SUPPLEMENTARY METHODS

Patient-derived tumor cells (PDC)

Upon receiving human BRAF-metastatic melanoma tissue, samples were mechanically disrupted and incubated in DMEM/F12 media (Gibco, Gaithersburg, MD) supplemented with B27 serum-free (Gibco, Gaithersburg, MD) and penicillin/streptomycin 10,000 u/mL (Gibco, Gaithersburg, MD) containing 0.25%, trypsin/EDTA (Gibco, Gaithersburg, MD), collagenase/hyaluronidase (StemCell Tech, Vancouver, BC), 1 μg/mL deoxyribonuclease I (BioChem, King of Prussia, PA) for 30 min and passed through a 40 μM cell strainer. Cell pellets were washed with phosphate buffered saline (PBS) without calcium and magnesium (Gibco, Gaithersburg, MD) and centrifuged at 300 x g for 5 min. Cell pellets were inspected for erythrocyte contamination and if present lysed utilizing lysis solution as per manufacturer's protocol (Miltenyi Biotech, Sunnyvale, CA). PDCs were cultured in a T75 ultra low attachment flasks (Corning, Tewksbury, MA) with DMEM/F12 media supplemented with B27, penicillin/streptomycin (10,000 u/mL), 50 μg/mL human epidermal growth factor (hEGF) (Peprotech, Rocky Hill, NJ), 50 μg/mL human fibroblast growth factor (hFGF) (Peprotech, Rocky Hill, NJ), and 5μg/mL heparin (Sigma, Carlsbad, CA). This media support the growth of tumorspheres (Supplementary Figure 1) but not stromal components. PDC were cultured for 3-7 days and then used to generate PDX or cryopreserved utilizing CellBanker2 without serum (AmsBio, Cambridge, MA).

Patient-derived xenograft generation and passaging

$1x10^6$ PDCs in 1:1 PBS:Matrigel (Corning, Tewksbury, MA) were injected subcutaneously (SQ) into the flank of female NOD *SCID* gamma mice (NSG) (Jackson Laboratories, Sacramento, CA). Before reaching 2000 mm^3 in volume, tumors were harvested and PDXC were processed in a manner identical to PDCs. PDXC were then either re-injected subcutaneously into the flank of NSG mice for an *in vivo* experiment, further *in vivo* passaging, plated for HTDS, or cryopreserved utilizing CellBanker2 without serum (AmsBio, Cambridge, MA). All PDXC were authenticated using short tandem repeat analysis (ATCC) and were mycoplasma-free. *In vivo* studies were carried out in accordance with the National Institutes of Health guidelines, Health Research Extension Act of 1985 and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (Policy), Office of Laboratory Animal Welfare assurance, and an approved Institutional Animal Care and Use Committee (IACUC) protocol.

HTDS screening platform

An Excel-based .csv for dosing PDXCs was automatically generated using specialized in-house VBA programmed Excel spreadsheets and submitted to the company Transcriptic (Menlo Park, CA). The protocol was then translated into a python script to generate autoprotocol, a data structure used to instruct a workcell to execute experiments. Compatible plates and tubes were supplied to the workcell and a robotic arm then moves the containers to and from the appropriate instruments without human intervention. Drugs were supplied to Transcriptic at 1000X their effective concentrations in standard microcentrifuge tubes. These were transferred to a 384-acoustic liquid handler source plate that was then moved to a multi-channel liquid handler to serially dilute the drugs. The standard dilution protocol was 1X, 0.2X, 0.1X, 0.02X, 0.01X, 0.002X, where 1X is equal to the C_{max} of the drug (Supplementary Table 1).

This source plate was used to dose 384-well microplates containing PDXC samples. Before dosing, the general health of the cells in a control lane are visually assessed. Using a simple .csv well map, the acoustic liquid handler automatically transferred each drug at each concentration from the source plate to the appropriate location on each of the cell-containing 384-well microplates. The drugged cell lines were then placed in an incubator for 72 hours, after which the CellTiter-Glo (Promega, San Luis Obispo, CA) assay was used to quantify cell viability/proliferation. Data from luminescence reads were subsequently rendered graphically in Transcriptic's web interface and made available for download in .csv format for further data analysis.

Culturing conditions for PDXC in HTDS

Blood serum albumin (BSA) in fetal bovine serum (FBS) is primarily responsible for binding and reducing activity of many drugs (11). Unlike standard cell lines, media used to propagate PDXCs does not contain FBS in order to more readily preserve the genomic and biological characteristics of the original tumor (12,13). Therefore, 0.1% purified BSA was added to PDC and PDXC growth media for HTDS in order that results could be more readily cross-compared to past and future studies using standard cell culturing techniques (14). Higher concentrations of BSA were not used because they significantly increase the cleaning maintenance of the automated cell dispenser cassettes.

Drug storage and preparation

Drugs were obtained from Selleckchem (Houston, TX) and master stocks were primarily made at half maximum solubility with DMSO or water diluent per manufacturer specifications for molecular weight, diluent and solubility. Drug stocks were then diluted to clinically relevant

maximum concentrations and transferred to 384-well stock drug plates at 65 μL. To prevent multiple freeze-thaw cycles of the master stocks, drugs are first aliquoted to a master plate, and then multiple working daughter 384-well plates were made, which were discarded monthly. For drug dosing, drugs from working passage plates were transferred at 25 nL to individual wells containing a 25 μL cell suspension media pre-seeded with tumorspheres. All drugs and drug plates were stored at -80 ℃. All drugs and drug plates were set to have one-year shelf life and discarded upon passing this point.

Next Generation Sequencing

Isolation of genomic DNA from fresh human and mouse PDX tissue samples was performed using DNeasy tissue kit (Qiagen, Redwood City, CA) after tissue disruption using ruptor disposable probes, and DNA was quantified using PicoGreen (Thermo Fisher Scientific, South San Francisco, CA). The integrity was determined using agarose gels.

Illumina (Foster City, CA) MiSeq 2x151 base paired-end sequencing results were validated to detect single-nucleotide variant (SNV) and insertion/deletion (indel) variants at 5% allelic frequency or higher in target regions with sufficient read coverage. The gene targets covered by this assay were as follows: ABL1, AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, JAK2, JAK3, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53, VHL. Concordance between the original sample and its derivative was calculated as described by Calapre et al (17):

Concordance: C = 100% * ($x/\ y$)

x = number of variants confirmed in both the initial tumor tissue AND the derivative tissue

y = number of similar variants confirmed in initial tumor tissue OR the derivative tissue

When there is a threshold (0, 10%, 25%) then there are different definitions of when variants are confirmed in both the initial tumor tissue and the derivative mouse tissue. The variants are confirmed in both tissues if the variant is above the threshold in at least one tissue and above zero in the other tissue.

SUPPLEMENTARY FIGURES

Supplementary Figure 1. Tumorspheres. Metastatic melanoma MM337X1 were cultured in T75 ultra low attachment flasks with DMEM/F12 media supplemented with B27, penicillin/streptomycin, hEGF, hFGF, and heparin. Microphotographs were captured 72 hours following initial cell plating utilizing a Zeiss AxioObserver Z1 with a 10X objective. Bar, 300 μm.

Supplementary Figure 2. PDX tumor growth rate. PDXCs were injected *in vivo* into the flank of NSG mice and monitored for growth. The number of days that were required to reach 500 mm^3 is indicated, illustrating the variability in growth rates between patient samples.

Supplementary Figure 3. Correlation of HTDS response between PDXC generations. The ability of multiple drugs to inhibit cell viability/proliferation was assessed. Scatter plots of the

correlation in drug score between different PDXCs, and PDCs and corresponding PDXCs. **A)** 500 versus 1000 MM300X cells, **B)** 250 versus 1000 MM300X cells, **C)** MM302X cells screened on 10/30 versus 11/6, **D)** MM337X cells screened on 1/21 versus 2/8, **E)** MM302X cells versus MM302X3 cells, and **F)** MM358 (PDC) versus MM358X (PDXC). A Pearson's correlation coefficiency test was performed.

Supplementary Figure 4. Patient treatment history timeline for MM334. Treatment with BRAF (dabrafenib) and MEK (trametinib) inhibitors is highlighted (red). Responses to treatments are also highlighted (* blue). MM334 was collected on October 2015 (red arrow): complete response (CR) and stable disease (SD) are indicated.

Supplementary Figure 5. Drug combinations that inhibit the growth of BRAF inhibitor-resistant melanoma. Response of single agent or drug combinations on melanoma cell viability/proliferation in **A)** MM358X PDXC and **B)** MM337X PDXC. Drug score of 0 equals no effect and 100 represents killing all the cells. Drugs that stimulate cell growth produce a score < 0. Darkest red of the heat map indicates greatest inhibition of cell viability/proliferation and white equals no response. **C)** CI values (range 0-4) for drug combinations in MM358X PDXC and **D)** MM337X PDXC . A CI value of <1, 1 and >1 indicates, synergism, additivity and antagonism respectively.

SUPPLEMENTARY TABLES

Supplementary Table 1. Drug list. Drugs list with corresponding C_{max} values and PubMed references. C_{max}: maximum plasma concentration; PMID: PubMed identifier; PMCID: PubMed identifier for all works published in the free-to-access PubMed Central.

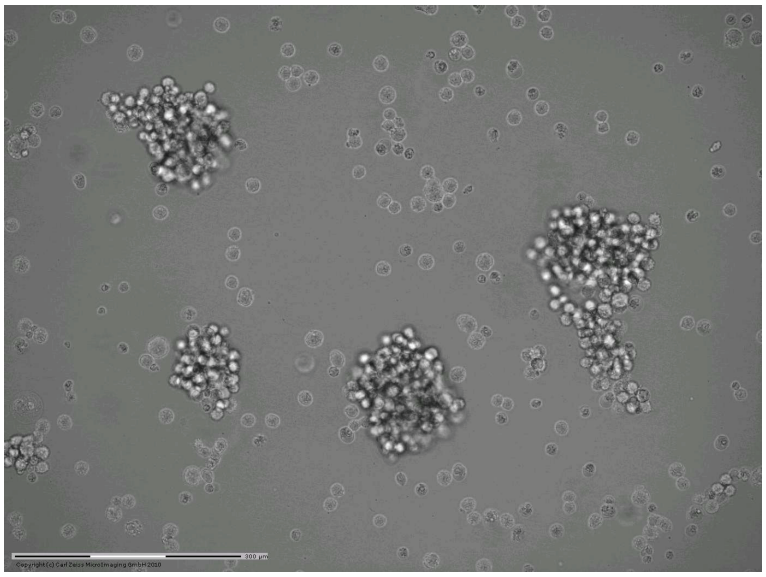
Supplementary Table 2. Clinical annotation and genetic information for patients. M: male, F: Female. BRAF status was identified using standard clinical analysis using a CLIA certified test. GM-CSF: Granulocyte-macrophage colony-stimulating factor. All samples were collect after the specified therapy.

Supplementary Table 3. Comparison of single-nucleotide variant (SNV) and insertion/deletion (ins/del) variants of DNA mutational hotspots from patient tumors and first (X) and second (X1) generation PDX derivatives. Patient tumors and corresponding first generation (X) PDXs as well as X and X1 PDXs where compared. The match pairs are grouped using colored columns. The mutations identified are listed by row. Allele frequencies are also listed by row (for example 0.14 = 14%). Allele frequencies of SNV or ins/del that are present in matched samples are highlighted in yellow. Concordance (%) = ($x \div y \times 100$). Concordance at ≥ 10% AF and ≥ 25% AF was calculated for each matched pair and for all samples (Total Concordance).

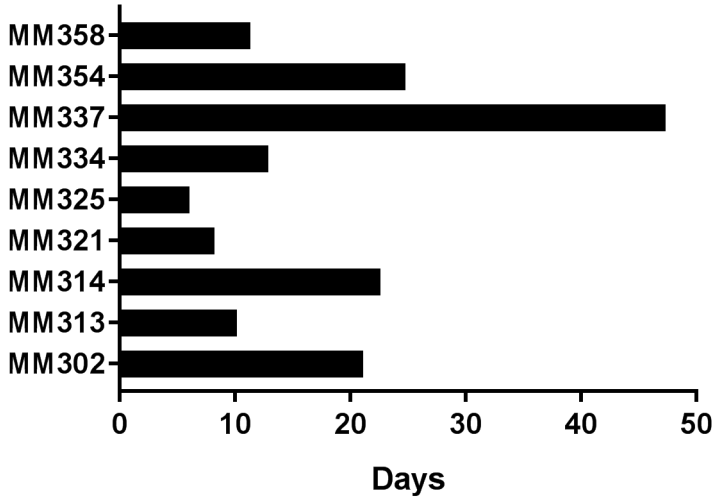
Supplementary Table 4. Drug score and AUC for HTDS in 8 BRAF mutant melanoma PDXCs. Drug scores and AUC values were calculated for single agents and vemurafenib + combimetinib

when assessing melanoma cell viability/proliferation. Drug score of 0 equals no effect and 100 represents killing all the cells. Drugs that stimulate cell growth produce a score < 0. An AUC value of 0 represents killing all the cells, a value of 270 represents no cell kill, values > 270 represent stimulation of cell growth.

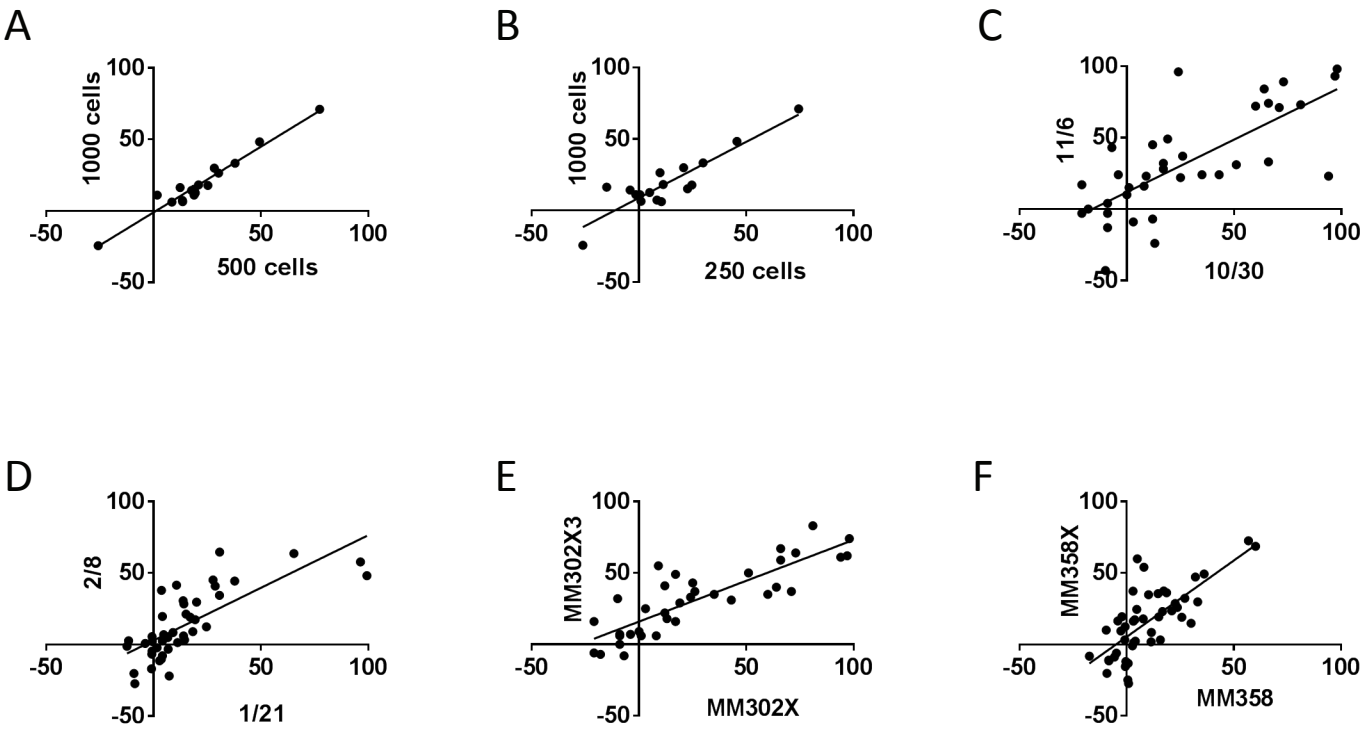
Supplementary Table 5. Drug score and AUC for single agents and drug combinations in PDXC. Drug scores and AUC values were calculated for PDXC MM302X, MM358X, and MM337X. Drug score of 0 equals no effect and 100 represents killing all the cells. Drugs that stimulate cell growth produce a score < 0. An AUC value of 0 represents killing all the cells, a value of 270 represents no cell kill, values > 270 represent stimulation of cell growth. Drug responses in the presence or absence of vemurafenib were compared statistically using AUC and corresponding confidence limits.



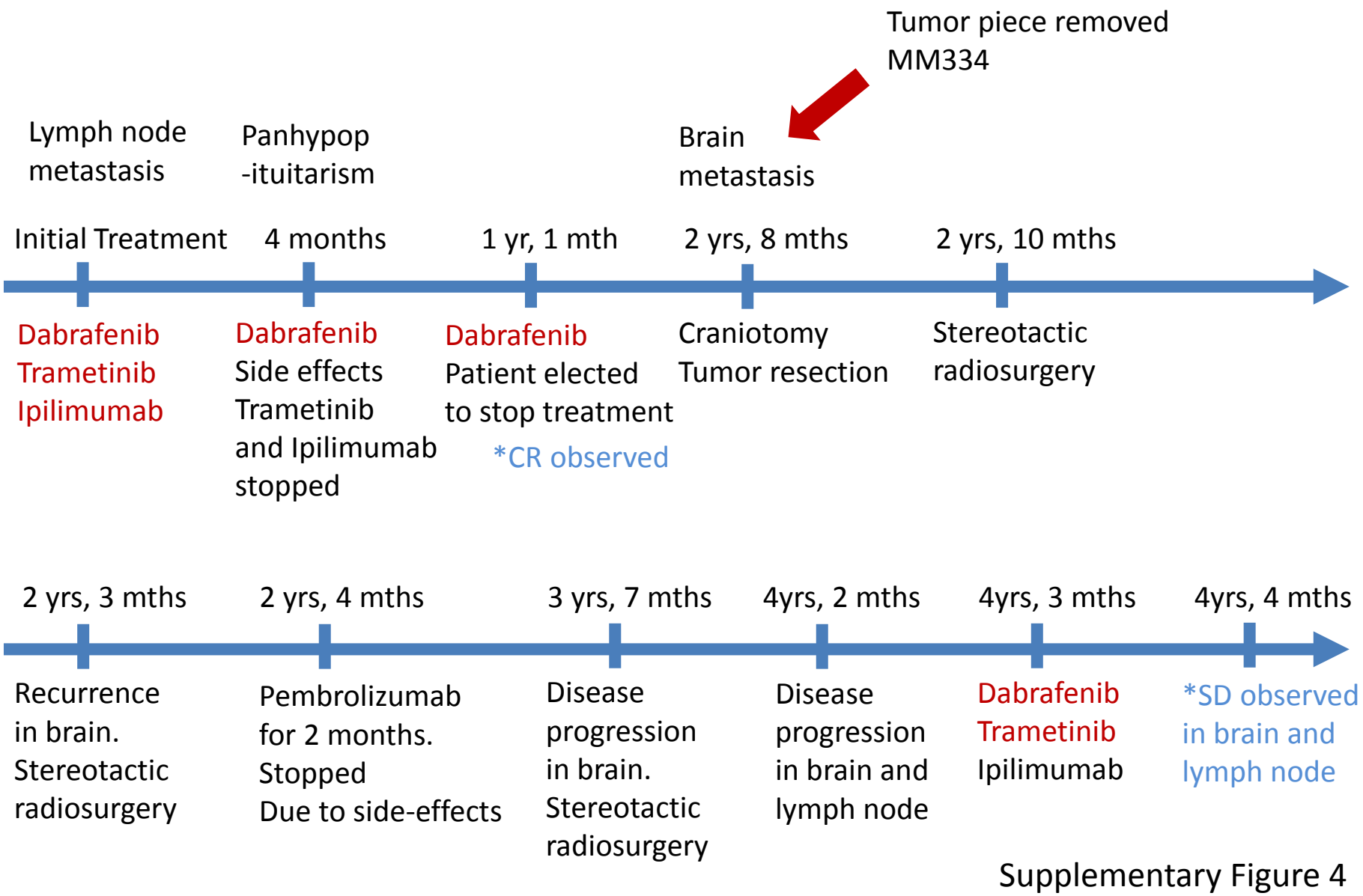
Supplementary Figure 1



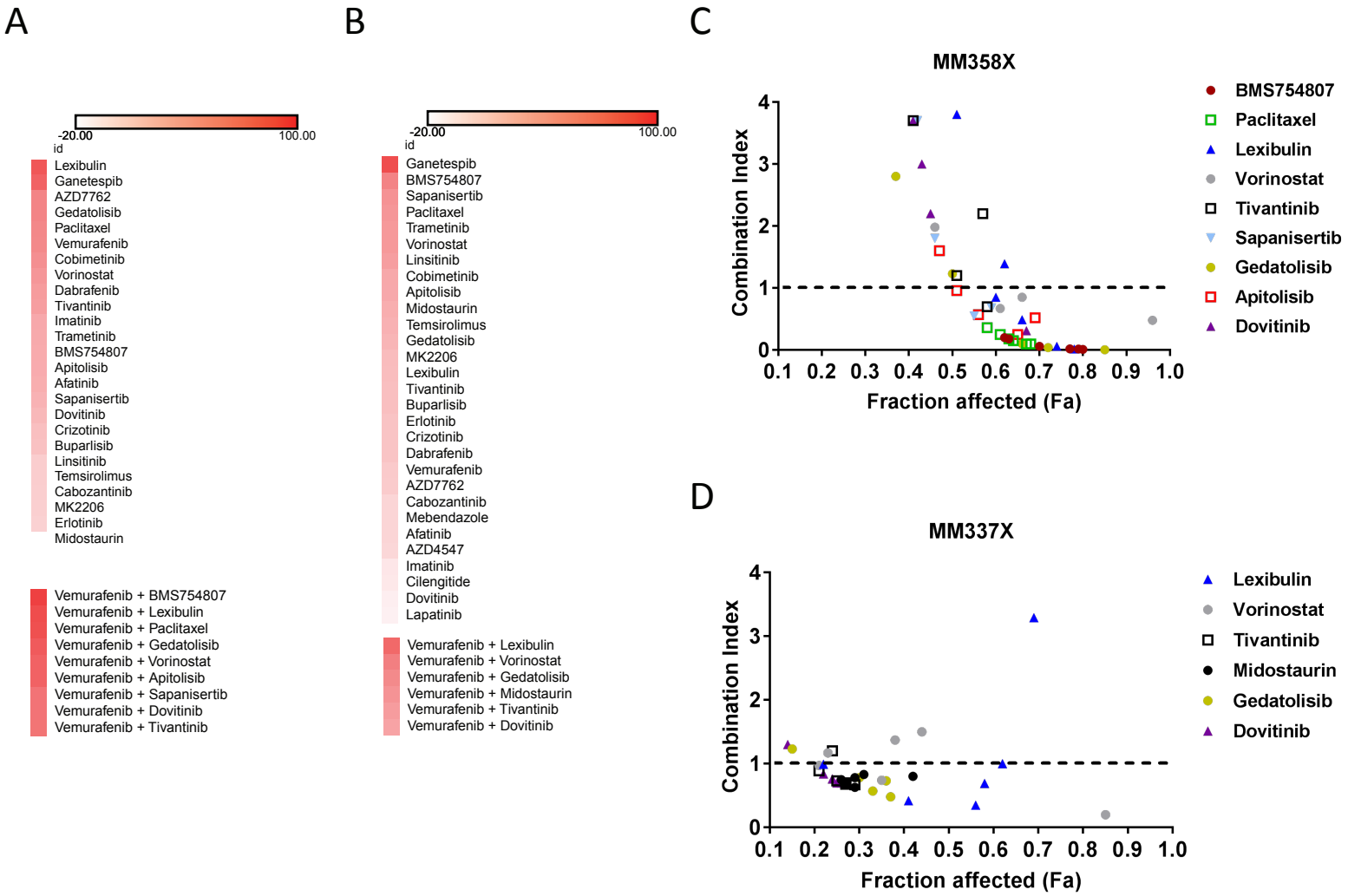
Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4



Supplementary Figure 5

Drug	Cmax μM	PMID	PMCID
Afatinib	1	28364015	PMC5511563
Apitolisib	1	26787751	PMC4876928
Axitinib	0.2	28364015	PMC5511563
AZD4547	0.5	28070720	PMC5502072
AZD7762	0.5	24448638	PMC4486055
Bosutinib	0.4	28364015	PMC5511563
Buparlisib	2	24405565	PMC4317947
Cabozantinib	1	28364015	PMC5511563
Cilengitide	50	12706360	N/A
Cobimetinib	1	28364015	PMC5511563
Crizotinib	1	28364015	PMC5511563
Dabrafenib	10	28364015	PMC5511563
Dacomitinib	0.05	22249430	PMC3523469
Dasatinib	0.3	28364015	PMC5511563
Dinaciclib	1	25217392	N/A
Dovitinib	1	23339124	N/A
Doxorubicin	15	28364015	PMC5511563
Erlotinib	2	28364015	PMC5511563
Everolimus	0.06	28364015	PMC5511563
Ganetespib	10	23530663	PMC3626541
Gedatolisib	1	27103175	N/A
Imatinib	7.5	28364015	PMC5511563
Ipatasertib	1.5	27872130	PMC5463454
Lapatinib	2	28364015	PMC5511563
Lexibulin	1	20733579	PMC2938266
Linsitinib	10	25795408	N/A
LY2228820	2	26581242	N/A
Mebendazole	1	7094986	N/A
Midostaurin	10	20733134	PMC4135183
MK2206	0.4	25239610	PMC4233149
Olaparib	10	28364015	PMC5511563
Paclitaxel	5	28364015	PMC5511563
Palbociclib	0.1	28364015	PMC5511563
PX866	0.1	22693357	N/A
Regorafenib	10	28364015	PMC5511563
Sapanisertib	0.3	26800393	N/A
Semagacestat	0.2	18695053	PMC2682361
Sunitinib	0.2	28364015	PMC5511563
Temsirolimus	0.5	28364015	PMC5511563
Tivantinib	19	23413279	N/A
Tozasertib	4	20386909	PMC3050703
Trametinib	0.02	28364015	PMC5511563
Veliparib	10	27803064	N/A
Vemurafenib	50	28364015	PMC5511563
Vismodegib	35	28364015	PMC5511563
Vorinostat	10	15857402	PMC6040651

Case	Age	Gender	Primary Tumor Type	Site of Tissue Biopsy	Therapies	BRAF status
MM300	69	M	Cutaneous (right cheek)	LN	dabrafenib + Ipilimumab	BRAF V600K
MM302	69	M	Cutaneous (right foot)	Distant Met	dabrafenib, dabrafenib + ipilimumab	BRAF V600E
MM313	69	F	Cutaneous (back)	Distant Met	Naïve	BRAF V600E
MM314	69	M	Unknown Primary	LN	Naïve	BRAF V600E
MM321	79	M	Unknown Primary	LN	dabrafenib + trametinib	BRAF V600E
MM325	69	F	Cutaneous (left leg)	LN	ipilimumab, nivolumab, Ipilimumab + nivolumab, nivolumab	BRAF V600E
MM334	69	M	Unknown Primary	Brain	high-dose interferon-alpha, dabrafenib + trametinib + ipilimumab	BRAF V600K
MM337	49	F	Cutaneous (left ear)	LN	biochemotherapy, pulse interleukin-2/GM-CSF, vemurafenib, ipilimumab, pembrolizumab, pembrolizumab + dabrafenib, carboplatin + paclitaxel, nivolumab + ipilimumab, nivolumab	BRAF V600E
MM354	39	M	Cutaneous (chest)	Distant Met	pembrolizumab, dabrafenib + trametinib, ipilimumab + nivolumab	BRAF V600E
MM358	59	M	Cutaneous (back)	Brain	dabrafenib + trametinib	BRAF V600K

GENE	MM300	MM300X	MM313	MM313X	MM314	MM314X	MM325	MM325X	MM334	MM334X	MM354	MM354X1	MM358	MM358X
ABL1	0.14													
ABL1	0.13													
ABL1										0.09				
APC					0.50	0.68								
APC			0.21											
ATM							0.83	0.98						
BRAF			0.17	0.57	0.26	0.78	0.60	0.67			0.65	0.67		
BRAF	0.54	1.00							0.83	0.84			0.77	0.61
CTNNB1	0.06													
ERBB4		0.27												
FBXW7				0.09										
FGFR3		0.18												
FLT3	0.14													
GNA11										0.09				
GNAQ										0.07				
GNAQ			0.06											
HNF1A												0.05	0.09	
HNF1A					0.05									
HNF1A			0.06	0.08	0.17	0.05								
KDR	0.09													
KDR			0.08	0.28	0.51	0.65	0.50	0.51						
KIT			0.05											
KIT				0.24										
KIT			0.06											
MET	0.11													
NPM1			0.20											
NPM1			0.18											
NRAS			0.06											
NRAS	0.10													
NRAS	0.26													
PTEN									0.41	0.56				
RB1	0.05													
RB1	0.06													
RB1	0.06													
RB1											0.12			
SMAD4	0.11													
SMARCB1									0.42	0.51				
STK11	0.10													
TP53	0.54	0.97												

Number of variants (any variant)	15	4	10	5	5	4	3	3	3	6	2	2	2	1
Number of variants (variant ≥ 10%)	9	4	4	3	4	3	3	3	3	3	2	1	1	1
	3	3	0	2	3	3	3	3	3	3	1	1	1	1

	MM300	MM300X	MM313	MM313X	MM314	MM314X	MM325	MM325X	MM334	MM334X	MM354	MM354X1	MM358	MM358X
Concordance (any variant)	0.12		0.3		0.8		1.0		0.5		0.3		0.5	
Concordance (variant ≥ 10%)	0.2		1.0		1.0		1.0		1.0		0.5		1.0	
Concordance (variant ≥ 25%)	0.5		1.0		1.0		1.0		1.0		1		1	

Total Concordance (any variant)	0.35
Total Concordance (variant ≥ 10%)	0.48
Total Concordance (variant ≥ 25%)	0.88

Supplementary Table 3

GENE	MM300X	MM300X1	MM302X	MM302X1	MM313X	MM313X1	MM314X	MM314X1	MM325X	MM325X1	MM334X	MM334X1	MM337X	MM337X1
ABL1											0.09			
APC							0.68	0.66						
ATM									0.98	1.00				
BRAF			0.61	0.64	0.57	0.50	0.78	0.79	0.67	0.66			0.24	0.23
BRAF	1.00	0.99									0.84	0.87		
CTNNB1													0.25	0.25
EGFR						0.12								
ERBB4	0.27	0.29												
FBXW7					0.09									
FGFR3	0.18													
GNA11											0.09			
GNAQ											0.07			
HNF1A		0.08			0.08		0.05			0.05				
KDR			0.52	0.50	0.28	0.54	0.65	0.63	0.51	0.49			0.99	1.00
KIT					0.24	0.40								
NRAS													0.23	0.25
PTEN											0.56	0.46		
RB1														0.09
RB1								0.05						
SMARCB1											0.51	0.68		
TP53	0.97	0.97												

Number of variants (any variant)	4	4	2	2	5	4	4	4	3	4	6	3	4	5
Number of variants (variant ≥ 10%)	4	3	2	2	3	4	3	3	3	3	3	3	4	4
Number of variants (variant ≥ 25%)	3	3	2	2	2	3	3	3	3	3	3	3	2	3

	MM300	MM300X	MM302X	MM302X1	MM313X	MM313X1	MM314	MM314X	MM325	MM325X	MM334	MM334X	MM337X	MM337X1
Concordance (any variant)	0.6		1.0		0.5		0.6		0.8		0.5		0.8	
Concordance (variant ≥ 10%)	0.8		1.0		0.8		1.0		1.0		1.0		1.0	
Concordance (variant ≥ 25%)	1		1.0		1		1		1		1		0.7	

Total Concordance (any variant)	0.64
Total Concordance (variant ≥ 10%)	0.91
Total Concordance (variant ≥ 25%)	0.95

Supplementary Table 3

	MM314X1	MM337X1	MM321X2	MM358X	MM302X	MM334X1	MM313X	MM325X
Vemurafenib	56.2	23.0	38.1	18.4	8.5	91.8	51.8	92.7
Dabrafenib	64.6	28.6	33.6	23.3	28.7	79.7	52.6	94.6
Trametinib	40.2	14.7	23.2	23.8	50.5	53.0	38.4	69.9
Cobimetinib	80.9	48.0	37.4	23.0	77.2	90.9	50.5	95.1
Vemurafenib + Cobimetinib	91.2	60.9	36.6	27.8	78.4	97.5	54.3	95.1
Crizotinib	-2.5	9.3	15.9	-9.8	22.7	18.7	12.5	19.7
Tivantinib	9.6	9.4	-8.3	-1.6	-1.7	15.6	-3.3	-27.7
Dasatinib	-9.4	-10.0	22.6	-21.9	-12.6	2.4	-13.9	8.0
Bosutinib	-7.1	0.4	25.3	-11.7	-15.7	-13.7	-6.2	1.7
Erlotinib	13.5	34.7	20.9	2.8	18.6	30.1	-0.1	18.9
Lapatinib	-2.2	-17.1	-4.8	-7.7	-17.6	-1.1	-3.8	-7.7
Axitinib	1.5	4.1	13.6	-12.8	-13.0	2.9	-5.1	4.7
Regorafenib	24.5	22.5	28.2	3.2	44.3	23.0	17.2	23.7
Sunitinib	17.9	34.8	30.9	5.0	-6.6	5.4	23.3	18.4
Imatinib	0.5	-9.7	-8.1	-6.9	-28.8	-3.4	-8.6	-17.6
Linsitinib	2.2	40.4	17.2	21.4	77.5	34.4	2.8	40.2
LY2228820	-2.4	-10.3	-0.9	-6.1	-6.6	6.4	-11.7	-20.4
Dacomitinib	-6.0	-5.2	7.6	-3.5	-18.7	-25.3	-3.2	-7.0
Temsirolimus	21.0	48.0	29.9	0.6	29.4	20.5	26.6	40.9
Buparlisib	9.0	26.1	6.3	8.0	17.4	6.3	30.4	17.9
Everolimus	19.5	48.2	2.7	14.0	15.0	-6.2	26.7	29.0
Ipatasertib	3.2	-4.7	8.3	-0.2	-4.4	1.6	4.5	-13.2
MK2206	-4.7	-11.1	14.7	-5.9	-9.0	-2.2	3.1	-4.8
Sapanisertib	34.3	46.7	16.0	15.1	40.3	34.1	35.4	32.8
PX866	-12.8	-0.6	-2.0	-1.3	-18.6	-9.6	-1.4	-1.3
Palbociclib	-3.0	-11.5	12.0	-11.6	-4.6	5.9	-5.0	6.0
Dinaciclib	60.6	81.1	44.9	49.9	54.1	63.7	47.9	43.4
Doxorubicin	63.9	94.1	69.8	18.9	37.1	16.3	49.7	44.4
Vismodegib	0.7	4.7	25.4	-8.7	-0.4	-2.2	6.7	13.9
Ganetespib	80.4	66.7	-6.3	29.9	72.6	52.7	47.9	69.4
Olaparib	2.6	13.1	30.0	-12.0	-12.9	-9.9	-9.7	3.0
Veliparib	7.4	5.1	-1.6	0.0	-5.7	-1.7	-6.0	-19.2
Semagacestat	26.3	21.1	11.1	14.6	-3.3	24.6	19.0	24.0
Tozasertib	18.9	36.3	23.3	-2.7	32.9	7.4	14.4	17.4
Vorinostat	74.4	58.6	72.8	28.6	31.1	27.5	67.1	52.4

Supplementary Table 4

	MM314X1	MM337X1	MM321X2	MM358X	MM302X	MM334X1	MM313X	MM325X
Vemurafenib	118.3	207.9	167.2	220.2	247.1	22.1	130.1	19.7
Dabrafenib	95.5	192.7	179.2	207.0	192.6	54.9	128.0	14.6
Trametinib	161.5	230.4	207.4	205.7	133.6	126.9	166.3	81.3
Cobimetinib	51.5	140.5	168.9	207.8	61.6	24.5	133.6	13.3
Vemurafenib + Cobimetinib	23.7	105.6	171.2	195.0	58.3	6.9	123.4	13.3
Crizotinib	276.7	245.0	227.0	296.5	208.7	219.6	236.2	216.9
Tivantinib	244.0	244.7	292.4	274.4	274.5	228.0	278.9	344.7
Dasatinib	295.3	296.9	209.1	329.2	303.9	263.4	307.6	248.5
Bosutinib	289.2	268.9	201.7	301.5	312.5	307.1	286.7	265.3
Erlotinib	233.6	176.2	213.5	262.4	219.7	188.7	270.3	219.1
Lapatinib	276.0	316.1	283.0	290.7	317.4	273.1	280.2	290.7
Axitinib	265.9	258.9	233.4	304.6	305.0	262.2	283.9	257.3
Regorafenib	203.9	209.2	193.9	261.4	150.4	207.8	223.5	206.1
Sunitinib	221.6	176.0	186.7	256.6	287.8	255.4	207.2	220.2
Imatinib	268.7	296.2	292.0	288.5	347.8	279.2	293.3	317.6
Linsitinib	264.1	160.8	223.6	212.2	60.9	177.1	262.5	161.5
LY2228820	276.6	297.8	272.3	286.5	287.7	252.7	301.6	325.1
Dacomitinib	286.1	284.0	249.4	279.4	320.6	338.2	278.7	289.0
Temsirolimus	213.2	140.3	189.3	268.3	190.6	214.6	198.1	159.5
Buparlisib	245.7	199.5	253.1	248.3	223.1	253.0	187.9	221.7
Everolimus	217.4	139.9	262.8	232.1	229.5	286.8	197.8	191.8
GDC0068 (Ipatasertib)	261.4	282.6	247.6	270.5	282.0	265.6	257.9	305.7
MK2206	282.6	299.9	230.3	285.8	294.2	275.9	261.5	283.0
MLN0128 (Sapanisertib)	177.4	143.8	226.8	229.2	161.1	177.8	174.5	181.4
PX866	304.5	271.6	275.5	273.4	320.1	295.8	273.7	273.5
Palbociclib	278.1	301.0	237.7	301.3	282.3	254.1	283.5	253.8
Dinaciclib	106.5	51.1	148.7	135.4	124.0	98.0	140.7	152.7
Doxorubicin	97.4	16.0	81.7	219.0	169.7	226.0	135.7	150.2
Vismodegib	268.2	257.4	201.4	293.6	271.1	276.0	252.0	232.5
Ganetespib	52.9	89.9	286.9	189.4	74.1	127.8	140.6	82.8
Olaparib	262.9	234.6	189.1	302.3	304.7	296.7	296.3	261.9
Veliparib	250.1	256.1	274.3	270.1	285.4	274.7	286.1	321.9
Semagacestat	199	213.1	240	230.7	279	203.7	218.6	205.1
Tozasertib	219.1	172.1	207.2	277.3	181.1	250	231.1	223
Vorinostat	69	111.9	73.33	192.7	186	195.7	88.88	128.4

Supplementary Table 4

	MM302X Score	MM302X AUC
Ganetespib	97.5	6.8
BMS-754807	81.0	51.3
Trametinib	72.8	73.6
Paclitaxel	71.4	77.3
Cobimetinib	66.3	90.9
Lexibulin	66.1	91.4
Sapanisertib	59.5	109.3
Gedatolisib	51	132.4
Vorinostat	43.1	153.6
Midostaurin	40.3	161.2
Tivantinib	35.2	175
Apitolisib	26	199.9
Everolimus	25.5	201.2
Dabrafenib	24.5	203.9
Linsitinib	17.4	222.9
MK2206	17.1	223.8
Afatinib	12.7	235.7
Buparlisib	12.3	236.9
Dovitinib	11.9	237.8
Temsirolimus	8.7	246.5
AZD7762	3.2	261.4
Lapatinib	1.5	266
Erlotinib	1.3	266.5
Cilengitide	-0.4	271
Cabozantinib	-3.7	279.9
XL765	-4.6	282.4
Mebendazole	-6.8	288.3
Vemurafenib	-9.5	295.6
AZD4547	-9.7	296.1
Imatinib	-20.9	326.5
Crizotinib	-21.1	326.9

	MM358X Score	MM358X AUC
Lexibulin	59.9	108.2
Ganetespib	54.0	124.2
AZD7762	37.4	168.9
Gedatolisib	37.3	169.2
Paclitaxel	35.6	174
Vemurafenib	34.9	175
Cobimetinib	32.4	182.6
Vorinostat	28.6	192.7
Dabrafenib	25.9	200.1
Tivantinib	24.6	203.6
Everolimus	23.6	206.4
Imatinib	19.4	217.6
Trametinib	19.0	218.7
Apitolisib	18.0	221.5
Afatinib	17.3	223.2
Sapanisertib	14.9	229.9
Dovitinib	12.4	236.5
Crizotinib	9.4	244.5
Buparlisib	8.5	247.1
Linsitinib	3.2	261.3
Temsirolimus	3.2	261.3
Cabozantinib	2.4	263.6
MK2206	1.9	265
Erlotinib	1.3	266.5
Midostaurin	-27.4	343.9

	MM337X Score	MM337X AUC
Ganetespib	65.4	93.5
Sapanisertib	30.8	186.8
BMS754807	37.8	168.0
Paclitaxel	28.7	192.6
Trametinib	27.7	195.3
Vorinostat	27.4	196.1
Linsitinib	24.6	203.6
Cobimetinib	20.1	215.8
Apitolisib	19.4	217.6
Midostaurin	17.1	223.9
XL765	16.0	226.7
Temsirolimus	15.1	229.2
Gedatolisib	13.8	232.8
MK2206	11.2	239.7
Lexibulin	10.7	241.0
Tivantinib	9.4	244.7
Buparlisib	9.1	245.5
Erlotinib	7.3	250.4
Crizotinib	6.8	251.6
Dabrafenib	6.6	252.2
Vemurafenib	4.7	257.2
AZD7762	4.1	258.8
Everolimus	3.7	259.9
Cabozantinib	-0.6	271.6
Mebendazole	-0.7	271.9
Afatinib	-0.8	272.1
AZD4547	-1.0	272.7
Imatinib	-8.7	293.4
Cilengitide	-9.1	294.6
Dovitinib	-11.6	301.3
Lapatinib	-12.4	303.4

MM302X

Drug	Score	AUC	AUC CL	Drug combination	Score	AUC	AUC CL
BMS754807	81.0	51.3	44.52 to 58.12	Vemurafenib + BMS754807	86.01	37.78	34.07 to 41.5
Paclitaxel	71.4	77.3	67.1 to 87.5	Vemurafenib + Paclitaxel	83.9	43.5	41.2 to 45.8
Lexibulin	66.1	91.44	80.07 to 102.8	Vemurafenib + Lexibulin	81.4	50.15	43.7 to 56.6
Vorinostat	43.1	153.6	127.6 to 179.5	Vemurafenib + Vorinostat	73.6	71.37	43.3 to 99.4
Tivantinib	35.2	175	145.3 to 204.8	Vemurafenib + Tivantinib	68.9	98.6	88.0 to 109.2
Midostaurin	40.3	161.2	148.8 to 173.6	Vemurafenib + Midostaurin	68.5	92.4	80.3 to 104.5
Sapanisertib	59.5	109.3	101.7 to 116.9	Vemurafenib + Sapanisertib	65.8	84.1	72.9 to 95.2
Gedatolisib	51.0	132.4	122 to 142.8	Vemurafenib + Gedatolisib	63.5	85.1	76.6 to 93.7
Apitolisib	26.0	199.9	186.1 to 213.8	Vemurafenib + Apitolisib	58.0	113.5	100.6 to 126.4
Dovitinib	11.9	237.8	208.9 to 266.7	Vemurafenib + Dovitinib	53.2	126.3	106.7 to 145.8

MM358X

Drug	Score	AUC	AUC CL	Drug combination	Score	AUC	AUC CL
BMS754807	36.2	172.2	153.9 to 190.5	Vemurafenib + BMS754807	71.9	75.9	70.17 to 81.58
Paclitaxel	35.6	174	154.3 to 193.7	Vemurafenib + Paclitaxel	63.56	98.38	85.5 to 111.3
Lexibulin	59.9	108.2	93.9 to 122.5	Vemurafenib + Lexibulin	65.59	92.9	71.93 to 113.9
Vorinostat	28.6	192.7	176 to 209.3	Vemurafenib + Vorinostat	53.89	124.5	106.1 to 142.9
Tivantinib	24.6	203.6	164.7 to 242.5	Vemurafenib + Tivantinib	44.52	149.8	139.2 to 160.5
Sapanisertib	14.9	229.9	183.4 to 276.3	Vemurafenib + Sapanisertib	45.26	147.8	135.1 to 160.4
Gedatolisib	37.3	169.2	146.2 to 192.1	Vemurafenib + Gedatolisib	58.11	113.1	104.4 to 121.7
Apitolisib	18.0	221.5	184.1 to 259	Vemurafenib + Apitolisib	53.85	124.6	112.5 to 136.7
Dovitinib	12.4	236.5	217.5 to 255.5	Vemurafenib + Dovitinib	45.22	147.9	134.8 to 161.1

MM337X

Drug	Score	AUC	AUC CL	Drug combination	Score	AUC	AUC CL
Lexibulin	10.74	241	220.2 to 261.8	Vemurafenib + Lexibulin	51.2	131.7	127 to 136.5
Vorinostat	27.37	196.1	176.3 to 215.8	Vemurafenib + Vorinostat	39.9	162.4	152.6 to 172.2
Tivantinib	9.37	244.7	222.7 to 266.6	Vemurafenib + Tivantinib	25.8	200.3	186.5 to 214.1
Midostaurin	17.07	223.9	205.8 to 241.9	Vemurafenib + Midostaurin	30.4	188	175.9 to 200
Gedatolisib	13.78	232.8	219.1 to 246.4	Vemurafenib + Gedatolisib	34.5	176.8	162.3 to 191.3
Dovitinib	-11.59	301.3	285 to 317.6	Vemurafenib + Dovitinib	22.8	208.5	197.4 to 219.7