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blood advances

Risk classification at diagnosis predicts post-HCT outcomes in intermediate-, adverse-risk, and *KMT2A*-rearranged AML

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The full-text version of this article contains a data supplement.

Key Points

- Patients with *KMT2A*-rearranged AML have post-HCT leukemia-free and overall survival rates similar to those with adverse risk AML.
- Adverse-risk AML confers a 71% higher risk of relapse and a 45% higher risk of death after HCT than intermediate-risk AML.

Little is known about whether risk classification at diagnosis predicts post-hematopoietic cell transplantation (HCT) outcomes in patients with acute myeloid leukemia (AML). We evaluated 8709 patients with AML from the CIBMTR database, and after selection and manual curation of the cytogenetics data, 3779 patients in first complete remission were included in the final analysis: 2384 with intermediate-risk, 969 with adverse-risk, and 426 with *KMT2A*-rearranged disease. An adjusted multivariable analysis detected an increased risk of relapse for patients with *KMT2A*-rearranged or adverse-risk AML as compared to those with intermediate-risk disease (hazards ratio [HR], 1.27; $P = .01$; HR, 1.71; $P < .001$, respectively). Leukemia-free survival was similar for patients with *KMT2A* rearrangement or adverse risk (HR, 1.26; $P = .002$, and HR, 1.47; $P < .001$), as was overall survival (HR, 1.32; $P < .001$, and HR, 1.45; $P < .001$). No differences in outcome were detected when patients were stratified by *KMT2A* fusion partner. This study is the largest conducted to date on post-HCT outcomes in AML, with manually curated cytogenetics used for risk stratification. Our work demonstrates that risk classification at diagnosis remains predictive of post-HCT outcomes in AML. It also highlights the critical need to develop novel treatment strategies for patients with *KMT2A*-rearranged and adverse-risk disease.

Introduction

Cytogenetic abnormalities are the most useful prognostic indicators for patients with acute myeloid leukemia (AML) and can provide insight into overall patient outcomes.[1-7] There are few studies, and no large, AML-specific studies, that analyzed how well cytogenetics at the time of diagnosis predicts outcomes after allogeneic hematopoietic cell transplant (HCT).[8,9]

The 2010 AML-Medical Research Council classification system categorized patients with AML based purely on cytogenetic characteristics as either intermediate or adverse risk.[2] One subset, patients with 11q23 translocations (site of the lysine (K)-specific methyltransferase 2A [*KMT2A*] gene), could be classified in either category, based on the translocation partner.

Translocations of 11q23 involve *KMT2A*, which encodes a histone 3, a lysine 4 methyltransferase that is involved in epigenetic regulation of transcriptional activation.[10-12] These translocations are frequently referred to as rearrangements of *MLL*, the mixed-lineage leukemia gene, as this was the name before changes in the Human Genome Organization gene nomenclature. *KMT2A* translocations are seen in patients with de novo AML, secondary AML after myelodysplastic syndrome (MDS), or therapy-related AML (tAML) after treatment with a topoisomerase II inhibitor.[13-15]

KMT2A rearrangements can occur with many translocation partners; at least 135 have been described.[16] Among the most common in adult AML are *KMT2A-AF9* t(9;11)(p22;q23), *KMT2A-ENL* t(11;19)(q23; p13.3), *KMT2A-AF6* t(6;11) (q27;q23), and *KMT2A-AF10* t(10;11) (p12;q23). Recent prognostic classification systems for AML have made distinctions between translocation partners. Some have noted that outcomes for t(9;11), and possibly for t(11;19), are similar to intermediate-risk AML, whereas all other translocation partners are classified as poor or adverse risk.[1,2]

We hypothesized that risk classification at diagnosis of patients with AML would be predictive of post-HCT outcomes among patients with intermediate- and adverse-risk disease, but that outcomes for patients with *KMT2A* rearrangement would depend on the translocation partner present. In this report, we present an analysis from the Center for International Blood and Marrow Transplant Research (CIBMTR) database comparing adult patients who underwent HCT in the first complete remission (CR1) with those with intermediate- or adverse-risk or *KMT2A*-rearranged AML, with a focus on the differences in relapse, leukemia-free survival (LFS), nonrelapse mortality (NRM), and overall survival (OS). To date, this is the largest annotated cohort of post-HCT outcomes of patients with AML and is reflective of real-world outcomes based on contemporary practice.

Methods

Data sources

This was a retrospective registry study approved and conducted through the CIBMTR. The CIBMTR is a collaborative research effort between the National Marrow Donor Program/Be the Match Registry and the Medical College of Wisconsin. More than 450 centers around the world contribute detailed clinical, pathological, and outcomes data to the CIBMTR on their patients who undergo stem cell transplant.

All patients included in this study signed a written, informed consent for data capture in the CIBMTR database. The National Marrow Donor Program Institutional Review Board approved the study. As with all CIBMTR studies, this work was performed in compliance with all applicable federal regulations pertaining to the protection of human research subjects.

Study population

Adult patients with AML aged 18 to 70 years who were in CR1 and had undergone the first HCT from 2007 through 2016 were considered for additional review (n = 8709). Patients with acute promyelocytic leukemia, favorable risk or unknown cytogenetics, syngeneic transplants, mismatched unrelated donors (<7 of 8), multiple donors, ex vivo T-cell depletion, or previous allogeneic transplants

were excluded. Data were not used for patients from whom consent for research was not obtained, whose data were associated with an embargoed center, or who did not have the appropriate data forms available (supplemental Table 1).

Manual curation (*KM*, *YZ*, *AGA*, and *RMM*) to define *KMT2A* rearrangements and the presence of additional cytogenetic abnormalities was performed on the data of 3999 patients, according to the AML-Medical Research Council 2010 classification system.[2] Chromosomal data from forms submitted on each patient were used to determine their cytogenetic classification. Images of the karyotypes and fluorescence in situ hybridization data were not available for confirmation. Patients were classified as carrying *KMT2A*-rearranged, intermediate-risk or adverse-risk AML. An additional 86 patients with favorable cytogenetics and 9 patients with an ambiguous classification were excluded.

A total of 426 patients were identified as having an 11q23 translocation, based on available cytogenetics data from the CIBMTR forms. Translocations involving 11q23 were categorized as t(6;11), t(9;11), t(10,11), or t(11;19); the remaining rearrangements for which a partner was known were categorized as "other." Patients with an 11q23 rearrangement and no information regarding translocation partner were categorized as "undefined." Manual curation for complex karyotypes (CKs) was limited by the available data, as was identification of deletion or loss of chromosomes 5, 7, and 17p.

Measurable residual disease

The CIBMTR operational definition of measurable residual disease (MRD) at the time of HCT for AML was used to define the presence or absence of MRD. During the study period, participating centers may have defined MRD by flow cytometry, cytogenetics, or molecular sequencing. Additional information on the criteria used can be found in the supplemental Information.

End points and definitions

The primary outcome was OS, defined as time from HCT to death from any cause. Secondary outcomes included LFS, defined as time to disease relapse or death from any cause; relapse, defined as the reappearance of at least 5% blasts on morphological, cytogenetic, flow, or molecular evaluation in bone marrow, blood, or an extramedullary site, per the treating center; NRM, defined as time to death without evidence of disease relapse; and a composite outcome of graft-versus-host disease (GVHD)–free, relapse-free survival (GRFS), defined as time to development of grades 3 to 4 acute GVHD, systemic therapy-requiring chronic GVHD, relapse, or death within the first 12 months after HCT.[17]

Statistical considerations

Patient- and transplant-related variables were compared using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Kaplan-Meier curves were used to estimate the probability of OS and LFS. Cumulative incidence was used to estimate the probability of relapse and NRM, with each treated as a competing risk for the other. For all 4 outcomes, patients were censored at the time of last follow-up. In addition, 95% confidence intervals (CI) were reported for all probability estimates.

A Cox proportional hazards model was built for the outcomes of relapse, NRM, LFS, and OS with the main effect of *KMT2A*-rearranged vs intermediate-risk vs adverse-risk disease. The model considered the covariates of age at time of HCT, sex, Karnofsky performance status score at time of HCT, HCT comorbidity index (HCT-CI) score, time from diagnosis to achieving CR1, time from CR1 to HCT, white blood cell (WBC) count at the time of diagnosis, de novo vs therapy-related vs secondary AML, MRD status at time of HCT, *KMT2A* subtype, year of transplant, donor type, recipient cytomegalovirus (CMV) serostatus, conditioning intensity (myeloablative [MA] with total body irradiation (TBI) vs MA with chemotherapy only vs reduced-intensity/non-MA [RIC/NMA] conditioning), use of in vivo T-cell depletion, and choice of GVHD prophylaxis. Interactions between main effect and all covariates were tested at a stringent significance level of $P < .01$, given the number of comparisons. Adjusted probabilities of outcomes were calculated with the final Cox models, stratified by main effect and weighted by the pooled sample proportion value for each prognostic factor. Imputation was not performed for missing data; only available data were analyzed. Analyses were performed in SAS, version 9.4.[18,19]

Results

Patient characteristics

Of the 8709 adult patients with AML considered for inclusion in the study, 3779 were selected as outlined in supplemental Table 1, with completeness of follow-up shown in supplemental Table 2.

Patient characteristics are shown in Table 1. A total of 426 patients with *KMT2A* rearrangement were studied, compared with 2384 patients without *KMT2A* rearrangement who had intermediate-risk disease and 969 patients without *KMT2A* rearrangement who had adverse-risk disease.

Patients with *KMT2A* rearrangement were younger, with a median age of 46, and more than half the patients presented before age 60. tAML was most frequently seen in the *KMT2A*-rearrangment group, 21% compared with 4% in the intermediate-risk group and 6% in the adverse-risk group. More patients with *KMT2A* rearrangement had been treated for breast cancer (11%, as opposed to 2% and 3% in patients with intermediate or adverse risk, respectively), and more women were diagnosed with *KMT2A*-rearranged AML whereas the other 2 groups had a slight male predominance.

Antecedent MDS was less common in patients with rearrangement in *KMT2A*, found in 6%, but was noted in 19% of the intermediate-risk group and 23% of the adverse-risk group.

Although all 3 groups achieved CR1 at similar rates, patients with adverse-risk disease more commonly required 2 inductions and were less likely to achieve CR1 within 4 weeks.

Patient characteristics by *KMT2A* translocation partner

Of the 426 patients found to have a *KMT2A* rearrangement (Table 2), 112 patients (26%) had t(9;11) and comprised the largest subtype group. Translocation t(11;19) was the next most common (62 patients, 15%), followed by t(6;11) with 41 patients (10%) and t(10;11) with 28 patients (7%). Translocation partners other than chromosomes 6, 9, 10, and 11 were detected in 47 patients (11%), designated "*KMT2A* other." An additional 136 patients had 11q23 rearrangements with an unspecified translocation partner and were categorized as "*KMT2A* undefined."

Table 1. Characteristics of study population

Characteristic	*KMT2A*	Intermediate	Adverse	*P**
Patients, n	426	2384	969	
Centers, n	112	165	141	
Patient characteristics				
Patient age at HCT, n (%)				<.001
Median (min-max)	46.4 (18.2-70)	54.5 (18-70)	55.3 (18.5-70)	
18-29	72 (17)	237 (10)	90 (9)	
30-39	70 (16)	249 (10)	97 (10)	
40-49	108 (25)	418 (18)	155 (16)	
50-59	118 (28)	730 (31)	328 (34)	
60-69	58 (14)	750 (31)	299 (31)	
Sex, n (%)				<.001
Male	179 (42)	1222 (51)	532 (55)	
Female	247 (58)	1162 (49)	437 (45)	
Karnofsky score, n (%)				.004
<90	136 (32)	773 (32)	375 (39)	
≥90	280 (66)	1576 (66)	577 (60)	
Missing	10 (2)	35 (1)	17 (2)	
HCT-CI, n (%)				<.001
0	89 (21)	659 (28)	227 (23)	
1-2	116 (27)	679 (28)	225 (23)	
3+	182 (43)	832 (35)	418 (43)	
Missing	39 (9)	214 (9)	99 (10)	
Recipient CMV serostatus, n (%)				.73
Negative	147 (35)	840 (35)	340 (35)	
Positive	277 (65)	1516 (64)	620 (64)	
Missing	2 (0)	28 (1)	9 (1)	
Disease characteristics				
Type of AML, n (%)				<.001
tAML	88 (21)	106 (4)	87 (9)	
Antecedent MDS	27 (6)	449 (19)	221 (23)	
De novo disease	311 (73)	1829 (77)	661 (68)	
KMT2A subtype, n (%)				
KMT2A t(9;11)	112 (26)			
KMT2A t(10;11)	28 (7)			
KMT2A t(6;11)	41 (10)			
KMT2A t(11;19)	62 (15)			
KMT2A other	47 (11)			
KMT2A undefined	136 (32)			
Prior disease, n (%)				<.001
AML, not therapy related	338 (79)	2278 (96)	882 (91)	
HD	5 (1)	8 (0)	5 (1)	
NHL	14 (3)	11 (0)	12 (1)	
Breast cancer	48 (11)	36 (2)	27 (3)	
Solid tumor	9 (2)	20 (1)	18 (2)	
Other	11 (3)	31 (1)	25 (3)	
Missing	1 (0)	0 (0)	0 (0)	

ATG, antithymocyte globulin; CSA, cyclosporine; HD, Hodgkin disease; *KMT2A*, mixed lineage leukemia; NA, not available; NHL, non-Hodgkin lymphoma; Tac, tacrolimus; Post tx-cy, Post-transplant cyclophosphamide.

*Hypothesis testing: Pearson χ^2 test.

Table 1. (continued)

Characteristic	*KMT2A*	Intermediate	Adverse	*P**
Therapy for previous disease, n (%)				<.001
AML, not therapy related	338 (79)	2278 (96)	882 (91)	
Chemotherapy	43 (10)	45 (2)	39 (4)	
Chemotherapy+radiation	40 (9)	39 (2)	32 (3)	
Radiation alone	2 (0)	4 (0)	7 (1)	
Auto HCT	0 (0)	5 (0)	2 (0)	
Other	3 (1)	13 (1)	7 (1)	
Extramedullary disease at diagnosis, n (%)				.35
No	394 (92)	2195 (92)	909 (94)	
Yes	23 (5)	148 (6)	43 (4)	
Missing	9 (2)	41 (2)	17 (2)	
White blood count at diagnosis, AML ($\times 10^9$/L), n (%)				<.001
Median (min-max)	1.2 (0.1-432)	8.9 (0-427.5)	3.6 (0-450)	
≤10	191 (45)	1117 (47)	646 (67)	
10-100	153 (36)	831 (35)	212 (22)	
>100	41 (10)	213 (9)	31 (3)	
Missing	41 (10)	223 (9)	80 (8)	
Time to achieve CR1 (wk), n (%)				<.001
Median (min-max)	5.6 (0.4-45.6)	6 (0.1-51.4)	7 (0.1-50.7)	
≤4	103 (24)	493 (21)	157 (16)	
4-8	199 (47)	1067 (45)	415 (43)	
>8	121 (28)	769 (32)	381 (39)	
Missing	3 (1)	55 (2)	16 (2)	
Time from CR1 to HCT (mo), n (%)				.04
Median (min-max)	2.8 (0.3-16.8)	2.8 (0-86.3)	2.6 (0.2-20.4)	
<3	239 (56)	1290 (54)	576 (59)	
3-6	146 (34)	823 (35)	305 (31)	
>6	38 (9)	216 (9)	72 (7)	
Missing	3 (1)	55 (2)	16 (2)	
Number of courses of induction for CR1 cases, n (%)				<.001
1	312 (73)	1636 (69)	593 (61)	
2	64 (15)	451 (19)	245 (25)	
3	13 (3)	66 (3)	28 (3)	
4	0	14 (1)	6 (1)	
5	0	2 (0)	0	
Missing	37 (9)	215 (9)	97 (10)	
MRD at time of HCT, n (%)				<.001
Negative	296 (69)	1289 (54)	594 (61)	
Positive	69 (16)	632 (27)	210 (22)	
Missing	61 (14)	463 (19)	165 (17)	
Transplant characteristics				
Donor type, n (%)				<.001
HLA-identical sibling	107 (25)	736 (31)	245 (25)	
Haploidentical	23 (5)	136 (6)	68 (7)	
Other related	9 (2)	90 (4)	22 (2)	
Well-matched unrelated (8/8)	173 (41)	912 (38)	377 (39)	

ATG, antithymocyte globulin; CSA, cyclosporine; HD, Hodgkin disease; *KMT2A*, mixed lineage leukemia; NA, not available; NHL, non-Hodgkin lymphoma; Tac, tacrolimus; Post tx-cy, Post-transplant cyclophosphamide.

*Hypothesis testing: Pearson χ^2 test.

Table 1. (continued)

Characteristic	*KMT2A*	Intermediate	Adverse	*P**
Partially matched unrelated (7/8)	39 (9)	192 (8)	99 (10)	
Cord blood	75 (18)	318 (13)	158 (16)	
Conditioning intensity, n (%)				<.001
MA-TBI	105 (25)	450 (19)	175 (18)	
MA-chemotherapy	183 (43)	922 (39)	370 (38)	
RIC/NMA	129 (30)	986 (41)	416 (43)	
Under review	9 (2)	26 (1)	8 (1)	
GVHD prophylaxis, n (%)				.33
Post tx-cy	35 (8)	144 (6)	66 (7)	
Tac based	295 (69)	1682 (71)	662 (68)	
CSA based	89 (21)	491 (21)	219 (23)	
Other	2 (0)	32 (1)	7 (1)	
Missing	5 (1)	35 (1)	15 (2)	
ATG/alemtuzumab, n (%)				.62
ATG alone	90 (21)	557 (23)	227 (23)	
Alemtuzumab alone	9 (2)	46 (2)	20 (2)	
No ATG or alemtuzumab	326 (77)	1773 (74)	722 (75)	
Missing	1 (0)	8 (0)	0	
Graft type, n (%)				<.001
Bone marrow	80 (19)	318 (13)	120 (12)	
Peripheral blood	271 (64)	1748 (73)	691 (71)	
Cord blood	75 (18)	318 (13)	158 (16)	
Year of transplant, n (%)				.02
2007	39 (9)	214 (9)	99 (10)	
2008	57 (13)	266 (11)	123 (13)	
2009	56 (13)	262 (11)	121 (12)	
2010	60 (14)	226 (9)	107 (11)	
2011	16 (4)	132 (6)	50 (5)	
2012	22 (5)	115 (5)	38 (4)	
2013	42 (10)	269 (11)	86 (9)	
2014	56 (13)	316 (13)	143 (15)	
2015	38 (9)	321 (13)	119 (12)	
2016	40 (9)	263 (11)	83 (9)	
Follow-up - median (min-max)	49.24 (3.32-126.41)	37.96 (1.84-122.63)	48.09 (2.89-120.23)	

ATG, antithymocyte globulin; CSA, cyclosporine; HD, Hodgkin disease; *KMT2A*, mixed lineage leukemia; NA, not available; NHL, non-Hodgkin lymphoma; Tac, tacrolimus; Post tx-cy, Post-transplant cyclophosphamide.
*Hypothesis testing: Pearson χ^2 test.

Patients with t(10;11) had the youngest median age, at 34; the patients classified as *KMT2A* other had the highest median age, at 54. For t(9;11), t(11;19), t(6;11), and t(10;11), there were nearly twice as many female as male patients per category.

tAML was found most frequently in those with t(9;11), with 38 (34%) patients having received prior therapy. Breast cancer was the most common prior malignancy. Other prior diagnoses included lymphoma (both Hodgkin and non-Hodgkin) and solid tumors.

Extramedullary disease was present at diagnosis at a single-digit frequency in all groups.

The majority of patients in all subcategories required only 1 course of induction to achieve CR1. Most patients with *KMT2A* rearrangement achieved MRD^- status before transplant, regardless of translocation partner.

Donor type and graft type were similar in all subgroups, as were rejection and GVHD prophylaxis regimens and year of transplant. The percentage of patients who underwent MA conditioning was similar for all translocation partners, but the use of chemotherapy vs TBI varied somewhat. CMV^+ status was more common than CMV^- status in all groups.

Table 2. Patient characteristics by translocation partner

Characteristic	*KMT2A* t(9;11)	*KMT2A* t(10;11)	*KMT2A* t(6;11)	*KMT2A* t(11;19)	*KMT2A* Other	*KMT2A* undefined
Patients, n	112	28	41	62	47	136
Centers, n	63	24	31	39	37	64
Patient characteristics						
Patient age at HCT, n (%)						
Median (min-max)	45.8 (20.1-69.9)	34.3 (18.4-67.4)	45.5 (18.3-62.7)	45.2 (18.4-69.8)	53.7 (18.3-69.3)	49.6 (18.2-70)
18-29	18 (16)	9 (32)	7 (17)	9 (15)	5 (11)	24 (18)
30-39	19 (17)	9 (32)	7 (17)	12 (19)	6 (13)	17 (13)
40-49	36 (32)	5 (18)	13 (32)	17 (27)	7 (15)	30 (22)
50-59	26 (23)	3 (11)	13 (32)	18 (29)	19 (40)	39 (29)
60-69	13 (12)	2 (7)	1 (2)	6 (10)	10 (21)	26 (19)
Sex, n (%)						
Male	43 (38)	8 (29)	11 (27)	23 (37)	25 (53)	69 (51)
Female	69 (62)	20 (71)	30 (73)	39 (63)	22 (47)	67 (49)
Karnofsky score, n (%)						
<90	36 (32)	12 (43)	13 (32)	23 (37)	17 (36)	35 (26)
≥90	73 (65)	16 (57)	27 (66)	37 (60)	29 (62)	98 (72)
Missing	3 (3)	0	1 (2)	2 (3)	1 (2)	3 (2)
HCT-CI, n (%)						
0	15 (13)	9 (32)	9 (22)	11 (18)	8 (17)	37 (27)
1-2	29 (26)	6 (21)	14 (34)	21 (34)	13 (28)	33 (24)
3+	59 (53)	8 (29)	14 (34)	24 (39)	20 (43)	57 (42)
Missing	9 (8)	5 (18)	4 (10)	6 (10)	6 (13)	9 (7)
Recipient CMV serostatus, n (%)						
Negative	41 (37)	8 (29)	10 (24)	27 (44)	17 (36)	44 (32)
Positive	71 (63)	20 (71)	31 (76)	35 (56)	29 (62)	91 (67)
Missing	0	0	0	0	1 (2)	1 (1)
Disease characteristics						
Type of AML, n (%)						
tAML	38 (34)	3 (11)	4 (10)	9 (15)	10 (21)	24 (18)
Antecedent MDS	1 (1)	3 (11)	1 (2)	6 (10)	6 (13)	10 (7)
De novo disease	73 (65)	22 (79)	36 (88)	47 (76)	31 (66)	102 (75)
Prior disease, n (%)						
AML, not therapy related	74 (66)	25 (89)	37 (90)	53 (85)	37 (79)	112 (82)
HD	2 (2)	0	0	0 (0)	0 (0)	3 (2)
NHL	5 (4)	0	1 (2)	2 (3)	3 (6)	3 (2)
Breast cancer	24 (21)	1 (4)	3 (7)	3 (5)	6 (13)	11 (8)
Solid tumor	2 (2)	0	0	3 (5)	0 (0)	4 (3)
Other	4 (4)	2 (7)	0	1 (2)	1 (2)	3 (2)
Missing	1 (1)	0	0	0 (0)	0 (0)	0 (0)
Therapy for previous disease, n (%)						
AML, not therapy related	74 (66)	25 (89)	37 (90)	53 (85)	37 (79)	112 (82)
Chemotherapy	19 (17)	2 (7)	2 (5)	2 (3)	5 (11)	13 (10)
Chemotherapy + radiation	16 (14)	1 (4)	2 (5)	6 (10)	4 (9)	11 (8)
Radiation alone	2 (2)	0	0	0 (0)	0 (0)	0 (0)
Other	1 (1)	0	0	1 (2)	1 (2)	0 (0)
Extramedullary disease at diagnosis, n (%)						
No	101 (90)	25 (89)	36 (88)	59 (95)	44 (94)	129 (95)

ATG, anti-thymocyte globulin; CSA, cyclosporine; NA, not available; HD, Hodgkin disease; NHL, non-Hodgkin lymphoma; Post tx-cy, Post-transplant cyclophosphamide.

Table 2. (continued)

Characteristic	*KMT2A* t(9;11)	*KMT2A* t(10;11)	*KMT2A* t(6;11)	*KMT2A* t(11;19)	*KMT2A* Other	*KMT2A* undefined
Yes	8 (7)	2 (7)	3 (7)	3 (5)	3 (6)	4 (3)
Missing	3 (3)	1 (4)	2 (5)	0	0	3 (2)
WBC count at diagnosis, AML (x 10^9/L), n (%)						
Median (min-max)	7.4 (0.6-432)	7.1 (0.8-128)	37.3 (1-284)	17.8 (0.7-270)	12.3 (0.4-228)	7.2 (0.1-318.2)
≤ 10	57 (51)	13 (46)	13 (32)	24 (39)	19 (40)	65 (48)
10-100	38 (34)	10 (36)	16 (39)	27 (44)	23 (49)	39 (29)
> 100	7 (6)	2 (7)	8 (20)	5 (8)	3 (6)	16 (12)
Missing	10 (9)	3 (11)	4 (10)	6 (10)	2 (4)	16 (12)
Time to achieve CR1 (weeks), n (%)						
Median (min-max)	5 (1.6-20.4)	6.8 (1.9-36.4)	7.1 (2-18.6)	5 (2-30)	6.7 (2-45.6)	5.6 (0.4-29.9)
≤4 wk	31 (28)	6 (21)	5 (12)	18 (29)	8 (17)	35 (26)
4-8 wk	54 (48)	11 (39)	20 (49)	31 (50)	18 (38)	65 (48)
>8 wk	26 (23)	11 (39)	15 (37)	13 (21)	21 (45)	35 (26)
Missing	1 (1)	0	1 (2)	0	0	1 (1)
Time from CR1 to HCT (months), n (%)						
Median (min-max)	3 (0.3-16.8)	2.9 (0.7-8.7)	2.4 (0.5-7.3)	2.6 (0.5-7.6)	2.5 (0.5-11.1)	2.8 (0.4-12.8)
<3 mo	56 (50)	16 (57)	26 (63)	35 (56)	30 (64)	76 (56)
3-6 mo	41 (37)	9 (32)	9 (22)	25 (40)	13 (28)	49 (36)
>6 mo	14 (13)	3 (11)	5 (12)	2 (3)	4 (9)	10 (7)
Missing	1 (1)	0	1 (2)	0	0	1 (1)
Number of courses of induction for CR1 cases, n (%)						
1	85 (76)	21 (75)	27 (66)	47 (76)	33 (70)	99 (73)
2	12 (11)	2 (7)	10 (24)	6 (10)	8 (17)	26 (19)
3	5 (4)	0	1 (2)	3 (5)	1 (2)	3 (2)
Missing	10 (9)	5 (18)	3 (7)	6 (10)	5 (11)	8 (6)
MRD at time of HCT, n (%)						
Negative	82 (73)	18 (64)	28 (68)	38 (61)	33 (70)	97 (71)
Positive	13 (12)	4 (14)	6 (15)	12 (19)	8 (17)	26 (19)
Missing	17 (15)	6 (21)	7 (17)	12 (19)	6 (13)	13 (10)
Transplant characteristics						
Donor type, n (%)						
HLA-identical sibling	23 (21)	9 (32)	13 (32)	18 (29)	9 (19)	35 (26)
Haplo-identical	9 (8)	0	0	6 (10)	2 (4)	6 (4)
Other related	4 (4)	0	0	1 (2)	0	4 (3)
Well-matched unrelated (8/8)	43 (38)	10 (36)	16 (39)	26 (42)	23 (49)	55 (40)
Partially matched unrelated (7/8)	10 (9)	2 (7)	6 (15)	3 (5)	5 (11)	13 (10)
Cord blood	23 (21)	7 (25)	6 (15)	8 (13)	8 (17)	23 (17)
Conditioning intensity, n (%)						
MA-TBI	23 (21)	12 (43)	12 (29)	19 (31)	11 (23)	28 (21)
MA-Chemo	54 (48)	11 (39)	15 (37)	25 (40)	16 (34)	62 (46)
RIC/NMA	32 (29)	5 (18)	13 (32)	16 (26)	20 (43)	43 (32)
Under review	3 (3)	0	1 (2)	2 (3)	0	3 (2)
GVHD prophylaxis, n (%)						
Post tx-cy	17 (15)	0	3 (7)	6 (10)	2 (4)	7 (5)
Tac based	71 (63)	16 (57)	31 (76)	43 (69)	36 (77)	98 (72)
CSA based	21 (19)	11 (39)	6 (15)	13 (21)	9 (19)	29 (21)
Other	1 (1)	0	0	0	0	1 (1)

ATG, anti-thymocyte globulin; CSA, cyclosporine; NA, not available; HD, Hodgkin disease; NHL, non-Hodgkin lymphoma; Post tx-cy, Post-transplant cyclophosphamide.

Table 2. (continued)

Characteristic	*KMT2A* t(9;11)	*KMT2A* t(10;11)	*KMT2A* t(6;11)	*KMT2A* t(11;19)	*KMT2A* Other	*KMT2A* undefined
Missing	2 (2)	1 (4)	1 (2)	0	0	1 (1)
ATG/Campath, n (%)						
ATG alone	18 (16)	8 (29)	8 (20)	9 (15)	11 (23)	36 (26)
Alemtuzumab alone	3 (3)	0	0	1 (2)	0	5 (4)
No ATG or alemtuzumab	91 (81)	19 (68)	33 (80)	52 (84)	36 (77)	95 (70)
Missing	0	1 (4)	0	0	0	0
Graft type, n (%)						
Bone marrow	26 (23)	3 (11)	6 (15)	11 (18)	7 (15)	27 (20)
Peripheral blood	63 (56)	18 (64)	29 (71)	43 (69)	32 (68)	86 (63)
Cord blood	23 (21)	7 (25)	6 (15)	8 (13)	8 (17)	23 (17)
Year of transplant, n (%)						
2007	9 (8)	5 (18)	4 (10)	6 (10)	6 (13)	9 (7)
2008	14 (13)	3 (11)	9 (22)	7 (11)	6 (13)	18 (13)
2009	13 (12)	7 (25)	5 (12)	6 (10)	7 (15)	18 (13)
2010	13 (12)	2 (7)	4 (10)	10 (16)	6 (13)	25 (18)
2011	6 (5)	1 (4)	2 (5)	1 (2)	1 (2)	5 (4)
2012	5 (4)	1 (4)	3 (7)	4 (6)	2 (4)	7 (5)
2013	9 (8)	3 (11)	1 (2)	7 (11)	4 (9)	18 (13)
2014	23 (21)	1 (4)	4 (10)	9 (15)	8 (17)	11 (8)
2015	11 (10)	2 (7)	2 (5)	7 (11)	5 (11)	11 (8)
2016	9 (8)	3 (11)	7 (17)	5 (8)	2 (4)	14 (10)
Follow-up, median (min-max)	49.24 (6.12-126.41)	52.57 (3.36-100.07)	55.89 (3.42-90)	47.4 (3.32-99.28)	71.45 (3.49-97.86)	48.19 (5.92-116.18)

ATG, anti-thymocyte globulin; CSA, cyclosporine; NA, not available; HD, Hodgkin disease; NHL, non-Hodgkin lymphoma; Post tx-cy, Post-transplant cyclophosphamide.

Table 3. Univariable analysis

	KMT2A (n = 426)		Intermediate (n = 2384)		Adverse (n = 969)		
Outcomes, y	**n**	**Prob, % (95% CI)**	**n**	**Prob, % (95% CI)**	**n**	**Prob, % (95% CI)**	***P***
Relapse	426		2383		968		<.001
1	225	25 (21-30)	1292	24 (22-26)	433	34 (31-37)	<.001
3	115	34 (30-39)	660	31 (29-33)	198	44 (40-47)	<.001
5	74	37 (32-42)	393	33 (31-35)	128	46 (42-49)	<.001
NRM	426		2383		968		.411
1	225	16 (13-20)	1292	14 (13-16)	433	17 (14-19)	.295
3	115	23 (19-28)	660	20 (18-22)	198	23 (21-26)	.070
5	74	25 (21-29)	393	24 (22-26)	128	25 (22-28)	.801
LFS	426		2383		968		<.001
1	223	59 (54-63)	1284	62 (60-64)	431	49 (46-53)	<.001
3	114	43 (38-48)	659	49 (47-52)	197	33 (30-36)	<.001
5	73	38 (33-44)	393	43 (41-46)	127	30 (27-33)	<.001
OS	426		2384		969		<.001
1	259	68 (63-72)	1472	70 (68-72)	521	60 (57-63)	<.001
3	119	45 (40-51)	748	55 (53-57)	225	38 (35-41)	<.001
5	79	42 (37-48)	443	48 (46-50)	141	34 (30-37)	<.001

NE, nonevaluable; Prob, probability.

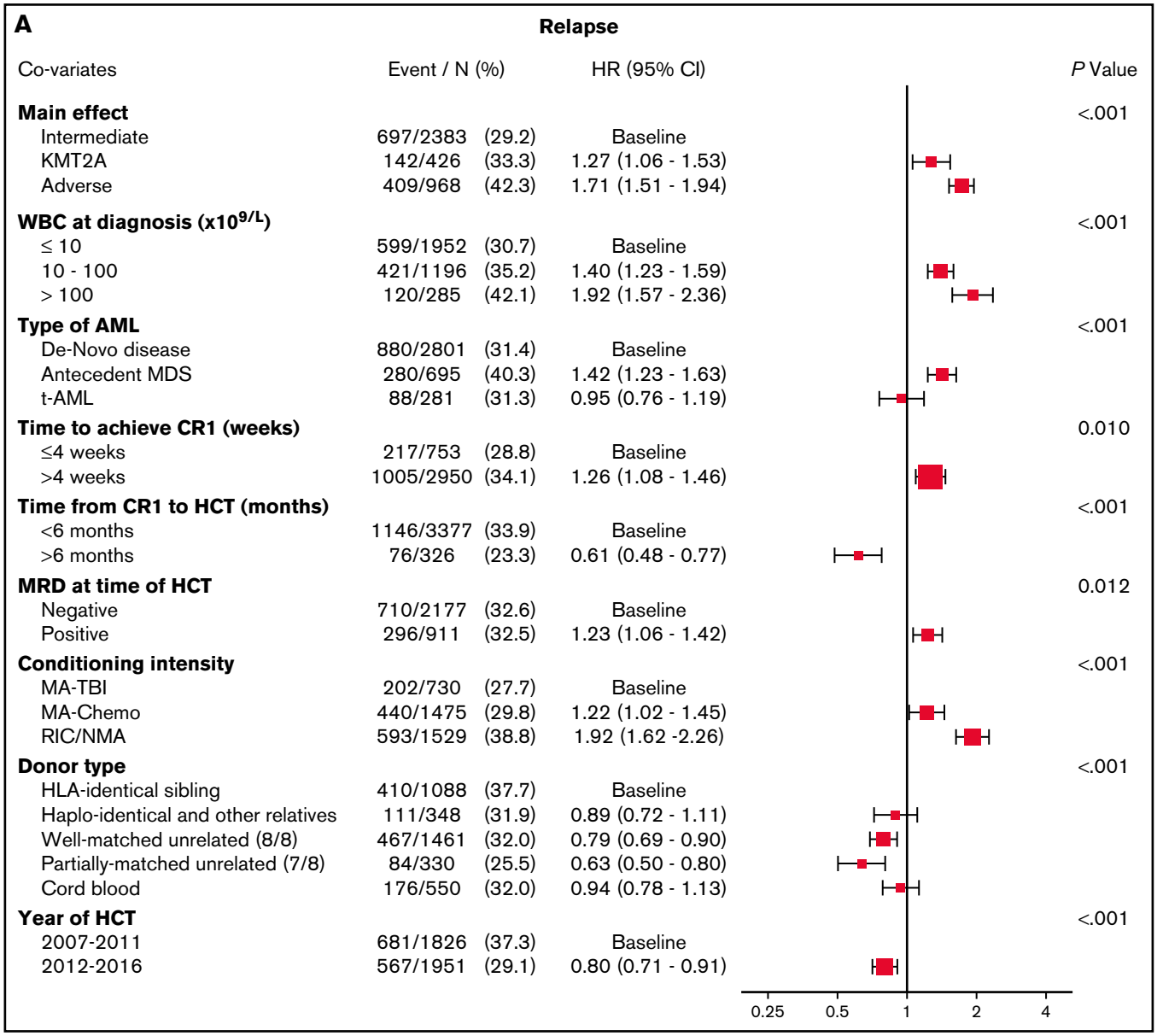

Figure 1. Multivariable analyses. (A) The outcome of relapse, with the main effect of cytogenetic category and including the listed covariates. The HR for relapse among those with *KMT2A* rearrangement was 1.27, and among those with adverse risk was 1.71. (B) The outcome of NRM, with the main effect of cytogenetic category and including the listed covariates. The HR for NRM was not significantly different among the groups. (C) The outcome of LFS, with the main effect of cytogenetic category and including the listed covariates. The HR among those with *KMT2A* rearrangement was 1.26, and among patients with adverse risk was 1.47. (D) The outcome of OS, with the main effect of cytogenetic category and including the listed covariates. The HR for death among those with *KMT2A* rearrangement was 1.32 and among patients with adverse risk was 1.45.

Relapse of AML

A univariable analysis of the risk of relapse at 1, 3, and 5 years after transplantation found that it was comparable in patients with *KMT2A* translocation and intermediate risk but higher at all time points in patients with adverse-risk disease (Table 3). The probability of relapse at 1 year was similar across *KMT2A* subtypes.

In the multivariable analysis, the *KMT2A*-rearranged and adverse-risk groups had an increased hazard ratio (HR) for relapse of 1.27 (95% CI, 1.06-1.53; $P = .01$) and 1.71 (95% CI, 1.51-1.94; $P < .001$), respectively, when compared with the intermediate-risk group (Figure 1A). Other predictors of relapse included higher WBC count at diagnosis, a longer time to achieve CR1, pre-HCT MRD positivity, conditioning other than TBI-based MA conditioning, and donors other than HLA-identical siblings. Relapse risk was also more apt to occur in those with a history of prior MDS, but not in those with therapy-related disease. Data on therapies used in the post-HCT relapse setting outside of the second transplant were not available for analysis.

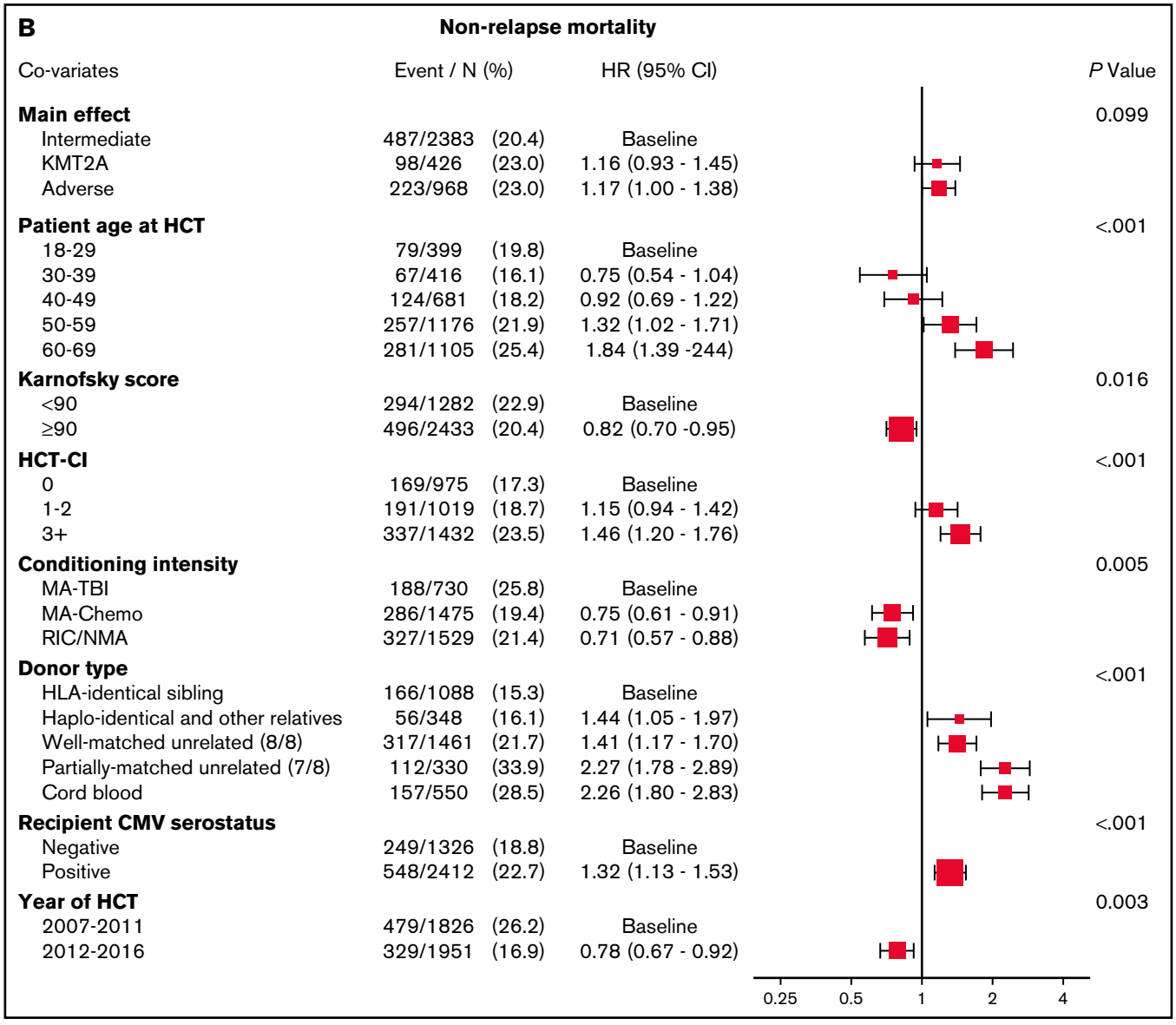

Figure 1 (continued)

The adjusted cumulative incidence function (CIF) for relapse is shown in Figure 2A.

NRM

NRM rates were similar for patients with *KMT2A*-rearrangement, intermediate-risk, or adverse-risk disease at 1, 3, and 5 years after transplant by univariable analysis (Table 3). NRM risk was similar for all translocation partners in patients with *KMT2A* rearrangement (Table 4). The CIF curve is shown in Figure 2B.

Figure 1B demonstrates that the results of multivariable analysis for NRM was not significantly different among cytogenetic groups, with HR, 1.16 (95% CI, 0.93-1.45) for *KMT2A*-rearranged disease and HR, 1.17 (95% CI, 1.00-1.38) for adverse-risk disease ($P = .099$). Predictors of NRM included older age, poor performance status, higher HCT-CI score, conditioning regimen, donor type, CMV positivity, and year of transplant.

LFS

LFS at 1, 3, and 5 years after transplantation was worse for patients with adverse-risk disease (Figure 2C). The 1-year probability of LFS overlapped for the *KMT2A*-rearranged and intermediate-risk groups but was worse for those in the adverse-risk group. Similar trends were seen at 3 and 5 years in the univariable analysis (Table 3). No differences in LFS according to translocation partner were noted (Table 4).

As shown in Figure 1C, the multivariable analysis detected worse LFS for the *KMT2A*-rearranged and adverse-risk groups, compared with the intermediate-risk group (HR, 1.26; 95% CI, 1.09-1.46; $P = .002$, and HR, 1.47; 95% CI, 1.33-1.62; $P < .001$, respectively). Increasing WBC count was a predictor of LFS, as was longer time to CR1. MRD^+ patients, those who underwent RIC/NMA, and those with a cord blood donor also had worse LFS. In addition, patients with prior MDS had worse LFS.

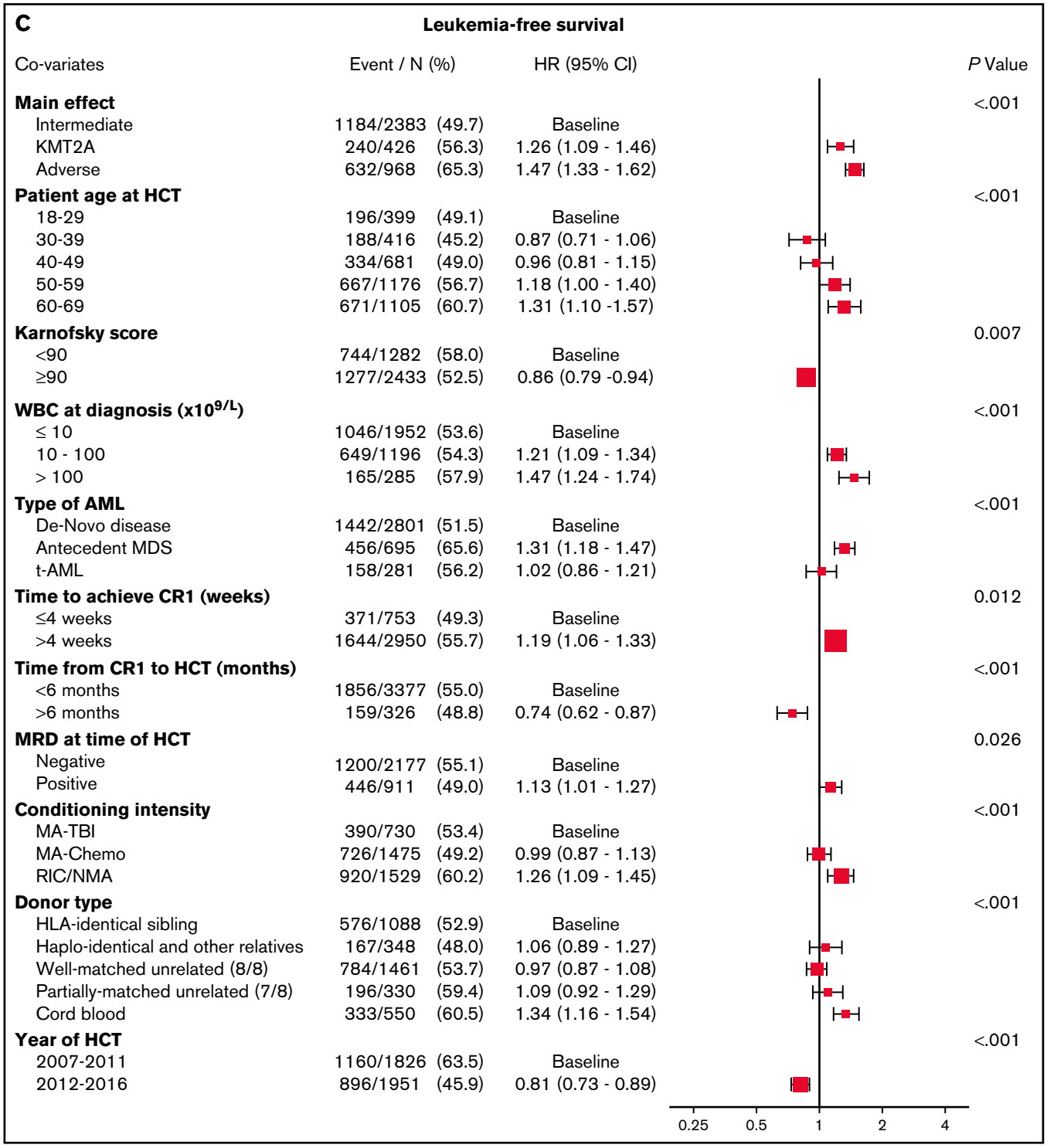

Figure 1 (continued)

GRFS

GRFS at 1, 3, and 5 years was similarly poor for patients with *KMT2A*-rearranged or adverse-risk disease and was somewhat better for those with intermediate-risk disease (Table 5). Five-year GRFS could be compared only between the intermediate- and adverse-risk groups, given the number of patients available for analysis, and was significantly worse among patients with adverse risk (9% vs 15%).

A multivariable analysis for GRFS detected that it was not significantly worse in patients with *KMT2A* rearrangement but it was worse for patients in the adverse-risk group, compared with those in the intermediate-risk group (HR, 1.14; 95% CI, 1.01-1.28; $P = .03$,

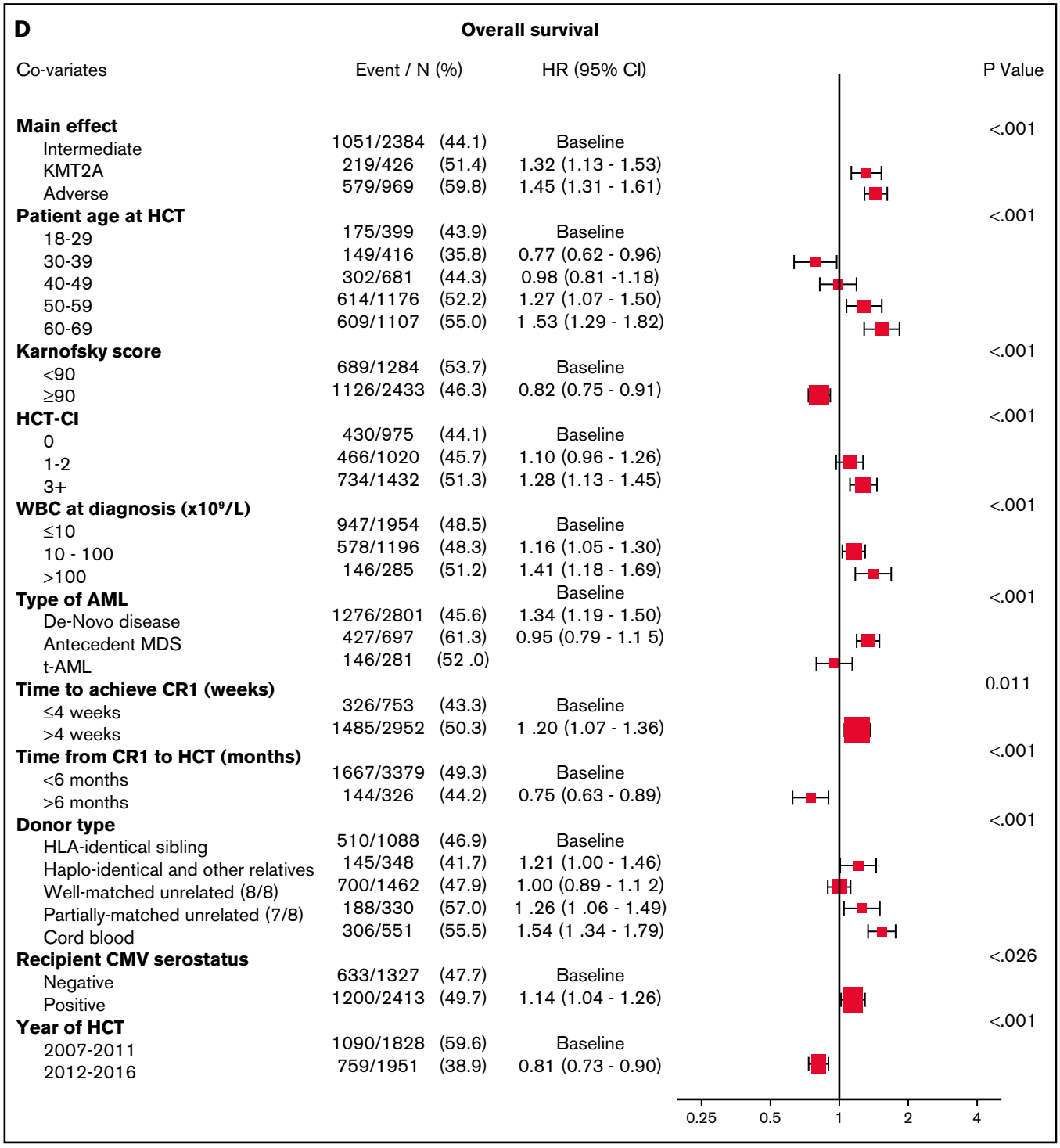

Figure 1 (continued)

and HR, 1.23; 95% CI, 1.14-1.34; $P < .001$, respectively) (Table 6). Age was included in the model but was not statistically significant. Later transplant was associated with improved GRFS, and a history of antecedent MDS was associated with a significantly worse outcome (HR, 1.19; 95% CI, 1.08-1.30; $P < .001$).

OS

A univariable analysis showed a 42% 5-year OS for the *KMT2A*-rearranged group, compared with 48% for the intermediate-risk group and 34% for the adverse-risk group (Table 3). No difference in OS was detected according to *KMT2A* translocation partner (Table 4).

Table 4. Univariable analysis by translocation partner

Outcomes, y	t(9;11) (n = 112) n	Prob, % (95% CI)	t(10;11) (n = 28) n	Prob, % (95% CI)	t(6;11) (n = 41) n	Prob, % (95% CI)	t(11;19) (n = 62) n	Prob, % (95% CI)	Other (n = 47) n	Prob, % (95% CI)	Undefined (n = 136) n	Prob, % (95% CI)	P
Relapse	112		28		41		62		47		136		.265
1	71	22 (14-30)	16	22 (9-40)	19	29 (15-44)	34	30 (19-42)	27	13 (5-25)	62	30 (22-38)	.148
2	48	27 (19-36)	9	NE	12	NE	22	38 (26-51)	19	26 (14-40)	48	32 (24-40)	.295
NRM	112		28		41		62		47		136		.606
1	71	14 (8-22)	16	15 (4-31)	19	16 (6-29)	34	13 (6-23)	27	24 (13-37)	62	17 (11-24)	.818
2	48	21 (13-29)	9	NE	12	NE	22	17 (8-28)	19	26 (15-40)	48	22 (15-30)	.838
LFS	112		28		41		62		47		136		.432
1	70	64 (55-73)	15	63 (44-80)	18	55 (39-71)	33	57 (44-69)	26	63 (49-76)	61	54 (45-62)	.62
2	47	53 (43-62)	8	NE	11	NE	21	45 (32-58)	18	48 (33-63)	47	46 (37-55)	.72
OS	112		28		41		62		47		136		.295
1	79	72 (63-80)	17	70 (52-86)	21	63 (47-78)	39	70 (57-81)	28	67 (53-80)	75	65 (56-73)	.85
2	51	58 (48-67)	10	NE	14	NE	25	59 (45-71)	20	57 (42-71)	50	48 (39-57)	.649

NE, nonevaluable; Prob, probability.

Table 5. Univariable analysis of GRFS

Outcomes	*KMT2A* (n = 426) n	Prob (95% CI)	Intermediate (n = 2384) n	Prob (95% CI)	Adverse (n = 969) n	Prob (95% CI)	P value
GVHD-free, relapse-free survival	410	–	2326	–	948	–	<.001
1	72	21 (17-25)	527	27 (25-29)	150	19 (16-21)	<.001
3	26	12 (9-16)	187	17 (15-19)	54	10 (8-12)	<.001
5	13	NE	103	15 (13-16)	39	9 (7-11)	<.001

Univariable analysis of GRFS by translocation partner is not provided, as not enough cases remained at risk at 1 y (most events occurred earlier).

Table 6. Multivariable analysis for GRFS

Covariates	n	HR, (95% CI)	P
Main effect			<.001
Intermediate	2326	Reference	
KMT2A	410	1.14 (1.01-1.28)	.03
Adverse	948	1.23 (1.14-1.34)	<.001
Patient age at HCT, y			.04
18-29	387	Reference	
30-39	411	0.93 (0.80-1.09)	.40
40-49	657	0.97 (0.84-1.12)	.70
50-59	1156	1.06 (0.93-1.21)	.36
60-69	1073	1.11 (0.97-1.27)	.12
Year of HCT			<.001
2007-2011	1790	Reference	
2012-2016	1894	0.83 (0.77-0.89)	<.001
Type of AML			.002
De novo disease	2741	Reference	
Antecedent MDS	683	1.19 (1.08-1.30)	<.001
tAML	260	1.03 (0.90-1.19)	.64

OS in a multivariable model (Figure 1D) was again worse for the *KMT2A*-rearranged and adverse-risk groups (HR, 1.32; 95% CI, 1.13-1.53; $P < .001$, and HR, 1.45; 95% CI, 1.31-1.61; $P < .001$, respectively). Poorer OS was also noted in those >50 years of age, with poor performance status, higher HCT-CI, score, higher WBC at diagnosis, and longer time to achieve CR1. Patients who underwent HCT <6 months after CR1 had worse OS, as did those with donors who were not well-matched or identical. Secondary AML was again a poor predictor, whereas tAML was not.

The Kaplan-Meier curve for OS is shown in Figure 2D.

MRD

The proportion of patients with MRD positivity was similar between the groups: 21% of patients with a *KMT2A* rearrangement, 30% of patients with intermediate-risk disease, and 30% of patients with adverse-risk disease. Pre-HCT MRD positivity was associated with relapse but did not meet statistical significance for LFS (HR, 1.23; 95% CI, 1.06-1.42; $P = .006$, and HR, 1.13; 95% CI, 1.01-1.27; $P = .04$, respectively). MRD was not associated with NRM or OS.

Outcomes among *KMT2A* translocation partners

A secondary analysis was performed to determine the influence of translocation partner on outcomes for patients with *KMT2A* rearrangement. We excluded the patients whose translocation partner had not been defined from the secondary analysis. We then compared the 112 patients with t(9;11) against the remaining patients with *KMT2A* rearrangement and the 62 patients with t(11;19) with the remaining patients with *KMT2A* rearrangement and then combined both the t(9;11) and t(11;19) groups and compared them

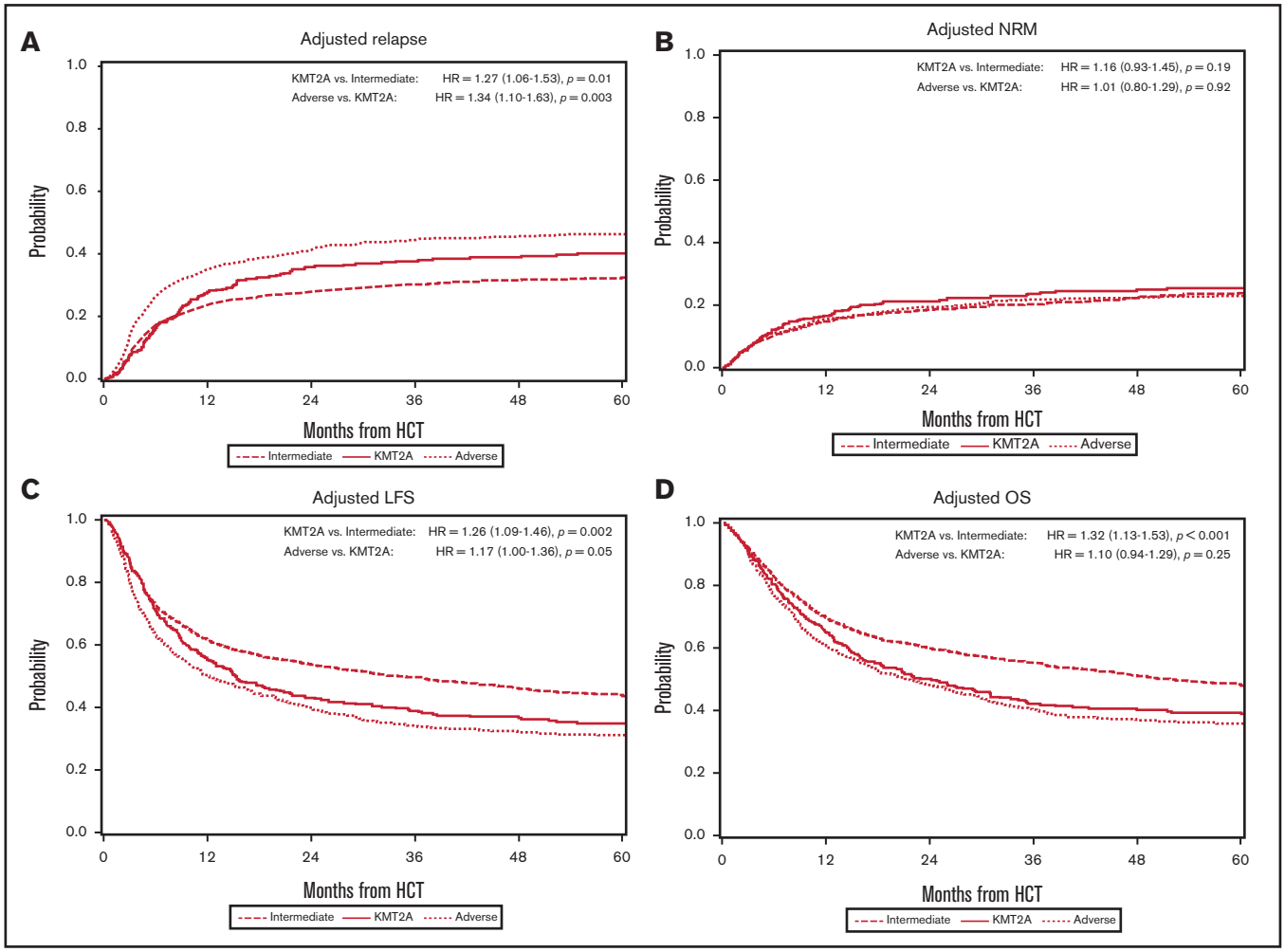

Figure 2. Adjusted multivariable analysis by cytogenetic group. (A) Curves of the CIF for the outcome of relapse, showing the highest risk of relapse was among patients with adverse risk. *KMT2A*-rearranged patients also had an increased risk of relapse after 12 months. (B) Curves of the CIF for the outcome of NRM, showing no significant difference among the intermediate-risk, adverse-risk, or *KMT2A*-rearranged groups. (C) Kaplan-Meier curves for the outcome of LFS, demonstrating that patients with *KMT2A* rearrangements did worse than those with intermediate risk but similarly to patients with adverse risk. (D) Kaplan-Meier curves for the outcome of OS, where the *KMT2A*-rearranged group's survival closely approximated that of the adverse-risk group.

with the remaining 116 patients for whom a translocation partner had been defined. We looked at the risk of relapse, NRM, LFS, and OS and found no difference between the groups for any outcome (Table 4; Figure 3; multivariable analysis results in supplemental Table 3).

We also performed a multivariable analysis for our main 4 outcomes that included only patients in the *KMT2A*-rearranged group who had t(9;11) as compared to those with intermediate-risk disease (Table 7). In this analysis, NRM, relapse, LFS, and OS were not significantly different between patients with t(9;11) and those with intermediate risk.

Additional chromosomal abnormalities and CK analysis

Of the 426 patients with *KMT2A* rearrangement in our study, 145 had additional karyotypic abnormalities, and 281 had an 11q23 translocation alone. The most common additional chromosomal abnormality was trisomy 8, which occurred as an isolated abnormality in 39 patients and with other abnormalities in 23 others. Monosomy 7 was detected in 10 patients, del(7q) in 3; monosomy 5 was found in 3 patients and del(5q) in 10. In supplemental Table 4, we present exploratory multivariable analyses for patients in the intermediate- and adverse-risk groups in comparison with all the patients in the *KMT2A*-rearranged group, those in the *KMT2A*-rearranged group without additional abnormalities, and those in the group with additional abnormalities. *KMT2A* with additional abnormalities had outcomes similar to those of patients with intermediate risk for all 4 outcomes at our level of significance ($P < .01$). LFS and OS were significantly shorter for the patients in the *KMT2A*-rearranged group who did not have additional abnormalities.

We performed a manual review to determine cytogenetic complexity in the *KMT2A*-rearranged group and found 29 instances of CK among them: 7 with t(9;11), 1 with t(11;19), 3 each with t(6;11) and t(10;11), 2 with a different translocation partner, and 13 in whom the translocation partner was not defined. We

Table 7. Multivariable analysis of t(9;11) vs intermediate risk vs adverse risk

Covariates	n	HR, (95% CI)	P
NRM			
Main effect	–	–	.15
Intermediate	2384	Reference	
t(9;11)	112	1.04 (0.70-1.55)	.85
Adverse	968	1.18 (1.00-1.38)	.05
Relapse			
Main effect	–	–	<.001
Intermediate	2384	Reference	
t(9;11)	112	0.98 (0.67-1.42)	.91
Adverse	968	1.67 (1.48-1.89)	<.001
LFS			
Main effect	–	–	<.001
Intermediate	2384	Reference	
t(9;11)	112	1.05 (0.79-1.38)	.74
Adverse	968	1.45 (1.31-1.60)	<.001
OS			
Main effect	–	–	<.001
Intermediate	2384	Reference	
t(9;11)	112	1.12 (0.84-1.49)	.45
Adverse	969	1.45 (1.30-1.61)	<.001

The same adjusting factors as those in the main model were selected, but only the main effect is presented in the table.

performed a univariable analysis to evaluate our main outcomes in those in the *KMT2A*-rearranged group with CK, compared with those without CK; no significant differences were detected (supplemental Table 5).

Discussion

For most patients with AML with intermediate- or adverse-risk prognostic features, allogeneic HCT remains the only curative therapy.[20-22] Until now, there have been limited quantitative data to compare post-HCT outcomes between these groups. This study is the largest presentation to date of real-world evidence on post-HCT AML outcomes using curated cytogenetics data. We used a refined stratification by diagnostic risk after expert manual curation and robust clinical and outcomes data collected from 165 centers by the CIBMTR to provide quantitative comparisons. Our results show that patients with adverse risk have a 71% increased risk of relapse, 47% increased risk of death from recurrent leukemia, and 45% increased risk of death overall, compared with those with intermediate-risk disease. Although HCT remains an essential component of curative therapy for patients with AML, it may not fully overcome the differences in disease biology detected at diagnosis.

Patients with a *KMT2A* rearrangement may fall into either the intermediate- or adverse-risk category at the time of diagnosis, based on translocation partner, and thus provide a compelling subgroup for further analysis. We found that LFS and OS for patients with *KMT2A* rearrangement are similar to those with adverse risk in the posttransplant setting. The *KMT2A*-rearranged group had a higher risk of relapse than the intermediate-risk group, but a lower relapse risk than the adverse-risk group. No differences in NRM were seen based on cytogenetic grouping. Patients with *KMT2A* rearrangement with t(9;11) were analyzed as a separate group in a multivariable model, and their outcomes were indistinguishable from those in the intermediate-risk group, suggesting that their risk classification at diagnosis remains predictive of their post-HCT outcomes. When all patients with *KMT2A* rearrangement were stratified by translocation partner, our study did not detect differences between the groups in any outcome.

We also provide quantitative, real-world data on the long-term outcomes of patients with AML who undergo HCT. For those with intermediate or adverse risk, our univariable analysis showed that 5-year post-HCT OS was 48% and 34%, respectively. Patients with *KMT2A* rearrangement had a 5-year OS of 42%. Although we could not perform a direct comparison with non-transplant treatment approaches with our available dataset, we noted that large studies of patients with AML have shown a 5-year OS for patients with *KMT2A* rearrangement of 20% to 25%.[7]

In addition, our real-world data show that *KMT2A*-rearranged disease was more common among women and that antecedent breast cancer had been detected in 4 to 6 times as many patients in the *KMT2A*-rearranged group as in the intermediate- or adverse-risk groups. These data reinforce the association between *KMT2A* translocations and antecedent chemotherapy and highlight the necessity of counseling women who have been treated with anthracycline-based regimens about the risks of developing tAML.[23-27]

Prior studies looking at whether translocation partner is predictive of outcomes in the posttransplant setting are mixed. A 2015 study of 159 patients with *KMT2A*-rearranged AML drew from the European Group for Blood and Marrow Transplantation database.[28] They found that patients with t(11;19) had the highest 2-year OS at 73% ± 10%, followed by t(9;11) at 64% ± 6%, t(10;11) at 40% ± 13%, and t(6;11) at 24% ± 11%. The results suggested that the stratification was driven by a high relapse risk in the latter 2 groups of ~50% at 2 years. Our study found lower rates of relapse that were similar for different translocation partners: ~20% to 30% at 1 year. A multivariable analysis of 49 patients in the *KMT2A*-rearranged group who underwent allo-HCT by the German Acute Myeloid Leukemia Intergroup did not find a significant difference in post-HCT OS based on *KMT2A* subtype.[29] Our analysis also did not detect a significant difference in post-HCT outcomes based on the *KMT2A* partner, despite having more patients per translocation subgroup than any other cohort in the published literature.

The relatively poor OS of patients with *KMT2A* rearrangement suggests that novel therapies are needed to treat this high-risk population. *KMT2A* rearrangements lead to the recruitment of the H3K79 histone methyltransferase DOT1L, which alters histone methylation and results in the overexpression of HoxA9 and Meis1 and a subsequent block in cellular differentiation.[30] A phase 1 study of the DOT1L inhibitor pinometostat found that it is well tolerated, with modest clinical activity as a single agent.[31] A combination study of pinometostat and azacitidine in patients with relapsed/refractory disease is ongoing, as is a trial of pinometostat with induction therapy in patients who were previously untreated.[32,33] Preclinical studies have shown that targeting menin, a protein that binds to the

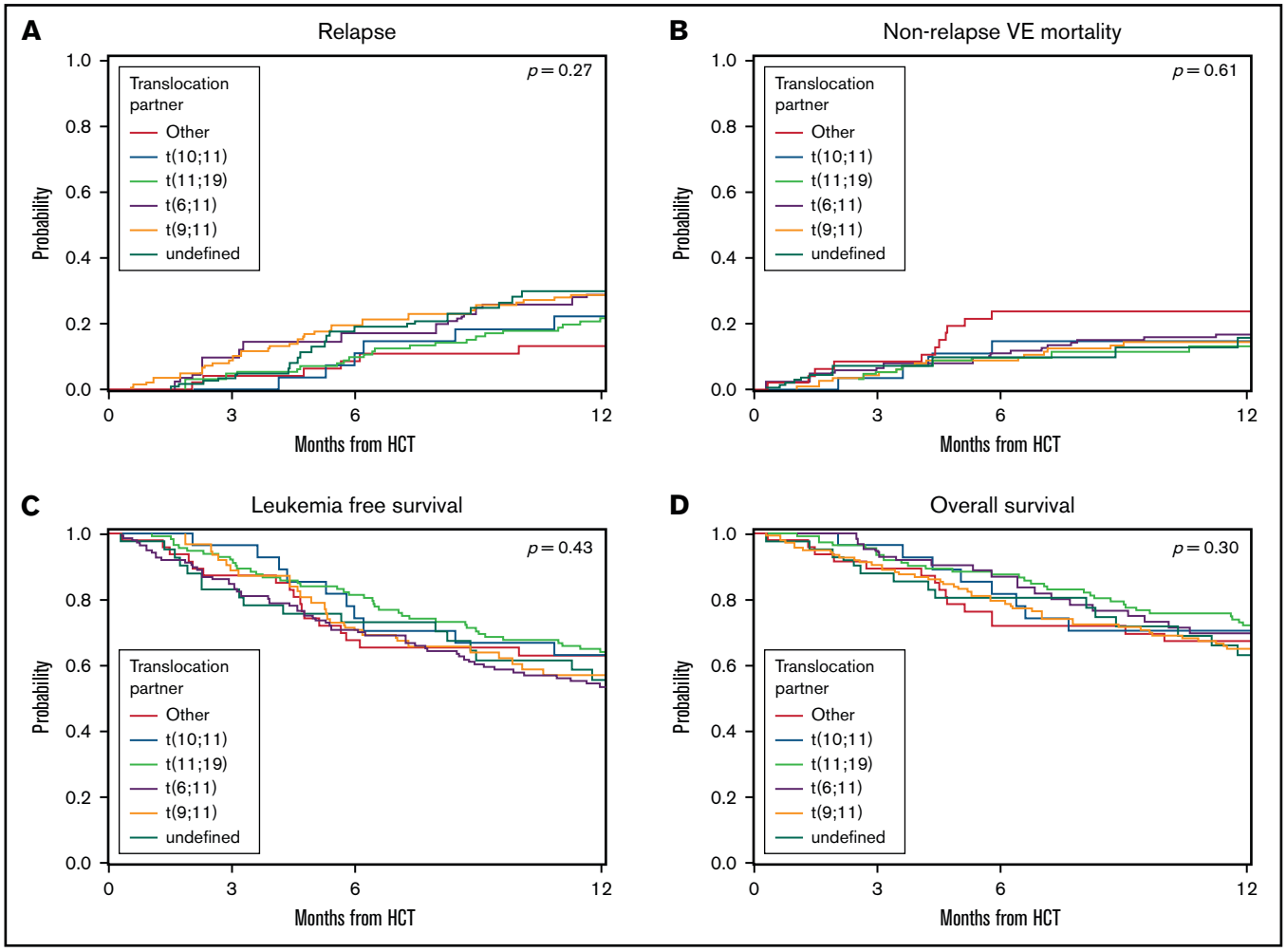

Figure 3. Univariable analysis by translocation partner. (A) CIF curves for the outcome of relapse, where patients with *KMT2A* rearrangement were stratified by translocation partner. No significant differences were noted between the groups. Log-rank, $P = .27$. (B) CIF curves for the outcome of NRM, where patients with *KMT2A* rearrangement were stratified by translocation partner. No significant differences were noted between the groups. Log-rank, $P = .61$. (C) Kaplan-Meier curves for the outcome of LFS, where patients with *KMT2A* rearrangement were stratified by translocation partner. No significant differences were noted between the groups. Log-rank, $P = .43$. (D) Kaplan-Meier curves for the outcome of OS, where patients with *KMT2A* rearrangement were stratified by translocation partner. No significant differences were noted between the groups. Log-rank, $P = .27$.

N-terminus of *KMT2A* fusion proteins, may also provide an avenue for directed therapy in these patients.[34] Clinical trials are also ongoing with menin inhibitors, and preclinical data suggest that combining DOT1L and menin inhibition may ultimately result in better outcomes for these patients than the use of either class of agent alone.[35-37] The spleen tyrosine kinase inhibitor entospletinib is also in early-phase trials in this population.[38] Although these studies are taking place in patients before HCT, including their use as a bridge to transplant, studies of their use in the post-HCT setting as maintenance therapies are clearly needed.

As trials of targeted therapies are ongoing, our study provides insights into transplant strategies that may be effective in this population. A subgroup analysis showed that those who underwent MA conditioning, especially with TBI, had improved LFS and lower relapse risk, compared with those who received RIC/NMA transplants. The benefits of MA conditioning, however, must be considered against the risk of NRM, which was higher in this group; on balance, conditioning intensity did not play a role in OS in our analysis. MA conditioning may be most useful for patients selected based on age, HCT-CI, and other patient- and disease-related factors, such as MRD positivity. Patients who go into transplant with MRD have been described to be more likely to relapse and have a decreased OS.[39] In a recent study, Hourigan et al found that these risks may be mitigated by the use of MA conditioning in patients with molecular MRD.[40] Prospective studies are needed to evaluate whether MA regimens should be preferred among patients with *KMT2A* rearrangement, and the role of MRD in this setting should be examined. In addition, as patients with *KMT2A* rearrangement do worse than those with intermediate-risk disease, use of donor lymphocyte infusions or posttransplant maintenance may also be considered as early interventions in this population.

In conclusion, our analysis is the largest to date of the posttransplant outcomes of patients with AML. Diagnostic risk classification remains predictive of transplant outcomes, but 5-year OS

after HCT is robust and provides evidence of the curative potential of this strategy. Post-HCT outcomes for t(9;11) patients hew closely to those of patients with intermediate-risk disease. In aggregate, however, patients with *KMT2A* rearrangement have LFS and OS similar to patients with adverse-risk disease. Stratification of all patients with *KMT2A* rearrangement by translocation partner did not show significant differences. This may be because, despite having the largest analysis published to date, we remain underpowered to detect such a difference. We recognize that our analysis of registry data may be limited by the heterogeneity of the contributing centers, changes in MRD assessment over the study period, and missing data, as well as the lack of genomic information. However, our study highlights the need to consider whether prognostic scoring systems for patients with AML who undergo HCT should include all cytogenetic data from the time of diagnosis. Further studies are needed to evaluate the role of genomic data and clonal evolution in refining risk prediction for this population. In the case of *KMT2A*, we posit that targeted approaches to treatment and transplantation in this unfavorable patient subset represent a critical unmet need.

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Authorship

Contribution: K.M., initiated the project, manually curated and analyzed the data, and drafted the manuscript; A.G.-A. manually curated and interpreted the data and edited the manuscript; R.M.-M. manually curated the data; M.-J.Z. performed the statistical analyses and interpreted the data; H.-L.W. managed the project, performed statistical analyses, curated and interpreted the data, and created the tables and figures; K.B.-S. managed the project, curated the data, performed the statistical analysis, and created the tables; J.S. managed the project, performed statistical analyses, and curated the data; C.H., B.S., M.L., P.K., and D.W. provided project oversight, interpreted the data, and reviewed the manuscript; Y.Z. initiated and designed the project, manually curated and interpreted the data, and reviewed the manuscript; M.S.T. provided project oversight, reviewed the statistical analyses, interpreted the data, and reviewed the manuscript; and all remaining authors interpreted the data and reviewed the manuscript.

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