

Supplemental Table 1. AML Treatment and Clinical Outcome for the UPENN Cohort

	Total Cohort (n=166)		Age ≤ 60, Intermediate Cytogenetics (n=82)	
	n	%	n	%
First Induction				
Dauno 45 / Ara-C	51	30.7	15	18.4
Dauno 60 / Ara-C	8	4.8	0	0.0
Dauno 90 / Ara-C	25	15.1	18	22.0
Ida 12 / Ara-C	71	42.8	46	56.1
Mito 10 / Ara-C	9	5.4	1	2.3
Unconfirmed	2	1.2	2	1.8
Second Induction				
Yes	45	27.1	21	25.6
Anthracycline / Ara-C	26	15.7	9	11.1
MEC	11	6.6	6	7.3
High-dose Ara-C	8	4.8	6	7.3
No	119	71.7	59	72.0
Unknown	2	1.2	2	1.8
Allogeneic Transplant				
Yes	107	64.5	44	53.7
No	59	35.5	38	46.3
CR				
Yes	118	71.1	65	79.3
No	48	28.9	17	20.7
2-Year OS				
Yes	62	38.0	35	43.2
No	101	62.0	46	56.8

AML, acute myeloid leukemia; Dauno 45/Ara-C, 3 once daily doses of daunorubicin 45 mg/m² plus 7 daily doses of cytarabine 100 mg/m² by continuous infusion; Dauno 60/Ara-C, 3 once daily doses of daunorubicin 60 mg/m² plus 7 daily doses of cytarabine 100 mg/m² by continuous infusion; Dauno 90/Ara-C, 3 once daily doses of daunorubicin 90 mg/m² plus 7 daily doses of cytarabine 100 mg/m² by continuous infusion; Ida 12/Ara-C, 3 once daily doses of idarubicin 12 mg/m² plus 7 daily doses of cytarabine 100 mg/m² by continuous infusion; Mito 10/Ara-C; 3 once daily doses of mitoxantrone 10 mg/m² plus 7 daily doses of cytarabine 100 mg/m² by continuous infusion; MEC, 6 once daily doses of mitoxantrone 6 mg/m², 8 daily doses of etoposide 80 mg/m²; plus 6 daily doses of cytarabine 1 g/m²; High-dose Ara-C, 1.5 or 3 gm/m² twice daily on days 1, 3, and 5;

Supplemental Table 2. UPENN Cohort: Sample Characteristics (n = 166)

	Bone Marrow	Peripheral Blood	Pheresis Sample	<i>P</i>
Number (%)	76 (45.8)	68 (41.0)	22 (13.3)	
M-score (Mean, 95% CI)	93.2 (85.2 - 101.1)	92.6 (85.1 – 100.2)	88.2 (77.3 – 99.1)	<i>P</i> = .809
Blast % (Mean, 95% CI)	66.2 (60.4 – 72.1)	53.0 (45.7 – 60.3)	N/A	<i>P</i> = .005

CI, confidence interval

Supplemental Table 3: Mean M-score by Mutant Status of DNA Methylation Regulatory Genes for UPENN Cohort (n=136)

	n	%	M-score (Mean)	95% CI	P
DNMT3A					
Mutant	42	30.1	101.5	91.1 – 111.9	.031
Wildtype	94	69.1	88.3	81.7 – 94.9	
TET2					
Mutant	19	14.0	103.3	89.5 – 117.0	.122
Wildtype	117	86.0	90.6	84.5 – 96.7	
IDH2					
Mutant	15	11.0	101.2	89.0 – 113.4	.275
Wildtype	121	89.0	91.3	85.2 – 97.4	
IDH1					
Mutant	11	8.1	113.7	85.7 – 141.6	.025
Wildtype	125	91.9	90.5	84.9 – 96.1	
WT1					
Mutant	8	5.9	87.2	66.1 – 108.3	.649
Wildtype	128	94.1	92.7	86.9 – 98.6	

CI, confidence interval; *DNMT3A*, DNA methyltransferase 3A; *TET2*, tet methylcytosine dioxygenase 2; *IDH2*, isocitrate dehydrogenase 2; *IDH1*, isocitrate dehydrogenase 2; *WT1*, wilms tumor1.

Supplemental Table 4. UPENN Cohort: Expanded Cox Model for Overall Survival (n=136, events=108)

	Univariate		Multivariable		Reduced		
Parameter	HR	P	Adj HR	P	Adj HR	95% CI	P
M-score^A	1.1	<.0001	1.1	.002	1.1	1.1 – 1.2	<.0001
Age^B	1.3	<.0001	1.3	.002	1.3	1.1 – 1.5	.001
Female	1.1	.503	1.0	.868	-	-	-
WBC, diagnosis^A	1.0	.289	1.0	.150	1.03	1.00 – 1.06	.035
Cytogenetic Risk (ref unfavorable)^C							
Intermediate	0.8	.400	9.8	.414	-	-	-
Favorable	0.4	.014	0.6	.256	-	-	-
FLT3-ITD+	1.6	.026	1.3	.351	-	-	-
NPM1+/FLT3-ITD-	0.5	.033	0.6	.107	0.6	0.3 – 1.0	.048
DNMT3A	1.3	.192	1.0	.897	-	-	-
IDH1	1.2	.536	1.3	.464	-	-	-

^Adivided by 10; ^B10-year increase; ^CMedical Research Council criteria (2010)

HR, hazard ratio; CI, confidence interval; WBC, white blood cell; *FLT3*-ITD, FMS-like kinase 3-internal tandem duplication; *NPM1*, nucleophosmin1; *DNMT3A*, DNA methyltransferase 3A; *IDH1*, isocitrate dehydrogenase 1

Supplemental Table 5. UPENN Cohort: Expanded Logistic Model for Failure to Achieve Complete Remission (n=136, events=38)

	Univariate		Multivariable		Reduced		
Parameter	OR	P	Adj OR	P	Adj OR	95% CI	P
M-score^A	1.2	.001	1.2	.036	1.2	1.1 – 1.4	.002
Age^B	1.7	.002	1.8	.002	1.7	1.2 – 2.5	.003
Female	0.9	.886	0.7	.559	-	-	-
WBC, diagnosis^A	1.0	.620	1.0	.412	-	-	-
Cytogenetics (ref unfavorable)^C							
Intermediate	0.4	.087	0.5	.180	-	-	-
Favorable	0.1	.012	0.1	.030	-	-	-
FLT3-ITD+	0.9	.761	0.8	.663	-	-	-
NPM1+/FLT3-ITD-	0.4	.141	0.3	.123	-	-	-
DNMT3A	0.6	.260	0.4	.088	-	-	-
IDH1	3.5	.051	6.4	.028	-	-	-

^Adivided by 10; ^B10-year increase; ^CMedical Research Council criteria (2010)

OR, odds ratio; CI, confidence interval; WBC, white blood cell; *FLT3*-ITD, FMS-like kinase 3-internal tandem duplication; *NPM1*, nucleophosmin1; *DNMT3A*, DNA methyltransferase 3A; *IDH1*, isocitrate dehydrogenase 1

Supplemental Table 6. Patient and Disease Characteristics by Optimal M-score for the UPENN Cohort

	Total Cohort			Age ≤ 60 years			Achieved CR		
	Low M-score (n=74) %	High M-score (n=92) %	<i>P</i>	Low M-score (n=35) %	High M-score (n=47) %	<i>P</i>	Low M-score (n=62) %	High M-score (n=56) %	<i>P</i>
Age									
≤ 60 years	77.0	62.0	.037	-	-	-	82.3	66.1	.044
> 60 years	23.0	38.0		-	-	-	17.7	33.9	
Sex									
Male	62.2	56.5	.463	60.0	53.2	.539	62.9	57.1	.523
Female	37.8	43.5		40.0	46.8		37.1	42.9	
WBC (x 10⁹/L), diagnosis									
<100	79.7	78.3	.818	74.3	70.2	.685	82.3	75.0	.335
≥100	20.3	21.7		25.7	29.8		17.7	25.0	
Cytogenetic risk group^A									
Favorable	25.7	2.2	<.0001	-	-	-	29.0	3.6	.001
Intermediate	60.8	79.3		-	-	-	59.7	83.9	
Unfavorable	13.5	18.5		-	-	-	11.3	12.5	
FLT3-ITD									
Mutant	25.7	40.2	.049	40.0	48.9	.421	72.6	57.1	.079
Wildtype	74.3	59.8		60.0	51.1		27.4	42.9	
NPM1									
Mutant	32.4	37.0	.543	54.3	40.4	.213	61.3	55.4	.514
Wildtype	67.7	63.0		45.7	59.6		38.7	44.6	
NPM1+, FLT3-ITD-									
Yes	17.6	13.0	.418	28.6	14.9	.131	79.0	85.7	.353
No	82.4	87.0		71.4	85.1		21.0	14.3	

^AMedical Research Council criteria (2010)

AML, acute myeloid leukemia; WBC, white blood cell; *FLT3*-ITD, FMS-like kinase 3-internal tandem duplication; *NPM1*, nucleophosmin1

Supplemental Table 7. E1900 Cohort: M-score by Patient, Disease, and Sample Characteristics (n=383)

	n	%	M-score (Mean)	95% CI	P
All Subjects	383	-	98.2	94.1 – 102.3	-
Sex					
Male	201	52.5	96.3	90.8 – 101.8	.347
Female	182	47.5	100.2	94.0 – 106.5	
WBC (x 10⁹/L), diagnosis					
<100	360	94.0	97.2	93.0 – 101.5	.06
≥100	23	6.0	113.6	95.9 – 131.4	
Cytogenetic risk group^A					
Favorable	66	17.2	65.1	59.3 – 70.9	<.0001
Intermediate	254	66.3	103.4	98.3 – 108.4	
Unfavorable	63	16.5	112.0	102.1 – 122.0	
FLT3-ITD					
Mutant	113	29.5	111.9	87.8-97.2	<.0001
Wildtype	270	70.5	92.5	103.9-119.8	
NPM1					
Mutant	115	30.0	107.2	99.7 – 114.8	.005
Wildtype	268	70.0	94.3	89.4 – 99.2	
NPM1+/FLT3-ITD-					
Yes	66	17.2	98.0	88.8 - 107.2	.964
No	317	82.8	98.2	93.6 – 102.9	
Induction Treatment					
Standard Dose	188	49.1	98.0	92.5-104.2	.946
High Dose	195	50.9	98.4	92.2-103.9	

^ASlovak et al. (2000)

CI, confidence interval; AML, acute myeloid leukemia; WBC, white blood cell; *FLT3*-ITD, FMS-like kinase 3-internal tandem duplication; *NPM1*, nucleophosmin1

Supplemental Table 8. E1900 Cohort: Cox Model for Overall Survival (n=383, events=275)

	Univariate		Multivariable		Reduced		
Parameter	HR	P	Adj HR	P	Adj HR	95% CI	P
M-score^A	1.1	<.0001	1.1	<.0001	1.1	1.05 – 1.1	<.0001
Age^B	1.2	.004	1.1	.015	1.1	1.03 – 1.3	.010
Female	0.9	.443	0.9	.287	-	-	-
WBC, diagnosis^A	1.1	<.0001	1.05	.003	1.05	1.02 – 1.08	.001
Cytogenetic Risk (reference unfavorable)^C							
Intermediate	0.4	<.0001	0.5	<.0001	0.5	0.4 – 0.7	<.0001
Favorable	0.3	<.0001	0.4	<.0001	0.4	0.2 – 0.6	<.0001
FLT3-ITD+	1.6	<.0001	1.1	.383	-	-	-
NPM1+/FLT3-ITD-	0.5	<.0001	0.5	<.0001	0.4	0.3 – 0.6	<.0001

^Adivided by 10; ^B10-year increase; ^C Slovak et al. (2000)

HR, hazard ratio; CI, confidence interval; WBC, white blood cell; *FLT3*-ITD, FMS-like kinase 3-internal tandem duplication; *NPM1*, nucleophosmin1

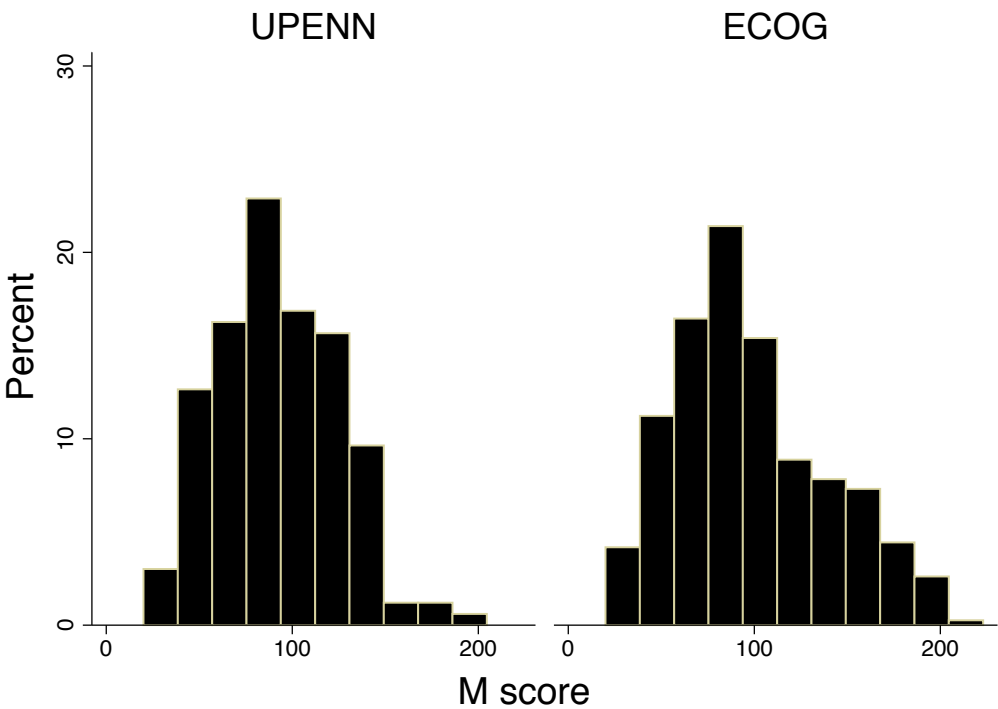
Supplemental Table 9. E1900 Cohort: Logistic Model for Failure to Achieve Complete Remission (n=383, events=140)

	Univariate		Multivariable		Reduced		
Parameter	OR	P	Adj OR	P	Adj OR	95% CI	P
M-score^A	1.1	.001	1.05	.076	-	-	-
Age^B	1.1	.127	1.1	.369	-	-	-
Female	0.8	.241	0.8	.251	-	-	-
WBC, diagnosis^A	1.1	.045	1.1	.066	-	-	-
Cytogenetic Risk (ref unfavorable)^C							
Intermediate	0.6	.054	0.8	.508	0.7	0.4 – 1.3	.32
Favorable	0.2	<.0001	0.3	.006	0.2	0.1 - 0.5	<.0001
FLT3-ITD+	1.6	.044	0.9	.674	-	-	-
NPM1+/FLT3-ITD-	0.3	.001	0.3	.001	0.3	0.1 – 0.6	<.0001

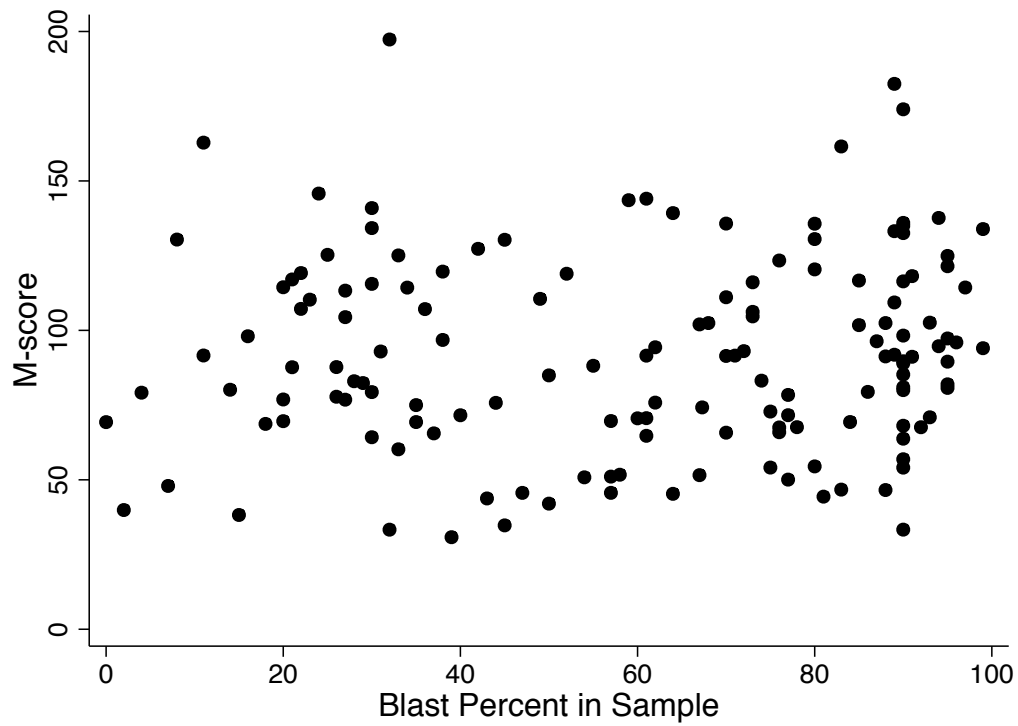
^Adivided by 10, ^B10-year increase, ^CSlovak et al. (200)

OR, odds ratio; CI, confidence interval; WBC, white blood cell; *FLT3*-ITD, FMS-like kinase 3-internal tandem duplication; *NPM1*, nucleophosmin1; WT, wildtype; ref, reference

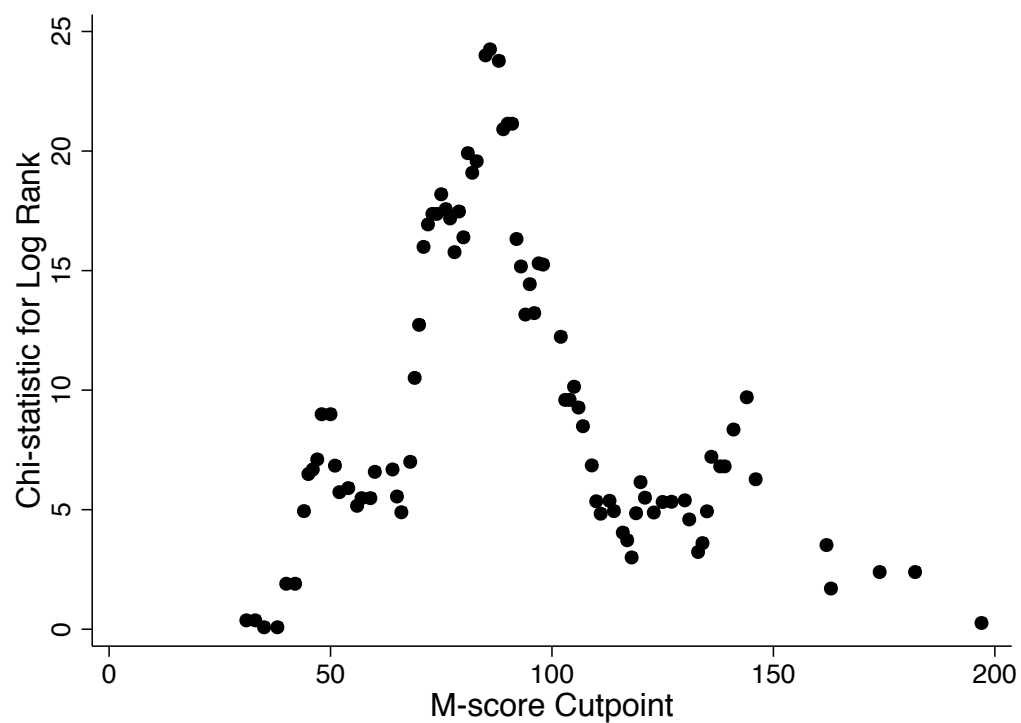
Supplemental Figures:



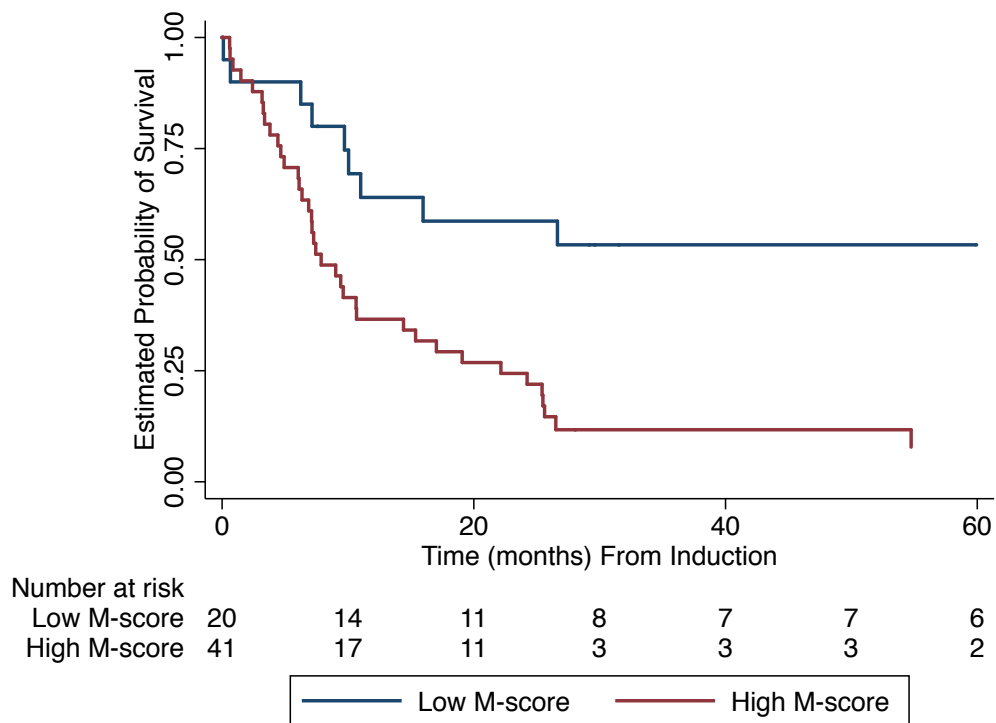
Supplemental Figure 1. M-score Distribution for UPENN and E1900 Cohorts.



Supplemental Figure 2. M-score by Blast Percent in Analyzed Diagnostic Sample in UPENN Cohort

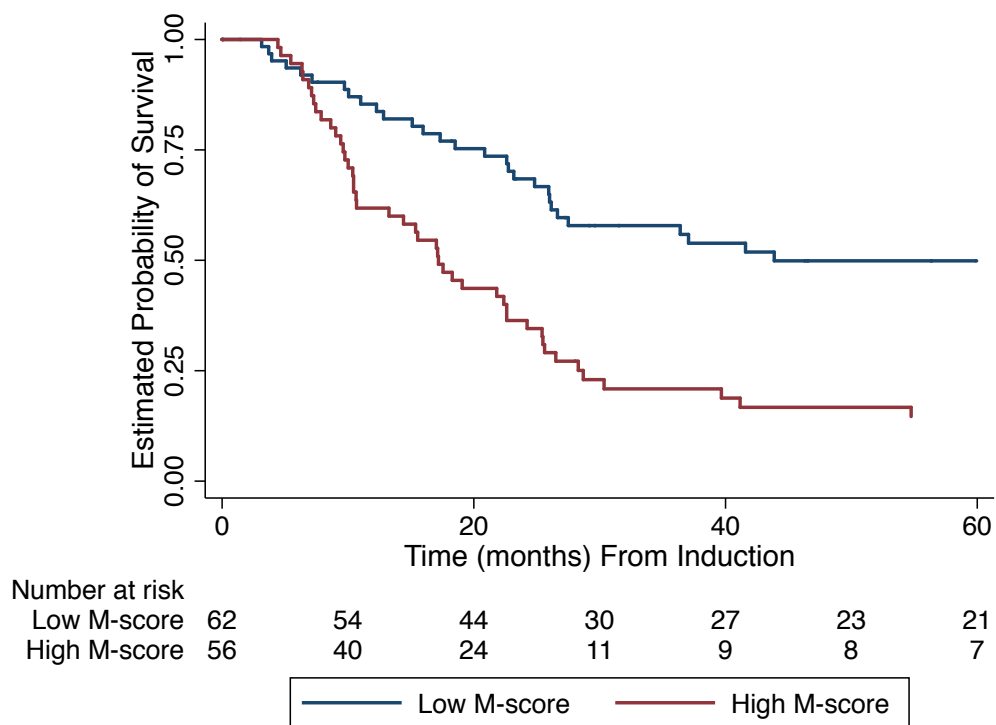


Supplemental Figure 3. Chi-statistic by M-score Cut-point in UPENN Cohort
(Optimal cut-point determined to be 86)



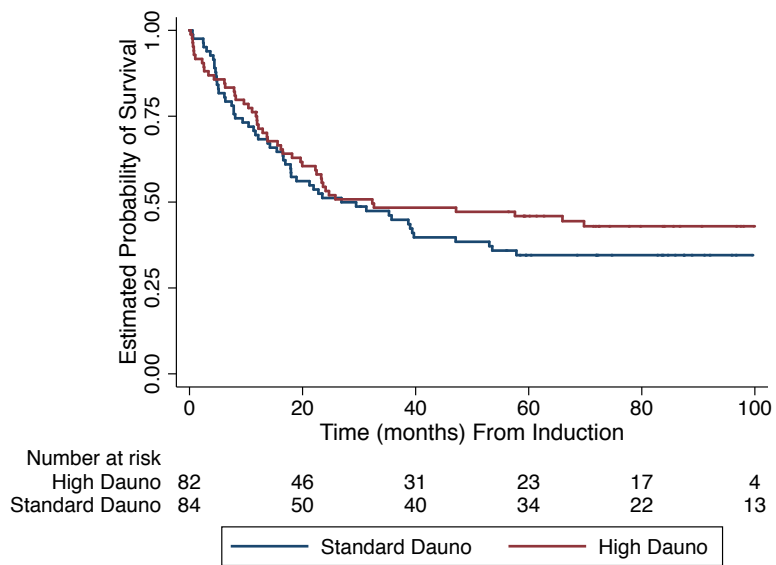
Supplemental Figure 4. Kaplan-Meier Curves of Overall Survival in UPENN

Patients with Intermediate Cytogenetics and *FLT3*-ITD mutation (n=61; log-rank P=0.001)

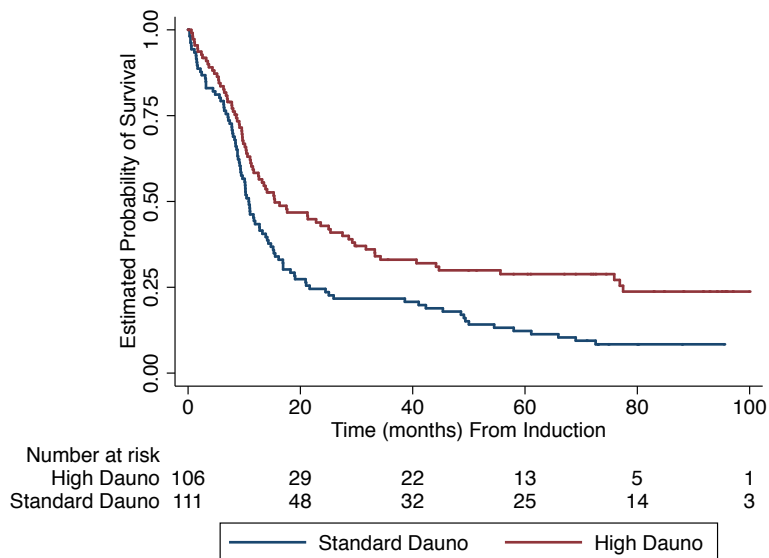


Supplemental Figure 5. Kaplan-Meier Curves of Overall Survival in UPENN Patients Who Achieved Complete Remission (n=118; log-rank $P < 0.00001$)

A)



B)



Supplemental Figure 6. E1900 Cohort: Kaplan Meier Curves of Overall Survival

by Daunorubicin Dose Stratified by Low and High M-score A) Low M-score;

n=166, log-rank P=.328 B) High M-score; n=217, log-rank P=.001