

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

Silvia Coma¹, Deborah K Morrison², Monica Musteanu^{3,4}, Chongkai Wang⁵, Julien Dilly⁶, Xiuting Liu⁷, Udai Banerji⁸, Ardaman Shergill⁹, Andrew Aguirre⁶, David G DeNardo⁷, Mariano Barbacid³, Marwan Fakih⁵, Jonathan A Pachter¹

¹ Verastem Oncology, Needham, MA, USA; ² Laboratory of Cell and Developmental Signaling, NCI-Frederick, Frederick, Frederick, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Complutense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Complutense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Complutense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Complutense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Complutense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Complutense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Complutense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Complutense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Completense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Completense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Completense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Completense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Completense University Madrid, Spain; ⁴ Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Completense University Madrid, Spain; ⁴ Department of Biochemistry and Bio ⁵ Department of Medical Oncology, City of Hope National Medical Center, Duarte, USA; ⁶ Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; ⁷ Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA; ⁸ Drug Development Unit, The Institute of Cancer Research/The Royal Marsden Hospital NHS Foundation Trust, UK; ⁹ University of Chicago Medical Centre, Chicago, USA

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 NFI 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 for combinability with inhibitors of multiple target classes (5).



Figure I. (A) Western blot analyses in serum-starved HeLa cells treated with 1 µMVS-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.



REFERENCES

- I. Ryan et al., Clinical Cancer Research 2019
- 2. Ishii et al., Cancer Research 2013
- 3. Lito et al., Cancer Cell 2014
- 4. Coma et al., AACR Annual Meeting 2022
- 5. Shinde et al., AACR Annual Meeting 2020
- 6. AACR GENIE v9.0 LGSOC cohort
- 7. Steward et al., AACR Annual Meeting 2022
- 8. Pachter et al., RAS Development Summit 2021
- 9. Minchom et al., ASCO Annual Meeting 2022





Α

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 GI2C 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 nMVS-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 GI2C 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 + FAK inhibition in LGSOC

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 + GI2C inhibition in KRAS GI2C NSCLC

The Fourth RAS Initiative Symposium; October 17-19, 2022



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 GI2D CRC tumor-bearing mice treated with VS-6766 (0.3 mg/kg PO, QD) ± MRTXII33 (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 + mTOR inhibition in KRAS mt NSCLC

Figure 6. (A) VS-6766 enhances efficacy of the mTOR inhibitor everolimus in a KRAS mt nonsmall 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).

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) \pm 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).

- combinations for multiple RAS pathway-driven cancers
- multiple target classes





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).



CONCLUSIONS

VS-6766 is a unique RAF/MEK clamp which has the potential to be a backbone of therapy with distinct rational

Intermittent oral dosing schedule confers manageable clinical safety profile with potential combinability with inhibitors of

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