ARTICLE

Bortezomib with standard chemotherapy for children with acute myeloid leukemia does not improve treatment outcomes: a report from the Children's Oncology Group

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ABSTRACT

New therapeutic strategies are needed for pediatric acute myeloid leukemia (AML) to reduce disease recurrence and treatment-related morbidity. The Children's Oncology Group Phase III AAML1031 trial tested whether the addition of bortezomib to standard chemotherapy improves survival in pediatric patients with newly diagnosed AML. AAML1031 randomized patients younger than 30 years of age with *de novo* AML to standard treatment with or without bortezomib. All patients received the identical chemotherapy backbone with either four intensive chemotherapy courses or three courses followed by allogeneic hematopoietic stem cell transplantation for high-risk patients. For those randomized to the intervention arm, bortezomib 1.3 mg/m^2 was given on days 1, 4 and 8 of each chemotherapy course. For those randomized to the control arm, bortezomib was not administered. In total, 1,097 patients were randomized to standard chemotherapy (n=542) or standard chemotherapy with bortezomib (n=555). There was no difference in remission induction rate between the bortezomib and control treatment arms (89% *vs.* 91%, *P*=0.531). Bortezomib failed to improve 3-year event-free survival (44.8±4.5% *vs.* 47.0±4.5%, *P*=0.236) or overall survival (63.6±4.5 *vs.* 67.2±4.3, *P*=0.356) compared with the control arm. However, bortezomib was associated with significantly more peripheral neuropathy (*P*=0.006) and intensive care unit admissions (*P*=0.025) during the first course. The addition of bortezomib to standard chemotherapy increased toxicity but did not improve survival. These data do not support the addition of bortezomib to standard chemotherapy in children with *de novo* AML. (Trial registered at *clinicaltrials.govNCT01371981; https://www.cancer.gov/clinicaltrials/ NCT01371981*).

Introduction

Pediatric acute myeloid leukemia (AML) is the second most common pediatric leukemia and requires intensive therapy for cure.[1,2] Despite the intensity of AML chemotherapy, which includes a very high cumulative lifetime anthracycline exposure in patients treated with chemotherapy alone or allogeneic donor stem cell transplantation (SCT) in first remission, approximately 50% of patients will experi-

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ence disease recurrence.[3,4] Moreover, treatment-related mortality limits the ability to further intensify therapy.[5] Thus, new therapies are needed to improve the outcomes of children with AML.

The development and evaluation of targeted therapies for children with AML is the highest clinical research priority for the Myeloid Committee in the Children's Oncology Group (COG).[6] After successfully demonstrating an improvement in event-free survival (EFS) in children treated with gemtuzumab,[3,4] COG sought to evaluate the efficacy of bortezomib, a first-generation proteasome inhibitor approved for multiple myeloma and non-Hodgkin lymphoma. Bortezomib was selected based on preliminary data demonstrating that AML blasts have increased proteasomes and are more sensitive to proteasome inhibitor-mediated apoptosis,[7] AML stem cells have increased NF-κB that is selectively targeted with proteasome inhibitors,[8-11] preclinical data from the pediatric preclinical testing program showing activity against leukemia cell lines,[12,13] and studies in adults with AML demonstrating clinical benefit.[14-16] At the time of the opening of the AAML1031 study, a COG pediatric phase I single agent bortezomib trial had determined the single agent maximum tolerated dose,[17] and a phase II trial (AAML07P1), combining bortezomib with AML chemotherapy for patients with relapsed AML, was nearing completion.[18]

Since the available safety and efficacy data for combining bortezomib with standard AML chemotherapy was limited, COG, in collaboration with the Cancer Therapy Evaluation Program (CTEP), designed AAML1031 as a definitive efficacy phase III trial with an interim toxicity analysis to ensure that combining bortezomib with standard AML chemotherapy was safe. The primary objective of AAML1031 was to definitively assess the impact of bortezomib in combination with standard AML chemotherapy on EFS for children with newly diagnosed AML without high allelic ratio (HAR) FLT3 ITD. A second objective was to evaluate the impact of bortezomib on overall survival (OS). Based on the available preliminary data at the time of study initiation, bortezomib was hypothesized to improve both EFS and OS. Multiple secondary objectives included an expanded safety assessment, multiple biology correlative studies, and secondary clinical data analyses.

Methods

The AAML1031 study was an open-label multi-center randomized trial including patients aged 0 to 29.5 years with previously untreated primary AML. Exclusion criteria were: prior chemotherapy, acute promyelocytic leukemia [t(15;17)], juvenile myelomonocytic leukemia, bone marrow failure syndromes, or secondary AML. The National Cancer Institute's central institutional review board (IRB) and IRB at each enrolling center approved the study; patients and families provided informed consent or assent as appropriate. The trial was conducted in accordance with the Declaration of Helsinki. The trial was registered at *clinicaltrials.gov identifier: NCT01371981.*

Patients were randomly assigned at enrollment to either standard AML treatment or standard treatment with bortezomib. Randomization was conducted in blocks of four. Bortezomib was administered at a dose of 1.3 mg/m^2 once on days 1, 4, and 8 of each chemotherapy course.

Patients with high allelic ratio FLT3 ITD were offered enrollment on a phase I sorafenib treatment arm if that arm was open. Patients with HAR FLT3 ITD who declined enrollment in the sorafenib arm, or who enrolled while the arm was suspended, continued to receive treatment according to their initial randomization. These patients were included in safety analyses but were excluded from all efficacy analyses.

Patients were classified as low- or high-risk after Induction I. Low-risk patients received four courses of chemotherapy and high-risk patients received three courses of chemotherapy followed by allogeneic SCT. High-risk patients without an appropriate donor received four courses of chemotherapy.

The primary end point was EFS from study entry. EFS was defined as the time from study entry until death, refractory disease, or relapse of any type, whichever occurred first. The secondary end points were OS, remission rates, relapse risk, post induction disease-free survival (DFS), and treatment-related mortality (TRM). OS was defined as time from study entry until death. Relapse risk was defined as the time from the end of Induction II for patients in complete remission (CR) to relapse, where deaths without a relapse were considered competing events. DFS was defined as the time from end of Induction II for patients in CR until relapse or death. Refractory disease was defined as the persistence of central nervous system (CNS) disease after Induction I, or the presence of morphologic bone marrow blasts ≥5% or any extramedullary disease at the end of Induction II. Patients with refractory disease were removed from protocol therapy. TRM was defined as the time from either study entry, or from end of Induction II for patients in CR, to deaths without a relapse, with relapses considered as competing events. Patients without an event were censored at their date of last known contact. However, for TRM analyses, patients were censored 30 days post end of therapy or 200 days post SCT.

Statistical analysis

The study was designed with 1-sided testing and 2.5% type I error rate and 80% power to detect a 9% difference in EFS plateaus (52% *vs.* 61%, hazard ratio = 0.78) between patients without HAR FLT3 ITD randomized to standard therapy *versus* bortezomib/standard combination therapy. All *P*-values are two-sided. Please see the *Online Supplementary Appendix* for additional details of the methods used.

Results

Between February 2011 and January 2016, 1,231 patients were enrolled on the AAML1031 study; patients were aged 0 to 29.5 years and had previously untreated primary AML at 184 institutions. Data for this analysis were frozen at December 31, 2017, with a median follow-up period of 3.0 years (range, 0-6.0 years) for patients alive at last contact. A total of 132 patients were excluded: 32 patients not meeting eligibility criteria, 102 patients with HAR FLT3 ITD who either enrolled (n=60) or did not enroll (n=42) on the phase I sorafenib treatment arm that concluded enrollment on July 31, 2017; this left 1,097 patients eligible for analysis. Figure 1 illustrates the reasons for exclusion and shows that 555 participants were randomized to the bortezomib arm and 542 to the control arm.

Accrual to the main randomization was completed on January 15, 2016. As of March 14, 2016, the projected relapse event horizon was reached and outcome analyses indicated that the addition of bortezomib did not improve EFS, DFS or OS, but did demonstrate a higher incidence of

non-fatal treatment-related toxicities. Therefore, institutions were notified on this date that patients receiving protocol therapy on the bortezomib arm should switch to the standard chemotherapy arm immediately. There were 22 patients who were receiving protocol therapy on the bortezomib arm at this time.

Table 1 and *Online Supplementary Table S1* summarizes the demographic characteristics of patients by study arm; no significant differences were observed in these demographic characteristics. Of note, 33% and 13% of patients had favorable cytogenetic or molecular features, respectively, and <5% had unfavorable cytogenetic features.

Table 1. Patient demographics and clinical characteristics by treatment arm.

Characteristic	Overall		Arm A		Arm B		*P*
	N	%	N	%	N	%	
Gender							
Male	572	52%	285	53%	287	52%	0.773
Female	525	48%	257	47%	268	48%	
Age at diagnosis, years							
Median	9.2		9.5		9.1		0.511
Range	0 - 29.5		0.03 - 29.5		0 - 29.2		
0-1 [0-730 day old]	237	22%	107	20%	130	23%	0.139
2-10	372	34%	189	35%	183	33%	0.507
11-15	273	25%	139	26%	134	24%	0.565
16-20	188	17%	91	17%	97	17%	0.763
≥21	27	2%	16	3%	11	2%	0.300
Race							
American Indian or Alaskan Native	9	1%	3	1%	6	1%	0.506
Asian	51	5%	24	5%	27	6%	0.699
Native Hawaiian or other Pacific Islander	8	1%	3	1%	5	1%	0.726
Black or African American	136	14%	69	14%	67	14%	0.793
White	767	79%	384	80%	383	78%	0.652
Multiple Races	1	0%	0	0%	1	0%	1.000
Unknown	125		59		66		
Ethnicity							
Hispanic or Latino	199	19%	99	19%	100	19%	0.945
Not Hispanic or Latino	863	81%	427	81%	436	81%	
Unknown	35		16		19		
Leukemic burden, WBC, x $10^9/\mu L$							
Median	17.7		17		19.2		0.185
Range	0.6 - 2730		0.6 - 2730		0.6 - 2600		
N. of patients with >100 x $10^9/\mu L$	178	16%	85	16%	93	17%	0.620
CNS disease classification at study entry							
CNS1	730	69%	358	70%	372	69%	0.617
CNS2	215	20%	100	20%	115	21%	0.507
CNS3	108	10%	53	10%	55	10%	0.905
Unknown	44		31		13		
Non-CNS extramedullary disease	170	15%	82	15%	88	16%	0.720
Risk factors and classification							
Cytogenetics affecting risk classification							
t(8;21)	166	20%	84	16%	82	15%	0.725
Inv(16), t(16;16)	114	13%	57	11%	57	11%	0.883
-7	21	3%	9	2%	12	2%	0.545
-5/5q-	13	1%	6	1%	7	1%	0.814
Institution mutation results							
Low FLT3-ITD allelic ratio (≤0.4)	77	7%	37	7%	40	7%	0.805
NPM	80	7%	37	7%	43	8%	0.558
CEBPα	66	6%	29	5%	37	7%	0.364
MRD at end of induction I							
Negative	782	75%	386	75%	396	75%	0.929
Positive	261	25%	128	25%	133	25%	
MRD positive %, median	2.3		2.8		1.9		0.247
MRD positive %, range	0.1 - 93		0.1 - 93		0.1 - 92		
Unknown	54		28		26		
Risk group assignment							
Low	836	78%	417	79%	419	78%	0.664
High	230	22%	111	21%	119	22%	

AML: acute myeloid leukemia; CNS: central nervous system; ITD high AR: internal tandem duplication with high allelic ratio; MRD: minimum residual disease; WBC: white blood cell count.

Minimal residual disease (MRD) assessment at the end of Induction I was available in 95% of patients, and was negative in 75%. Thus, approximately 78% of all patients were classified as low-risk based on cytogenetic, molecular, and disease response features, while 22% were classified as high-risk.

Of the 1,097 patients enrolled on AAML1031, approximately 84% survived and achieved a remission at the end of two courses of induction. For the 1,024 patients who initiated the second course of induction therapy and were evaluable at the end of Induction II, the remission rate was 90% and there was no difference between study arms. No differences in EFS and OS were observed by study arm (Table 2 and Figure 2). Specifically, the 3-year EFS from study entry for the no bortezomib and bortezomib arms were 44.8%±4.5% *versus* 47.0%±4.5% (*P*=0.236) and the

Table 2. Event-free survival, overall survival, and treatment-related mortality by study arm.

	Overall		Arm A		Arm B		*P*
	N	% ± 2 SE%	N	% ± 2 SE%	N	% ± 2 SE%	
3-year EFS from study entry	1097	45.9 ± 3.2	542	44.8 ± 4.5	555	47.0 ± 4.5	0.236
3-year OS from study entry	1097	65.4 ± 3.1	542	63.6 ± 4.5	555	67.2 ± 4.3	0.356
3-year CI of relapse from study entry	1097	47.2 ± 3.2	542	48.0 ± 4.5	555	46.4 ± 4.4	0.378
1-year TRM from study entry	1097	11.8 ± 5.2	542	13.3 ± 8.2	555	10.5 ± 6.6	0.577
3-year DFS from end of Induction I	1015	47.8 ± 3.3	506	46.9 ± 4.6	509	48.7 ± 4.6	0.261
3-year OS from end of Induction I	1015	66.6 ± 3.2	506	65.2 ± 4.6	509	68.0 ± 4.5	0.451
3-year DFS from end of Induction II	910	52.4 ± 3.5	453	51.8 ± 4.9	457	53.0 ± 4.9	0.444
3-year OS from end of Induction II	910	70.5 ± 3.3	453	69.3 ± 4.8	457	71.7 ± 4.7	0.453
1-year TRM from end of Induction II	910	9.7 ± 5.2	453	10.4 ± 7.6	457	9.0 ± 7.2	0.331

EFS: event-free survival; OS: overall survival; CI: cumulative incidence; TRM: treatment-related mortality; DFS: disease-free survival; SE: standard error.

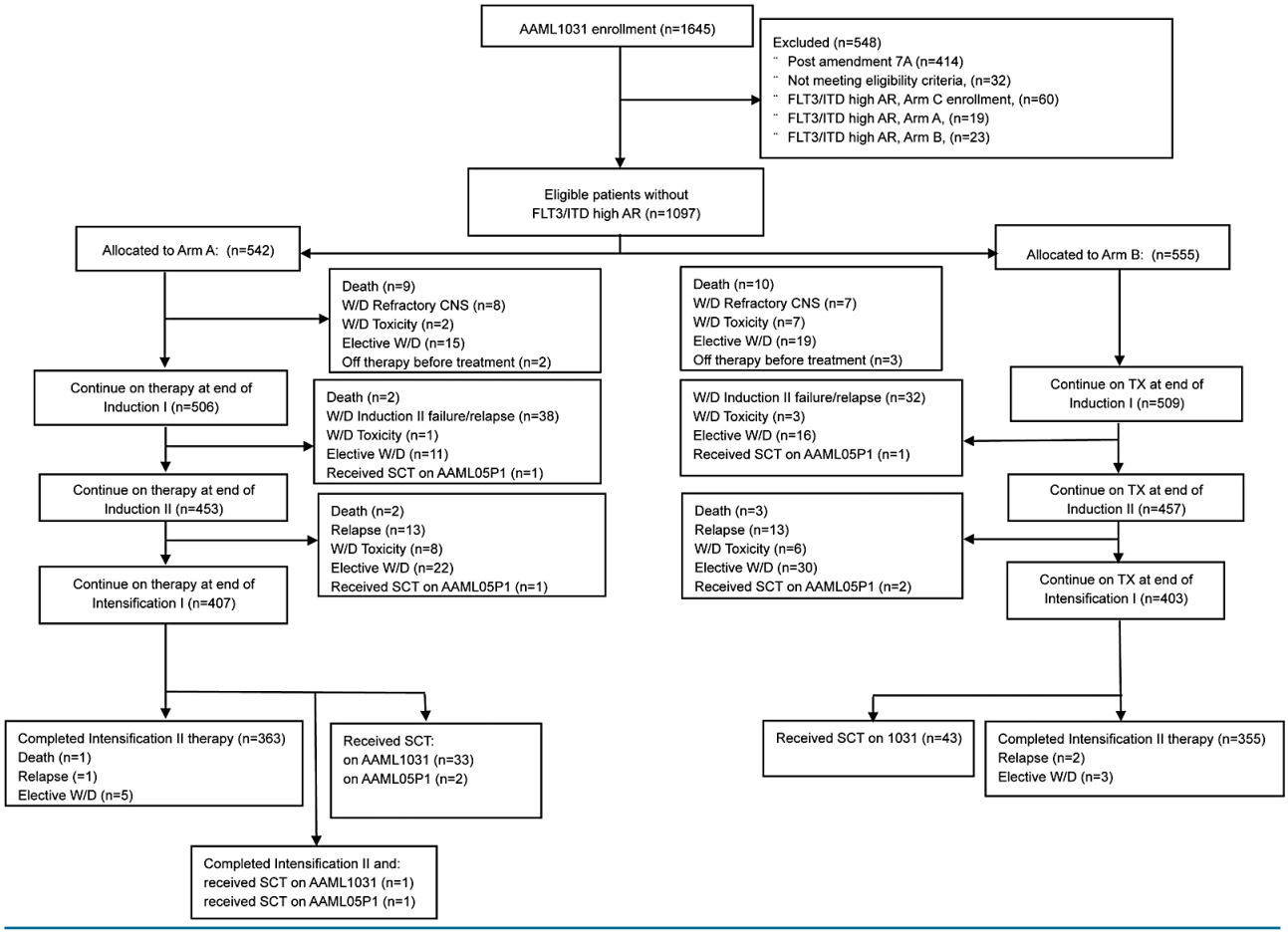

Figure 1. Consort diagram – AAML1031, as of December 31, 2017. High AR: W/D: Elective withdrawal. Reasons include terminating therapy to due to physician's choice or patient's refusal of further protocol therapy. SCT: stem cell transplantation; TX: therapy; n: number.

3-year OS from study entry were 63.6%±4.5% *versus* 67.2%±4.3% (*P*=0.356). Similar outcomes by randomization arm were observed for the cumulative incidence of relapse, 1-year TRM, and DFS/OS from the end of Induction II (Table 2).

Subgroup analyses by risk group (*Online Supplementary Table S2*) showed similar outcomes between treatment arms for both low- and high-risk patients. Combining the two arms, 3-year DFS and OS for low-risk patients was 52.9%±3.7% and 74.1%±3.4%, respectively while 3-year DFS and OS for high-risk patients was 27.8%±6.6% and 36.9%±7.6%. Subgroup analyses by NPM, CEBPA, CBF, and KMT2A molecular subtypes (*Online Supplementary Table S3*) and by age category (*Online Supplementary Table S4*) did not show any evidence of subtype- or age-specific bortezomib responses.

Univariable and multivariable Cox analyses from study entry and end of Induction II are shown in Table 3 and *Online Supplementary Table S5*. Initial white blood cell count (WBC) >100x10^9/L was significantly associated with an increased risk of relapse, treatment-related mortality, and decreased survival from study entry. Age greater or equal to 11 years old was associated with a decreased risk of relapse and increased survival. Black race, a previously observed risk factor,[3,19] was no longer a significant risk factor for relapse or death. The magnitude and significance of these associations remained stable between univariate and multivariable analyses.

Interim analyses of TRM and acute respiratory distress syndrome (ARDS) after 100 patients were randomized to bortezomib did not cross predefined toxicity thresholds. Overall TRM and targeted toxicity data are shown in Table 4 and *Online Supplementary Table S6*. No differences were observed in overall or course-specific TRM. While most toxicity rates did not differ by treatment arm, peripheral neuropathy, dose reductions, and pediatric Intensive Care Unit (PICU) admissions were consistently increased in patients receiving bortezomib in combination with standard chemotherapy. Course-specific increased rates of ARDS and hypoxia were observed in the patients treated with bortezomib together with standard chemotherapy. However, the reported rates of these toxicities was relatively low and did not differ from rates in patients treated with standard chemotherapy alone. No differences in infectious complications, renal toxicities, or decline in shortening fraction/ejection fraction were observed between treatment arms (*Online Supplementary Table S7*). Subgroup toxicity analyses by patient age demonstrated increased toxicities in Arm B patients with increasing age (*Online Supplementary Table S8*) amongst patients who completed all four courses of chemotherapy.

Discussion

The AAML1031 trial data demonstrate that the addition of bortezomib to standard chemotherapy does not improve EFS or OS. However, bortezomib caused additional treatment-related toxicity, specifically peripheral neuropathy, dose reductions, and PICU admissions. Given the lack of clinical benefit and increased toxicity observed in the bortezomib treatment arm, bortezomib was discontinued in all patients who remained on protocol mandated therapy. While the preliminary data regarding bortezomib efficacy in adults with AML was promising,[14-16] and pediatric preclinical models demonstrated a potential biological rationale for combining bortezomib with pediatric AML chemotherapy,[12,13] the results of AAML1031 do not support the addition of bortezomib to current pediatric AML chemotherapy. This trial result illustrates the need for specific pediatric clinical trials in AML, even in the context of a promising efficacy signal in adult AML.

Several important additional conclusions may be drawn from these data. First, the outcomes seen on the AAML1031 trial are generally similar to those seen on the standard arm of the immediately antecedent phase III trial, AAML0531, and are slightly inferior to outcomes reported in other pediatric co-operative oncology groups.[3,20-22] The observed differences in outcomes between other pediatric co-operative oncology group clinical trials and AAML1031 are still not completely understood but stem, in part, from the elimination of chemotherapy cycle 5 (Capizzi AraC) for low-risk patients with uninformative molecular features.[23] Further investigations will evaluate differences in

Table 3. Multivariable analyses.

		OS from study entry			EFS from study entry			TRM from study entry		
	N	HzR	95% CI	*P*	HzR	95% CI	*P*	HzR	95% CI	*P*
Treatment arm										
Arm A	482	1			1			1		
Arm B	487	0.91	0.73 - 1.13	0.383	0.95	0.80 - 1.13	0.567	0.87	0.49 - 1.57	0.652
Age at diagnosis, years										
2-10	318	1			1			1		
0-1	209	1.26	0.94 - 1.68	0.118	1.21	0.96 - 1.53	0.100	0.80	0.32 - 1.99	0.638
≥11	442	0.86	0.66 - 1.11	0.231	0.78	0.64 - 0.96	0.017	1.25	0.65 - 2.40	0.498
WBC at diagnosis, x10^9/L										
≤ 100	805	1			1			1		
> 100	164	1.42	1.08 - 1.86	0.013	1.64	1.32 - 2.03	<0.001	1.79	0.92 - 3.48	0.089
Race										
Non-black	832	1			1			1		
Black	137	1.30	0.97 - 1.75	0.084	1.02	0.79 - 1.31	0.884	1.86	0.95 - 3.62	0.068

OS: overall survival; EFS: event-free survival; TRM: treatment-related mortality; HzR: hazard ratio; CI: confidence interval; WBC: white blood cell count.

Table 4. Targeted toxicity by phase of therapy.

	Phase of therapy	Induction I			Induction II			Intensification I			Intensification II		
	Treatment arm	Arm A	Arm B	A *vs.* B *P*	Arm A	Arm B	A *vs.* B *P*	Arm A	Arm B	A *vs.* B *P*	Arm A	Arm B	A *vs.* B *P*
Toxicity	N	574	580		518	529		460	469		373	361	
Cardiac	Heart failure	4	4		3	6		5	10		10	13	
		0.7%	0.7%	1.000	0.6%	1.1%	0.506	1.1%	2.1%	0.206	2.7%	3.6%	0.474
	EF decreased	4	6		1	5		8	19		4	11	
		0.7%	1.0%	0.753	0.2%	0.9%	0.218	1.7%	4.1%	0.036	1.1%	3.0%	0.059
	Cardiac LVSD	5	8		4	4		13	15		9	16	
		0.9%	1.4%	0.413	0.8%	0.8%	1.000	2.8%	3.2%	0.740	2.4%	4.4%	0.132
Neurologic	Peripheral neuropathy/	6	20		4	17		8	14		5	10	
	Paresthesia/neuralgia	1.0%	3.4%	0.006	0.8%	3.2%	0.005	1.7%	3.0%	0.212	1.3%	2.8%	0.171
	Seizure	2	1		1	0		0	0		0	3	
		0.3%	0.2%	0.623	0.2%	0.0%	0.495	0.0%	0.0%	1.000	0.0%	0.8%	0.119
Pulmonary	ARDS	2	12		2	3		6	3		3	1	
		0.3%	2.1%	0.008	0.4%	0.6%	1.000	1.3%	0.6%	0.337	0.8%	0.3%	0.624
	Hypoxia	21	35		7	10		7	24		15	17	
		3.7%	6.0%	0.060	1.4%	1.9%	0.490	1.5%	5.1%	0.002	4.0%	4.7%	0.648
	Respiratory failure	10	18		2	3		4	5		8	5	
		1.7%	3.1%	0.133	0.4%	0.6%	1.000	0.9%	1.1%	1.000	2.1%	1.4%	0.435
Renal	Acute kidney injury	9	10		0	4		1	6		2	1	
		1.6%	1.7%	0.835	0.0%	0.8%	0.124	0.2%	1.3%	0.124	0.5%	0.3%	1.000
	Creatinine increased	0	5		1	2		0	2		0	1	
		0.0%	0.9%	0.062	0.2%	0.4%	1.000	0.0%	0.4%	0.500	0.0%	0.3%	0.492
Microbiologically documented sterile site infections (at least 1 occurrence)	Viridans group Streptococcus	21	25		55	53		70	78		83	75	
		3.7%	4.3%	0.572	10.6%	10.0%	0.750	15.2%	16.6%	0.556	22.3%	20.8%	0.627
	Gram Negative Bacilli	9	16		23	31		41	49		53	43	
		1.6%	2.8%	0.165	4.4%	5.9%	0.299	8.9%	10.4%	0.429	14.2%	11.9%	0.356
	Fungi	16	7		3	7		0	2		6	6	
		2.8%	1.2%	0.055	0.6%	1.3%	0.342	0.0%	0.4%	0.500	1.6%	1.7%	0.955
Dose reductions		8	31		8	33		4	37		9	47	
		1.4%	5.3%	<0.001	1.5%	6.2%	<0.001	0.9%	7.9%	<0.001	2.4%	13.0%	<0.001
PICU admissions		121	155		43	66		53	84		72	71	
		21.1%	26.7%	0.025	8.3%	12.5%	0.027	11.5%	17.9%	0.006	19.3%	19.7%	0.901

ARDS: adult respiratory distress syndrome; EF: ejection fraction; LVSD: left ventricular cystolic dysfunction; PICU: pediatric intensive care unit.

study populations, including characteristics such as obesity, molecularly-defined risk differences between study populations, efficacy of the backbone treatment regimen, variations in supportive care practices, and the potential impact of structural differences in the provision of health services. Additional analyses including comparisons focusing on the efficacy of dexrazoxane as a cardioprotectant,[24] specific cytogenetic abnormalities (MLL translocation subgroups), the use of MRD testing for outcome prediction, optimizing risk classification, the intensification of Induction II therapy with cytarabine and mitoxantrone, and the role of allogeneic donor SCT, are ongoing.

Second, COG, in partnership with the Cancer Therapy Evaluation Program (CTEP) can conduct complex clinical trials that contain phase I, phase II, and phase III components. The sorafenib study arm, which will be reported separately, served as a phase I trial of the feasibility and initial efficacy assessment of incorporating sorafenib into pediatric AML. Moreover, at the initiation of AAML1031, the only published data for bortezomib in pediatric AML was as a single agent.[17] While limited safety data were available during the 2-year planning process prior to the opening of the AAML1031 trial in June, 2011, full safety and efficacy data were not available until the subsequent closure of the AAML07P1 trial in December, 2011.[18] Given these limited toxicity data, the AAML1031 trial included a planned targeted toxicity (ARDS and TRM) analyses after the randomization of 100 patients to the bortezomib treatment arm. The successful monitoring of bortezomib-associated toxicities on the AAML1031 trial highlights the ability of COG, in partnership with the CTEP, to conduct complex clinical trials that provide definitive efficacy testing of a novel agent in the setting of limited preliminary toxicity data.

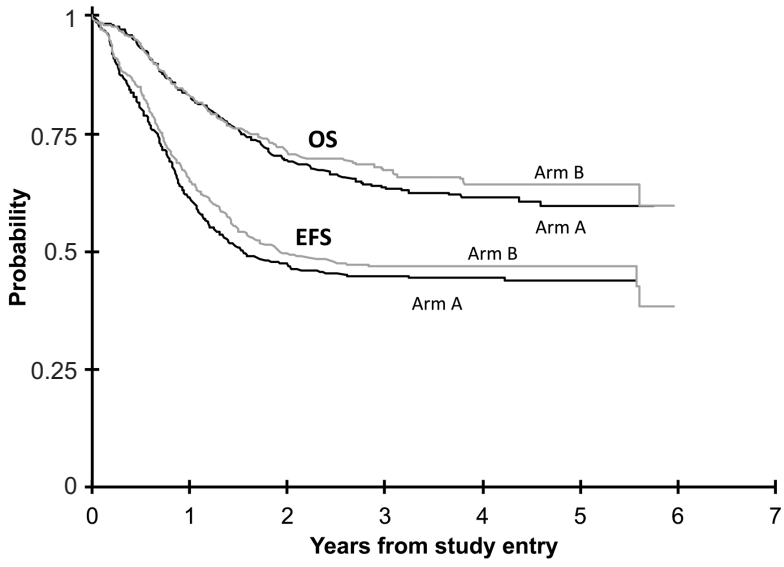

Figure 2. Event-free survival (EFS) and overall survival (OS) by treatment arm.

Several limitations of this clinical trial require acknowledgment. First, correlative biology data on the unfolded protein response and other biomarkers of bortezomib efficacy are currently ongoing and thus could not be included in this report. These ongoing studies may define subgroup populations who may benefit from bortezomib.[25] Second, comprehensive molecular profiling of each individual AML case is ongoing but is still not complete.[26] The completion of this work will likely enable the next generation of risk prediction and therapy individualization. Finally, the ongoing analyses of changes in chemotherapy course sequence and use of allogeneic donor SCT will face the well documented challenges of limitations in chemotherapy toxicity reporting,[27,28] and the challenges faced by all cooperative oncology groups to collect and account for variable supportive care practices and particular factors at the level of each individual center that may impact treatment outcomes.

In conclusion, the AAML1031 trial demonstrates that bortezomib can be combined safely with standard pediatric AML chemotherapy but that this combination does not improve EFS or OS and is associated with increased toxicity. Thus, these data do not support the use of bortezomib in pediatric AML therapy at this time. Despite this, the successful conduct of this very complex trial highlights the clinical trial capabilities of COG in partnership with the CTEP, and may serve as a paradigm for definitive efficacy clinical trials initiated in the setting of limited preliminary data. Finally, the AAML1031 clinical trial data set, in conjunction with ongoing biology studies, will serve as an invaluable data platform for future clinical and translational investigations.

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