FGFR-related *in vivo* models

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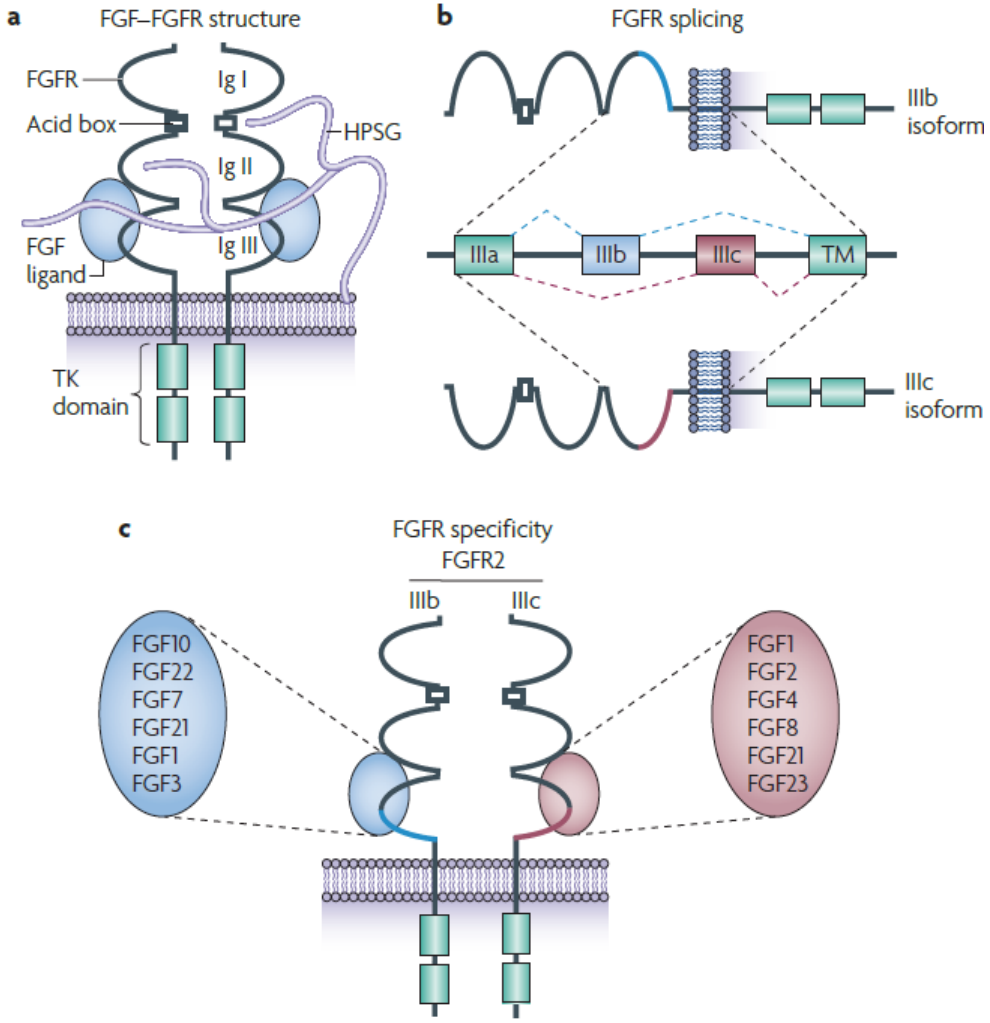
Outline

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

FGFR family and its ligands

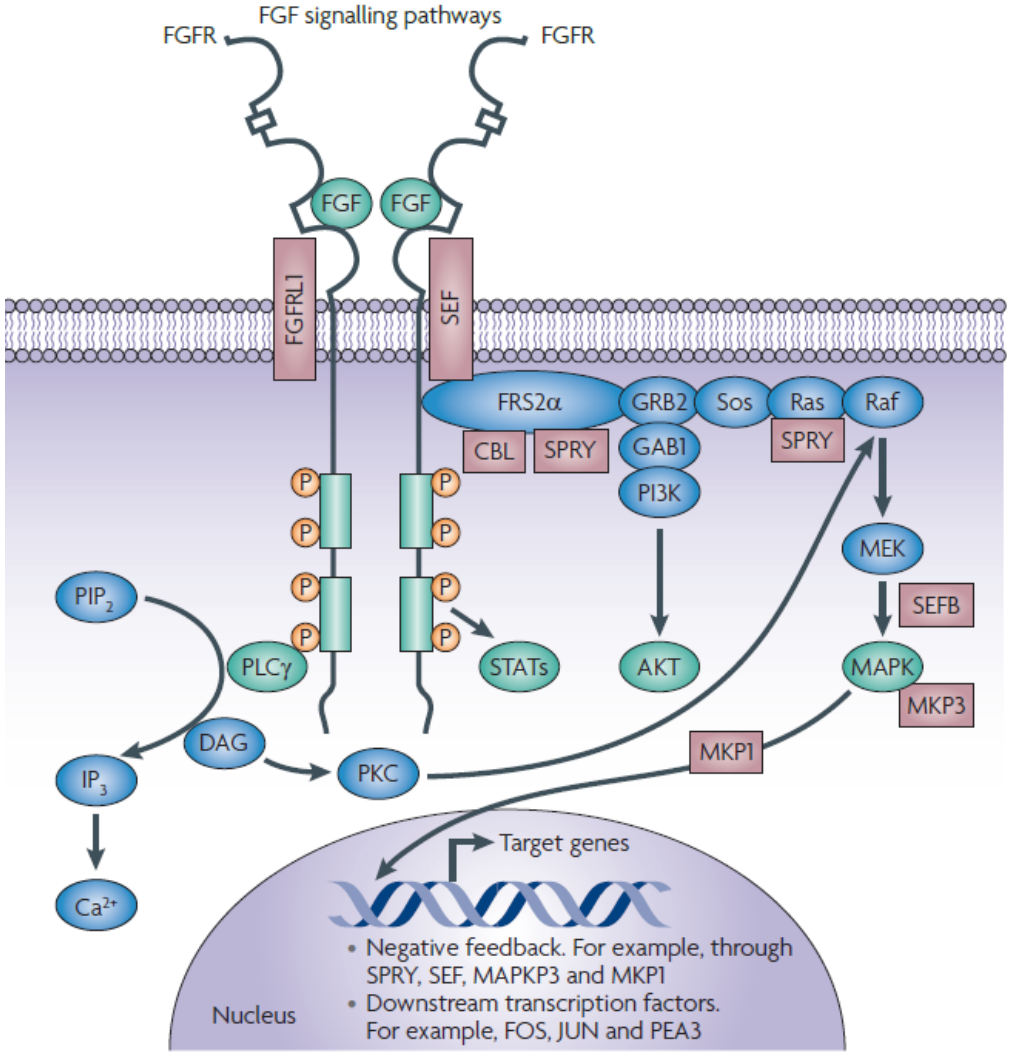
- Fibroblast growth factor receptor (FGFR) belongs to the receptor tyrosine kinases (RTKs) family, and has four isoforms, FGFR1, FGFR2, FGFR3 and FGFR4.
- FGFR is composed of an extracellular ligand binding domain, a single transmembrane domain and a cytoplasmic domain containing the catalytic protein 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 signaling.



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

FGFR Pathway

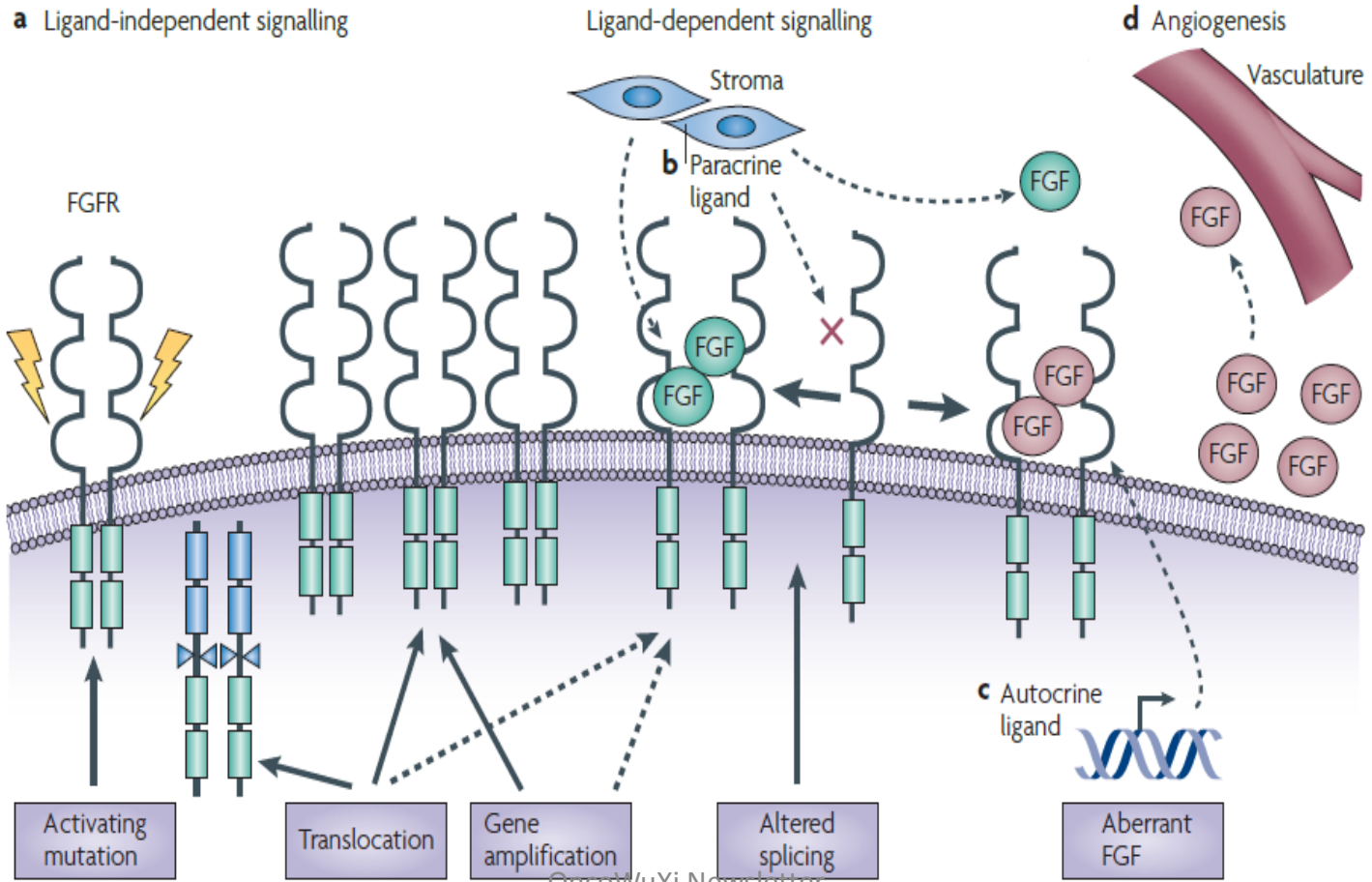
- Following ligand binding and receptor dimerization, the kinase domains transphosphorylate each other, leading to the docking of adaptor proteins and the activation of four key downstream pathways: RAS–RAF–MAPK, PI3K–AKT, signal transducer and activator of transcription (STAT) and phospholipase Cγ (PLCγ) (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.



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

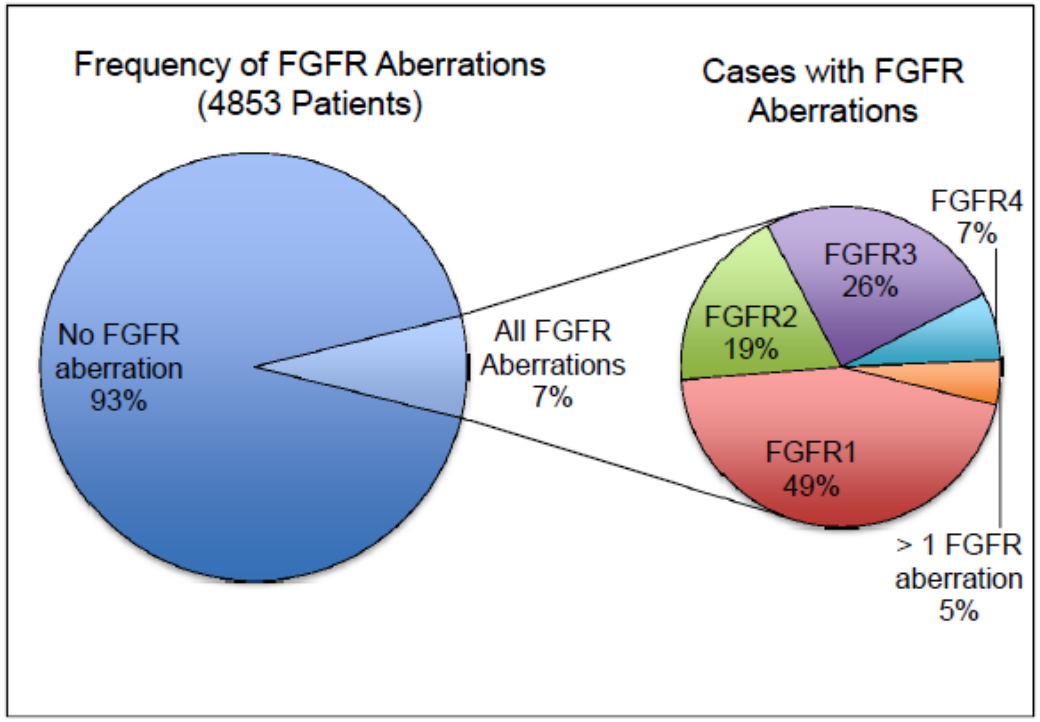
FGFR role in cancer

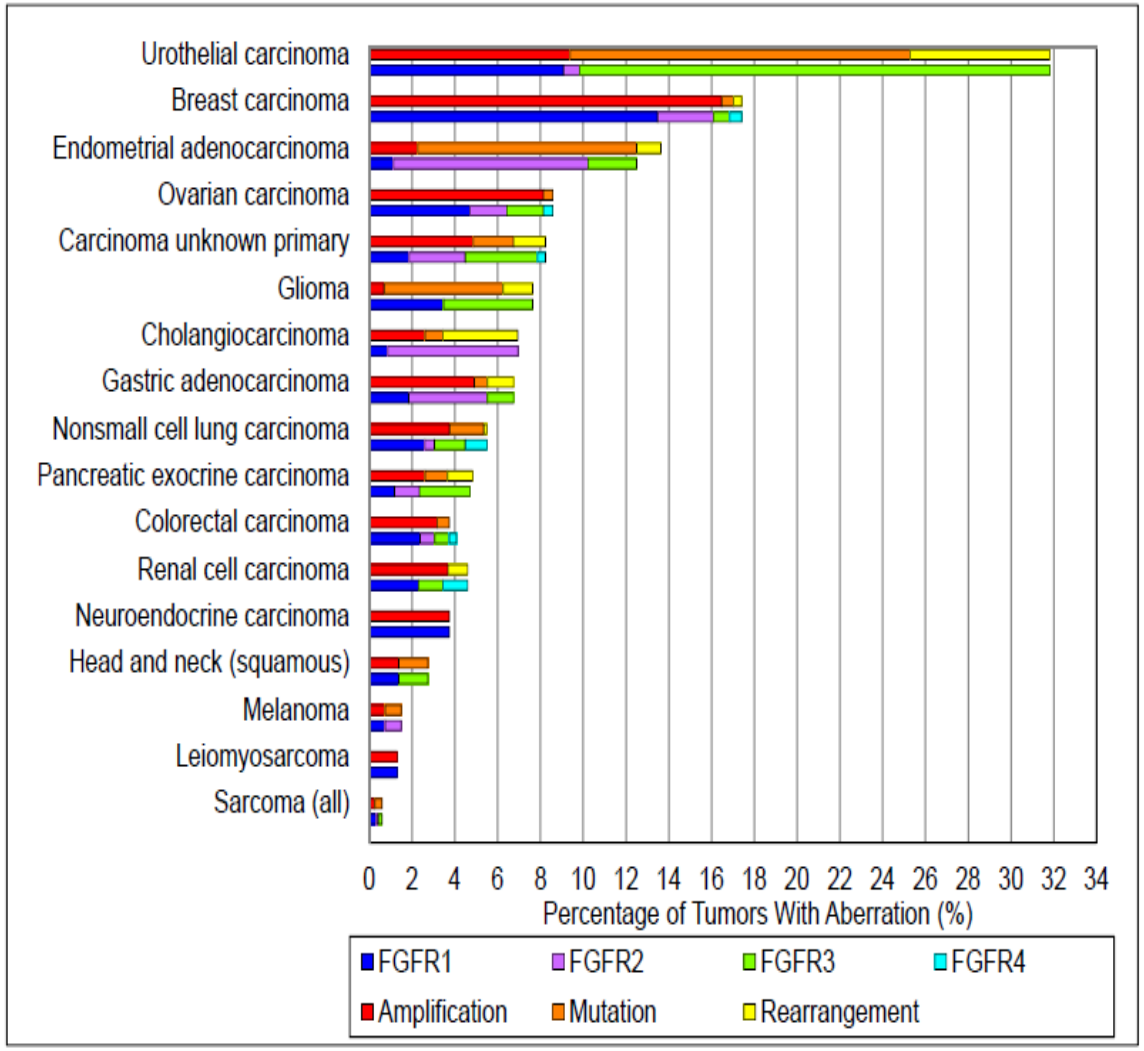
- There are several types of genetic evidence that support an oncogenic function for FGFRs: identification of gene amplifications, activating mutations, chromosomal translocations, single nucleotide polymorphisms and aberrant splicing at the post-transcriptional level.



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

FGFR abnormality prevalence in cancer



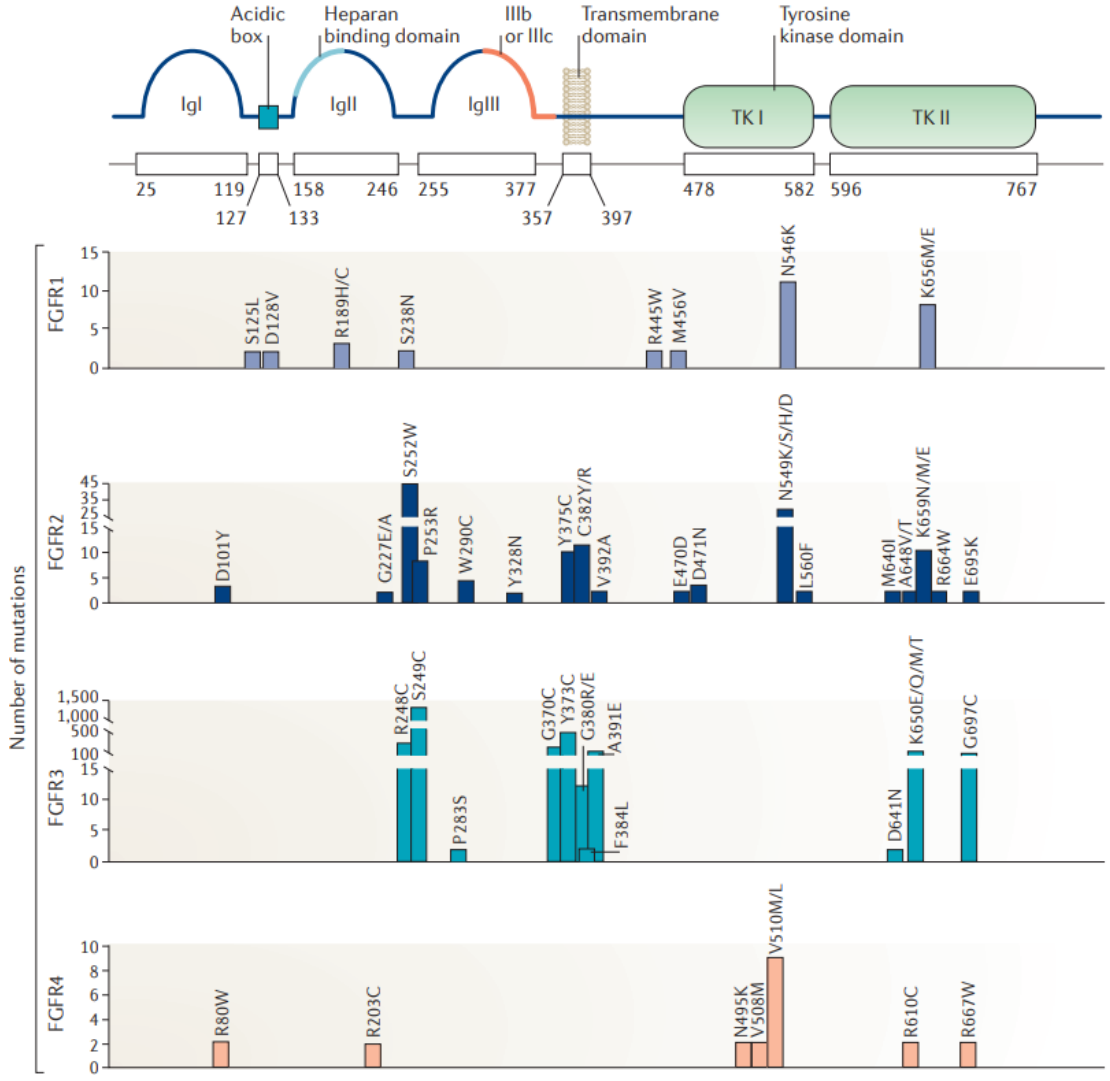


FGFR aberrations were found in 7.1% of cancers, with the majority being gene amplification (**66**% of the aberrations), followed by mutations (26%) and rearrangements (8%). FGFR1 (mostly amplification) was affected in 3.5% of 4,853 patients; FGFR2 in 1.5%; FGFR3 in 2.0%; and FGFR4 in 0.5%. Almost every 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.

Frequency of FGFR somatic mutations

- The figure shows the frequency of FGFR somatic mutations reported in cancer patients and their relative location on the proteins. Residue locations correspond to various regions on the receptors, using the FGFR1 molecule as a reference. Mutations in FGFR1 and FGFR4 are not frequently reported, but mutations in FGFR2 and FGFR3 are common and occur predominantly in the ligand-binding and transmembrane domains of the receptors, with fewer mutations reported in the kinase domains.



Nat Rev Cancer. 2017 May;17(5):318-332.

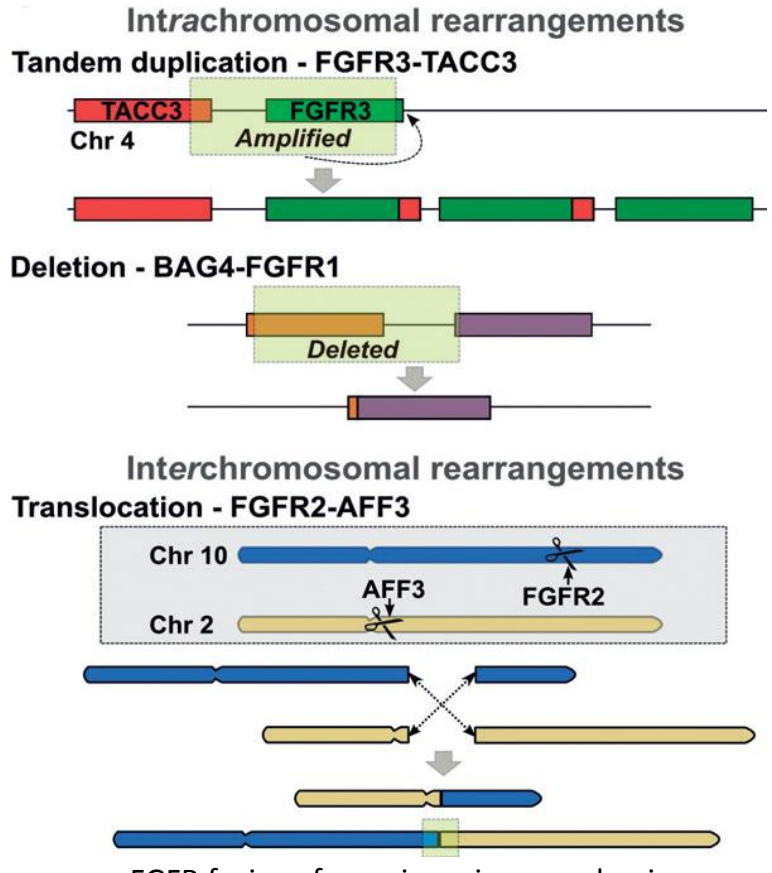
FGFR mutations and their functional significance

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	FGFR1/2/3/4	Breast cancer, NSCLC, Gastric cancer	Phase 2/3
CH5183284	Debiopharm International SA	FGFR1/2/3	Solid Tumors	Phase 1
JNJ-42756493 (Erdafitinib)	Janssen Scientific Affairs, LLC	FGFR1/2/3/4	Advanced Cancers and FGFR Genetic Alterations	Approved for marketing
NVP-BGJ398	Novartis Pharmaceuticals	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 Pharmaceuticals	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)	Institut de Recherches Internationales Servier	FGFR1/2, VEGFR1-3, PGFRα/β	Solid Tumor	Phase 1/2

https://clinicaltrials.gov/

FGFR-targeted drugs

Drug	Inventor	Target/Mechanism	Indications	Status
BLU-554	Blueprint Medicines Corporation	FGFR4	Hepatocellular Carcinoma (HCC)	Phase 1
FGF401	Novartis Pharmaceuticals	Positive FGFR4	Hepatocellular Carcinoma, Solid Malignancies	Phase 1/2
U3-1784	Daiichi Sankyo Inc.	FGFR4	Advanced Solid Tumors, Hepatocellular Cancer (HCC)	Phase 1 （Terminated ）
TAS-120	Taiho Oncology, Inc.	FGFR1/2/3/4	Advanced solid tumors, Metastatic Breast Cancer	Phase2
Debio 1347	Debiopharm International SA	FGFR1/2/3	Solid tumors	Phase 1/2
H3B-6527	Eisai Inc.	FGFR4	Advanced Hepatocellular Carcinoma	Phase 1
ASP5878	Astellas Pharma Inc	FGFR1/2/3/4	Solid tumors	Phase 1
PRN1371	Principia Biopharma Inc.	FGFR1/2/3/4	Solid tumors	Phase 1 （Terminated ）
Rogaratinib (BAY1163877)	Bayer	FGFR1/3	Carcinoma	Phase 2/3
BAY1179470	Bayer	FGFR2	Neoplasms	Phase 1
FPA144	Five Prime Therapeutics, Inc.	FGFR2	Gastric cancer, Bladder cancer	Phase 1

https://clinicaltrials.gov/

FGFR-targeted drugs

Drug	Inventor	Target/Mechanism	Indications	Status
Vofatamab (B-701)	Rainier Therapeutics	FGFR3	Advanced or Metastatic Urothelial Cell Carcinoma	Phase 2 （Terminated ）
Pemigatinib	Incyte Corporation	FGFR1/2/3	Solid tumors, Myeloid/Lymphoid Neoplasms	Phase 2
Derazantinib	Basilea Pharmaceutica	FGFR2	Intrahepatic Cholangiocarcinoma Combined Hepatocellular and Cholangiocarcinoma, Solid Tumor	Phase 2
LY3076226	Eli Lilly and Company	FGFR3	Advanced Cancer	Phase 1
ASP5878	Astellas Pharma Inc	FGFR1/2/3/4	Solid Tumors	Phase 1
E7090	Eisai Co., Ltd.	FGFR1/2/3	Solid Tumors, Cholangiocarcinoma	Phase1/2
CPL304110	Celon Pharma SA	FGFR1/2/3	Solid Tumors	Phase 1
INCB062079	Incyte Corporation	FGFR4	Solid Tumors	Phase 1 (Terminated)
Infigratinib (BGJ398）	QED Therapeutics, Inc.	FGFR2	Advanced Cholangiocarcinoma	Phase 3
HMPL-453	Hutchison Medipharma Limited	FGFR2	Advanced Intrahepatic Cholangiocarcinoma	Phase 2

https://clinicaltrials.gov/

FGFR-targeted drugs

Drug	Inventor	Target/Mechanism	Indications	Status
RLY-4008	Relay Therapeutics, Inc.	FGFR2	ICC, Advanced Solid Tumors	Phase 1
TKI258	Novartis Pharmaceuticals	FGFR1/2	Solid Tumors, Advanced Endometrial Cancer, Metastatic Breast Cancer, Gastric Cancer	Phase 2
Ponatinib	Mayo Clinic	FGFR1/2/3/4, RET, KIT	Advanced Biliary Cancer, Malignant Neoplasm	Phase 2
Erdafitinib	National Cancer Institute (NCI)	FGFR1/2/3/4	Advanced Solid Tumors, Non-Hodgkin Lymphoma	Phase 2
Lucitanib	Institut de Recherches Internationales Servier	FGFR1	Breast Cancer	Phase 2
Rogaratinib	Swiss Group for Clinical Cancer Research	FGFR1/2/3/4	SQCLC	Phase 2
EVER4010001	EverNov Medicines (Zhuhai Hengqin) Co., Ltd	FGFR4	Solid Tumors	Phase1/2
Rogaratinib (BAY1163877)	Bayer	FGFR1/2/3/4	Neoplasms, Breast Cancer Metastatic	Phase 1
ASP5878	Astellas Pharma Inc	FGFR1/2/3/4	Solid Tumors	Phase 1
AL3810	Haihe Biopharma Co., Ltd.	Dual -VEGFR-FGFR	Solid Tumors	Phase 1

https://clinicaltrials.gov/

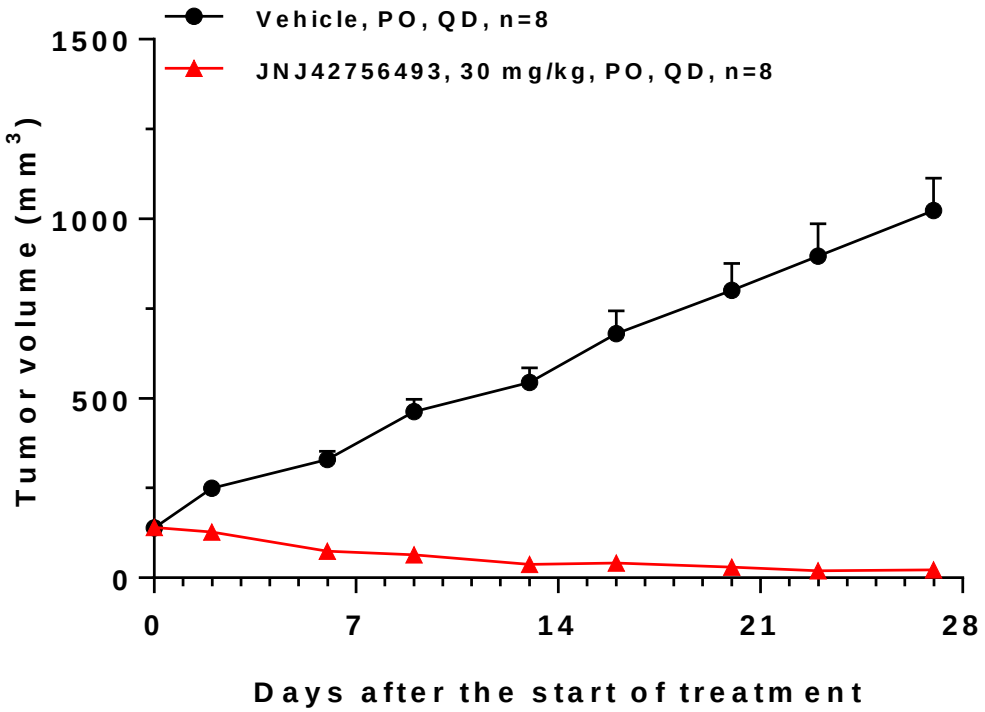
FGFR-related human cancer cell lines

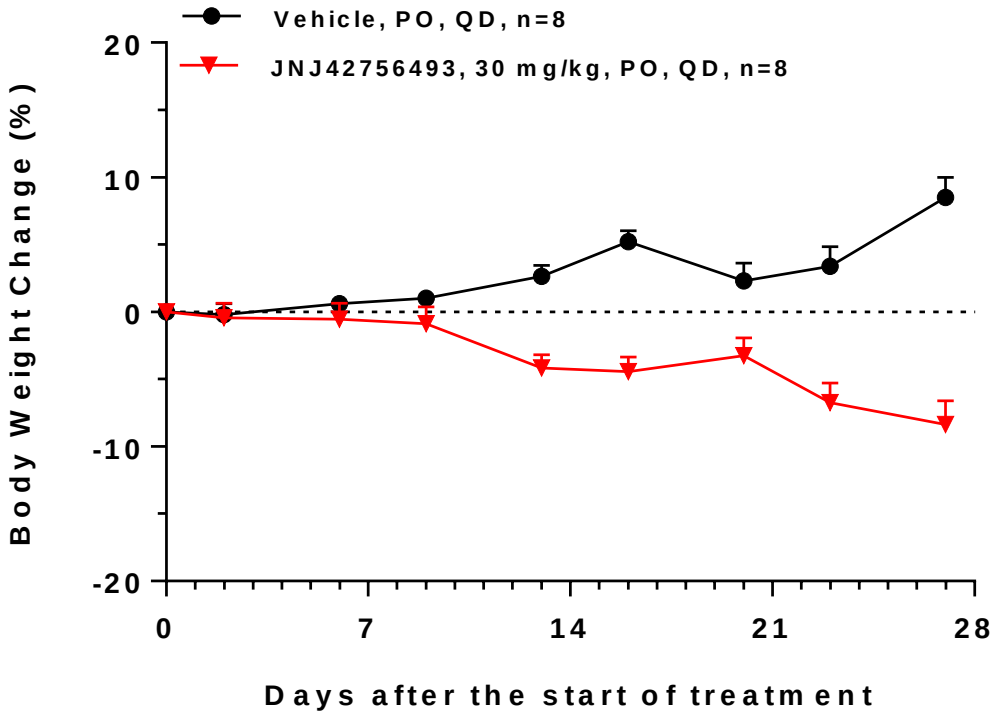
Cell line	FGFR genotype	Tissue
MDA-MB-134	FGFR1 amplification[2]	Breast
NCI-H1581	FGFR1 amplification[2]	NSCLC
DMS 114	FGFR1 amplification[1]	SCLC
KG-1	FGFR1 translocation[1,3] (FGFROP2-FGFR1 fusion)	AML
MFE-280	FGFR2:S252W[3]	Endometrium
MFE-296	FGFR2:N549K[3]	Endometrium
NCI-H716	FGFR2 gene amplification[1,3, 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

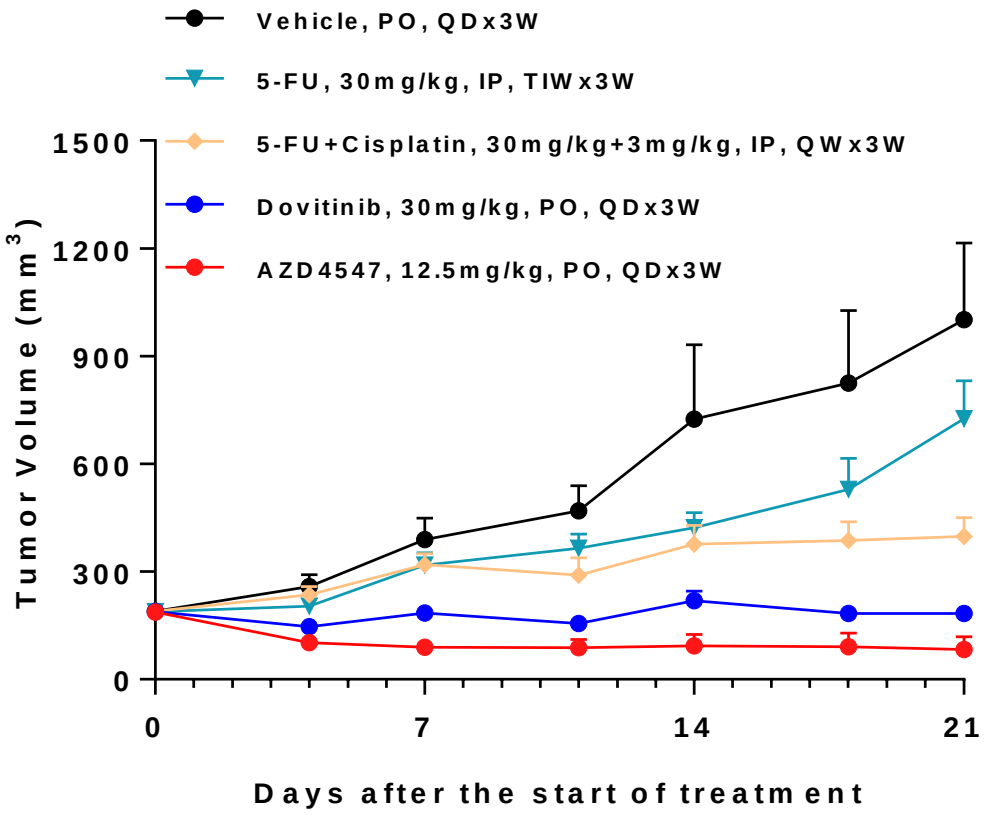
1: 2010 AACR, poster 220;
2: 2014 AACR, poster 3124;
3: 2013 AACR, poster 818;
4: 2014 AACR, poster 483;
5: PLoS One. 2014; 26;9(6):e98515;
6: Cancer Discov. 2013;3(6):636-47.
7: 2015 AACR, abstract 784;
8: Cancer Discov; 2015 Apr;5(4):424-37.

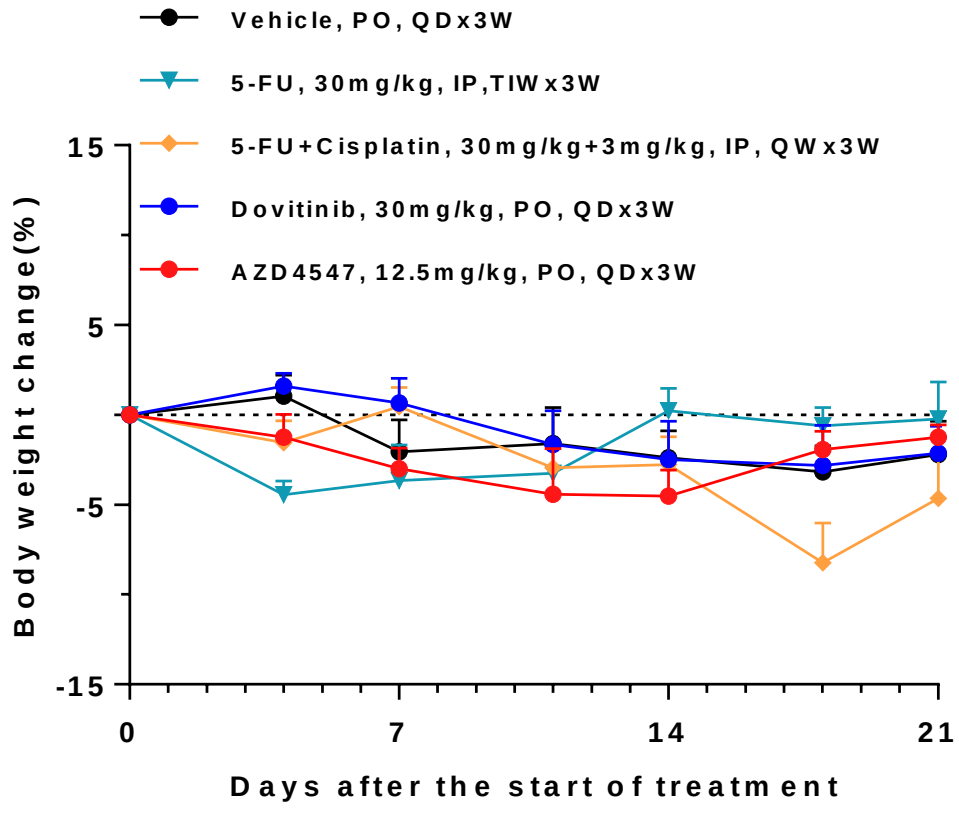
JNJ42756493 in RT112/84 xenograft model



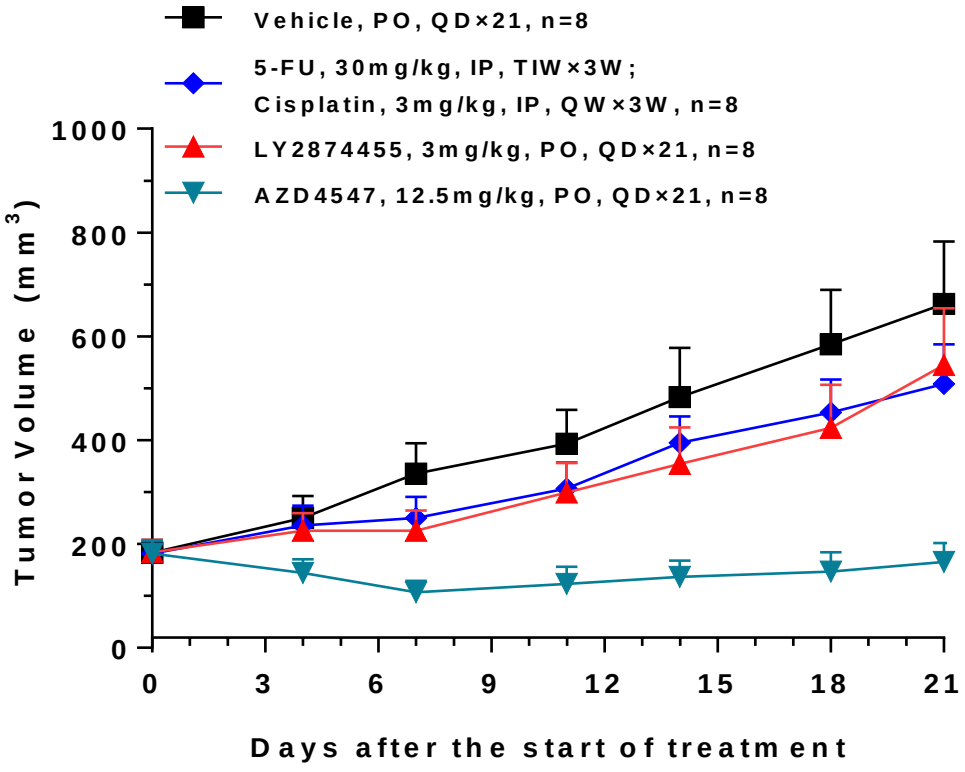


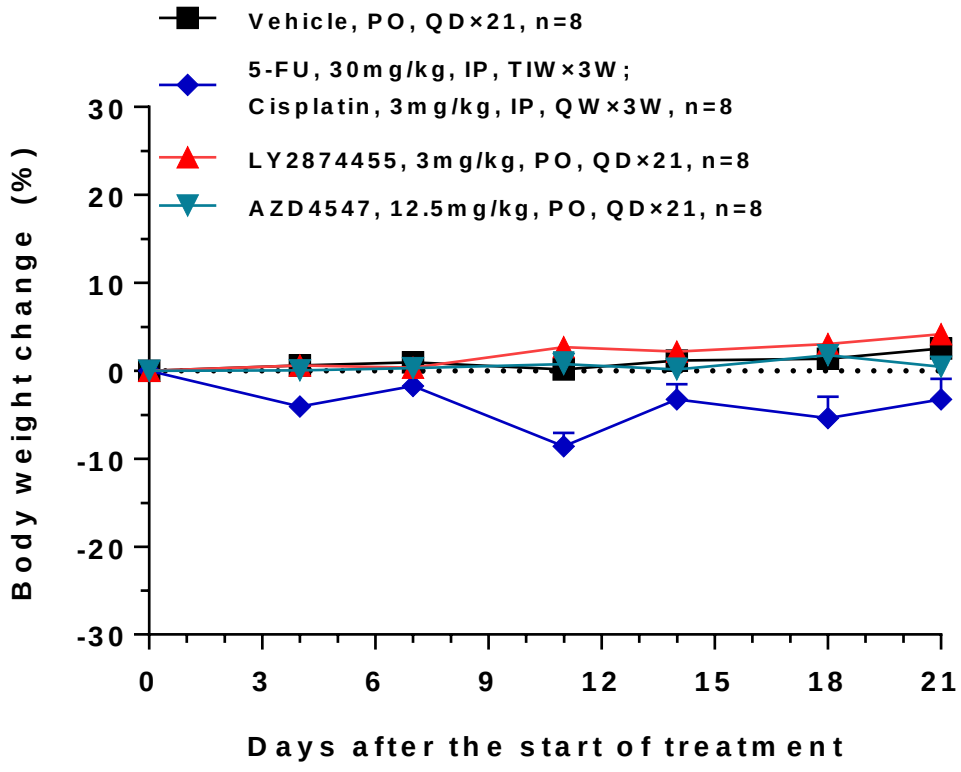
Dovitinib and AZD4547 in SNU-16 xenograft model



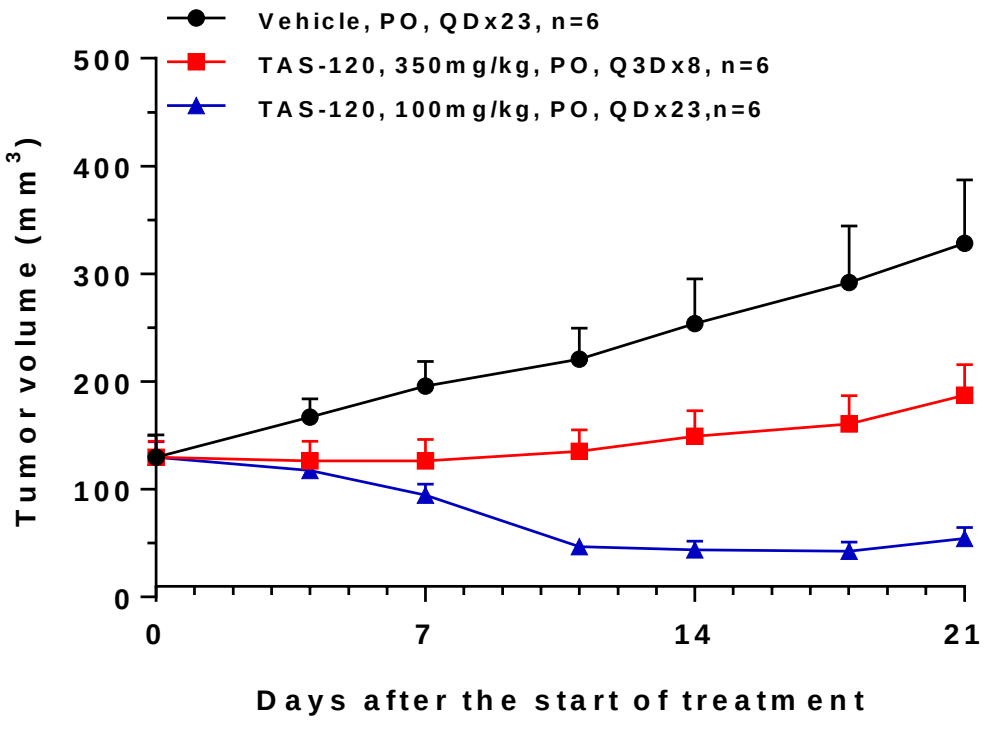


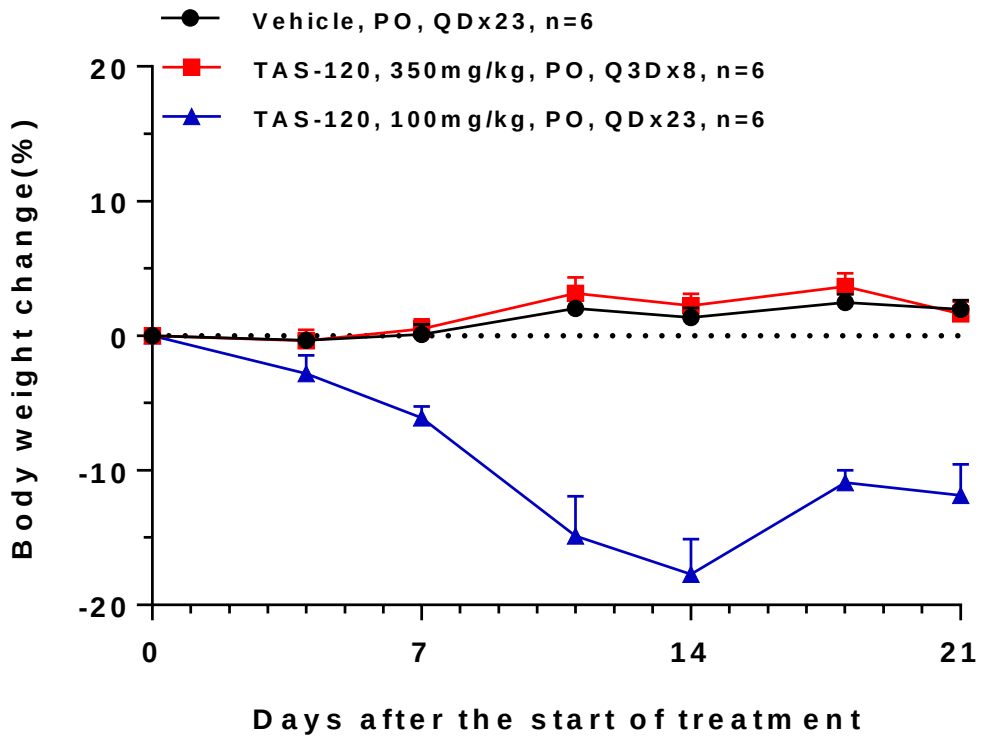
LY2874455 and AZD4547 in SNU-16 xenograft model



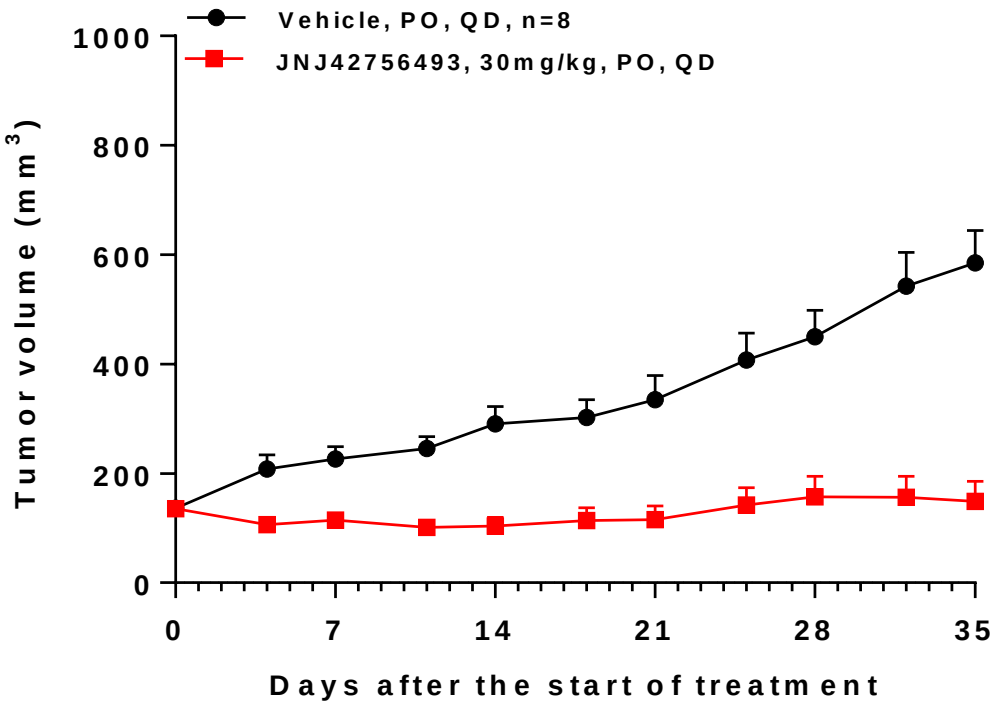


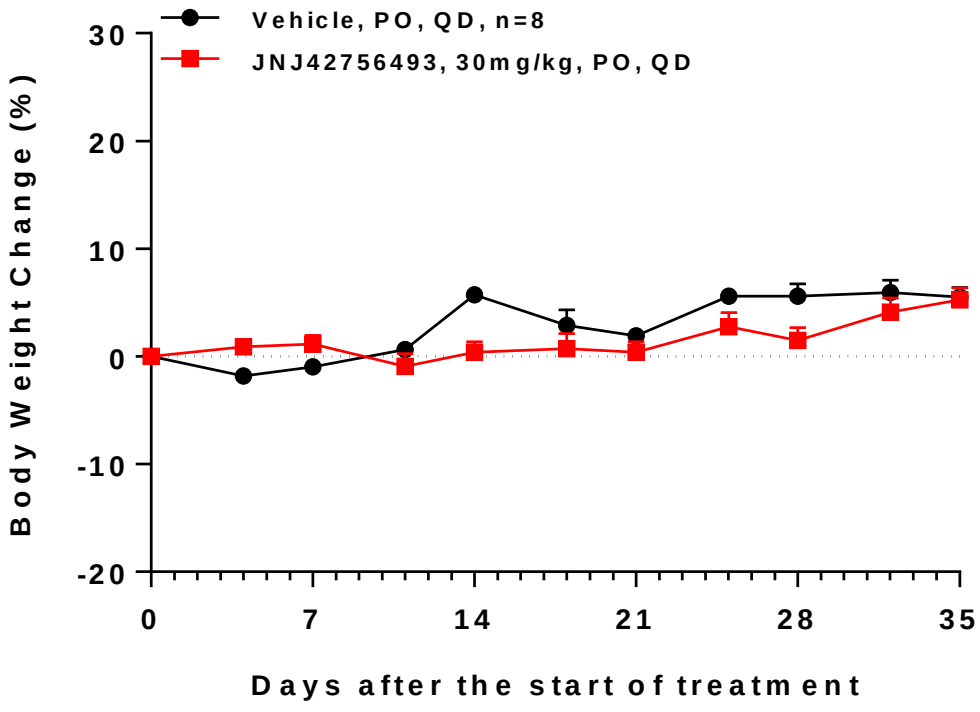
TAS-120 in SNU-16 xenograft model



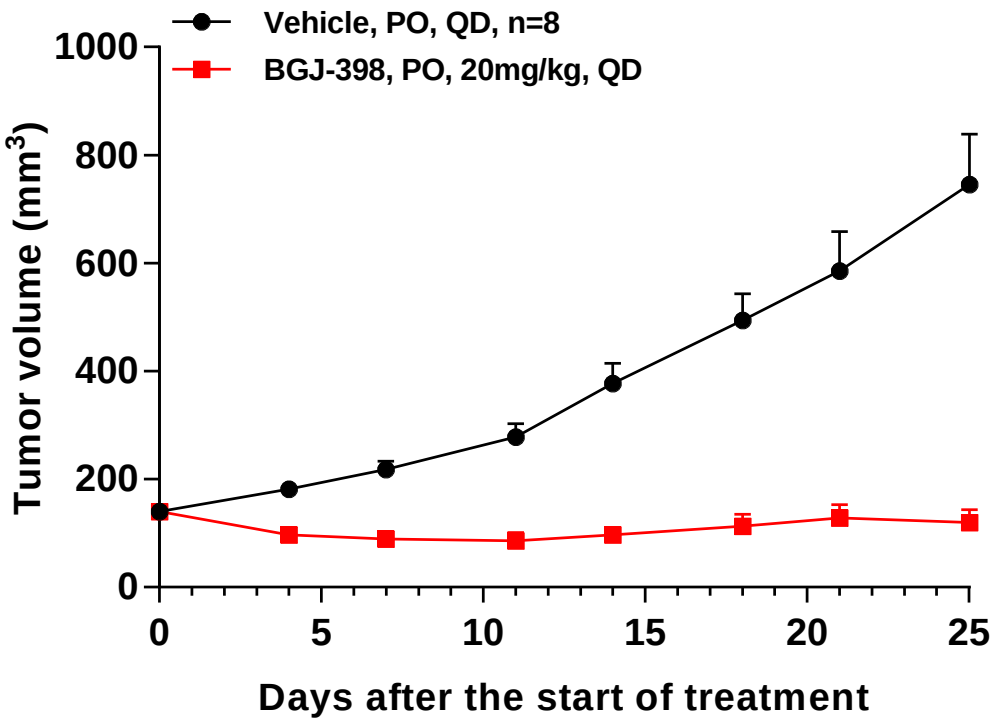


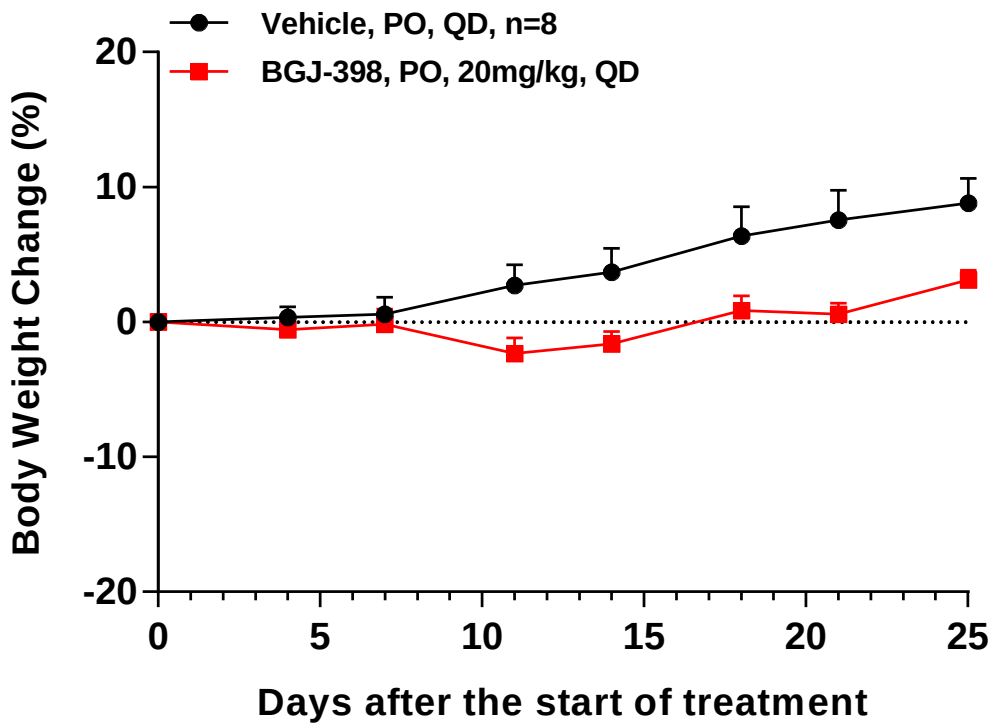
JNJ43756493 in SNU-16 xenograft model



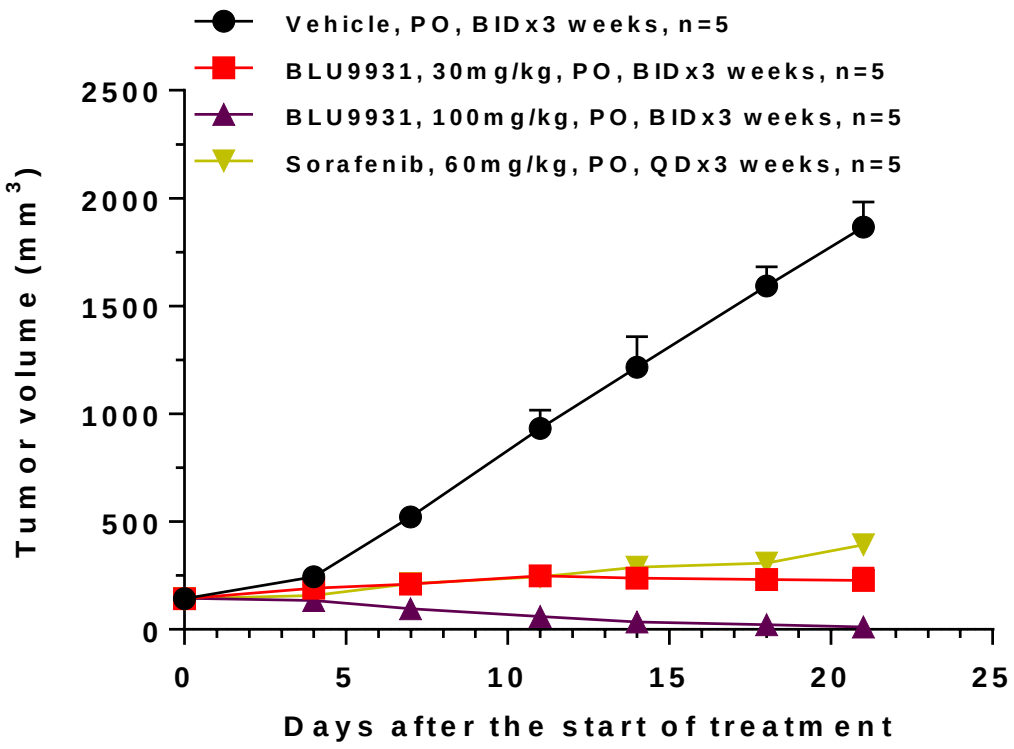


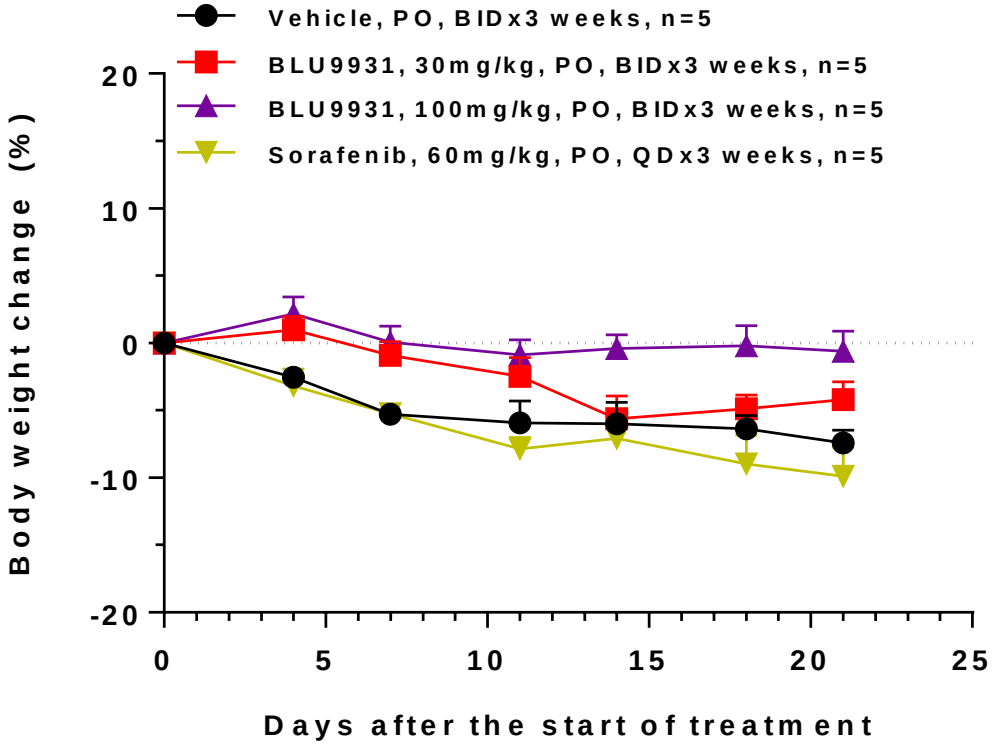
BGJ-398 in SNU-16 xenograft model



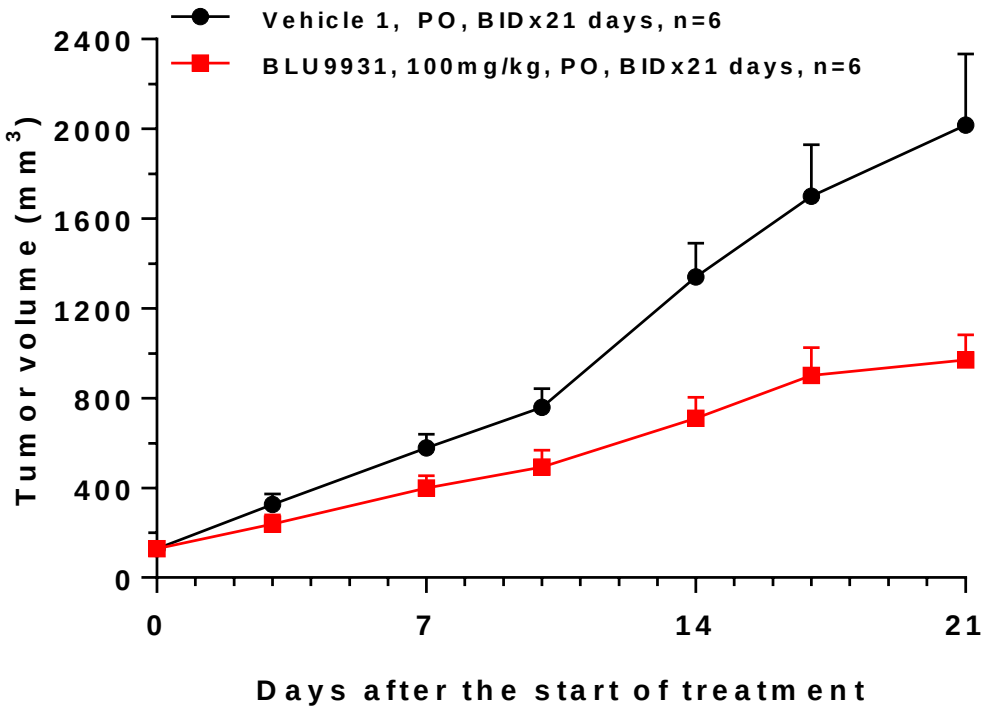


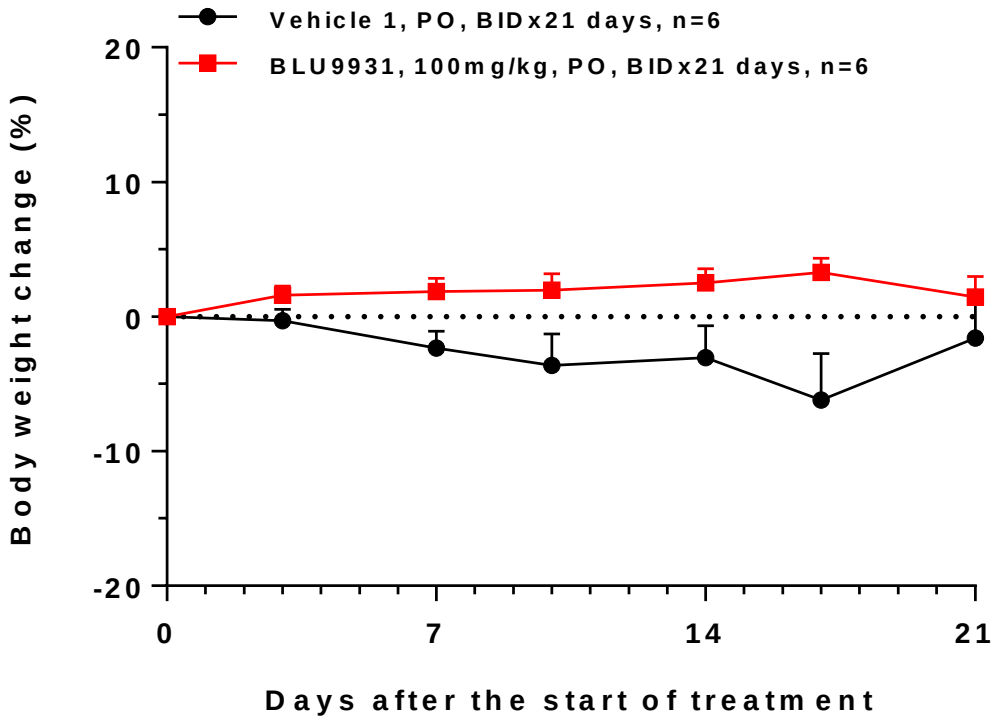
BLU9931 in Hep 3B xenograft model



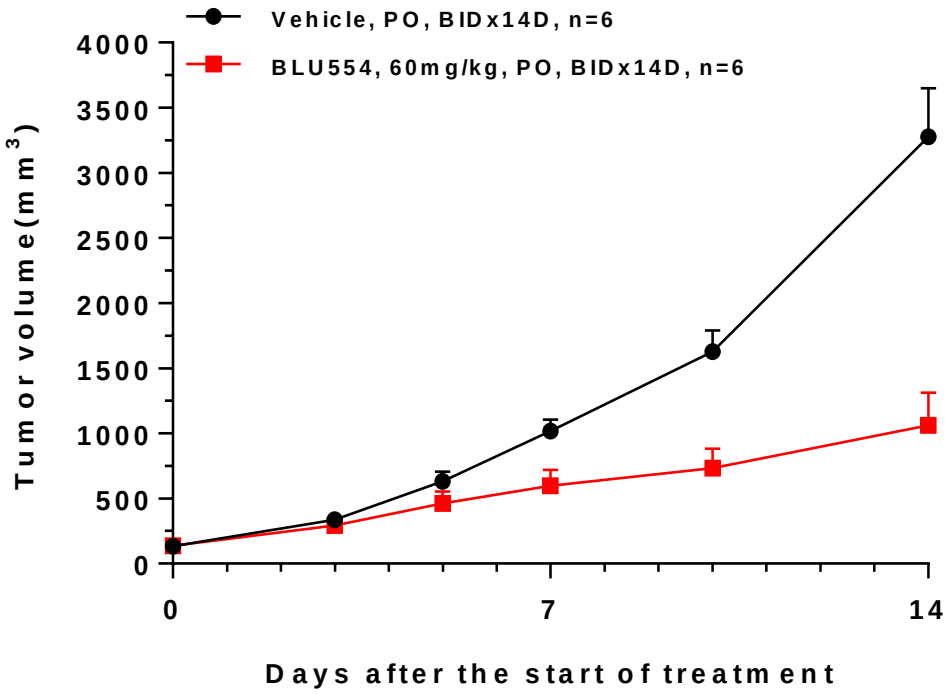


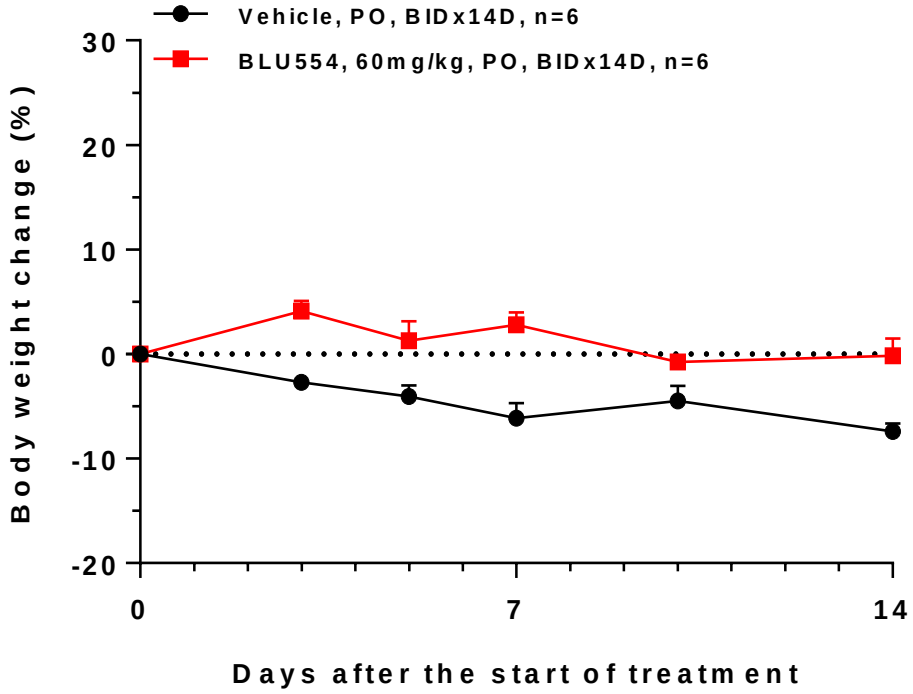
BLU9931 in Huh-7 xenograft model





BLU554 in JHH-7 xenograft model





FGFR-overexpressing PDX and PDC models

Model ID	Cancer type	Growth curve	FGFR overexpression	CNV (SNP6.0)	RNAseq (FPKM)
LU-01-0016_PDC	NSCLC	Yes	FGFR1	4.3	154.9
LU-01-0016	NSCLC	Yes	FGFR1	4.1	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	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	110.6
LI-03-0159	HCC	Yes	FGFR4	1.0	140.3
LI-03-0185	HCC	Yes	FGFR4	1.5	115.0
LI-03-0220	Liver cancer	Yes	FGFR4	2.1	114.9
LI-03-0842	HCC	Yes	FGFR3 FGFR4	3.3 2.3	219.1 211.3

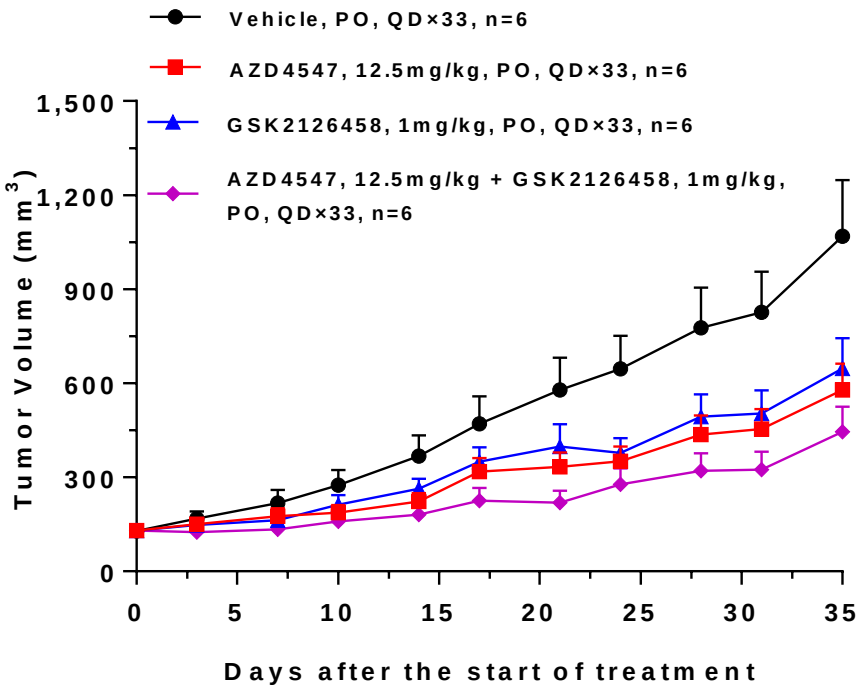
Note: FPKM > 100 was considered as overexpression.

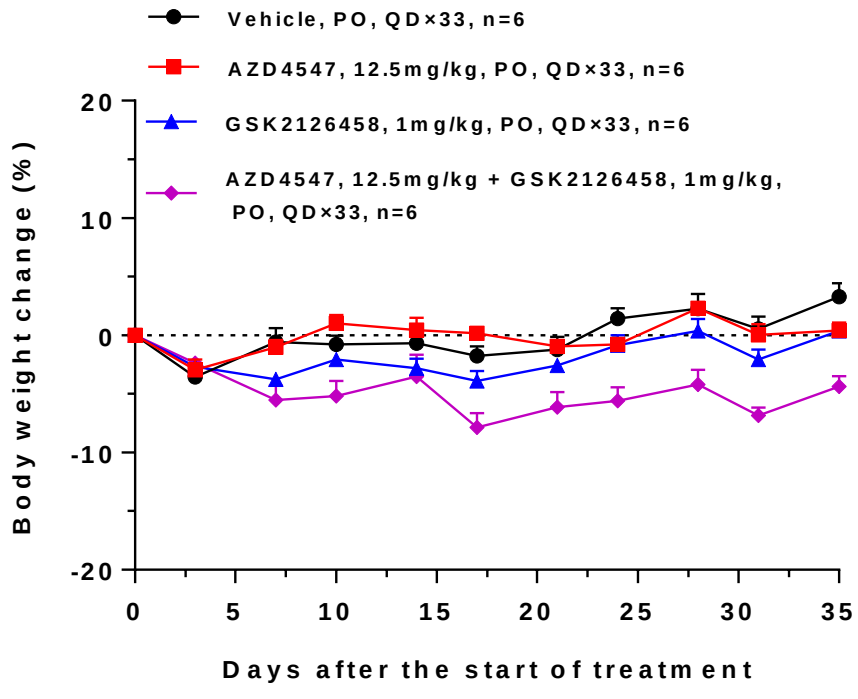
FGFR fusion/mutation PDX models

Model ID	Cancer type	Growth curve	FGFR alteration
LU-01-0010	NSCLC	Yes	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	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 inhibitor in LU-01-0010

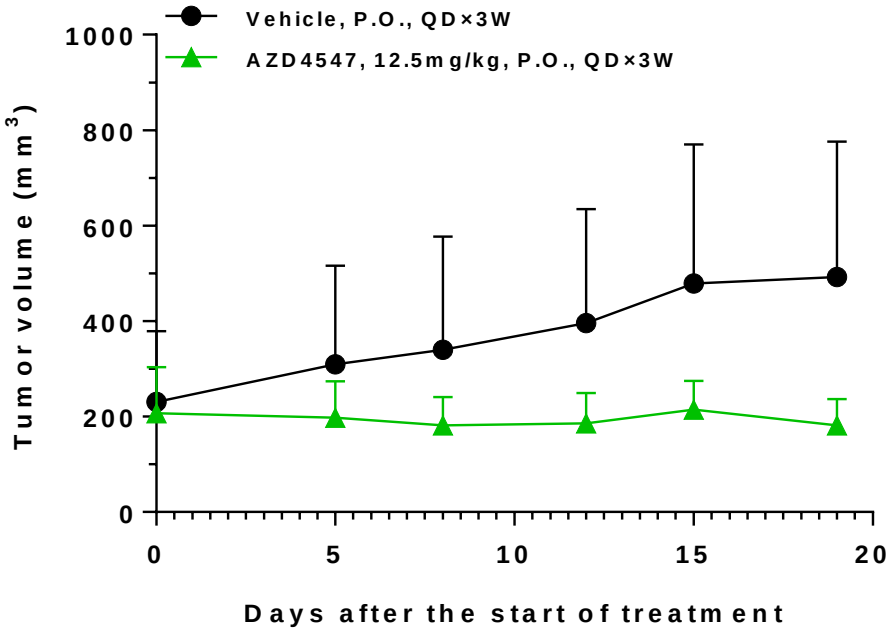
Model ID	Cancer type	Gender	Age	Tumor Grade	Tumor Stage	Model Genetics
LU-01-0010	NSCLC	Male	38	G3	T2N0M0	COL25A1-exon3->FGFR2-exon3 PIK3CA E545K mutation

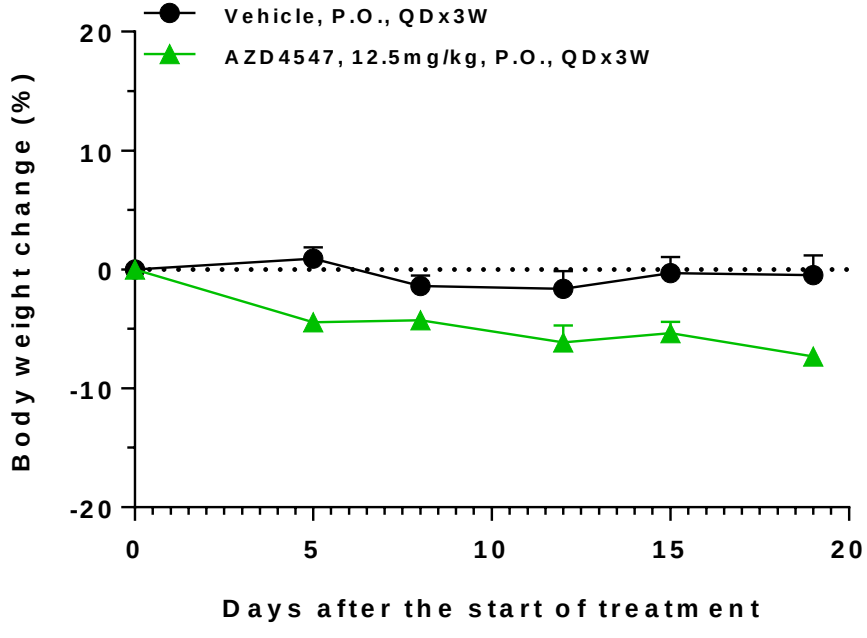




FGFR inhibitor in LU-01-0048

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





OUR COMMITMENT

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