RAF-MEK1/2 related *in vivo* models

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Outline

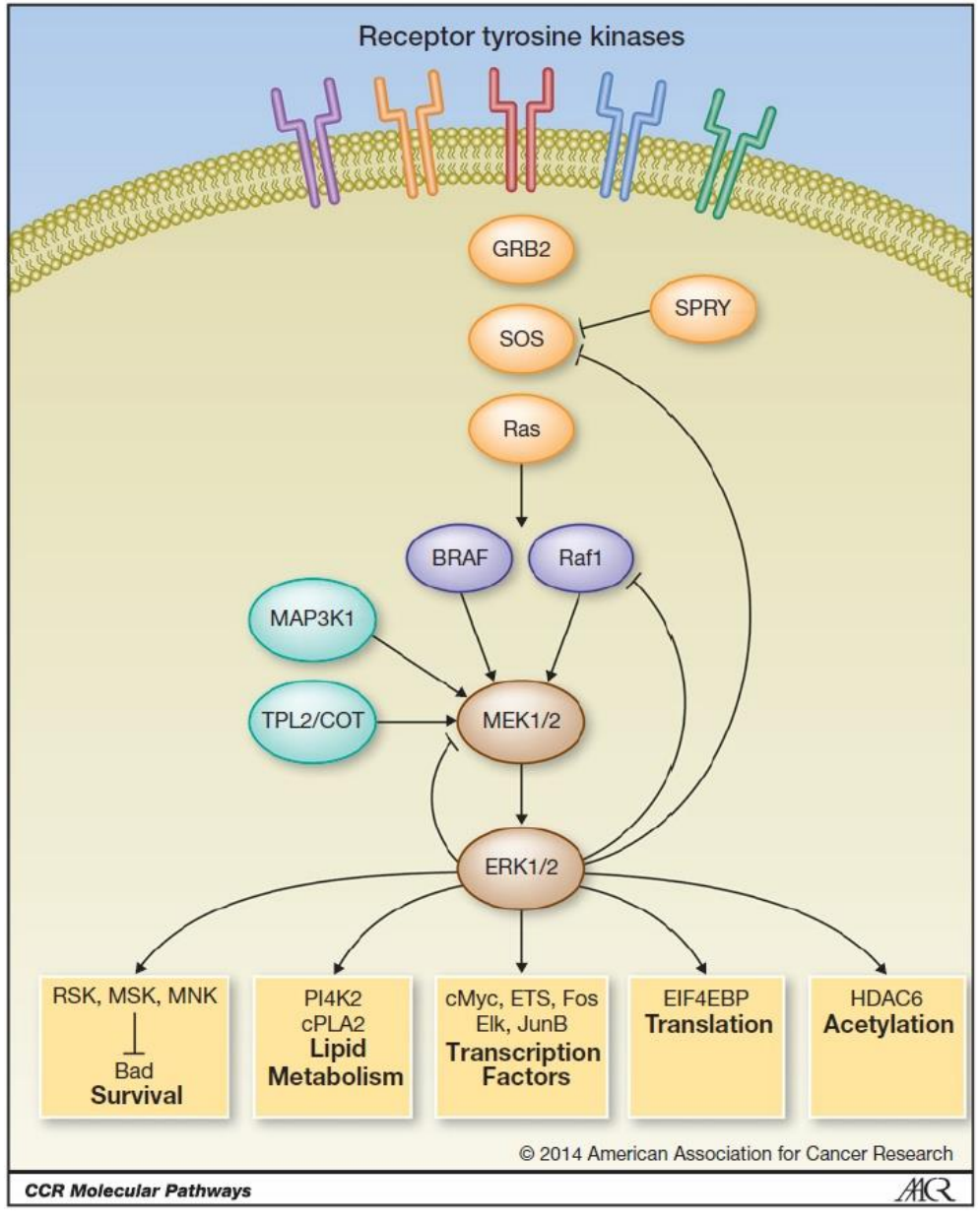
- RAF-MEK1/2 biology and inhibitors
- RAF-MEK1/2 related CDX models and SOC data
- RAF-MEK1/2 related PDX models and SOC data

RAF-MEK1/2 pathway biology

- MAPKKK (MAP3K) is a family of kinases which phosphorylate MAPKK. BRAF, RAF1 and ARAF are among the best understood MAP3K in oncology.

- MEK (MAPKK) is a family of kinases which phosphorylate MAPK. Among the 7 members of MEK family, MEK1/2 plays key role in mediating RAS-RAF-MEK1/2-ERK1/2 signaling pathway.

- Upon activation, MEK1/2 can phosphorylate ERK1/2 at Ser and Thr residues, which further stimulates cell growth and inhibits cell apoptosis.



RAF-MEK1/2 role in disease

- RAF-MEK1/2 inhibitors have been proven effective in suppressing the growth of cancers with aberrant RAS-RAF-MEK1/2-ERK1/2 signaling

- RAS-RAF-MEK1/2-ERK1/2 pathway aberrance includes, but not limited to:
  - BRAF mutation: melanoma 44%, papillary thyroid cancer 35-70%, ovarian cancer 30%, colon cancer 14%
  - KRAS mutation: pancreatic cancer 90%, colon cancer 35%, NSCLC 35%
  - NRAS mutation: ALL, AML 30%, melanoma 15%

- Currently, RAF-MEK1/2 inhibitors patient selection biomarkers majorly focus on BRAF mutation. Some trials also include KRAS/NRAS mutations.

RAF-targeted drugs

Drug	Inventor	Indications	Status
Sorafenib	Bayer	HCC and other advanced tumors	Launched
Vemurafenib	Plexxikon/Genentech	BRAF V600 mutant metastatic melanoma	Launched
Dabrafenib	GSK	BRAF V600 mutant metastatic melanoma	Launched
RAF265	Novartis	Advanced melanoma	Phase II
XL281	Exelixis	Solid tumor	Phase I
ARQ-736	ArQule	Advanced solid tumors	Phase I
LGX818	Novartis	Advanced melanoma	Phase I
RO5212054	Roche	Advanced solid tumors	Phase I

MEK1/2-targeted drugs

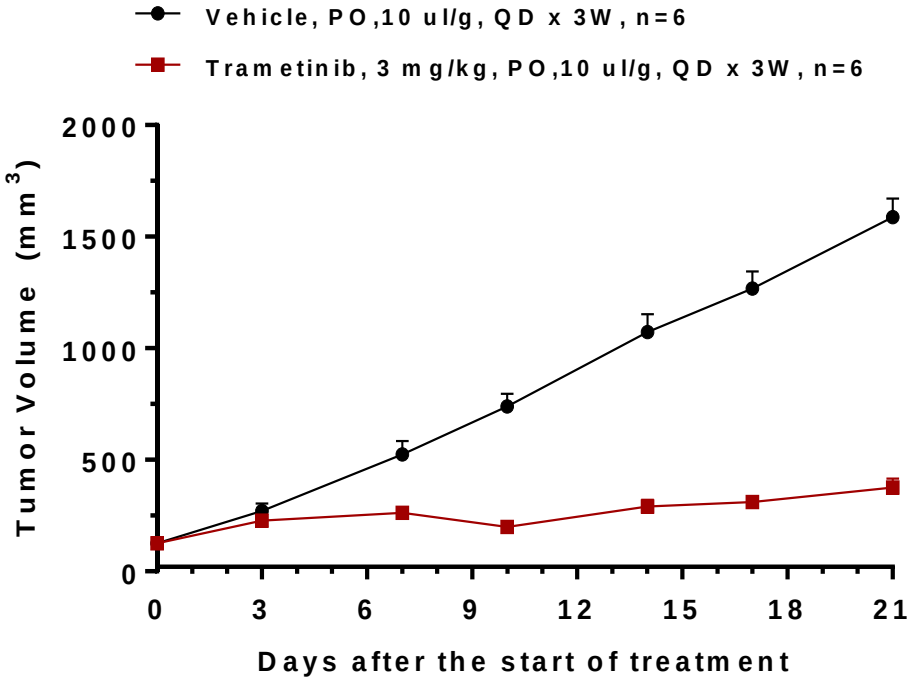
Drug	Inventor	Indications	Status
Trametinib	GSK	BRAF V600 mutant metastatic melanoma	Launched
Cobimetinib	Exelixis/GNT/Roche	BRAF V600 mutant metastatic melanoma	Phase III
Binimetinib	Array/Novartis	Serous ovarian cancer, BRAF mutant melanoma, and NRAS mutant melanoma	Phase III
Selumetinib	Array/Astra Zeneca	KRAS mutant NSCLC, differentiated thyroid cancer, and neurofibromatosis type 1	Phase III
Pimasertib	Merck Serono	N-Ras mutant cutaneous melanoma	Phase II
Refametinib	Bayer	RAS mutant HCC, pancreatic cancer, biliary tract cancer	Phase II
TAK-733	Takeda	Solid tumors	Phase I
RG7304	Chugai/Roche	Solid tumors	Phase I
E6201	Eisai	Solid tumors	Phase I

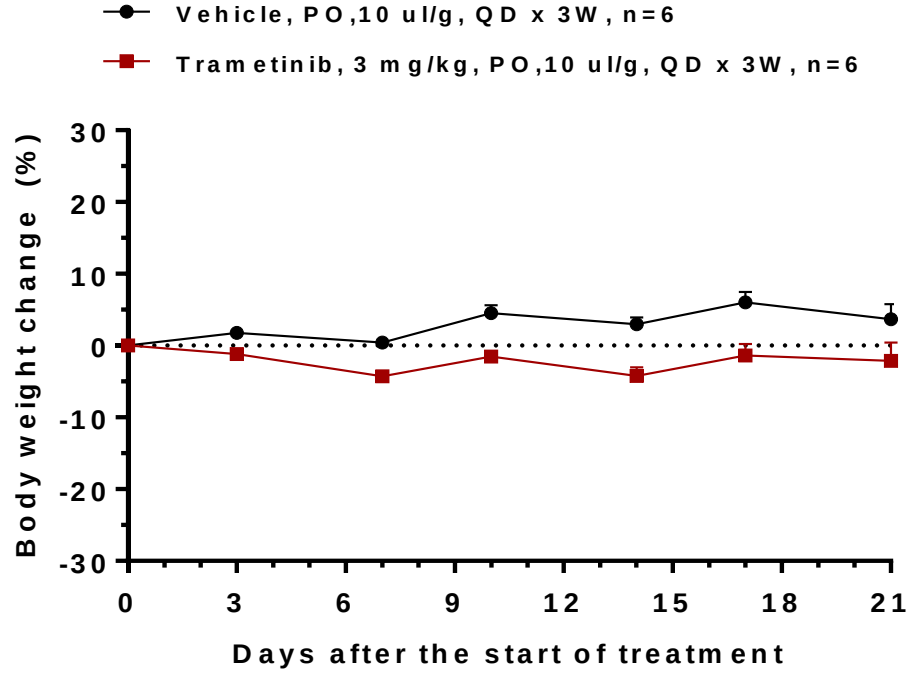
RAF-MEK1/2 related CDX models

Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	TGI	Model genetics
Colon	HT29	Yes	Trametinib	3 mg/kg, PO, QD	83%	BRAF V600E
				0.2 mg/kg, PO, QD	59%	BRAF V600E
Melanoma	A375	Yes	Trametinib	0.6 mg/kg, PO, QD	91%	BRAF V600E
Lung	A549	Yes	Trametinib	0.6 mg/kg, PO, QD	64%	KRAS G12S
Lung	NCI-H358	Yes	Trametinib	1 mg/kg, PO, QD	93%	KRAS G12C
Melanoma	COLO 829	Yes	Dabrafenib	30 mg/kg, PO, QD	63%	BRAF V600E
Breast	DU4475	Yes	Dabrafenib	100 mg/kg, PO, QD	64%	BRAF V600E
Colon	COLO 205	Yes				BRAF V600E
Melanoma	SK-MEL-28	Yes				BRAF V600E

MEK1/2 inhibitors in HT29 model

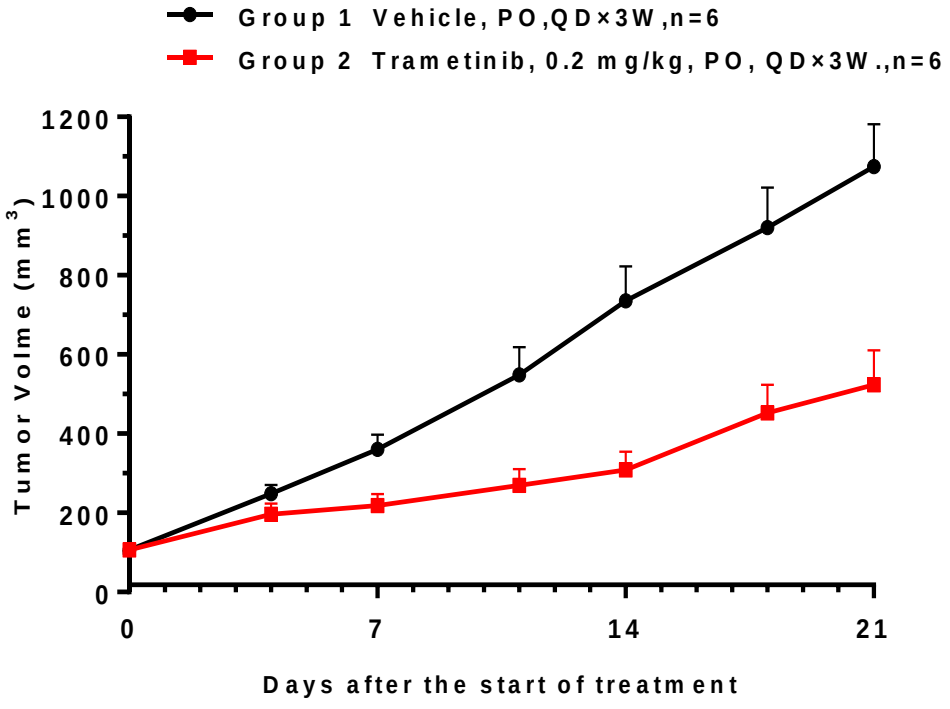
Cancer type	Model ID	Drugs tested	Dosage	TGI	Model genetics
Colon	HT29	Trametinib	3 mg/kg, PO, QD	83%	BRAF V600E

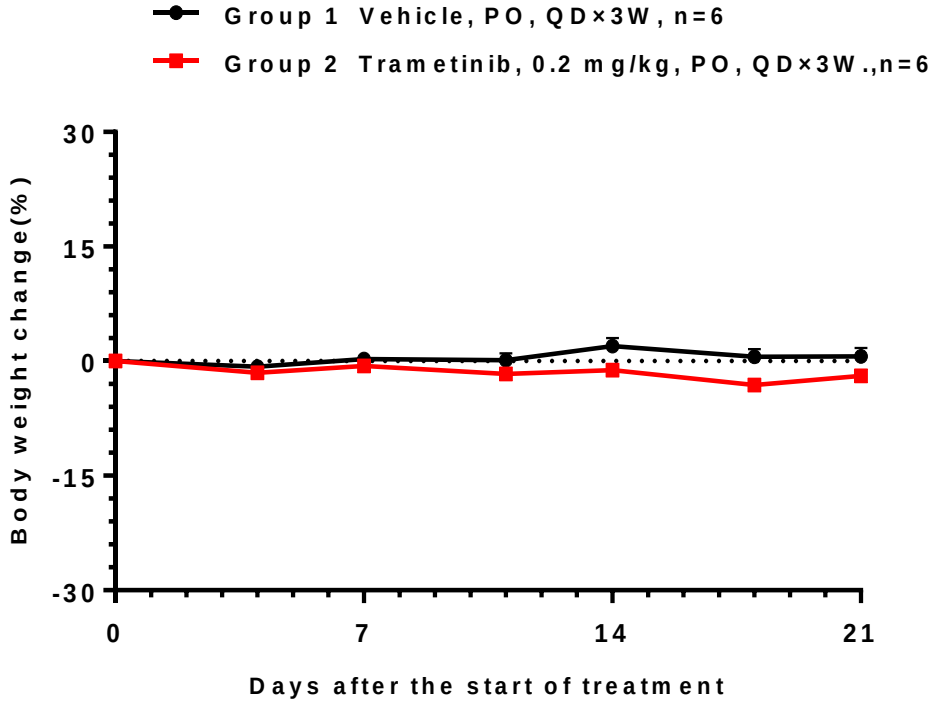




MEK1/2 inhibitors in HT29 model

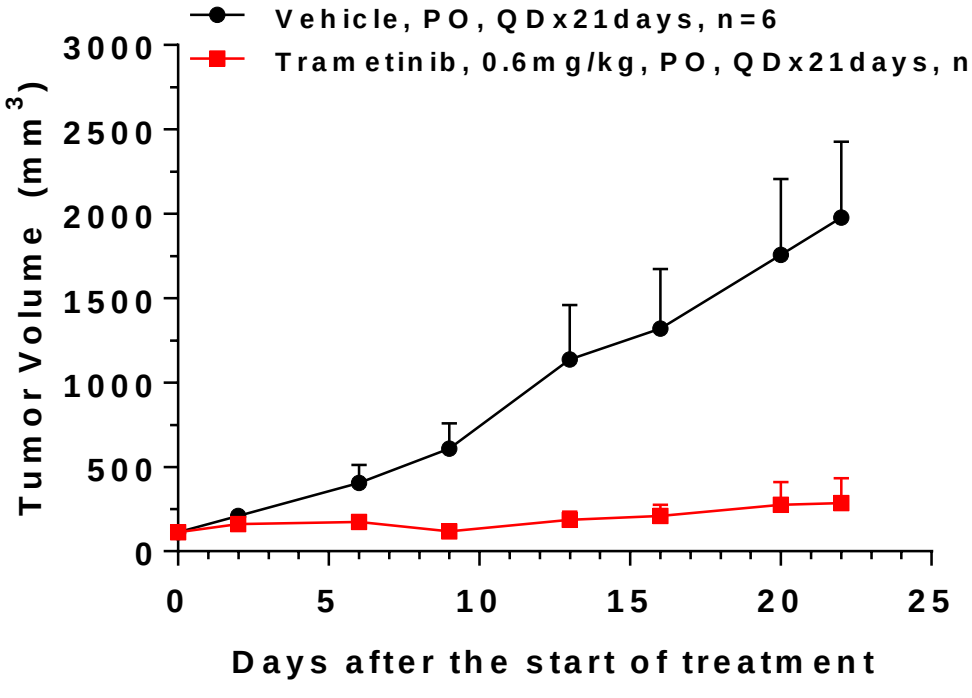
Cancer type	Model ID	Drugs tested	Dosage	TGI	Model genetics
Colon	HT29	Trametinib	0.2 mg/kg, PO, QD	59%	BRAF V600E

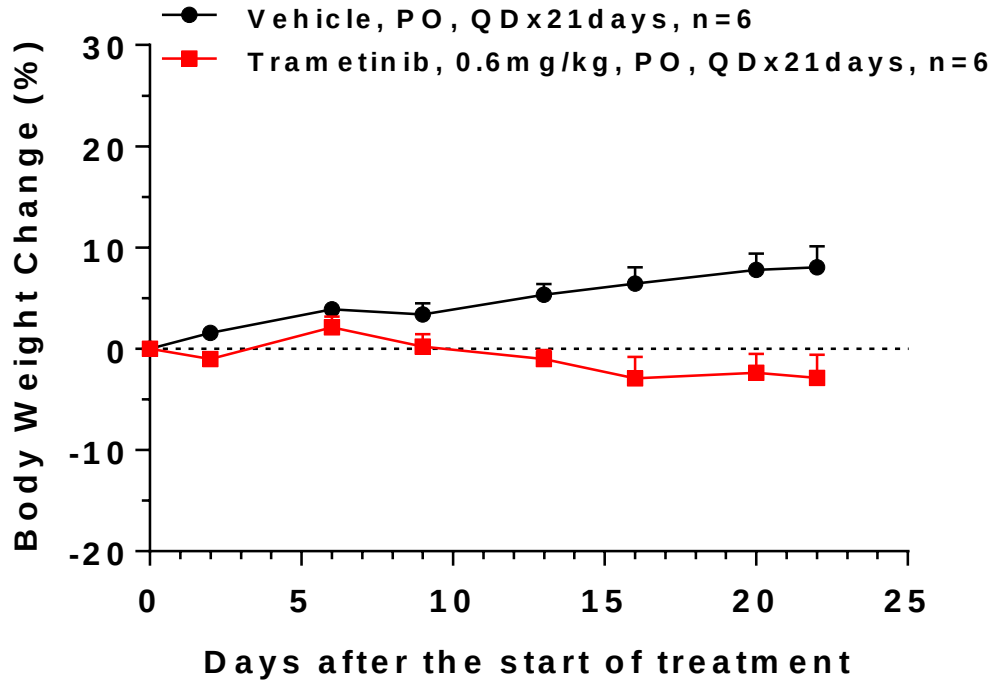




MEK1/2 inhibitors in A375 model

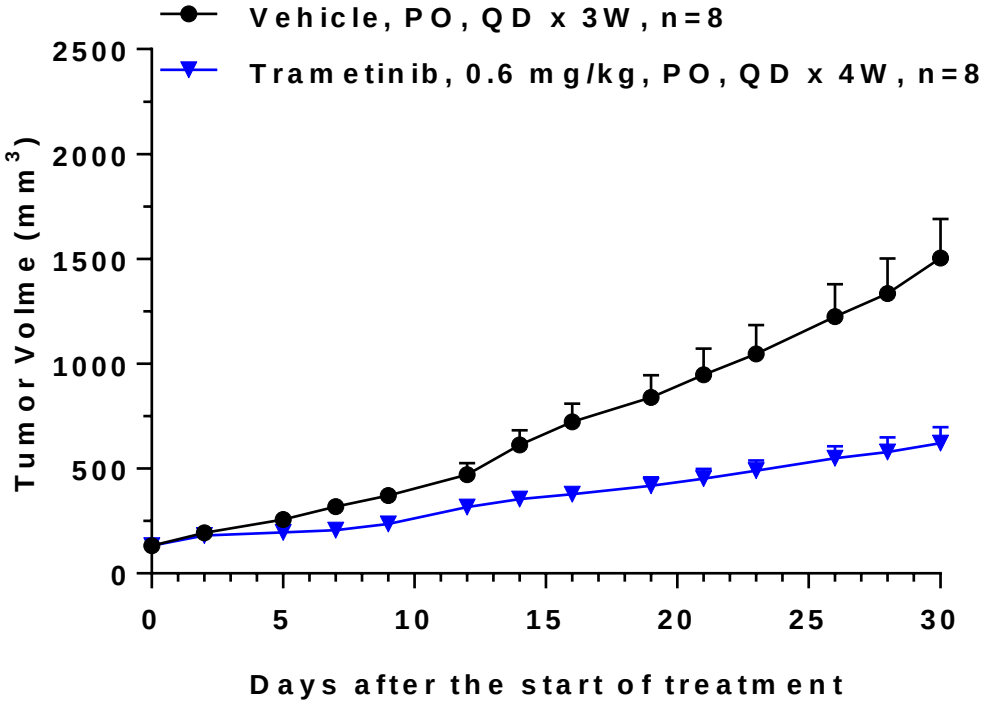
Cancer type	Model ID	Drugs tested	Dosage	TGI	Model genetics
Melanoma	A375	Trametinib	0.6 mg/kg, PO, QD	91%	BRAF V600E

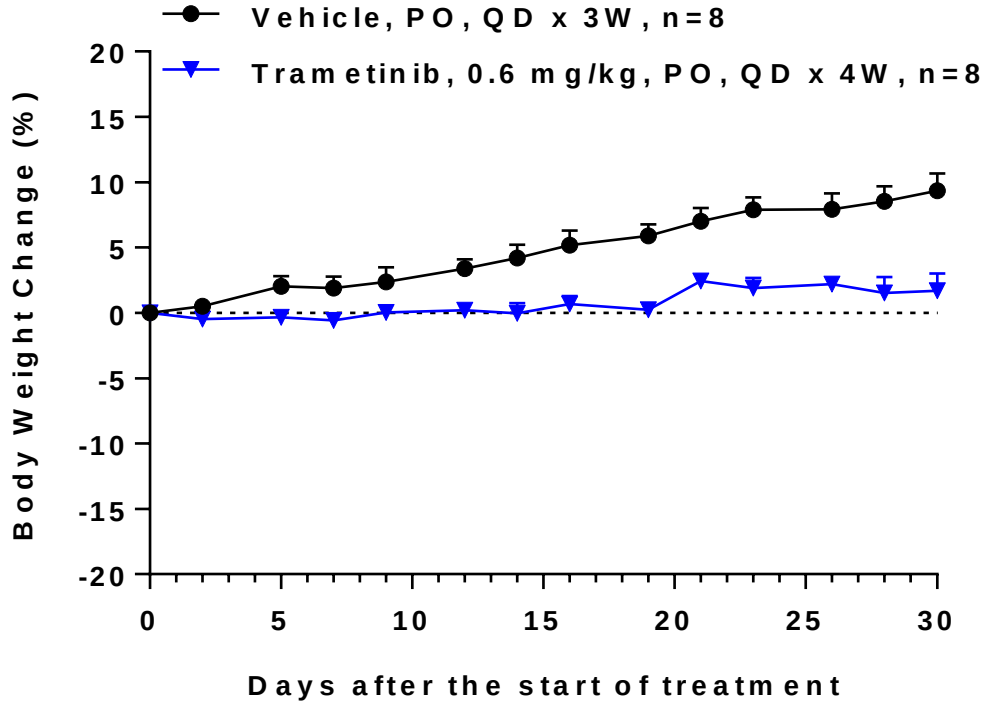




MEK1/2 inhibitors in A549 model

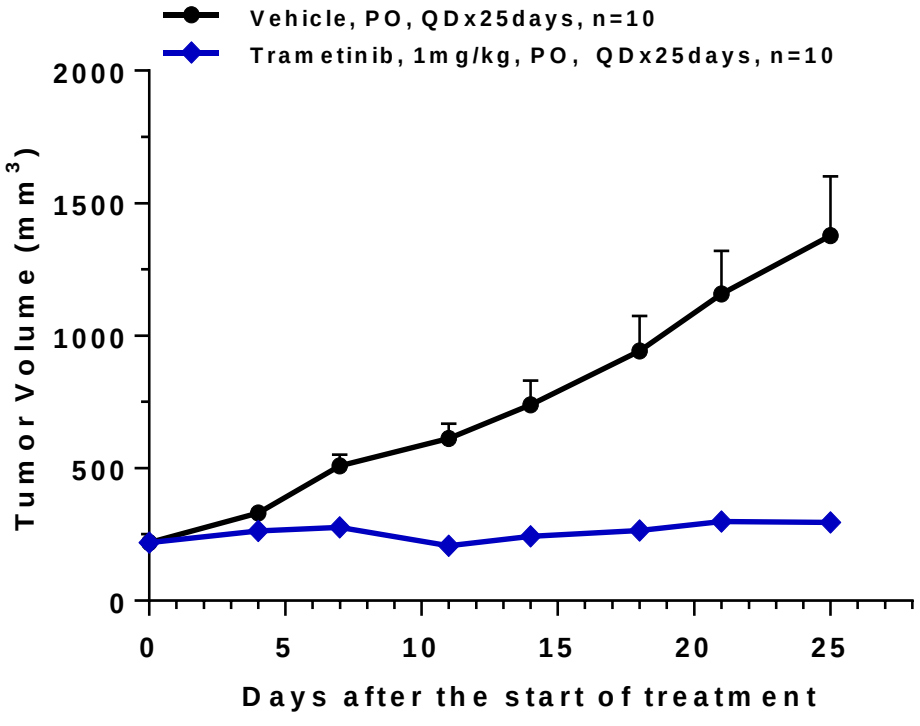
Cancer type	Model ID	Drugs tested	Dosage	TGI	Model genetics
Lung	A549	Trametinib	0.6 mg/kg, PO, QD	64%	KRAS G12S

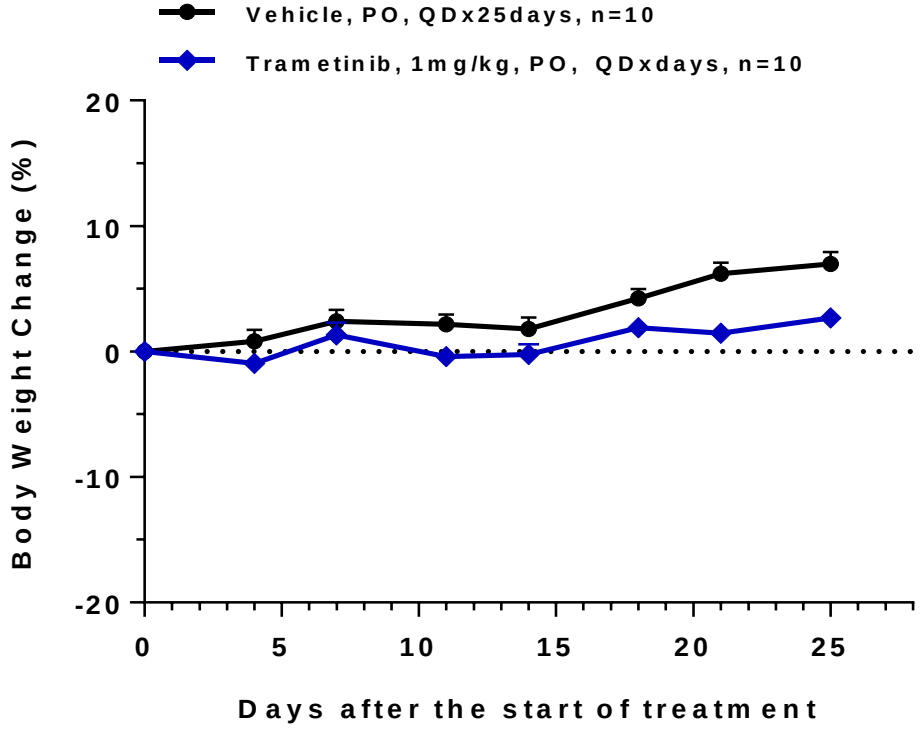




MEK1/2 inhibitors in NCI-H358 model

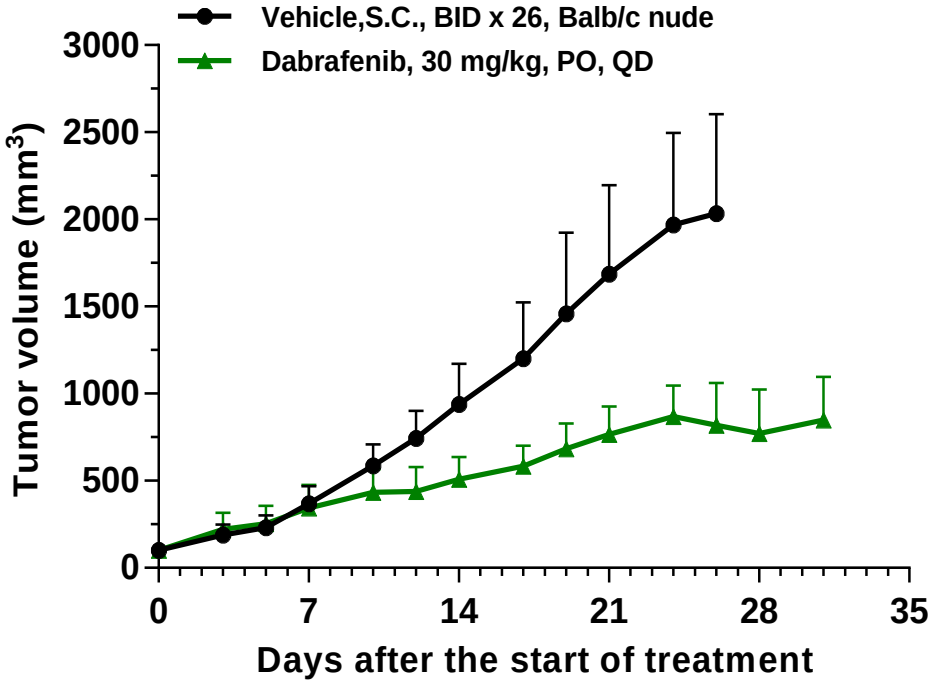
Cancer type	Model ID	Drugs tested	Dosage	TGI	Model genetics
Lung	NCI-H358	Trametinib	1 mg/kg, PO, QD	93%	KRAS G12C

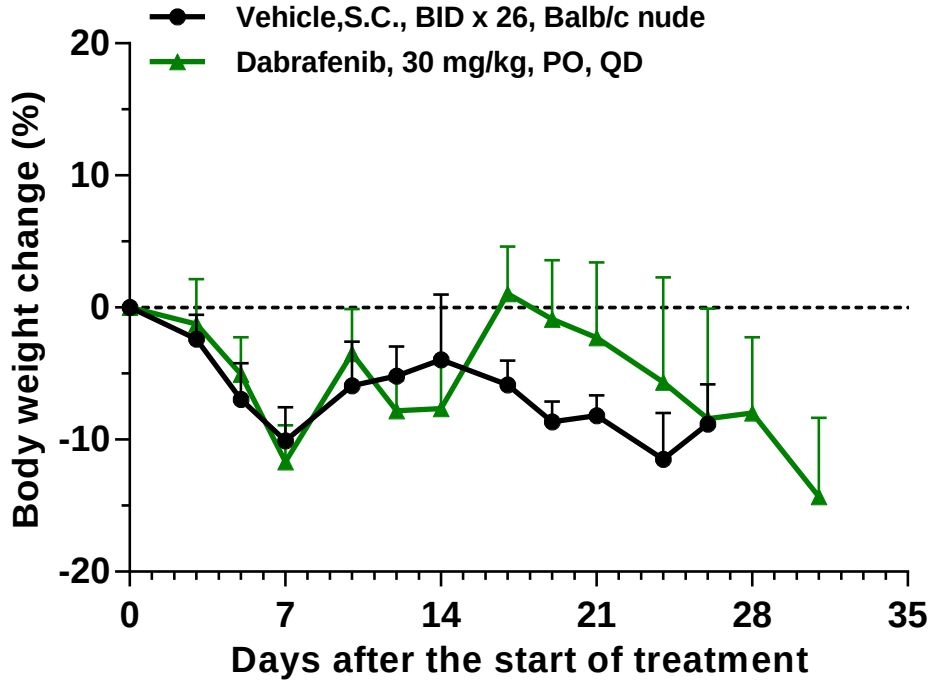




RAF inhibitors in COLO 829 model

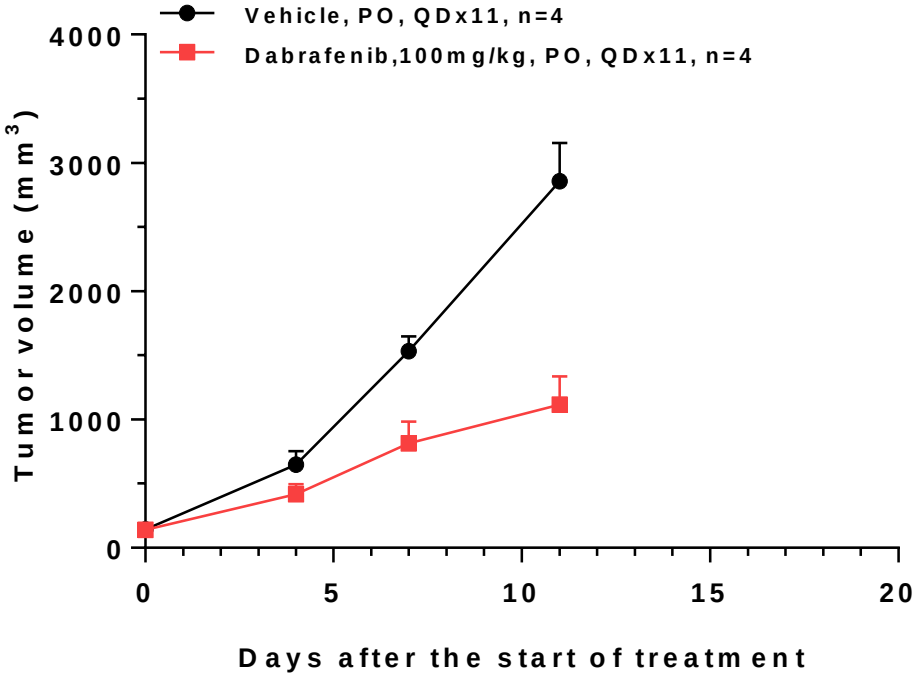
Cancer type	Model ID	Drugs tested	Dosage	TGI	Model genetics
Melanoma	COLO 829	Dabrafenib	30 mg/kg, PO, QD	63%	BRAF V600E

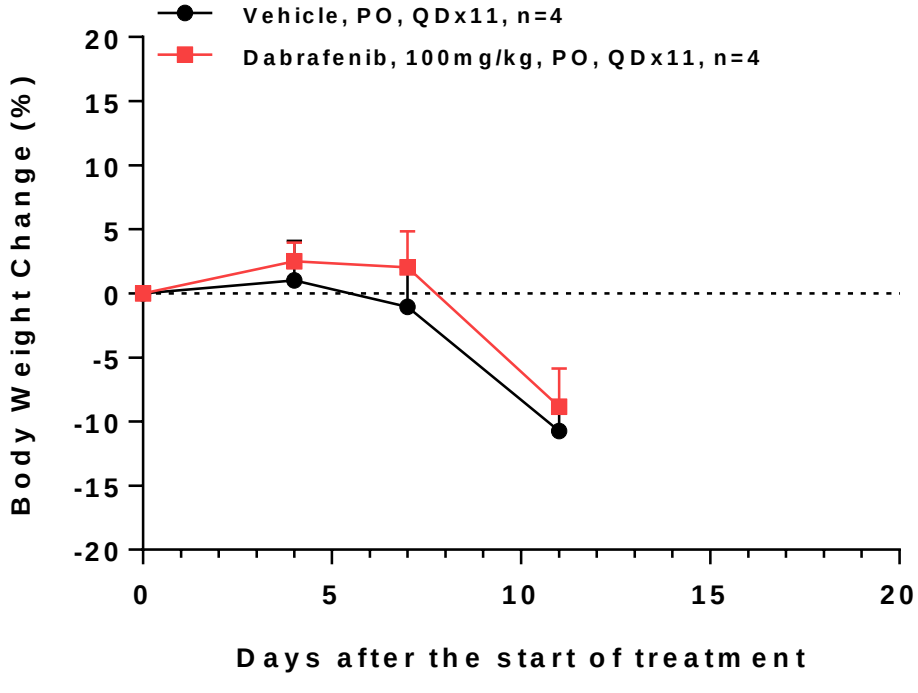




RAF inhibitors in DU4475 model

Cancer type	Model ID	Drugs tested	Dosage	TGI	Model genetics
Breast	DU4475	Dabrafenib	100 mg/kg, PO, QD	64%	BRAF V600E





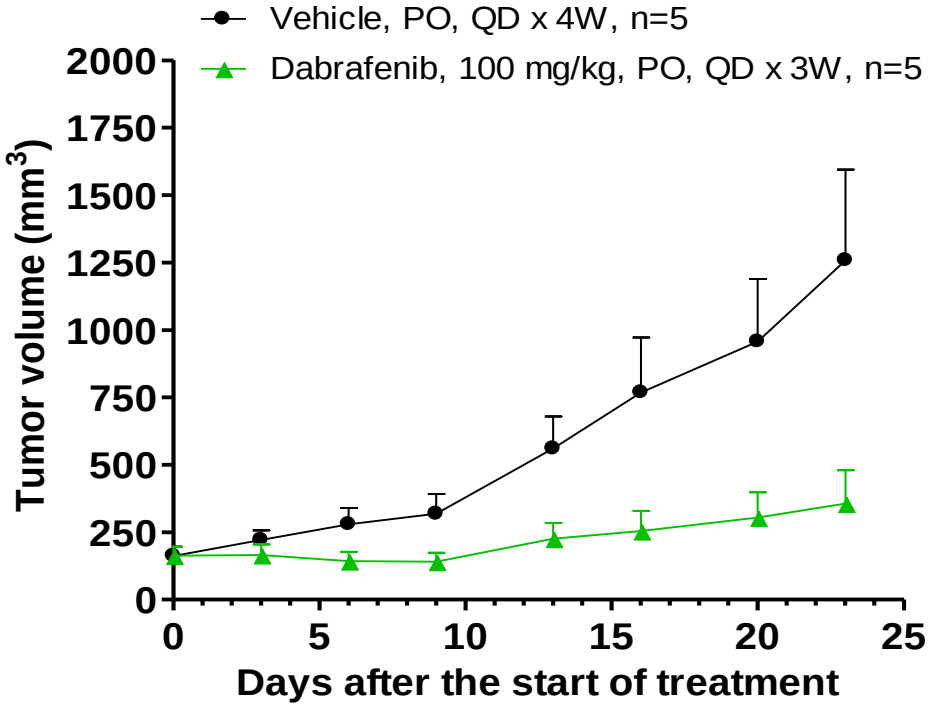
RAF-MEK1/2 Patient Derived Xenograft Models

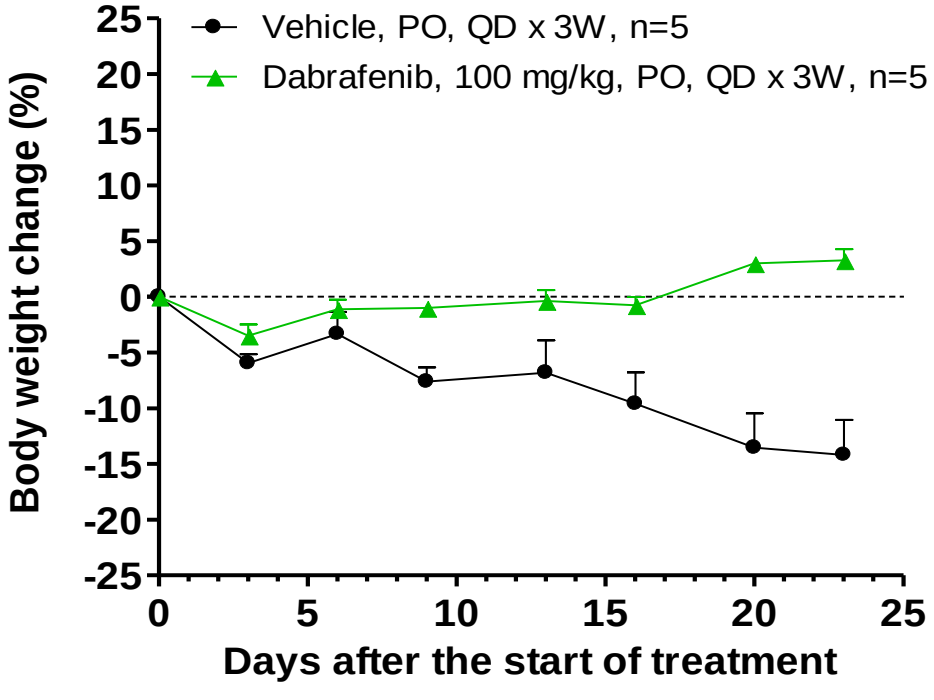
Cancer type	Model ID	Drugs tested	Dosage	TGI	Model genetics
Melanoma	ME-21-0001#	Dabrafenib	100 mg/kg, PO, QD	82%	BRAF V600E
	ME-21-0003	/			BRAF V600E
	ME-21-0004	/			BRAF V600E
Pancreatic	PC-07-0020#	/			BRAF V600E
Colon	CO-04-0032	/			BRAF V600E, PIK3CA H1047R
	CO-04-0283#	/			BRAF V600E PIK3CA E545K
	CO-04-0306	/			BRAF V600E

with PDC (cell line derived from the PDX models) as well.

BRAF inhibitor in ME-21-0001 model

Model ID	Cancer type	Gender	Age	Metastasis	Tumor Stage	Target
ME-21-0001	Chest malignant melanoma	female	21	Lymph node	IV	BRAF V600E





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