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

Jonathan Pachter, PhD, Chief Scientific Officer

July 14, 2021

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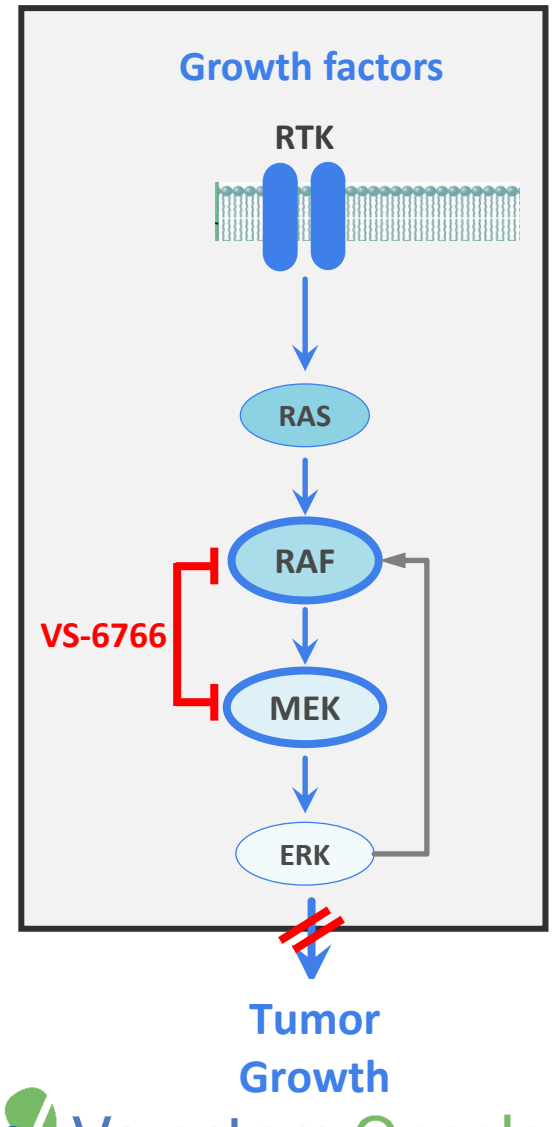
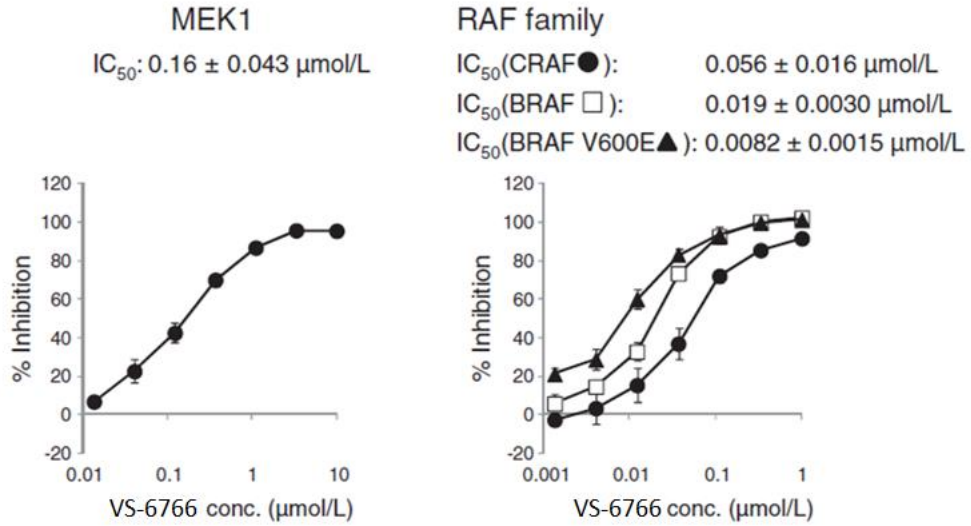
VS-6766 is a Unique Small Molecule RAF/MEK Inhibitor



- 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



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

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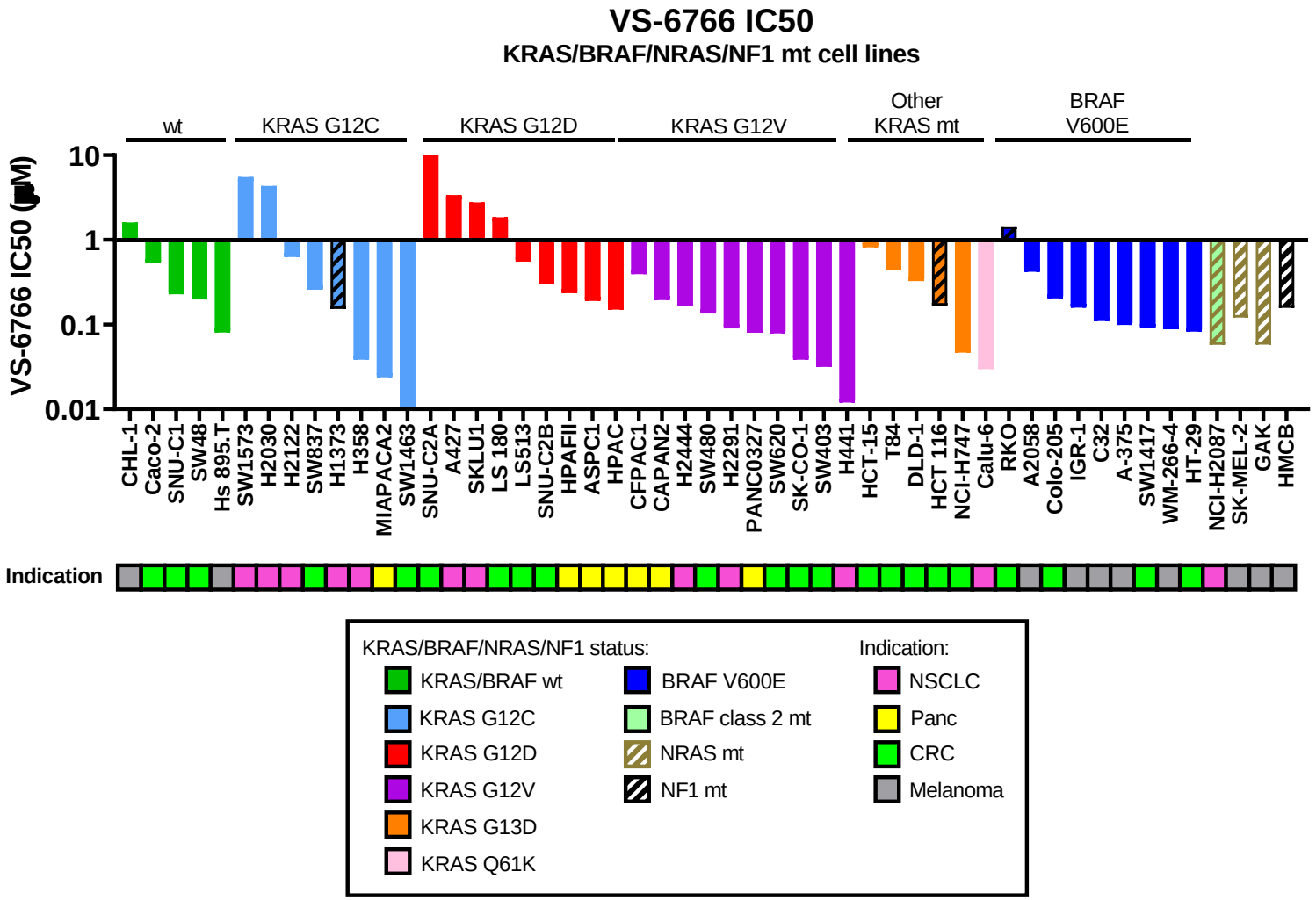
Anti-tumor effects of VS-6766 across multiple indications and multiple MAPK pathway alterations



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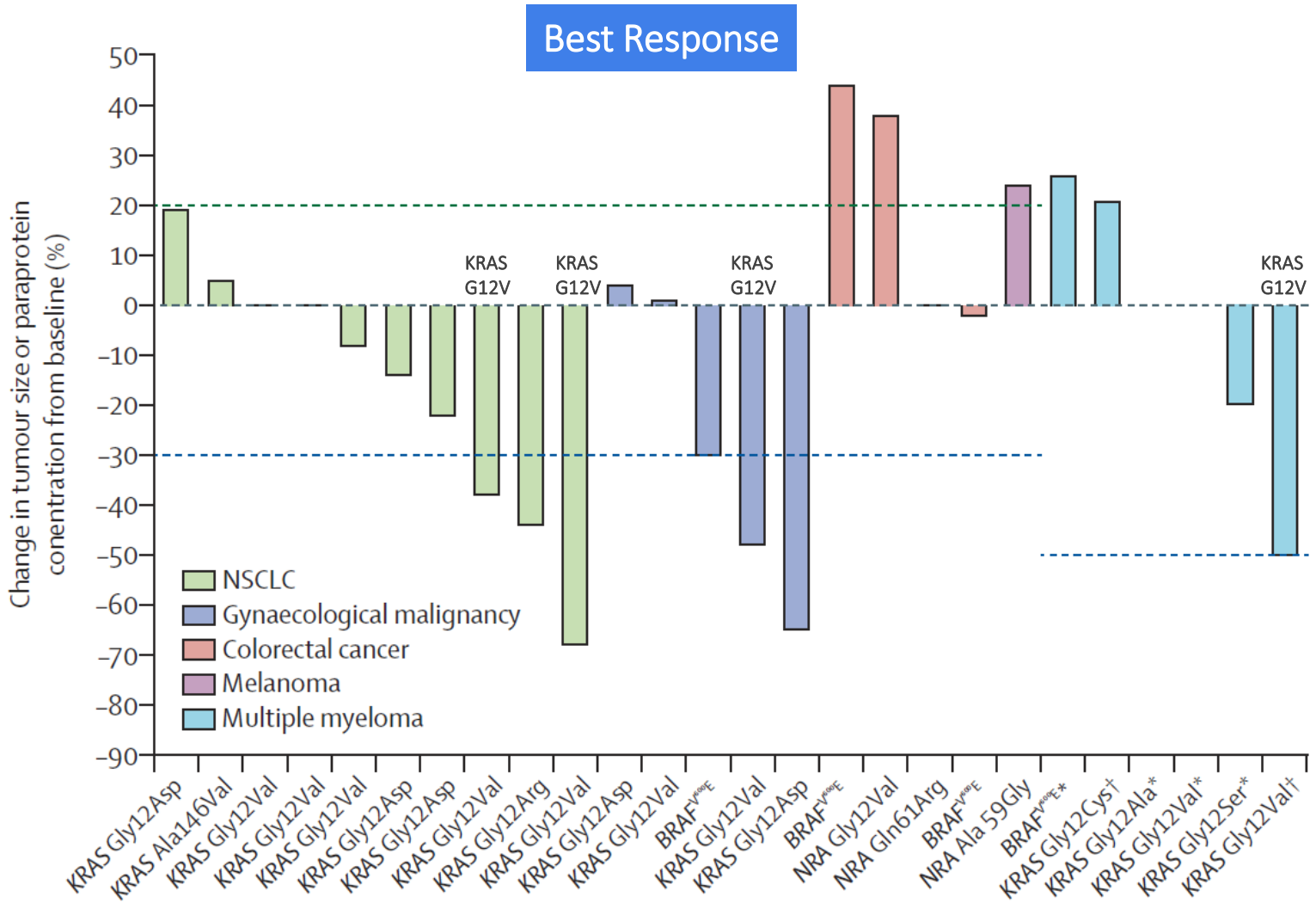
VS-6766 monotherapy has shown clinical activity in several cancer indications, including NSCLC



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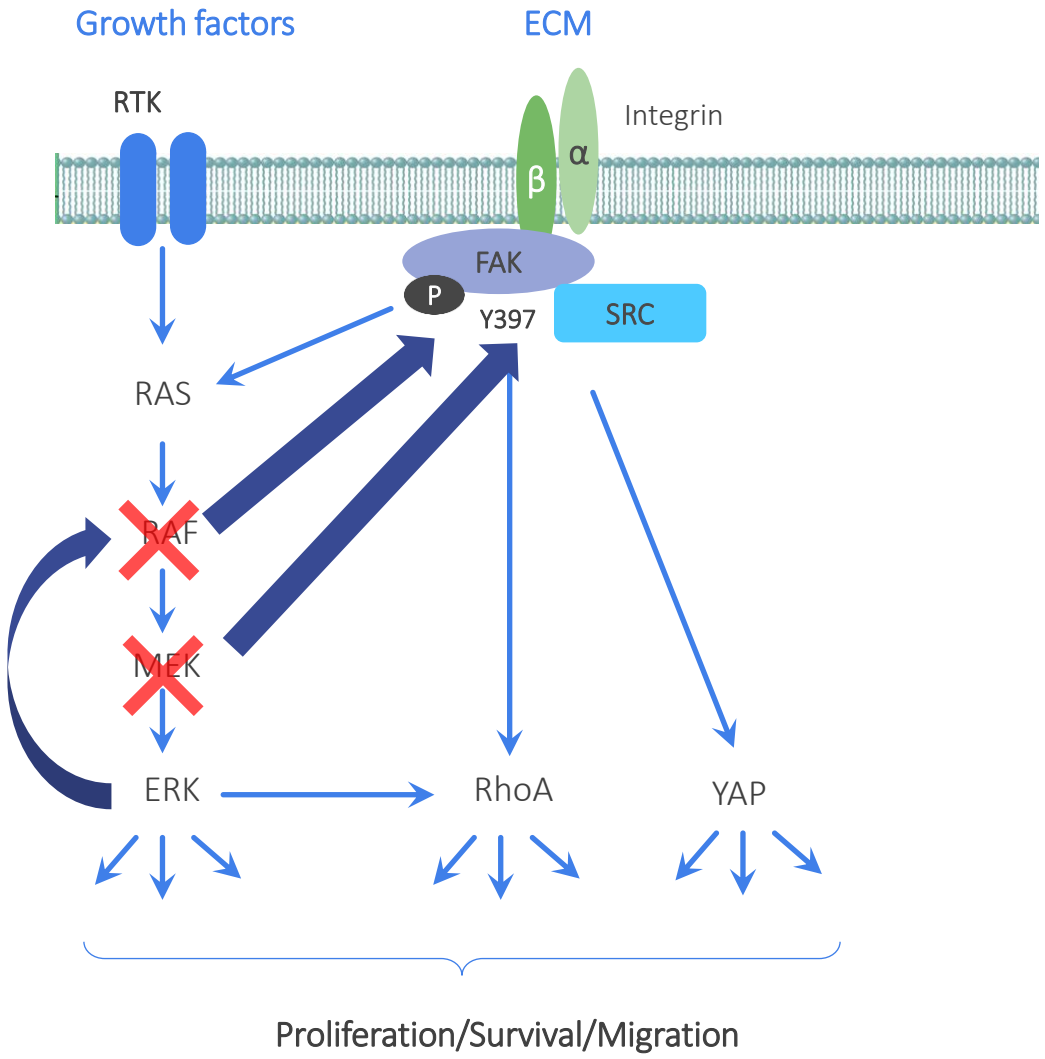
Guo et al., Lancet Oncology 2020

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

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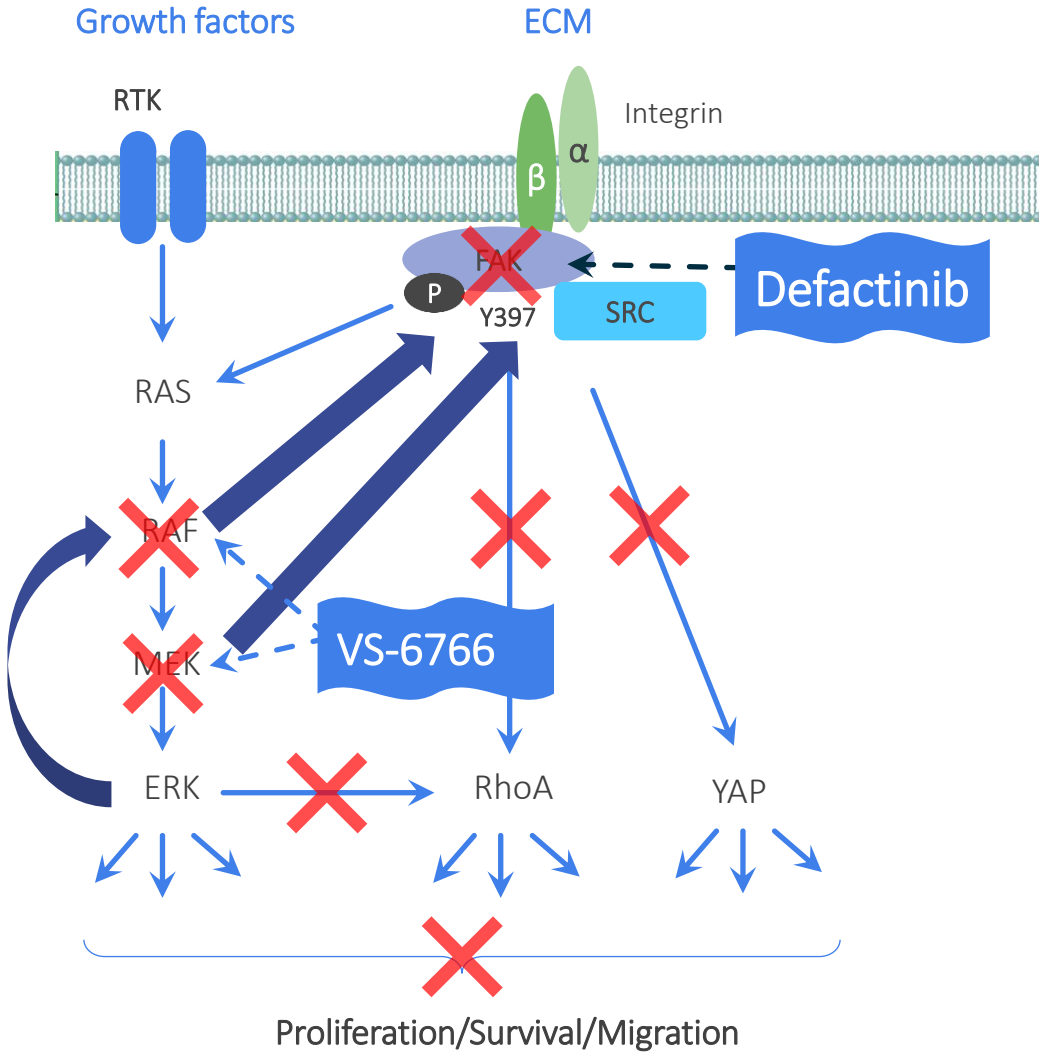
More Complete Shutdown of Tumor Growth Requires Addressing Multiple Resistance Mechanisms



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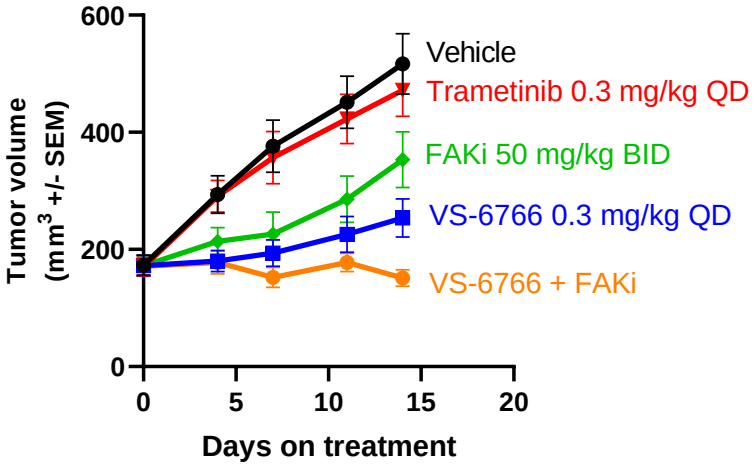
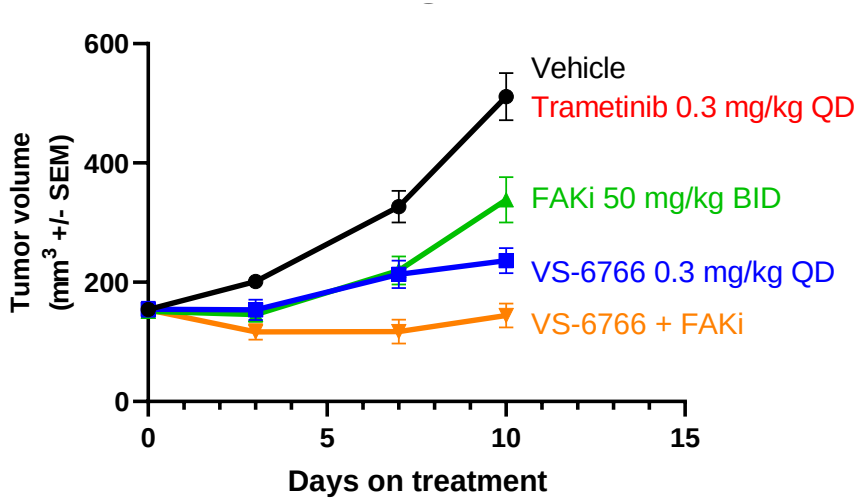
Combination of VS-6766 with FAK Inhibitor Leads to More Robust Anti-Tumor Efficacy *In vivo* & Suppresses pFAK in Patient's Tumors

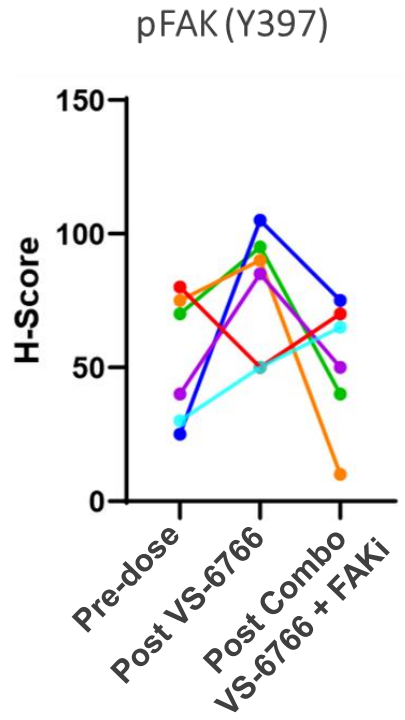
NSCLC cancer model
H358 KRAS G12C mt



NSCLC cancer model
H2122 KRAS G12C mt



VS-6766 induces pFAK in patient's tumors



U. Banerji, AACR 2020

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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%)

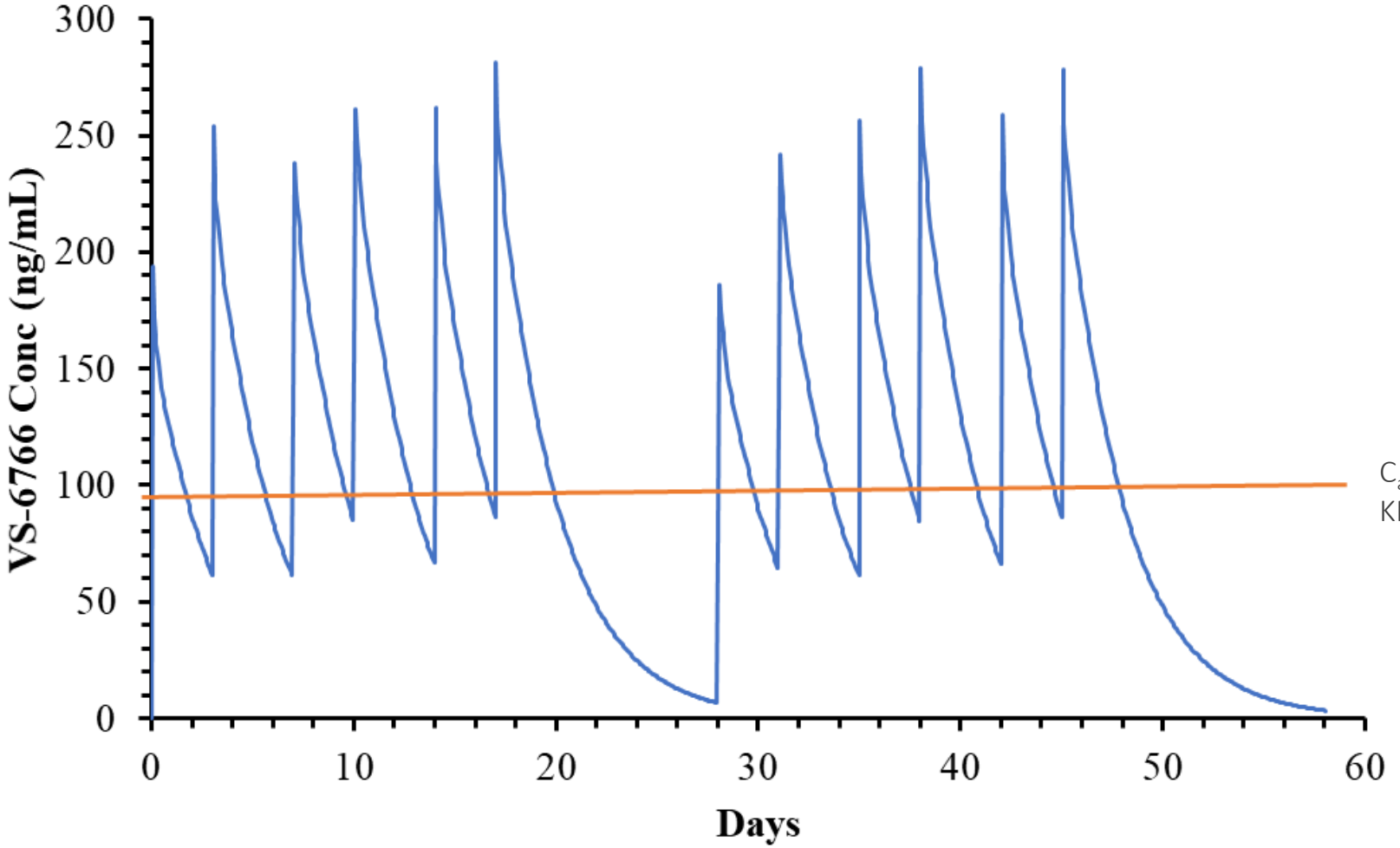
Summary of FRAME Safety Profile

Most Adverse Events (AE) were Grade 1/2

Few patients have discontinued due to AEs in the study

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

Target exposure for preclinical tumor regression is covered by twice weekly dosing of 4 mg VS-6766 3 wks on/1 wk off



C_{av} for tumor regression from KRAS G12V mt NSCLC GEMM model

- Modeling of PK for 4 mg VS-6766 2/wk, 3 wks on/1 wk off, based on 4 mg single dose PK data (study NO21895)
- Relationship to average exposure for tumor regression in KRAS G12V mt NSCLC mouse model

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Reference: Martinez-Garcia et al., Clin Cancer Res 2012; Coma et al. AACR 2021

Clinical Activity of VS-6766 + Defactinib in Low-Grade Serous Ovarian Cancer (LGSOC)

- Overall response rate (ORR) is 52% (11 of 21 response evaluable patients)
  - **KRAS mutant ORR at 70% (7 of 10 response evaluable patients)**
  - **KRAS wild-type ORR at 44% (4 of 9 response evaluable patients)**
  - KRAS status undetermined ORR at 0% (0 of 2 response evaluable patients)
- As reported previously, the most common side effects seen in the study were rash, creatine kinase elevation, nausea, hyperbilirubinemia and diarrhea, most being NCI CTC Grade 1/2 and all were reversible

May 2021: 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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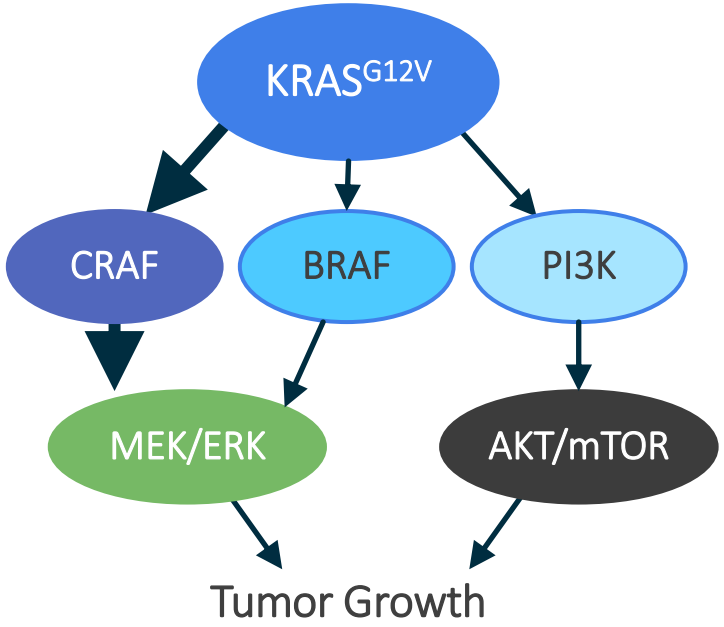
Dec 2020 data cut

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

A Precision Approach to KRAS-G12V Driven NSCLC



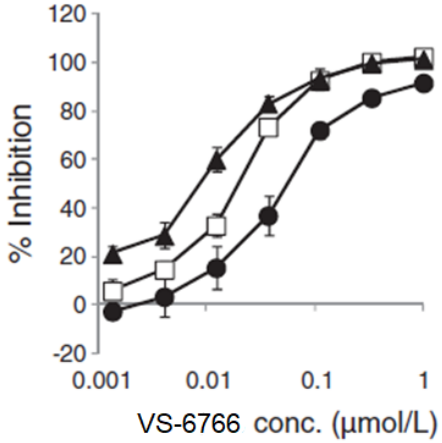
- $KRAS^{G12V}$ signals mainly through RAF/MEK in contrast to other variants, such as KRAS-G12D, which signal more through PI3K/AKT
- $KRAS^{G12V}$ models are especially dependent on CRAF

RAF family

IC_{50}(CRAF●): 0.056 ± 0.016 µmol/L

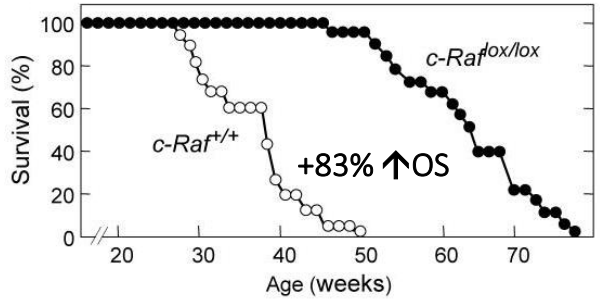
IC_{50}(BRAF □): 0.019 ± 0.0030 µmol/L

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

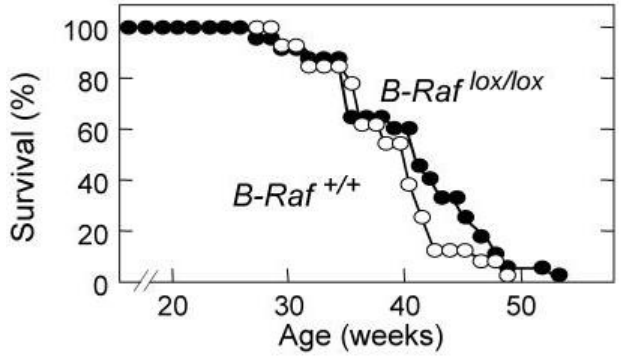


CRAF Drives $KRAS^{G12V}$ NSCLC[1,3]

CRAF KO vs. WT



BRAF KO vs. WT



CRAF, but not BRAF, ablation improves survival of mice with $KRAS^{G12V}$ 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)

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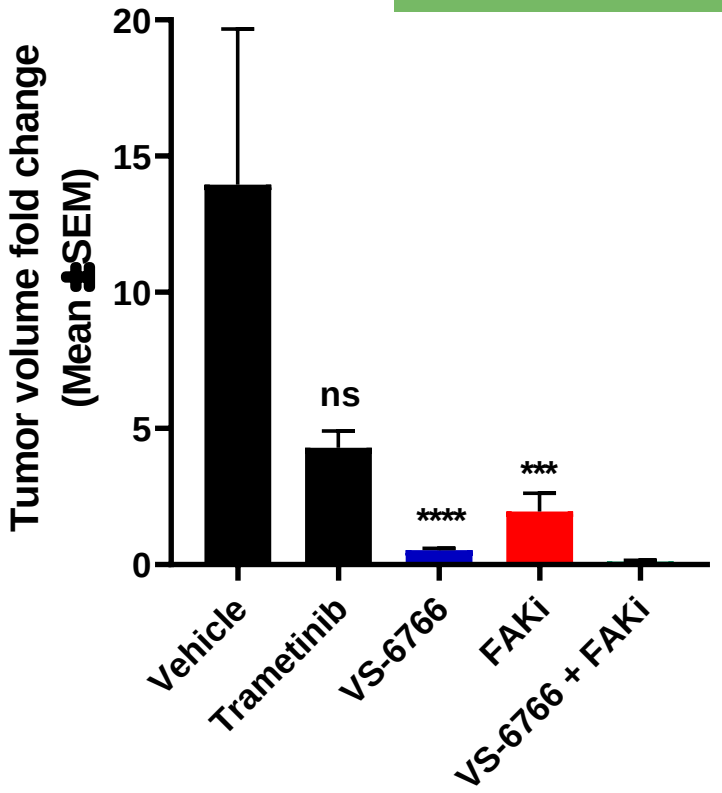
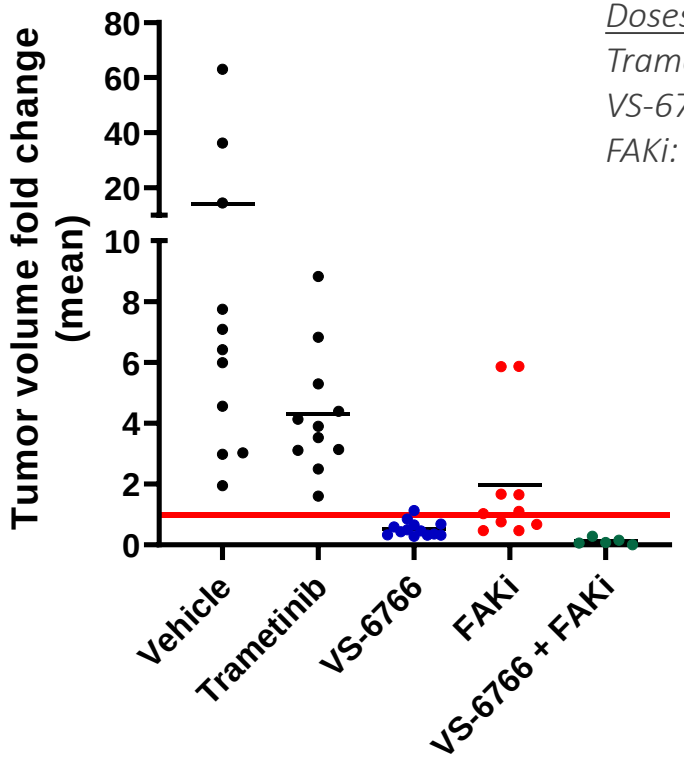
VS-6766 +/- FAKi confers strong tumor regression in CRAF-dependent KRAS G12V mutant NSCLC *in vivo*

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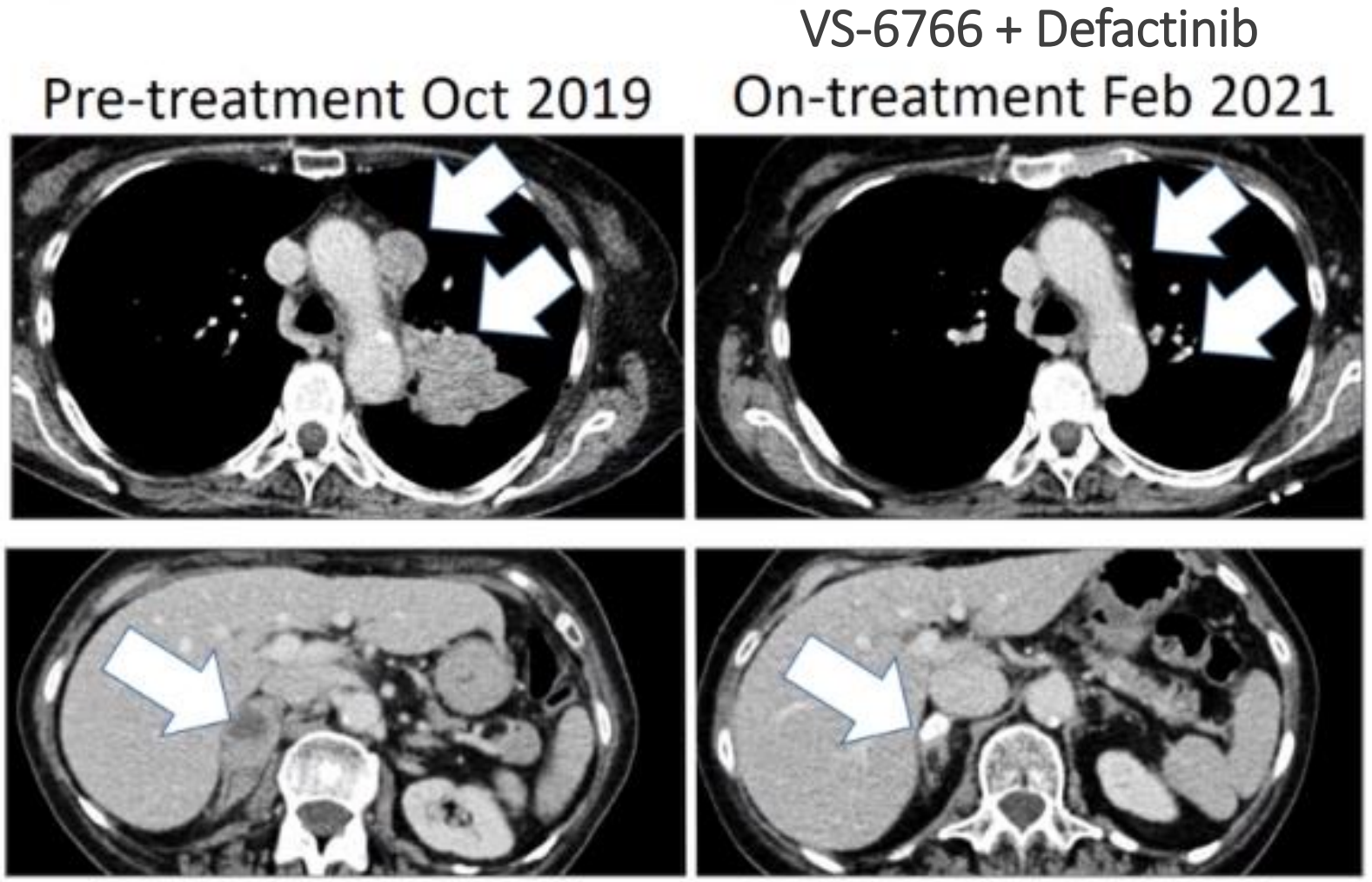
Response to VS-6766 + Defactinib in a Patient with KRAS G12V mt NSCLC

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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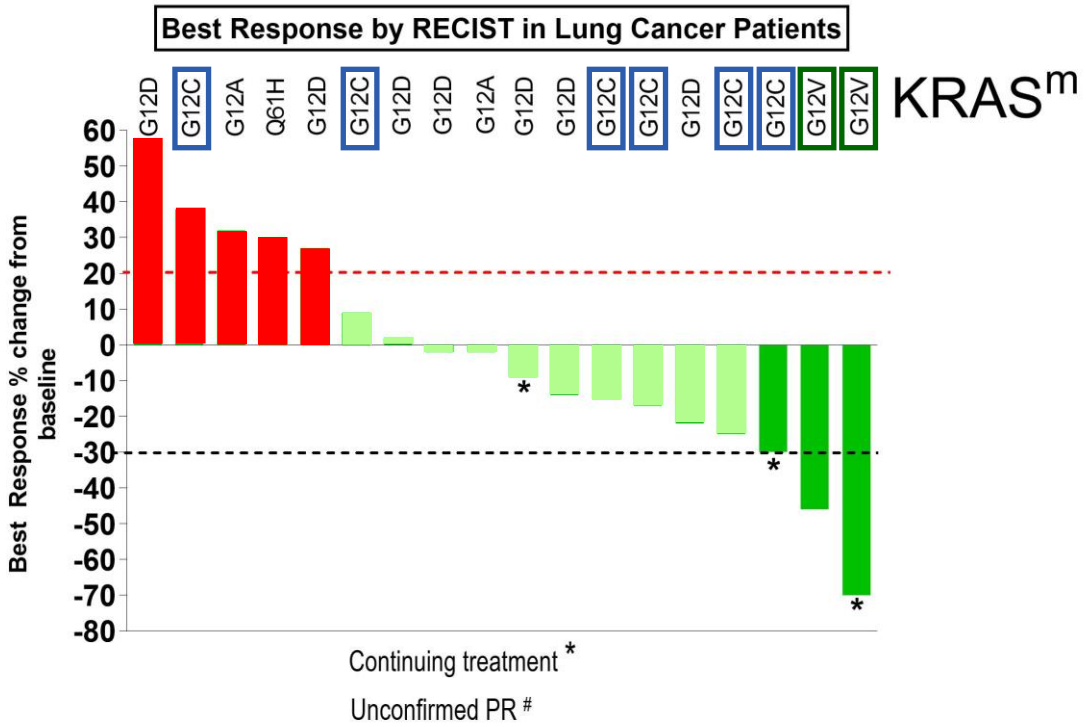
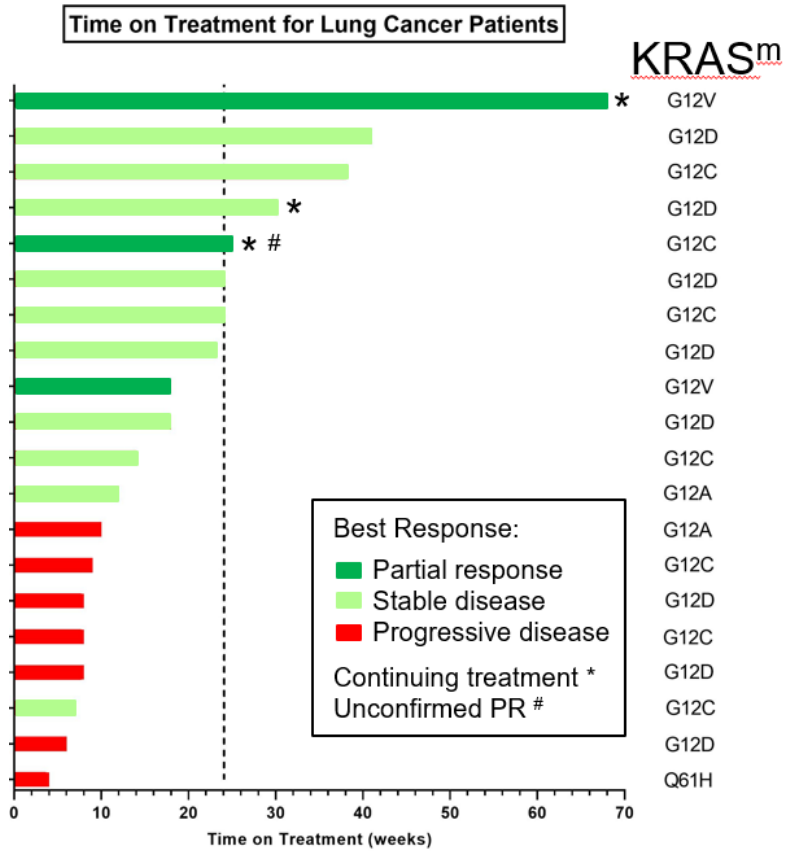
NSCLC Responses with VS-6766 + Defactinib Combination (n=20)

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

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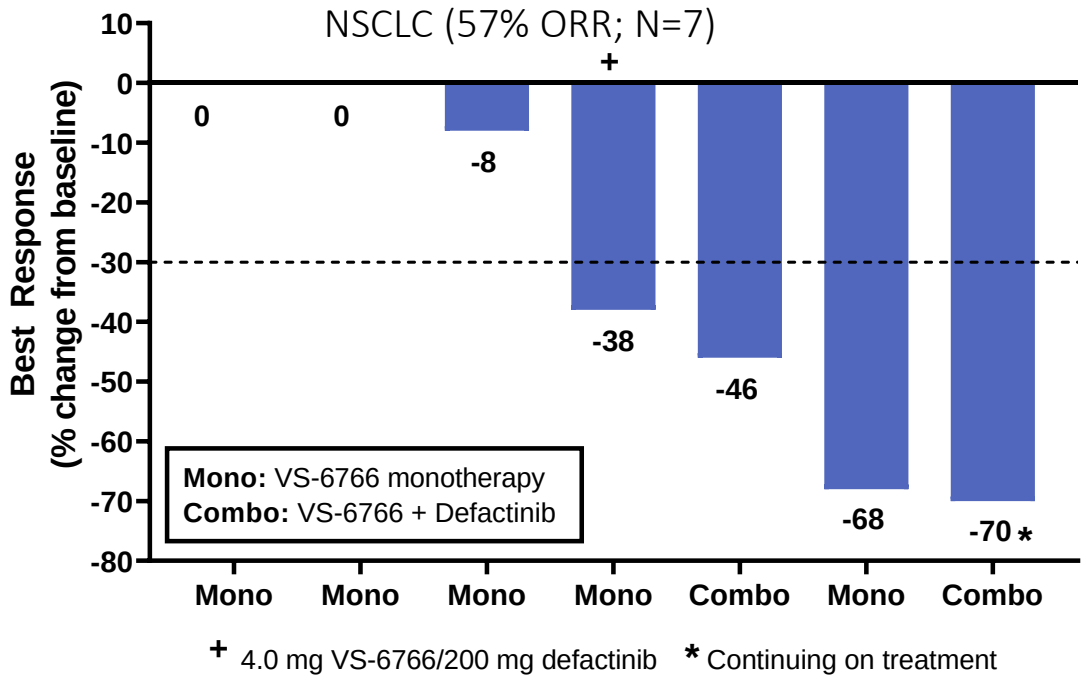
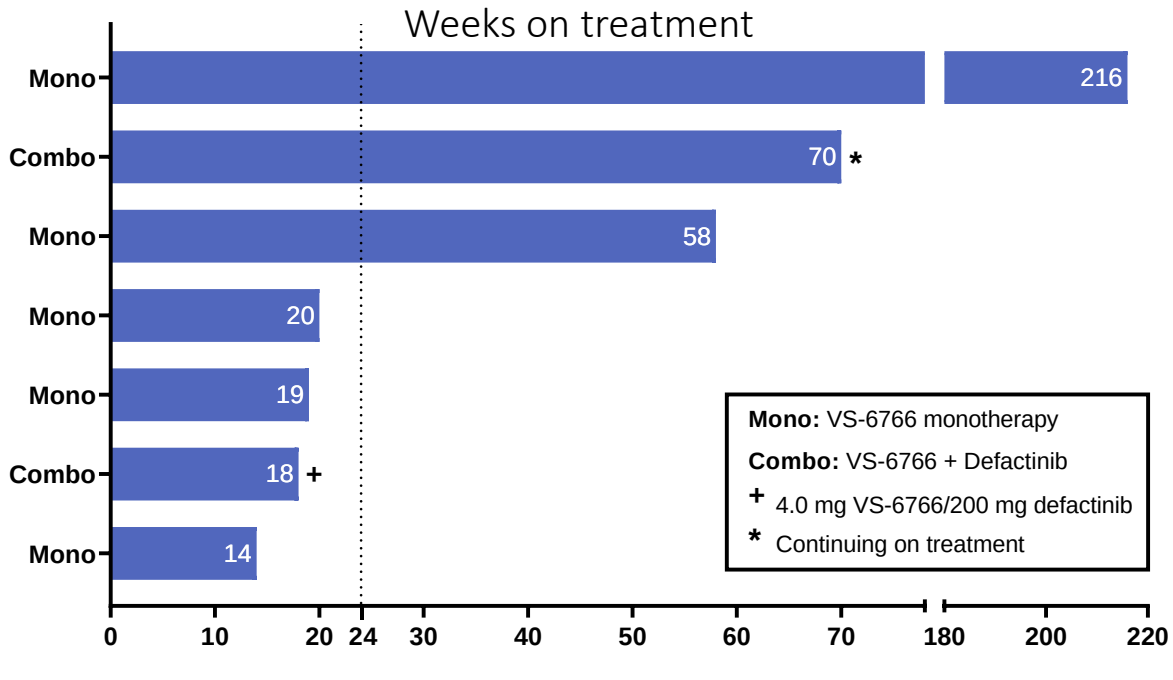
Strong Signal in KRAS G12V NSCLC to be Further Validated

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

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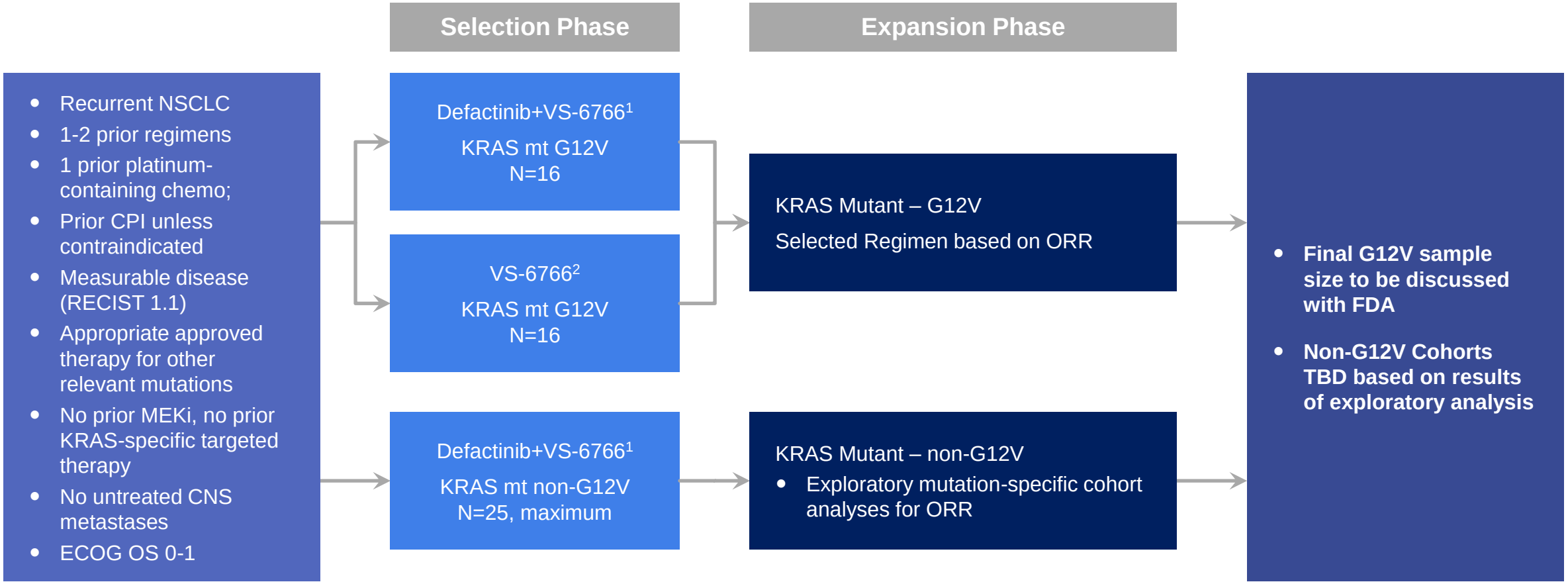
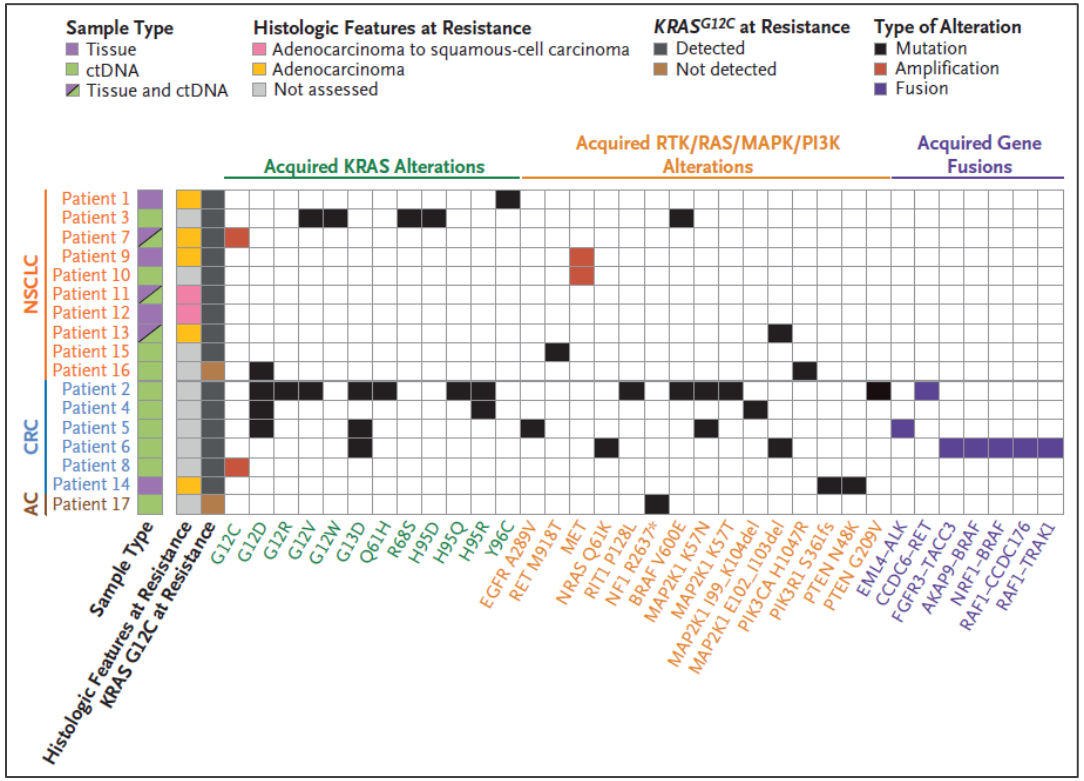
NSCLC Clinical Strategy: KRAS Mutant (mt), Enriched G12V, Phase 2, Recurrent NSCLC for Potential Accelerated Approval



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

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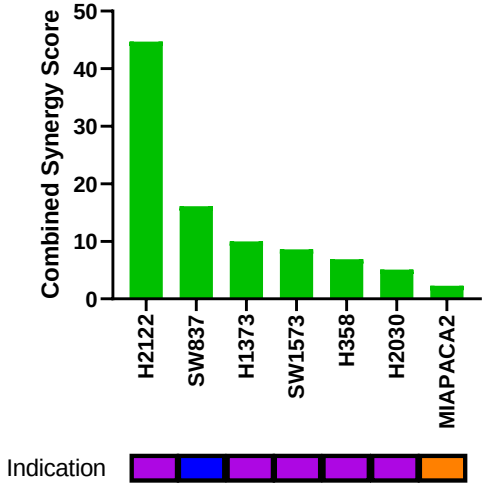
[1]Awad MM et al., N Engl J Med 2021; 384: 2382-93; [2]Tanaka et al., Cancer Discov 2021;11:1–10

Preclinical synergy of VS-6766 + G12C inhibitors observed in KRAS G12C mutant NSCLC, CRC and pancreatic cancer cell lines

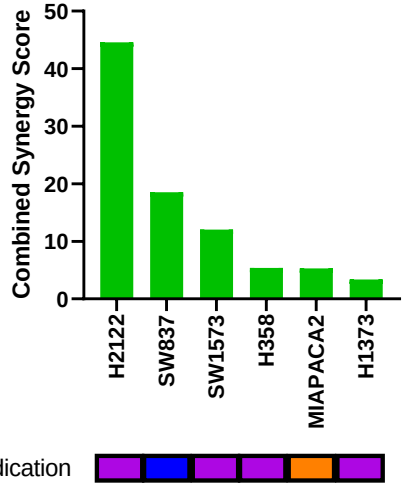
Cell line	Indication	Sensitivity to G12C inhibitors	Combined Synergy Score: VS-6766 + AMG 510	Combined Synergy Score: VS-6766 + MRTX849
H2122	NSCLC	Moderately sensitive	44.7	44.6
H1373	NSCLC	Sensitive	10.0	3.4
SW1573	NSCLC	Insensitive	8.6	12.0
H358	NSCLC	Sensitive	6.9	5.4
H2030	NSCLC	Moderately sensitive	5.1	ND
SW837	CRC	Sensitive	16.1	18.5
MIAPACA2	Panc	Sensitive	2.3	5.3

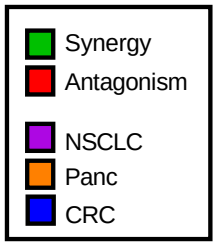
ND: not determined

VS-6766 + AMG 510

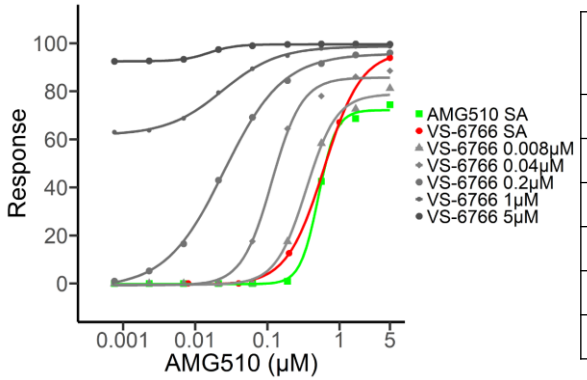


VS-6766 + MRTX849



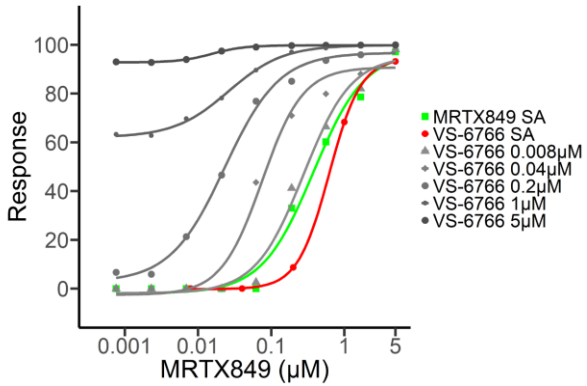


VS-6766 + AMG 510
H2122 KRAS G12C mt NSCLC



	AMG 510 IC50 (nM)
AMG 510 Single Agent (SA)	**631**
+ VS-6766 0.008 μM	439
+ VS-6766 0.04 μM	134
+ VS-6766 0.2 μM	28
+ VS-6766 1 μM	0.4
+ VS-6766 5 μM	<0.1

VS-6766 + MRTX849
H2122 KRAS G12C mt NSCLC



	MRTX849 IC50 (nM)
MRTX849 Single Agent (SA)	**397**
+ VS-6766 0.008 μM	290
+ VS-6766 0.04 μM	83
+ VS-6766 0.2 μM	23
+ VS-6766 1 μM	0.40
+ VS-6766 5 μM	<0.1

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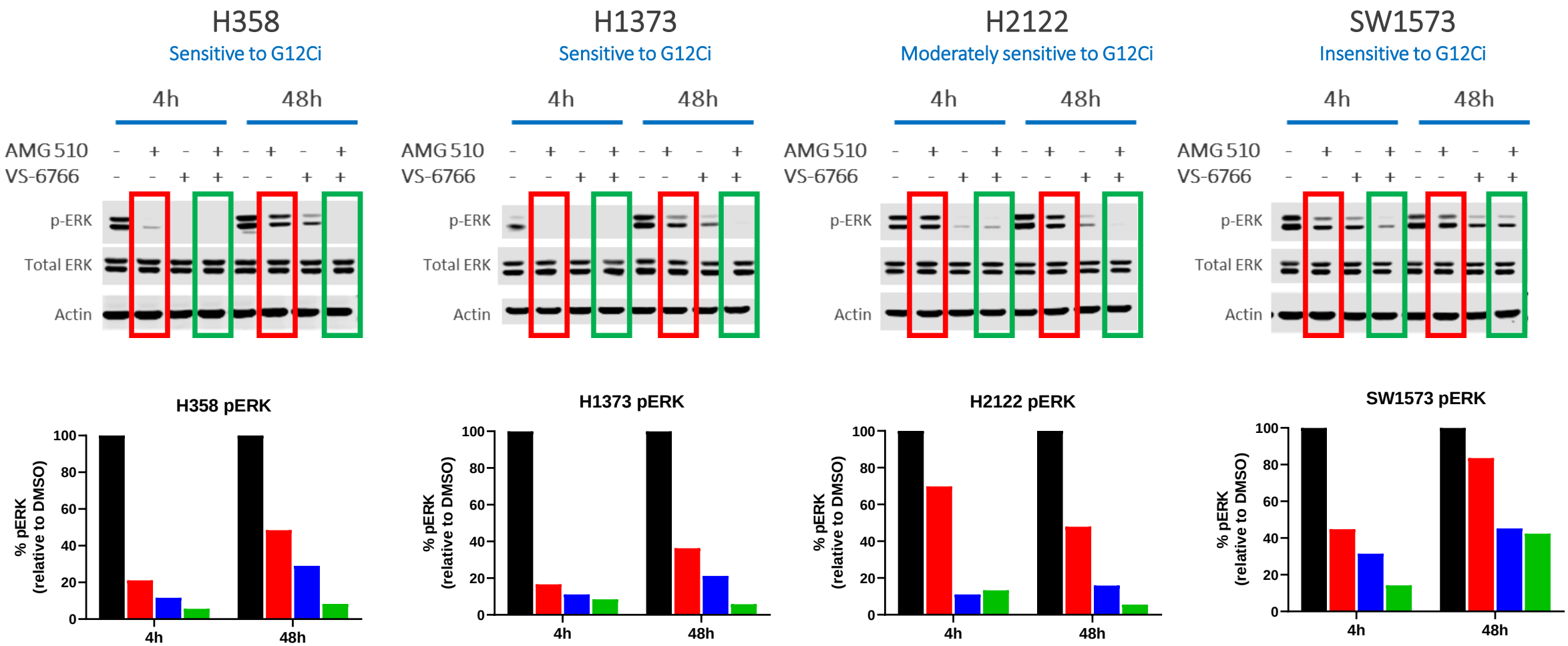
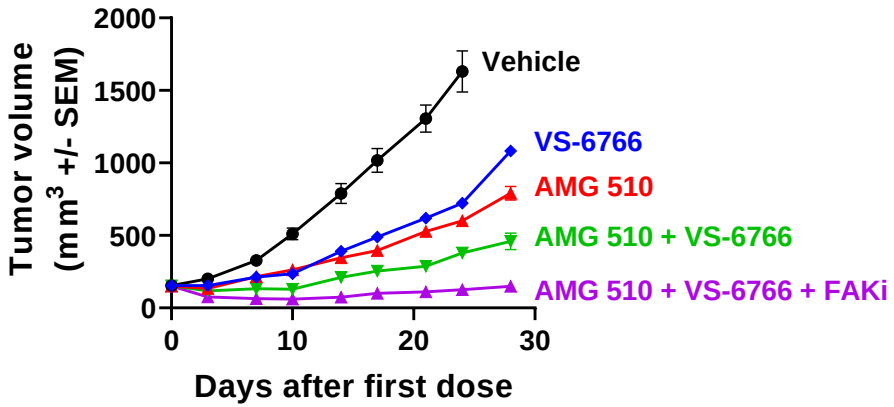
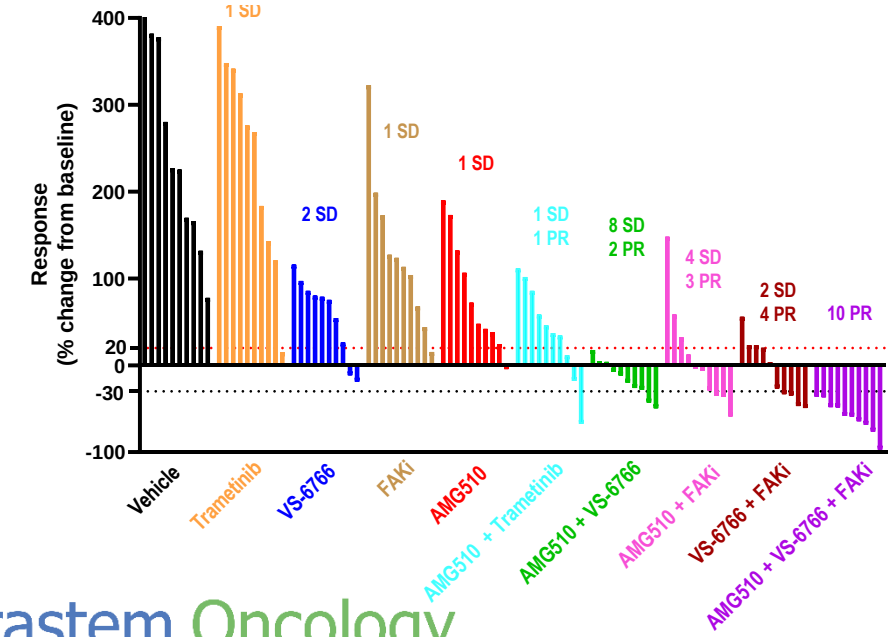
Addition of VS-6766 to AMG 510 increases depth & duration of pERK inhibition relative to AMG 510 alone across a panel of KRAS G12C mutant NSCLC cell lines



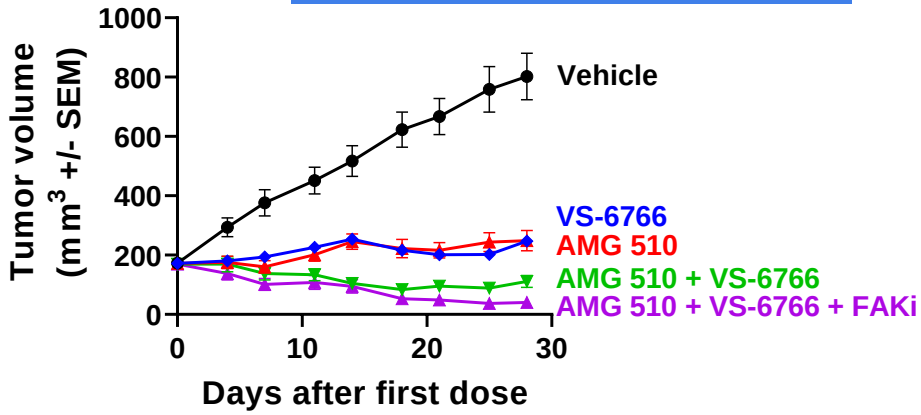
VS-6766 & FAKi potentiate AMG 510 efficacy in KRAS G12C mutant NSCLC in vivo
Tumor regression in all mice with triple combination

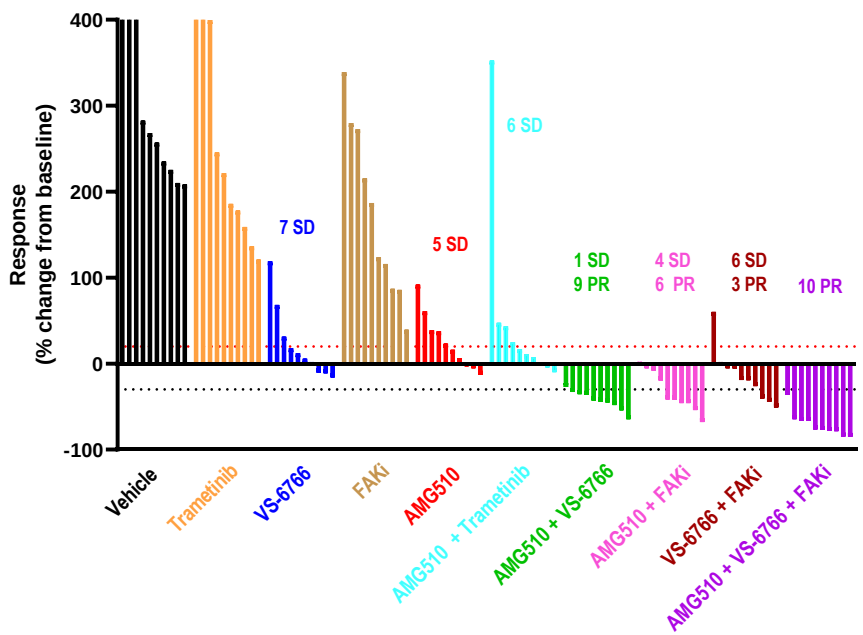
H2122 KRAS G12C mt NSCLC





H358 KRAS G12C mt NSCLC





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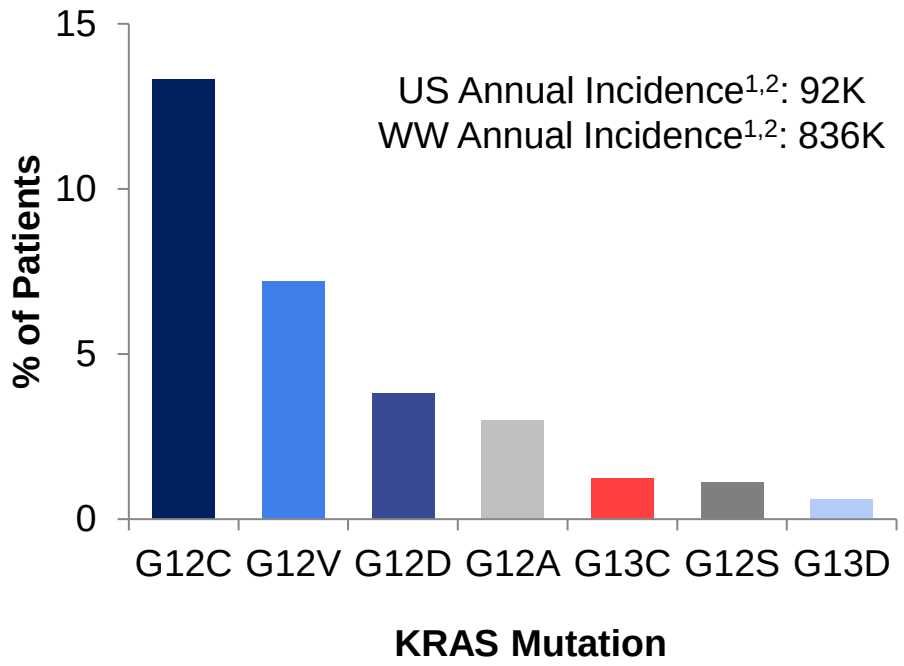
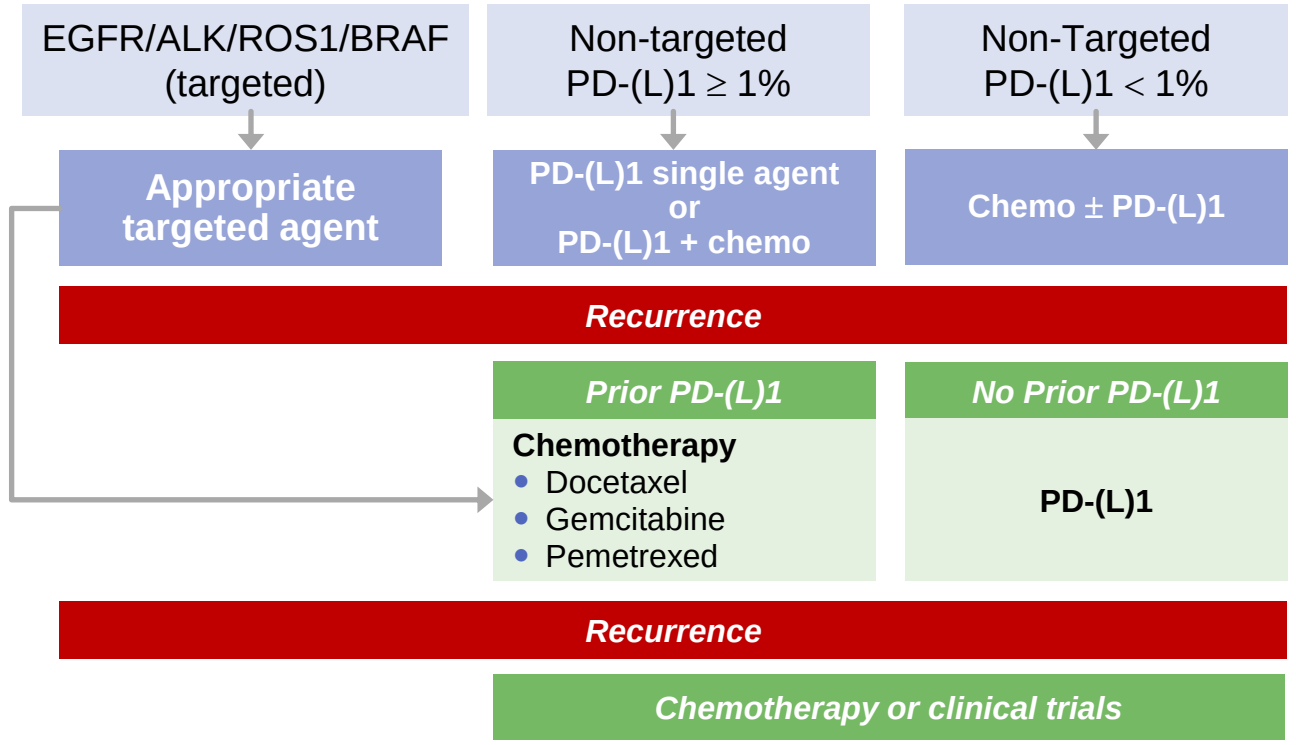
High Unmet Need in Refractory KRAS mut NSCLC Adenocarcinoma

NSCLC Adenocarcinoma[3]



KRAS Mutations Represent 25% of Lung Cancer Adenocarcinoma (EGFR 17%, ALK 7%)[4]

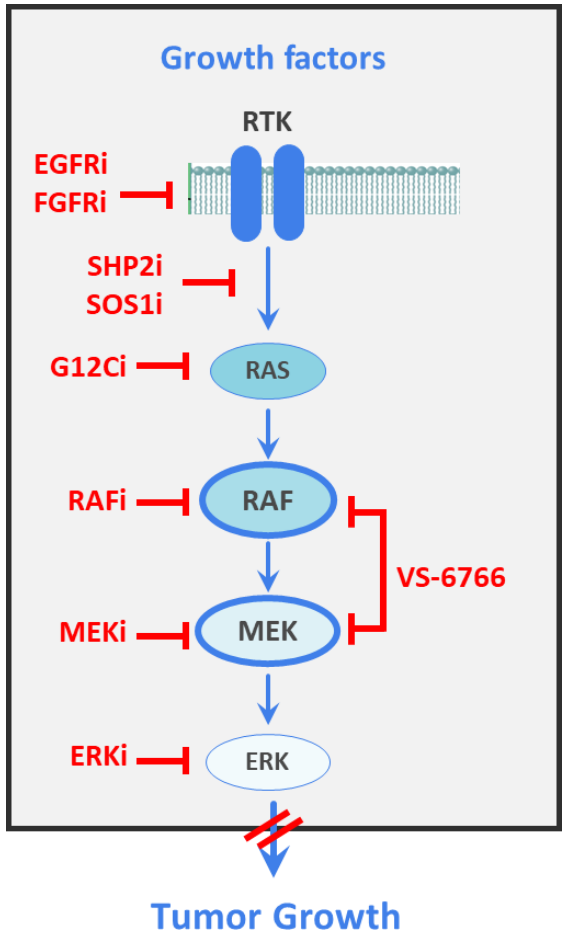
Advanced or Metastatic NSCLC Recommend Histologic and Molecular Subtyping[5]

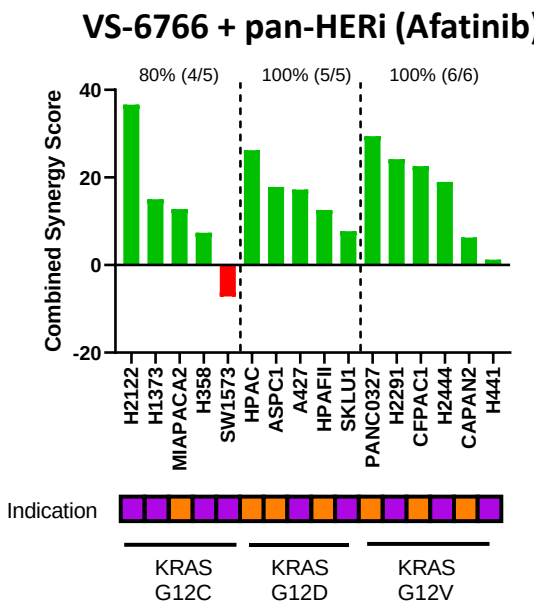


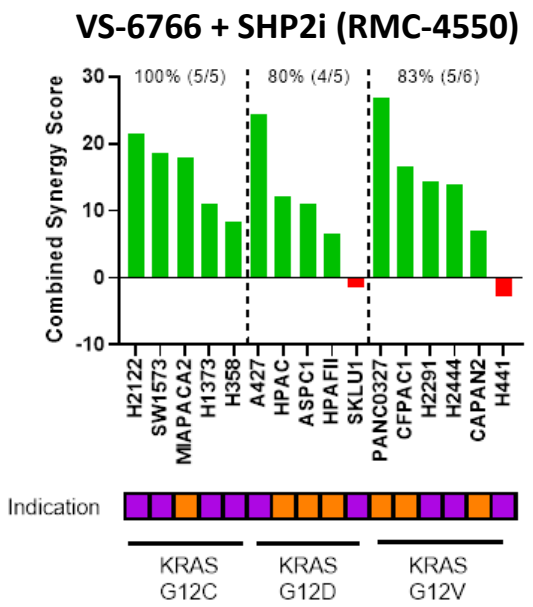
- SOC in recurrent disease is chemotherapy
- Pre-PD-(L)1 era, chemotherapy response rate ~10% in recurrent disease; 12w PFS of 30–45%

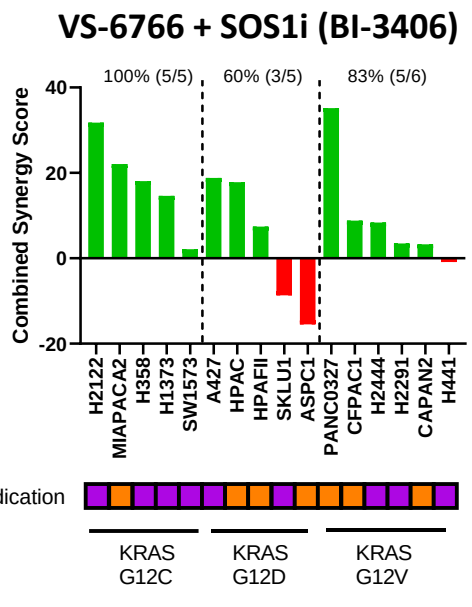
[1] Globocan, 2018
[2] https://www.ncbi.nlm.nih.gov/books/NBK519578/
[3] TCGA PanCancer Atlas (cBioPortal analysis)
[4] www.thelancet.com Vol 389 January 21, 2017
[5] Adapted from NCCN Non-small cell lung cancer guidelines Version 3.2020

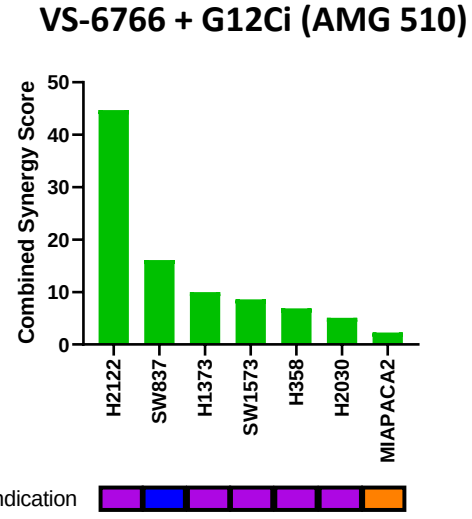
Vertical Blockade: Preclinical synergy of VS-6766 with inhibitors of several promising targets

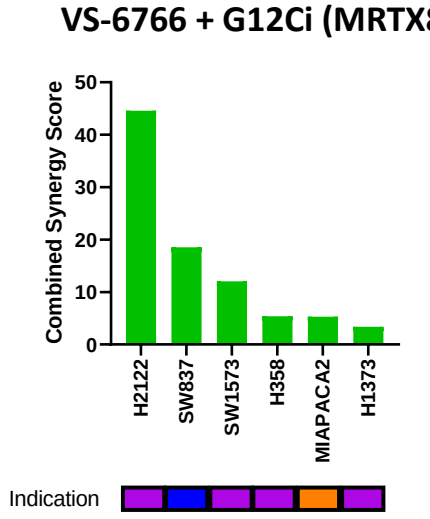


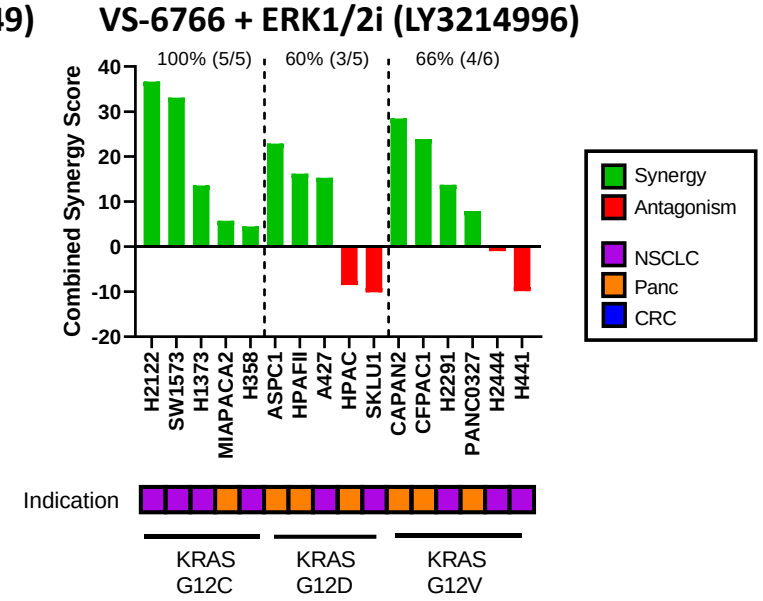












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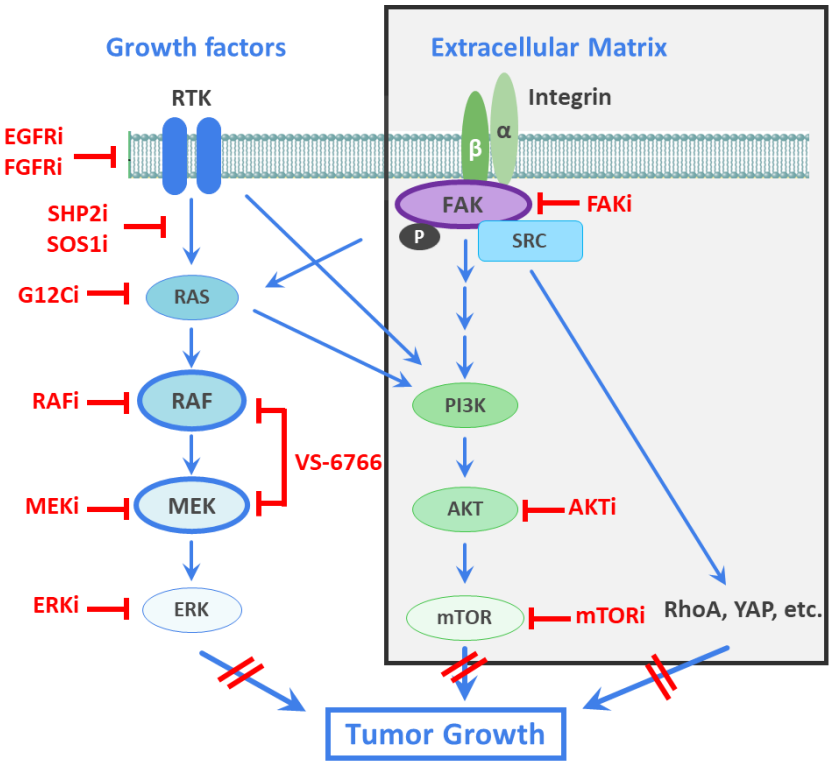
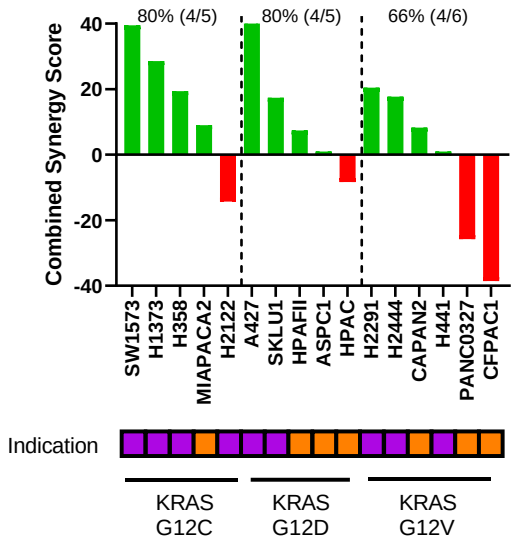
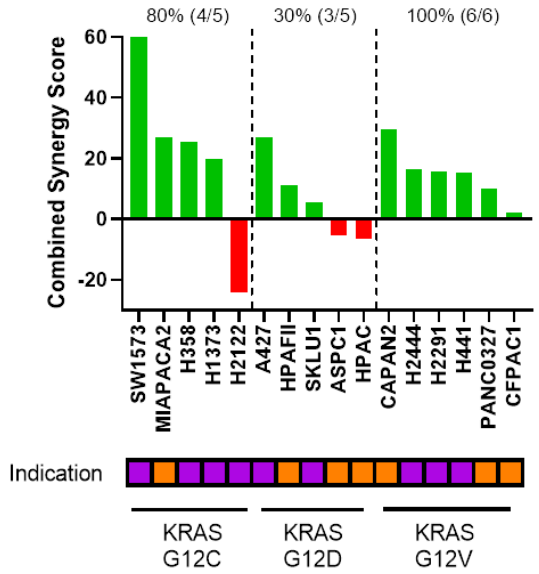
Parallel Pathway Blockade: Preclinical synergy of VS-6766 with inhibitors of several promising targets



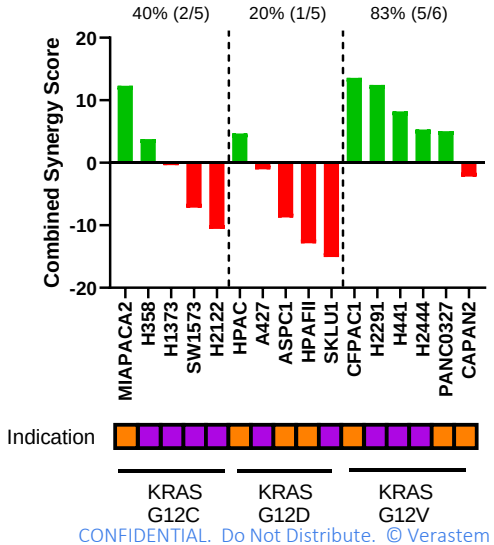
VS-6766 + p70S6K/AKTi (M2698)



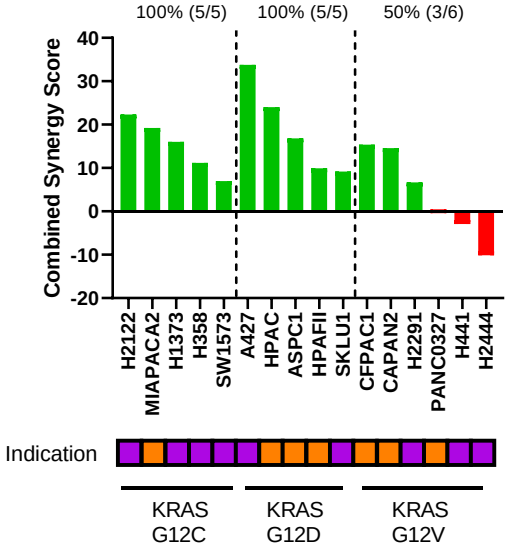
VS-6766 + mTORi (Everolimus)

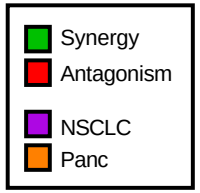


VS-6766 + FAKi (Defactinib)



VS-6766 + CDK4/6i (Palbociclib)





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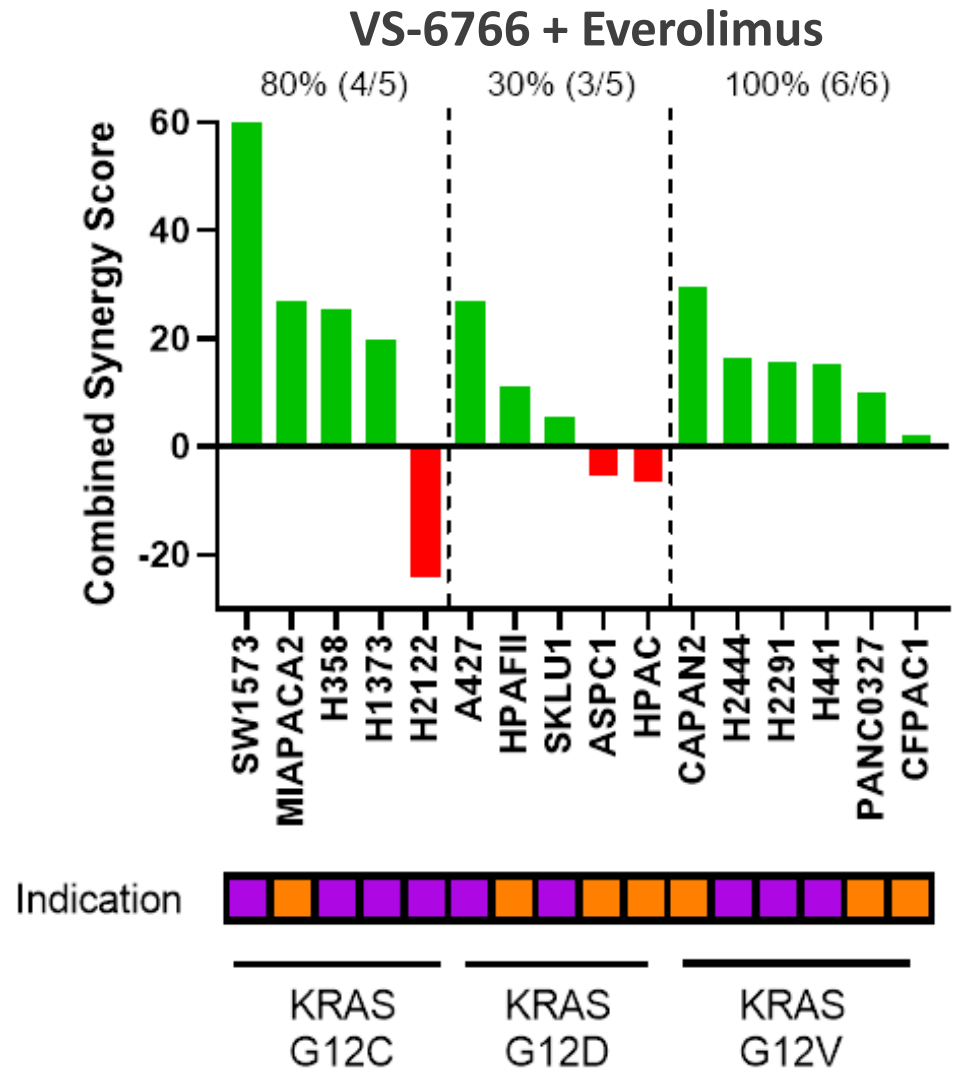
Combination of VS-6766 with Everolimus (mTOR inhibitor) now being evaluated in patients with KRAS mt NSCLC

- 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



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

- 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 main 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 in the UK testing a RP2D of VS-6766 + everolimus (mTOR inhibitor) in patients with KRAS mutant NSCLC
  - Other combinations with VS-6766 (e.g. with SOS1i; SHP2i) also supported by preclinical data

Acknowledgments

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Thanks for your attention!