

Supporting Information Table 1 – List of publications included in the analysis.

Year of publication	Reference	Number of patients	Case number(s)	Number of regimens
2010	Godbert et al. ⁱ	1	12	3
	Wagner et al. ⁱⁱ	3	29,30,32	5
2011	Villarreal et al. ⁱⁱⁱ	1	24	3
2012	Garrido-Laguna et al. ^{iv}	1	33	1
2013	Falchook et al. ^v	1	14	3
	Artioli et al. ^{vi}	1	54	5
2014	Falchook et al. ^{vii}	1	2	4
	Hagemann et al. ^{viii}	1	7	4
	Loaiza-Bonilla et al. ^{ix}	1	18	2
	Voss et al. ^x	4	42,43,44,53	8
	Wagle et al. ^{xi}	1	61	2
	Subbiah et al. ^{xii}	1	63	4
2015	Wheler et al. ^{xiii}	10	10,25,26,27,50,55,56,60,65,66	30
	Davar et al. ^{xiv}	1	13	3
	Mitsis et al. ^{xv}	1	15	2
	Steenbruggen et al. ^{xvi}	1	16	2
	Subbiah et al. ^{xvii}	1	23	2
	VanderWeele et al. ^{xviii}	1	36	1
	Palma et al. ^{xix}	1	37	4
	Wheler et al. ^{xx}	3	49,51,57	17
	Knoechel et al. ^{xxi}	1	62	1
	Van Allen et al. ^{xxii}	1	64	1
	Kadakia et al. ^{xxiii}	1	68	2
2016	Cheng et al. ^{xxiv}	3	3,8,40	13
	Ikeda et al. ^{xxv}	1	5	5
	Sharabi et al. ^{xxvi}	1	17	2
	Mehnert et al. ^{xxvii}	1	21	1
	Colton et al. ^{xxviii}	1	22	1
	Ravi et al. ^{xxix}	1	34	4
	Kieler et al. ^{xxx}	1	45	3
	Lim et al. ^{xxxi}	1	52	2
	Loaiza-Bonilla et al. ^{xxxii}	1	59	2
	Biswas et al. ^{xxxiii}	1	67	14
	Pietanza et al. ^{xxxiv}	1	69	1
	Wen et al. ^{xxxv}	1	70	1
2017	Lheureux et al. ^{xxxvi}	3	1,41,47	7
	Gibson et al. ^{xxxvii}	1	4	4
	Kollipara et al. ^{xxxviii}	1	6	4
	Knepper et al. ^{xxxix}	1	9	3
	Dos Santos Fernandes et al. ^{xl}	1	11	3
	Wilkes et al. ^{xli}	1	19	1
	George et al. ^{xlii}	1	20	1
	Wander et al. ^{xliii}	1	28	3
	Patel et al. ^{xliv}	1	31	1
	Seim et al. ^{xlv}	1	35	2
	Parachoniak et al. ^{xlvi}	1	38	6
	Rodríguez-Moreno et al. ^{xlvii}	1	39	3
	Sorscher et al. ^{xlviii}	1	46	2
	Pishvaian et al. ^{xl ix}	1	48	1
	Korphaisarn et al. ^l	1	58	3

Supporting Information Table 2 – Description of the 70 exceptional responders reviewed.

Case number	Age	Sex	Diagnosis	Stage/TNM class	Altered biomarkers	Treatment lines & responses (best response, tumor change, time to treatment failure in months)
1	49	F	High-grade serous ovarian cancer	M1	BRCA1, TMB high	[cisplatin + paclitaxel (SD, TTF=6mo)] [carboplatin + gemcitabine (SD, TTF=8mo)] [cisplatin + paclitaxel (SD, TTF=8mo)] [olaparib (PR, TTF=41mo)]
2	55	M	High-grade salivary duct carcinoma	M1	ERBB2	[lapatinib + trastuzumab + bevacizumab (PR, TTF=25+mo)] [cisplatin + docetaxel (PD)] [carboplatin + docetaxel + trastuzumab (PR)] [zoledronic acid + trastuzumab +/- paclitaxel (SD, TTF=14mo)]
3	70	M	Prostate adenocarcinoma	M1	BRCA2	[androgen deprivation (SD, TTF=6mo)] [docetaxel + carboplatin (PR, TTF=24+mo)] [cisplatin + etoposide (SD, TTF=6mo)] [paclitaxel (SD, TTF=6mo)]
4	62	F	High-grade anaplastic thyroid carcinoma		BRAF, PIK3CA	[dabrafenib + trametinib + everolimus (PR, TTF=2mo)] [carboplatin + paclitaxel (PD, TTF=1mo)] [everolimus (PD)] [dabrafenib + trametinib (PD, TTF=1.5mo)]
5	58	M	Basal cell carcinoma	M1	CDKN1A, CDKN2A, CTNNA1, FLT1, JAK2, LRP1B, MLL2, NOTCH1, PDGFRA, PD-L1, PD-L2, PIK3R2, PTCH1, SLIT2, SMARCA4, TERT, TMB high	[nivolumab (PR, TTF=18+mo)] [vismodegib (PD, TTF=2mo)] [cisplatin + paclitaxel (PR, TTF=2mo)] [sonidegib + buparlisib (PD, TTF=1.5mo)] [paclitaxel + vismodegib (PD, TTF=2mo)]
6	62	M	Poorly-differentiated thyroid papillary adenocarcinoma	T2N0M0	BIRC5, BRAF, PD-L1, TUBB3, TYMP	[doxorubicin + cisplatin (PD)] [paclitaxel (PD)] [vemurafenib (PD)] [nivolumab (CR, TTF=20+mo)]
7	55	F	Poorly differentiated squamous cell carcinoma of thymus	M1	KIT	[imatinib (SD, -20%, TTF=12+mo)] [paclitaxel + carboplatin (PR, -50%, TTF=4mo)] [pemetrexed (PD)] [gemcitabine (PD, TTF=3mo)]

8	66	M	Prostate adenocarcinoma	M1	BRCA2	[docetaxel (SD, TTF=4mo)] [abiraterone (PD, TTF=1mo)] [enzalutamide (PD, TTF=1mo)] [docetaxel + carboplatin (SD, TTF=12mo)]
9	60	M	Basal squamous cell carcinoma		KDR	[pazopanib (CR, TTF=6mo)] [vismodegib (CR, TTF=5mo)] [carboplatin + paclitaxel (PD)]
10			Melanoma		BRAF, NF1	[dabrafenib + trametinib (CR, -100%, TTF=6mo)] [unknown/unmatched (PD)] [unknown/unmatched (PD)]
11	50	F	Gastric cancer		MTB high	[epirubicin + oxaliplatin + capecitabine (PD)] [fluorouracil + oxaliplatin (SD)] [pembrolizumab (CR)]
12	71	F	Anaplastic thyroid cancer	IVB / pT4aN1bM1	ALK	[crizotinib (PR, -90%, TTF=24+mo)] [cisplatin + etoposide (SD, TTF=6mo)] [carboplatin + etoposide (PD, TTF=3mo)]
13	77	F	Lung adenocarcinoma	M1	KRAS, PD-L1, TP53	[carboplatin + pemetrexed (PD)] [docetaxel + FAK inhibitor + gemcitabine + pemetrexed (PD)] [nivolumab (PR)]
14	53	F	Lung adenocarcinoma	M1	ERBB2	[lapatinib + trastuzumab + bevacizumab (PR, TTF=7+mo)] [cisplatin+docetaxel (SD)] [carboplatin+pemetrexed (SD)]
15	69	M	High-grade sarcoma abdominal wall		BRAF	[gemcitabine + docetaxel (PD)] [dabrafenib + trametinib (CR, TTF=14mo)]
16	32	F	Breast ductal carcinoma	M1	BRCA1	[fluorouracil + epirubicin + cyclophosphamide (PD)] [thiothepa + cyclophosphamide + carboplatin (CR)]
17	48	F	High-grade large-cell neuroendocrine cervical carcinoma	M1	"ABL2, ATRX, BLM, CTNNB1, FBXW7, FGF6, JAK1, MEN1, MLL2, MLL3, MSH2, MSI high, NOTCH1, NRAS, PD-L1, PIK3CA, PREX2, PTEN, QKI, SETD2, SMARCA4, STK11, TET2, TMB high, octreotide scan positive	[nivolumab + octreotide (PR, -95%, TTF=17+mo)] [cisplatin + etoposide (PD)]
18	47	F	Poorly differentiated intrahepatic cholangiocarcinoma	"		[dabrafenib + trametinib (PR, TTF=8.5+mo)] [fluorouracil (PD)]
19		M	Small-cell neuroendocrine prostate cancer	M1	BRAF	[cisplatin (CR)]

20		F	Uterine leiomyosarcoma		FANCA	[pembrolizumab (PR, TTF=9mo)]
21	53	F	High-grade endometrioid adenocarcinoma	M1	MYC, PD-L1, PD-L2, PTEN, TP53	[pembrolizumab (PR, TTF=14mo)]
22	53	M	Stomach adenocarcinoma	IB / pT1N0	PD-L1, POLE, TMB high	[fluorouracil + oxaliplatin (PR, TTF=4+mo)]
23	74	F	lung adenocarcinoma		PALB2	[carboplatin + pemetrexed + zoledronic acid + docetaxel (PD)] [vandetanib + everolimus (PR)]
24	61	M	Ductal pancreatic adenocarcinoma	M1	AKT2, RET	[mitomycin C (PR, TTF=22mo)] [cisplatin (PR, TTF=36+mo)] [gemcitabine (SD, TTF=4mo)]
25			Melanoma	pT3N1M0	PALB2	[dabrafenib (CR, -100%, TTF=29+mo)] [unknown/unmatched (PD)] [unknown/unmatched (PD)]
26			Melanoma		BRAF	[dabrafenib (CR, -100%, TTF=24+mo)] [unknown/unmatched (PD)] [unknown/unmatched (PD)]
27			Melanoma		BRAF	[trametinib (PR, -53%, TTF=7mo)] [unknown/unmatched (PD)] [unknown/unmatched (PD)]
28	44	F	Therapy-related myeloid neoplasm, progressing in acute myeloid leukemia		BRAF	[dabrafenib + trametinib (PR, TTF=1mo)] [decitabine (PD)] [cytarabine + topotecan (PD)]
29	65	M	Perivascular epithelioid cell tumor		BRAF, KRAS, MLLT3-KMT2A	[sirolimus (PR, TTF=16+mo)] [MET inhibitor (PD)]
30	70	M	Perivascular epithelioid cell tumor		mTORC1, TSC2	[sirolimus (PR, -40%, TTF=10mo)] [sunitinib (PD, TTF=1.5mo)]
31	50	F	Cutaneous Castleman's disease		mTORC1, TSC2	[siltuximab (CR, TTF=84mo)]
32	61	F	Perivascular epithelioid cell tumor		JAK1	[sirolimus (PR, TTF=7mo)]
33			Pancreatic cancer		mTORC1, TSC1, TSC2	[trametinib (PR, TTF=10mo)]

34			Angiosarcoma		KRAS	[paclitaxel (SD, TTF=12mo)] [sorafenib (PD, TTF=3mo)] [pazopanib (SD, TTF=6mo)] [gemcitabine + docetaxel (PD, TTF=2mo)]
35	60	M	Squamous cell carcinoma		ARID1A, MCL1, TP53, VEGFR2, VEGFR3	[lapatinib (SD, TTF=3mo)] [lapatinib + fluorouracil + irinotecan (CR, TTF=60+mo)]
36	82	M	Prostate adenocarcinoma	T2N2M1	"HPV positive	[carboplatin + gemcitabine + veliparib (CR)]
37	67	F	high-grade papillary urothelial carcinoma	ERBB2, ERCC1, TOPO1, TOP2A, TYMS"		[methotrexate + vinblastine + doxorubicin + cisplatin (PD)] [doxorubicin + iphosphamide (PD)] [paclitaxel + methotrexate + gemcitabine + cyclophosphamide (PD)] [pazopanib (PR)]
38	49	F	Breast ductal carcinoma / undifferentiated carcinoma	M1	AR, BRCA2, TMPRSS2-ERG, TP53	[exemestane + everolimus (CR, TTF=14+mo)] [carboplatin + gemcitabine (PR, TTF=9mo)] [anastrozole + fulvestrant (PD, TTF=3mo)] [anastrozole + fulvestrant + capecitabine (CR, TTF=12mo)] [paclitaxel (SD, TTF=8mo)] [megestrol + gencitabine + carboplatin (SD, TTF=7mo)]
39	57	F	Clear cell renal carcinoma	M1	CCND1, FGF19, FGFR3	[sunitinib (PD)] [sorafenib (PD)] [temsirolimus (CR)]
40	53	M	Prostate adenocarcinoma	III / T1bN1M1	ER, PR, STK11	[androgen deprivation (SD, TTF=36mo)] [abiraterone (SD, TTF=18mo)] [enzalutamide (SD, TTF=12mo)] [docetaxel (PD, TTF=2mo)] [carboplatin + doxorubicin (PR, TTF=6mo)]
41	51	F	High-grade serous ovarian cancer	IV	BAP1, MTOR, VHL1	[olaparib (CR, TTF=77mo)] [carboplatin + paclitaxel (SD, TTF=4mo)]
42	73	F	Renal clear cell cancer	M1	BRCA2	[temsirolimus (SD, TTF=34mo)] [sunitinib (SD, TTF=3mo)]
43	58	F	Renal clear cell cancer		BRCA2, TP53	[temsirolimus (SD, TTF=27mo)] [sunitinib (SD, TTF=14mo)]
44	66	M	Renal clear cell cancer	M1	TP53, TSC1, VHL	[everolimus (SD, TTF=20mo)] [sunitinib (SD, TTF=5mo)]
45	42	F	Colorectal cancer	M1	PBRM1, TSC1, VHL	[pembrolizumab (PR, -30%, TTF=9+mo)] [capecitabine + oxaliplatin (SD, TTF=9mo)] [fluorouracil + irinotecan (SD, TTF=9mo)]
46	83	F	Colon adenocarcinoma		BAP1, MTOR, TSC1, VHL	[nivolumab (PR, TTF=6+mo)] [fluorouracil + oxaliplatin (SD, TTF=7mo)]

47	65	F	High-grade serous ovarian cancer	III / M1	KRAS, MLH1, PMS2	[olaparib (CR, TTF=86mo)]
48	63	F	Pancreatic cancer	IIIB / T4bN1M1	APC, CDK8, EPHA3, ETV6, FLT3, KRAS, PD-L1, PD-L2, STAG2, TMB intermediate, TP53	[fluorouracil + oxaliplatin + veliparib (PR, TTF=15mo)]
49	48	F	Breast ductal carcinoma		BRCA1, TP53	[anastrozole + everolimus (PR, -38%, TTF=14mo)] [anastrozole + everolimus + fulvestrant (PR, TTF=5+mo)] [tamoxifen (PD, TTF=2mo)] [paclitaxel + bevacizumab (PD)] [vinorelbine (PD)] [fulvestrant (PD, TTF=3mo)] [ixabepilone (PD)] [docetaxel (SD, TTF=9mo)] [docetaxel + doxorubicin + cyclophosphamide (PD, TTF=3mo)]
50			Melanoma	M1	BRCA2, KRAS, TP53	[dabrafenib + trametinib (PR, -34%, TTF=11mo)] [unknown/unmatched (PD)] [unknown/unmatched (PD)]
51	38	F	Breast ductal carcinoma	M1	CCND1, ER, FGFR1, MYC, PIK3CA, PIK3R1, PR	[anastrozole + everolimus (PR, -56%, TTF=11mo)] [paclitaxel (PD, TTF=3mo)] [fluorouracil + doxorubicin + cyclophosphamide (PD, TTF=1mo)] [tamoxifen (PD, TTF=3mo)] [capecitabine (PD, TTF=3mo)]
52	51	M	Ductal adenocarcinoma of the lacrimal gland		APC, BRAF, NRAS, PTEN, RB1	[? (PD)] [everolimus (PR)]
53	60	F	Renal clear cell cancer	M1	CCND1, ER, FGFR1, PR, PRKDC, PTEN	[temsirrolimus (SD, TTF=28mo)] [sunitinib (SD, TTF=11mo)]
54	29	F	Breast ductal carcinoma	M1	NF1, TP53	[cisplatin + nab-paclitaxel + zoledronic acid (CR, TTF=4.5mo)] [tamoxifen + zoledronic acid (SD, TTF=7mo)] [fulvestrant (SD, TTF=7mo)] [fluorouracil + epirubicin + cyclophosphamide then docetaxel (SD, TTF=54 for 2 linesmo)] [fluorouracil + epirubicin + cyclophosphamide then triptorelin + tamoxifen (SD, TTF=54mo for 2 lines)]
55			Melanoma	M1	PBRM1, VHL	[dabrafenib (CR, -100%, TTF=27+mo)] [unknown/unmatched (PD)] [unknown/unmatched (PD)]
56			Melanoma	pT2N2aM1	BRCA2, ER, PR, TP53	[dabrafenib (PR, -48%, TTF=6mo)] [unknown/unmatched (PD)] [unknown/unmatched (PD)]

57	44	F	Breast ductal carcinoma		AURKA, BRAF	[anastrozole + everolimus (CR, -100%, TTF=9+mo)] [tamoxifen + zoledronic acid (SD, TTF=6mo)] [letrozole (SD, TTF=4mo)]
58	53	M	Rectal cancer		BRAF, MITF	[fluorouracil + oxaliplatin (SD, TTF=4mo)] [fluorouracil + oxaliplatin + irinotecan (SD, TTF=8mo)] [regorafenib (PR, TTF=20mo)]
59	84	F	High-grade colorectal adenocarcinoma	M1	CCNE1, ER, IRS2, MCL1, TP53	[fluorouracil + bevacizumab (PD, TTF=3mo)] [regorafenib (low dose) (PR, TTF=9+mo)]
60			Melanoma	M1	APC, FLT4, KRAS, PPP1R3A, TP53	[dabrafenib (PR, -54%, TTF=3mo)] [unknown/unmatched (PD)] [unknown/unmatched (PD)]
61	57	F	Anaplastic thyroid cancer	pT4bN1bM1	APC, ERBB2, KDR, KRAS	[everolimus (PR, TTF=18mo)] [carboplatin + paclitaxel (PD, TTF=3mo)]
62	53	M	Early T-cell progenitor acute lymphoblastic leukemia		BRAF, CDKN2A, MYC	[BMS-906024 (pan-Notch inhibitor) + dexamethasone (CR, TTF=19mo)]
63	52	M	Testicular germ cell tumor	N1M1	FLCN, PTEN, TMB high, TSC2	[sunitinib (PR, TTF=17mo)] [bleomycin + ifosfamide + etoposide + cisplatin (SD, TTF=4mo)] [paclitaxel + ifosfamide + cisplatin (PD, TTF=2mo)] [actinomycin D + cyclophosphamide + etoposide (PD, TTF=3mo)]
64	32	M	Head and neck squamous cell carcinoma		CSF3R, DNMT3A, NOTCH1, PTPN11	[erlotinib (CR)]
65			Melanoma	N1M1	AKT1, EGFR, KRAS, PTEN, RET	[vemurafenib (PR, -38%, TTF=8mo)] [unknown/unmatched (PD)] [unknown/unmatched (PD)]
66			Melanoma	IVA / T1N2cM0	ABL2, ARID1A, MAPK1, TP53	[dabrafenib (PR, -75%, TTF=4mo)] [unknown/unmatched (PD)] [unknown/unmatched (PD)]
67	50	M	Lung adenocarcinoma		BRAF, CDKN2A, CDKN2B, NF1, PAX5	[carboplatin + paclitaxel + bevacizumab (SD, TTF=6mo)] [erlotinib (PD, TTF=3mo)] [dacomitinib (SD, TTF=7mo)] [trastuzumab (PD, TTF=3mo)] [trastuzumab + vinorelbine (SD, TTF=18mo)] [lapatinib (SD, TTF=4mo)] [crizotinib (PD, TTF=1mo)] [lapatinib + capecitabine (SD, TTF=10mo)] [lapatinib + nab-paclitaxel (PD, TTF=3mo)] [lapatinib + pemetrexed (PD, TTF=3mo)] [pertuzumab + trastuzumab +

						docetaxel (SD, TTF=12mo)] [trastuzumab emtansine (PD, TTF=3mo)] [pertuzumab + trastuzumab + afatinib (SD, TTF=4mo)] [trastuzumab + vinorelbine + everolimus (SD, TTF=12mo)]
68	47	M	Prostate adenocarcinoma		ATM, BRAF, CDKN2A, CDKN2B, MET	[anti-androgen + leuprolide (PR)] [etoposide + carboplatin + leuprolide (PD)]
69			Small cell lung cancer	IV	ABL1, CDK12, CIITA, CTSG, DNMT3A, ELN, ERBB2, FAM20C, HIP1, IL2, MET, MLL3, NF2, PDE4DIP, PHKG1, RB1, ROS1, SBDS, TP53	[sonidegib + etoposide + cisplatin (PR, TTF=27+mo)]
70		M	Head and neck squamous cell carcinoma	M1	AR, MAP2K4, MYCL, PTEN, RB1, SMAD4, TP53,	[erlotinib (PR, TTF=24+mo)]

Abbreviations: CR = complete response; F = female; M = male; mo = month(s); MMR = mismatch repair; MSI = microsatellite instability; PD = progressive disease; PR = partial response; SD = stable disease; TMB = tumor mutation burden; TTF = time to treatment failure.

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