

Background: IME, a first-in-class, direct, and competitive inhibitor of telomerase activity, was approved in the US for the tx of red blood cell (RBC)-TD LR-MDS in pts who are R/R or ineligible for ESA based on the results of the pivotal IMerge trial (NCT02598661). IMerge demonstrated significant and durable efficacy of IME (n=118) versus placebo (n=60) for ≥8-week, ≥24-week, and ≥1-year RBC-transfusion independence (TI), with a generally manageable safety profile in this pt population. Here, we pooled data from the 3 parts of the IMerge trial (phase 2, phase 3, and QTc substudy) to investigate the effect of prior txs on the clinical activity of IME. **Methods:** In IMerge, pts received IME intravenously every 4 weeks at 7.1 mg/kg active dose (7.5 mg/kg IME sodium equivalent). Prior lenalidomide (LEN) and prior hypomethylating agent (HMA) use were exclusion criteria in phase 3 only. In this analysis, pooled data from IME-treated pts (phase 2, phase 3, and QTc substudy) were analyzed by prior tx: ± ESA, luspatercept (LUSP), LEN, and HMA; pts may have received >1 prior tx. Outcomes included ≥8-week, ≥24-week, and ≥1-year RBC-TI, rates of hematologic improvement-erythroid (HI-E) based on the revised International Working Group (IWG) 2018 criteria, transfusion reduction of ≥4 U/8 weeks, and a hemoglobin (Hb) rise of ≥1.5 g/dL for ≥8 weeks. **Results:** The data cutoff dates were 10/13/2023 (phase 2/3) and 10/13/2024 (QTc substudy). A total of 226 IME-treated pts pooled in IMerge were included in this analysis; most pts (n=188) had a high transfusion burden (TB) per revised IWG 2018 at baseline (vs low TB [n=38]; Table). Of all pts, 39% achieved ≥8-week RBC-TI (median duration of response, 55 weeks), and 28% and 18% achieved ≥24-week and ≥1-year RBC-TI, respectively. Among all IME-treated pts, 204 had prior tx with an ESA and 22 were ineligible for ESAs; 36 had prior LUSP, 26 had prior LEN, and 22 had prior HMA. Pt characteristics and efficacy by prior tx are shown in the table. **Conclusions:** Pts who were ESA ineligible or who had prior tx with LUSP, LEN, or HMA, and were largely high TB, in IMerge experienced clinical benefit from IME tx, though the number of pts was small. Given the limited efficacy data available in later lines of tx for LR-MDS, these results have important clinical implications, suggesting that IME has clinical activity regardless of prior txs. Clinical trial information: NCT02598661. Research Sponsor: This study was funded by the Geron Corporation. All authors contributed to and approved the abstract; writing and editorial support were provided by Casandra Monzon, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by the Geron Corporation.

	ESA ineligible (n=22)	Prior ESA (n=204)	Prior LUSP (n=36)	Prior LEN (n=26)	Prior HMA (n=22)
TB at baseline, n					
Low TB	3	35	5	4	3
High TB	19	169	31	22	19
≤8-week RBC-TI, %					
Median duration of RBC-TI for ≥8-week TI responders, weeks	36	40	31	23	14
≥24-week RBC-TI, %	32	60	70	41	41
≥1-year RBC-TI, %	14	29	22	19	9
HI-E (IWG 2018), %	9	19	14	8	0
Transfusion reduction of ≥4 U/8 weeks (IWG 2006), %	41	44	31	35	23
Hb rise ≥1.5 g/dL for ≥8 weeks (IWG 2006), %	64	64	69	54	50
	27	34	31	19	14

Real-world (RW) outcomes of patients (pts) with lower-risk myelodysplastic syndrome (LR-MDS) receiving first-line (1L) luspatercept (LUSPA) or 1L erythropoiesis-stimulating agents (ESA) in the US.

Idoroenyi Usua Amanam, Chidera Agu, Siddhi Korgaonkar, Abigail Hitchens, Svetlana Gavrilov, Derek Tang, Rohan Parikh, Keith L. Davis, Samantha Slaff; City of Hope Cancer Center, Duarte, CA; Bristol Myers Squibb, Princeton, NJ; RTI Health Solutions, Research Triangle Park, NC

Background: LR-MDS pts receiving ESAs for anemia often experience treatment (tx) resistance or relapse. Evidence from the COMMANDS trial led to LUSPA's US FDA approval in August 2023 as 1L tx for anemia in pts with LR-MDS. This is the first study assessing RW characteristics and outcomes in pts with LR-MDS receiving 1L LUSPA or ESA after 1L LUSPA approval. **Methods:** Interim data from an ongoing, retrospective medical records review of pts with LR-MDS receiving 1L LUSPA or ESA was collected (17 Oct 2024-19 Dec 2024; target sample size = 200 pts per cohort). Eligible adult pts had IPSS/IPSS-R-defined diagnosis of LR-MDS and initiated 1L LUSPA or ESA between 28 Aug 2023-31 Jul 2024 (tx initiation date = index date). Outcomes were descriptively analyzed; pt characteristics and changes in hemoglobin (Hb) and red blood cell (RBC) transfusion requirements during the first 6 months (mos) of 1L anemia tx are reported. **Results:** 103 pts (1L LUSPA: 46; 1L ESA: 57) were included in the interim data.In the LUSPA and ESA cohorts, respectively,median age at index was 67.7 and 62.9 yrs; 63.0% and 66.7% were White; 54.3% and 40.4% were female; 28.3% and 10.5% had *SF3B1* mutation; 93.5% and 68.4% had ECOG 0/1; and median follow-up was 7.9 and 8.4 mos. IPSS/IPSS-R risk status was intermediate-1/intermediate for 21.7% of LUSPA pts and 8.8% of ESA pts. Of pts with known ring sideroblast (RS) level, 62.2% (23/37) of LUSPA pts and 71.8% (28/39) of ESA pts were RS negative. Baseline (BL) sEPO was <200 IU/L for 30.6% (11/36) of LUSPA pts and 78.9% (30/38) of ESA pts. Most ptsreceiving 1L LUSPA achieved Hb increase of ≥1.5 g/dL (LUSPA: 89.1%; ESA: 56.1%) in the first 6 mos of tx. Of pts who were RBC transfusion-dependent (RBC-TD) at BL, a greater proportion of LUSPA pts became RBC transfusion-independent (RBC-TI) vs ESA pts (91.7% vs 71.4%) in the first 3 mos (Table). Updated results for the full cohort to be presented at the meeting. **Conclusions:** During the first 6 mos of tx,a higher proportion of ptsreceiving 1L LUSPA showed improvement in Hb and a reduced need for RBC compared to those receiving 1L ESA. This analysis corroborates the results of the COMMANDS trial and demonstrates the favorable RW effectiveness of 1L LUSPA vs 1L ESA for anemia treatment in LR-MDS. Research Sponsor: Bristol Myers Squibb.

	1L LUSPA (n=46)	1L ESA (n=57)
Mean (SD) BL Hb,[a] g/dL	7.7 (0.9)	8.2 (1.2)
Pts with Hb increase by ≥1.5 g/dL after tx, n (%)	41 (89.1)	32 (56.1)
Pts with Hb increase by ≥1.5 g/dL for ≥8 wks, n (%)	37 (80.4)	27 (47.4)
Mean (SD) Hb change from BL during first 6 mos of tx, g/dL	1.7 (1.0)	1.0 (1.0)
BL RBC-TD pts with follow-up RBC data known, n	12	14
Became RBC-TI (0 transfusions for ≥8 wks) within first 3 mos of tx, n (%)	11 (91.7)	10 (71.4)
Median time to RBC-TI, mos	0.8	1.9
RBC-TI for ≥12 wks, n (%)	11 (91.7)	9 (64.3)
Decreased RBC need by ≥50% in first 16 wks of tx among pts with ≥1 BL transfusion, n (%)	9 (75.0)	6 (42.9)

[a]Evaluable pts (LUSPA, n=42; ESA, n=53).

6571 Poster Session

An exploratory analysis of myelofibrosis (MF) patient subgroups by baseline hemoglobin levels in the gecacitinib phase 3 trial.

Yi Zhang, Hu Zhou, Junling Zhuang, Linhua Yang, Aili He, Qingchi Liu, Yuqing Chen, Xin Du, Sujun Gao, Yarong Li, Yan Li, Wen Wu, Huanling Zhu, Zhi-Jian Xiao, Jie Jin; The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Hematology, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China; Department of Hematology, The Second Affiliated Hospital of Shanxi Medical University, Taiyuan, China; The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; The First Hospital of Hebei Medical University, Shijiazhuang, China; Department of Hematology, Henan Province People's Hospital, Zhengzhou, China; Guangdong Provincial People's Hospital, Guangzhou, China; The First Hospital of Jilin University, Changchun, China; Department of Hematology and Oncology, The Second Hospital of Jilin University, Changchun, China; The First Affiliated Hospital of China Medical University, Shenyang, China; Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; West China Hospital of Sichuan University, Chengdu, China; Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China

Background: Anemia is a key prognostic indicator of MF. In the double-blind, randomized phase 3 ZGJAK016 trial, gecacitinib (GCA), a dual JAK/ACVR1 inhibitor, demonstrated superior spleen response over hydroxyurea, and a trend toward improvement in constitutional symptom and anemia associated with MF in JAK inhibitor-naive patients (pts). To further elucidate the impact of GCA on anemia, we conducted a post-hoc analysis of the data from this trial, examining outcomes in relation to the severity of anemia. **Methods:** Pts in the GCA group were categorized post subgroups based on their baseline hemoglobin (Hb) levels: less than 100 g/L (moderate to severe anemia), 100 g/L to lower limit of the normal (LLN) (mild anemia), LLN to upper limit of the normal (ULN) (normal), and more than ULN for (Hb elevated). The primary endpoint was the proportion of pts with a spleen volume reduction of $\geq$ 35% from baseline (SVR35) at week (wk) 24. Secondary endpoints included the proportion of pts with a $\geq$ 50% reduction in Total Symptom Score (TSS50), and transfusion independence (TI) rate at wk 24 (no red blood cell transfusions and no Hb levels of $<$80 g/L in the last 12 wks before wk 24). **Results:** Of all the 71 pts randomly assigned to GCA in the intent-to-treat (ITT) population, 47 (66.2%) were moderately/severely anemic at baseline (including 16 pts [22.5%] with severe anemia [Hb levels of $<$ 80 g/L]), 11 (15.5%) were mildly anemic and 13 (18.3%) were nonanemic (including three pts [3.8%] with Hb levels of $>$ ULN). In the moderately/severely anemic subgroup, a higher proportion of pts were classified as DIPSS high risk, transfusion dependent, and had a diagnosis with primary MF at baseline. Most pts in the mildly anemic group were TI, as were all in the nonanemic subgroup. The three pts with elevated Hb all had post- polycythemia vera MF. Mean Hb levels increased by wk 2 across all GCA subgroups, then remained stable in the anemic subgroups, or slightly decreased but still $>$ 110 g/L in the normal subgroup and markedly decreased in the Hb elevated subgroup. Mean platelet counts decreased by wk 2 except in the Hb elevated subgroup and then maintained stability. In the moderately/severely and mild anemic subgroup, 24 of 36 (66.7%) pts who were TI at baseline maintained this status at wk 24 and 8 of 22 (36.4%) who were non-TI at baseline achieved TI at wk 24. The SVR35 rates and TSS50 rates at wk 24 were comparable across subgroups and consistent with those observed in the ITT population. **Conclusions:** In summary, GCA delivers a threefold benefit in terms of spleen and symptom management, as well as anemia, to JAK inhibitor-naive pts with MF who have mild, moderate/severe, or no anemia at baseline, particularly those with Hb levels below LLN. Clinical trial information: NCT04617028. Research Sponsor: Suzhou Zelgen Biopharmaceuticals Co, Ltd.

	ITT (n =71)	Hb <100 g/L (n =47)	Hb ≥100 g/L to LLN (n =11)	LLN to ULN (n =10)	>ULN (n =3)
SVR35 rate at wk 24	64.8%	59.6%	81.8%	70.0%	66.7%
TSS50 rate at wk 24	62.0%	57.4%	90.9%	50.0%	66.7%
TI rate at wk 24	60.6%	48.9%	81.8%	90.0%	66.7%

Efficacy of BTI615 on malignant cells expansion and bone marrow fibrosis in a myelofibrosis mice model.

Xiaomei Li, Qiu Jiang, Rui Chen, Yi Ding; Chengdu Brilliant Inspiration Biotherapeutics Co., Ltd., Chengdu, Sichuan, China

Background: Due to the limitation of Janus kinase inhibitors and allogeneic transplant, critical unmet needs are remained in myelofibrosis (MF) patients, particularly for those with cytopenias, non-response or intolerance issues. Novel therapeutic avenues could arise from promoting bone marrow regeneration, which is dysregulated by pro-tumorigenic, fibrotic niche networked by vicious cycle of transforming growth factor β (TGF-β) signaling. Here we verified that BTI615, a synthetic active TGF-β modulating peptide, rescued malignant cells expansion and bone marrow fibrosis to restore hematopoiesis in a romiplostim-induced MF model. **Methods:** Mice (5-6 weeks old C57BL/6J, male) were treated with romiplostim (s.c., 90 μg/kg, Q3D), and simultaneously dosed with BTI615 (i.v., 30 or 120 mg/kg, TIW) for 4 weeks. The bloods, femurs, and spleens were collected for cell counting, Hematoxylin and Eosin staining, Gordon & Sweet's silver staining, immunofluorescence imaging and cytokines quantification. **Results:** In blood, BTI615 restored the declined peripheral red blood cells and hemoglobin, and suppressed inflammatory increase of white blood cells (incl. monocytes and granulocytes). Histological examination of bone marrow and spleen revealed that BTI615 remarkably suppressed megakaryocytes hyperplasia and atypia. Moreover, there was a significant reduction in the deposition of reticular fibers, fibronectin and collagen IV over the femurs by BTI615. Notably, in BTI615 treated bone marrow, the specialized niches erythroblastic islands and total Ter-119 positive cells markedly increased, accompanied by declining trends of splenomegaly. Aligned with those symptom relieves, BTI615 decreased the amount of active TGF-β_1 and the intensity of phospho-Smad2, as well as the expression of interleukin (IL)-1α and monocyte chemoattractant protein (MCP)-1 in bone marrow. **Conclusions:** Given its effective suppression on hyperplasia of atypical megakaryocytes, inflammation, marrow fibrosis and the ultimate recovery of hematopoietic function via modulating TGF-β signaling, BTI615 has a great potential to be the next generation therapeutic approach for MF. Research Sponsor: None.

6573 Poster Session

Ropeginterferon alfa-2b for pre-fibrotic primary myelofibrosis and DIPSS low/intermediate-risk myelofibrosis.

Harinder Gill, Lester Au, Rita Yim, Paul Lee, Vivian Li, Lynn Chin, Qi Zhang, Po-Yan Chan, Chun-Kei Au, Tony Wu, Carmen Lee, Garret Leung, Hsin-An Hou, Yok-Lam Kwong; Department of Medicine, School of Clinical Medicine, LKS Faculty of Medicine, the University of Hong Kong, Hong Kong, China; Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

Background: There is currently no consensus on the optimal treatment for primary myelofibrosis (PMF) in pre-/early fibrotic stage (pre-PMF) and DIPPS low/intermediate-1 risk MF. Ropeginterferon alfa 2b (Ropeg-IFN-α2b) is a next-generation monopegylated interferon alfa-2b developed specifically to treat myeloproliferative neoplasms (MPN). **Methods:** Key eligibility included morphologically confirmed pre-PMF, and DIPSS low/intermediate-1 risk overt PMF, post-polycythemia vera MF (PPV-MF), and post-essential thrombocythemia MF (PET-MF) in patients requiring cytoreduction. The primary end-points were responses in hemoglobin (from 10 g/dL to upper reference range), white blood cell (to $< 10 \times 10^9$/L) and platelet (to $\leq 400 \times 10^9$/L) at 24 and 52 weeks. Secondary endpoints included safety (adverse events, AEs), reductions in variant allele frequencies (VAF) of driver and non-driver genes, spleen length by palpation, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPNSAF-TSS), and bone marrow fibrosis. Patients received Ropeg-IFN-α2b at a dose of 250 mcg at Week 0, followed by 350 mcg at Week 2 and 500 mcg every 2 weeks from Week 4 onwards. **Results:** At the data cut-off of 30 June 2024, 71 patients (40 men and 31 women) with a median age of 60 (range: 31-86) years were enrolled. At a median follow up of 119 (10-131) weeks, responses in hemoglobin, white blood cell and platelet counts were 73.9%, 82.6% and 100% at Week 24; and 76.2%, 79.4% and 100% at Week 52, respectively. Reduction in *JAK2*V617F VAF was found in 16 of 47 evaluable patients (34%) at Week 24, and 20 of 41 evaluable patients (44%) at Week 52. Reduction in *CALR* VAF was found in 10 of 19 evaluable patients (53%) at Week 24, and 6 of 14 evaluable patients (43%) at Week 52. Reduction of spleen size was found in 9 of 19 patients (47%) at Week 24, and 9 of 17 patients (53%) at Week 52. Reduction in MPNSAF-TSS of $\geq$50% was found in 27 of 63 evaluable patients (42.9%) at Week 24, and 23 of 57 patients (42.1%) at Week 52. The most common non-hematologic AEs included transaminitis (grade 1-2, N=35, 49.2%); malaise (grade 1-2, N=29, 40.8%; grade 3-4, N=1, 1.4%), and hair loss (grade 1-2, N=24, 33.8%). The most common hematologic AEs were anemia (grade 1-2, N=15, 21.1%; grade 3-4, N=6, 8.5%), neutropenia (grade 1-2, N=15, 21.1%; grade 3-4, N=4, 5.6%) and thrombocytopenia (grade 1-2, N=8, 11.2%; grade 3-4, N=3, 4.2%). Thrombohemorrhagic events or progression to blast-phase MF was not observed during the study. **Conclusions:** Ropeg-IFN-α2b was well-tolerated and induced clinical, hematologic and molecular responses in patients with pre-PMF and low/intermediate-1-risk MF. Clinical trial information: NCT04988815. Research Sponsor: Health and Medical Research Fund (HMRF); 09201046.

6574 Poster Session

Safety and efficacy of bromodomain and extra-terminal (BET) inhibitor INCB057643 in patients (pts) with relapsed or refractory myelofibrosis (r/r-MF) and other advanced myeloid neoplasms: A phase (Ph) 1 study.

Justin M. Watts, Alessandro M. Vannucchi, Anthony Hunter, Vikas Gupta, Srinivas Kiran Tantravahi, Junichiro Yuda, Alessandra Iurlo, Prithviraj Bose, María Teresa Gómez Casares, Brandon McMahon, Francesca Palandri, Emma Searle, Blanca Xicoy, Andrew Srisuwananukorn, Anna B. Halpern, Rosa Ayala Diaz, Jesus Maria Hernandez, Akihiro Tomita, Fred Zheng, Pankit Vachhani; Sylvester Cancer Center, University of Miami, Miami, FL; AOU Careggi, University of Florence, Florence, Italy; Emory University School of Medicine, Atlanta, GA; Princess Margaret Cancer Centre, Toronto, ON, Canada; University of Utah Huntsman Cancer Institute, Salt Lake City, UT; National Cancer Center Hospital East, Kashiwa, Japan; Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; The University of Texas MD Anderson Cancer Center, Houston, TX; Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas De Gran Canaria, Spain; University of Colorado School of Medicine, Division of Hematology, Aurora, CO; IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; The Christie Hospital NHS Foundation Trust; University of Manchester, Manchester, United Kingdom; Hospital Germans Trias I Pujol, Institut Català Oncologia, Josep Carreras Leukemia Research Institute, Universitat Autònoma de Barcelona, Badalona, Spain; The Ohio State University Comprehensive Cancer Center, Columbus, OH; University of Washington; Fred Hutchinson Cancer Cente, Seattle, WA; Hospital Universitario 12 de Octubre, Madrid, Spain; University of Salamanca, Salamanca, Spain; Fujita Health University School of Medicine, Toyoake, Japan; Incyte Corporation, Wilmington, DE; O'Neal Comprehensive Cancer Center at University of Alabama, Birmingham, AL

Background: BET proteins are epigenetic readers that regulate expression of oncoproteins involved in hematologic malignancies, including MF. The oral, small-molecule BET inhibitor INCB057643 had favorable tolerability and encouraging clinical activity in pts with advanced MF in a previous Ph 1/2 trial. **Methods:** This ongoing Ph 1, open-label 3+3 dose-escalation/expansion study (NCT04279847) is evaluating INCB057643 monotherapy (mono; part 1; 4 mg→12 mg once daily [qd]) in adults with r/r-MF, essential thrombocythemia (ET), myelodysplastic syndrome (MDS), or MDS/myeloproliferative neoplasm (MPN) overlap syndrome, or combination therapy (combo; part 2; 4 mg qd→part 1 maximum tolerated dose) with ruxolitinib (RUX) in adults with MF and suboptimal response to RUX or who were Janus kinase inhibitor (JAKi) naive. Primary endpoint is safety/tolerability. Secondary endpoints: spleen volume (SV) response (≥35% reduction from baseline [BL; SVR35] at Week [Wk] 24), symptom response (≥50% reduction from BL in MPN-Symptom Assessment Form total symptom score [TSS50] at Wk 24), and anemia response (sustained hemoglobin increase ≥1.5 g/dL from BL [if transfusion (TF) independent at BL] or TF independence [if dependent at BL] for ≥12 wks). **Results:** As of 9Sep2024, 18 pts were treated in mono dose escalation, 20 in mono dose expansion, and 23 in combo dose escalation. 48 (79%) pts had MF, 5 (8%) MDS or MDS/MPN, and 8 (13%) ET. Median (range) INCB057643 exposure was 196 (15–812) days (d) in mono dose escalation, 155 (14–341) d in mono dose expansion, and 176 (25–560) d in combo dose escalation. The most common treatment (tx)-emergent adverse event (TEAE) was thrombocytopenia (TCP; 46%). Grade ≥3 TEAEs occurred in 57%, most commonly TCP (26%) and anemia (20%). Serious TEAEs occurred in 31%; 3 (5%) were tx related. No fatal events were tx related. 9 TEAEs lead to discontinuation. 2 dose-limiting toxicities occurred with mono (12 mg, TCP, hyperbilirubinemia) and 1 with combo (6 mg, TCP). 3 pts had acute myeloid leukemia transformation (4-mg mono MDS/MPN, 10-mg mono MDS, 4-mg combo MF). Wk 24 SVR35 was achieved by 3/20 evaluable MF pts treated with any mono dose (3/7 receiving ≥10 mg) and by 4/17 treated with any combo dose. Wk 24 TSS50 was achieved by 7/19 evaluable MF pts treated with any mono dose (5/8 receiving ≥10 mg) and by 8/16 treated with any combo dose. Durable anemia response occurred in 6/22 evaluable mono pts (2 TF-dependent at BL) and 4/20 combo pts. **Conclusions:** INCB057643 mono or combo with RUX was generally well tolerated, with no tx-related fatal events. Improvements in anemia, spleen size, and symptom burden were observed with mono and combo. Dose expansion is ongoing for 6- and 10-mg mono and 4- and 8-mg combo groups (add-on and JAKi naive). A Ph 3 study of INCB057643 mono in advanced post-JAKi MF pts is being initiated. Clinical trial information: NCT04279847. Research Sponsor: Incyte Corporation.

A simplified scoring system to predict in-hospital mortality of leukapheresis in patients with leukemia.

Barath Prashanth Sivasubramanian, Gagan Kumar, Achuta Kumar Guddati; Northeast Georgia Medical Center, Gainesville, GA; Northeast Georgia Health System, Atlanta, GA; Stony Brook University, Stony Brook, NY

Background: The 2019 consensus guidelines from the American Society for Apheresis recommend leukapheresis as a category II recommendation (acceptable second-line therapy) for patients with symptomatic hyperleukocytosis or leukostasis. Mortality in these patients has been reported to vary between 8-29%. However, no tool is currently available to assess the mortality risk following the procedure. **Methods:** The National Inpatient Sample Database (2016-2021) and ICD-10 coding were utilized to identify adults (age ≥18 years) with leukemia who underwent leukapheresisprocedure. Different types of leukemia were identified along with various demographic and clinical characteristics of patients including symptoms of leucostasis such as acute encephalopathy, respiratory failure, cardiac failure, and renal failure using ICD-10 codes. Also included were complications associated with leukapheresissuch as hemorrhage. Multivariate logistic regression models were constructed to identify independent factors associated with mortality. A scoring system was constructed to identify the risks of mortality using the variables in the model and their associated odds ratio (OR). Splines were used to identify the knots which were used as cutoff values. The cumulative risk score was divided into three strata: low (mortality < 10%), intermediate (10-40%), and high risk (>40%). **Results:** Of the estimated 4,705 patients who underwent leukapheresis, 14.2% had lymphoid leukemia, 6.2% had monocytic leukemia, 52.2% had myeloid leukemia, and 3.6% had other types of leukemia. The overall in-hospital mortality was 24.2% and the median length of hospital stay was 10 days (IQR 5-24). 71.3% received leukapheresiswithin the first 48 hours of hospitalization. Variables identified as significantly associated with mortality included the type of leukemia: monocytic leukemia (OR 3.1), myeloid leukemia (OR 2.6), lymphoid leukemia (OR 1.8) other types of leukemia (OR 3.8). Organ failure associated with hospital mortality included acute respiratory failure (OR 12.7), acute renal failure (OR 2.3), cardiogenic shock (OR 8), acute encephalopathy (OR 2.2), and disseminated intravascular coagulation (OR 1.8). The cumulative mortality score ranged from 0 to 33, categorizing patients into high risk (score ≥ 5), intermediate risk (score 2-4) and low risk (score 0-1). The risk score demonstrated a performance with an area under the curve of 0.79. of note, age, gender, and race were non-contributory in this scoring system. **Conclusions:** A novel simplified scoring tool to predict in-hospital mortality in leukemia patients requiring leukapheresis is proposed. This tool can assist in preprocedural risk assessment and help guide management planning along with consideration for the role of other treatment modalities. Research Sponsor: None.

Efficacy and safety outcomes of obecabtagene autoleucel (obe-cel) stratified by age in patients (pts) with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL).

Bijal D. Shah, Deborah Yallop, Elias Jabbour, Pere Barba, Eleni Tholouli, Max S. Topp, Karamjeet S. Sandhu, Sridhar Chaganti, Jae H. Park, Tobias Menne, Aaron Logan, Daniel J. DeAngelo, Pierre Lao-Sirieix, Ping Wang, Wolfram Brugger, Claire Roddie; Moffitt Cancer Center, Tampa, FL; King's College Hospital NHS Foundation Trust, London, United Kingdom; University of Texas MD Anderson Cancer Center, Houston, TX; Hospital Universitari Vall d'Hebron-Universitat Autónoma de Barcelona, Barcelona, Spain; Manchester Royal Infirmary, Manchester, United Kingdom; University Hospital of Würzburg, Würzburg, Germany; City of Hope National Medical Center, Duarte, CA; University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; Memorial Sloan Kettering Cancer Center, New York, NY; Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle, United Kingdom; Hematology, Blood and Marrow Transplantation, and Cellular Therapy Program, University of California San Francisco, San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA; Autolus Therapeutics, London, United Kingdom; Autolus Therapeutics, Rockville, MD; Autolus Therapeutics, Munich, Germany; University College London Cancer Institute, London, United Kingdom

Background: CD19 chimeric antigen receptor T-cell therapy (CAR T) exhibits good efficacy in adults with R/R B-ALL but is associated with higher toxicity with increasing age. Obe-cel, an autologous anti-CD19 CAR T, has shown high and durable response rates with low incidence of immunotoxicity in adult R/R B-ALL, and was recently approved by the US FDA. Here, we report a post-hoc analysis of the Phase Ib/II FELIX trial (NCT04404660) evaluating efficacy, safety, and persistence outcomes with obe-cel stratified by pt age. **Methods:** Adult R/R B-ALL pts received obe-cel using a tumor burden-guided dosing strategy to minimize toxicity. Overall remission rate (ORR; complete remission [CR]/CR with incomplete hematologic recovery), event-free survival (EFS), safety, and persistence are reported for pts aged <55 and ≥55 years (yrs; data cut-off: 7 Feb 2024). **Results:** Of 127 obe-cel infused pts, 79 (62.2%) were aged <55 yrs (median 36.0 [range: 20–54]) and 48 (37.8%) were aged ≥55 yrs (median 65.0 [range: 55–81]). A higher proportion of pts aged <55 yrs were Hispanic/Latino (36.7% vs 18.8%), had extramedullary disease at lymphodepletion (LD; 29.1% vs 8.3%), received prior blinatumomab (53.2% vs 22.9%), and prior inotuzumab ozogamicin (35.4% vs 25.0%) than those ≥55 yrs, while a higher proportion of pts aged ≥55 yrs had Philadelphia chromosome-positive disease (47.9% vs 16.5%). Median bone marrow blast burden at LD was higher in pts aged ≥55 yrs (45.5%) vs <55 yrs (30.0%). At 21.5 months' (mos) median follow-up (range: 8.6–41.4), the ORR (95% CI) was 72.2% (60.9–81.7) in pts aged <55 yrs vs 87.5% (74.8–95.3) in pts aged ≥55 yrs. In responders, 84.2% of pts <55 yrs and 83.3% ≥55 yrs with ≥1 post-infusion next-generation sequencing result achieved measurable residual disease-negative remission to 10^{-6} leukemic cells by Month 3. Durable remission at 1 yr post infusion was observed in 68.3% and 51.8% of pts aged <55 and ≥55 yrs, respectively. EFS was comparable in pts aged <55 and ≥55 yrs: median (95% CI) 14.3 mos (6.0–not estimable [NE]) vs 11.7 mos (6.6–NE), respectively. While in remission, 29.8% of pts aged <55 yrs and 2.4% aged ≥55 yrs proceeded to consolidative stem cell transplant (SCT). Incidence of Grade ≥3 cytokine release syndrome (CRS; 2.5% vs 2.1%) and immune effector cell-associated neurotoxicity syndrome (ICANS; 5.1% vs 10.4%) were low for pts aged <55 and ≥55 yrs, respectively. Treatment-related mortality within 3 mos post obe-cel infusion was 0% in pts aged <55 yrs vs 4.2% in pts aged ≥55 yrs. CAR T-cell persistence was similar in both age groups. **Conclusions:** Obe-cel treatment resulted in favorable ORR and EFS with low Grade ≥3 CRS/ICANS incidence in both age groups. These findings indicate that obe-cel is effective and has a positive benefit/risk profile regardless of age, including in older adults with R/R B-ALL despite few receiving consolidative SCT. Clinical trial information: NCT04404660. Research Sponsor: Autolus Therapeutics PLC. Third-party medical writing assistance, under the direction of the authors, was provided by Michaella Hulley, PhD, of Ashfield MedComms, an Inizio company, funded by Autolus Therapeutics PLC.

6577 Poster Session

Updated results of a phase 2 study: Timdarpacept (IMM01) combined with azacitidine (AZA) as the first-line treatment in adults with chronic myelomonocytic leukemia (CMML).

Hongyan Tong, Sujun Gao, Wei Yang, Junmin Li, Qingsong Yin, Xingli Zhao, Xiaojing Yan, Sanfang Tu, Fei Li, Haiping Yang, Ronghua Hu, Shaoyuan Wang, Liya Ma, Zheng Dong, Qiying Lu, Wenzhi Tian, Zhi-Jian Xiao, Jianxiang Wang; The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; The First Hospital of Jilin University, Changchun, China; Second Department of Hematology, Shengjing Hospital of China Medical University, Shenyang, China; Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; Department of Hematology, Oncology Center, Tianjin Union Medical Center, Nankai University, Tianjin, China; The First Hospital of China Medical University, Shenyang, China; Zhujiang Hospital of Southern Medical University, Guangzhou, China; Department of Hematology, The First Affiliated Hospital of Nanchang University, Nanchang, China; The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China; Xuanwu Hospital of Capital Medical University, Beijing, China; Fujian Medical University Union Hospital, Fuzhou, China; The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; ImmuneOnco Biopharmaceuticals (Shanghai) Inc., Shanghai, China; Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Disease, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China

Background: Timdarpacept is a recombinant signal regulatory protein α (SIRPα) IgG1 fusion protein that exerts anti-tumor activity via blocking "Don't eat me" signal and activating the "Eat me" signal to induce strong antibody-dependent cellular phagocytosis (ADCP). **Methods:** The study (NCT05140811) assessed the safety and efficacy of Timdarpacept combined with AZA as first-line treatment for newly diagnosed CMML patients. Timdarpacept was administered intravenously at a dosage of 2.0mg/kg/week, while subcutaneous AZA was given at a dosage of 75 mg/m^2 on D1-7 per 28-day cycle. **Results:** At the cut-off date on Dec 31, 2024, 24 patients, with a median age of 62, males 62.5%, and 75.0% ECOG≥1, were enrolled. 33.3% and 66.7% patients were and high risk (HR), respectively. Majority of patients had poor baseline of hematologic conditions with a median hemoglobin (Hb) level of 69.5 (32-132) g/L and a median platelet (PLT) count of 73.5 (5-667)×10^9/L. The median duration of follow-up was 21.0 months (95%CI, 19.3-23.3). Among 22 efficacy evaluable patients, overall response rate (ORR) was 72.7%, including 27.3% complete response (CR), 13.6% marrow CR (mCR) with hematologic improvement (HI), 4.5% HI and 27.3% mCR alone. The median time to response (TTR) was 1.8 months and the median duration of response (DoR) was 16.9 months (95%Cl, 5.1-not reached [NR]). The median time to CR (TTCR) was 3.7 months and the median duration of CR (DoCR) was 13.6 months (95%Cl, 5.7-NR). The median of progression-free survival (PFS) was 17.8 months (95%Cl, 5.3-NR), with an estimated 12-month PFS of 59.0% (95%Cl, 33.4-77.6). Median OS has not been reached yet. The most common ≥Grade 3 TRAEs (≥10%) included lymphopenia (66.7%), leukopenia (62.5%), neutropenia (58.3%), thrombocytopenia (50.0%), anemia (29.2%) and pneumonia (16.7%). Without using of a low dose priming regimen, Grade ≥3 hemolysis occurred in 1 patient (4.2%). **Conclusions:** Timdarpacept, without a low-dose priming, combined with AZA, was well tolerated in 1L CMML. The combination, when compared to the historical data of AZA monotherapy, showed promising efficacy results for patients with treatment-naive CMML-1 and -2. Clinical trial information: NCT05140811. Research Sponsor: ImmuneOnco Biopharmaceuticals (Shanghai) Inc., Shanghai, China.

Maintenance therapy with azacitidine and valproic acid after allogeneic stem cell transplant in patients with high-risk myelodysplastic syndrome and acute myelogenous leukemia.

Timothy Edward O'Connor, Cody Whitcomb, Kayeromi Gomez, Stephanie Tsai, Patrick J. Stiff, Patrick Hagen; Loyola University Medical Center, Maywood, IL

Background: Relapse is a major cause of death after allogeneic stem cell transplant (allo-SCT) in patients with high-risk myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). Chemotherapy maintenance to prevent relapse has had limited success to date, with a phase 3 hypomethylating agent (HMA) study showing no improvement in relapse rate or survival (Oran et al.). A subgroup analysis, however, showed that high-risk patients may indeed benefit (Pasvolsky et al.). We tested a combination of an HMA [azacitidine (AZA)] and a histone deacetylase (HDAC) inhibitor [valproic acid (VPA)] as a novel maintenance following allo-SCT for high-risk AML and MDS patients based on previously reported in vitro synergism between these agents. **Methods:** This investigator-initiated, single-center, phase II trial included only patients with high-risk MDS and AML who were enrolled following day+40 of allo-SCT to receive AZA and VPA for 4, 28 day cycles. Exclusions included no grade 3-4 acute GVHD, active infection, low risk AML in CR1, a neutrophil count $< 1500/\mu l$, or platelets $< 50\,000/\mu l$. Risk was assessed via DRI at time of transplant. AZA was administered at 40 mg/m2 daily for 5 days SQ with daily oral VPA starting at 15 mg/kg and dose-adjusted to achieve a trough level of bound VPA of 100 μg/mL. Tacrolimus and methotrexate were used as GVHD prophylaxis. The primary endpoints were 1-year relapse rate, overall (OS), and progression-free (PFS) survival. **Results:** Fifty patients were enrolled. The median age was 52 with 28 (56%) male. The median hematopoietic cell transplantation-specific comorbidity index was 2. Graft types: 21 (42%) matched related, 21 (42%) matched unrelated, and 8 (12%) cord blood. Thirty grafts were from peripheral blood and 12 marrow. Myeloablative conditioning was used in 36 (72%) and reduced intensity conditioning in 14 (28%). At time of transplant for AML patients, 21 (46%) were in CR1, 5 (11%) in CR2, 2 (4%) in CRi, and 18 (39%) were relapsed/refractory. Four had high grade MDS. Baseline DRI: 42 (84%) were very high risk or high risk and 8 (16%) were intermediate risk. Eight (16%) patients did not receive all four cycles: 5 (10%) due to progression of disease, 1 (2%) due to acute GVHD, 1 each (2%) due to fatigue and cytopenias. One-year PFS and OS were 80% and 86% and 5-year PFS and OS were 47% and 61%, respectively. The one-year relapse rate was 18%. Most toxicities were grade I or II: fatigue, cytopenias, and acute kidney injury. **Conclusions:** The co-administration of AZA and VPA as a short-term maintenance strategy following allo-SCT in patients with high risk MDS and AML is safe and feasible. While a comparative trial is warranted, the use of this HMA+HDAC regimen seems to validate prior data that HMA-based maintenance may improve the outcomes of high-risk MDS and AML patients. Clinical trial information: NCT02124174. Research Sponsor: None.

Hydroxyurea vs. hypomethylating vs. other agents in chronic myelomonocytic leukemia: A retrospective inspection of treatment strategies among 457 Mayo Clinic patients.

Muhammad Yousuf, Ayalew Tefferi, Naseema Gangat, Animesh Dev Pardanani, Abhishek A Mangaonkar, Priyansh Faldu, Maymona Abdelmagid, Fnu Aperna, Fathima Saubia, Ali Alsugair, Clifford Michael Csizmar, Terra L. Lasho, Kaaren Reichard, Rong He, Mrinal Patnaik; Mayo Clinic, Rochester, MN; Division of Hematopathology, Mayo Clinic, Rochester, MN

Background: Treatment strategies in chronic myelomonocytic leukemia (CMML) are not standardized and include hydroxyurea (HU) and hypomethylating agents (HMA). In a phase 3 study comparing HU and decitabine, in proliferative CMML, response rates were higher for decitabine (56% vs 31%; $p<0.01$) but overall survival was similar ($p=0.67$) between the two groups (Itzykson, R. JCO, 2023. 41:1888). In the current retrospective study, we examined the survival impact of different treatment strategies among 457 Mayo Clinic patients with CMML. **Methods:** The current study was conducted under institutional review board approved minimum risk protocols allowing retrospective patient data collection and analysis. Diagnostic criteria were according to the International Consensus Classification (Arber et al. Blood 2022. 140:1200). All statistical analyses were conducted using JMP 17 software. For survival analysis, patients were censored at time of allogeneic stem cell transplant (ASCT). **Results:** A total of 457 patients were considered (median age 72 years; 68% males). 209 patients received CMML-directed therapy: HU (N=102), HMA (N=78; azacitidine 32 and decitabine 46). Responses were adjudicated separately for leukocytosis and anemia; normalization of leukocyte count was achieved in 21% vs. 16 % ($p<0.01$) for HU vs. HMA and overall response in anemia in 1% vs. 9% ($p=0.02$), respectively. Overall survival did not appear to be impacted by different treatment strategies at any stage of CMML; (i) treated vs. untreated ($p=0.3$), (ii) HU vs. HMA for first-line therapy ($p=0.3$), and (iii) HU/HMAs vs. other drugs as first-line therapy ($p=0.1$). Blast transformation-free survival (BTFS) was also similar between HU vs. HMA as well as HU/HMA vs. other drugs. In univariate analysis, BTFS was inferior in patients receiving CMML-directed therapy ($p<0.01$); the particular association (HR 2; 95% CI 1.2-3.3) retained its significance in multivariable analysis that also included other risk factors for BTFS: bone marrow blast ≥10% (HR 4.3), circulating blast ≥2% (HR 2.7), WBC ≥13 x 10^9/L (HR 1.8), and ASXL1 mutation (HR 1.7). **Conclusions:** In the current retrospective study that included a large number of patients with CMML, chemotherapy with HU or HMA did not appear to affect overall survival but might have increased the risk of blast transformation. The study also suggests superiority of HU for the treatment of leukocytosis and HMA for anemia. Research Sponsor: None.

Predictors of blast transformation-free survival (BTFS) in 457 patients diagnosed with chronic myelomonocytic leukemia (CMML).

BTFS	Univariable analysis *p-value* (HR)	Multivariable analysis *p-value* (HR)
CMML-directed therapy	**<0.01** (2.9; 1.8-4.7)	**<0.01** (2; 1.2-3.3)
Bone marrow blasts ≥10%	**<0.01** (12.4)	**0.01** (4.3)
Circulating blasts ≥2%	**<0.01** (5.2)	**<0.01** (2.7)
WBC ≥13 x 10^9/L	**<0.01** (2.9)	**0.02** (1.8)
ASXL1mut	**<0.01** (2.1)	**0.02** (1.7)

TPS6580 **Poster Session**

QuANTUM-Wild: A phase 3, randomized, double-blind, placebo-controlled trial of quizartinib in combination with chemotherapy and as single-agent maintenance in *FLT3*-ITD–negative acute myeloid leukemia (AML).

Pau Montesinos, June-Won Cheong, Naval Guastad Daver, Amir Fathi, Mark J. Levis, Selina M. Luger, Toshihiro Miyamoto, Esther Natalie Oliva, Alexander E. Perl, Christian Recher, Richard F. Schlenk, Jianxiang Wang, Amer Methqal Zeidan, Li Liu, Yvonne Duong, Karima Imadalou, Karenza Alexis, Akash Nahar, Kristy Burns, Harry Paul Erba; Hematology, Hospital Universitari I Politécnic La Fe and Programa Español de Tratamientos en Hematología (PETHEMA) Group, Valencia, Spain; Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, 50 Yonsei-ro, Seodaemun-gu, Seoul, South Korea; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital Cancer Center, Boston, MA; Johns Hopkins University, Baltimore, MD; University of Pennsylvania, Philadelphia, PA; Department of Hematology, Institute of Medical Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Ishikawa, Japan; U.O.C. Ematologia, Grande Ospedale Metropolitano Bianchi Melacrino Morelli, Reggio Di Calabria, Italy; Service d'hématologie, Centre Hospitalo-universitaire de Toulouse, Institut Universitaire du Cancer de Toulouse-Oncopole, Université de Toulouse, UPS, Service d'hématologie, Toulouse, France; NCT-Trial Center, National Center of Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany; State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Disease, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; Department of Internal Medicine, Section of Hematology, Yale School of Medicine, New Haven, CT; Daiichi Sankyo, Inc., Basking Ridge, NJ; Duke Cancer Institute, Durham, NC

Background: Quizartinib (Quiz) is an oral, selective, type-II FLT3 inhibitor with potent activity against wild-type (wt) FLT3, FLT3-ITDs, and other kinase domain variants. Quiz is approved for patients (pts) with *FLT3*-ITD+ newly diagnosed (ND) AML based on results from the QuANTUM-First trial (NCT02668653). Mutations in the *FLT3* gene are observed in ~30% of AML cases, most commonly as ITDs, but they are not the only mechanism affecting FLT3 activation. Elevated expression of the FLT3 receptor is observed in nearly all cases of AML, and high levels of *FLT3* gene expression are detected in 70–100% of AML blasts, independent of the presence of *FLT3* gene mutations, potentially contributing to leukemic cell survival and proliferation. Evidence from preclinical and clinical studies supports Quiz activity in *FLT3*-ITD–negative (*FLT3*-ITDneg) AML. In the phase 2 QUIWI trial, the addition of Quiz to standard chemotherapy and as single-agent maintenance significantly prolonged overall survival (OS) vs placebo (Pbo) in ND *FLT3*-ITDneg AML. QuANTUM-Wild is a global, phase 3, double-blind, Pbo-controlled trial evaluating Quiz with standard induction/consolidation chemotherapy and as maintenance in ND *FLT3*-ITDneg AML (NCT06578247). **Methods:** Eligible pts are aged 18–70 years with *FLT3*-ITD allelic frequency $< 5\%$. Treatment includes standard induction with cytarabine and an anthracycline plus Quiz/Pbo, followed by up to 4 cycles of consolidation (+/– allo-HSCT) with high-dose cytarabine and Quiz/Pbo, and then single-agent maintenance with Quiz/Pbo in 28d cycles for up to 36 cycles. Pts are randomized 2:2:1 into 3 arms: Arm A (Quiz in all phases), Arm B (Pbo in all phases), or Arm C (Quiz in induction/consolidation and Pbo in maintenance). Quiz is administered at 60 mg/day, reduced to 30 mg if combined with strong CYP3A inhibitors. The primary endpoint is OS, and secondary endpoints include event-free survival (EFS), relapse-free survival (RFS), complete remission (CR) rate and duration, measurable residual disease (by *FLT3*-ITD in all pts and by *NPM1* and *CBF* if present), and safety. Planned enrollment is ~700 pts, with 280 each in Arms A and B, and 140 pts in Arm C. The primary OS analysis compares Arms A and B, while Arm C is descriptive. Enrollment is expected to continue through 2028. Clinical trial information: 2023-507936-20-00; NCT06578247. Research Sponsor: Daiichi Sankyo.

TPS6581 **Poster Session**

First-in-human study of autologous chimeric engulfment receptor T-cell CER-1236 targeting TIM-4-l in acute myeloid leukemia (CertainT-1).

Abhishek Maiti, Jeremy L. Ramdial, Brandon Cieniewicz, Edson Oliveira, Ankit Bhatta, Hongxiu Ning, Yazan Migdady, Jacob Appelbaum; Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Department of Stem Cell Transplantation & Cellular Therapy, Houston, TX; CERo Therapeutics Holdings, Inc, South San Francisco, CA; Colorado Blood Cancer Institute (CBCI), Denver, CO; Fred Hutchinson Cancer Center, Seattle, WA

Background: Acute myeloid leukemia (AML) is the most common adult acute leukemia. Patients with relapsed or refractory (R/R) disease have dismal outcomes with complete remission (CR) rates of 5%- 15% and median overall survival of 3 to 6 months with best available therapies. In addition, patients in remission with measurable residual disease (MRD) have poor outcomes with no approved therapies. CER-1236 is an autologous chimeric engulfment receptor T cell (CER-T) which fuses external domain of TIM-4 with intracellular domains from T cells and innate immune cells including Toll-like receptor 2 (TLR2), CD28 and CD3ζ. This receptor binds TIM-4-ligand (phosphatidylserine) on tumor cells leading to phagocytosis and lysis of target cells followed by tumor antigen processing and cross-presentation to induce an adaptive immune response. CER-1236 was shown to eliminate AML cell in vitro, and in vivo in a xenograft model. TIM-4 is the key receptor which binds to TIM-4-L and leads to target cell engulfment. TIM-4-L is expressed in 88% of primary patient AML samples, across TP53 mutated and other mutational subgroups, with significantly higher expression than bone marrow from healthy donors. **Methods:** This is an open label phase I study to evaluate the safety and preliminary activity of CER-1236 in patients with R/R AML. We will evaluate 3 doses levels from 1 to 5 x10^6/kg CER+ T cells using a BOIN dose escalation design. Subsequently we will evaluate patients in 3 expansion cohorts including R/R AML, TP53 mutated AML, and AML in composite CR (cCR), i.e., CR/CRi/CRh with positive MRD. For the dose escalation study we will enroll adults with R/R AML or myelodysplastic syndrome (MDS)/AML per ICC 2022 criteria who have exhausted standard therapeutic options and patients with treated secondary AML who have progressed to AML after receiving AML directed therapy for antecedent hematological disorder, e.g, MDS. Patients will need an ECOG performance status of 0 to 1 and adequate end organ function. We will exclude patients with t(15;17), proliferative disease or active infections. For the MRD dose expansion cohorts we will enroll patients with cCR with MRD $\geq$0.1% by validated multiparametric flow cytometry. Study treatment: Patients will receive lymphodepleting chemotherapy (LDC) with fludarabine 30 mg/m^2/d and cyclophosphamide 400 mg/m^2/d for 3 days followed by a single infusion of CER-1236 2 days later. Patients may receive standard treatments as bridging therapy after apheresis and prior to LDC. The primary objective of the study is the safety of CER-1236 in terms of dose-limiting toxicities, cytokine release syndrome, and Immune effector cell-associated neurotoxicity syndrome. Secondary objectives are to measure objective response rate per the ELN 2022 criteria including CR+CRh+CRi+MLFS, cCR, MRD negativity by flow cytometry, and PK/PD profile and biomarkers of response. Research Sponsor: None.

TPS6582 **Poster Session**

Tagraxofusp and low-intensity chemotherapy for the treatment of CD123-positive relapsed or refractory acute myeloid leukemia.

Wooin Cho, Ritika Dutta, Veronica de Santiago, Kyle Denzel Cobarrubias, Jihyun Choi, Emily Bianca Inlow, Blake Shaw, Kristen Cunanan, Vivek Charu, Asiri Ediriwickrema, Tian Yi Zhang, Gabriel N. Mannis; Stanford Cancer Institute, Clinical Trial Office, Stanford University School of Medicine, Palo Alto, CA; Stanford Cancer Institute, Division of Hematology, Department of Medicine, Stanford University School of Medicine, Palo Alto, CA; Quantitative Science Unit, Department of Medicine, Stanford University School of Medicine, Stanford, CA

Background: The combination of venetoclax and a hypomethylating agent (Ven/HMA) is the standard frontline (1L) therapy for patients with acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy (IC). However, outcomes after Ven/HMA failure are poor, with a median overall survival of only 2-3 months. Cladribine (CLAD) with LDAC has previously been shown to be well-tolerated and effective in IC-ineligible patients with newly diagnosed AML. Resistance to Ven/HMA is commonly driven by mutations in the RAS/MAPK pathway and the presence of monocytic subclones that are less dependent on BCL2, both of which may retain sensitivity to cladribine-based therapy following 1L Ven/HMA. Tagraxofusp (TAG), a CD-123 targeted therapy, selectively induces apoptosis in CD123-expressing cells by irreversibly inhibiting protein synthesis through EF-2 inactivation. CD123 is highly expressed on AML blasts and leukemia stem cells compared to normal hematopoietic stem cells in the majority of AML patients. TAG in combination with Ven/HMA has shown efficacy in 1L adverse-risk AML. With its minimal additive myelosuppression and targeted specificity, TAG represents an ideal partner to combine with traditional cytotoxic chemotherapies such as CLAD and LDAC. This investigator-initiated study aims to determine the safety and tolerability of TAG in combination with CLAD and LDAC for IC-ineligible patients with relapsed or refractory (R/R) CD123 positive AML after 1L treatment with Ven/HMA. **Methods:** This single-center, open-label Phase 1b/2 trial will enroll up to 20 patients. Key inclusion criteria are: age≥18 years, R/R AML after 1L Ven/HMA with no prior salvage therapies with the exception of monotherapy with targeted inhibitors, ECOG 0-2; serum albumin≥3.2g/dL; and adequate cardiac, renal, and liver function. The phase 1b dose-exploration will determine the safety and tolerability of CLAD, LDAC, and TAG. The first 3 patients will all be treated at Dose Level 1, consisting of CLAD 5mg/m2 IV daily on days 1-3, LDAC 20mg/m2 IV daily days 1-5, TAG 12mcg/kg IV daily days 4-6. Dose escalation will proceed as tolerated to a target dose level of Dose Level 3, consisting of CLAD 5mg/m2 IV daily on days 1-5, LDAC 20mg/m2 IV daily days 1-10, TAG 12mcg/kg IV daily days 4-6. Dose-escalation and de-escalation will be determined by the BOIN design. The primary objective is determination of the RP2D based on the safety of TAG+CLAD+LDAC, as assessed by DLT evaluation. Secondary objectives include ORR, CR, composite CR (CR+CRi+CRh), and rate of MRD negativity in responders. Duration of RFS, OS, and responses according to mutational profile, karyotype, CD123 expression, and patient demographics will be reported. Once the RP2D is determined, a dose expansion cohort will begin enrolling. The study began enrolling patients in January 2025 and is actively recruiting. Clinical trial information: NCT06561152. Research Sponsor: None.

TPS6583 **Poster Session**

A phase II open-label study of olutasidenib post-transplant maintenance therapy for patients with IDH1-mutated myeloid malignancies.

Jeremy L. Ramdial, Kelly Sharon Chien, Ruitao Lin, Jennie Thy Duong, Rohtesh S. Mehta, Betul Oran, Uday R. Popat, Partow Kebriaei, Katy Rezvani, Gheath Alatrash, George Chen, Yago Nieto, Abhishek Maiti, Nicholas James Short, Ghayas C. Issa, Gautam Borthakur, Hagop M. Kantarjian, Richard E. Champlin, Elizabeth J. Shpall, Courtney Denton Dinardo; Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; MD Anderson Cancer Center, Houston, TX; Department of Stem Cell Transplantation & Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Allogeneic hematopoietic stem cell transplantation (alloSCT) remains one of the most effective treatments for patients with myeloid malignancies. Much of the benefit is due to the immune-mediated graft-versus-leukemia effect to prevent relapse. Nevertheless, despite advances in conditioning therapy, disease relapse remains the most important cause of treatment failure after alloSCT. Maintenance therapy post alloSCT aims to reduce relapse incidence and strengthen the potential for cure. With modern treatment regimens, expected complete remission (CR) rates for newly diagnosed AML patients are 60-70%, however, long-term cure rates are only ~30% and improved treatments are needed. IDH1 mutations occur in >7% of older patients with AML and up to 4% of patients with high-risk CMML or MDS. A multicenter phase I trial of another IDH1 inhibitor used as maintenance treatment following alloSCT for IDH1-mutated AML demonstrated a two-year progression-free survival (PFS) of 81%, and two-year overall survival (OS) of 88%. The 2-year cumulative incidence of disease relapse was 19% (95% CI, 4%–41%) and the 2-year cumulative incidence of non-relapse mortality (NRM) was 0%. Olutasidenib is a well-tolerated, highly selective, non-cytotoxic, and potent FDA-approved oral inhibitor of mutant IDH1, with an overall response rate in relapsed/refractory AML of 48%. **Methods:** In our single center, investigator-initiated study under the MDACC-Rigel Research Alliance we aim to determine the safety and tolerability of olutasidenib as maintenance post-allo-SCT and to determine the rate of progression-free survival (PFS). Eligibility includes patients 18-75 years old with IDH1 mutation presence at diagnosis with acceptable organ function. Patients must also have a diagnosis of AML, MDS, MPN, or CMML according to World Health Organization (WHO) classification that underwent first or second alloSCT with either peripheral blood or bone marrow hematopoietic stem cell source, regardless of donor type/match, conditioning regimen, or GVHD prophylaxis and is at least 30 days post stem cell transplant until day 120. A safety lead-in phase will be given for the first 6 patients to investigate whether the starting dose of 150 mg BID is safe and tolerable. After the safety lead-in phase, the remaining patients will be enrolled at the same dose and the safety and tolerability will be monitored. We also would like to determine response rate, overall survival (OS), cumulative incidence of relapse, NRM, GVHD relapse-free survival (GRFS), rate and grading of aGVHD grade 2-4 and 3-4 at day 100, incidence and grading chronic GVHD (cGVHD) all grades. The goal enrollment is 25 total patients. The study was activated and enrollment began in December 2024. Clinical trial information: NCT06668584. Research Sponsor: None.

TPS6584 Poster Session

Phase 3 study of either ivosidenib monotherapy or azacitidine monotherapy in patients with IDH1-mutant myelodysplastic syndromes who are hypomethylating agent naive (PyramIDH).

Valeria Santini, Marie Sébert, David Valcárcel, Uma Borate, Weishi Yuan, Stephanie M. Kapsalis, Lorene Simonot, Prapti Arvind Patel, Guillermo Garcia-Manero; DMSC, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy; Groupe Francophone des Myélodysplasies (GFM), Hôpital Saint-Louis, Paris, France; Hematology Department, Vall d'hebron University Hospital, Vall d'hebron Institut of Oncology (VHIO) Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; Ohio State University Comprehensive Cancer Center/James Cancer Hospital Ohio State University, Columbus, OH; Servier BioInnovation, Boston, MA; Servier Pharmaceuticals LLC, Boston, MA; Servier International Research Institute, Gif-Sur-Yvette, France; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal myeloid disorders that occur predominantly in older patients with variable risk of progression to acute myeloid leukemia (AML). According to International Prognostic Scoring Systems, patients with lower-risk MDS (LR-MDS) and cytopenias can be treated with different drugs and in some cases hypomethylating agents (HMAs). However, in higher-risk MDS (HR-MDS), HMAs are the only available standard of care therapy. The complete response (CR) + partial response (PR) rate of azacitidine in treatment-naive MDS ranges between 16% and 22%. These low response rates, combined with the short duration of responses observed with these approaches highlight an unmet medical need for this population. Ivosidenib (IVO) is an oral, targeted small molecule inhibitor of mutant IDH1 that is currently FDA approved in relapsed/refractory MDS with a complete remission (CR) + partial remission (PR) rate of 38.9% (95% CI: 17.3%, 64.3%) with all responses being CR. In the phase 2 IDIOME study, 72% of patients with previously untreated *mIDH1* HR-MDS obtained CR+PR with IVO monotherapy; median OS and DOR were not reached after median follow-up of 25.2 months. The aim of PyramIDH is to confirm the safety and clinical activity of IVO monotherapy in HMA–naive *mIDH1* MDS in a larger cohort. **Methods:** PyramIDH (NCT06465953) is a phase 3, multicenter, open-label, randomized, non-comparative two-arm study of IVO or azacitidine (AZA) monotherapy in patients with HMA-naive *mIDH1* MDS. Key eligibility criteria include diagnosis of HMA-naive *IDH1 R132* mutated MDS. HR-MDS (moderate high-, high- and very-high-risk MDS per IPSS-Molecular (IPSS-M) score), will be eligible if the bone marrow blast count is <20% regardless of blood cell counts. LR-MDS (low- and moderate-low-risk MDS per IPSS-M score), must have cytopenias related to MDS, defined as: <100 platelets/μL, or absolute neutrophil count (ANC) <1000/mm^3, or hemoglobin <10g/dL, have a blast count between 5% and 19%, and be eligible for HMA therapy. Very-low-risk MDS per IPSS-M will not be eligible for enrollment. Enrolled patients (n=~48) will be randomized (2:1) to IVO or AZA monotherapy and they will be stratified by IPSS-M risk status (HR versus LR). The primary endpoint is CR+PR at 4 months as per IWG 2006 criteria. Key secondary endpoints include duration of CR+PR per IWG 2006 criteria, time to CR+PR per IWG 2006 criteria, transfusion independence rate, AML transformation rate, and number of patients going to transplant. Other secondary endpoints are CR+PR at 6 months per IWG 2006 criteria; CR+PR at 4 and 6 months per IWG 2023 criteria; overall response rate per IWG 2023 criteria, duration of response, EFS, OS, duration of transfusion independence (TI), time to TI, AML transformation, quality of life, PK/PD, and safety. Clinical trial information: NCT06465953. Research Sponsor: Servier.

TPS6585 **Poster Session**

Phase II study evaluating olutasidenib in patients with *IDH1*-mutated clonal cytopenia of undetermined significance or lower-risk myelodysplastic syndromes/ chronic myelomonocytic leukemia.

Kelly Sharon Chien, Jeremy L. Ramdial, Wei Qiao, Lizabeth Romero, Guillermo Montalban-Bravo, Nicholas James Short, Ghayas C. Issa, Farhad Ravandi-Kashani, Naval Guastad Daver, Tapan M. Kadia, Hagop M. Kantarjian, Guillermo Garcia-Manero, Courtney Denton Dinardo; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Observational studies have demonstrated that individuals with clonal cytopenia of undetermined significance (CCUS) involving high-risk mutations, such as *IDH1*, are more likely to transform to acute myeloid leukemia (AML), with one study showing a progression rate of 100% in *IDH1*/2-mutated patients after 5 years of follow-up. However, there are no Food and Drug Administration (FDA)-approved strategies for the prevention of hematologic malignancies in the setting of CCUS. *IDH1* mutations are detected in 3-4% of patients with myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML). Despite the safety and efficacy of IDH1 inhibitors in acute myeloid leukemia and the recent FDA approval of ivosidenib for relapsed/refractory *IDH1*-mutated MDS, no IDH1-directed therapies are approved in lower-risk, treatment-naïve MDS/CMML. Olutasidenib, an FDA-approved oral, highly selective, potent inhibitor of mutant IDH1, is well-tolerated, non-cytotoxic and effective, with overall response rates in relapsed/refractory AML of 48% as monotherapy. We consequently hypothesize olutasidenib to be effective in both improving hematologic parameters and decreasing the risk of progression to high-risk MDS/CMML and AML in *IDH1*-mutated patients. **Methods:** This multicenter investigator-initiated study under the MDACC-Rigel Research Alliance is a phase II single-arm study evaluating the efficacy of olutasidenib monotherapy in patients with *IDH1*-mutated CCUS or lower-risk MDS/CMML. Eligibility includes adult patients with acceptable organ function and confirmed *IDH1* mutation with CCUS (by World Health Organization criteria) or lower-risk MDS/CMML (by Revised International Prognostic Scoring System [IPSS-R] and Molecular International Prognostic Scoring System [IPSS-M] criteria). The primary objective of the study is to determine the response rate by International Working Group 2018 criteria. Secondary objectives include rates of transfusion independence, safety and tolerability, overall survival, progression-free survival, duration of response, rates of leukemic transformation, and changes in *IDH1* clone size. All patients will receive olutasidenib 150 mg orally twice daily. CCUS patients will receive up to 18 months of olutasidenib, while lower-risk MDS/CMML patients can receive olutasidenib indefinitely. Response assessments will be performed approximately every 3 months for the first year, then yearly thereafter. Once off treatment, survival follow-up will occur every 3 months for 3 years. The goal enrollment is 15 total patients with at least 8 CCUS patients across 5-6 centers in the United States. The study was activated and enrollment began in December 2024. Clinical trial information: NCT06566742. Research Sponsor: None.

TPS6586 **Poster Session**

Phase II study evaluating olutasidenib and azacitidine in patients with *IDH1*-mutated higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia, or advanced myeloproliferative neoplasms.

Kelly Sharon Chien, Jeremy L. Ramdial, Wei Qiao, Rosmy John, Guillermo Montalban-Bravo, Nicholas James Short, Ghayas C. Issa, Farhad Ravandi-Kashani, Naval Guastad Daver, Tapan M. Kadia, Hagop M. Kantarjian, Guillermo Garcia-Manero, Courtney Denton Dinardo; Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: *IDH1* mutations are detected in 3-4% of patients with myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML) and approximately 9% of patients with myeloproliferative neoplasms (MPN). *IDH1* mutations have been associated with shortened survival and increased rates of transformation to acute myeloid leukemia (AML). Despite the use of IDH1 inhibitors in AML and the recent FDA approval of ivosidenib for relapsed/refractory *IDH1*-mutated MDS, no IDH1-directed therapies are approved in MPN or treatment-naïve MDS/CMML, and no combination treatment regimens are commercially available. Olutasidenib, an FDA-approved oral, highly selective, potent inhibitor of mutant IDH1, is well-tolerated, non-cytotoxic and effective, with overall response rates in relapsed/refractory AML of 51% in combination with azacitidine. Olutasidenib alone or with azacitidine demonstrated overall response rates of 86% in treatment-naïve and 47% in relapsed/refractory MDS. We consequently hypothesize olutasidenib to be effective in patients with *IDH1*-mutated higher-risk MDS/CMML or advanced MPN. **Methods:** This multicenter investigator-initiated study under the MDACC-Rigel Research Alliance is a phase II non-randomized study evaluating the efficacy of olutasidenib in combination with azacitidine in patients with *IDH1*-mutated higher-risk MDS/CMML or advanced MPN. Patients will be divided into 2 arms: treatment naïve and previously treated. Eligibility includes adult patients with acceptable organ function and confirmed *IDH1* mutation with higher-risk MDS/CMML (by International Prognostic Scoring System [IPSS], Revised IPSS [IPSS-R], or Molecular IPSS [IPSS-M] criteria) or advanced MPN (with bone marrow blast percentage $\geq 10\%$). The primary objective of the study is to determine the overall response rate by International Working Group 2023 criteria (MDS), 2015 MDS/MPN uniform response criteria (CML), and European Leukemia Network 2017 AML criteria (advanced MPN). Secondary objectives include rates of complete remission, safety and tolerability, overall survival, progression-free survival, duration of response, and changes in *IDH1* clone size. All patients will receive azacitidine 75 mg/m^2 intravenously or subcutaneously daily on days 1-7 of each treatment cycle and olutasidenib 150 mg orally twice daily. Response assessments will be performed after cycle 1, then every 3 cycles up through cycle 12, then every 12 cycles thereafter. Once off treatment, survival follow-up will occur every 3 months for 3 years. The goal enrollment is 45 patients (25 treatment-naïve and 20 previously-treated with no more than 5 MPN patients in each arm) across 5-6 centers in the United States. The study was activated and enrollment began in January 2025. Clinical trial information: NCT06597734. Research Sponsor: None.

TPS6587 **Poster Session**

Shorespan-007: Phase 3 study of bomedemstat versus hydroxyurea in essential thrombocythemia naive to cytoreductive therapy.

Kristen M. Pettit, Yuka Sugimoto, Eran Zimran, Yoshimitsu Shimomura, Hiroki Yamaguchi, Hans Carl Hasselbach, Jean-Jacques Kiladjian, Steffen Koschmieder, Harinder Gill, Natalia Curto-Garcia, Alejandro Berkovits, Ahmet Muzaffer Demir, Tsai-Yun Chen, Stefan Scheding, Claudia Barrera Carmona, Alessandro M. Vannucchi, Keita Kirito, Shiyu Zhang, Uzor Ogbu, David M. Ross; University of Michigan, Ann Arbor, MI; Mie University Graduate School of Medicine, Tsu, Japan; Hadassah Medical Center, Jerusalem, Israel; Kobe City Medical Center General Hospital, Kobe, Japan; Nippon Medical School, Tokyo, Japan; Zealand University Hospital, Roskilde, Denmark; Hôpital Saint-Louis, Université Paris Cité, Paris, France; Faculty of Medicine, RWTH Aachen University, Aachen, Germany; Department of Medicine, School of Clinical Medicine, LKS Faculty of Medicine, University of Hong Kong, Hong Kong, Hong Kong; Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; Immunocel Chile, Providencia, Chile; Trakya University, Edirne, Turkey; National Cheng Kung University Hospital Clinical Trial Center, Tainan, Taiwan; Skånes Universitetssjukhus Lund, Lund, Sweden; Higiea Oncologia, Mexico City, Mexico; AOU Careggi, University of Florence, Florence, Italy; Department of Hematology and Oncology, University of Yamanashi Hospital, Yamanashi, Japan; Merck & Co., Inc., Rahway, NJ; Royal Adelaide Hospital and SA Pathology, Adelaide, Australia

Background: Lysine-specific demethylase 1 (LSD1) is an enzyme that regulates hematopoietic stem and progenitor cell proliferation and maturation. Bomedemstat (MK-3543) is an LSD1 inhibitor shown to have manageable safety and improve symptoms, durably reduce platelet and white blood cell (WBC) count, and reduce mutation burden in patients with essential thrombocythemia (ET) in a phase 2 study. Here, we describe the methodology of the randomized, double-blind, phase 3 Shorespan-007 study (NCT06456346), which has been designed to evaluate the efficacy and safety of bomedemstat compared with hydroxyurea in participants with ET naive to cytoreductive therapy. **Methods:** Key eligibility criteria include patients aged ≥18 years with an ET diagnosis per WHO diagnostic criteria for myeloproliferative neoplasms, an indication for cytoreductive therapy, no prior cytoreductive therapy, a bone marrow fibrosis score of 0 or 1, a platelet count of $>450 \times 10^9$/L, and an absolute neutrophil count of $\geq 0.75 \times 10^9$/L. Key exclusion criteria include a documented increased risk of bleeding or an active infection necessitating systemic therapy. Approximately 300 participants will be enrolled. Participants will be randomly assigned 1:1 to bomedemstat at a starting dose of 50 mg/day by mouth titrated to a target platelet count of $\geq 150 \times 10^9$/L to $\leq 350 \times 10^9$/L or hydroxyurea at a starting dose of 500 mg/day by mouth titrated per the approved product labeling. The primary end point is durable clinicohematologic response, defined as the following: a confirmed reduction of platelet count to $\leq 400 \times 10^9$/L; absence of a WBC count elevation to $>10 \times 10^9$/L locally assessed to be due to ET; and, if WBC count is elevated to $>10 \times 10^9$/L at screening, a reduction of WBC count to $\leq 10 \times 10^9$/L (confirmed by first subsequent visit a minimum of 2 weeks apart, starting by week 24 and maintained for ≥24 weeks to at least week 48; absence of any thrombotic or major hemorrhagic events or disease progression to myelofibrosis [MF] or myelodysplastic syndrome [MDS]/acute myeloid leukemia (AML) by week 52). Secondary end points include change in fatigue from baseline per the MFSAF v4.0, change in total fatigue score from baseline per the PROMIS Fatigue SF-7a scale, change in total symptom score from baseline per the MFSAF v4.0, duration of clinicohematologic response, duration of hematologic remission, incidence of thrombotic events, incidence of major hemorrhagic events, transformation to post-ET MF or MDS/AML, and safety and tolerability. Clinic visits will occur every 2 weeks for the first 12 weeks and every 4 weeks thereafter. Adverse events will be monitored throughout the study and for ≤30 days after treatment end and will be graded per NCI CTCAE v5.0. Recruitment for Shorespan-007 is ongoing or planned in sites in Asia, Australia, Europe, North America, and South America. Clinical trial information: NCT06456346. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS6588 Poster Session

IMpactMF, randomized, open-label, phase 3 trial of imetelstat (IME) versus best available therapy (BAT) in patients (pts) with intermediate-2 (INT-2) or high-risk (HR) myelofibrosis (MF) relapsed or refractory (R/R) to Janus kinase inhibitors (JAKi).

John Mascarenhas, Claire Harrison, Prithviraj Bose, Jean-Jacques Kiladjian, Alessandro Lucchesi, Alessandro Vannucchi, Michelle Mudge-Riley, Jennifer Riggs, Lixian Peng, Fei Huang, Ying Wan, Vivian Rodolf, Judy Ho, Shyamala Chendeal Navada, Rami S. Komrokji; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Guy's and St Thomas' National Health Service Foundation Trust, London, United Kingdom; The University of Texas MD Anderson Cancer Center, Houston, TX; Hôpital Saint-Louis, Assitance Publique-Hôpitaux de Paris, Université de Paris, Paris, France; Hematology Unit, IRCCS Istituto Romagnolo per lo Studio e la Cura dei Tumori (IRST) "Dino Amadori", Meldola, Italy; University of Florence, Florence, Italy; Geron Corporation, Foster City, CA; Geron, Foster City, CA; Geron, Forest City, CA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: IME is a first-in-class telomerase inhibitor approved in 2024 for pts with transfusion-dependent lower-risk myelodysplastic syndromes who are R/R or ineligible for erythropoiesis-stimulating agents. In the phase 2 IMbark trial (NCT02426086) in pts with MF, IME (9.4 mg/kg every 3 weeks [q3w]; N=59) at wk 24 showed median overall survival (OS) of 29.9 mo (median follow-up, 27.4 mo), total symptom score reduction ≥50% in 32% of pts, and spleen volume reduction ≥35% in 10% of pts. IME treatment dose-dependently improved bone marrow (BM) fibrosis and reduced MF driver mutation variant allele frequency, which correlated with improved OS. The most common grade ≥3 adverse events were thrombocytopenia, anemia, and neutropenia; cytopenias were generally manageable, short-lived, and resolved to grade ≤2 in <4 wks. These data support further evaluation of IME. **Methods:** IMpactMF (MYF3001; NCT04576156) is a phase 3, open-label, randomized (2:1) trial of IME versus BAT in ≈320 adults with INT-2 or HR MF R/R to JAKi or ineligible for allogeneic stem cell transplantation or further JAKi. Randomization is to IME sodium 9.4 mg/kg (8.9 mg/kg active dose) intravenously q3w or investigator-selected BAT (eg, hypomethylating agents, hydroxyurea, interferon, thalidomide, danazol, chemotherapy, or other non–JAKi-containing therapy, but not hematopoietic stem cell transplantation or splenectomy). Eligibility criteria include peripheral blood and marrow blast counts <10% and Eastern Cooperative Oncology Group performance status ≤2. Chronic liver disease unrelated to underlying MF, active systemic hepatitis infection, or clinically significant cardiovascular disease are not allowed. Pts are stratified at randomization based on INT-2 or HR MF per the Dynamic International Prognostic Scoring System and baseline platelet count. Crossover to IME may be permitted for pts who meet progressive disease criteria (≥25% increase in spleen volume from baseline) or a palpable increase in splenomegaly after 6 mo of BAT. IMpactMF is the first MF phase 3 trial evaluating OS as the primary endpoint. Secondary endpoints include wk 24 symptom and spleen response rates, progression-free survival, clinical response assessments per modified 2013 International Working Group-Myeloproliferative Neoplasms Research and Treatment criteria, time to and duration of response, reduction in BM fibrosis, safety, pharmacokinetics, and pt-reported outcomes. Biomarkers and mutation analyses will be performed. As of December 2024, 172 sites in North and South America, Europe, Middle East, Australia, and Asia have enrolled ≈75% of pts. The planned interim analysis (when ≈35% of pts planned to be enrolled have died) is expected in early 2026 and final analysis is expected in early 2027. Clinical trial information: NCT04576156. Research Sponsor: This study was funded by the Geron Corporation; writing and editorial support were provided by Meredith Rogers, MS, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by the Geron Corporation.

TPS6589 **Poster Session**

Anti-tumor activity of CoREST inhibitor, JBI-802 (dual epigenetic modifier of LSD1/HDAC6): An opportunity to treat essential thrombocythemia and MPN/MDS patients with thrombocytosis in ongoing phase 1/2 clinical trial.

Melda S. Dolan, Sridharan Rajagopal, Abhijit B., Deepak Mittal, Shawnavaz Vazeer, Mohd Zainuddin, G. Chandru, Naveen Sadhu, Syed Kazmi; Jubilant Therapeutics and Jubilant Radiopharmaceuticals, Yardley, NJ; Jubilant Therapeutics Inc, Bedminster, NJ; Jubilant Radioharma, Yardley, PA; Jubilant Therapeutics India Limited 96 Industrial Suburb, Bangalore, India; Jubilant Therapeutics India Limited, Bangalore, India

Background: Lysine specific demethylase 1 (LSD1) and histone deacetylase 6 (HDAC6) are epigenetic proteins associated with several diseases, including cancer. JBI-802 is a highly potent CoREST inhibitor with LSD1/HDAC6 selective dual inhibition that shows superior anti-tumor activity in several pre-clinical models with significant modulation of PD biomarkers that include CD11b, CD86 and acetylated alpha-tubulin. JBI-802 in first-in-human phase I clinical trial (NCT05268666) demonstrated a dose-proportional increase in exposure across cohorts and its correlation with on-target effects in therapy resistant advanced lung cancers patients. 2/2 immunotherapy resistant NSCLC patients displayed improvement in tumor-related symptoms with confirmed partial response (PR) in one NSCLC patient at 10 mg dose. Overall, JBI-802 was well tolerated and showed remarkable safety profile without affecting hemoglobin, with grade 3/4 thrombocytopenia as the only adverse event observed in 38% of patients at the higher dose. Dose-dependent decrease in platelets as a part of MOA of LSD1 and HDAC6 inhibition demonstrated that JBI-802 is pharmacologically active and provided an opportunity to treat patients with hematological malignancies like essential thrombocythemia (ET) and other myelodysplastic/myeloproliferative neoplasms (MDS/MPN) characterized by thrombocytosis. **Methods:** The ongoing phase 1/2 clinical trial will assess the safety and preliminary efficacy of orally administered JBI-802 in ET and MDS/MPN patients with thrombocytosis (ACTRN12624000478516) in a standard 3+3 design in 30 patients in two phases. Part 1: Dose Escalation Phase - Primary objective is to determine the recommended phase 2 dose (RP2D) of JBI-802 and safety in subjects with ET and MDS/MPN neoplasms with thrombocytosis, with dose-limiting toxicity as the primary endpoint during the monitoring period. Secondary objective is to evaluate the overall safety and tolerability, and to determine the preliminary antitumor activity along with characterization of pharmacokinetic (PK) profile of JBI-802 and its metabolites as well as clinical and hematologic responses. Part 2: Dose Expansion Phase – The objective is to obtain preliminary evidence of efficacy as defined by MDS/MPN IWG response criteria, which includes platelet count reduction, and response assessments of spleen size and volume, evaluation of hematology parameters and bone marrow aspiration/biopsy, and to further evaluate the overall safety and tolerability of JBI-802, along with characterization of PK and PD profile and changes in mutant allele frequencies. Study results will provide insights into the clinical potential of JBI-802 in treating ET and MDS/MPN patients relapsed and/or refractory to standard of care therapies. Clinical trial information: ACTRN12624000478516. Research Sponsor: None.