Synergistic Combinations with the Dual RAF/MEK Inhibitor VS-6766 to Overcome Resistance Mechanisms

Jonathan Pachter, PhD, Chief Scientific Officer – Verastem Oncology

RAS-Targeted Drug Development, Sept 16, 2020

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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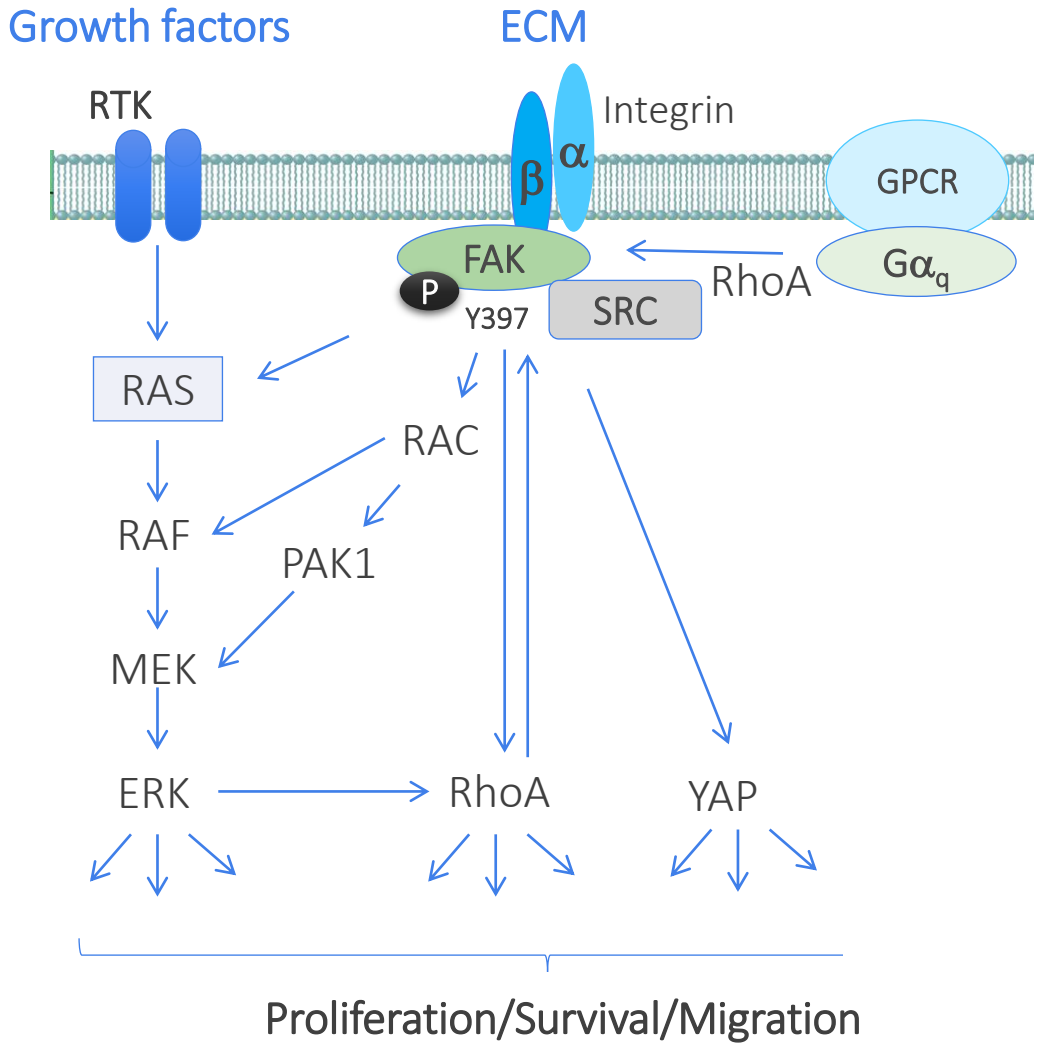
More Complete Shutdown of RAS Pathway-Driven Tumor Growth Requires Addressing Multiple Resistance Mechanisms



- BRAF & MEK inhibitors can block Growth Factor-stimulated ERK signaling, but Cell Attachment can also stimulate ERK signaling through a FAK-dependent pathway (Slack-Davis, JCB 162:281, 2003)
- GPCR-mediated activation of RhoA and YAP pathways through FAK (Feng, Cancer Cell, 2019) may also confer cancer cell proliferation and survival bypassing the ERK pathway
- Signaling through a RhoA-FAK axis is required for maintenance of KRAS-dependent lung adenocarcinomas (Konstantinou, Cancer Discovery 3:444, 2013)
- BRAF inhibition generates a drug-tolerant microenvironment for melanoma cells which can be abolished by FAK inhibition (Hirata, Cancer Cell 27:574, 2015)

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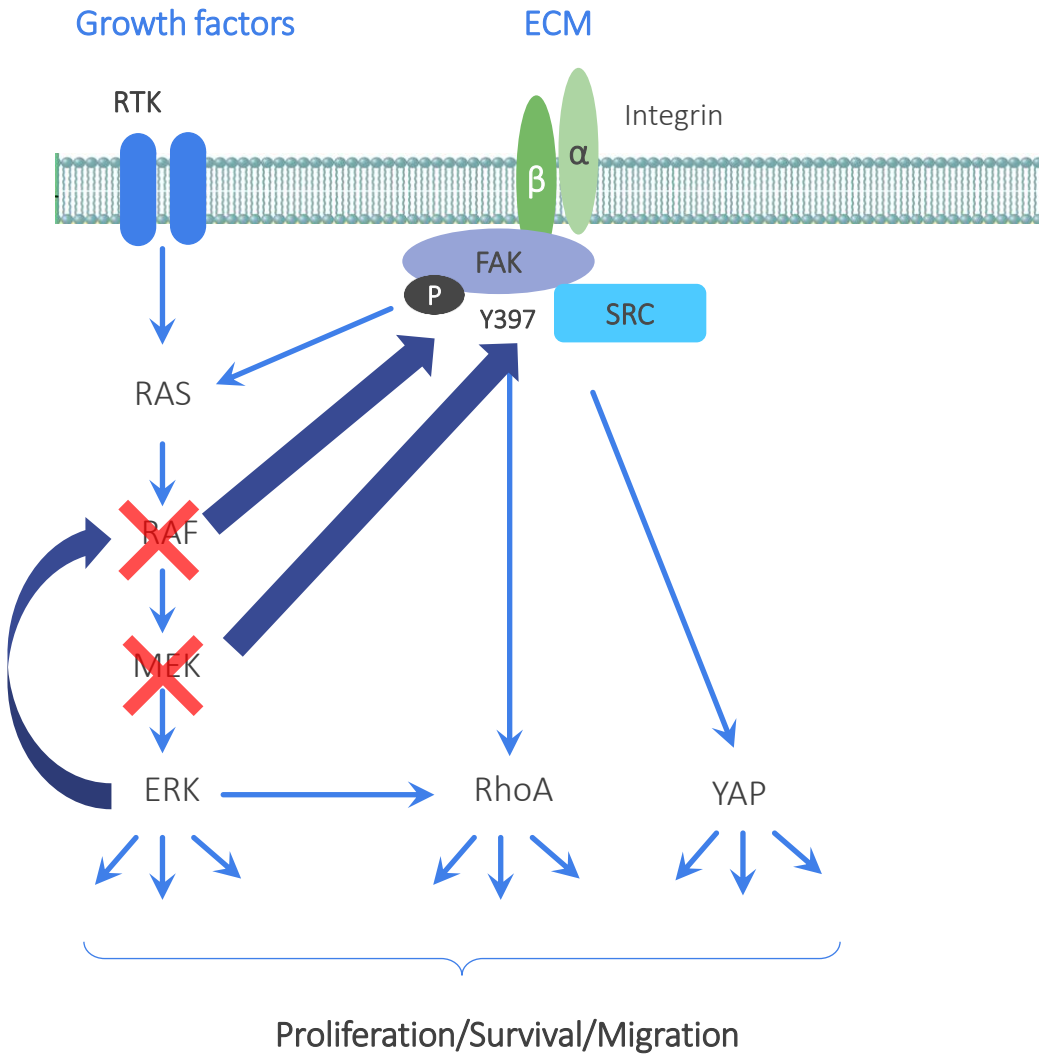
More Complete Shutdown of RAS Pathway-Driven Tumor Growth Requires Addressing Multiple Resistance Mechanisms



- 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, ERK 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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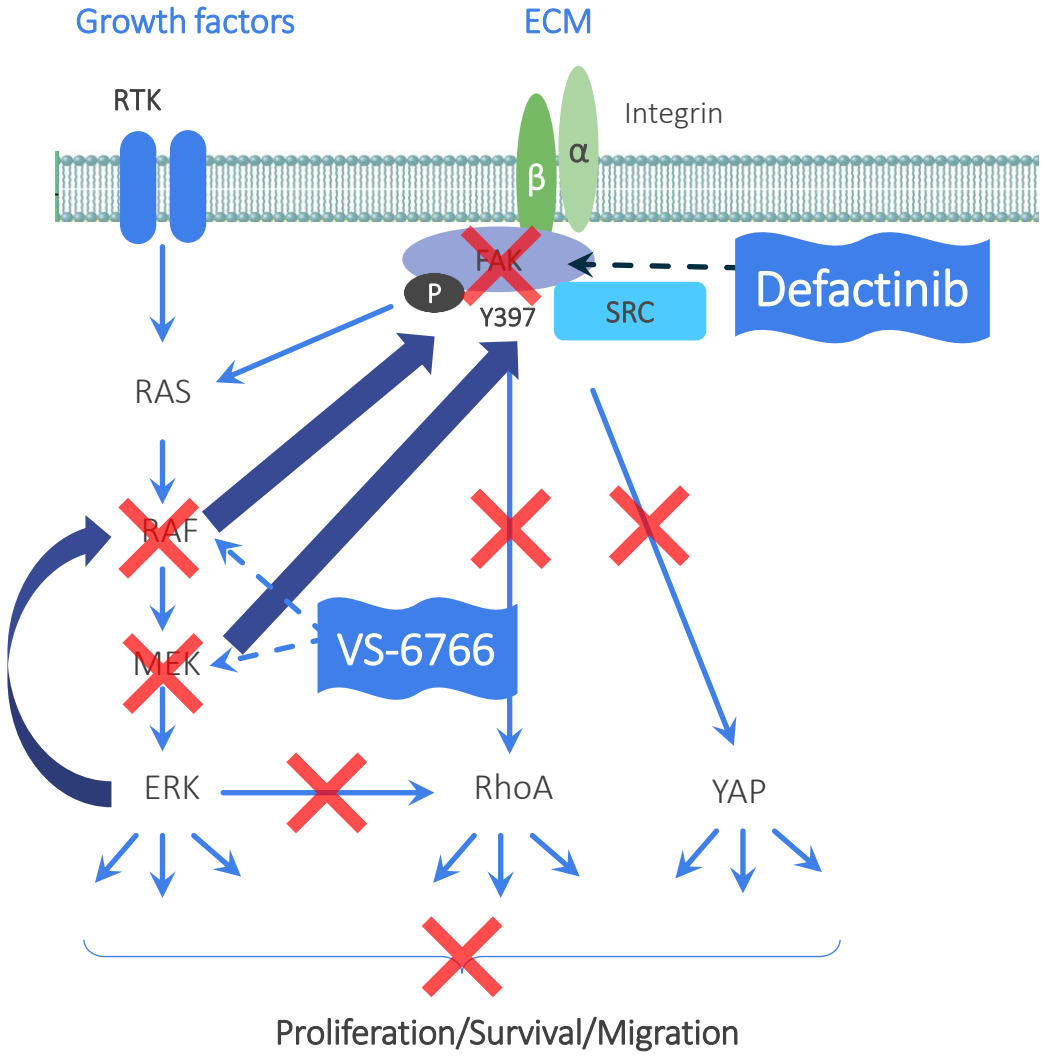
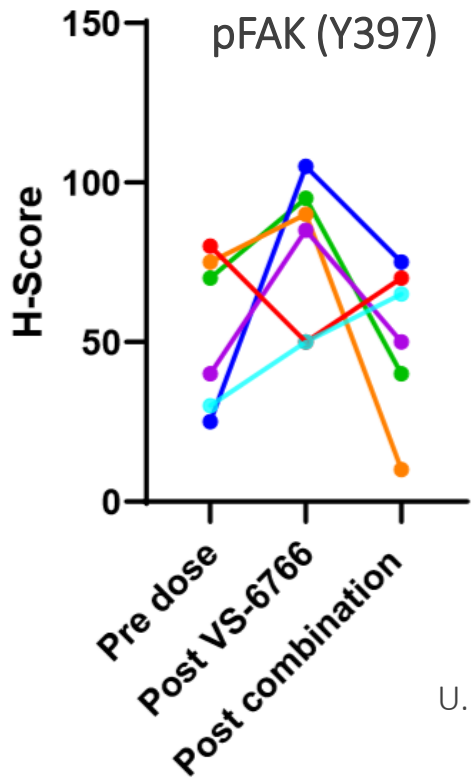
More Complete Shutdown of RAS Pathway-Driven Tumor Growth Requires Addressing Multiple Resistance Mechanisms



- In patients with KRAS mt tumors
  - VS-6766 induced ↑ pFAK (Y397) as a potential resistance mechanism in the majority of patients
  - Combination of VS-6766 with defactinib reduced this compensatory pFAK signal



U. Banerji, AACR 2020

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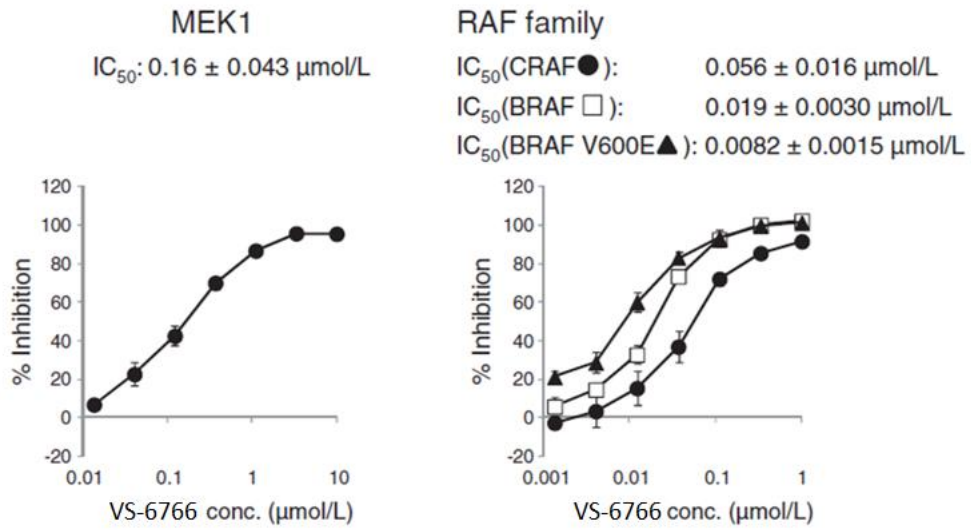
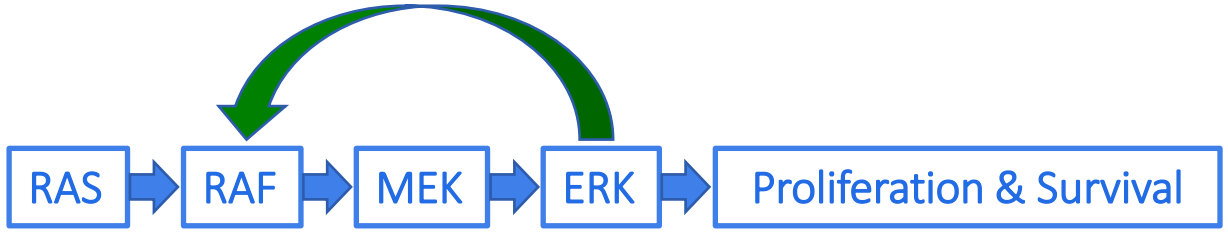
VS-6766 is a Unique Small Molecule RAF/MEK Dual Inhibitor

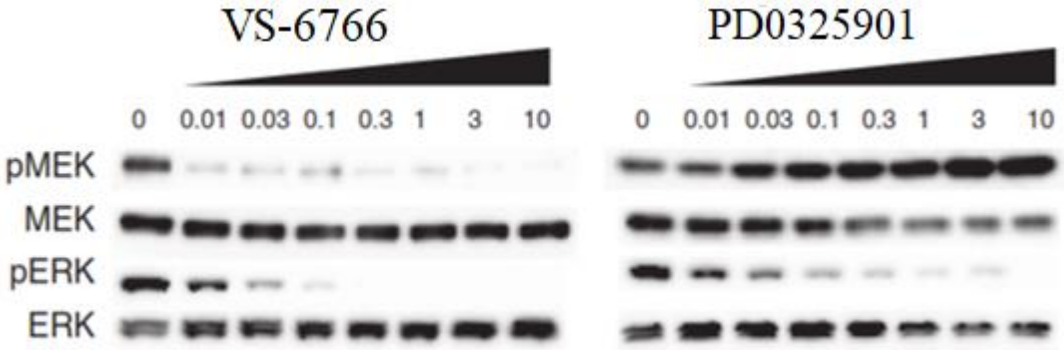
- VS-6766 inhibits both MEK & RAF kinase activities



- Most MEK inhibitors paradoxically induce MEK phosphorylation (pMEK) by relieving ERK-dependent feedback inhibition of RAF



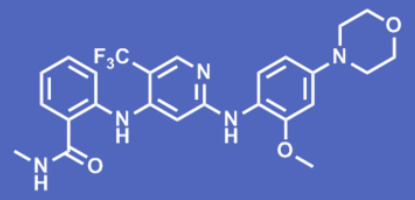
- By inhibiting RAF phosphorylation of MEK, VS-6766 has advantage of not inducing pMEK
- VS-6766 inhibits ERK signaling more completely; may confer enhanced therapeutic activity

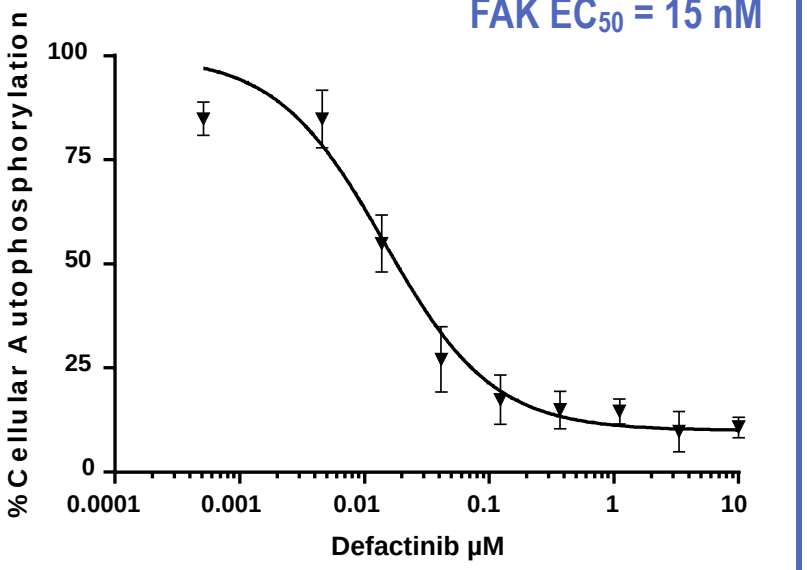


Reference:
Ishii et al., *Cancer Res*, 2013; Lito et al., Cancer Cell, 2014; Blasco, R. B. *et al. Cancer Cell* (2011); Sanclemente, M. *et al. Cancer Cell* (2018)

Defactinib (VS-6063) – Selective FAK Inhibitor

Defactinib

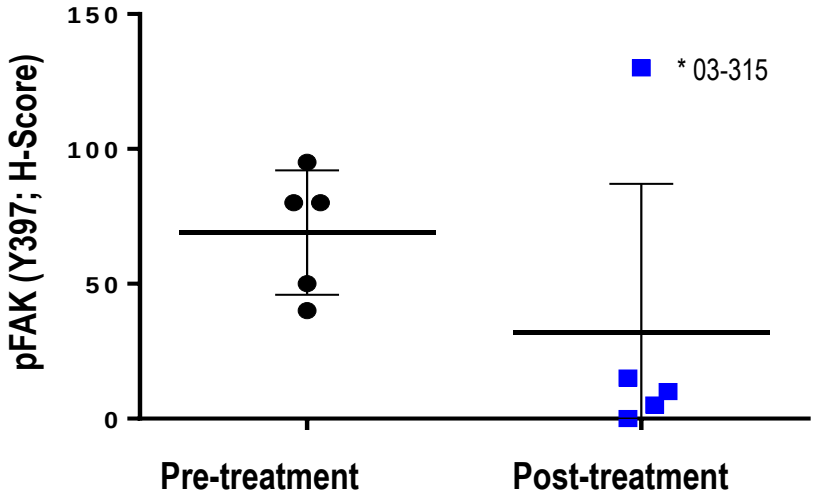




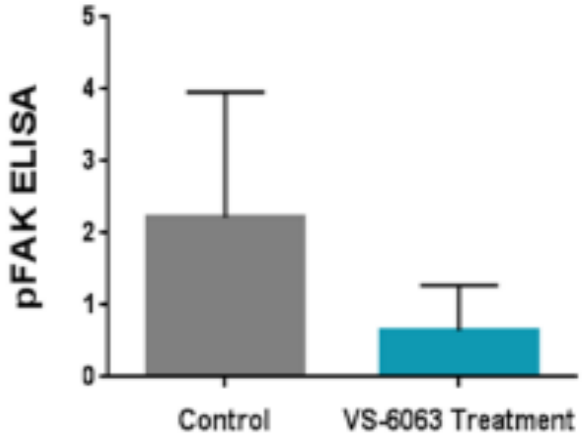
Dosage: Oral, 400mg BID

- Studied in 300+ patients with good safety profile observed to date
- DLT not reached
- Early signs of clinical efficacy
- Well established safety profile as a single agent and in combination:
  - MEK/RAF, PD-1, Chemotherapy

OVARIAN CANCER: TUMOR BIOPSIES



MESOTHELIOMA: TUMOR BIOPSIES



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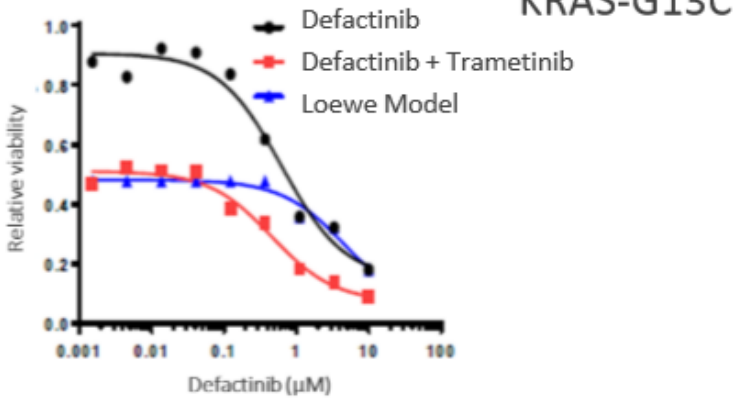
Combination of defactinib with VS-6766 or trametinib shows synergy in KRAS mt and BRAF mt cell lines

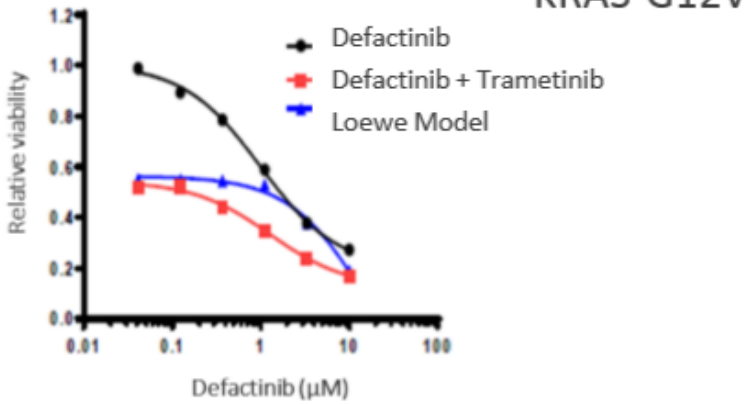
TOV-21G CELLS KRAS-MUTANT OVARIAN CANCER

KRAS-G13C

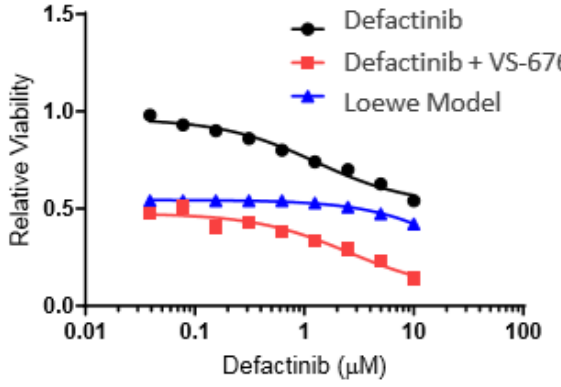


H441 CELLS KRAS-MUTANT NON-SMALL-CELL LUNG CANCER

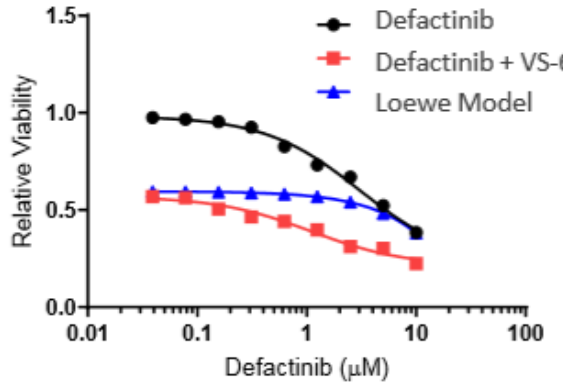
KRAS-G12V



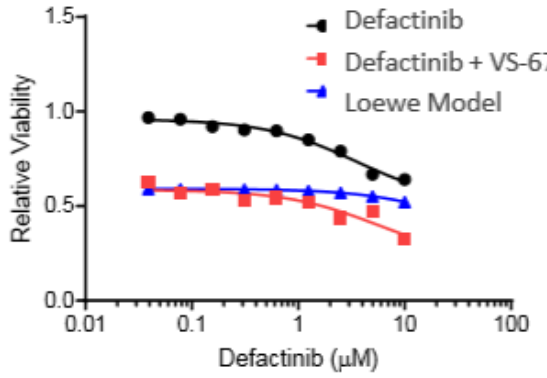
SW982 CELLS SARCOMA BRAF:pV600E



MERO-14 CELLS MESOTHELIOMA



CAL-51 CELLS TRIPLE NEGATIVE BREAST CANCER



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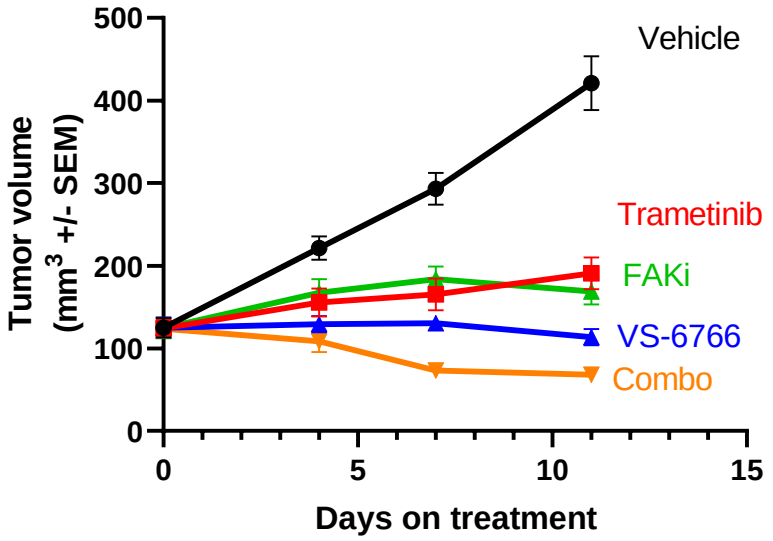
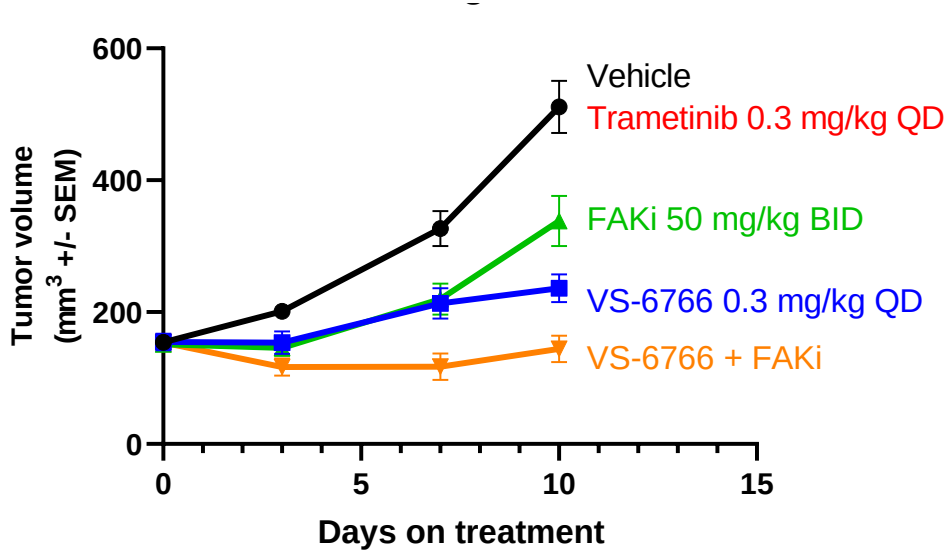
VS-6766 and FAK inhibitor combination leads to more robust anti-tumor efficacy *in vivo*

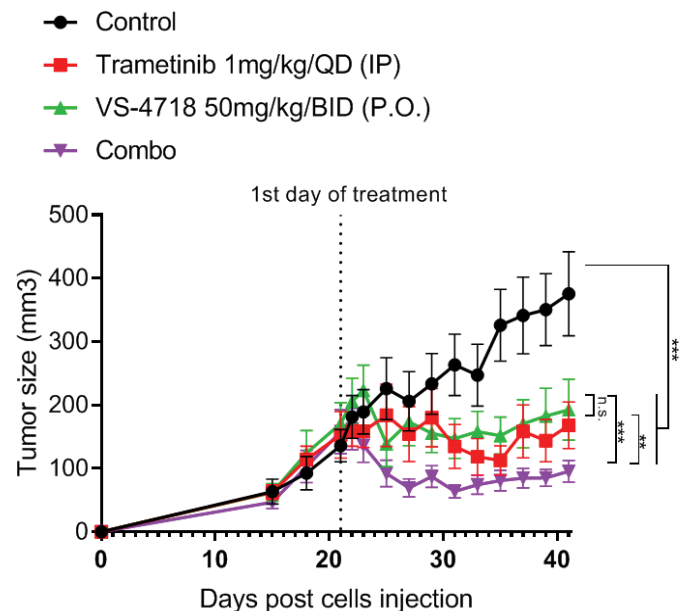
Ovarian cancer model
(TOV-21g KRAS(G13C) mutant)



NSCLC cancer model
(H2122 KRAS(G12C) mutant)



Uveal melanoma model
(92.1 GNAQ mutant)



Updated label x-axis

J. Paradis, AACR 2020

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VS-6766 and FAK inhibitor combination leads to more robust anti-tumor efficacy *in vivo*

Ovarian cancer model
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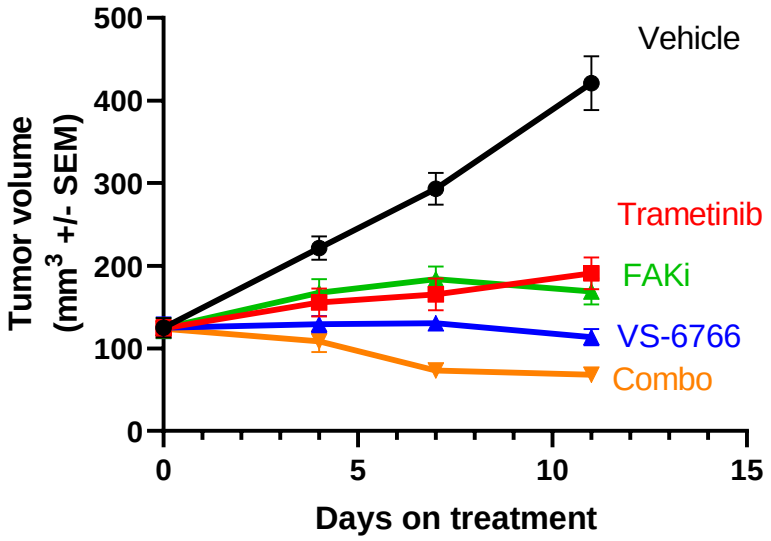

NSCLC cancer model
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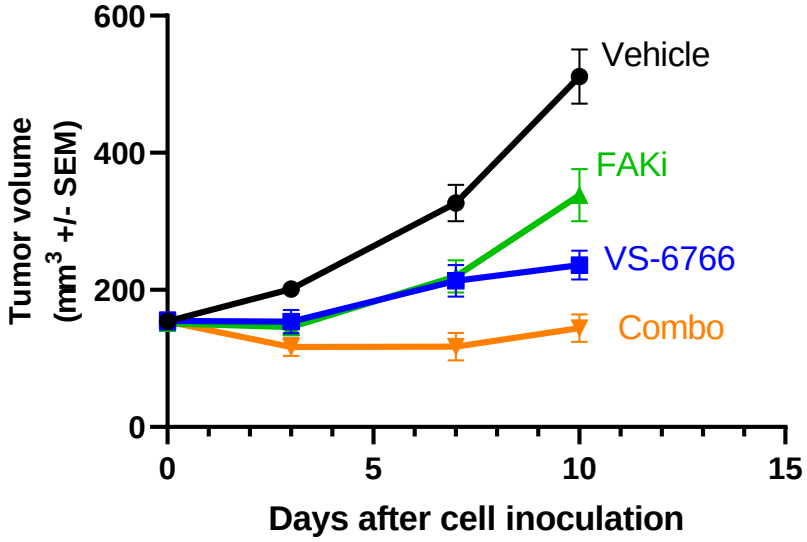

Uveal melanoma model
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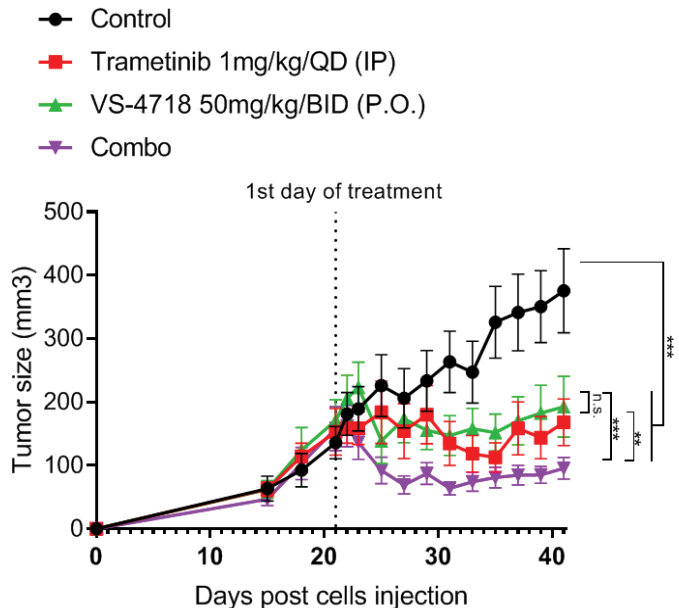

J. Paradis, AACR 2020

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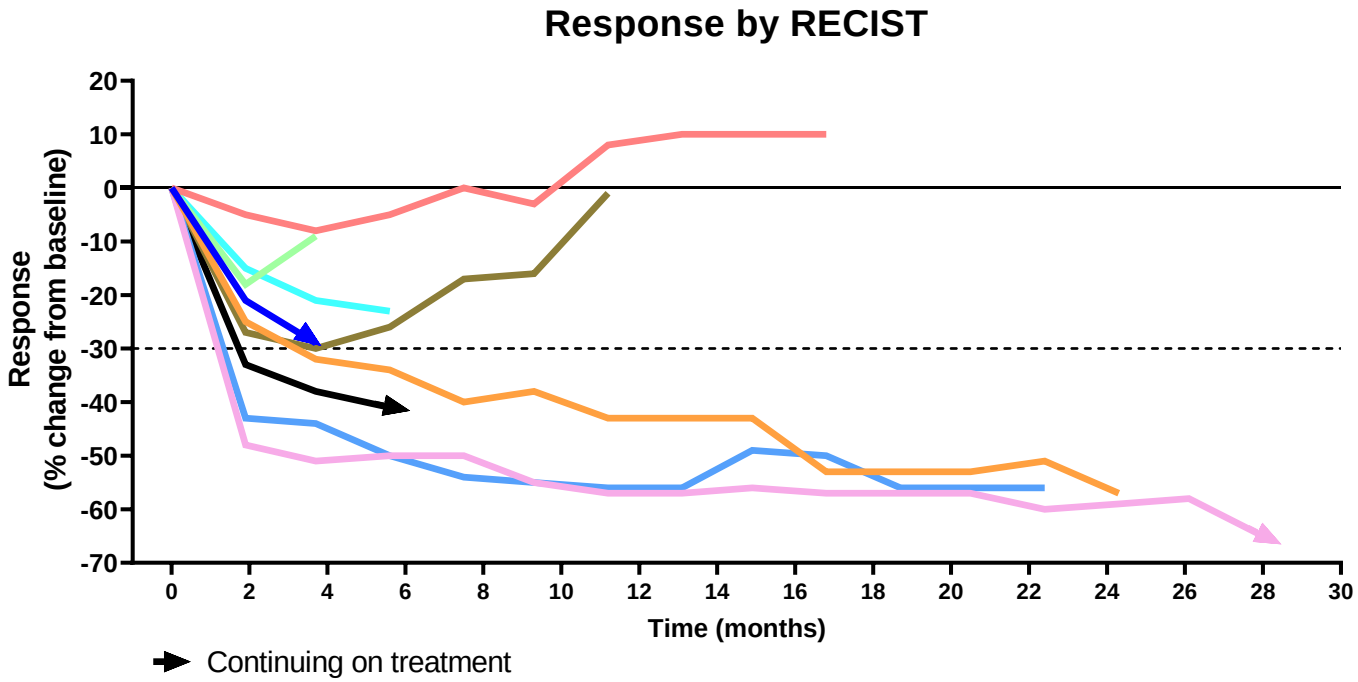
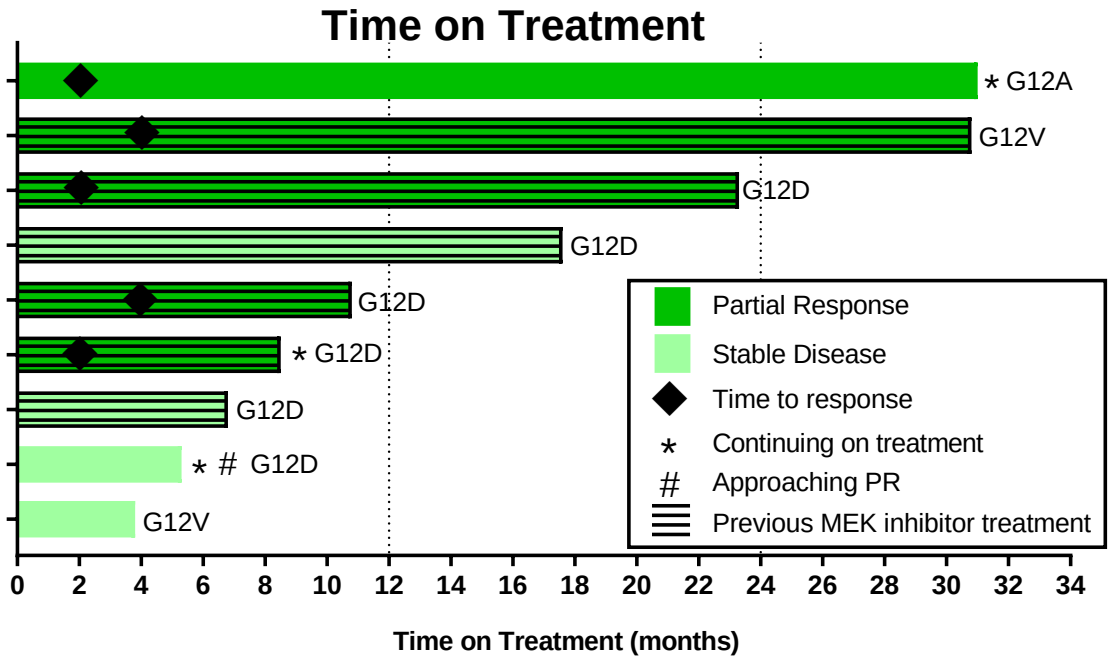
VS-6766 in Combination with Defactinib Shows Robust ORR with Durability in Patients with Refractory KRAS Mutant Low Grade Serous Ovarian Cancer





Udai Banerji, RAS-Targeted Drug Development, 2020
9/16/20, 3:35 pm ET

- 9 pts with KRAS-G12 mutations
- ORR = 56% (5/9); data still maturing
- 4/5 PRs in pts who had previous MEKi
- 2 pts on treatment for 2.5 yrs

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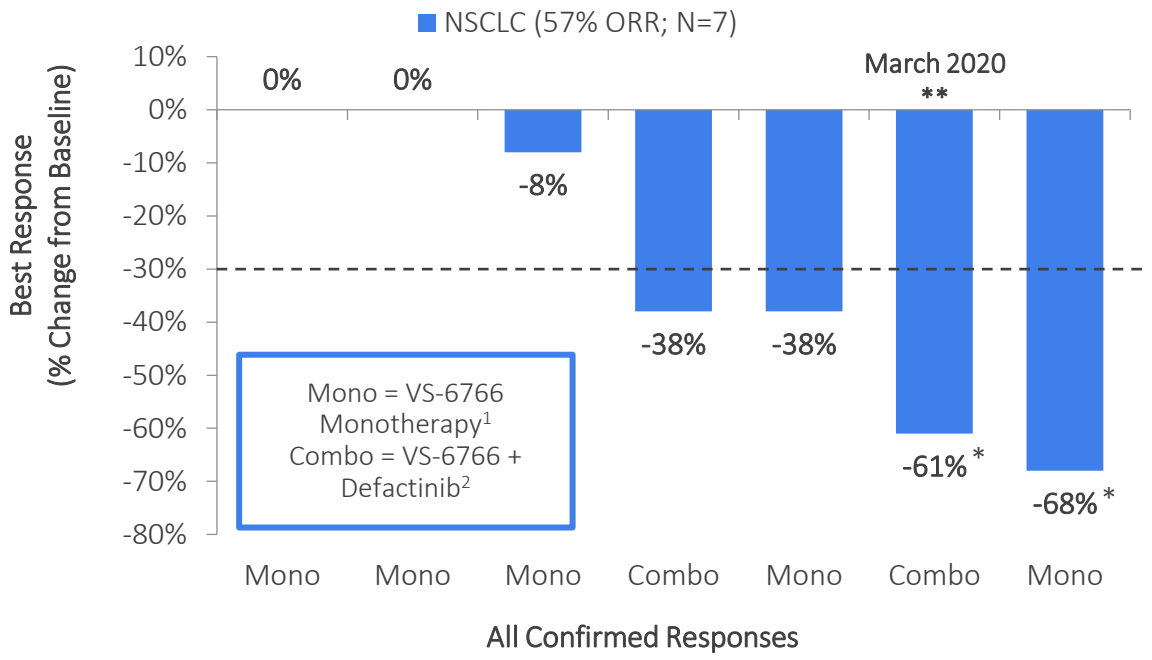
Cut-off August 17, 2020

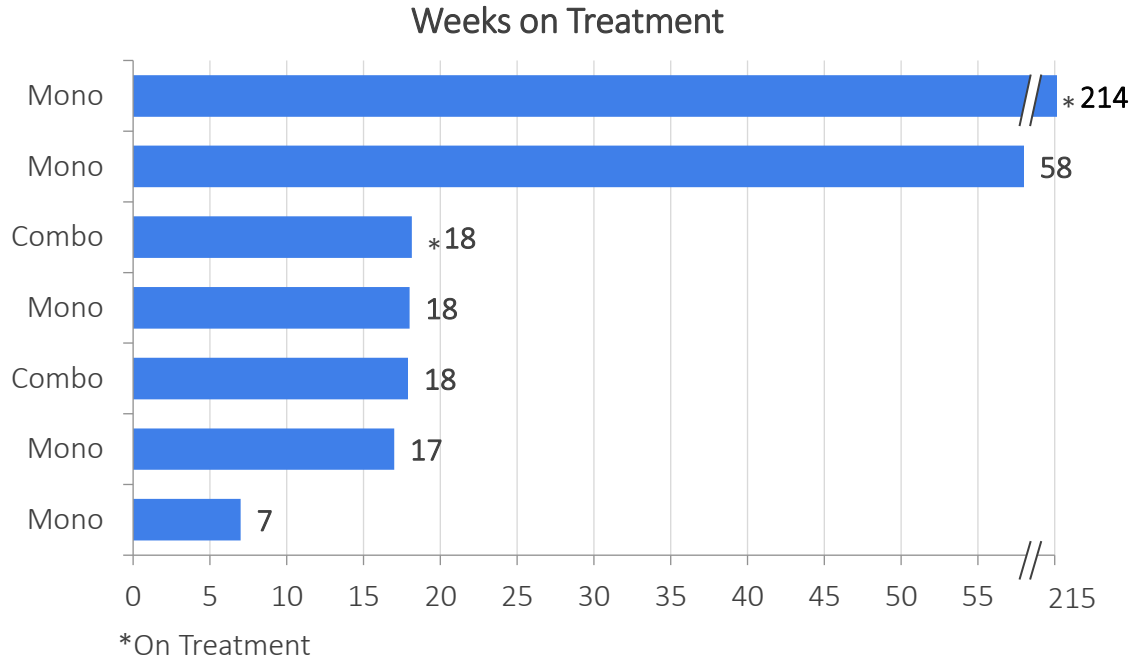
Strong Signal Identified in KRAS^{G12V} NSCLC to Be Further Validated

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



- Preclinical evidence suggests combination with Defactinib may improve efficacy in KRAS^{G12V}
- Activity of VS-6766 as a single agent and in combo with Defactinib in KRAS^{G12V}
- 1 additional confirmed PR in KRAS^{G12V} mutant patient as of Mar-2020

Source: [1] Martinez-Garcia, M. et al. *Clin. Cancer Res*. (2012); [2] Banerji, AACR VM 1, April 27, 2020, CT143

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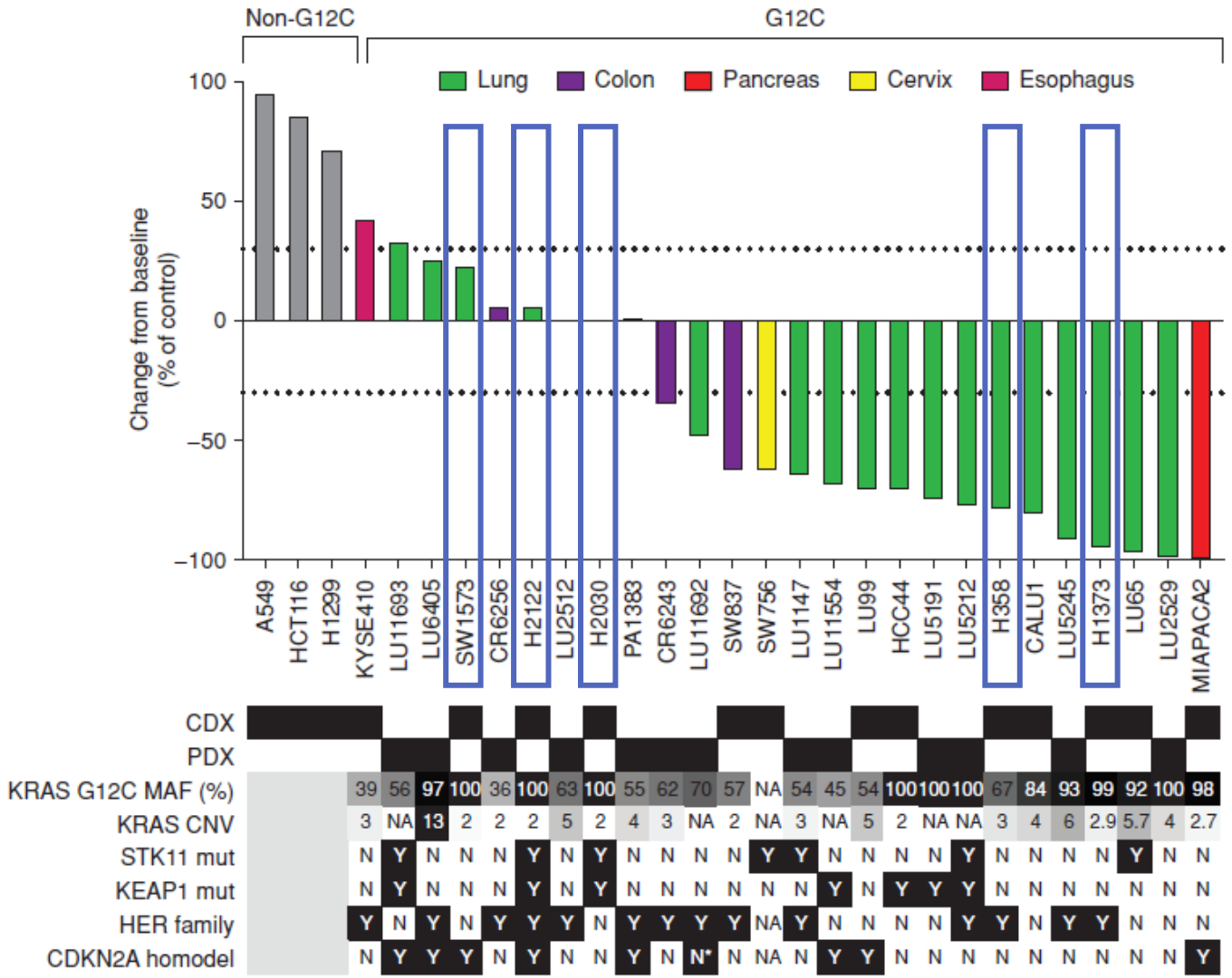
KRAS-G12C mutant tumor models differ in their sensitivity to G12C inhibitors



MRTX849
100 mg/kg QD

Hallin et al., Cancer Discovery 2020

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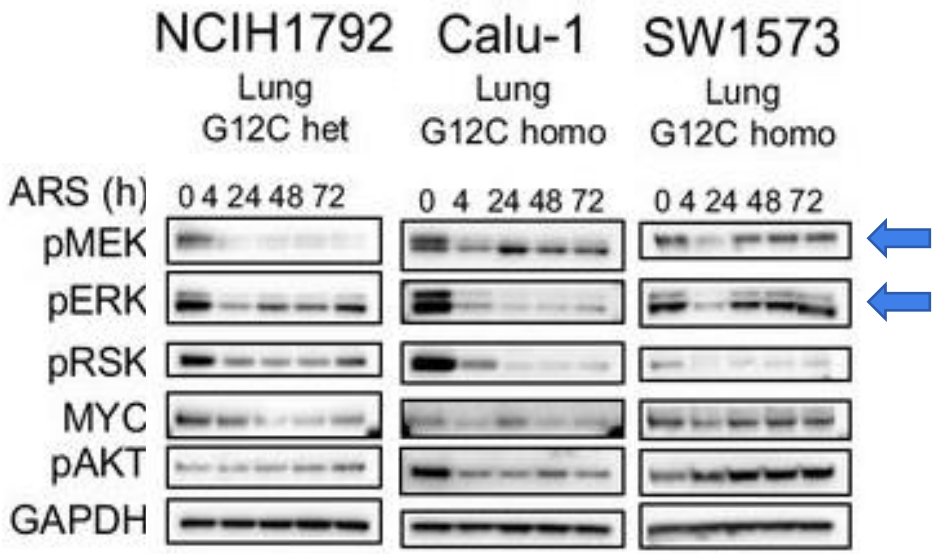
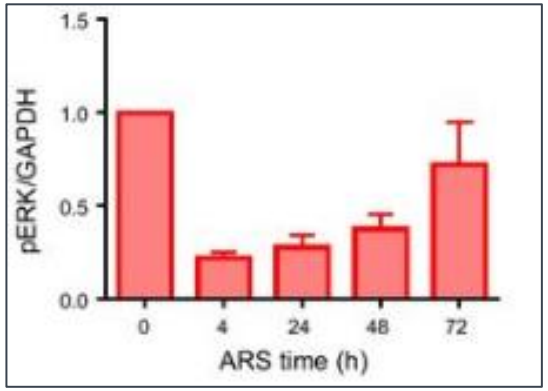
G12C inhibitors do not maintain sustained inhibition of pMEK & pERK

ARS-1620 at 1 µM





Densitometry of p-ERK normalized to GAPDH for blots; results represent an **average of pERK across 8 cell lines**

Source: Ryan, M. B. *et al. Clin. Cancer Res.* (2020)

- Sustained inhibition of pMEK & pERK may be essential for durable response in KRAS-G12C mutant NSCLC & colorectal cancer
- KRAS-G12C inhibitors as monotherapy transiently inhibit pMEK & pERK *in vitro*

- VS-6766 yields more complete blockade of pMEK & pERK than other MEKi in preclinical models
- Tested hypothesis that VS-6766 combination with G12C inhibitors should yield deeper & durable inhibition of ERK pathway signaling with corresponding synergy in KRAS-G12C tumor cell lines

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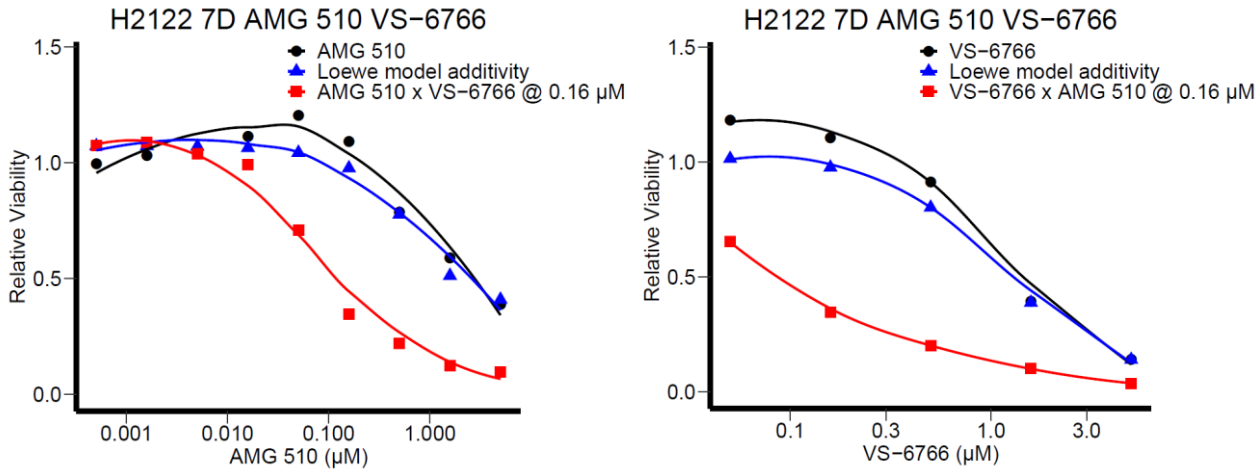
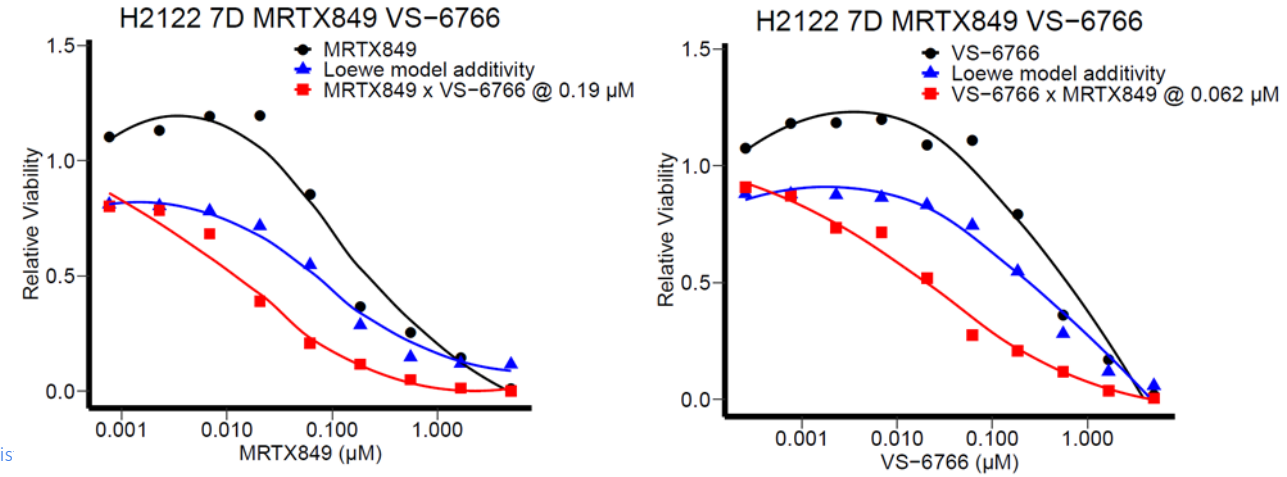
G12C inhibition is synergistic with VS-6766 in KRAS G12C mutant NSCLC & CRC cell lines

Cell line	Indication	Sensitivity to G12C inhibitors	Synergy Score (Loewe model)	
			VS-6766 + AMG 510	VS-6766 + MRTX849
H2122	NSCLC	Moderately sensitive	43.9	46.9
H358	NSCLC	Sensitive	14.5	11.9
H2030	NSCLC	Moderately sensitive	12.1	ND
H1373	NSCLC	Sensitive	9.3	9.6
SW1573	NSCLC	Insensitive	5	ND
SW837	CRC	Sensitive	14.9	ND
SW1463	CRC	Moderately sensitive	11.5	ND

H2122: AMG 510 + VS-6766 (RAF/MEKi)



H2122: MRTX849 + VS-6766 (RAF/MEKi)



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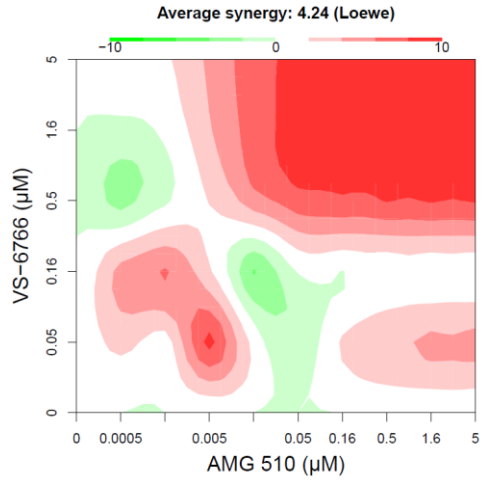
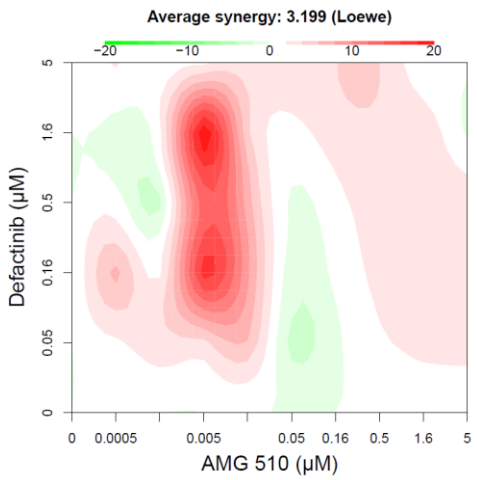
G12C inhibition is synergistic with VS-6766 & defactinib in KRAS G12C mutant NSCLC & CRC cell lines

H358 (KRAS G12C NSCLC)

AMG 510 + VS-6766

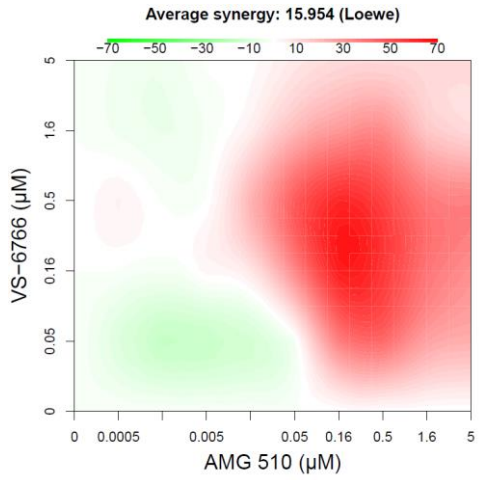


AMG 510 + Defactinib

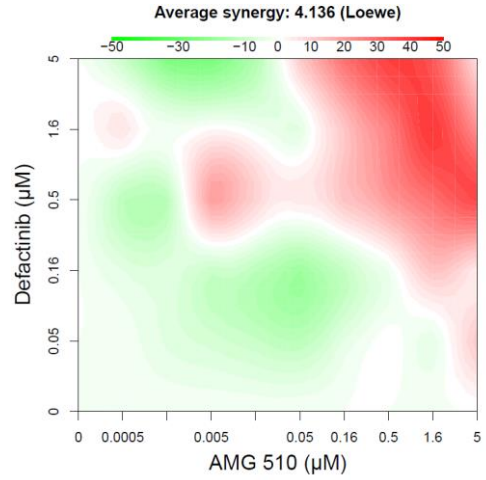


H2122 (KRAS G12C NSCLC)

AMG 510 + VS-6766

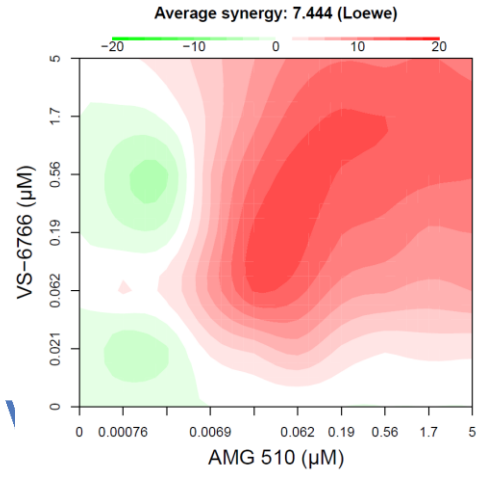


AMG 510 + Defactinib

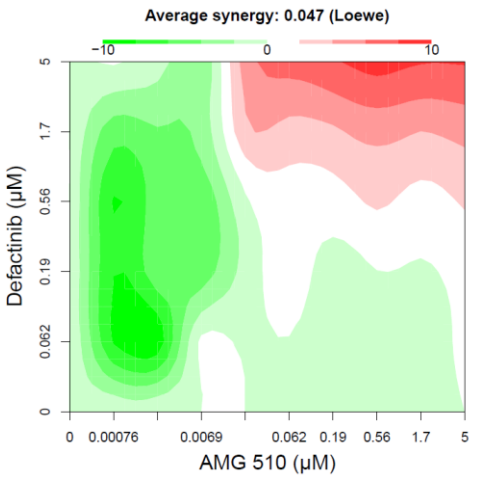


SW837 (KRAS G12C CRC)

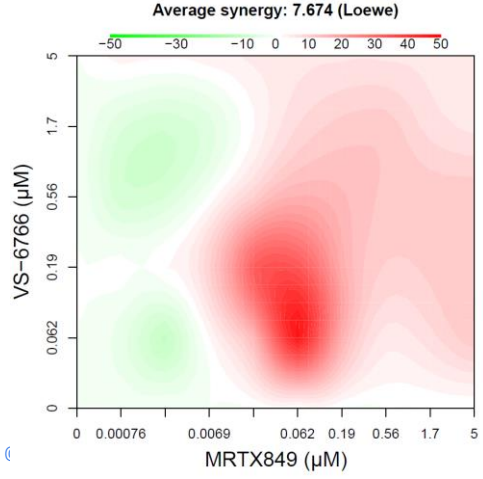
AMG 510 + VS-6766



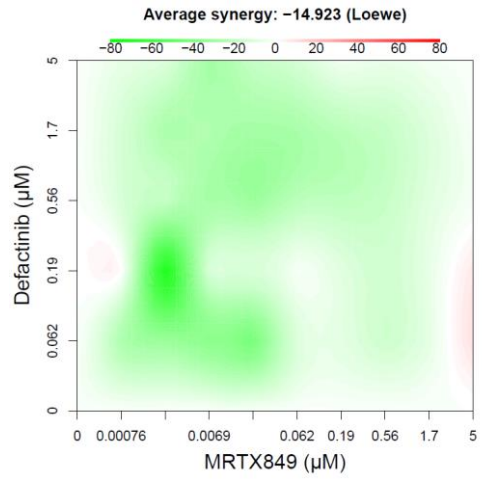
AMG 510 + Defactinib



MRTX849+ VS-6766

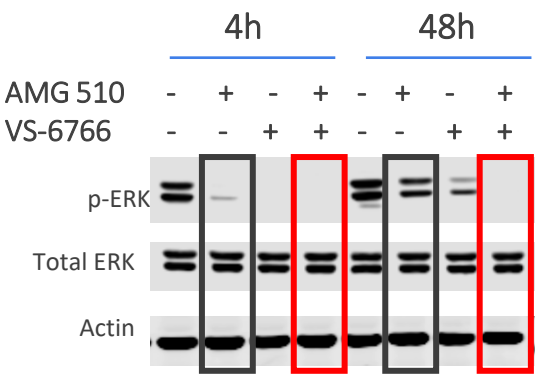


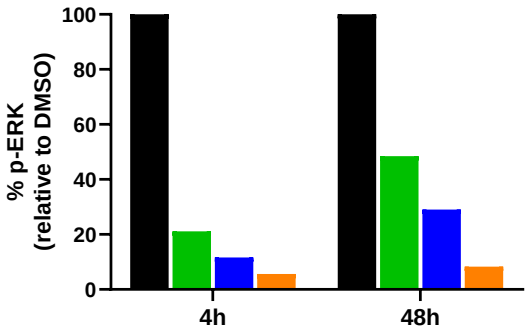
MRTX849 + Defactinib



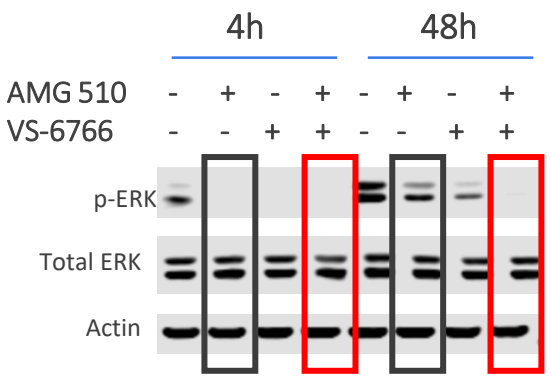
Addition of VS-6766 to AMG 510 increases depth & duration of inhibition of p-ERK relative to AMG 510 across a panel of KRAS-G12C mt NSCLC cell lines

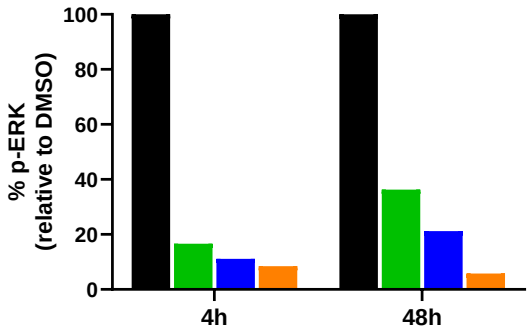
H358
Sensitive



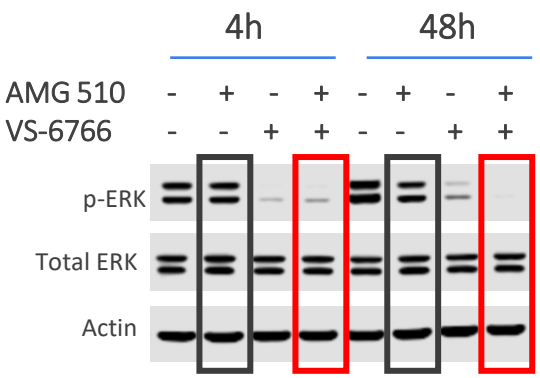


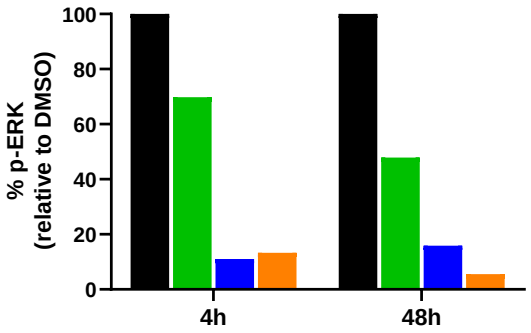
H1373
Sensitive



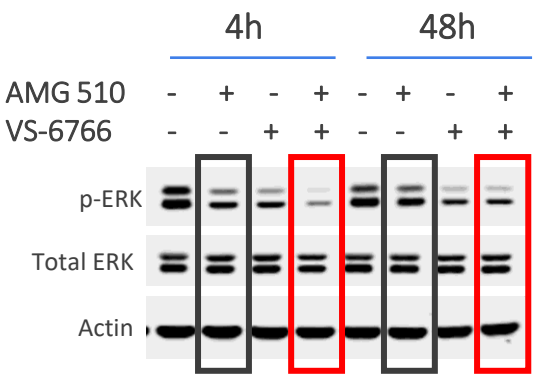


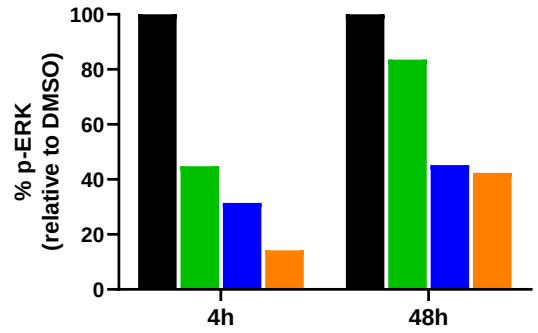
H2122
Moderately sensitive

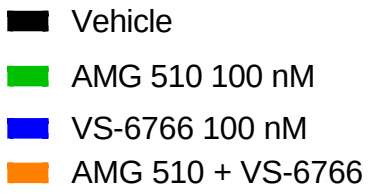




SW1573
Insensitive

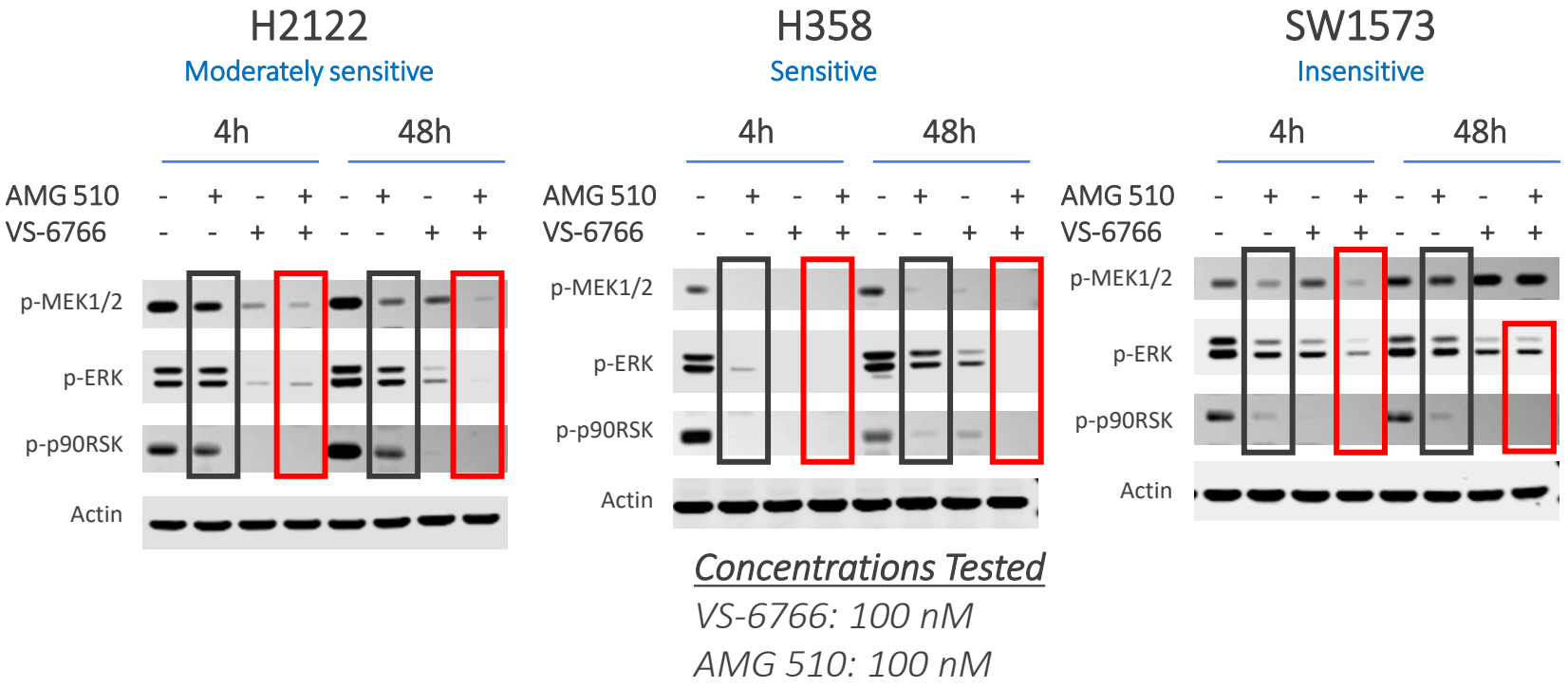






Verastem Oncology

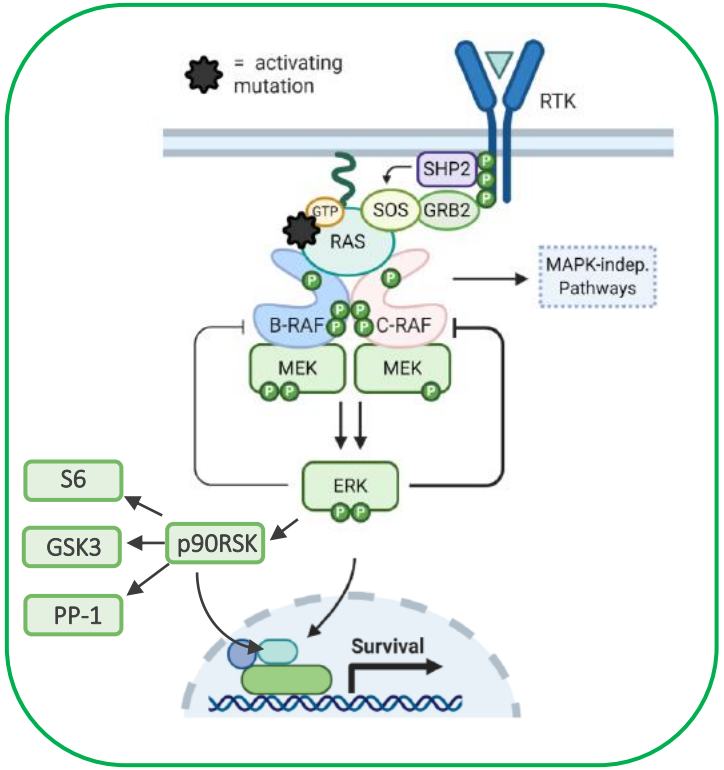
Addition of VS-6766 to AMG 510 increases depth & duration of inhibition of MEK/ERK signaling relative to AMG 510 across a panel of KRAS-G12C mt NSCLC cell lines



Concentrations Tested

VS-6766: 100 nM

AMG 510: 100 nM



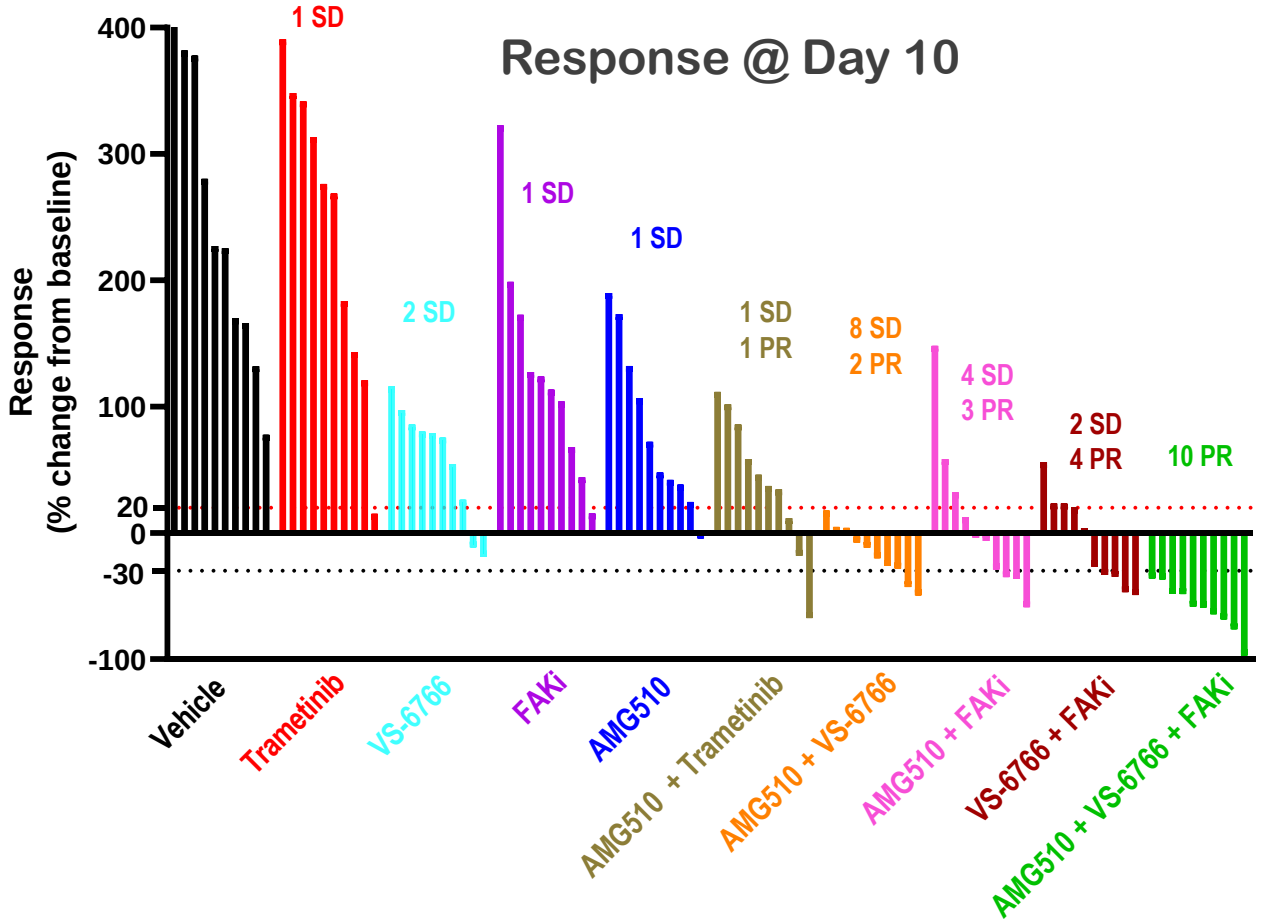
- In G12C cell lines sensitive to AMG 510 (e.g. H358), addition of VS-6766 to AMG 510 increases duration of inhibition of the MEK/ERK/RSK pathway
- In G12C cell lines less sensitive to AMG 510 (e.g. H2122), addition of VS-6766 to AMG 510 increases inhibition of the MEK/ERK/RSK pathway at both early and late time points

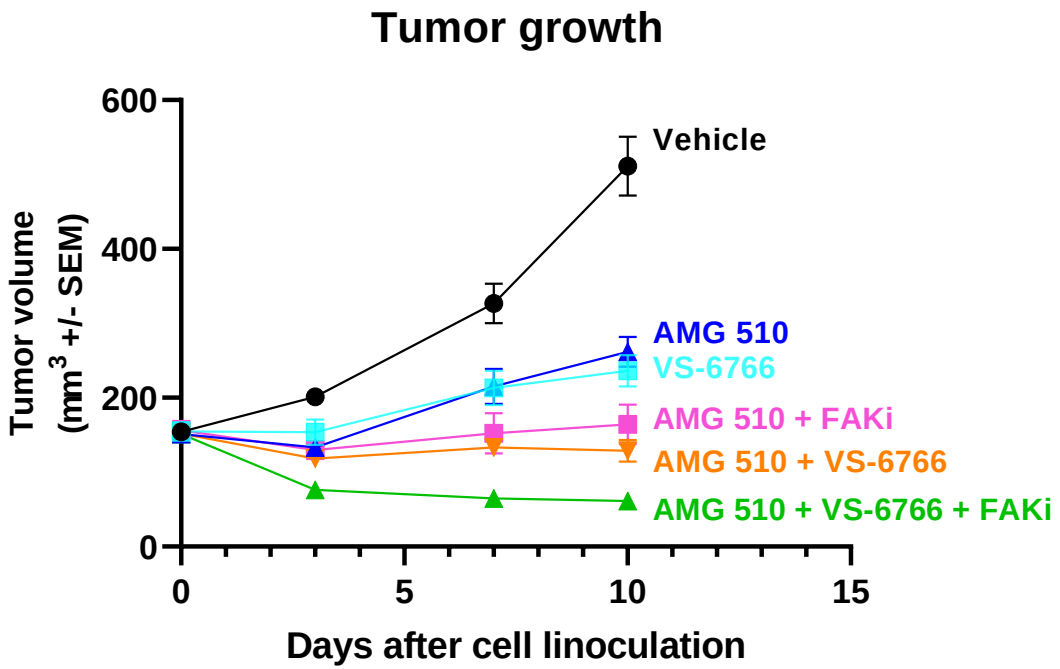
Verastem Oncology

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 mutant NSCLC





- VS-6766 is more effective than trametinib at equal dose
- VS-6766 or FAKi each potentiate the efficacy of AMG 510
- Triple combination of AMG 510 + VS-6766 + FAKi yields tumor regression in all mice

Doses Tested

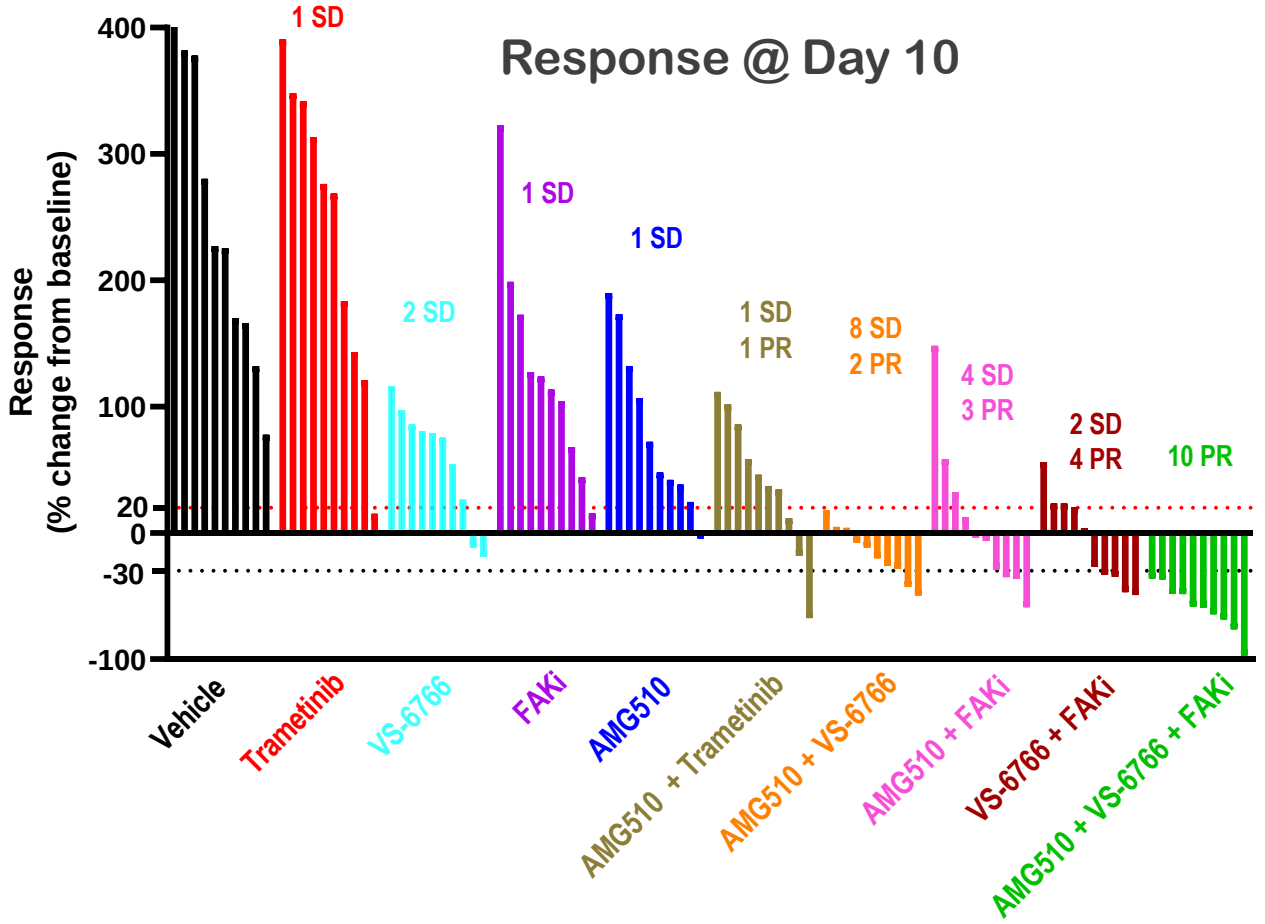
Trametinib: 0.3 mg/kg QD
VS-6766: 0.3 mg/kg QD
FAKi: 50 mg/kg BID
AMG 510: 30 mg/kg QD

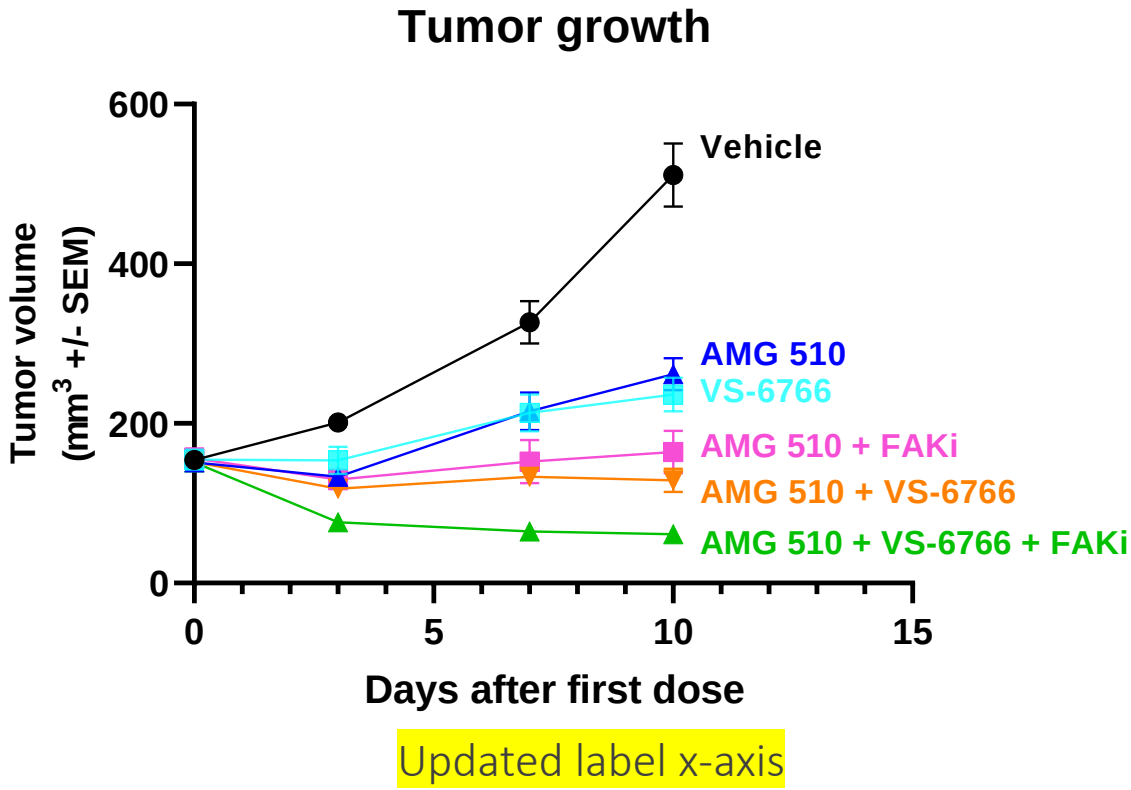
Verastem Oncology

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 mutant NSCLC





Updated label x-axis

- VS-6766 is more effective than trametinib at equal dose
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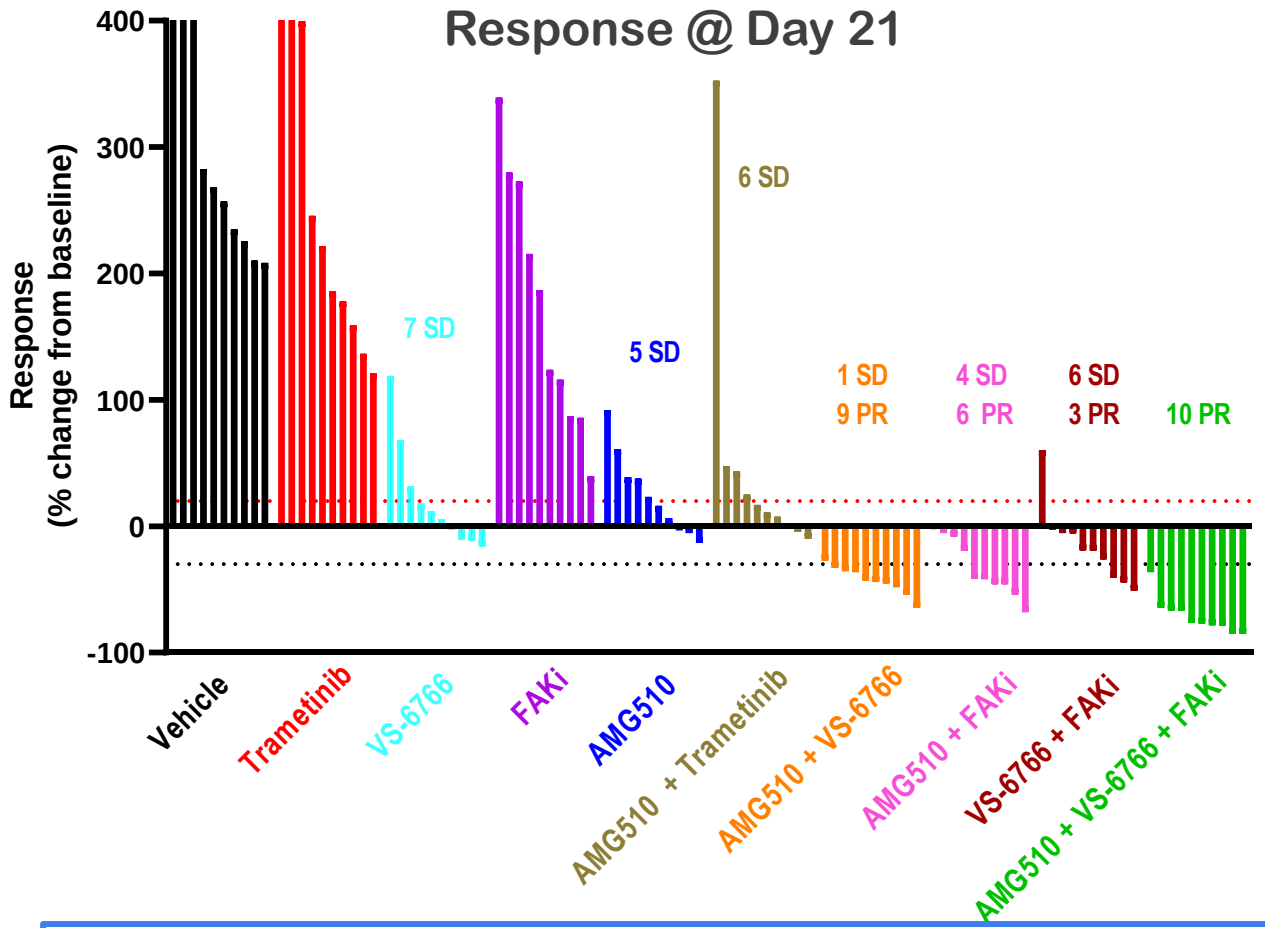
AMG 510: 30 mg/kg QD

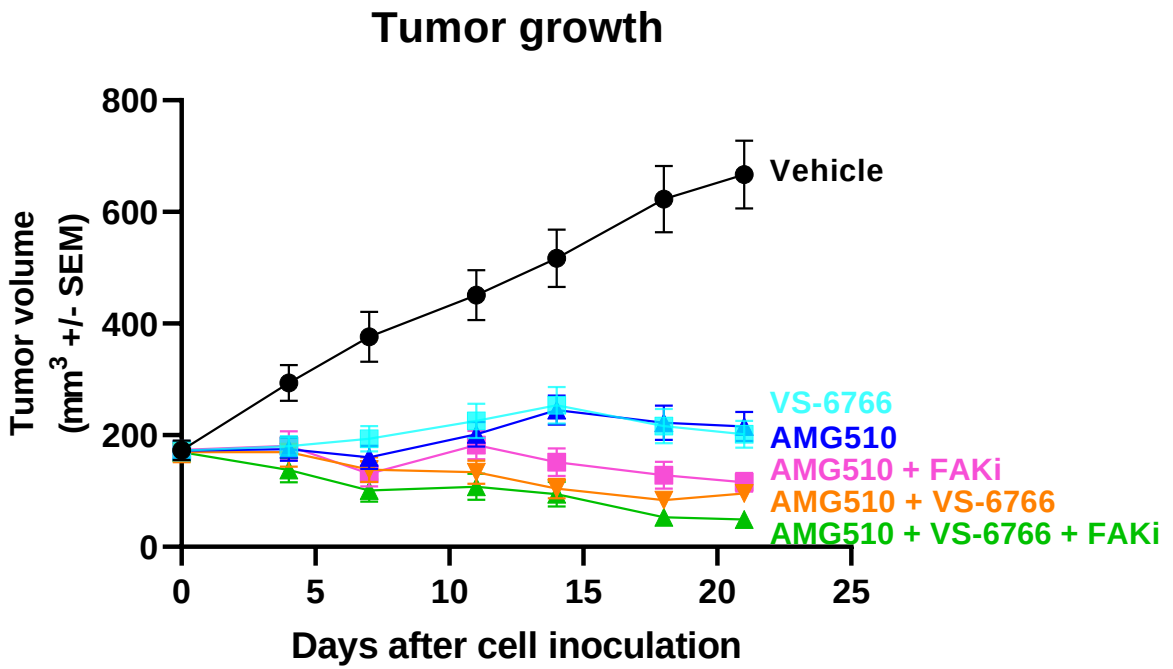
Verastem Oncology

VS-6766 & FAKi potentiate AMG 510 efficacy in KRAS G12C mutant NSCLC in vivo

Tumor regression in all mice with triple combination

H358 KRAS G12C mutant NSCLC





- VS-6766 is more effective than trametinib at equal dose
- VS-6766 or FAKi each potentiate the efficacy of AMG 510
- Triple combination of AMG 510 + VS-6766 + FAKi yields tumor regression in all mice

Doses Tested

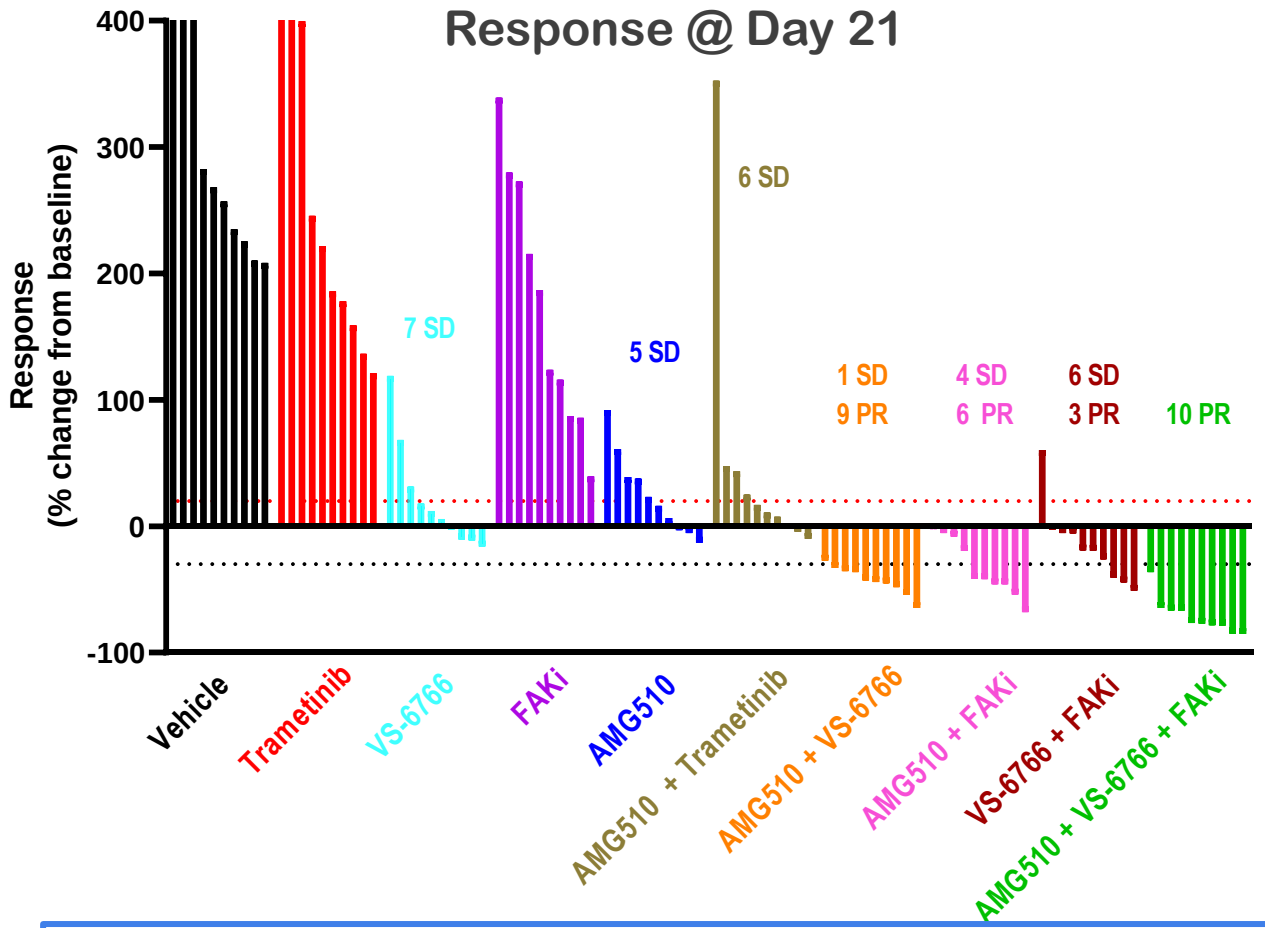
Trametinib: 0.3 mg/kg QD
VS-6766: 0.3 mg/kg QD
FAKi: 50 mg/kg BID
AMG 510: 10 mg/kg QD

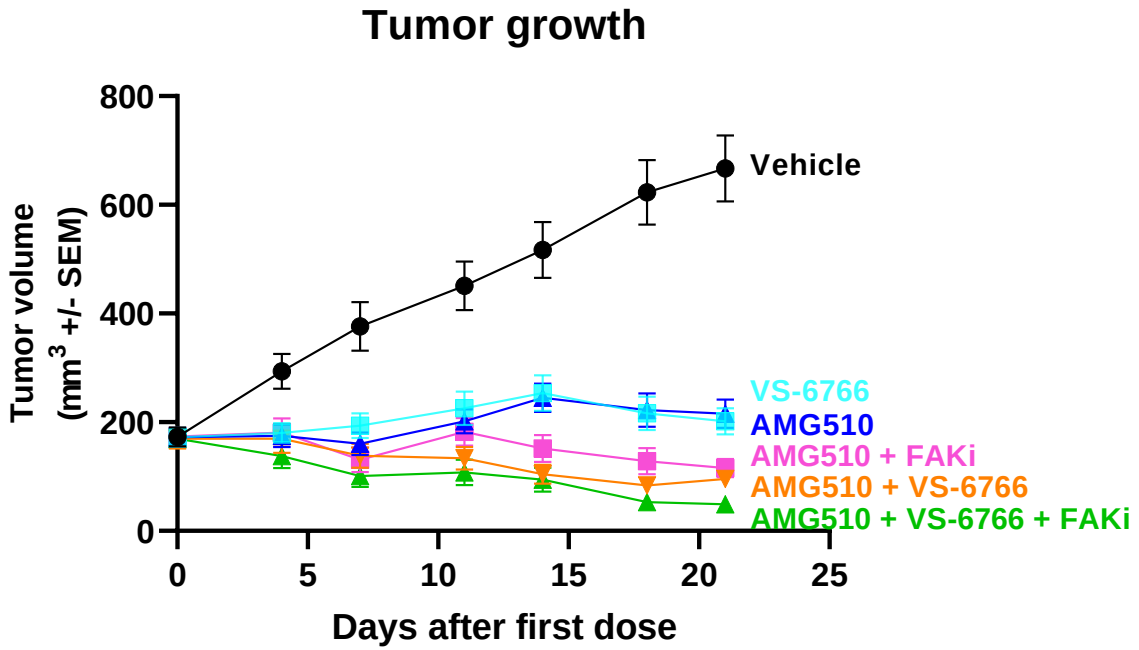
Verastem Oncology

VS-6766 & FAKi potentiate AMG 510 efficacy in KRAS G12C mutant NSCLC in vivo

Tumor regression in all mice with triple combination

H358 KRAS G12C mutant NSCLC





Updated label x-axis

- VS-6766 is more effective than trametinib at equal dose
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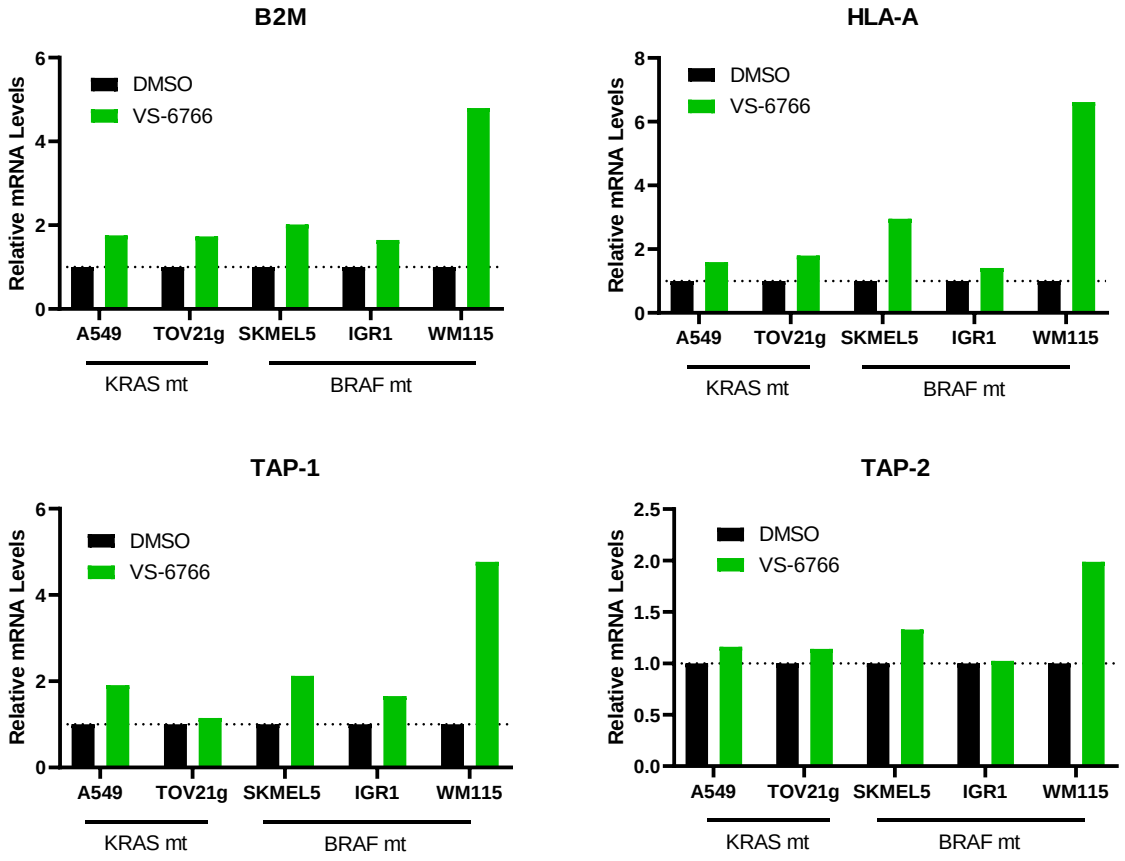
Doses Tested

Trametinib: 0.3 mg/kg QD
VS-6766: 0.3 mg/kg QD
FAKi: 50 mg/kg BID
AMG 510: 10 mg/kg QD

Verastem Oncology

Role of VS-6766 in Immuno-Oncology: VS-6766 upregulates antigen presentation machinery (MHC-I) including β2 microglobulin

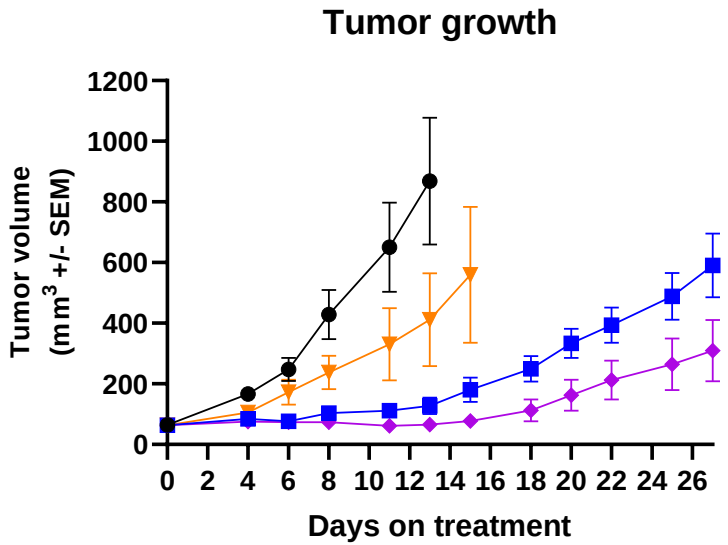


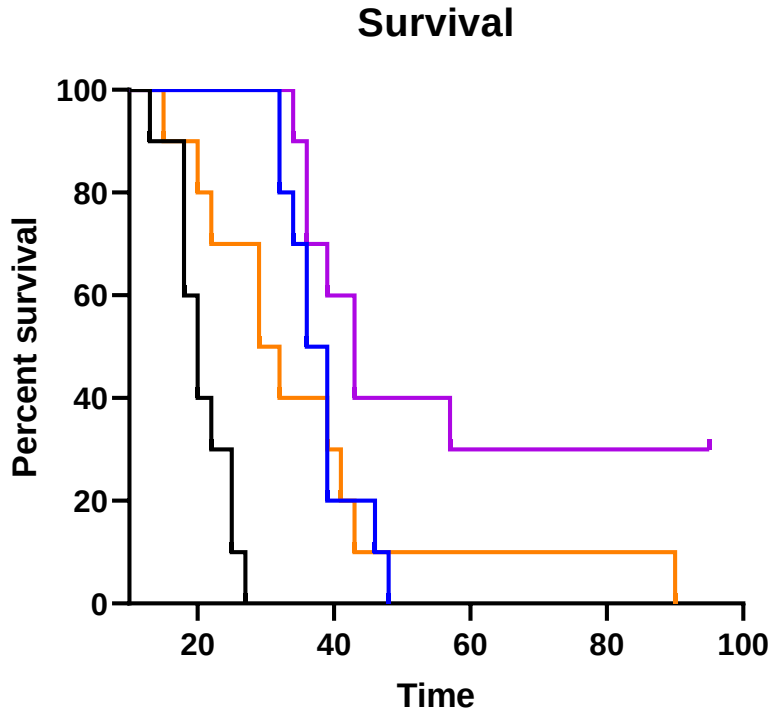
Cell Line	Tumor type	RAS/RAF mutation status
A549	Lung	KRAS mt G12S
TOV21g	Ovarian	KRAS mt G13C
SKMEL5	Melanoma	BRAF mt V600E
IGR-1	Melanoma	BRAF mt V600E
WM115	Melanoma	BRAF mt V600E

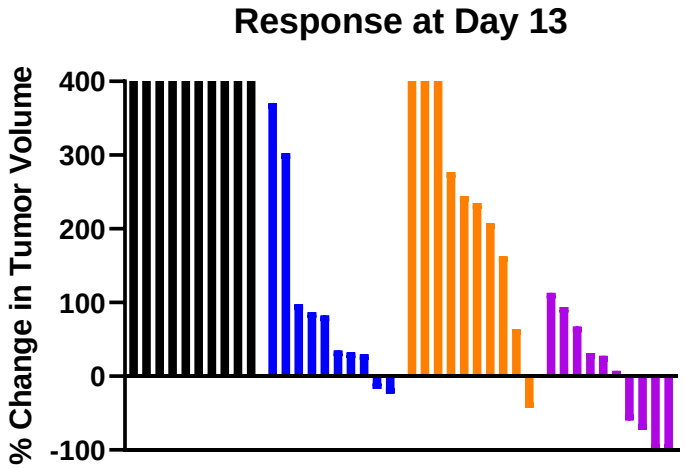
VS-6766 1 µM (except SKMEL5 and IGR-1, 300 nM)

Verastem Oncology

VS-6766 enhances tumor growth inhibition when combined with anti-PD-1 in the CT26 KRAS (G12D) syngeneic model



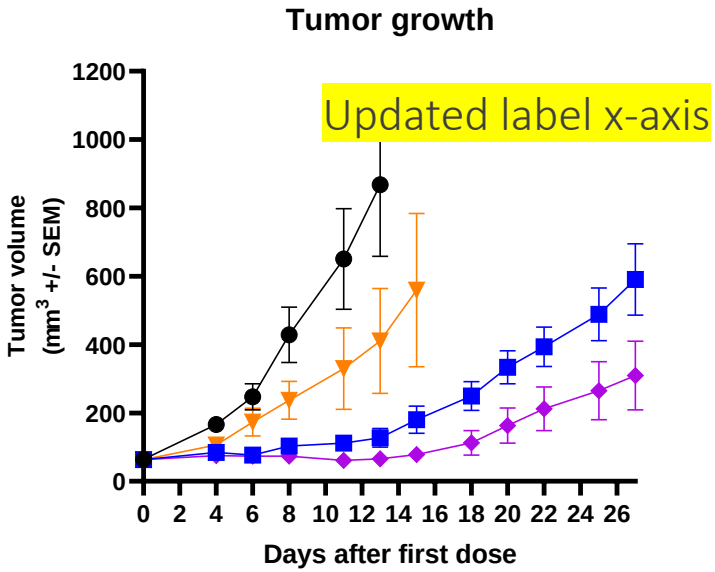




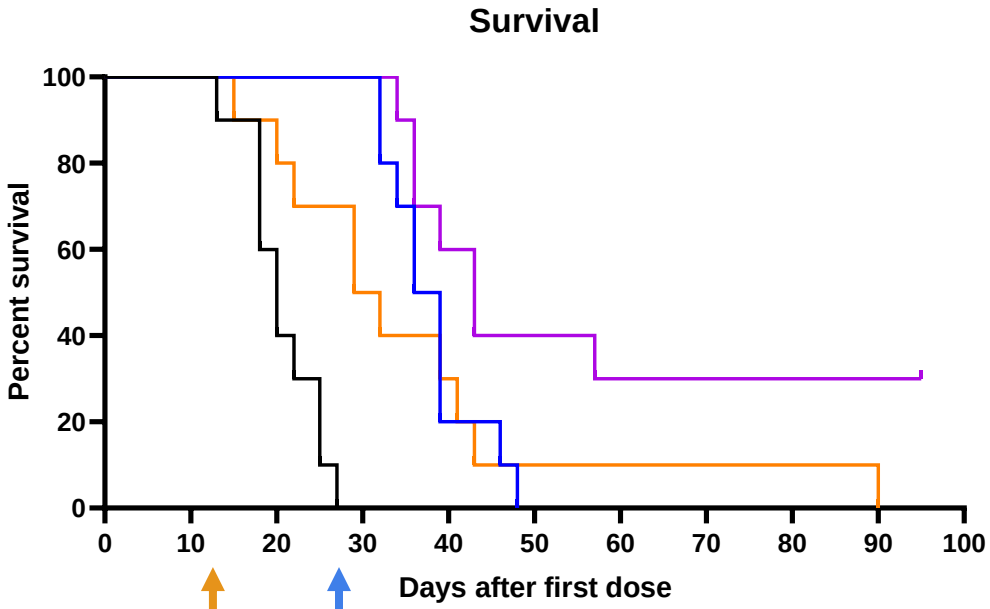
Vehicle
VS-6766 0.5 mg/kg QD x 28 days
anti-PD-1 3 mg/kg 2xW x 4 doses
VS-6766 + anti-PD-1

Verastem Oncology

VS-6766 enhances tumor growth inhibition when combined with anti-PD-1 in the CT26 KRAS (G12D) syngeneic model



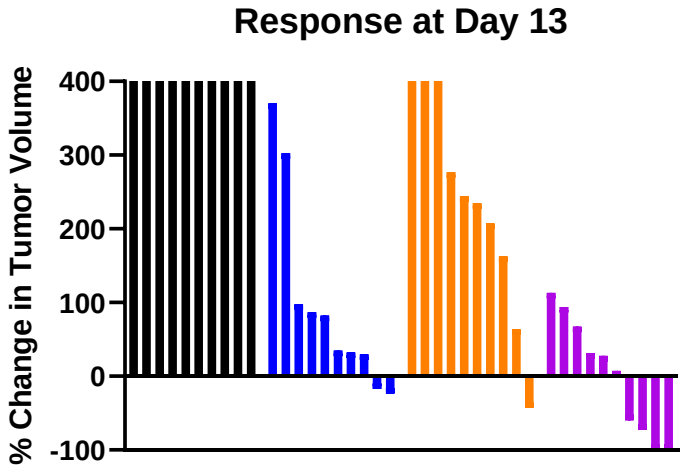
Updated label x-axis



Day 11, Last dose anti-PD-1

Day 28, Last dose VS-6766

Updated label x-axis
Added last day of dosing

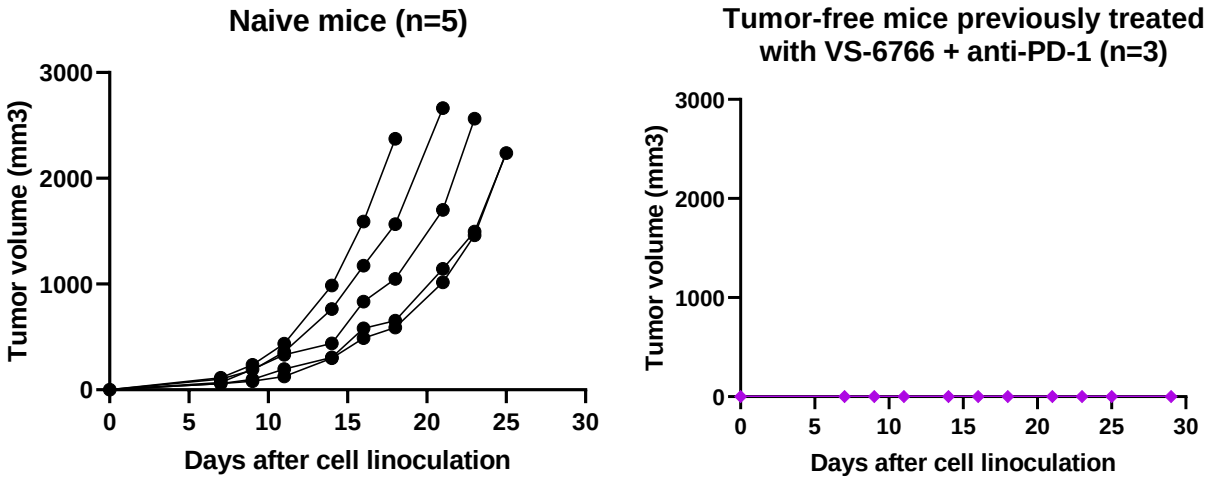


- Vehicle
- VS-6766 0.5 mg/kg QD x 28 days
- anti-PD-1 3 mg/kg 2xW x 4 doses
- VS-6766 + anti-PD-1

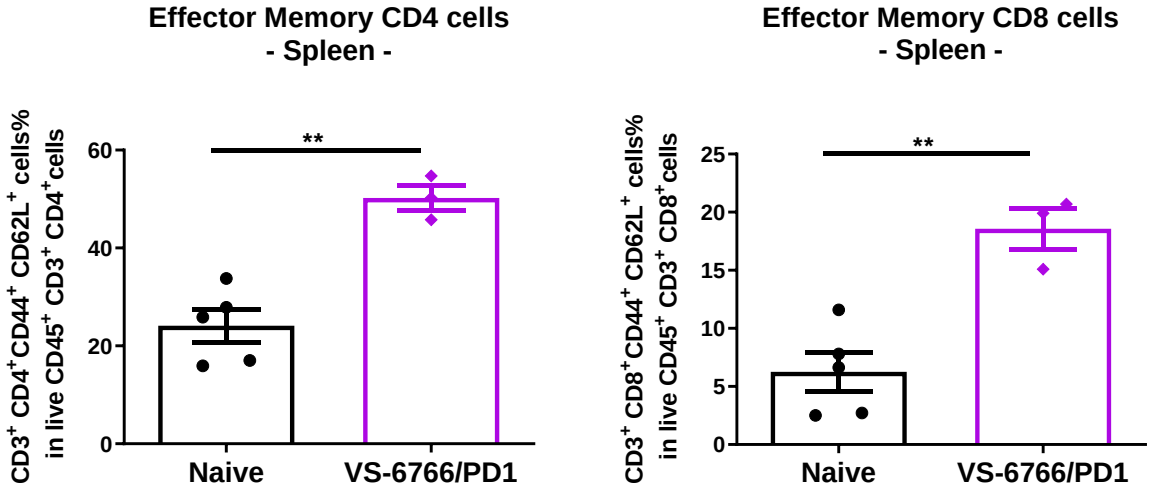
Verastem Oncology

Combination of VS-6766 + anti-PD-1 induces long-lasting immune memory in the CT26 colorectal cancer model

Tumor re-challenge: Tumor-free mice show durable immune memory



Tumor-free mice show increase in effector memory T cells



Verastem Oncology

VS-6766 Combinatons to Overcome Resistance Mechanisms: Conclusions

- **Combination of dual RAF/MEK inhibitor VS-6766 + FAKi may yield more complete RAS pathway shutdown**
  - Synergy in cellular models with tumor regression *in vivo*
  - Clinical activity in KRAS mt ovarian cancer & KRAS G12V mt NSCLC patients
- **Combination of RAF/MEK inhibitor VS-6766 is synergistic with KRAS-G12C inhibitors across G12C mt NSCLC & CRC cell lines**
  - Strong & durable inhibition of pERK pathway signaling
  - Tumor regressions in KRAS G12C mt NSCLC models *in vivo*
  - In KRAS G12C NSCLC models, triple combination of G12Ci + VS-6766 + FAKi yields PRs in all mice
- **Combination of RAF/MEK inhibitor with anti-PD-1 yields enhanced efficacy & immune memory *in vivo***
  - VS-6766 increases MHC-I expression across KRAS & BRAF mt cell lines

Acknowledgments

Verastem Oncology

- Silvia Coma
- Sanjib Chowdhury
- Winnie Tam

Royal Marsden Hospital

- Udai Banerji

UCSD

- J. Silvio Gutkind

Thanks for your attention!