c-Met-related *In Vivo* Models

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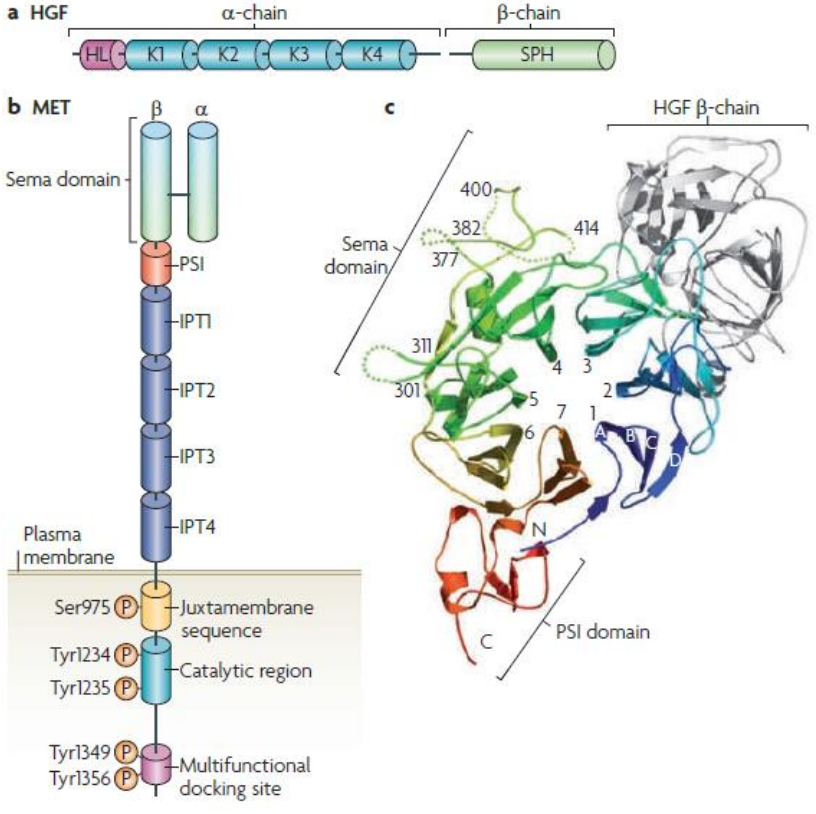
Outline

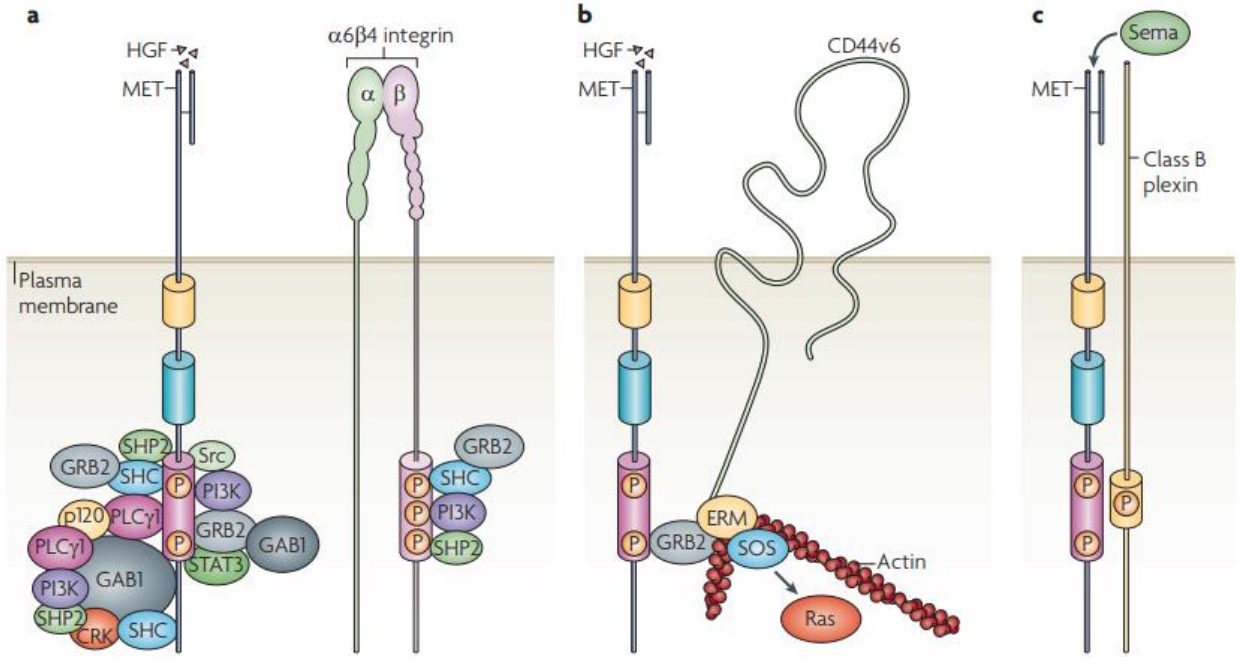
- **c-Met background as a drug target**
- **c-Met-related CDX models**
- **c-Met-related PDX models**
  - c-Met overexpression or amplification PDX models
  - c-Met exon 14 skipping PDX models
  - Clinically acquired Capmatinib-resistant LU-01-0751 PDX model

c-Met Background

c-Met biology

- c-Met, also called **tyrosine-protein kinase Met** or **hepatocyte growth factor receptor (HGFR)**, is a protein that in humans is encoded by the MET gene located on chromosome 7q31.
- MET is a single-pass heterodimer comprising an entirely extracellular α-subunit and a transmembrane β-subunit, which contains the intracellular catalytic activity.
- MET promotes tissue remodeling, which underlies developmental morphogenesis, wound repair, organ homeostasis and cancer metastasis, by a network of signaling amplifiers and co-receptors.



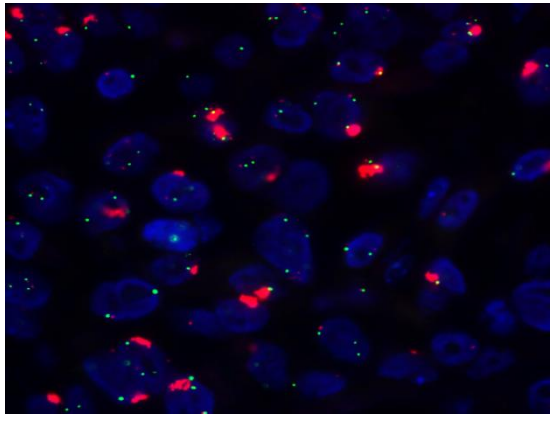


NATURE REVIEWS, Molecular cell Biology. (2010);

c-Met Background

MET oncogene activation in cancer

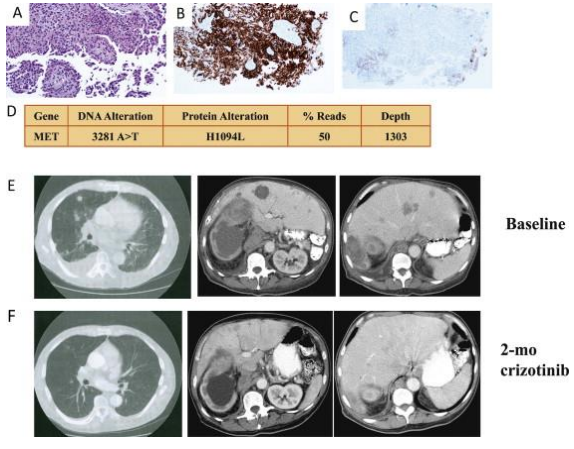
Amplification



WuXi internal data

MET AMP rate in Cancer:
Liver cancer: ~5–10%
Lung cancer: ~2–4%
Gastroesophageal cancer (GEC): ~2%
Renal Cell Carcinoma: ~2%

Point mutation



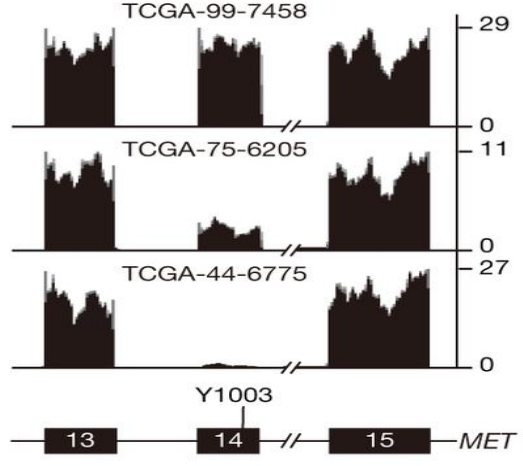
Eur Urology 2015; 67: 353-4

MET resistant mutation (H1094L) case report in Papillary Renal Cell Cancer

Papillary Renal Cell Carcinoma: ~10%

N Engl J Med. 2015 Nov 4. (TCGA)

Exon 14 skipping

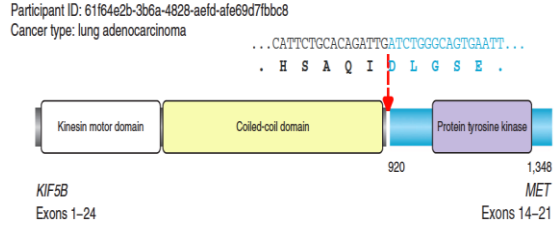


Nature. 2014 Jul 31;511(7511):543-50.

MET exon 14 skipping occurs ~4% in western lung adenocarcinoma, and 22% in pulmonary sarcomatoid carcinoma (PSC)

Cancer Discovery 2015 Aug;5(8):842-9
J Clin Oncol. 2015.62.0674

Rearrangement



Nat Commun 2014; 10;5:4846

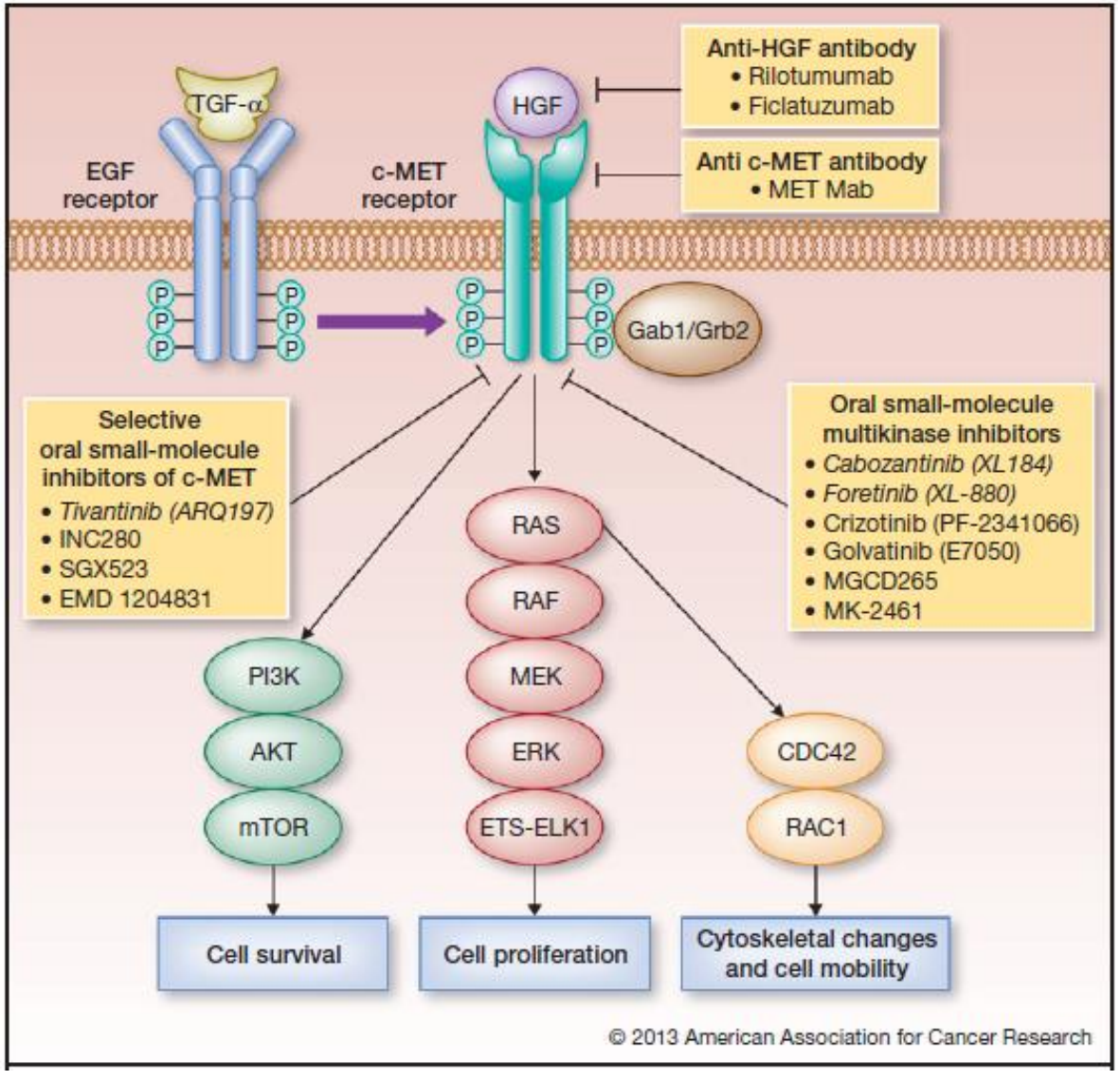
MET fusion occurs ~1% in Kidney papillary cell carcinoma, and rarely in thyroid, glioma, lung and liver cancer.

c-Met Background

Therapeutic inhibitors of the c-Met signaling pathway

- Binding of HGF to c-Met, homo-dimerization, and auto-phosphorylation elicit downstream signaling mediated by adaptor proteins (Gab1 and Grb2) to induce activation of the PI3K, Ras/ Raf/ MEK/ ERK, and Cdc42/ Rac1 pathways.

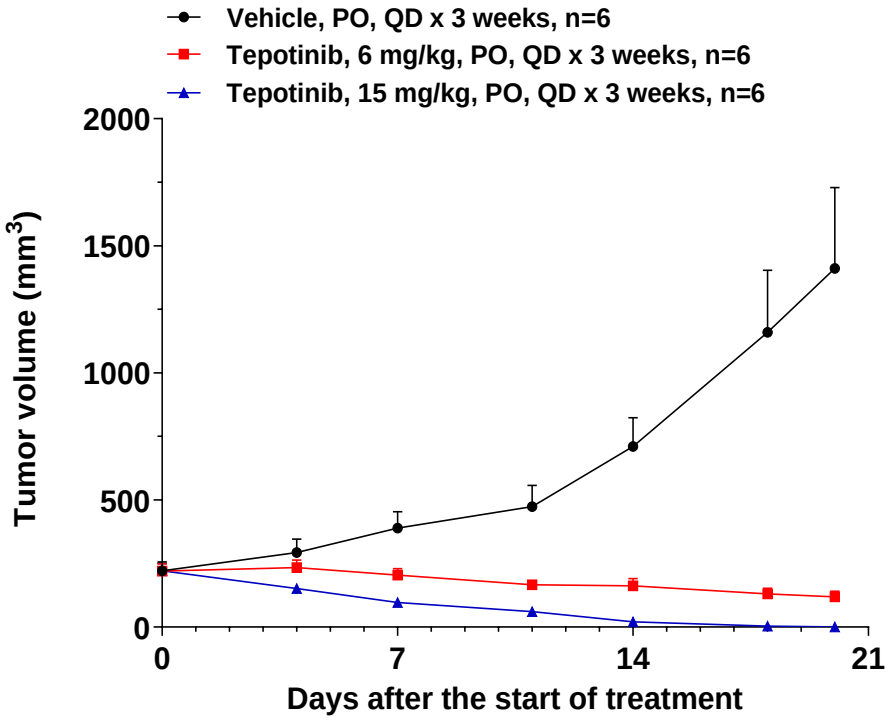
- HGF-independent signaling can be mediated by phosphorylated EGFR, which can be activated by the ligand TGF-α.

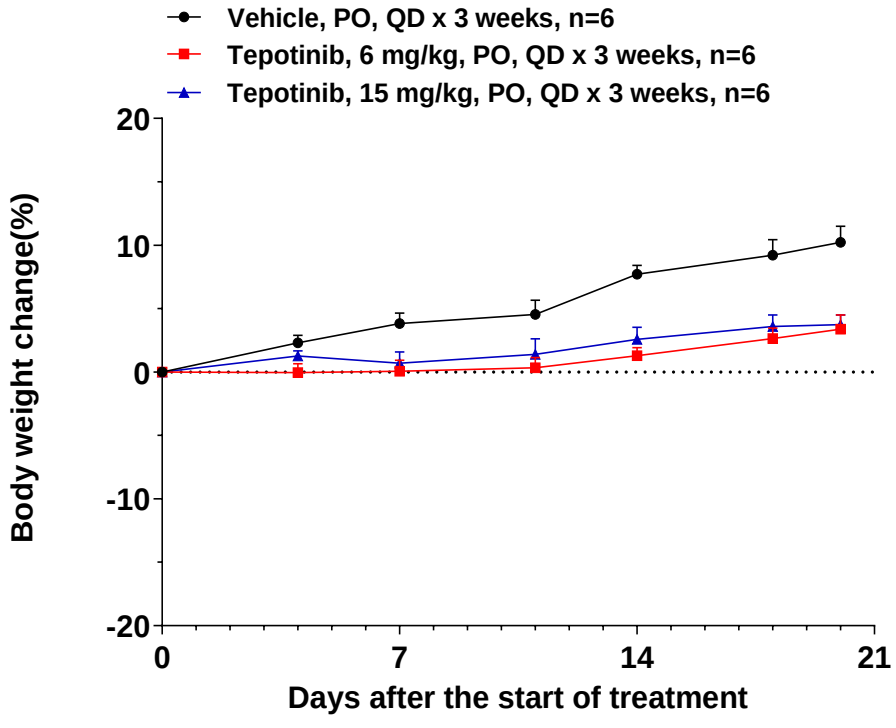


c-Met-related CDX models

Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	TGI	Model genetics
Gastric cancer	MKN45	Yes	BMS-777607	25 mg/kg, PO, QD	72% (D18)	MET amplification
			LY2801653	12.5 mg/kg (D0-D15) / 100 mg/kg (D16-D18)	98% (D18)	
	Hs746T	Yes	Tepotinib	3 mg/kg, PO, QD	69% (D24)	MET amplification, MET exon 14 skipping
			Capmatinib	1 mg/kg, PO, QD 3 mg/kg, PO, QD	105% 105%	
			Cabozantinib	10 mg/kg, PO, QD	81%	
	SNU-5	Yes	--			MET amplification
	GTL-16	No	--			
HCC	MHCC97H	Yes	Tepotinib	3 mg/kg, PO, QD	73% (D28)	c-Met overexpression
				10 mg/kg, PO, QD	105% (D28)	
	MHCC97-L	No	--			
	HCCLM3	No	--			
Glioblastoma	U87MG	Yes	Crizotinib	60 mg/kg, PO, QD	98% (D18)	c-Met autocrine
Lung cancer	NCI-H441	Yes	--			MET amplification
	EBC-1	Yes	Tepotinib	6 mg/kg, PO, QD 15 mg/kg, PO, QD	109% 119%	MET amplification
	NCI-H820	Yes	Capmatinib	15 mg/kg, PO, QD	107%	EGFR exon 19 del, EGFR T790M, MET amplification
			Cabozantinib	30 mg/kg, PO, QD	109%	
	NCI-H1573	No	--			MET amplification
	NCI-H596	No	--			MET exon 14 skipping, PIK3CA mutated
Pancreatic cancer	KP4	Yes	Capmatinib	3 mg/kg, PO, QD	53%	c-Met autocrine

Anti-tumor efficacy of Tepotinib in EBC-1 xenograft model





c-Met-related PDX models

MET overexpression or amplification

Cancer type	Model ID	Growth curve	CNV	RNASeq (FPKM)	Model genetics
Liver cancer	LI-03-0117	Yes	5.05	506.88	MET amplification
Liver cancer	LI-03-0228	Yes	5.25	225.32	
Liver cancer	LI-03-0317	Yes	5.48	896.57	
Liver cancer	LI-03-0839	Yes	5.39	457.89	
Lung cancer	LU-01-0506	Yes	5.54	838.88	
Lung cancer	LU-01-0781	Yes	12.04	510.63	
Lung cancer	LU-01-1377	Yes	17.90	543.51	
Lung cancer	LU-01-1649	Yes	8.14	361.39	
Lung cancer	LU-01-1178	Yes	5.20	403.72	
Gastric cancer	ST-02-0168	Yes	5.45	1217.68	
Lung cancer	LU-01-0439	Yes	3.28	157.3	MET overexpression

For more MET-related PDX models, please check ***https://onco.wuxiapptec.com***

c-Met-related PDX models

H-score of c-Met IHC staining

Model ID	MET Expression (RNAseq_FPKM)	0 positive rate (%)	1+ positive rate (%)	2+ Positive rate (%)	3+ positive rate (%)	H-score (0-300)
LU-01-1649	361.39	1	4	21	74	268
LU-01-1178	403.72	1	5	19	75	268
ST-02-0168	1217.86	2	5	43	50	241
LI-03-0317	896.57	3	7	35	55	242
LU-01-0506	838.88	1	5	39	55	248
LU-01-1640	624.7	0	0	35	65	265
LY-24-0109	620.73	2	35	43	20	181
LY-24-0059	611.23	1	5	50	44	237
KI-12-0094	570.99	1	2	42	55	251
LU-01-1377	543.51	1	0	44	55	253
LU-01-0781	510.63	1	3	41	55	250
LI-03-0117	506.8	2	15	58	25	206
LU-01-1674	484.62	1	5	19	75	268
LI-03-0839	457.89	60	5	20	15	90
SA-22-0074	316.51	0	9	90	1	192
LU-01-0598	309.34	0	8	47	45	237
LU-01-1529	306.99	1	0	54	45	243
LU-01-1534	300.54	0	10	55	35	225
LI-03-0228	225.32	1	10	49	40	228
LI-03-0240	NA	1	8	41	50	240
LU-01-0439	157.3	1	17	52	30	211

c-Met-related PDX models

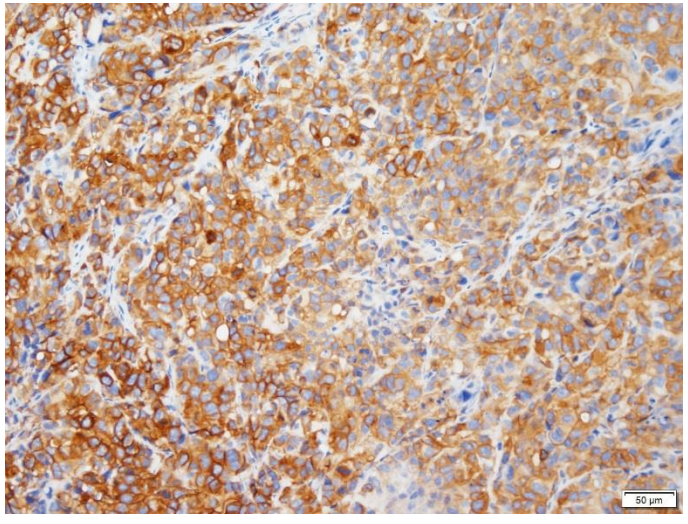
H-score of c-Met IHC staining

Model ID	MET Expression (RNAseq_FPKM)	0 positive rate (%)	1+ positive rate (%)	2+ Positive rate (%)	3+ positive rate (%)	H-score (0-300)
LU-01-1476	361.39	20	35	37	8	133
LU-01-1623	156.15	30	35	30	5	110
NP-23-0075	670.19	1	6	18	75	267

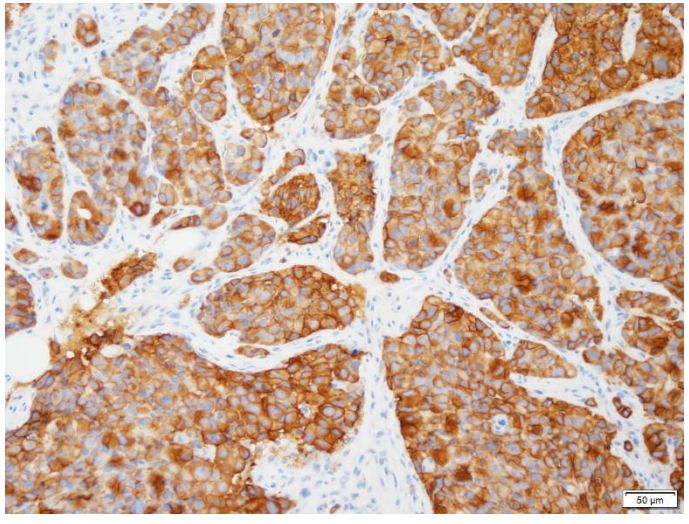
- **H-score Criteria**: low (1+): 0-50, medium (2+): 50-150, high (3+): 150-300.
- 0 for “no staining”, 1+ for “light staining”, 2+ for “intermediate staining” and 3+ for “dark staining”.
- The percentage of cells at different staining intensities was determined by visual assessment, with the H-score calculated using this formula: 1x (percentage of “1+” cells) + 2x (percentage of “2+” cells) + 3x (percentage of “3+” cells).

c-Met-related PDX models

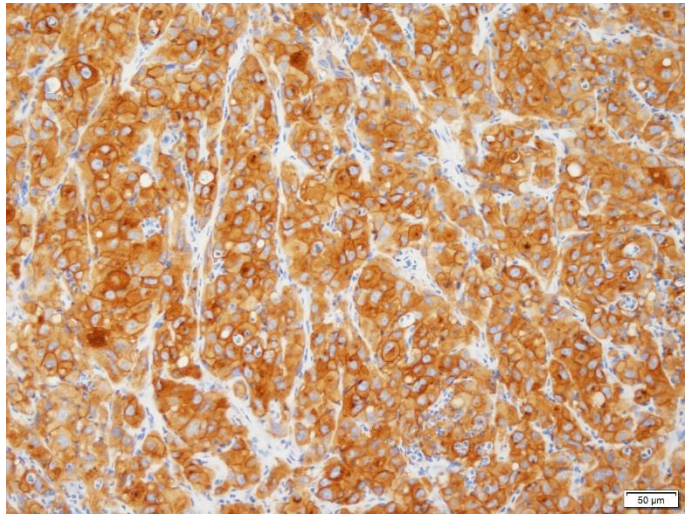
Representative images of c-Met IHC staining



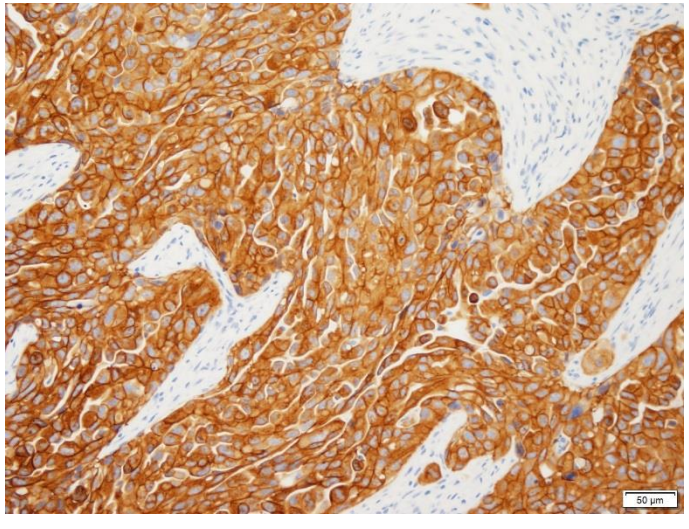
ST-02-0168 c-Met 200x



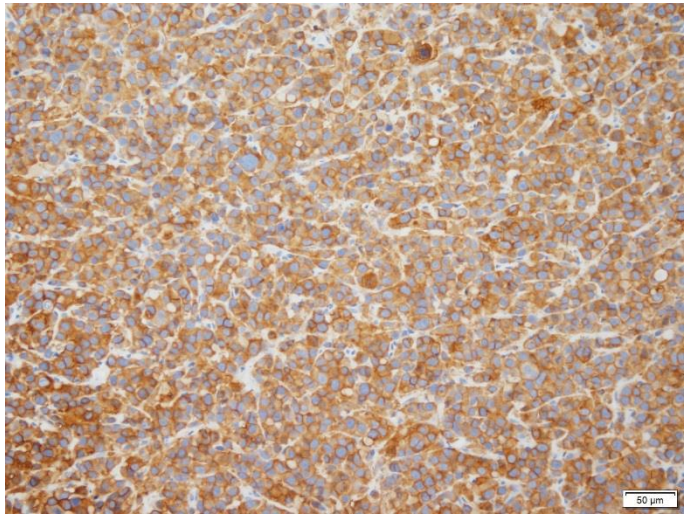
LI-03-0317 c-Met 200x



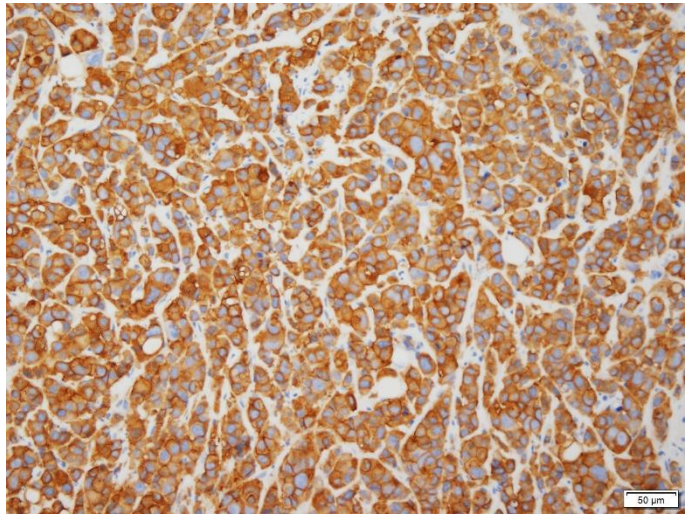
LU-01-0506 c-Met 200x



LU-01-1640 c-Met 200x



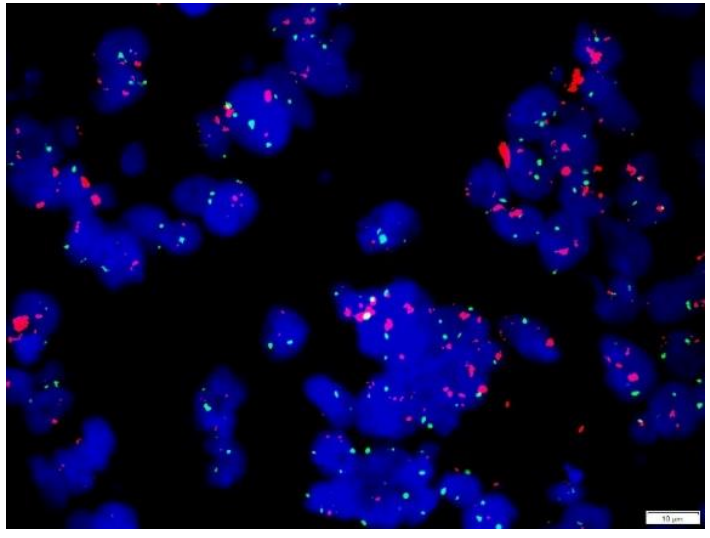
LY-24-0109 c-Met 200x



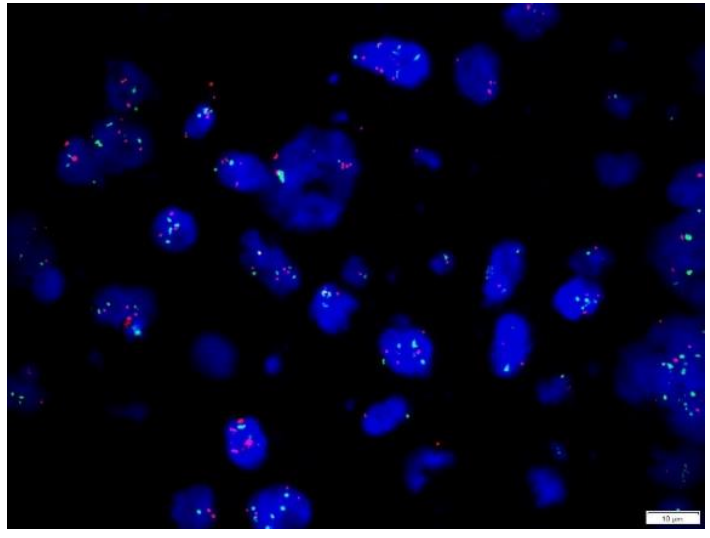
LY-24-0059 c-Met 200x

c-Met amplification detection (by FISH) in lung cancer PDX models

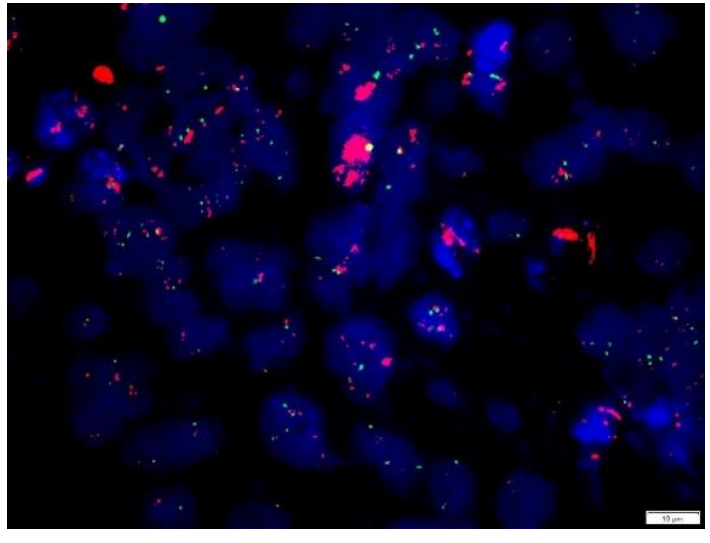
LU-01-0781



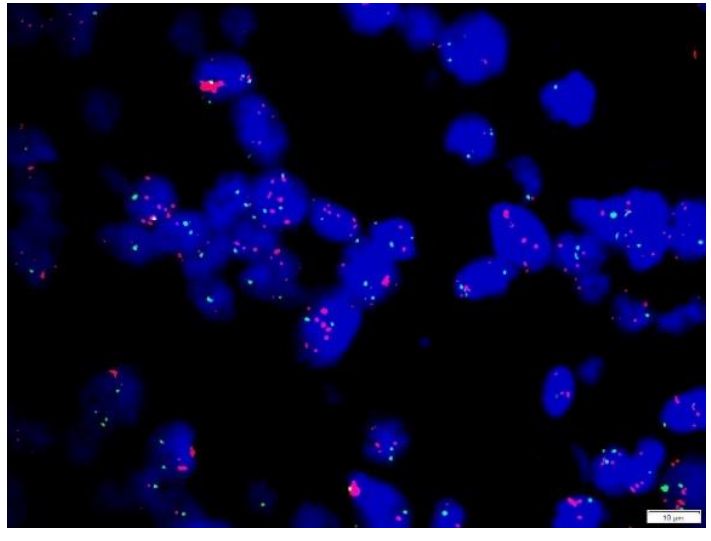
LU-01-1178



LU-01-1377

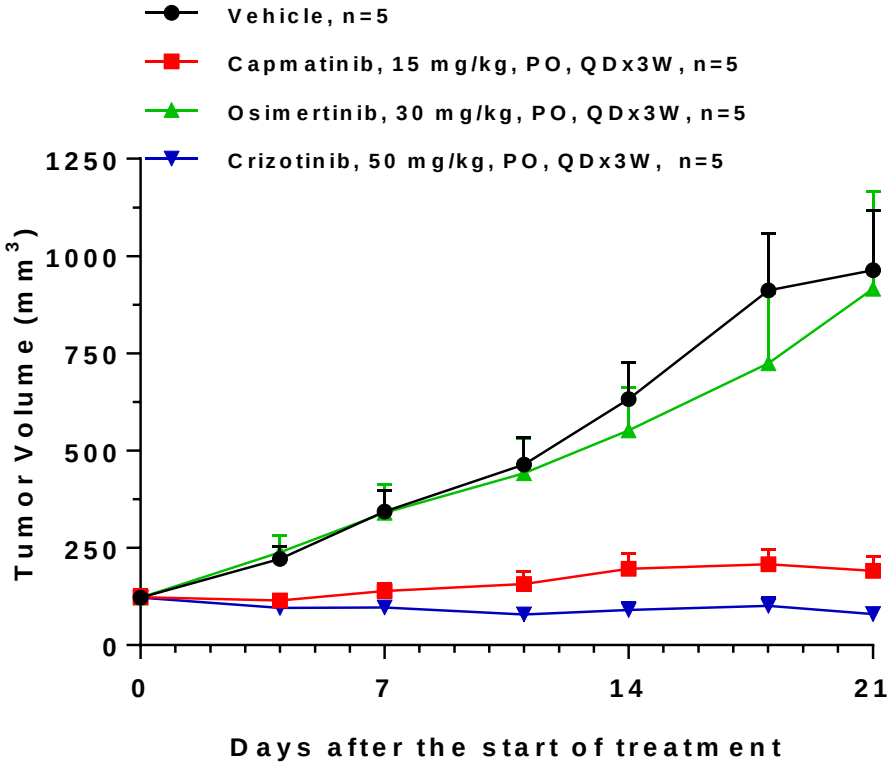


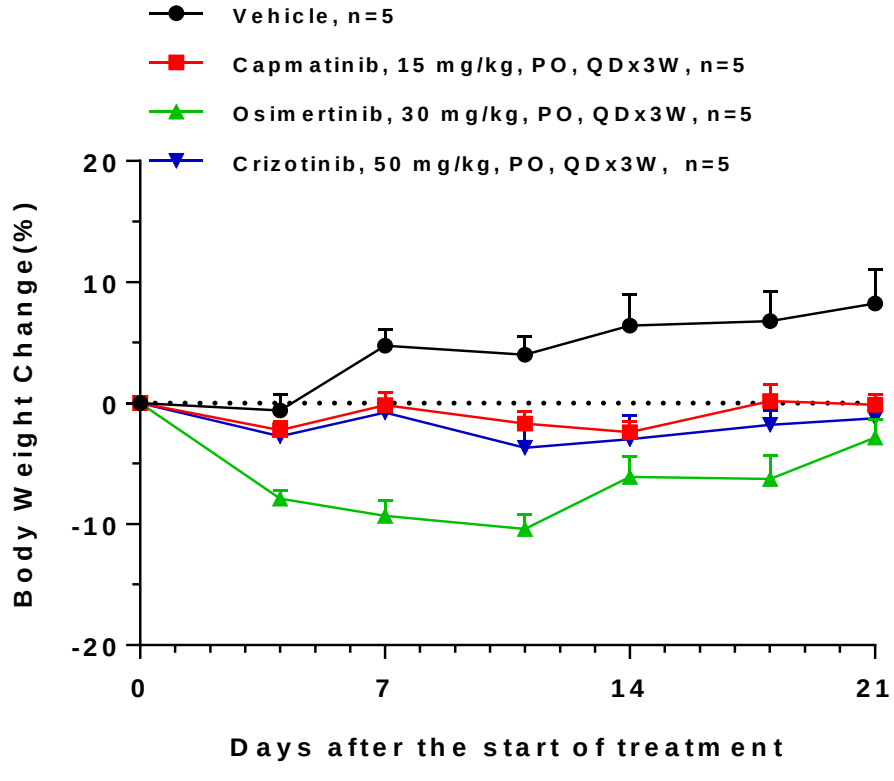
LU-01-1649



Anti-tumor efficacy of c-MET inhibitors in LU-01-0506 PDX model

Model ID	Cancer type	Gender	Age	Tumor grade	Tumor stage	Model genetics
LU-01-0506	Lung cancer (Adenocarcinoma)	Female	54	G3	T2N0M0	MET amplification





c-Met-related PDX models

MET exon 14 skipping

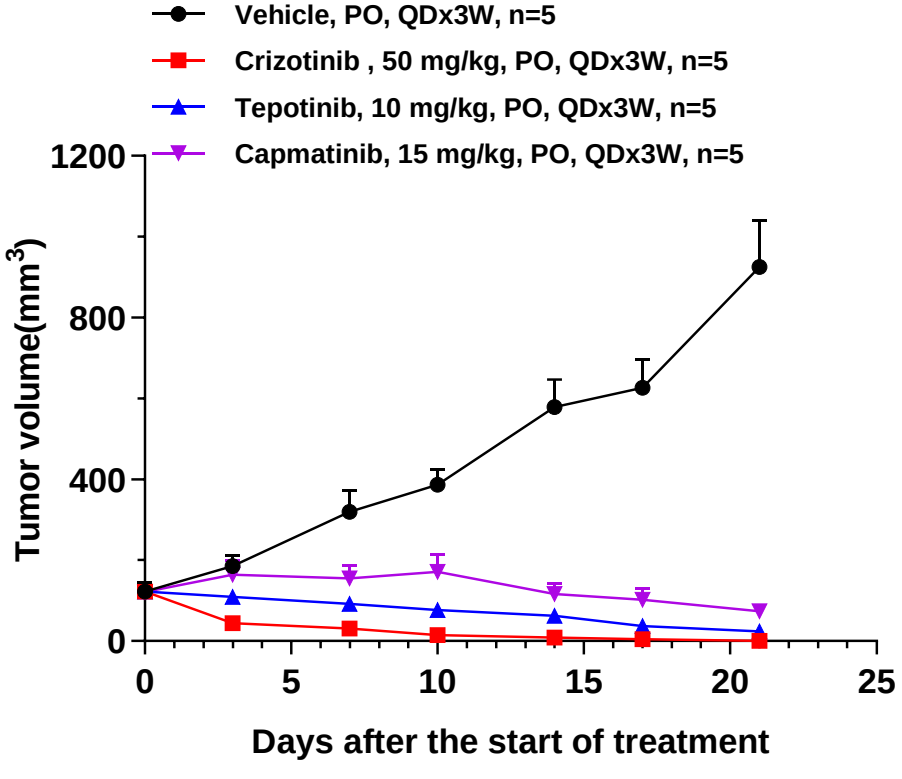
Model ID	Cancer type	Gender	Age	Tumor grade	Tumor stage	Model genetics
LU-01-1375	Lung Cancer (Adenocarcinoma)	Female	68	NA	NA	MET exon 14 skipping
LU-01-1476	Lung Cancer (Adenocarcinoma)	Female	68	NA	NA	MET exon 14 skipping
LU-01-1616	Lung Cancer (Adenocarcinoma)	Female	67	NA	IV	MET exon 14 skipping

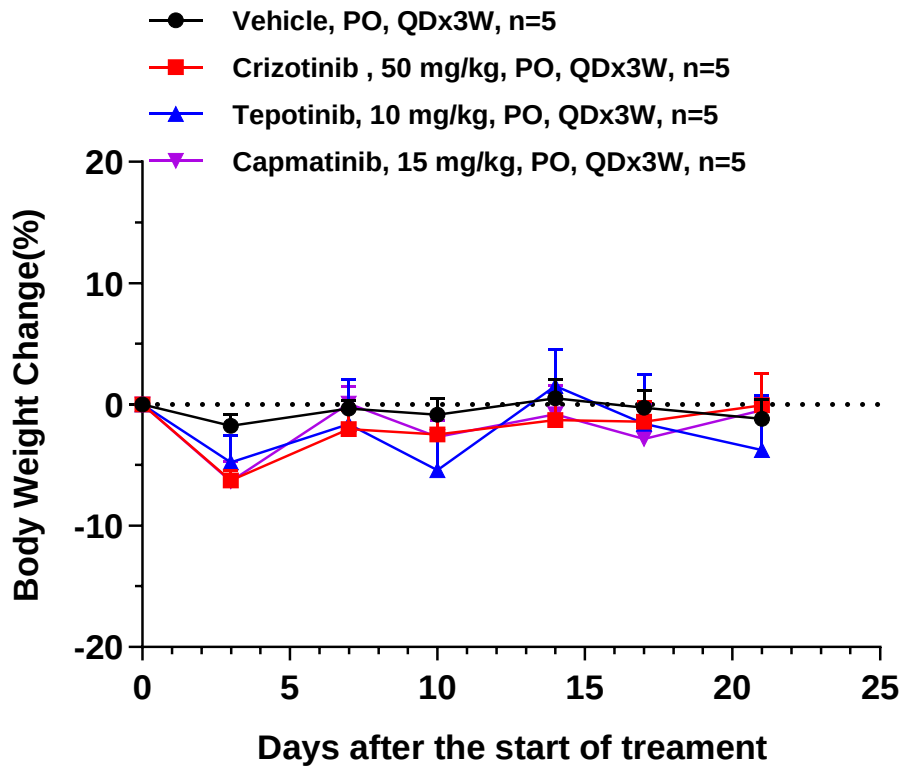
Note: LU-01-1476 model was established from the same patient of LU-01-1375 model after Crizotinib therapy.

c-Met targeted inhibitors in LU-01-1375 PDX model

MET exon 14 skipping PDX models

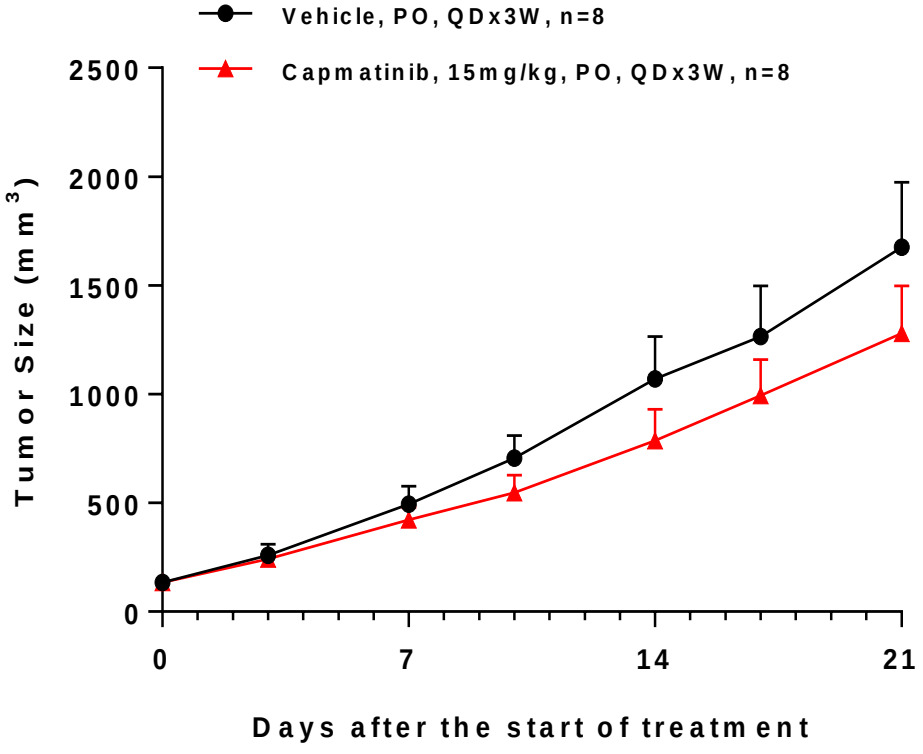
Model ID	Cancer type	Gender	Age	Tumor grade	Tumor stage	Model genetics
LU-01-1375	Lung Cancer (Adenocarcinoma)	Female	68	NA	NA	MET exon 14 skipping

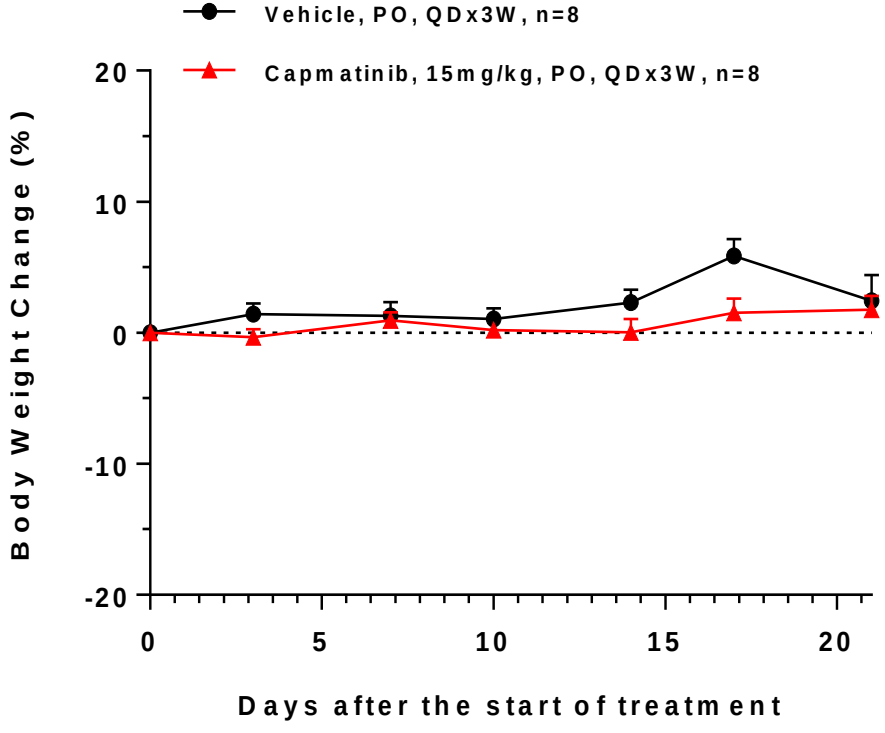




Anti-tumor efficacy of Capmatinib in clinically acquired Capmatinib-resistant LU-01-0751 PDX model

Model ID	Cancer type	Gender	Age	Tumor grade	Tumor stage	Model genetics
LU-01-0751	Lung Cancer (Adenocarcinoma)	Female	67	NA	IV	MET mutation: exon2_p.N375S, exon19_p.D1228N





Xu, Z., Hu, P., Fang, D. et al. Electrostatic explanation of D1228V/H/N-induced c-Met resistance and sensitivity to type I and type II kinase inhibitors in targeted gastric cancer therapy. J Mol Model 25, 13 (2019). https://doi.org/10.1007/s00894-018-3893-3

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