The RAF/MEK Clamp VS-6766 as a Backbone of Therapy for RAS Pathway-Driven Cancers: Tumor/Biomarker-Specific Combination Strategies

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Poster #21

BACKGROUND

The RAS/RAF/MEK/ERK (RAS) pathway is the most mutated oncogenic pathway in cancer. Although RAS, RAF and MEK have been validated as anticancer targets and KRAS G12C (G12Ci), BRAF (BRAFi) and MEK (MEKi) inhibitors are approved, it has been shown that simultaneous targeting of multiple nodes in the RAS pathway or combinations with agents targeting parallel pathways may be optimal for deep and durable response (1).

VS-6766 is a unique RAF/MEK clamp (Figure 1). In contrast to MEK-only inhibitors (MEKi), VS-6766 is a potent allosteric inhibitor of MEK kinase activity and induces a dominant negative RAF/MEK complex preventing phosphorylation of MEK by ARAF, BRAF and CRAF (2-4). VS-6766 has shown strong anti-proliferative potency across tumor cell lines carrying KRAS, BRAF, CRAF, NRAS or NF1 alterations, supporting the use of VS-6766 as a backbone of therapy for RAS pathway-driven cancers (Figure 2). An intermittent oral dosing schedule confers a manageable clinical safety profile with potential combinability with inhibitors of multiple target classes (5).

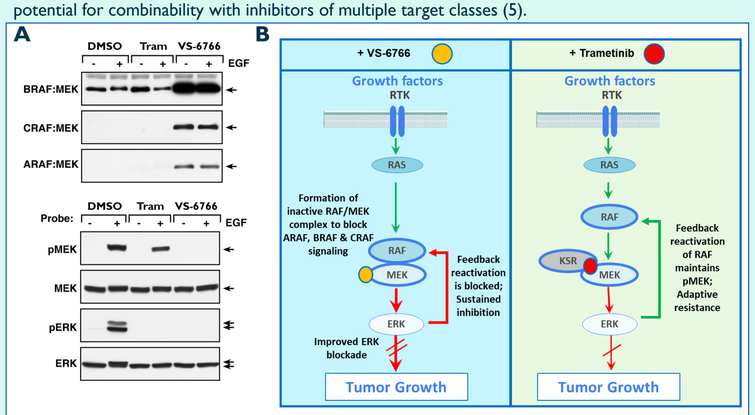

Figure 1. (A) Western blot analyses in serum-starved HeLa cells treated with 1 μM VS-6766 or 1 μM trametinib (Tram) for 3 hours and with EGF for 5 minutes (4). **(B)** Schematic showing that in contrast to MEKi (e.g. trametinib), VS-6766 is a unique RAF/MEK clamp that induces inactive complexes of MEK with ARAF, BRAF and CRAF.

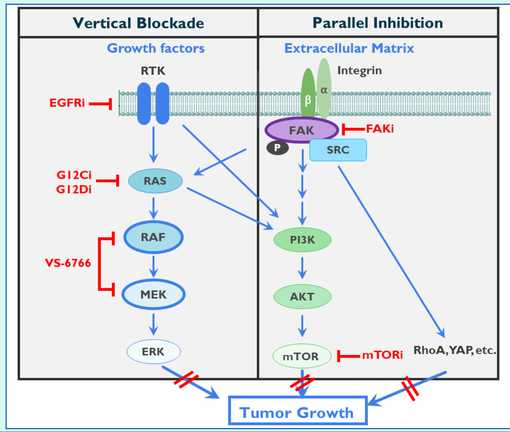

Figure 2. Establishing VS-6766 as a backbone of therapy for RAS pathway-driven cancers. (Left) Combinations of VS-6766 with agents targeting other nodes in the RAS pathway (e.g. EGFRi, G12Ci, G12Di). (Right) Combinations of VS-6766 with agents targeting parallel resistance pathways, including the FAK and PI3K/mTOR pathways.

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VS-6766 + FAK inhibition in LGSOC

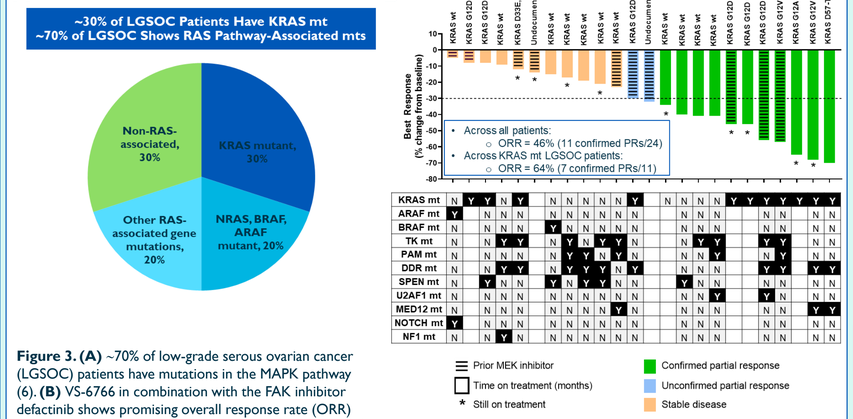

Figure 3. (A) ~70% of low-grade serous ovarian cancer (LGSOC) patients have mutations in the MAPK pathway (6). **(B)** VS-6766 in combination with the FAK inhibitor defactinib shows promising overall response rate (ORR) with durability in patients with refractory LGSOC (n = 24). Waterfall plot showing best target lesion response by RECIST from the ongoing Phase 1/2 clinical study investigating VS-6766 in combination with defactinib in patients with LGSOC (NCT03875820; September 2021 cut-off) (7). Mutation status by Foundation Medicine testing from 17 patients with available tissue are shown. Combination of VS-6766 + defactinib has Breakthrough Therapy Designation in LGSOC based on promising clinical data. An ongoing registration-directed Phase 2 study is assessing VS-6766 ± defactinib for patients with recurrent LGSOC regardless of KRAS status (NCT04625270).

VS-6766 + G12C inhibition in KRAS G12C NSCLC

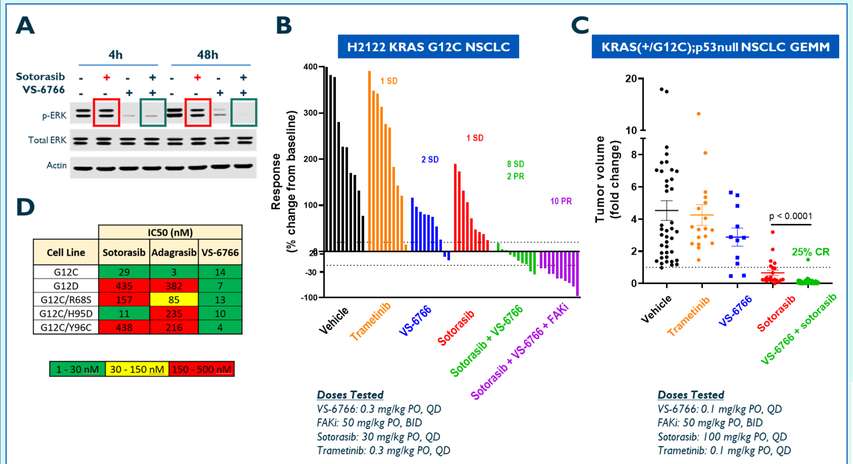

Figure 4. VS-6766 enhances antitumor efficacy of KRAS G12C inhibitors through vertical inhibition of RAS, RAF and MEK (4). These data support ongoing clinical testing of VS-6766 in combination with sotorasib (NCT05074810) or adagrasib (NCT05375994) for treatment of patients with KRAS G12C non-small cell lung cancer (NSCLC). **(A)** Addition of VS-6766 to sotorasib increases depth & duration of inhibition of p-ERK in KRAS G12C NSCLC cell lines. Western blot analyses of pERK and total ERK in H2122 KRAS G12C NSCLC cells treated with 100 nM VS-6766 ± 100 nM sotorasib. **(B, C)** VS-6766 & FAKi potentiate sotorasib efficacy in vivo. Changes in tumor volume in H2122 KRAS G12C NSCLC tumor-bearing mice (B) and KRAS(+/G12C);p53null NSCLC GEMM mice (C). N = 10 mice/group. PO: oral dosing; QD: every day; BID: twice per day. **(D)** VS-6766 is effective against acquired mutations in the MAPK pathway that occur clinically upon progression on G12C inhibitors. Proliferation assays were performed to calculate IC50 of sotorasib, adagrasib and VS-6766 in Ba/F3 cell lines expressing different KRAS variants found in G12Ci-resistant patients and cultured in RPMI 10% FBS in the absence of IL-3 for 4 days.

VS-6766 + G12D inhibition in KRAS G12D CRC

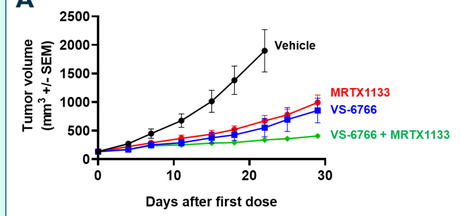

Figure 5. (A) VS-6766 enhances efficacy of the G12D inhibitor MRTX1133 in a KRAS G12D colorectal carcinoma (CRC) PDX model. Changes in tumor volume in CR3300 KRAS G12D CRC tumor-bearing mice treated with VS-6766 (0.3 mg/kg PO, QD) ± MRTX1133 (30 mg/kg PO, twice weekly; collaboration with Mirati). N = 10 mice/group. **(B)** Combination of VS-6766 with anti-EGFR mAb induces tumor regression in a KRAS mt CRC PDX model. Changes in tumor volume in KRAS G12V CRC tumor-bearing mice treated with VS-6766 (0.3 mg/kg PO, QD) ± panitumumab (20 mg/kg IP, twice weekly). N = 10 mice/group (8). These data support ongoing clinical testing of VS-6766 + anti-EGFR (cetuximab) for treatment of patients with KRAS mt CRC (NCT05200442).

VS-6766 + EGFR inhibition in KRAS mt CRC

VS-6766 + mTOR inhibition in KRAS mt NSCLC

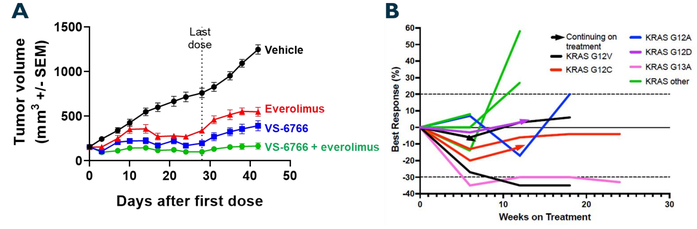

Figure 6. (A) VS-6766 enhances efficacy of the mTOR inhibitor everolimus in a KRAS mt non-small cell lung cancer (NSCLC) model. Changes in tumor volume in H441 KRAS G12V NSCLC tumor-bearing mice treated with VS-6766 (0.3 mg/kg PO, QD) ± everolimus (2.5 mg/kg PO, QD). N = 10 mice/group. **(B)** VS-6766 in combination with everolimus shows promising ORR with durability in patients with KRAS mt NSCLC (n = 11). Spider plot showing best target lesion response by RECIST from the ongoing Phase 1/2 clinical study investigating VS-6766 in combination with everolimus in patients with KRAS mt NSCLC (NCT02407509; April 2022 cut-off) (9).

VS-6766 + chemotherapy + FAK inhibition in first line PDAC

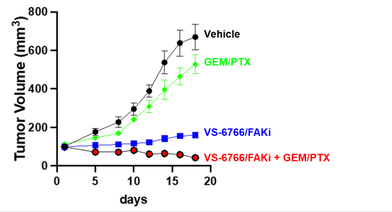

Figure 7. Combination of VS-6766 with chemotherapy and FAK inhibitor induces tumor regression in a KRAS mt pancreatic cancer (PDAC) model. Changes in tumor volume in KP2 KRAS G12D/p53 pancreatic cancer tumor-bearing mice treated with VS-6766 (0.3 mg/kg PO, QD) + FAKi (50 mg/kg PO, BID) ± gemcitabine/paclitaxel (GEM/PTX; 75 mg/kg / 10 mg/kg IP, every 5 days). Paclitaxel was used as a surrogate for nab-paclitaxel in mice. N = 10 mice/group. These data support initiation of clinical testing of VS-6766 + gemcitabine/nab-paclitaxel + defactinib for treatment of patients with first line pancreatic cancer (RAMP-205).

CONCLUSIONS

- VS-6766 is a unique RAF/MEK clamp which has the potential to be a backbone of therapy with distinct rational combinations for multiple RAS pathway-driven cancers
- Intermittent oral dosing schedule confers manageable clinical safety profile with potential combinability with inhibitors of multiple target classes
- The VS-6766 clinical trial program includes rational combinations with 1) defactinib (FAKi) in low-grade serous ovarian cancer *(NCT03875820, NCT04625270)*, 2) sotorasib or adagrasib (G12Ci) in KRAS G12C NSCLC *(NCT05074810 & NCT05375994, respectively)*, 3) cetuximab (anti-EGFR) in KRAS mt CRC *(NCT05200442)*, 4) everolimus (mTORi) in KRAS mt NSCLC *(NCT02407509)*, and 5) chemotherapy and defactinib in first line pancreatic cancer *(RAMP-205)*
- Preclinical data also support combination of VS-6766 with G12Di in KRAS G12D cancers including CRC