$KRAS^{G12C}$ Related *In Vivo* Tumor Models

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Outline

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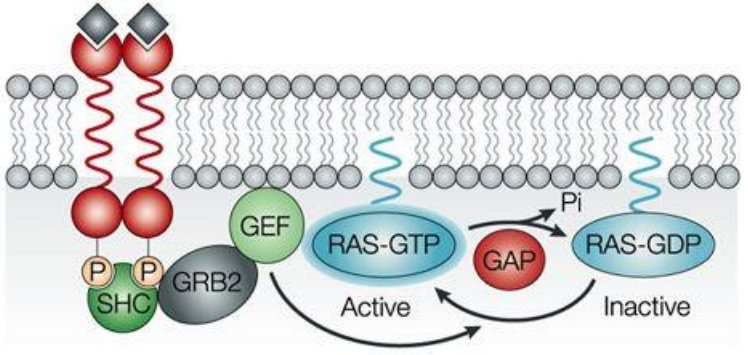
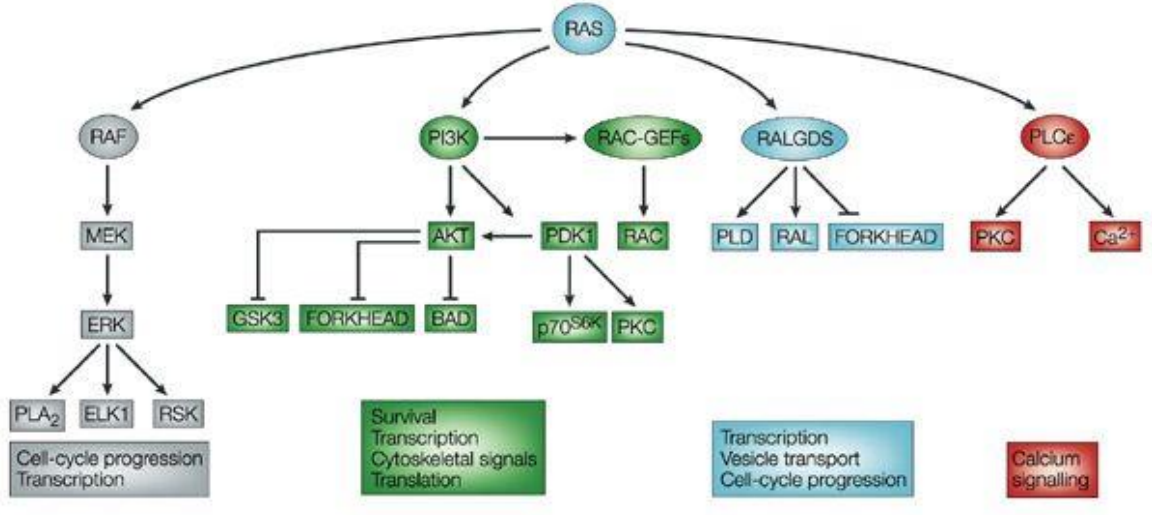
  - KRAS biology
  - Selective KRAS^{G12C} inhibitors in clinical trail
- **KRAS^{G12C} related models**
  - AMG 510 3D CTG validation across KRAS^{G12C} cell lines
  - KRAS^{G12C} related CDX models and SOC data
  - KRAS^{G12C} related PDX models and SOC data
  - AMG 510 *in vivo* validation across KRAS^{G12C} models

KRAS biology and related signaling pathway

- The *KRAS* gene, which encoded an 21kDa membrane-localized GTPase transforming protein called KRAS, was first discovered and identified as a human proto-oncogene in 1982.
- KRAS belongs to the Ras superfamily functioning as on/off switches in regulating diverse cellular pathways for **cell growth, differentiation, proliferation and survival.** KRAS links growth promoting signals from the cell surface to the nucleus.
- KRAS is an enzyme (a GTPase) that converts a molecule called GTP into GDP. When KRAS is attached (bound) to GDP, it's in its "off" position and can't send signals to the nucleus. But when a GTP molecule arrives and binds to KRAS, KRAS is activated and sends its signal, and then it converts the GTP into GDP and returns to the "off" position.



Signalling upstream of RAS



Signalling downstream of RAS

Targeting RAS signalling pathways in cancer therapy. *Nat Rev Cancer.* 2003 Jan;3(1):11-22.

KRAS mutation identified in human cancer

- When mutated, KRAS can act as an oncogene, causing normal cells to become cancerous. The mutations can shift the KRAS protein into the "on" position all the time. KRAS mutations are common in **pancreatic adenocarcinomas (98%), colorectal cancers (45%) and lung cancers (31%)**.

Table 1 | **Frequency of RAS mutations in human cancers***

Cancer	% *KRAS*	% *NRAS*	% *HRAS*	% All RAS
Pancreatic ductal adenocarcinoma	97.7	0.0	0.0	97.7
Colorectal adenocarcinoma	44.7	7.5	0.0	52.2
Multiple myeloma	22.8	19.9	0.0	42.6
Lung adenocarcinoma	30.9	0.9	0.3	32.2
Skin cutaneous melanoma	0.8	27.6	1.0	29.1
Uterine corpus endometrioid carcinoma	21.4	3.6	0.4	24.6
Uterine carcinosarcoma	12.3	1.8	0.0	14.3
Thyroid carcinoma	1.0	8.5	3.5	12.5
Acute myeloid leukaemia	3.1	6.7	1.6	11.4
Bladder urothelial carcinoma	3.1	1.4	5.9	10.6
Gastric adenocarcinoma	11.4	0.9	0.0	10.0
Cervical adenocarcinoma	8.3	0.0	0.0	8.3
Head and neck squamous cell carcinoma	0.5	0.3	4.7	5.5
Diffuse large B cell lymphoma	5.2	0.0	0.0	5.2
Oesophageal adenocarcinoma	3.8	0.0	0.6	4.4
Chronic lymphocytic leukaemia	1.9	2.5	0.0	4.4
Lung squamous cell carcinoma	2.2	0.0	2.2	4.4
Small cell lung carcinoma	1.4	0.0	1.4	2.8

KRAS^{G12C} mutation and opportunity

- The G12C mutation results in an amino acid substitution at position 12 in KRAS, from a **glycine (G)** to a **cysteine (C)**, which occurs in 2% of all human cancers.
- In non-small cell lung cancer (NSCLC), KRAS^{G12C} is the most common mutation, comprising nearly half of all KRAS mutations.
- KRAS^{G12C} was recently identified to be potentially druggable by allele-specific covalent targeting of Cys-12 in vicinity to an inducible allosteric **Switch II Pocket (S-IIP)**.
- The series of Switch-II Pocket KRAS^{G12C} Inhibitors bind to and covalently react with the GDP-bound state of KRAS^{G12C} trapping it in an inactive conformation.

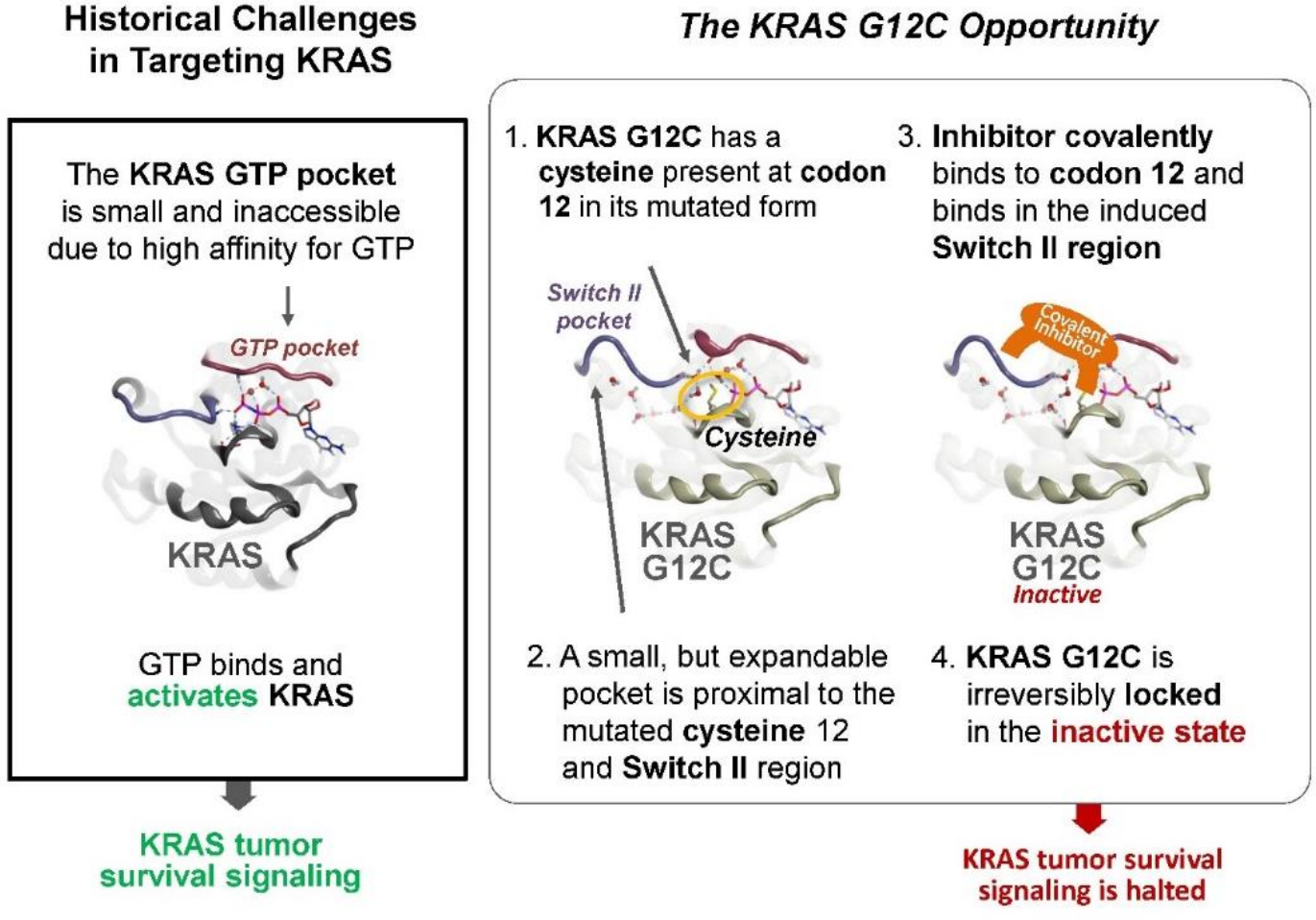


Image from https://www.mirati.com

Selective KRAS^{G12C} Inhibitors in clinical trail

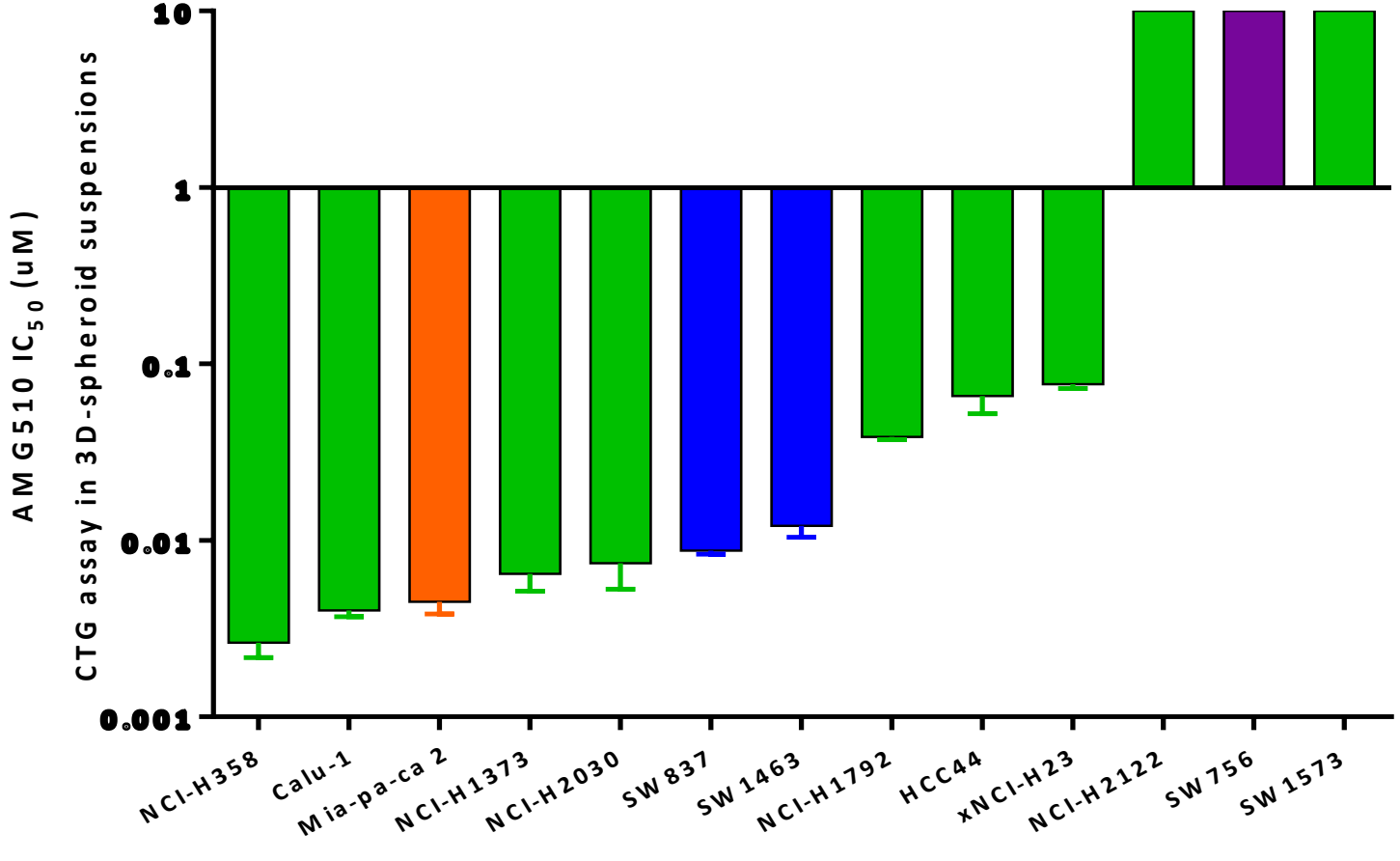
Drug	Inventor	Indications	Intervention/ treatment	Status	Clinical trials identifier
AMG 510	Amgen	Advanced Solid Tumors With KRAS p.G12C Mutation	AMG 510	Phase 1/2	NCT03600883
		Monotherapy and in Combination With Other Anti-cancer Therapies in Advanced Solid Tumors With KRAS p.G12C Mutation	AMG 510 PD1 inhibitor MEK inhibitor SHP2 inhibitor Pan-ErbB inhibitor	Phase 1	NCT04185883
		Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC With KRAS p.G12C Mutation	AMG 510 Docetaxel	Phase 3	NCT04303780
		Chinese Descent With Advanced/Metastatic Solid Tumors With KRAS p.G12C Mutation	AMG 510	Phase 1	NCT04380753
MRTX849	Mirati Therapeutics Inc.	Advanced Cancer Metastatic Cancer Malignant Neoplastic Disease	MRTX849 Pembrolizumab Cetuximab Afatinib	Phase 1/2	NCT03785249
		Advanced Cancer Metastatic Cancer Malignant Neoplastic Disease	MRTX849 TNO155	Phase 1/2	NCT04330664

Selective KRAS^{G12C} Inhibitors in clinical trail

Drug	Inventor	Indications	Intervention/ treatment	Status	Clinical trials identifier
JNJ-74699157	Janssen Research & Development, LLC	Neoplasms Advanced Solid Tumors Non-small Cell Lung Cancer Colorectal Cancer	JNJ-74699157	Phase 1	NCT04006301
LY3499446	Eli Lilly and Company	Advanced Solid Tumor Non-Small Cell Lung Cancer Colorectal Cancer	LY3499446 Abemaciclib Cetuximab Erlotinib Docetaxel	Phase 1/2	NCT04165031

https://clinicaltrials.gov/

AMG 510 3D CTG validation across KRAS^{G12C} cell lines



Cell line	IC_{50} (μM)
NCI-H358	0.00264
Calu-1	0.00402
Mia-pa-ca-2	0.00449
NCI-H1373	0.00647
NCI-H2030	0.00741
SW837	0.00876
SW1463	0.01211
NCI-H1792	0.03860
HCC44	0.06583
xNCI-H23	0.07661
NCI-H2122	>10
SW756	>10
SW1573	>10

KRAS^{G12C} related CDX models

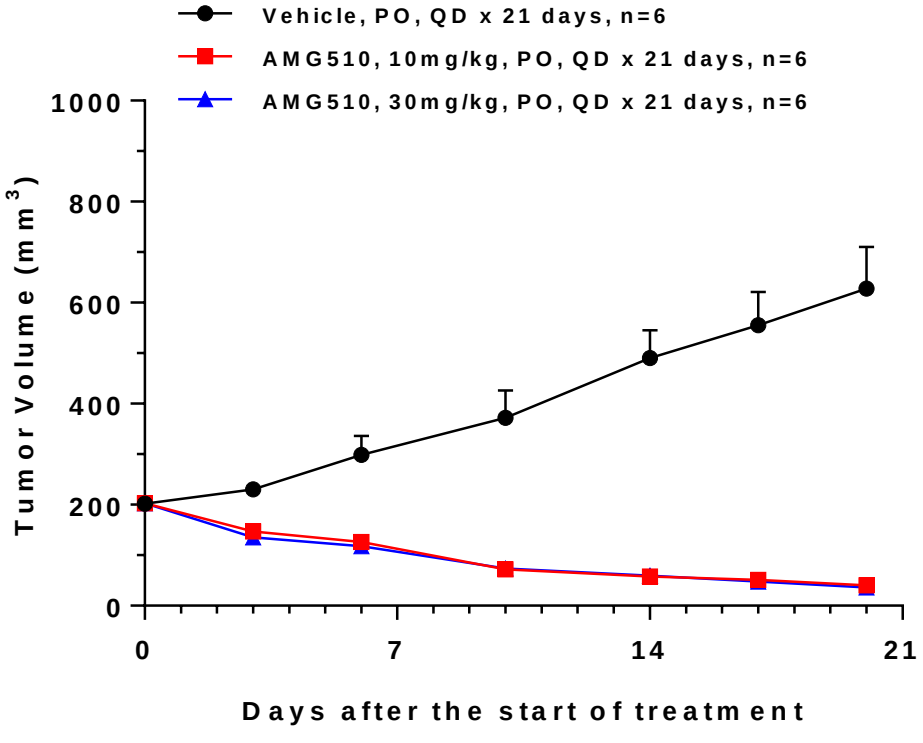
Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	T/C (%)	Model genomics
Lung cancer	HCC44	Yes	AMG 510	10 mg/kg 30 mg/kg	6.7% 5.8%	KRAS p.G12C
	NCI-H358	Yes	AMG 510	10 mg/kg 30 mg/kg	13.6% 7.0%	
			ARS-1620	15 mg/kg 20 mg/kg	56.4% 25.7%	
	NCI-H2030	Yes	AMG 510	10 mg/kg 30 mg/kg	24.5% 14.0%	
	NCI-H2122	Yes	AMG 510	10 mg/kg 30 mg/kg	56.6% 41.1%	
	xNCI-H23	Yes	AMG 510	10 mg/kg 30 mg/kg	48.5% 48.7%	
	SW1573	Yes	AMG 510	10 mg/kg 30 mg/kg	62.3% 73.3%	
	NCI-H1373	Yes	In plan			

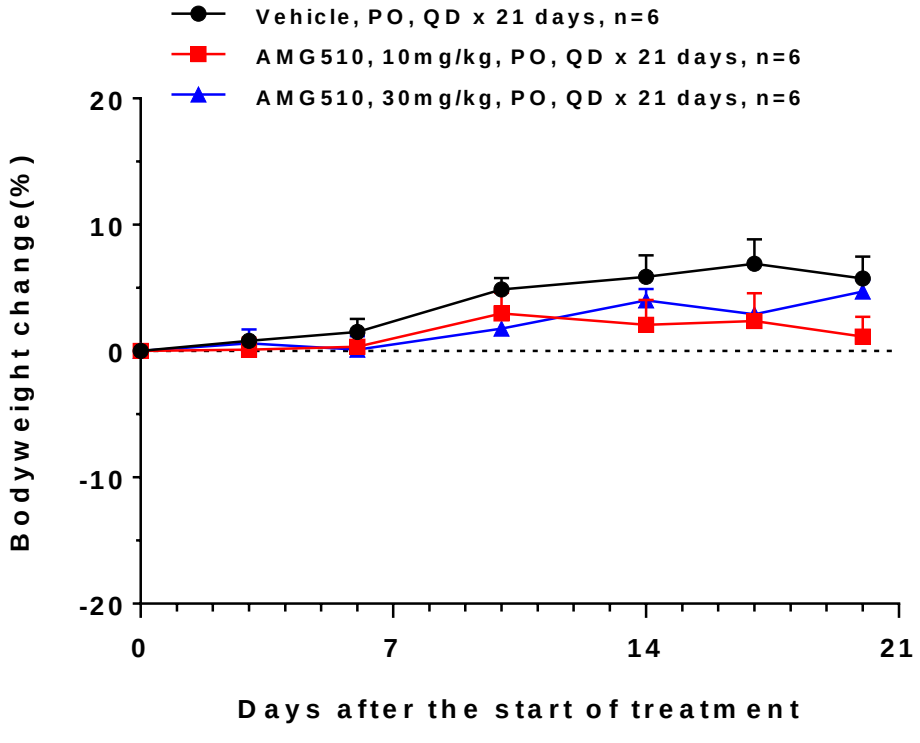
$KRAS^{G12C}$ related CDX models

Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	T/C (%)	Model genomics
Pancreatic cancer	Mia-pa-ca-2	Yes	AMG 510	10 mg/kg 30 mg/kg	8.0% 3.3%	KRAS p.G12C
			ARS-1620	50 mg/kg 200 mg/kg	8.0% 5.2%	
Colorectal cancer	SW1463	Yes	AMG 510	10 mg/kg 30 mg/kg	29.9% 13.8%	
	SW837	Yes	AMG 510	10 mg/kg 30 mg/kg	22.0% 14.4%	
Cervical cancer	SW756	Yes	AMG 510	10 mg/kg 30 mg/kg	24.9% 7.8%	

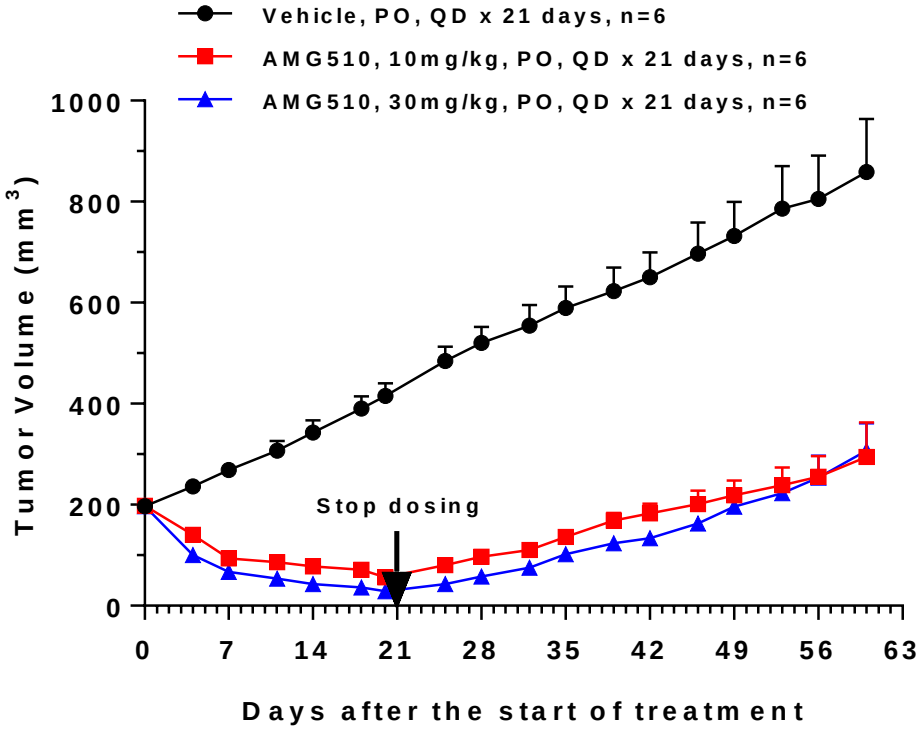
$T/C\ (\%) = T_{RTV} / C_{RTV} \times 100\ \%$, $RTV = V_t / V_0$
T_{RTV} : relative tumor volume of treatment group, C_{RTV} : relative tumor volume of control group

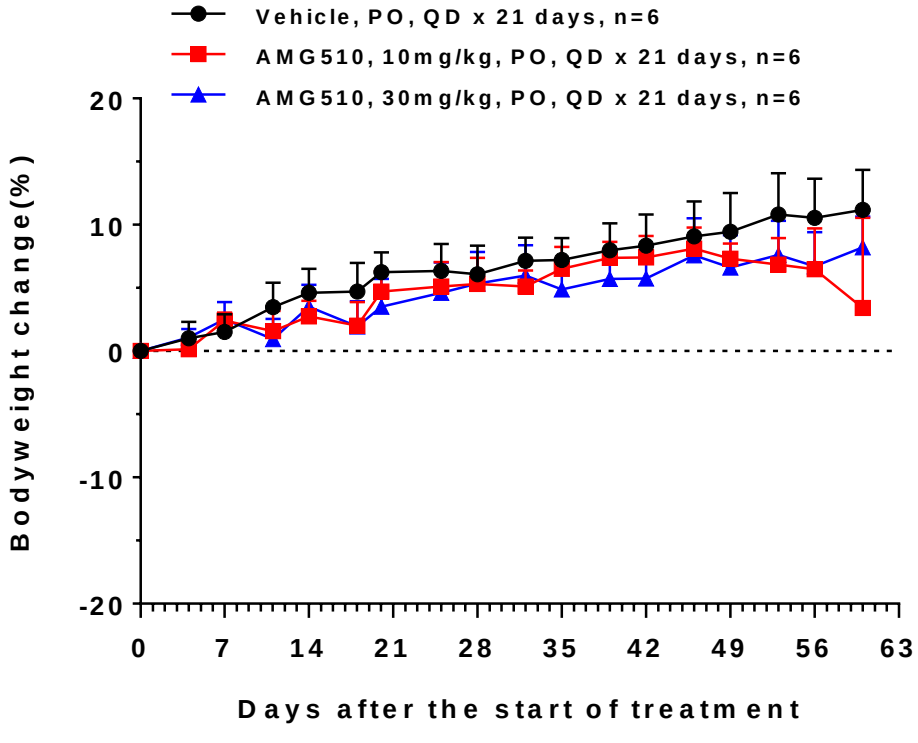
AMG 510 in HCC44 non-small cell lung cancer xenograft model



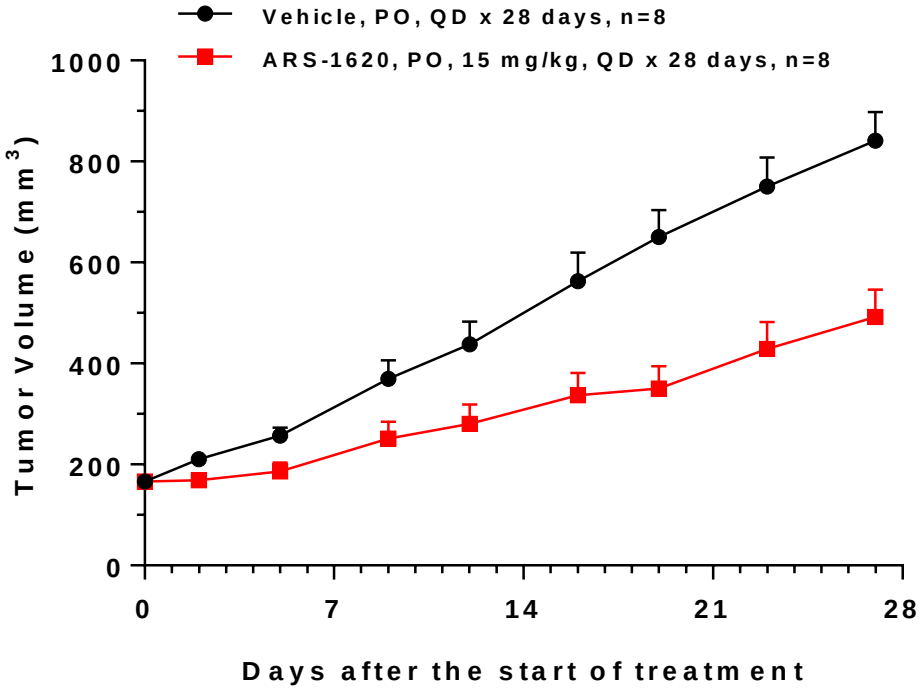


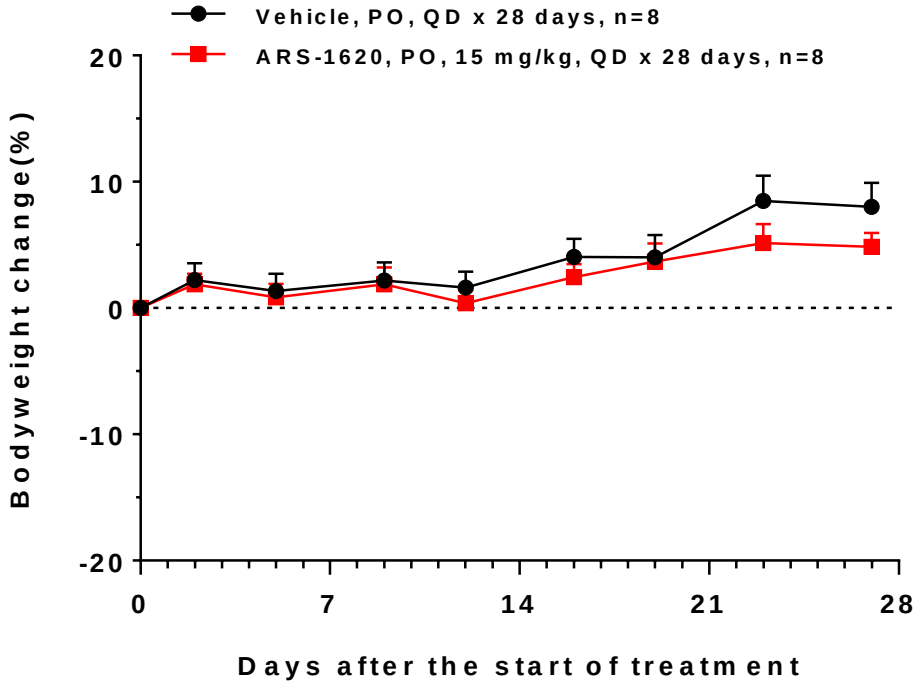
AMG 510 in NCI-H358 non-small cell lung cancer xenograft model



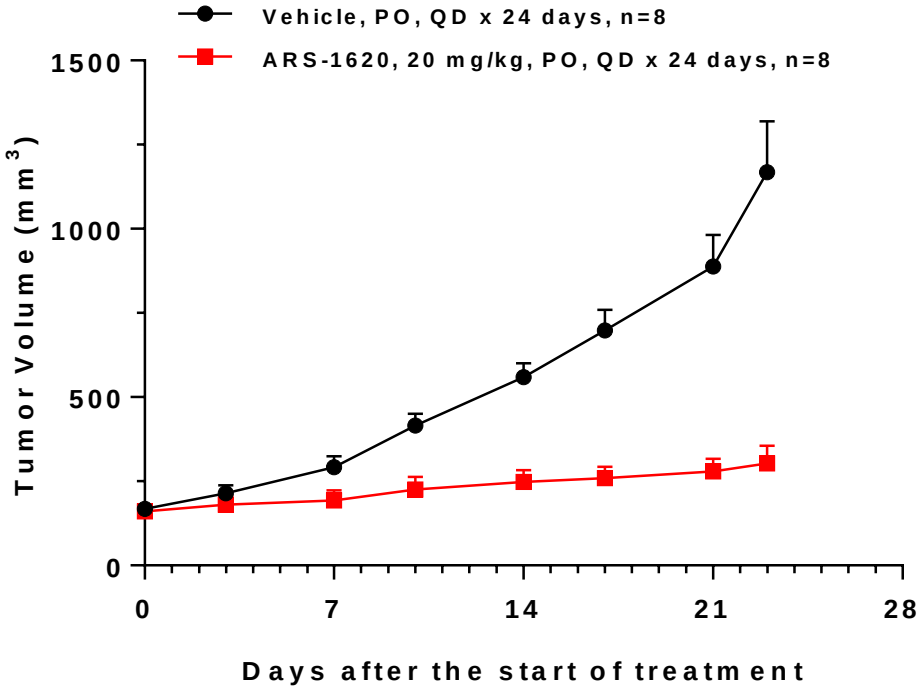


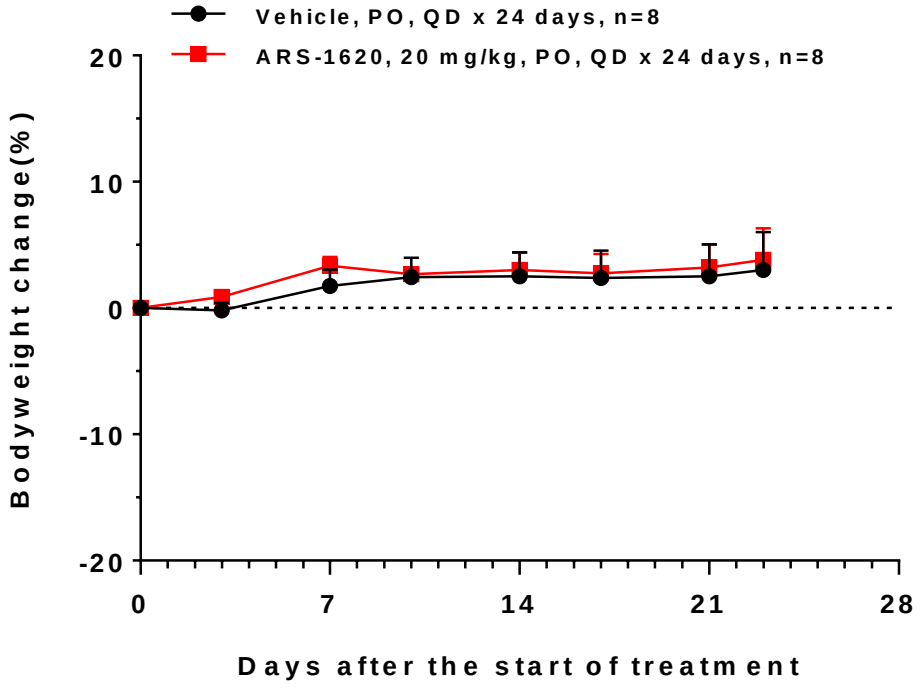
ARS-1620 in NCI-H358 non-small cell lung cancer xenograft model



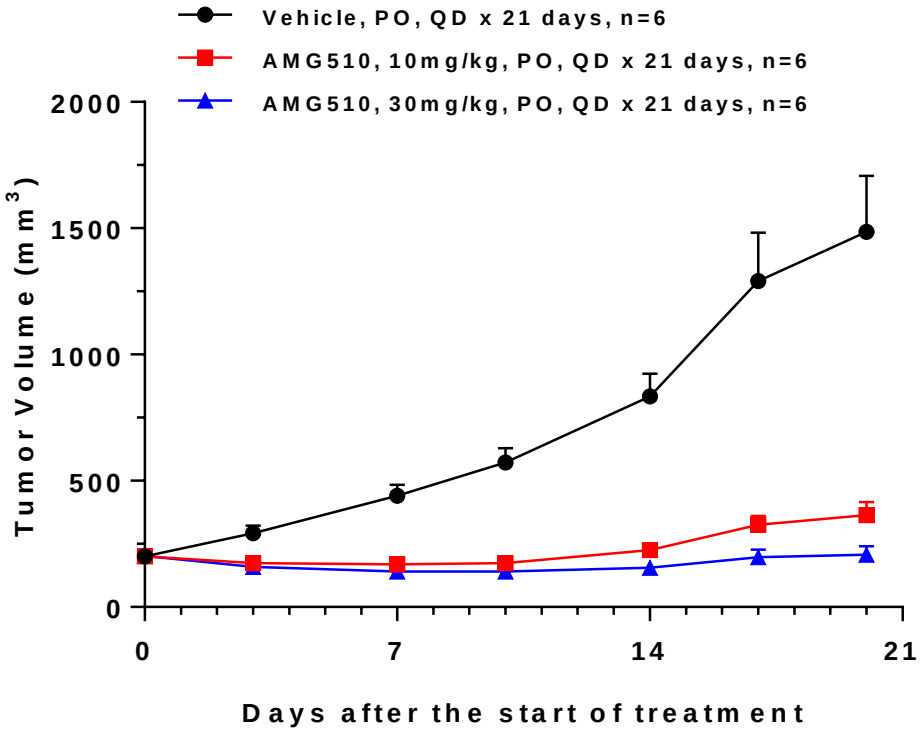


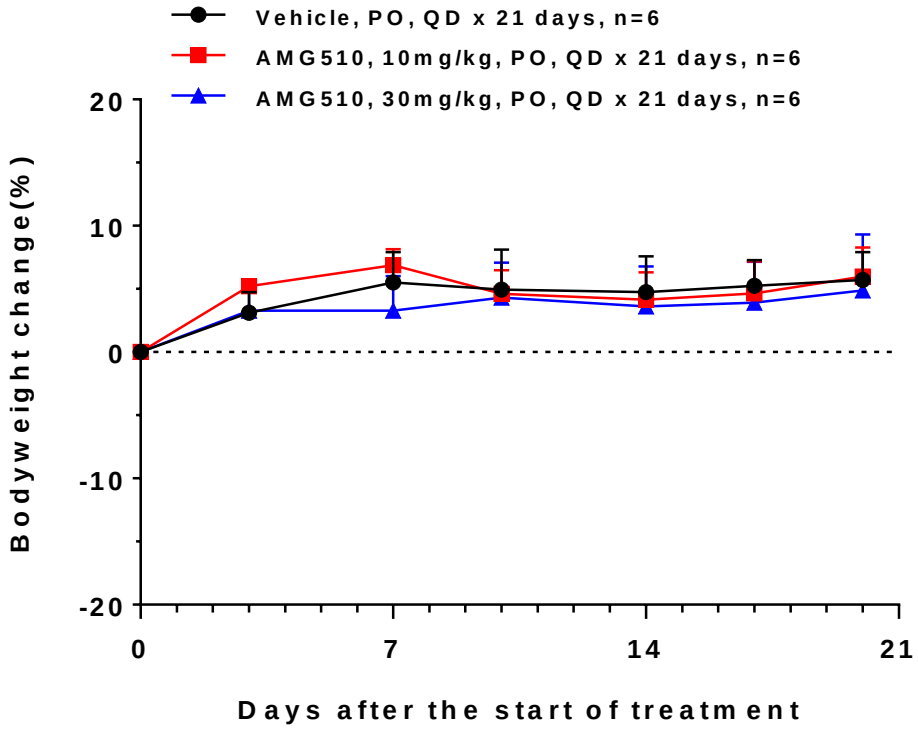
ARS-1620 in NCI-H358 non-small cell lung cancer xenograft model



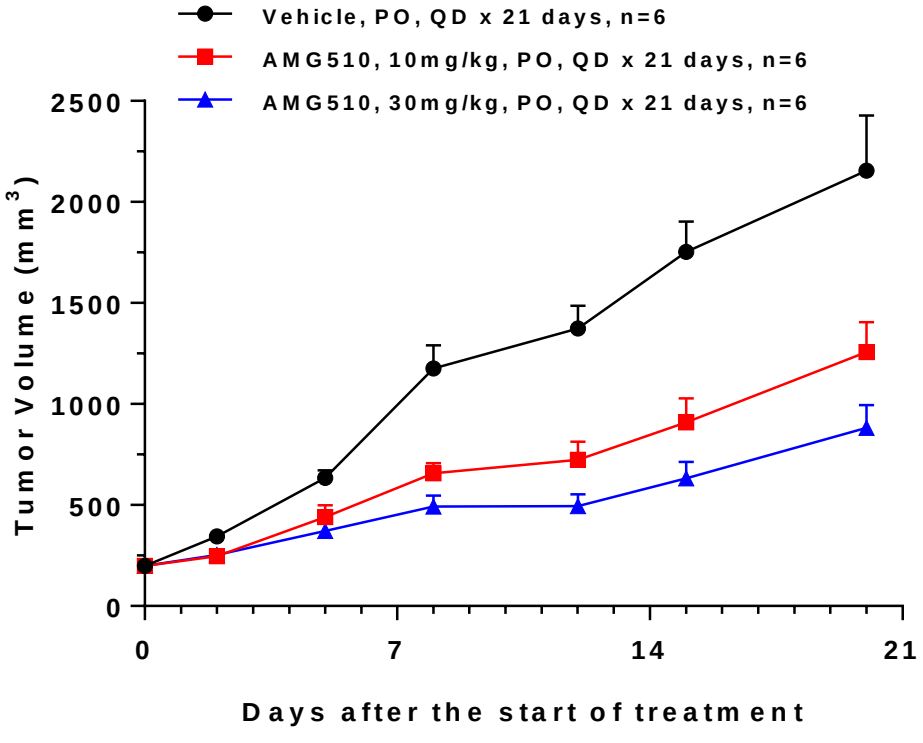


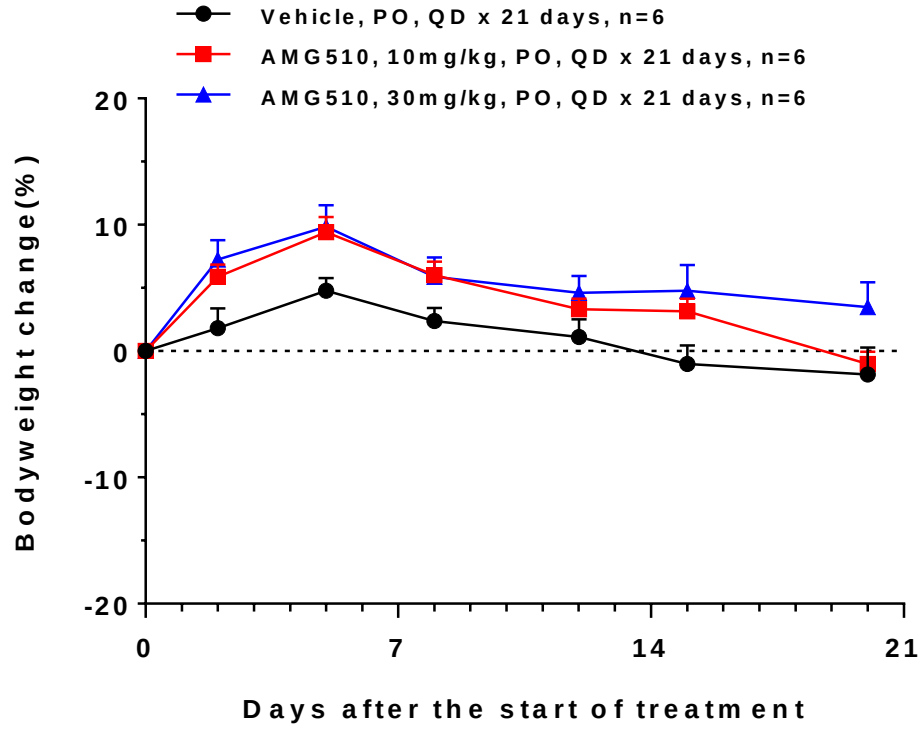
AMG 510 in NCI-H2030 non-small cell lung cancer xenograft model



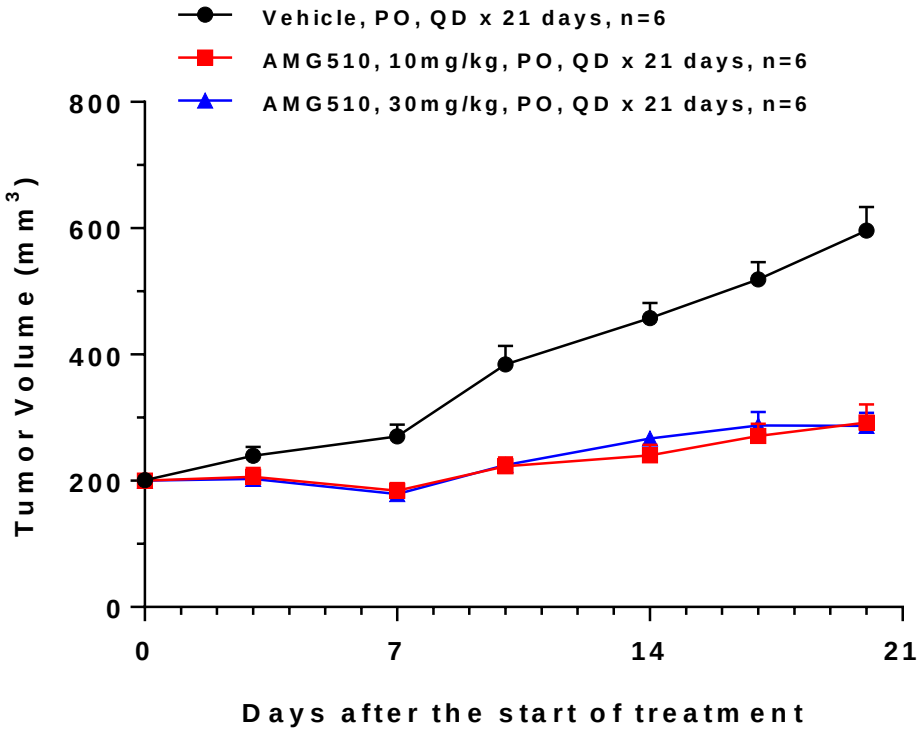


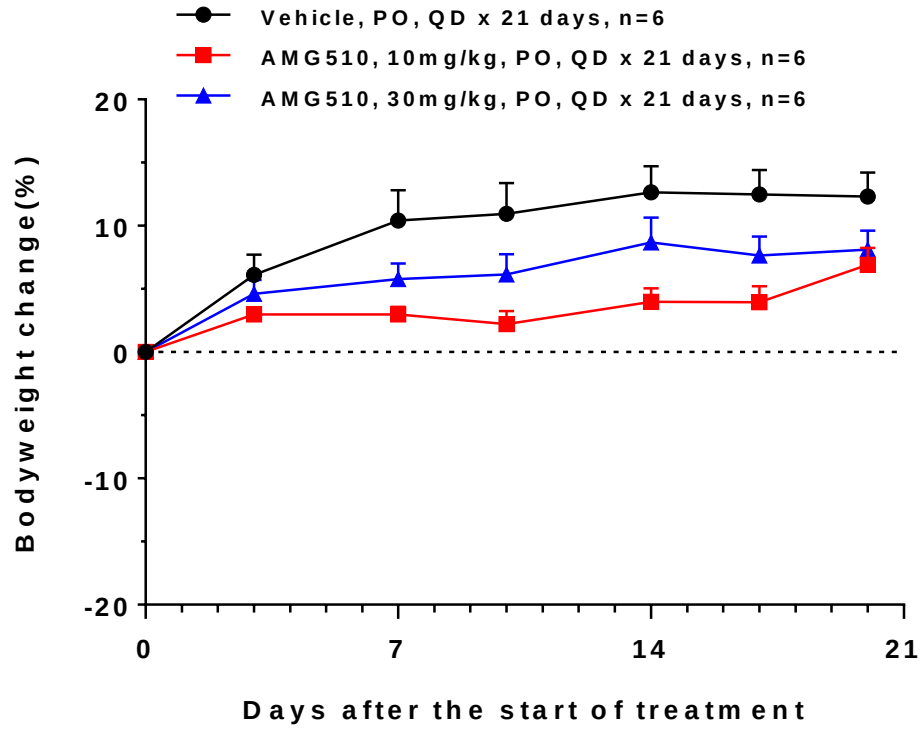
AMG 510 in NCI-H2122 non-small cell lung cancer xenograft model





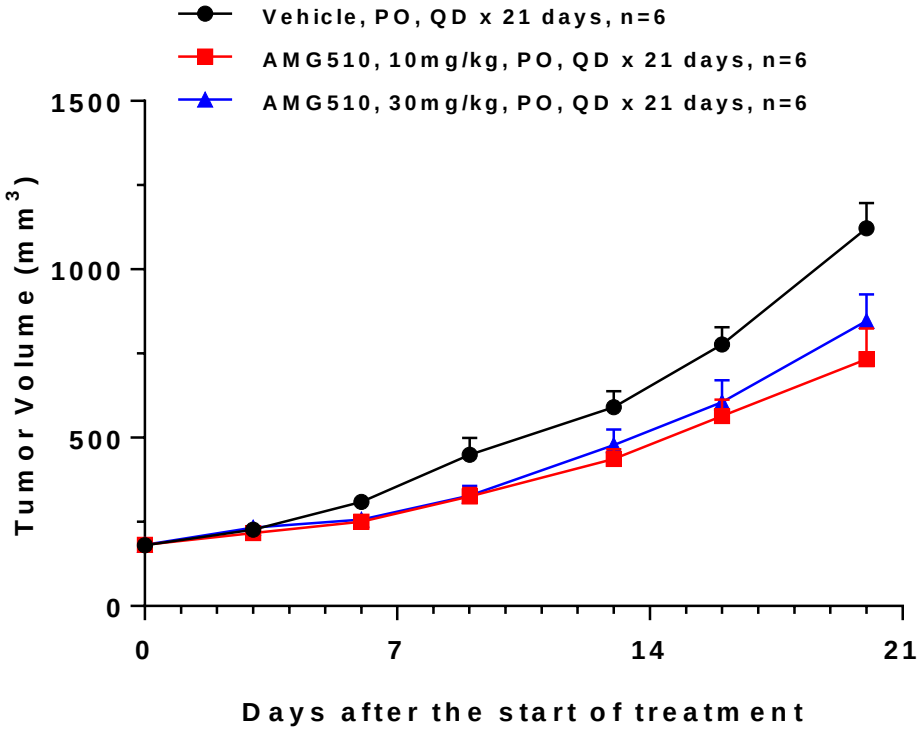
AMG 510 in xNCI-H23 non-small cell lung cancer xenograft model

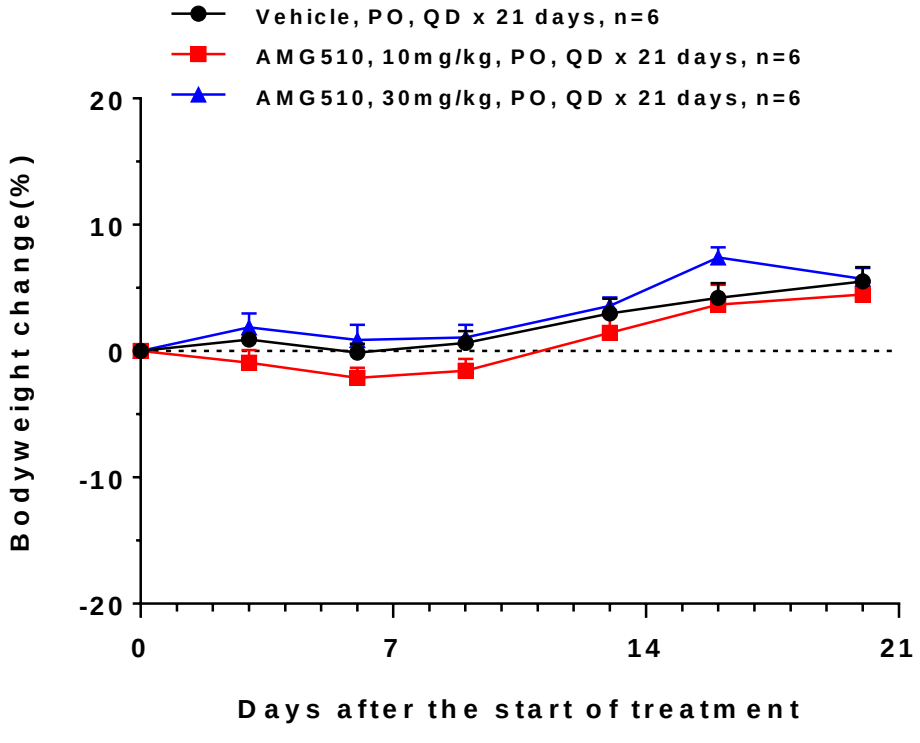




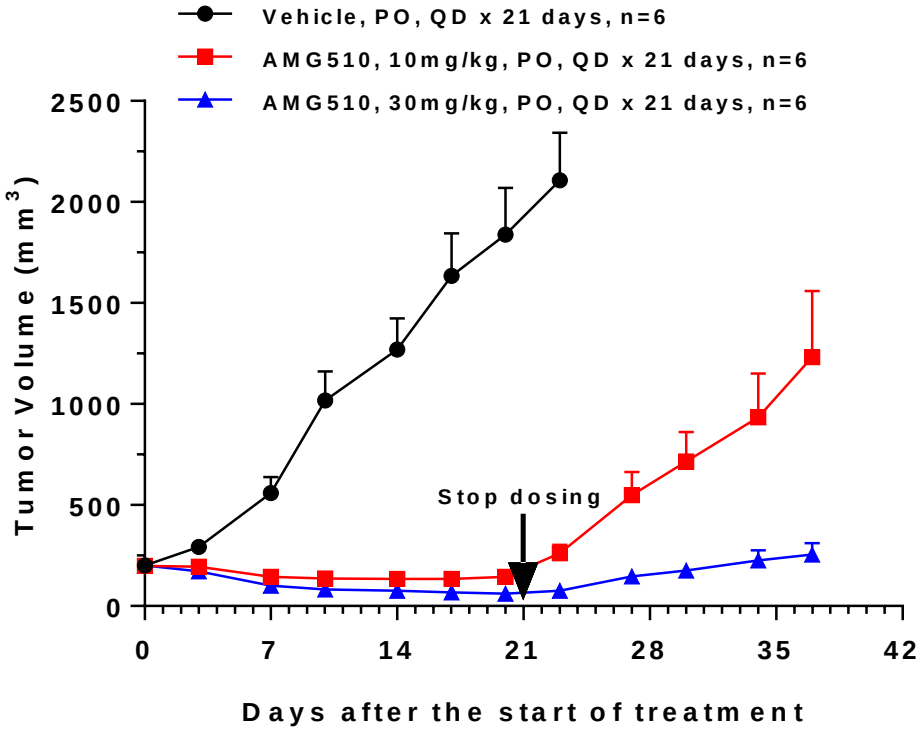
Note: Model was established from **xNCI-H23** which went through *in vivo* passage once.

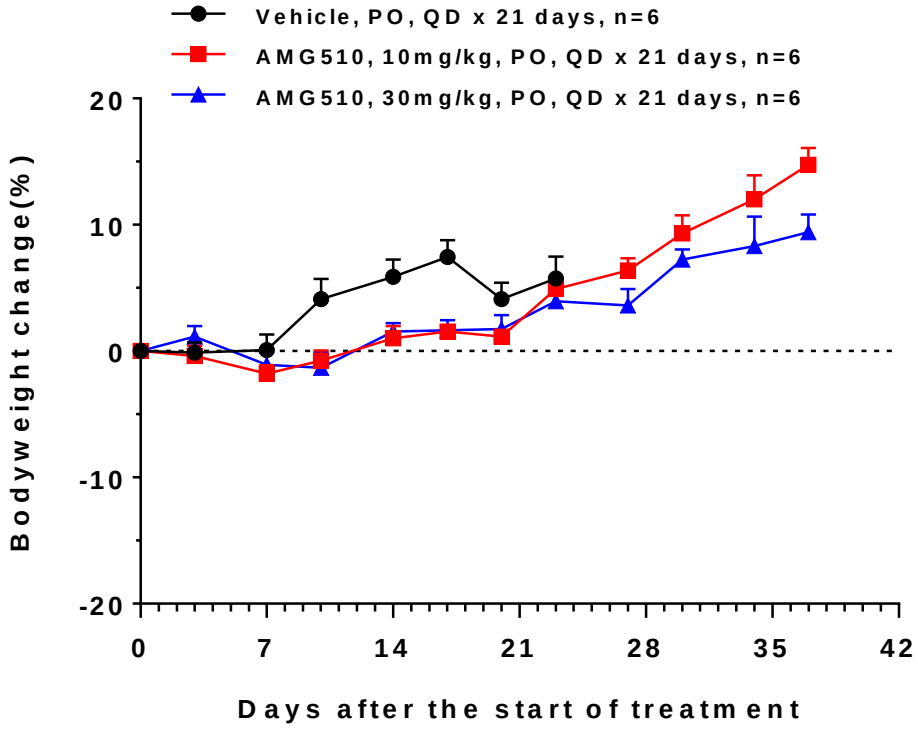
AMG 510 in SW1573 non-small cell lung cancer xenograft model



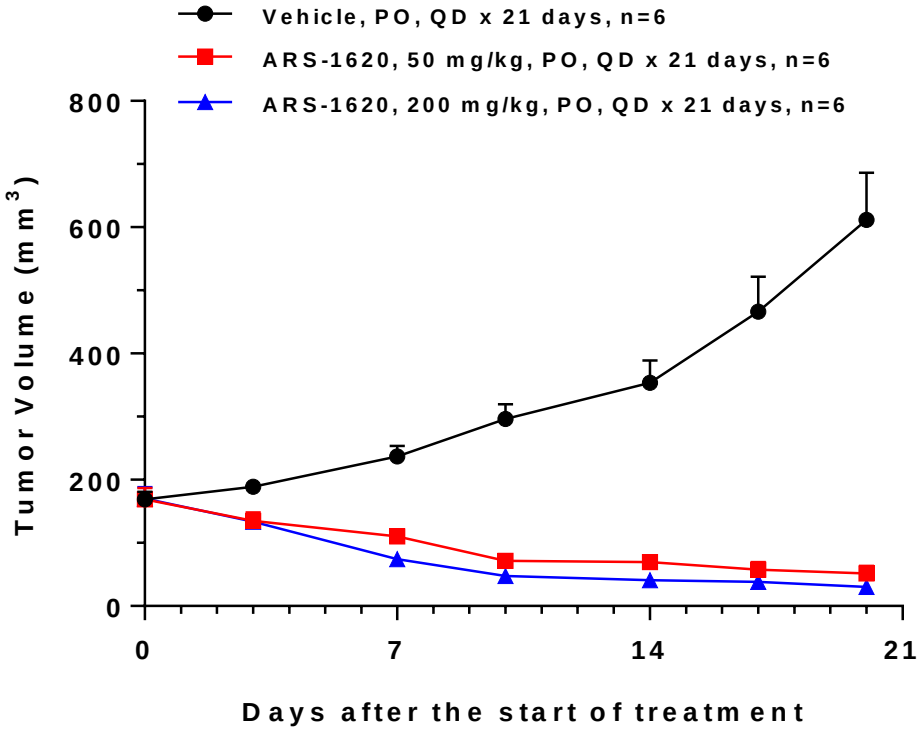


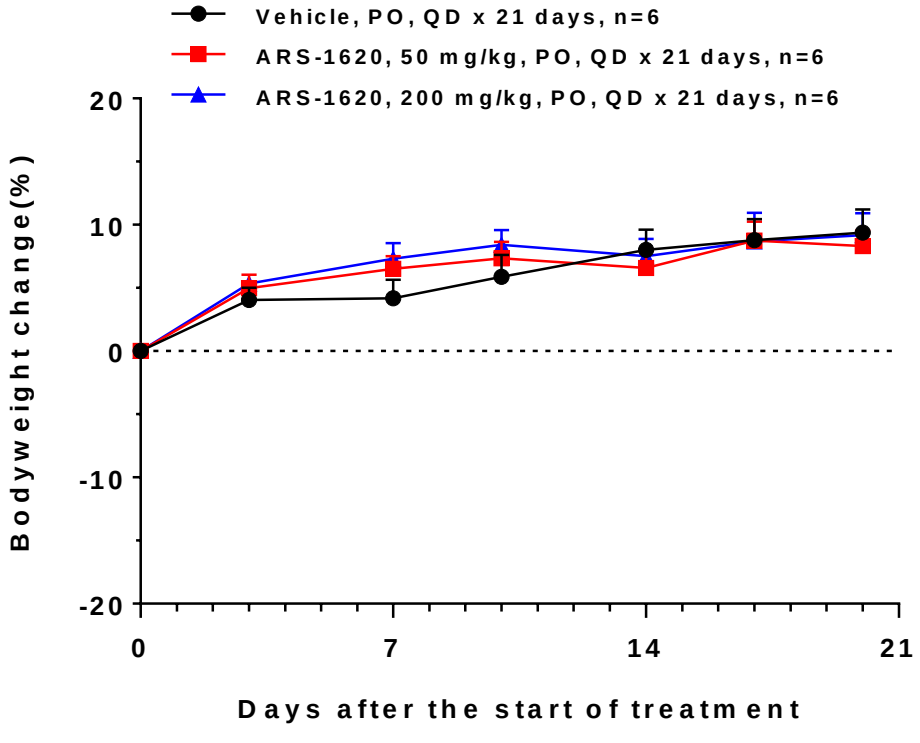
AMG 510 in Mia-pa-ca-2 pancreatic cancer xenograft model



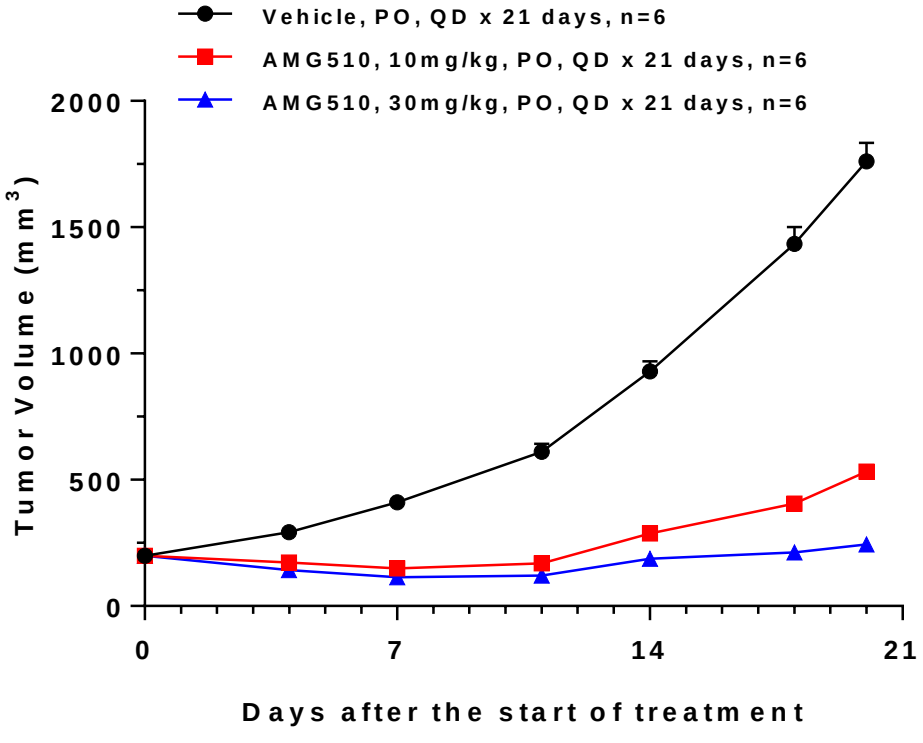


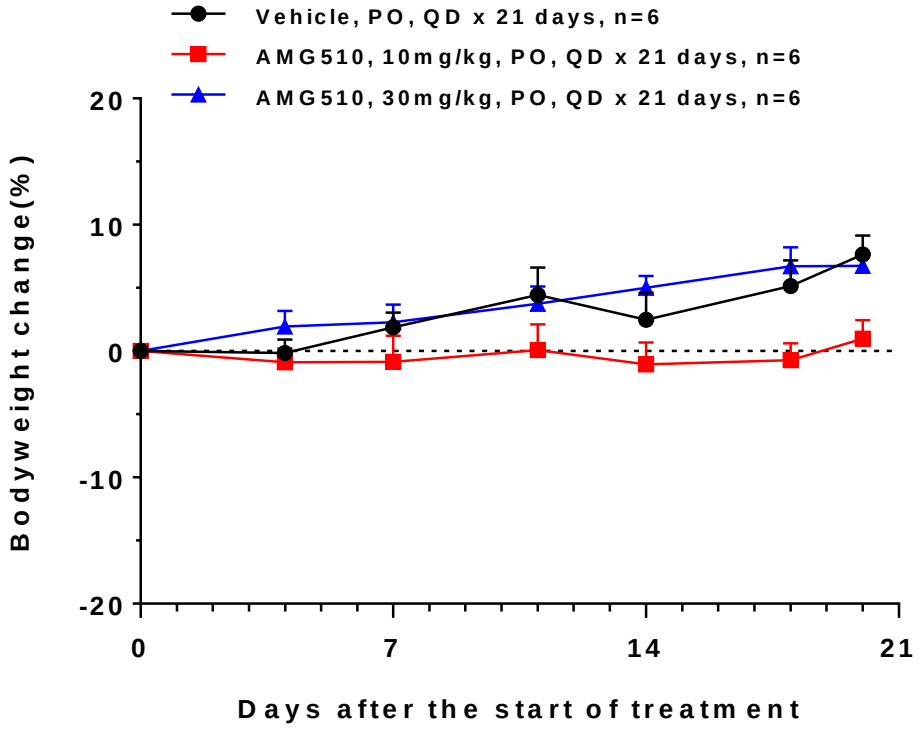
ARS-1620 in Mia-pa-ca-2 pancreatic cancer xenograft model



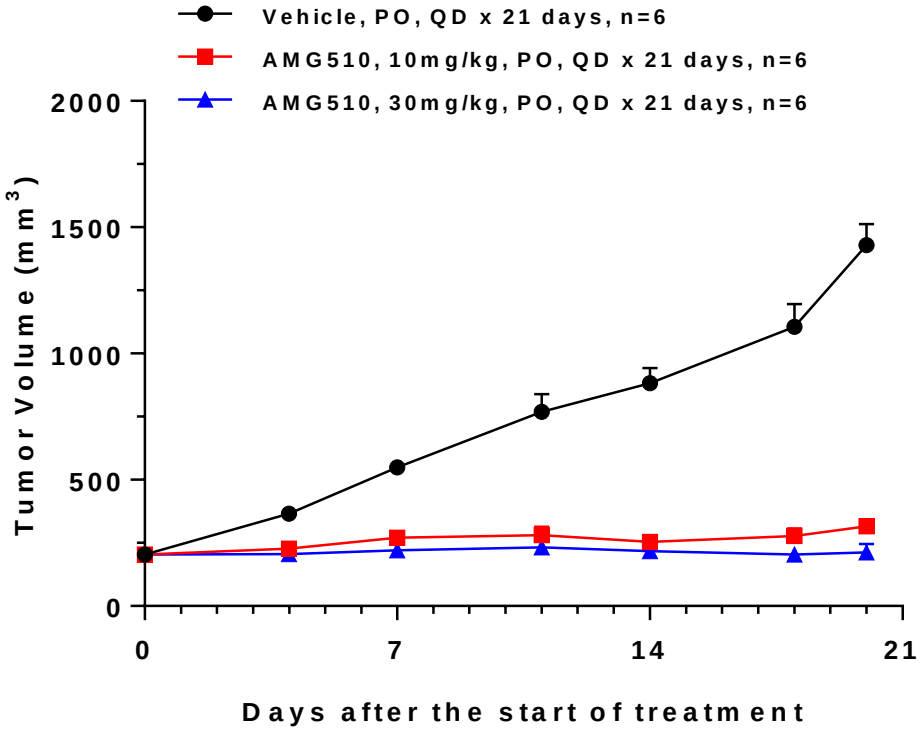


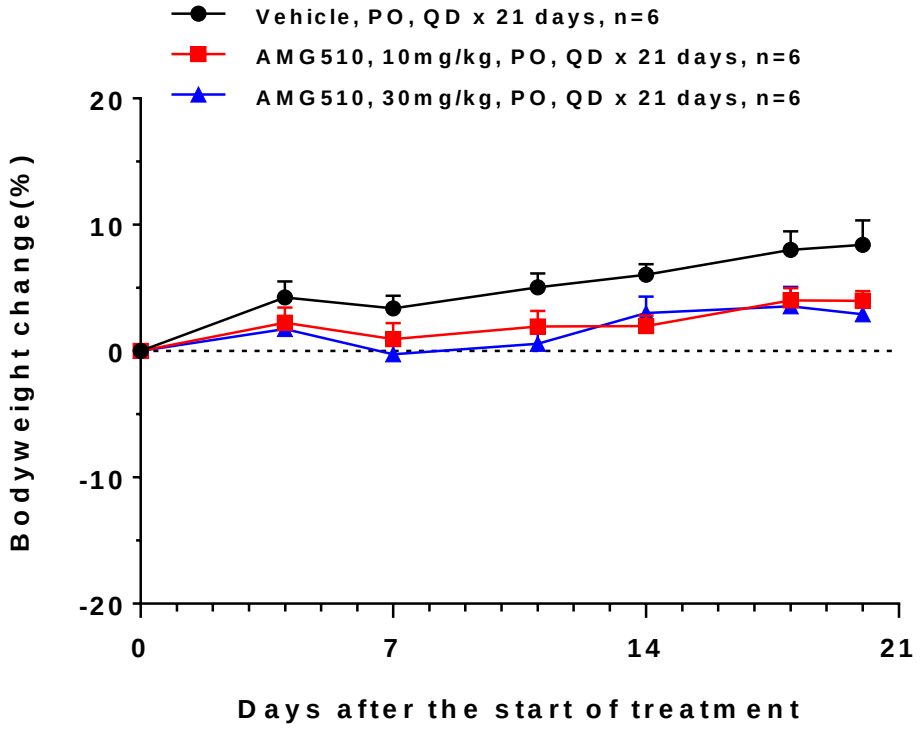
AMG 510 in SW1463 colorectal cancer xenograft model



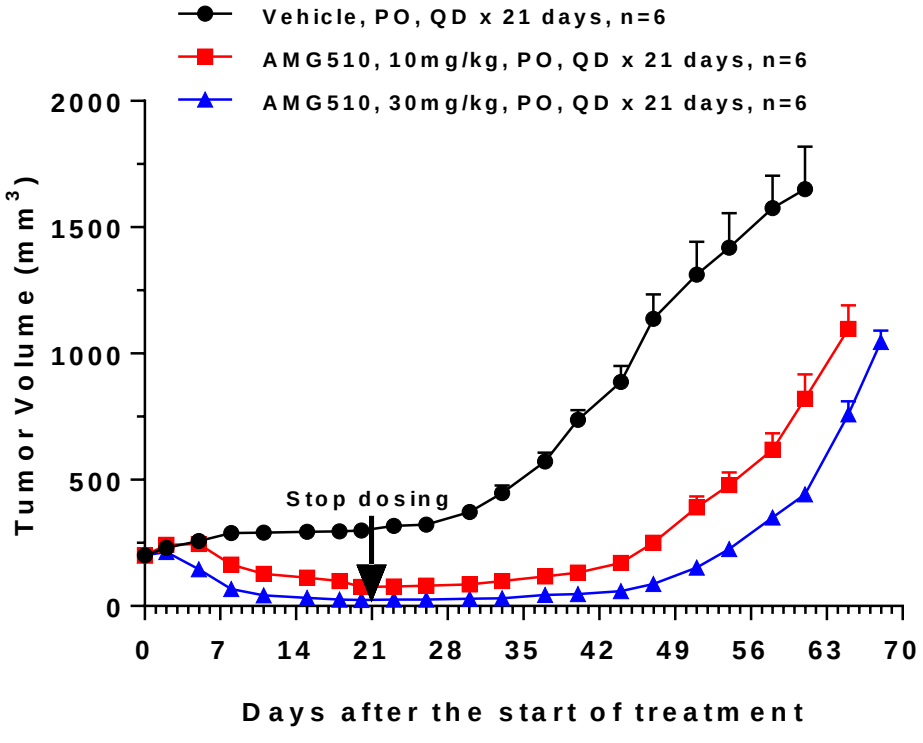


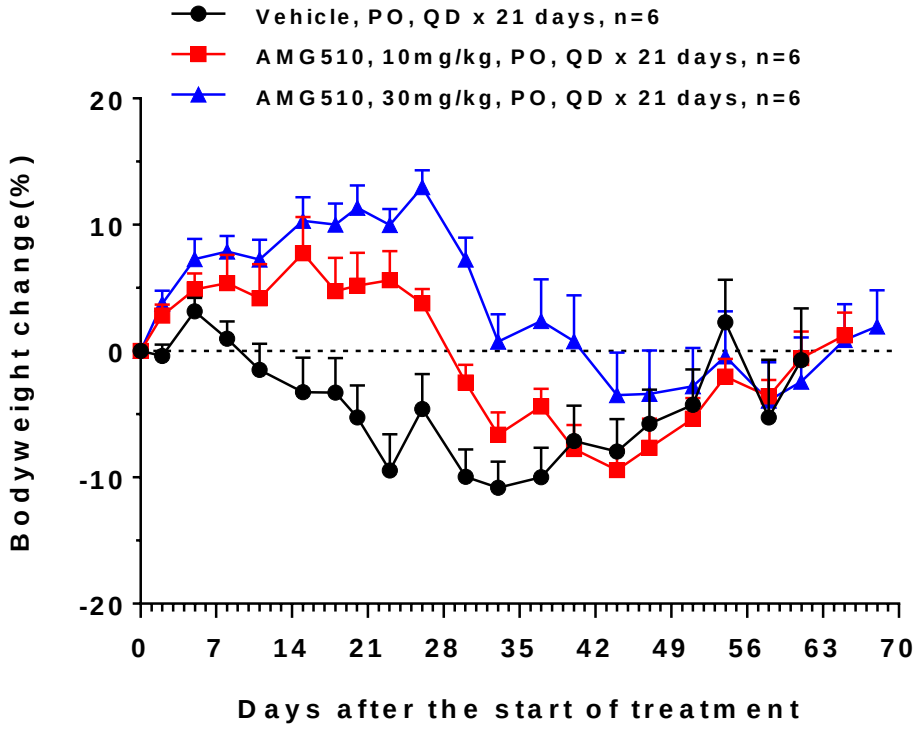
AMG 510 in SW837 colorectal cancer xenograft model





AMG 510 in SW756 cervical cancer xenograft model





KRAS^{G12C} Mutation PDX models

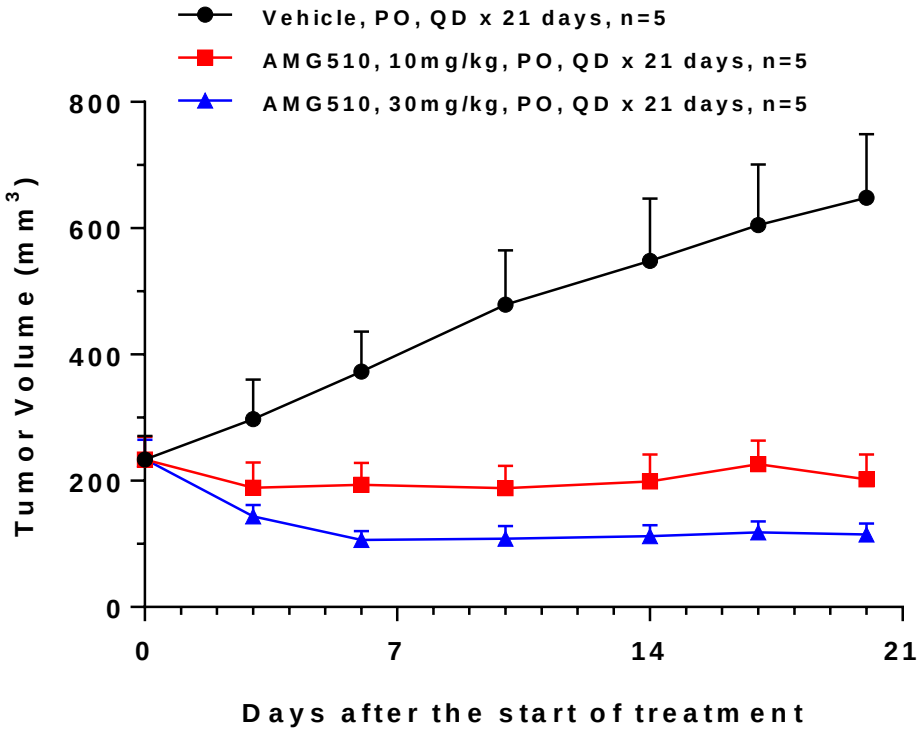
Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	T/C (%)	Model genomics
Lung cancer	LU-01-0030	Yes	AMG 510	10 mg/kg 30 mg/kg	29.8% 17.6%	KRAS p.G12C
			ARS-1620	200 mg/kg	22.5%	
	LU-01-0046	Yes	AMG 510	10 mg/kg 30 mg/kg	41.6% 46.4%	
			ARS-1620	100 mg/kg	45.9%	
	LU-01-0361	Yes	In plan			
	LU-01-0462	Yes	AMG 510	30 mg/kg 100 mg/kg	15.8% 13.0%	

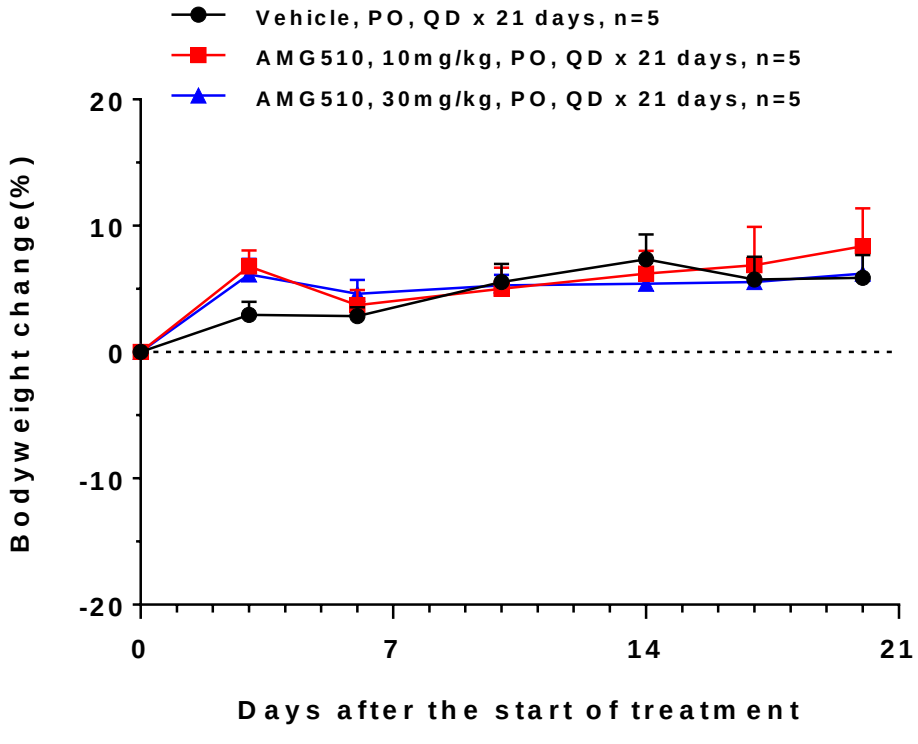
$KRAS^{G12C}$ Mutation PDX models

Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	T/C (%)	Model genomics
Colorectal cancer	CO-04-0070	Yes	AMG 510	10 mg/kg 30 mg/kg	22.2% 7.9%	KRAS p.G12C
	CO-04-0307	Yes	AMG 510	10 mg/kg 30 mg/kg	31.0% 11.3%	
	CO-04-0310	Yes	In plan			
	CO-04-0315	Yes	AMG 510	10 mg/kg 30 mg/kg	29.7% 18.4%	
Gastric cancer	ST-02-0331	Yes	In plan			

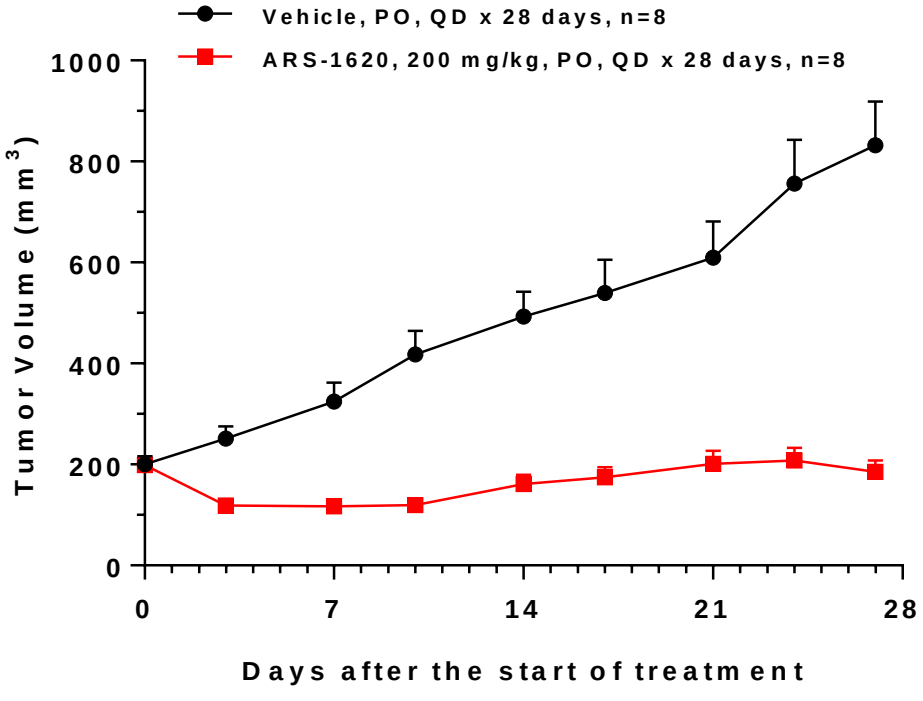
$T/C\ (\%) = T_{RTV} / C_{RTV} \times 100\ \%$, $RTV = V_t / V_0$
T_{RTV} : relative tumor volume of treatment group, C_{RTV} : relative tumor volume of control group

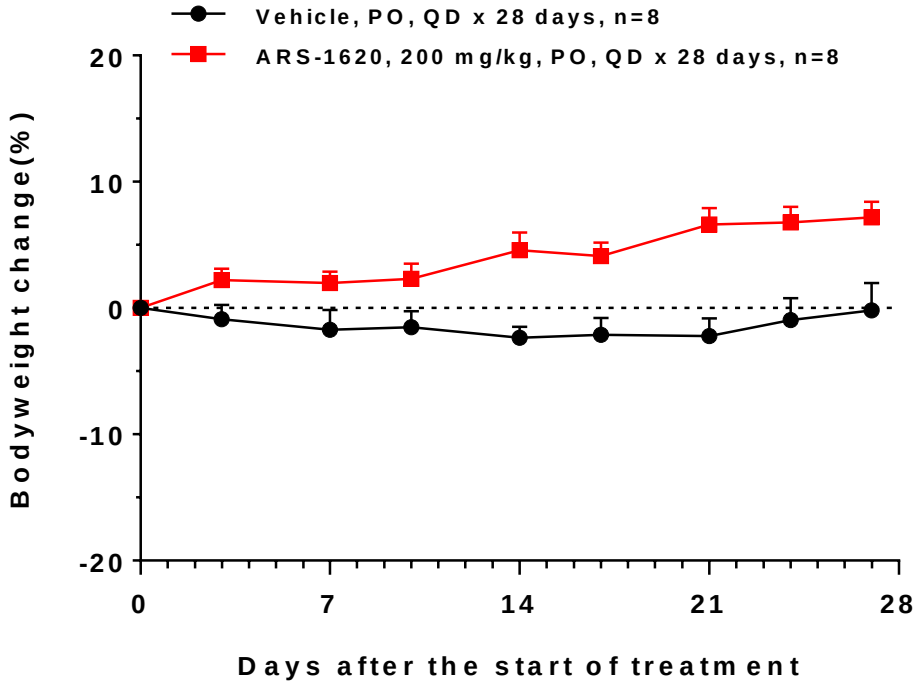
AMG 510 in LU-01-0030 non-small cell lung cancer xenograft model



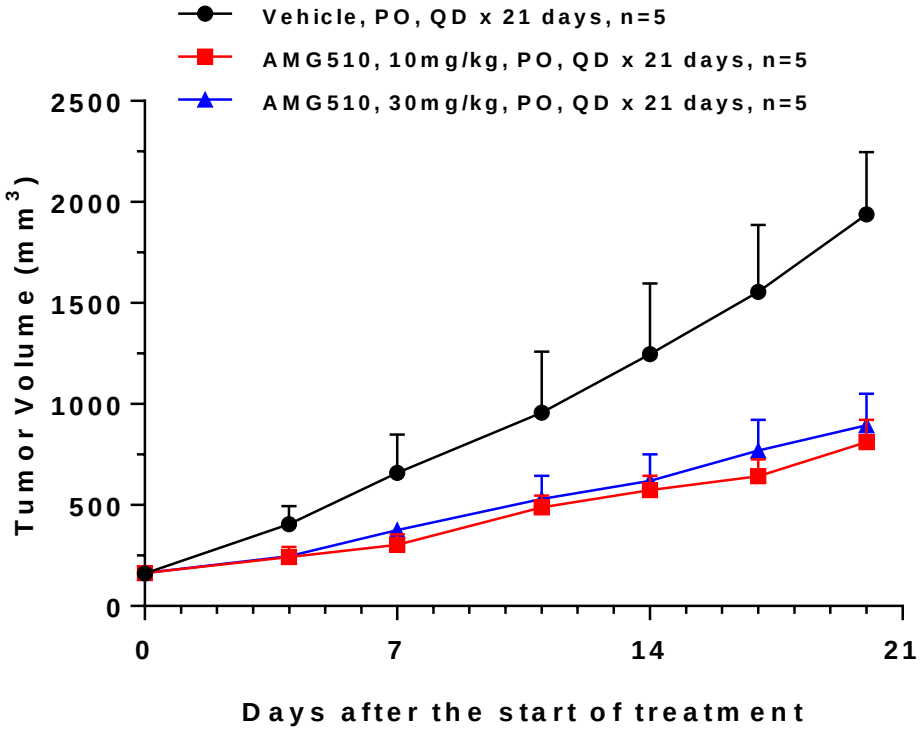


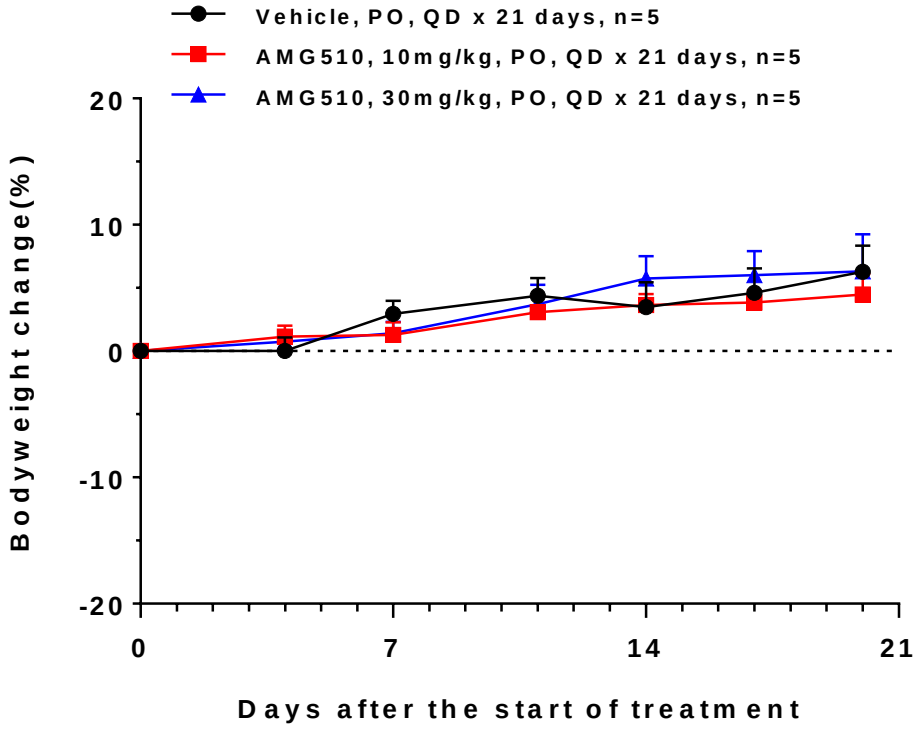
ARS-1620 in LU-01-0030 non-small cell lung cancer xenograft model



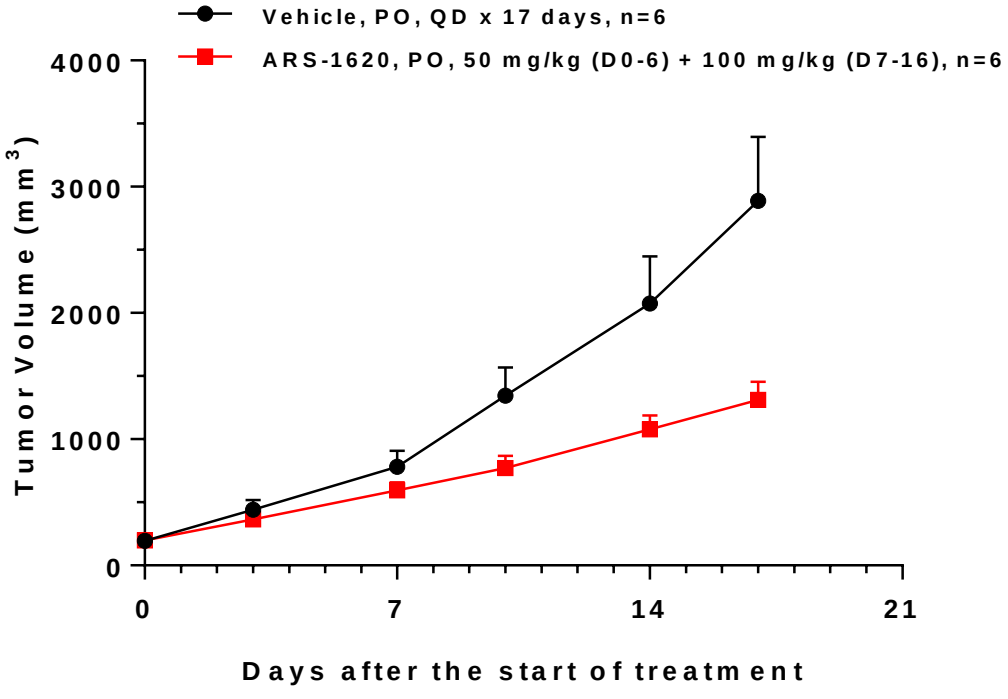


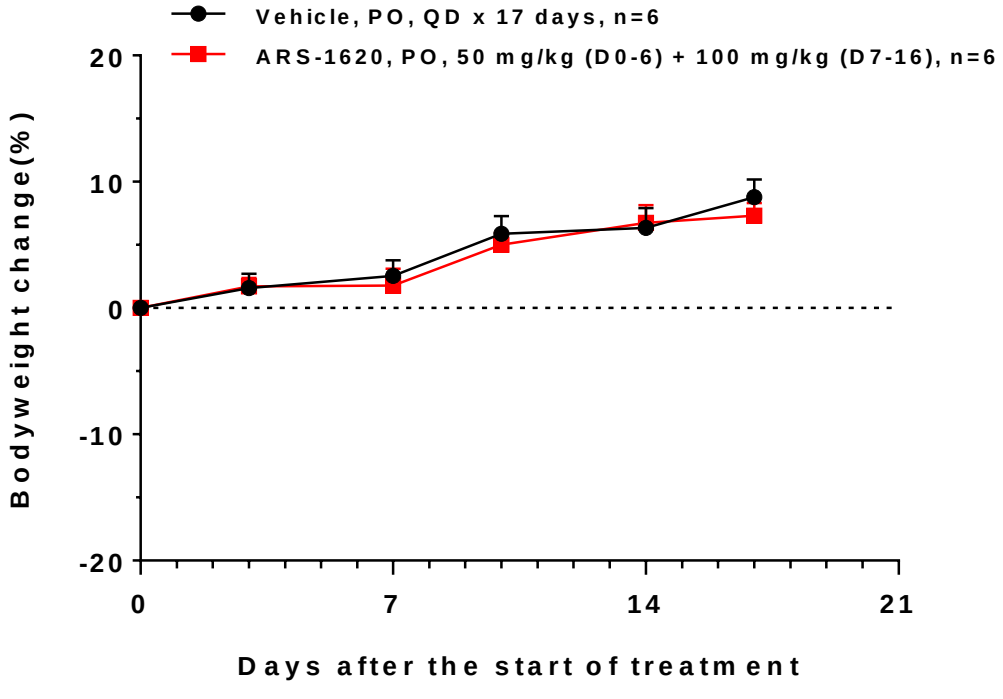
AMG 510 in LU-01-0046 non-small cell lung cancer xenograft model



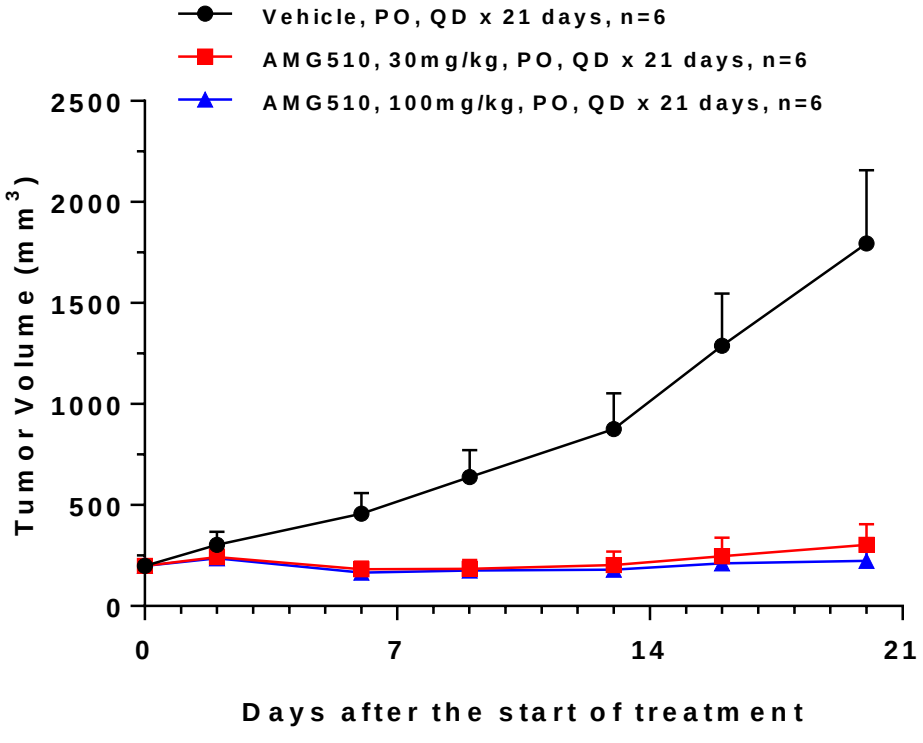


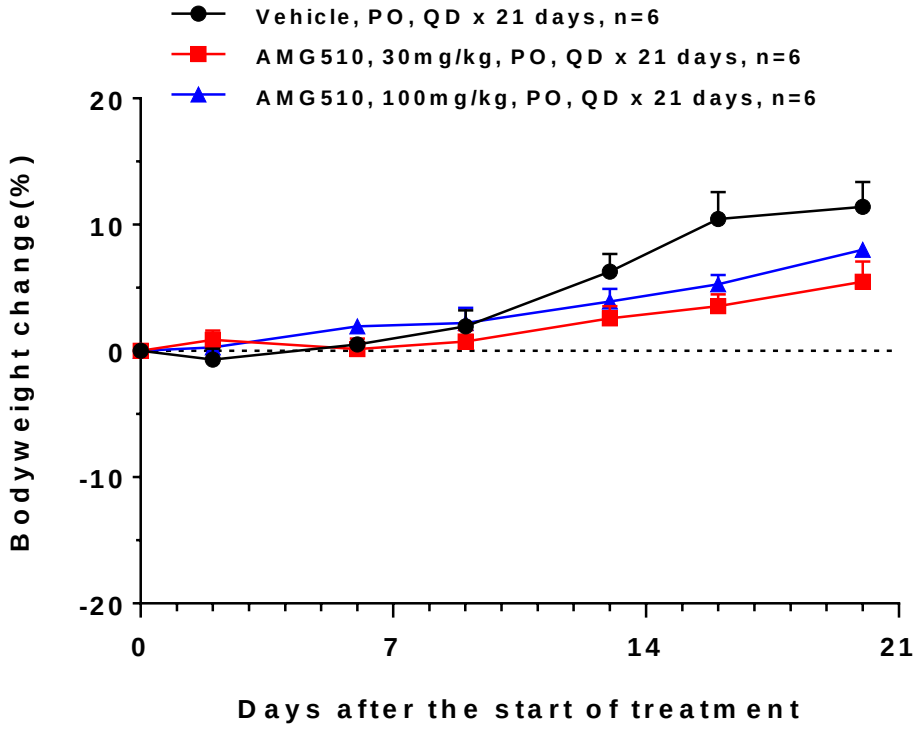
ARS-1620 in LU-01-0046 non-small cell lung cancer xenograft model



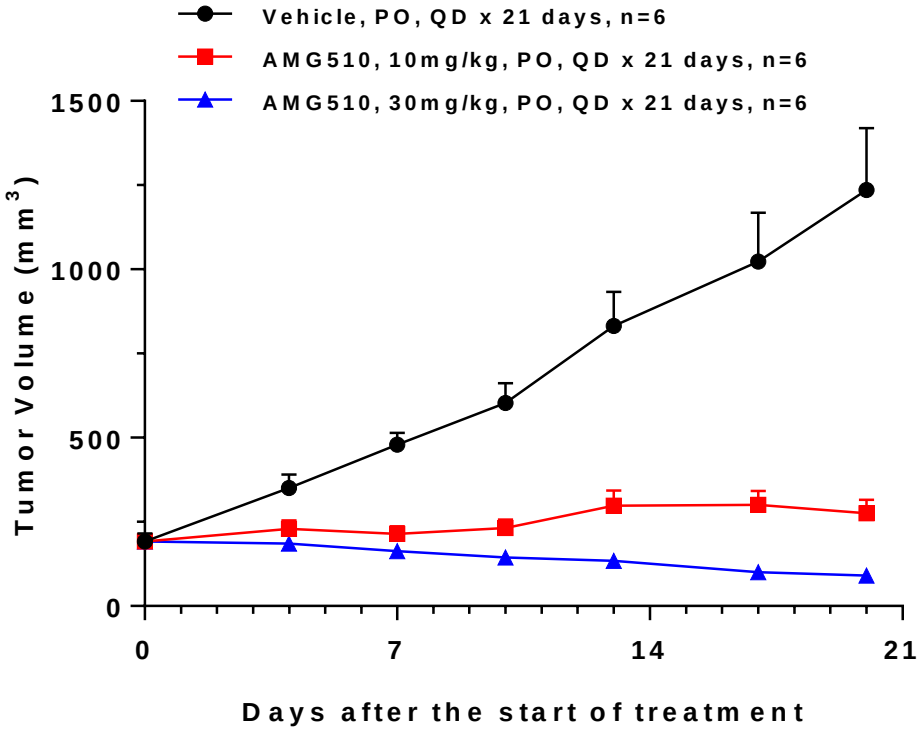


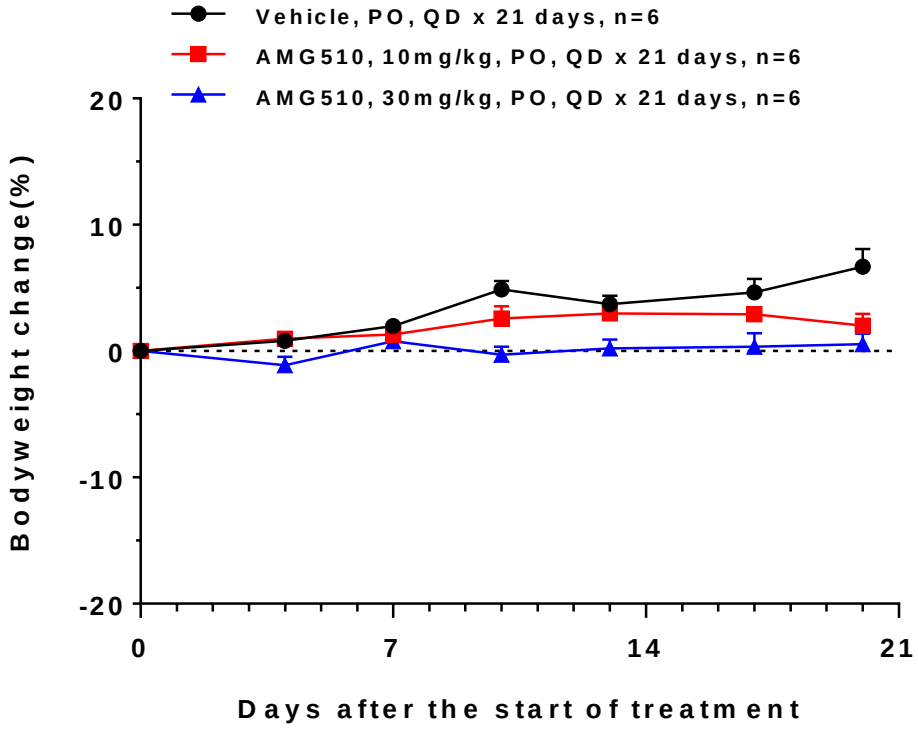
AMG 510 in LU-01-0462 non-small cell lung cancer xenograft model



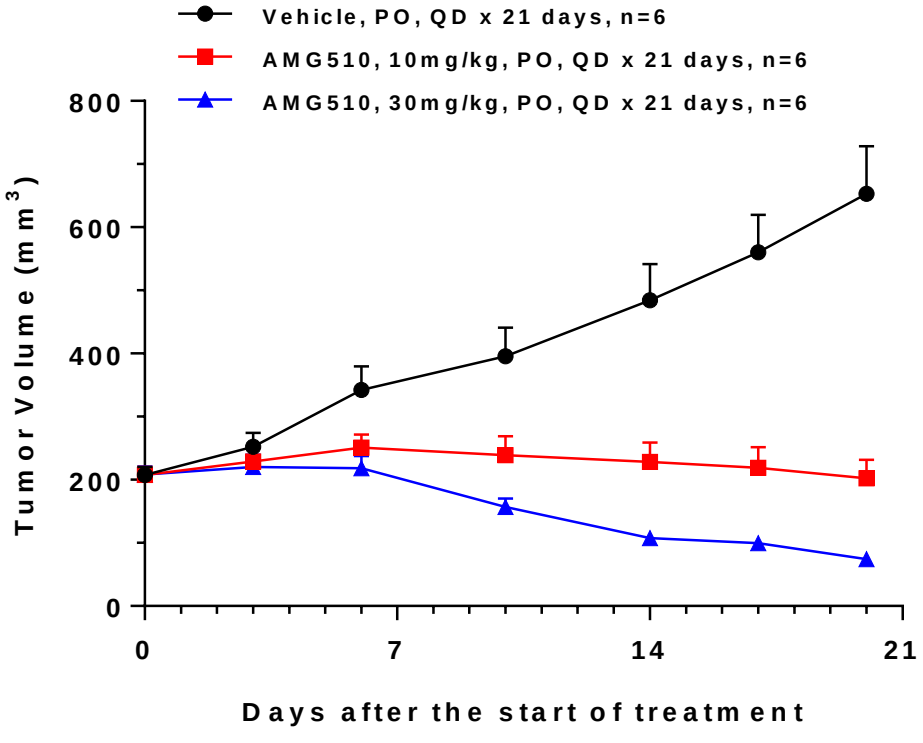


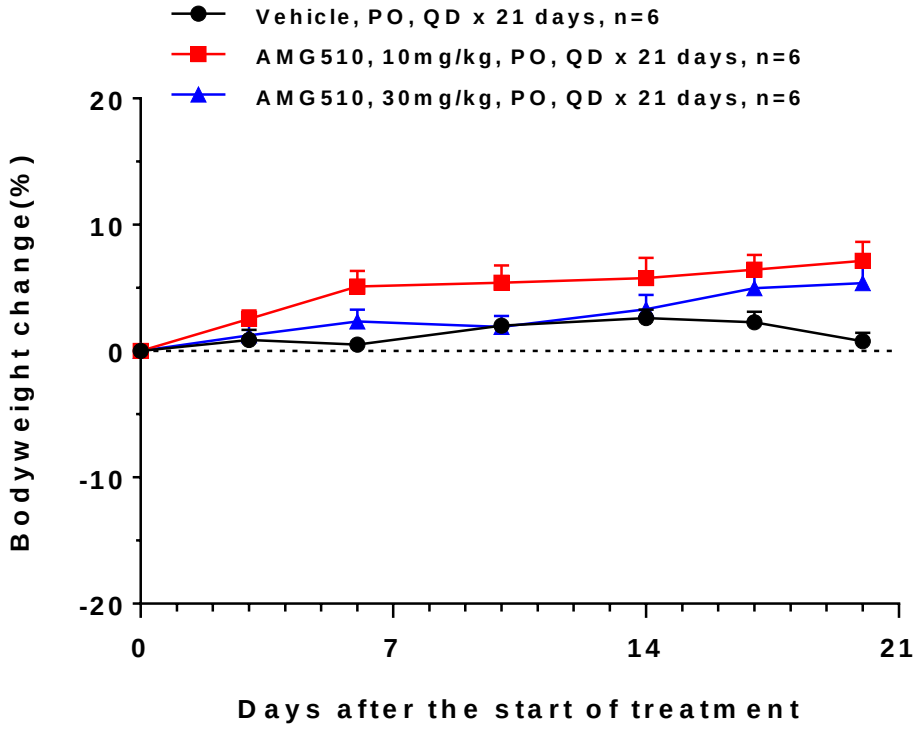
AMG 510 in CO-04-0070 colorectal cancer xenograft model



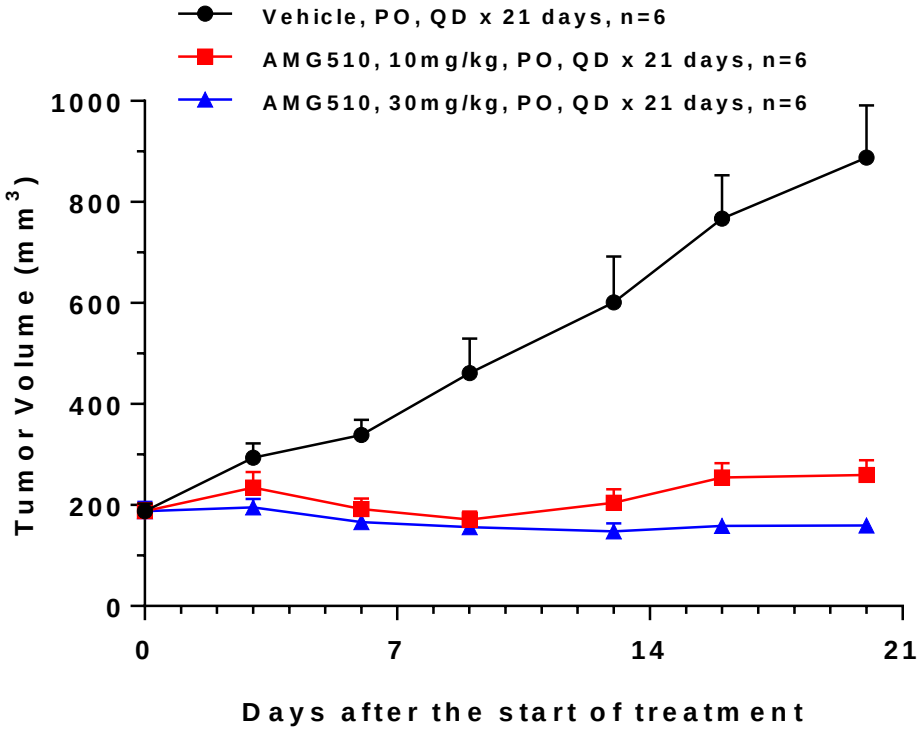


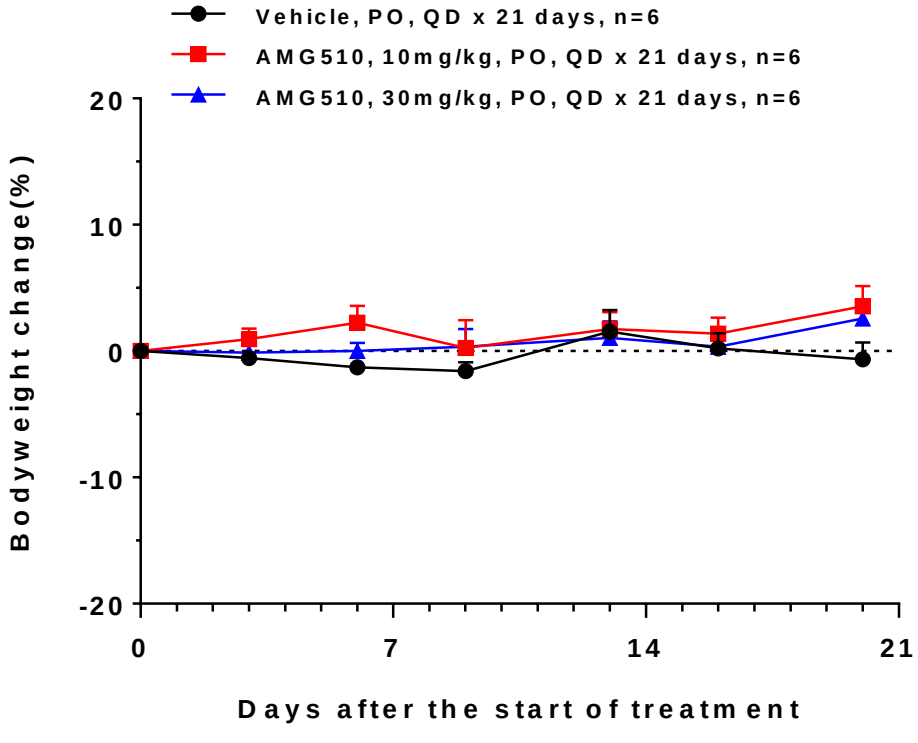
AMG 510 in CO-04-0307 colorectal cancer xenograft model



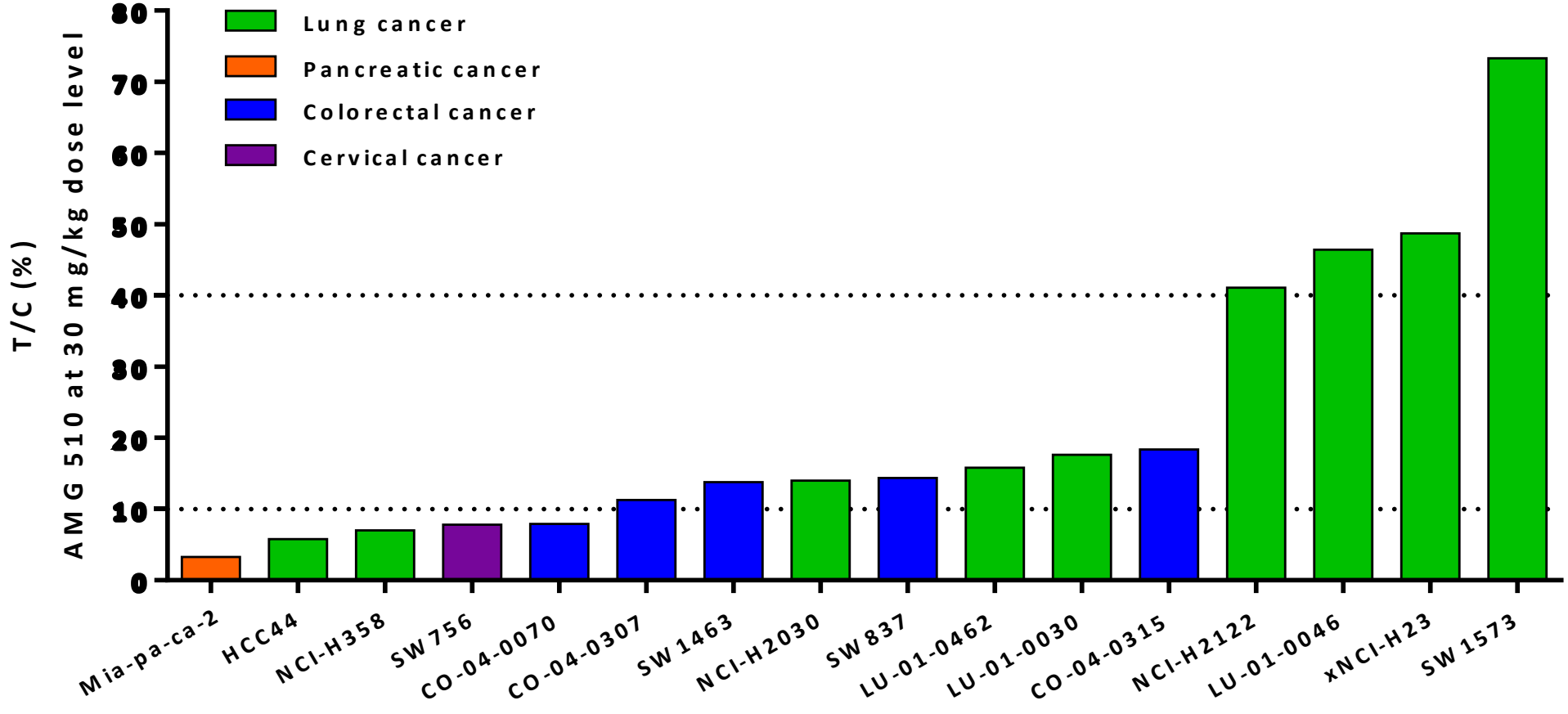


AMG 510 in CO-04-0315 colorectal cancer xenograft model





AMG 510 *in vivo* validation across KRAS^{G12C} models



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