

### Supplementary Table 1

Antibodies and standardized protocols on the Ventana Benchmark<sup>®</sup> Ultra system

Protein name	Clone	Company	Titer	Art. No.	antigen retrieval	primary
mTOR (phospho Ser2448)	49F9	Cell signaling	1/300	2976	36 min Cc1	1h
4EBP1 (phoshpo Ser65)	174A9	Cell signaling	1/1000	9456	36 min Cc1	1h
S6K1 (phospho Thr389)	1A5	Cell signaling	1/300	9206	36 min Cc1	32 min

**Supplementary table 2:** Multivariate linear regression model for the difference in p-mTOR expression between metastatic and primary tumor tissue

		95% Confidence Interval for Beta			
		Beta	p-value	Lower Bound	Upper Bound
(Constant)		-25.60	0.29	-73.47	22.28
<b>age</b>	< 55 versus ≥ 55 year	-5.54	0.72	-36.40	25.32
<b>location</b>	non-skin versus skin	-3.80	0.76	-29.03	21.42
<b>grade</b>	grade 3 versus grade 1-2	15.77	0.19	-8.27	39.81
<b>T-stage</b>	T3-4 versus T1-2	7.92	0.69	-31.00	46.83
<b>lymph node status</b>	positive versus negative	-10.78	0.57	-48.63	27.06
<b>HER2 status</b>	positive versus negative	3.28	0.88	-38.68	45.24
<b>progesterone receptor</b>	positive versus negative	44.78	0.02	7.37	82.20
<b>endocrine therapy</b>	treated versus untreated	39.41	0.01	9.11	69.70
<b>chemotherapy</b>	treated versus untreated	-17.67	0.32	-52.63	17.29

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**Supplementary table 3:** Multivariate linear regression model for the difference in p-4EBP1 expression between metastatic and primary tumor tissue

		95% Confidence Interval for Beta			
		Beta	p-value	Lower Bound	Upper Bound
(Constant)		3.93	0.85	-36.06	43.93
<b>age</b>	< 55 versus ≥ 55 year	-9.63	0.46	-35.56	16.30
<b>location</b>	non-skin versus skin	-11.11	0.30	-32.42	10.21
<b>grade</b>	grade 3 versus grade 1-2	21.76	0.04	1.01	42.51
<b>T-stage</b>	T3-4 versus T1-2	12.42	0.45	-20.21	45.04
<b>lymph node status</b>	positive versus negative	-7.76	0.64	-40.82	25.29
<b>HER2 status</b>	positive versus negative	9.18	0.63	-28.21	46.56
<b>progesterone receptor</b>	positive versus negative	4.50	0.77	-26.56	35.55
<b>endocrine therapy</b>	treated versus untreated	29.16	0.03	3.39	54.93
<b>chemotherapy</b>	treated versus untreated	-11.04	0.48	-41.96	19.89

**Supplementary table 4:** Multivariate linear regression model for the difference in p-p70S6K expression between metastatic and primary tumor tissue

		95% Confidence Interval for Beta			
		Beta	p-value	Lower Bound	Upper Bound
(Constant)		0.05	0.87	-0.59	0.69
<b>age</b>	< 55 versus ≥ 55 year	-0.34	0.11	-0.75	0.08
<b>location</b>	non-skin versus skin	-0.30	0.08	-0.63	0.04
<b>grade</b>	grade 3 versus grade 1-2	0.10	0.55	-0.23	0.42
<b>T-stage</b>	T3-4 versus T1-2	0.25	0.33	-0.26	0.76
<b>lymph node status</b>	positive versus negative	-0.41	0.11	-0.92	0.10
<b>HER2 status</b>	positive versus negative	0.50	0.10	-0.10	1.09
<b>progesterone receptor</b>	positive versus negative	0.25	0.31	-0.24	0.75
<b>endocrine therapy</b>	treated versus untreated	0.74	0.001	0.34	1.14
<b>chemotherapy</b>	treated versus untreated	0.05	0.84	-0.42	0.52

**Supplementary table 5:** Multivariate linear regression model for the difference in p-4EBP1 expression between metastatic and primary tumor tissue in patients who did not receive chemotherapy.

		95% Confidence Interval for Beta			
		Beta	p-value	Lower Bound	Upper Bound
(Constant)		13.33	0.60	-37.91	64.57
<b>age</b>	< 55 versus ≥ 55 year	1.33	0.94	-31.84	34.49
<b>location</b>	non-skin versus skin	-16.63	0.22	-43.43	10.16
<b>grade</b>	grade 3 versus grade 1-2	13.86	0.33	-14.43	42.15
<b>T-stage</b>	T3-4 versus T1-2	40.51	0.05	0.24	80.78
<b>lymph node status</b>	positive versus negative	-12.53	0.57	-57.44	32.39
<b>HER2 status</b>	positive versus negative	-3.55	0.91	-66.74	59.63
<b>progesterone receptor</b>	positive versus negative	-3.95	0.84	-42.42	34.52
<b>endocrine therapy</b>	treated versus untreated	20.21	0.38	-26.31	66.72

**Supplementary table 6:** Multivariate linear regression model for the difference in p-p70S6K expression between metastatic and primary tumor tissue in patients who did not receive chemotherapy.

		95% Confidence Interval for Beta			
		Beta	p-value	Lower Bound	Upper Bound
(Constant)		0.10	0.79	-0.62	0.81
<b>age</b>	< 55 versus ≥ 55 year	0.06	0.81	-0.42	0.53
<b>location</b>	non-skin versus skin	-0.35	0.06	-0.72	0.02
<b>grade</b>	grade 3 versus grade 1-2	-0.12	0.53	-0.52	0.28
<b>T-stage</b>	T3-4 versus T1-2	0.19	0.49	-0.36	0.73
<b>lymph node status</b>	positive versus negative	-0.31	0.29	-0.88	0.27
<b>HER2 status</b>	positive versus negative	-0.04	0.93	-0.91	0.83
<b>progesterone receptor</b>	positive versus negative	0.21	0.44	-0.33	0.74
<b>endocrine therapy</b>	treated versus untreated	0.50	0.12	-0.13	1.13

**Supplementary table 7:** Multivariate linear regression model for the difference in p-mTOR expression between metastatic and primary tumor tissue in patients who did not receive chemotherapy.

		95% Confidence Interval for Beta			
		Beta	p-value	Lower Bound	Upper Bound
(Constant)		-34.59	0.23	-92.45	23.28
<b>age</b>	< 55 versus ≥ 55 year	-20.39	0.28	-58.36	17.58
<b>location</b>	non-skin versus skin	-7.61	0.61	-37.60	22.38
<b>grade</b>	grade 3 versus grade 1-2	32.97	0.05	0.78	65.15
<b>T-stage</b>	T3-4 versus T1-2	16.99	0.45	-28.07	62.04
<b>lymph node status</b>	positive versus negative	-36.73	0.13	-84.24	10.78
<b>HER2 status</b>	positive versus negative	-19.25	0.52	-79.62	41.13
<b>progesterone receptor</b>	positive versus negative	52.27	0.02	8.67	95.88
<b>endocrine therapy</b>	treated versus untreated	75.21	0.005	24.04	126.39

# Supplementary Figure 1: Data flow

