Dual RAF/MEK inhibitor VS-6766 as a Backbone of Therapy for RAS Pathway-Driven Cancers

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Disclosures

- I am an employee of Verastem Oncology
- I will be discussing investigational/off-label uses of VS-6766 (RAF/MEK inhibitor) and defactinib (focal adhesion kinase inhibitor)

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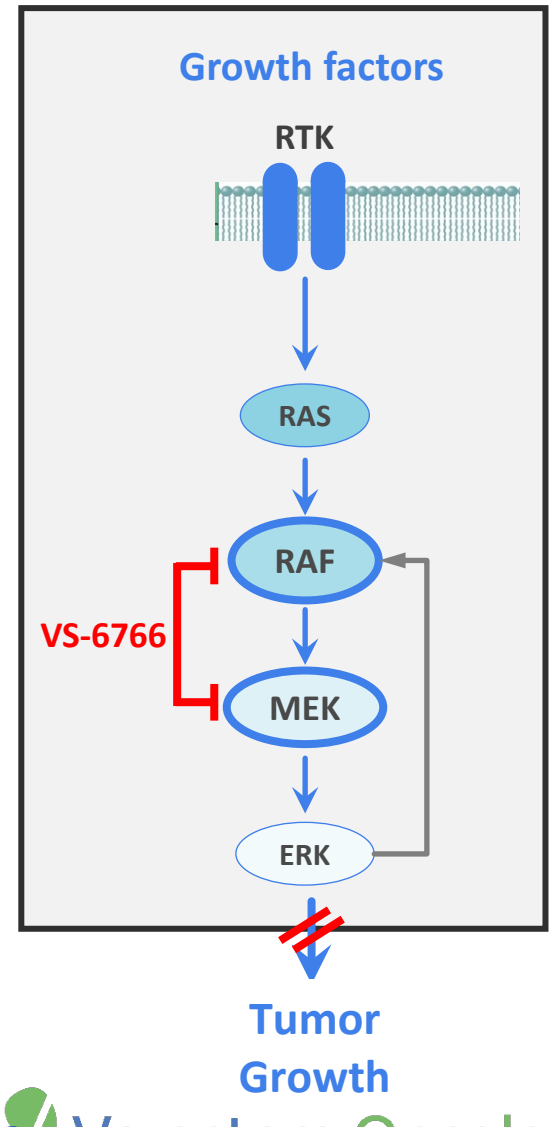
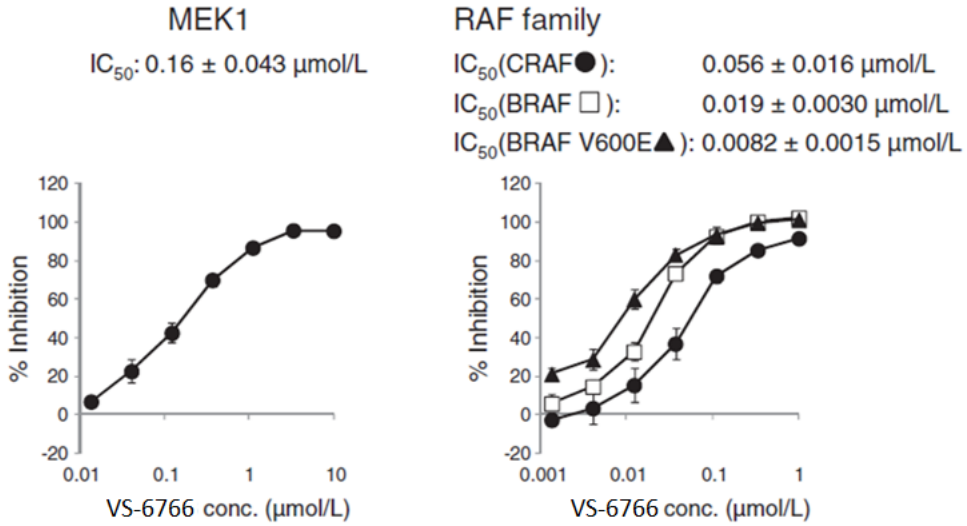
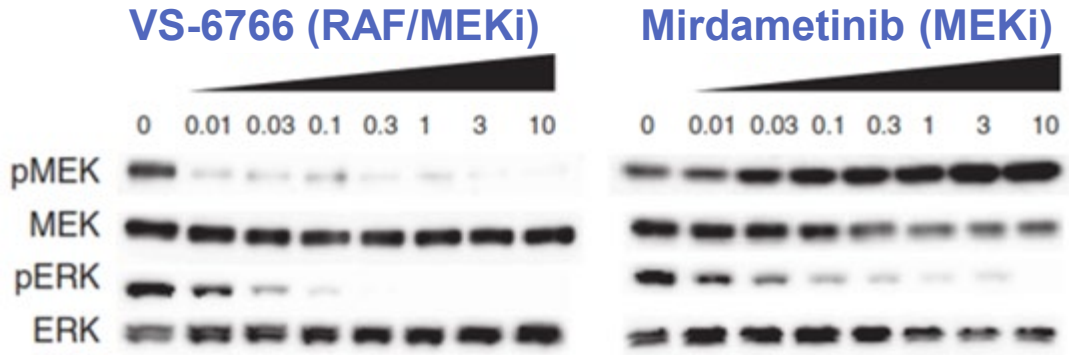
VS-6766 is a Unique Small Molecule RAF/MEK Inhibitor



- VS-6766 inhibits both MEK & RAF kinase activities
- MEK inhibitors paradoxically induce MEK phosphorylation (pMEK) by relieving ERK-dependent feedback inhibition of RAF
- By inhibiting RAF phosphorylation of MEK, VS-6766 has advantage of not inducing pMEK
- VS-6766 inhibits ERK signaling more completely; may confer enhanced therapeutic activity





References: Ishii et al., Cancer Res, 2013; Lito et al., Cancer Cell, 2014

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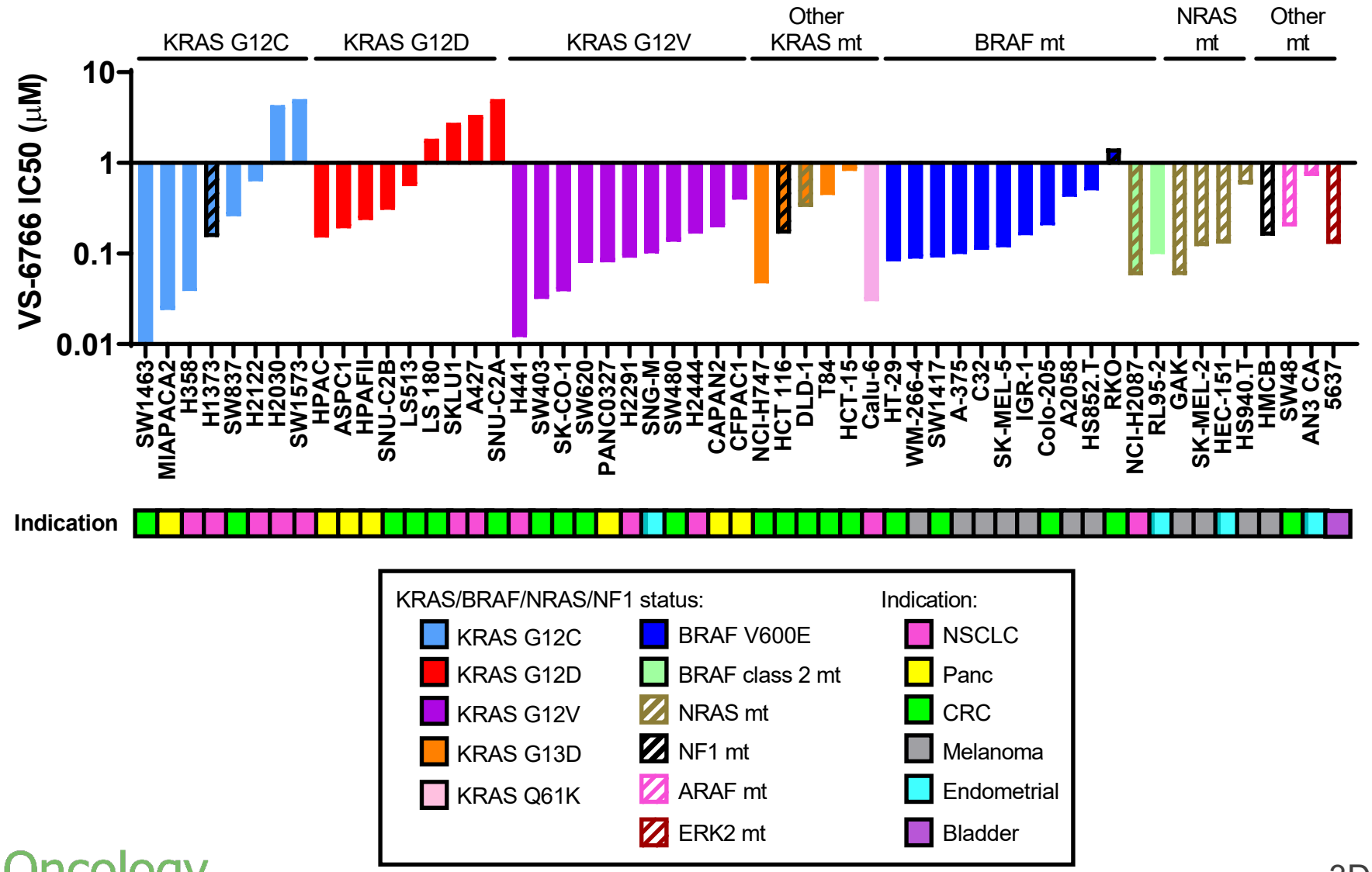
VS-6766 inhibits cell proliferation across multiple MAPK pathway alterations and multiple solid tumor indications



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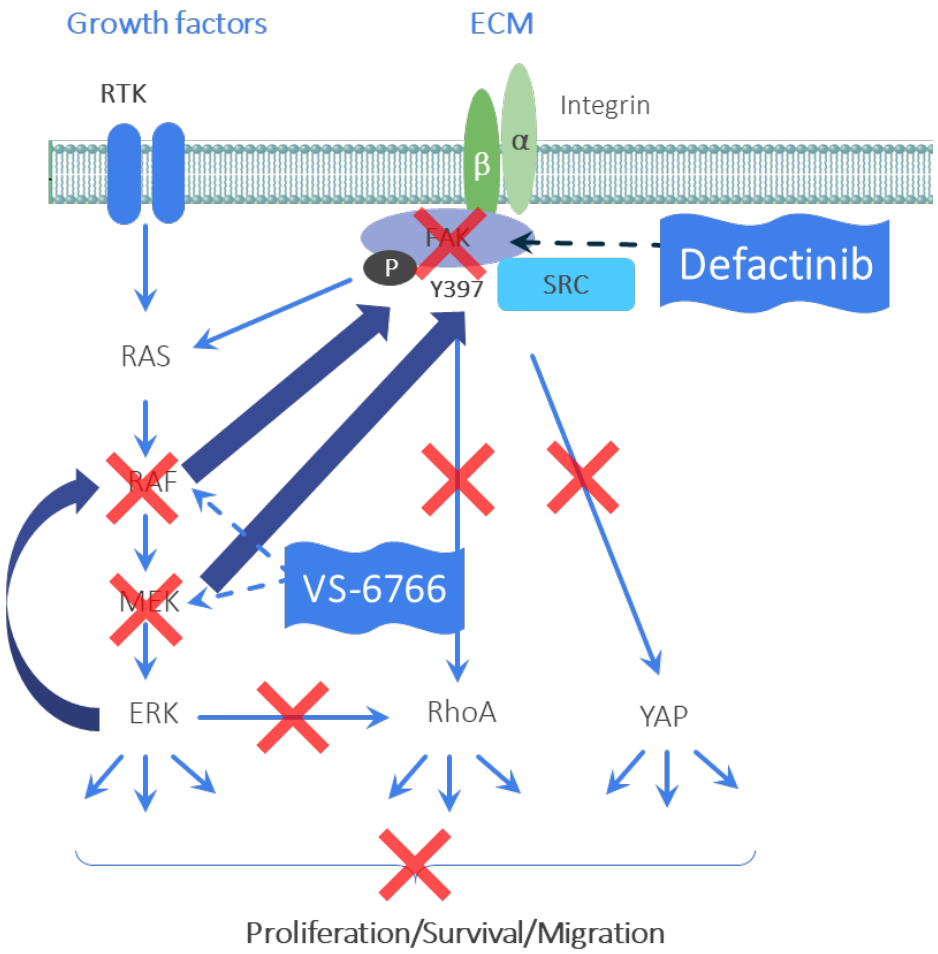
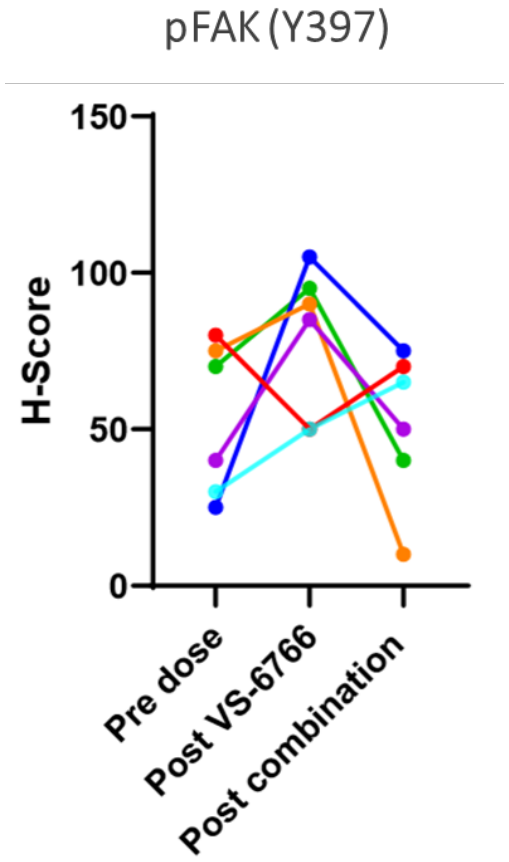
3D proliferation assay

Combination of VS-6766 with FAK Inhibitor Leads to More Robust Anti-Tumor Efficacy *In vivo* & Suppresses pFAK in Patients' Tumors



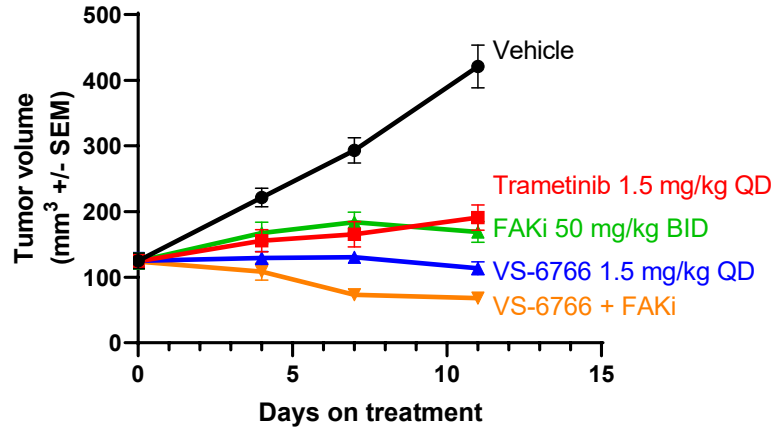
➡ = Feedback Reactivation

VS-6766 induces pFAK in patients' tumors

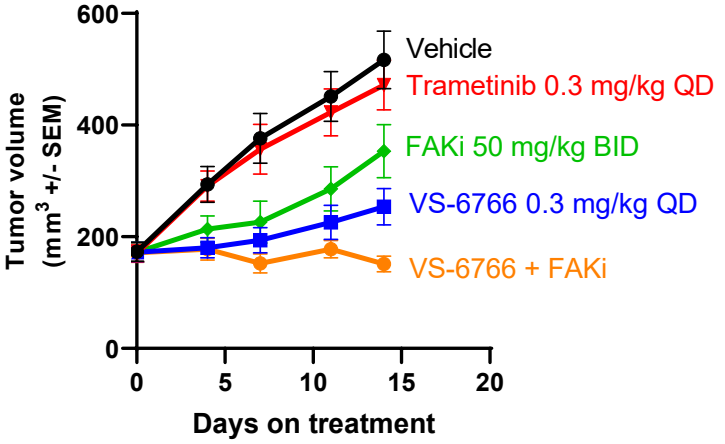


U. Banerji, AACR 2020

Ovarian cancer model (TOV21G KRAS mutant)



NSCLC cancer model (H358 KRAS mutant)



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Favorable Tolerability Profile with Novel Intermittent Dosing Regimen

Summary of Adverse Events Grade ≥ 3 Occurring in ≥ 5% of patients

	VS-6766 monotherapy Daily at MTD N=6 28-day cycle	RP2D VS-6766 monotherapy 4mg twice weekly N=26 28-day cycle	RP2D (VS-6766 3.2mg twice weekly + defactinib 200mg twice daily) N=38 21 days of 28-day cycle
Treatment Related Adverse Event	Grade ≥3	Grade ≥3	Grade ≥3
Rash	3 (50%)	5 (19%)	2 (5%)
CK elevation (Creatine phosphokinase)	1 (17%)	2 (8%)	2 (5%)

- Summary of FRAME (VS-6766+Defactinib) Safety Profile (>60 pts)
  - Most Adverse Events (AE) were Grade 1/2
  - Only 1 patient has discontinued due to AEs in the study

References: Chenard-Poirier, et al. ASCO 2017; Banerji, Q4 2020 report; Data on file

RP2D: recommended phase 2 dosing

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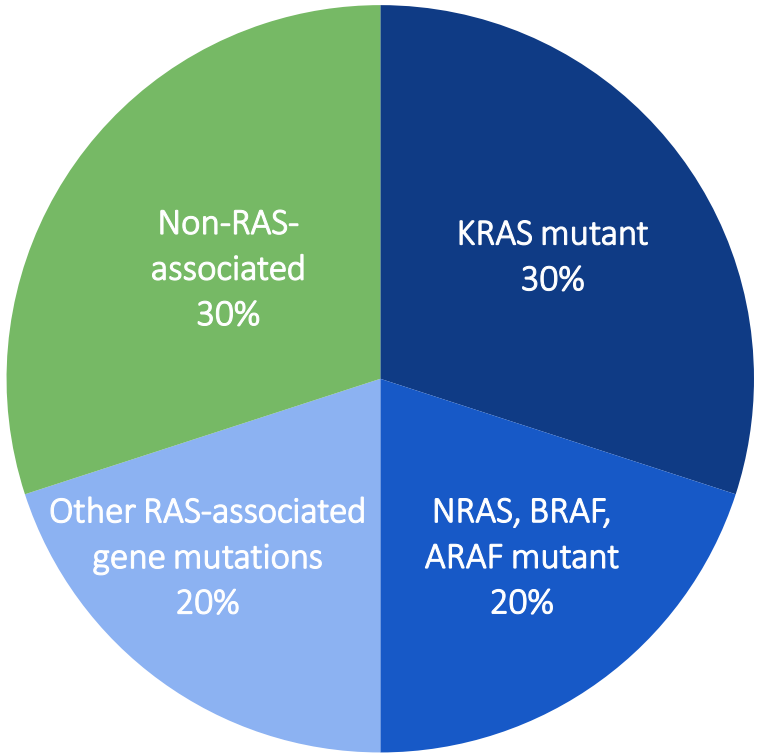
Low-Grade Serous Ovarian Cancer (LGSOC) is a RAS Pathway-Driven Cancer with Limited Treatment Options

~30% of LGSOC Patients Have KRAS mt
~70% of LGSOC Shows RAS Pathway-Associated mts



Therapy	Response Rate ORR	Median PFS Months (95% CI)	Discontinuation Rate due to AEs
Standard of Care[1]	6%	7.2 (5.6-9.9)	12 %
Trametinib[1]	26%	13.0 (9.9-15.0)	35%
Standard of Care[2]	13%	10.6 (9.2 to 14.5)	17%
Binimetinib[2]	16%	9.1 (7.3-11.3)	31%

[1] Gershenson, et al. ESMO 2019.
[2] Monk et al., J Clin Oncol 2020.

Standard of Care = letrozole, tamoxifen, chemotherapy
CI = confidence interval
PFS = progression-free survival

References: AACR Project GENIE Cohort v9.0-public and Verastem unpublished analysis

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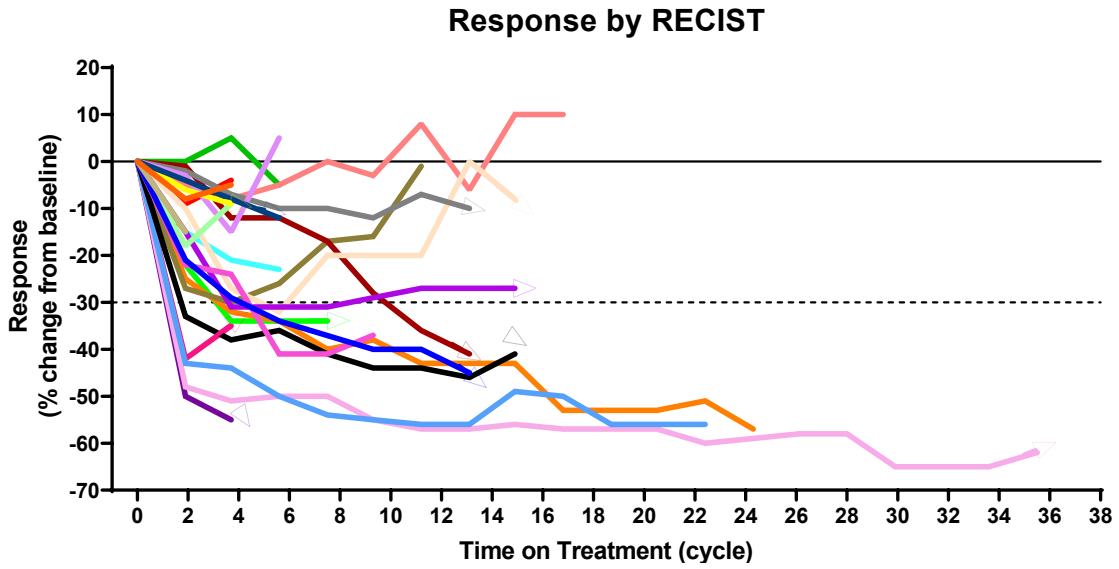
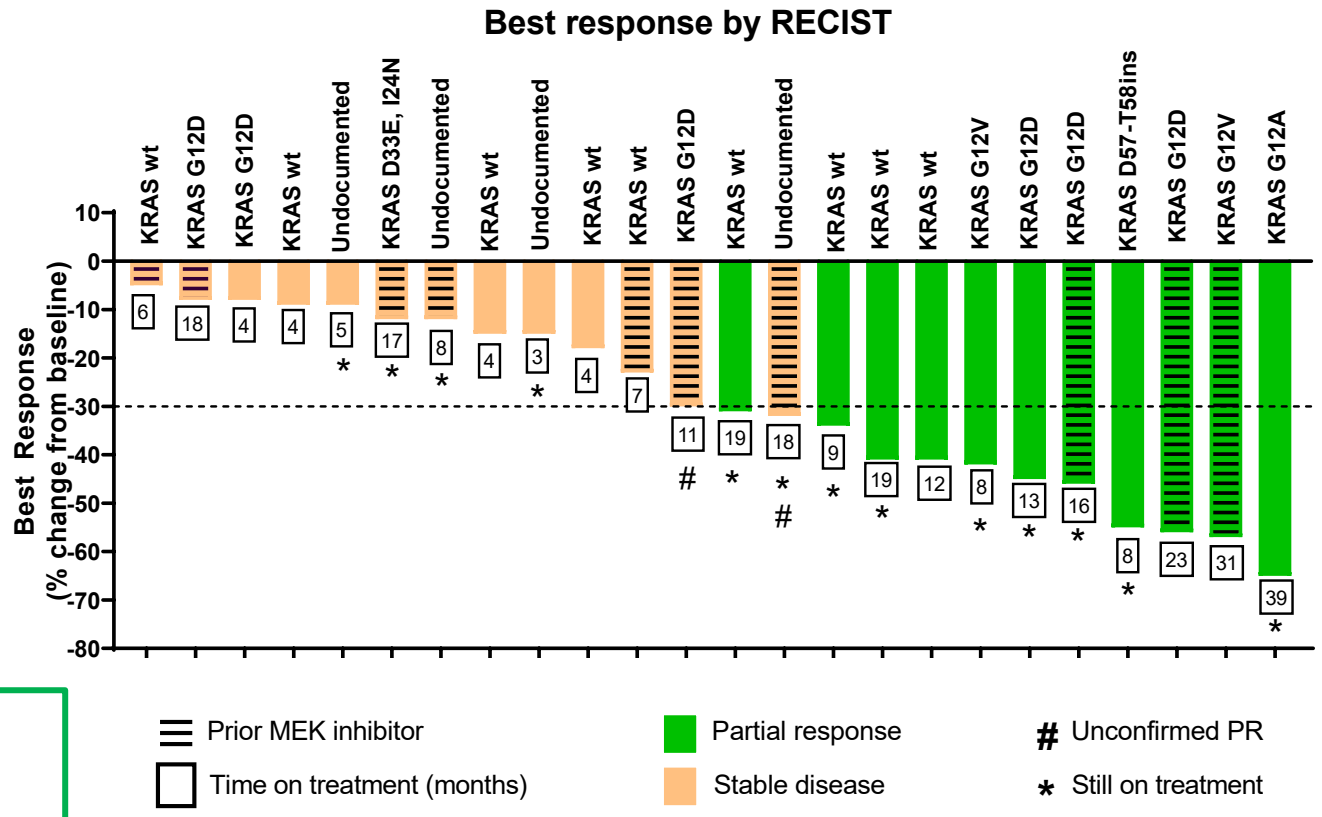
VS-6766 in Combination with Defactinib Shows Robust ORR with Durability in Refractory LGSOC with Expanded Number of Patients (n=24)





- Overall response rate (ORR) = 46% (11 confirmed PRs/24)
  - KRAS mutant ORR = 64% (7/11)
  - KRAS wild-type ORR = 44% (4/9)
  - KRAS status undetermined (3 SD; 1 unconfirmed PR)
- Responses in patients previously treated with MEKi
- Median PFS = 23 months (95% CI 10.6-NR) across all LGSOC

Data cut off April 2021
PFS: Progression free survival
NR: Not reached

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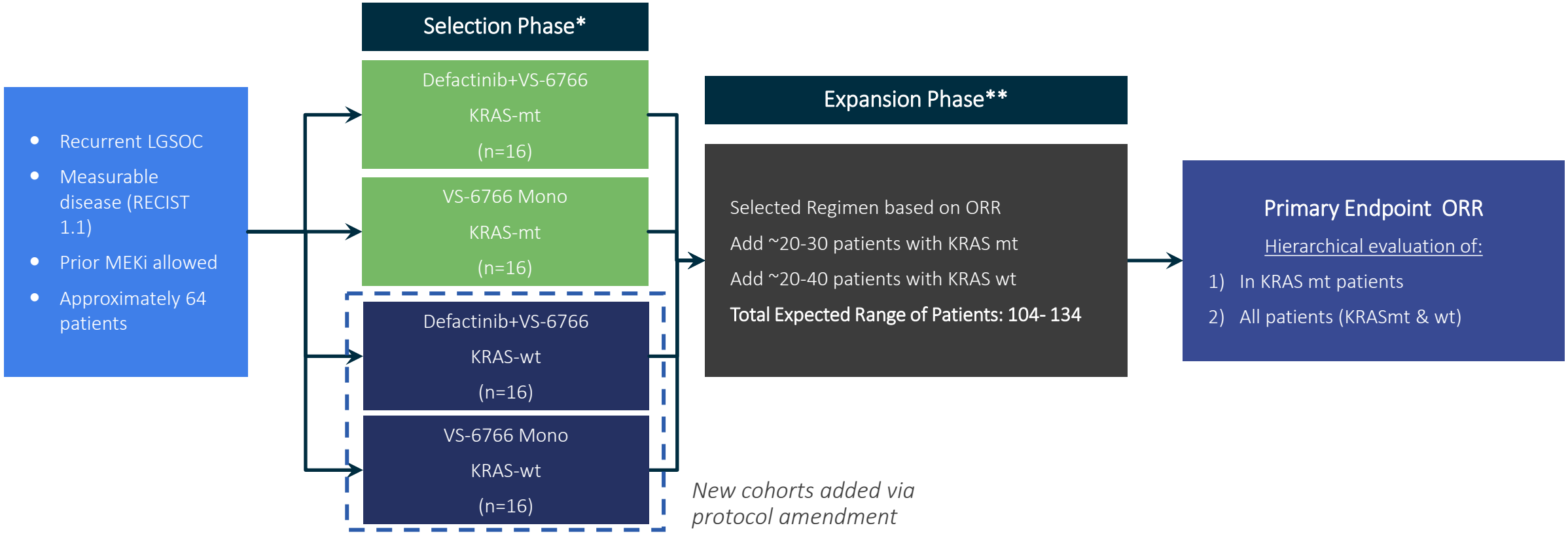
Reference: Banerjee et al., ESMO Sept 2021

RAMP 201: KRAS Mutated (mt) and Wild-type (wt), Phase 2, Recurrent LGSOC Adaptive Design for Potential Accelerated Approval



- Registration-directed Study Commenced in Nov. 2020 with estimated Primary Completion Date for the Expansion Phase of June 2023 (clinicaltrials.gov)
- FDA granted Breakthrough Therapy designation for VS-6766 + defactinib for treatment of patients with recurrent low-grade serous ovarian cancer (LGSOC) after one or more prior lines of therapy, including platinum-based chemotherapy

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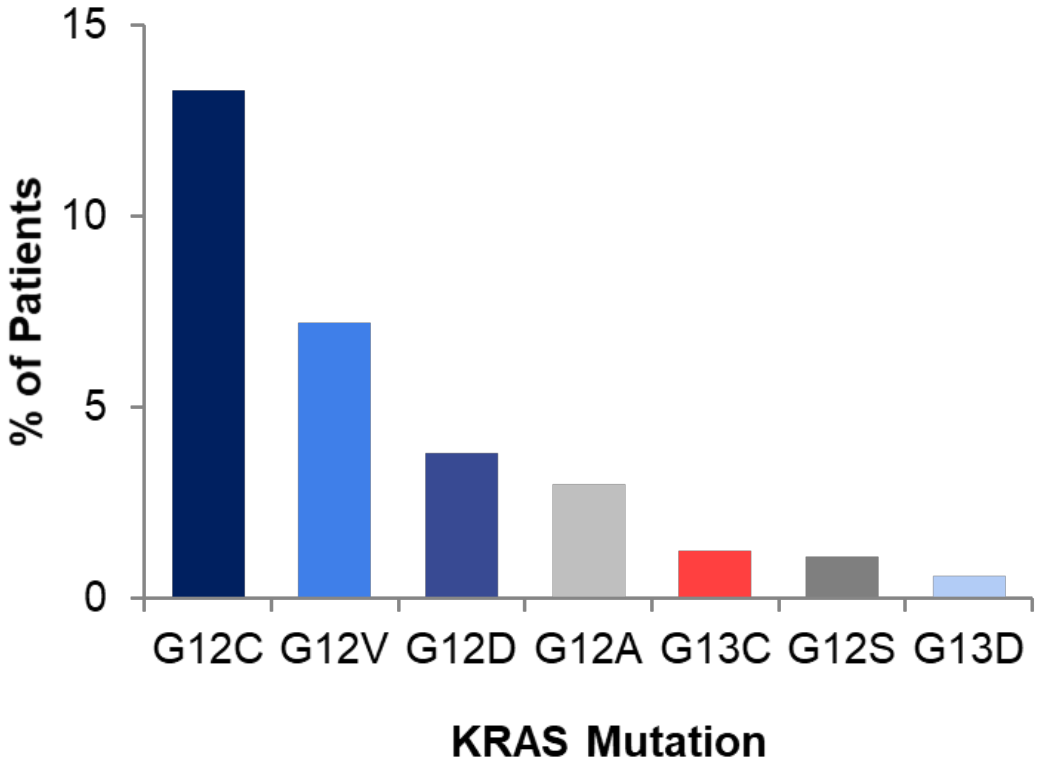
*Dosing: Defactinib + VS-6766 combo: Defactinib 200mg PO BID: 21/28 days + VS-6766 3.2mg PO 2x/wk 21/28 days; VS-6766 monotherapy: VS6766 4.0 mg PO 2x/wk 21/28 days

**Expansion Phase – final sample size to be adjusted based on adaptive design

High Unmet Need in Refractory KRAS mt NSCLC Adenocarcinoma

KRAS mutations in NSCLC Adenocarcinoma



Reference: TCGA PanCancer Atlas (cBioPortal analysis)

- KRAS is mutated in ~25% of NSCLC adenocarcinoma
  - ~13% G12C mutation
  - ~ 7% G12V mutation
- Sotorasib is now approved for treatment of KRAS G12C mt NSCLC
- There are no approved drugs for treatment of KRAS G12V mt NSCLC
- SOC for advanced or metastatic KRAS non-G12C mt NSCLC is chemotherapy and/or anti-PD(L)1

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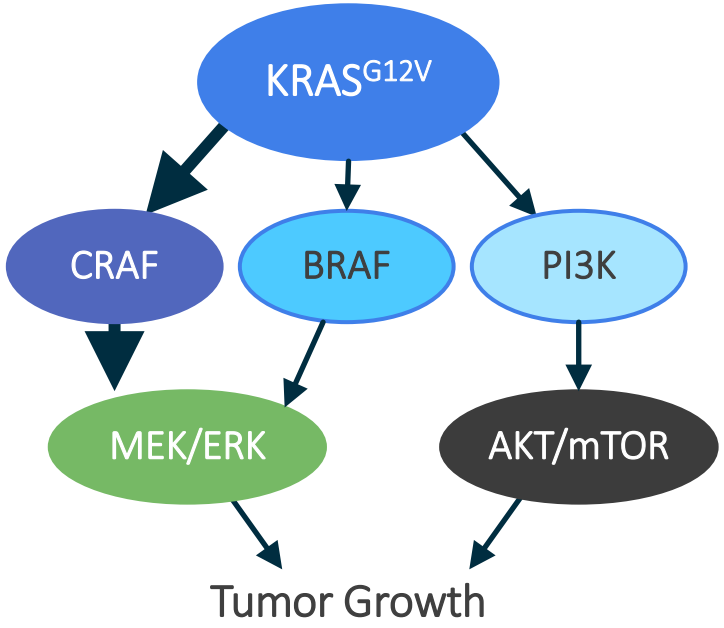
VS-6766 Inhibits CRAF - Key driver of KRAS G12V mutant NSCLC



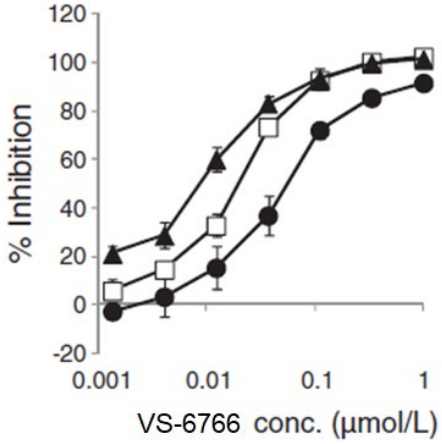
- KRAS G12V signals mainly through RAF/MEK in contrast to other variants, such as KRAS-G12D, which signal more through PI3K/AKT
- KRAS G12V models are especially dependent on CRAF

RAF family

IC_{50}(CRAF●): 0.056 ± 0.016 µmol/L

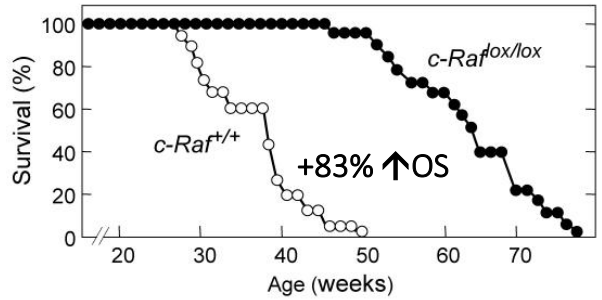
IC_{50}(BRAF □): 0.019 ± 0.0030 µmol/L

IC_{50}(BRAF V600E▲): 0.0082 ± 0.0015 µmol/L

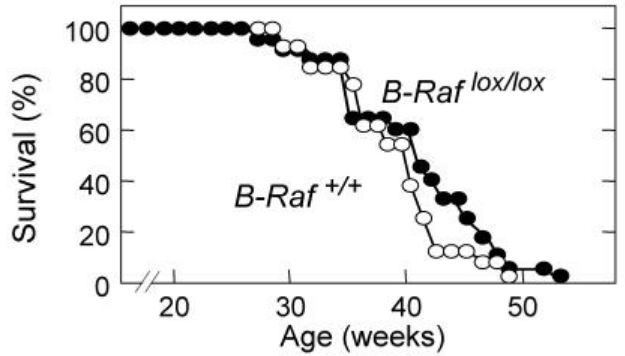


CRAF Drives KRAS^{G12V} NSCLC[1,3]

CRAF KO vs. WT



BRAF KO vs. WT



CRAF, but not BRAF, ablation improves survival of mice with KRAS G12V mt lung cancer *in vivo*

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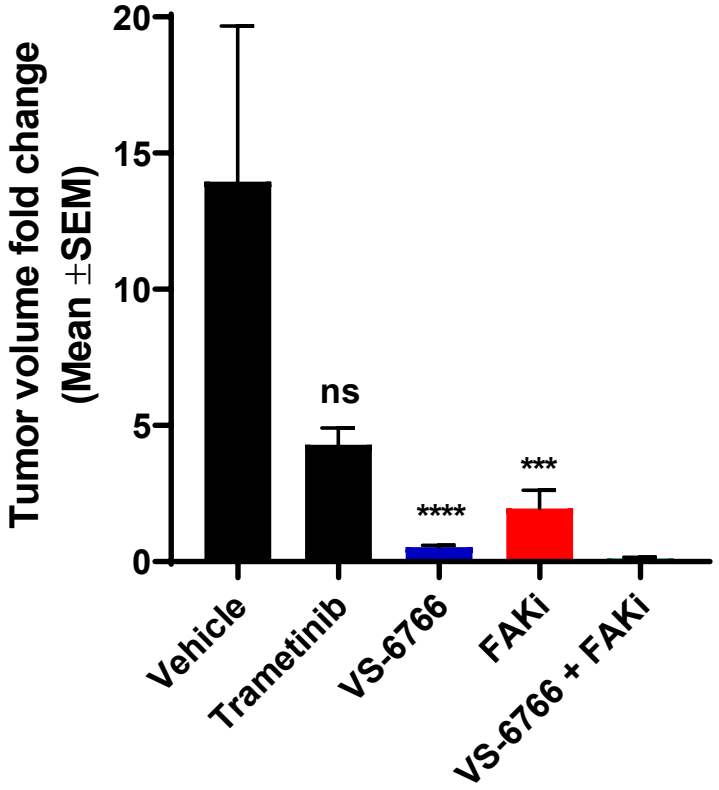
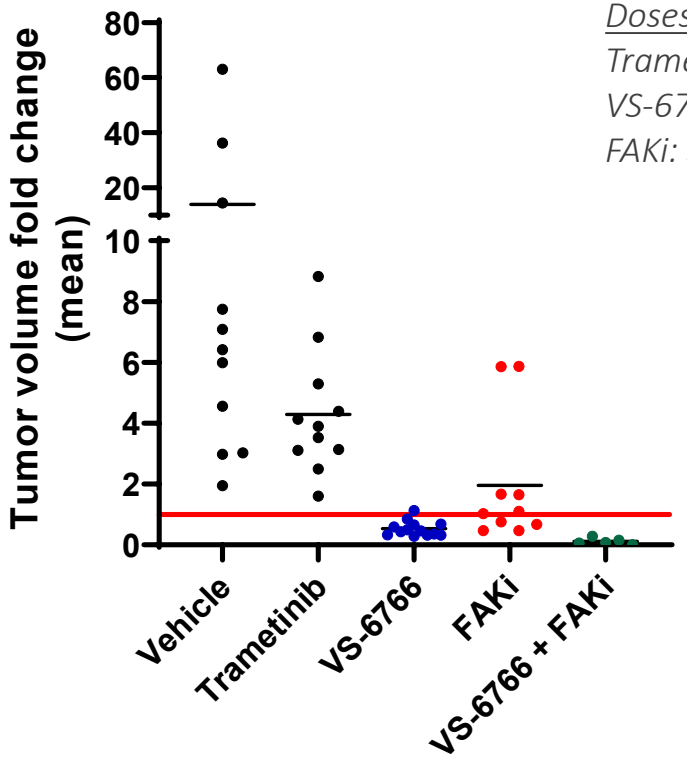
References: Ishii et al. Cancer Res (2013), Blasco, R. B. et al. Cancer Cell (2011), Lito, P. et al. Cancer Cell (2014), Sanclemente, M. et al. Cancer Cell (2018)

VS-6766 +/- FAKi confers strong tumor regression in CRAF-dependent KRAS G12V mutant NSCLC *in vivo*

KRAS G12V mutant; Trp53 KO NSCLC





Doses Tested
Trametinib: 0.1 mg/kg QD (5 days/week)
VS-6766: 0.1 mg/kg QD (5 days/week)
FAKi: 50 mg/kg BID (5 days/week)

- VS-6766 monotherapy caused tumor regression
- VS-6766 + FAKi showed stronger regression
- Anti-tumor effect of trametinib not significant at same dose level

4 weeks of treatment

Statistics: Mann-Whitney test

Collaboration with Mariano Barbacid

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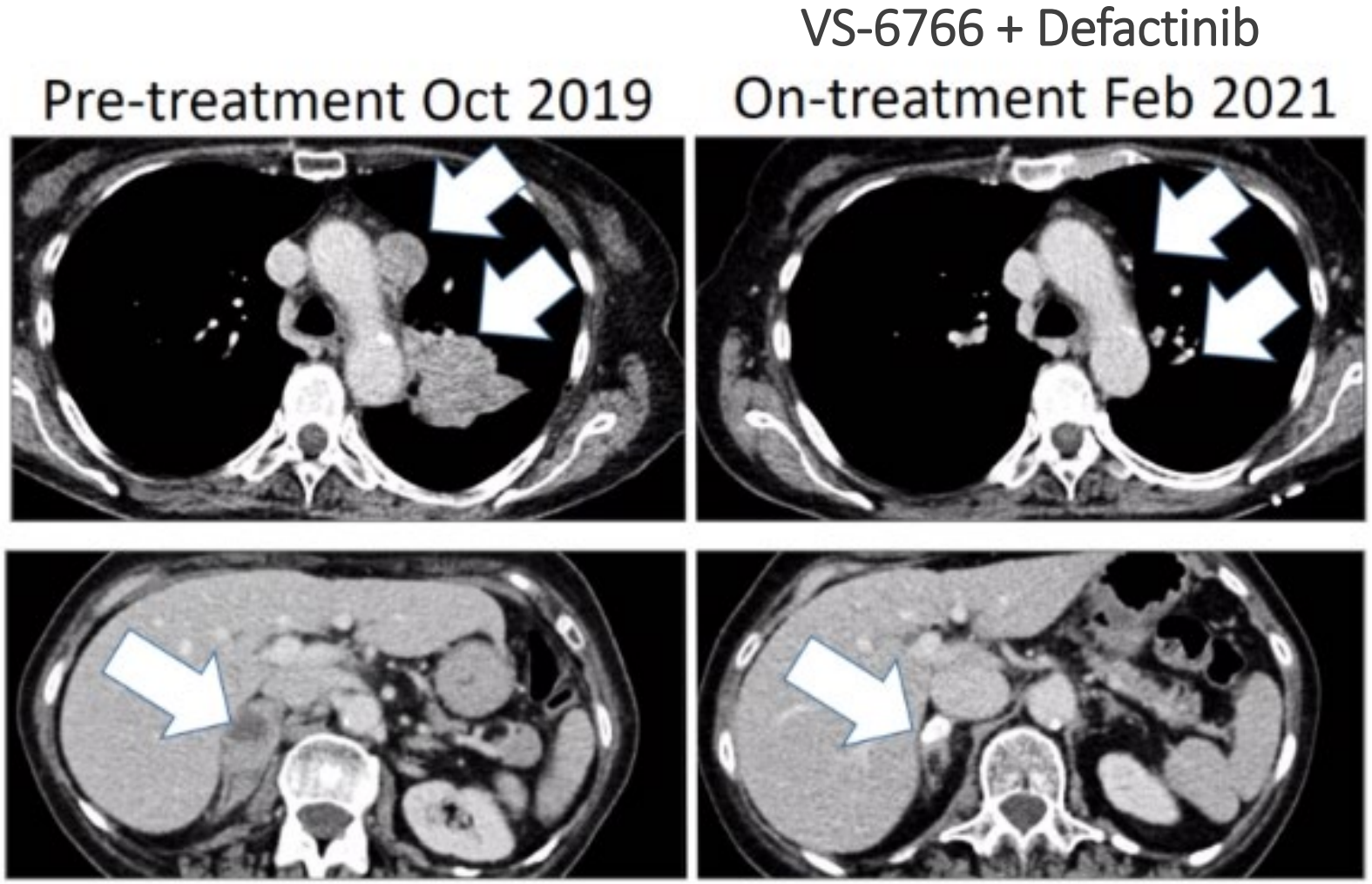
Response to VS-6766 + Defactinib in a Patient with KRAS G12V mt NSCLC

May 2019- Diagnosed with NSCLC

June 2019- Sept 2019 treated with first line Carbopltin + Pemetrexed + Pembrolizumab

Oct 2019- Progression, palliative RT to right hip

Nov 2019- To present on treatment on FRAME study VS-6766 + Defactinib



Presented by Matt Krebs in oral AACR 2021 presentation

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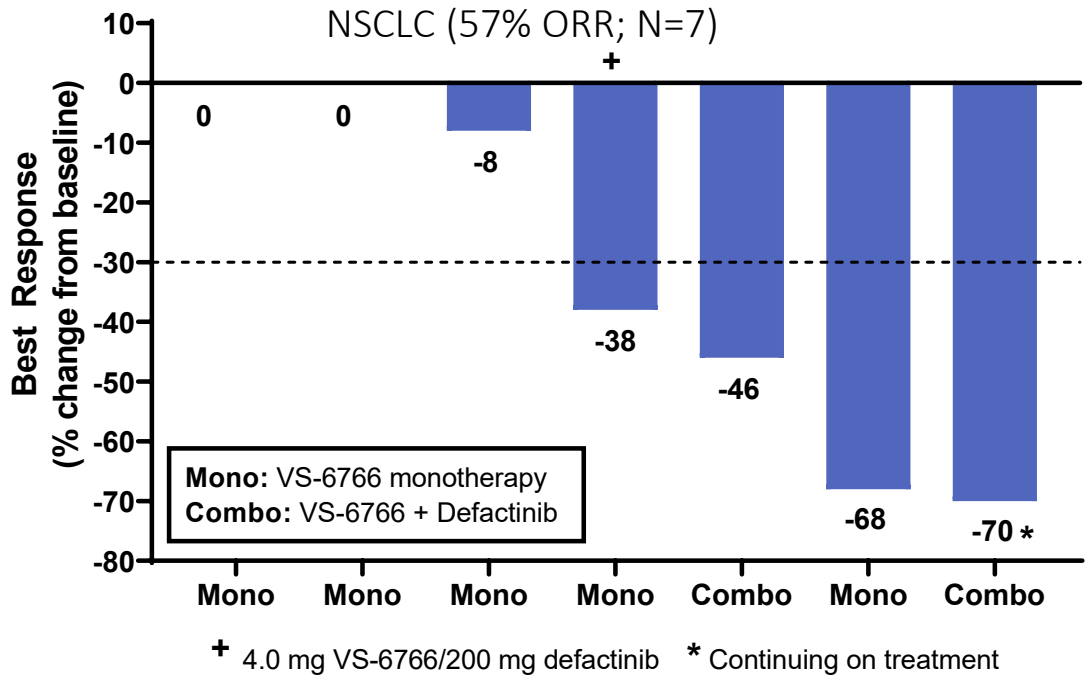
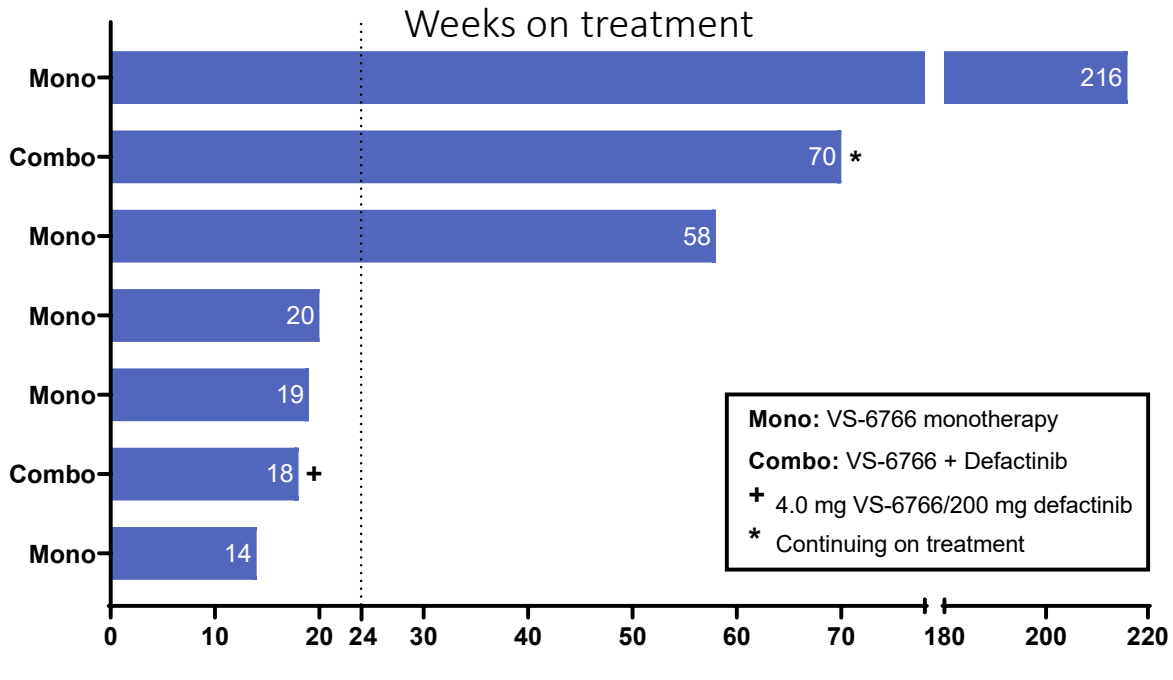
Strong Signal in KRAS G12V NSCLC to be Further Validated

VS-6766 ± Defactinib Has a Confirmed 57% ORR in KRAS G12V mt NSCLC in Integrated Analysis

Best Response by RECIST in KRAS G12V mt NSCLC



Time on Treatment for KRAS G12V mt NSCLC



Activity of VS-6766 as a single agent and in combo with defactinib in KRAS G12V mt NSCLC

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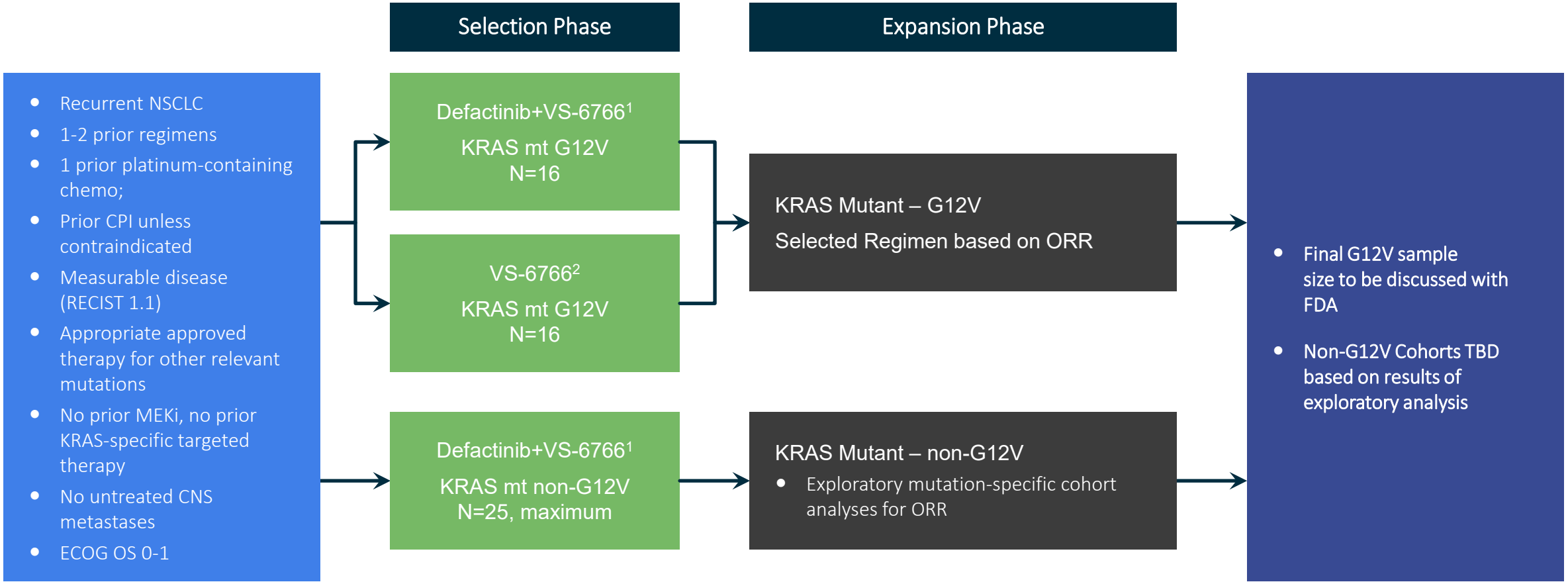
References: Guo, et al Lancet Oncology 2020; Krebs, AACR April 2021 (March 18, 2021 cutoff)

RAMP-202: KRAS Mutant (mt), Enriched G12V, Phase 2, Recurrent NSCLC for Potential Accelerated Approval



This registration-directed Phase 2 study commenced December 2020 with an estimated primary completion date for the expansion phase of March 2023 (clinicaltrials.gov)

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[1] Defactinib 200 mg PO BID (21/28 days) + VS-6766 3.2 mg PO 2x/wk (21/28 days)
[2] VS-6766 4.0 mg PO 2x/wk (21/28 days)

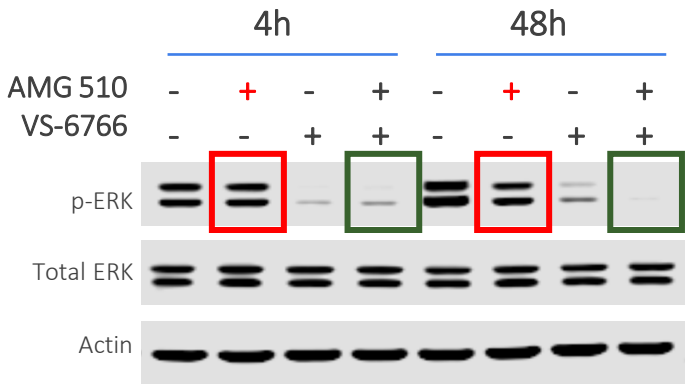
Preclinical synergy of VS-6766 + G12C inhibitors in KRAS G12C mt models

Synergy of VS-6766 + G12C inhibitors across KRAS G12C mt NSCLC, CRC & pancreatic cancer cell lines

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

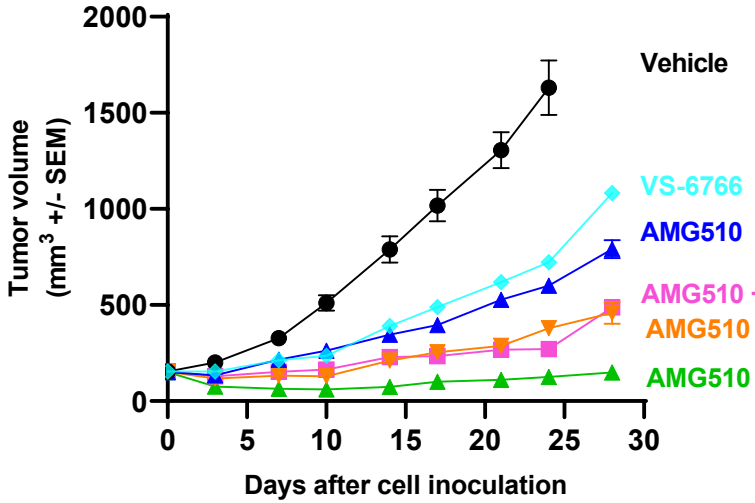
VS-6766 + AMG 510 yields deeper and more sustained inhibition of pERK signaling



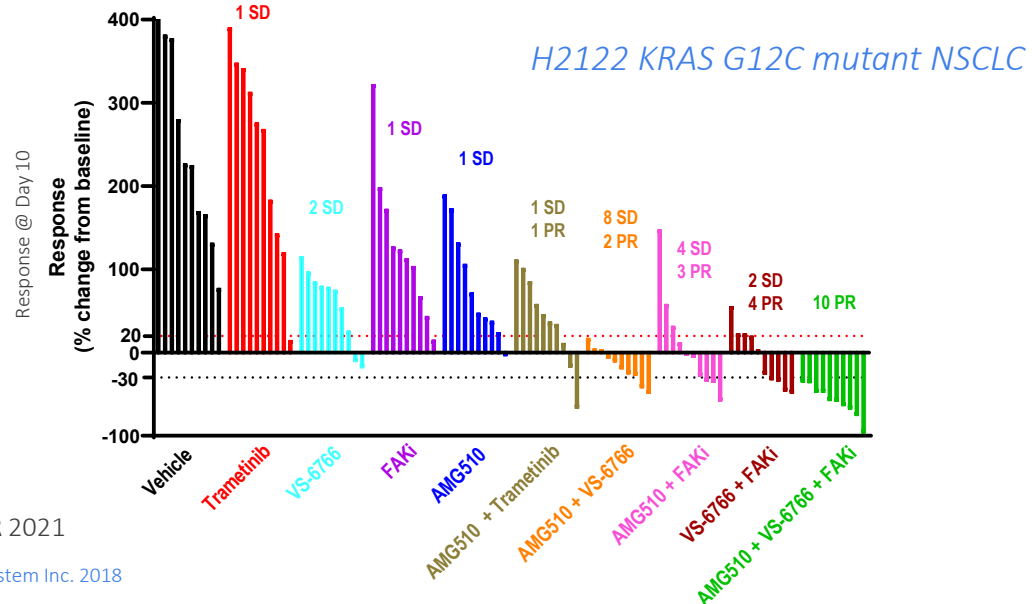
H2122 KRAS G12C mutant NSCLC

Concentrations Tested
AMG 510: 100 nM
VS-6766: 100 nM

VS-6766 & FAKi potentiate AMG 510 efficacy in KRAS G12C mt NSCLC *in vivo*
Tumor regression in all mice with triple combination



Doses Tested
Trametinib: 0.3 mg/kg QD
VS-6766: 0.3 mg/kg QD
FAKi: 50 mg/kg BID
AMG 510: 30 mg/kg QD



H2122 KRAS G12C mutant NSCLC

Reference: Coma et al., AACR 2021

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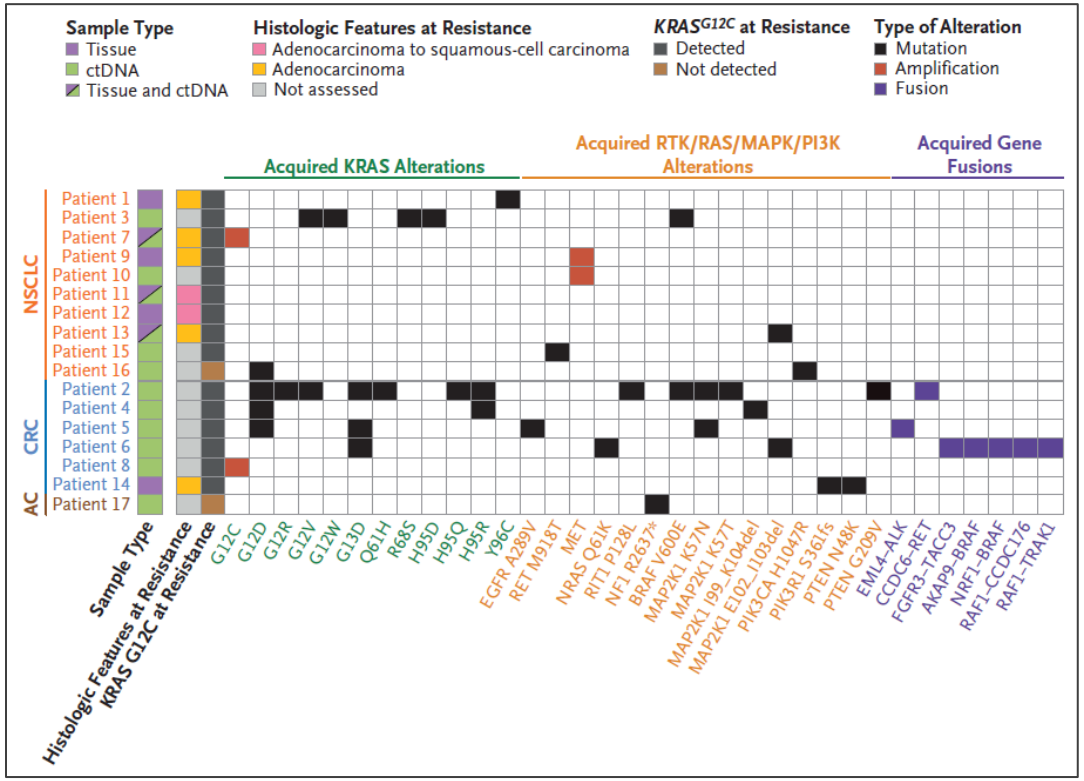
Mechanisms of acquired resistance to KRAS G12Ci treatment in patients

Supports combination of KRAS G12Ci with VS-6766



Summary of Putative Mechanisms of Acquired Resistance to Adagrasib Treatment
(Fig 3 in Awad MM et al., N Engl J Med 2021; 384: 2382-93)

- Mechanisms of acquired resistance to KRAS G12Ci adagrasib treatment in patients recently reported[1,2]
- The main resistance alterations occurred in
  - RTK mts or amplifications
  - KRAS mts or amplification
  - NRAS mt
  - BRAF V600E mt, BRAF or CRAF fusions
  - MAP2K1 (MEK1) mt/deletion
- VS-6766 is expected to be effective against these KRAS, NRAS, BRAF and CRAF modifications

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References: [1]Awad MM et al., N Engl J Med 2021; 384: 2382-93; [2]Tanaka et al., Cancer Discov 2021;11:1–10

Clinical Evaluation of VS-6766 in Combination with Sotorasib in Patients with KRAS G12C mt NSCLC

Expansion cohorts in patients with or without prior G12Ci treatment

- Patients must have known G12C KRAS mutation determined using validated test
- Treatment with at least 1 but no more than 3 prior systemic regimens, for Stage 3B-C or 4 NSCLC
- Patient may have previously received adjuvant chemotherapy for earlier-stage disease
- Measurable disease according to RECIST 1.1
- ECOG performance status ≤ 1

Part A: Dose Evaluation (3+3 DLT Assessment)

Dose Level 1
(N = 3 to 6)
VS-6766 3.2 mg BIW +
Sotorasib 960 mg QD

AMGEN

RP2D Selection

Part B: Dose Expansion at RP2D (Primary Endpoint ORR)

Cohort 1
Patients without prior KRAS G12C inhibitor treatment
Stage 1: ~20 patients
Stage 2: expand

Cohort 2
Patients whose NSCLC progressed on KRAS G12C inhibitor treatment
Stage 1: ~20 patients
Stage 2: expand

Part A (Dose Evaluation) portion of study expected to initiate in 4Q 2021

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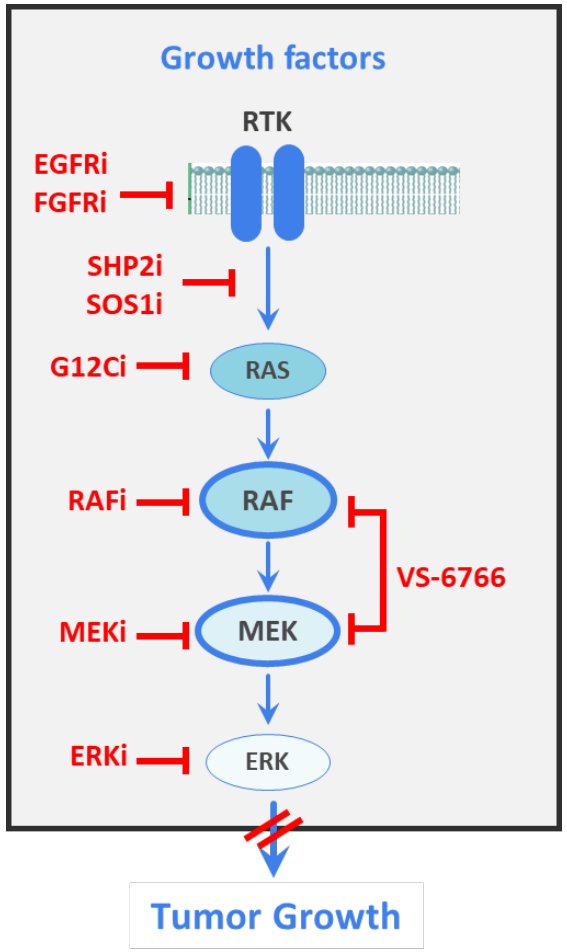
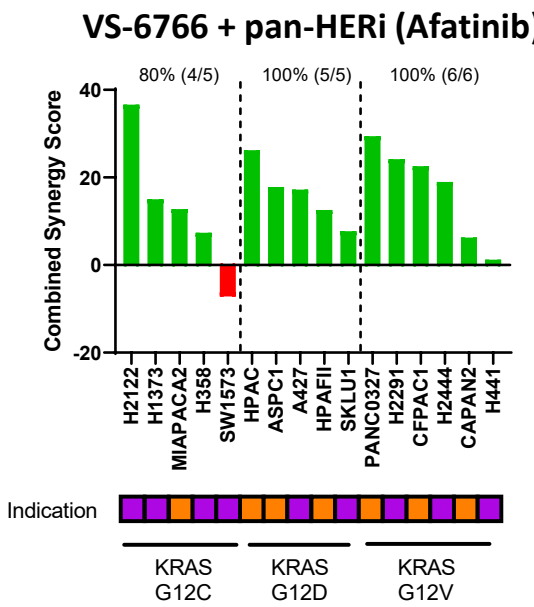
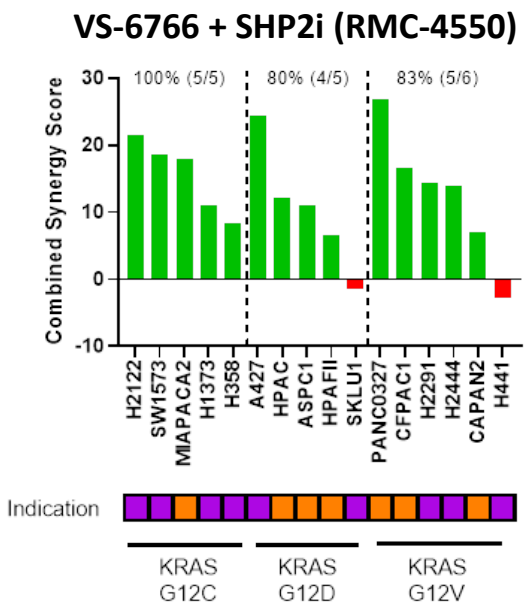
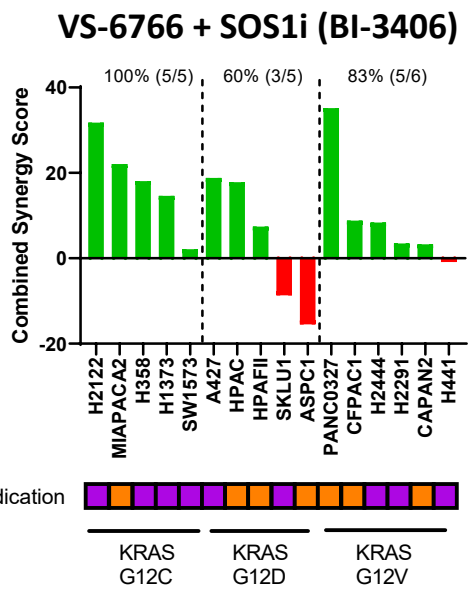
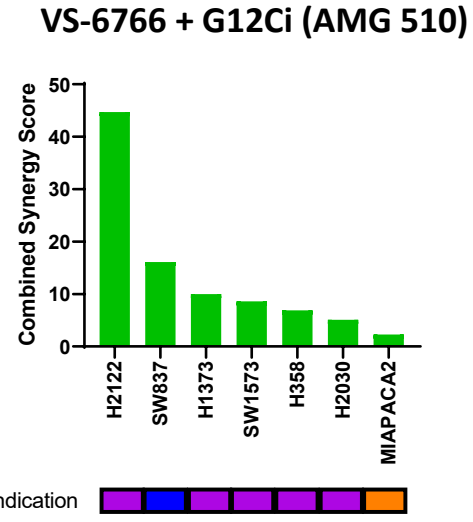
Vertical Blockade: Preclinical synergy of VS-6766 with inhibitors of several promising targets

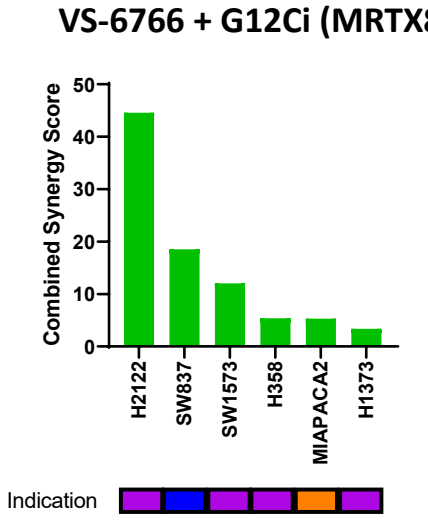


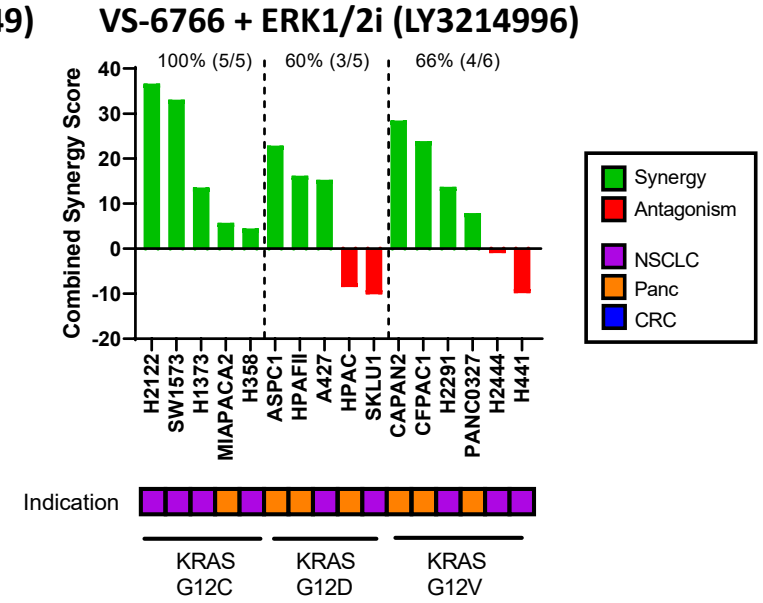












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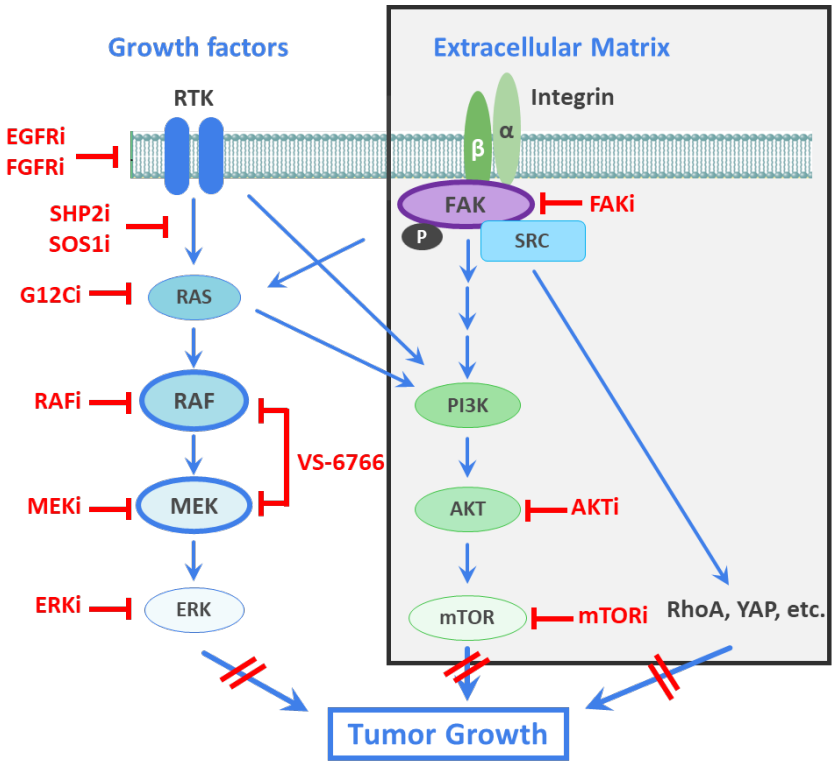
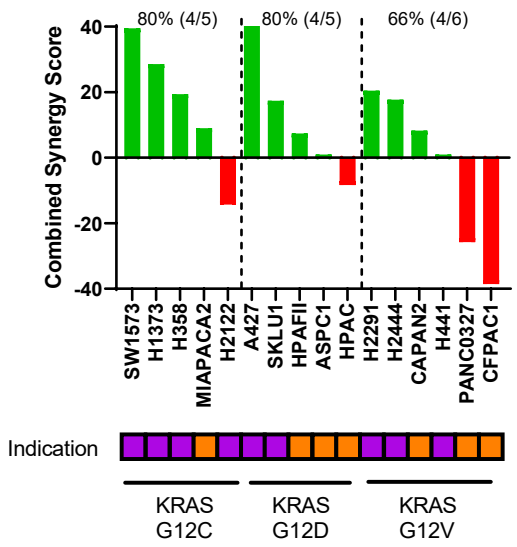
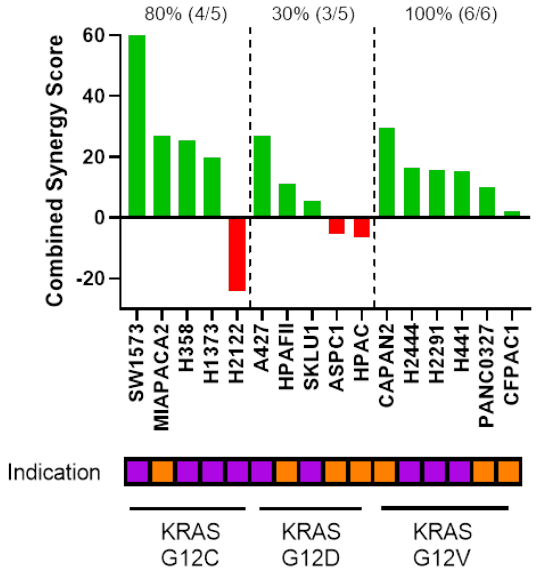
Parallel Pathway Blockade: Preclinical synergy of VS-6766 with inhibitors of several promising targets



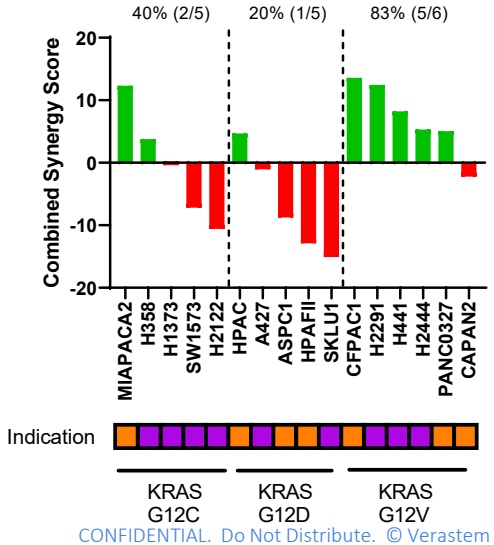
VS-6766 + p70S6K/AKTi (M2698)



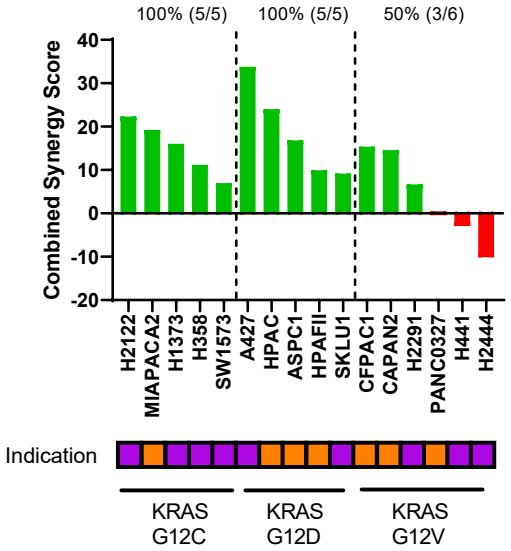
VS-6766 + mTORi (Everolimus)

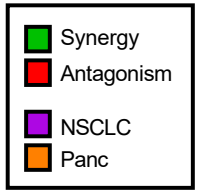


VS-6766 + FAKi (Defactinib)



VS-6766 + CDK4/6i (Palbociclib)





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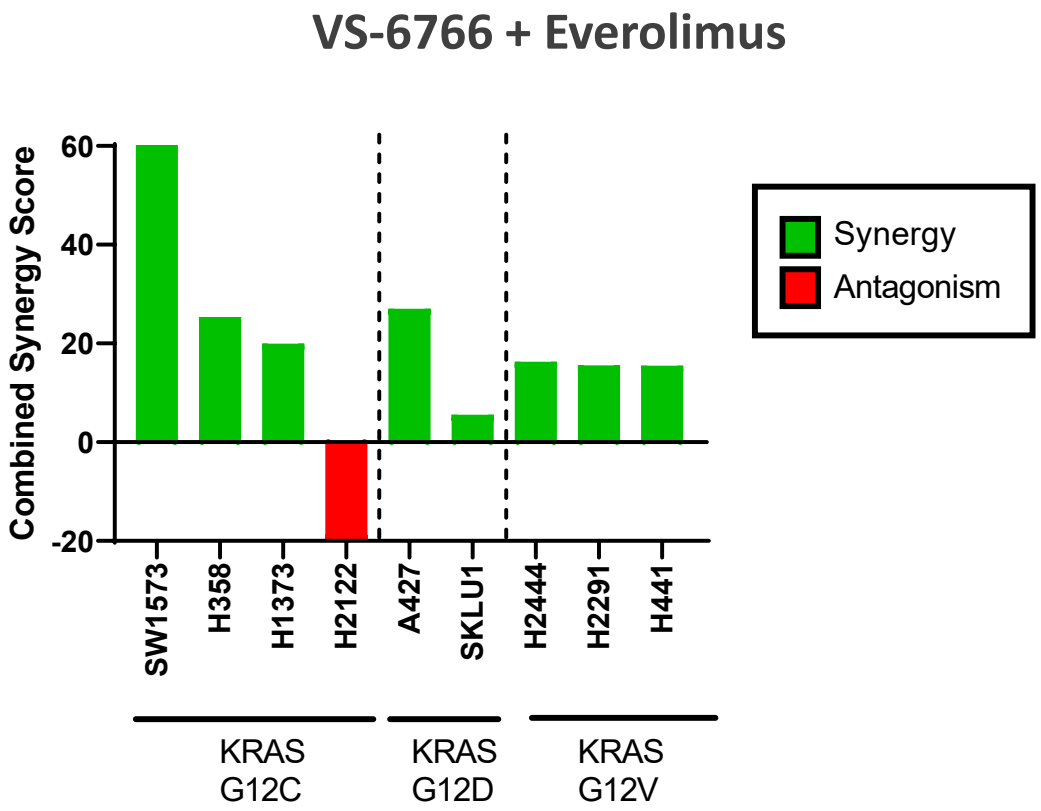
Combination of VS-6766 with Everolimus (mTOR inhibitor) now being evaluated in patients with KRAS mt NSCLC

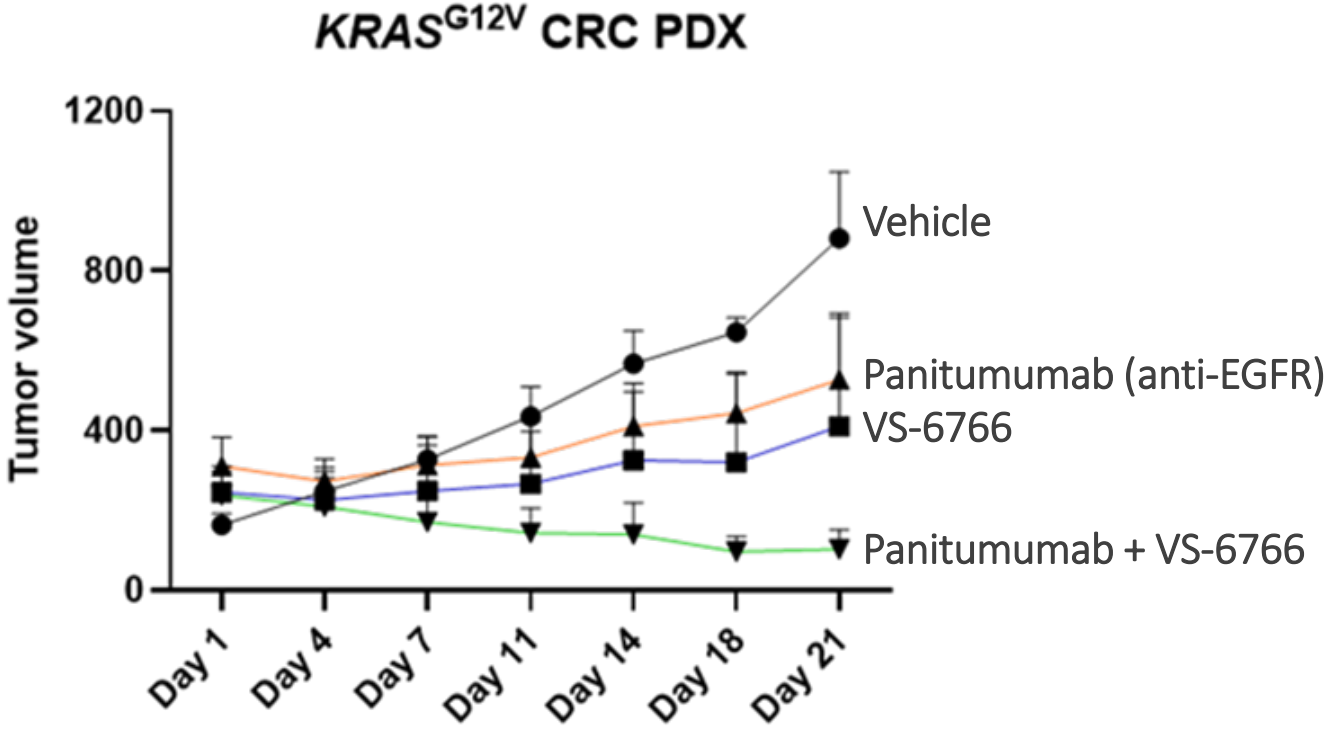


- VS-6766 + everolimus are synergistic across multiple KRAS mt NSCLC cell lines
- A well-tolerated RP2D for VS-6766 + everolimus has been established with intermittent dosing of both agents (twice weekly; 3 wks on/1 wk off)
- KRAS mutant NSCLC expansion cohort is currently ongoing with VS-6766 + everolimus

PI: Udai Banerji, Institute of Cancer Research, UK

Verastem Oncology

Combination of VS-6766 with anti-EGFR mAb induces tumor regression in a KRAS mt Colorectal PDX model



- VS-6766 + anti-EGFR (panitumumab) induces tumor regression in a KRAS G12V mt CRC patient-derived xenograft model
- G12Ci + anti-EGFR (sotorasib + panitumumab and adagrasib + cetuximab) have shown partial responses in KRAS G12C mt CRC (Fakih et al. ESMO 2021; Weiss et al. ESMO 2021)
- **These data support clinical testing of VS-6766 + anti-EGFR for treatment of KRAS mt CRC**

Collaboration with Marwan Fakih, City of Hope

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Conclusions: VS-6766 as a potential backbone of therapy for RAS pathway-driven cancers

- VS-6766 is a dual RAF/MEK with anti-tumor activity across multiple MAPK pathway alterations and multiple solid tumor indications
- VS-6766 + defactinib (FAKi) has shown 46% ORR (11/24) [64% ORR (7/11) in KRAS mt] with 23 months mPFS in LGSOC
  - Registration-directed clinical trial in progress (RAMP-201; NCT04625270)
- VS-6766 ± defactinib (FAKi) has shown 57% ORR (4/7) in KRAS G12V mt NSCLC
  - Registration-directed clinical trial in progress (RAMP-202; NCT04620330)
- Preclinical synergy of VS-6766 + G12Ci in KRAS G12C mt NSCLC models
  - Verastem & Amgen partnering to evaluate VS-6766 + sotorasib in patients with KRAS G12C mt NSCLC
- Additional combinations with VS-6766
  - Ongoing clinical trial testing VS-6766 + everolimus in KRAS mt NSCLC
  - Tumor regression with VS-6766 + anti-EGFR mAb in KRAS mt CRC PDX model supports clinical testing

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Thanks for your attention!