Molecular Features of Cancers Exhibiting Exceptional Responses to Treatment

David A. Wheeler, Naoko Takebe, Toshinori Hinoue, Alina M. Hamilton, Maria F. Cardenas, Peter W. Laird, Katherine A. Hoadley, Linghua Wang, Adrienne Johnson MS, Ninad Dewal, Vincent Miller ,[7] David Piñeyro,[8,10] Manuel Castro de Moura, Manel Esteller, Hui Shen, Jean Claude Zenklusen, Roy Tarnuzer, Lisa M. McShane, James V. Tricoli, Paul M. Williams, Irina Lubensky, Geraldine O'Sullivan-Coyne, Elise C. Kohn, Richard Little, Jeffrey White, Shakun Malik, Lyndsay Harris, Carol Weil, Alice P. Chen, Chris Karlovich, Brian Rodgers, Lalitha Shankar, Paula Jacobs, Tracy Nolan, Donna M. Muzny, Harshavardnan Doddapaneni, Viktoriya Korchina, Julie Gastier-Foster, Jay Bowen, Kristen Leraas, Elijah F. Edmondson, James H. Doroshow, Barbara A. Conley, S. Percy Ivy, Louis M. Staudt.
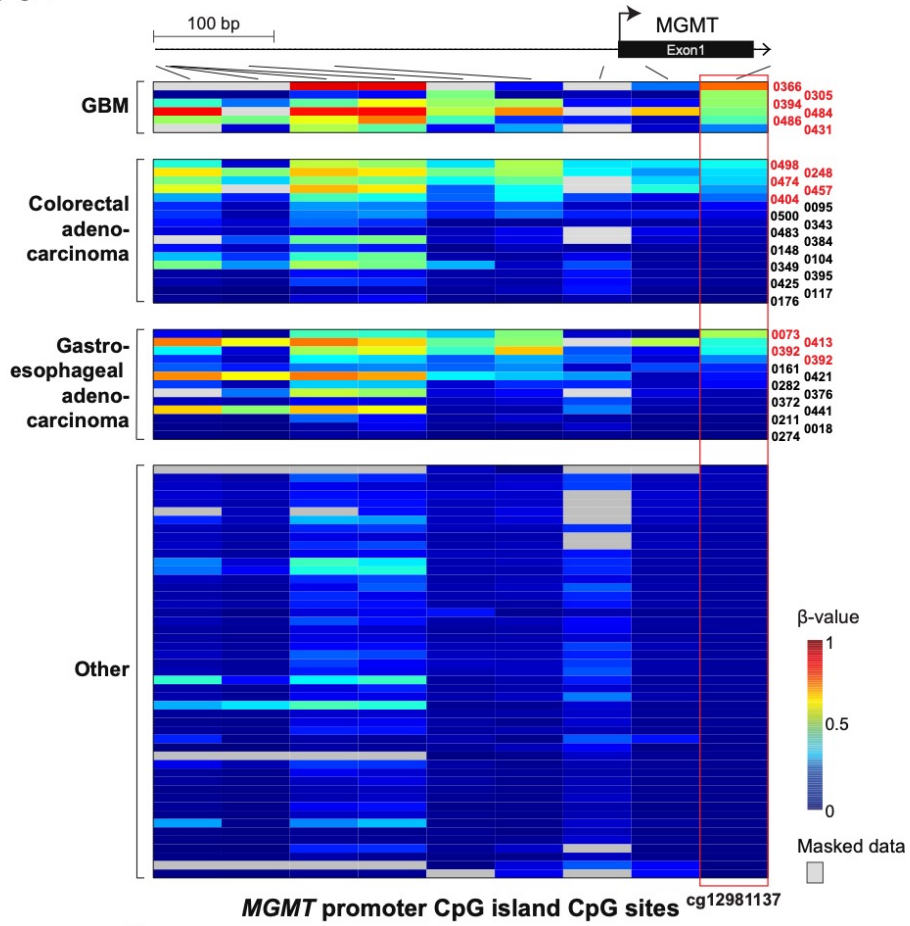
Figure S1

Figure S1. Agents used in treatments leading to exceptional response, Related to STAR Methods. Treatment agents are listed on the left and categorized by mechanism of action as indicated on the right. Treatments involving standard combinations of drugs are evident from systematic correlation across multiple patients. FOLFOX, 5-FU, Folinic acid, oxaliplatin; FOLFIRI, 5-FU, Folinic acid, Irinotecan; FOLFIRINOX, 5-FU, Folinic acid, Irinotecan, Oxaliplatin; EOX, Epirubicin, Oxaliplatin, Capecitabine (Xeloda). Some agents could be classified in more than one category, for example Carmustine alkylates N1 of guanine and N3 of cytosine but also forms inter-strand crosslinks. Note, methoxyamine (TRC102) binds to apurinic/apyrimidinic sites formed in the first step of base excision repair, thereby blocking this repair pathway, leading to double stranded breaks. Further, bound methoxyamine poisons topoisomerase 2, preventing it from re-joining double strand breaks during replication and transcription. It is classified with the alkylating agents because it is often given in combination with alkylating agents. Carmustine is administered infused in a biodegradable, Gliadel, wafer layered onto the site from which the brain tumor was resected. CP, cyclophosphamide; XRT, X-ray treatment. The mechanism of action of Thalidomide is unknown.

Figure S2

A

100 bp

MGMT
Exon1

GBM
0366 0305
0394 0484
0486 0431

Colorectal adeno-carcinoma
0498 0248
0474 0457
0404 0095
0500 0343
0483 0384
0148 0104
0349 0395
0425 0117
0176

Gastro-esophageal adeno-carcinoma
0073 0413
0392 0392
0161 0421
0282 0376
0372 0441
0211 0018
0274

Other

β-value
1

0.5

0

Masked data

MGMT promoter CpG island CpG sites cg12981137

B

MGMT Expression

DNA Methylation (cg12981137)

Brain Tumors

TCGA
LGG
GBM

Exceptional Responders
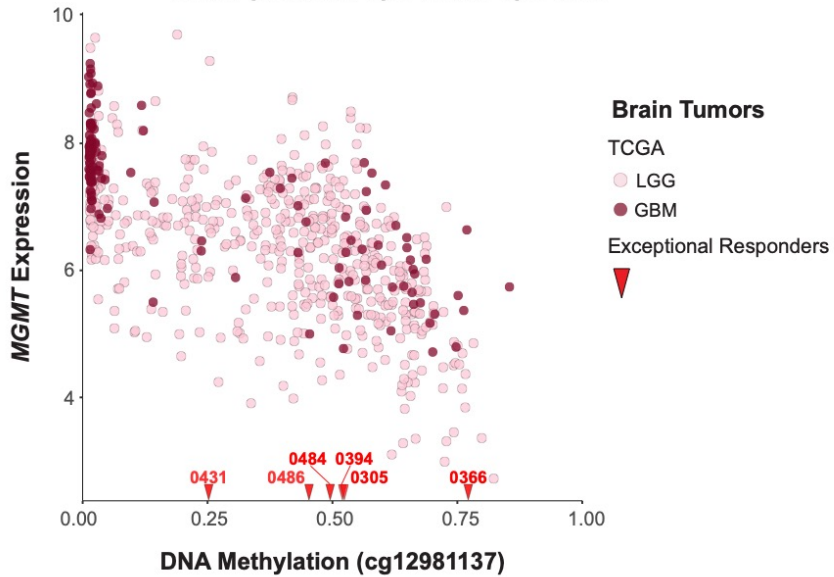
0431 0484 0394
0486 0305 0366

Figure S2. *MGMT* CpG island promoter DNA hypermethylation analysis, Related to Figure 1D.

(A) DNA methylation patterns at the *MGM*T promoter CpG island in the Exceptional Responder tumors. Tumors with a probe success rate lower than 10% were omitted from the analysis (see Table S10). The DNA methylation β values are represented by using a color scale from dark blue (low DNA methylation) to red (high DNA methylation). The red box highlights probe cg12981137, which was selected in a previous TCGA study as the optimal probe for evaluation of *MGMT* epigenetic silencing (See Methods, "Epigenetic silencing in DNA damage repair pathways"). Tumors in each disease group are arranged from top to bottom in order of decreasing DNA methylation level at cg12981137. Patient IDs in the selected disease groups are listed to the right of the heatmap, in which hypermethylated cases are indicated in red.

(B) Scatter plots exhibiting an inverse relationship between DNA methylation (cg12981137) and *MGMT* expression [log2(RSEM+1)] in TCGA brain tumors. The DNA methylation levels of Exceptional Responder cases are indicated by the red triangles on the horizontal axis. Three Exceptional Responder cases (ER0072, ER0151, and ER0256) are missing DNA methylation data.
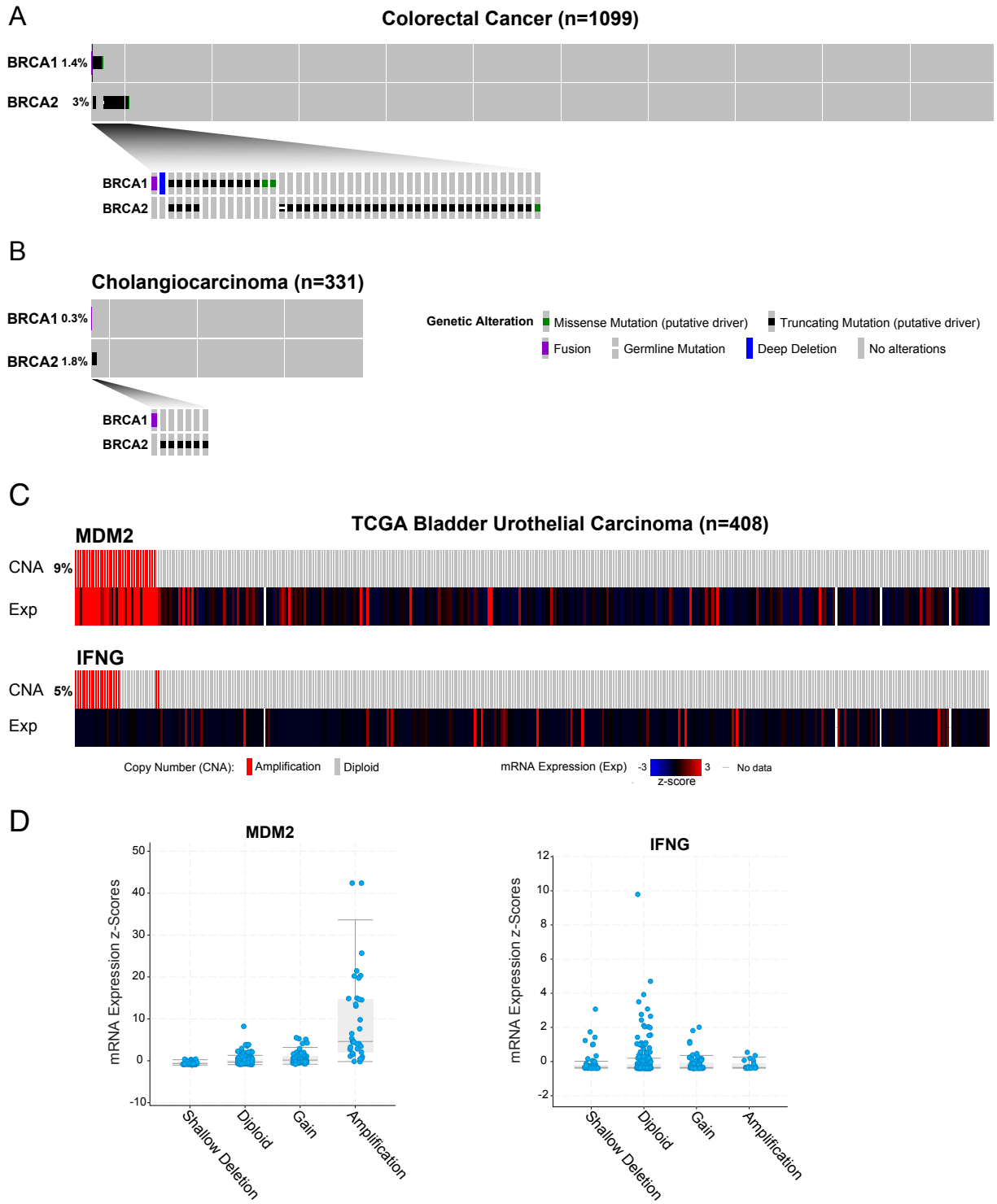
Figure S3

Figure S3. ER Cases 0075, 0399, 0483. Inactivating mutation in *BRCA1* and *BRCA2* are rare in colorectal cancers and cholangiocarcinomas, Related to Table 1.

(A) Colorectal cancers, data from MSKCC Impact (n = 1099). In MSKCC impact, BRCA1 had 13 inactivating of 1099 CRC patients (inactivating = homozygous deletion, nonsense, fs, splice site = 10 of 13 are fs. 5/10 are MLH1 or MSH2 inactivating mutations (<1% of patients), 1.4% of patients.

(**B)** Cholangiocarcinoma, data from 3 studies, MSKCC Impact, TCGA, and the Shanghai Intrahepatic Cholangiocarcinoma study were pooled for a combined cohort of 334 samples. Data is rendered from cBioPortal.

Occurrence of *MDM2* and *INFG* amplification in TCGA bladder cancer, Figures C and D are also related to Figures 4B-F, case 0401.

(C) *MDM2* and *IFNG* are located about 690kb apart on Chr 12q15 and co-amplified in about 5% of bladder cancers from TCGA (copy number alteration [CNA] tracks). *MDM2* is almost always upregulated when amplified, whereas *IFNG* was never upregulated when amplified in this data set (expression [exp] tracks). Nonetheless, in ER0401, *IFNG* was robustly expressed in tumor cells.

(D) Overall relationship between gene copy number and gene expression for MDM2 and IFNG in the TCGA bladder cancer cohort, n=404. The box marks the 25th and 75th quartiles and the whiskers are the 1.5 times the inter-quartile range.
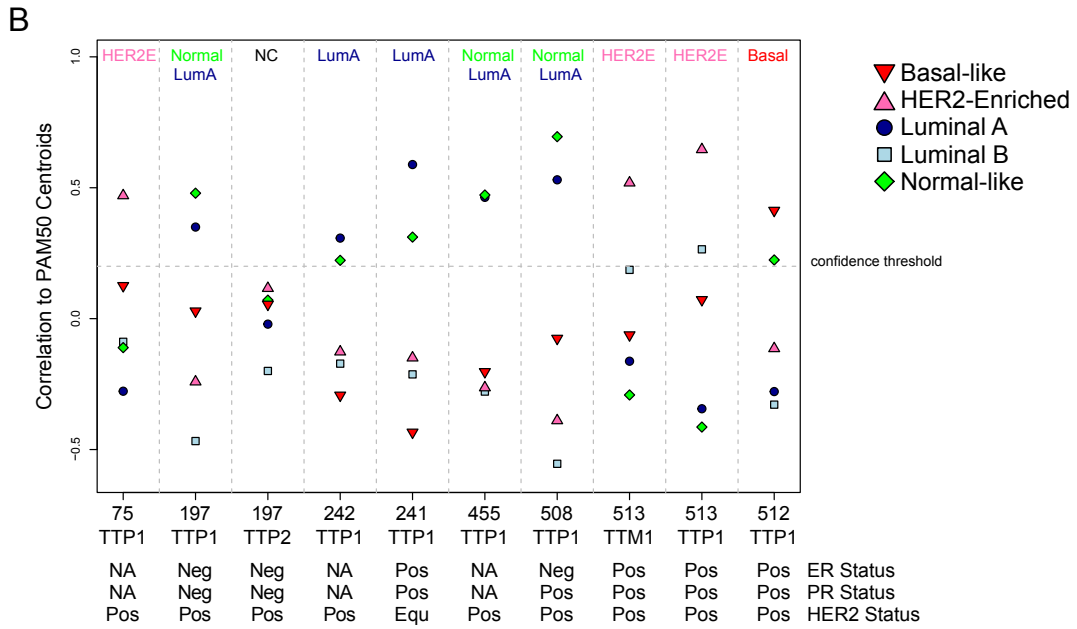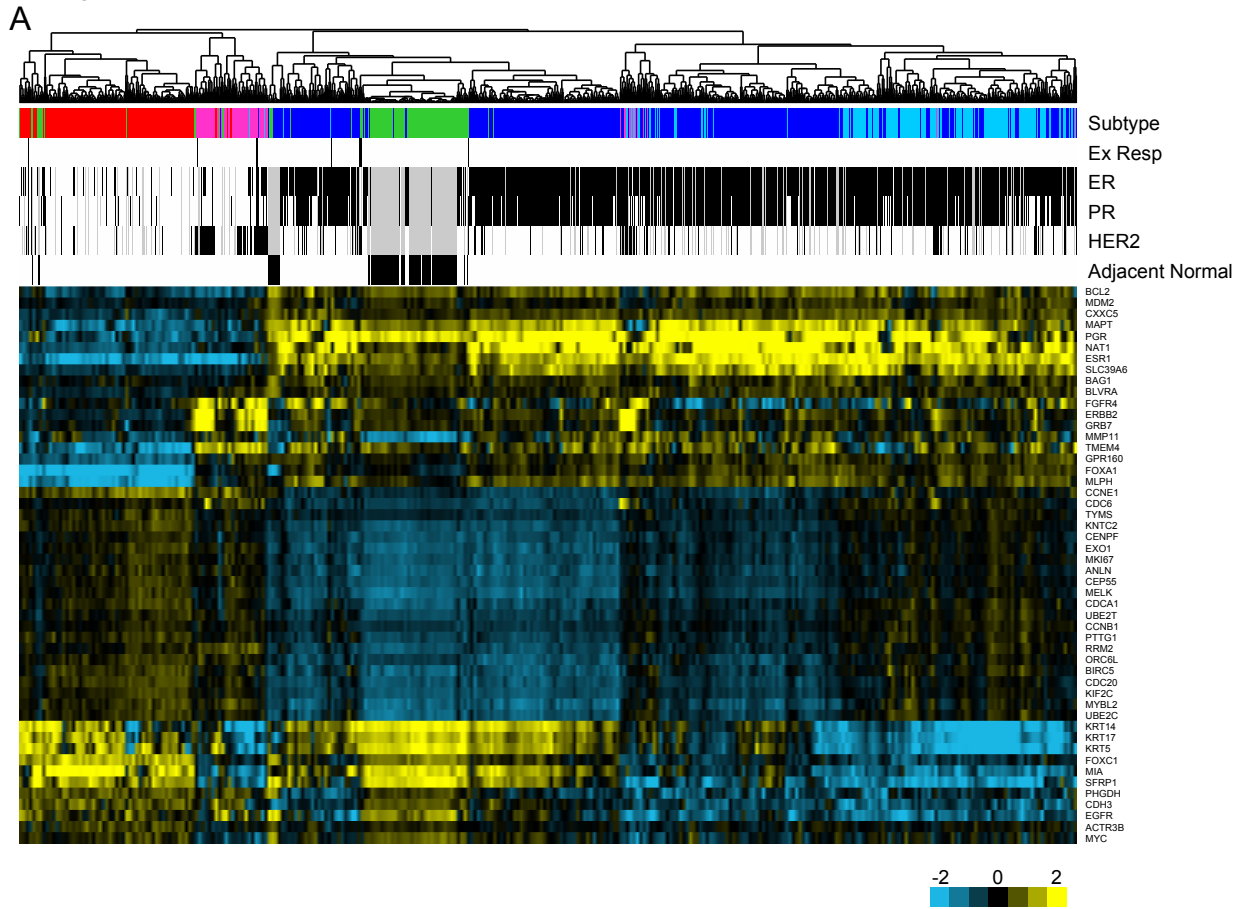
Figure S4

A

B

Figure S4. Breast cancer subtypes among Exceptional Responders, Related to Figures 3A and B.

(**A**) Exceptional responder breast cancer samples co-clustered with the TCGA breast cancer and adjacent normal breast samples for the 50 PAM50 genes. Annotation bars above cluster indicate PAM50 subtype, Exceptional Responder Cohort (Ex Resp), Clinical status for ER, PR and HER2, and indicator adjacent normal samples.

(**B**) The expression profiles of the Exceptional Responder breast cancer cases were fit to the PAM50 classifier based on correlation to centroids of each of 5 subtypes listed in the figure Key at the upper right. Below the plot clinical status for estrogen receptor (ER), progesterone receptor (PR) and Her2 (ERBB2) are given. The final call for the PAM50 subtype, based on this highest correlation, is given at the top of the figure. Note: In this test a normal centroid was included, and 3 of the tumors matched the normal most closely. The commercial Prosigna test does not include a Normal-like centroid. Using the Prosigna criteria the 3 Normal like would match the Luminal A. NC – not well correlated (AC0F, had poorer quality RNA); HER2E -- Her2-enriched.

Figure S5

Matched Tumor Types

B Cell Score

FDR=0.085

B Cell Score

ER
n=38

TCGA
n=35

CD56dim NK Cell Score

FDR=0.011

CD56dim NK Score

ER
n=38
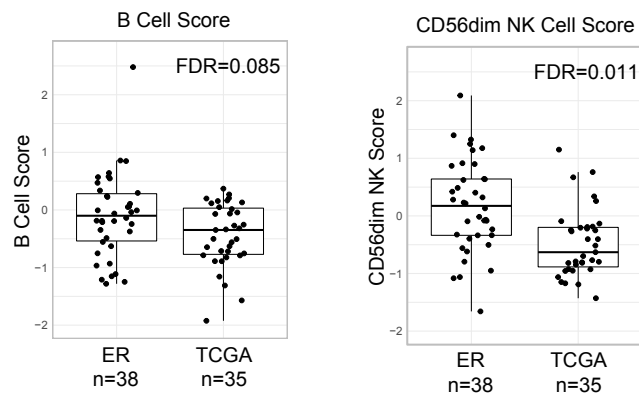
TCGA
n=35

Figure S5. Comparison of immune signatures for B-cell and CD56dim NK cells.

Related to Figure 4A Exceptional Responders (ER) and TCGA FFPE samples compared among the same 6 tumor types shared by both cohorts. "n", is the number of tumors tested. Expression levels were based on NanoString IO360 array with modifications (see also Star Methods, and Tables S3A, B).

Figure S6

A

Lower Grade Glioma (n=507)

ATRX 41%

TP53 49%

IDH1 78%

Glioblastoma (n=378)

ATRX 9%

TP53 33%

IDH1 6%

Genetic Alteration

- ■ Truncating Mutation (putative driver)
- ■ Missense Mutation (putative driver)
- ■ Missense Mutation (unknown significance)
- ■ Inframe Mutation (putative driver)
- ■ Inframe Mutation (unknown significance)
- ■ Amplification ■ Fusion
- ■ Deep Deletion ■ No alterations

B

Pan-Lung Cancer (n=1144)

Missense mutation (n=60)

Truncating mutation (n=18)

ATRX Mutations

density

SNF2_N   He

0   400   800   1200   1600   2000   2492aa

Figure S6. Co-occurrence of ATRX, TP53, IDH1 in LGG and GBM; Related to Figure 5 and Table S5.

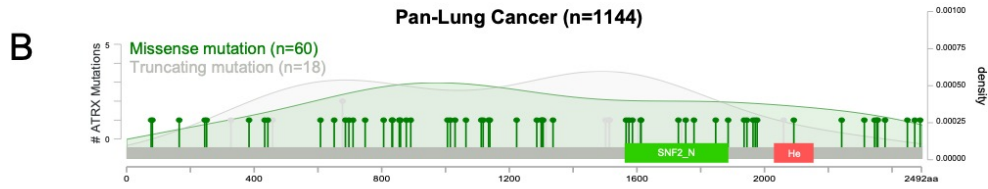**(A)** Mutation occurrence plot showing the TCGA mutation frequencies for the 3 genes is significantly different between low- and high-grade glioma: ATRX, TP53 and IDH1 are all commonly mutated in low grade glioma, and much less frequent in primary GBM in the TCGA data.

(B) ATRX mutations in lung adenocarcinoma (TCGA Pan Lung Cancer) where the gene plays a much smaller role and inactivating mutations are rare compared to missense mutations. Note that in spite of many more missense mutations in this cancer, there is no clustering of missense mutations in the SNF2_N or Helicase domains as was observed in glioma. The distribution of missense mutations mirrors the distribution of truncating mutations.

Table S3. Comparison of immune expression signatures between ER and TCGA samples, Related to Figures 4, S5 and STAR Methods, "Evaluation of Immune Cell Markers."

Signature[a]	ER vs TCGA Comparison[b]	MEAN ER[c]	SD ER[d]	MEAN TCGA[e]	SD TCGA[f]	p Ttest[g]	p Ttest FDR[h]	p LR Group adj[i]	p LR Group adj FDR[j]
B Cell	All	0.0493	0.6617	-0.4348	0.5481	0.0002	0.0016	n/a	n/a
NKCD56dim	All	0.1628	0.7042	-0.4762	0.5893	0	0.0001	n/a	n/a
CD45	All	-0.0537	1.0043	-0.0701	0.8904	0.9325	0.9325	n/a	n/a
CD8 T Cell	All	0.0242	0.6174	-0.2166	0.7439	0.0657	0.1805	n/a	n/a
Cytotoxic Cell	All	-0.025	0.5715	-0.0069	0.6702	0.8791	0.9325	n/a	n/a
Dentritic Cell	All	0.0176	0.5092	-0.0713	0.8108	0.4602	0.6372	n/a	n/a
Exhausted CD8	All	-0.0784	0.6114	-0.1459	0.7444	0.6014	0.7732	n/a	n/a
Macrophage	All	-0.0513	0.5498	0.1127	0.6187	0.1488	0.2976	n/a	n/a
Mast Cell	All	-0.0637	0.7752	-0.0879	0.9114	0.8812	0.9325	n/a	n/a
Neutrophil	All	0.0612	0.5257	-0.3025	0.5935	0.001	0.0061	n/a	n/a
Nk Cell	All	0.0671	0.8084	-0.2025	0.7639	0.0904	0.2034	n/a	n/a
T Cell	All	0.0056	0.6556	-0.1277	0.6944	0.315	0.5154	n/a	n/a
T helper	All	-0.0984	0.7707	0.1735	0.6174	0.0636	0.1805	n/a	n/a
T fh	All	0.0157	0.707	-0.1034	0.6161	0.3817	0.5726	n/a	n/a
Th1	All	0.1027	0.9971	-0.3539	0.9742	0.0217	0.0978	n/a	n/a
T reg	All	-0.019	0.6411	0.1278	0.6225	0.2467	0.4441	n/a	n/a
IFNG	All	-0.0388	0.992	0.0511	1.0992	0.6582	0.7899	n/a	n/a
TNF	All	0.1047	0.8996	-0.2495	1.1643	0.0702	0.1805	n/a	n/a
B Cell	Match Histo	-0.1058	0.7378	-0.4348	0.5481	0.0352	0.3166	0.0095	0.0858
NKCD56dim	Match Histo	0.1648	0.8035	-0.4762	0.5893	0.0002	0.0045	0.0007	0.0118
CD45	Match Histo	-0.1922	1.0241	-0.0701	0.8904	0.5897	0.7582	0.858	0.858
CD8 T Cell	Match Histo	-0.0386	0.5922	-0.2166	0.7439	0.2601	0.6681	0.1322	0.4758
Cytotoxic Cell	Match Histo	-0.0167	0.4746	-0.0069	0.6702	0.9421	0.9421	0.5103	0.7065
Dentritic Cell	Match Histo	-0.0023	0.4934	-0.0713	0.8108	0.6587	0.7673	0.3047	0.6255
Exhausted CD8	Match Histo	-0.1138	0.6193	-0.1459	0.7444	0.8413	0.8908	0.7726	0.858
Macrophage	Match Histo	-0.0559	0.528	0.1127	0.6187	0.2137	0.6681	0.4347	0.652
Mast Cell	Match Histo	0.051	0.7889	-0.0879	0.9114	0.4876	0.7308	0.658	0.7896
Neutrophil	Match Histo	-0.0587	0.5192	-0.3025	0.5935	0.0654	0.3303	0.1087	0.4758
Nk Cell	Match Histo	-0.0861	0.7993	-0.2025	0.7639	0.5278	0.7308	0.3299	0.6255
T Cells	Match Histo	0.0327	0.63	-0.1277	0.6944	0.3043	0.6681	0.0796	0.4758
T helper	Match Histo	-0.087	0.6065	0.1735	0.6174	0.0734	0.3303	0.2613	0.6255
T fh	Match Histo	0.0469	0.6972	-0.1034	0.6161	0.3341	0.6681	0.1792	0.5377
Th1	Match Histo	-0.2541	1.0892	-0.3539	0.9742	0.682	0.7673	0.8392	0.858
T reg	Match Histo	0.0402	0.556	0.1278	0.6225	0.527	0.7308	0.6201	0.7896
IFNG	Match Histo	-0.2017	0.9037	0.0511	1.0992	0.2852	0.6681	0.3822	0.6255
TNF	Match Histo	-0.0403	0.8339	-0.2495	1.1643	0.3776	0.6797	0.3634	0.6255

a, Cell-type signatures from Nanostring IO360

b, Cell-type signatures were compared in two ways: All ER vs All TCGA available; and by using indentical histologies

c, Mean of scores for the ER cases

d, Standard deviation of scores for the ER cases

e, Mean of scores for the TCGA cases

f, Standard deviation of scores for the TCGA cases

g, P-value for standard t-test (assuming equal variance) comparing mean score in ER cases to that in TCGA cases

h, Benjamin- Hochberg FDR-adjusted p-value computed from the 18 unadjusted p-values in column F (p Ttest)

i, P-value for a likelihood ratio (LR) test comparing mean score in ER cases to that in TCGA cases *after* adjusting for tumor type. The LR test tends to be slightly more powerful than the standard ANOVA

j, Benjamin- Hochberg FDR-adjusted p-value computed from the 18 unadjusted p-values in column H (p LR Group adj)

Table S5. Exceptional Responder Brain Cancers, Related to Figure 5 and Figure S6A,B.

Disease	Case ID	Age Gender	Treatment	1p/19q loss	IDH1	Tel maint[a]	TP53	MGMT	DNA Damage Response[b]	L1 Category	Comments
GBM	366	48 F	RT, Gliadel wafer, TMZ	N	-	TERTp	-	dn me	APEX1,[c] EXO5 me	DDR	High profilereation score
GBM	431	51 M	TMZ	N	-	TERTp	-	dn	-	-	Lowest MGMT among GBM, high IFNG
GBM	484	73 M	RT, TMZ	N	-	TERTp	mut		-	-	Highest proliferation score among GBM
GBM	187	26 F	Cediranib Cilengitide	N	R132H	-	mut		-	PG	
GBM	394	27 F	TMZ, RT	N	R132H	ATRX pM1839K	mut	me	DDB2 me	PG	ATRX VUS in SNF2 domain
GBM	486	35 M	RT TMZ, Irinotecan	N	R132C	ATRX fs	mut	dn me	DDB2 me POLE4 me, XRCC4 fs	PG	
Astrocytoma (G3)	151	45 F	Irinotecan Bevacusumab	N	R132H	ATRX fs	mut		-	PG	
Astrocytoma (anaplastic G3/4)	305	28 F	Carbozantinib	N	R132L	ATRX p.I2050N	mut		MLH3 me, DDB2 me	PG	High mutation burden 7.9/Mb, ATRX (VUS) in helicase domain
Astrocytoma (G3/4)	256	25 F	TMZ, Irinotecan Bevacizumab	N	-	-	mut		POLE V411L	PG	MSI and POLE exonuclease domain mutant tumor likely indolent
Low Grade Glioma	72	40 M	Irinotecan	Y	R132H	-	-		POLQ ns	PG	High mutation burden. REV1 R167S (VUS)

Abbreviations: DDR, DNA Damage Response; down reg, down-regulation of mRNA expression; fs, frame shift; me, promoter methylation; ns, nonsense mutation; ss, splice site mutation; VUS, variant of unknown significance. See footnotes to Table 1 for drug definitions.

a, TERTp, promoter region mutations upregulating TERT. Inactivation of ATRX promotes activation of the ALT telomere maintenance pathway.

b, Inactivation of known DNA damage response genes by mutation or DNA methylation.

c, APEX1 is the 3' partner of a translocation with ACTN4. APEX1 transcriptionally silenced (see Figure 1.)

Table S9. Probe success rates for Exceptional Responder cases with methylation data. Related to Star Methods, "DNA Methylation, Data production."

ER Case ID	Sample ID	IDAT barcode	Probe success rate
012	ER-ABCU-TTM1-A-1-0-D-A508-38	200512330144_R01C01	0.104
012	ER-ABCU-TTP1-A-1-0-D-A508-38	200512330144_R02C01	0.199
018	ER-ABDN-TTP1-A-2-0-D-A508-38	200512330144_R03C01	0.577
073	ER-ABDV-NT1-A-2-0-D-A508-38	200512330144_R04C01	0.521
073	ER-ABDV-TTP1-A-1-0-D-A508-38	200512330144_R05C01	0.559
064	ER-ABDX-NT1-A-1-0-D-A508-38	200512330144_R06C01	0.085
064	ER-ABDX-TTP1-A-2-0-D-A508-38	200512330144_R07C01	0.162
099	ER-ABEA-TTM1-A-1-0-D-A508-38	200512330144_R08C01	0.065
095	ER-ABEN-TTP1-A-1-0-D-A76T-38	202915460135_R06C01	0.936
060	ER-ABEO-TTM1-A-1-0-D-A508-38	200514030011_R01C01	0.066
060	ER-ABEO-TTP1-A-1-0-D-A508-38	200514030011_R02C01	0.057
075	ER-ABF0-TTP1-A-1-0-D-A508-38	200514030011_R03C01	0.529
075	ER-ABF0-NB1-A-1-0-D-A76T-38	202915600004_R04C01	0.984
104	ER-ABMI-NT1-A-1-0-D-A732-38	202277800017_R03C01	0.786
104	ER-ABMI-TTP1-A-1-0-D-A76T-38	202915460135_R05C01	0.799
131	ER-ABNX-TTP1-A-1-0-D-A508-38	200514030011_R04C01	0.395
009	ER-ABO1-NT1-A-1-0-D-A508-38	200514030011_R05C01	0.625
009	ER-ABO1-TTP1-A-1-0-D-A508-38	200514030011_R06C01	0.641
100	ER-ABO4-NT1-A-1-0-D-A508-38	200514030011_R07C01	0.464
100	ER-ABO4-TTP1-B-1-0-D-A508-38	200514030011_R08C01	0.098
190	ER-ABOM-TTP1-A-1-0-D-A508-38	200514030133_R01C01	0.233
176	ER-ABON-TTM1-A-1-0-D-A508-38	200514030133_R02C01	0.058
176	ER-ABON-TTP1-A-1-0-D-A508-38	200514030133_R03C01	0.429
137	ER-ABOT-TTM1-A-1-0-D-A508-38	200514030133_R04C01	0.394
120	ER-ABOU-NT1-A-2-0-D-A508-38	200514030133_R05C01	0.119
120	ER-ABOU-TTP1-A-1-0-D-A508-38	200514030133_R06C01	0.155
122	ER-ABPA-TTP1-A-2-0-D-A508-38	200514030133_R07C01	0.067
010	ER-ABS8-TTP1-A-1-0-D-A508-38	200514030133_R08C01	0.086
117	ER-ABSE-TTM1-A-1-0-D-A508-38	200514030157_R01C01	0.393
118	ER-ABSF-TTM1-A-1-0-D-A508-38	200514030157_R02C01	0.558
143	ER-ABU7-TMM1-A-1-0-D-A508-38	200514030157_R03C01	0.610
132	ER-ABV2-TTM1-A-1-0-D-A508-38	200514030157_R04C01	0.223
211	ER-ABV6-TTP1-A-1-0-D-A508-38	200514030157_R05C01	0.706
108	ER-ABWP-TTM1-A-1-0-D-A508-38	200514030157_R06C01	0.409

108	ER-ABWP-NB1-A-1-0-D-A76T-38	202915600004_R03C01	0.986
192	ER-ABXO-TTM1-A-1-0-D-A508-38	200514030157_R07C01	0.059
151	ER-ABXP-TTP1-A-1-0-D-A508-38	200514030157_R08C01	0.055
150	ER-ABXQ-TTP1-A-1-0-D-A508-38	200516380104_R01C01	0.167
197	ER-AC0F-TTP2-A-1-0-D-A732-38	202176290117_R08C01	0.904
072	ER-AC3K-TTP1-A-1-0-D-A508-38	200516380104_R02C01	0.057
222	ER-AC3P-TTP1-A-1-0-D-A508-38	200516380104_R03C01	0.054
078	ER-AC6N-TTM1-A-1-0-D-A76T-38	202915600004_R02C01	0.888
242	ER-AC81-TTP1-A-1-0-D-A508-38	200516380104_R05C01	0.446
274	ER-ACFR-NT1-A-1-0-D-A508-38	200512330133_R06C01	0.790
274	ER-ACFR-TTP1-A-1-0-D-A508-38	200516380104_R07C01	0.367
226	ER-ACGR-TTM1-A-1-0-D-A508-38	200512330133_R01C01	0.745
226	ER-ACGR-NB1-A-1-0-D-A508-38	200516380104_R08C01	0.421
248	ER-ACH5-TTP1-A-8-0-D-A508-38	200512330133_R02C01	0.600
305	ER-ACHG-TTP1-A-1-0-D-A508-38	200512330133_R03C01	0.844
343	ER-AD0G-TTP1-A-1-0-D-A508-38	200512330133_R04C01	0.940
161	ER-AD0W-TTP1-A-1-0-D-A508-38	200512330133_R05C01	0.830
291	ER-AD3L-TTM1-A-1-0-D-A508-38	200512330133_R07C01	0.848
148	ER-AD7D-TTM1-A-1-0-D-A508-38	200512330133_R08C01	0.723
148	ER-AD7D-NT1-A-1-0-D-A732-38	202232360155_R02C01	0.888
309	ER-ADBL-NT1-A-2-0-D-A508-38	200512330139_R01C01	0.897
309	ER-ADBL-TTM1-A-2-0-D-A508-38	200512330139_R02C01	0.895
214	ER-ADBU-TTP1-A-8-0-D-A508-38	200512330139_R03C01	0.697
214	ER-ADBU-TTR1-A-8-0-D-A508-38	200512330139_R04C01	0.836
330	ER-ADC2-TTM1-A-1-0-D-A508-38	200512330139_R05C01	0.905
170	ER-ADIN-NT1-A-1-0-D-A732-38	202176290160_R01C01	0.872
170	ER-ADIN-TTM1-A-1-0-D-A732-38	202277800017_R01C01	0.853
324	ER-ADJ2-TTM1-A-1-0-D-A732-38	202410000035_R02C01	0.721
204	ER-ADRU-NT1-A-1-0-D-A732-38	202176290117_R03C01	0.913
204	ER-ADRU-TTP1-A-1-0-D-A732-38	202277800091_R02C01	0.773
384	ER-ADXD-NT1-A-1-0-D-A732-38	202232360155_R05C01	0.884
384	ER-ADXD-TTP1-A-1-0-D-A732-38	202277800091_R06C01	0.668
356	ER-ADXR-TTP1-A-1-0-D-A732-38	202176290160_R03C01	0.736
356	ER-ADXR-TTM1-A-1-0-D-A732-38	202232360108_R07C01	0.838
372	ER-AE02-TTP1-A-1-0-D-A732-38	202277800091_R01C01	0.625
282	ER-AE2I-TTP1-A-1-0-D-A732-38	202232360108_R06C01	0.800
102	ER-AE67-TTP1-A-1-0-D-A732-38	202277800091_R07C01	0.862
421	ER-AE6D-TTP1-A-1-0-D-A732-38	202277800091_R05C01	0.819
390	ER-AE7D-NT1-A-2-0-D-A732-38	202176290160_R05C01	0.709
390	ER-AE7D-TTM1-A-1-0-D-A732-38	202232360108_R02C01	0.643

059	ER-AE8Q-TTP1-A-1-0-D-A732-38	202232360155_R01C01	0.853
024	ER-AE8R-TTM1-A-1-0-D-A732-38	202176290117_R04C01	0.906
024	ER-AE8R-TTP1-A-1-0-D-A732-38	202232360155_R06C01	0.837
062	ER-AE8U-TTM1-A-1-0-D-A732-38	202232360155_R07C01	0.883
413	ER-AE91-TTP1-A-1-0-D-A732-38	202232360155_R03C01	0.874
322	ER-AEK6-TTM1-A-2-0-D-A732-38	202277800017_R02C01	0.790
349	ER-AEND-TTP1-A-1-0-D-A732-38	202176290160_R06C01	0.799
454	ER-AF1I-TTP1-A-1-0-D-A76T-38	202915460135_R08C01	0.739
454	ER-AF1I-NT1-A-1-0-D-A76T-38	202915590155_R01C01	0.804
457	ER-AFAH-TTP1-A-1-0-D-A732-38	202277800091_R03C01	0.656
376	ER-B0AT-TTP1-A-1-0-D-A732-38	202277800091_R04C01	0.802
399	ER-B0BO-TTM1-A-2-0-D-A732-38	202277800017_R08C01	0.765
428	ER-B0BP-TTM1-A-1-0-D-A732-38	202277800017_R06C01	0.899
441	ER-B0BV-TTM1-A-1-0-D-A732-38	202176290160_R08C01	0.779
441	ER-B0BV-NT1-A-1-0-D-A732-38	202277800017_R07C01	0.784
441	ER-B0BV-NB1-A-1-0-D-A76T-38	202915590155_R02C01	0.978
481	ER-B0C1-TTP1-A-1-0-D-A732-38	202232360108_R03C01	0.683
187	ER-B0C2-TTR1-A-1-0-D-A732-38	202277800017_R05C01	0.907
496	ER-B0C3-NB1-A-1-0-D-A76T-38	202915590155_R03C01	0.982
404	ER-B0CR-NT1-A-1-0-D-A732-38	202176290117_R05C01	0.909
404	ER-B0CR-TTP1-A-1-0-D-A732-38	202232360108_R01C01	0.819
366	ER-B0DO-TTP1-A-1-0-D-A732-38	202277800091_R08C01	0.743
223	ER-B0EH-TTM1-A-1-0-D-A76T-38	202915460135_R04C01	0.924
483	ER-B0FX-TTP1-A-9-0-D-A732-38	202410000035_R03C01	0.639
498	ER-B0FY-TTM1-A-1-0-D-A732-38	202410000035_R01C01	0.776
395	ER-B0GE-TTP1-A-1-0-D-A732-38	202176290117_R01C01	0.885
396	ER-B0GF-TTM1-A-1-0-D-A732-38	202277800017_R04C01	0.822
431	ER-B0GH-TTP1-A-1-0-D-A732-38	202232360108_R08C01	0.813
425	ER-B0GI-TTP1-A-1-0-D-A732-38	202232360155_R08C01	0.873
385	ER-B0GM-TTM1-A-1-0-D-A732-38	202176290117_R07C01	0.927
455	ER-B0GQ-TTP1-A-1-0-D-A76T-38	202915460135_R07C01	0.894
392	ER-B0HF-TTP1-A-1-0-D-A732-38	202176290160_R04C01	0.827
392	ER-B0HF-TTM1-A-1-0-D-A732-38	202232360108_R05C01	0.810
401	ER-B1HQ-TTP1-A-1-0-D-A76T-38	202915590155_R07C01	0.908
394	ER-B1HR-TTP1-A-1-0-D-A732-38	202232360155_R04C01	0.817
402	ER-B1HS-TTP1-A-1-0-D-A732-38	202232360108_R04C01	0.892
486	ER-B1I4-TTP1-A-1-0-D-A732-38	202176290117_R02C01	0.912
466	ER-B1I5-TTM1-A-1-0-D-A732-38	202176290160_R02C01	0.763
474	ER-B1I8-TTP2-A-1-0-D-A732-38	202176290160_R07C01	0.782
500	ER-B1IK-TTM1-A-6-0-D-A732-38	202176290117_R06C01	0.946

521	ER-B1MD-TTP1-A-14-0-D-A76T-38	202915590155_R06C01	0.763
515	ER-B1ME-TTM1-A-1-0-D-A76T-38	202915590155_R05C01	0.898
520	ER-B1MF-TTR1-A-11-0-D-A76T-38	202915600004_R01C01	0.716
484	ER-B1MG-TTP1-A-1-0-D-A76T-38	202915590155_R04C01	0.827
513	ER-B1PV-TTM1-A-10-0-D-A76T-38	202915590155_R08C01	0.812

Table S10. DNA methylation probe success rates for Exceptional Responder cases, Related to Figure S2 and STAR Methods.

Case Number	Tumor tissue	Heatmap sample order	Disease group	MGMT DNA methylation at cg12981137
366	Primary	1	GBM	0.7712
305	Primary	2	GBM	0.5237
394	Primary	3	GBM	0.5199
484	Primary	4	GBM	0.4953
486	Primary	5	GBM	0.4534
431	Primary	6	GBM	0.2526
498	Metastatic	7	Colorectal adenocarcinoma	0.3879
248	Primary	8	Colorectal adenocarcinoma	0.3481
474	Primary	9	Colorectal adenocarcinoma	0.3367
457	Primary	10	Colorectal adenocarcinoma	0.2800
404	Primary	11	Colorectal adenocarcinoma	0.2292
095	Primary	12	Colorectal adenocarcinoma	0.1180
500	Metastatic	13	Colorectal adenocarcinoma	0.0997
343	Primary	14	Colorectal adenocarcinoma	0.0587
483	Primary	15	Colorectal adenocarcinoma	0.0567
384	Primary	16	Colorectal adenocarcinoma	0.0446
148	Metastatic	17	Colorectal adenocarcinoma	0.0376
104	Primary	18	Colorectal adenocarcinoma	0.0355
349	Primary	19	Colorectal adenocarcinoma	0.0329
395	Primary	20	Colorectal adenocarcinoma	0.0296
425	Primary	21	Colorectal adenocarcinoma	0.0290
117	Metastatic	22	Colorectal adenocarcinoma	0.0149
176	Primary	23	Colorectal adenocarcinoma	0.0097
073	Primary	24	Gastroesophageal adenocarcinoma	0.5417
413	Primary	25	Gastroesophageal adenocarcinoma	0.4071
392	Primary	26	Gastroesophageal adenocarcinoma	0.3920
392	Metastatic	27	Gastroesophageal adenocarcinoma	0.2527
161	Primary	28	Gastroesophageal adenocarcinoma	0.1616
421	Primary	29	Gastroesophageal adenocarcinoma	0.1371
282	Primary	30	Gastroesophageal adenocarcinoma	0.1197
376	Primary	31	Gastroesophageal adenocarcinoma	0.0523
372	Primary	32	Gastroesophageal adenocarcinoma	0.0424
441	Metastatic	33	Gastroesophageal adenocarcinoma	0.0390
211	Primary	34	Gastroesophageal adenocarcinoma	0.0178

018	Primary	35	Gastroesophageal adenocarcinoma	0.0164
274	Primary	36	Gastroesophageal adenocarcinoma	0.0115
064	Primary	37	Other	0.0586
396	Metastatic	38	Other	0.0548
481	Primary	39	Other	0.0547
399	Metastatic	40	Other	0.0517
322	Metastatic	41	Other	0.0477
390	Metastatic	42	Other	0.0472
204	Primary	43	Other	0.0439
170	Metastatic	44	Other	0.0413
466	Metastatic	45	Other	0.0404
356	Primary	46	Other	0.0378
402	Primary	47	Other	0.0369
062	Metastatic	48	Other	0.0364
059	Primary	49	Other	0.0349
078	Metastatic	50	Other	0.0337
324	Metastatic	51	Other	0.0332
024	Primary	52	Other	0.0328
521	Primary	53	Other	0.0323
454	Primary	54	Other	0.0311
024	Metastatic	55	Other	0.0308
520	Recurrence	56	Other	0.0306
455	Primary	57	Other	0.0305
356	Metastatic	58	Other	0.0303
385	Metastatic	59	Other	0.0303
428	Metastatic	60	Other	0.0303
102	Primary	61	Other	0.0301
401	Primary	62	Other	0.0300
223	Metastatic	63	Other	0.0287
197	Primary	64	Other	0.0278
226	Metastatic	65	Other	0.0253
515	Metastatic	66	Other	0.0248
214	Recurrence	67	Other	0.0224
309	Metastatic	68	Other	0.0215
132	Metastatic	69	Other	0.0201
137	Metastatic	70	Other	0.0199
012	Primary	71	Other	0.0198
330	Metastatic	72	Other	0.0194
291	Metastatic	73	Other	0.0181
214	Primary	74	Other	0.0174

143	Metastatic	75	Other	0.0171
118	Metastatic	76	Other	0.0158
513	Metastatic	77	Other	0.0147
009	Primary	78	Other	0.0130
075	Primary	79	Other	0.0127
108	Metastatic	80	Other	0.0118
242	Primary	81	Other	0.0098
120	Primary	82	Other	0.0095
131	Primary	83	Other	0.0084
150	Primary	84	Other	0.0084
190	Primary	85	Other	0.0048