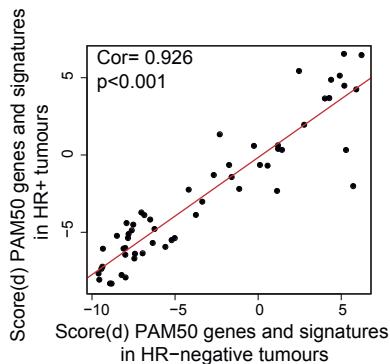
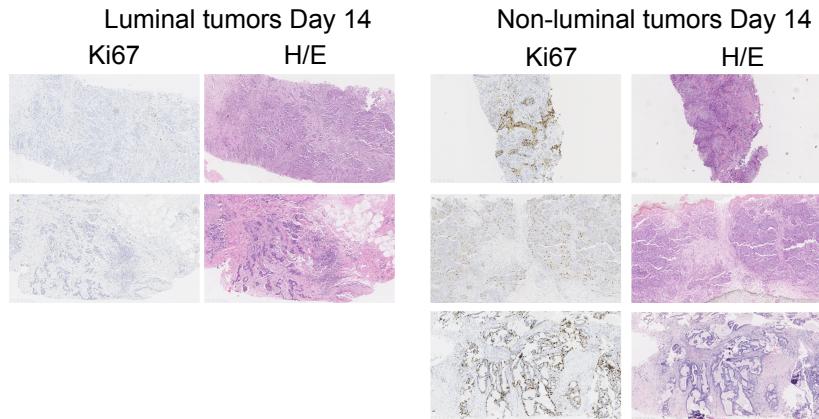
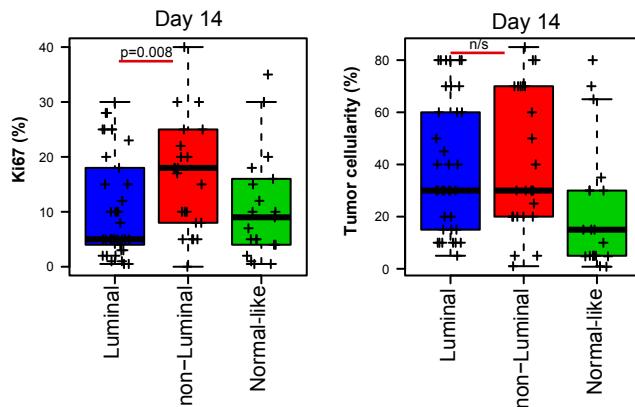
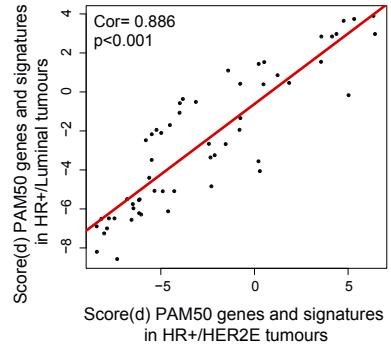


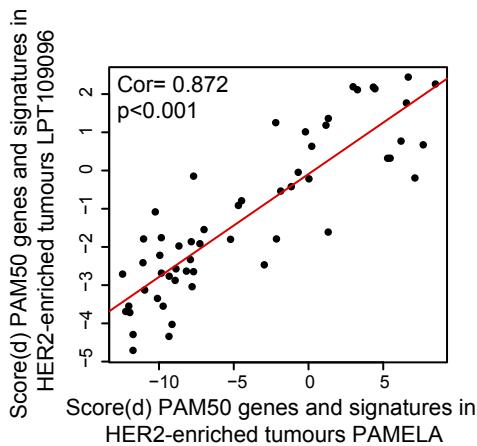
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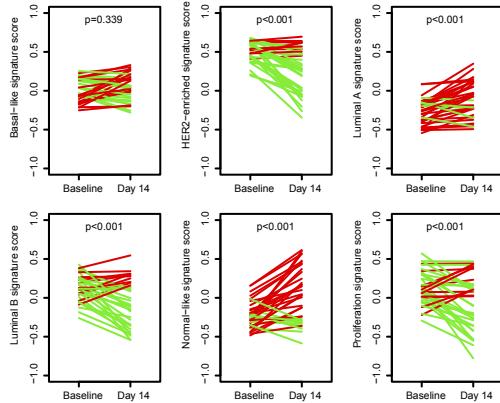
a**b****c****d**

Supplementary Figure 1. Molecular changes in HER2-E tumors upon dual HER2-blockade.

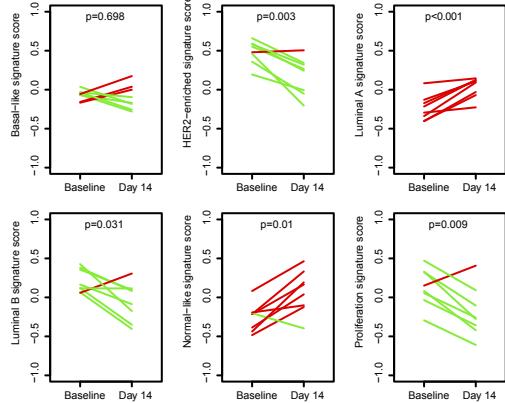
(a) Pearson correlation between differential PAM50 gene and signatures expression (Score [d]) in HER2+/HR+/HER2-E and HER2+/HR-negative/HER2-E tumors after 2 weeks of treatment with trastuzumab plus lapatinib. **(b)** Representative images of Ki67 and H/E stainings in Luminal and non-Luminal tumors of the PAMELA trial at day 14 **(c)** Ki67 (%) and tumor cellularity (%) at day 14 across molecular subtypes. P-values were determined by two-tailed unpaired t-tests. **(d)** Pearson correlation between differential PAM50 gene and signatures expression (Score [d]) in HER2+/HR+/HER2-E and HER2+/HR+/Luminal tumors after 2 weeks of treatment with trastuzumab plus lapatinib. Source data are provided as a Source Data file.

a**b**

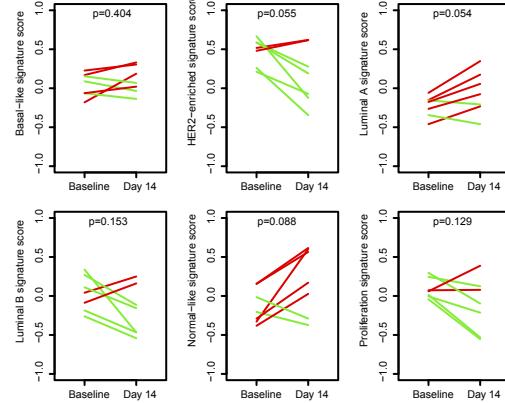
HER2+/HER2-E LPT109096

**c**

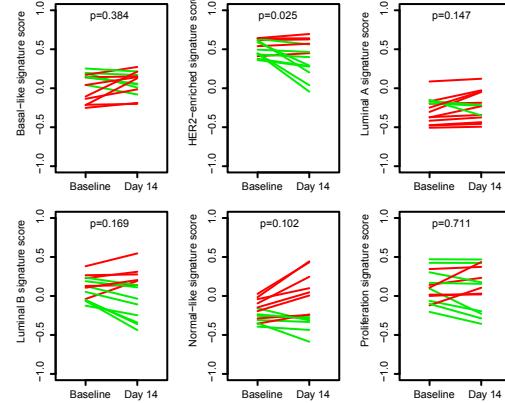
HER2+/HER2-E trastuzumab plus lapatininib

**d**

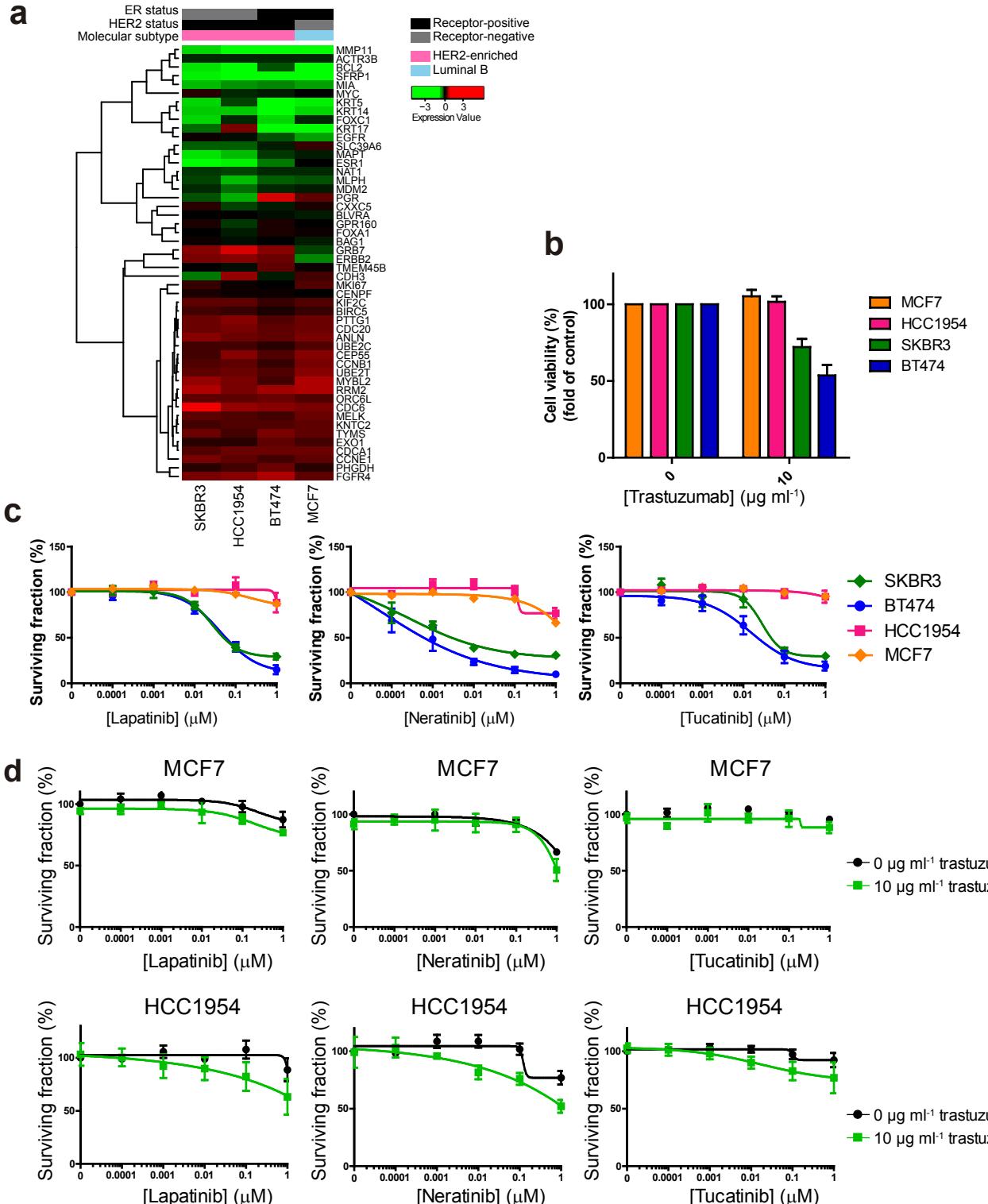
HER2+/HER2-E lapatininib

**e**

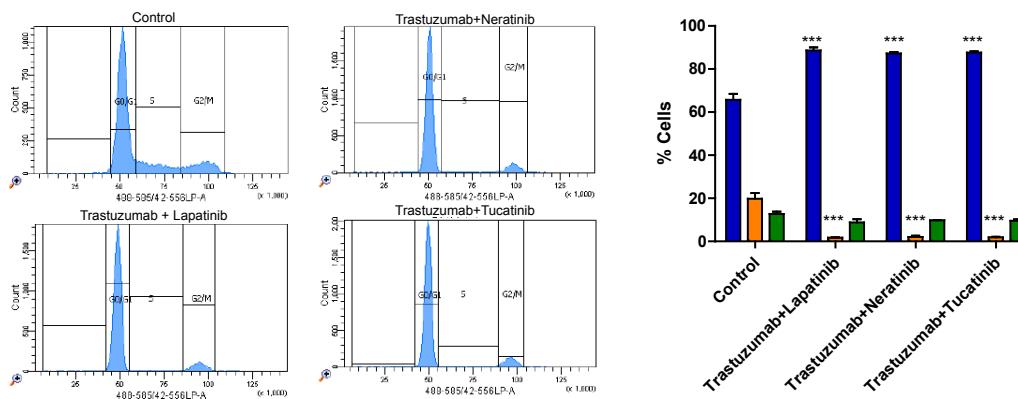
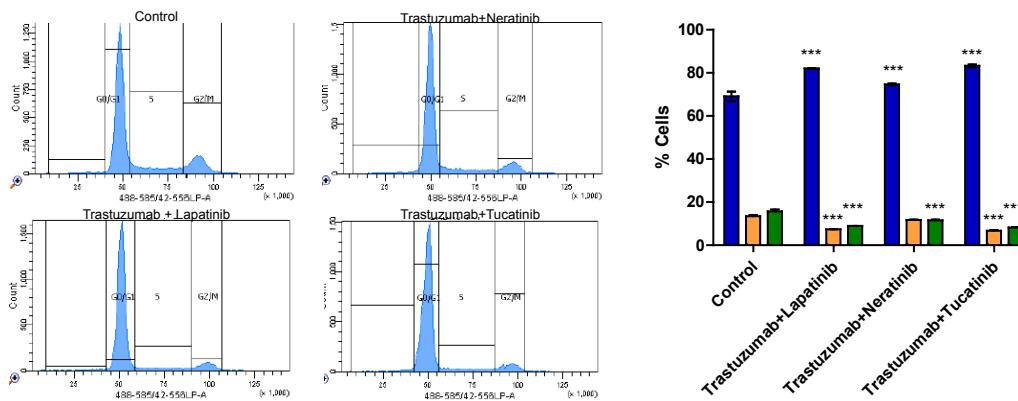
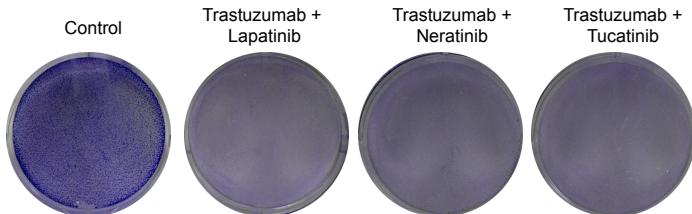
HER2+/HER2-E trastuzumab



Supplementary Figure 2. HER2 blockade led to a more luminal-like phenotype in HER2-E tumors of the LPT109096 trial. (a) Pearson correlation between differential PAM50 gene and signatures expression (Score [d]) in HER2-E tumors of the PAMELA study and HER2-E tumors of the LPT109096 study. (b) PAM50 signature expression changes between baseline and day 14 tumors treated with lapatininib, trastuzumab or the combination of both. Each line represents a tumor sample. P-values were determined by two-tailed paired t-tests. (c) PAM50 signature expression changes between baseline and day 14 tumors treated with lapatininib plus trastuzumab. (d) PAM50 signature expression changes between baseline and day 14 tumors treated with lapatininib. (e) PAM50 signature expression changes between baseline and day 14 tumors treated with trastuzumab. Each line represents a tumor sample. P-values were determined by two-tailed paired t-tests.

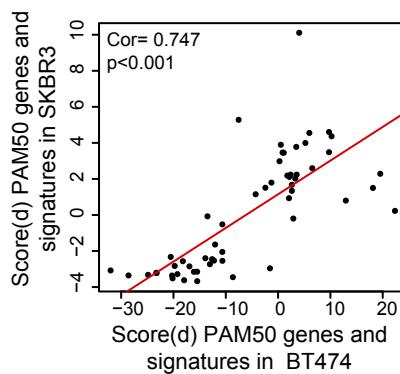
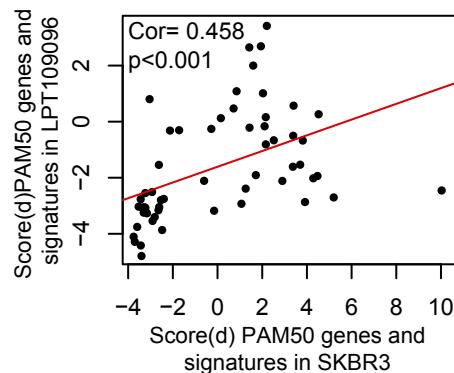
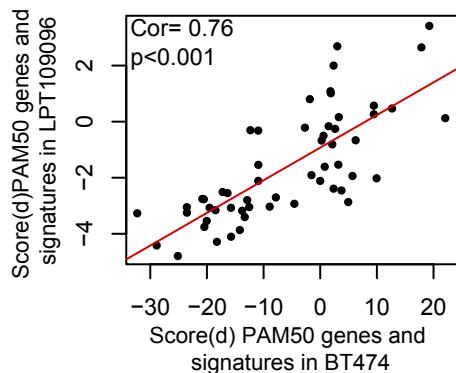
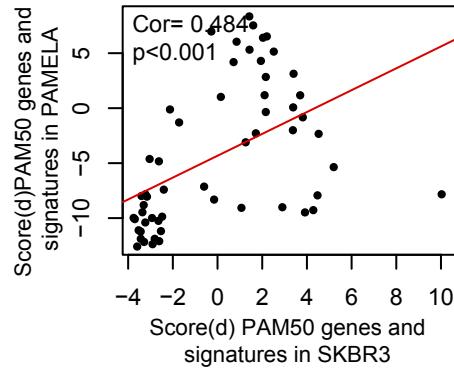
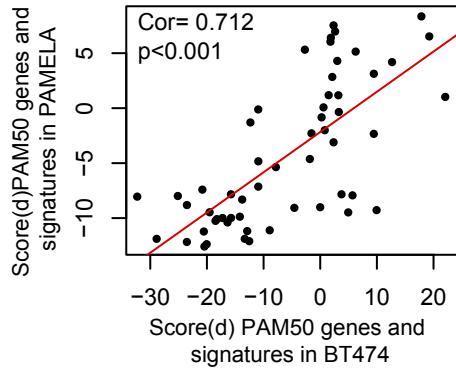


Supplementary Figure 3. Characterization of breast cancer cell lines. (a) Unsupervised hierarchical clustering of BT474, SKBR3, HCC1954 and MCF7 cell lines. The heatmap shows high (red) to low (green) expression of mRNAs in each sample. The molecular subtype call and HER2 and HR expression of each sample are shown. (b) Cell viability (%) of BT474 SKBR3, HCC1954 and MCF7 cells upon treatment with 10 $\mu\text{g ml}^{-1}$ trastuzumab or (c) increasing concentrations of lapatinib, neratinib or tucatinib for 72 hours. (d) Cell viability (%) of HCC1954 and MCF7 cells upon treatment with increasing concentrations of the TKI lapatinib, neratinib or tucatinib as monotherapy or in combination with 10 $\mu\text{g ml}^{-1}$ trastuzumab for 72 hours. Data points in (b), (c) and (d) represent the mean; error bars represent the standard error of the mean of 3 independent experiments. Source data are provided as a Source Data file.

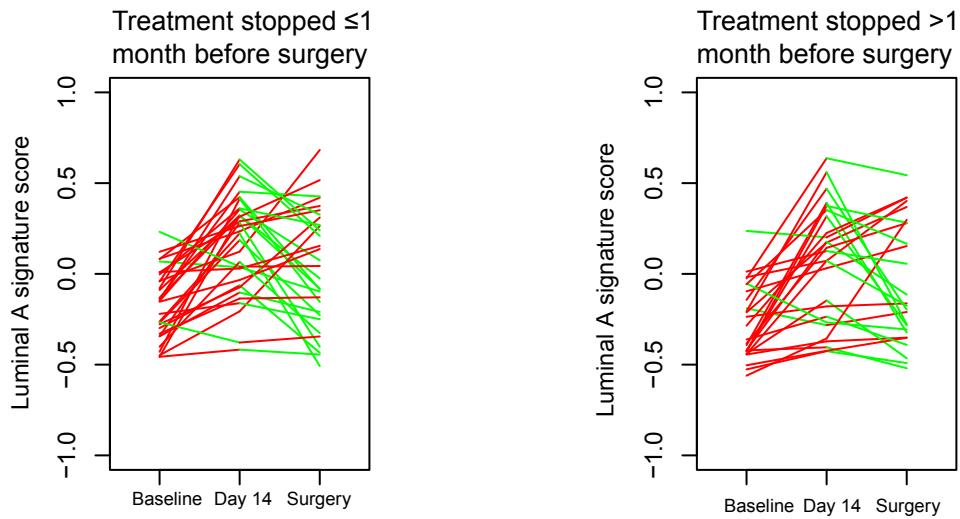
a**BT474****SKBR3****b****BT474****Supplementary Figure 4. Effects of anti-HER2 treatments on cell cycle and clonogenic potential.**

(a) Cell cycle analysis of BT474 and SKBR3 control and treated with 10 $\mu\text{g ml}^{-1}$ trastuzumab plus TKI (10 nM lapatinib, 2 nM neratinib or 10 nM tucatinib) or DMSO control and quantification of % of cells in each cell cycle phase. Column bars represent the mean of 3 independent experiments; error bars represent the standard error of the mean. P-values (**>: p<0.001) were determined by two-way ANOVAs.

(b) Representative images of BT474 treated with DMSO control or combinations of 10 $\mu\text{g ml}^{-1}$ trastuzumab and TKI (10 nM lapatinib, 2 nM neratinib or 10 nM tucatinib) and stained with 0.5% crystal violet solution after 10 days. Source data are provided as a Source Data file.

a**b**

Supplementary Figure 5. Gene and signatures changes in HER2+/HR+/HER2-E and HER2+/HR-negative/HER2-E cell lines and tumors upon dual HER2-blockade. (a) Pearson correlation between differential PAM50 gene and signatures expression (Score [d]) in BT474 and SKBR3 cells. **(b)** Pearson correlations between differential PAM50 gene and signatures expression (Score [d]) in TKI and trastuzumab-treated breast cancer cell lines and HER2-E tumors of the PAMELA and LPT109096 trials.



Supplementary Figure 6. Biological changes after dual HER2 blockade. Luminal A signature expression changes between baseline, day 14 and surgery in residual tumors, separated by time from end of treatment to surgery. Source data are provided as a Source Data file.

Supplementary Table 1. Gene expression profiles between day 14 and baseline in tumors of the PAMELA trial. Lists of differentially expressed genes between day 14 and baseline in tumors HER2+/HR+/HER2-E and tumors HER2+/HR-negative/HER2-E determined by SAM analysis.

SAM results HER2+/HR+/HER2E			SAM results HER2+/HR-/HER2E		
PAM50 gene or signature	Score (d)	q-value (% FDR)	PAM50 gene or signature	Score (d)	q-value (% FDR)
SFRP1	6.46970618	0	Normal	6.15800003	0
Normal	6.3872984	0	KRT14	5.84216192	0
EGFR	5.35663022	0	ESR1	5.65647281	0
BCL2	5.06052018	0	PGR	5.22656919	0
FOXC1	4.79417774	0	Luma	5.12669179	0
LumA	4.41129528	0	SFRP1	5.10093245	0
KRT14	4.17549989	0	BCL2	4.85173226	0
KRT5	3.60365709	0	FOXC1	4.32964763	0
MIA	3.58795374	0	KRT5	4.21822733	0
BAG1	1.88401491	0.33673772	MIA	3.95104105	0
PHGDH	1.26924536	1.8978564	BAG1	2.70717314	0
KRT17	0.55727256	10.0937572	EGFR	2.39800331	0.04977261
Basal	0.51615725	11.2848065	MDM2	1.3710356	2.19966358
MYC	0.32153393	13.5441796	MYC	1.13949548	3.58489853
MDM2	0.25715744	14.9731305	KRT17	1.12936489	3.58489853
PGR	0.24875259	14.9731305	NAT1	1.07697888	3.58489853
ANLN	-8.392227	0	CXXC5	0.50455003	11.4058563
MYBL2	-8.3792142	0	BLVRA	0.04393207	14.4021793
CCNB1	-8.1403335	0	UBE2C	-9.6658332	0
MKI67	-7.9912978	0	CCNB1	-9.6213003	0
BIRC5	-7.8405124	0	CENPF	-9.4923592	0
UBE2C	-7.7368716	0	RRM2	-9.4309033	0
CENPF	-7.4374211	0	UBE2T	-9.4026078	0
RRM2	-7.2959853	0	MYBL2	-8.9779165	0
KIF2C	-6.7642229	0	ANLN	-8.882521	0
CEP55	-6.5278776	0	CDCA1	-8.5615767	0
KNTC2	-6.4604716	0	BIRC5	-8.2813934	0
CDC20	-6.4274859	0	EXO1	-8.1651828	0
UBE2T	-6.1347616	0	ORC6L	-8.057896	0
EXO1	-6.124016	0	CEP55	-8.0559901	0
ORC6L	-6.0978949	0	MKI67	-8.0426157	0
TYMS	-6.0167558	0	FGFR4	-7.9837552	0
Her2	-5.765923	0	ERBB2	-7.8954499	0
Proliferation.	-5.5845645	0	GRB7	-7.8623169	0
LumB	-5.4551036	0	FOXA1	-7.6709285	0
ERBB2	-5.4505663	0	CDC6	-7.5776642	0
CDCA1	-5.3032377	0	KIF2C	-7.5096191	0
GRB7	-5.1956307	0	KNTC2	-7.476962	0
FOXA1	-4.9427805	0	TMEM45B	-7.088461	0
PTTG1	-4.8639359	0	CDC20	-7.0125249	0
CDC6	-4.5760108	0	MLPH	-6.90992	0
FGFR4	-4.4812287	0	MELK	-6.5593125	0
MELK	-4.2474824	0	Her2	-6.4054409	0
MLPH	-3.9638204	0	PTTG1	-6.3005764	0
GPR160	-3.9515314	0	TYMS	-5.6443705	0
TMEM45B	-3.7870791	0	Proliferation.	-5.2700002	0
MMP11	-3.0931685	0	LumB	-5.0820503	0
NAT1	-2.3986462	0	CCNE1	-4.2419873	0
CCNE1	-2.3133168	0	GPR160	-3.811707	0
MAPT	-2.2670435	0	MMP11	-3.4240648	0
ESR1	-2.0921499	0.10616361	CDH3	-2.7305932	0
SLC39A6	-1.5042711	0.64653641	PHGDH	-2.3708076	0
CDH3	-1.3705641	1.17909376	ACTR3B	-1.8091845	0.18725818
CXXC5	-0.7606059	6.78580491	SLC39A6	-1.6584347	0.49329089
ACTR3B	-0.7238199	6.78580491	MAPT	-1.2022239	1.52018129
BLVRA	-0.7188276	6.78580491	Basal	-0.3165352	10.6355494

n (%) genes which expression significantly changed at day 14		
PAM50 genes and signatures	HER2+/HR+/HER2-E	HER2+/HR-/HER2-E
significantly upregulated	11 (19.6%)	16 (28.6%)
significantly downregulated	37 (66.1%)	37 (66.1%)
significantly changed	48 (85.7%)	53 (94.7%)

Supplementary Table 2. Gene expression profiles between day 14 and baseline in tumors of the LPT109096 trial. Lists of differentially expressed genes between day 14 and baseline in tumors HER2+/HER2-E determined by SAM analysis.

SAM results HER2+/HER2E			changed at day 14	
PAM50 gene or signature	Score (d)	q-value (% FDR)	PAM50 genes and signatures	HER2+/HER2-E
LumA	2.41838424	0.364256025	significantly upregulated	11 (19.6%)
Normal	2.236725985	0.689984971	significantly downregulated	37 (66.1%)
ESR1	2.165060269	0.689984971	significantly changed	48 (85.7%)
PGR	2.156161758	0.689984971		
EGFR	2.112983956	1.116242352		
BAG1	2.087011993	1.116242352		
BCL2	1.741287709	2.3084056		
MDM2	1.335338364	6.211924392		
MAPT	1.225459931	8.045340075		
MYC	1.158344635	8.045340075		
BLVRA	0.985612937	11.9013993		
FOXC1	0.743408576	17.53002912		
SFRP1	0.64600633	19.56687468		
CXXC5	0.606938823	21.45793777		
KRT5	0.296018843	28.84689165		
MIA	0.294162017	28.84689165		
RRM2	-4.734293694	0		
ERBB2	-4.367722434	0		
ANLN	-4.317934529	0		
GRB7	-4.054252844	0		
CENPF	-3.743732209	0		
UBE2C	-3.715674287	0		
KNTC2	-3.576202236	0		
MYBL2	-3.574679304	0		
EXO1	-3.374244041	0		
MKI67	-3.154297258	0		
MLPH	-3.067889774	0		
FGFR4	-2.902270025	0		
CDC20	-2.792382984	0		
CCNB1	-2.736870423	0		
KIF2C	-2.710805965	0		
TMEM45B	-2.674148145	0		
Her2	-2.659903209	0		
FOXA1	-2.600037815	0		
CDH3	-2.494727115	0		
BIRC5	-2.439357783	0		
TYMS	-2.357887728	0		
ORC6L	-2.245064323	0.227083661		
CDC6	-2.000992396	0.364256025		
Proliferation.Score	-1.942576112	0.364256025		
PTTG1	-1.88976293	0.689984971		
GPR160	-1.827838843	0.689984971		
SLC39A6	-1.816706527	0.689984971		
UBE2T	-1.816652365	0.689984971		
CDCA1	-1.78452686	1.116242352		
KRT17	-1.637900104	1.611761767		
LumB	-1.57289301	2.3084056		
CEP55	-1.109609116	8.045340075		
CCNE1	-0.941149962	11.9013993		
MMP11	-0.818230781	15.58135075		
ACTR3B	-0.564088278	22.93979819		
PHGDH	-0.44914754	25.99564997		
Basal	-0.244066193	32.09534609		
KRT14	-0.221571796	32.09534609		
MELK	-0.174463958	33.01686895		
NAT1	-0.073726747	34.14101136		

Supplementary Table 3. Gene expression profiles between anti-HER2-treated and control cell lines.

Lists of differentially expressed genes between treated and untreated BT474 and SKBR3 determined by SAM analysis.

SAM results BT474			SAM results SKBR3		
PAM50 gene or signature	Score (d)	q-value (% FDR)	PAM50 gene or signature	Score (d)	q-value (% FDR)
MYC	22.3093313	0	TMEM45B	10.0915537	0
LumA	19.4924567	0	GPR160	5.26141284	0
Normal	18.0966483	0	MAPT	4.58506588	0
PGR	12.9120696	0	MLPH	4.5349134	0
GRB7	10.191529	0	GRB7	4.3477998	0
BAG1	9.70542779	0	ERBB2	3.97622206	0
MAPT	9.69600973	0	NAT1	3.87621467	0
MIA	6.49544207	0	KRT17	3.76005902	0
MLPH	5.93731448	0	BAG1	3.46366279	0
ERBB2	5.18130394	0	CXXC5	3.44629861	0
TMEM45B	3.99625975	0	ACTR3B	3.43351463	0
BLVRA	3.51777631	0	FOXA1	2.96195992	0
KRT17	3.4346435	0	MIA	2.57853407	0
EGFR	3.24853725	0	LumA	2.26626769	0
KRT14	2.87140641	0	ESR1	2.22124563	0
CDH3	2.59820706	0	BLVRA	2.21929742	0
SFRP1	2.59077176	0	MDM2	2.16674336	0
ESR1	2.36648054	0	BCL2	2.09600592	0
BCL2	2.11642018	0	EGFR	2.00173608	0
FOXC1	2.04696068	0	SLC39A6	1.77622477	0.31055901
MDM2	1.72646494	0	SFRP1	1.65735565	0.31055901
ACTR3B	1.03365261	0.58309038	KRT5	1.49284381	0.58309038
CXXC5	0.81751484	0.85714286	Normal	1.48261777	0.58309038
NAT1	0.48534011	2.38095238	CDH3	1.32020875	0.58309038
FOXA1	0.23442552	2.38095238	FGFR4	1.13126342	0.85714286
TYMS	-32.061148	0	FOXC1	0.91334586	2.1978022
RRM2	-28.634145	0	PGR	0.77909601	2.1978022
PTTG1	-24.892848	0	MYC	0.20920028	11.9480519
MYBL2	-23.299509	0	KIF2C	-3.6938286	0
CDC6	-23.28624	0	ORC6L	-3.6409611	0
Proliferation.	-20.562718	0	CCNB1	-3.5339459	0
BIRC5	-20.309112	0	MKI67	-3.4688951	0
CCNB1	-20.206106	0	BIRC5	-3.3777159	0
UBE2C	-19.802115	0	RRM2	-3.3736596	0
CDC20	-19.282807	0	PTTG1	-3.3409174	0
EXO1	-18.248942	0	CDC20	-3.3005879	0
ORC6L	-17.997795	0	CDC6	-3.2433842	0
CDCA1	-16.992776	0	MYBL2	-3.2245953	0
CEP55	-16.130011	0	CEP55	-3.1708805	0
MELK	-15.51551	0	MELK	-3.1673059	0
KIF2C	-15.503251	0	TYMS	-3.0971865	0
KNTC2	-13.946895	0	MMP11	-2.9792742	0
Her2	-13.538759	0	CDCA1	-2.8695331	0
ANLN	-13.083033	0	UBE2C	-2.8459982	0
UBE2T	-12.651167	0	ANLN	-2.7497298	0
CENPF	-12.291133	0	EXO1	-2.583306	0
PHGDH	-12.085984	0	CCNE1	-2.5630939	0
Basal	-10.703039	0	CENPF	-2.5489344	0
LumB	-10.697143	0	UBE2T	-2.4714759	0
CCNE1	-10.684727	0	KNTC2	-2.4181577	0
MKI67	-8.6796733	0	Proliferation.	-2.3439252	0
GPR160	-7.5904084	0	Basal	-2.0669437	0
FGFR4	-4.3265546	0	PHGDH	-1.6582951	0.31746032
KRT5	-2.470231	0	LumB	-0.5401174	5.92991914
MMP11	-1.5908671	0	KRT14	-0.2170521	11.9480519
SLC39A6	-1.3072353	0	Her2	-0.093242	12.5

n (%) genes which expression significantly changed at 72 h		
PAM50 genes and signatures	BT474	SKBR3
significantly upregulated	25 (44.6%)	27 (48.2%)
significantly downregulated	31 (55.4%)	25 (44.6%)
significantly changed	56 (100%)	52 (92.8%)

Supplementary Table 4. Gene expression profiles between surgery and day 14 in residual tumors of the PAMELA trial. Lists of differentially expressed genes between surgery and day 14 in residual HER2+/HER2-E tumors determined by SAM analysis.

SAM results day 14 vs residual tumor			n (%) genes which expression significantly changed	
PAM50 gene or signature	Score (d)	q-value (% FDR)	PAM50 genes and signatures	HER2+/HER2-E
MYC	5.9969978	0	significantly upregulated	46 (82.1%)
KRT17	4.16496599	0	significantly downregulated	6 (10.7%)
KRT5	3.62457159	0	significantly changed	52 (92.8%)
UBE2T	3.2318067	0		
MIA	2.99023234	0		
KRT14	2.98090971	0		
EXO1	2.79177628	0		
FOXC1	2.78401243	0		
PHGDH	2.74123057	0		
CDCA1	2.68866523	0		
MAPT	2.33025674	0		
SFRP1	2.27962982	0		
TYMS	2.20944238	0		
BLVRA	2.17584252	0		
CEP55	1.95103282	0		
PGR	1.82393423	0		
RRM2	1.81633076	0		
BIRC5	1.7594765	0		
CDC20	1.72158454	0		
UBE2C	1.66039707	0		
TMEM45B	1.52234215	0.060299		
BCL2	1.50609152	0.060299		
MKI67	1.4726498	0.060299		
MYBL2	1.42804655	0.060299		
ESR1	1.42751414	0.060299		
MLPH	1.3978971	0.060299		
FOXA1	1.35480731	0.060299		
CCNB1	1.33468156	0.060299		
KNTC2	1.33205903	0.060299		
CDC6	1.28713127	0.10611059		
EGFR	1.28514889	0.10611059		
MELK	1.17950362	0.10611059		
FGFR4	1.12902328	0.10611059		
GRB7	1.03156326	0.37033496		
CCNE1	0.96221905	0.37033496		
CDH3	0.83782518	0.61169632		
ANLN	0.81149944	0.61169632		
Basal	0.73394152	0.61169632		
KIF2C	0.53338263	0.61169632		
Normal	0.47183479	0.61169632		
CENPF	0.40750995	0.61169632		
Proliferation.	0.39116135	0.61169632		
BAG1	0.37724082	0.61169632		
CXXC5	0.3684763	0.61169632		
PTTG1	0.34998073	0.61169632		
ORC6L	0.31363867	0.61169632		
MMP11	-4.3451389	0		
MDM2	-2.8387937	0		
GPR160	-1.2155317	0.76999619		
ACTR3B	-1.1722067	0.76999619		
SLC39A6	-0.700598	2.19902495		
LumA	-0.5086705	3.94816837		
Her2	-0.4185061	4.62754837		
LumB	-0.3504179	5.20758105		
NAT1	-0.3113614	5.95026643		
ERBB2	-0.1898128	7.06591756		

Supplementary Table 5. Gene expression profiles after anti-HER2 treatment discontinuation in breast cancer cell lines. Lists of differentially expressed genes between cells after treatment discontinuation and treated with anti-HER2 therapy for 72 hours determined by SAM analysis.

SAM results BT474			SAM results SKBR3		
PAM50 gene or signature	Score (d)	q-value (% FDR)	PAM50 gene or signature	Score (d)	q-value (% FDR)
UBE2T	5.64771526	0	BIRC5	3.62129373	0
RRM2	5.24025011	0	PTTG1	3.48268016	0
TYMS	4.24155798	0	ORC6L	3.41702299	0
CDC6	3.94945638	0	PHGDH	3.25301632	0
FGFR4	3.93932464	0	CDC20	3.22496063	0
MYBL2	3.67725006	0	UBE2T	3.06679189	0
PTTG1	3.56187941	0	ANLN	3.06503655	0
CDC20	3.45738846	0	CDCA1	2.88292653	0
MELK	3.34569468	0	CCNB1	2.88220608	0
EXO1	3.30394814	0	TYMS	2.87625166	0
BIRC5	3.27321788	0	CEP55	2.86025669	0
PHGDH	3.26564704	0	EXO1	2.82205515	0
MKI67	3.25073895	0	CENPF	2.73825151	0
ANLN	3.1825882	0	CCNE1	2.60727219	0
CEP55	3.15995457	0	CDC6	2.57438742	0
KIF2C	3.1153988	0	MELK	2.50763625	0
ORC6L	2.88117683	0.74336283	RRM2	2.47517231	0
Proliferation.	2.84342528	0.74336283	KNTC2	2.40691848	0
CDCA1	2.7689423	0.74336283	MYBL2	2.35049619	0
CCNB1	2.68177325	0.74336283	KIF2C	2.33974306	0
KNTC2	2.63064025	0.74336283	Basal	1.93332396	0.46082949
GPR160	2.50463998	0.74336283	UBE2C	1.93086974	0.46082949
Her2	2.45978513	0.74336283	Proliferation.	1.89036537	0.46082949
BCL2	2.45378207	0.74336283	SLC39A6	1.75907523	0.46082949
CENPF	2.42081411	0.74336283	ACTR3B	1.15951435	4.34782609
UBE2C	2.40523987	0.74336283	MYC	1.0266555	4.34782609
LumB	2.06449157	1.85840708	LumB	1.0146316	4.34782609
Basal	1.76540029	2.73295159	ESR1	0.92097902	4.34782609
KRT5	1.71286567	2.73295159	MKI67	0.90548013	4.34782609
MMP11	1.67434709	2.73295159	MMP11	0.76955818	4.34782609
ACTR3B	1.01839603	11.192679	CXXC5	0.48956207	4.34782609
SLC39A6	0.62333832	20.1327434	EGFR	0.28047244	4.34782609
PGR	0.43927746	23.7569565	BLVRA	0.21647794	4.34782609
NAT1	0.27404084	26.8241777	BCL2	0.03462159	4.34782609
ESR1	0.254545274	26.8241777	KRT14	0.02832246	4.34782609
FOXA1	0.22928433	26.8241777	MDM2	-5.8174899	0
GRB7	-8.952422	0	FGFR4	-4.4747558	0
ERBB2	-3.0556566	0.86437539	MLPH	-4.1277234	0
Normal	-2.9893113	0.86437539	FOXA1	-4.0080666	0
LumA	-2.8594964	0.86437539	TMEM45B	-3.6545581	0
EGFR	-2.5975391	0.86437539	GRB7	-3.5113559	0
MIA	-2.5708598	0.99557522	KRT17	-2.7378484	0
CDH3	-2.509935	0.99557522	MIA	-2.2003798	0.89285714
KRT14	-1.7950501	2.73295159	LumA	-2.0920206	0.89285714
BLVRA	-1.6474238	2.73295159	NAT1	-2.0350607	0.89285714
TMEM45B	-1.6443933	2.73295159	ERBB2	-2.0012702	0.89285714
BAG1	-1.3957195	3.76704138	MAPT	-1.887994	0.89285714
MLPH	-1.3093719	4.46017699	BAG1	-1.7256374	0.89285714
MDM2	-1.1663668	5.24166099	SFRP1	-1.6069372	0.89285714
SFRP1	-0.9930443	5.24166099	Normal	-1.5736336	4.34782609
MYC	-0.7388819	11.192679	GPR160	-1.4821297	4.34782609
FOXC1	-0.5256456	15.4208247	KRT5	-1.4577348	4.34782609
MAPT	-0.5018061	15.4208247	FOXC1	-1.1323695	4.86322188
CXXC5	-0.3430367	15.4208247	CDH3	-0.4231845	4.86322188
KRT17	-0.1465987	15.4208247	PGR	-0.2600519	4.86322188
CCNE1	-0.0076394	15.4208247	Her2	-0.1188024	4.86322188

n (%) genes which expression significantly changed upon discontinuation		
PAM50 genes and signatures	BT474	SKBR3
significantly upregulated	30 (53.6%)	35 (62.5%)
significantly downregulated	12 (35.7%)	21 (37.5%)
significantly changed	56 (75%)	56 (100%)

Supplementary Table 6. Gene expression profiles in BT474-L^{RT}R and BT474-Tu^{RT}R. Lists of differentially expressed genes between BT474-L^{RT}R and parental BT474 cells and between BT474-Tu^{RT}R and parental BT474 cells determined by SAM analysis.

SAM results BT474 vs BT474-LRTR			SAM results BT474 vs BT474-TuRTR		
PAM50 genes	Score (d)	q-value (% FDR)	PAM50 genes	Score (d)	q-value (% FDR)
FGFR4	12.7323407	0	FGFR4	7.03476586	0
FOXA1	9.11196718	0	KRT5	5.53855821	0
GRB7	6.45458	0	KRT14	3.9474193	0
ERBB2	5.91971466	0	SFRP1	3.9474193	0
MLPH	5.49257597	0	ERBB2	3.26755369	0
KRT5	4.58430964	0	MAPT	3.10027698	0
EGFR	4.3881213	0	EGFR	3.02649972	0
MDM2	3.90096637	0	MDM2	3.01789419	0
MAPT	3.77590049	0	FOXA1	2.16563796	1.03448276
SFRP1	3.59380934	0	MLPH	1.56457514	7.21732157
BAG1	2.39454049	1.14942529	GRB7	1.43635636	7.21732157
GPR160	1.9489275	1.64576803	FOXC1	1.26297565	7.21732157
BLVRA	1.87658348	1.64576803	ESR1	0.86045578	13.7931035
MIA	1.57990066	2.09895053	MMP11	0.73539923	16.1637931
CXXC5	1.50736934	2.09895053	NAT1	0.62401171	16.1637931
NAT1	1.22941738	2.51436782	MIA	0.6210077	16.1637931
PGR	1.08497893	2.51436782	BAG1	0.49898233	18.3673469
ESR1	0.81518396	2.51436782	KRT17	0.3191269	18.3673469
ACTR3B	0.2820106	2.51436782	GPR160	0.18611141	18.3673469
MYC	0.09596955	2.51436782	PGR	0.13378854	18.3673469
KRT14	-0.0777179	1.17746005	MYC	-0.1918202	7.95755968
KRT17	-0.1676905	1.17746005	CXXC5	-0.4822267	7.95755968
FOXC1	-0.3858942	1.17746005	ACTR3B	-0.569305	7.95755968
SLC39A6	-0.4864237	1.17746005	PHGDH	-0.6870804	7.95755968
TMEM45B	-0.4948573	1.17746005	TMEM45B	-0.8212657	7.95755968
MMP11	-1.0146634	1.17746005	PTTG1	-0.836089	7.95755968
BCL2	-1.1802496	1.17746005	BCL2	-0.9263621	7.95755968
PHGDH	-1.2890688	1.17746005	SLC39A6	-1.0662884	4.31034483
CDH3	-1.8645395	0.60344828	BLVRA	-1.127455	3.54679803
MKI67	-3.7996034	0	BIRC5	-1.166172	3.54679803
CCNE1	-4.6235586	0	CENPF	-1.3409063	1.88087774
UBE2T	-5.0562345	0	UBE2C	-1.4564618	1.88087774
UBE2C	-6.4896599	0	MKI67	-1.6871412	1.14942529
KNTC2	-7.7897848	0	EXO1	-1.9595977	1.14942529
CDC6	-10.018136	0	CCNB1	-2.2910507	0
KIF2C	-10.976417	0	CDC20	-2.3393368	0
PTTG1	-11.189744	0	UBE2T	-2.3679123	0
CDC20	-12.55016	0	RRM2	-2.5099799	0
ORC6L	-14.127434	0	CDC6	-2.5760795	0
CENPF	-14.251581	0	CCNE1	-2.6132856	0
MELK	-14.81298	0	CDCA1	-2.660327	0
RRM2	-15.219372	0	ANLN	-2.7131414	0
BIRC5	-16.038778	0	CDH3	-2.9998097	0
ANLN	-16.857195	0	KIF2C	-3.1565632	0
EXO1	-18.261239	0	CEP55	-3.3461766	0
CEP55	-19.811407	0	MYBL2	-3.405738	0
TYMS	-21.079682	0	ORC6L	-4.2898388	0
CDCA1	-22.710382	0	MELK	-4.3151181	0
MYBL2	-25.104831	0	TYMS	-4.3920362	0
CCNB1	-26.321783	0	KNTC2	-7.0013982	0