original reports

Sorafenib in Combination With Standard Chemotherapy for Children With High Allelic Ratio *FLT3*/ITD+ Acute Myeloid Leukemia: A Report From the Children's Oncology Group Protocol AAML1031

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abstract

PURPOSE High allelic ratio (HAR) *FLT3*/ITD (AR > 0.4) mutations confer poor prognosis in pediatric acute myeloid leukemia (AML). COG AAML1031 studied the feasibility and efficacy of adding sorafenib, a multikinase tyrosine kinase inhibitor to standard chemotherapy and as single-agent maintenance therapy in this population.

MATERIALS AND METHODS Patients were treated in three cohorts. The initial safety phase defined the maximum tolerated dose of sorafenib starting in induction 2. Cohorts 2 and 3 added sorafenib in induction and as single-agent maintenance. Clinical outcome analysis was limited to n = 72 patients in cohorts 2/3 and compared with n = 76 HAR *FLT3*/ITD+ AML patients who received identical chemotherapy without sorafenib. Sorafenib pharmacokinetics and plasma inhibitory activity were measured in a subset of patients.

RESULTS The maximum tolerated dose of sorafenib was 200 mg/m^2 once daily; dose-limiting toxicities included rash (n = 2; 1 grade 3 and 1 grade 2), grade 2 hand-foot syndrome, and grade 3 fever. Pharmacokinetics/plasma inhibitory activity data demonstrated that measured plasma concentrations were sufficient to inhibit phosphorylated FLT3. Although outcomes were superior with sorafenib in cohorts 2 and 3, patients treated with sorafenib also underwent hematopoietic stem-cell transplant more frequently than the comparator population. Multivariable analysis that accounted for both hematopoietic stem-cell transplant and favorable co-occurring mutations confirmed sorafenib's benefit. Specifically, risk of an event was approximately two-fold higher in HAR *FLT3*/ITD+ patients who did not receive sorafenib (event-free survival from study entry: hazard ratio [HR] 2.37, 95% CI, 1.45 to 3.88, $P < .001$, disease-free survival from complete remission: HR 2.28, 95% CI, 1.08 to 4.82, $P = .032$, relapse risk from complete remission: HR 3.03, 95% CI 1.31 to 7.04, $P = .010$).

CONCLUSION Sorafenib can be safely added to conventional AML chemotherapy and may improve outcomes in pediatric HAR *FLT3*/ITD+ AML.

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ASSOCIATED CONTENT

See accompanying article on page 2058

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Fms-like tyrosine kinase 3 (*FLT3*) is a receptor tyrosine kinase, and mutations in *FLT3* occur in 10%-15% of pediatric de novo acute myeloid leukemia (AML) patients.[1,2] Children with high allelic ratio (HAR; AR > 0.4) *FLT3* internal tandem duplication (ITD) mutant AML have inferior outcomes with survival of approximately 25%-30% historically; hematopoietic stem-cell transplant (HSCT) has improved outcomes to 50%-65%.[1,3-6] Co-occurrence of an *NPM1* mutation, seen in 20%-30% of *FLT3*/ITD+ AML, confers more favorable outcome, with event-free survival (EFS) of approximately 60%.[7]

FLT3/ITD alterations constitutively activate *FLT3*, and tyrosine kinase inhibitors (TKIs) are approved for adults with *FLT3*-mutated AML.[8,9] Type I inhibitors, including gilteritinib, inhibit both *FLT3*/ITD mutations and tyrosine kinase domain–activating mutations. By contrast, type II inhibitors, such as sorafenib, are largely inactive against the latter.[10] Sorafenib targets *KIT*, *PDGFR*, *VEGF*, *RET*, and *RAF* pathway signaling along with *FLT3*. Studies of sorafenib in adults with *FLT3*-mutant AML demonstrate safety despite targeting multiple pathways but impact on outcome is variable.[11-16] After two early pediatric studies demonstrated feasibility of administering sorafenib in

CONTEXT

Key Objective

Pediatric high allelic ratio (HAR) *FLT3*/ITD+ acute myeloid leukemia (AML) is a high-risk disease subset. Children's Oncology Group protocol AAML1031 tested sorafenib, a tyrosine kinase inhibitor (TKI), in the treatment of children with this AML subtype. Patients who consented to treatment received sorafenib in combination with conventional chemotherapy; a subset of patients were also eligible for sorafenib maintenance.

Knowledge Generated

Sorafenib was safe and tolerable and significantly improved event-free survival and disease-free survival while lowering relapse risk in children with HAR *FLT3*/ITD+ AML. Multivariable analysis that accounted for stem-cell transplant and favorable co-occurring mutations confirmed sorafenib's benefit. The utility of maintenance treatment warrants further investigation, given limited patient exposure.

Relevance

Treatment of pediatric HAR *FLT3*/ITD+ AML should entail consideration of TKIs. Contemporary pediatric AML trials are studying the feasibility and efficacy of second-generation TKIs in combination with chemotherapy and as a post-consolidation maintenance approach.

pediatric AML,[17,18] COG AAML1031 broadened this experience by adding sorafenib to chemotherapy for patients with HAR *FLT3*/ITD+ AML and as single-agent maintenance. We hypothesized that sorafenib could be added safely and would improve remission induction and survival outcomes.

MATERIALS AND METHODS

Patients and Treatment

Details of the primary AAML1031 randomization are published.[19] At enrollment, patients were randomly assigned to either arm A (standard chemotherapy) or arm B (standard chemotherapy with bortezomib) and underwent centralized *FLT3*/ITD mutation testing. Dexrazoxane use as a cardioprotectant was per treating physician discretion. Patients with an *FLT3*/ITD AR $>$ 0.4 were eligible for enrollment on arm C. If consented, patients initially randomly assigned to arm A continued standard chemotherapy with sorafenib, whereas arm B patients discontinued bortezomib when signing arm C consent. After arms A/B closed,[19] patients were enrolled on arm D (same as arm A) until *FLT3*/ITD results returned; if positive, they were eligible for arm C. AAML1031 was approved by the National Cancer Institute's Central Institutional Review Board (IRB) and local IRBs (n = 184). Patients and families provided informed consent and assent as appropriate. The trial was conducted in accordance with the Declaration of Helsinki and was registered at ClinicalTrials.gov (identifier: NCT01371981). The clinical Protocol (online only) included three aims for patients with HAR *FLT3*/ITD+ AML: (1) feasibility of sorafenib administration, (2) assessment of antileukemic activity of sorafenib, and (3) analysis of pharmacokinetics (PK) and plasma inhibitory activity (PIA) in subjects receiving sorafenib. Analytic plans/power analyses are provided in the protocol.

Treatment Cohorts

The initial safety phase (cohort 1 [C1], n = 12, Data Supplement, online only) defined the maximum tolerated dose of sorafenib when administered in induction 2 and subsequent courses. Targeted toxicities were compared against predetermined rates that would mandate treatment arm closure. During the safety phase, sorafenib was initiated at 200 mg/m^2 once daily; given lack of protocol defined dose-limiting toxicities that would warrant treatment de-escalation, the recommended dosing of sorafenib for subsequent cohorts remained 200 mg/m^2. Following completion of C1, the study was amended (cohort 2 [C2], Data Supplement) to start sorafenib on day 11 of induction 1 and to administer concomitantly with chemotherapy in subsequent cycles. This design maximized sorafenib exposure while allowing for delayed drug start during induction 1, given centralized *FLT3* testing. Moreover, by starting sorafenib after chemotherapy in induction 1, risk for overlapping toxicities of two investigational drugs (sorafenib and bortezomib) was lessened. A year of sorafenib maintenance, administered after HSCT or completion of chemotherapy (if no HSCT donor was identified) was added for patients enrolled in C2 given preliminary evidence for benefit of maintenance therapy.[20-23] Maintenance dosing was 100 mg/m^2/daily with potential intrapatient escalation to a maximum of 150 mg/m^2 twice daily. After interim analyses suggested potential cardiac risk with this dosing schedule, the study was subsequently amended (cohort 3 [C3], Data Supplement) to start sorafenib after chemotherapy completion each cycle. Patients eligible for arm C but diagnosed during periods of arm C closure were eligible to transition to arm C after induction when the arm reopened but were not included in efficacy analysis. Targeted toxicities of all arm C cohorts were described in evaluable patients. To minimize potential confounding influence of

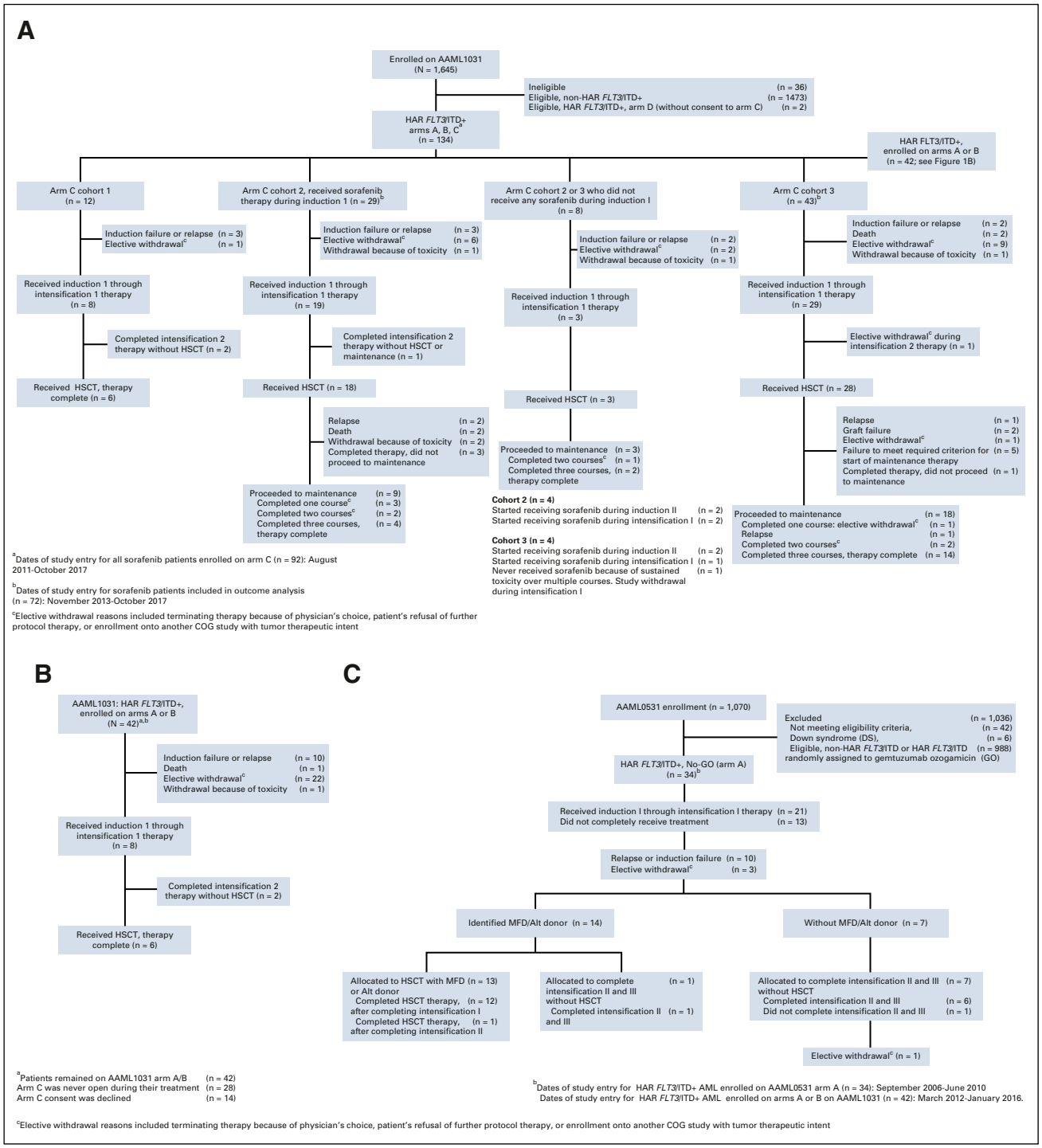

FIG 1. Distribution of HAR *FLT3*/ITD+ AML patients included in analysis. (A) CONSORT diagram of AAML1031 overall and by Arm C cohort, (B) Flow diagram of AAML1031 Arms A/B (sorafenib-unexposed), and (C) Flow diagram for AAML0531 (sorafenib-unexposed). Alt, alternative donor (donor availability defined for intermediate- and high-risk patients only); AML, acute myeloid leukemia; HAR, high allelic ratio; HSCT, hematopoietic stem-cell transplant; MFD, matched family donor.

bortezomib, toxicities of n = 53 *FLT3*/ITD+ patients enrolled on arm C after initial treatment assignment to arm A were compared with those of 34 arm A patients with HAR *FLT/*ITD+ AML who either declined arm C participation or were treated on arm A while arm C was closed.

Sorafenib-Exposed Versus Sorafenib-Unexposed Patients

Long-term clinical outcome analysis was limited to C2/C3, given lack of induction 1 sorafenib exposure in C1. Patients in C2/C3 who did not receive drug during induction I were also excluded. Outcome measures for patients with

TABLE 1. Targeted Toxicities for *FLT3*/ITD+ Patients Who Transitioned From Arm A to C Versus HAR *FLT3*/ITD+ Patients Who Remained on Arm A

Phase of Therapy	Induction I			Induction II			Intensification I			Maintenance 1	Maintenance 2	Maintenance 3
Treatment Arm	Arm A to Arm C (n = 53)	HAR *FLT3*/ITD: Arm A (n = 34)	Arm C *v* Arm A *P*	Arm A to Arm C (n = 62)	HAR *FLT3*/ITD: Arm A (n = 12)	Arm C *v* Arm A *P*	Arm A to Arm C (n = 53)	HAR *FLT3*/ITD: Arm A (n = 6)	Arm C *v* Arm A *P*	Arm A to Arm C (n = 23)	Arm A to Arm C (n = 21)	Arm A to Arm C (n = 19)
Cardiac												
Heart failure[a]	1	0		2	1		2	0		0	0	0
	1.9%	0.0%	1.000	3.2%	8.3%	.417	3.8%	0.0%	1.000	0.0%	0.0%	0.0%
EF decreased	0	1		1	0		2	1		0	0	0
	0.0%	2.9%	.391	1.6%	0.0%	1.000	3.8%	16.7%	.279	0.0%	0.0%	0.0%
Cardiac LVSD[a]	0	0		4	0		1	1		0	0	0
	0.0%	0.0%	—	6.5%	0.0%	1.000	1.9%	16.7%	.195	0.0%	0.0%	0.0%
Prolong QTc[a]	4	2		8	0		8	1		1	1	0
	7.5%	5.9%	1.000	12.9%	0.0%	.339	15.1%	16.7%	1.000	4.3%	4.8%	0.0%
Rash/skin pain												
Palmar-plantar erythrodysesthesia	0	0		0	0		0	0		0	0	0
	0.0%	0.0%	—	0.0%	0.0%	—	0.0%	0.0%	—	0.0%	0.0%	0.0%
Rash maculopapular	4	3		2	0		2	0		1	0	0
	7.5%	8.8%	1.000	3.2%	0.0%	1.000	3.8%	0.0%	1.000	4.3%	0.0%	0.0%
Pain of skin	1	0		0	0		1	0		0	0	0
	1.9%	0.0%	1.000	0.0%	0.0%	—	1.9%	0.0%	1.000	0.0%	0.0%	0.0%
Renal												
Hypertension	2	0		2	0		2	0		1	0	0
	3.8%	0.0%	1.000	3.2%	0.0%	1.000	3.8%	0.0%	1.000	4.3%	0.0%	0.0%
Microbiologically documented sterile site infections (at least 1 occurrence)												
Viridans group Streptococcus	0	2		6	2		5	0		0	0	0
	0.0%	5.9%	.150	9.7%	16.7%	.608	9.4%	0.0%	1.000	0.0%	0.0%	0.0%
Gram-negative bacilli	0	0		3	2		5	0		0	0	0
	0.0%	0.0%	—	4.8%	16.7%	.183	9.4%	0.0%	1.000	0.0%	0.0%	0.0%
Fungi	1	0		1	0		0	0		0	0	0
	1.9%	0.0%	1.000	1.6%	0.0%	1.000	0.0%	0.0%	—	0.0%	0.0%	0.0%

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TABLE 1. Targeted Toxicities for *FLT3*/ITD+ Patients Who Transitioned From Arm A to C Versus HAR *FLT3*/ITD+ Patients Who Remained on Arm A (continued)

Phase of Therapy	Induction I			Induction II			Intensification I			Maintenance 1	Maintenance 2	Maintenance 3
Treatment Arm	Arm A to Arm C (n = 53)	HAR *FLT3*/ITD: Arm A (n = 34)	Arm C *v* Arm A *P*	Arm A to Arm C (n = 62)	HAR *FLT3*/ITD: Arm A (n = 12)	Arm C *v* Arm A *P*	Arm A to Arm C (n = 53)	HAR *FLT3*/ITD: Arm A (n = 6)	Arm C *v* Arm A *P*	Arm A to Arm C (n = 23)	Arm A to Arm C (n = 21)	Arm A to Arm C (n = 19)
Dose reductions	5	0		13	0		9	0		5	3	3
	9.4%	0.0%	.152	21.0%	0.0%	.110	17.0%	0.0%	.577	21.7%	14.3%	15.8%
PICU admissions	10	11		7	1		9	1		1	1	0
	18.9%	32.4%	.152	11.3%	8.3%	1.000	17.0%	16.7%	1.000	4.3%	4.8%	0.0%
Dexrazoxane received	16	2		15	1		1	0		0	0	0
	30.2%	5.9%	**.006**	24.2%	8.3%	.443	1.9%	0.0%	1.000	0.0%	0.0%	0.0%
Median course duration, days	38.0	38.0	.464	41.5	40.5	.977	48.0	58.5	.067	112.0	112.0	141.0
	range, 26-64	range, 10-53		range, 15-67	range, 32-56		range, 28-100	range, 46-71		87-120	28-134	34-182

NOTE. Bold value is statistically significant.

Abbreviations: EF, ejection fraction; HAR, high allelic ratio; LVSD, left ventricular systolic dysfunction; QTc, heart rate corrected QT interval.

[a]Reported AE grades 1-5 (AEs not denoted with [a] are grade 3 and higher).

FLT3/ITD+ AML enrolled on arm C2 and C3 were compared with children with *FLT3*/ITD+ AML (AR > 0.4) who received similar treatment without sorafenib. Specifically, this unexposed group included patients who enrolled on AAML1031 but remained on their initial treatment arm (arm A: n = 19, arm B: n = 23) because of declination of arm C enrollment (n = 14) or closure of arm C during their time on protocol therapy (n = 28). Since AAML1031 observed equivalent outcomes between arms A and B,[19] patients with HAR *FLT3*/ITD+ AML from both arms were included in the response comparison. In addition, n = 34 HAR *FLT3*/ITD+ patients on AAML0531 arm A (standard chemotherapy without gemtuzumab ozogamicin) were also defined as the unexposed cohort.[24] Ultimately, a total of 72 patients from AAML1031 arm C were included in the sorafenib-exposed analyses and compared with n = 76 patients on AAML1031/AAML0531 who did not receive sorafenib (sorafenib-unexposed, Data Supplement).

Statistical Analyses

Data were current as of June 30, 2021. The significance of observed difference in proportions was tested using the chi-squared test and Fisher's exact test when data were sparse. The Kruskal-Wallis test was used to determine the significance between differences in medians of groups. The Kaplan-Meier method was used to calculate overall survival (OS), EFS, and disease-free survival (DFS).[25] Nonparametric maximum likelihood estimation was used to estimate the cumulative incidence of relapse risk (RR).[26] OS was defined as time from study entry until death. EFS was defined as time from study entry until either death, refractory disease, or relapse of any type, whichever occurred

TABLE 2. Outcome Data for Sorafenib-Exposed Versus -Unexposed

Response	Sorafenib-Exposed (n = 72), No. (%)	Sorafenib-Unexposed (n = 76), No. (%)	*P*
End of IND1 marrow response and evaluation			
CR, < 5% blasts	53 (75)	40 (57)	**.028**
Persistent disease, ≥ 5% blasts	16 (23)	27 (39)	**.039**
Refractory CNS leukemia	0 (0)	3 (4)	.120
Death	2 (3)	0 (0)	.497
Not evaluable	1	6	
MRD at the end of induction I			
Positive	29 (48)	29 (45)	.742
Negative	32 (52)	36 (55)	
Unknown	11	11	

Outcome	No.	% (95% CI)	No.	% (95% CI)	*P*
Clinical outcome data—Complete *FLT3*/ITD+ cohort (N = 148)					
3-year OS from study entry	72	65.8 (53.4 to 75.6)	76	55.3 (39.9 to 68.2)	.244
3-year EFS from study entry	72	55.9 (43.5 to 66.6)	76	31.9 (19.0 to 45.7)	**.001**
3-year DFS from EOI1 (CR patients)	53	70.9 (56.4 to 81.3)	40	49.4 (28.4 to 67.3)	**.032**
3-year RR from EOI1 (CR patients)	53	17.6 (8.6 to 29.2)	40	44.1 (23.4 to 63.0)	**.012**
Clinical outcome data—NPM1 wild-type/*FLT3*/ITD+ (N = 115)					
3-year OS from study entry	55	61.8 (47.6 to 73.1)	60	49.3 (32.1 to 64.4)	.213
3-year EFS from study entry	55	50.8 (36.9 to 63.1)	60	23.3 (10.7 to 38.6)	**< .001**
3-year DFS from EOI1 (CR patients)	37	67.6 (50.0 to 80.1)	29	38.6 (16.4 to 60.6)	**.019**
3-year RR from EOI1 (CR patients)	37	21.6 (10.0 to 36.1)	29	56.3 (28.4 to 76.9)	**.008**
Clinical outcome data—NPM1+/*FLT3*/ITD+ (N = 33)					
3-year OS from study entry	17	81.6 (53.0 to 93.7)	16	75.0 (39.8 to 91.4)	.783
3-year EFS from study entry	17	75.3 (46.8 to 89.9)	16	56.3 (24.1 to 79.3)	.399
3-year DFS from EOI1 (CR patients)	16	80.0 (50.0 to 93.1)	11	75.8 (30.5 to 93.7)	.715
3-year RR from EOI1 (CR patients)	16	6.7 (0.4 to 26.9)	11	15.2 (0.5 to 51.5)	.607

NOTE. Bold values are statistically significant.

Abbreviations: CR, complete remission; DFS, disease-free survival; EFS, event-free survival; MRD, minimal residual disease; NA, not available; OS, overall survival; RR, relapse risk.

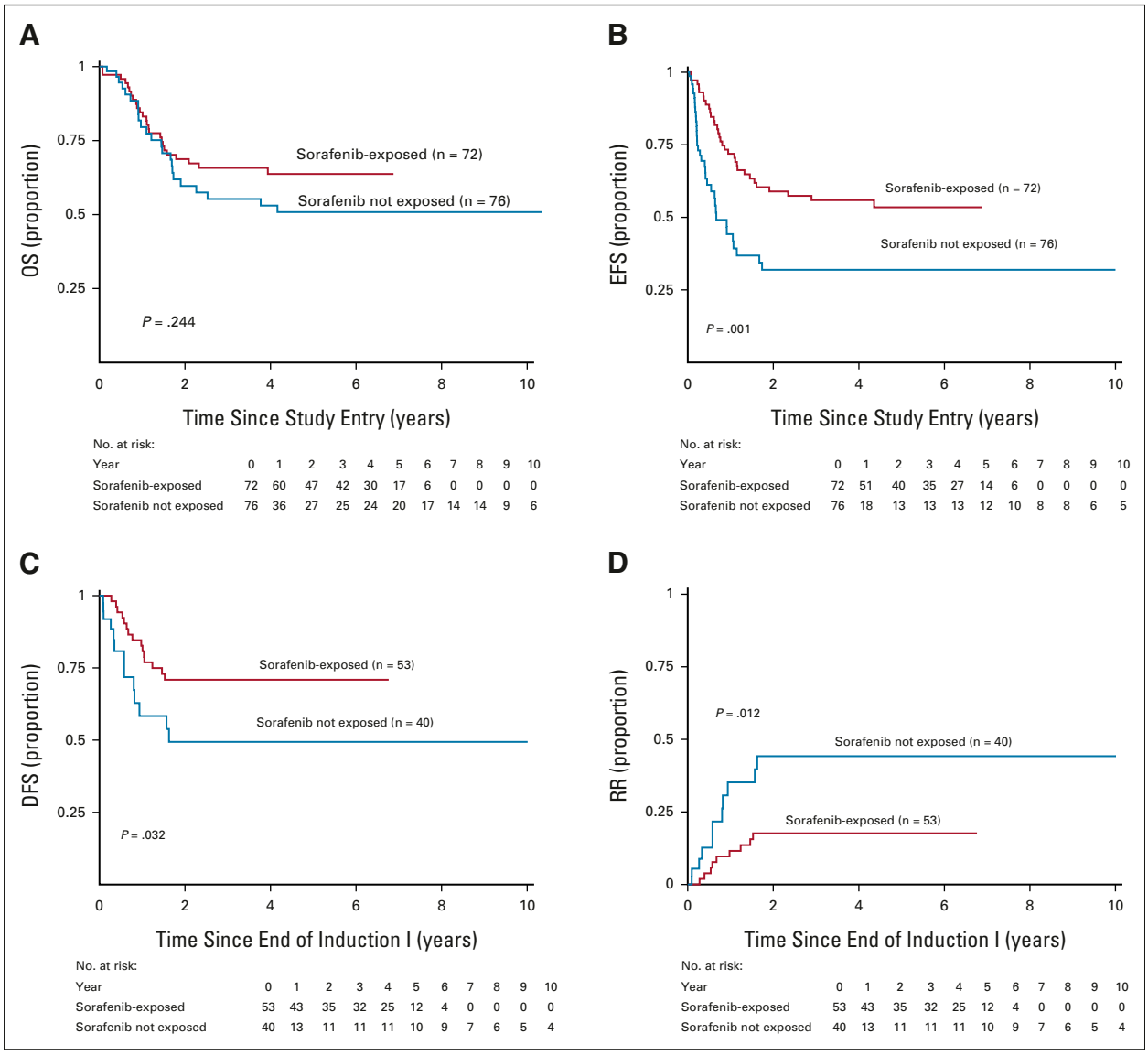

FIG 2. Outcomes for sorafenib-exposed versus -unexposed patients: (A-D) Overall and (E-H) by NPM1 status. (A) OS from study entry, (B) EFS from study entry, (C) DFS from CR, (D) RR from CR, (E) OS from study entry, (F) EFS from study entry by *NPM1* status, (G) DFS from CR by *NPM1* status, and (H) RR from CR by *NPM1* status. CR, complete remission; DFS, disease-free survival; EFS, event-free survival; OS, overall survival; RR, relapse risk; WT, wild-type. (continued on following page)

first. DFS was defined as time from end of induction 1 for patients in complete remission (CR) until relapse or death. RR was defined as time from the end of induction 1 for patients in CR to relapse, where deaths without a relapse were considered competing events. The statistical significance of predictor variables was tested with the log-rank statistic for OS, EFS, and DFS, and with Gray's statistic for RR.[26] Three-year estimates were summarized with their corresponding log-log 95% CIs. Cox proportional hazards models were used to estimate hazard ratios (HRs) for univariable and multivariable analyses of OS, EFS, and DFS.[27] Competing risk regression models were used to estimate the subgroup HR for univariable and multivariable analyses of RR. Receipt of HSCT on protocol therapy was analyzed as a time-varying covariate (TVC) to control for HSCT effect. To minimize impact of TKI exposure after removal from protocol therapy, sorafenib-unexposed patients were censored at date of elective withdrawal from protocol therapy. All *P* values were two-sided.

PK and Pharmacodynamic Analysis

Sorafenib PK and PIA were measured in a subset of patients who consented to this optional study and provided evaluable samples at prescribed time points. A non-compartmental PK analysis characterized the concentration × time profile and trough concentrations at steady state for sorafenib and the N-oxide metabolite.[28] Pharmacodynamic

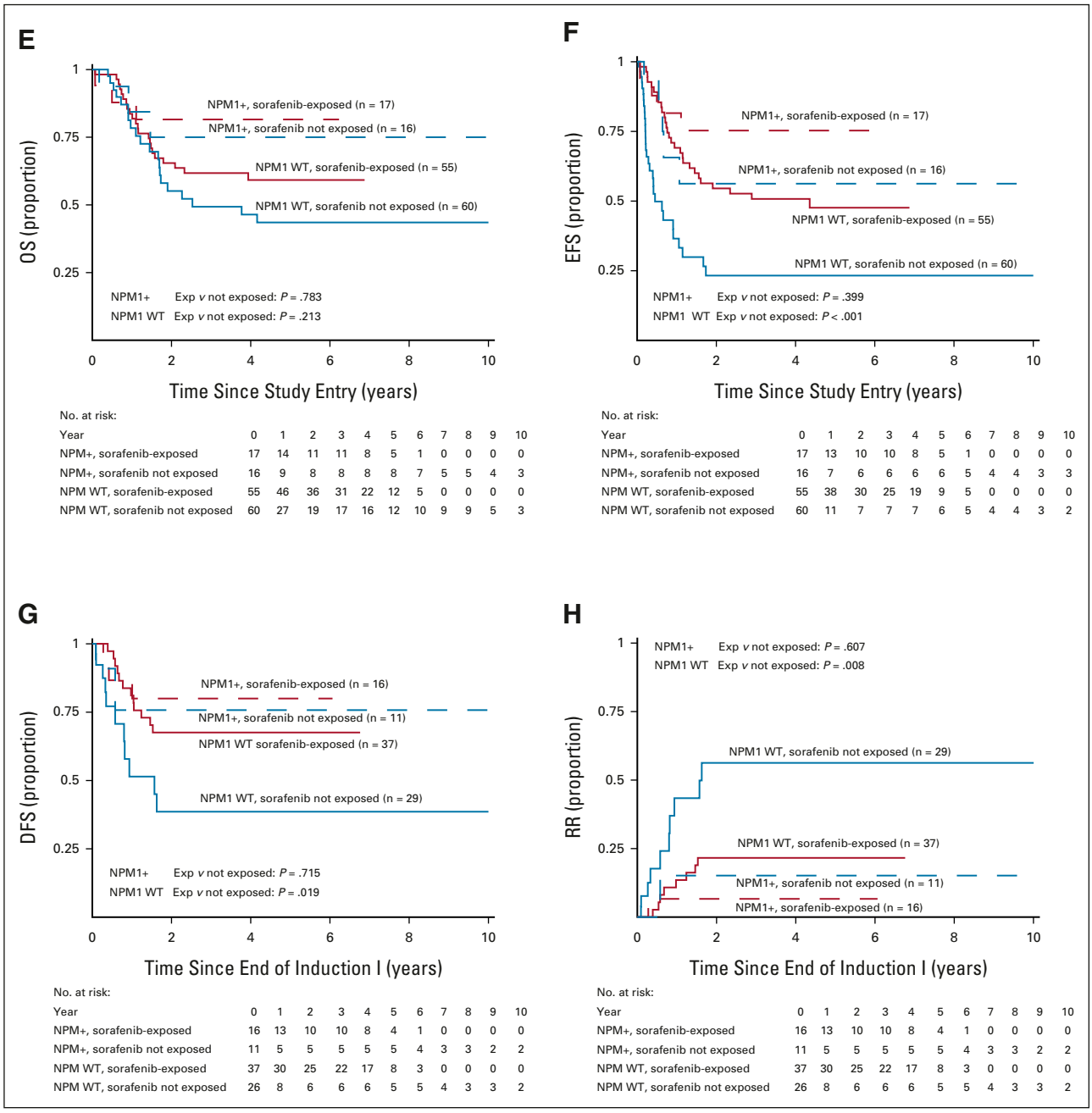

FIG 2. (Continued)

testing was conducted by determining PIA using previously described techniques.[29]

RESULTS

Study Distribution

A total of 1,645 de novo AML patients enrolled on AAML1031; 1,609 were study-eligible. Of the 1,609 enrolled, n = 136 (8.5%) had HAR *FLT3*/ITD+ AML (AR > 0.4) and were eligible for arm C enrollment, of which 92 patients (68%) consented. An additional n = 42 HAR *FLT3*/ITD+ patients enrolled on arm A/B patients did not participate in arm C (Fig 1B). Of 24 HAR *FLT3*/ITD+ patients randomly assigned to bortezomib before arm C enrollment, only 19 received bortezomib in close proximity to sorafenib.

Arm C C1 Analysis (safety phase)

The maximum tolerated dose of sorafenib in C1 was 200 mg/m^2 once daily. Dose-limiting toxicities observed in C1 included rash (grade 2 [n = 1] and grade 3 [n = 1]), grade 2 hand-foot syndrome (n = 1), and grade 3 fever (n = 1). Rates of targeted toxicities for C1 were similar to that of arm C patients in later cohorts (Data Supplement).

Targeted Toxicity for *FLT3*/ITD+ Patients on Arm A Versus C

FLT3/ITD+ patients initially enrolled on arm A before arm C enrollment (n = 53) were compared with n = 34 *FLT3*/ITD+ patients who remained on arm A (standard therapy). Targeted toxicities were similar, both overall (Table 1) and across cohorts and treatment phases for arm C patients who initially were treated on arm A (Data Supplement). Moreover, rates of chemotherapy dose reduction and intensive care unit admission were similar (Table 1). Interestingly, patients on arm C were more likely to receive dexrazoxane as a cardioprotectant with anthracycline therapy during induction I ($P = .006$, Table 1). No significant unanticipated toxicities were identified in the sorafenib cohort.

Interim cardiac toxicity analyses identified a preliminary signal of increased cardiac toxicity in 7/33 (22%) C2 patients as defined by grade 3 ejection fraction (EF) decline (n = 3), grade 2 EF decline (n = 2), grade 3 left-ventricular systolic dysfunction (n = 1), grade 2 cardiac other (shortening fraction decline, n = 1), and grade 1 cardiac other (shortening fraction decline, n = 1). Two patients met criteria for permanent discontinuation of sorafenib and two tolerated restart. The remaining five discontinued protocol therapy before rechallenge was possible. This toxicity concern prompted amendment of the chemotherapy schedule to start sorafenib after completion of standard chemotherapy in a given cycle (cohort 3, C3, Data Supplement). Ultimately, the cardiac toxicity observed in arm C was comparable to that of arm A (Table 1). Differences in median EF were also comparable between arms C and A and similar across arm C cohorts (Table 1, Data Supplement).

Feasibility of Sorafenib Maintenance

Sorafenib maintenance was restricted to 80 patients in C2/C3; 30/80 (38%) received at least one cycle (4 months of therapy) and 20/80 (25%) completed all maintenance treatment. Approximately 62% of patients did not receive any maintenance treatment; 45/80 (56%) went off protocol therapy prior to being eligible for maintenance (Fig 1) and the remaining 5/80 (6%) failed to meet maintenance eligibility criteria. Maintenance toxicity rates were similar to that of earlier treatment cycles (Table 1, Data Supplement).

Arm C Clinical Characteristics and Induction Response by Cohort

To identify potential confounders that could have clinical impact, clinical covariates were compared between sorafenib cohorts. No statistically significant differences were observed with the exception of patients who received sorafenib during induction 1 (eg, C2 or C3) had decreased burden of disease if found to be minimal residual disease–positive (Data Supplement).

Clinical Characteristics and Treatment Response for Sorafenib-Exposed Versus -Unexposed Cohorts

Clinical characteristics were similar for the sorafenib-exposed versus sorafenib-unexposed cohorts with the

TABLE 3. Multivariable Analysis

		EFS From Study Entry			OS From Study Entry		
Patient Characteristic	**No.**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Sorafenib-exposed	72	1			1		
Sorafenib-unexposed	76	2.37	1.45 to 3.88	**< .001**	1.21	0.67 to 2.20	.525
NPM1-positive	33	1			1		
NPM1-negative	115	2.58	1.27 to 5.23	**.009**	1.96	0.82 to 4.67	.128
HSCT not received on study	83	1			1		
HSCT received on study (TVC)	65	0.64	0.34 to 1.20	.165	0.58	0.31 to 1.09	.900

		DFS from EOI1 (CR pts)			RR from EOI1 (CR pts)		
Patient Characteristic	**No.**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Sorafenib-exposed	53	1			1		
Sorafenib-unexposed	40	2.28	1.08 to 4.82	**.032**	3.03	1.31 to 7.04	**.010**
NPM1-positive	27	1			1		
NPM1-negative	66	2.03	0.77 to 5.35	.153	4.16	0.94 to 18.4	.061
HSCT not received on study	43	1			1		
HSCT received on study (TVC)	50	0.96	0.38 to 2.43	.936	0.71	0.27 to 1.87	.491

NOTE. Bold values are statistically significant. Unexposed sorafenib patients were censored at the time of elective withdrawal for OS, EFS, DFS, and RR analyses.

Abbreviations: CR, complete remission; DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; HSCT, hematopoietic stem-cell transplant; OS, overall survival; RR, relapse risk; TVC, time-varying covariate.

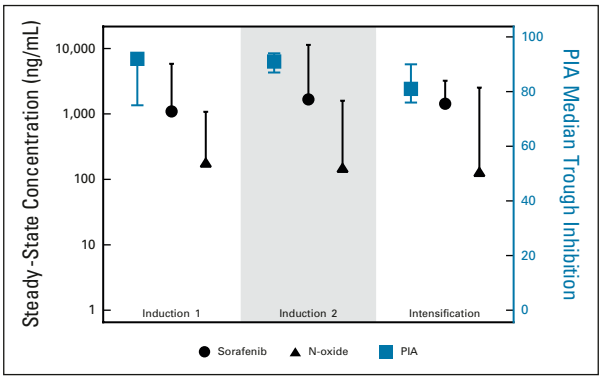

FIG 3. PK/PD effects of sorafenib. The median and upper range steady-state concentration of sorafenib and the N-oxide metabolite in induction I (n = 23), induction 2 (n = 33), and intensification I (n = 28) is noted in black. PIA median trough inhibition and associated 95% CI are noted in red. Data are contributed by a total of n = 52 patients enrolled at 10 different institutions. PIA, plasma inhibitory activity; PK, pharmacokinetics.

exception that children of Hispanic ethnicity were more common in the unexposed cohort and HSCT occurred more frequently in those treated with sorafenib. Notably, prevalence of co-occurring *NPM1* mutation was similar for the two cohorts (Data Supplement). Patients who received sorafenib were more likely to achieve morphologic CR at the end of induction 1 and were less likely to have persistent disease. However, rates of minimal residual disease were not significantly different (Table 2) for the two groups.

The median (range) of follow-up time for patients alive at last contact was 5.3 (0.3-13.1) years. There were 32 EFS events among patients exposed to sorafenib (n = 72) and 35 events among patients who were unexposed (n = 76). Comparison of long-term outcomes suggested that sorafenib exposure was associated with improved EFS from study entry as well as DFS and RR from CR but not OS (Table 2, Figs 2A-2D). Secondary analyses, in which sorafenib-exposed versus -unexposed were both censored at the date of last contact, demonstrated similar findings (Data Supplement) as did censoring of both groups at the time of elective withdrawal (Data Supplement). Subanalysis by *NPM1* status demonstrated that *FLT3*/ITD+ *NPM1*+ patients treated with sorafenib did not show a statistically significant improvement in outcome with sorafenib (Table 2, Figs 2E-2H). Although outcomes appeared overall superior for those children with *FLT3*/ITD+ AML who were treated with sorafenib, they also underwent HSCT more frequently than the comparator population (64% *v* 25%, $P < .001$). In multivariable analysis including *NPM*1 status and HSCT as a TVC, there was significantly worse EFS, DFS, and RR in sorafenib-unexposed patients (EFS from study entry: HR 2.37, 95% CI, 1.45 to 3.88, $P < .001$, DFS from CR: HR 2.28, 95% CI, 1.08 to 4.82, $P = .032$, RR from CR: HR 3.03, 95% CI, 1.31 to 7.04, $P = .010$, Table 3).

Correlative Studies: PK and PIA Analysis

Optional PK and PIA data that were obtained during the first 3 courses of chemotherapy demonstrated that the steady-state concentrations of sorafenib and N-oxide metabolite were similar across treatment cycles and that measured plasma concentrations were sufficient to inhibit phosphorylated FLT3 (Fig 3). With PIA assay, the median trough *FLT3* inhibition was 92%, 91%, and 81%, respectively, for the first 3 courses of therapy, suggesting sorafenib, at the dosing prescribed, was able to, in a subset of patients, target FLT3 and inhibit its function. There were no significant differences in clinical characteristics or outcome for arm C patients who contributed to PK/PD data (n = 52) versus not (n = 40; Data Supplement).

DISCUSSION

These data demonstrate that sorafenib dosing of 200 mg/m^2/day was tolerable in conjunction with conventional chemotherapy, significantly improved EFS, RR, and DFS, and provided potent *FLT3* inhibition. Importantly, HSCT use and *NPM1* status did not explain the clinical benefit seen. Although sorafenib did not improve OS, this may reflect use of TKI therapy after withdrawal from protocol therapy or at time of relapse. Our findings build on previously published pediatric studies of sorafenib that demonstrated tolerability and on-target effects.[17,18] Studies of TKI efficacy in younger adults with AML previously demonstrated benefit of midostaurin in FLT3-mutant AML[30] and sorafenib in younger adults with AML, regardless of FLT3 mutation status.[14,15] However, a more recent study of sorafenib in adults with HAR *FLT3*/ITD+ AML shows less clear benefit.[16] Although our results are compelling, we recognize that the higher-than-anticipated rates of attrition and intermittent periods of study closure are limitations in our study. Despite this, the improved EFS and DFS and reduced RR observed with treatment would support its use.

Importantly, first-generation FLT3 inhibitors have off-target effects that may increase systemic toxicity by targeting multiple signaling pathways. Despite this risk, the sorafenib/chemotherapy toxicity profile observed was overall comparable to that of standard therapy, although an early cardiac toxicity signal in C2 prompted change in dosing schedule for induction 2 and beyond. Interestingly, a majority of patients experiencing cardiac toxicity had preceding exposure to bortezomib (6/7; 86%), which was associated with higher rates of overall study toxicity.[19] Despite this early concern for cardiac dysfunction, rates of cardiac toxicity were ultimately comparable for *FLT3*/ITD+ patients treated with and without sorafenib. Interestingly, more patients enrolled on arm C received dexrazoxane compared with arms A and B, a difference that may reflect practice change after the cardiac toxicity concern was raised as well as evolving data regarding various mechanisms of TKI cardiotoxicity.[31-34] Additional

data regarding long-term cardiac function after completion of sorafenib treatment are being sought.

To our knowledge, our study is also the first prospective trial of sorafenib maintenance for *FLT3*/ITD+ AML in children, an effective intervention in adult *FLT3*/ITD+ AML.[35-37] As the majority of children (62%) did not receive any maintenance therapy, a greater understanding of barriers that preclude maintenance treatment are needed. As early relapse was seen in a subset of patients after HSCT before sorafenib start, earlier initiation of TKI therapy after HSCT (eg, before day 40) may be warranted. Moreover, as a subset of patients failed to meet criteria for drug start within the window of time allowed after HSCT or were removed from protocol therapy after HSCT before eligible, a greater understanding of barrier to maintenance treatment is needed. Use of a second-generation TKI with less off-target effects, such as gilteritinib, may enable initiation of maintenance treatment at an earlier stage of hematopoietic recovery and ensure greater compliance. Discontinuous dosing of sorafenib during maintenance treatment may also facilitate greater compliance, albeit with a potential risk of resistance mutation development.

The efficacy analyses presented have the well-established limitation of historical controls and incomplete TKI exposure data after study withdrawal. To control for differential rates of HSCT between sorafenib-exposed/-unexposed patients, HSCT was treated as a TVC. Although this analytic approach appropriately adjusts for the differential HSCT exposure, it does not address differences resulting from changes in HSCT conditioning or supportive care. We also electively censored sorafenib-unexposed patients at the time of elective withdrawal to minimize the impact of unobserved TKI exposure after study withdrawal. We performed secondary analyses using different censoring approaches (Data Supplement) that suggest outcomes remained superior in the sorafenib-exposed cohort. We recognize that although sorafenib improved EFS, DFS, and RR, it had less definitive impact on OS, suggesting that those who did not receive sorafenib might benefit from FLT3 inhibition at the time of recurrence. Moreover, the role of sorafenib in the more favorable *NPM1*+/*FLT3*/ITD+ AML is less clear and warrants further study in a larger subset of patients.

Despite these limitations, these data are the largest analysis of sorafenib efficacy in pediatric *FLT3*/ITD+ AML. The presently open COG phase III study, AAML1831, builds on our sorafenib experience by testing gilteritinib in both *FLT3*/ITD+ AML and children with clinically relevant *FLT3*-activating mutations. For treatment of pediatric *FLT3*/ITD+ AML outside of a study context, these data provide compelling support for sorafenib combined with conventional chemotherapy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Sorafenib in Combination With Standard Chemotherapy for Children With High Allelic Ratio *FLT3*/ITD+ Acute Myeloid Leukemia: A Report From the Children's Oncology Group Protocol AAML1031

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