p53 suppresses type II endometrial carcinomas in mice and governs endometrial tumour aggressiveness in humans

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Supporting Information: Materials and Methods

TP53 deep sequencing primers

	p53 primers
MID1	
p53 Ex.5 F_MID1	5'-CGTATCGCCTCCCTCGCGCCATCAGACGAGTGCGTcacttgtgccctgactttca-3'
p53 Ex.5 R_MID1	5'-CTATGCGCCTTGCCAGCCCGCTCAGACGAGTGCGTaaccagccctgtcgtctct-3'
p53 Ex.5 Fs2_MID1	5'-CGTATCGCCTCCCTCGCGCCATCAGACGAGTGCGTcagctgtgggttgattcca-3'
p53 Ex.5 Rs1_MID1	5'-CTATGCGCCTTGCCAGCCCGCTCAGACGAGTGCGTtcatgtgctgtgactgcttg-3'
p53 Ex.6 F_MID1	5'-CGTATCGCCTCCCTCGCGCCATCAGACGAGTGCGTcaggcctctgattcctcact-3'
p53 Ex.6 R_MID1	5'-CTATGCGCCTTGCCAGCCCGCTCAGACGAGTGCGTcttaacccctcctcccagag-3'
p53 Ex.7 F_MID1	5'-CGTATCGCCTCCCTCGCGCCATCAGACGAGTGCGTccacaggtctccccaagg-3'
p53 Ex.7 R_MID1	5'-CTATGCGCCTTGCCAGCCCGCTCAGACGAGTGCGTcagcaggccagtgtgcag-3'
MID2	
p53 Ex.5 F_MID2	5'-CGTATCGCCTCCCTCGCGCCATCAGACGCTCGACAcacttgtgccctgactttca-3'
p53 Ex.5 R_MID2	5'-CTATGCGCCTTGCCAGCCCGCTCAGACGCTCGACAaaccagccctgtcgtctct-3'
p53 Ex.5 Fs2_MID2	5'-CGTATCGCCTCCCTCGCGCCATCAGACGCTCGACAcagctgtgggttgattcca-3'
p53 Ex.5 Rs1_MID2	5'-CTATGCGCCTTGCCAGCCCGCTCAGACGCTCGACAtcatgtgctgtgactgcttg-3'
p53 Ex.6 F_MID2	5'-CGTATCGCCTCCCTCGCGCCATCAGACGCTCGACAcaggcctctgattcctcact-3'
p53 Ex.6 R_MID2	5'-CTATGCGCCTTGCCAGCCCGCTCAGACGCTCGACActtaacccctcctcccagag-3'
p53 Ex.7 F_MID2	5'-CGTATCGCCTCCCTCGCGCCATCAGACGCTCGACAccacaggtctccccaagg-3'
p53 Ex.7 R_MID2	5'-CTATGCGCCTTGCCAGCCCGCTCAGACGCTCGACAcagcaggccagtgtgcag-3'
p53 Ex.8 F_MID2	5'-CGTATCGCCTCCCTCGCGCCATCAGACGCTCGACAgcctcttgcttctcttttcc-3'
p53 Ex.8 R_MID2	5'-CTATGCGCCTTGCCAGCCCGCTCAGACGCTCGACAtaactgcaccctggtctcc-3'
MID3	
p53 Ex.5 F_MID3	5'-CGTATCGCCTCCCTCGCGCCATCAGAGACGCACTCcacttgtgccctgactttca-3'
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p53 Ex.5 R_MID3_short*	5'-CTATGCGCCTTGCCAGCCCGCTCAGAGACGCACTCctgctcaccatcgctatctg-3'
p53 Ex.5 Fs2_MID3	5'-CGTATCGCCTCCCTCGCGCCATCAGAGACGCACTCcagctgtgggttgattcca-3'
p53 Ex.5 Rs1_MID3	5'-CTATGCGCCTTGCCAGCCCGCTCAGAGACGCACTCtcatgtgctgtgactgcttg-3'
p53 Ex.6 F_MID3	5'-CGTATCGCCTCCCTCGCGCCATCAGAGACGCACTCcaggcctctgattcctcact-3'
p53 Ex.6 R_MID3	5'-CTATGCGCCTTGCCAGCCCGCTCAGAGACGCACTCcttaacccctcctcccagag-3'
p53 Ex.7 F_MID3	5'-CGTATCGCCTCCCTCGCGCCATCAGAGACGCACTCccacaggtctccccaagg-3'
p53 Ex.7 R_MID3	5'-CTATGCGCCTTGCCAGCCCGCTCAGAGACGCACTCcagcaggccagtgtgcag-3'
p53 Ex.8 F_MID3	5'-CGTATCGCCTCCCTCGCGCCATCAGAGACGCACTCgcctcttgcttctcttttcc-3'
p53 Ex.8 R_MID3	5'-CTATGCGCCTTGCCAGCCCGCTCAGAGACGCACTCtaactgcaccctggtctcc-3'
MID4	
p53 Ex.8 F_MID4**	5'-CGTATCGCCTCCCTCGCGCCATCAGAGCACTGTAGgcctcttgcttctcttttcc-3'
p53 Ex.8 R_MID4**	5'-CTATGCGCCTTGCCAGCCCGCTCAGAGCACTGTAGtaactgcaccctggtctcc-3'

*MID3_short primer combination was used with Fs2 for p53 exon 5 amplification due to better PCR performance
**MID4 primer combinations were used instead of MID1 in p53 exon 8 multiplexing due to better PCR performance

Statistical determination of risk score based on analysis of multiple immunohistochemical variables

One of the major statistical challenges in large scale immunohistochemical studies are missing values in the design matrix due to missing or corrupt spots on the TMA. The more markers that are investigated the higher the chance that at least one value is missing per patient. Frequently this problem is tackled by either sacrificing a larger number of patient records or by employing unreliable multiple imputation techniques. In this study, ignoring missing values would reduce the set of patients with all measurements from 410 to 302. To overcome this problem we developed a novel statistical approach based on a learning model that is invariant to missing values and results in an easily interpretable and practically applicable linear model. Prognostic power of the individual and combined clinico-pathologic variables was assessed by learning univariate proportional hazard models, yielding eight markers significantly associated with overall survival. To correct for multiple testing, the false discovery rate (FDR) procedure was applied with a FDR of 0.01, reducing the set of significantly associated markers to four. A risk score was calculated for each patient by a linear combination of the univariate Cox regression coefficients β and the corresponding IHC measurements $x = \{x_1, x_2, \ldots, x_D\}$, where D is the number of markers in the signature. Single x_i might be unavailable due to missing TMA spots. Finally, the score was normalized by the number of markers measured:

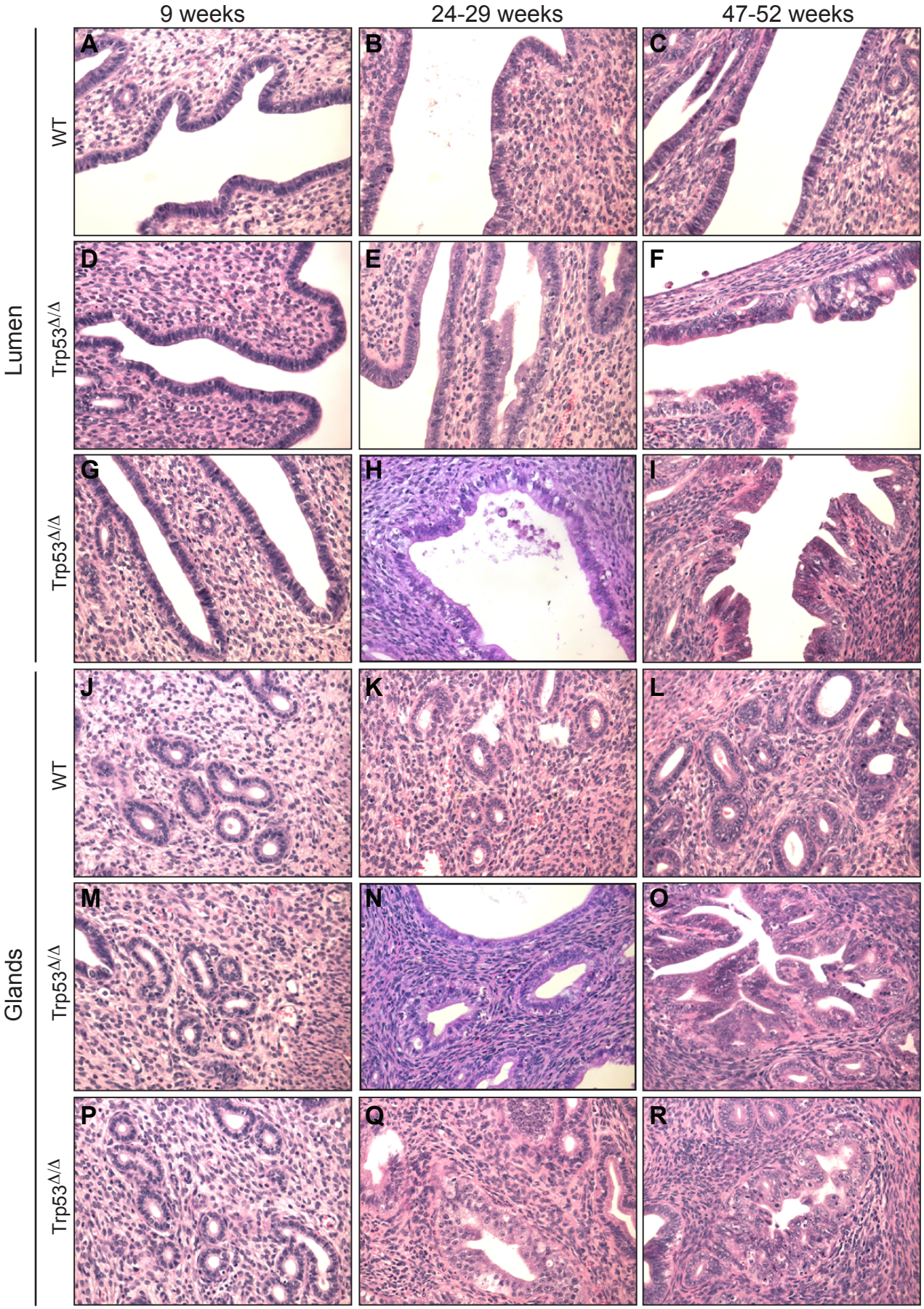
$$\text{score}(x) = \left(\sum_{i=1}^{D} (\beta_i x_i) \alpha_i \right) \Bigg/ \left(\sum_{i=1}^{D} \alpha_i \right), \quad \alpha_i = \begin{cases} 1, & \text{if } x_i \text{ exists} \\ 0, & \text{if } x_i \text{ is missing} \end{cases}$$

Based on this risk score, patients were assigned to a high risk group and a low risk group, split at the 50th percentile (median) of all scores. Thus, the final model consisted of the coefficient vector β and the median threshold θ. The model was thoroughly evaluated with cross validation experiments and a multivariate Cox regression analysis. The cross validation experiments were conducted as follows:

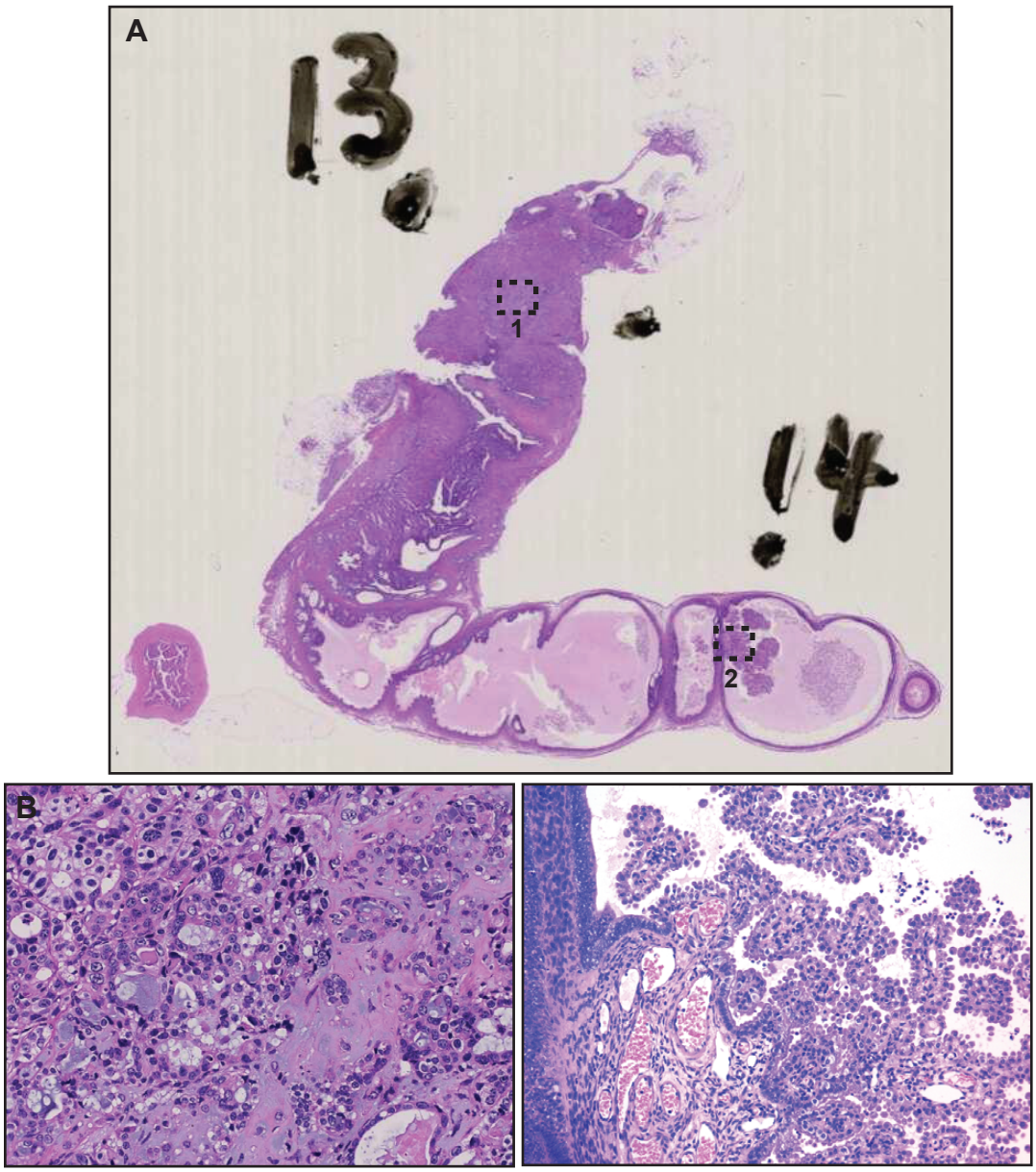
1. Divide the patients into K cross-validation folds (groups) at random.

2. For each fold k = 1, 2, …, K
    a. Find a subset of univariate statistically significant (LRT $p < 0.05$) predictors for the overall survival, using all of the patients except those in fold k.
    b. Filter the selected predictors based on a FDR of 0.01.
    c. Using just this subset of predictors, build a multivariate linear model using the formulation in score equation, using all of the patients except those in fold k.
    d. Use the model to predict the score for the patients in fold k.
3. Aggregate the out-of-bag predictions of all patients and split them in two groups based on the median predicted score.
4. Calculate the Kaplan-Meier estimator for each group and report the LRT p-value of their difference in survival expectation.

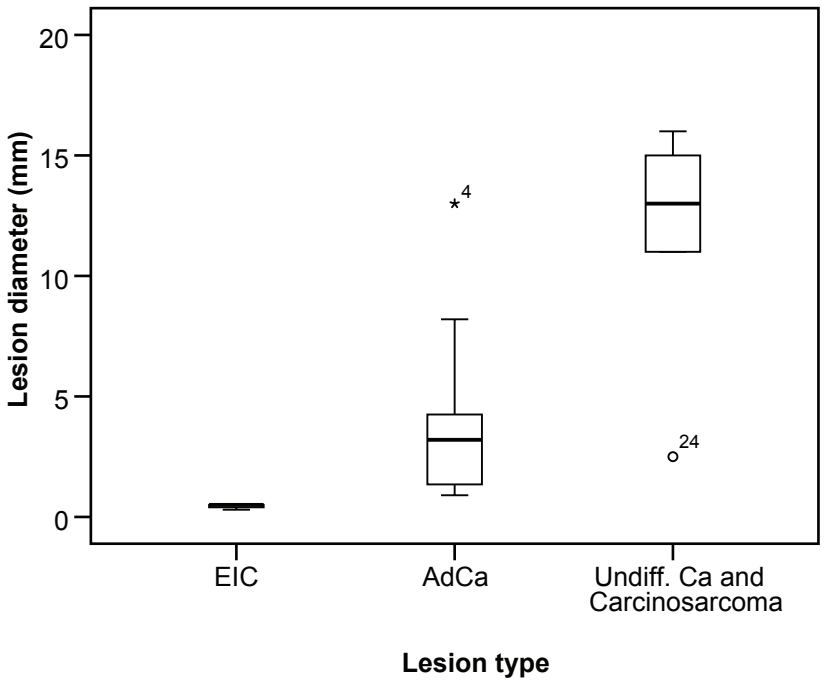
10-fold cross validation was conducted by partitioning the dataset into 10 parts of equal size using 90% of the patients for learning and 10% for validation. The procedure was repeated 10 times resulting in a 10-fold score for each patient. The resulting differentiation between high risk and low risk patient was still highly significant as shown in Fig. 6C ($p=0.000011$).



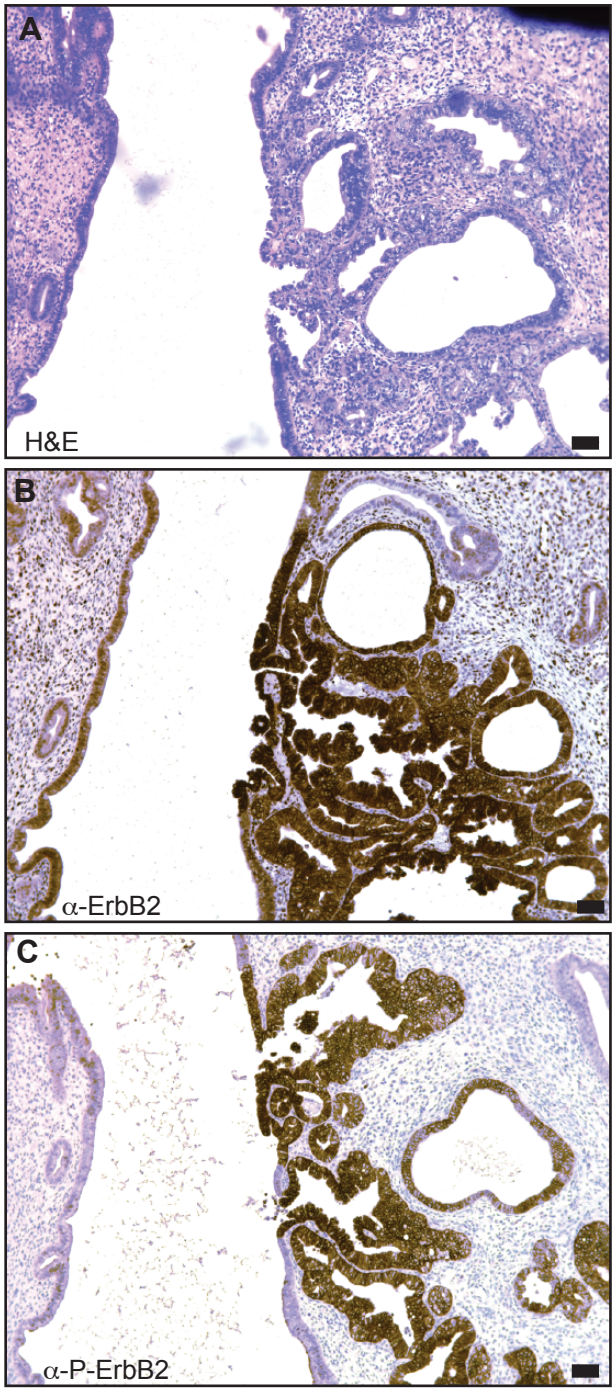
Supporting Information Figure 1 Representative histological appearances of lumenal (**A-J**) and glandular (**J-R**) endometria in wild type (**A-C, J-L**) and Trp53Δ/Δ (**D-I, M-R**) mice. Pictures are representative of cohorts of mice aged 9 weeks (**A,D,G,J,M,P**), 24-29 weeks (**B,E,H,K,N,Q**) or 47-52 weeks (**C,F,I,L,O,R**).



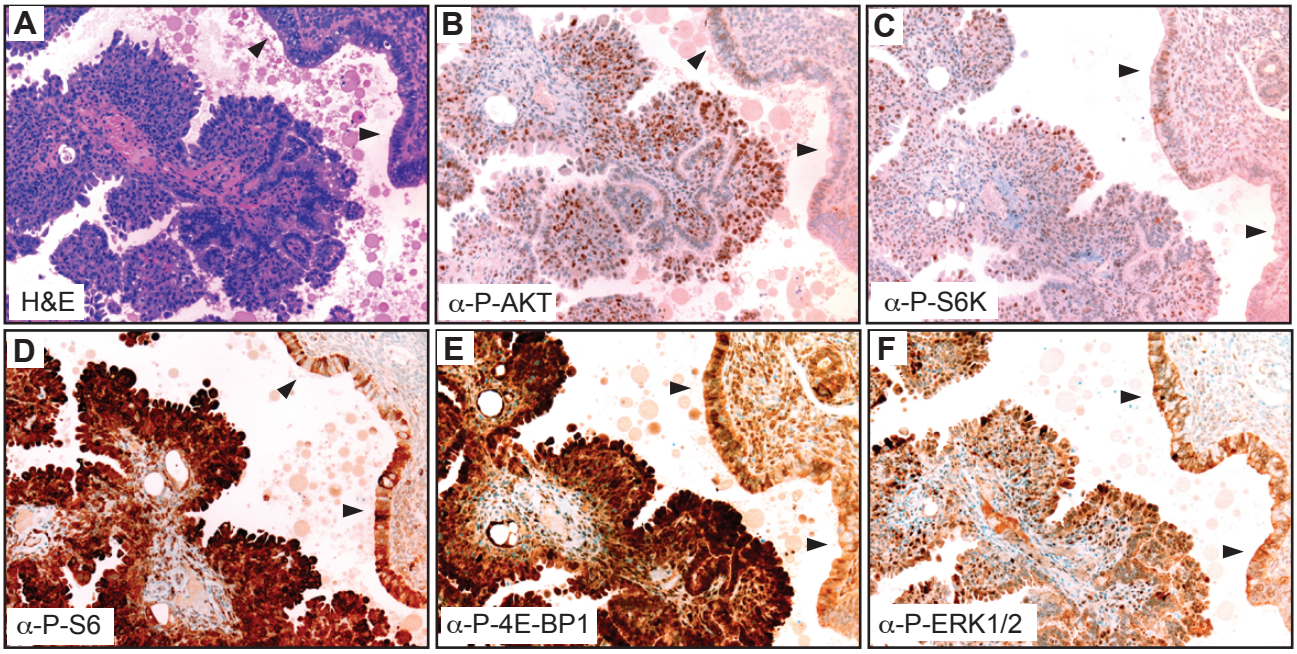
Supporting Information Figure 2 Example of a carcinosarcoma and of a serous, partly clear cell adenocarcinoma arising in the uterus of a 68 week-old Trp53Δ/Δ mouse. (**A**) Low power magnification of a longitudinal cross section of the uterus, displaying the carcinosarcoma in the upper uterine branch and a papillary serous, partly clear cell adenocarcinoma in the lower uterine branch. (**B**) Zoom of the region from box 1 in **A** showing a mixed clear cell adenocarcinoma and chondrosarcoma phenotype. (**C**) Zoom of the region from box 2 in **A** showing a papillary serous and partly clear cell adenocarcinoma.



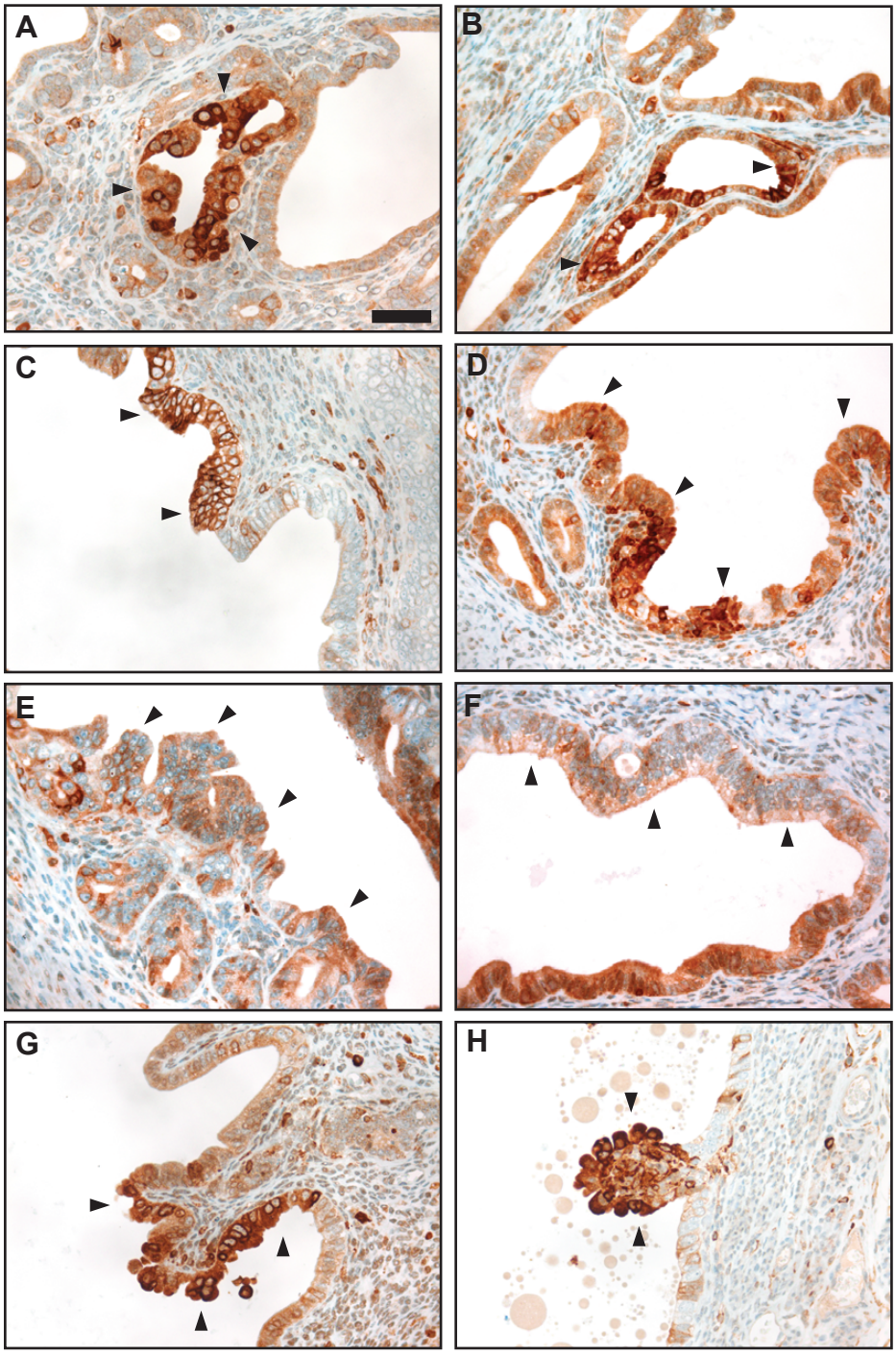
Supporting Information Figure 3 Sizes of lesions in *Trp53* mutant mice. Box plot showing the maximum diameter (mm) of lesions identified in mice aged 58-72 weeks, grouped according to lesion type. EIC: endometrial intraepithelial carcinoma, AdCa: adenocarcinoma, Undiff. Ca and Carcinosarcoma: undifferentiated carcinoma and carcinosarcoma.



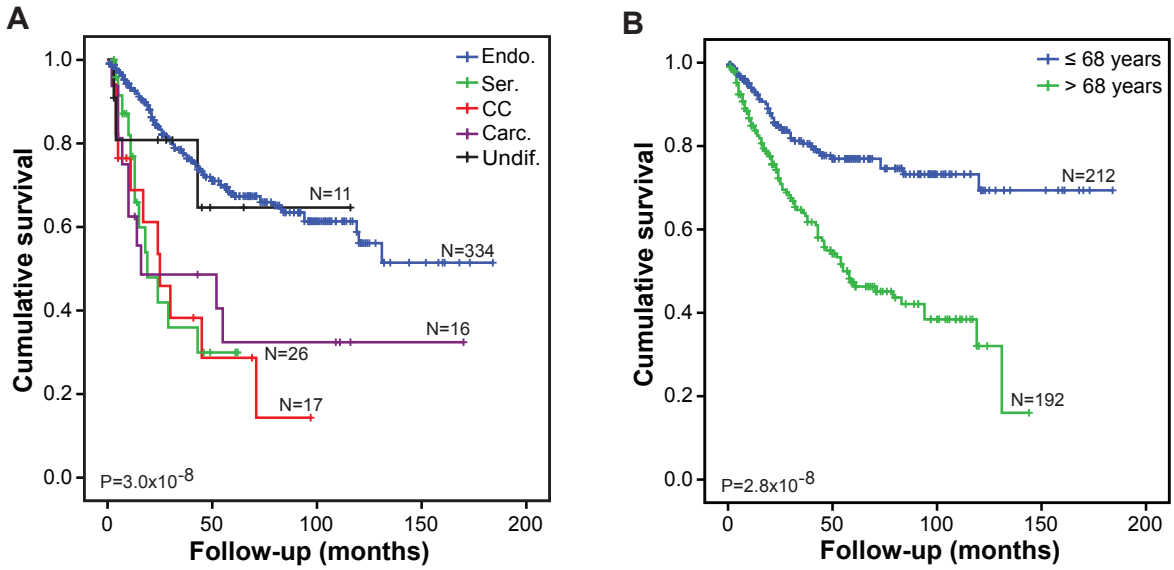
Supporting Information Figure 4 Activation of ErbB2 in a tumour from a *Trp53* mutant mouse. (**A**) Haemotoxlin and eosin stain of a clear cell EIC lesion. (**B**) Immunohistochemical staining using an antibody against ErbB2. (**C**) Immunohistochemical staining using an antibody against phospho-Tyr1248-ErbB2, a marker of ErbB2 activation. This staining is classified as DAKO 3+ on the Hercep test criteria. Scale bars represent 200 μm.



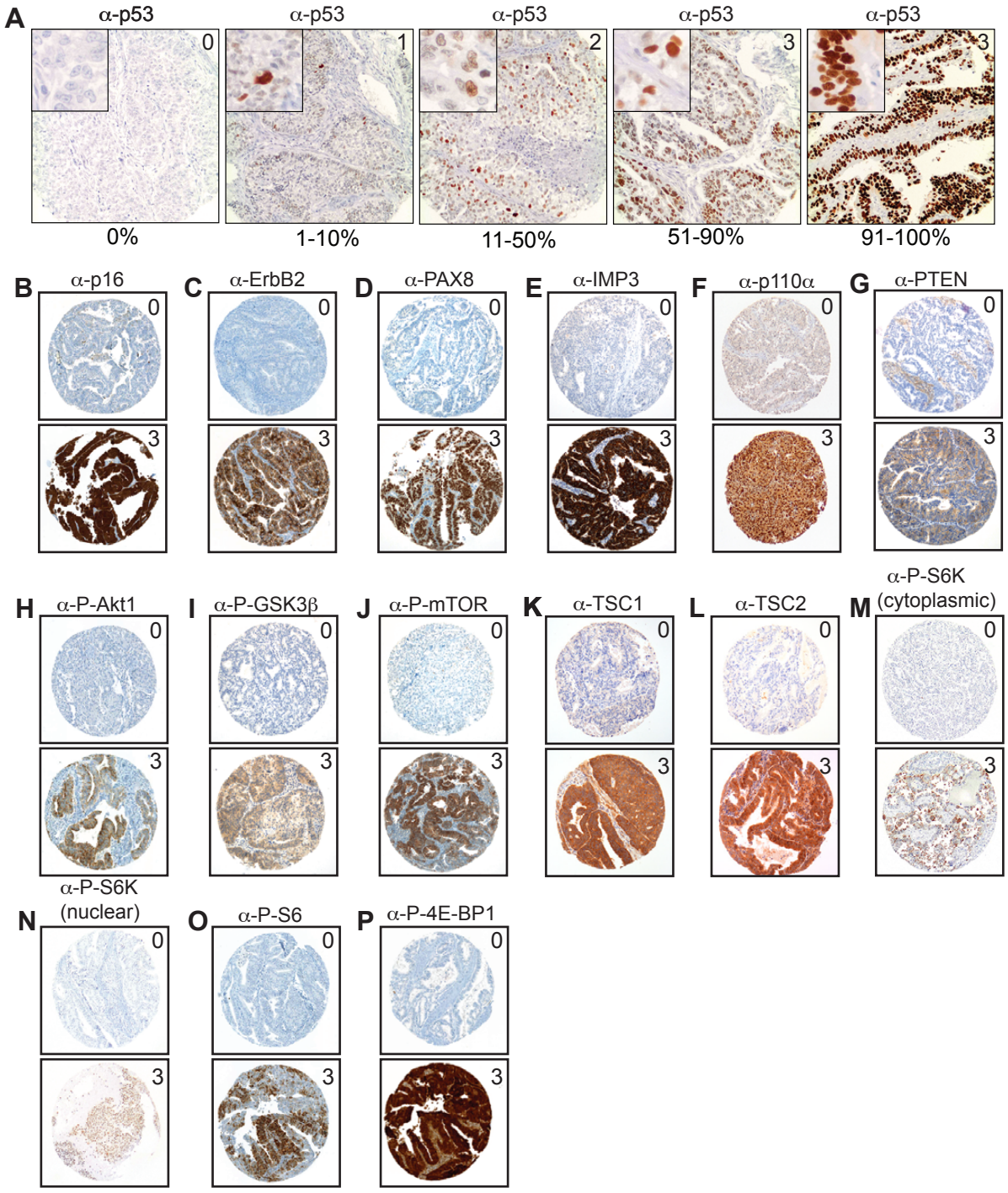
Supporting Information Figure 5 Activation of the PI3K-AKT-mTOR signalling pathway in a tumour from a *Trp53* mutant mouse. Adjacent sections of a serous adenocarcinoma were stained with (**A**) haematoxylin and eosin or immunohistochemically with antibodies against (**B**) phospho-Ser473-AKT, (**C**) phospho-Thr421/Ser424-p70 S6 Kinase, (**D**) phospho-Ser240/244-ribosomal S6 protein, (**E**) phospho-Thr37/46-4E-BP1, (**F**) phospho-Thr202/Tyr204-ERK1/2. Arrowheads depict the normal-appearing, non-dysplastic surface epithelium adjacent to the tumour.



Supporting Information Figure 6 Upregulation of P-S6 at discrete early lesions in *Trp53* mutant mice. (**A-H**) Immunohistochemical staining of various early lesions using an antibody against phospho-Ser240/244-ribosomal S6 protein. (**A,B**) Examples of upregulated expression in endometrial glandular dysplasia arising in glands. (**C,D**) Examples of upregulated expression in endometrial glandular dysplasia arising in luminal surface epithelium. (**E,F**) Examples of endometrial glandular dysplasia that do not show elevated staining. (**G,H**) Upregulation P-S6 expression was observed in all very early papillary endometrial intraepithelial carcinoma lesions. Arrowheads in **A-F** highlight regions of endometrial glandular dysplasia and in **G,H** sites of papillary endometrial intraepithelial carcinoma. All images are the same magnification, scale bar represents 50 μm.

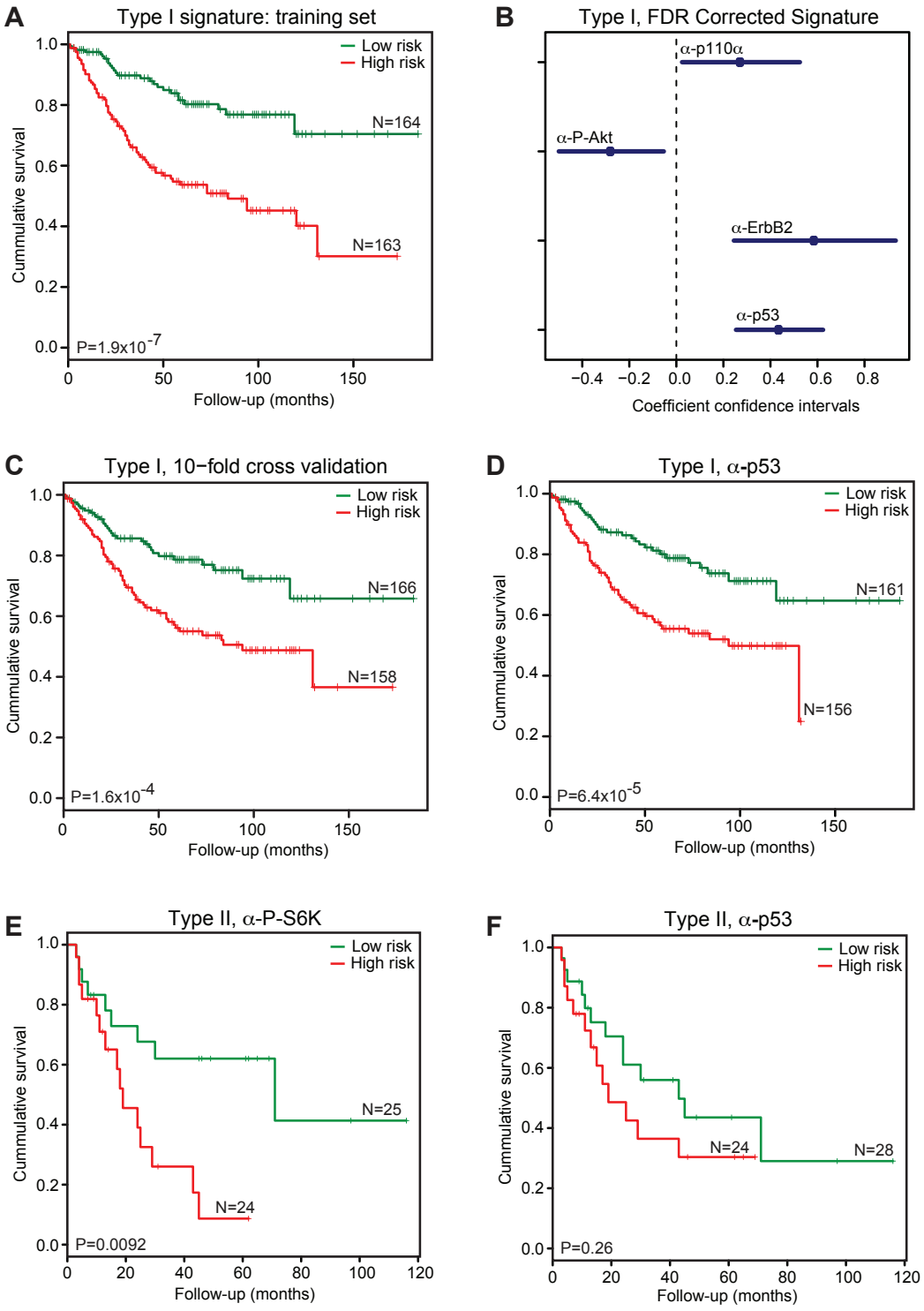


Supporting Information Figure 7 Patient survival correlated to clinical parameters. Kaplan-Meier plots of patient survival over time after diagnosis when patients were grouped according to histologic tumour subtype (**A**) or age at diagnosis (**B**). P values are from the Log Rank (Mantel-Cox) test to test the equality of survival distributions of each group. Abbreviations: Endo. endometrioid carcinoma, Ser. serous carcinoma, CC. clear cell carcinoma, Carc. carcinosarcoma, Undif. undifferentiated carcinoma.

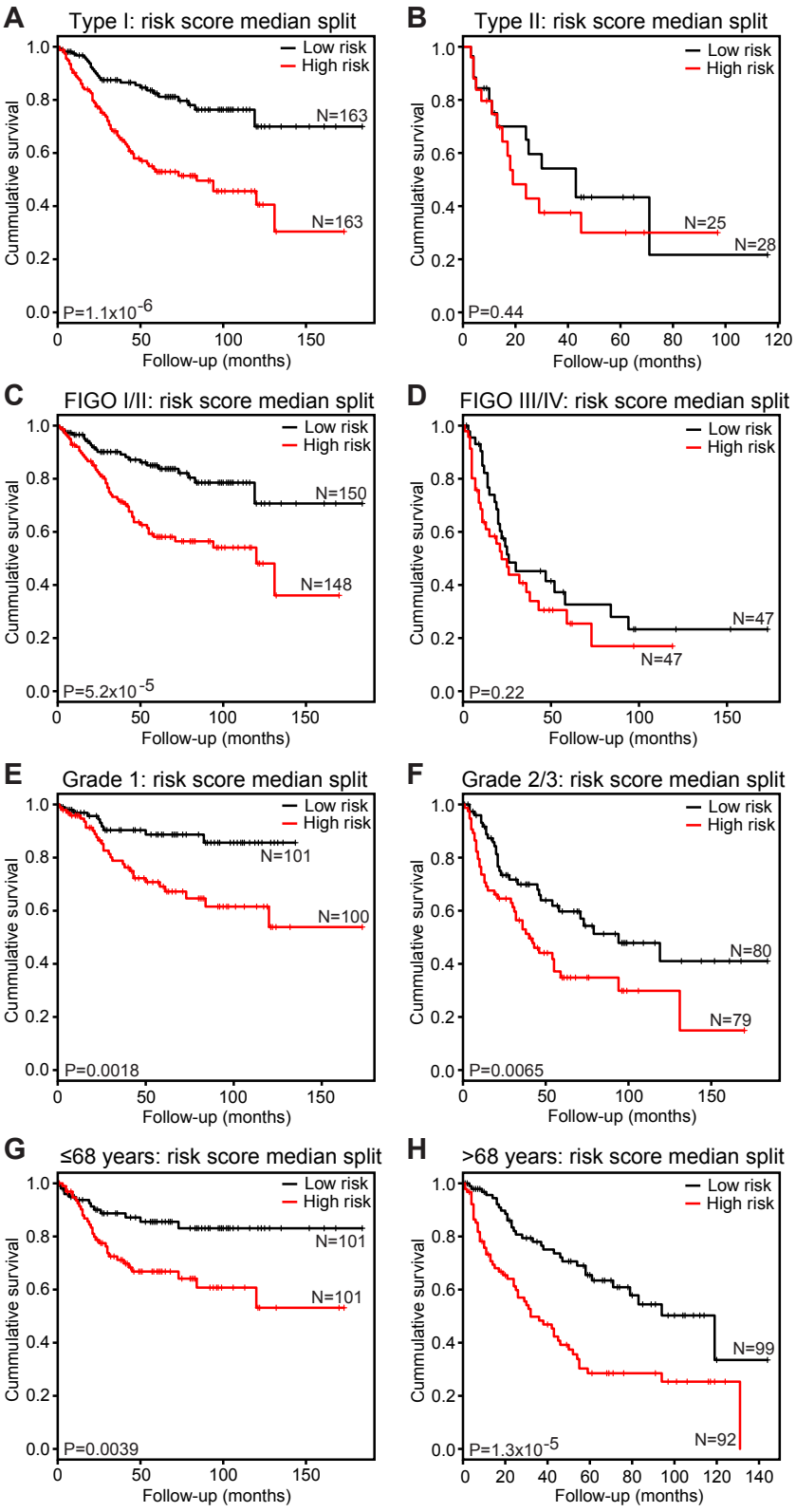


Supporting Information Figure 8

(**A**) Examples of representative TMA spots (inset is zoom) showing different p53 IHC staining patterns classified according to frequency of cells exhibiting strong nuclear immunoreactivity. Cells were classified in 4 groups (IHC score 0-3) for analysis in Fig 4 and in 5 groups (IHC score as % groups) for analysis in all other Figures. (**B-N**) Examples of TMA spots with negative (score 0) and strongly positive (score 3) immunoreactivity for antibodies against p16 (**B**), ErbB2 (**C**), PAX8 (**D**), IMP3 (**E**), p110α (**F**), PTEN (**G**), phospho-Ser473-AKT (**H**), phospho-Ser9-GSK3β (**I**), phospho-Ser2448-mTOR (**J**), TSC1 (**K**), TSC2 (**L**), phospho-Thr421/Ser424-p70 S6 Kinase (cytoplasmic staining) (**M**), phospho-Thr421/Ser424-p70 S6 Kinase (nuclear staining) (**N**), phospho-Ser240/244-ribosomal S6 protein (**O**) and phospho-Thr37/46-4E-BP1 (**P**).



Supporting Information Figure 9 Kaplan-Meier plots based on risk-model analysis of survival of patients with type I endometrial carcinomas (**A-D**) or type II carcinomas (**E,F**). (**A**) Patient stratification using a risk-model four-marker signature based on staining patterns for p110α, phospho-Ser473-AKT, ErbB2 and p53. (**B**) Contribution of each marker to the signature represented by coefficients and confidence intervals. (**C**) Patient stratification based on 10-fold cross-validation of the linear risk score model. (**D**) Patient stratification based on the median split of p53 expression frequency only, showing equal prognostic power to the four-marker model. (**E**) Patient stratification in type II tumours based on the median split of phospho-Thr421/Ser424-p70 S6 Kinase nuclear staining. (**F**) Patient stratification in type II tumours based on the median split of p53 staining frequency. Log Rank (Mantel-Cox) tests were conducted to test for equality in the survival expectation of both groups. N values represent the number of patients in each group.



Supporting Information Figure 10 Kaplan-Meier plots for high-risk and low-risk endometrial carcinoma patients based on the four-marker signature consisting of p110α, phospho-Ser240/244-ribosomal S6 protein, ErbB2 and p53. (**A**) Kaplan-Meier plots for subgroups of patients based on low and high risk scores in type I tumours, (**B**) in type II tumours, (**C**) in FIGO stage I and II tumours, (**D**) in FIGO stage III and IV tumours, (**E**) in grade 1 tumours, (**F**) in grade 2 and 3 tumours, (**G**) in tumours arising in patients 68 years or younger or (**H**) in tumours arising in patients older than 68 years, respectively. Log Rank (Mantel-Cox) tests were conducted to test for equality in the survival expectation of both groups. N values represent the number of patients in each group.

Supporting Information Table 1. Clinicopathologic and immunohistochemical features in endometrial cancer patients

Variable	*n*	*%*
Follow-up data:		
No. of patients	**521**	
No. of patients with follow-up (%)	410 (78.7%)	
Median follow-up	38 months	
(range)	(1-184 months)	
Clinicopathological characteristics:		
Age at diagnosis (median 68 years, range 33-92)		
≥ 68 years	268	51.4
> 68 years	252	48.4
unknown	1	0.2
FIGO stage		
I	263	50.5
II	65	12.5
III	76	14.6
IV	18	3.5
unknown	99	19.0
Histologic subtype		
Endometrioid adenocarcinoma	436	83.7
Serous adenocarcinoma	34	6.5
Clear cell adenocarcinoma	19	3.6
Undifferentiated carcinoma	16	3.1
Carcinosarcoma	16	3.1
unknown	0	0
Grading FIGO		
1	270	51.8
2	128	24.6
3	88	16.9
unknown	35	6.7
Immunohistochemical data:		
Nuclear p53 (%)		
negative	231	44.3
1-10%	129	24.8
11-50%	50	9.6
51-90%	28	5.4
91-100%	44	8.4
unknown	39	7.5
Cytoplasmic p16 (intensity)		
negative	51	9.8
score 1+	160	30.7
score 2+	211	40.5
score 3+	41	7.9
unknown	58	11.1
ErbB2 (Dako HercepTest criteria)		
negative	391	75.0
score 1+	55	10.6
score 2+	9	1.7
score 3+	10	1.9
unknown	56	10.7
Nuclear PAX8 (intensity)		
negative	74	14.2
score 1+	127	24.4
score 2+	173	33.2
score 3+	94	18.0
unknown	53	10.2
Cytoplasmic IMP3 (intensity)		
negative	269	51.6
score 1+	90	17.3
score 2+	64	12.3
score 3+	38	7.3
unknown	60	11.5

Variable	*n*	*%*
Immunohistochemical data (continued):		
Nuclear p110α (intensity)		
negative	21	4.0
score 1+	141	27.1
score 2+	163	31.3
score 3+	120	23.0
unknown	76	14.6
Cytoplasmic PTEN (intensity)		
negative	353	67.8
score 1+	63	12.1
score 2+	41	7.9
score 3+	8	1.5
unknown	56	10.7
Cytoplasmic P-Akt1 (Ser473) (intensity)		
negative	135	25.9
score 1+	177	34.0
score 2+	124	23.8
score 3+	43	8.3
unknown	42	8.1
Cytoplasmic P-GSK3β (intensity)		
negative	391	75.0
score 1+	55	10.6
score 2+	15	2.9
score 3+	3	0.6
unknown	57	10.9
Cytoplasmic P-mTOR (intensity)		
negative	182	34.9
score 1+	135	25.9
score 2+	114	21.9
score 3+	43	8.3
unknown	47	9.0
Cytoplasmic P-S6K (intensity)		
negative	397	76.2
score 1+	45	8.6
score 2+	13	2.5
score 3+	4	0.8
unknown	62	11.9
Nuclear P-S6K (intensity)		
negative	252	48.4
score 1+	144	27.6
score 2+	58	11.1
score 3+	4	0.8
unknown	63	12.1
Cytoplasmic P-S6 ribosomal protein (Ser235/236) (intensity)		
negative	251	48.2
score 1+	87	16.7
score 2+	82	15.7
score 3+	50	9.6
unknown	51	9.8
Cytoplasmic P-4E-BP1 (Thr37/46) (intensity)		
negative	110	21.1
score 1+	86	16.5
score 2+	196	37.6
score 3+	96	18.4
unknown	33	6.3
Cytoplasmic TSC1		
negative	14	2.7
score 1+	77	14.8
score 2+	213	40.9
score 3+	95	18.2
unknown	122	23.4
Cytoplasmic TSC2		
negative	114	21.9
score 1+	155	29.8
score 2+	88	16.9
score 3+	17	3.3
unknown	147	28.2

Supporting Information Table 2. ***TP53*** **Deep sequencing analyses**

TMA Spot No.	Histology	Grade	Grade_d1	p53 IHC groups	Dominant mutation frequency (%)	Dominant mutation	Functional impact of dominant mutation	Number of mutations in coding region	Cumulative mutation frequency in coding region (%)	Number of mutations with functional impact (N)	Cumulative mutation frequency with functional impact (%)	Mutations with functional impact														
3	Endom	1	G1	>10% - 50%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9	Serous	-	-	>90% - 100%	98	G266E	high	10	396	8	362	G279E	G266E	G262S	T253A	Y220C	P219L	P152S	P142L	-	-	-	-	-	-	-	-
17	Endom	1	G1	negative	19	R196*	high	11	118	5	35	R196*	G245S	H214Y	A161T	L130F	-	-	-	-	-	-	-	-	-	-	-
19	Endom	3	G2-3	>10% - 50%	6	A161V	medium	16	74	9	35	E286K	P250S	M246I	V225I	P219L	T211I	R202C	G187D	A161V	-	-	-	-	-	-	-
21	Endom	1	G1	<=10%	16	P151L	medium	6	50	5	32	G302E	G293R	G266R	G262D	P151L	-	-	-	-	-	-	-	-	-	-	-
23	Endom	1	G1	<=10%	6	G279E	high	17	61	10	34	P300S	G279E	G262S	E258K	T230I	V225I	R202C	P191L	T155I	S127F	-	-	-	-	-	-
25	Endom	1	G1	<=10%	12	Q192*	high	12	105	6	21	Q192*	Q165*	L252F	M243I	T211I	D207N	-	-	-	-	-	-	-	-	-	-
27	Endom	1	G1	negative	19	G266E	high	13	180	5	43	R282Q	G266E	R158C	T155I	S149F	-	-	-	-	-	-	-	-	-	-	-
29	Endom	1	G1	>10% - 50%	43	G226S	medium	12	297	5	168	D228N	G226S	T155I	P151S	W146R	-	-	-	-	-	-	-	-	-	-	-
31	Serous	-	-	>50% - 90%	35	Pro191_Pro191del	high	21	151	9	81	R213*	Q165*	Pro191_Pro191del	R283H	S260F	L252F	S215N	P152L	P151L	-	-	-	-	-	-	-
33	Endom	1	G1	<=10%	9	H297Y	low	21	99	8	29	R196*	W146*	H297Y	C238Y	T155I	G154S	P151L	P151S	-	-	-	-	-	-	-	-
37	Endom	1	G1	<=10%	10	M246I	medium	15	70	9	48	Q192*	H297Y	G262D	M246I	D208N	P191S	P190L	C141Y	P128S	-	-	-	-	-	-	-
39	Endom	1	G1	>10% - 50%	6	P177L	high	20	104	10	43	Q144*	G302E	D259N	T231I	G226S	P177L	A63C	T155I	P153S	P151L	-	-	-	-	-	-
45	Endom	1	G1	negative	3	R248W	high	1	4	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
47	Endom	2	G2-3	>10% - 50%	6	S260F	medium	8	33	5	20	R306Q	D281N	S215G	P177L	P151L	-	-	-	-	-	-	-	-	-	-	-
49	Endom	1	G1	negative	28	P191S	medium	27	195	17	138	G302E	T284I	R283C	D259N	R248Q	T230I	D228N	V225I	R213Q	P191S	R181C	H179Y	H178Y	R158H	P153S	T150I	V143M
51	Endom	1	G1	<=10%	4	R306Q	medium	17	70	12	48	R306Q	S303N	A276T	S227F	P223L	D208N	E198K	R196Q	E171K	T170M	V157I	T155I	-	-	-	-	-
55	Endom	-	-	negative	9	R282Q	high	7	41	4	22	R282Q	V274A	R248Q	G226S	-	-	-	-	-	-	-	-	-	-	-	-
59	Endom	2	G2-3	<=10%	29	D207N	medium	13	129	6	83	R273H	G262S	S241F	V218M	V217M	D207N	-	-	-	-	-	-	-	-	-	-
61	Endom	2	G2-3	>50% - 90%	53	R280K	high	28	344	17	245	Q192*	Q144*	R280K	G266E	G262S	S260F	D259N	T253A	G245S	S227F	Y220C	D207N	P152S	V143M	P142L	A138T	L130F
63	Endom	1	G1	<=10%	3	R196*	high	6	25	2	4	R196*	G245S	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
65	Endom	1	G1	negative	4	A276T	medium	17	54	6	18	R306*	G293R	E286K	C277Y	A276T	R273H	-	-	-	-	-	-	-	-	-	-	-
73	Endom	2	G2-3	negative	10	P151L	medium	2	14	2	14	C277Y	P151L	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
75	Endom	1	G1	negative	24	E285K	medium	29	191	16	127	R213*	W146*	W146*	H296Y	E285K	G279E	P250S	G226D	V225I	P219S	R213Q	G199R	L194F	P190L	A159T	T150I	-
77	Endom	1	G1	negative	6	Q165*	high	14	52	5	11	Q192*	L252F	H233Y	G226S	V225I	-	-	-	-	-	-	-	-	-	-	-	-
79	Endom	1	G1	negative	7	T155I	high	18	66	7	26	P278S	G266E	M243I	P191L	P191S	R158C	T155I	-	-	-	-	-	-	-	-	-	-
85	Endom	1	G1	negative	15	R306Q	medium	5	58	1	15	R306Q	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
91	Endom	2	G2-3	>10% - 50%	49	C135Y	high	14	114	5	71	T256I	T231I	T230I	C176F	C135Y	-	-	-	-	-	-	-	-	-	-	-	-
95	Endom	3	G2-3	<=10%	6	P278S	high	14	45	9	28	P278S	R267Q	G266E	M246I	P219L	I195T	L194F	V157I	S127F	-	-	-	-	-	-	-	-
97	Endom	3	G2-3	negative	3	E286K	high	27	62	12	25	E286K	R282H	G266E	G262D	S241F	C238Y	H214Y	A159V	R158C	P142L	T140I	P128S	-	-	-	-	-
99	Endom	1	G1	<=10%	6	A189V	medium	15	73	2	5	C176F	H168Y	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
101	Endom	1	G1	>10% - 50%	4	E285R	medium	2	6	1	4	E285K	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
107	Endom	3	G2-3	>90% - 100%	65	M237I	high	17	183	9	132	W146*	E286K	A276T	C275G	S260P	R248Q	M237I	V225I	R158C	-	-	-	-	-	-	-	-
109	Endom	1	G1	negative	3	A189V	medium	10	28	5	11	A189V	C182Y	E180K	C176Y	G154D	-	-	-	-	-	-	-	-	-	-	-	-
111	Endom	1	G1	negative	10	G302R	low	19	116	7	39	P300S	E286K	T284I	S260F	R248Q	V225I	S149F	-	-	-	-	-	-	-	-	-	-
113	Endom	1	G1	<=10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
115	Endom	2	G2-3	>10% - 50%	19	C277Y	high	18	115	9	67	W146*	C277Y	P250S	P222L	L194F	P191S	A161V	M160I	P128S	-	-	-	-	-	-	-	-
117	Endom	1	G1	<=10%	2	V216M	high	6	7	3	4	V216M	H193Y	P142S	-	-	-	-	-	-	-	-	-	-	-	-	-	-
119	Endom	1	G1	<=10%	5	E286K	high	30	50	14	26	Q144*	E286K	G279E	R273C	E271K	M246I	M237I	T230I	A161V	P152L	P152S	P151S	T150I	A138V	-	-	-
123	Endom	1	G1	negative	11	G279E	high	11	52	6	30	R290C	G279E	G279R	G262S	S260F	S241F	-	-	-	-	-	-	-	-	-	-	-
125	Endom	1	G1	negative	6	R248Q	high	10	32	5	22	Q136*	R306Q	A276T	R248Q	A138V	-	-	-	-	-	-	-	-	-	-	-	-
131	Endom	1	G1	<=10%	4	R213*	high	12	46	6	18	R213*	Q144*	E286K	G226D	E221K	H214Y	-	-	-	-	-	-	-	-	-	-	-
133	Endom	1	G1	<=10%	18	R273H	high	13	150	6	71	E286K	D281N	R273H	V173M	P153L	P152L	-	-	-	-	-	-	-	-	-	-	-
135	Endom	1	G1	<=10%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
137	Endom	1	G1	negative	3	H214Y	medium	12	24	6	11	G266E	G262S	S241F	V225I	H214Y	R213Q	-	-	-	-	-	-	-	-	-	-	-
143	Endom	2	G2-3	>50% - 90%	67	Y220C	high	20	121	12	95	H297Y	R282W	P250S	R249K	R248Q	M246I	C238Y	M237I	D228N	V225I	Y220C	R213Q	-	-	-	-	-
167	Endom	1	G1	>50% - 90%	50	R248Q	high	16	92	8	70	S303N	C277Y	A276V	D259N	E258K	R248Q	D207G	A189V	-	-	-	-	-	-	-	-	-
191	Endom	2	G2-3	>50% - 90%	38	R282W	high	2	74	2	74	R282W	A161T	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
207	Serous	-	-	<=10%	13	T253I	medium	25	202	16	106	R267Q	T253I	T230I	E224K	S215N	V197M	L194F	H193Y	P191L	D93N	V172I	R158C	G154D	P153S	P151S	L130F	-
211	Serous	-	-	>90% - 100%	85	R248Q	high	5	124	4	113	R248Q	T170M	R156H	T140I	-	-	-	-	-	-	-	-	-	-	-	-	-
213	Endom	2	G2-3	>10% - 50%	8	R267Q	medium	18	57	10	34	H296Y	C275Y	S269N	R267Q	R267W	S260F	L252F	G244D	M243T	P151S	-	-	-	-	-	-	-
217	Endom	3	G2-3	>90% - 100%	35	A276D	high	2	68	1	35	A276D	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
247	Endom	1	G1	>50% - 90%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
283	Endom	2	G2-3	>90% - 100%	73	S241F	high	2	76	1	73	S241F	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
285	Endom	1	G1	>10% - 50%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
287	Endom	-	-	>10% - 50%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
289	Endom	1	G1	>90% - 100%	44	R273H	high	4	51	4	51	A276T	R273H	L252F	R248W	-	-	-	-	-	-	-	-	-	-	-	-	-
297	Endom	2	G2-3	>10% - 50%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
335	Serous	-	-	>90% - 100%	70	D281E	high	1	70	1	70	D281E	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
337	Serous	-	-	>90% - 100%	89	R273H	high	1	89	1	89	R273H	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
359	Endom	1	G1	>10% - 50%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
361	Endom	3	G2-3	>50% - 90%	45	S241A	high	7	63	3	50	R213*	G302E	S241A	-	-	-	-	-	-	-	-	-	-	-	-	-	-
367	Serous	-	-	>90% - 100%	26	Y220C	high	1	26	1	26	Y220C	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-