

VEGF-VEGFR Related *in vivo* Models



WuXi AppTec Research Service Division, Oncology & Immunology Unit



2020.08

OncoWuXi Newsletter

■ VEGF-VEGFR background as drug targets

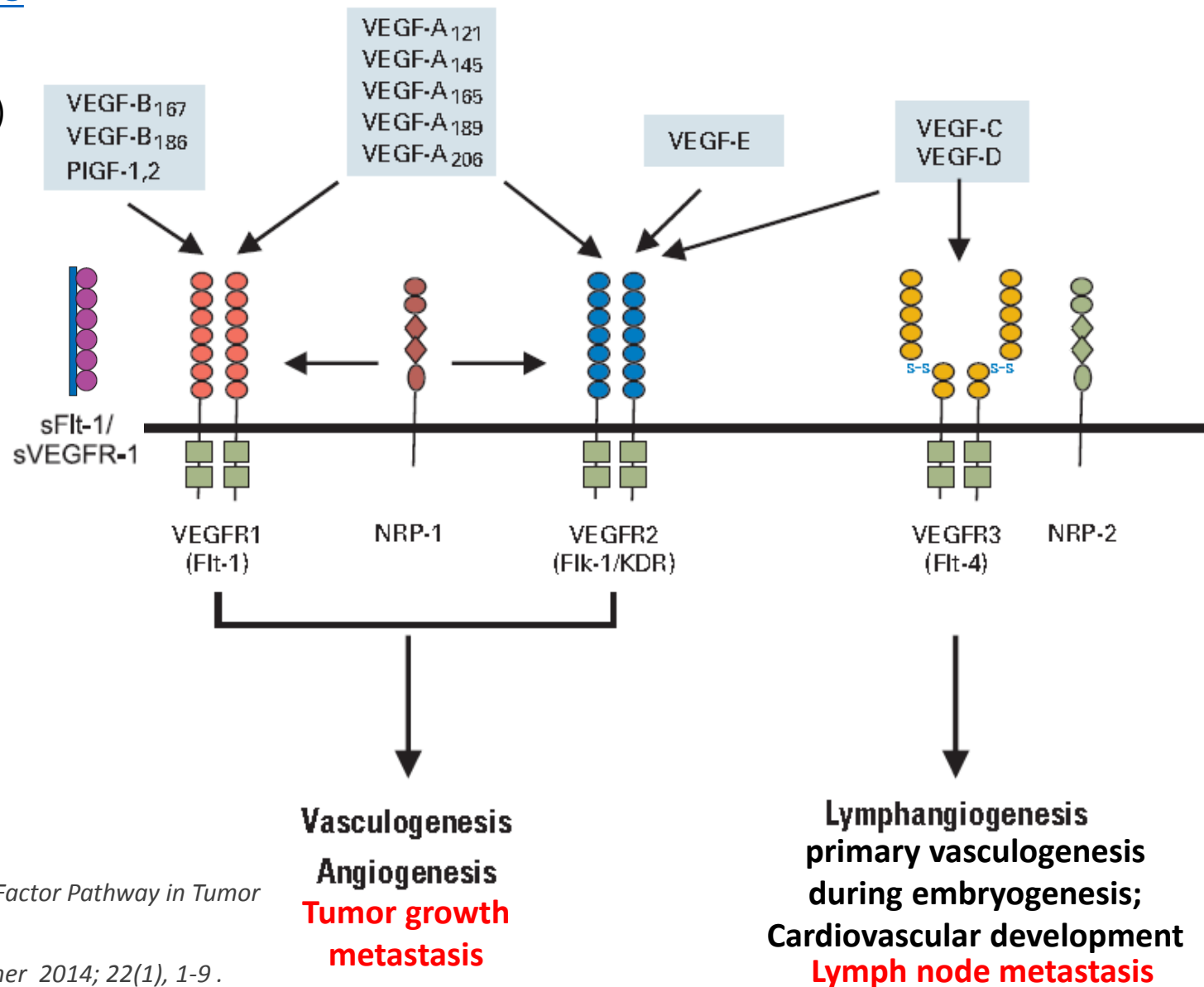
- [VEGF-VEGFR biology](#)
- [VEGF-VEGFR Inhibitors](#)

■ VEGF-VEGFR inhibitors in tumor models

- [SOC data in CDX models](#)
- [SOC data in PDX models](#)

VEGF Family and Its Receptors

- Vascular endothelial growth factor (VEGF) is an important signaling protein involved in both vasculogenesis (the formation of the circulatory system) and angiogenesis (the growth of blood vessels from pre-existing vasculature).
- VEGF receptors are receptors for VEGF. There are three main subtypes of VEGFR, numbered 1, 2 and 3. Also, they may be membrane-bound (mbVEGFR) or soluble (sVEGFR), depending on alternative splicing.

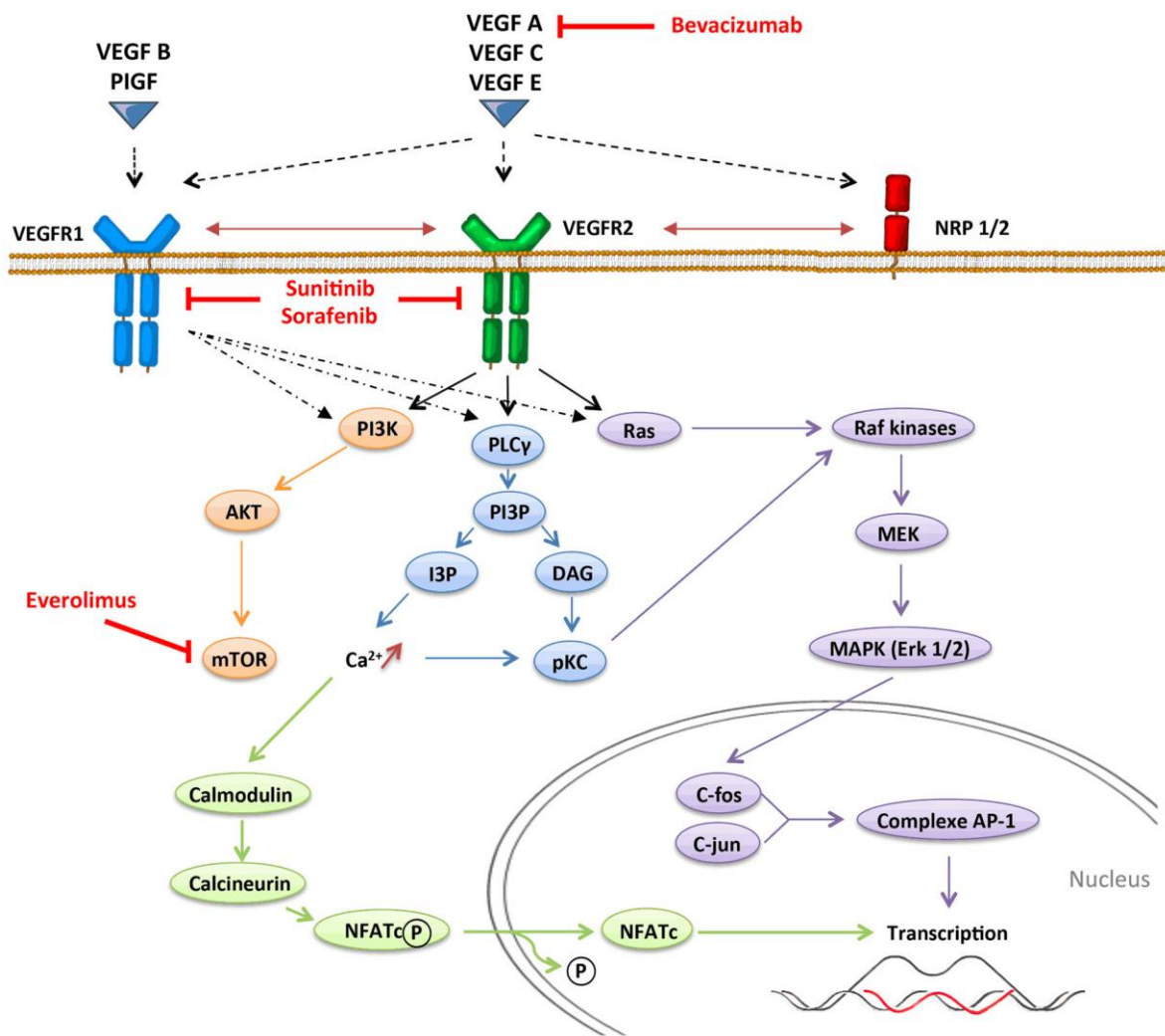


Daniel J. Hicklin et al. Role of the Vascular Endothelial Growth Factor Pathway in Tumor Growth and Angiogenesis. *J Clin Oncol* 2005; 23:1011-1027.

Shibuya. VEGF-VEGFR Signals in Health and Disease. *Biomol Ther* 2014; 22(1), 1-9.

VEGF-VEGFR Pathway Biology

- Activation of the VEGF-receptor pathway triggers a network of signaling processes that promote endothelial cell growth, migration, and survival from pre-existing vasculature.
- VEGF mediates vessel permeability, and has been associated with malignant effusions.
- The well-established role of VEGF in promoting tumor angiogenesis and the pathogenesis of human cancers has led to the rational design and development of agents that selectively target this pathway.

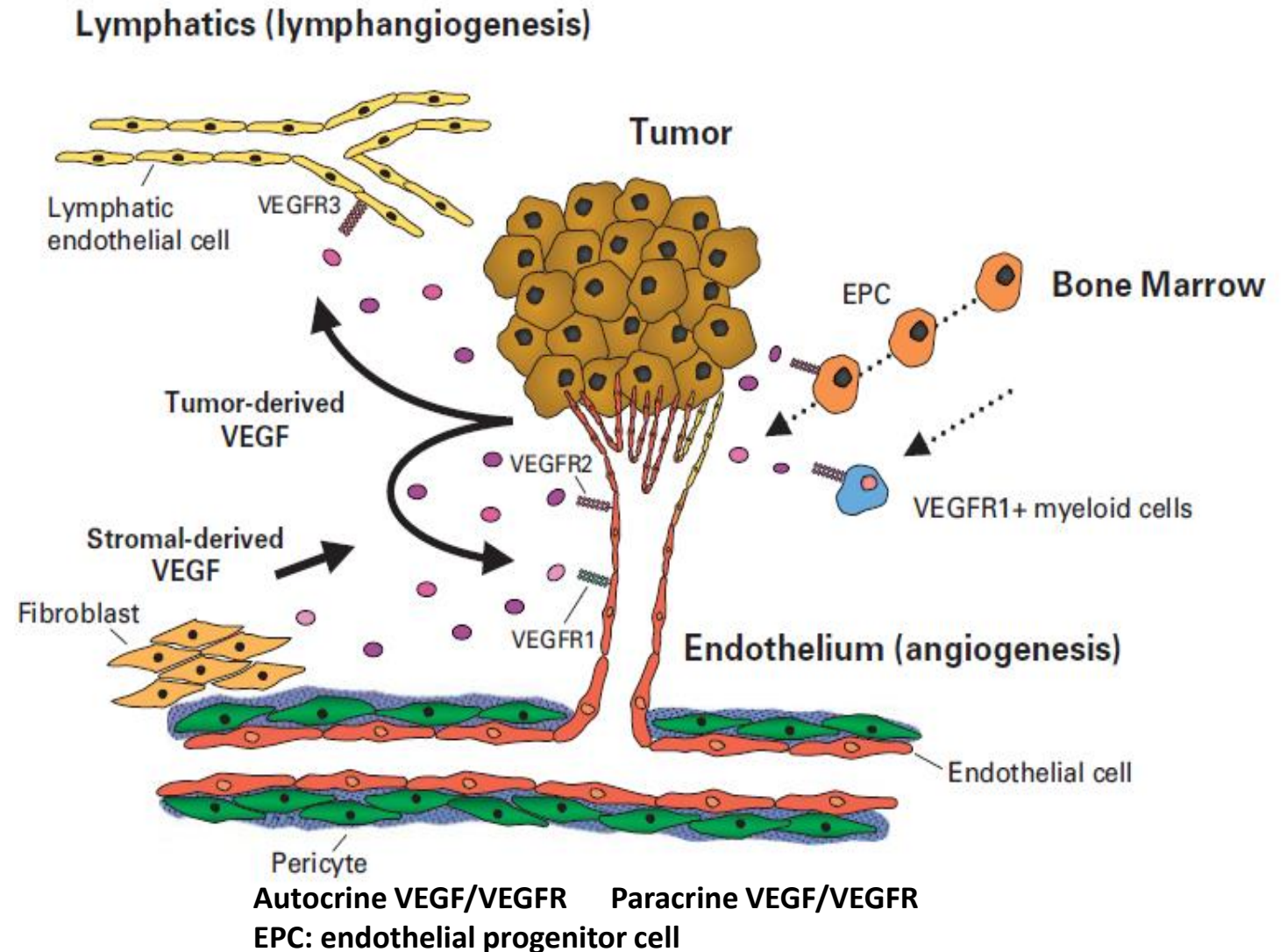


Thibault Voron et al. Control of the immune response by pro-angiogenic factors. *Frontiers in Oncology* 2014; 4: 1-9

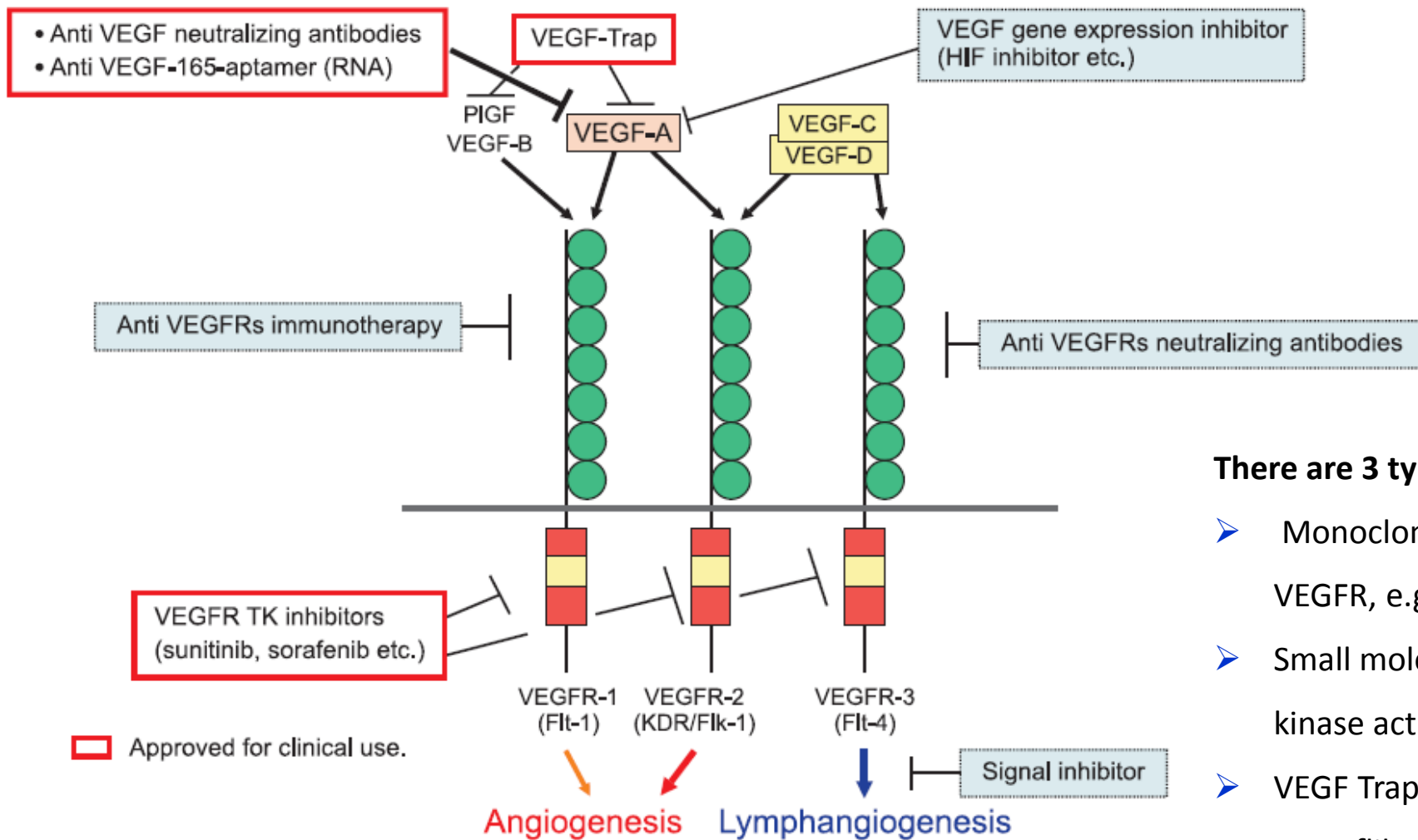
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VEGF-VEGFR Role in Tumor Angiogenesis

- VEGF stimulation of VEGFR-1 and VEGFR-2 on endothelial cells induces endothelial cell proliferation, migration, and survival, as well as vascular permeability—all effects that lead to tumor angiogenesis.
- VEGF may also recruit endothelial progenitor cells and VEGFR-1–expressing myeloid cells to sites of tumor neovascularization.
- Finally, VEGF-C and VEGF-D interact with VEGFR-3 on the surface of lymphatic endothelial cells, leading to lymph angiogenesis.



VEGF-VEGFR as Therapeutic Targets



There are 3 types of VEGF/VEGFR inhibitors:

- Monoclonal antibodies against VEGF and VEGFR, e.g. Bevacizumab
- Small molecule inhibitors of VEGF tyrosine kinase activity, e.g. Sorafenib
- VEGF Trap, e.g. VEGFR1-R2 fusion peptide, e.g. Aflibercept

Shibuya. VEGF-VEGFR Signals in Health and Disease. *Biomol Ther* 2014; 22(1), 1-9.

VEGF-VEGFR Inhibitors (1)

Drug	Inventors	Target/mechanism	Indication	Status
Bevacizumab (Avastin®)	Genentech	Anti-VEGF mAb	Breast, colorectal, bladder cancer etc.	FDA-approved
Ranibizumab (Lucentis®)	Genentech	Anti-VEGF (VEGFR-2)	AMD HCC, Melanoma, NSCLC, RCC	FDA-approved Phase III
Thalidomide (Thalomid®)	Celgene	Anti-angiogenic and oxidative stress-inducing effects	Multiple myeloma	FDA-approved
Lenalidomide (Revlimid®)	Celgene	Analogue of thalidomide-complex actions	Myelodysplastic syndromes multiple myeloma	FDA-approved
Sorafenib (Nexavar®)	Bayer	VEGFR and PDGFR inhibitor	HCC and RCC	FDA-approved
Sunitinib (Sutent®)	CPPI CV	VEGFR and PDGFR inhibitor-multikinase	RCC and GI cancer	FDA-approved
Pazopanib (Votrient®)	Novartis	Multi-targeted RTK inhibitor	RCC, advanced soft tissue sarcomas	FDA-approved
Regorafenib (Stivarga®)	Bayer	VEGFR inhibitor-multikinase	Metastatic colorectal cancer	FDA-approved
Ramucirumab (Cyramza®)	Eli Lilly	VEGFR2 inhibitor	Gastric cancer	FDA-approved

VEGF-VEGFR Inhibitors (2)

Drug	Inventors	Target/mechanism	Indication	Status
Lenvatinib (Lenvima®)	Eisai	VEGFR inhibitor	Thyroid cancer	FDA-approved
Aflibercept (Eylea®)	Regeneron	VEGF trap	AMD Colorectal cancer	FDA-approved Phase III
Axitinib (Inlyta®)	Pfizer	VEGFR/PDGFR/KIT inhibitor	RCC	FDA-approved
Nintedanib (OFEV®, Vargatef®)	Boehringer Ingelheim	VEGFR/PDGFR/FGFR inhibitor	Idiopathic Pulmonary Fibrosis Colorectal Cancer Adeno NSCLC	FDA-approved Phase III EU-approved
Vandetanib (Caprelsa®, ZACTIMA®)	AstraZeneca	VEGFR/EGFR/RET inhibitor	Medullar Thyroid Cancer (MTC) NSCLC	FDA-approved Phase III
Cabozantinib (XL184)	Exelixis	VEGFR2/MET/RET inhibitor	Medullar Thyroid Cancer (MTC)	FDA-approved
Foretinib (GSK1363089)	GSK	MET/VEGFR2 inhibitor	NSCLC	Phase II
ENMD-2076	CASI	VEGFR, Flt-3 and FGFR3 inhibitor	HCC, OC, TNBC	Phase II
Apatinib (Aitan®, Rivoceranib)	LSK	VEGFR2 inhibitor	Gastric cancer, Hepatocellular carcinoma Adenoid cystic carcinoma	Phase III Phase II
Anlotinib	Chia-tai Tianqing Pharmaceutic	VEGFR and multiple RTKs	Advanced NSCLC Advanced soft tissue sarcoma	CFDA-approved Phase II

Therapeutic Antibodies and Small Molecule Inhibitors in CDX Models

Cancer Type	Model ID	Drugs tested	Dosage	TGI (%)
CRC	HCT-15	Avastin 5-FU + Avastin	6 mg/kg, BIW 35 mg/kg, TIW + 6 mg/kg, BIW	61.1 69
	SW620	Avastin 5-FU + Avastin	6 mg/kg, BIW 35 mg/kg, TIW + 6 mg/kg, BIW	80 87.5
	LS174T	Avastin 5-FU + Avastin	6 mg/kg, BIW 20 mg/kg, QW + 6 mg/kg, BIW	61 62.4
	HT-29	Regorafenib	10 mg/kg, QD	87.7
Liver cancer	Huh7	Avastin	6 mg/kg, BIW	52.7
		Cisplatin + Avastin	3 mg/kg, QW + 6 mg/kg, BIW	83.9
		Sorafenib	30 mg/kg, QD	62.8
	BEL-7404	Avastin	6 mg/kg, BIW	54.9
		Cisplatin + Avastin	4 mg/kg, Q2W + 6 mg/kg, BIW	64.0
		Sorafenib	60 mg/kg, QD	78.0
	Hep-3B	Sorafenib	60 mg/kg, QD	70.0
	JHH-7	Sorafenib	30 mg/kg, QD	81.5

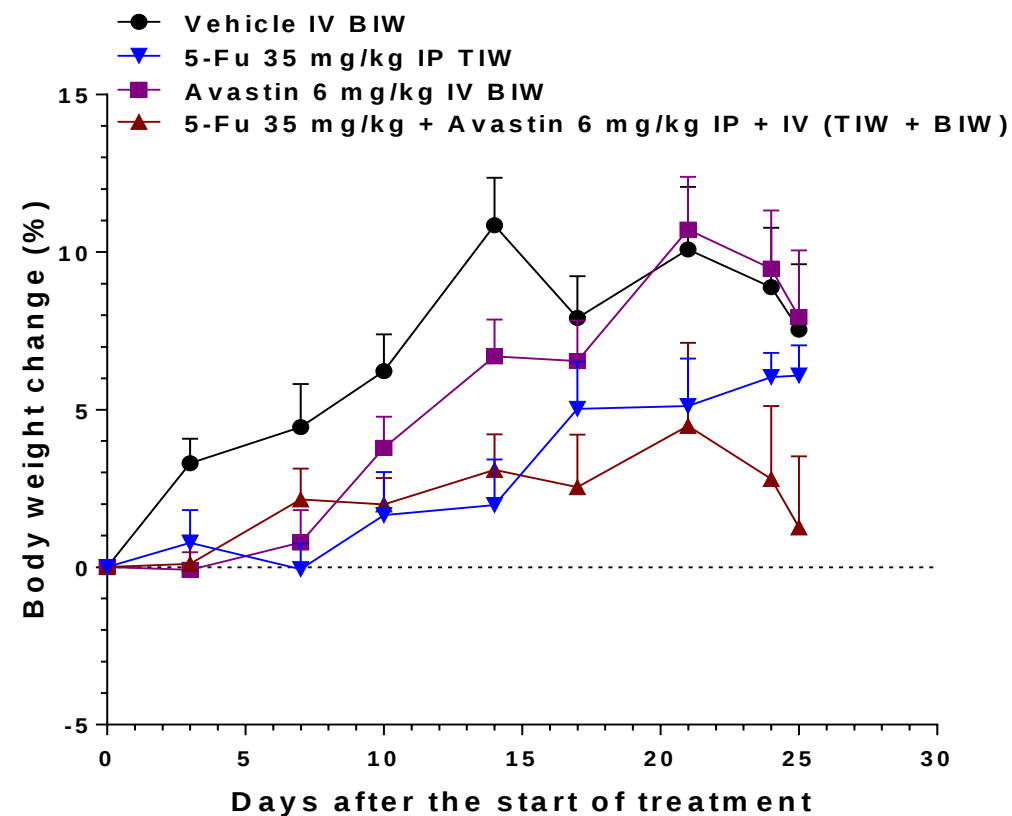
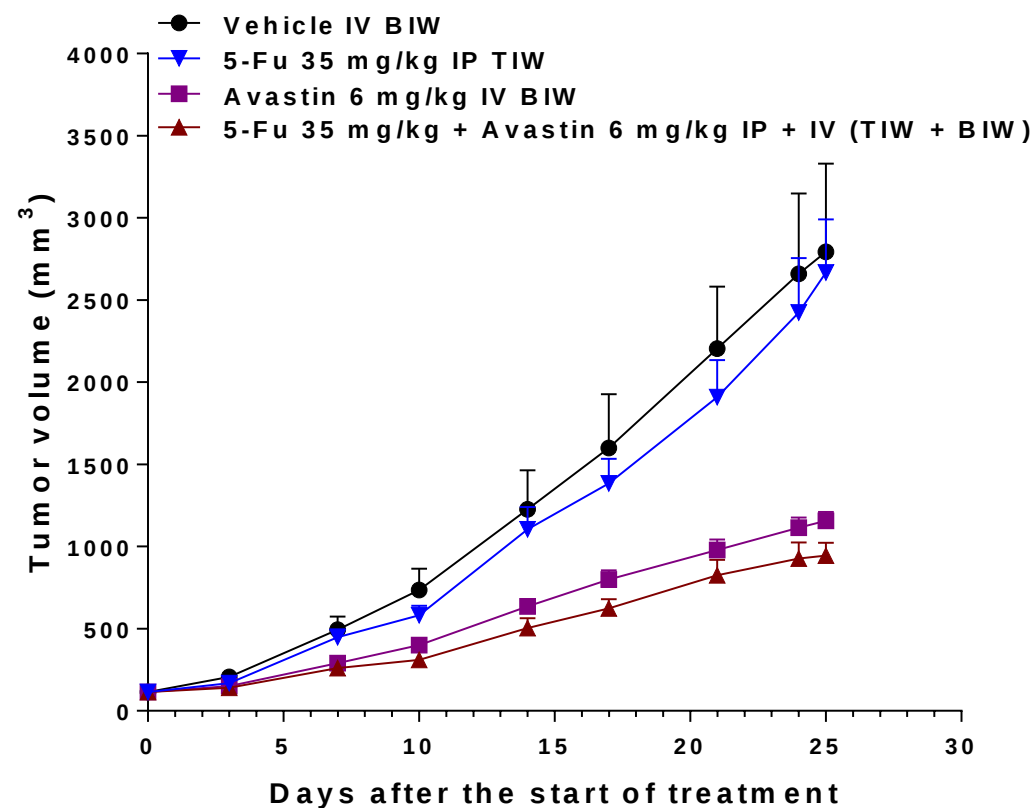
Therapeutic Antibodies and Small Molecule Inhibitors in CDX Models

Cancer Type	Model ID	Drugs tested	Dosage	TGI (%)
NSCLC	Calu-6	Nintedanib	50 mg/kg, QD 100 mg/kg, QD	83.5 93.5
	A549	Nintedanib	100 mg/kg, QD	80.6
	NCI-H520	Nintedanib Axitinib Sunitinib	100 mg/kg, QD 100 mg/kg, QD 80 mg/kg, QD	62 58 104
	PC-9	Apatinib	50 mg/kg, QD 100 mg/kg, QD	40.9 48.35
	NCI-H358	Avastin	0.5 mg/kg, TIW	72.87
Renal cancer	786-O	Sorafenib Sunitinib Malate Avastin	60 mg/kg (D0-7), 30 mg/kg (D8-16), QD 60 mg/kg, QD 6 mg/kg, BIW	76.0 88.4 47.7
	ACHN	Avastin	10 mg/kg, QW	25.9
Breast cancer	MCF-7	Avastin	10 mg/kg, QW	45.4
GBM	U87	Avastin	10 mg/kg, BIW	-
SCLC	NCI-H69	Anlotinib	1 mg/kg, QD 3 mg/kg, QD	54 99

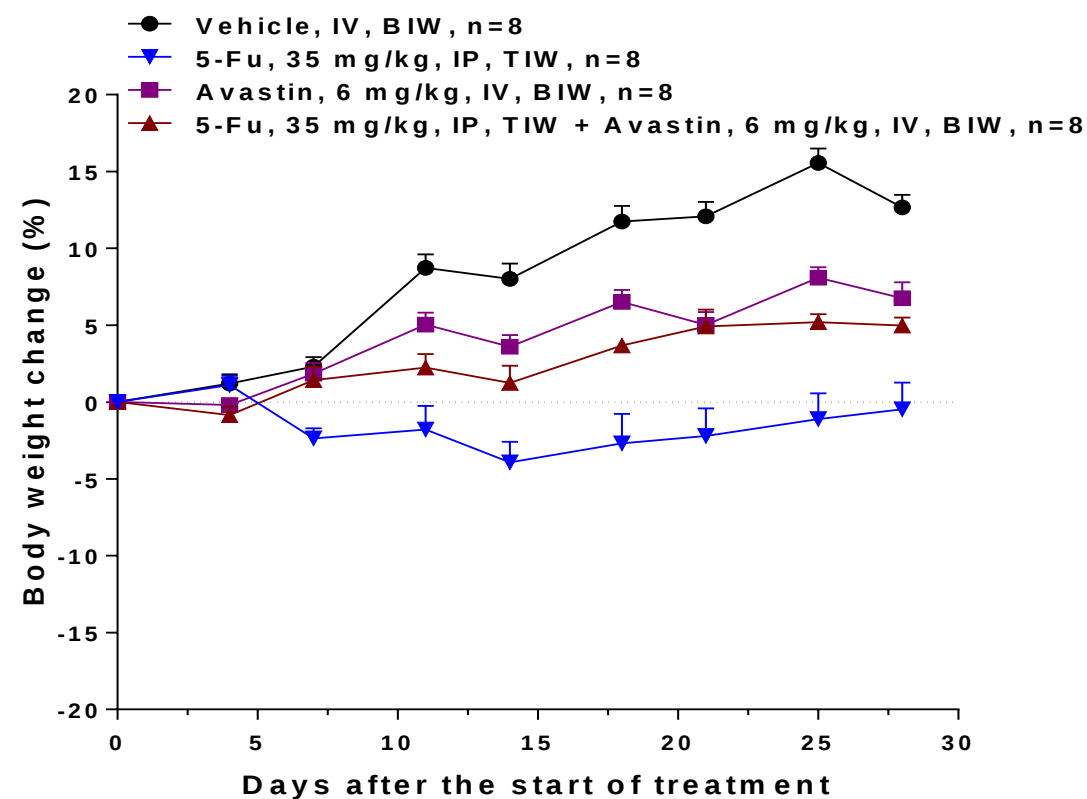
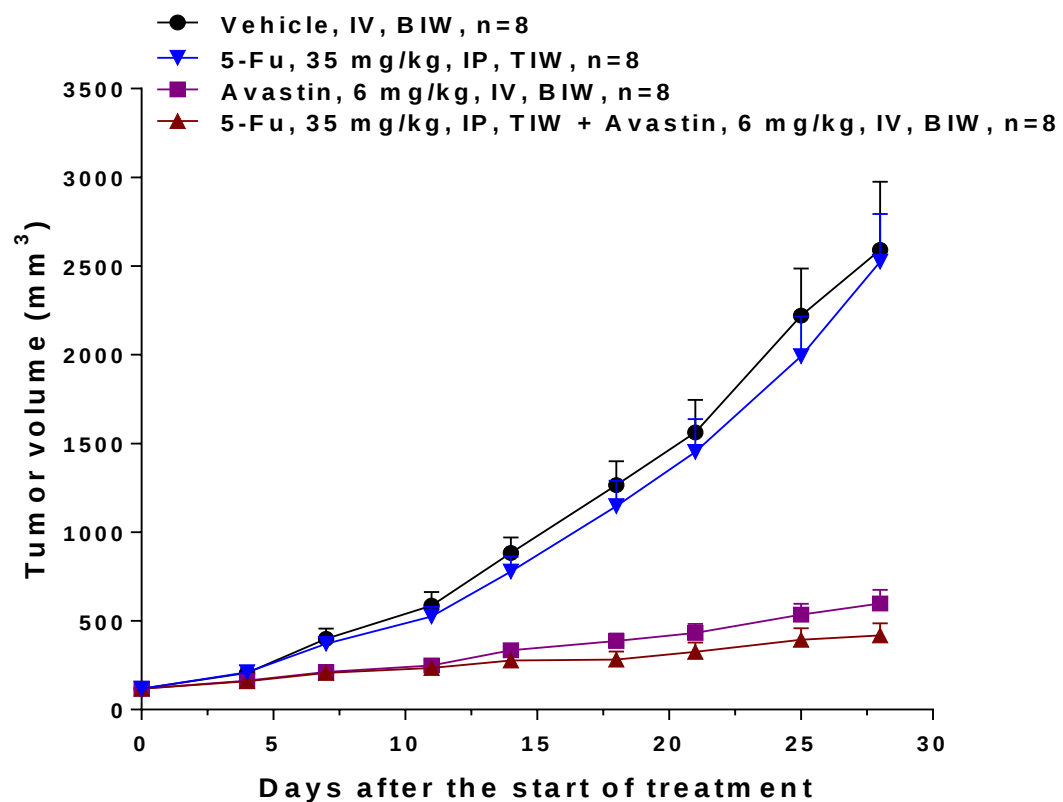
Therapeutic Antibodies and Small Molecule Inhibitors in CDX Models

Cancer Type	Model ID	Drugs tested	Dosage	TGI (%)
Gastric cancer	MKN-45	Sunitinib	20 mg/kg, QD	51.8
			40 mg/kg, QD	81.8
		Apatinib	100 mg/kg, QD	79.5
Thyroid cancer	FTC-238	Lenvatinib	30 mg/kg, QD	94.5

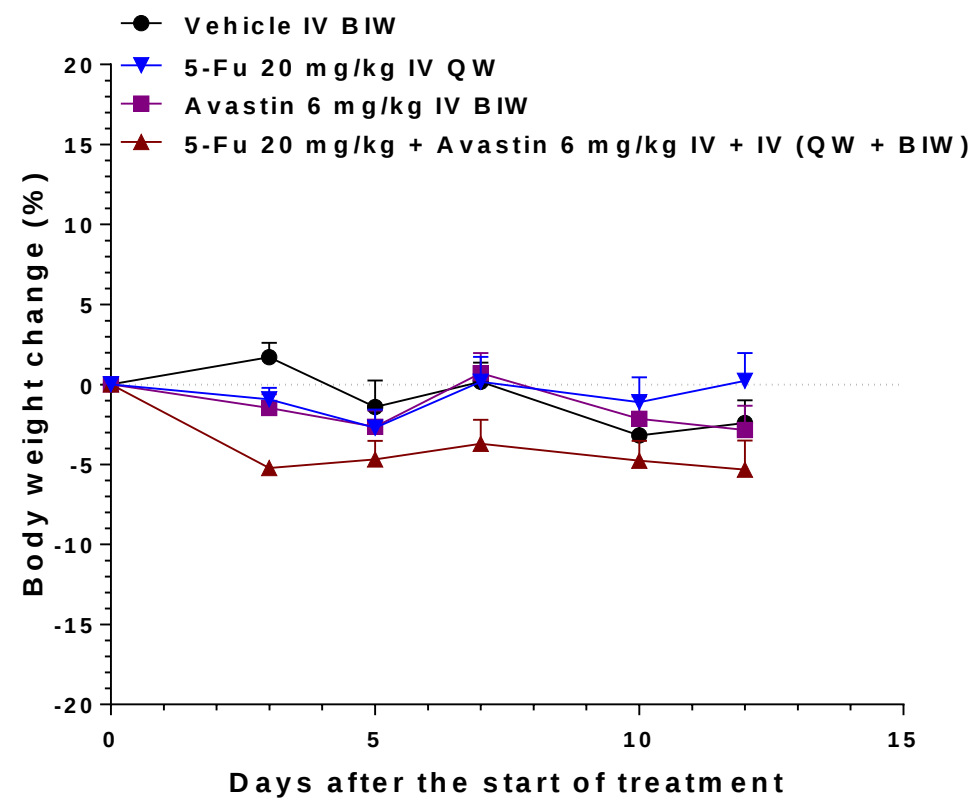
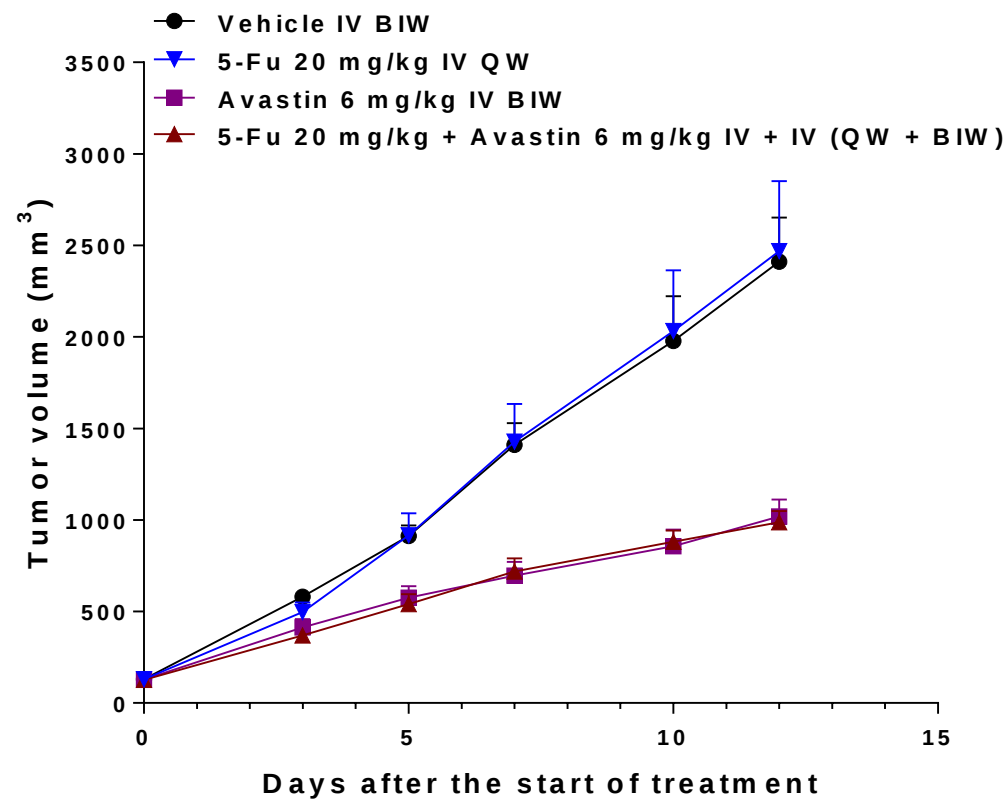
5-FU and Avastin in the HCT-15 Colorectal Cancer Model



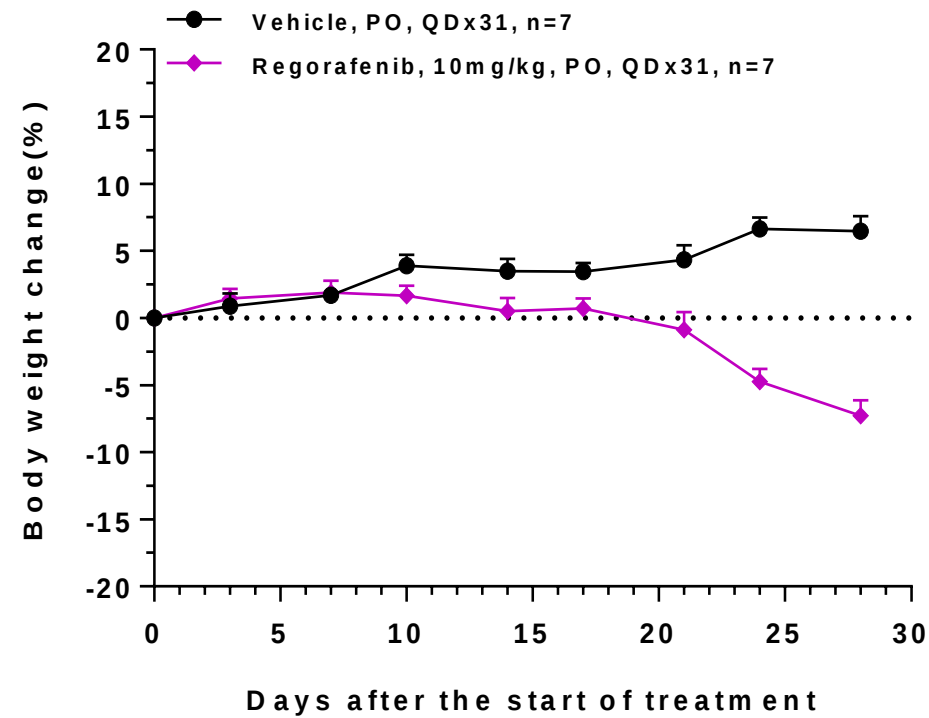
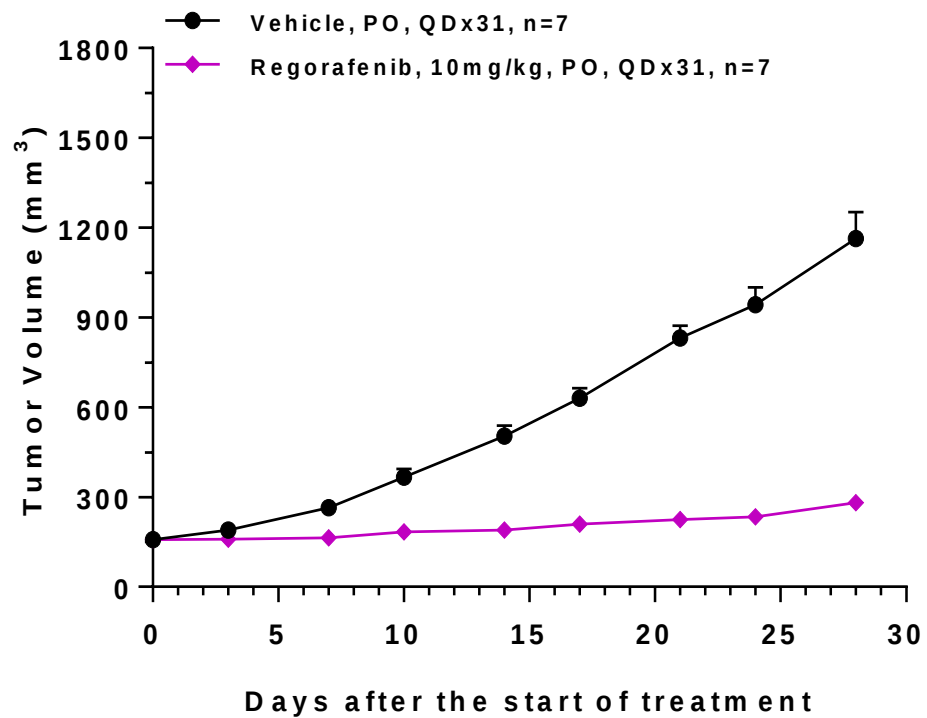
5-FU and Avastin in the SW620 Colorectal Cancer Model



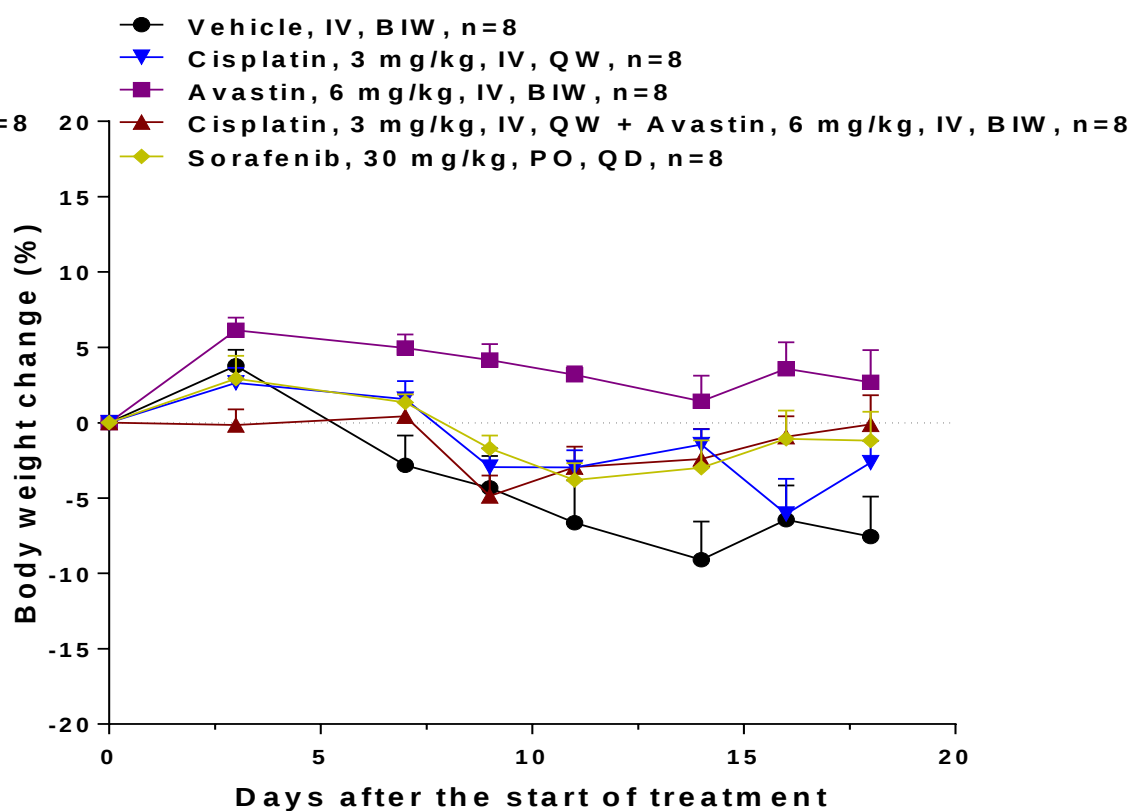
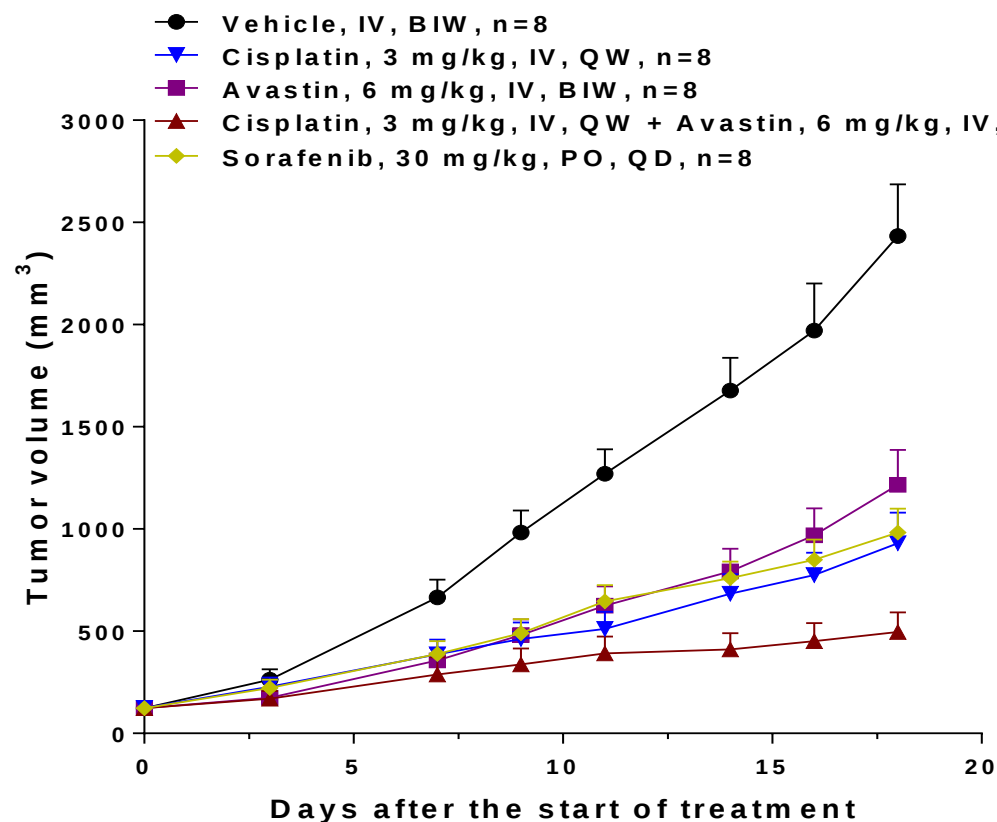
5-FU and Avastin in the LS174T Colorectal Cancer Model



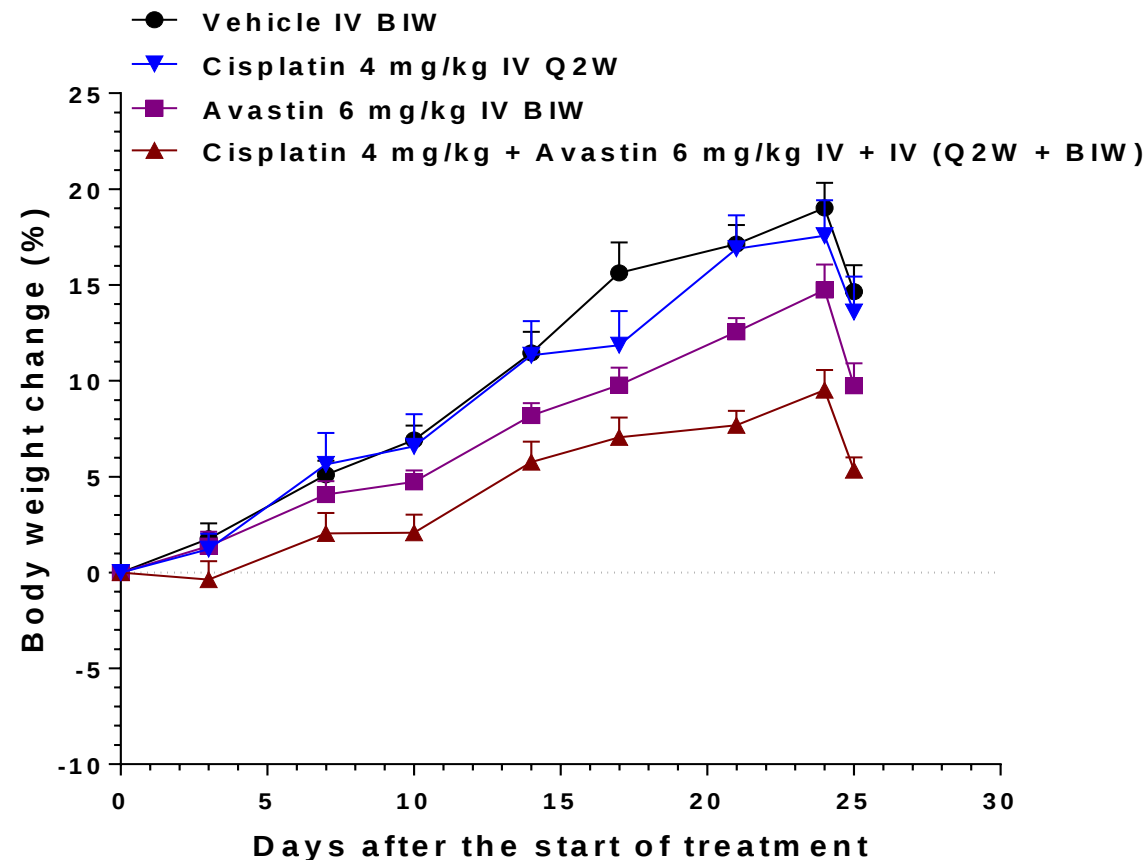
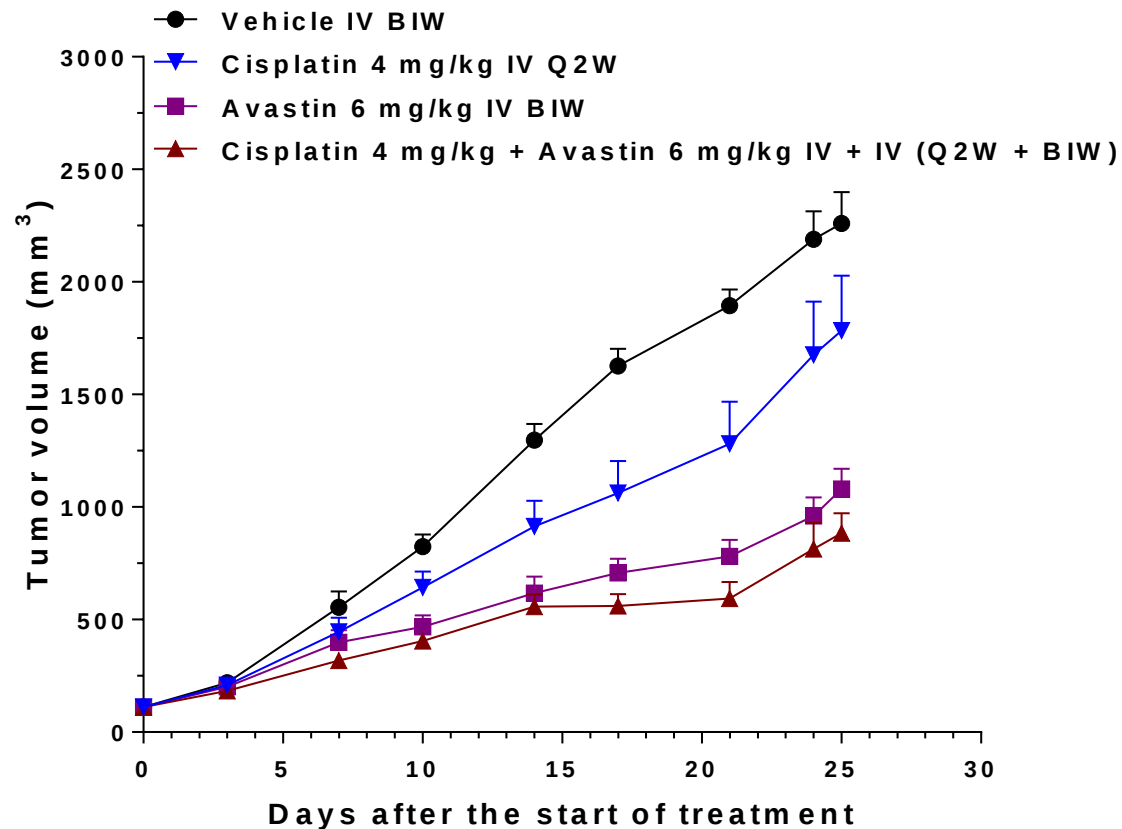
Regorafenib in the HT-29 Colorectal Cancer Model



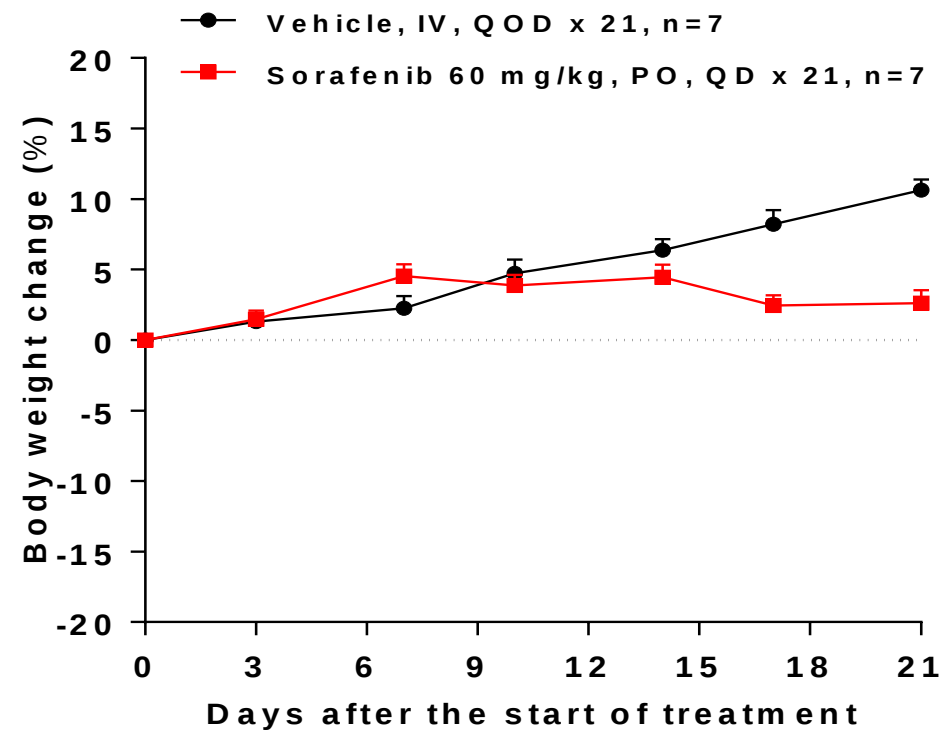
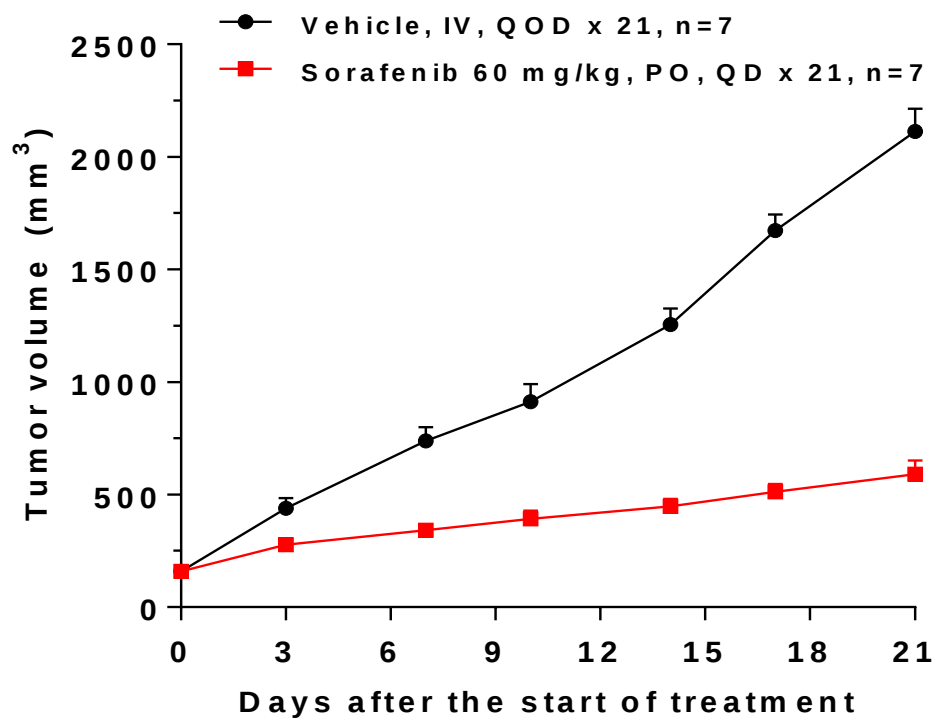
Cisplatin, Sorafenib and Avastin in the Huh7 Liver Cancer Model



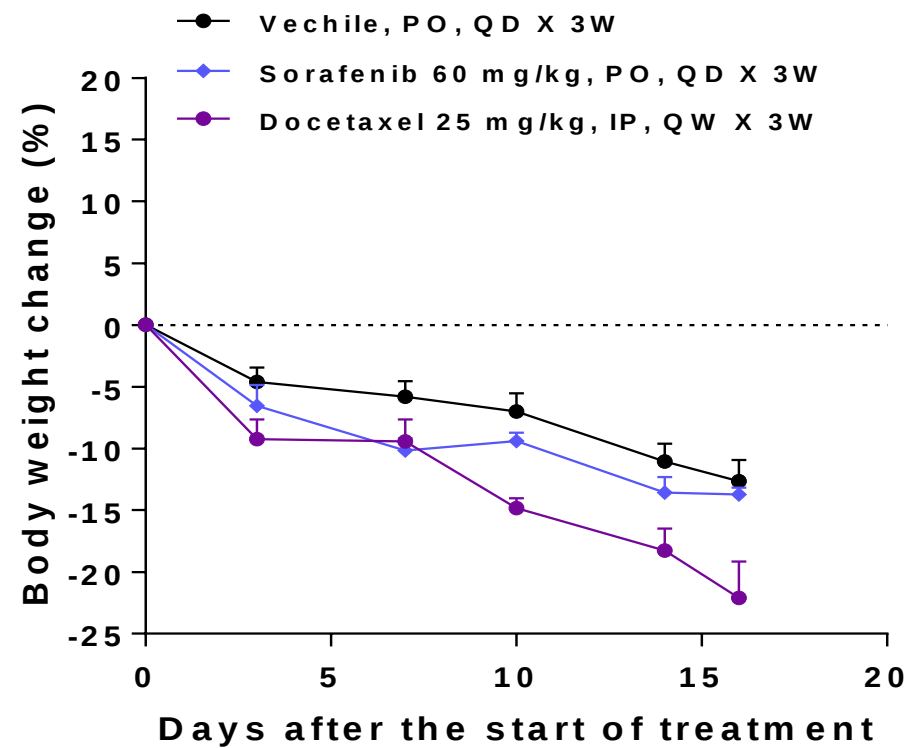
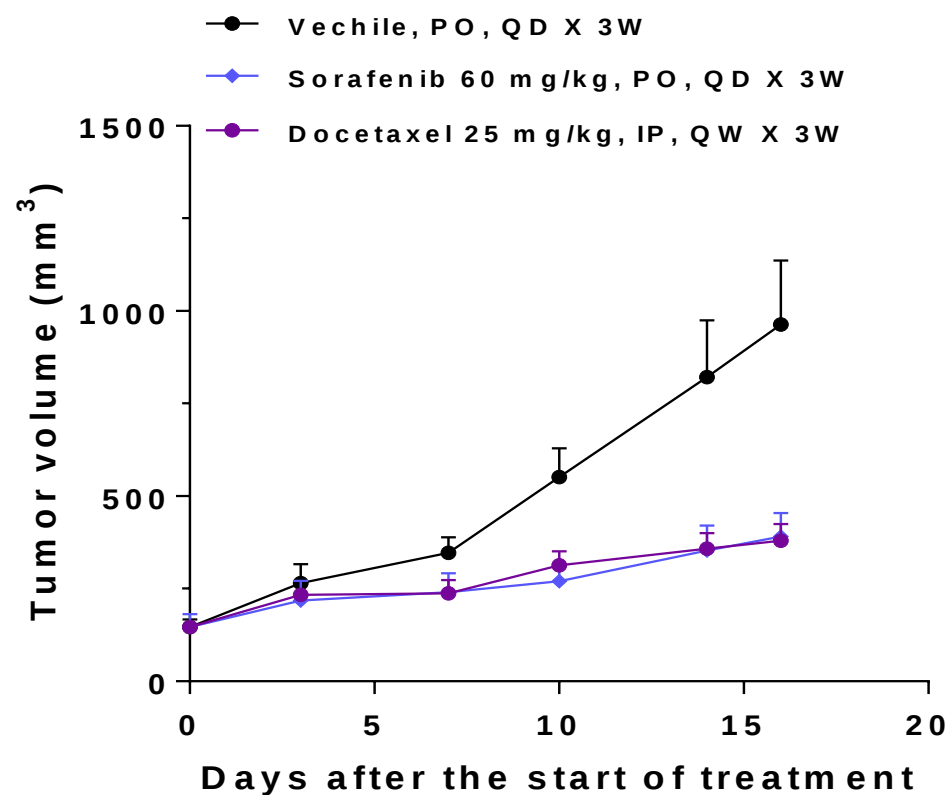
Cisplatin and Avastin in the BEL-7404 Human Liver Cancer Model



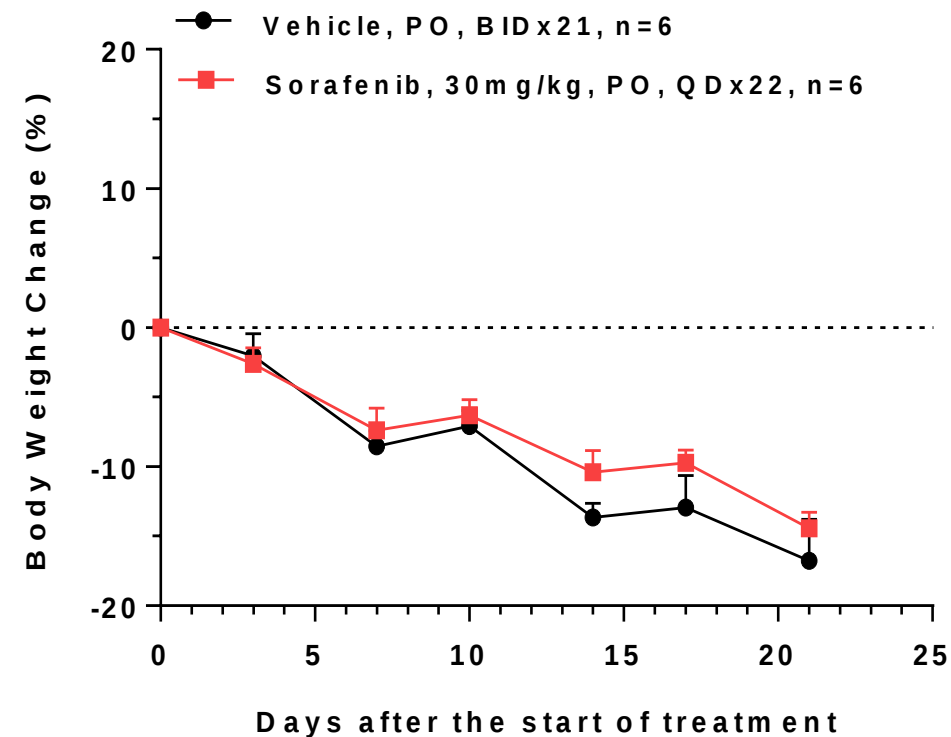
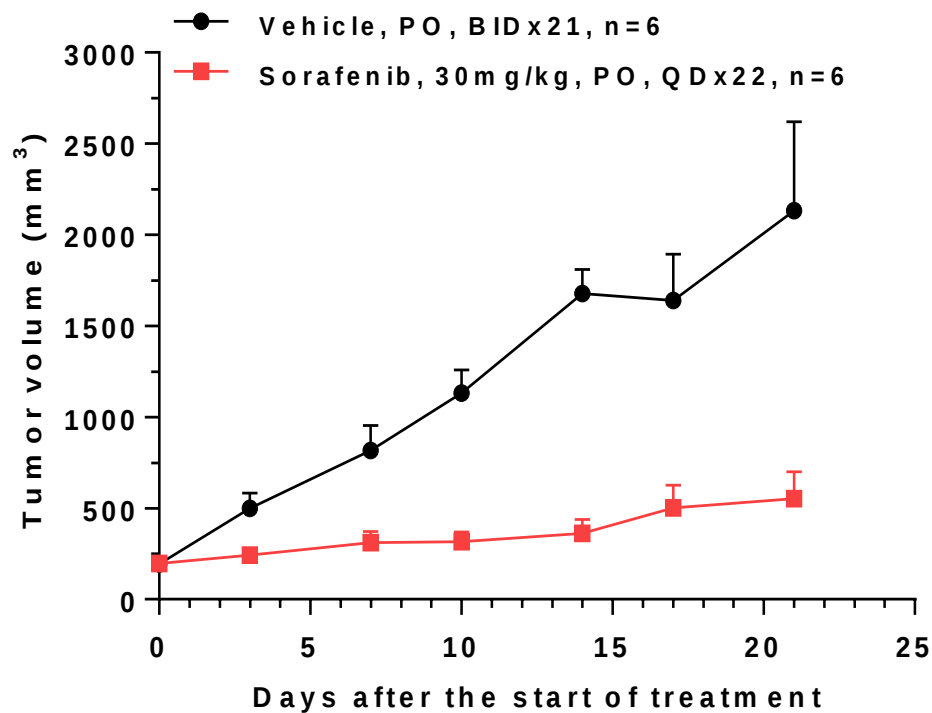
Sorafenib in the BEL-7404 Human Liver Cancer Model



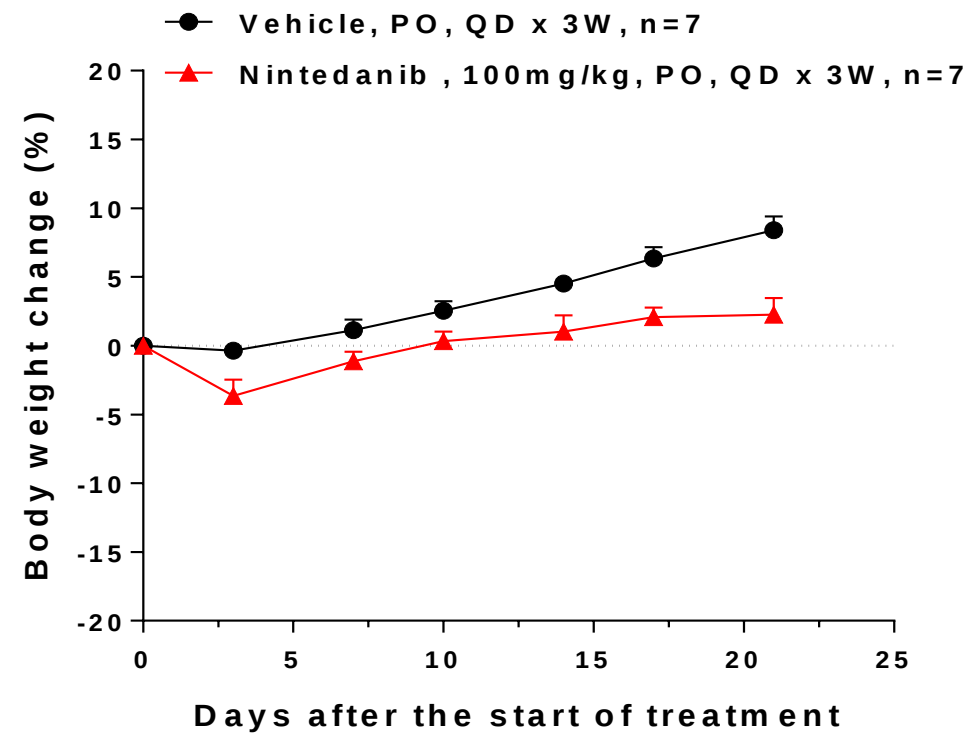
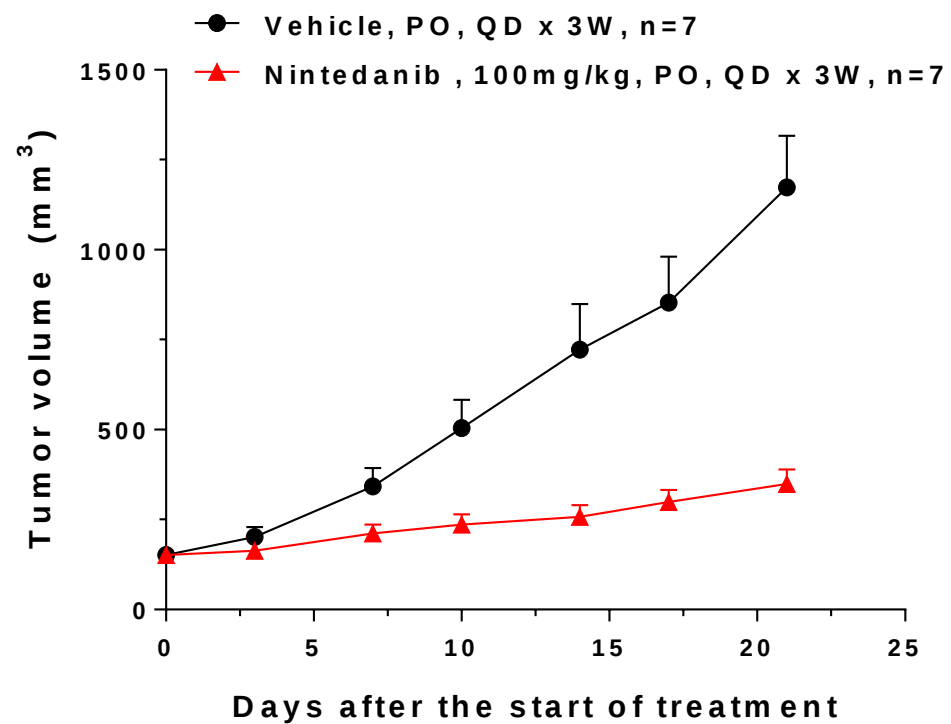
Sorafenib in the Hep3B Human Liver Cancer Model



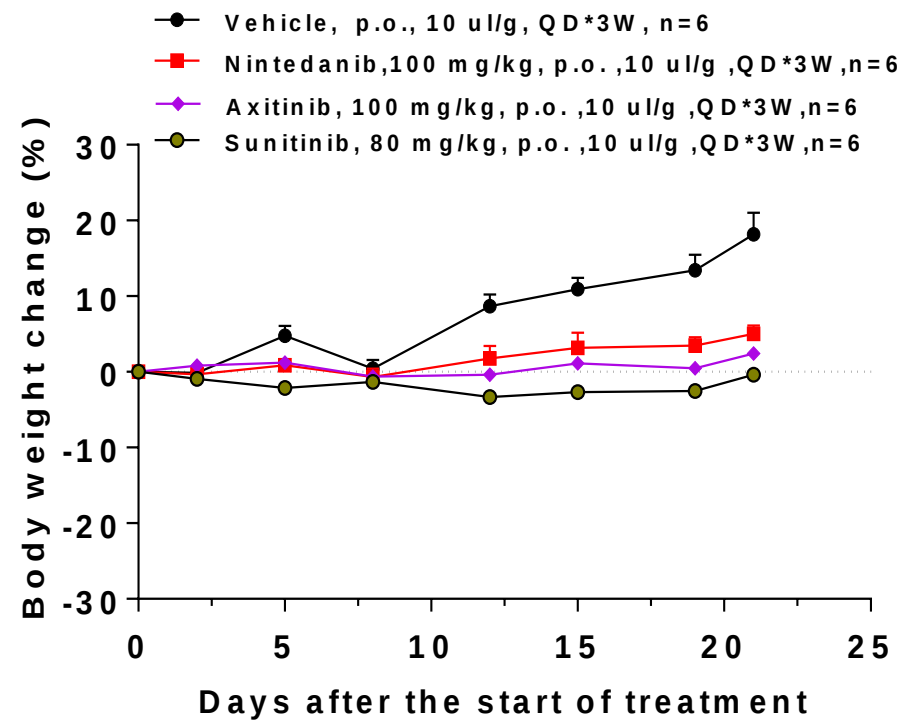
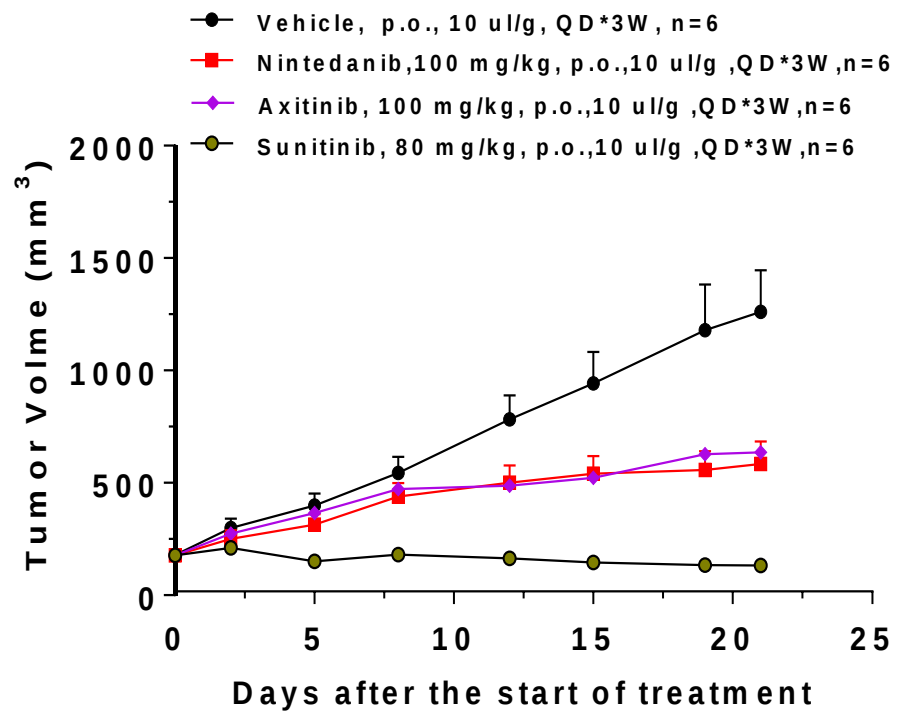
Sorafenib in the JHH-7 Human Liver Cancer Model



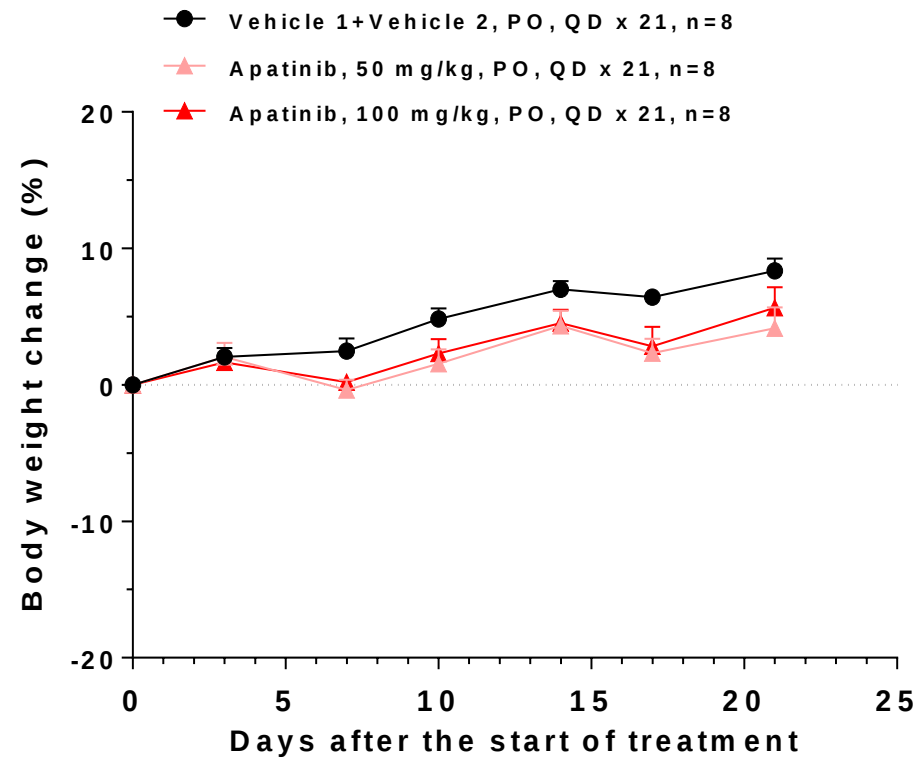
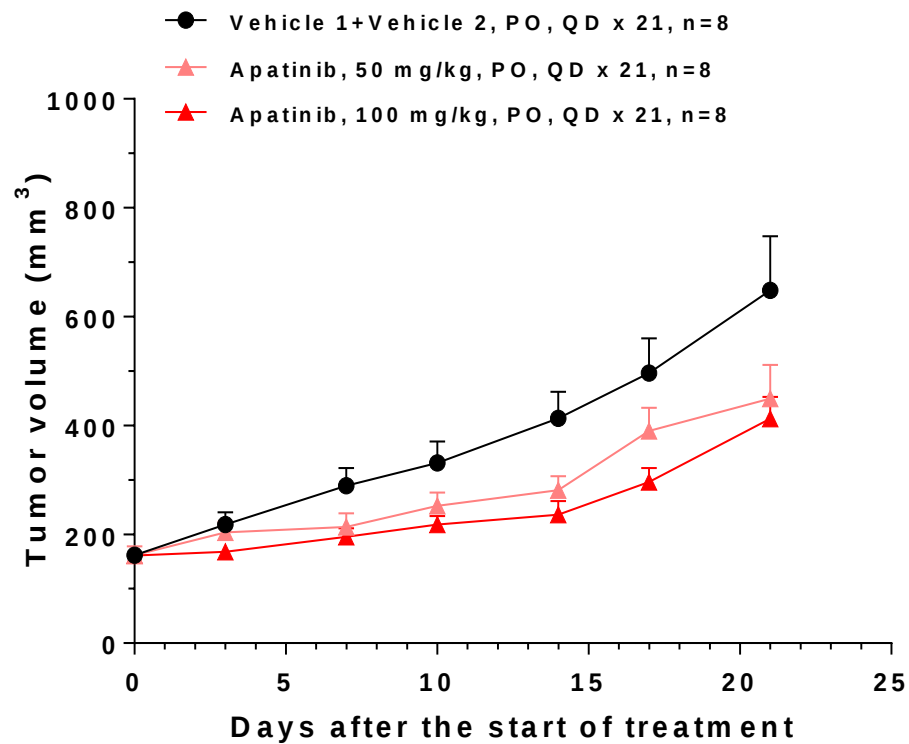
Nintedanib in the A549 NSCLC Adenocarcinoma Model



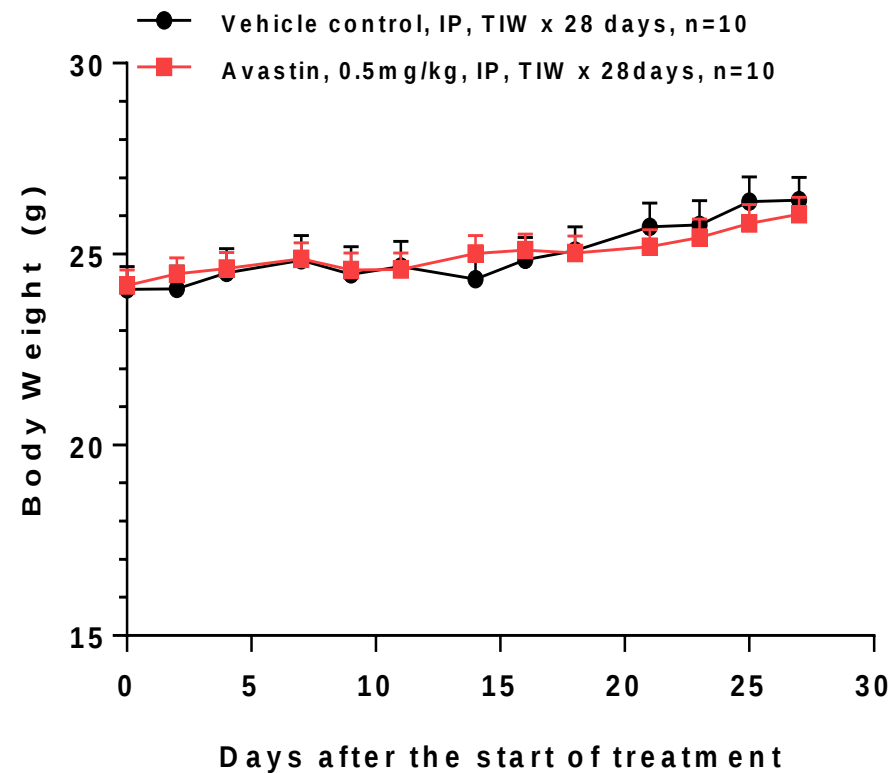
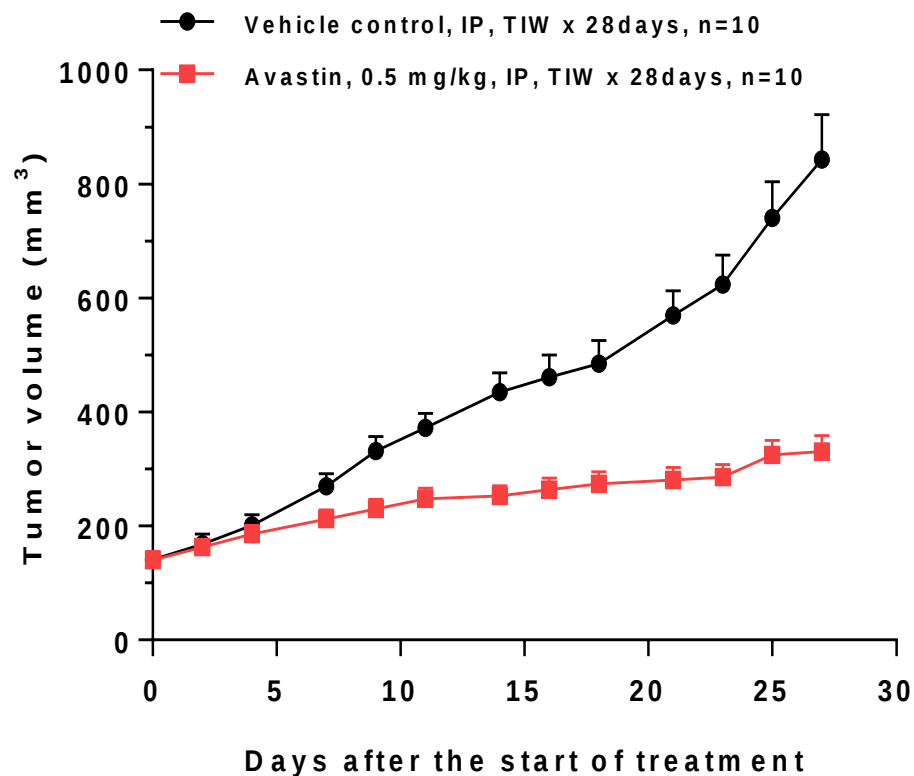
Nintedanib, Axitinib, Sunitinib in the NCI-H520 NSCLC Model



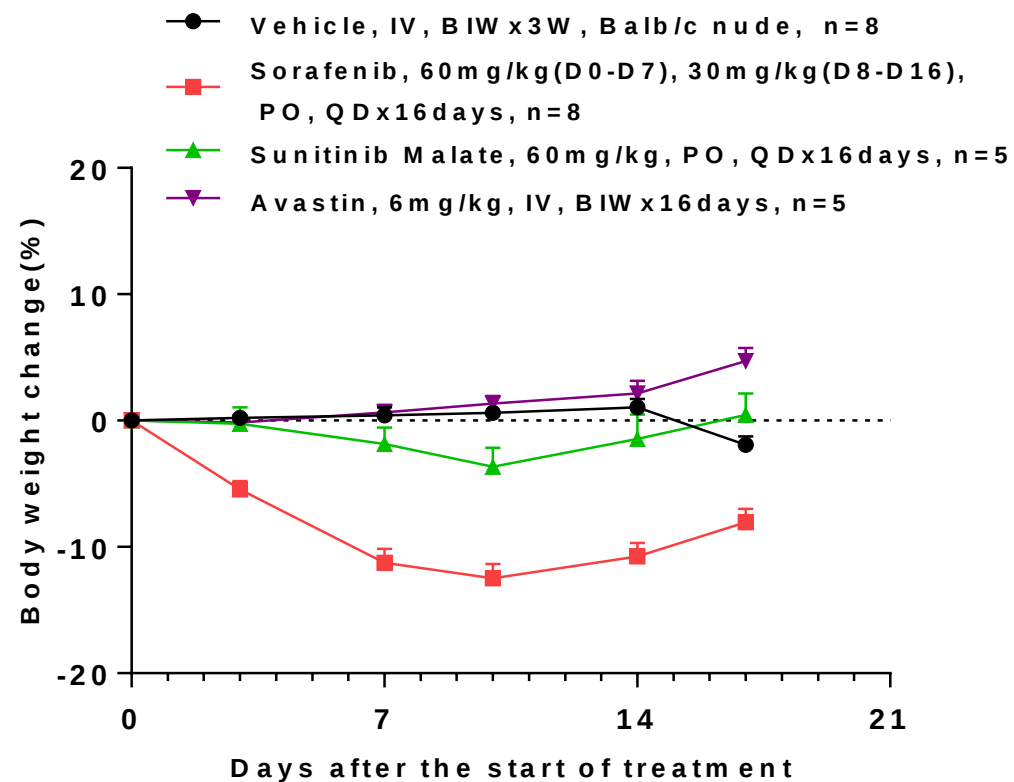
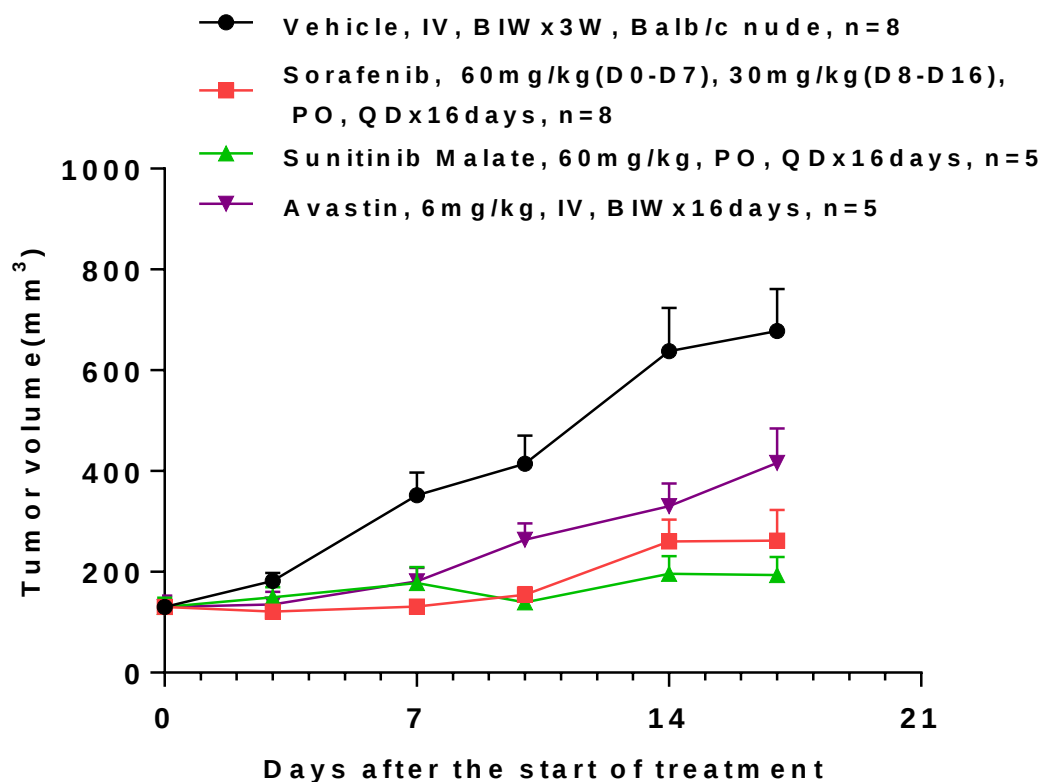
Apatinib in the PC-9 NSCLC Model



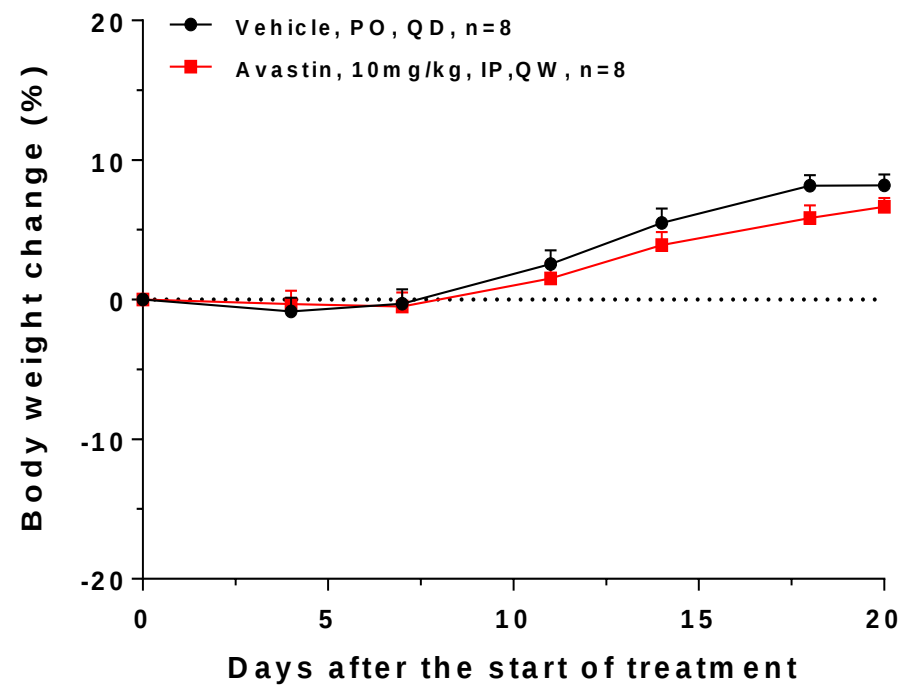
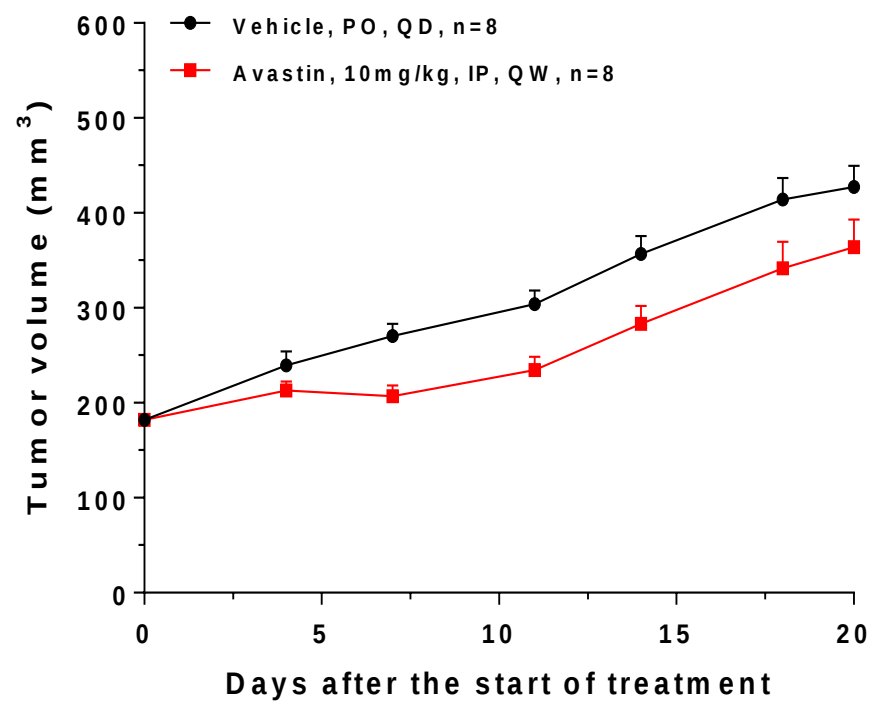
Avastin in NCI-H358 Human NSCLC Xenograft Model



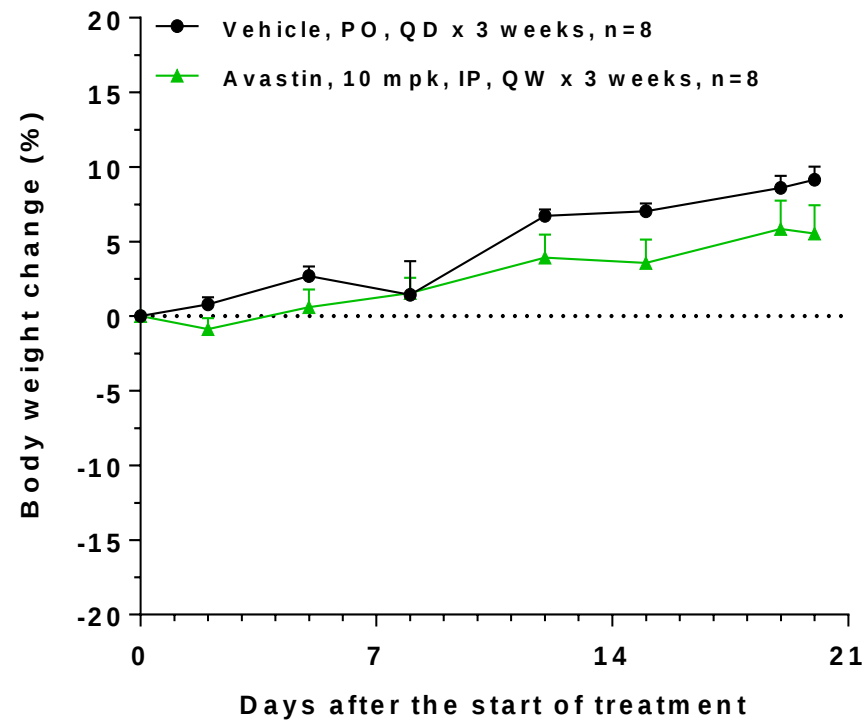
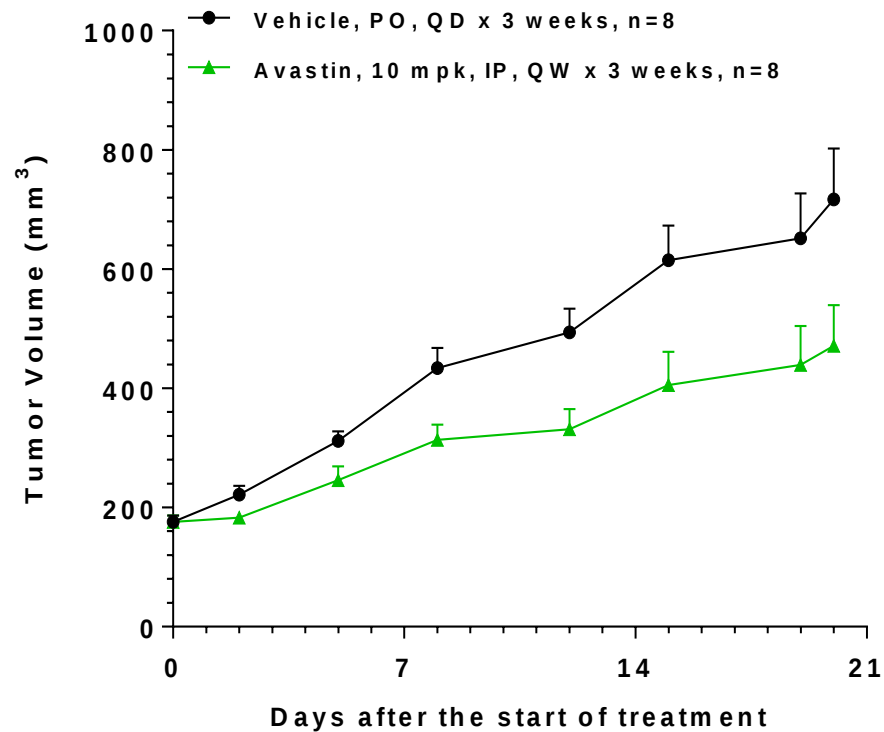
Sorafenib, Sunitinib Malate and Avastin in the 786-O Renal Cancer Model



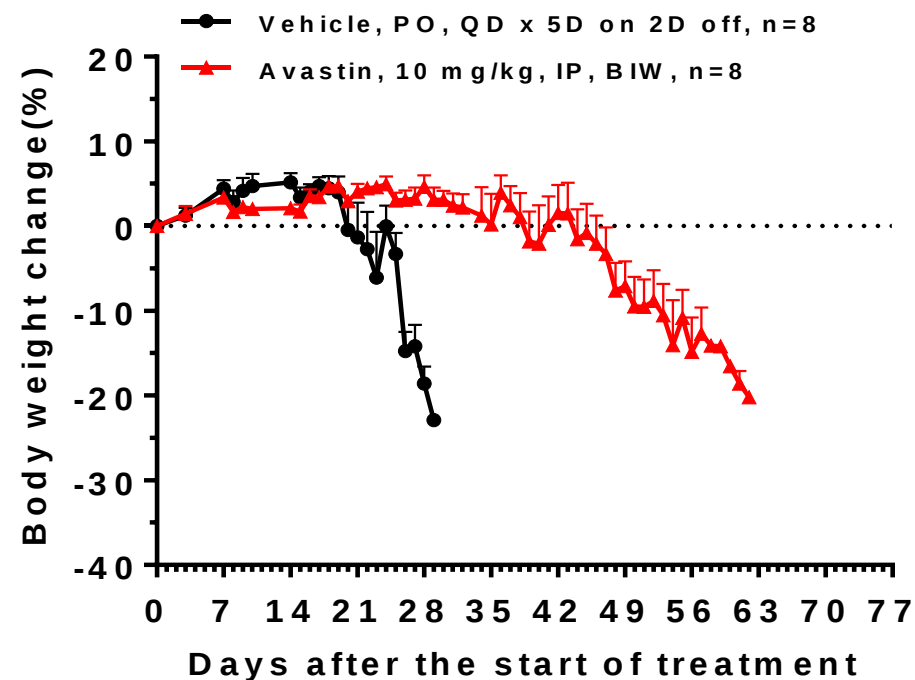
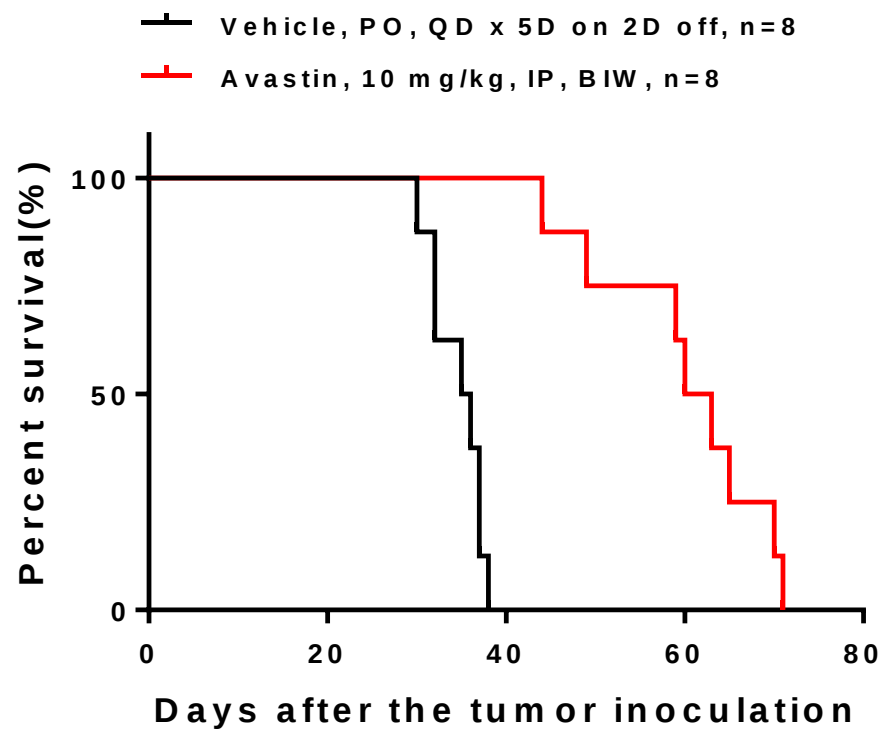
Avastin in the ACHN Human Renal Cancer Model



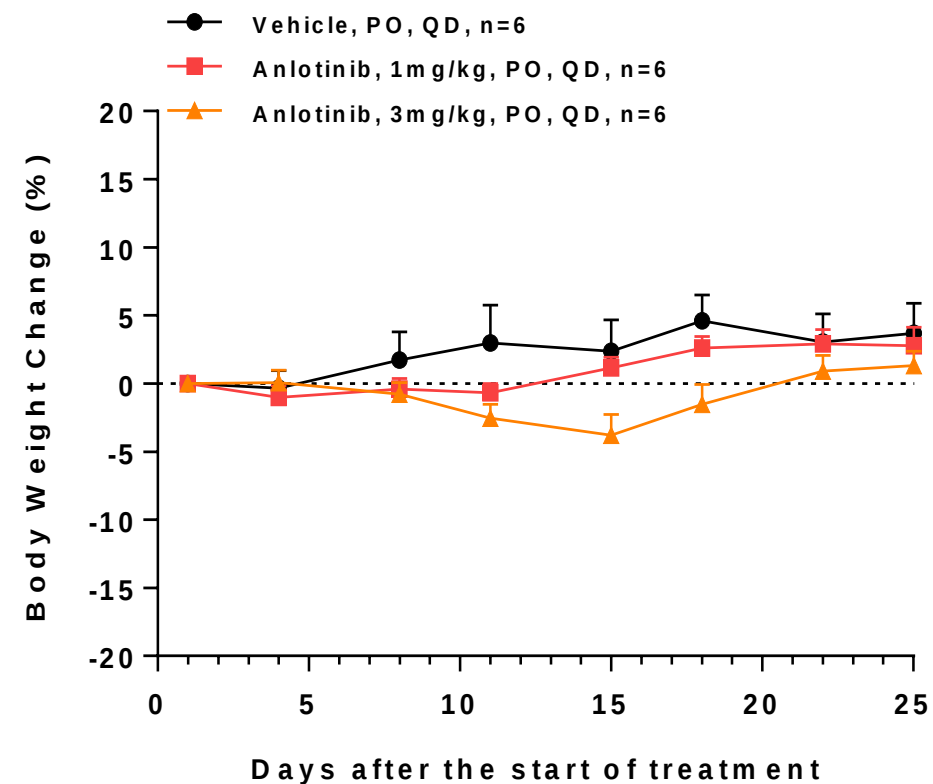
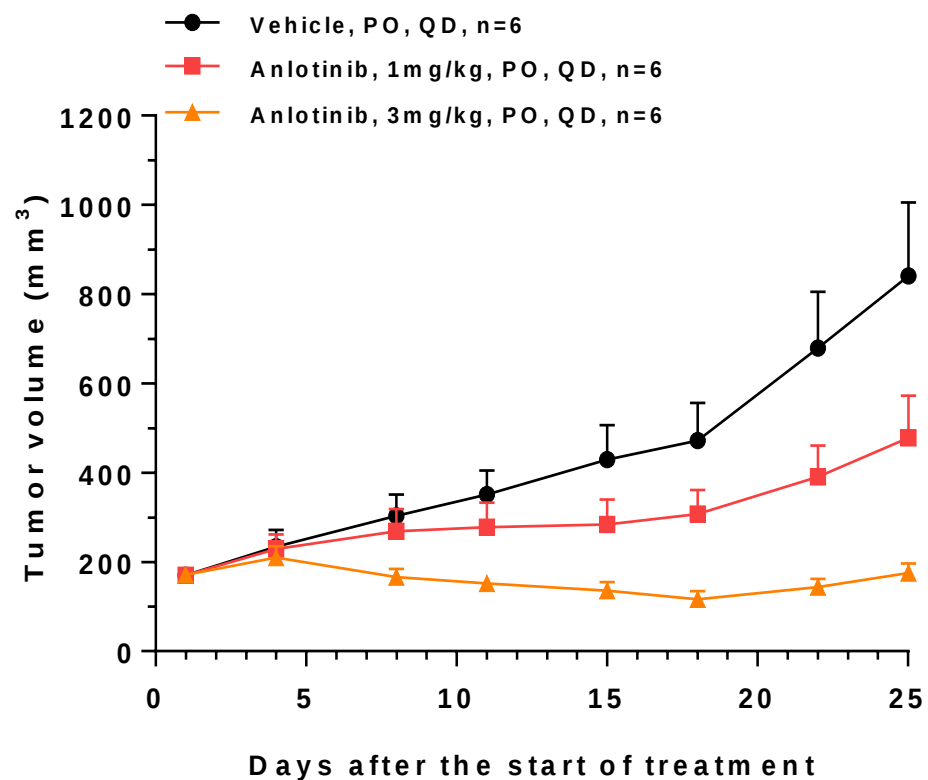
Avastin in the MCF-7 Human Breast Cancer Model



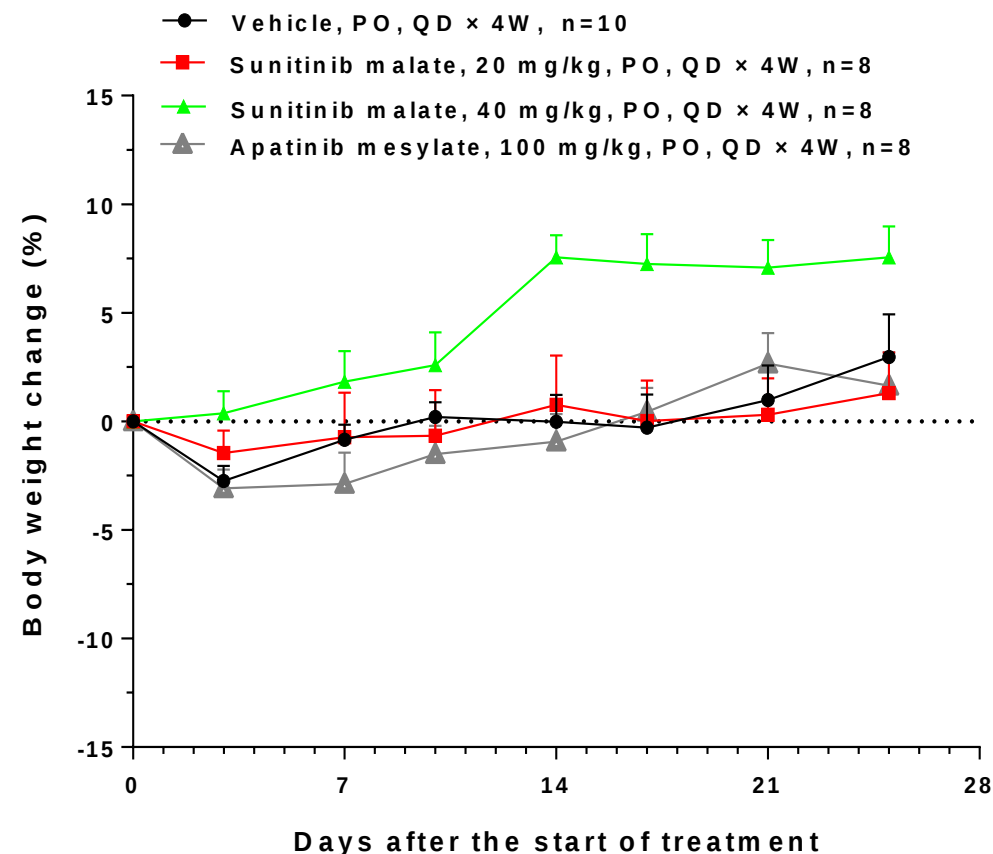
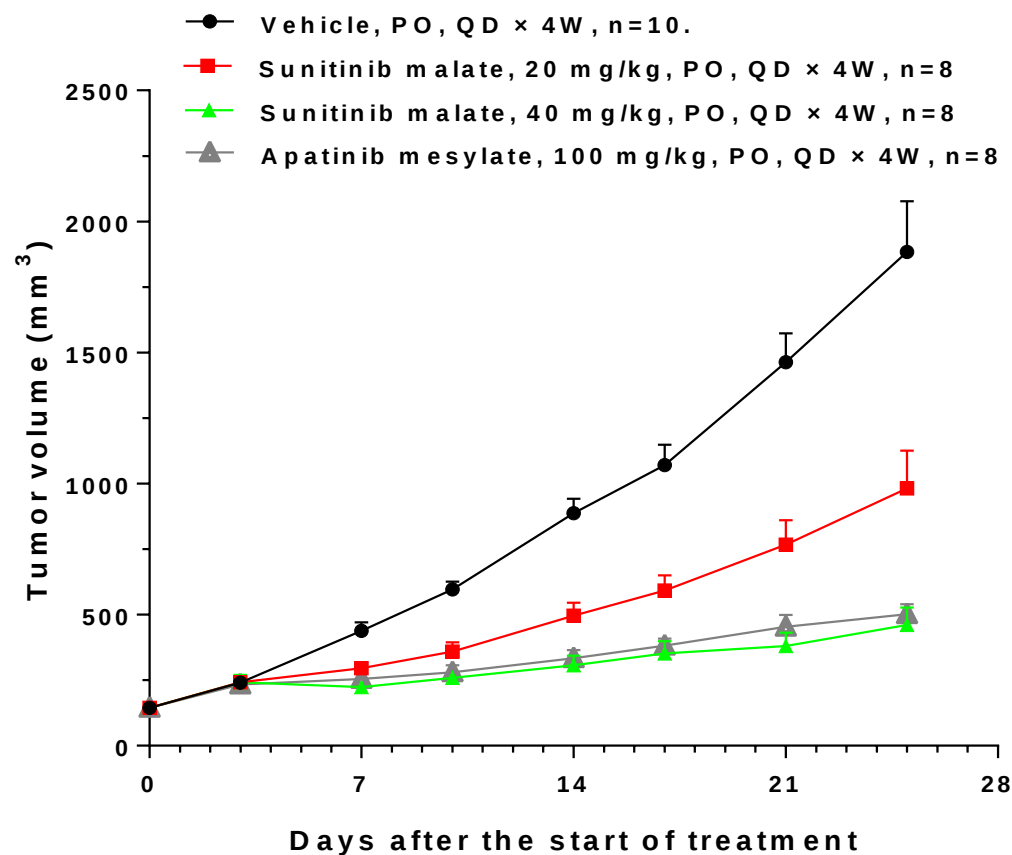
Avastin in the U87 Human GBM Model



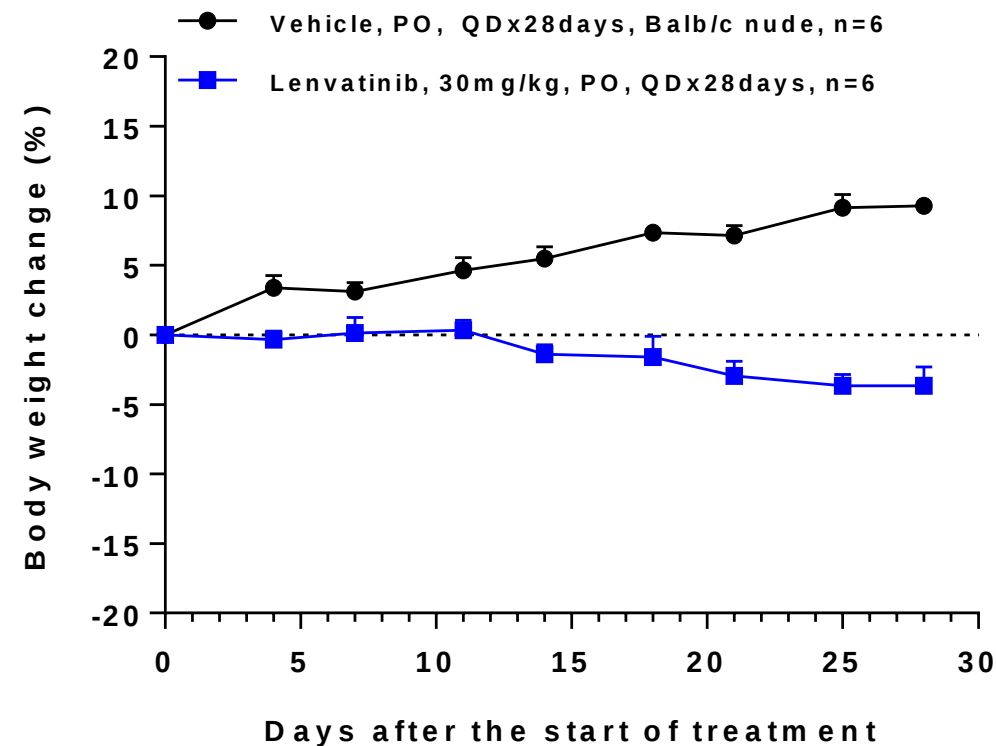
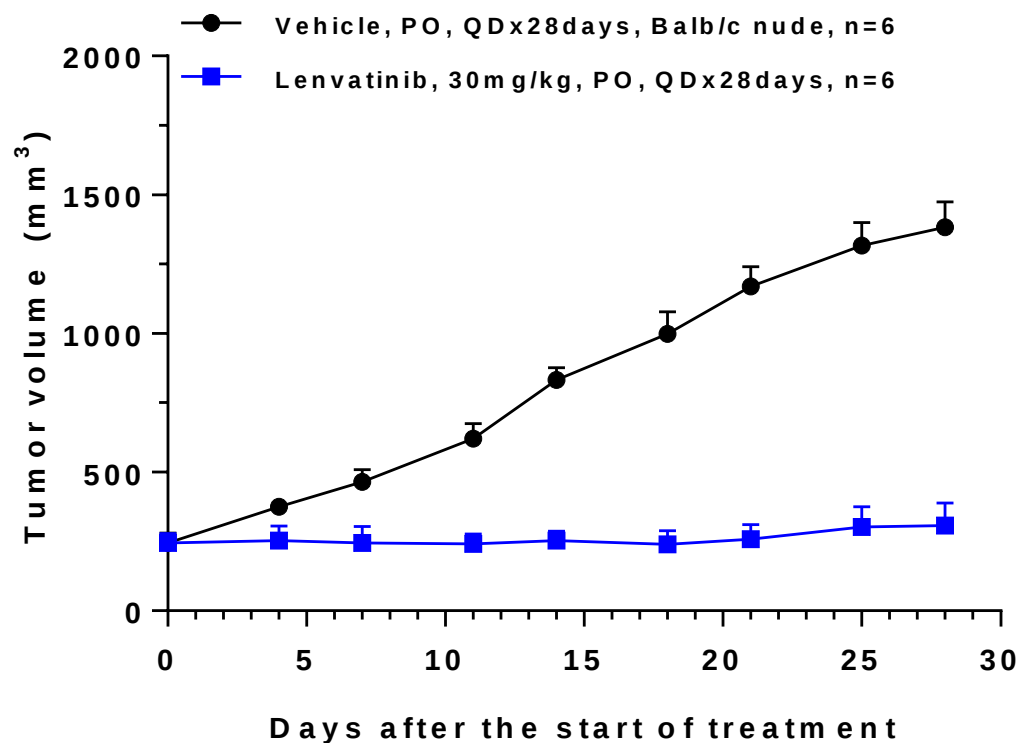
Anlotinib in the NCI-H69 SCLC Model



Sunitinib or Apatinib in MKN-45 Gastric Cancer Xenograft Model



Lenvatinib in FTC-238 Thyroid Cancer Xenograft Model



Summary of Small Molecule Inhibitors in PDX Models

Cancer Type	Model ID	Drugs tested	Dosage	TGI (%)
HCC	LI-03-0004	Lenvatinib	30 mg/kg, QD x 3W	60.9
		Nintedanib	100 mg/kg, QD x 3W	7.4
		Dovitinib	30 mg/kg, QD x 3W	17
		ENMD-2076	100 mg/kg, QD x 3W	47.8
		Sorafenib	60 mg/kg, QD x 3W	54.4
	LI-03-0005	Sorafenib	30 mg/kg, PO, QD x 4W	106.3
		Regorafenib	10 mg/kg, PO, QD x 4W	118.8
	LI-03-0010	Sorafenib	30 mg/kg, QD x 4W	78.1
		Regorafenib	10 mg/kg, PO, QD x 4W	91.2
		Vismodegib	100 mg/kg, QD x 2W	0
		Sorafenib	30 mg/kg, QD x 2W	91
		Sorafenib + Vismodegib	30 mg/kg, QD x 2W + 50 mg/kg, QD x 2W	91
		Lenvatinib	30 mg/kg, QD x 3W	103.7
		Dovitinib	30 mg/kg, QD x 3W	78
		Sorafenib	60 mg/kg, QD x 3W	79.4
	LI-03-0012	Lenvatinib	30 mg/kg, QD x 3W;	97.7
		Sorafenib	60 mg/kg, QD x 3W	95.8
		Foretinib	60 mg/kg, QD x 3W	110
		Cabozantinib	60 mg/kg, QD x 3W	110
		Sorafenib	60/30 mg/kg, QD x 3W	53.2
	LI-03-0016	Vismodegib	50 mg/kg, QD x 27D	0
		Sorafenib	60 mg/kg, QD x 26D	36
		Sorafenib + Vismodegib	60+50 mg/kg, QD x 26D +19D	42
		Lenvatinib	30 mg/kg, QD x 3W + QOD x 2W	116
		Sorafenib	60 mg/kg, PO, QD x 3W + QOD x 2W	103

Summary of Small Molecule Inhibitors in PDX Models

Cancer Type	Model ID	Drugs tested	Dosage	TGI (%)
HCC	LI-03-0018	Sorafenib	60 mg/kg, QD x 3W	62.4
	LI-03-0019	Sorafenib	30 mg/kg, PO, QD x 4W	47.3
		Regorafenib	10 mg/kg, PO, QD x 4W	28.1
	LI-03-0020	Sorafenib	30 mg/kg, QD x 4W	0
		Lenvatinib	30 mg/kg, QD x 3W	99.2
		Nintedanib	100 mg/kg, QD x 3W	57.8
		Dovitinib	30 mg/kg, QD x 3W	80
		ENMD-2076	100 mg/kg, QD x 3W	84.6
		Sorafenib	60 mg/kg, QD x 3W	60.2
	LI-03-0022	Vismodegib	50 mg/kg, QD x 2W	0
		Sorafenib	60 mg/kg, QD x 12D	62
		Sorafenib + Vismodegib	60 mg/kg, QD x 12D + 50 mg/kg, QD x 2W	62
	LI-03-0061	Lenvatinib	30 mg/kg, PO, QD x 3W	84.2
		Nintedanib	100 mg/kg, PO, QD x 3W	77
		Dovitinib	30 mg/kg, PO, QD x 3W	77
		ENMD-2076	100 mg/kg, PO, QD x 3W	64.6
		Sorafenib	60 mg/kg, PO, QD x 3W	46.8
		Sorafenib	30 mg/kg, PO, QD x 4W	77.5
	LI-03-0101	Regorafenib	10 mg/kg, PO, QD x 4W	85.4
		Sorafenib	30 mg/kg, PO, QD x 4W	64.7
		Regorafenib	10 mg/kg, PO, QD x 4W	91.9

Summary of Small Molecule Inhibitors in PDX Models

Cancer Type	Model ID	Drugs tested	Dosage	TGI (%)
HCC	LI-03-0115	Lenvatinib	30 mg/kg, QD x 3W	81.5
		Nintedanib	100 mg/kg, QD x 3W	35.5
		Dovitinib	30 mg/kg, QD x 3W	68
		ENMD-2076	100 mg/kg, QD x 3W	66
		Sorafenib	60 mg/kg, QD x 3W	79.6
	LI-03-0117	Avastin	10 mg/kg, QW	80.1
	LI-03-0141	Sorafenib	30 mg/kg, PO, QD x 4W	79.2
		Regorafenib	10 mg/kg, PO, QD x 4W	100.2
	LI-03-0155	Sorafenib	60 mg/kg, QD x 4W	46.2
	LI-03-0159	Sorafenib	30 mg/kg, PO, QD x 4W	22.6
		Regorafenib	10 mg/kg, PO, QD x 4W	32.3
	LI-03-0164	Lenvatinib	30 mg/kg, PO, QD x 3W	72.8
		Dovitinib	30 mg/kg, PO, QD x 3W	22
		ENMD-2076	100 mg/kg, PO, QD x 3W	0
		Sorafenib	60 mg/kg, PO, QD x 3W	55.9
	LI-03-0189	Sorafenib	30 mg/kg, PO, QD x 4W	67.5
		Regorafenib	10 mg/kg, PO, QD x 4W	72.0
	LI-03-0217	Lenvatinib	30 mg/kg, QD x 3W	84
		Nintedanib	100 mg/kg, QD x 3W	80
		Dovitinib	30 mg/kg, QD x 3W	70
		ENMD-2076	100 mg/kg, QD x 3W	59

Summary of Small Molecule Inhibitors in PDX Models

Cancer Type	Model ID	Drugs tested	Dosage	TGI (%)
HCC	LI-03-0217	Sorafenib	30 mg/kg, PO, QD x 4W	52.3
		Regorafenib	10 mg/kg, PO, QD x 4W	60.2
	LI-03-0191	Sorafenib	30 mg/kg, PO, QD x 4W	128
	LI-03-0254	Lenvatinib	3.75 mg/kg, QD x 25D	87.7
			7.5 mg/kg, QD x 25D	91.9
			15 mg/kg, QD x 25D	94.8
		Sorafenib	25 mg/kg, QD x 25D	91.9
			50 mg/kg, QD x 25D	89.9
	LI-03-0257	Sorafenib	30 mg/kg, PO, QD x 4W	62.8
Cholangiocarcinoma	LI-03-0271	Sorafenib	30 mg/kg, PO, QD x 4W	77.1
	LI-03-0317	Sorafenib	30 mg/kg, PO, QD x 4W	94.8
	LI-03-0332	Sorafenib	3 mg/kg, PO, QD x 3W	92.3
		BLU554	30 mg/kg, PO, QD x 3W	101.9
	CH-17-0001	Cabozantinib	30 mg/kg, PO, QD x 27D	89.9
	CH-17-0003	Cabozantinib	10 mg/kg, PO, QD x 20D	102.1
			30 mg/kg, PO, QD x 20D	111.7
	CH-17-0004	Cabozantinib	60 mg/kg, PO, QD x 20D	115.2
	CH-17-0004	Cabozantinib	30 mg/kg, PO, QD x 30D	97.1
	CH-17-0033	Cabozantinib	30 mg/kg, PO, QD x 31D	103.7

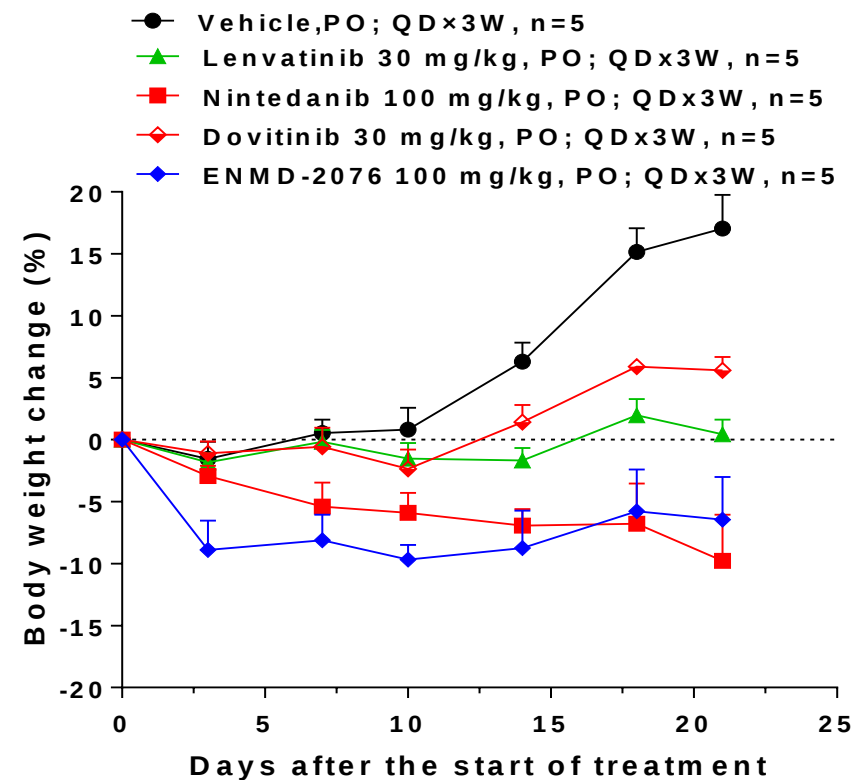
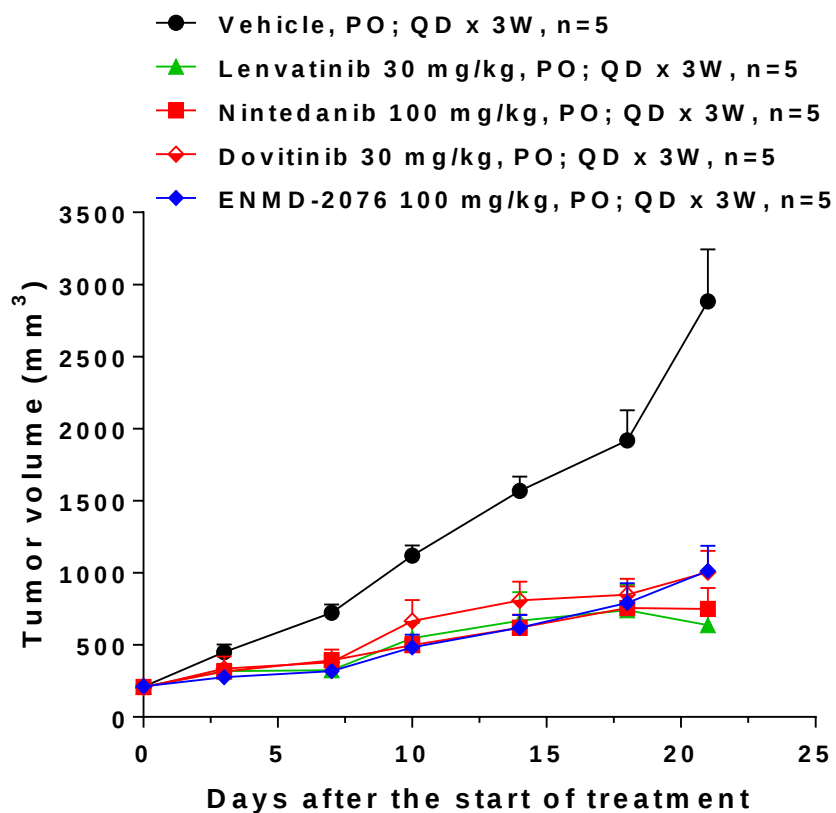
Summary of Small Molecule Inhibitors in PDX Models

Cancer Type	Model ID	Drugs tested	Dosage	TGI (%)
Cholangiocarcinoma	CH-17-0036	Cabozantinib	30 mg/kg, PO, QD x 15D	70.3
	CH-17-0038	Cabozantinib	30 mg/kg, PO, QD x 42D	113
	CH-17-0044	Cabozantinib	10 mg/kg, PO, QD x 21D	88.3
			30 mg/kg, PO, QD x 21D	104.8
			60 mg/kg, PO, QD x 21D	105.8
	CH-17-0073	Cabozantinib	15+30 mg/kg, PO,QD x (0-10)+(11-17) D	66.59
Nasopharyngeal cancer	NP-23-0055	Sorafenib	50 mg/kg, PO, QD x 3W	48.6
		Sorafenib + X ray	50 mg/kg, PO, QD x 3W; 2 Gy, D0,1	82.9
Lung adenocarcinoma	LU-01-0486	Avastin	5 mg/kg, IP, QW	33.9
Gastric cancer	ST-02-0350	Avastin	5 mg/kg, IP, QW	60.1
Colorectal cancer	CO-04-0105	Avastin	5 mg/kg, IP, QWx 3W	28.1
Pancreatic cancer	PC-07-0048	Avastin	5 mg/kg, IP, QW	39.7
Kidney cancer	KI-12-0073	Cabozantinib	30 mg/kg, PO, QD x 3W	33.7
		Pazopanib	30 mg/kg, PO, QD x 3W	24.6

- For model genomic information, VEGFA/B is ubiquitously expressed in all tumor tissue, so usually patient selection is not necessary for VEGF-VEGFR Inhibitors.

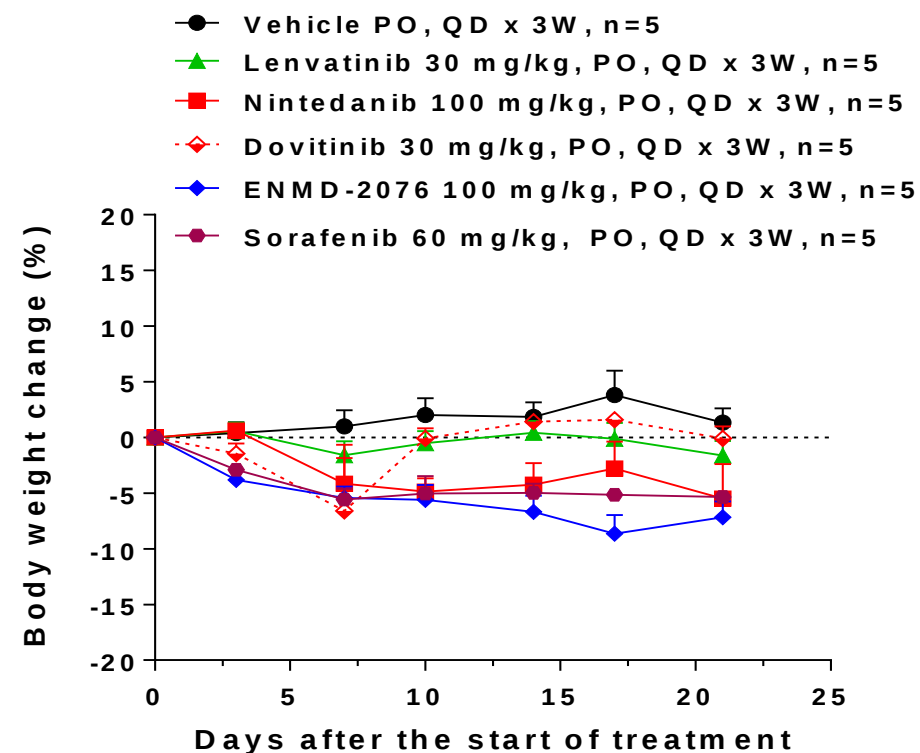
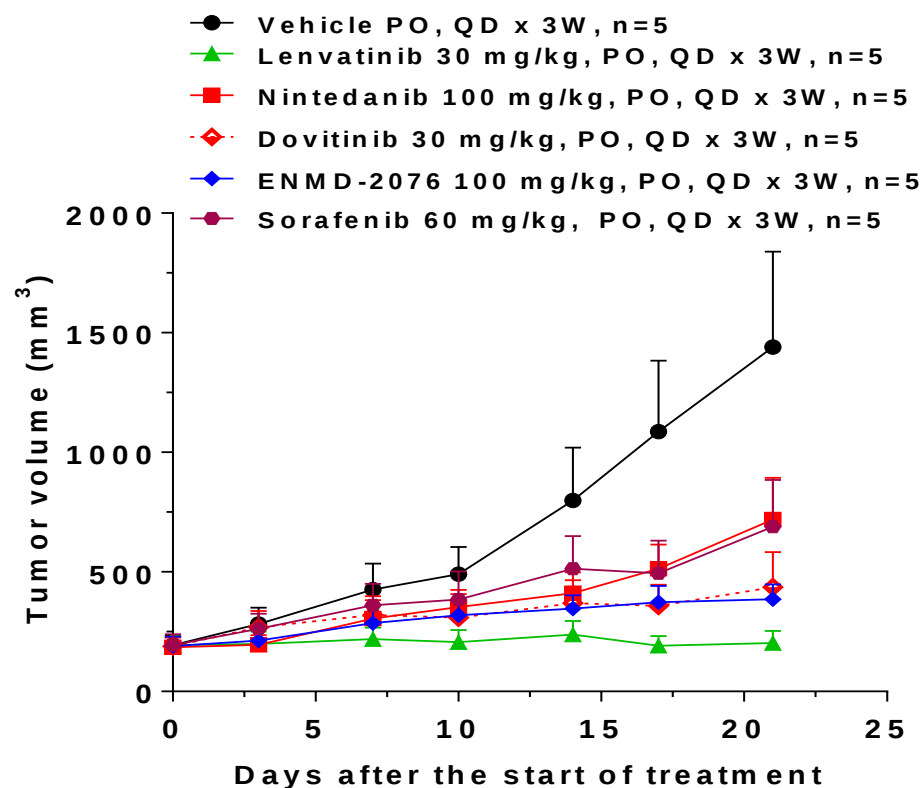
Lenvatinib, Nintedanib, Dovitinib, ENMD-2076 in LI-03-0217

Model ID	Cancer Type	Gender	Age	Tumor Grade	Tumor Stage	Pathological Diagnosis	Molecular Diagnosis
LI-03-0217	Liver cancer	male	56	IV	T3N1M0	NA	IHC: Hep1(+), HBsAg(+), CK18(+), CK19(-), CD46(+), PCEA(+), HBcAg(-), MUC(-)



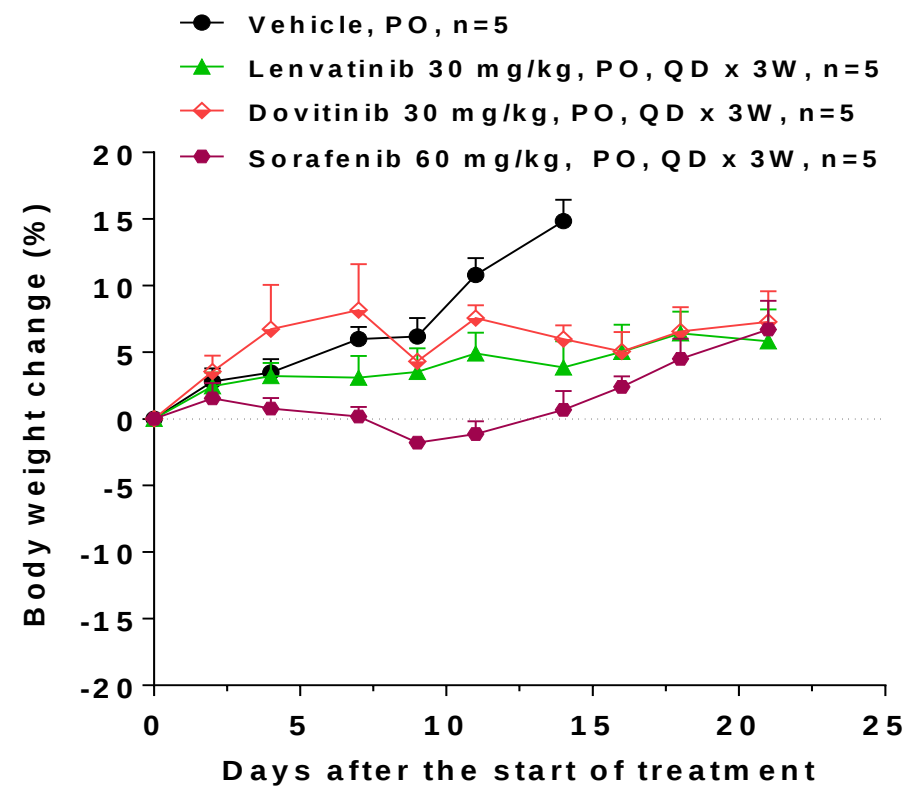
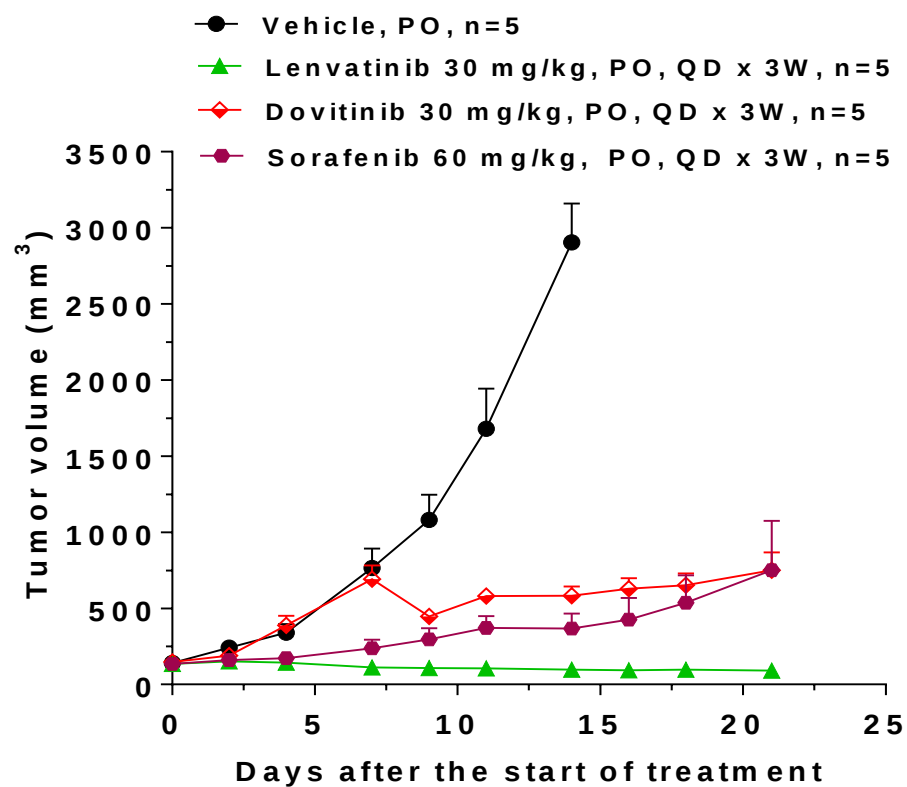
Lenvatinib, Nintedanib, Dovitinib, ENMD-2076, Sorafenib in LI-03-0020

Model ID	Cancer Type	Gender	Age	Tumor Grade	Tumor Stage	Pathological Diagnosis	Molecular Diagnosis
LI-03-0020	Liver cancer	male	69	III	T3N0M0	Thick trabecular type	NA



Lenvatinib, Dovitinib, Sorafenib in LI-03-0010

Model ID	Cancer Type	Gender	Age	Tumor Grade	Tumor Stage	Pathological Diagnosis	Molecular Diagnosis
LI-03-0010	Liver cancer	male	47	NA	NA	NA	IHC: Hep1(-), HBsAg(-), CK18(-), CK19(-), CD34(-), PCEA(-), HBcAg(-), CK20(-), MUC(-)





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