Prognostic impact of complete remission with MRD negativity in patients with relapsed or refractory AML

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Key Points
• In relapsed/refractory AML, CR and MRD negativity are associated with lower risk of relapse and better relapse-free survival.
• Patients who underwent HSCT in second remission had the best outcomes, irrespective of hematologic or MRD response.

In relapsed/refractory acute myeloid leukemia (AML), the prognostic impact of complete remission (CR) and measurable residual disease (MRD) negativity is not well established. We retrospectively analyzed 141 patients with relapsed/refractory AML who received first salvage therapy and had MRD assessed by multiparameter flow cytometry at the time of response. Patients who achieved CR with full hematologic recovery as best response vs those with incomplete hematologic recovery had lower cumulative incidence of relapse (P = .01) and better relapse-free survival (P = .004) but not overall survival (P = .15); a similar trend was observed in patients who achieved MRD negativity vs those who were MRD positive (P = .01, P = .05, and P = .21, respectively). By multivariate analysis, CR and MRD negativity were each independently associated with lower cumulative incidence of relapse (P = .001 and P = .003, respectively) and better relapse-free survival (P < .001 and P = .02) but not overall survival. Patients who achieved CR with MRD negativity had the lowest rates of relapse and best survival (2-year overall survival rate, 37%), which was driven largely by lower rates of early relapse and an increased ability in this group to undergo hematopoietic stem cell transplantation (HSCT); however, post-HSCT outcomes were similar regardless of response to salvage chemotherapy. Overall, in patients with relapsed/refractory AML, CR with MRD negativity was associated with the best outcomes, supporting it as the optimal response in this setting.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease, with widely variable disease biology and response to conventional therapies.1 Although cytogenetics and gene mutations are among the primary disease-related factors that influence prognosis,2 how well the disease responds to initial therapy is also a vital determinant of long-term outcomes and provides useful information about the chemosensitivity of an individual’s leukemia that cannot necessarily be predicted from pretreatment characteristics.3 In the frontline setting, the achievement of complete remission (CR) with full hematologic recovery has been shown to confer better long-term outcomes than morphologic remission (ie, <5% bone marrow blasts) with incomplete peripheral blood count recovery.4,5 Among patients who achieve morphologic remission, assessment of measurable (or “minimal”) residual disease (MRD) also provides important prognostic information, and multiple studies have shown that the achievement of MRD negativity is a strong predictor of better long-term outcomes in patients with AML undergoing frontline therapy.6–15

Because achievement of CR and MRD negativity are both independently associated with lower rates of relapse and superior survival in the frontline setting,5 recent consensus guidelines have supported
prognostic impact of these responses.

For patients with AML in first relapse, established prognostic factors include: cytogenetics at diagnosis, prior allogeneic hematopoietic stem transplantation (HSCT), age at relapse, and length of relapse-free interval after first relapse. Together, these factors can stratify patients into widely disparate risk groups, with 5-year overall survival (OS) rates ranging from 4% to 46%. Although it may be reasonably assumed that the posttreatment factors which influence prognosis in the frontline setting would translate to patients with relapsed/refractory disease is largely unknown.

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Response and outcome definitions
CR, CRi, and MLFS were defined according to European LeukemiaNet consensus guidelines. The best response achieved within 1 to 2 cycles of first salvage chemotherapy was used for this analysis. Relapse was defined as recurrence of bone marrow blasts >5% or extramedullary AML. Cumulative incidence of relapse (CIR) was calculated from the time of best response until relapse, censored for death in morphologic remission, or if the patient was alive at last follow-up. Relapse-free survival (RFS) was calculated from the time of best response until relapse or death from any cause, censored if the patient was alive at last follow-up. OS was calculated from the time of treatment initiation until death from any cause, censored if the patient was alive at last follow-up. Survival estimates were not censored at the time of HSCT.

Statistical methods
Patient characteristics were summarized by using median (range) for continuous variables and frequencies (percentages) for categorical variables. To compare 2 groups, Fisher’s exact test was performed for categorical variables, and the Wilcoxon rank sum test was performed for continuous variables. Univariate Cox proportional hazards models were used to evaluate the risk factors associated with survival outcomes. A multivariate proportional hazards model was obtained by first including the factors with $P < .20$ on univariate analysis and then finalizing via backward elimination until all remaining factors had $P < .05$. Subgroup analysis was performed for transplanted patients and nontransplanted patients; the survival outcomes for transplanted patients were redefined from the time of HSCT. Landmark analysis was conducted for nontransplant patients using landmark time of 1.4 months, which was the median time to HSCT among patients undergoing transplant. Statistical analyses were conducted in R version 3.5.1.

Results
Patient characteristics and study cohort
Between August 2011 and July 2018, we identified 192 patients with relapsed/refractory AML who achieved CR/CRi/MLFS after first salvage therapy. Fifty-one patients were excluded due to no available MRD information ($n = 30$), equivocal MRD assessment ($n = 20$), and extramedullary disease only ($n = 1$). Overall, 141 patients with relapsed or refractory AML met inclusion criteria and were included in this analysis. Baseline characteristics of the study population are shown in Table 1. The median age was 58 years (range, 17-84 years). For first-line therapy, 90 patients (64%) received intensive cytotoxic chemotherapy, and 51 patients (36%) received lower intensity therapy, primarily with a hypomethylating agent. Eighty-eight patients (62%) were refractory to induction therapy or had a first remission duration <1 year. Among 80 patients who had responded to frontline therapy and in whom the duration of first response was known, 42 (53%) had a first remission previously described. When available, the phenotypic profiles of pretreatment blasts were compared with those of specimens submitted for MRD testing. A distinct cluster of at least 20 cells showing altered expression of ≥2 antigens was regarded as an aberrant population. The sensitivity of this assay is 0.1% or higher. All specimens with unequivocally positive results were included in this analysis. However, specimens with indeterminate MRD assessment or with negative results but suboptimal cell counts were excluded.
Eighty-six patients (61%) achieved MRD negativity at the time of best response. Best response was CR\(_{\text{MRD-}}\) in 61 patients (43%), CR with MRD positivity in 34 patients (24%), CRi with MRD negativity in 12 patients (9%), CRi with MRD positivity in 14 patients (10%), MLFS with MRD negativity in 13 patients (9%), and MLFS with MRD positivity in 7 patients (5%). Notably, the rates of MRD negativity among patients achieving CR, CRi, and MLFS were not significantly different (64%, 46%, and 65%, respectively; \(P = .22\)), suggesting a lack of association between hematologic recovery and MRD response. Among MRD-positive patients, 53 had a quantifiable MRD value. MRD levels at best response were <0.1% in 4 patients (8%), 0.1% to 0.99% in 27 patients (51%), and ≥1% in 22 patients (42%). There was no difference in median level of MRD for patients who achieved CR, CRi, or MLFS (0.66%, 0.70%, and 1.50%; \(P = .68\)).

### Factors associated with hematologic recovery and MRD status

Predictors for achievement of CR (vs CRi/MLFS) included diploid karyotype (78% vs 59% for patients with non-diploid karyotype; \(P = .02\)) and first remission duration ≥1 year (87% vs 57% for patients who were refractory to frontline therapy or with first remission duration <1 year; \(P = .001\)) (supplemental Table 2). Higher pretreatment bone marrow percentage was associated with a significantly increased rate of MRD negativity (median bone marrow blast percentage for MRD-negative vs MRD-positive cases, 35% vs 26%; \(P = .03\)) (supplemental Table 3). However, achievement of MRD negativity was not associated with any other pretreatment parameter.

### Outcomes by hematologic recovery and MRD status for the entire cohort

Given the similar outcomes for patients with CRi and MLFS in this cohort, these patients were combined for survival analyses. Patients who achieved CR vs CRi/MLFS had significantly lower CIR (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.34-0.88; \(P = .01\)) (Figure 1A) and better RFS (HR, 0.54; 95% CI, 0.35-0.82; \(P = .004\)) (Figure 1B) but not OS (HR, 0.72; 95% CI, 0.46-1.12; \(P = .15\)) (Figure 1C). A similar trend was observed in patients who achieved MRD negativity vs those who were MRD positive (CIR HR, 0.55 [95% CI, 0.36-0.85; \(P = .01\)]; RFS HR, 0.67 [95% CI, 0.45-0.99; \(P = .05\)]; OS HR, 0.76 [95% CI, 0.50-1.16; \(P = .21\)]) (Figure 1D-F). Notably, among MRD-positive patients, level of MRD (ie, <0.1% vs 0.1%-0.99% vs ≥1%) did not affect CIR (\(P = .88\)), RFS (\(P = .85\)), or OS (\(P = .91\)).

### Impact of HSCT on outcomes

Sixty-two patients (44%) underwent allogeneic HSCT after first salvage therapy, with a median time of 1.4 months between achievement of second remission and HSCT. HSCT after first salvage therapy was the strongest prognostic factor identified for CIR, RFS, and OS (\(P < .001\) for all). HSCT rate was higher in those who achieved CR vs CRi/MLFS (52% vs 28%, respectively; \(P = .008\)) and in those who were MRD negative vs MRD positive (52% vs 31%; \(P = .01\)).

Overall, 15 patients relapsed within 1.4 months after achievement of second remission. The relapse rate in this period was significantly higher in patients who achieved only CRi/MLFS and/or were MRD positive compared with those who achieved CR\(_{\text{MRD-}}\). The relapse rates within 1.4 months of second remission for patients who

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**Table 1. Patient characteristics**

| Characteristic       | Value (N = 141) |
|----------------------|-----------------|
| Age, y               | 58 [17-84]      |
| WBC, \(\times 10^9/L\)| 2.3 [0.3-20.7]  |
| Hemoglobin, g/dL     | 9.6 [3.8-14.3]  |
| Platelets, \(\times 10^9/L\)| 43 [3-464]    |
| BM blasts, %         | 32 [1-91]       |

**Cytogenetics**

- Diploid: 59 (42%)
- Poor risk: 38 (27%)
- Others: 42 (30%)
- Insufficient metaphases/not done: 2 (1%

**CR1 response**

- Refractory or CR1 duration <1 y: 88 (62%)
- CR1 duration ≥1 y: 38 (27%)
- Unknown: 15 (11%)
- Prior HSCT: 13 (9%)
- 2 cycles to best response: 19 (13%)

**Mutations**

- NPM1: 22/57 (39)
- NRAS/KRAS: 15/64 (23)
- IDH2: 16/79 (20)
- IDH1: 14/79 (18)
- ASXL1: 11/61 (18)
- TET2: 9/62 (15)
- FLT3-ITD: 12/86 (14)
- DNMT3A: 10/71 (14)
- CEBPA: 9/69 (13)
- RUNX1: 8/62 (13)
- WT1: 6/81 (10)
- PTPN11: 6/68 (9)
- FLT3-TKD: 7/85 (8)
- EZH2: 5/87 (7)
- GATA2: 4/62 (6)

Continuous variables are listed as median [range] and categorical variables as n (%). BM, bone marrow; CR1, first complete remission; WBC, white blood cell.

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duration <1 year, and 38 (48%) had a first remission duration ≥1 year. Thirteen patients (9%) had undergone prior HSCT. The majority of patients (87%) achieved best response after 1 cycle of salvage therapy.

The median duration of follow-up of the entire cohort was 30.5 months (range, 0.3-80.3 months). The 1- and 2-year CIR rates were 59% and 67%, respectively. Median RFS was 5.6 months, with 1- and 2-year RFS rates of 34% and 23%. Median OS was 11.2 months, with 1- and 2-year OS rates of 48% and 29%.

### Response rates

Ninety-five patients (67%) achieved CR, 26 (18%) achieved CRi, and 20 (14%) achieved MLFS as best response to salvage therapy.
Figure 1. Outcomes of patients according to hematologic recovery and MRD status. CIR (A), RFS (B), and OS (C) for the entire cohort, stratified according to hematologic response to salvage chemotherapy. CIR (D), RFS (E), and OS (F) for the entire cohort, stratified according to MRD response to salvage chemotherapy.
achieved CR\textsubscript{MRD-}, CR with MRD positivity, CR\textsubscript{i}/MLFS with MRD negativity, and CR\textsubscript{i}/MLFS with MRD positivity were 3%, 15%, 8%, and 29%, respectively. Overall, 2 (3%) of 61 patients with CR\textsubscript{MRD-} relapsed in this period, compared with 13 (16%) of 80 patients with CR\textsubscript{i}/MLFS and/or MRD positivity (P = .01). This increased rate of very early relapse was a major driver of the inferior outcomes observed in this latter group.

In a landmark HSCT analysis, 22 patients who relapsed (n = 15), died in remission (n = 4), or were lost to follow-up (n = 3) within 1.4 months of second remission were excluded. Among the remaining 57 patients who did not undergo HSCT in second remission, stratification of patients into 4 groups according to hematologic response (CR vs CR\textsubscript{i}/MLFS) and MRD response (positive vs negative) was associated with significant differences in CIR (P = .004) and RFS (P = .008) but not OS (P = .8) (supplemental Figure 1A-C). As expected, outcomes in patients who did not undergo HSCT in second remission were very poor, regardless of their response to salvage chemotherapy, with only 1 patient alive without relapse or death at 2 years.

Overall, 62 patients underwent HSCT in first remission. The conditioning regimen was myeloablative in 37 of these patients (60%) and reduced-intensity in 25 patients (40%). Twelve patients (19%) received post-HSCT maintenance therapy (azacitidine, n = 6; sorafenib, n = 3; ceranolab, n = 2; SGI-110, n = 1). Outcomes were significantly better for patients who underwent HSCT, regardless of their response to first salvage therapy (Figure 2). Interestingly, among patients who underwent HSCT, neither hematologic nor MRD response after salvage therapy was associated with CIR (P = .94), RFS (P = .77), or OS (P = .54) (supplemental Figure 2A-C). Fifty-nine of these patients also had pre-HSCT MRD information available (defined as MRD assessment within 6 weeks before HSCT), which was analyzed for impact on clinical outcomes. Forty-two of the 59 patients with pre-HSCT MRD information had at least one additional MRD assessment performed before HSCT. Thirty patients who were MRD negative remained MRD negative before HSCT, 1 patient converted from MRD negative to MRD positive, 7 patients converted from MRD positive to MRD negative, and 4 patients who were MRD positive remained MRD positive before HSCT. Overall, 50 patients (85%) were MRD negative and 9 patients (15%) were MRD positive before HSCT. Among MRD-positive patients, the median level of pre-HSCT MRD was 0.5% (range, 0.04%-2%). MRD status before HSCT was not associated with differential outcomes with respect to either CIR (P = .70), RFS (P = .46), or OS (P = .48) (supplemental Figure 3A-C).

**Multivariate analysis and integration of hematologic recovery and MRD response**

According to multivariate analysis, including established predictors for outcomes in relapsed/refractory AML (modified from Breems et al\textsuperscript{17}) and using HSCT as a time-dependent variable, both CR and MRD negativity were independently associated with lower CIR (HR of 0.45 [95% CI, 0.28-0.73; P = .001] and HR of 0.50 [95% CI, 0.32-0.79; P = .003], respectively) and better RFS (HR of 0.46 [95% CI, 0.30-0.71; P < .001] and HR of 0.62 [95% CI, 0.41-0.93; P = .02]) but not with OS (Table 2; supplemental Tables 4-6).

In light of the favorable and independent prognostic impact of achieving CR and of achieving MRD negativity, as well as to assess whether CR\textsubscript{MRD-} might be the optimal response for patients with
relapsed/refractory AML, these variables were combined for analyses of relapse and survival outcomes. Integration of hematologic recovery and MRD information appeared to stratify patients into 3 groups according to CIR and RFS, ranging from most favorable outcomes to poorest outcomes: (1) CRMRD−; (2) CR with MRD positivity or CRi/MLFS with MRD negativity; and (3) CRi/MLFS with MRD positivity (Figure 3A-B). The 1-year CIR rates for these groups were 47%, 67%, and 76%, respectively ($P = .001$), and the median RFS were 10.1 months, 5.1 months, and 2.4 months ($P = .004$). However, OS was not significantly different between groups when stratified according to hematologic recovery and MRD status ($P = .29$) (Figure 3C).

Patients who achieved CRMRD− as best response ($n = 61$ [43% of the entire cohort]) had better outcomes than those who achieved CR/MLFS and/or MRD positivity. Patients who achieved CRMRD− had significantly lower CIR (2-year CIR rate, 58% vs 73% [HR, 0.52; 95% CI, 0.33-0.82; $P = .004$]) (Figure 4A) and better RFS (2-year RFS rate, 30% vs 15% [HR, 0.58; 95% CI, 0.39-0.87; $P = .008$]) (Figure 4B). A trend for better OS was also observed in patients who achieved CRMRD− (2-year OS rate, 37% vs 21% [HR, 0.70; 95% CI, 0.46-1.07; $P = .10$]) (Figure 4C).

The impact of achieving CRMRD− vs lesser responses was similar in both younger and older populations. Achievement of CRMRD− was associated with better RFS in patients aged <60 years (HR, 0.60; 95% CI, 0.35-1.05; $P = .07$) and in patients aged ≥60 years (HR, 0.57; 95% CI, 0.33-1.01; $P = .05$). Patients with diploid cytogenetics who achieved CRMRD− had a trend toward better RFS compared with those with lesser responses (HR, 0.66; 95% CI, 0.35-1.25; $P = .20$); this benefit of CRMRD− was also observed in patients with non-diploid cytogenetics (HR, 0.60; 95% CI, 0.36-0.99; $P = .047$).

**Discussion**

CR with full hematologic recovery and achievement of MRD negativity have both been shown in several studies to be associated

| Characteristic | HR (95% CI) | $P$ |
|---------------|------------|-----|
| **CIR**       |            |     |
| MRD status (negative vs positive) | 0.50 (0.32-0.79) | .003 |
| Response (CR vs CRi/MLFS) | 0.45 (0.28-0.73) | .001 |
| Log of platelets | 0.74 (0.59-0.94) | .01 |
| HSCT after salvage therapy (time-dependent) | 0.20 (0.11-0.35) | <.001 |
| **RFS**       |            |     |
| MRD status (negative vs positive) | 0.62 (0.41-0.93) | .02 |
| Response (CR vs CRi/MLFS) | 0.46 (0.30-0.71) | <.001 |
| Log of platelets | 0.77 (0.63-0.96) | .02 |
| HSCT after salvage therapy (time-dependent) | 0.25 (0.15-0.41) | .02 |
| **OS**        |            |     |
| Cytogenetics (diploid vs others) | 0.58 (0.38-0.88) | .01 |
| HSCT after salvage therapy (time-dependent) | 0.28 (0.18-0.46) | <.001 |

Variables included in multivariate analysis were: age, white blood cell count, platelet count, hemoglobin, bone marrow blast percentage, cytogenetics (diploid vs others), response to first induction (relapsed with first remission duration ≥1 year vs relapsed with first remission duration <1 year or refractory), prior HSCT, HSCT after salvage therapy (as time-dependent variable), hematologic response (CR vs CRi/MLFS), and MRD response (negative vs positive).
with superior outcomes in patients with AML undergoing frontline therapy. In contrast, established prognostic factors in the relapsed/refractory setting have historically been limited to pre-treatment clinical variables. In this study of patients with relapsed/refractory AML treated with first salvage chemotherapy, we showed that achievement of CR and MRD negativity by MFC are both independently associated with lower rates of relapse and superior RFS, even when accounting for subsequent HSCT. When hematologic recovery and MRD status were integrated, the best outcomes were observed in patients who achieved CRMRD (43% of patients in the cohort), and the superior outcomes in these patients were driven, at least in part, by their ability to be bridged to allogeneic HSCT. Together, these data support the European LeukemiaNet consensus guidelines defining CRMRD as the optimal response in AML and provide evidence that this response definition is also applicable to patients with relapsed/refractory disease.

In nearly all fit patients with relapsed/refractory AML (with the possible exception of select patients with core binding factor AML), the goal of salvage therapy is to induce a response and bridge to potentially curative allogeneic HSCT. Because coordination of HSCT may take ≥6 weeks, transient responses may not provide adequate disease control to proceed with HSCT and thus may require additional lines of treatment before HSCT can be performed. We found that the rate of very early relapse (ie, within 1.4 months, which was the median time to HSCT in our study) was lower in patients who achieved CRMRD vs those who achieved lesser responses (relapse rate within 1.4 months, 3% and 16%, respectively), which increased the ability of patients with CRMRD to undergo HSCT after first salvage. In contrast, the suboptimal disease control associated with achieving only CRi/MLFS or MRD positivity contributed to the poorer outcomes of these patients, largely because fewer patients with these responses were able to undergo potentially curative HSCT. Not surprisingly, the outcomes of patients who did not undergo subsequent HSCT were poor, regardless of initial response to salvage chemotherapy. Although risk of relapse was lower, and RFS was superior for patients who achieved CR and/or MRD negativity, outcomes were still universally poor in all groups who did not undergo HSCT, with only 1 patient being alive without relapse 2 years after first salvage. Previous reports, including a meta-analysis of 19 studies, have largely shown that achievement of MRD negativity before HSCT is associated with superior post-HSCT outcomes. In contrast, we found that MRD response after salvage chemotherapy or immediately before HSCT did not affect relapse rates or survival after HSCT. Our finding is consistent with another retrospective report that showed no difference in post-HSCT outcomes according to pre-HSCT MRD status (measured by MFC) in patients with relapsed or refractory AML. There are also emerging data that a myeloablative conditioning regimen may overcome the poor prognostic impact of pre-HSCT MRD when HSCT is performed in first remission, although similar analyses in patients in second remission or beyond are lacking. One limitation of our study is that the number of patients with pre-HSCT MRD information available was relatively small (n = 59), with only 9 patients who were MRD positive before HSCT; it was therefore not possible to perform meaningful subgroup analyses evaluating the interaction between conditioning regimen and pre-HSCT MRD status. One recent study has suggested that myeloablative and reduced-intensity

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**Figure 4.** Outcomes of patients achieving CRMRD vs lesser responses. CIR (A), RFS (B), and OS (C) for the entire cohort, stratified according to CRMRD vs lesser responses.
conditioning regimens result in similar survival outcomes in patients who undergo transplant in second remission.\textsuperscript{30} Further analyses integrating both conditioning intensity and MRD status in the salvage setting are therefore warranted. When comparing our results vs those of other reported studies on the impact of pre-HSCT MRD, it is important to note that most of these other studies were limited to patients who underwent transplant in first remission or combined patients who underwent transplant in first or later remissions in their analysis. However, AML disease biology is significantly different in patients who have not responded to or who relapsed after frontline therapy and is characterized by increased clonal complexity and chemoresistance.\textsuperscript{31} We therefore hypothesize that patients who achieve “MRD negativity” after frontline therapy and those who seemingly achieve the same response after salvage chemotherapy likely possess very different quantities of residual disease that are present below the level of detection of the MRD assay (in our study, sensitivity of at least 0.1%). This could similarly explain why patients in our study who were able to proceed to HSCT had similar post-HSCT outcomes, regardless of response to salvage chemotherapy. It is very possible that in the relapsed/refractory setting in which the disease is generally more chemoresistant, the difference in total quantity of residual disease between patients who are “MRD negative” and “MRD positive” is less pronounced than in the frontline setting, and these differences therefore may be more easily negated by HSCT. Additional studies using ultrasensitive MRD assays would be needed to better characterize and quantify the true level of residual disease that persists after chemotherapy, how these differ between frontline and relapsed/refractory patients, and how these very small amounts of residual disease affect outcomes after HSCT. Such an approach will be particularly important in the frontline setting in which deep MRD-negative responses identified by using highly sensitive assays may help to inform the decision for HSCT in first remission.

There are several important implications of our findings. First, the strong and independent impact of both CR and MRD negativity on risk of relapse and RFS support the use of CR\textsubscript{MRD}–as a valuable end point for clinical trials in patients with relapsed/refractory AML, which may allow for more rapid clinical evaluation and approval of novel agents. Although the impact of achieving CR\textsubscript{MRD}–was not statistically associated with OS (2-year OS rate, 37% vs 21%; \(P = .10\)), there was a strong trend toward better OS in patients who achieved CR\textsubscript{MRD}–, with these patients having nearly twice the 2-year OS rate as those with lesser responses. The lack of a significant difference may be in part due to the increasing availability of effective salvage regimens for these patients, including the development of novel FMS-like tyrosine kinase 3 inhibitors (eg, gilteritinib), IDH1 and IDH2 inhibitors (eg, ivosidenib and enasidenib), and venetoclax-based regimens, which became available in clinical trials and commercially over the study period.\textsuperscript{32} However, it remains possible that with a larger cohort of patients, an OS benefit might have been observed, which would further support the importance of CR\textsubscript{MRD}– in this context. Our findings that hematologic recovery and MRD status do not significantly affect post-HSCT outcomes also inform the optimal timing of HSCT in the salvage setting. In contrast with the frontline setting, where outcomes after HSCT are significantly better in patients who achieve MRD negativity, we found no difference in post-HSCT outcomes according to response to salvage chemotherapy or pre-HSCT MRD. Our data therefore suggest that, whenever possible, immediate HSCT should be considered for any patient with relapsed/refractory AML who achieves a marrow remission, regardless of hematologic recovery or MRD response. In light of the high rates of early relapse in patients who achieve only CR/MLFS and/or MRD positivity, our findings argue against a practice of attempting to administer additional cycles of chemotherapy in an effort to deepen a patient’s response before undergoing HSCT in the salvage setting; this may sometimes be necessary, however, when HSCT is not yet available.

In conclusion, among patients with relapsed/refractory AML receiving first salvage chemotherapy, both CR and MRD negativity were independently associated with a lower risk of relapse and longer RFS. Patients who achieved CR\textsubscript{MRD}– had the best outcomes, which were driven in part by an increased ability to undergo subsequent HSCT. Given the superior outcomes in patients who achieve CR\textsubscript{MRD}–, this response end point should be considered in clinical trials evaluating novel agents and combinations in relapsed/refractory AML.

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Authorship

Contribution: N.J.S., H.R., and F.R. designed the study, collected and analyzed the data, and wrote the manuscript; H.H. and J.N. performed statistical analyses; J.L.J. and S.A.W. performed MRD analyses; N.D., J.C., T.M.K., C.D.D., E.J., U.P., B.O., M.K., M.Y., G.C.I., and H.K. treated patients; and all authors reviewed and approved the manuscript.

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