SUPPLEMENTAL DATA

Title: Transcriptomic analysis identifies a potential target for bevacizumab resistant glioblastoma

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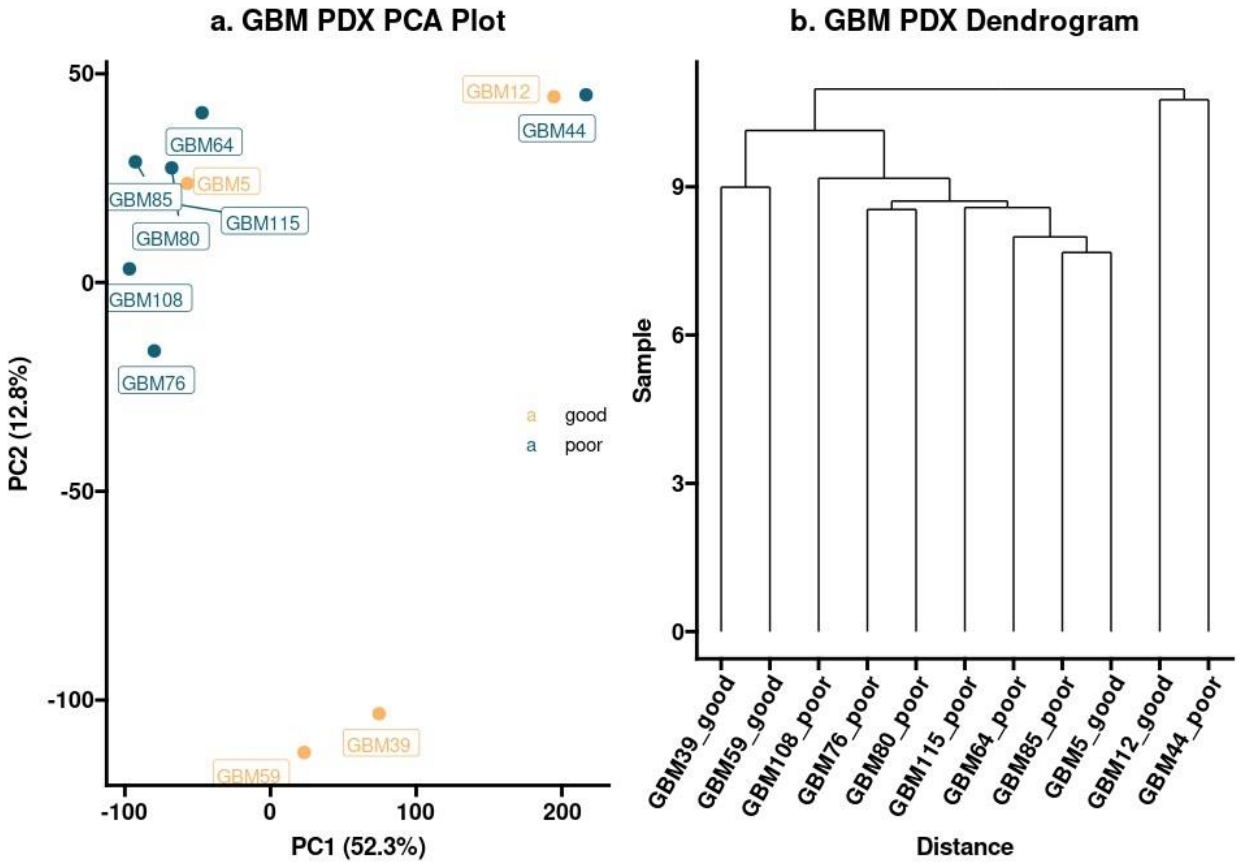
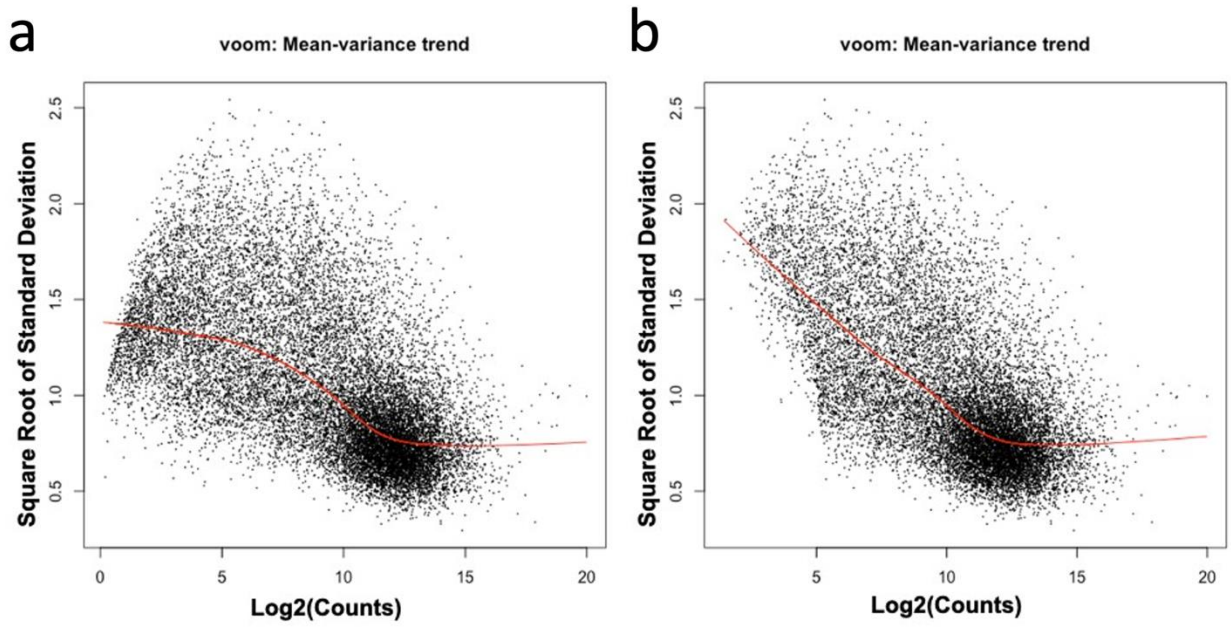
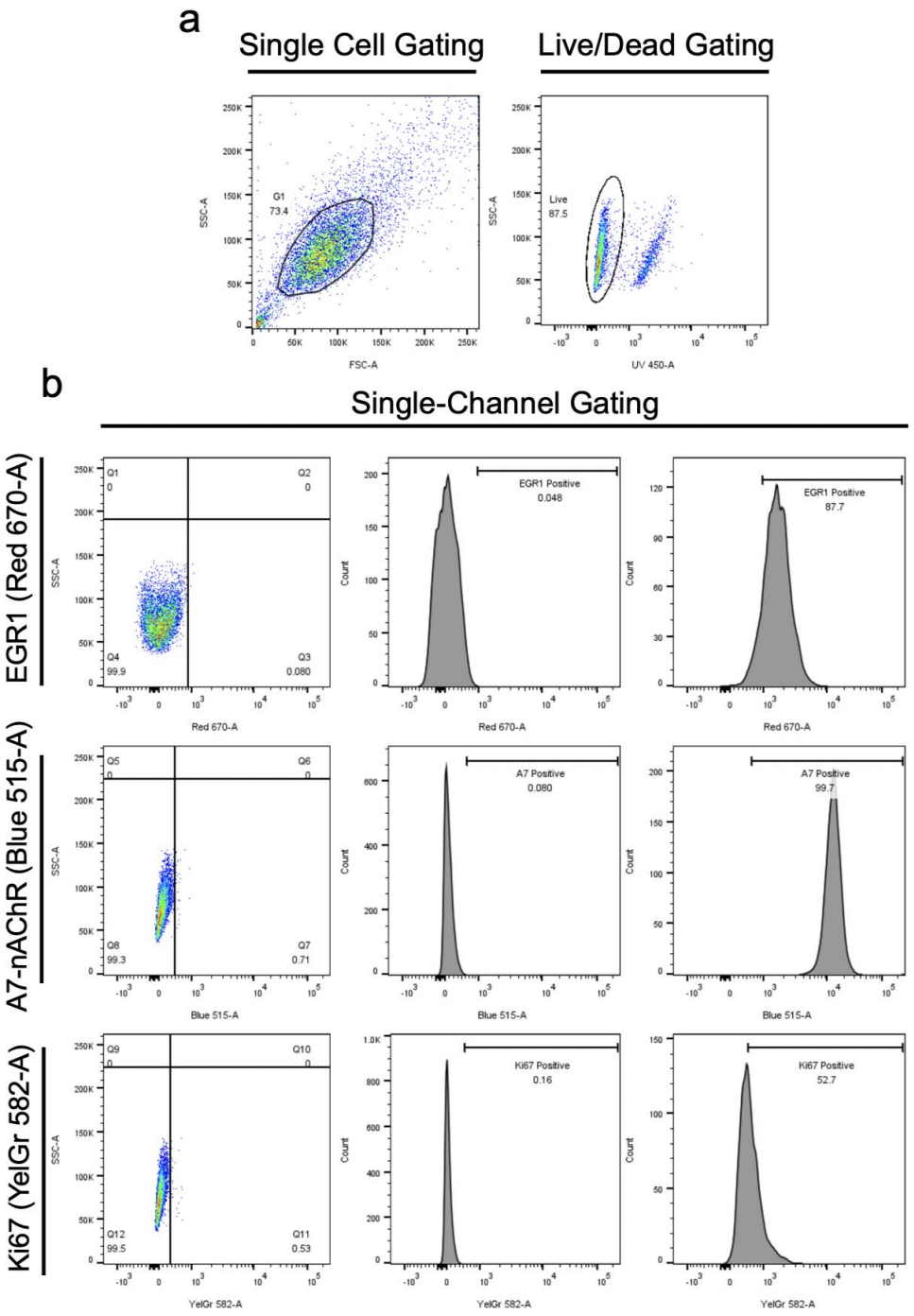


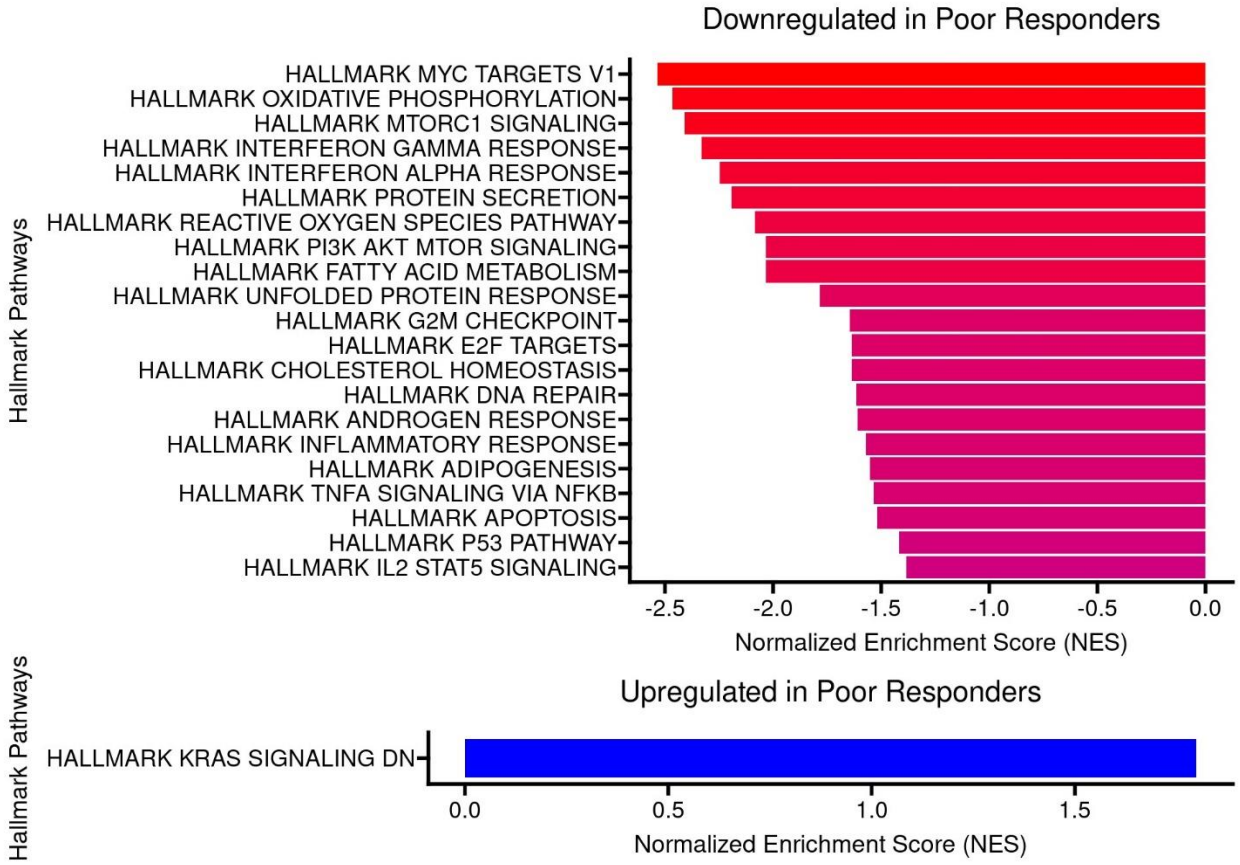
SFig. 1. Analysis of GBM PDX samples before filtering. **a**, The first two principal components of each mouse are plotted with color indicating the response group. Samples GBM44, poor-responder, and GBM5, good-responder, do not cluster in their respective group. **b**, The same data is shown as a dendrogram.



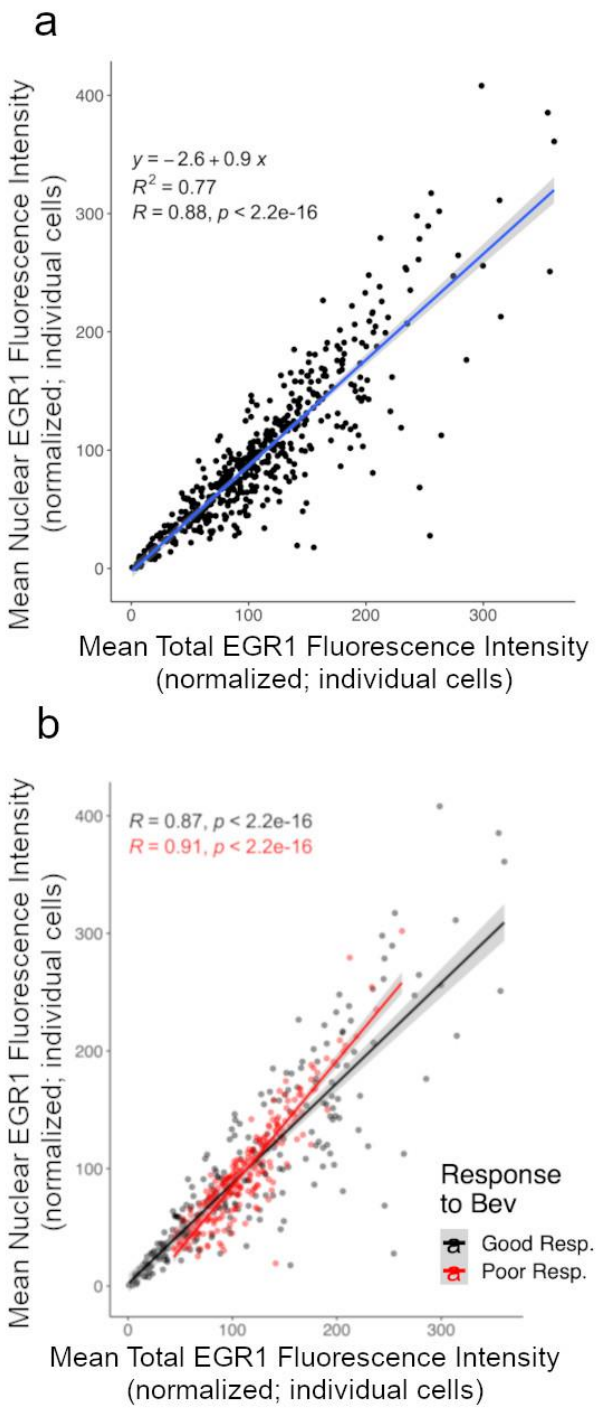
SFig. 2. Comparison of mean-variance trend before and after hyperparameter optimization. Mean-variance trends before (**a**) and after (**b**) transcript filtering based on hyperparameter optimization.



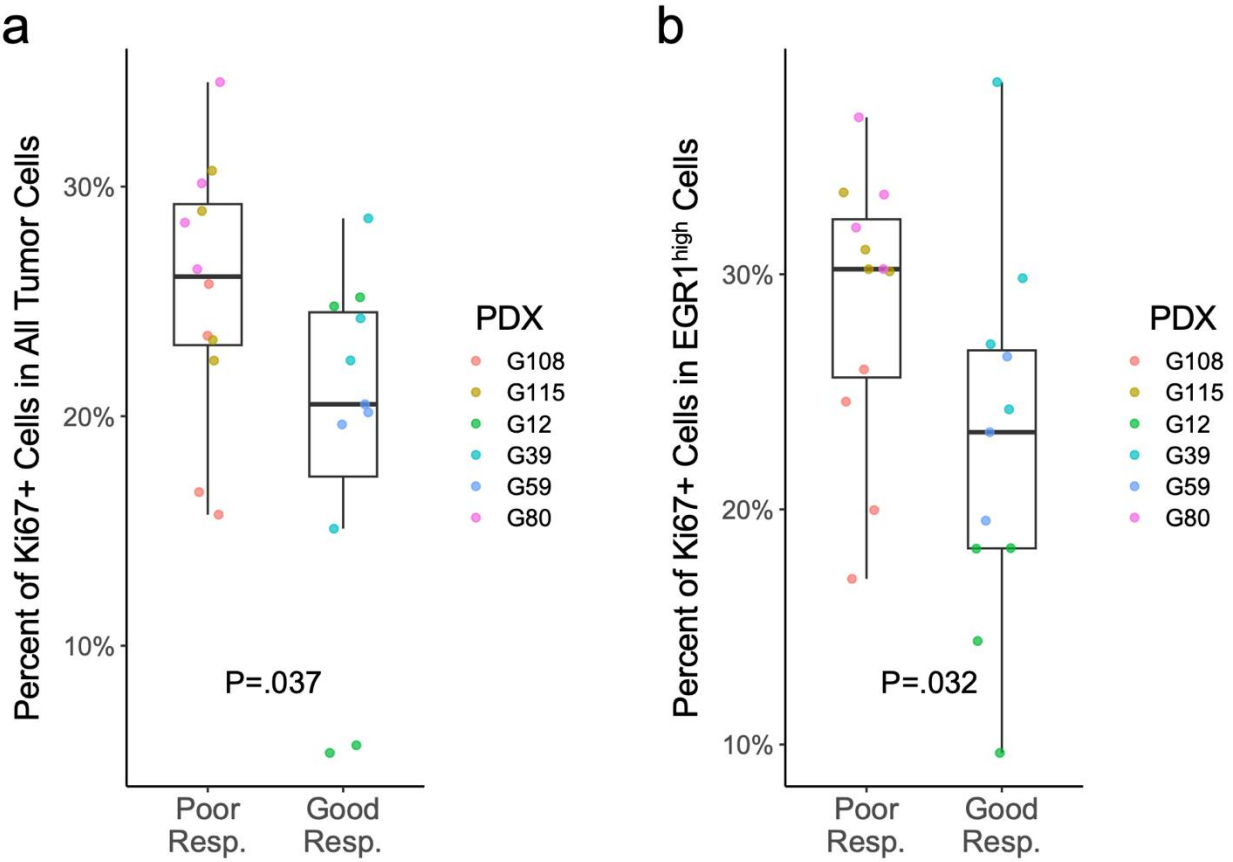
SFig. 3. Flow Cytometry gating strategy for EGR1, α7-nAChR, and Ki67 antibodies. a, Events were first gated based on forward scatter (FSC) and side scatter (SSC) to exclude debris and select for single cells followed by gating of live cells based on negative staining for live/dead fixable UV dead cell stain. **b,** Gates were set using unstained and single-stained controls. Gating was performed using FlowJo (v10.10.0), and fluorescence intensity values were exported for further analyses.



SFig. 4. Gene set enrichment and pathway analysis using the Hallmark gene-sets in tumors that were poor- and good-responders to bevacizumab therapy. Significantly enriched pathways in the Hallmark gene sets (https://www.gsea-msigdb.org/gsea/msigdb/human/genesets.jsp?collection=H) are shown in red. Alterations in expression between the poor-and good-responders were found in 23 pathways, with 22 pathways being downregulated in the poor-responder tumors. Using the Hallmark Gene-set, only one pathway, Downregulated Under the KRAS Pathway Activation, showed upregulation in the poor-responder tumors, shown in blue. The graph was generated in R using the mSigDBr package using the shrunken log fold change as stat.

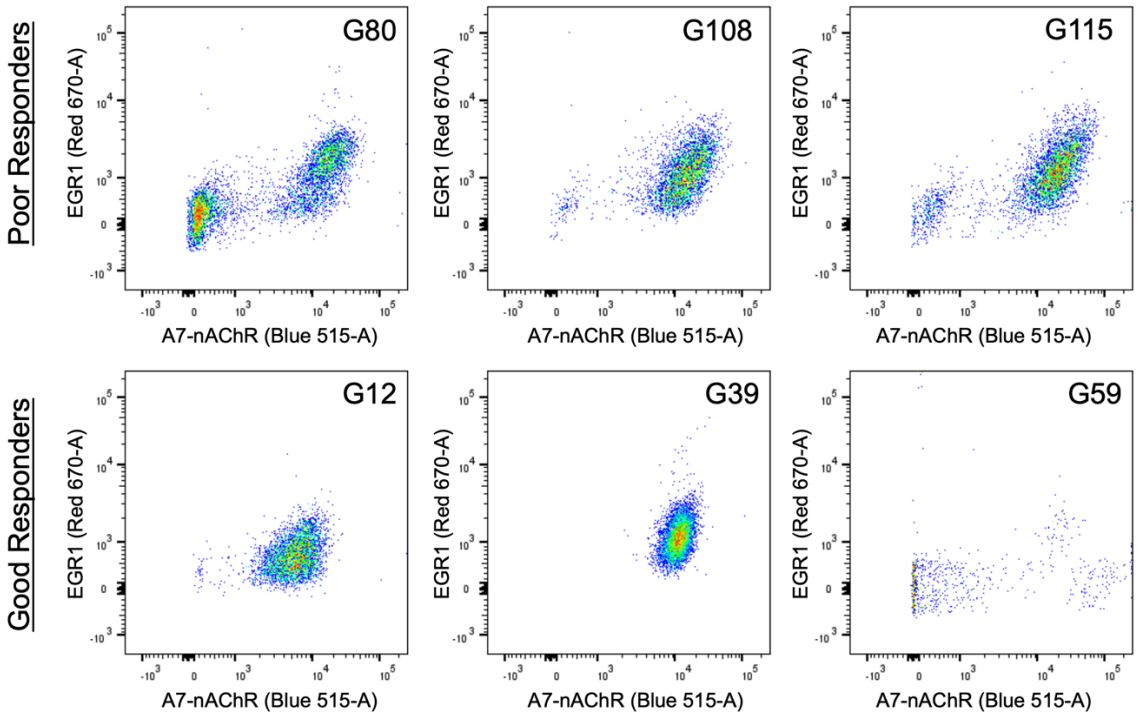


SFig. 5. Mean nuclear EGR1 and mean total EGR1 signal intensities are correlated in GBM PDX tumors. **a**, Mean nuclear and mean total EGR1 signal intensities in individual tumor cells have a strong positive correlation, both poor- and good-responder PDX tumors included. **b**, Mean nuclear and mean total EGR1 signal intensities in individual tumor cells have a stronger positive correlation in the poor-responder tumors as compared to the good-responder tumors (p = 0.031). Statistical analyses: Fisher Z Transformation Test.



SFig. 6. Elevated Ki67 signal in tumors that were poor-responders to bevacizumab therapy, based on flow cytometry. PDX cells were propagated as neurospheres in neural basal media with EGF and bFGF [8] and harvested for flow cytometry. Cells were stained with a live/dead marker (LIVE/DEAD™ Fixable Violet Kit, Thermo # L34955) and then fixed and permeabilized (True Nuclear Buffer Set, BioLegend # 424401), and stained with Alexa Fluor® 647 anti-EGR1 Antibody (BioLegend # 943906) and PE Ki67 (Thermo # 12-5698-82) and then analyzed on a BD Fortessa (BD Biosciences) flow cytometer. Data were analyzed using the FlowJo software as described in the Methods and graphed as box and whisker plots (the median is shown in the box plots). **a**, Percent of Ki67+ cells above the mean Ki67 fluorescent intensity ($Ki67^{high}$) in all tumor cells from poor- and good-responder tumors to bevacizumab therapy, irrespective of EGR1 expression. The median percent of tumor cells that were $Ki67^{high}$ irrespective of EGR1 expression in the poor-responders was 26.1% and the median percent of tumor cells that were $Ki67^{high}$ irrespective of EGR1 expression in the good-responders was 20.5%. There is a 27% increase in tumor cells that are $Ki67^{high}$ irrespective of EGR1 expression in the poor-responders, as compared to the good-responders. **b**, Percent of $Ki67^{high}$ cells (cells with Ki67 mean fluorescent intensity above the mean) in $EGR1^{high}$ cells (cells with top 15% of EGR1 signal intensity) in tumors that were poor- and good-responders to bevacizumab therapy. The median percent of tumor cells that were $EGR1^{high}$ and $Ki67^{high}$ in the poor-responders was 30.2%, the median percent of tumor cells that were $EGR1^{high}$ and $Ki67^{high}$ in the good-responders was 23.3%. There is a 30% increase in tumor cells that are $Ki67^{high}$ and $EGR1^{high}$ in the poor-responders as compared to the good-responders. Statistical analyses: Wilcoxon Rank Sum Test.

a

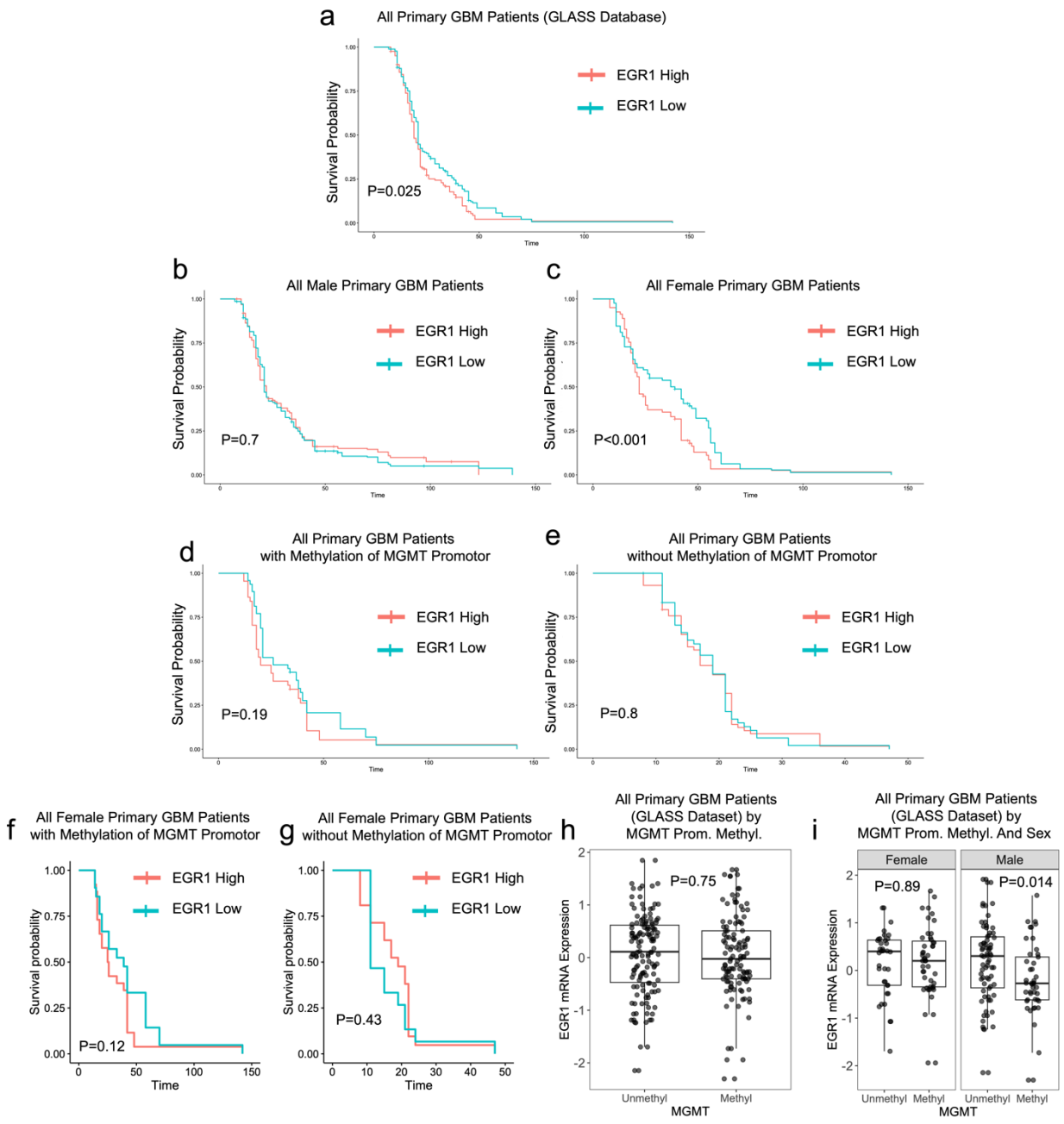


b

Poor Responders		
G80	G108	G115
R = 0.79	R = 0.44	R = 0.62

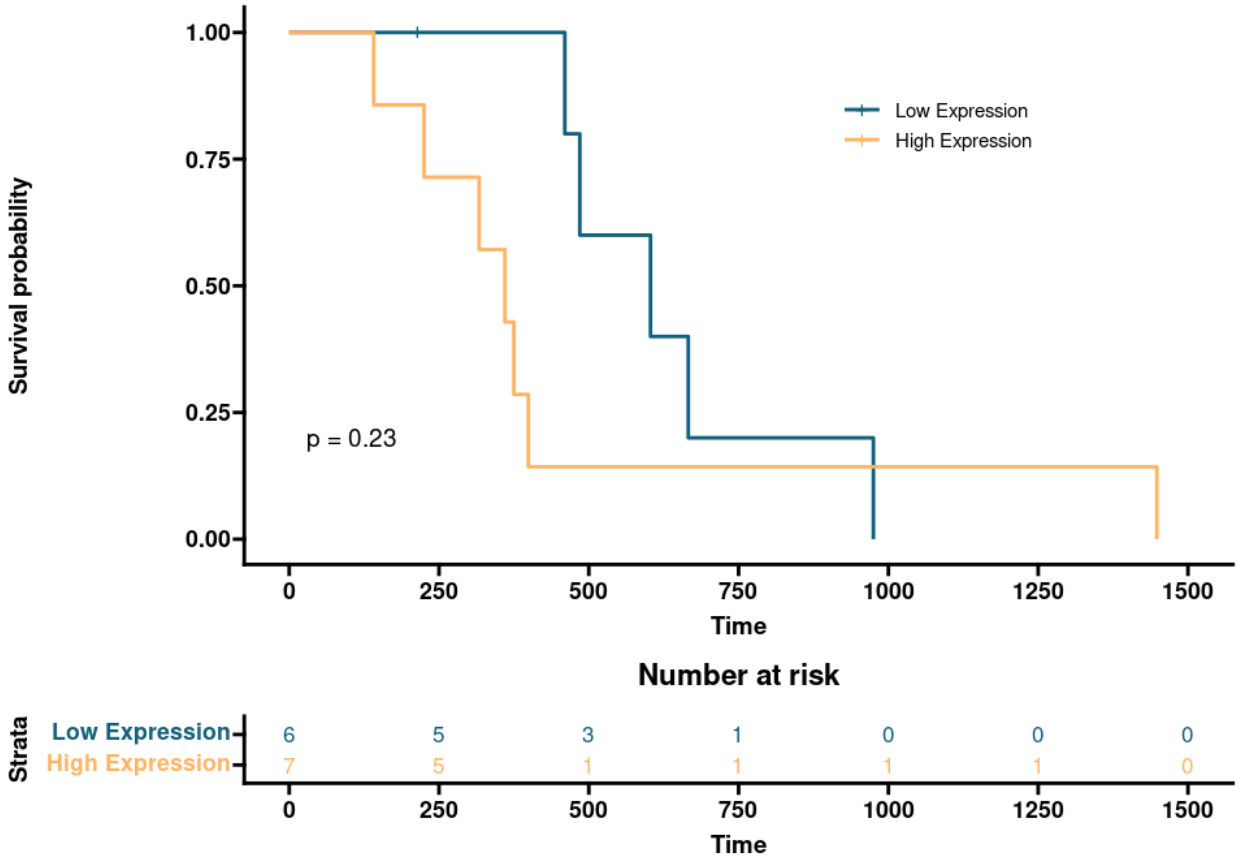
Good Responders		
G12	G39	G59
R = 0.35	R = 0.37	R = 0.14

SFig. 7. Expression of α7-nAChR protein directly correlates with EGR1 protein in poor- and good-responder tumors to bevacizumab therapy, based on flow cytometry. PDX cells were propagated as neurospheres in neural basal media with EGF and bFGF (8) and harvested for flow cytometry. Cells were stained with a live/dead marker (LIVE/DEAD™ Fixable Violet Kit, Thermo # L34955) and then fixed and permeabilized (True Nuclear Buffer Set, BioLegend # 424401), and stained with Alexa Fluor® 647 anti-EGR1 Antibody (BioLegend # 943906) and FITC a7-nAChR (Thermo # ANC-007-F-50UL) and then analyzed on a BD Fortessa (BD Biosciences) flow cytometer. Data were analyzed using the FlowJo software, as described in the Methods. **a**, Representative flow cytometry plots showing EGR1 fluorescence intensity on the y-axis and α7-nAChR fluorescence intensity on the x-axis for the primary cells from each PDX. **b**, Median linear correlation R values for each PDX (2 biologic replicates, 2 technical replicates for each PDX).

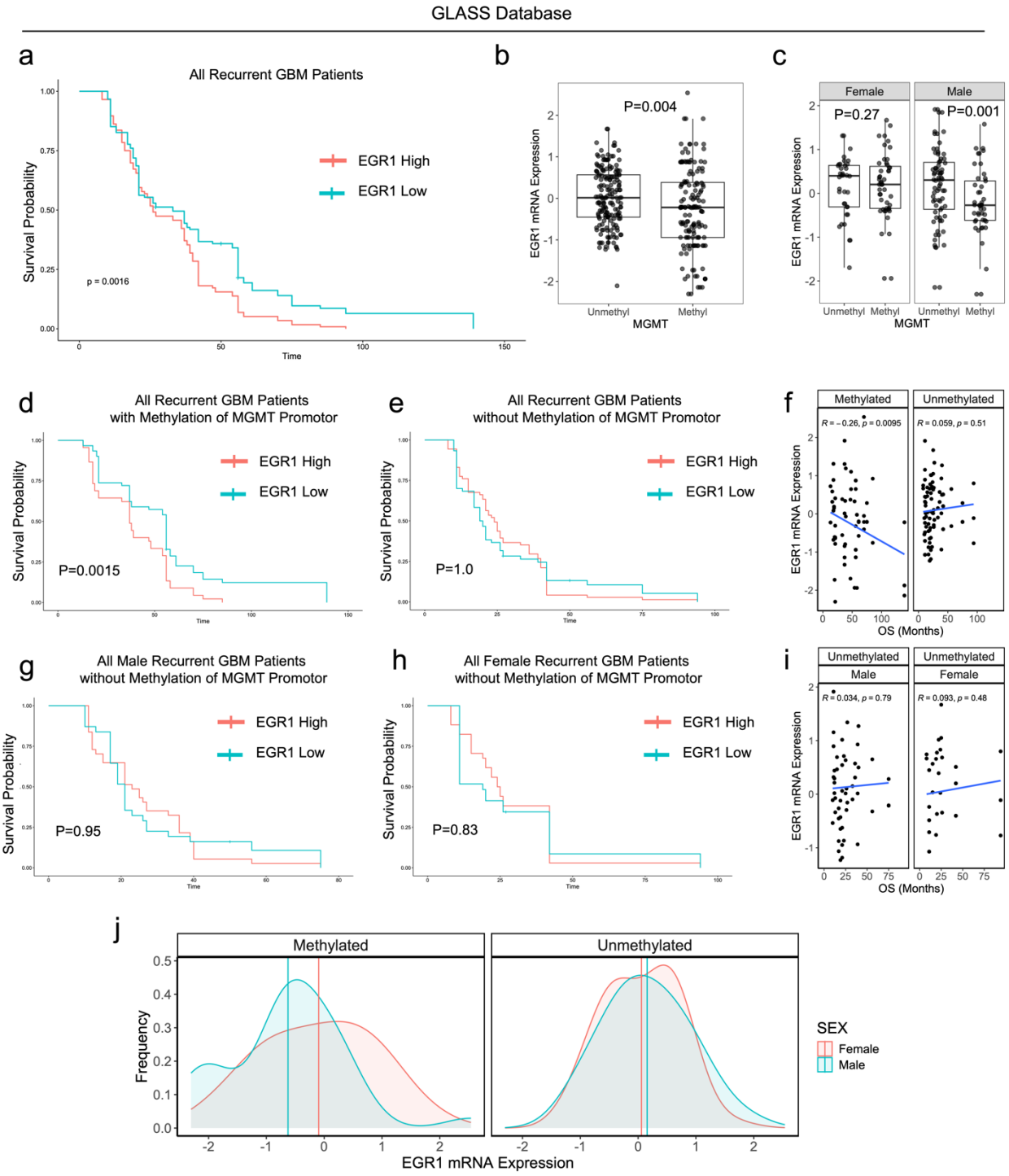


SFig. 8. Survival analysis in newly diagnosed GBM with elevated levels of *EGR1* mRNA defined as ≥ mean (GLASS database). **a**, The overall survival difference between low *EGR1* expression (< mean) and high *EGR1* expression (≥ mean) in newly-diagnosed tumors is significant (P=0.025; statistical analysis: Log-Rank test). **b&c**, When stratified by sex, the overall survival difference between low *EGR1* expression (< mean) and high *EGR1* expression (≥ mean) in newly-diagnosed tumors was significant only for females (P < 0.001; statistical analyses: Log-Rank test). **d&e**, When stratified by *MGMT* promoter methylation status, the overall survival difference between low *EGR1* expression (< mean) and high *EGR1* expression (≥ mean) in newly-diagnosed tumors was not significant (statistical analyses: Log-Rank test). **f&g**, When stratified by *MGMT* promoter methylation status in newly-diagnosed tumors in females,

the overall survival difference between low *EGR1* expression (< mean) and high *EGR1* expression (≥ mean) was not significant (statistical analyses: Log-Rank test). **h&i**, *EGR1* mRNA levels were unchanged by *MGMT* promoter methylation status overall but when stratified by sex, *EGR1* mRNA levels were significantly reduced in tumors with methylation of the *MGMT* promoter in males only (P=0.014; statistical analyses: Student T-test). Data gathered from GLASS database through cBioPortal and filtered for GBM tumors (186 patients with primary tumor information, of which 102 patients also had *MGMT* promoter methylation status data). Plots generated and stratified using ggsurv and ggplot2 in R.

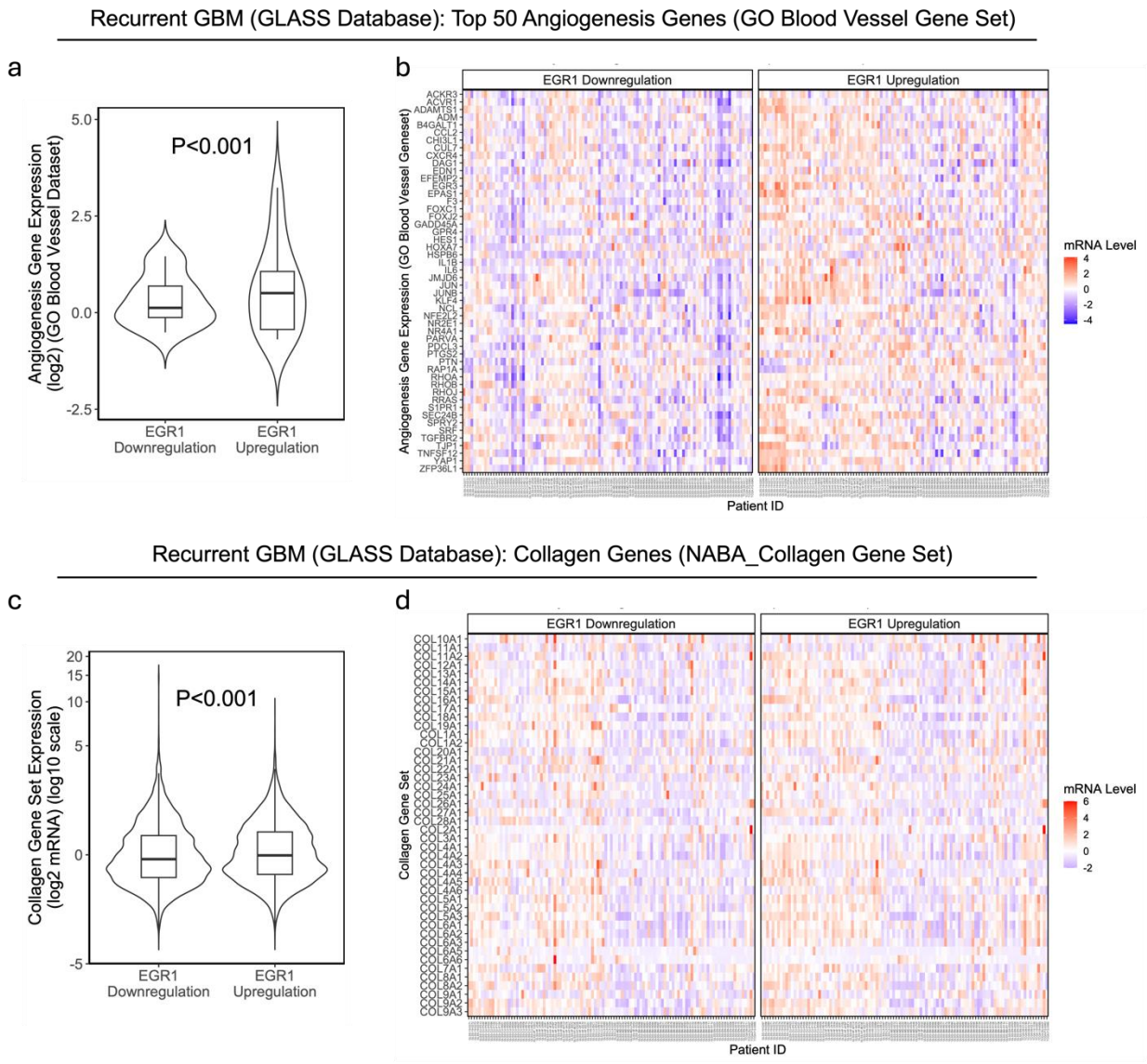


SFig. 9. Survival curve of patients with recurrent GBM stratified by *EGR1* mRNA expression. The overall survival difference between low *EGR1* expression and high *EGR1* expression is not significant, but the survival curves do not overlap. Data gathered from TCGA GBM database. Plots generated and recurrence status stratified using GDCdownload in R.

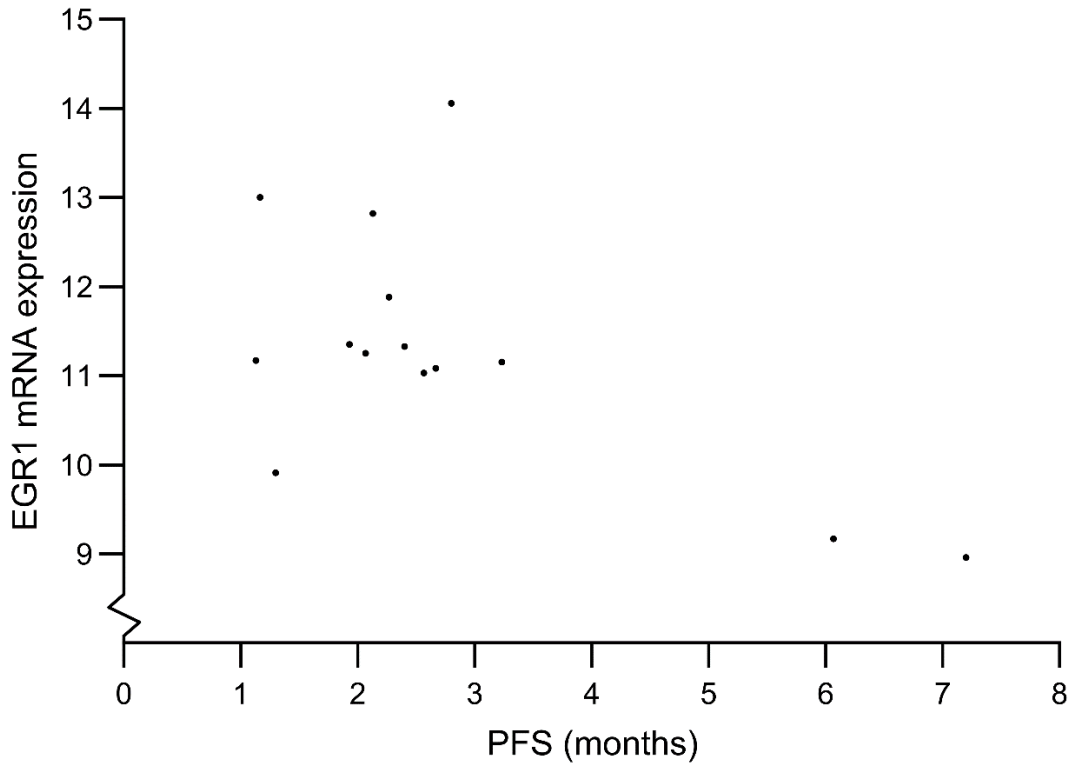


SFig. 10. Shorter survival in recurrent GBM with elevated levels of *EGR1* mRNA defined ≥ mean and a methylated *MGMT* promoter (GLASS database). **a**, The overall survival difference between low *EGR1* expression (< mean) and high *EGR1* expression (≥ mean) in recurrent tumors was significant (P=0.0016; statistical analysis: Log-Rank test). See Fig. 6 for data showing this was specific for females. **b**, *EGR1* mRNA levels were lower in recurrent tumors with a methylated *MGMT* promoter (P=0.004;

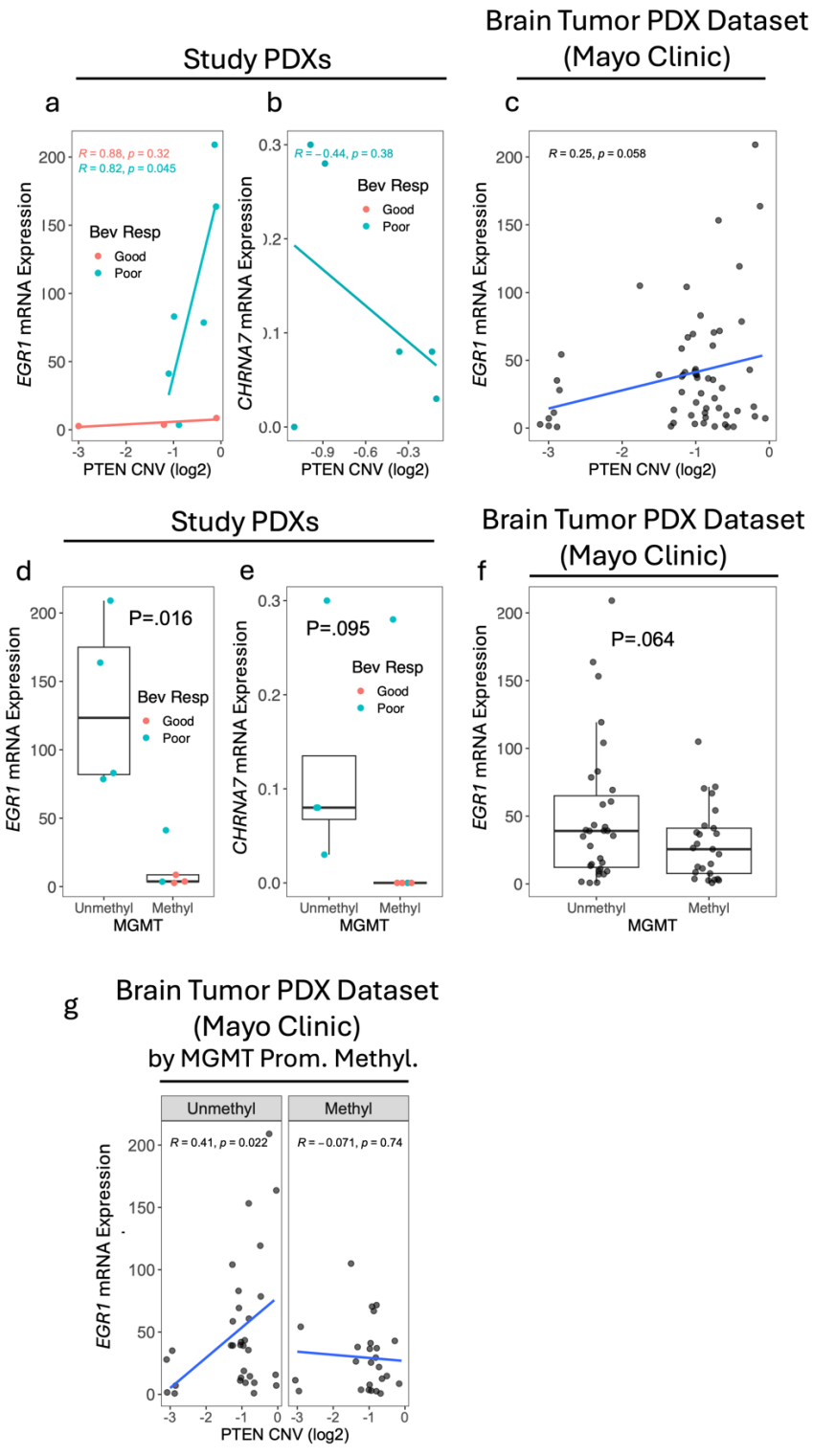
statistical analysis: Student's T-test). **c**, When stratified by sex in recurrent tumors, *EGR1* mRNA levels were lower only in males with a methylated *MGMT* promoter (P=0.001; statistical analyses: Student's T-test). **d&e**, When stratified by *MGMT* promoter methylation status, the overall survival difference between low *EGR1* expression (< mean) and high *EGR1* expression (≥ mean) in recurrent tumors was significant only in tumors with methylation of the *MGMT* promoter (P=0.0015; statistical analysis: Log-Rank test). **f**, When stratified by *MGMT* promoter methylation status in recurrent tumors, higher *EGR1* mRNA levels correlated with shorter overall survival only in tumors with methylation of the *MGMT* promoter (R = -0.26, P=0.0095; statistical analyses: Pearson Correlation). See Fig. 6 for data showing that only females with recurrent GBM and methylation of the *MGMT* promoter had a shorter overall survival. **g&h**, When recurrent tumors without methylation of the *MGMT* promoter were stratified by sex, there was no overall survival difference between low *EGR1* expression (< mean) and high *EGR1* expression (≥ mean) in recurrent tumors in males or females (statistical analysis: Log-Rank test). **i**, When tumors without methylation of the *MGMT* promoter are stratified by sex, *EGR1* mRNA levels did not correlate with overall survival for males or females (statistical analyses: Pearson Correlation). **j,** *EGR1* mRNA levels have different distributions in females as compared to males in patients with recurrent GBM and a methylated *MGMT* promoter versus the distribution in females as compared to males in patients with recurrent GBM and an unmethylated *MGMT* promoter (D = 0.30, P = 0.0271 for tumors with a methylated *MGMT* promoter and D = 0.16, P = 0.312 for tumors with an unmethylated *MGMT* promoter, by the Kolmogorov-Smirnov test). Mean *EGR1* mRNA levels of -0.095 and -0.626 in females and males, respectively (represented by vertical lines) in tumors with a methylated *MGMT* promoter (P = 0.018 by the Student's T-test). The Kolmogorov D statistic measures the distance describing the difference in distribution. Data gathered from GLASS database through cBioPortal and filtered for GBM tumors (247 patients with recurrent tumor information, of which 89 patients also had *MGMT* promoter methylation status data). Plots generated and stratified using ggsurv and ggplot2 in R.



SFig. 11. In recurrent GBM, elevated *EGR1* levels correlate with upregulation of the GO-Angiogenesis-Blood Vessel geneset and NABA_Collagen geneset (GLASS database). a, Log 2 expression of angiogenesis (GO Blood Vessel) gene set in recurrent GBM patients shows upregulation in patients with elevated levels of *EGR1* mRNA ($p<0.001$; statistical analyses: Student T-test). **b,** Heatmap of concordant angiogenesis (GO Blood Vessel) genes shows upregulation of the 50 genes with the largest differential expression in tumors with elevated levels of *EGR1* mRNA. **c,** Log 2 expression of collagen (NABA_COLLAGEN) gene set in recurrent GBM patients shows upregulation in patients with elevated levels of *EGR1* mRNA ($p<0.001$; statistical analyses: Student T-test). **d,** Heatmap of concordant collagen (NABA_COLLAGEN gene-set) genes shows upregulation in tumors with elevated levels of *EGR1* mRNA.

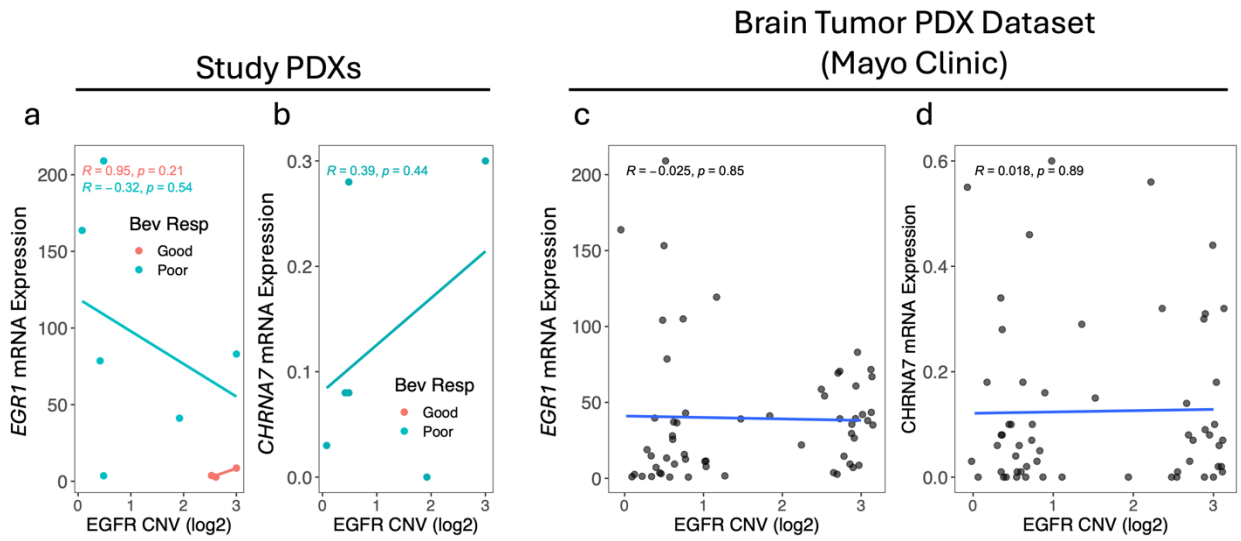


SFig. 12. Low *EGR1* mRNA expression levels correlate with a longer PFS in recurrent GBM treated with bevacizumab monotherapy. Fourteen patients with recurrent GBM who had received bevacizumab monotherapy as a cancer treatment and who had been tested for *EGR1* mRNA expression levels by the Biomarker Discovery Laboratory at the Mayo Clinic were identified. Their electronic medical records were retrospectively reviewed to collect demographic, clinical, imaging, histological and molecular data. We found a significant correlation between low *EGR1* mRNA expression levels and PFS in recurrent GBM (Pearson's correlation coefficient = 0.598, p=0.024).

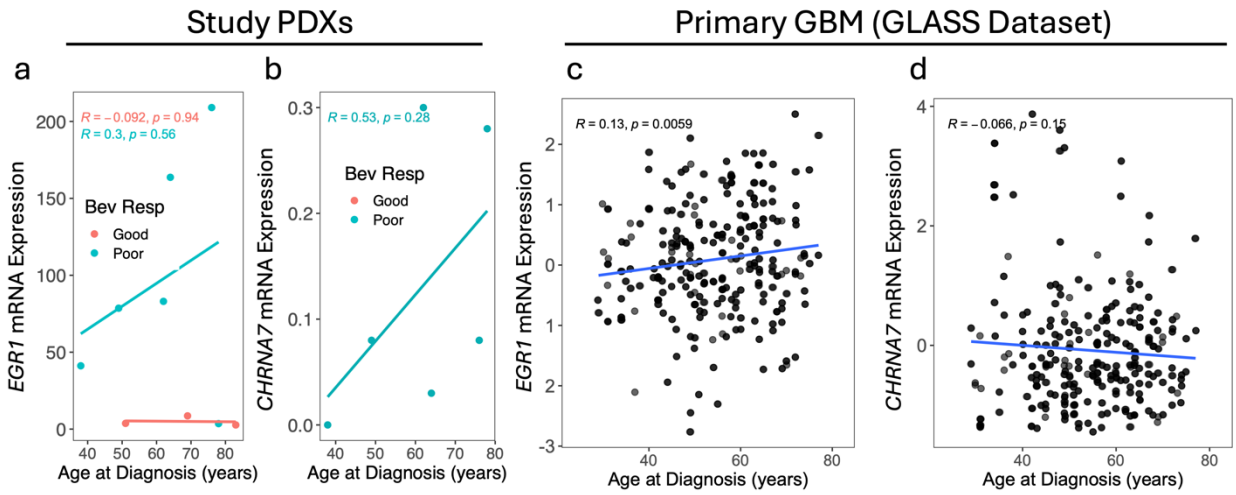


SFig. 13. High *EGR1* mRNA levels correlate with low CNV of *PTEN* in GBM PDX tumors. a, EGR1 mRNA levels were positively correlated with PTEN copy number (lower EGR1 mRNA levels were correlated with PTEN loss and higher EGR1 mRNA levels correlated with PTEN^{wt}/CNV = 0) in poor-

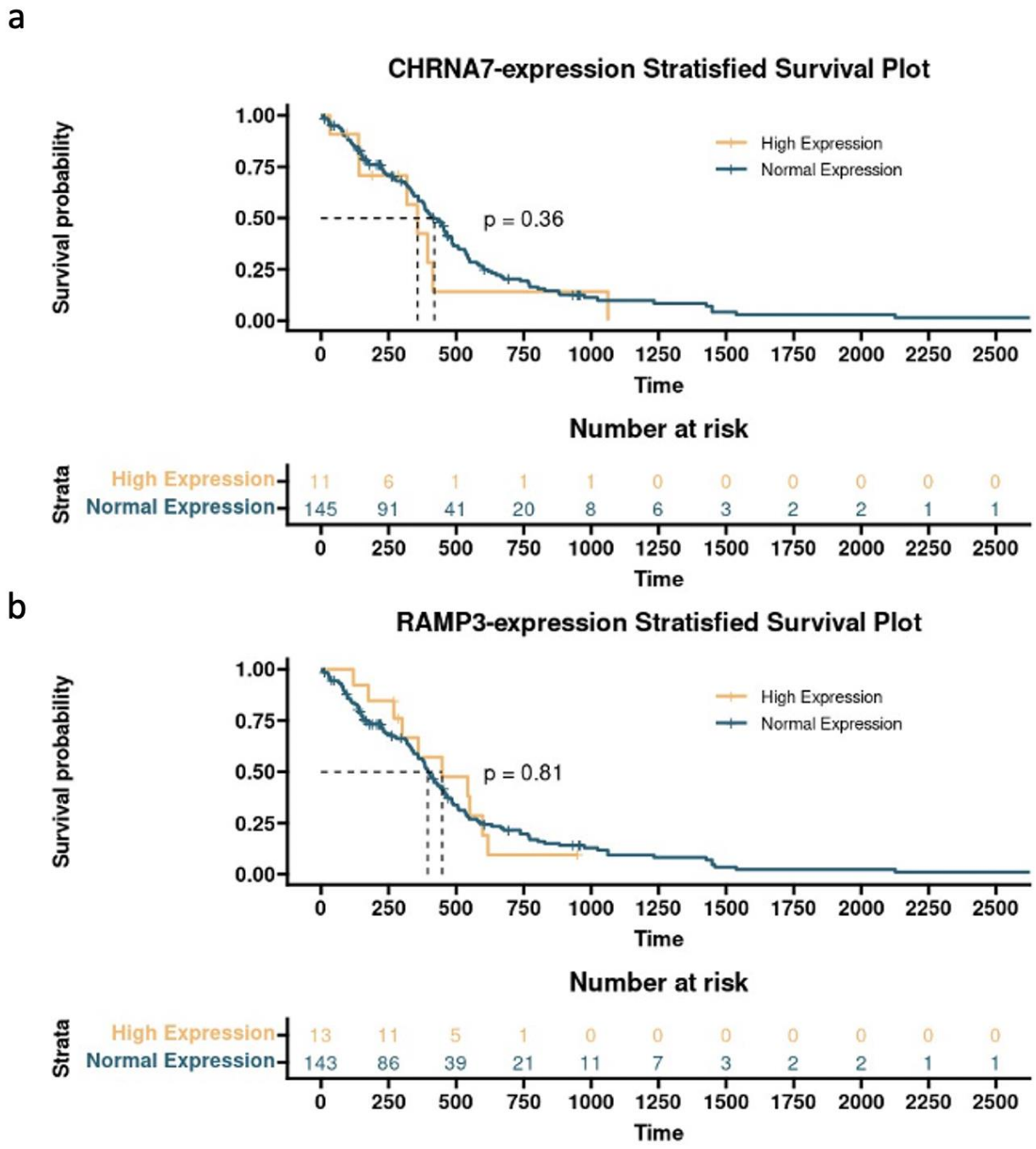
responder tumor PDXs from this study (R=0.82, P=0.045; Statistical analyses: Pearson Correlation). **b,** CHRNA7 mRNA levels were not significantly correlated with PTEN copy number in tumor PDXs from this study (Statistical analyses: Pearson Correlation). **c,** There was a trend toward EGR1 mRNA levels positively correlating with PTEN copy number (lower EGR1 mRNA levels were correlated with PTEN loss and higher EGR1 mRNA levels correlated with $PTEN^{wt}$/CNV = 0) in all GBM PDXs from the Brain Tumor PDXs database (Mayo Clinic data in cBioPortal) (R=0.25, P=0.058; Statistical analyses: Pearson Correlation). **d,** High EGR1 mRNA levels were associated with absence of methylation of the MGMT promoter in the 9 tumor PDXs from this study (P=0.016; Statistical analyses: Wilcoxon-Rank Sum test). **e,** CHRNA7 mRNA levels were not significantly associated with MGMT promoter methylation status in tumor PDXs from this study (Statistical analyses: Wilcoxon-Rank Sum test). **f,** There was a trend towards higher EGR1 mRNA levels being associated with an unmethylated MGMT promoter in GBM PDXs from the Brain Tumor PDXs database (Mayo Clinic data in cBioPortal) (P=0.064; statistical analysis: Student's T-test). **g,** When stratified by MGMT promoter methylation status, EGR1 mRNA levels had a moderate positive correlation with PTEN copy number (lower EGR1 mRNA levels were correlated with PTEN loss and higher EGR1 mRNA levels correlated with $PTEN^{wt}$/CNV = 0) in tumor PDXs without methylation of the MGMT promoter from the Brain Tumor PDXs database (Mayo Clinic data in cBioPortal) (R=0.41, P=0.022; Statistical analyses: Pearson Correlation). The Brain Tumor PDX database (Mayo Clinic) contained 109 GBM PDXs, and 78 of these samples contained data regarding the MGMT methylation status.



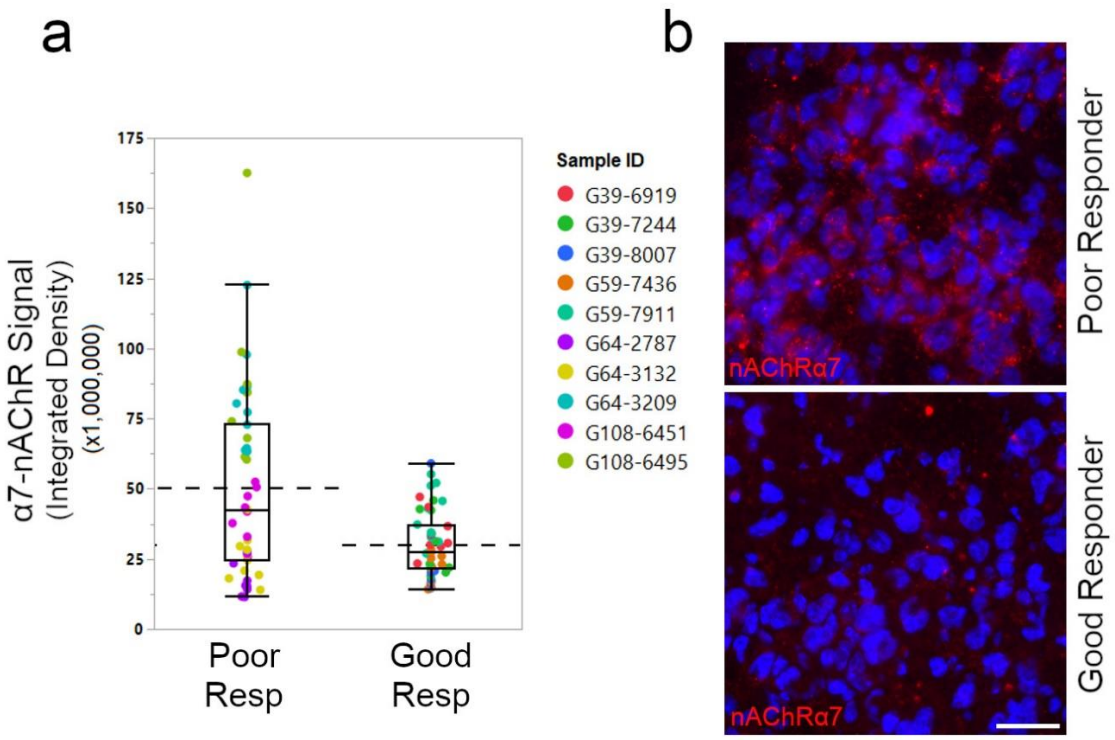
SFig. 14. No correlation between *EGR1* mRNA levels and amplification of *EGFR*. **a,** *EGR1* mRNA levels were not significantly correlated with *EGFR* copy number in poor-responder tumor PDXs from this study (Statistical analyses: Pearson Correlation). **b,** *CHRNA7* mRNA levels were not significantly correlated with *EGFR* copy in tumor PDXs from this study (Statistical analyses: Pearson Correlation). **c&d,** *EGR1* and *CHRNA7* mRNA levels were not significantly correlated with *EGFR* copy number in all GBM PDXs from the Brain Tumor PDXs database (Mayo Clinic data in cBioPortal) (Statistical analyses: Pearson Correlation).



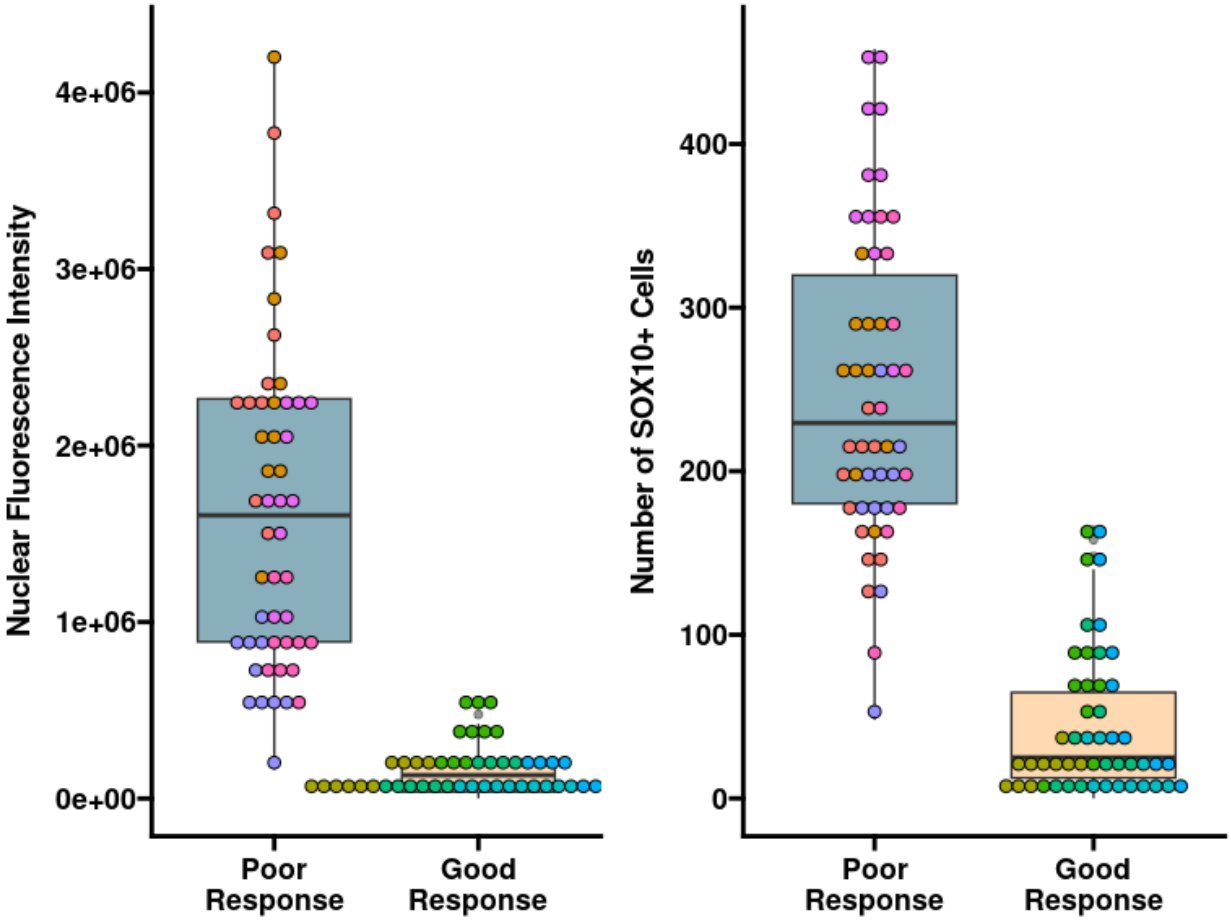
SFig. 15. *EGR1* mRNA levels very weakly correlate with age at diagnosis in newly-diagnosed GBM. **a,** *EGR1* mRNA levels were not significantly correlated with age at diagnosis in the poor-responder tumor PDXs used for this study (Statistical analyses: Pearson Correlation). **b,** *CHRNA7* mRNA levels were not significantly correlated with age at diagnosis in the poor-responder tumor PDXs used for this study (Statistical analyses: Pearson Correlation). **c,** *EGR1* mRNA levels were positively correlated with age at diagnosis in all primary (newly-diagnosed) GBM tumors from the GLASS database (R=0.13, P=0.006; Statistical analyses: Pearson Correlation). **d,** *CHRNA7* mRNA levels were not correlated with age at diagnosis in all primary GBM tumors from the GLASS database (Statistical analyses: Pearson Correlation). Data gathered from GLASS database through cBioPortal and filtered for GBM tumors (186 patients with recurrent tumor information). Plots generated and stratified using ggplot2 in R.



SFig. 16. Survival curves for patients with GBM with upregulated *CHRNA7* or *RAMP3* mRNA. a, The overall survival difference between high *CHRNA7* expression and normal *CHRNA7* expression is not significant. **b**, The overall survival difference between high *RAMP3* expression and normal *RAMP3* expression is not significant. Data gathered from TCGA GBM database. Plots generated using UCSC Xena Tools in R.



SFig. 17. Expression of α7-nAChR in GBM PDX xenograft tumors that were poor- or good-responders to bevacizumab therapy. Sections were reacted with the primary antibody to α7-nAChR followed by the secondary antibody as described in the Methods. Images were acquired with the Leica microscope and analyzed using ImageJ, as described in the Methods. **a**, Data are plotted as a box and dot plot. The dotted line represents the mean. There was an increase in the mean α7-nAChR signal in the poor-responder tumors that was significant by a two-sided t-test (p=0.004), but it was not significant by the linear mixed model (p=0.15). **b**, Representative images are shown. Scale bar denotes 30 μm.



SFig. 18. **Increased nuclear SOX10 expression in tumors that were poor-responders to bevacizumab therapy**. Sections were permeabilized, blocked, reacted with rabbit anti-SOX10 antibody overnight (4ºC), washed, reacted with Alexa-488-conjugated anti-rabbit secondary antibody, followed by DAPI nuclear stain and coverslipped, as described in the Methods. Images were acquired on a Leica fluorescent microscope and analyzed with ImageJ. The mean nuclear fluorescence intensity in poor- and good-responder tumors is shown on the readers left, and there is a significant increase in the poor-responder tumors as compared to the good-responder tumors ($p<0.001$). The mean number of SOX10+ tumor nuclei is shown in poor- and good-responder tumors on the readers right, and there is a significant increase in the poor-responder tumors as compared to the good-responder tumors ($p<0.001$). Statistical analyses: linear mixed model.

Characteristics of GBM PDX Tumors

Sample	*Group*	*SRA*	*Pri/ Rec*	*Molecular Subtype (RNAseq / Methylo)*	*TERT Prom Status*	*Sex*	*Age*	*Patient Survival*
GBM64	poor	SRR9294073.1	Rec	P / P	Mut	F	64	1.02
GBM76	poor	SRR9294072.1	Rec	C / C	Mut	M	38	3.23
GBM80	poor	SRR9294077.1	Pri	P / P	Mut	M	49	0.98
GBM85	poor	SRR9294060.1	Pri	P / P	Mut	M	78	0.13
GBM108	poor	SRR9294041.1	Pri	N/A / N/A	Mut	M	62	0.67
GBM115	poor	SRR9294043.1	Pri	N/A / C	Mut	F	76	0.34
GBM12	good	SRR9294075.1	Pri	M / C	Mut	M	69	0.24
GBM39	good	SRR9294069.1	Pri	M / C	Mut	M	51	2.4
GBM59	good	SRR9294032.1	Pri	M / C	Mut	F	83	1.03

STable 1. **GBM patient derived xenograft (PDX) samples reference table**. Abbreviations: N/A, denotes not available; SRA, Sequence Read Archive; Pri, Primary or Newly-diagnosed GBM; Rec, Recurrent GBM; Molecular Subtype based on RNA sequencing (RNAseq) or Methylomics (Methylo) -P, Proneural; C, Classical; M, Mesenchymal; *TERT*, telomerase reverse transcriptase; Prom, promoter; Mut, mutant. The Age and Overall Survival are in years. Below is the link to the description of the GBM PDX tumors:

https://www.mayo.edu/research/labs/translational-neuro-oncology/mayo-clinic-brain-tumor-patient-derived-xenograft-national-resource/overview.

Differential Gene Expression

Gene	*Fold Change*	*P-value*	*Adjusted P-value*	*Mean Expression*
MXRA5	1868.27	< .001	< .001	1759.89
FIGNL2	1569.38	< .001	< .001	436.46
DPP10	1492.07	< .001	< .001	2903.70
SHD	1490.51	< .001	<.001	3325.96
IGLON5	1353.83	< .001	< .001	2933.21
SYT13	1308.00	< .001	< .001	925.22
NCAN	1187.78	< .001	< .001	38401.23
SIX6	1050.67	< .001	< .001	646.75
SCN3B	923.04	< .001	< .001	1313.92
VGF	878.53	< .001	< .001	27375.38
MMD2	784.09	< .001	< .001	300.90
B3GAT1	733.52	< .001	< .001	9828.08
NAT16	699.09	< .001	< .001	1335.63
USP43	683.91	< .001	< .001	816.73
ABCC8	630.66	< .001	< .001	2770.25
ATCAY	624.96	< .001	< .001	10365.40
EXTL1	621.35	< .001	< .001	622.66
KCNA6	619.83	< .001	< .001	1845.29
TLX1	570.41	< .001	< .001	795.25
SCG3	567.91	< .001	< .001	10645.30

STable 2. **List of the top 20 differentially expressed genes identified through differential gene expression analysis in tumors that were poor-responders to bevacizumab treatment**. Fold-change represents the ratio of expression in the poor-responder tumors to the good-responder tumors.

Gene-Set Enrichment

Genset	*Normalized Enrichment*	*Adjusted P-value*	*Core Enrichment*
HALLMARK INTERFERON GAMMA RESPONSE	-2.34	0.00	IRF9/CMPK2/BPGM/CXCL11/IFIH1/PNPT1/USP18/JAK2/HLA-A/CASP3/IL7/MX2/MYD88/STAT1/NLRC5/CASP4/IFI44L/SPPL2A/PARP14/ST8SIA4/RTP4/MT2A/NOD1/IFI35/CASP8/EPSTI1/PTPN2/HERC6/PML/HIF1A/CASP7/IFIT2/PLSCR1/IRF1/PARP12/PTPN1/LGALS3BP/IFI44/RSAD2/UPP1/LAP3/SP110/NCOA3/ICAM1/EIF2AK2/IFITM2/DDX58/ZNFX1/RIPK1/PSMB10/IFITM3/IL15/OAS2/PSME1/PSMA2/MX1/NMI/IFIT3/VAMP5/FAS/NAMPT/PSMA3/IFI30/OASL/SOD2/PNP/ISG20/PSMB2/B2M/NFKB1/IFIT1/ISG15/NFKBIA/GBP4/MVP/IFI27/PSME2/TNFAIP2
HALLMARK MTORC1 SIGNALING	-2.45	0.00	RDH11/CCT6A/NIBAN1/STIP1/PITPNB/COPS5/LGMN/EEF1E1/EDEM1/HMBS/CACYBP/SLC9A3R1/BHLHE40/CYP51A1/USO1/RAB1A/DDX39A/CYB5B/PDK1/MTHFD2L/PLK1/BTG2/HSPA5/PSMA4/HSP90B1/SDF2L1/RPN1/SQLE/M6PR/GPI/FKBP2/G6PD/AK4/BUB1/GLRX/PSMD13/ERO1A/STC1/PSMG1/MAP2K3/ARPC5L/TBK1/EGLN3/POLR3G/ATP6V1D/SEC11A/GMPS/PRDX1/SSR1/PPIA/HSPA4/ENO1/HSPD1/GBE1/P4HA1/ELOVL5/ACTR3/PNO1/CALR/IMMT/GAPDH/LDLR/UBE2D3/PSMC2/GTF2H1/HSPE1/ETF1/STARD4/CD9/PSMB5/EIF2S2/EBP/PSMD12/PSMC4/NAMPT/PSMA3/IFI30/TPI1/CCNG1/ACTR2/PSMC6/GLA/PNP/SQSTM1/HPRT1/AURKA/RIT1/LDHA/ELOVL6/ALDOA/SLC2A1/PSMD14/PGK1
HALLMARK MYC TARGETS V1	-2.54	0.00	ORC2/EIF3B/DEK/DDX21/CNBP/TXNL4A/SRPK1/NME1/NOP56/CANX/RPL22/PRDX3/RPL14/SYNCRIP/COPS5/RPS10/EIF3D/VBP1/APEX1/HNRNPA2B1/TYMS/EIF1AX/RPS5/PTGES3/PCBP1/G3BP1/RPS2/EEF1B2/ILF2/POLE3/KARS1/PRPF31/TCP1/KPNA2/PWP1/YWHAE/EIF2S1/SSBP1/GOT2/PSMA4/RPLP0/SRSF1/TARDBP/EIF3J/UBA2/TRA2B/CUL1/AIMP2/SERBP1/RPL34/PCNA/NPM1/YWHAQ/RPS6/ERH/HNRNPC/DHX15/RACK1/VDAC1/SNRPD3/MRPL9/SSB/HSP90AB1/HDDC2/ACP1/UBE2L3/SNRPB2/PPM1G/PPIA/CDC20/EIF4E/LSM7/SLC25A3/HSPD1/PRPS2/RPL18/SRSF3/NOP16/CCT4/NDUFAB1/CCNA2/CCT7/PSMA2

			/HSPE1/SNRPD1/PSMD7/PSMD1/ETF1/PSMA1/GLO1/VDAC3/ABCE1/AP3S1/XRCC6/SRSF7/EIF4G2/EIF2S2/MAD2L1/H2AZ1/PSMC4/PSMD8/SNRPG/PSMC6/SNRPD2/PSMB3/PSMB2/HPRT1/LDHA/SNRPA1/PSMA6/PRDX4/PSMA7/PSMD14/PGK1
HALLMARK OXIDATIVE PHOSPHORYLATION	-2.47	0.00	NDUFA2/MRPS22/COX11/NDUFC2/PDHX/ATP6V0B/PRDX3/MRPL35/DLD/ATP5MC3/ACAT1/SDHC/BAX/NDUFB2/SUCLG1/ISCA1/COX7C/DLST/NDUFS4/NDUFS6/NDUFB5/MRPL11/NDUFB8/ATP6V1F/NDUFB3/ATP5MG/NDUFS1/GOT2/COX5B/ATP6V1E1/TIMM50/GPI/NDUFA8/MRPS12/MDH2/ATP5F1C/NDUFS8/VDAC2/DLAT/MRPS30/CASP7/ECHS1/TIMM8B/MGST3/ATP5ME/ATP5MF/UQCRC2/VDAC1/NDUFA9/ATP6AP1/HADHA/NDUFA3/AFG3L2/NDUFA7/UQCR10/CYCS/CPT1A/ATP6V1D/TIMM9/NDUFB4/ATP5PB/ATP5F1A/NDUFA4/NDUFB7/NDUFA6/UQCRFS1/SLC25A3/COX7A2/NDUFC1/TOMM22/ETFDH/COX4I1/HSD17B10/IMMT/SLC25A5/NDUFB1/OXA1L/NDUFAB1/TIMM17A/CYB5A/UQCRQ/GPX4/ETFA/ABCB7/PDP1/MDH1/ATP5PD/DECR1/COX6C/NDUFV2/PDHA1/UQCRH/GRPEL1/ATP6V0E1/UQCR11/AIFM1/FH/VDAC3/MRPL15/NQO2/COX6B1/NDUFA1/IDH3G/ECH1/ACAA2/HCCS/MPC1/NDUFB6/COX7B/COX7A2L/MRPL34/SDHB/ATP5F1E/LDHA/MRPS15
HALLMARK INTERFERON ALPHA RESPONSE	-2.23	0.00	WARS1/SAMD9L/TRIM25/IRF2/CD47/CXCL10/TRIM21/IRF9/CMPK2/CXCL11/IFIH1/PNPT1/USP18/SAMD9/IL7/PARP9/IFI44L/PARP14/CSF1/RTP4/IFI35/CASP8/EPSTI1/ELF1/HERC6/IFIT2/PLSCR1/IRF1/PARP12/LGALS3BP/IFI44/RSAD2/LAP3/SP110/EIF2AK2/IFITM2/GMPR/IFITM3/IL15/PSME1/MX1/NMI/IFIT3/PROCR/PSMA3/IFI30/OASL/ISG20/B2M/ISG15/IFITM1/GBP2/GBP4/IFI27/PSME2
HALLMARK PROTEIN SECRETION	-2.18	0.00	ANP32E/OCRL/GALC/TSG101/AP3B1/ARFGAP3/IGF2R/ARCN1/SCAMP3/BET1/PAM/USO1/GOLGA4/SEC31A/CLTC/RER1/M6PR/BNIP3/TMED10/ZW10/SOD1/COPB1/VPS4B/NAPA/SEC22B/YIPF6/RAB22A/ARF1/TMED2/LMAN1/SEC24D/ADAM10/CD63/ARFGEF2/TMX1/COPE/SNX2/ARFIP1/CLTA/AP2S1/RAB9A/AP3S1/ERGIC3/KRT18/GLA/LAMP2

HALLMARK FATTY ACID METABOLISM	-2.01	0.00	IDI1/SERINC1/RETSAT/NBN/SMS/DLD/RDH11/SDHC/SUCLG1/NTHL1/HSP90AA1/APEX1/DLST/ERP29/MIF/HMGCL/HSD17B11/HSD17B7/MDH2/GRHPR/G0S2/ACSL1/ACOT8/ECHS1/HADH/ACAT2/CRYZ/PTS/YWHAH/METAP1/CPT1A/EPHX1/ETFDH/ELOVL5/HSD17B10/ADSL/UROD/MDH1/PSME1/DECR1/RAP1GDS1/PDHA1/FH/IDH3G/ECH1/ACAA2/HCCS/H2AZ1/NSDHL/PRDX6/OSTC/LGALS1/S100A10/ACSL4/LDHA/ALDOA/ECI2
HALLMARK PI3K AKT MTOR SIGNALING	-2.00	0.00	PDK1/CLTC/HSP90B1/NOD1/ATF1/RALB/PPP1CA/MAP2K3/TBK1/MKNK1/EIF4E/ARF1/ARPC3/RIPK1/ACTR3/CALR/UBE2D3/YWHAB/ACTR2/SQSTM1/PPP2R1B/RIT1/SLC2A1/PFN1
HALLMARK KRAS SIGNALING DN	1.81	0.00	SOX10/CLSTN3/CAMK1D/TLX1/THRB/MACROH2A2/SLC29A3/GDNF/YBX2/MYH7/RYR1/KCNN1/GPR19/ARHGDIG/RGS11/COL2A1/THNSL2/ACTC1/YPEL1/RIBC2/ALOX12B/HSD11B2/TEX15/KCND1/FGFR3/MYO15A/PDE6B/SLC30A3/GAMT/SPTBN2/C5/NR4A2/DLK2/NRIP2/PDK2/ARPP21/SKIL/STAG3/TGM1/SYNPO/CPA2/WNT16/IDUA/MAST3/TFAP2B/SNCB/CHST2/DCC/EFHD1/PRODH/CPEB3

STable 3. List of the top 10 differentially expressed Hallmark gene-sets identified through gene set enrichment analysis in tumors that were poor-responders to bevacizumab therapy as compared to tumors that were good-responders to bevacizumab therapy. Positive normalized enrichment indicates upregulation in poor-responders to bevacizumab, and negative normalized enrichment indicates downregulation in poor-responders to bevacizumab. Genes listed in core enrichment are sorted in decreasing order of differential expression. Link to the Hallmark gene-set pathway analysis resource: https://www.gsea-msigdb.org/gsea/msigdb/human/genesets.jsp?collection=H.