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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Supplemental Table 1. Patient Enrollment and WHO classification

Characteristic	Overall		Arm A		Arm B		*P*-value
	N	%	N	%	N	%	
Total enrolled							
Ineligible	32		19		13		
Eligible, ITD high AR (enrolled on Arm C)	60		36		24		
Eligible, ITD high AR	42		19		23		
Eligible, without ITD high AR	1097		542		555		
WHO classification							
AML, not otherwise categorized: Acute erythroid leukemia (Erythroleukemia, erythroid/myeloid)	12	1%	7	1%	5	1%	0.538
AML, not otherwise categorized: Acute erythroid leukemia (Pure erythroid leukemia)	3	0%	3	1%	0	0%	0.121
AML, not otherwise categorized: AML without maturation	68	6%	28	5%	40	7%	0.156
AML, not otherwise categorized: AML with maturation	66	6%	36	7%	30	5%	0.398
AML, not otherwise categorized: AML, with minimal differentiation	31	3%	14	3%	17	3%	0.624
AML, not otherwise categorized: Acute myelomonocytic leukemia	71	6%	32	6%	39	7%	0.440
AML, not otherwise categorized: Acute monoblastic/acute monocytic leukemia	172	16%	89	16%	83	15%	0.521
AML, not otherwise categorized: Acute megakaryoblastic leukemia	57	5%	25	5%	32	6%	0.382
AML with t(8;21)(q22;q22); RUNX1-RUNX1T1	154	14%	78	14%	76	14%	0.758
AML with inv(16)(p13q22) or t(16;16)(p13;q22); CBFB-MYH11	101	9%	53	10%	48	9%	0.530
AML with t(9;11)(p22;q23); MLLT3-MLL	94	9%	46	8%	48	9%	0.909
AML with t(6;9)(p23;q34); DEK-NUP214	12	1%	8	1%	4	1%	0.232
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1	1	0%	0	0%	1	0%	1.000
AML (megakaryoblastic) with t(1;22)(p13;q13); RMB15-MKL	13	1%	6	1%	7	1%	0.808
AML with myelodysplasia-related changes	88	8%	41	8%	47	8%	0.570
Provisional entity: AML with mutated CEBPA	37	3%	19	4%	18	3%	0.819
Provisional entity: AML with mutated NPM1	32	3%	16	3%	16	3%	0.954
AML, not otherwise categorized	69	6%	35	6%	34	6%	0.833
Myeloid sarcoma	14	1%	6	1%	8	1%	0.617
Unknown	2		0		2		

Abbreviations: AML, acute myeloid leukemia; WHO, World Health Organization.

Supplemental Table 2: Outcome by Risk Group:

Low Risk	Overall		Arm A		Arm B		p-value
	N	% ± 2 SE%	N	% ± 2 SE%	N	% ± 2 SE%	
3 year DFS from end of Induction I	805	52.9 ± 3.7	403	50.7 ± 5.2	402	55.1 ± 5.2	0.129
3 year OS from end of Induction I	805	74.1 ± 3.4	403	71.9 ± 4.9	402	76.3 ± 4.6	0.264
3 year CI of relapse from end of Induction I	805	44.1 ± 3.7	403	45.7 ± 5.2	402	42.4 ± 5.2	0.214

High Risk	Overall		Arm A		Arm B		p-value
	N	% ± 2 SE%	N	% ± 2 SE%	N	% ± 2 SE%	
3 year DFS from end of Induction I	210	27.8 ± 6.6	103	31.7 ± 9.5	107	24.6 ± 8.9	0.279*
3 year OS from end of Induction I	210	36.9 ± 7.6	103	38.0 ± 10.9	107	36.2 ± 10.5	0.924
3 year CI of relapse from end of Induction I	210	58.8 ± 7.2	103	55.0 ± 10.2	107	62.1 ± 10.0	0.311*

*Landmark analyses as proportional hazards assumption violated

Supplemental Table 3: Outcome by Cytogenetic Risk Group:

NPM+ patients only	Overall		Arm A		Arm B		p-value
	N	% ± 2 SE%	N	% ± 2 SE%	N	% ± 2 SE%	
3 year EFS from study entry	80	72.2 ± 10.4	37	72.6 ± 14.8	43	72.0 ± 14.4	0.833
3 year OS from study entry	80	86.8 ± 7.8	37	83.4 ± 12.4	43	89.8 ± 9.8	0.404
3 year CI of relapse from study entry	80	20.2 ± 9.5	37	16.6 ± 12.6	43	23.3 ± 13.9	0.615
0.5 year TRM from study entry	80	5.3 ± 5.2	37	5.8 ± 8.2	43	4.7 ± 6.5	0.748
3 year DFS from end of Induction II	76	74.9 ± 10.3	36	74.6 ± 14.7	40	75.5 ± 14.3	0.708
3 year OS from end of Induction II	76	88.9 ± 7.4	36	85.8 ± 11.8	40	91.8 ± 9.1	0.397
0.5 year TRM from end of Induction II	76	21.0 ± 36.7	36	24.7 ± 44.2	40	2.5 ± 5.0	0.816

CEBPα+ patients only	Overall		Arm A		Arm B		p-value
	N	% ± 2 SE%	N	% ± 2 SE%	N	% ± 2 SE%	
3 year EFS from study entry	66	61.5 ± 12.7	29	61.3 ± 18.3	37	60.7 ± 18.0	0.952
3 year OS from study entry	66	91.5 ± 7.3	29	96.2 ± 7.5	37	88.1 ± 11.4	0.319
3 year CI of relapse from study entry	66	35.5 ± 12.6	29	38.7 ± 18.8	37	33.9 ± 18.0	0.558
0.5 year TRM from study entry	66	1.6 ± 3.1	29	0 ± 0	37	2.9 ± 5.7	0.116
3 year DFS from end of Induction II	64	60.1 ± 13.0	28	59.6 ± 18.8	36	59.9 ± 18.2	0.903
3 year OS from end of Induction II	64	91.3 ± 7.5	28	96.0 ± 7.8	36	87.8 ± 11.5	0.345
0.5 year TRM from end of Induction II	64	4.9 ± 7.3	28	0 ± 0	36	10.9 ± 17.0	0.140

CBF (t(8;21) or inv(16)) patients only	Overall		Arm A		Arm B		p-value
	N	% ± 2 SE%	N	% ± 2 SE%	N	% ± 2 SE%	
3 year EFS from study entry	280	64.8 ± 5.9	141	60.9 ± 8.6	139	68.8 ± 8.0	0.219
3 year OS from study entry	280	85.6 ± 4.4	141	83.9 ± 6.8	139	87.2 ± 5.8	0.736
3 year CI of relapse from study entry	280	30.9 ± 5.7	141	34.8 ± 8.5	139	26.9 ± 7.7	0.185
1 year TRM from study entry	280	6.0 ± 3.8	141	4.8 ± 3.9	139	7.1 ± 6.5	0.960
3 year DFS from end of Induction II	262	67.9 ± 6.0	133	63.1 ± 8.8	129	72.8 ± 8.0	0.129
3 year OS from end of Induction II	262	85.3 ± 4.9	133	83.8 ± 7.2	129	86.7 ± 6.6	0.569
1 year TRM from end of Induction II	262	4.3 ± 3.1	133	4.0 ± 3.6	129	4.5 ± 4.9	0.757

MLL (t(9;11) or 11q23) patients only	Overall		Arm A		Arm B		p-value
	N	% ± 2 SE%	N	% ± 2 SE%	N	% ± 2 SE%	
3 year EFS from study entry	280	32.1 ± 5.8	147	31.8 ± 7.9	133	32.5 ± 8.4	0.507
3 year OS from study entry	280	52.5 ± 6.4	147	49.8 ± 8.8	133	55.5 ± 9.4	0.431
3 year CI of relapse from study entry	280	62.5 ± 6.0	147	62.0 ± 8.3	133	63.0 ± 8.8	0.709
1 year TRM from study entry	280	9.6 ± 8.0	147	9.1 ± 9.8	133	10.1 ± 13.1	0.919
3 year DFS from end of Induction II	221	37.9 ± 6.7	117	38.0 ± 9.2	104	37.8 ± 9.9	0.675
3 year OS from end of Induction II	221	58.8 ± 7.1	117	56.2 ± 9.7	104	61.6 ± 10.5	0.539
0.5 year TRM from end of Induction II	221	7.1 ± 8.8	117	6.1 ± 8.8	104	7.2 ± 14.5	0.346

Supplemental Table 4: Outcome by Age Group:

0-1 yrs	Overall		Arm A		Arm B		*P*-value
	N	% ± 2 SE%	N	% ± 2 SE%	N	% ± 2 SE%	
3-year EFS from study entry	237	39.1 ± 6.6	107	34.4 ± 9.8	130	42.8 ± 8.9	0.326
3-year OS from study entry	237	55.9 ± 7.1	107	53.2 ± 10.6	130	58.2 ± 9.5	0.390
2-10 yrs							
	N	% ± 2 SE%	N	% ± 2 SE%	N	% ± 2 SE%	
3-year EFS from study entry	372	42.3 ± 5.4	189	42.6 ± 7.5	183	41.9 ± 7.8	0.672
3-year OS from study entry	372	64.4 ± 5.4	189	64.7 ± 7.6	183	64.0 ± 7.7	0.587
11-15 yrs							
	N	% ± 2 SE%	N	% ± 2 SE%	N	% ± 2 SE%	
3-year EFS from study entry	273	49.0 ± 6.3	139	46.6 ± 8.8	134	51.4 ± 9.0	0.360
3-year OS from study entry	273	70.0 ± 5.9	139	64.3 ± 8.7	134	75.8 ± 7.6	0.054
≥16 yrs							
	N	% ± 2 SE%	N	% ± 2 SE%	N	% ± 2 SE%	
3-year EFS from study entry	215	56.0 ± 7.3	107	57.2 ± 10.0	108	54.7 ± 10.5	0.747
3-year OS from study entry	215	71.5 ± 6.9	107	70.9 ± 9.7	108	72.2 ± 9.7	0.858

Supplemental Table 5. Univariable Analyses and Multivariable Analyses from End of Induction II

Univariable analyses	OS from study entry				EFS from study entry			TRM from study entry		
	N	HzR	95% CI	*P*-value	HzR	95% CI	*P*-value	HzR	95% CI	*P*-value
Treatment Arm										
Arm A	542	1			1			1		
Arm B	555	0.91	0.74 - 1.12	0.356	0.91	0.77 - 1.07	0.236	0.85	0.49 - 1.49	0.577
Age at diagnosis, years										
2-10	372	1			1			1		
0-1	237	1.25	0.95 - 1.63	0.106	1.20	0.97 - 1.49	0.098	0.68	0.28 - 1.63	0.385
≥11	488	0.80	0.63 - 1.02	0.068	0.76	0.63 - 0.92	**0.004**	1.10	0.60 - 2.02	0.769
WBC at diagnosis, µL										
≤ 100,000	916	1			1			1		
> 100,000	178	1.43	1.10 - 1.86	**0.007**	1.66	1.35 - 2.03	**<0.001**	2.00	1.06 - 3.76	**0.033**
Race										
Non-black	835	1			1			1		
Black	137	1.31	0.97 - 1.76	0.077	1.03	0.80 - 1.33	0.796	1.87	0.95 - 3.67	0.069

Univariable analyses		OS from end induction II			DFS from end induction II			RR from end induction II			TRM from end induction II		
	N	HzR	95% CI	*P*-value	HzR	95% CI	*P*-value	HzR	95% CI	*P*-value	HzR	95% CI	*P*-value
Treatment Arm													
Arm A	453	1			1			1			1		
Arm B	457	0.91	0.71 - 1.17	0.454	0.93	0.76 - 1.13	0.444	0.96	0.79 - 1.18	0.727	0.70	0.34 - 1.45	0.335
Age at diagnosis, years													
2-10	304	1			1			1			1		
0-1	185	1.28	0.92 - 1.79	0.143	1.17	0.91 - 1.52	0.225	1.25	0.95 - 1.65	0.108	0.43	0.09 - 2.01	0.285
≥11	421	0.87	0.65 - 1.17	0.357	0.84	0.67 - 1.05	0.122	0.77	0.61 - 0.98	**0.029**	1.57	0.69 - 3.59	0.283
WBC at diagnosis, µL													
≤ 100,000	781	1			1			1			1		
> 100,000	128	0.92	0.63 - 1.34	0.662	1.42	1.10 - 1.83	**0.008**	1.54	1.18 - 2.02	**0.002**	0.47	0.11 - 1.96	0.298
Race													
Non-black	696	1			1			1			1		
Black	107	1.19	0.81 - 1.73	0.375	0.87	0.64 - 1.20	0.402	0.81	0.57 - 1.15	0.239	1.11	0.38 - 3.24	0.846

Risk group													
Low	769	1			1			1			1		
High	141	2.80	2.12 - 3.71	**<0.001**	1.60	1.25 - 2.04	**<0.001**	1.19	0.89 - 1.59	0.238	1.12	0.44 - 2.85	0.809

Multivariable analyses		OS from end induction II			DFS from end induction II			RR from end induction II			TRM from end induction II		
	N	HzR	95% CI	*P*-value	HzR	95% CI	*P*-value	HzR	95% CI	*P*-value	HzR	95% CI	*P*-value
Treatment Arm													
Arm A	401	1			1			1			1		
Arm B	401	0.95	0.73 - 1.24	0.723	1.01	0.82 - 1.24	0.957	1.03	0.83 - 1.28	0.807	0.82	0.38 - 1.79	0.623
Age at diagnosis, years													
2-10	258	1			1			1			1		
0-1	162	1.37	0.95 - 1.96	0.090	1.22	0.93 - 1.62	0.158	1.26	0.93 - 1.69	0.132	0.55	0.11 - 2.69	0.458
≥11	382	0.95	0.70 - 1.30	0.760	0.87	0.69 - 1.10	0.244	0.78	0.61 - 1.00	**0.046**	1.98	0.79 - 4.96	0.145
WBC at diagnosis, µL													
≤ 100,000	683	1			1			1			1		
> 100,000	119	0.88	0.59 - 1.30	0.507	1.34	1.02 - 1.76	**0.035**	1.46	1.10 - 1.95	**0.010**	0.44	0.10 - 1.89	0.268
Race													
Non-black	695	1			1			1			1		
Black	107	1.14	0.78 - 1.65	0.509	0.84	0.61 - 1.16	0.294	0.79	0.55 - 1.13	0.195	1.19	0.41 - 3.47	0.745
Risk group													
Low	682	1			1			1			1		
High	120	2.81	2.08 - 3.80	**<0.001**	1.67	1.28 - 2.17	**<0.001**	1.16	0.84 - 1.59	0.377	1.39	0.53 - 3.66	0.502

Abbreviations: OS, overall survival; EFS, event-free survival; TRM, treatment-related mortality; DFS, disease-free survival; RR, relapse risk; HzR, hazard ratio; CI, confidence interval; WBC, white blood cell count

Supplemental Table 6. Treatment-Related Mortality (TRM) by Treatment Phase

	Induction I		Induction II		Intensification I		Intensification II	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
Patients (N)	540	552	506	509	453	456	372	360
Patients with TRM (N)	9	11	1	0	3	3	9	6
% TRM	1.7%	2.0%	0.2%	0.0%	0.7%	0.7%	2.4%	1.7%

Supplemental Table 7. Ejection Fraction/Shortening Fraction by Course and Treatment Arm

Arm A: Lowest EF and SF in Each Course								
	Induction I		Induction II		Intensification I		Intensification II	
	EF	SF	EF	SF	EF	SF	EF	SF
Patients (N)	574		518		460		373	
ECHO result (N)	475	525	395	430	359	401	278	300
Mean	64.3	35.8	62.57	34.61	61.1	33.68	59.07	32.72
Median	65	35.4	63	34.1	62	33.5	61	32.82

Arm B: Lowest EF and SF in Each Course								
	Induction I		Induction II		Intensification I		Intensification II	
	EF	SF	EF	SF	EF	SF	EF	SF
Patients (N)	580		529		469		361	
ECHO result (N)	483	539	408	464	384	418	284	307
Mean	63.45	35.3	61.34	33.6	59.58	32.44	58.37	31.37
Median	64	34.9	62	33.9	61	32.9	59.8	32

Abbreviations: EF, Ejection fraction; SF, Shortening fraction

Supplemental Table 8. Toxicities in Arm B by Age Category

Toxicity	**Treatment Arm**	**Arm B**				
	Age group	**Age: 0-1 yrs**	**Age: 2-10 yrs**	**Age: 11-15 yrs**	**Age: ≥16 yrs**	***P*-value**
	N	81	115	91	74	
Cardiac	Heart Failure	1	10	4	4	
		1.2%	8.7%	4.4%	5.4%	0.139
	EF Decreased	0	10	9	5	
		0.0%	8.7%	9.9%	6.8%	**0.044**
	Cardiac LVSD	1	11	5	10	
		1.2%	9.6%	5.5%	13.5%	**0.021**
Neurologic	Peripheral Neuropathy/ Paresthesia/Neuralgia	2	7	12	16	
		2.5%	6.1%	13.2%	21.6%	**<0.001**
	Seizure	1	1	1	1	
		1.2%	0.9%	1.1%	1.4%	0.990
Pulmonary	ARDS	0	5	2	3	
		0.0%	4.3%	2.2%	4.1%	0.269
	Hypoxia	13	14	20	14	
		16.0%	12.2%	22.0%	18.9%	0.289
	Respiratory Failure	2	8	3	8	
		2.5%	7.0%	3.3%	10.8%	0.096
Renal	Acute kidney injury	0	0	4	7	
		0.0%	0.0%	4.4%	9.5%	**<0.001**
	Creatinine increased	0	0	2	4	
		0.0%	0.0%	2.2%	5.4%	**0.020**
Microbiologically documented sterile site infections (at least 1 occurrence)	Viridans group Streptococcus	25	60	36	31	
		30.9%	52.2%	39.6%	41.9%	**0.026**
	Gram Negative Bacilli	19	23	30	18	
		23.5%	20.0%	33.0%	24.3%	0.192
	Fungi	4	1	4	3	
		4.9%	0.9%	4.4%	4.1%	0.353
Dose Reductions		12	31	22	26	
		14.8%	27.0%	24.2%	35.1%	**0.033**

PICU Admissions		34	56	54	47	
		42.0%	48.7%	59.3%	63.5%	**0.023**

Induction I:	All patients Cytarabine 100 mg/m2 BID x 10 days Daunorubicin 50 mg/m2 daily on days 1, 3 and 5 Etoposide 100 mg/m2 daily on days 1-5
Induction II	Low Risk patients Cytarabine 100 mg/m2 BID x 8 days Daunorubicin 50 mg/m2 daily on days 1, 3 and 5 Etoposide 100 mg/m2 daily on days 1-5 High Risk patients Cytarabine 1000 mg/m2 daily on days 1-4 Mitoxantrone 12 mg/m2 daily on days 3-6
Intensification I	All patients Cytarabine 1000 mg/m2 BID x 5 days Etoposide 150 mg/m2 daily on days 1-5
Intensification II	Low Risk patients Cytarabine 1000 mg/m2 daily on days 1-4 Mitoxantrone 12 mg/m2 daily on days 3-6 High Risk patients Best allogenic donor stem cell transplant

Methods:

This was an open-label multi-center randomized trial conducted by COG in the United States, Canada, Australia and New Zealand. AAML1031 included patients aged 0 to 29.5 years who had previously untreated primary AML. Data were entered through the COG Web portal by each enrolling institution and were frozen December 31, 2017. No minimal performance status was required. Exclusion criteria were prior chemotherapy (except intrathecal cytarabine and hydroxyurea), acute promyelocytic leukemia [t(15;17)], juvenile myelomonocytic leukemia, bone marrow failure syndromes, or secondary AML. Pathologic (84.3%) and cytogenetic findings (97.6%) were centrally reviewed. The National Cancer Institute's central institutional review board and institutional review boards at each enrolling center (n = 184) approved the study; patients and their families provided informed consent or assent as appropriate. The trial was conducted in accordance with the Declaration of Helsinki. The trial was registered at www.clinicaltrials.gov as NCT01371981.

Patients were randomly assigned at enrollment to either standard AML treatment or standard treatment with bortezomib given in each chemotherapy course. The allocation sequence was computer generated and randomization was conducted in blocks of 4. For those allocated to the intervention arm, bortezomib was given at a dose 1.3 mg/m^2 administered once on days 1, 4, and 8 of each chemotherapy course.

Patients with high allelic ratio FLT3 ITD were offered enrollment in 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 (defined below). Low risk patients received four courses of chemotherapy. Patients classified as high risk received three courses of chemotherapy followed by allogeneic SCT. Choice of alternative donors were at the transplantation center's discretion and included matched or 1-antigen mismatched unrelated donors, 4-to-6 antigen matched cord blood, or mismatched family donor with at least one haplotype match or 5-of-6 antigen phenotypic match. High risk patients without an appropriate donor received four courses of chemotherapy.

Supplemental table 9 presents protocol mandated chemotherapy courses and doses. Targeted toxicity monitoring for infectious and other toxicities was employed as previously described.(1) In addition, an echocardiogram was mandated prior to each course of protocol therapy and values for the lowest shortening fraction and ejection fraction in each course were submitted by treating centers.

Patients were classified as either low risk or high risk based on diagnostic cytogenetic and molecular risk features and disease response after Induction I. Low risk was defined by the presence of t(8;21)(q22;q22), inv(16)(p13.1q22), or t(16;16)(p13.1;q22), NPM, or CEBPA mutations. Low risk was also defined by negative minimal residual

disease (MRD) in the bone marrow specimen at the end of Induction I in patients with uninformative cytogenetic and molecular features (MRD level < 0.1%).(2, 3) MRD detection was performed in a centralized lab using a "different from normal" algorithm employed as previously reported.(3) High risk was defined by the presence of monosomy 7, monosomy 5/5q deletion, or uninformative cytogenetic/molecular features with MRD >0.1% after Induction I. Pathologic and cytogenetic findings were centrally reviewed. Cytogenetics and molecular features outweighed minimal residual disease in risk classification,(4) and FLT3-ITD HAR outweighed favorable cytogenetics.(5)

Refractory disease was defined as the persistence of 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.

The primary endpoint 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 endpoints 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. 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.

Because of the limited data on the safety of combining bortezomib with standard AML chemotherapy in pediatric patients at the time of study initiation, an interim toxicity analyses was performed after 100 patients had been randomized to receive bortezomib. Specifically, rates of TRM and adult respiratory distress syndrome (ARDS) were compared against predetermined rates that would require study closure and the rates of other targeted toxicities were compared between treatment arms.

Statistical Analysis: The study had a goal to enroll 1,200 eligible patients and 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. The study was monitored by a data safety monitoring committee. The alpha-spending function αt^2 (truncated at three standard deviations) and 2.5% type I error was used to monitor OS and EFS while futility monitoring was performed by testing the alternative hypothesis at the 0.005 level.

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. Estimates of OS,

EFS, and DFS were calculated using the Kaplan-Meier procedure along with corresponding two Greenwood SEs.(6) The significance of predictor variables was tested with the log-rank statistic for OS, EFS, DFS and with Gray's statistic for RR and TRM.(7) Cox proportional hazards models were used to estimate hazard ratios (HzR) for univariable and multivariable analyses of OS, EFS, and DFS.(8) Competing risk regression models were used to estimate the subgroup HzR for univariable and multivariable analyses of RR and TRM. A landmark analysis comparing 3 year point estimates was used for any analyses that did not satisfy the proportional hazards assumption. All p values are two-sided.

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