ARTICLE

ACUTE MYELOID LEUKEMIA

Impact of pre-transplant induction and consolidation cycles on AML allogeneic transplant outcomes: a CIBMTR analysis in 3113 AML patients

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We investigated the impact of the number of induction/consolidation cycles on outcomes of 3113 adult AML patients who received allogeneic hematopoietic cell transplantation (allo-HCT) between 2008 and 2019. Patients received allo-HCT using myeloablative (MAC) or reduced-intensity (RIC) conditioning in first complete remission (CR) or with primary induction failure (PIF). Patients who received MAC allo-HCT in CR after 1 induction cycle had 1.3-fold better overall survival (OS) than 2 cycles to CR and 1.47-fold better than ≥3 cycles. OS after CR in 2 or ≥3 cycles was similar. Relapse risk was 1.65-fold greater in patients receiving ≥3 cycles to achieve CR. After RIC allo-HCT, the number of induction cycles to CR did not affect OS. Compared to CR in 1 cycle, relapse risk was 1.24-1.41-fold greater in patients receiving 2 or ≥3 cycles. For patients receiving only 1 cycle to CR, consolidation therapy prior to MAC allo-HCT was associated with improved OS vs. no consolidation therapy. Detectable MRD at the time of MAC allo-HCT did not impact outcomes while detectable MRD preceding RIC allo-HCT was associated with an increased risk of relapse. For allo-HCT in PIF, OS was significantly worse than allo-HCT in CR after 1–3 cycles.

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INTRODUCTION

The goal of intensive induction chemotherapy in patients with newly diagnosed acute myeloid leukemia (AML) is complete remission (CR) with restoration of a normal bone marrow function. Attainment of a CR is an important first step in the treatment of AML. CR using intensive induction chemotherapy is achieved in 60–80% of younger adults and in 40–60% of adults over 60 years [1, 2]. Post-remission strategies for patients that achieve CR include consolidation chemotherapy and for some, allogeneic hematopoietic cell transplantation (allo-HCT) [3, 4]. Allo-HCT is also the only curative options for patients with primary induction failure (PIF) after induction chemotherapy. Despite the intensification of therapy with allo-HCT, the 3-year overall survival (OS) published in 2010 for patients who received allo-HCT in PIF between 1995 and 2004 reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) was only 19% [5].

The decision to perform allo-HCT is based on cytogenetic and molecular genetic features as well as patient's age, performance status, and donor availability [4]. Advances in limiting the toxicity of conditioning regimens, managing graft-versus-host disease (GVHD), and new donor options have widened the pool of AML patients who are eligible for allo-HCT.

Leukemia relapse and non-relapse mortality (NRM) are the major obstacles for successful allo-HCT. The number of induction cycles to achieve CR plus the number of post-CR consolidation cycles and the disease status at the time of allo-HCT may influence both NRM and post allo-HCT relapse rates. Higher risk leukemia may require multiple induction therapies to achieve CR and thus might have higher post allo-HCT relapse rates. In addition, extended induction treatments may result in end-organ damage or infection leading to greater susceptibility to post-allo-HCT complications and higher NRM.

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We investigated the impact of the number of induction and consolidation cycles on the outcomes of allo-HCT in 3113 AML patients reported to the CIBMTR.

METHODS

Data sources

This study was conducted through the CIBMTR, a collaborative research effort between the National Marrow Donor Program/Be the Match Registry and the Medical College of Wisconsin. Over 450 centers around the world contribute detailed clinical, pathological, and outcomes data to CIBMTR. All patients included in this study signed written, informed consent for data capture in the CIBMTR database.

Patient selection

Patients with AML who were ≥18 year old and underwent allo-HCT in first CR or allo-HCT with PIF receiving either myeloablative (MAC) or reduced-intensity (RIC) conditioning between 2008 and 2019 were studied. Peripheral blood, bone marrow, and umbilical cord blood (UCB) grafts and all related donor and unrelated donor (URD) types were included with a total of 3113 patients. Patients who received only hypomethylating agents ($n = 78$) to achieve CR, or had ex vivo T cell depletion ($n = 163$) were excluded as were patients who were missing pre-HCT blast counts, number of induction and consolidation cycles, or pre-HCT disease status information (Supplementary Table 1). CIBMTR consensus criteria were used to define the conditioning intensity as MAC or RIC [6]. Cytogenetic risks of AML were classified as described previously [7]. CR was defined as absolute neutrophil count ≥1000/μl and platelet count ≥100,000/μl along with no peripheral blasts and <5% blasts on morphologic assessment of the bone marrow. CRi was defined as <5% blast percentage in the marrow, but incomplete recovery of peripheral blood neutrophils or platelets. PIF was defined as failure to achieve initial CR after 2 induction cycles [8]. In the current study, 35% of the patients reported had undergone allo-HCT using MAC or RIC in PIF after receiving only 1 cycle of induction chemotherapy; thus this analysis of PIF included failure to achieve CR after 1 or ≥2 induction cycles. Pre allo-HCT measurable residual disease (MRD) was reported from transplant centers using institutional flow cytometry, cytogenetic or molecular testing. The vast majority (>90%) of patients did not receive post allo-HCT maintenance therapy.

Study endpoints

Clinical outcomes included non-relapse mortality (NRM), incidence of relapse, disease-free survival (DFS), and overall survival (OS). NRM was defined as the time from allo-HCT to death from any cause without evidence of AML relapse, considering relapse as a competing event. Relapse was defined as recurrence of AML after allo-HCT, and death in remission was considered a competing event. DFS was defined as the time to relapse of AML or death from any cause, and OS was defined as the time from HCT to death from any cause. Surviving patients were censored at the time of last follow-up.

Statistical analysis

The primary question addressed the number of induction cycles and consolidation therapies prior to allo-HCT analyzing outcomes in CR and PIF patients. Since the development of reduced-intensity regimens has made the use of allo-HCT accessible to older patients, MAC and RIC were analyzed separately as various demographic (age and other factors) differed substantially between the two cohorts. For allo-HCT during PIF, because post allo-HCT CR was not always confirmed, the incidence of relapse, NRM, or DFS could not be reliably calculated and OS was reported. Univariable analysis of OS and DFS was performed using the Kaplan–Meier method. Cumulative incidence of NRM and relapse were calculated while accounting for competing risks and were compared using Gray's method. Multivariable analysis (MVA) was performed using the Cox proportional hazards model to adjust for patient-, disease-, and transplant-related factors. Clinically relevant covariates considered in the Cox models included age at HCT, sex, race, Karnofsky performance score (KPS), hematopoietic cell transplantation comorbidity index (HCT-CI), cytogenetic risk group, MRD status, de novo vs. transformed vs. therapy-related AML, conditioning intensity/regimen, donor type, donor age, donor and recipient cytomegalovirus status, graft type, GVHD prophylaxis and year of transplant. The proportional hazards assumption was tested for the main effect. The number of induction cycles to CR was retained in all models as the main effect. Covariates that were identified as significant ($p < 0.01$) with a stepwise model selection procedure were used in the final models. Interactions between the main effect and significant covariates were tested. Analyses were performed using SAS version 9.4 (Cary, NC, USA).

RESULTS

Outcomes of AML patients in CR with myeloablative conditioning allo-HCT

AML patients in first CR ($n = 1473$) received MAC allo-HCT and Table 1 shows their demographic and clinical characteristics. Eight hundred sixty-two patients (median age 48 years, range 18–81) achieved CR after 1 cycle of induction chemotherapy; 454 (median age 47 years, range 18–72) achieved CR after 2 cycles, while 157 (median age 46 years, range 19–70) achieved CR after ≥3 cycles of induction chemotherapy.

A total of 64% of patients had HCT-CI 0–2, and 68% had KPS ≥90%. Well-matched URD (39%) and HLA-identical sibling donor (32%) were the predominant donor types for the MAC allo-HCT. Graft sources were mobilized peripheral blood stem cells (PBSC) (70%), bone marrow (18%) and UCB (12%). European Leukemia Net (ELN) risk classification was only available in 766 (42%) patients. Cytogenetic scores (available in 97%) showed that 95% had intermediate (65%) or high risk (30%) cytogenetics.

Patients who achieved CR after 1 cycle of induction chemotherapy had 3-year probabilities of relapse of 26.5% (95% CI, 23.6–29.6%) vs. 31% (26.8–35.4%) in CR patients receiving 2 induction cycles and 41.3% (33.5–49.3%) in CR patients after ≥3 cycles ($p < 0.001$). Corresponding 3-year probabilities of NRM were: 1 cycle CR 15.5% (95% CI, 13.1–18.1%); 2 cycles CR 20.7% (17–24.6%); and ≥3 cycles CR 14.8% (9.7–20.9%) ($p = 0.009$). Univariate analyses for OS, DFS, relapse and NRM by induction cycle number and post-transplant years are shown in Supplementary Table 2.

Multivariate analysis demonstrated that achieving CR after 1 cycle led to higher OS vs. 2 cycles (HR 1.32, 95% CI 1.11–1.56, $p < 0.01$) or ≥3 cycles (HR 1.47, 95% CI 1.16–1.87, $p < 0.01$). OS after 2 cycles or ≥3 cycles were similar (HR 1.12 95% CI 0.87–1.4, $p = 0.38$) (Table 2A and Fig. 1A). Multivariate analysis also demonstrated that relapse risk was greater in those receiving ≥3 cycles to achieve CR ($p < 0.01$) (Table 2A and Fig. 1B). Higher NRM was observed in patients receiving 2 vs. only 1 cycle to CR (HR 1.34, 95% CI 1.05–1.72, $p < 0.02$) (Table 2A and Fig. 1C).

Twenty percent of patients after 1 cycle were in CRi at the time of allo-HCT, 24% after 2 cycles and 26% after ≥3 cycles. Multivariate analysis demonstrated no statistically significant differences in OS, NRM and relapse between the CR or CRi patients receiving one or more induction cycles (data not shown).

Outcomes of AML patients in CR with reduced-intensity conditioning allo-HCT

AML patients in first CR ($n = 1162$) received RIC allo-HCT and Table 3 shows their demographic and clinical characteristics. Seven hundred fourteen patients (median age 62 years, range 18–78) achieved CR after 1 cycle of induction chemotherapy; 310 (median age 62, range 18–76) achieved CR after 2 cycles; while 138 (median age 64 years, range 22–80) achieved CR after ≥3 cycles. Fifty-two percent had HCT-CI 0–2, and 55% had KPS ≥90%. Well-matched URD (36%) and HLA-identical sibling donor (23%) were the predominant donor types for the RIC allo-HCT. Graft sources were mobilized PBSC (69%), UCB (18%) and bone marrow (13%). Sixty-nine percent of patients had intermediate risk and 31% had poor risk cytogenetics. MRD was detectable pre-HCT in 22-37% of the 3 CR cohorts. ELN classification was available in only 741 (56%) patients.

For patients who achieved CR with 1 cycle of induction, the 3-year probabilities of relapse were 36.4% (95% CI, 32.8–40%) vs.

Table 1. Characteristics of AML patients receiving myeloablative allo-HCT in PIF or CR.

Characteristic	PIF	CR1 w/ 1 cycle	CR1 w/ 2 cycles	CR1 w/ ≥3 cycles
No. of patients	328	862	454	157
No. of centers	94	109	105	66
Age at HCT, *n* (%)				
Median (min–max)	51 (18–82)	48 (18–81)	47 (18–72)	46 (19–70)
18–29	44 (13)	116 (13)	83 (18)	35 (22)
30–39	42 (13)	144 (17)	75 (17)	25 (16)
40–49	65 (20)	218 (25)	107 (24)	36 (23)
50–59	105 (32)	282 (33)	142 (31)	38 (24)
60–69	68 (21)	96 (11)	46 (10)	23 (15)
≥70	4 (1)	6 (1)	1 (0)	0 (0)
Recipient sex, *n* (%)				
Male	174 (53)	417 (48)	238 (52)	85 (54)
Female	154 (47)	445 (52)	216 (48)	72 (46)
Race, *n* (%)				
White	267 (81)	705 (82)	386 (85)	123 (78)
Other	61 (19)	157 (18)	68 (15)	34 (22)
Karnofsky score, *n* (%)				
<90	174 (53)	260 (30)	156 (34)	41 (26)
≥90	148 (45)	588 (68)	292 (64)	116 (74)
Missing	6 (2)	14 (2)	6 (1)	0 (0)
HCT-CI, *n* (%)				
0	85 (26)	253 (29)	130 (29)	44 (28)
1–2	84 (26)	291 (34)	141 (31)	53 (34)
3+	153 (47)	314 (36)	180 (40)	59 (38)
Missing	6 (2)	4 (0)	3 (1)	1 (1)
Clinical onset of AML, *n* (%)				
De novo	190 (58)	691 (80)	384 (85)	123 (78)
Transformed from MDS/MPN	121 (37)	101 (12)	46 (10)	25 (16)
Therapy related	17 (5)	70 (8)	24 (5)	9 (6)
White blood count at diagnosis, *n* (%)				
Median (min–max)	6 (0–399)	11 (0–409)	6 (0–334)	10 (0–271)
Cytogenetic score, *n* (%)				
Favorable	8 (2)	38 (4)	13 (3)	2 (1)
Intermediate	179 (55)	584 (68)	261 (57)	106 (68)
Poor	132 (40)	221 (26)	172 (38)	45 (29)
Missing	9 (3)	19 (2)	8 (2)	4 (3)
Time from diagnosis to HCT, *n* (%)				
Median (range)	4 (1–173)	4 (2–31)	4 (2–23)	5 (3–34)
<6 months	262 (80)	709 (82)	366 (81)	102 (65)
6–12 months	54 (16)	143 (17)	82 (18)	47 (30)
>12 months	12 (4)	10 (1)	6 (1)	8 (5)
Time to achieve CR1, *n* (%)				
Median (range)	–	4 (1–8)	8 (4–37)	17 (8–111)
≤4 weeks	–	332 (39)	0 (0)	0 (0)
4–8 weeks	–	530 (61)	210 (46)	0 (0)
>8 weeks	–	0 (0)	244 (54)	157 (100)
Blasts in pre-HCT bone marrow, median (range)[a]	8 (0–94)	1 (0–4)	1 (0–4)	1 (0–4)
Pre-HCT status, *n* (%)				
CR	–	685 (79)	339 (75)	110 (70)
CRi	–	172 (20)	111 (24)	41 (26)
Missing	–	5 (1)	4 (1)	6 (4)

Table 1. continued

Characteristic	PIF	CR1 w/ 1 cycle	CR1 w/ 2 cycles	CR1 w/ ≥3 cycles
Measurable residual disease (MRD) pre HCT, *n* (%)				
Negative	–	634 (74)	326 (72)	108 (69)
Positive	–	178 (21)	100 (22)	32 (20)
Missing	–	50 (6)	28 (6)	17 (11)
Initial induction therapy, *n* (%)				
7 + 3 ± other	257 (78)	790 (92)	422 (93)	135 (86)
High-dose cytarabine	4 (1)	16 (2)	3 (1)	2 (1)
Hypomethylating agent + other	22 (7)	1 (0)	1 (0)	7 (4)
Other	45 (14)	55 (6)	28 (6)	13 (8)
Total cycles of induction, *n* (%)				
1	113 (34)	862 (100)	0 (0)	0 (0)
2	97 (30)	0 (0)	454 (100)	0 (0)
3+	118 (36)	0 (0)	0 (0)	157 (100)
Total cycles of consolidation, *n* (%)				
0	328 (100)	183 (21)	233 (51)	134 (85)
1	0 (0)	308 (36)	125 (28)	12 (8)
2	0 (0)	216 (25)	64 (14)	9 (6)
3+	0 (0)	155 (18)	32 (7)	2 (1)
Total cycles: induction + consolidation therapy, *n* (%)	97 (30)	308 (36)	233 (51)	0 (0)
Median	2	2	2	3
1	113 (34)	183 (21)	0 (0)	0 (0)
2	97 (30)	308 (36)	233 (51)	0 (0)
3	65 (20)	216 (25)	125 (28)	80 (51)
4	32 (10)	105 (12)	64 (14)	35 (22)
5+	21 (6)	50 (6)	32 (7)	42 (27)
Conditioning regimen, *n* (%)				
TBI/Cy ± Flu	61 (19)	180 (21)	107 (24)	33 (21)
TBI ± Flu ± other	47 (14)	77 (9)	31 (7)	10 (6)
Bu/Cy	102 (31)	284 (33)	158 (35)	46 (29)
Flu/Bu ± other	93 (28)	299 (35)	144 (32)	64 (41)
Flu/Mel ± other	5 (2)	16 (2)	7 (2)	1 (1)
Other	20 (6)	6 (1)	7 (2)	3 (2)
Donor type, *n* (%)				
HLA-identical sibling	98 (30)	288 (33)	141 (31)	47 (30)
Haploidentical	33 (10)	76 (9)	32 (7)	7 (4)
Well-matched unrelated (8/8)	129 (39)	329 (38)	185 (41)	64 (41)
Mis-matched unrelated (≤7/8)	35 (11)	64 (7)	48 (11)	19 (12)
Cord blood	33 (10)	105 (12)	48 (11)	20 (13)
Graft type, *n* (%)				
Bone marrow	45 (14)	160 (19)	81 (18)	25 (16)
Peripheral blood	250 (76)	597 (69)	325 (72)	112 (71)
Cord blood	33 (10)	105 (12)	48 (11)	20 (13)
GVHD prophylaxis, *n* (%)				
Tac or CSA based with ATG/alemtuzumab	74 (23)	174 (20)	97 (21)	49 (31)
Tac or CSA based without ATG/alemtuzumab	209 (64)	581 (67)	315 (69)	94 (60)
Post HCT-Cy	36 (11)	101 (12)	42 (9)	13 (8)
Missing	9 (3)	6(0)	0 (0)	1 (1)
Year of HCT, *n* (%)				
2008–2013	197 (60)	454 (53)	269 (59)	97 (62)
2014–2019	131 (40)	408 (47)	185 (41)	60 (38)
Follow-up, median (range)	58 (3–121)	54 (3–126)	60 (3–124)	58 (3–122)

CRi CR with incomplete count recovery.
[a]49/328 (15%) of PIF patients had 0–5% blasts in the bone marrow, but had circulating blasts.

Table 2. **A** Multivariate analysis—AML patients receiving myeloablative allo-HCT, **B** Overall survival and non-relapse mortality by total number of induction plus consolidation cycles in CR patients.

	HR (95% CI)	*p* value
A		
Overall survival[a]		
PIF vs. CR1, 1 cycle	2.41 (2.02–2.87)	<0.01
PIF vs. CR1, 2 cycles	1.83 (1.51–2.21)	<0.01
PIF vs. CR1, 3+ cycles	1.63 (1.27–2.11)	<0.01
CR1, 2 cycles vs. CR1, 1 cycle	1.32 (1.11–1.56)	<0.01
CR1, 3+ cycles vs. CR1, 1 cycle	1.47 (1.16–1.87)	<0.01
CR1, 3+ cycles vs. CR1, 2 cycles	1.12 (0.87–1.44)	0.38
Non-relapse mortality[b]		
CR1, 2 cycles vs. CR1, 1 cycle	1.34 (1.05–1.72)	0.02
CR1, 3+ cycles vs. CR1, 1 cycle	1.09 (0.73–1.65)	0.67
CR1, 3+ cycles vs. CR1, 2 cycles	0.81 (0.53–1.25)	0.34
Relapse[c]		
CR1, 2 cycles vs. CR1, 1 cycle	1.19 (0.97–1.46)	0.10
CR1, 3+ cycles vs. CR1, 1 cycle	1.65 (1.26–2.16)	<0.01
CR1, 3+ cycles vs. CR1, 2 cycles	1.39 (1.05–1.86)	0.02
Disease-free survival[d]		
CR1, 2 cycles vs. CR1, 1 cycle	1.24 (1.05–1.45)	0.01
CR1, 3+ cycles vs. CR1, 1 cycle	1.42 (1.13–1.78)	<0.01
CR1, 3+ cycles vs. CR1, 2 cycles	1.15 (0.90–1.46)	0.26
B		
Overall survival		
Number of cycles		
1 cycle induction vs. 1 cycle induction plus ≥1 consolidation cycles	1.57 (1.24–1.99)	<0.01
2 or more induction cycles vs. 1 cycle induction plus ≥1 consolidation cycles	1.01 (0.81–1.26)	0.94
Non-relapse mortality		
Number of cycles		
1 cycle induction vs. 1 cycle induction plus ≥1 consolidation cycles	1.36 (0.95-1.96)	0.10
2 or more induction cycles vs. 1 cycle induction plus ≥1 consolidation cycles	0.94 (0.66-1.35)	0.75

[a]Adjusted for age, HCT-CI, conditioning regimen, AML onset, cytogenetic risk.
[b]Adjusted for age, HCT-CI, conditioning regimen.
[c]Adjusted for cytogenetic risk.
[d]Adjusted for age, HCT-CI, conditioning regimen, AML onset, cytogenetic risk, race.

46.1% (40.4–51.8%) in CR patients receiving 2 induction cycles and 46.1% (37.7–54.7%) in CR patients after ≥3 cycles ($p < 0.001$). Cycles to CR did not influence 3-year NRM with: 1 cycle CR 20.9% (95% CI, 17.9–24%); 2 cycles CR 19.1% (14.9–23.8%); and ≥3 cycles CR 22.3% (15.6–29.7%) ($p = 0.25$). Univariate analyses for OS, DFS, relapse and NRM by induction cycle number and post-transplant years are shown in Supplementary Table 3.

After RIC allo-HCT, multivariate analysis demonstrated that the number of induction cycles did not significantly influence either OS or NRM (Fig. 2A, C). Relapse risk was greater in patients requiring ≥2 cycles to achieve CR vs. those with only 1 cycle to CR (Table 4A and Fig. 2B).

Twenty-nine percent of patients after 1 cycle were in CRi at the time of HCT, 32% after 2 cycles and 34% after ≥3 cycles. Multivariate analysis demonstrated no statistically significantly differences in OS, NRM or relapse between the CR or CRi patients receiving one or more induction cycles (data not shown).

Effect of post-remission consolidation therapy before allo-HCT

The use of consolidation therapy in MAC allo-HCT recipients that received 1 cycle to achieve CR was associated with improved OS vs. no consolidation therapy (HR 1.57, 95% CI 1.24–1.99, $p < 0.01$). However, for MAC allo-HCT recipients receiving 2 or ≥3 induction cycles to CR, the addition of consolidation therapy had no impact on post allo-HCT NRM compared to patients receiving only 2+ cycles of induction therapy (HR 0.94, 95% CI 0.66–1.35–1.72, $p \leq 0.75$) (Table 2B). After RIC allo-HCT, 2 or more induction cycles combined with or without consolidation therapy did not influence either OS or NRM (Table 4B).

Effect of MRD on outcomes

MRD status determined at each HCT center was available in 1378 (94%) patients who received MAC allo-HCT. Detectable MRD was noted pre-HCT in 21% of those in CR. MRD status at the time of MAC allo-HCT did not have an independently significant impact on OS (HR 1.01, $p = 0.91$), NRM (HR 1.01, $p = 0.95$) or relapse incidence (HR 1.04, $p = 0.77$).

MRD status was available in 1097 (95%) patients who received RIC allo-HCT. Detectable MRD was noted pre-HCT in 27 % of those in CR. Pre-HCT detectable MRD at the time of RIC allo-HCT was associated with a significantly increased risk of relapse (HR 1.35 (1.10–1.65), $p = 0.037$. MRD status at the time of RIC allo-HCT did

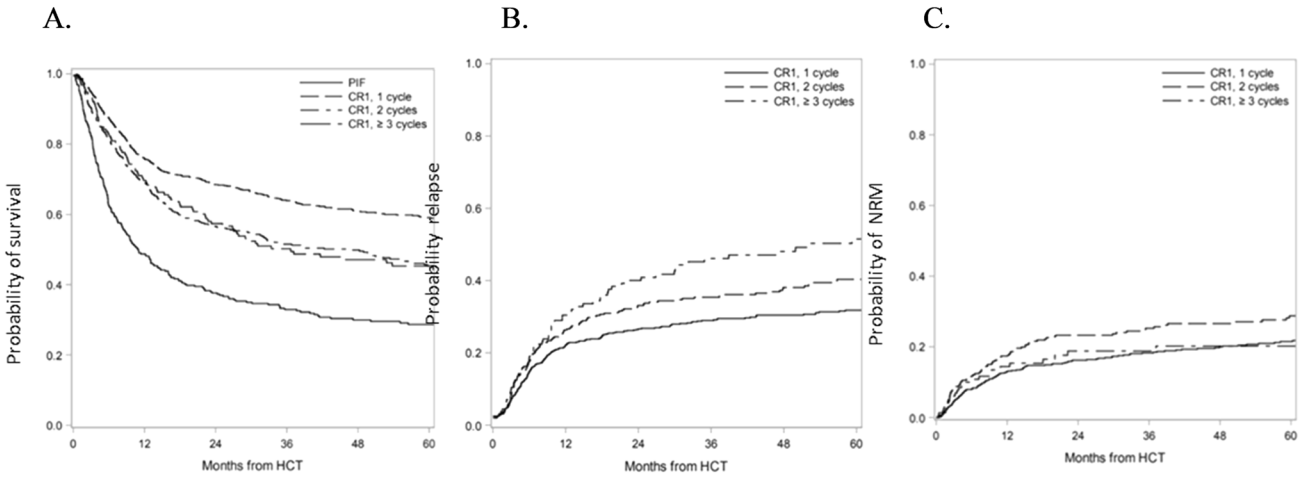

Fig. 1 AML patients in CR ($n = 1473$; 862 after 1 cycle, 454 after 2 cycles, 157 after ≥3 cycles) and in PIF ($n = 328$) with myeloablative conditioning. A Patients achieving CR after 1 cycle of induction chemotherapy had better overall survival (OS) compared to patients requiring 2 or more cycles ($p < 0.01$). Patients undergoing HCT in PIF had worse OS vs. those in CR ($p < 0.01$). **B** Relapse was higher in patients needing ≥3 cycles to achieve CR. **C** Higher NRM was observed in patients receiving 2 vs. only 1 cycle to achieve CR ($p < 0.02$).

not have an independently significant impact on OS (HR 1.09, $p > 0.63$) or NRM (HR 0.93, $p > 0.38$).

AML patients in primary induction failure (PIF) with MAC or RIC conditioning allo-HCT

Patient population. A total of 478 AML patients received allo-HCT after PIF; 328 patients with MAC (median age of 51 years, range 18-82). Thirty four percent of patients received only 1 induction cycle prior to HCT during PIF, while 30% received 2 cycles and 36% ≥3 cycles of induction chemotherapy (Table 1). Fifty-two percent of those in PIF had HCT-CI 0–2, and only 47% had KPS ≥90%. Well-matched URD (39%) and HLA-identical sibling donor (30%) were the predominant donor types for the MAC allo-HCT. Graft sources were mobilized PBSC (76%), followed by bone marrow (14%) and UCB (19%). Fifty-five percent had intermediate risk and 40% poor risk cytogenetics.

One hundred fifty PIF patients received RIC (median age 65 years, range 19-75). Thirty-seven percent received only 1 induction cycle prior to allo- HCT, 27% 2 cycles and 36% ≥3 cycles of induction chemotherapy (Table 3). Forty-nine percent had HCT-CI 0–2, and only 42% KPS ≥90%. Well-matched URD (41%) and HLA-identical sibling donor (27%) were the predominant donor types for the RIC allo- HCT. Graft sources were mobilized PBSC (76%), bone marrow (14%) and UCB (10%). 62% of patients had intermediate risk and 35% poor risk cytogenetics.

Outcomes. After MAC HCT, 3-year probability of OS was 30% (95% CI, 25.1–35.1%, Supplementary Table 2) and after RIC the 3-year probability of OS was 26.3% (95% CI, 19.1–34.2%, Supplementary Table 3) ($p = 0.43$).

Outcomes of CR vs. PIF patients

After MAC, OS was significantly worse in PIF patients compared to any patients that achieved CR after ≥1 induction cycles ($p < 0.01$) (Table 2 and Fig. 1A). After RIC, OS were significantly worse in PIF patients compared to patients that achieved CR after 1 or 2 induction cycles (Table 4 and Fig. 2A).

DISCUSSION

We have quantitatively evaluated the impact of the pre-transplant number of induction and consolidation cycles on post allo-HCT AML outcomes. In the current study, we demonstrate that achieving CR after 1 induction cycle in MAC allo-HCT recipients is associated with superior OS, relapse, and NRM compared to allo-HCT in CR achieved after 2 or more induction cycles. In addition, allo-HCT recipients who received consolidation therapy prior to allo-HCT had improved OS. Among RIC allo-HCT recipients, induction chemotherapy beyond cycle 1 was associated with increased relapse risk, independent of MRD, which was also associated with relapse risk. The number of induction and consolidation cycles did not influenced OS or NRM in patients receiving RIC allo-HCT. Allo-HCT in PIF is done less often due to various selection factors determined at each center. We find that achieving CR with any number of induction cycles conferred superior allo-HCT outcomes as compared to allo-HCT after PIF.

The prognostic impact of early remission achievement after 1 or 2 cycles without allo-HCT has been examined using data from cooperative group trials. Rowe et al. reported outcomes of 1980 newly diagnosed patients with AML registered in six consecutive Eastern Cooperative Oncology Group (ECOG) AML studies between 1983 and 1993 [9]. The 5- and 10-year DFS and OS for each study was not significantly affected by the need for either 1 or 2 cycles to achieve a CR. In contrast, data from 1711 patients in the Medical Research Council (MRC) AML 10 trial, which included double induction chemotherapy regimens, showed that patients who achieved a CR with the first induction cycle were less likely to relapse than those requiring 2 cycles of therapy to achieve CR [10]. Othus et al. analyzed 1247 newly diagnosed AML patients randomized to the 7 + 3 treatment arms of five Southwest Oncology Group (SWOG) trials between 1983 and 2015. In the more recent SWOG trials, those who achieved remission after the first cycle of 7 + 3 chemotherapy had better survival than those needing 2 cycles of chemotherapy to achieve CR, even after adjustment for other risk factors [11].

The number of induction cycles influencing post allo-HCT outcomes was investigated by Walter et al. in 220 consecutive adults with AML transplanted in first CR following MAC or non-ablative conditioning [12]. Survival was significantly worse with >2 induction courses and relapse was worse ≥2 induction courses. In another study, 122 patients achieving CR with one course had a DFS at 3 years of 67% post-HCT; significantly better than 44% for 47 patients needing ≥2 cycles to CR. Relapse was less with 1 cycle to CR (16 vs. 40% at 3 years), while NRM at 2 years was similar (21 vs. 27%) [13]. Nagler et al. compared outcomes of 635 adults with AML receiving haploidentical HCT in CR1 following 1 or 2 induction courses. Two-year relapse incidence was significantly higher in patients receiving 2 induction courses to achieve

Table 3. Characteristics of AML patients receiving reduced-intensity conditioning allo-HCT.

Characteristic	PIF	CR1 w/ 1 cycle	CR1 w/ 2 cycles	CR1 w/ ≥3 cycles
No. of patients	150	714	310	138
No. of centers	70	110	87	59
Age at HCT, *n* (%)				
Median (min–max)	65 (19–76)	62 (18–78)	62 (18–76)	64 (22–80)
18–29	7 (5)	31 (4)	14 (5)	3 (2)
30–39	7 (5)	27 (4)	9 (3)	2 (1)
40–49	5 (3)	69 (10)	27 (9)	9 (7)
50–59	31 (21)	169 (24)	69 (22)	27 (20)
60–69	78 (52)	347 (49)	166 (54)	71 (51)
≥70	22 (15)	71 (10)	25 (8)	26 (19)
Recipient sex, *n* (%)				
Male	97 (65)	373 (52)	187 (60)	83 (60)
Female	53 (35)	341 (48)	123 (40)	55 (40)
Race, *n* (%)				
White	112 (75)	587 (82)	267 (86)	114 (83)
Other	38 (25)	127 (18)	43 (14)	24 (17)
Karnofsky score, *n* (%)				
<90	87 (58)	300 (42)	144 (46)	64 (46)
≥90	61 (41)	404 (57)	166 (54)	71 (51)
Missing	2 (1)	10 (1)	0 (0)	3 (2)
HCT-CI, *n* (%)				
0	37 (25)	162 (23)	68 (22)	30 (22)
1–2	36 (24)	199 (28)	97 (31)	49 (36)
3+	75 (50)	343 (48)	145 (47)	59 (43)
Missing	2 (1)	10 (1)	0 (0)	0 (0)
Clinical onset of AML, *n* (%)				
De novo	67 (45)	519 (73)	221 (71)	91 (66)
Transformed from MDS/MPS	74 (49)	127 (18)	65 (21)	35 (25)
Therapy related	9 (6)	68 (10)	24 (8)	12 (9)
White blood count at diagnosis				
Median (min–max)	5 (0–230)	7 (0–1230)	5 (0–451)	5 (0–363)
Cytogenetic score, *n* (%)				
Favorable	3 (2)	27 (4)	3 (1)	1 (1)
Intermediate	93 (62)	506 (71)	192 (62)	98 (71)
Poor	53 (35)	166 (23)	112 (36)	38 (28)
Missing	1 (1)	15 (2)	3 (1)	1 (1)
Time from diagnosis to HCT, *n* (%)				
Median (min–max)	4 (2–106)	4 (1–20)	5 (2–33)	6 (3–24)
<6 months	104 (69)	550 (77)	217 (70)	73 (53)
6–12 months	41 (27)	156 (22)	83 (27)	56 (41)
>12 months	5 (3)	8 (1)	10 (3)	9 (7)
Time to achieve CR1, *n* (%)				
Median (min–max)	–	5 (1–8)	9 (4–119)	20 (9–75)
≤4 weeks	–	212 (30)	0 (0)	0 (0)
4–8 weeks	–	502 (70)	135 (44)	0 (0)
>8 weeks	–	0 (0)	175 (56)	138 (100)
Blasts in pre-HCT bone marrow, median (min–max)[a]	7 (0–100)	1 (0–4)	1 (0–4)	1 (0–4)
Pre HCT status, *n* (%)				
CR	–	495 (69)	207 (67)	89 (64)
CRi[b]	–	209 (29)	99 (32)	47 (34)
Missing	–	10 (1)	4 (1)	2 (1)

Table 3. continued

Characteristic	PIF	CR1 w/ 1 cycle	CR1 w/ 2 cycles	CR1 w/ ≥3 cycles
Measurable residual disease (MRD) pre HCT, *n* (%)				
Negative	–	515 (72)	209 (67)	80 (58)
Positive	–	160 (22)	82 (26)	51 (37)
Missing	–	39 (5)	19 (6)	7 (5)
Initial induction therapy, *n* (%)				
7 + 3 ± other	110 (73)	631 (88)	263 (85)	100 (72)
Other	40 (27)	83 (12)	47 (15)	38 (28)
Total cycles of induction, *n* (%)				
1	55 (37)	714 (100)	0 (0)	0 (0)
2	41 (27)	0 (0)	310 (100)	0 (0)
3+	54 (36)	0 (0)	0 (0)	138 (100)
Total cycles of consolidation, *n* (%)				
0	150 (100)	191 (27)	163 (53)	119 (86)
1	0 (0)	257 (36)	78 (25)	13 (9)
2	0 (0)	158 (22)	48 (15)	2 (1)
3+	0 (0)	108 (15)	21 (7)	4 (3)
Total cycles induction + consolidation therapy, *n* (%)				
Median	2	2	2	4
1	55 (37)	191 (27)	0 (0)	0 (0)
2	41 (27)	257 (36)	163 (53)	0 (0)
3	18 (12)	158 (22)	78 (25)	49 (36)
4	14 (9)	78 (11)	48 (15)	38 (28)
5+	22 (15)	30 (4)	21 (7)	51 (37)
Conditioning regimen, *n* (%)				
TBI/Cy ± Flu ± other	48 (32)	281 (39)	120 (38)	59 (43)
Flu/Bu ± other	46 (31)	251 (35)	97 (31)	50 (36)
Flu/Mel ± other	50 (33)	143 (20)	76 (25)	24 (17)
Other	6 (4)	39 (5)	17 (5)	5 (4)
Donor type, *n* (%)				
HLA-identical sibling	40 (27)	167 (23)	78 (25)	26 (19)
Haploidentical	24 (16)	110 (15)	46 (15)	19 (14)
Well-matched unrelated (8/8)	61 (41)	256 (36)	103 (33)	55 (40)
Mis-matched unrelated (≤7/8)	11 (7)	56 (8)	27 (9)	9 (7)
Cord blood	14 (9)	125 (18)	56 (18)	29 (21)
Graft type, *n* (%)				
Bone marrow	14 (9)	92 (13)	41 (13)	12 (9)
Peripheral blood	122 (81)	497 (70)	213 (69)	97 (70)
Cord blood	14 (9)	125 (18)	56 (18)	29 (21)
GVHD prophylaxis, *n* (%)				
Tac or CSA based w/ ATG/alemtuzumab	35 (23)	192 (27)	80 (26)	36 (26)
Tac or CSA based w/o ATG/alemtuzumab	86 (57)	381 (53)	175 (56)	82 (59)
Post HCT-Cy	25 (17)	125 (18)	53 (17)	19 (14)
Other	4 (2)	16 (3)	2 (0)	1 (1)
Year of HCT, *n* (%)				
2008–2013	66 (44)	297 (42)	138 (45)	58 (42)
2014–2019	84 (56)	417 (58)	172 (55)	80 (58)
Follow-up, months, median (range)	37 (3–122)	46 (3–126)	48 (3–121)	48 (3–123)

[a]31/150 (21%) of PIF patients had 0–5% blasts in the bone marrow, but had circulating blasts.
[b]*CRi* CR with incomplete count recovery.

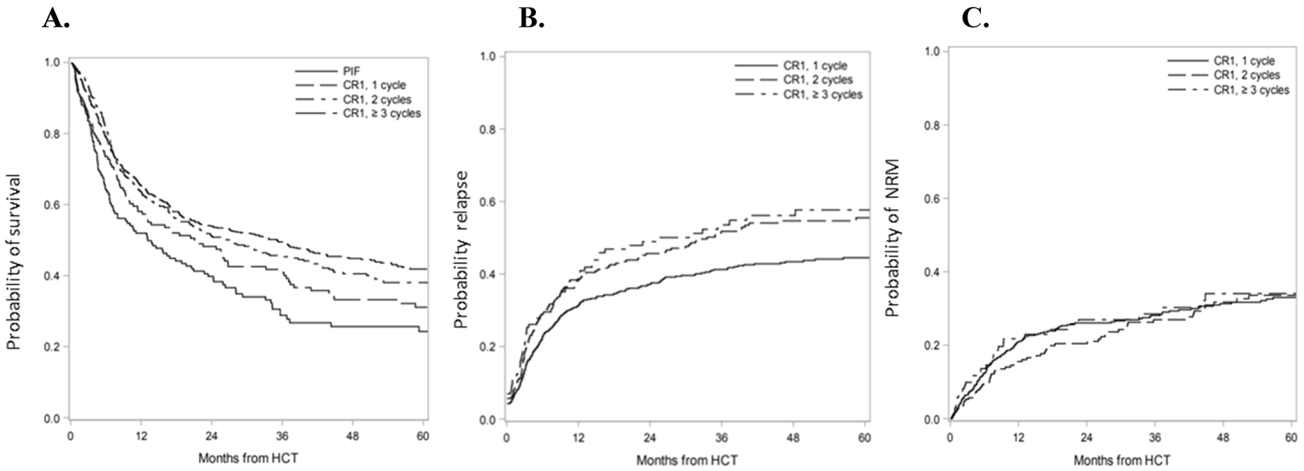

Fig. 2 AML patients in CR ($n = 1162$; 714 after 1 cycle, 310 after 2 cycles, 138 after ≥3 cycles) and in PIF ($n = 150$) with reduced-intensity conditioning. A The number of induction cycles to achieved CR did not influence OS. Patients in PIF had worse OS compared to patients in CR. **B** Relapse was more frequent in patients needing ≥2 cycles to achieve CR. **C** The number of induction cycles to achieve CR did not significantly influence NRM.

Table 4. A Multivariate analysis—AML patients receiving reduced-intensity allo-HCT, **B** Overall survival and non-relapse mortality by total number of induction and consolidation cycles in CR patients.

	HR (95% CI)	*p* value
A		
Overall survival[a]		
PIF vs. CR1, 1 cycle	1.50 (1.19–1.87)	<0.01
PIF vs. CR1, 2 cycles	1.46 (1.14–1.86)	<0.01
PIF vs. CR1, 3+ cycles	1.20 (0.90–1.60)	0.21
CR1, 2 cycles vs. CR1, 1 cycle	1.03 (0.86–1.23)	0.77
CR1, 3+ cycles vs. CR1, 1 cycle	1.24 (0.99–1.57)	0.06
CR1, 3+ cycles vs. CR1, 2 cycles	1.21 (0.94–1.56)	0.13
Non-relapse mortality[b]		
CR1, 2 cycles vs. CR1, 1 cycle	0.98 (0.74–1.30)	0.89
CR1, 3+ cycles vs. CR1, 1 cycle	1.10 (0.76–1.61)	0.61
CR1, 3+ cycles vs. CR1, 2 cycles	1.12 (0.74–1.71)	0.58
Relapse[c]		
CR1, 2 cycles vs. CR1, 1 cycle	1.24 (1.01–1.52)	0.04
CR1, 3+ cycles vs. CR1, 1 cycle	1.41 (1.07–1.85)	0.01
CR1, 3+ cycles vs. CR1, 2 cycles	1.14 (0.85–1.52)	0.39
Disease-free survival[d]		
CR1, 2 cycles vs. CR1, 1 cycle	1.14 (0.96–1.34)	0.13
CR1, 3+ cycles vs. CR1, 1 cycle	1.30 (1.05–1.62)	0.02
CR1, 3+ cycles vs. CR1, 2 cycles	1.15 (0.90–1.45)	0.26
B		
Overall survival		
Number of cycles		
1 cycle induction vs. 1 cycle induction plus ≥1 consolidation cycles	1.15 (0.92–1.43)	0.21
2 or more induction cycles vs. 1 cycle induction plus ≥1 consolidation cycles	1.04 (0.82–1.32)	0.76
Non-relapse mortality		
Number of cycles		
1 cycle induction vs. 1 cycle induction plus ≥1 consolidation cycles	1.10 (0.78–1.56)	0.57
2 or more induction cycles vs. 1 cycle induction plus ≥1 consolidation cycles	1.15 (0.88–1.49)	0.75

[a]Adjusted for age, Karnofsky score, AML onset, cytogenetic risk, graft type, year of transplant.
[b]Adjusted for age, conditioning regimen, donor type, year of transplant.
[c]Adjusted for cytogenetic risk, conditioning regimen.
[d]Adjusted for cytogenetic risk, graft type, AML onset, Karnofsky score.

CR vs. those receiving only 1 induction course with lower LFS and OS [14]. These reports are compatible with our findings that early response to induction therapy is associated with favorable post allo-HCT outcomes.

Post-remission consolidation therapy after induction decreases leukemia relapse and improves survival [15]. However, several earlier studies have demonstrated no survival advantage of post-remission consolidation therapy for AML and no significant protection against post allo-HCT relapse [16–20]. For patients receiving RIC allo-HCT, one or more induction cycles with or without consolidation therapy did not influence OS or NRM. In contrast, for patients that received MAC allo-HCT, consolidation therapy improved OS. The decision to administer consolidation and its impact could be influenced by the leukemia phenotypic risk, detectable measurable residual disease and timing of donor availability factors not fully addressable in this analysis.

Historically, patients with AML refractory to initial induction chemotherapy have dismal prognoses without allo-HCT, and the prognoses have only modestly improved with the addition of allo-HCT [5], confirmed in a more recent UK NCRI study [21]. Thus, the decision to proceed with allo-HCT in patients not in CR is multifactorial, relying substantially on patient' choice, donor availability, and the transplant center's practice, thus adding these uncontrolled uncertainly to any analyses. The current study demonstrated that allo-HCT can achieve long-term survival in 26% and 30% of PIF AML patients receiving RIC and MAC conditioning, respectively. Importantly, all outcomes of PIF AML patients were worse than those who were able to achieve a CR prior to allo-HCT. These data suggest that achieving CR remains a critical goal for all AML patients being considered for allo-HCT.

The presence of MRD prior to allo-HCT may identify patients at a higher risk of relapse [22–27].

In a meta-analysis that included 1431 AML patients, pre-transplant MRD was associated with worse leukemia-free survival, OS and cumulative incidence of relapse, but not NRM [26]. These associations were noted using variable detection methods and conditioning regimens. In the current study, after adjusting for other pertinent covariates, MRD at the time of allo-HCT after MAC HCT had no significant impact on relapse, OS, or NRM. However, detectable MRD prior to RIC conditioning was associated with increased relapse suggesting that MAC may more effectively overcome residual leukemia and limit leukemia relapse, an impact not observed with RIC allo-HCT. Heterogeneous MRD methodology at the transplant centers with varying levels of sensitivity could not be addressed in this analysis.

Several limitations of this retrospective study warrant comment. Variations in induction regimens cannot be directly addressed nor the toxicities of extended multi-cycle induction therapy which might have excluded patients from allo-HCT. Factors influencing the decision making regarding the number of consolidation cycles after CR or the choice of allo-HCT in PIF are unavailable. Finally, a potential selection bias is that we can only analyze outcomes in those receiving an allo-HCT, thus excluding PIF patients and those who achieved CR, yet did not proceed to allo-HCT.

These data have practical clinical implications. We suggest that the development of alternative induction strategies to achieve CR for resistant AML may be valuable. In addition, modified conditioning regimens might also improve the outcomes post allo-HCT and guide decisions about when to proceed with allo-HCT for AML patients not in CR.

DATA AVAILABILITY

The final analysis dataset will be posted to the CIBMTR website at https://www.cibmtr.org/ReferenceCenter/PubList/PubDsDownload/Pages/default.aspx.
CIBMTR supports accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

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AUTHOR CONTRIBUTIONS

The study was proposed by MB, revised by MB and DJW, statistical analysis by KC and M-JZ. All authors reviewed the analysis, revised the manuscript and approved the final submission. Additional contributing co-authors from the Writing Committee: A. Samer Al-Homsi, Hassan B. Alkhateeb, Yasuyuki Arai, Jean-Yves Cahn, Moussab Damlaj, Firas El Chaer, Jong Wook Lee, Hongtao Liu, Leland Metheny, Fotios V. Michelis, Pashna Munshi, Alberto Mussetti, David Rizzieri, Sachiko Seo, Leo F. Verdonck.

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COMPETING INTERESTS

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VB reports as member of the American Board of Pediatrics Pediatric Hematology/Oncology subboard; National Leader of Pediatric and AYA oncology disease section with Caris Precision Oncology Alliance. JC reports as a member Data Safety Monitoring Board with Allovir, consulting fees with advisory board membership with Jazz Pharmaceuticals, Pfizer, and Amgen; and stocks with Actinium Pharmaceuticals, Bluebird Bio/2Seventy, Dynavax Technologies, aTyr Pharma, Gamida Cell, Miragen Therapeutics, Mustang Bio, Novavax, Ovid Therapeutics, Sorrento Therapeutics, TG Therapeutics, Vaxart, and Veru. RPG reports consulting fees with Ascentage Pharma Group, BeiGene Ltd., Kite Pharma, Inc., Fusion Pharma LLC, LaJolla NanoMedical, Inc., Mingsight Pharma, Inc., Prolacta Bioscience, Inc., CStone Pharmaceuticals. Board participation on FFF Enterprises, Azca, Inc., RakFond Foundation, Antegene Biotech LLC, Stem Rad LTD; and stock or stock options with Bristol Myers. SG reports participation on advisory board with Astellas, Daiichi Sankyo, Bristol Myers Squibb, Sanofi Aventis, AstraZeneca, and Kite Pharma. MRGr reports consulting fees and/or advisory board with Abbvie, Agios/Servier, Amgen, Astellas, Blueprint Medicines, Bristol Myers Squibb, Cardinal Health, CTI Biopharma, Daiichi Sankyo, Gamida Cell, Gilead, Incyte, Invitae, Karius, Novartis, Ono Pharmaceutical, Pfizer, Pharmacosmos, Premier, Sierra Oncology, and Stemline; stock ownership in Medtronic; medical writing with Incyte, Amgen, Jazz, Janssen, Genentech/Roche; and support with Incyte, Genetech/Roche, Janssen. Shahrukh Hashmi reports honorarium for educational talks (all non-promotional, majority on "quality of life" or "survivorship") in CME accredited educational seminars/conferences. This is over the past 10 years: Pfizer, Novartis, Gilead, Sanofi, Therakos, Janssen, MSD; Relationships: No financial but only volunteer: ASTCT, WBMT, CIBMTR. GH reports grants or contracts from Incyte, Acerta/Astra Zeneca, Takeda, Jazz Pharmaceuticals, and Pharmacyclics; consulting fees from Incyte, Morphosys, Alexio n Pharmaceutcials, Karyopharm, Seattle Genetics, Janssen; participation on a Data Safety Monitoring Board or Advisory Board with Rapa Therapauetics, serves as Vice President, Kentucky Society for Clinical Oncology; Axim Biotechnologies, GW Pharmaceuticals, Cardinal Health, Clovis Oncology, Pfizer, Cellectis, CVS Health, Bluebird Bio, Biogen, Charlottes Webb, Almmune Therapeutics Inc, Medical PPTYS TR Inc, Caretrust Reit Inc, Moderna Therapeutics, Zoom. MK-D reports consulting fees with Darrchi Sankyo. HML reports honoraria for consulting fees from Jazz Pharmaceuticals, CSL Behring, Partner Therapeutics, Actinium, Pluristem, Seattle Genetics; payment or honoraria from speakers' bureau with Jazz Pharmaceuticals, Seattle Genetics, AstraZeneca; travel reimbursement from Jazz Pharmaceuticals and Seattle Genetics; honoraria for participation on a Data Safety Monitoring Board or Advisory Board with BMS-Celgene and Biosight; and stock options with Partner Therapeutics. DM reports honoraria for AstraZeneca; advisory board for Morphosys and Seagen; and research funding with Genentech, ADC therapeutics, and Karyopharm. AS is the St. Jude Children's Research Hospital site principal investigator of clinical trials sponsored by Vertex Pharmaceuticals/CRISPR Therapeutics (NCT03745287) and by Novartis (NCT04443907). The industry sponsors provide funding for the clinical trial, which includes salary support paid to AS's institution. AS has received consultant fee from Spotlight Therapeutics, Medexus Inc. and Vertex Pharmaceuticals. He has also received research funding from CRISPR Therapeutics and honoraria from Vindico Medical Education. None of these are related to the work presented in this manuscript. Kirsten Williams reports grants for immunotherapy in AML unrelated to current project with Leukemia Lymphoma Society; payment for educational seminar in lung complications of HCT with ASH; ASTCT board of directors meeting; ASH for educational seminar; patents pending for MRD test for AML and ALL unrelated to this work; and leadership roles with ASTCT, CIBMTR, and PTCTC. CH reports the National Heart, Lung, and Blood Institute receives research funding for the laboratory of Dr Hourigan from Sellas; and the National Heart, Lung, and Blood Institute receives research funding for the laboratory of Dr Hourigan from the Foundation of the NIH AML MRD Biomarkers Consortium. PK reports participation on advisory board with Kite, Pfizer, and Jazz. Marcos de Lima

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ADDITIONAL INFORMATION

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