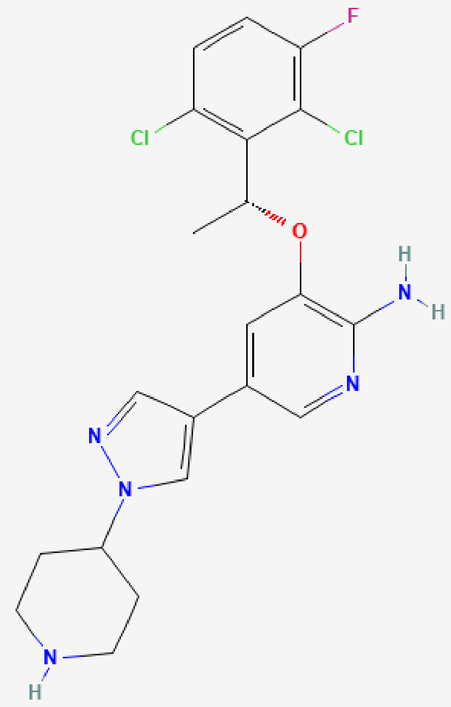
Supplementary Table S1

Tyrosine kinase inhibitor	IC50			
Crizotinib	ROS1	c-MET	ALK	
	Cell-free assay	A549, MDA-MB-231, GTL-16, HT29, 786-O, Colo-205, A498 cells	Karpas299 cells	
	<0.025 nM(Ki)	11 nM	24 nM	
	PMID: 25733882	PMID: 17483355		
Savolitinib	c-MET	p-MET	c-MET	
	Cell-free assay	Cell-free assay	NCI-H441	
	5 nM	3 nM	6 nM	
	PMID: 25148209		PMID: 25148209	
Capmatinib	c-MET	c-MET		
	cell-free assay	MKN45, NCI-H1993, SNU5		
	0.13 nM	1.7-2.7 nM		
	PMID: 21918175	PMID: 28411455, 30871613		
Cabozantinib	VEGFR2/KDR	c-Met	Axl	c-Met
	Cell-free assay	Cell-free assay	Cell-free assay	TPR-MET BA/F3, EBC1, MKN45, Hs746T, SNU5
	0.035 nM	1.3 nM	7 nM	6.9-51.4 nM
	PMID: 21613405			PMID: 30248654; 27068889, 21926191
Glesatinib	c-MET	RON	VEGFR1/2/3	c-MET
	Cell-free assay	Cell-free assay	Cell-free assay	MKN45, MNNG-HOS, and SNU-5
	1 nM	2 nM	3-4 nM	6-30 nM
	Bonfils C. et al. AACR 2012 Annual Meeting, 2012. Abstract 1790.			Beaulieu N. et al. 20th EORTC-NCI-AACR Symposium, 2008.
Merestinib	c-MET	DDR1	AXL	FLT3
	Cell-free assay	Cell-based assay	Cell-based assay	Cell-based assay
	2 nM (Ki)	0.1 nM	2 nM	7 nM
	PMID: 23275061	PMID: 23275061		

Supplementary Table S1. Cell-free and/or cell-based IC50 values for MET TKIs and some of their tyrosine kinase targets

Supplementary Figure S1

Crizotinib



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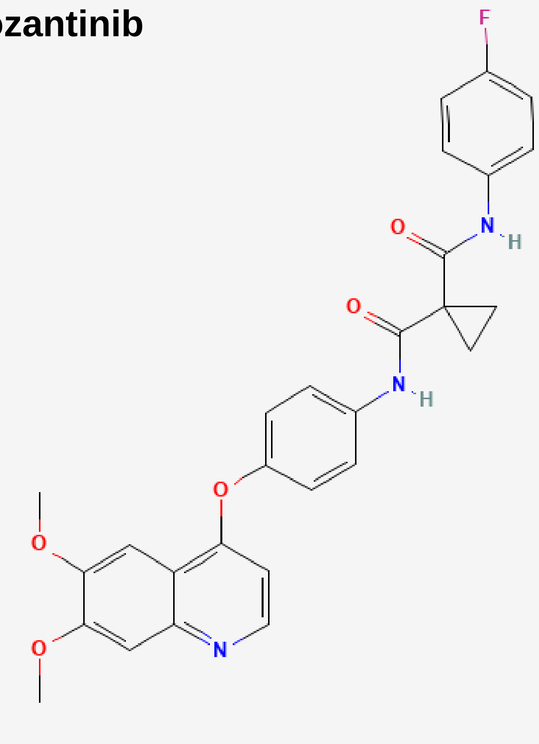
Cabozantinib



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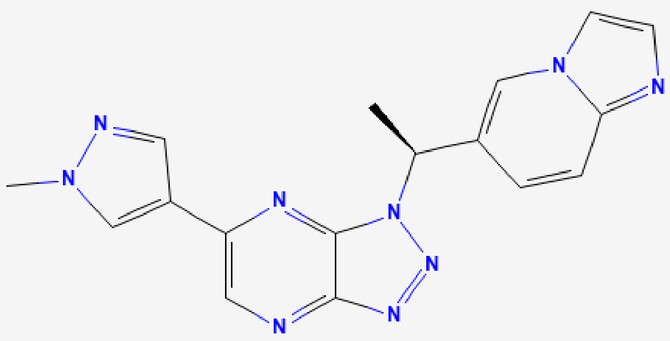
Savolitinib



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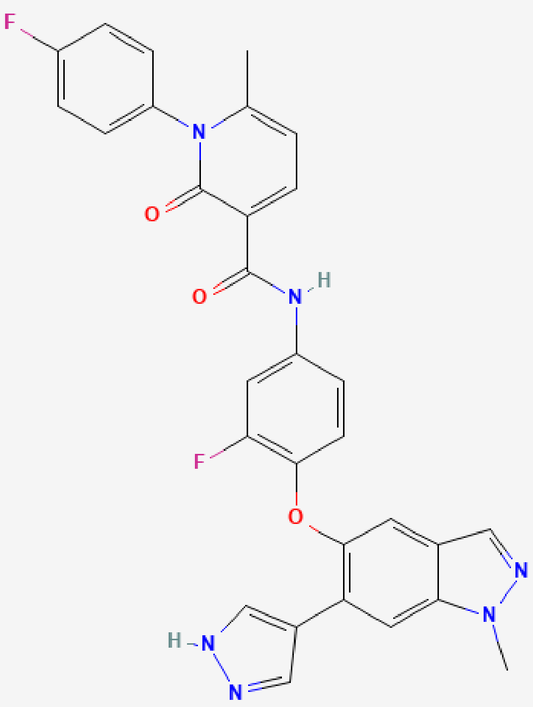
Merestinib



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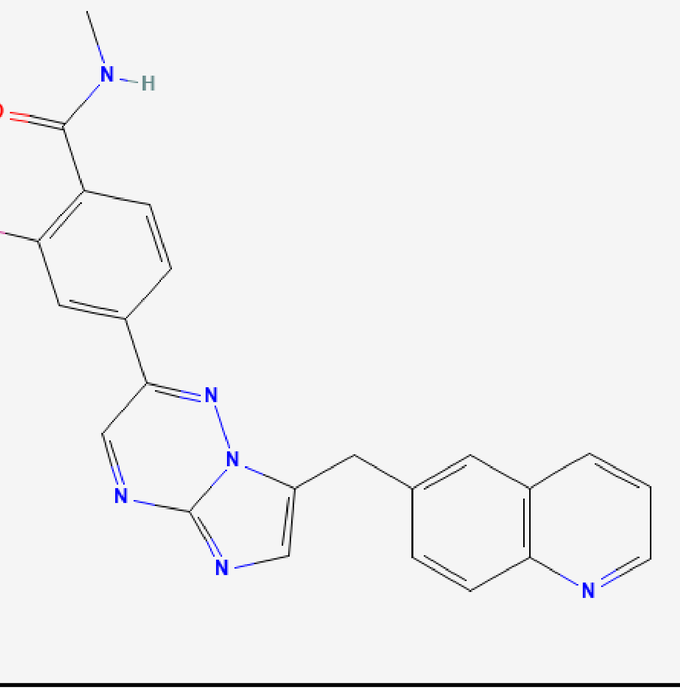
Capmatinib



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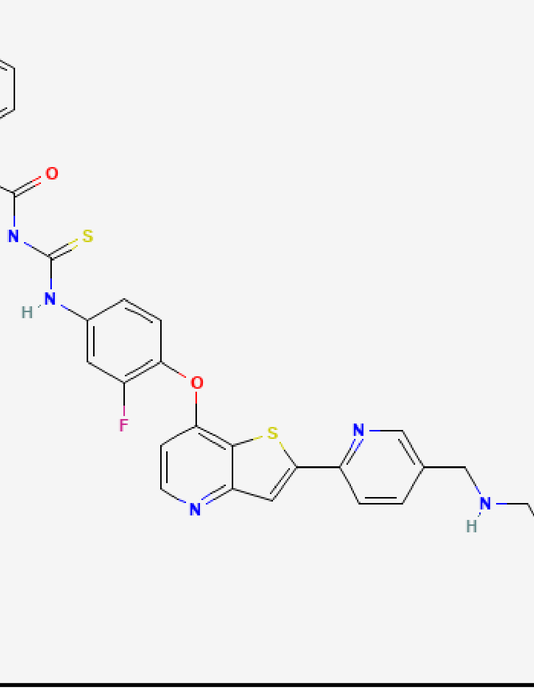
Glesatinib



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Supplementary Figure S1. Chemical structures of MET tyrosine kinase inhibitors

Supplementary Table S2

Assay	Mutation/ Amplicon	Forward Primer	Reverse Primer	Probe
Subcloning	TPR-MET	5'-GCATGATCTCGAGTATGGCGGCGGTGTTGCAGCAAGTCCT-3'	5'-GCATGATAAGCTTTCTTACTTGTCATCGTCATCCTTGTAATCTGATGTCTCCCAGAAGGAGGCTGGTCGTGTG-3'	
Mutagenesis	V1155L	5'-AAGGGTCTCCGCTGCTGGTCCTACCATAC-3'	5'-GTATGGTAGGACCAGCAGCGGAGACCCTT-3'	
Mutagenesis	M1211L	5'-GAGACTTGGCTGCAAGAAACTGTCTGCTGGATGAAA-3'	5'-TTTCATCCAGCAGACAGTTTCTTGCAGCCAAGTCTC-3'	
Mutagenesis	Y1159N	5'-CCGCTGGTGGTCCTACCAAACATGAAACATGGAG-3'	5'-CTCCATGTTTCATGTTTGGTAGGACCACCAGCGG-3'	
Mutagenesis	Y1230H	5'-TTTTGGTCTTGCCAGAGACATGCATGATAAAGAATACTATAGTGTA-3'	5'-TACACTATAGTATTCTTTATCATGCATGTCTCTGGCAAGACCAAAA-3'	
Mutagenesis	D1228N	5'-GGTTGCTGATTTTGGTCTTGCCAGAAACATGTATGATAAAGAATAC-3'	5'-GTATTCTTTATCATACATGTTTCTGGCAAGACCAAAATCAGCAACC-3'	
Mutagenesis	F1200I	5'-ATATCTTGCAAGCAAAAAGATTGTCCACAGAGACTTGGC-3'	5'-GCCAAGTCTCTGTGGACAATCTTTTTGCTTGCAAGATAT-3'	
Mutagenesis	L1195V	5'-CTTCAAGTAGCCAAAGGCATGAAATATGTTGCAAGCAAAAAGTT-3'	5'-AACTTTTTGCTTGCAACATATTTCATGCCTTTGGCTACTTGAAG-3'	
Mutagenesis	G1163R	5'-TGGTGGTCCTACCATACATGAAACATAGAGATCTTCGAAAT-3'	5'-ATTTCGAAGATCTCTATGTTTCATGTATGGTAGGACCACCA-3'	
PCR amplification	MET TKD	5'-TCTCAGAACGGTTCATGCCG-3'	5'-CCGTCATGGTCTTTGTAGTCTG-3'	
Sanger sequencing	MET TKD	5'-TGCAGCATGTAGTGATTGGGC-3'	5'-ACGGAGCGACACATTTTACG-3'	
ddPCR	Y1230H	5′- CAGTCAAGGTTGCTGATTTTGGT-3′	5′-TGCACCTGTTTTGTTGTGTACACTA-3′	5′-VIC-TGCCAGAGACATGTATGATA-MGB-NFQ-3′
				5′-FAM- CCAGAGACATGCATGATA-MGB-NFQ-3′
ddPCR	D1228N	5′- CAGTCAAGGTTGCTGATTTTGGT-3'	5′- TGCACCTGTTTTGTTGTGTACACTA-3′	5′-VIC- CTTGCCAGAGACATGT-MGB-NFQ-3′
				5′-FAM- CTTGCCAGAAACATGT-MGB-NFQ-3′
ddPCR	F1200I	5’- GATCTTATTGGCTTTGGTC-3’	5’- ACAGTTTCTTGCAGCCAAGT-3’	5’-VIC- TGTGGACAAACTTTTT-MGB-NFQ-3’
				5’-FAM- TGTGGACAATCTTTTT-MGB-NFQ-3’
ddPCR	L1195V	5′- AGATCTTATTGGCTTTGGTCTTCAAGTAG-3′	5′- GCCAAGTCTCTGTGGACAAACT-3′	5′-VIC- TTGCTTGCAAGATATTT-MGB-NFQ-3′
				5′-FAM- TGCTTGCAACATATTT-MGB-NFQ-3′
ddPCR	G1163R	5′- TCTCCGCTGGTGGTCCTA-3′	5′- ATGAGTCTCATTTCGAATGAAATTTCGA-3′	5′-VIC- CATGAAACATGGAGATCT-MGB-NFQ-3′
				5′-FAM- CATGAAACATAGAGATCT-MGB-NFQ-3′

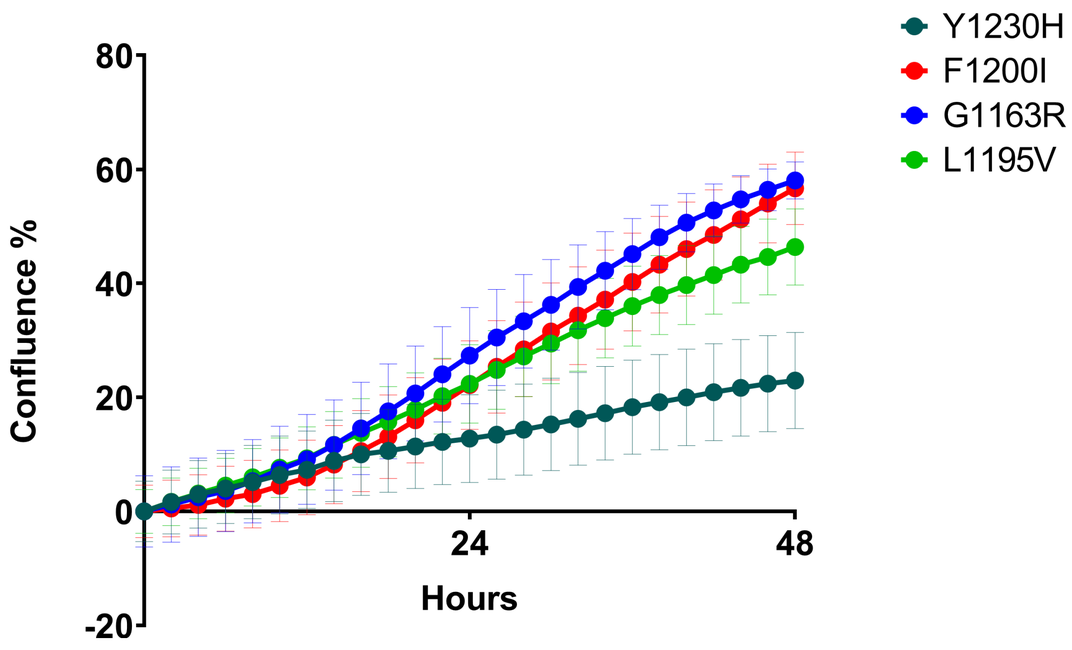
Supplementary Table S2. Primers and probes used in the study

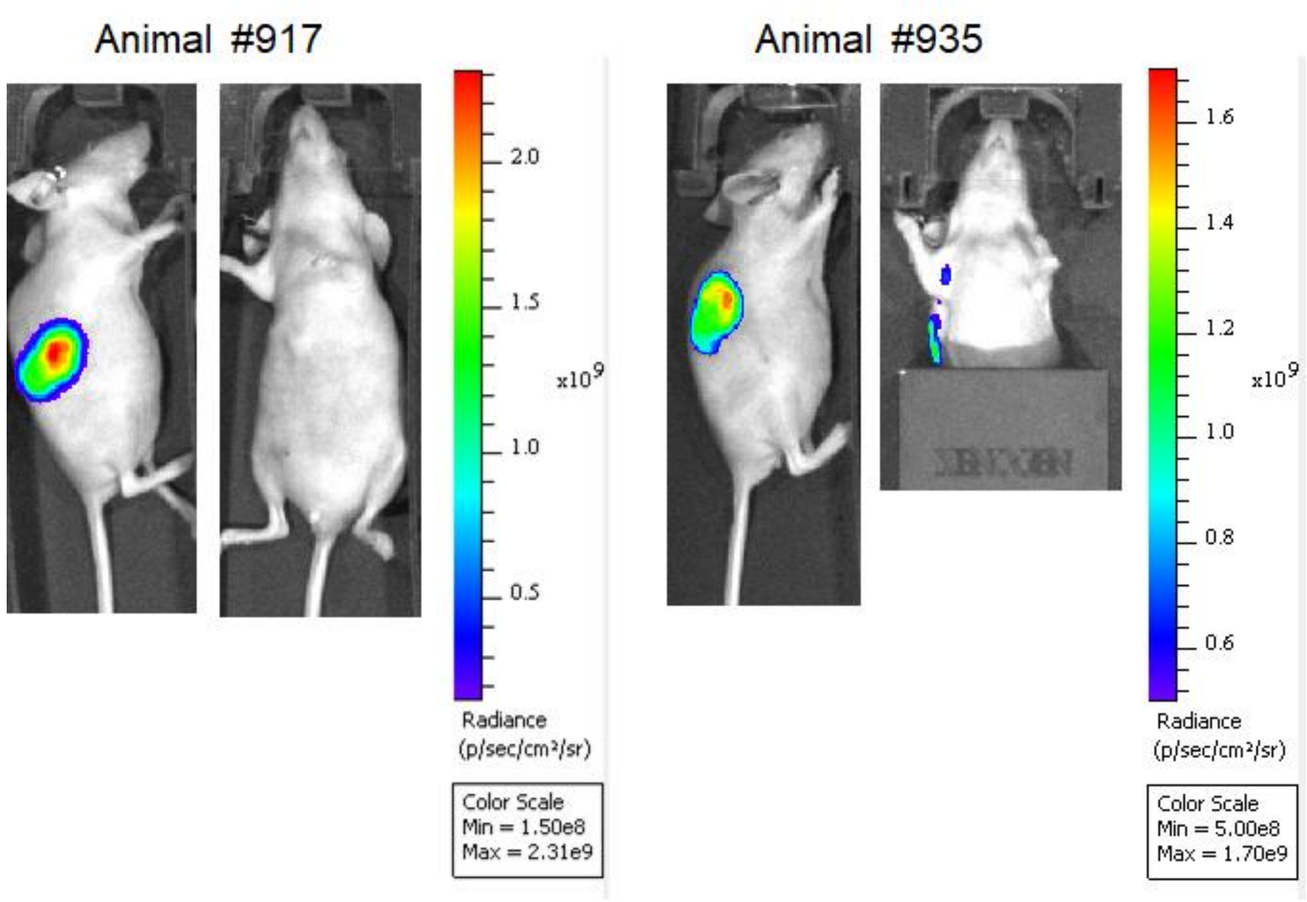
Supplementary Table S3

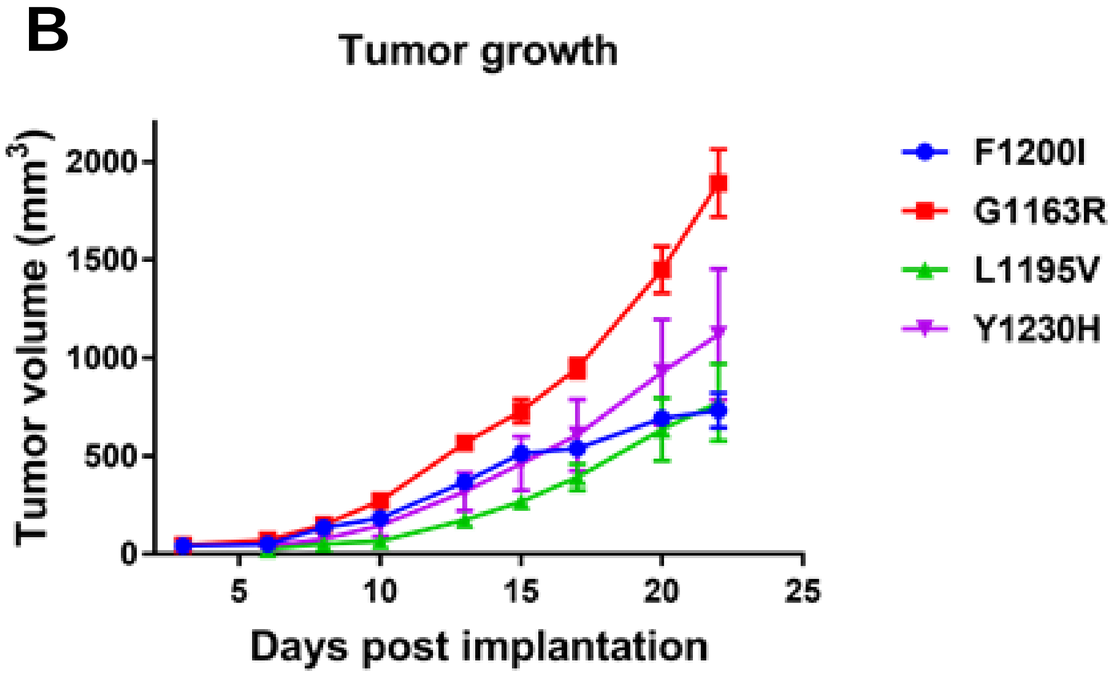
	N	%
Total sequenced	**153**	
Detected by both Sanger and ddPCR	145	95
Detected by ddPCR, not by Sanger	4	3
Detected by Sanger, not by ddPCR	5	3
Probe detects multiple aa substitutions	11	7
L1195V probe detecting L1195F	2/5	40
Y1230H probe detecting Y1230C	2/3	67
F1200I probe detecting F1200L/V	7/8	88

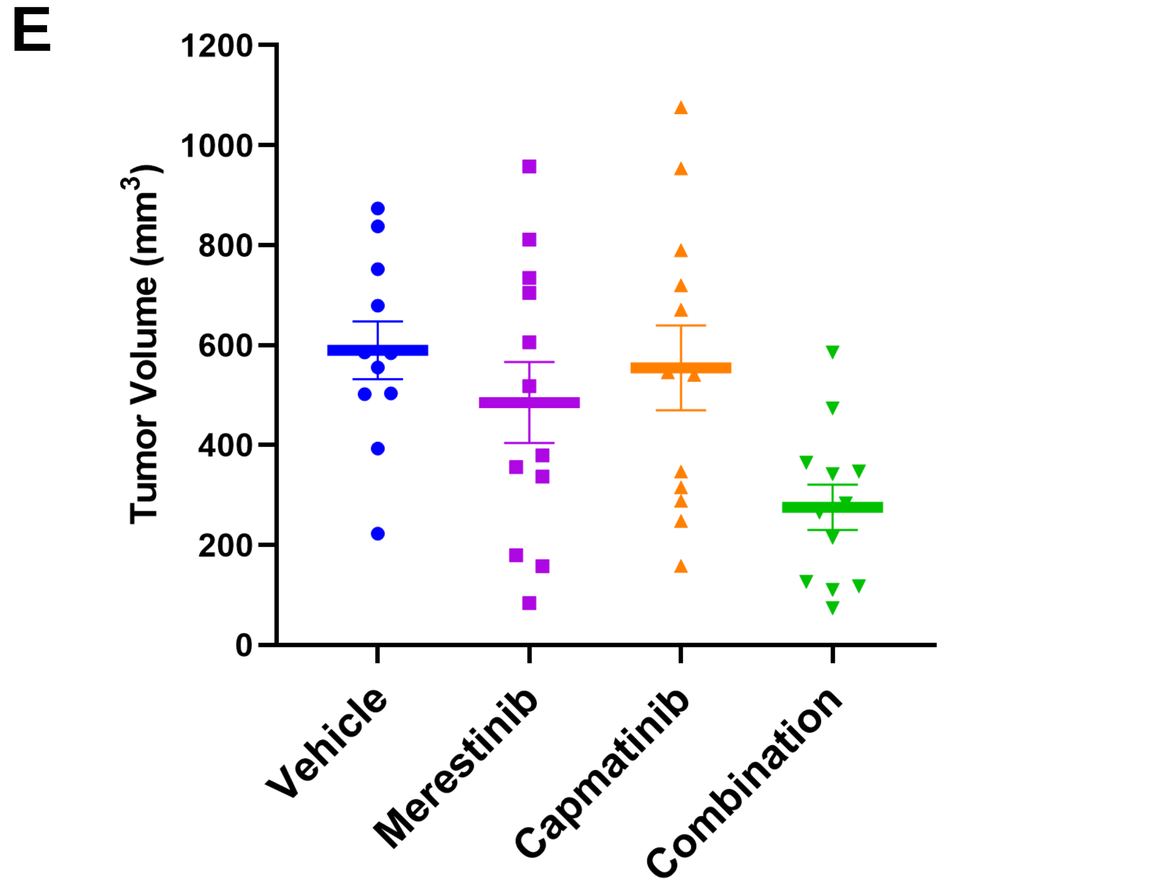
Supplementary Table S3. Comparison of Sanger and ddPCR sequencing as sequencing tools to detect MET secondary mutations.

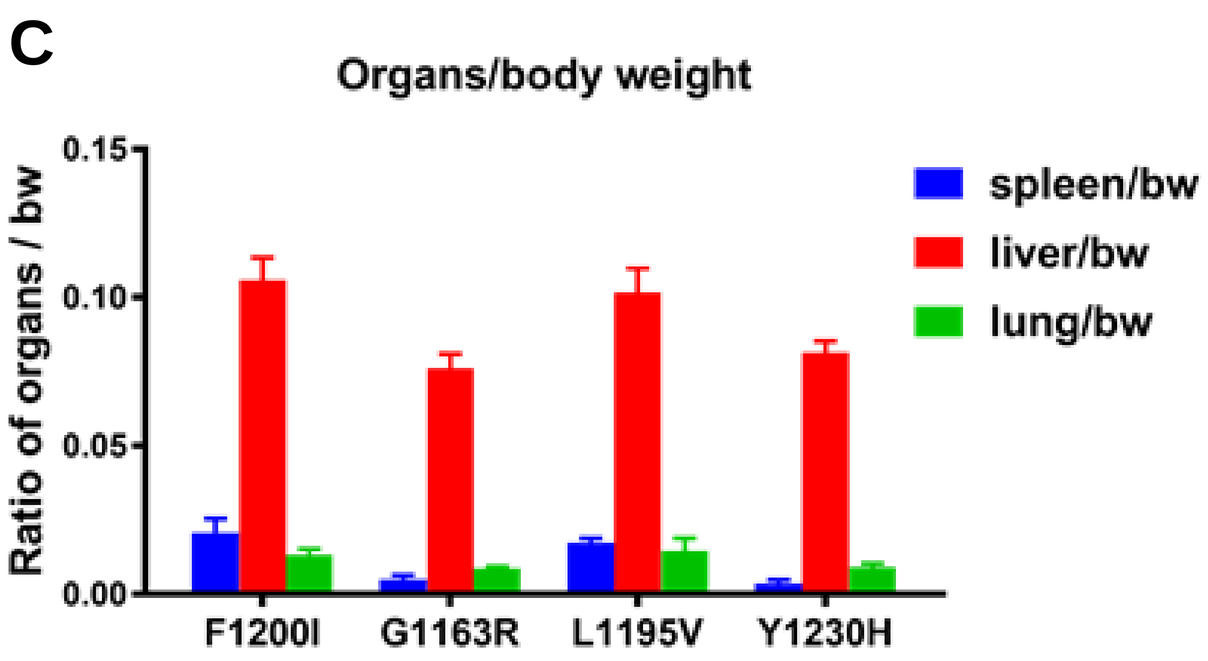
Supplementary Figure S2

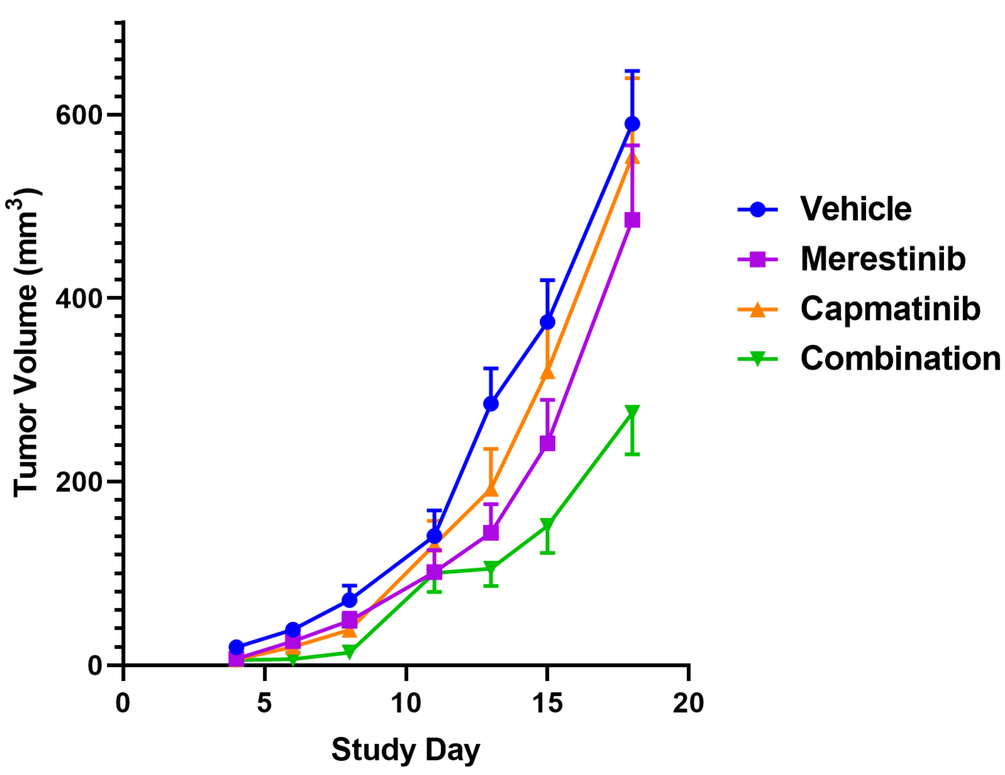








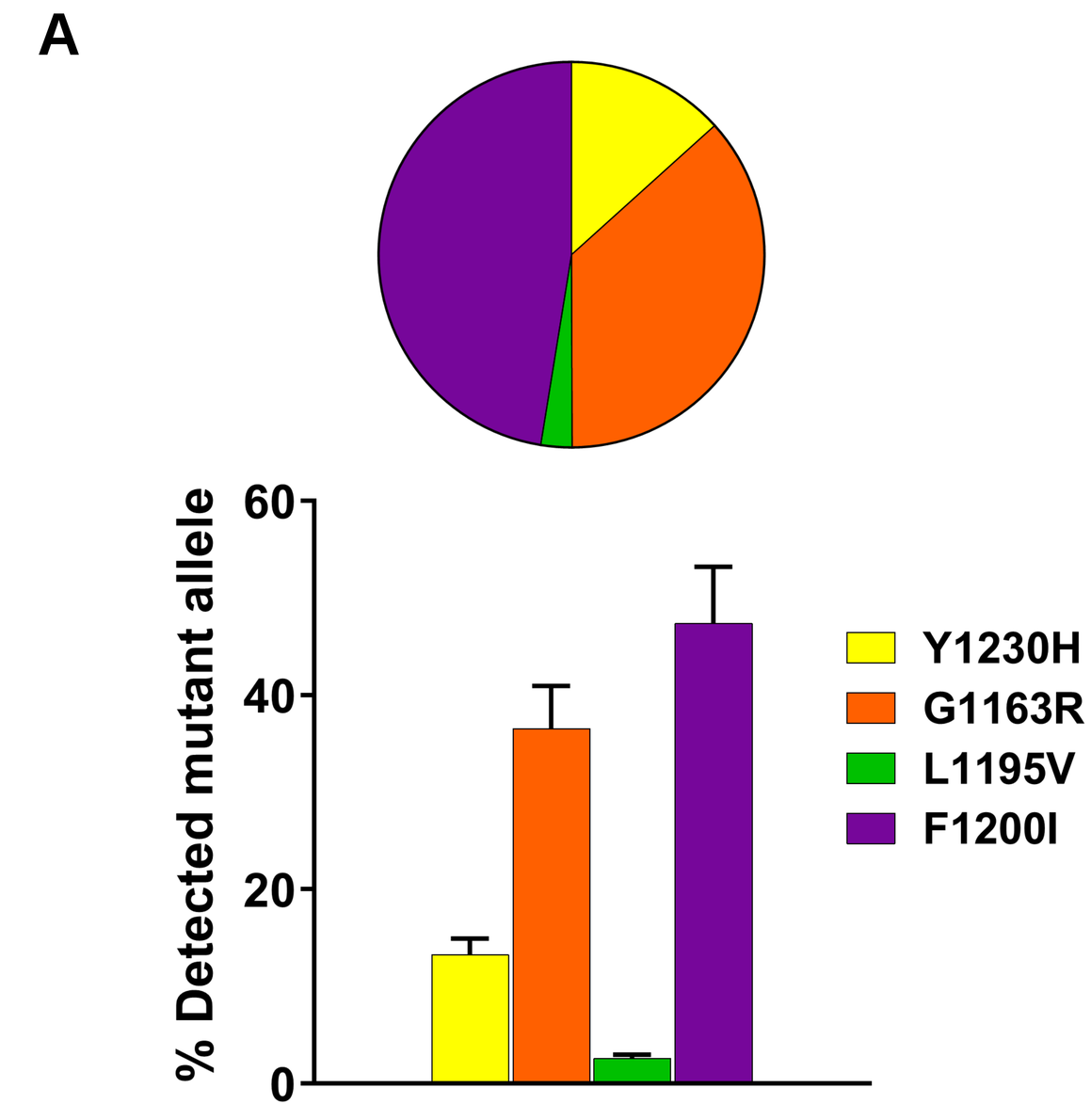




Supplementary Figure S2.

Extension of *in vivo* study data. **A,** Incucyte-based comparison of proliferation rates of TPR-MET mutant Ba/F3 cell lines. **B,** Comparison of *in vivo* growth rates of individually implanted TPR-MET mutant Ba/F3 xenografts. **C,** Surrogate for metastasis assessment – ratio of organ to body weight harvested from mice implanted with TPR-MET mutant Ba/F3 cell lines. **D,** Representative bioluminescence images of luciferized TPR-MET L1195V mutant Ba/F3 cell xenografts on day 17 of vehicle treatment showing no metastases. **E,** Column scatter plot (line = mean) of the tumor volume distribution for each treatment arm, **F,** Plot of tumor volume measurements as a function of time in days.

Supplementary Figure S3



Supplementary Figure S3. The merestinib/capmatinib combination shows tolerability and efficacy against TPR-MET L1195V mutant *in vivo*. **A,** The Y1230H; G1163R; L1195V; F1200I TPR-MET Ba/F3 cell mixture was let proliferate *in vitro* in the absence of treatment for 18 days. The individual contribution of each TPR-MET mutant was determined by ddPCR at the end of the study and expressed as parts of a whole and percent of total mutant TPR-MET cell population. Error bars represent standard deviation of the mean. **B,** A box plot of volume of tumors harvested from mice on day 17 of treatment. P-values of < 0.05 were considered significant; ns = not significant. **C,** Plot of body weight percent change of treated mice as a function of treatment time.