



Corporate Presentation

August 2022



Safe Harbor Statement

This presentation includes forward-looking statements about, among other things, Verastem Oncology's programs and product candidates, including anticipated regulatory submissions, approvals, performance and potential benefits of Verastem Oncology's product candidates, that are subject to substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Applicable risks and uncertainties include the risks and uncertainties, among other things, regarding: the success in the development and potential commercialization of our product candidates, including defactinib and other compounds in combination with VS-6766; the occurrence of adverse safety events and/or unexpected concerns that may arise from additional data or analysis or result in unmanageable safety profiles as compared to their levels of efficacy; or our ability to obtain, maintain and enforce patent and other intellectual property protection for our product candidates.

Other risks and uncertainties include those identified under the heading "Risk Factors" in the Company's Annual Report on Form 10-K for the year ended December 31, 2021, as filed with the Securities and Exchange Commission (SEC) on March 28, 2022, and in any subsequent filings with the SEC, which are available at www.sec.gov and www.verastem.com.

The forward-looking statements in this presentation speak only as of the original date of this presentation, and we undertake no obligation to update or revise any of these statements.

Verastem Oncology

Well Positioned to Capitalize on Growth Opportunities

We are a biopharmaceutical company committed to developing and commercializing new medicines for patients battling cancer

Lead clinical program has best-in-class potential

VS-6766 (RAF/MEK clamp) and defactinib (FAK inhibitor) are clinically active against RAS mutant cancers

Rapid development paths to market

FDA Breakthrough Therapy Designation in LGSOC; Supported by clinical results (FRAME study) achieved in low-grade serous ovarian cancer (LGSOC), strong signal in KRAS G12V mutant NSCLC; registration-directed trials initiated in 4Q 2020

Significant downstream market opportunity and blockbuster potential

30% of all human cancers are driven by mutations in RAS; VS-6766 combinations potentially broadly applicable across a variety of tumor types.
Clinical collaborations with Amgen & Mirati evaluating the combinations of VS-6766 with sotorasib & adagrasib, respectively, in KRAS G12C mutant NSCLC supported by strong pre-clinical rationale
Multiple clinical opportunities within NSCLC and other tumor areas based on preclinical data

Strong balance sheet

Up to \$150 million of non-dilutive funding available from new credit facility
Cash balance of \$94.3 million as of June 30, 2022
Company ended Quarter 2 2022 with \$19.6 million non-GAAP operating expenses
Cash position, credit facility and expected COPIKTRA milestones extend expected cash runway through 2025 to support continued development and potential commercial launches

* Q2 2022 GAAP operating expenses - \$21.4M minus Q2 2022 stock compensation - \$1.8M = \$19.6M Q2 2022 non-GAAP operating expenses


Key VSTM Milestones 2021-2022

	1H2021	2H2021	1Q2022	2Q2022	2H2022
LGSOC	<ul style="list-style-type: none"> ✓ RAMP 201 Amended to Include KRAS wt patients in Selection Phase ✓ FDA Breakthrough Therapy Designation 	<ul style="list-style-type: none"> ✓ Updated data from FRAME LGSOC cohort Presenting at ESMO 	<ul style="list-style-type: none"> ✓ RAMP 201 Target enrollment of Selection Phase Complete Initiated enrollment of Expansion Phase 	<ul style="list-style-type: none"> ✓ RAMP 201 Selection Phase Update* ✓ Translational data from FRAME LGSOC cohort presented at AACR 	<ul style="list-style-type: none"> RAMP 201 Complete enrollment of Expansion Phase
NSCLC	<ul style="list-style-type: none"> ✓ Updated data from FRAME NSCLC cohort Presented at AACR 	<ul style="list-style-type: none"> ✓ VS-6766 + Adagrasib Collaboration w/Mirati ✓ VS-6766 + Sotorasib Collaboration w/Amgen 	<ul style="list-style-type: none"> ✓ RAMP 202 Complete enrollment of Selection Phase ✓ Initiate RAMP 203 (VS-6766 + sotorasib) in KRAS G12C (Amgen) 	<ul style="list-style-type: none"> ✓ RAMP 202 Amended to include BRAF mt cohorts ✓ Top-Line Data from VS-6766 + everolimus in KRAS mt 	<ul style="list-style-type: none"> Initiate RAMP 204 (VS-6766 + adagrasib) in KRAS G12C (Mirati) Top-Line Data from RAMP 202 Selection Phase Initial readout of RAMP 203 data Initiate combo study of VS-6766 + abemaciclib and fulvestrant in ER+ breast cancer Initiate basket trial of VS-6766 + defactinib in RAS pathway-driven gynecological cancers Initiate combo study of VS-6766 + cetuximab in KRAS mt CRC
Additional Indications*				<ul style="list-style-type: none"> ✓ PanCAN Agreement Executed 	

VS-6766 is a Differentiated, Potentially Best-in-Class Asset Applicable Across Multiple Patient Populations

- Unique RAF/MEK clamp mechanism of action
- Novel intermittent dosing schedule; convenient oral regimen
- Breakthrough Therapy Designation in recurrent low-grade serous ovarian cancer
- Potential best-in-class safety & tolerability profile relative to marketed MEK inhibitors, with potential for combinability with agents from multiple target classes
- Promising signals of clinical activity in various RAS-driven cancers, including in patients whose tumors previously progressed on other MEK inhibitors
- Preclinical anti-proliferative activity across multiple MAPK pathway alterations (e.g. KRAS, NRAS, BRAF, NFI mt) and multiple solid tumor indications
- Strong preclinical combination data with other agents targeting RAS pathway and parallel pathways

Robust Clinical Program in Two Lead Indications: Gynecologic Oncology & Non-Small Cell Lung Cancer

INDICATION	REGIMEN	STUDY NAME	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	CLINICAL COLLABORATION WITH
LGSOC ^{1,2}	VS-6766 +/- defactinib	RAMP 201	<div></div>				
R/R LGSOC	VS-6766 + defactinib	FRAME	<div></div>				
R/R endometrioid cancer (RAS/RAF mt)	VS-6766 + defactinib	FRAME	<div></div>				
Gynecological cancers (RAS Pathway-driven) ⁴	VS-6766 + defactinib	IST	<div></div>				
Mesonephric ⁴	VS-6766 + defactinib	IST	<div></div>				
R/R NSCLC (KRAS G12V mt) ²	VS-6766 +/- defactinib	RAMP 202	<div></div>				
R/R NSCLC (KRAS non-G12V mt)	VS-6766 + defactinib	RAMP 202	<div></div>				
R/R NSCLC (BRAF mt)	VS-6766 + defactinib	RAMP 202	<div></div>				
R/R NSCLC (KRAS G12C mt)	VS-6766 + sotorasib	RAMP 203	<div></div>				
R/R NSCLC (KRAS G12C mt) ³	VS-6766 + adagrasib	RAMP 204	<div></div>				
R/R NSCLC (KRAS mt)	VS-6766 + everolimus (mTORi)	IST	<div></div>				
R/R NSCLC (KRAS mt)	VS-6766 + defactinib	FRAME	<div></div>				

¹ FDA Breakthrough Therapy Designation

² Registration-directed trial

³ In Startup

⁴ Preclinical studies underway, ph. 2 investigator-sponsored trials in preparation

Key Financial Statistics

As of and for the quarter ended June 30, 2022

Cash, cash equivalents & investments	\$94.3M
Non-GAAP Operating Expenses	\$19.6M
Shares Outstanding	187.6M

Oxford Finance LLC Credit Facility

<u>Loan Tranches</u>	<u>Event</u>
A	\$25M
B	\$15M
C	\$25M
D	\$35M
E	\$50M
Total	\$150M

Interest rate: floating rate, which is subject to a floor and a cap; 5% final payment charge, and loan subject to 1-3% early payment fee

Term: 5 Years; Interest only two years initially, extendable up to four years based on achievement of milestones

Financial covenants: None

VS-6766 RAF/MEK Clamp Program Overview

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Broad Development Opportunities Across Multiple RAS/MAPK Driven Cancers

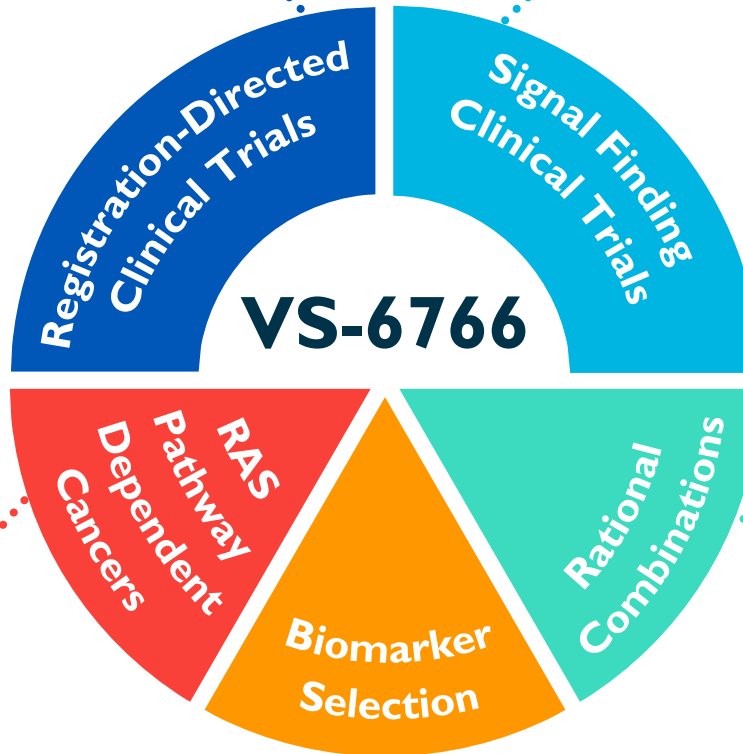
High Priority Registration Indications

Registration-Directed Trials Initiated in 4Q20

- LGSOC^{1,2} (RAMP 201)
- KRAS G12V mt NSCLC^{1,2} (RAMP 202)

RAS Pathway Dependent Cancers

- Gynecological^{1,2}
- NSCLC^{1,2}
- Colorectal^{1,2}
- Melanoma^{1,2}
- Pancreatic²
- Thyroid^{1,2}



Key Signal Finding

- VS-6766 + G12Ci KRAS G12C mt NSCLC² (RAMP 203-sotorasib) & (RAMP 204-adagrasib)
- KRAS non-G12V^{1,2} mt NSCLC (RAMP 202)
- BRAF mt (V600E & non V600E) NSCLC^{1,2} (RAMP 202)
- Pancreatic²
- RAS/RAF mt endometrioid¹
- Uveal Melanoma²
- VS-6766 + everolimus KRAS mt NSCLC^{1,2}
- VS-6766 + cetuximab KRAS mt CRC²

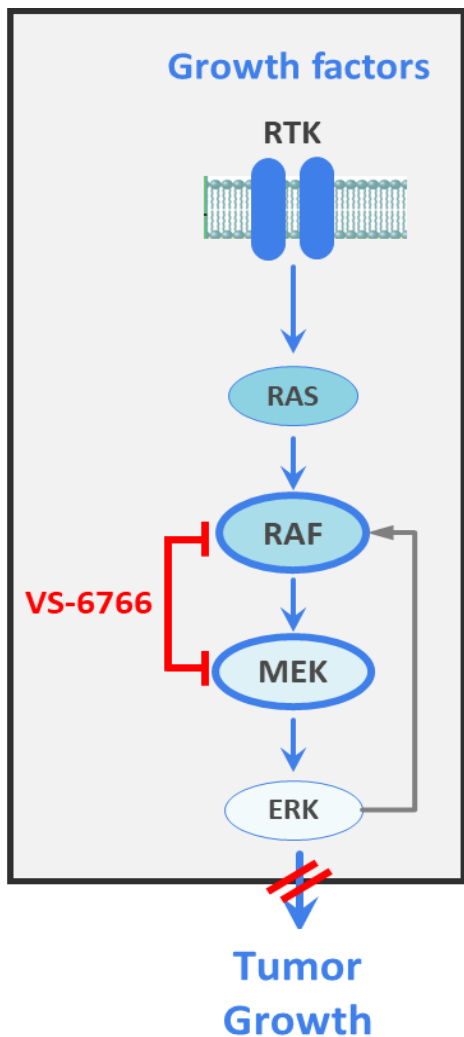
Rational Combinations

- G12Ci^{1,2}
- G12Di²
- Anti-EGFR²
- Everolimus^{1,2}
- CDK4/6 inhibitor²
- Anti-PD-1^{1,2}
- Chemotherapy²

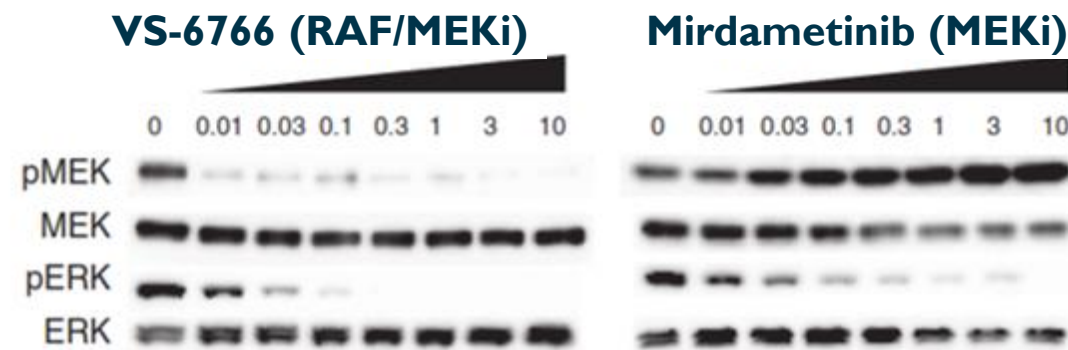
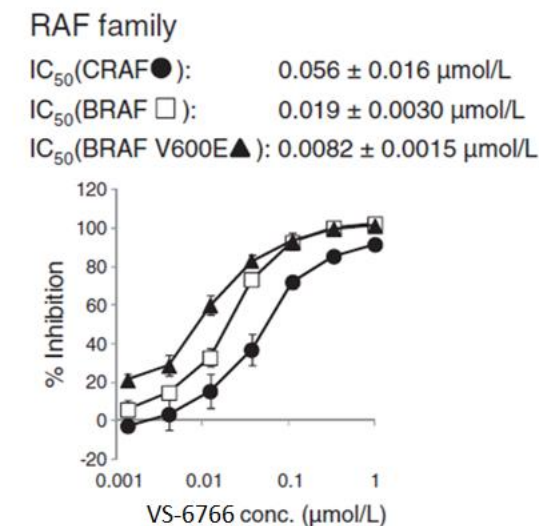
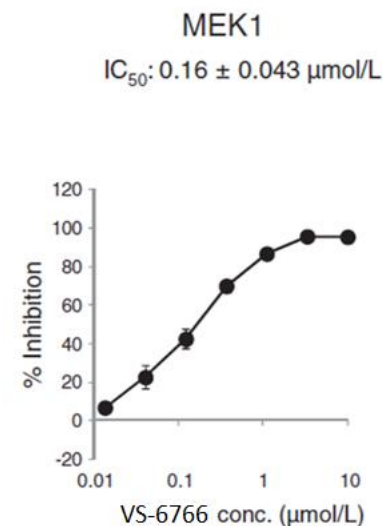
Biomarker Selection

- KRAS mt^{1,2}
- BRAF mt (V600 & non-V600)^{1,2}
- NRAS mt^{1,2}
- CRAF mt/fusions²

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

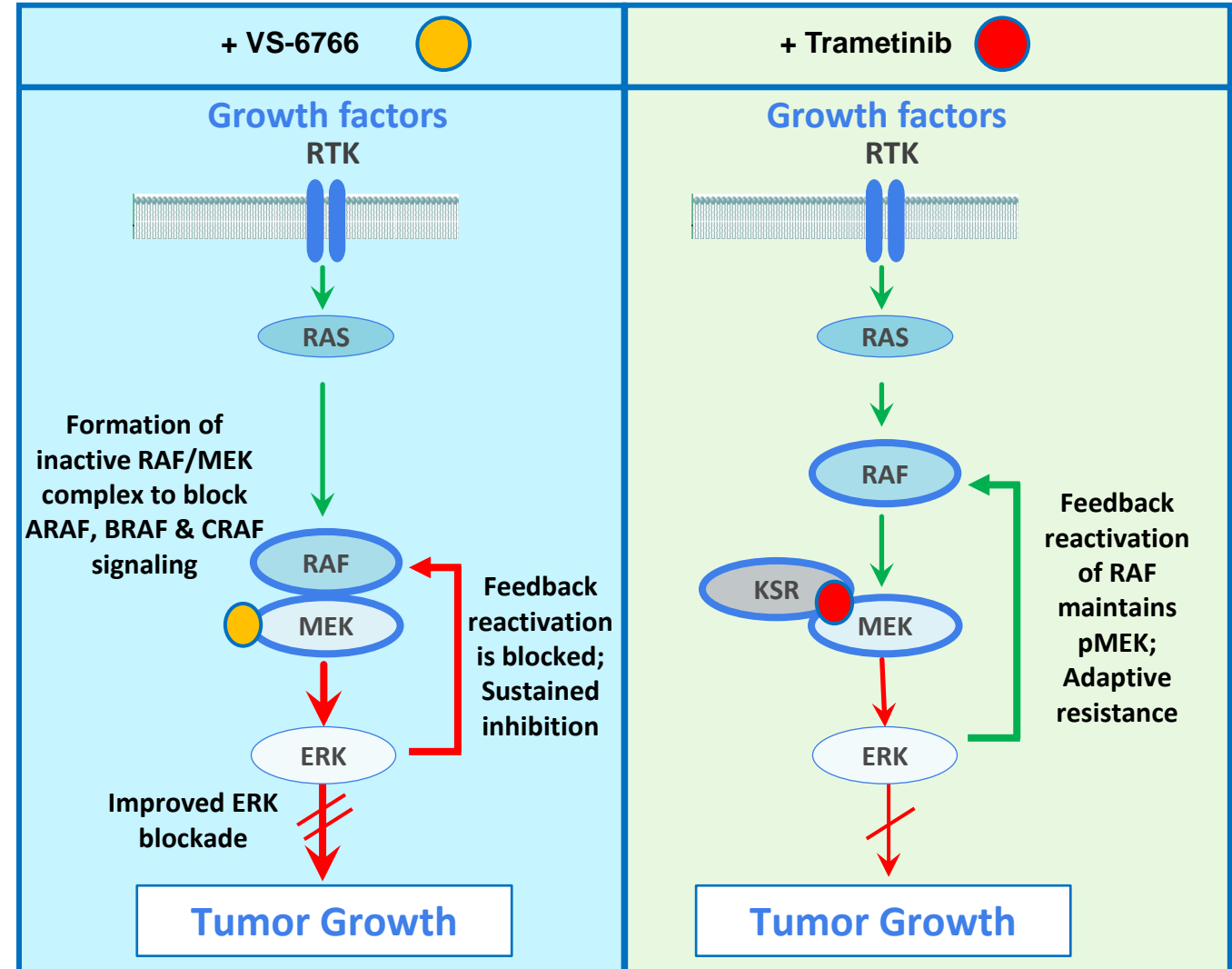
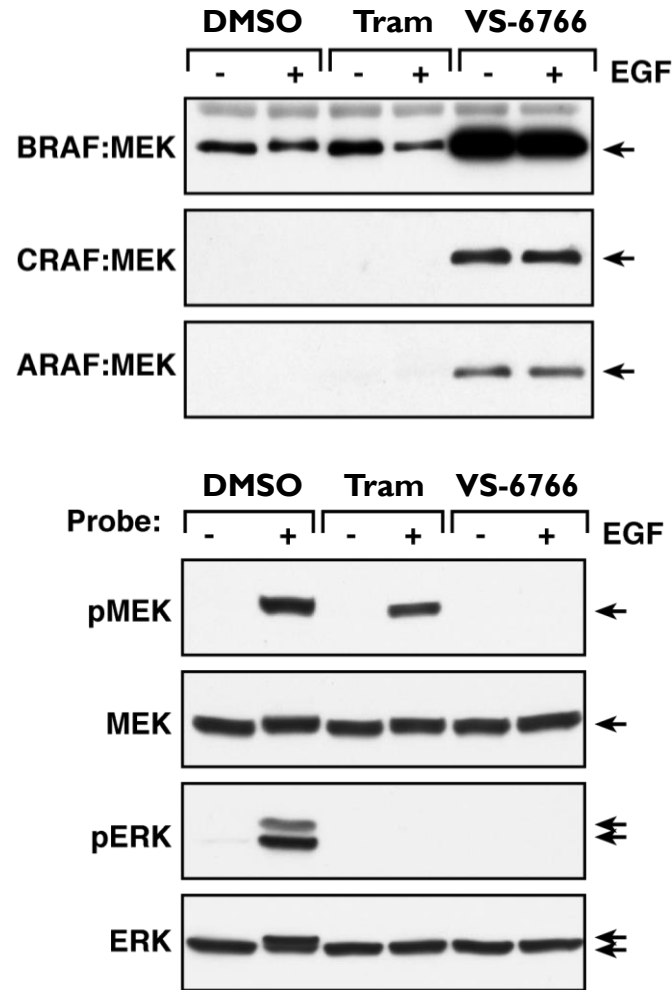


- VS-6766 inhibits MEK, BRAF & CRAF by trapping these molecules in inactive complexes
- MEK inhibitors paradoxically induce MEK phosphorylation (pMEK) by relieving ERK-dependent feedback inhibition of RAF
- By inhibiting RAF phosphorylation of MEK, VS-6766 has advantage of not inducing pMEK
- VS-6766 inhibits ERK signaling more completely; may confer enhanced therapeutic activity

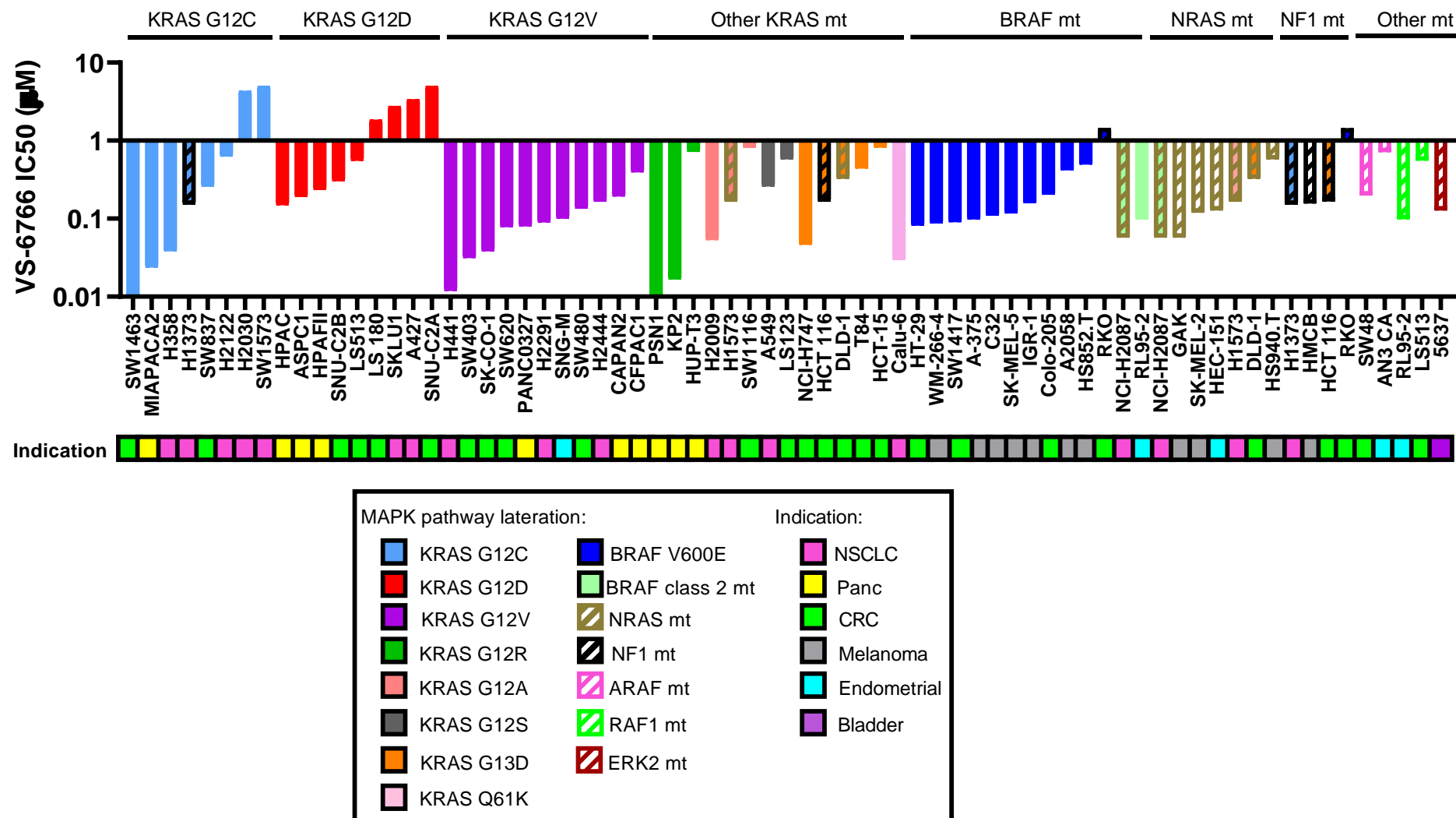


VS-6766 is a Unique RAF/MEK Clamp which Induces Inactive Complexes of MEK with ARAF, BRAF & CRAF

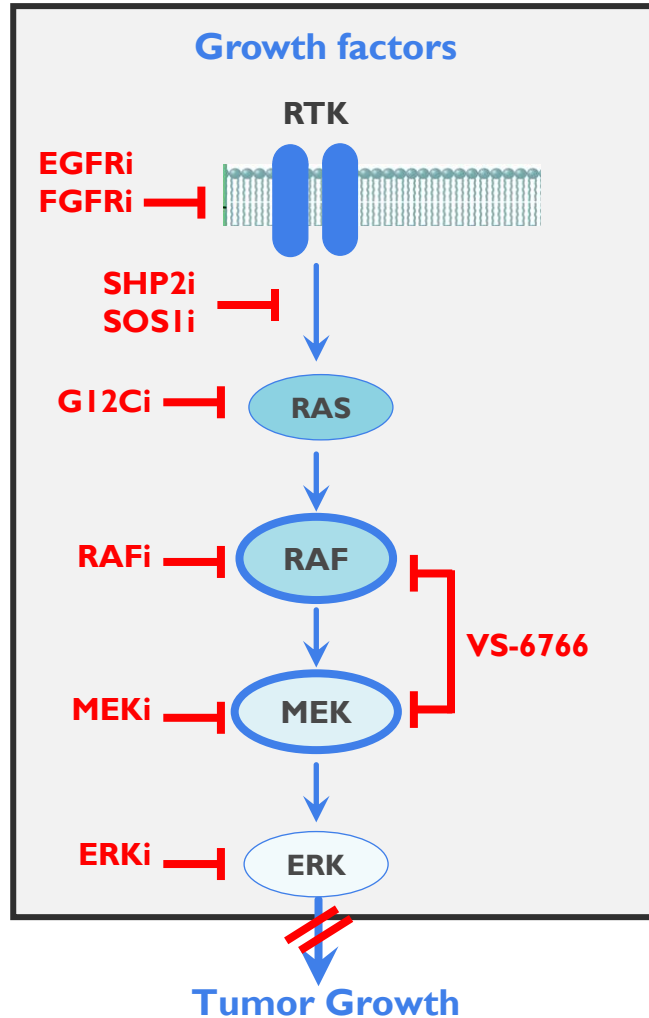
Contrasting mechanism of action vs. trametinib



VS-6766 Inhibits Cell Proliferation Across Multiple MAPK Pathway Alterations and Multiple Solid Tumor Histologies



Vertical Blockade: Establishing VS-6766 as the Backbone of Therapy for RAS Pathway-Driven Tumors



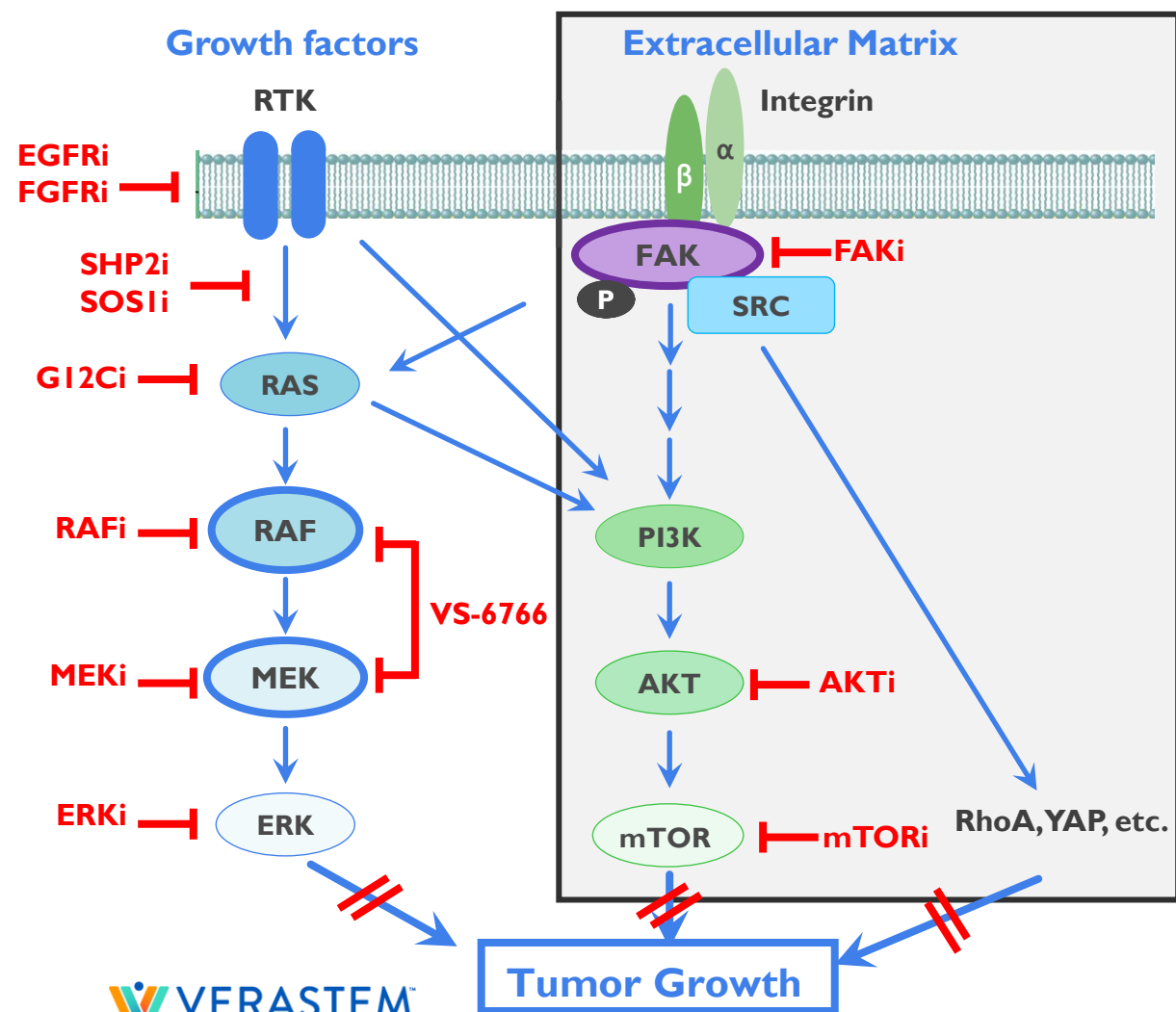
▪ Current Challenges

- Blocking any single target in the pathway is insufficient for maximum depth and duration of anti-tumor efficacy
 - e.g., SHP2i, KRAS-G12Ci, RAFi, MEKi, ERKi
- Vertical blockade concept is now well established
 - Necessary to block more than 1 target in the pathway
- Many of these agents (e.g., SHP2i, MEKi) have poor tolerability as monotherapy and in combination

▪ Solutions offered by VS-6766

- Vertical blockade (RAF and MEK blockade) in a single drug
- Potential best-in-class tolerability with recommended twice weekly dosing regimen
 - Should enable tolerable combinations
- Compelling synergy data (preclinical) for VS-6766 combinations (e.g., with KRAS-G12C inhibitors) supporting clinical combinations

Parallel Pathway Inhibition: Establishing VS-6766 as the Backbone of Therapy for RAS Pathway-Driven Tumors



Current Challenges

- Blocking Ras pathway can be circumvented through parallel pathways
 - e.g., PI3K/AKT/mTOR, FAK, RhoA, YAP
- Combinations of MEKi + AKTi have shown poor tolerability

Solutions offered with VS-6766

- Good tolerability with twice weekly VS-6766 opens up intermittent dosing options for combinations
- Compelling preclinical synergy data with VS-6766 in combination with FAK inhibition and with AKT pathway inhibition (e.g., everolimus)
- RP2D established for VS-6766 + defactinib and for VS-6766 + mTORi (everolimus) with twice weekly regimen



VS-6766 +/- Defactinib in Low-Grade Serous Ovarian Cancer

Favorable Tolerability Profile with Novel Intermittent Dosing Regimen

Summary of Adverse Events Grade ≥ 3 Occurring in $\geq 5\%$ 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

Favorable Tolerability Profile at Recommended Phase 2 Dose for VS-6766 plus Defactinib Combination Regimen

Treatment Related Adverse Events Details* (≥10% patients in cohort 3.2mg 6766 and Def 200mg)	VS-6766 4mg Twice Weekly (4 wks of every 4 wks) ¹ n=22		VS-6766 3.2mg Twice Weekly Def 200mg BID (3 wks of every 4 wks) ² n=38	
	Gr1/2	Gr3/4	Gr1/2	Gr3/4
Rash	15	5	32	2
CK Elevation	13	2	19	2
AST Elevation	1		13	
Hyperbilirubinemia			14	1
Visual Disturbance	13		9	
ALT Elevation	2		5	
Diarrhoea	6	1	14	1
Fatigue	5	1	8	1
Oral Mucositis [^]	7	1	11	
Nausea	5		5	
Vomiting	2		4	
Peripheral Edema	9		10	
Paronychia	3		4	
Thrombocytopenia			6	
Pruritus	3	0	5	

Summary of FRAME Safety Profile

- Most Adverse Events (AE) were Grade 1/2
- Few patients have discontinued due to AEs in the study

RP2D

- **VS-6766 3.2 mg** oral twice wkly (3 wks of every 4 wks)
- **Defactinib 200 mg** oral BID (3 wks of every 4 wks)

*AEs were graded by NCI CTC v4; highest grade only recorded for each patient; AEs presented in ≥10% Patient (cohort 3.2mg 6766 and Def 200mg) data preliminary and subject to change;

[^]also includes glossitis/mouth ulcers

70% of LGSOC Tumors Driven by Mutations in the RAS Pathway



LGSOC is a type of ovarian cancer that disproportionately affects younger women



1,000 to 2,000 patients in the U.S. and 15,000 to 30,000 worldwide diagnosed with LGSOC each year



A slow growing cancer, that has a median survival of almost 10 years, so patients remain in treatment for a long time (10-yr prevalence ~80,000 worldwide, ~6,000 US)

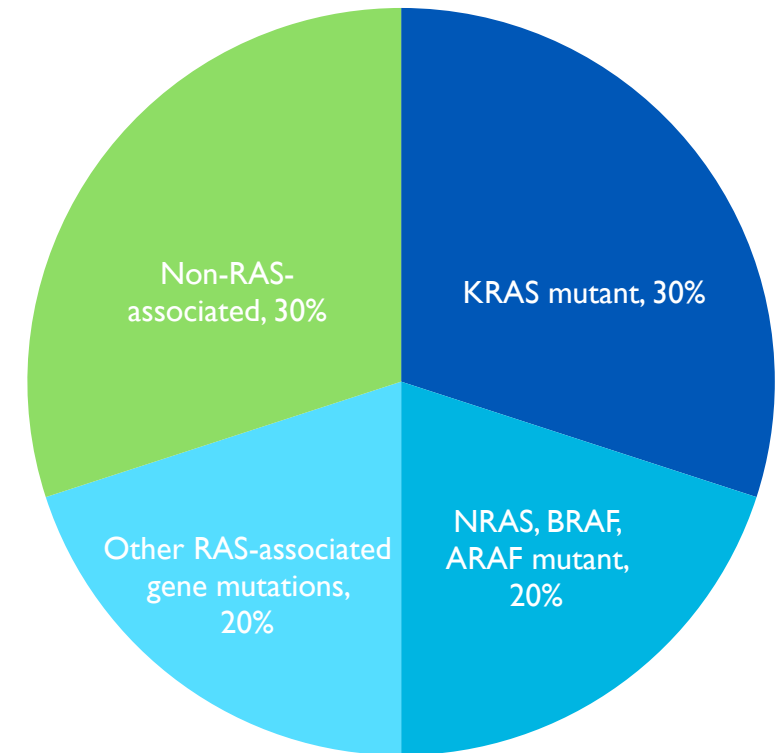


Patients often experience significant pain and suffering from their disease over time



Most prior research has focused on high grade serous ovarian cancer (HGSOC). However, LGSOC is clinically, histologically and molecularly unique from HGSOC with limited treatments available

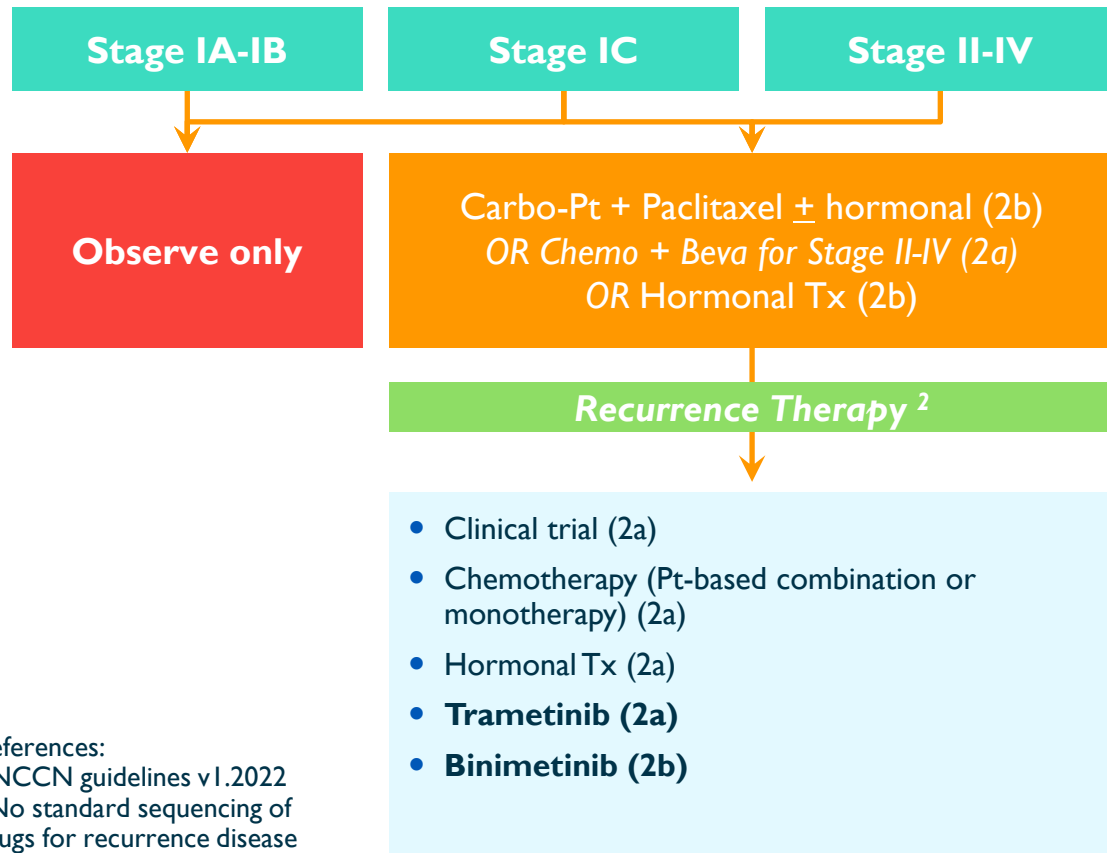
~30% of LGSOC Patients Have KRAS mt
~70% of LGSOC Shows RAS Pathway-Associated mts



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

LGSOC: Limited Treatment Options with High Unmet Need

Low-Grade Ovarian Cancer – Treatment Algorithm¹



Recent Clinical Trials in Recurrent LGSOC

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%

* Not confirmed by central review

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

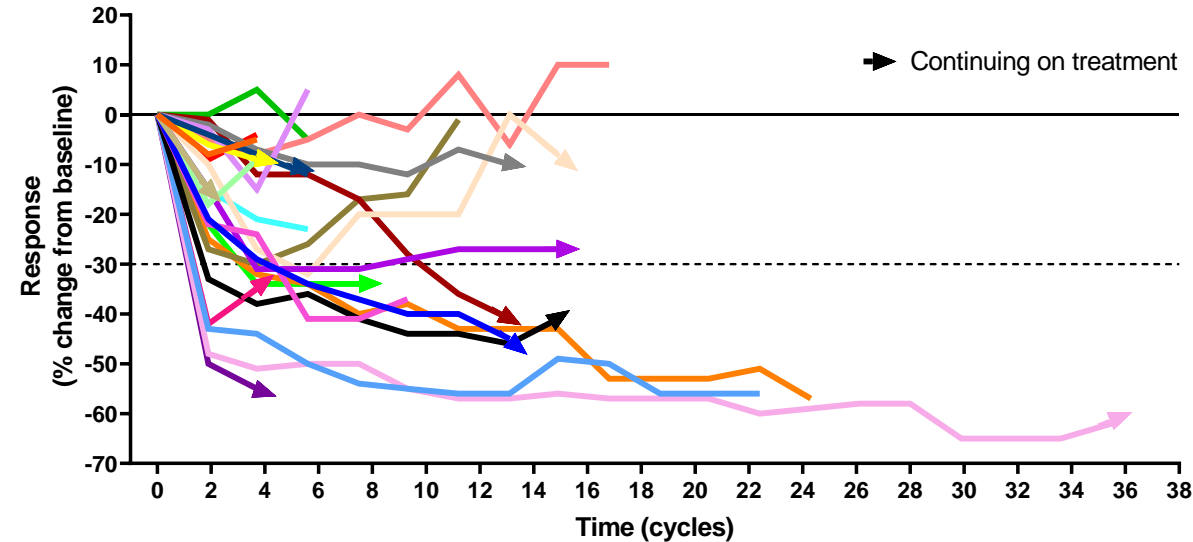
¹ Study GOG 281 trial Gershenson et al., Lancet 2022

² MILO Study Monk et al., J Clin Oncol 2020.

References:
¹ NCCN guidelines v1.2022
² No standard sequencing of
drugs for recurrence disease

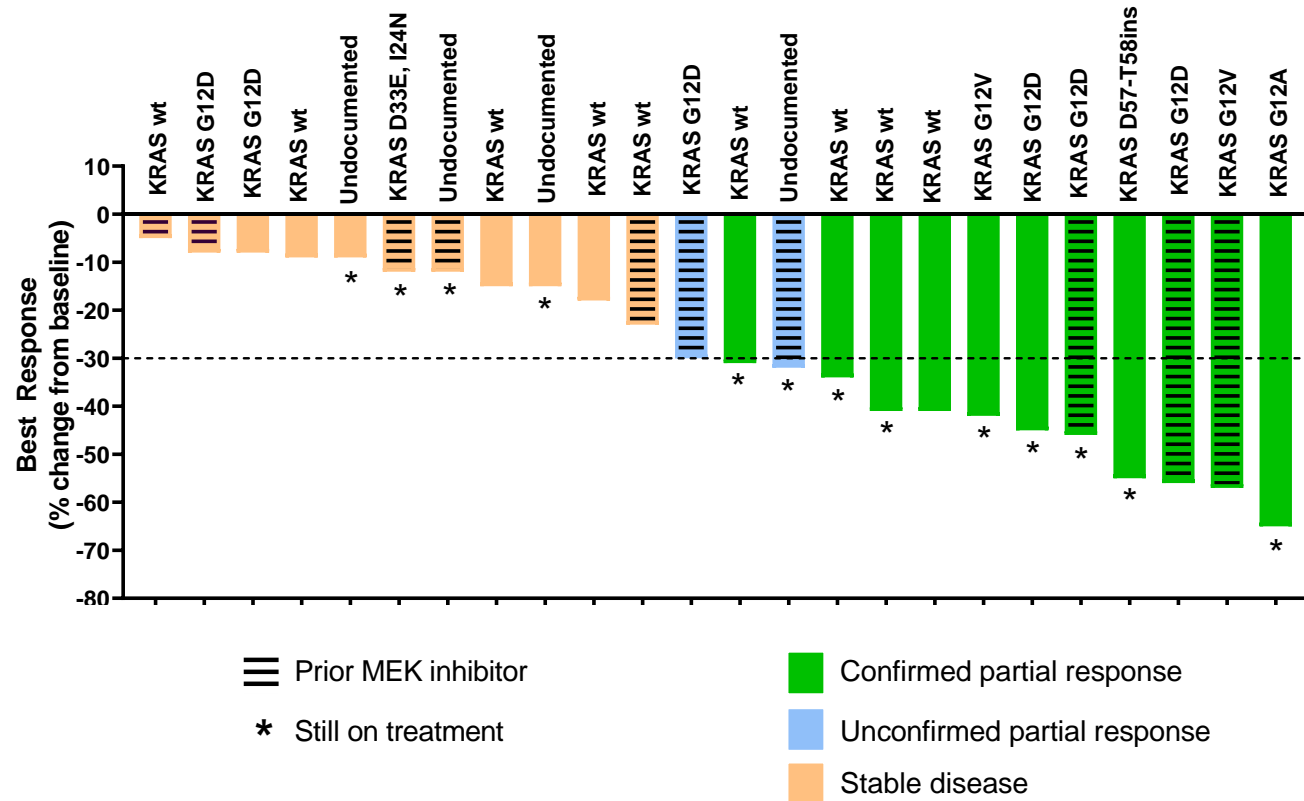
VS-6766 in Combination with Defactinib Shows Promising ORR with Durability in Refractory LGSOC with Expanded Number of Patients (n=24)

Response by RECIST



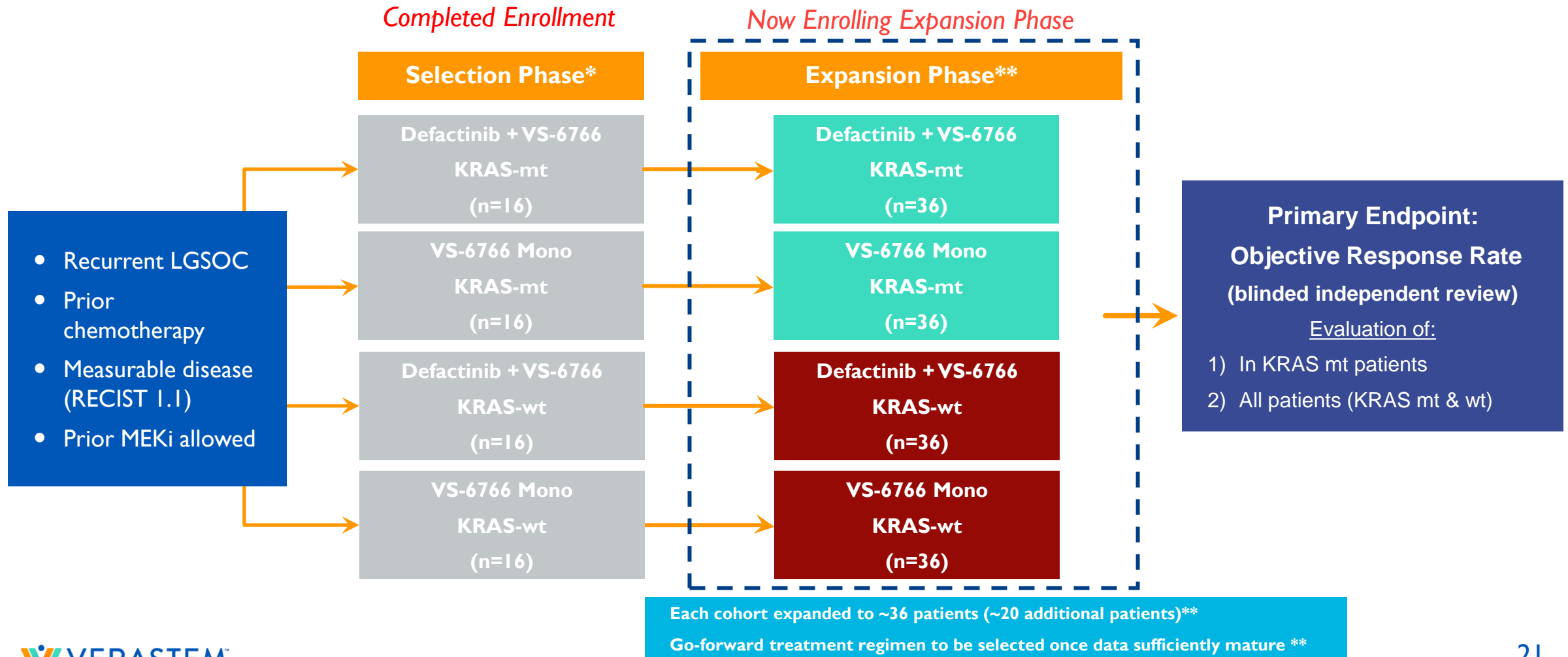
- Overall response rate (ORR) = 46% (11 confirmed PRs/24)
 - KRAS mutant ORR = 64% (7 confirmed PRs/11)
 - KRAS wild-type ORR = 44% (4 confirmed PRs/9)
 - KRAS status undetermined (1 unconfirmed PR/4)
- Response too early to determine for 2 pts on study for ≤ 5 months
- Responses in patients previously treated with MEKi
- 54% (13/24) patients still on treatment
- 1 patient discontinuing for adverse events as of April 2021
- Median PFS 23 months (95% CI 10.6-NR) across all LGSOC

Best response by RECIST



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

RAMP 201 Registration-directed Phase 2 Trial of VS-6766 +/- Defactinib in Recurrent LGSOC - KRAS Mutant (mt) and Wild Type (wt): adaptive design modified based on interim analysis findings



RAMP 201 Selection Phase: Interim Analysis Findings - June 2022

Findings

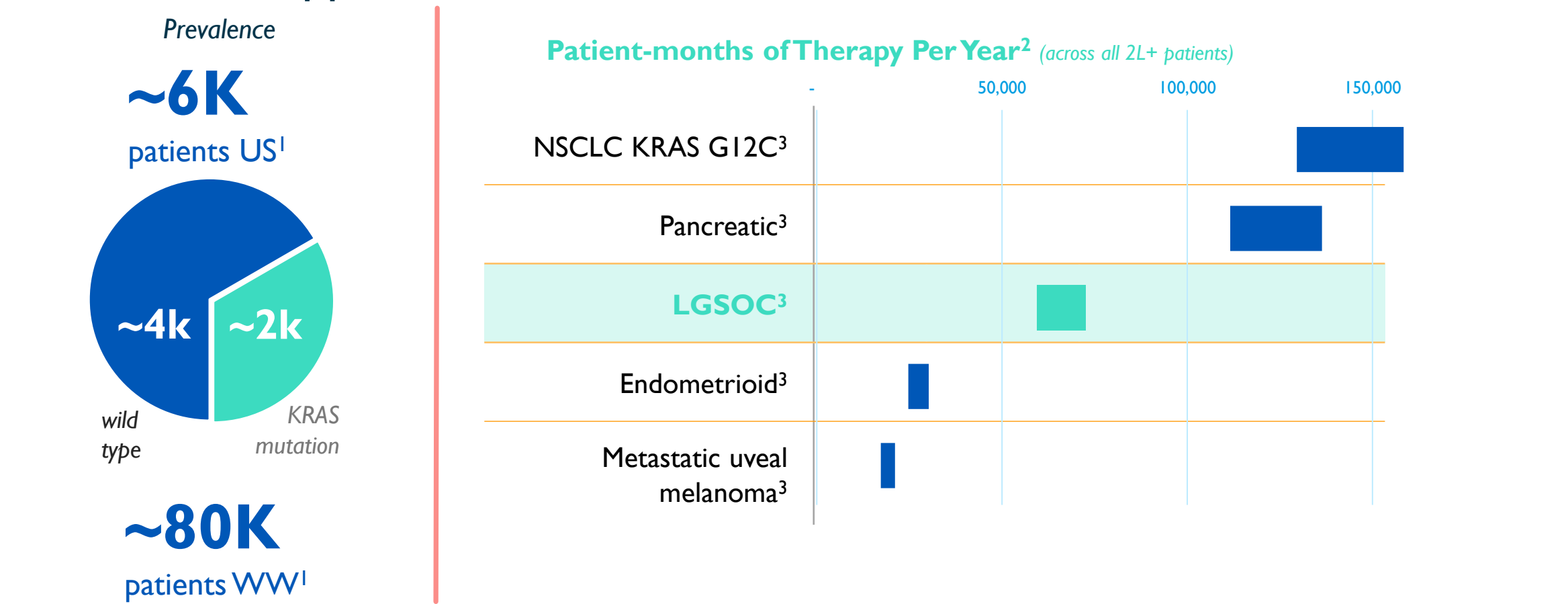
- Support continued evaluation of both VS-6766 monotherapy and VS-6766 + defactinib combination therapy treatment arms
- Encouraging efficacy results include confirmed responses in:
 - Monotherapy and combo therapy
 - KRAS mt and KRAS wt tumors
- No addl. safety signals to date, continued favorable safety profile for both monotherapy and combination treatment arms (~ 6% of patients discontinuing due to AEs)
- Substantial majority (~ 80%) of patients remain on study treatment



Next Steps

- All four cohorts from Selection Phase will be enrolled for Expansion Phase (add ~ 20 patients/cohort)
- Fully enroll all four Expansion Phase cohorts in 2H 2022
- Select go-forward treatment regimen, timing driven by data maturity
- Next update to be provided once go-forward treatment regimen determined

LGSOC Market Opportunity Larger or Comparable to Other High Unmet Need KRAS Opportunities



¹ References: Monk, Randall, Grisham, The Evolving Landscape of Chemotherapy in Newly Diagnosed Advanced Epithelial Ovarian Cancer, Am Soc Clin Oncol Educ Book; 2019; Slomovitz, Gourley, Carey, Malpica, Shih, Huntsman, Fader., Grisham et al, Low-Grade serous ovarian cancer: State of the Science; Gynecol Oncol; 2020. Grisham, Iyer, Low-Grade Serous Ovarian Cancer: Current Treatment Paradigms and Future Directions; Curr Treat Options Oncology; 2018; Globocan 2020

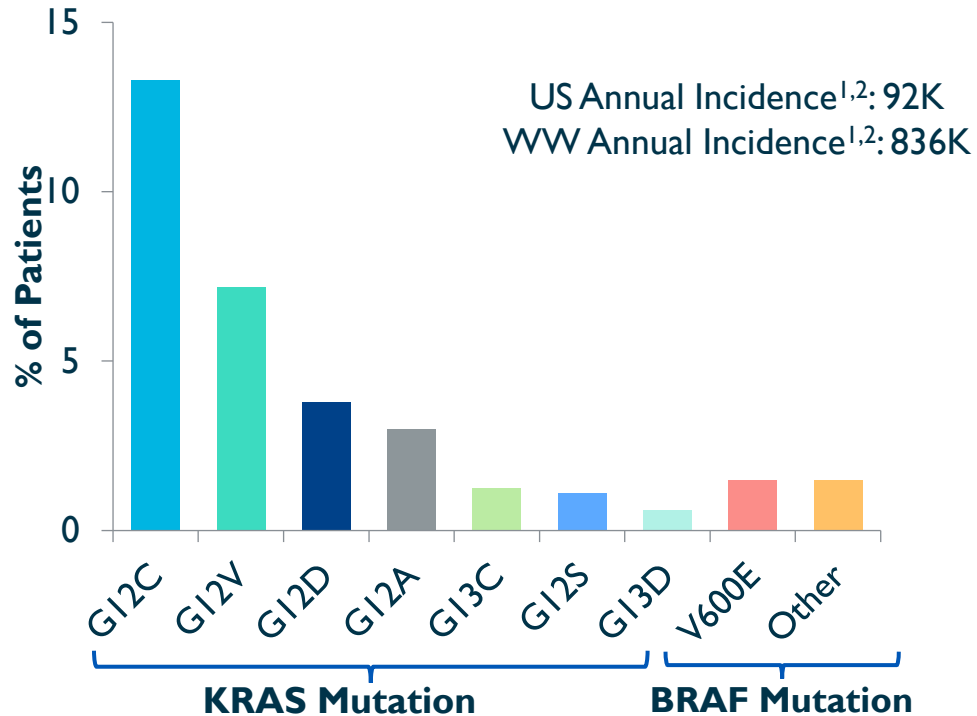
² Patient-months of Therapy metric calculated by multiplying relevant incidence/prevalence rate times estimated duration of therapy; represents US market opportunity only; patient population estimates from Globocan 2020, American Cancer Society 2021, AACR Genie Cohort V9.0 public, and scientific publications. Duration of therapy estimates from clinical studies and clinician experience. Patient-months on therapy is for 2nd-line+ patients

³ NSCLC KRAS G12C 2nd line patients (incidence); Pancreatic RAS/RAF mutant 2nd-line patients (incidence); LGSOC KRAS mutant and wild-type patients (prevalence); Endometrioid RAS/RAF mutant 2nd-line patients (incidence); Uveal melanoma RAS/RAF mutant 2nd-line patients (incidence)

VS-6766 +/- Defactinib in NSCLC

High Unmet Need in Refractory mt NSCLC Adenocarcinoma

NSCLC Adenocarcinoma³



KRAS Mutations Represent 25% of Lung Cancer Adenocarcinoma & BRAF Represent 2-4% (EGFR 17%, ALK 7%)^{4,6}

References:

¹ Globocan, 2018

² <https://www.ncbi.nlm.nih.gov/books/NBK519578/>

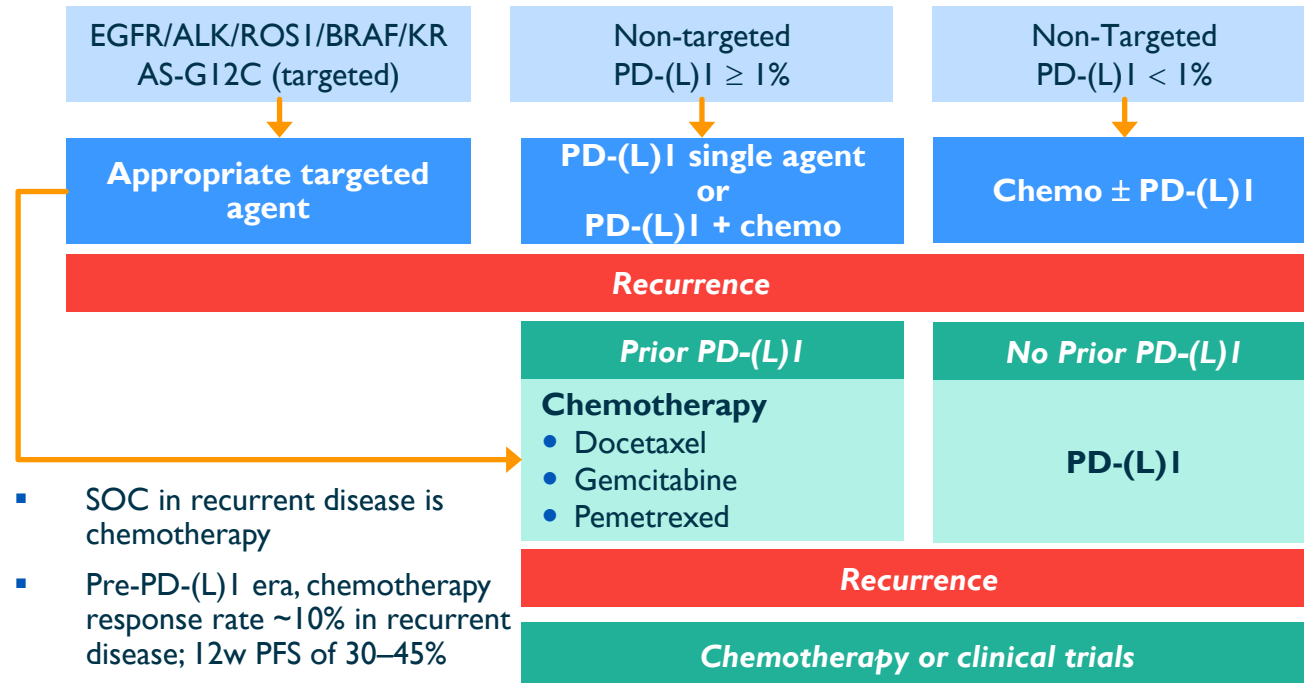
³ TCGA PanCancer Atlas (cBioPortal analysis)

⁴ www.thelancet.com Vol 389 January 21, 2017

⁵ Adapted from NCCN Non-small cell lung cancer guidelines Version 3.2020

⁶ Clinical Cancer Research DOI 10.1158/1078-0432.CCR-18-2062

Advanced or Metastatic NSCL Cancer Recommend Histologic and Molecular Subtyping⁵

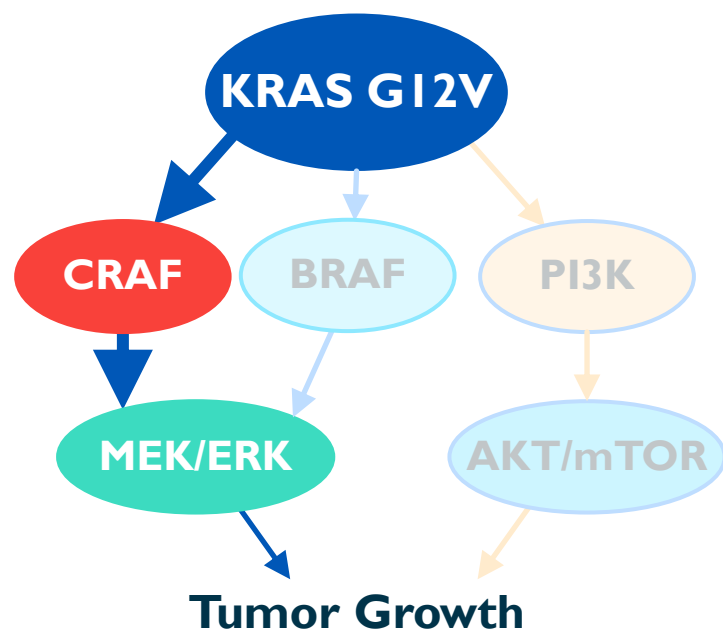


Verastem Clinical Trials:

- RAMP 202:
 - KRAS G12V—VS-6766 monotherapy & VS-6766 + Defactinib
 - Other KRAS mutations—VS-6766 + Defactinib
 - BRAF V600E and BRAF non-V600E—VS-6766 + Defactinib
- RAMP 203—KRAS G12C: VS-6766 + sotorasib
- RAMP 204—KRAS G12C: VS-6766 + adagrasib

VS-6766 Inhibits CRAF - The key driver of KRAS G12V mt NSCLC

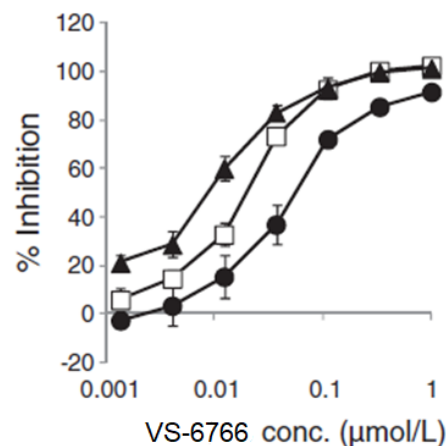
A Precision Approach to KRAS G12V Driven NSCLC



- 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

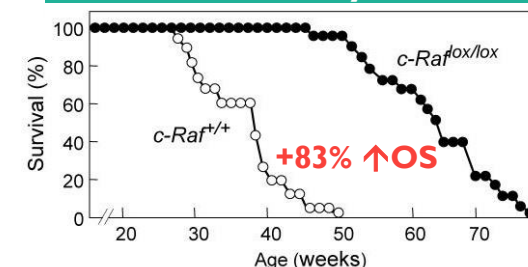
IC_{50} (CRAF●): $0.056 \pm 0.016 \mu\text{mol/L}$
 IC_{50} (BRAF□): $0.019 \pm 0.0030 \mu\text{mol/L}$
 IC_{50} (BRAF V600E▲): $0.0082 \pm 0.0015 \mu\text{mol/L}$



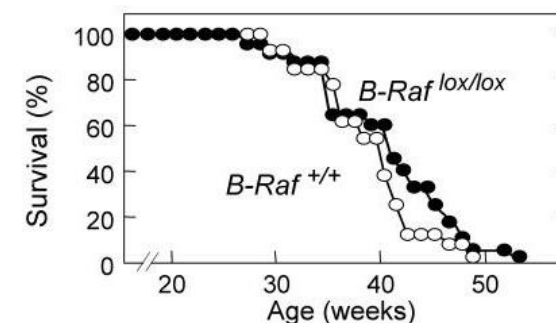
CRAF, but not BRAF, ablation improves survival of mice with KRAS G12V induced lung cancer *in vivo*

CRAF Drives KRAS G12V mt NSCLC¹

CRAF KO Shows Strong Efficacy

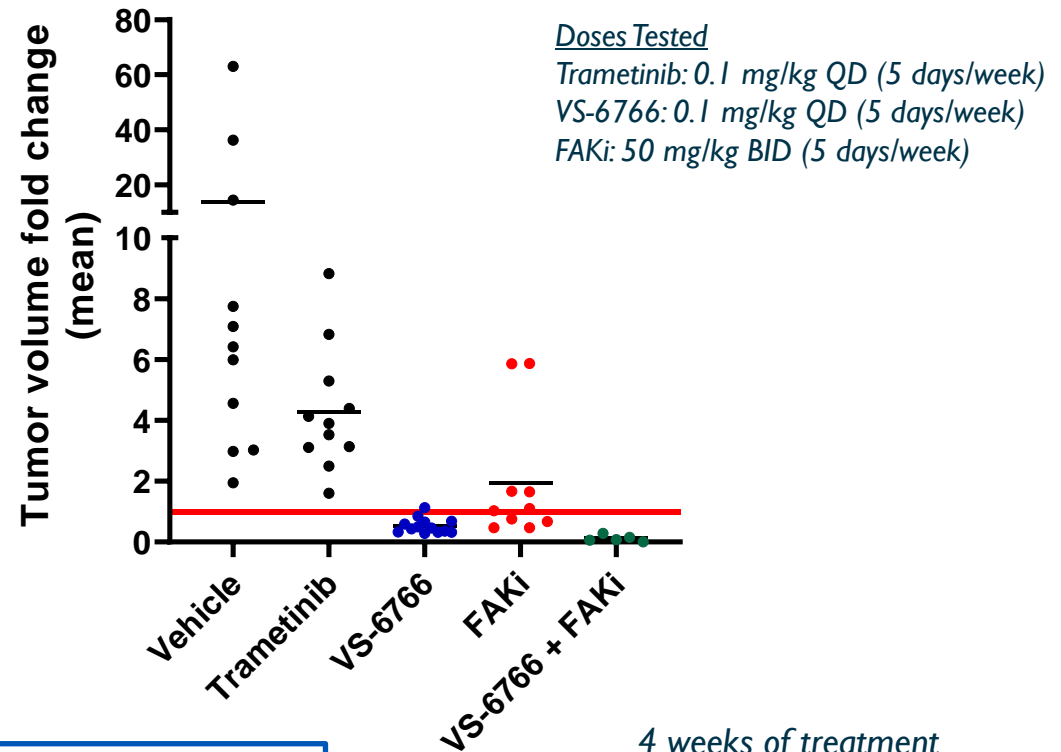
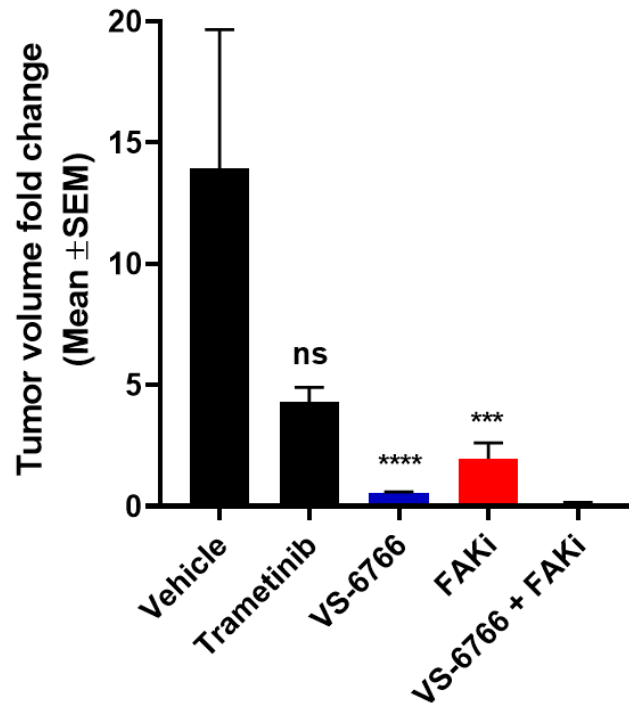


BRAF KO Has No Effect



VS-6766 +/- FAKi Induces Significant Tumor Regression in KRAS G12V mt NSCLC in vivo Model, with Clear Differentiation from Trametinib

KRAS G12V mutant;Tp53 KO NSCLC



- VS-6766 monotherapy caused tumor regression
- VS-6766 + FAKi showed stronger regression
- No significant anti-tumor effect of trametinib at same dose level

4 weeks of treatment

Statistics: Mann-Whitney test

Collaboration with Mariano Barbacid

Case Study: Response to VS-6766 + Defactinib in a Patient with KRAS G12V mutant NSCLC

May 2019: Diagnosed with NSCLC

June 2019 - Sept 2019: Treated with first line Carboplatin + Pemetrexed + Pembrolizumab

Oct 2019: Progression, palliative RT to right hip

Nov 2019 – present: On treatment in FRAME study VS-6766 + Defactinib

Pre-treatment Oct 2019



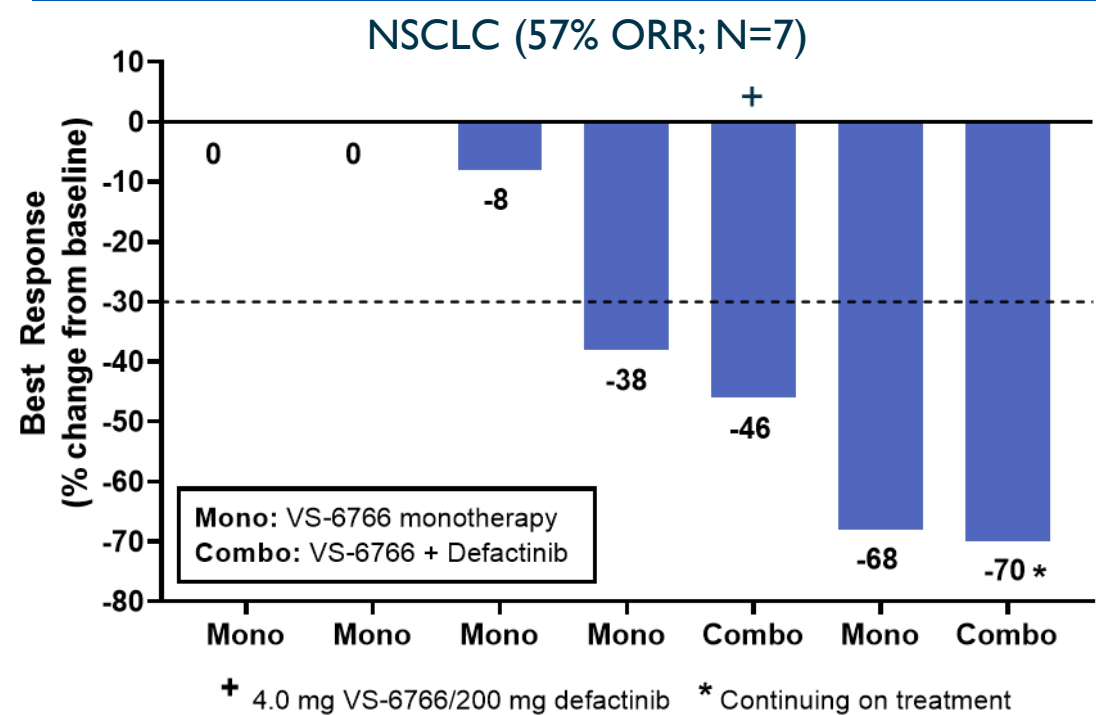
VS-6766 + Defactinib
On-treatment Feb 2021



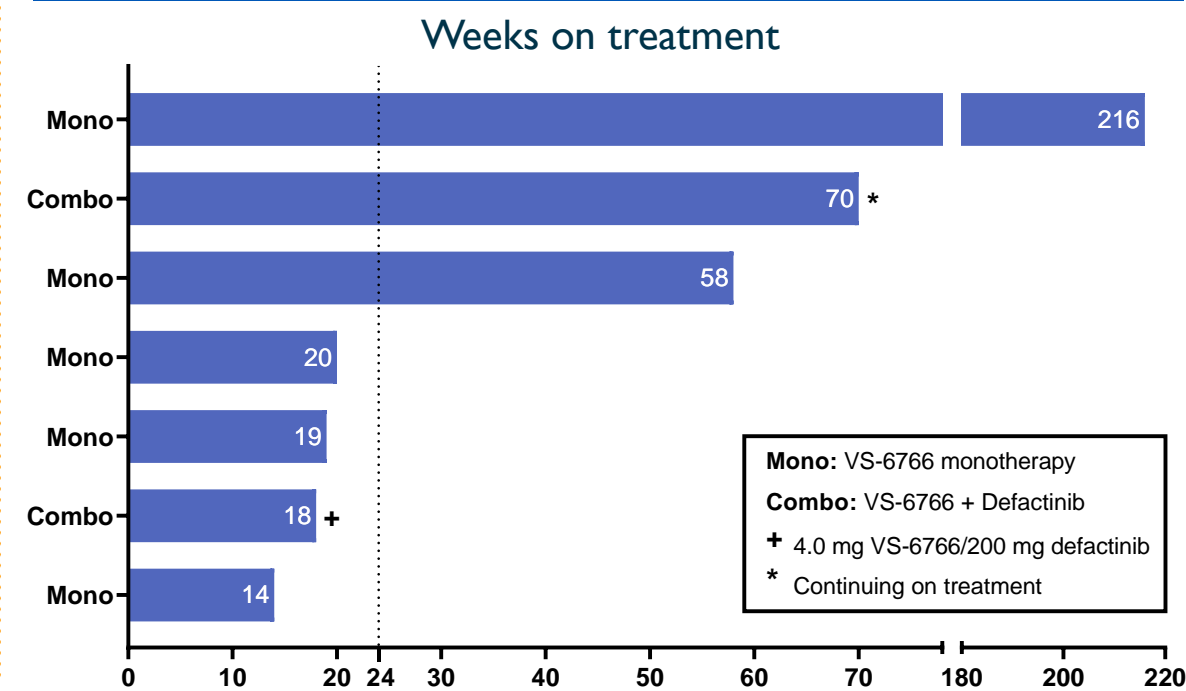
Strong Signal Identified in KRAS G12V NSCLC

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

Best Response by RECIST in KRAS G12V mt NSCLC

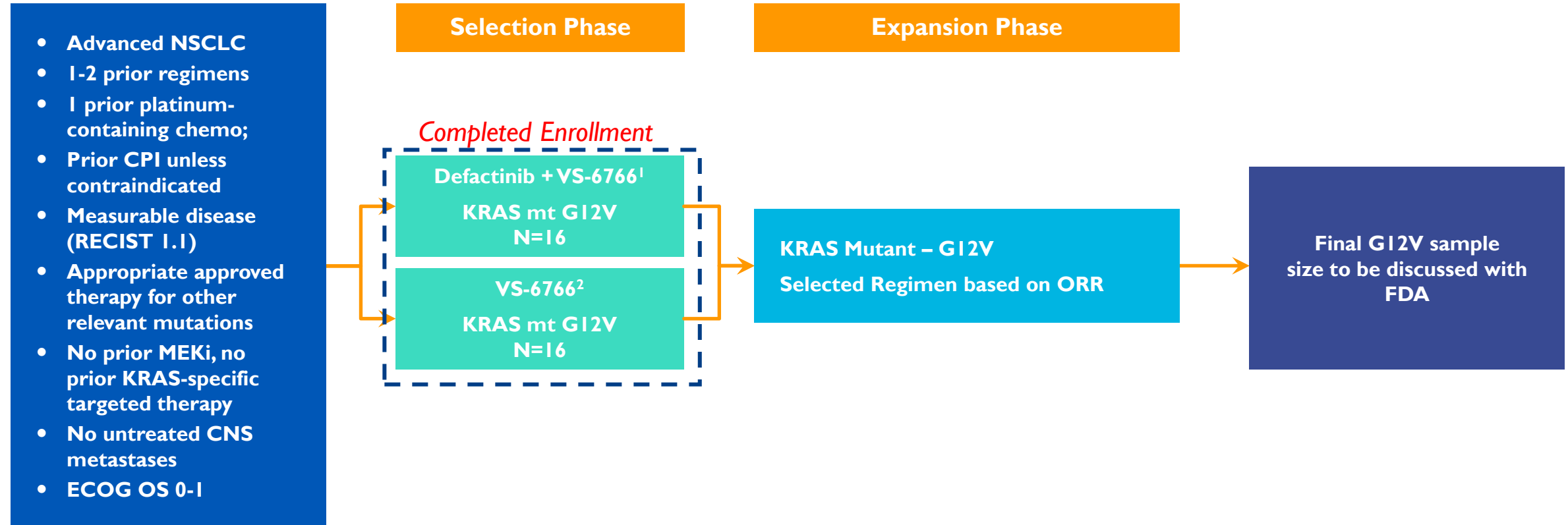


Time on Treatment for KRAS G12V mt NSCLC

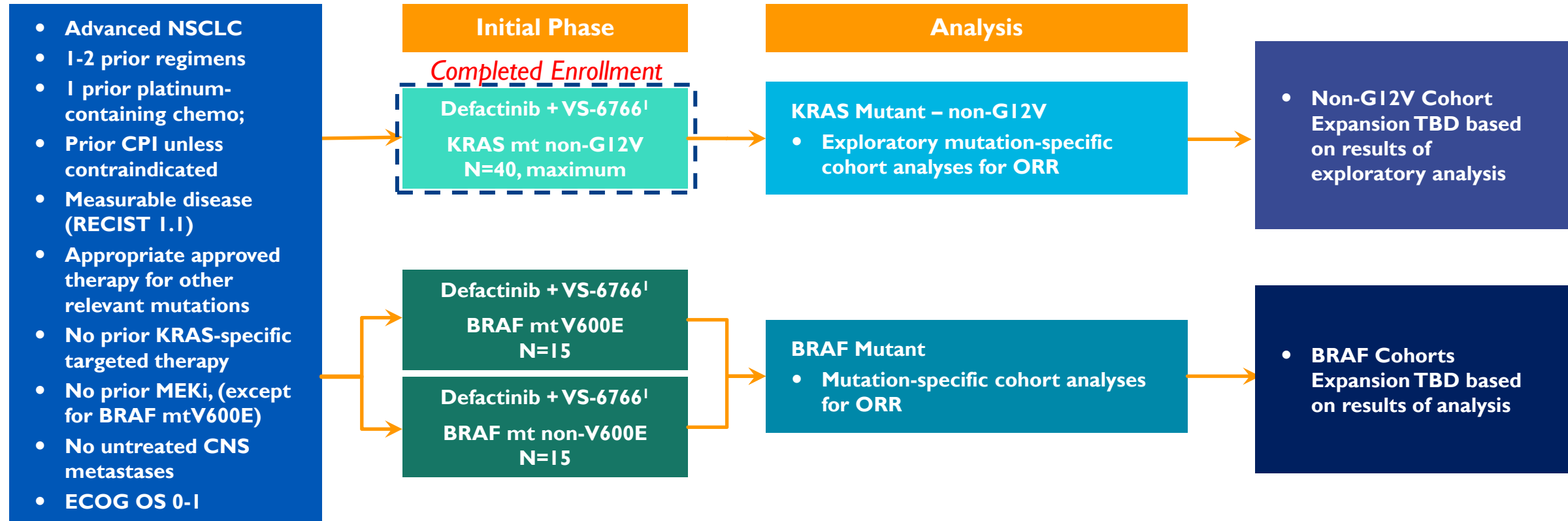


- Preclinical evidence suggests combination with Defactinib may improve efficacy in KRAS G12V mt NSCLC
- Activity of VS-6766 as a single agent and in combo with Defactinib in KRAS G12V mt NSCLC

RAMP 202: Registration-directed Phase 2 Trial of VS-6766 +/- Defactinib in Advanced NSCLC Primary Cohort: KRAS G12V mt NSCLC



RAMP 202: Additional Cohorts of VS-6766 + Defactinib in KRAS non-G12V mt & BRAF mt NSCLC



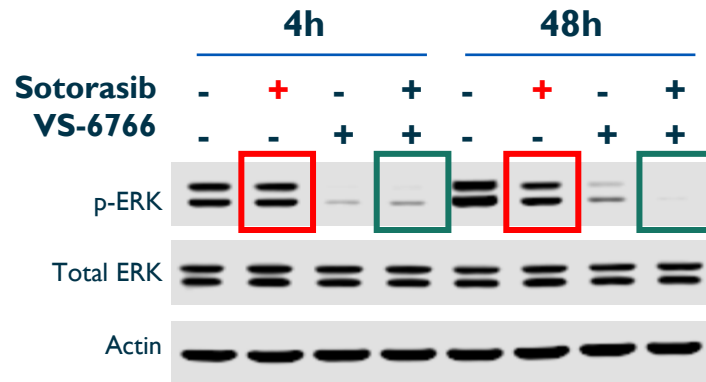
Preclinical Synergy of VS-6766 + G12C Inhibitors in KRAS G12C mt Models

Synergy of VS-6766 + G12C inhibitors across G12C mutant NSCLC, CRC & Pancreatic cancer cell lines

Cell line	Indication	Sensitivity to G12C inhibitors	Combined Synergy Score	
			VS-6766 + sotorasib	VS-6766 + adagrasib
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 + sotorasib yields deeper and more sustained inhibition of ERK signaling pathway



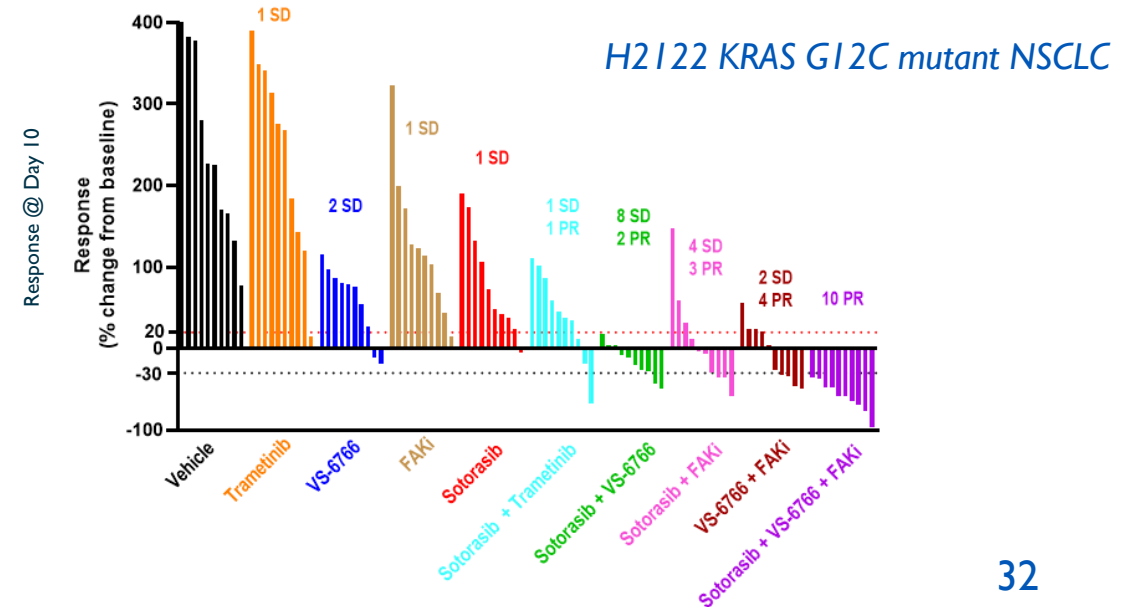
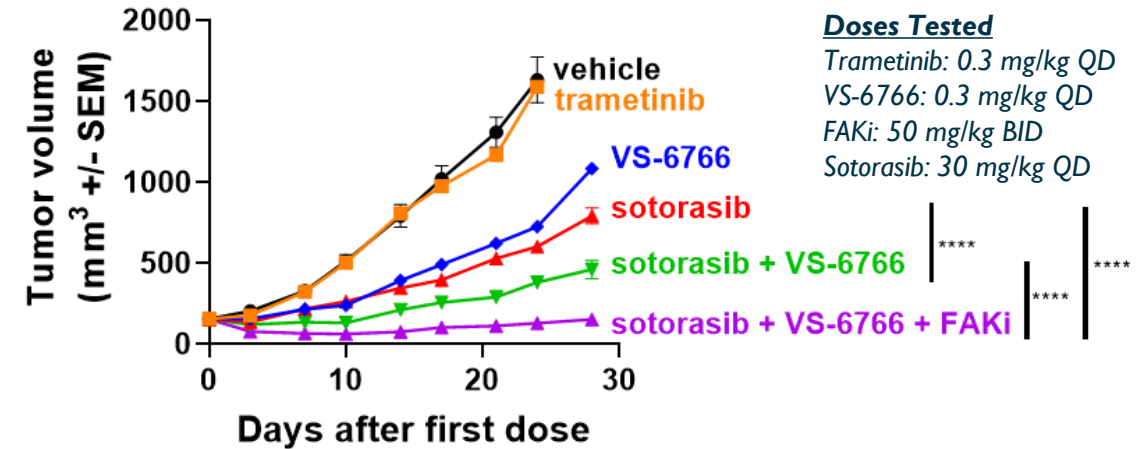
H2122 KRAS G12C mutant NSCLC

Concentrations Tested

Sotorasib: 100 nM

VS-6766: 100 nM

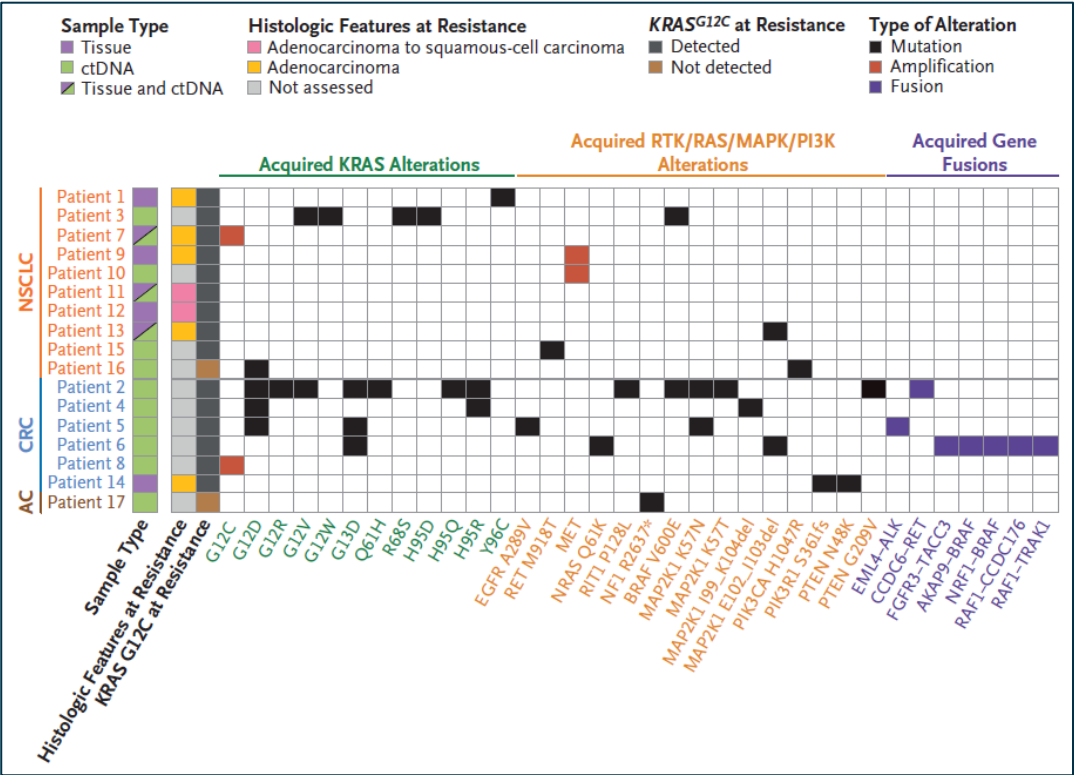
VS-6766 & FAKi potentiate sotorasib efficacy in KRAS G12C mutant NSCLC in vivo; Tumor regression in all mice with triple combination



Acquired Resistance Mechanisms to KRAS G12Ci Treatment in Patients

Further Support Combination of KRAS G12Ci with VS-6766

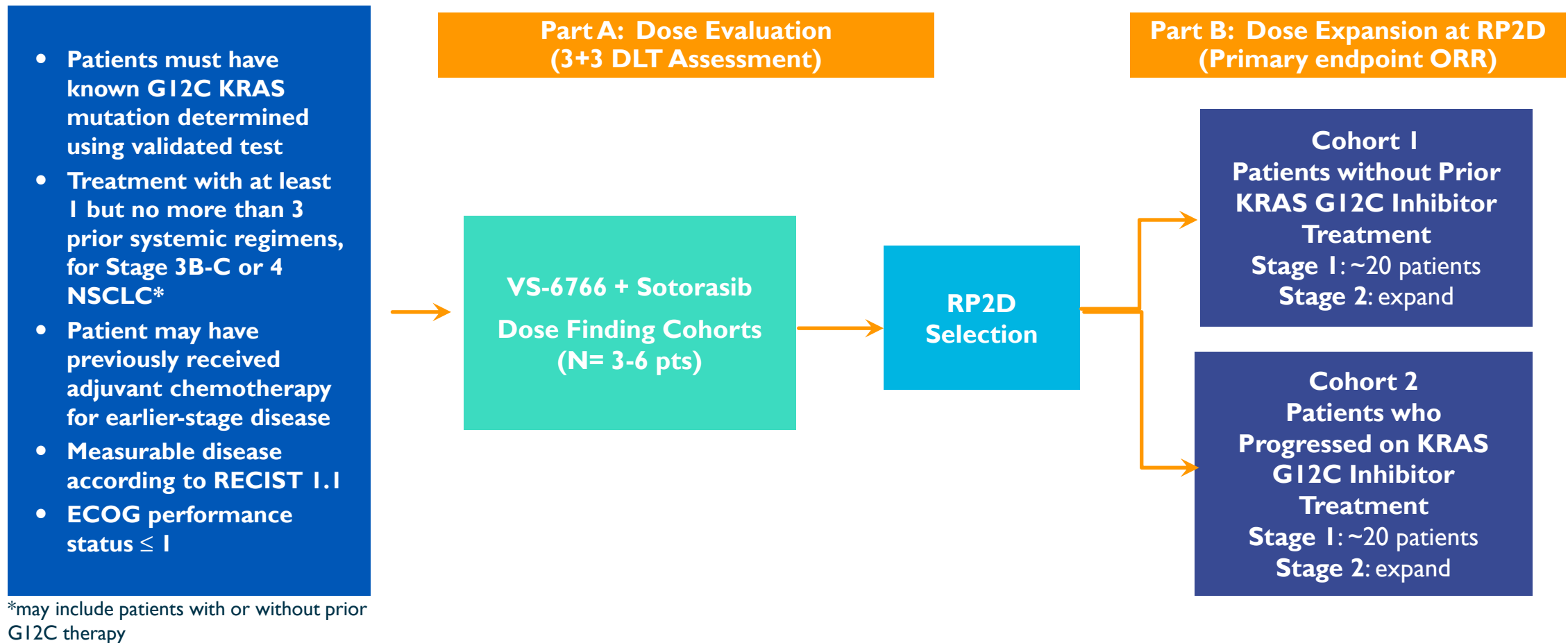
Summary of Putative Mechanisms of Acquired Resistance to Adagrasib Treatment



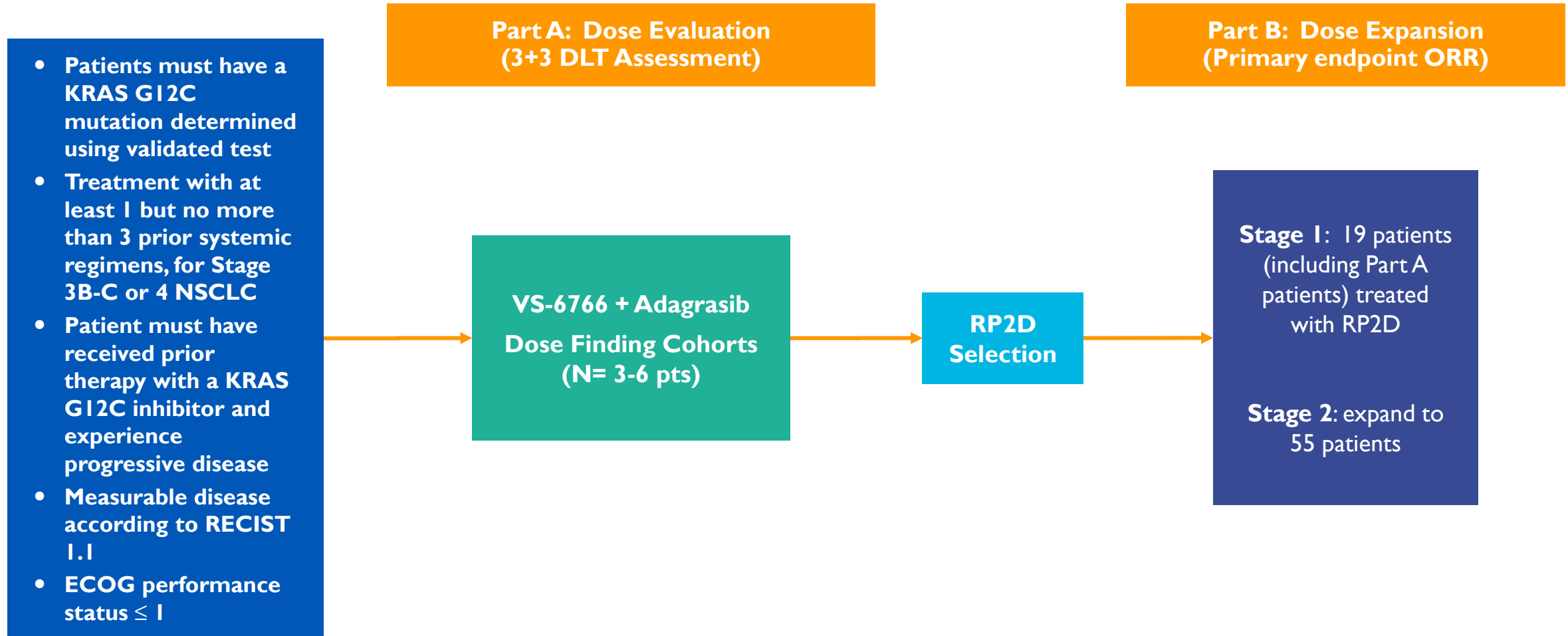
- Mechanisms of acquired resistance to KRAS G12Ci adagrasib treatment in patients recently reported^{1,2}
- The main resistance alterations occurred in
 - RTK mts or amplifications
 - KRAS mts or amplification
 - NRAS mt
 - BRAF V600E mt, BRAF or CRAF fusions
 - MAP2KI (MEK1) mt/deletion
- VS-6766 has shown activity against these KRAS, NRAS, BRAF and CRAF modifications

Cell Line	IC50 (nM)		
	Sotorasib	Adagrasib	VS-6766
G12C	29	3	14
G12D	435	382	7
G12C/R68S	157	85	13
G12C/H95D	11	235	10
G12C/Y96C	438	216	4

RAMP 203: Phase I/2 Trial of VS-6766 + LUMAKRAS™ (sotorasib) in KRAS G12C-mutated Advanced NSCLC



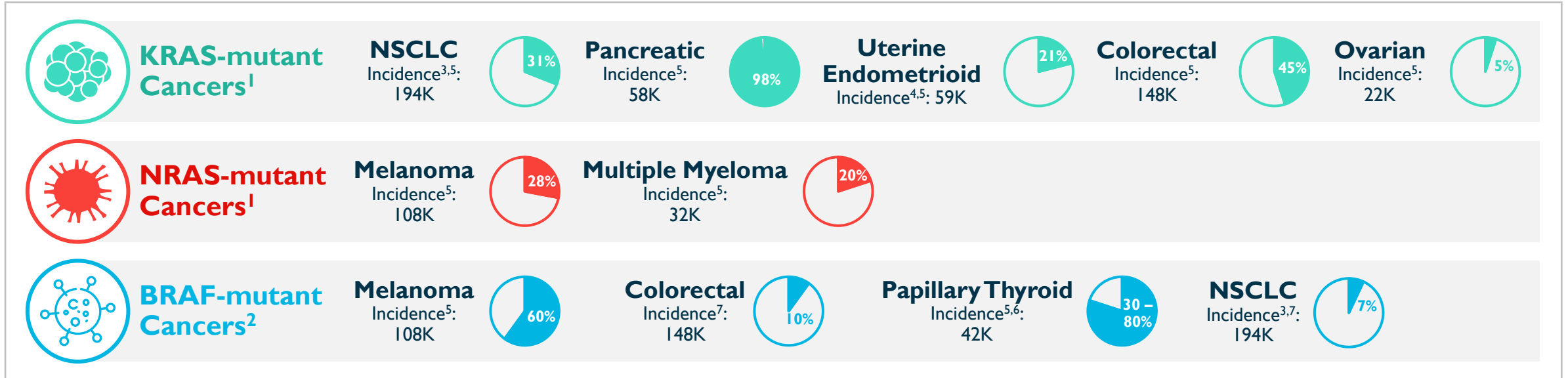
RAMP 204: Phase I/2 Trial of VS-6766 + Adagrasib in KRAS G12C-mutated Advanced NSCLC





Future Opportunities: VS-6766 as Backbone of RAS Therapy

High Unmet Needs in RAS/RAF/MEK/ERK-Driven Cancers



Breadth of potential opportunity

- 30% of all human cancers are driven by mutations of the RAS family of genes⁶

Established prognostic significance

- Patients with mutations of the RAS family have an overall worse prognosis

Challenges with conventional approaches

- Modest progress; limited number of approved therapies
- Single agent therapies (e.g., MEK inhibitors) associated with resistance
- Tolerable combination regimens with MEK inhibitors have been challenging
- Current RAS inhibitors in development address only a minority of all RAS mutated cancers

Incidence References:

¹Reference for RAS mt frequencies – Cox et al. *Nature Reviews* 13: 828, 2014; ²Reference for BRAF mt frequencies – Turski et al. *Mol Cancer Ther* 15: 533, 2016

³85% of lung cancer is NSCLC (Lu et. al. *Cancer Manag Res*. 2019); ⁴90% of all uterine cancers are of the endometrial type (ACS); ⁵Cancer Statistics 2020, Siegel et. al. *CA Cancer J Clin* 2020;70:7-30; ⁶8 out of 10 thyroid cancers are of the papillary type (ACS)⁷CbioPortal

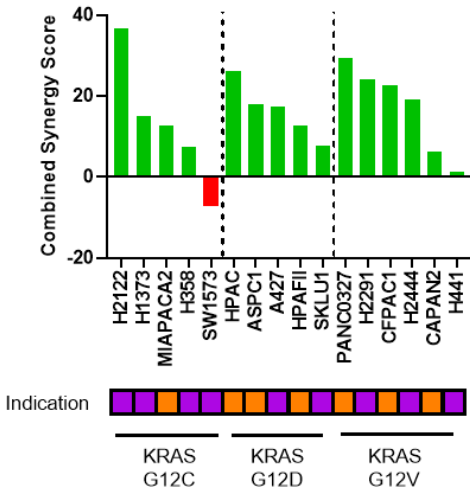
References:

McCormick F *Clin Cancer Res* 15April2015; ⁶Adderley H et al. *EBioMedicine* 01Mar2019; Papke B et al. *Science* 17Mar2017; Ryan M et al. *Nature Reviews Clinical Oncology* 01Oct2018; NIH cancer.gov/research/key-initiatives/ras

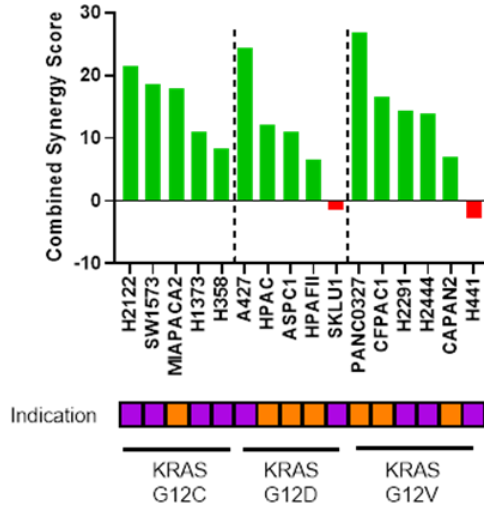
Preclinical Synergy of VS-6766 in Combination with Promising Agents for Clinical Investigation

Vertical MAPK Pathway Inhibition

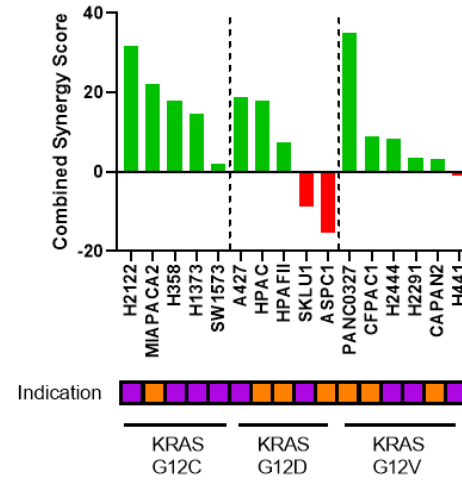
VS-6766 + pan-HERi (Afatinib)



VS-6766 + SHP2i (RMC-4550)

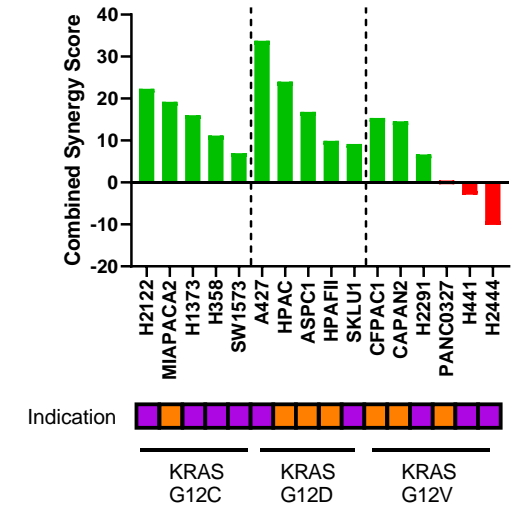


VS-6766 + SOS1i (BI-3406)

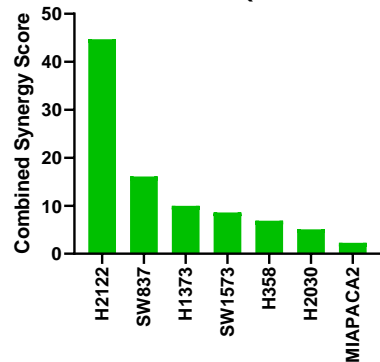


Parallel Pathway Inhibition

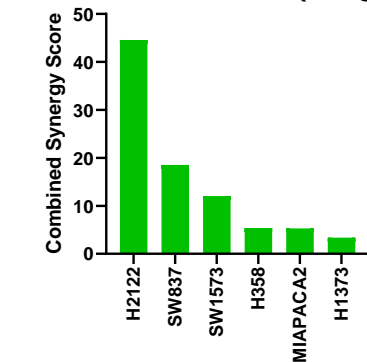
VS-6766 + CDK4/6i (Palbociclib)



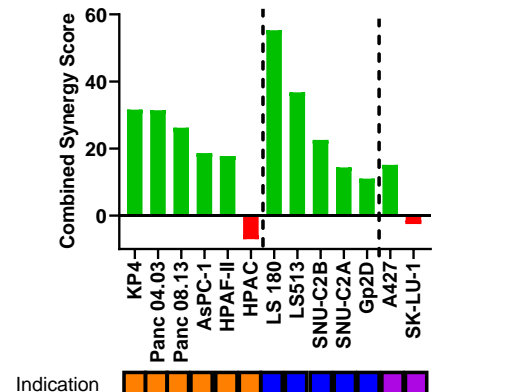
VS-6766 + G12Ci (sotorasib)



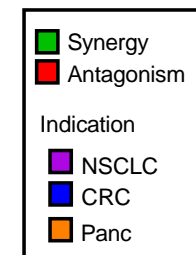
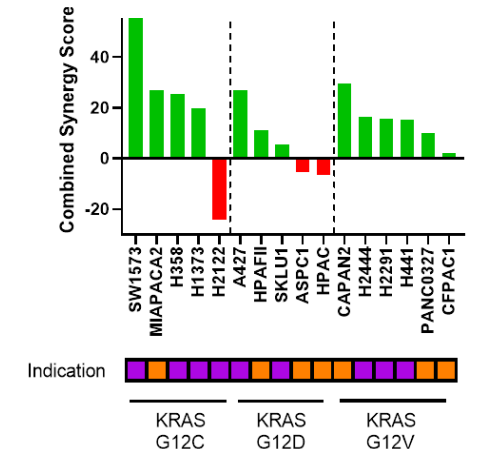
VS-6766 + G12Ci (adagrasib)



VS-6766 + G12Di (MRTX1133)



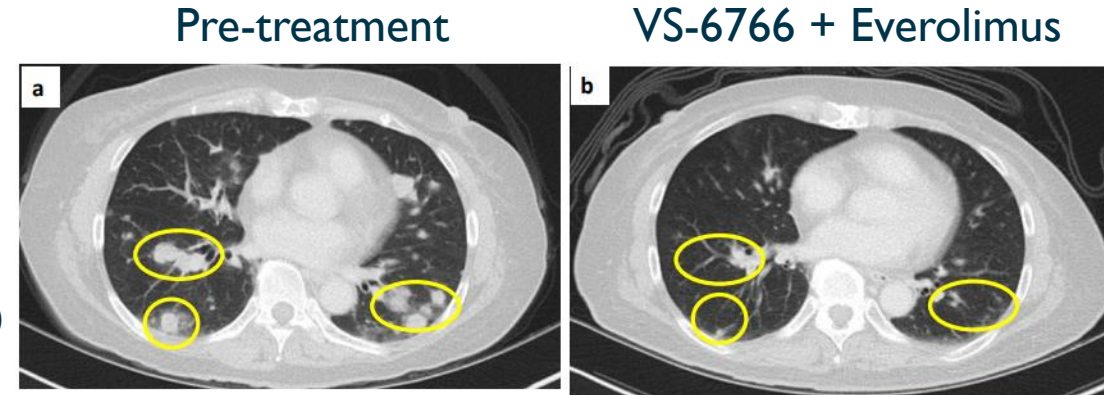
VS-6766 + mTORi (Everolimus)



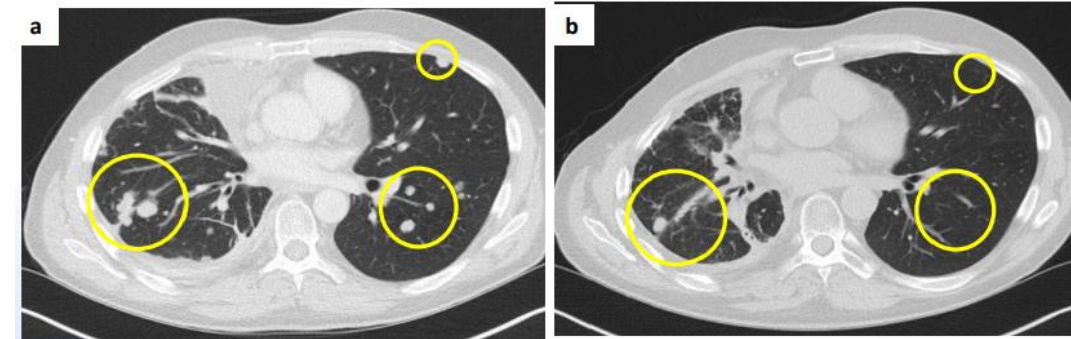
VS-6766 + Everolimus Clinical Data Presented at ASCO

- Well-tolerated RP2D established for VS-6766 + everolimus with intermittent dosing of both agents (twice weekly; 3 wks on/1 wk off)
 - No DLTs reported at RP2D
- VS-6766 + everolimus combo induced PRs in patients with various RAS mutations in NSCLC, LGSOC and thyroid cancers
- Both LGSOC pts showed PRs with 69% and 79% reduction and have been on treatment for ≥3 years with treatment ongoing
- KRAS mutant NSCLC expansion cohort is currently ongoing – expanding to 20 pts
 - Currently 2 PRs/11
 - Median progression free interval of 6.25 months in heavily pre-treated patients

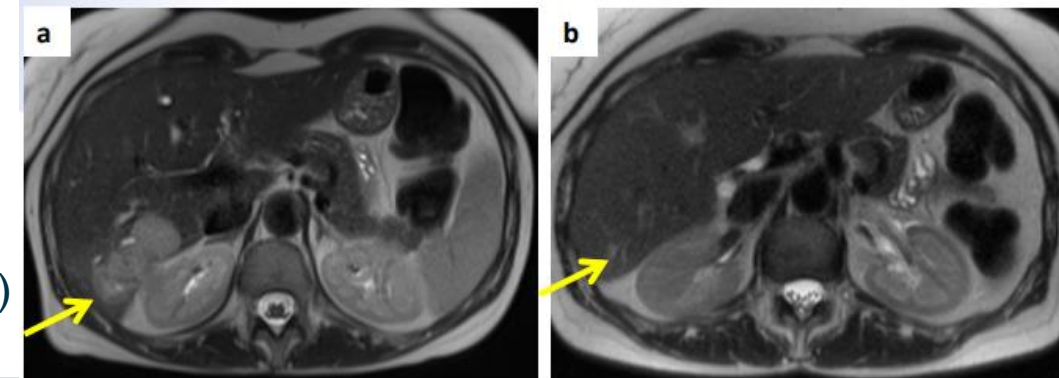
NRAS Q61K
Anaplastic
thyroid cancer
(lung metastasis)



KRAS G13A
NSCLC

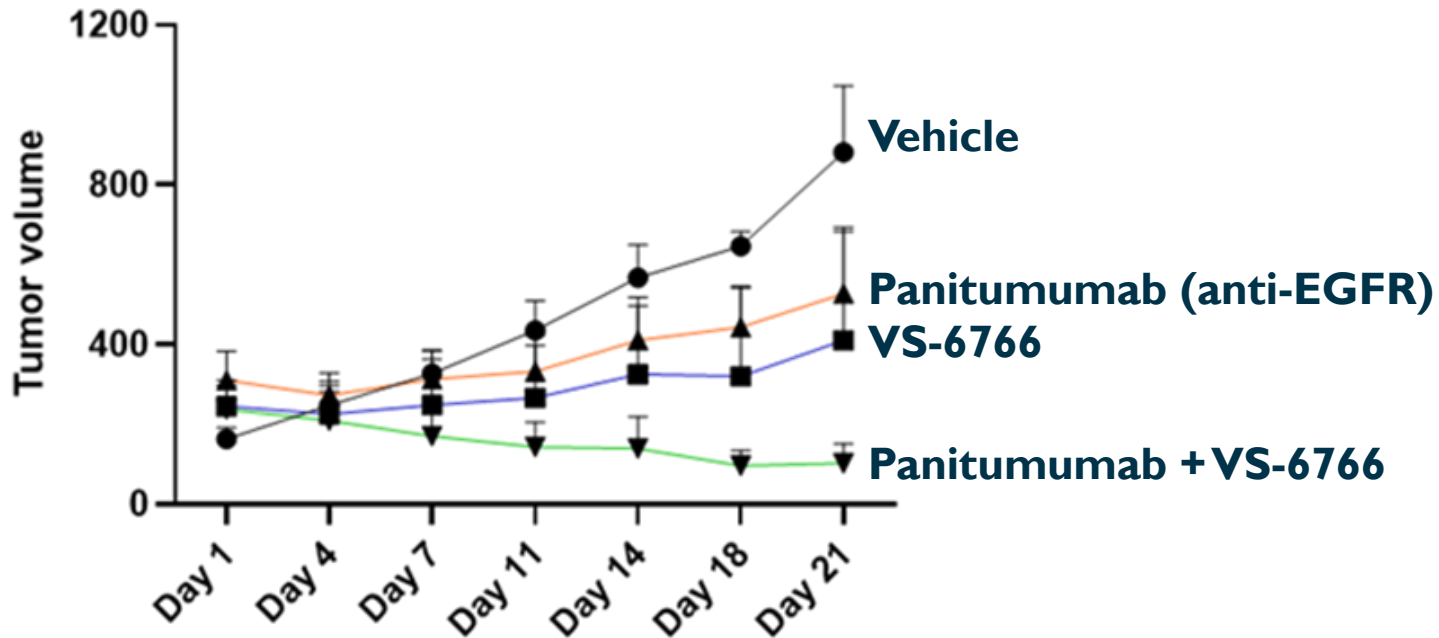


KRAS G12D
LGSOC
(liver metastasis)



Combination of VS-6766 with anti-EGFR mAb Induces Tumor Regression in a KRAS mt Colorectal PDX Model

KRAS^{G12V} CRC PDX



- 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 (cetuximab) for treatment of KRAS mt CRC (NCT05200442)**

Backup Slides

Verastem Oncology Strategic Transformation



**Q1 2020: In-licensed global rights to VS-6766, best-in-class RAF/MEK inhibitor, from Chugai
PIPE financing based on data for new clinical program**



Q3 2020: Divested global rights to Copiktra to Secura Bio



**Q4 2020: Initiated registration-directed ph. 2 study in LGSOC
Initiated registration-directed ph. 2 study in NSCLC**



Q1 2021: LGSOC study updated to include KRAS wild type patients



**Q2 2021: FDA Breakthrough Therapy Designation granted for VS-6766 + Defactinib in
LGSOC**



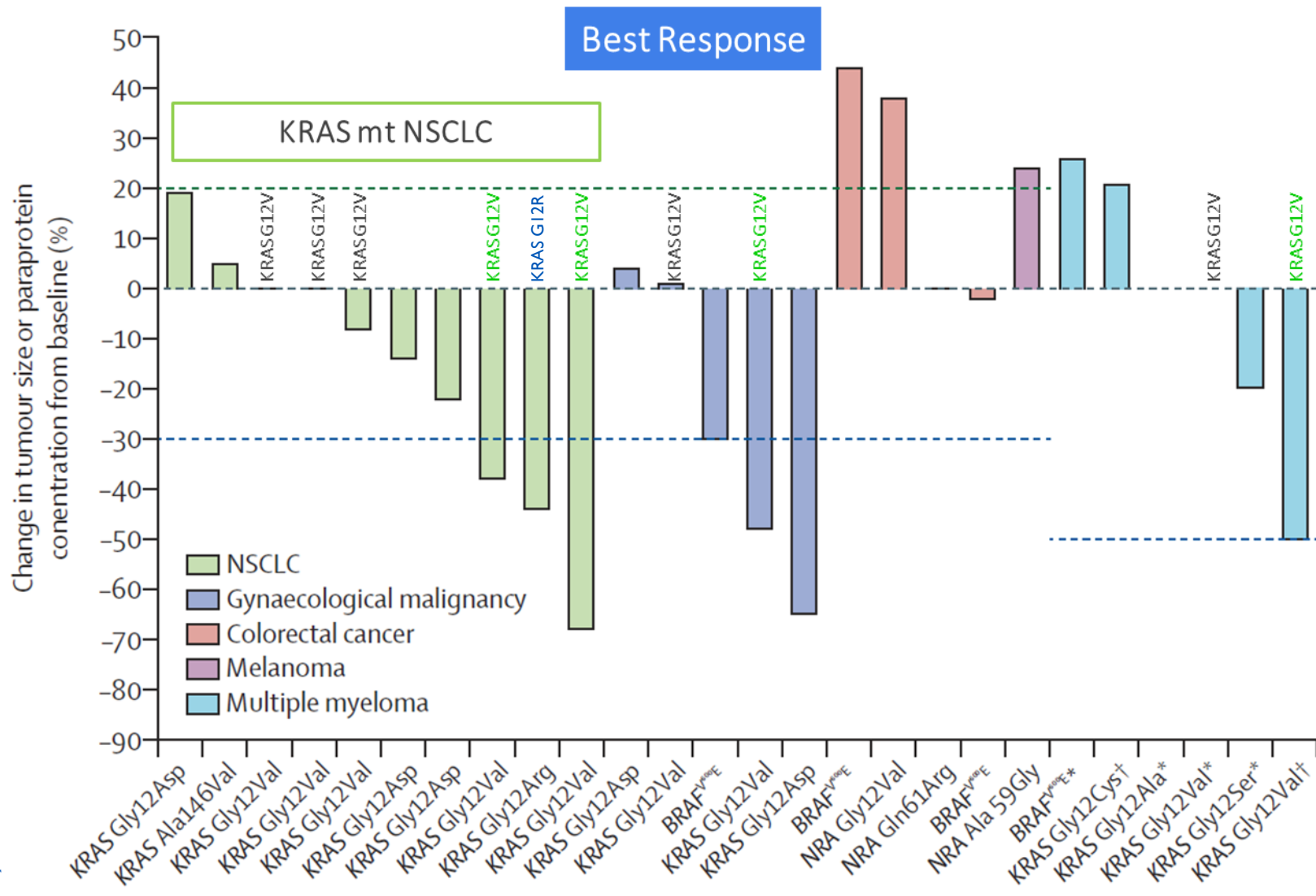
**Q3 2021: Remaining outstanding debt retired
VS-6766 + sotorasib Collaboration agreement with Amgen**



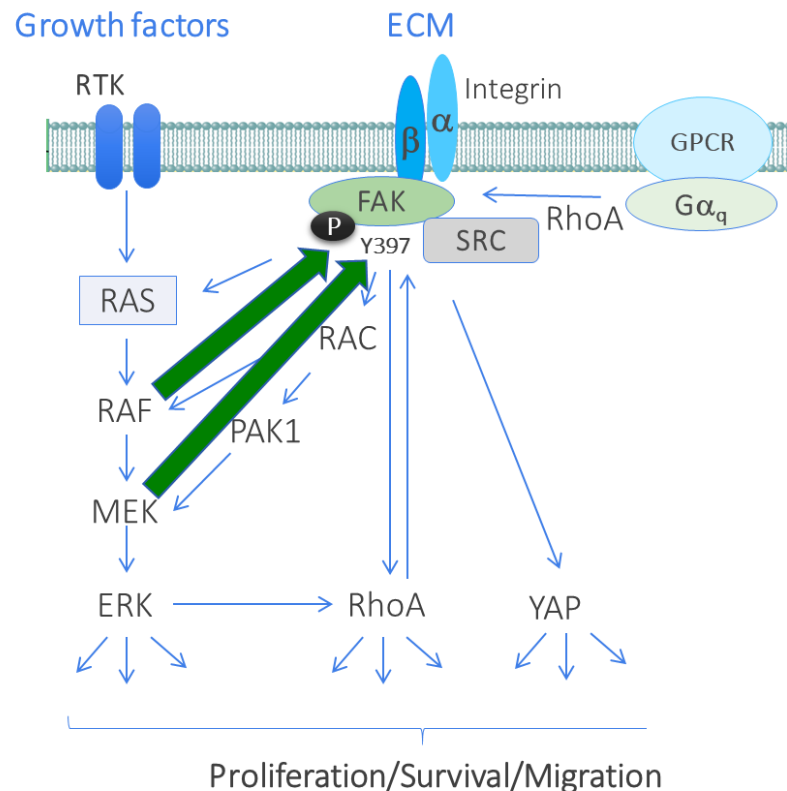
Q4 2021: VS-6766 + adagrasib Collaboration agreement with Mirati

VS-6766 Monotherapy Has Shown Clinical Activity in Several RAS/RAF Mutant Cancer Indications, Including NSCLC and Gynecologic Cancers

Confirmed responses especially in patients with KRAS G12V mutation

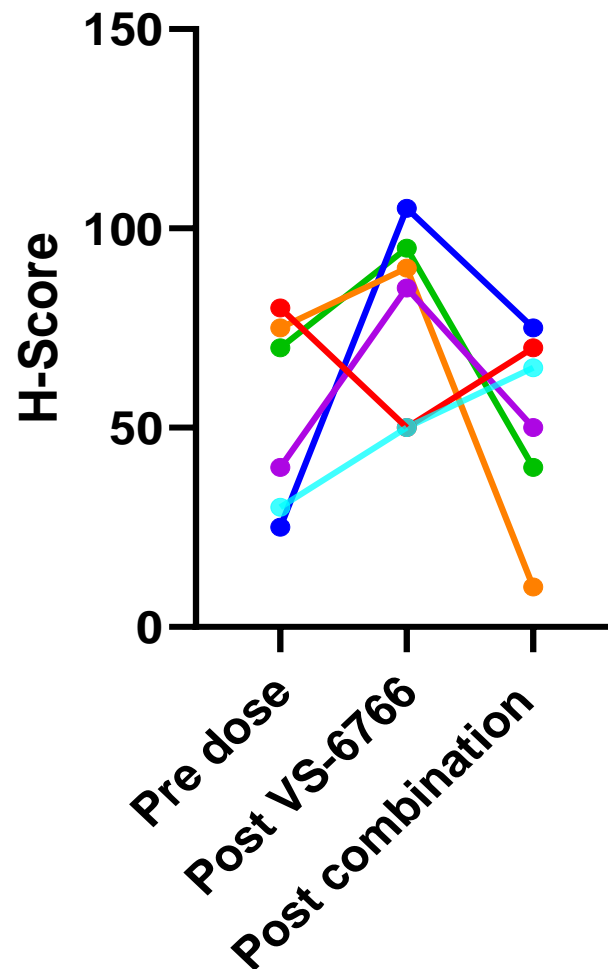


Overcoming Key Resistance Mechanisms to MEK Inhibitors



**➡ = Feedback
Reactivation**

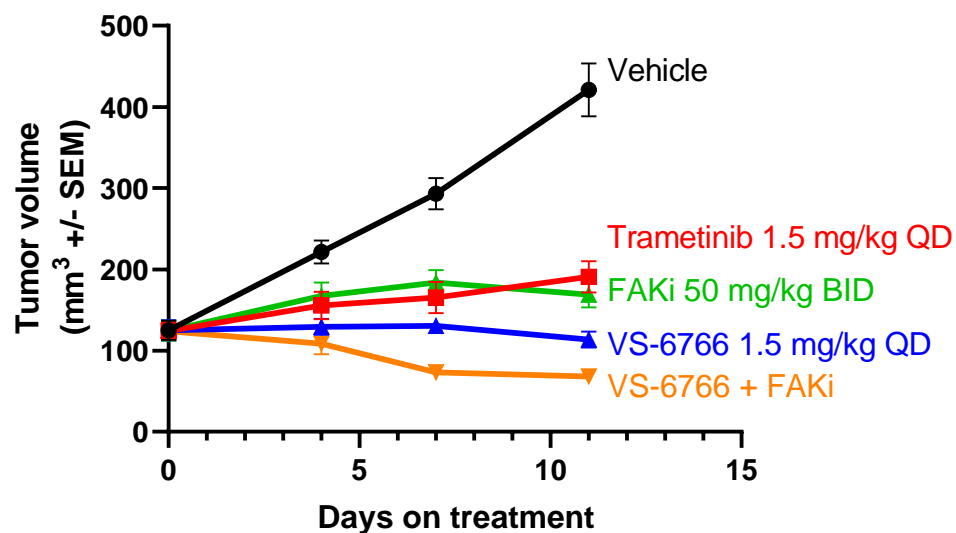
p-FAK



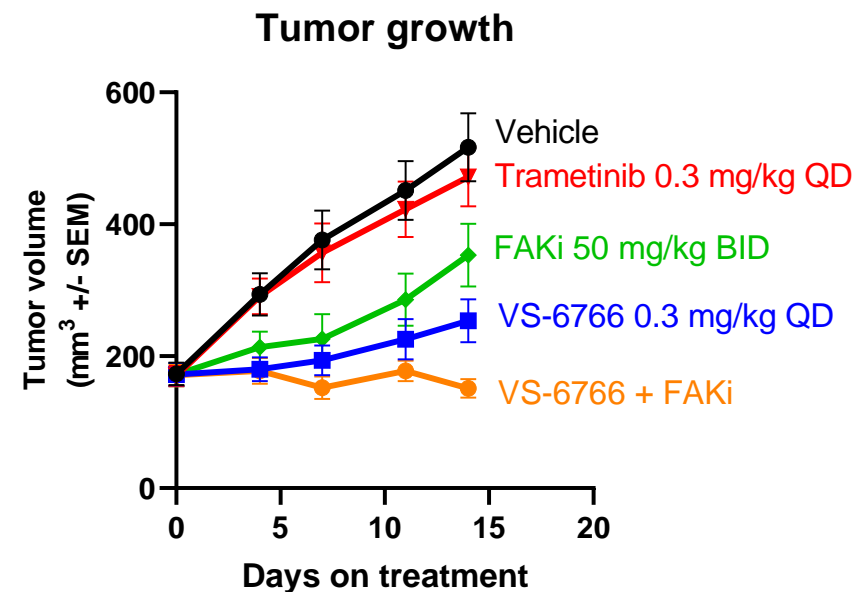
- **MEK inhibition induces compensatory activation of pFAK preclinically and clinically**
 - Trametinib induced ↑ pFAK (Y397) preclinically in KRAS mt NSCLC cell lines
 - **Also observed in patients**
 - **VS-6766 induced ↑ pFAK (Y397) as a potential resistance mechanism in the majority of patients**
 - **Combination with defactinib reduced this compensatory pFAK signal**

VS-6766 and FAK Inhibitor Combination Leads to More Robust Anti-Tumor Efficacy in vivo

KRAS^{mt} Ovarian TOV-21G *in vivo* Model¹



KRAS^{mt} NSCLC H358 *in vivo* Model²



Pharmacokinetic Profiles of VS-6766 + Defactinib in Combination Similar to that Seen in Single Agent Studies

VS-6766

Cohort	Dose (mg)	N	Subject	AUC _{0-24h} (h*ng/mL)	C _{max} (ng/mL)
I	3.2 (with 200mg VS)	3	Mean	6179	354
			CV%	32.1	30.4
2a	4 (with 200mg VS)	5	Mean	5353	289
			CV%	15.8	16.0
2b	3.2 (with 400mg VS)	1	FRA101-007	3302	229

Defactinib

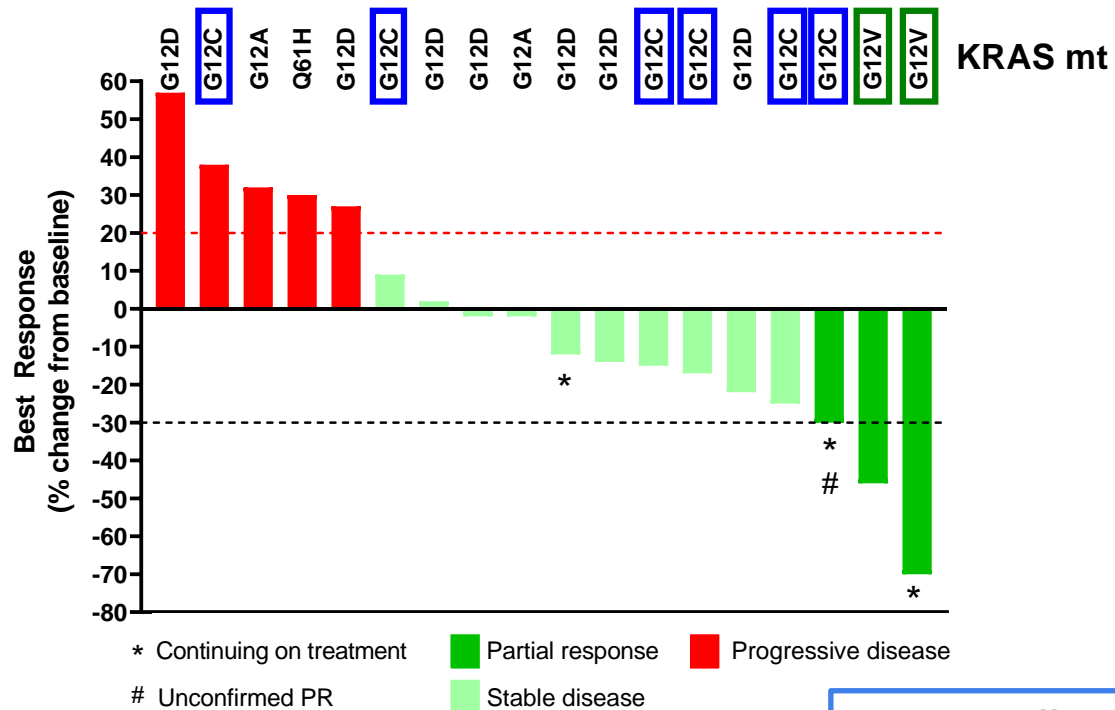
Cohort	Dose (mg)	N	Subject	AUC _{last} (h*ng/mL)	C _{max} (ng/mL)
I	200 (with 3.2mg RO)	3	Mean	2071	273
			CV%	103	80
2a	200 (with 4mg RO)	5	Mean	2252	318
			CV%	124	117
2b	400 (with 3.2mg RO)	3	Mean	2807	360
			CV%	31	32

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

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

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

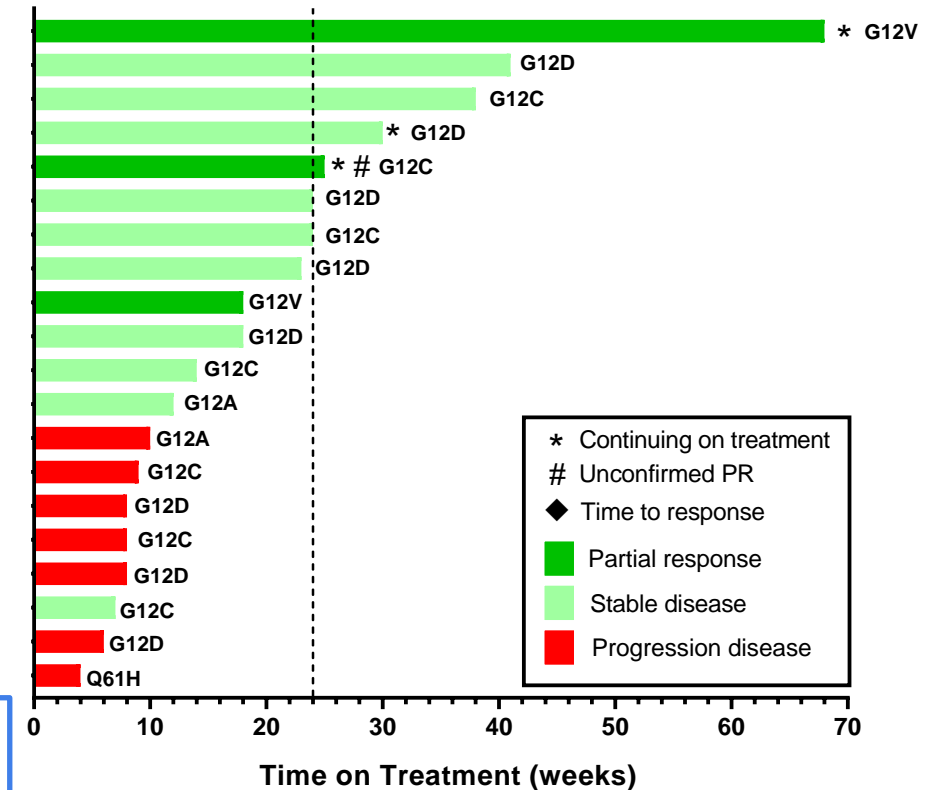
Best response by RECIST in KRAS mt NSCLC



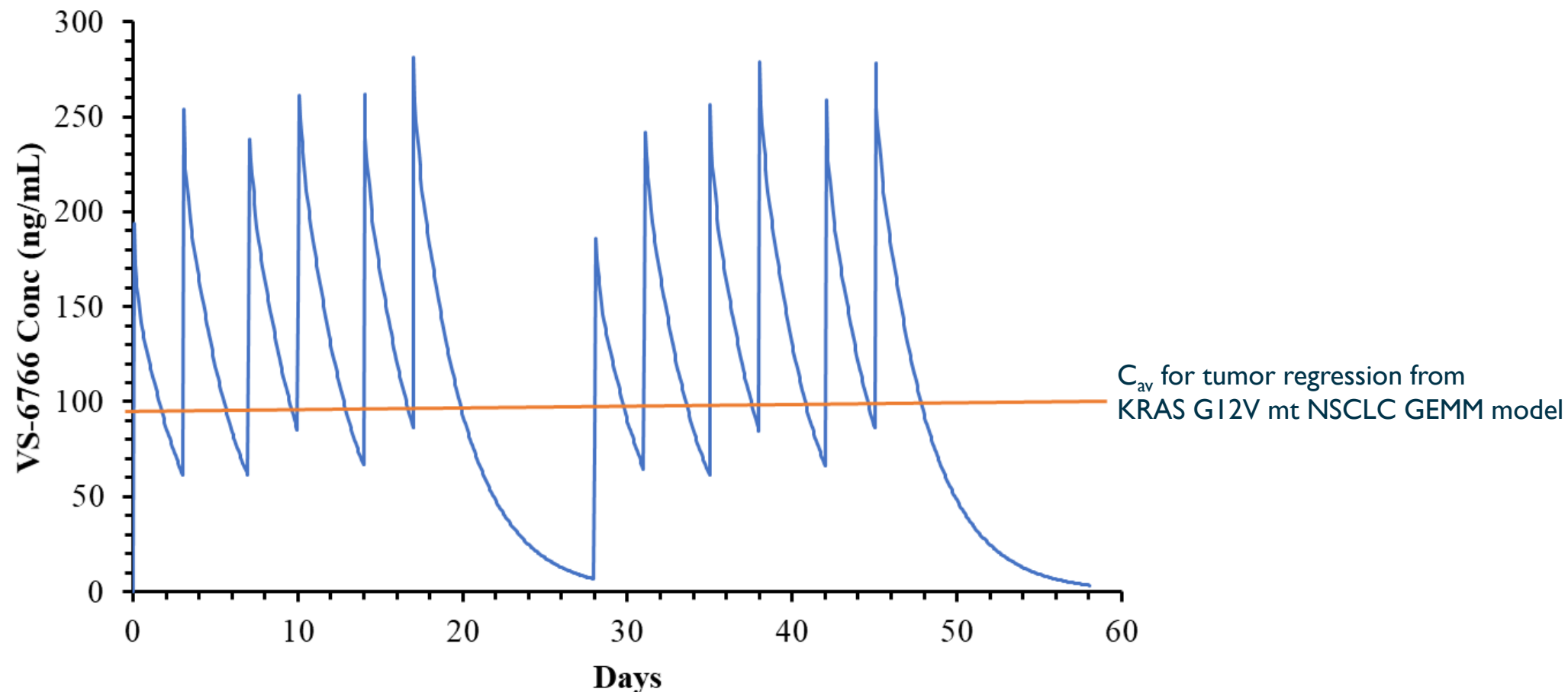
Data cut off March 5, 2021

- 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

Time on Treatment

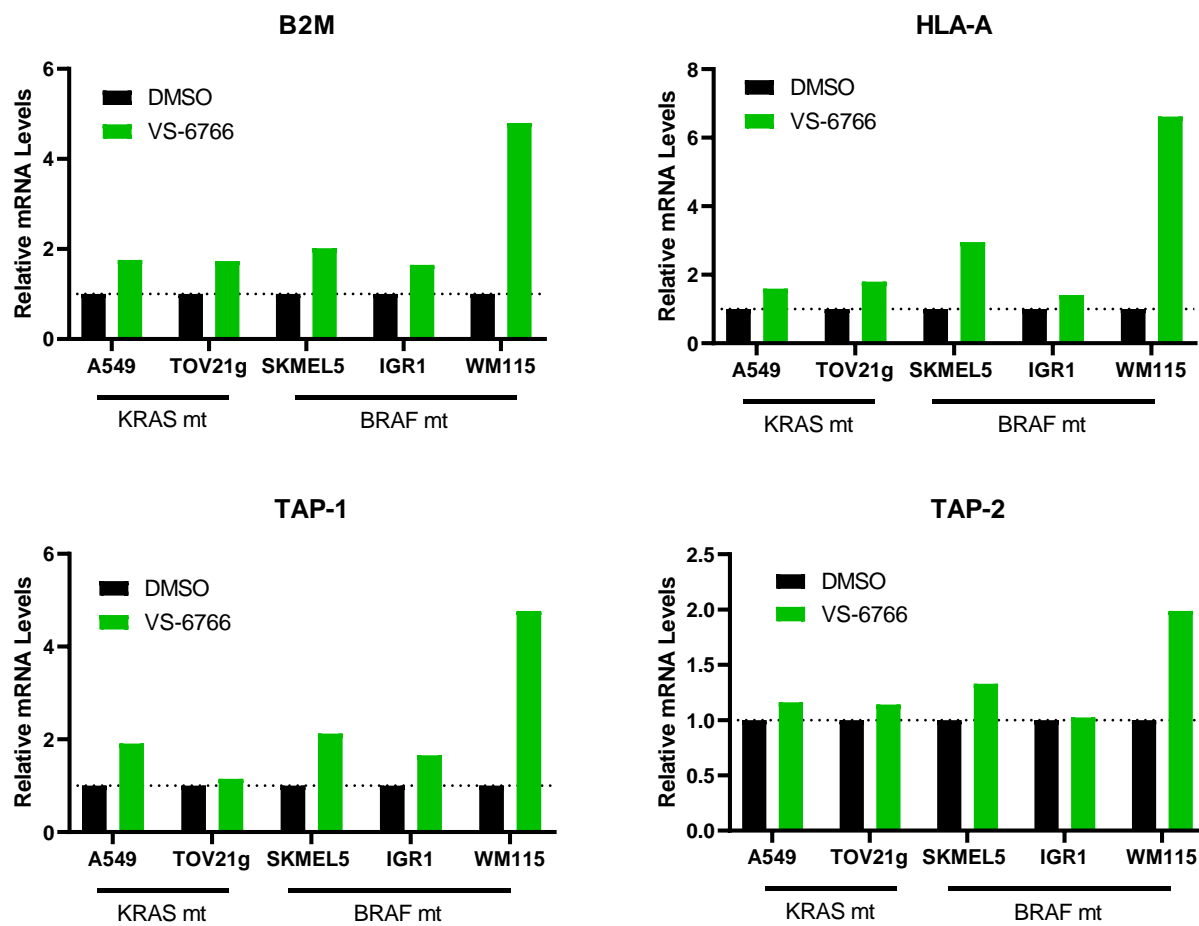


Target Exposure for Preclinical Tumor Regression is Covered by Twice Weekly Dosing of 4 mg VS-6766 3 wks on/1 wk off



- 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

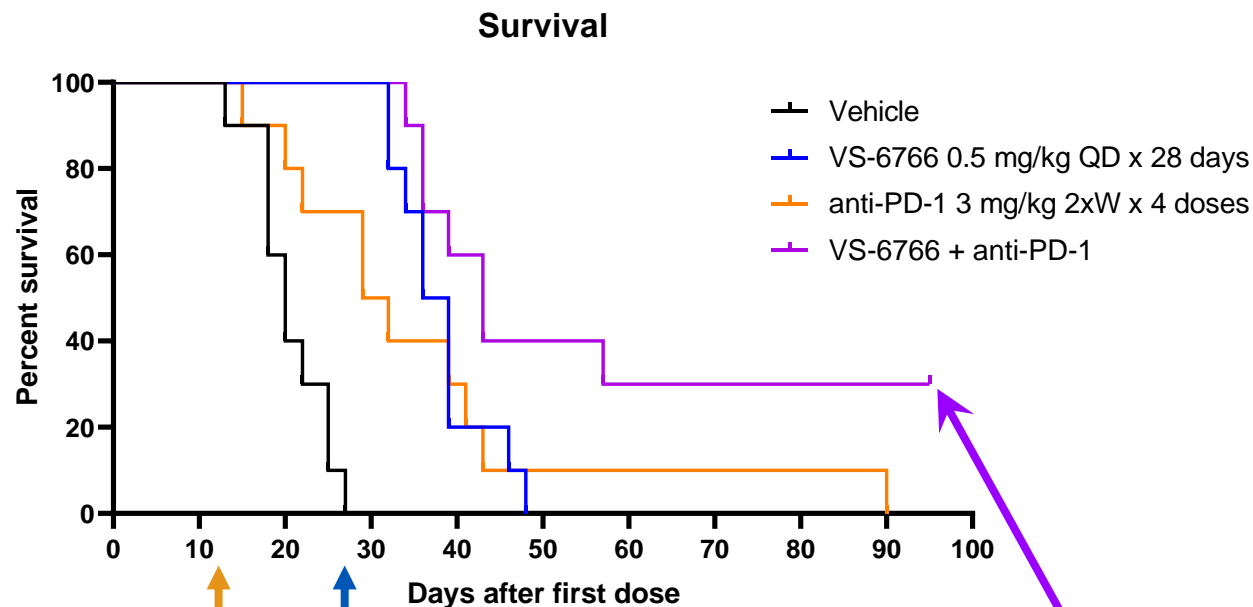
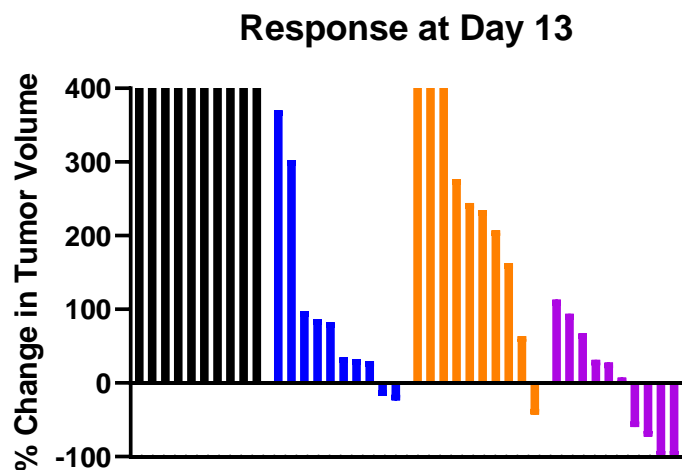
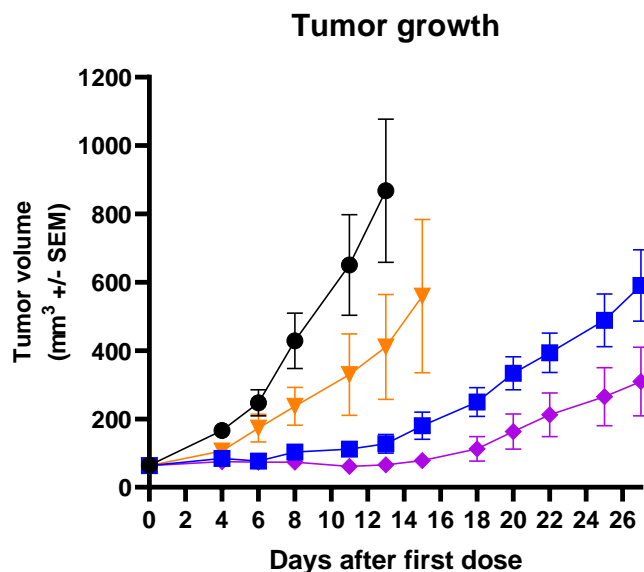
VS-6766 Upregulates MHC Class I Antigens on Tumor Cells: a mechanism for potentiation of I/O efficacy



Cell Line	Tumor type	RAS/RAF mutation status
A549	Lung	KRASmt G12S
TOV21g	Ovarian	KRASmt G13C
SKMEL5	Melanoma	BRAFmt V600E
IGR-I	Melanoma	BRAFmt V600E
WM115	Melanoma	BRAFmt V600E

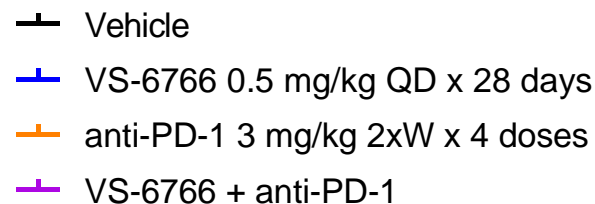
VS-6766 @ 1 μ M (except SKMEL5 and IGR-I, 300 nM)

VS-6766 Enhances Tumor Growth Inhibition when Combined with Anti-PD-1 in the CT26 KRAS (G12D) Syngeneic Model



Day 11,
Last dose
anti-PD-1

Day 28,
Last dose
VS-6766



Tumor re-challenge in tumor-free mice showed immune memory with increased memory T cells

Strong Patent Protection

- COM for VS-6766 to 2027 & defactinib to 2028, Hatch Waxman should extend to 2032
- VS-6766 intermittent dosing regimen until 2038
- FAK/MEK combination to 2035
- VS-6766/defactinib combination until 2040 if granted
- Method of manufacture for VS-6766 to 2032
- Other activity related to patent protection is ongoing and will continue into the future

Experienced Senior Management Team



Brian Stuglik
Chief Executive Officer

- Global VP & Chief Marketing Officer – Lilly Oncology
- Founding Member – Proventus Health Solutions



Daniel Paterson
President and Chief Operating Officer

- CEO – The DNA Repair Co. (now On-Q-ity)
- PharMetrics (now IMS), Axion



Rob Gagnon
Chief Business and Financial Officer

- CFO – Harvard Bioscience, Clean Harbors
- VP of Finance – Biogen Idec



Cathy Carew
Chief Organizational Effectiveness Officer

- Principal – HR Collaborative
- Ironwood, ActiveBiotics, Dynogen, Tufts Health Plan



Jonathan Pachter, Ph.D.
Chief Scientific Officer

- Head of Cancer Biology – OSI (now Astellas)
- Schering-Plough



Louis Denis, M.D.
Chief Medical Officer

- CMO, Asana BioSciences
- Boehringer-Ingelheim, Pfizer



Hagop Youssoufian, MSc, M.D.
Head of Medical Strategy

- CMO, BIND Therapeutics, EVP, Progenics,
- CMO & EVP, Ziopharm Oncology, SVP, Imclone



THANK YOU