Capmatinib-induced resistant Hs 746T model

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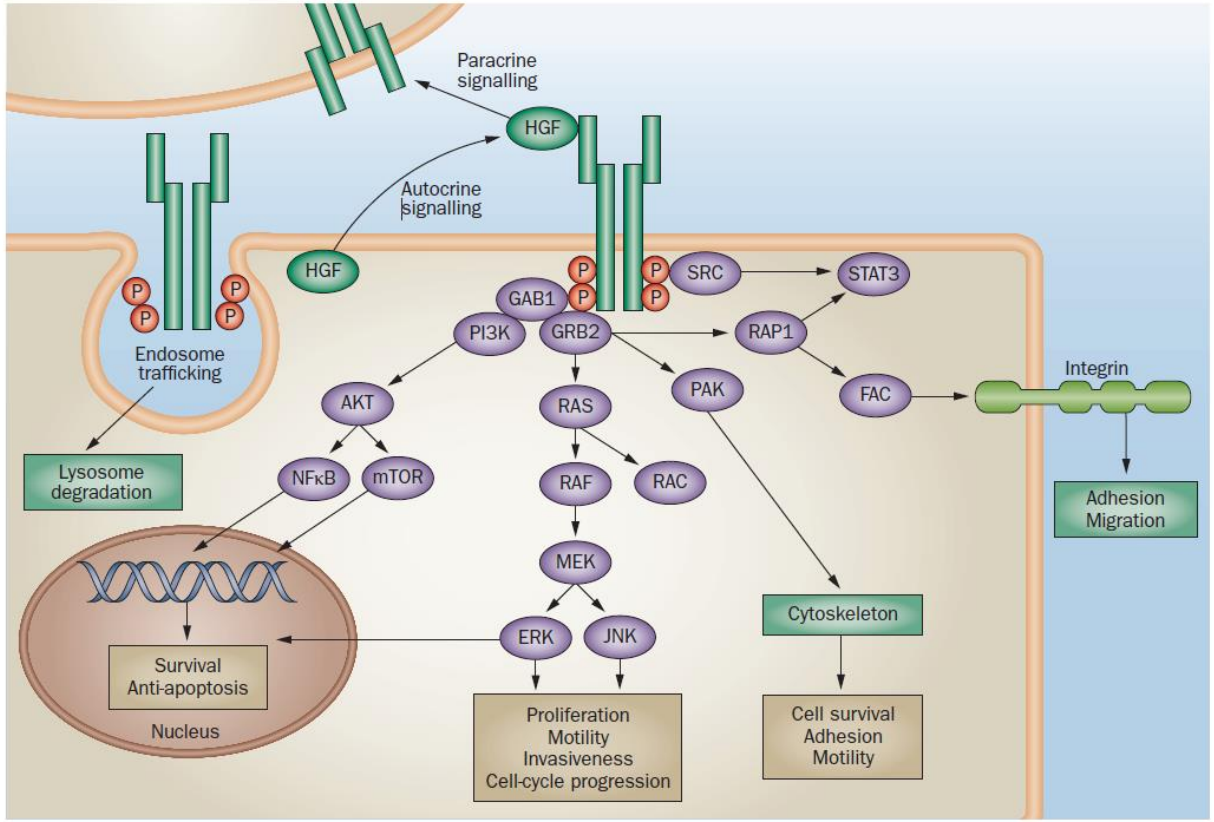
Outline

- **Background**
  - MET signaling and types of MET aberrations in cancer
  - MET TKIs
  - Mechanisms of resistance to MET TKIs
- **Development of Capmatinib-induced resistant Hs 746T model**
  - Capmatinib-R-Hs 746T model validation

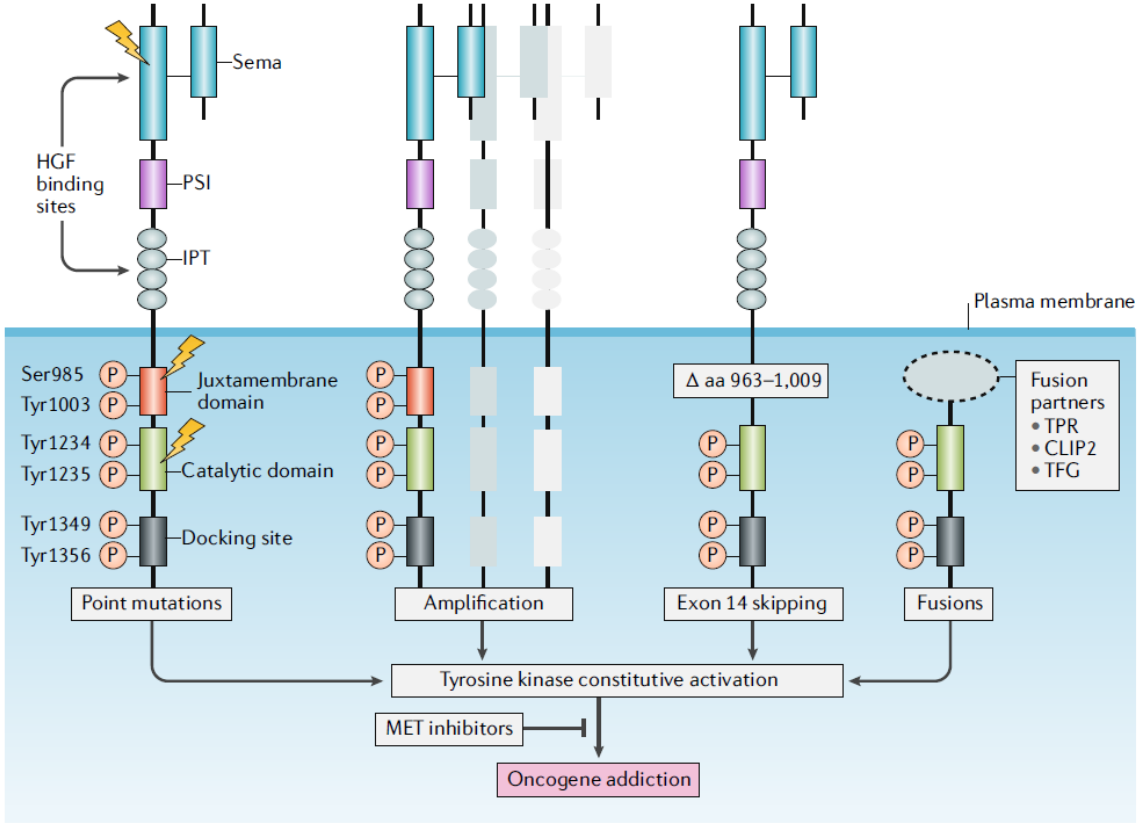
MET signaling and types of MET aberrations in cancer

MET signaling pathway



Nat. Rev. Clin. Oncol. 9, 314–326 (2012)

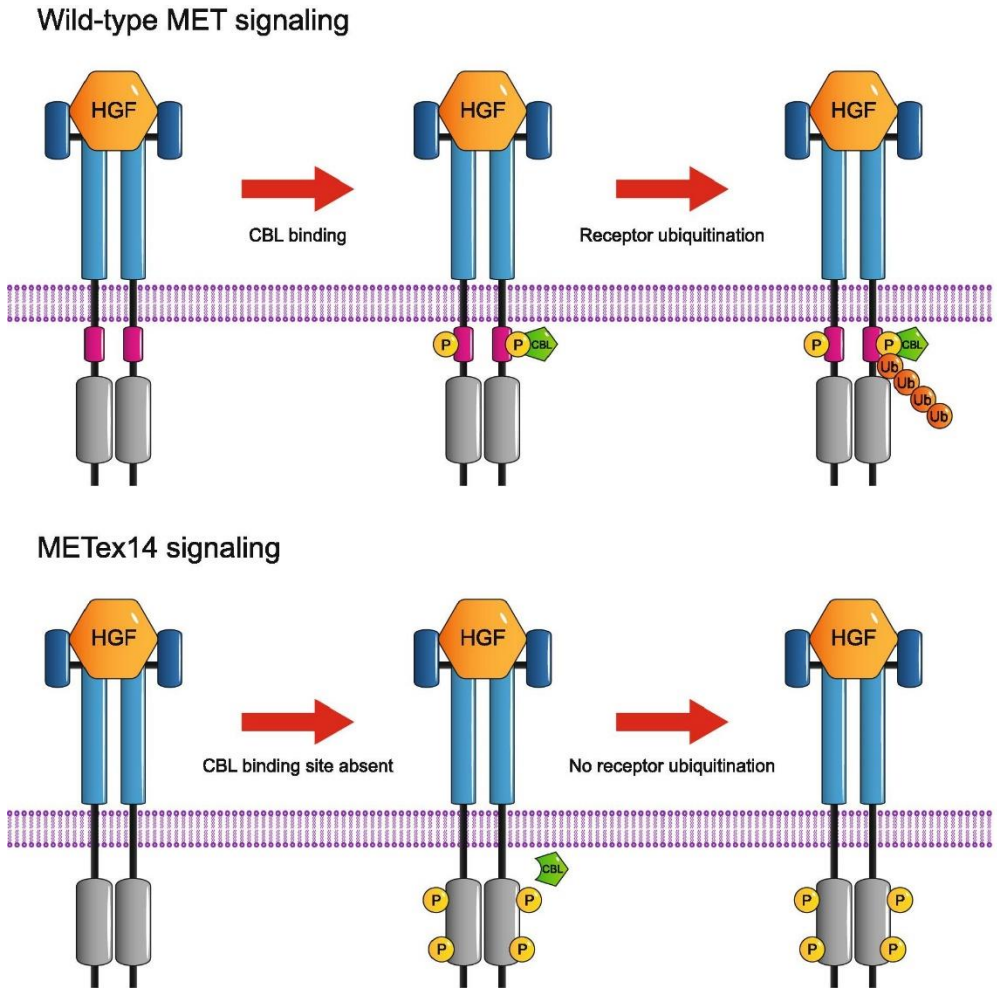
MET structural aberrations and oncogene addiction



Nature Reviews Cancer volume 18, pages341–358 (2018)

- MET is the only known receptor for HGF. Activation of the MET receptor by HGF binding triggers a large, multistep, tightly regulated signal transduction cascade.
- MET exon 14 skipping and high-level MET amplification have been found to be independent prognostic factors of poor survival in a multivariable analysis.

MET signaling and types of MET aberrations in cancer



Endocytosis
↓
Proteasomal degradation of receptor
↓
Termination of signaling

- Reduced endocytosis
- Increased receptor half-life
- Continuing signaling
- Hyper-responsiveness to ligand binding
- Transactivation by other kinases
- Potential for targeted therapeutics

Cancer Treat Rev. 2020 Jul;87:102022.

MET exon 14 alterations in lung adenocarcinoma	2.94%	(172/5838)
Exon 14 skipping mutations	2.36 %	(138/5838)
Exon 14 point mutations	0.58 %	(34/5838)
Y1003F/N/X (1/ 1 /1)	0.07 %	
D1010H/N/Y (13/10/ 7)	0.51 %	

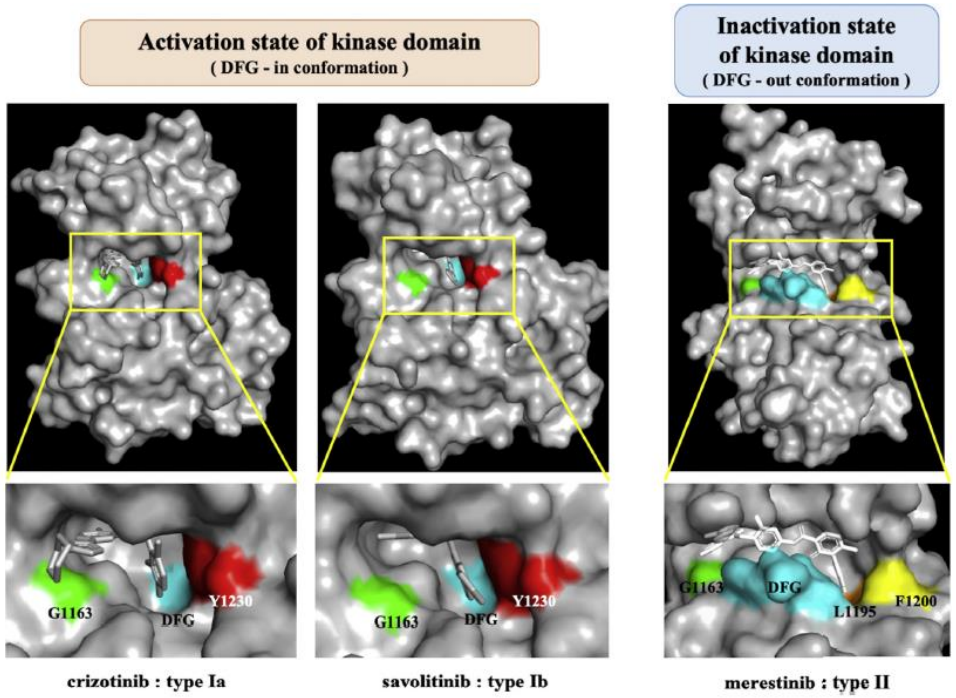
Above data consists of following molecular profiling cohort.

1. Foundation Medicine Inc. study (n=4402) (ref. 6)
2. The Memorial Sloan Kettering Cancer Center integrated mutation profiling of actionable cancer targets (MSK-IMPACT) study (n=860) (ref. 7)
3. The Cancer Genome Atlas (TCGA) study (n=230) (ref. 8)
4. The Broad Institute of Harvard and MIT study (n=183) (ref. 9)
5. The Genome Center at Washington University study (n=163) (ref. 10)

J Thorac Oncol. 2019 Oct;14(10):1753-1765.

- MET exon 14 skipping alterations are distinct from other MET aberrations and are strong oncogenic drivers.

MET TKIs



J Thorac Oncol. 2019 Oct;14(10):1753-1765.

- Type I TKIs: bind to the active state of kinase (DFG-in)
  - Type Ia inhibitors interact more with G1163
    eg. Crizotinib
  - Type Ib inhibitors interact more with Y1230 but have no interaction with G1163 (more specific)
    eg. Capmatinib, Tepotinib, Savolitinib
- Type II TKIs: bind to the inactive state of kinase (DFG-out)
  - eg. Cabozantinib, Merestinib, and Glesatinib

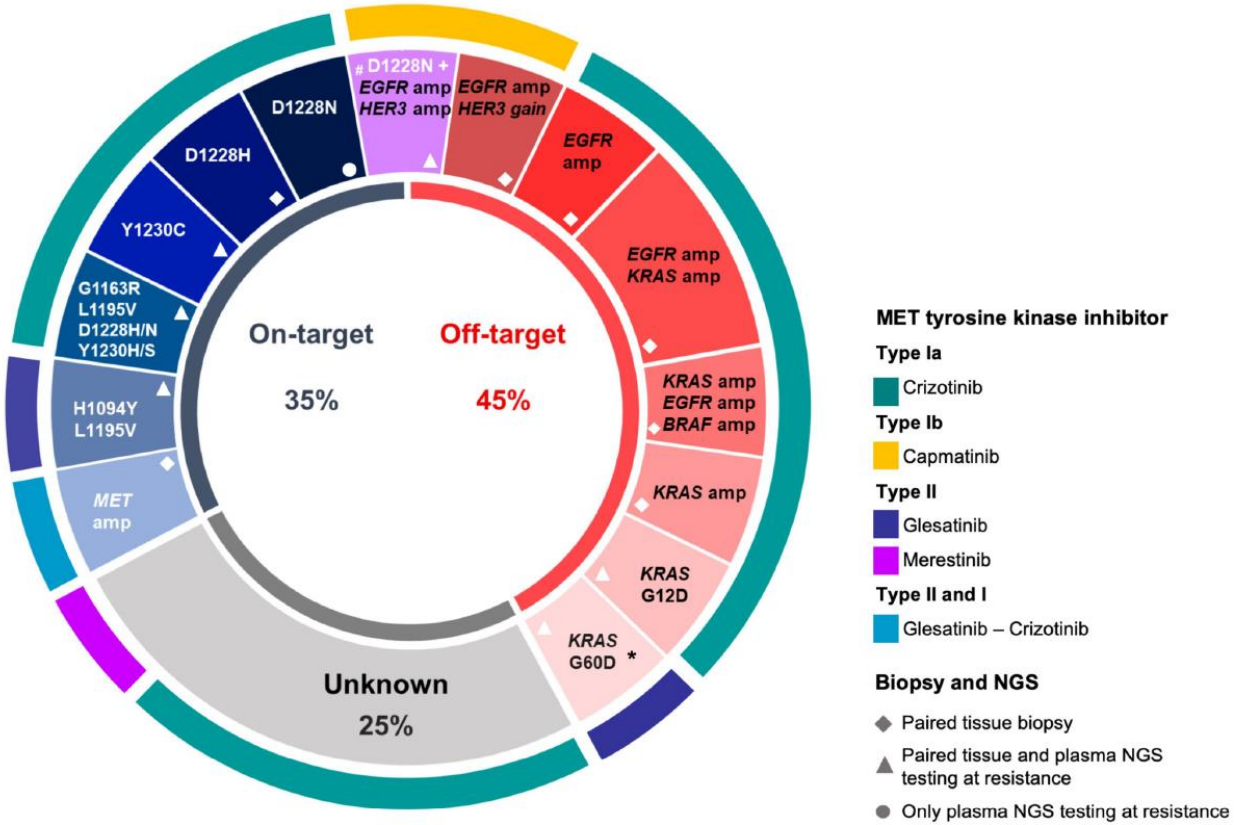
Table 1 Summary of MET inhibitors in use and in development.

Compound name	Company	Targeted kinase(s)
Crizotinib (PF-02341066)	Pfizer (New York City, New York, USA)	MET, ALK, RON, AXL, TIE2, ROS1
Cabozantinib (XL184)	Exelixis (Alameda, California, USA)	MET, RET, VEGFR1–3, KIT, FLT3, TIE2, TRKB, AXL
Foretinib (XL880)	Exelixis/GlaxoSmithKline (London, UK)	MET, VEGFR2, RON, ERK, AKT, PDGFRβ, c-KIT, TIE2
Glesatinib (MGCD265)	MethylGene/Mirati Therapeutics (San Diego, California, USA)	MET, RON, VEGFR1–2, PDGFR, KIT, FLT3, TIE2, AXL
Golvatinib (E-7050)	Eisai (Tokyo, Japan)	MET, VEGFR2, RON, EPH, KIT
Merestinib (LY2801653)	Eli Lilly	MET, MST1R, FLT3, AXL, MERTK, TIE2, ROS1, NTRK1/2/3, DDR1/2, MKNK1/2, VEGFR2
PF-04217903	Pfizer	MET, ALK
AMG 208	Amgen	MET, VEGFR1–3, RON, TIE2
Capmatinib (INC280/ INCB28060)	Incyte (Wilmington, Delaware, USA) /Novartis (Basel, Switzerland)	MET
Tepotinib (EMD1214063)	EMD Serono (Darmstadt, Germany)	MET
AMG 337	Amgen	MET
Savolitinib/Volitinib (AZD6094)	AstraZeneca (Cambridge, UK)	MET
OMO-1 (JNJ-38877618)	Johnson & Johnson (New Brunswick, New Jersey, USA)	MET

Oncogene volume 39, pages2845–2862 (2020)

- The selective MET TKIs **Capmatinib**, **Tepotinib** and **Savolitinib** have been granted approval for treatment of NSCLC with MET exon 14–skipping alterations.

Mechanisms of resistance to MET TKIs



Clin Cancer Res. 2020 Jun 1;26(11):2615-2625.

- On-target secondary mutations and activation of bypass signaling have been clinically documented and preclinically characterized to confer resistance to type I and type II MET TKIs.

Table 2. Studies reporting mechanisms of resistance in MET ex14+ NSCLC to MET-TKI

Reference	MET inhibitor	Patients	Resistance alteration	Treatment after resistance to MET-TKI	Efficacy
Dong et al. 2016 [46]	Crizotinib	1	D1228N/H and Y1230H	NA	NA
Liu et al. 2016 [8]	Crizotinib	1	PIK3CA mutation	NA	NA
Ou et al. 2017 [47]	Crizotinib	1	MET Y1230C	Radiation	NA
Engstrom et al. 2017 [37]	Crizotinib	1	MET Y1230H	Glesatinib 1050 mg twice daily	PR for 7 months
Lu et al. 2017 [48]	Crizotinib	1	D1228N, Y1230H, Y1230S, and G1163R	NA	NA
Schrock et al. 2017 [49]	Crizotinib	1	MET Y1230H mutation	Palliative chemotherapy with carboplatin and pemetrexed	NA
Zhang et al. 2017 [50]	Crizotinib	1	MET exon 17 p.G1181R missense mutation, MET exon 19 p.D1246H missense mutation, MET exon 19 p.D1246A missense mutation, MET exon 19 p.Y1248H missense mutation.	Palliative treatment	NA
Jiang et al. 2018 [51]	Crizotinib	1	MET exon 14 inserting mutation (c.3019_3028+29delinsACCTA, p.Phe1007fs)	NA	NA
Suzawa et al. 2019 [52]	Crizotinib	5	KRAS mutation	NA	NA
Ding et al. 2019 [53]	Crizotinib	1	HER2 gene amplification	NA	NA
Jin et al. 2019 [54]	Crizotinib	1	D1246N mutation	Cabozantinib with cisplatin injecting to the chest	A large cavity was found in the lung tumor by CT after 1 month
Han et al. 2019 [55]	Savolitinib	1	FGFR1, EGFR and KRAS gene amplification	Crizotinib 250 mg, orally, twice daily	PD after 2 months
Bahcall et al. 2018 [56]	Crizotinib	Patient-derived cell line and xenografts	KRAS amplification	NA	NA
Fujino et al. 2019 [57••]	Type I/II TKIs	Ba/F3 cells	D1228 and Y1230 (type I TKIs); L1195 and F1200 (type II TKIs)	NA	NA
Rotow et al. 2019 [58]	Crizotinib	Preclinical model	KRAS overexpression or NF1 downregulation hyperactivated MAPK signaling	Crizotinib and the MEK inhibitor trametinib	Resistance was overcome in preclinical model

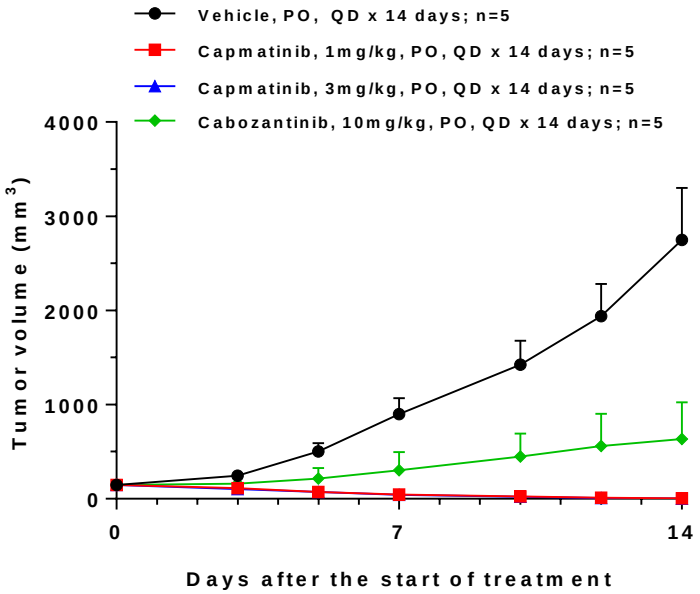
NA, not assessed; *PR*, partial response; *PD*, progressive disease

CurrTreat Options Oncol. 2020;21(4): 33.

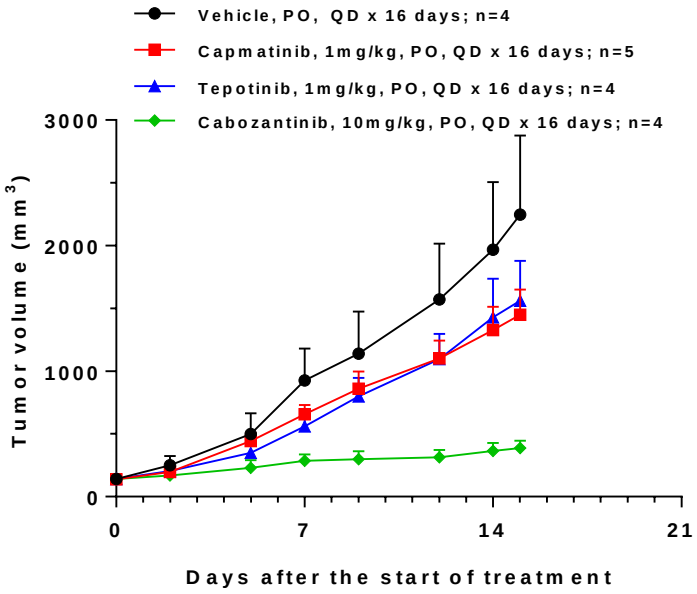
Establishment of *in vivo* induced Capmatinib-R-Hs 746T model

MET TKIs in Parental Hs 746T model vs. Capmatinib-R-Hs 746T model

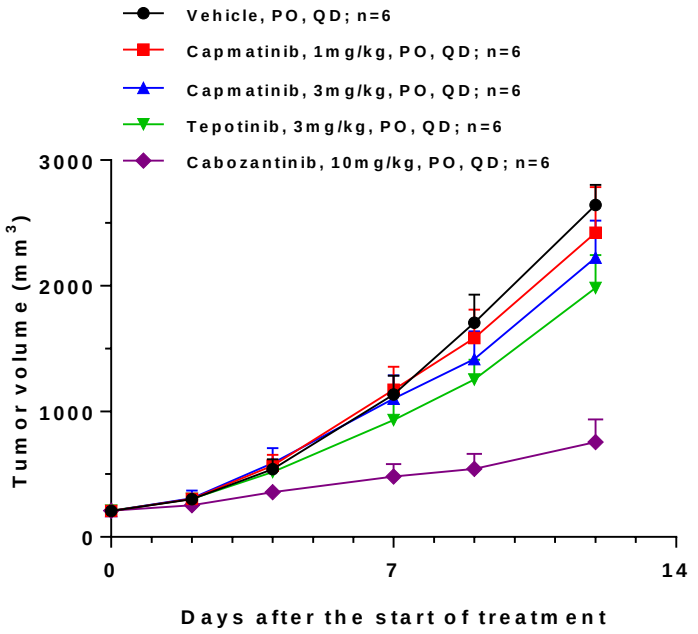
Parental Hs 746T



Capmatinib-R-Hs 746T (P5)



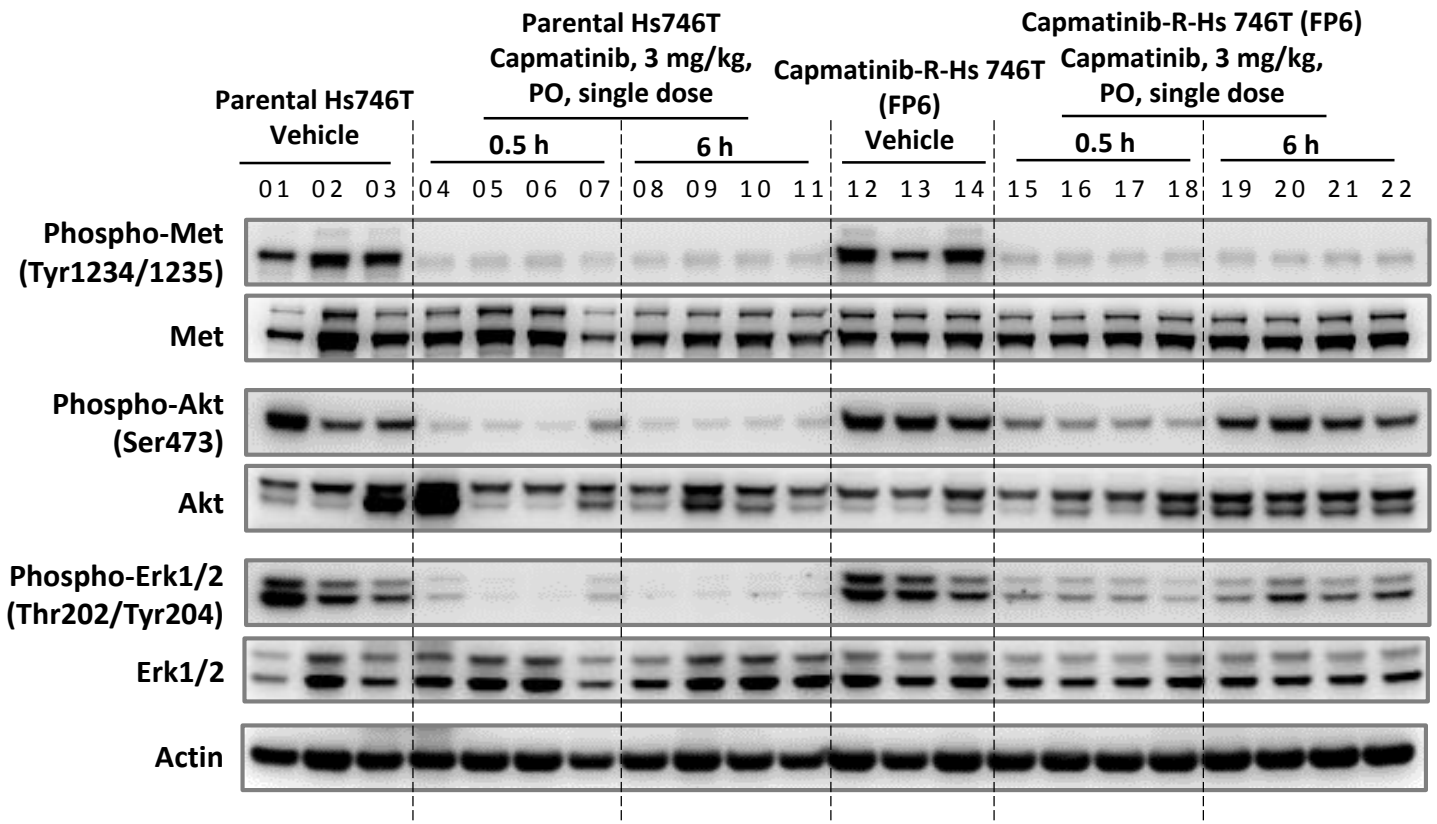
Capmatinib-R-Hs 746T (FP6) *

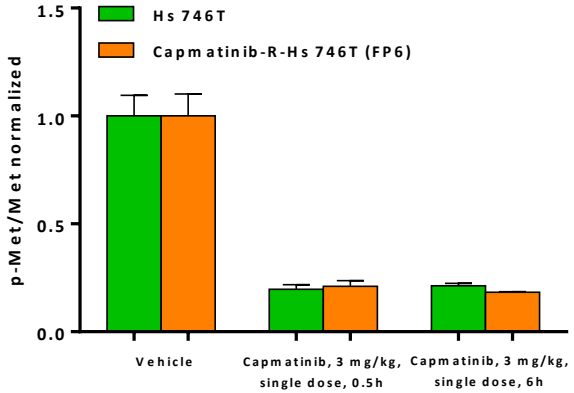


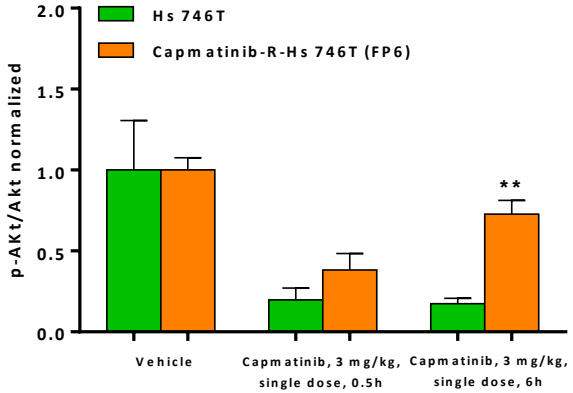
- The established Capmatinib-R-Hs 746T model is resistant to Type Ib MET TKIs Capmatinib and Tepotinib, while is still sensitive to Type II MET TKI Cabozantinib.
- *Tumor fragment revival validation test: P4 frozen tumor fragments were implanted into mice and the revival passage was defined as FP5. Tumors were passaged to FAP6 for the validation study. Data shows that the resistant phenotype of Capmatinib-R-Hs 746T model is stable.

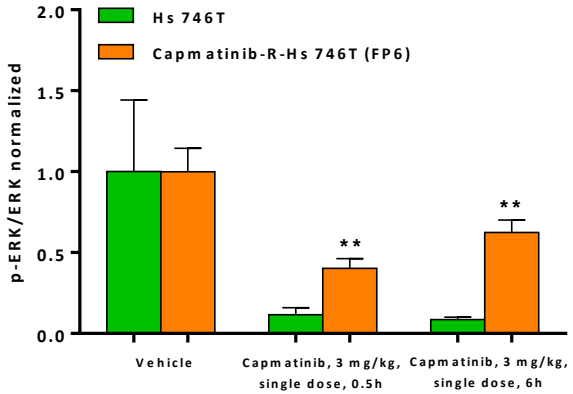
Establishment of *in vivo* induced Capmatinib-R-Hs 746T model

MET signaling Western blotting analysis in Parental Hs 746T and Capmatinib-R-Hs 746T model









- Capmatinib showed less inhibitory effect on Akt and Erk phosphorylation in Capmatinib-R-Hs 746T model.
- Capmatinib effectively inhibited Met phosphorylation in both Parental Hs746T and Capmatinib-R-Hs 746T model, suggesting a MET-independent mechanism of resistance.

Data summary of model validation

Induce method	Model ID	Cancer type	Inoculation	Drugs tested	Dosage	TGI (%)
Parental	Parental Hs 746T (MET exon 14 skipping, MET amplification)	Gastric cancer	Cell line	Capmatinib Cabozantinib	1, 3 mg/kg 10 mg/kg	105, 105 81
***In vivo* induce**	Capmatinib-R-Hs 746T (P5)	Gastric cancer	Tumor fragment	Capmatinib Tepotinib Cabozantinib	1 mg/kg 1 mg/kg 10 mg/kg	38 32 88
	Capmatinib-R-Hs 746T (FP6)	Gastric cancer	Tumor fragment	Capmatinib Tepotinib Cabozantinib	1, 3 mg/kg 3 mg/kg 10 mg/kg	9, 17 30 78

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