AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

Dual RAF/MEK inhibitor VS-6766 for treatment of solid tumors with diverse MAPK pathway alterations

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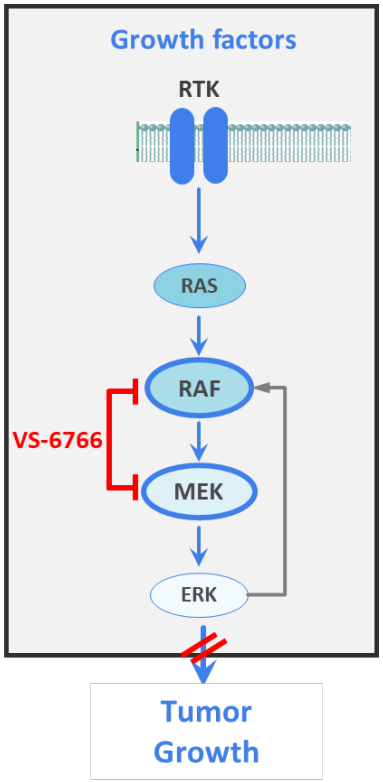
Jonathan A. Pachter, Ph.D.

I have the following financial relationships to disclose:

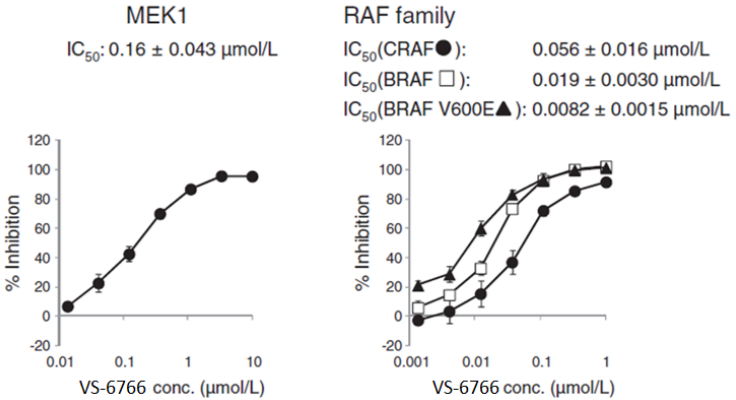
Employee of: Verastem Oncology

I will discuss the following off label use and/or investigational use in my presentation: VS-6766 (dual RAF/MEK inhibitor)

VS-6766 is a Unique Small Molecule RAF/MEK Inhibitor

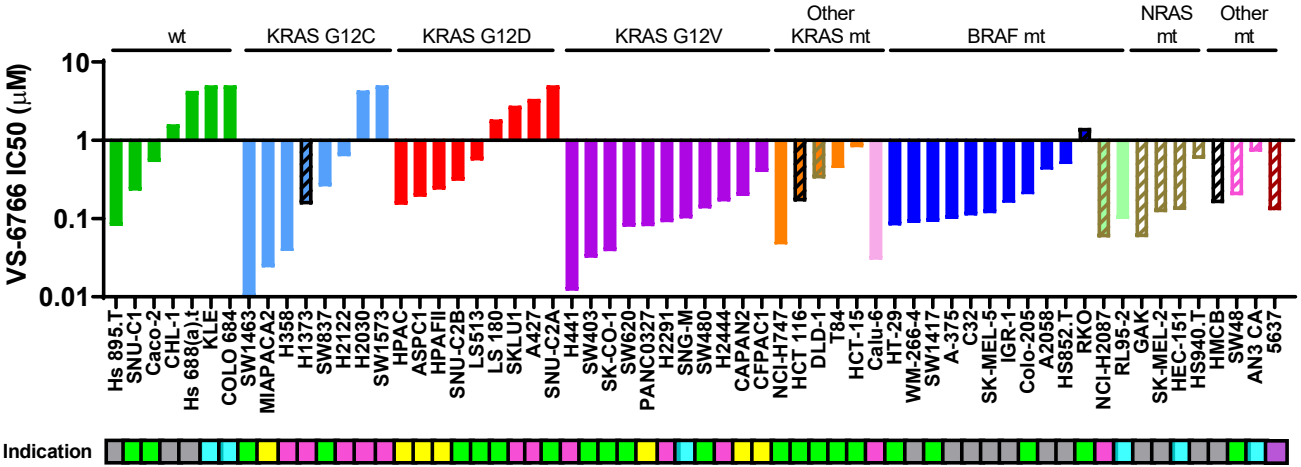


- VS-6766 inhibits both MEK & RAF kinase activities
- MEK inhibitors paradoxically induce MEK phosphorylation (pMEK) by relieving ERK-dependent feedback inhibition of RAF
- By inhibiting RAF phosphorylation of MEK, VS-6766 has advantage of not inducing pMEK
- VS-6766 inhibits ERK signaling more completely; may confer enhanced therapeutic activity



Reference: Ishii et al., Cancer Res, 2013; Lito et al., Cancer Cell, 2014

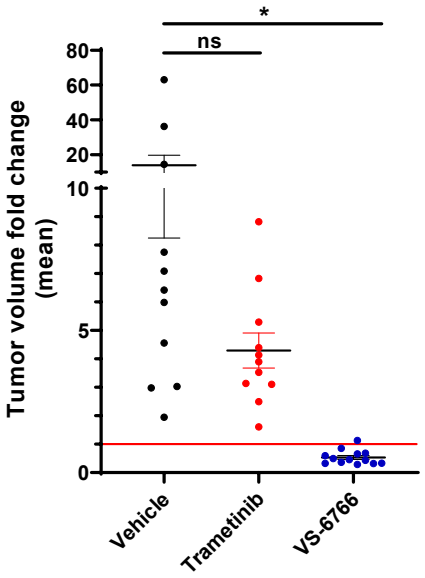
VS-6766 inhibits cell proliferation across multiple MAPK pathway alterations and multiple solid tumor indications



3D proliferation assay

VS-6766 shows strong single agent anti-tumor activity across KRAS mt NSCLC, ovarian, pancreatic and colorectal cancer models *in vivo*

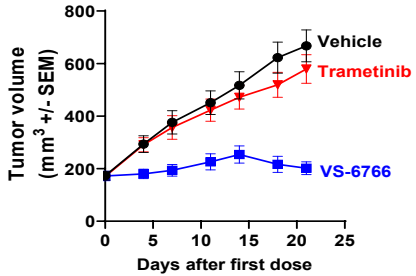
KRAS G12V mt/Trp53KO NSCLC GEMM[1]



VS-6766 @ 0.1 mg/kg QD
Trametinib @ 0.1 mg/kg QD

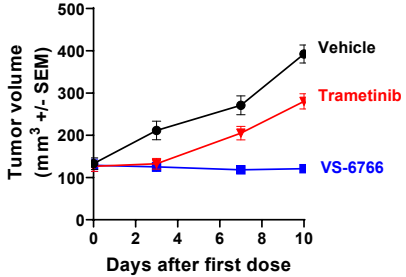
[1] *Sanclemente, M. et al. Cancer Cell (2018)*

H358 KRAS G12C mt NSCLC



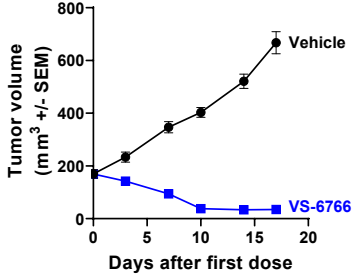
VS-6766 @ 0.3 mg/kg QD
Trametinib @ 0.3 mg/kg QD

TOV21G KRAS G13D mt ovarian cancer



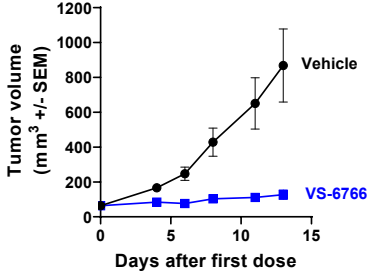
VS-6766 @ 0.5 mg/kg QD
Trametinib @ 0.5 mg/kg QD

MiaPaca2 KRAS G12C mt pancreatic cancer



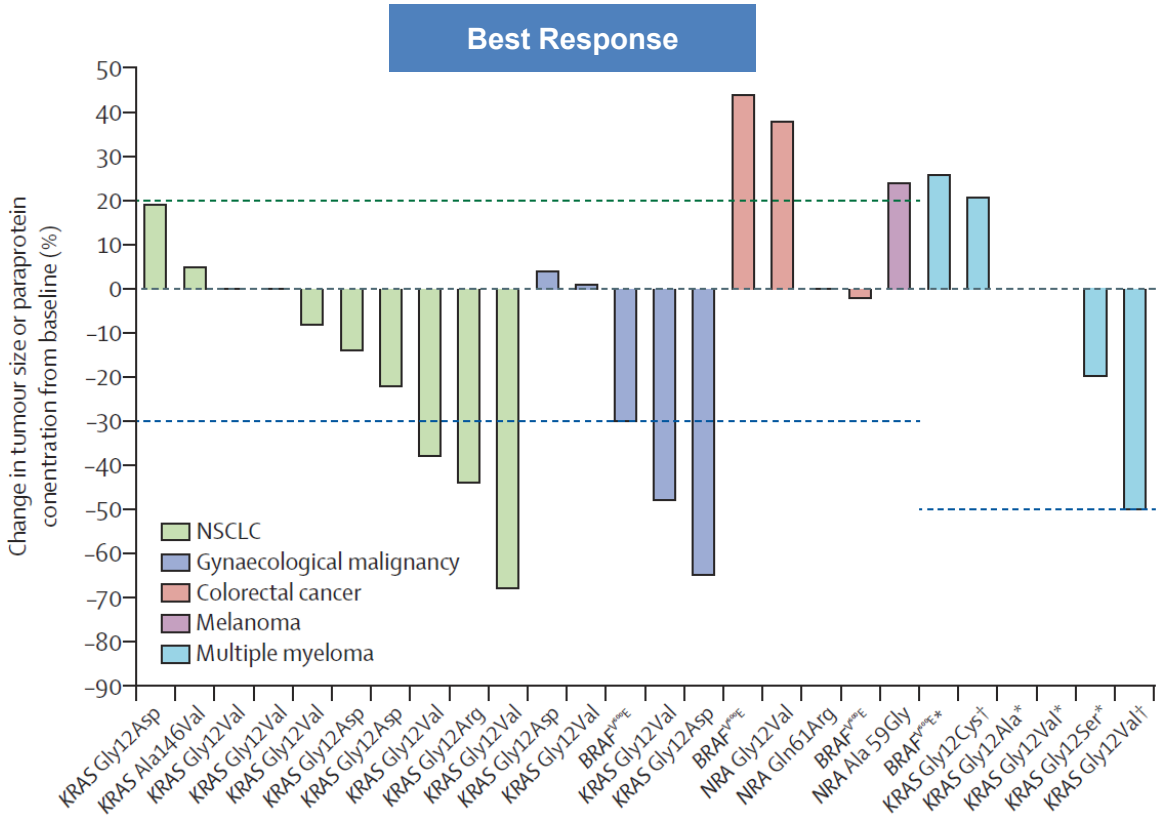
VS-6766 @ 0.3 mg/kg QD

CT26 KRAS G12D mt colorectal cancer



VS-6766 @ 0.3 mg/kg QD

VS-6766 monotherapy has shown clinical activity in patients with several RAS/RAF mutant cancers



- Twice weekly intermittent dosing of VS-6766 shows objective responses with good tolerability
- This opens up options for selected combinations with agents targeting key nodes in the MAPK pathway or parallel pathways

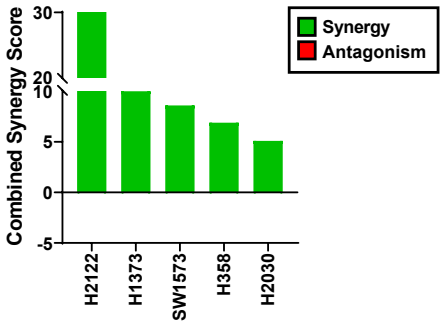
Guo et al., Lancet Oncology 2020

Distinct combinations with VS-6766 for biomarker-selected cancer subsets

- Registration-directed trials ongoing with VS-6766 + defactinib (FAK inhibitor) in low-grade serous ovarian cancer (NCT04625270) and KRAS G12V mt NSCLC (NCT04620330)
- With its activity against tumor cells with diverse MAPK pathway mutations, VS-6766 has potential to be the backbone of rational combinations for various biomarker-selected cancer patient subsets
- Preclinical synergy with VS-6766 in biomarker-selected subsets supports clinical combination studies

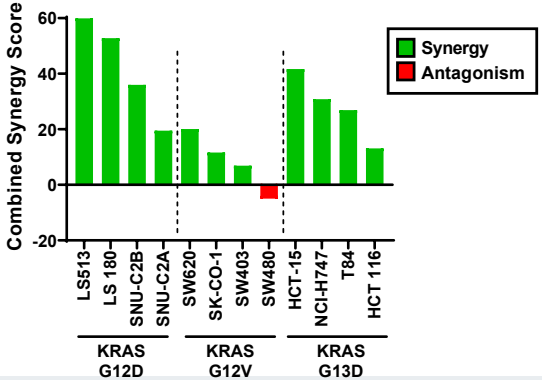
KRAS G12C mt NSCLC

VS-6766 + G12Ci (sotorasib)



KRAS mt Colorectal

VS-6766 + EGFRi (afatinib)



ER+ Breast Cancer

VS-6766 + CDK4/6i (abemaciclib)