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Abstract #1263

Dual RAF/MEK Inhibitor VS-6766 Enhances Anti-Tumor Efficacy of KRAS G12C Inhibitors through a Vertical Pathway Inhibition Strategy

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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. G12C inhibitors (G12Ci), sotorasib (AMG 510) and adagrasib (MRTX849), have demonstrated promising anti-tumor activity in patients with KRAS G12C mutant (mt) non-small cell lung cancer (NSCLC)[1,2]. However, several recent studies have shown that simultaneous targeting of multiple nodes in the RAS/RAF/MEK/ERK pathway may be optimal for durable pathway inhibition and response[3].
- VS-6766 is a dual RAF/MEK inhibitor that uniquely confers vertical inhibition of the MAPK pathway with a single drug (Figure 1)[4]. 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[5,6]. See also poster #1425 and oral presentation #CT01 describing synergy of VS-6766 + FAK inhibition for the treatment of RAS-driven cancers.
- Here, we tested the hypothesis that vertical pharmacological blockade of RAS, RAF and MEK with G12Ci in combination with VS-6766 might yield superior pathway blockade and anti-tumor efficacy.
- Additional studies are underway testing the combination of VS-6766 with agents targeting other nodes in the RAS pathway (vertical blockade), including tyrosine kinase receptor inhibitors, SHP2 inhibitors, SOS1 inhibitors and ERK1/2 inhibitors. Since signaling varies by tumor type and KRAS mutation variants[7,8], a panel of 16 different cell lines with 14 different agents was tested.

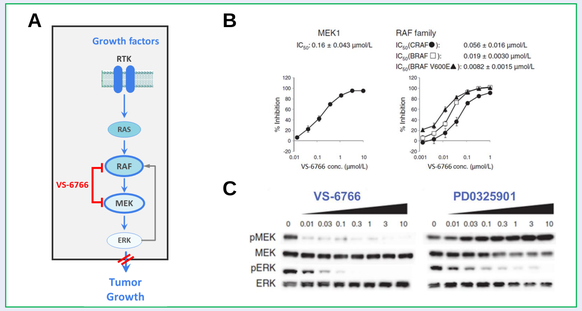


Figure 1. (A, B) VS-6766 is a unique small molecule dual RAF/MEK inhibitor. (C) MEK-only inhibitors paradoxically induce MEK phosphorylation (pMEK) by relieving ERK-dependent feedback inhibition of RAF. By also inhibiting RAF phosphorylation of MEK, VS-6766 has the advantage of not inducing pMEK, enabling more robust inhibition of pERK.

CONCLUSIONS

- VS-6766 is a dual RAF/MEK inhibitor that uniquely confers vertical inhibition of the MAPK pathway with a single drug
- Synergy of VS-6766 + G12Ci observed across KRAS-G12C mt NSCLC, pancreatic cancer & CRC cell lines
- VS-6766 combination confers better ERK pathway blockade relative to G12Ci alone
- Both VS-6766 & FAKi enhance efficacy of G12Ci in H2122 & H358 xenograft models. Triple combination of G12Ci + VS-6766 + FAKi yields tumor regression in all mice in both models.
- These results support the clinical evaluation of VS-6766 ± a FAK inhibitor (e.g. defactinib) in combination with a G12C inhibitor for treatment of KRAS G12C mutant cancers

DISCLOSURES

S Coma, S Chowdhury & JA Pachter are employees of Verastem Oncology

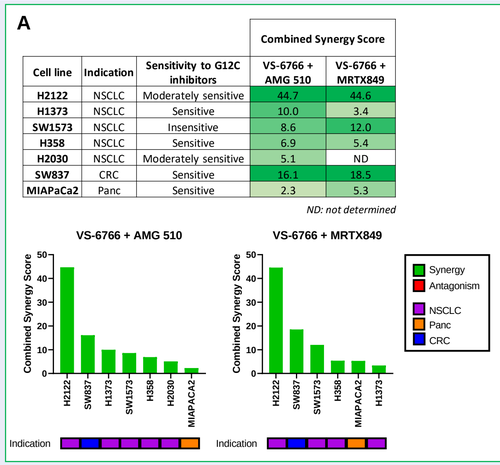
RESULTS

1. Preclinical synergy of VS-6766 + G12C inhibitors observed in KRAS G12C mutant NSCLC, CRC and pancreatic cancer cell lines

A

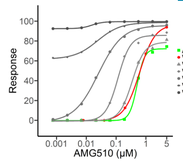
Cell line	Indication	Sensitivity to G12C inhibitors	Combined Synergy Score: VS-6766 + AMG 510	Combined Synergy Score: VS-6766 + MRTX849
H2122	NSCLC	Moderately sensitive	44.7	44.6
H1373	NSCLC	Sensitive	10.0	3.4
SW1573	NSCLC	Insensitive	8.6	12.0
H358	NSCLC	Sensitive	6.9	5.4
H2030	NSCLC	Moderately sensitive	5.1	ND
SW837	CRC	Sensitive	16.1	18.5
MIAPaCa2	Panc	Sensitive	2.3	5.3

ND: not determined



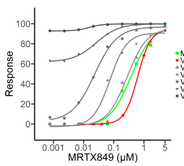
B

VS-6766 + AMG 510
H2122 KRAS G12C mt NSCLC



AMG 510 Single Agent (SA)	AMG 510 IC50 (nM)
	631
+ VS-6766 0.008 µM	439
+ VS-6766 0.04 µM	134
+ VS-6766 0.2 µM	28
+ VS-6766 1 µM	0.4
+ VS-6766 5 µM	<0.1

VS-6766 + MRTX849
H2122 KRAS G12C mt NSCLC



MRTX849 Single Agent (SA)	MRTX849 IC50 (nM)
	397
+ VS-6766 0.008 µM	290
+ VS-6766 0.04 µM	83
+ VS-6766 0.2 µM	23
+ VS-6766 1 µM	0.40
+ VS-6766 5 µM	<0.1

Figure 2. (A) 3D proliferation assays were performed to calculate synergy score between VS-6766 with AMG 510 or MRTX849 in KRAS G12C mt non-small cell lung cancer (NSCLC), colorectal cancer (CRC) and pancreatic cancer (Panc) cell lines. Bliss, Loewe, HSA and ZIP synergy analysis were performed to generate a composite synergy score. (B) Dose responses of AMG 510 (top) and MRTX849 (bottom) alone (SA) or combined with VS-6766 on tumor cell viability in H2122 KRAS G12C mt NSCLC show that combination with VS-6766 enhances the apparent potencies of the G12C inhibitors.

2. Addition of VS-6766 to AMG 510 increases depth & duration of inhibition of p-ERK relative to AMG 510 alone across a panel of KRAS G12C mutant NSCLC cell lines

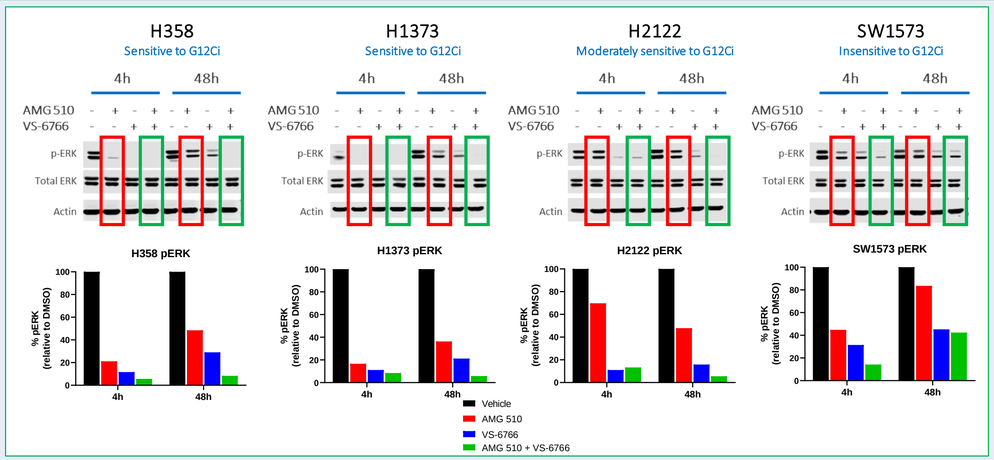


Figure 3. Western blot analyses of pERK and total ERK in KRAS G12C mt NSCLC cells treated for 4 and 48 hours with 100 nM VS-6766 and 100 nM AMG 510 as single agents or in combination.

3. VS-6766 & FAKi potentiate AMG 510 efficacy in KRAS G12C mutant NSCLC in vivo

Tumor regression in all mice with triple combination

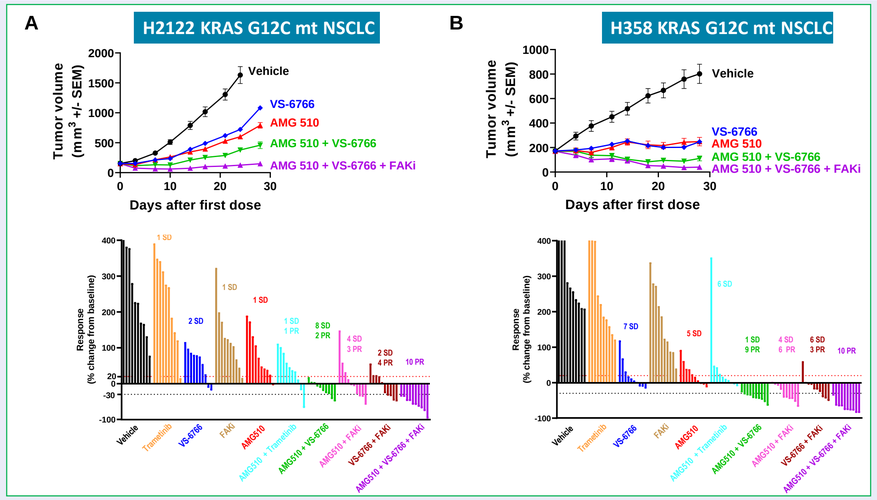


Figure 4. Changes in tumor volume in KRAS mt NSCLC H2122 (A) and H358 (B) tumor bearing mice treated with VS-6766 (0.3 mg/kg QD) +/- FAKi (50 mg/kg BID) +/- AMG 510 (30 mg/kg QD for H2122 and 10 mg/kg QD for H358). Trametinib was tested at 0.3 mg/kg QD.

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

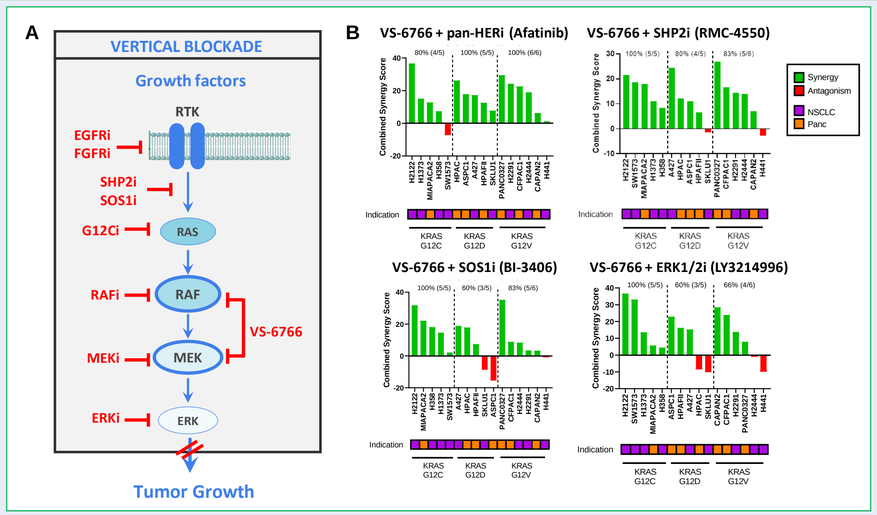


Figure 5. (A) Establishing VS-6766 as the backbone of targeted therapy combinations for the treatment of RAS-driven cancers. Rationale for combinations. (B) Synergy between VS-6766 and several key agents/mechanisms in the RAS pathway. Waterfall plots summarize the combination synergy results for VS-6766 with agents targeting other nodes in the RAS pathway across a panel of KRAS G12C, G12D & G12V mt NSCLC and pancreatic cell lines. Bliss, Loewe, HSA and ZIP synergy analyses were performed to generate a composite synergy score.

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