

Examining the impact of age on the prognostic value of ELN-2017 and ELN-2022 acute myeloid leukemia risk stratifications: a report from the SWOG Cancer Research Network

Christina M. Termini,^{1,2} Anna Moseley,³ Megan Othus,³ Frederick R. Appelbaum,^{4,5} Thomas R. Chauncey,^{4,6} Harry P. Erba,⁷ Min Fang,^{1,2} Stanley C. Lee,^{1,2} Jasmine Naru,¹ Era L. Pogossova-Agadjanyan,¹ Jerald P. Radich,^{1,4} Cheryl L. Willman,⁸ Feinan Wu,⁹ Soheil Meshinchi^{1,10} and Derek L. Stirewalt^{1,4}

¹Translational Science and Therapeutics Division, Fred Hutch Cancer Center, Seattle, WA; ²Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA; ³SWOG Statistical Center, Fred Hutch Cancer Center, Seattle, WA; ⁴Departments of Oncology and Hematology, University of Washington, Seattle, WA; ⁵Clinical Research Division, Fred Hutch Cancer Center, Seattle, WA; ⁶VA Puget Sound Health Care System, Seattle, WA; ⁷Duke Cancer Institute, Durham, NC; ⁸Department of Laboratory Medicine and Pathology, Mayo Clinic Comprehensive Cancer Center, Rochester, MN; ⁹Genomics and Bioinformatics Shared Resource, Fred Hutchinson Cancer Research Center, Seattle, WA and ¹⁰Department of Pediatrics, University of Washington, Seattle, WA, USA

Correspondence:

C.M. TERMINI - ctermini@fredhutch.org

<https://doi.org/10.3324/haematol.2023.282733>

Supplemental Table 1: Characteristics of patients analyzed using ELN-2017 and ELN-2022 guidelines. Data was procured from n=351 patients. Abbreviations: CR, complete remission.

Factor	Level	Number (%) of patients (n=351)	
Age	Age	Median 56 years (range 18-88)	
SWOG Study ID	S0106	205 (58)	
	S0112	24 (7)	
	S9031	57 (16)	
	S9333	65 (19)	
Hispanic Ethnicity	Hispanic	14 (4)	
	Not Hispanic	288 (82)	
	Hispanic ethnicity unknown	49 (14)	
FLT3 Status	FLT3-ITD mutated	110 (31)	
	FLT3-ITD not mutated	238 (68)	
	FLT3 ITD not tested	2 (1)	
NPM1 status	NPM1 mutated	124 (35)	
	NPM1 not mutated	223 (64)	
	NPM1 not tested	2 (1)	
	NPM1 status unknown	1 (0)	
Cytogenic risk (ELN2017)	Favorable	42 (12)	
	Intermediate	184 (52)	
	Unfavorable	49 (14)	
	Unknown	76 (22)	
Cytogenic risk (ELN2022)	Favorable	43 (12)	
	Intermediate	184 (52)	
	Unfavorable	48 (14)	
	Unknown	76 (22)	
			5-year overall survival
ELN2017	Favorable	117 (33)	53% (95% CI 44% - 63%)
	Intermediate	64 (18)	22% (95% CI 14% - 35%)
	Unfavorable	91 (26)	12% (95% CI 7% - 21%)
	Unknown	79 (23)	22% (95% CI 15% - 34%)
ELN2022	Favorable	106 (30)	57% (95% CI 49% - 68%)
	Intermediate	67 (19)	21% (95% CI 13% - 34%)
	Unfavorable	99 (28)	12% (95% CI 7% - 21%)
	Unknown	79 (23)	22% (95% CI 15% - 34%)
ELN changed 2017-2022	Changed from 2017-2022	33 (9)	
	Did not change from 2017-2022	318 (91)	
Response to therapy	CR/Unconfirmed CR	210 (60)	
	No CR	141 (40)	
Overall survival	Overall survival	Median 1.4 years (95% CI 1.1-1.8)	

Supplemental Table 2: Molecular mutation profiles of patients analyzed with ELN-2017 and ELN-2022.

Factor	Level	Number (%) of patients (n = 351)
ASXL1	ASXL1 mutated	33 (9)
	ASXL1 not mutated	314 (89)
	ASXL1 not tested	3 (1)
	ASXL1 status unknown	1 (0)
RUNX1	RUNX1 mutated	40 (11)
	RUNX1 not mutated	307 (87)
	RUNX1 not tested	3 (1)
	RUNX1 status unknown	1 (0)
TP53	TP53 mutated	26 (7)
	TP53 not mutated	321 (91)
	TP53 not tested	3 (1)
	TP53 status unknown	1 (0)
BCOR	BCOR mutated	12 (3)
	BCOR not mutated	335 (95)
	BCOR not tested	3 (1)
	BCOR status unknown	1 (0)
EZH2	EZH2 mutated	12 (3)
	EZH2 not mutated	335 (95)
	EZH2 not tested	3 (1)
	EZH2 status unknown	1 (0)
SF3B1	SF3B1 mutated	15 (4)
	SF3B1 not mutated	332 (95)
	SF3B1 not tested	3 (1)
	SF3B1 status unknown	1 (0)
SRSF2	SRSF2 mutated	36 (10)
	SRSF2 not mutated	311 (89)
	SRSF2 not tested	3 (1)
	SRSF2 status unknown	1 (0)

STAG2	STAG2 mutated	7 (2)
	STAG2 not mutated	340 (97)
	STAG2 not tested	3 (1)
	STAG2 status unknown	1 (0)
U2AF1	U2AF1 mutated	11 (3)
	U2AF1 not mutated	336 (96)
	U2AF1 not tested	3 (1)
	U2AF1 status unknown	1 (0)
ZRSR2	ZRSR2 mutated	1 (0)
	ZRSR2 not mutated	346 (99)
	ZRSR2 not tested	3 (1)
	ZRSR2 status unknown	1 (0)

Supplemental Table 3: Univariate and multivariate analyses with ELN-2017 and ELN-2022 with FLT3 patients removed. Univariate analyses for complete response, overall survival, and relapse-free survival for patients excluding those with FLT3 mutations. Multivariate analyses for complete response, overall survival, and relapse-free survival for patients excluding those with FLT3 mutations. Analyses were performed using data from n= 238 patients.

Univariate analyses

Variable	Level	Complete Response OR (95% CI; P-value)	Overall Survival HR (95% CI; P-value)	Relapse-free Survival HR (95% CI; P-value)
Age	Continuous	0.96 (0.94-0.98; <0.01)	1.05 (1.04-1.06; <0.01)	1.03 (1.02-1.05; <0.01)
	By decade	0.66 (0.55-0.80; <0.01)	1.61 (1.43-1.81; <0.01)	1.39 (1.20-1.62; <0.01)
Cytogenetic risk 2017¹	Favorable	5.47 (1.58-18.93; <0.01)	0.26 (0.13-0.50; <0.01)	0.51 (0.29-0.89; 0.017)
	Unfavorable	0.16 (0.07-0.36; <0.01)	2.57 (1.73-3.82; <0.01)	1.70 (0.84-3.45; 0.14)

	Unknown	0.34 (0.17-0.71; <0.01)	1.36 (0.89-2.06; 0.15)	1.02 (0.55-1.91; 0.95)
Cytogenetic risk 2022¹	Favorable	3.94 (1.30-11.91; 0.015)	0.28 (0.15-0.53; <0.01)	0.50 (0.29-0.87; 0.014)
	Unfavorable	0.14 (0.06-0.32; <0.01)	2.64 (1.77-3.94; <0.01)	1.51 (0.72-3.17; 0.28)
	Unknown	0.33 (0.16-0.68; <0.01)	1.36 (0.90-2.07; 0.14)	1.00 (0.54-1.88; 0.99)
Performance Status	Numeric	0.90 (0.65-1.24; 0.51)	1.17 (0.98-1.41; 0.089)	1.02 (0.78-1.32; 0.89)
	2-3 v 0-1	0.70 (0.36-1.38; 0.31)	1.45 (0.98-2.14; 0.06)	1.12 (0.65-1.96; 0.68)
AML Onset	Yes v No	0.06 (0.01-0.26; <0.01)	3.34 (2.03-5.50; <0.01)	0.90 (0.13-6.49; 0.92)
	S0106	2.64 (1.17-5.96; 0.019)	0.25 (0.16-0.38; <0.01)	0.30 (0.16-0.54; <0.01)

Study²	S0112	0.71 (0.23-2.26; 0.57)	0.94 (0.53-1.69; 0.84)	0.76 (0.31-1.88; 0.55)
	S9333	0.87 (0.34-2.19; 0.76)	0.77 (0.48-1.25; 0.29)	0.81 (0.41-1.62; 0.56)
ELN 2017¹	Favorable	2.78 (1.13-6.85; 0.026)	0.42 (0.25-0.70; <0.01)	0.59 (0.33-1.05; 0.072)
	Adverse	0.26 (0.11-0.65; <0.01)	1.80 (1.10-2.92; 0.018)	1.26 (0.63-2.52; 0.52)
	Unknown	0.41 (0.16-1.07; 0.07)	1.09 (0.63-1.87; 0.76)	0.85 (0.40-1.82; 0.68)
ELN 2022¹	Favorable	2.33 (0.86-6.25; 0.094)	0.41 (0.24-0.71; <0.01)	0.55 (0.29-1.05; 0.069)
	Adverse	0.26 (0.10-0.69; <0.01)	1.69 (1.00-2.86; 0.049)	1.27 (0.63-2.57; 0.5)
	Unknown	0.35 (0.12-1.00; 0.049)	1.09 (0.61-1.95; 0.77)	0.84 (0.38-1.86; 0.66)

ELN 2017 (excluding unknowns)¹	Favorable	2.78 (1.13-6.85; 0.026)	0.41 (0.25-0.68; <0.01)	0.58 (0.33-1.04; 0.069)
	Adverse	0.26 (0.11-0.65; <0.01)	1.82 (1.12-2.95; 0.016)	1.26 (0.63-2.52; 0.52)

ELN 2022 (excluding unknowns)¹	Favorable	2.33 (0.86-6.25; 0.094)	0.40 (0.23-0.69; <0.01)	0.55 (0.29-1.03; 0.063)
	Adverse	0.26 (0.10-0.69; <0.01)	1.70 (1.01-2.88; 0.047)	1.26 (0.62-2.55; 0.52)

¹Reference level = Intermediate

²Reference level = S9031

Multivariate analyses

Model	AUC or C-statistic	AUC or C-statistic (excluding unknowns)
--------------	---------------------------	--

Complete Response (CR, AUC)

ELN 2017	0.75	0.75
ELN 2022	0.74	0.74
Age + ELN 2017	0.79	0.78

Age + ELN 2022	0.77	0.77
Overall Survival (OS, C-Statistic)		
ELN 2017	0.66	0.67
ELN 2022	0.66	0.67
Age + ELN 2017	0.73	0.73
Age + ELN 2022	0.72	0.72
Relapse-free Survival (RFS, C-Statistic)		
ELN 2017	0.57	0.57
ELN 2022	0.58	0.59
Age + ELN 2017	0.65	0.66
Age + ELN 2022	0.65	0.67