




ORIGINAL ARTICLE OPEN ACCESS

Second- and Third-Line Salvage Chemotherapy Followed by Allogeneic Stem Cell Transplantation Leads to High Survival Rates in Primary Refractory AML—A Population-Based Study

Markus Liew-Littorin^{1,2}  | Linn Deleskog-Spångberg³ | Stefan Deneberg³ | Judit Janosi⁴ | Vladimir Lazarevic⁵  | Gustav Nilsson⁶ | Aristeia Papageorgiou⁷ | Anna Robelius⁶  | Lovisa Vennström⁸ | Gunnar Juliusson⁵ | Bertil Ugglå¹ | Martin Höglund⁶ | Sören Lehmann^{3,6}

¹Department of Medicine, Division of Hematology, Örebro University Hospital, Örebro, Sweden | ²School of Medical Sciences, Örebro University, Örebro, Sweden | ³Karolinska University Hospital, Stockholm, Sweden | ⁴Gävle County Hospital, Gävle, Sweden | ⁵Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, Sweden | ⁶Department of Medical Sciences, Uppsala University, Uppsala, Sweden | ⁷Halmstad County Hospital, Halmstad, Sweden | ⁸Sahlgrenska University Hospital, Gothenburg, Sweden

Correspondence: Markus Liew-Littorin (markus.liew-littorin@regionorebrolan.se)

Received: 23 April 2025 | **Revised:** 8 July 2025 | **Accepted:** 14 July 2025

Funding: The data collecting part of the study was sponsored by Amgen Inc. Data curation, statistics, and manuscript writing were done without external funding.

Keywords: acute | leukemia | myeloid | refractory | retrospective study

ABSTRACT

Refractory acute myeloblastic leukemia (AML) is poorly studied. In this study, we characterized primary refractory AML and investigated treatment and outcome in a population-based setting. Based on all AML patients receiving intensive induction therapy at 12 Swedish hospitals from 2011 to 2018 ($N=1221$), we identified 306 patients that failed to achieve composite complete remission (CRc) after first-line therapy. Two-hundred-sixteen (71%) of these patients received salvage treatment with intensive chemotherapy (ICT), of which 126 (58%) achieved CRc and 85 (39%) underwent allogeneic stem cell transplantation (HSCT). One- and 3-year overall survival (OS) in patients receiving salvage ICT were 56.8% and 28.9%, respectively. Secondary AML and adverse ELN risk were associated with worse OS after salvage ICT, while fludarabine-based FAIDA versus amsacrine-based ACE salvage and HSCT were associated with better OS. Three-year OS after first or second salvage chemotherapy, followed by HSCT were 55% and 71%, respectively. Refractory patients responding to salvage ICT showed only a nonsignificant trend toward inferior OS compared to patients in CRc after the first cycle. In conclusion, refractory AML patients eligible for further intensive therapy have a reasonable chance of obtaining remission and long-term survival when followed by HSCT. The results can serve as a basis for evaluation of new treatments in refractory AML.

1 | Introduction

Despite recent improvements in the treatment of acute myeloblastic leukemia (AML), including the introduction of new targeted drugs [1–5], the long-term prognosis for a majority of AML patients remains poor. In particular, this seems to be true

for patients who fail to achieve complete remission (CR) after the first line (i.e., one or more cycles of the same regimen) of induction chemotherapy [6] and even more so after the second line [7]. However, studies of primary refractory AML patients are scarce [8, 9], and in previous works, data on patients with primary refractory and relapsed AML are presented together,

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2025 The Author(s). *European Journal of Haematology* published by John Wiley & Sons Ltd.

despite the fact that the two entities represent two different clinical situations and may have biologically different resistance mechanisms [8, 10, 11]. To our knowledge, this is the largest and the first population-based cohort that characterizes and reports the outcome of primary refractory AML.

Since decades, the combination of cytarabine and an anthracycline, most commonly the 3+7 schedule [12], has constituted the standard induction chemotherapy for patients with newly diagnosed AML. Over the past two decades, AML patients in Sweden have been treated using a modified version of the 3+7 schedule, according to the national guidelines. This regimen, named the 3+5 schedule, consists of intermediate-dose cytarabine administered over 5 days, combined with the standard 3 days of anthracycline [13].

The definition of refractory AML varies between studies and includes definitions such as failure to achieve CR after two cycles of intensive induction therapy (ICT) [12], failure to achieve at least a partial remission after the first cycle or no CR after 2 cycles [14], no CR after one induction cycle [6] or no CR after the first line of induction [15]. In this study, refractory disease was defined as the absence of composite CR (CRc) after the first line of ICT, regardless of the number of cycles with the same ICT regimen. Which of these definitions of refractory disease is the most appropriate or the most clinically useful remains unresolved.

The primary aim in this study was to determine the response rate and long-term outcome following salvage treatment for primary refractory AML. Additionally, we compared the efficacy of two commonly used salvage regimens: ACE and FAIDA. We also characterized the patients, including their treatment as well as their response to treatment, in the later stages of refractoriness.

2 | Methods

2.1 | Patient Cohort, Data Collection and Treatment

All adults (≥ 18 years) with AML diagnosed between 2011 and 2018 at 12 hospitals (5 university hospitals and 7 regional county hospitals) covering 65%–70% of the Swedish population were identified from the Swedish AML Registry [16]. All patients who received ICT but failed to achieve a composite complete remission (CRc) after the first line were identified through medical records at the respective hospital. Patients with APL, isolated myeloid sarcoma, or CNS-leukemia were excluded. Clinical and laboratory data were collected from medical records, and death dates were acquired from the Swedish population registry. A control cohort consisting of all intensively treated non-APL AML patients diagnosed between 2011 and 2018, and who had achieved a CRc after one cycle of the first-line induction therapy were extracted from the Swedish AML Registry. Data were transferred to a central pseudonymized database for analysis. The study was approved by the Swedish Ethics Review Authority (d-nr 2020-00621). Intensive induction treatment according to the national guidelines consisted of daunorubicin 60 mg/m²/day day 1–3 and cytarabine 1 g/m² twice daily day 1–5. The ACE regimen included amsacrine 150 mg/m² once

daily day 1–5, cytarabine 100 mg/m² daily day 1–5 as continuous infusion, and etoposide 110 mg/m² once daily day 1–5. The FAIDA regimen included fludarabine 30 mg/m² once daily day 1–5, cytarabine 2 g/m² once daily day 1–5, and idarubicin 10 mg/m² once daily day 1–3.

2.2 | Definitions

Refractory AML was defined as failure to achieve a complete remission after the first line of intensive chemotherapy (one or more cycles of the same regimen). Available data did not permit a reliable distinction between CR, CRi, and CRh [17] in all cases, which is why composite CR (CRc) was used as the main response definition. CRc includes CR, CRi, or CRh. MRD analyses were only sporadically performed during the study period, which is why the results are not included in this study. For salvage treatment, patients were grouped according to treatment intensity. Intensive chemotherapy (ICT) was defined as at least one cycle of intensive combination chemotherapy (anthracycline or amsacrine + cytarabine or high-dose cytarabine alone), non-intensive treatment (NIT) was defined as at least one cycle with a hypomethylating agent (HMA) or low-dose cytarabine \pm additional oral agent, and best supportive care (BSC) as no treatment, hydroxyurea, or thioguanine. Overall survival (OS) was defined as the time from established refractory AML to the date of death or last follow-up (up until the end of 2020), except in the comparison of early versus salvage responders, where survival was calculated from the date of CR1.

Risk stratification was conducted according to the ELN 2017 genetic risk classification [17]. During the study period, the ELN 2010 [18] classification was predominantly used in clinical practice; however, during data collection, all patients were reclassified according to the ELN 2017 classification. Due to incomplete molecular data, it was not possible to reliably classify the patients according to the ELN 2022 classification [12].

2.3 | Statistics

Data were collected using a case report form (CRF) in Microsoft Excel (version 16.0). Statistical analyses were conducted using the R software (version 4.3.1). Descriptive statistics were used to describe the cohort and subgroups. *t*-test and Chi-square test were used to determine *p*-values. Survival analyses were conducted using the Kaplan–Meier method. Multivariate Cox regression was used to compare treatment options, with HSCT included as a time-dependent covariate. Two-tailed *p*-values with a significance level of 0.05 were used throughout the analyses.

3 | Results

3.1 | Characterization of Study Cohort

During the study period from 2011 to 2018, 2001 patients were diagnosed with non-APL AML at the included 12 centers, as identified by the Swedish AML Registry. Of these, 1221 (61%) received intensive induction therapy. Three hundred six (25%) of the

intensively treated patients were refractory to the first line of therapy, consisting of either one or two cycles of the same ICT regimen; these patients constitute the main study cohort (Figure 1). As this was a population-based retrospective study, the time point of remission assessment was not standardized. However, the median time from the start of induction to established refractory disease was 25 days. Patients who died during the induction phase, that is, before the first bone marrow evaluation (4%), were not included as refractory. Two hundred ninety-eight (97%) of the primary refractory patients had received induction therapy according to national guidelines with 3 days of daunorubicin at a dose of 60 mg/m² once daily and 5 days of cytarabine at a dose of 1 g/m² twice daily. Five patients (1.6%) received idarubicin and cytarabine according to a clinical trial protocol, and three patients (1.0%) received ACE treatment due to previous anthracycline treatment of a previous malignancy. Thirty-six (12%) received two cycles of daunorubicin and cytarabine before being considered refractory, while the remaining received only one cycle. Baseline characteristics of the 306 primary refractory patients in the study cohort are shown in Table 1. The median age was 65 years, and 56 (18%) of the patients had a secondary AML (AML with antecedent myeloid disorder or

therapy-related AML). One hundred fifty-three patients (50%) had adverse-risk AML, according to ELN 2017, while 121 (40%) and 15 (5%) had intermediate and favorable risk, respectively.

3.2 | First Salvage Therapy—Intensive Versus Nonintensive

Of the 306 patients who were refractory to the first line of induction therapy, 216 (71%) received ICT salvage, 47 (15%) NIT salvage (37 HMA only, 3 HMA + venetoclax, and 7 low-dose cytarabine) and 43 (14%) BSC. Patients receiving ICT were younger ($p < 0.001$), and had less often secondary AML ($p = 0.02$) compared to those receiving NIT. There were no significant differences in performance status or genetic risk profile between ICT and NIT patients (Table 1). CRc rates after salvage therapy were 58% in the ICT group compared to 17% in the NIT group. OS in the three treatment groups is shown in Figure 2A, displaying significant differences in OS between ICT, NIT, and BSC ($p < 0.001$ for ICT vs. NIT and $p < 0.001$ for NIT vs. BSC). One-year OS was 57%, 29%, and 2% for the

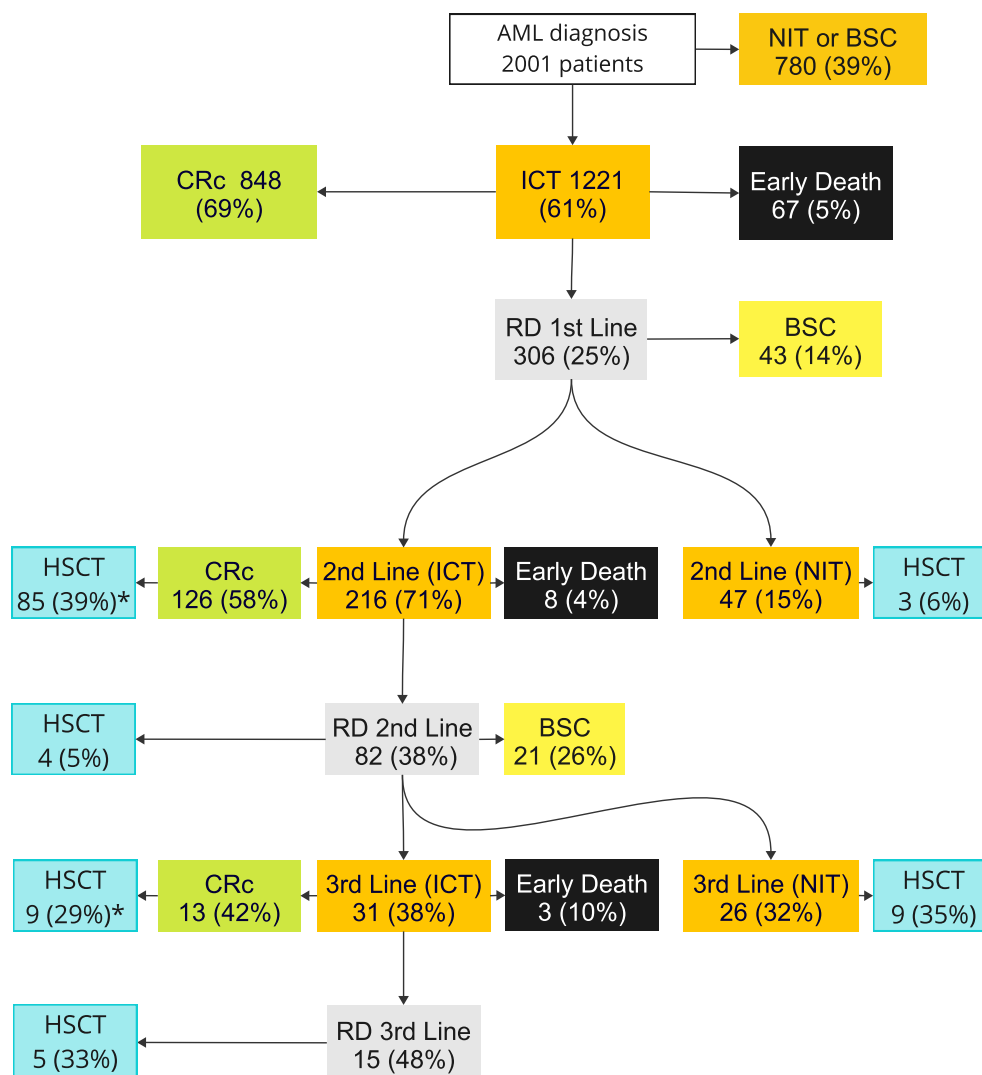


FIGURE 1 | Flowchart of screened patients and outcomes of the main study cohort. BSC: best supportive care; CRc: composite complete remission; Early death: death before response evaluation; HSCT: allogeneic stem cell transplantation; ICT: intensive chemotherapy; NIT: nonintensive therapy; RD: refractory disease. *HSCT percentages based on patients receiving treatment.

TABLE 1 | Baseline characteristics and outcomes of the main cohort and subgroups of treatment choice.

Characteristic	Total	ICT second line	NIT second line	BSC
	n = 306	n = 216	n = 47	n = 43
Age, years, median (range)	65 (19–84)	61 (19–81)	69 (41–82)	73 (32–84)
Sex, male, n (%)	174 (57)	120 (56)	28 (60)	26 (60)
Bone marrow blasts after first line, mean percentage	32.2	41.4	21.7	37.9
ECOG ≥ 2 at start of second line, %	—	28.2	38.3	—
Secondary AML ^a , n (%)	56 (18)	29 (13)	13 (28)	14 (33)
ELN 2017 risk group ^b , n (%)				
Favorable	15 (5)	13 (6)	1 (2)	1 (2)
Intermediate	121 (42)	92 (44)	18 (41)	11 (29)
Adverse	153 (53)	102 (49)	25 (57)	26 (68)
CRc after salvage treatment, n (%)		126 (58)	8 (17)	
1-year survival from refractory disease, % (95% CI)	45.0 (40–51)	56.8 (51–64)	28.9 (18–46)	2.33 (0–16)
3-year survival from refractory disease, % (95% CI)	22.7 (18–28)	31.4 (26–38)	0	0
Early death (within 45 days from treatment start), n (%)		20 (9)	7 (15)	
HSCT after second line, n (%)		89 (41)	3 (6)	0
HSCT after third line or later, n		22	0	0

Abbreviations: BSC: best supportive care; CRc: composite complete remission; ECOG: Eastern Cooperative Oncology Group; ELN: European Leukemia Net; HSCT: allogeneic stem cell transplantation; ICT: intensive chemotherapy; NIT: nonintensive therapy.

^aSecondary AML includes therapy-related AML and AML after myelodysplastic syndrome and myeloproliferative neoplasms.

^bPercentages are based on classifiable patients. In total, 17/306 patients were not able to be classified due to missing genetic data.

groups receiving ICT, NIT, and BSC, respectively, whereas 3-year OS was 31%, 0%, and 0%. The rate of HSCT was 41% in the ICT group and 6% in the NIT group after first salvage therapy, with an additional 10% in the ICT group receiving a transplant after additional lines of therapy. Median time to transplant after first salvage was 133 days, which was used as a landmark in the landmark analysis shown in Figure 2B. Patients who received intensive salvage therapy and were transplanted had a 3-year survival of 57%, while patients who received ICT without transplantation did very poorly, showing no long-term survival and an OS similar to NIT patients. Multivariate Cox regressions were performed for ICT and NIT combined and ICT patients alone (Figure 3). Salvage treatment modality (ICT vs. NIT) did not influence OS in the multivariable analysis, whereas adverse genetic risk according to ELN 2017 and secondary AML were associated with significantly worse OS and HSCT with better OS. In addition, FAIDA salvage therapy was associated with a significantly better OS compared to ACE, whereas ECOG ≥ 2 was a significant negative factor for OS in the analysis with both ICT and NIT patients.

3.3 | Intensive Salvage Therapy—FAIDA Versus ACE

Of the 216 patients who received ICT as salvage, 141 (65%) received ACE, 65 (30%) FAIDA, and 10 (5%) another ICT regimen.

Patients who received FAIDA were younger than those in the ACE group, but the two groups had a similar distribution of ELN 2017 genetic risk groups, rate of secondary AML, performance status, and proportion of bone marrow blasts prior to the start of salvage therapy (Table S1). The FAIDA group had a higher rate of CRc (70.7% vs. 52.4%, $p=0.02$) and a better 3-year survival (43.2% vs. 27.5%, $p=0.01$) compared to the ACE group. Survival in the two treatment groups is shown in Figure 2C. In a multivariate analysis, patients receiving FAIDA had a significantly better outcome compared to those treated with ACE, with an HR of 0.58 (0.38–0.88, $p=0.01$) (multivariate analysis included secondary AML, HSCT (as time-dependent covariate), age, performance status, and genetic risk) (Figure 3).

3.4 | Outcome of Early Responders Versus Responders to Salvage Therapy

To compare characteristics and outcomes of primary refractory patients that achieved CRc after salvage therapy to those of early responders, 848 newly diagnosed AML patients treated with intensive induction chemotherapy between 2011 and 2018 and achieving CRc after one cycle of first-line therapy (early responders) were extracted from the Swedish AML registry. Patients who achieved CRc after the first cycle were older than those who achieved CRc after the first salvage

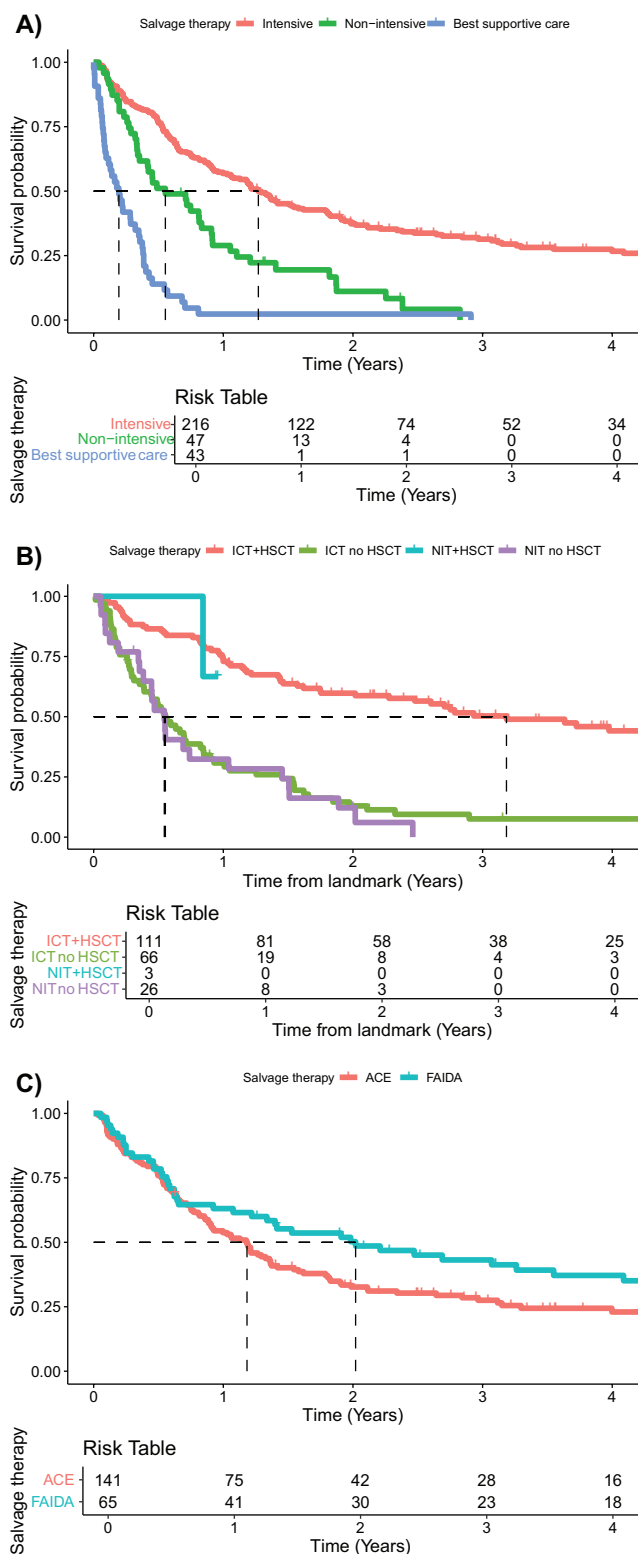


FIGURE 2 | Overall survival according to treatment choice in first salvage. Panel (A) shows survival in intensively treated (ICT), nonintensively treated (NIT) and patients with best supportive care (BSC), (B) ICT and NIT patients with and without hematopoietic stem cell transplantation (HSCT) from landmark 133 days from refractory disease, and (C) ICT patient treated with either ACE or FAIDA regimens.

therapy (salvage responders) ($p=0.002$) (Table 2), likely due to the selection of patients who received salvage therapy. Early responders had a more favorable ELN 2017 risk profile with

more frequent favorable-risk and less frequent high-risk disease ($p<0.001$), while patients in CRc after the second line of therapy were transplanted at a significantly higher rate ($p<0.001$).

Characteristics and outcomes of early responders compared to salvage responders are shown in Table 2 and Figure 4A–D. One and three-year survival post-CRc was significantly better in early versus salvage responders with 73.8 versus 66.5 and 52.0 versus 40.0%, respectively ($p=0.02$, Figure 4A). However, this difference disappeared when ELN favorable-risk patients were excluded (Figure 4B). When analyzing transplanted and nontransplanted patients separately, there was a significant difference in favor of early responders in both patient groups ($p=0.006$, Figure 4C and $p<0.001$, Figure 4D, respectively).

In a multivariate analysis, adjusting for risk groups, age, and HSCT rate (time-dependent covariate), comparing early responders to salvage responders, there was a trend, while not statistically significant, in survival favoring the early responders (HR 1.29, 95% CI [0.99–1.68], $p=0.06$), which contrasts with the general clinical perception of a clear difference in outcome between a patient that responds to the first cycle of intensive treatment compared to those that need a second line to achieve CRc.

3.5 | Second Salvage Therapy

Out of the 216 patients receiving intensive salvage therapy, 126 (58%) achieved CRc, 8 (4%) died before evaluation, and 82 (38%) had refractory disease (RD2) as defined by lack of at least CRc after salvage therapy (Figure 1). Thirty-one (38%) of the patients who were refractory to the first ICT salvage therapy received a third line of ICT, in most cases either ACE or FAIDA, depending on what regimen the patient received as first salvage (third line: 5 ACE, 21 FAIDA, and 5 mitoxantrone-based regimens). Twenty-six (32%) of the RD2 patients received NIT (2 with venetoclax), and the remaining 21 (26%) patients received BSC. Patients receiving ICT were younger compared to those receiving NIT (52 vs. 66.5 years, $p<0.02$), but they had comparable performance status and the same risk group distribution (Table S2). Notably, the CRc rate after the second salvage therapy was 42% for ICT patients compared to 15% for NIT patients. Among patients receiving ACE, 2 out of 5 achieved CRc; in the FAIDA group, 11 out of 21 achieved CRc; while none of the 5 patients treated with mitoxantrone-based regimens achieved CRc.

While the CRc rate was significantly higher in the ICT group ($p=0.02$), 1-year survival of patients of ICT versus NIT did not differ (52% vs. 50%, respectively, $p=0.81$). However, the ICT group had a significantly better 3-year survival rate of 35% compared to 4% in the NIT group ($p=0.003$), despite the fact that the transplantation rate was not different between ICT and NIT patients (45% vs. 35%, $p=0.5$). This may be explained by the fact that, among transplanted patients, ICT patients had a better survival compared to NIT patients (HR 3.73 $p=0.02$), with 3-year survival of transplanted patients as high as 71% (Figure S1). Similar to patients after the first

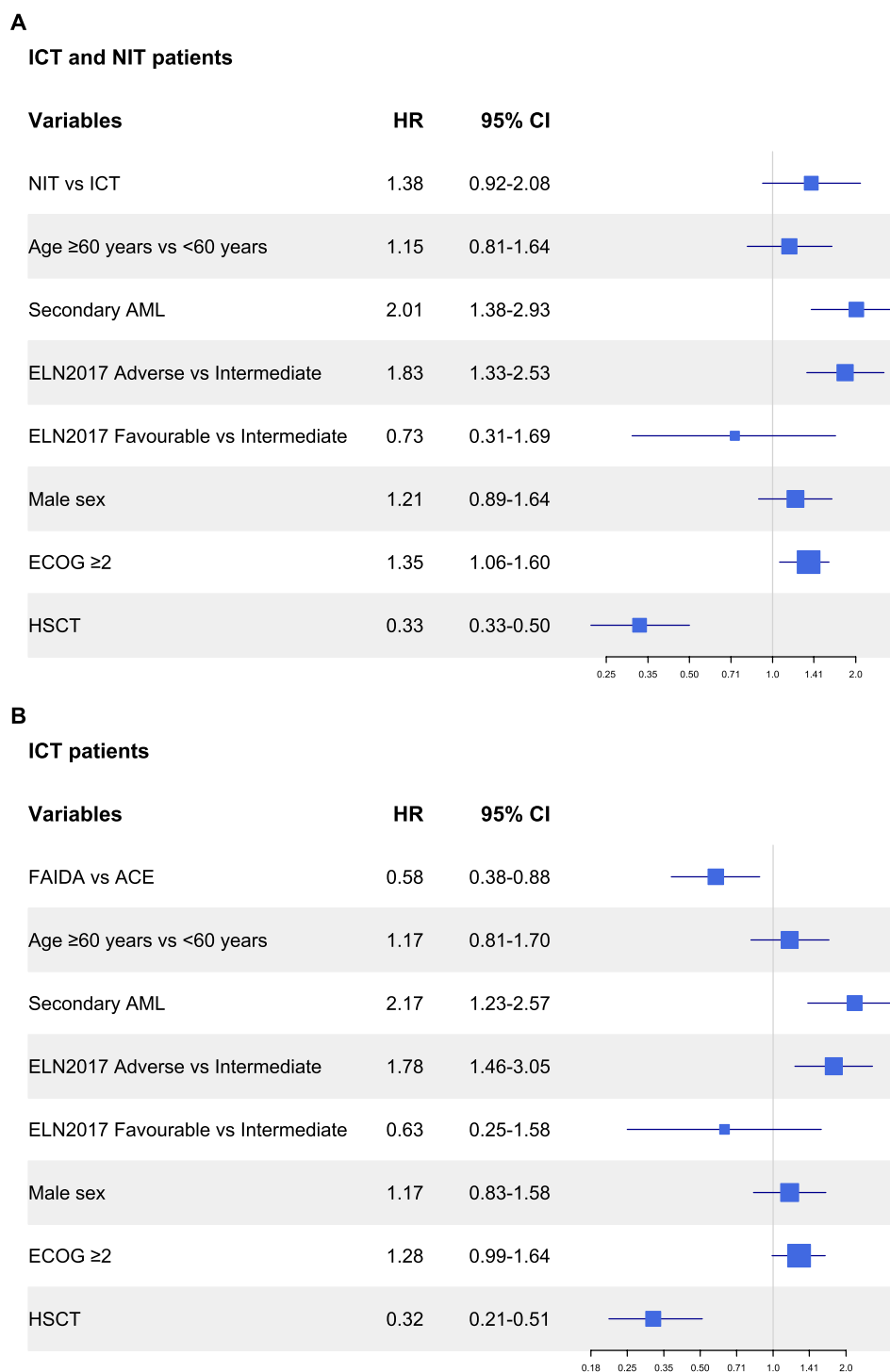


FIGURE 3 | Forest plots for intensively treated (ICT) and nonintensively treated (NIT) patients together (above) and for ICT patients alone (below) showing HR values with 95% CI for variables impacting on overall survival after salvage therapy. ACE: amsacrine, cytarabine, etoposide; ECOG: Eastern Cooperative Oncology Group; ELN: European Leukemia Net; FAIDA: fludarabine, idarubicin, cytarabine; HSCT: allogeneic stem cell transplantation. *With age included as a continuous variable the HR per year was 1.00 (0.99–1.01) for ICT and 1.00 (0.99–1.02) for ICT + NIT.

salvage therapy, those who proceed to a second-line salvage do as poorly with ICT as with NIT if not followed by transplantation. This suggests that, although representing a highly selected patient group, a third line of intensive therapy may result in a significant remission rate and long-term survival in patients who proceed to a transplant.

4 | Discussion

In this study, we present, to our knowledge, the first real-world cohort of AML patients receiving salvage therapy for primary refractory AML as well as one of the largest cohorts of refractory AML reported to date. Refractory disease was defined as failure

TABLE 2 | Baseline characteristics and survival data on early responders (CRc after first cycle), salvage responders (CRc after first salvage therapy), and patients refractory to two lines of therapy.

Characteristic	Early responders	Salvage responders	RD second line
	<i>n</i> = 848	<i>n</i> = 126	<i>n</i> = 82
Age, years, median (range)	64 (18–84)	59.5 (19–81)	62 (20–79)
Sex, male <i>n</i> (%)	455 (54)	66 (52)	49 (60)
Bone marrow blasts after first line, mean percentage	NA	37.8	47.2
ECOG \geq 2 at start of second line, %	NA	25.2	28.0
Secondary AML, <i>n</i> (%) ^a	NA ^a	11 (9)	16 (20)
ELN 2017 Risk group at diagnosis, <i>n</i> (%) ^b			
Favorable	203 (29)	10 (8)	3 (4)
Intermediate	324 (47)	55 (45)	33 (42)
Adverse	162 (24)	56 (46)	43 (54)
CRc1 achieved after third line or later, %			18
1-year survival from first CRc, % (95% CI)	73.8 (71–77)	66.5 (59–75)	37.8 (29–50) ^c
3-year survival from first CRc, % (95% CI)	52.0 (49–55)	40 (32–50)	16.3 (10–27) ^c
HR, multivariate (95% CI)	—	1.29 (0.99–1.68)	3.04 (2.32–3.97)
HSCT in CR1, <i>n</i> (%)	259 (31)	85 (67)	25 (30)

Abbreviations: CRc: composite complete remission; ECOG: Eastern Cooperative Oncology Group; ELN: European Leukemia Net; HSCT: allogeneic stem cell transplantation.

^aSecondary AML rate was not reliably reported in this cohort.

^bPercentages are based on classifiable patients. The number of patients that could not be classified due to missing genetic data was 159 of 848 in early responders, 5 of 126 in salvage responders, and 3 of 82 patients in patients with RD to second line treatment.

^cSurvival rates from response assessment after second line.

to achieve CRc after the first line of therapy, which differs from the ELN definition of failure to achieve CR after two cycles of intensive chemotherapy, regardless of the chemotherapy regimen used [17]. This relatively broad definition was chosen because it reflects a setting in which the treating hematologist considers the patient refractory to first-line therapy and therefore decides to switch to a salvage regimen.

Approximately, two-thirds of the patients refractory to the first line of therapy received a second line of intensive salvage therapy, resulting in a CRc rate as high as 58%, as compared to 71% after first-line therapy. The response rate of 58% observed in our study is higher than that reported in most previous studies, where response rates have ranged from 15% to 78% [6, 8, 15, 19–22]. Notably, the 78% represents an outlier from a recent study using the FLAVIDA regimen [22], whereas all other studies report response rates between 15% and 56%. However, comparisons between the studies are challenging due to differences in patient selection, treatment schedules, definitions of CR, and definitions of refractory disease, with many studies requiring at least 2 cycles of intensive chemotherapy to be classified as refractory. Nonetheless, two studies are more relevant for comparison, as they employed induction therapies with higher doses of cytarabine, similar to our Swedish protocol, and defined refractoriness in a comparable way [6, 15]. First, a study from the United States reported a CR rate of only 15% in patients receiving intensive salvage therapy. The CRc rate was 24%; however, this study also included patients who received nonintensive therapy as well as

those who proceeded directly to HSCT when diagnosed with refractory disease [6]. Second, a more recent study from Germany [15] reported a CR+CRi rate of 56% in a cohort that included both relapsed and refractory disease. However, their definition of refractory disease also included patients with PR and those without blast clearance at day 15—patients that would not have been included in our study cohort. Notably, among the other studies, only one reported data exclusively on refractory disease [20], whereas all other studies included both relapsed and refractory patients, often with a predominance of relapsed cases. In the previous studies, no significant prognostic factors were found to influence outcomes following salvage therapy [8, 15]. In contrast, our findings suggest that the established main leukemia-related risk factors for newly diagnosed AML, namely cytogenetic risk and secondary disease, also have prognostic impact in the refractory setting.

While we observed a relatively high CRc rate among patients who received intensive salvage treatment, long-term survival depended on undergoing HSCT after salvage treatment. Survival was not improved in patients receiving intensive salvage therapy compared to those receiving nonintensive therapy, unless followed by HSCT. This supports the notion that intensive salvage, which inevitably is associated with more toxicity, should not be given to refractory patients without aiming for an allogeneic transplantation. This is especially true given the more recent development of more efficient nonintensive therapies, mainly the introduction of venetoclax in combination with a

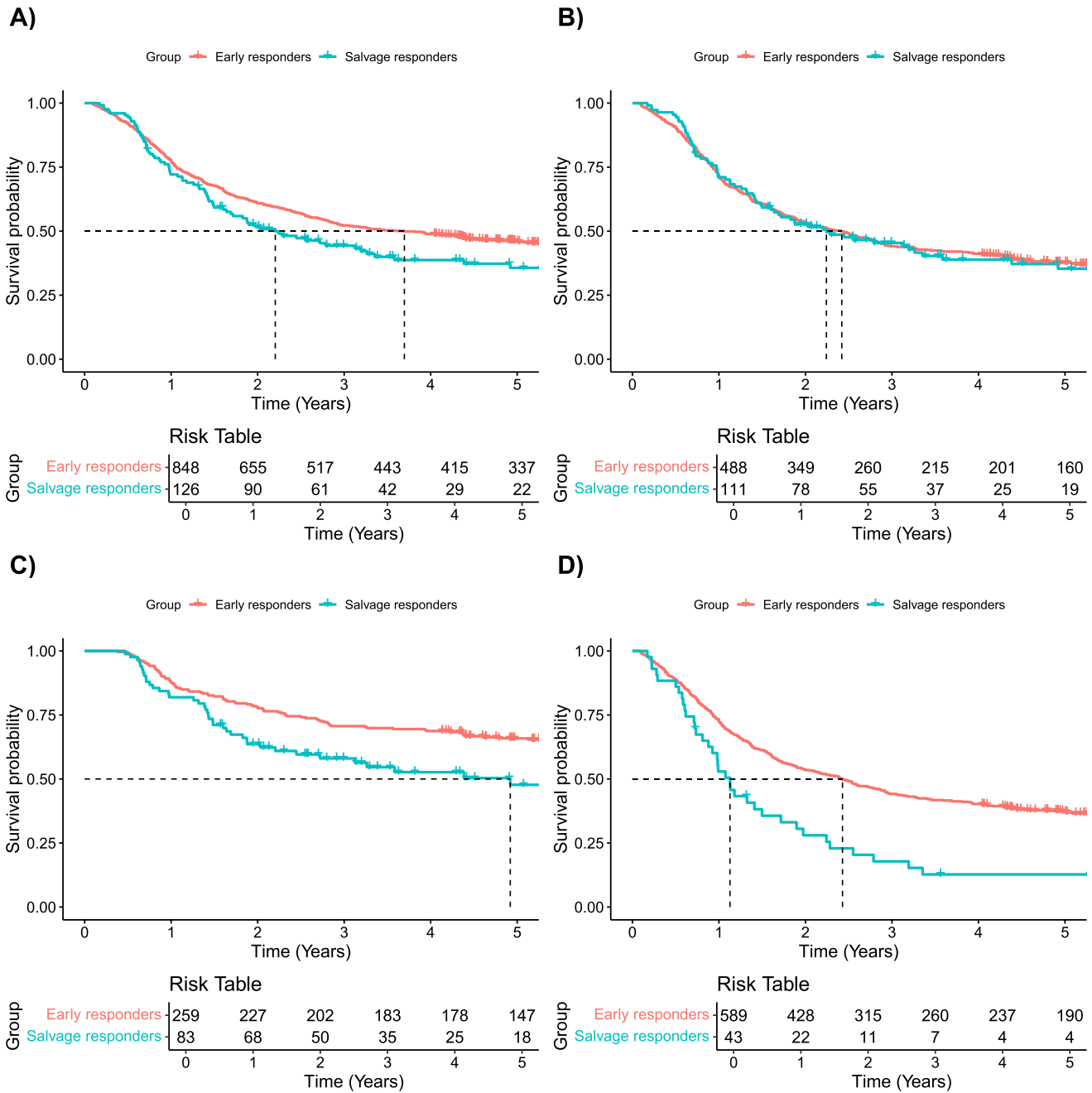


FIGURE 4 | (A–D) Overall survival for groups of early responders (red line), salvage responders (light blue). (A) Whole cohort, (B) patients with high or intermediate ELN 2017 genetic risk, (C) patients who underwent allogeneic stem cell transplant, (D) patients who did not receive a stem cell transplant.

hypomethylating drug, which may even serve as bridge to transplantation. In this study, nonintensive treatment consisted primarily of hypomethylating therapy alone, which is a limitation. However, although other nonintensive treatment options for refractory AML exist, the survival rates for patients who receive first- and second-line salvage chemotherapy followed by HSCT remain high, and this serves as the standard against which new treatments for refractory AML should be measured.

For the patients who did not respond to the first salvage therapy and received a third line of intensive chemotherapy, the response rate remained relatively favorable, with a 3-year survival of 37%

increasing to 78% among those who also underwent HSCT. This group is obviously highly selected for younger patients and those in good physical condition and with few complications from previous therapies. Still, the results show that in a carefully selected group of fit patients, the chance of response and even cure with further chemotherapy remains, despite being refractory to 1 or even 2 previous lines of therapy.

In this study, we also compared two salvage regimens: FAIDA and ACE. FAIDA or variants such as FLAG-IDA have been commonly used for relapsed/refractory AML. In addition, fludarabine-based regimens have also demonstrated favorable

results as induction therapy in newly diagnosed AML, with high response rates in multiple studies [23, 24]. The ACE regimen has been widely used in Sweden in the refractory setting since the 1990s. We found a higher response rate as well as better OS in patients receiving FAIDA as compared to ACE. This was also true in a multivariable analysis, adjusting for other prognostic factors such as the use of HSCT. Interestingly, although the response rate was higher in the FAIDA group, the difference in survival curves (Figure 2C) becomes apparent only after 9 months. This may be attributable to the fact that HSCT was the primary factor contributing to long-term cure. While not statistically significant, there was a trend toward a higher transplant rate in the FAIDA group (48% vs. 35%), which is similar to the difference in 3-year survival (43% vs. 29%). The reason for the higher transplant rate is likely due to the higher CRc and lower age in the FAIDA group. The results favor the use of fludarabine-based treatment for the first salvage chemotherapy. However, ACE treatment may still be an alternative, particularly for patients who have previously received anthracyclines, in whom cumulative cardiotoxicity is a significant concern.

Furthermore, we compared the responders to salvage therapy to early responders, who achieved CRc already after the first cycle of intensive chemotherapy. Interestingly, there was a relatively small difference in survival outcome between these groups, and this difference disappeared entirely once ELN favorable-risk patients were excluded. However, the transplant rate was significantly higher in the salvage responders, which partly explains the minimal difference in outcome. The reason for the high transplant rate in salvage responders compared to primary responders likely depends on several factors such as the selection of patients aimed for transplantation, better performance status, younger age, and worse cytogenetic risk. A tendency to choose a nontransplant approach in some very good responders could be another factor. Clearly, the recommendation in the national guidelines during the whole study period has been to transplant all patients except favorable-risk patients in first CR. However, the emphasis on transplantation has become stronger, and the transplantation rates have increased during the last 15 years in Sweden. In a multivariable analysis, no significant difference was observed between the two groups. However, there was a trend toward a favorable survival among early responders compared to patients who responded to the second-line therapy. These results suggest that the key factor for long-term outcome is the achievement of a CRc and consolidation with HSCT, rather than the number of therapies required to achieve the first CRc.

The main strength of this study is the unique and large real-world cohort of solely refractory AML, a disease entity previously sparsely described in the literature. The major limitations of the study are that the studied period spanned a period before the introduction of novel nonintensive therapy options, primarily the combination of hypomethylating agent plus venetoclax [5] as well as venetoclax in addition to intensive salvage regimens [22] and the lack of more extensive molecular data that was not available at the time of the study. The treatment landscape for refractory AML may also change during the years to come, hopefully increasing the treatment options and further improving the outcomes in the refractory setting.

In conclusion, this study demonstrates that AML patients refractory to first-line induction chemotherapy retain a meaningful chance of achieving remission and potential cure after intensive salvage therapy when followed by an allogeneic stem cell transplantation. The outcomes observed, only marginally inferior to those of first-cycle responders, provide a valuable real-world benchmark for evaluating novel treatment options in the refractory setting.

Author Contributions

Sören Lehmann, Martin Höglund, and Bertil Uggla designed the study. Markus Liew-Littorin, Linn Deleskog-Spångberg, Stefan Deneberg, Judit Janosi, Vladimir Lazarevic, Gustav Nilsson, Aristeia Papageorgiou, and Lovisa Vennström collected data. Markus Liew-Littorin curated data and performed the analyses. Markus Liew-Littorin, Sören Lehmann, Bertil Uggla, and Martin Höglund interpreted the data and wrote the manuscript. Markus Liew-Littorin, Sören Lehmann, Bertil Uggla, Martin Höglund, Stefan Deneberg, Vladimir Lazarevic, Anna Robelius, Lovisa Vennström, and Gunnar Juliusson further reviewed and edited the manuscript.

Acknowledgments

The authors thank Sandra Eketorp Sylvan (Swedish Amgen) for advice and administrative support.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. J. E. Cortes, S. Khaled, G. Martinelli, et al., "Quizartinib Versus Salvage Chemotherapy in Relapsed or Refractory FLT3-ITD Acute Myeloid Leukaemia (QuANTUM-R): A Multicentre, Randomised, Controlled, Open-Label, Phase 3 Trial," *Lancet Oncology* 20, no. 7 (2019): 984–997.
2. A. E. Perl, G. Martinelli, J. E. Cortes, et al., "Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML," *New England Journal of Medicine* 381, no. 18 (2019): 1728–1740.
3. X. Thomas, "Small Molecule Menin Inhibitors: Novel Therapeutic Agents Targeting Acute Myeloid Leukemia With KMT2A Rearrangement or NPM1 Mutation," *Oncology and Therapy* 12, no. 1 (2024): 57–72.
4. G. K. Abou-Alfa, T. Macarulla, M. M. Javle, et al., "Ivosidenib in IDH1-Mutant, Chemotherapy-Refractory Cholangiocarcinoma (ClarIDHy): A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Phase 3 Study," *Lancet Oncology* 21, no. 6 (2020): 796–807.
5. C. D. DiNardo, B. A. Jonas, V. Pullarkat, et al., "Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia," *New England Journal of Medicine* 383, no. 7 (2020): 617–629.
6. F. Ravandi, J. Cortes, S. Faderl, et al., "Characteristics and Outcome of Patients With Acute Myeloid Leukemia Refractory to 1 Cycle of High-Dose Cytarabine-Based Induction Chemotherapy," *Blood* 116, no. 26 (2010): 5818–5823.
7. H. M. Kantarjian, C. D. DiNardo, G. M. Nogueras-Gonzalez, et al., "Results of Second Salvage Therapy in 673 Adults With Acute Myelogenous Leukemia Treated at a Single Institution Since 2000," *Cancer* 124, no. 12 (2018): 2534–2540.

8. J. M. Brandwein, L. Saini, M. N. Geddes, et al., "Outcomes of Patients With Relapsed or Refractory Acute Myeloid Leukemia: A Population-Based Real-World Study," *American Journal of Blood Research* 10, no. 4 (2020): 124–133.
9. A. J. Klink, A. Gajra, R. L. Knoth, et al., "Real-World Clinical Outcomes With Enasidenib in Relapsed or Refractory Acute Myeloid Leukemia," *Leukemia Research* 122 (2022): 106946.
10. J. E. Megías-Vericat, D. Martínez-Cuadrón, M. Sanz, and P. Montesinos, "Salvage Regimens Using Conventional Chemotherapy Agents for Relapsed/Refractory Adult AML Patients: A Systematic Literature Review," *Annals of Hematology* 97, no. 7 (2018): 1115–1153.
11. E. N. Oliva, S. M. Ronnebaum, O. Zaidi, et al., "A Systematic Literature Review of Disease Burden and Clinical Efficacy for Patients With Relapsed or Refractory Acute Myeloid Leukemia," *American Journal of Blood Research* 11, no. 4 (2021): 325–360.
12. H. Döhner, A. H. Wei, F. R. Appelbaum, et al., "Diagnosis and Management of AML in Adults: 2022 Recommendations From an International Expert Panel on Behalf of the ELN," *Blood* 140, no. 12 (2022): 1345–1377.
13. C. Abé, J. Keto, M. Lilja, et al., "Cytarabine Dose Intensification Improves Survival in Older Patients With Secondary/High-Risk Acute Myeloid Leukemia in Matched Real-World Versus Clinical Trial Data," *Leukemia & Lymphoma* 65 (2024): 1493–1501.
14. M. Wattad, D. Weber, K. Döhner, et al., "Impact of Salvage Regimens on Response and Overall Survival in Acute Myeloid Leukemia With Induction Failure," *Leukemia* 31, no. 6 (2017): 1306–1313.
15. R. Mühleck, S. Scholl, I. Hilgendorf, et al., "Outcome of Patients With Relapsed or Refractory Acute Myeloid Leukemia Treated With Mito-FLAG Salvage Chemotherapy," *Journal of Cancer Research and Clinical Oncology* 148, no. 9 (2022): 2539–2548.
16. E. Hulegardh, C. Nilsson, V. Lazarevic, et al., "Characterization and Prognostic Features of Secondary Acute Myeloid Leukemia in a Population-Based Setting: A Report From the Swedish Acute Leukemia Registry," *American Journal of Hematology* 90, no. 3 (2015): 208–214.
17. H. Döhner, E. Estey, D. Grimwade, et al., "Diagnosis and Management of AML in Adults: 2017 ELN Recommendations From an International Expert Panel," *Blood* 129, no. 4 (2017): 424–447.
18. C. Röllig, M. Bornhäuser, C. Thiede, et al., "Long-Term Prognosis of Acute Myeloid Leukemia According to the New Genetic Risk Classification of the European LeukemiaNet Recommendations: Evaluation of the Proposed Reporting System," *Journal of Clinical Oncology* 29, no. 20 (2011): 2758–2765.
19. A. Thiel, J. Schetelig, W. Pönisch, et al., "Mito-FLAG With Ara-C as Bolus Versus Continuous Infusion in Recurrent or Refractory AML—Long-Term Results of a Prospective Randomized Intergroup Study of the East German Study Group Hematology/Oncology (OSHO) and the Study Alliance Leukemia (SAL)," *Annals of Oncology* 26, no. 7 (2015): 1434–1440.
20. S. Zhong, H. Kurish, R. Walchack, et al., "Efficacy and Safety of Mitoxantrone, Etoposide, and Cytarabine for Treatment of Relapsed or Refractory Acute Myeloid Leukemia," *Leukemia Research* 139 (2024): 107468.
21. B. Bhatnagar, Q. Zhao, A. S. Mims, et al., "Phase 1 Study of Selinexor in Combination With Salvage Chemotherapy in Adults With Relapsed or Refractory Acute Myeloid Leukemia," *Leukemia & Lymphoma* 64, no. 13 (2023): 2091–2100.
22. R. Shahswar, G. Beutel, R. Gabdoulline, et al., "Fludarabine, Cytarabine, and Idarubicin With or Without Venetoclax in Patients With Relapsed/Refractory Acute Myeloid Leukemia," *Haematologica* 109, no. 1 (2024): 72–83.
23. P. Minetto, A. Candoni, F. Guolo, et al., "Fludarabine, High-Dose Cytarabine and Idarubicin-Based Induction May Overcome the Negative Prognostic Impact of FLT3-ITD in NPM1 Mutated AML, Irrespective of FLT3-ITD Allelic Burden," *Cancers (Basel)* 13, no. 1 (2020): 34.
24. A. K. Burnett, N. H. Russell, R. K. Hills, et al., "Optimization of Chemotherapy for Younger Patients With Acute Myeloid Leukemia: Results of the Medical Research Council AML15 Trial," *Journal of Clinical Oncology* 31, no. 27 (2013): 3360–3368.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.