

Supplementary Figure S1: Consort diagram of the study

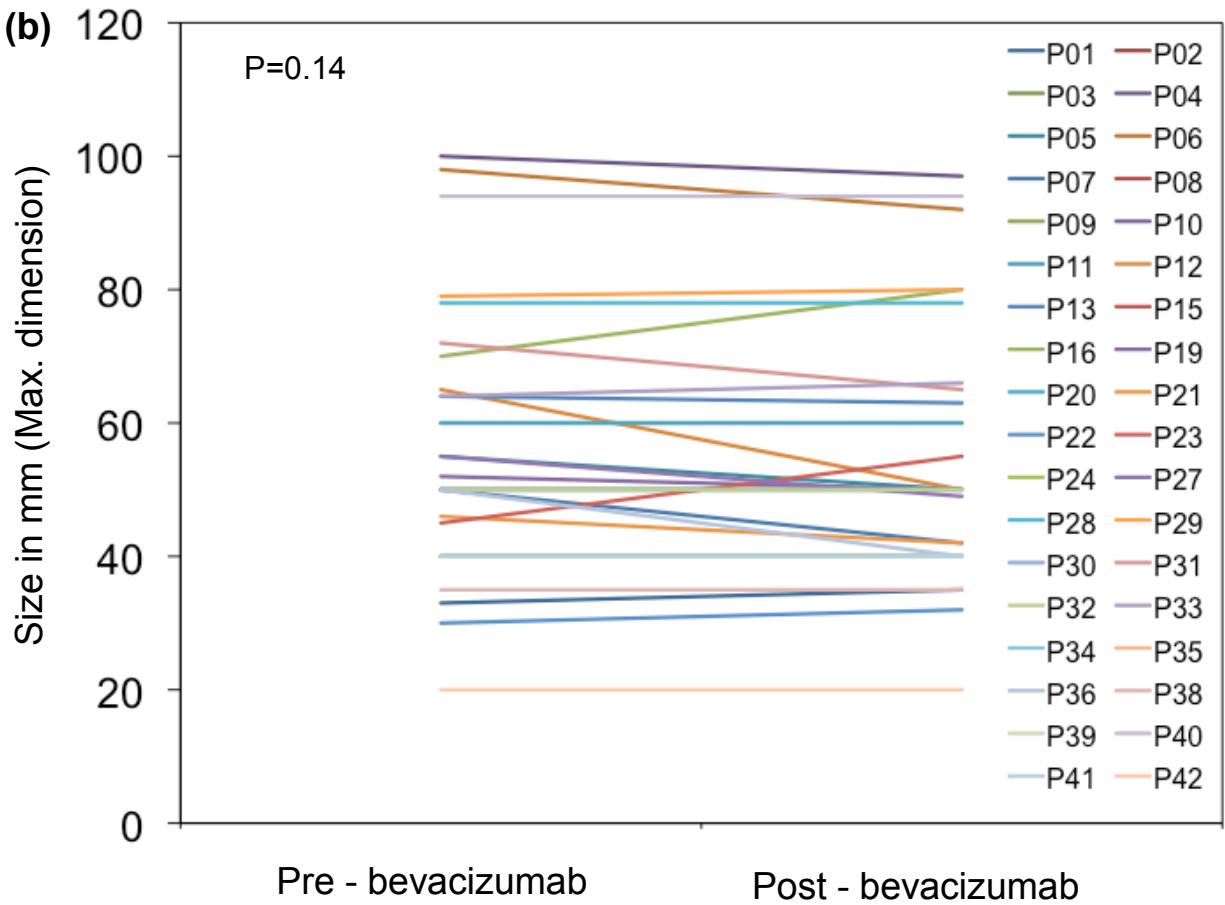
(a)



Pre - bevacizumab

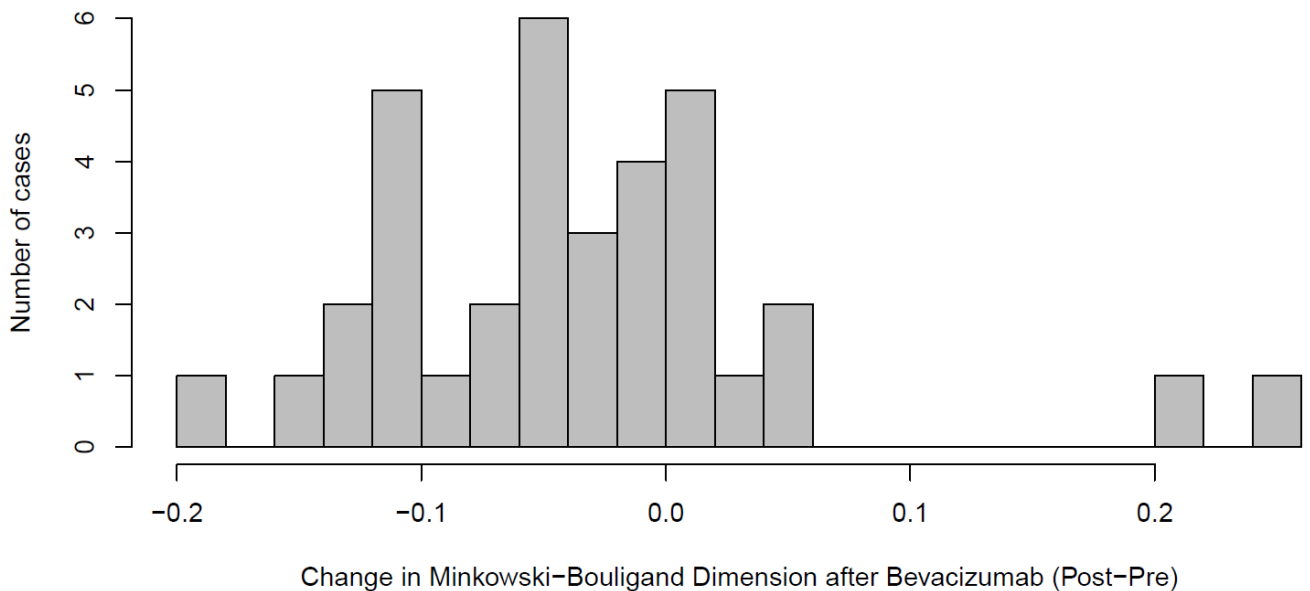


Post - bevacizumab

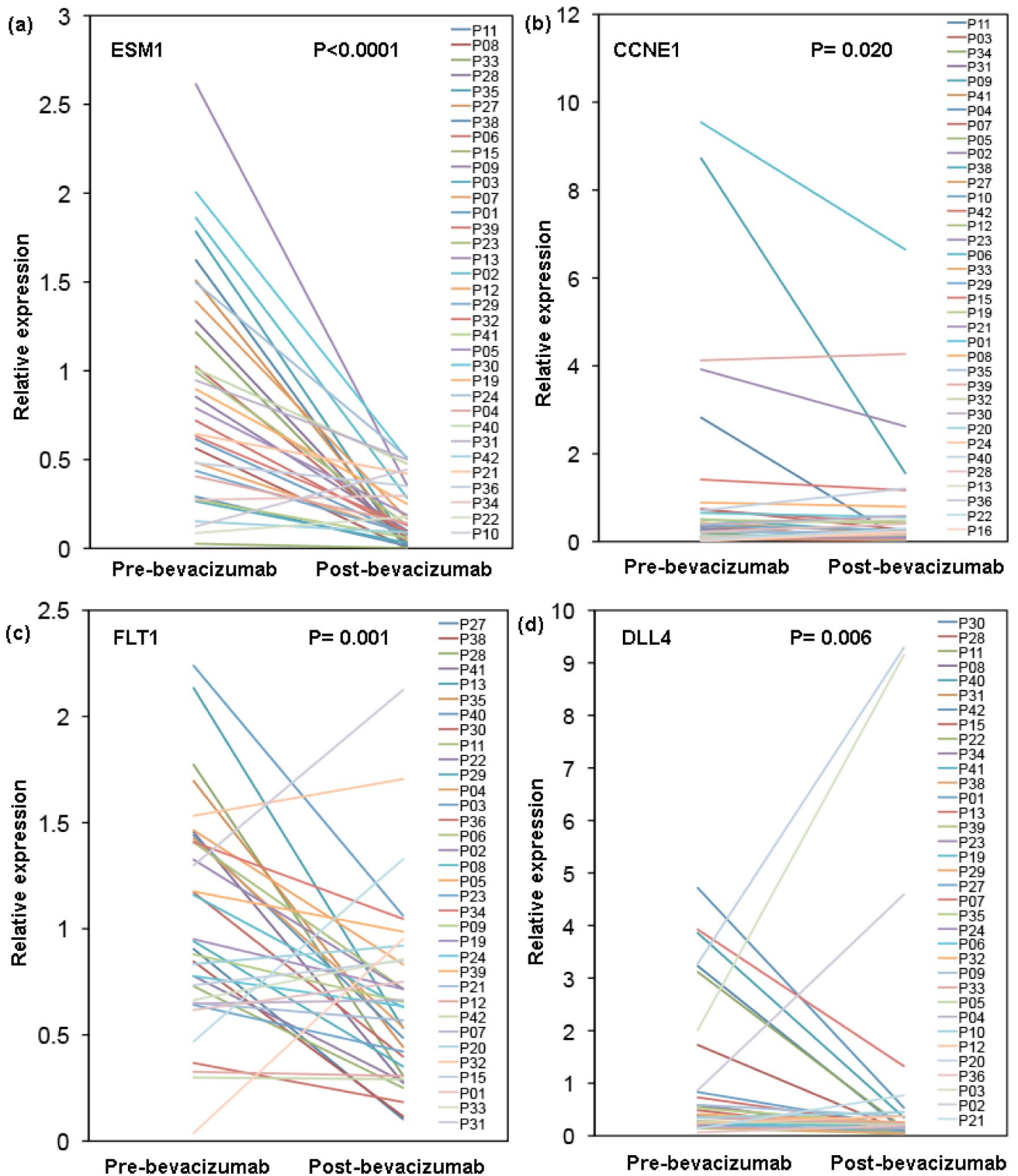


Supplementary Figure S2: Clinical response two weeks after one cycle of bevacizumab. (a) Marked reduction in erythema two weeks after bevacizumab. (b) Line plot showing patient-by-patient change in maximum dimension after bevacizumab. P-value, Wilcoxon paired samples test.

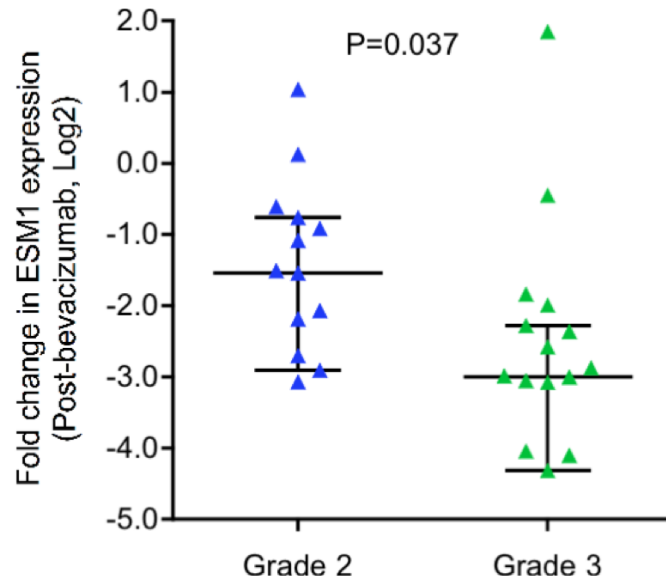
Distribution of Changes in Minkowski–Bouligand Dimension after Bevacizumab



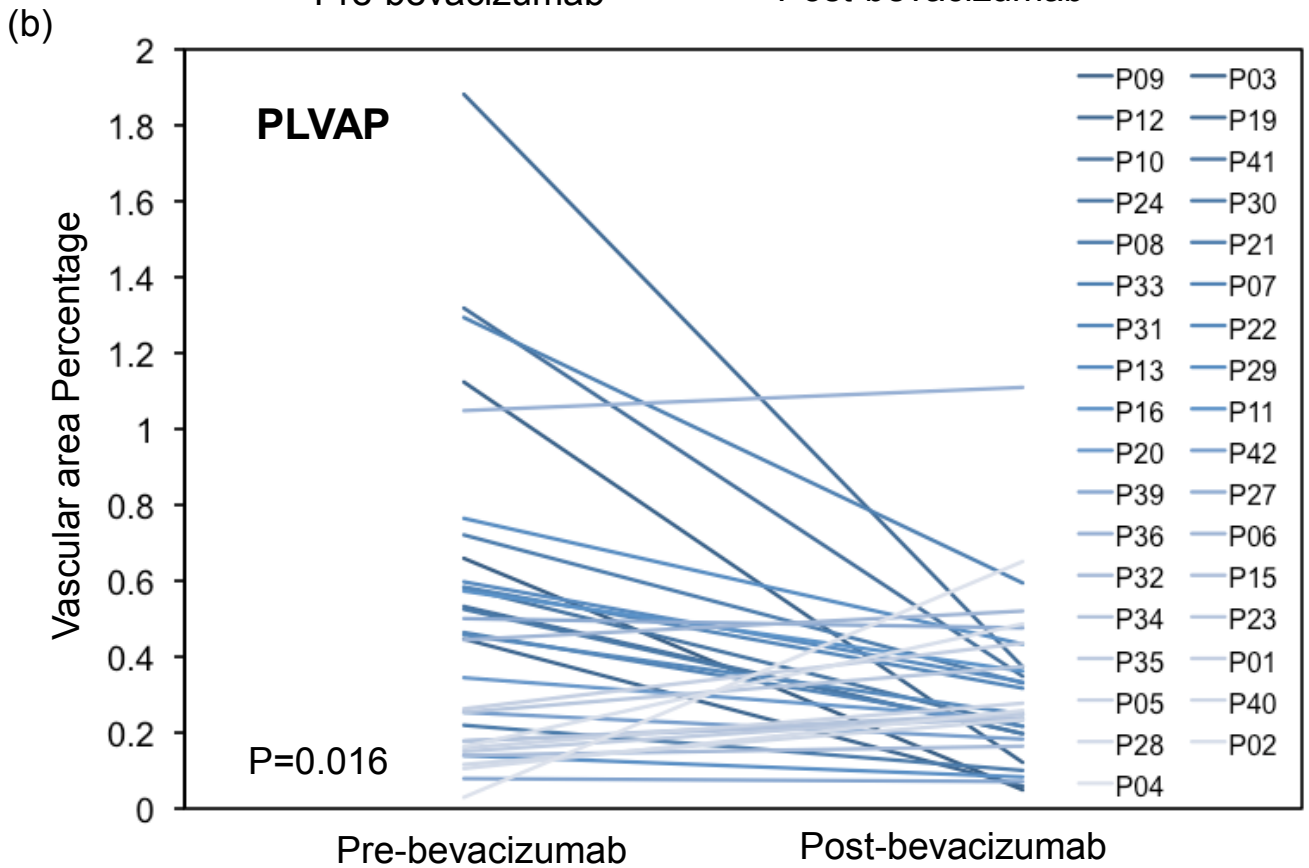
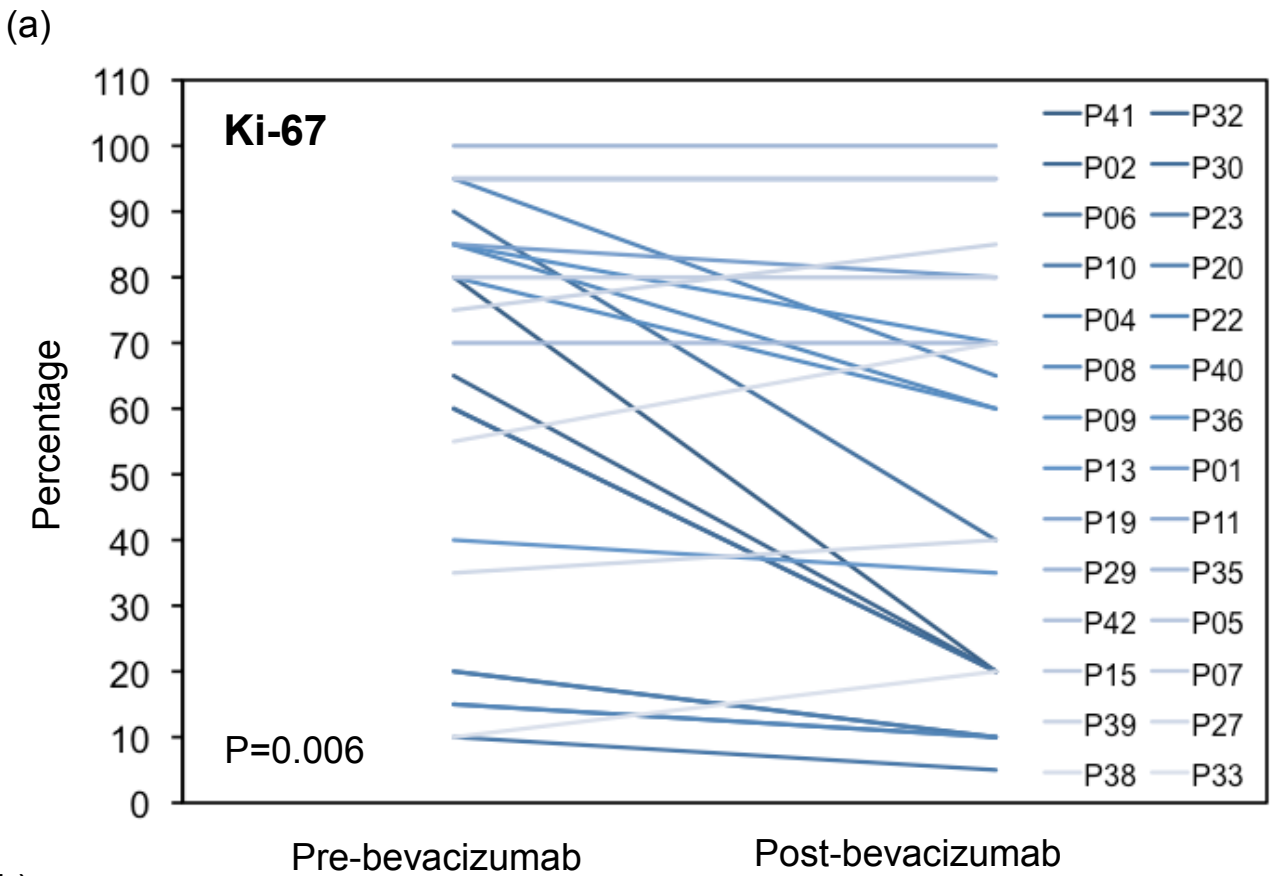
Supplementary Figure S3: Distribution of changes in fractal dimension two weeks after bevacizumab. The Minkowski–Bouligand (M-B) dimension was used as an indication of the fractal dimension of the Ktrans 3D volume. For each tumour, the M-B dimension is shown. To calculate this the full 3D voxel parametric 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, $P=0.012$).



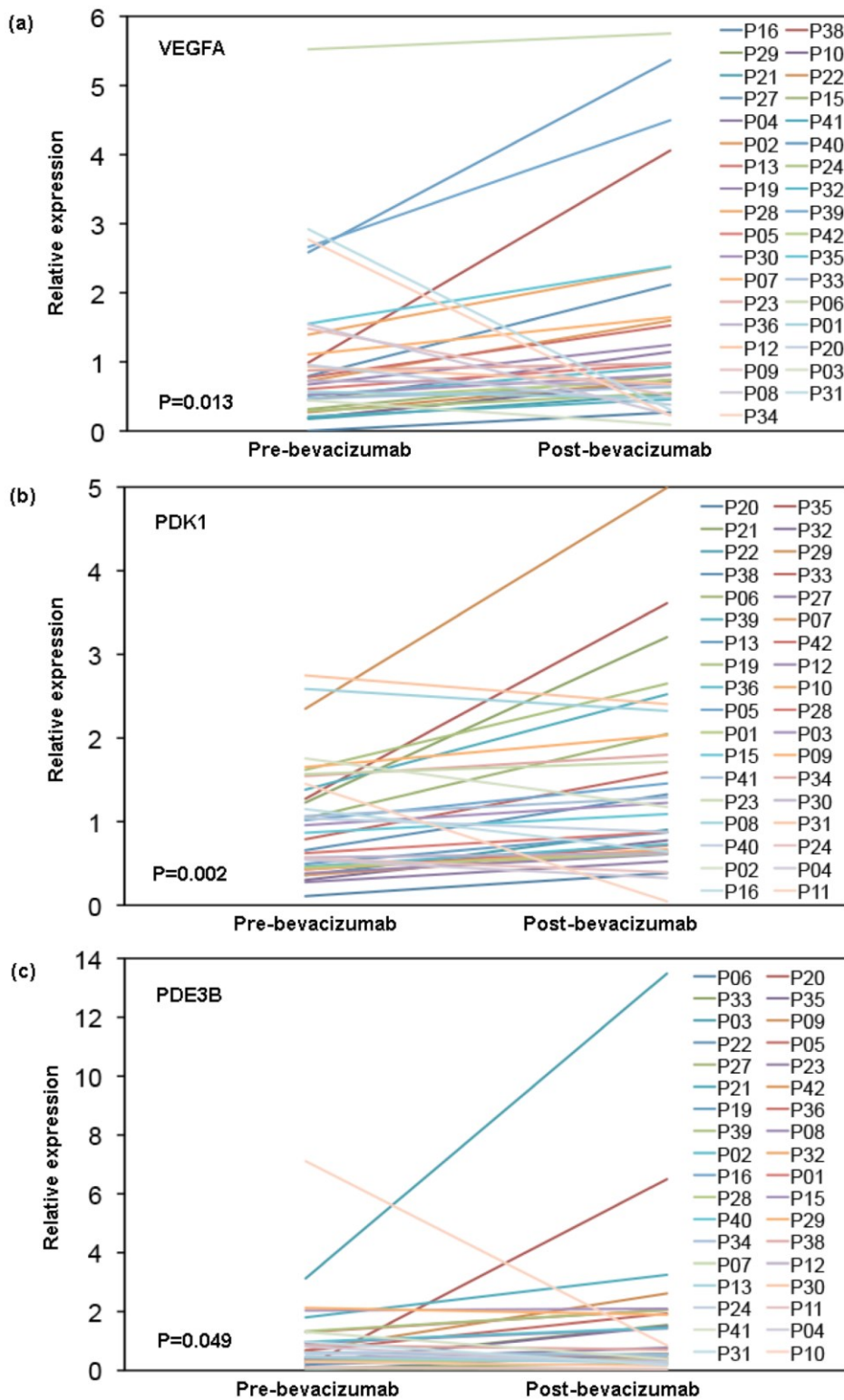
Supplementary Figure S4: Significantly down-regulated genes two weeks after bevacizumab as validated by qRT-PCR. Plots showing patient-by-patient changes in the relative expression for (a) ESM-1 (b) CCNE1 (c) FLT-1 and (d) DLL4 (P-value, Mann-Whitney test).



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

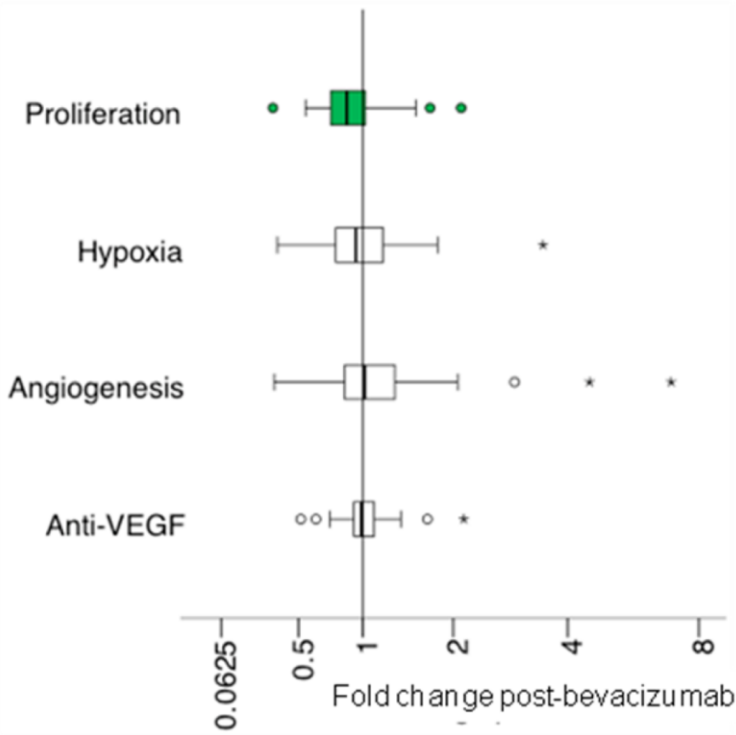


Supplementary Figure S6: Significant down-regulation of Proliferation and Angiogenesis in response to bevacizumab. (a) Plot showing patient-by-patient change in Ki-67 percentage (b) Plot showing patient-by-patient change in vascular area percentage of PLVAP in response to bevacizumab assessed after 2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

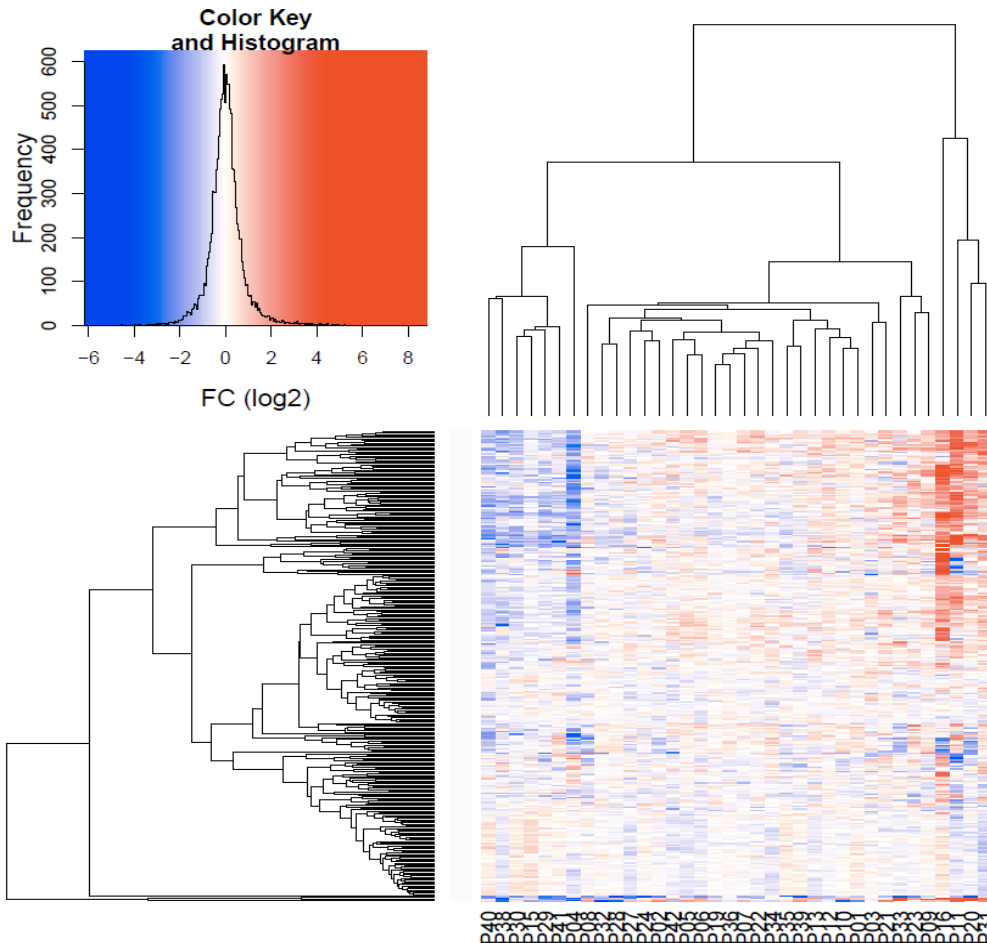


Supplementary Figure S7: Significantly up regulated genes two weeks after bevacizumab as assessed by qRT-PCR. Plots showing patient-by-patient changes in the relative expression for (a) VEGFA (b) PDK1 and (c) PDE3B, (P-value, Mann-Whitney test).

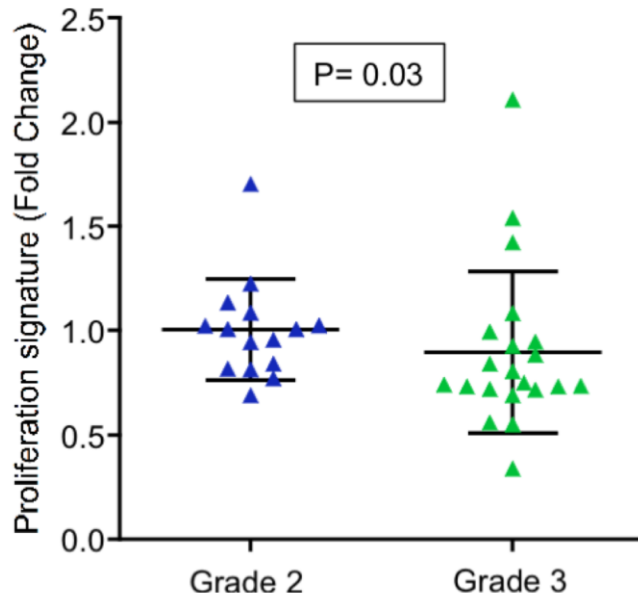
(a)



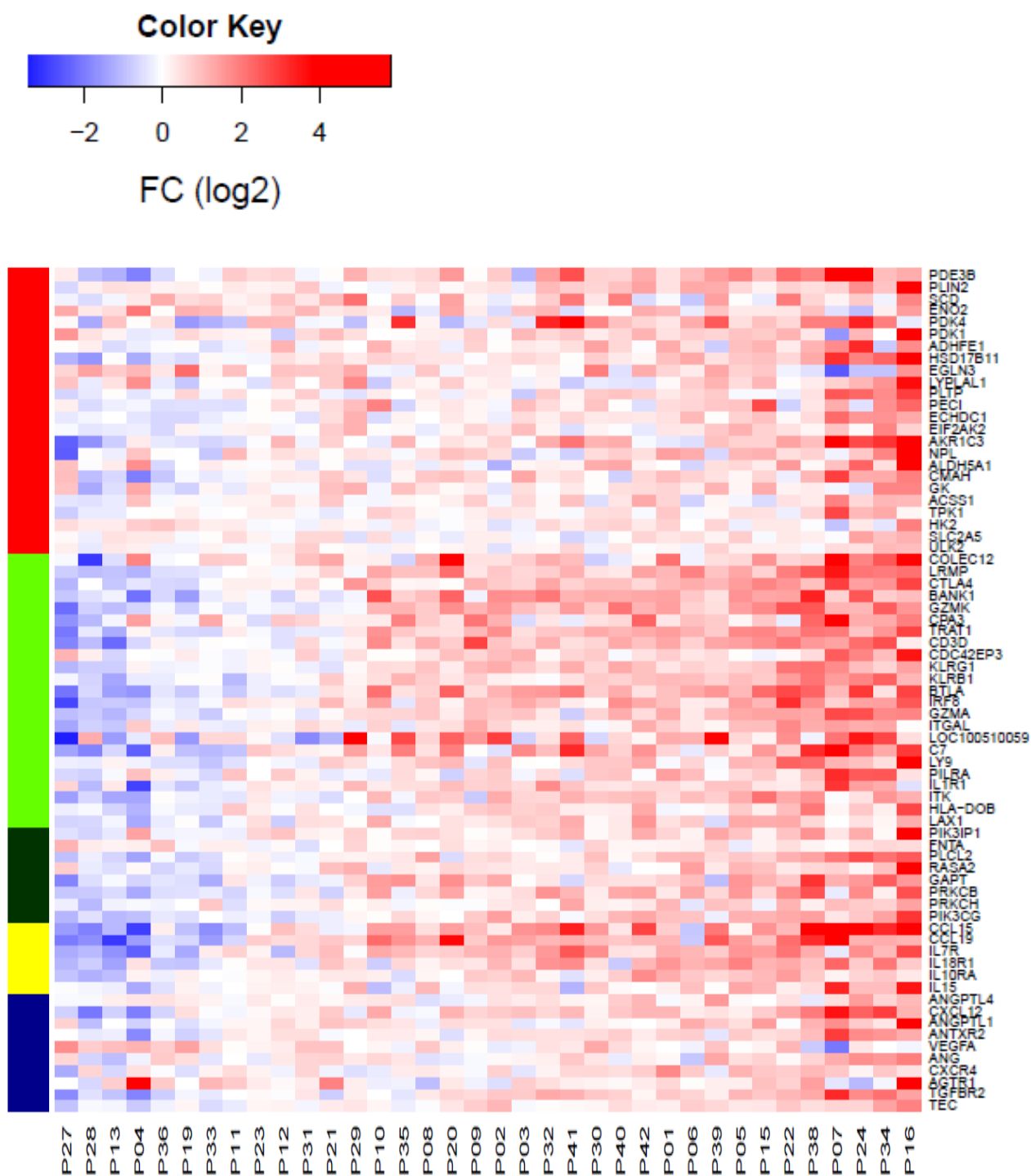
(b)



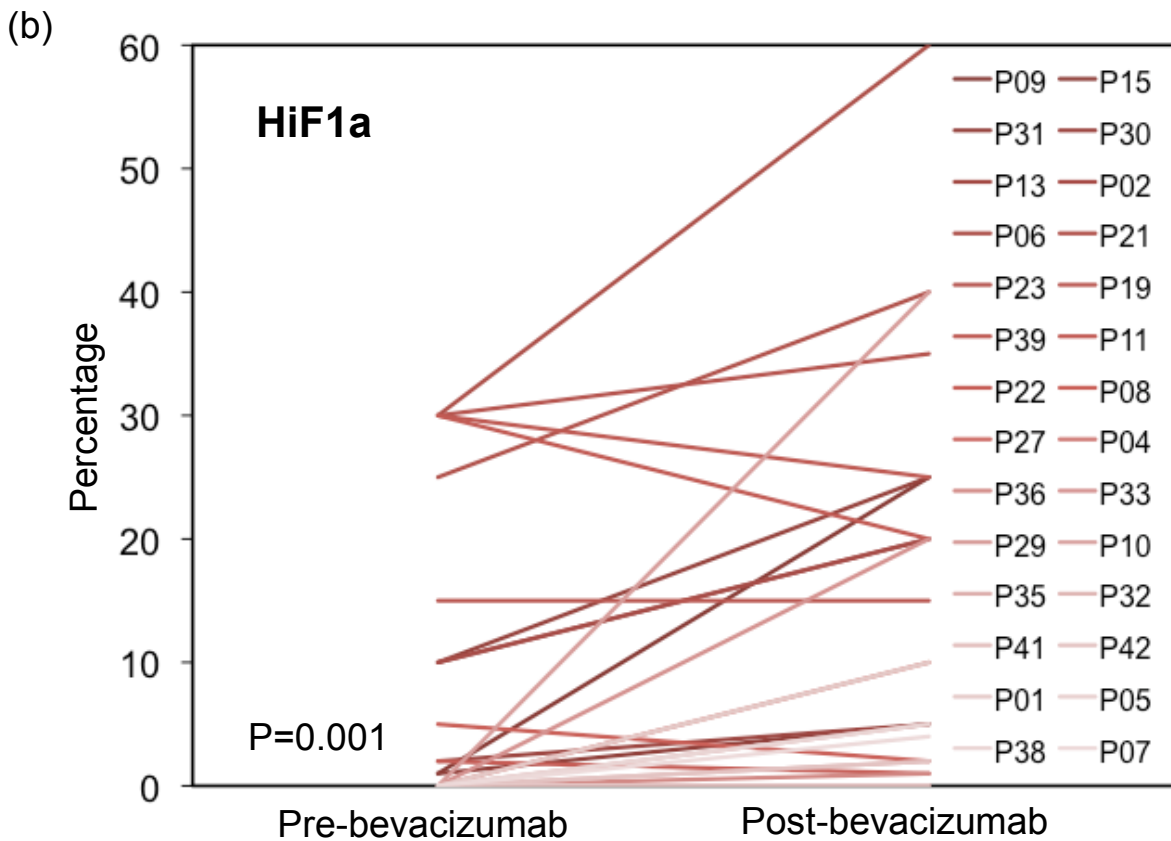
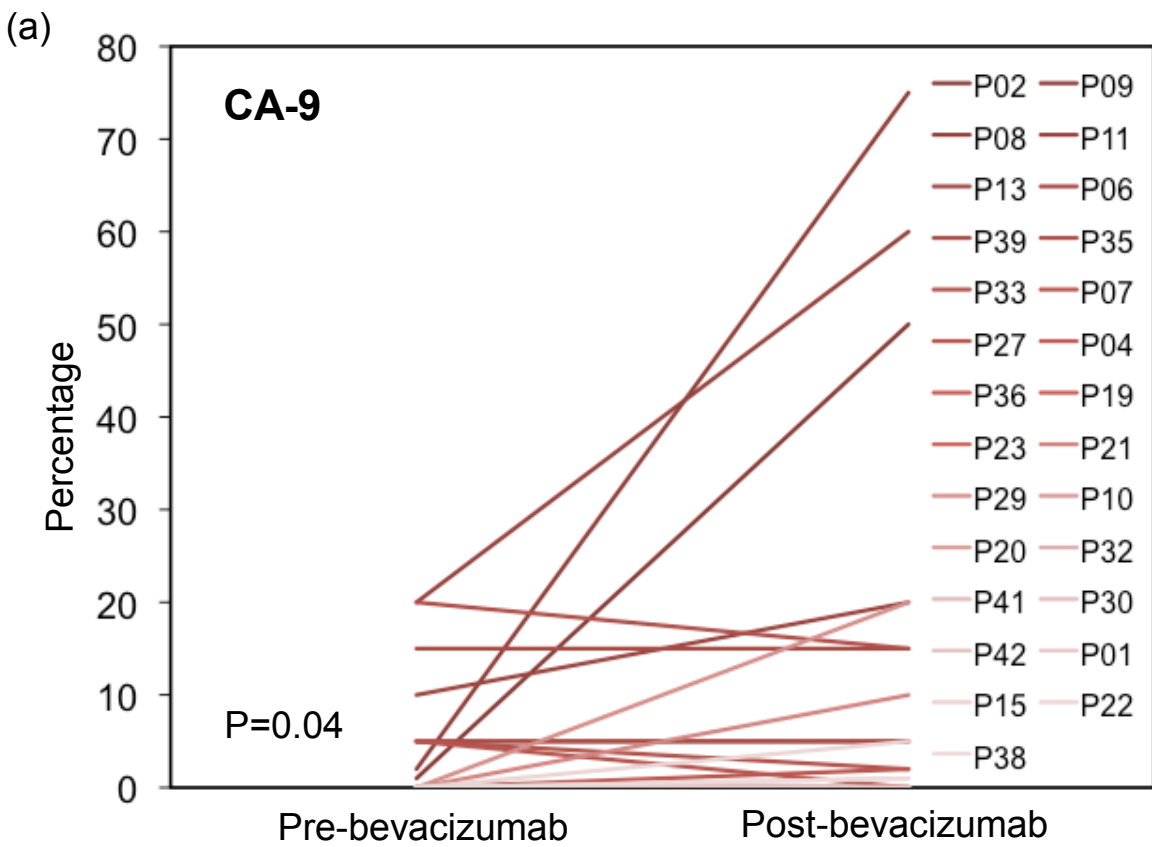
Supplementary Figure S8: Box plot showing global changes in gene signatures post-bevacizumab. (a) Bars depicting median \pm interquartile range of fold changes for each signature. Signature summary scores are calculated as the median expression of all genes in the signature. Fold changes are calculated 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-1 α 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).

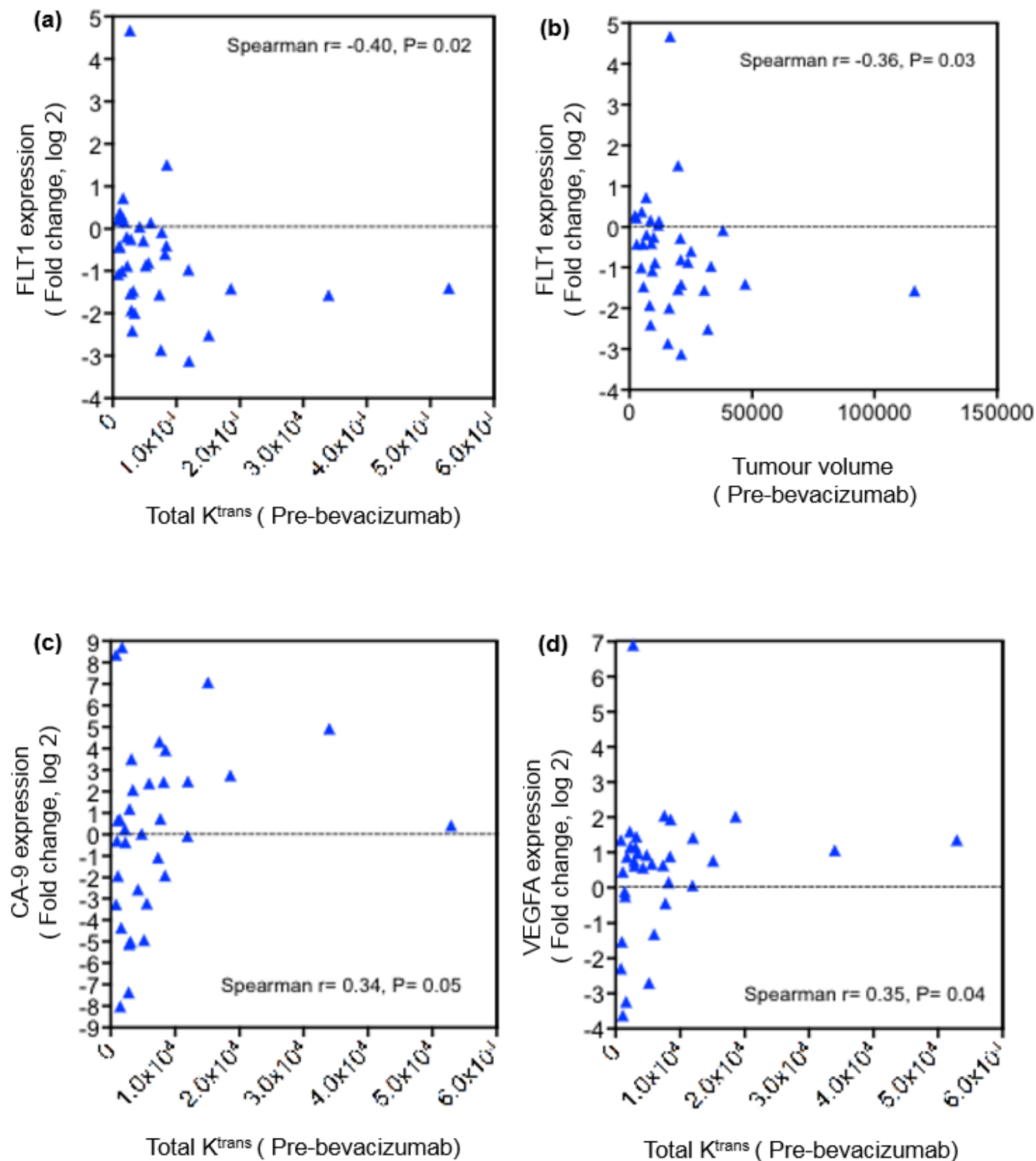
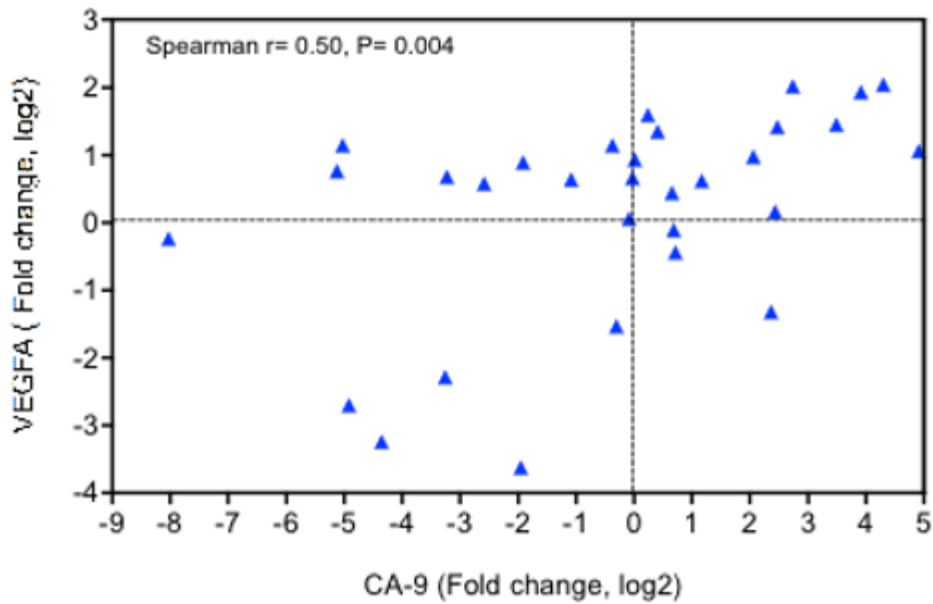


Figure S13: Association of baseline MRI parameters with fold changes in genes after bevacizumab. (a,b) Significant negative correlation between baseline total K^{trans} and tumour volume with the fold change in FLT1 after bevacizumab; (c) Significant positive correlation between baseline total K^{trans}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



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