**Supplementary Figure 1. IHC for Cleaved Caspase 3 (CC3) in serial biopsies by treatment arm and time.** Points represent individual observations, and horizontal lines indicates the mean in each group. T-tests were used to compare Combo and Fulv for each outcome and timepoint. One outlier was removed and paired t-tests were used to evaluate within-group changes over time. "n.s." indicates non-significance ($p>0.05$). One patient's paired samples over time are shown in the images below the x-axis as an example. Magnification = 400x.
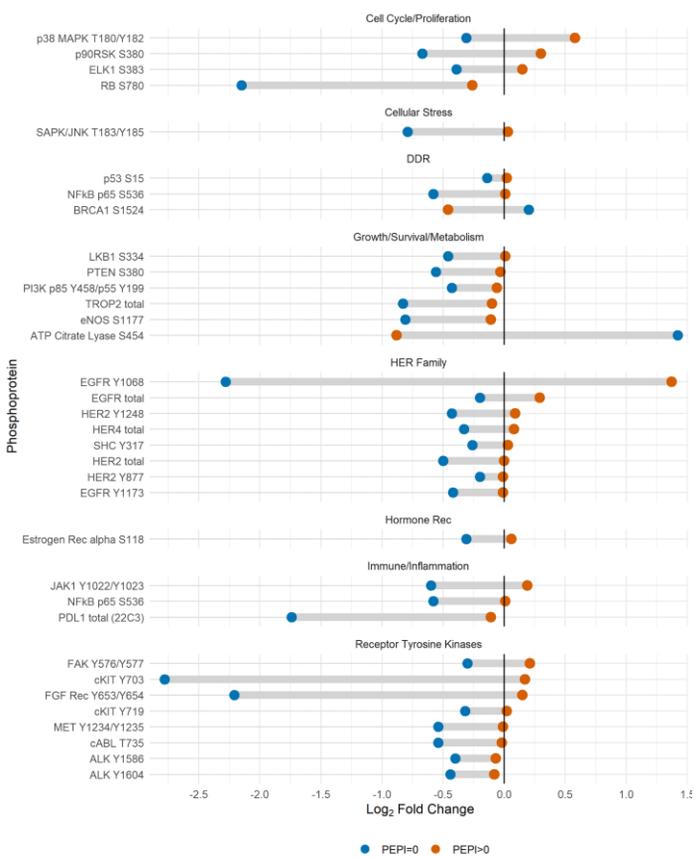
Phosphoprotein	PEPI=0 (N=7) Mean(SD)	PEPI>0 (N=22) Mean(SD)	Mean Diff	p-value
MET Y1234/Y1235	-0.54 (0.46)	-0.01 (0.29)	-0.52	0.002
EGFR Y1068	-2.28 (3.24)	1.37 (2.47)	-3.64	0.003
ALK Y1586	-0.4 (0.29)	-0.07 (0.21)	-0.33	0.005
EGFR total	-0.2 (0.19)	0.29 (0.36)	-0.49	0.005
cKIT Y719	-0.32 (0.34)	0.02 (0.22)	-0.34	0.007
FGF Rec Y653/Y654	-2.21 (3.96)	0.15 (0.5)	-2.35	0.007
EGFR Y1173	-0.42 (0.43)	-0.01 (0.37)	-0.41	0.022
ALK Y1604	-0.44 (0.41)	-0.08 (0.31)	-0.36	0.023
HER4 total	-0.33 (0.35)	0.08 (0.41)	-0.41	0.026
SAPK/JNK T183/Y185	-0.79 (1.23)	0.03 (0.65)	-0.82	0.026
eNOS S1177	-0.81 (0.87)	-0.11 (0.63)	-0.69	0.027
Estrogen Rec alpha S118	-0.31 (0.47)	0.06 (0.29)	-0.37	0.029
cABL T735	-0.54 (0.84)	-0.02 (0.41)	-0.52	0.032
RB S780	-2.15 (3.98)	-0.26 (0.69)	-1.89	0.032
PI3K p85 Y458/p55 Y199	-0.43 (0.62)	-0.06 (0.25)	-0.37	0.033
LKB1 S334	-0.46 (0.78)	0.01 (0.39)	-0.47	0.043
FAK Y576/Y577	-0.3 (0.69)	0.21 (0.54)	-0.52	0.048
PDL1 total (22C3)	-1.74 (3.85)	-0.11 (0.38)	-1.62	0.048
HER2 Y877	-0.2 (0.29)	-0.01 (0.14)	-0.19	0.050
p90RSK S380	-0.67 (1.26)	0.3 (1.07)	-0.97	0.050
ATP Citrate Lyase S454	1.42 (3.81)	-0.88 (2.31)	2.29	0.056
BRCA1 S1524	0.2 (1.12)	-0.46 (0.65)	0.66	0.058
NFkB p65 S536	-0.58 (0.81)	0.01 (0.62)	-0.59	0.063
cKIT Y703	-2.78 (5.2)	0.17 (3.04)	-2.95	0.066
p53 S15	-0.14 (0.22)	0.02 (0.13)	-0.16	0.069
HER2 Y1248	-0.43 (0.31)	0.09 (0.71)	-0.52	0.071
HER2 total	-0.5 (0.63)	0 (0.63)	-0.50	0.072
JAK1 Y1022/Y1023	-0.6 (0.41)	0.19 (1.01)	-0.79	0.072
p38 MAPK T180/Y182	-0.31 (1.02)	0.58 (1.07)	-0.88	0.075
PTEN S380	-0.56 (0.86)	-0.03 (0.59)	-0.52	0.076
SHC Y317	-0.26 (0.28)	0.03 (0.35)	-0.29	0.084
ELK1 S383	-0.39 (0.93)	0.15 (0.59)	-0.54	0.089
TROP2 total	-0.83 (0.52)	-0.1 (1.07)	-0.74	0.089
Cyclin D1 total	-1.53 (1.01)	-0.79 (1.02)	-0.74	0.101
ERK 1/2 T202/Y204	-0.77 (2.55)	0.47 (1.42)	-1.24	0.102
HER3 total	-0.76 (0.78)	-0.16 (0.87)	-0.60	0.106
VEGF Rec2 Y996	-0.27 (0.23)	-0.02 (0.32)	-0.25	0.107
p70S6K T412	-0.29 (0.89)	0.19 (0.6)	-0.48	0.110
PTEN total	-0.72 (0.95)	-0.21 (0.65)	-0.51	0.117
mTOR S2448	-0.42 (0.5)	-0.09 (0.46)	-0.33	0.118
HER3 Y1289	-0.28 (0.33)	-0.03 (0.35)	-0.25	0.119
M-CSF Rec Y723	-0.16 (0.18)	0.02 (0.23)	-0.18	0.126
4EBP1 S65	-0.49 (1.23)	0.11 (0.87)	-0.60	0.156
PRK1 T774/PRK2 T816	-0.54 (0.6)	-0.13 (0.62)	-0.42	0.156
eIF4G S1108	-0.54 (0.42)	-0.01 (0.89)	-0.54	0.160
RAF S259	-0.35 (0.44)	-0.05 (0.44)	-0.30	0.167
FOXO1 T24/FOXO3a T32	-0.16 (0.26)	0.16 (0.6)	-0.33	0.175
GSK3aB S21/S9	-0.61 (1.08)	-0.04 (0.95)	-0.58	0.177
AMPKalpha1 S485	2.12 (3.94)	-0.39 (4.04)	2.51	0.179
PKA C T197	-0.37 (0.25)	-0.03 (0.61)	-0.34	0.200

Supplementary Figure 2. RPPA change with treatment in the combination arm for PEPI=0 vs. PEPI>0. Dumbbell plot of the mean log$_2$ fold change in expression with treatment (W5–BL) in the Combo arm by PEPI score (blue: PEPI=0 (N=7), orange: PEPI>0 (N=22)) and phosphoprotein. Presented phosphoproteins on the left-hand side were significantly ($p<0.1$) differently expressed with treatment by the Empirical Bayes moderated t-test. The corresponding table on the right presents all phosphoproteins with $p<0.2$. Results are summarized in log2 units with the mean and standard deviation (SD) among patients with PEPI=0 and PEPI>0 in the 2nd and 3rd columns, respectively. "Mean Diff" is the mean change among PEPI>0 patients (column 3) subtracted from the mean change among patients with PEPI=0 (column 2).

Phosphoprotein	PEPI=0 (N=9) Mean(SD)	PEPI>0 (N=45) Mean(SD)	Mean Diff	p-value
Cyclin B1 total	11.79 (1.6)	13.65 (0.93)	-1.85	<0.001
Ki67 total	11.47 (1.71)	13.67 (1.59)	-2.21	<0.001
Cyclin D1 total	10.28 (5.91)	13.57 (1.1)	-3.29	0.001
H2A.X S139	11.45 (1.98)	13.06 (1.06)	-1.61	0.001
RB S780	11.68 (1.31)	12.91 (0.9)	-1.23	0.001
PDL1 total (22C3)	10.6 (4.23)	12.69 (0.78)	-2.09	0.002
p70S6K S371	11.42 (1.61)	12.82 (1.19)	-1.39	0.003
p53 S15	14.26 (0.27)	14.49 (0.14)	-0.23	0.004
LKB1 S334	11.76 (1.99)	13.04 (0.95)	-1.29	0.004
EGFR Y992	11.3 (0.58)	9.87 (1.48)	1.43	0.006
FOXO3a S253	13.81 (0.24)	14.02 (0.15)	-0.21	0.006
FOXM1 T600	12.33 (1.13)	13.11 (0.66)	-0.79	0.006
SGK1 S78	13.7 (0.7)	14.17 (0.37)	-0.48	0.006
HER2 Y877	14.24 (0.43)	14.57 (0.28)	-0.33	0.007
4EBP1 S65	11.2 (1.88)	12.54 (1.26)	-1.34	0.009
PRAS40 T246	11.3 (4.33)	13.06 (0.89)	-1.76	0.013
RAS-GRF1 S916	11.98 (1.03)	12.7 (0.7)	-0.72	0.013
PLK1 T210	13.44 (0.7)	13.87 (0.42)	-0.43	0.019
Androgen Rec S81	13.6 (0.48)	13.93 (0.34)	-0.33	0.021
MLH1 total	12.01 (1.32)	12.78 (0.77)	-0.76	0.021
HER3 total	13.76 (1.6)	14.58 (0.8)	-0.82	0.023
SMAD2 S245/S250/S255	12.61 (0.73)	13.18 (0.67)	-0.57	0.028
MSH2 total	12.65 (1.18)	13.33 (0.77)	-0.68	0.033
FOXO1 S256	13.53 (1.12)	14.21 (0.8)	-0.67	0.035
Acetyl CoA Carboxylase S79	12.67 (1.58)	13.79 (1.39)	-1.12	0.035
HSP90a T5/T7	10.57 (2.22)	12.16 (2)	-1.59	0.035
Androgen Rec S650	12.22 (2.22)	13.78 (2)	-1.56	0.038
S6RP S240/S244	4.85 (5.92)	8.66 (5.01)	-3.81	0.045
EGFR Y1068	11.68 (1.39)	8.43 (4.78)	3.25	0.046
FGF Rec Y653/Y654	11.57 (1.47)	12.3 (0.89)	-0.73	0.049
PRK1 T774/PRK2 T816	12.74 (1.37)	13.32 (0.62)	-0.58	0.049
cKIT Y719	13.2 (0.65)	13.54 (0.41)	-0.35	0.05
PDK1 S241	13.12 (1.34)	13.81 (0.85)	-0.68	0.052
RAF S259	12.72 (1.08)	13.2 (0.53)	-0.48	0.054
4EBP1 T70	12.07 (1.1)	12.92 (1.21)	-0.85	0.067
Androgen Rec alpha total DAKO	13.36 (1.22)	13.92 (0.75)	-0.56	0.071
ALK Y1604	12.6 (0.65)	12.23 (0.55)	0.37	0.079
MEK 1/2 S217/S221	13.38 (1.09)	13.94 (0.83)	-0.56	0.084
MET Y1234/Y1235	12.41 (1.42)	13.02 (0.85)	-0.61	0.088
PTEN S380	13.64 (1.06)	14.16 (0.79)	-0.52	0.092
STAT3 S727	11.32 (4.48)	12.67 (1.53)	-1.35	0.104
HER4 total	13.98 (0.79)	14.38 (0.64)	-0.40	0.108
cABL T735	13.62 (0.79)	13.92 (0.48)	-0.31	0.127
ATR S428	13.45 (0.97)	13.86 (0.68)	-0.41	0.13
eNOS S1177	12.7 (1.34)	13.32 (1.08)	-0.62	0.134
IGF1 Rec Y1135/Y1136-Insulin Rec Y1150/Y1151	2.79 (5.56)	5.78 (5.6)	-2.99	0.144
PKA C T197	13.38 (0.91)	13.8 (0.77)	-0.42	0.155
CREB S133	13 (1.37)	13.44 (0.79)	-0.44	0.19
mTOR S2448	13.89 (0.98)	14.19 (0.54)	-0.30	0.196

Supplementary Figure 3. RPPA by PEPI at baseline. Phosphoproteins that were significantly (p<0.2, eBayes moderated t-test) differentially expressed at BL between patients with PEPI =0 (N=9) and PEPI>0 (N=45) are presented in log2 units. The mean and standard deviation (SD) among patients with PEPI=0 and PEPI>0 are presented in columns 2 and 3, respectively. "Mean Diff" is the mean among patients with PEPI>0 (column 3) subtracted from the mean among patients with PEPI =0 (column 2).

Phosphoprotein	PEPI=0 (N=9) Mean(SD)	PEPI>0 (N=45) Mean(SD)	Mean Diff	p-value
Androgen Rec total CST	-4.09 (4.17)	-0.87 (2.4)	-3.23	0.002
cKIT Y719	-0.25 (0.34)	0.03 (0.23)	-0.29	0.005
ALK Y1586	-0.37 (0.3)	-0.09 (0.25)	-0.28	0.006
FGF Rec Y653/Y654	-1.62 (3.63)	0 (0.66)	-1.62	0.006
MET Y1234/Y1235	-0.41 (0.54)	-0.03 (0.33)	-0.38	0.008
SAPK/JNK T183/Y185	-0.82 (1.07)	-0.12 (0.76)	-0.70	0.021
VEGF Rec2 Y996	-0.26 (0.2)	-0.02 (0.27)	-0.24	0.029
EGFR Y1173	-0.42 (0.38)	-0.09 (0.4)	-0.33	0.030
HER3 total	-1.03 (0.86)	-0.27 (0.95)	-0.76	0.030
EGFR total	-0.22 (0.17)	0.23 (0.58)	-0.45	0.036
HER2 Y1248	-0.53 (0.4)	-0.02 (0.7)	-0.52	0.036
PRK1 T774/PRK2 T816	-0.78 (1.53)	-0.13 (0.6)	-0.66	0.037
TROP2 total	-1.35 (1.39)	-0.22 (1.48)	-1.13	0.038
PTEN S380	-0.56 (0.89)	-0.05 (0.63)	-0.51	0.043
4EBP1 S65	-1.1 (2.84)	-0.07 (0.92)	-1.04	0.045
cABL T735	-0.4 (0.78)	-0.01 (0.45)	-0.39	0.046
ERK 1/2 T202/Y204	-1.19 (2.36)	0.12 (1.67)	-1.31	0.048
PRAS40 T246	1.45 (4.21)	0.17 (0.65)	1.28	0.049
SRC Y527	-1.1 (3.9)	1.94 (4.01)	-3.04	0.050
YAP S127	-0.36 (0.5)	0.13 (0.67)	-0.49	0.054
ALK Y1604	-0.41 (0.38)	-0.13 (0.38)	-0.28	0.058
EGFR Y1068	-2.04 (2.92)	0.58 (3.94)	-2.62	0.061
RB S780	-1.46 (3.72)	-0.35 (0.84)	-1.12	0.067
eNOS S1177	-0.73 (0.78)	-0.16 (0.86)	-0.57	0.069
FAK Y576/Y577	-0.28 (0.61)	0.09 (0.56)	-0.37	0.082
HER3 Y1289	-0.4 (0.38)	-0.08 (0.5)	-0.31	0.084
HER4 total	-0.29 (0.33)	0.04 (0.55)	-0.34	0.085
PTEN total	-0.62 (0.96)	-0.18 (0.64)	-0.44	0.089
Androgen Rec alpha total DAKO	-0.8 (0.68)	-0.27 (0.82)	-0.53	0.090
FOXO1 T24/FOXO3a T32	-0.27 (0.4)	0.15 (0.72)	-0.41	0.101
HER2 Y877	-0.16 (0.27)	-0.03 (0.17)	-0.13	0.102
LKB1 S334	-0.3 (0.79)	-0.01 (0.37)	-0.28	0.104
cKIT Y703	-1.95 (4.81)	0.13 (3.26)	-2.08	0.109
PKA C T197	-0.45 (0.42)	-0.02 (0.72)	-0.43	0.109
RET Y905	-0.76 (1)	0.32 (2)	-1.08	0.117
HER2 total	-0.5 (0.57)	-0.05 (0.82)	-0.45	0.125
PI3K p85 Y458/p55 Y199	-0.27 (0.63)	-0.06 (0.28)	-0.21	0.126
Estrogen Rec alpha S118	-0.2 (0.5)	0.02 (0.34)	-0.22	0.133
p90RSK S380	-0.52 (1.45)	0.17 (1.28)	-0.70	0.147
RAF S259	-0.35 (0.53)	-0.06 (0.51)	-0.29	0.151
mTOR S2448	-0.41 (0.47)	-0.15 (0.51)	-0.25	0.177
M-CSF Rec Y723	-0.12 (0.18)	0.01 (0.24)	-0.13	0.197

Supplementary Figure 4. RPPA by PEPI with treatment. Phosphoproteins that were significantly (P<0.2, eBayes moderated t-test) differentially expressed with treatment (W5 – BL) between patients with PEPI=0 (N=9) and PEPI>0 (N=45) are presented in log2 units. The mean and standard deviation (SD) among patients with PEPI=0 and PEPI>0 are presented in columns 2 and 3, respectively. "Mean Diff" is the mean change among patients with PEPI>0 (column 3) subtracted from the mean change among patients with PEPI =0 (column 2).

Phosphoprotein	High BL/Low W5 (N=13) Mean(SD)	High BL/High W5 (N=9) Mean(SD)	Mean Diff	p-value
RB S780	12.65 (0.74)	13.71 (0.68)	-1.07	0.002
Ki67 total	13.57 (1.15)	14.93 (0.79)	-1.37	0.005
ATR S428	13.83 (0.5)	14.41 (0.45)	-0.59	0.010
4EBP1 S65	12.38 (1.15)	13.56 (0.88)	-1.18	0.015
HER2 Y1248	14.29 (0.69)	13.62 (0.42)	0.67	0.016
Cyclin B1 total	13.63 (0.97)	14.51 (0.45)	-0.88	0.019
p70S6K S371	12.84 (0.9)	13.67 (0.65)	-0.83	0.025
PDK1 S241	13.95 (0.51)	14.52 (0.6)	-0.57	0.028
CHK1 S345	1.42 (3.48)	5.64 (5.4)	-4.22	0.031
NFkB p65 S536	12.92 (0.72)	13.54 (0.62)	-0.62	0.046
cABL T735	13.94 (0.28)	14.25 (0.37)	-0.31	0.048
p70S6K T412	12.85 (0.6)	13.51 (0.89)	-0.65	0.048
MEK 1/2 S217/S221	14.01 (0.6)	14.56 (0.65)	-0.56	0.049
HSP90a T5/T7	12.14 (1.25)	13.62 (2.22)	-1.47	0.052
RAS-GRF1 S916	12.74 (0.51)	13.22 (0.56)	-0.48	0.055
Androgen Rec S650	14.28 (1.16)	12.99 (2.24)	1.29	0.082
VEGF Rec2 Y996	14.17 (0.31)	13.84 (0.5)	0.33	0.087
p27 T187	11.82 (0.87)	12.49 (0.93)	-0.68	0.090
PRK1 T774/PRK2 T816	13.44 (0.4)	13.75 (0.35)	-0.31	0.091
Estrogen Rec alpha S118	13.6 (0.5)	13.99 (0.53)	-0.38	0.102
PLK1 T210	13.89 (0.27)	14.14 (0.38)	-0.25	0.112
Androgen Rec alpha total DAKO	14.25 (0.45)	13.86 (0.65)	0.39	0.117
FOXO3a S253	13.98 (0.13)	14.11 (0.1)	-0.13	0.119
STAT6 Y641	11.94 (2.06)	9.95 (3.97)	1.99	0.125
VEGF Rec2 Y951	12.49 (0.92)	11.82 (1.22)	0.66	0.151
B-RAF S445	12.76 (0.5)	13.24 (1.03)	-0.48	0.153
EGFR Y1173	13.03 (0.57)	12.66 (0.6)	0.37	0.155
eNOS/NOSIII S116	10.89 (3.82)	12.8 (1.46)	-1.91	0.155
HIF-1 alpha total	10.95 (3.65)	8 (6.11)	2.95	0.156
SGK1 S78	14.21 (0.32)	14.42 (0.24)	-0.21	0.161
S6RP S235/S236	7.41 (5.69)	11.1 (6.46)	-3.69	0.165
p53 S15	14.49 (0.16)	14.6 (0.12)	-0.12	0.178
MLH1 total	12.8 (0.63)	13.17 (0.6)	-0.37	0.181
MET Y1234/Y1235	13.39 (0.38)	13.01 (0.89)	0.38	0.182
STAT3 Y705	11.94 (3.67)	9.4 (5.46)	2.54	0.189
MSH2 total	13.5 (0.59)	13.83 (0.54)	-0.33	0.196

Supplementary Figure 5. RPPA by Ki67 at baseline. Phosphoproteins that were significantly (*p*<0.2, eBayes moderated t-test) differentially expressed at BL between patients with High BL/Low W5 Ki67 (N=13) and High BL/High W5 Ki67 (N=9) are presented in log2 units. The mean and standard deviation (SD) among patients with High BL/Low W5 and High BL/High W5 Ki67 are presented in columns 2 and 3, respectively. "Mean Diff" is the mean among patients with High BL/High W5 (column 3) subtracted from the mean among patients with High BL/Low W5 (column 2).

Phosphoprotein	High BL/Low W5 (N=13) Mean(SD)	High BL/High W5 (N=9) Mean(SD)	Mean Diff	p-value
FGF Rec Y653/Y654	-0.41 (0.73)	0.23 (0.35)	-0.63	0.024
MET Y1234/Y1235	-0.26 (0.34)	0.06 (0.21)	-0.32	0.031
eIF4G S1108	-0.54 (0.51)	0.23 (1.11)	-0.77	0.039
HER2 Y1248	-0.24 (0.7)	0.31 (0.45)	-0.55	0.046
CHK1 S345	0.83 (4.75)	-3.51 (4.95)	4.34	0.048
FOXO1 S256	-0.29 (0.68)	0.24 (0.5)	-0.52	0.059
Androgen Rec total CST	-1.34 (1.56)	-0.08 (1.58)	-1.26	0.068
Ki67 total	-2.72 (1.49)	-1.55 (1.41)	-1.17	0.072
Androgen Rec S650	-1.45 (1.25)	-0.54 (1)	-0.91	0.074
mTOR S2448	-0.36 (0.37)	-0.06 (0.33)	-0.29	0.076
RAS-GRF1 S916	-0.32 (0.52)	0.07 (0.42)	-0.40	0.076
MEK 1/2 S217/S221	-0.78 (0.7)	-0.24 (0.65)	-0.54	0.077
AXL Y702	0.24 (1.16)	-0.56 (0.8)	0.79	0.081
IGF1 Rec Y1135/Y1136-Insulin Rec Y1150/Y1151	-0.12 (0.71)	1.78 (3.79)	-1.90	0.081
ATR S428	-0.45 (0.43)	-0.14 (0.3)	-0.31	0.085
LKB1 S334	-0.33 (0.48)	0.04 (0.49)	-0.37	0.096
eNOS S1177	-0.44 (0.83)	0.15 (0.73)	-0.58	0.099
PTEN S380	-0.29 (0.54)	0.13 (0.64)	-0.43	0.101
PRK1 T774/PRK2 T816	-0.27 (0.42)	0.04 (0.42)	-0.32	0.109
AMPKalpha T172	-0.39 (0.71)	0.16 (0.86)	-0.55	0.117
MLH1 total	-0.56 (0.5)	-0.13 (0.78)	-0.43	0.124
CHK2 S33/S35	-0.89 (1.71)	0.2 (0.33)	-1.09	0.136
PI3K p85 Y458/p55 Y199	-0.3 (0.46)	-0.04 (0.18)	-0.26	0.139
Androgen Rec alpha total DAKO	-0.37 (0.5)	0.02 (0.67)	-0.39	0.141
RET Y905	-0.13 (0.5)	0.15 (0.31)	-0.28	0.148
RAF S259	-0.19 (0.41)	0.07 (0.35)	-0.26	0.149
Caspase 3, cleaved D175	-1.01 (2.9)	0.5 (1.32)	-1.50	0.153
SHC Y317	-0.15 (0.32)	0.06 (0.29)	-0.22	0.153
GSK3aB S21/S9	-0.27 (0.92)	0.32 (1.01)	-0.60	0.155
SMAD2 S245/S250/S255	-0.44 (0.4)	-0.12 (0.61)	-0.32	0.155
S6RP S240/S244	-4.9 (4.99)	-2.07 (3.84)	-2.83	0.156
S6RP S235/S236	-3.52 (7.57)	0.55 (4.69)	-4.07	0.159
VEGF Rec2 Y996	-0.14 (0.28)	0.03 (0.19)	-0.17	0.172
Glucocorticoid Rec S211	-0.21 (1.11)	0.34 (0.58)	-0.55	0.184
PTEN total	-0.42 (0.54)	-0.05 (0.75)	-0.37	0.188
HER3 Y1289	-0.19 (0.52)	0.08 (0.32)	-0.27	0.190
RB S780	-1.39 (2.95)	-0.08 (0.54)	-1.31	0.194

Supplementary Figure 6. RPPA by Ki67 with treatment. Phosphoproteins that were significantly (p<0.2, eBayes moderated t-test) differentially expressed with treatment (W5 – BL) between patients with High BL/Low W5 Ki67 (N=13) and High BL/High W5 Ki67 (N=9) are presented in log2 units. The mean and standard deviation (SD) among patients with High BL/Low W5 and High BL/High W5 Ki67 are presented in columns 2 and 3, respectively. "Mean Diff" is the mean change among patients with High BL/High W5 (column 3) subtracted from the mean change among patients with High BL/Low W5 (column 2).
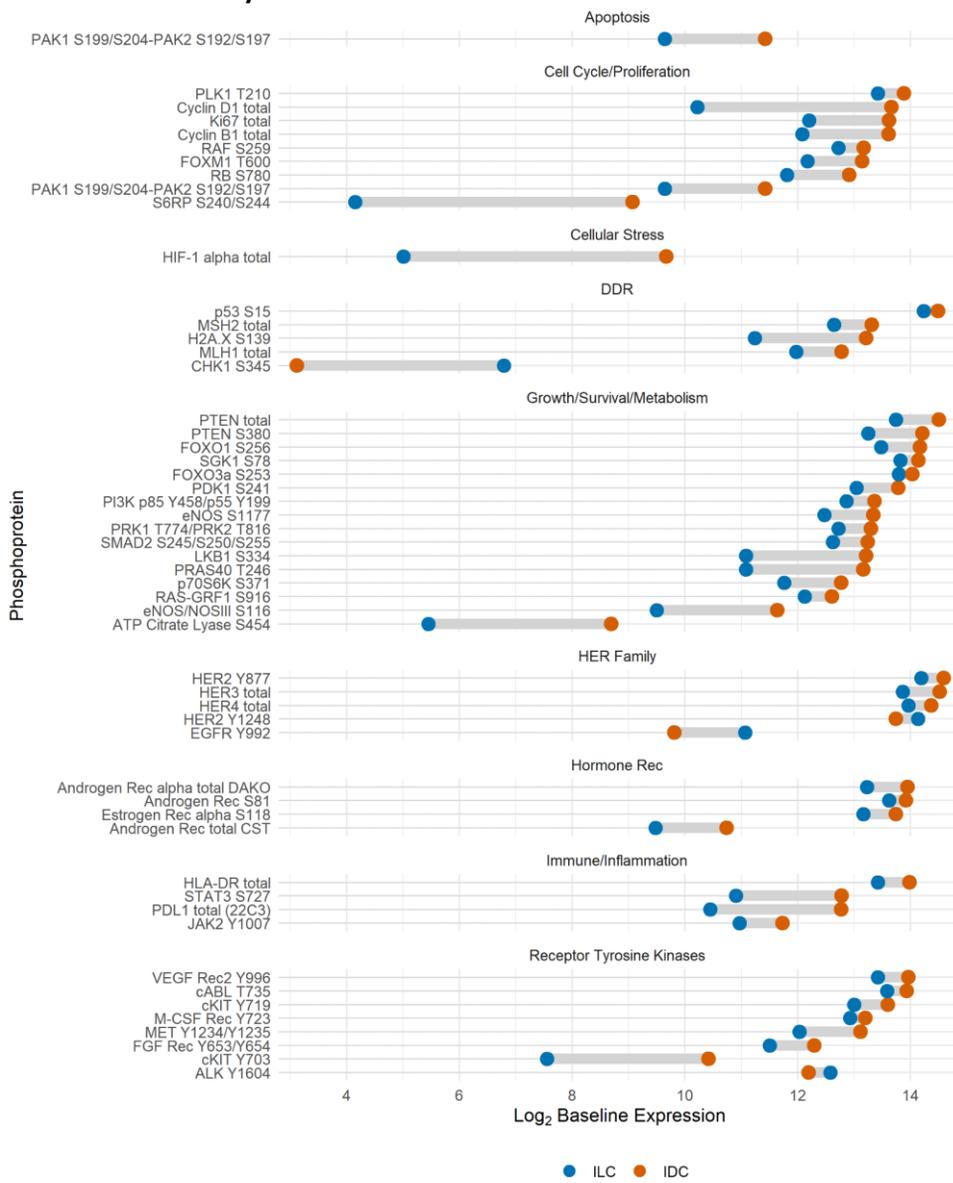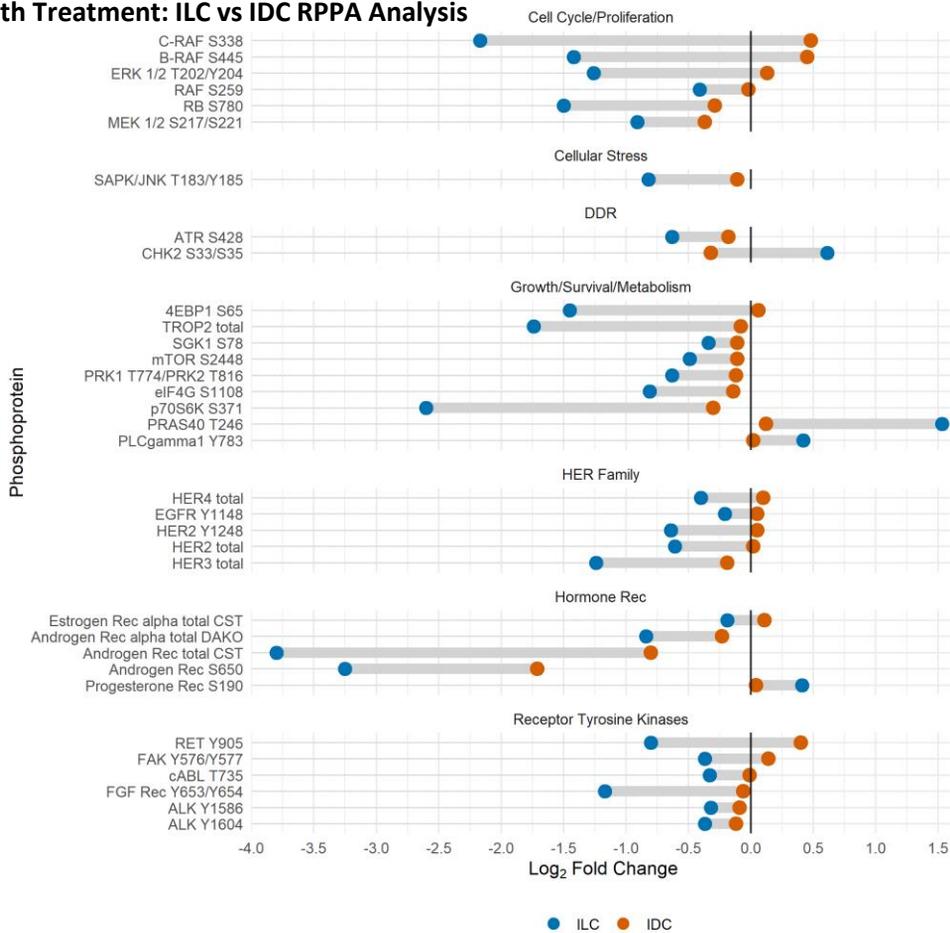
Supplementary Figure 7. RPPA by Histology (ILC vs IDC). Reverse phase phospho-protein analysis (RPPA) was performed on laser-captured, fresh frozen tumor that was split into two groups for comparison: ILC (blue, N=10) tumors, and IDC (orange, N=41) tumors. Tumors came from patients in both arms. Presented phosphoproteins were significantly (*p*<0.1) differentially expressed by the Empirical Bayes moderated t-test. **a** Dumbbell plot of the mean log2 baseline expression for patients with ILC and IDC for each significant phosphoprotein. **b** Dumbbell plot of the mean log2 change in expression among patients with ILC and IDC for each significant phosphoprotein.

Phosphoprotein	ILC (N=10) Mean(SD)	IDC (N=41) Mean(SD)	Mean Diff	p-value
p53 S15	14.23 (0.23)	14.49 (0.14)	-0.26	<0.001
cKIT Y719	13 (0.5)	13.6 (0.4)	-0.60	<0.001
Cyclin B1 total	12.08 (1.81)	13.61 (0.93)	-1.52	<0.001
Cyclin D1 total	10.22 (5.6)	13.66 (0.94)	-3.44	<0.001
FOXM1 T600	12.17 (1.08)	13.14 (0.61)	-0.97	<0.001
H2A.X S139	11.24 (1.76)	13.21 (0.94)	-1.97	<0.001
LKB1 S334	11.08 (1.63)	13.21 (0.74)	-2.14	<0.001
PDL1 total (22C3)	10.45 (3.85)	12.77 (0.74)	-2.33	<0.001
FOXO3a S253	13.79 (0.21)	14.03 (0.15)	-0.25	0.001
HER2 Y877	14.19 (0.36)	14.59 (0.28)	-0.39	0.001
PTEN S380	13.25 (1)	14.21 (0.69)	-0.96	0.001
MET Y1234/Y1235	12.03 (0.98)	13.11 (0.89)	-1.08	0.001
PRAS40 T246	11.08 (4.12)	13.16 (0.71)	-2.07	0.003
RB S780	11.81 (1.49)	12.91 (0.85)	-1.10	0.003
PTEN total	13.74 (0.81)	14.5 (0.74)	-0.76	0.006
S6RP S240/S244	4.15 (5.46)	9.07 (4.89)	-4.92	0.007
MLH1 total	11.97 (1.09)	12.78 (0.83)	-0.82	0.011
SMAD2 S245/S250/S255	12.62 (0.46)	13.24 (0.7)	-0.62	0.011
PLK1 T210	13.42 (0.62)	13.88 (0.44)	-0.46	0.012
EGFR Y992	11.07 (0.97)	9.81 (1.51)	1.26	0.014
HIF-1 alpha total	5.01 (5.43)	9.67 (5.29)	-4.66	0.015
Androgen Rec alpha total DAKO	13.23 (1.12)	13.95 (0.72)	-0.71	0.016
VEGF Rec2 Y996	13.42 (0.67)	13.96 (0.59)	-0.54	0.016
PI3K p85 Y458/p55 Y199	12.86 (0.61)	13.36 (0.57)	-0.50	0.021
STAT3 S727	10.9 (3.98)	12.78 (1.62)	-1.87	0.021
Estrogen Rec alpha S118	13.16 (0.8)	13.74 (0.66)	-0.58	0.023
HLA-DR total	13.42 (0.58)	13.98 (0.68)	-0.56	0.023
Ki67 total	12.2 (1.94)	13.62 (1.68)	-1.42	0.023
FOXO1 S256	13.48 (0.71)	14.17 (0.87)	-0.69	0.024
PDK1 S241	13.04 (1.1)	13.78 (0.87)	-0.74	0.027
FGF Rec Y653/Y654	11.5 (1.2)	12.29 (0.94)	-0.79	0.028
Androgen Rec S81	13.62 (0.47)	13.92 (0.34)	-0.30	0.029
CHK1 S345	6.79 (4.81)	3.12 (4.68)	3.67	0.029
MSH2 total	12.64 (0.9)	13.31 (0.84)	-0.67	0.03
eNOS S1177	12.47 (0.85)	13.34 (1.16)	-0.87	0.031
p70S6K S371	11.76 (1.78)	12.77 (1.23)	-1.01	0.037
PRK1 T774/PRK2 T816	12.72 (1.06)	13.3 (0.71)	-0.59	0.042
PAK1 S199/S204-PAK2 S192/S197	9.64 (3.56)	11.42 (2.19)	-1.78	0.046
cKIT Y703	7.55 (5.29)	10.42 (3.75)	-2.87	0.048
Androgen Rec total CST	9.48 (3.54)	10.74 (1.26)	-1.26	0.061
HER3 total	13.86 (1.45)	14.52 (0.85)	-0.66	0.061
RAF S259	12.72 (0.87)	13.17 (0.59)	-0.45	0.061
ALK Y1604	12.58 (0.83)	12.19 (0.5)	0.39	0.062
HER2 Y1248	14.13 (0.6)	13.74 (0.57)	0.39	0.062
SGK1 S78	13.82 (0.57)	14.14 (0.43)	-0.31	0.067
cABL T735	13.58 (0.62)	13.93 (0.52)	-0.35	0.076
RAS-GRF1 S916	12.12 (0.95)	12.61 (0.72)	-0.50	0.076
HER4 total	13.96 (0.75)	14.37 (0.65)	-0.41	0.086
ATP Citrate Lyase S454	5.45 (5.85)	8.69 (5.22)	-3.24	0.087
M-CSF Rec Y723	12.93 (0.44)	13.2 (0.42)	-0.27	0.087
eNOS/NOSIII S116	9.5 (5.09)	11.64 (3.16)	-2.14	0.092
JAK2 Y1007	10.97 (0.93)	11.73 (1.36)	-0.76	0.097
EGFR Y1068	10.88 (4)	8.28 (4.66)	2.59	0.106
HSP90a T5/T7	10.97 (1.97)	12.14 (2.14)	-1.17	0.117
TYK2 Y1054/Y1055	13.61 (0.37)	13.86 (0.46)	-0.25	0.135
Cyclin A1 total	14.04 (0.23)	14.22 (0.31)	-0.17	0.144
IGF1 Rec Y1135/Y1136-Insulin Rec Y1150/Y1151	3.07 (4.98)	5.95 (5.74)	-2.88	0.146
CHK2 S33/S35	9.99 (1.42)	10.93 (1.5)	-0.95	0.157
Glucocorticoid Rec S211	12.38 (0.82)	11.84 (1.15)	0.55	0.161
EGFR Y1148	14.9 (0.2)	14.69 (0.47)	0.22	0.17
S6RP S235/S236	4.32 (5.71)	7.68 (6.19)	-3.36	0.18
STAT3 Y705	8.44 (5.94)	10.72 (4.72)	-2.28	0.193

Supplementary Figure 8. RPPA by Histology (ILC vs IDC) at baseline. Phosphoproteins that were significantly (*p*<0.2, eBayes moderated t-test) differentially expressed at BL between patients with ILC (N=10) and IDC (N=41) are presented in log2 units. The mean and standard deviation (SD) among patients with ILC and IDC are presented in columns 2 and 3, respectively. "Mean Diff" is the mean among patients with IDC (column 3) subtracted from the mean among patients with ILC (column 2).

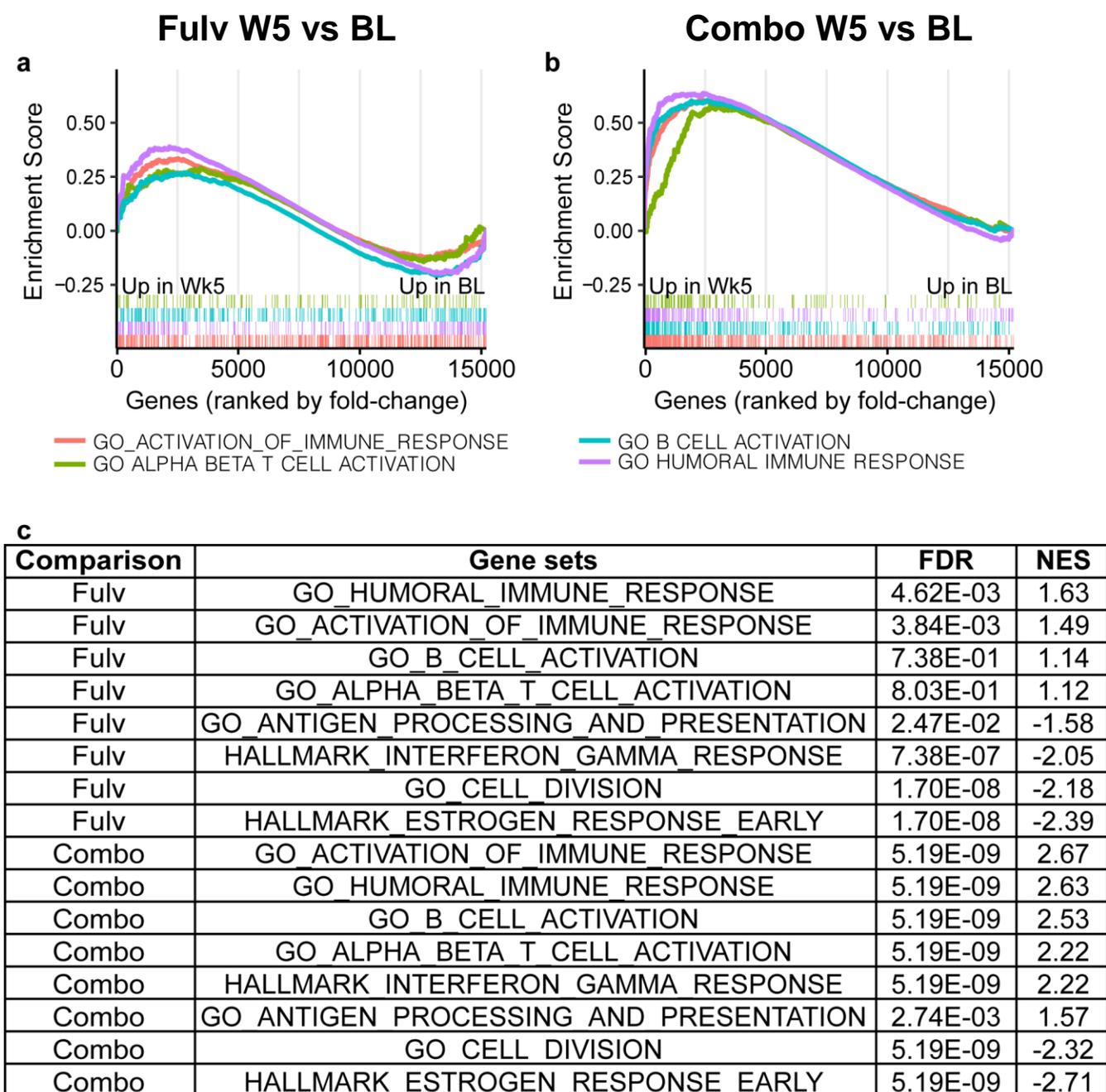| Phosphoprotein	ILC (N=10) Mean(SD)	IDC (N=41) Mean(SD)	Mean Diff	p-value
p70S6K S371	-2.6 (3.86)	-0.3 (1)	-2.30	0.001
4EBP1 S65	-1.45 (2.62)	0.06 (0.85)	-1.51	0.002
HER3 total	-1.24 (1.31)	-0.19 (0.8)	-1.05	0.002
TROP2 total	-1.74 (2.35)	-0.08 (1.11)	-1.66	0.002
HER2 Y1248	-0.64 (0.64)	0.05 (0.64)	-0.69	0.003
Androgen Rec total CST	-3.8 (4.38)	-0.8 (2.36)	-3.00	0.004
HER4 total	-0.4 (0.56)	0.1 (0.49)	-0.50	0.007
FAK Y576/Y577	-0.37 (0.75)	0.14 (0.51)	-0.51	0.014
SAPK/JNK T183/Y185	-0.82 (1.1)	-0.11 (0.75)	-0.71	0.018
ALK Y1586	-0.32 (0.36)	-0.09 (0.24)	-0.23	0.023
HER2 total	-0.61 (1.14)	0.02 (0.67)	-0.63	0.025
ATR S428	-0.63 (0.71)	-0.18 (0.52)	-0.45	0.027
PRAS40 T246	1.53 (3.94)	0.12 (0.63)	1.42	0.027
MEK 1/2 S217/S221	-0.91 (0.82)	-0.37 (0.65)	-0.54	0.028
PLCgamma1 Y783	0.42 (0.54)	0.02 (0.47)	0.40	0.032
ERK 1/2 T202/Y204	-1.26 (2.3)	0.13 (1.7)	-1.39	0.033
mTOR S2448	-0.49 (0.53)	-0.11 (0.5)	-0.38	0.037
Androgen Rec alpha total DAKO	-0.84 (1.13)	-0.23 (0.73)	-0.62	0.042
RB S780	-1.5 (3.65)	-0.29 (0.69)	-1.20	0.045
RAF S259	-0.41 (0.67)	-0.02 (0.48)	-0.39	0.051
Androgen Rec S650	-3.25 (3.63)	-1.71 (1.84)	-1.54	0.057
FGF Rec Y653/Y654	-1.17 (3.6)	-0.06 (0.65)	-1.11	0.060
eIF4G S1108	-0.81 (1.26)	-0.14 (0.8)	-0.67	0.064
CHK2 S33/S35	0.61 (0.61)	-0.32 (1.16)	0.93	0.065
EGFR Y1148	-0.21 (0.43)	0.05 (0.4)	-0.26	0.075
RET Y905	-0.8 (0.98)	0.4 (2.07)	-1.20	0.078
B-RAF S445	-1.42 (3.22)	0.45 (2.83)	-1.87	0.081
ALK Y1604	-0.37 (0.5)	-0.12 (0.37)	-0.25	0.082
C-RAF S338	-2.17 (3.58)	0.48 (4.22)	-2.65	0.083
Estrogen Rec alpha total CST	-0.19 (0.72)	0.11 (0.41)	-0.30	0.089
Progesterone Rec S190	0.41 (0.77)	0.04 (0.57)	0.37	0.092
cABL T735	-0.33 (0.75)	-0.01 (0.48)	-0.32	0.094
PRK1 T774/PRK2 T816	-0.63 (1.5)	-0.12 (0.61)	-0.52	0.098
SGK1 S78	-0.34 (0.46)	-0.11 (0.36)	-0.23	0.099
HER2 Y877	-0.14 (0.28)	-0.02 (0.17)	-0.12	0.115
AXL Y702	-0.5 (1.23)	0.1 (1.07)	-0.61	0.120
p90RSK S380	-0.54 (1.44)	0.19 (1.32)	-0.74	0.122
PDK1 S241	-0.58 (0.84)	-0.15 (0.75)	-0.44	0.130
eNOS/NOSIII S116	-1.75 (4.07)	-0.2 (2.59)	-1.55	0.134
PKA C T197	-0.41 (0.87)	-0.02 (0.66)	-0.39	0.138
SRC Y527	-0.32 (4.61)	1.95 (4.08)	-2.27	0.143
AKT T308	-0.35 (0.48)	0.4 (1.62)	-0.75	0.149
MET Y1234/Y1235	-0.25 (0.61)	-0.04 (0.33)	-0.21	0.150
FOXM1 T600	0.07 (0.65)	-0.14 (0.32)	0.22	0.155
EGFR total	-0.07 (0.44)	0.21 (0.6)	-0.28	0.179

Supplementary Figure 9. RPPA by Histology (ILC vs IDC) with treatment. Phosphoproteins that were significantly (P<0.2, eBayes moderated t-test) differentially expressed with treatment (W5 – BL) between patients with ILC (N=10) and IDC (N=41) are presented in log2 units. The mean and standard deviation (SD) among patients with ILC and IDC are presented in columns 2 and 3, respectively. "Mean Diff" is the mean change among patients with IDC (column 3) subtracted from the mean change among patients with ILC(column 2).

Metabolite	PEPI=0 (N=9) Mean(SD)	PEPI>0 (N=41) Mean(SD)	Mean Diff	p-value
acyl-C5:1	-1.49 (1.72)	-0.02 (1.17)	-1.47	0.002
L-asparagine	-0.44 (0.43)	0.04 (0.44)	-0.48	0.005
Succinate	-0.44 (0.45)	0 (0.41)	-0.44	0.007
Malate	-0.44 (0.37)	0.11 (0.57)	-0.56	0.008
L-alanine	-0.36 (0.27)	0 (0.37)	-0.36	0.012
L-Carnitine	-0.36 (0.42)	0 (0.37)	-0.35	0.018
Sphinganine 1-phosphate	0.33 (0.38)	-0.18 (0.64)	0.50	0.027
Dodecanedioic acid	-0.34 (0.55)	0.01 (0.37)	-0.34	0.030
2-Oxoglutaramate	0.39 (0.94)	-0.13 (0.7)	0.52	0.059
Lactate	-0.28 (0.28)	0.15 (0.65)	-0.43	0.061
Mannitol	0.55 (1.4)	-0.1 (0.84)	0.65	0.064
Sphingosine 1-phosphate	-0.31 (0.5)	0.16 (0.73)	-0.47	0.068
2',3'-Cyclic CMP	0.5 (1.17)	-0.14 (0.97)	0.64	0.085
gamma-L-Glutamyl-D-alanine	-0.28 (0.59)	0.12 (0.66)	-0.41	0.090
Octanoic acid (caprylate)	0.46 (1.67)	-0.31 (1.17)	0.77	0.096
L-lysine	-0.28 (0.46)	-0.05 (0.34)	-0.23	0.101
UDP	-0.1 (0.43)	0.21 (0.52)	-0.31	0.102
Glycolate	-0.16 (0.29)	0.07 (0.38)	-0.23	0.107
4-Acetamidobutanoate	0.84 (1.46)	-0.31 (2.08)	1.15	0.111
Guanidinoacetate	-0.22 (0.55)	0.04 (0.43)	-0.25	0.137
5-6-Dihydrothymine	-0.07 (0.33)	0.17 (0.45)	-0.24	0.138
Citrate	-0.19 (0.26)	0 (0.35)	-0.19	0.145
L-Citrulline	-0.3 (0.41)	-0.07 (0.42)	-0.23	0.148
Heptanoic acid	0.24 (0.44)	0.02 (0.4)	0.22	0.151
L-valine	-0.23 (0.39)	-0.03 (0.35)	-0.20	0.156
L-tryptophan	0.09 (0.52)	-0.14 (0.42)	0.24	0.159
Choline	-0.13 (0.31)	0.08 (0.43)	-0.22	0.168
Anthranilate	1 (2.27)	0.06 (1.91)	0.94	0.190
Inosine	0.58 (1.19)	-0.09 (1.43)	0.66	0.191
2-Hydroxyglutarate/Citramalate	-0.08 (0.52)	0.13 (0.4)	-0.21	0.194
5-Hydroxyisourate	-0.23 (0.46)	0.11 (0.76)	-0.34	0.197

Supplementary Figure 10. Metabolomics by PEPI. Metabolites that were significantly ($p<0.2$, eBayes moderated t-test) differentially expressed with treatment (W5-BL) between patients with PEPI=0 (N=9) and PEPI>0 (N=41) are presented in log2 units. The mean and standard deviation (SD) among patients with PEPI=0 and PEPI> 0 are presented in columns 2 and 3, respectively. "Mean Diff" is the mean change among patients with PEPI> 0 (column 3) subtracted from the mean change among patients with PEPI=0 (column 2).

Metabolite	Combination (N=29) Mean(SD)	Fulvestrant (N=21) Mean(SD)	Mean Diff	p-value
L-Citrulline	-0.3 (0.39)	0.16 (0.3)	-0.46	<0.001
acyl-C5:1	-0.83 (1.37)	0.47 (1.04)	-1.30	<0.001
octenoyl-l-carnitine (acyl-C8:1)	-0.65 (0.59)	-0.06 (0.65)	-0.59	0.001
acyl-C4-OH	-1.02 (1.34)	0.09 (1.26)	-1.11	0.004
Bilirubin	0.46 (0.73)	-0.19 (0.85)	0.66	0.004
butanoyl-l-carnitine (acyl-C4)	-0.5 (0.75)	0.13 (0.81)	-0.63	0.006
L-lysine	-0.22 (0.39)	0.07 (0.27)	-0.29	0.007
Ornithine	-0.31 (0.4)	0.05 (0.47)	-0.35	0.007
N-Methylethanolamine phosphate	-0.37 (0.6)	0.11 (0.6)	-0.48	0.007
5-Hydroxyisourate	-0.17 (0.67)	0.35 (0.69)	-0.52	0.009
L-octanoylcarnitine (acyl-C8)	-1.18 (0.87)	-0.45 (1.11)	-0.73	0.011
gamma-Glutamyl-Se-methylselenocysteine	-0.33 (0.43)	0.03 (0.54)	-0.36	0.012
O-Decenoyl-L-carnitine (acyl-C10:1)	-0.97 (1.03)	-0.28 (1.01)	-0.69	0.02
5-Hydroxyindoleacetate	-0.12 (0.8)	0.39 (0.72)	-0.51	0.023
Picolinic acid	0.12 (0.54)	-0.31 (0.79)	0.44	0.023
L-proline	-0.28 (0.48)	0.01 (0.4)	-0.29	0.031
Guanidinoacetate	-0.13 (0.49)	0.16 (0.35)	-0.28	0.031
L-valine	-0.17 (0.39)	0.06 (0.29)	-0.23	0.035
Succinate	-0.19 (0.43)	0.07 (0.45)	-0.26	0.045
Sphinganine 1-phosphate	0.06 (0.56)	-0.29 (0.68)	0.36	0.045
S-Glutathionyl-L-cysteine	0.36 (1.12)	-0.24 (0.95)	0.59	0.049
Dodecanedioic acid	-0.15 (0.43)	0.08 (0.38)	-0.24	0.055
3-Methyleneoxindole	-0.27 (1.03)	0.24 (0.76)	-0.51	0.058
L-phenylalanine	-0.14 (0.35)	0.05 (0.34)	-0.19	0.065
Hypoxanthine	0.04 (0.6)	0.34 (0.56)	-0.30	0.074
L-methionine	-0.25 (0.62)	0.02 (0.4)	-0.27	0.087
L-Carnitine	-0.15 (0.43)	0.05 (0.33)	-0.20	0.087
Urate	-0.07 (0.28)	0.09 (0.33)	-0.16	0.089
L-glutamate	0.04 (0.54)	0.31 (0.57)	-0.27	0.095
Mannitol	-0.17 (1.11)	0.27 (0.71)	-0.43	0.115
4-Acetamidobutanoate	-0.48 (1.94)	0.41 (2.05)	-0.89	0.115
propionyl-carnitine (acyl-C3)	-0.3 (0.74)	0 (0.61)	-0.31	0.122
Sphingosine 1-phosphate	-0.05 (0.76)	0.25 (0.62)	-0.30	0.136
2-Hydroxyglutarate/Citramalate	0.17 (0.51)	-0.01 (0.24)	0.18	0.144
Glycolate	-0.04 (0.36)	0.12 (0.38)	-0.16	0.144
Allantoate	-0.27 (0.47)	-0.05 (0.61)	-0.23	0.149
L-aspartate	0.23 (0.46)	0.05 (0.4)	0.18	0.167
Glycerol 3-phosphate	0.29 (0.5)	0.1 (0.48)	0.20	0.167
N-Acetylornithine	-0.38 (1.27)	0.11 (1.19)	-0.48	0.169
L-Homocysteine	-0.35 (1.14)	0.07 (1.02)	-0.42	0.175
D-Ribose	-0.04 (0.39)	0.13 (0.45)	-0.17	0.177
L-Adrenaline	-0.21 (0.48)	-0.02 (0.53)	-0.19	0.195
Diphosphate	0.3 (1.08)	-0.09 (1.05)	0.39	0.196

Supplementary Figure 11. Metabolomics by arm. Metabolites that were significantly ($p<0.2$, eBayes moderated t-test) differentially expressed with treatment between patients with Combo (N=29) and Fulv (N=21) arms are presented in log2 units. The mean and standard deviation (SD) among patients with Combo and Fulv are presented in columns 2 and 3, respectively. "Mean Diff" is the mean change among Fulv patients (column 3) subtracted from the mean change among patients in the Combo arm (column 2).

Fulv W5 vs BL

Combo W5 vs BL

a

b

GO_ACTIVATION_OF_IMMUNE_RESPONSE
GO ALPHA BETA T CELL ACTIVATION

GO B CELL ACTIVATION
GO HUMORAL IMMUNE RESPONSE

c

Comparison	Gene sets	FDR	NES
Fulv	GO_HUMORAL_IMMUNE_RESPONSE	4.62E-03	1.63
Fulv	GO_ACTIVATION_OF_IMMUNE_RESPONSE	3.84E-03	1.49
Fulv	GO_B_CELL_ACTIVATION	7.38E-01	1.14
Fulv	GO_ALPHA_BETA_T_CELL_ACTIVATION	8.03E-01	1.12
Fulv	GO_ANTIGEN_PROCESSING_AND_PRESENTATION	2.47E-02	-1.58
Fulv	HALLMARK_INTERFERON_GAMMA_RESPONSE	7.38E-07	-2.05
Fulv	GO_CELL_DIVISION	1.70E-08	-2.18
Fulv	HALLMARK_ESTROGEN_RESPONSE_EARLY	1.70E-08	-2.39
Combo	GO_ACTIVATION_OF_IMMUNE_RESPONSE	5.19E-09	2.67
Combo	GO_HUMORAL_IMMUNE_RESPONSE	5.19E-09	2.63
Combo	GO_B_CELL_ACTIVATION	5.19E-09	2.53
Combo	GO_ALPHA_BETA_T_CELL_ACTIVATION	5.19E-09	2.22
Combo	HALLMARK_INTERFERON_GAMMA_RESPONSE	5.19E-09	2.22
Combo	GO_ANTIGEN_PROCESSING_AND_PRESENTATION	2.74E-03	1.57
Combo	GO_CELL_DIVISION	5.19E-09	-2.32
Combo	HALLMARK_ESTROGEN_RESPONSE_EARLY	5.19E-09	-2.71

Supplementary Figure 12. Select immune pathway enrichment by treatment of Fulvestrant-only or in combination with enzalutamide. GSEA plots displaying select pathways in each comparison (**a**, **b**). Below the enrichment score are ticks indicating the ranked positions of genes from each gene set (positive to negative fold-change). **c** Table displaying GSEA statistics for select gene sets. FDR, false discovery rate; NES, normalized enrichment score.

Supplementary Discussion 1. Ki67 Agreement Analysis

A linear mixed effect model with a random intercept for subject was used to assess the univariate association between RPPA Ki67 and IHC Ki67. RPPA Ki67 was log-transformed to improve model fit and one leverage point was removed. The regression line and its 95% prediction interval was plotted to assess agreement.[1] The model was fit with the lme4[2] R package and plots were constructed with the ggeffects[3] package. High levels of agreement between RPPA and IHC Ki67 at the given threshold are demonstrated.

IHC and RPPA Ki67 Agreement
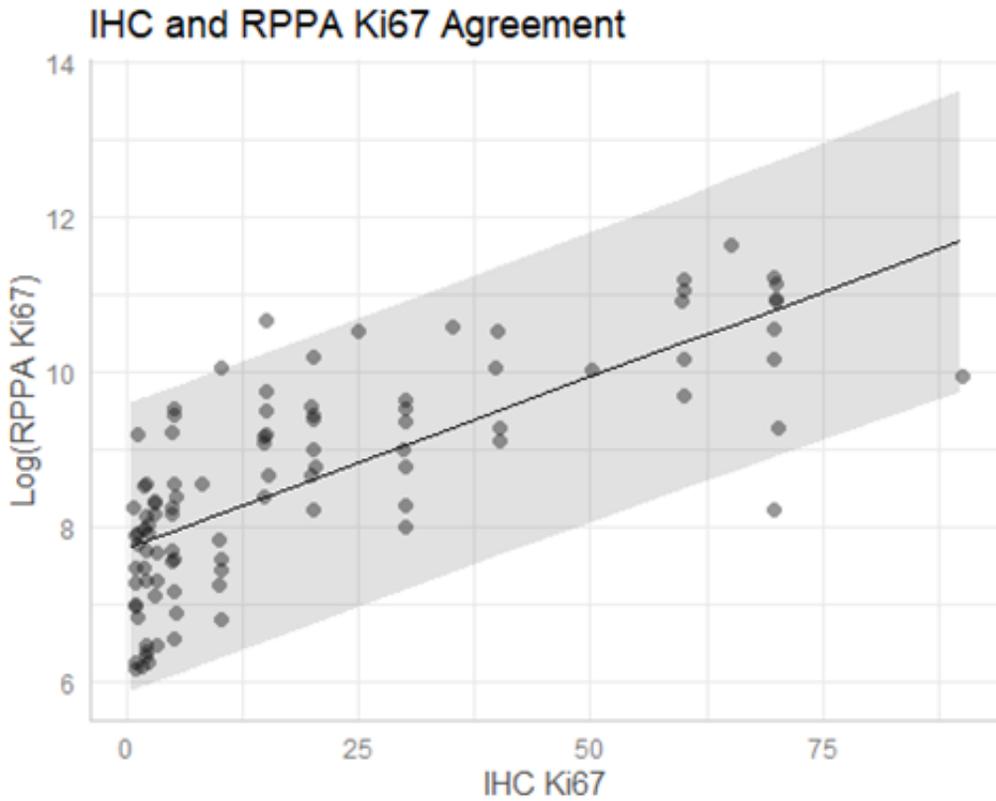
Predictor	Estimate	CI	p-value
IHC	1.05	1.04 – 1.05	<0.001

IHC Ki67 is a highly significant predictor of RPPA Ki67 (p<0.001). The agreement between RPPA Ki67 and IHC Ki67 is visualized by a plot of the regression line and corresponding 95% prediction bands. The regression line estimates the expected value of log(RPPA Ki67) based on IHC Ki67. The 95% prediction interval shows the uncertainty around the prediction estimate and the scattered points represent the observed values. Since the observed values generally fall within the prediction interval, this plot indicates good agreement at the given threshold.

References

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2. Bates, D., Mächler, M., Bolker, B. & Walker, S. Fitting Linear Mixed-Effects Models Using lme4. **67**(2015).
3. Lüdecke, D. ggeffects: Tidy Data Frames of Marginal Effects from Regression Models. *Journal of Open Source Software* **3**, 772 (2018).

Supplementary Data 1. Gene expression analysis from RNA from baseline (BL) and week 5 (W5) of treatment tumors. Differential gene expression of fulvestrant-treated samples at W5 as compared to matched baseline analyzed as described in methods.

Supplementary Data 2. Gene expression analysis from RNA from baseline (BL) and week 5 (W5) of treatment tumors. Differential gene expression of combination-treated samples at W5 as compared to matched baseline analyzed as described in methods.

Supplementary Data 3. Gene set enrichment analysis (GSEA) from gene expression analysis of RNA from baseline (BL) versus week 5 (W5) of treatment. Fulvestrant-treated samples at W5 as compared to matched BL.

Supplementary Data 4. Gene set enrichment analysis (GSEA) from gene expression analysis of RNA from baseline (BL) versus week 5 (W5) of treatment. Combination-treated samples at W5 as compared to matched BL.