

Selinexor plus ruxolitinib in JAK inhibitor–naïve myelofibrosis: Phase 3 SENTRY trial.

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RALLY-MF: Initial efficacy of a phase 2 study of DISC-0974, an anti-hemojuvelin antibody, to treat anemia in myelofibrosis.

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Background: Hepcidin, a central regulator of iron homeostasis, is pathologically elevated in patients with myelofibrosis (MF) and anemia. Chronic hepcidin elevation limits iron availability for red blood cell (RBC) production and contributes to anemia onset and severity. DISC-0974 is an investigational, first-in-class, monoclonal antibody that blocks hemojuvelin, a co-receptor in the bone morphogenetic protein-signaling pathway driving hepcidin expression. **Methods:** RALLY-MF (NCT05320198) is an ongoing Phase 2, open-label study conducted in the US. The primary aim is to evaluate DISC-0974 efficacy in participants with MF and anemia. Secondary aims include evaluating safety, pharmacokinetics (PK), and pharmacodynamics (PD). Eligible participants are ≥ 18 years of age with primary or secondary MF and hemoglobin (Hgb) < 10 g/dL or RBC transfusion requirement. Participants enroll into 3 cohorts based on RBC units transfused in the 84 days prior to screening: non-transfusion dependent (nTD, 0 units and Hgb < 10 g/dL), low transfusion burden (TD low, 1-2 units), high transfusion burden (TD high, 3-12 units). Stable dose of concomitant Janus kinase inhibitor (JAKi) is allowed. DISC-0974 is administered subcutaneously at 50 mg monthly for up to 6 doses, with escalation to 75 mg for inadequate or lost response. Primary endpoints include major hematologic response defined as transfusion independence (TI) during any consecutive 16 weeks (TD low) or 12 weeks (TD high), or a mean Hgb increase of ≥ 1.5 g/dL from baseline for ≥ 12 weeks (nTD). Secondary endpoints include PK/PD markers of iron regulation and safety assessments. Data were summarized using descriptive statistics. **Results:** At data cut (16 Oct 2025), 47 participants enrolled in the nTD (n=30), TD low (n=10), and TD high (n=7) cohorts, with 53% on concomitant JAKi therapy. DISC-0974 led to sustained hepcidin reduction and iron mobilization across cohorts. DISC-0974 resulted in meaningful hematologic responses among evaluable participants: 50% of nTD participants achieved a mean Hgb increase of ≥ 1.5 g/dL for ≥ 12 weeks, 71% of TD low participants achieved TI for ≥ 16 weeks, and 67% of TD high participants experienced a $\geq 50\%$ reduction in transfusion burden, with follow-up ongoing. Major hematologic response rates were 50% for participants on and off concomitant JAKi therapy (n=18 and n=16, respectively). DISC-0974 was associated with meaningful improvement in FACIT-Fatigue scores for nTD and TD low participants. Serious adverse events (AEs, n=9) and $\geq$ Grade 3 AEs (n=16) were considered unrelated to DISC-0974. There were no early withdrawals due to AEs. **Conclusions:** DISC-0974 was well tolerated and shows a favorable safety profile. Anemia response and fatigue scores improved across patients with MF and anemia, including those receiving JAKi therapy. These data validate hepcidin reduction as a promising approach to treating anemia in MF. Clinical trial information: NCT05320198. Research Sponsor: Disc Medicine.

A phase II trial of tagraxofusp, hyper-CVAD, and venetoclax for patients with newly diagnosed or relapsed/refractory BPDCN.

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Background: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive hematologic malignancy with (w/) historically dismal outcomes, including median (med) overall survival (OS) of 8 – 12 months (mos) and frequent central nervous system (CNS) involvement (Martin-Martin *Oncotarget* 2016, Pemmaraju *Blood* 2021). Tagraxofusp (TAG; first CD123-targeted therapy approved for BPDCN) improves responses (Pemmaraju *JCO* 2022), but relapse remains common. Venetoclax (VEN) demonstrates activity in BPDCN (Montero *Cancer Disc* 2017), and intensified chemotherapy may improve outcomes. We report the results of a phase II investigator-initiated trial (NCT04216524) of TAG, Hyper-CVAD, and VEN in newly diagnosed (ND) or relapsed/refractory (R/R) BPDCN. **Methods:** Adults (≥ 18 years [yrs]) w/ ND or R/R BPDCN received: Cycle [C] 1: TAG days [d] 1–5; C2, 4, 6, 8: TAG d1 – 5 w/ VEN d2 – 14 (C2) and d1 – 7 (C4, 6, 8); C3, 7: VEN d1 – 7 w/ Hyper-CVAD or mini-hyper-CVD; C5: VEN d1 – 7 w/ high-dose methotrexate/cytarabine or mini-methotrexate/cytarabine. Cycles were 28 days for up to 8 cycles, followed by POMP, VEN, and TAG maintenance. Pts received ≥ 8 intrathecal. **Results:** Nineteen pts were enrolled (14 ND; 5 R/R). Med age was 61 yrs (range, 20 – 79); 79% male. Disease sites included 84% skin, 63% bone marrow, 16% CNS, 16% extramedullary. Co-occurring mutations were *TET2* (60%), *ASXL1* (33%), *DNMT3A* (20%), *NRAS* (13%), *KRAS* (13%). Two pts had prior/concomitant MDS. For ND, overall response rate (ORR; complete remission [CR] plus CR w/ incomplete count recovery [CRi] plus partial response [PR]) was 93% (13/14, all CR/CRi). Pts received a med of 2 (1 – 6) cycles w/ 2 (1 – 3) cycles to best response. The 30- and 60-day mortality was 0%. After a 55-mos med follow-up, (19.5 – NR), med OS was 15 mos w/ 24-month OS of 42%. Med EFS was 14.6 mos w/ 24-month EFS of 42%. Nine pts (65%) went to stem cell transplant (SCT) (2 died in CR, 6 remain alive in CR; of these, 3 remain alive in CR almost 5 yrs; with only 1 post-SCT relapse). In the 4 responding pts who did not go to SCT, 3 relapsed, 1 died in CR. For R/R, ORR was 100%; CR/CRi of 50%. Pts received a med of 2 (2 – 4) prior lines; 3 (60%) had prior SCT. Pts received a med of 3 (1 – 7) cycles w/ 3 (1 – 3) to best response. Two pts went to SCT (1 auto, 1 allo); 1 pt is alive on active treatment. The 30- and 60-day mortality was 0% and 20%. With f/u ranging 1.4 – 21.8 mos, med OS and EFS is 8.9 mos; 12-month OS and EFS was 30%. In responding pts, causes of death were progression n = 4; died in CR n = 5 (3 ND, 2 R/R, 1 post SCT, 1 unknown, 3 sepsis). The most common any grade adverse events (AE) were edema (n = 13) and fatigue (n = 11). There were 2 grade 5 AE (progression, respiratory failure). Two grade 3 capillary leak events were observed. **Conclusions:** As frontline therapy, TAG with Hyper-CVAD, and VEN shows promising safety with no early mortality or high-grade CLS, with high response rates enabling frequent SCT consolidation and no CNS relapse. Clinical trial information: NCT04216524. Research Sponsor: Stemline.

A multicenter phase Ib/II trial of azacitidine, venetoclax, and ivosidenib in *IDH1*-mutated acute myeloid leukemia (AML).

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Background: Outcomes for patients with *IDH1*^{mut} AML have improved with the advent of targeted therapies. Two doublet regimens are approved for *IDH1*^{mut} AML: venetoclax (VEN) with a hypomethylating agent (HMA), and azacitidine (AZA) plus ivosidenib (IVO). Both regimens are effective, yet a substantial proportion of patients fail to respond or eventually relapse. Combining all three agents into a “triplet” regimen may improve outcomes. Herein, we report results from the fully enrolled newly diagnosed (ND) cohort of the multicenter phase Ib/II study of AZA+VEN+IVO for *IDH1*^{mut} AML (NCT03471260). **Methods:** Adults ≥18 years with ND *IDH1*^{mut} AML not eligible for standard induction chemotherapy and treated at the RP2D in the phase Ib or II cohorts were included. Patients received AZA 75 mg/m² days 1–7, VEN 400mg days 1–14, and IVO 500mg continuously starting C1D14. Dose attenuations in remission were permitted to minimize myelosuppression. The primary objectives were to determine the safety and overall response rate (ORR: CR + CRh + CRi + MLFS). **Results:** From November 2019 to October 2025, 40 patients with ND AML at four U.S. academic centers initiated treatment (Phase Ib: 9, Phase II: 31). The median age was 72 years (range, 51–80), and 26 patients (65%) were male. AML was classified as *de novo* in 21 (53%), therapy-related in 4 (10%), and secondary to antecedent myeloid neoplasm in 15 (38%). Six (15%) had received a prior HMA. The ORR was 95% (38/40) with 93% (37/40) achieving a composite CR (CRc; CR+CRh+CRi). The median number of cycles to best response was two (range, 1–7). Measurable residual disease (MRD) negativity by flow cytometry (sensitivity <0.1%) was achieved in 92% (34/37) of CRc responders. With a median follow up of 35 months, median overall survival (OS) and duration of remission (DOR) were not reached. The 3-year OS was 79% (95% CI 64–96%). Three patients relapsed during follow-up with *IDH1*-negative clones, and 18 patients (45%) transitioned to SCT. The 3-year DOR censored and not-censored at SCT was 82% (95% CI 68–98%) and 83% (95% CI 64–100%), respectively. Among the 22 patients who did not undergo SCT, the median number of cycles received is 14, with 10 patients (45%) remaining on study. Reasons for discontinuation included lack of response/relapse (n=5), development of another malignancy (n=2), adverse events (AEs; n=2), and patient preference (n=1). Non-hematologic AEs occurred in 32 patients (80%), with 12 (30%) experiencing grade ≥3 AEs. Most grade ≥3 AEs were infectious (n=7, 23%), although two patients each experienced grade ≥3 QTc prolongation, tumor lysis syndrome, and differentiation syndrome, all successfully managed with supportive care and/or with dose modifications. **Conclusions:** Triplet therapy with AZA+VEN+IVO demonstrates high MRD negative response rates, durable remissions, and comparable safety to doublet regimens in this multicenter study for patients with ND *IDH1*^{mut} AML. Clinical trial information: NCT03471260. Research Sponsor: None.

Quizartinib in combination with decitabine and venetoclax for newly diagnosed and relapsed/refractory *FLT3*-mutated AML.

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Background: Hypomethylating agents (HMAs; azacitidine/decitabine) plus venetoclax (VEN) are standard for newly diagnosed acute myeloid leukemia (AML) unfit for intensive chemotherapy; however *FMS*-like tyrosine kinase-3 internal tandem duplication (*FLT3-ITD*) confers resistance and poor overall survival (OS). Addition of quizartinib (QUIZ), a potent *FLT3* inhibitor, may improve outcomes. **Methods:** Phase I/II study of QUIZ+decitabine+VEN in two cohorts: newly diagnosed *FLT3-ITD* AML pts unfit for intensive chemotherapy and relapsed/refractory (R/R) *FLT3-ITD* AML pts. Primary endpoints were maximum tolerated dose (MTD) and overall response rate (ORR). **Results:** Eighty-eight patients (pts) were enrolled (frontline N=42; R/R N=46). QUIZ 26.5mg/day was selected as the recommended phase II dose (RP2D). In the frontline cohort, median age was 70y (62–85); 15 pts (36%) were ≥ 75 y; 25 (60%), 12 (N=28%), and 5 (12%) had de novo, secondary, and therapy-related AML, respectively. *DNMT3A* (43%), *NPM1* (33%), and *RUNX1* (31%) were the most common co-mutations. Complete remission (CR), CR with incomplete count recovery (CRi), morphologic leukemia-free state (MLFS), end-of-cycle-1 (EOC1) measurable residual disease (MRD) negativity by multicolor flow cytometry (MFC; 0.01%), and next-generation sequencing (NGS) *FLT3-ITD* negativity (5×10^{-8}) were 72% (N=29), 17% (N=7), 2% (N=1), 58% (19/32), and 27% (5/18), respectively; 2 pts in cycle 1 were not evaluable. Best MRD negativity by MFC and *FLT3*-NGS were 68% (23/34) and 83% (15/18). Median time to absolute neutrophil count (ANC) >500 , ANC >1000 , and platelets $>50K$ were 40 (19–72), 41 (14–72), and 35 (16–71) days, respectively. The median relapse-free survival (RFS) and OS were 24.7 and 36.5mo. Fifteen pts (36%) proceeded to allogeneic stem cell transplant (ASCT) in CRi, with OS not reached vs 36.6mo without ASCT ($p=0.65$, landmark analysis). Median 3 cycles (1–39) were delivered; 11 pts remain on study. Thirty-one pts discontinued protocol due to ASCT (N=15), relapse (N=9), physician/pt choice (N=3), induction death (N=1), death in CR (N=1), death with disease (N=1), or hospice (N=1). Grade ≥ 3 non-hematologic adverse events ($>5\%$) included febrile neutropenia (37%), pneumonia (33%), infections (17%), pain (10%), ALT increase (10%), fracture (10%), sepsis (9%), hypertension (7%), hypotension (7%), hyponatremia (7%), gait disturbance (7%), oral mucositis (7%), and pleural effusion (7%). In the R/R cohort, CR/CRi was 28% (N=13) with 33% (N=15) MLFS; 37% (N=17) proceeded to ASCT; median OS was 6.3mo (further data will be provided at the time of presentation). **Conclusions:** QUIZ+decitabine+VEN combination resulted in high CR/CRi, deep MRD responses, and encouraging survival in older pts with newly diagnosed *FLT3-ITD* AML. Clinical trial information: NCT03661307. Research Sponsor: None.

Revumenib as maintenance for AML following allogeneic stem cell transplantation.

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Background: Relapse after allogeneic stem cell transplantation (SCT) remains common in acute myeloid leukemia (AML). Revumenib is approved for relapsed/refractory (R/R) *NPM1*mt or *KMT2A*r acute leukemia however its safety and efficacy as post-SCT maintenance has not been characterized. We report outcomes of revumenib maintenance post-SCT in adult and pediatric patients (pts) at our institution. **Methods:** Pts with *NPM1*mt, *KMT2A*r or *NUP98*r AML could continue post-SCT revumenib maintenance following response pre-SCT to revumenib monotherapy or combination on clinical trial. Revumenib was resumed at pre-SCT dose with adjustment for azoles. **Results:** Twenty-one pts were included (11 adult, 10 pediatric); median age 20 years (range, 1 – 69), 62% female. Most (n = 16, 76%) had *KMT2A*r, 4 (19%) had *NPM1*mt, and 1 peds pt had *NUP98*r. Pre-SCT, revumenib was given as monotherapy per AUGMENT-101 (NCT04065399, n = 8) or Expanded Access (NCT05918913, n = 2) or with oral decitabine and venetoclax per SAVE (NCT05360160, n = 11). Pts received a median of 3 (1 – 11) prior therapies, 12 pts (57%) had prior SCT, and 4 pts received SAVE frontline. Maintenance post-SCT on SAVE was planned for 1 yr. At current SCT, 19% were in first complete remission (CR1 following SAVE), 81% were in CR2+ (SAVE or monotherapy). Median time to initiate post-SCT revumenib was 2.8 months (1.4 – 5.7) with median duration of therapy of 6.7 months (0.5 – 36). With a median follow-up of 18.2 months (95% CI 17.2 – 44.3), median overall survival (OS) and event-free survival (EFS) from SCT have not been reached; 1- and 2-year OS were 89%; 1- and 2-year EFS were 84% and 73%, respectively. The 1-year cumulative incidence of relapse (CIR) was 11% and death was 5%. In CR2+, 2-year OS was 93% and 1-year CIR was 13%. At last follow up, 29% remain on revumenib, and 71% have discontinued (relapse 14%, toxicity 14%, completion 14%, pt choice 14%, other illness 9%). The most common any grade adverse event (AE) was thrombocytopenia (86%; grade >3 43%), leading to dose modification in 48% and discontinuation in 10%. Graft-versus-host-disease occurred in 14% (grade >3 5%), however no other AE led to dose modification. Infections occurred in 14% (grade ≥3 10%); one pt discontinued due to grade 4 septic shock. No QTc prolongation was seen. In contrast, in a historical SCT cohort with the same genotypes treated prior to the advent of menin inhibitors (Table 1), pts transplanted at CR2+ had 2-year OS of 33% and 1-year CIR of 46%. **Conclusions:** Revumenib maintenance post-SCT was feasible in this heavily pretreated cohort. Thrombocytopenia was common often requiring dose modification, but no other significant toxicities were observed. Outcomes appear favorable compared to historical cohorts, supporting prospective evaluation of menin inhibition as maintenance. Clinical trial information: NCT04065399, NCT05918913. Research Sponsor: Syndax Pharmaceuticals.

Rev vs. historical cohort.

	N	1-yr OS (%)	2-yr OS (%)	1-year CIR (%)	Median F/U (mos)
Rev	21	89	89	11	18.2
Rev CR2+	17	93	93	13	33.3
Hist.	320	60	51	39	76
Hist. CR2+	124	45	33	46	92

Safety, tolerability, and efficacy of mesutoclax (ICP-248) in combination with azacitidine in patients with myeloid malignancies.

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Background: Venetoclax has been approved for the treatment of newly diagnosed acute myeloid leukemia (AML) in elderly or unfit pts but failed in the high-risk myelodysplastic syndromes (MDS). Mesutoclax is a novel, potent, highly selective BCL-2 inhibitor. It exhibits favorable pharmacokinetic profile without any major metabolites. **Methods:** ICP-CL-01205 (NCT06656494) is an ongoing, global, phase I study evaluating mesutoclax in combination with azacitidine (AZA) in pts with AML or MDS. In the dose escalation part, mesutoclax at 100 mg, 125 mg, and 150 mg in combination with AZA were evaluated for safety and tolerability. 100 mg and 125 mg were selected as Recommended dose for expansion (RDE) for further evaluation. Antitumor activity in AML and MDS is assessed based on ELN 2017 and IWG 2006/2023 criteria, respectively. Herein, we report safety, tolerability and efficacy for mesutoclax with AZA in pts with AML and MDS in this phase 1 study. **Results:** As of January 12, 2026, a total of 59 pts were enrolled including 8 R/R AML, 39 TN AML and 12 TN MDS. The median age of AML and MDS pts was 65 (range: 23, 81) and 67 years (range: 54, 75), respectively. Adverse risk per 2017 ELN was identified in 51.1% AML pts. Azole prophylaxis and G-CSF treatment were used in 5% and 22% pts. Among the 35 evaluable TN AML pts, 30 (85.7%) achieved composite CR (cCR, CR+CRi) with central assessment of CR rate of 65.7% (23/35). Among those who achieved cCR, 86.7% (26/30) were MRD negative per flow cytometry. MRD negative in CR (CR_{MRD-}) was 60% (21/35). cCR was 75% in adverse risk per 2017 ELN classification. The DOR rate at 3-months was 91.7%. The 6-month OS rate was 94.1%. Among 10 response evaluable TN MDS pts, the overall response rate (ORR) per IWG 2006 criteria was 100%, including CR in 20%, marrow CR in 80%. The composite CR rate was 70% per IWG 2023 criteria including 30% CR even when most pts only received 1 cycle treatment. There were no DLT or TLS events. The most common ($\geq 10\%$) grade ≥ 3 TEAEs in pooled analysis of 59 AML and MDS were neutrophil count decreased (62.7%), platelet count decreased (50.8%), anemia (33.9%), infection (16.9%), and lymphocyte count decreased (11.9%). There were 5.1% grade ≥ 3 febrile neutropenia and no TEAEs lead to dose discontinuation. SAEs were reported in 25.4% pts. For pts with TN AML, the median intervals between cycle 1 and cycle 2 initiation (requiring neutrophil $\geq 1 \times 10^9/l$ and platelet $\geq 100 \times 10^9/l$) was 39 days and the median duration of grade 4 neutropenia and thrombocytopenia were 17 and 9 days, respectively. **Conclusions:** The combination of mesutoclax and azacitidine demonstrated a favorable safety profile and encouraging anti-tumor activity not only in AML but also in MDS pts, supporting its continued development for the treatment of myeloid malignancies. These preliminary results warrant further investigation in larger, randomized trials. Clinical trial information: NCT06656494. Research Sponsor: None.

Safety and efficacy of eganelisib in adults with higher-risk myelodysplastic syndrome (HR-MDS) or relapsed/refractory (R/R) acute myeloid leukemia (AML).

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Background: The gamma isoform of PI3K (PI3K γ) directs a myeloid-specific signaling node (PI3K γ -AKT1-PAK1) identified as a core dependency in AML responsible for LSC self-renewal, medullary homing, and resistance to venetoclax and nucleoside analogues (Luo 2024; Gu 2024; Kelly 2024; Qiu 2025). Eganelisib is a highly potent isoform-specific inhibitor of PI3K γ that demonstrated safety and effective target modulation in solid tumors. Here we report results of a Phase I study of eganelisib monotherapy in R/R AML or HR-MDS using doses previously shown to be biologically active [NCT06533761]. **Methods:** Eligible patients had ECOG PS <2, R/R AML or IPSS-R Int-Very High risk MDS that was R/R to prior therapy with $\geq 10\%$ BM blasts. Eganelisib was administered orally in two cohorts of 45 mg and 60 mg QD in 28-day cycles. The primary endpoints were safety and efficacy per ELN 2022 (AML) and IWG 2023 (HR-MDS) and recommended dose for expansion (RDE). Additional endpoints included PK and PD effects assessed by AKT^{S273} phosphorylation in monocytes. **Results:** 15 patients have been treated to date (n=7, 45 mg; n=8, 60 mg); patient characteristics are summarized in the table below. There were no DLTs at either dose level. PD studies revealed dose-dependent reduction in AKT phosphorylation of ~90% at the 60 mg dose. Of the 10 patients who completed a 28-day cycle, anti-leukemic activity and evidence of clinical benefit was observed in 4 patients, including a CR in 1 patient at 45 mg. Three patients at 60 mg demonstrated anti-leukemic activity: 1 patient achieved <5% bone marrow blasts by flow cytometry, major cytogenetic response, rapid subclonal clearance, with full trilineage count recovery and low levels of persistent circulating blasts; two patients (both with TP53 mutations) with stable/decreasing marrow blasts had a progressive rise in neutrophils while on therapy. Longest duration of treatment is 5 cycles. Exposure to eganelisib was variable across both dose levels, and both doses showed overlapping plasma concentrations. **Conclusions:** Eganelisib demonstrates effective inhibition of PI3K γ with single agent activity in heavily treated, poor-risk patients, validating PI3K γ as a key vulnerability in MDS and AML. Importantly, eganelisib had no intrinsic hematologic toxicity, consistent with previous studies and pre-clinical observations that PI3K γ is dispensable for normal hematopoiesis. Given the capacity to potentiate activity of nucleoside analogues and venetoclax, combined therapy in previously untreated HR-MDS & AML patients at the RDE of 60 mg QD is planned. Clinical trial information: NCT06533761. Research Sponsor: Stelexis BioSciences, Inc.

	45 mg (n=7)	60 mg (n=8)	All (n=15)
Age (median/range)	78 (71-85)	59 (20-74)	72 (20-85)
AML MDS	7 0	7 1	14 1
Prior MDS or MDS-related changes	6	5	10
Prior therapies (median/range)	2 (1-3)	2 (1-6)	2 (1-6)
Adverse-risk ELN	86%	71%	79%
TP53 mutation	43%	43%	43%
Prior intensive chemo/venetoclax	14%/71%	50%/100%	33%/87%

First-in-human dual-epitope nanobody anti-CD5 CAR-T for relapsed/refractory T-ALL/PTCL: Phase I dose-escalation and expansion results from the CONQUER trial.

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Background: Patients with relapsed or refractory T-lymphoblastic leukemia/Peripheral T-Cell Lymphoma (R/R T-ALL/PTCL) experience dismal outcomes. Previously, we demonstrated naturally selected anti-CD7 CAR-T could overcome fratricide without gene editing or protein blockade, yielding encouraging clinical activity (Blood, 2022; 2025). CD5 is a critical pan-T-cell marker highly expressed in T-ALL/PTCL and represents a rational target beyond CD7. **Methods:** We developed SL105 injection, an autologous CD5-directed CAR-T cell product incorporating a tandem camelid-derived dual-epitope nanobody through a natural selection platform. This first-in-human phase I study evaluates the safety, preliminary efficacy, and recommended phase II dose (RP2D) of SL105 injection in patients with R/R T-ALL/PTCL (NCT06874946). **Results:** As of January 27, 2026, 37 patients provided informed consent; 18 patients received a single infusion of SL105 and completed the 28-day dose-limiting toxicity (DLT) assessment and constituted the enrolled population for analysis. Three dose levels (0.5, 1.0, and 2.0×10^6 CAR-T cells/kg) were evaluated, with a minimum of two patients with T-ALL/LBL or PTCL enrolled at each dose level. Median age was 32 years (range, 16–57); 33.3% had prior hematopoietic stem cell transplantation. Diagnoses included T-ALL/LBL (n=11) and PTCL (n=7). Median follow-up was 6 months (range, 2–11). No DLTs were observed, and the recommended RP2D was established at 2.0×10^6 CAR-T cells/kg. Median time to peak CAR-T expansion was 14 days by qPCR, with a median peak level of 6.3×10^4 copies/ μ g (range, $6-5.5 \times 10^5$). Cytokine release syndrome (CRS) occurred in 66.7% of patients; grade 2 CRS was observed in 21.7%, with no grade ≥ 3 CRS. One patient (5.5%) experienced grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS). Grade 1–4 early immune-cell-associated hematotoxicity (ICAHT) events occurred in 7 (38.9%), 2 (11.1%), 4 (22.2%), and 5 (27.8%) patients, respectively. EBV-related events occurred in 50% of patients, and CMV viremia in 33.3%. The best overall response rate (ORR) was 77.8% (14/18), including a CR/CRi/CMR rate of 61.1% (11/18) and PR with extranodal disease in 16.7% (3/18). All responding patients with bone marrow involvement achieved MRD negativity by flow cytometry. All four non-responders (two T-ALL/LBL and two PTCL) demonstrated low CAR-T expansion, with peak levels < 500 copies/ μ g genomic DNA. At the RP2D, ORR was 100%, with CR/CMR achieved in 85.7% (6/7). Five responding patients underwent consolidative allogeneic HSCT. **Conclusions:** SL105, an autologous dual-epitope nanobody CD5 CAR-T therapy, demonstrated a favorable safety profile and encouraging efficacy in R/R T-ALL/PTCL. The RP2D has been established, supporting further evaluation in an ongoing phase II study. Clinical trial information: NCT06874946. Research Sponsor: Beijing Research Ward Excellence Program; National key research and development plan of China.

A phase 2 study of fedratinib in patients with MDS/MPN and chronic neutrophilic leukemia.

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Background: MDS/MPNs are complex diseases that exhibit proliferative symptoms and aggressive clinical courses. Treatment options are limited. Ruxolitinib, a JAK1/JAK2 inhibitor, showed clinical benefit in pts with chronic neutrophilic leukemia (CNL) and atypical CML (aCML); yet survival remained poor (mOS 18.8 mo). Fedratinib (Fed) is a JAK2 inhibitor approved for MF that, compared to ruxolitinib, has a broader kinase inhibition profile which may provide enhanced efficacy in molecularly complex disease. Fed potently inhibits FLT3 and BRD4 and potently suppresses c-Myc, a critical upregulated pathway in MDS/MPN. Here, we present the primary results of NCT05177211 assessing the efficacy of Fed in pts with MDS/MPNs. **Methods:** NCT05177211 is a phase 2, multi-institutional study that enrolled pts with aCML, CNL, MDS/MPN-unclassifiable (MDS/MPN-U), and MDS/MPN-ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) who have splenomegaly (spleen volume > 450cc) and/or significant symptom burden (MPN TSS $\geq$ 10). The primary endpoint is overall response defined as complete/partial response or clinical benefit at 24 weeks per MDS/MPN IWG response criteria. Exploratory endpoints include progression-free survival (PFS), overall survival (OS), and duration of response (DOR). Fed was given at a dose of 400 mg daily on day 1–28 of 28-day cycles. **Results:** The data cutoff was 1/1/2026. Among 25 pts, 6 had aCML, 5 had CNL, 6 had MDS/MPN-RS-T, and 8 had MDS/MPN-U. Median age was 68.8 y. $\geq$ 3 mutations were present in 19 (76%) pts. Three (12%) pts remain on study. Median duration of treatment was 7.4 months. Eleven (44%) pts responded at week 24: 6 (30%) spleen responses (SVR35) and 9 (47%) symptom responses (TSS50). Four (25%) pts had both spleen and symptom response. Among 16 pts with splenomegaly treated for $\geq$ 24 weeks, spleen volume decreased by an average of 30% (+9% to -61%). Among 16 pts with symptomatic disease treated for $\geq$ 24 weeks, TSS improved by an average of -41% (range +35% to -80%). CSF3R mutations were enriched among pts with SVR35 (n = 4; 67%). Median PFS and OS were 36.9 mo (95% CI 19.3–NR) and 36.9 mo (95% CI 18.4–NR), respectively. Among responders, the duration of response was 7.6 mo (95% CI: 3.72–not reached). When stratified by diagnosis, OS for aCML, CNL, MDS/MPN-RS-T, and MDS/MPN-U was 19.8, 36.9, NR and NR, respectively. SAEs occurred in 13 (52%) pts. SAEs possibly related to Fed included acute kidney injury (n = 2), low thiamine (n = 1), colitis (n = 1), diarrhea (n = 1), arthralgias (n = 1), and edema (n = 1). Any grade nausea, vomiting, diarrhea, and constipation were seen in 52%, 16%, 44%, and 48% of pts, respectively. **Conclusions:** Fed demonstrates promising clinical efficacy in MDS/MPN and CNL pts with proliferative features. The safety profile is consistent with prior experience. Fed's unique kinase inhibition profile may provide a mechanism for enhanced effectiveness in this pt population. Clinical trial information: NCT05177211. Research Sponsor: BMS.

Updated efficacy and safety of olverembatinib (HQP1351) as second-line therapy in patients with chronic-phase chronic myeloid leukemia (CP-CML).

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Background: Olverembatinib is a third-generation BCR::ABL1 tyrosine kinase inhibitor (TKI) approved in China for chronic myeloid leukemia (CML) resistant/intolerant to ≥ 2 TKIs or with the T315I mutation. This study assessed olverembatinib as second-line treatment in patients with CP-CML resistant/intolerant to first-line TKIs without the T315I mutation. **Methods:** This single-arm, multicenter, open-label study enrolled patients (ECOG PS 0–2, adequate hepatic/renal function) who receive olverembatinib 40 mg orally every other day in 28-day cycles. Efficacy and safety were assessed every 3 cycles. The primary endpoint was complete cytogenetic response (CCyR) rate. **Results:** From August 4, 2022, through January 14, 2026, 47 patients were enrolled (91.5% first-line TKI resistant, 8.5% intolerant). The median age was 42.0 (19–70) years; 66.0% were male. Twelve (25.5%) received first-line imatinib, and 35 (74.5%) received first-line second-generation TKIs. Thirty-six (76.6%) had no baseline BCR::ABL1 kinase domain mutations, and 11 (23.4%) had non-T315I mutations. At data cutoff, 33 (70.2%) continued treatment, while 14 (29.8%) discontinued because of adverse events (n = 3), treatment failure (n = 4), progression (n = 2), or other reasons (n = 5). Among 42 evaluable patients, 76.2% achieved CCyR and 47.6% major molecular response (MMR). CCyR/MMR rates increased progressively: cycle 6 (57.5%/25.0%), cycle 9 (60.4%/33.3%), cycle 12 (75.0%/37.5%), cycle 15 (83.3%/46.7%), cycle 18 (89.3%/50.0%), cycle 21 (92.0%/64.0%), and cycle 24 (91.3%/60.9%). Complete hematologic response was achieved in 83.3% (15/18) and major cytogenetic response in 83.3% (35/42). Among 32 patients pretreated with first-line second-generation TKIs, 81.3% achieved CCyR and 50% MMR. The median treatment duration was 16.0 (6–38) cycles. Any-grade treatment-related adverse events (TRAEs) occurred in 42 (89.4%) patients; 21 (44.7%) had grade ≥ 3 TRAEs; and 6 (12.8%) had serious adverse events (SAEs). Nonhematologic TRAEs (mainly grade 1–2) included skin hyperpigmentation (51.1%), hyperuricemia (31.9%), and creatine phosphokinase increased (27.7%). Grade ≥ 3 hematologic toxicities included platelet count decreased (42.6%), neutropenia (25.5%), and anemia (8.5%). Olverembatinib-related SAEs included platelet count decreased (6.4%), anemia, myelosuppression, and pyrexia (2.1% each). Most hematologic TRAEs were manageable with supportive care. Two cardiovascular events (grade 1 hypertension) were possibly treatment-related. No deaths occurred. **Conclusions:** Olverembatinib shows good tolerability and leads to high MMR and CCyR in patients with CP-CML without T315I mutation that is resistant/intolerant to first-line TKIs. Clinical trial information: ChiCTR2200061655. Research Sponsor: None.

A prospective observational study to compare the efficacy, time toxicity, and cost of conventional 3+7 regimen versus azacitidine + venetoclax (AZA + VEN) as induction therapy in patients with acute myeloid leukemia (AML).

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Background: In low-middle income countries, 3+7 induction therapy for AML is associated with high induction mortality (7–40%), more so in patients with infections at diagnosis. Given the activity of AZA+VEN, a considerable proportion of patients with high-risk features (infections at diagnosis, poor-risk AML, poor performance status, multiple comorbidities, elderly) or long-waiting for admission to start induction are treated with AZA+VEN and 3+7 regimen use is limited to young, fit and good/intermediate risk groups. However, it is important to understand if use of AZA+VEN in this setting provides similar efficacy and is safe without increasing the cost of therapy and time-toxicity as defined by the contact days with healthcare system. Ideally a randomized controlled trial is needed to answer this question, however physicians' unwillingness to randomize patients at high-risk of induction mortality to 3+7 regimen would challenge the feasibility of such trial. **Methods:** A prospective observational study enrolled consecutive de-novo AML patients aged ≥ 18 -years after written informed consent who were planned for treatment by a multi-disciplinary joint clinic with either 3+7 or AZA+VEN. The primary endpoint was induction mortality, with secondary endpoints of grade 3/4 toxicity, treatment cost, time toxicity, complete response/complete response rate with incomplete count recovery rates (CR/CRi) assessed after one course. **Results:** 154 participants were included (3+7 -73, AZA+VEN-83). Median age was 35 years in 3+7 as compared to 44 years in Aza-Ven group. The AZA+VEN group was enriched for high-risk features – ECOG PS ≥ 2 (10.9% vs 33.3%), baseline fungal pneumonia (4.1% vs 50%), poor-risk profile as per ELN 2022 (12.3% vs 24.7%). The primary reasons for starting AZA+VEN were active infection (65.4%), poor-risk disease (28.4%), delay in admission (16%), and poor performance status (8.6%). Induction mortality was comparable between 3+7 and AZA+VEN (8.2% vs 7.5%). Toxicities were higher with 3+7; febrile neutropenia (95.9% vs 79.7%), new-onset bacterial infections (49.3% vs 19.0%) with multidrug resistant bacterial sepsis (32.9% vs 9.1%), and new-onset fungal pneumonia (27.4% vs 15.2%). The median treatment cost was higher with 3+7 (227,790 INR) compared to AZA+VEN (184,694 INR). Time toxicity (26.0 ± 0.8 vs 19.0 ± 0.9 days) and duration of hospitalization (26.0 ± 0.9 vs 18.0 ± 2.1 days) were higher in the 3+7. CR/CRi rates were higher with 3+7 (80.6% vs 57.1%), including higher CR (52.2% vs 27.1%) and flow-MRD negativity (71.6% vs 41.9%) driven by the favorable risk profile in this group. **Conclusions:** The study demonstrated that AZA+VEN in patients who are at high-risk of induction mortality provides a valuable alternative with better safety and reduced financial burden and time toxicity. Research Sponsor: None.

A randomized phase II study of selinexor added to standard induction and consolidation chemotherapy in adults with acute myeloid leukemia (AML).

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Background: Preclinical and early clinical data suggest that inhibition of nuclear export by the XPO1 inhibitor selinexor may enhance chemosensitivity in AML. We conducted a randomized phase II study evaluating the addition of selinexor to standard intensive induction and consolidation chemotherapy. **Methods:** This was an open-label, randomized (3:1) phase II trial in adults with newly diagnosed non-APL, AML. Good risk patients, those with FLT3 mutations or those with an indication for CPX-351 were excluded. Patients were assigned to standard induction with cytarabine and an anthracycline (7+3) followed by high-dose cytarabine (HDAC) consolidation (control arm) or the same regimen with the addition of selinexor (study arm). Selinexor was administered at a fixed dose of 60 mg orally on days 1, 3, 8, 10, 15, and 17 during induction and consolidation cycles. Randomization was not stratified. The primary endpoint was overall survival, analyzed in the intention-to-treat population. Secondary endpoints included overall response rate, complete remission with or without complete count recovery and safety. **Results:** A total of 57 patients were randomized (study arm n = 43; control arm n = 14). The study was discontinued early after results of the PARADIGM study raised concerns regarding the use of intensive chemotherapy in intermediate- and poor-risk AML patients. Baseline characteristics except for gender were generally balanced (Table 1). Median overall survival was 991 days in the study arm compared with 649 days in the control arm (log-rank p = 0.2267). Thirty-day mortality occurred in 5 patients (11.6%) in the study arm and 2 patients (14.3%) in the control arm. The response rate was 77% (33/43) in the study arm and 50% (7/14) in the control arm, corresponding to a risk ratio of 1.53 (95% CI, 1.01–4.57); this difference did not reach statistical significance by Fisher's exact test (p = 0.09). The addition of selinexor was feasible, with early mortality rates consistent with intensive induction therapy and no unexpected safety signals observed. **Conclusions:** In this randomized phase II study, the addition of selinexor to standard induction and consolidation chemotherapy was associated with numerically higher response rates and longer median overall survival compared with chemotherapy alone. Small study size and early termination limit definitive conclusions. However, these findings suggest biological activity of nuclear export inhibition in AML and support further evaluation of selinexor-containing combinations. Clinical trial information: NCT02835222. Research Sponsor: Karyopharm.

Characteristic	Control arm (n = 14)	Study arm (n = 43)
Median age, years (range)	69 (22–75)	65 (24–73)
Female sex, n (%)	11 (78.6%)	17 (39.5%)
ELN 2022 Risk group		
Good	5 (35.7%)	9 (20.9%)
Intermediate	3 (21.4%)	20 (46.5%)
Poor	6 (42.9%)	14 (32.6%)

Olverembatinib (HQP1351) combined with blinatumomab in patients with lymphoid blast phase chronic myeloid leukemia (CML-LBP) or Philadelphia chromosome-positive B-cell precursor acute lymphoblastic leukemia (Ph⁺ BCP-ALL).

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Background: Olverembatinib, a third-generation BCR::ABL1 TKI, has demonstrated clinical activity in TKI-resistant Ph⁺ hematologic malignancies. This study evaluated olverembatinib combined with blinatumomab in patients with relapsed/refractory (R/R) Ph⁺ B-cell precursor ALL (BCP-ALL) or CML-LBP outside China. **Methods:** In this phase 1b study (HQP1351CU101; NCT04260022), adults with R/R Ph⁺ BCP-ALL or CML-LBP received olverembatinib from 30 mg QOD, with planned escalation to 40 mg QOD, combined with standard-dose blinatumomab in 6-week cycles. Using a 3+3 design, dose-limiting toxicities (DLTs) were assessed during cycle 1. Objectives included evaluation of safety and tolerability, complete response (CR) rate, and minimal residual disease (MRD) negativity rate. MRD was assessed by flow cytometry. **Results:** Between January 2023 and June 2025, 9 patients were enrolled (8 Ph⁺ BCP-ALL, 1 CML-LBP). Median age was 47 years (range 32–60); 66.7% were male. Median time from diagnosis to olverembatinib treatment initiation was 2.46 (range 0.5–6.2) years; median leukocyte count $3.5 \times 10^9/L$ (range 2–171); median prior regimens 4 (range 2–10); and median TKIs 3 (range 1–6). BCR::ABL1 transcripts were P190 (n = 7), P210 (n = 2); one patient had the T315I mutation. Notably, 6 patients had received prior blinatumomab and relapsed during maintenance or subsequent therapy. The combination demonstrated a manageable safety profile, with most adverse events (AEs) being grade 1–2, consistent with the known toxicities of each agent. Four patients experienced grade 3 AEs related to olverembatinib, including increased lipase, neutropenia, thrombocytopenia, and pancreatitis. In the 30 mg QOD cohort (n = 3), no DLTs occurred. One patient in the 40 mg QOD cohort developed grade 3 pancreatitis (considered treatment related and a DLT) on day 4, which resolved with supportive care and dose reduction to 30 mg without recurrence; this patient achieved CR and MRD negativity by end of cycle 1. With median olverembatinib treatment duration of 15.7 weeks (range 1.4–37.1), 4 patients discontinued because of disease progression (n = 1) or bridge to CAR-T/transplantation (n = 3). Among 9 enrolled patients, 5 had positive MRD at study entry without CR. In this subgroup, 4 achieved CR and 2 achieved MRD negativity. One patient died due to disease progression, assessed as unrelated to study treatment. **Conclusions:** Olverembatinib combined with blinatumomab shows promising clinical activity in patients with R/R Ph⁺ BCP-ALL or CML-LBP outside China, with encouraging response rates and MRD clearance. The regimen was generally well tolerated, with a safety profile consistent with individual agent toxicities. These findings support further investigation of this chemotherapy-free approach. Clinical trial information: NCT04260022. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

Updated results of the chemotherapy-free regimen of blinatumomab and ponatinib in patients with newly diagnosed Philadelphia-positive B-cell acute lymphoblastic leukemia.

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Background: Chemotherapy-free regimens incorporating blinatumomab (blina) and ponatinib have demonstrated promising activity in frontline Philadelphia-positive (Ph+) B-cell acute lymphoblastic leukemia (B-ALL). We report the long-term outcomes from an ongoing, phase II study of blina with ponatinib in adults with newly diagnosed (ND) Ph+ B-ALL. **Methods:** Patients (pts) ≥ 18 yrs with Ph+ B-ALL received up to 5 simultaneous cycles of blina with ponatinib 30 mg daily, reduced to 15 mg daily upon complete molecular response (CMR). Pts continued ponatinib for at least 5 yrs. IT chemo was increased from 12 to 15 with pt #64 to reduce the risk of central nervous system (CNS) relapse. Protocol was amended to add 2 cycles of high-dose methotrexate (MTX) and cytarabine for pts with WBC $> 70 \times 10^9/L$. **Results:** As of January 2025, 88 pts were enrolled (median age of 50 yrs [range, 18–83]; 19% > 70 yrs). Median baseline WBC was $15.2 \times 10^9/L$ (0.6–322). 78% of pts had BCR::ABL1 p190 transcripts, 20% had p210. 25 out of 48 pts (52%) with SNP array testing had IKZF1+ genotype. The objective response rate was 96%, with a complete remission (CR) rate of 95%. Measurable residual disease (MRD)-negativity by next-generation sequencing (NGS) was achieved in 95% of evaluable pts; 43% after 1 cycle. CMR rates by RT-PCR was 83%, 67% after 1 cycle. Median follow-up was 3 yrs. 70 pts (79%) remain in molecular remission without allogeneic stem cell transplant (SCT). Of these, 1 received inotuzumab for MRD-positivity and 1 received CAR T-cell therapy. 2 pts (2%) went to SCT in CR1 due to persistent positive p190 transcripts; neither pt had NGS-MRD available. 11 pts (12%) relapsed (10 with p190 transcripts) after a median of 20 months (8–33) from CR: 5 were bone marrow only, 5 CNS only, and 1 extramedullary only; 7/11 relapsed pts (64%) had baseline WBC $> 70 \times 10^9/L$. Three of the 11 relapsed pts died. There were 2 early deaths, and 3 pts died in CR. Since increasing IT chemo to 15, there has been 1 CNS relapse. 3 pts received 2 cycles of high-dose MTX and cytarabine for WBC $> 70 \times 10^9/L$; none have relapsed. Median event-free survival (EFS) and overall (OS) have not yet been reached; 3-yr EFS and OS rates are 79% and 89%, respectively. Outcomes did not differ significantly by transcript type nor by NGS MRD clearance after C1. For pts with WBC $\geq 70 \times 10^9/L$ vs. WBC $< 70 \times 10^9/L$, the 3-yr cumulative incidence of relapse (CIR) was 31% vs. 6.7% ($p=0.005$). The CIR for IKZF1+ vs non-*IKZF1*+ was 16% vs. 21% ($p=0.6$). **Conclusions:** Frontline blina with ponatinib induced deep, durable remission in Ph+ B-ALL, allowing most patients to avoid SCT. Relapses are seen with high presenting WBC, supporting the use of baseline-risk intensified strategies, including increased IT chemo, incorporation of high-dose chemo into consolidation, as well as CAR T-cell therapy. Clinical trial information: NCT03263572. Research Sponsor: Amgen; Takeda Oncology.

Long-term outcomes with addition of inotuzumab ozogamicin to HCVAD and sequential blinatumomab in adults with newly diagnosed B-ALL.

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Background: Despite high remission rates with intensive chemotherapy and blinatumomab (blina) in newly diagnosed (ND) Philadelphia-negative (Ph-) B-ALL, relapse remains a major cause of treatment failure. Inotuzumab ozogamicin (InO) demonstrates efficacy in the relapsed setting and may improve outcomes in frontline. We report long-term results with 4.5 years of follow-up from the phase II study of HCVAD plus blina +/- InO for adults with ND Ph- B-ALL. **Methods:** Patients (pts) 18-59 years (yrs) with ND Ph- B-ALL received HCVAD alternating with high-dose methotrexate (MTX) and cytarabine (Ara-C) for up to 4 cycles, followed by 4 cycles of blina. Blina was initiated after 2 cycles of HCVAD for pts with high-risk features or persistent measurable residual disease (MRD) by multiparameter flow cytometry (FC). Starting with pt #39, InO was administered during the 2 MTX/Ara-C cycles and 2 blina cycles. Pts received 15 maintenance cycles with POMP and blina after every third cycle. Pts received 12 IT chemotherapies. **Results:** As of January 2025, 75 pts were treated (38 without InO [cohort 1] and 37 with InO [cohort 2]). The median age was 33 yrs (range, 18-59); 37 for cohort 1 (18-59) and 25 (18-57) for cohort 2 ($p=0.01$). All other characteristics were similar. All pts (100%) achieved complete remission (CR). MRD-negativity by FC was achieved in 95% of pts at any time (66% at CR): 97% (76%) in cohort 1 and 94% (56%) in cohort 2. By next generation sequencing (NGS), 76% achieved MRD-negativity (26% at CR): 50% in cohort 1 and 79% in cohort 2. There were no early deaths. The median follow-up for cohorts 1 and 2 was 76 months (28-109) and 47 months (31-61), respectively. Of the 38 pts in cohort 1, 14 (37%) proceeded to allogeneic stem cell transplantation (SCT); of these, 11 (79%) remain alive in CR, 1 (7%) died in CR and 2 relapsed, 1 of which died. A total of 24 pts (63%) did not proceed to SCT; of these, 16 (67%) remain alive in CR, 3 (13%) died in CR, and 5 (20%) relapsed, 4 of which died. Of the 37 pts in cohort 2, 10 (27%) proceed to SCT; all alive in CR. A total of 27 pts (65%) did not proceed to SCT; 24 (89%) remain alive in CR (1 pt received CAR T-cell) and 3 (11%) relapsed, all of them alive in CR2. Median OS and event-free survival (EFS) have not been reached for either cohort. 4-year OS rates for the entire cohort, cohort 1 and cohort 2 are 91%, 82% and 100% ($p=0.007$), respectively, with 4-year EFS rates of 83%, 74%, and 91% ($p=0.034$), respectively. At 24 months, CIR was with InO vs without InO (8.1% vs 18.4%; $p = 0.18$). No deaths were observed in the InO group, whereas pts without InO had a 24-month cumulative incidence of death of 7.9% ($p = 0.08$). **Conclusions:** Incorporation of InO into frontline HCVAD with sequential blina is associated with improved survival and durable remission in adults with ND Ph- B-ALL, supporting its role in the frontline setting. Confirmatory randomized trial comparing HCVAD-blina to HCVAD-blina-InO is ongoing. Clinical trial information: NCI-2017-00596. Research Sponsor: Amgen; Pfizer.

The impact of MRD and post-remission strategies on outcomes following dose-dense mini-hyper-CVD inotuzumab and blinatumomab in relapsed B-cell acute lymphoblastic leukemia.

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Background: Advances in immunotherapy have improved outcomes for relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL). However, the optimal sequence of immunotherapies remains undefined, particularly the role of chimeric antigen receptor (CAR) T-cell therapy in the era of sensitive assessment of measurable residual disease (MRD). Here, we provide an update of the phase II trial the dose dense mini-CVD with inotuzumab ozogamicin (InO) and blinatumomab (blina) regimen in R/R B-ALL. **Methods:** Adults (>18 years) with R/R Philadelphia (Ph) positive (+) or negative (-) B-ALL were treated with dose-dense mini-hyper-CVD with InO and blina. Cycles 1, 3, 5 consisted of mini-hyper-CVD, InO and blina; cycles 2, 4, 6 consisted of mini-methotrexate and ara-C, InO, and blina with Peg-G-CSF administered after each course. Patients (Pts) received 12 IT chemotherapy administrations and rituximab if CD20 positive. Pts with Ph+ ALL received a concomitant BCR::ABL1 tyrosine kinase inhibitor. MRD was assessed by flow cytometry (FC) and next-generation sequencing (NGS). **Results:** Between September 2021 and January 2026, 27 pts were enrolled (median age 42 years; range, 19–63). Three pts (11%) had Ph+ ALL, and among Ph- pts, 30% had Ph-like disease. Five pts (19%) had adverse risk cytogenetics and (24%) had a TP53 mutation. Twenty-four pts (89%) were in salvage 1. Three pts (11%) had previously undergone allogeneic stem cell transplant (SCT) and 9 (33%) had received blina. All pts achieved complete remission (CR) or CR with incomplete count recovery (CRi), including 22 (81%) CR. MRD negativity was achieved in 96% of pts by FCM and 95% by NGS; 80% and 44% achieved FCM and NGS MRD negativity, respectively, after the first cycle. With a median follow-up of 32 months, 11 pts (41%) proceeded to CAR T-cell consolidation, 5 (18%) to SCT, and 11 (41%) received no further consolidation. Among CAR T recipients, 70% were NGS MRD-negative prior to lymphodepletion. Post CAR T-cells infusion, 10/11 (91%) pts achieved/maintained NGS MRD negativity, while 1 (9%) pt had MRD below level of detection at last follow-up. The 2-year overall survival (OS) and event-free survival (EFS) rates for the entire cohort were 68% and 79%, respectively. The 2-year EFS rates for pts receiving CAR T-cell, ASCT, or no further consolidation were 81%, 80% and 50%, respectively, while the corresponding 2-year OS rates were 89%, 100%, and 55%. **Conclusions:** Dose-dense mini hyper-CVD combined with InO and blina induces high rates of deep NGS-MRD negative remission in patients with R/R B-ALL, allowing for consolidative strategies including CAR T-cell therapy, leading to favorable survival outcomes at a follow-up of almost 3 years. Clinical trial information: NCT01371630. Research Sponsor: Amgen.

The effect of obecabtagene autoleucel (obe-cel) on adult patients (pts) with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) and extra-medullary disease (EMD).

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Background: Pts with R/R B-ALL and EMD have limited treatment options and are a population with an unmet need. Obe-cel is an autologous chimeric antigen receptor (CAR) T-cell therapy with a fast off-rate CAT19 binding domain and a 4-1BB- ζ co-stimulatory domain designed to improve persistence and reduce severe immunotoxicity. Here, we report a post-hoc analysis of the Phase Ib/II FELIX study (NCT04404660), evaluating efficacy and safety of obe-cel in pts with R/R B-ALL, by EMD status at lymphodepletion (LD). **Methods:** Following LD, adults with R/R B-ALL 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 [CRI]), event-free survival (EFS), overall survival (OS), and safety are reported for pts with or without (w/o) EMD. **Results:** Of 127 obe-cel infused pts, 27 (21%) had EMD at LD and 100 (79%) did not. At screening, the median age (range) was 36.0 years (20–73) in pts with EMD, and 50.5 years (20–81) in pts w/o EMD. Of the pts with EMD, 13 (48%) were male and 11 (41%) were Hispanic or Latino; of those w/o EMD, 53 (53%) were male and 27 (27%) were Hispanic or Latino. The median number of prior lines of therapy (range) was 3.0 (1–6) and 2.0 (1–6) for pts with and w/o EMD at LD, respectively; prior SCT was received by 12 (44%) and 44 (44%) pts, respectively. At LD, the median bone marrow (BM) blast percentage (range) was 54% (0–100) in pts with EMD and 39% (0–100) in pts w/o EMD; Philadelphia chromosome-positive disease was observed in 6 (22%) and 30 (30%) pts, respectively. At 32.8 months' (mos) median follow-up (range 20–53), the ORR (95% confidence interval [CI]) was 59% (39–78) in pts with EMD and 83% (74–90) in pts w/o EMD. Median DoR (95% CI) among responders was 42.5 mos (3.4–not evaluable [NE]) and NE, in those with (n=16) and w/o (n=83) EMD at LD, respectively. Overall, median EFS (95% CI) was 4.5 mos (0.0–NE) and 14.3 mos (9.0–NE) in pts with and w/o EMD at LD, respectively; however, median EFS appeared to be comparable in responders with (44.6 mos [6.0–NE]) and w/o EMD (NE). Overall, median OS (95% CI) was 15.3 mos (7.9–NE) and 21.0 mos (13.2–NE) in pts with and w/o EMD at LD, respectively. The incidence of Grade $\geq$ 3 cytokine release syndrome in pts with and those w/o EMD was 3.7% and 2.0%; the incidence of Grade $\geq$ 3 immune effector cell-associated neurotoxicity syndrome was 19% and 4.0%, respectively. Cerebrospinal fluid pharmacokinetic analyses are underway; data will be presented. **Conclusions:** Obe-cel treatment demonstrated favorable efficacy and safety outcomes in pts with and w/o EMD in the FELIX trial. Among responders, DoR in pts with EMD was comparable with that observed in pts w/o EMD. Overall, these findings support a positive benefit-risk profile for obe-cel, irrespective of EMD status at LD. Clinical trial information: NCT04404660. Research Sponsor: Funding: Autolus Therapeutics PLC. Third-party medical writing assistance, under the direction of the authors, was provided by Emily Fang, MPharm, of Ashfield Med-Comms, an Inizio company, and was funded by Autolus Therapeutics PLC.

Early G-CSF after venetoclax-based induction for acute myeloid leukemia: Multi-center associations with infections, neutrophil recovery, and early mortality.

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Background: Venetoclax-based induction has improved remission rates in acute myeloid leukemia (AML) but is associated with prolonged neutropenia and infectious mortality. Optimal G-CSF timing remains uncertain. **Methods:** Multicenter real-world cohort (2018–2025) using TriNetX data across 21 U.S. institutions. Adults with newly diagnosed AML treated with venetoclax + hypomethylating agent or low-dose cytarabine were included. Early G-CSF was defined as initiation $\leq$ day 7 of cycle 1; deferred/none = $>$ day 7 or none. The primary endpoint was grade ≥ 3 infection through day 42 (death as a competing risk, Fine–Gray models). Secondary endpoints: febrile neutropenia (FN), time to ANC $\geq 1.0 \times 10^9/L$, ICU admission $\leq$ day 42, 60-day mortality, CR/CRi by day 60, and overall survival (OS). Multivariable models adjusted for age, ECOG, ELN risk, cytogenetics, baseline ANC/WBC, TP53/IDH/NPM1 mutations, antibacterial prophylaxis, and center effects. **Results:** N = 2,934; median age = 69 y (range 34–87). Early G-CSF = 39 %, deferred/none = 61 %. Early G-CSF lowered grade ≥ 3 infections (sHR 0.61 [95 % CI 0.49–0.76], $p < 0.001$) and shortened ANC recovery ($\Delta -3.2$ days [-4.6 to -1.9], $p < 0.001$). FN risk was similar (aOR 0.94 [0.79–1.12], $p = 0.49$). CR/CRi by day 60 (aOR 1.06 [0.90–1.25], $p = 0.47$), OS (aHR 0.97 [0.85–1.11], $p = 0.65$), and 60-day mortality (aOR 0.92 [0.73–1.16], $p = 0.49$) were comparable. Findings persisted in age ≥ 75 and ELN-adverse subsets and remained robust after inverse-probability weighting and landmark analyses. **Conclusions:** Early ($\leq$ day 7) G-CSF after venetoclax-based AML induction reduced severe infections and accelerated neutrophil recovery without affecting remission or survival. Results support standardized early G-CSF use to improve supportive-care safety, especially for older or high-risk patients. Research Sponsor: None.

Early G-CSF timing and clinical outcomes after venetoclax-based AML induction.

Outcome	Deferred/None	Early G-CSF	Adjusted effect (95 % CI)	P value
Grade ≥ 3 infection $\leq$ day 42, %	31.4	21.2	sHR 0.61 (0.49–0.76)	<0.001
Time to ANC ≥ 1.0 (days, median)	11.8	8.6	$\Delta -3.2$ (-4.6 to -1.9)	<0.001
Febrile neutropenia, %	38.9	37.4	aOR 0.94 (0.79–1.12)	0.49
ICU admission $\leq$ day 42, %	14.6	11.9	aOR 0.80 (0.65–0.99)	0.04
60-day mortality, %	10.1	9.3	aOR 0.92 (0.73–1.16)	0.49
CR/CRi by day 60, %	63.8	64.9	aOR 1.06 (0.90–1.25)	0.47

Abbreviations: sHR = sub-hazard ratio; aOR = adjusted odds ratio; aHR = adjusted hazard ratio; Δ = difference in medians. All models adjusted for baseline covariates (age, ELN risk, ECOG, cytogenetics, molecular subtype, prophylaxis use) and center effects.

Molecular landscape and outcomes of Black and White adults diagnosed with acute myeloid leukemia.

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Background: Acute myeloid leukemia (AML) is characterized by poor survival with Black patients (pts) experiencing worse outcomes compared to White pts. While patient-specific factors such as race have emerged as important predictors for survival in AML, the biologic mechanisms driving these factors are not well characterized. Here, we analyzed the molecular profiles of adults diagnosed with AML to identify potential differences in the frequency of genes commonly mutated in AML and their impact on survival. **Methods:** This was a retrospective cohort study of adults diagnosed with AML at the Cleveland Clinic between 2008 and 2022. Patients were identified as Black or White based on self-reported race/ethnicity. Molecular data were obtained from next-generation sequencing (NGS) performed at the time of diagnosis. Survival analysis was limited to pts receiving intensive induction chemotherapy and estimated using the Kaplan-Meier method and compared with the log-rank test. **Results:** 1,144 pts were included in this study: 10% (n = 115) Black and 90% (n = 1029) White. Median age at diagnosis (years) was lower in Black pts compared to White pts (62 vs 66) (p = 0.005). Cytogenetics analysis (MRC 2010) showed a higher proportion of Black pts with favorable-risk disease compared to White pts (15% vs. 8%; p = 0.04) while rates of poor-risk cytogenetics were similar (31% vs. 30%). Mutations in *IDH1*, *CBL*, *CEBPA*, and *NOTCH1* were more common in Black pts than in White pts (p < 0.05). Conversely, mutations in *NPM1* were lower in Black pts (16%) vs. White pts (24%) (p = 0.22). We did not observe a difference in the type of induction chemotherapy received (p = 0.23). However, more White pts underwent hematopoietic cell transplant (HCT) compared to Black pts (32% vs. 21%; p = 0.02). The median overall survival (OS) for the whole cohort was 18 months (95% CI: 16-21 months) with a 5-year OS of 31% (95% CI: 27-34%); median follow up time of 63 months. Univariable analysis showed that worse overall survival was associated with older age, poor risk cytogenetics, therapy-related and secondary AML, and not undergoing HCT (p < 0.05), but median OS and 5-year OS rates were similar between Black and White pts (24 months, 28% vs. 17 months, 31%). After adjusting for prognostic variables, age, HCT status and cytogenetic risk remained significant (p < 0.05). **Conclusions:** Unlike previously reported studies, we did not observe a survival disparity in race in our study cohort. However, we observed lower rates of treatment with HCT in Black pts. We also identified a higher frequency of mutations in genes involved in myeloid transcriptional regulation, epigenetic modification, and cellular signaling. Adequate assessment of the prognostic relevance of these genes is limited by a small sample size and variability in NGS platforms over time. Future studies may explore pooled genetic data across several institutions and genetic ancestry testing over self-reported race/ethnicity. Research Sponsor: None.

The association of *IDH* co-mutations with treatment outcomes and overall survival in *TP53*-mutated acute myeloid leukemia.

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Background: In acute myeloid leukemia (AML), *TP53* mutations confer a dismal prognosis, with a median survival of ~6 months. While characteristics of *TP53* aberrancy (multi-hit status) define an even more aggressive subset, little is known about the effect of *IDH* co-mutations on outcomes. An analysis of the Consortium on Myeloid Malignancies and Neoplastic Diseases (COMMAND) cohort suggests that *TP53*+/*IDH*+ subjects (n = 24) have prolonged survival compared to *TP53*+/*IDH*wt, a finding that could inform our treatment approach in these patients. We therefore aimed to validate this finding in a larger cohort within the Flatiron Health Research Database. **Methods:** Patients over 18 years with *TP53*+ AML and *IDH*1 or 2 testing at diagnosis were selected within Flatiron Health. Demographics, cytogenetic/molecular testing, and treatments were compared using standardized mean difference (SMD), with SMD > 0.2 indicating meaningful difference. Cox proportional hazards models controlling for age, sex, socioeconomic status, ECOG, multi-hit *TP53*, secondary AML, and induction strategy were built to test the association of *IDH* co-mutations with Event Free Survival (EFS) and overall survival (OS). Sensitivity analyses considering receipt of an *IDH* inhibitor (*IDHi*) and stem cell transplant (SCT) as time-varying covariates were also constructed. Finally, two subgroup analyses in the *IDH*+ subcohort were performed to test associations between 1) *IDHi* in first line, and 2) hypomethylating agent/venetoclax (HMA/ven) in first line, and EFS and OS. **Results:** 753 *TP53*+ AML subjects with *IDH* testing at diagnosis were included. There were meaningful differences in the cytogenetic/mutational landscape of the *IDH*wt (n = 659) and *IDH*+ (n = 94) cohorts, the latter with a lower incidence of multi-hit *TP53* and myelodysplasia-related changes, and a higher incidence of *ASXL1*, *DNMT3A*, and *TET2* co-mutations. In multivariable modeling, *IDH* co-mutations were not independently associated with EFS, though were strongly associated with improved overall survival (mOS 9.8 vs 6.1 months, HR 0.69, CI 0.52 – 0.92, p = 0.01). These associations persisted in sensitivity analyses treating *IDHi* and SCT as time-varying covariates. In analyses of the *IDH*+ subcohort, receipt of *IDHi* or HMA/ven during first line did not associate with improved OS or EFS. **Conclusions:** In these data, *IDH* co-mutations are associated with improved OS in *TP53*+ AML, though there was no signal suggesting this was driven by choice of therapy. Our analysis is limited by its retrospective nature and a definition of “multi-hit” status that relied on concomitant presence of del17 and a *TP53* point mutation. Though these results require further validation, they may currently inform the clinical approach to *TP53*+/*IDH*+ AML by framing goals-of-care conversations. However, more work is needed to characterize the effect of treatment selection on outcomes in this population. Research Sponsor: None.

A targeted phosphoproteomic assay to enable the prediction of response to intensive chemotherapy in acute myeloid leukemia.

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Background: Intensive chemotherapy (IC; cytarabine plus an anthracycline) remains a standard first-line therapy for fit patients with acute myeloid leukemia (AML), a heterogeneous hematologic malignancy with poor long-term survival. IC induces composite complete remission (cCR) in ~60–70% of cases, and IC response variability persists within genetic/ELN risk strata. As emerging regimens increasingly challenge IC as a default therapy, biology-informed predictors are needed to identify patients unlikely to benefit from IC to avoid unnecessary toxicity. Mass spectrometry (MS)-based phosphoproteomics enables quantitative profiling of phosphopeptides (PPs) from patient samples, providing a functional readout of tumor biology. Thus, we sought to develop a PP-based clinically-deployable assay, orthogonal to genetic risk stratification, to predict response to IC in AML. **Methods:** 261 retrospective samples were collected from patients with newly-diagnosed AML (Table) treated with standard “7+3” IC in 9 centers in Europe, Australia, and North America. Response was assessed at the end of induction by the treating physician. Samples underwent phosphoproteomics using: 1) global MS for biomarker discovery or 2) targeted, clinically-compatible MS for validation. Predictive model performance was evaluated using rebalanced leave-one-out cross-validation. **Results:** During discovery, 3205 PPs were detected. Using Bayesian approaches, we identified an 80-PP multi-analyte signature of IC response (refractory vs cCR), and achieved an AUROC of 0.68 (95% CI 0.54–0.83). The signature was enriched for DNA damage signalling and repair (DNA-PK-S2612, ATM/cohesin, nucleotide excision and double-strand break repair proteins), and cellular stress pathways (phospho-p38, IL-16, AP-1/c-Jun). In an independent validation cohort, the targeted assay reliably detected the biomarker set and preserved its association with outcome (AUROC 0.69; 95% CI 0.53–0.84). Biomarker-based classification was associated with improved event-free survival (HR 0.45; 95% CI 0.26–0.78). **Conclusions:** We identified and validated a signature of response to IC in AML, and translated it into a targeted, clinically-deployable assay. This approach captures signaling states relevant to IC mechanisms of action that are not directly inferred from standard clinical or genetic variables. Ongoing analyses are evaluating its relationship to established genetic and ELN risk stratification. These findings support diagnostic phosphoproteomics and suggest functional biomarkers may complement existing approaches for treatment selection in AML. Research Sponsor: Innovate UK; Application number: 10054602.

Cohort characteristics.		
Cohort	Discovery	Validation
Median age at diagnosis (years, quartiles)	54 (23, 65)	59 (47, 68)
Median diagnosis year (range)	2014 (1999, 2023)	2013 (2001, 2024)
No of patients/samples	135/165	102/106
No of cCR/Refractory	94/41	79/23
PPs	3205	80

Investigation of the role of IFITM3 and the PI3K/Akt axis in the acute myeloid leukemia tumor microenvironment.

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Background: Interferon-induced transmembrane protein 3 (IFITM3) is overexpressed in acute myeloid leukemia (AML) and is associated with poor prognosis. Previous studies have implicated IFITM3 in oncogenic processes and immune modulation; however, the mechanisms through which IFITM3 contributes to leukemogenesis and shapes the immune microenvironment in AML remain unclear. **Methods:** The clinical and immunological significance of IFITM3 in AML was analyzed using scRNA-seq and bulk transcriptomic datasets. IFITM3-knockdown Kasumi-1 and ME-1 cells were established to evaluate their impact on cell proliferation and cycle progression via MTT and flow cytometry. A Transwell co-culture system was employed to assess AML-induced M0 macrophage polarization, quantified by surface markers (CD80/CD163) and cytokine profiling (ELISA/qRT-PCR). Mechanistically, GSEA were performed to identify downstream pathways, followed by Western blot validation. The functional role of the PI3K/Akt axis was further verified using the specific inhibitor LY294002. **Results:** Our results revealed for the first time that IFITM3^{high} AML cell lines polarize M0 macrophages into an M2-like phenotype. Knockdown of IFITM3 led to a significant reduction of the M2 marker CD163, accompanied by an increase of the M1 marker CD80. In parallel, IFITM3-deficient AML cells exhibited decreased M2-associated gene expression and diminished secretion of TGF- β and IL-10, together with lower viability and G0/G1 cell-cycle arrest. Molecular mechanism studies revealed that loss of IFITM3 markedly reduced Akt and p-Akt protein levels. Crucially, pharmacological inhibition of the PI3K/Akt pathway using a PI3K inhibitor rescued the IFITM3-mediated effects, suppressing AML cell proliferation and M2 macrophage polarization. Clinically, we extended the adverse prognostic effect of IFITM3 to AML patients with intermediate molecular risk. **Conclusions:** These findings provide comprehensive evidence that IFITM3 promotes leukemic cell proliferation and contributes to a tumor-supportive AML microenvironment by driving M2 macrophage polarization via the PI3K/Akt signaling axis. These results highlight IFITM3 as a promising therapeutic target and suggest that PI3K inhibitors may offer a precision medicine approach for AML patients with elevated IFITM3 expression. Research Sponsor: None.

Association of acute myeloid leukemia (AML) patient, disease, and molecular characteristics with a long-term (LT) response to olutasidenib.

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Background: Mutations in isocitrate dehydrogenase 1 (*mIDH1*) occur in 7%-14% of patients with AML. Olutasidenib is a potent, oral small-molecule *mIDH1* inhibitor that selectively inhibits *IDH1* variants but preserves wild-type *IDH1* function. The registrational phase 2 trial (NCT02719574) of olutasidenib in patients with relapsed/refractory (R/R) *mIDH1* AML reported a complete remission (CR)/CR with partial hematologic recovery (CRh) rate of 35% and a median CR/CRh duration of 25.3 mo. This analysis examines patient, disease, and molecular characteristics of patients with a LT CR/CRh response to olutasidenib without transplant. **Methods:** Adults with R/R *mIDH1* AML treated with olutasidenib 150 mg twice daily who had a CR/CRh and a duration of response (DOR) >12 mo were included. Overall survival (OS), DOR, event-free survival (EFS), and adverse events (AEs) were assessed. Univariate and multivariate logistic regression analyses were used to examine baseline factors that predicted DOR >12 vs ≤12 mo. **Results:** Of 147 evaluable patients, 51 (35%) achieved a CR/CRh; of these, 32 (63%) maintained a CR/CRh >12 mo. Excluding 6 patients who proceeded to transplant, 26 (51%) had a DOR >12 mo (Table). Among these patients at baseline, median age was 72 y; 69% were female; 73% had an R132C mutation; 12% had prior venetoclax; 88% were platelet transfusion independent (TI); 73% were red blood cell (RBC) TI. Patients had a median (range) of 2 (0, 5) comutations, most commonly *DNMT3A* (n=6) or *NPM1* (n=5); 2 patients with *NPM1* also had *FLT3* mutations. Median (95% CI) time to response was 1.9 (1.0, 1.9) mo. Median OS and EFS were not reached. Estimated 48-mo OS was 74% (95% CI: 51%, 88%). Estimated 48-mo EFS was 69% (95% CI: 47%, 83%). 5 (19%) patients relapsed (including 1 after 24 mo); 10 (38%) patients were on treatment at data lock. Significant predictors of response >12 vs ≤12 mo by multivariate analysis were relapsed AML vs refractory AML (odds ratio [OR]: 0.19) and female sex (OR: 0.21). Age, number of comutations, *mIDH1* variant, RTK pathway mutations, number of prior therapies, and baseline TI were not significant predictors. Common AEs were nausea (35%), increased ALT, asthenia, constipation, and cough (31% each). Common grade ≥3 AEs were increased ALT, gamma glutamyltransferase increased (19% each), and RBC count decreased (15%). 9 (35%) patients experienced grade ≥3 all-cause AEs after 12 mo (only 1 AE in >1 patient [Coronavirus infection]). **Conclusions:** Olutasidenib enabled LT CR/CRh in half of R/R *mIDH1* AML patients with CR/CRh without transplant (longest response >54 mo). Multivariate analysis identified relapsed (vs refractory) AML and female sex but not baseline TI or molecular factors as a significant predictor of LT response with olutasidenib. Clinical trial information: NCT02719574. Research Sponsor: Rigel Pharmaceuticals, Inc.

Patients with LT response.

DOR Group	Patients, n (%)
>12 mo	26 (100)
>24 mo	19 (73)
>36 mo	15 (58)
>48 mo	5 (19)

Comparing induction strategies in acute myeloid leukemia: 10-year real-world experience with 7+3 and HMA/venetoclax.

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Background: Hypomethylating agents (HMA) combined with venetoclax are the standard of care for AML in adults ineligible for intensive chemotherapy, but use is expanding to fit patients given prospective data suggesting comparable outcomes. Whether these findings are reproducible in real-world practice remains under investigation. **Methods:** We conducted a retrospective cohort study of adults with newly diagnosed AML treated at the University of Kentucky from 2016–2025 with either 7+3 or HMA/venetoclax. Overlap propensity score weighting balanced age, sex, ECOG, ELN risk group, prior MDS, and therapy-related AML. Primary endpoints were CR/CRi, RFS, OS, and 30-day mortality. Cox models included allogeneic HSCT as a time-varying covariate. Survival outcomes were stratified by ELN risk group and mutational risk group according to venetoclax sensitivity (favorable: *NPM1* and *IDH1/2*, adverse: *TP53* and *FLT3*). **Results:** Prior to weighting, patients treated with HMA/venetoclax were older (68 vs. 50 years), had worse performance status (mean ECOG 1.2 vs. 0.7), and were more likely to have prior MDS, therapy-related AML, and less favorable ELN risk. Unweighted data demonstrated a median OS of 13.3 months for HMA/venetoclax and 19.6 months for 7+3. After overlap weighting of 379 patients (250 received 7+3 and 129 received HMA/venetoclax), acceptable covariate balance was achieved with all standardized differences < 0.01. HMA/venetoclax was associated with numerically higher odds of achieving CR/CRi compared with 7+3 (OR 1.84, $p=0.09$), and this reached significance in adverse-risk disease (OR 2.31, $p=0.006$). 30-day mortality was similar between 7+3 and HMA/venetoclax groups (8.3% vs. 8.0%, $p=0.96$). Among patients who achieved CR/CRi, no significant difference in relapse was noted ($p=0.24$). RFS and OS did not differ significantly between treatment groups ($p=0.76$ and 0.18 , respectively). Analysis of ELN risk subgroups and mutation subgroups incorporating venetoclax sensitivity demonstrated no association with treatment group in survival outcomes (for OS, $p=0.53$ and 0.43 , respectively), suggesting no effect modification from these variables. Allogeneic HSCT was strongly associated with improved OS (HR 0.26, $p<0.001$), which persisted after adjusting for ELN risk (HR 0.39, $p<0.001$) and mutational subgroups (HR 0.44, $p=0.001$). Across all models, treatment assignment did not significantly impact OS once transplant was modeled as a time-dependent variable. **Conclusions:** After accounting for baseline confounding and allogeneic HSCT as a time-varying covariate, survival in AML is primarily driven by molecular risk profile and transplant rather than initial induction strategy. These results support further investigation of HMA/venetoclax as a frontline alternative in fit patients with AML and the intention to proceed to transplant. Research Sponsor: None.

HMA plus venetoclax for 7- vs 14- vs 21- vs 28-day cycles in newly-diagnosed acute myeloid leukemia: ELN- and Mayo Genetic Risk–stratified analysis in 540 patients.

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Background: Venetoclax plus hypomethylating agent (Ven-HMA) is the standard treatment for unfit patients with newly diagnosed acute myeloid leukemia (ND-AML), with Ven typically administered for 28 days (d) per cycle (*DiNardo NEJM 2020*). However, the optimal duration of Ven across risk groups remains unclear. We examined survival outcomes with Ven 7, 14, 21, and 28d in ND-AML, in the context of European LeukemiaNet (ELN) and Mayo Genetic risk models. **Methods:** ND-AML patients receiving Ven-HMA at the Mayo Clinic were retrospectively studied. Patients were stratified by ELN 2024 (*Döhner Blood 2024*) and Mayo Genetic risk (*Gangat Am J Hematol 2025*), and analyzed using standard statistical methods. **Results:** 540 patients (median age 75 years, 52% *de novo*) received HMA with Ven for 7d (n=33), 14d (n=117), 21d (n=96), or 28d (n=294). ELN and Mayo risk distributions were 22%/35% high, 18%/56% intermediate, 60%/9% low risk, respectively. Baseline characteristics were comparable. CR/CRi rates were comparable across Ven durations, with the exception of lower CR/CRi with 7d vs 21d (p=0.04). Risk-stratified CR/CRi showed variations across Mayo and ELN groups but without significant differences based on Ven duration (Table). Allogeneic transplant rates were 15%, 18%, 18%, 20% for 7, 14, 21, 28d (p=0.86). At a median followup of 37.7 months, median overall survival (OS) differed by ELN risk (6.6, 11.9, 20 months) and Mayo genetic risk (7.8, 17.4 months, not reached (NR)), for high, intermediate, low risk (p<0.01), respectively. Median OS was comparable across Ven 7, 14, 21, 28 d (13, 13, 17, 14 months; p=0.84), with corresponding 1/3/5-year survival rates (Table). 30/60d mortality differed by Ven duration; 7d 10%/20%, 14d 7%/15%, 21d 4%/13%, 28d 4%/6%. Compared with 28d, 30d mortality was higher with 7d and 14d (p=0.07/0.03), and 60d mortality was higher with 7d, 14d, and 21d (p=0.02/0.01/0.05). OS was comparable across Ven durations within ELN intermediate/low risk and all Mayo risk groups, except among ELN high risk, patients receiving 14d Ven had inferior OS compared with 21d and 28d (p<0.01). Cumulative incidence of relapse at 1 year was similar among patients receiving 14, 21, 28d Ven (16%, 18%, 18%;p >0.1). **Conclusions:** Survival outcomes were comparable across Ven 7, 14, 21, 28 d in ND-AML, with outcomes driven by Mayo Genetic and ELN risk. Despite differences by Ven duration in high-risk groups, higher early mortality with 7d and 14d likely reflects treatment selection. Prospective trials are needed to establish risk adapted Ven dosing strategies. Research Sponsor: None.

			7 (N=33)	14 (N=117)	21 (N=96)	28 (N=294)	P- value	
CR/CRi (%)	Mayo Risk	High	52 33	63 49	72 58	65 55	0.19 0.53	7≠21 -
		Intermediate	55	69	80	69	0.17	7≠21
		Low	100	85	80	84	0.84	-
	ELN Risk	High	33	30	57	53	0.21	-
		Intermediate	33	59	64	56	0.63	-
		Low	62 13	74 13	80 17	73 14	0.46 0.84	- -
Median OS (months)								
1/3/5-year survival (%)			53/NR/NR	51/25/22	56/23/20	55/27/20	>0.1	-

ASCERTAIN: Real-world asciminib (ASC) effectiveness in patients (pts) with Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL).

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Background: ATP-competitive tyrosine kinase inhibitors (TKIs) in combination with chemo-immunotherapy have improved outcomes in Ph+ ALL; still, some pts relapse despite appropriate frontline therapy and have limited options. ASC is approved for Ph+ chronic myeloid leukemia in chronic phase. The ASC managed access program (MAP) allowed adults with Ph+ ALL refractory/resistant or intolerant to available treatment (Tx) to receive ASC as monotherapy or combination under individual request when the potential benefit outweighed the risk. **Methods:** This was a non-interventional, multi-country, retrospective chart review in eligible pts with Ph+ ALL aged ≥ 18 who were refractory/resistant or intolerant to available Tx and who received ≥ 1 dose of ASC within the MAP. Index date (date of first ASC administration) occurred between 1 March 2019 and 30 June 2023. Existing data were extracted from index date up to 13 months (mo), or until discontinuation, death or last visit, whichever occurred first. The primary endpoint was complete hematologic remission (CR) and CR with incomplete count recovery (CRi) anytime in the first 3 mo of Tx based on peripheral blood assessments. **Results:** A total of 37 pts were enrolled. At Tx start, 25 pts (67.6%) received ASC as monotherapy. Median ASC dose intensity was 400 mg/day (range 71.6–400.0). Overall, 23 pts (62.2%) achieved CR/CRi within 3 months (95% CI: 44.8, 77.5). Median duration of response was 7.4 mo. Median overall survival was 7.7 mo. Nineteen pts were assessed for minimal residual disease (MRD) at time of CR/CRi and 7 (36.8%) were MRD-. Of the 13 pts with T315I mutation, 10 achieved CR or CRi at any time during follow-up. Thirty-three pts (89.2%) permanently discontinued ASC; reasons for permanent discontinuation included disease progression (n=16) and adverse events (AEs, n=5). Any-grade Tx-emergent AEs were reported in 73.0% (Grade ≥ 3 , 56.8%) of pts; the most common any-grade AE was neutropenia (21.6%). No new safety signals were observed. Most deaths (22/28) were Ph+ ALL related. **Conclusions:** Adults with Ph+ ALL that was relapsed, resistant/refractory or intolerant to previous Tx achieved high rates of CR/CRi with ASC as monotherapy or in combination with chemotherapy/immunotherapy, despite most pts being heavily pretreated and/or harboring poor prognosis markers (Table). The safety profile was consistent with previous studies. Results, while positive, should be cautiously interpreted given the retrospective nature of the study and heterogenous population. Research Sponsor: Novartis Pharma AG.

Pt baseline characteristics.

	Pts N=37
Median age (range), years	53 (19–84)
Disease status (bone marrow blasts), %	
$\geq 5\%$	67.6
$< 5\%$	24.3
Unknown	8.1
Prior treatment lines, %	
1	2.7
2	32.4
3	21.6
≥ 4	43.2
Ponatinib pretreatment, %	94.6
T315I mutation, %	35.1
Reason for starting ASC, %	
Relapse	67.6
Specific mutations	27.0
Resistance	24.3
Intolerance	18.9
Other	13.5

Response to HiDAC/mitoxantrone/venetoclax (HMV) in patients with relapsed/refractory (R/R) acute myeloid leukemia (AML).

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Background: Outcomes for patients (pts) with R/R AML are dismal, especially after failure of Venetoclax (Ven)-based regimens. Effective strategies are urgently needed particularly in the absence of targetable mutations. An early-phase study of HMV demonstrated a 75% remission rate in pts with R/R AML, however the majority of these pts were Ven-naïve (Ruhnke et al, EHA 2024). We aimed to study a real-world cohort of pts with R/R AML treated with HMV. **Methods:** A retrospective cohort of 16 pts with R/R AML treated with HMV at the University of Chicago (2020–2025) was analyzed. Clinical and disease characteristics were collected; European Leukemia Net (ELN) 2022 criteria were used for risk stratification and response assessment. Overall response rate (ORR) was defined as complete response (CR) + CR with partial hematologic recovery (CRh) + CR with incomplete hematologic recovery (CRi). Overall survival (OS) was estimated using Kaplan–Meier methods. **Results:** Sixteen pts with R/R AML were included; 2 pts had ALL with lineage switch to AML. Median age at diagnosis was 54.5 years. Amongst the 14 pts with AML at initial diagnosis, 28.6%, 14.3%, and 50.0% had favorable, intermediate, and adverse ELN 2022 risk, respectively. Our cohort of pts was heavily pre-treated with 56.2% receiving ≥3 lines of therapy prior to HMV; two pts had received prior allogeneic hematopoietic stem cell transplant (allo-SCT). The ORR was 43.8%; in addition, 6.3% attained morphologic leukemia-free state (MLFS), 6.3% obtained a partial response (PR), and 43.7% had no response/not evaluable (NR/NE). Among pts that received prior intensive AML chemotherapy (n=8), the ORR was 50.0% with HMV. The ORR was 41.6% in pts with prior Ven exposure (n=12). Median OS from HMV initiation was 5.1 months (95% CI: 2.2–9.2) with two deaths within 30 days of HMV initiation; 62.5% of patients received subsequent therapy and 37.5% proceeded to allo-SCT. Two patients are alive in remission at time of data analysis; both underwent allo-SCT after HMV. **Conclusions:** In this heavily pretreated R/R AML cohort, HMV produced encouraging response rates and facilitated transition to allo-SCT in a subset of pts. These data warrant further evaluation of HMV as an R/R option even in pts with prior Ven exposure. Research Sponsor: National Cancer Institute; 3P30CA014599–49S1.

Patient characteristics and efficacy outcomes.	
Median Age at Time of Receiving HMV (N=16)	54.5 years (Range 21-66)
Gender (N=16)	Male 69%; Female 31%
# of Lines of Therapy Received Prior to HMV (N=16)	1 Line 25%; 2 Lines 18.8%; ≥3 Lines 56.2%
Best Response to HMV (N=16)	CR 31.2%; CRh 6.3%; CRi 6.3%; MLFS 6.3%; PR 6.3%; NR/NE 43.7%
Best Response to HMV in Patients Who Received Prior AML-Based Intensive Chemotherapy (N=8)	CR 25%; CRh 12.5%; CRi 12.5%; MLFS 0%; PR 0%; NR/NE 50%
Best Response to HMV in Patients Who Received Prior Venetoclax (N=12)	CR 25%; CRh 8.3%; CRi 8.3%; MLFS 0%; PR 8.3%; NR/NE 50%

Pharmacokinetic (PK) assessment of revumenib in patients with relapsed/refractory (R/R) acute leukemias harboring a *KMT2A* rearrangement (*KMT2Ar*) or *NPM1* mutation (*NPM1m*): Impact of food and concomitant medications.

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Background: Revumenib is a first-in-class, oral, potent, and selective inhibitor of the menin-*KMT2A* interaction that disrupts multiple drivers of leukemogenesis such as *KMT2A* rearrangements (*KMT2Ar*) and *NPM1* mutations (*NPM1m*). Revumenib is approved in the United States in patients 1 year and older for the treatment of R/R acute leukemia with a *KMT2A* translocation or R/R acute myeloid leukemia with a susceptible *NPM1* mutation who have no satisfactory alternative treatment options. Given the severity of disease, frequent polypharmacy, and variable clinical status in this population, dosing flexibility is essential to support consistent treatment delivery and optimize outcomes. This analysis characterizes the PK of revumenib and its major metabolite (M1), with emphasis on factors that may influence dosing flexibility, including food and concomitant medications such as CYP3A4 inhibitors (CYP3A4i) and gastric acid-reducing agents such as antacids, H2 blockers (H2Bs), and proton pump inhibitors (PPIs). **Methods:** PK data were obtained from 286 adult (≥ 18 years) and 49 pediatric (< 18 years) patients with *KMT2Ar* or *NPM1m* acute leukemia enrolled in the phase 1/2 AUGMENT-101 trial (NCT04065399) following single and multiple doses of revumenib. Non-compartmental analyses were performed in selected subgroups, while population PK modeling was conducted using data from all patients to systematically quantify PK variability and evaluate covariate effects. **Results:** As compared to fasted state, a low-fat meal (400–500 calories with $< 25\%$ fat content) reduced revumenib C_{max} and AUC by 27% and 12%, respectively, and M1 C_{max} and AUC by 14% and 18%, respectively, although exposure ranges overlapped under fasted and fed (low-fat meal) conditions. Median T_{max} was unchanged for revumenib and delayed by 1.8 hours for M1. Co-administration with strong CYP3A4i (eg, voriconazole, posaconazole, itraconazole) resulted in ~2-fold increase in revumenib C_{max} and AUC, whereas moderate CYP3A4i (eg, fluconazole, isavuconazole) had no meaningful effect. M1 exposure was unaffected by strong or moderate CYP3A4i. Approximately 52% of patients received antacids, H2Bs, or PPIs; revumenib and M1 C_{max} and AUC were not altered, consistent with the high solubility of revumenib across physiological pH range (1.2–6.8). **Conclusions:** Revumenib exposure increases ~2-fold with strong CYP3A4i, supporting dose reduction in this setting, while M1 exposure remains unaffected. Low-fat meals do not cause clinically meaningful changes in revumenib or M1 PK. Similarly, antacids, H2Bs, and PPIs, which are frequently used in this patient population, had no impact on revumenib or M1 PK. These findings reinforce the flexible administration of revumenib that may support treatment adherence and patient convenience. Clinical trial information: NCT04065399. Research Sponsor: Syndax Pharmaceuticals, Inc.

Preliminary results of an open-label, single-arm phase 2/3 trial (SPARK-ALL) of calaspargase pegol in adults with newly diagnosed Philadelphia chromosome-negative acute lymphoblastic leukemia.

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Background: Asparaginase is an important component of many regimens for acute lymphoblastic leukemia (ALL). In patients (pts) <21 years, calaspargase pegol (Cal-PEG) provides more sustained asparagine depletion than pegaspargase. SPARK-ALL is a multicenter phase 2/3 study (NCT04817761) assessing the safety and anti-leukemic activity of Cal-PEG in pts aged ≥ 22 years with newly diagnosed Philadelphia chromosome-negative (Ph-) ALL. **Methods:** Part 1 was a dose-finding study in pts with a body mass index (BMI) ≤ 35 kg/m² aged 22–39 and 40–54 years (Cal-PEG 2000 and 1500 U/m², respectively) and pts with BMI > 35 kg/m² or aged ≥ 55 years (Cal-PEG 1000 U/m²). Part 2 was a dose-expansion study in pts with BMI ≤ 35 kg/m² aged 22–39 years (Cal-PEG 1750 U/m²) or 40–54 years (Cal-PEG 1500 U/m²). Six Cal-PEG IV infusions were given as part of a multiagent chemotherapy regimen based on CALGB 10403 (Stock W, et al. *Blood* 2019;133(14):1548–1559). The primary objectives are assessment of safety in all pts, and anti-leukemic activity using the surrogate marker of nadir plasma asparaginase activity (NPAA) ≥ 0.1 U/mL 21 days after the D43 consolidation dose in all evaluable pts who were treated at the recommended dose (primary NPAA [PNPAA] analysis set). **Results:** A total of 42 pts received Cal-PEG treatment: 26 and 16 in parts 1 and 2, respectively. Overall, 31 (73.8%) and 16 (38.1%) pts experienced grade 3/4 treatment-related adverse events (TRAEs) and serious TRAEs, respectively. Overall, 15 pts (35.7%) had TRAEs leading to study drug discontinuation, including hypersensitivity-type events in 6 pts (14.3%); 4 (9.5%) had nervous system events, including cerebral venous sinus thrombosis in 2 pts (4.8%). Three pts (7.1%) had a grade 3 pulmonary embolism, which, per protocol, required study drug discontinuation. The most common grade 3/4 TRAEs included hypertriglyceridemia (9 pts; 21.4%), alanine aminotransferase increase (7 pts; 16.7%), and blood fibrinogen decrease (5 pts; 11.9%). In part 1, intolerable toxicities considered related to Cal-PEG were experienced by 2/8 pts who were older and 2/8 pts with a BMI > 35 kg/m²; 1 (11.1%) pt aged between 22–39 years experienced an event of hypersensitivity. One Cal-PEG-related death was reported as likely related to complications from embolic stroke in a pt aged 71 years with comorbidities. Dose expansion was pursued in the first two cohorts. At 21 days after the D43 post-consolidation dose, all pts in the PNPAA set had NPAA values above the 0.1 U/mL efficacy threshold. **Conclusions:** Cal-PEG has a safety profile consistent with asparaginase class toxicity and, as part of multidrug chemotherapy regimen, provides sustained asparagine depletion in newly diagnosed Ph- ALL pts aged ≥ 22 years. In light of the observed high-grade TRAEs, future studies will evaluate different Cal-PEG doses for this pt population. Clinical trial information: NCT04817761. Research Sponsor: Servier.

Older age as a predictor of post-transplant survival in newly diagnosed acute myeloid leukemia treated with HMA-venetoclax.

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Background: Venetoclax (Ven) plus hypomethylating agents (HMA) is standard frontline therapy for newly diagnosed AML (ND-AML) patients unfit for intensive chemotherapy and is also being considered in younger and fit patients (Fathi, Blood 2025). However, consolidation with allogeneic stem cell transplant (ASCT) is often required to secure durable remission. The current study examines predictors of post-transplant survival (PTS) in the particular scenario.

Methods: ND-AML patients who received upfront Ven+HMA and underwent ASCT were retrospectively studied. PTS, relapse rate, and non-relapse mortality (NRM) were evaluated.

Results: 111 ND-AML patients (58% male, 60% secondary/therapy-related, median age 70 [37–80 years]) received median 3 cycles of Ven-HMA. 22% had complex karyotype. Mutations at diagnosis included *RUNX1* (18%), *SRSF2* (17%), *TP53* (16%), *ASXL1*, *IDH2*, *K/NRAS* and *TET2* (14% each), *STAG2* (11%), *DNMT3A* (8%) and at time of ASCT (N=78 evaluable); *RUNX1* (8%), *NPM1* (6%), *TP53* and *ASXL1* (5% each), and *SRSF2* and *TET2* (4% each). At ASCT, all patients were in CR/CRi; 88% after Ven-HMA and 12% after additional bridging therapy. MRD by flow cytometry was detected in 18 (24%) of 76 evaluable patients and complex karyotype in 8 (9%) of 94. Donors were mostly HLA-matched unrelated (75%), with 51% receiving fludarabine/melphalan conditioning and 67% post-transplant cyclophosphamide (PTCy). At a median follow-up of 30 months, 42 patients (38%) have died including 18 (40%) from relapse. Median PTS was not reached (NR) with 1–2–3-year survival of 69%/60%/57%. On multivariate analysis, age ≥ 65 years (median NR vs 10 months $p < 0.01$), *STAG2* (NR vs 44 months; $p = 0.04$), and *DNMT3A* mutations (NR vs NR $p = 0.05$) were associated with superior PTS. In analysis limited to variables at time of ASCT, age ≥ 65 years remained significant ($p < 0.01$) while *TP53* mutations, donor type, and MRD status were not ($p > 0.1$). Patients < 65 years more often received bridging therapy compared to ≥ 65 years (23% vs 7%; $p < 0.05$); excluding salvage-treated patients did not change survival results. 18 patients (16%) experienced post-ASCT relapse with median RFS of 7 months. Relapse rates at 1/2/3 years were 22%, 30% and 31% and NRM 13%, 24%, 46%, respectively. Patients < 65 years had a higher 1 yr relapse incidence than those ≥ 65 years (36% vs 18%; $p = 0.01$), with similar NRM ($p = 0.58$). PTCy was not associated with relapse ($p = 0.66$) but showed a borderline association with higher NRM (1–2–3-year 17%/31%/58% vs 4%/7%/16% in non-PTCy recipients; $p = 0.06$). GVHD rate was 44% (50% $\geq$ grade 2) with no association with relapse ($p = 0.43$) or NRM ($p = 0.99$). **Conclusions:** In the current study, older age (> 65 years), including > 75 years, was independently associated with superior PTS in ND-AML patients receiving Ven-HMA. By contrast, PTS was not affected by genetic profile at the time of ASCT, donor type, conditioning regimen, or GVHD prophylaxis. Research Sponsor: None.

Myelodysplasia-related mutation dynamics and outcomes in newly diagnosed (ND) acute myeloid leukemia (AML) treated with low-intensity therapy (LIT).

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Background: Outcomes of patients (pts) with ND AML with myelodysplasia related gene mutations (MRMs), while traditionally adverse, appear to be better with LIT regimens + venetoclax (Ven). The impact of MRMs as a minimal residual disease (MRD) marker warrants investigation. **Methods:** We retrospectively analyzed the impact of persistence/clearance of MRM at VAF <2% at best response of CR/CRi, in pts with LIT treated ND AML (with available genomic data), treated at our institution between 2017 – 2025 and had ≥ 1 MRM (*ASXL1*, *BCOR*, *EZH2*, *STAG2*, *SF3B1*, *SRSF2*, *U2AF1*, and/or *ZRSR2*) at diagnosis, at a VAF of $\geq 2\%$. We excluded pts with CBF-AML, APL, or treated secondary AML. MRM dynamics were tracked at baseline and best response (CR/CRi) and correlated with relapse free/overall survival (RFS/OS). **Results:** A total of 185 pts, median (med) age 69 yrs (range, 56–87 yrs), were included; 96% were ≥ 60 yrs. The common baseline MRM were *SRSF2* (54%), *ASXL1* (32%), *STAG2* (16%) and *BCOR* (14%); 16% had >1 MRM. Overall, 17% had concurrent *NPM1* mutation (mut), 9% *FLT3*-ITD (AR >0.05), 22% *RAS*, 32% *RUNX1*, 8% *TP53*, and 32/183 pts (17%) had ELN2017 adverse cytogenetics (CTG). 171 pts (92%) were treated with LIT+Ven and 14 (8%) LIT without Ven; 105 (57%) received hypomethylating agents based, and the rest (43%) received cladribine + low-dose cytarabine based LIT. Overall, 148 (80%) achieved CR and 37 (20%) CRi. 117/168 (70%) pts with available data were MRD negative (-) by flow cytometry (FCM; $<0.01\%$) at CR/CRi. At CR/CRi, 49 (26%) cleared their MRMs (MRM-) while 136 (74%) retained MRMs (MRM+); among pts with FCM MRD- CR/CRi, 33/117 (28%) were MRM- and 84/117 (72%) MRM+. Med cycle to CR/CRi was 1 (IQR 1–2). Pts with MRM- at CR/CRi had superior med RFS (24 [95% CI 9–18] vs. 14 mos [16–NR], $p=0.008$) and OS (54 [25–NR] vs. 21 mos [15–27], $p=0.01$) compared to MRM+ pts. Among 117 FCM MRD- pts, med RFS (NR vs. 14 mos [9–23], $p=0.001$) and med OS (NR vs. 19 mos [14–36], $p=0.003$) was still superior among MRM- pts ($n=33$) vs. MRM+ ($n=84$). 67 pts (36%) underwent a hematopoietic stem cell transplantation (HSCT) in CR1, 26/49 (53%) MRM- and 41/136 (30%) MRM+. Among FCM MRD- pts who did not undergo HSCT, 2-yr OS rate (86% vs. 48%, $p=0.04$) was better in MRM- pts ($n=15$) vs. MRM+ pts ($n=58$); among FCM MRD- pts who had HSCT, 2-yr OS rate trended to favor MRM- pts ($n=18$) (77% vs. 55%, $p=.14$) vs. MRM+ pts ($n=26$). On backward selected Cox MVA, clearance of MRMs at CR/CRi was independently associated with favorable OS (HR=0.54, 95% CI 0.31–0.95, $p=0.03$), along with *BCOR*, *IDH2* mut, and HSCT, while *RAS* mut, *FLT3*-ITD, and adverse CTG were unfavorable. Finally, among FCM-MRD- pts at CR/CRi, using the same Cox model, clearance of MRMs was independently favorable for OS (HR=0.42, 95%CI 0.20–0.93, $p=0.03$). **Conclusions:** In our analysis, the status of MRM clearance at CR/CRi in LIT treated AML with baseline MRM affected survival outcomes, including in pts FCM MRD- at CR/CRi. Research Sponsor: None.

Impact of concomitant *NPM1* mutations on genomic and transcriptomic patterns of *PTPN11*-mutant myeloid leukemias.

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Background: *PTPN11* mutations are associated with worse treatment outcomes in acute myeloid leukemia (AML) and frequently co-occur with *NPM1* mutations. However, the impact of concurrent *NPM1* mutations in *PTPN11*^{mut} myeloid leukemia is not well understood. This work aims to 1) characterize genomic features of a single-center cohort of patients with *PTPN11*^{mut}/*NPM1*^{wt} and *PTPN11*^{mut}/*NPM1*^{mut}-myeloid leukemia and 2) assess associated transcriptomic patterns.

Methods: Patients with myeloid leukemia with *PTPN11* and/or *NPM1* mutations observed in blood (PB) or bone marrow (BM) were identified from the UMass Leukemia Registry. Next-generation sequencing (NGS) data were annotated for co-occurring variants and cytogenetic abnormalities. RNA-seq data from PB and BM samples from the Beat AML 1.0 trial were accessed via The Cancer Genome Atlas. Sample IDs with *PTPN11*^{mut}, *NPM1*^{mut} and *PTPN11*^{mut}/*NPM1*^{mut} were identified using the Vizome platform. High-throughput analysis of these samples and *NPM1*/*PTPN11*^{wt} was then performed using DESeq2. **Results:** 107 patients with myeloid leukemias at UMass Cancer Center harboring *PTPN11* mutations (n = 34) or *NPM1* mutations (n=74) were identified, 14 of whom had both. Subgroup analysis of chromosomal maps of *PTPN11*^{mut}/*NPM1*^{mut} cohort and *PTPN11*^{mut}/*NPM1*^{wt} cohort showed that the *PTPN11*^{mut}/*NPM1*^{wt} group had a higher cytogenetic abnormality burden compared to the *PTPN11*^{mut}/*NPM1*^{mut} group, demonstrating 18 observations of 12 distinct abnormalities compared to 5 observations of 3 distinct abnormalities, respectively. Analysis of RNA-seq from BM tissue of *PTPN11*^{mut}/*NPM1*^{wt} AML (n = 6) from the Beat AML 1.0 dataset revealed only 22 differentially expressed genes compared to *PTPN11*^{wt}/*NPM1*^{wt} samples. Of these, 12 were mitigated in the *PTPN11*^{mut}/*NPM1*^{mut} (n = 9) group. This trend was less pronounced in analysis of PB tissue. However, review of 20 most differentially expressed genes of both BM and PB in the *PTPN11*^{mut}/*NPM1*^{wt} group revealed many changes in long intergenic non-coding RNAs (lincRNAs).

Conclusions: Genomic analysis of *PTPN11*^{mut}/*NPM1*^{wt} BM and PB highlighted widespread cytogenetic heterogeneity compared to the *PTPN11*^{mut} *NPM1*^{mut} subgroup. RNAseq analysis of *PTPN11*^{mut} BM and PB revealed significant differential expression in multiple lincRNAs, particularly in BM. These changes were mitigated in the double mutant group. Larger studies are needed to validate these findings and investigate whether presence of subtle regulatory shifts serve as a driving factor in the poor outcomes underlying *PTPN11*^{mut} AML. Further chromatin accessibility profiling studies may help elucidate the regulatory mechanisms driving these transcriptomic changes. Research Sponsor: None.

Can transcriptome-based risk modeling improve survival stratification across cytogenetic groups in acute myeloid leukemia?

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Background: Cytogenetic risk stratification is central to prognostication in acute myeloid leukemia (AML), yet survival outcomes vary considerably within each group. We hypothesized that transcriptomic features could further stratify survival within these cytogenetic categories, independent of clinical factors. **Methods:** We analyzed gene expression microarray data for 172 AML patients from the TCGA-LAML cohort (dbGaP phs000178). Multivariable Cox proportional hazards modeling incorporating age, gender, and CALGB cytogenetic risk was used to identify genes independently associated with overall survival. LASSO regression was applied to derive a transcriptomic gene signature and compute a patient-level transcriptomic risk score. Kaplan-Meier survival analysis, log-rank testing, and Cox modelling were performed in the overall cohort and within each cytogenetic subgroup. Model performance was assessed using concordance index (C-index) and likelihood ratio testing. Differential expression and Gene Ontology Biological Process (GOBP) enrichment were performed between high and low transcriptomic risk groups. **Results:** The transcriptomic risk score significantly stratified overall survival and, importantly, retained prognostic significance within favorable, intermediate, and poor cytogenetic risk groups (Table). The concordance index improved from 0.69 with clinical variables (age, gender, cytogenetics) alone to 0.82 after adding the transcriptomic risk score. Likelihood ratio testing confirmed a highly significant improvement in model fit with the inclusion of the transcriptomic score ($\chi^2 = 98.7$, $p < 2.2 \times 10^{-16}$). GOBP enrichment of DEGs between high and low transcriptomic risk groups revealed upregulation of CD4-positive T-cell activation (STAT6, IL12RB1, ZBTB7B), negative regulation of immune response (LGALS9, PTPN6, FGL2), regulation of leukocyte and lymphocyte differentiation (ZC3H12A, VNN1, HCLS1), and response to bacterial molecules and lipopolysaccharide (NLRP3, MYD88, CASP1) confirming dysregulated immune signaling as a hallmark of adverse prognosis. **Conclusions:** A transcriptomic risk score provides powerful, independent prognostic information beyond cytogenetics and clinical factors in AML. These findings support the integration of transcriptomic biomarkers into existing risk models to refine AML prognostication. Research Sponsor: None.

Survival association of transcriptomic risk score across CALGB groups in AML patients.

CALGB Group	HR* (95% CI)	p value**
All AML patients (N =172)	3.74 (2.48–5.63)	2.81×10^{-10}
Favourable (N= 34)	14.53 (1.87–112.83)	1.05×10^{-2}
Intermediate (N = 97)	6.49 (3.43–12.26)	8.43×10^{-9}
Poor (N = 38)	2.68 (1.26–5.69)	1.01×10^{-2}

*HR: High vs Low genomic risk.

**Cox p from multivariable Cox model.

Mutation landscape and pathway-level disparities in Black versus White patients with acute myeloid leukemia.

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Background: Racial disparities in acute myeloid leukemia (AML) outcomes are well-documented, yet race-specific genomic differences remain incompletely characterized. Current risk stratification systems, developed from European-ancestry cohorts, may inadequately classify patients (pts) of African ancestry (Stiff, *Nature Genetics*, 2024). We performed comprehensive clinicogenomic analysis to identify race-specific mutation patterns and their clinical impact in AML. **Methods:** We analyzed genomic and outcomes data on AML pts in AACR Project GENIE database. Mutation frequencies, co-mutation patterns, and pathway alterations were compared between racial groups. Survival analyses used Cox proportional hazards models adjusted for age and sex. Multiple comparison correction used Benjamini-Hochberg false discovery rate (FDR). **Results:** Our study included 2,359 pts (Black, n=243; White, n=2,116). Black pts demonstrated a distinct mutational landscape with fewer splicing factor (*SRSF2*, *U2AF1*, *SF3B1*) mutations (11.1% vs 20.1%, FDR p=0.003) and tumor suppressor (*TP53*, *WT1*) mutations (11.9% vs. 18.2%, FDR p=0.038). Signaling/RAS pathway mutations were nominally higher in Blacks. A notable finding was the emergence of MDS-related gene mutations in Black pts at a younger age, suggesting distinct disease biology. Among pts aged <40 years, *ASXL1* mutations were more prevalent in Blacks (10.2% vs. 1.8%, p=0.006). Co-mutation architectures differed substantially by race: in Black pts, *ASXL1* and *RUNX1* frequently co-occurred with RAS/MAPK pathway mutations (*ASXL1*+RAS: 7.8% vs. 3.4%, FDR p=0.006), whereas White pts had predominant co-occurrence of *ASXL1* and *RUNX1* with splicing factor mutations. Critical survival disparities emerged by mutation status. *NPM1*+*FLT3* co-mutation was less common in Blacks (3.3% vs. 7.0%, FDR p=0.028) and conferred markedly inferior survival when present (median OS 6.7 vs. 14.6 months, p=0.008). Strikingly, favorable-risk mutations showed race-specific effects. *NPM1*-only (HR 0.79, p=0.014), *IDH1*-only (HR 0.68, p=0.005), and *NPM1*+*IDH1* (HR 0.61, p=0.013) were protective in White but not in Black pts: *NPM1*-only (HR 0.89, p=0.76), *IDH1*-only (HR 0.84, p=0.71), *NPM1*+*IDH1* (HR 0.34, p=0.13), challenging current risk stratification's universal applicability. Overall survival (OS) was similar (median OS- 18 vs. 16.7 months), though propensity-matched analysis trended toward worse outcomes in Blacks (18 vs. 25 months, p=0.091). **Conclusions:** Black AML pts exhibit fundamentally distinct molecular biology with differential pathway involvement, earlier MDS-related mutations, unique co-mutation patterns, and loss of prognostic value for traditionally favorable mutations. These findings demonstrate that race-blind risk stratification may systematically misclassify Black pts, supporting urgent need for ancestry-informed precision medicine approaches in AML. Research Sponsor: None.

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

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Background: For adults with ND Ph- B-ALL, frontline regimens now often include the CD19/CD3 bispecific blinatumomab (blin). However, blin administration is challenging, particularly for less-experienced centers. DA-EPOCH ± R is safe and active in these patients (pts; Cassaday, et al, *Leuk Lymphoma*, 2023) and easier to deliver. Tafa is a CD19 monoclonal antibody active in B-cell lymphomas. We hypothesized that the addition of tafa to DA-EPOCH ± R will yield higher rates of measurable residual disease negativity (MRD-) without increasing toxicity or administration complexity. **Methods:** This is a phase II investigator-initiated study (NCT05453500) in adults (>18 years) with ND CD19+ Ph- B-ALL not eligible for a pediatric regimen. DA-EPOCH ± R was given as cited above; tafa 12 mg/kg was given IV on day (d) 1, 8, and 15 of each cycle (C). After blin consolidation was FDA approved, pts could receive this off-study. The primary endpoint was MRD- by multiparameter flow cytometry (MFC) per EuroFlow ($\sim <10^{-4}$) after C1 (~d 20); secondary endpoints included MRD- by MFC after C4 (~d 80); non-hematologic adverse events (AEs, CTCAE v5); and relapse-free (RFS) and overall survival (OS). Exploratory endpoints included high-throughput sequencing (HTS; $<10^{-6}$) by clonoSEQ in marrow and cerebrospinal fluid (CSF). If ^{313} of 30 evaluable pts (343%) are MRD- after C1, the primary endpoint is met (vs 28% with DA-EPOCH ± R alone; 80% power and one-sided $\alpha = 0.05$). **Results:** From 3/2023 to 12/2025, 30 pts enrolled: 2 pts did not finish C1 due to grade (G) 4 AST elevation (related) and G5 *C. perfringens* sepsis (unrelated); 27 were evaluable for response and are the focus here. Median age was 67 (44-84), 70% male, 56% poor risk cytogenetics by NCCN, and 9 received R. Complete response (CR) rate was 85% (23/27); MRD- by MFC after C1 was 44% (12/27) and 80% (20/25) by C4 in pts with sufficient follow-up (f/u). In pts MRD- by MFC, 53% (8/15) were MRD- by HTS. Other G3+ AEs seen in >2 pts: infection (9); febrile neutropenia (8); low fibrinogen (6); hypotension (5); and syncope (4). Initial CSF MFC was positive in 3 pts; HTS was positive in these plus 4 more (7 total). With a median f/u among survivors of 10 mo (1-37), there were 3 relapses: 1 post-HCT and 1 after only 2 treatment cycles; all were CD19+, and 0 involved CNS. Only 2 pts got blin consolidation. 6 pts died: 4 non-relapse causes (3 post-HCT) and 2 from refractory ALL. No deaths were due to study treatment. 1-year RFS and OS were estimated to be 67% and 76%, respectively. **Conclusions:** DA-EPOCH ± R + tafa yields high rates of MRD-. Follow-up is immature, but early survival rates are comparable to more complex strategies. This study is on pace to reach its primary endpoint, with enrollment ending before the conference. HTS on CSF can identify CNS disease more frequently. Clinical trial information: NCT05453500. Research Sponsor: None.

Impact of variant topography of *NPM1* mutations in acute myeloid leukemia.

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Background: *NPM1* is a frequent driver mutation in AML and conveys favorable prognosis in the absence of *FLT3* mutations. Currently, *NPM1* subtypes (Type A, B, D and non-ABD) are approached uniformly. A granular analysis evaluating *NPM1* subtypes (ST) is essential to improve molecular risk stratification in AML. We seek to evaluate the molecular intricacies of *NPM1* variants and genomic architecture to determine how these influence outcomes in AML.

Methods: The cohort had patient data from Karmanos Cancer Institute, meta-analytic cohorts (Awada et al., 2021; Kewan et al., 2023), cBioPortal, and AACR GENIE (v17) (Cerami et al., 2012; Gao et al., 2013; de Bruijn et al., 2023). Clinical and genomic characteristics of *NPM1*^{MT} AML were reviewed. Insertions between nucleotides 863 and 864 determined the ST classification: TCTG (A), CATG (B), CCTG (D) and others (non-ABD). Stratification of *NPM1* by VAF was performed by quartiles from the median. Clonal hierarchy was defined as a difference in VAF $\geq 5\%$ and differences $< 5\%$ were designated as codominant. **Results:** Of 7653 patients with AML, 5342 (84.2%) had de novo AML. *NPM1*^{MT} was present in 1570. Type A was most common (73%), followed by non-ABD (18%), B (5%) and D (4%). Median age was 66 years (IQR 53.8–73.7) and was similar across groups. Females more frequently had non-ABD than B or D (67% vs 45% and 53%, $p=0.0008$ and 0.04 , respectively). Non-ABD had the least proliferative bone marrow compared to A, B or D (blast percentage 54 vs 79, 75.5, 70, $p<0.0001$, $p=0.0015$, $p=0.02$). Type A had lower VAF than other ST (29% vs 34%, $p<0.0001$), while B and D had higher VAF than other ST (38% vs 30%, $p<0.0001$ and 33% vs 30% $p=0.0004$). The most common co-mutation with *NPM1* was *DNMT3A* (48%). Type A was enriched for *DNMT3A* compared to other ST (54% vs 34%, $p<0.00001$). Type A and D had more *IDH1*, *IDH2*, and *NRAS* mutations than B and non-ABD (17% vs 10%, $p=0.01$; 23% vs 9%, $p<0.00001$; 16% vs 10%, $p=0.03$, respectively). B and non-ABD were more enriched in *WT1* compared to A and D (12% vs 4%, $p=0.00002$). Non-ABD was more enriched for *FLT3* mutations than other ST (39% vs 24%, $p=0.00012$). *DNMT3A*^{R882} was enriched in high VAF (HV) compared to low VAF (LV) *NPM1* (54% vs 46%, $p=0.01$). *FLT3* was more common in HV *NPM1* (34% vs 17%, $p<0.0001$). *NPM1* was often a subclone (82%), but was more likely to be dominant in B (29%, $p=0.001$). The median OS of *NPM1*^{MT} AML was 19 mo, similar across ST (A: 18 vs B: 14 mo, $p=0.3896$). OS was numerically higher in D (26 mo) and non-ABD (25 mo). LV *NPM1* ($Q1 \leq 22.8\%$) had significantly better OS than HV ($Q3 \geq 38\%$): 21 vs 10 mo ($p<0.0001$). This trend was most pronounced in D and non-ABD (D: 58 vs 10 mo, $p=0.009$; non-ABD: 29 vs 7 mo, $p=0.005$). **Conclusions:** As survival differences between *NPM1* mutation subtypes were numerically different, enrichment of Type A and D for *IDH1/2* and *NRAS*, non-ABD for *FLT3*, B and D for *WT1* probes the question of the impact of these co-mutations and VAF on *NPM1* outcomes. Further work will evaluate the impact of *NPM1* ST on de novo and therapy-related AML. Research Sponsor: None.

Impact of transplant on *TP53*^{MT} configurational dynamics in myeloid neoplasms.

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Background: Multihit *TP53* clonal configurations in myeloid neoplasms (MN) confers poor prognosis but therapy alters allelic burden in general. Using our previously described algorithm, patients with up-trending or stable (UT/S) *TP53*^{MT} had worse OS than those who down-trended (DT); HSCT was associated with DT. We evaluated whether this pattern reflects intrinsic *TP53*-driven disease biology or from treatment/transplant effects. **Methods:** We analyzed a serially sequenced *TP53*^{MT} AML/MDS cohort from four academic centers using targeted NGS (Illumina MiSeqDx; 54-gene TruSight panel). *TP53* configurations were defined per Bahaj et al.: single-hit *TP53*^{MT} as obligatory biallelic (VAF >50%), probable biallelic (23–50%), or probable monoallelic (<23%); combined VAF was used for double-hit *TP53*^{MT}. *TP53* clearance was defined as VAF <3%. Associations were tested with chi-square/Fisher tests and survival by Kaplan–Meier analysis. Clonal velocity (CV) was defined as the change in VAF from diagnosis to final serial sample post-transplant (Δ VAF) over post-HSCT survival time and categorized as stable (0 to –1), moderately downtrended (MD) (–1 to –5), or highly downtrended (HD) ($\leq$ –5). **Results:** Among 119 *TP53*^{MT} MN patients, 58 (49%) had pAML, 38 (32%) sAML, and 23 (19%) MDS. Median age was 65 years, 55% were male, and 20% had del(17p). Initial therapy included 7+3/CPX (34%), HMA+VEN (30%), or HMA alone (29%). 71 pts (60%) underwent HSCT (mOS 17 vs 5 mos in non-HSCT group; $p < 0.001$). Among 62 with serial samples, 76% down trended *TP53* post-HSCT and 72% achieved *TP53* clearance. Patients in the UT/S group more often had complex karyotype (93% vs 64%; $p = 0.04$) and numerically shorter time to HSCT (4 vs 5 mos; $p = 0.11$). In the DT group, pre-HSCT therapy included 7+3 (30%), HMA alone (23%), and HMA+VEN (25%); HMA monotherapy was more common in UT/S vs DT (53% vs 23%; $p = 0.03$). Mismatched/haploidentical transplants (in 45%) had numerically lower mOS than matched donor transplant (13 vs 52 mos; $p = 0.27$); class II mismatch showed numerically better survival than class I or haploidentical (37 vs 12 mos; $p = 0.27$). mOS was worse in UT/S (14 vs 22 mos; $p = 0.03$). When stratified by clonal velocity (CV), the DT group showed stepwise differences in mOS: stable (78 mos), MD (26 mos), and HD (11 mos; $p < 0.0001$). Stable CV was enriched for monoallelic *TP53* at diagnosis (60% vs 14% vs 6%; $p = 0.004$), higher chronic GVHD (60% vs 24% vs 13%; $p = 0.03$), and greater *TP53* clearance (100% vs 71% vs 56%; $p = 0.05$), whereas HD CV was enriched for obligatory biallelic *TP53* ($p = 0.001$). PTCy use was highest in the MD group (30% vs 76% vs 50%; $p = 0.04$). **Conclusions:** UT/S patients had higher pre-HSCT HMA monotherapy use and complex karyotypes. Stable CV was associated with monoallelic *TP53*, lower PTCy use, higher chronic GVHD, greater *TP53* clearance, and superior survival, suggesting that the rate of *TP53* clonal contraction rather than clearance alone best predicts OS and reflects intrinsic *TP53*^{MT} disease biology. Research Sponsor: None.

Distinction of FLT3-ITD transcriptomic signature from FLT3-TKD and the frequency of this signature in acute myeloid leukemia without *FLT3* mutation.

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Background: The FLT3 gene plays a major role in acute myeloid leukemia and frequently overexpressed irrespective of its mutation status. FLT3 internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutation are both associated with adverse prognosis, but the ITD is associated with more aggressive disease and higher relapses than the TKD. Therapeutically, FLT3-TKD has different resistance implications from FLT3-ITD. We used transcriptomic data to compare AML FLT3-ITD-positive (ITD+) with FLT3-TKD-positive (TKD+), then tested if AML FLT3-negative (FLT3-) may have RNA signature similar to those seen in ITD+ or TKD+ AML. **Methods:** Between 2023 and 2025, 906 AML samples were RNA profiled using next generation sequencing. A targeted NGS panel of approximately 1,600 genes was used. More than 100 million reads were required to accept RNA results. The required percentage of spliced RNA reads was above 20%. Of these samples, 171 had FLT3-ITD and 115 had FLT3-TKD mutations and 619 were FLT3-. **Results:** We first explored if expression profiling can define a subgroup of TKD+ cases that are similar to those with ITD+ AML. Using 22 genes in random forest modeling, expression profiling segregated ITD+ AML from TKD+ AML with AUC of 0.734 (95% CI: 0.638–0.831, Precision: 0.940). The top genes relevant for this segregation were GRB10, PTK7, WT1, TEC, CASP3, NR6A1, and CD47. We then build a random-forest-based model to distinguish ITD+ from FLT3- cases. We used the 171 ITD+ AML and a set of 220 FLT3- AML cases to distinguish between the two groups. Using 45 genes in this model we were able to segregate with the ITD+ cases based on expression with AUC of 0.889 (95% CI: 0.833–0.945, precision : 0.935). Top genes were LUC7L2, NFYC, PRPF40B, PRPF8, SF3A1, SMAD5, THRA, ACVR1, EVI2A, MCM3AP. This highly predictive model was then used to test independent set of 399 FLT3- AML cases. Of these cases 319 (80%) had a signature similar to ITD+ AML. Similarly, we used the 115 TKD+ with the 220 FLT3- AML cases and built a random forest-based model to distinguish between the two groups. This model required 70 genes and was less robust but segregated the TKD+ AML with AUC of 0.784 (95% CI: 0.701–0.868, precision: 0.842). Testing an independent set of 399 FLT3- cases using this model showed TKD signature in 236 (59%) of FLT- cases. All these positive TKD signature cases were also positive for the ITD signature. **Conclusions:** This data suggests that significant number of AML cases are biologically driven by changes similar to those seen in FLT3-mutant cases. While clinical trial is needed for confirmation, these cases with FLT3-ITD signature may respond efficiently if treated with therapy including FLT3 inhibitors in fashion similar to that seen ITD+ cases. Furthermore, this data suggests that ITD signature might be a better biomarker than TKD mutation for selecting patients to be treated with FLT3 inhibitors. Research Sponsor: None.

Real-world outcomes of early unfractionated heparin use in NSTEMI patients with acute leukemia and severe thrombocytopenia.

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Background: Current AHA/ACC guidelines provide limited guidance for acute non-ST-segment elevation myocardial infarction (NSTEMI) management in patients with active hematologic malignancy and concurrent severe thrombocytopenia, as these individuals have been systematically excluded from randomized trials. Consequently, decisions regarding anticoagulation rely on expert opinion and limited observational data. We evaluated real-world outcomes in patients with acute leukemia, severe thrombocytopenia, and NSTEMI, comparing early unfractionated heparin use with no parenteral anticoagulation. **Methods:** We conducted a multicenter retrospective cohort study using the TriNetX Research Network to identify adults (≥ 18 years) with acute leukemia who experienced a first NSTEMI following leukemia diagnosis. Severe thrombocytopenia was defined as a platelet count $< 50 \times 10^3/\mu\text{L}$ measured within 24 hours of NSTEMI. Patients with prior intracranial hemorrhage or on chronic anticoagulation were excluded. The primary exposure was unfractionated heparin administered within 24 hours of NSTEMI diagnosis versus no parenteral anticoagulation. Propensity score matching (1:1) was performed for demographics, cardiovascular risk factors and chronic co-morbidities. Primary efficacy outcomes were all-cause mortality at 30 days, 90 days, and 1 year. The primary safety outcome was major bleeding, defined as a composite of intracranial and gastrointestinal hemorrhage at 7 days, 30 days, and 90 days. Kaplan-Meier analysis, hazard ratios (HR), risk ratios (RR), and 95% confidence intervals (CI) were used to assess outcomes. **Results:** Among 1,734 patients who met the inclusion criteria, 639 received unfractionated heparin and 1095 did not. Following, PSM 528 patients remained in each group. Kaplan-Meier overall survival at 30 days, 90 days, and 1 year was significantly improved in patients receiving early unfractionated heparin (30-day HR = 0.78 [0.64-0.96]; 90-day HR = 0.77 [0.64-0.92]; 1-year HR = 0.75 [0.64-0.87]). Composite major bleeding events at 7 days, 30 days, and 90 days were similar between groups (7-day RR = 1.56 [0.95-2.56]; 30-day RR = 1.15 [0.81-1.77]; 90-day RR = 1.24 [0.88-1.83]). **Conclusions:** In this large real-world study of patients with acute leukemia, severe thrombocytopenia, and NSTEMI, early unfractionated heparin administration within 24 hours was associated with improved survival without an increased risk of major bleeding, addressing a critical evidence gap in this high-risk population. Research Sponsor: None.

Overall Survival			
Timepoint	Heparin (%) [n=446]	No Heparin (%) [n=446]	HR (95% CI)
30-day	66.9%	59.3%	0.78 [0.64-0.96]
90-day	55.3%	45.6%	0.77 [0.64-0.92]
1-year	36.9%	23.8%	0.75 [0.64-0.87]
Major Bleeding			
Timepoint	Heparin (%) [n=446]	No Heparin (%) [n=446]	RR (95% CI)
7-days	7.6%	5%	1.56 [0.95-2.56]
30-day	10.9%	9.8%	1.19 [0.81-1.77]
90-day	14.1%	11.6%	1.27 [0.88-1.83]

A two-axis machine learning framework for cell-of-origin inference in AML: A proof-of-concept study.

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Background: Leukemogenesis mirrors hematopoietic differentiation yet proceeds through dysregulated programs. Multiparameter flow cytometry (MFC) allows leukemia immunophenotypes projection onto normal myeloid ontogeny. Here, we apply machine-learning (ML) models trained on MFC data to reconstruct a preliminary data-driven representation of inferred cell-of-origin (COO). Additionally, we explore integration of monocytic differentiation into canonical COO framework to identify dysregulated commitment programs not explained by developmental maturity alone. **Methods:** After IRB approval, MFC data from 261 AML patients were aligned to immunophenotypic signatures of normal myeloid ontogeny (HSC, MPP, CMP, GMP, GP, MP) as previously described (Simoes *et al.*, *Blood Neoplasia*, 2024; Vergez *et al.*, *Blood Cancer Journal*, 2022). Probabilistic COO states were inferred from core markers (CD34, HLA-DR, MPO, CD33, CD117) using ensemble Random Forest classifiers with gradient boosting [Training/Validation=70/30]. Because canonical COO algorithms omit monocytic features, we implemented a secondary Mono-Risk Layer trained on monocytic markers (CD14, CD64) and stemness/invasiveness surrogates (CD56, reflecting adhesion, migration propensity) and CD123, to generate complementary phenotypic labels. Models were trained with cross-validation in Python, and mutation enrichment was projected onto inferred COO states. **Results:** Mean age was 63.8 years. 114/261 (44%) were male. 123/261 (47.1%) of cases produced multidimensional P-COO achieving "Ensembled (RF+ Boosting Gradient)" AUC=0.74. Confusion matrix revealed a structured pattern of misclassification predominantly between adjacent COO states, consistent with a continuous differentiation manifold (Recall for MPP, CMP, GMP, GP, MP, 50% 83%, 62%, 65%, 76%, respectively). Mono-Risk-Layer (MRL) improved discriminatory ability for MP (AUC 0.94, Recall 86%, F1 0.75). *NPM1* was mapped to GMP (60%), MP (34%) and CMP (27%), $p=2.61\text{e-}09$, *FLT3 ITD* GMP (43.3%), CMP (32.4%) and MP (12.3%), $p=4.72\text{e-}05$, *TP53* HSC (50%), MPP (24.3%) and GMP (16%), $p=3.6\text{e-}04$, *RUNX1* MPP (26.1%), HSC (25%) and MP (13%), $p=7.7\text{e-}03$, *RAS* MP (35%), MPP (19%) and HSC (13%), $p=5.18\text{e-}03$. **Conclusions:** Machine-learning-based probabilistic cell-of-origin inference from routine flow cytometry is feasible and biologically informative in AML. Incorporation of a monocytic risk layer improves resolution of monocytic programs not captured by canonical COO and reveals distinct mutation-differentiation relationships. *NPM1* and *FLT3-ITD* are enriched in GMP/MP-like states, *TP53* in primitive HSC/MPP compartments, *RUNX1* in early progenitors, and *RAS* in monocytic-skewed trajectories. These findings link genomic drivers to specific developmental niches and establish a scalable framework for biologically grounded AML classification and therapeutic modeling. Research Sponsor: None.

Impact of cell-type–specific circadian disruption in pediatric B-ALL on clock-based biomarkers with implications for chronotherapy.

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Background: B-cell acute lymphoblastic leukaemia (B-ALL) is the most common paediatric malignancy. While cure rates exceed 90%, treatment remains intensive and is frequently associated with relapse, toxicity, and long-term adverse effects. The circadian clock regulates DNA repair, metabolism, immune function, and drug pharmacokinetics—processes central to cancer therapy. Although treatment timing has been shown to influence outcomes in childhood ALL, the molecular circadian landscape of malignant versus healthy hematopoietic cells in paediatric patients remains unexplored. **Methods:** We performed an integrated molecular and clinical circadian profiling study in paediatric ALL patients (N=7) and age-matched healthy controls (N=10). Peripheral blood, bone marrow, and saliva samples were collected at diagnosis. CD19⁺ (leukemic B cells) and paired CD19⁻ (non-B cells) populations were isolated and used to establish an internal, patient-specific circadian baseline. Expression of ~800 cancer-, immune-, and clock-related genes was quantified using NanoString SPRINT technology. Rhythmicity parameters (acrophase, amplitude, MESOR), differential expression, and machine-learning–based classification were integrated with longitudinal clinical and physiological data. **Results:** Malignant CD19⁺ cells exhibited marked circadian dysregulation compared with paired CD19⁻ cells from the same patients. Core clock architecture was altered specifically in leukemic cells, including disrupted BMAL1–PER2 phase relationships and reduced rhythmic amplitude. CD19 expression itself displayed cell-type–specific circadian modulation, with higher amplitude and phase variability in CD19⁺ cells. In contrast, CD19⁻ cells retained more coherent circadian organization, supporting their use as an internal normalization reference. Preliminary analyses suggest that the degree of circadian misalignment between CD19⁺ and CD19⁻ compartments correlates with treatment dynamics, including early response and therapy duration. **Conclusions:** Our findings reveal profound, cell-intrinsic circadian disruption in paediatric B-ALL and demonstrate that comparing malignant CD19⁺ cells against paired non-malignant CD19⁻ cells enables robust detection of clock dysregulation. These results provide a molecular framework for developing circadian biomarkers and support the rational design of chronotherapy strategies aimed at optimising efficacy while minimising toxicity in paediatric leukaemia. Research Sponsor: Dr. Rolf Schwiete Stiftung.

Cladribine (CLAD) + low-dose AraC (LDAC) + venetoclax (VEN) in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome: Real-world analysis from a large community-based oncology practice.

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Background: A lower intensity combination cladribine (CLAD), low dose cytarabine (LDAC), and venetoclax (VEN), alternating with hypomethylating agents (HMA) + VEN has been shown to be highly effective in the treatment of older and/or unfit patients with newly diagnosed AML, producing high rates of MRD negative complete remission (CR), low early mortality, and successful transition to allogeneic stem cell transplant. While this was conducted in a large academic center in a prospective phase II study, we aimed to assess the efficacy and safety of this approach in a community practice setting, with important implications of broader applicability. **Methods:** This is a single-center retrospective study evaluating the efficacy and safety of using the CLAD/LDAC/VEN alternating with HMA/VEN regimen in a large oncology practice in the community setting. Dosing of CLAD/LDAC/VEN was according to published experience (Kadia, et al. JCO 2022). Patients with high risk MDS or AML treated in our institution from January 13, 2023–November 18, 2025 were included. Pts with prior treatment, including HMA for prior MDS transforming to AML (treated secondary AML, ts-AML) were also included. **Results:** A total of 72 patients received at least 1 cycle of CLAD/LDAC/VEN. The median age was 74 yrs (range: 43–90). Median PS was 1 (0–2), including 21 (29%) pts with ECOG PS of 2 (29%). 58 pts had AML, including 44 (78%) with untreated AML, 10 (18%) with ts-AML, and 12 (22%) with relapsed AML; 14 pts had high risk MDS, of which 5 (36%) had failed prior HMA. 37 pts (51%) had adverse risk karyotype by ELN 2022, 16 (22%) had TP53 mutation and 29 (40%) had secondary AML. Twenty-nine (40%) pts had received prior therapy, including 13 pts (18%) with prior HMA. The median number of cycles received was 2 (range 1–14). Among untreated AML and MDS, the composite CR (CRc) rates were 63% and 58%, respectively. Six out of 16 pts with p53 (38%) achieved CRc and of 16 pts with prior HMA 6 (38%) achieved CRc. The median survival (OS) was 8 months (range 0.16–33m). Eleven pts (15%) went on to have allo-SCT. Five pts (7%) died within 28 days of first treatment. Three of these died of infectious complications, 1 died of an acute coronary event and 1 patient decided to go on comfort care mid-way through treatment. **Conclusions:** CLAD/LDAC/VEN was feasible and effective in a high-risk, older patient population including pts with prior treatment who were able to achieve meaningful disease control and used as a bridge to transplant. The regimen translated well to a community setting, with relatively low 28-day mortality and good tolerability. Research Sponsor: None.

Age and the genomic landscape of AML in precision oncology: An analysis using ASH HematOmics Program.

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Background: Age is a major determinant of prognosis and treatment selection in acute myeloid leukemia (AML), yet the extent to which chronological age reflects underlying genomic and transcriptomic features remains incompletely characterized. The American Society of Hematology HematOmics Program (ASHOP) provides a centralized, clinically annotated genomic resource enabling systematic evaluation of age-associated AML biology across molecular subtypes. **Methods:** We conducted a cross-sectional analysis of adults with AML using ASHOP data. Patients were categorized by age (<40, 40–59, 60–74, and ≥75 years). AML molecular subtypes were defined based on recurrent cytogenetic and genomic alterations (NPM1, PML::RARA, CBFB::MYH11, MECOM, CEBPA, AML-MR, KMT2A, DEK::NUP214, TP53, and other recurrent translocations), aligned with WHO classification. Adverse genomic risk was defined by AML-MR, MECOM, and TP53. Gene expression levels for epigenetic regulators (DNMT3A, TET2, IDH1, IDH2, FLT3) and stemness-associated genes (HOXA9, MEIS1, HLF, GATA2, PROM1) were standardized as z-scores, and composite scores generated. Associations were assessed using chi-square tests, linear regression, and multivariable models adjusted for sex. **Results:** Among 302 patients (mean age 71.1 ± 17.3 years; 47.7% aged ≥75; 54.3% male), the most common subtypes were NPM1 (20.5%), PML::RARA (16.6%), CBFB::MYH11 (15.6%), MECOM (14.2%), CEBPA (10.9%), AML-MR (9.6%), and KMT2A (7.6%). Subtype distribution varied modestly across age groups ($p=0.053$) but not by sex ($p=0.858$). Adverse genomic risk increased significantly with age ($p=0.016$). In multivariable logistic regression adjusted for sex, patients aged ≥75 had significantly higher odds of adverse genomic features (OR 2.78, 95% CI 1.26, 6.12; $p=0.011$), while sex was not independently associated ($p=0.325$). In transcriptomic analyses ($n=265$), age was not associated with individual epigenetic or stemness genes, with age and sex explaining minimal variance in composite scores (epigenetic score $R^2=0.013$, $p=0.506$; stemness score $R^2=0.003$, $p=0.957$). In contrast, molecular subtype showed strong associations. Subtype along with age and sex explained 16.4% of epigenetic score variance ($R^2=0.164$; $p<0.001$) and 38.0% of the stemness score variance ($R^2=0.380$; $p<0.001$). Key stemness genes were highly subtype-dependent (HOXA9 $R^2=0.709$; MEIS1 $R^2=0.599$; both $p<0.001$), driven primarily by NPM1 and KMT2A subtypes. **Conclusions:** Advanced age in AML is associated with adverse genomic risk accumulation but explains minimal variance in stemness or epigenetic transcriptional programs. Instead, these programs are largely determined by molecular subtype. Hence, stemness and epigenetic programs are intrinsic properties of AML molecular subtypes rather than age, supporting subtype-driven risk stratification and therapeutic decision-making in the precision oncology era. Research Sponsor: None.

From infancy to young adulthood: Exploring the divergent genomic mechanisms that drive AML.

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Background: Pediatric & young adult Acute Myeloid Leukemias (pAML & YA AML) are an uncommon, heterogenous, & clinically challenging group of malignancies, as age ranges widely & proper therapy selection (i.e. pediatric vs. adult regimens, etc.) can be unclear. The genomics of these disorders can help understand distinct disease biology, better risk stratification, & improve outcomes. **Methods:** Bone marrow, peripheral blood, or FFPE samples from 870 suspected AML patients were sequenced using a 302 gene panel to detect SNVs/indels. 466 underwent RNA fusion detection of 184 genes & DNA analysis for CNV detection of 24 genes. Only pathogenic/likely pathogenic variants were included in the analysis. AML patients were split into 4 groups based on age: Infant (≤ 3 , n=30), Childhood (4-14, n=51), Adolescent (15-19, n=51), YA (20-35, n=738). 4750 DNA/RNA sequenced adult AML patients (>35) were also included in the analysis. Statistics were performed using Fisher's exact test. **Results:** pAML patients (infant, childhood, & adolescent) had a high prevalence of FLT3 & NRAS variants (17.4% & 15.2%) & fusions (26.2%) while YA AML had a high prevalence of fusions (29.2%), FLT3 (20%), NRAS (12.5%), & WT1 (12.6%) variants. Adult AML had a high prevalence of TET2 (18.4%), DNMT3A (18.3%), ASXL1 (16.8%), SRSF2 (14.8%), & TP53 (14.2%) variants, highlighting an increased prevalence of mutations associated with clonal hematopoiesis or prior chronic myeloid neoplasms. Infant AML had a higher number of GATA1 variants (33.3% vs. 0% - 2%, $p<0.00001$) vs. childhood, adolescent, & YA AML; trisomy 21 was present in 90% of patients by CNV detection. Fusions were only found in 5% of infant AML ($p=0.02$) vs. 29.2% - 34.5% in other groups. FLT3 variants were lower in infant (10%) and childhood AML (13.7%) vs. adolescent (25.5%) & YA (20%) while NRAS variants were higher in adolescent AML (21.6% vs. 6.7% - 13.7%). Childhood AML had a higher prevalence of RUNX1 fusions (16.1% vs. 0 - 5.4%, $p=0.03$) & Adolescent AML had a higher prevalence of PML::RARA fusions (13.8% vs. 0% - 6.5%) vs. other groups. YA AML had a higher prevalence of WT1 variants (12.6% vs. 0% - 7.8%, $p=0.02$). CNV loss in IKZF1 (7p12) were more prevalent in adolescent AML (10.3% vs. 0 - 0.5%, $p=0.002$); EZH2 CNV loss (7q36) were more prevalent in YA & childhood AML (4.7% & 3.4% vs. 0%). Upon aggregating genes by their molecular function, infant AML had a lower prevalence of variants in epigenetic genes (6.7% vs. 15.57-24.8%, $p=0.02$), RAS (10% vs. 23.2%-25.5%), & signaling genes (16.7% vs. 27.5% - 41.2%). Variants in DNA repair genes were more frequent in adolescent AML (13.7% vs. 3.9% - 6.7%, $p=0.01$). **Conclusions:** Infant, childhood, adolescent, & YA AML harbor unique genetic profiles that distinguish themselves from each other and reflect divergent and evolutionarily favored mechanisms behind leukemogenesis. Understanding these genetic profiles can help predict prognosis & help tailor more effective treatments. Research Sponsor: None.

TP53 mutation adoption of stromal-adhesion/neuronal-like programs as a driver of stress adaptation and acute myelogenous leukemia cell survival.

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Background: TP53-mutated AML is associated with early relapse and poor survival, highlighting the need to define p53-driven transcriptional programs that may reveal targetable therapeutic vulnerabilities. Systematic deconvolution of the TP53-associated transcriptome provides a critical framework to uncover dependencies associated with drug resistance. **Methods:** After IRB approval, 311 AML patients were screened; 93 (30%) with available NGS were included (32 TP53-mutated, 61 TP53-wild type). Bulk transcriptome data were available for 11 TP53+ and 13 TP53-WT cases. Overall survival was analyzed using Kaplan–Meier and multivariable Cox regression. Transcriptional modules predictive of TP53+ AML were identified using Random Forest and pathway enrichment via KEGG/Reactome with confirmation by ToppGene. Public single-cell RNA-seq datasets from the MIT Single Cell Portal were queried to assess whether low TP53 expression states recapitulate bulk TP53-mutated transcriptional programs. **Results:** OS was 168 and 624 days (d) in TP53+ and TP53 WT cases (HR = 4.2, $p = 0.02$). Only CK retained independent effect for OS (HR = 0.33, 95% CI = 0.13–0.82, $p = 0.014$) when accounting for TP53 mut status and age. TP53 mut status imprinted a deep transcriptomic signature (AUC = 0.94). Top upregulated genes included FHL2 ($p = 4.0 \times 10^{-6}$, FDR = 0.004), HMGA2 ($p = 1.4 \times 10^{-3}$, FDR = 0.02), ARHGEF12 ($p = 5.2 \times 10^{-3}$, FDR = 0.04), RYR3 ($p = 2.1 \times 10^{-3}$, FDR = 0.03), LRRC7 ($p = 7.7 \times 10^{-3}$, FDR = 0.05), ALDH1A1 ($p = 1.4 \times 10^{-3}$, FDR = 0.02). Top downregulated genes included CSF1 ($p = 4.7 \times 10^{-4}$, FDR = 0.007), CD34 ($p = 1.2 \times 10^{-3}$, FDR = 0.01). To uncover pathway-level shifts co-opted by TP53+ AML, we contrasted pathway-level projection against TP53 WT cases. Upregulated pathways included adhesion / stromal dependence ($p = 0.0004$; FDR = 0.0028), neurotrophin / calcium signaling / Ca²⁺-coupled survival ($p = 0.0006$, FDR = 0.0021). However, downregulated pathways included cytokine-cytokine receptor interaction ($p = 4.7 \times 10^{-4}$, FDR = 0.007) and myeloid differentiation ($p = 1.2 \times 10^{-3}$, FDR = 0.01) [Fig. 2]. Interestingly, in lineage-resolved single-cell reference, low TP53 GE was visually colocalized with perivascular/stromal cells exhibiting high FHL2 and THY1 (CD90) expression. This data reconfirms prior data suggesting that reduced TP53 function favors niche-adapted perivascular/MSC-like reprogramming (THY1-high) that protects “resistant AML clones” (Mizuno et al., ASH 2024). **Conclusions:** These findings unveil that TP53+ AML co-opts leukemic blasts toward a stromal-adhesive and neuronal-like state, allowing survival under metabolic and therapeutic stress. Reversing stromal adhesive / neuronal-like rewiring may attenuate TP53+ blasts hijacking on vascular niche that maintains relapse potential. Research Sponsor: None.

Induction failure (IF) as a prognostic marker in adult acute lymphoblastic leukemia (ALL).

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Background: Despite advances in the treatment of adult ALL, risk factors for IF and optimal management are poorly understood. We aimed to characterize patients (pts) with IF after therapy for newly diagnosed (nd)ALL and their outcomes. **Methods:** We performed a retrospective chart review of adult ndALL pts treated at Weill Cornell Medicine from 2012–2025. We defined IF as failure to achieve < 5% bone marrow blasts, count recovery and extramedullary disease clearance after 1 cycle of induction. Fisher's exact test was used for analysis of discrete variables and Wilcoxon rank-sum test for continuous ones. **Results:** Among 220 pts, 48.2% were female, mean age at diagnosis was 50.5 (18–87) yrs, 74.5% had B-cell ALL (of which 41.5% Ph+), with median follow-up 24.5 months. 34 pts (15.5%) had IF (22 B cell, 12 T cell). B-cell IF patients were more likely to have Ph– (77.3% vs 50%, $p=0.0211$) or Ph-like phenotype (13.6% vs 3.5%, $p=0.0753$). IF pts were more likely to have CNS disease at diagnosis ($p=0.034$). There was no significant difference in baseline median white cell count (13.18 vs 9.60 $p=0.4$) or LDH (448 vs 517 $p=0.17$) in IF vs non-IF pts. IF was not associated with age, asparaginase-treatment, BMI, abnormal cytogenetics, pertinent mutations, or year of diagnosis. On multivariable logistic analysis controlling for age and lineage, CNS disease at diagnosis remained associated with IF (OR 2.81, $p=0.0343$). Overall survival (OS) was significantly worse in IF vs non-IF pts at 3-years (29.2% vs 66.8%, $p=0.0002$). OS did not vary by CNS disease at diagnosis in IF pts. Of IF pts, 27/34 (79.4%) achieved CR with subsequent therapy (median time to CR 68.5 days, range 21–228), with improved survival vs the 7 pts (5 B cell, 2 T cell) who did not ($p=0.00001$). 4/7 patients without CR died within 4 months, and none of these 7 patients received allo-SCT. In the 27 IF pts attaining later CR, there was a trend towards worse OS vs non-IF pts (1029 days vs not reached, $p=0.0659$), though importantly a subset of 10 pts who achieved minimal residual disease (MRD)-negativity had OS similar to the non-IF group ($p=0.95$). IF patients were more likely to receive allo-SCT than non-IF patients (51.4% vs 29.7%, $p=0.0164$). Receiving allo-SCT tended to be associated with improved survival in this group ($p=0.0578$) vs no allo-SCT. 16/22 B cell IF patients received blinatumomab and/or inotuzumab. These were not associated with MRD-negative status or allo-SCT, but did show a trend towards subsequent CR ($p=0.1$) and better OS ($p=0.1119$). **Conclusions:** In our single-center retrospective cohort of ALL pts, 15.5% had IF. 29.4% of these patients (4.5% of the total cohort) were able to achieve MRD- status with subsequent treatment, resulting in outcomes comparable to pts without IF. ALL-IF patients should be closely monitored for MRD and may benefit from early application of immunotherapeutic approaches and/or allo-SCT. Research Sponsor: None.

Phase 1 study of venetoclax combined with a 10-day regimen of decitabine in subjects with high-risk acute myeloid leukemia.

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Background: We and others have reported the antileukemic activity of a 10-day regimen of the hypomethylating agent (HMA), decitabine (DEC), in high-risk acute myeloid leukemia (AML). Venetoclax (VEN), at a standard (std) dose of 400 mg, combined with HMA, at a std schedule, has improved AML outcomes. We aimed to investigate the safety of adding VEN to the 10-day regimen of DEC and explore the effects of BCL2 inhibition on the immune repertoire. **Methods:** This was a multicenter, investigator-initiated, dose-escalation study in adults with high-risk AML defined as, disease with a *TP53* mutation, adverse-risk cytogenetics or relapsed/refractory (R/R). Patients (pts) were naïve to HMA and VEN. The primary endpoint was to establish the maximum tolerated dose (MTD) of VEN when combined with a 10-day DEC schedule. Dose-limiting toxicities (DLT) were evaluated during cycle 1. In the absence of a DLT, 3–6 evaluable pts were enrolled per dose level (DL) or until the 400mg DL of VEN was reached (Table 1). Peripheral blood mononuclear cells (PBMCs) were isolated before and after treatment. Shifts in the immune landscape and BCL2 family expression were profiled with spectral flow cytometry. **Results:** 14 pts were enrolled, with a median age of 66.5 years (range 19–77); including 9 pts (64%) with R/R AML, 8 (57%) with adverse-risk cytogenetics and 6 (43%) with a *TP53* mutation. One pt had a DLT at DL1, due to grade (G) 4 neutropenia and persistent marrow aplasia in the absence of leukemia beyond day 42. One patient with R/R AML and pre-existing elevated alanine aminotransferase (ALT) secondary to known graft-versus-host disease developed G2 ALT elevation. 3 pts were then enrolled at DL-1, before reescalation back up to DL1. 2 pts at DL1 were deemed not eligible for DLT evaluation, requiring an additional 2 pts enrolled at DL1, without DLT, to confirm safety. The MTD was determined to be DL2 (400 mg). 5 pts (36%) had a complete remission (CR) or CR with incomplete count recovery (CRi). Non-hematologic or infectious G1–2 toxicities included fatigue (43%), diarrhea (43%) and decreased appetite (36%). 1 pt died of suspected sepsis outside of the DLT evaluation period. 7 pts had serial PBMCs available for multiparameter flow cytometric immune and BCL2 family profiling. Of these, 3 responders had strong induction of BCL2 in CD4+/CD8+ lymphocytes and B cells after 1 cycle and were enriched for a population of “senescent” CD8+ T cells that had relatively low expression of coinhibitory markers (PD-1, LAG3, TIM3). **Conclusions:** A 10-day DEC+VEN regimen is feasible in high-risk AML, with myelosuppression being the major DLT. The recommended phase 2 dose is 400mg VEN (DL2), but responses were also seen at 200mg. The immune profile of responders have demonstrated intriguing patterns that merit investigation in a larger HMA+VEN cohort. Clinical trial information: NCT03844815. Research Sponsor: Abbvie.

DL	DEC dose(D1-10)mg/m2	VEN dose (D1-21)mg	# of pts	DLT	CR	CRi	No Response
-1	15	100	3	0	0	0	3
1	20	200	8	1	1	3	4
2	20	400	3	0	0	1	2

Time to response with HMA/venetoclax as a predictor of survival in acute myeloid leukemia: Analysis of 1- vs 2-cycle responders.

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Background: Hypomethylating agents (HMA) with venetoclax are the standard of care for patients with AML ineligible for intensive chemotherapy. However, the prognostic significance of time to response and the optimal duration of venetoclax, often modified in real-world practice due to myelosuppression, remain unclear. **Methods:** We conducted a retrospective analysis of adults with AML achieving CR/CRi with HMA/venetoclax at University of Kentucky from 2016–2025. Patients were stratified by cycle of response: 1 vs 2 cycles, using ELN 2022 response criteria. These groups were compared by demographics, cytogenetic and mutational profiles, and allogeneic HSCT. RFS and OS were estimated using Kaplan–Meier methods and compared with log-rank tests. Cox models evaluated associations between cycle of response, response type (CR vs CRi), and survival outcomes. **Results:** Eighty-six responding patients were included, with 69 (80%) achieving response after 1 cycle and 17 (20%) achieving response after 2 cycles. Median age was 66.7 vs. 67.1 years, male sex was 58% vs. 76%, and ELN risk distribution was similar: favorable 25% vs. 18% and adverse 64% vs. 65% ($p=0.671$). Frequent cytogenetic profiles included normal karyotype (44% vs. 41%) and complex karyotype (27% vs. 24%), and common mutations included *IDH1/2* (23% vs. 18%), *DNMT3A* (19% vs. 24%), and *NPM1* (22% vs. 12%). Overall, baseline demographics and cytogenetic/mutational profile were similar between 1-cycle and 2-cycle responders, supporting comparability of these groups for outcome analyses. With a median follow-up of 23.8 months, relapse occurred in 36% of 1-cycle responders vs. 82% of 2-cycle responders ($p=0.002$). Inferior RFS was noted in 2-cycle responders (HR 3.04, $p=0.002$), which remained after adjusting for total venetoclax exposure (HR 3.26, $p=0.002$). Median OS was 22.8 months (95% CI 14.0–NR) for 1-cycle responders and 12.7 months (95% CI 7.2–NR) for 2-cycle responders ($p=0.01$). In Cox models, 2-cycle response was associated with significantly inferior OS (HR 2.33, $p=0.012$), which persisted after adjusting for venetoclax exposure (HR 2.26, $p=0.018$). Hematologic recovery at time of CR was assessed and was not significantly associated with cycle of response or survival outcomes. Increased venetoclax exposure was associated with improved OS (HR 0.82 per day; $p=0.049$). When venetoclax exposure was dichotomized, receipt of ≤ 14 days was associated with inferior OS (HR 2.49; $p=0.028$). In this cohort, 6% of 1-cycle responders and 18% of 2-cycle responders proceeded to allogeneic HSCT ($p=0.14$). **Conclusions:** Delayed response beyond 1 cycle in patients receiving HMA/venetoclax identifies AML patients at higher risk of relapse and inferior survival. Time to response can inform early risk-adapted strategies, including venetoclax optimization. Research Sponsor: None.

Cladribine/cyclophosphamide lymphodepletion efficacy and toxicity in CD19 CAR-T therapy for B-ALL.

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Background: During an international fludarabine (Flu) shortage, our center adopted cladribine (Cla) as a substitute for Flu with cyclophosphamide (Cy) for lymphodepletion (LD) prior to CAR-T therapy in patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL). We evaluated clinical outcomes and toxicity with Cla/Cy LD. **Methods:** We conducted a retrospective, single-center analysis of R/R B-ALL patients who received CD19-directed CAR-T therapy between January 2018 and April 2025. The Cla/Cy regimen substituted Flu 30 mg/m² with Cla 5 mg/m²/day on days -5 to -3. ALL-HT risk was calculated (Nair et al, 2025). CRS and ICANS were graded per ASTCT; cytopenias per CTCAE v5.0. Early (<30 days) and late (31-100 days) infections were assessed. Overall survival (OS), Event free survival (EFS, event=progression or death) and Minimal residual disease (MRD) status by clonoSEQ assay at Day 30 bone marrow biopsy were assessed. **Results:** We analyzed 53 patients (brexu-cel n=49; tisa-cel n=4). 28 received Flu/Cy and 25 received Cla/Cy. Baseline characteristics are outlined in Table 1. Three patients died before day 30 and two before day 100. Ten patients underwent allo-SCT within 6 months of CAR-T. Rates of grade ≥3 CRS (4% vs 12%, p=0.29) and ICANS (40% vs 24%, p=0.25) did not differ. MRD negativity at day 30 was comparable (Cla/Cy 81.8% vs Flu/Cy 75.0%, p=0.71). Early infection rates were similar; however, late infections were more frequent with Flu/Cy (48% vs 17.4%, p=0.034), with a persistent trend after ALL-HT adjustment (adjusted OR 3.54, p=0.073). Grade ≥3 thrombocytopenia (35.7% vs 8.0%, p=0.022) and neutropenia (25.0% vs 4.0%, p=0.05) at day 90 were higher with Flu/Cy, with similar trends after adjustment (adjusted OR 4.71, p = 0.082 and adjusted OR 7.88, p = 0.067, respectively). Neutrophil recovery (ANC >1000) time was comparable (median 17 vs 18 days, p=0.10). With a median follow-up of 14.6(Flu/Cy) and 13.1 months(Cla/Cy), EFS (6.8 vs 18.1 months, p=0.45) and OS (33.9 months vs not reached, p=0.25) were similar. **Conclusions:** Cla/Cy demonstrated comparable efficacy to Flu/Cy with lower toxicity, including fewer late infections and severe cytopenias. These findings suggest Cla/Cy may represent a safer alternative lymphodepletion strategy. Prospective studies are warranted to validate these observations. Research Sponsor: None.

Baseline characteristics of study cohort.			
Characteristic	Flu/Cy (n=28)	Clad/Cy (n=25)	p-value
Age, median (IQR)	38.0 (30.2–58.5)	47.0 (26.0–64.0)	0.77
Male sex, n (%)	18 (64.3)	13 (52.0)	0.53
White race, n (%)	25 (89.3)	20 (80.0)	0.35
KPS ≥80, n (%)	24 (85.7)	21 (84.0)	1.00
Marrow blasts pre-LD, median (IQR)	2.0 (1.0–3.5)	1.5 (0.5–11.0)	0.67
Ph+ ALL, n (%)	11 (39.3)	12 (48.0)	0.78
Prior allo-HSCT, n (%)	6 (21.4)	7 (28.0)	0.56
Prior lines of therapy, median (IQR)	2 (2–3)	3 (2–3)	0.96
High-risk ALL-HT, n (%)	12 (42.9)	3 (12.0)	0.016

A phase II, single-arm study of romiplostim N01 for cancer treatment–induced thrombocytopenia in leukemia patients.

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Background: Cancer Treatment–Induced Thrombocytopenia (CTIT) poses a significant challenge in leukemia treatment, increasing bleeding risk and potentially disrupting therapy. Romiplostim N01 is recommended for CTIT but lacking specific clinical data in leukemia patients. This study evaluates its efficacy and safety in this population. **Methods:** This is a multi-center, single-arm, phase II study conducted from February 2025 to February 2027. We plan to enroll 97 adult patients (18 – 75 years) with leukemia who developed CTIT (platelets $< 50 \times 10^9/L$) after antitumor therapy. Patients received subcutaneous Romiplostim N01 at a starting dose of 5 $\mu g/kg$ once weekly for up to 8 weeks. The primary endpoint is the proportion of patients achieving platelet recovery ($\geq 50 \times 10^9/L$) after two week. Secondary endpoints include response rate within 7 days, median time to platelet recovery ($\geq 50 \times 10^9/L$ and $\geq 100 \times 10^9/L$), platelet transfusion requirements, and safety. **Results:** As of January 27, 2026, a total of 49 subjects were enrolled (18 males, 31 females) with a median age of 57 years (range, 17–75). Primary tumor types included acute myeloid leukemia (AML, n=40), acute lymphoblastic leukemia (ALL, n=7), mixed phenotype acute leukemia (MPAL, n=1), and myelodysplastic syndromes (MDS, n=1). All patients received standard chemotherapy and had an ECOG performance status of 0–2 at enrollment; 35 of 49 patients had an ECOG score of 0–1. All subjects received Romiplostim N01 (5 $\mu g/kg/week$): 13 subjects received one dose, 14 received two doses, and 22 received ≥ 3 doses. The median baseline platelet count was $15 \times 10^9/L$ (range, $1–49 \times 10^9/L$). 40.8% (20/49) of patients achieved a response within 7 days. 23 subjects (46.9%, 23/49) achieved the primary endpoint (platelet count $\geq 50 \times 10^9/L$) within two weeks. The median time to platelet recovery $\geq 50 \times 10^9/L$ was 7 days (95% CI, 6–9). A total of 21 patients achieved a platelet count of $\geq 100 \times 10^9/L$; the median time to recovery was 13 days (95% CI, 10–22). The median platelet transfusion dose was 2.0 units (95% CI, 1–3). Adverse events were mild to moderate, most commonly infections. No treatment-related serious adverse events (SAEs) were reported. **Conclusions:** Preliminary findings suggest Romiplostim N01 may be effective in promoting platelet recovery with a manageable safety profile in leukemia patients with CTIT. Final results will provide further evidence for its clinical application. Clinical trial information: NCT06898983. Research Sponsor: National Natural Science Foundation of China (82270223 82500286); Anhui Provincial Health Research Project (AHWJ2024BAa10021); Anhui Provincial Department of Education Scientific Research Project (2023AH010079); Anhui Provincial Natural Science Foundation (2308085J09); USTC Research Funds of the Double First-Class Initiative (YD9110002109).

Comparative effectiveness and toxicity of CAR-T therapy versus blinatumomab in adult B-cell acute lymphoblastic leukemia: A real-world propensity-matched analysis.

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Background: Chimeric antigen receptor T-cell (CAR-T) therapy and blinatumomab are established treatment options for relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL). While CAR-T therapy offers durable disease control, it is associated with significant immune-mediated toxicities, including cytokine release syndrome (CRS) and neurotoxicity. Comparative real-world data evaluating long-term mortality and toxicity outcomes between CAR-T therapy and blinatumomab remain limited. **Methods:** We conducted a retrospective cohort study using the TriNetX Analytics Network. Adult patients with B-cell acute lymphoblastic leukemia treated with either CAR-T therapy or blinatumomab were identified. Propensity score matching (1:1) was performed to balance baseline demographic and clinical characteristics, yielding 306 patients in each cohort. Primary outcomes included all-cause mortality at 1 and 3 years. Secondary outcomes included cytokine release syndrome at 1 year and neurotoxicity (including delirium, encephalopathy, and altered mental status) at 3 months, 1 year, and 3 years. Outcomes were assessed using risk ratios (RR), odds ratios (OR), Kaplan–Meier survival analysis, and Cox proportional hazards models. **Results:** After propensity matching, 612 patients were analyzed (306 per cohort). At 1 year, all-cause mortality was significantly higher with CAR-T than blinatumomab (50.98% vs 17.97%; RR 2.84, 95% CI 2.18–3.69; $p < 0.0001$). Kaplan–Meier analysis showed inferior survival with CAR-T (HR 3.48, 95% CI 2.56–4.74; log-rank $p < 0.0001$). This excess mortality persisted at 3 years (52.61% vs 18.95%; RR 2.78, 95% CI 2.15–3.58; $p < 0.0001$; HR 3.43, 95% CI 2.54–4.63). CAR-T was associated with higher cytokine release syndrome at 1 year (20.59% vs 5.88%; RR 3.50, 95% CI 2.12–5.77; $p < 0.0001$). Neurotoxicity was consistently more frequent with CAR-T: 27.78% vs 13.40% at 3 months (RR 2.07, 95% CI 1.48–2.91; $p < 0.0001$), 25.16% vs 11.44% at 1 year (RR 2.20, 95% CI 1.52–3.18; $p < 0.0001$), and 27.78% vs 13.40% at 3 years (RR 2.07, 95% CI 1.49–3.15; $p < 0.0001$). Kaplan–Meier analyses confirmed a persistently higher cumulative neurotoxicity risk with CAR-T across all time points. **Conclusions:** In this large real-world propensity-matched analysis, CAR-T therapy for B-cell ALL was associated with significantly higher short- and long-term mortality compared with blinatumomab, as well as markedly increased risks of cytokine release syndrome and neurotoxicity. These findings highlight the substantial toxicity burden associated with CAR-T therapy in routine clinical practice and underscore the importance of careful patient selection, early toxicity recognition, and risk-benefit stratification when choosing between advanced immunotherapeutic options for B-ALL. Research Sponsor: None.

Frailty-comorbidity discordance and non-relapse mortality after allogeneic hematopoietic cell transplantation.

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Background: Non-relapse mortality (NRM) is a barrier to successful allogeneic hematopoietic cell transplantation (HCT). The HCT-Comorbidity Index (HCT-CI) is used for pre-HCT risk assessment but does not capture physiological reserve. Frailty, assessed by the validated Hematopoietic Cell Transplantation-Frailty Scale (HCT-FS), independently predicts post-HCT outcomes; however, the clinical consequences of frailty-comorbidity discordance remain poorly defined. We hypothesized that such discordance identifies patients whose transplant risk may be misclassified by HCT-CI alone. **Methods:** We retrospectively analyzed 692 patients undergoing first allogeneic HCT at our center. Frailty was assessed using HCT-FS and categorized as fit, pre-frail, frail. For discordance analyses, HCT-FS was dichotomized as fit vs pre-frail/frail. HCT-CI was dichotomized as low (<3) vs high (≥ 3). Patients were classified into 4 groups: fit+low HCT-CI (group I), fit+high HCT-CI (group II), pre-frail/frail+low HCT-CI (group III), and pre-frail/frail+high HCT-CI (group IV). Fine-Gray competing-risk models and Cox regression was used for NRM and overall survival (OS), respectively. **Results:** The median age was 61 years (Q1-Q3: 52-67), and 399 (58%) were male. At baseline, 287 (42%) patients had an HCT-CI ≥ 3 . HCT-FS classified 252 (36%) as fit, 373 (54%) as pre-frail, and 67 (10%) as frail. Overall, 355 (51%) patients demonstrated discordant HCT-FS and HCT-CI scores: 78 (11%) as group II, and 277 (40%) classified as group III. At 2 years, NRM and OS were 11.2% (95% CI, 7-16) and 79.3% (95% CI, 73-84) in fit patients, 17.4% (95% CI, 14-22) and 67.0% (95% CI, 62-72) in pre-frail patients, and 33.5% (95% CI, 22-45) and 54.9% (95% CI, 42-66) in frail patients, respectively ($p < 0.01$ for both). In multivariable analyses, HCT-FS, HCT-CI, and age at HCT were independently associated with NRM and OS. Compared with fit patients with low HCT-CI (group I), pre-frail/frail patients with HCT-CI ≥ 3 (group IV) experienced the highest risk of NRM (sub-distribution hazard ratio (sHR) 2.7, 95% CI 1.5-5, $p < 0.01$). Pre-frail/frail patients with HCT-CI < 3 (group III) also had an increased risk of NRM (sHR 1.9, 95% CI 1.1-3.5, $p = 0.01$). Fit patients with HCT-CI ≥ 3 (group II) did not have a significant increase in NRM risk (sHR 1.7, 95% CI 0.8-3.7, $p = 0.15$). The corresponding HR for OS were 2.1 (95% CI 1-3; $p < 0.01$) for group IV, 1.7 (95% CI 1-3; $p < 0.01$) for group III, and 1.4 (95% CI 0.8-2.5; $p = 0.18$) for group II, compared with group I. **Conclusions:** Frailty-comorbidity discordance was observed in 51% of patients and has prognostic implications. Pre-frail and frail patients with low HCT-CI experience higher NRM than would be predicted by HCT-CI alone, suggesting underestimation of transplant risk when frailty is not assessed. Integrating HCT-FS with HCT-CI may improve risk stratification and better identify patients at high risk for NRM. Research Sponsor: None.

Clinical outcomes of *TP53*-mutated myeloid neoplasms after allogeneic hematopoietic cell transplantation: A Canadian multicenter propensity score–matched analysis.

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Background: *TP53* mutations define a biologically aggressive subset of myeloid malignancies with poor outcomes. We evaluated clinical, disease-related, and transplant-associated variables influencing post-allogeneic hematopoietic cell transplant (HCT) outcomes in this high-risk group. **Methods:** We conducted a retrospective multicenter study across 10 Canadian transplant centers, including 153 individuals with *TP53*-mutated and 2,207 patients with *TP53* wild-type acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) from the Cell Therapy and Transplant Canada (CTTC) registry. Propensity score matching was performed to account for baseline differences. The primary outcomes were relapse and overall survival (OS) after HCT. **Results:** Presence of *TP53* mutation was associated with increased risk of relapse compared with *TP53* wild-type (HR 2.21; 95% CI: 1.5–3.1; $p < 0.01$). Among *TP53*-mutated patients ($n=153$), with a median follow-up of 35.8 months (Q1–Q3: 29–48), the 2-year cumulative incidence of relapse was 53.2% (95% CI: 44.4–61.2), and OS 40.1% (95% CI: 31.6–48.4). In multivariable analysis, multi-hit *TP53* mutations (HR 2.17, 95% CI: 1.3–3.7; $p < 0.01$), and graft-vs-host disease (GVHD) prophylaxis regimens containing anti-thymocyte globulin (ATG) with (HR 3.53, 95% CI: 1.5–8.1; $p < 0.01$) or without (HR 2.59, 95% CI: 1.2–5.6; $p = 0.01$) post-transplant cyclophosphamide were associated with higher relapse risk. Conditioning regimen intensity, and chronic GVHD, modelled as a time-dependent covariable, did not significantly impact relapse, while chronic GVHD was associated with improved OS (HR 0.46; 95% CI: 0.2–0.9, $p = 0.03$). **Conclusions:** In patients with myeloid malignancies, *TP53* mutations are associated with a high risk of relapse and poor survival after HCT, while chronic GVHD appears to be protective, underscoring the importance of careful selection of GVHD prophylaxis and the need for effective post-transplant strategies in this high-risk population. Research Sponsor: None.

Multivariable analysis.			
Variable	Hazard Ratio	95% CI	p value
Relapse			
<i>TP53</i> mutation status			
Single hit	Ref	Ref	Ref
Multi hit	2.17	1.27–3.71	0.005
Disease risk index			
Intermediate	Ref	Ref	Ref
High/very high	1.53	0.77–3.03	0.220
GVHD prophylaxis			
CNI-MTX	Ref	Ref	Ref
ATG-CNI-MTX	2.59	1.21–5.56	0.014
ATG-PTCY-CNI	3.53	1.52–8.17	0.003
PTCY-CNI-MMF	1.66	0.58–4.74	0.350
Chronic GVHD (time dependent)	1.25	0.63–2.45	0.526
Overall survival			
<i>TP53</i> mutation status			
Single hit	Ref	Ref	Ref
Multi hit	2.26	1.30–3.90	0.003
Disease risk index			
Intermediate	Ref	Ref	Ref
High/very high	0.93	0.49–1.77	0.823
GVHD prophylaxis			
CNI-MTX	Ref	Ref	Ref
ATG-CNI-MTX	2.18	1.12–4.24	0.021
ATG-PTCY-CNI	1.62	0.73–3.61	0.236
PTCY-CNI-MMF	1.04	0.36–2.99	0.949
Chronic GVHD (time dependent)	0.46	0.23–0.93	0.030

Allele-specific targeting of CD33 as a novel approach to enhance CAR-T selectivity in relapsed acute myeloid leukemia post–allogeneic transplantation.

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Background: Relapse after allogeneic hematopoietic cell transplant (HCT) represents the most common treatment failure in acute myeloid leukemia (AML), urging the need for new therapies. Chimeric antigen receptor (CAR) T cells have shown efficacy in lymphoid and plasma cell malignancies but have not yet successfully translated to myeloid disease. This could in part be due to the expression of target antigens on normal myeloid cells, which might result in significant on-target but off-tumor effects. Exploiting a single nucleotide polymorphism (SNP) in *SIGLEC3*, which encodes CD33, to target relapsing AML cells while selectively sparing donor-derived hematopoietic cells could improve the efficacy of anti-CD33 CAR-T cells in treating AML. **Methods:** We evaluated the *in vitro* efficacy and specificity of CAR-T cells that target each of two alleles of a common SNP in CD33 (rs2455069, *CD33 Arg69Gly*). Controls included untransduced activated T-cells (UTD, negative control) and CAR-T cells targeting a different CD33 epitope (CART33^{Pan} positive control). Effector cells were incubated with CD33-expressing AML targets for 24 hours at serial effector-to-target ratios, and surviving target cells were quantified via flow cytometry to calculate percent cell killing. Initial screens used Jurkat cells lentivirally transduced with CD33 of each polymorphism (Jurkat33^{Gly} or Jurkat33^{Arg}) to characterize CAR-T efficacy and specificity. Subsequent tests used MOLM-13 (homozygous CD33^{Arg}) and KG-1 (homozygous CD33^{Gly}) AML cell lines. Statistical comparisons of generated CAR-T cytotoxicity curves were performed with two-way ANOVA. Killing assays were performed with at least six biologic replicates. **Results:** CART33^{Gly} and CART33^{Arg} cells each showed statistically equivalent killing against their concordant Jurkat33 targets compared to CART33^{Pan} cells. Each CAR directed minimal killing of discordant Jurkat33 targets, similar to UTD controls. In KG-1 (CD33^{Gly}) cells, CART33^{Gly} showed similar killing efficacy as CART33^{Pan} cells, while CART33^{Arg} were statistically equivalent to UTD cells at multiple E:T ratios. In MOLM-13 (CD33^{Arg}) cells, CART33^{Gly} and CART33^{Arg} exhibited mixed efficacy and specificity: at lower E:T ratios (1:16 to 1:8), CART33^{Gly} was statistically equivalent to untransduced controls, but began to demonstrate more nonspecific toxicity at E:T above 1:4. CART33^{Arg} exhibited significant cytotoxicity once above E:T of 1:8, but only achieved similar toxicity to CART33^{Pan} at E:T ratios over 1:2. **Conclusions:** Allele-specific CART33 cells demonstrate promising efficacy and specificity in killing AML cells expressing either CD33^{Gly} or CD33^{Arg}. Further studies are underway to test efficacy *in vivo* against primary AML cells and safety toward normal hematopoietic progenitor cells that express the alternative CD33 allele. Research Sponsor: None.

Pre-transplant MRD negativity and TP53 mutation status determine survival after CAR-T therapy bridged to allo-HSCT for refractory/relapse B-ALL.

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Background: The feasibility and outcomes of bridging relapsed/refractory (R/R) B-lineage acute lymphoblastic leukemia (B-ALL) patients to allogeneic hematopoietic stem cell transplantation (allo-HSCT) following CAR-T therapy require further investigation. This study evaluated long-term outcomes and prognostic factors in this setting. **Methods:** We conducted a retrospective analysis of 300 consecutive R/R B-lineage leukemia patients (295 B-ALL, 98.3%) who underwent allo-HSCT after CAR-T therapy. Somatic mutation screening via next-generation sequencing was performed on 179 patients. Univariate Cox regression analyzed factors associated with transplant outcomes. A contemporaneous cohort of 36 transplanted patients without prior CAR-T served as a comparator. **Results:** Median age at transplant was 14 years (range, 1-68). Prior to HSCT, 220 (73.3%), 75 (25.0%), and 5 (1.7%) patients received CD19-, CD22-, and Mix-CAR-T, respectively; 265 (88.3%) achieved complete remission (CR), and 39 (13.0%) were minimal residual disease (MRD)-positive. The 3-year disease-free survival (DFS), overall survival (OS), cumulative incidence of relapse (CIR), and non-relapse mortality (NRM) for the CAR-T bridging cohort were 64.0% (95%CI, 58.6-69.8%), 74.5% (95%CI, 69.5-79.9%), 28.4% (95%CI, 23.6-34.1%), and 7.6% (95%CI, 5.04-11.3%), respectively. Outcomes did not differ significantly from the non-CAR-T cohort (OS, $p=0.54$; DFS, $p=0.24$). Failure to achieve CR pre-HSCT ($HR=3.31$, $p<0.0001$) and MRD-positivity ($HR=3.69$, $p<0.0001$) were risk factors for relapse, while chronic graft-versus-host disease was protective ($HR=0.35$, $p=0.0002$). Pre-HSCT MRD-positivity, fungal infection, and viral cystitis increased NRM risk. TP53 (15.1%), KMT2D (14.5%), NRAS (14.0%), KRAS (13.4%), and ABL1 (9.5%) were the most frequently mutated genes. TP53 mutation was a significant risk factor for inferior DFS ($HR=3.37$, $p<0.0001$) and OS ($HR=3.56$, $p<0.0001$). GNAS and KDM6A mutations predicted higher CIR, while ETV6 mutation was associated with increased NRM. **Conclusions:** Bridging to allo-HSCT after CAR-T therapy is a feasible and effective strategy for R/R B-ALL, providing substantial long-term survival. Achieving pre-transplant CR and MRD-negative status is critical for outcome. Somatic mutations, particularly TP53, hold significant prognostic value, aiding in risk stratification and treatment optimization for these patients. Research Sponsor: None.

MSNPseq: An NGS-based assay for chimerism detection and risk assessment in allogeneic HSCT.

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Background: Chimerism (CHIM) analysis assesses the ratio of donor to recipient hematopoietic cells, confirming engraftment and detecting impending graft failure or relapse, in allogeneic hematopoietic stem cell transplantation (aHSCT). However, the conventional short tandem repeat (STR) analysis, has limited sensitivity (1–5%), often missing low-level CHIM. In this retrospective study, Multiple Single Nucleotide Polymorphism sequencing (MSNPseq), an NGS-based assay targeting DNA fragments each harboring 4–8 SNPs, demonstrated superior sensitivity and specificity compared with STR analysis, enabling reclassification of STR-negative cases and improved prognostic stratification. **Methods:** MSNPseq, based on Ion AmpliSeq technology, amplifies 100 fragments for sequencing on the Ion Torrent PGM platform, achieving $>2000\times$ depth for 96.8% of loci. Its sensitivity and accuracy were validated in simulated chimeric and post-transplant samples against STR analysis. Calibration models used pre-transplant donor/recipient data to generate tailored correction coefficients. CHIM was assessed via MSNPseq at three 30-day time points (TP1, 2, 3) post-transplant, in 741 aHSCT patients (AML 49.9%, ALL 27.4%, MDS 13.5%, lymphoma 4.7%, others 4.5%). PFS and OS were stratified by CHIM status and its dynamics to evaluate transplant outcomes, prognostic significance, and late relapse. **Results:** CHIM sensitivity was assessed using BCR-ABL1-positive standards. MSNPseq achieved a 0.01% detection limit, outperforming STR (1%) with strong correlation ($R^2 = 0.9953$). CHIM status was classified by donor fraction as complete (cCHIM, 100%), microchimerism (mCHIM, 99% to $<100\%$), subthreshold chimerism (sCHIM, 95% to $<100\%$; below STR sensitivity), and incomplete chimerism (iCHIM, $\leq 95\%$) across three time points. While iCHIM was consistently associated with inferior PFS and OS, sCHIM and mCHIM also showed worse outcomes compared with cCHIM, defining distinct high-risk subsets. CHIM dynamics revealed decreasing sCHIM/mCHIM and increasing cCHIM/iCHIM over time. Notably, a sustained CHIM decrease $>0.5\%$ over two consecutive time points was associated with significantly poorer OS and PFS. Interestingly, sCHIM and mCHIM status, as well as a sustained CHIM decrease $>0.5\%$ over two consecutive time points, were also associated with a high risk of acute graft-versus-host disease (aGvHD). Overall, MSNPseq enables more precise CHIM stratification than STR, improving post-transplant risk assessment. **Conclusions:** MSNPseq's superior sensitivity enables more precise chimerism classification and detection of clinically relevant sCHIM and mCHIM subsets that STR often misses. These refined CHIM categories, along with sustained CHIM decline, correlate with poorer survival and higher aGvHD risk, supporting MSNPseq as a superior tool for post-aHSCT risk stratification and therapeutic guidance. Research Sponsor: None.

Impact of Ori-TTV particles on in vivo CAR-T cell engineering for the treatment of hematologic malignancies.

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Background: CAR-T cell therapy has revolutionized hematological malignancy treatment, yet traditional autologous therapies face substantial logistical and financial challenges. An efficient in vivo CAR-T cell generation platform represents a transformative approach to make immunotherapies more accessible. Here, we report the design and validation of Ori-TTV, a T cell-specific lentiviral vector system capable of directly generating functional CAR-T cells within the body. **Methods:** Ori-TTV was engineered with five synergistic components: (1) an Ori Multiple Targeting Domain (Ori-MTD) for selective delivery to T lymphocytes; (2) a de-targeted fusogen; (3) a T cell-specific synthetic promoter; (4) phagocytosis-resistant modifications; and (5) serum-resistant surface engineering. Ori-TTV encodes a dual-target CAR recognizing CD19 and BCMA, enabling treatment of B-cell malignancies (e.g., non-Hodgkin lymphoma) and plasma cell-derived cancers (e.g., multiple myeloma) with potential extension to autoimmune diseases. **Results:** Ori-TTV particles are produced at high functional titers comparable to conventional broad-tropism lentiviruses and demonstrate significant resistance to macrophage phagocytosis (>50% reduction). The T cell-specific synthetic promoter drives CAR/GFP expression comparable to the EF-1 α promoter in primary T cells while maintaining minimal off-target expression in non-T cells, including HEK293T producer cells and various tumor lines. Ori-TTV efficiently transduces resting T cells, achieving >80% CAR expression in PBMCs in vitro. The resulting CAR-T cells exhibit a predominantly memory phenotype with increased TSCM cells compared to Kymriah-like ex vivo CAR-T cells. Serial killing assays demonstrated potent, multi-round cytotoxicity against CD19+ and BCMA+ target cell lines with varying antigen densities. In vivo efficacy was evaluated in humanized mouse models of NHL and MM. The PBMC humanized mice were challenged with tumors and administered Ori-TTV. Bioluminescence imaging demonstrated robust tumor regression, with complete remissions in the majority of treated animals. Pharmacodynamics revealed efficient in vivo transduction, with CAR-T expansion kinetics showing peak levels at day 13 (20–30% of circulating T cells). Expanded CAR-T cells maintained a memory-enriched phenotype with significantly increased TSCM cells. Long-term monitoring confirmed durable responses without toxicity or vector-related adverse events. Furthermore, in CD34+ humanized mice, single-injection Ori-TTV caused durable depletion of peripheral B cells. **Conclusions:** These findings establish Ori-TTV as a next-generation lentiviral vector system enabling safe, efficient, and selective in vivo CAR-T cell generation. It has the potential to redefine CAR-T therapy by eliminating manufacturing barriers, reducing costs, and expanding patient access. Research Sponsor: None.

Pharmacogenetic (PGx) markers of cardiovascular side effects (CVSEs) in allogeneic hematopoietic cell transplant (HCT) patients receiving post-transplant cyclophosphamide (PTCy).

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Background: PTCy is used to prevent graft versus host disease (GVHD) post-HCT. CVSEs can be observed with Cy. We previously showed 16% of PTCy-treated patients experienced CVSEs within 30 days post-HCT. PGx determinants of Cy metabolism have been explored, but data are lacking on the impact of PGx on PTCy-related CVSEs. This study aims to identify PGx markers of CVSE risk in adult patients undergoing HCT. **Methods:** This is a retrospective PGx study of patients who underwent HCT between January 2014 and July 2024. Germline DNA was extracted from buccal swabs, and genotyping was performed using the Illumina Global Diversity Array with Enhanced PGx. The analysis focused on 99 single nucleotide polymorphisms (SNPs) in 13 candidate genes involved in Cy metabolism: GSTM1, GSTA1, GSTP1, GSTT1, CYP3A5, CYP3A4, CYP2C9, CYP2C8, CYP2C19, CYP2A6, CYP2B6, ALDH1A1, and ALDH3A1. The primary endpoint was time to CVSE occurrence at 90 days, 180 days, and 5 years post-HCT, including acute or chronic ischemic heart disease, acute myocardial infarction, angina pectoris, atrial fibrillation or flutter, other arrhythmias, cardiomyopathy, heart failure, hypertensive heart disease, pericardial effusion, pericarditis, peripheral vascular disease, and pulmonary edema. Covariates included age, sex, ancestral variation, diabetes, dyslipidemia, hypertension, atherosclerosis, and CVSEs within 2 years prior to HCT. Using an additive genetic model, a Cox proportional hazards model was generated to evaluate the association between each SNP and time to CVSE, adjusting for covariates. A CVSE risk score was developed using the total number of risk alleles from statistically significant SNPs and tested for association with time to CVSE using a Cox proportional hazards model. **Results:** Of 86 evaluable patients, the median age was 60 (range 24-78), 78% were male, 77% White, and 20% Black; 54% received haploidentical and 24.4% matched related donor HCT. The incidence of CVSEs was 27% at 90 days post-HCT, 31% at 180 days, and 58% at 5 years. The table describes three SNPs significantly associated with time to CVSE ($p<0.05$). The CVSE risk score ($n=19$ for low risk, 0-1 risk alleles; $n=49$ for intermediate, 2-3 risk alleles; $n=18$ for high, 4-6 risk alleles) was significantly associated with time to CVSE (HR 2.30, 95% CI 1.43-3.71, $p=0.0006$). **Conclusions:** PTCy-related CVSEs were common post-HCT. Single nucleotide polymorphisms in CYP2A6, GSTT1, and ALDH1A1 may influence CVSE risk post-HCT. These findings require further validation in independent datasets and may be used to develop a clinicogenomic risk model for CVSE post-HCT. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; NIH/NCI P30CA012197; Swim Across America.

SNP	Gene	Risk allele frequency	Hazard ratio (95% CI)	p value
rs1137115	CYP2A6	0.215	2.78 (1.48-5.23)	0.0015
rs1007888	GSTT1	0.494	1.78 (1.13-2.81)	0.0129
rs1330283	ALDH1A1	0.506	1.82 (1.06-3.12)	0.0301

Outcomes after unrelated donor allogeneic hematopoietic cell transplantation in age ≥ 65 using post-transplant cyclophosphamide.

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Background: The use of allogeneic hematopoietic cell transplantation (allo-HCT) in older adults has increased with reduced-intensity conditioning and post-transplant cyclophosphamide (PTCy) based GVHD prophylaxis. While PTCy has demonstrated excellent GVHD control across multiple disease types, age-related toxicities and non-relapse mortality remain significant challenges in older patients with acute leukemia and myelodysplastic syndrome (MDS). Understanding age-associated risks in contemporary unrelated donor (URD) HCT platforms may help guide patient selection, counseling, and future refinements in transplant practice. **Methods:** We analyzed adults undergoing first URD allo-HCT (8/8 or 7/8 HLA-matched) with PTCy-based GVHD prophylaxis for acute myeloid leukemia, acute lymphoblastic leukemia, or myelodysplastic syndrome reported to CIBMTR, 2017–2021, using the P-5891 dataset. Patients were grouped into <65 and ≥ 65 years. Outcomes included overall survival (OS), non-relapse mortality (NRM), relapse, acute GVHD, and chronic GVHD. Univariable and multivariable Cox proportional hazards or Fine-Gray competing risks models were used as appropriate. Variables with $p < 0.2$ in univariable analysis and clinically relevant factors were included in multivariable models. **Results:** Of 2,271 patients, 849 (37%) were ≥ 65 years. Older patients were more frequently treated with reduced-intensity or non-myeloablative conditioning, had a Hematopoietic Cell Transplantation–Comorbidity Index (HCT-CI) ≥ 3 , and had a Karnofsky Performance Status (KPS) < 90 . On multivariable analysis, age ≥ 65 was associated with significantly inferior OS (HR 1.20, 95% CI 1.02–1.40, $p=0.029$), with 3-year OS of 52.1% vs 63.4% (log-rank $p<0.001$). Other independent predictors of worse OS included reduced-intensity conditioning, higher disease risk index, KPS < 90 , and HCT-CI ≥ 3 ; graft source was not significant. Competing-risk analyses showed significantly higher NRM in ≥ 65 years (3-year cumulative incidence 22.7% vs 13.6%; HR 1.56, 95% CI 1.21–2.01, $p<0.001$), which was the primary driver of inferior survival. Importantly, relapse incidence was similar (HR 0.90, $p=0.249$), and no differences were found in GVHD rates: grade II–IV acute GVHD (HR 0.98, 95% CI 0.81–1.17, $p=0.785$), grade III–IV acute GVHD (HR 0.91, 95% CI 0.64–1.30, $p=0.600$), or moderate-to-severe chronic GVHD (HR 0.90, 95% CI 0.68–1.20, $p=0.467$). **Conclusions:** In patients undergoing unrelated donor HCT with PTCy-based GVHD prophylaxis for acute leukemia or MDS, those aged ≥ 65 years had significantly lower overall survival and higher non-relapse mortality compared to younger patients, with similar relapse and GVHD rates. These findings suggest the need to optimize the PTCy-based prophylaxis platform, such as reduced PTCy dosing with the addition of novel agents, in patients with advanced age. Research Sponsor: None.

Post-prophylaxis CMV in the letermovir era: Incidence, risk factors, and outcomes following HCT.

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Background: Cytomegalovirus (CMV) is a major infectious complication after allogeneic hematopoietic cell transplantation (HCT). Letermovir prophylaxis (ppx) effectively reduces clinically significant CMV infection (csCMVi) within 100 days, but csCMVi after ppx discontinuation occurs in 7–16%. Extended letermovir ppx has been proposed for high-risk patients, though optimal patient selection is uncertain. Our study aims to define the incidence, risk factors, and outcomes for post-ppx csCMVi to guide extended ppx strategies. **Methods:** We analyzed adult CMV-seropositive (+) HCT recipients at Cleveland Clinic who received ≥ 45 days of Letermovir primary ppx between 1/1/2018–12/31/2024. The primary outcome was post-ppx csCMVi, defined as CMV disease or asymptomatic viremia requiring preemptive therapy. Secondary outcomes included overall and non-relapse mortality. Patients with csCMVi during standard ppx were excluded. Associations with csCMVi were evaluated using competing-risk models accounting for mortality, with multivariable Cox analyses adjusting for age, sex, Karnofsky score. **Results:** Among 311 CMV+ recipients of HCT, 62% were donor-CMV negative and 50% were male. Median age was 59 (47–67) years. HCT was most commonly for AML (48%), with matched unrelated donors (54%), peripheral blood graft (76%), myeloablative conditioning (45%), and GVHD ppx with post-transplant cyclophosphamide (PTCy) (63%). Grade ≥ 2 acute GVHD (36%), chronic GVHD (53%), and relapse (22%) were common in the cohort. Post-ppx infection occurred in 64 patients (21%), including 8 (13%) with tissue-invasive disease. Median duration of Letermovir was 75 days, typically initiated on day 28 post-transplant. Median time to csCMVi was 123 days from transplant. Cumulative incidence of post-ppx csCMVi was 9% at 60 days, 11% at 90 days, and 12% at 180 and 360 days. Risk factors included older age (HR 1.04 per year, 95% CI=1.01–1.07, $p=0.014$), female sex (HR 3.3, 95% CI=1.5–7.1, $p=0.003$), chronic GVHD (HR 9.9, 95% CI=1.2–5.6, $p=0.024$), and GVHD treated with steroids (HR 9.86, 95% CI=1.4–71.5, $p=0.024$) or ruxolitinib (HR 2.8, 95% CI= 1.3–6.3, $p=0.011$). Primary disease, donor CMV status, donor relationship, graft source, conditioning intensity, ATG, and PTCy were not associated with csCMVi. All-cause mortality was high in the cohort (37%), particularly in the late csCMVi group (52%). Post-ppx csCMVi was associated with increased non-relapse (HR 2.36, 95% CI= 1.37–4.07, $p=0.002$) and overall mortality (HR 2.41, 95% CI= 1.43–4.06, $p<0.001$) in multivariable analysis adjusted for age and sex. **Conclusions:** Late csCMVi occurs in 12% of CMV+ HCT recipients after prophylaxis discontinuation and may confer additional mortality risk. These findings support risk-adapted surveillance and extended prophylaxis in high-risk groups, particularly recipients who are older, female, and have chronic GVHD requiring immunosuppression. Research Sponsor: None.

Impact of *NPM1* co-mutation on post-transplant outcomes in MRG-mutated AML.

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Background: Myelodysplasia-related gene (MRG) mutations are classified as adverse risk per ELN 2022, and allogeneic cell transplantation (allo-HCT) is recommended. However, it remains unclear whether post-transplant outcomes in MRG-mutated AML are inferior compared with other ELN-defined higher-risk AML without MRG mutations, and whether the presence of a favorable co-mutation *NPM1* modifies prognosis after transplantation. **Methods:** We conducted a retrospective study of adult patients with AML who underwent allo-HCT at our institution between January 2015 and January 2025. MRG mutations defined per ELN. Patients were categorized into four molecular groups: MRG-mutated/*NPM1* wild-type (MRG^{mut}*NPM1*^{wt}), MRG-mutated/*NPM1*-mutated (MRG^{mut}*NPM1*^{mut}), MRG-wild-type/*NPM1*-mutated (MRG^{wt}*NPM1*^{mut}), and MRG-wild-type/*NPM1* wild-type (MRG^{wt}*NPM1*^{wt}). Overall survival (OS) and RFS were calculated using the Kaplan–Meier. Adjusted OS and RFS were estimated using propensity score matching accounting for age, sex, remission status at transplant (CR1 vs others), and conditioning intensity. **Results:** A total of 146 patients with complete molecular and cytogenetic data were included. Forty-two percent were MRG^{wt}*NPM1*^{wt}, 16% were MRG^{wt}*NPM1*^{mut}, 23% were MRG^{mut}*NPM1*^{mut}, and 19% were MRG^{mut}*NPM1*^{wt}. Cytogenetic risk distribution was 11% favorable, 71% intermediate, and 18% adverse. Among patients with favorable cytogenetics, 86% were either MRG^{wt}*NPM1*^{wt} or MRG^{wt}*NPM1*^{mut}, and none had MRG^{mut}*NPM1*^{wt} disease. In contrast, among patients with adverse cytogenetics, 17% had MRG^{wt}*NPM1*^{wt}, 23% had MRG^{wt}*NPM1*^{mut}, and 45% had MRG^{mut}*NPM1*^{wt} disease ($p = 0.07$). There was no significant difference in OS across molecular subgroups, with median OS of 70 months (95% CI 40–NR) for MRG^{wt}*NPM1*^{wt}, 101 months (95% CI 20–NR) for MRG^{wt}*NPM1*^{mut}, 69 months (95% CI 27–NR) for MRG^{mut}*NPM1*^{wt}, and 94 months (95% CI 59–NR) for MRG^{wt}*NPM1*^{wt} ($p = 0.5$). However, patients with MRG^{wt}*NPM1*^{wt} demonstrated a trend toward inferior RFS, with a median RFS of 17 months (95% CI 13–NR), compared with RFS not reached in the MRG^{wt}*NPM1*^{mut}, MRG^{wt}*NPM1*^{wt}, and MRG^{wt}*NPM1*^{wt} groups ($p = 0.1$). These findings remained consistent after propensity score adjustment. **Conclusions:** Our findings suggest that the presence of an *NPM1* mutation may mitigate post-transplant relapse risk in patients with MRG-mutated AML. In contrast, patients with MRG-mutated/*NPM1* wild-type disease appear to have inferior relapse-free survival after allo-HCT compared with other ELN-defined adverse-risk AML subgroups. These results indicate biologic heterogeneity within adverse-risk AML and highlight the need for refined post-transplant risk stratification and relapse-prevention strategies in MRG-mutated/*NPM1* wild-type AML. Research Sponsor: None.

Myeloablative vs reduced-intensity conditioning in PTCy-based allogeneic HCT: A CIBMTR analysis.

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Background: Post-transplant cyclophosphamide (PTCy) is widely used in matched unrelated and haploidentical HCT. However, the optimal conditioning intensity in the PTCy era remains unclear. This study compared outcomes of myeloablative versus reduced-intensity conditioning in MUD and haploidentical HCT recipients. **Methods:** This retrospective multicenter study utilized the Center for International Blood and Marrow Transplant Registry (CIBMTR) to analyze patients who underwent HCT and received PTCy, based on the P-6219 dataset by Modi et al. Clinical outcomes were compared between patients who received MAC and RIC. Kaplan–Meier analysis was used to determine mean overall survival (OS) and graft-vs-host disease (GVHD)–free relapse–free survival (GRFS). Cox proportional hazards regression models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI). Statistical analyses were conducted using SPSS, with p-values less than 0.05 considered statistically significant.

Results: A total of 5,873 patients were included, comprising 1,973 MUD recipients (797 MAC, 1,176 RIC) and 3,900 haploidentical recipients (1,485 MAC, 2,415 RIC). All patients received PTCy GVHD prophylaxis. Among MUD recipients, MAC was associated with significantly OS compared with RIC, with a mean OS of 27.8 months (95% CI 26.9–28.7) versus 24.8 months (95% CI 24.1–25.6, $p<0.001$). RIC was associated with a higher risk of mortality compared with MAC (HR 1.45, 95% CI 1.24–1.68, $p<0.001$). GRFS was also worse with RIC (mean 21.5 months, 95% CI 20.4–22.5 vs 18.3 months, 95% CI 17.4–19.2; HR 1.33, 95% CI 1.17–1.51, $p<0.001$). There were no significant differences between MAC and RIC in rates of grade 2–4 acute GVHD (HR 1.00, 95% CI 0.85–1.18, $p=1.0$), grade 3–4 acute GVHD (HR 1.04, 95% CI 0.72–1.51, $p=0.84$), or moderate/severe chronic GVHD (HR 0.97, 95% CI 0.86–1.08, $p=0.59$). Among haploidentical recipients, MAC was also associated with improved OS compared with RIC, with a mean OS of 26.1 months (95% CI 25.4–26.8) versus 24.1 months (95% CI 23.6–24.7, $p<0.001$), and RIC conferred a higher mortality risk (HR 1.29, 95% CI 1.16–1.43, $p<0.001$). GRFS was superior with MAC (18.4 months, 95% CI 17.6–19.2 vs 16.5 months, 95% CI 15.9–17.2; HR 1.17, 95% CI 1.08–1.27, $p<0.001$). Rates of grade 2–4 acute GVHD were lower with RIC (HR 0.88, 95% CI 0.78–0.98, $p=0.018$). Rates of grade 3–4 acute GVHD (HR 1.06, 95% CI 0.85–1.32, $p=0.61$) and moderate/severe chronic GVHD (HR 0.98, 95% CI 0.90–1.07, $p=0.70$) were similar between MAC and RIC. **Conclusions:** MAC was associated with improved OS and GRFS compared with RIC in MUD and haploidentical transplant recipients, with similar rates of severe acute and chronic GVHD. These findings support the use of MAC when patient comorbidities and performance status permit. Research Sponsor: None.

Differentiating donor age on AML patient outcomes in the post-transplant cyclophosphamide contemporary era.

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Background: alloHCT provides curative potential for patients with AML. PTCy GVHD prophylaxis has changed this paradigm. Impact of donor age is unknown in the PTCy era. **Methods:** Utilizing the publicly available CIBMTR dataset, de-identified AML patients receiving alloHCT between 2017–2021 with PTCy-based GVHD prophylaxis were identified. Patients with primary induction failure or relapsed disease status at time of transplant were excluded. The main effect of donor age was examined across outcomes at 24-months. Univariate and multivariate analyses were performed. **Results:** 5,702 patients were included in the analysis. The median age at alloHCT was 59 years (IQR, 46–66). Median donor age was 33 years (IQR, 22–42). CI of relapse at 24 months was 36.4% (95% CI, 33.1%–39.8%) for donors aged ≥ 45 yrs, 32.9% (95% CI, 24.6%–41.2%) for donors aged 0–19 yrs, 30.5% (95% CI, 28.6%–32.4%) for donors aged 20–34 yrs, and 30.1% (95% CI, 27.3%–32.9%) for donors aged 35–44 yrs; $p=0.003$ (Gray's test). Overall survival (OS) at 24 months was 45.9% (95% CI, 42.6%–49.6%) for donors aged ≥ 45 yrs, 55.4% (95% CI, 47.1%–65.2%) for donors aged 0–19 yrs, 58.5% (95% CI, 56.5%–60.6%) for donors aged 20–34 yrs, and 53.3% (95% CI, 50.3%–56.5%) for donors aged 35–44 yrs; $p<0.001$. Leukemia-free survival at 24 months was 39.4% (95% CI, 36.2%–43.0%) for donors aged ≥ 45 yrs, 48.2% (95% CI, 40.1%–57.9%) for donors aged 0–19 yrs, 51.4% (95% CI, 49.4%–53.5%) for donors aged 20–34 yrs, and 49.2% (95% CI, 46.2%–52.4%) for donors aged 35–44 yrs; $p<0.001$. In multivariable analysis, as compared to donor age >45 , the 2 younger age groups, age 20–34 years (HR 0.41, 95%CI, 0.69–0.87; $p=.004$) and 35–44 years (HR 0.78, 95% CI, 0.66–0.92; $p=.004$) were independently associated with reduced relapse and superior LFS (HR 0.77, 95% CI, 0.69–0.87; $p<.001$) and (HR 0.77, 95% CI, 0.68–0.87; $p<.001$) respectively, and OS (HR 0.76, 95%CI, 0.67–0.86; $p<.001$) and (HR 0.80, 95% CI, 0.70–0.91; $p<.001$) respectively. In contrast, there was no significant difference between outcomes when the donor belonged to the age group 0–19 for relapse (HR 0.87, 95%CI, 0.61–1.22; $p=.410$, LFS (HR 0.84, 95% CI, 0.65–1.09; $p=.188$), and OS (HR 0.79, 95%CI, 0.60–1.05; $p=.108$) (Table 1). **Conclusions:** In this homogeneous analysis, patients with AML undergoing PTCy-based GVHD prophylaxis in the contemporary era, younger donor between age groups 20–44 years conferred a significantly reduced relapse risk and superior LFS and OS. The findings inform optimal donor selection. Research Sponsor: None.

Multivariate analyses (ref: donor age ≥ 45).

Donor age	0-19	P	20-34	P	35-44	P
OS	0.79 (0.60-1.05)	0.108	0.76 (0.67-0.86)	<0.001	0.80 (0.70-0.91)	<0.001
LFS	0.84 (0.65-1.09)	0.188	0.77 (0.69-0.87)	<0.001	0.77 (0.68-0.87)	<0.001
Relapse	0.87 (0.61-1.22)	0.410	0.81 (0.69-0.93)	0.004	0.78 (0.66-0.92)	0.004

Adjusted for donor age, year of transplant, DRI, year of HCT, donor type, graft type, conditioning intensity, and ethnicity.

Early neutrophil incompetence following allogeneic stem cell transplant.

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Background: Neutrophils are key immune effector cells against fungal pathogens such as *Candida albicans*. After allogeneic stem cell transplant (allo-SCT), absolute neutrophil count (ANC) is used to measure myeloid engraftment and estimate infection risk, but post-transplant neutrophil function remains poorly understood. Our prior work showed impaired neutrophil function after both myeloablative (MAC) and reduced-intensity conditioning (RIC) regimens. Here, we assess broader neutrophil functions and hypothesize post-transplant neutrophil impairment persists for at least one month despite numeric recovery. **Methods:** Peripheral blood was collected from patients undergoing RIC or MAC allo-SCT and healthy donors at four time points: immediately post-engraftment (P1), and at one (P2), three (P3), and seven (P4) months. Neutrophil function was analyzed by multiparametric flow cytometry to assess phagocytosis, degranulation (CD66b), reactive oxygen species (ROS) production (dihydrorhodamine-123), and ectodomain shedding (CD62L) after incubation with fluorescent *C. albicans*. At P1, neutrophil deformability was quantified to generate a sepsis risk index: Band 1 (low risk, 0.1–4.9), Band 2 (intermediate risk, 5–6.2) and Band 3 (high risk, 6.3–10). Neutrophil antifungal activity was assessed *in vitro* using microscale platforms to quantify and image swarming (cumulative neutrophil response) during restriction of *C. albicans* growth over 12 hours. **Results:** Nineteen subjects were included. The most common underlying malignancy was acute myeloid leukemia (12/19, 63%). Conditioning regimens included fludarabine/melphalan (14/19, 74%), busulfan/fludarabine (4/19, 21%), or fludarabine/total body irradiation (1/19, 5%), with post-transplant cyclophosphamide and tacrolimus. The majority received grafts from matched unrelated donors (14/19, 74%). Median ANC (K/uL) was 3.59 at P1 (15/19 subjects, 79%), 4.55 at P2 (14/19, 74%), 4.03 at P3 (5/19, 26%) and 2.94 at P4 (7/19, 37%). Functional analyses revealed significant impairment in allo-SCT recipients compared with controls at P1, with trends of persistent impairment at P2, and evidence of recovery by P3–P4. At P1, eight recipients demonstrated altered neutrophil deformability, yielding a higher sepsis risk index [median (IQR) 5.93 (3.88–6.80)] versus controls [median (IQR) 0.95 (0.33–2.33)]. Swarming analysis revealed impaired collective behavior in fungal containment compared with controls. **Conclusions:** Despite normalization of ANC after allo-SCT, early post-engraftment neutrophils exhibit significant functional and biophysical impairments, indicating transient immune incompetence. This early window of vulnerability may persist for at least one month post-transplant. Ongoing follow-up and expanded analyses will further characterize the underlying mechanisms and define the trajectory of delayed functional neutrophil recovery. Research Sponsor: U.S. National Institutes of Health; Cytovale.

Updated overall survival (OS) and long-term transfusion-independence (TI) from the phase 3 COMMANDS trial in erythropoiesis-stimulating agent (ESA)–naïve patients (pts) with lower-risk myelodysplastic syndromes (LR-MDS).

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Background: In the phase 3 COMMANDS trial (NCT03682536), luspatercept (LUSPA) significantly improved RBC-TI ≥ 12 wks with concurrent mean hemoglobin (Hb) increase ≥ 1.5 g/dL during wks 1–24 (primary endpoint) vs epoetin alfa (EA) in pts with ESA-naïve transfusion-dependent (TD) LR-MDS. Longer follow-up (> 2.5 yrs) showed a favorable OS trend and durable TI responses with LUSPA vs EA. We report updated results with 6 additional mos of follow-up (> 3 yrs). **Methods:** Eligible pts (≥ 18 yrs; ESA-naïve; TD; LR-MDS) were stratified by baseline (BL) transfusion burden (TB), ring sideroblasts (RS), and serum erythropoietin (sEPO). Pts were randomized 1:1 to LUSPA (1.0–1.75 mg/kg; SC Q3W) or EA (450–1050 IU/kg; SC QW) for ≥ 24 wks. OS (from randomization), RBC-TI responses and Hb improvement (all from wk 1 to end of treatment), predictive BL biomarkers of OS, and safety were evaluated. **Results:** At cutoff (Oct 6, 2025), median (min–max) follow-up was 35.9 (1–73; LUSPA) and 30.8 (0–77; EA) mos. Median OS was not reached (NR) for LUSPA and 46.0 mos for EA (HR, 0.78; 95% CI, 0.56–1.09), with similar trends in subgroups (Table). RBC-TI ≥ 12 wks (LUSPA vs EA) occurred in 76.4% vs 55.8% of pts, and in 60.4% vs 39.2% with concurrent mean Hb ≥ 10 g/dL. Median cumulative duration (95% CI) of RBC-TI ≥ 12 wks was 184.4 (118.4–NE) wks for LUSPA and 95.1 (74.9–180.1) wks for EA (HR, 0.54; 95% CI, 0.36–0.80). RBC-TI ≥ 2.5 yrs (LUSPA vs EA) was achieved by 25.3% vs 10.5% of pts. Mean Hb increase ≥ 1.5 g/dL (LUSPA vs EA) was achieved by 80.2% vs 58.6% of pts; median duration (95% CI) of Hb increase ≥ 1.5 g/dL was 72.9 (53.9–89.9) and 47.9 (35.9–60.0) wks (HR, 0.61; 95% CI, 0.44–0.85). Improved OS was associated with BL biomarkers of favorable immune (LUSPA) and CV function (LUSPA and EA), less aggressive disease (EA), and preserved megakaryopoiesis (EA); these characteristics may enhance response to therapy. At cutoff, 17.6% (LUSPA) and 7.8% (EA) of pts remained on treatment; 84.6% and 83.2% had ≥ 1 dose escalation. No new safety concerns emerged. Deaths (any cause) occurred (LUSPA, 36.3%; EA, 43.0%), fewer LUSPA pts progressed to HR-MDS (3.3%; 7.3%), and AML progression was comparable (4.9%; 5.5%). **Conclusions:** Long-term follow-up demonstrated improved OS trends and sustained responses with LUSPA vs EA, overall and in subgroups. No new safety concerns emerged, reinforcing superior clinical benefit as first-line treatment in LR-MDS. Clinical trial information: NCT03682536. Research Sponsor: Bristol Myers Squibb.

Median OS, mos	LUSPA	EA	HR (95% CI)
Overall	(n=182) NR	(n=181) 46.0	0.78 (0.56–1.09)
Stratification subgroup			
TB <4 RBC U/8 wks	(n=118) 57.5	(n=111) 47.2	0.87 (0.57–1.33)
TB ≥ 4 RBC U/8 wks	(n=64) NR	(n=70) 39.9	0.62 (0.37–1.05)
RS+	(n=133) NR	(n=130) 47.2	0.70 (0.47–1.04)
RS–	(n=49) 54.8	(n=50) 46.2	0.96 (0.53–1.72)
sEPO ≤ 200 U/L	(n=145) NR	(n=144) 51.4	0.81 (0.55–1.20)
sEPO > 200 U/L	(n=37) 43.0	(n=37) 35.4	0.67 (0.35–1.28)

Impact of shallow whole genome sequencing on diagnostic yield and prognostic precision in myelodysplastic syndromes.

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Background: Accurate cytogenetic characterization is critical for risk stratification in myelodysplastic syndromes (MDS). Conventional karyotyping and fluorescence in situ hybridization (FISH) are limited in resolution, target specific loci, and cannot detect copy-neutral loss of heterozygosity (CN-LOH). LeukoPrint, a CE-IVD-marked shallow whole-genome sequencing (sWGS, 1×coverage) test, enables genome-wide detection of copy number alterations (CNAs) and CN-LOH. Previously validated in acute myeloid leukemia and multiple myeloma, it improved CNA detection and prognostic accuracy. This study evaluated its ability to enhance diagnostic yield and refine prognostic precision in a large MDS cohort. **Methods:** Bone marrow samples from 461 MDS patients were profiled for genome-wide CNA/CN-LOH using LeukoPrint. Results were compared with conventional karyotyping and FISH to assess detection yield and concordance. The impact of additional LeukoPrint findings on Revised International Prognostic Scoring System (IPSS-R) cytogenetic risk stratification and MDS subclassification was evaluated. **Results:** LeukoPrint detected cytogenetic abnormalities in 63.3% of patients, comprising CNAs in 50.3%, CN-LOH in 23.9%, with 10.8% harboring both. Recurrent CNAs included del(5q) (10.0%), del(20q) (10.0%), +8 (8.9%), and del(7q) (7.8%), among others. CN-LOH frequently affected regions that overlapped common CNA loci, such as 5q (3.7%), 7q (3.7%), and 17p (0.7%). Compared with conventional cytogenetics, LeukoPrint showed 94.4% concordance ($\kappa=0.854$) with FISH for five key loci (−5/del(5q), −7/del(7q), +8, del(20q), −Y) and a higher detection rate than karyotyping (65.7% vs 39.2%). For the 11 IPSS-R defined cytogenetic abnormalities (del(3q), del(5q), del(7q), del(11q), del(12p), del(17p), del(20q), +8, +19, −7, and −Y), it identified all karyotype-detected lesions and increased detection yield by 49.4%. These newly identified abnormalities led to IPSS-R cytogenetic risk reclassification in 32.4% (33/102) of comparable cases, predominantly upgrading patients to higher-risk categories. Specifically, 26 patients were reassigned from Good to Intermediate (n = 17), Poor (n = 2), or Very Poor (n = 7); 5 from Intermediate to Poor (n = 4) or Very Poor (n = 1); and 1 from Poor to Very Poor. Furthermore, by detecting additional aberrations such as del(17p) or 17p CN-LOH, LeukoPrint enabled more accurate molecular classification, including the reclassification of one case from MDS-IB1 to MDS-biTP53. **Conclusions:** sWGS-based LeukoPrint substantially enhances cytogenetic detection in MDS, outperforming conventional karyotyping and FISH. By identifying additional clinically relevant cytogenetic abnormalities, it improves prognostic risk stratification and refines disease classification, supporting its integration into routine MDS cytogenetic assessment. Research Sponsor: None.

Phlebotomy, adherence, and hematocrit control in patients with polycythemia vera in the United States: Real-world analysis.

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Background: Polycythemia Vera (PV) is characterized by erythrocytosis. A key treatment goal in PV, for which phlebotomy (PHL) is recommended, is achieving and maintaining hematocrit (HCT) levels $< 45\%$ to reduce thrombotic risk. However, real-world evidence suggests PHL alone may not achieve consistent and durable HCT control. Repeated PHL may also increase treatment burden and present logistical challenges. **Methods:** Data were collected using the Adelphi PV Disease Specific Programme, a United States (US) cross-sectional survey (August 2025–January 2026) with retrospective chart review. Physicians reported demographics, clinical characteristics, and treatment history for the next five patients (pts) with PV that met the inclusion criteria. Interim analyses are presented descriptively. Of those receiving ≥ 1 PHL in the 12 months prior to survey, pts receiving frequent PHL were defined as ≥ 3 in 6 months or ≥ 5 in 12 months; all other pts were classified as receiving infrequent PHL. Uncontrolled HCT was defined as any HCT $\geq 45\%$ within the prior 12 months. **Results:** Twenty-seven physicians provided data for 143 pts; 86 (60%) received ≥ 1 PHL in the prior 12 months; median (interquartile range (IQR)) age was 65.0 (52.0–70.0) years, 77% were male, median (IQR) time since PV diagnosis was 11.0 (4.0–33.5) months, and 62% were high risk (defined as ≥ 60 years old or history of thrombosis). Half experienced ≥ 1 barrier to receiving PHL, including care coordination challenges (22%), lack of resources (12%), travel time burden (12%) and vein access challenges (10%). In prior 12 months, physicians reported that 38% of pts were not fully adherent to PHL (attended PHL appointments as recommended $< 90\%$ of the time). At the most recent consultation, 51% of pts were receiving cytoreductive therapy in addition to PHL. Frequent PHL occurred in 24% of pts and infrequent in 76% of pts. Overall, 90% (75/83) had uncontrolled HCT: 89% for frequent (17/19) vs 91% for infrequent PHL (58/64). Since their PV diagnosis, 13% (11/86) of pts had experienced a thromboembolism (TE), and of these 11 pts, 45% (5/11) had experienced a TE within the 12 months prior to survey. For all pts who had ever experienced a TE, the median (IQR) time since their most recent TE was 20.0 (2.5–32.0) months. **Conclusions:** Within this study, pts receiving PHL for PV commonly experienced access and logistical barriers, and incomplete PHL adherence. Nearly all pts had evidence of uncontrolled HCT in the 12 months prior to survey, including both frequent and infrequent PHL groups, and TEs were observed despite PHL treatment. These findings highlight the need for more effective and sustainable approaches to prevent consequences, such as TEs, commonly associated with uncontrolled HCT, while also reducing pt burden. Research Sponsor: Takeda Pharmaceuticals America, Inc.

Multimodal immunotherapy for high-risk acute myeloid leukemia and myelodysplastic syndrome.

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Background: CD117 is highly expressed on myeloid leukemia cells (MLC) with limited expression on normal tissues. Our group has developed an anti-CD117 monoclonal antibody and demonstrated its safety in a phase 1 clinical trial for myelodysplastic syndrome (MDS). To potentiate engagement with MLC and immune effector cells, we engineered bispecific antibodies (bsAb) to bind CD117 and CD33 or CD38 and recruit natural killer (NK) cells using an active Fc and CD16 (CM1/3/16/16) and/or Nkp46 scFv (CM1/3/16/17). NK cell cytotoxicity against MLC increases several-fold when activated by IL2, IL15 or IL21. We studied the *in vitro* and *in vivo* efficacy of bsAbs with fresh NK cells or IL2, IL15 and IL21 (IL21521) activated NK cells (cNK) to deplete MLC. **Methods:** *In vitro* cytotoxicity assays were performed on Kasumi-1 (CD117 high) and MOLM-13 (CD117 negative) acute myeloid leukemia (AML) cell lines and a primary AML sample (CD117 low) with bsAb and NK or cNK cells. cNK were exposed to IL21521 for 7 days. To mimic *in vivo* exposure, cNK were removed from IL21521 for 24, 48 and 72 hours prior to cytotoxicity assays. Using immune deficient NBSGW mice and primary patient sample of high risk (HR)-MDS transformed to AML (MDS/AML), a patient derived xenograft (PDX) model of HR-MDS/AML was created and allowed to progress to >80% CD45+ human leukemia chimerism (HLC) before treatment. Treatment groups included CM1/3/16/16 at 1mg and/or 2e6 NK or cNK given as a single dose per animal. Weekly blood HLC and a terminal 4-week blood, marrow and spleen HLC were performed. **Results:** In *in vitro* cytotoxicity assays, among the bsAbs, CM1/3/16/16 at 100nM with NK cells at 1:1 target:effector (TE) ratio produced the highest cytotoxicity against Kasumi-1 (70%) and MOLM13 (50%). cNK cells alone produced >90% cytotoxicity of Kasumi-1 cells at 1:1 TE ratio even at 72 hours after IL21521 washout. In the HR-MDS/AML PDX advanced leukemia model, the group receiving CM1/3/16/16 with cNK demonstrated the highest depletion of MLC, with 70% reduction of HLC seen at 4 weeks post-treatment. Mice in this treatment group had 100% survival at 4 weeks at which time they were euthanized for analysis. **Conclusions:** Both CM1/3/16/16 and cNK cells independently killed MLC with high efficacy *in vitro*. A single dose of CM1/3/16/16 combined with cNK cells depleted human MLC in PDX model of HR-MDS/AML with advanced leukemia. Further clinical investigation of this bsAb with allogeneic donor cNK cells in HR-MDS/AML is warranted. Research Sponsor: California Institute of Regenerative Medicine; Edward P Evans Foundation.

Whole genome sequencing to identify novel, clinically relevant findings missed by standard of care for patients with myelodysplastic syndrome.

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Background: Genomic analysis is critical for accurate diagnosis and risk stratification for patients with myeloid malignancies. Whole genome sequencing (WGS) has the ability to capture a breadth of alterations and has the potential to complement or replace current genomic profiling techniques. We sought to validate the molecular findings from Tempus xH, a WGS based assay, with standard of care [SOC] results from a major academic institution (MDACC). **Methods:** We retrospectively sequenced 43 patient samples from MDACC using the Tempus xH WGS assay. SOC data from cytogenetics (karyotype +/- FISH), 81-gene panel sequencing, and/or optical genome mapping OGM (n=10), was regarded as the source of truth. We performed a two-part study: an initial unblinded analysis (n=10) comparing WGS to SOC, followed by a blinded unbiased comparative review (n=33). Clinically relevant alterations were compared between the SOC and xH reportable range workflows. We excluded mutations with $\leq 10\%$ VAF and filtered copy number alterations (CNAs) $< 5\text{Mb}$, and combined OGM and cytogenetics ($10 \geq$ metaphases). Structural variants (SVs) were included if they overlapped orthogonal truth or were recurrent myeloid fusions. **Results:** In the unblinded analysis (n=10), WGS detected 53 clinically reported alterations, yielding 94% sensitivity. Single nucleotide variants (SNVs) had 100% sensitivity, and 18/20 CNA events and 6/7 SVs were detected. The single missed SV event was a derivative chromosome (chr), between chr1 and chr20, identified by cytogenetics with breakpoints over the masked centromere region of the WGS. However, WGS detected CNAs in chr arms of 1 and 20, signalling the event was captured yet not resolved as a derivative chr. Two copy losses on chr 19 (complete loss and p-arm) and an *ASXL1* frameshift were detected by WGS but not by SOC. In the blinded study (n=33), WGS detected 143 events, including 124 true positives and no alterations from SOC went undetected by WGS demonstrating 100% sensitivity. WGS identified 24/24 of the CNAs detected by cytogenetics. Among all specimens, 21 novel, high confidence variants were identified in 11 specimens (39%) by WGS that were not detected by SOC; including 14 CNAs, two SNVs, and five SVs, including diagnostically and/or prognostically critical alterations: 2 *MECOM* rearrangements, 1 *KMT2A-PTD*, an 11MB deletion in chr 17p (*TP53* locus), and a focal *RUNX1* deletion highlighting the potential clinical benefit of WGS. **Conclusions:** WGS accurately recapitulates results from targeted NGS panels, OGM and cytogenetics and advances our understanding of MDS biology. xH WGS uncovered a significant number of novel, clinically relevant and potentially targetable findings undetected by SOC. WGS provides a complementary view of the genome, identifying actionable and prognostic markers helping clinicians make more informed treatment decisions. Research Sponsor: None.

Multi-modal AI foundation models approach for diagnosis of myelodysplastic syndromes across whole bone marrow aspirate and biopsy slides.

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Background: Morphologic diagnosis of myelodysplastic syndromes (MDS) from bone marrow aspirates and biopsies is subjective and error prone. Compared to narrow/specific predictive AI methods used in the literature, recently developed pathology foundation models pretrained on large, diverse histopathology corpora have the potential to improve generalizability while reducing task-specific annotation requirements. Here, we evaluate and compare multiple pretrained foundation models across bone marrow aspirate and biopsy whole-slide images (WSI), incorporate a cell-level bag-of-cells (BoC) foundation model, and assess tri-modal ensemble strategies. **Methods:** Digitized bone marrow aspirate (Asp) and biopsy (Bx) WSIs from patients with MDS and non-MDS cytopenias were analyzed using four pretrained pathology foundation models (GigaPath, H-Optimus-o, Virchow2-CLS, MUSK) for tile-level feature extraction. Cell-level features from aspirate-derived BoCs were extracted using DinoBloom-B, a foundation model pretrained for hematologic cell representations. Tile- or cell-level features were aggregated using attention-based multiple instance learning (ABMIL). Models were evaluated on 645 patients (319 MDS, 326 non-MDS) from the NHLBI MDS Natural History Study (NCT02775383) using 5-fold cross-validation (CV) and a held-out test set (n=129). For each modality, the best-performing model was selected based on test performance. Predictions were evaluated individually and combined using soft-probability ensembles. An oracle ensemble estimated the upper bound of multimodal complementarity. **Results:** Performance of the foundation models is summarized in Table 1. A soft-vote tri-modal ensemble of the selected models improved performance beyond any single modality (AUC 0.83; accuracy 0.73). Error analysis demonstrated partially non-overlapping failure modes across modalities, and an oracle ensemble achieved substantially higher accuracy (0.94), indicating unrealized multi-modal complementarity. **Conclusions:** Foundation models enable robust AI-based diagnosis of MDS across bone marrow specimen types. Tri-modal ensembling improves diagnostic performance, while oracle analysis motivates TriPath, a unified framework for joint modeling of aspirate, biopsy, and cellular morphology to support standardized and generalizable MDS diagnosis. Research Sponsor: Edward P. Evans Foundation; The National MDS Natural History, NIH/NHLBI/NCI.

Performance summary.						
Model	Bx WSI CV AUC	Bx WSI Test AUC	Asp WSI CV AUC	Asp WSI Test AUC	Asp-derived BoC CV AUC	Asp-derived BoC Test AUC
GigaPath+ABMIL	0.80+/-0.05	0.82	0.77+/-0.06	0.66		
H-Optimus-0+ABMIL	0.82+/-0.04	0.79	0.77+/-0.07	0.68		
Virchow2-CLS+ABMIL	0.81+/-0.04	0.76	0.78+/-0.05	0.74		
MUSK+ABMIL	0.77+/-0.05	0.81	0.76+/-0.04	0.72		
DinoBloom-B+ABMIL					0.83+/-0.05	0.78
Tri-modal Soft Ensemble	Test AUC 0.83					
Oracle ensemble (upper bound)	Test Accuracy 0.94					

Characterizing the genomic landscape of Langerhans cell histiocytosis using the AACR Project GENIE database.

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Background: Langerhans cell histiocytosis (LCH) is a rare neoplasm characterized by the abnormal clonal proliferation of bone marrow-derived Langerhans cells and occurs predominantly in pediatric patients. Clinical manifestations range from localized bone lesions to multisystem involvement. Given the high frequency of MAPK pathway mutations, particularly BRAF V600E, next-generation sequencing is recommended for LCH patients to identify actionable targets. This study utilizes the American Association for Cancer Research (AACR) Project Genomic Evidence Neoplasia Information Exchange (GENIE) database to address existing gaps in the genomic profiling of LCH, aiming to inform long-term risk stratification, uncover prognostic markers, and guide avenues for targeted therapy. **Methods:** AACR Project GENIE was accessed via cBioPortal (v18.0-public) on November 18, 2025 to identify all LCH patients. Gene mutations and demographic variables were tabulated, and statistical correlations were assessed using two-sided t-tests and non-parametric analyses with Benjamini-Hochberg false discovery rate correction. Entries with unknown values were excluded from analysis; discrepancies in percentage reflect unreported data. **Results:** This study identified 326 LCH samples from 290 patients, of whom 140 (48.3%) were female and 139 (47.9%) were male. By race, 140 (48.3%) identified as White, 9 (3.1%) as Black, and 9 (3.1%) as Asian. Of the samples, 152 (46.6%) originated from primary tumors and 20 (6.1%) were from metastatic tumors. The cohort included samples from 113 pediatric patients (34.7%) and 212 (65.0%) adults. Frequent mutations included *BRAF* (n=126; 38.7%), *MAP2K1* (n=57; 17.5%), *TET2* (n=17; 5.2%), and *FAT1* (n=8; 2.5%). No significant difference was identified between the genomic profiles of males and females ($p>0.05$), although comparisons by race revealed several unique somatic point mutations in Asian and Black patients. Among Asian patients, mutations in *MUTYH*, *PDGFRB*, and *TERT* were significantly enriched, while *BORCS8-MEF2B*, *BRCA1*, and *DDR2* mutations were enriched in Black patients. Within this cohort, pediatric patients were more likely to present with *PTEN* mutations, while adults ≥ 34 years old were more likely to have *VTI1A* or *ATM* mutations. *BRAF* mutations were mutually exclusive with *MAP2K1* mutations (n=124/124; $p<0.001$), while *TET2* mutations frequently co-occurred with *ASXL1* mutations (n=2/18, $p<0.05$). There were no significant differences in mutations between primary and metastatic samples ($p>0.05$). **Conclusions:** Our findings support the classification of *BRAF* and *MAP2K1* mutations as key driver mutations and identify several additional mutations that are significantly enriched across demographic groups. Further research into these genomic associations is crucial to address existing knowledge gaps and translate into novel treatment modalities for patients with LCH. Research Sponsor: None.

Updated analysis of overall survival (OS) with imetelstat (IME) in relapsed/refractory (R/R) myelofibrosis (MF) versus real-world (RW) data, and assessment of RW treatment (tx) patterns.

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Background: IME showed significantly longer median OS (mOS) in patients (pts) with Janus kinase inhibitor (JAKi) R/R intermediate-2-risk or high-risk MF in the IMbark trial (NCT02426086) vs closely matched RW pts treated with best available therapy (BAT) after ruxolitinib (RUX; HR, 0.35; *P*=.0019). The MF tx landscape changed considerably in recent years, potentially impacting OS. We present an updated OS analysis of IMbark pts vs a larger RW pt cohort after extended follow-up. **Methods:** The updated RW dataset included 126 pts who discontinued RUX and were subsequently treated with BAT at Moffitt Cancer Center between 2010 and 2025. To assess changes in RW tx patterns, baseline/disease characteristics and OS of pts diagnosed before/after 2016 and 2019 were compared. To update the IMbark vs RW OS analysis, a closely matched cohort was identified using IMbark eligibility criteria, including pts diagnosed before 2016 who received RUX but were R/R. The mOS was measured from time of JAKi discontinuation to death or censored at last follow-up. Propensity score approaches using average tx effect for overlap population (ATO) or stabilized inverse probability tx weighting (sIPTW) were implemented to adjust for baseline covariates/prognostic factors that may impact outcomes. **Results:** The RW tx pattern assessment included 96 pts. Time from diagnosis to start of RUX and duration of RUX tx were significantly shorter after 2016 vs before (Table). Similar changes were observed after 2019 vs before. The mOS in pts diagnosed after 2016 and 2019 was significantly longer vs before. The updated mOS analysis included 59 IMbark pts and 54 closely matched RW pts. With a median follow-up of 46.2 mo for IMbark pts and 48.2 mo for RW pts, mOS (95% CI) was 30.7 mo (25.5-36.9) with IME in IMbark vs 15.4 mo (13.1-30.5) with BAT in RW (HR, 0.512; *P*=.003) per the unweighted analysis. Propensity-weighted analyses (ATO, sIPTW) had similar results. **Conclusions:** This updated post hoc analysis confirms a significantly more favorable OS benefit with IME vs BAT in pts with R/R MF and poor prognosis consistent with the previous report (Kuykendall 2021). A significant improvement in OS in RW pts over the last decade was also demonstrated, potentially due to shorter time from diagnosis to start of RUX and earlier switch to next-line JAKi or clinical trial. Evolving tx patterns are key considerations for interpreting future clinical trial outcomes. Clinical trial information: NCT02426086. Research Sponsor: This study was funded by Geron Corporation. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Casandra M. Monzon, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Geron Corporation.

Updated RW data by time of diagnosis.				
	Before 2016 (N=54)	After 2016 (N=42)	Before 2019 (N=69)	After 2019 (N=27)
Time from diagnosis to RUX start (mean), mo	46.7	10.5	39.7	8.2
RUX duration (mean), mo	30.4	13.5	26.1	15.0
Transplant, n (%)	3 (5.6)	4 (9.5)	5 (7.2)	2 (7.4)
mOS (95% CI), mo	15.4 (13.1-30.5)	34.2 (24.2-NA)	16.6 (14.2-30.0)	39.8 (34.2-NA)

mOS, median overall survival; NA, not available; RUX, ruxolitinib; RW, real world.

Pregnancy outcomes in women with myeloproliferative neoplasms: A multicenter real-world analysis.

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Background: Pregnancy in women with myeloproliferative neoplasms (MPNs) is associated with increased thrombotic and obstetric risk, yet contemporary real-world data describing maternal and fetal outcomes remain limited. We evaluated pregnancy-related outcomes in women with MPNs and examined potential risk predictors. **Methods:** We conducted a retrospective cohort study using the TriNetX network, a federated multicenter network of de-identified electronic health records from participating healthcare organizations. Pregnant women with essential thrombocythemia (ET), polycythemia vera (PV), or myelofibrosis (MF) were identified. The primary outcome was all-cause mortality. Secondary outcomes included deep vein thrombosis (DVT), miscarriage, pre-eclampsia, eclampsia, preterm labor, and intrauterine growth restriction (IUGR). Subgroup analyses were performed using propensity score matching for age, race, ethnicity, and comorbidities to compare outcomes by Low Molecular Weight Heparin (LMWH) exposure, race, maternal age, and MPN subtype. Risk ratios (RR) with 95% confidence intervals (CI) were calculated. **Results:** A total of 1,904 pregnancies were identified (mean age 31.1 ± 7.0 years). The cohort was predominantly non-Hispanic (66.2%) and White (59.1%). ET accounted for 90.3% of cases, followed by PV (8.0%) and MF (1.7%). Overall rates of maternal mortality and DVT were 2.8% and 2.6%, respectively. Adverse obstetric outcomes included miscarriage (9.6%), pre-eclampsia (12.4%), eclampsia (1.3%), preterm labor (9.1%), and IUGR (8.5%). In matched analyses, LMWH use was associated with a numerically lower risk of miscarriage compared with no LMWH (6.8% vs 10.4%; RR 0.66, 95% CI 0.42–1.04), without significant differences in pre-eclampsia, preterm labor, or IUGR. Outcomes were similar between White and African American patients. Advanced maternal age (>35 years) was associated with a lower risk of preterm labor (3.7% vs 9.2%; RR 0.40, 95% CI 0.21–0.75). Obstetric outcomes were comparable between ET and PV. **Conclusions:** In this real-world cohort, pregnancies in women with MPNs were associated with measurable rates of thrombotic and obstetric outcomes. LMWH use was associated with a numerically lower risk of miscarriage without statistically significant differences in other outcomes. These findings provide contemporary outcome estimates and may inform risk stratification and future prospective studies. Limitations include the retrospective design, potential misclassification due to inherent limitation of the database, limited MF representation, and inability to assess disease activity, aspirin use, or pregnancy-specific dosing strategies. Research Sponsor: None.

Treatment patterns and outcomes in pacritinib-treated patients with MF and higher platelet count: MY-PAC study.

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Background: Pacritinib (PAC), a JAK1-sparing JAK2/IRAK1/ACVR1 inhibitor has shown spleen volume and symptom improvement in clinical trials of in patients (pts) with myelofibrosis (MF) with similar benefits in the real-world. This analysis evaluated real-world outcomes in pts with MF and platelet counts (PLT) $\geq 50 \times 10^9/L$ at PAC initiation. **Methods:** This was a multisite chart review of pts with MF treated with PAC for ≥ 1 month between 06/01/2022 and 07/31/2024 with ≥ 6 months of follow-up through 01/31/2025. Pts were followed from PAC initiation (index) until the earliest of end of the study, the end of data availability for the pt, or death. Evaluated data included Pt characteristics, treatment patterns, palpable spleen length (total spleen length minus 10cm) and spleen size category based on palpation or palpable spleen length below costal margin (not palpable/minimally palpable < 5 cm below costal margin; mild: 5–10 cm palpable; moderate: 11–20 cm palpable; severe: > 20 cm palpable), PLT, hemoglobin (Hb), MF-related symptoms, and overall survival through Day 180. Results for pts with PLT $\geq 50 \times 10^9/L$ at index are described using counts and percentages, medians and interquartile range (IQR), and survival probabilities. **Results:** Of 169 pts with MF treated with PAC, 27% (45/169) had PLT $\geq 50 \times 10^9/L$ at index. Median age was 67 years (IQR: 62–74) at diagnosis and median time from diagnosis to index was 6 months (IQR: 1.3–14.3). The median duration of follow-up from index was 7.6 months (IQR: 6.7–11.0) and 82% of pts (n=37) were still on PAC at end of follow-up. Of 12 pts with spleen length measured by ultrasound at index and Day 180, median spleen length reduction (SLR) was 39% (IQR: 30.4–48.3) with 83% (10/12) achieving SLR $\geq 25\%$ by Day 180. Among those with categorical spleen size based on palpation (n=5) or ultrasound (n=12), 53% (9/17) achieved a reduction in spleen size category. No pts had a worsening in spleen size category, and spleen size category remained stable for 47% (8/17) of pts. At index, all but one pt had ≥ 1 MF-related symptom. By Day 180, 80% (35/44) experienced a reduction in the number of symptoms, with a median reduction of 67% (IQR: 33–75). Median PLT at index was $72 \times 10^9/L$ (IQR: 53–110) and from index to Day 180, median increase in PLT was 14% (n=38, IQR: 0–30). Among pts with PLT $\leq 100 \times 10^9/L$ at index 20% (6/30) achieved an increase of $\geq 30 \times 10^9/L$. At index, median Hb was 8.8 g/dL (IQR: 8.0–9.7). Among 29 pts with Hb < 10 g/dL at index and Hb at Day 180, Hb increased by a median of 0.8 g/dL (IQR: -0.1–1.0), with 31% (9/29) achieving an increase ≥ 1.0 g/dL. Overall survival by the end of follow-up was 89% (40/45), and 6-month survival probability was 93% (95% confidence interval: 81, 98). **Conclusions:** Similar to clinical trials, pts with MF and higher PLT counts treated with PAC in the real-world also experienced reduction or stabilization in spleen size category, decreased MF-symptom burden, PLT stability, and improved Hb. Research Sponsor: Sobi Inc.

Integrated analysis of the ropeginterferon alfa-2b clinical program in essential thrombocythemia to demonstrate molecular and hematologic responses with safety profile information across treatment lines, ethnicities, and driver mutation types.

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Background: Patients with essential thrombocythemia (ET) have limited disease-modifying options. This integrated analysis of 182 ET patients from 2 trials evaluated consistency the efficacy of ropeginterferon alfa-2b (ropeg, BESREMI) across treatment lines and examined the impact of ethnicity and molecular subtype on outcomes. **Methods:** Data were pooled from the phase 3 randomized SURPASS-ET study (ropeg vs anagrelide [ANA] in HU-resistant/intolerant high-risk ET) and the phase 2b single-arm EXCEED-ET study enrolling both treatment-naïve and previously treated patients in North America. Endpoints included durable modified ELN response, hematologic and molecular responses, thrombotic events, and safety. **Results:** In SURPASS-ET, ropeg achieved a significantly higher durable modified ELN response at months 9 and 12 than ANA (42.9% vs 6.0%; $p < 0.0001$), with superior platelet and WBC control, greater *JAK2V617F* allelic burden reduction, and fewer major thrombotic events. In EXCEED-ET, durable objective modified ELN responses reached 60.2%, with ELN2009 molecular response rates of 35.0% for *JAK2V617F*, 16.0% for *CALR*, and 25.0% for *MPL*, demonstrating consistent efficacy across treatment lines and mutation subtypes (Table 1). Safety profiles were comparable between studies, with mostly low-grade, manageable AEs. In the integrated analysis across studies, grade ≥ 3 TEAEs occurred in 28.6% of ropeg recipients and 33.8% of ANA. TEAEs leading to discontinuation (8.8% vs 20.0%) and serious AEs (12.6% vs 30.0%) were less frequent in the ropeg group. Fatal AEs occurred only in the ANA group (3.8%). **Conclusions:** Across the two studies, consistent molecular and hematologic efficacy with a favorable and manageable safety profile was demonstrated in treatment-naïve and pretreated ET populations, across ethnicities and disease drivers. These findings support ropeg as a disease-modifying treatment option with a favorable benefit-risk profile for all ET patients regardless of ethnicity, treatment line, driver mutation status, and mutational complexity. Clinical trial information: NCT04285086, NCT05482971. Research Sponsor: PharmaEssentia Corporation.

Key efficacy outcomes from both trials.

Outcome	SURPASS-ET		EXCEED-ET
	Ropeg N=91	ANA N=83	Ropeg N=91
Durable modified ELN response, %	42.9	6.0	60.2
Subgroup analysis by race, % (n)			57.2 (41/71)
Caucasian	44.2 (38/86)	6.2 (5/81)	53.0 (4/7)
Asian	-	-	100.0 (5/5)
African American	-	-	66.7 (2/3)
Hispanic	-	-	100.0 (5/5)
Other	-	-	-
Platelet control $\leq 400 \times 10^9/L$, %	56.0	21.7	48.4
WBC normalization, %	73.6	13.3	48.4
Molecular response*, % (n)			
<i>JAK2V617F</i>	30.6 (19/62)	0 (0/42)	35.0 (7/20)
<i>CALR</i>	30.0 (3/10)	0 (0/4)	16.0 (4/25)
<i>MPL</i>	0 (0/1)	0 (0/1)	25.0 (2/8)
Major thrombotic events, %	1.1	10.0	1.1

*The molecular response per the 2009 ELN criteria includes complete and partial responses.

Activating MPN patients through empowering, patient-centered education.

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Background: Patients living with myeloproliferative neoplasms (MPNs) face complex disease management, evolving treatment options, and barriers to accessing reliable, culturally relevant information. These challenges disproportionately affect underrepresented populations, including Black, Latinx, Indigenous, rural, LGBTQIA+, and veteran communities. The [ACT]IVATED MPN program was developed to improve health literacy, patient activation, and self-advocacy among individuals newly diagnosed with MPNs, while remaining relevant across all stages of disease. **Methods:** The [ACT]IVATED MPN program delivers expert-verified, multimedia educational content designed to support patient and care partner engagement in care. Program components include multilingual expert interview videos, real-world patient vignettes, downloadable health literacy tools, and a comprehensive resource guide available in English and Spanish. Content is distributed digitally and through culturally trusted community organizations to increase reach among underserved populations. Program reach and impact are assessed through digital engagement analytics and post-program participant feedback. **Results:** To date, the [ACT]IVATED MPN program has reached over 5,000 patients and care partners. Preliminary program evaluation data indicate that 100% rated their overall experience as positive or somewhat positive, with 83.3% reporting a positive experience. Following participation, 90.9% of respondents agreed or strongly agreed that the program increased their understanding of MPNs. Indicators of patient activation were high, with 100% of participants reporting increased confidence to speak up with questions about their care and 95.7% reporting greater knowledge and confidence to take an active role in treatment decisions. **Conclusions:** The [ACT]IVATED MPN program demonstrates the feasibility and value of a patient-centered, equity-focused education model in supporting health literacy, self-advocacy, and engagement in care among individuals living with MPNs. Scalable, multilingual educational interventions may complement clinical care by promoting shared decision-making and reducing disparities in access to MPN-related information and resources. Hibbard, J. H., & Greene, J. (2013). What the evidence shows about patient activation: Better health outcomes and care experiences; fewer data on costs. *Health Affairs*, 32(2), 207–214. <https://doi.org/10.1377/hlthaff.2012.1061>. Research Sponsor: Incyte; Merck; Sanofi.

Association of neutrophil-to-lymphocyte ratio and thrombotic events in US veterans with polycythemia vera.

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Background: Neutrophil-to-lymphocyte ratio (NLR) is a novel predictor of thrombosis in patients with Polycythemia Vera (PV), an uncommon myeloproliferative neoplasm distinguished by excessive red blood cell production within the bone marrow. However, there is no guideline-endorsed NLR cut-off that mandates cytoreduction. This study aims to assess the association of NLR and risk of thrombotic events, and evaluate the impact of different therapies based on electronic health records from the United States (US) Veterans Affairs Healthcare System (VAHS). **Methods:** Veterans with PV were identified based on either 2 outpatient codes separated by 30 or more days or 1 inpatient code in the VAHS databases (2017–2023). The first PV diagnosis was considered as the index date. Patients with myelofibrosis or leukemia diagnosis before the index date were excluded from the analysis. Veterans with at least one NLR value were examined for the occurrence of thrombotic events. Baseline characteristics were defined over the two-year period preceding the first PV diagnosis code. Treatments were defined within two years of the index date and categorized as: cytoreductive therapy (including hydroxyurea, interferons, or ruxolitinib), phlebotomy interventions, or neither. Cox proportional hazards regression was used to evaluate the associations between therapies and the risks of thrombotic events, controlled by the pre-index use of individual therapy. **Results:** A total of 11,809 Veterans with PV were identified from the VAHS, with a mean (SD) age of 67.4 (11.1) years, 96.7% male, 9.0% Black, 81.1% White, and 5.1% Hispanic. The rate of thrombotic events (per 1000 person-year) was 45 for patients treated with cytoreductive therapy, 32 for phlebotomy-treated patients, and 51 for those who received no treatment. Patients were delineated into five groups based on NLR: <1, 1–2.9, 3–4.9, 5–19.9, and above 19.9. The rate of thrombotic events was closely at 39% amongst each group with NLR below 5. For those with NLR at 5–19.9 and >19.9, thrombotic events were reported in 48% and 61% of veterans, respectively. Cytoreductive therapy and therapeutic phlebotomy were each associated with significantly lower risks of thrombotic events compared to none of these two treatments among PV patients. Adjusted risk of thrombotic events was 45% (HR: 0.55, 95%CI: 0.48–0.62, $P < 0.01$) and 34% (HR: 0.66, 95%CI: 0.57–0.78, $P < 0.01$) lower for patients with cytoreductive and phlebotomy therapy compared to no treatment. **Conclusions:** The real-world evidence from VAHS yields a cut-off value of NLR at 5 to predict risks of thrombotic events among Veterans with PV. Patients receiving cytoreductive therapy or therapeutic phlebotomy had reduced risk of thrombotic events. Research Sponsor: PharmaEssentia, Inc.

Real-world outcomes of 7+3 versus azacitidine/venetoclax in CML transformed to AML.

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Background: Although tyrosine kinase inhibitors (TKIs) have markedly improved outcomes in chronic myeloid leukemia (CML), transformation to acute myeloid leukemia (AML) remains a devastating event with poor prognosis. Intensive induction chemotherapy with cytarabine and anthracycline (7+3) is standard, but many patients are older or frail and unable to tolerate intensive therapy. Azacitidine plus venetoclax (aza-ven) has emerged as a low-intensity alternative; however, real-world comparative outcome data in CML-transformed AML remain limited. We conducted a large real-world analysis to compare survival and early clinical outcomes with 7+3 versus aza-ven. **Methods:** Adult patients with CML transformed to AML who received induction therapy between January 1, 2010, and June 1, 2025, were identified using the TriNetX Research Network. Patients were classified by receipt of 7+3 or azacitidine plus venetoclax within one year before or after allogeneic hematopoietic stem cell transplantation. Overall survival (OS) was evaluated using Kaplan–Meier analysis with hazard ratios (HRs) and log-rank testing. Early clinical outcomes were compared using z-tests with risk differences (RD), risk ratios (RR), and 95% confidence intervals (CI). **Results:** A total of 280 patients were included, of whom 222 received 7+3 and 58 received azacitidine plus venetoclax (aza-ven). Patients treated with aza-ven had a higher comorbidity burden and lower baseline albumin, consistent with a frailer population. Early infectious complications within 30 days occurred in 53.2% of patients receiving 7+3 and 58.6% receiving aza-ven (risk difference [RD] –5.47%, 95% CI –19.74% to 8.81%; risk ratio [RR] 0.91, 95% CI 0.71–1.16; $p=0.46$). One-year overall survival was similar between groups (66.2% vs 68.1%; hazard ratio [HR] 1.03, 95% CI 0.62–1.72; log-rank $p=0.91$). Hospitalization within 30 days occurred less frequently with 7+3 than with aza-ven (71.6% vs 84.5%; RD –12.86%, 95% CI –23.91% to –1.82%; RR 0.85, 95% CI 0.74–0.97; $p=0.046$), while hospitalization between days 31–180 was identical in both groups (50.0% vs 50.0%; $p=1.00$). Infection between days 14–30 occurred in 34.7% versus 43.1%, respectively (RD –8.42%, 95% CI –22.62% to 5.78%; $p=0.24$). **Conclusions:** In this real-world cohort of patients with CML transformed to AML, azacitidine plus venetoclax achieved comparable 1-year survival and early infectious outcomes to intensive 7+3 induction despite being used in a frailer population. Larger multicenter studies are needed to confirm comparative effectiveness and refine patient selection. Research Sponsor: None.

Clinical features, management, and outcomes of adolescents and young adults with myeloproliferative neoplasms.

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Background: Myeloproliferative neoplasms (MPNs)—polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (MF)—are chronic myeloid malignancies mainly occurring in older adults. However, up to 20% of pts are diagnosed as adolescents and young adults (AYA; ages 13–39). Thus, treatment guidelines and outcome data primarily apply to older subjects, leaving clinical features, outcomes, and management of younger pts poorly defined. We describe the characteristics, risk stratification, and treatment of AYA pts at a tertiary academic center. **Methods:** We conducted a retrospective study of AYA pts with MPN treated at Mass General Brigham between 2007–2025. Pts diagnosed at ages 13–39 and meeting 2022 WHO criteria for MPN were included. Data abstracted from the electronic medical record included demographics, diagnostics, cardiovascular (CV) risk factors, thrombotic and bleeding events, risk stratification, and management. Descriptive statistics were applied. **Results:** 90 AYA pts with MPN were identified. Median age at diagnosis was 27 years (range 16–39), 53 (58.9%) were female and 64 (71.1%) were White. ET was the most frequent (65.6%), followed by PV (22.2%), MF (6.7%), and MPN-unclassified (5.6%). Most pts (73.3%) were diagnosed incidentally with abnormal blood counts. At least one CV risk factor—HTN, HL, DM, BMI >25, tobacco use—was present in 53 pts (58.9%). JAK2 mutation was present in 55 pts (61.1%), CALR in 26 (28.9%), MPL in 3 (3.3%), and triple-negative in 7 (7.8%). Across 18 (20.0%) pts, 23 thrombotic events occurred; arterial (n= 9) and venous (n= 14); 13 in the year prior to diagnosis and 10 after; 3 pts (3.3%) experienced events in both time periods and 4 (4.4%) pts experienced more than one event. Seven (7.8%) experienced major bleeding in the year prior to diagnosis or any time after, defined by ISTH criteria. Of the 23 pts with thrombotic and/or bleeding events, 19 were subsequently cytoreduced, most often with interferon (peginterferon n=10; peginterferon n=3). One pt received ruxolitinib and 12 hydroxyurea. Of 71 pts classified as low-risk, 34 (47.9%) received cytoreduction. Indications included extreme thrombocytosis (32.4%), inadequate control with phlebotomy (23.5%), symptom burden (23.5%), bleeding risk/history (17.6%), and disease modification (14.7%). Median follow-up was 3.6 years (IQR 1.9–7.6), 4 (4.4%) pts progressed to MF, and 1 (1.1%) to accelerated phase MPN. Two (2.2%) of these pts have undergone allogeneic stem cell transplantation. One (1.1%) death was reported during follow-up. **Conclusions:** In this AYA MPN cohort, > 20% were high-risk due to thrombotic events. CV comorbidities were common despite young age. Nearly half of low-risk pts received cytoreductive therapy, highlighting potential limitations of standard risk stratification in young pts. These findings support the need for age-specific guidelines for AYA pts with MPN. Research Sponsor: None.

Beyond haematological control: Long-term renal outcomes of imatinib therapy in chronic myeloid leukaemia.

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Background: Imatinib has transformed outcomes in chronic myeloid leukaemia (CML), enabling long-term survival and durable molecular responses. With therapy often extending over decades, late toxicities affecting organ function have gained increasing importance. However, real-world data on long-term renal outcomes with prolonged imatinib exposure remain limited. **Objectives:** To evaluate long-term changes in renal function in patients with CML receiving imatinib therapy for at least 10 years. **Methods:** This retrospective observational study included patients with CML treated with imatinib for ≥ 10 years at a single tertiary care centre. Clinical and treatment-related data were obtained from medical records. Renal function at baseline and at latest follow-up was assessed using estimated glomerular filtration rate (eGFR) calculated by the CKD-EPI formula. Data on diabetes and hypertension were collected. Patients with pre-existing chronic kidney disease, those receiving chemotherapy, those diagnosed with a second malignancy and patients in treatment-free remission (TFR) were excluded. **Results:** A total of 440 patients were analysed. The median age at diagnosis was 36 years (range, 5–70), with a male-to-female ratio of 1.39:1. At diagnosis, 95% were in chronic phase. Sokal risk stratification classified 32%, 31%, and 37% of patients as low, intermediate, and high risk, respectively. The median duration of imatinib therapy was 15 years (range, 10–24), with a median daily dose of 400 mg (range, 200–800 mg). At last follow-up, 91% of patients had achieved major molecular response. Overall, 62 patients (14%) developed a clinically significant decline in renal function ($\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$). In this subgroup, median eGFR declined from 90 range, 70–122 to 44 mL/min/1.73 m² (range, 13–54); representing a median reduction of 46 mL/min over 15 years (approximately 3 mL/min/year). Comorbidities were present in 11 patients (18%). A greater decline in eGFR was observed among males ($p < 0.001$), patients aged < 35 years at diagnosis ($p < 0.0001$), and those achieving major molecular response ($p < 0.0002$). Treatment modification was undertaken in < 37 patients (60%), including TFR in 13 (21%), dose reduction in 20 (32%), and switching to an alternate tyrosine kinase inhibitor in 4 (6%). Partial renal recovery was documented in 9 patients (24%). All patients in whom TFR was attempted continue to maintain TFR at last follow-up. **Conclusions:** Long-term imatinib therapy is associated with a gradual but clinically meaningful decline in renal function in a subset of patients with CML. Dose modification, switching TKIs, or attempting TFR may result in partial reversibility, without compromising disease control. These findings highlight the importance of long-term renal monitoring and treatment optimisation in patients with sustained molecular responses. Research Sponsor: None.

Durable treatment-free remission in CML beyond clinical trials: Lessons from a large single-center real-world experience.

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Background: Treatment-free remission (TFR) has become a major therapeutic objective in chronic-phase chronic myeloid leukemia (CML). While clinical trials have established the feasibility of TFR, real-world data evaluating the influence of deep molecular response (DMR) duration, cumulative tyrosine kinase inhibitor (TKI) exposure, and adherence to molecular monitoring remain limited, particularly in resource-constrained settings. **Methods:** We conducted a retrospective single-centre analysis of chronic-phase CML patients who electively discontinued TKI therapy between May 2019 and October 2025 after achieving sustained DMR (BCR-ABL $\leq 0.01\%$ IS). Collected variables included demographics, ELTS risk score, TKI type, duration of DMR (<5 vs ≥ 5 years), cumulative TKI exposure (<8 vs ≥ 8 years), molecular relapse (loss of major molecular response [MMR]), time to relapse, and time to MMR regain following TKI resumption. Monitoring compliance was defined as completion of at least five PCR assessments in the first year following TKI discontinuation. Relapse-free survival was analyzed using Kaplan–Meier methods. **Results:** Eighty-eight patients were included (median age 36 years; 53.4% male). Median cumulative TKI exposure prior to discontinuation was 14.5 years, and median DMR duration was 13 years. At a median follow-up of 40 months, 72 patients (81.8%) remained in sustained TFR. TFR rates were 92% at 6 months, 87% at 12 months, and 82% at 24 months. Fourteen patients (15.9%) restarted TKI therapy due to molecular relapse, one due to withdrawal symptoms, and two died from causes unrelated to CML. Median time to relapse was 4.5 months, with the majority occurring within the first six months. No patient progressed to accelerated or blast phase. All evaluable patients who resumed TKI therapy rapidly regained MMR (median 3 months). TFR rates did not differ significantly according to DMR duration (<5 vs ≥ 5 years; $p=0.67$), cumulative TKI exposure (<8 vs ≥ 8 years; $p=0.70$), or compliance with molecular monitoring (compliant vs non-compliant; $p=0.82$). Notably, 30.6% of patients were non-compliant with recommended monitoring schedules, yet high TFR rates and excellent salvage outcomes were maintained. **Conclusions:** In this large single-centre real-world cohort, over 80% of chronic-phase CML patients achieved durable TFR with predictable early relapses, excellent salvage outcomes, and no disease progression. Neither prolonged DMR duration, extended TKI exposure, nor strict adherence to intensive molecular monitoring significantly influenced relapse risk. These findings support broader, pragmatic implementation of TFR strategies and suggest that less stringent molecular monitoring may be safely adopted in carefully selected patients, particularly in resource-limited settings. Research Sponsor: None.

ASC4FIRST wk 144 analysis: Efficacy and safety and tolerability with asciminib (ASC) vs investigator-selected tyrosine kinase inhibitors (IS TKIs) in newly diagnosed (ND) chronic myeloid leukemia in chronic phase (CML-CP).

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Background: In ASC4FIRST (NCT04971226) primary (wk 48) (Hochhaus A et al. *N Engl J Med*. 2024) and key secondary (wk 96) (Cortes JE et al. *Blood*. 2025) analyses, ASC had superior efficacy and improved safety/tolerability vs IS TKIs. ASC was approved for ND CML-CP in numerous countries. We report the ASC4FIRST wk 144 analysis (cutoff: Sep 29, 2025). **Methods:** In this multicenter, open-label, phase 3 study, patient (pts) with ND CML-CP were randomized 1:1 to ASC 80 mg once daily or an IS TKI at label doses, stratified by ELTS risk category and prerandomization-selected TKI (imatinib [IMA] or a second generation [2G] TKI). Primary endpoints were major molecular response (MMR) rates at wk 48 with ASC vs all IS TKIs, and ASC^{IMA} vs IS TKI^{IMA}. **Results:** Pts were randomized to ASC (n=201) or IS TKIs (n=204). Median follow-up was 38.1 mo with ASC vs 37.4 mo with all IS TKIs, 36.2 mo with ASC^{IMA} vs 35.3 mo with IS TKI^{IMA}, and 39.2 mo with ASC^{2G} vs 38.5 mo with IS TKI^{2G}. At cutoff, more pts were ongoing tx with ASC vs all IS TKIs (78.6% vs 55.9%), ASC^{IMA} vs IS TKI^{IMA} (81.2% vs 50.0%), and ASC^{2G} vs IS TKI^{2G} (76.0% vs 61.8%). MMR rate at wk 144 continued to be superior with ASC vs all IS TKIs (77.1% vs 53.4%; tx difference, 23.9%; P<.001) and ASC^{IMA} vs IS TKI^{IMA} (79.2% vs 47.1%; tx difference, 32.6%; P<.001), and higher with ASC^{2G} vs IS TKI^{2G} (75.0% vs 59.8%; tx difference, 15.2%; P=.01). MR⁴ and MR^{4.5} rates at wk 144 were higher with ASC vs all IS TKIs (56% vs 36%; 42% vs 25%), ASC^{IMA} vs IS TKI^{IMA} (58% vs 33%; 44% vs 20%), and ASC^{2G} vs IS TKI^{2G} (53% vs 39%; 41% vs 29%). Long-term outcomes with ASC vs all IS TKIs, ASC^{IMA} vs IS TKI^{IMA}, and ASC^{2G} vs IS TKI^{2G} included probability of event-free survival at wk 144 post randomization (85% vs 69%; 83% vs 63%; 87% vs 75%), and estimated progression-free survival (98% vs 95%; 97% vs 93%; 99% vs 97%) and overall survival (99% vs 97%; 99% vs 96%; 99% vs 99%), at 3 yrs post randomization. No new postbaseline mutations emerged with ASC after wk 96; 1 each emerged with IMA and nilotinib. Safety/tolerability remained favorable with ASC vs IMA vs 2G TKIs including grade ≥3 AEs (49% vs 52% vs 63%), AEs leading to discontinuation (6% vs 13% vs 14%), and AEs leading to dose adjustment/interruption (37% vs 44% vs 63%); exposure-adjusted arterial occlusive event rates were 1.3, 0.5, and 1.1 cases per 100 pt-tx yr, respectively. Median exposure duration was 37.4 mo, 33.8 mo, and 37.3 mo, respectively. No deaths occurred during tx or ≤30 d after last dose. **Conclusions:** At wk 144, ASC had consistently higher molecular response rates and favorable safety/tolerability vs all IS TKIs with no new tx-emergent mutations. Together with wk 48 and 96, this analysis reinforces ASC's improved benefit-risk profile and supports ASC as a tx option for ND CML. Clinical trial information: NCT04971226. Research Sponsor: Novartis Pharma AG.

Upfront low-dose diet-modified nilotinib versus standard imatinib in Indian patients with newly diagnosed chronic-phase chronic myeloid leukemia: The NILLOW phase II randomised trial.

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Background: Upfront use of second-generation tyrosine kinase inhibitors in chronic myeloid leukemia (CML) is limited in resource-constrained settings due to cost, fasting requirements, and tolerability concerns. Food increases nilotinib bioavailability, enabling effective dose reduction. **Methods:** NILLOW was a single-center, open-label, randomized phase II study. Newly diagnosed CML-CP patients were randomized 1:1 to receive nilotinib 150 mg twice daily with meals or imatinib 400 mg once daily. The primary endpoint was EMR at 3 months (BCR-ABL1 IS $\leq 10\%$). Safety and hematologic recovery were evaluated as secondary endpoints. **Results:** EMR at 3 months was significantly higher with nilotinib compared to imatinib (73.8% vs 46.2%; absolute difference 27.6%; $p=0.001$). Patients receiving nilotinib demonstrated faster hemoglobin recovery during follow-up ($p<0.01$). Grade 3/4 anemia was lower with nilotinib (5.5% vs 17.8%; $p=0.02$). Imatinib was associated with higher rates of peripheral edema, periorbital edema, rash, pruritus, and headache (all $p<0.05$). **Conclusions:** Low-dose fed nilotinib improves early molecular response with superior tolerability compared to imatinib. This approach represents a cost-effective frontline strategy for CML in low-resource settings. Further studies as phase 3 maybe be followed up to confirm the signal. Clinical trial information: CTRI/2024/03/064707. Research Sponsor: None.

Clinical fidelity of large language models in chronic myeloid leukemia: A multimodel comparative study.

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Background: Large language models (LLMs) are emerging as promising tools for clinical decision-making. These models are increasingly investigated for their potential in diagnosis, prognosis, and personalized treatment of chronic myeloid leukemia (CML). This study evaluates the efficacy of five leading LLMs and examines the impact of incorporating up-to-date clinical guidelines into LLM prompts to enhance clinical decision-making. **Methods:** We developed fifty standardized clinical vignettes on CML, staging, tyrosine kinase inhibitor (TKI) selection, monitoring, adverse events, and treatment-free remission. Five LLMs (DeepSeek-R1, Gemini-2.5-Pro, Claude 4.0, GPT-OSS-120B, and LLAMA 4) generated responses under two distinct prompt conditions. In the baseline prompt, the clinical vignette was entered, and a response was obtained. In the guideline-augmented prompt, models were instructed to extract information from the NCCN v1.2026 and ESMO 2017 guidelines. A blinded expert panel evaluated the responses using a peer-reviewed answer key, assigning scores of 0 for incorrect, 1 for partial, and 2 for correct answers. The maximum possible score was 100. **Results:** The use of guideline-augmented prompting increased accuracy across all models, raising performance from 79.8% to 97.6% (mean difference: 17.8 percentage points, 95% CI: 3.9-31.7, p=0.024). Improvements for individual models ranged from 5 to 33 percentage points. Notably, only Gemini-2.5-Pro achieved perfect accuracy (100%). Knowledge drift was observed in four out of five models (80%), primarily due to reliance on outdated WHO classification criteria instead of current NCCN standards. This discrepancy resulted in staging errors in 32% of baseline cases. The diagnostic workup category exhibited the highest baseline accuracy (94%), whereas the treatment-free remission criteria showed the most substantial improvement following guideline integration, increasing from 72% to 96%. **Conclusions:** LLMs possess substantial medical knowledge that can facilitate clinical decision-making. However, these AI systems remain vulnerable to errors such as knowledge drift and hallucinations. This scalable framework demonstrates that mandatory compliance with guidelines, supported by structured prompting, is essential for safe LLM integration into oncology workflows. Institutions implementing LLM-based clinical decision support should require guideline integration rather than relying solely on pre-trained knowledge. Future studies should validate these findings in prospective clinical settings and evaluate mechanisms for automated guideline updating. Research Sponsor: None.

Comparative accuracy of LLM responses under baseline vs. guideline-augmented prompts.			
LLM	Baseline response accuracy	Guideline augmented response accuracy	Delta
Claude 4.0	82	97	+15
DeepSeek-R1	72	97	+25
Gemini-2.5 Pro	89	100	+11
GPT-OSS-120B	90	95	+5
LLAMA-4	66	99	+33

Molecular response and outcomes in patients with myeloproliferative neoplasms treated with interferon in the real-world setting.

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Background: Myeloproliferative neoplasms are clonal stem cell disorders driven by constitutive JAK-STAT signaling, classically via acquisition of the *JAK2* V617F mutation. *JAK2* variant allele frequency (VAF) correlates with disease phenotype and clinical risk. Interferon (IFN) therapies are immunomodulatory agents with disease-modifying potential, demonstrating reductions in *JAK2* allele burden in limited prospective trials. However, IFN therapies are underutilized in clinical practice, and molecular responses are poorly defined. Therefore, we evaluated clinical outcomes and molecular response to IFN therapy in real-world practice, emphasizing long-term *JAK2* VAF kinetics. **Methods:** We conducted a single-center, retrospective study of consecutive patients diagnosed with essential thrombocythemia (ET), polycythemia vera (PV), or pre-fibrotic myelofibrosis (pre-MF) treated with peginterferon alfa-2a or ropeginterferon alfa-2b, regardless of prior therapy. Serial *JAK2* V617F was measured in peripheral blood using allele-specific PCR. Clinical outcomes, treatment persistence, and longitudinal molecular responses were evaluated. **Results:** Eighty-two patients were included (median age 50.5 years, 73% female), with diagnosis of PV (76.8%), ET (17.1%), or pre-MF (6.1%); 44 patients (53.7%) were treatment naïve. Median follow-up was 92 mos. from diagnosis and 59 mos. from IFN initiation. At 48 mos., 82% of patients remained on treatment; 12 patients (14.6%) discontinued due to intolerance. Disease progression occurred in one patient. Complete hematologic remission (CHR) was achieved in 80.5% of patients. Median baseline *JAK2* VAF was 28%, declining to a median nadir of 4.2% at 41.5 months. Median absolute and relative percent reductions were -18.7 and -81.6%, respectively. VAF reduction $\geq 50\%$ was achieved by 79% of patients, 19.5% achieved a nadir $<1\%$, and 53.2% achieved nadir $<5\%$. VAF declined progressively until 48 mos. and then remained stable through 72 mos., with later increases mostly attributable to treatment discontinuation. No baseline clinical, molecular, or treatment-related variables predicted depth of molecular response. Treatment-free remission (TFR) was attempted in seven patients after a median of 45 mos. of therapy (mean VAF 0.52%), and median TFR duration was 39 mos. **Conclusions:** This real-world analysis demonstrates that interferon therapy is feasible and effective in real-world practice. Most patients achieved durable CHR with low rates of treatment discontinuation. Disease progression was exceedingly rare. IFN was associated with substantial and sustained reductions in *JAK2* allele burden, supporting its disease-modifying activity outside of the trial setting. These findings reinforce the clinical relevance of serial molecular monitoring and inform emerging approaches to treatment de-escalation in select patients. Research Sponsor: None.

Timing of TP53 mutation acquisition as a determinant of outcomes in patients with myeloproliferative neoplasms and myelodysplastic syndromes.

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Background: While *TP53* mutations have been studied in MDS and AML, their clinical significance in MPN and MDS/MPN remains incompletely understood. Emerging evidence suggests that *TP53* mutations are often not present at diagnosis, acquired over the disease course, and enriched in older patients (pts). The primary objective of this study was to evaluate whether the interval between diagnosis and the detection of *TP53* mutation impacts OS and/or PFS.

Methods: All patients with a *TP53* mutation were identified via our in-house NGS panel between 2018–2024 were included (n=497). Spearman correlation, Kruskal–Wallis, and chi-square tests were used to evaluate associations between age, VAF, and the presence of co-mutations with the interval from diagnosis to *TP53* detection. The Kaplan–Meier method and Cox proportional hazards models were used to analyze OS and PFS. **Results:** A total of 54 pts, including ET (n=27), PV (n=7), MF (n=9), and CMML (n=9) were identified. The median age at diagnosis was 65.1 yrs, 56% were males (n=30), 81% Caucasian (n=44). 22% (n=12) of pts were diagnosed with their MPN or MDS/MPN at the time of *TP53* identification. 52% pts were treated with hydroxyurea prior to *TP53* identification. At the time of *TP53* detection, 13 pts had progressed to AML and 11 pts to MF. The most common co-mutations were *JAK2* (n=19), *CALR* (n=11), *TET2* (n=10) and *ASXL1* (n=9). The median time from initial diagnosis to *TP53* detection was 6.7 yrs (interquartile range [IQR], 0.8–13.4; range, 0–38 yrs). Pts were divided into 4 quartiles depending on timing of *TP53* acquisition, with 13 pts in the <6-mo, 15 pts in the 6 mo–7 yrs, 13 in the 7.1–14 yrs and 13 pts in the >14 yrs quartiles. Older pts had a significantly shorter interval between diagnosis and *TP53* detection (Spearman $r = -0.61$, $p < 0.0001$). In addition to older age in *TP53* time < 6 months (Median 74.9 vs 64.0, $p=0.005$), pts in the <6-month group also had higher VAF (> median of 41: 69.2% vs 43.9%) and had higher number of co-mutations at diagnosis (≥ 3 : 53.8% vs 26.8%), although this did not reach statistical significance. Older age at *TP53* detection was associated with significantly worse OS (3.6 vs 27.2 mo; $p=0.002$) and PFS (3.6 vs 17.5 mo; $p<0.001$). After adjusting for age at the time of *TP53* detection, a longer interval between diagnosis and *TP53* detection was associated with worse OS (HR for the 2nd, 3rd, and 4th quartiles vs. the 1st quartile: 1.2, 2.5, and 4.3; p for trend = 0.002) and worse PFS (HR 1.2, 2.9, and 4.5, p for trend = 0.001). **Conclusions:** This study demonstrates that after adjusting for age, a longer interval between MPN or MDS/MPN diagnosis and *TP53* detection is associated with worse OS and PFS. Older age has previously been identified as an adverse prognostic factor, however our findings suggest that timing of *TP53* acquisition may also be an important predictor of clinical outcomes in pts with MPNs and MDS/MPNs. Research Sponsor: None.

One vs. 2 vs. ≥ 3 *TET2* mutations in chronic myelomonocytic leukemia: Co-mutation patterns and prognostic correlates.

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Background: *TET2* is the most frequently mutated gene in chronic myelomonocytic leukemia (CMML) and has been associated with favorable outcome, with recent studies suggesting a more pronounced prognostic impact in the presence of ≥ 2 *TET2* mutations (Csizmar *et al. leukemia* 2025;39:2030; Kynning *et al. Br J Haematol.* 2025 Nov 25. doi: 10.1111/bjh.70264). We sought to determine if this particular observation extended to patients with ≥ 3 *TET2* mutations (*TET2*^{MUT}) and also held true in the context of recently reiterated genetic risk factors. **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 18 software. **Results:** 536 CMML patients who underwent CLIA-approved NGS testing were stratified according to the number of *TET2*^{MUT}: 221 (41%) wild-type, 148 (28%) with one, 153 (29%) 2, and 14 (2%) ≥ 3 *TET2*^{MUT}. Co-mutation frequencies with significant differences between one vs. two *TET2*^{MUT} included ASXL1 (46% vs. 29%; $p < 0.01$), KRAS (7% vs. 14%; $p = 0.02$) and SETBP1 (5% vs. 0.6%; $p = 0.02$). Phenotypic comparisons revealed preponderance of prognostically favorable traits associated with wild-type *TET2* but no significant differences between one vs. two *TET2*^{MUT}. In age-adjusted univariate analysis, transplant-censored overall survival (TCOS), calculated from the time of mutation detection, was superior in patients with one ($p < 0.01$; HR 0.7) or 2 ($p < 0.01$; HR 0.4) but not ≥ 3 ($p = 0.4$) *TET2*^{MUT}, vs. those with wild-type *TET2*. TCOS was also superior with 2 vs. 1 ($p = 0.02$; HR 0.7) but not with ≥ 3 vs. 1 ($p = 0.7$) *TET2*^{MUT}; the results were similar when TCOS was calculated from the time of diagnosis. Multivariable analysis confirmed the survival advantage of exactly two *TET2*^{MUT} vs. wild-type *TET2* ($p < 0.01$; HR 0.5), one *TET2*^{MUT} ($p < 0.01$; HR 0.6), or ≥ 3 *TET2*^{MUT} ($p < 0.01$; HR 0.4), after adjusting for age, sex, anemia, circulating blasts $\geq 2\%$, and leukocyte count $\geq 13 \times 10^9/L$. The favorable impact of exactly two *TET2*^{MUT} persisted in CMML-MD and CMML-MP and remained independent of *TET2* VAF, mutation type, karyotype, and other prognostically relevant mutations. This association was sustained in the BLAST ($p < 0.01$; HR 0.5) and CPSS-mol ($p = 0.02$; HR 0.7) models, but not in BLAST-mol model ($p = 0.12$). **Conclusions:** Mechanistic explanation for this novel observation includes the possibility that *TET2* mutational categories based on mutation count reflect distinct biological states rather than having a simple linear effect. The persistence of this signal despite adjustment for established molecular and genetic risk factors supports its consideration in the development of future CMML prognostic models. Research Sponsor: None.

Phase II trial of asciminib for newly diagnosed chronic myeloid leukemia.

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Background: Asciminib is safe and effective across all lines of therapy of chronic myeloid leukemia (CML). Here, we report interim results from an investigator-initiated phase II trial of asciminib in patients (pts) with newly diagnosed (ND) CML. **Methods:** Asciminib was given at 80 mg/day in pts with ND CML in chronic phase or accelerated phase (clonal evolution only). The primary endpoint was the rate of major molecular response (MMR) by 12 months of therapy. AEs were recorded according to the CTCAE version 5.0 criteria. The data cutoff was January 20, 2026. **Results:** A total of 59 pts were treated with a median age at diagnosis of 49 years (range, 21–79); 33 (56%) were male. Sokal score was low in 29 pts (49%), intermediate in 21 (36%), and high in 9 (15%). With a median follow-up of 12 months, the cumulative best overall response was MCyR in 57 pts (97%), CCyR in 54 (92%), MMR in 40 (68%), MR4 in 21 (36%), and MR4.5 in 17 (29%). Among pts who completed at least 1 year of asciminib therapy, the MMR rate by 12 months was 71%. By 3 months, among 58 evaluable pts, 51 (88%) achieved MCyR or transcript levels below 10% on the international scale (IS), 42 (72%) CCyR or transcript levels below 1% IS, 16 (28%) MMR, 5 (9%) MR4, and 2 (3%) MR4.5. Seven pts (12%) had transcript levels above 10%. By 6 months, among 53 evaluable pts, the rate of CCyR was 85% (45/53), MMR 64% (34/53), MR4 34% (18/53), and MR4.5 26% (14/53). By 12 months, CCyR was achieved in 27 pts (87%), MMR in 22 (71%), MR4 in 13 (42%), and MR4.5 in 10 (32%). *ASXL1* mutation was detected in 3 of 41 pts (7%) evaluated for cancer gene variants. Of them, two achieved a complete molecular response and one achieved CCyR as best response but later lost it with the acquisition of *A337T* and *F497L* mutations. The most frequent adverse events related or possibly related to asciminib included elevated lipase (Grade[G]2, n=9; G3, n=3; G4, n=1) and fatigue (G1, n=7; G2, n=2); 3 pts developed pancreatitis (G2, n=1; G3, n=2). A 71-year-old pt with a previous medical history of hypertension developed G5 acute coronary syndrome after 2.5 months of asciminib therapy. Overall, 8 of 59 pts (14%) discontinued asciminib due to: 1) adverse events in 4 (including 1 fatal acute coronary syndrome); 2) loss of CCyR in 2 (one with the emergence of *A337T* and *F497L* mutations and another with *P465A* and *D381E* mutations); 3) failure to achieve CCyR in 1 patient in the setting of cytopenias and asciminib dose reduction to 40 mg/day; and 4) withdrawal of consent by 1 patient due to inability to return to clinic for treatment due to social constraints and was in MR4 at the time of asciminib discontinuation. The 12-month rates of failure-free survival, event-free survival, transformation-free survival, and overall survival were 92%, 96%, and 98%, respectively. **Conclusions:** Treatment with asciminib in ND CML showed a MMR rate of 71% by 12 months of therapy with no new safety signals. Disease resistance was associated with the emergence of myristoyl pocket mutations. Clinical trial information: NCT06236724. Research Sponsor: None.

Thromboelastography-guided platelet transfusion and associations with utilization and outcomes in patients with hematologic malignancies.

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Background: Thromboelastography (TEG) is a viscoelastic assay assessing clot formation and global hemostasis. In patients with hematologic malignancies, transfusion support is essential, yet evidence guiding optimal transfusion strategies is limited. This study evaluated transfusion utilization and outcomes associated with TEG use in hematologic oncology patients. **Methods:** We conducted a retrospective cohort study at a tertiary care hospital (October 2022–2025) including hospitalized patients with acute and chronic leukemias or multiple myeloma who received blood product transfusions. Primary outcomes were platelet transfusion utilization (standardized units) and platelet response. Secondary outcomes included hospital length of stay (LOS) and in-hospital mortality. Welch's t-test and chi-square testing were used, with multivariable regression adjusting for demographic and clinical covariates. **Results:** Among 975 platelet transfusion episodes, 68 (5.3%) were TEG-guided. Unadjusted analyses showed slightly lower platelet utilization with TEG-guided transfusions compared with standard care (1.03 vs 1.06 units, $p<0.001$). Platelet count increments did not differ significantly (Δ 17.9 vs 16.3, $p=0.57$). TEG-guided patients had longer LOS (39.8 vs 31.9 days, $p<0.001$) and higher in-hospital mortality ($p<0.001$), reflecting greater illness severity. After adjustment, differences in utilization, platelet response, and LOS were no longer significant. TEG use remained strongly associated with in-hospital mortality (adjusted OR 29.8, 95% CI 8.83–100.77, $p<0.001$). **Conclusions:** TEG use in hospitalized patients with hematologic malignancies receiving platelet transfusions was uncommon and not associated with improved transfusion efficiency or platelet response. TEG-guided transfusions occurred primarily in high-acuity settings with prolonged hospitalization and increased mortality, suggesting TEG functions more as a marker of illness severity than a routine tool for optimizing platelet transfusion. Further studies are needed to clarify its role in malignant hematology care. Research Sponsor: None.

Platelet transfusion outcomes by TEG use in hematological malignancy encounters.

Outcome	TEG guided (n=68)	Non-TEG guided (n=1214)	P Value (unadjusted)	P value (adjusted)
Number of encounters	68	1214	—	—
Standardized platelet units, mean	1.03	1.06	0.14	0.34
Platelet count response (DELTA), mean	17.9	16.3	0.57	0.93
Length of stay, mean days	39.8	31.9	<0.001	0.51
In-hospital mortality, %	94.1	44.7	<0.001	0.0008

Adjusted p values from multivariable regression models including demographics, malignancy subtype, baseline platelet count, transfusion dose, care location, transfusion priority, and timing variables. DELTA = post-pre platelet count.

Safety and efficacy of asciminib in veterans with chronic myeloid leukemia.

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Background: Asciminib was approved for use in previously treated patients with chronic myeloid leukemia (CML) in 2021. It employs a novel allosteric mechanism that can overcome resistance and intolerance to conventional tyrosine kinase inhibitors (TKIs). We assessed the efficacy and clinical outcomes of asciminib in Veterans with CML following failure of first- and second-generation TKIs. **Methods:** Utilizing the VA Informatics and Computing Infrastructure (VINCI), we reviewed all 116 Veterans nationwide with a diagnosis of CML who were treated with asciminib prior to August 2025. Demographic and clinical data collected included age at diagnosis, gender, race, prior CML treatments, and BCR-ABL transcript levels at treatment initiation and at 3 and 6 months. Safety outcomes included the development of thrombocytopenia and neutropenia. Mortality data were collected when applicable. Since more than half of the patients were still alive at the time of chart abstraction, median survival could not be reliably estimated (median 3.4 years, lower limit 2.8 years, upper limit NA). We therefore report the restricted mean survival time (RMST). **Results:** 110 Veterans were included in the analysis after excluding 6 for missing data. The median age at diagnosis was 65 years (IQR, 52–71) and 95% of participants were male (Table 1). 70% of participants received a first-generation TKI as first-line therapy; in the second-line setting, 12% received a first-generation TKI and 83% received a second-generation TKI. The median BCR-ABL level at asciminib initiation was 1.03 (IQR, 0.08–29.95) and decreased to 0.05 (IQR, 0–0.69) at 6 months. 11 patients developed thrombocytopenia and 3 developed neutropenia. Assuming 5 years of follow-up from the start of asciminib, RMST is 3.3 years (standard error, 0.23 years). **Conclusions:** Asciminib demonstrated clinically meaningful activity in a heavily pretreated Veteran population with CML. By 6 months, the median BCR-ABL level was 0.05%, consistent with major molecular response (MMR; BCR-ABL ≤0.1%), a well-established positive prognostic indicator. Despite prior exposure to multiple therapies, overall survival (using RMST) remained favorable at a mean of 3.3 years following treatment initiation. Rates of any-grade neutropenia and thrombocytopenia were low, supporting a favorable safety profile. Research Sponsor: None.

Patient characteristics and outcomes.	
Characteristic	Total (N = 110)
Age at diagnosis, median (IQR)	65 (52–71)
Gender, n (%)	
Male	105 (95%)
Female	5 (4.5%)
Race	
Black	19 (17%)
White	85 (77%)
American Indian or Alaska Native	1 (0.9%)
Unspecified	5 (4.5%)
Treatment Exposure	
First-line therapy	
1 st generation TKI	77 (70%)
2 nd generation TKI	33 (30%)
Second-line therapy	
1 st generation TKI	13 (11.8%)
2 nd generation TKI	91 (82.7%)
3 rd generation TKI (ponatinib)	6 (5.5%)
Outcomes	
Thrombocytopenia	11 (10%)
Neutropenia	3 (2.7%)
RMST (5 years), years	3.3 (95% CI, 2.9–3.8)

Glucagon-like peptide-1 receptor agonist (GLP-1 RA) and hematologic cancer risk among older adults with type 2 diabetes.

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Background: Recent preclinical and clinical evidence suggests that glucagon-like peptide-1 receptor agonists (GLP-1 RA) may reduce cancer risk through inflammation modulation. However, comparative effectiveness research evaluating hematologic malignancy risks of GLP-1 RAs remain limited in real-world populations. **Methods:** Using 15% random samples of Medicare Part D beneficiaries from 2013 to 2022, we identified older adults with type 2 diabetes who initiated GLP-1 RA or DPP-4i. The primary outcomes included myelodysplastic syndromes (MDS), lymphoma, and leukemia. We performed 1:1 propensity score matching for confounding control. We estimated the hazard ratios (HR) and 95% confidence intervals (CI) with Cox proportional hazard model. We examined the heterogeneity in treatment effects by pre-specified patient demographic and baseline factors. Subgroup analyses were conducted for: a) age (≥ 75 vs. < 75 years), b) sex (female vs. male), c) race/ethnicity (non-Hispanic Black vs. non-Hispanic White vs. Hispanic ethnicity), d) obesity status (overweight vs. obese vs. severe obesity), and e) specific GLP-1 RA class (e.g., liraglutide, dulaglutide, and semaglutide). In the sensitivity analysis, we used cause-specific Cox model to account for death as a competing risk and calculated E-values to examine the potential influence of unmeasured confounders. **Results:** After propensity score matching, there were 29,212 patients included in the cohort (14,606 GLP-1 RA users and 14,606 DPP-4i users). Of the cohort, mean (SD) age was 77.3 (7.4) years; 53.9% were female, 69.9% were non-Hispanic White, 11.1% were non-Hispanic Black, and 3.9% were Hispanic. Compared to DPP-4i, GLP-1 RA showed reduced risks in MDS (HR: 0.70, 95% CI [0.53-0.94]), lymphoma (0.71 [0.57-0.89]), and leukemia (0.85 [0.74-0.99]). Overall, no statistically significant heterogeneity of treatment effect was detected in subgroup analyses. After accounting for death as a competing event, the hazard ratios are consistent with the conventional Cox models except monocytic leukemia (HR: 1.4 [0.45-4.56], $p=0.48$). E-values suggest moderate robustness to potential unmeasured confounding. **Conclusions:** GLP-1 RA initiation was associated with a reduced risk of hematologic malignancies compared with DPP-4i use among real-world patients with type 2 diabetes. These findings suggest a potential protective effect of GLP-1 RAs on hematologic cancer risk and warrant further mechanistic and prospective investigation. Research Sponsor: None.

Clinical and genetic landscape of individuals evaluated in a CHIP cardiology clinic: A single-center experience, 2020 to 2025.

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Background: Despite growing observational data linking clonal hematopoiesis of indeterminate potential (CHIP) to adverse cardiovascular outcomes, the cardiovascular evaluation and management of individuals with clonal hematopoiesis remain undefined. We report the experience of a dedicated CHIP Cardiology Clinic. **Methods:** We conducted a retrospective review of patients evaluated in the CHIP Cardiology Clinic at the Brigham and Women's Hospital. Baseline demographics, comorbidities, medication use, and treatment interventions were extracted from the electronic medical record. **Results:** Fifty-three patients were evaluated between 2020 and 2025, of whom 39 (73.6%) had clonal hematopoiesis (CH), out of which 12 (30.8%) met criteria for CHIP. Among individuals with CH, the most frequently identified mutations were DNMT3A (30, 76.9%), TET2 (23, 59.0%), and ASXL1 (6, 15.4%). The mean age was 65.9 years (range 40–81), and 23 (58.9%) were male. Hypertension and dyslipidemia were each present in 23 (59.0%) patients. Existing cardiovascular diseases included coronary artery disease (7, 18.0%) and arrhythmias (3, 7.7%). Following evaluation in the CHIP Clinic, and shared decision-making discussion in view of the dearth of evidence regarding outcome improvement in those with CHIP, lipid-lowering therapies were initiated or increased in 28 (71.8%) patients, with statins initiated or dose escalated in 21 (53.8%) and ezetimibe in 11 (28.2%). Blood pressure medications were initiated or intensified in 5 (12.8%) patients. Ischemic evaluation was performed in 3 (7.7%) patients due to suggestive symptoms. We developed a “patient page” to acquaint the patients and families with CHIP. (<https://doi.org/10.1001/jamacardio.2024.3773>). **Conclusions:** In this first longitudinal report from a dedicated CHIP Cardiology Clinic, a substantial proportion of patients harbored somatic mutations associated with elevated cardiovascular risk. Institution of preventive cardiovascular medications, in particular lipid-lowering therapies, was a frequent intervention. These findings support the feasibility of CHIP-focused cardiovascular care but underscore the need for prospective trials to evaluate the impact of targeted preventive strategies in this population. Research Sponsor: None.

Clinical outcomes in *TP53*-mutated clonal hematopoiesis: Single-center retrospective study.

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Background: Clonal hematopoiesis (CH), including CH of indeterminate potential (CHIP) and clonal cytopenia of undetermined significance (CCUS), is defined by myeloid neoplasm (MN)-associated somatic mutations in the absence of known hematologic malignancy and may precede MNs, such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). *TP53*-mutated (*TP53m*) CH has been assumed to be high risk, but clinical outcomes are poorly characterized. **Methods:** We retrospectively evaluated patients (pts) with *TP53m* CH seen at a tertiary cancer center. Inclusion required pathogenic or likely pathogenic *TP53* mutations of presumed hematopoietic origin identified on bone marrow, peripheral blood, or plasma next-generation sequencing. **Results:** 62 pts with *TP53m* CH were included; 26 (42%) CHIP and 36 (58%) CCUS. Median age was 68 years (range, 23–81) with 30 male pts (48%). History of tobacco, alcohol, and illicit drug use was noted in 30 (48%), 31 (50%), and 7 (11%) pts, respectively. Common comorbidities included cardiovascular disease (n=51, 82%), diabetes (n=17, 27%), and rheumatologic disorders (n=13, 21%). 53 pts (85%) had a history of non-myeloid malignancy, with 41 (77%) receiving prior cytotoxic chemotherapy, 20 radiation (32%), and 13 (21%) stem cell transplant/cellular therapy (SCTCT). By CH Risk Score (CHRS), 4 (7%), 38 (61%), and 20 (32%) pts were considered low-, intermediate-, and high-risk of myeloid transformation. The 36 CCUS pts were classified as 10 (28%) low, 9 (25%) intermediate, and 17 (47%) high risk by Clonal Cytopenia Risk Score (CCRS). Median *TP53* VAF was 5% (range, 1–54), and 30 pts (46%) had additional somatic mutations. 12 pts (19%) were *TP53* double-hit. Median time from prior malignancy to CH detection was 42.3 months (mo; range, 0.2–365.0). With a median follow-up time of 60.1 mo (95% confidence interval [CI], 43.0–70.5), median overall survival (mOS) from CH detection was 67.5 mo (95% CI, 59.0–not estimable [NE]). A total of 15 pts (24%) progressed to MNs (12 MDS [80%], 3 AML [20%]) with a median time to transformation of 20.2 mo (95% CI: 6.8–53.9). mOS from time of MN diagnosis was 20.1 mo (95% CI, 7.3–NE) for MDS and 0.3 mo (95% CI, 0.3–NE) for AML pts. Pts who transformed to MNs were more likely to have had tobacco (p=0.026) or illicit drug use (p=0.031), higher comorbidity burdens (p=0.031), rheumatologic disorders (p=0.016), previous SCTCT (p=0.042), and CCUS (p=0.035). No differences were observed by *TP53* VAF. Of those who transformed, 7 (47%) were intermediate- and 8 (53%) high-risk by CHRS. CCRS showed low, intermediate, and high risk in 4 (33%), 1 (9%), and 7 (58%) of the 12 *TP53m* CCUS pts who progressed to MNs, respectively. **Conclusions:** *TP53m* CH is associated with significant comorbidity burdens and oncologic history. Existing risk stratification tools poorly predict myeloid transformation in these pts. Further clinicopathologic characterization of *TP53m* CH is warranted. Research Sponsor: None.

Genomic landscape and precision therapeutics in polycythemia vera: Insights from the AACR Project GENIE.

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Background: Polycythemia vera (PV) is a myeloproliferative neoplasm associated with blood thickening and increased risk of life-threatening blood clots and bleeding. PV is rare and affects roughly 50 per 100,000 people in the US. PV is most commonly associated with a somatic mutation in the *JAK2* gene and the mean age of diagnosis is 60. The *JAK2* gene is critical for cell signaling, and cell maturation. Treatments for PV include immunotherapy, radiation and chemotherapy but this can only slow growth, underscoring the need to define molecular drivers for targeted therapies. Using the AACR GENIE database, this study characterizes the mutational landscape of PV to identify genetic markers and therapeutic targets. **Methods:** The American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database was accessed from cBioPortal (v18.1-public) on November 20, 2025 to identify all patients with PV. The most common gene mutations, demographic correlations, and mutual exclusivities were analyzed using a two-sided T-test and non-parametric tests, with Benjamini-Hochberg false discovery rate (FDR) correction. **Results:** The cohort comprised 491 PV samples from 341 patients. The patient population consisted of adults (19–88 years old, $n=341, 100\%$). Males ($n=171, 50.1\%$) were represented as equally as females ($n=163, 47.8\%$), with some unknown cases ($n=7, 2.1\%$). By race, the cohort consisted primarily of White ($n=236, 69.2\%$), Black ($n=13, 3.8\%$), and Asian ($n=17, 5.0\%$) patients, with the remaining patients ($n=75, 22.0\%$) categorized as having an unspecified or other race. Of the samples derived from 90 tumors which were classified as primary ($n=80, 16.3\%$) or metastatic ($n=10, 2.0\%$), the most frequent somatic mutations were observed in *JAK2* (87.17%, $n=428$), *TERT2* (18.53%, $n=91$), *DNMT3A* (14.87%, $n=73$), *ASXL1* (5.50%, $n=27$), and *TP53* (3.05%, $n=15$). When stratified by sex, sex-associated mutational variability was observed. Specifically, mutations in *NF1* ($n=13, p < 0.001$) were detected only in females. *DNMT3A* mutations occurred at a higher frequency in females compared to males ($n=48$ v. $n=23$; $p < 0.001$). *ASXL1* mutations occur at a higher frequency in males compared to females ($n=23$ v. $n=4$; $p < 0.001$). **Conclusions:** To the best of our knowledge, this is the first GENIE database analysis of polycythemia vera, thus addressing a significant research gap regarding its genomic landscape. The predominance of *JAK2* and *TERT2* align with earlier descriptions in prior genetic profiling studies. Sex specific mutations underscore the importance of demographic-specific molecular features. Collectively, these findings suggest that *JAK2* and *TERT2* could serve as key genomic targets for the development of novel precision therapeutics. Further research is needed to validate these genomic associations and advance precision medicine approaches for patients with PV. Research Sponsor: None.

Universal adipogenic and immunologic remodeling in the recurrent myeloid leukemia microenvironment of recurrent versus primary myeloid leukemias: An age-stratified analysis.

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Background: Disease recurrence is the primary cause of mortality in myeloid leukemias. While molecular studies suggest leukemic cells actively reprogram marrow stroma to create a self-reinforcing niche, natural age-related adiposity confounds whether this remodeling is disease-intrinsic or a byproduct of aging. We sought to validate the "disease-intrinsic" hypothesis by delineating the landscape of recurrent disease across a large-scale transcriptomic cohort, rigorously distinguishing leukemic reprogramming from physiologic aging. **Methods:** We analyzed 2,378 myeloid leukemia samples (2,007 primary, 371 recurrent) from NCI genomic datasets via xCell computational deconvolution. To control for ontogenic marrow changes, the cohort was stratified into Pediatric (<18 years, n = 2,071) and Adult (≥ 18 years, n = 307) subgroups. Demographic analysis confirmed balanced gender and race distributions (p > 0.05); age disparity was explicitly corrected via the stratified design. Differences in tumor microenvironment (TME) composition were assessed using Mann-Whitney U tests, with Bonferroni-corrected p-values (Padj) calculated to ensure statistical rigor. **Results:** Recurrent tumors exhibited a profound, convergent stromal remodeling independent of age. The 'adipogenic shift' via Preadipocyte enrichment was observed in both Pediatric (P < 10⁻⁴⁸) and Adult (P < 10⁻⁴) recurrences. Conversely, vascular collapse was universal, characterized by a significant reduction of Pericytes in both Pediatric (P < 10⁻⁷²) and Adult (P < 10⁻⁸) cohorts. Immunologically, CD4+ Memory T cells were consistently enriched in both Pediatric (P < 10⁻²⁶) and Adult (P < 10⁻⁴) groups, suggesting a convergent mechanism of adaptive immune persistence in the relapsed setting. **Conclusions:** We demonstrate that recurrent myeloid leukemia drives a convergent microenvironmental evolution characterized by vascular collapse, pathologic adiposity, and immune persistence, independent of patient age. These findings corroborate that stromal remodeling is a dominant, disease-intrinsic program actively driven by leukemic cells rather than a passive reflection of aging. Validating this "adipogenic shift" as a universal resistance mechanism identifies the adipogenic and vascular niches as priority targets for therapeutic intervention across the spectrum of myeloid malignancies. Research Sponsor: None.

Differential enrichment of microenvironmental populations in recurrent vs. primary myeloid neoplasms.				
Cohort	Cell Type	Direction	Mean Diff (Rec - Pri)	Padj
Pediatric (<18y)	Preadipocytes	Recurrence- High	+0.064	p < 0.05
	Pericytes	Primary- High	-0.085	p < 0.05
	CD4+ Memory T-cells	Recurrence- High	+0.849	p < 0.05
Adult (≥18y)	Preadipocytes	Recurrence- High	+0.056	p < 0.05
	Pericytes	Primary- High	-0.078	p < 0.05
	CD4+ Memory T-cells	Recurrence- High	+1.184	p < 0.05

Molecular characteristics of therapy-related myeloid neoplasms in PARP inhibitor-treated patients.

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Background: Poly ADP-ribose polymerase inhibitors (PARPi) are part of standard therapy in solid tumors, and is associated with development of therapy-related myeloid neoplasm (t-MN), including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). The contribution of pre-existing clonal hematopoiesis (CH) in t-MN with PARPi exposure is unknown. We report outcomes of a real-world cohort of t-MN patients following PARPi therapy. **Methods:** We performed a retrospective single-center analysis of 23 patients with solid tumors treated with PARPi (olaparib, rucaparib, niraparib, talazoparib) who subsequently developed t-MN. Chart review was performed to collect clinical data. Blood samples collected as a somatic control prior to the first chemotherapy or radiation for targeted next-generation sequencing (NGS) using the MSK-IMPACT platform were analyzed for pre-existing CH in a subset of evaluable patients (n=17). CH was defined as a somatic mutation with variant allelic frequency of 2% or more in peripheral blood. **Results:** Median age was 63 years at initial solid tumor diagnosis and 68 years at t-MN diagnosis. Primary malignancies included Ovarian/Fallopian Tube (83%, n=19), Breast (17%, n=4), Prostate (9%, n=2), and Esophageal (n=1) cancer. 3 patients had a history of both Breast and Ovarian cancer. Germline BRCA1/2 mutations were present in 48% (n=11) and 1 patient had Li-Fraumeni. Median time from PARPi initiation to t-MN diagnosis was 23.7 months (range: 1.6–45.3 months). At t-MN diagnosis, 52% (12/23) presented with MDS (including one case of clonal cytopenias of undetermined significance) and 48% (11/23) with AML. Genomic profiling of t-MN showed 78% (18/23) of patients had *TP53* mutations, and 65% (15/23) had complex karyotype. 90% of evaluable AML cases were classified as adverse risk by ELN 2022 and most MDS cases (9/11) had High/Very High risk by IPSS-R. Median overall survival in this cohort was 6 months from t-MN diagnosis. Among 17 patients with evaluable baseline blood samples, 41% (7/17) had detectable CH prior to t-MN, while 59% (10/17) did not. Of those with pre-existing CH, 57% (4/7) harbored mutations in DNA damage response genes (2 with *TP53*, 2 with *PPM1D*). Other mutations included *DNMT3A* (N=2), *ASXL1* (N=1), *SRSF2* (N=1), and *JAK2* (N=1). 43% (3/7) had a single CH mutation, while 57% (4/7) had 2 or more CH mutations. 6/7 of those with pre-existing CH had molecular testing at t-MN diagnosis, all of which (6/6) had a detectable *TP53* mutation at t-MN diagnosis, even when not previously detected. Cytogenetic features of t-MN for those with and without pre-existing detectable CH were similar. **Conclusions:** This is the largest single center cohort of post-PARPi t-MN with molecular characteristics described to date. Further study on the effect of PARPi therapy in the pathogenesis of t-MN is needed. Research Sponsor: None.

Outcomes and responsiveness of standard tyrosine kinase inhibitor dose versus dose de-escalation in chronic myeloid leukemia: A single-center retrospective study.

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Background: Treatment with tyrosine kinase inhibitors (TKIs) enables patients with chronic myeloid leukemia (CML) to achieve durable remission and a normal life expectancy. Despite this success, chronic TKI therapy is associated with cumulative toxicities. Although TKI dose de-escalation can be implemented to mitigate adverse events, its impact on the attainment and durability of response milestones is not completely defined. This study explored the impact of dose de-escalation of TKIs on clinical response milestones and treatment-free remission (TFR) outcomes. **Methods:** We retrospectively analyzed 407 adult CML patients treated with TKIs at Oregon Health & Science University. Outcomes of interest were TFR and achievement of undetectable *BCR::ABL1* transcripts. Odds ratios (OR) or Cox proportional hazards regression hazard ratios (HR) were used to analyze covariates and predictors. **Results:** Overall, the median age at diagnosis was 48 years (range: 18–91) and 1st-line therapies included: imatinib (n=252; 62%), dasatinib (n=95; 23%), nilotinib (n=42; 10%), and bosutinib (n=10; 2%); the remaining 2% of patients were treated with 3rd generation or later TKIs. Median follow-up since diagnosis was 11.3 years (0.2–35.8); 189 patients (46%) remained on their initial TKI, while 218 patients (54%) received ≥ 2 TKIs. Only 13 patients (3.2%) received a bone marrow transplant. With respect to the primary outcome of TFR, 133 patients attempted TFR and were further analyzed with respect to de-escalation of dose. Fifty-two patients (39%) remained on standard dose while 81 patients (61%) underwent dose de-escalation prior to the 1st TFR attempt. TFR rates were not significantly different between patients receiving standard dose vs de-escalated dose TKI (HR: 1.07 (95% CI: 0.59–1.96); p=0.818) at either 1 year (77% vs 74%) or 2 years (69% vs 69%). At the last follow-up, 89 patients remained in TFR, 62% of which had undergone dose de-escalation. Among the remaining 274 patients who have yet to attempt TFR, 162 (59%) continued treatment with their initial TKI: 98 (60%) on imatinib, 39 (24%) on dasatinib, 17 (10%) on nilotinib, 5 (3%) on bosutinib, 2 (1%) on ponatinib, 1 (1%) on asciminib. Among these patients, 56 (34%) had dose reduction, 9 (16%) of whom achieved undetectable disease. For the 106 patients on standard doses, only 5 (5%) had undetectable disease (OR: 3.83 (95% CI: 1.08–15.40); p= 0.020). More importantly, dose de-escalation led to significant reduction of adverse events. **Conclusions:** Our results show that patients who underwent dose de-escalation did not have significant differences in TFR duration and rate and are more likely to achieve undetectable diseases when compared with patients on standard doses. These findings support rational dose de-escalation as a strategy that preserves achievement of clinical outcomes while reducing adverse events. Research Sponsor: None.

A phase I study of HPB-092, a dual FLT3/IRAK4 inhibitor, in relapsed or refractory acute myeloid leukemia.

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Background: Fms-like tyrosine kinase 3 (FLT3) is a clinically validated oncogenic driver in acute myeloid leukemia (AML). While FLT3 kinase inhibitors have been approved for AML patients with FLT3 mutations, resistance remains a significant challenge. Interleukin-1 receptor-associated kinase 4 (IRAK4) has emerged as a key signaling node in treatment-induced resistance. Moreover, a subset of AML patient population harbors mutations in RNA splicing factors U2AF1 or SF3B1. These mutations result in expression of an oncogenic long form of IRAK4. Therefore, co-targeting FLT3 and IRAK4 can potentially both address resistance and treat a broader population in AML. HPB-092 is a highly selective dual-target small-molecule kinase inhibitor designed to target mutant FLT3 and IRAK4. HPB-092 demonstrated robust potency against FLT3-ITD ($IC_{50} = 0.24$ nM), FLT3-D835Y ($IC_{50} = 0.18$ nM), and IRAK4 ($IC_{50} = 3.1$ nM). In vivo, HPB-092 elicited dose-dependent regression of the MV4-11 tumor model. HPB-092 received IND clearance in both China and the US, showing a favorable safety profile with no significant genotoxicity or hERG inhibition, supporting its clinical evaluation. **Methods:** This ongoing, first-in-human, phase 1 study evaluates oral HPB-092 monotherapy in adults with RR-AML. The primary objectives are to evaluate safety, tolerability, pharmacokinetics (PK), and to determine the recommended phase II dose (RP2D). Secondary objectives include preliminary antileukemic activity (ORR, DOR) and exploratory biomarkers analyses. Part A is a dose-escalation phase spanning five dose levels (30–200 mg), utilizing an accelerated titration design followed by a 3+3 scheme in patients with R/R AML, regardless of FLT3, U2AF1 or SF3B1 mutation status. The study initiates with a single-dose administration on cycle 1 day 1 for SAD-PK assessment, followed by multiple ascending doses administered twice daily for MAD-PK and dose-limiting toxicities (DLTs) over a 28-day observation window. Part B is a randomized dose-expansion phase to evaluate selected dose levels in patients with FLT3-mutant AML and those with U2AF1 or SF3B1 mutations. Correlative pharmacodynamic and biomarker analyses are planned. No formal hypothesis testing or sample size calculation was performed. Safety, PK, and efficacy analyses will be descriptive in patients receiving at least one dose of HPB-092. AEs will be graded according to NCI CTCAE v5.0. PK parameters will be derived using noncompartmental methods. Time-to-event endpoints will be estimated using Kaplan-Meier methods, where applicable. Site initiation is complete; enrollment is initiated and ongoing, with the first patient anticipated in Q1 2026. Clinical trial information: NCT07137637. Research Sponsor: None.

A phase 3 study of revumenib plus venetoclax/azacitidine in adults with newly diagnosed *NPM1*-mutated or *KMT2A*-rearranged acute myeloid leukemia ineligible for intensive chemotherapy (EVOLVE-2/HO177/AMLSG35-24/ACT-HOV-AML-002).

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Background: Optimal treatment for patients (pts) with acute myeloid leukemia (AML) unfit for intensive chemotherapy (IC) remains challenging and depends on pt and disease characteristics and pt preference. In AML with a nucleophosmin-1 mutation (*NPM1m*) or lysine methyltransferase 2A (*KMT2A*) rearrangement (*KMT2Ar*), menin-*KMT2A* fusion proteins upregulate *HOX/MEIS* gene expression, resulting in hematopoietic differentiation arrest and leukemogenesis. Revumenib is a first-in-class, oral, potent, and selective inhibitor of the menin-*KMT2A* interaction. In the phase 1/2 AUGMENT-101 study (NCT04065399), revumenib monotherapy demonstrated clinically meaningful response rates and was generally well tolerated in pts with relapsed/refractory *NPM1m* AML or *KMT2Ar* acute leukemia. To further improve outcomes, combination regimens are being studied as front-line therapy for newly diagnosed (ND) pts. In the phase 1b Beat AML study (NCT03013998), revumenib plus venetoclax/azacitidine (VEN/AZA) demonstrated deep responses in pts ≥ 60 years (y) of age with ND *NPM1m* or *KMT2Ar* AML. EVOLVE-2 will assess whether revumenib plus VEN/AZA prolongs overall survival (OS) and improves complete remission (CR) rates in pts with ND *NPM1m* or *KMT2Ar* AML ineligible for IC.

Methods: EVOLVE-2 is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT06652438/EU-CT 2024-512733-32-00). Eligible pts are ≥ 75 y of age (18–74 y with comorbidities), have ND AML with centrally confirmed *NPM1m* or *KMT2Ar* (excluding *KMT2A* partial tandem duplications/deletions), are ineligible for IC, and are AML treatment-naïve. Pts will be randomized 1:1 to revumenib or placebo in combination with VEN/AZA and stratified by age (< 75 vs ≥ 75 y), genotype (*NPM1m* vs *KMT2Ar*), and region (Europe vs Australia vs United States). In Cycle (C) 1, VEN is given daily on Days (D) 1–28 and AZA daily on D1–7, $\pm$ revumenib twice daily on D1–28. In C2+, responders (per 2022 European LeukemiaNet criteria) may adjust VEN based on remission status/count recovery. Treatment continues until disease progression, unacceptable toxicity, pt withdrawal, or death. The dual primary endpoints are OS and CR rate. Key secondary endpoints include event-free survival and rate of CR/CR with partial hematologic recovery (CRh). Other endpoints include rates of CRh and CR/CR with incomplete hematologic recovery (CRi), measurable residual disease (MRD) negativity (CR, CR/CRh, CR/CRi with MRD negativity), time to/duration of response, adverse events, time to hematopoietic recovery, and incidence of platelet and red blood cell transfusions. Overall, 448 pts will be enrolled. As of January 27, 2026, the study is open to enrollment. Clinical trial information: NCT06652438. Research Sponsor: Syndax Pharmaceuticals, Inc.

Phase 1, open-label, multi-center trial of RPT1G in patients with relapsed/refractory acute myeloid leukemia and higher-risk myelodysplastic syndromes/neoplasms.

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Background: Nicotinamide phosphoribosyltransferase (NAMPT), the rate limiting enzyme in the NAD salvage pathway, regulates cellular energy metabolism and is overexpressed in blood cancers. Because cancer cells depend on elevated NAD-flux, they are highly sensitive to NAMPT inhibition. Since normal cells also require NAD for survival, prior clinical trials of complete NAMPT inhibitors lead to dose-limiting toxicities. We developed RPT1G, a novel hyperbolic inhibitor with an improved therapeutic window that enables therapeutically effective NAD depletion in malignant cells while sparing normal tissues (Crimmins, ASH 2023). A first-in-human, Phase 1, randomized, double-blind, placebo-controlled, SAD and MAD study in healthy volunteers of RPT1G showed that oral administration of RPT1G is safe and well-tolerated with a favorable pharmacokinetics (PK) profile. Target engagement results showed that RPT1G inhibits NAMPT at doses predicted to be therapeutically relevant. **Methods:** RPT1G is being investigated in a Phase 1, multi-center, open-label clinical trial (NCT07107126) for treatment of Relapsed/Refractory Acute Myeloid Leukemia (R/R AML) and Higher-Risk Myelodysplastic Syndromes/Neoplasms (HR-MDS). It is the first NAMPT hyperbolic inhibitor to be studied for the treatment of R/R-AML and HR-MDS patients. With a standard 3+3 design, this study explores escalating oral doses of RPT1G, given twice daily in 28-day cycles. Other dosing schedules will be studied based on observed PK, PK/pharmacodynamic relationships, safety, and tolerability to identify the maximum tolerated dose or presumptive biologically effective dose and select the recommended phase 2 dose (RP2D). The starting dose of 120 mg BID was active in healthy adults. Primary objectives include: 1) defining safety and tolerability; 2) determining the RP2D, optimal schedule and/or BED. Key secondary objectives include: 1) evaluating PK; 2) assessing preliminary efficacy by European LeukemiaNet 2022, including overall response rate, duration of response, and hematologic improvement, and clinical benefit by transfusion independence and the International Working Group 2023 HR-MDS response criteria. Enrollment criteria: adults ≥ 18 years old, with a histological confirmation of R/R-AML (ELN 2022 criteria) or HR-MDS (International Consortium for MDS 2023 criteria) that have received appropriate standard of care therapy(s) or declined receipt of these. Adequate organ function is required. Exclusion criteria: ongoing AEs from prior therapies; received radiation < 14 days from the first RPT1G dose; known active infections; or have uncontrolled cardiac issues, or other medical comorbidities that preclude safety evaluation. Clinical trial information: NCT07107126. Research Sponsor: None.

A phase 3 study of revumenib in combination with intensive chemotherapy in patients with newly diagnosed *NPM1*-mutated acute myeloid leukemia (REVEAL-ND NPM1).

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Background: There are currently no approved targeted therapies for newly diagnosed (ND) acute myeloid leukemia (AML) harboring a nucleophosmin-1 mutation (*NPM1m*), which occurs in ~30% of ND adult AML cases. In *NPM1m* AML, the *NPM1m*/XPO1 protein complex binds to DNA to sustain the interaction of menin and wild-type KMT2A that drives upregulation of *HOX/MEIS* gene expression, resulting in hematopoietic differentiation arrest and leukemogenesis. Revumenib is a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction. In the phase 1/2 AUGMENT-101 study (NCT04065399), revumenib monotherapy demonstrated clinically meaningful response rates and was generally well tolerated in relapsed/refractory *NPM1m* AML, leading to US Food and Drug Administration approval for that patient population on October 24, 2025. Standard AML treatment for younger, non-frail adults is based on intensive chemotherapy (IC) regimens and hematopoietic stem cell transplant (HSCT). The addition of revumenib to standard IC may further improve treatment responses specifically in the ND setting. This study is designed to assess the safety and efficacy of revumenib in combination with IC in patients with ND *NPM1m* AML. **Methods:** REVEAL-ND NPM1 is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT07211958). Eligible patients are ≥ 12 years of age, weigh ≥ 40 kg, and have treatment-naïve ND AML with locally determined (centrally confirmed) *NPM1m*. Patients will be randomized 1:1 to revumenib or placebo in combination with IC. Induction consists of 1 to 2 cycles of revumenib or placebo (dosed orally) alongside IC with cytarabine and daunorubicin or idarubicin (dosed intravenously). Consolidation consists of 1 to 3 cycles of revumenib or placebo plus cytarabine. HSCT may be performed after initial induction or consolidation. Treatment with revumenib or placebo monotherapy will continue for up to 2 years, with long-term follow-up until death, withdrawal of consent, or study closure. The dual primary endpoints are event-free survival and measurable residual disease-negative complete remission (CR) in the bone marrow, both assessed by independent reviewers. A key secondary endpoint is overall survival. Additional investigator-assessed endpoints include CR rate, composite complete remission (CRc) rate, overall response rate, duration of response (CR, CRc), safety, and quality of life. Overall, ~468 patients will be enrolled. As of January 27, 2026, the study is open to enrollment. Clinical trial information: NCT07211958. Research Sponsor: Syndax Pharmaceuticals, Inc.

A phase 2 study of olutasidenib in combination with azacitidine followed by olutasidenib maintenance after venetoclax plus a hypomethylating agent regimen for *IDH1*-mutated acute myeloid leukemia (University of California Hematologic Malignancies Consortium Study 2441).

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Background: Acute myeloid leukemia (AML) with isocitrate dehydrogenase-1 (IDH1) mutations represents a subset of up to approximately 7–14% of patients. For patients with IDH1m AML ineligible for first line intensive induction, the combination of a hypomethylating agent (HMA) and venetoclax (VEN) is a standard of care based on the VIALE-A study. In patients with IDH1m, the HMA azacitidine (AZA) plus VEN regimen leads to a complete remission (CR) plus CR with incomplete count recovery (CRi) rate of 66.7%, duration of remission (DoR) 21.9 months, and median overall survival (OS) of 15.2 months. However, one of the limiting features of HMA-VEN is myelosuppression, leading to dose delays and reductions, and adverse events (AEs) led to discontinuation in up to 30% of patients on the VIALE-A study. Approaches to increase tolerability and improve outcomes are of interest. Oltasidenib (OLU) is a potent, oral and selective small-molecule IDH1m inhibitor currently approved for relapsed/refractory AML patients with an IDH1 mutation, based on the pivotal cohort of a Phase 1/2 study. Overall, this study showed that OLU alone or in combination with AZA in patients with IDH1m AML was well-tolerated and showed meaningful clinical activity, including in those with prior VEN treatment. We hypothesize that, after achieving a response on HMA-VEN, de-escalating and switching maintenance from HMA-VEN to OLU-AZA followed by OLU monotherapy will lead to improved outcomes for patients with IDH1m AML. **Methods:** This multicenter investigator-initiated study through the University of California Hematologic Malignancies Consortium (UCHMC) is a phase II single-arm study evaluating the combination of OLU in combination with AZA followed by OLU monotherapy as a switch maintenance approach after HMA-VEN for patients with IDH1m AML. Key eligibility criteria include a diagnosis of IDH1m AML, achievement of CR or CRi to first-line HMA-VEN with no more than 4 cycles of HMA-VEN at the time of enrollment, IDH1m inhibitor naïve, age 18+, and performance status 0–2. The primary endpoint is treatment failure, defined as AML-related death, relapse, or treatment discontinuation due to AE within 12 months from the time of CR/CRi. Secondary endpoints include treatment-related AE, time to treatment failure, relapse-free survival, DoR, OS, and rate of allotransplant. Patients will receive OLU 150mg BID in combination with standard AZA during the first 4 cycles followed by OLU 150mg BID monotherapy until any discontinuation criteria are met. Disease assessments will be performed at baseline, following cycles 4, 8, and 12, and then as clinically indicated. The trial will enroll up to 28 patients across the UCHMC. The trial is currently enrolling. Clinicaltrials.gov ID is NCT07304011. Clinical trial information: NCT07304011. Research Sponsor: Rigel.

Updated protocol: IMPROVEMF, a phase 1b trial of imetelstat (IME)+ ruxolitinib (RUX) in patients (pts) with intermediate (INT)-1/2 or high-risk (HR) myelofibrosis (MF).

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Background: In preclinical evaluations, sequential treatment (tx) with RUX, a Janus kinase inhibitor (JAKi), and IME, a telomerase inhibitor, selectively reduced MF hematopoietic stem cells (HSC) and progenitor cells. In the Phase 2 IMbark trial (NCT02426086), IME monotherapy showed clinical activity and disease-modifying potential in pts with INT-2 or HR MF relapsed/refractory to JAKi. These findings, and the nonoverlapping mechanisms of action, supported the evaluation of IME+RUX in frontline MF. IMPROVEMF (NCT05371964) is an open-label study of IME+RUX in pts with INT-1/INT-2/HR MF. In Phase 1 (dose finding), IME+RUX was generally well tolerated, with no dose-limiting toxicities at any dose, and a safety profile consistent with reports from other IME trials. Notably, a dose-dependent signal of clinical activity was observed. The pharmacokinetics for the combination were similar to those of previous monotherapy studies. Thus, the recommended Phase 1b dose of 8.9 mg/kg IME active dose (equivalent to 9.4 mg/kg IME sodium) was chosen. **Methods:** Phase 1b (dose confirmation and expansion) will enroll adult pts with INT-1/INT-2/HR MF with an Eastern Cooperative Oncology Group performance status ≤ 2 and peripheral blood and bone marrow blasts $< 10\%$, ≥ 2 active symptoms with a score of ≥ 3 , or a total score of ≥ 10 on the MF Symptom Assessment Form v4.0, an absolute neutrophil count of $\geq 1.5 \times 10^9/L$ independent of growth factor support and platelets of $\geq 75 \times 10^9/L$ (updated criterion), no active systemic hepatitis infection, acute or chronic liver disease unrelated to underlying MF, and no prior history of HSC transplantation. The study was planned to evaluate 2 cohorts. In cohort A (JAKi-naïve pts), upon enrollment, pts will start RUX for ≥ 12 weeks (24 weeks max); once the RUX dose is stable for 4 weeks, 8.9 mg/kg IME intravenously (IV) every 4 weeks will be added. Per the updated protocol (November 2025), the study will no longer recruit pts into cohort A. Existing enrollees will continue in the study per schedule. In cohort B, ~15 pts will be enrolled who are currently on first-line RUX per standard of care for ≥ 12 weeks, with ≥ 4 weeks at a stable dose, and will begin 8.9 mg/kg IME IV every 4 weeks after enrollment. Tx will continue until toxicity, disease progression, or withdrawal. The primary endpoint includes safety and symptom response rate at week 24 (proportion of pts with $\geq 50\%$ reduction in total symptom score [TSS] at week 24 from start of IME+RUX tx). Secondary endpoints include absolute change in TSS at week 24, average absolute change in TSS over 24 weeks, spleen response ($\geq 35\%$ spleen volume reduction) at week 24, and progression-free survival. The primary analysis is planned ~6 months after the last pt's first dose of IME+RUX; the final analysis will occur after the study ends. Cohort B is actively enrolling. Clinical trial information: NCT05371964. Research Sponsor: This study was funded by Geron Corporation. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Mohamed Abdelmegeed, MD, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Geron Corporation.

A phase 2 study to assess the safety and efficacy of bomedemstat (IMG-7289) in combination with momelotinib in patients with myelofibrosis.

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Background: Myelofibrosis (MF) is a chronic myeloproliferative neoplasm characterized by splenomegaly, cytopenias, inflammatory symptoms, and progressive marrow fibrosis. Momelotinib, a JAK1/JAK2 and ACVR1 inhibitor, improves splenomegaly and anemia; however, a substantial proportion of patients experience inadequate spleen, symptom, or hematologic responses. Bomedemstat (IMG-7289), an oral irreversible inhibitor of lysine-specific demethylase 1 (LSD1), has demonstrated disease-modifying activity in MF, including effects on megakaryopoiesis, inflammatory signaling, and fibrosis. Preclinical and clinical data support complementary mechanisms between JAK inhibition and LSD1 inhibition. **Methods:** This is an open-label, single-arm, multicenter phase 2 study enrolling approximately 50–60 adults with primary or secondary MF (post-polycythemia vera or post-essential thrombocythemia) with intermediate-2 or high-risk disease. All patients receive momelotinib 200 mg orally once daily. After 12 weeks of momelotinib monotherapy, patients with protocol-defined suboptimal response—based on spleen volume reduction, symptom improvement, hematologic parameters, or transfusion requirements—initiate combination therapy with bomedemstat 50 mg orally once daily, with dose titration per MF-specific guidelines, through week 24. Two cohorts are included: (1) patients previously treated with momelotinib who demonstrate suboptimal response after ≥ 12 weeks of therapy, and (2) patients with baseline cytopenias initiating momelotinib within the study who demonstrate suboptimal response at week 12. The primary endpoint is the proportion of patients achieving $\geq 35\%$ spleen volume reduction at week 24 by MRI or CT. Secondary endpoints include $\geq 50\%$ reduction in total symptom score, changes in symptom burden, transfusion independence, hematologic responses, overall response rate, duration of response, progression-free survival, overall survival, and safety and tolerability. Exploratory endpoints include molecular and biomarker analyses assessing changes in driver mutation allele burden, inflammatory cytokines, and markers of differentiation and fibrosis. The study will run in 5 Countries (UK, France, Spain, Dubai, USA), for a total of 20 Sites. Enrollment expected to start in September 2026. Clinical trial information: ISRCTN98283910. Research Sponsor: MSD; MISP 103465.

ASC4Kids-2: Asciminib in pediatric chronic myeloid leukemia with or without T315I.

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Background: Adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitors (TKIs), including imatinib, dasatinib, nilotinib, and bosutinib, are the standard of care for pediatric patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP), with efficacy and safety profiles generally comparable to those observed in adults. However, TKIs can cause long-term adverse effects in pediatric pts, including delayed growth and development. Effective therapies that minimize long-term adverse effects in pediatric pts are needed. No TKI is approved for pediatric pts with the T315I mutation, which is linked with lower progression-free and overall survival. Asciminib represents an alternative to ATP-competitive TKIs that works by Specifically Targeting the ABL Myristoyl Pocket (STAMP). Asciminib is approved for adults with newly diagnosed and previously treated CML-CP (at 80 mg daily), and those harboring T315I (at 200 mg twice daily). In ASC4Kids (NCT04925479), asciminib was well-tolerated and efficacious in pediatric pts resistant or intolerant (R/I) to 1 prior TKI without T315I. Here, we describe ASC4Kids-2 (NCT07354074), a phase 2 study evaluating asciminib in pediatric pts with CML-CP. **Methods:** Approximately 50 pediatric pts aged 1 to <18 years with Philadelphia chromosome positive (Ph+) CML-CP who are (1) newly diagnosed without known T315I, (2) R/I to ≥ 1 prior TKI without known T315I, or (3) with T315I irrespective of prior TKIs, will be enrolled in this multicenter, open-label, single-arm study. Asciminib will be administered at 80 mg once daily, or at 200 mg twice daily for pts with T315I using the adult formulation under fasting conditions, or as a body weight-based pediatric formulation (2.6 mg/kg once daily or 6.5 mg/kg twice daily for pts with T315I, rounded to the nearest 5 mg) in the fed state. ASC4Kids-2 consists of a 22-day screening period followed by a treatment period with visits at weeks 1, 2, 4, 8, 12, 24, 36, and 48, then every 12 weeks. A posttreatment follow-up period includes a 30-day safety follow-up call and survival assessments every 12 weeks until study end, which is 240 weeks after the last pt receives the first dose. The primary objective is to assess treatment efficacy via MMR at week 48 (defined as the proportion of pts who meet MMR criteria at week 48, excluding those who discontinued earlier or lost response at/before week 48). Secondary endpoints include MMR at week 96; hematologic, cytogenetic, and molecular responses at and by scheduled time points; time to response, progression, or treatment failure; duration of response; event-free and overall survival; growth and sexual maturation (assessed via height, weight, bone age measured by x-ray, and Tanner staging); safety; and pharmacokinetic parameters. Clinical trial information: NCT04925479. Research Sponsor: Novartis Pharma AG.

Phase Ib study of momelotinib during and following hematopoietic stem cell transplantation for patients with primary or secondary myelofibrosis.

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Background: Despite progress in the treatment of myelofibrosis (MF) with multiple approved JAK inhibitors (JAKi), the only curative therapy is allogeneic hematopoietic cell transplantation (HCT). Discontinuation of JAKi's before HCT is challenging as patients experience return of symptoms, moreover, hematopoietic recovery post-HCT is challenging as fibrosis takes many months to resolve. Although we have shown that ruxolitinib can be safely used during and after HCT with excellent survival, low rates of GVHD, and no adverse impact on engraftment (Hobbs et al., JCO Advances 2025), important unmet needs persist: better prevention of GVHD and improved management of post-transplant anemia and residual symptoms. Momelotinib is a JAK1/JAK2, ROCK2 and ACVR1 inhibitor that may help prevent GVHD via JAK1 and ROCK2 inhibition, which play key roles in immune cell function and inflammatory signaling. Moreover, in addition to momelotinib's efficacy in spleen and symptom control, this agent improves anemia through ACVR1 inhibition. Thus, we aim to conduct a phase Ib study to determine the safety and tolerability of momelotinib in the peri/post-HCT period along with its impact on reducing transfusion needs. **Methods:** This is a phase Ib, single institution study investigating momelotinib given pre-, during- and for 1-year post-HCT for patients with primary or secondary MF (NCT 07104799). The primary endpoint is 1-year GVHD-free, relapse-free survival (GRFS). Secondary endpoints include overall (OS) and progression free survival (PFS), engraftment, and incidence of acute and chronic GVHD. Patients will be treated with reduced intensity conditioning with fludarabine (30mg/m²/d x 5 days) and melphalan (100 or 140mg/m² x 1). Patients will receive peripheral blood stem cell grafts from either 7/8 or 8/8 HLA-matched donors. GVHD prophylaxis will consist of standard tacrolimus and methotrexate. We will conduct a 3+3 dose escalation of momelotinib starting on day -7 of HCT through engraftment to test the safety of momelotinib at 100 mg, 150 mg and 200 mg during the peri and early post-HCT period. Once patients achieve engraftment, dose escalation to the approved dose of 200 mg daily will be allowed and continued for one-year post-HCT. We will collect samples for correlative analysis at baseline, day +100 and 1 year post-HCT. This study is the first to test momelotinib use pre-, during- and post-HCT in patients with MF. We have demonstrated that ruxolitinib use during and after-HCT leads to excellent GRFS and OS, however, post-HCT cytopenias remain an issue. Moreover, as more JAKi become available, it is important to evaluate the safety and efficacy of different JAKi during the time of HCT. This trial is open to accrual as of January of 2026. Funding and Product for this study is provided by GSK. Clinical trial information: NCT 07104799. Clinical trial information: NCT 07104799. Research Sponsor: GlaxoSmithKline LLC.

A phase 3 study of olverembatinib (HQP1351) in patients with chronic-phase chronic myeloid leukemia: POLARIS-2 trial in progress.

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Background: Chronic myeloid leukemia (CML) is driven by the BCR::ABL1 oncogenic fusion protein. Although tyrosine kinase inhibitors (TKIs) have transformed CML management, normalizing life expectancy for many patients, treatment resistance and intolerance remain significant clinical challenges. Olverembatinib is a novel third-generation BCR::ABL1 TKI with activity against wild-type BCR::ABL1, multiple resistance-conferring mutations including T315I, and challenging compound mutations. The POLARIS-2 study evaluates olverembatinib efficacy and safety in patients with relapsed/refractory chronic phase CML (CP-CML). **Methods:** This global, multicenter, open-label, randomized phase 3 registrational study includes two patient cohorts based on T315I mutation status (ClinicalTrials.gov identifier: NCT06423911; internal study number: HQP1351CG301). Part A randomly allocates patients with CP-CML previously treated with at least two approved TKIs to receive either olverembatinib or bosutinib (2:1 randomization). The primary endpoint is major molecular response (MMR) rate at 24 weeks. Part B is a single-arm study evaluating olverembatinib in patients with CP-CML with the T315I mutation at screening, and the primary endpoint is MMR rate by 24 weeks. Key inclusion criteria include age ≥ 18 years, diagnosis of CP-CML, Eastern Cooperative Oncology Group performance status ≤ 2 , and adequate organ function. Key exclusion criteria include prior hypersensitivity to study drugs and pregnancy or lactation. Patients in Part A receiving bosutinib who do not achieve MMR by 24 weeks are eligible to cross over to olverembatinib. The study hypothesis posits that olverembatinib will demonstrate superior MMR compared to bosutinib in Part A and provide clinical benefit in T315I-positive patients in Part B. Clinical trial information: NCT06423911. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).