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Abstract 398

Prognostic Significance of Genetic Alterations in Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia Treated with Hyper-CVAD Plus Dasatinib or Hyper-CVAD Plus Ponatinib

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Introduction: Clinical outcomes of patients with Philadelphia chromosome positive (Ph+) B-ALL have been significantly improved with the addition of tyrosine kinase inhibitors (TKIs). The treatments with a TKI alone or a TKI with chemotherapy result in morphological complete response in nearly all patients with Ph+ B-ALL. However, persistence of measurable residual disease (MRD) and disease relapse remain major clinical problems (Ravandi et al. Blood 2019). Identification of predictive and prognostic biomarkers for Ph+ B-ALL is urgently needed.

Recurring genetic abnormalities such as deletions in *IKZF1*, *CDKN2A/2B*, *PAX5*, *BTG1*, and *EBF1* have been identified in Ph+ B-ALL (Mullighan et al. Nature 2008). Among those, *IKZF1* deletion has been associated with poor prognosis in Ph+ B-ALL patients treated with imatinib-based or dasatinib-based regimens. However, molecular determinants for clinical outcomes in ponatinib (potent TKI)-treated patients are not known. Here, we have systematically analyzed genetic alterations in adult Ph+ B-ALL patients uniformly treated in clinical trials with Hyper-CVAD plus dasatinib or Hyper-CVAD plus ponatinib regimens and investigated the molecular determinants for treatment outcomes and prognosis.

Methods: We analyzed pretreatment bone marrow or peripheral blood specimens collected from adults with Ph+ B-ALL, who participated in clinical trials with either NCT00390793 (Hyper-CVAD plus dasatinib, N=55) or NCT01424982 (Hyper-CVAD plus ponatinib, N=50). Targeted capture DNA sequencing of 295 genes (N=102) or whole exome sequencing (WES, N=3) was performed. Genome-wide copy number analysis (CNA) was performed using either SNP microarray (N=102) or WES (N=3).

Results: Baseline clinical characteristics of these patients are described in **Table 1**. The landscape of genetic alterations, which summarizes the CNAs and point mutations detected is shown in **Figure 1**. The most frequently detected alterations were *IKZF1* deletion. Among the 63 cases with *IKZF1* deletion, we addressed detailed deletion site in 53 cases. Ik6 subtype, which is characterized by deletion of exon 4–7 (N=28, 23%) was most frequently detected followed by Ik2 subtype, which involves deletion of exon 2 (N=20, 32%).

Figure 2A and 2B show the impact of each genetic alteration on event-free survival (EFS) and overall survival (OS). Cases harboring Ik2 subtype deletion or Ik6 subtype deletion showed significantly worse EFS (hazard ratio [HR]=1.91; p=0.048) and OS (HR=2.36; p=0.019) than non-*IKZF1* deletion cases or cases with *IKZF1* deletion other than Ik2 or Ik6 subtype. We defined the *IKZF1*^{plus} group as the group consisting of the cases with deletion of *IKZF1* and other deletions.

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Then, we performed univariate analysis for cases with *IKZF1* deletion in order to find the significant deletion partner of *IKZF1* deletion in terms of prognosis (**Figure 3A and 3B**) and we defined *IKZF1*$^{plus(rev)}$ group as cases *IKZF1* deletion with both *CDKN2A/2B* deletions and *VPREB1* deletion or, or at least one of them. *IKZF1*$^{plus(rev)}$ group showed worse prognosis on EFS and OS than non-*IKZF1*$^{plus(rev)}$ group (**Table 2A**).

Combining the results of the impact of Ik subtype and *IKZF1*$^{plus(rev)}$ group on EFS and OS, we defined *IKZF1*-driven high-risk group as cases harboring either alteration of Ik2/Ik6 subtype or *IKZF1*$^{plus(rev)}$. *IKZF1*-driven high-risk group showed worse prognosis on EFS and OS than *IKZF1*-driven low-risk group (**Table 2B**).

Next, we performed univariate analysis and multivariate analysis combining baseline features, TKI type, and MRD status to assess their impact on outcome (**Figure 4A and 4B**). Multivariate analysis showed TKI type, MRD status at 3 months, and *IKZF1*-driven high-risk group were independent factors for OS. (**Figure 4B**).

Figures 5A and 5B show EFS and OS according to TKI type and *IKZF1*-driven risk. In patients treated with Hyper-CVAD plus ponatinib and categorized into *IKZF1*-driven low-risk group, the 5-year EFS and OS rates were 92.0% and 96.0%, respectively (**Table 2C**).

Discussion: In this study, unlike with dasatinib-based therapy, we demonstrated that *IKZF1*-driven high-risk group was associated with worse EFS and OS than *IKZF1*-driven low-risk in the context of Hyper-CVAD plus ponatinib. Evaluation of the prognostic implication of Ph+ B-ALL using *IKZF1*-driven risk group at the time of the diagnosis may be useful to personalize treatment in order to improve the clinical outcome of Ph+ B-ALL in the era of ponatinib.

Table 1. Patient characteristics

	Entire cohort	**HCVAD plus dasatinib**	**HCVAD plus ponatinib**	**p. value (dasatinib vs ponatinib)**
Patients	105	55	50	
Age (range)	51.9 (22–80)	53.49 (22–80)	50.08 (23–80)	0.252
AYA, age <40 (%)	24 (22.9)	12 (21.8)	12 (24.0)	0.82
Sex, female (%)	41 (39.0)	27 (49.1)	24 (48.0)	1
PS ≥2 (%)	15 (14)	8 (14.5)	7 (14.0)	1
WBC x 10^9/L (range)	68.40 (0.9–658.1)	71.63 (1.1–658.1)	64.85 (0.9–629.4)	0.771
HGB g/dl	10.21 (5.7–15.8)	10.19 (5.9–15.7)	10.24 (5.7–15.8)	0.913
PLT x 10^9/L (range)	83.19 (3–416)	91.91 (3–416)	73.60 (3–324)	0.28
BM, blast % (range)	79.61 (15–98)	78.78 (27–98)	80.52 (15–98)	0.584
Cytogenetic abnormality				
Isolated Ph+	28	16	12	0.721
Ph+ and ACA	72	36	36	
IM	4	2	2	
Not done	1	1	0	
Transcript subtype				
B2A2	14	6	8	0.898
B3A2	11	7	4	
B2A2 + B3A2	2	1	1	
E1A2	76	40	36	
E1A3	2	1	1	
CNS leukemia (%)	0	9 (16.4)	3 (6.0)	0.128
CD20 expression	26.22 (0–99.4)	30.71 (0–99.4)	21.27 (0–98.2)	0.154
Rituximab or ofatumumab therapy (%)	34 (32.4)	19 (34.5)	15 (30.0)	0.679

Table 2A. Clinical outcome according to *IKZF1*$^{plus(rev)}$ status and *IKZF1*-driven risk group

Non-*IKZF1* plus (rev)			*IKZF1* plus (rev)	
median EFS months (95% CI)	5-year EFS rate % (95% CI)		median EFS months (95% CI)	5-year EFS rate % (95% CI)
118 (118–NA)	65.1 (52.9–74.8)		14 (10–79)	29.8 (11.9–50.2)
		p=0.000907		
median OS months (95% CI)	5-year OS rate % (95% CI)		median OS months (95% CI)	5-year OS rate % (95% CI)
119 (119–NA)	69.9 (57.8–79.1)		26 (11–80)	44.0 (23.4–62.9)
		p=0.00183		

Table 2B. Clinical outcome according to *IKZF1*$^{plus(rev)}$ status and *IKZF1*-driven risk group

IKZF1-driven low-risk			*IKZF1*-driven high-risk	
median EFS months (95% CI)	5-year EFS rate % (95% CI)		median EFS months (95% CI)	5-year EFS rate % (95% CI)
NA (52–NA)	66.3 (49.5–78.7)		19 (12–118)	43.4 (28.7–57.3)
		p=0.0176		
median OS months (95% CI)	5-year OS rate % (95% CI)		median OS months (95% CI)	5-year OS rate % (95% CI)
NA (NA–NA)	73.6 (57.3–84.4)		67 (20–NA)	50.8 (35.3–64.4)
		p=0.0125		

Table 2C. Clinical outcome according to *IKZF1*$^{plus(rev)}$ status and *IKZF1*-driven risk group

	IKZF1-driven low-risk		*IKZF1*-driven high-risk	
TKI type	median EFS months (95% CI)	5-year EFS rate % (95% CI)	median EFS months (95% CI)	5-year EFS rate % (95% CI)
Dasatinib	20 (12–NA)	36.9 (16.6–57.6)	16 (10–84)	40.0 (22.6–56.9)
Ponatinib	NA (NA–NA)	92.0 (71.6–97.9)	24 (7–NA)	48.7 (23.6–69.9)
		p=0.0114		
TKI type	median OS months (95% CI)	5-year OS rate % (95% CI)	median OS months (95% CI)	5-year OS rate % (95% CI)
Dasatinib	32 (18–NA)	47.4 (24.4–67.3)	36 (13–119)	47.0 (28.5–63.4)
Ponatinib	NA (NA–NA)	96.0 (74.8–99.4)	NA (8–NA)	58.6 (30.3–78.8)
		p=0.0125		

Figure 1. Landscape of genetic alterations

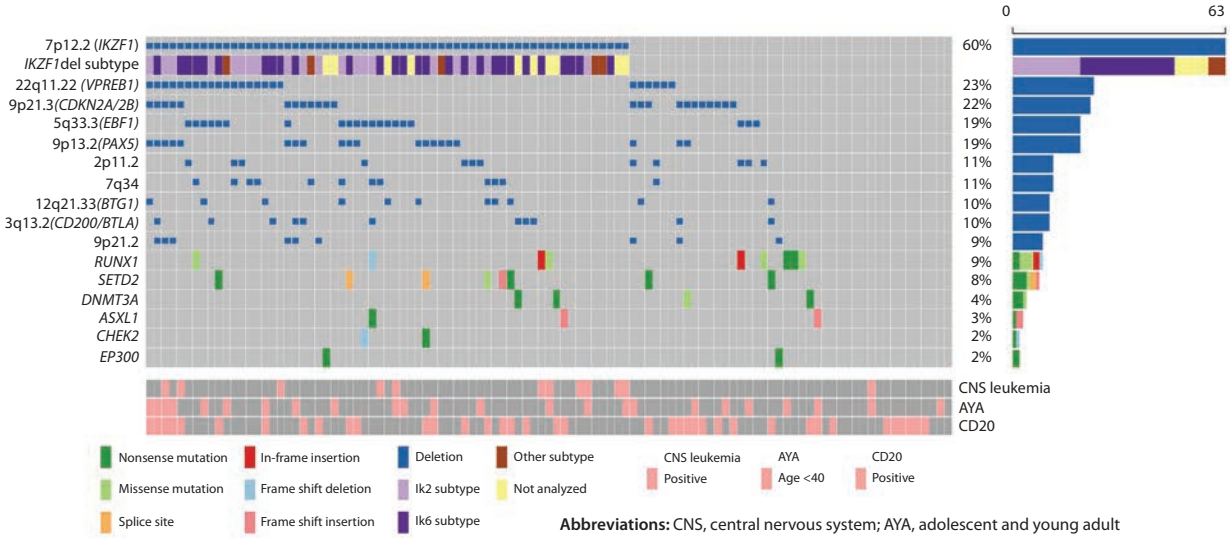


Figure 2. The impact of genetic alterations on event-free survival (EFS) and overall survival (OS)

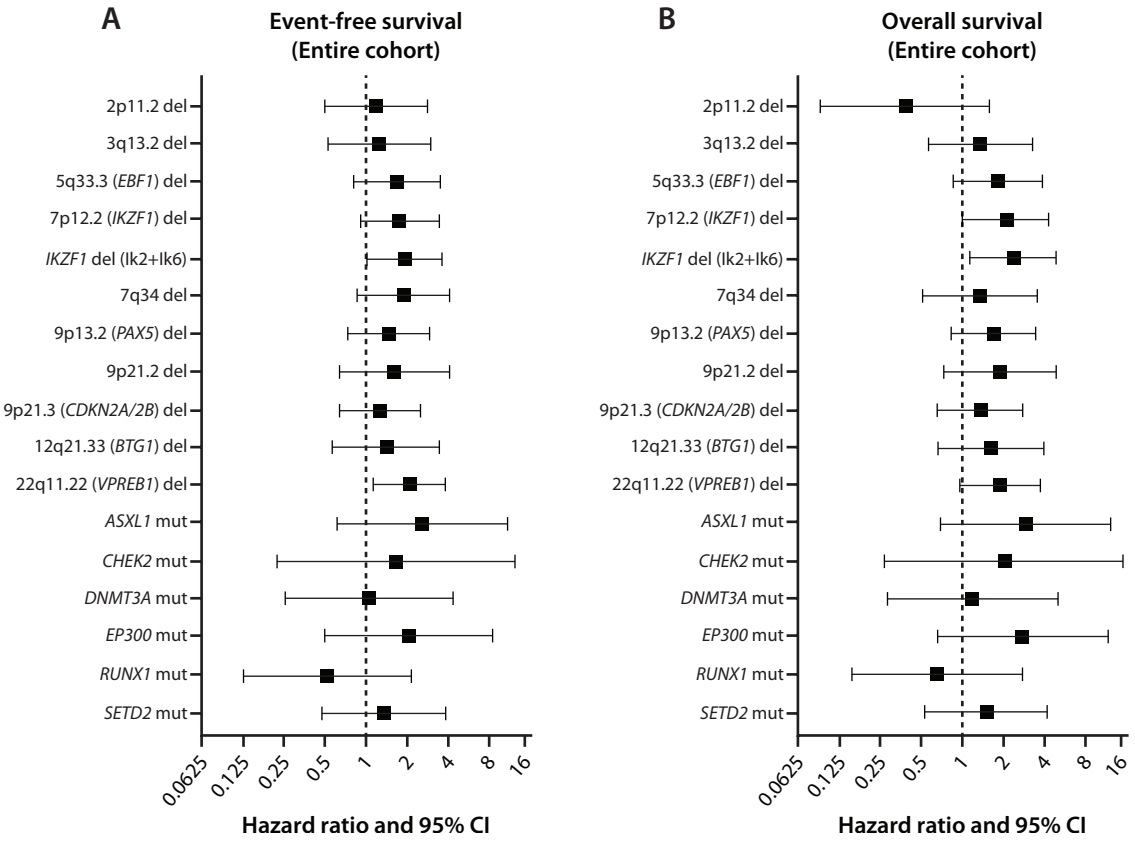


Figure 3. The impact of deletion on EFS and OS in addition to *IKZF1* deletion

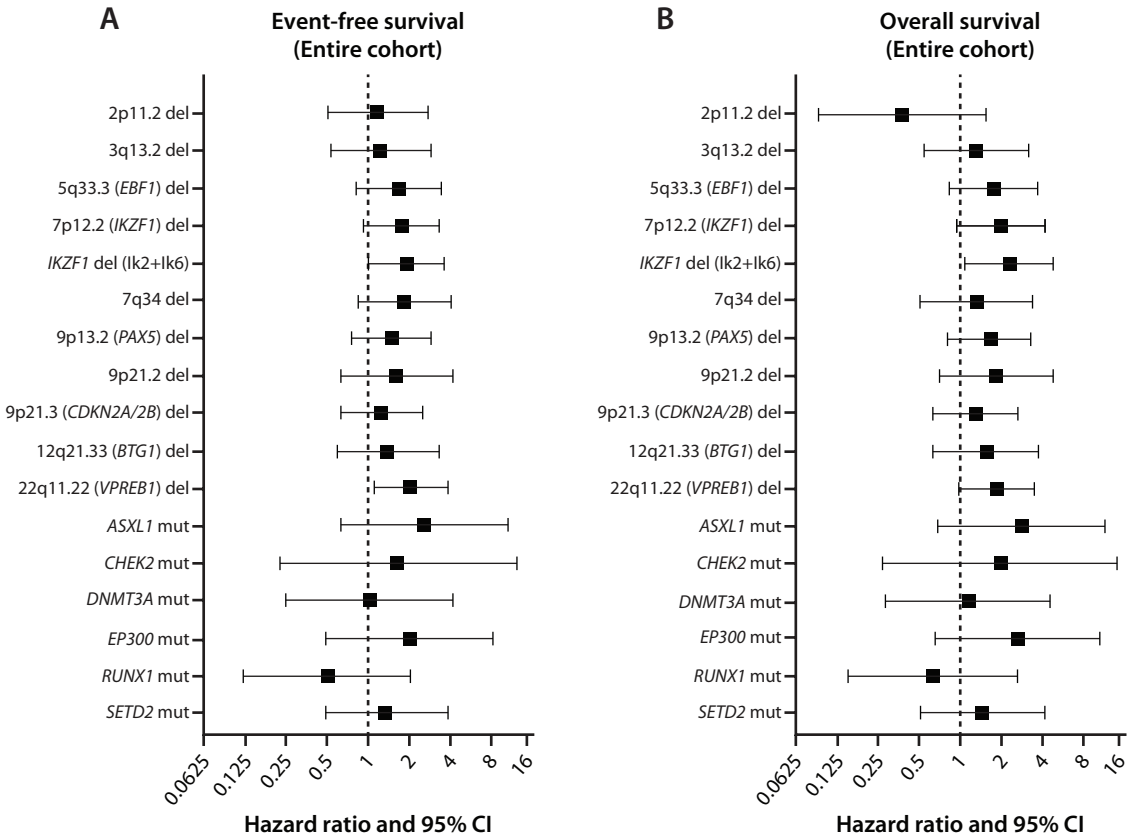


Figure 4. Univariate analysis and multivariate analysis for EFS and OS

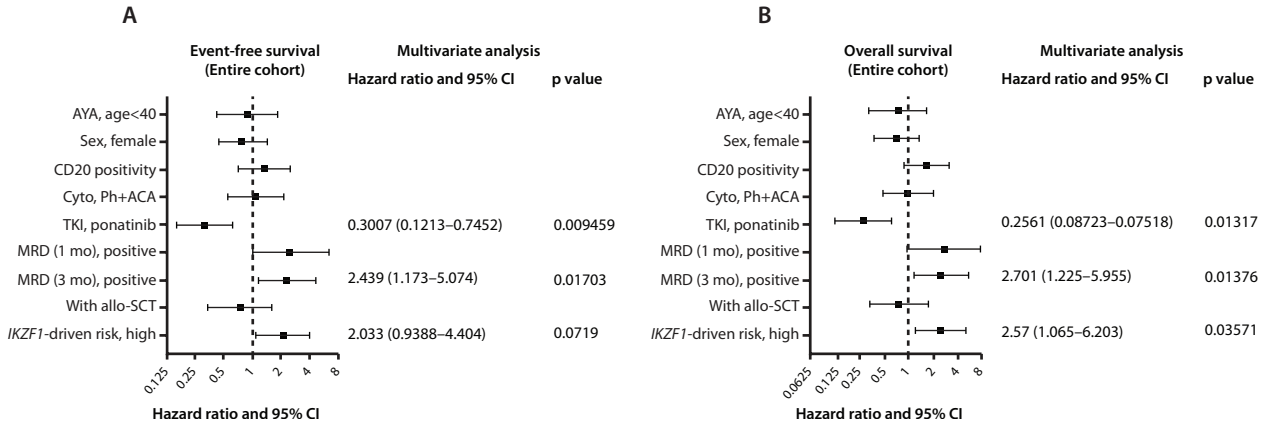
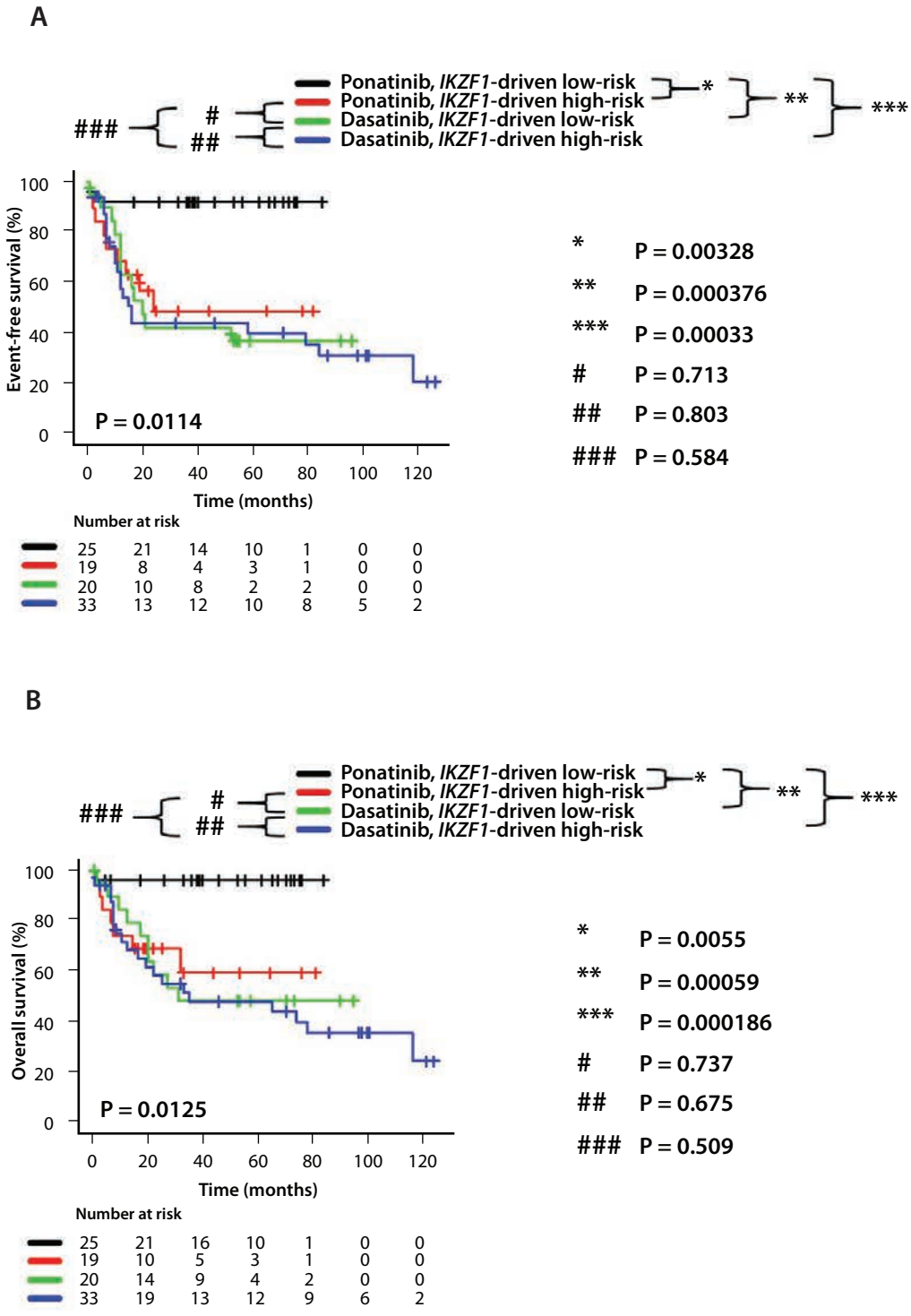


Figure 5. EFS and OS according to tyrosine kinase inhibitor type and IKZF1-driven risk group



Abbreviations: HCVAD, Hyper-CVAD; AYA, adolescents and young adults; PS, performance status; WBC, white blood cell count; HGB, hemoglobin; PLT, platelet; BM, bone marrow; Ph, Philadelphia chromosome; ACA, additional chromosomal abnormality; IM, insufficient metaphase; CNS, central nervous system; del, deletion; mut, mutation; CI, confidence interval; Cyto, cytogenetics; TKI, tyrosine kinase inhibitor; MRD, measurable residual disease; mo, month; allo-SCT, allogenic stem cell transplantation; NA, not applicable.

Disclosures: Kantarjian: *Pfizer:* Honoraria, Research Funding; *Novartis:* Honoraria, Research Funding; *Adaptive biotechnologies:* Honoraria; *Actinium:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Research Funding; *Amgen:* Honoraria, Research Funding; *Abbvie:* Honoraria, Research Funding; *Jazz:* Research Funding; *Immunogen:* Research Funding; *Ascentage:* Research Funding; *BMS:* Research Funding; *Daiichi-Sankyo:* Honoraria, Research Funding; *Janssen:* Honoraria; *Delta Fly:* Honoraria; *Oxford Biomedical:* Honoraria; *Aptitute Health:* Honoraria; *BioAscend:* Honoraria. **Short:** *Takeda Oncology:* Consultancy, Honoraria, Research Funding; *Amgen:* Honoraria; *Astellas:* Research Funding; *AstraZeneca:* Consultancy. **Jain:** *TG Therapeutics:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Genentech:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Fate Therapeutics:* Research Funding; *Pharmacyclics:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Adaptive Biotechnologies:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *AstraZeneca:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Precision Bioscienes:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *BMS:* Research Funding; *Pfizer:* Research Funding; *AbbVie:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Verastem:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Aprea Therapeutics:* Research Funding; *ADC Therapeutics:* Research Funding; *Incyte:* Research Funding; *Servier:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Cellectis:* Research Funding; *BeiGene:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Sasaki:** *Daiichi Sankyo:* Consultancy; *Otsuka:* Honoraria; *Novartis:* Consultancy, Research Funding; *Pfizer Japan:* Consultancy. **Ravandi:** *BMS:* Consultancy, Honoraria, Research Funding; *Celgene:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria, Research Funding; *Xencor:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria, Research Funding; *Astellas:* Consultancy, Honoraria, Research Funding; *Orsenix:* Consultancy, Honoraria, Research Funding; *Jazz Pharmaceuticals:* Consultancy, Honoraria, Research Funding; *Macrogenics:* Research Funding. **Konopleva:** *Ascentage:* Research Funding; *Calithera:* Research Funding; *Reata Pharmaceutical Inc.;:* Patents & Royalties: patents and royalties with patent US 7,795,305 B2 on CDDO-compounds and combination therapies, licensed to Reata Pharmaceutical; *Forty-Seven:* Consultancy, Research Funding; *Amgen:* Consultancy; *AstraZeneca:* Research Funding; *F. Hoffmann La-Roche:* Consultancy, Research Funding; *Agios:* Research Funding; *Cellectis:* Research Funding; *Kisoji:* Consultancy; *Sanofi:* Research Funding; *Ablynx:* Research Funding; *Rafael Pharmaceutical:* Research Funding; *Genentech:* Consultancy, Research Funding; *AbbVie:* Consultancy, Research Funding; *Stemline Therapeutics:* Consultancy, Research Funding; *Eli Lilly:* Research Funding. **Garcia-Manero:** *AbbVie:* Honoraria, Research Funding; *Onconova:* Research Funding; *Bristol-Myers Squibb:* Consultancy, Research Funding; *Amphivena Therapeutics:* Research Funding; *Acceleron Pharmaceuticals:* Consultancy, Honoraria; *Celgene:* Consultancy, Honoraria, Research Funding; *H3 Biomedicine:* Research Funding; *Helsinn Therapeutics:* Consultancy, Honoraria, Research Funding; *Astex Pharmaceuticals:* Consultancy, Honoraria, Research Funding; *Jazz Pharmaceuticals:* Consultancy; *Novartis:* Research Funding; *Genentech:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Merck:* Research Funding. **Jabbour:** *BMS:* Other: Advisory role, Research Funding; *Amgen:* Other: Advisory role, Research Funding; *Genentech:* Other: Advisory role, Research Funding; *Pfizer:* Other: Advisory role, Research Funding; *AbbVie:* Other: Advisory role, Research Funding; *Adaptive Biotechnologies:* Other: Advisory role, Research Funding; *Takeda:* Other: Advisory role, Research Funding.

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