Mechanistic evaluation of VS-6766 (RAF/MEK clamp) and defactinib (FAK inhibitor) in low-grade serous ovarian cancer models with correlations to clinical response

Abstract #3476

Adam Stewart[1], Sara Diaz-Sanchez[1], Lisa Pickard[1], Ekta Paranjape[1], Victoria Sanchez Perez[2], Sanjib Chowdhury[3], Stephanie Lustgarten[3], Silvia Coma[3], Jonathan A Pachter[3], Mark Carey[4], Gabriel DiMattia[5], Hannah Badham[1], Toby Prout[1], Mona Parmar[1], Muneeb Mahmud[1], Christina Yap[1], Matthew Krebs[6], Susana Banerjee[2], Udai Banerji[1,2]

[1]The Institute of Cancer Research, London UK; [2]The Royal Marsden Hospital NHS Foundation Trust, London UK; [3]Verastem Oncology, Needham, MA, USA; [4]University of British Columbia, Canada; [5]University of Western Ontario, London, Canada; [6]Christie Hospital, Manchester, UK

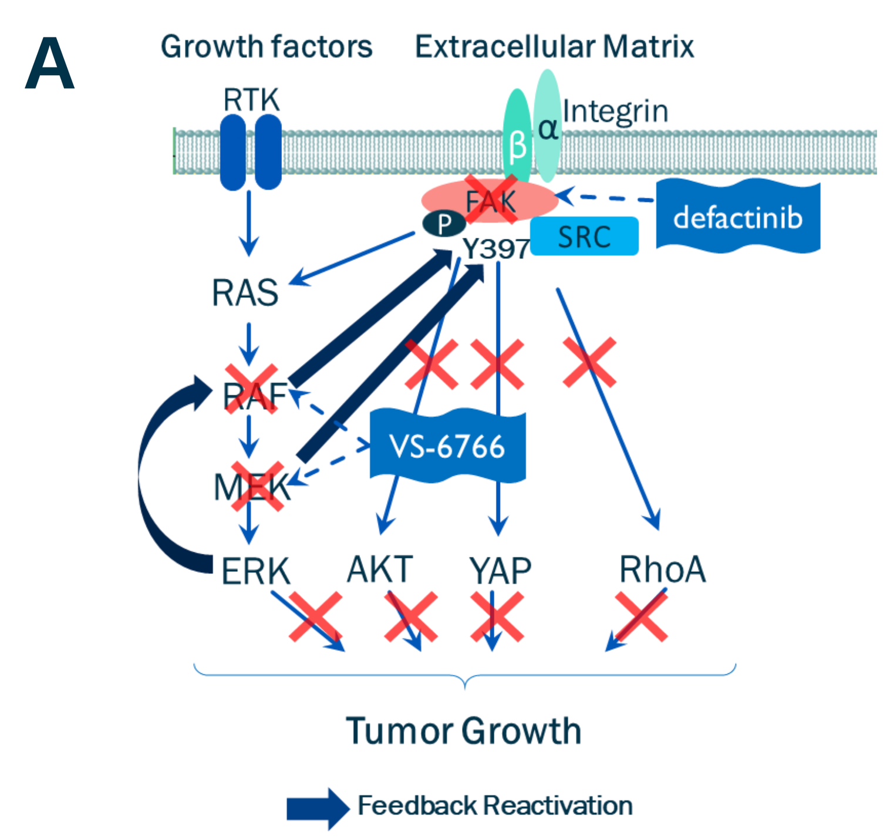
BACKGROUND

Low-grade serous ovarian cancer (LGSOC) constitutes ~10% of all ovarian cancer and has clinical and molecular characteristics (resistance to chemotherapy, presence of RAS/RAF mutations, lack of TP53 mutations) distinct from high-grade serous ovarian cancer.

Patients with LGSOC have limited response to conventional chemotherapy and hormonal therapy. Recently, MEK inhibitors (MEKi) have shown an overall response rate (ORR) of 16-26% (Gershenson, et al. Lancet 2022; Monk et al., J Clin Oncol 2020). Activation of p-FAK is a possible mechanism of resistance to MEKi and we hypothesized that the combination of VS-6766 (RAF/MEK clamp) (Ishii et al., Cancer Res, 2013; Lito et al., Cancer Cell, 2014). with defactinib (FAK inhibitor) would overcome this mechanism of resistance observed with MEKi (Figure 1A). Indeed, FAK inhibition enhances anti-tumor activity of VS-6766 in a KRAS mutant ovarian cancer xenograft model in vivo (Figure 1B).

Clinical studies are ongoing evaluating VS-6766 and defactinib for the treatment of various solid tumors. The combination of VS-6766 with defactinib with an intermittent schedule has shown clinical activity for patients with KRAS G12V and KRAS G12C non-small cell lung cancer (NSCLC) and LGSOC with a manageable safety profile relative to MEK-only inhibitors (Krebs et al., AACR 2021; Banerjee et al., ESMO 2021).

Here, we characterized the effects of VS-6766 and defactinib on signal transduction and viability in LGSOC cell lines and patient-derived organoids. To correlate molecular characteristics with clinical response, we characterized genomic alterations in archival tumor samples from patients with LGSOC treated with the combination of VS-6766 and defactinib on the Phase 1/2 FRAME study.



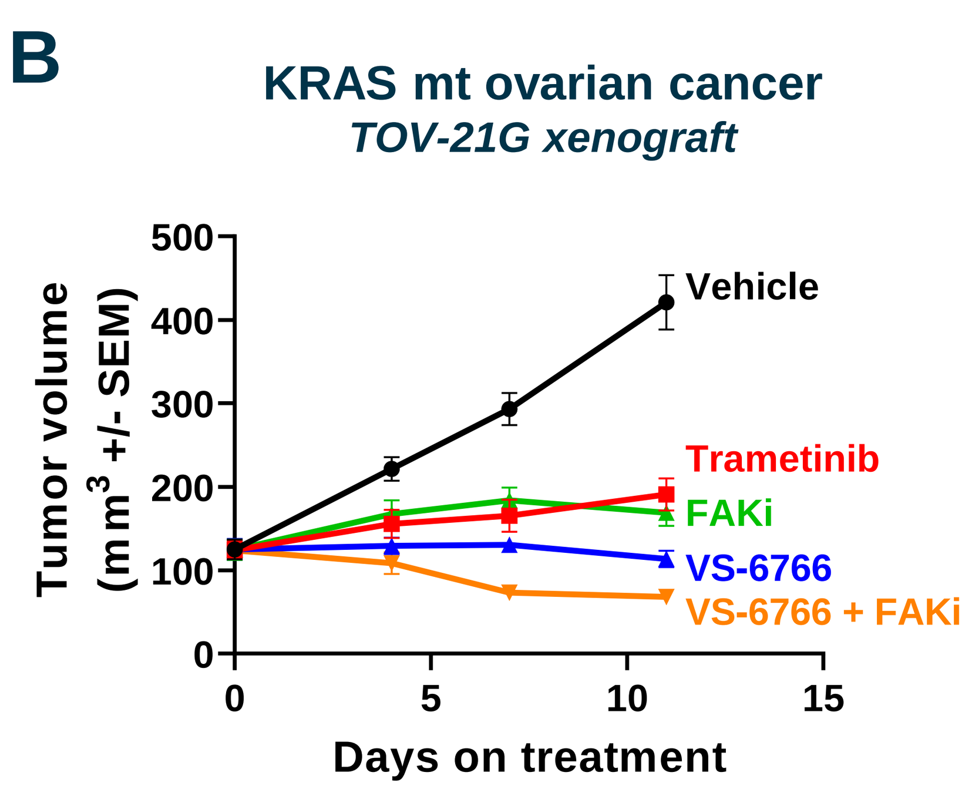


Figure 1. (A) Combination of VS-6766 (RAF/MEK clamp) with defactinib (FAK inhibitor) to overcome mechanisms of resistance to MAPK pathway inhibition. (B) Changes in tumor volume in TOV-21G tumor bearing mice treated with VS-6766 (1.5 mg/kg QD) ± FAKi (50 mg/kg BID) as compared with trametinib (1.5 mg/kg QD). Combination of VS-6766 + FAKi induces tumor regression.

RESULTS

Synergy between VS-6766 (RAF/MEK clamp) and defactinib (FAK inhibitor) in a patient-derived LGSOC organoid model

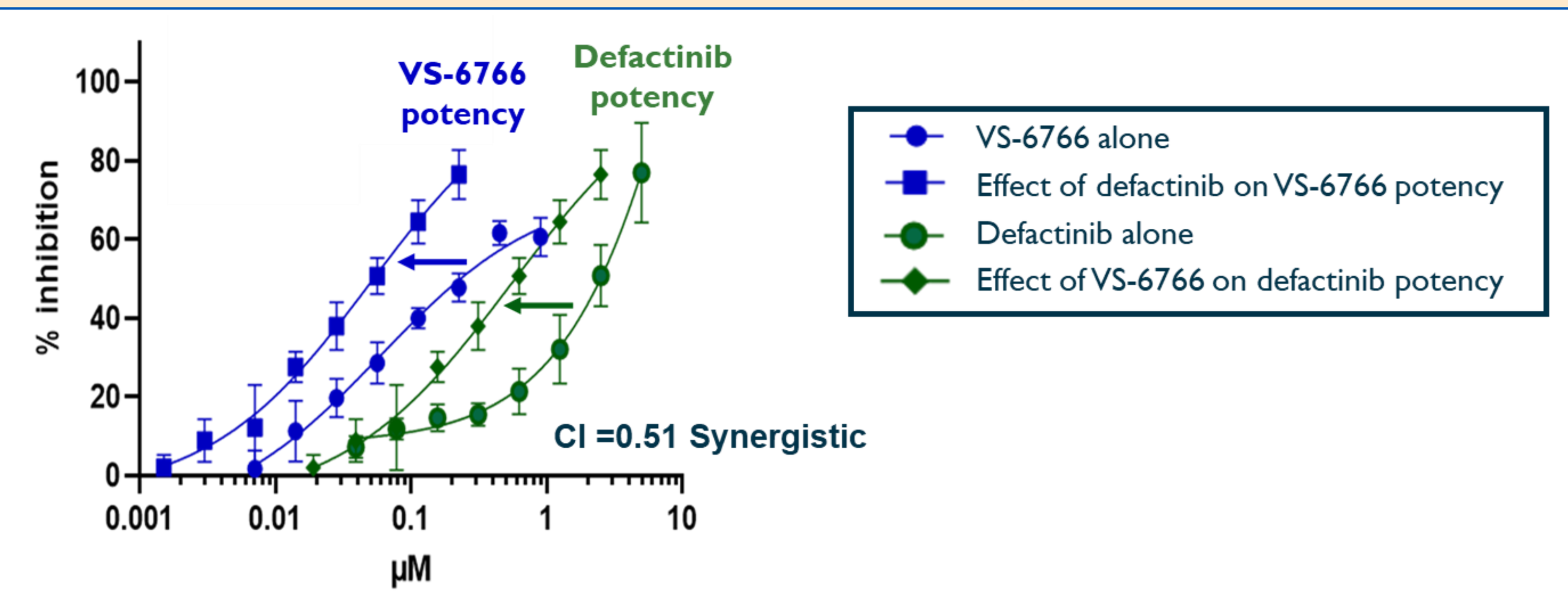
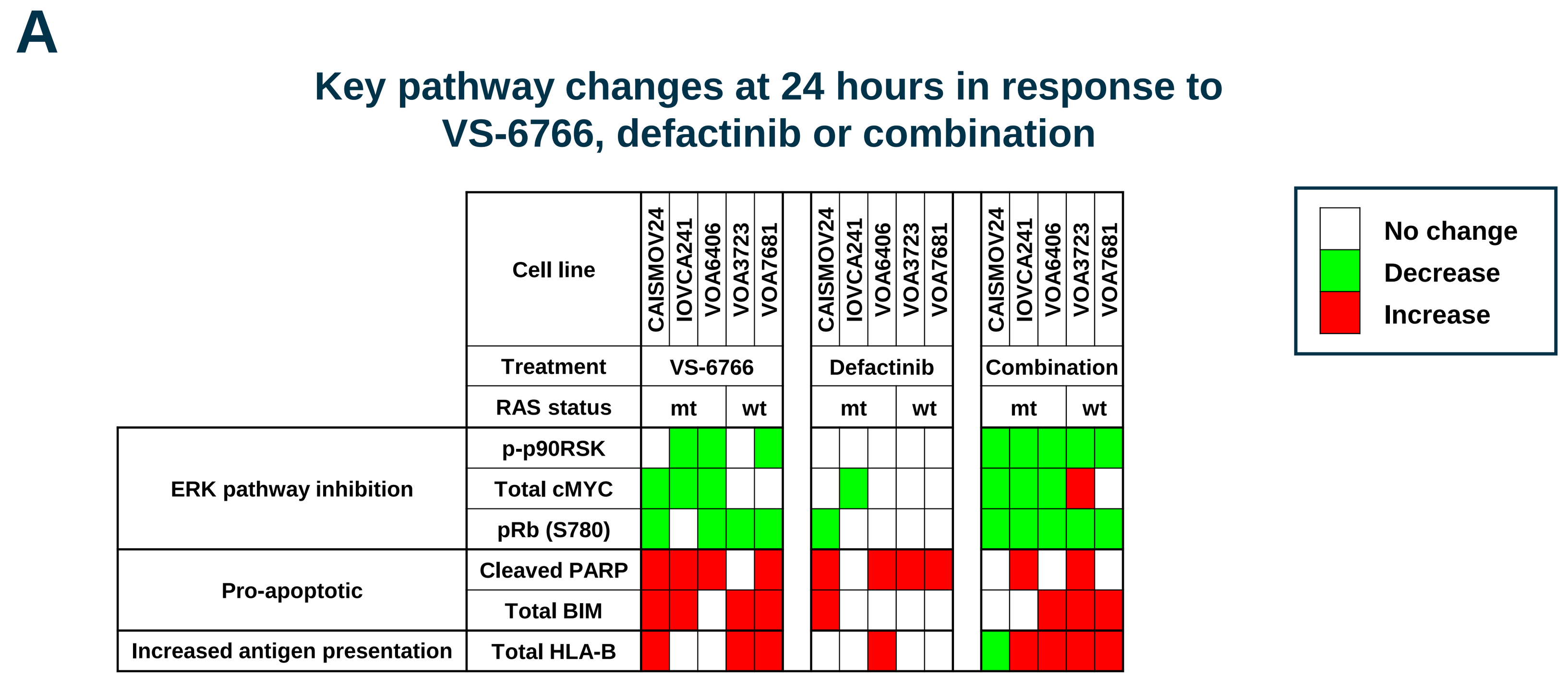
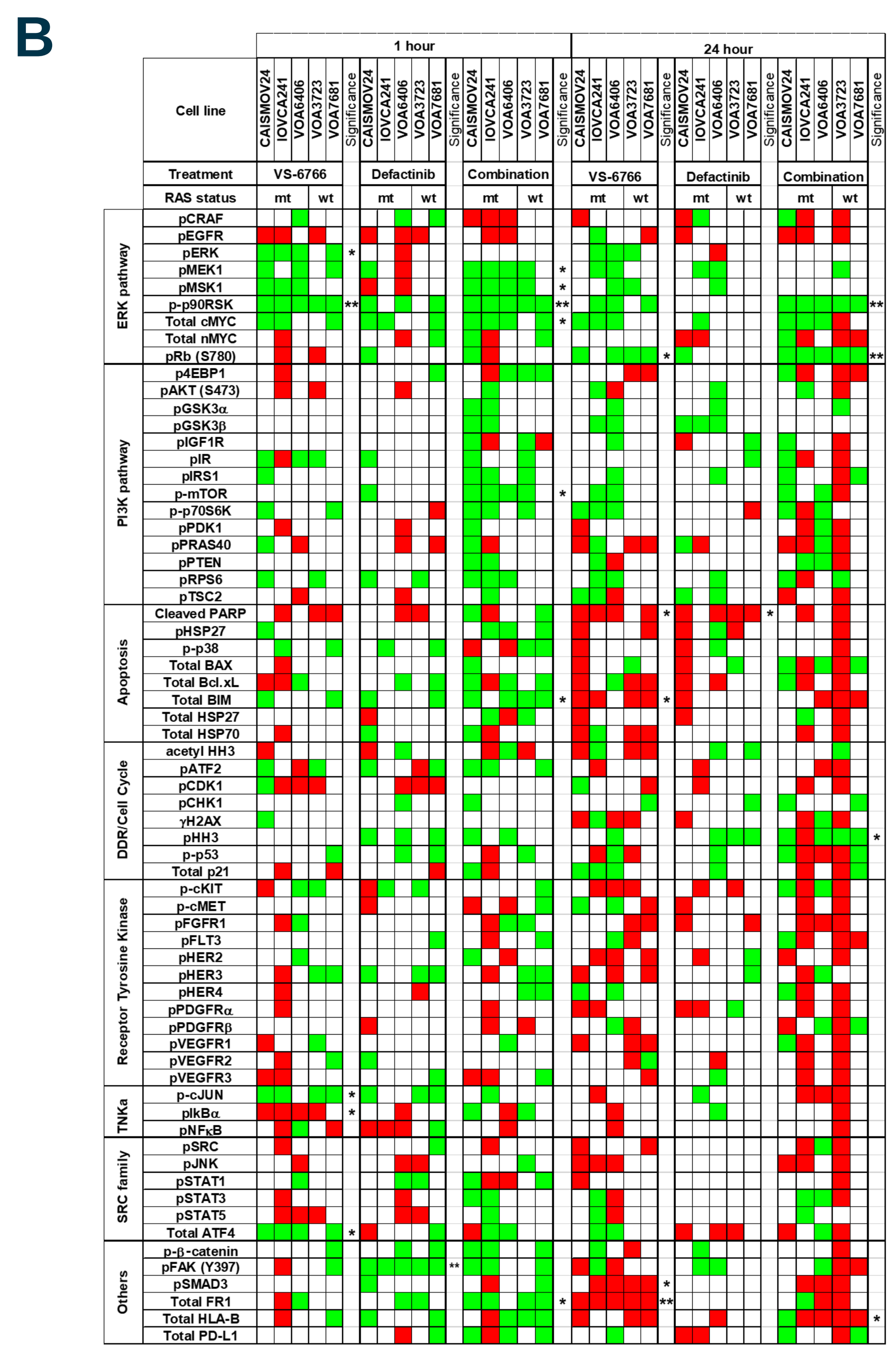


Figure 2. Strong synergy between VS-6766 and defactinib in a patient-derived LGSOC KRAS G12V mt organoid model *in vitro*. Addition of each agent improves the potency of the other. Combination index (CI) was calculated using Chou and Talalay method (CI > 1: antagonistic & CI = <1: synergistic).

RESULTS

In LGSOC cell lines, VS-6766 ± defactinib inhibits ERK pathway signaling and increases pro-apoptotic and antigen presentation markers





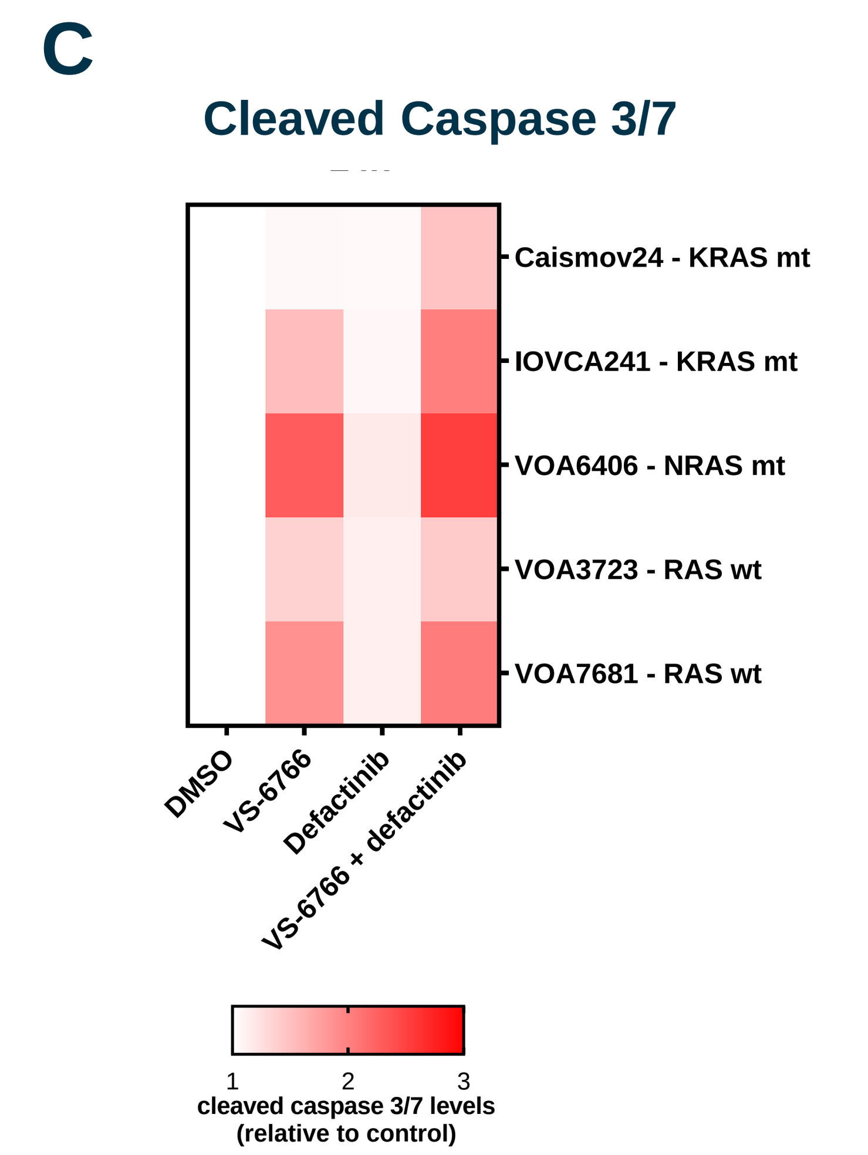
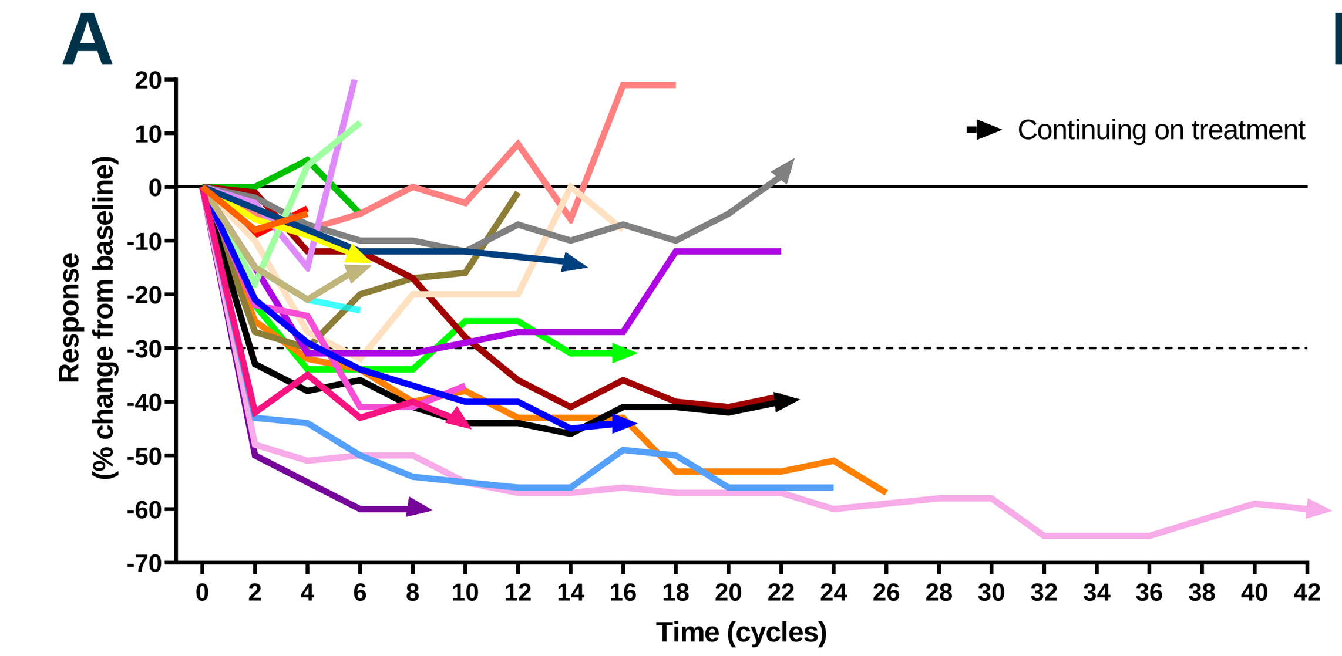
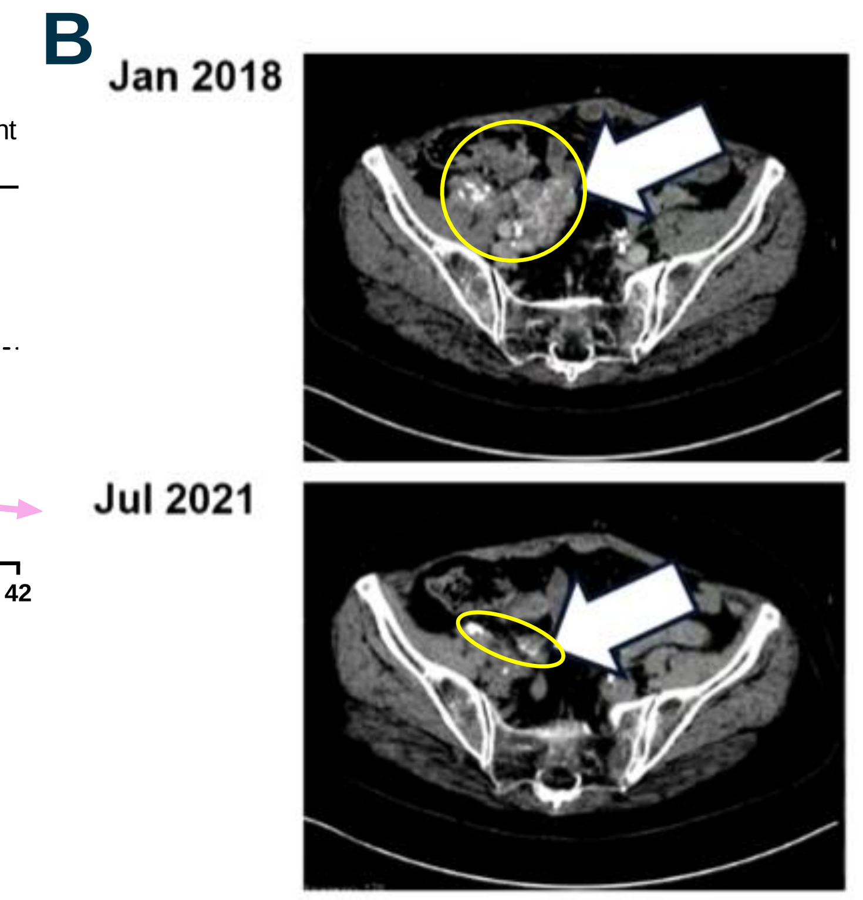


Figure 3. (A, B) Luminex analysis (protein levels) in human LGSOC cell lines treated for 1 or 24 hours with the clinical Cmax equivalent for each agent (156 nM VS-6766 or 769 nM defactinib) or in combination. (A) Key pathway changes at 24 hours in response to VS-6766, defactinib or combination. (B) Full Luminex analysis. Statistically significant changes by Mann Whitney U tests (Wilcoxon rank sum) are shown. (C) Cleaved caspase 3/7 in human LGSOC cell lines treated for 24 hours with the clinical Cmax equivalent for each agent (156 nM VS-6766 or 769 nM defactinib) or in combination.

VS-6766 in combination with defactinib shows robust ORR and durability in refractory LGSOC

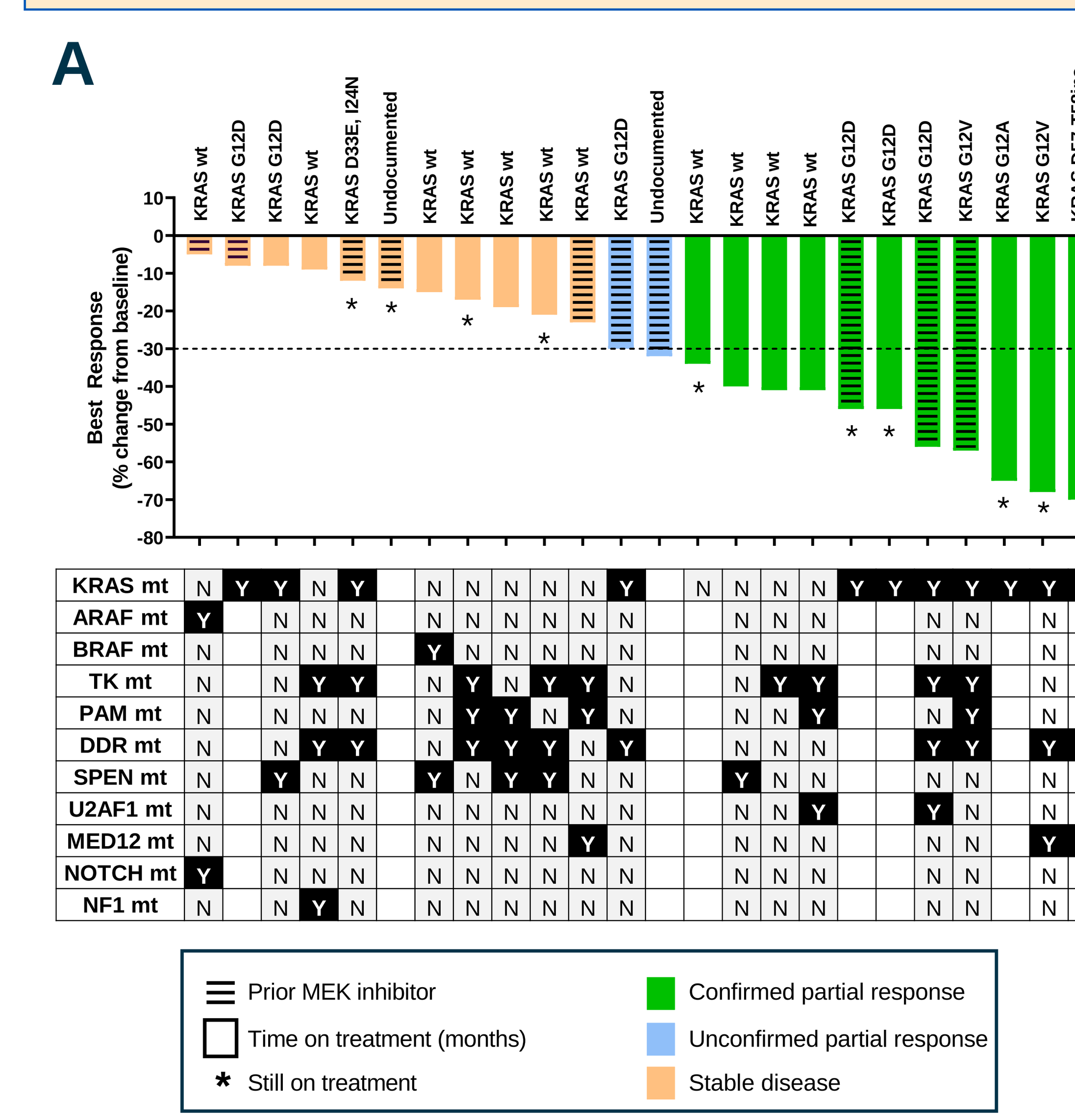




- Across all patients:
  - ORR = 46% (11 confirmed PRs/24)
- Across KRAS mt LGSOC patients:
  - ORR = 64% (7 confirmed PRs/11)

Figure 4. (A) Spider plot depicting response (% change from baseline in target lesions) of individual patients 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). ORR = Objective response rate; PRs = partial response. (B) Case study of an LGSOC patient treated with VS-6766 + defactinib showing tumor reduction. Confirmed partial response was observed.

Correlation between response to VS-6766 + defactinib and mutation status



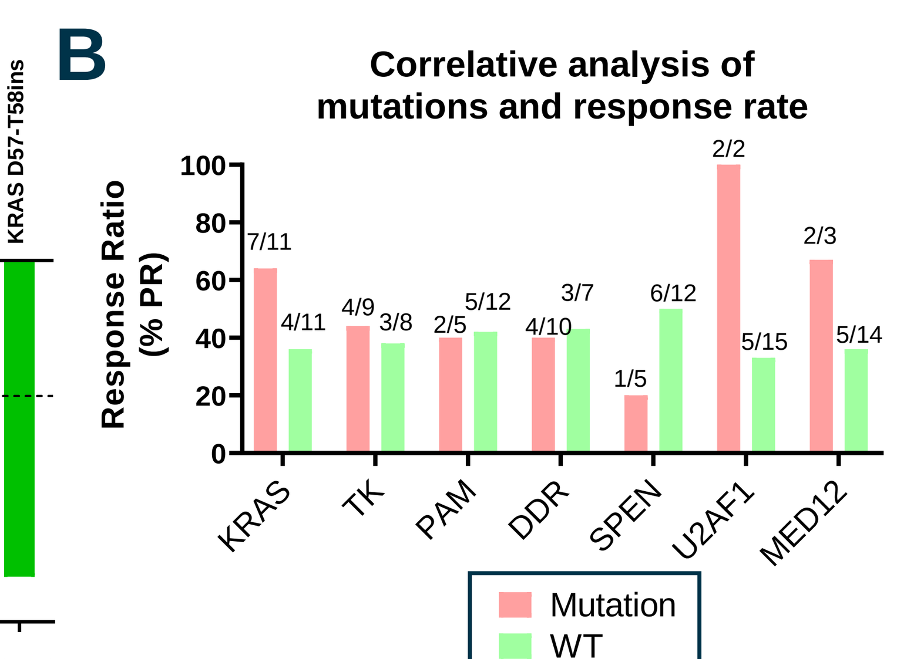


Figure 5. (A) Waterfall plot showing best target lesion response by RECIST from the ongoing Phase 1/2 clinical study investigating VS-6766 in combination with defactinib in patients with LGSOC (NCT03875820; September 2021 cut-off). Mutation status by Foundation Medicine testing from 17 patients with available tissue are shown below. (B) Response ratio (% PR) in patients with mutation (mt) vs. wild-type (WT) for KRAS, TK (tyrosine kinase), PAM (PI3K/AKT/mTOR), DDR (DNA damage response), SPEN, U2AF1 and MED12 genes.

CONCLUSIONS

- VS-6766 + defactinib shows robust anti-tumor efficacy in preclinical LGSOC models and patients with LGSOC in both KRAS mt and KRAS wt backgrounds.
  - VS-6766 + defactinib synergistically inhibit proliferation of organoids derived from a patient with LGSOC.
  - VS-6766 inhibits ERK pathway signaling, increases apoptosis and increases antigen presentation markers in both KRAS mt and KRAS wt LGSOC cell lines, and combination with defactinib enhances these effects.
  - Clinically, VS-6766 + defactinib shows an ORR of 11/24 (46%) across all patients with LGSOC, and an ORR of 64% (7/11) for patients with KRAS mt LGSOC (n=11) (NCT03875820; September 2021 cut-off).
  - Confirmed clinical responses are observed for LGSOC patients with a wide variety of signaling node mutations, including KRAS, tyrosine kinases, DNA damage response genes as well as U2AF1 and MED12.
- These results provide mechanistic insights into the encouraging response rates and progression free survival observed in patients with LGSOC treated with VS-6766 + defactinib (NCT03875820). These data support the ongoing registration-directed Phase 2 RAMP 201 study assessing VS-6766 ± defactinib for patients with recurrent LGSOC regardless of KRAS status (NCT04625270).