BRAF related *in vivo* models

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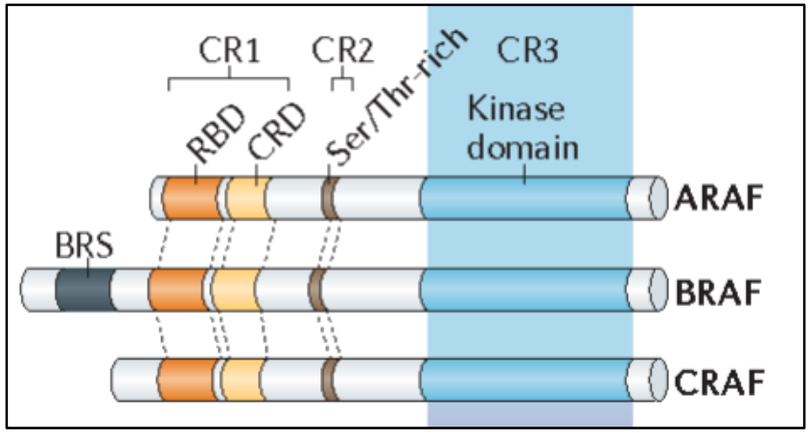
OncoWuXi Newsletter

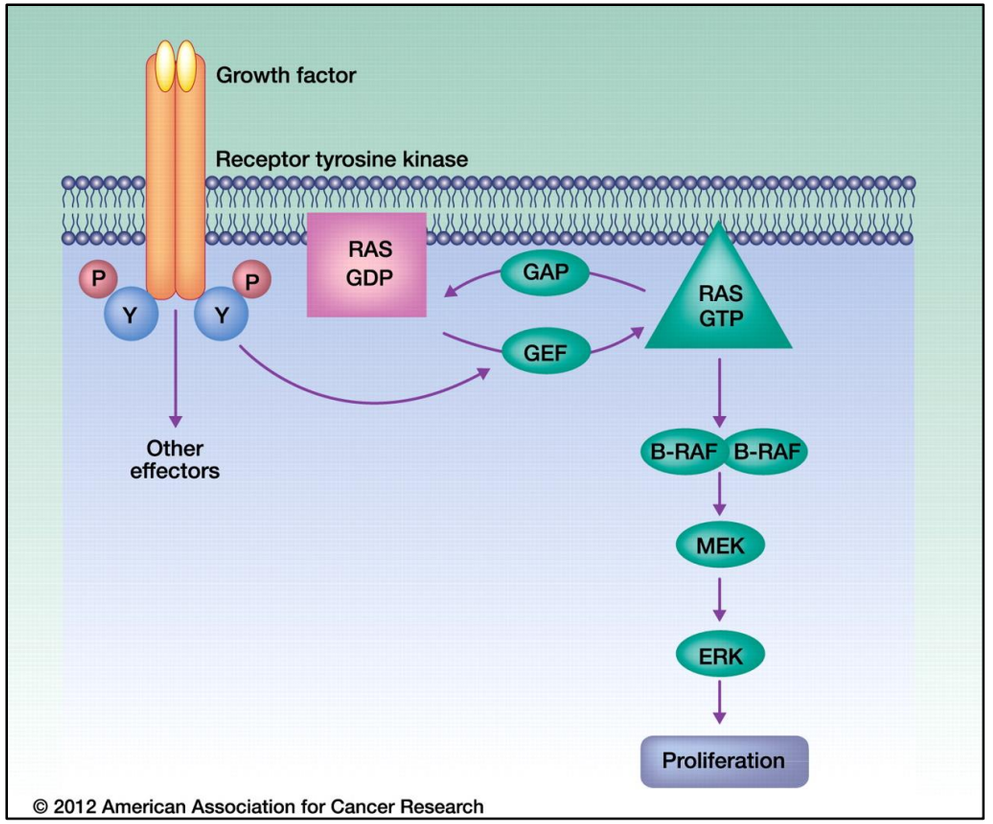
Outline

- **RAF background as a drug target**
  - RAF signaling pathway
  - BRAF role in cancers
- **BRAF mutant CDX and PDX models**
- **Case studies with BRAF and MEK inhibitors**

RAF signaling pathway

- The RAF family members are highly conserved serine/threonine kinases of the MAPK [RAS-RAF-MEK-ERK] pathway, a pathway widely utilized to control many cellular processes, including proliferation, differentiation and survival.
- Of the Raf kinases, B-Raf has the highest intrinsic kinase activity and is mutated in 50–70% of malignant melanomas, 40% of thyroid carcinomas, 30% of ovarian tumors, and nearly 100% of hairy cell leukemia.

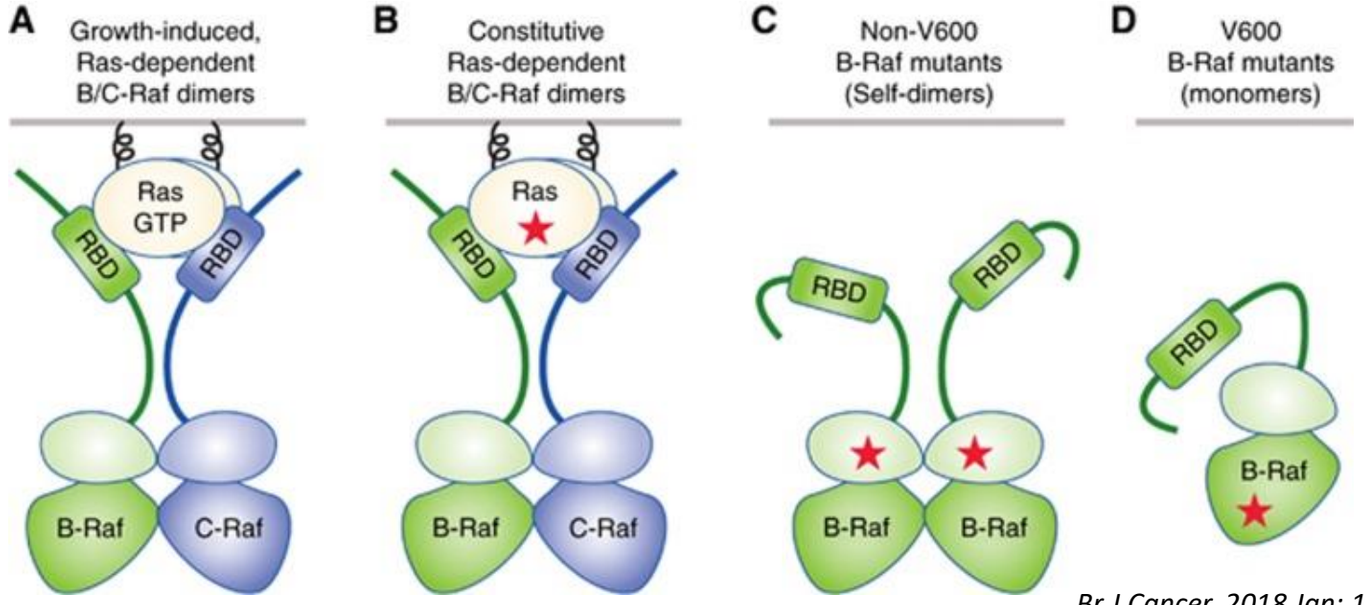




Cancers 2019, 11(8), 1197

RAF signaling pathway

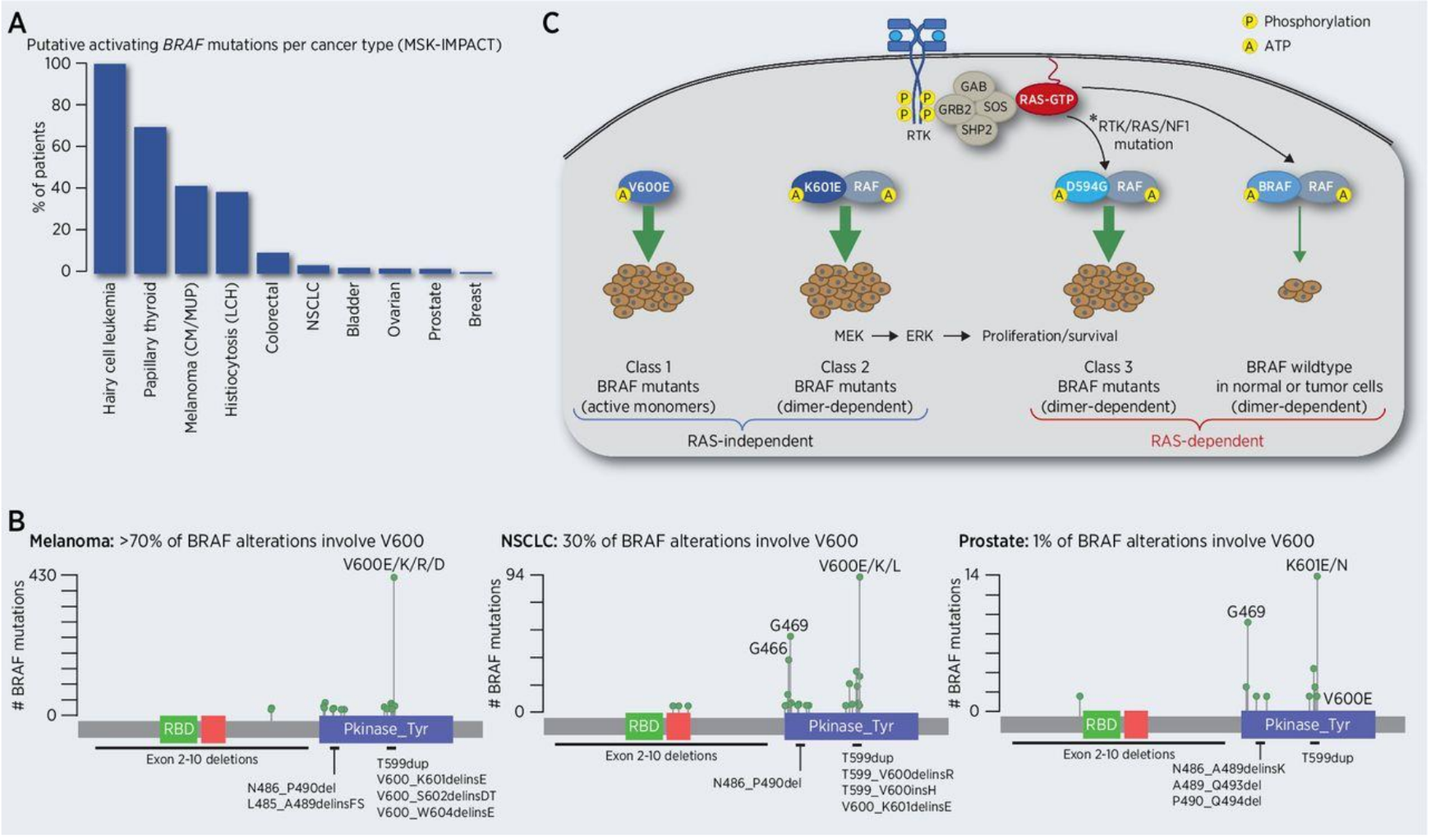
- All members of the Raf family, which include A-Raf, B-Raf and C-Raf, possess a Ras-binding domain (RBD) in their N-terminal regulatory region. Ras binding also promotes changes in Raf phosphorylation and induces Raf dimer formation.
- However, when oncogenic signalling is driven by B-Raf, the requirement for Raf dimerisation can vary. BRAF V600 mutations allow B-Raf to adopt an active kinase conformation in the absence of dimerization and, as a result, these mutants can signal as Ras-independent monomers. With limited exceptions, all other oncogenic B-Raf proteins, including non-V600 mutants and B-Raf truncation or fusion proteins, depend on dimerisation for their transforming activity, which can involve Ras-independent self-dimerisation or Ras-dependent heterodimerisation with C-Raf.



Br J Cancer. 2018 Jan; 118(1): 3–8.

BRAF role in cancers

Landscape of BRAF mutations in human cancer and mechanisms of mutant BRAF activation



https://doi.org/10.1158/0008-5472.CAN-21-3377

BRAF mutant CDX models

Class I (carrying BRAF V600E)

Model ID	Cancer Type	Model ID	Cancer Type
A2058	Melanoma	LS411N	Colorectal cancer
A375	Melanoma	COLO201	Colorectal cancer
COLO829	Melanoma	COLO205	Colorectal cancer
SKMEL24	Melanoma	HT29	Colorectal cancer
SKMEL28	Melanoma	RKO	Colorectal cancer
SKMEL3	Melanoma	SKHEP1	Liver cancer
SKMEL5	Melanoma	ES2	Ovarian cancer
DU4475	Breast cancer	A673	Sarcoma
MDAMB361	Breast cancer	8505C	Thyroid cancer

Class II and Class III

Type	Model ID	Cancer Type	Model genetics
Class II	NCIH1395	Lung cancer	BRAF G469A
	NCIH1755	Lung cancer	BRAF G469A
	MDAMB231	Breast cancer	BRAF G464V
Class III	CAL12T	Lung cancer	BRAF G466V
	NCIH1666	Lung cancer	BRAF G466V
	NCIH508	Colorectal cancer	BRAF G596R
	HT55	Colorectal cancer	BRAF N581Y

BRAF mutant PDX models

Class I

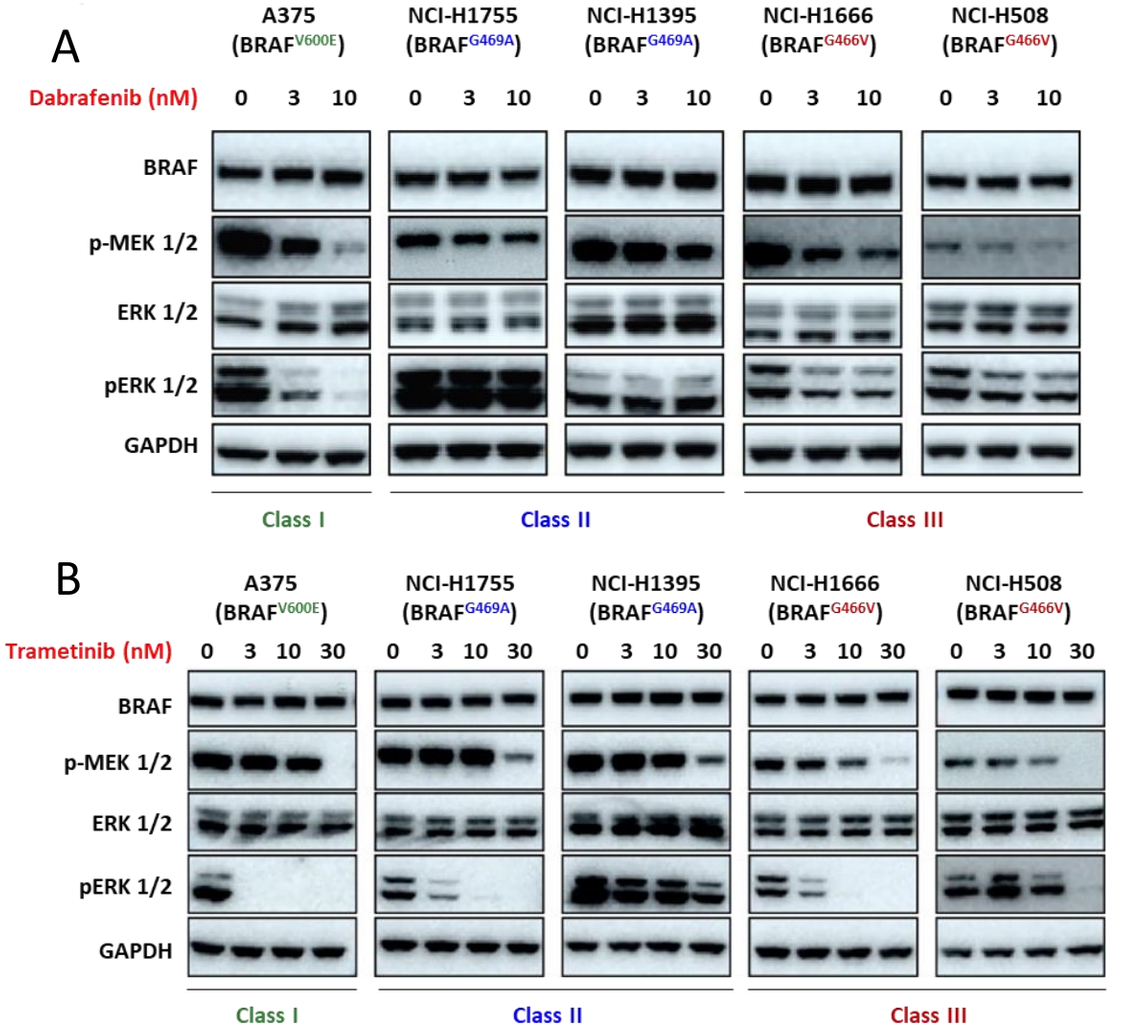
Type	Model ID	Cancer Type	Model genetics
Class I	ME-21-0001	Melanoma	BRAF V600E
	ME-21-0003	Melanoma	BRAF V600E
	ME-21-0004	Melanoma	BRAF V600E
	ME-21-0222	Melanoma	BRAF V600E
	ME-21-0223	Melanoma	BRAF V600E
	PC-07-0020	Pancreatic cancer	BRAF V600E
	CO-04-0032	Colorectal cancer	BRAF V600E
	CO-04-0283	Colorectal cancer	BRAF V600E
	CO-04-0306	Colorectal cancer	BRAF V600E
	CO-04-0342	Colorectal cancer	BRAF V600E

Class II and Class III

Type	Model ID	Cancer Type	Model genetics
Class II	LU-01-0002	Lung cancer	BRAF G469A
	LU-01-1397	Lung cancer	BRAF G469A
	ME-21-0234	Melanoma	BRAF G469A
Class III	HN-13-0336	Head and neck cancer	BRAF G469E
	HN-13-0032	Head and neck cancer	BRAF D594N
	CO-04-0314	Colorectal cancer	BRAF D594N
	LY-24-0303	Lymphoma	BRAF D594N
	LU-01-1320	Lung cancer	BRAF N581S

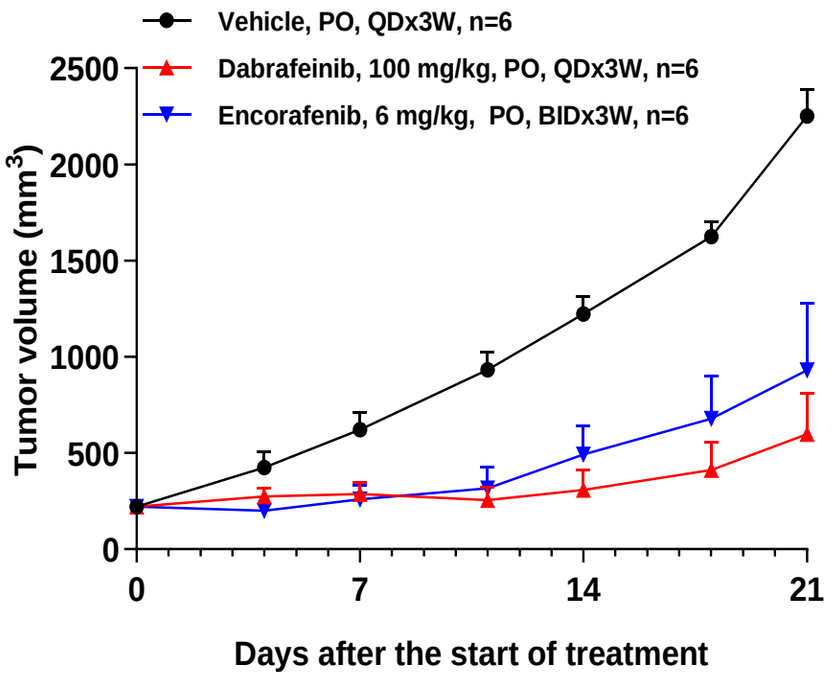
BRAF and MEK inhibitors in BRAF mutant cancer cell lines

- **Class I** BRAF mutations affect amino acid V600 and signal as RAS-independent active monomers, **Class II** mutations function as RAS-independent activated dimers, and **Class III** mutations are kinase impaired but increase signaling through the MAPK pathway.
- **Fig A.** Inhibition of MEK/ERK signaling in a panel of cancer cell lines harboring indicated BRAF mutants, exposed to Dabrafenib for 4 h at indicated doses. MEK/ERK signaling in tumors with class I BRAF mutants is sensitive to BRAF inhibitor
- **Fig B.** Inhibition of MEK/ERK signaling in cancer cell lines, exposed to Trametinib for 4 h at indicated doses. MEK/ERK signaling in tumors with class I, class II and III BRAF mutants is sensitive to MEK inhibitor.

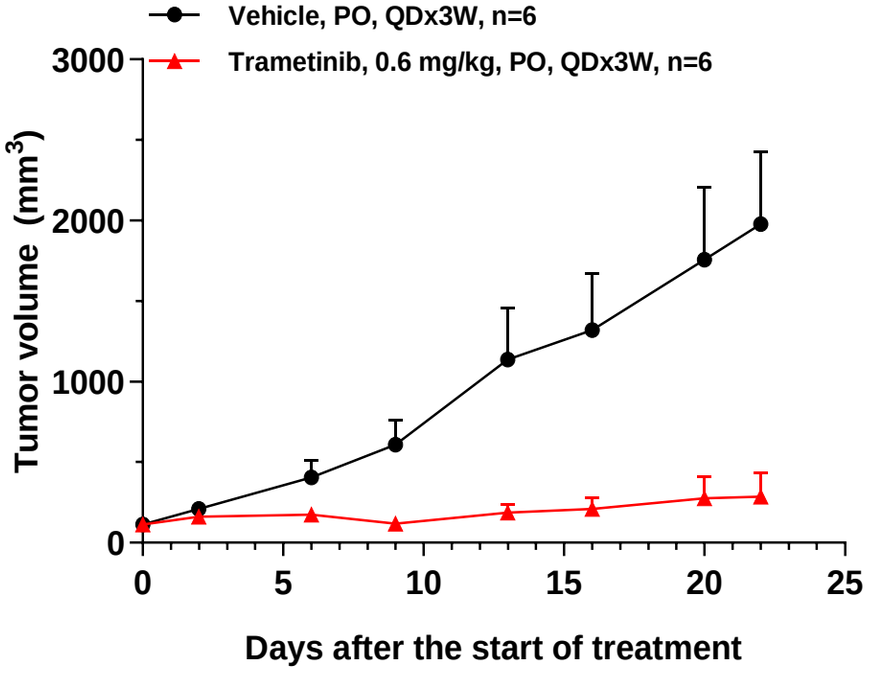


BRAF and MEK inhibitors in BRAF Class I mutant CDX models

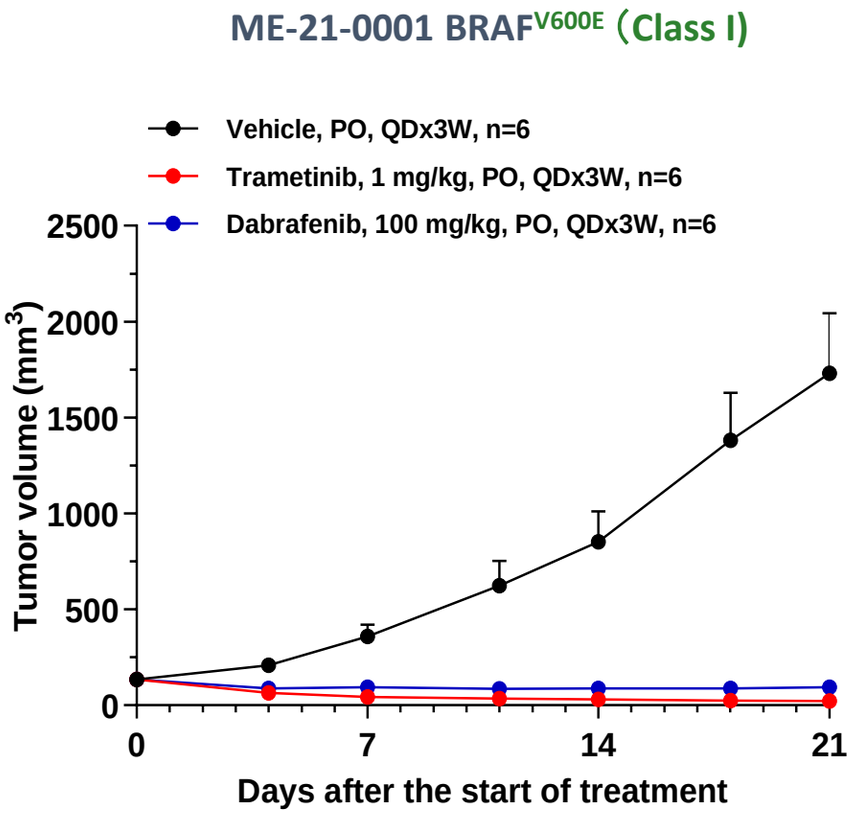
A375 BRAF^{V600E} (Class I)

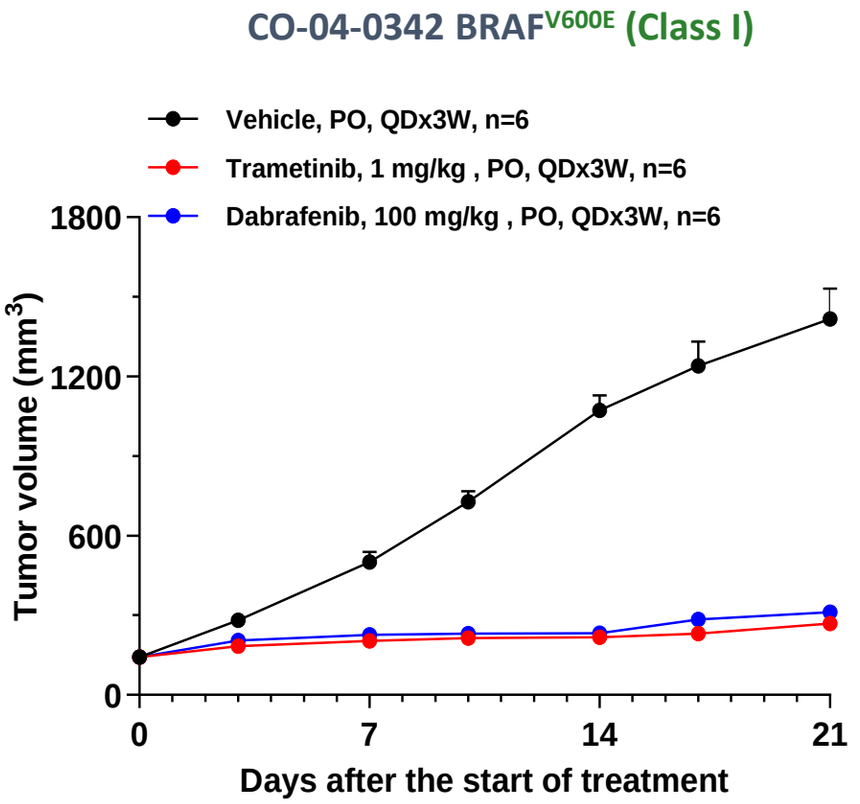


A375 BRAF^{V600E} (Class I)



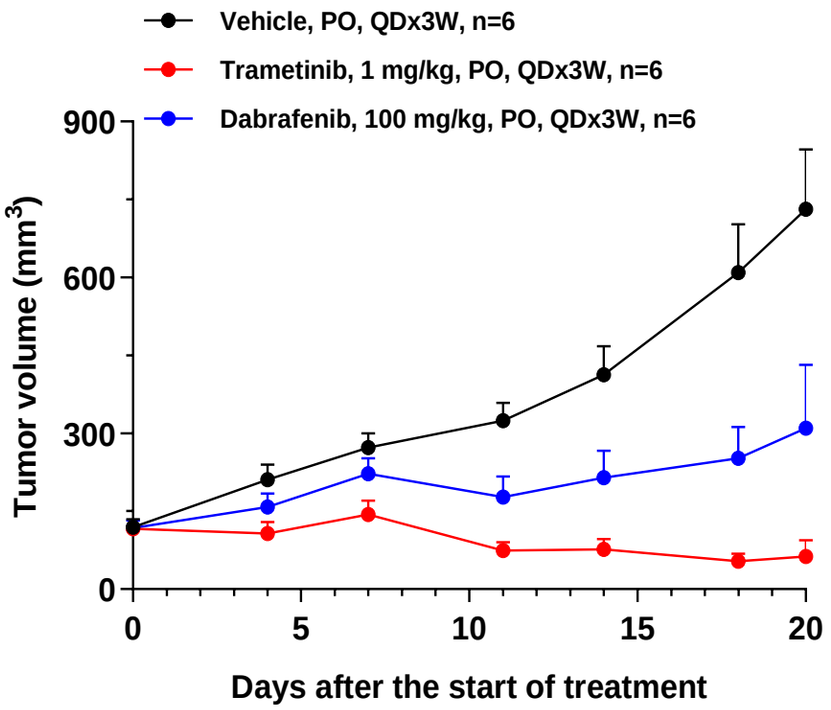
BRAF and MEK inhibitors in BRAF Class I mutant PDX models



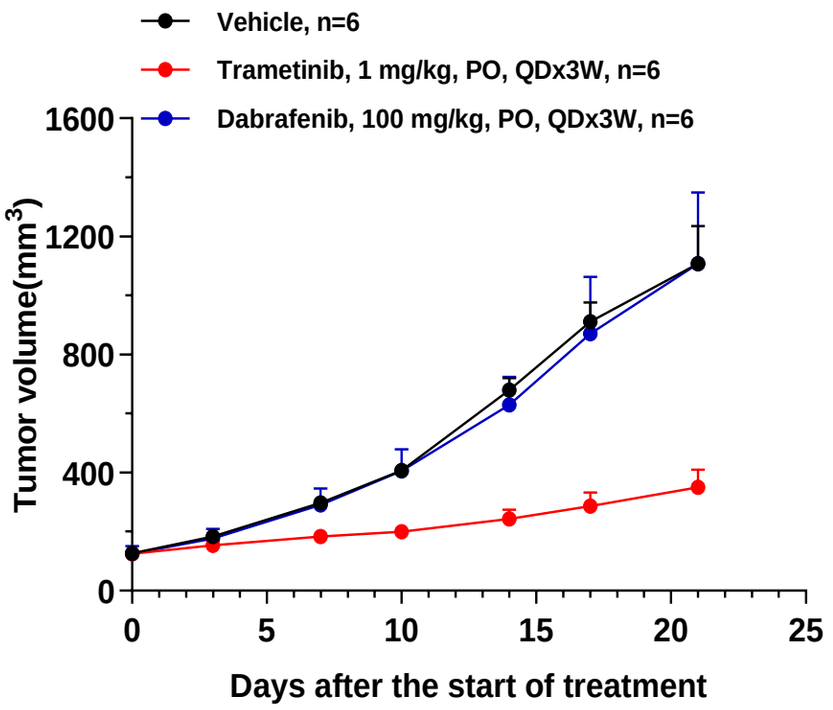


BRAF and MEK inhibitors in BRAF Class II mutant PDX models

ME-21-0234 BRAF^{G469A} (Class II)

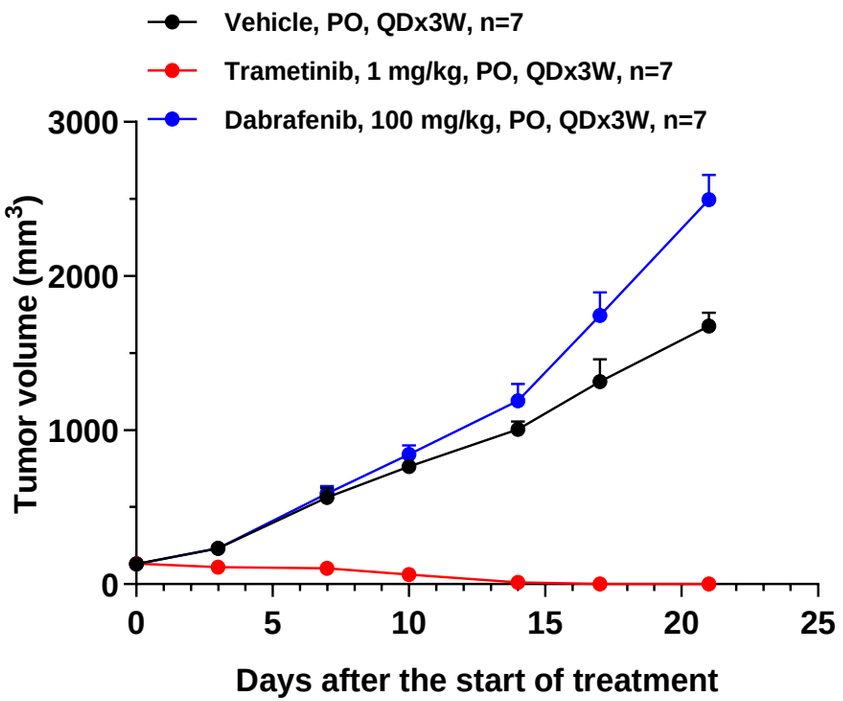


LU-01-1397 BRAF^{G469A} (Class II)

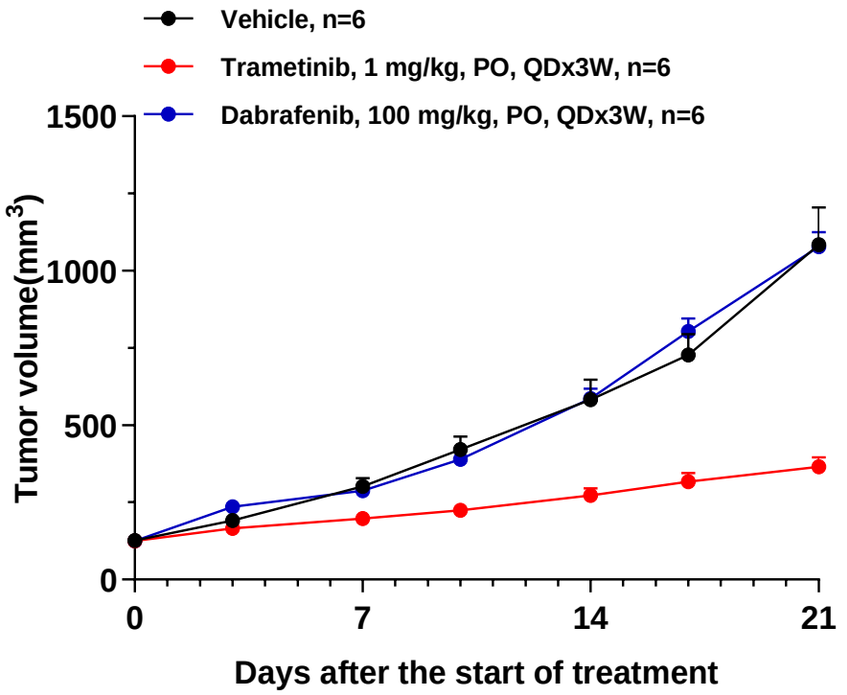


BRAF and MEK inhibitors in BRAF Class III mutant PDX models

HN-13-0336 BRAF^{G469E} (Class III)



CO-04-0314 BRAF^{D594N} (Class III)



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