Dual RAF/MEK inhibitor VS-6766 for treatment of KRAS mutant NSCLC: Novel combinations targeting G12C or G12V variants

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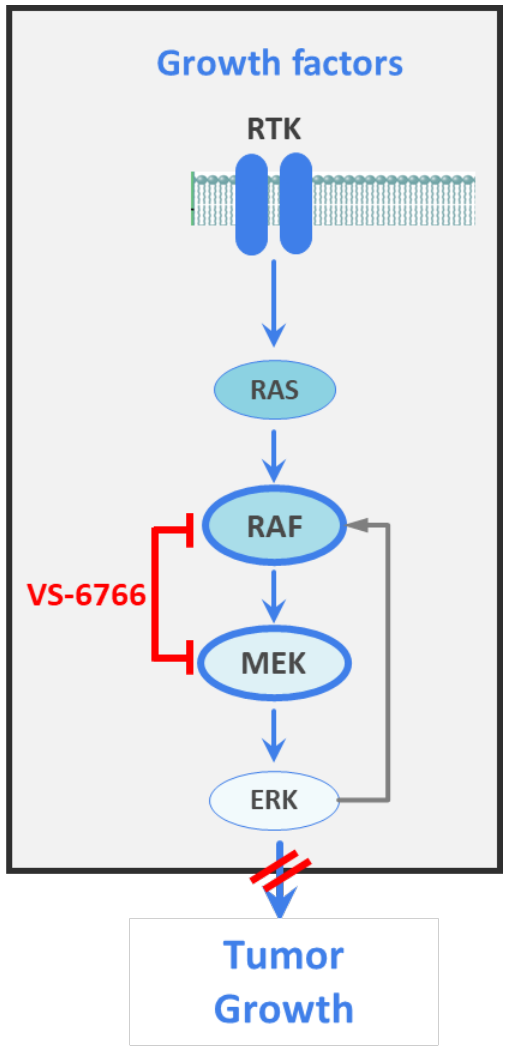
Presenter DISCLOSURES

Ineligible Company (formerly: Commercial Interest)	**Relationship(s)**
Verastem Oncology	Employee, Stock Interest

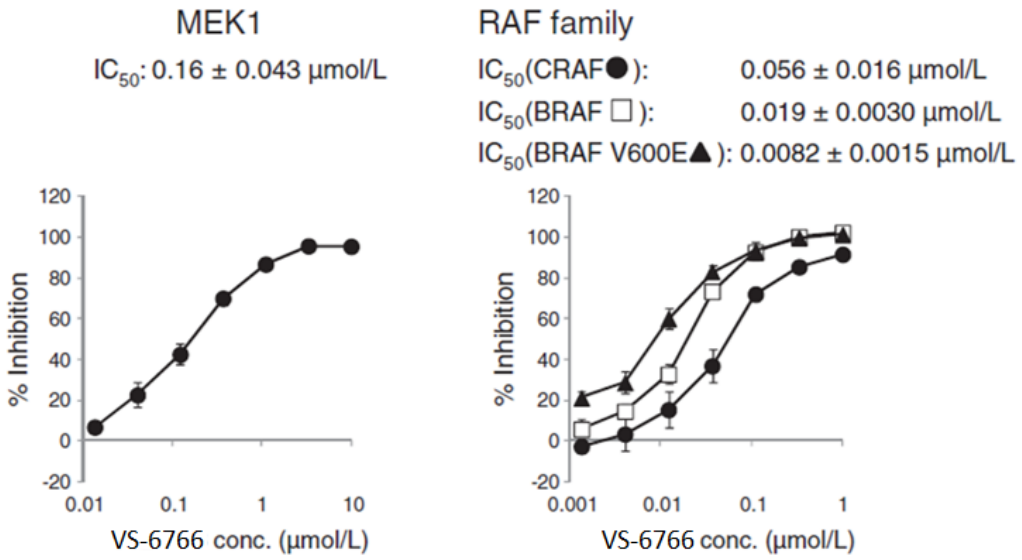
Outline

- Mechanism of action of VS-6766 (RAF/MEK inhibitor)
- Clinical activity of VS-6766 monotherapy in RAS/RAF mutant cancers
- VS-6766 + defactinib (FAK inhibitor) in KRAS G12V mutant NSCLC
- VS-6766 + G12C inhibitor in KRAS G12C mutant NSCLC
- VS-6766 + everolimus (mTOR inhibitor) in KRAS mutant NSCLC
- Conclusions

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

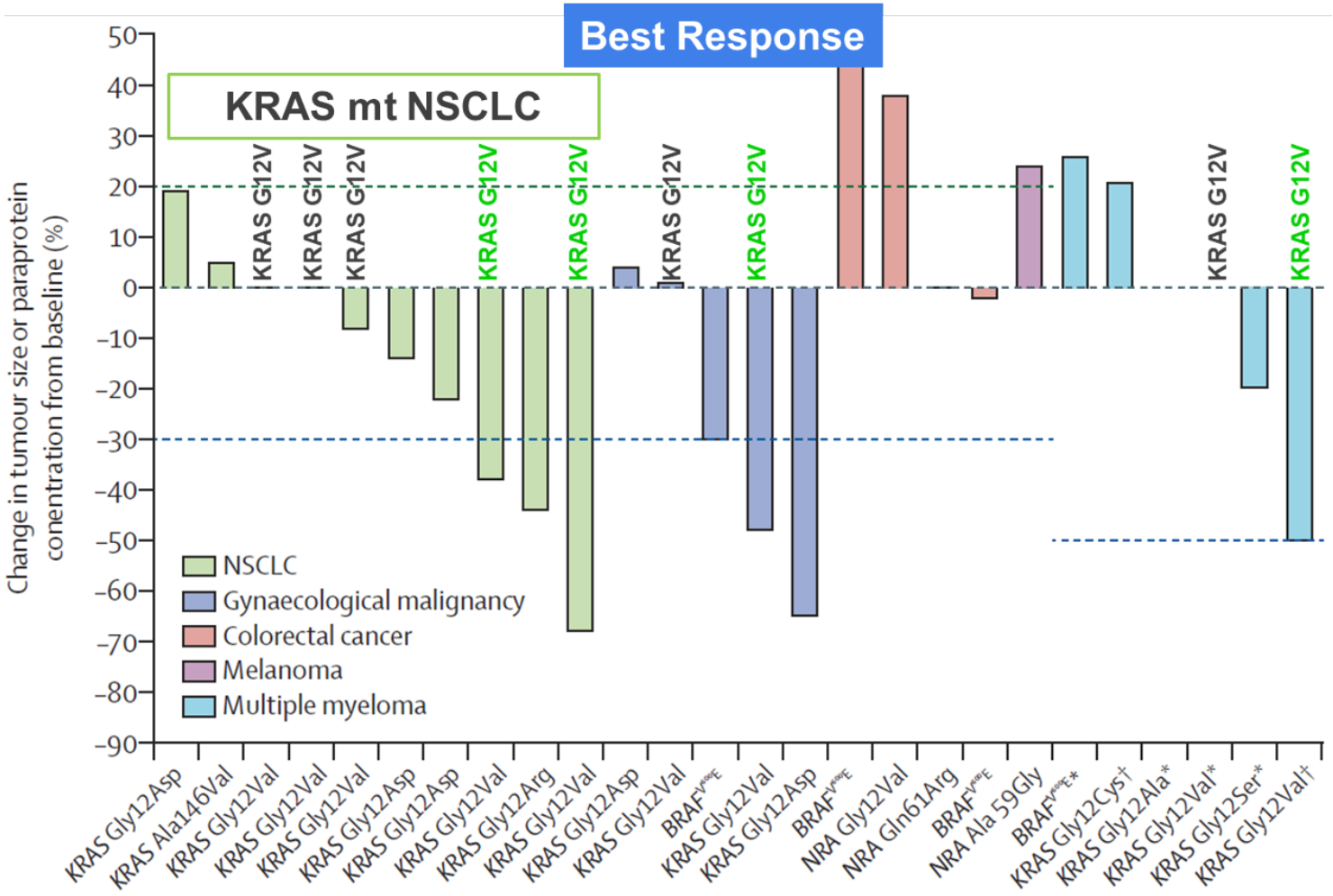


- VS-6766 inhibits both MEK & RAF kinase activities
- MEK inhibitors paradoxically induce MEK phosphorylation (pMEK) by relieving ERK-dependent feedback inhibition of RAF
- By inhibiting RAF phosphorylation of MEK, VS-6766 has advantage of not inducing pMEK
- VS-6766 inhibits ERK signaling more completely;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



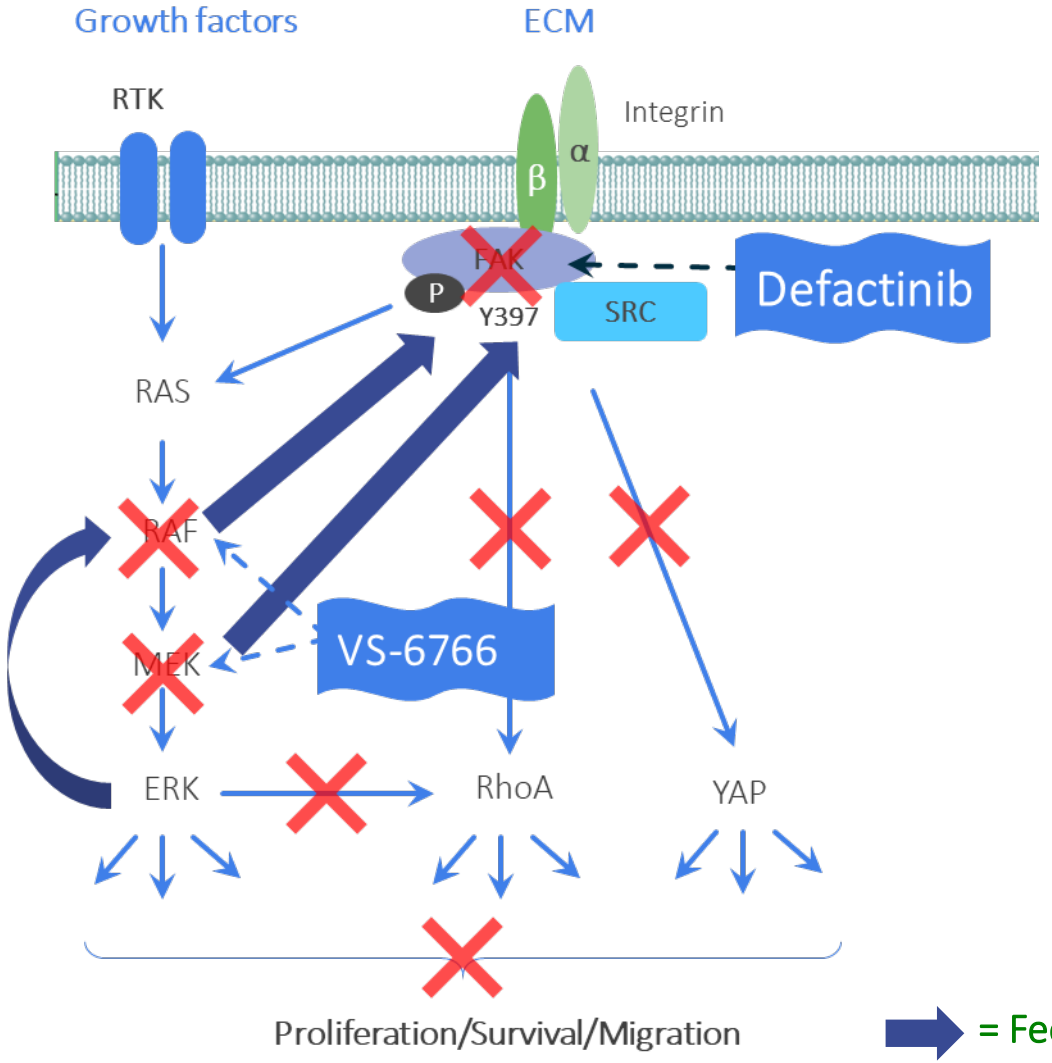
VS-6766 monotherapy has shown clinical activity in several RAS/RAF mutant cancers, including NSCLC

Objective responses especially in patients with KRAS G12V mutation



Guo et al., Lancet Oncology 2020

More Complete Shutdown of Tumor Growth Requires Addressing Multiple Resistance Mechanisms



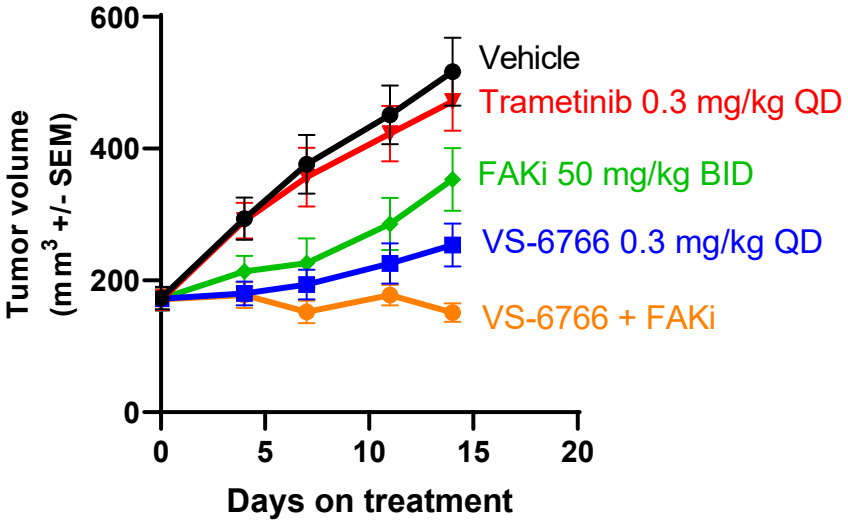
- BRAF inhibition induces compensatory activation of pFAK[1]
- MEK inhibition induces compensatory activation of pFAK preclinically and clinically[2]
  - Trametinib induced ↑ pFAK (Y397) preclinically in KRAS mt NSCLC cell lines
  - Also observed in patients
    - VS-6766 induced ↑ pFAK (Y397) as a potential resistance mechanism in the majority of patients
    - Combination with defactinib reduced this compensatory pFAK signal
- Upon MEK blockade, pERK inhibition feeds back to activate RAF kinase

➡ = Feedback Reactivation

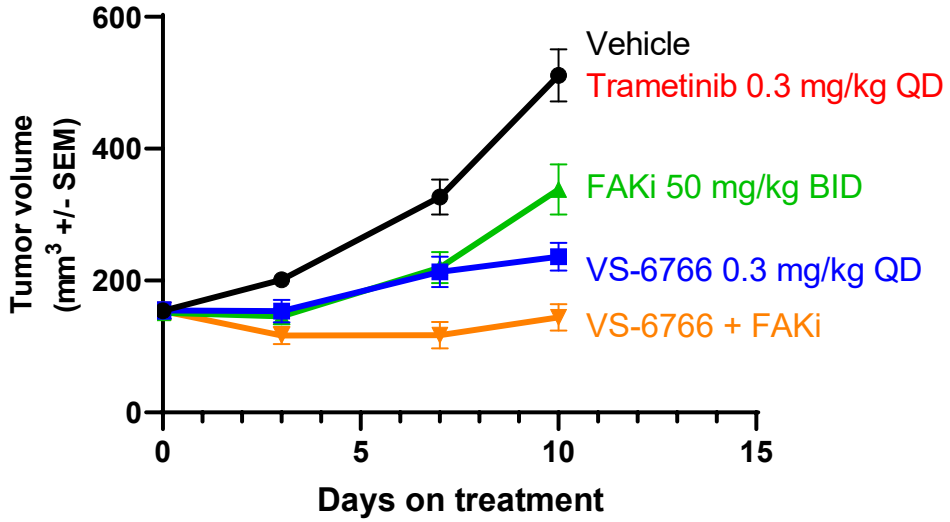
References: [1] Chen, *Mol Cancer Res* 2018; [2] Banerji, BTOG Dublin, Jan 23, 2019

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

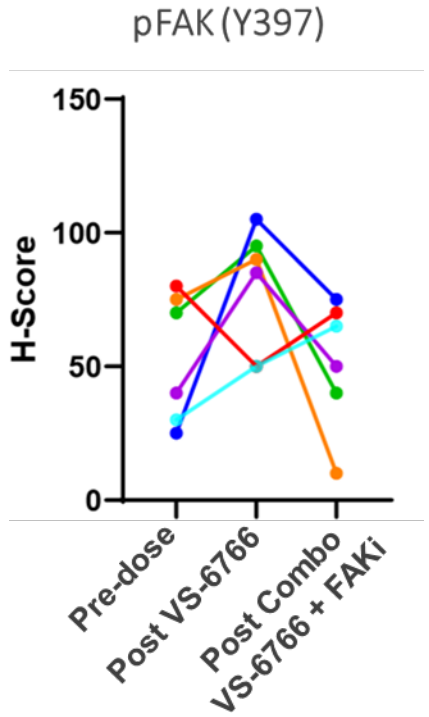
NSCLC cancer model
H358 KRAS G12C mt



NSCLC cancer model
H2122 KRAS G12C mt



VS-6766 induces pFAK
in patients' tumors



U. Banerji, AACR 2020

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 Study Safety Profile

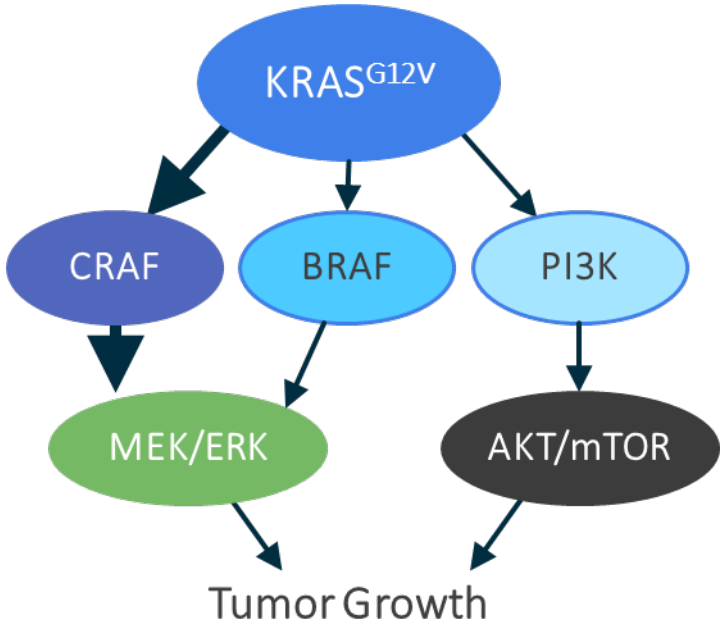
Most Adverse Events (AE) were Grade 1/2

Only one patient has discontinued due to AEs in this VS-6766 + defactinib combination study

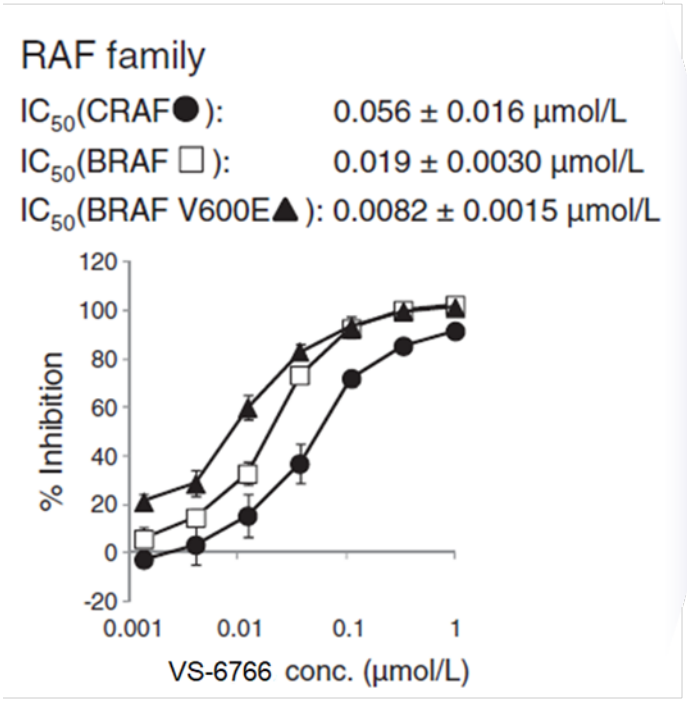
[1] Chenard-Poirier, *et al*. ASCO 2017
References: Banerji, Q4 2020 report; Data on file
RP2D: recommended phase 2 dosing

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

A Precision Approach to KRAS-G12V Driven NSCLC

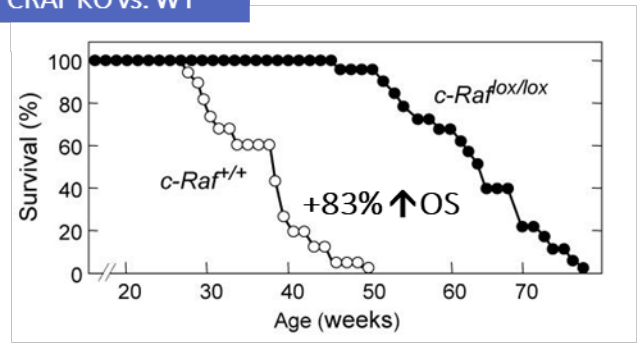


- KRAS^{G12V} signals mainly through RAF/MEK in contrast to other variants, such as KRAS-G12D, which signal more through PI3K/AKT
- KRAS^{G12V} models are especially dependent on CRAF

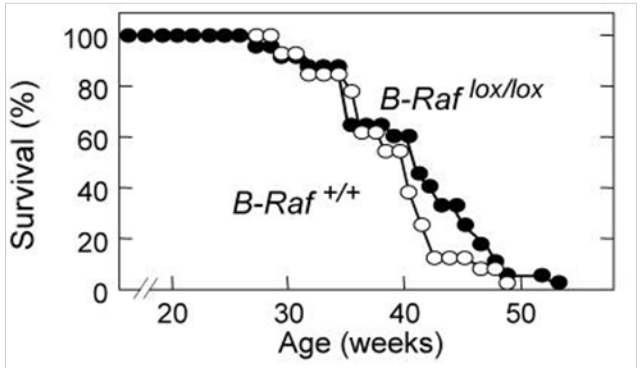


CRAF Drives KRAS^{G12V} NSCLC[1,3]

CRAF KO vs. WT



BRAF KO vs. WT

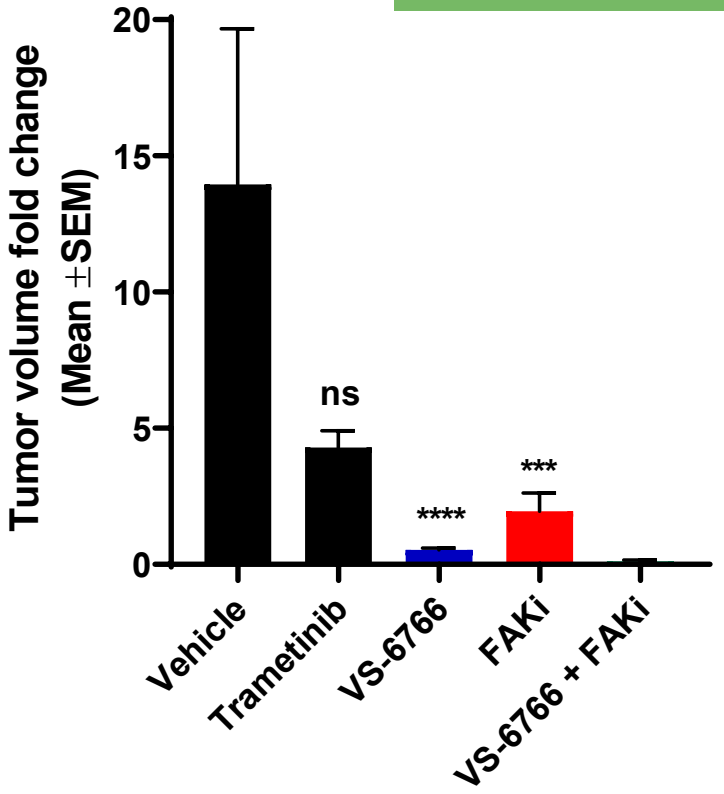


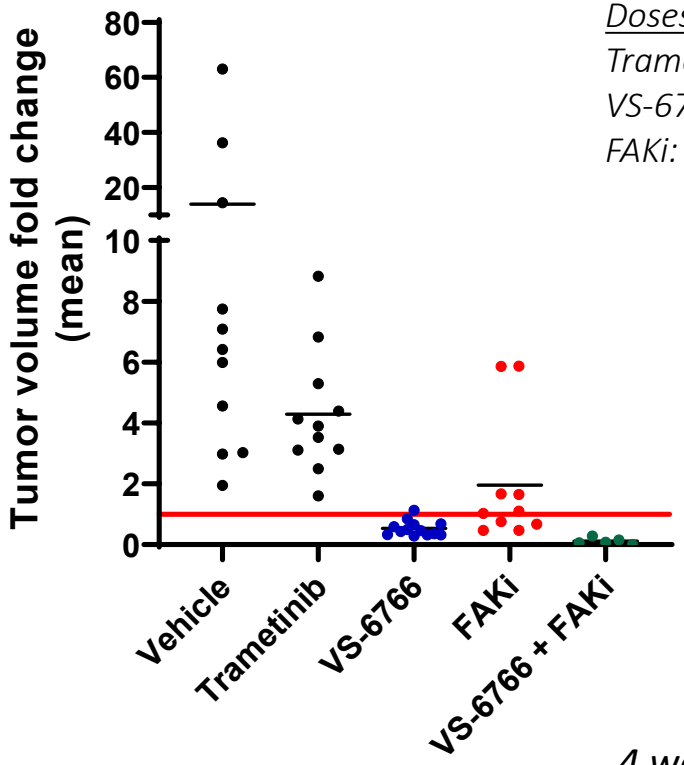
CRAF, but not BRAF, ablation improves survival of mice with KRAS^{G12V} induced lung cancer *in vivo*

Source: 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

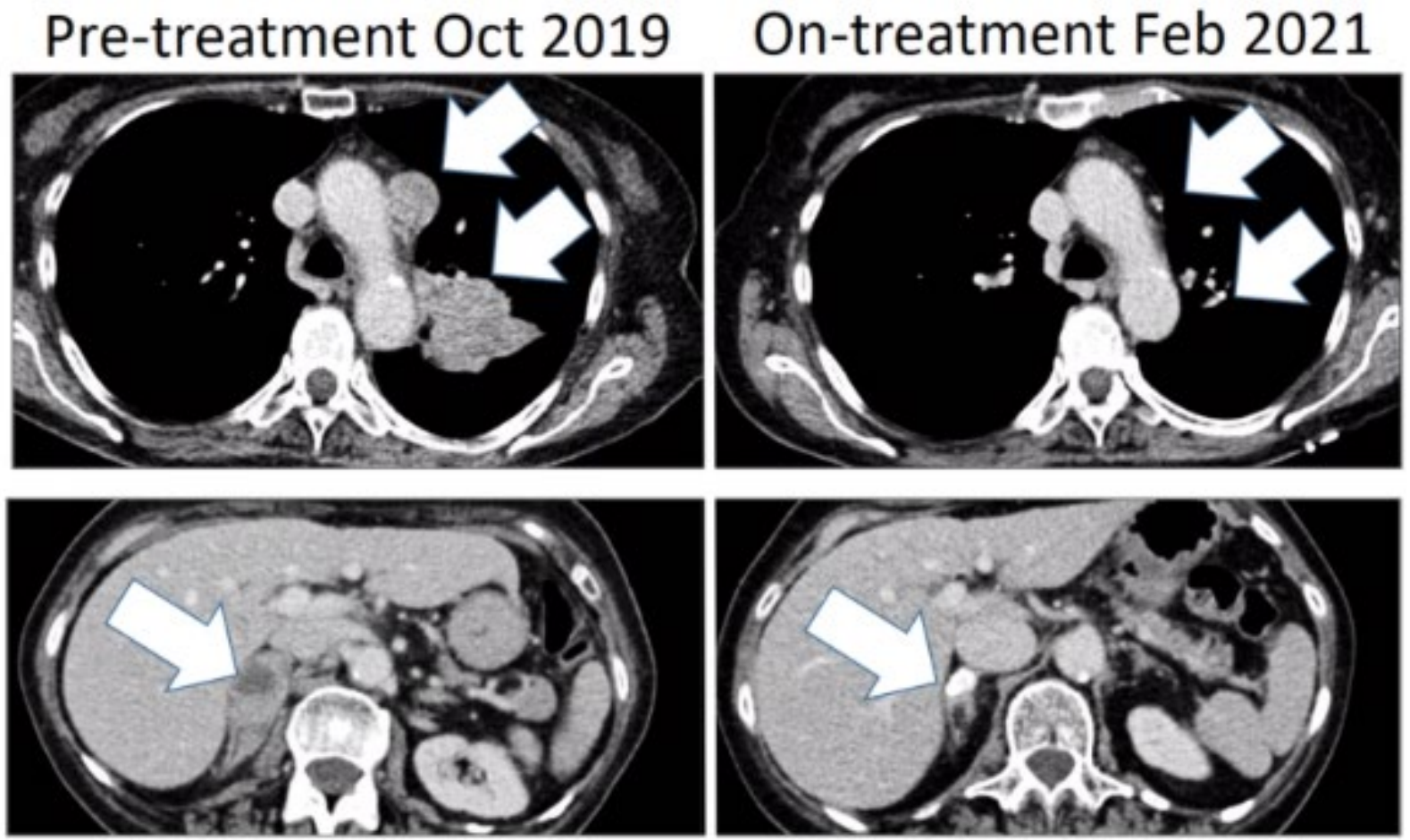
Response to VS-6766 + Defactinib in a Patient with KRAS G12V mt NSCLC

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

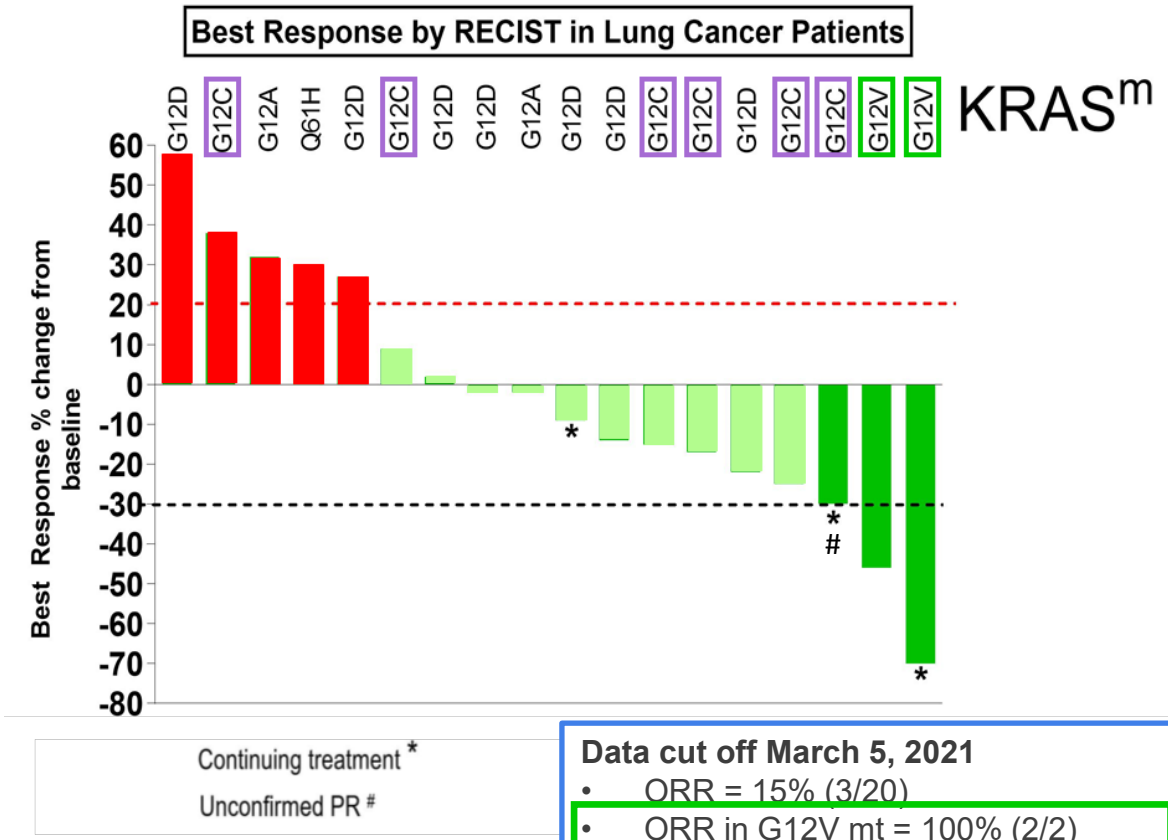


Presented by Matt Krebs in oral AACR 2021 presentation

NSCLC Responses with VS-6766 + Defactinib Combination

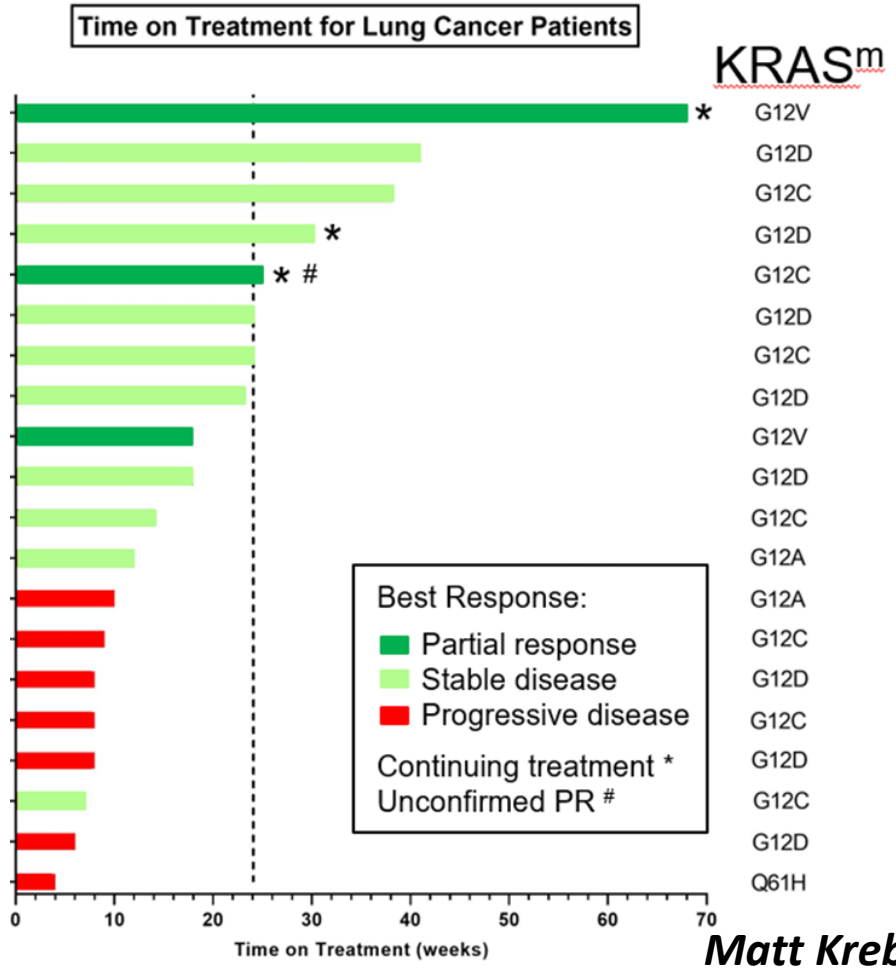
Confirmed responses in 2/2 patients with KRAS-G12V NSCLC

Tumor reduction in 4/6 patients with KRAS-G12C NSCLC



Data cut off March 5, 2021

- ORR = 15% (3/20)
- ORR in G12V mt = 100% (2/2)
- DCR =65% (13/20)
- 3/20 (15%) still on study
- 7 pts on treatment ≥ ~24 weeks

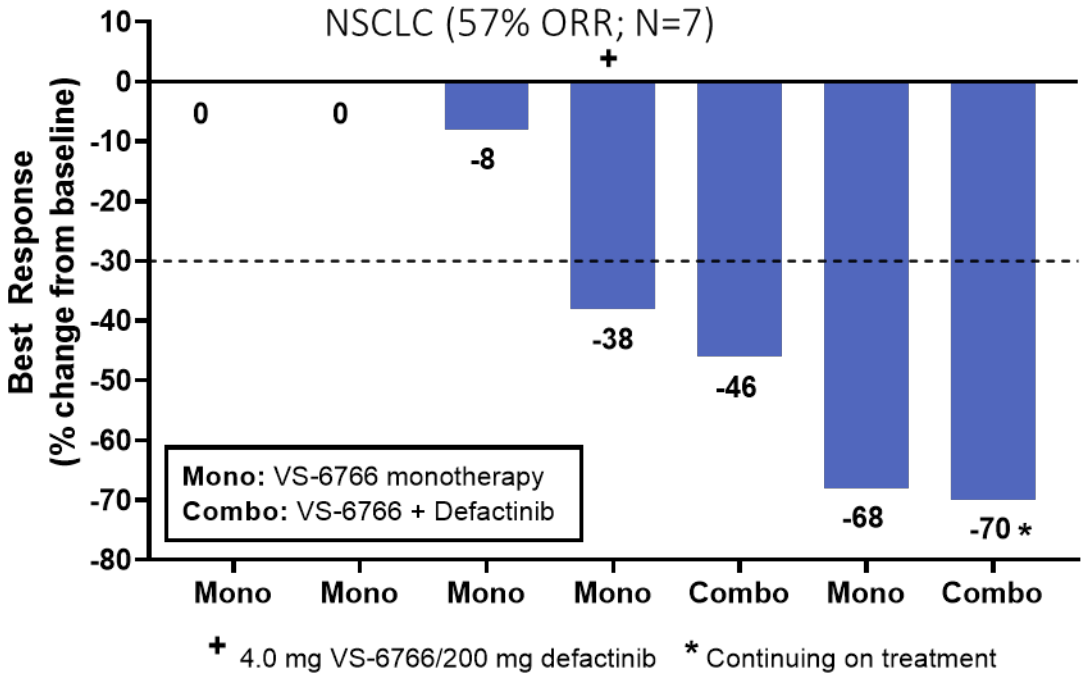


Matt Krebs, AACR 2021

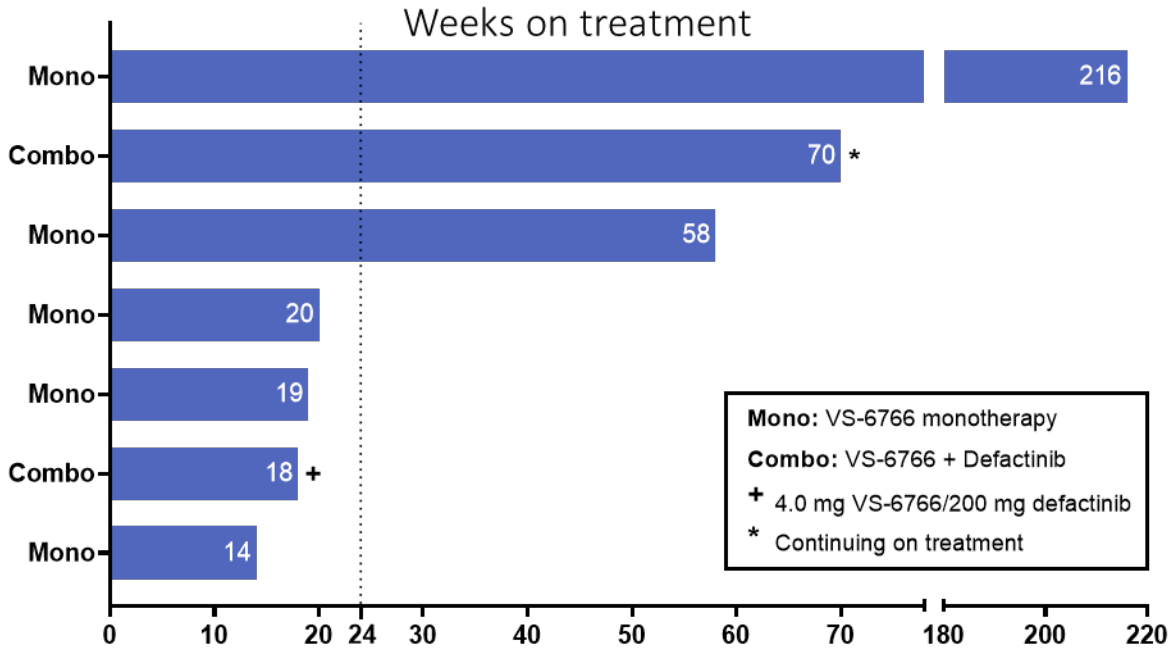
Strong Signal in KRAS G12V NSCLC to be Further Validated

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

Best Response by RECIST in KRAS^{G12V} NSCLC



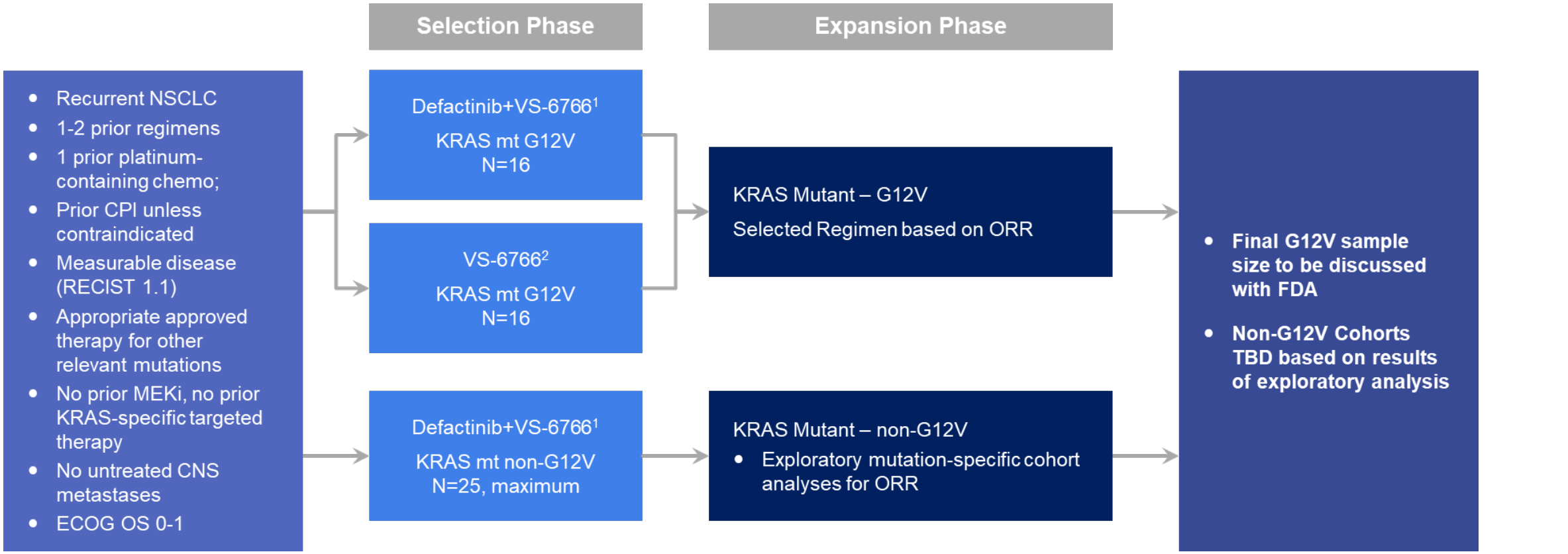
Time on Treatment for KRAS^{G12V} NSCLC



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

Source: [1] Guo, et al Lancet Oncology 2020 [2] Krebs, AACR April 2021(March 18, 2021 cutoff)

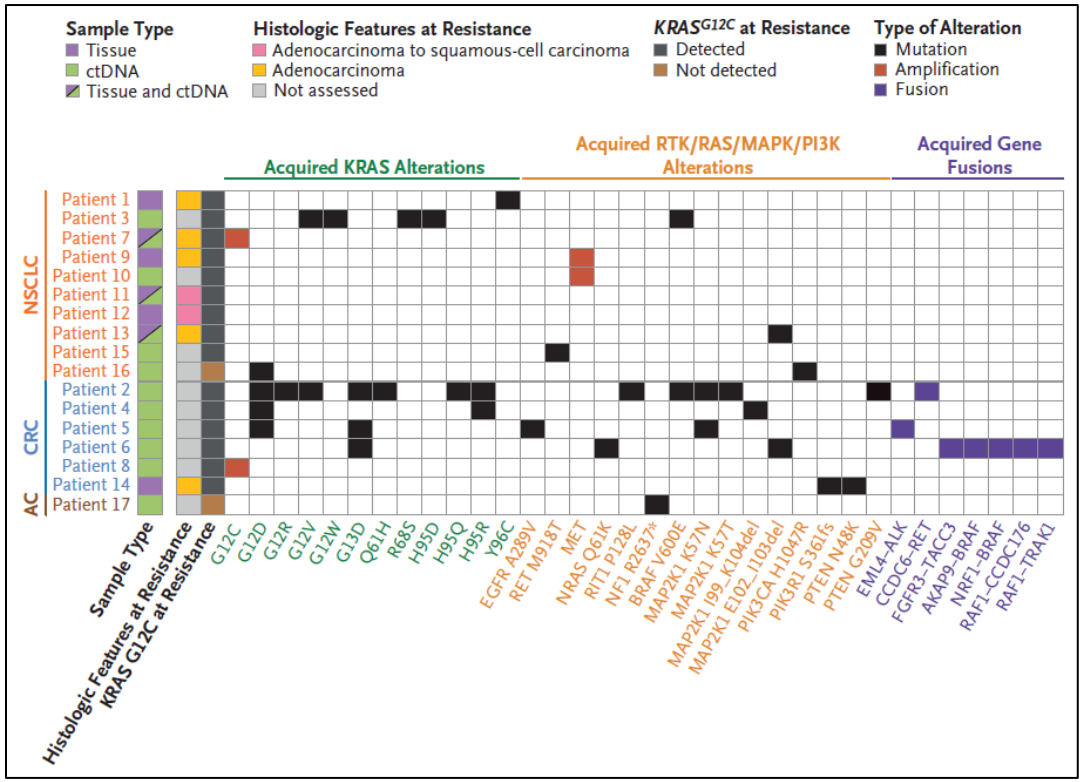
NSCLC Clinical Strategy: KRAS Mutant (mt), Enriched G12V, Phase 2, Recurrent NSCLC for Potential Accelerated Approval



This Registration-directed Phase 2 Study commenced December 2020 with an estimated Primary Completion Date for the Expansion Phase of March 2023 (clinicaltrials.gov)

[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)

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**

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

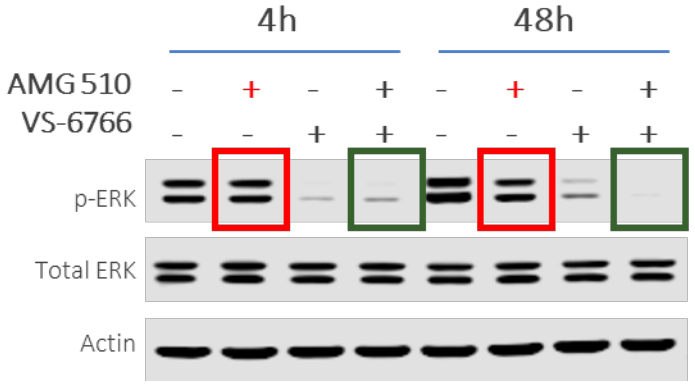
Preclinical synergy of VS-6766 + G12C inhibitors in KRAS G12C mt models

Synergy of VS-6766 + G12C inhibitor AMG 510 across G12C mutant 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 ERK signaling pathway



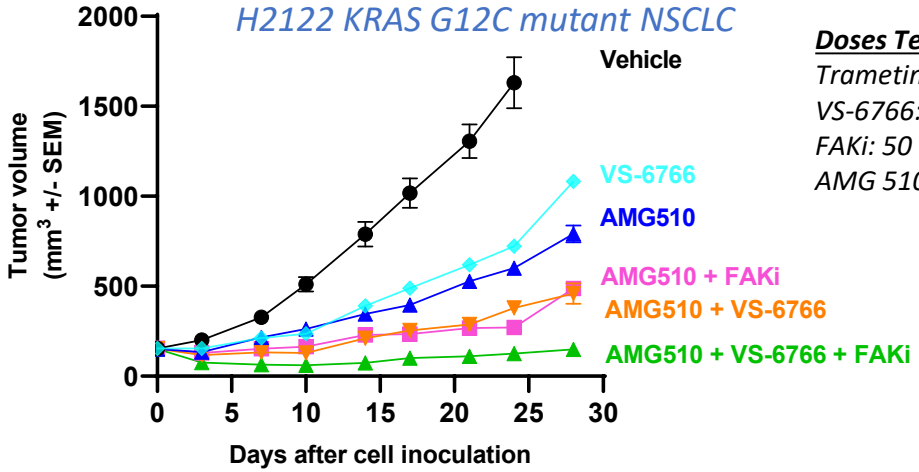
H2122 KRAS G12C mutant NSCLC

Concentrations Tested

AMG 510: 100 nM

VS-6766: 100 nM

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



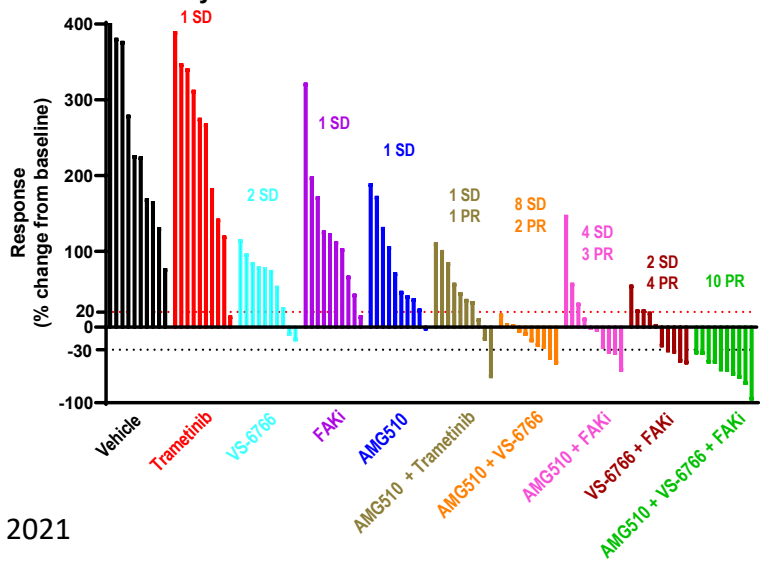
Doses Tested

Trametinib: 0.3 mg/kg QD

VS-6766: 0.3 mg/kg QD

FAKi: 50 mg/kg BID

AMG 510: 30 mg/kg QD

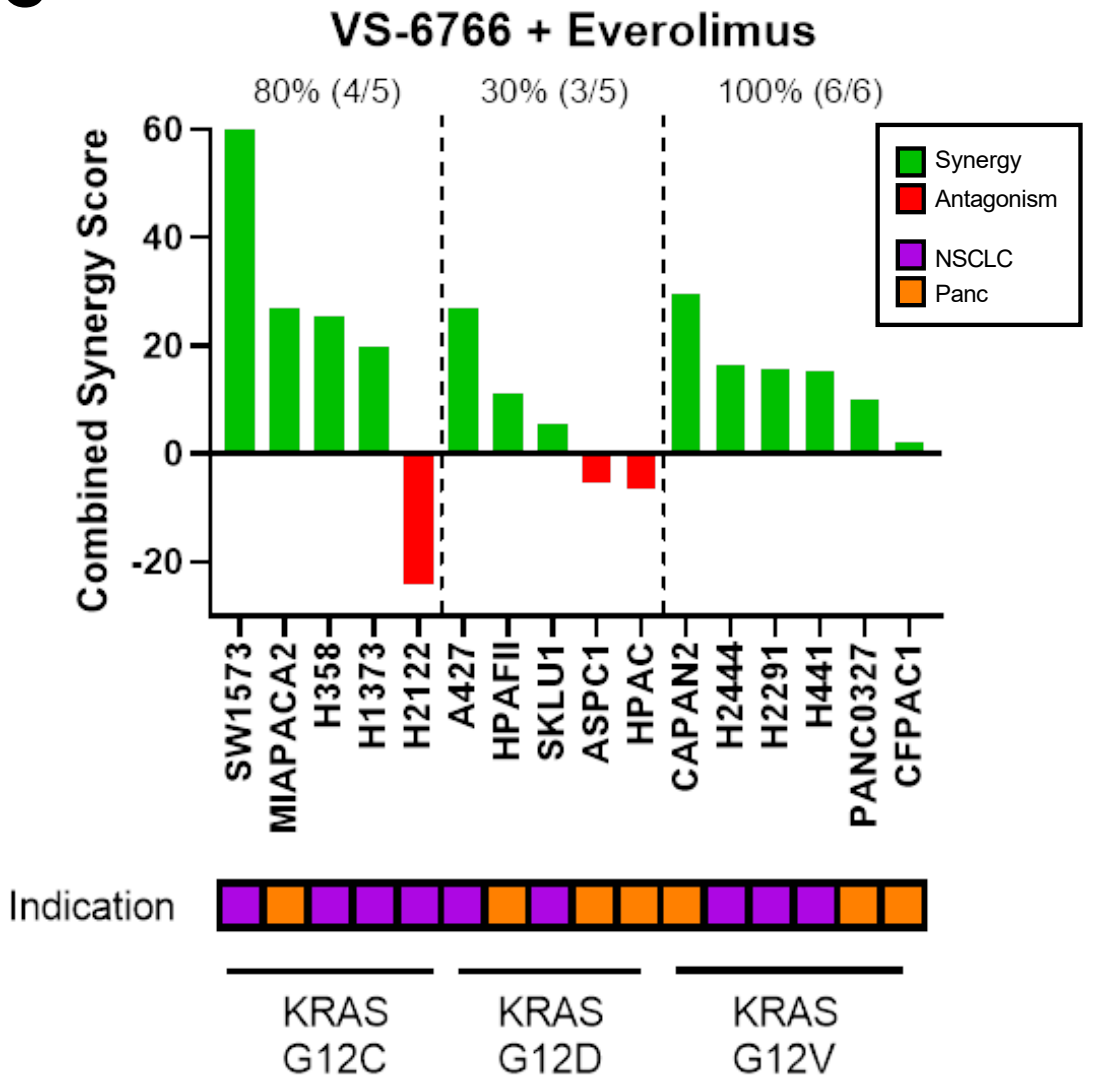


Reference: Coma et al., AACR 2021

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

- Synergy of VS-6766 + everolimus observed broadly across cancer cell lines with various KRAS mutation variants
- 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



Conclusions

- **For KRAS G12V mt NSCLC**
  - VS-6766 ± FAKi induces tumor regression in KRAS G12V mt NSCLC genetically engineered mouse model: Consistent with the strong dependence of KRAS G12V mt NSCLC on CRAF
  - VS-6766 ± defactinib has elicited confirmed responses in patients with KRAS G12V mt NSCLC (4/7 pts; 57% ORR)
  - A registration-directed trial of VS-6766 ± defactinib is ongoing with focus on recurrent KRAS G12V mt NSCLC (NCT04620330)
- **For KRAS G12C mt NSCLC**
  - Preclinical synergy of VS-6766 with G12C inhibitors across KRAS G12C mt cell lines correlates with deeper/sustained pERK inhibition and tumor regressions in KRAS G12C mt NSCLC xenograft models
  - Clinical data (Awad, NEJM, 2021) show that acquired resistance to adagrasib in patients with KRAS G12C mt NSCLC is largely mediated by additional RAS and/or RAF mutations – predicted to be sensitive to VS-6766
  - With the recent approval of sotorasib, VS-6766 + sotorasib would no longer be a novel:novel combination
- **For other KRAS mutations**
  - A cohort is currently ongoing testing a RP2D of VS-6766 + everolimus (mTOR inhibitor) in patients with KRAS mutant NSCLC
  - Other combinations with VS-6766 (e.g. with SOS1i) also supported by preclinical data

VS-6766 as potential backbone of therapy for KRAS mutant NSCLC