

Table S2. Results summary of univariate and multivariate analysis of combined PI-risk predictor for systemic recurrence

1. Univariate analysis

Univariate Cox model incorporating the dichotomized combined-PI as predictor

```
coxph(formula = Surv(time, event == 1) ~ combined_PI, data = tmp)
```

```
n= 77, number of events= 34
(4 observations deleted due to missingness)
```

```

              coef exp(coef) se(coef)      z Pr(>|z|)
combined_PI:high risk 1.0365    2.8194  0.3678 2.819  0.00482 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

              exp(coef) exp(-coef) lower .95 upper .95
combined_PI:high risk    2.819    0.3547    1.371    5.797
```

```

Rsquare= 0.106 (max possible= 0.971 )
Likelihood ratio test= 8.61 on 1 df,  p=0.003341
Wald test              = 7.94 on 1 df,  p=0.004824
Score (Logrank) test = 8.67 on 1 df,  p=0.003242
```

Test proportional hazards assumption for individual univariate Cox models reported in the univariate comparison part

```

$combined_PI
              rho chisq  p
combined_PI:high risk -0.0483 0.0781 0.78
$tumorSize
              rho chisq  p
tumorSizepT2  -0.15344 0.77843 0.378
tumorSizepT3-pT4  0.00864 0.00253 0.960
GLOBAL          NA 2.10350 0.349
$histoGrade
              rho chisq  p
histoGrade2  0.210  1.50 0.220
histoGrade3  0.204  1.42 0.233
GLOBAL          NA  1.53 0.465
$TP53
              rho chisq  p
TP53mutation -0.144 0.661 0.416
$node
              rho chisq  p
nodepN1      -0.0746 0.1871 0.665
nodepN2-pN3  -0.0398 0.0523 0.819
nodeOther    -0.2007 1.2908 0.256
GLOBAL          NA 1.3267 0.723
$ER
              rho chisq  p
ERpositive  0.475  6.85 0.00887
$stage
              rho chisq  p
stage2     -0.11936 0.39224 0.531
stage3     -0.13508 0.49363 0.482
```

```

stage4 -0.00722 0.00143 0.970
GLOBAL      NA 1.11034 0.775
$AOL_risk
      rho chisq  p
AOL_risk -0.0275 0.0201 0.887
$RS
      rho chisq  p
RS1 -0.00289 0.000281 0.987
$AMST
      rho chisq  p
AMST1 -0.0502 0.0836 0.772
$ROT
      rho chisq  p
ROT1 -0.239 1.87 0.172
$Grade
      rho chisq  p
Grade1 -0.0475 0.0746 0.785
$Robust
      rho chisq  p
Robust1 -0.065 0.139 0.709
$Hypoxia
      rho chisq  p
Hypoxia1 -0.354 4.18 0.0409
$Stem
      rho chisq  p
Stem1 -0.0384 0.0491 0.825
$Intrinsic
      rho chisq  p
Intrinsic1 0.174 1.02 0.312
$WR
      rho chisq  p
WR1 0.0921 0.286 0.593

```

Summary of univariate comparison

	Deviance	PVE	p	Cindex	HR	HR_lowerCI	HR_upperCI		type
combined_PI	8.611	0.106	0.003	0.746	2.819	1.371	5.797	GeneSet	predictor
AOL_risk	2.283	0.033	0.131	0.734	2.629	0.622	11.106	Clinical	parameter
TP53	7.470	0.092	0.006	0.759	2.872	1.415	5.830	Clinical	parameter
tumorSize	9.358	0.117	0.009	0.706	NA	NA	NA	Clinical	parameter
stage	7.501	0.111	0.058	0.698	NA	NA	NA	Clinical	parameter
node	6.090	0.076	0.107	0.605	NA	NA	NA	Clinical	parameter
ER	0.227	0.003	0.634	0.403	0.838	0.406	1.727	Clinical	parameter
histoGrade	1.979	0.025	0.372	0.480	NA	NA	NA	Clinical	parameter
RS	4.827	0.061	0.028	0.686	2.146	1.072	4.296	GeneSet	predictor
AMST	2.092	0.027	0.148	0.630	1.646	0.838	3.232	GeneSet	predictor
ROT	3.591	0.046	0.058	0.686	1.933	0.966	3.865	GeneSet	predictor
Grade	6.174	0.077	0.013	0.712	2.377	1.185	4.767	GeneSet	predictor
Robust	5.391	0.068	0.020	0.703	2.257	1.114	4.573	GeneSet	predictor
Hypoxia	1.060	0.014	0.303	0.626	1.426	0.727	2.795	GeneSet	predictor
Stem	0.115	0.001	0.734	0.535	1.124	0.573	2.205	GeneSet	predictor
Intrinsic	0.437	0.006	0.508	0.538	1.261	0.631	2.519	GeneSet	predictor
WR	3.093	0.039	0.079	0.640	1.835	0.926	3.636	GeneSet	predictor

2. Multivariate analysis

Correlation between TP53 & combined-PI predictor

	low risk	high risk
WT	38	22
Mut	2	18

Fisher's Exact Test for Count Data
p-value = 5.308e-05
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
3.137077 145.691741
sample estimates:
odds ratio
15.026

Full model: Risk = tumor size + Tp53 + combined_PI + strata(ER)

	coef	exp(coef)	se(coef)	z	p
tumorSize:pT2	1.005	2.73	0.575	1.75	0.080
tumorSize:pT3-pT4	1.200	3.32	0.658	1.82	0.068
TP53:mutation	0.732	2.08	0.575	1.27	0.200
combined_PI:high risk	0.974	2.65	0.468	2.08	0.037

Likelihood ratio test=16.1 on 4 df, p=0.00296 n= 68, number of events= 31 (13 observations deleted due to missingness)

Model 2: Risk = tumor size + Tp53 + strata(ER)

	coef	exp(coef)	se(coef)	z	p
tumorSize:pT2	1.14	3.14	0.576	1.98	0.047
tumorSize:pT3-pT4	1.43	4.17	0.660	2.16	0.030
TP53:mutation	1.33	3.79	0.519	2.57	0.010

Likelihood ratio test=11.8 on 3 df, p=0.00793 n= 68, number of events= 31 (13 observations deleted due to missingness)

Model comparison by AIC and Analysis of Deviance: Full model vs Model 2

```
> stepAIC(model_full)
Start: AIC=191.8
Surv(time, event == 1) ~ tumorSize + TP53 + combined_PI + strata(ER)

> stepAIC(model2)
Start: AIC=194.01
Surv(time, event == 1) ~ tumorSize + TP53 + strata(ER)
```

Analysis of Deviance Table

```
Cox model: response is Surv(time, event == 1)
Model 1: ~ tumorSize + TP53 + combined_PI + strata(ER)
Model 2: ~ tumorSize + TP53 + strata(ER)
loglik Chisq Df P(>|Chi|)
1 -91.902
2 -94.003 4.2011 1 0.0404 *
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Model selection by AIC:

```
stepAIC(model_full, direction = "both")
Start: AIC=191.8
Surv(time, event == 1) ~ tumorSize + TP53 + combined_PI + strata(ER)
      Df  AIC
- TP53    1 191.46
<none>    191.80
- tumorSize  2 192.25
- combined_PI  1 194.01

Step: AIC=191.46
Surv(time, event == 1) ~ tumorSize + combined_PI + strata(ER)
      Df  AIC
<none>    191.46
- tumorSize  2 191.51
+ TP53    1 191.80
- combined_PI  1 198.66
Call:
coxph(formula = Surv(time, event == 1) ~ tumorSize + combined_PI + strata(ER), data = tmp)
```

	coef	exp(coef)	se(coef)	z	p
tumorSize:pT2	0.952	2.59	0.563	1.69	0.0910
tumorSize:pT3-pT4	1.090	2.97	0.640	1.70	0.0890
combined_PI:high risk	1.206	3.34	0.413	2.92	0.0035

Likelihood ratio test=14.4 on 3 df, p=0.00241 n= 68, number of events= 31

Final model: Risk = tumor size + combined_PI + strata(ER)

n= 68, number of events= 31 (13 observations deleted due to missingness)

	coef	exp(coef)	se(coef)	z	Pr(> z)
tumorSize:pT2	0.9524	2.5920	0.5628	1.692	0.09059 .
tumorSize:pT3-pT4	1.0897	2.9734	0.6398	1.703	0.08853 .
combined_PI:high risk	1.2060	3.3402	0.4132	2.919	0.00351 **

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

	exp(coef)	exp(-coef)	lower .95	upper .95
tumorSize:pT2	2.592	0.3858	0.8602	7.811
tumorSize:pT3-pT4	2.973	0.3363	0.8485	10.420
combined_PI:high risk	3.340	0.2994	1.4862	7.507

Rsquare= 0.191 (max possible= 0.947)
Likelihood ratio test= 14.39 on 3 df, p=0.002415
Wald test = 12.9 on 3 df, p=0.004867
Score (logrank) test = 14.57 on 3 df, p=0.002222

Test proportional hazards assumption for Final model

	rho	chisq	p
tumorSize:pT2	-0.0402	0.0477	0.827
tumorSize:pT3-pT4	0.0378	0.0389	0.844
combined_PI:high risk	0.1143	0.4301	0.512
GLOBAL	NA	0.7959	0.850