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Abstract #1425

Synergistic Antitumor Efficacy of the Dual RAF/MEK Inhibitor VS-6766 with FAK inhibition for Treatment of RAS-Dependent Solid Tumors

Silvia Coma[1], Monica Musteanu[2], Justine S. Paradis[3], J. Silvio Gutkind[3], Mariano Barbacid[2], Jonathan A. Pachter[1]

[1] Verastem Oncology, Needham MA; [2] Centro Nacional de Investigaciones Oncológicas, Madrid; [3] Moores Cancer Center, University of California San Diego, La Jolla, CA

Verastem Oncology

VS-6766 (RAF/MEKi) and Defactinib (FAKi) in Low-Grade Serous Ovarian Cancer

Low-grade serous ovarian cancer is a RAS-driven subtype of ovarian cancer

- Low-grade serous ovarian cancer (LGSOC) is a slow-growing cancer with ~30% of patients harboring KRAS mutations and an additional ~40% of patients harboring mutations in other RAS-pathway associated genes[1].
- Here, we present preclinical and clinical data supporting the combination of VS-6766 and defactinib in LGSOC. VS-6766 is a unique dual RAF/MEK inhibitor which allows VS-6766 to block MEK signaling without the compensatory MEK activation that limits the efficacy of other MEK inhibitors (Figure 1A)[2]. Defactinib is a selective FAK inhibitor (FAKi). RAF and MEK inhibition have been shown to induce compensatory activation of pFAK preclinically and clinically (Figure 1B) and VS-6766 and defactinib have been combined to overcome this potential resistance mechanism[3,4,5].

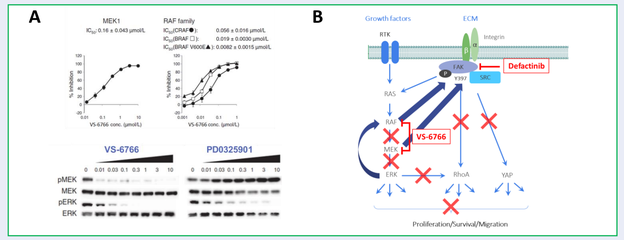

Figure 1. (A) VS-6766 is a unique dual RAF/MEK inhibitor which allows VS-6766 to block MEK signaling without the compensatory MEK activation that limits the efficacy of other MEK inhibitors. **(B)** RAF and MEK inhibition induce compensatory activation of pFAK preclinically and clinically, providing rationale for the combination of RAF/MEK + FAK inhibitors.

VS-6766 and FAK inhibitor combination leads to more robust anti-tumor efficacy in KRAS mutant ovarian cancer models

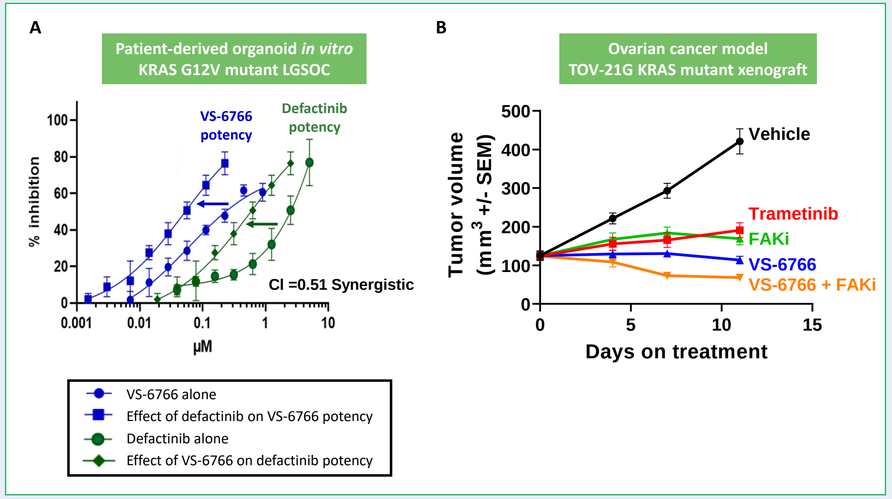

Figure 2. (A) Strong synergy between VS-6766 and FAKi (defactinib) in a patient-derived LGSOC G12V mt organoid *in vitro*. Addition of each agent improves the potency of the other. Combination index (CI) was calculated using Chou and Talalay method (>1 = antagonistic & <1 = synergistic). Data kindly provided by Lisa Pickard and Udai Banerji (The Institute of Cancer Research, UK). **(B)** Changes in tumor volume in TOV-21G tumor bearing mice treated with VS-6766 (1.5 mg/kg QD) ± FAKi (50 mg/kg BID) as compared with trametinib (1.5 mg/kg QD). Combination of VS-6766 + FAKi induces tumor regression.

VS-6766 in combination with defactinib shows robust ORR with durability in refractory LGSOC[6]

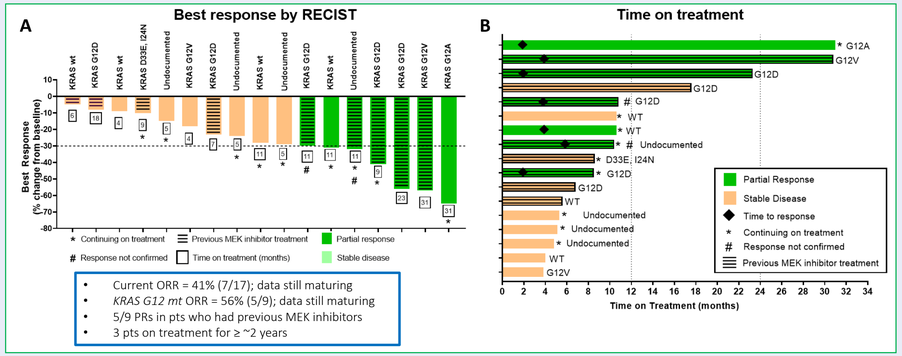

Figure 3. Best response **(A)** and time on treatment **(B)** from the ongoing investigator-initiated Phase 1/2 clinical study investigating VS-6766 in combination with defactinib in patients with LGSOC (NCT03875820; data cutoff August 17, 2020)[6]. Patients with KRAS G12 mutant tumors (n=9) had an overall response rate (ORR) of 56% (5/9).

CONCLUSIONS

- FAK inhibition enhances anti-tumor activity of VS-6766 in a KRAS mutant patient-derived LGSOC organoid *in vitro* and in a KRAS mutant ovarian cancer xenograft model *in vivo*
- In LGSOC, the combination of VS-6766 + defactinib has shown clinical activity in patients with KRAS mutant LGSOC regardless of the specific KRAS mutation variant
- These preclinical and clinical data support the ongoing registration-directed phase 2 study evaluating VS-6766 ± defactinib for the treatment of recurrent LGSOC with or without a KRAS mutation (NCT04625270)

VS-6766 (RAF/MEKi) and Defactinib (FAKi) in KRAS G12V mutant Non-Small Cell Lung Cancer

KRAS G12V mutant NSCLC is especially dependent on CRAF

- KRAS G12V mutation occurs in 7% of non-small cell lung carcinoma (NSCLC) adenocarcinoma[7]. KRAS G12V mt signals mainly through RAF/MEK in contrast to other variants, such as KRAS G12D, which signal through PI3K/AKT (Figure 4A)[8,9]. KRAS G12V NSCLC models are especially dependent on CRAF (Figure 4B)[10,11].
- Here, we present preclinical and clinical data supporting the use of VS-6766 alone and/or in combination with defactinib in KRAS G12V mt NSCLC. VS-6766 is a unique dual RAF/MEK inhibitor that inhibits CRAF in addition to inhibiting MEK (Figure 1A)[2]. Defactinib is a selective FAK inhibitor (FAKi) and preclinical and clinical data support the combination of RAF/MEK + FAK inhibition (Figure 1B)[3,4,5].

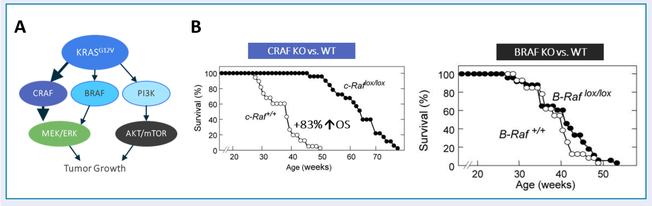

Figure 4. (A) KRAS G12V mutant signals mainly through RAF/MEK in contrast to other variants, such as KRAS G12D, which signal through PI3K/AKT. **(B)** KRAS G12V mutant models are especially dependent on CRAF.

VS-6766 and FAK inhibitor combination induces robust anti-tumor efficacy in CRAF-dependent KRAS G12V mutant NSCLC models *in vitro* and *in vivo*

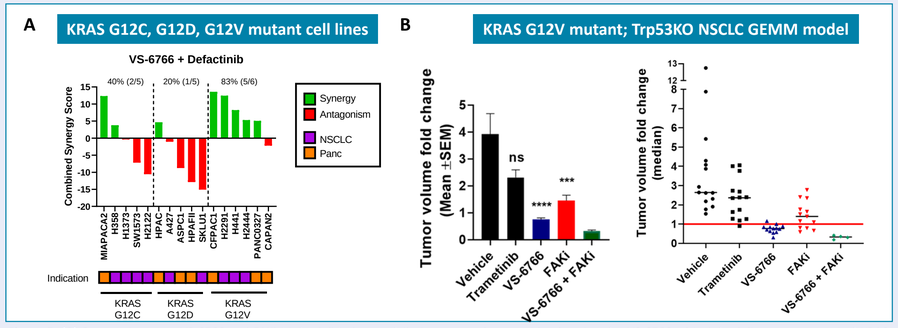

Figure 5. (A) Synergy between VS-6766 and FAKi (defactinib). A waterfall plot summarizes combination data for VS-6766 with defactinib across a panel of KRAS G12C, G12D & G12V NSCLC and PDAC cell lines. Bliss, Loewe, HSA and ZIP synergy analyses were performed to generate a composite synergy score. Synergy between VS-6766 and defactinib was strongest in KRAS G12V mt cell lines. **(B)** Changes in tumor volume in KRAS G12 mutant; Trp53KO NSCLC mice treated with VS-6766 (0.1 mg/kg QD) +/- FAKi (50 mg/kg BID) as compared with trametinib (0.1 mg/kg QD). VS-6766, but not trametinib, significantly inhibits tumor growth.

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Strong signal identified in KRAS G12V NSCLC patients treated with VS-6766 alone or in combination with defactinib[12,13]

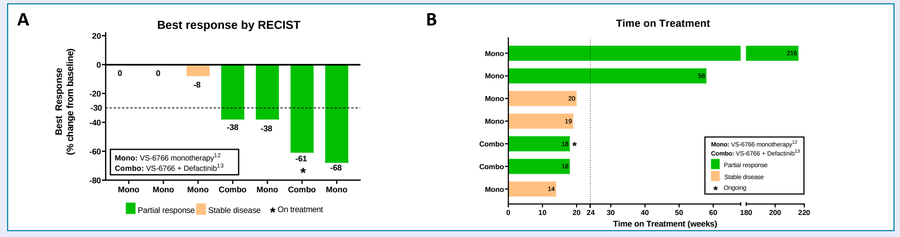

Figure 6. Best response **(A)** and time on treatment **(B)** in KRAS G12V mutant NSCLC patients from the completed investigator-initiated Phase 1 clinical study investigating VS-6766 monotherapy (NCT02407509)[12] and the ongoing investigator-initiated Phase 1/2 clinical study investigating VS-6766 in combination with defactinib (NCT03875820)[13]. Patients with KRAS G12V mutant tumors (n=7) had an overall response rate (ORR) of 57% (4/7). For an update on the status of NSCLC patients receiving VS-6766 + defactinib, please attend oral presentation #CT01 by Matthew Krebs on April 10, 2021 at 2:35 pm (Channel 08).

CONCLUSIONS

- Strong synergy observed between VS-6766 (RAF/MEKi) and defactinib (FAKi) in KRAS G12V mutant cell lines
- VS-6766 and FAK inhibitor combination induces robust anti-tumor efficacy in CRAF-dependent KRAS G12V mutant NSCLC cancer model *in vivo*, in contrast to trametinib
- Strong activity signal in KRAS G12V mt NSCLC patients. For an update on the status of NSCLC patients receiving VS-6766 + defactinib, please attend oral presentation #CT01 by Matthew Krebs on April 10, 2021 at 2:35pm (Channel 08).
- These preclinical and clinical data support the ongoing registration-directed phase 2 study evaluating VS-6766 ± defactinib for the treatment of recurrent NSCLC with KRAS G12V or other KRAS mutation (NCT04620330)