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Does FLT3 Mutation Impact Survival after Hematopoietic Cell Transplant for AML? A CIBMTR Analysis

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Abstract

1. FLT3 mutation status does not impact overall survival after allogeneic hematopoietic stem cell transplant.

2. Pre-emptive strategies to reduce relapse need to be investigated in FLT3 mutated patients to further improve post HCT outcomes.

Background—Patients (pts) with FMS like tyrosine kinase 3 (FLT3) mutated acute myeloid leukemia (AML) have poor prognosis and are referred for early allogeneic hematopoietic cell transplant (HCT).

Methods—Using data from the Center for International Blood and Marrow Transplant Research (CIBMTR), we evaluated 511 adult pts with *de novo* AML who underwent HCT during 2008-2011 to determine if FLT3 mutations (mut.) impact HCT outcomes.

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Results—158 (31%) pts had FLT3 mut. Univariate analysis and multivariate analysis showed increased relapse risk at 3 years(yr.) in FLT3 mut. group when compared to wild type (WT) group (38% (95% confidence intervals [CI] 30-45) vs. 28% (95% CI 24-33), P =0.04; and relative risk [RR] 1.60 (95% CI 1.15-2.22), P =0.0048). However, FLT3 mut. status was not significantly associated with non-relapse mortality, leukemia-free survival, or overall survival (OS). Though more pts in the FLT3 mut. group died from relapsed primary disease (60% vs. 46%) as compared to WT, the 3-year OS of pts was comparable 49% (95% CI 40-57) and 55% (95% CI 50-60%) P=0.20.

Conclusions—Our data shows that FLT3 mut. status did not adversely impact the OS after HCT and about 50% of pts with this mut. who underwent HCT were long term survivors.

Keywords

Acute Myeloid Leukemia; Allogeneic stem cell transplantation; FLT3

INTRODUCTION

HCT remains the most effective post remission therapy for high-risk AML. FLT3 mut. occur in about 30% of pts with AML and the 2 most common variants are the internal tandem duplications (FLT3-ITD) and the point mut. in the tyrosine kinase domain (FLT3-TKD). FLT3-ITD mut. occur more frequently than the TKD mut. (˜25% vs. ˜7%), and the clinical manifestations of a FLT3-ITD mut. have a more characteristically unfavorable risk profile.[1-9] In contrast with AML with FLT3-TKD, FLT3-ITD mut. is associated with short-lived remissions, resistant relapsed disease and a dismal prognosis. [2, 3, 10-14] Pts with FLT3-ITD are therefore commonly offered HCT in CR1. [15-21]

Pre-HCT disease characteristics in AML such as disease status (CR1, CR2, MRD) and cytogenetics are predictors of post-HCT outcomes.[22, 23] The impact of FLT3 mut. on outcomes of HCT was previously reported in predominantly normal karyotype AML in CR1 and was associated with high post-HCT relapses and poor OS (Table 1).[20, 24-27] We sought to analyze within the CIBMTR database the independent impact of FLT3 mut. on HCT outcomes in AML.

PATIENTS AND METHODS

The CIBMTR® is a research collaboration between the NMDP®/Be The Match® and the Medical College of Wisconsin. It comprises a group of ≥ 450 transplant centers worldwide that contribute detailed data on HCT. Studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

Inclusion Criteria

Adults ≥ 18 yr. with a diagnosis of *de novo* AML in CR1 or CR2 (M3 was excluded), with available FLT3 mut. status who underwent a HLA identical sibling or an 8/8 or 7/8 matched

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unrelated donor (URD) HCT after myeloablative (MAC), non-myeloablative (NMA), or reduced intensity conditioning (RIC) as previously defined[28] reported to the CIBMTR from 2008-2011 were included. Graft source could be either bone marrow or peripheral blood stem cells, and any graft-versus-host-disease (GVHD) prophylaxis excluding *ex- vivo* T cell depletion was permitted. Cord blood and haploidentical transplants were excluded to decrease heterogeneity and due to small numbers of pts. Centers that never reported FLT3 mut. were excluded to avoid ascertainment bias. As CIBMTR data collection does not distinguish between ITD and TKD mut. or allelic ratios, all pts with FLT3 mut. were included.

Endpoints and Statistical Analysis

Patient- and HCT-related characteristics were identified, and the primary endpoints included the risk of relapse, non-relapse mortality (NRM), leukemia-free survival (LFS), and OS. Cumulative incidence (*CI*) of relapse was defined as the onset of recurrent AML through morphologic evidence in the bone marrow or extra medullary sites, and NRM was considered a competing risk. *CI* of NRM was defined as time to death from any cause while in remission, and disease relapse was considered a competing risk. LFS was calculated as the interval from HCT to time of relapse or death from any cause. OS was calculated as the interval from HCT to death from any cause. Endpoints were calculated at 3 yr.

The Kaplan-Meier estimator was used to calculate the probability of LFS and OS. Probabilities of disease relapse, NRM, incidences of acute and chronic GVHD were calculated using the *CI* estimates to account for competing risks. Clinical outcomes following HCT for FLT3 mut. and FLT3 WT AML pts were compared adjusting as indicated for significant patient-, disease-, and HCT-related variables. Cox proportional hazards regression was used to compare the two groups. Backward elimination was used to select significant covariates. Proportional hazards assumption was checked. If violated, it was added as time-dependent covariate in the Cox model. Interactions between the main effect and significant covariates were examined. Due to the strong correlation with FLT3 mut. status, WBC count at diagnosis was excluded in multivariate analysis (MVA).

RESULTS

Patient Characteristics

511 pts from 48 reporting centers worldwide between 2008 and 2011 were included in the analysis. Median follow-up of survivors was 37 months (12-65). 158 (31%) pts were FLT3 mut. Patient-, disease- and HCT- characteristics are outlined in Table 2.

Transplant Outcomes

The MVA of outcomes are shown in Table 3.

Relapse Risk

The *CI* of relapse at 3 yr. was 38% (95% CI 30-45) in the FLT3 mut. group compared to 28% (95% CI 24-33) in the FLT3 WT group, P=0.04. In MVA, relapse was higher in FLT3 mut. group (RR 1.6; 95% CI 1.15-2.22, P =0.005) shown in figure 1. Disease status at time

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of HCT (CR2 vs.CR1, RR 1.52; 95% CI 1.08-2.14, *P*=0.016) and conditioning intensity (RIC/NMA vs. MAC, RR 2.14; 95% CI 1.57-3.70, *P*<0.001) were associated with increased risk of relapse while, HCT from a URD compared to HLA-Identical sibling led to reduced relapse risk (RR 0.64; 95% CI 0.45-0.90, *P*=0.0095). For pts who underwent HCT in CR1, relapse was significantly impacted by the number of consolidation cycles, with pts who received ≥ 3 consolidations having lower risk of relapse compared to those with no consolidation (*P*= 0.046, 1 cycle [RR 0.76, 95% CI 0.47-1.23], 2 cycles [RR 0.53, 95% CI 0.28-1.00], and ≥3 cycles [RR 0.45, 95% CI 0.22-0.95]). Pts who underwent HCT in CR2 with mut. FLT3 also had higher relapse risk (RR 1.83 95% CI 1.00- 1.83, *P*=0.049) compared to pts in CR2 who were FLT3 WT. There was no significant statistical interaction between FLT3 status and cytogenetics (*P*=0.85), FLT3 status and disease status (*P*=0.18) nor cytogenetics and disease status (*P*=0.99).

GVHD

There was no difference in the incidence of acute GVHD between the FLT3 mut. (38% (95%CI 30-45)) and WT groups (32% (95% CI 28-37)) at 100 days (P =0.27). There was no difference in chronic GVHD between the FLT3 mut. (61% (95%CI 52-69)) and WT groups (60% (95% CI 54-65)) at 3 yr. (P =0.86).

Non-Relapse Mortality

Univariate analysis(UVA) showed no significant difference in the *CI* of NRM between the FLT3 mut.(11% (95% CI 7-17)) and WT groups (13% (95% CI 10-17)) at 1 year (*P*=0.65). In MVA, there was no significant association between FLT3 mut. status and NRM (RR 0.77; 95% CI 0.48-1.22, *P*=0.26) (Table 3). Compared to HCT from HLA-identical sibling donors, risk of NRM was higher in 7/8 URD (RR 2.82; 95% CI 1.48-5.37, *P*=0.001). Other adverse prognostic factors included the use of total body irradiation based MAC (p=0.047) and HCT comorbidity index scores of 1 or greater (P<0.001). *In vivo* T cell depletion was associated with higher NRM within 6 months of HCT (*P* <0.001).

Leukemia Free Survival

UVA showed no significant difference in the 3 year-LFS between the FLT3 mut. (47%, 95% CI 39-55) and WT groups (51%, 95 % CI 45-56) (*P*=0.42) which was confirmed in MVA (RR 1.25; 95% CI 0.96-1.67, *P*=0.1). LFS was inferior among pts who were transplanted in CR2 (RR 1.44; 95% CI 1.09-1.90, *P*=0.011), among those who underwent RIC/NMA preparative regimen (RR 1.52; 95% CI 1.07-2.16, *P* = 0.021) or had HCT from 7/8 unrelated donor (RR 1.58; 95% CI 1.08-2.30, *P* =0.018). In this model there was no significant interaction between FLT3 status and cytogenetics (*P*= 0.70).

Overall Survival

UVA showed similar OS between the FLT3 mut. (49% (95%CI 40-57)) and WT groups (55% (95% CI 50-60)) at 3 yr. (P =0.20). In MVA OS was not significantly associated with FLT3 mut. status (RR 1.17; 95% CI 0.89-1.53) as shown in figure 2. OS was inferior among pts older than 40 yr. (RR 1.77; 95% CI 1.32-2.37, *P* < 0.001), and after 7/8 URD (RR 2.33; 95% CI 1.60-3.40, *P* < 0.001).

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We re-ran the models for LFS and OS after excluding pts with poor risk cytogenetics and there was no significant difference between the two groups (data not shown)

Causes of Death

More pts in the FLT3 mut. group (60% versus 46%) died from their leukemia compared to FLT3 WT group (Table 4).

DISCUSSION

Many physicians favor early HCT as the most optimal consolidation[18, 19, 29] for pts with FLT3 mut. AML though this strategy remains controversial.[20, 21, 30-32] In our study, we were able to examine the impact of regimen intensity, consolidation, and disease status (CR1 vs. CR2) on HCT outcomes in FLT3 mut. AML, with long median follow-up of 37 months. This study shows that though pts with FLT3 mut. AML have higher relapse risk after HCT, there is no difference in NRM, LFS, or OS, and 49% pts were alive at 3 yr. Furthermore, our results show that RIC/NMA conditioning may be a feasible strategy in pts who are unsuitable for MAC.

A possible explanation for the increase in relapse risk without concomitant detriment in OS may be the differences in post relapse intervention such as early withdrawal of immunosuppression; institution of tyrosine kinase inhibitor (TKI) based therapy in FLT3 mutated pts, or salvage treatment (chemo/donor lymphocyte infusion (DLI), second HCT), which are all difficult to capture explicitly in a registry study and may have played a role. We reviewed the CIBMTR database to determine if the pts included in this analysis received salvage DLI or a 2nd HCT post relapse, and observed that 16 /60 (27%) pts in the FLT3 mut. group who relapsed and 39/102 (38%) in the FLT3 WT group who relapsed received a DLI or 2nd HCT after relapse.

Brunet et al from the EBMT analyzed outcomes of 206 pts who underwent HLA identical sibling and matched URD HCT with only cytogenetically normal FLT3-ITD mut. AML in CR1 after MAC. They showed a higher relapse (30% vs. 16%, P=0.0006) but also noted inferior LFS (58% vs. 71%, P=0.04) in the FLT3-ITD mut. pts.[24]

Many pts with FLT3-ITD mut. relapse within 6 months of diagnosis and it is postulated that more consolidation in these pts may promote relapse due to upregulation of the FLT3 ligand.[29] In our study, we analyzed the impact of the number of consolidations cycles in pts who underwent HCT in CR1 and found that more cycles (≥ 2) of consolidation chemo were associated with decreased the risk of relapse. However, it is noted that this data includes only pts who survived and received HCT in CR1 and cannot account for those pts who died early due to relapse.

Furthermore, our results showed that some pts with FLT3 mut. are able to achieve CR2 and undergo HCT. Our study showed that pts with mut. FLT3 in either CR1 or CR2 had similar increased relapse risk without adverse effect on NRM, LFS, and OS. While recognizing that the cohort of CR2 pts (n=134) is likely to be representative of highly selected pts (those who have chemo-sensitive disease that was kinetically stable to allow time for HCT in CR2), our

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data suggests that pts with FLT3 mut. AML who are able to achieve CR2 should be considered for HCT.

Though our study population included FLT3 mut. pts with abnormal cytogenetics, different conditioning regimens, and pts in CR1 or CR2, our MVA showed no significant interaction among these variables. The limitations of our study include those that are inherent in a retrospective registry study. Unfortunately, the data collected by CIBMTR during the study period did not include information about type of FLT3 mut. (ITD vs. TKD), allelic ratios, and minimal residual status at time of HCT, which precludes comment on these variables.

In summary, we show that HCT may be able to overcome the negative prognostic impact of FLT3 mut. in AML with promising LFS and OS. Because most relapses in the FLT3 mut. group were early, usually within the first year, continued investigation of pre-emptive strategies, such as post -HCT maintenance therapy with FLT3 inhibitors or hypomethylating agents, early withdrawal of immunosuppression, and DLI may have value. FLT3 inhibitors such as sorafenib[33, 34], quizartinib[35] and midostaurin are under investigation in the post-HCT maintenance setting, and may improve outcomes of these high risk pts.

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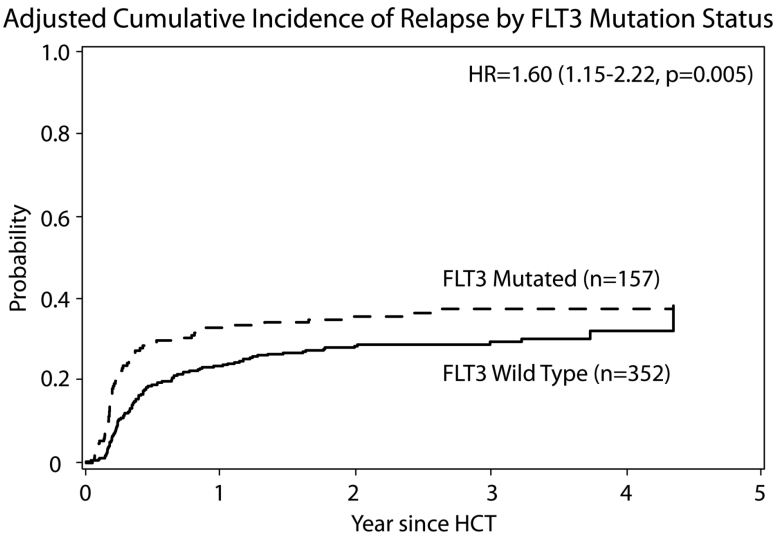

Figure 1.
Adjusted CI of Relapse by FLT3 mut. status

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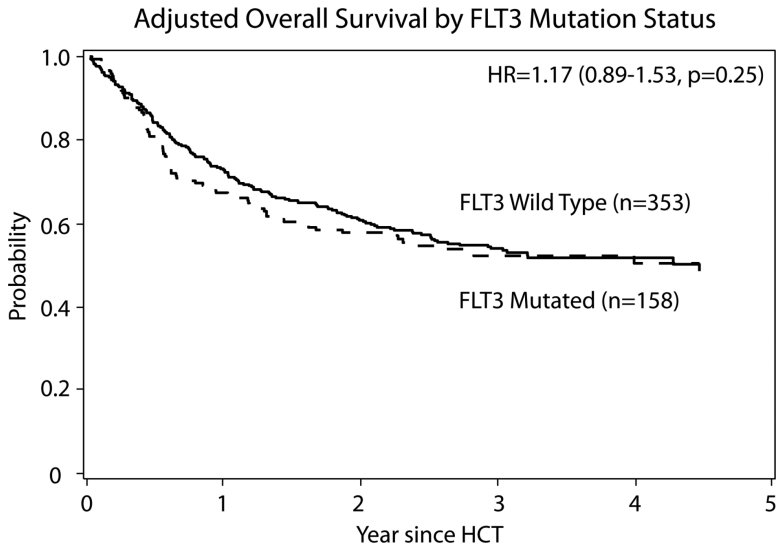

Figure 2.
Adjusted Overall Survival by FLT3 mut. status

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Table 1

Studies addressing Post HCT outcomes of pts with FLT3 mut.

Reference	Total pts	FLT3 Mut. underwent HCT	Cytogenetics of FLT3 mut. pts	Relapse in FLT3 Mut.pts	OS of FLT3 Mut. pts
[20]	103	40	Intermediate	Increased	No Difference
[24]	206	86	Normal	Increased	Worse
[26]	75	16	Normal (12) Monosomal karyotype (4)	Increased	Worse
[25]	171	50	Intermediate (41) Unknown (9)	Increased	Worse (p =.334)
[27]	702	344	Normal	Increased	Worse

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Table 2

Patient Characteristics

Variable	FLT3 mut Wild type	Mut.	p-value
Number of pts	353	158	
Median Age(range)	46 (18-60)	47 (18-60)	0.47
Gender			0.05
Male	190 (54)	70 (44)	
Female	163 (46)	88 (56)	
Recipient race			0.78
Caucasian	320 (91)	142 (90)	
Non-Caucasian	29 (8)	15 (9)	
Karnofsky score			0.92
<90%	103 (29)	49 (31)	
≥90%	234 (66)	102 (65)	
Missing	16 (5)	7 (4)	
White blood count at diagnosis (×10^9/L)			<0.001
Median (range)	10 (<1-344)	34 (<1-305)	<0.001
HCT Co-morbidity Index			0.95
0	131 (37)	57 (36)	
1	91 (26)	40 (25)	
2+	10 (3)	6 (4)	
Missing	121 (34)	55 (35)	
Cytogenetic abnormalities			<0.001
Favorable	25 (7)	5 (3)	
Intermediate	216 (61)	128 (81)	
Normal	*114 (32)*	*102(65)*	
Poor	101 (29)	20 (13)	
Missing	11 (3)	5 (3)	
Disease status prior to HCT			0.07
CR1	252 (71)	125 (79)	
CR2	101 (29)	33 (21)	
Status at CR1			<0.001
Hematologic CR only	123 (35)	68 (43)	
Cytogenetic and molecular CR	94 (27)	64 (41)	
Cytogenetic CR	130 (37)	22 (14)	
Molecular CR	6 (2)	4 (3)	
Time from diagnosis to HCT (for CR1 HCT), months			0.82
Median (range)	4 (2-17)	4 (2-19)	0.59
<6 months	199 (79)	100 (80)	
≥6 months	53 (21)	25 (20)	
Time to achieve CR1 (for CR1 HCT), weeks			0.05

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Variable	FLT3 mut Wild type	Mut.	p-value
Median (range)	6 (1-71)	5 (1-22)	0.07
Time from CR1 to HCT (for CR1 HCT), weeks			0.12
Median (range)	11 (1-53)	13 (1-76)	0.02
Lines of induction prior to CR1 (for CR1 HCT)			0.06
1	177 (70)	102 (82)	
2	63 (25)	20 (16)	
≥3	12 (5)	3 (2)	
Type of induction therapy (for CR1 HCT)			0.12
7+3	156 (62)	72 (58)	
7+3 + other	78 (31)	50 (40)	
Other	16 (6)	3 (2)	
Cycle of consolidation therapy prior to CR1 HCT			0.02
No consolidation given	86 (34)	24 (19)	
1	71 (28)	49 (39)	
2	32 (13)	23 (18)	
≥3 cycles	33 (13)	17 (14)	
Missing	30 (12)	12 (10)	
Duration of CR1 (for CR2 HCT), months			0.006
Median (range)	11 (1-98)	6 (<1-42)	0.006
Time from relapse to HCT (for CR2 HCT), months			0.59
Median (range)	3 (1-17)	3 (1-19)	0.76
0-3 months	41 (41)	14 (42)	
3-6 months	43 (43)	13 (39)	
>6 months	9 (9)	5 (15)	
Missing	8 (8)	1 (3)	
Conditioning regimen intensity			0.19
MAC with TBI	140 (40)	74 (47)	
MAC without TBI	162 (46)	62 (39)	
RIC/NMA	51 (14)	21 (13)	
Type of donor			0.69
HLA-identical sibling	150 (42)	67 (42)	
8/8 URD	165 (47)	70 (44)	
7/8 URD	38 (11)	21 (13)	
Donor age of unrelated donor HCT			0.19
Median (range)	30 (19-56)	33 (19-52)	0.04
GVHD prophylaxis			0.75
Tacrolimus ± others	302 (86)	139 (88)	
CSA ± others	42 (12)	16 (10)	
Others	9 (3)	3 (2)	
In vivo T cell Depletion			0.84
ATG alone	80 (23)	34 (22)	

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	FLT3 mut		
Variable	**Wild type**	**Mut.**	**p-value**
Alemtuzumab alone	4 (1)	1 (<1)	
No ATG or alemtuzumab	268 (76)	123 (78)	
Graft type			0.33
Bone marrow	59 (17)	21 (13)	
Peripheral blood	294 (83)	137 (87)	
Donor/Recipient CMV serostatus			0.60
R+	193 (55)	96 (61)	
R-D+	46 (13)	16 (10)	
R-D−	108 (31)	44 (28)	
Donor/Recipient sex match			0.16
M/M	121 (34)	43 (27)	
M/F	93 (26)	56 (35)	
F/M	69 (20)	27 (17)	
F/F	70 (20)	32 (20)	

CSA: cyclosporine; ATG: anti-thymocyte globulin; CMV: cytomegalovirus

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Table 3

MVA of Effect of FLT3 Mut. on Outcomes

	N	RR (95%CI)	p-value
1. Relapse (All pts)			
Main effect:			
FLT3 mut.			
No	352	1	
Yes	157	1.60 (1.15-2.22)	0.0048
Other factors:			
Disease status			
CR1	375	1	
CR2	134	1.52 (1.08-2.14)	0.016
Conditioning intensity			
MAC with TBI	214	1	$P_{overall}$=0.0003
MAC without TBI	224	1.31 (0.92-1.89)	0.14
RIC/NMA	71	2.41 (1.57-3.70)	<.0001
Donor type			
HLA-id sibling	217	1	$P_{overall}$=0.032
8/8 URD	233	0.64 (0.45-0.90)	0.0095
7/8 URD	59	0.89 (0.53-1.49)	0.65
2. Non Relapse mortality (All Pts)			
Main effect:			
FLT3 mut			
No	352	1	
Yes	157	0.77 (0.48-1.22)	0.26
Other factors:			
HCT comorbidity index			
0	187	1	$P_{overall}$=0.0018
1	131	1.77 (1.06-2.94)	0.028
2+	16	4.50 (1.99-10.18)	0.0003
Missing	175	1.24 (0.74-2.09)	0.41
Conditioning intensity			
MAC with TBI	214	1	$P_{overall}$=0.047
MAC without TBI	224	0.58 (0.37-0.90)	0.015
RIC/NMA	71	0.66 (0.35-1.26)	0.21
Donor type			
HLA-id sibling	217	1	$P_{overall}$=0.0064
8/8 URD	233	1.47 (0.91-2.38)	0.12
7/8 URD	59	2.82 (1.48-5.37)	0.0016

In-vivo T-cell depletion, NRM≤ 6 months

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	N	RR (95%CI)	p-value
No	390	1	
Yes	115	3.30 (1.71-6.34)	0.0003
In-vivo T-cell depletion, NRM> 6 months			
No	280	1	
Yes	76	0.69 (0.34-1.43)	0.32
3. LeukemiaFree Survival			
Main effect:			
FLT3 mut			
No	352	1	
Yes	157	1.25 (0.96-1.67)	0.099
Cytogenetic abnormalities			
Normal	216	1	$P_{overall}$=0.026
Favorable	30	0.49 (0.26-0.92)	0.027
Intermediate (excludingnormal)	127	0.94 (0.68-1.29)	0.68
Poor	121	1.21 (0.88-1.68)	0.25
Missing	15	1.69 (0.92-3.13)	0.094
Disease status			
CR1	375	1	
CR2	134	1.44 (1.09-1.90)	0.011
Conditioning intensity			
MAC with TBI	214	1	$P_{overall}$=0.028
MAC without TBI	224	0.96 (0.73-1.27)	0.78
RIC/NMA	71	1.52 (1.07-2.16)	0.021
Donor type			
HLA-id sibling	217	1	$P_{overall}$=0.0081
8/8 or well matched URD	233	0.88 (0.67-1.16)	0.36
7/8 URD	59	1.58 (1.08-2.30)	0.018
4. Overall mortality			
Main effect:			
FLT3 mut			
No	352	1	
Yes	157	1.17 (0.89-1.53)	0.25
Other factors:			
Recipient age			
18-39	177	1	
40-60	332	1.77 (1.32-2.37)	0.0001
White blood count at diagnosis			
<30	299	1	$P_{overall}$=0.006
30-100	114	1.43 (1.04-1.95)	0.027
>100	61	1.82 (1.26-2.61)	0.0013

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	N	RR (95%CI)	p-value
Missing	35	1.05 (0.62-1.77)	0.87
Donor type			
HLA-id sibling	217	1	$P_{overall}$<.0001
8/8 or well matched URD	233	1.17 (0.89-1.55)	0.27
7/8 URD	59	2.33 (1.60-3.40)	<.0001

RR: relative risk

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Table 4

Causes of Death

	FLT3 mut.	
	WT	**Mut.**
Total deaths	154	77
Primary disease	71 (46)	46 (60)
GVHD	21 (14)	8 (10)
Idiopathic pneumonia syndrome	11 (7)	4 (5)
Infection	21 (14)	8 (10)
Organ failure	14 (9)	8 (10)
Others	14 (9)	2 (3)
Missing	2	1