Synergistic combinations with the novel dual RAF/MEK inhibitor VS-6766: Establishing VS-6766 as the backbone of therapy for RAS-driven cancers

Silvia Coma[1], Sanjib Chowdhury[1], Jonathan A Pachter[1]
[1]Verastem Oncology, Needham MA

Verastem Oncology

BACKGROUND

- KRAS is one of the most frequently mutated oncogenes in cancer, stimulating tumor growth through activation of the RAS/RAF/MEK/ERK (MAPK) pathway. Drugs targeting the MAPK pathway have shown clinical benefit in KRAS-driven cancers, including RAF, MEK and KRAS G12C inhibitors[1,2].
- However, it appears that blocking a single node in the RAS pathway may be insufficient for deep and durable response, and simultaneous targeting of multiple nodes in the MAPK pathway (**vertical blockade; Figure 1A**) may improve response[3].
- Additionally, the efficacy of MAPK pathway blockade may be circumvented through activation of resistance pathways and thus, co-targeting the MAPK pathway and relevant parallel pathways, such as the AKT/mTOR pathway (**parallel inhibition; Figure 1B**) may be necessary[4].
- VS-6766 is a dual RAF/MEK inhibitor that uniquely confers vertical inhibition of the MAPK pathway with a single drug **(Figure 2)[5].** Clinically, VS-6766 has shown a favorable tolerability profile and objective responses as monotherapy or in combination with the focal adhesion kinase (FAK) inhibitor defactinib in the treatment of heavily pretreated patients with various KRAS mutant solid tumors[6,7].
- Here, we tested the hypothesis that combination of VS-6766 with agents targeting other nodes in the RAS pathway (vertical blockade) and agents targeting parallel pathways (parallel inhibition) might yield superior antitumor efficacy. Since signaling varies by tumor type and KRAS mutation variants, a panel of 16 different cell lines with 14 different agents was tested.

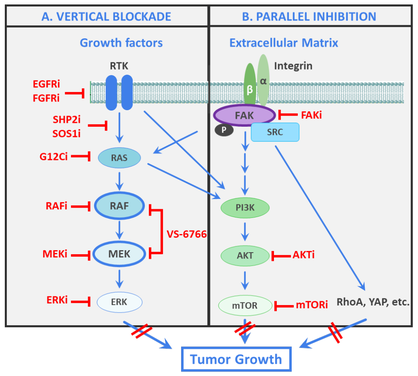


Figure 1. Establishing VS-6766 as the backbone of targeted therapy combinations for the treatment of KRAS-driven cancers. Rationale for combinations.

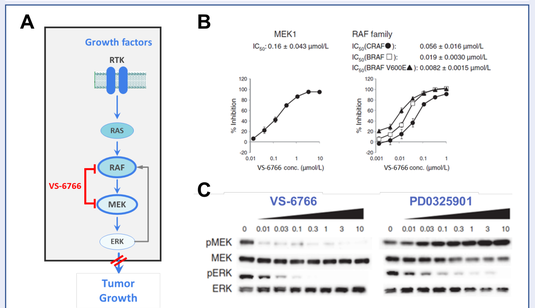


Figure 2. (A,B) VS-6766 is a unique small molecule dual RAF/MEK inhibitor that inhibits tumor growth. (C) MEK-only inhibitors paradoxically induce MEK phosphorylation (pMEK) by relieving ERK-dependent feedback inhibition of RAF. By also inhibiting RAF phosphorylation of MEK, VS-6766 has advantage of not inducing pMEK, enabling more robust inhibition of pERK.

REFERENCES

1. Cox et al., Nat Rev Drug Discovery 2014
2. Moore et al., Nat Rev Drug Discov. 2020
3. Ryan et al., Clinical Cancer Research 2019
4. Yaeger & Solit, Clinical Cancer Research 2020
5. Ishi et al., Cancer Research 2013
6. Guo, et al Lancet Oncology 2020
7. Banerji, AACR VM 1, April 27, 2020

RESULTS

1. Broad synergy observed with VS-6766 in combination with agents targeting other nodes in the RAS pathway (vertical blockade) and parallel pathways (parallel blockade)

A

VS-6766 (RAF/MEKi) +

Mechanism (Vertical Inhibition)	Compounds
Pan-HER	Afatinib
Pan-FGFR	Erdafitinib
SHP2	TNO155, RMC-4550
SOS1	BI-3406
KRAS G12C	AMG 510, MRTX849
ERK1/2	LY-3214996

Mechanism (Parallel Inhibition)	Compounds
FAK	Defactinib
AKT	Ipatasertib, M2698
mTOR	Everolimus
CDK4/6	Palbociclib, Abemaciclib

B

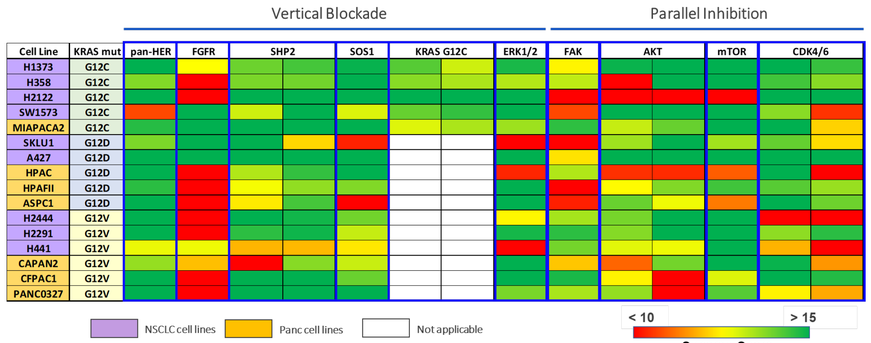


Figure 3. (A) Synergy between VS-6766 and agents targeting other nodes in the RAS pathway, including pan-HER, SHP2, SOS1, KRAS-G12C and ERK1/2 inhibitors, and agents targeting parallel pathways, including inhibitors of CDK4/6, AKT and mTOR. (B) Heatmap shows synergy scores for VS-6766 combinations across a panel of KRAS G12C, G12D & G12V non-small cell lung cancer (NSCLC) and pancreatic cancer (Panc) cell lines. Bliss, Loewe, Highest Single Agent (HSA) and ZIP synergy analysis were performed to generate a composite synergy score.

2. Strong synergy observed between VS-6766 and agents targeting other nodes in the RAS pathway (vertical blockade), including pan-HER, SHP2, SOS1, KRAS G12C and ERK1/2 inhibitors

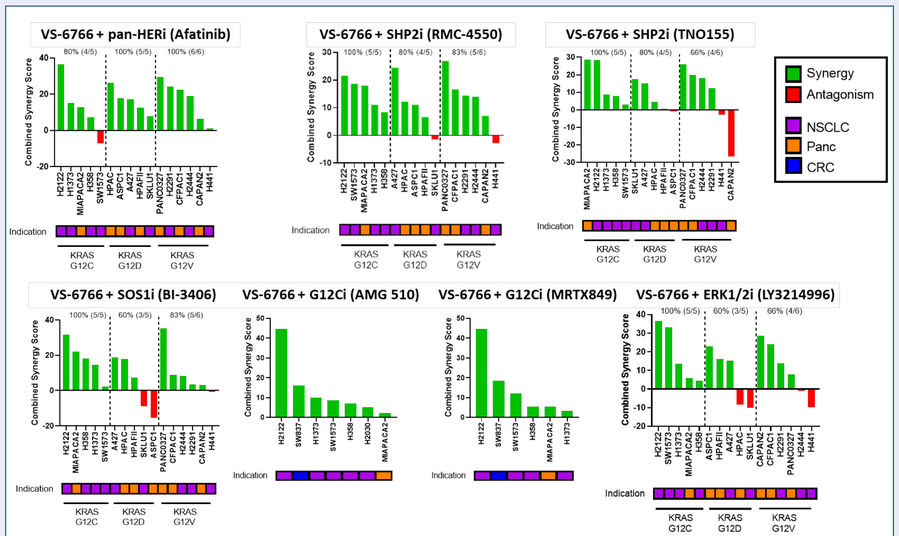


Figure 4. Synergy between VS-6766 and several key agents/mechanisms in the RAS pathway. Waterfall plots summarize the combination synergy results for VS-6766 with agents targeting other nodes in the RAS pathway across a panel of KRAS G12C, G12D & G12V NSCLC, PDAC and colorectal (CRC) cell lines. Bliss, Loewe, HSA and ZIP synergy analyses were performed to generate a composite synergy score.

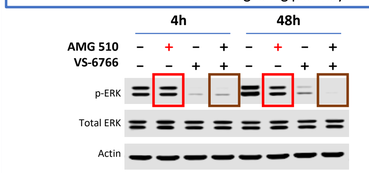
3. VS-6766 enhances anti-tumor efficacy of KRAS G12C inhibitors through a vertical pathway inhibition strategy

A. Synergy of VS-6766 + G12C inhibitor AMG 510 or MRTX849 across G12C mutant NSCLC, CRC, and PDAC cell lines

Cell line	Indication	Sensitivity to G12C inhibitors	Combined Synergy Score: VS-6766 + AMG 510	Combined Synergy Score: VS-6766 + MRTX849
H2122	NSCLC	Moderately sensitive	44.7	44.6
H1373	NSCLC	Sensitive	10.0	3.4
SW1573	NSCLC	Insensitive	8.6	12.0
H358	NSCLC	Sensitive	6.9	5.4
H2030	NSCLC	Moderately sensitive	5.1	ND
SW837	CRC	Sensitive	16.1	18.5
MIAPACA2	Panc	Sensitive	2.3	5.3

ND: not determined

B. VS-6766 + AMG 510 yields deeper and more sustained inhibition of ERK signaling pathway



H2122 KRAS G12C mutant NSCLC

Concentrations Tested
AMG 510: 100 nM
VS-6766: 100 nM

C. VS-6766 & FAKi potentiate AMG 510 efficacy in KRAS G12C mutant NSCLC in vivo; Tumor regression in all mice with triple combination

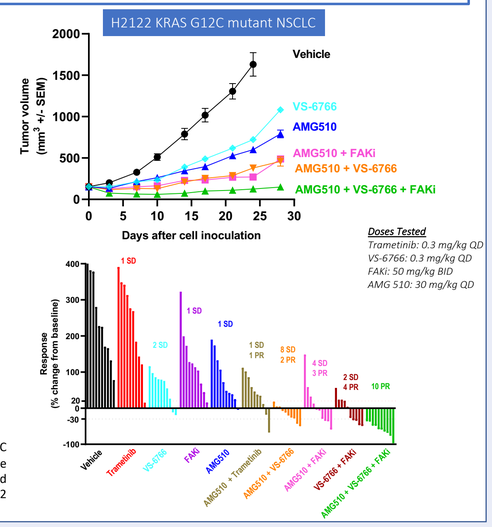


Figure 5. (A) Synergy score between VS-6766 and AMG 510 or MRTX849 in KRAS G12C mutant NSCLC, CRC and PDAC cell lines. Bliss, Loewe, HSA and ZIP synergy analysis were performed to generate a composite synergy score. (B) Western blot analyses of pERK and total ERK in H2122 KRAS G12C mt NSCLC cells treated for 4 and 48 hours with 100 nM VS-6766 and 100 nM AMG 510. (C) Changes in tumor volume in H2122 tumor bearing mice treated with VS-6766 +/- FAKi +/- AMG 510.

4. Strong synergy observed between VS-6766 and agents targeting parallel pathways, including inhibitors of AKT, mTOR & CDK4/6

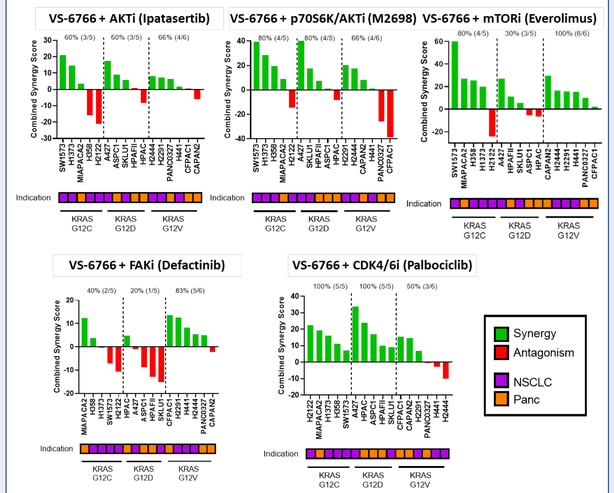


Figure 6. Synergy between VS-6766 and several agents targeting parallel pathways. Waterfall plots summarize the combination synergy results for VS-6766 with agents targeting parallel pathways across a panel of KRAS G12C, G12D & G12V NSCLC and PDAC cell lines. Bliss, Loewe, HSA and ZIP synergy analyses were performed to generate a composite synergy score.

5. VS-6766 and FAK inhibitor combination leads to more robust anti-tumor efficacy *in vivo*

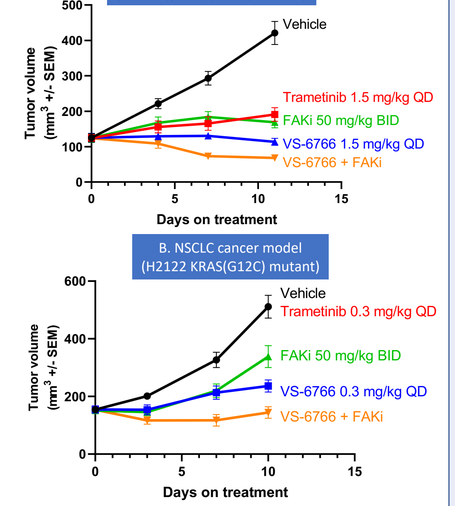


Figure 7. Changes in tumor volume in (A) TOV-21g and (B) H2122 tumor bearing mice treated with VS-6766 +/- FAKi as compared with trametinib.

CONCLUSIONS

- VS-6766 is a dual RAF/MEK inhibitor that uniquely confers vertical inhibition of the MAPK pathway with a single drug.
- Strong synergy was observed between VS-6766 and agents targeting other nodes in the RAS pathway including pan-HER, SHP2, SOS1, KRAS-G12C and ERK1/2 inhibitors.
- Among agents targeting parallel pathways, strong synergy with VS-6766 was observed with inhibitors of AKT, mTOR, CDK4/6 and FAK. Interestingly, in NSCLC, synergy between VS-6766 and the FAK inhibitor defactinib was especially striking in cell lines with KRAS G12V mutation as compared with G12C or G12D. This correlates well with clinical activity of VS-6766 + defactinib that has been observed in patients with KRAS G12V mutant NSCLC[6,7]. In low-grade serous ovarian cancer (LGSOC), the combination of VS-6766 + defactinib has shown clinical activity in patients with KRAS mutant LGSOC regardless of the specific KRAS mutation variant[7].
- All together, these results support the clinical evaluation of VS-6766 in combination with agents that target other nodes in the MAPK pathway or parallel pathways and may establish VS-6766 as the backbone of therapy for RAS-driven cancers.