Clinical interrogation of *TP53* aberrations and its impact on survival in patients with myeloid neoplasms

Jayastu Senapati,[1*] Sanam Loghavi,[2*] Guillermo Garcia-Manero,[1] Guillin Tang,[2] Tapan Kadia,[1] Nicholas J. Short,[1] Hussein A. Abbas,[1] Naszrin Arani,[3] Courtney D. DiNardo,[1] Gautam Borthakur,[1] Naveen Pemmaraju,[1] Betul Oran,[4] Elizabeth Shpall,[4] Uday Popat,[4] Richard Champlin,[4] Sherry Pierce,[1] Sankalp Arora,[3] Ghayas Issa,[1] Musa Yilmaz,[1] Keyur Patel,[1] Koichi Takahashi,[1] Guillermo Montalban-Bravo,[1] Danielle Hammond,[1] Fadi G. Haddad,[1] Farhad Ravandi,[1] Hagop M. Kantarjian[1] and Naval G. Daver[1]

[1]Department of Leukemia; [2]Department of Hematopathology; [3]Department of Cancer Medicine and [4]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

**JS and SL contributed equally as first authors.*

Correspondence: N.G. Daver
ndaver@mdanderson.org

Received: August 14, 2024.
Accepted: December 3, 2024.
Early view: December 12, 2024.

https://doi.org/10.3324/haematol.2024.286465

Abstract

In myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) with *TP53* aberrations, dissecting the interaction amongst patient, disease and treatment factors are important for therapeutic decisions and prognostication. This retrospective analysis included patients with newly diagnosed MDS (>5% blasts) and AML with *TP53* mutation(s) treated at MD Anderson Cancer Center. We factored patient age, *TP53* aberration burden, therapy intensity and use of venetoclax in the AML subgroup, and allogeneic hematopoietic stem cell transplantation (HSCT) to interrogate outcomes. *TP53* was annotated as high-risk (TP53^{HR}) if >1 mutation, one mutation plus allelic deletion or a single mutation with variant allele frequency (VAF) ≥40%; *TP53* low-risk (*TP53*^{LR}) included a single *TP53* mutation VAF <40%. Four-hundred and thirteen patients (291 AML, 122 MDS) at a median age of 69.4 years were included, 350 (85%) with *TP53*^{HR} (253 AML [87%], 97 [79%] MDS). Overall response (OR) rate was 53% in AML and 62% in MDS. OR and composite complete response (CRc) rates was similar in patients with AML irrespective of treatment intensity, but higher when treated with venetoclax. At a median follow-up of 77 months, median OS was superior in patients with MDS than AML (10.8 *vs*. 5.9 months). On multivariate analysis (MVA) MDS had lower hazards of death compared to AML, as was *TP53*^{LR} and HSCT. In the AML cohort, *TP53*^{LR} and HSCT were favorable on MVA, though venetoclax did not improve survival. Both the diagnosis of MDS or AML and burden of *TP53* aberrations dictated outcomes in our analysis and HSCT consistently led to improved survival outcomes.

Introduction

The approval of several novel agents has improved the outcomes of patients with newly diagnosed acute myeloid leukemia (AML), though the outcomes of most patients with adverse-risk AML remain dismal.[1-5] AML with *TP53* aberrations has particularly dismal outcomes due to resistance to various treatments, including cytotoxic chemotherapy, epigenetic therapies, and apoptosis-inducing therapies such as venetoclax.[2,6-8] Recent attempts to improve the outcomes of patients with *TP53*-mutated (*TP53*^{mut}) AML have failed to improve survival, however extensive efforts are ongoing to leverage non-chemotherapy-based approaches to improve outcomes in these patients.[9-12] Mutation-agnostic agents including venetoclax, in combination with low-intensity therapy have failed to improve outcomes of patients with *TP53*^{mut} AML.[12-16] However, whether these outcomes are homogenously dismal regardless of the type of *TP53* aberrations, treatment intensity, or type of therapy needs to be better understood. Despite allogeneic hematopoietic stem cell transplantation (HSCT) being the only potentially curative option for patients with *TP53*^{mut} AML, post-HSCT survival remains generally poor. In addition, the impact of baseline *TP53* mutational burden and concomitant cytogenetics on HSCT outcomes remains poorly defined.

Previous studies have annotated the allelic status of *TP53* using the mutational burden (variant allele fraction [VAF]) and *TP53* allelic loss (*TP53*^{loss}) through cytogenetic assess-

ment.[17-19] These studies have made important contributions in correlating the burden of *TP53* aberrations with clinical outcomes; however, the interplay of blast burden and treatment regimens in conjunction with the burden of *TP53* aberrations is not well known and needs further characterization. A number of studies have suggested minimizing or even obviating the need for blast cutoffs in distinguishing *TP53*^{mut} AML from *TP53*^{mut} myelodysplastic neoplasms (MDS) with increased blasts, mostly due to their similarly poor outcomes irrespective of blast percentage and need for inclusion in clinical trials.[20-24]

Routine laboratory methods such as conventional karyotyping, fluorescence *in situ* hybridization (FISH), bulk next-generation sequencing (NGS), and array-specific comparative genomic hybridization (aCGH) can be used to infer the allelic status and the burden of *TP53* aberrations, which along with patient age, fitness, blood and/or bone marrow (BM) blast percentage, can be used for prognostication and to guide treatment decision-making. In view of evolving data dissecting the outcomes of patients with *TP53*^{mut} MDS and AML based solely on the burden of *TP53* aberrations, we attempted to more comprehensively study the outcomes of patients with newly diagnosed MDS and AML with *TP53* mutation at MD Anderson Cancer Center (MDACC) incorporating not just *TP53* burden, but also age, pathologic diagnosis (MDS *vs*. AML), treatment intensity, use of venetoclax and HSCT. The primary objective of the study was to compare the outcomes of patients with MDS and AML with *TP53* mutations and then to focus on factors affecting outcomes of patients in the AML cohort.

Methods

Patients and treatment

We performed a retrospective analysis of adult patients (≥18 years) with newly diagnosed MDS (and ≥5% blasts) and AML as per World Health Organization 2016 criteria[25] at MDACC harboring a pathogenic *TP53* mutation +/- concurrent deletion. Baseline parameters, including complete blood counts, BM blast percentage, cytogenetics and mutations, treatment intensity, use of frontline venetoclax and HSCT in first remission, were obtained from the electronic medical records. The study was approved by the Institutional Review Board and conducted in accordance with the declaration of Helsinki. Informed consent was obtained from all participants.

Assessment of *TP53* aberrations

TP53 mutation analysis

NGS was performed using our clinically-validated myeloid panels, interrogating the entire exonic or hotspot regions of 28, 53 or 81 genes (depending on the time of presentation) frequently mutated in myeloid malignancies, including *TP53*, with a lower limit of detection of VAF ≥2%, as described previously and detailed in the *Online Supplementary Appendix*.[26,27]

TP53 allelic loss/deletion

Allelic loss/deletion at the *TP53* locus was studied using a combination of conventional karyotyping, FISH and aCGH. Allelic loss/deletion was defined as described previously and detailed in the *Online Supplementary Appendix*.[28,29]

Annotation of TP53 aberrations

We classified our patient population based on the burden of *TP53* aberrations into *TP53* low-risk (*TP53*^{LR}) and *TP53* high-risk (*TP53*^{HR}) with a focus on clinical relevance. Multihit *TP53* aberrations included patients with >1 mutation, one *TP53* mutation plus deletion, and a *TP53* mutation plus copy neutral loss of heterozygosity (cnLOH) (assessed either through a-CGH or with high VAF [≥40%] as a surrogate).[19] Thus, our *TP53*^{HR} group included patients with documented multihit status (group 1: >1 *TP53* mutation with VAF ≥2%, [*Online Supplementary Figure S1*]; group 2: 1 *TP53* mutation [VAF ≥2%] and concurrent 17p.13 deletion, and group 3: *TP53* single hit mutations with VAF ≥40%).[19] The *TP53*^{LR} group included patients with a single mutation with a VAF <40% and no concurrent 17p.13 deletion.

Response and outcomes

Response was annotated per the European LeukemiaNet (ELN) 2017 guidelines for AML[30] and the 2006 International Working Group criteria for MDS.[31] Best response after frontline therapy was recorded, prior to HSCT. Overall response (OR) included a combination of complete remission (CR), complete remission with incomplete counts recovery (CRi) and morphological leukemia-free state (MLFS) for AML, and CR and BM CR for MDS. Relapse-free survival (RFS) was calculated from the time of best response to relapse, transformation to AML (for MDS patients) or death. We did not censor for HSCT. Overall survival (OS) was calculated from the time of therapy initiation to death from any cause and censored at last follow-up.

Statistical analysis

Mann-Whitney U test and a two-sided Fisher *t* test were used to compare continuous and categorical baseline variables. A *P* value of <0.05 was considered significant. Survival data were calculated using the Kaplan Meier test and compared using the Mantel Cox log-rank test. Follow-up was calculated using reverse Kaplan-Meier method. Cox proportional hazard was used to study disease and treatment factors associated with OS through univariate (UVA) and multivariate analysis (MVA). For MVA, factors biologically relevant on the UVA model and/or those with *P*<0.1 were used. We used a classification and regression tree (CRT) model as a predictive decision-making tool for survival at 1-year. Propensity score analysis was done by comparing logit of propensity scores from baseline covariates and

using a caliper width of sigma 0.1 with an optimal selection algorithm. Analysis was done using GraphPad Prism version 9.3.1 (GraphPad Software, Boston, MA) and the Lumivero (New York, NY) (2023) XLSTAT statistical solution.

Results

We identified 413 unique patients with newly diagnosed AML (291 [70.5%]) and MDS (122 [29.5%]) harboring a known pathogenic *TP53* mutation with available cytogenetic (CTG) data between January 2013 to July 2022. Baseline characteristics are summarized in Table 1. The median age at diagnosis was 69.4 years (range, 18.2-90.4 years); 321 patients (78%) were ≥60 years. In the AML group, the median age was 70 years (range, 20.1-87 years). The median age in the MDS cohort was 69 years (range, 18.2-90.4 years). The median BM aspirate blast percentage in the MDS cohort was 9 (range, 5-18), 57 patients (47%) had ≥10% BM blasts at diagnosis.

TP53 allelic status

Three-hundred and fifty-eight patients (87%) had a complex karyotype (CK) including 190 patients (46%) with *TP53* deletion. Only two patients (1%) with a *TP53* deletion did not have a CK. Based on our HR *versus* LR algorithm, 63 patients (15%) had $TP53^{LR}$ (38 patients [13%] with AML and 25 patients [20%] with MDS; *P*=0.07) (*Online Supplementary Figure S1*). The median VAF in the patients with $TP53^{LR}$ was 21% (range, 2-39%) and 45 of 63 patients (71%) had a VAF ≥10%. The median $TP53^{LR}$ VAF was 20% (range, 2-37%) in the MDS group and 23% (range, 2-39%) in the AML group; *P*=0.40. In the $TP53^{LR}$ group 37 patients (59%) had a CK (20 of 38 [53%] with $TP53^{LR}$ AML and 17 of 25 [68%] with $TP53^{LR}$ MDS).

A total of 350 patients (85%) had a $TP53^{HR}$ aberration, of whom 111 patients (32%) had multiple *TP53* mutations (group 1). Among these, 65 patients (59%) had a VAF sum of ≥50% (43 with AML and 35 with MDS) and 47 (41%) had a VAF sum <50% (35 with AML and 12 with MDS). There was no difference in OS based on *TP53* VAF sum in the

Table 1. Baseline characteristics of the patients.

Parameters		MDS N=122	AML N=291	*P*
		N (%) or median (range)		
Age in years		69 (18-90)	70 (20-87)	0.48
	≥60	94 (77)	227 (78)	0.90
Sex	Female	58 (47)	138 (47)	0.99
Race	White	99 (81)	219 (75)	-
	Black	9 (7)	27 (9)	-
	Hispanic	5 (4)	10 (3)	-
	Other	9 (7)	24 (8)	-
Baseline CBC	Hb g/L	9.2 (6.9-13.8)	9.6 (6.3-13.2)	-
	WBC x10^9/L	3.8 (0.6-13.5)	6.8 (0.1-77.3)	-
	Platelet x10^9/L	37 (2-647)	30 (1-271)	-
BM blasts* %		9 (5-18)	32 (7-97)#	-
Cytogenetics	Complex	104 (85)	254 (87)	0.63
TP53 aberrations	-17/del17p	42 (34)	148 (51)	0.002
	Single mutation	87 (71)	215 (74)	0.63
	>1 mutation	35 (29)	76 (26)	-
Myeloid mutations	*ASXL1*	2 (2)	6 (2)	-
	DNMT3A	6 (5)	29 (10)	-
	FLT3 TKD	0	6 (2)	-
	FLT3 ITD	0	9 (3)	-
	IDH1	0	14 (5)	-
	IDH2	2 (2)	6 (2)	-
	NPM1	0	6 (2)	-
	RAS	4 (3)	20 (7)	-
	RUNX1	5 (4)	8 (3)	-
	SF3B1	2 (2)	5 (2)	-
	TET2	4 (3)	26 (9)	-

*Blast percentages mentioned here are as per estimates on aspirate smear. #For patients with <20% blasts on aspirate smear, bone marrow morphology or immunohistochemistry showed features suggestive of higher blast counts. MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; CBC: complete blood count; Hb: hemoglobin; WBC: white blood cell count; BM: bone marrow; TKD: tyrosine kinase domain; ITD: internal tandem duplication.

full cohort or the AML and MDS cohorts, when analyzed separately (*Online Supplementary Figure S2*). Based on this, all patients with multiple *TP53* mutations were considered to have multihit *TP53* status irrespective of the VAF sums, for subsequent analysis. The *TP53*^{HR} cohort also included 112 (32%) patients with a single *TP53* mutation and a *TP53* deletion (group 2; median *TP53* VAF of 33% [range, 2-93%]; 71 of 112 [63%] with *TP53* VAF <40%) and 127 patients (36%) with a single *TP53* mutation ≥40% (group 3; median *TP53* VAF: 69% [range, 40-97%]). We validated the VAF cutoff for patients with a single *TP53* mutation in the AML cohort using decision trees from a CRT model. A *TP53* VAF >37.5% (very close to our VAF cutoff of 40% for calling *TP53*^{HR}) had the best discriminatory power to predict OS at 1 year and was associated with OS <1 year in 78% patients (*Online Supplementary Figure S3*). Further details are provided in *Online Supplementary Figures S4, S5*.

Missense mutations were the most common, occurring in 361 patients (87%), followed by frameshift in 42 patients (10%), nonsense in 31 patients (7%) and splice site mutations in ten patients (2%) (*Online Supplementary Figure S6*).

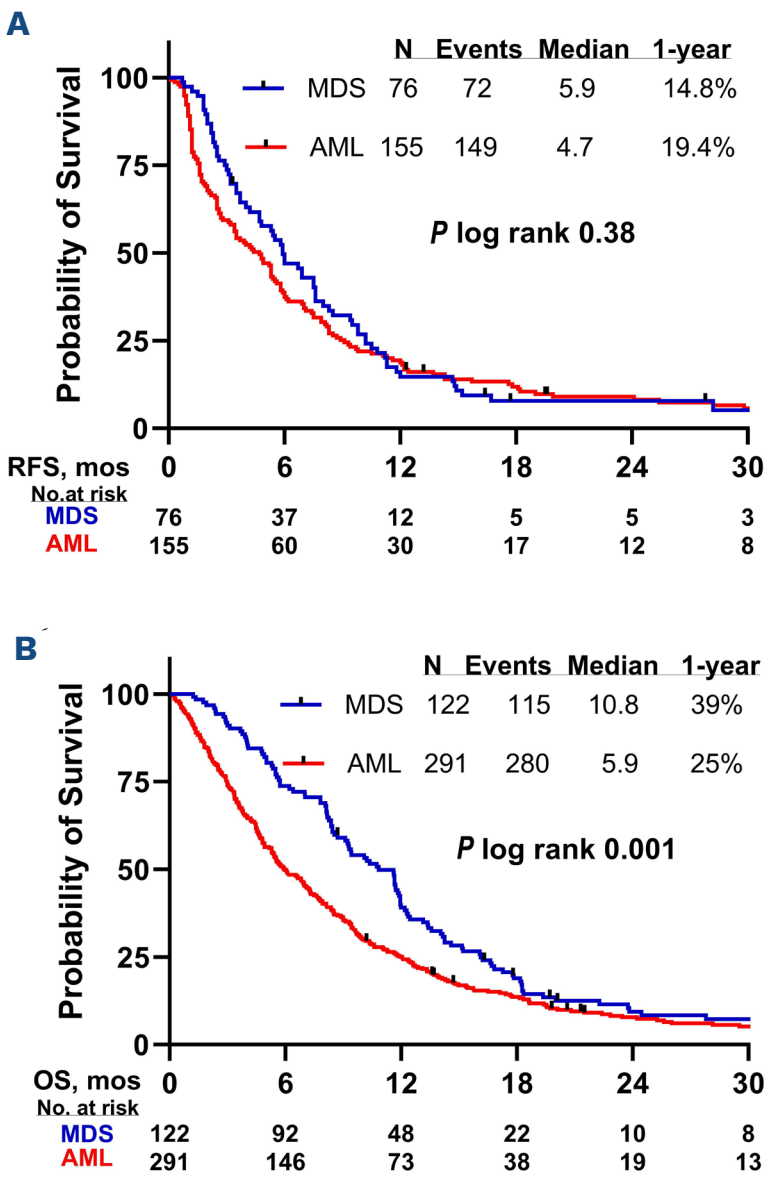

Figure 1. Comparative relapse-free survival and overall survival of the full myelodysplastic syndrome and acute myeloid leukemia cohorts. (A) Relapse-free survival (RFS). (B) Overall survival (OS). MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; mos: months.

Treatment and response outcomes

Overall, 319 patients (77%) were treated on a clinical trial, 219 (75%) patients with AML and 100 patients (82%) with MDS. In the AML group, 234 patients (80%) were treated with low-intensity therapy, 201 (86%) of whom received hypomethylating agent (HMA)-based therapy. Amongst these 234 patients, 81 (35%) received venetoclax and 213 patients (91%) were ≥60 years old. The other 57 patients with AML were treated with intensive chemotherapy-based approaches; 42 (74%) patients were <60 years and only nine patients (15%) received concurrent venetoclax (*Online Supplementary Table S1*).

Amongst patients with AML, an OR was attained in 155 patients (53%) and a composite complete response (CRc) [CRc=CR+CRi] in 129 (44%) (*Online Supplementary Figure S7*). Thirty-one patients (11% of full AML group and 20% of responders) proceeded to HSCT in first remission. The median age of the transplanted patients at AML diagnosis was 61.4 years (range, 20-74 years) and 20 patients (64%) had been treated on a low-intensity regimen prior to HSCT (*Online Supplementary Figure S8A*).

The most common treatment in the MDS group was HMA, used in 114 patients (93%) and cumulatively eight patients (6%) had received venetoclax as part of frontline therapy. An OR was attained in 76 patients (62%), of whom 43 patients (30%) had a CR (*Online Supplementary Figure S7*). Overall, 23 responders (20% of full MDS group) proceeded to an HSCT. Twenty-two patients (18%) transformed to an AML, 16 of whom were responders and six patients amongst them had transformed after HSCT (*Online Supplementary Figure S8B*).

TP53 aberration status and survival outcomes

The median follow-up of the whole cohort was 77.8 months (95% confidence interval [CI]: 77-90 months); 78 months for AML and not reached for the MDS group. The median RFS and OS in the patients with AML was 4.7 months (95% CI: 2.5-5.6 months) and 5.9 months respectively (95% CI: 5.3-7.3 months); for patients with MDS the median RFS and OS were 5.9 months (95% CI: 3.9-7.7 months) and 10.8 months (95% CI: 9.1-11.9 months) respectively (Figure 1).

In the full cohort, the median OS was significantly longer in patients with *TP53*^{LR} compared with *TP53*^{HR} (12.1 months *vs.* 6.8 months; *P*<0.001) while there was no significant difference between type of *TP53*^{HR} (Figure 2A; *Online Supplementary Figure S9A*). Stratifying by diagnosis, in the MDS cohort, OS was significantly better in *TP53*^{LR} compared to the *TP53*^{HR} (14.3 *vs.* 9.3 months; *P*=0.06) (Figure 2B). There was no difference amongst the three *TP53*^{HR} groups (11.6 months in group 1 *vs.* 10.1 months in group 2 and 8.4 months in group 3; *P* log-rank for trend =0.67) (*Online Supplementary Figure S9B*). Patients with *TP53*^{LR} AML had better OS of 10.4 months compared to 5.4 months in patients with *TP53*^{HR} AML (*P*=<0.01) (Figure 2C). The median OS was slightly better in group 2 *TP53*^{HR} at 6.9 months

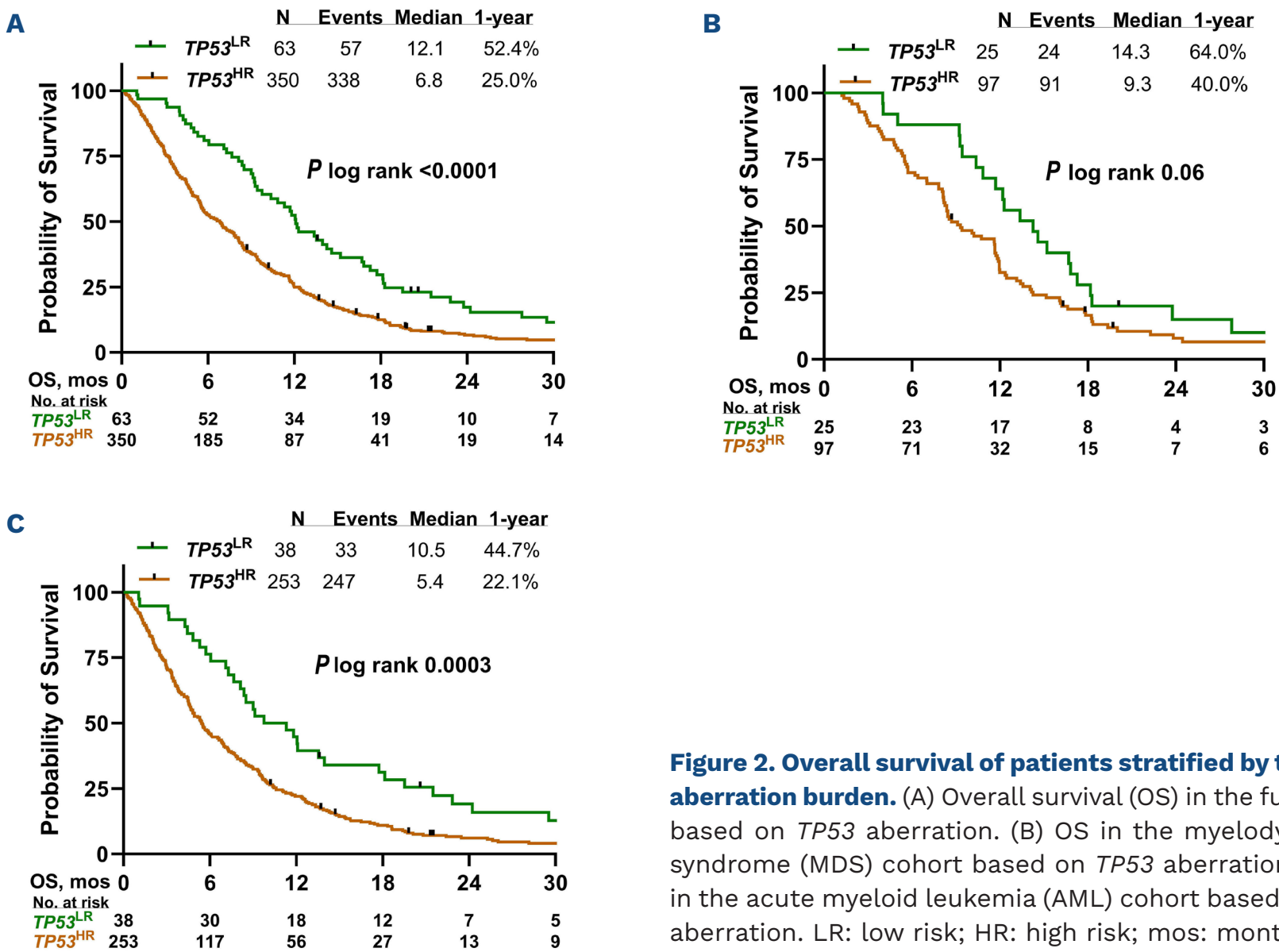

Figure 2. Overall survival of patients stratified by the *TP53* aberration burden. (A) Overall survival (OS) in the full cohort based on *TP53* aberration. (B) OS in the myelodysplastic syndrome (MDS) cohort based on *TP53* aberration. (C) OS in the acute myeloid leukemia (AML) cohort based on *TP53* aberration. LR: low risk; HR: high risk; mos: months.

compared with 5.6 months (group 3) and 4.4 months (group 1) (*P* for trend =0.02). Despite statistical significance the absolute durations of response were short and dismal in all three *TP53*^{HR} sub-groups (*Online Supplementary Figure S9C*). Twenty of 38 (53%) patients with AML *TP53*^{LR} had a CK (without *TP53* deletion) and an inferior survival of 8.2 months, compared to the remainder *TP53*^{LR} patients with AML who did not have a CK (12.7 months; *P*=0.04). The median *TP53* VAF was not different between the two groups (25% *vs*. 22%; *P*=0.63) (*Online Supplementary Figure S10A*). Though limited by very small patient numbers, there was no difference in OS in the MDS *TP53*^{LR} group based on CK (*Online Supplementary Figure S10B*).

Myelodysplastic syndrome *versus* acute myeloid leukemia survival outcomes

In patients with MDS, there was no difference in median OS based on 5-10% and ≥10% BM blasts (10.7 *vs*. 11.6 months; *P*=0.21). However, OS was superior in patients with MDS, irrespective of blast percentage, compared to AML (*Online Supplementary Figure S11*). Amongst patients with *TP53*^{HR}, there was a significant difference in OS between the MDS and AML group (9.3 and 5.4 months respectively; *P*=0.001), however there was no significant difference in OS between *TP53*^{LR} MDS and AML (14.3 *vs*. 10.5 months respectively; *P*=0.83) (*Online Supplementary Figure S12*). We then selected the patients with *TP53*^{HR} AML (N=23) and MDS (N=16) who underwent HSCT; the median survival was similar at 12.6 months and 15.4 months respectively; *P*=0.73 (*Online Supplementary Figure S13*). The numbers in the *TP53*^{LR} HSCT arms were too small for a salient comparison.

We performed Cox regression analysis accounting for MDS or AML diagnosis, age (</≥60 years), *TP3* status (*TP53*^{HR} *vs*. *TP53*^{LR}), CTG (CK or not), use of venetoclax and HSCT; on MVA patients with MDS had significantly reduced risk of death (hazard ratio [HR]=0.76, 95% CI: 0.61-0.94) compared to patients with AML, along with *TP53*^{LR} (HR=0.66, 95% CI: 0.48-0.89) and HSCT (HR=0.42, 95% CI: 0.30-0.57) while other covariates were not significant (Table 2). We subsequently performed a propensity matched comparison of patients in the MDS cohort to the AML cohort, including age (continuous), *TP53* status (*TP53*^{HR} *vs*. *TP53*^{LR}), attainment of OR and HSCT as variables; amongst 23 matched pairs there was no difference of median OS between the two groups (17.3 *vs*. 13.9 months respective; *P*=0.69); incidentally this matching selected 23 patients in each group who had undergone an HSCT. We thus matched again discounting the patients who had undergone HSCT and maintaining

Table 2. Multivariate Cox proportional hazard model to analyze factors affecting overall survival in the full patient cohort (N=413).

Univariate analysis				Multivariate analysis				Evaluable	Covariate frequency N/N	Events N/N	Events %/%
Covariates	HR	95% CI	*P*	Covariates	HR	95% CI	*P*				
MDS	0.70	0.56-0.87	0.001	MDS	0.76	0.61-0.94	0.01	413	122/291	115/280	94/96
Age ≥60 years	1.07	0.84-1.36	0.59	-	-	-	-	413	322/91	307/88	95/97
TP53^{LR}	0.54	0.41-0.71	<0.0001	*TP53*^{LR}	0.66	0.48-0.89	0.008	413	63/350	57/338	90/97
CK	1.63	1.21-2.27	0.002	CK	1.23	0.89-1.74	0.23	410	357/53	347/46	97/87
Venetoclax	1.15	0.90-1.44	0.26	-	-	-	-	413	98/315	91/304	93/96
HSCT	0.37	0.27-0.51	<0.0001	HSCT	0.42	0.30-0.57	<0.0001	413	55/358	45/350	82/98

HR: hazard ratio; CI: confidence interval; MDS: myelodysplastic syndrome; CK: complex karyotype; LR: low risk; HSCT: allogeneic hematopoietic stem cell transplantation.

the other variables; all 99 non-transplanted patients in the MDS group could be adequately matched to 99 of 260 non-transplanted patients in the AML group. The median OS was significantly shorter in the AML compared to the MDS group; 5.3 *versus* 9.3 months respectively; *P*=0.001 (Figure 3). Finally, we used the full dataset of 413 patients (AML + MDS) and proceeded with a CRT using the diagnosis (MDS *vs*. AML), age ≥/< 60 years and *TP53* aberration status; the primary decision node was *TP53* status, with a 75% mortality within 1 year in patients with *TP53*^{HR}. The TP53 status predicted survival at 1 year more strongly than the diagnosis of MDS or AML (*Online Supplementary Figure S14*).

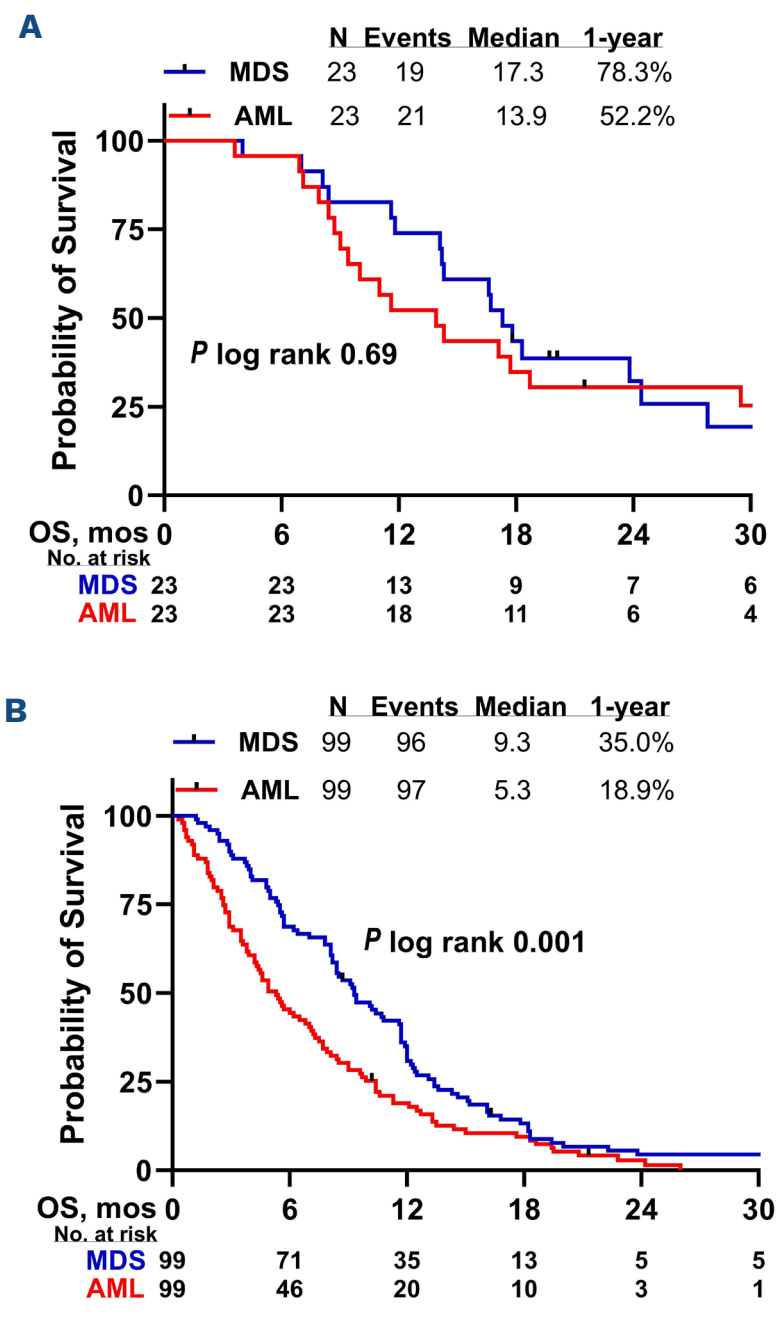

Figure 3. Propensity matched survival outcomes between patients with myelodysplastic syndrome and acute myeloid leukemia. (A) Unselected propensity matching. This matching incidentally selected all transplanted patients in both groups (matched 23/23 transplanted patients in the myelodysplastic syndrome [MDS] group to 23/31 transplanted patients in the acute myeloid leukemia [AML] group). (B) Propensity matching excluding transplanted patients. All 99 non-transplanted patients in the MDS cohort could be adequately matched to 99 of 260 non-transplanted patients in the AML group. OS: overall survival; mos: months.

Hematopoietic stem cell transplantation, *TP53* status and outcomes in acute myeloid leukemia and myelodysplastic syndrome

A total of 32 patients (11%) (9 of 38 [24%] patients with *TP53*^{LR} and 23 of 253 [9%] patients with *TP53*^{HR}; *P*=0.02) with AML at a median age of 61.3 years (range, 20-73.6 years) could proceed to HSCT at a median of 3.7 months of therapy (range, 2.1-7.4 months) leading to a median survival of 14 months and 2-year OS of 32%; this was significantly superior to a landmark comparison of patients <70 years who attained a response but did not undergo HSCT (14 *vs*. 9.4 months; *P* log-rank =0.001) (Figure 4A, B). When comparing the *TP53*^{HR} AML, again HSCT led to a statistically significant improvement in OS (12.6 *vs*. 9 months; *P*=0.009). Amongst the patients with AML who underwent an HSCT, 17 (7 *TP53*^{LR} and 16 *TP53*^{HR}) had a best response of MRD-negative CRc before HSCT, and the other 15 patients (3 *TP53*^{LR} and 12 *TP53*^{HR}) were positive for MRD by flow cytometry (13 CRc, 1 MLFS and 1 stable disease). The median OS of patients with MRD-negative CRc before HSCT was 29.5 months compared to 10.0 months for those who were MRD-positive before HSCT (*P*<0.001). Selecting only patients with *TP53*^{HR}, the median OS was 26.4 months who were MRD-negative

compared to 9.5 months who were MRD-positive before HSCT (*P*=0.003) (Figure 4C, D).

In the MDS group 23 patients (18.8%) (median age of 63.4 years, range 18.2-76 years) underwent an HSCT (7 of 25 [28%] patients with *TP53*^{LR} and 16 of 97 [16%] patients with *TP53*^{HR}) with a median OS of 17.3 months and 2-year OS of 32%. The median time to HSCT post therapy initiation was 5.4 months (range, 2.9-17.7 months). On a landmark analysis comparing transplanted patients to non-transplanted patients who had a response and <70 years of age at diagnosis, HSCT significantly improved OS (17.3 *vs*. 12.4 months; *P*=0.02) (Figure 4E, F). On selecting only *TP53*^{HR} patients in the transplanted and comparator group, again transplanted patients had a superior OS (15.5 *vs*. 11.9 months; *P*=0.05) on landmark analysis.

Assessment of factors affecting survival in acute myeloid leukemia

Focusing on the AML cohort we analyzed disease and treatment related factors that affected the rates of HSCT and survival.

Venetoclax, treatment intensity and outcomes in acute myeloid leukemia

A CRc and OR was attained in 21 of 38 (55%) and 27 of 38 (71%) patients with *TP53*^{LR} compared to 108 of 253 (43%) (*P*=0.16) and 128 of 253 (36%) (*P*=0.02) patients with *TP53*^{HR}. On UVA, *TP53*^{LR} and use of venetoclax was associated with higher odds of response in AML while CK was associated with lower odds for OR. On MVA including CTG, *TP53* status, use of venetoclax and treatment intensity as variables, *TP53*^{LR} continued to favor odds of response compared to *TP53*^{HR} (odds ratio=2.415, 95% CI: 0.99-4.95) along with venetoclax (odds ratio=2.09, 95% CI: 1.30-3.78) while other variables were not independently significant (*Online Supplementary Table S2*).

Two-hundred and thirty-four (80%) patients with AML received a low-intensity therapy of whom 202 (86%) had *TP53*^{HR} (*Online Supplementary Table S3*). Amongst the 57 patients treated with intensive therapy, 51 (89%) patients had *TP53*^{HR}. An OR was seen in 130 patients (56%) (CRc: 44%) treated with low-intensity therapy and 107 of 202 (53%) (CRc: 43%) patients with *TP53*^{HR} treated with low-intensity therapy. In the intensively treated arm, an OR was seen in 25 of 57 (44%) (CRc: 44%) and in 21 of 51 (41%) (CRc: 41%) patients with *TP53*^{HR}. There was no difference in RFS and OS based on treatment intensity (*Online Supplementary Figure S15*). The rates of HSCT were higher for patients treated with intensive therapy compared to low-intensity therapy (19% *vs*. 9%; *P*=0.03) despite comparable response rates between the two-arm, possibly because of the lower median age in the intensively treated patients (56.6 years *vs*. 72.2 years; *P*<0.0001). In patients <60 years of age (N=63), there was no difference in OS between intensive and low-intensity therapy, irrespective of *TP53* burden (*Online Supplementary Figure S16*).

With respect to venetoclax, overall, 90 patients (31%) had received venetoclax of whom 81 patients (90%) were treated with low-intensity therapy (*Online Supplementary Table S4*). The rates of CRc and OR was higher in the patients treated with venetoclax containing regimens (54% and 66%) compared to those who did not receive venetoclax (40%; *P*=0.02 and 48%; *P*=0.005, respectively). When selecting only patients with *TP53*^{HR}, again, rates of CRc and OR was higher when patients were treated with venetoclax (54% *vs*. 37%; *P*=0.02 and 63% *vs*. 44%; *P*=0.005, respectively). However, HSCT rates, RFS and OS were similar between patients treated with or without venetoclax in the full AML cohort as well as *TP53*^{HR} AML group (*Online Supplementary Figure S17*). The 60-day mortality was similar in patients who received low-intensity therapy with or without venetoclax (15/81 [18%] *vs*. 22/153 [14%]; *P*=0.45). Characteristics and outcomes of patients treated only with HMA based low-intensity therapy is described in *Online Supplementary Table S5*.

Finally, we did a Cox proportional hazard analysis to understand the independent significance of disease and treatment factors affecting survival in patients with AML. On UVA, using age </≥60 years, *de novo versus* secondary or therapy-related AML, *TP53*^{HR} *versus TP53*^{LR}, CTG (CK *vs*. others), use of venetoclax and HSCT, *de novo* AML and HSCT were favorable risk factors while CK was adverse. Including these significant factors on a stepwise multivariate Cox, *de novo* AML (HR=0.73, 95% CI: 0.57-0.93), *TP53*^{LR} (HR=0.58, 95% CI: 0.38-0.86) and HSCT (HR=0.40, 95% CI: 0.26-0.60) continued to remain significant (Table 3A). MVA for factors affecting survival only in patients who attained ORR is in Table 3B.

Discussion

We present a comprehensive analysis on the impact of *TP53* aberrations on outcomes among a large contemporary cohort of patients with *TP53*^{mut} MDS and AML. Our report includes well curated data at a single large academic center with >75% patients treated on clinical trials with a median follow-up of >6 years. Importantly, we have tried to analyze the clinical relevance of the *TP53* allele status on survival outcomes, and better define what constitutes truly high-risk *TP53* mutations in MDS and AML from a clinical standpoint. The focus of our analysis was to understand the interplay between MDS and AML (based on historical blast percentage cutoffs) and baseline *TP53* burden on clinical outcomes, and to study the impact of therapeutic interventions including HSCT, intensive *versus* non-intensive therapy, and venetoclax use on response and survival in relation to the baseline *TP53* burden in patients with AML. Using a machine learning algorithm, we also validated the cutoff of a single *TP53*

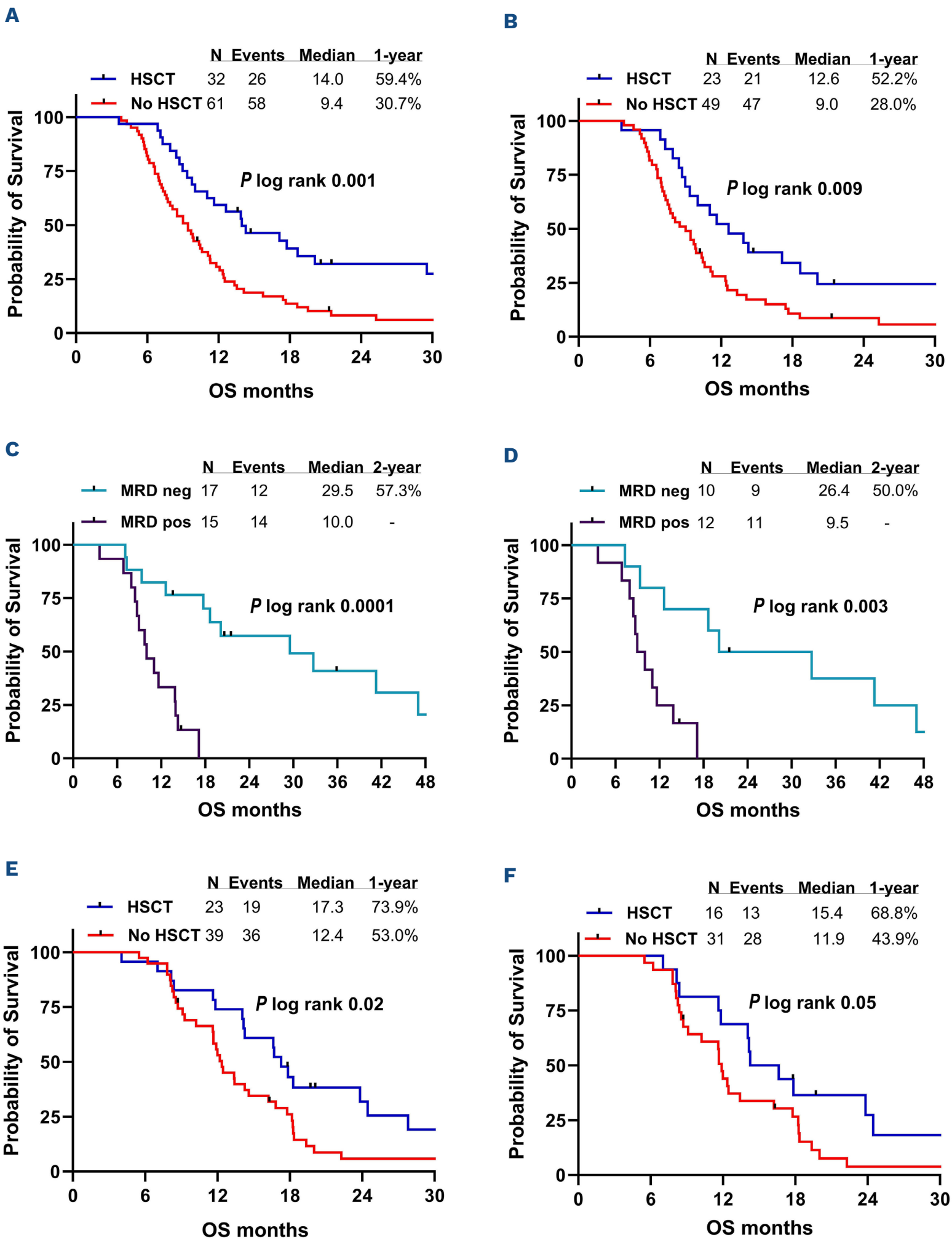

Figure 4. Outcomes with allogeneic hematopoietic stem cell transplantation. (A, B) Landmark comparison based on transplant in the acute myeloid leukemia (AML) cohort. (A) Overall survival (OS) of transplanted *versus* non-transplanted patients. (B) OS of transplanted *versus* non-transplanted patients with *TP53* high-risk (*TP53*^{HR}). (C, D) Outcomes with allogeneic hematopoietic stem cell transplantation (HSCT) in the AML cohort stratified by the pre-transplant measurable residual disease. (C) OS in the transplanted AML cohort. (D) OS in the transplanted AML cohort with *TP53*^{HR}. (E, F) Landmark comparison based on HSCT in the myelodysplastic syndrome (MDS) cohort. (E) OS of transplanted *versus* non-transplanted patients. (F) OS *versus* transplanted *versus* non-transplanted patients with *TP53*^{HR}. MRD: measurable residual disease; pos: positive; neg: negative.

Table 3. Multivariate Cox proportional hazard model of factors affecting overall survival in acute myeloid leukemia.

(A) Cox proportional hazard model of factors affecting OS in all patients with AML											
Univariate analysis				Multivariate analysis				Evaluable	Covariate frequency N/N	Events N/N	Events %/%
Covariates	HR	95% CI	*P*	Covariates	HR	95% CI	*P*				
Age ≥60 years	1.31	0.85-1.52	0.40	-	-	-	-	291	228/63	219/61	96/97
De novo AML	0.74	0.59-0.94	0.01	*De novo* AML	0.73	0.57-0.93	0.01	291	158/133	150/130	95/98
TP53^{LR}	0.51	0.35-0.73	0.0004	*TP53*^{LR}	0.58	0.38-0.86	0.009	291	38/253	33/247	87/98
CK	1.73	1.20-2.58	0.005	CK	1.16	0.77-1.80	0.50	290	254/36	249/30	98/83
Venetoclax	1.06	0.82-1.37	0.65	-	-	-	-	291	90/201	85/195	94/97
HSCT	0.36	0.23-0.53	<0.0001	HSCT	0.40	0.26-0.60	<0.0001	291	32/259	26/254	81/98
(B) Cox proportional hazard model of factors affecting OS in patients with AML who had an overall response											
Univariate analysis				Multivariate analysis				Evaluable	Covariate frequency N/N	Events N/N	Events %/%
Covariates	HR	95% CI	*P*	Covariates	HR	95% CI	*P*				
Age ≥60 years	1.22	0.81-1.91	0.36	-	-	-	-	155	126/29	118/27	94/93
De novo AML	0.57	0.41-0.80	0.001	*De novo* AML	0.49	0.34-0.70	<0.0001	155	85/70	78/67	92/96
TP53^{LR}	0.51	0.31-0.79	0.004	*TP53*^{LR}	0.50	0.29-0.83	0.01	155	27/128	22/123	81/96
CK	1.80	1.14-2.99	0.02	CK	0.78	0.45-1.33	0.41	155	129/26	125/20	97/77
Venetoclax	1.19	0.84-1.66	0.32	-	-	-	-	155	59/96	54/91	91/95
HSCT	0.46	0.29-0.70	0.0006	HSCT	0.48	0.30-0.73	<0.0001	155	31/124	25/120	81/97

OS: overall survival; AML: acute myeloid leukemia; HR: hazard ratio; CI: confidence interval; CK: complex karyotype; HSCT: allogeneic hematopoietic stem cell transplantation; LR: low risk.

mutation (without an allelic loss) in AML that is associated with inferior outcomes; our present finding of 37.5% is close to the 40% reported in previous analysis.

TP53^{HR} was associated with inferior ORR in patients with AML but not with MDS, and this remained significant even on MVA. Though median survival was <12 months in both the MDS and AML group, in mutation burden unstratified analysis, median survival for AML (defined as >/=20% blasts) was significantly shorter than MDS (5.9 *vs*. 10.8 months). There was no difference in survival within the MDS group based on the blast percentage either for the entire population (5-10% *vs*. >10% both with median OS approximately 11 months; *Online Supplementary Figure S6*) or for the *TP53*^{HR}. Although studies have claimed diminutive (in some cases even irrelevant) effects of blast percentage defining MDS and AML on OS in patients with high-burden *TP53* aberrations, in our analysis with a large number of well-annotated and contemporary patients we see a statistically better survival in patients with MDS (5-19%) compared to patients with AML (>/=20% blasts). Although the outcomes remain dismal for both MDS and AML with *TP53*^{HR} it is important to have the OS expectations clearly defined and differentiated between these two populations to enable critical and realistic appraisal of emerging data from phase I/II single arm studies in the right context. For example, an OS of 12 months may be considered encouraging in a study of frontline *TP53*^{HR} AML but is very similar to expected historical outcomes in frontline *TP53*^{HR} MDS. In further interrogation towards this effect, we found on MVA that both the diagnosis (MDS or AML) as well as the *TP53* allele status had an independent impact on OS. However, on the CRT analysis, the *TP53*^{HR} status indeed carried more weight and had the most discriminatory role in predicting poor survival at 1 year. Putting these into perspective, we can draw the conclusion that both the diagnosis of AML and MDS as well as the *TP53* allele status at baseline are important prognostic variables.

Our study shows important evidence in assessing *TP53* aberration burden and that patients with *TP53*^{LR} have better outcomes in both MDS and AML, validated with independent statistical models. The lack of convergence of OS of patients with high-blast MDS and AML was surprising and different from analysis by other groups.[17] Though few patients in both disease groups proceeded to HSCT, we show that transplanted patients with MDS and AML had similar survival to each other, and led to improved OS on a landmark analysis comparing to patients who did not undergo HSCT; the independent benefit from HSCT was also maintained on multivariate Cox regression analysis. This again underlines the need to facilitate HSCT in patients with *TP53* aberrations whenever feasible. Though HSCT in *TP53*^{mut} myeloid disorders is often debated, it remains the only line of management which has the potential to offer an improved survival over any other form of non-trans-

plant therapy and should be the goal after some form of BM remission is attained in a transplant eligible patient. The presence of *TP53* aberrations should in isolation not preclude patients from an HSCT. Next, we show that treatment intensity does not have a significant bearing on long-term survival outcomes. In patients <60 years of age, intensive and low-intensity therapy fared equivocally both in terms of response rates as well as OS. Though more patients treated with intensive therapy proceeded to an HSCT, this was a function of the lower median age and more patients <60 years of age in the intensive treated arm compared to the low-intensity treatment arm, which would have driven their therapy choice in the first place. In the context of venetoclax, we showed that despite the higher rates of CRc and OR in patients with AML who received venetoclax along with their treatment, these responses were not durable and did not lead to higher rates of HSCT or improved survival.

Our study had few limitations, primarily being the retrospective nature of this analysis. However, the majority of our patients were treated on clinical trials and the analyses stem from well curated prospectively collected data. Enrollment of patients on clinical trials could however be associated with potential selection biases secondary to trial enrollment criteria, though clinical trials remain the ideal treatment decision for patents with high-risk AML (including *TP53*^{mut} AML) given dismal outcomes with standard of care therapy. Secondly the *TP53* allele loss call was from a combination of cytogenetic data, FISH and aCGH and might have missed some cn-LOH. Nonetheless the use of routine laboratory tools for the annotation of *TP53* aberration in our patients make the interpretation of this data clinically robust and widely adaptable.

In summary, our study shows that *TP53* aberrations (mutations and/or allelic loss) is an independent factor that affects survival outcomes, and this impact is dependent on the burden of this aberration. Secondly, the diagnosis of MDS or AML, and the burden of *TP53* aberration independently affect survival, and HSCT lead to equivalent improved outcomes in both diagnosis groups.

Disclosures

GGM has received research funding from Astex Pharmaceuticals, Novartis, AbbVie, BMS, Genentech, Aprea Therapeutics, Curis, and Gilead Sciences; has been a consultant for Astex Pharmaceuticals, Acceleron Pharma, and BMS; and has received honoraria from Astex Pharmaceuticals, Acceleron Pharma, AbbVie, Novartis, Gilead Sciences, Curis, Genentech, and BMS. TMK has been a consultant for AbbVie, Agios, BMS, Genentech, Jazz Pharmaceuticals, Novartis, Servier, and PinotBio; has received research funding from AbbVie, BMS, Genentech, Jazz Pharmaceuticals, Pfizer, Cellenkos, Ascentage Pharma, GenFleet Therapeutics, Astellas Pharma, AstraZeneca, Amgen, Cyclacel Pharmaceuticals, Delta-Fly Pharma, Iterion Therapeutics, GlycoMimetics, and Regeneron Pharmaceuticals; and has received honoraria from Astex Pharmaceuticals. NJS has been a consultant for Takeda Oncology, AstraZeneca, Amgen, Novartis, and Pfizer; and received research funding from Takeda Oncology, Astellas, and Stemline Therapeutics as well as honoraria from Amgen. CDD has been a board of directors or advisory committee member for Genmab, GSK, Kura Oncology, and Notable Labs; has received honoraria from Kura, Astellas Pharma, Bluebird Bio, Bristol Myers Squibb, Foghorn Therapeutics, Immune-Onc Therapeutics, Novartis, Takeda Oncology, Gilead Sciences, and Jazz Pharmaceuticals; is a current holder of stock options for Notable Labs; has been a consultant for AbbVie and Servier; and has received research funding from Servier, Bristol Myers Squibb, Foghorn, Immune-Onc Therapeutics, Loxo Oncology, Astex Pharmaceuticals, Cleave, and Forma. GB has received research funding from Astex Pharmaceuticals, Ryvu Therapeutics, and PTC Therapeutics; has been a board of directors or advisory committee member for Pacyclex Pharmaceuticals, Novartis, CytomX, and Bio Ascend; and has been a consultant for Catamaran Bio, AbbVie, PPD Development, Protagonist Therapeutics, and Janssen. NP has received Consultancy/Scientific Advisory Board/Speaking from Pacylex Pharmaceuticals, Astellas, Pharma US, Aplastic Anemia & MDS International Foundation, CareDx, ImmunoGen, Inc, Bristol-Myers Squibb Co., Cimeio Therapeutics AG, EUSA Pharma, Menarini Group, Blueprint Medicines, CTI BioPharma, ClearView Healthcare Partners, Novartis Pharmaceutical, Neopharm, Celgene Corporation, AbbVie Pharmaceuticals, Pharma Essentia, Curio Science, DAVA Oncology, Imedex, Intellisphere, CancerNet, Harborside Press, Karyopharm, Aptitude Health, Medscape, Magdalen Medical Publishing, and Morphpsys. GCI has been a consultant for Novartis, Kura Oncology, and NuProbe; and received research funding from Celgene, Kura Oncology, Syndax, Merck, Cullinan, and Novartis. MY has received research funding from DaiichiSankyo and Pfizer. HMK has received research funding from AbbVie, Amgen, Ascentage Pharma, BMS, Daiichi Sankyo, ImmunoGen, Jazz Pharmaceuticals, and Novartis as well as honoraria from AbbVie, Amgen, Amphista Therapeutics, Ascentage Pharma, Astellas Pharma, Biologix, Curis, Ipsen, KAHR, Novartis, Pfizer, Precision Biosciences, Shenzhen TargetRx, and Takeda Oncology. ND has received research funding from Astellas Pharma, AbbVie, Genentech, Daiichi Sankyo, Gilead Sciences, ImmunoGen, Pfizer, Bristol Myers Squibb, Trovagene, Servier, Novimmune, Incyte, Hanmi Pharm, Fate Therapeutics, Amgen, Kite Pharma, Novartis, Astex Pharmaceuticals, KAHR, Shattuck, Sobi, GlycoMimetics, and Trillium; has been an advisor for Astellas Pharma, AbbVie, Genentech, Daiichi Sankyo, Novartis, Jazz Pharmaceuticals, Amgen, Servier, Karyopharm Therapeutics, Trovagene, Trillium, Syndax, Gilead Sciences, Pfizer, Bristol Myers Squibb, Kite Pharma, Actinium Pharmaceuticals, Arog Pharmaceuticals, ImmunoGen, Arcellx, and Shattuck; has been a data monitoring committee member for Kartos Therapeutics and Jazz Pharmaceuticals; has been a con-

sultant or board of directors or advisory committee member for Agios, Celgene, Sobi, and STAR Therapeutics; and has received research funding from Karyopham Therapeutics and Newave Pharmaceutical. The other authors have no conflicts of interest to disclose.

Contributions

JS, SL and ND designed the manuscript. JS and SP collected the data. JS, SL and ND analyzed the data. SL and GT provided the laboratory data. JS, NA and SA made the figures. JS, GGM, GT, TK, NJS, HA, CDD, GB, NP, BO, ES, UP, RC, GI, MY, KP, KT, GMB, DH, FGH, FR, HMK and ND provided patients. JS wrote the first manuscript draft. SL and ND revised the drafts. All others reviewed the final draft and approved the final draft

Funding

The study was supported by University of Texas MD Anderson Cancer Center grant (CA016672) and the University of Texas MD Anderson SPORE (C1100632).

Data-sharing statement

Data available from corresponding author on reasonable request.

References

1. Daver NG, Iqbal S, Huang J, et al. Clinical characteristics and overall survival among acute myeloid leukemia patients with TP53 gene mutation or chromosome 17p deletion. Am J Hematol. 2023;98(8):1176-1184.
2. Daver NG, Maiti A, Kadia TM, et al. TP53-mutated myelodysplastic syndrome and acute myeloid leukemia: biology, current therapy, and future directions. Cancer Discov. 2022;12(11):2516-2529.
3. Kantarjian H, Kadia T, DiNardo C, et al. Acute myeloid leukemia: current progress and future directions. Blood Cancer J. 2021;11(2):41.
4. Bazinet A, Kantarjian HM. Moving toward individualized target-based therapies in acute myeloid leukemia. Ann Oncol. 2023;34(2):141-151.
5. Lachowiez CA, Long N, Saultz J, et al. Comparison and validation of the 2022 European LeukemiaNet guidelines in acute myeloid leukemia. Blood Adv. 2023;7(9):1899-1909.
6. Nechiporuk T, Kurtz SE, Nikolova O, et al. The TP53 apoptotic network is a primary mediator of resistance to BCL2 inhibition in AML Cells. Cancer Discov. 2019;9(7):910-925.
7. Prokocimer M, Molchadsky A, Rotter V. Dysfunctional diversity of p53 proteins in adult acute myeloid leukemia: projections on diagnostic workup and therapy. Blood. 2017;130(6):699-712.
8. Desai PN, Wang B, Reville PK, et al. Single-cell characterization of TP53-mutated AML patients treated with frontline azacitidine, venetoclax, and magrolimab reveals mechanisms of response and resistance. Blood. 2023;142(Suppl 1):64.
9. Daver N, Senapati J, Maiti A, et al. Phase I/II study of azacitidine (AZA) with venetoclax (VEN) and magrolimab (Magro) in patients (pts) with newly diagnosed (ND) older/unfit or high-risk acute myeloid leukemia (AML) and relapsed/refractory (R/R) AML. Blood. 2022;140(Suppl 1):141-144.
10. Senapati J, Loghavi S, Reville PK, et al. Outcomes of patients (pts) with newly diagnosed acute myeloid leukemia (AML) and TP53 mutation/loss treated on the phase 2 study of venetoclax (Ven) added to alternating cladribine (Clad) plus low-dose cytarabine (LDAC) and azacitidine (Aza): a subgroup analysis. Blood. 2023;142(Suppl 1):4282.
11. Garcia-Manero G, Goldberg AD, Winer ES, et al. Eprenetapopt combined with venetoclax and azacitidine in TP53-mutated acute myeloid leukaemia: a phase 1, dose-finding and expansion study. Lancet Haematol. 2023;10(4):e272-e283.
12. Daver NG, Iqbal S, Renard C, et al. Treatment outcomes for newly diagnosed, treatment-naïve TP53-mutated acute myeloid leukemia: a systematic review and meta-analysis. J Hematol Oncol. 2023;16(1):19.
13. Pollyea DA, Pratz KW, Wei AH, et al. Outcomes in patients with poor-risk cytogenetics with or without TP53 mutations treated with venetoclax and azacitidine. Clin Cancer Res. 2022;28(24):5272-5279.
14. Wei AH, Panayiotidis P, Montesinos P, et al. Long-term follow-up of VIALE-C in patients with untreated AML ineligible for intensive chemotherapy. Blood. 2022;140(25):2754-2756.
15. Döhner H, Pratz KW, DiNardo CD, et al. ELN risk stratification is not predictive of outcomes for treatment-naïve patients with acute myeloid leukemia treated with venetoclax and azacitidine. Blood. 2022;140(Suppl 1):1441-1444.
16. Bataller A, Bazinet A, DiNardo CD, et al. Prognostic risk signature in patients with acute myeloid leukemia treated with hypomethylating agents and venetoclax. Blood Adv. 2024;8(4):927-935.
17. Grob T, Al Hinai ASA, Sanders MA, et al. Molecular characterization of mutant TP53 acute myeloid leukemia and high-risk myelodysplastic syndrome. Blood. 2022;139(15):2347-2354.
18. Bahaj W, Kewan T, Gurnari C, et al. Novel scheme for defining the clinical implications of TP53 mutations in myeloid neoplasia. J Hematol Oncol. 2023;16(1):91.
19. Short NJ, Montalban-Bravo G, Hwang H, et al. Prognostic and therapeutic impacts of mutant TP53 variant allelic frequency in newly diagnosed acute myeloid leukemia. Blood Adv. 2020;4(22):5681-5689.
20. DiNardo CD, Garcia-Manero G, Kantarjian HM. Time to blur the blast boundaries. Cancer. 2022;128(8):1568-1570.
21. Estey E, Hasserjian RP, Döhner H. Distinguishing AML from MDS: a fixed blast percentage may no longer be optimal. Blood. 2022;139(3):323-332.
22. DiNardo CD, Garcia-Manero G, Pierce S, et al. Interactions and relevance of blast percentage and treatment strategy among younger and older patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Am J Hematol. 2016;91(2):227-232.
23. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.
24. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias:

integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
25. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.
26. ISCN 2016: an International System for Human Cytogenomic Nomenclature (2016): S.Karger AG; 2016.
27. Ok CY, Loghavi S, Sui D, et al. Persistent IDH1/2 mutations in remission can predict relapse in patients with acute myeloid leukemia. Haematologica. 2019;104(2):305-311.
28. Montalban-Bravo G, Kanagal-Shamanna R, Benton CB, et al. Genomic context and TP53 allele frequency define clinical outcomes in TP53-mutated myelodysplastic syndromes. Blood Adv. 2020;4(3):482-495.
29. Short NJ, Montalban-Bravo G, Hwang H, et al. Prognostic and therapeutic impacts of mutant TP53 variant allelic frequency in newly diagnosed acute myeloid leukemia. Blood Adv. 2020;4(22):5681-5689.
30. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.
31. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108(2):419-425.