

Clinical relevance of proteomic profiling in *de novo* pediatric acute myeloid leukemia: a Children's Oncology Group study

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Supplemental methods

Statistical analysis

Proportions were compared between protein SIGs and categorical variables using Pearson's Chi-square test or continuous variables using the Kruskal-Wallis test. Networks were constructed based the STRING database¹ and computationally reconstructed interactions from the RPPA data using graphical lasso² and StARS.³ Networks were visualized using Cytoscape (version 3.8.0).^{4,5} Proteins significantly aberrantly regulated compared to the normal CD34+ samples were identified using the Wilcoxon signed-rank test with a Bonferroni adjusted *p*-value. Statistical analyses were performed in R version 1.3.959 2009-2020 (RStudio, Inc., Boston, MA) or SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Supplemental Table S2 summarize cox analyses for outcome reported in the paper in Figures 3D, 5, S3, S7 and S8. We arbitrarily set a baseline group for each of the analyses where there were 3 or more groups being compared. Some of these groups did not have any events (100% survival or 0% RR) and in such cases, there is no convergence of HR estimates.

Quality control

Samples with a highly significantly greater number (>20%) of proteins with extremely high or low expression ($\geq 3SD$ from the median) might have problematic "handling" effects.⁶ This metric identified six pre-treatment samples with quality control issues which were excluded.

Gene expression profiling

Ribodepleted RNA-sequencing expression data was generated for 390 of the 500 RPPA-patients as described. Data was generously provided by Meshinchi et al.⁷

Transcriptome mutation calls

Single-nucleotide variants and indels were analyzed utilizing a custom pipeline (British Columbia Cancer Agency, British Columbia, Canada). Targeted alignment of custom in silico probes were produced for 1160 physical positions across 166 genes to detect a “hit count” of variant reads and compared with positive controls (patient samples with validated mutations) and negative controls (normal BM). A cut-off of seven variant hit counts was used.

List of References

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Supplemental table and figure legends

Supplemental Table S1. “Rosetta Stone” for the antibody and protein nomenclature together with the RPPA staining details/

Supplemental Table S2. Cox analyses for outcome reported in Figures 3D, 5, S3, S7 and S8.

Supplemental Table S3. Patient characteristics and disease features for the four heat shock protein clusters.

Supplemental Table S4. List of the 116 protein clusters that form the 12 protein constellations.

Supplemental Table S5. Cross tables Proteomic-Risk groups, AAML1031 risk groups and conventional cytogenetics risk groups.

Supplemental Table S6. (A) Proteins that significantly changed between the pre-treatment samples and the 10hr-post-treatment samples. (B) Proteins that significantly changed between the pre-treatment samples and the 24hr-post-treatment samples. (C) Seventy-six proteins that had changed significantly after chemotherapy exposure after both 10 hours and 24 hours. To show the number of proteins that had changed within each PFG, proteins were grouped within their PGFs.

Supplemental Table S7. List of existing drugs used in the clinical setting that are potentially testable within specific patient subgroups, based on protein expression significantly different from normal.

Supplemental Figure S1. Relative protein expression in pediatric AML and normal CD34+ samples. (A) Unsupervised hierarchical clustering, and (B) PCA of the 500 pediatric AML patient samples (light blue) and the 30 normal CD34+ cells.

Supplemental Figure S2. PFG associated *p*-values. Bar graph showing the associated *p*-values for (A) OS, (B) EFS and (C) CR duration. Light blue bars indicate all 410 patients, dark blue bars the ADE-treated patients and red bars patients treated with ADEB.

Supplemental Figure S3. Kaplan-Meier survival curves for EFS and RR for the four heat shock PCs. (A) EFS and (B), RR for all patients (left), treated with ADE alone (middle) or ADE plus bortezomib addition (right). Each line indicates patients in one of the four identified heat shock PCs: red (C1), pink (C2), yellow (C3) and green (C4).

Supplemental Figure S4. Cluster stability for the identified PrCONs and PrSIGs. Robustness of the PrCONs and PrSIG was evaluated tested using a training set (n=355) and test set (n=145). Sets were created by using random sampling. (A) To test PrCON-membership stability, block-clustering was first applied to the training set. PrCON-membership for the 12 PrCONs is shown in the left column. Secondly, block-clustering algorithm was applied to the test set. Pearson's chi-square between PrCON-membership of the training and test set resulted in a p -value <0.0001 . (B) To assess PrSIG-stability, PrSIG-membership of the training set (based on the block-clustering algorithm used in A) was used. Linear-discriminant analysis of the test set was applied to the test set to predict PrSIG-membership of the test set. Pearson's chi-square was used to compare overlapping PrSIG-membership in the training and test set to PrSIG-membership of the 500 patients. This resulted in a significant p -value <0.0001 . Left column: PrSIG-membership of the 500 patients. Middle column: PrSIG-membership of the training and test set. Right column indicates whether sample was assigned to the training (blue) or test set (red).

Supplemental Figure S5. Correlation between RPPA protein abundance and mRNA. Histogram showing the Pearson's correlation coefficient in 390 of the 500 AML patients for 205 total protein targets. Positive correlation was found between 171 of the mRNA and protein levels.

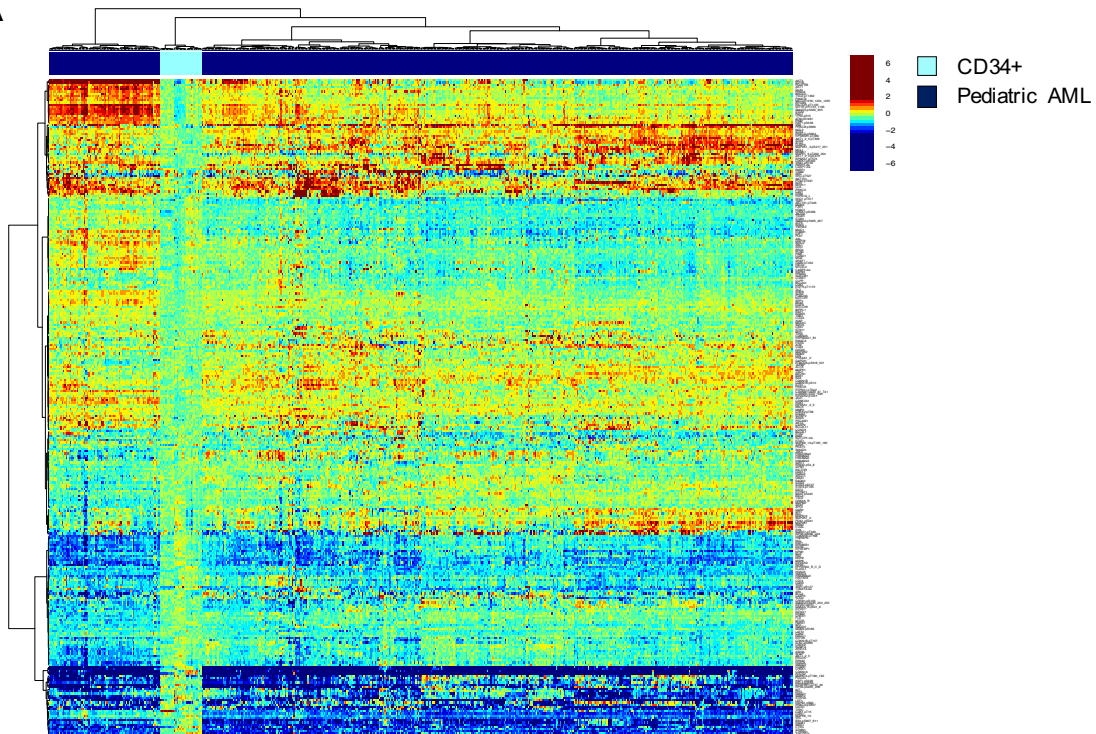
Supplemental Figure S6. MetaGalaxy annotated with clinical, disease and molecular characteristics. MetaGalaxy annotated with cytogenetics, mutational state for CEBPA, FLT3-ITD, NPM1 and KIT, fusion genes CBFA2T3-GLIS2, NUP98-KDM5A, NUP98-NSD1, age, gender, FAB classification, ethnicity, CNS status, race and WBC count.

Supplemental Figure S7. Kaplan-Meier survival curves for OS, EFS and RR for the 9 PrSIGs. Survival analysis for (A) all, (B) ADE and, (C) ADEB treated patients. Curves are shown for OS (left), EFS (middle) and RR (right).

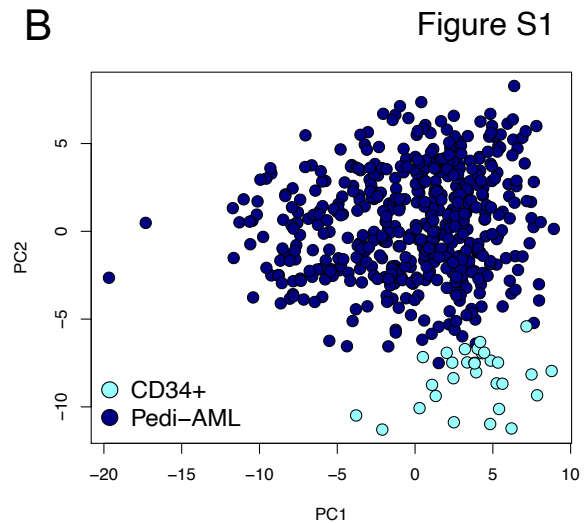
Supplemental Figure S8. Kaplan-Meier overall survival curves the 3 Proteomic Risk groups within the normal karyotype patients (n=114).

Supplemental Figure S9. Kaplan-Meier survival curves for OS, EFS and RR for the 9 PrSIGs. Survival analysis for all (left), ADE (middle), and ADEB (right) treated patients in **(A)** AAML1031 low and **(B)** high-risk patients

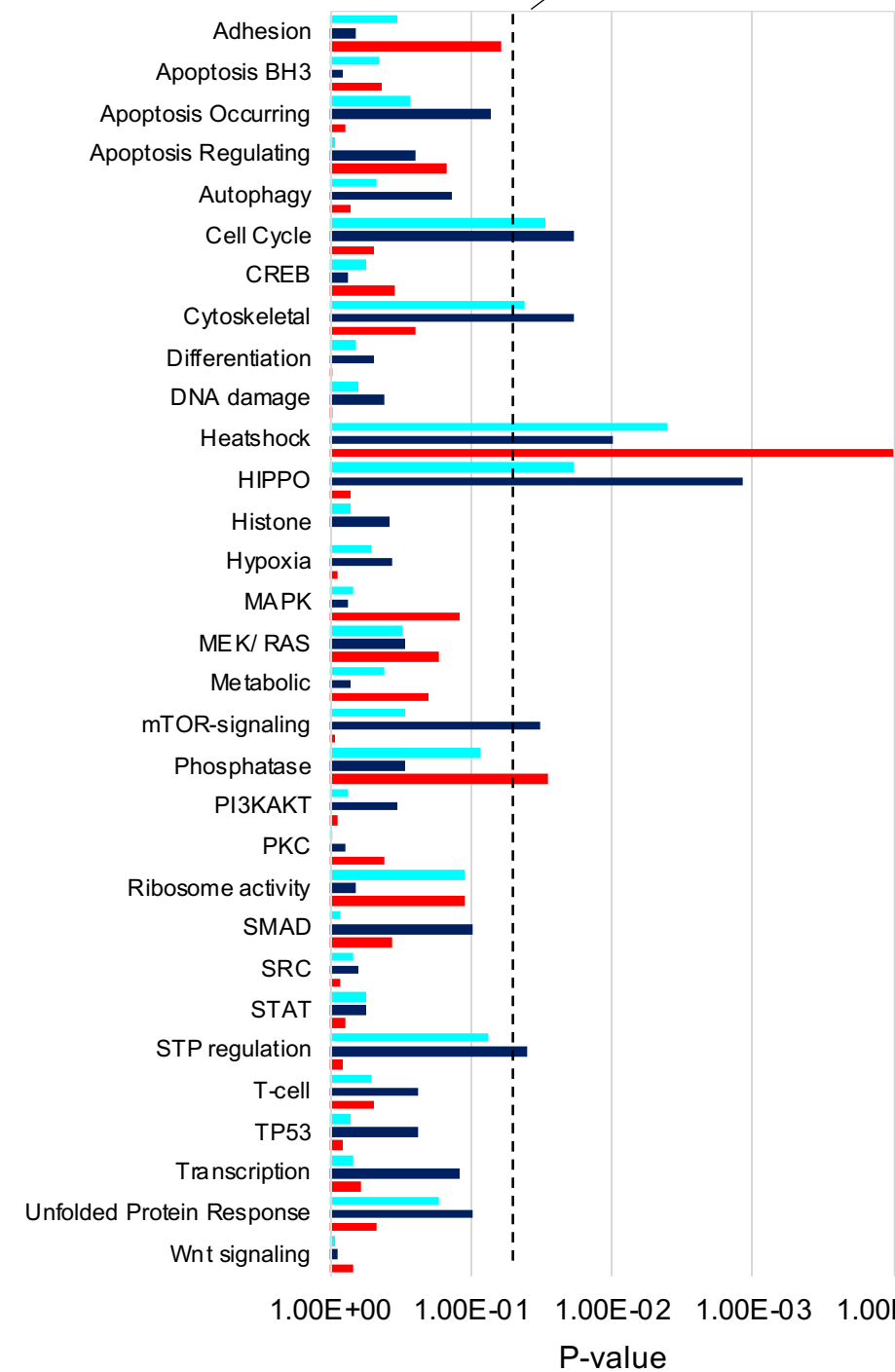
A



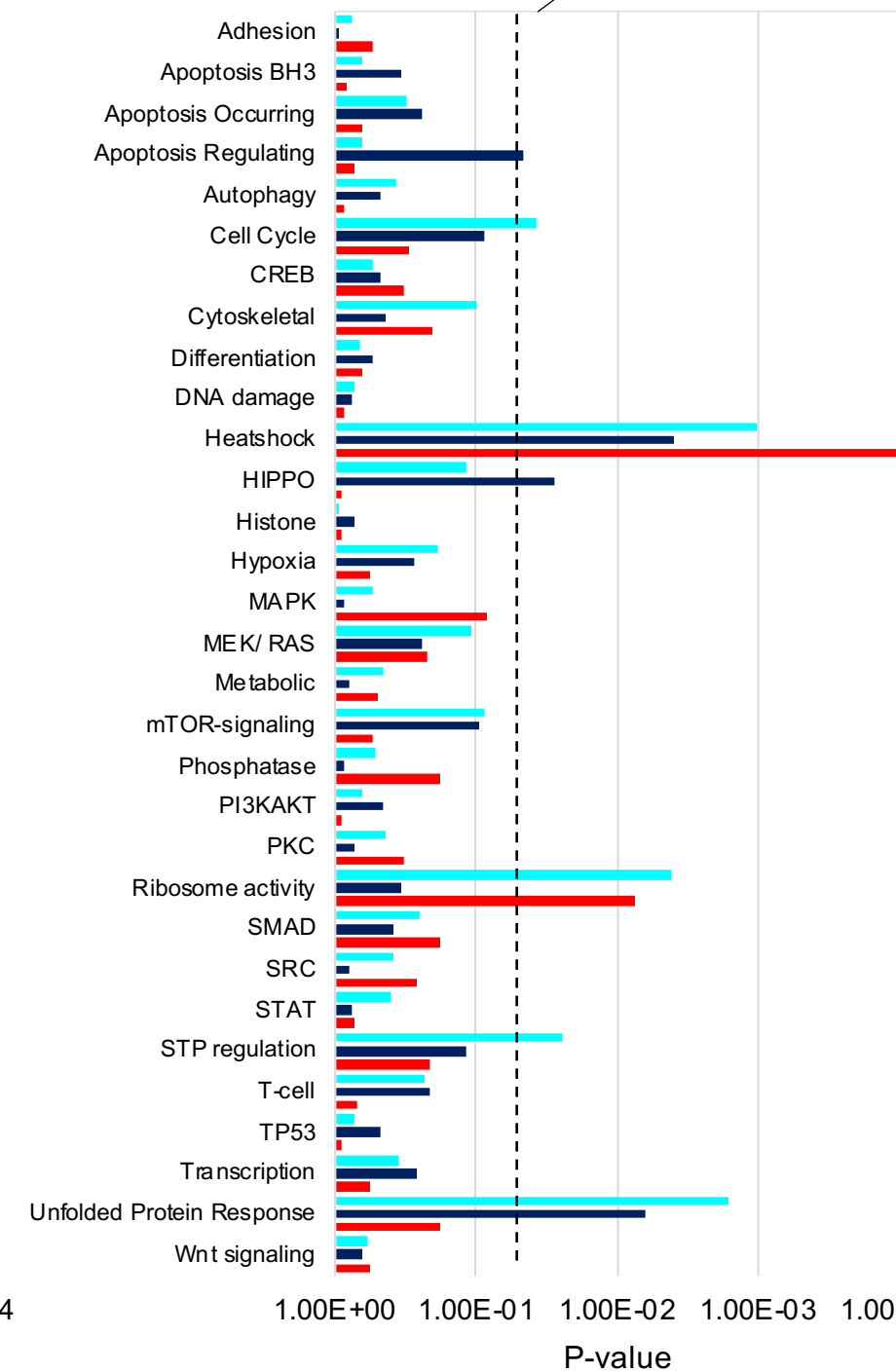
B



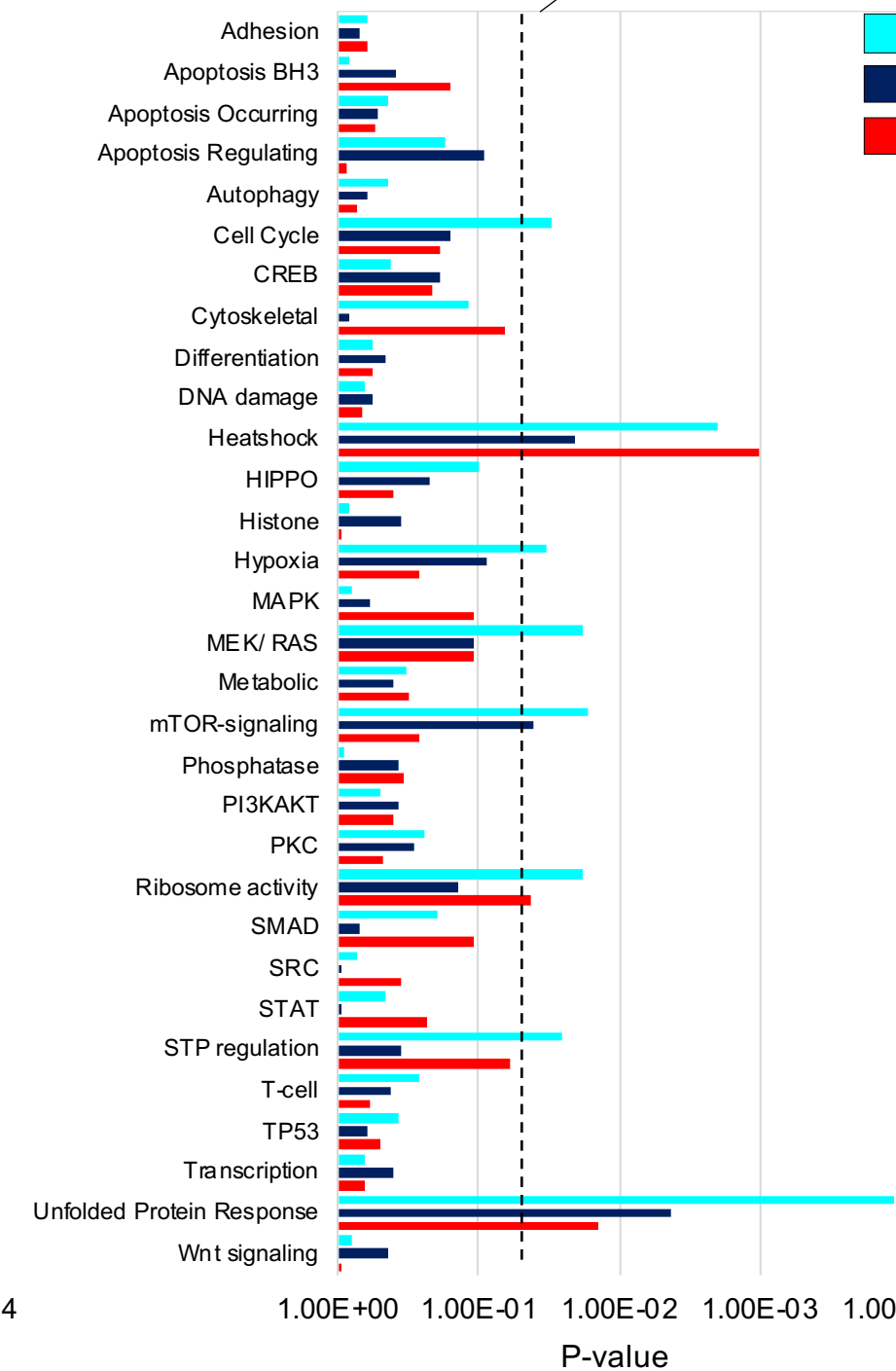
PFG associated with OS 0.5E-1



PFG associated with EFS 0.5E-1

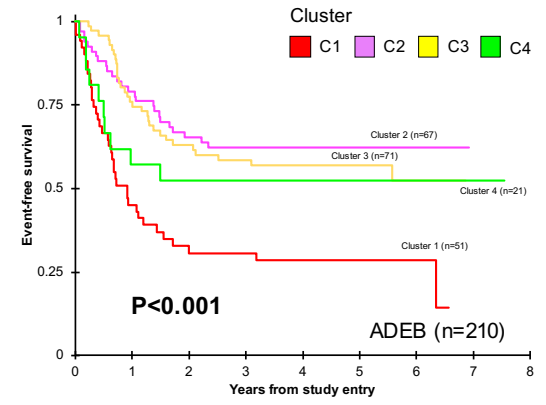
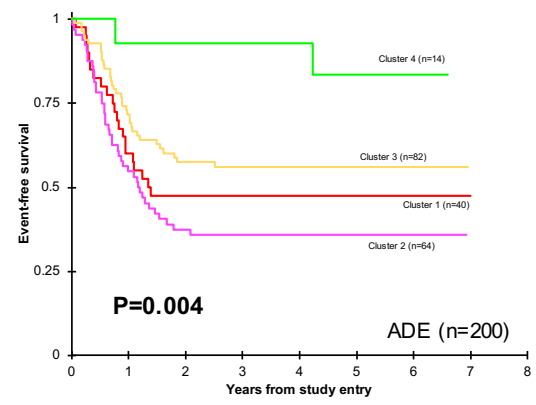
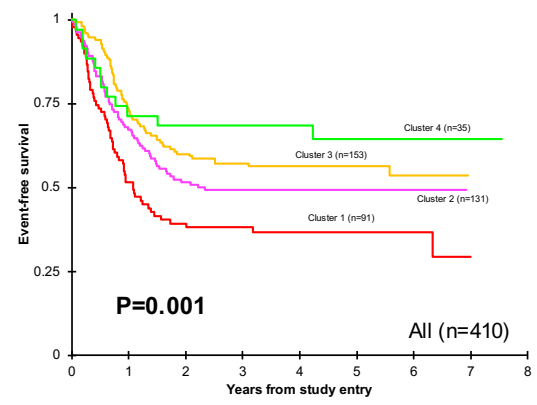


PFG associated with CR 0.5E-1



All
ADE
ADEB

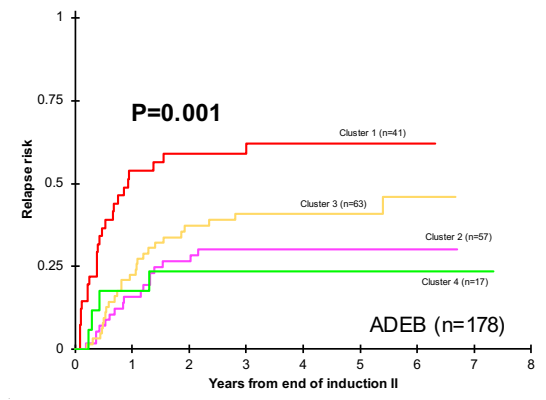
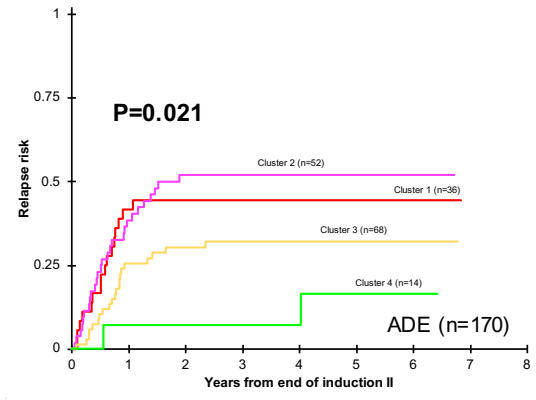
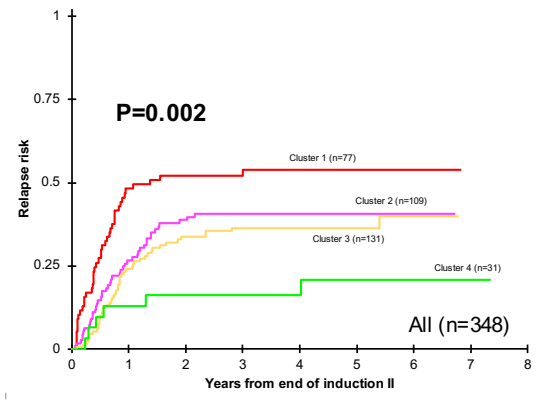
A



Cluster

■ C1 ■ C2 ■ C3 ■ C4

B



A

TRAIN (n=355)





TEST (n=145)

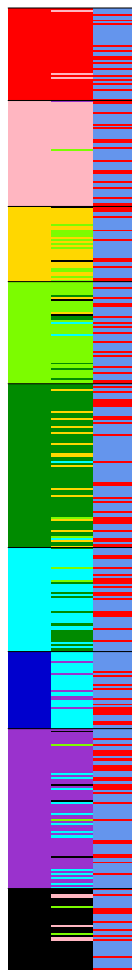
Protein Constellations (n=116)

**B**

øæ'!^Åj|

 Train set
 Test set

Signatures (n=500)



$\hat{\rho}_{\hat{A}\hat{B}}$

Mean = 0.17

Probability density

3

2

1

0

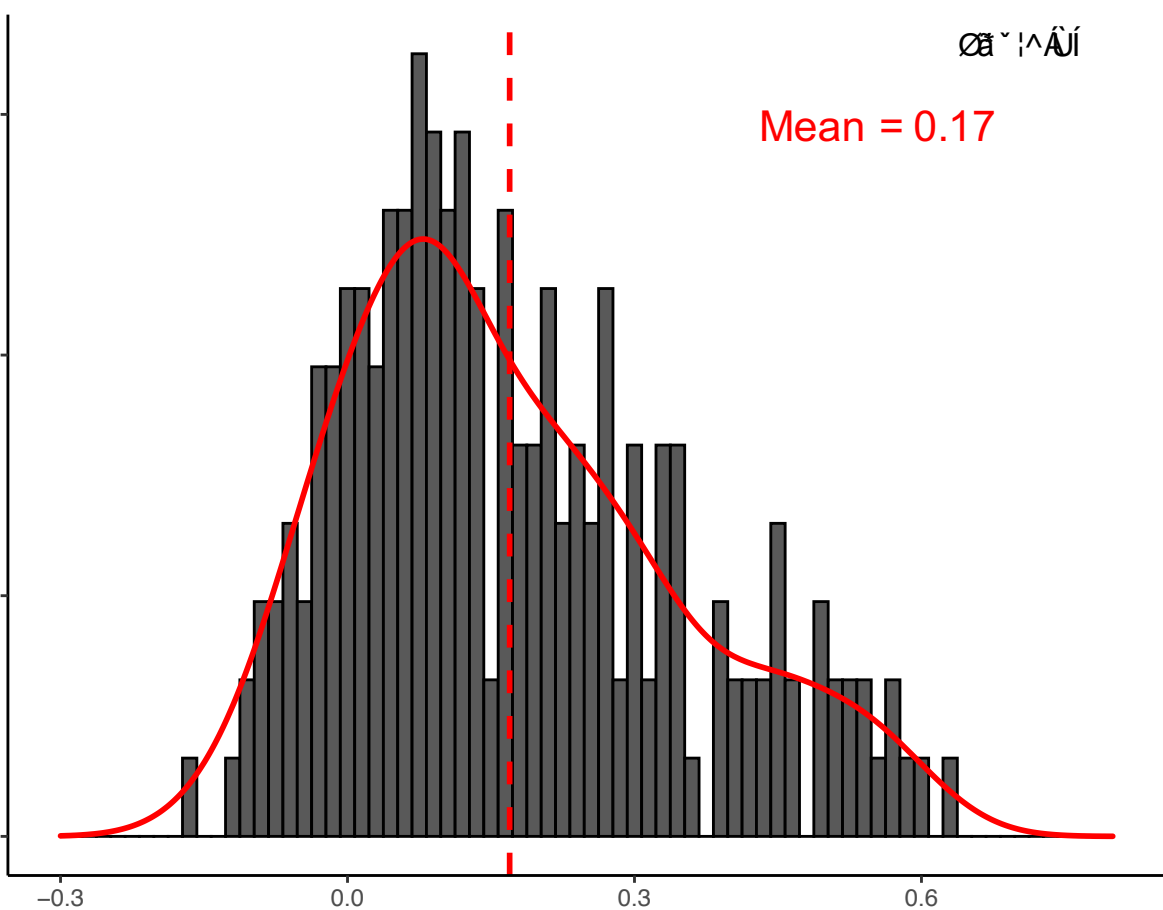
-0.3

0.0

0.3

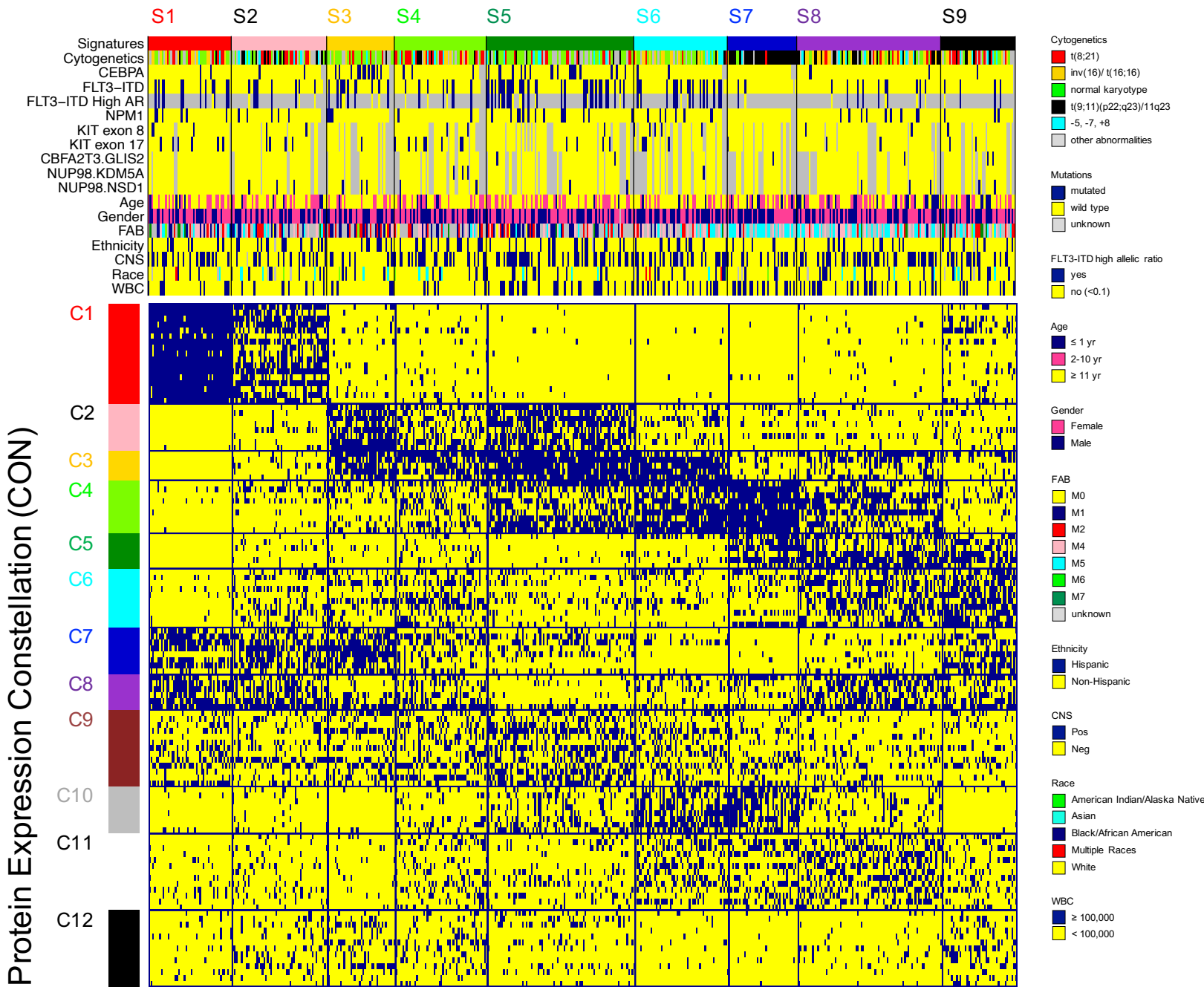
0.6

Pearson's correlation coefficient



Protein Expression Signature (SIG)

øã ~ |^ÀÛ



Overall survival

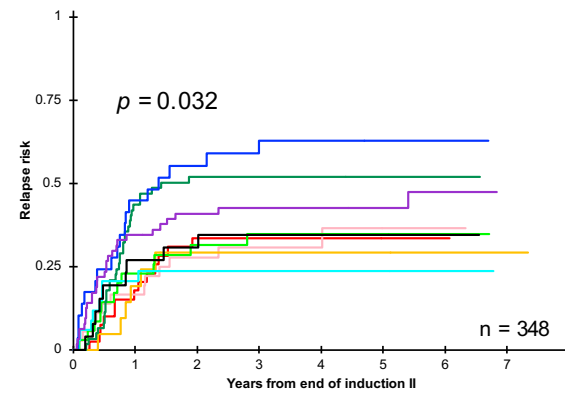
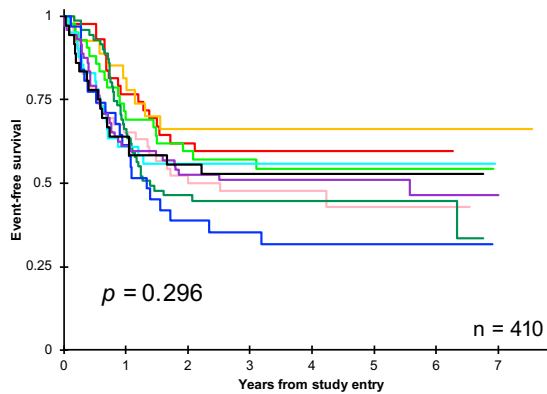
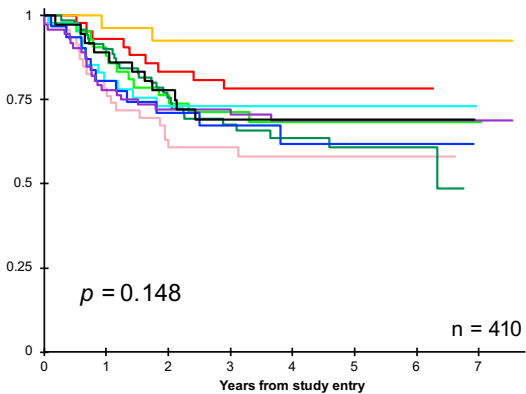
Event free survival

Relapse risk

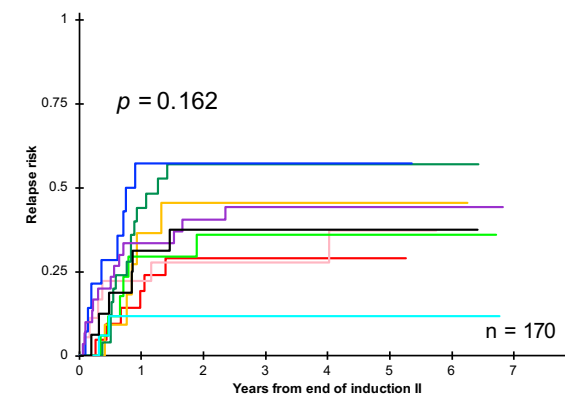
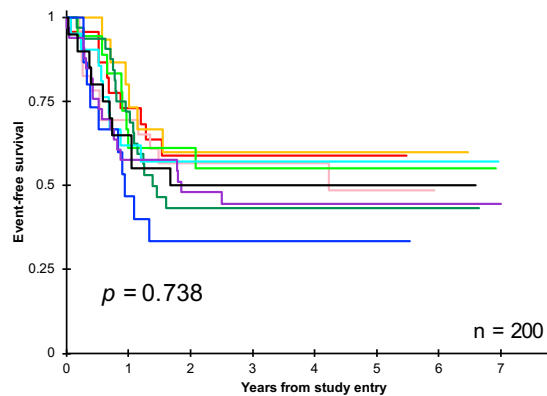
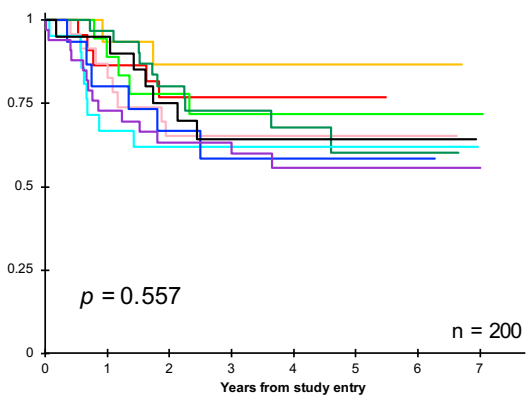
Signature

- S1
- S2
- S3
- S4
- S5
- S6
- S7
- S8
- S9

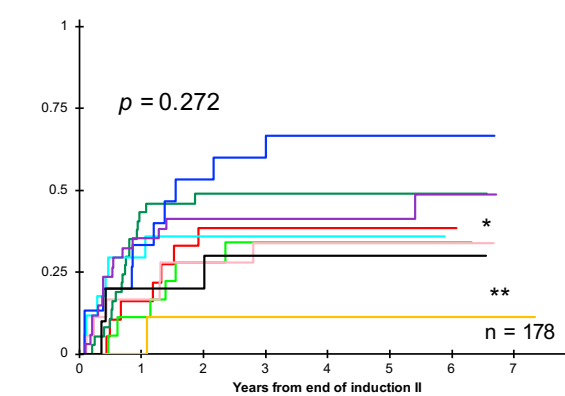
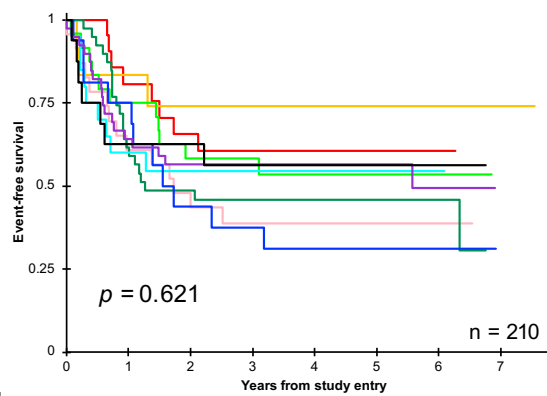
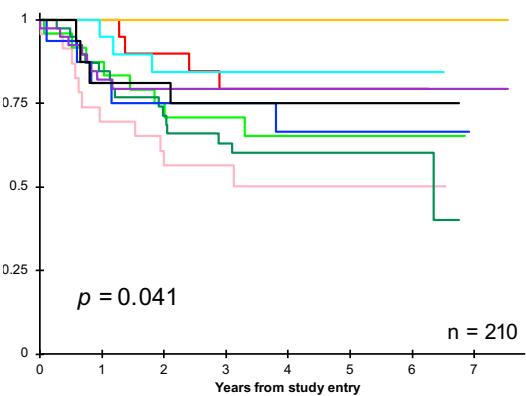
AI1

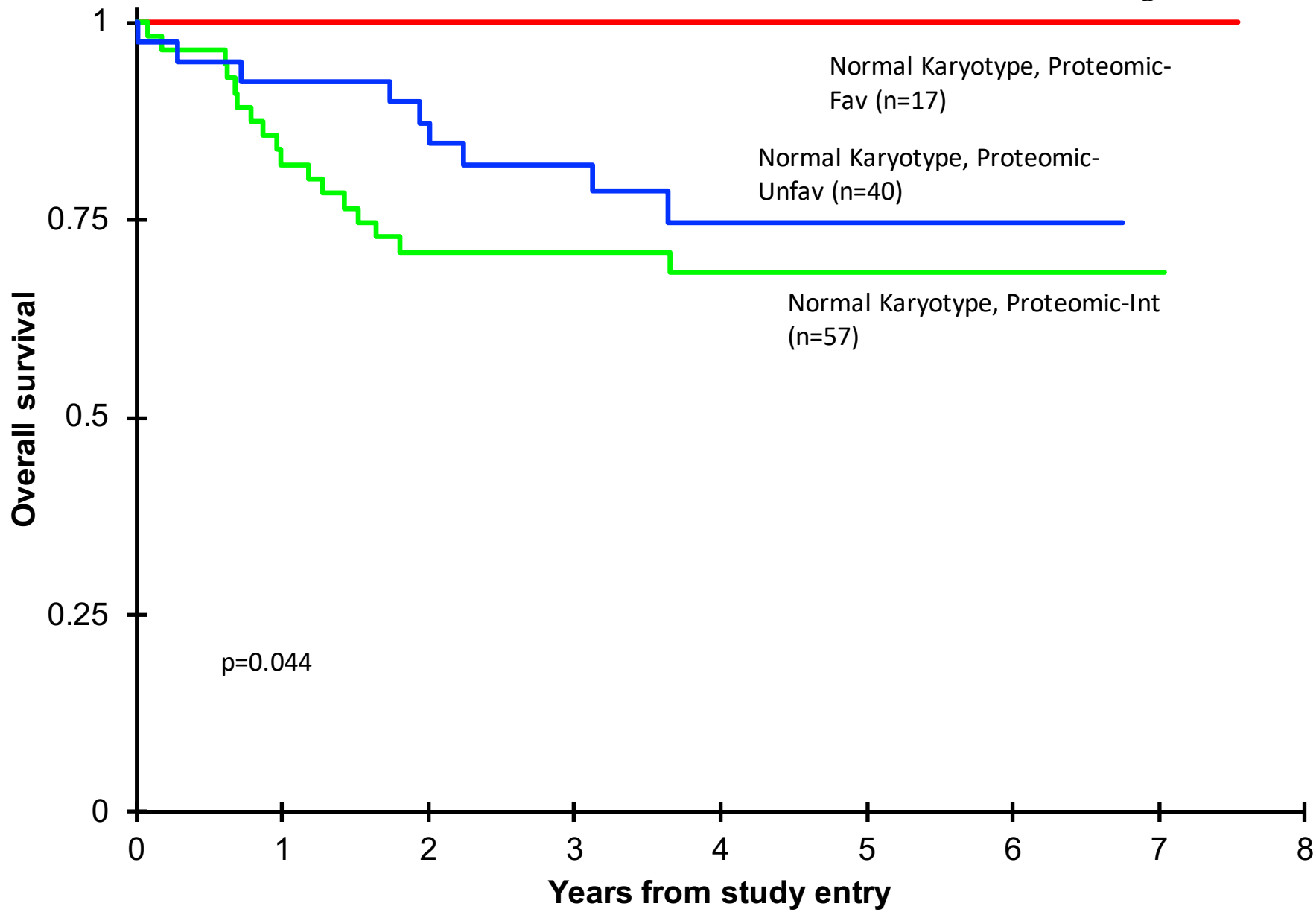


ADE



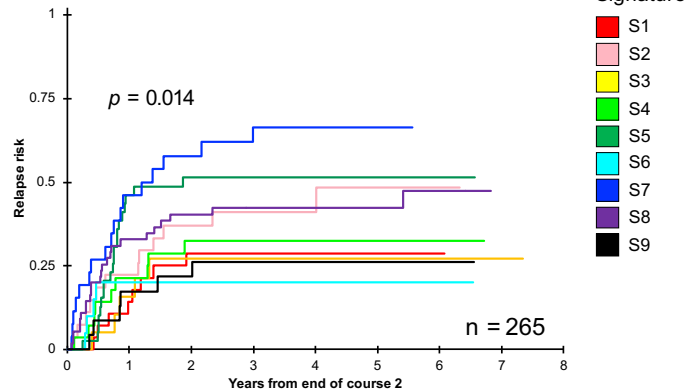
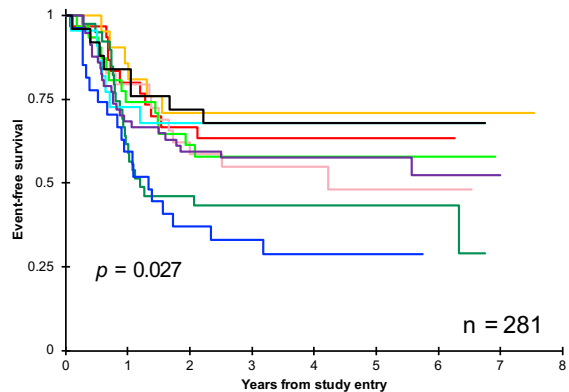
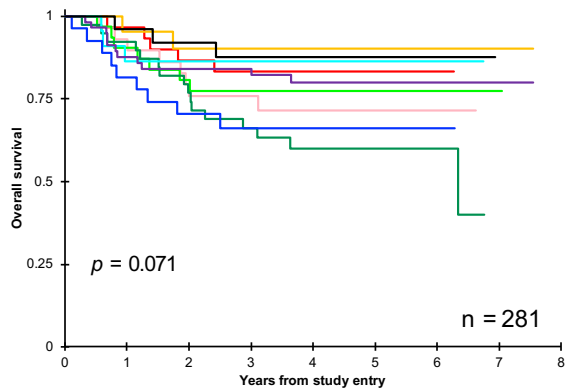
ADEB





A

AAML1031 low-risk



B

AAML1031 high-risk

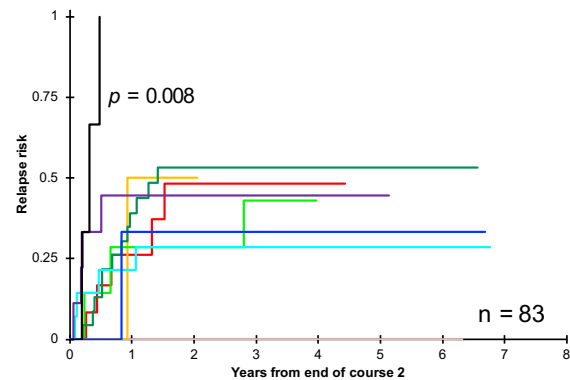
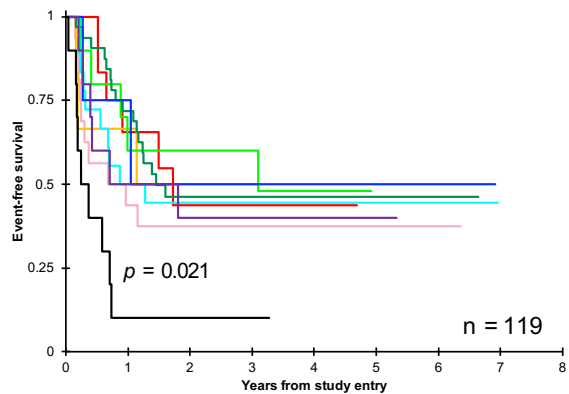
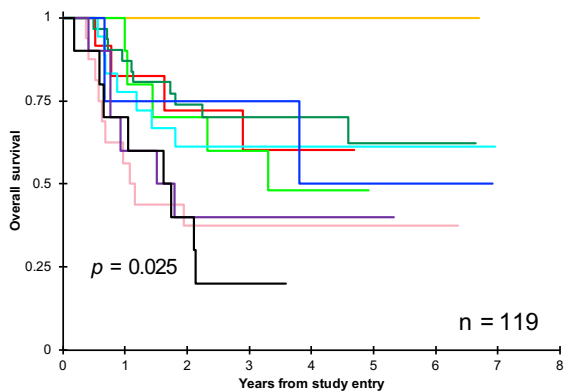


Table S2

Figure 3D

All patients (n=410)		OS from study entry			
	N	HR	95% CI	p	
Cluster					
3	153	1			
1	91	2.10	1.34 - 3.29	0.001	
2	131	1.32	0.84 - 2.06	0.227	
4	35	0.83	0.37 - 1.87	0.657	

Cluster 3 is selected as baseline group (largest group with good outcome)

ADE (n=200)		OS from study entry			
	N	HR	95% CI	p	
Cluster					
3	82	1			
1	40	1.42	0.74 - 2.75	0.291	
2	64	1.84	1.05 - 3.22	0.033	
4	14	no convergence			

No convergence because of no events in Cluster 4 for this group (100% survival)

ADEB (n=210)		OS from study entry			
	N	HR	95% CI	p	
Cluster					
3	71	1			
1	51	2.98	1.57 - 5.65	<0.001	
2	67	0.83	0.39 - 1.78	0.635	
4	21	1.88	0.77 - 4.61	0.168	

Cluster 2 (n=131)		OS from study entry			
	N	HR	95% CI	p	
Treatment					
ADE	64	1			
ADEB	67	0.33	0.17 - 0.66	0.002	

Cluster 4 (n=35)		OS from study entry			
	N	HR	95% CI	p	
Treatment					
ADEB	21	1			
ADE	14	no convergence			

No convergence because of no events in Cluster 4 for this group (100% survival)

Figure 5A

All patients	OS from study entry				RR from end of Induction II			
	N	HR	95% CI	p	N	HR	95% CI	p
Signature								
S1	44	1			41	1		
S2	46	2.32	1.05 - 5.12	0.038	36	1.02	0.48 - 2.18	0.960
S3	27	0.34	0.07 - 1.55	0.162	21	0.85	0.34 - 2.15	0.729
S4	42	1.52	0.65 - 3.55	0.336	35	1.07	0.50 - 2.30	0.861
S5	71	1.86	0.87 - 3.97	0.110	62	1.82	0.98 - 3.37	0.056
S6	41	1.38	0.57 - 3.33	0.477	34	0.75	0.30 - 1.85	0.530
S7	31	1.87	0.78 - 4.52	0.163	29	2.41	1.21 - 4.79	0.012
S8	72	1.61	0.74 - 3.51	0.227	64	1.57	0.82 - 2.99	0.176
S9	36	1.51	0.62 - 3.63	0.364	26	1.09	0.47 - 2.53	0.837

Figure 5B

All patients	OS from study entry				RR from end of Induction II			
	N	HR	95% CI	p	N	HR	95% CI	p
Proteomic risk class								
Intermediate	235	1			200	1		
Favorable	27	0.24	0.06 - 0.96	0.044	21	0.74	0.33 - 1.65	0.462
Unfavorable	148	1.41	0.98 - 2.01	0.061	127	1.47	1.04 - 2.06	0.028

Figure 5C

	Signatures=8				Signatures=3			
	OS from study entry				RR from end of Induction II			
	N	HR	95% CI	p	N	HR	95% CI	p
Treatment								
ADE	33	1			11	1		
ADEB	39	0.43	0.18 - 1.03	0.058	10	0.18	0.02 - 1.37	0.098

Figure 5D

Since there are no events (100% survival, 0% RR) for the ADEB group, OS and RR analyses do not converge

Figure S3A

All patients (n=410)		EFS from study entry			
	N	HR	95% CI	p	
Cluster					
3	153	1			
1	91	1.90	1.34 - 2.71	<0.001	
2	131	1.26	0.90 - 1.78	0.179	
4	35	0.79	0.43 - 1.46	0.450	

ADE (n=200)		EFS from study entry			
	N	HR	95% CI	p	
Cluster					
3	82	1			
1	40	1.34	0.78 - 2.31	0.285	
2	64	1.80	1.15 - 2.83	0.011	
4	14	0.26	0.06 - 1.08	0.064	

ADEB (n=210)		EFS from study entry			
	N	HR	95% CI	p	
Cluster					
3	71	1			
1	51	2.50	1.55 - 4.04	<0.001	
2	67	0.85	0.50 - 1.44	0.551	
4	21	1.34	0.66 - 2.73	0.423	

Figure S3B

CR patients (n=348)		RR from end of Induction II			
	N	HR	95% CI	p	
Cluster					
3	131	1			
1	77	1.89	1.23 - 2.89	0.004	
2	109	1.16	0.78 - 1.73	0.468	
4	31	0.49	0.21 - 1.14	0.099	

ADE (n=170)		RR from end of Induction II			
	N	HR	95% CI	p	
Cluster					
3	68	1			
1	36	1.64	0.85 - 3.17	0.141	
2	52	1.92	1.10 - 3.37	0.022	
4	14	0.39	0.10 - 1.58	0.189	

ADEB (n=178)		RR from end of Induction II			
	N	HR	95% CI	p	
Cluster					
3	63	1			
1	41	2.11	1.21 - 3.68	0.009	
2	47	0.68	0.38 - 1.22	0.196	
4	17	0.55	0.18 - 1.64	0.282	

Figure S7 - all (OS and RR are same as Figure 5A)

All patients	OS from study entry				EFS from study entry			RR from end of Induction II				
	N	HR	95% CI	p	HR	95% CI	p	N	HR	95% CI	p	
Signature												
S1	44	1			1			41	1			
S2	46	2.32	1.05 - 5.12	0.038	1.58	0.85 - 2.93	0.145	36	1.02	0.48 - 2.18	0.960	
S3	27	0.34	0.07 - 1.55	0.162	0.83	0.37 - 1.86	0.650	21	0.85	0.34 - 2.15	0.729	
S4	42	1.52	0.65 - 3.55	0.336	1.19	0.62 - 2.28	0.611	35	1.07	0.50 - 2.30	0.861	
S5	71	1.86	0.87 - 3.97	0.110	1.56	0.88 - 2.75	0.126	62	1.82	0.98 - 3.37	0.056	
S6	41	1.38	0.57 - 3.33	0.477	1.30	0.67 - 2.52	0.440	34	0.75	0.30 - 1.85	0.530	
S7	31	1.87	0.78 - 4.52	0.163	2.10	1.11 - 3.98	0.023	29	2.41	1.21 - 4.79	0.012	
S8	72	1.61	0.74 - 3.51	0.227	1.46	0.82 - 2.60	0.200	64	1.57	0.82 - 2.99	0.176	
S9	36	1.51	0.62 - 3.63	0.364	1.38	0.71 - 2.71	0.344	26	1.09	0.47 - 2.53	0.837	

Figure S7 - ADE only

All patients	OS from study entry				EFS from study entry			RR from end of Induction II				
	N	HR	95% CI	p	HR	95% CI	p	N	HR	95% CI	p	
Signature												
S1	23	1			1			22	1			
S2	23	1.62	0.53 - 4.95	0.399	1.27	0.53 - 3.07	0.594	18	1.26	0.40 - 3.91	0.694	
S3	15	0.55	0.11 - 2.82	0.472	0.92	0.33 - 2.58	0.868	11	1.67	0.55 - 5.09	0.363	
S4	18	1.18	0.34 - 4.07	0.797	1.08	0.42 - 2.81	0.870	17	1.29	0.43 - 3.89	0.654	
S5	32	1.37	0.47 - 4.01	0.564	1.43	0.64 - 3.19	0.378	25	2.29	0.92 - 5.68	0.074	
S6	21	1.98	0.65 - 6.06	0.231	1.14	0.45 - 2.87	0.785	17	0.39	0.08 - 1.98	0.255	
S7	15	1.97	0.60 - 6.44	0.265	2.15	0.87 - 5.30	0.096	14	2.82	0.96 - 8.29	0.060	
S8	33	2.21	0.80 - 6.14	0.128	1.57	0.71 - 3.51	0.267	30	1.83	0.70 - 4.77	0.219	
S9	20	1.54	0.49 - 4.85	0.462	1.38	0.56 - 3.39	0.488	16	1.40	0.46 - 4.27	0.551	

Figure S7 - ADEB only

All patients	OS from study entry				EFS from study entry			RR from end of Induction II				
	N	HR	95% CI	p	HR	95% CI	p	N	HR	95% CI	p	
Signature												
S1	21	1			1			19	1			
S2	23	3.24	1.03 - 10.2	0.045	1.93	0.81 - 4.59	0.140	18	0.83	0.30 - 2.29	0.719	
S3	12	no convergence			0.67	0.18 - 2.53	0.557	10	0.24	0.03 - 1.84	0.169	
S4	24	1.91	0.58 - 6.35	0.290	1.30	0.52 - 3.23	0.572	18	0.89	0.31 - 2.57	0.832	
S5	39	2.43	0.81 - 7.26	0.113	1.68	0.75 - 3.77	0.212	37	1.48	0.65 - 3.39	0.351	
S6	20	0.79	0.18 - 3.54	0.760	1.53	0.59 - 3.97	0.381	17	1.13	0.37 - 3.46	0.834	
S7	16	1.78	0.48 - 6.65	0.388	2.09	0.84 - 5.19	0.114	15	2.07	0.85 - 5.00	0.108	
S8	39	1.14	0.34 - 3.78	0.833	1.38	0.60 - 3.17	0.451	34	1.35	0.56 - 3.22	0.506	
S9	16	1.38	0.35 - 5.54	0.646	1.37	0.50 - 3.78	0.546	10	0.79	0.21 - 3.01	0.729	

Figure S8 - low risk patients only

Low risk	OS from study entry				EFS from study entry				RR from end of Induction II			
	N	HR	95% CI	p	HR	95% CI	p	N	HR	95% CI	p	
Signature												
S1	30	1			1			28	1			
S2	29	1.76	0.58 - 5.38	0.322	1.35	0.61 - 2.97	0.457	27	1.75	0.74 - 4.15	0.203	
S3	21	0.57	0.11 - 2.92	0.498	0.74	0.27 - 1.99	0.546	19	0.93	0.32 - 2.75	0.898	
S4	31	1.41	0.45 - 4.44	0.558	1.18	0.53 - 2.63	0.693	28	1.20	0.47 - 3.04	0.709	
S5	39	2.66	0.98 - 7.27	0.056	1.86	0.91 - 3.82	0.091	39	2.16	0.98 - 4.75	0.056	
S6	22	0.85	0.20 - 3.56	0.822	0.93	0.36 - 2.39	0.876	20	0.75	0.22 - 2.59	0.649	
S7	27	2.40	0.80 - 7.15	0.117	2.58	1.23 - 5.42	0.013	26	3.20	1.42 - 7.19	0.005	
S8	57	1.20	0.42 - 3.46	0.735	1.30	0.64 - 2.65	0.465	55	1.84	0.84 - 4.01	0.128	
S9	25	0.69	0.17 - 2.91	0.617	0.84	0.34 - 2.09	0.710	23	0.90	0.32 - 2.51	0.837	

Figure S8 - high risk patients only

High risk	OS from study entry				EFS from study entry				RR from end of Induction II			
	N	HR	95% CI	p	HR	95% CI	p	N	HR	95% CI	p	
Signature												
S1	13	1			1			13	1			
S2	16	2.53	0.79 - 8.08	0.117	1.72	0.63 - 4.75	0.292	9	no convergence			
S3	6	no convergence			1.20	0.30 - 4.82	0.794	2	1.11	0.18 - 6.89	0.907	
S4	10	1.35	0.36 - 5.03	0.655	0.99	0.30 - 3.25	0.987	7	0.95	0.25 - 3.67	0.940	
S5	32	0.87	0.27 - 2.77	0.811	1.05	0.41 - 2.66	0.923	23	1.27	0.49 - 3.34	0.626	
S6	18	1.12	0.33 - 3.83	0.857	1.33	0.48 - 3.65	0.586	14	0.64	0.17 - 2.46	0.520	
S7	4	1.30	0.24 - 7.09	0.766	1.05	0.21 - 5.22	0.951	3	0.68	0.09 - 5.19	0.714	
S8	10	2.17	0.61 - 7.70	0.231	1.44	0.46 - 4.46	0.530	9	1.29	0.31 - 5.44	0.731	
S9	10	3.18	0.96 - 10.6	0.060	4.63	1.64 - 13.1	0.004	3	8.74	3.09 - 24.7	<0.001	

No convergence because of no events in S2 for this group (0% RR)

No convergence because of no events in S3 for this group (100% survival)

Table S3

	Variable	Total (n=500)	PC-1	PC-2	PC-3	PC-4	P	P*
Treatment arm (n=410)	ADE	40%	38%	42%	39%	40%	0.061	0.242
	ADEB	51%	56%	51%	46%	60%		
	ADES	9%	5%	7%	14%	0%		
Gender (n=498)	Female	49%	46%	52%	48%	56%	0.618	0.719
Age (years)	0-1	12%	16%	14%	8%	8%	0.059	0.096
	2-10	33%	35%	36%	30%	23%		
	11+	55%	48%	50%	61%	69%		
Ethnicity (n=497)	Hispanic	20%	24%	18%	19%	18%	0.660	1.000
Race (n=488)	Black	12%	16%	13%	11%	8%	0.489	0.509
CNS status (at Dx) (n=497)	Positive	39%	38%	40%	43%	26%	0.242	0.136
WBC (at study entry)	>100000	24%	24%	23%	29%	8%	0.034	0.058
FAB classification (n=339)	M0	2%	3%	1%	2%	0%	0.022	0.266
	M1	15%	13%	11%	19%	21%		
	M2	13%	7%	13%	16%	21%		
	M4	16%	16%	14%	19%	8%		
	M5	18%	22%	20%	14%	21%		
	M6	1%	0%	1%	1%	0%		
	M7	3%	2%	7%	1%	0%		
NA	32%	37%	32%	29%	31%			
AAML1031 risk group (n=485)	High risk	27%	21%	28%	32%	18%	0.088	0.287
Cytogenetics (n=492)	t(8;21)	16%	28%	19%	3%	33%	0.000	0.242
	inv16	13%	8%	16%	17%	23%		
	normal karyotype	28%	32%	23%	7%	15%		
	t(9;11)(p22;q23)/11q23	18%	8%	10%	10%	5%		
	-5, -7 or +8	9%	12%	17%	11%	10%		
other	15%	12%	15%	51%	13%			
FLT3-ITD (n=489)	ITD	21%	11%	18%	35%	5%	0.000	0.082
NPM1 (n=483)	Mutant	10%	4%	6%	19%	5%	0.000	1.000
CEBPA (n=483)	Mutant	9%	0%	2%	22%	3%	0.000	1.000
c-Kit (exon 8) (n=399)	Mutant	4%	3%	5%	4%	3%	0.963	1.000
c-Kit (exon 17) (n=399)	Mutant	8%	13%	10%	2%	15%	0.006	0.625
c-Kit (combined) (n=399)	Mutant	12%	16%	14%	6%	18%	0.053	0.762
KRAS (n=390)	Mutant	7%	15%	8%	3%	6%	0.008	1.000
NRAS (n=390)	Mutant	25%	29%	23%	27%	16%	0.448	0.548
NRAS.KRAS (n=390)	Mutant	31%	41%	28%	29%	19%	0.089	0.421
PTPN11 (n=390)	Mutant	7%	12%	3%	9%	3%	0.062	1.000
MYH11 (n=390)	Mutant	4%	5%	6%	3%	3%	0.582	0.839
GATA2 (n=390)	Mutant	3%	1%	2%	5%	3%	0.407	1.000
IDH1/2 (combined) (n=390)	Mutant	4%	1%	3%	4%	10%	0.169	0.259

* P-value PC-2 vs PC-4

Table S4

Constellation	Protein Cluster
CON-1	adhesion C4 apopreg C4 celleycle C3 creb C2 differentiation C3 histone C4 hypoxia C1 mek C4 metabolic C4 mtor C2 pi3kakt C3 smad C4 stat C2 stp C2 tcell C4 tp53 C2 transcription C4
CON-2	adhesion C2 apopreg C3 dna damage C2 histone C1 metabolic C1 pi3kakt C1 smad C1 transcription C2
CON-3	celleycle C2 hypoxia C2 stat C1 stp C1 tp53 C1
CON-4	creb C1 cytoskeletal C2 differentiation C4 hippo C3 mek C1 metabolic C2 mtor C1 tcell C1 upr C1
CON-5	adhesion C3 dna damage C4 hypoxia C3 smad C3 stp C3 transcription C3
CON-6	apopreg C1 bh3 C3 creb C3 histone C5 mapk C4 mtor C3 pi3kakt C2 stat C3 tcell C3 tp53 C3
	autophagy C1 cytoskeletal C1 hippo C1

CON-7	mapk C2 mek C2 pkc C1 ribosome C4 src C2
CON-8	apopoccur C1 bh3 C2 dna damage C3 heatshock C2 upr C2 wnt C2
CON-9	apopoccur C2 apopoccur C3 autophagy C3 bh3 C1 differentiation C2 dna damage C1 heatshock C3 mapk C1 phosphatase C1 phosphatase C2 pkc C3 ribosome C3 src C1
CON-10	celleycycle C1 heatshock C1 mapk C3 pi3kakt C4 ribosome C2 smad C2 transcription C1 wnt C3
CON-11	adhesion C1 apopreg C2 autophagy C2 autophagy C5 cytoskeletal C3 histone C3 mek C3 phosphatase C3 pkc C2 pkc C4 ribosome C1 src C4 stat C4
CON-12	apopoccur C4 autophagy C4 differentiation C1 heatshock C4 hippo C2 histone C2 metabolic C3 mtor C4 src C3 tcell C2 upr C3 upr C4 wnt C1

Table S5

A

		AAML1031 risk groups				
		Total (n=410)	Total (100%)	Low (n=281)	High (n=122)	Unknown (n=7)
Prot-SIG risk	Favorable (S3)	27	7%	78%	22%	0%
	Intermediate (S1, 4, 6, 8, 9)	235	57%	70%	27%	4%
	Unfavorable (S2, 5, 7)	148	36%	65%	35%	2%

B

		Conventional cytogenetics				
		Total (n=410)	Total (100%)	Fav (n=217)	Int (n=170)	Unfav (n=105)
Prot-SIG risk	Favorable (S3)	27	7%	70%	15%	15%
	Intermediate (S1, 4, 6, 8, 9)	235	57%	53%	33%	14%
	Unfavorable (S2, 5, 7)	148	36%	32%	47%	21%

Table S6

A

Proteins significantly changed between 0hr vs 10hr			
Antibody	Estimate mean of the differences	P value (uncorrected)	Bonferroni corrected P-value
MDM4	0.4271	0.0000	0.0000
TP53	-0.5267	0.0000	0.0000
BBC3	-0.2576	0.0000	0.0000
TP53.pS15	-0.4373	0.0000	0.0000
WEE1	0.2982	0.0000	0.0000
ATM.pS1981	-0.2528	0.0000	0.0000
CHEK1	0.3206	0.0000	0.0000
SRC.pT527	-0.3274	0.0000	0.0000
CCND3	-0.2015	0.0000	0.0000
CHEK2	0.1273	0.0000	0.0000
RB1.pS807_811	0.4107	0.0000	0.0000
MCL1	-0.1703	0.0000	0.0000
CDKN1A	-0.3349	0.0000	0.0000
CCNB1	0.2988	0.0000	0.0000
KDM1A	0.1307	0.0000	0.0000
MYC	0.1511	0.0000	0.0000
TFRC	0.1969	0.0000	0.0000
CHEK2.pT68	-0.1335	0.0000	0.0000
EEF2K	0.1392	0.0000	0.0000
RB1	0.1056	0.0000	0.0000
NOTCH1	-0.0824	0.0000	0.0000
CDK1.pT15	0.1674	0.0000	0.0000
NOTCH1.cle	-0.2016	0.0000	0.0000
RAD51	0.2115	0.0000	0.0000
ASH2L	0.1060	0.0000	0.0000
PRKCB.pS660	-0.1728	0.0000	0.0000
RPS6KB1.pT389	-0.1042	0.0000	0.0000
ATM	0.1362	0.0000	0.0000
GATA3	0.1195	0.0000	0.0000
PKM2	-0.1364	0.0000	0.0000
GATA1	0.1492	0.0000	0.0000
AKT1_2_3.pT308	-0.1657	0.0000	0.0000
STAT3.pS727	-0.0812	0.0000	0.0000
MSH2	0.0958	0.0000	0.0000
STAT3	-0.0965	0.0000	0.0000
NCL	0.1065	0.0000	0.0000
VIM	0.1325	0.0000	0.0000
SIRT1	0.0970	0.0000	0.0000
HSPB1.pS82	-0.1518	0.0000	0.0000
LEF1	0.2221	0.0000	0.0001
DDX17	0.0712	0.0000	0.0001
TIGAR	-0.0684	0.0000	0.0001
BCL2	0.1218	0.0000	0.0001
ABL1	-0.0977	0.0000	0.0001
ETS1	0.0781	0.0000	0.0002
JUNB	-0.1043	0.0000	0.0002
MTOR	0.0814	0.0000	0.0003
PTK2.pT397	-0.1388	0.0000	0.0003
STAT3.pT705	-0.0805	0.0000	0.0003
ASNS	0.1372	0.0000	0.0003
HSF1	0.0775	0.0000	0.0003
PRKCB	0.0764	0.0000	0.0003
PIK3CA	0.1049	0.0000	0.0006
SMAD3	0.0604	0.0000	0.0006
KDR	0.1065	0.0000	0.0008
EIF2S1	0.1155	0.0000	0.0008
MAPK14.pT180_182	-0.2249	0.0000	0.0010
SYK	-0.1150	0.0000	0.0011
SPP1	-0.0796	0.0000	0.0012
HNRNPK	0.0911	0.0000	0.0016
ERCC1	0.0496	0.0000	0.0017
KIT	0.1498	0.0000	0.0018
LCK	0.1094	0.0000	0.0022
FLI1	0.0585	0.0000	0.0028
BRD4	0.0528	0.0000	0.0028
WTAP	0.0839	0.0000	0.0034
ACTB	-0.0658	0.0000	0.0034
RAF1	-0.0500	0.0000	0.0034
AIFM1	0.0659	0.0000	0.0060
CASP7.cle	0.1101	0.0000	0.0073
SMAD1	-0.0740	0.0000	0.0131
SOD2	-0.0848	0.0000	0.0133
MDM2	-0.0845	0.0000	0.0146
RICTOR.pT1135	-0.1037	0.0001	0.0161
OMA1	0.0580	0.0001	0.0186
PIK3CB	-0.0708	0.0001	0.0208

PPP2R2A_B_C_D	0.0740	0.0001	0.0223
FOXO3A.pS318_321	0.0808	0.0001	0.0230
PTPN11.pT542	-0.0609	0.0001	0.0261
BID	-0.0918	0.0001	0.0295
ARAF	-0.0594	0.0001	0.0326
MEF2C	0.0572	0.0001	0.0337
CDKN1B.pT157	0.0745	0.0001	0.0384
SSBP2	0.0829	0.0001	0.0441
RICTOR	0.0559	0.0002	0.0446
RPA32.pS4_8	0.0658	0.0002	0.0459
CREB1	0.0615	0.0002	0.0488

B

Proteins significantly changed between 0hr vs 24hr			
Antibody	Estimate mean of the differences	P value (uncorrected)	Bonferroni corrected P-value
MDM4	0.38567	0.00000	0.00000
SRC.pT527	-0.7086	0.0000	0.0000
WEE1	0.5199	0.0000	0.0000
TFRC	0.5190	0.0000	0.0000
KDM1A	0.2871	0.0000	0.0000
CHEK2	0.2513	0.0000	0.0000
TP53	-0.4115	0.0000	0.0000
CHEK1	0.5741	0.0000	0.0000
BBC3	-0.2610	0.0000	0.0000
RB1	0.2453	0.0000	0.0000
MSH6	0.2244	0.0000	0.0000
PTK2.pT397	-0.4671	0.0000	0.0000
PTPN11.pT542	-0.2435	0.0000	0.0000
RB1.pS807_811	0.5873	0.0000	0.0000
SSBP2	0.2792	0.0000	0.0000
AKT1_2_3.pT308	-0.3463	0.0000	0.0000
EEF2K	0.2329	0.0000	0.0000
ASH2L	0.2196	0.0000	0.0000
TP53.pS15	-0.3510	0.0000	0.0000
MSH2	0.2028	0.0000	0.0000
RPS6KB1.pT389	-0.1942	0.0000	0.0000
BCL2	0.2775	0.0000	0.0000
WTAP	0.2539	0.0000	0.0000
CDKN1B.pS10	-0.1385	0.0000	0.0000
TIGAR	-0.1729	0.0000	0.0000
NCL	0.2218	0.0000	0.0000
KIT	0.3770	0.0000	0.0000
RAD50	0.1773	0.0000	0.0000
PRKCB.pS660	-0.2871	0.0000	0.0000
OMA1	0.1764	0.0000	0.0000
AIFM1	0.1778	0.0000	0.0000
PRKCA.pS657	-0.3323	0.0000	0.0000
XRCC1	0.1909	0.0000	0.0000
PKM2	-0.2319	0.0000	0.0000
PRKCD.pS664	-0.1305	0.0000	0.0000
DDX17	0.1423	0.0000	0.0000
PRKCA	-0.2167	0.0000	0.0000
SRC	-0.3898	0.0000	0.0000
ATM.pS1981	-0.1779	0.0000	0.0000
ERG	0.2053	0.0000	0.0000
H3K36Me3	0.2114	0.0000	0.0000
CCNB1	0.3892	0.0000	0.0000
STAT3.pS727	-0.1372	0.0000	0.0000
NPM1	0.1801	0.0000	0.0000
MAP2K1	-0.2084	0.0000	0.0000
ACTB	-0.1437	0.0000	0.0000
ERCC1	0.1090	0.0000	0.0000
MAPK14.pT180_182	-0.4390	0.0000	0.0000
ARID1A	0.1849	0.0000	0.0000
PIK3CA	0.2095	0.0000	0.0000
HNRNP	0.1868	0.0000	0.0000
PECAM1	-0.1940	0.0000	0.0000
ELK1.pS383	0.1662	0.0000	0.0000
GATA1	0.2197	0.0000	0.0000
RICTOR.pT1135	-0.2526	0.0000	0.0000
CDK1.pT15	0.2257	0.0000	0.0000
NOTCH1.cle	-0.2269	0.0000	0.0000
PLK1	-0.2230	0.0000	0.0000
RAD51	0.2939	0.0000	0.0000
HDAC2	0.1081	0.0000	0.0000
JMJD6	-0.1076	0.0000	0.0000
CDKN1A	-0.3025	0.0000	0.0000
SMAD5.pS463_465	-0.2058	0.0000	0.0000
STAT3.pT705	-0.1351	0.0000	0.0000
ABL1	-0.1746	0.0000	0.0000
PDL1	-0.1800	0.0000	0.0000
IGF1R.pY1135_1136	-0.1960	0.0000	0.0000
FLI1	0.1068	0.0000	0.0000
ERN1	-0.3143	0.0000	0.0000
ERCC5	0.1185	0.0000	0.0000
RELA.pS536	-0.2273	0.0000	0.0000
STMN1	0.1730	0.0000	0.0000
RPA32	0.1218	0.0000	0.0000
EIF2S1	0.1678	0.0000	0.0000
CCND3	-0.1556	0.0000	0.0000
MAPK8_10.pT183_185	-0.1734	0.0000	0.0000

NOTCH1	-0.0834	0.0000	0.0000
HIST3H3	0.1690	0.0000	0.0000
ITGA2	-0.1584	0.0000	0.0000
HDAC3	0.0931	0.0000	0.0000
STK4	-0.0926	0.0000	0.0000
CDKN1B	-0.1064	0.0000	0.0000
MCL1	-0.1372	0.0000	0.0000
SIRT1	0.1270	0.0000	0.0000
ITGAL	-0.1437	0.0000	0.0000
VIM	0.1823	0.0000	0.0000
TAPBP	0.1023	0.0000	0.0000
MYC	0.1315	0.0000	0.0000
TSC2.pT1462	-0.1376	0.0000	0.0000
SIRT6	0.1061	0.0000	0.0000
SMAD4	0.0860	0.0000	0.0000
PIK3CB	-0.1399	0.0000	0.0000
ATM	0.1293	0.0000	0.0000
CREB1	0.1097	0.0000	0.0000
STAT3	-0.1205	0.0000	0.0000
GAB2.pT452	-0.1643	0.0000	0.0000
IGF1R	-0.2939	0.0000	0.0000
MTOR	0.1022	0.0000	0.0000
ASNS	0.1742	0.0000	0.0000
EIF2S1.pS51	0.1280	0.0000	0.0000
RAF1.pS338	-0.1185	0.0000	0.0000
MAP2K1_2	-0.1060	0.0000	0.0000
ELAVL1	0.1449	0.0000	0.0000
AKT1	-0.1575	0.0000	0.0000
DUSP6	-0.1510	0.0000	0.0000
AKT1S1.pT246	-0.1436	0.0000	0.0000
EIF2AK2	0.1101	0.0000	0.0000
JAG1	-0.1140	0.0000	0.0000
SHC1.pT317	-0.1350	0.0000	0.0000
HDAC6	0.1219	0.0000	0.0000
LCK	-0.1350	0.0000	0.0000
EP300	0.1095	0.0000	0.0000
MDM2	-0.1154	0.0000	0.0000
SYK	-0.1387	0.0000	0.0000
BAX	-0.1141	0.0000	0.0000
AKT1S1	-0.1474	0.0000	0.0001
STK11	-0.1217	0.0000	0.0001
IGFBP2	-0.1319	0.0000	0.0001
RPS6	0.1481	0.0000	0.0002
HSF1.pS326	-0.1902	0.0000	0.0003
MMP2	-0.0967	0.0000	0.0003
H3K4Me3	0.1392	0.0000	0.0003
BRAF	-0.0759	0.0000	0.0003
HIF1A	-0.1310	0.0000	0.0004
CDKN1B.pT198	0.1137	0.0000	0.0004
RAF1	-0.0646	0.0000	0.0004
H3K27Me3	0.1116	0.0000	0.0005
AKT3	-0.2692	0.0000	0.0005
TUBA1A.de	-0.1346	0.0000	0.0007
CREB1.pS133	-0.1256	0.0000	0.0008
RPS6KB1	0.0909	0.0000	0.0009
NOL3	-0.0901	0.0000	0.0009
FOXO3A.pS318_321	0.0940	0.0000	0.0010
SPP1	-0.0918	0.0000	0.0010
HSF1	0.0885	0.0000	0.0011
EGLN1	-0.0726	0.0000	0.0012
EIF4G1	0.0832	0.0000	0.0013
PK1.pS241	-0.0846	0.0000	0.0014
HSPA1A_L	-0.1870	0.0000	0.0014
CDKN1B.pT157	0.0979	0.0000	0.0016
ATF3	-0.1157	0.0000	0.0016
PARP1	0.1278	0.0000	0.0017
LATS1	0.0617	0.0000	0.0023
MS12	-0.0928	0.0000	0.0025
PRKCB	0.0755	0.0000	0.0033
YWHAE	-0.0818	0.0000	0.0034
RHEB	-0.0665	0.0000	0.0036
BAK1	0.0688	0.0000	0.0037
CDK1	0.0891	0.0000	0.0039
EIF4EBP1	0.0928	0.0000	0.0040
NFE2L2	-0.1066	0.0000	0.0042
HSPB1.pS82	-0.1469	0.0000	0.0043
ASS1	-0.0898	0.0000	0.0046
NLN	0.0746	0.0000	0.0049
HSP90AA1_B1	0.1249	0.0000	0.0054
ITGB1	-0.1084	0.0000	0.0065

PK1	-0.0807	0.0000	0.0065
PPARA	-0.1022	0.0000	0.0071
RPS6.pS240_244	0.2000	0.0000	0.0096
COG3	0.0564	0.0000	0.0113
CDH2	0.0822	0.0000	0.0114
RICTOR	0.0643	0.0000	0.0132
BIRC2	-0.1188	0.0000	0.0135
RPSKA1_2_3	-0.0728	0.0000	0.0144
RPA32.pS4_8	0.0732	0.0001	0.0164
GATA3	0.0824	0.0001	0.0185
PPP2R2A_B_C_D	0.0819	0.0001	0.0206
FOXO3A	-0.0513	0.0001	0.0214
EIF4EBP1.pT37_46	0.1664	0.0001	0.0215
CBX7	-0.0737	0.0001	0.0230
CHEK2.pT68	-0.0644	0.0001	0.0241
SMAD3	0.0635	0.0001	0.0436
BECN1	0.0793	0.0002	0.0485

C

Proteins significantly changed after both 10 and 24 hours by protein functional group				
PFG	Protein	Absolute number of proteins that changed	Size group	%
DNA damage	ATM, ATM-pS1981, CHEK1, CHEK2, CHEK2-pT68, ERCC1, MSH2, RAD51, RPA32-pS4_8, SSBP2	10	19	53%
Cell cycle	CCNB1, CCND3, CDK1-pT15, CDKN1A, CDKN1B-pT157, RB1, RB1-pS807_810, Wee1, FOXO3A-pS318_321	9	23	39%
TP53	ATM, ATM-pS1981, MDM2, MDM4, TP53, TP53-pS15	6	8	75%
Histone	ASH2L, HNRNPK, KDM1A, NCL, SIRT1, WTAP	6	23	26%
STP	ABL1, KIT, PTK2-pT397, PTPN11-pT542, SYK	5	18	28%
Ribosome	DDX17, EEF2K, EIF2S1, HNRNPK, RPS6KB1.pT389	5	24	21%
PI3KAKT	AKT1_2_3-pT308, FOXO3A.pS318_321, PIK3CA, PIK3CB	4	15	27%
Metabolic	ASNS, OMA1, PKM2, TIGAR	4	16	25%
STAT	STAT3, STAT3.pS727, STAT3.pT705	3	7	43%
BH3	BBC3, BCL2, MCL1	3	9	33%
mTOR	MTOR, RICTOR, RICTOR-pT1135	3	11	27%
Differentiation	GATA1, GATA3	2	5	40%
SRC	LCK, SRC.pT527	2	5	40%
PKC	PRKCB, PRKCB.pS660	2	6	33%
Cytoskeletal	ACTB, VIM	2	7	29%
Heat shock	HSF1, HSPB1-pS82	2	7	29%
T-cell	NOTCH1, NOTCH1-cle	2	8	25%
Transcription	MYC, FLI1	2	15	13%
Phosphatase	PPP2R2A_B_C_D	1	2	50%
Apoptosis Regulating	AIFM1	1	4	25%
Creb	Creb1	1	4	25%
UPR	EIF2S1	1	6	17%
SMAD	SMAD3	1	8	13%
Adhesion	SPP1	1	11	9%
MEK	RAF1	1	11	9%
MAPK	MAPK14-pT180_182	1	13	8%
Apoptosis Occurring	-	0	6	0%
Autophagy	-	0	7	0%
HIPPO	-	0	8	0%
Hypoxia	-	0	5	0%
Wnt	-	0	4	0%

TP53			-			Yellow							
TP53.pS15			-	Red	Magenta							Black	
TSC1			-			Yellow	Green		Cyan	Blue	Purple		
TSC2.pT1462			-	Red	Magenta								
VCP	21	Yes	CB-5339				Green	Cyan	Blue				
VIM*	49	No	20(R)-Rg3, Silibinin, Volasertib	Red	Magenta	Yellow	Green	Dark Green	Cyan	Blue	Purple	Black	
YBX1.pS102*			-	Red	Magenta	Yellow	Green	Dark Green	Cyan	Blue	Purple	Black	

* Universal
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2 <https://clinicaltrials.gov/ct2/show/NCT01870596?term=chk1&draw=2&rank=2>
3 <https://clinicaltrials.gov/ct2/show/NCT02797964?term=chk1&draw=2&rank=5>
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67 DOI: 10.1038/s41420-019-0232-0
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