Triple negative PAM50 non-basal breast cancer subtype predicts benefit from extended adjuvant capecitabine

SUPPLEMENTARY TABLES

Supplementary Table S1: Gene list for the NanoString custom nCounter codeset included in the study.

Codeset gene	**Gene/Metagene details**
CTSW	Cytotoxic cells signature
GNLY	Cytotoxic cells signature
GZMA	Cytotoxic cells signature
GZMB	Cytotoxic cells signature
GZMH	Cytotoxic cells signature
KLRB1	Cytotoxic cells signature
KLRD1	Cytotoxic cells signature
KLRK1	Cytotoxic cells signature
NKG7	Cytotoxic cells signature
PRF1	Cytotoxic cells signature
BCL6B	Endothelial signature
CDH5	Endothelial signature
CLEC14A	Endothelial signature
CXorf36	Endothelial signature
FAM124B	Endothelial signature
KDR	Endothelial signature
MMRN2	Endothelial signature
MYCT1	Endothelial signature
PALMD	Endothelial signature
ROBO4	Endothelial signature
TIE1	Endothelial signature
CPA3	Mast cells
HDC	Mast cells
MS4A2	Mast cells
TPSAB1	Mast cells
CD8A	CD8 T cells
CD8B	CD8 T cells
LAG3	Exhausted CD8 T cells
ANGPT1	Capecitabine sensitivity
BCL2A1	Capecitabine sensitivity
BMP2	Capecitabine sensitivity
CACNA2D3	Capecitabine sensitivity
CCNA1	Capecitabine sensitivity
CCR5	Capecitabine sensitivity
CES1	Capecitabine sensitivity
CXCL10	Capecitabine sensitivity
CXCL5	Capecitabine sensitivity
GRIA3	Capecitabine sensitivity
HAS1	Capecitabine sensitivity
HOXA9	Capecitabine sensitivity
IL22RA2	Capecitabine sensitivity
IL24	Capecitabine sensitivity
IL6	Capecitabine sensitivity

JAK1	Capecitabine sensitivity
LEP	Capecitabine sensitivity
LIFR	Capecitabine sensitivity
MME (CD10)	Capecitabine sensitivity
NRCAM	Capecitabine sensitivity
PLCB1	Capecitabine sensitivity
PSMB9	Capecitabine sensitivity
SLC28A1	Capecitabine sensitivity
SOCS3	Capecitabine sensitivity
STC1	Capecitabine sensitivity
TGFB2	Capecitabine sensitivity
TWIST2	Capecitabine sensitivity
TYMP	Capecitabine sensitivity
VIT	Capecitabine sensitivity
MAPK1	Capecitabine resistance
PLCE1	Capecitabine resistance
FXYD3	Capecitabine resistance
AR	Additional biologically-important
BRCA1	Additional biologically-important
BRCA2	Additional biologically-important
CAV1	Additional biologically-important
CCL5	Additional biologically-important
CD27	Additional biologically-important
CD274	Additional biologically-important
CD276	Additional biologically-important
CMKLR1	Additional biologically-important
CXCL9	Additional biologically-important
CXCR6	Additional biologically-important
DDR2	Additional biologically-important
FHL1	Additional biologically-important
FSTL1	Additional biologically-important
HEG1	Additional biologically-important
HLA-DMA	Additional biologically-important
HLA-DOA	Additional biologically-important
HLA-DPA1	Additional biologically-important
HLA-DPB1	Additional biologically-important
HLA-DQA1	Additional biologically-important
HLA-DQB1	Additional biologically-important
HLA-DRA	Additional biologically-important
HLA-DRB1	Additional biologically-important
HLA-DRB5	Additional biologically-important
HLA-E	Additional biologically-important
IDO1	Additional biologically-important
JAM2	Additional biologically-important
PDCD1	Additional biologically-important
PDCD1LG2	Additional biologically-important
PSMB10	Additional biologically-important
SNAI2	Additional biologically-important
STAT1	Additional biologically-important
TCF4	Additional biologically-important
TIGIT	Additional biologically-important
VCAN	Additional biologically-important
VIM	Additional biologically-important

ACTR3B	PAM50
ANLN	PAM50
BAG1	PAM50
BCL2	PAM50
BIRC5	PAM50
BLVRA	PAM50
CCNB1	PAM50
CCNE1	PAM50
CDC20	PAM50
CDC6	PAM50
CDCA1	PAM50
CDH3	PAM50
CENPF	PAM50
CEP55	PAM50
CXXC5	PAM50
EGFR	PAM50
ERBB2	PAM50
ESR1	PAM50
EXO1	PAM50
FGFR4	PAM50
FOXA1	PAM50
FOXC1	PAM50
GPR160	PAM50
GRB7	PAM50
KIF2C	PAM50
KNTC2	PAM50
KRT14	PAM50
KRT17	PAM50
KRT5	PAM50
MAPT	PAM50
MDM2	PAM50
MELK	PAM50
MIA	PAM50
MKI67	PAM50
MLPH	PAM50
MMP11	PAM50
MYBL2	PAM50
MYC	PAM50
NAT1	PAM50
ORC6L	PAM50
PGR	PAM50
PHGDH	PAM50
PTTG1	PAM50
RRM2	PAM50
SFRP1	PAM50
SLC39A6	PAM50
TMEM45B	PAM50
TYMS	PAM50
UBE2C	PAM50
UBE2T	PAM50
ABCF1	Reference genes
ACTB	Reference genes
G6PD	Reference genes

GUSB	Reference genes
MRPL19	Reference genes
NRDE2	Reference genes
OAZ1	Reference genes
POLR2A	Reference genes
PSMC4	Reference genes
PUM1	Reference genes
RPLP0	Reference genes
SDHA	Reference genes
SF3A1	Reference genes
STK11IP	Reference genes
TBC1D10B	Reference genes
TBP	Reference genes
TFRC	Reference genes
UBB	Reference genes

Supplementary Table S2: Patient characteristics in the GEICAM/CIBOMA translational study cohort versus the original trial.

Characteristic	GEICAM/CIBOMA Translational Population (n=658)	GEICAM/CIBOMA Whole Population (n=876)
Treatment		
Observation	321 (49%)	428 (49%)
Capecitabine	337 (51%)	448 (51%)
Age		
Mean (years)	50.51	50.27
Region		
Spain	423 (64%)	532 (61%)
Latin America	235 (36%)	344 (39%)
Race		
White	491 (74%)	622 (71%)
Hispanic	136 (21%)	204 (23%)
African American	14 (2%)	27 (3%)
Other	17 (3%)	23 (3%)
Karnofsky performance status		
80	23 (4%)	25 (3%)
90	95 (14%)	124 (14%)
100	540 (82%)	727 (83%)
Menopausal status at diagnosis		
Postmenopausal	210 (32%)	276 (32%)
Premenopausal	448 (68%)	600 (68%)
Histological type		
Invasive Ductal	569 (87%)	764 (87%)
Invasive Lobular	16 (2%)	19 (2%)
Other	73 (11%)	93 (11%)
Histological grade		
G1	16 (3%)	27 (3%)
G2	108 (16%)	163 (19%)
G3	493 (75%)	622 (71%)
GX	41 (6%)	64 (7%)
Tumor size		
≤ 2 cm	248 (38%)	353 (40%)
> 2 cm and ≤ 5 cm	361 (55%)	462 (53%)
> 5 cm	39 (6%)	47 (5%)
Unknown	10 (1%)	14 (2%)
Phenotype by IHC		
Triple negative Basal	496 (75%)	647 (74%)
Triple negative Non-basal	162 (25%)	229 (26%)
Stage at diagnosis		
I	107 (16%)	136 (16%)
II	407 (62%)	541 (62%)
III	137 (21%)	186 (21%)

Unknown	7 (1%)	13 (1%)
Nodal status		
Negative	352 (53%)	486 (55%)
1-3	195 (30%)	246 (28%)
≥ 4	106 (16%)	138 (16%)
Unknown	5 (1%)	6 (1%)
pCR in patients with neoadjuvant chemotherapy		
No	72 (11%)	123 (14%)
Yes	17 (3%)	41 (5%)
Unknown	569 (86%)	712 (81%)
Type of prior chemotherapy		
Adjuvant	564 (86%)	706 (80%)
Neoadjuvant	89 (13%)	164 (19%)
Unknown	5 (1%)	6 (1%)
Chemotherapy regimen		
Anthracyclines and Taxanes	442 (67%)	591 (67%)
Anthracyclines without Taxanes	216 (33%)	285 (33%)
Breast surgery		
Conservative	372 (56%)	479 (55%)
Mastectomy	280 (43%)	390 (44%)
Unknown	6 (1%)	7 (1%)
Axillary surgery		
ALND ± SLNB	486 (74%)	655 (75%)
SLNB	172 (26%)	221 (25%)
Radiation therapy		
No	518 (79%)	698 (80%)
Yes	135 (20%)	172 (19%)
Unknown	5 (1%)	6 (1%)
Distant relapse events		
No	507 (77%)	674 (77%)
Yes	151 (23%)	202 (23%)
Recurrence events		
No	491 (75%)	651 (74%)
Yes	167 (25%)	225 (26%)
Death events		
No	555 (84%)	732 (84%)
Yes	103 (16%)	144 (16%)

Abbreviations: IHC, immunohistochemistry; pCR, pathologic complete response; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

Supplementary Table S3: Distribution of PAM50 intrinsic subtypes in the GEICAM/CIBOMA translational study cohort.

	Observation (n=321)	Capecitabine (n=337)	*P*-value
PAM50 intrinsic subtype			
Basal-like	274 (85.36%)	279 (82.79%)	0.84
Her2-Enriched	19 (5.92%)	27 (8.01%)	
Luminal A	5 (1.56%)	7 (2.08%)	
Luminal B	1 (0.31%)	1 (0.3%)	
Normal-like	22 (6.85%)	23 (6.82%)	
PAM50 intrinsic subtype			
PAM50 Basal	274 (85.36%)	279 (82.79%)	0.43
PAM50 Non-basal	47 (14.64%)	58 (17.21%)	

Supplementary Table S4: Differential gene expression analysis performed on the 164 genes included in the custom codeset comparing PAM50 non-basal vs. basal-like subtype and their biological processes. Only genes with significant results when adjusted for multiple testing are displayed.

Gene	Log2 fold change	std error (log2)	Lower confidence limit (log2)	Upper confidence limit (log2)	*P*-value	Adjusted *P*-value	Biological Process
FOXA1	5.55	0.27	5.03	6.08	6.53E-73	7.99E-71	ER mediated signaling, Breast cancer subtyping
AR	3.68	0.168	3.35	4.01	2.00E-80	7.35E-78	Androgen receptor signalling
MLPH	3.6	0.168	3.27	3.93	7.96E-78	1.95E-75	Breast cancer subtyping
FGFR4	3	0.149	2.71	3.29	2.69E-70	2.82E-68	PI3K-AKT signaling, Breast cancer subtyping
ESR1	2.84	0.147	2.55	3.13	6.00E-66	4.89E-64	ER mediated signaling
MAPT	2.63	0.166	2.31	2.96	3.95E-48	1.61E-46	Breast cancer subtyping
NAT1	2.61	0.125	2.37	2.86	7.79E-75	1.14E-72	Breast cancer subtyping
CES1	2.4	0.191	2.02	2.77	1.35E-32	3.68E-31	Capecitabine metabolism
ERBB2	1.81	0.0991	1.61	2	2.39E-60	1.59E-58	Her2 signalling, PI3K-AKT signaling, Breast cancer subtyping
GPR160	1.78	0.12	1.54	2.01	3.27E-43	1.26E-41	Breast cancer subtyping
CPA3	1.73	0.157	1.42	2.04	3.36E-26	6.86E-25	Mast cell signature

TPSAB1	1.69	0.154	1.39	1.99	5.87E-26	1.17E-24	Mast cell signature, Extracellular matrix organization
GRB7	1.1	0.111	0.887	1.32	9.31E-22	1.55E-20	Her2 signalling, PI3K-AKT signaling, Breast cancer subtyping
JAM2	1.04	0.0969	0.846	1.23	1.01E-24	1.86E-23	Extracellular matrix organization
SLC39A6	0.947	0.0724	0.805	1.09	6.48E-35	1.90E-33	Transport of small molecules, Breast cancer subtyping
BLVRA	0.922	0.0719	0.781	1.06	9.87E-34	2.79E-32	Breast cancer subtyping
CXXC5	0.902	0.079	0.747	1.06	1.10E-27	2.37E-26	ER mediated signaling, Breast cancer subtyping
HOXA9	0.867	0.104	0.663	1.07	5.53E-16	7.81E-15	Transcription Misregulation pathway
MYCT1	0.834	0.0935	0.651	1.02	4.52E-18	6.77E-17	Tumor angiogenesis, endothelial signature
FHL1	0.813	0.125	0.569	1.06	1.39E-10	1.50E-09	Triple negative biology, Cancer progression EMT, tumor proliferation
MMRN2	0.8	0.084	0.635	0.965	3.17E-20	4.95E-19	Tumor angiogenesis, endothelial signature
CLEC14A	0.782	0.081	0.623	0.941	1.05E-20	1.71E-19	Tumor angiogenesis, endothelial signature
CXorf36	0.703	0.0852	0.536	0.87	8.28E-16	1.15E-14	Tumor angiogenesis, endothelial signature
TIE1	0.671	0.0872	0.5	0.842	5.24E-14	6.31E-13	Tumor angiogenesis, endothelial signature
ROBO4	0.666	0.0863	0.497	0.835	4.62E-14	5.65E-13	Tumor angiogenesis, endothelial signature
CDH5	0.661	0.0842	0.496	0.826	1.64E-14	2.08E-13	Tumor angiogenesis, endothelial signature
VCAN	0.641	0.0938	0.457	0.825	1.86E-11	2.11E-10	Extracellular matrix organization, Cancer progression EMT, Tumor angiogenesis
FAM124B	0.641	0.117	0.411	0.871	6.50E-08	6.45E-07	Tumor angiogenesis, endothelial signature
BCL6B	0.586	0.13	0.331	0.84	7.68E-06	6.96E-05	Tumor angiogenesis, endothelial signature
TCF4	0.566	0.0753	0.418	0.713	1.91E-13	2.26E-12	Cancer progression EMT
MMP11	0.552	0.158	0.241	0.862	0.000526	0.00429	Extracellular matrix organization, Breast cancer subtyping
LIFR	0.543	0.116	0.315	0.771	3.75E-06	3.44E-05	JAK1/STAT3 pathway
KDR	0.518	0.0767	0.367	0.668	3.24E-11	3.61E-10	VEGF receptor 2, tumor angiogenesis,

							endothelial signature, Extracellular matrix organization
CAV1	0.477	0.0948	0.291	0.663	6.45E-07	6.23E-06	Extracellular matrix organization, Cancer progression EMT
DDR2	0.465	0.0828	0.303	0.628	2.81E-08	2.82E-07	Extracellular matrix organization, Cancer progression EMT
FSTL1	0.449	0.083	0.287	0.612	8.67E-08	8.48E-07	Cancer progression EMT, Tumor angiogenesis
STC1	0.428	0.115	0.201	0.654	0.00023	0.00194	Tumor angiogenesis, JAK1/STAT3 pathway
GRIA3	0.405	0.162	0.0883	0.722	0.0124	0.0923	Transcription misregulation pathway
BCL2	0.396	0.116	0.168	0.624	0.000701	0.00566	Apoptosis, ER mediated signaling, Breast cancer subtyping
HEG1	0.372	0.0742	0.226	0.517	6.97E-07	6.64E-06	Cancer progression EMT
PALMD	0.372	0.116	0.146	0.599	0.00133	0.0106	Tumor angiogenesis, endothelial signature
KLRB1	0.331	0.124	0.0879	0.573	0.00777	0.0588	Adaptive Immune System, Cytotoxic cell signature
PLCB1	0.289	0.114	0.0658	0.512	0.0114	0.0852	Signaling by WNT
MDM2	0.246	0.0526	0.143	0.349	3.50E-06	3.25E-05	Breast cancer subtyping, Cell cycle pathway
JAK1	0.154	0.0418	0.0716	0.235	0.000258	0.00215	JAK1/STAT3 signalling, PI3K sognalling, immune response
CD276	0.153	0.0657	0.0244	0.282	0.02	0.145	B7-H3 immune checkpoint molecule suppressing T cell activation and proliferation
CCR5	-0.229	0.115	-0.455	-0.00341	0.0471	0.335	C-C chemokine receptor type 5 involved in immune response
GZMA	-0.283	0.138	-0.554	-0.0119	0.0411	0.296	Immune response, Cytotoxic cell signature
TYMP	-0.316	0.0839	-0.481	-0.152	0.00018	0.00153	Capecitabine metabolism, Tumor proliferation
PDCD1LG2	-0.343	0.0909	-0.521	-0.165	0.000175	0.00151	Programmed cell death 1 ligand 2,

							Immune checkpoint receptor molecule
PDCD1	-0.35	0.145	-0.634	-0.0667	0.0157	0.115	Programmed cell death 1, Immune checkpoint molecule
KLRD1	-0.368	0.122	-0.608	-0.129	0.0027	0.0213	Immune response, Cytotoxic cell signature
PRF1	-0.387	0.14	-0.661	-0.112	0.00594	0.0454	Immune response, Cytotoxic cell signature
NKG7	-0.394	0.142	-0.672	-0.115	0.00577	0.0446	Natural killer cell granule protein 7, Cytotoxic cell signature
TGFB2	-0.503	0.14	-0.776	-0.229	0.000338	0.00279	Extracellular matrix organization
GZMH	-0.505	0.17	-0.839	-0.172	0.0031	0.0242	Immune response, Cytotoxic cell signature
STAT1	-0.556	0.0986	-0.749	-0.363	2.58E-08	2.63E-07	STAT pathway, Immune infiltration
CCL5	-0.575	0.137	-0.843	-0.307	2.98E-05	0.000264	Immune response
GNLY	-0.597	0.154	-0.899	-0.294	0.00012	0.00105	Immune response, Cytotoxic cell signature
PSMB9	-0.617	0.106	-0.824	-0.409	8.66E-09	9.08E-08	Immune response
RRM2	-0.629	0.0808	-0.787	-0.471	2.73E-14	3.40E-13	Breast cancer subtyping, DNA damage repair
ACTR3B	-0.639	0.0682	-0.773	-0.506	1.18E-19	1.80E-18	Breast cancer subtyping
CD8B	-0.665	0.152	-0.962	-0.367	1.36E-05	0.000122	CD8 T cells signature
CD274	-0.753	0.133	-1.01	-0.493	2.05E-08	2.12E-07	Programmed cell death 1 ligand 1, Immune checkpoint receptor molecule
PLCE1	-0.765	0.117	-0.995	-0.535	1.33E-10	1.46E-09	Ras/MAPK signalling
BRCA2	-0.825	0.0664	-0.955	-0.695	6.09E-32	1.54E-30	DNA damage repair
CCNB1	-0.848	0.076	-0.997	-0.699	1.43E-26	3.00E-25	Breast cancer subtyping, Cell Cycle
MYBL2	-0.904	0.0942	-1.09	-0.719	1.70E-20	2.72E-19	Breast cancer subtyping, Cell Cycle
PHGDH	-0.957	0.119	-1.19	-0.724	4.12E-15	5.40E-14	Breast cancer subtyping
LAG3	-0.983	0.136	-1.25	-0.716	1.35E-12	1.55E-11	Exhausted CD8 cells
MYC	-1.03	0.0951	-1.22	-0.846	2.44E-25	4.71E-24	Breast cancer subtyping, Cell Cycle
ORC6	-1.06	0.0868	-1.23	-0.895	2.65E-31	6.47E-30	Breast cancer subtyping, Cell Cycle
UBE2T	-1.09	0.0939	-1.27	-0.907	1.74E-28	3.88E-27	Breast cancer subtyping, Cell Cycle

GZMB	-1.1	0.179	-1.45	-0.753	1.25E-09	1.33E-08	Immune response, Cytotoxic cell signature
SFRP1	-1.14	0.154	-1.44	-0.839	4.18E-13	4.87E-12	Breast cancer subtyping, Cancer progression EMT, Signaling by WNT
PTTG1	-1.19	0.0818	-1.35	-1.03	1.12E-41	3.74E-40	Breast cancer subtyping, Cell Cycle
CDH3	-1.22	0.122	-1.46	-0.98	4.32E-22	7.38E-21	Breast cancer subtyping
ANLN	-1.25	0.0845	-1.42	-1.08	6.12E-43	2.25E-41	Breast cancer subtyping, DNA damage repair
UBE2C	-1.28	0.0899	-1.45	-1.1	4.47E-40	1.37E-38	Breast cancer subtyping
MKI67	-1.29	0.0808	-1.45	-1.14	5.28E-49	2.28E-47	Breast cancer subtyping, Tumor proliferation
CEP55	-1.3	0.0895	-1.47	-1.12	1.41E-41	4.51E-40	Breast cancer subtyping
CXCL10	-1.3	0.153	-1.6	-1	1.21E-16	1.78E-15	Immune response
BIRC5	-1.32	0.105	-1.52	-1.11	2.02E-32	5.30E-31	Breast cancer subtyping
BMP2	-1.33	0.165	-1.65	-1.01	3.19E-15	4.26E-14	Extracellular matrix organization
EXO1	-1.39	0.0821	-1.55	-1.23	2.27E-53	1.11E-51	Breast cancer subtyping, Cell Cycle
MELK	-1.39	0.0864	-1.56	-1.22	1.44E-49	6.62E-48	Breast cancer subtyping
ANGPT1	-1.39	0.176	-1.74	-1.04	1.34E-14	1.72E-13	Tumor angiogenesis
TYMS	-1.54	0.0892	-1.72	-1.37	1.88E-55	1.06E-53	Breast cancer subtyping, DNA damage repair
IDO1	-1.55	0.186	-1.91	-1.18	5.42E-16	7.80E-15	Immune response
KIF2C	-1.56	0.0811	-1.71	-1.4	1.59E-65	1.17E-63	Immune response, DNA damage repair
CDC20	-1.61	0.0912	-1.79	-1.44	1.37E-57	8.39E-56	Breast cancer subtyping
KRT5	-1.62	0.197	-2.01	-1.24	8.74E-16	1.19E-14	Breast cancer subtyping
CCNE1	-1.63	0.111	-1.84	-1.41	1.84E-42	6.43E-41	Breast cancer subtyping, Cell Cycle
KRT14	-1.63	0.336	-2.29	-0.976	1.45E-06	1.37E-05	Breast cancer subtyping
CENPF	-1.66	0.0841	-1.83	-1.5	1.01E-68	9.26E-67	Breast cancer subtyping
BCL2A1	-1.66	0.161	-1.98	-1.35	2.65E-23	4.74E-22	Transcription misregulation pathway
NDC80	-1.77	0.0833	-1.94	-1.61	6.96E-77	1.28E-74	Breast cancer subtyping
NUF2	-1.82	0.107	-2.03	-1.61	3.04E-54	1.59E-52	Breast cancer subtyping, Cell Cycle

KRT17	-2.07	0.192	-2.45	-1.7	4.05E-25	7.63E-24	Breast cancer subtyping
CCNA1	-2.16	0.18	-2.51	-1.81	2.98E-30	7.07E-29	Cell Cycle, DNA damage repair
MIA	-2.35	0.199	-2.74	-1.96	2.24E-29	5.13E-28	Breast cancer subtyping
FOXC1	-2.69	0.12	-2.93	-2.46	6.21E-83	4.56E-80	Breast cancer subtyping
CXCL5	-2.89	0.287	-3.45	-2.33	2.66E-22	4.66E-21	Immune response

Supplementary Table S5: Multivariate survival analysis and interaction tests for the four genes and metagenes included in the prespecified hypotheses testing their association with DFS.

Multivariate analysis for DFS endpoint for selected biologically important genes and metagenes					
Gene/ metagene	**$\mathrm{HR}_{\mathrm{capecitabine}}$ (95%CI), *P*-value**	**Adjusted BH (capecitabine)**	**$\mathrm{HR}_{\mathrm{observation}}$ (95%CI), *P*-value**	**Adjusted BH (observation)**	***P*-interaction**
Mast cells score	1.18 (0.98-1.42), 0.08	0.13	1.3 (1.09-1.55), 0.003	0.01	0.31
Endothelial score	1.39 (0.94-2.05), 0.10	0.36	1.25 (0.9-1.75), 0.18	0.26	0.57
PDL2 score	0.87 (0.65-1.17), 0.36	0.13	0.84 (0.65-1.09), 0.19	0.26	0.94
Cytotoxic cells score	0.84 (0.68-1.03), 0.09	0.13	0.93 (0.78-1.11), 0.45	0.45	0.48
Mast cells score in PAM50 Non-basal	0.99 (0.5-1.96), 0.98	---	2.68 (1-7.21), 0.01	---	0.09
Mast cells score in PAM50 basal	1.13 (0.93-1.37), 0.21	---	1.16 (0.96-1.4), 0.14	---	0.87

Abbreviations: DFS, distant free survival.

Supplementary Table S6: Multivariate survival analysis and interaction tests for the continuous expression of the 38 individual genes included in the prespecified hypotheses testing their association with DRFS.

Multivariate analysis for the primary endpoint DRFS for selected biologically important genes and metagenes					
Gene/ metagene	**$\mathrm{HR}_{\text{capecitabine}}$ (95%CI), *P*-value**	**Adjusted BH (capecitabine)**	**$\mathrm{HR}_{\text{observation}}$ (95%CI), *P*-value**	**Adjusted BH (observation)**	***P*-interaction**
IL24	1.29 (1-1.66), 0.06	0.58	1.2 (0.94-1.53), 0.16	0.65	0.39
IL22RA2	0.97 (0.81-1.16), 0.73	0.87	1.06 (0.89-1.24), 0.53	0.80	0.61
NRCAM	0.88 (0.73-1.07), 0.19	0.72	1 (0.83-1.2), 0.96	0.98	0.78
GRIA3	1.12 (0.93-1.34), 0.23	0.72	1.12 (0.93-1.35), 0.23	0.67	0.74
SOCS3	1.09 (0.83-1.43), 0.55	0.87	1.12 (0.86-1.47), 0.38	0.74	0.74
CXCL5	1.12 (1-1.25), 0.06	0.58	0.95 (0.84-1.07), 0.38	0.74	0.03
VIT	1.1 (0.87-1.4), 0.43	0.86	1.09 (0.9-1.3), 0.38	0.74	0.79
MME	1.08 (0.89-1.31), 0.45	0.86	1 (0.82-1.2), 0.96	0.98	0.37
PLCB1	1.08 (0.85-1.38). 0.51	0.87	1.12 (0.92-1.38), 0.25	0.68	0.88
SLC28A1	0.97 (0.75-1.25), 0.82	0.89	0.93 (0.74-1.17), 0.54	0.80	0.85
CTSW	1.04 (0.85-1.26), 0.71	0.88	0.91 (0.77-1.08), 0.28	0.71	0.53
CES1	0.95 (0.8-1.13), 0.55	0.88	1.15 (0.99-1.33), 0.07	0.63	0.06
BMP2	1.09 (0.89-1.33), 0.40	0.86	0.94 (0.78-1.14), 0.51	0.80	0.33
GZMH	0.93 (0.76-1.13), 0.45	0.86	0.83 (0.69-1), 0.04	0.56	0.68
TGFB2	1.02 (0.84-1.23), 0.87	0.90	1.13 (0.94-1.35), 0.19	0.65	0.50
HAS1	1.16 (0.95-1.42), 0.15	0.72	1.04 (0.87-1.25), 0.67	0.93	0.55
CCNA1	1.19 (0.98-1.44). 0.09	0.58	1 (0.83-1.21), 0.98	0.98	0.28
CXCL10	0.91 (0.78-1.07), 0.27	0.72	0.95 (0.83-1.08), 0.42	0.74	0.50
IL6	1.12 (0.92-1.35), 0.25	0.72	1.12 (0.93-1.36), 0.23	0.67	0.88
CCR5	0.84 (0.66-1.07), 0.17	0.72	0.92 (0.74-1.13), 0.41	0.74	0.34
CACNA2D3	0.94 (0.75-1.17), 0.59	0.87	1.02 (0.84-1.23), 0.87	0.98	0.76
JAK1	1.09 (0.59-2.02),	0.89	1.33 (0.77-2.29),	0.71	0.45

	0.79		0.30		
HOXA9	1.15 (0.88-1.5), 0.30	0.72	1.12 (0.89-1.42), 0.33	0.74	0.75
TWIST2	1.16 (0.91-1.48), 0.22	0.72	1.04 (0.85-1.26), 0.74	0.93	0.64
PDL2	0.94 (0.69-1.28), 0.69	0.88	0.82 (0.62-1.08), 0.16	0.65	0.80
BCL2A1	0.9 (0.74-1.1), 0.30	0.72	0.99 (0.85-1.16), 0.93	0.98	0.28
ANGPT1	1.26 (1.03-1.54), 0.03	0.50	1.11 (0.95-1.29), 0.18	0.65	0.20
LIFR	1.05 (0.82-1.35), 0.68	0.88	0.98 (0.8-1.19), 0.82	0.97	0.71
IDO1	0.97 (0.85-1.11), 0.65	0.88	0.88 (0.79-0.99), 0.04	0.56	0.55
PSMB9	0.99 (0.78-1.26), 0.93	0.93	0.96 (0.79-1.17), 0.69	0.93	0.90
LEP	1.21 (1.04-1.41), 0.01	0.50	1.02 (0.87-1.21), 0.77	0.95	0.20
STC1	0.95 (0.75-1.21), 0.70	0.88	1.31 (1.03-1.66), 0.03	0.56	0.12
VIM	0.96 (0.69-1.33), 0.81	0.89	1 (0.75-1.33), 0.98	0.98	0.88
KLRK1	0.84 (0.68-1.03), 0.09	0.58	0.88 (0.74-1.05), 0.17	0.65	0.42
PDL1	0.92 (0.74-1.16), 0.49	0.88	0.85 (0.7-1.04), 0.11	0.65	0.88
TYMP	1.03 (0.75-1.42), 0.86	0.90	0.96 (0.75-1.22), 0.73	0.93	0.88
STAT1	0.95 (0.72-1.25), 0.72	0.88	0.93 (0.75-1.15), 0.51	0.80	0.88
NKG7	0.89 (0.73-1.07), 0.21	0.72	0.88 (0.75-1.03), 0.11	0.65	0.85

Abbreviations: DRFS, distant recurrence free survival.

Supplementary Table S7: Multivariate survival analysis and interaction tests for the continuous expression of the 38 individual genes included in the prespecified hypotheses testing their association with OS.

Multivariate analysis for the primary endpoint OS for selected biologically important genes and metagenes					
Gene/ metagene	**HR$_{\text{capecitabine}}$ (95%CI), *P*-value**	**Adjusted BH (capecitabine)**	**HR$_{\text{observation}}$ (95%CI), *P*-value**	**Adjusted BH (observation)**	***P*-interaction**
IL24	1.29 (0.96-1.72), 0.10	0.34	1.07 (0.77-1.47), 0.70	0.89	0.10
IL22RA2	0.98 (0.8-1.21), 0.87	0.89	1.04 (0.84-1.28), 0.72	0.89	0.88
NRCAM	0.91 (0.74-1.13), 0.41	0.65	0.92 (0.72-1.18), 0.52	0.89	0.40
GRIA3	1.26 (1.02-1.56), 0.04	0.27	1.07 (0.85-1.35), 0.56	0.89	0.57
SOCS3	1.19 (0.86-1.65), 0.29	0.56	1.03 (0.75-1.42), 0.83	0.91	0.55
CXCL5	1.11 (0.97-1.27), 0.13	0.37	0.92 (0.78-1.08), 0.29	0.89	0.01
VIT	1.19 (0.89-1.59), 0.26	0.56	1.07 (0.84-1.36), 0.60	0.89	0.51
MME	1.09 (0.87-1.37), 0.46	0.67	0.95 (0.75-1.21), 0.67	0.89	0.13
PLCB1	1.24 (0.93-1.66), 0.15	0.37	1.14 (0.88-1.49), 0.31	0.89	0.44
SLC28A1	0.91 (0.68-1.21), 0.51	0.67	1.04 (0.77-1.4), 0.80	0.89	0.49
CTSW	0.94 (0.75-1.19), 0.63	0.77	0.89 (0.71-1.11), 0.29	0.89	0.88
CES1	1.08 (0.9-1.29), 0.43	0.65	1.06 (0.89-1.27), 0.49	0.89	0.61
BMP2	1.18 (0.95-1.47), 0.14	0.37	1.04 (0.83-1.3), 0.73	0.89	0.26
GZMH	0.88 (0.7-1.12), 0.29	0.56	0.8 (0.63-1.01), 0.06	0.77	0.80
TGFB2	1.03 (0.81-1.29), 0.83	0.89	1.18 (0.95-1.48), 0.14	0.77	0.50
HAS1	1.02 (0.81-1.3), 0.85	0.89	1.06 (0.84-1.34), 0.63	0.89	0.78
CCNA1	1.24 (0.99-1.55), 0.07	0.28	1.1 (0.86-1.39), 0.46	0.89	0.40
CXCL10	0.82 (0.68-0.99), 0.04	0.27	0.97 (0.82-1.14), 0.70	0.89	0.26
IL6	1.1 (0.88-1.37), 0.41	0.65	1.01 (0.8-1.28), 0.93	0.94	0.60
CCR5	0.74 (0.56-0.98) 0.03	0.27	0.96 (0.74-1.25), 0.78	0.89	0.09
CACNA2D3	1.02 (0.8-1.3), 0.85	0.89	0.96 (0.75-1.22), 0.72	0.89	0.55
JAK1	0.81 (0.39-1.65),	0.70	0.89 (0.47-1.7),	0.89	0.45

	0.56		0.73		
HOXA9	1.04 (0.75-1.45), 0.80	0.89	1.07 (0.8-1.43), 0.63	0.89	0.95
TWIST2	1.15 (0.86-1.53), 0.33	0.61	1.04 (0.81-1.35), 0.74	0.89	0.62
PDL2	0.71 (0.49-1.03), 0.07	0.28	0.85 (0.59-1.21), 0.37	0.89	0.54
BCL2A1	0.92 (0.72-1.16), 0.48	0.67	1.05 (0.86-1.28), 0.63	0.89	0.37
ANGPT1	1.25 (0.99-1.59), 0.07	0.28	1.26 (1.04-1.52), 0.02	0.77	0.30
LIFR	0.99 (0.74-1.32), 0.93	0.93	0.85 (0.65-1.11), 0.22	0.89	0.71
IDO1	0.89 (0.76-1.04), 0.16	0.38	0.87 (0.75-1.01), 0.08	0.77	0.83
PSMB9	0.81 (0.61-1.07), 0.14	0.37	0.96 (0.75-1.24), 0.77	0.89	0.53
LEP	1.3 (1.09-1.57), 0.006	0.23	1.01 (0.82-1.24), 0.94	0.94	0.23
STC1	0.88 (0.65-1.18), 0.37	0.65	1.05 (0.78-1.4), 0.74	0.89	0.87
VIM	0.87 (0.59-1.3), 0.50	0.67	0.93 (0.65-1.33), 0.69	0.89	0.96
KLRK1	0.75 (0.59-0.96), 0.02	0.27	0.83 (0.66-1.03), 0.09	0.77	0.27
PDL1	0.76 (0.58-0.99), 0.04	0.27	0.82 (0.64-1.05), 0.12	0.77	0.62
TYMP	0.95 (0.66-1.38), 0.80	0.89	0.96 (0.7-1.31), 0.79	0.89	0.81
STAT1	0.8 (0.59-1.1), 0.18	0.40	0.99 (0.75-1.3), 0.93	0.94	0.51
NKG7	0.82 (0.66-1.02), 0.07	0.28	0.85 (0.69-1.05), 0.13	0.77	0.76

Abbreviations: OS, overall survival.

Supplementary Table S8: Multivariate survival analysis and interaction tests for the continuous expression of the 38 individual genes included in the prespecified hypotheses testing their association with DFS.

Multivariate analysis for the primary endpoint DFS for selected biologically important genes and metagenes					
Gene/ metagene	**HR$_{\text{capecitabine}}$ (95%CI), *P*-value**	**Adjusted BH (capecitabine)**	**HR$_{\text{observation}}$ (95%CI), *P*-value**	**Adjusted BH (observation)**	***P*-interaction**
IL24	1.29 (1.01-1.63), 0.05	0.47	1.12 (0.89-1.41), 0.34	0.81	0.27
IL22RA2	0.96 (0.81-1.14), 0.66	0.78	1.07 (0.91-1.25), 0.41	0.82	0.49
NRCAM	0.87 (0.72-1.05), 0.14	0.47	1.02 (0.86-1.22), 0.79	0.88	0.47
GRIA3	1.1 (0.93-1.32), 0.28	0.63	1.07 (0.9-1.28), 0.43	0.82	0.90
SOCS3	1.05 (0.81-1.38), 0.70	0.78	1.08 (0.84-1.38), 0.57	0.85	0.76
CXCL5	1.1 (0.98-1.22), 0.11	0.47	0.96 (0.86-1.08), 0.50	0.85	0.09
VIT	1.1 (0.87-1.38), 0.45	0.76	1.04 (0.88-1.24), 0.63	0.8	0.70
MME	1.05 (0.87-1.26), 0.63	0.77	0.97 (0.81-1.16), 0.71	0.87	0.40
PLCB1	1.08 (0.86-1.35), 0.53	0.76	1.14 (0.94-1.38), 0.18	0.61	0.94
SLC28A1	0.93 (0.73-1.18), 0.54	0.76	0.95 (0.77-1.17), 0.62	0.85	0.82
CTSW	0.99 (0.82-1.19), 0.91	0.92	0.9 (0.77-1.06), 0.21	0.61	0.56
CES1	0.97 (0.82-1.14), 0.71	0.78	1.13 (0.98-1.3), 0.10	0.61	0.11
BMP2	1.12 (0.93-1.35), 0.25	0.63	0.95 (0.79-1.13), 0.54	0.85	0.28
GZMH	0.89 (0.73-1.07), 0.21	0.63	0.84 (0.71-0.99), 0.03	0.49	0.77
TGFB2	0.98 (0.82-1.18), 0.82	0.87	1.14 (0.96-1.35), 0.14	0.61	0.25
HAS1	1.16 (0.96-1.4), 0.13	0.47	1.1 (0.92-1.3), 0.30	0.81	0.79
CCNA1	1.18 (0.98-1.42), 0.09	0.47	0.95 (0.79-1.14), 0.59	0.85	0.15
CXCL10	0.89 (0.76-1.04), 0.13	0.47	0.97 (0.86-1.1), 0.64	0.85	0.33
IL6	1.08 (0.9-1.3), 0.40	0.75	1.09 (0.92-1.3), 0.32	0.81	0.83
CCR5	0.8 (0.63-1), 0.05	0.47	0.92 (0.76-1.12), 0.42	0.82	0.26
CACNA2D3	0.93 (0.76-1.15), 0.51	0.76	1 (0.84-1.2), 0.98	0.98	0.69
JAK1	0.97 (0.54-1.74),	0.92	1.4 (0.84-2.34),	0.61	0.23

	0.92		0.19		
HOXA9	1.1 (0.85-1.43), 0.45	0.76	1.06 (0.85-1.32), 0.63	0.85	0.65
TWIST2	1.1 (0.87-1.39), 0.42	0.76	1 (0.83-1.21), 0.97	0.98	0.77
PDL2	0.87 (0.65-1.17), 0.36	0.73	0.84 (0.65-1.09), 0.19	0.61	0.94
BCL2A1	0.9 (0.75-1.09), 0.27	0.63	0.98 (0.85-1.13), 0.79	0.88	0.37
ANGPT1	1.23 (1.02-1.48), 0.04	0.47	1.11 (0.97-1.28), 0.15	0.61	0.28
LIFR	1.14 (0.9-1.45), 0.27	0.63	0.96 (0.8-1.16), 0.70	0.87	0.36
IDO1	0.94 (0.83-1.07), 0.36	0.73	0.89 (0.8-0.99), 0.04	0.49	0.66
PSMB9	0.93 (0.74-1.17), 0.53	0.76	0.94 (0.78-1.14), 0.54	0.85	0.86
LEP	1.21 (1.05-1.4), 0.01	0.42	0.99 (0.84-1.15), 0.86	0.94	0.09
STC1	0.94 (0.75-1.18), 0.58	0.77	1.28 (1.02-1.61), 0.03	0.49	0.13
VIM	0.92 (0.67-1.26), 0.61	0.77	1.02 (0.78-1.33), 0.90	0.95	0.70
KLRK1	0.83 (0.69-1.01), 0.06	0.47	0.88 (0.75-1.03), 0.12	0.61	0.54
PDL1	0.89 (0.72-1.1), 0.28	0.63	0.84 (0.7-1.01), 0.07	0.61	0.83
TYMP	0.95 (0.7-1.28), 0.72	0.78	0.97 (0.77-1.22), 0.78	0.88	0.65
STAT1	0.93 (0.71-1.2), 0.57	0.77	0.92 (0.75-1.13), 0.43	0.82	0.98
NKG7	0.86 (0.72-1.02), 0.09	0.47	0.88 (0.76-1.03), 0.11	0.61	0.78

Abbreviations: DFS, distant free survival.

Supplementary Table S9: Multivariate survival analysis and interaction tests restricted to the PAM50 non-basal subgroup. Selected genes tested in an exploratory analysis where their high expression was found to be significantly associated with a higher survival on the capecitabine arm over observation are presented. Expression status was derived from the median gene expression scores. Hazard ratios, 95% confidence intervals and *P*-values are derived from Cox regression analyses adjusted for age, menopausal status, histological grade, tumor size, stage, breast surgery, region, nodal status, chemotherapy regimen and phenotype by IHC.

Gene	**Subgroup**	**$HR_{capecitabine}$ (95%CI), *P*-value**	***P*-interaction**
Multivariate analysis for DRFS (PAM50 non-basal subgroup)			
STC1	High	0.51 (0.33-0.8), 0.003	0.01
	Low	1.24 (0.74-2.09), 0.41	
CES1	High	0.56 (0.35-0.89), 0.01	0.12
	Low	1 (0.61-1.62), 0.99	
JAK1	High	0.57 (0.35-0.92), 0.02	0.28
	Low	0.96 (0.6-1.53), 0.85	
CCR5	High	0.61 (0.37-0.99), 0.04	0.39
	Low	0.89 (0.57-1.41), 0.63	
SOCS3	High	0.6 (0.37-0.97), 0.04	0.58
	Low	0.79 (0.49-1.26), 0.32	
Multivariate analysis for DFS (PAM50 non-basal subgroup)			
STC1	High	0.54 (0.35-0.82), 0.004	0.02
	Low	1.19 (0.74-1.93), 0.47	
CES1	High	0.59 (0.38-0.93), 0.02	0.17
	Low	0.96 (0.61-1.51), 0.85	
JAK1	High	0.57 (0.36-0.91), 0.02	0.28
	Low	0.93 (0.6-1.45), 0.75	
CCR5	High	0.58 (0.36-0.93), 0.02	0.27
	Low	0.93 (0.6-1.42), 0.73	
SOCS3	High	0.6 (0.37-0.96), 0.03	0.62
	Low	0.79 (0.51-1.22), 0.28	
Multivariate analysis for OS (PAM50 non-basal subgroup)			
CCR5	High	0.49 (0.26-0.89), 0.02	0.05
	Low	1.29 (0.75-2.23), 0.36	
PDL2	High	0.53 (0.29-0.98), 0.04	0.07
	Low	1.27 (0.74-2.18), 0.39	

Supplementary Table S10: Exploratory analysis for the prognostic capacity of the continuous expression of genes and metagenes restricted to the PAM50 non-basal subgroup. Selected genes and metagenes tested in the exploratory prognostic analysis that were significantly associated with survival are displayed.

Endpoint	Gene/ Metagene	Variable type	Univariate HR (95%CI) PAM50 Non-basal	Univariate *P*-value PAM50 Non-basal	Multivariate HR (95%CI) PAM50 Non-basal	Multivariate *P*-value PAM50 Non-basal
DRFS	Mast cells	Continuous	1.62 (1.09-2.4)	0.01	1.56 (0.96-2.54)	0.05
OS	Mast cells	Continuous	1.87 (1.16-3.01)	0.005	1.78 (0.99-3.18)	0.03
DRFS	Endothelial	Continuous	1.73 (1.03-2.92)	0.05	2.15 (1.06-4.36)	0.04
OS	Endothelial	Continuous	1.73 (0.94-3.2)	0.09	2.52 (1.09-5.86)	0.03
DRFS	*KLRK1*	Continuous	1.01 (0.73-1.4)	0.96	0.6 (0.36-0.98)	0.04
DRFS	*ANGPT1*	Continuous	1.53 (0.97-2.43)	0.07	1.88 (1.03-3.44)	0.04