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RESEARCH ARTICLE

Real-world outcomes of intensive induction approaches in core binding factor acute myeloid leukemia

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Abstract

Core-binding factor acute myeloid leukemia (CBF-AML) is characterized by the presence of inv(16)/t(16;16) or t(8;21) and is classified as a favorable risk by the 2022 European LeukemiaNet (ELN) guidelines. The CD33-targeting antibody-drug conjugate, gemtuzumab ozogamicin (GO), is commonly added to intensive chemotherapy (IC) in CBF-AML. We sought to compare outcomes in patients treated with IC with or without GO in CBF-AML. We included 200 patients with CBF-AML treated with IC across seven academic centers. Induction treatment regimens were categorized as IC alone, IC with GO, or IC with KIT inhibitor (dasatinib or midostaurin). Median follow-up for the whole cohort was 2.5 years. Three-year overall survival (OS) was 70% and 3-year event-free survival (EFS) was 51%. Patients treated with IC with GO experienced a 3-year EFS of 50% compared to those treated with IC alone who experienced a 3-year EFS of 47%, with no statistically significant difference ($p = 0.62$). Similarly, those treated with IC with GO did not experience an improved OS compared to those treated with IC alone ($p = 0.67$). Patients treated with IC with KIT inhibitor experienced a significantly improved 3-year EFS of 85% compared to those with IC with or without GO ($p = 0.04$). We find in our study that there is no survival benefit in patients

treated with IC with the addition of GO; improved EFS was seen in patients with CBF-AML treated with IC plus KIT inhibitors, consistent with outcomes noted in prospective studies utilizing this approach.

KEYWORDS
acute myeloid leukemia, core binding factor, intensive chemotherapy

1 | INTRODUCTION

Core-binding factor acute myeloid leukemia (CBF-AML) is characterized by the presence of inv(16)/t(16;16) or t(8;21) and is classified as a favorable risk by the 2022 European LeukemiaNet (ELN) guidelines [1]. High remission rates are observed in the setting of cytarabine or anthracycline-based induction regimens [2]. The CD33-targeted antibody-drug conjugate gemtuzumab ozogamicin (GO) is approved by the United States Food and Drug Administration for use in CD33+ AML [3]. Based upon subgroup and meta-analyses, GO is frequently added to intensive chemotherapy (IC) in patients with CBF-AML despite not being investigated prospectively in a randomized fashion exclusively in CBF-AML.

Notably, a meta-analysis of five randomized trials investigating GO-containing regimens reported a 5-year overall survival (OS) of 76.3% in patients with favorable-risk cytogenetics treated with GO-containing regimens compared to 55.2% in those with non-GO-containing regimens ($p = 0.0005$) [4]. Bothakur et al. reported on fludarabine, cytarabine, and granulocyte-colony stimulating factor (FLAG)+GO with a 5-year event-free survival (EFS) of 78% [5]. In addition, Russell et al. reported on a prospective trial comparing FLAG+idarubicin+GO to 7+3+GO in patients with newly diagnosed AML and there was no difference in OS across the treatment arms; the 3-year OS for CBF-AML was 94% for 7+3+GO and 86% for FLAG+idarubicin+GO [6]. There are conflicting data in the literature regarding differences in toxicity and efficacy when using a fractionated dosing GO schedule versus a single dose of GO [4, 7–9]. GO has also been studied in *NPM1*-mutated AML in the AMLSG 09-09 study and was not shown to improve remission rates or survival, however, it did reduce the cumulative incidence of relapse [10].

Prior work has also investigated the role of response kinetics and measurable residual disease (MRD) in CBF-AML. Achievement of a 3-fold reduction of quantitative polymerase chain reaction (qPCR) testing of bone marrow samples for CBF is associated with improved outcomes [11, 12]. In addition, qPCR testing is feasible outside of a clinical trial setting and has been incorporated into disease assessment for CBF-AML [13].

Mutations in *KIT* are found in 17–36% of CBF-AML cases [14–17], with adverse outcomes noted for patients harboring mutations in *KIT*, particularly in inv(16) CBF-AML and when occurring in exon 8 and 17 [16]. The AMLSG 11-08 trial investigated the addition of the KIT inhibitor, dasatinib, to IC in CBF-AML. Although this was a phase I/II study, this approach showed promising efficacy with a 4-year EFS of 74% [18]. Similarly the Cancer and Leukemia Group B (CALGB) 10801 trial also evaluated the addition of dasatinib to IC and found a 3-year EFS of 75% and a 3-year OS of 77% [19]. Intriguingly, only 19% of patients in the CALGB study harbored *KIT* mutations and outcomes between patients in this study with or without mutations were comparable.

Based on the heterogeneity of data regarding intensive treatment approaches in CBF-AML, we sought to investigate outcomes utilizing the Consortium on Myeloid Malignancies and Neoplastic Diseases (COMMAND). Specifically, we focused on patients treated with IC ± GO or a KIT inhibitor. With this real-world data on treatment outcomes of diverse induction therapy practices for those fit for IC, we set out to provide insight into comparative outcomes for different regimens. In particular, outcomes of patients treated with IC+GO versus IC+KIT inhibitor have not been compared previously.

2 | METHODS

A retrospective chart review was done to identify patients with AML harboring inv(16)/t(16;16) or t(8;21) who were treated with IC from January 2010 through April 2023. Patients treated at seven sites participating in COMMAND were included. Clinical data were abstracted by individual chart review, and all participating centers obtained approval from their Institutional Review Board (IRB). Patient demographics, disease characteristics, and treatment approaches were collected. Cytogenetic abnormalities were characterized in metaphase cells and classified as follows: CBF rearrangement, complex karyotype, chromosome 5 abnormalities, chromosome 7 abnormalities, recurring translocations, and other cytogenetic abnormalities. A subset of patients had molecular testing via next-generation sequencing (NGS) testing available. NGS was done according to each institution's available platform and varied in coverage. Information was collected for each patient with available testing on the following genes: *FLT3*, *NPM1*, *IDH1*, *IDH2*, *TP53*, *CEBPA*, *NRAS*, *KRAS*, *PTPN11*, *SRSF2*, *SF3B1*, *U2AF1*, and *KIT*.

The World Health Organization (WHO) 2016 diagnostic criteria were used [20]; response to therapy, EFS, and OS was assessed based on 2022 ELN AML guidelines [1]. EFS and OS analyses were analyzed by CBF cytogenetics, induction treatment regimen, MRD status, and mutational status of *KIT*, *NRAS*, and *FLT3*. EFS and OS were both analyzed using Kaplan-Meier analysis with log-rank tests of significance at the designated time points per 2022 ELN AML guidelines [1], as well as

by Cox proportional hazards risk modeling. Categorical variables were compared between groups with chi-squared tests of independence, when appropriate. All analyses were conducted with R version 4.2.1.

3 | RESULTS

Two hundred consecutive patients with CBF-AML were identified across seven institutions from 2010 to 2023. One hundred and five patients (53%) of patients harbored inv(16) on their cytogenetics, while 95 harbored t(8;21) (47%). The median age of patients was 47 years (range 18–80 years); additional characteristics are summarized in Table 1. Sixty-seven (33%) patients harbored additional cytogenetic abnormalities, with 25/67 (37%) harboring a complex karyotype, and 16/67 (24%) with deletion 5, 7, or a monosomal karyotype. One hundred twenty-eight patients (64%) had NGS data available, and among these 31 (24%) had *KIT* mutations identified, with an additional five cases with *KIT* mutations on targeted mutation testing. Altogether, when excluding CBF status, 42 (21%) patients harbored an additional genetic abnormality classified as adverse risk by ELN22 guidelines (Table 1). The most common mutation observed across all patients was *NRAS*, with 35 patients (26%) harboring mutations. The second most common somatic mutation was in *KIT*, as above. Twenty-five (19%) of patients had mutations in *FLT3*, (12 *FLT3*-ITD and 13 *FLT3*-TKD). All patients were treated with IC, with the most common regimen being a 7+3 backbone, and additional details of chemotherapy backbones used are listed in Table S1.

3.1 | Survival outcomes

All patients underwent induction with IC. Sixty-three patients received IC+GO, 21 received IC+KIT inhibitor (14 received dasatinib, seven received midostaurin; six of these 21 patients had known *KIT* mutations), and the remaining 116 received IC without a targeted agent. Of those receiving IC+GO, 56/63 (89%) received a 3 mg/m^2 GO dose capped at 4.5 mg, and 30 of these patients received three doses during induction. Patients receiving dasatinib received doses of 100 mg on days 8–21 of induction, days 6–26 of consolidation, and 100 mg daily for up to 12 months after consolidation. Patients receiving midostaurin received 50 mg twice daily on days 8–21 of induction and consolidation.

One hundred and sixty-five (82%) patients achieved a complete response (CR) or CR with incomplete hematopoietic recovery (CRi) to induction therapy, and three (1.5%) patients experienced induction-related mortality. Of those treated with IC+GO, 90% achieved CR/CRi, while 79% of those treated with IC without GO achieved a CR/CRi to induction ($p = 0.07$). The subset of patients who were treated with IC+KIT inhibitor experienced a CR/CRi rate of 95%, which was significantly higher compared to those treated with IC without KIT inhibitor – either IC+GO or IC alone ($p = 0.01$) (Table 2). Among patients receiving GO with induction, only one patient developed veno-occlusive disease (VOD), and one patient developed grade 3 liver enzyme abnormalities.

One hundred seventy-seven (89%) patients underwent consolidation with an intermediate or high-dose cytarabine-based regimen for a median of three cycles of chemotherapy (inter-quartile range [IQR] 2–4 cycles). Of patients who received consolidation chemotherapy, 32 (17%) patients received GO as part of their regimen for a median of two cycles, and 16 (9%) received a KIT inhibitor as part of their regimen for a median of four cycles (15 of whom had also received a KIT inhibitor with induction chemotherapy) (Figure 1). Of note, 1 patient who received GO with induction later went on to receive a KIT inhibitor with consolidation, although further details were not available regarding the treatment rationale.

Sixty (30%) patients underwent allogeneic stem cell transplantation (alloSCT), with 23 in first CR, and 37 after second-line or beyond therapy, with four undergoing second transplants. Seventy-eight (39%) patients experienced disease relapse at any point following induction therapy, with 13 of these having disease refractory to first induction.

The median follow-up for the whole cohort was 2.5 years (range: 0.1–14.2 years). The median EFS for the whole cohort was 4.1 years, and the median OS for the whole cohort was not reached in the study period. The 3-year EFS for the whole cohort was 51% (95% confidence interval [CI]: 44%–60%), and the 3-year OS was 70% (95% CI: 54%–78%). We observed a significant difference in 3-year EFS among induction treatment groups, with those treated with IC+KIT inhibitor having a 3-year EFS of 85% (95% CI: 70%–100%), compared to 50% (95% CI: 37%–69%) for IC+GO, and 47% (95% CI: 38%–57%) for IC alone ($p = 0.04$) (Figure 2A). We also observed superior 3-year EFS among patients harboring inv(16) on their cytogenetics (3-year EFS of 56% (95% CI: 46%–68%)) compared to those with t(8;21) (3-year EFS 46% (95% CI: 36%–59%)) ($p = 0.04$) (Figure 2B). We observed no difference in 3-year OS for those treated with IC+GO at 71% (95% CI: 58%–86%), compared to 67% (95% CI: 58%–77%) for those treated with IC alone ($p = 0.11$) (Figure 3A). Those treated with IC+KIT inhibitor had a 3-year OS of 95% (95% CI: 85%–100%), which was significantly longer than the 3-year OS in all patients treated without a KIT inhibitor ($p = 0.03$). Additionally, we found that patients with inv(16) had improved 3-year OS of 76% (95% CI: 67%–86%) compared to those harboring t(8;21) with a 3-year OS of 64% (95% CI: 54%–76%) ($p = 0.05$) (Figure 3B).

We also evaluated the impact of patient and disease characteristics, as well as induction therapies, on survival outcomes with Cox proportional hazard risk modeling. We found that in a multivariate model, factors associated with EFS were the use of IC+KIT inhibitor, CBF cytogenetic abnormality—t(8;21) vs inv(16), and the presence of other cytogenetic abnormalities ($p < 0.05$). Factors significantly associated with OS on multivariate analysis were the presence of other cytogenetic abnormalities, sex, and race ($p < 0.05$).

3.2 | Residual disease by fluorescence in-situ hybridization and polymerase chain reaction

Fluorescence in-situ hybridization (FISH) data was available in 113 (56%) patients at the end of induction with 82% of these patients

TABLE 1 Baseline patient characteristics by induction regimen.

Characteristic	All, $N = 200$ (%)	Intensive + GO, $N = 63$ (%)	Intensive + KIT, $N = 21$ (%)	Intensive alone, $N = 116$ (%)
Sex				
Male	123 (61)	41 (65)	11 (52)	71 (61)
Female	76 (38)	21 (33)	10 (48)	45 (39)
Not available	1 (1)	1 (2)		
Race/Ethnicity				
non-Hispanic White	145 (72)	49 (78)	16 (76)	80 (69)
non-Hispanic Black	23 (12)	5 (8)	5 (24)	13 (11)
Hispanic	16 (8)	6 (9)	0	10 (9)
non-Hispanic other	14 (7)	3 (5)	0	11 (9)
Not available	2 (1)			2 (2)
Age at diagnosis, years				
Median (range)	47 (18–80)	53 (18–71)	52 (23–75)	45 (18–80)
White blood cell count, $\times 10^9$/L	14 (4–46)	14 (7–44)	12 (4–31)	16 (4–46)
Median (IQR)				
Platelet count, $\times 10^9$/L				
Median (IQR)	32 (20–56)	35 (18–61)	29 (23–52)	33 (20–51)
Bone marrow blast, %				
Median (IQR)	59 (36–70)	58 (36–67)	52 (33–67)	58 (34–70)
Cytogenetics				
inv(16)	105 (53)	37 (59)	9 (43)	59 (51)
t(8;21)	95 (47)	26 (41)	12 (57)	57 (49)
Complex karyotype	25 (13)	3 (5)	4 (19)	18 (16)
5, −7, or monosomal karyotype	16 (8)	2 (3)	5 (24)	9 (8)
other abnormalities	26 (13)	17 (27)	3 (14)	16 (14)
KIT mutation				
Present	36 (18)	11 (17)	6 (29)	19 (16)
Absent	97 (49)	46 (73)	9 (43)	42 (36)
Not available	67 (33)	6 (10)	6 (29)	55 (47)
ECOG performance status				
0	67 (33)	24 (38)	8 (38)	35 (30)
1	59 (30)	13 (21)	11 (52)	35 (30)
2	10 (5)	5 (8)	1 (5)	4 (4)
3	4 (2)	4 (6)	0	0
Not available	60 (30)	17(27)	1(5)	42(36)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GO, gemtuzumab ozogamicin.

achieving FISH negativity. Measurable residual disease (MRD) testing done by polymerase chain reaction (PCR) was available in 71 (35%) patients with 70% of these patients achieving MRD-negativity. Sixty-five (32%) patients had neither FISH nor PCR testing available at the end of induction for residual disease analysis (Table 2).

A comparison of survival outcomes by residual disease status showed no difference in either EFS or OS. The 3-year EFS of those who were either FISH- or PCR-negative was 59% (95% CI: 50%–71%) compared to 47% (95% CI: 30%–73%) for those who were FISH- or PCR-positive at the end of induction ($p = 0.31$) (Figure 4A). Three-year OS for those who were FISH- or PCR-negative was 81% (95% CI: 72%–90%) compared to 72% (95% CI: 55%–93%) for those who were FISH- or PCR-positive at the end of induction ($p = 0.24$) (Figure 4B). Given the difference in sensitivity between PCR and FISH testing (PCR testing had at least a sensitivity of 10^{-4}), we additionally limited the analysis to patients who had PCR-based MRD testing done at the end of

TABLE 2 Response rates and assessment of disease by fluorescence in-situ hybridization (FISH) and polymerase chain reaction (PCR).

	All, *N* = 200 *(%)*	Intensive + GO, *N* = 63 (%)	Intensive + KIT, *N* = 21 (%)	Intensive alone, *N* = 116 (%)
Response to induction				
CR	152 (76)	55 (87)	18 (86)	79 (68)
CRi	13 (7)	2 (3)	2 (9)	9 (8)
MLFS	7 (3)	2 (3)	1 (5)	4 (3)
PR	11 (5)	2 (3)	0	9 (8)
SD	3 (2)	0	0	3 (3)
PD/death	5 (3)	1(2)	0	4 (3)
Not evaluable	9 (4)	1 (2)	0	8 (7)
Residual disease testing				
FISH	113 (57)	38 (60)	16 (76)	59 (51)
PCR	71 (36)	31 (49)	6 (29)	32 (28)
None	65 (33)	14 (22)	4 (19)	47 (41)
Disease Assessment by FISH				
Detectable	20 (18)	2 (5)	3 (19)	15 (25)
Not detectable	93 (82)	36 (95)	13 (81)	44 (75)
MRD—by PCR				
Detectable	21 (30)	9 (29)	2 (33)	9 (28)
Not detectable	50 (70)	22 (71)	4 (67)	23 (72)

Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematopoietic recovery; FISH, fluorescence in situ hybridization; GO, gemtuzumab ozogamicin; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; PCR, polymerase chain reaction; PD, progressive disease; PR, partial remission; SD, stable disease.

induction. We did not find statistically significant differences in 3-year EFS (52% for MRD-negative vs. 31% for MRD-positive, $p = 0.27$) or OS (75% for both groups, $p = 0.24$) between patients who were PCR-negative or positive at the end of induction.

3.3 | Somatic mutations

Molecular testing via NGS was available for 133 (67%) patients per each institution's available testing panels and standards (Figure 5). Nineteen (14%) patients had mutations classified as adverse risk by ELN22 guidelines, excluding CBF status. The most common mutations observed across all patients were *NRAS*, *KIT*, and *FLT3*. The following adverse-risk mutations by ELN22 were noted in our cohort: *ASXL1* ($n = 9$), *RUNX1* ($n = 5$), *SRSF2* ($n = 5$), *TP53* ($n = 2$), and *U2AF1* ($n = 1$). Three patients harbored two adverse-risk mutations simultaneously. Of the 36 patients who had an identified *KIT* mutation (through NGS or targeted mutation analysis), only 6 were treated with IC + KIT inhibitor.

We evaluated survival outcomes by *KIT* mutation status among patients with NGS available and found that the 3-year EFS of patients harboring a *KIT* mutation was 45% (95% CI: 27%–75%), compared to 53% (95% CI: 43%–66%) for those without a *KIT* mutation ($p = 0.71$). For those with *KIT* mutations, the 3-year OS was 68% (95% CI: 51–91%), compared to those without *KIT* mutations who experienced a 3-year OS of 69% (95% CI: 59%–81%) ($p = 0.91$) (Figure S1).

We also evaluated outcomes by the next most frequent somatic mutations, namely *NRAS* and *FLT3*. We found no difference in EFS for those who harbored an *NRAS* mutation, with a 3-year EFS of 49% (95% CI: 30%–80%) for those with an *NRAS* mutation, compared to 51% (95% CI: 40%–64%) for those without an *NRAS* mutation ($p = 0.31$). Similarly, the 3-year EFS for those with either a *FLT3*-ITD or *FLT3*-TKD mutation was 47% (95% CI: 26%–84%), while for those without either mutation, it was 52% (95% CI: 42–65%) ($p = 0.55$) (Figure S2).

4 | DISCUSSION

In this multi-center retrospective study of patients with CBF-AML undergoing induction with IC regimens with diverse national treatment practices, we find that the addition of GO to IC is not associated with improved 3-year EFS or OS. Notably, patients treated with IC with a KIT inhibitor had significantly improved 3-year EFS and 3-year OS compared to those treated with IC with or without GO. Although this subgroup was small in our study cohort, the striking difference in survival benefit is noteworthy for future study and evaluation, and the first time to our knowledge that outcomes of IC with KIT inhibitor-treated patients have been directly compared to other induction approaches.

The addition of GO to IC exclusively in CBF-AML patients has never been studied prospectively in a randomized fashion, and as such, our understanding and use of this agent as a part of induction therapy

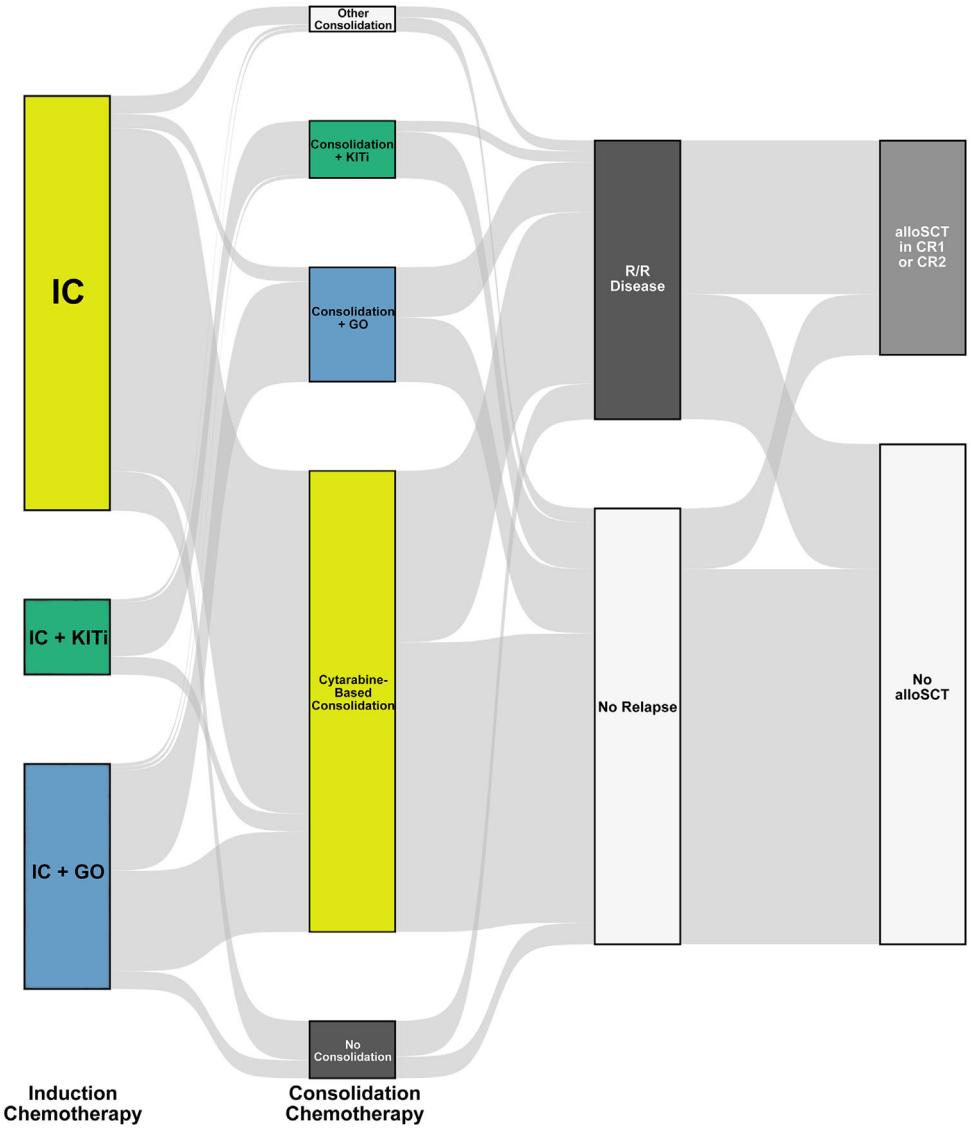

FIGURE 1 Sankey plot of treatment patterns from induction chemotherapy through consolidation therapy, and relapse outcomes. *IC = intensive chemotherapy; KITi = KIT inhibitor (dasatinib or midostaurin); GO = gemtuzumab ozogamicin; R/R = relapsed/refractory disease; CR1 = first complete remission; CR2 = second complete remission; alloSCT = allogeneic stem cell transplantation.

has been based on subgroup and meta-analyses. Prospective studies completed to date [7, 21–23] did not exclusively enroll CBF-AML patients, and thus conclusions from such studies do not fully account for the heterogeneity of biology and outcomes among patients with AML subtypes. Given the variable inclusion of GO with IC in different real-world practices nationally, our study examines the observed outcomes acknowledging these variable treatment practices across diverse, national institutions. Our real-world data set did not demonstrate a clinical benefit from the addition of GO to IC, suggesting that there may be heterogeneity in which patients with CBF-AML benefit most from this approach. Observed rates of VOD were low; this is likely due to the largely split-dosing strategy undertaken by most centers participating in this study, consistent with prior work.

The benefit in both EFS and OS observed for the subgroup of patients treated with IC+KIT inhibitor (either dasatinib or midostaurin) is promising and consistent with previous prospective efforts [18, 19]. A phase III, randomized study evaluating the addition of dasatinib to IC (NCT02013648) is ongoing and will be informative in defining the role of dasatinib with IC in patients with CBF-AML.

We also find in our analysis of residual disease data for a subset of patients, that the achievement of FISH- or PCR-negativity did not translate to a benefit in either EFS or OS. Prior studies have suggested a survival benefit for those achieving MRD-negativity after induction [11, 13, 24, 25], however, most of these studies have focused on a PCR-based approach which is more sensitive, whereas our study of real-world treatment practices did not demonstrate the widespread use of PCR testing for MRD status after induction at many institutions. Although FISH testing after induction was more widely available, this does not reflect the same depth of testing for residual disease, and thus while informative, is not as sensitive, and is a limitation of our available

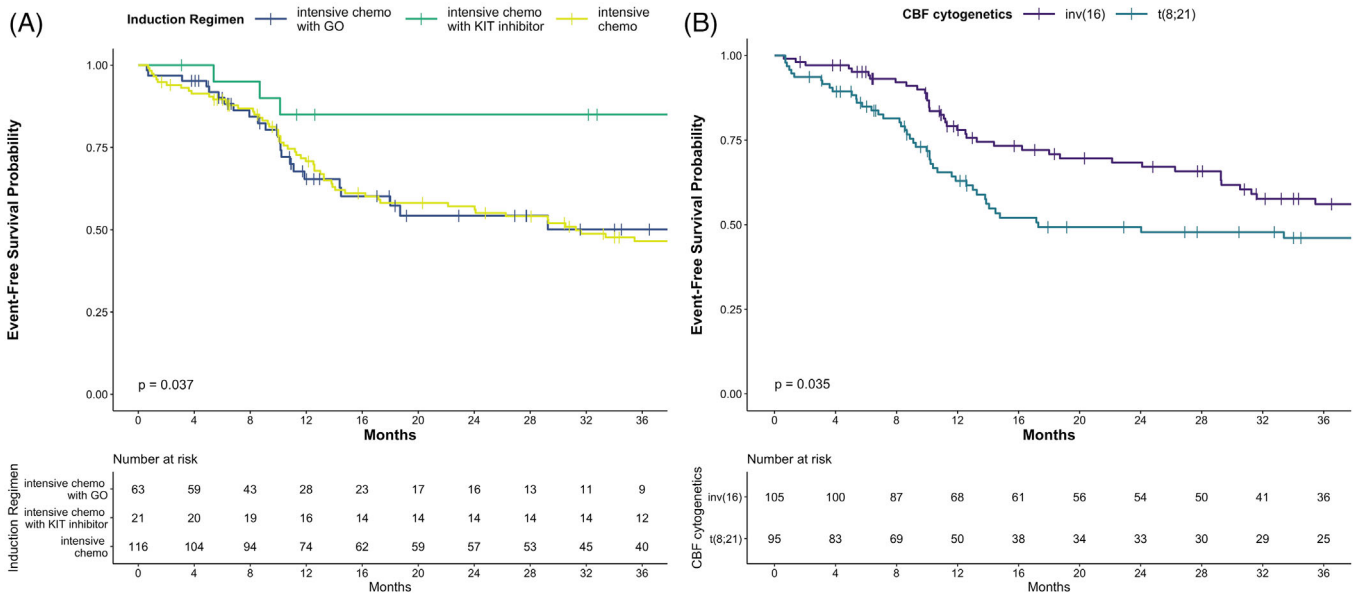

FIGURE 2 Event-free survival outcomes of CBF-AML patients. (A) By induction chemotherapy regimen—intensive chemotherapy (IC) with gemtuzumab ozogamicin (GO), IC with KIT inhibition, or IC without a targeted inhibitor; (B) by CBF cytogenetic abnormality.
*CBF-AML = core-binding factor acute myeloid leukemia; IC = intensive chemotherapy.

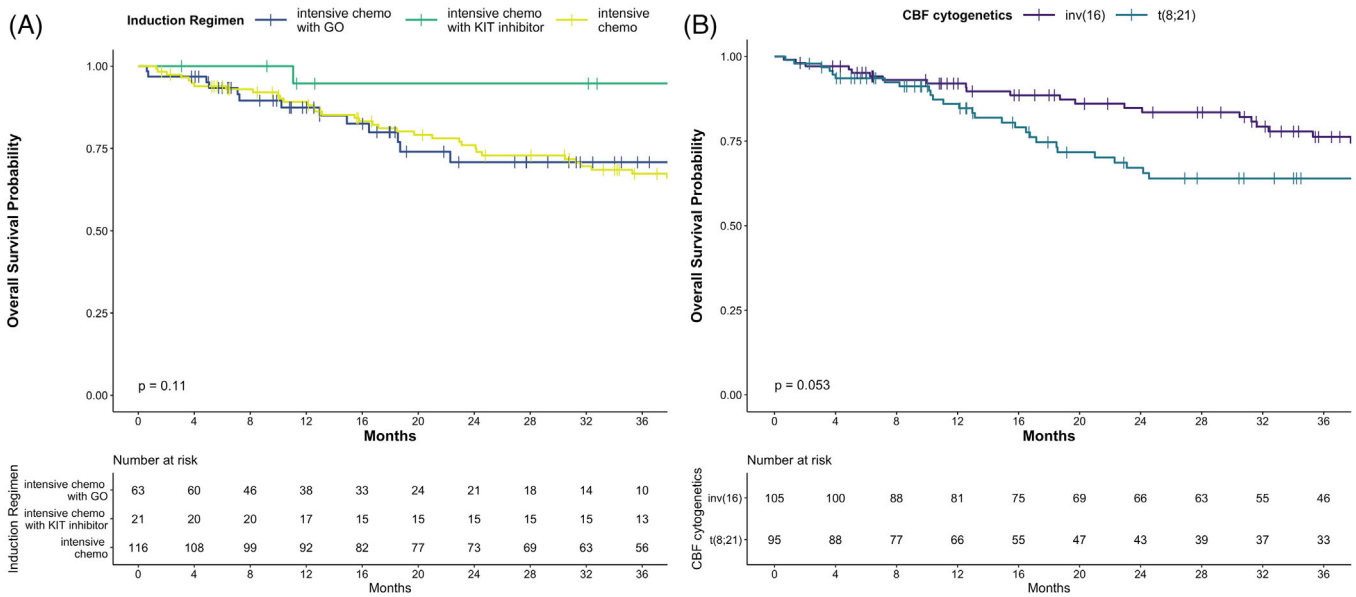

FIGURE 3 Overall survival outcomes of CBF-AML patients. (A) By induction chemotherapy regimen—intensive chemotherapy (IC) with gemtuzumab ozogamicin (GO), IC with KIT inhibition, or IC without a targeted inhibitor; (B) by CBF cytogenetic abnormality.
*CBF-AML = core-binding factor acute myeloid leukemia; IC = intensive chemotherapy.

data. Additionally, our study was limited by the incomplete coverage of either FISH or PCR testing for all patients included in the cohort, with approximately 30% having neither FISH- nor PCR-based residual disease testing available.

We do not find a survival difference based on *KIT* mutation status. One of the first studies to evaluate the effect of *KIT* mutations on CBF-AML outcomes noted the impact of *KIT* mutations among inv(16) cases [16], whereas a majority of the patients in our cohort who harbored *KIT* mutations were t(8;21) cases. However, CALGB 10801 did not observe differences in outcomes of patients treated with dasatinib based on *KIT* mutation status [19], consistent with our findings.

Our cohort was dominantly non-Hispanic White, despite several participating study centers being located in historically underserved and racially diverse communities. Prior work has shown increased rates of CBF-AML in Black patients [26, 27] with inferior outcomes. These disparities may be primarily driven by social factors including

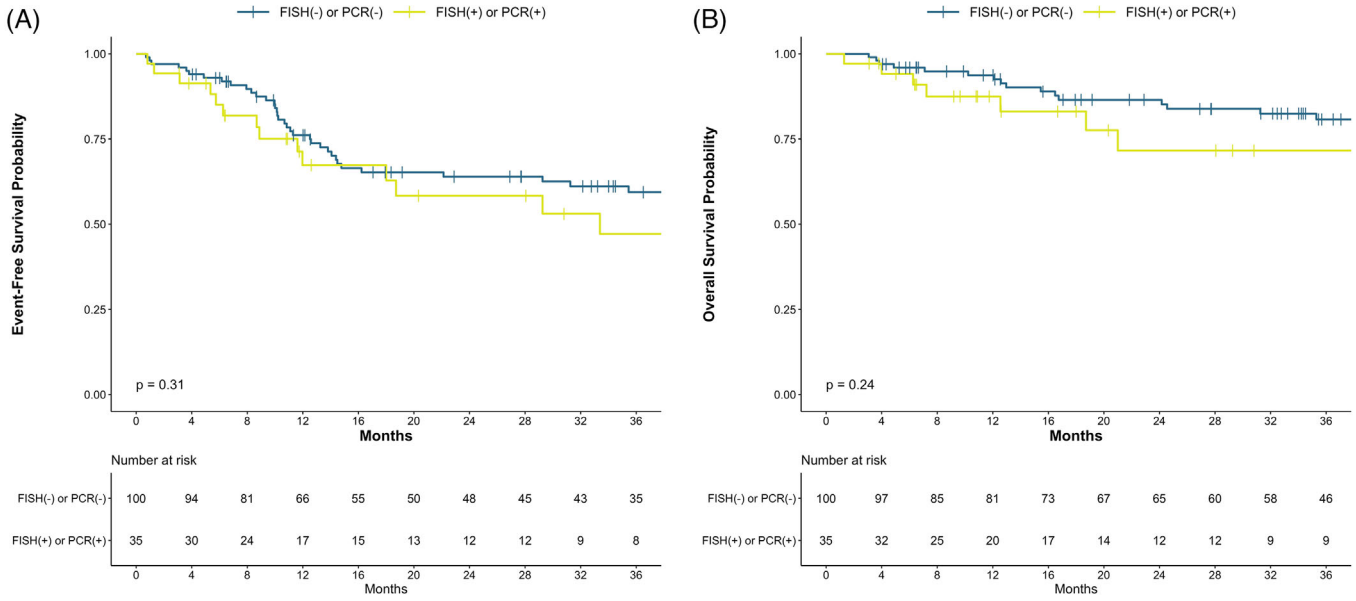

FIGURE 4 Survival outcomes by post-induction FISH- and PCR-based residual disease status in evaluable patients. (A) Event-free survival, (B) Overall survival. *FISH = fluorescence in situ hybridization; PCR = polymerase chain reaction.

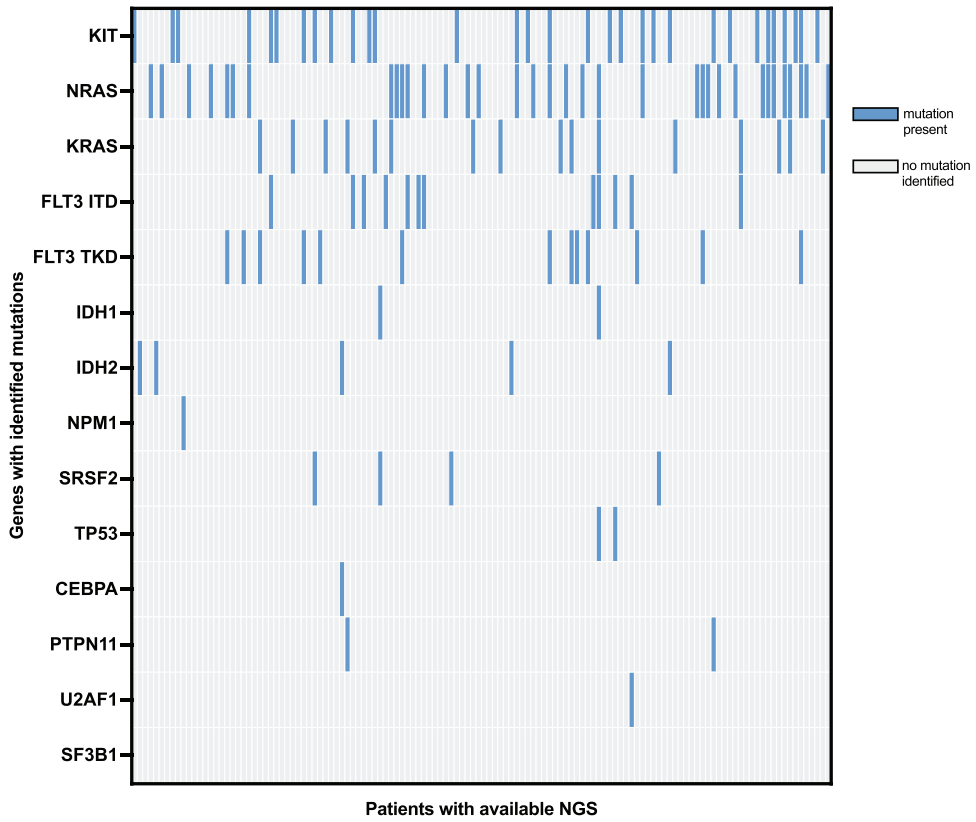

FIGURE 5 Somatic mutations in patients with CBF-AML. Somatic mutations are shown in blue and non-mutated genes are in gray. *CBF-AML = core-binding factor acute myeloid leukemia.

structural racism [28]. We also note in our multivariate Cox proportional hazards model that race/ethnicity and sex were significant variables when assessing OS but not EFS. Prior studies have suggested sex may be linked to differential risk of specific mutations [29] and disparate survival outcomes by race continue to be noted [27, 28, 30]; these disparities are linked to structural racism and other factors such as access to care. Further work in this subgroup of patients with CBF-AML is needed to better understand the interplay of social and biological factors for these patients.

Given that this is a retrospective analysis and there is inherent selection bias with this approach, there are limitations to our findings. These include heterogeneity in IC and GO dosing with a lack of available details on anthracycline dosing along with the lack of KIT inhibitor-specific toxicity data. Additionally, MRD testing was incomplete across the study cohort, with institutional variability regarding MRD testing methods and laboratory variation of negativity thresholds. Comprehensive molecular testing was only available for a portion of patients, with variable mutation panels available at various institutions.

Despite these limitations, our real-world study demonstrates that survival outcomes are similar between IC+GO and IC without GO regimens for CBF-AML. In addition, there was a survival benefit noted with IC+KIT inhibitor and an ongoing Phase III study investigating this approach may definitively establish this regimen. While CBF-AML is a favorable risk subtype of the disease, there remains an opportunity to further improve upon the outcomes noted in our cohort.

AUTHOR CONTRIBUTIONS

Alexandra E. Rojek and Anand A. Patel designed the study, collected data, analyzed all data, and wrote the manuscript. Benjamin J. McCormick, Joanna Cwykiel, Oluwatobi Odetola, Yasmin Abaza, Nhi Nai, Charles E. Foucar, Rohan K. Achar, Rory M. Shallis, Danielle Bradshaw, Meaghan Standridge, Vamsi Kota, Guru Subramanian Guru Murthy, and Talha Badar collected data, reviewed the manuscript, and provided edits.

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CONFLICT OF INTEREST STATEMENT

Alexandra E. Rojek, Benjamin J. McCormick, Joanna Cwykiel, Oluwatobi Odetola, Nhi Nai, Rohan K. Achar, Danielle Bradshaw, Meaghan Standridge, and Guru Subramanian Guru Murthy declare no conflict of interest.

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Talha Badar served on an advisory board for Takeda, Morphosys, and Pfizer.

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DATA AVAILABILITY STATEMENT

Data are available upon reasonable request from the corresponding author, Anand A. Patel (Anand.Patel@bsd.uchicago.edu).

ETHICS STATEMENT

All participating centers obtained approval from their respective Institutional Review Boards (IRB). The study was conducted in accordance with the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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REFERENCES

1. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345–77.
2. Begna KH, Xu X, Gangat N, Alkhateeb H, Patnaik MM, Al-Kali A, et al. Core-binding factor acute myeloid leukemia: long-term outcome of 70 patients uniformly treated with "7+3". Blood Cancer J. 2022;12(4):55.
3. Center for Drug Evaluation and Research. FDA approves gemtuzumab ozogamicin for CD33-positive AML. Silver Spring, MD: U.S. Food and Drug Administration; 2019. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-gemtuzumab-ozogamicin-cd33-positive-aml
4. Hills RK, Castaigne S, Appelbaum FR, Delaunay J, Petersdorf S, Othus M, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. Lancet Oncol. 2014;15(9):986–96.
5. Borthakur G, Ravandi F, Patel K, Wang X, Kadia T, DiNardo C, et al. Retrospective comparison of survival and responses to Fludarabine, Cytarabine, GCSF (FLAG) in combination with gemtuzumab ozogamicin (GO) or Idarubicin (IDA) in patients with newly diagnosed core binding factor (CBF) acute myelogenous leukemia: MD Anderson experience in 174 patients. Am J Hematol. 2022;97(11):1427–34.
6. Russell NH, Wilhelm-Benartzi C, Othman J, Dillon R, Knapper S, Batten LM, et al. Fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin with gemtuzumab ozogamicin improves event-free survival in younger patients with newly diagnosed AML and overall survival in patients with NPM1 and FLT3 mutations. J Clin Oncol. 2024;JCO2300943.

7. Lambert J, Pautas C, Terré C, Raffoux E, Turlure P, Caillot D, et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. Haematologica. 2019;104(1):113–19.
8. Burnett A, Cavenagh J, Russell N, Hills R, Kell J, Jones G, et al. Defining the dose of gemtuzumab ozogamicin in combination with induction chemotherapy in acute myeloid leukemia: a comparison of 3 mg/m2 with 6 mg/m2 in the NCRI AML17 Trial. Haematologica. 2016;101(6):724–31.
9. Freeman SD, Thomas A, Thomas I, Hills RK, Vyas P, Gilkes A, et al. Fractionated vs single-dose gemtuzumab ozogamicin with determinants of benefit in older patients with AML: the UK NCRI AML18 trial. Blood. 2023;142(20):1697–707.
10. Döhner H, Weber D, Krzykalla J, Fiedler W, Kühn MWM, Schroeder T, et al. Intensive chemotherapy with or without gemtuzumab ozogamicin in patients with NPM1-mutated acute myeloid leukaemia (AMLSG 09-09): a randomised, open-label, multicentre, phase 3 trial. Lancet Haematol. 2023;10(7):e495–509.
11. Boddu P, Gurguis C, Sanford D, Cortes J, Akosile M, Ravandi F, et al. Response kinetics and factors predicting survival in core-binding factor leukemia. Leukemia. 2018;32(12):2698–701.
12. Jourdan E, Boissel N, Chevret S, Delabesse E, Renneville A, Cornillet P, et al. Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia. Blood. 2013;121(12):2213–23.
13. Höllein A, Jeromin S, Meggendorfer M, Fasan A, Nadarajah N, Kern W, et al. Minimal residual disease (MRD) monitoring and mutational landscape in AML with RUNX1-RUNX1T1: a study on 134 patients. Leukemia. 2018;32(10):2270–74.
14. Ishikawa Y, Kawashima N, Atsuta Y, Sugiura I, Sawa M, Dobashi N, et al. Prospective evaluation of prognostic impact of KIT mutations on acute myeloid leukemia with RUNX1-RUNX1T1 and CBFB-MYH11. Blood Adv. 2020;4(1):66–75.
15. Boissel N, Leroy H, Brethon B, Philippe N, de Botton S, Auvrignon A, et al. Incidence and prognostic impact of c-Kit, FLT3, and Ras gene mutations in core binding factor acute myeloid leukemia (CBF-AML). Leukemia. 2006;20(6):965–70.
16. Paschka P, Marcucci G, Ruppert AS, Mrózek K, Chen H, Kittles RA, et al. Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): a Cancer and Leukemia Group B Study. J Clin Oncol. 2006;24(24):3904–11.
17. Duployez N, Marceau-Renaut A, Boissel N, Petit A, Bucci M, Geffroy S, et al. Comprehensive mutational profiling of core binding factor acute myeloid leukemia. Blood. 2016;127(20):2451–59.
18. Paschka P, Schlenk RF, Weber D, Benner A, Bullinger L, Heuser M, et al. Adding dasatinib to intensive treatment in core-binding factor acute myeloid leukemia-results of the AMLSG 11-08 trial. Leukemia. 2018;32(7):1621–30.
19. Marcucci G, Geyer S, Laumann K, Zhao W, Bucci D, Uy GL, et al. Combination of dasatinib with chemotherapy in previously untreated core binding factor acute myeloid leukemia: CALGB 10801. Blood Adv. 2020;4(4):696–705.
20. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.
21. Burnett AK, Hills RK, Milligan D, Kjeldsen L, Kell J, Russell NH, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. J Clin Oncol. 2011;29(4):369–77.
22. Burnett AK, Russell NH, Hills RK, Hunter AE, Kjeldsen L, Yin J, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. J Clin Oncol. 2013;31(27):3360–68.
23. Petersdorf SH, Kopecky KJ, Slovak M, Willman C, Nevill T, Brandwein J, et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. Blood. 2013;121(24):4854–60.
24. Yin JAL, O'Brien MA, Hills RK, Daly SB, Wheatley K, Burnett AK. Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: results of the United Kingdom MRC AML-15 trial. Blood. 2012;120(14):2826–35.
25. Marcucci G, Caligiuri MA, Döhner H, Archer KJ, Schlenk RF, Döhner K, et al. Quantification of CBFbeta/MYH11 fusion transcript by real time RT-PCR in patients with INV(16) acute myeloid leukemia. Leukemia. 2001;15(7):1072–80.
26. Larkin KT, Nicolet D, Kelly BJ, Mrózek K, LaHaye S, Miller KE, et al. High early death rates, treatment resistance, and short survival of Black adolescents and young adults with AML. Blood Adv. 2022;6(19):5570–81.
27. Bhatnagar B, Kohlschmidt J, Mrózek K, Zhao Q, Fisher JL, Nicolet D, et al. Poor survival and differential impact of genetic features of black patients with acute myeloid leukemia. Cancer Discov. 2021;11(3):626–37.
28. Abraham IE, Rauscher GH, Patel AA, Pearse WB, Rajakumar P, Burkart M, et al. Structural racism is a mediator of disparities in acute myeloid leukemia outcomes. Blood. 2022;139(14):2212–26.
29. Ozga M, Nicolet D, Mrózek K, Yilmaz AS, Kohlschmidt J, Larkin KT, et al. Sex-associated differences in frequencies and prognostic impact of recurrent genetic alterations in adult acute myeloid leukemia (Alliance, AMLCG). Leukemia. 2024;38(1):45–57.
30. Abraham IE, Patel AA, Wang H, Galvin JP, Frankfurt O, Liu L, et al. Impact of race on outcomes in intermediate-risk acute myeloid leukemia. Cancer Causes Control. 2021;32(7):705–12.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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