Prognostic impact of 'multi-hit' *versus* 'single-hit' *TP53* alteration in patients with acute myeloid leukemia: results from the Consortium on Myeloid Malignancies and Neoplastic Diseases

Talha Badar,[1] Ahmad Nanaa,[2] Ehab Atallah,[3] Rory M. Shallis,[4] Emily C. Craver,[5] Zhuo Li,[5] Aaron D. Goldberg,[6] Antoine N. Saliba,[7] Anand Patel,[8] Jan P. Bewersdorf,[6] Adam Duvall,[8] Madelyn Burkart,[9] Danielle Bradshaw,[10] Yasmin Abaza,[9] Maximilian Stahl,[11] Neil Palmisiano,[12] Guru Subramanian Guru Murthy,[3] Amer M. Zeidan,[4] Vamsi Kota,[10] Mrinal M. Patnaik[6] and Mark R. Litzow[6]

[1]Division of Hematology-Oncology and Blood and Marrow Transplantation and Cellular Therapy Program, Mayo Clinic, Jacksonville, FL; [2]John H. Stroger, Jr. Hospital of Cook County, Chicago, IL; [3]Division of Hematology and Medical Oncology, Medical College of Wisconsin, Milwaukee, WI; [4]Section of Hematology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT; [5]Division of Clinical Trials and Biostatistics, Mayo Clinic, Jacksonville, FL; [6]Division of Hematologic Malignancies, Department of Medicine Memorial Sloan Kettering Cancer Center, New York, NY; [7]Division of Hematology, Mayo Clinic, Rochester, MN; [8]Section of Hematology and Oncology, Department of Medicine, University of Chicago, Chicago, IL; [9]Robert H. Lurie Comprehensive Cancer Center, Northwestern Hospital, Chicago, IL; [10]Division of Hematology and Oncology, Georgia Cancer Center, Augusta, GA; [11]Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA and [12]Division of Hematology and Oncology, Jefferson University Hospital, Philadelphia, PA, USA

Correspondence: T. Badar
badar.talha@mayo.edu

Received: January 6, 2024.
Accepted: May 21, 2024.
Early view: May 30, 2024.

https://doi.org/10.3324/haematol.2024.285000

Prognostic impact of 'multi-hit' *versus* 'single hit' *TP53* alteration in patients with acute myeloid leukemia: results from the Consortium on Myeloid Malignancies and Neoplastic Diseases.

Talha Badar,[1]Ahmad Nanaa,[2] Ehab Atallah,[3]Rory M. Shallis,[4] Emily C. Craver,[5] Zhuo Li,[5] Aaron D. Goldberg,[6] Antoine N. Saliba,[7]Anand Patel,[8]Jan P. Bewersdorf,[6] Adam Duvall,[8] Madelyn Burkart,[9] Danielle Bradshaw,[10] Yasmin Abaza,[9] Maximilian Stahl,[11] Neil Palmisiano,[12] Guru Subramanian Guru Murthy,[3] Amer M. Zeidan,[4] Vamsi Kota,[10] Mrinal M. Patnaik, [6] Mark R. Litzow.[6]

[1]Division of Hematology-Oncology and Blood and Marrow Transplantation and Cellular Therapy Program, Mayo Clinic, Jacksonville, FL, USA.
[2]John H. Stroger, Jr. Hospital of Cook County, IL, USA.
[3]Division of Hematology and Medical Oncology, Medical College of Wisconsin, Milwaukee, WI, USA
[4]Section of Hematology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA.
[5]Division of Clinical Trials and Biostatistics, Mayo Clinic, Jacksonville, FL, USA
[6]Division of Hematologic Malignancies, Department of Medicine Memorial Sloan Kettering Cancer Center, NY, USA.
[7]Division of Hematology, Mayo Clinic, Rochester, MN, USA
[8]Section of Hematology and Oncology, Department of Medicine, University of Chicago, Chicago, IL, USA.
[9]Robert H. Lurie Comprehensive Cancer Center, Northwestern Hospital, Chicago, Illinois.
[10] Division of Hematology and Oncology, Georgia Cancer Center, GA, USA.
[11]Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA
[12]Division of Hematology and Oncology, Jefferson University Hospital, Philadelphia, PA, USA

Address Correspondence:
Talha Badar, MD
Assistant Professor of Medicine
Mayo Clinic
4500 San Pablo Rd, Jacksonville
Florida, USA. 32224.
Email: badar.talha@mayo.edu

Running title: *TP53* allelic state and outcome in AML
Key words: AML, *TP53* allelic state, genomic landscape of AML, t-AML, *TP53* and *IDH1* mutation and allogeneic HCT.
Figures: 3
Tables: 1
Supplementary material: 5

Author contribution

TB: Conceptualization, data curation, writing original draft, and submission. AN: helped in data collection and making figures. EA, RMS, AP, ANS, MS, JPB: contributed patients, review and edit manuscript. MB, MS, GCC, GM, YA, AD, DB, VK, SD, ADG, NP, AAK, AZ, MP: contributed patients and review manuscript. MRL: contributed patients, supervise, review, and edit the manuscript.

Conflict of interest

TB: Serve in advisory board for Pfizer, Morphosys and Takeda AP: Consulting for Abbvie, research funding from Kronos Bio, Pfizer, Celgene/BMS, Servier, VK: Advisory board for Novartis and Pfizer. Anand Patel: COI: honoraria from AbbVie and BMS, research funding (institutional) from Pfizer and Kronos Bio. Amer Zeidan: Amer Zeidan is a Leukemia and Lymphoma Society Scholar in Clinical Research. Amer M. Zeidan received research funding (institutional) from Celgene/BMS, Abbvie, Astex, Pfizer, Medimmune/AstraZeneca, Boehringer-Ingelheim, Cardiff oncology, Incyte, Takeda, Novartis, Shattuck Labs, Geron, and Aprea. AMZ participated in advisory boards, and/or had a consultancy with and received honoraria from AbbVie, Pfizer, Celgene/BMS, Jazz, Incyte, Agios, Servier, Boehringer-Ingelheim, Novartis, Astellas, Daiichi Sankyo, Geron, Taiho, Seattle Genetics, BeyondSpring, Takeda, Ionis, Amgen, Janssen, Genentech, Epizyme, Syndax, Gilead, Kura, Chiesi, ALX Oncology, BioCryst, Notable, Orum, Mendus, Foran, Syros, and Tyme. AMZ served on clinical trial committees for Novartis, Abbvie, Gilead, Syros, BioCryst, Abbvie, ALX Oncology, Geron and Celgene/BMS. AMZ received travel support for meetings from Pfizer, Novartis, and Cardiff Oncology.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

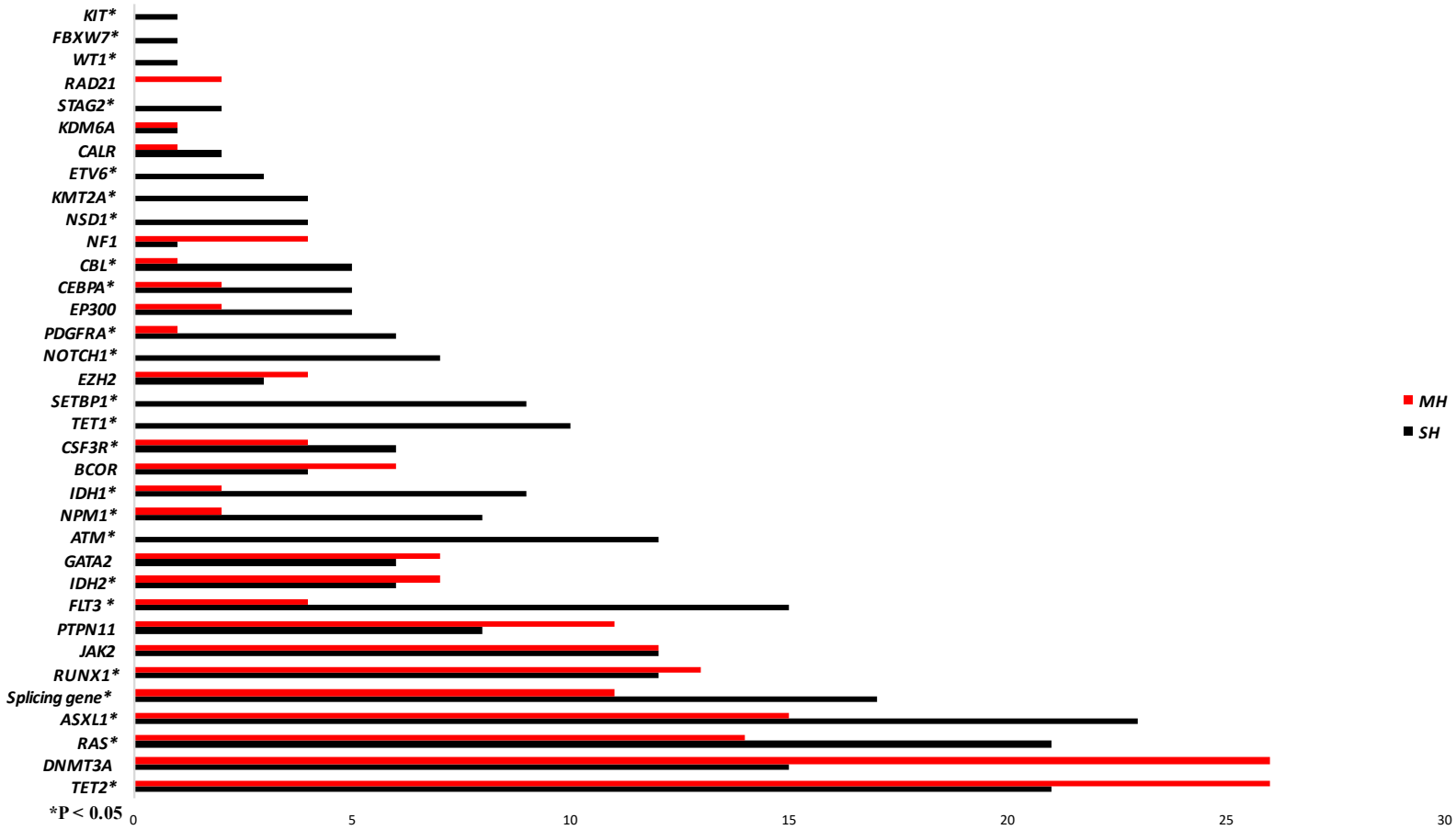
Supplementary Table 1. Baseline characteristics and outcome with *IDH1* (N=11) and *IDH2* (13) mutations			
Variables	IDH1	IDH2	P Value
Age	66 [24-73]	70 [36-85]	>0.99
sAML	3 (27)	6 (46)	0.15
Complex CG	3 (27)	7 (54)	0.24
TP53 VAF (%)	24 [5-32]	68 [7-89]	0.52
Multi-hit *TP53*	2 (18)	7 (53)	0.10
Co-mutations other than *IDH1/2*			
ASXL1	5 (45)	5 (38)	>0.99
TET2	5 (45)	4 (31)	0.41
FLT3 ITD	4 (36)	3 (23)	0.65
DNMT3A	4 (36)	6 (46)	0.69
NPM1	3 (27)	2 (15)	0.63
RAS	2 (18)	5 (38)	0.40
RUNX1	2 (18)	2 (15)	>0.99
Splicing factor (U2AF1, SF3B1, SRSF2)	1 (9)	4 (31)	0.33
GATA2	1 (9)	1 (7)	>0.99
EZH2	1 (9)	0	0.45
JAK2	0	5 (38.5)	0.04
PTPN11	0	3 (23)	0.59
CSF3R1	0	2 (15)	0.48
CEBPA	0	1 (7)	>0.99
BCOR	0	0	-
Venetoclax plus HMA (1st line)	2 (18)	1 (7)	0.21
Venetoclax, HMA, IDH1 inhibitor (Salvage)	1 (9)	-	-
HMA plus IDH2 inhibitor (Salvage)	-	1 (7)	-
IDH1 inhibitor alone (Salvage)	1 (9)	-	-
IDH2 inhibitor alone (Salvage)	-	1 (7)	-
CR/CRi rate	6 (54.5)	0	0.003
Allogeneic-HCT	2 (18)	1 (8)	0.57
sAML; secondary acute myeloid leukemia, HMA; hypomethylating agent, CR; complete remission, i; incomplete count recovery, HCT; hematopoietic stem cell transplantation			

Supplementary Table 2. Predictors of complete remission (N= 91/382; 24%)				
Variable	Total (N= 382)	CR/CRi	No CR/CRi	p value
Age ≥ 65 years	206 (54)	49 (24)	156 (76)	>0.99
Gender (Male)	224 (59)	40 (18)	118 (82)	0.62
sAML	109 (30)	28 (26)	81 (74)	0.58
tAML	85 (22)	20 (23.5)	65 (76.5)	>0.99
Complex cytogenetics	307 (80)	73 (24)	234 (76)	>0.99
Single hit *TP53*	137 (36)	38 (28)	99 (72)	0.211
Multi hit *TP53*	245 (64)	53 (22)	192 (78)	0.211
Co-mutated	239 (63)	55 (23)	183 (77)	0.71
Myeloid co-mutations				
TET2	47 (12)	7 (15)	40 (85)	0.19
DNMT3A	41 (11)	9 (22)	32 (78)	>0.99
ASXL1	38 (10)	11 (29)	27 (71)	0.41
RAS	35 (9)	3 (9)	32 (91)	0.02
Splicing factor *(U2AF1, SF3B1, SRSF2)*	28 (7)	5 (18)	23 (82)	0.64
JAK2	24 (6)	5 (21)	19 (79)	>0.99
RUNX1	25 (7)	6 (24)	19 (76)	>0.99
IDH1	11 (3)	6 (55)	5 (45)	0.02
IDH2	13 (3)	0	13 (100)	0.03
FLT3 ITD	19 (5)	8 (42)	11 (68)	0.09
PTPN11	19 (5)	3 (16)	16 (84)	0.58
GATA2	13 (4)	2 (15)	11 (85)	0.74
NPM1	10 (3)	3 (30)	7 (70)	0.70
BCOR	10 (3)	5 (50)	5 (50)	0.06
CSF3R	10 (3)	2 (20)	8 (80)	>0.99
CEBPA	7 (2)	3 (43)	4 (57)	0.36
EZH2	7 (2)	2 (28.5)	5 (71.5)	>0.99
Type of Induction				
Intensive induction	97 (25)	25 (26)	72 (74)	0.67
HMA based	50 (13)	9 (18)	41 (82)	0.37
HMA plus venetoclax	102 (27)	37 (36)	65 (64)	<0.001
Other low intensity chemotherapy	21 (5)	2 (10)	19 (90)	0.12
WBC; white blood cell, sAML; secondary acute myeloid leukemia, HMA; hypomethylating agent, CR; complete remission, i; incomplete count recovery, HCT; hematopoietic stem cell transplantation				

Supplementary Table 3. Cox regression models predicting for event free survival				
Variable	Univariate analysis for EFS		Multivariate analysis for EFS	
	EFS (mo)	P value	HR (95% CI)	P value
Age (every 10 years)	-	0.27		
Gender (Male vs Female)	1.80 vs 2.27	0.99		
sAML	1.73 vs 2.13	0.20		
tAML	2.27 vs 1.93	0.17		
Complex cytogenetics	1.97 vs 2.27	0.04	1.42 (0.98, 2.07)	0.06
Single hit *vs* Multi hit *TP53*	2.27 vs 1.90	0.40		
Co-mutated	2.13 vs 1.93	0.39		
Myeloid co-mutations				
TET2	1.97 vs 2.13	0.69		
DNMT3A	1.87 vs 2.13	0.72		
ASXL1	3.00 vs 2.03	0.02	0.73 (0.44, 1.21)	0.22
RAS	1.97 vs 2.13	0.98		
Splicing factor *(U2AF1, SF3B1, SRSF2)*	1.90 vs 2.13	0.51		
JAK2	1.30 vs 2.13	0.68		
RUNX1	1.17 vs 2.13	0.17		
IDH1	8.23 vs 2.07	0.01	0.44 (0.19, 1.01)	0.05
IDH2	1.17 vs 2.13	0.17		
FLT3 ITD	2.13 vs 2.0	0.04	0.98 (0.48, 2.01)	0.96
PTPN11	1.97 vs 2.13	0.87		
GATA2	1.20 vs 2.13	0.35		
NPM1	2.83 vs 2.03	0.06		
BCOR	1.47 vs 2.07	0.20		
CSF3R	2.13 vs 2.03	0.91		
CEBPA	3.67 vs 2.13	0.25		
EZH2	1.50 vs 2.10	0.52		
Type of Induction				
Intensive induction	1.33 vs 2.20	0.20		
HMA based	5.10 vs 1.80	0.09		
HMA plus venetoclax	3.73 vs 1.63	<0.001	0.53 (0.41, 0.70)	<0.001
Other low intensity chemotherapy	1.43 vs 2.13	0.11		
Allogeneic-HCT[1]	-	0.002	0.34 (0.18, 0.62)	<0.001
mo; months, HR; hazard ratio, CI; confidence interval, WBC; white blood cell, sAML; secondary acute myeloid leukemia, HMA; hypomethylating agent, HCT; hematopoietic stem cell transplantation [1]Allogeneic- HCT was treated as a time-dependent covariate.				

Supplementary Table 4. Cox regression models predicting for overall survival				
Variable	Univariate analysis for OS		Multivariate analysis for OS	
	OS (mo)	P value	HR (95% CI)	P value
Age (every 10 years)	-	0.002	1.07 (0.95, 1.21)	0.27
Gender (Male vs Female)	6.57 vs 8.07	0.59		
sAML	5.90 vs 7.53	0.06		
tAML	8.20 vs 6.60	0.86		
Complex cytogenetics	6.67 vs 10.07	0.002	1.56 (1.01, 2.40)	0.044
Single hit vs Multi hit TP53	6.87 vs 7.13	0.35		
Co-mutated	6.70 vs 8.0	0.60		
Myeloid co-mutations				
TET2	6.57 vs 6.63	0.35		
DNMT3A	5.90 vs 7.10	0.89		
ASXL1	11.33 vs 6.60	0.18		
RAS	4.03 vs 6.90	0.78		
Splicing factor (*U2AF1, SF3B1, SRSF2*)	6.57 vs 6.67	0.34		
JAK2	5.87 vs 7.10	0.58		
RUNX1	9.93 vs 6.57	0.01	0.73 (0.42, 1.25)	0.25
IDH1	55.73 vs 7.10	<0.001	0.24 (0.08, 0.71)	0.010
IDH2	23.07 vs 7.03	0.52		
FLT3 ITD	22.53 vs 6.90	0.003	0.90 (0.39, 2.12)	0.82
PTPN11	3.37 vs 6.70	0.45		
GATA2	4.40 vs 6.70	0.07		
NPM1	NR vs 7.10	0.02	0.31 (0.07, 1.37)	0.12
BCOR	6.57 vs 6.90	0.20		
CSF3R	6.70 vs 7.03	0.97		
CEBPA	8.83 vs 6.90	0.35		
EZH2	2.73 vs 7.03	0.29		
Type of Induction				
Intensive induction	9.13 vs 6.47	0.007	0.86 (0.62, 1.18)	0.34
HMA based	9.17 vs 6.67	0.85		
HMA plus venetoclax	7.53 vs 6.87	0.28		
Other low intensity chemotherapy	1.93 vs 7.30	0.01	3.66 (2.09, 6.39)	<0.001
Allogeneic-HCT[1]	-	<0.001	0.28 (0.16, 0.47)	<0.001

mo; months, HR; hazard ratio, CI; confidence interval, WBC; white blood cell, sAML; secondary acute myeloid leukemia, HMA; hypomethylating agent, HCT; hematopoietic stem cell transplantation, NR; not reached.
[1]Allogeneic- HCT was treated as a time-dependent covariate.



Supplementary Figure 1. *Patterns and frequency of co-mutations identified in the TP53 cohort by allelic state. Single-hit TP53 are depicted in black and those co-mutated with multi-hit TP53 in red. *P < 0.05, Chi Square approximation & two-sided Fisher's exact test.*