Supplementary Online Content

Sorror ML, Storer BE, Fathi AT, et al. Development and validation of a novel acute myeloid leukemia–composite model to estimate risks of mortality. *JAMA Oncol*. Published online September 7, 2017. doi:10.1001/jamaoncol.2017.2714

This supplementary material has been provided by the authors to give readers additional information about their work.

SUPPLEMENTAL ONLINE-ONLY MATERIAL for SORROR et al.,
" The Acute Myeloid Leukemia – Composite Model: A New Tool for Risk-Assessment"

List of ONLINE-ONLY Items

SUPPLEMENTAL MATERIALS AND METHODS (eMaterials and Methods)

Predictors: Comorbidities and Other Covariates

Comorbidities were evaluated per the definitions of comorbidities for the HCT-CI;[1,2] with the exception of renal comorbidities that were defined by creatinine clearance (mild = <60-46, moderate = <46-31, and severe = <31) when available and by serum creatinine when creatinine clearance was not available. Data on additional comorbidities not included in the HCT-ICI were collected including hyperlipidemia, hypertension, coagulopathy, gastroesophageal reflux disease, hypothyroidism, hypoalbuminemia, elevated lactate dehydrogenase (LDH), thrombocytopenia, neutropenia, anemia, and smoking history. These additional comorbidities were defined as follows:

Hyperlipidemia: Diagnosis of hyperlipidemia at any time in the patient past medical history. Patient had to have been on a specific treatment for hyperlipidemia for at least 4 consecutive weeks before start of induction therapy.

Hypertension: Diagnosis of hypertension at any time in the patient past medical history. Patient had to have been on a specific treatment for hypertension for at least 4 consecutive weeks before start of induction therapy.

Coagulopathy: Diagnosis of deep venous thrombosis or pulmonary embolism at any time in the patient past medical history.

Gastroesophageal reflux disease (GERD): Diagnosis of GERD at any time in the patient past medical history. Patient had to have been on a specific treatment for GERD for at least 4 consecutive weeks before start of induction therapy.

Hypothyroidism: Diagnosis of hypothyroidism at any time in the patient past medical history. Patient had to have been on a specific treatment for hypothyroidism for at least 4 consecutive weeks before start of induction therapy.

Hypoalbuminemia: We evaluated the closest value of albumin before start of induction therapy. We categorized albumin values into three categories: 3.5-<4, 3-<3.5, and <3 g/dL.

Elevated lactate dehydrogenase (LDH): We evaluated the closest value of LDH before start of induction therapy. We categorized LDH values into three categories: >200-500, >500-1000, and >1000 U/L.

Thrombocytopenia: We evaluated the closest value of platelet count before start of induction therapy. We categorized platelet count values into three categories: <100,000-50,000, <50,000-20,000, and <20,000 cells/μL.

Neutropenia: We evaluated the closest value of neutrophil count before start of induction therapy. We categorized neutrophil count values into three categories: <1,500-1,000, <1,000-500, and <500 cells/μL.

Anemia: We evaluated the closest value of hemoglobin before start of induction therapy. We categorized hemoglobin values into three categories: <10-9, <9-8, and <8 g/dL.

Smoking: We evaluated smoking status before start of induction therapy. We categorized smoking status into three categories: current (within 3 months before start of

induction therapy), former (cessation of smoking more than 3 months before start of induction therapy), and never.

Induction treatment regimens were categorized into 3 levels of intensity: low, intermediate, and high (eTable 1). Cytogenetic-molecular risks were categorized into favorable 19%, intermediate 38%, and adverse 43% following the European Leukemia Network (ELN) classification.[3]

Other Covariates are described in Supplemental eTable 6.

Sample Size

Sample size was determined based on the total number of patients seen at each of the five institutions during the study, conducted from 2008-2012. Supplemental eTable 10 gives the minimal increment in the 1-year risk of mortality detectable with at least 80% power at the 2-sided 0.05 level of significance in the training set of 733 patients. Since there is almost no loss to follow-up for the primary endpoint, the power calculations are based on a binomial assumption; the actual analysis based on Cox regression should provide somewhat higher power. Supplemental eTable 10 demonstrates sufficient power to identify a minimal increase in risk for a risk factor of specified prevalence compared to the remainder of the cohort. As noted in Supplemental eTable 2 there was an all-cause mortality rate of 40% (428/1100) in the first year.

Missing Data

Data collected from all 1100 pateints were used in the study analyses. Supplemental eTables 5 and 6 describe the distribution of all covariates, comorbidities as well other covariates, and describe the number and percentage of missing data per covariate. The components of the

HCT-CI were almost complete, and the HCT-CI could be computed for all patients except for a few (n=41), who were missing body mass index that defines obesity. Univariate analyses of risk factors excluded patients with missing data for the risk factor. In the multivariate analysis performed within the training set, missing value indicator variables were included for albumin, platelets, LDH, and cytogenetic risk group. In the validation set, we used complete data analysis in computing the various indices for comparisons of discriminative capacity.

SUPPLEMENTAL RESULTS (eResults)

Use of the AML-CM in Describing Outcomes of Patients of ≥65 years of age

We have looked at data on patients 60-75 years old within the validation set. Those patients constituted about 50% of the validation set population. The AUC for 1-year mortality was 0.68. The reduced AUC compared to the general population of AML is expected since this group is homogenous with respect to an important component of the AML-CM, alas age.

Per the AML-CM four risk groups, 1-year survival among patients 60-75 years old were; for those with scores 1-4, 86%; scores 5-6, 50%; scores 7-9, 46%; scores ≥10, 23%.

These results suggest that for older patients, AML-CM categorization into 3 risk groups with AML-CM scores of 1-4, 5-9, and ≥10 is more appropriate for decision-making given similar outcomes between those with scores 5-6 and 7-9.

Patients with scores 1-4 could benefit from intensive standard treatment combinations. Patients with scores ≥10 would benefit from being enrolled in novel clinical trials using novel targeted therapies to improve their outcomes. The concurrent use of palliative care might be warranted in this patient population. Patients with scores of 5-9 could be good candidates for randomized controlled trial comparing intensive versus less-intensive induction therapies for AML.

Supplemental References

1. Sorror M. How I assess comorbidities prior to hematopoietic cell transplantation. *Blood.* 2013;121(15):2854-2863.
2. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood.* 2005;106(8):2912-2919.
3. Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet (Review). *Blood.* 2010;115(3):453-474.

eTable 1. Initial Therapy Regimens as Stratified into Low, Intermediate, and High Intensity

Low Intensity		
Regimen		Patients
Main agent	Added agents	N
LDAC		**44**
	Alone	15
	+ Clofarabine	11
	+ Tosedostat	11
	+ Barasertib	2
	+ Lintuzumab	2
	+ Rigosertinib	2
	+ Azacitedine	1
Azacitidine		**67**
	Alone	51
	+ Gemtuzumab Ozogamicin	10
	+ Gemtuzumab Ozogamicin + vorinostat	3
	+ Decitabine	1
	+ Lenalidomide	1
	+ Vorinostat	1
Decitabine		**40**
	Alone	33
	+ Bortezomib	6
	+ Gemtuzumab Ozogamicin	1
Bendamustine + Idarubicin		**30**
Clofarabine	**Alone**	**12**
Gemtuzumab Ozogamicin + vorinostat		**16**
Others		**19**
Moderate Intensity		
"7+3"		**578**
	Alone	490
	+ Gemtuzumab Ozogamicin	28
	+ Bortezomib	12
	+ Etopsoside	12
	+ Midostaurine vs placebo	9
	+ Decitabine	5
	+ Cladribine	4
	+ Sorafenib	4
	+ Dasatinib	3
	+ Panobinostat	3
	+ Plerixafor	3
	+ Pravastatin	2
	+ Imatinib	2
	+ Vincristrine, Dexamethasone	1
Cytarabine (100 mg/m^2/dose)		**45**
	+ Mitoxantrone	37

	+ Amonafide	5
	+ Clofarabine	1
	+ Methotrexate	1
	+ Pravastatin	1
"4+3"		**40**
	Alone	37
	+ Dasatinib	3
Others		**12**
High Intensity		
Cytarabine (≥1 g/m^2/dose)		**199**
	Alone	2
	+ Purine analog (fludarabine, cladrabine, or clofarabine)	116
	+ Idarubicin	66
	+ Others	15

LDAC indicates low-dose cytarabine; "7+3" or "4+3", Cytarabine, + Daunorubicin, Doxorubicin, Idarubicin or Mitoxantrone.

eTable 2. Distribution of mortality events (n=679) according to time among all patients (n=1100)

Interval, months	Deaths	Cumulative
02	135	135
>2–4	71	206
>4–6	67	273
>6–8	56	329
>8–10	56	385
>10–12	53	438
>12–18	100	538
>18–24	45	583
>24–36	55	638
>36	41	679

eTable 3. Comparison of Characteristics and Outcome of Patients within the Training and Validation Sets

Patient Characteristics	All patients (n=1100)	Training (n-733)	Validation (n=367)
Age, median (range)	60 (20–89)	60 (20–88)	59 (20–89)
	%		
Sex			
Female	45	45	45
Male	55	55	55
Race			
Caucasian	80	80	81
Other	20	20	19
Cytogenetic risk, %			
Favorable	19	20	17
Intermediate	38	40	36
High	43	41	47
Regimen Intensity, %			
Low	20	20	20
Intermediate	62	63	60
High	19	18	20
Outcome			
1-year mortality	39.5	39	40

eTable 4. Patient Characteristics at Diagnosis of Acute Myeloid Leukemia for All Patients as well as and per Institution.

	All patients (1100)	FHCRC (n=366)	Cleveland Clinic (n=216)	MGH (n=232)	Stanford University (n=198)	Utah University (n=88)
Age, median (range)	60 (20-89)	61 (20–84)	59 (23–82)	64 (20–89)	55 (20–72)	59 (20–88)
	%					
Sex						
Female	45	40	49	46	49	44
Male	55	60	52	54	52	56
Race						
Caucasian	80	82	85	88	58	94
Other	20	18	15	12	42	6
Cytogenetic/molecular risk						
Favorable	19	18	24	13	22	23
Intermediate	38	42	39	39	31	37
Adverse	43	41	37	49	47	40
Regimen Intensity						
Low	20	33	4	25	5	25
Intermediate	62	31	93	72	70	69
High	19	37	3	4	25	7

FHCRC indicates Fred Hutchinson Cancer Research Center; MGH, Massachusetts General Hospital.

Supplemental eTable 5. Distribution and Classification of HCT-CI and Other Comorbidities (n=1100 patients)

Comorbidities	Missing data among patients		Prevalence of comorbidity	Grade of severity		
				Mild	Moderate	Severe
	Number	%	%	%	%	%
Arrhythmia	0	0	8	—	—	—
Coronary Artery	0	0	13	—	—	—
Heart valve disease	0	0	3	—	—	—
Cerebrovascular	0	0	4	—	—	—
Inflammatory Bowel	0	0	3	—	—	—
Hepatic	0	0	29	22	4	3
Renal (serum creatinine)*	0	0	19	16	2	1
Pulmonary	0	0	17	8	5	4
Rheumatoid	0	0	16	—	—	—
Diabetes	0	0	11	—	—	—
Tumor	0	0	21	—	—	—
Peptic Ulcer	0	0	3	—	—	—
Psychiatric	0	0	13	—	—	—
Infection	0	0	28	—	—	—
Obesity	41	3.7	13	—	—	—
Renal (creatinine clearance)*	195	17.7	19	9	7	3
Hyperlipidemia	0	0	27			
HTN	0	0	35			
DVT	0	0	4			
GERD	0	0	13			
Hypothyroid	0	0	11			
Hyperthyroid	88	8.0	1			
Hypoalbuminemia	65	5.9	72	31	24	17
Elevated lactate dehydrogenase (LDH)	114	10.4	80	44	21	15
Thrombocytopenia	38	3.5	70	27	29	14
Neutropenia	71	6.5	60	10	22	28
Anemia	39	3.5	67	26	24	17
Smoking£	47	4.3	46			

In Blue are comorbidities included under the HCT-CI while in Red are other comorbidities

*Both values were used to define renal comorbidity where preference was given to creatinine clearance when available or serum creatinine used if not.

£Smoking is categorized into never (50%), former (32%), current (14%).

Hypoalbuminemia was defined as a comorbidity if albumin value was <4 g/dL; mild if 3.5-<4; moderate, 3-<3.5; and severe, <3 g/dL.

Elevated LDH was defined as a comorbidity if LDH value was >200 U/L; mild if >200-500; moderate, >500-1000; and severe, >1000 U/L.

Thrombocytopenia was defined as a comorbidity if platelet value was <100,000 cells/μL; mild if <100,000-50,000; moderate, <50,000-20,000; and severe, <20,000 cells/μL

Neutropenia was defined as a comorbidity if neutrophil count value was <1,500 cells/μL; mild if <1,500-1,000; moderate, <1,000-500; and severe, <500 cells/μL.

Anemia was defined as a comorbidity if hemoglobin value was <10 g/dL; mild if <10-9; moderate, <9-8; and severe, <8 g/dL.

Supplemental eTable 6. Distribution and Classification of Other Study Covariates (n=1100 patients)

Covariate	Missing data among patients		Categories	% of patients
	Number	%		
Gender	1	0.1	Female	45
			Male	55
Age, years	0	0	0–49	25
			50–59	23
			60–69	31
			≥70	20
Race	27	2.5	White	80
			Asian	5
			Others	15
Cytogenetic/molecular risk	52	4.7	Favorable	19
			Intermediate	38
			Adverse	43
Initial regimen intensity	2	0.2	Low	20
			Intermediate	62
			High	19
WBC at diagnosis, X 1000 cells/μL	20	1.8	0–5	45
			>5–10	13
			>10–25	14
			>25–50	10
			>50–100	10
			>100	9
Peripheral blast count at diagnosis, X 1000 cells/μL	84	7.6	0–5	61
			>5–10	7
			>10–25	12
			>25–50	7
			>50–100	9
			>100	4
Marrow blasts at diagnosis, %	107	9.7	≥ 20	19
			>20–50	39
			>50	43

eTable 7: Univariate Analysis of Associations between Individual Comorbidities and Other Covariates with Post-Initial Therapy Mortality (288 Deaths Over 1 Year)

Comorbidities		HR	95% confidence interval	P	Overall P
Arrhythmia		1.14	(0.7–1.8)	0.54	
Cardiac		2.28	(1.7–3.0)	<0.0001	
Inflammatory Bowel		1.03	(0.5–2.1)	0.93	
Diabetes		1.67	(1.2–2.3)	0.004	
Cerebrovascular		1.37	(0.8–2.4)	0.27	
Psychiatric		1.21	(0.9–1.7)	0.26	
Hepatic	Mild	1.47	(1.1–1.9)	0.003	
	Moderate/Severe	1.44	(1.0–2.2)	0.08	0.004
Obesity		0.96	(0.7–1.4)	0.81	
Infection		1.27	(1.0–1.6)	0.06	
Rheumatologic		1.02	(0.6–1.7)	0.94	
Peptic Ulcer		2.05	(1.2–3.4)	0.01	
Renal	Mild	1.38	(1.0–1.8)	0.03	
	Moderate/Severe	1.44	(0.8–2.6)	0.22	0.06
Pulmonary	Mild	1.20	(0.8–1.8)	0.35	
	Moderate/Severe	1.32	(0.9–1.9)	0.11	0.20
Prior Malignancy		1.53	(1.2–2.0)	0.002	
Heart Valve Disease		2.86	(1.7–4.8)	0.0006	
Hyperlipidemia		1.58	(1.2–2.0)	0.0003	
Hypertension		1.62	(1.3–2.0)	<0.0001	
Coagulopathy		0.98	(0.5–1.7)	0.94	
GERD		1.13	(0.8–1.6)	0.46	
Hypothyroid		1.17	(0.8–1.7)	0.42	
Albumin, g/dL	<4–3.5	1.22	(0.9–1.7)	0.24	
	<3.5–3	1.42	(1.0–2.0)	0.04	
	<3	1.73	(1.2–2.5)	0.003	0.02
Platelets, cells/μL	<100,000–50,000	1.19	(0.9–1.6)	0.27	
	<50,000–20,000	1.15	(0.8–1.6)	0.38	
	<20,000	1.64	(1.1–2.4)	0.008	0.08
ANC, μL	<1,500–1,000	0.90	(0.6–1.4)	0.63	

	<1,000–500	1.11	(0.8–1.5)	0.50	
	<500	0.78	(0.6–1.1)	0.11	0.20
Hemoglobin, g/dL	<10–9	1.25	(0.9–1.7)	0.16	
	<9–8	1.44	(1.1–2.0)	0.02	
	<8	1.20	(0.8–1.7)	0.32	0.14
LDH, U/L	>200–500	1.64	(1.2–2.3)	0.006	
	>500–1000	1.67	(1.1–2.5)	0.01	
	>1000	2.02	(1.3–3.1)	0.001	0.005
Smoker	Former	1.28	(1.0–1.7)	0.006	
	Current	1.06	(0.7–1.5)	0.75	0.19
Other Covariates					
Gender	Female	1.0	—	—	
	Male	1.25	(1.0–1.6)	0.06	
Age, years	0–49	1.0	—	—	
	50–59	1.81	(1.2–2.7)	0.003	
	60–69	2.42	(1.7–3.5)	<0.0001	<0.0001
	≥70	3.49	(2.4–5.1)	<0.0001	
Race	White	1.0	—		
	Others	0.93	(0.7–1.2)	0.61	
Cytogenetic/molecular risks	Favorable	1.0	—	—	
	Intermediate	1.82	(1.25–2.5)	0.006	<0.0001
	Adverse	1.64	(1.3–2.1)	0.0002	
Initial regimen intensity	Low	1.93	(1.5–2.5)	<0.0001	
	Intermediate	1.0	—	—	<0.0001
	High	1.02	(0.7–1.4)	0.88	
WBC, cells/μL	0–5	1.0	—		
	>5–25	1.04	(0.8–1.4)	0.79	
	>25–100	1.07	(0.8–1.5)	0.68	0.98
	>100	1.04	(0.7–1.6)	0.87	
Peripheral blast count, cells/μL	0–5	1.0	—		
	>5–25	1.0	(0.7–1.4)	0.99	0.59
	>25–100	1.21	(0.9–1.7)	0.23	
	>100	1.31	(0.7–2.5)	0.41	
Marrow blasts, %	0–20	1.0	—		
	>20–50	0.96	(0.7–1.4)	0.81	0.76

	>50	1.06	(0.8–1.5)	0.73	

Covariates with different levels of severity and with an overall p-value are in blue.

GERD indicates gastro-esophageal reflux disease; ANC, absolute neutrophil count; LDH, lactate dehydrogenase; BMI, body mass index; WBC, and white blood count.

Supplemental eTable 8. Components of the HCT-CI, Augmented HCT-CI, and the AML-CM and their Corresponding Scores

Comorbidity	Definition	Score
The HCT-CI		
Arrhythmia	Any type of arrhythmia that has necessitated the delivery of a specific anti-arrhythmia treatment at any time point in the patient's past medical history.	1
Cardiac	Coronary artery disease,[§] congestive heart failure, myocardial infarction, or EF ≤50%	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis requiring treatment at any time point in patient's past medical history.	1
Diabetes	Requiring treatment with insulin or oral hypoglycemic agents continuously for 4 weeks before start of treatment	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Any disorder requiring continuous treatments for 4 weeks before start of treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT> ULN to 2.5 × ULN; using the closest value before start of treatment.	1
Obesity	Patients with a body mass index >35 kg/m2 for patients older than 18 years or a BMI-for-age of ≥ 95th percentile for patients of ≤ 18 years of age	1
Infection	Requiring antimicrobial treatment starting from before treatment and continued beyond day 0	1
Rheumatologic	Requiring specific treatment at any time point in the patient's past medical history	2
Peptic ulcer	Based on prior endoscopic or radiologic diagnosis	2
Moderate/severe renal	Creatinine clearance <45, if not available then serum creatinine > 2 mg/dL using the closest value before start of treatment, on dialysis, or prior renal transplantation	2
Moderate pulmonary	Corrected D_LCO (via Dinakara equation) and/or FEV1 of 66%-80% or dyspnea on slight activity	2
Prior malignancy	Any prior malignancy to AML treated at any time point in the patient's past history,	3

Comorbidity	Definition	Score
	excluding non-melanoma skin cancer and other myeloid malignancies.	
Heart valve disease	Of at least moderate severity, prosthetic valve, or symptomatic mitral valve prolapse as detected by echocardiogram	3
Severe pulmonary	Corrected D_LCO (via Dinakara equation) and/or FEV1 ≤ 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN; using the closest value before start of treatment.	3
The Augmented HCT-CI = all the above + the following		
Comorbidity	**Definition**	**Score**
Hypoalbuminemia	Value of <3.5 g/dL; using the closest value before start of treatment.	1
Thrombocytopenia	Value of <20,000 cells/μL; using the closest value before start of treatment	1
Elevated LDH	Values of >200-1000 U/L; using the closest value before start of treatment.	1
Elevated LDH	Value of >1000 U/L; using the closest value before start of treatment.	2
The AML-CM = all the above + the following		
Component	**Definition**	**Score**
Age	50-59 years old	1
Age	≥60 years old	2
ELN cytogenetic/molecular risk groups	Intermediate	1
ELN cytogenetic/molecular risk groups	Adverse	2

Abbreviations: HCT-CI = hematopoietic cell transplantation-comorbidity index; EF = ejection fraction; ULN= upper limit of normal; BMI = body mass index; D_LCO= diffusion capacity of carbon monoxide; FEV1 = forced expiratory volume in one second; g/dL =

gram/ deciliter; μL = microliter; LDH = lactate dehydrogenase; U/L = unit/liter; AML-CM = acute myeloid leukemia- composite model; and ELN = European leukemia network.

§One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.

Supplemental eTable 9: Comparisons of Kaplan Meier Survival Rates per Different Risk Factors and Models.

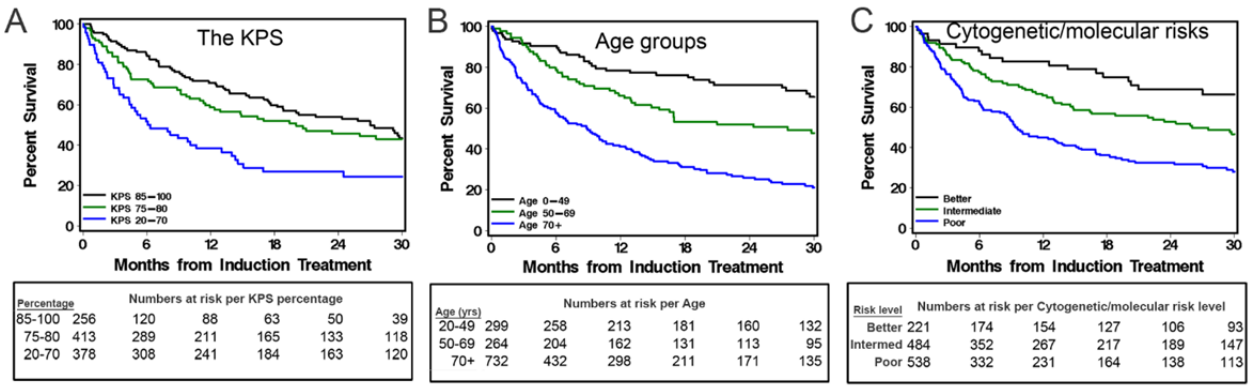
AML-CI			HCT-CI			Augmented HCT-CI			AML-CM		
Score	Patients, %	OS, %	Score	Patients, %	OS, %	Score	Patients, %	OS, %	Score	Patients, %	OS, %
0-1	30	69	0	17	70	0-2	32	73	1–4	27	84
2	32	55	1-2	37	74	3-4	30	65	5–6	24	65
3	18	61	3-4	26	50	5-6	20	57	7–9	31	52
≥4	20	40	≥5	19	30	≥7	18	20	≥10	18	21
Age (groups)			**Cytogenetics (groups)**			**KPS (groups)**					
Group, years	Patients, %	OS, %	Group	Patients, %	OS, %	Group, %	Patients, %	OS, %			
20-49	26	78	Favor	17	83	90-100	41	71			
50-59	24	66	Intermediate	36	66	75-80	35	59			
60+	50	41	Adverse	47	45	≤70	24	38			

AML-CI indicates acute myeloid leukemia-comorbidity index; HCT-CI, hematopoietic cell transplantation-comorbidity index; AML-CM, acute myeloid leukemia-composite model; and KPS, Karnofsky performance status.

Supplemental eTable 10: Power Calculation

Prevalence of risk factor or group	Minimal detectable risk increment[1] (risk ratio)
10%	0.17 (1.5)
20%	0.13 (1.35)
30%	0.11 (1.3)
40%	0.10 (1.25)

[1] with 80% power at 2-sided 0.05 level of significance and overall risk of 40%



eFigure 1: Kaplan Meier Estimates of Survival. Figure compares Kaplan-Meier estimates of survival by **A)** Karnofsky performance status percentages, **B)** age groups, and **C)** Cytogenetic/molecular risk groups.