FGFR Related Models

WuXi AppTec Research Service Division, Oncology & Immunology Unit

药明康德 WuXi AppTec

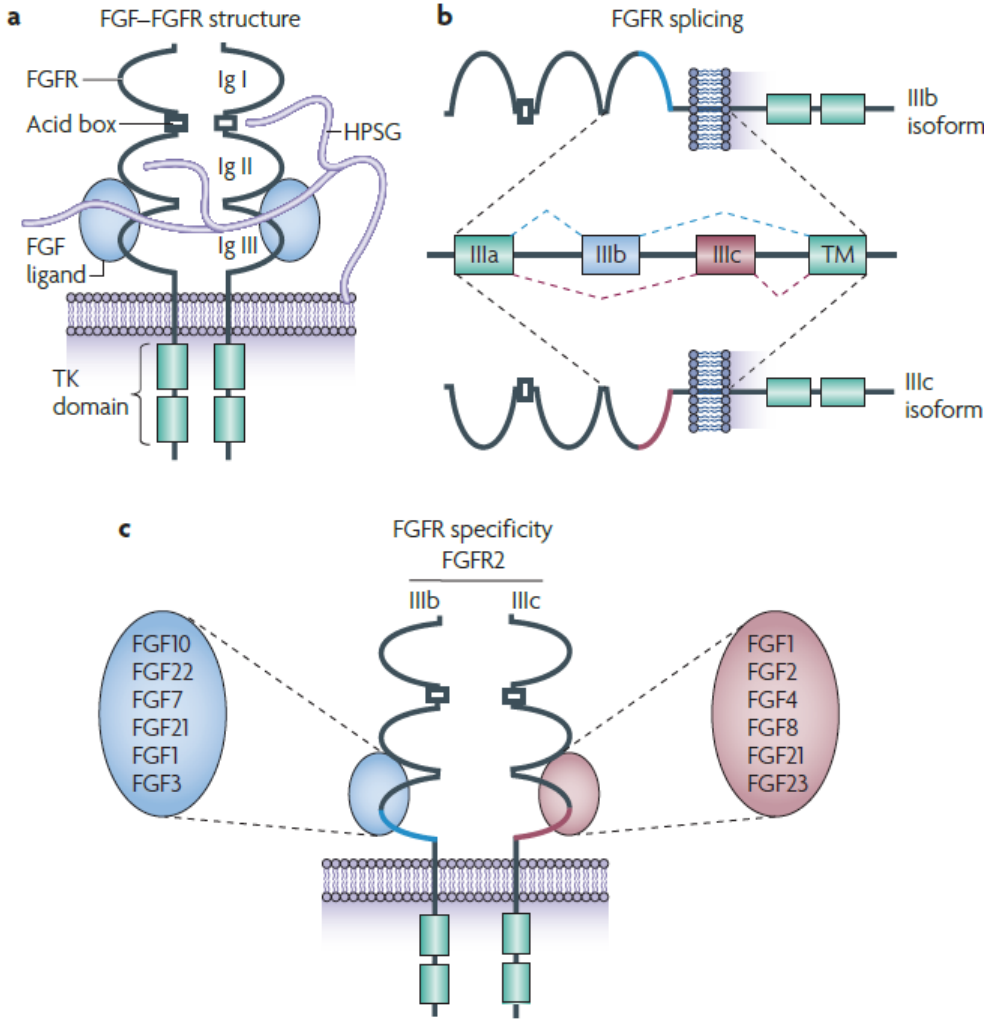
2020.02

Outline

- **FGFR background as a drug target**
  - FGFR biology
  - FGFR Inhibitors in clinical trial
- **FGFR CDX models**
  - FGFR related cancer cell lines
  - FGFR related CDX models
- **FGFR PDX models**
  - Summary of FGFR overexpression PDX models
  - Summary FGFR fusion/mutation PDX models
  - PDX models validated with FGFR inhibitors
  - PDX characterization and SOC data

FGFR Family and Its Ligands

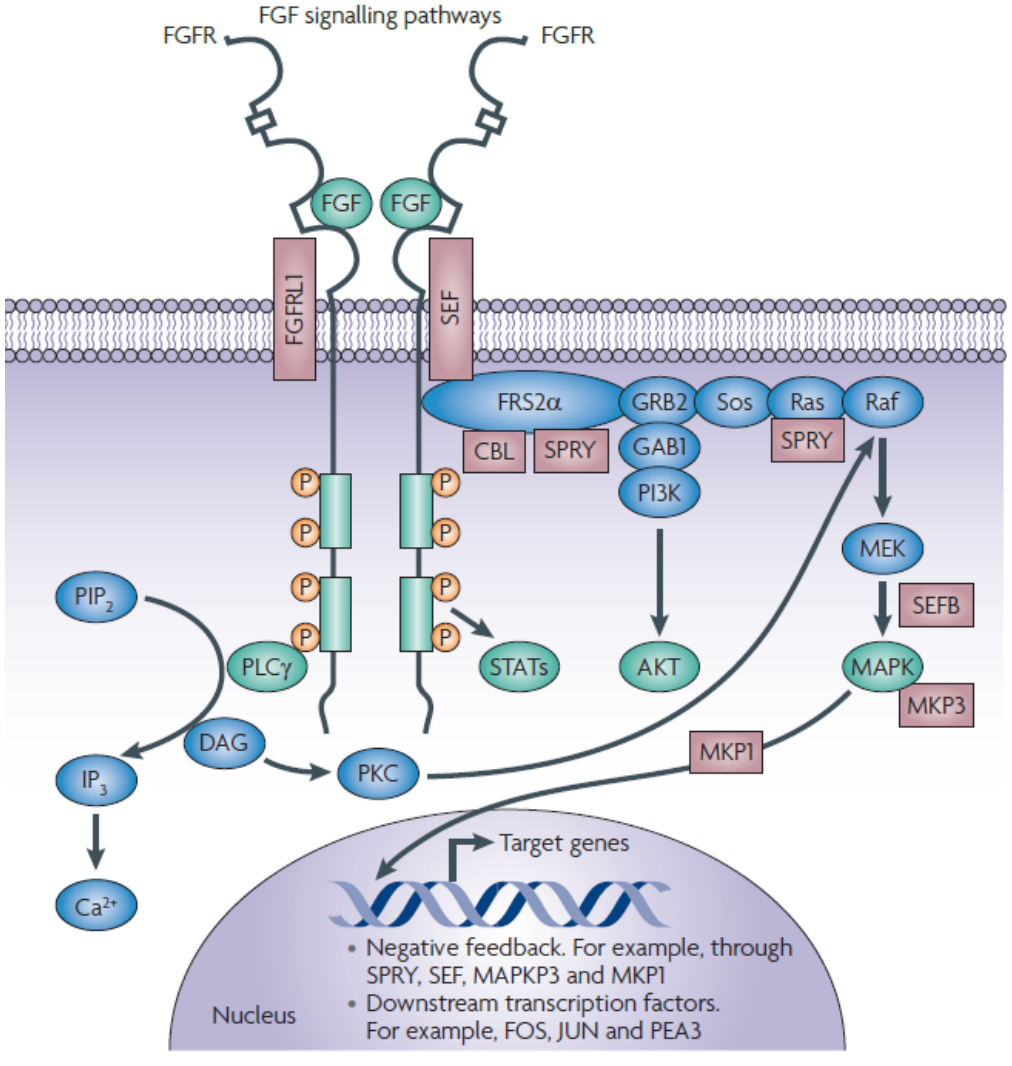
- Fibroblast growth factor receptor(FGFR) belongs to receptor tyrosine kinases (RTKs) and has four isoforms, FGFR1, FGFR2, FGFR3 and FGFR4.
- FGFR is composed of an extracellular ligand binding domain, a single transmembrane domain and a cytoplasmic domain containing the catalytic protein tyrosine kinase core as well as additional regulatory sequences.
- There are 22 members of the fibroblast growth factor (FGF) family, mediating their cellular responses by binding to FGFR.
- A fifth related receptor, FGFR5 (also known as FGFRL1), can bind FGFs, but has no tyrosine kinase domain, and might negatively regulate signalling.



Cytokine Growth Factor Rev. 2005;16(2):139-49.
Nat Rev Cancer. 2010;10(2):116-29.

FGFR Pathway

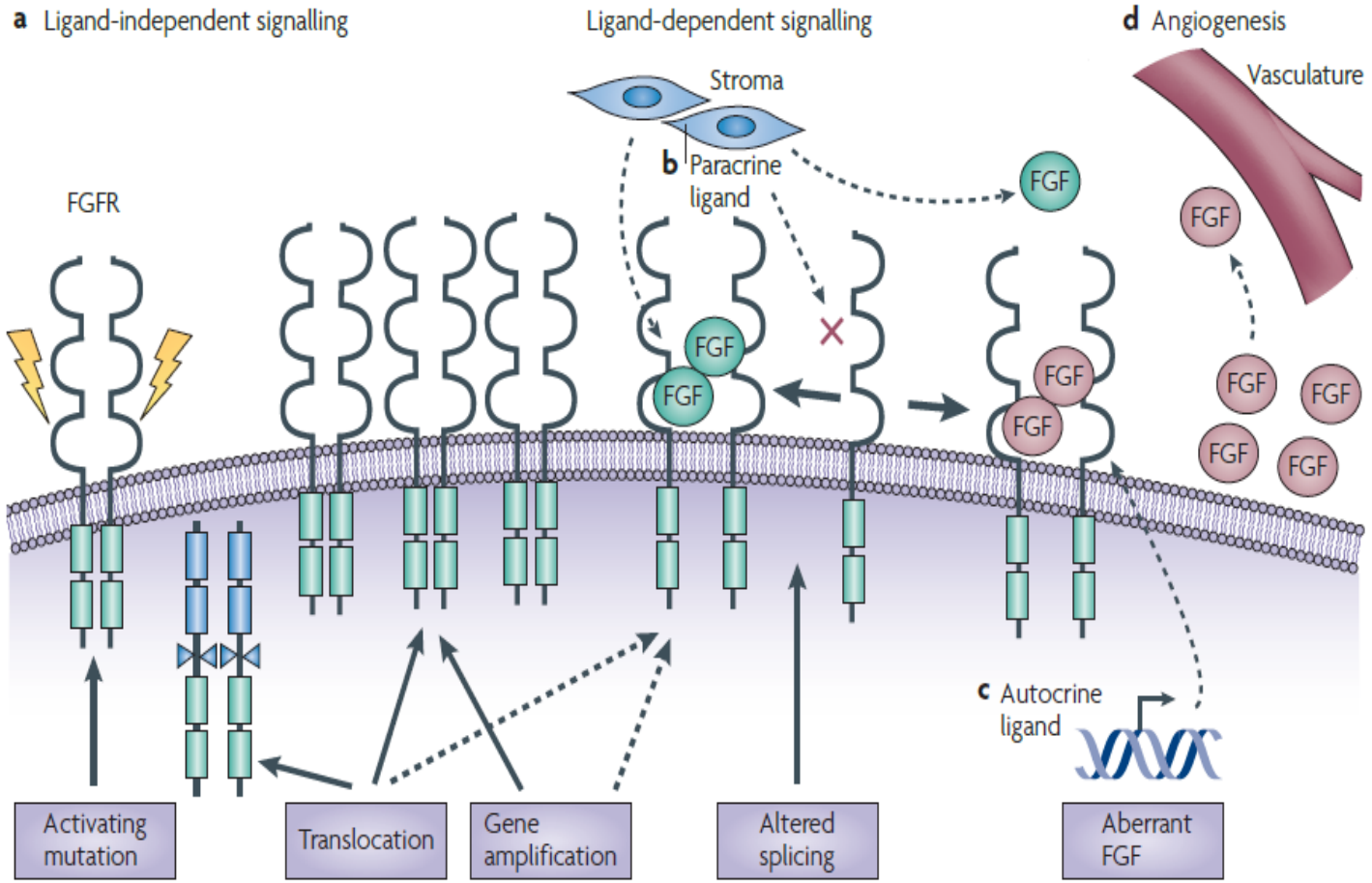
- Following ligand binding and receptor dimerization, the kinase domains transphosphorylate each other, leading to the docking of adaptor proteins and the activation of four key downstream pathways: RAS–RAF–MAPK, PI3K–AKT, signal transducer and activator of transcription (STAT) and phospholipase Cγ (PLCγ) (green).
- Signaling can be negatively regulated at several levels by receptor internalization or the induction of negative regulators, including FGFR-like 1 (FGFRL1), SEF, Sprouty (SPRY), CBL, MAPK phosphatase 1 (MKP1) and MKP3 (brown).



Nat Rev Cancer. 2010 Feb;10(2):116-29.

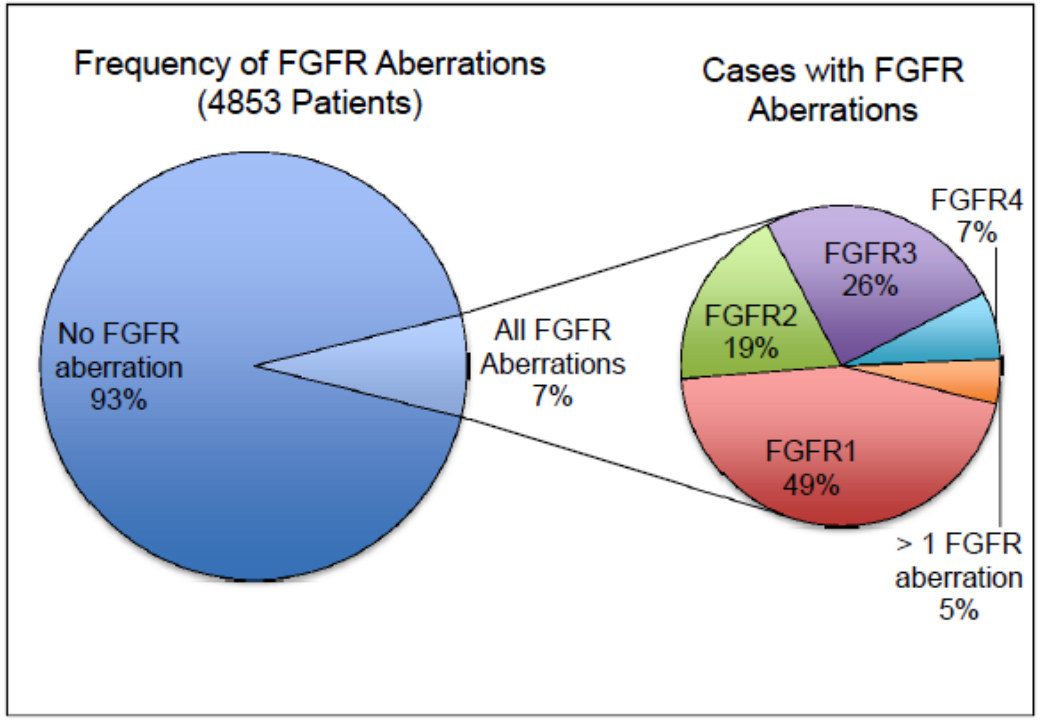
FGFR Role in Cancer

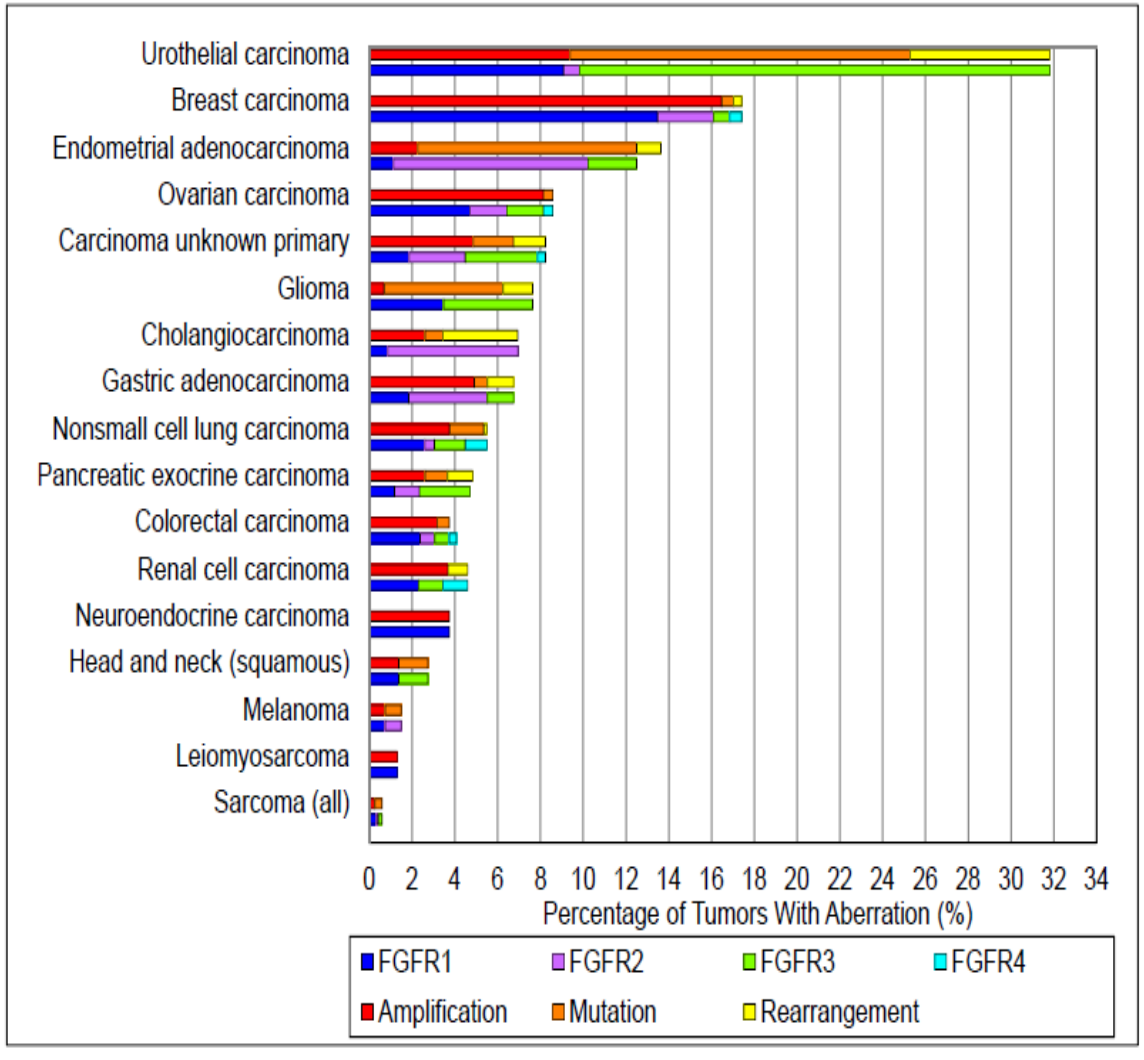
- There are several types of genetic evidence that support an oncogenic function for FGFRs: identification of gene amplifications, activating mutations, chromosomal translocations, single nucleotide polymorphisms and aberrant splicing at the post-transcriptional level.



Nat Rev Cancer. 2010 Feb;10(2):116-29.

FGFR abnormality prevalence in cancer





FGFR aberrations were found in 7.1% of cancers, with the majority being gene amplification (**66**% of the aberrations), followed by mutations (26%) and rearrangements (8%). FGFR1 (mostly amplification) was affected in 3.5% of 4,853 patients; FGFR2 in 1.5%; FGFR3 in 2.0%; and FGFR4 in 0.5%. Almost every type of malignancy examined showed some patients with FGFR aberrations, but the cancers most commonly affected were urothelial (32% FGFR-aberrant); breast (18%); endometrial (~13%), squamous lung cancers (~13%), and ovarian cancer (~9%).

Clin Cancer Res. 2016 22:1 259-267.

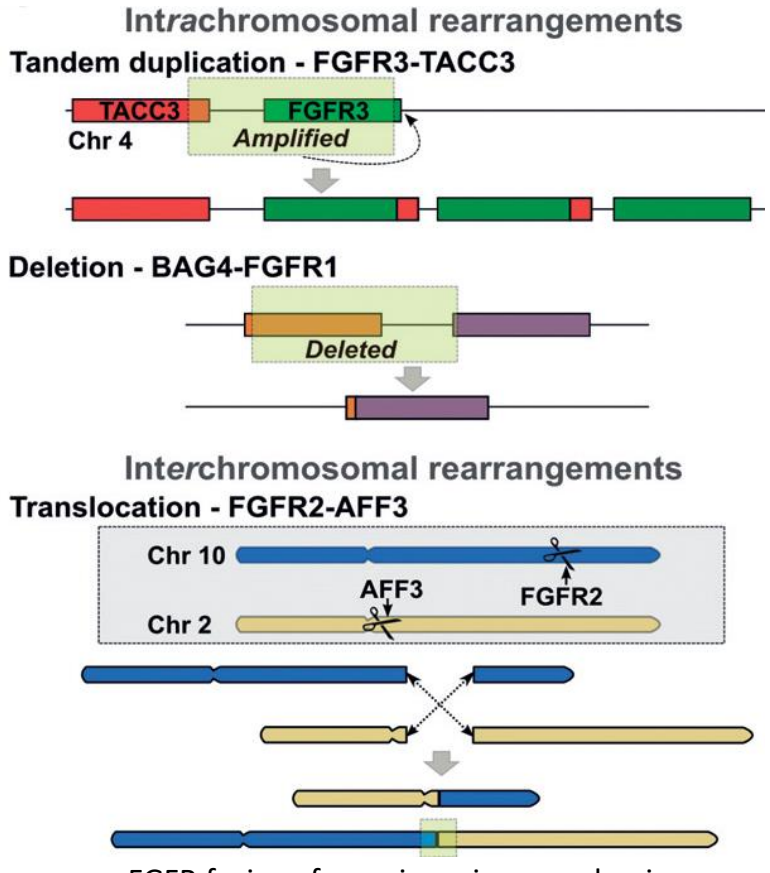
FGFR mutations and their functional significance

Gene	Transcript	Protein Change	Location in Protein	Reported in COSMIC	Functional Effect of Alteration	Able to Transform Cells *in vitro*
FGFR1	NM_023110	N546K	kinase	Yes	Activating	Yes
FGFR1	NM_023110	K656E	kinase	Yes	Activating	Yes
FGFR2	NM_000141	S252W	extracellular	Yes	Activating	Yes
FGFR2	NM_000141	P253R	extracellular	Yes	Activating	Yes
FGFR2	NM_000141	A315T	extracellular	Yes	Activating	Unknown
FGFR2	NM_000141	Y375C	extracellular	Yes	Activating	Unknown
FGFR2	NM_000141	C382R	transmembrane	Yes	Activating	Yes
FGFR2	NM_000141	N549K	kinase	Yes	Activating	Yes
FGFR2	NM_000141	K659E	kinase	Yes	Activating	Yes
FGFR3	NM_000142	R248C	extracellular	Yes	Activating	Yes
FGFR3	NM_000142	S249C	extracellular	Yes	Activating	Yes
FGFR3	NM_000142	G370C	extracellular	Yes	Activating	Unknown
FGFR3	NM_000142	S371C	extracellular	Yes	Activating	Unknown
FGFR3	NM_000142	Y373C	extracellular	Yes	Activating	Yes
FGFR3	NM_000142	G380R	transmembrane	Yes	Activating	Unknown
FGFR3	NM_000142	K650E	kinase	Yes	Activating	Yes
FGFR3	NM_000142	K650M	kinase	Yes	Activating	Unknown

Clin Cancer Res. 2016 22:1 259-267

FGFR fusion

FGFR family	Fusion partner	Disease
FGFR1	BAG4	lung squamous cell carcinoma
FGFR1	ERLIN2	Breast cancer
FGFR1	TACC1	Glioblastoma
FGFR2	TACC3, MGEA5, KIAA1598, AHCYL1, CCDC6, BICC1	cholangiocarcinoma
FGFR2	CCDC6, AFF3, CASP7	Breast cancer
FGFR2	CCAR2, CIT	Lung cancer
FGFR2	CD44	Gastric cancer
FGFR2	SLC45A3	Prostate cancer
FGFR2	OFD1	Thyroid cancer
FGFR3	TACC3, BAIAP2L1	Bladder cancer
FGFR3	TACC3	lung squamous cell carcinoma, oral cancer, head and neck squamous cell carcinoma, glioblastoma, cervical cancer



FGFR fusions form via various mechanisms.
Examples of each mechanism are listed.

Cancer Discov. 2013;3(6):636-47.
J Pathol. 2014 Jan;232(1):4-15.
PLoS Genet. 2014;10(2):e1004135.
Oncologist. 2014;19(3):235–242.
Genome Res. 2012;22(11):2109–2119
Onco Targets Ther. 2015 Oct 19;8:3009-16.

The FGFR fusions discovered thus far have numerous 3’ partner genes that are not recurrent, suggesting the importance of the FGF kinase in the fusion allowing the selection of FGFR fusion-containing tumour cells.

FGFR targeted drugs

Drug	Inventor	Target/Mechanism	Indications	Status
AZD4547	AstraZenca	FGFR1/2/3	Breast cancer, NSCLC, Gastric cancer	Phase 2/3
LY2874455	Lilly	FGFR1/2/3/4; VEGFR2	Advanced Cancer, Leukemia	Phase 1
CH5183284	Debiopharm	FGFR1/2/3	Solid Tumors	Phase 1/2
JNJ-42756493 (Erdafitinib)	JNJ	FGFR1/2/3/4	Advanced Cancers and FGFR Genetic Alterations	Approved for marketing
NVP-BGJ398	Novartis	FGFR1/2/3	Solid tumors, Bladder Cancer	Phase 2/3
Nintedanib (BIBF 1120)	Boehringer Ingelheim	FGFR1/2/3; VEGFR1/2/3; PDGFRα/β	Solid tumors	Phase 3
Dovitinib	Novartis	FLT3, cKIT, FGFR1/3, VEGFR1-4	Solid tumors	Phase 2/3
BAY1187982	Bayer	FGFR2	Advanced Solid Tumors	Phase 1 (Terminated)
Ponatinib Hydrochloride	Ariad pharmaceuticals	FGFR1, Abl, PDGFRα, VEGFR2, Src	Malignant Hepatobiliary Neoplasm	Phase 2/3
Lenvatinib (E7080)	Eisai	VEGFR1/2/3, FGFR1, PDGFRα/β	Thyroid Cancer	Approved for marketing
ENMD-2076	CASI Pharmaceuticals, Inc.	VEGFR2/3, FGFR1/2, PDGFRα, Flt3/4, Aurora A/B	Advanced Cancer	Phase 2
Lucitanib(E-3810)	Servier, Clovis Oncology	FGFR1/2, VEGFR1-3, PGFRα/β	Breast cancer, NSCLC	Phase 2/3

https://clinicaltrials.gov/

FGFR targeted drugs

Drug	Inventor	Target/Mechanism	Indications	Status
BLU9931	Blueprint Medicines	FGFR4	Hepatocellular Carcinoma (HCC)	-
BLU-554	Blueprint Medicines	FGFR4	Hepatocellular Carcinoma (HCC)	Phase 1/2
FGF401	Novartis	Positive FGFR4 and KLB Expression	Hepatocellular Carcinoma, Solid Malignancies	Phase 1/2
U3-1784	Daiichi Sankyo Inc.	FGFR4	Advanced Solid Tumors, Hepatocellular Cancer (HCC)	Phase 1
TAS-120	Taiho Oncology, Inc.	FGFR1/2/3/4	Advanced solid tumors	Phase2
Debio 1347	Debiopharm International SA	FGFR1/2/3	Solid tumors	Phase 1/2
H3B-6527	H3 Biomedicine Inc.	FGFR4	Advanced Hepatocellular Carcinoma	Phase 1
ASP5878	Astellas	FGFR1/2/3/4	Solid tumors	Phase 1
PRN1371	Principia Biopharma Inc.	FGFR1/2/3/4	Solid tumors	Phase 1
Rogaratinib (BAY1163877)	Bayer	FGFR1/2/3/4	Carcinoma	Phase 2/3
BAY1179470	Bayer	FGFR2	Neoplasms	Phase 1
FPA144	Five Prime Therapeutics, Inc.	FGFR2	Gastric cancer, Bladder cancer	Phase 1
Vofatamab (B-701)	Rainier Therapeutics	FGFR3	Advanced or Metastatic Urothelial Cell Carcinoma	Phase 1

https://clinicaltrials.gov/

FGFR targeted drugs

Drug	Inventor	Target/Mechanism	Indications	Status
Pemigatinib	Incyte Corporation	FGFR1/2/3	Solid tumors	Phase 2
Derazantinib	Basilea Pharmaceutica	FGFR1/2/3	Solid tumors	Phase 1/2
LY3076226	Lilly	FGFR3	Advanced Cancer	Phase 1
ASP5878	Astellas Pharma Inc	FGFR1/2/3/4	Solid Tumors	Phase 1
E7090	Eisai	FGFR1/2/3	Solid Tumors	Phase1/2
CPL304110	Celon Pharma SA	FGFR1/2/3	Solid Tumors	Phase 1
INCB062079	Incyte Corporation	FGFR4	Solid Tumors	Phase 1

https://clinicaltrials.gov/

In vitro activity of FGFR inhibitors

BIBF1120 (Nintedanib)	Targets	VEGFR1/2/3	FGFR1/2/3	PDGFRα/β			
	IC50	34 nM/13 nM/13 nM	69 nM/37 nM/108 nM	59 nM/65 nM			
Dovitinib (TKI258)	Targets	VEGFR1/2/3	FGFR1/3	PDGFRα/β	Flt3	c-Kit	
	IC50	10 nM/13 nM/8 nM	8 nM/9 nM	210 nM/27 nM	1 nM	2 nM	
Lenvatinib (E7080)	Targets	VEGFR1/2/3	FGFR1	PDGFRα/β			
	IC50	22nM/4 nM/5.2nM	46 nM	51 nM/39nM			
ENMD-2076	Targets	VEGFR2/3	FGFR1/2	PDGFRα	Flt3/4	Aurora A	Aurora B
	IC50	58.2 nM/15.9nM	93 nM/71 nM	56.4nM	1.86nM/15.9nM	14 nM	350 nM
LY2874455	Targets	VEGFR2	FGFR1/2/3/4				
	IC50	7nM	2.8 nM/2.6 nM/6.4 nM/6 nM				
AZD4547	Targets	VEGFR2	FGFR1/2/3/4				
	IC50	24 nM	0.2 nM/2.5 nM/1.8 nM/165 nM				
BGJ398	Targets	VEGFR2	FGFR1/2/3/4				
	IC50	180 nM	0.9 nM/1.4 nM/1 nM/60 nM				
CH5183284	Targets	FGFR1/2/3					
	IC50	9.3 nM/7.6 nM/22 nM					
Ponatinib Hydrochloride	Targets	VEGFR2	FGFR1	PDGFRα	Abl	Src	
	IC50	1.5 nM	2.2 nM	1.1 nM	0.37 nM	5.4 nM	
Debio 1347	Targets	FGFR1/2/3/4					
	IC50	9 nM/8 nM/22 nM/290 nM					
H3B-6527	Targets	FGFR1/4					
	IC50	320 nM/<=1 nM					

In vitro activity of FGFR inhibitors

ASP5878	Targets	FGFR1/2/3/4	VEGFR2
	IC50	<1 nM/1 nM/1 nM/4 nM	25 nM
PRN1371	Targets	FGFR1/2/3/4	VEGFR2
	IC50	1 nM/1 nM/4 nM/19 nM	705 nM
Rogaratinib	Targets	FGFR1/2/3/4	VEGFR2
	IC50	15 nM/<1 nM/19 nM/33 nM	120 nM

FGFR related human cancer cell lines

Cell line	FGFR genotype	Tissue
MDA-MB-134	FGFR1 amplification[2]	Breast
NCI-H1581	FGFR1 amplification[2]	NSCLC
DMS 114	FGFR1 amplification[1]	SCLC
KG-1	FGFR1 translocation[1,3] (FGFROP2-FGFR1 fusion)	AML
MFE-280	FGFR2:S252W[3]	Endometrium
MFE-296	FGFR2:N549K[3]	Endometrium
NCI-H716	FGFR2 gene amplification[1,3, 5]	colon
KATO III	FGFR2 gene amplification[1,3]	gastric
SNU-16	FGFR2 gene amplificatio[1,2,3]	Gastric
MFM-223	FGFR2 gene amplification[1,3]	Breast
AN3CN	FGFR2 activating mutation(N548K/K310R)[1,2,3]	Endometrium

Cell line	FGFR genotype	Tissue
J82	FGFR3:K560E[3,6]	bladder
RT-112	FGFR3 amplification[1.2]	bladder
RT-112/84	FGFR3-TACC3 fusion[7]	bladder
KMS-11	FGFR3:Y375P[4]	Multiple myeloma
JIM-1	FGFR3 positive[4]	Multiple myeloma
SW780	FGFR3-BAIAP2L1 fusion,[6,7]	Bladder cancer
OPM-2	FGFR3 translocation and activating mutation[1]	Multiple myeloma
RT-4	FGFR3 overexpression[2] FGFR3-TACC3 fusion[6,7]	bladder
Huh-7	FGFR4 overexpression[1] FGF19 amplification[8]	Hepatic
Hep3B	FGF19 amplification[8]	Hepatic
JHH-7	FGF19 amplification[8]	Hepatic

1: 2010 AACR, poster 220;
2: 2014 AACR, poster 3124;
3: 2013 AACR, poster 818;
4: 2014 AACR, poster 483;
5: PLoS One. 2014; 26;9(6):e98515;
6: Cancer Discov. 2013;3(6):636-47.
7: 2015 AACR, abstract 784;
8: Cancer Discov; 2015 Apr;5(4):424-37.

FGFR related CDX models

Cancer type	Model ID	Tumor growth curve in WuXi	Drugs tested	Dosage(mg/kg)	TGI	Model genomics
Multiple myeloma	JIM-1	n/a	n/a	--	--	FGFR3 positive[1]
Multiple myeloma	KMS-11	Yes	n/a	--	--	FGFR3 positive(Y375P)[1]
Colorectal cancer	NCI-H716	n/a	EXEL-6484[2]	200	>100%	FGFR2 amplification[2,4,5]
			ARQ087[4]	75	96%	
			MK2461[5]	800	>100%	
Bladder cancer	RT-4	n/a	PRN1371[3]	12.5	>100%	FGFR3 overexpression[3]
			PD173074[6]	20	60%	FGFR3-TACC3 fusion[6]
			BGJ398[7]	10/20	64%	FGFR3-TACC3 fusion[7]
	RT112/84	Yes	Lucitanib[7] BGJ398[7]	25 15	>100% 20%	FGFR3-TACC3 fusion[7]
Gastric cancer	SNU-16	Yes	PRN1371[3]	15	>100%	FGFR2 amplification[3]
			AZD4547[8]	12.5	101	
			Dovitinib[8]	30	114	
			LY2874455[8]	3	24	
			TAS-120[8]	100	139	
			JNJ-42756493[8]	30	97	
			BGJ398[8]	20	103	
Bladder cancer	SW780	n/a	PD173074[6]	60	60%	FGFR3-BAIAP2L1 fusion[6]
			BGJ398[7]	20	92%	FGFR3-BAIAP2L1 fusion[7]

1: 2010 AACR, poster 3626; 3: 2014 AACR, poster 483; 5. PLoS One. 2014; 26;9(6):e98515; 7: 2015 AACR, abstract 784;
2: 2010 AACR, poster 220; 4: 2013 AACR, poster 818; 6. Cancer Discov. 2013;3(6):636-47; 8: WuXi internal data

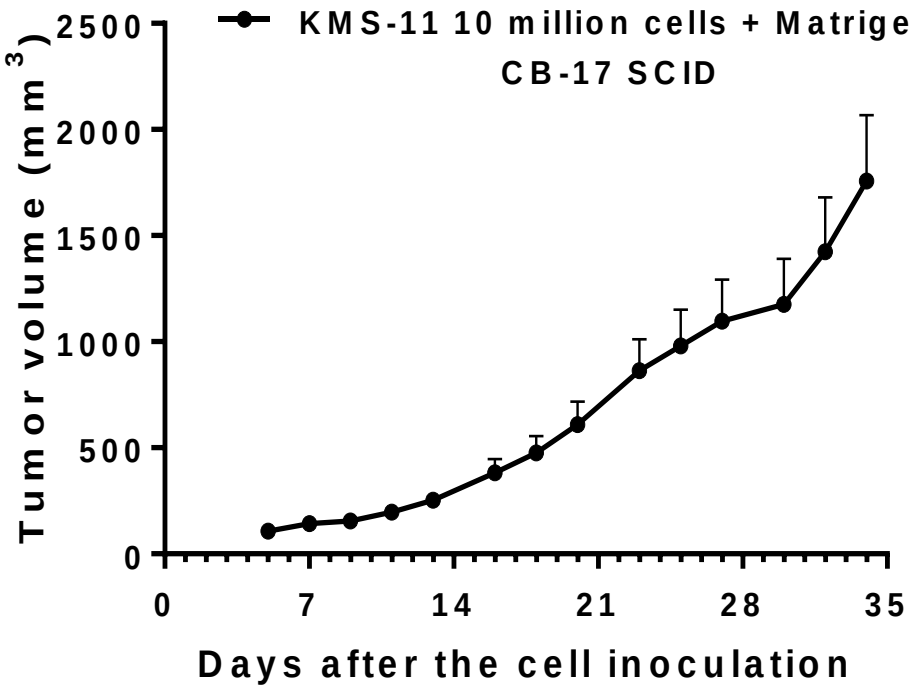
FGFR related CDX models

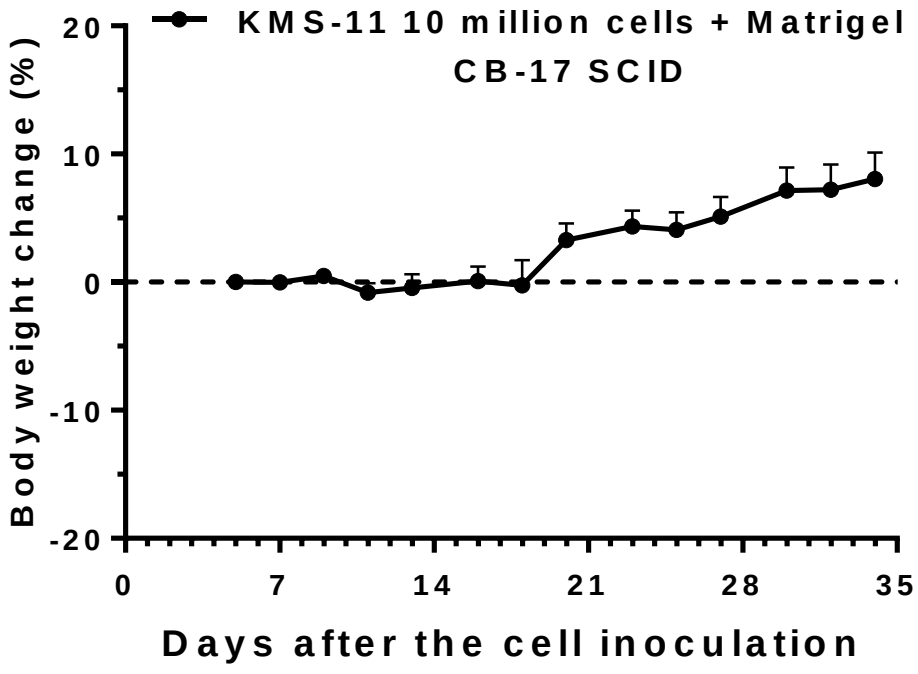
Cancer type	Model ID	Tumor growth curve in WuXi	Drugs tested	Dosage(mg/kg)	TGI (%)	Model genomics
Liver cancer	Hep 3B	Yes	BLU9931	30	95	FGF19 amplification, with concomitant expression of KLB[1,2]
			BLU9931	100	108	
			Sorafenib	60	85	
	Hep 3B		BLU9931	30	87	
	Hep 3B		BLU9931	100	92	
	Huh-7	Yes	BLU9931	100	55	FGF19 amplification, with concomitant expression of KLB[1,2]
	JHH-7	Yes	--	--	--	FGF19 amplification, with concomitant expression of KLB[1,2]

***1: Cancer Discov**; 2012 Dec;2(12):1118-33.*

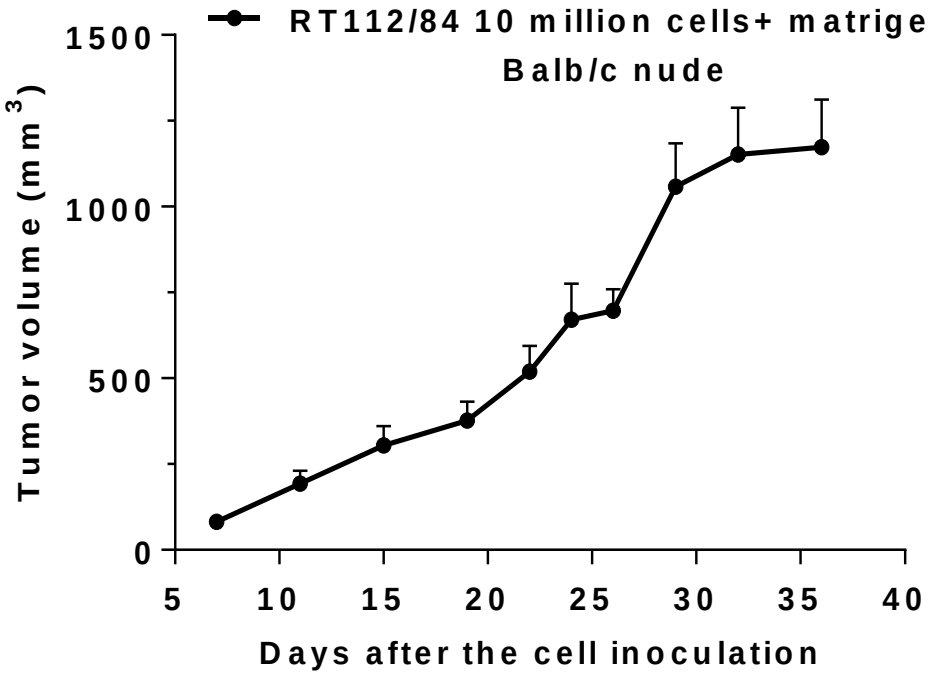
***2: Cancer Discov**; 2015 Apr;5(4):424-37.*

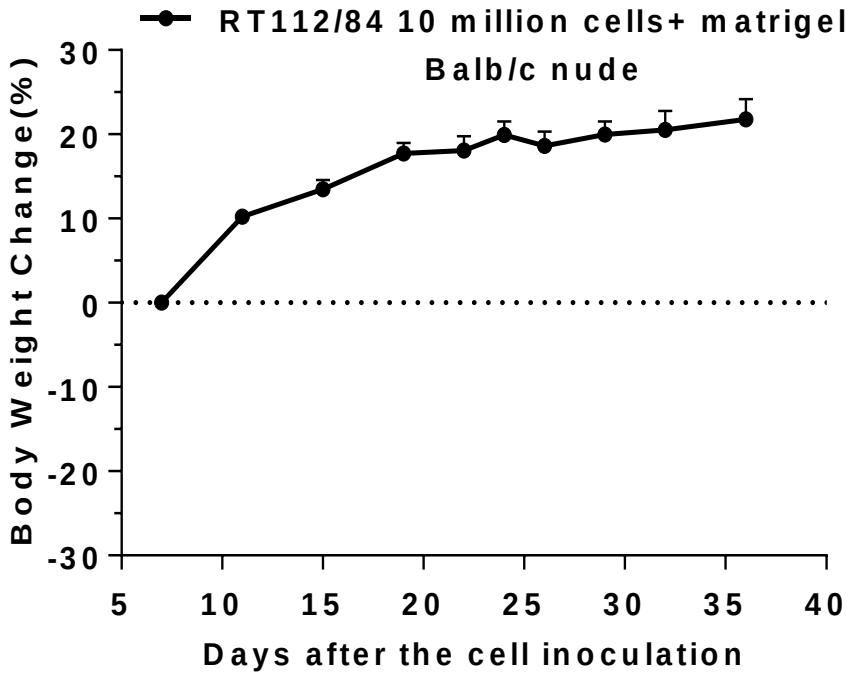
KMS-11 human myeloma xenograft model



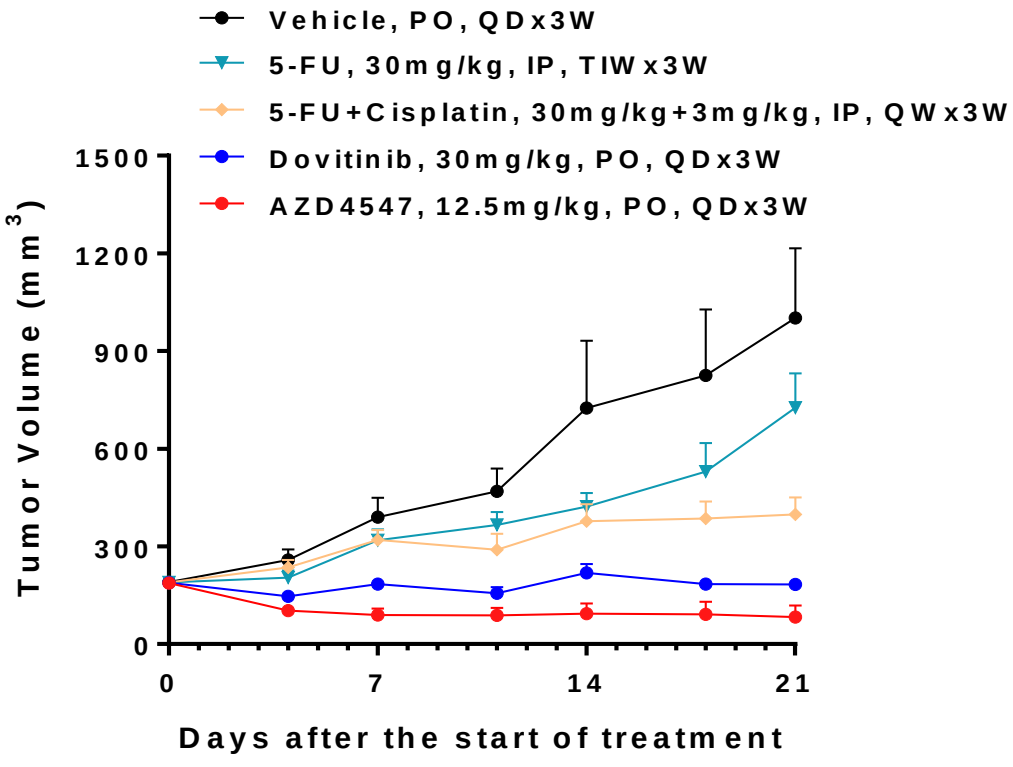


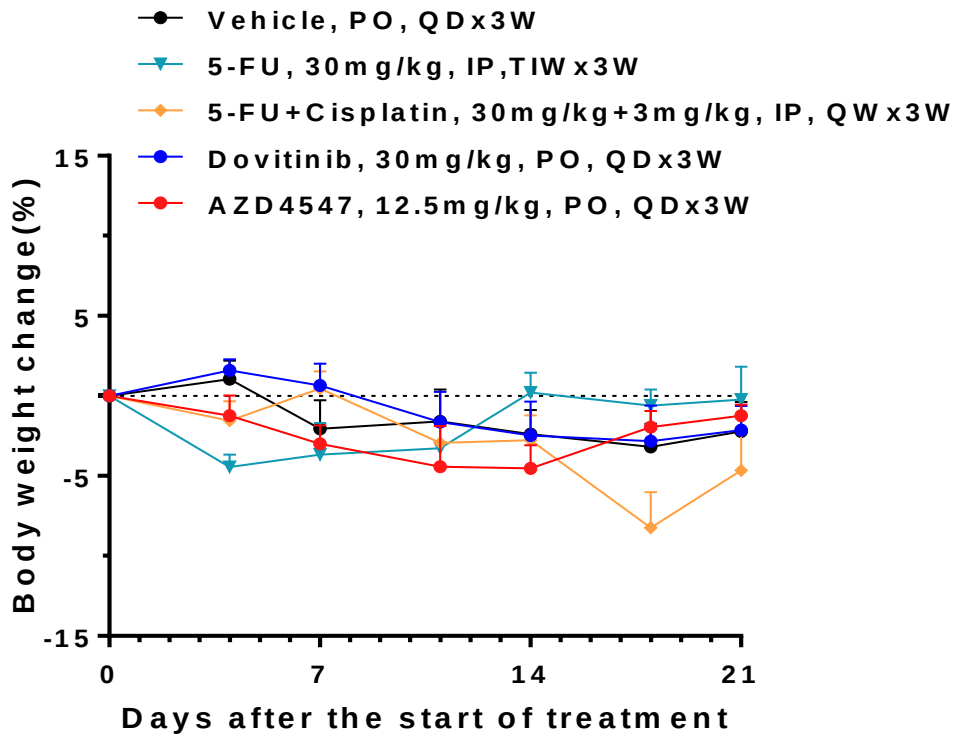
RT112/84 human urinary bladder carcinoma xenograft model



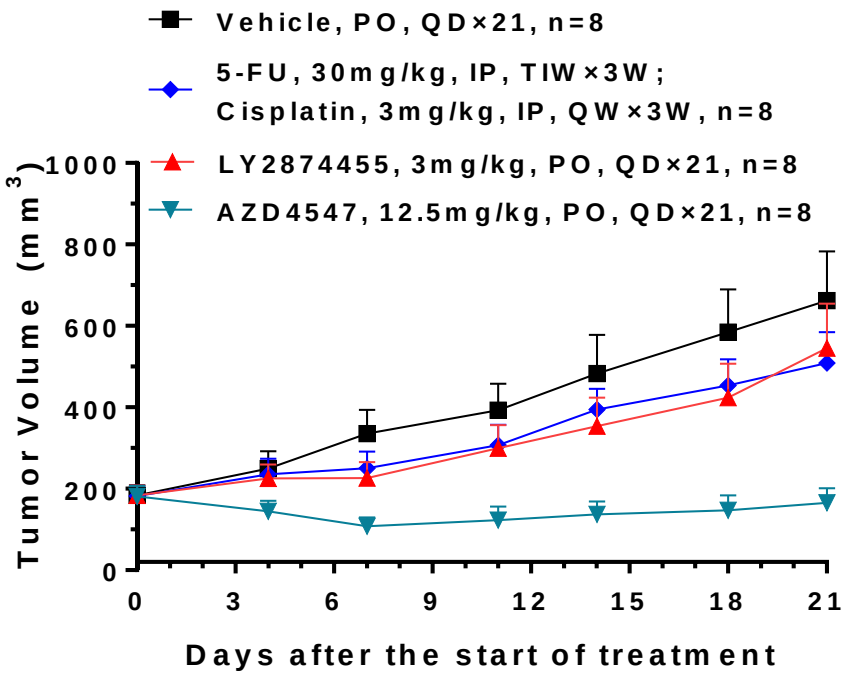


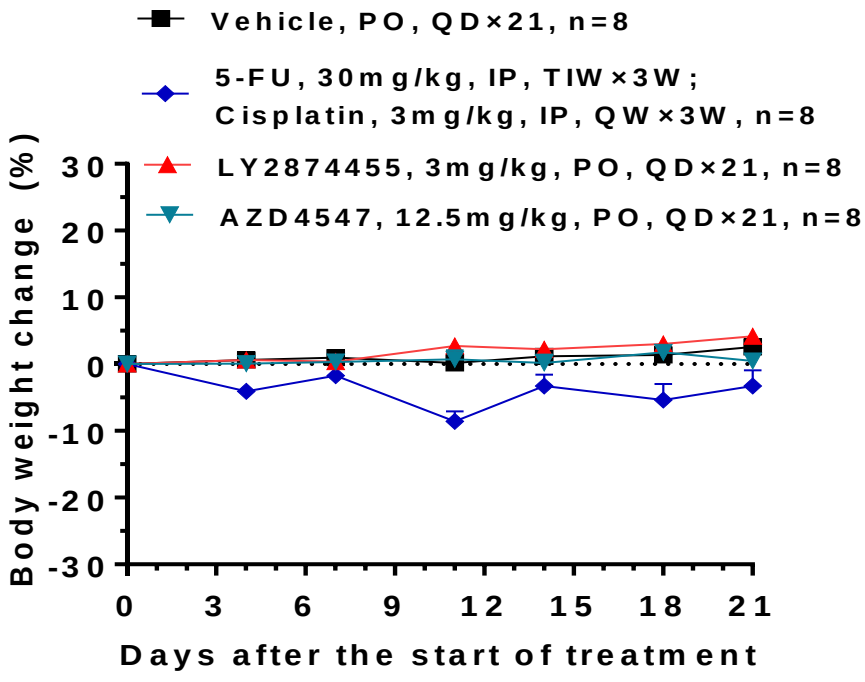
FGFR Inhibitors in SNU-16 xenograft model



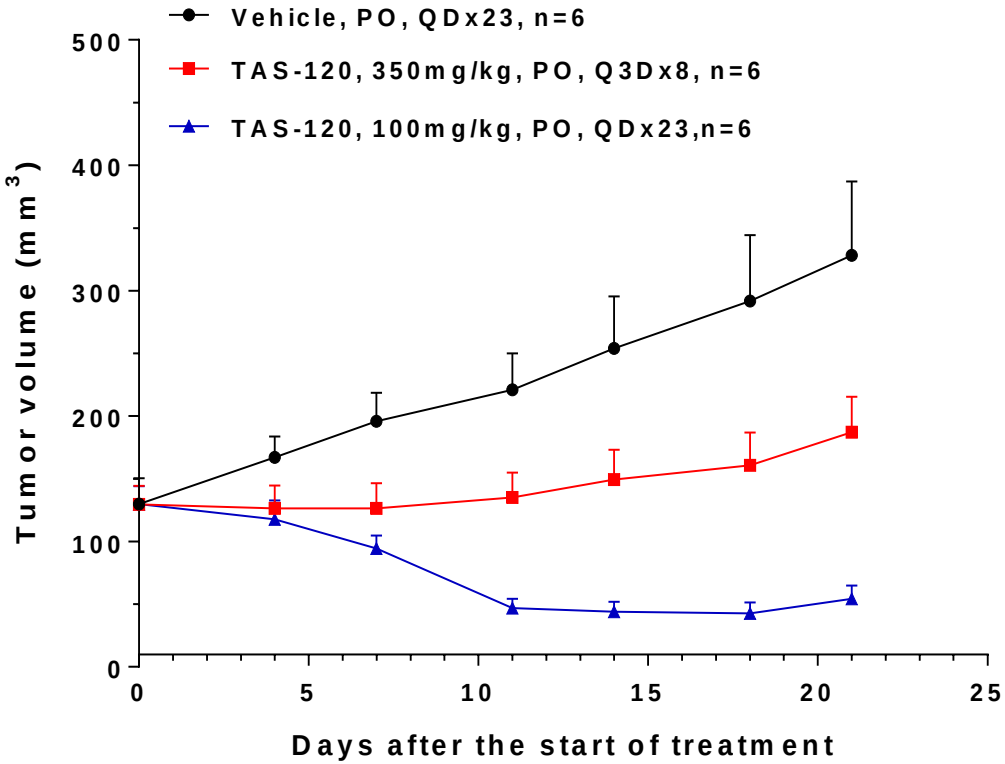


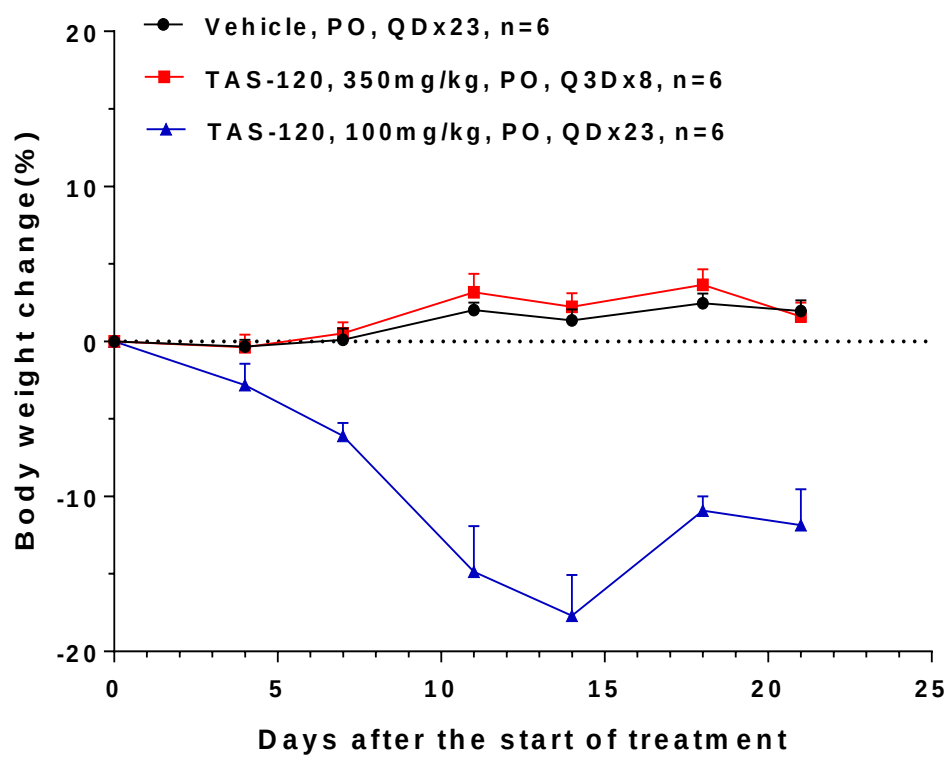
FGFR Inhibitors in SNU-16 xenograft model



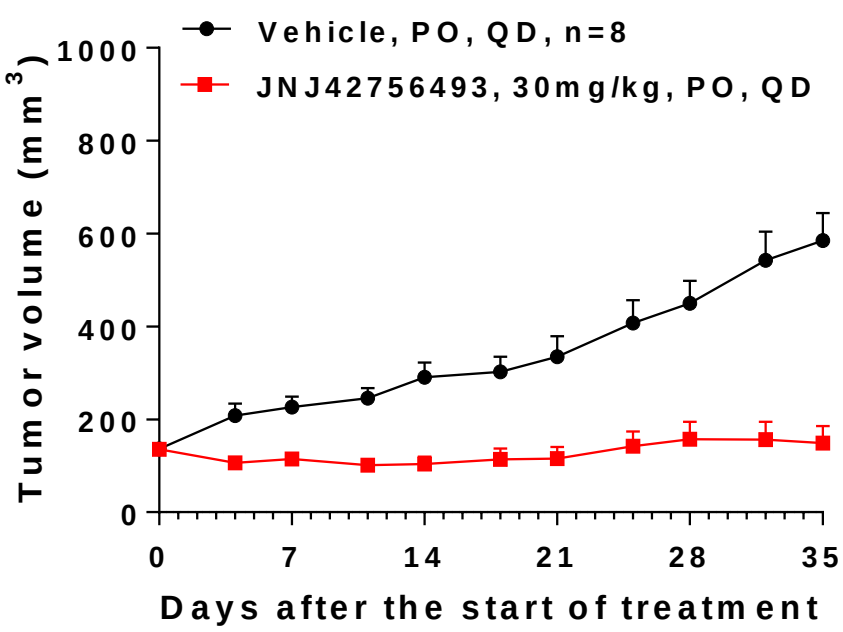


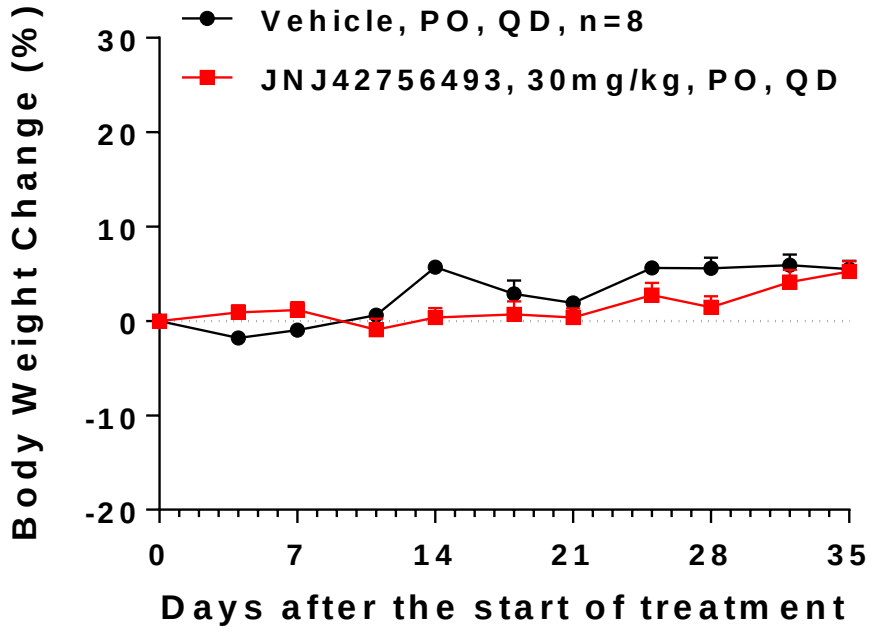
FGFR Inhibitors in SNU-16 xenograft model



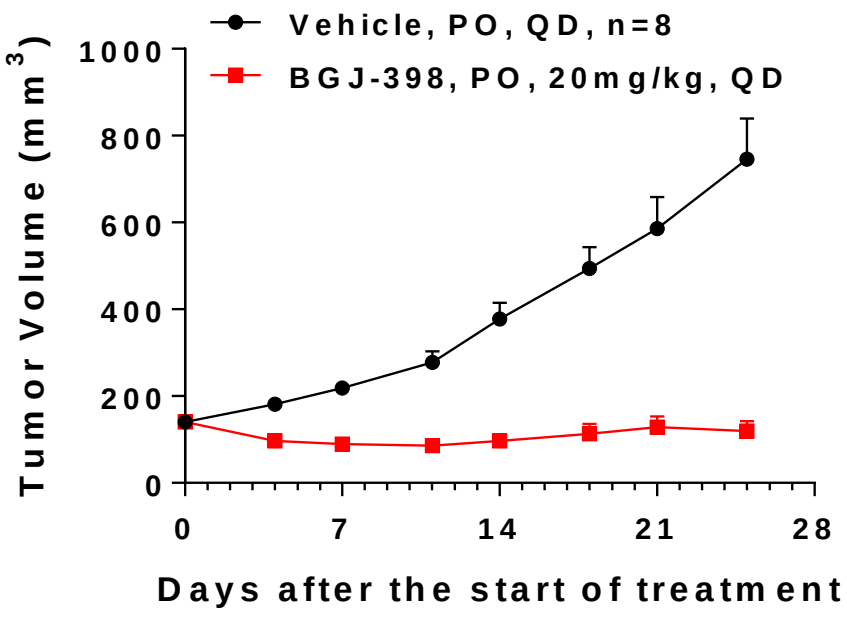


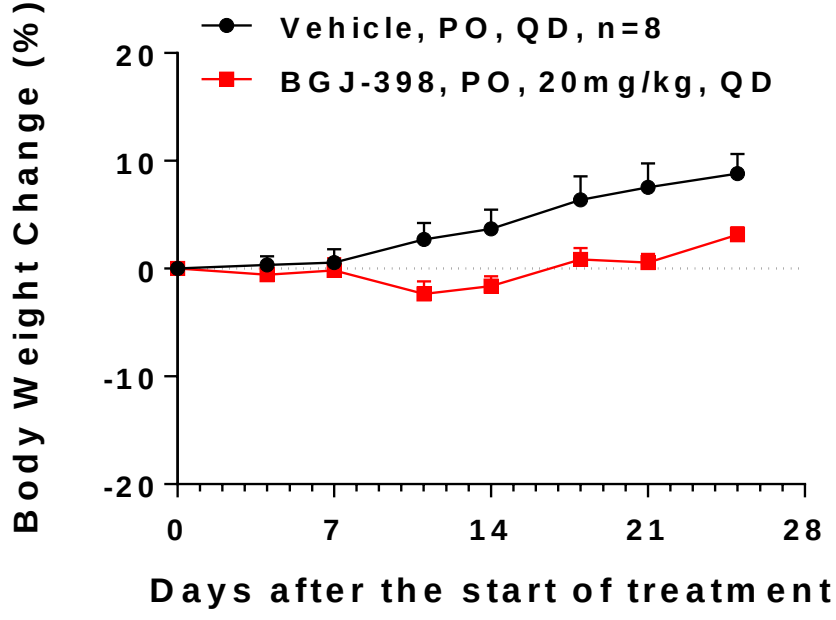
FGFR Inhibitors in SNU-16 xenograft model



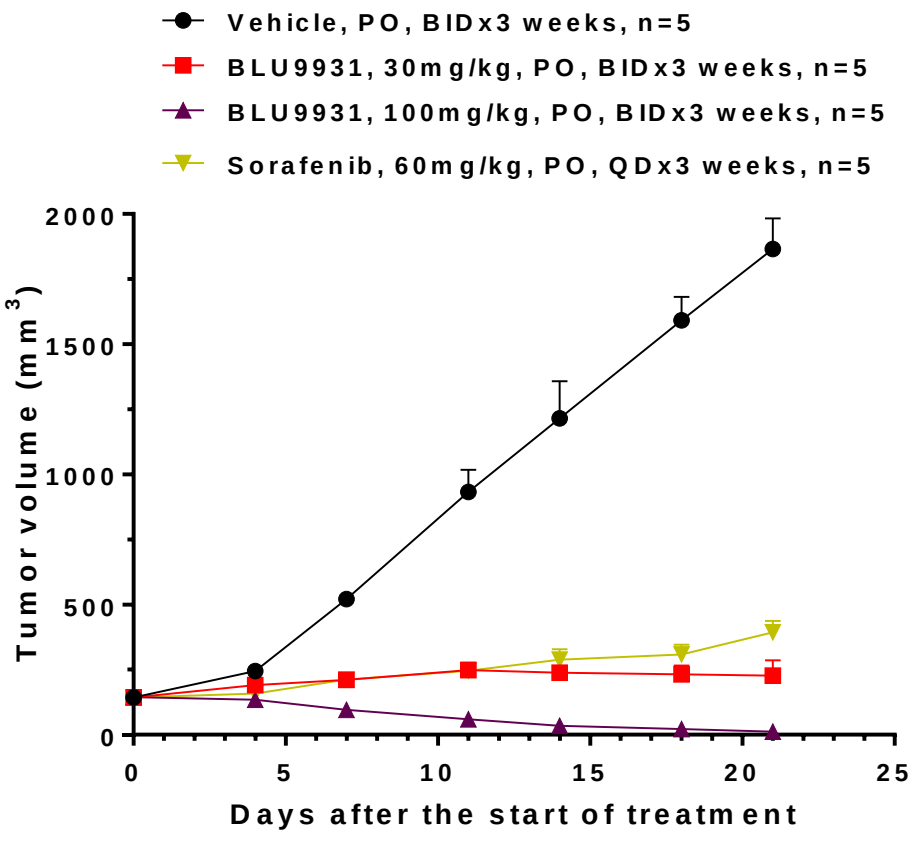


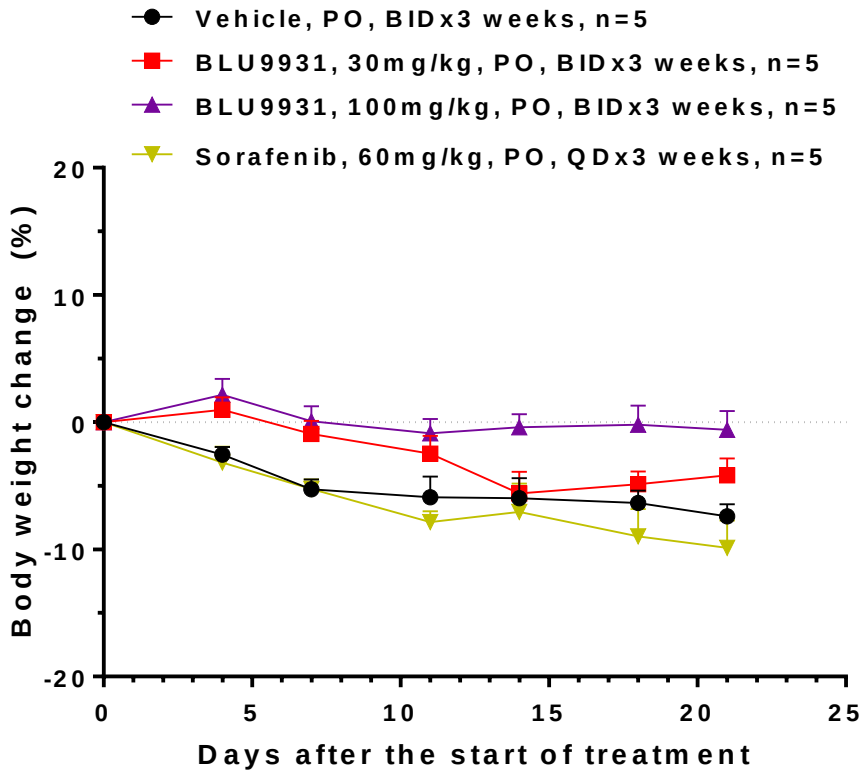
FGFR Inhibitors in SNU-16 xenograft model



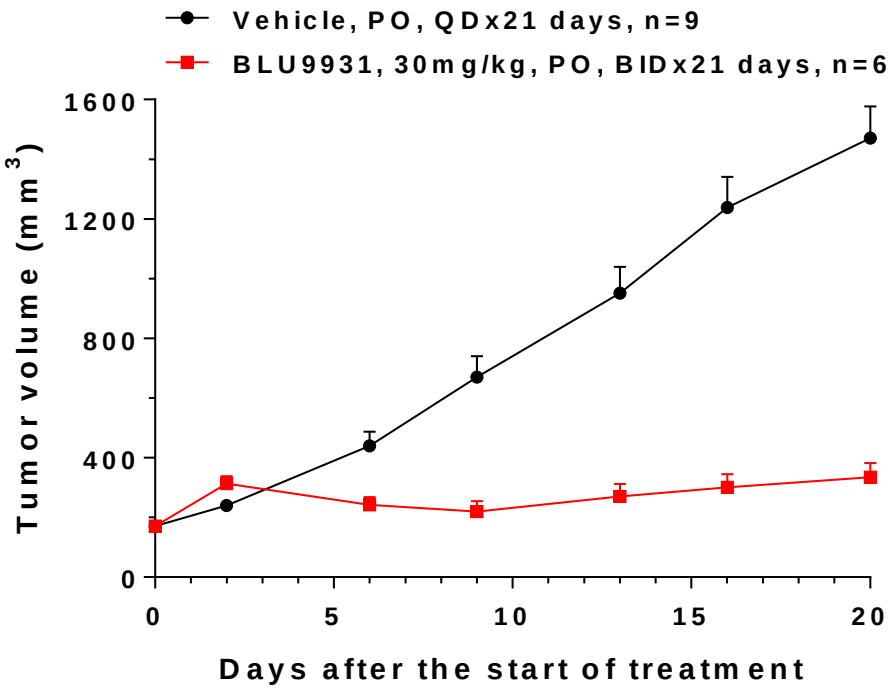


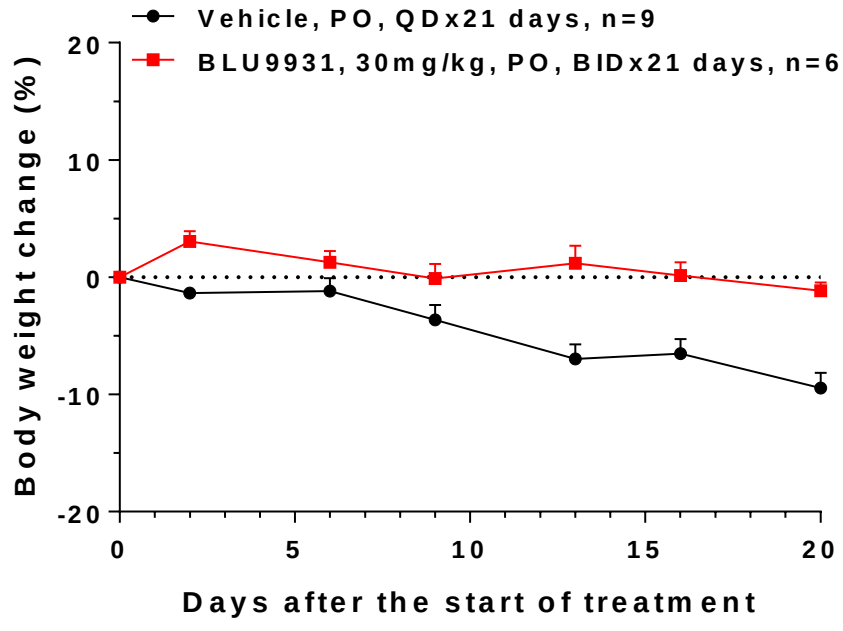
BLU9931 and Sorafenib in Hep 3B Xenograft model



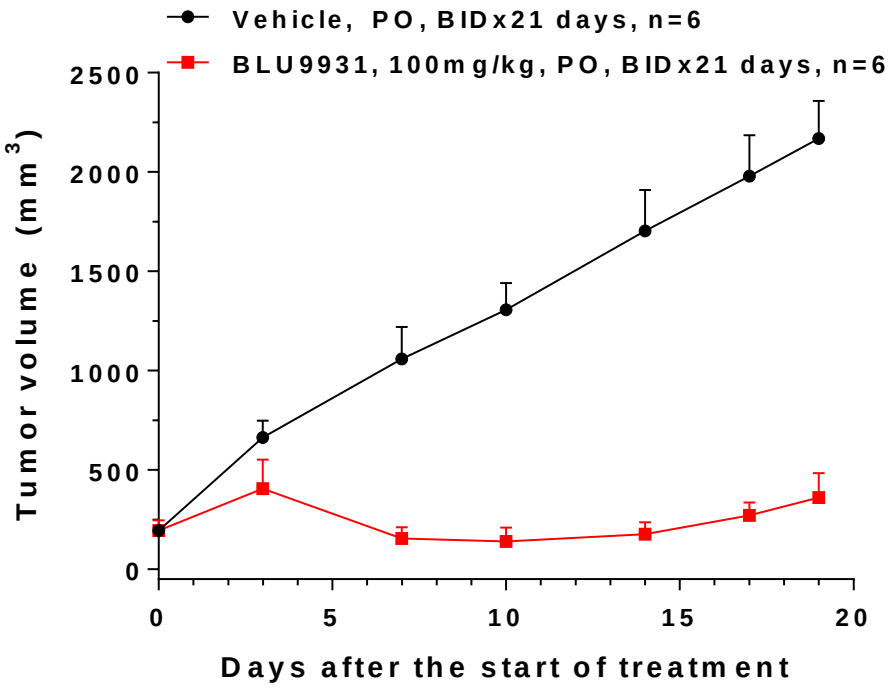


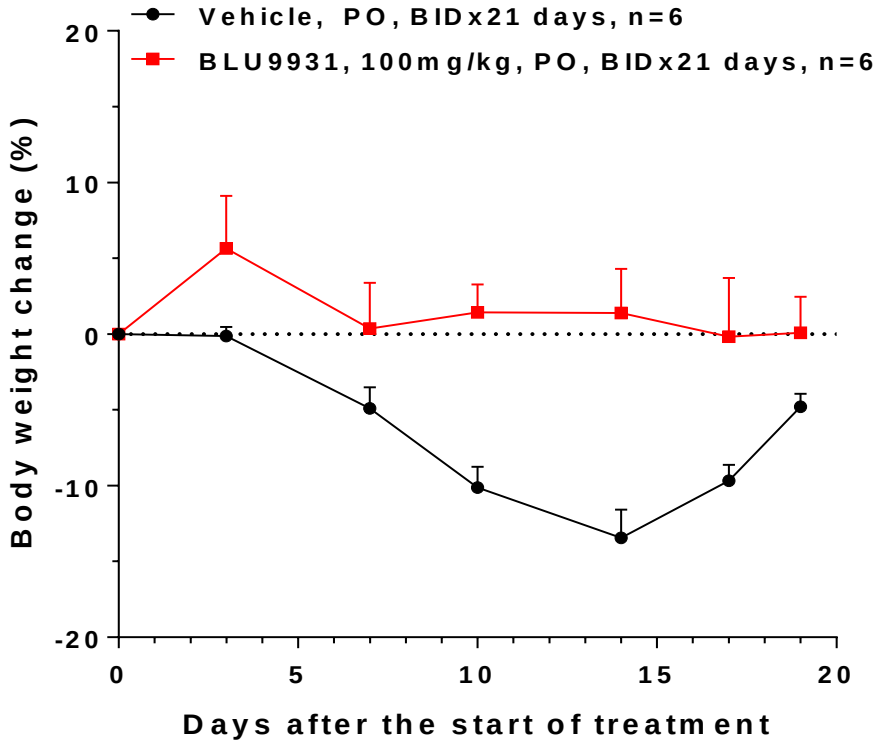
BLU9931 in Hep 3B xenograft model



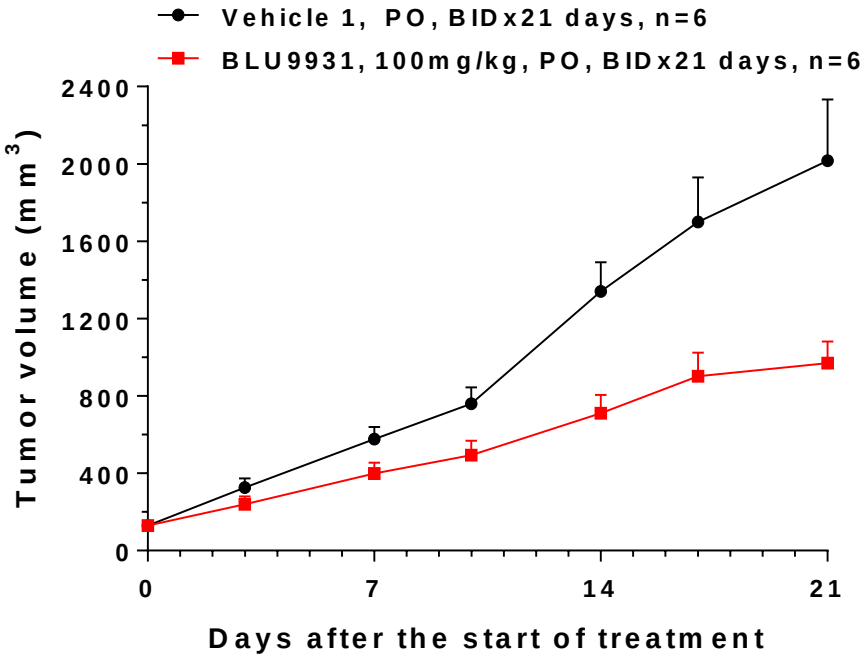


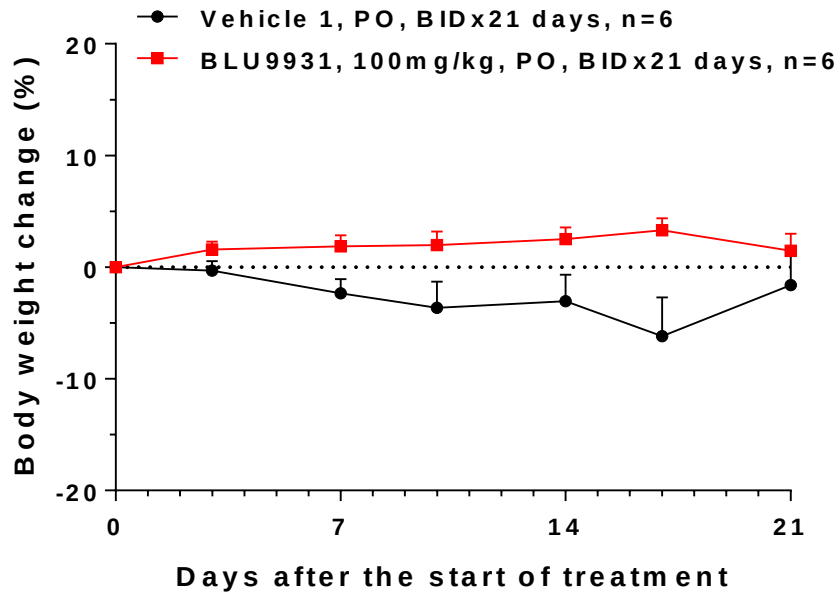
BLU9931 in Hep 3B xenograft model



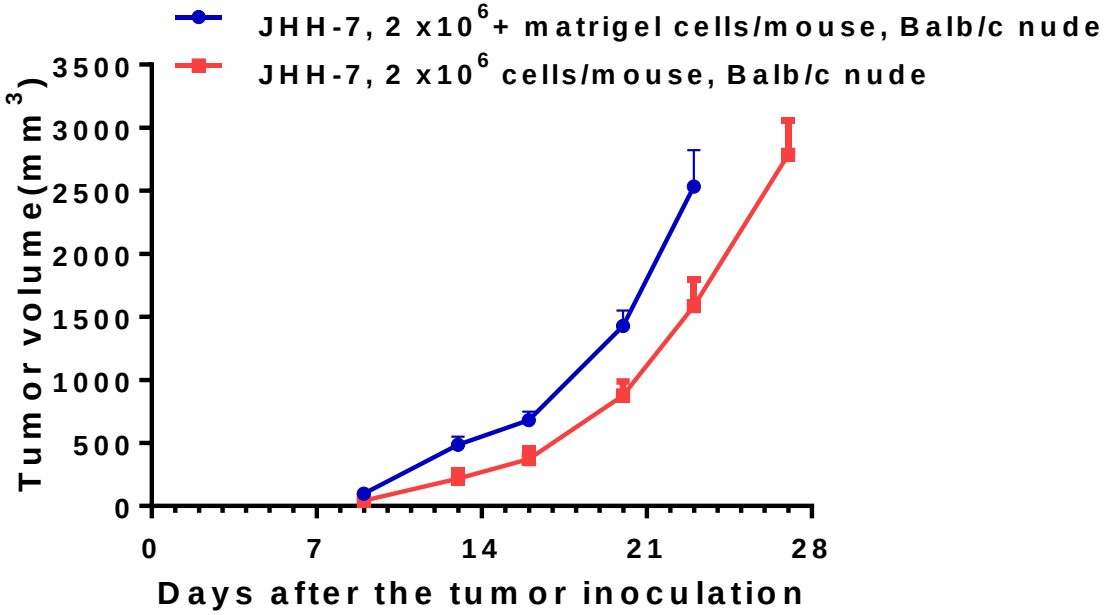


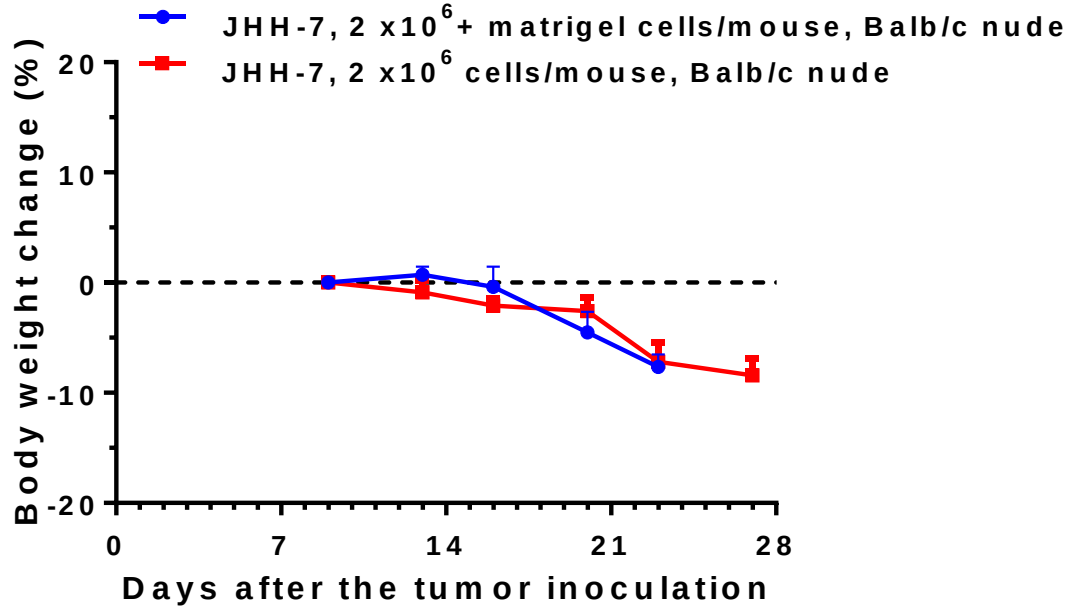
BLU9931 in Huh-7 xenograft model





JHH-7 Liver Cancer Xenograft model





FGFR overexpression PDX and PDC models

Model ID	Cancer type	Growth curve	Drug tested	FGFR overexpression	CNV (SNP6.0)	Microarray (Log2Ratio)	RNAseq (FPKM)
LU-01-0016_PDC	NSCLC	Yes		FGFR1	4.3		154.9
LU-01-0016	NSCLC	Yes		FGFR1	4.1	8.4	124.9
GI-20-0006	GIST	Yes		FGFR1	2.8		133.7
GI-20-0008	GIST	Yes		FGFR1	2.5		120.3
ES-06-0164_PDC	Esophageal cancer	Yes		FGFR3	2.2		120.9
LU-01-0030	NSCLC	Yes		FGFR3	2.4	7.5	107.9
LI-03-1054TM	HCC	Yes		FGFR3	2.7		104.3
LU-01-0695	NSCLC	Yes		FGFR3	2.2		180.1
LI-03-0140	HCC	Yes		FGFR3	3.5	8.5	110.6
LI-03-0159	HCC	Yes	Regorafenib Sorafenib	FGFR4	1.0	7.8	140.3
LI-03-0185	HCC	Yes		FGFR4	1.5	8.3	115.0
LI-03-0220	Liver cancer	Yes		FGFR4	2.1	8.2	114.9
LI-03-0842	HCC	Yes		FGFR3 FGFR4	3.3 2.3		219.1 211.3

Note: FPKM > 100 was considered as overexpression.

FGFR fusion/mutation PDX models

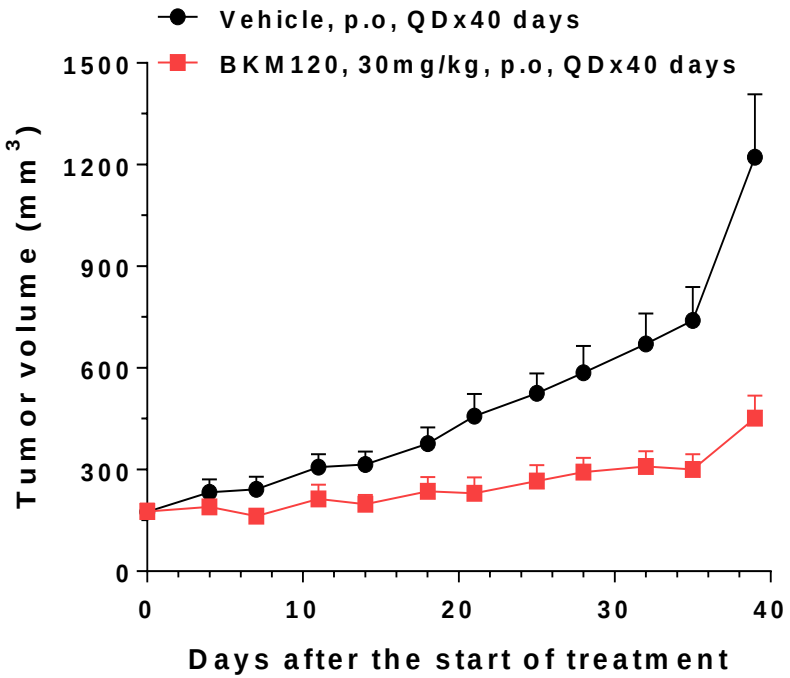
Model ID	Cancer type	Growth curve	Drug tested	FGFR status
LU-01-0010	NSCLC	Yes	BKM120, AZD4547	COL25A1-exon3->FGFR2-exon3 PIK3CA E545K mutation
LU-01-0248	NSCLC	Yes		FGFR3(NM_000142) R248C
LI-03-0196	HCC	Yes		FGFR3(NM_000142) S249C
LU-01-0048	NSCLC	Yes	AZD4547	FGFR3(NM_000142) S249C
LU-01-0280	NSCLC	Yes		FGFR3(NM_000142) S249C
LU-01-0514	NSCLC	Yes		FGFR3(NM_000142) S249C
LU-01-0594	NSCLC	Yes		FGFR2(NM_000141) C382R

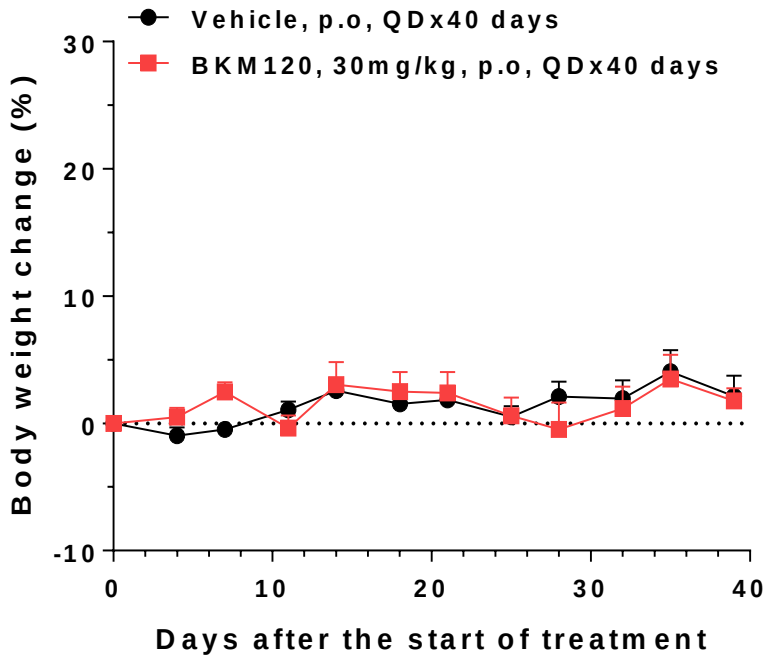
FGFR PDX models: summary of validation data

Model ID	Cancer type	Tumor growth curve	Drugs tested	Dosage(mg/kg)	TGI (%)	Model genomics
LU-01-0010	NSCLC	Yes	BKM120	30	63	COL25A1-exon3->FGFR2-exon3 PIK3CA E545K mutation
LU-01-0010			AZD4547	12.5	52	
LU-01-0048	NSCLC	Yes	AZD4547	12.5	110	FGFR3 S249C

PI3K inhibitor in LU-01-0010

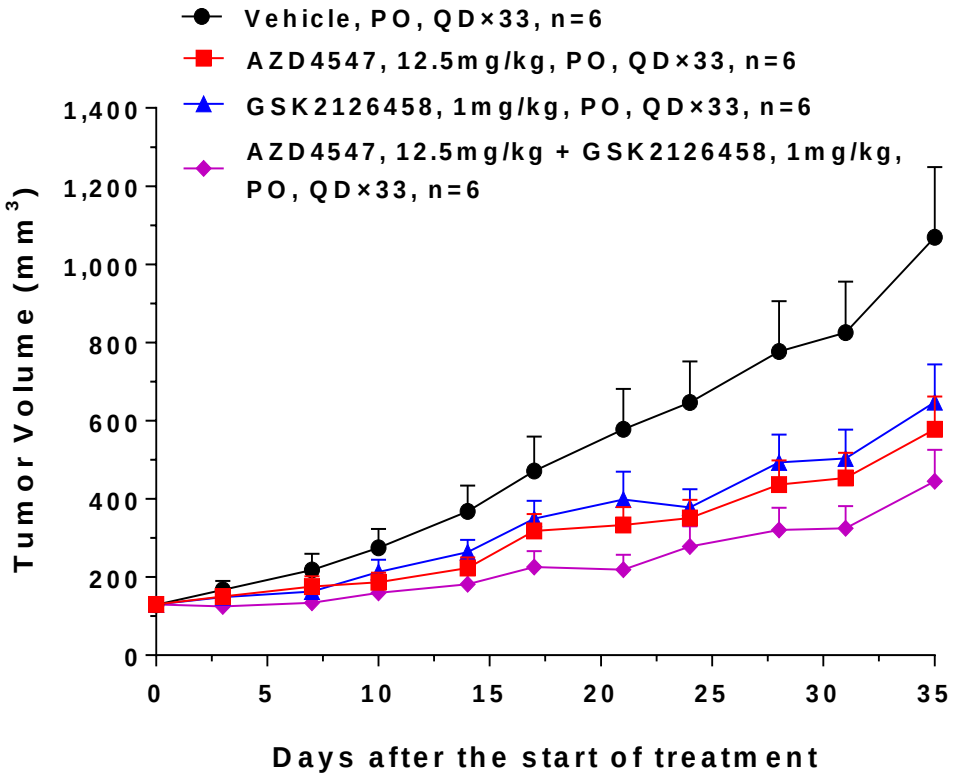
Model ID	Cancer type	Gender	Age	Tumor Grade	Tumor Stage	Target
LU-01-0010	NSCLC	Male	38	G3	T2N0M0	COL25A1-exon3->FGFR2-exon3 PIK3CA E545K mutation

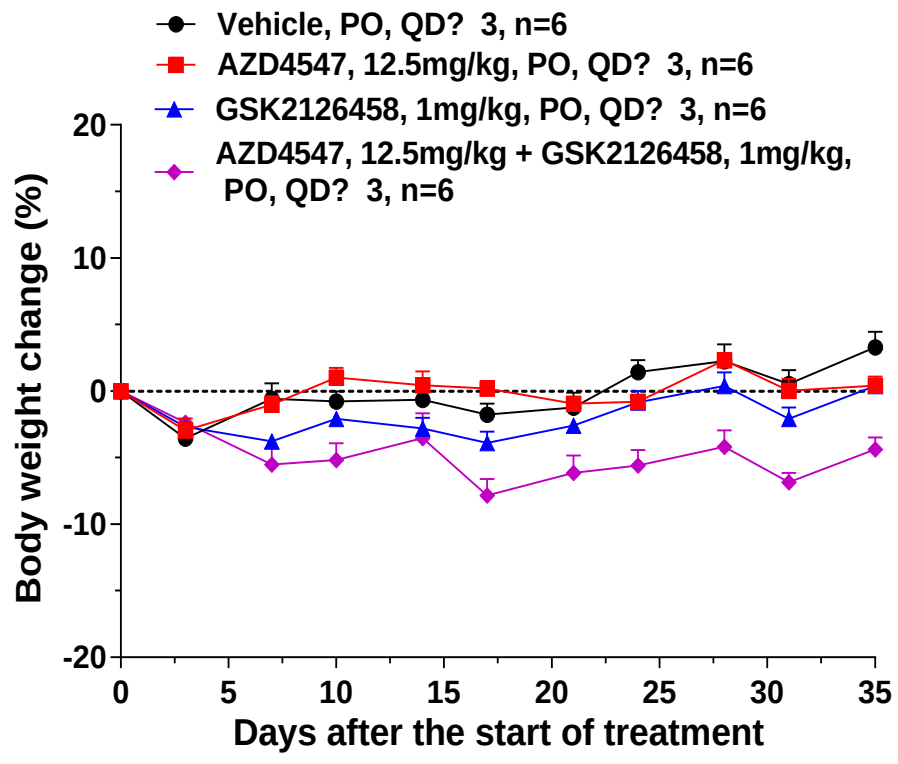




FGFR inhibitor in LU-01-0010

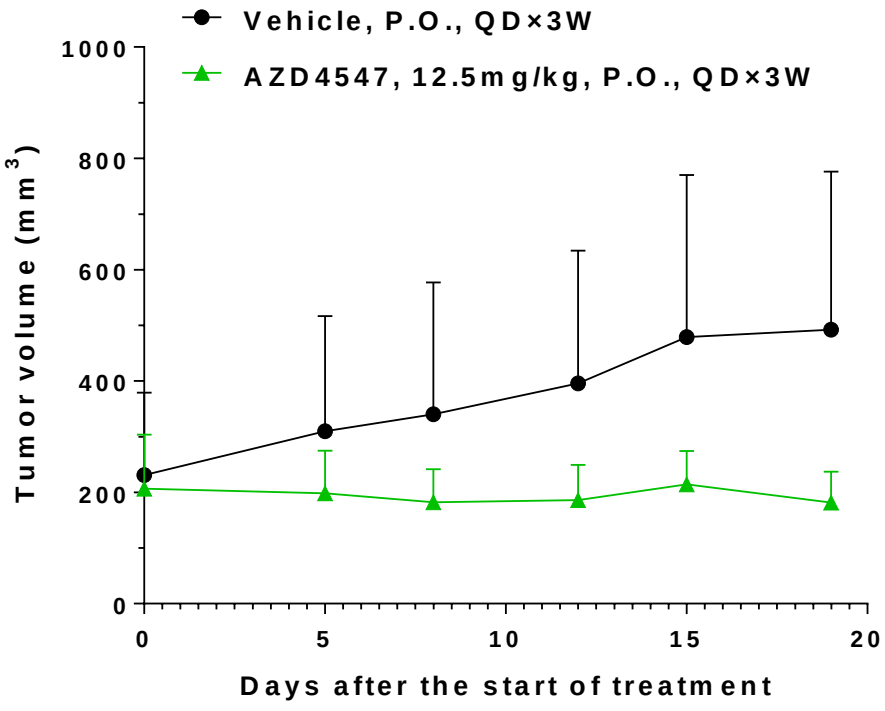
Model ID	Cancer type	Gender	Age	Tumor Grade	Tumor Stage	Target
LU-01-0010	NSCLC	Male	38	G3	T2N0M0	COL25A1-exon3->FGFR2-exon3 PIK3CA E545K mutation

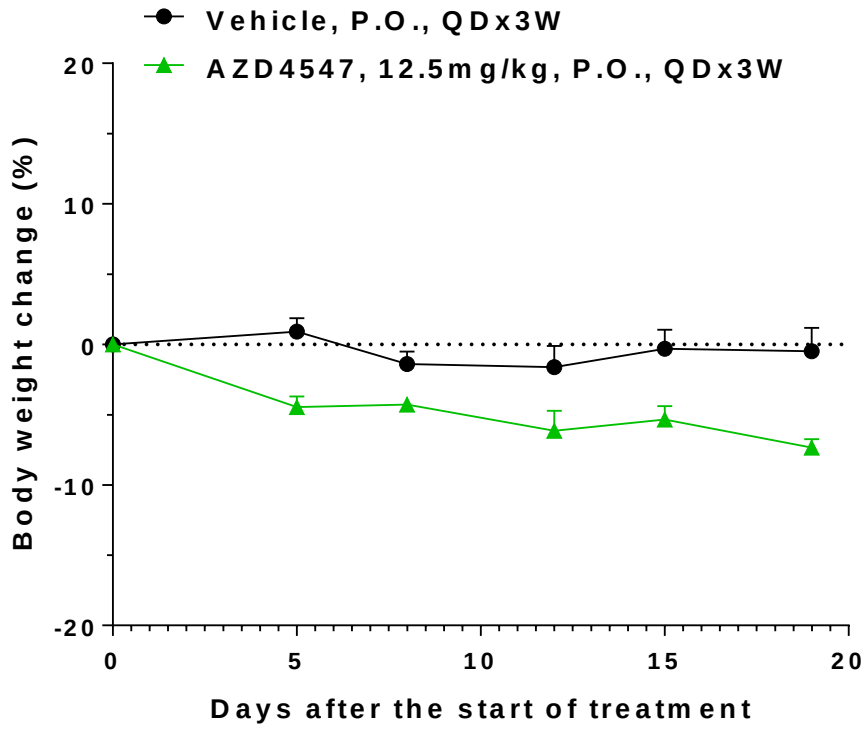




FGFR inhibitor in LU-01-0048

Model ID	Cancer type	Gender	Age	Tumor Grade	Tumor Stage	Target
LU-01-0048	NSCLC	Male	78	G2	T2N0M0	FGFR3 S249C





OUR COMMITMENT

Improving Health. Making a Difference.

For questions and requests, please email to info_onco@wuxiapptec.com

https://onco.wuxiapptec.com

Mobile App

药明康德
WuXi AppTec

www.wuxiapptec.com