Appendix:

Supplementary table 1: **Summary outcomes for patients in discovery (COMPARZ) and validation cohort (RECORD3) - biomarker and full populations**

Outcomes	**COMPARZ biomarker cohort** **n=377***		**COMPARZ total** **n=927**		**RECORD3 biomarker cohort** **n=258***		**RECORD3 total** **n=471**	
Combined treatment arms								
Median PFS in months (95% CI)	9·1 (8·3, 11·0)		8·6 (8·3, 10·9)		9·8 (8·1, 10·9)		8·2 (8·0, 10·1)	
Median OS in months (95% CI)	28·2 (26·2, 34·9)		28·7 (26·6, 32·4)		29·9 (22·4, 33·4)		27·7 (21·9, 31·4)	
Treatment arms	Sunitinib n=189	Pazopanib n=188	Sunitinib n=463	Pazopanib n=464	1st line Sunitinib then Everolimus n=130	1st line Everolimus then Sunitinib n=128	1st line Sunitinib then Everolimus n=233	1st line Everolimus then Sunitinib n=238
Median PFS in months (95% CI)	9·0 (8·1, 11·2)	10·7 (8·3,11·1)	9·3 (8·2, 11·0)	8·6 (8·3, 11·0)	10·9 (8·1, 13·3)	8·1 (5·4, 10·5)	10·7 (8·2, 11·5)	7·9 (5·6, 8·2)
Median OS in months (95% CI)	27·4 (21·0, 31·5)	32·6 (26·7, NE)	29·1 (24·7, 32·1)	28·4 (26·0, 35·6)	31·4 (23·1, 34·9)	26·9 (16·9, 34·7)	29·5 (22·8, 33·1)	22·4 (18·6, 33·3)

CR, complete response; mPFS, median progression free survival; mOS, median overall survival; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease.

* Biomarker cohort is all the patients from ITT population that have available NGS data.

***Supplementary table 2:* Multivariate Cox regression model testing clinical, laboratory and genomic parameters for OS in the discovery cohort (COMPARZ)**

Parameter [reference level]	**Effect size**	**Two-sided p-value**	**HR**	**95% HR Confidence Limits**	
TP53+BAP1 [Continuous 0, 1, 2]	0·45072	0·0008	1·569	1·207	2·042
*PBRM1*_status [MT]	0·45472	0·0035	1·576	1·161	2·138
KPS [≥80%]	0·40704	0·0204	1·502	1·065	2·119
Hgb [High]	0·15662	0·3326	1·170	0·852	1·606
LDH [≤1·5 ULN]	0·51181	0·0769	1·668	0·946	2·941
Time from diagnosis [≥1 y]	0·37766	0·0192	1·459	1·064	2·001
Corrected Ca [≤10 mg/DL]	0·73286	0·0002	2·081	1·416	3·059

Ca, calcium; HR=hazard ratio; Hgb, haemoglobin; LDH, lactate dehydrogenase; KPS, karnofsky performance status; MT=mutated
Listed are individual parameters considered favourable per the original model/univariate testing, used as reference level for the hazard ratio estimate of each variable in the multivariate Cox PH model.

Supplementary table 3: **Distribution of risk groups in the discovery cohort (COMPARZ), per original and annotated MSKCC risk models**

MSKCC original risk	**MSKCC annotated risk by adding TP53, BAP1 and PBRM1 (n=357)**				
	Favourable (annotated=0) n (%)	**Good (annotated=1) n (%)**	**Intermediate (annotated=2) n (%)**	**Poor (annotated ≥3) n (%)**	**Total n (%)**
Favourable (original=0), n (%)	36 (10·08)	37 (10·36)	14 (3·92)	0	87 (24·37)
Intermediate (original=1-2), n (%)	0	40 (11·2)	94 (26·33)	83 (23·25)	217 (60·78)
Poor (original ≥3), n (%)	0	0	0	53 (14·85)	53 (14·85)
Total, n (%)	36 (10·08)	77 (21·57)	108 (30·25)	136 (38·1)	357 (100)

MSKCC=Memorial Sloan Kettering Cancer Center

Supplementary table 4: **The p-value of Hosmer-Lemeshow overall goodness of fit test**

Model	**p-value of Hosmer-Lemeshow test**
COMPARZ MSKCC original model	0·0662
COMPARZ MSKCC annotated model	0·1702
RECORD3 MSKCC original model	0·4706
RECORD3 MSKCC annotated model	0·4319

No model test has significant p-value, which means no model has poor fit in the assessment of calibration.

Supplementary table 5: **OS and PFS outcomes by original and annotated MSKCC risk groups in the discovery cohort (COMPARZ)**

Original Group	**Median OS (95% CI)**	**25th quartile OS (95% CI)**	**Median PFS (95% CI)**	**25th quartile PFS (95% CI)**
Favourable Risk n=87	NE (30·55, NE)	26·15 (18·69, 28·71)	11·10 (8·38, 16·59)	8·21 (5·39, 8·38)
Intermediate Risk n=217	26·64 (21·03, 32·03)	11·61 (9·53, 13·27)	8·54 (8·15, 10·97)	2·86 (2·63, 4·17)
Poor Risk n=53	18·10 (11·86, 25·20)	10·25 (4·21, 12·65)	5·39 (2·86, 10·55)	2·60 (1·38, 3·12)
Changing Group	**Median OS (95% CI)**	**25th quartile OS (95% CI)**	**Median PFS (95% CI)**	**25th quartile PFS (95% CI)**
Fav (original) to Fav (annotated)	NE (31·61, NE)	28·02 (26·15, NE)	16·59 (11·04, 26·25)	11·01 (8·12, 11·10)
Fav (original) to Good (annotated)	NE (34·89, NE)	26·05 (13·08, NE)	8·38 (5·65, 15·05)	5·49 (2·07, 8·31)
Fav (original) to Inter (annotated)	22·95 (11·24, 30·56)	17·35 (10·02, 22·34)	5·52 (3·84, NE)	4·37 (1·35, 5·52)
Inter (original) to Good (annotated)	35·48 (21·55, NE)	19·75 (13·17, 23·10)	8·97 (7·72, 22·05)	5·49 (1·54, 8·28)
Inter (original) to Inter (annotated)	32·03 (24·15, NE)	12·52 (9·53, 18·23)	10·97 (8·28, 13·77)	4·04 (2·69, 7·89)
Inter (original) to Poor (annotated)	16·46 (12·75, 23·79)	8·77 (6·90, 11·53)	5·59 (4·04, 10·02)	2·56 (1·41, 2·83)
Poor (original) to Poor (annotated)	18·10 (11·86, 25·20)	10·25 (4·21, 12·65)	5·39 (2·86, 10·55)	2·60 (1·38, 3·12)

Fav, favourable; Inter, intermediate, mOS, median overall survival; mPFS, median progression free survival; NE, not estimable.

Supplementary table 6: **RECORD3 distribution and outcome for good/intermediate/poor for MSKCC and MSKCC 2·0**

MSKCC risk	**MSKCC original model**		**MSKCC annotated with *BAP1*, *TP53*, *PBRM1* mutation status**	
	n (%)	mOS (95% CI) [months]	n (%)	mOS (95% CI) [months]
Favourable	82 (32)	45 (36-NE)	28 (11)	45 (34-NE)
Good			81 (31)	36 (33-46)
Intermediate	145 (56)	23 (19-31)	66 (26)	32 (20-40)
Poor	31 (12)	8 (4-12)	83 (32)	11 (9-16)
p-value	<0·0001		<0·0001	
C-index OS (95% CI)	0·658 (0·616-0·699)		0·670 (0·625-0·715)	

mOS, median overall survival; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable.

Supplementary Table 7: **OS by original and annotated MSKCC risk groups for validation cohort (RECORD3)**

Original grouping	**Median OS (95% CI)**	**25th quartile OS (95% CI)**
Favourable n=82	45·04 (36·30, NE)	28·29 (17·22, 34·69)
Intermediate n=145	23·06 (19·19, 31·44)	10·87 (7·75, 14·00)
Poor n=31	8·08 (3·84, 11·47)	3·45 (1·71, 7·03)
Changing Group	**Median OS (95%CI)**	**25th quartile OS (95% CI)**
Inter (original) to Good (Annotated)	34·86 (27·66, 46·13)	20·53 (10·58, 30·19)
Inter (original) to Inter (Annotated)	27·70 (17·71, 37·19)	11·30 (5·49, 17·71)
Inter (original) to Poor (Annotated)	16·89 (9·76, 20·44)	7·33 (5·65, 9·76)

CI=confidence interval; Inter, intermediate, mOS=median overall survival; MSKCC=Memorial Sloan Kettering Cancer Center; NE, not estimable.

Supplementary table 8: **Objective response by risk category and trend-testing from validation cohort (RECORD3)**

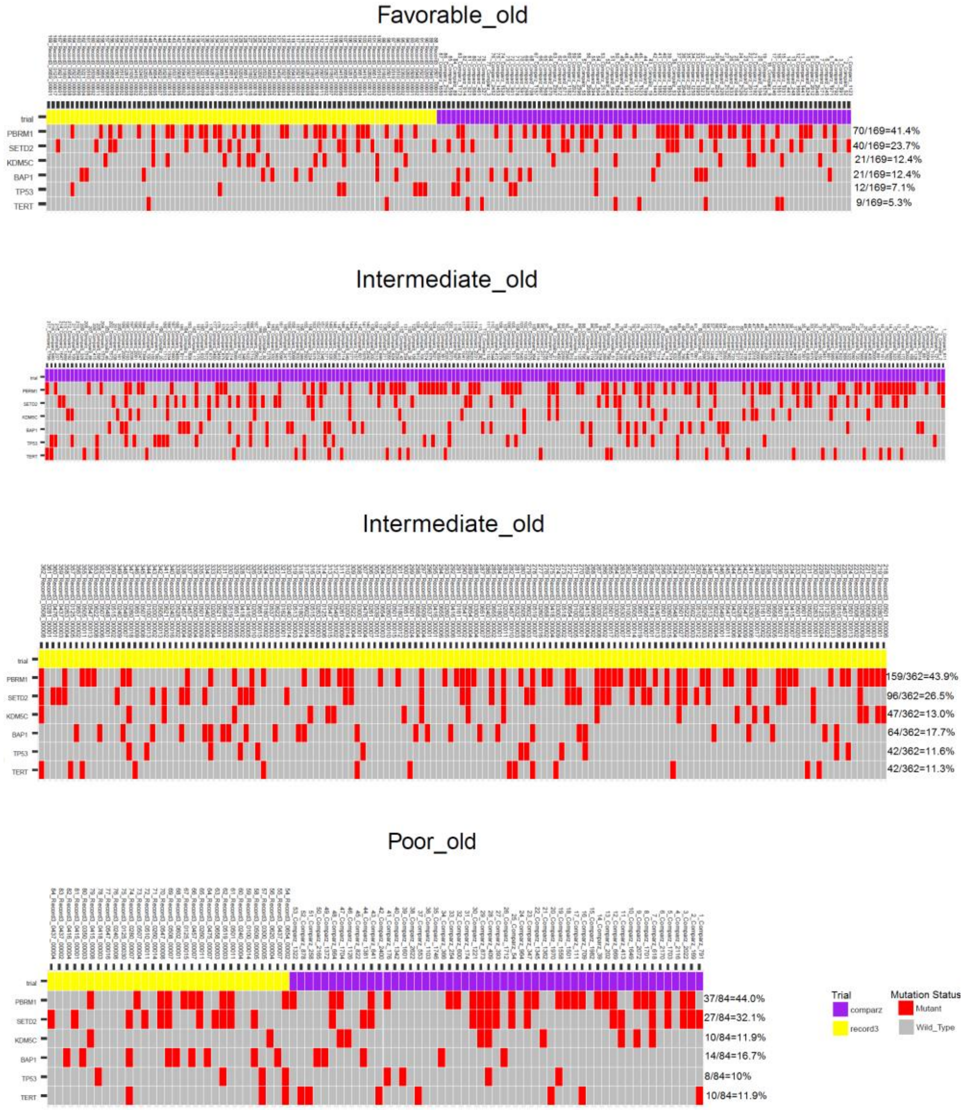
MSKCC Risk	**Original MSKCC risk model - RECORD3**	**New MSKCC risk model 2 - RECORD3**
Risk status	ORR	ORR
Favourable risk	24 (31·6)	14 (51·9)
Good		18 (24·0)
Intermediate risk	25 (18·7)	14 (23·7)
Poor risk	1 (3·9)	4 (5·3)
Total	50 (21·2)	50 (21·2)
CA one-sided p	0·0007	<0·0001

MSKCC, Memorial Sloan Kettering Cancer Center; ORR, overall response rate.

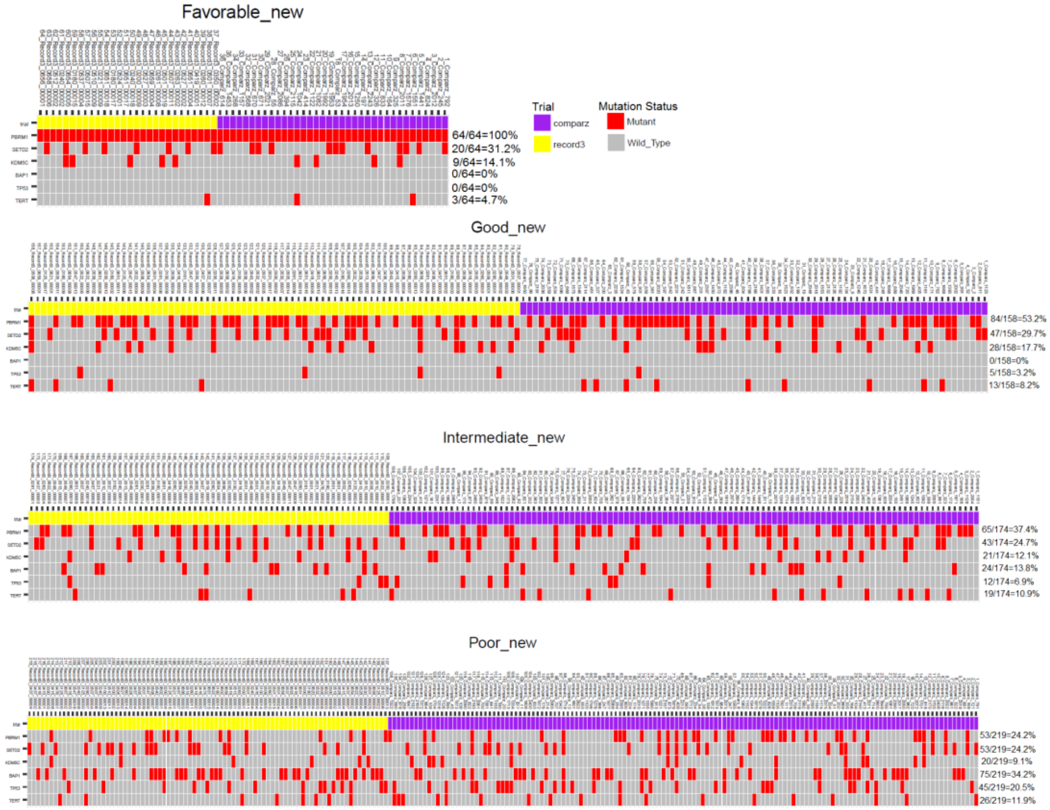
Supplementary Figure 1:

Panel A) Oncoprint: Original MSKCC risk model Panel B) Oncoprint: Annotated MSKCC risk model

A



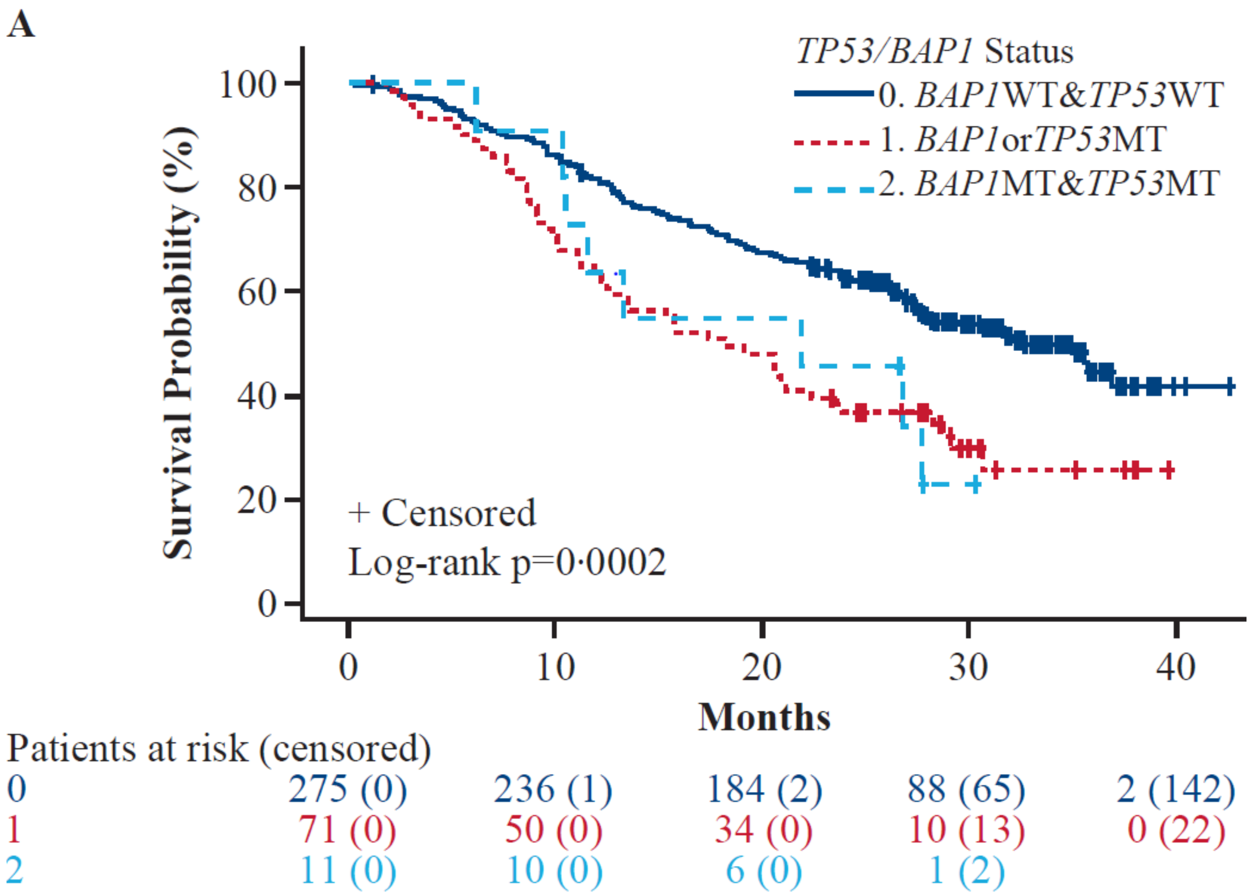
B


Favorable_new
trial
PBRM1
SETD2
KDM5C
BAP1
TP53
TERT
64/64=100%
20/64=31.2%
9/64=14.1%
0/64=0%
0/64=0%
3/64=4.7%
Trial
comparz
record3
Mutation Status
Mutant
Wild_Type
Good_new
84/158=53.2%
47/158=29.7%
28/158=17.7%
0/158=0%
5/158=3.2%
13/158=8.2%
Intermediate_new
65/174=37.4%
43/174=24.7%
21/174=12.1%
24/174=13.8%
12/174=6.9%
19/174=10.9%
Poor_new
53/219=24.2%
53/219=24.2%
20/219=9.1%
75/219=34.2%
45/219=20.5%
26/219=11.9%

Supplementary Figure 2: **Overall survival by mutation status in the discovery cohort (COMPARZ)**

Panel A) Kaplan-Meier plot of OS by BAP1 and TAP53 mutation status. Panel B) Kaplan-Meier plot of OS by PBRM1 mutation status and comutant BAP1 or TP53 mutation status.

Legend: A) The KM plot for the three category groupings of *BAP1*/*TP5*3 are presented including, *BAP1* and *TP53* are both wild type (0); *BAP1* or *TP53* is mutated (1); *BAP1* and *TP53* are both mutated (2). Adding a point for poorer prognosis if one or both of *BAP1*/*TP53* are mutated was considered based on this plot.
B) The KM plot of OS by *PBRM1* status and *BAP1*/*TP53* joint status
MSKCC, Memorial Sloan Kettering Cancer Center



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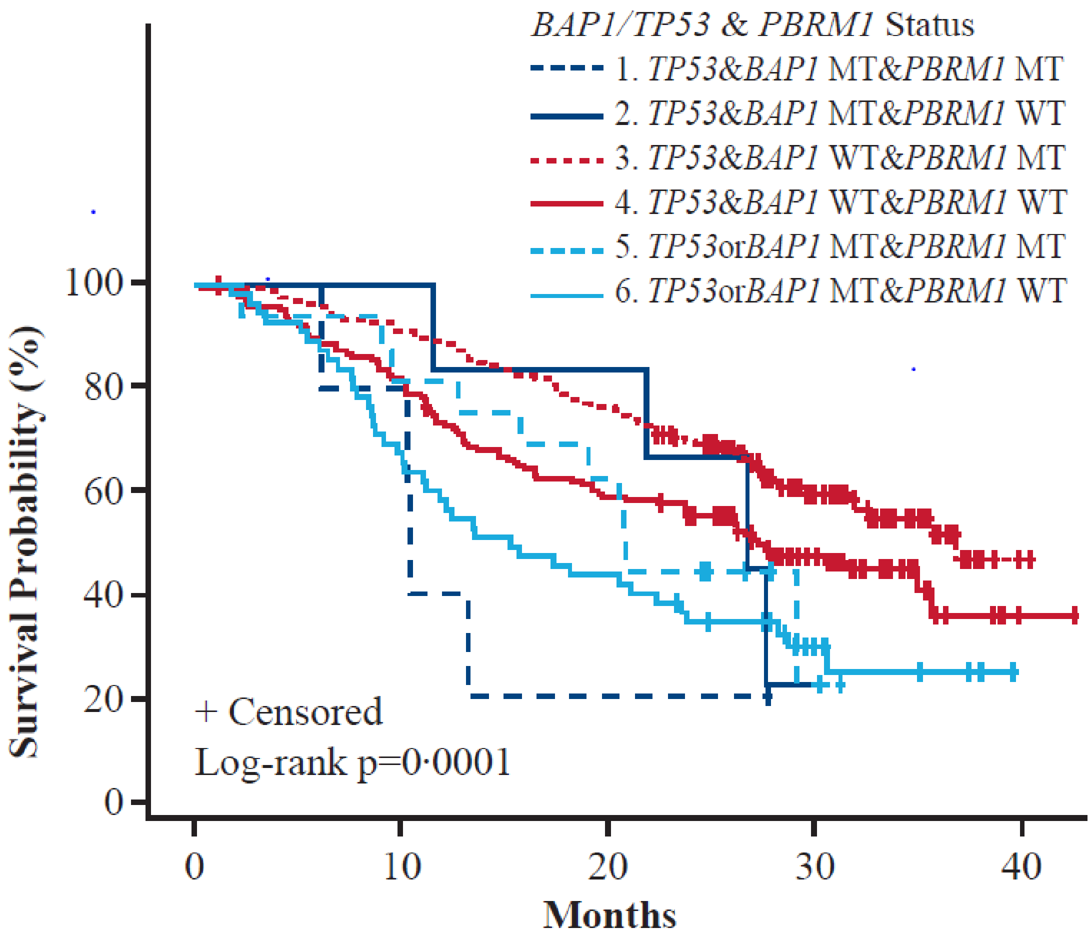
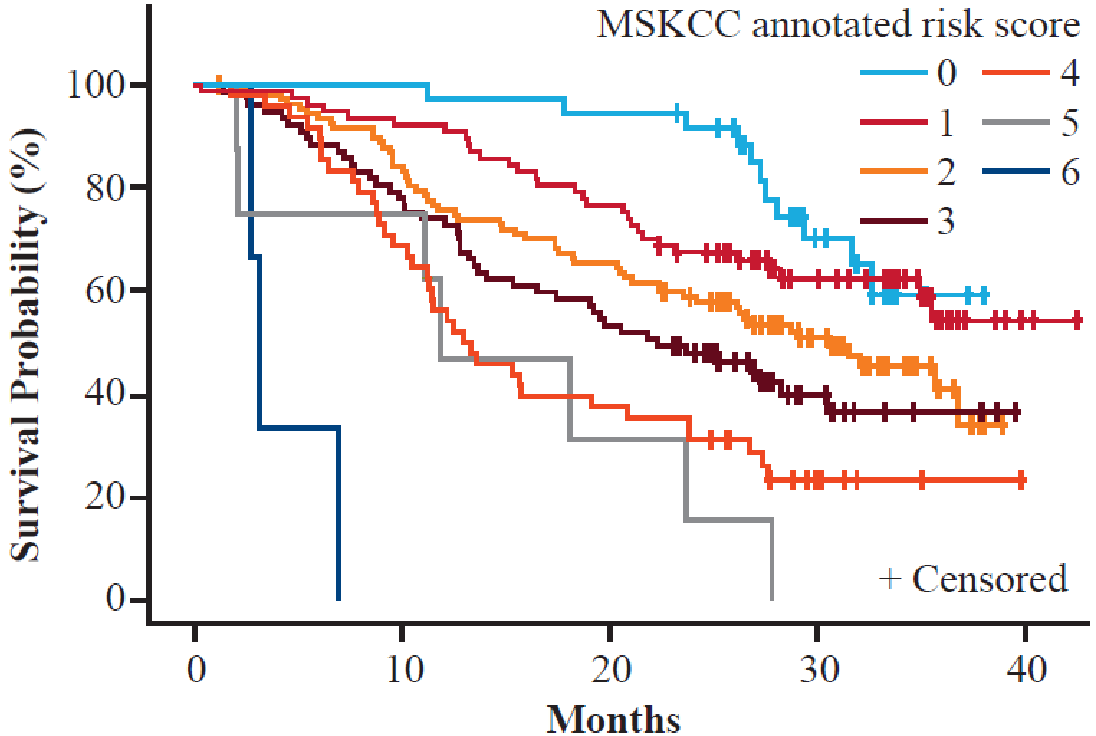


Patients at risk (censored)

1	5 (0)	4 (0)	1 (0)	0 (1)	
2	6 (0)	6 (0)	5 (0)	1 (1)	
3	139 (0)	125 (1)	105 (1)	50 (36)	1 (80)
4	136 (0)	111 (0)	79 (1)	38 (29)	1 (62)
5	16 (0)	13 (0)	10 (0)	1 (5)	0 (6)
6	55 (0)	37 (0)	24 (0)	9 (8)	0 (16)

Supplementary Figure 3: **Kaplan-Meier plot of overall survival by MSKCC annotated risk scores in the discovery cohort (COMPARZ)**

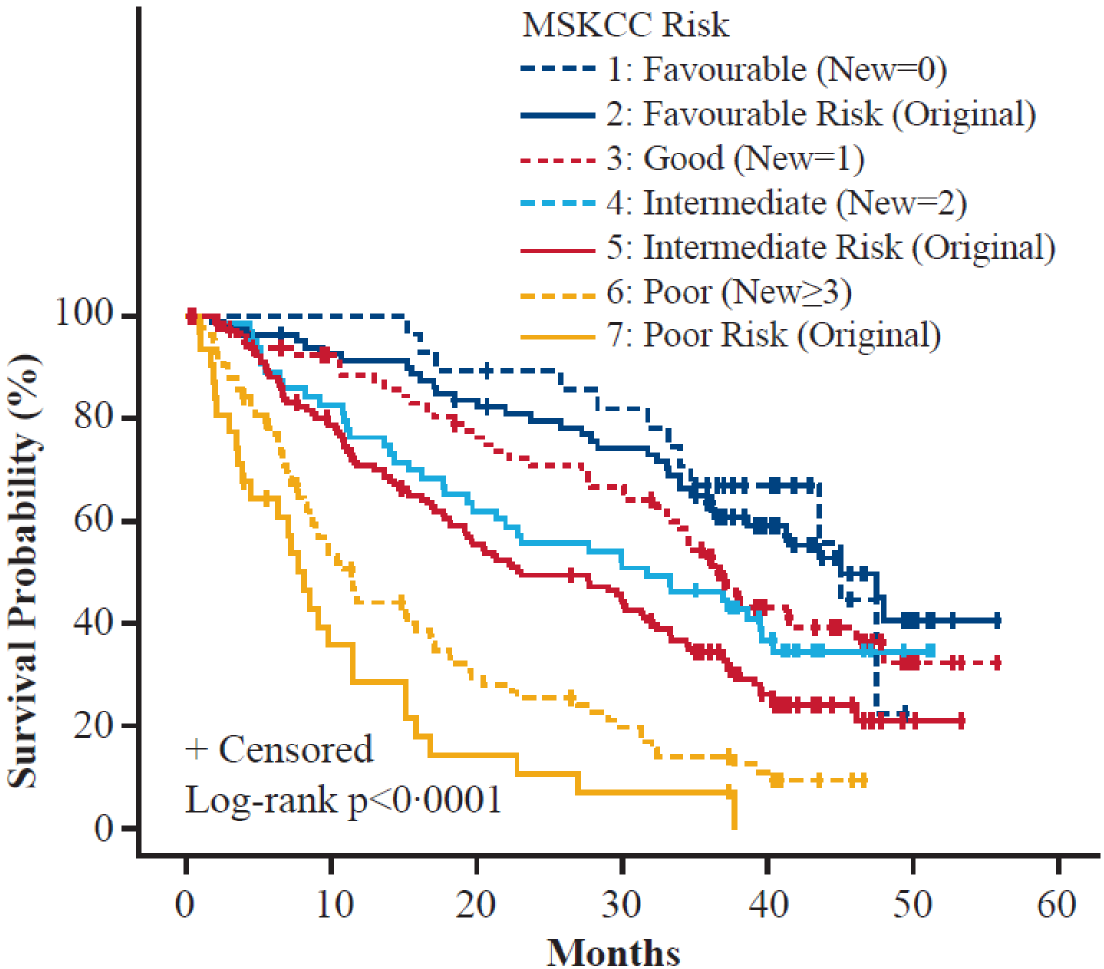
Legend: Patients were separated by individual score on the annotated model (0-6); no patient scored 7, though technically it would have been possible. MSKCC, Memorial Sloan Kettering Cancer Center



Patients at risk (censored)

0	36 (0)	36 (0)	34 (0)	16 (11)	0 (25)
1	77 (0)	71 (0)	59 (0)	30 (19)	2 (45)
2	108 (0)	90 (1)	70 (1)	35 (22)	0 (52)
3	77 (0)	60 (0)	41 (0)	13 (20)	0 (32)
4	48 (0)	33 (0)	18 (0)	5 (7)	0 (12)
5	8 (0)	6 (0)	2 (1)	0 (1)	
6	3 (0)	0 (0)			

Supplementary Figure 4: **Kaplan-Meier plot of overall survival comparing original and new MSKCC risk models in validation cohort (RECORD3)**



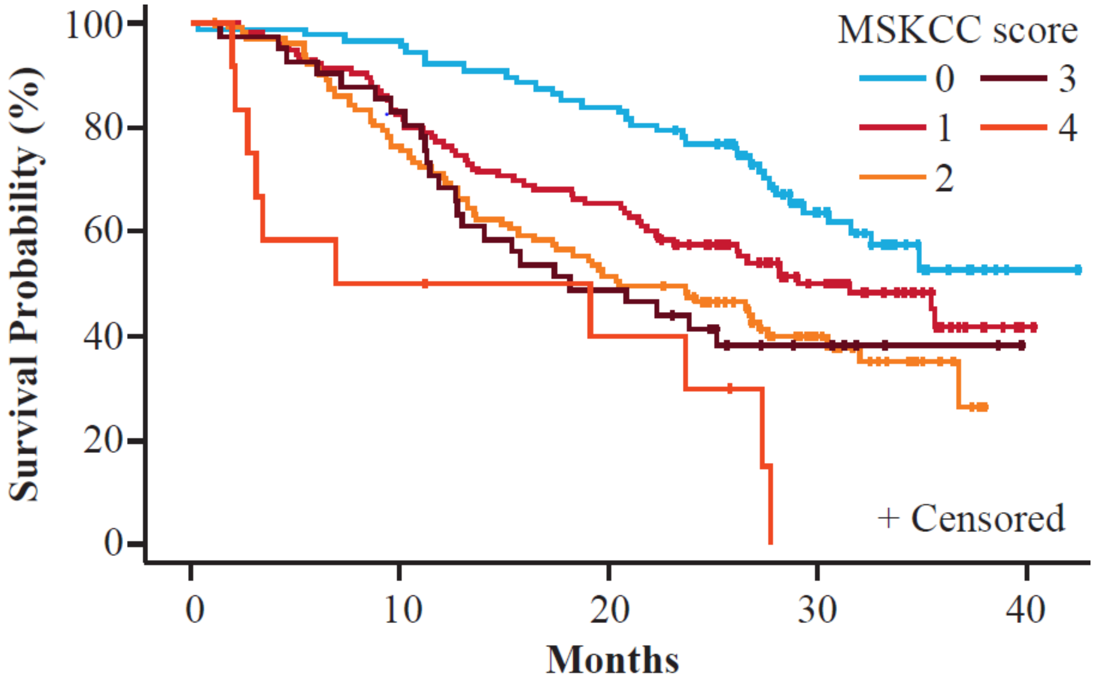
Patients at risk (censored)

1	28 (0)	28 (0)	25 (0)	22 (1)	12 (7)	0 (16)	
2	82 (0)	72 (4)	64 (5)	56 (6)	33 (18)	5 (40)	0 (45
3	81 (0)	69 (6)	57 (7)	49 (7)	22 (18)	5 (31)	0 (36
4	66 (0)	52 (3)	39 (3)	32 (3)	18 (9)	2 (24)	0 (26
5	145 (0)	109 (6)	75 (8)	59 (9)	26 (20)	2 (41)	0 (43
6	83 (0)	42 (3)	22 (5)	14 (6)	7 (7)	0 (13)	
7	31 (0)	10 (2)	4 (2)	2 (2)	0 (3)		

MSKCC, Memorial Sloan Kettering Cancer Center

Supplementary Figure 5: **Kaplan-Meier plot of overall survival for original MSKCC risk score in the discovery cohort (COMPARZ)**

Legend: Patients were separated by individual score on the annotated model (0-4); no patient scored 5, though technically it would have been possible. MSKCC, Memorial Sloan Kettering Cancer Center



Patients at risk (censored)					
0	87 (0)	84 (0)	73 (0)	36 (22)	1 (53)
1	115 (0)	95 (0)	75 (0)	35 (25)	1 (56)
2	102 (0)	77 (1)	52 (1)	19 (24)	0 (40)
3	41 (0)	34 (0)	20 (0)	9 (7)	0 (16)
4	12 (0)	6 (0)	4 (1)	0 (2)	