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Characteristics and prognostic impact of *IDH* mutations in AML: a COG, SWOG, and ECOG analysis

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Key Points

- *IDH* mutation did not abrogate the favorable prognostic impact of *NPM1* mutation in AML for patients aged <60 years.
- Patients with *IDH*-mutated AML without cooccurring *NPM1* or triple-mutated *IDH*/*NPM1*/*DNMT3A* or *IDH*/*NPM1*/*FLT3*-ITD AML had inferior outcomes.

Somatic mutations in isocitrate dehydrogenase (*IDH*) genes occur frequently in adult acute myeloid leukemia (AML) and less commonly in pediatric AML. The objective of this study was to describe the prevalence, mutational profile, and prognostic significance of *IDH* mutations in AML across age. Our cohort included 3141 patients aged between <1 month and 88 years treated on Children's Cancer Group/Children's Oncology Group (n = 1872), Southwest Oncology Group (n = 359), Eastern Cooperative Oncology Group (n = 397) trials, and in Beat AML (n = 333) and The Cancer Genome Atlas (n = 180) genomic characterization cohorts. We retrospectively analyzed patients in 4 age groups (age range, n): pediatric (0-17, 1744), adolescent/young adult (18-39, 444), intermediate-age (40-59, 640), older (≥60, 309). *IDH* mutations (IDH^{mut}) were identified in 9.2% of the total cohort (n = 288; *IDH1* [n = 123, 42.7%]; *IDH2* [n = 165, 57.3%]) and were strongly correlated with increased age: 3.4% pediatric vs 21% older, $P < .001$. Outcomes were similar in IDH^{mut} and *IDH*-wildtype (IDH^{WT}) AML (event-free survival [EFS]: 35.6% vs 40.0%, $P = .368$; overall survival [OS]: 50.3% vs 55.4%, $P = .196$). *IDH* mutations frequently occurred with *NPM1* (47.2%), *DNMT3A* (29.3%), and *FLT3*-internal tandem duplication (ITD) (22.4%)

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The data used for analysis in this manuscript are available in a variety of publicly available databases. The Database for Genotypes and Phenotypes (dbGaP; https://www.ncbi.nlm.nih.gov/gap/) houses data for the AML TARGET (phs000465.v22.p8), Beat AML (phs001657.v2.p1), and The Cancer Genome Atlas (TCGA)-LAML (phs000178.v11.p8) projects. These data sets are also available through the Genomic Data Commons (GDC; https://portal.gdc.cancer.gov/). The Beat AML data set can also be viewed in an interactive browser available at: http://www.vizome.org/. In addition, the TCGA has an interactive browser available at: https://software.broadinstitute.org/software/igv/tcga. The ECOG E1900 mutation data are published here https://doi.org/10.1182/blood.V116.21.851.851. Transfer of the SWOG S0106 data into dbGaP is underway.

Data are available on request from the corresponding author, Sara Zarnegar-Lumley (sara.zarnegar@vumc.org).

The full-text version of this article contains a data supplement.

mutations. Patients with *IDH*^{mut} AML with *NPM1* mutation (*IDH*^{mut}/*NPM1*^{mut}) had significantly improved survival compared with the poor outcomes experienced by patients without (*IDH*^{mut}/*NPM1*^{WT}) (EFS: 55.1% vs 17.0%, $P < .001$; OS: 66.5% vs 35.2%, $P < .001$). *DNTM3A* or *FLT3*-ITD mutations in otherwise favorable *IDH*^{mut}/*NPM1*^{mut} AML led to inferior outcomes. Age group analysis demonstrated that *IDH* mutations did not abrogate the favorable prognostic impact of *NPM1*^{mut} in patients aged <60 years; older patients had poor outcomes regardless of *NPM1* status. These trials were registered at www.clinicaltrials.gov as #NCT00070174, #NCT00372593, #NCT01371981, #NCT00049517, and #NCT00085709.

Introduction

Enhanced genomic and epigenomic profiling of acute myeloid leukemia (AML) has led to identification of recurrent mutations that are prognostic and are candidates for targeted therapy. Somatic mutations in isocitrate dehydrogenase (*IDH*) genes, *IDH1* and *IDH2,* occur in ~6% to 16% and ~8% to 19% of adult patients with AML, respectively.[1-5] In pediatric AML, *IDH* mutations are rare, occurring in <4% of patients.[6-11]

Mutations in active site arginine residues of IDH1 (R132) and IDH2 (R140, R172) enzymes lead to neomorphic production of the oncometabolite 2-hydroxyglutarate.[12-15] Accumulation of 2-hydroxyglutarate alters DNA and histone methylation, which impairs myeloid differentiation and contributes to leukemogenesis.[14,16] Inhibitors of IDH-mutant protein including ivosidenib, olutasidenib (IDH1), and enasidenib (IDH2) can be used as single agents in adult patients with *IDH*-mutant AML, either in the upfront or relapsed/refractory setting.[17-20] Clinical trials investigating IDH inhibitors combined with varying intensity chemotherapy are underway for adult patients with newly diagnosed *IDH*-mutated AML.[21-23]

Several groups have reported on the prognostic influence of *IDH* mutations alone and in combination with frequently cooccurring mutations and have found varying results.[1-5,24-33] Data on younger patients (aged <30 years) are limited, making it difficult to prognosticate outcomes based on *IDH* mutation status in these patients.[6-11] The aim of the current study is to describe the prevalence, cooccurring mutational profile, and prognostic impact of *IDH* mutations in a large cohort of patients with AML across the age spectrum. We hypothesize that improved understanding of *IDH*-mutated AML will allow for optimal integration of targeted agents into risk and age-adapted treatment strategies.

Patients and methods

Characteristics of study cohort

The total patient cohort included 3141 patients with AML ranging in age from <1 month to 88 years. For analysis, patients were divided into 4 age-defined groups: pediatric (0-17 years, n = 1744), adolescent/young adult (AYA; 18-39 years, n = 444), intermediate-age (40-59 years, n = 640), and older (≥60 years, n = 309). The cohort comprised 1872 (59.5%) patients enrolled in Children's Cancer Group (CCG) or Children's Oncology Group (COG) trials CCG2961,[34] AAML03P1 (NCT00070174),[35] AAML0531 (NCT00372593),[36] and AAML1031 (NCT01371981)[37]; 397 (12.6%) patients enrolled on the Eastern Cooperative Oncology Group (ECOG) E1900 trial (NCT00049517)[38]; 359 (11.4%) patients on the Southwest Oncology Group (SWOG) trial, S0106 (NCT00085709)[39]; 333 (10.6%) patients included in the Beat AML genomic characterization cohort[40]; and 180 (5.7%) patients from TCGA AML cohort.[41] Details of chemotherapy regimens and randomizations for each treatment protocol and methods for genomic characterization cohorts were previously described.[34-41] (supplemental Table 1). Institutional review boards of participating institutions approved clinical protocols. Written informed consent was obtained from study participants in accordance with the Declaration of Helsinki.

Clinical characteristics and treatment outcomes were collected and evaluated per standard practices of respective studies. For our analysis by cytomolecular risk category, we assigned patients to favorable, intermediate, adverse, or indeterminate risk, independent of *IDH* mutation status. Patients in the ECOG, SWOG, Beat AML, and TCGA cohorts were assigned risk classification based on their designation at the time of the original studies. Earlier CCG/COG studies made very limited use of cytomolecular risk classification; therefore, the current COG risk classification schema was used to classify patients in the CCG/COG cohort for this study (supplemental Table 2).

Mutational analysis was performed per each study or subsequent analyses. Cytogenetic analysis, fluorescence in situ hybridization, and reverse transcriptase polymerase chain reaction assays for recurrent cytogenetic lesions were performed as previously described.[34-37,39,42] Samples from patients on CCG/COG trials underwent mutational profiling by targeted capture (n = 788), whole-genome (n = 329), and/or transcriptome (n = 1659) sequencing.[43] Targeted mutation sequencing was conducted on banked ECOG E1900 samples.[44] Samples from SWOG S0106 underwent next-generation sequencing. TCGA employed whole-genome sequencing (n = 50) or whole-exome sequencing (n = 150).[41] For Beat AML, whole-exome and RNA sequencing as well as targeted mutation polymerase chain reactions were performed.[40] Mutation prevalence was reported as the proportion of patients positive for mutation among patients with available mutation data.

Statistical analysis

IDH and cooccurring mutation prevalence was determined, and overall survival (OS), 5-year event-free survival (EFS), and cumulative incidence of relapse risk (RR) were analyzed across the total cohort and each study-defined age group. EFS and RR data were not available for Beat AML samples, and RR data were not available for TCGA samples, thus Beat AML samples were excluded from all outcome analyses and TCGA samples from RR analyses. OS was measured from date of initial randomization or study entry until death from any cause. EFS was measured from date of randomization or study entry until refractory disease, relapse, or death. Complete remission (CR) was defined as hematopoietic recovery with <5% morphologic leukemic blasts in the bone marrow and no extramedullary disease after induction chemotherapy; response data were not available for the TCGA cohort. RR was measured for all patients who achieved CR from date of CR until first relapse. Observations were censored at date of last contact for patients last known to be alive (OS, EFS, and RR) without report of relapse (EFS and RR). The Kaplan-Meier method was used to estimate survival outcomes.[45] The significance of predictor variables was tested with log-rank statistic for OS and EFS and Gray statistic for RR.[46] The significance of observed differences in proportions was tested by χ^2 test and Fisher exact test when data were sparse. The Mann-Whitney (vs Kruskal-Wallis) test was used to determine the significance between differences in medians. Cox proportional hazard models were used to estimate hazard ratios of OS, EFS for univariable and multivariable analyses.[47] Competing risk regression was used to estimate hazard ratios of RR.[48] A P value of <.05 was considered statistically significant. Statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc., Cary, NC).

Results

Mutation prevalence and characteristics

Among the total cohort, there were 286 patients (9.1%) with *IDH*-mutant (*IDH*^{mut}) and 2855 (90.9%) with *IDH*-wildtype (*IDH*^{WT}) AML (Table 1). There were 288 *IDH* mutations identified; 2 patients had cooccurring *IDH1* and *IDH2* mutations and were excluded from outcomes analyses.

There were 123 (42.7%) *IDH1* mutations, nearly all point mutations at conserved active site residue R132 (n = 117, 95.1%; R132H [50.4%], R132C [36.8%], R132S [9.4%], and R132G [3.4%]). The remaining *IDH1* mutations (n = 6, 4.9%) occurred at alternative residues (V71I [n = 4], F86S [n = 1], and S122N [n = 1]) previously confirmed to be nonfunctional (V71I)[49] or outside the active site and were thus excluded from outcomes analyses. There were 165 (57.3%) *IDH2* mutations, 164 (99%) located at conserved active site residues R140 (n = 142, 86%; R140Q [95%], R140W [2.1%], R140G [1.4%], and R140L [1.4%]) and R172 (n = 22, 13.3%); 1 frameshift mutation distal to the active site at G145 with unknown functional significance was excluded from outcomes analyses.

IDH mutation frequency increased significantly with age: pediatric (3.4%, 60 of 1744), AYA (11.3%, 50 of 444), intermediate-age (17.7%, 113 of 640), and older adults (21%, 65 of 309); $P <$ .001. This observed age-dependent mutation prevalence was similar for *IDH1* and *IDH2* (Figure 1A). *IDH* mutations were virtually absent (0.3%) in patients aged <5 years.

To identify cooccurring mutations, we conducted mutational profiling of *IDH*^{mut} AML (Figure 2). In the total cohort, *NPM1* was the most frequently cooccurring mutation, identified in 47.2% (n = 135) of all patients with *IDH*^{mut} (*IDH*^{mut}/*NPM1*^{mut}), in 53.7% of patients with *IDH1*^{mut}, and 41.8% of patients with *IDH2*^{mut}, and was more common in *IDH*^{mut} than in *IDH*^{WT} (n = 398) AML (47.2% vs 14.0%; $P <$ .001) (Figure 1B). *NPM1* and *IDH1* mutations cooccurred with *IDH1*^{R132H} at 68.8% vs with *IDH1*^{R132C} at 12.5% ($P <$ .001). *NPM1* and *IDH2* mutations cooccurred primarily with *IDH2*^{R140} (98.6%), and once with *IDH2*^{R172K}. When analyzed by age group, a greater proportion of younger patients with *IDH*^{mut} AML had cooccurring *NPM1* mutation (56.7% pediatric, 55.1% AYA, 48.7% intermediate-age, and 29.7% older; P = .001).

DNMT3A mutations (n = 78) were the next most common mutation cooccurring in *IDH*^{mut} AML and was more prevalent in *IDH*^{mut} AML than in *IDH*^{WT} AML (29.3% vs 8.1%; $P <$ .001; Figure 1B). Of the patients with *IDH*^{mut}/*DNMT3A*^{mut} AML, 44.8% had triple mutations in *IDH*, *NPM1*, and *DNMT3A* (*IDH*^{mut}/*NPM1*^{mut}/*DNMT3A*^{mut}), mostly in the intermediate-age group (60%), and most were *IDH1*^{mut} (71.4%). *DNTM3A* mutation status was assessed in 1281 (68.5%) patients in the CCG/COG trials in the TARGET AML analysis and only 2 overlapping *IDH* and *DNMT3A* mutations were identified.

FLT3 internal tandem duplication (ITD) and tyrosine kinase domain mutations occurred with similar frequency in *IDH*^{mut} and *IDH*^{WT} AML (ITD: 22.4% vs 19.1%, P = .188; tyrosine kinase domain: 10.9% vs 8.9%, P = .259) (Figure 1B). Of the patients with *IDH*^{mut}/*FLT3*-ITD AML, these mutations also cooccurred with *NPM1* (*IDH*^{mut}/*NPM1*^{mut}/*FLT3*-ITD) in 63.9%.

Mutations that more frequently occurred in *IDH*^{mut} vs *IDH*^{WT} AML included *ASXL1* (8.9% vs 2.5%, $P <$ .001), *RUNX1* (9.7% vs 3.3%, $P <$ .001), and *KMT2A*-partial tandem duplication (11.5% vs 4.3%, $P <$ .001) (Figure 1B). The poor risk mutations *RUNX1* and *ASXL1* were prevalent in intermediate-age and older patients, particularly with *IDH*^{mut}/*NPM1*^{WT} (Figure 2). Other comutations were less prevalent in *IDH*^{mut} than *IDH*^{WT} AML, namely *WT1* (3.8% vs 9.0%, P = .003) and *NRAS* (11.6% vs 20.0%, P = .001) (Figure 1B).

IDH^{mut} AML was more frequently associated with normal karyotype than with *IDH*^{WT} AML (62.6% vs 30.3%, $P <$ .001; Figure 1B). Data on cytomolecular risk classification were available in 2976 (94.7%) patients overall and 256 (89.5%) patients with *IDH*^{mut} AML (Table 1). A greater proportion of *IDH*^{mut} AML was classified as intermediate risk compared with *IDH*^{WT} AML in the total cohort (51.6% vs 35.6%, $P <$ .001) and in AYA and intermediate-age groups (AYA: 62.8% vs 36.4%, P = .001; intermediate-age: 74.5% vs 50.5%, $P <$ .001). Among pediatric patients, a greater proportion of those with *IDH*^{mut} AML had favorable risk classification compared with those with *IDH*^{WT} AML (71.7% vs 37.4%, $P <$ .001). This was, in large part, because of the combination of *NPM1* and *IDH* mutations (76.7% of pediatric patients with favorable risk *IDH*^{mut}); cooccurrence with core-binding factor (CBF) mutations accounted for 20.9% of pediatric patients with

Table 1. Clinical and disease characteristics of study cohort

	IDH1^{mut}		*IDH2*^{mut}		*IDH1/2*^{mut*}		*IDH*^{WT}		
	n	%	n	%	n	%	n	%	
	123		165		286		2855		
Study cohort									
CCG/COG	31	25.2%	44	26.7%	74	25.9%	1798	63.0%	
Beat AML	24	19.5%	32	19.4%	56	19.6%	277	9.7%	
ECOG	24	19.5%	34	20.6%	58	20.3%	339	11.9%	
SWOG	25	20.3%	35	21.2%	60	21.0%	299	10.5%	
TCGA	19	15.4%	20	12.1%	38	13.3%	142	5.0%	
Age category (y)									
Pediatric (0-17)	25	20.3%	35	21.2%	60	21.0%	1684	59.1%	
AYA (18-39)	25	20.3%	25	15.2%	49	17.1%	395	13.9%	
Intermediate-age (40-59)	48	39.0%	65	39.4%	113	39.5%	527	18.5%	
Older (≥60)	25	20.3%	40	24.2%	64	22.4%	245	8.6%	
									P value: *IDH*^{mut} vs *IDH*^{WT}
Age: median (range)	46.4 (4.3-87)		51.4 (4.2-83)		50.7 (4.2-87)		15.6 (0.01-88)		**<.001**
	IDH1^{mut}		*IDH2*^{mut}		*IDH1/2*^{mut*}		*IDH*^{WT}		
	n	%	n	%	n	%	n	%	
Sex									
Male	60	48.8%	89	53.9%	147	51.4%	1503	52.7%	.683
Female	63	51.2%	76	46.1%	139	48.6%	1351	47.3%	
WBC (×10^3/μL)									
Median (range), n = 3092	22.8 (0.6-201.1)		14.3 (0.8-191.8)		19.1 (0.6-201.1)		21.9 (0.2-918.5)		**.003**
Peripheral blast, %									
Median (range), n = 2961	63 (0-98)		45 (0-97)		55 (0-98)		38 (0-100)		**.002**
Bone marrow blast, %									
Median (range), n = 2582	79 (0-99)		74 (11-100)		76 (0-100)		68 (0-100)		**<.001**
Platelet count (×10^3/μL)									
Median (range), n = 1799	65 (9-650)		57.5 (8-9300)		62 (8-9300)		48 (0.7-7900)		**<.001**
Cytomolecular risk group									
Favorable	30	26.3%	42	29.2%	72	28.1%	916	33.7%	.071
Intermediate	61	53.5%	73	50.7%	132	51.6%	968	35.6%	**<.001**
Adverse	23	20.2%	29	20.1%	52	20.3%	836	30.7%	**.001**
Unknown	9		21		30		135		

Bolded values are statisically significant.

favorable risk *IDH*^{mut} because dual CBF and *IDH* mutations occurred in 15% (9 of 60) of the *IDH*^{mut} pediatric cohort. There was no difference among cytomolecular risk groups based on *IDH* mutation status in older patients (*IDH*^{mut} vs *IDH*^{WT}, favorable: 16.9% vs 18.2%, $P = .820$; intermediate: 44.1% vs 46.2%, $P = .77$; adverse: 39% vs 35.6%, $P = .628$).

Clinical outcomes

Outcomes analyses were conducted for nearly all patients aged <60 years (pediatric: n = 60/60 [100%], AYA: n = 44/49 [90%], and intermediate-age: n = 92/113 [89]); however, in older patients with *IDH*^{mut} AML, outcomes analyses were limited to 39% (n = 25/64). There was no significant difference in CR rates between *IDH*^{mut} and *IDH*^{WT} AML for the overall cohort (80.4% vs 84.3%; $P = .162$) or among age groups (supplemental Table 3). Outcome data were available for OS and EFS analysis in 2799 (89.1%) and for RR in 2162 (68.8%) of the total cohort. In the overall cohort, patients with *IDH*^{mut} or *IDH*^{WT} AML experienced similar OS (50.3%; 95% confidence interval [CI], 42.8-57.2 vs 55.4%; 95% CI, 53.3-57.3; $P = .196$) and EFS (35.6% [95% CI, 29-42.3] vs 40% [95% CI, 38.1-42]; $P = .368$). Further analysis by age group demonstrated no difference in OS or EFS between *IDH*^{mut} and *IDH*^{WT} AML (Table 2). There was no significant OS or EFS difference when comparing *IDH*^{WT} and *IDH*^{mut} by *IDH* isoform (*IDH1* vs *IDH2*) or mutation subtype (*IDH1*^{R132} vs *IDH2*^{R140} vs *IDH2*^{R172K}) overall (Figure 3) or in any age group (Table 2). Among the cohort for RR analysis, there was no RR difference based on *IDH* mutation status (*IDH*^{mut}: 47.3% [95% CI, 38.7-55.5] vs

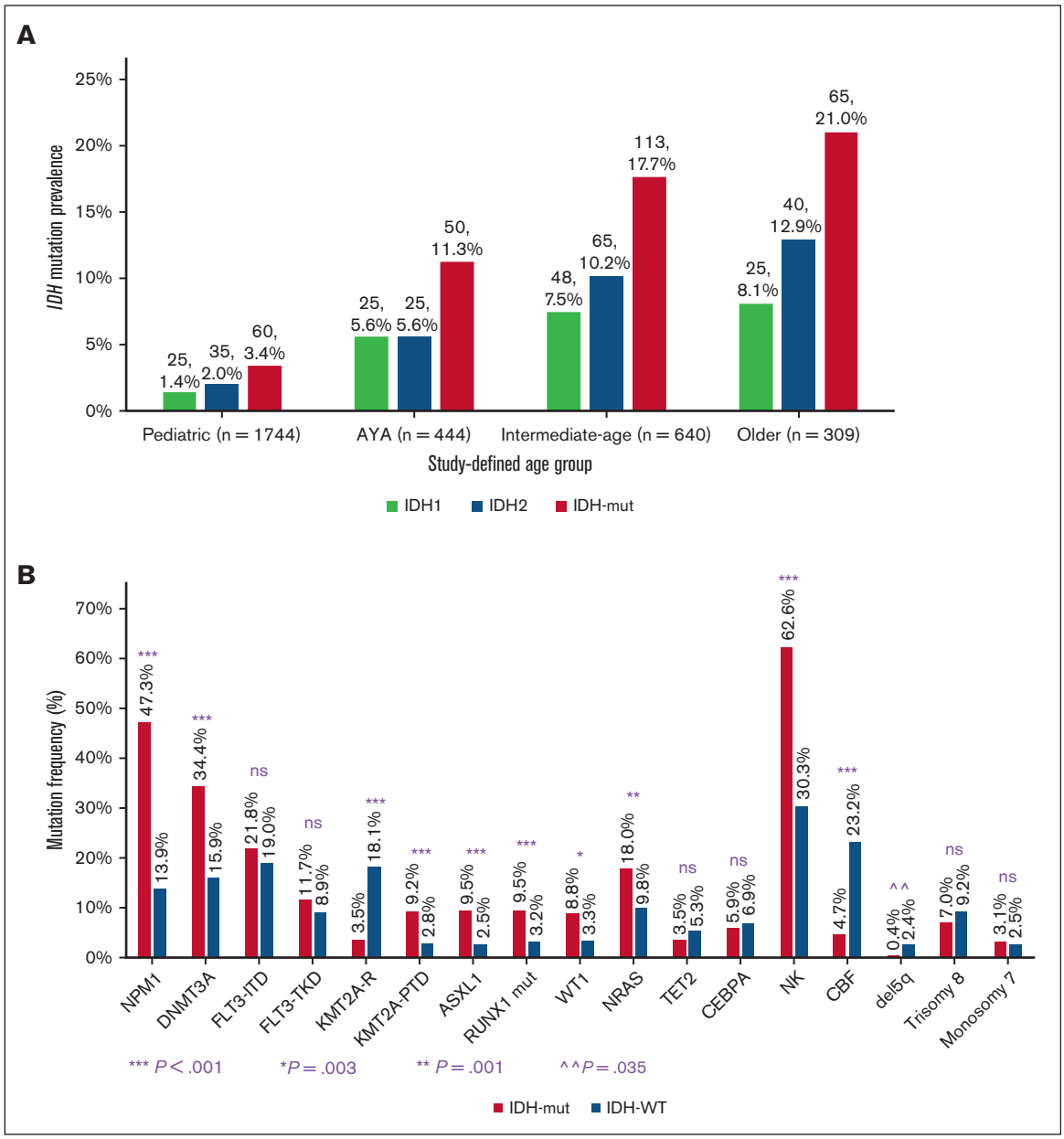

Figure 1. Profile of *IDH* mutations in AML according to age and cooccurring mutations. (A) *IDH* mutation prevalence increases with age shown as *IDH1, IDH2,* and combined *IDH1*/*IDH2* in study-defined age groups. (B) The cooccurring mutational profile of *IDH*^{mut} AML varies from that of *IDH*^{WT} AML. CBF, core-binding factor; *KMT2A*-R, *KMT2A*-rearranged; NK, normal karyotype; ns, nonsignificant; PTD, partial tandem duplication; TKD, tyrosine kinase domain.

IDH^{WT}: 45.5% [95% CI, 43.3-47.7]; P = .858; supplemental Table 4). When the cohort was analyzed by cytomolecular risk group, presence of *IDH* mutation did not significantly modify outcomes (OS for *IDH*^{mut} vs *IDH*^{WT}: favorable: 78.3% [95% CI, 63.1-87.8] vs 79.8% [95% CI, 76.8-82.5]; P = .705; intermediate: 44.1% [95% CI, 33.7-54] vs 52.5% [95% CI, 49.1-55.9]; P = .25; adverse: 36.8% [95% CI, 18.8-55.0] vs 36.2% [95% CI, 32.6-39.8]; P = .448). Those with *IDH*^{mut}/normal karyotype had better outcomes compared with those with *IDH*^{mut} with abnormal karyotype (EFS: 46.5% vs 22.9%, P = .002; OS: 58.4% vs 41.5%, P = .007).

Nearly half of all patients with *IDH*^{mut} AML had cooccurring *NPM1* mutation (*NPM1*^{mut}; 47.2%), thus we evaluated outcomes of *IDH*^{mut} AML based on presence of *NPM1* mutation. In the overall cohort, patients with dual mutant *IDH*^{mut}/*NPM1*^{mut} had significantly better EFS and OS compared with the particularly poor outcome of those with *IDH*^{mut}/*NPM1*^{WT} (EFS: 55.1% [95% CI, 44.9-64.2] vs 17% [95% CI, 10.4-25.1]; P < .001; Figure 4A; OS: 66.5% [95% CI, 55.4-75.4] vs 35.2% [95% CI, 25.9-44.6]; P < .001; Figure 4B). RR was significantly lower for *IDH*^{mut}/*NPM1*^{mut} vs *IDH*^{mut}/*NPM1*^{WT} AML (35.3% [95% CI, 25.2-45.6] vs 66% [95% CI, 51.3-77.3]; P < .001).

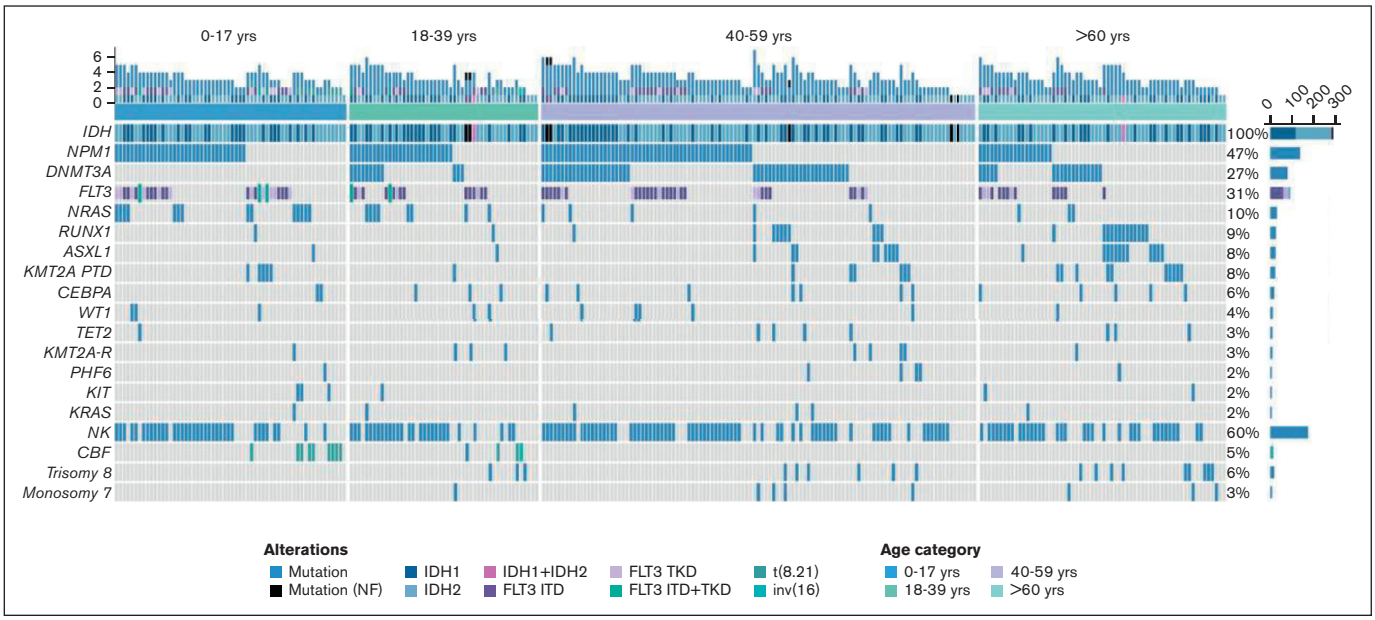

Figure 2. Mutational analysis of patient cohort. Combined *IDH1* and *IDH2* mutations with overlapping cytomolecular mutations per age cohort. NF, nonfunctional.

Similarly, when analyzed by age group, patients aged <60 years with $IDH^{mut}/NPM1^{mut}$ had superior EFS compared with those with $IDH^{mut}/NPM1^{WT}$ (pediatric: 70.6% [95% CI, 50.7-83.7] vs 23.1% [95% CI, 9.4-40.3], $P < .001$; AYA: 67.3% [95% CI, 45.0-82.2] vs 33.7% [95% CI, 13-56], $P = .048$; intermediate-age: 41.5% [95% CI, 26.0-56.4] vs 10.3% [95% CI, 3.3-22.0], $P < .001$; Figure 4C,E,G). OS was significantly better for $IDH^{mut}/NPM1^{mut}$ vs $IDH^{mut}/NPM1^{WT}$ AML in the pediatric (86.8% [95% CI, 68-95] vs 57.7% [95% CI, 36.8-73.9], $P = .011$; Figure 4D) and intermediate-age groups (62.5% [95% CI, 43.5-76.8] vs 23.4% [95% CI, 11.9-37.2], $P < .001$; Figure 4H); however, this effect was not observed in OS in the AYA group (57.2% [95% CI, 30.3-76.9] vs 57.1% [95% CI, 28.7-77.8], $P = .641$; Figure 4F). Among older patients with IDH^{mut} AML, outcomes were poor irrespective of cooccurring *NPM1* mutation $IDH^{mut}/NPM1^{mut}$ vs $IDH^{mut}/NPM1^{WT}$, EFS: 25% [95% CI, 3.7-55.8] vs 7.1% [95% CI, 0.5-27.0]; $P = .687$ and OS: 25% [95% CI, 3.7-55.8] vs 0%; $P = .55$; Figure 4I-J.

When comparing outcomes of IDH^{mut} AML by mutation subtypes, $IDH1^{R132}$ and $IDH2^{R140}$, the favorable prognostic impact of cooccurring *NPM1* was retained ($IDH1^{R132}/NPM1^{mut}$ vs $IDH1^{R132}/NPM1^{WT}$: OS, 65.1% [95% CI, 49.5-77] vs 26.1% [95% CI, 12.2-42.4]; $P < .001$; $IDH2^{R140}/NPM1^{mut}$ vs $IDH2^{R140}/NPM1^{WT}$: OS, 68.4% [95% CI, 51.8-80.4] vs 36.3% [95% CI, 23.7-49]; $P < .001$). $IDH2^{R172}/NPM1^{mut}$ occurred only once, thus precluding outcome analysis.

To further evaluate the effect of mutations in *IDH* in combination with *NPM1*, we analyzed outcomes for $NPM1^{mut}$ AML with or without *IDH* mutation. We found that EFS and OS were comparable between dual mutant $NPM1^{mut}/IDH^{mut}$ vs $NPM1^{mut}/IDH^{WT}$ in pediatric, AYA, and older patients (supplemental Table 5). In the intermediate-age cohort, $NPM1^{mut}/IDH^{mut}$ patients had improved OS compared with $NPM1^{mut}/IDH^{WT}$ (62.5% [95% CI, 43.5-76.8] vs 38.2% [95% CI, 29.3-47.0]; $P = .009$), but EFS differences did not achieve significance for $NPM1^{mut}/IDH^{mut}$ vs $NPM1^{mut}/IDH^{WT}$ (41.5% [95% CI, 26.0-56.4] vs 27.4% [95% CI, 19.7-35.6]; $P = .089$) (supplemental Figure 1). In the overall cohort, to which intermediate age patients contributed significantly, patients with $NPM1^{mut}/IDH^{mut}$ compared with $NPM1^{mut}/IDH^{WT}$ showed improved OS at 66.5% (95% CI, 55.4-75.5) vs 54.1% (95% CI, 48.2-59.6); $P = .017$ (supplemental Figure 1) and improved EFS, albeit just short of statistical significance at 55.1% (95% CI, 44.9-64.2) vs 44.3% (95% CI, 38.6-49.9); $P = .056$.

We considered the prognostic impact of *IDH* mutation in favorable risk AML without mutated *NPM1*. With the nontrivial overlap of CBF in IDH^{mut} AML in younger patients (11.2%, n = 12 of 107 pediatric/AYA patients with IDH^{mut} AML), we evaluated the outcomes of CBF AML in pediatric and AYA patients treated on COG trials (n = 11). The favorable prognosis of CBF AML was modulated by the addition of *IDH* mutation; cooccurrence of *IDH* mutation (CBF/IDH^{mut}) was associated with inferior outcomes when compared with wildtype *IDH* (CBF/IDH^{WT}); OS: 54.6% (95% CI, 22.9-78) vs 81.5% (95% CI, 77.6-84.7; $P = .03$) and EFS: 27.3% (95% CI, 6.5-53.9) vs 62.4% (95% CI, 57.9-66.6; $P = .001$).

We analyzed the prognostic impact of *DNMT3A* in the presence of cooccurring *IDH* and *NPM1* mutations in the intermediate-age cohort in which this mutation combination was most prevalent. Intermediate-age patients with $IDH^{mut}/NPM1^{mut}/DNMT3A^{mut}$ AML had inferior outcomes compared with those with $IDH^{mut}/NPM1^{mut}/DNMT3A^{WT}$; EFS: 19% (95% CI, 5.9-37.7) vs 64% (95% CI, 38.1-81.3; $P < .001$); and OS: 47.7% (95% CI, 24.5-67.8) vs 76.5% (95% CI, 40.8-92.3; $P = .019$) and higher RR (87.6% [95% CI, 49.3-97.1] vs 30.4% [95% CI, 11.9-51.3]; $P < .001$) (supplemental Figure 2).

Comparison of outcomes for IDH^{mut} AML based on the presence of cooccurring *FLT3*-ITD mutation demonstrated no difference based on presence of *FLT3*-ITD (OS: IDH^{mut}/*FLT3*-ITD vs IDH^{mut}/*FLT3*-non-ITD; 44.4% [95% CI, 22.6-55.9] vs 51.6% [95% CI, 43.2-59.3]; $P = .409$) (supplemental Figure 3). We evaluated the

Table 2. Comparison of survival outcomes of IDH^{mut} vs IDH^{WT} AML including by *IDH* isoform or mutation subtype in total cohort and by age group

	OS (n, 5-y estimated OS, 95% CI)									
	IDH^{WT}	IDH^{mut}	*P* value	$IDH1^{mut}$	$IDH2^{mut}$	*P* value	$IDH1^{R132}$	$IDH2^{R140}$	$IDH2^{R172K}$	*P* value*
Total	2578, 55.4%, (53.3-57.3)	221, 50.3%, (42.8-57.2)	.196	91, 50.6%, (38.9-61.2)	130, 50.1%, (40.4-59.1)	.778	91, 50.6%, (38.9-61.2)	110, 50.4%, (39.8-60.0)	19, 45.6%, (20.0-68.1)	.939
Pediatric	1681, 63.2%, (60.8-65.6)	60, 73.4%, (59.7-83.1)	.269	25, 78.7%, (56.1-90.6)	35, 69.2%, (50.0-82.3)	.471	25, 78.7%, (56.1-90.6)	34, 68.2%, (48.6-81.7)	1, 100%,	.610
AYA	358, 52.0%, (46.3-57.3)	44, 57.3%, (38.1-72.5)	.225	21, 58.3%, (27.7-79.7)	23, 56.6%, (31.5-75.5)	.548	21, 58.3%, (27.7-79.7)	17, 52.9%, (27.6-73.0)	5, 66.7%, (5.4-94.5)	.312
Intermediate age	446, 34.4%, (29.7-39.1)	92, 40.6%, (29.3-51.5)	.187	38, 33.8%, (18.2-50.1)	54, 46.4%, (31.2-60.3)	.425	38, 33.8%, (18.2-50.1)	43, 50.7%, (33.1-65.8)	11, 32.7%, (8.3-60.6)	.479
Older	91, 19.8%, (12.3-28.7)	25, 9.2%, (0.9-30.2)	.5	7, 14.3%, (0.7-46.5)	18, 0%	.751	7, 14.3%, (0.7-46.5)	16, 0%	2, 50.0%, (0.6-91)	.692
	EFS (n, 5-y estimate EFS, 95% CI)									
	IDH^{WT}	IDH^{mut}	*P* value	$IDH1^{mut}$	$IDH2^{mut}$	*P* value	$IDH1^{R132}$	$IDH2^{R140}$	$IDH2^{R172K}$	*P* value*
Total	2578, 40.0%, (38.1-42)	221, 35.6%, (29.0-42.3)	.368	91, 35.8%, (25.7-46.0)	130, 35.4%, (26.8-44.2)	.920	91, 35.8%, (25.7-46.0)	110, 36.5%, (27.2-45.8)	19, 12.4%, (5.8-50.1)	.892
Pediatric	1681, 45.6%, (43.2-48.0)	60, 49.5%, (35.8-61.7)	.484	25, 57.6%, (35.4-74.6)	35, 43.3%, (26.0-59.5)	.279	25, 57.6%, (35.4-74.6)	34, 44.6%, (26.8-61.0)	1, 0%	.342
AYA	358, 38.2%, (33.1-43.3)	44, 52.6%, (36.3-66.6)	.061	21, 61.1%, (36.9-78.4)	23, 46.4%, (25.0-65.4)	.473	21, 61.1%, (36.9-78.4)	17, 40.3%, (17.6-62.2)	5, 60.0%, (12.6-88.2)	.437
Intermediate age	446, 26.1%, (22-30.5)	92, 24.2%, (15.3-34.3)	.980	38, 12.2%, (3.6-26.4)	54, 33.4%, (20.5-46.9)	.086	38, 12.2%, (3.6-26.4)	43, 39.3%, (24.5-53.8)	11, 13.6%, (1.0-2.6)	.129
Older	91, 11.5%, (5.8-19.2)	25, 13.7%, (3.6-30.6)	.293	7, 14.3%, (0.7-46.5)	18, 13.3%, (2.3-34.0)	.636	7, 14.3%, (0.7-46.5)	16, 7.8%, (0.5-29.1)	2, 50.00%, (0.6-91.0)	.559

Five-year estimates of OS and EFS, 95% CI. *P* values calculated by log-rank test.

impact of *FLT3*-ITD in combination with both *IDH* and *NPM1* mutations in the overall cohort and found that IDH^{mut}/$NPM1^{mut}$/*FLT3*-ITD compared with IDH^{mut}/$NPM1^{mut}$/*FLT3*-non-ITD was associated with inferior OS (45.8% [95% CI, 24.6-64.7] vs 74.3% [95% CI, 61.4-83.4]; $P = .018$), whereas no significant difference in EFS was seen (45.7% [95% CI, 26.7-62.9] vs 58.5% [95% CI, 46.7-69.1]; $P = .274$, supplemental Figure 3). This difference in OS was largely driven by intermediate-age patients because those with IDH^{mut}/$NPM1^{mut}$/*FLT3*-ITD experienced inferior OS compared with those with IDH^{mut}/$NPM1^{mut}$/*FLT3*-non-ITD (33.3% [95% CI, 6.3-64.6] vs 73.2% [95% CI, 51.4-86.4]; $P = .021$). Pediatric and AYA patients with IDH^{mut}/$NPM1^{mut}$/*FLT3*-ITD AML experienced inferior OS compared with those with IDH^{mut}/$NPM1^{mut}$/*FLT3*-non-ITD, although these differences did not reach statistical significance. In a multivariable analysis, there was no statistical difference for EFS, OS, and RR by *IDH* mutation status when adjusting for age group, cooperative group, risk group, white blood cell count, blast percentage, *NPM1* mutation, or *FLT3*-ITD mutation (supplemental Table 6).

Discussion

In this study we investigated the prevalence, cooccurring mutational profile, and prognostic significance of *IDH* mutations in AML across the age spectrum, using a large cohort of 3141 patients. We demonstrated an age-associated prevalence of *IDH1* and *IDH2* mutations in AML and showed that *IDH* mutations increased in frequency from 3.4% in pediatric patients to 21% in those older than 60 years. Our findings are concordant with prior reports of mutation prevalence.[4,7,9,50] Furthermore, we identified cooccurring mutational patterns that were associated with prognostic outcomes. Although limited by small numbers, patients aged ≥60 years had poor outcomes regardless of mutational status. In patients younger than 60 years, those with dual IDH^{mut}/$NPM1^{mut}$ AML had better EFS compared with those with IDH^{mut}/$NPM1^{WT}$ AML; furthermore, *IDH* mutation did not abolish the favorable prognostic impact of *NPM1* mutation. Patients of all ages with IDH^{mut} AML who lacked a cooperating *NPM1* mutation, experienced unfavorable outcomes. We observed that the favorable outcomes of IDH^{mut}/$NPM1^{mut}$ AML were abrogated by cooccurrence of *DNMT3A* or *FLT3*-ITD.

Our age-expansive cohort showed that younger patients with IDH^{mut} AML had superior survival outcomes compared with older patients. This can be attributed to many factors including enrichment of favorable risk mutations and paucity of adverse risk mutations in the younger age cohorts. We found that favorable risk *NPM1* mutations were least prevalent in patients aged >60 years with IDH^{mut} AML, occurring in less than one-third of older patients, in contrast to at least half of patients aged <60 years. In contrast, adverse risk mutations including *RUNX1* and *ASXL1* were far more prevalent in intermediate-age and older adults with IDH^{mut} AML. The improved pediatric outcomes may also reflect better tolerance of more intensive therapeutic regimens, irrespective of *IDH* mutational profile.

When we compared patients with IDH^{mut} AML with those with IDH^{WT} AML, we found no difference in response to induction therapy or survival outcome in our total cohort or in any age group. Among our large cohort, there was no difference in OS or EFS between $IDH1^{mut}$ and $IDH2^{mut}$ AML, consistent with recent analysis from a large German cohort.[51] Furthermore, we demonstrated

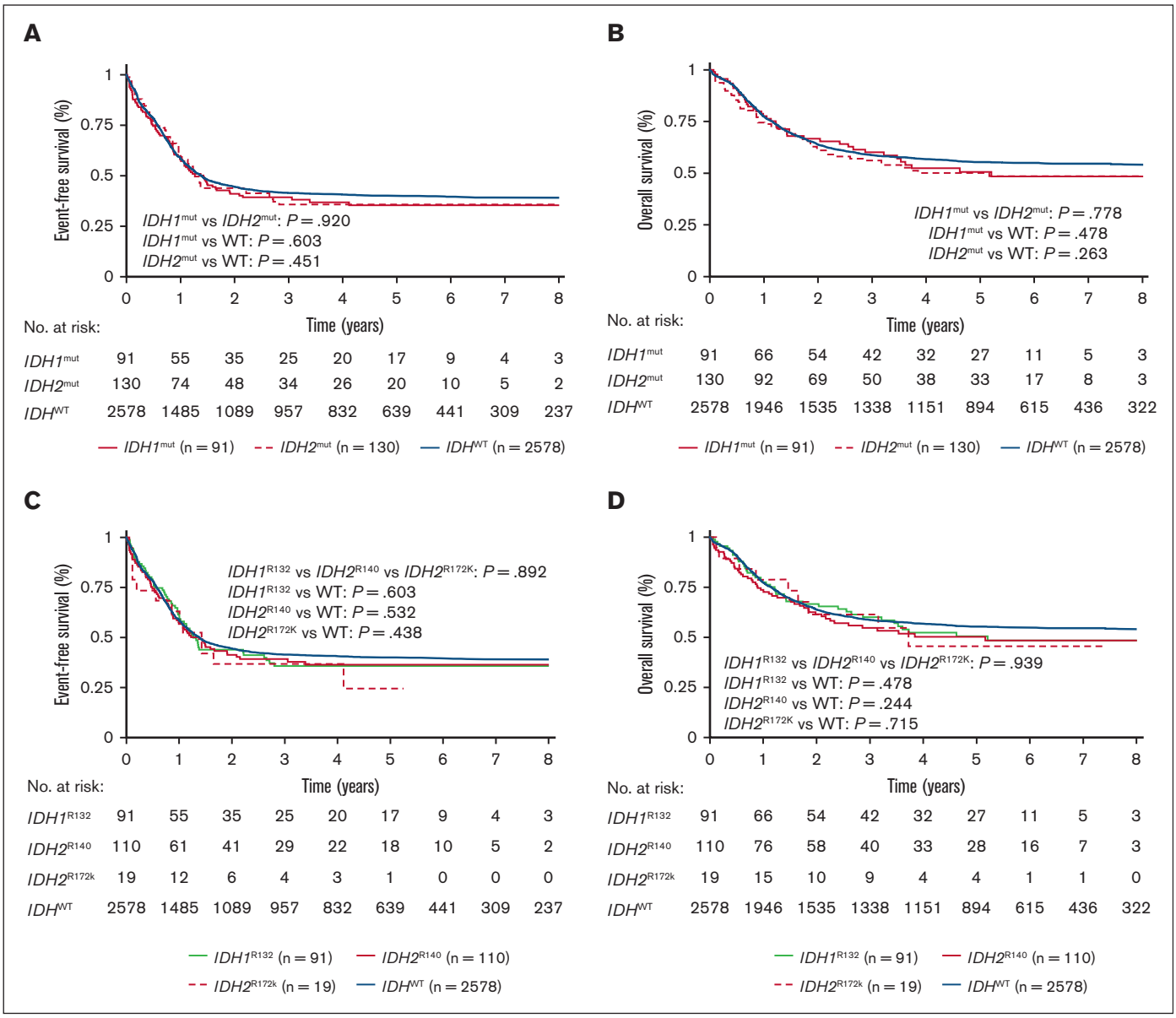

Figure 3. Survival outcomes of *IDH*^{mut} AML in the total study cohort based on *IDH* isoform and mutation subtype. There was no difference between isoform *IDH1* vs *IDH2* for (A) EFS or (B) OS. Similarly, there was no difference in outcomes according to mutation subtype *IDH1*^{R132} vs *IDH2*^{R140} vs *IDH2*^{R172} for (C) EFS or (D) OS. *P* values calculated by log-rank test.

no outcome differences among *IDH1*^{R132}, *IDH2*^{R140}, and *IDH2*^{R172K} for the overall study cohort or in any age group.

IDH and *NPM1* mutations frequently co-occur, but there has been lack of consensus on the prognostic significance of *IDH* mutations in conjunction with *NPM1*.[5,32,44] Recent reports from several large study cohorts have provided clarity about the favorable prognostic influence of cooccurring *NPM1* in *IDH*^{mut} AML in adult patients, most of whom were treated with intensive chemotherapy.[51-53] In our study, after separating patients with *IDH*^{mut} based on *NPM1* status, we observed that almost all patients with *IDH*^{mut}/*NPM1*^{WT}AML had dismal EFS, regardless of age, *IDH* isoform, or mutation subtype. This is consistent with previous reports in smaller cohorts of adult patients for *IDH*^{mut}/*NPM1*^{WT}AML, including when analyzed by subtype.[3,24,44,53,54] We found that patients aged <60 years with *IDH*^{mut}/*NPM1*^{mut} AML had significantly improved EFS compared with patients with *IDH*^{mut}/*NPM1*^{WT}. Of note, despite significantly worse EFS, the AYA cohort with *IDH*^{mut}/*NPM1*^{WT} AML had overlapping OS with those with *IDH*^{mut}/*NPM1*^{mut} AML, which suggests salvage strategies were effective in this group; however, the patient cohort was limited in number and by heterogenous treatment across several studies, thereby limiting our ability to better understand why dismal outcomes were salvageable in this age cohort. Although limited by smaller numbers of *NPM1* mutations compared with the younger age groups, patients aged >60 years in this study had poor survival outcomes regardless of *IDH* and *NPM1* mutation status, thus there were no discernible differences based on mutational profile.

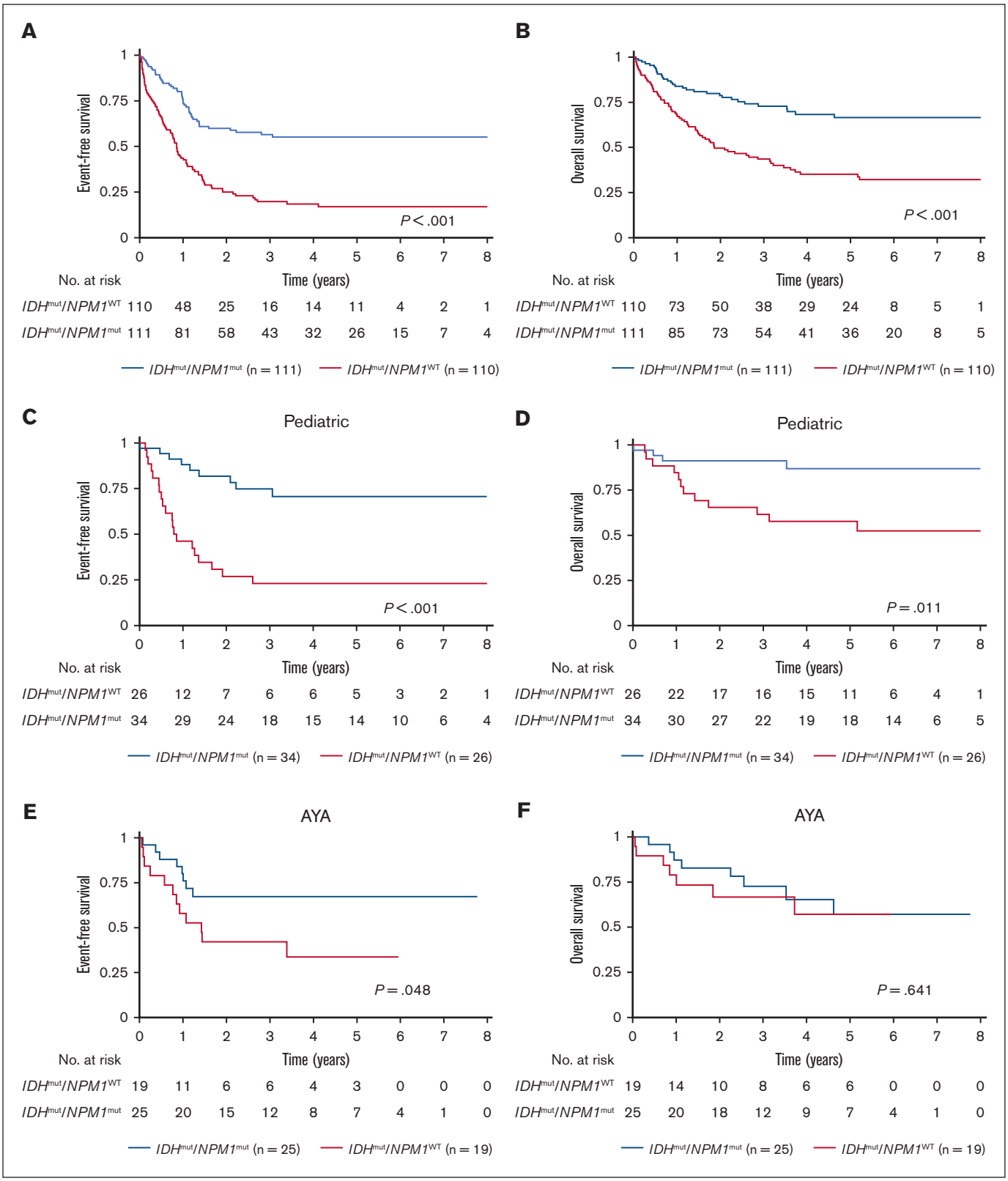

Figure 4. Cooccurrence of *NPM1* and *IDH* mutations is associated with improved survival outcomes in the total study cohort. Survival outcomes based on *NPM1* and *IDH* mutation status in AML (A) EFS and (B) OS for the total study cohort; EFS and OS in each age group: pediatric (C-D), AYA (E-F), intermediate-age (G-H), and older patients (I-J). *P* values calculated by log-rank test.

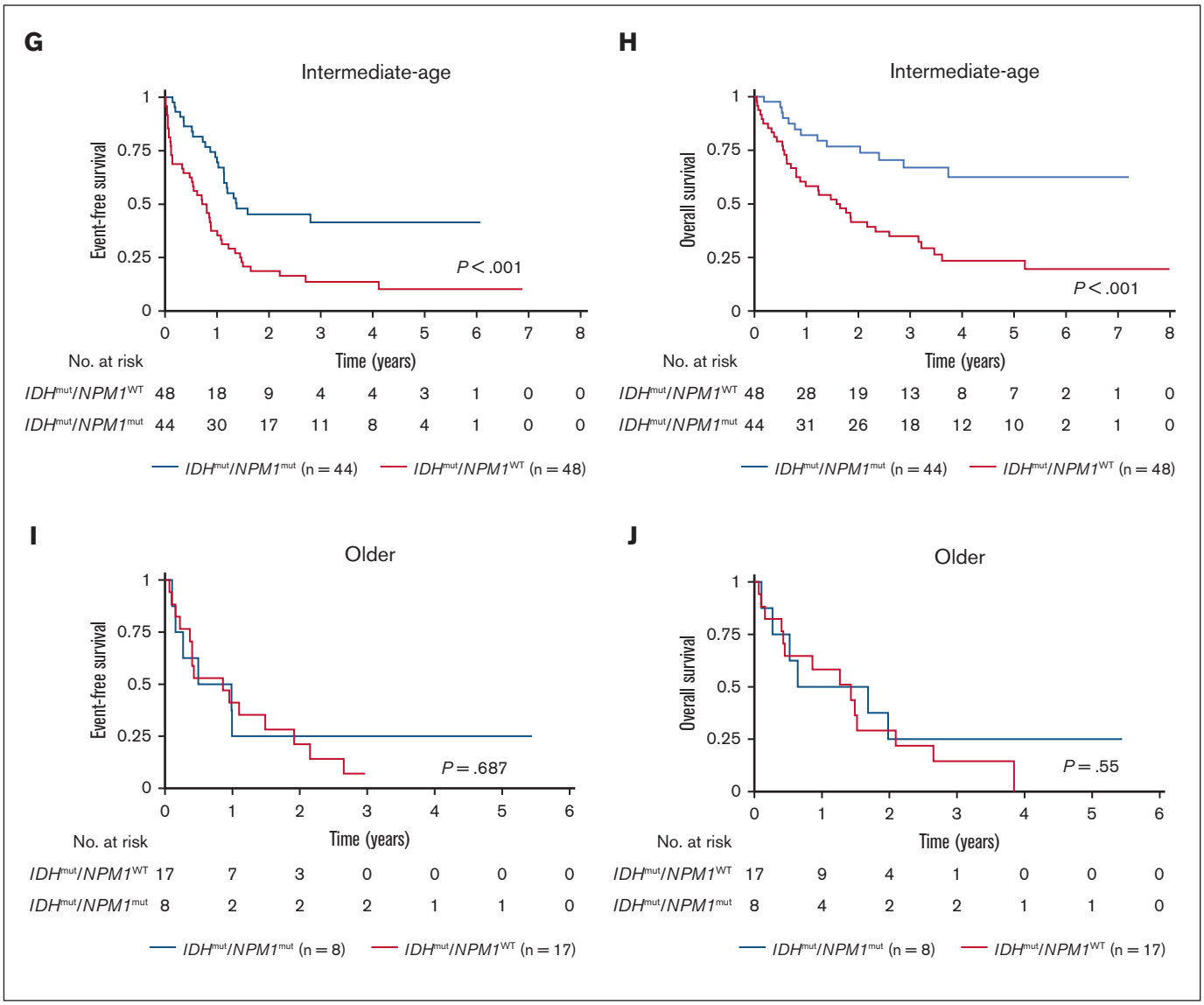

Figure 4 (continued)

Furthermore, in our study we found that *IDH* mutation did not abrogate the favorable prognostic impact of *NPM1* mutation in patients aged <60 years. We also observed that in the intermediate-age cohort, patients with *NPM1*^{mut} AML had improved outcomes in the presence of cooccurring *IDH* mutation compared with those with *NPM1*^{mut}/*IDH*^{WT} AML. Further analysis of this finding was limited by the small numbers of patients with dual *IDH*^{mut}/*NPM1*^{mut} AML, especially when divided by age; however, the favorable outcome in these patients is of interest for further study. In a multivariate analysis, our findings showed that cooccurrence with *NPM1* had a more powerful impact on prognosis than *IDH* mutation alone and suggests that risk stratification per *IDH* should incorporate *NPM1* mutational status.

Our findings demonstrated that in patients aged <60 years with *IDH*^{mut}/*NPM1*^{mut} AML, the frequently cooccurring *DNMT3A* and *FLT3*-ITD mutations could further inform prognostication. We demonstrated that patients with *IDH*^{mut}/*NPM1*^{mut}/*DNMT3A*^{mut} AML had inferior EFS and OS compared with those with *IDH*^{mut}/*NPM1*^{mut} AML, suggesting that *DNMT3A* mutation abrogated the positive prognostic effect of *NPM1*. Our findings align with previous findings of inferior survival for this mutation combination.[53,55] The addition of *FLT3*-ITD mutation in *IDH*^{mut}/*NPM1*^{mut} AML led to inferior OS in the total cohort. This decline in OS for *IDH*^{mut}/*NPM1*^{mut}/*FLT3*-ITD AML reached statistical significance in intermediate-age patients with a similar pattern in pediatric and AYA groups. Thus, *FLT3*-ITD mutation negated the favorable impact of *NPM1* mutation in *IDH*^{mut} AML. With the availability of *FLT3* and *IDH* inhibitors, patients with *IDH*^{mut}/*NPM1*^{mut}/*FLT3*-ITD AML may be ideal candidates for prospective clinical investigation to incorporate these therapeutic strategies.[56]

Our study included the largest cohort of pediatric and AYA patients to undergo *IDH* mutation analysis. With the inclusion of patients from several large pediatric trials, the distribution of ages for *IDH*^{WT}

AML was significantly skewed to younger age, and we conducted analyses by total cohort and age group to account for this whenever possible. Because of limited available data, we reported outcomes for only 25 patients aged >60 years; thus, these conclusions should be considered descriptive, particularly for subanalyses by mutation profile. We were unable to evaluate outcomes in the older patient (≥75 years) age group because only 2 patients had outcomes data available. The retrospective nature of our study was an inherent limitation and comparative outcomes must be interpreted with caution. Our analyses were confounded by nonuniform treatment of patients enrolled in studies conducted by various cooperative groups in different diagnostic and treatment eras. Given the time period represented in our study, we were unable to assess the impact of modern-day targeted therapies including IDH inhibitors. Certain analyses were limited by small patient numbers; for instance, we could not determine the impact of low-intensity approaches for older patients or higher-intensity treatments including hematopoietic stem cell transplant (HSCT) for younger adults. The role of HSCT on treatment outcomes could not be determined either because the clinical trials in our cohort did not capture data on HSCT, or too few patients with *IDH*^{mut} AML underwent transplantation in first CR. Future studies should pay special attention to these subsets to better understand differential outcomes with targeted therapies and treatment approaches of varying intensity.

This expansive study of *IDH*^{mut} AML across the age spectrum identified specific mutation combinations with inferior outcomes including patients with *IDH*^{mut}/*NPM1*^{WT} AML and *IDH*^{mut}/*NPM1*^{mut} with *DNTM3A*^{mut} or *FLT3*-ITD. These patients may derive benefit from risk-adapted and age-adjusted therapy modifications including consideration of IDH inhibitors in combination with intensive chemotherapy, hypomethylating agents, Bcl-2 inhibition,[22,50,52,57,58] and potentially HSCT for remission consolidation in younger or fit patients. Although rare in pediatric AML, our study demonstrates that subsets of *IDH*^{mut} AML portend an inferior prognosis in pediatric patients and may also warrant consideration of risk-adapted therapy modification. In our study, patients aged >60 years with *IDH*^{mut} all experienced poor outcomes, regardless of *NPM1* mutational status, underscoring the need to study targeted therapy combinations with tolerable profiles for these patients. Our report on outcomes in subsets of *IDH*^{mut} AML provides important historical comparator data as IDH inhibitors are studied for frontline use in adults and in the relapsed/refractory setting in pediatric patients.

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Authorship

Contribution: S.Z.-L., K.T., R.B.G., R.E.R., T.A.A., and S.M. designed the study; R.B.G., T.A.A., M.O., Z.S., and J.W. provided biostatistical support for the study; S.Z.-L., K.T., R.E.R., S.M., R.B.G., T.A.A., M.O., and Z.S. analyzed and interpreted the data; S.Z.-L., K.T., R.B.G., and S.M. wrote the manuscript; S.Z.-L., K.T., R.B.G., A.L., and R.E.R. created manuscript figures; and all authors collected clinical and/or genetic data, reviewed the manuscript, and approved the final version of the manuscript.

Conflict-of-interest disclosure: M.O. reports consulting or an advisory role for GlycoMimetics, Cascadia Labs, Merck, Daiichi Sankyo, and BioSight. J.P.R. reports personal fees from Novartis, Bristol Myers Squibb, Takeda, Amgen, Cepheid, and Genentech outside the submitted work. M.S.T. reports grant/research support from AbbVie, Orsenix, Biosight, GlycoMimetics, Rafael Pharmaceuticals, and Amgen; a scientific advisory role for AbbVie, Orsenix, Biosight, Daiichi Sankyo Co., KAHR, Novartis Pharmaceuticals, and Innate Pharmaceuticals; and royalty from UpToDate. M.L. reports consulting or an advisory role for Omeros and Jazz Pharmaceuticals; reports research funding form Amgen, Astellas Pharma, Actinium Pharmaceuticals, Pluristem Therapeutics, AbbVie/Genentech, Tolero Pharmaceuticals, and AbbVie; and served on the data monitoring committee for BioSight. E.A. reports consultancy for AbbVie, Takeda, Pfizer, Novartis, and Amgen; speakers' bureau role for AbbVie and Bristol Myers Squibb; received honoraria from Bristol Myers Squibb and Novartis; and received research funding from Takeda, Pfizer, and Novartis. O.A.-W. has served as a consultant for H3B Biomedicine, Foundation Medicine Inc., Merck, Prelude Therapeutics, and Janssen; is on the scientific advisory board of Envisagenics Inc., AIChemy, Harmonic Discovery Inc., and Pfizer Boulder; and has received prior research funding from H3B Biomedicine, Nurix Therapeutics, Minovia Therapeutics, and Loxo Oncology unrelated to the current manuscript. S.L. received honoraria from Syros, Agios, Daiichi Sankyo, Jazz Pharmaceuticals, Bristol Myers Squibb, Acceleron, Astellas, and Pfizer, and research funding from Onconova, Celgene, Biosight, Hoffman LaRoche, and Kura. H.E. reports consultancy or an advisory role for Agios, Astellas Pharma, Amgen, Celgene, Daiichi Sankyo, GlycoMimetics, Immunogen, Incyte, Jazz Pharmaceuticals, MacroGenics, Novartis, AbbVie/Genentech, Janssen Oncology, Pfizer, Trillium Therapeutics, Takeda, and Kura Oncology; a speakers' bureau role for Agios, Celgene, Incyte, Jazz Pharmaceuticals, Novartis, and AbbVie/Genentech; received research funding from AbbVie, Agios (Inst), Amgen (Inst), Daiichi Sankyo (Inst), Forma Therapeutics (Inst), Gilead/Forty Seven (Inst), Immunogen (Inst), Jazz Pharmaceuticals (Inst), MacroGenics (Inst), Novartis (Inst), PTC Therapeutics (Inst), AbbVie (Inst), GlycoMimetics (Inst), and ALX Oncology (Inst); declares other relationship with GlycoMimetics and Celgene; and reports an uncompensated relationship with Daiichi Sankyo. R.L. serves on the supervisory board of Qiagen; is a scientific adviser to Imago, Mission Bio, Syndax, Zentalis, Ajax, Bakx, Auron, Prelude, C4 Therapeutics, and Isoplexis for which he receives equity support; received research support from Ajax and AbbVie; reports consultancy for Incyte, Janssen, Morphosys, and Novartis; and received honoraria from AstraZeneca and Kura for invited lectures, and from Gilead for grant reviews. The remaining authors declare no competing financial interests.

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