

Supplementary Figure S1: Consort diagram of the study





Pre - bevacizumab





Supplementary Figure S2: Clinical response two weeks after one cycle of bevacizumab. (a) Marked reduction in erythema two weeks after bevacizumab.
(b) Line plot showing patient-by-patient change in maximum dimension after bevacizumab. P-value, Wilcoxon paired samples test.



Distribution of Changes in Minkowski-Bouligand Dimension after Bevacizumab

Change in Minkowski-Bouligand Dimension after Bevacizumab (Post-Pre)

Supplementary Figure S3: Distribution of changes in fractal dimension two weeks after bevacizumab. The Minkowski–Bouligand (M-B) dimension was used as an indication of the fractal dimension of the Ktrans 3D volume. For each tumour, the M-B dimension is shown. To calculate this the full 3D voxel parametric map was considered as inferred from the DCE-MRI compartmental model analysis (See Methods). A general downregulation of fractal dimension can be observed (Wilcoxon Signed Rank Sum test, P=0.012).



Supplementary Figure S4: Significantly down-regulated genes two weeks after bevacizumab as validated by qRT-PCR. Plots showing patient-by-patient changes in the relative expression for (a) ESM-1 (b) CCNE1 (c) FLT-1 and (d) DLL4 (P-value, Mann-Whitney test).



Supplementary Figure S5: Significantly greater down-regulation of ESM1 in grade 3 patients in comparison to grade 2 patients. Error bars showing median± Interquartile range; P-value: Mann-Whitney test



Supplementary Figure S6: Significant down-regulation of Proliferation and Angiogenesis in response to bevacizumab. (a) Plot showing patient-by-patient change in Ki-67 percentage (b) Plot showing patient-by-patient change in vascular area percentage of PLVAP in response to bevacizumab assessed after 2 weeks of therapy. Patients arranged by ascending order of fold change (P-value, Wilcoxon-signed rank test).



Supplementary Figure S7: Significantly up regulated genes two weeks after bevacizumab as assessed by qRT-PCR. Plots showing patient-by-patient changes in the relative expression for (a) VEGFA (b) PDK1 and (c) PDE3B, (P-value, Mann-Whitney test).



Supplementary Figure S8: Box plot showing global changes in gene signatures post-bevacizumab. (a) Bars depicting median±interquartile range of fold changes for each signature. Signature summary scores are calculated as the median expression of all genes in the signature. Fold changes are calculated as ratio of expression post/pre-bevacizumab. X-axis showing folds changes after bevacizumab. (b) Heatmap of fold change after bevacizumab for all genes in the anti-VEGF signature. X-axis: patients. Y-axis: genes.



Supplementary Figure S9: Proliferation signature fold change vs. grade. Plot showing significant down-regulation of proliferation in grade 3 (n=21) in comparison to grade 2 (n=15) after single cycle of bevacizumab. Error bars represent mean±SD; P-value, Mann-Whitney test.





Supplementary Figure S10: Up-regulation of genes in key cancer pathways after bevacizumab suggesting possible mechanism of resistance. Heatmap showing patient (X-axis) changes in significantly up-regulated genes (Y-axis) in hypoxia and metabolism (red), immune response (bright green), signalling (dark green), cytokines (yellow) and angiogenesis (blue) pathways. These genes were significantly upregulated (FDR<0.05) after bevacizumab when the whole population as considered, however there is a clear heterogeneity in the changes. Patients are visually ordered by increased median expression of these genes.



Supplementary Figure S11: Up-regulation of hypoxia markers CA-9 and HIF1a in response to bevacizumab. (a) Plot showing patient-by-patient change in CA-9 percentage (b) Plot showing patient-by-patient change in HIF-1α percentage in response to bevacizumab assessed after 2 weeks of therapy. Patients arranged by descending order of fold change (P-value, Wilcoxon-signed rank test).

gene expression signatures (red/blue:>15% up/down-regulation), Kegg pathway changes (red/blue: up/downregulated after bevacizumab as called by Minepath with p<0.05). See methods for further details.

Initial Clinical Classification	Her2 status	Estrogen Receptor status	Progesteron status	Tumour Stage	Tumour Grade

В	MRI Ktrans response	>30% Reduction	or <30% Reduction
Chan	nges in Cancer Gene Expression Signatures		
Proli	iferation		
	Proliferation_BreastCancer		
Hypo	oxia		
	Hypoxia 99metagene		
	Hypoxia_CancerCommon		
	Hypoxia BreastCancer		
Angi	iogenesis		
	GeneNT_antiVEGFA		

KEGG pathways (Top differentially regulated) Angiogenesis_CancerCommon

Sub-path	ATM ATM	RASSED STKD	INPPSD - NAPPAA	MAU'SKOP MAUNUM	GAD1 GGT6	PTEN - INPPOD - INPPARA - ISYNAT	PROCE PRINCIPAL	FAS FADO	NOON SYNCH STOCK	4.10 A.108A.0	a series of		PGM2L1 PGM1	OITA BF/5	MTHPD4 FTCD	FES PLANAT RIGH	PTH1R GRUAS	F2 - F15 - F2 - FGA	ZBTB17 CDH028	F9 F10	TEM -CHANCE PRIVACE Nev	1V61d - 2d - 055 - 6d	THF NGH	turner taury - taury		NA - DEE - DEE - DEE - DEE - DEE - DEE	The set of	tons - then - time - time - their - true - true	GALE GALT	131740 4740
vay ID	5206	0651	1562	1010	0430	1562	1562	5010	5131	5321		1360	0500	1612/hsa05152	0670	1360	1961	1610	1110	1610	1920	1610	1150		1620	0830	0830	3830	0052	1520
Pathv	18 hsa05	16 hsa04	14 hsa00	14 hsa04	12 hsa00	11 hsa00	11 hsa00	11 hsa05	11 hsa05	11 hsa05		os nsauk	59 hsa00	9 hsa04	6 hsa00	12 hsa04	2 hsa04	52 hsa04	6 hsa04	6 hsa04	6 hsa04	6 hsa04	52 hsa04		0 hsaU4	19 hsa00	19 hsa00	19 hsa00	15 hsa00	15 hsa00
Ranking	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4		0.0	0.5	0.5	0.5	0.5	0.5	-0.6	-0.5	-0.5	-0.5	-0.5	-0.5		2.0-	-0.4	-0.4	-0.4	-0.4	-0.4
	Deregulated								Bownregulated						a	sı	əpı pəş	lod ejn	səy Bə.	-uc Id N		Non-Responders Downregulated								

Antigen processing and presentation Taurine and hypotaurine metabolism Inflammatory bowel disease (IBD) Starch and sucrose metabolism Inositol phosphate metabolism Inositol phosphate metabolism Inositol phosphate metabolism One carbon pool by folate MAPK signaling pathway Hippo signaling pathway MicroRNAs in cancer Alzheimer's disease Pathway name Axon guidance Axon guidance Shigellosis

Endocrine and other factor-regulated calcium reabsorption Complement and coagulation cascades Cell cycle

Toll-like receptor signaling Galactose metabolism Galactose metabolism Retinol metabolism Retinol metabolism Retinol metabolism mTOR signaling

Complement and coagulation cascades Complement and coagulation cascades

Adipocytokine signaling pathway



Figure S13: Association of baseline MRI parameters with fold changes in genes after bevacizumab. (a,b) Significant negative correlation between baseline total K^{trans} and tumour volume with the fold change in FLT1 after bevacizumab; (c) Significant positive correlation between baseline total K^{trans} and CA-9 fold change after bevacizumab; (d) significant positive correlation between baseline total K^{trans} and K^{trans} and K^{trans} and K^{trans} and CA-9 fold change after bevacizumab; (d) significant positive correlation between baseline total K^{trans} and fold change in VEGFA after bevacizumab



Supplementary Figure S14: Significant positive correlation between CA-9 fold change with VEGFA fold change after bevacizumab.