

SUPPLEMENTARY APPENDIX

Table of Contents

Supplemental Methods	2
Supplemental Figures	4
Figure S1.....	4
Figure S2.....	5
Figure S3.....	6
Figure S4.....	7
Figure S5.....	8
Figure S6.....	9
Legends	10
Supplemental Tables	11
Table S1	11
Table S2	13
Table S3	22
Table S4	23
Table S5	24
Table S6	25

Supplemental Methods

Patient Derived Xenografts

Between one and 15 experiments were performed per xenograft. The radiation dose was 20Gy in 2Gy/fraction either daily or BID in almost all of experiments. The TMZ doses were more varied. However, since no relationship was seen between TMZ dose and survival benefit in either the TMZ alone or TMZ+RT cohorts, all dose levels were included and treated equally. Full treatment data and PDX experimental results will be made available online at the Mayo Clinic PDX National Resource website:

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

RNAseq library preparation was performed using the Illumina TruSeq RNA Sample Prep Kit V2. Mouse RNAseq reads were filtered out using Xenome 1.0.1¹, and mouse-only reads were excluded. RNAseq data were processed using a comprehensive bioinformatics pipeline from the Mayo Clinic: Map-RSeq². Gene expression was quantified using RPKM. The full dataset is in the process of being deposited in cBioPortal (<http://www.cbioportal.org>).

TCGA

Available clinical and molecular variables such as age, sex, treatment, prior treatment, surgery, IDH1, and MGMT were used. However, not all clinical variables had complete and well annotated data (e.g., performance status). MGMT promotor methylation was assessed using the same method as in TCGA utilizing the Illumina Infinium HumanMethylation27 and 450 BeadChip arrays^{3,4}. In the 5 samples where both 27k and 450k data were available for the same probes, the values were averaged. MGMT promoter methylation was scaled by the standard deviation to make hazard ratios comparable with gene expression and the signatures.

Gene signature development

Some PDXs had treatment responses assessed in multiple experiments and we treated each experiment, rather than each PDX, as an individual data point. Only genes that were available in both the PDX and TCGA samples were retained for analysis. Genes were ranked by the absolute value of the correlation coefficient in order to identify potential biomarkers for predicting treatment response. We did not utilize a more complex statistical model due to the significant technical differences between RNAseq (PDXs) and microarrays (TCGA) to prevent overfitting. Furthermore, since the correlation coefficients in the top genes were very similar, genes were weighted equally by utilizing a simple average. Genes with negative correlations were multiplied by -1 to invert their signs. Thus, increasing values are associated with increased treatment sensitivity, and decreasing values are associated with treatment resistance, allowing for combining of genes that were positively and negatively correlated to treatment resistance.

Centering and scaling was performed using the “scale” function in R applied to each gene with the default parameters. This function subtracts the mean expression for each gene (centering) and divides each gene by the standard deviation (scale).

The formulas for the three gene signatures are below (assuming centered and scaled gene expression data):

$$\text{Chemo-GS} = (-\text{GPRASP1} + -\text{MGMT}) / 2$$

$$\text{RT-GS} = (\text{CHGA} + \text{MAPK8}) / 2$$

$$\text{ChemoRT-GS} = (-\text{GPRASP1} + -\text{MGMT} + \text{CHGA} + \text{MAPK8} + -\text{ATP6V0A2} + -\text{FGF7}) / 6$$

Gene Set Enrichment Analysis

The ranked gene list by Spearman's correlation coefficient from above was also utilized to run GSEA pre-ranked. The default parameters were used, and the following gene sets were included for assessment: H1:Hallmarks, C2:Canonical Pathways, and C5:GO Biological Processes. Volcano plots were created by plotting the normalized enrichment scores versus the -log of the p-values from GSEA.

References

1. Conway T, Wazny J, Bromage A, et al. Xenome--a tool for classifying reads from xenograft samples. *Bioinformatics*. 2012;28(12):i172-178.
2. Kalari KR, Nair AA, Bhavsar JD, et al. MAP-RSeq: Mayo Analysis Pipeline for RNA sequencing. *BMC Bioinformatics*. 2014;15:224.
3. Bady P, Sciuscio D, Diserens AC, et al. MGMT methylation analysis of glioblastoma on the Infinium methylation BeadChip identifies two distinct CpG regions associated with gene silencing and outcome, yielding a prediction model for comparisons across datasets, tumor grades, and CIMP-status. *Acta Neuropathol*. 2012;124(4):547-560.
4. Brennan CW, Verhaak RG, McKenna A, et al. The somatic genomic landscape of glioblastoma. *Cell*. 2013;155(2):462-477.

Figure S1

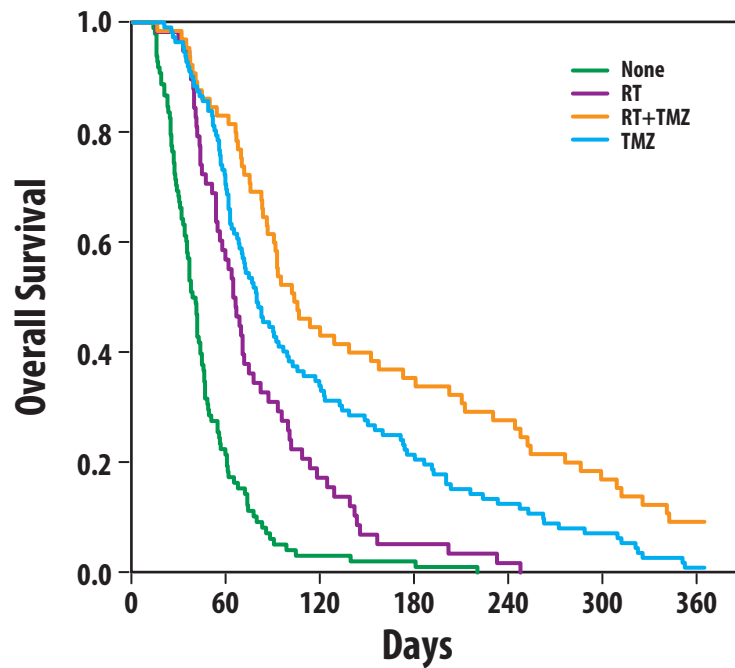
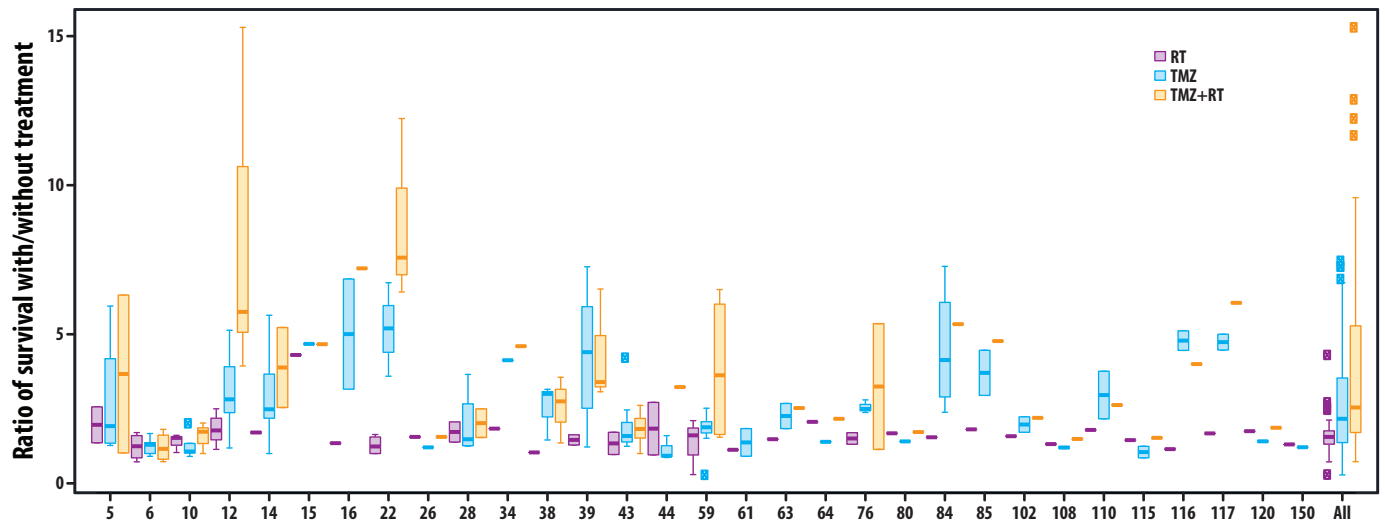


Figure S2

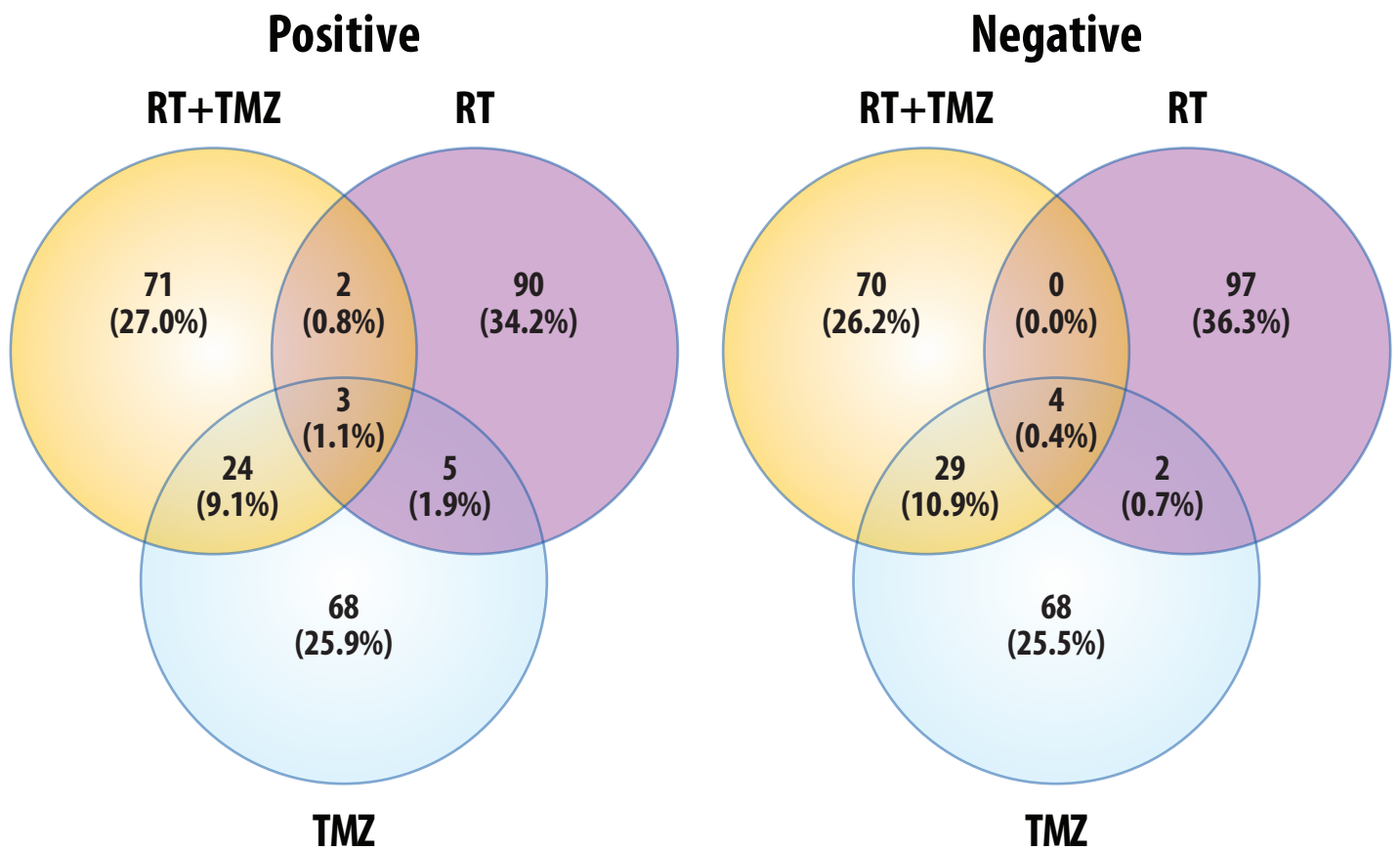


Figure S3

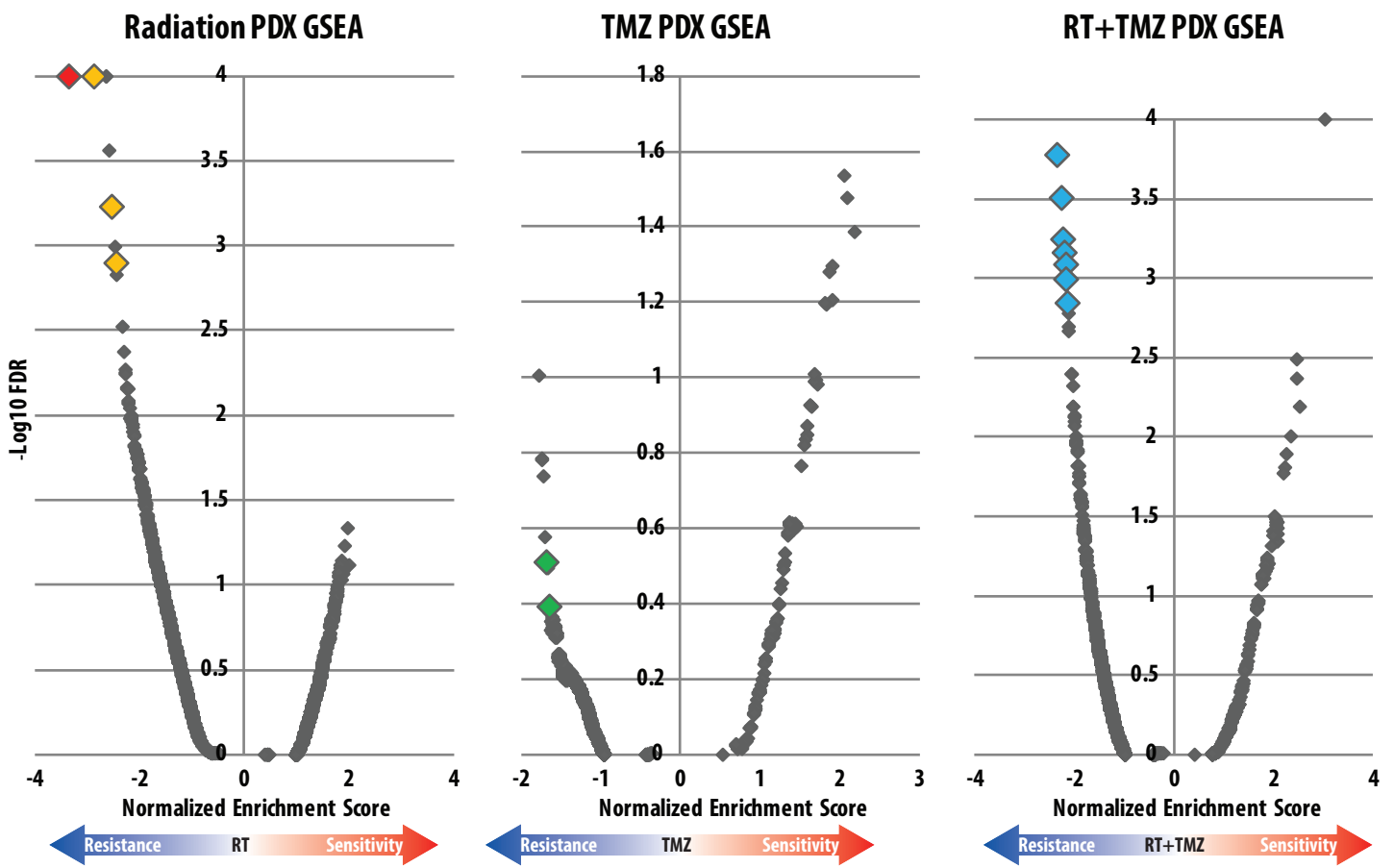


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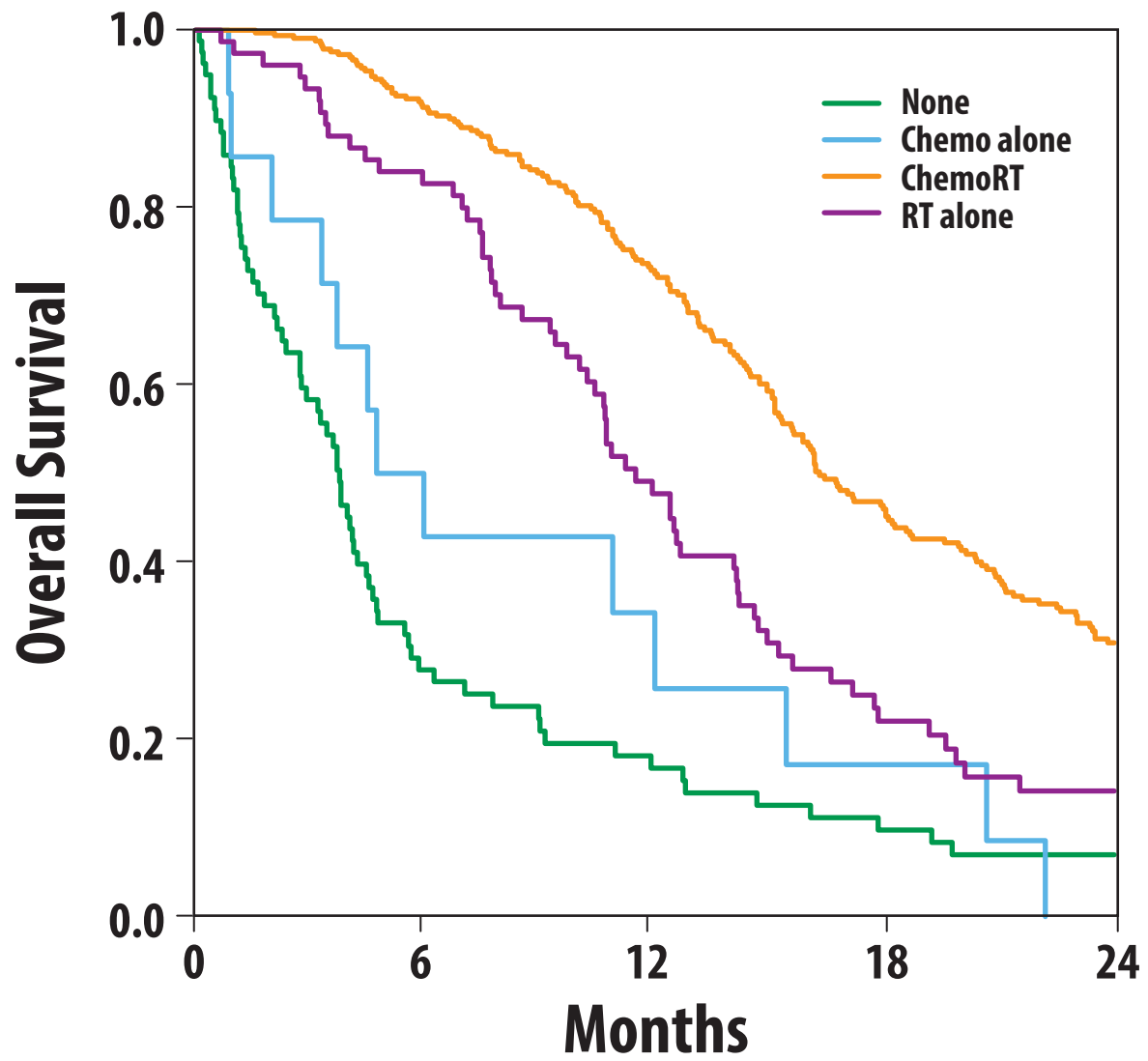


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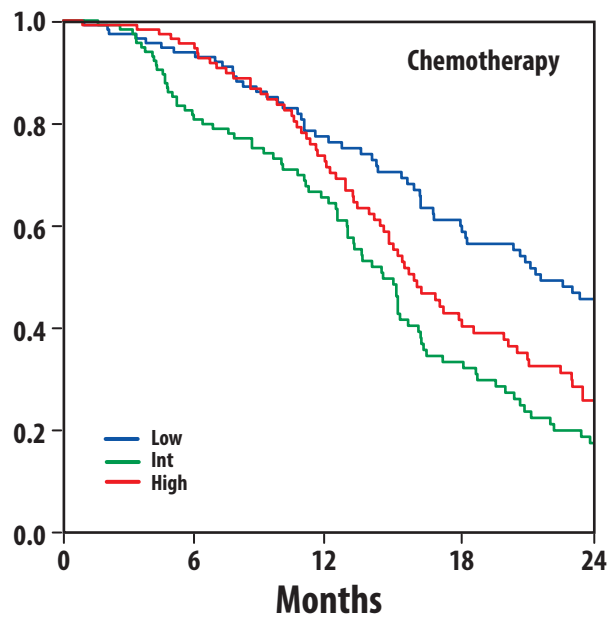
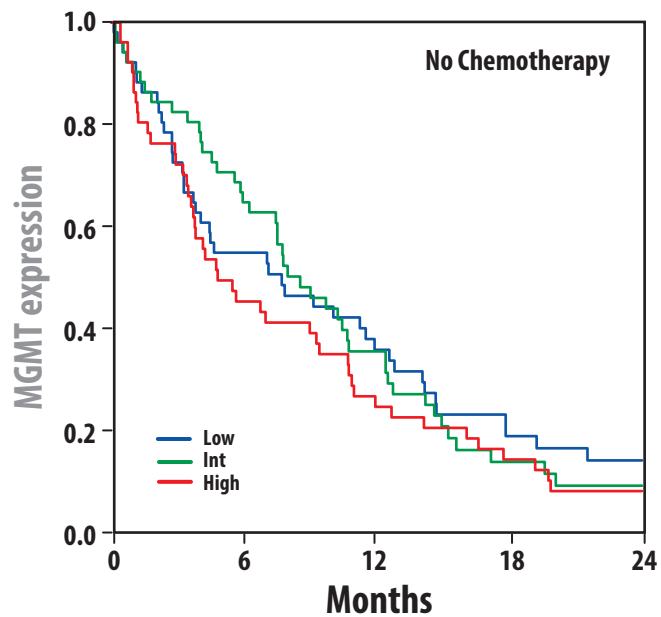
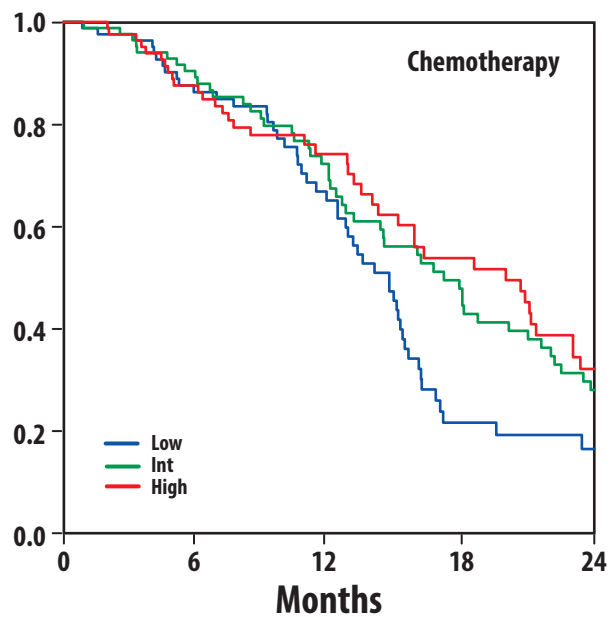
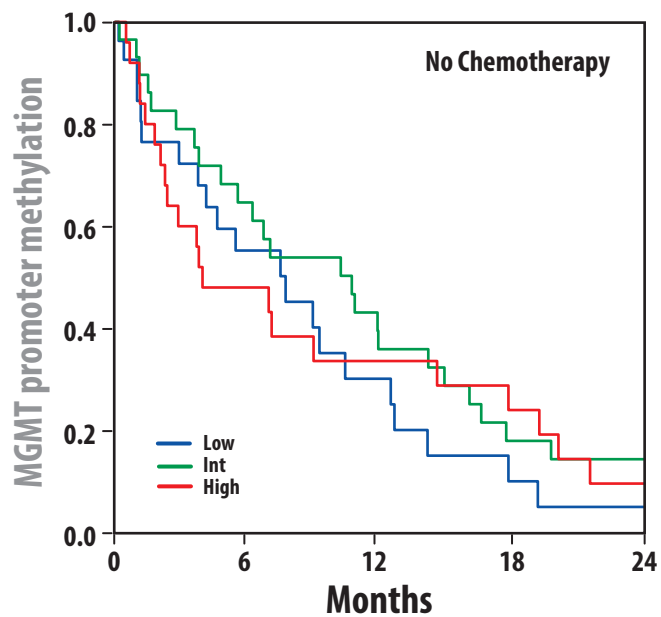
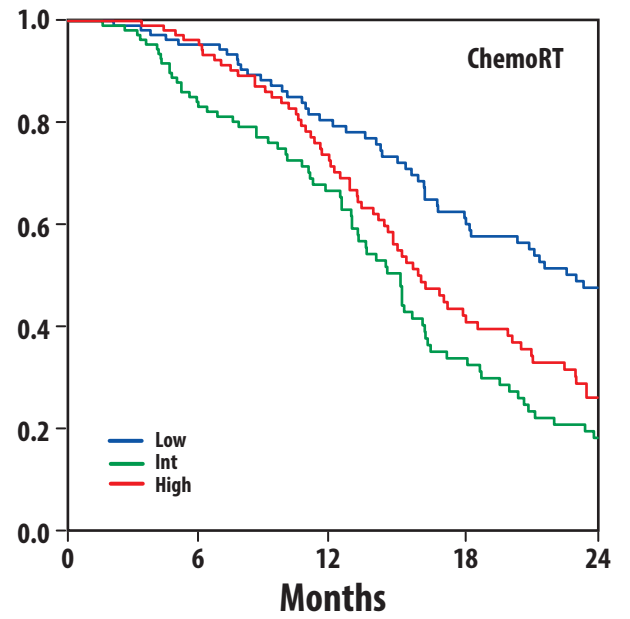
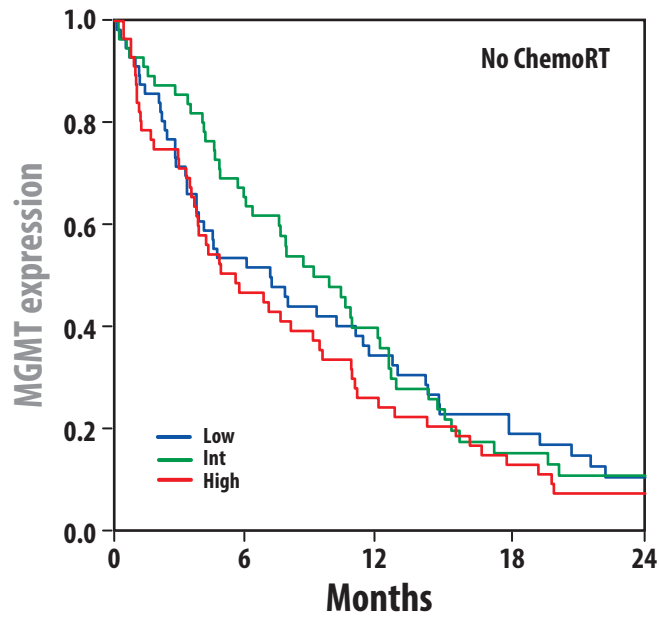
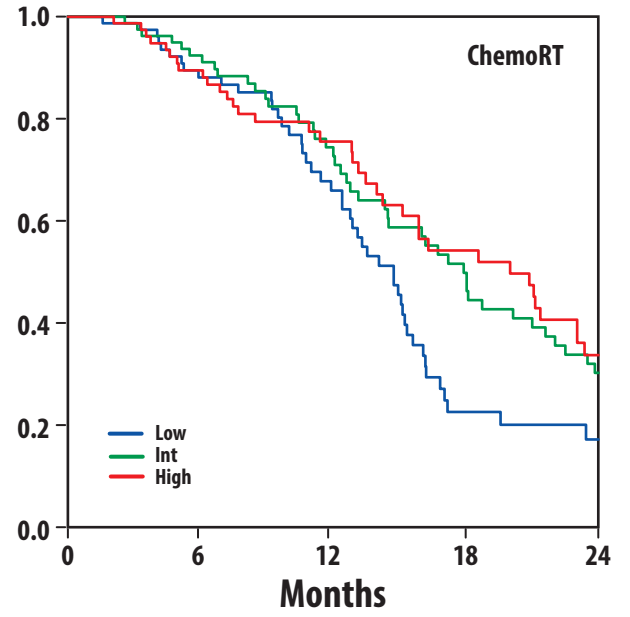
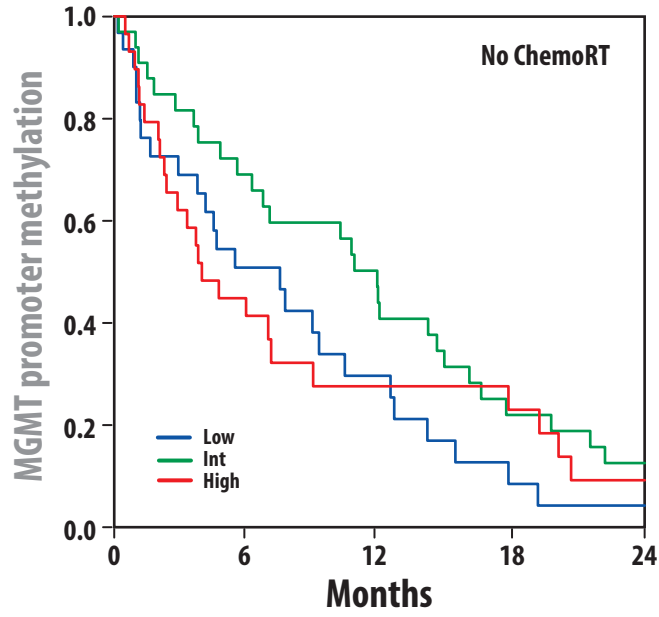


Figure S6



Supplemental Figure Legends

Figure S1: (A) Boxplots showing range of survival ratios between treated and untreated PDXs for RT, TMZ, and RT+TMZ. (B) Kaplan Meier curves showing survival of the PDXs with no treatment, RT, TMZ, and RT+TMZ.

Figure S2: Overlap between the top 100 most positively and negatively correlated genes with treatment response

Figure S3: GSEA was performed on gene lists ranked by correlation to treatment response in the PDX. Red = EMT; Orange = ECM; Green = RAS signaling; Blue = DNA replication.

Figure S4: Kaplan Meier curves showing survival in TCGA with no treatment, RT, chemotherapy, and ChemoRT

Figures S5: Assessment of performance of MGMT promoter methylation and expression in TCGA. Chemotherapy is defined as alkylating chemotherapy with or without RT. No chemotherapy is defined as RT alone or no treatment. Kaplan-meier curves showing that both MGMT promoter methylation and expression are not prognostic in patients who did not receive chemotherapy, and borderline prognostic in patients who did receive chemotherapy.

Figure S6: Assessment of performance of MGMT promoter methylation in TCGA. ChemoRT is defined as alkylating chemotherapy with RT. No ChemoRT is defined as chemo alone, RT alone, or no treatment. Kaplan-meier curves showing that both MGMT promoter methylation and expression are not prognostic in patients who did not receive ChemoRT, and prognostic or borderline prognostic in patients who did receive ChemoRT.

Table S1: Clinical and genomic characteristics of the PDXs

	Gender	Age	MGMT	IDH1	IDH2	EGFR	P53	PTEN	EGFR Amplification
GBM5	M	57	M	wt	wt	wt	wt	wt	no
GBM6	M	65	U	wt	wt	wt	ins/del	wt	yes
GBM10	M	41	U	wt	wt	wt	wt	ins/del	no
GBM12	M	69	M	wt	wt	ins/del	splice	wt	yes
GBM14	M	58	U	wt	wt	wt	wt	frameshift	no
GBM15	M		M	wt	wt	ins/del	wt	wt	yes
GBM16	F		M	wt	wt	wt	wt	wt	no
GBM22	M	80	M	wt	wt	wt	ins/del	wt	no
GBM26	M	49	U	wt	wt	ins/del	wt	wt	yes
GBM28	M	68	U	wt	wt	wt	ins/del	ins/del	no
GBM34	F	46	U	wt	wt	wt	wt	wt	yes
GBM38	F	72	U	wt	wt	ins/del	wt	wt	yes
GBM39	M	51	M	wt	wt	wt	wt	ins/del	yes
GBM43	M	69	U	wt	wt	wt	ins/del	wt	no
GBM44	F	80	U	wt	wt	wt	wt	wt	no
GBM59	F	83	M	wt	wt	wt	wt	wt	yes
GBM61	F	45	U	wt	wt	wt	wt	wt	yes
GBM63	F	50	M	wt	wt	wt	ins/del	wt	yes
GBM64	F	64	U	wt	wt	wt	wt	ins/del	yes
GBM76	M	38	M	wt	wt	wt	wt	ins/del	
GBM80	M	49	U	wt	wt	wt	wt	splice	
GBM84	F	49	M	wt	wt	ins/del	wt	frameshift	yes
GBM85	M	78	M	wt	wt	wt	ins/del	ins/del	
GBM102	M	68	M	wt	wt	wt	wt	wt	
GBM108	M	62	U	wt	wt	wt	wt	ins/del	
GBM110	F	64	U	wt	wt	wt	wt	wt	
GBM115	F	76	U	wt	wt	wt	wt	wt	
GBM116	F	56	M	wt	wt	wt	ins/del	frameshift	
GBM117	M	63	M	wt	wt	wt	ins/del	wt	
GBM120	M	57	U	wt	wt	wt	ins/del	wt	
GBM150	M	65	U	wt	wt	wt	wt	wt	

M=methylated

U=unmethylated

wt=wildtype

ins/del=in-frame insertion or deletion

splice=splice site mutation

Table S1:

	Grade	PDX Start	Primary vs. Recurrent	Days in Flank	OS from Dx (yr)	OS from PDX (yr)
GBM5	IV	2000	PRIMARY	20	2.57	2.57
GBM6	IV	2000	PRIMARY	30	1.05	1.05
GBM10	IV	2001	RECURRENT	30	2.50	0.62
GBM12	IV	2001	PRIMARY	20	0.24	0.24
GBM14	IV	2001	RECURRENT	30	0.90	0.38
GBM15	IV	2002	PRIMARY	30		
GBM16	IV	2002	PRIMARY	20		
GBM22	IV	2002	PRIMARY	40	0.21	0.21
GBM26	IV	2002	PRIMARY	40	0.73	0.73
GBM28	IV	2002	PRIMARY	30	0.67	0.50
GBM34	IV	2003	PRIMARY	60	0.88	0.88
GBM38	IV	2003	PRIMARY	60	1.38	1.38
GBM39	IV	2003	PRIMARY	30	2.41	2.41
GBM43	IV	2003	PRIMARY	20	0.26	0.26
GBM44	IV	2003	PRIMARY	30	1.40	1.36
GBM59	IV	2004	PRIMARY	30	1.03	1.03
GBM61	IV	2006	PRIMARY	120	2.88	2.88
GBM63	IV	2006	PRIMARY	60	1.34	1.34
GBM64	IV	2006	RECURRENT	90	1.02	0.13
GBM76	IV	2007	RECURRENT	30	3.23	1.62
GBM80	IV	2007	PRIMARY	120	0.98	0.98
GBM84	IV	2007	PRIMARY	30	6.30	6.29
GBM85	IV	2008	PRIMARY	30	0.13	0.13
GBM102	IV	2008	RECURRENT	90	1.75	0.36
GBM108	IV	2009	PRIMARY	60	0.67	0.67
GBM110	IV	2009	PRIMARY	120	2.16	2.16
GBM115	IV	2009	PRIMARY	120	0.34	0.34
GBM116	IV	2009	PRIMARY	60	0.87	0.87
GBM117	IV	2009	PRIMARY	90	0.81	0.81
GBM120	IV	2009	RECURRENT	60	0.76	0.15
GBM150	IV	2011	RECURRENT	90	1.22	1.22

Table S2: Top genes correlated with treatment benefit in the PDXs

Top 100 genes correlated with TMZ benefit

Negatively Correlated			Positively Correlated		
Gene	Spearman's Rho	P-value	Gene	Spearman's Rho	P-value
GPRASP1	-0.482497195	7.16E-08	TAC1	0.459133457	3.55E-07
MGMT	-0.472157143	1.47E-07	TRPC7	0.382735439	3.12E-05
PNPLA2	-0.468490489	1.90E-07	EPB41L3	0.357637075	0.00011
ELAC2	-0.45792981	3.84E-07	PITX2	0.329096833	0.0004
TRAF1	-0.450900032	6.07E-07	CRX	0.327476346	0.00042
RPH3AL	-0.447517169	7.53E-07	SERPINB7	0.316538797	0.00067
PMVK	-0.445481307	8.57E-07	KRT81	0.309204795	0.00091
PTPRT	-0.445303711	8.67E-07	CCIN	0.309038503	0.00092
NAALADL1	-0.444165737	9.31E-07	NDST4	0.299942552	0.00131
SCAP	-0.443781839	9.54E-07	RENBP	0.292083216	0.00178
SF3B4	-0.443011299	1.00E-06	SLC24A3	0.290266321	0.00191
SIPA1	-0.442768663	1.02E-06	DACH1	0.286523176	0.00219
RIC8A	-0.437523341	1.41E-06	GPR31	0.284034682	0.00241
CD3EAP	-0.43498484	1.65E-06	RALYL	0.28193429	0.0026
ITIH5	-0.433518494	1.80E-06	SLC22A1	0.280699797	0.00272
LASP1	-0.43267322	1.89E-06	MS4A6A	0.280063821	0.00278
ME1	-0.432474394	1.92E-06	GYP A	0.27948918	0.00284
MRM1	-0.431814339	2.00E-06	GIP	0.27711994	0.0031
CPT2	-0.429342774	2.32E-06	FABP2	0.27573438	0.00325
FES	-0.428279166	2.47E-06	NOV	0.275273067	0.00331
CUTC	-0.428139876	2.49E-06	MYL2	0.272592005	0.00364
CD82	-0.427219508	2.63E-06	PPARG	0.272030209	0.00371
CHD1L	-0.426440407	2.76E-06	TAAR5	0.26983701	0.00401
HCN2	-0.421320856	3.73E-06	AQP9	0.269403144	0.00407
DNAJC12	-0.420858906	3.83E-06	PRTN3	0.268824488	0.00416
PRCC	-0.420532933	3.90E-06	SLC6A12	0.260356263	0.00556
ANXA11	-0.420511529	3.91E-06	KLK2	0.258159597	0.00599
RSU1	-0.420490125	3.91E-06	ALOXE3	0.257502732	0.00613
GRN	-0.420464441	3.92E-06	LUZP2	0.255661378	0.00651
DOCK9	-0.420451598	3.92E-06	PRSS12	0.255551409	0.00654
HLTF	-0.419347157	4.18E-06	PAX3	0.254765999	0.00671
UBE2NL	-0.417698566	4.60E-06	GRIK1	0.254348849	0.00681
TIE1	-0.417392949	4.68E-06	MRPS17	0.254014948	0.00688
LRP8	-0.417266699	4.72E-06	SLCO1B1	0.252787564	0.00717
CCDC85B	-0.416804945	4.85E-06	CPVL	0.252516676	0.00723
PDE1C	-0.416675952	4.88E-06	APOA4	0.251295059	0.00753
NPR1	-0.415712777	5.16E-06	UGT2B17	0.250159721	0.00781
ERAL1	-0.415220487	5.31E-06	KLK3	0.249226483	0.00805
TNKS2	-0.415220487	5.31E-06	SLC17A4	0.248850366	0.00815
TRPM4	-0.415029058	5.37E-06	SERPINA10	0.246091972	0.00891
SPOCK2	-0.414325805	5.59E-06	KCNE2	0.245308751	0.00914
HSF4	-0.413947868	5.71E-06	TPSG1	0.24498129	0.00923
SLC12A9	-0.412626336	6.16E-06	EIF5	0.243103245	0.0098
DRP2	-0.412471138	6.21E-06	TBX3	0.241074911	0.01045
LRRC6	-0.412365801	6.25E-06	IL2RA	0.236630642	0.01201

G6PC3	-0.412330962	6.26E-06	ZG16	0.235603022	0.01239
IGSF1	-0.411920338	6.41E-06	ADM2	0.235107629	0.01258
POLDIP2	-0.411372068	6.61E-06	PRR4	0.23163076	0.014
LHPP	-0.409016228	7.55E-06	ARHGAP24	0.229531585	0.01491
SULF1	-0.408988589	7.56E-06	FCN1	0.229059766	0.01513
POLL	-0.407184092	8.37E-06	GRIN2B	0.226779055	0.01619
LGR4	-0.407104132	8.41E-06	KLK8	0.226440088	0.01636
CES3	-0.406853125	8.52E-06	MYCT1	0.22374226	0.01772
TSSC4	-0.405456033	9.21E-06	ZIC3	0.221485268	0.01893
ROR2	-0.405220192	9.34E-06	CIDEA	0.221401856	0.01898
CABYR	-0.404813916	9.55E-06	BDKRB1	0.2211034	0.01914
PFKM	-0.404813916	9.55E-06	GBAS	0.220119747	0.0197
CC2D1A	-0.403974884	1.00E-05	TH	0.219834919	0.01986
TM9SF3	-0.403148693	1.05E-05	EFCAB1	0.218392474	0.02071
RUSC1	-0.401111043	1.17E-05	RELN	0.216683142	0.02175
WWC1	-0.400912375	1.18E-05	SIX3	0.216369786	0.02194
KLK6	-0.400829753	1.19E-05	RIMS2	0.215706265	0.02236
FCRL2	-0.400470372	1.21E-05	ABCC9	0.215603527	0.02243
POMGNT1	-0.399531436	1.28E-05	LILRP2	0.215538687	0.02247
STAT5A	-0.398743773	1.33E-05	PLCL1	0.214945761	0.02285
MAPK4	-0.397410724	1.43E-05	INHBE	0.214677438	0.02303
HPS6	-0.397030851	1.46E-05	KRT2	0.212862072	0.02424
HPS1	-0.396475065	1.51E-05	NFIL3	0.21281674	0.02427
DNAH2	-0.396461127	1.51E-05	HMHB1	0.212302273	0.02462
ADAMTS13	-0.396342504	1.52E-05	CDH5	0.21059002	0.02583
C1orf54	-0.396218114	1.53E-05	HSPB8	0.210339219	0.02601
PADI4	-0.394863552	1.64E-05	BTBD3	0.210308204	0.02604
C21orf62	-0.394781098	1.65E-05	TPK1	0.210250375	0.02608
ADAMTS1	-0.393927897	1.73E-05	SLC17A7	0.209489245	0.02664
GPR137	-0.392780649	1.84E-05	PTGDR	0.209078169	0.02694
APH1A	-0.39251096	1.87E-05	RUNX1T1	0.208844178	0.02712
FHIT	-0.391549943	1.96E-05	MAN1A1	0.20869007	0.02723
LYL1	-0.389876091	2.15E-05	IRF8	0.208277946	0.02755
GPR3	-0.389617233	2.18E-05	ATXN7L1	0.208103603	0.02768
SCAMP4	-0.389574346	2.18E-05	CCL19	0.207616827	0.02805
SLC25A28	-0.3894288	2.20E-05	TMEM30B	0.207526522	0.02812
KIAA1279	-0.388902264	2.26E-05	CRNN	0.207367202	0.02825
GTF2E1	-0.388123888	2.35E-05	GCG	0.206743741	0.02873
AMT	-0.386278202	2.59E-05	STAC	0.206621396	0.02883
SEC24C	-0.385892877	2.65E-05	FGF13	0.2065454	0.02889
FUT2	-0.385855113	2.65E-05	SLC6A4	0.206450643	0.02897
RNMTL1	-0.385854871	2.65E-05	RBM39	0.203488925	0.0314
AP2B1	-0.385695961	2.67E-05	GH2	0.203346033	0.03152
PTPRR	-0.385539371	2.69E-05	APOC3	0.202491544	0.03226
PTPRN2	-0.385067137	2.76E-05	DLGAP2	0.202181529	0.03253
SLC39A1	-0.384814121	2.80E-05	CRIP1	0.201201227	0.0334
PSPN	-0.384446488	2.85E-05	B3GNT3	0.20028767	0.03423
UBE2M	-0.384231935	2.88E-05	CALCR	0.199757997	0.03472
ETFB	-0.384035019	2.91E-05	GPR32	0.199723966	0.03475

PRKAB1	-0.383829542	2.94E-05	SYT1	0.198643084	0.03576
NUDCD3	-0.383088967	3.06E-05	CDH17	0.197432882	0.03693
PLAGL1	-0.382868001	3.10E-05	SOX14	0.197085647	0.03727
PRR7	-0.382405331	3.17E-05	SLCO1A2	0.196973407	0.03738
ARR3	-0.382181428	3.21E-05	CSHL1	0.196729976	0.03762
PNPO	-0.382014492	3.23E-05	LAMB4	0.196091088	0.03825

Top 100 genes correlated with RT benefit

Negatively Correlated			Positively Correlated		
Gene	Spearman's Rho	P-value	Gene	Spearman's Rho	P-value
CD7	-0.321774058	0.01377	CHGA	0.467107816	0.00022
PTHLH	-0.319706258	0.01443	MAPK8	0.408350583	0.00146
GRPR	-0.317439472	0.01518	RCOR3	0.403047329	0.00171
NRAP	-0.309611124	0.01803	RBM14	0.392934146	0.00228
CCL24	-0.308321503	0.01854	NPPA	0.392121006	0.00233
PDE3A	-0.302504408	0.021	CLCN6	0.392070826	0.00234
DPP4	-0.300435524	0.02194	ZBTB17	0.388494213	0.00258
COL5A2	-0.2930973	0.02556	RAB33A	0.388327217	0.00259
MDFIC	-0.291131822	0.02661	HNRNPR	0.385287594	0.00282
RGS4	-0.291023667	0.02667	TSPAN15	0.383986808	0.00292
TXK	-0.290639265	0.02688	FUBP1	0.381032657	0.00317
PTGES	-0.290260798	0.02709	BMP8B	0.380477665	0.00322
HGF	-0.28906749	0.02775	RSBN1	0.380477665	0.00322
APOBEC3C	-0.286419994	0.02928	PRPF38B	0.378936022	0.00335
HOXB8	-0.283368092	0.03112	PCDH11X	0.377105478	0.00352
FOXC1	-0.280581108	0.03289	TRIM17	0.37538224	0.00369
HNF1B	-0.280457173	0.03297	SIM2	0.374804417	0.00375
JAK3	-0.277928005	0.03465	ZNF492	0.374510725	0.00378
A4GALT	-0.276224588	0.03583	RALYL	0.373541358	0.00387
KCNN4	-0.274349401	0.03715	PIK3C2B	0.37301611	0.00393
PTPRR	-0.273455347	0.0378	CHRNA4	0.3694994	0.00431
AXL	-0.273192317	0.03799	GNMT	0.368255964	0.00445
CD44	-0.272851433	0.03824	ADM2	0.367085231	0.00459
TNFSF4	-0.272065886	0.03883	PCDH11Y	0.365442837	0.00479
KRT7	-0.271298912	0.0394	TRIT1	0.365431223	0.00479
WNT11	-0.269849313	0.04051	DLK2	0.363837716	0.00499
GCNT1	-0.266908037	0.04283	MYB	0.361750755	0.00527
C6orf15	-0.264055471	0.04519	AZGP1	0.359726108	0.00555
RRAS	-0.263860387	0.04535	PLCL1	0.359477871	0.00558
C8orf4	-0.262757752	0.04629	PAIP2B	0.359281658	0.00561
CHRNA9	-0.261844199	0.04709	FBXO42	0.358586325	0.00571
IGFBP6	-0.259866733	0.04884	DCT	0.35784938	0.00582
COL4A5	-0.259489468	0.04918	FAT2	0.356429465	0.00603
CPN2	-0.259110725	0.04952	SPTB	0.356288185	0.00605
PROCR	-0.256622548	0.05183	ARVCF	0.353714731	0.00645
NPTX2	-0.256398953	0.05204	GAL3ST1	0.352079476	0.00672
OLFML3	-0.256104303	0.05232	HDAC2	0.351248101	0.00686
CTSZ	-0.255923102	0.0525	BRSK2	0.348473142	0.00735
C3AR1	-0.255417746	0.05298	C20orf27	0.347548156	0.00751
CHST4	-0.25156351	0.05679	KLK2	0.347126047	0.00759
LTBP2	-0.251539274	0.05682	GTDC1	0.346499838	0.00771
ORAI3	-0.249958791	0.05844	MADCAM1	0.346181385	0.00777
TGM2	-0.248181321	0.06032	SLC6A12	0.34600741	0.0078
PHACTR2	-0.247386466	0.06117	PBOV1	0.345020465	0.00799
CLCF1	-0.246469188	0.06217	FCHO1	0.343650233	0.00826

SLCO3A1	-0.245685991	0.06303	SRRM1	0.341998239	0.0086
MYL9	-0.245624066	0.0631	LUZP2	0.341680909	0.00866
PVRL3	-0.244196362	0.0647	TEX14	0.341366022	0.00873
EPHA5	-0.243588895	0.06539	FYN	0.341319915	0.00874
IL18	-0.242689809	0.06642	BAIAP3	0.340888255	0.00883
PVRL2	-0.242654718	0.06646	GALNT8	0.340063825	0.00901
COL4A6	-0.24202584	0.06719	OMG	0.338914951	0.00926
EMP3	-0.241236406	0.06811	RNF43	0.337291484	0.00962
PLS3	-0.238954774	0.07084	ADRBK2	0.337064979	0.00967
TRPA1	-0.238487418	0.07141	RAPGEF4	0.335831664	0.00996
MTMR11	-0.237819874	0.07223	RAP2A	0.335461669	0.01005
EMP1	-0.237228133	0.07297	SHC2	0.333981691	0.0104
ASB9	-0.235872063	0.07467	REC8	0.33385836	0.01043
LIF	-0.235537889	0.07509	RENBP	0.333537129	0.01051
CH25H	-0.235190485	0.07554	BCAS1	0.332614778	0.01074
CXCL1	-0.234699031	0.07617	CPM	0.33225505	0.01083
ANXA1	-0.23451484	0.07641	GPR17	0.3319864	0.0109
MFSD5	-0.234032363	0.07703	ABCG4	0.3279077	0.01198
CAV1	-0.233934332	0.07716	KHDRBS3	0.327876782	0.01199
KCNJ15	-0.233543174	0.07767	SLC17A6	0.327183581	0.01218
SHH	-0.23310109	0.07825	BLCAP	0.326581802	0.01235
PLAGL1	-0.232588186	0.07892	RANBP9	0.326581802	0.01235
TGFBR2	-0.23219959	0.07944	NPTX1	0.326031526	0.0125
ARSJ	-0.232109876	0.07956	MAZ	0.325286821	0.01272
BANK1	-0.231463731	0.08042	SPEN	0.324238503	0.01303
LRRC17	-0.231123224	0.08088	STC2	0.323462749	0.01326
DUSP6	-0.230938226	0.08113	PPY2	0.323155091	0.01335
VNN1	-0.230501691	0.08173	PODXL2	0.322943522	0.01341
SERPINA5	-0.230116124	0.08225	INSM1	0.322696859	0.01349
SNCA	-0.229457207	0.08316	LCP1	0.322490593	0.01355
ITGA4	-0.22928955	0.08339	VEZF1	0.320970218	0.01403
CAV2	-0.229229678	0.08347	JARID2	0.320476893	0.01418
CTGF	-0.22890504	0.08392	ELAVL3	0.31873784	0.01475
MYO1B	-0.228603728	0.08434	PPP1R16B	0.318269258	0.0149
TFPI	-0.228594928	0.08435	SSTR5	0.317346519	0.01521
BDNF	-0.227889241	0.08534	BAALC	0.316530285	0.01549
ADM	-0.226929953	0.0867	SP4	0.316036959	0.01566
ARPC1B	-0.226559958	0.08723	TRIB3	0.314590802	0.01617
COL13A1	-0.226386062	0.08748	ITGA2B	0.314572848	0.01617
NRP2	-0.226313295	0.08759	FBXO11	0.314495315	0.0162
FCGR2C	-0.22612829	0.08785	PDIA2	0.3141407	0.01633
CDSN	-0.226077953	0.08792	SGK3	0.313570329	0.01653
SLC7A8	-0.224012369	0.09094	GRIN2B	0.312623181	0.01688
TFPI2	-0.223422512	0.09182	DOCK3	0.31239868	0.01697
TCTN2	-0.223326184	0.09196	NKX2-2	0.312090351	0.01708
KRT16	-0.223086537	0.09232	CAND2	0.311967019	0.01713
ETV4	-0.222675016	0.09294	GPD1	0.311830209	0.01718
PSORS1C1	-0.221780267	0.09429	HBQ1	0.311571167	0.01728
CRIM1	-0.22014672	0.09681	SYN3	0.311194601	0.01742

BCAS4	-0.219591729	0.09767	RIC8B	0.310918702	0.01752
CLEC2B	-0.219204387	0.09828	TIA1	0.310178713	0.01781
RIN1	-0.21882357	0.09888	P2RX7	0.309993715	0.01788
ATP8B3	-0.218399103	0.09955	ST18	0.309386806	0.01812
GPR3	-0.218129528	0.09998	ARHGDIG	0.309239847	0.01817
HOXB9	-0.218082859	0.10006	ACOXL	0.308399306	0.01851

Top 100 genes correlated with TMZ+RT benefit

Negatively Correlated

Positively Correlated

Gene	Spearman's Rho	P-value	Gene	Spearman's Rho	P-value
ATP6V0A2	-0.701888657	7.33E-11	MBNL2	0.550767978	2.00E-06
FGF7	-0.693214594	1.56E-10	TAC1	0.547379652	2.38E-06
CD3EAP	-0.692545057	1.65E-10	EIF5	0.545109178	2.67E-06
ELAC2	-0.691558057	1.79E-10	FGF13	0.522166909	8.15E-06
COX10	-0.690034584	2.04E-10	SYT1	0.517736376	1.00E-05
PFKM	-0.689496323	2.13E-10	UBE2B	0.511309909	1.35E-05
CPT2	-0.689189256	2.19E-10	PTBP2	0.504686041	1.81E-05
THAP10	-0.687807456	2.46E-10	DDX3X	0.491284774	3.25E-05
RIC8A	-0.682455723	3.83E-10	CRX	0.4752574	6.32E-05
GAPVD1	-0.682148656	3.93E-10	S100A8	0.472255941	7.13E-05
ISG20L2	-0.681161656	4.26E-10	AP3S1	0.468583772	8.26E-05
FUBP3	-0.680350122	4.55E-10	PITX2	0.465138025	9.47E-05
GPR107	-0.679187656	5.00E-10	NOVA1	0.464789305	9.60E-05
FAM120A	-0.677323322	5.80E-10	KCNE2	0.462768532	0.0001
SLC25A44	-0.677279455	5.83E-10	SNAP25	0.461828304	0.00011
PTGER1	-0.674554483	7.24E-10	AMELX	0.458483509	0.00012
SCAP	-0.673528855	7.85E-10	SIX3	0.449984304	0.00017
NCAPG	-0.672870855	8.27E-10	SLC6A4	0.444725198	0.00021
TSSC4	-0.671379388	9.30E-10	MYT1L	0.44206637	0.00023
DDX31	-0.670458188	1.00E-09	PFN2	0.438820236	0.00026
RSU1	-0.670107255	1.03E-09	EPHA7	0.438447369	0.00026
APH1A	-0.669800188	1.05E-09	DACH1	0.438206103	0.00026
SLC12A9	-0.669558921	1.07E-09	ZIC3	0.435534308	0.00029
ATP2A2	-0.668067455	1.20E-09	ANKS1B	0.435376702	0.00029
TOR1B	-0.667146255	1.29E-09	RRAGB	0.430332035	0.00035
SLC39A1	-0.666663721	1.34E-09	TRPC7	0.426907943	0.00039
FLOT2	-0.664470388	1.59E-09	NPTN	0.421185834	0.00048
CIZ1	-0.663044721	1.77E-09	PRMT8	0.420637501	0.00049
SENP3	-0.661882254	1.93E-09	CLK4	0.418751234	0.00052
SV2A	-0.661487454	1.99E-09	NDST4	0.418002733	0.00053
NAALADL1	-0.661327622	2.02E-09	SLC22A1	0.416849761	0.00055
RNMTL1	-0.66078536	2.10E-09	POU6F2	0.416097301	0.00057
HLTF	-0.658372921	2.52E-09	RBM39	0.412916967	0.00063
TATDN2	-0.657429787	2.70E-09	TBR1	0.4118203	0.00065
WDR46	-0.65593832	3.01E-09	BCL11B	0.411184234	0.00067
MEPCE	-0.655587387	3.09E-09	EIF4A2	0.408289033	0.00073
C17orf53	-0.655571245	3.10E-09	AQP9	0.407745453	0.00075
MRM1	-0.655009345	3.23E-09	NRXN3	0.406512433	0.00078
GPRASP1	-0.654973254	3.24E-09	UBE2D3	0.4064905	0.00078
GEMIN4	-0.65363532	3.57E-09	PPP3CB	0.404604233	0.00083
APOC1	-0.653534939	3.60E-09	RELN	0.402685485	0.00088
KIAA0907	-0.65310892	3.71E-09	CXCL12	0.401730679	0.00091
LGR4	-0.65304312	3.73E-09	CCIN	0.400947236	0.00093
SNX27	-0.652823787	3.79E-09	EPB41L3	0.399397287	0.00098
AP2B1	-0.652297387	3.94E-09	ELAVL4	0.398199699	0.00102

ZNF324B	-0.650408231	4.52E-09	ELAVL2	0.397432033	0.00104
CEACAM1	-0.650010484	4.65E-09	GPM6B	0.396445032	0.00108
PTPRCAP	-0.649593679	4.79E-09	MBD5	0.393286632	0.00119
PMVK	-0.649511853	4.82E-09	RALYL	0.388088381	0.0014
MMACHC	-0.649445076	4.84E-09	GRIN1	0.387781365	0.00141
PLXNA1	-0.648459053	5.20E-09	MATR3	0.386246032	0.00148
CDK5RAP2	-0.64837132	5.23E-09	NR1D1	0.384754565	0.00155
ERMAP	-0.64817392	5.31E-09	IL26	0.382049338	0.00169
TRIM44	-0.647472053	5.58E-09	SCRT1	0.381267165	0.00173
COX7A1	-0.647427397	5.60E-09	PCBP3	0.377801698	0.00192
LASP1	-0.64685792	5.83E-09	RENBP	0.377172833	0.00195
RNF4	-0.646682453	5.91E-09	CXXC4	0.376573431	0.00199
GPR3	-0.646313459	6.07E-09	NNAT	0.376025097	0.00202
RPH3AL	-0.645917191	6.24E-09	ALOXE3	0.374227024	0.00213
INTS3	-0.645892853	6.25E-09	EBF2	0.372446201	0.00225
PNPLA2	-0.64580512	6.29E-09	RIMS1	0.37065143	0.00237
SF3B4	-0.645147119	6.59E-09	EFNA3	0.369554764	0.00245
TCAP	-0.644232265	7.03E-09	CPA4	0.369356614	0.00246
FBXO41	-0.643895576	7.20E-09	KCNK3	0.367418889	0.00261
MCM3AP	-0.643743386	7.28E-09	PPP3R1	0.366155097	0.0027
DHX8	-0.642909919	7.72E-09	PLP1	0.364685563	0.00282
TBRG4	-0.642734453	7.82E-09	PRSS12	0.36407143	0.00287
DOLK	-0.641462319	8.55E-09	GGCX	0.363391496	0.00293
TRAF1	-0.641051898	8.80E-09	POU2AF1	0.362185163	0.00303
SPTLC1	-0.640892052	8.90E-09	GRIA3	0.358807429	0.00333
FTCD	-0.640804099	8.95E-09	NEUROD6	0.358053397	0.00341
COPS7B	-0.640782386	8.97E-09	CNTN5	0.356424447	0.00357
TMPRSS6	-0.640154078	9.37E-09	HMGB1	0.356263163	0.00358
POLDIP2	-0.640124386	9.39E-09	OAZ2	0.354464629	0.00377
PRDM4	-0.640058586	9.43E-09	CDH5	0.353186112	0.0039
GMIP	-0.639685719	9.68E-09	MAP2K4	0.352753829	0.00395
ZNF749	-0.639680135	9.68E-09	CITED2	0.352051962	0.00403
CHMP1A	-0.639137386	1.01E-08	PRPF38B	0.346809895	0.00465
SIPA1L3	-0.638830319	1.03E-08	FEZF2	0.346357476	0.00471
ACOX3	-0.638764519	1.03E-08	DDX5	0.345099095	0.00487
LSG1	-0.638764519	1.03E-08	NR4A2	0.344528828	0.00495
TP53	-0.638523252	1.05E-08	MEF2C	0.342883828	0.00517
VAV2	-0.638435519	1.06E-08	MEMO1	0.340975628	0.00544
DPP3	-0.638368011	1.06E-08	AKAP6	0.340690495	0.00549
RUSC1	-0.638303919	1.07E-08	BTRC	0.338826161	0.00576
CC2D1A	-0.638040719	1.09E-08	SUMO4	0.337426142	0.00598
STARD3	-0.637645919	1.12E-08	FHL1	0.337071494	0.00604
HPS6	-0.637463469	1.13E-08	FMR1	0.335952894	0.00622
SLC2A8	-0.636832576	1.18E-08	SRRM1	0.334636894	0.00644
WFDC1	-0.636560865	1.20E-08	GRIA2	0.333057694	0.00671
GOLGA2	-0.636417652	1.21E-08	MEF2A	0.332597094	0.00679
SMG5	-0.635825452	1.26E-08	NOV	0.332531982	0.0068
SART3	-0.635781585	1.27E-08	MRPS17	0.33165396	0.00696
TSC1	-0.635079719	1.33E-08	GRM5	0.330480473	0.00717

WDR82	-0.634948119	1.34E-08	EIF1	0.33000896	0.00726
ODF2	-0.634838452	1.35E-08	SLC6A12	0.328329795	0.00758
GP5	-0.634776898	1.36E-08	SLITRK5	0.327947227	0.00766
DOLPP1	-0.634399785	1.39E-08	EVI2B	0.3279277	0.00766
PSPN	-0.63389351	1.44E-08	KCNC1	0.32750856	0.00774
DAG1	-0.633763719	1.46E-08	SLIT2	0.327135693	0.00782

Table S3: TCGA Demographics by Treatment

	Chemo	RT	Chemo+RT	None	Total	P-value
Age	68.6 +/- 12.6	59.8 +/- 13.2	55.4 +/- 14.1	64.9 +/- 14.3	58 +/- 14.5	<0.0001
MSP	0.63 +/- 0.461	0.261 +/- 0.39	0.459 +/- 0.458	0.398 +/- 0.45	0.436 +/- 0.454	0.032
MSP Missing	2 (0.143)	42 (0.545)	91 (0.277)	32 (0.39)	167 (0.333)	
IDH1 WT	13 (0.929)	42 (0.545)	239 (0.726)	62 (0.756)	356 (0.709)	0.17
IDH1 Mut	0 (0)	4 (0.052)	23 (0.07)	1 (0.012)	28 (0.056)	
IDH1 Missing	1 (0.071)	31 (0.403)	67 (0.204)	19 (0.232)	118 (0.235)	
Female	4 (0.286)	32 (0.416)	120 (0.365)	38 (0.463)	194 (0.386)	0.31
Male	10 (0.714)	45 (0.584)	209 (0.635)	44 (0.537)	308 (0.614)	
No prior tx	14 (1)	77 (1)	309 (0.939)	82 (1)	482 (0.96)	0.015
Prior tx	0 (0)	0 (0)	19 (0.058)	0 (0)	19 (0.038)	
Missing	0 (0)	0 (0)	1 (0.003)	0 (0)	1 (0.002)	
Biopsy	5 (0.357)	2 (0.026)	52 (0.158)	6 (0.073)	65 (0.129)	0.0004
Resection	9 (0.643)	75 (0.974)	277 (0.842)	74 (0.902)	435 (0.867)	
Resection Missing	0 (0)	0 (0)	0 (0)	2 (0.024)	2 (0.004)	

Table S4: Association of Chemo-GS with clinicopathologic variables

	T1	T2	T3	Total	P-value*
Age	59.9 +/- 13.5	58.7 +/- 13.9	55.3 +/- 15.7	58 +/- 14.5	0.0002
Female	56 (0.333)	63 (0.377)	75 (0.449)	194 (0.386)	0.12
Male	112 (0.667)	104 (0.623)	92 (0.551)	308 (0.614)	
MGMT promoter methylation	0.197 +/- 0.345	0.46 +/- 0.462	0.744 +/- 0.385	0.436 +/- 0.454	0.21
MGMT missing	34 (0.202)	62 (0.371)	71 (0.425)	167 (0.333)	
IDH1 Wildtype	139 (0.827)	112 (0.671)	105 (0.629)	356 (0.709)	<0.0001
IDH1 Mutant	3 (0.018)	8 (0.048)	17 (0.102)	28 (0.056)	
IDH1 Missing	26 (0.155)	47 (0.281)	45 (0.269)	118 (0.235)	
No Radiation	35 (0.208)	32 (0.192)	29 (0.174)	96 (0.191)	0.41
Radiation	133 (0.792)	135 (0.808)	138 (0.826)	406 (0.809)	
No Chemo	54 (0.321)	59 (0.353)	46 (0.275)	159 (0.317)	0.069
Alkylating Chemo	114 (0.679)	108 (0.647)	121 (0.725)	343 (0.683)	
No Chemo and RT	57 (0.339)	64 (0.383)	52 (0.311)	173 (0.345)	0.15
Chemo and RT	111 (0.661)	103 (0.617)	115 (0.689)	329 (0.655)	
No Prior Treatment	159 (0.946)	160 (0.958)	163 (0.976)	482 (0.96)	0.036
Prior Treatment	9 (0.054)	7 (0.042)	3 (0.018)	19 (0.038)	
Prior Treatment Missing	0 (0)	0 (0)	1 (0.006)	1 (0.002)	
Biopsy	25 (0.149)	22 (0.132)	18 (0.108)	65 (0.129)	0.71
Resection	143 (0.851)	145 (0.868)	147 (0.88)	435 (0.867)	
Resection Missing	0 (0)	0 (0)	2 (0.012)	2 (0.004)	

*P-values were assessed with Chemo-GS as a continuous variable as in the rest of the manuscript.

*Spearman's correlation was used to test continuous variables and a T-test was used for binary variables.

Note: T1, T2, T3 refer to the Chemo-GS tertiles, with T1 the lowest, and T3 the highest tertile.

Table S5: Association of RT-GS with clinicopathologic variables

	T1	T2	T3	Total	P-value*
Age	59.8 +/- 13.2	60.3 +/- 12	53.9 +/- 17.1	58 +/- 14.5	0.009
Female	70 (0.417)	68 (0.407)	56 (0.335)	194 (0.386)	0.02
Male	98 (0.583)	99 (0.593)	111 (0.665)	308 (0.614)	
MGMT promoter methylation	0.454 +/- 0.453	0.325 +/- 0.431	0.534 +/- 0.459	0.436 +/- 0.454	<0.0001
MGMT missing	52 (0.31)	54 (0.323)	61 (0.365)	167 (0.333)	
IDH1 Wildtype	127 (0.756)	125 (0.749)	104 (0.623)	356 (0.709)	0.0008
IDH1 Mutant	1 (0.006)	4 (0.024)	23 (0.138)	28 (0.056)	
IDH1 Missing	40 (0.238)	38 (0.228)	40 (0.24)	118 (0.235)	
No Radiation	31 (0.185)	36 (0.216)	29 (0.174)	96 (0.191)	0.61
Radiation	137 (0.815)	131 (0.784)	138 (0.826)	406 (0.809)	
No Chemo	54 (0.321)	58 (0.347)	47 (0.281)	159 (0.317)	0.41
Alkylating Chemo	114 (0.679)	109 (0.653)	120 (0.719)	343 (0.683)	
No Chemo and RT	57 (0.339)	63 (0.377)	53 (0.317)	173 (0.345)	0.52
Chemo and RT	111 (0.661)	104 (0.623)	114 (0.683)	329 (0.655)	
No Prior Treatment	165 (0.982)	160 (0.958)	157 (0.94)	482 (0.96)	0.16
Prior Treatment	2 (0.012)	7 (0.042)	10 (0.06)	19 (0.038)	
Prior Treatment Missing	1 (0.006)	0 (0)	0 (0)	1 (0.002)	
Biopsy	18 (0.107)	28 (0.168)	19 (0.114)	65 (0.129)	0.12
Resection	150 (0.893)	139 (0.832)	146 (0.874)	435 (0.867)	
Resection Missing	0 (0)	0 (0)	2 (0.012)	2 (0.004)	

*P-values were assessed with RT-GS as a continuous variable as in the rest of the manuscript.

*Spearman's correlation was used to test continuous variables and a T-test was used for binary variables.

Note: T1, T2, T3 refer to the RT-GS tertiles, with T1 the lowest, and T3 the highest tertile.

Table S6: Association of ChemoRT-GS with clinicopathologic variables

	T1	T2	T3	Total	P-value*
Age	60.3 +/- 13.7	58.2 +/- 13.6	55.4 +/- 15.7	58 +/- 14.5	0.004
Female	70 (0.417)	62 (0.371)	62 (0.371)	194 (0.386)	0.65
Male	98 (0.583)	105 (0.629)	105 (0.629)	308 (0.614)	
MGMT promoter methylation	0.266 +/- 0.397	0.495 +/- 0.463	0.639 +/- 0.432	0.436 +/- 0.454	<0.0001
MGMT missing	29 (0.173)	54 (0.323)	84 (0.503)	167 (0.333)	
IDH1 Wildtype	138 (0.821)	122 (0.731)	96 (0.575)	356 (0.709)	<0.0001
IDH1 Mutant	3 (0.018)	5 (0.03)	20 (0.12)	28 (0.056)	
IDH1 Missing	27 (0.161)	40 (0.24)	51 (0.305)	118 (0.235)	
No Radiation	32 (0.19)	30 (0.18)	34 (0.204)	96 (0.191)	0.79
Radiation	136 (0.81)	137 (0.82)	133 (0.796)	406 (0.809)	
No Chemo	58 (0.345)	51 (0.305)	50 (0.299)	159 (0.317)	0.21
Alkylating Chemo	110 (0.655)	116 (0.695)	117 (0.701)	343 (0.683)	
No Chemo and RT	60 (0.357)	56 (0.335)	57 (0.341)	173 (0.345)	0.52
Chemo and RT	108 (0.643)	111 (0.665)	110 (0.659)	329 (0.655)	
No Prior Treatment	160 (0.952)	160 (0.958)	162 (0.97)	482 (0.96)	0.46
Prior Treatment	8 (0.048)	7 (0.042)	4 (0.024)	19 (0.038)	
Prior Treatment Missing	0 (0)	0 (0)	1 (0.006)	1 (0.002)	
Biopsy	21 (0.125)	25 (0.15)	19 (0.114)	65 (0.129)	0.63
Resection	147 (0.875)	142 (0.85)	146 (0.874)	435 (0.867)	
Resection Missing	0 (0)	0 (0)	2 (0.012)	2 (0.004)	

*P-values were assessed with ChemoRT-GS as a continuous variable as in the rest of the manuscript.

*Spearman's correlation was used to test continuous variables and a T-test was used for binary variables.

Note: T1, T2, T3 refer to the ChemoRT-GS tertiles, with T1 the lowest, and T3 the highest tertile.