VERASTEM ONCOLOGY

Corporate Presentation

November 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 avutometinib (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	Avutometinib (VS-6766; RAF/MEK clamp) and defactinib (FAK inhibitor) are clinically active against RAS mutant cancers
Rapid development path to market	**FDA Breakthrough Therapy Designation in LGSOC;** Registration-directed trial initiated in 4Q 2020 in low-grade serous ovarian cancer (LGSOC)
Significant downstream market opportunity and blockbuster potential	**30% of all human cancers are driven by mutations in RAS**; Avutometinib combinations potentially broadly applicable across a variety of tumor types. **Clinical collaborations with Amgen & Mirati** evaluating the combinations of avutometinib with sotorasib & adagrasib, respectively, in KRAS G12C NSCLC supported by strong pre-clinical rationale **Multiple clinical opportunities** across RAS pathway-driven cancers based on preclinical data
Patent Update	Recently issued intermittent dosing IP for both avutometinib alone and avutometinib + defactinib extends patent coverage up to 2038 and 2040
Strong balance sheet	Up to $150 million of non-dilutive funding available from new credit facility Cash balance of $104.0 million as of September 30, 2022 Company ended Quarter 3 2022 with $16.4 million non-GAAP operating expenses

* Q3 2022 GAAP operating expenses - $17.71M minus Q3 2022 stock compensation - $1.36M = $16.35M Q3 2022 non-GAAP operating expenses

Key VSTM Milestones 2021-2022

	1H2021	2H2021	1H2022	4Q2022
LGSOC	✓RAMP 201 Amended to Include KRAS wt patients in Selection Phase	✓Updated data from FRAME LGSOC cohort Presenting at ESMO	✓RAMP 201 Target enrollment of Selection Phase Complete Initiated enrollment of Expansion Phase	✓RAMP 201 Second Interim Update
	✓FDA Breakthrough Therapy Designation		✓ RAMP 201 Selection Phase Update	RAMP 201 FDA Meeting
			✓Translational data from FRAME LGSOC cohort presented at AACR	RAMP 201 Complete enrollment of Expansion Phase
NSCLC	✓Updated data from FRAME NSCLC cohort Presented at AACR	✓Avutometinib + Adagrasib Collaboration w/Mirati	✓ RAMP 202 Complete enrollment of Selection Phase	✓Initiate RAMP 204 (avutometinib + adagrasib) in KRAS G12C (Mirati)
			✓ Initiate RAMP 203 (avutometinib + sotorasib) in KRAS G12C (Amgen)	✓Top-Line Data from RAMP 202 Selection Phase
		✓Avutometinib + Sotorasib Collaboration w/Amgen	✓Top-Line Data from avutometinib + everolimus in KRAS mt*	Initial readout of RAMP 203 data
			✓RAMP 202 Amended to include BRAF mt cohorts	Initiate combo study of avutometinib + abemaciclib and fulvestrant in ER+ breast cancer*
Additional Indications			✓PanCAN Agreement Executed	Initiate basket trial of avutometinib + defactinib in RAS pathway-driven gynecological cancers*
				✓Initiate combo study of avutometinib + cetuximab in KRAS mt CRC*
				Initiate combo study of avutometinib + gemcitabine/nab-paclitaxel + defactinib in metastatic pancreatic cancer*

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*Investigator-sponsored research

Avutometinib 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, NF1 mt) and multiple solid tumor indications
- Strong preclinical combination data with other agents targeting RAS pathway and parallel pathways

Robust Clinical Program: Avutometinib in multiple combinations across RAS/MAPK pathway-driven tumors

INDICATION	REGIMEN	STUDY NAME	PRECLINICAL / PHASE 1 / PHASE 2 / PHASE 3	CLINICAL COLLABORATION WITH
LGSOC[1,2]	Avutometinib +/- defactinib	RAMP 201		
R/R LGSOC	Avutometinib + defactinib	FRAME		
R/R endometrioid cancer (RAS/RAF mt)	Avutometinib + defactinib	FRAME		
Gynecological Cancers (RAS Pathway-driven)[4]	Avutometinib + defactinib	IST		
Mesonephric[4]	Avutometinib + defactinib	IST		
R/R NSCLC (BRAF mt)	Avutometinib + defactinib	RAMP 202		
R/R NSCLC (KRAS G12C)	Avutometinib + sotorasib	RAMP 203		AMGEN
R/R NSCLC (KRAS G12C)	Avutometinib + adagrasib	RAMP 204		MIRATI THERAPEUTICS
Pancreatic Ductal Adenocarcinoma[3]	Avutometinib + gemcitabine/nab-paclitaxel + defactinib	RAMP 205		PANCREATIC CANCER ACTION NETWORK
R/R NSCLC (KRAS mt)	Avutometinib + everolimus (mTORi)	IST		
R/R Colorectal Cancer	Avutometinib + cetuximab (EGFRi)	IST		
ER+ Breast Cancer	Avutometinib + abemaciclib + fulvestrant	IST		

[1] FDA Breakthrough Therapy Designation
[2] Registration-directed trial
[3] In Startup
[4] Preclinical studies underway, ph. 2 investigator-sponsored trials in preparation

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Key Financial Statistics

As of and for the quarter ended September 30, 2022

Cash, cash equivalents & investments	$104.0M
Non-GAAP Operating Expenses	$16.4M
Shares Outstanding	210.1M

Oxford Finance LLC Credit Facility

Loan Tranches		Event
A	$25M	At closing
B	$15M	COPIKTRA PTCL approval in U.S. or $50M equity proceeds
C	$25M	LGSOC accelerated or full approval
D	$35M	$50M product revenue on six months trailing basis
E	$50M	Lender discretion
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

* Q3 2022 GAAP operating expenses - $17.71M minus Q3 2022 stock compensation - $1.36M = $16.35M Q3 2022 non-GAAP operating expenses

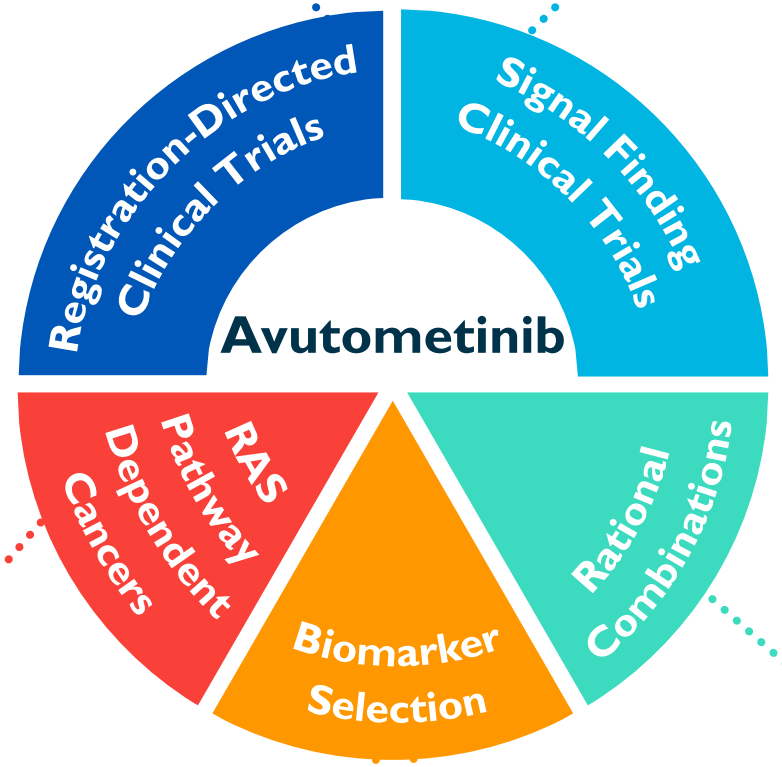
Avutometinib RAF/MEK Clamp Program Overview

Broad Development Opportunities Across Multiple RAS/MAPK Pathway-Driven Cancers

High Priority Registration Indication

Registration-Directed Trial Initiated in 4Q20

- LGSOC[1,2] (RAMP 201)



Key Signal Finding

- Avutometinib + G12Ci in KRAS G12C NSCLC[2] (RAMP 203 - sotorasib) & (RAMP 204 - adagrasib)
- Avutometinib + defactinib in BRAF mt (V600E & non-V600E) NSCLC[1,2] (RAMP 202)
- Avutometinib + defactinib and gemcitabine/nab-paclitaxel in first line pancreatic cancer (RAMP 205)[2]
- Avutometinib + defactinib in RAS/RAF mt endometrioid cancer[1]
- Uveal Melanoma[2]
- Avutometinib + everolimus in KRAS mt NSCLC[1,2]
- Avutometinib + cetuximab in KRAS mt CRC[2]
- Avutometinib + abemaciclib and fulvestrant in ER+ breast cancer

RAS Pathway Dependent Cancers

- Gynecological[1,2]
- NSCLC[1,2]
- Colorectal[1,2]
- Melanoma[1,2]
- Pancreatic[2]
- Thyroid[1,2]

Biomarker Selection

- KRAS mt[1,2]
- BRAF mt (V600 & non-V600)[1,2]
- NRAS mt[1,2]
- CRAF mt/fusions[2]

Rational Combinations

- G12Ci[1,2]
- G12Di[2]
- Anti-EGFR[2]
- Everolimus[1,2]
- CDK4/6 inhibitor[2]
- Anti-PD-1[1,2]
- Chemotherapy[2]

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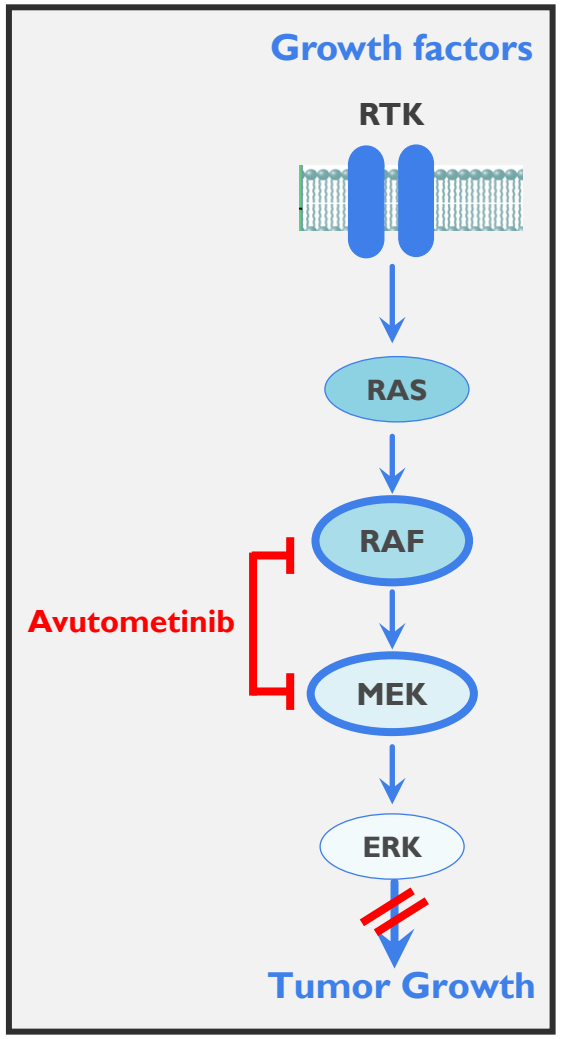
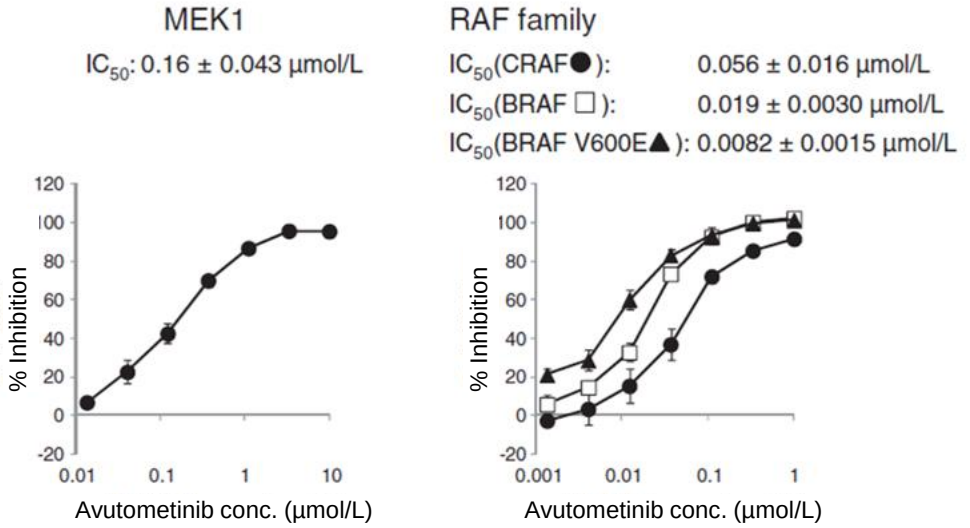
[1] Supported by clinical data

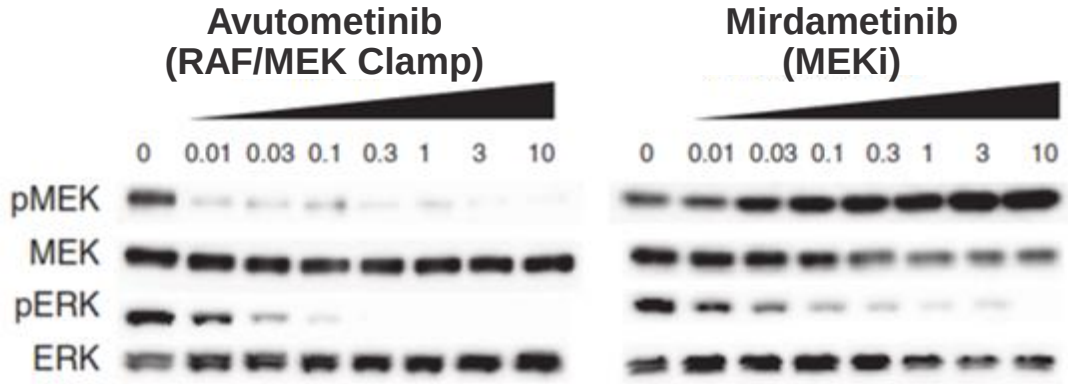
[2] Supported by preclinical data

Avutometinib is a Unique Small Molecule RAF/MEK Clamp



- Avutometinib 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, avutometinib has advantage of not inducing pMEK
- Avutometinib inhibits ERK signaling more completely; may confer enhanced therapeutic activity

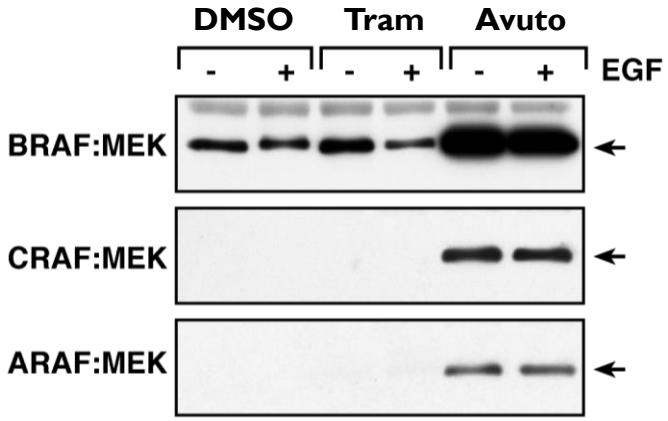


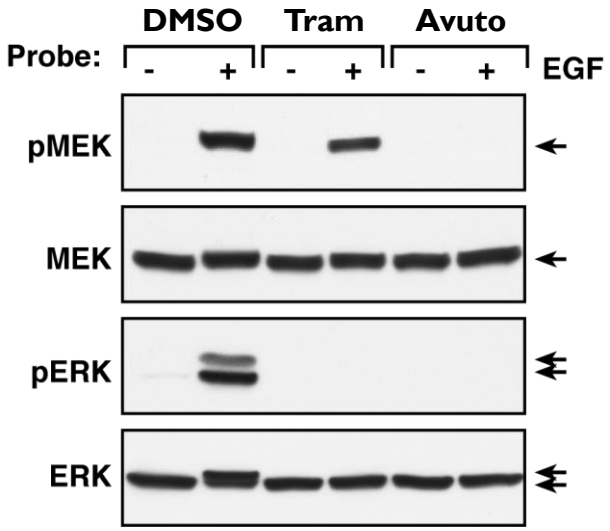


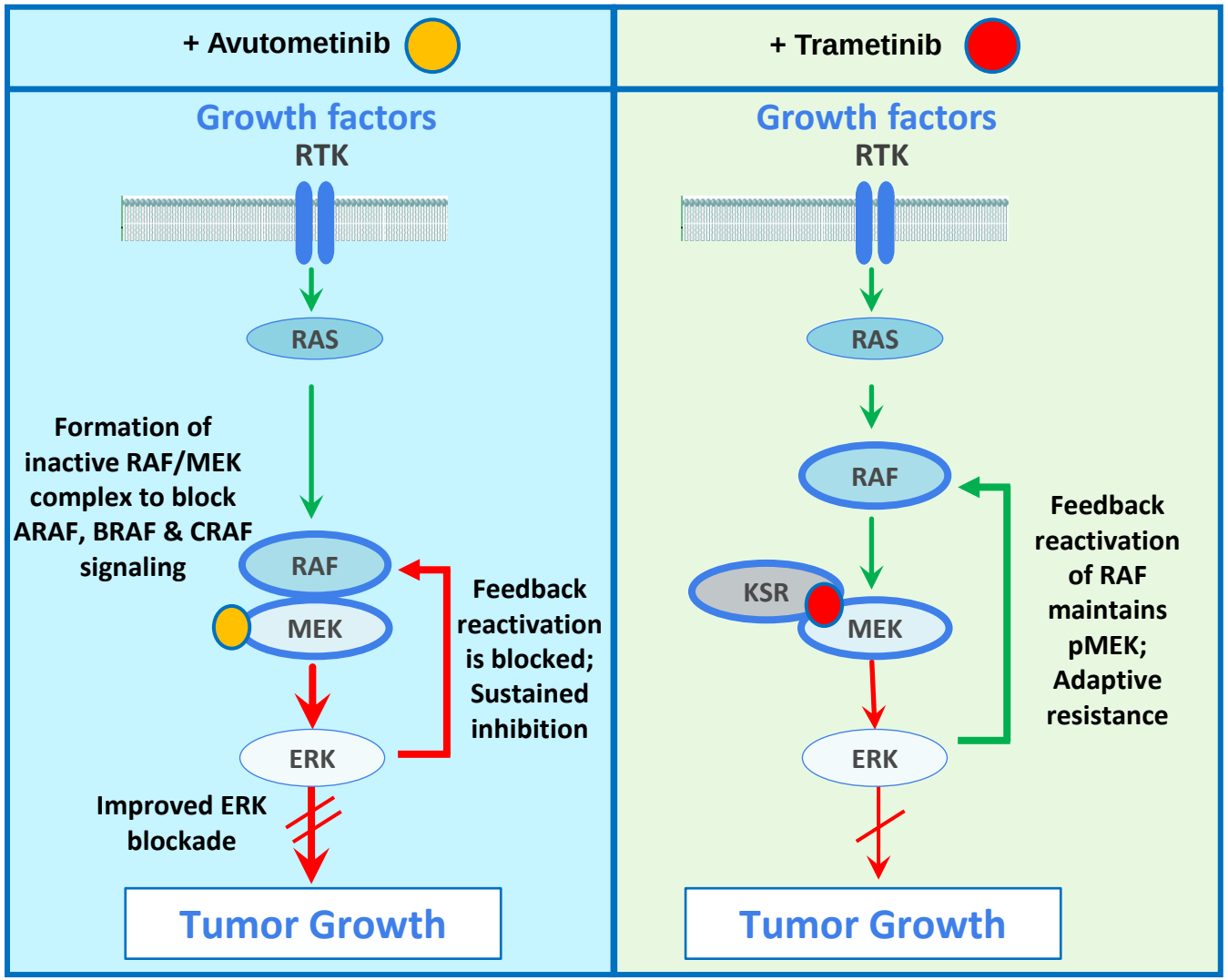
References: Ishii et al., *Cancer Res*, 2013; Lito et al., *Cancer Cell*, 2014

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

Contrasting mechanism of action vs. trametinib







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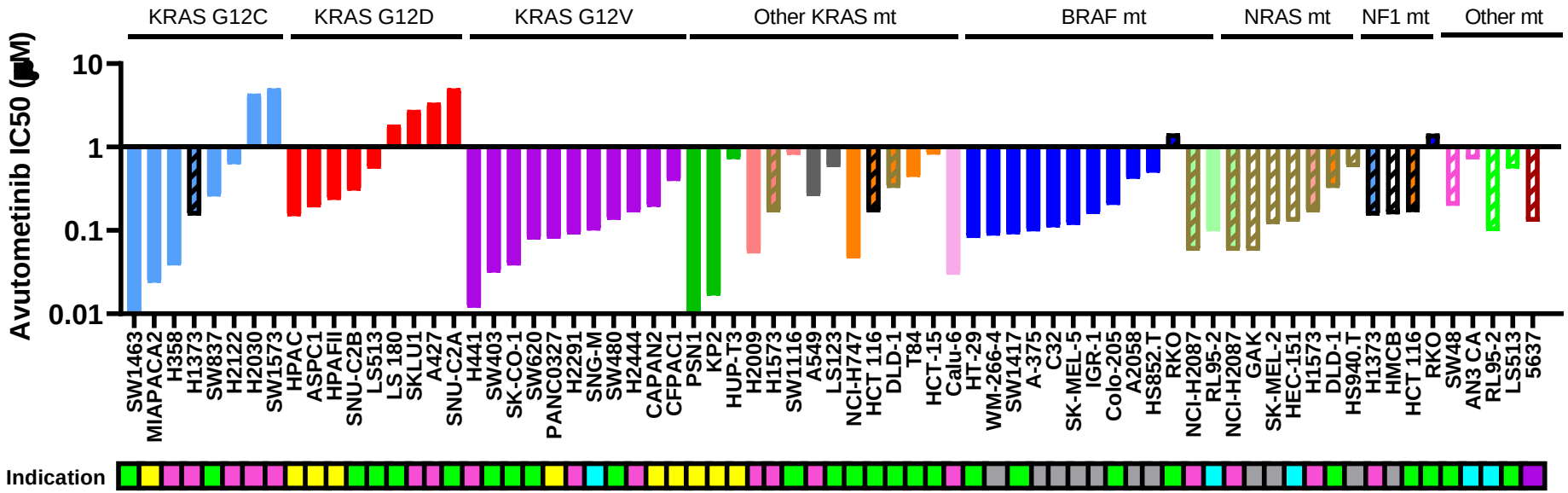
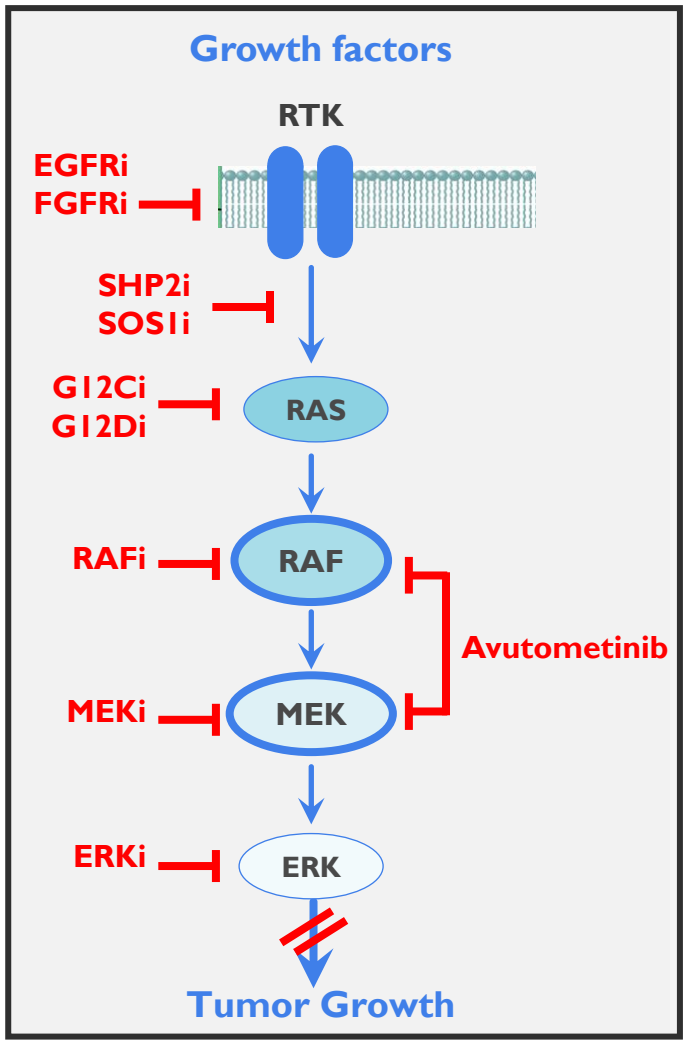
Deborah Morrison unpublished

Avutometinib Inhibits Cell Proliferation Across Multiple RAS/MAPK Pathway Alterations and Multiple Solid Tumor Histologies



Reference: Adapted from Pachter *RAS-Targeted Drug Discovery*, Sep 2021 3D proliferation assay

Vertical Blockade: Establishing Avutometinib as the Backbone of Therapy for RAS/MAPK 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, KRAS-G12Di, 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 Avutometinib**
  - 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 avutometinib combinations (e.g., with KRAS-G12C inhibitors) supporting clinical combinations

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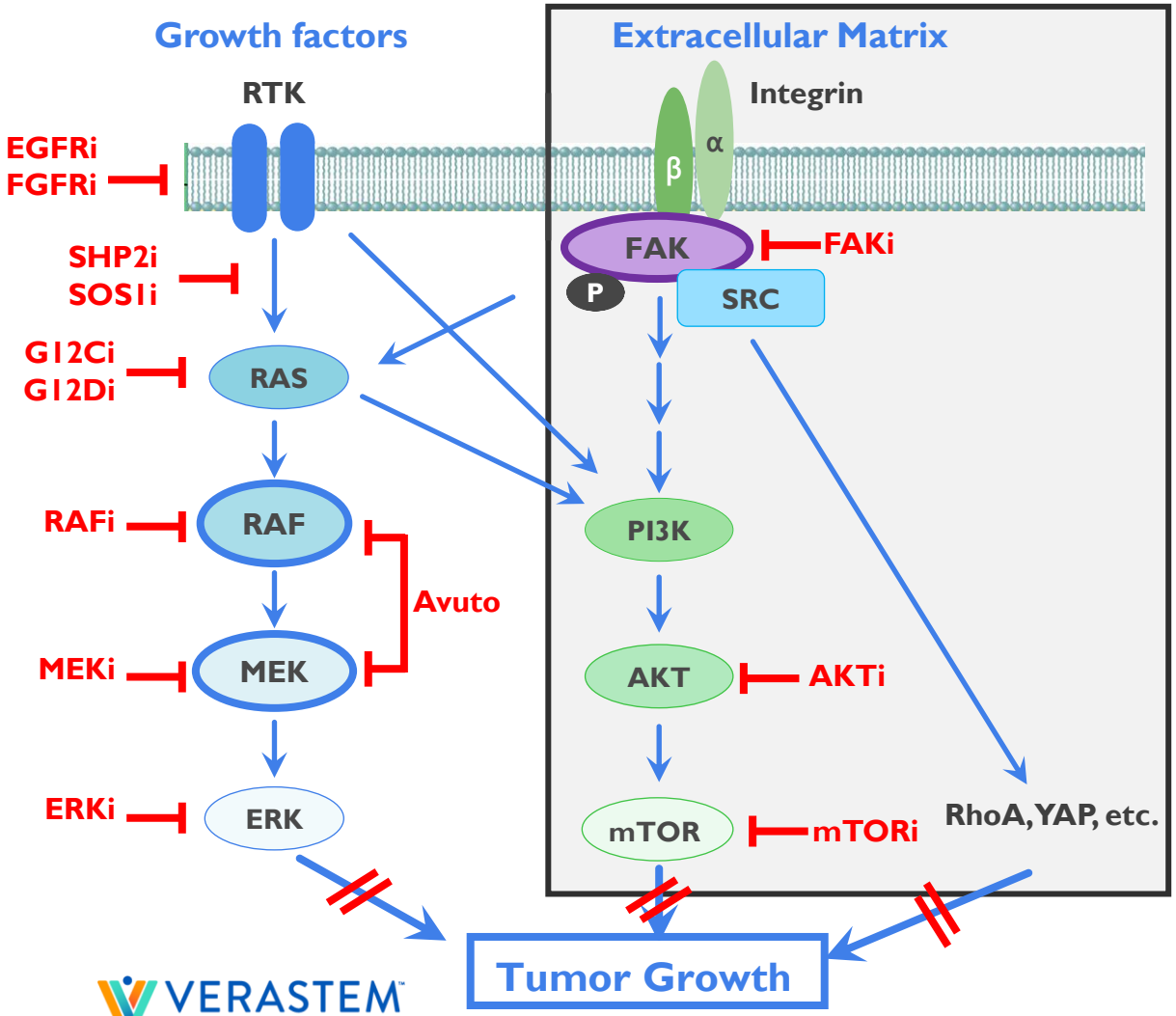
References: [1] Chen, *Mol Cancer Res* 2018; [2] Banerji, BTOG Dublin, Jan 23, 2019

Parallel Pathway Inhibition: Establishing Avutometinib as the Backbone of Therapy for RAS/MAPK 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 Avutometinib**
  - Good tolerability with twice weekly avutometinib opens up intermittent dosing options for combinations
  - Compelling preclinical synergy data with avutometinib in combination with several key anti-cancer agents
  - RP2D established for avutometinib + defactinib and for avutometinib + mTORi (everolimus) with twice weekly regimen

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

Favorable Tolerability Profile with Novel Intermittent Dosing Regimen

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

	Avutometinib monotherapy Daily at MTD N=6 28-day cycle	**RP2D Avutometinib monotherapy 4mg twice weekly N=26 28-day cycle**	**RP2D** (Avutometinib 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

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[1] Chenard-Poirier, *et al*. ASCO 2017

References: Banerji, Q4 2020 report; Data on file

RP2D: recommended phase 2 dosing

Favorable Tolerability Profile at Recommended Phase 2 Dose for Avutometinib plus Defactinib Combination Regimen

Treatment Related Adverse Events Details* (≥10% patients in cohort Avuto 3.2mg and Def 200mg)	Avutometinib 4mg Twice Weekly (4 wks of every 4 wks)[1] n=22		Avutometinib 3.2mg Twice Weekly Defactinib 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

- **Avutometinib 3.2 mg** oral twice weekly (3 weeks of every 4 weeks)
- **Defactinib 200 mg** oral BID (3 weeks of every 4 weeks)

* AEs were graded by NCI CTC v4; highest grade only recorded for each patient; AEs presented in ≥10% Patient (cohort 3.2mg avutometinib and Def 200mg) data preliminary and subject to change;
^ Also includes glossitis/mouth ulcers

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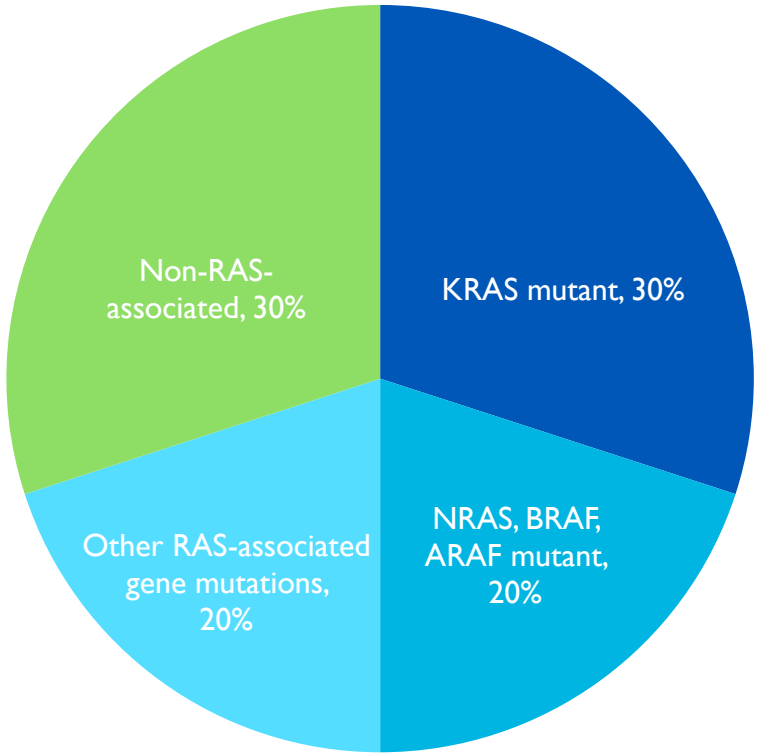
References: [1] Data on file Avutometinib Investigator's Brochure; [2]Banerji, Q4 2020 report

Avutometinib +/- Defactinib in Low-Grade Serous Ovarian Cancer

70% of LGSOC Tumors Driven by Mutations in the RAS/MAPK 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

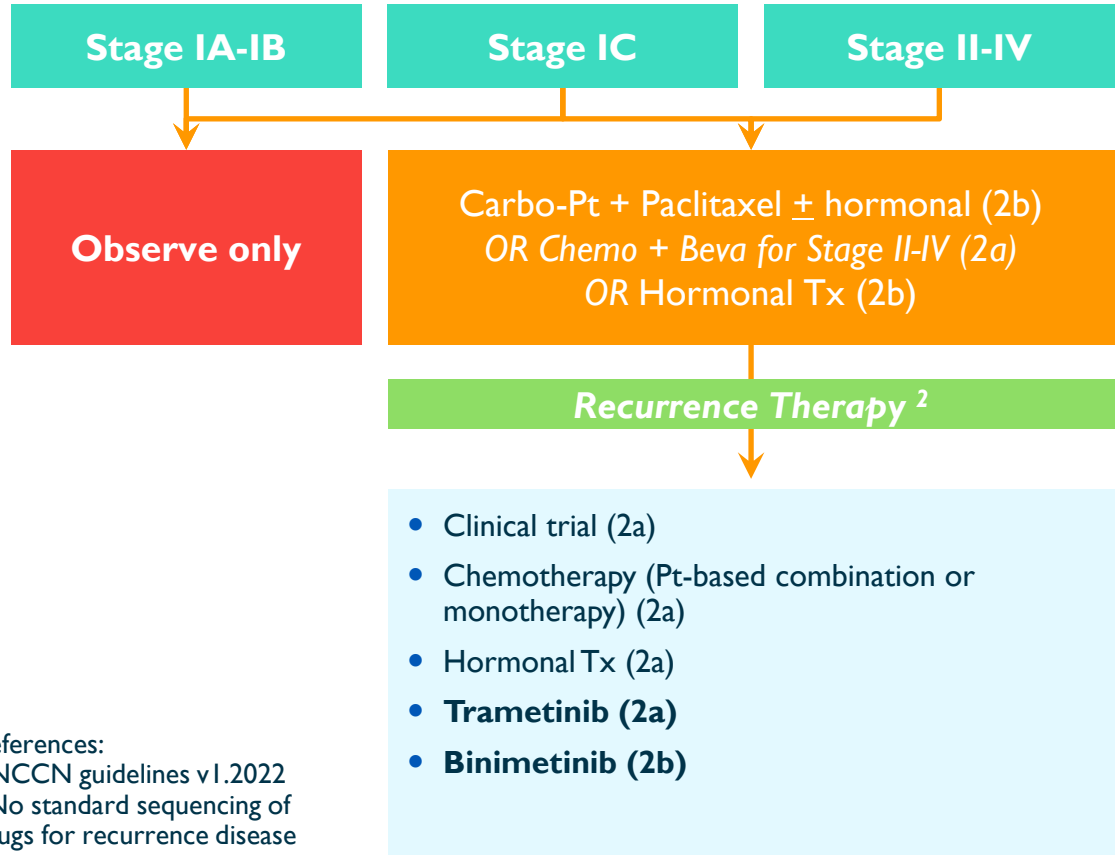


References: AACR Project GENIE Cohort v9.0-public and Verastem unpublished analysis

Reference: 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.

LGSOC: Limited Treatment Options with High Unmet Need

Low-Grade Ovarian Cancer – Treatment Algorithm[1]



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

Recent Clinical Trials in Recurrent LGSOC

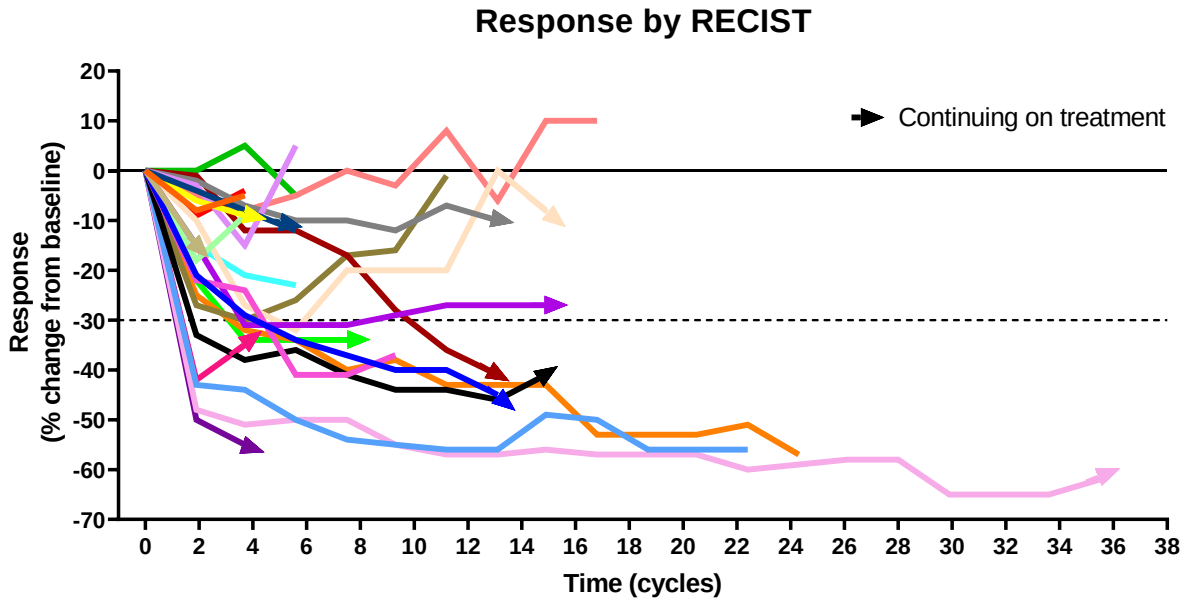
Therapy	Response Rate ORR	Median PFS Months (95% CI)	Discontinuation Rate due to AEs
Standard of Care[1]	6%	7.2 (5.6-9.9)	12 %
Trametinib[1]	26%*	13.0 (9.9-15.0)	35%
Standard of Care[2]	13%	10.6 (9.2 to 14.5)	17%
Binimetinib[2]	16%	9.1 (7.3-11.3)	31%

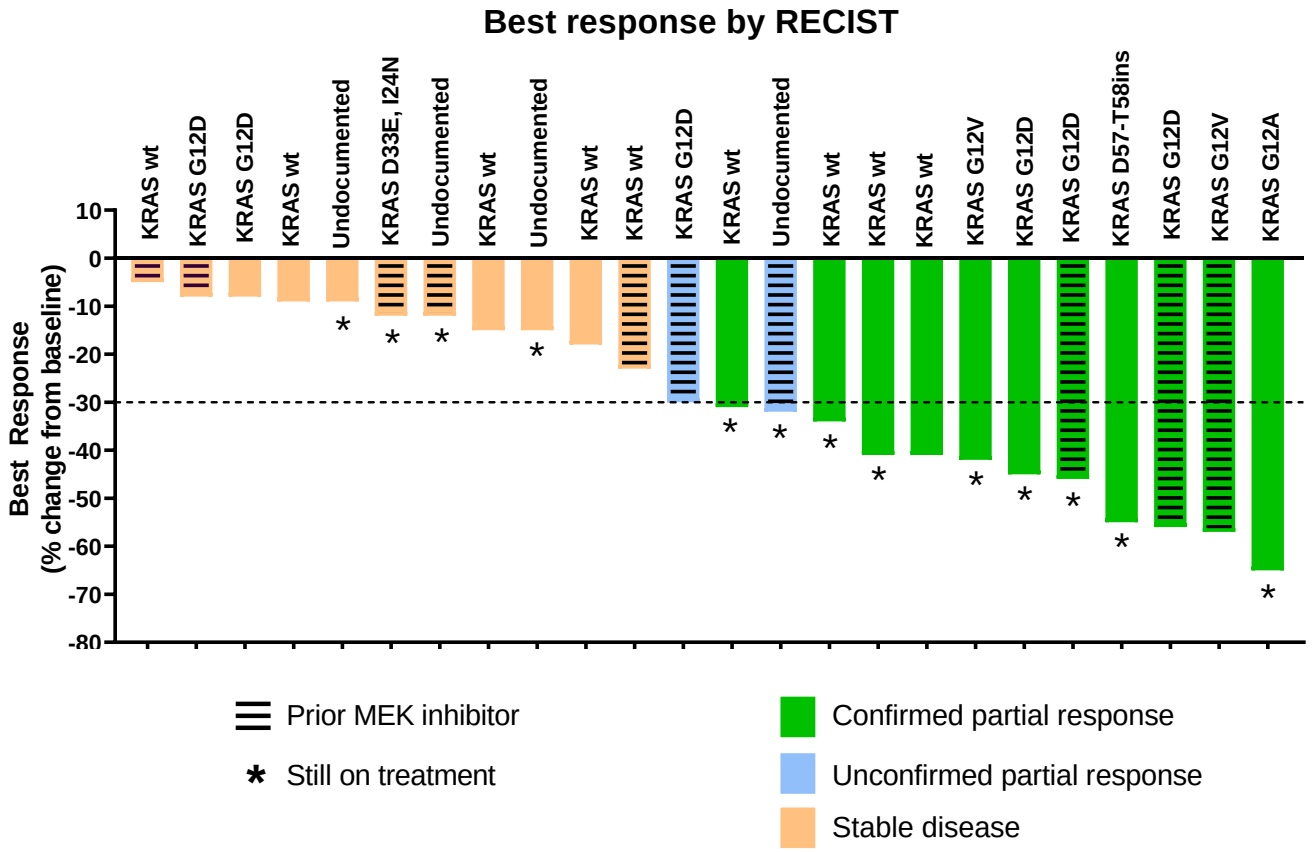
* *Not confirmed by central review*

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.

Avutometinib in Combination with Defactinib (FRAME) Shows Promising ORR with Durability in Refractory LGSOC with Expanded Number of Patients (n=24)





- Overall response rate (ORR) = 46% (11 confirmed PRs/24)
  - KRAS mutant ORR = 64% (7 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

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

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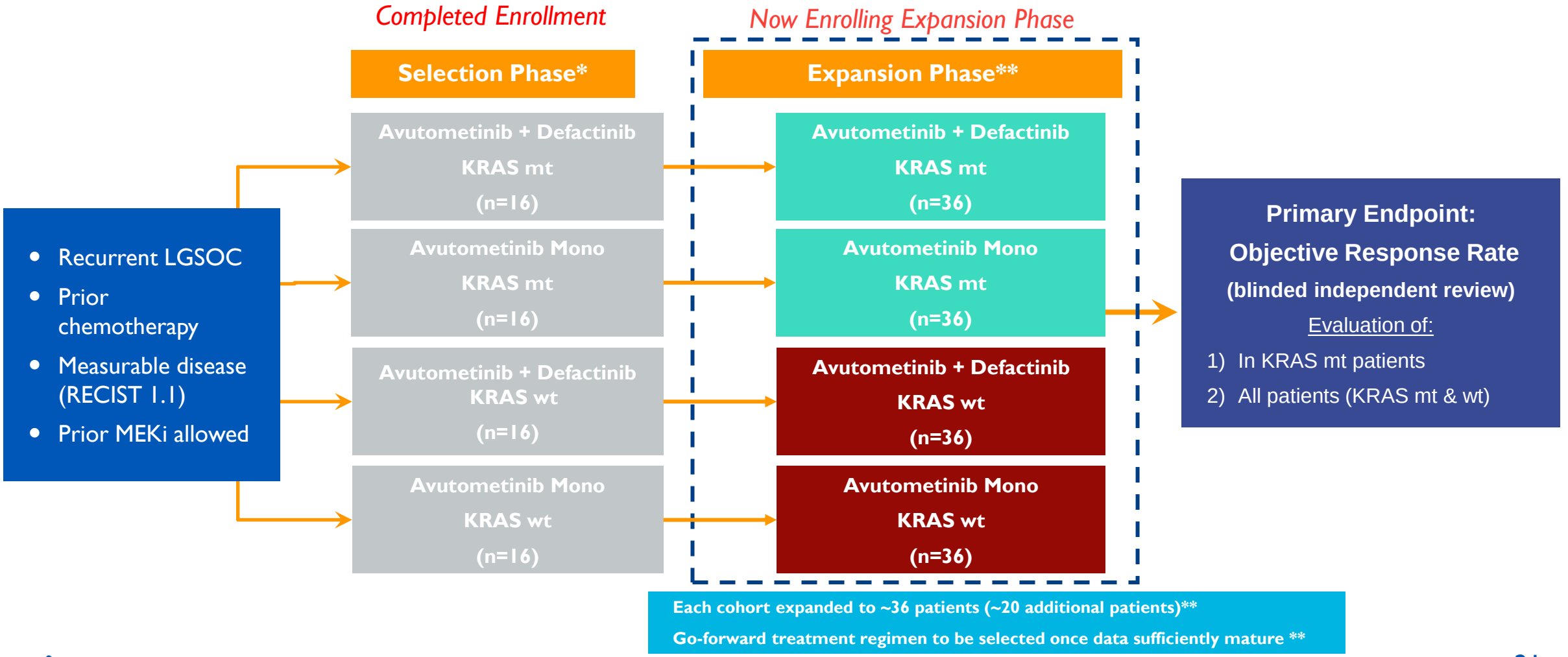
Reference: Banerjee et al., ESMO Sept 2021

RAMP 201 Registration-directed Phase 2 Trial of Avutometinib +/- Defactinib in Recurrent LGSOC KRAS Mutant (mt) and Wild Type (wt)



*Dosing: Avutometinib + Defactinib combination: Avutometinib 3.2mg PO 2x/wk (21/28 days) + Defactinib 200mg PO BID (21/28 days); Avutometinib monotherapy: Avutometinib 4.0 mg PO 2x/wk 21/28 days

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

RAMP 201 Update-October 2022

Update

- Completed second planned interim analysis
- Encouraging efficacy results include independently confirmed responses
- Enrollment continues towards completion of all four cohorts
- No new safety signals, continued favorable safety profile
- Majority of patients remain on treatment

Next Steps

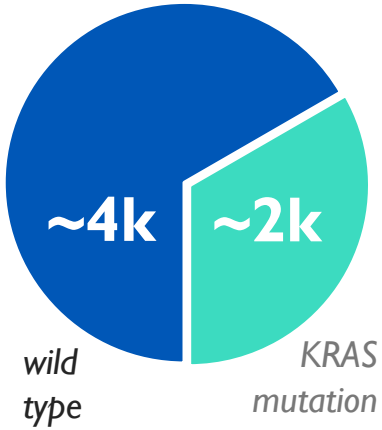
- Full enrollment based on the study protocol on track and expected by the end of the year
- FDA meeting 4Q-22 to align on regulatory path forward and go forward regimen

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

Prevalence

~6K

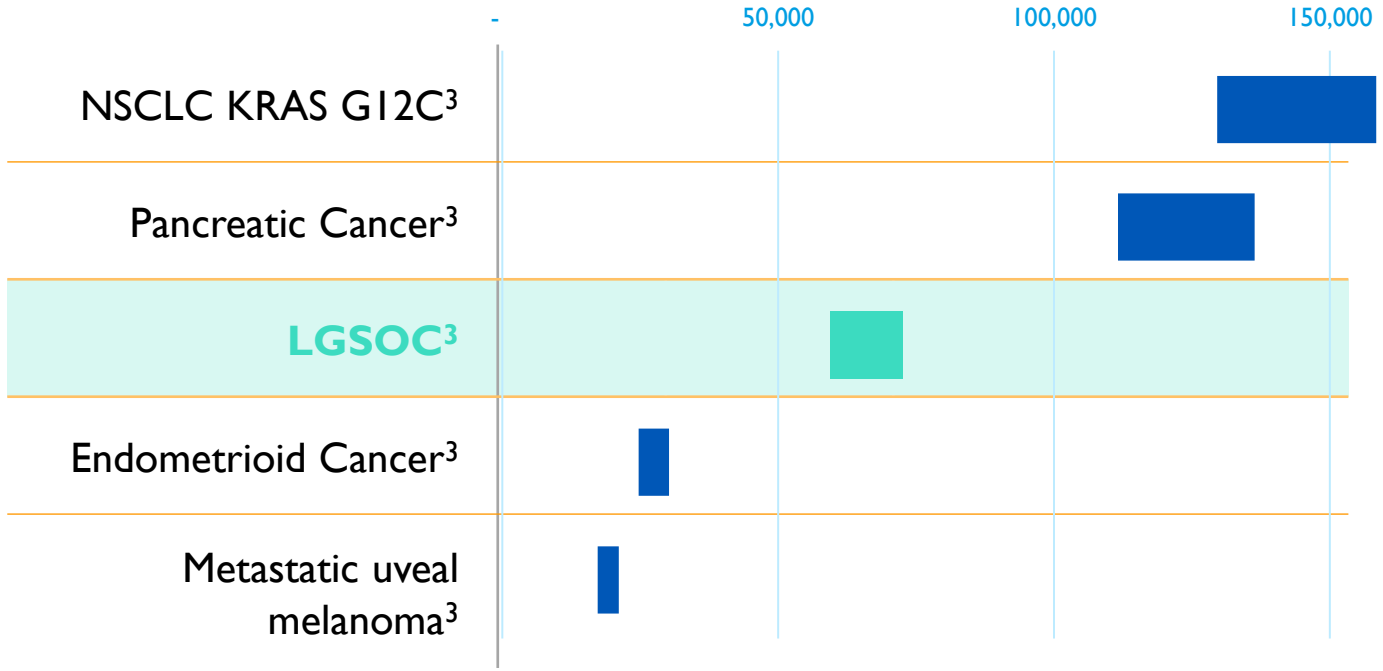
patients US[1]



~80K

patients WW[1]

Patient-months of Therapy Per Year[2] *(across all 2L+ patients)*



[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)

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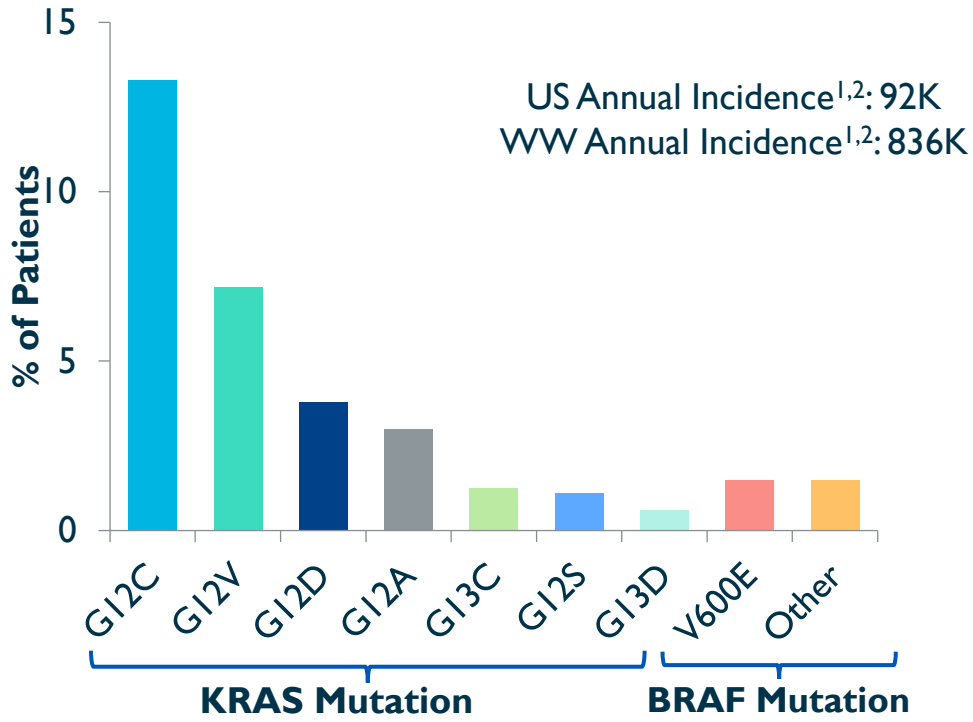
Avutometinib Combinations in NSCLC

High Unmet Need in Refractory mt NSCLC Adenocarcinoma

NSCLC Adenocarcinoma[3]



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

Advanced or Metastatic NSCL Cancer Recommend Histologic and Molecular Subtyping[5]

EGFR/ALK/ROS1/BRAF/ KRAS G12C (targeted)	Non-targeted PD-(L)1 ≥ 1%	Non-Targeted PD-(L)1 < 1%
Appropriate targeted agent	**PD-(L)1 single agent or PD-(L)1 + chemo**	**Chemo ± PD-(L)1**

Recurrence

Prior PD-(L)1	*No Prior PD-(L)1*
Chemotherapy • Docetaxel • Gemcitabine • Pemetrexed	**PD-(L)1**

Recurrence

Chemotherapy or clinical trials

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

Clinical Trials with Avutometinib:

- RAMP 202:
  - BRAF V600E and BRAF non-V600E - Avutometinib + defactinib
- RAMP 203: KRAS G12C - Avutometinib + sotorasib
- RAMP 204: KRAS G12C - Avutometinib + adagrasib
- KRAS mt - Avutometinib + everolimus

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

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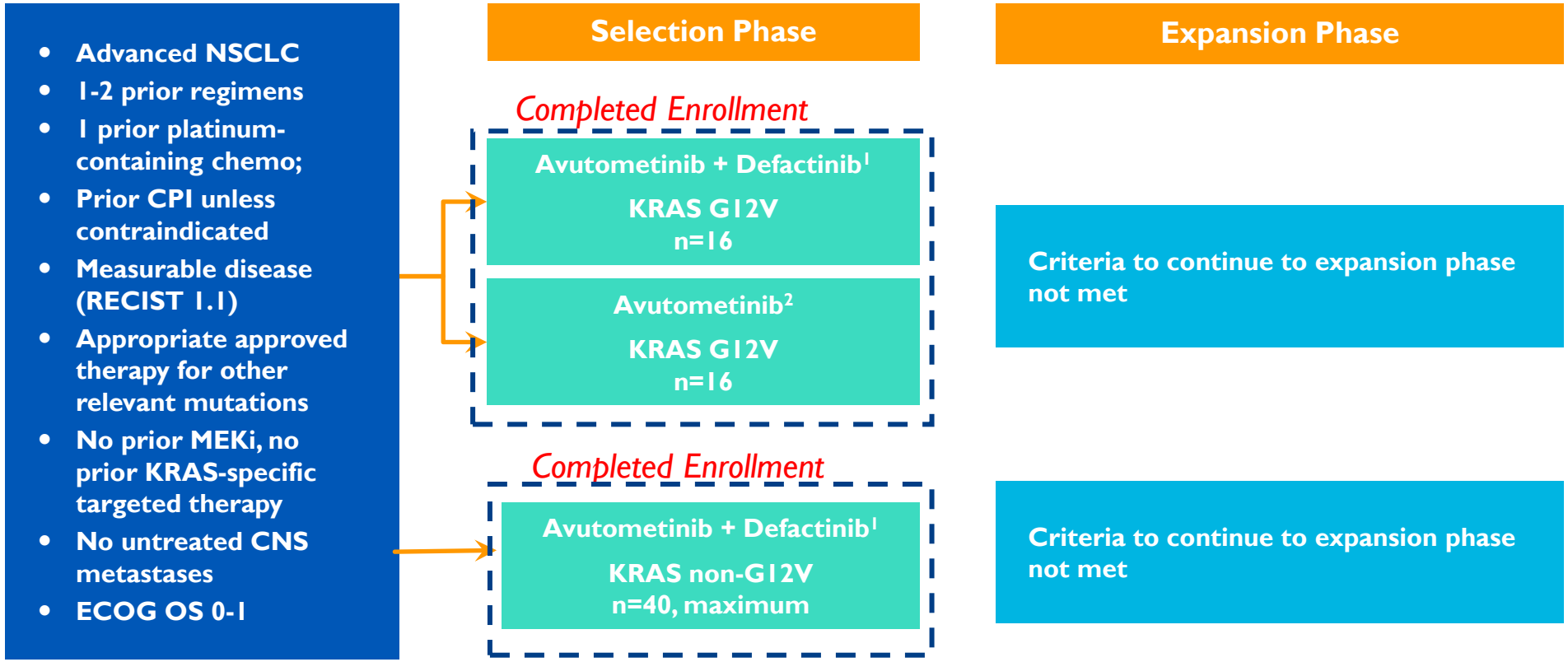
RAMP 202: Phase 2 Trial of Avutometinib +/- Defactinib in Advanced NSCLC Primary Cohort: KRAS G12V NSCLC



References:[1] Avutometinib 3.2 mg PO 2x/wk (21/28 days) + Defactinib 200 mg PO BID (21/28 days)

[2] Avutometinib 4.0 mg PO 2x/wk (21/28 days)

RAMP 202 Results–August 2022

Findings

- The confirmed ORR was 11% (2/19) in KRAS G12V NSCLC patients treated with avutometinib + defactinib with a disease control rate of 37%
- The ORR in KRAS non-G12V NSCLC patients treated with avutometinib + defactinib was 5% (2/37) with a disease control rate of 54%
    - No subtype was identified for further clinical evaluation of avutometinib + defactinib in this trial

Next Steps

- Results of Part A of RAMP 202 trial in KRAS G12V NSCLC show avutometinib ± defactinib did not meet criteria to continue to expansion phase
- Continue to analyze the results of the trial and integrate the findings into our development plans moving forward
- Continuing avutometinib development in NSCLC with other combinations:
    - Sotorasib
    - Adagrasib
    - Everolimus

RAMP 202: Avutometinib + Defactinib in BRAF mt NSCLC

- Advanced NSCLC
- 1-2 prior regimens
- 1 prior platinum-containing chemo;
- Prior CPI unless contraindicated
- Measurable disease (RECIST 1.1)
- Appropriate approved therapy for other relevant mutations
- No prior KRAS-specific targeted therapy
- No prior MEKi, (except for BRAF V600E)
- No untreated CNS metastases
- ECOG OS 0-1

Initial Phase

Avutometinib + Defactinib[1]
BRAF V600E
n=15

Avutometinib + Defactinib[1]
BRAF non-V600E
n=15

Analysis

BRAF Mutant
- Mutation-specific cohort analyses for ORR

- BRAF Cohorts Expansion TBD based on results of analysis

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References:[1] Avutometinib 3.2 mg PO 2x/wk (21/28 days) + Defactinib 200 mg PO BID (21/28 days)

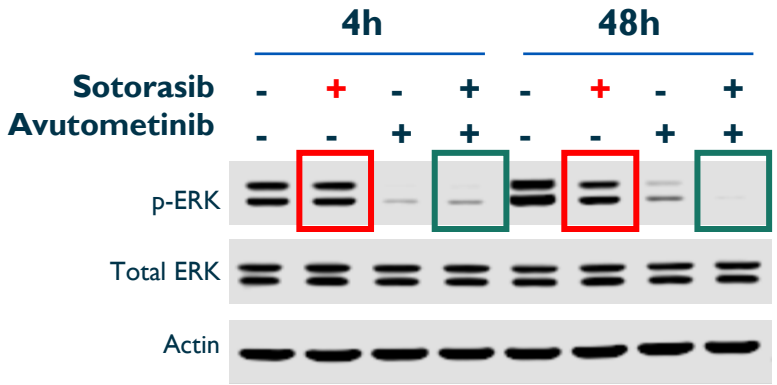
Preclinical Synergy of Avutometinib + G12C Inhibitors in KRAS G12C Models

Synergy of avutometinib + G12C inhibitors across G12C mutant NSCLC, CRC & Pancreatic cancer cell lines

Cell line	Indication	Sensitivity to G12C inhibitors	Combined Synergy Score: Avutometinib + sotorasib	Combined Synergy Score: Avutometinib + 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

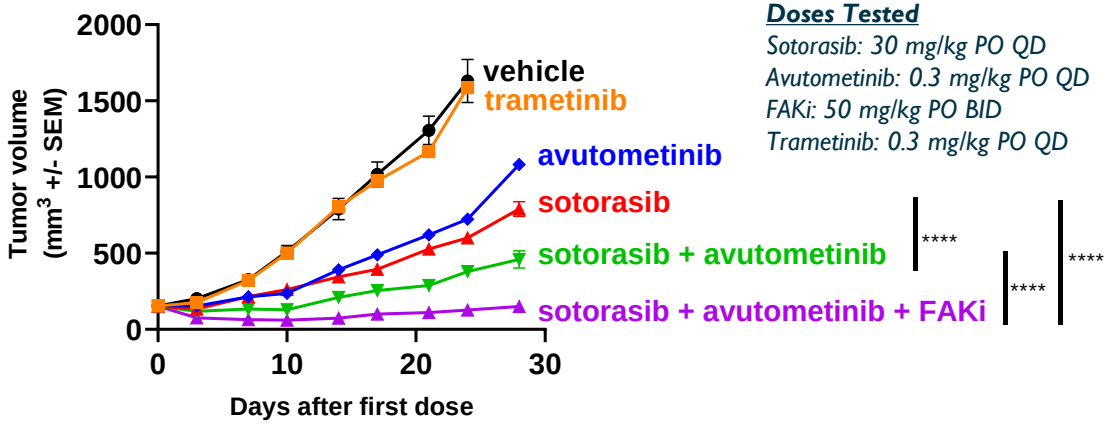
Avutometinib + sotorasib yields deeper and more sustained inhibition of ERK signaling pathway



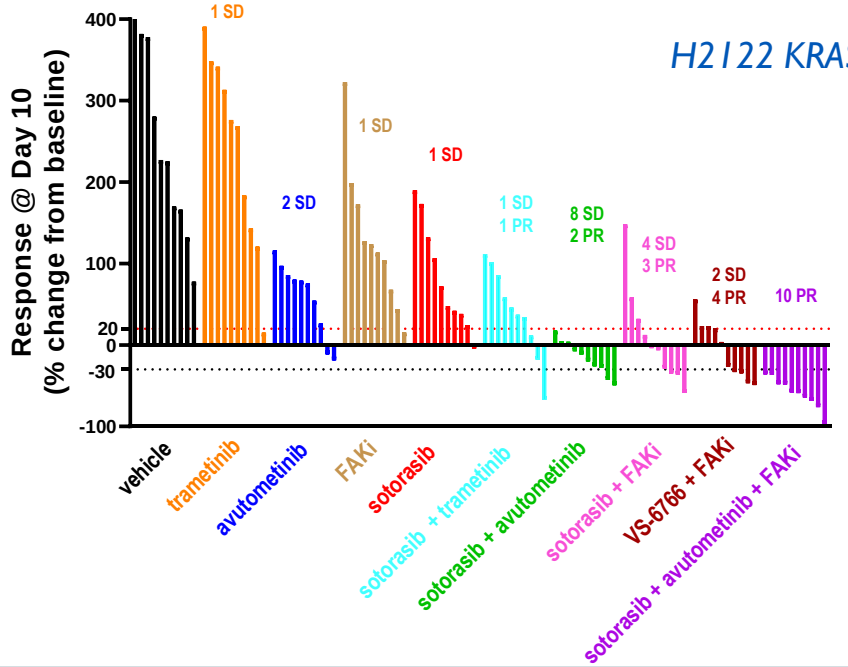
H2122 KRAS G12C NSCLC

Concentrations Tested
Sotorasib: 100 nM
Avutometinib: 100 nM

Avutometinib & FAKi potentiate sotorasib efficacy in KRAS G12C NSCLC in vivo; Tumor regression in all mice with triple combination



Doses Tested
Sotorasib: 30 mg/kg PO QD
Avutometinib: 0.3 mg/kg PO QD
FAKi: 50 mg/kg PO BID
Trametinib: 0.3 mg/kg PO QD



H2122 KRAS G12C NSCLC

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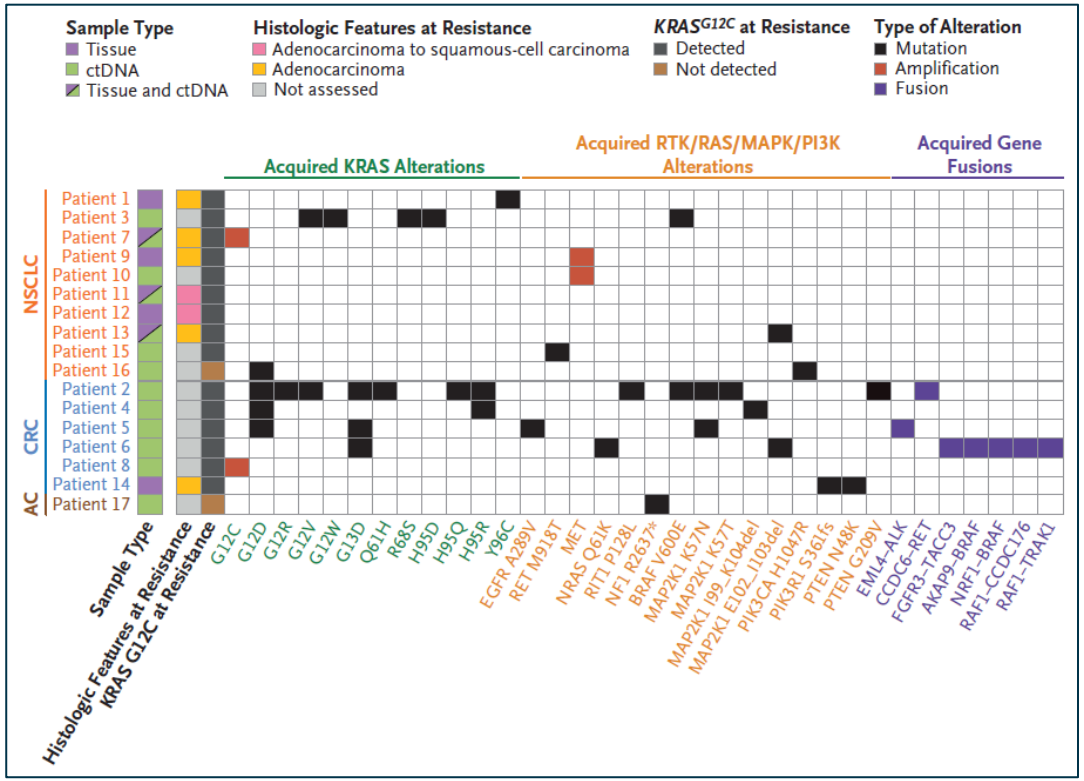
Reference: Coma et al., AACR 2021

Acquired Resistance Mechanisms to KRAS G12Ci Treatment in Patients Further Support Combination of KRAS G12Ci with Avutometinib

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, BRAF or CRAF fusions
  - MAP2K1 (MEK1) mt/deletion
- Avutometinib has shown activity against these KRAS, NRAS, BRAF and CRAF modifications

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

1 - 30 nM	30 - 150 nM	150 - 500 nM

Reference: Andrew Aguirre, unpublished

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

RAMP 203: Phase 1/2 Trial of Avutometinib + LUMAKRAS™ (sotorasib) in KRAS G12C Advanced NSCLC

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

*may include patients with or without prior G12C therapy

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

Avutometinib + Sotorasib

Dose Finding Cohorts (n=3-6)*

*Has advanced to Cohort 2: 4mg avutometinib/960mg sotorasib

RP2D Selection

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

Cohort 1
Patients without Prior KRAS G12C Inhibitor Treatment
Stage 1: ~20 patients
Stage 2: expand

Cohort 2
Patients who Progressed on KRAS G12C Inhibitor Treatment
Stage 1: ~20 patients
Stage 2: expand

RAMP 204: Phase 1/2 Trial of Avutometinib + Adagrasib in KRAS G12C Advanced NSCLC

- **Patients must have a KRAS G12C mutation determined using validated test**
- **Treatment with at least 1 but no more than 3 prior systemic regimens, for Stage 3B-C or 4 NSCLC**
- **Patient must have received prior therapy with a KRAS G12C inhibitor and experience progressive disease**
- **Measurable disease according to RECIST 1.1**
- **ECOG performance status ≤ 1**

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

Avutometinib + Adagrasib

Dose Finding Cohorts (n=3-6)

RP2D Selection

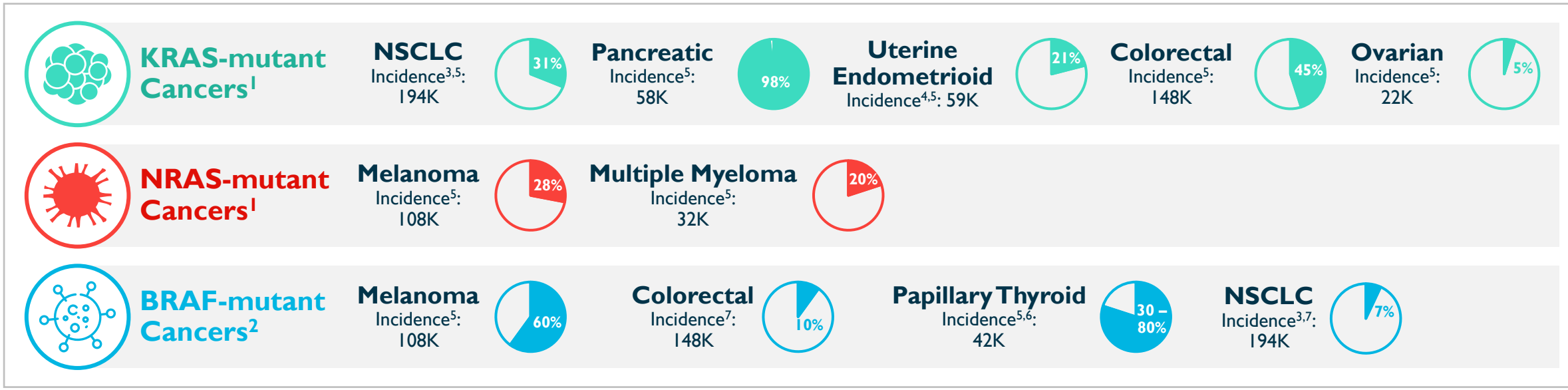
Part B: Dose Expansion (Primary endpoint ORR)

Stage 1: 19 patients (including Part A patients) treated with RP2D

Stage 2: expand to 55 patients

Future Opportunities: Avutometinib as Backbone of RAS Therapy

High Unmet Needs in RAS/MAPK Pathway-Driven Cancers



Breadth of potential opportunity

- 30% of all human cancers are driven by mutations of the RAS family of genes[6]

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:
[1]Reference for RAS mt frequencies – Cox et al. *Nature Reviews* 13: 828, 2014; [2]Reference for BRAF mt frequencies – Turski et al. *Mol Cancer Ther* 15: 533, 2016
[3]85% of lung cancer is NSCLC (Lu et. al. *Cancer Manag Res.* 2019); [4]90% of all uterine cancers are of the endometrial type (ACS); [5]Cancer Statistics 2020, Siegel et. al. *CA Cancer J Clin* 2020;70:7-30; [6]8 out of 10 thyroid cancers are of the papillary type (ACS)[7]CbioPortal

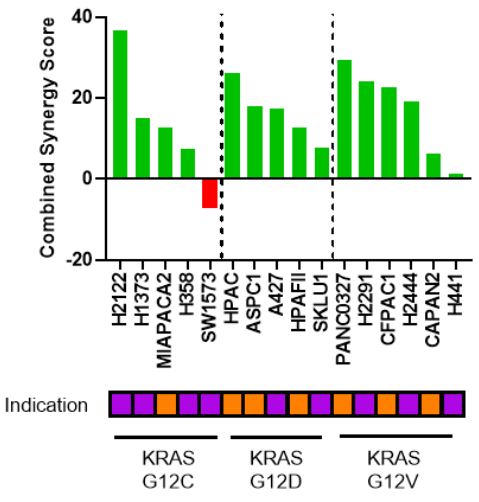
References:
McCormick F Clin Cancer Res 15April2015; [6]Adderley H et al. EBioMedicine 01Mar2019; Papke B et al. Science 17Mar2017; Ryan M et al. *Nature Reviews Clinical Oncology* 01Oct2018; NIH cancer.gov/research/key-initiatives/ras

VERASTEM ONCOLOGY

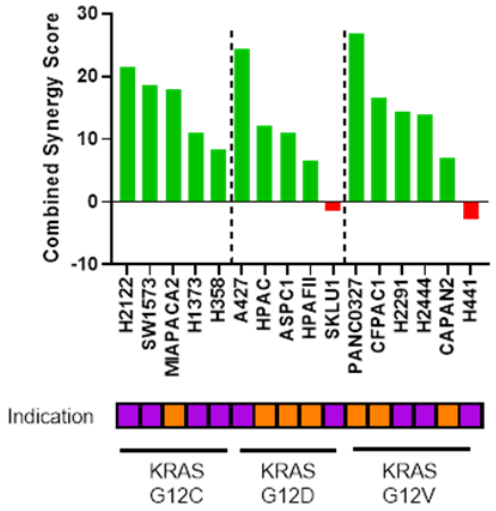
Preclinical Synergy of Avutometinib in Combination with Promising Agents for Clinical Investigation

Vertical MAPK Pathway Inhibition

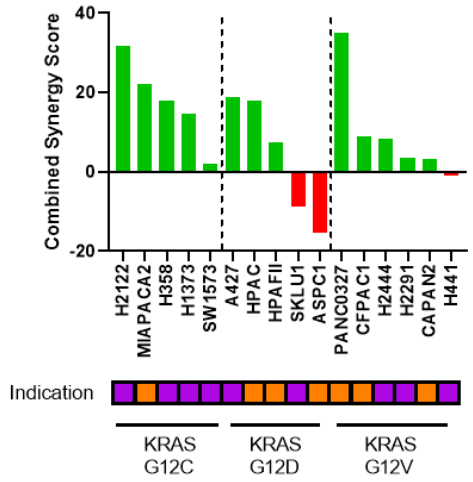
Avutometinib + pan-HERi (afatinib)



Avutometinib + SHP2i (RMC-4550)

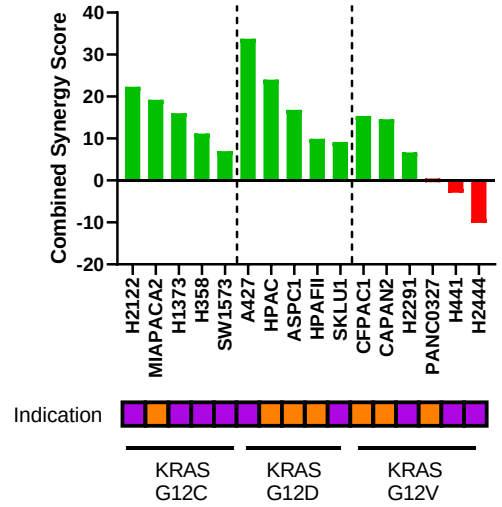


Avutometinib + SOS1i (BI-3406)

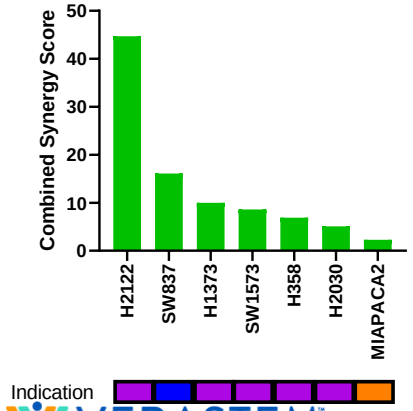


Parallel Pathway Inhibition

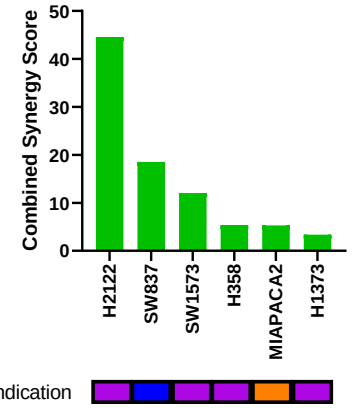
Avutometinib + CDK4/6i (palbociclib)



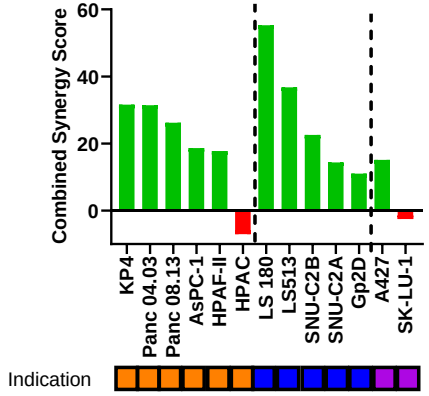
Avutometinib + G12Ci (sotorasib)

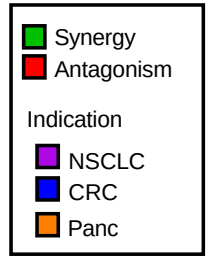


Avutometinib + G12Ci (adagrasib)

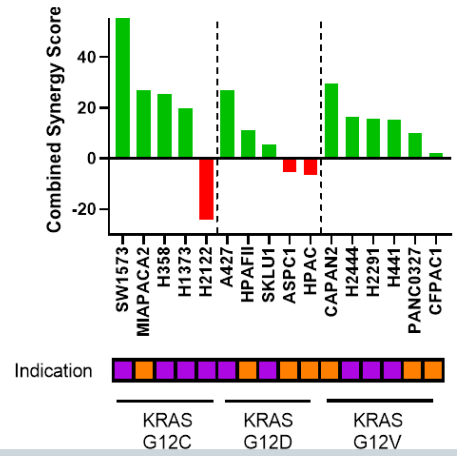


Avutometinib + G12Di (MRTX1133)





Avutometinib + mTORi (everolimus)



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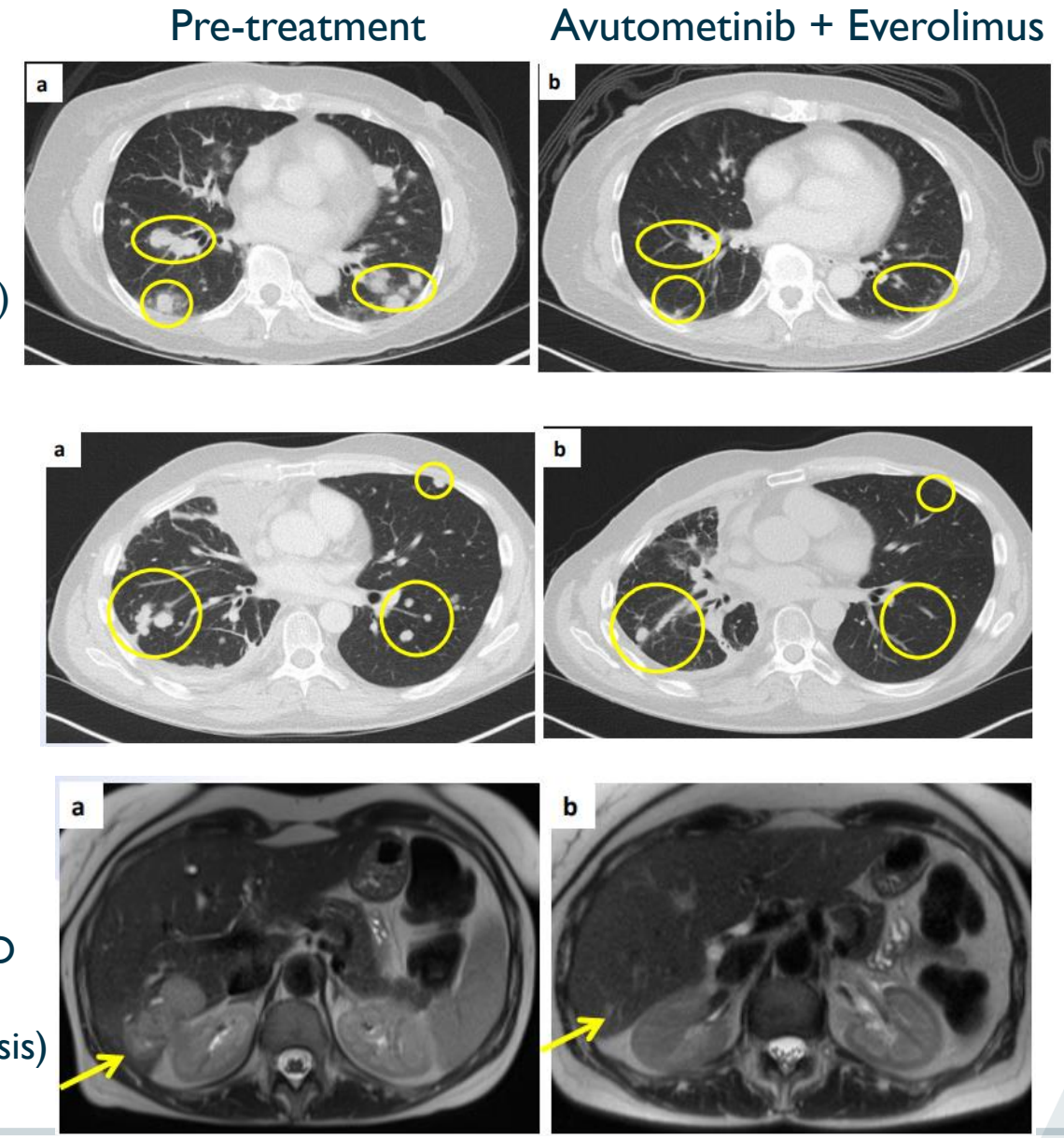
Avutometinib + Everolimus Clinical Data Presented at ASCO

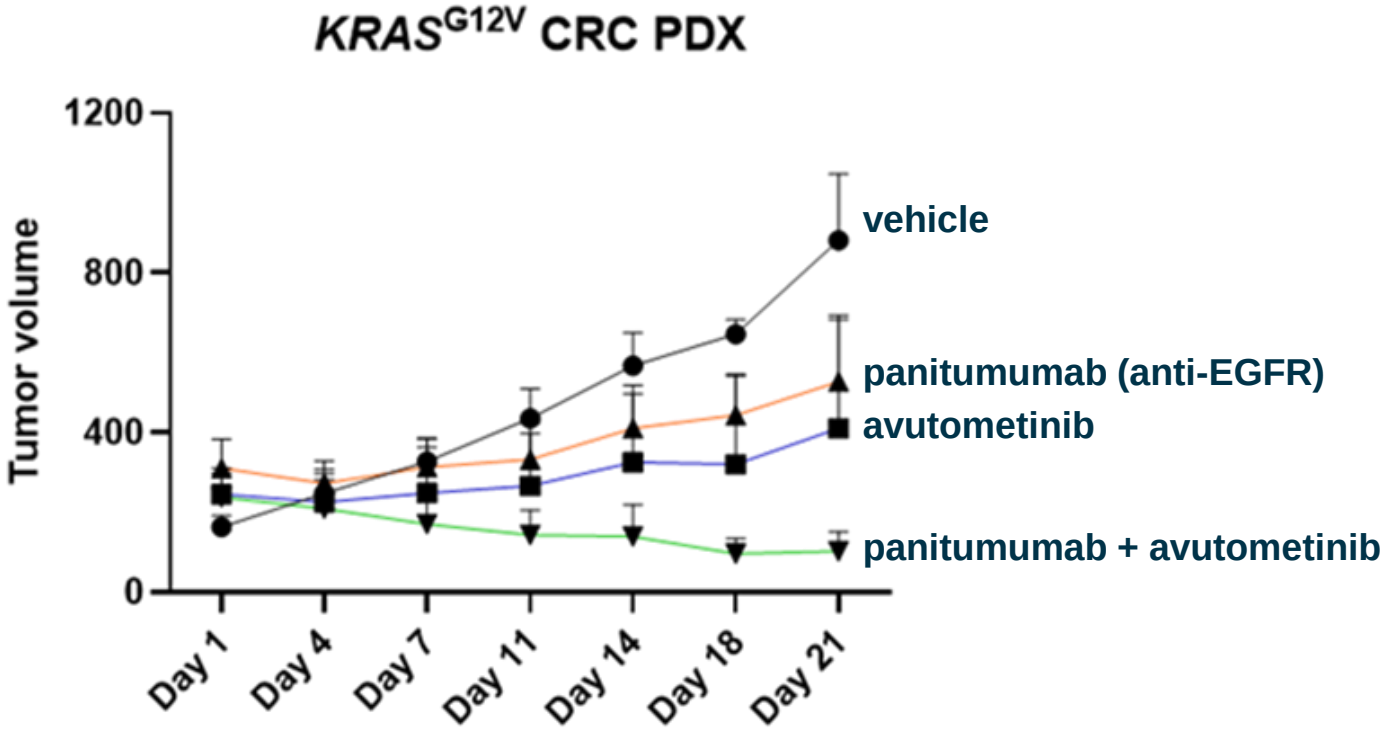
- Well-tolerated RP2D established for avutometinib + everolimus with intermittent dosing of both agents (twice weekly; 3 wks on/1 wk off)
  - No DLTs reported at RP2D
- Avutometinib + everolimus combo induced PRs in patients with various RAS mutations in NSCLC, LGSOC and thyroid cancers
- Both LGSOC 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



VERASTEM ONCOLOGY

Reference: Minchom et al., ASCO 2022

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

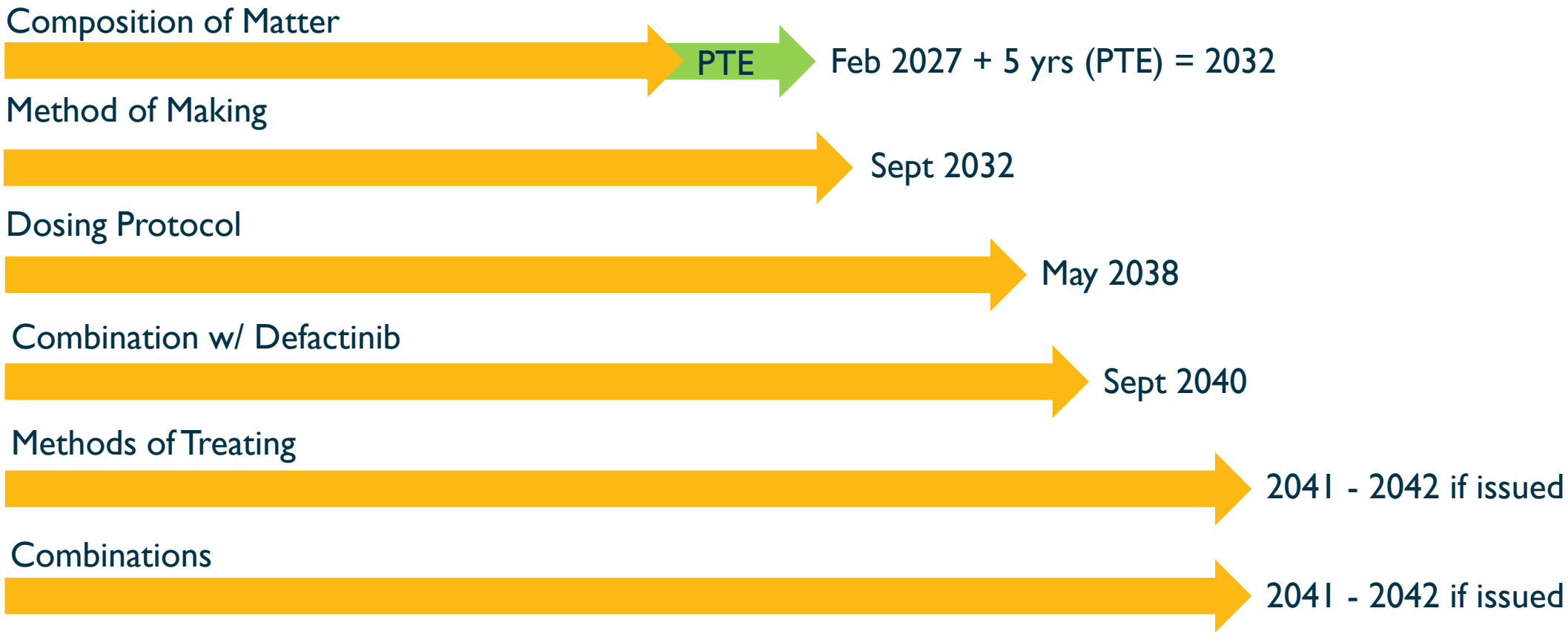


- Avutometinib + anti-EGFR (panitumumab) induces tumor regression in a KRAS G12V CRC patient-derived xenograft model
- G12Ci + anti-EGFR (sotorasib + panitumumab and adagrasib + cetuximab) have shown partial responses in KRAS G12C CRC (Fakih et al. ESMO 2021; Weiss et al. ESMO 2021)
- **These data support the ongoing clinical evaluation of avutometinib + anti-EGFR (cetuximab) for treatment of KRAS mt CRC (NCT05200442)**

Collaboration with Marwan Fakih, City of Hope

Pachter, RAS Development Summit, 2021

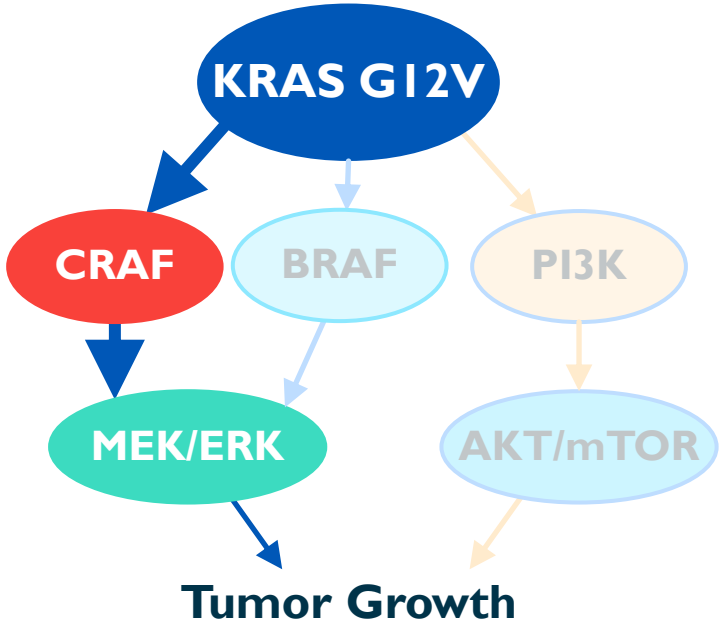
Avutometinib Patent Exclusivity



Backup Slides

Avutometinib Inhibits CRAF - The key driver of KRAS G12V NSCLC

A Precision Approach to KRAS G12V Driven NSCLC



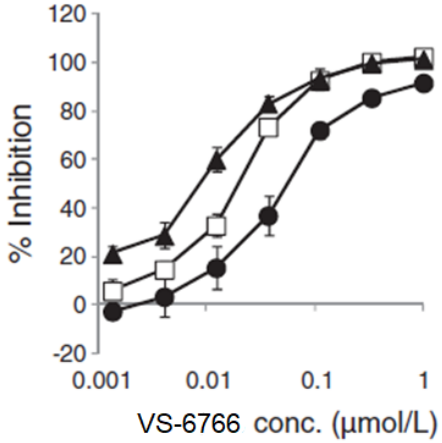
- KRAS G12V signals mainly through RAF/MEK in contrast to other variants, such as KRAS-G12D, which signal more through PI3K/AKT
- KRAS G12V models are especially dependent on CRAF

RAF family

IC_{50}(CRAF●): 0.056 ± 0.016 µmol/L

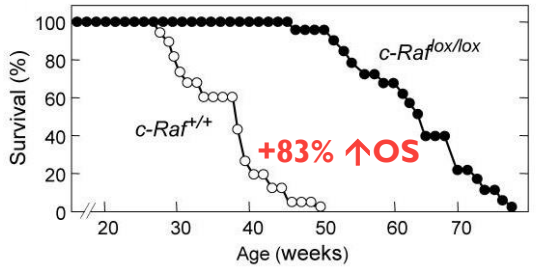
IC_{50}(BRAF □): 0.019 ± 0.0030 µmol/L

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

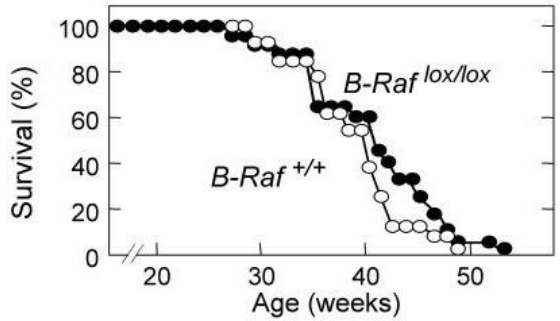


CRAF Drives KRAS G12V NSCLC[1]

CRAF KO Shows Strong Efficacy



BRAF KO Has No Effect

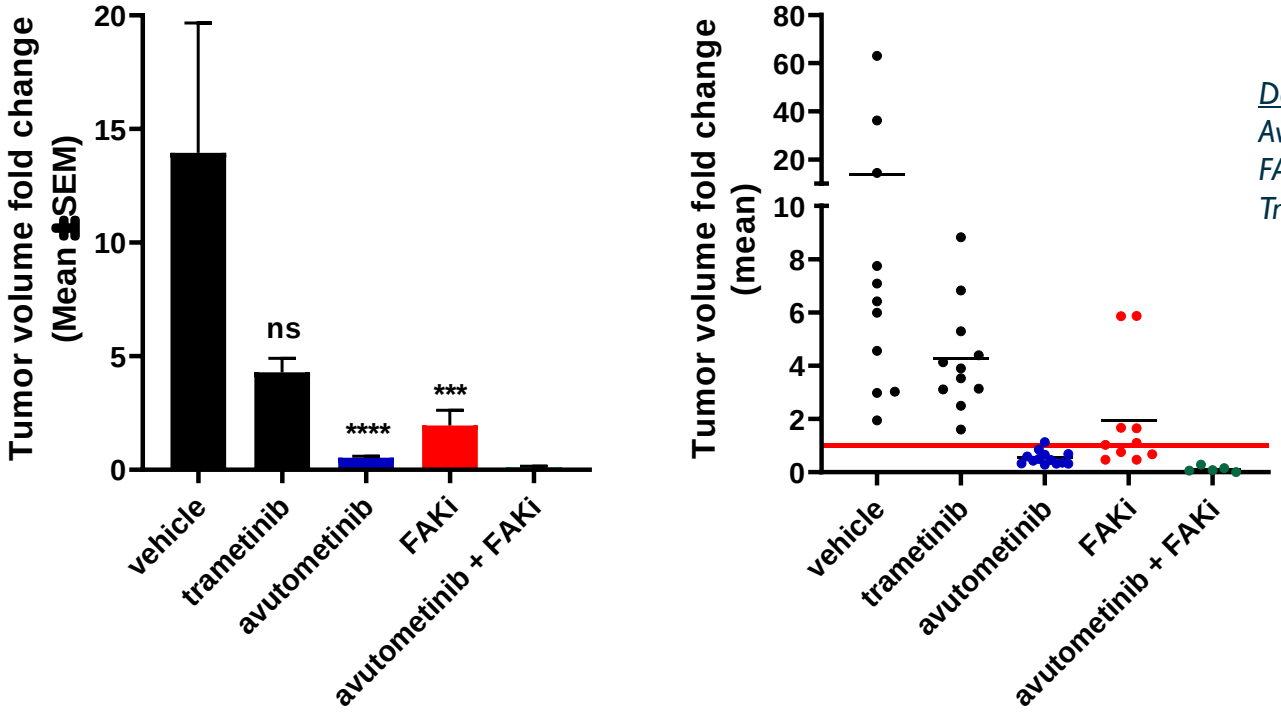


CRAF, but not BRAF, ablation improves survival of mice with KRAS G12V induced lung cancer *in vivo*

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

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

KRAS G12V;Tp53 KO NSCLC



Doses Tested
Avutometinib: 0.1 mg/kg PO QD (5 days/week)
FAKi: 50 mg/kg PO BID (5 days/week)
Trametinib: 0.1 mg/kg PO QD (5 days/week)

- **Avutometinib monotherapy caused tumor regression**
- **Avutometinib + 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

VERASTEM ONCOLOGY

Reference: Coma et al. AACR 2021

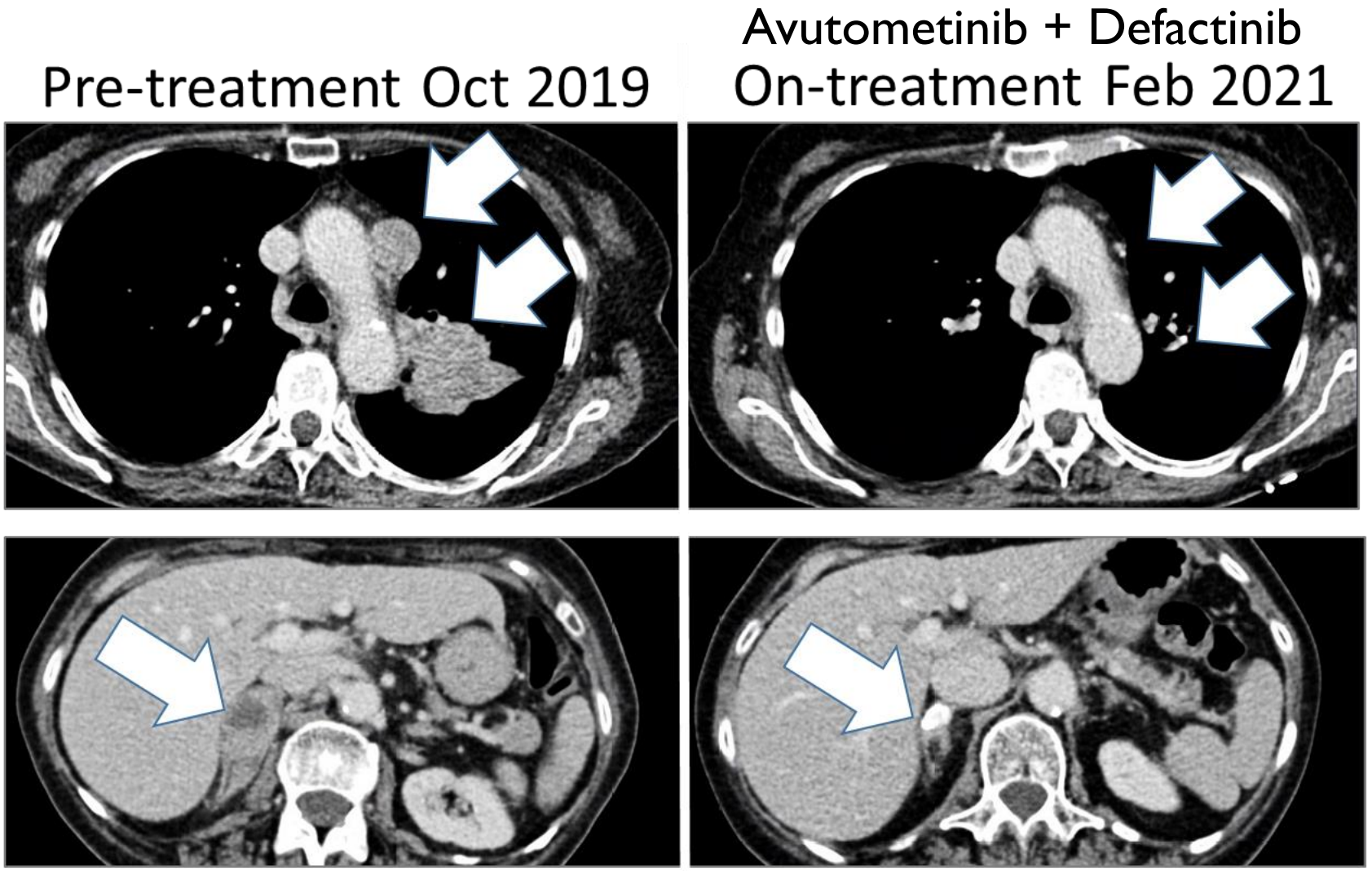
Case Study: Response to Avutometinib + Defactinib in a Patient with KRAS G12V NSCLC

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 avutometinib + defactinib

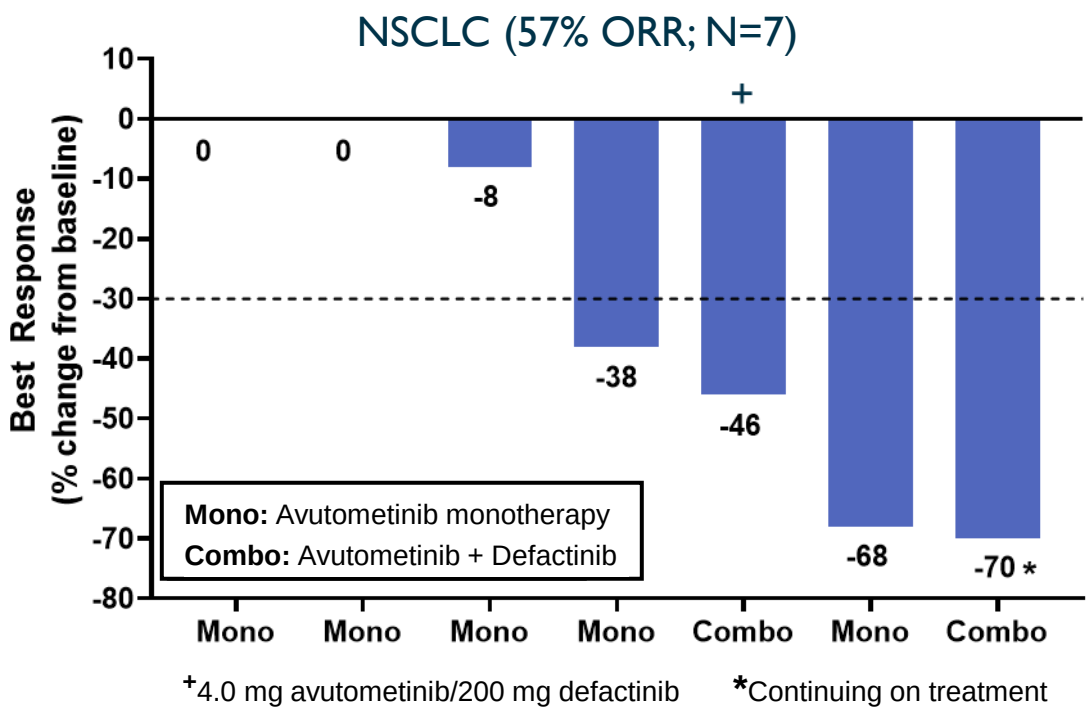


Reference: Krebs et al. AACR 2021

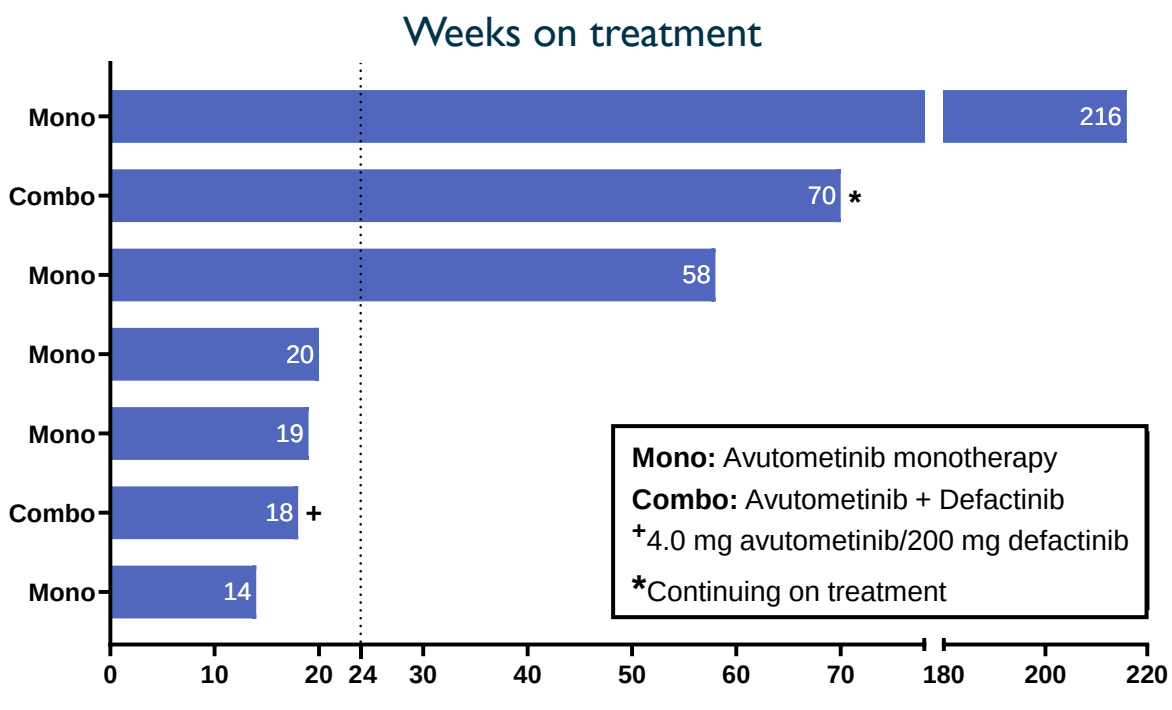
Strong Signal Identified in KRAS G12V NSCLC

Avutometinib ± Defactinib Has Shown a 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 NSCLC**
- **Activity of avutometinib as a single agent and in combination with defactinib in KRAS G12V NSCLC**

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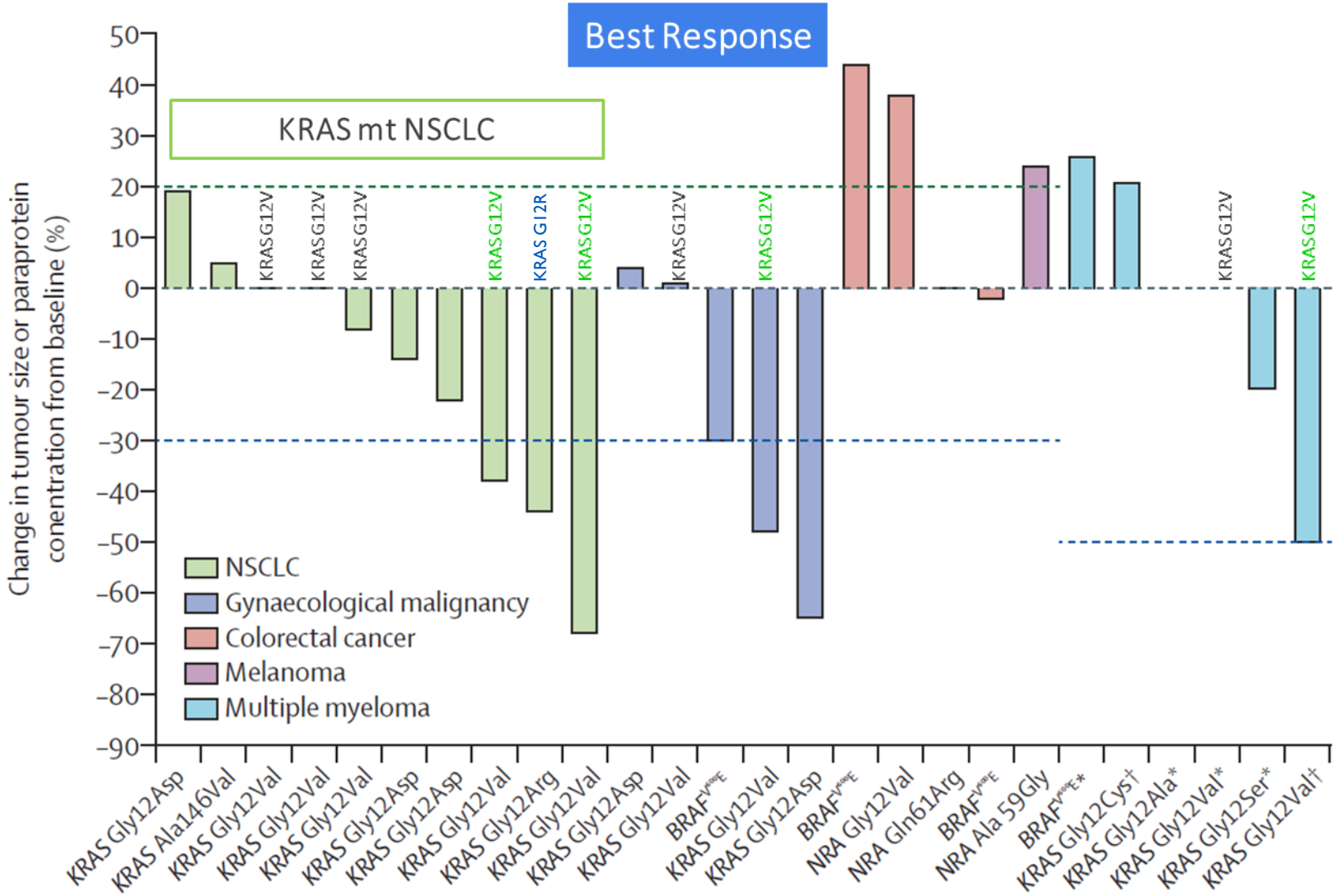
References: [1] Guo, et al Lancet Oncology 2020 [2] Krebs, AACR April 2021(March 18, 2021 cutoff)

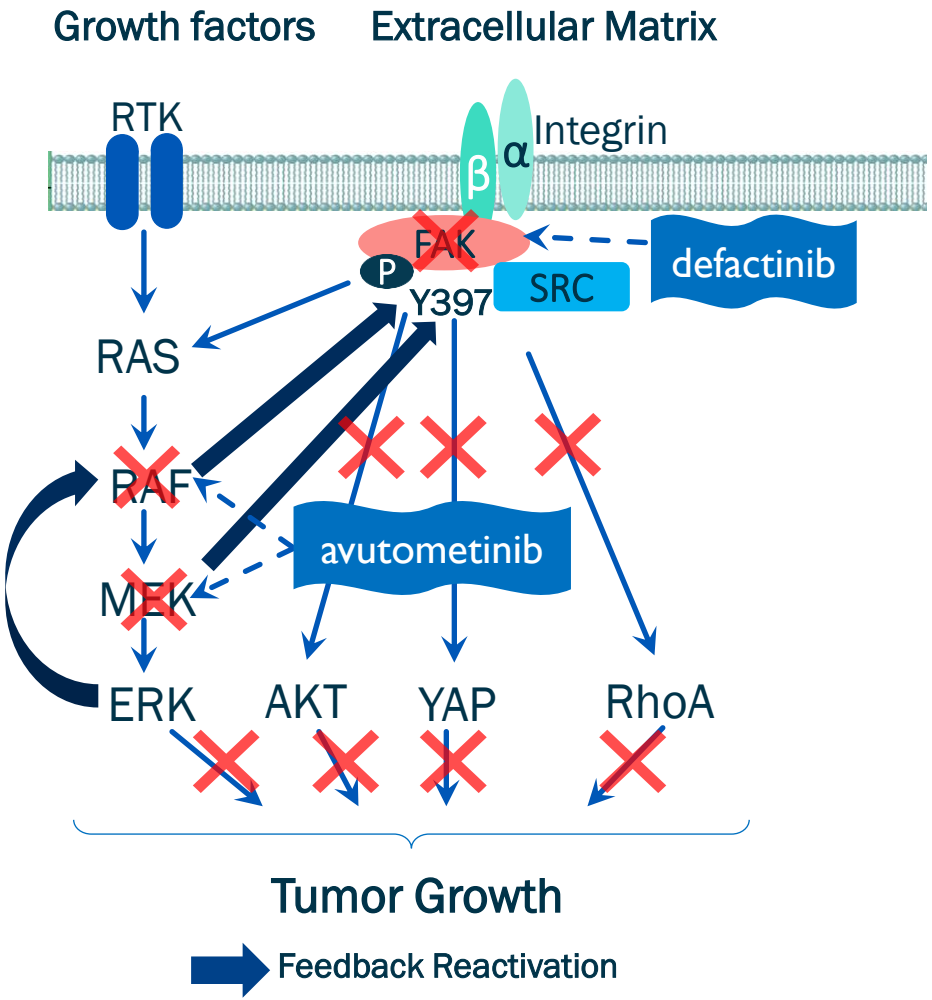
Avutometinib Monotherapy Has Shown Clinical Activity in Several RAS/RAF Mutant Cancer Indications, Including NSCLC and Gynecologic Cancers

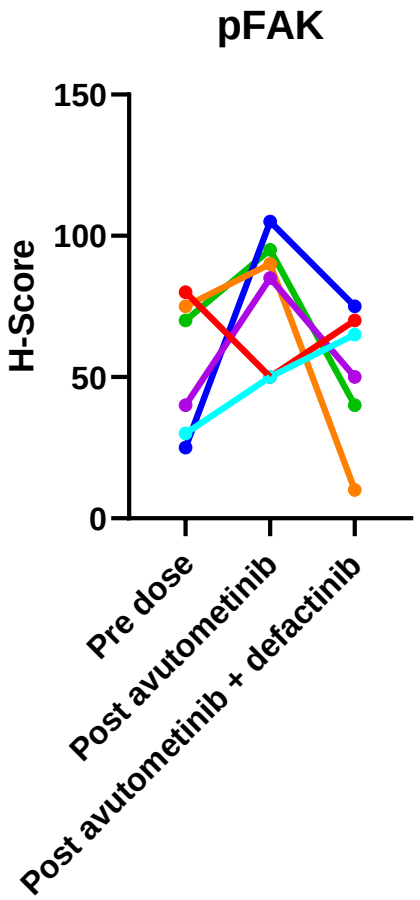
Confirmed responses especially in patients with KRAS G12V mutation



Guo et al., Lancet Oncology 2020

Overcoming Key Resistance Mechanisms to MEK Inhibitors





- **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**
    - **Avutometinib induced ↑ pFAK (Y397) as a potential resistance mechanism in the majority of patients**
    - **Combination with defactinib reduced this compensatory pFAK signal**

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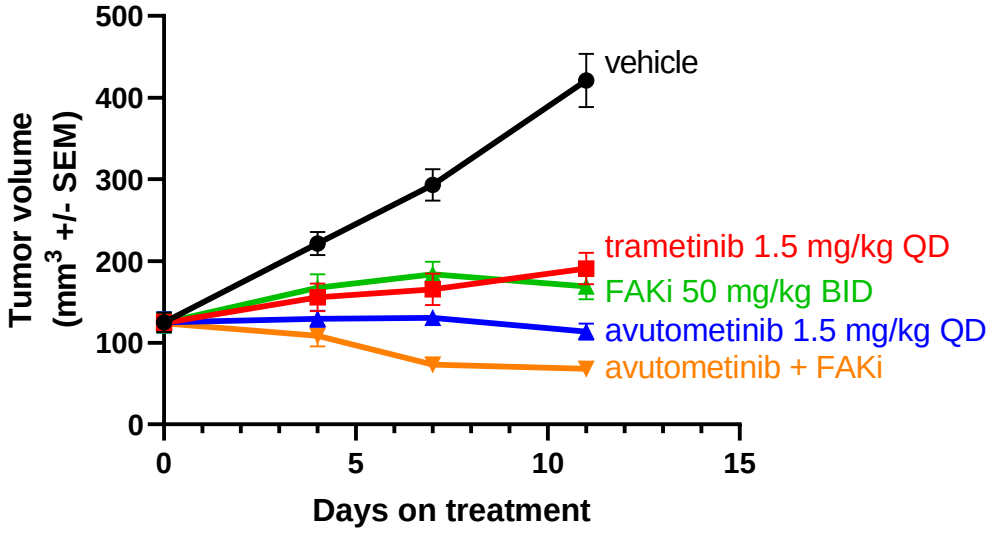
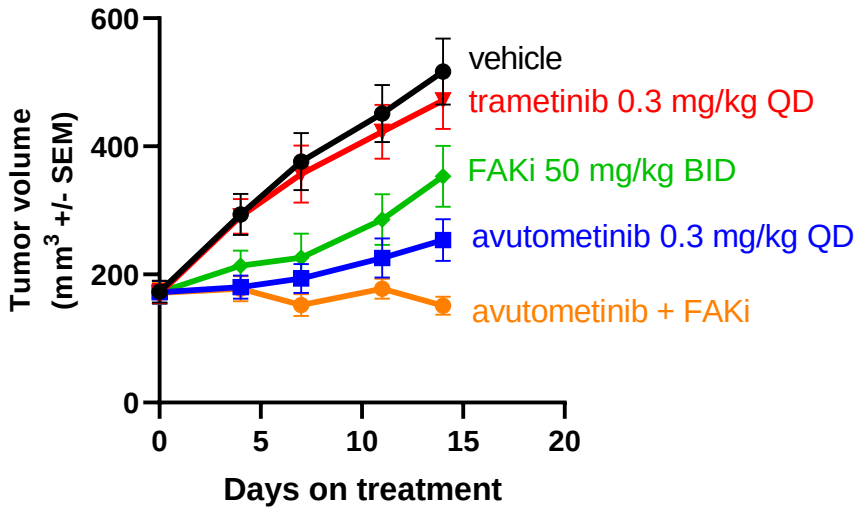
References:
Banerji, BTOG Dublin, Jan 23, 2019
Banerji, AACR VM 1, April 27, 2020, CT143

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

KRAS mt Ovarian TOV-21G *in vivo* Model[1]



KRAS mt NSCLC H358 *in vivo* Model[2]



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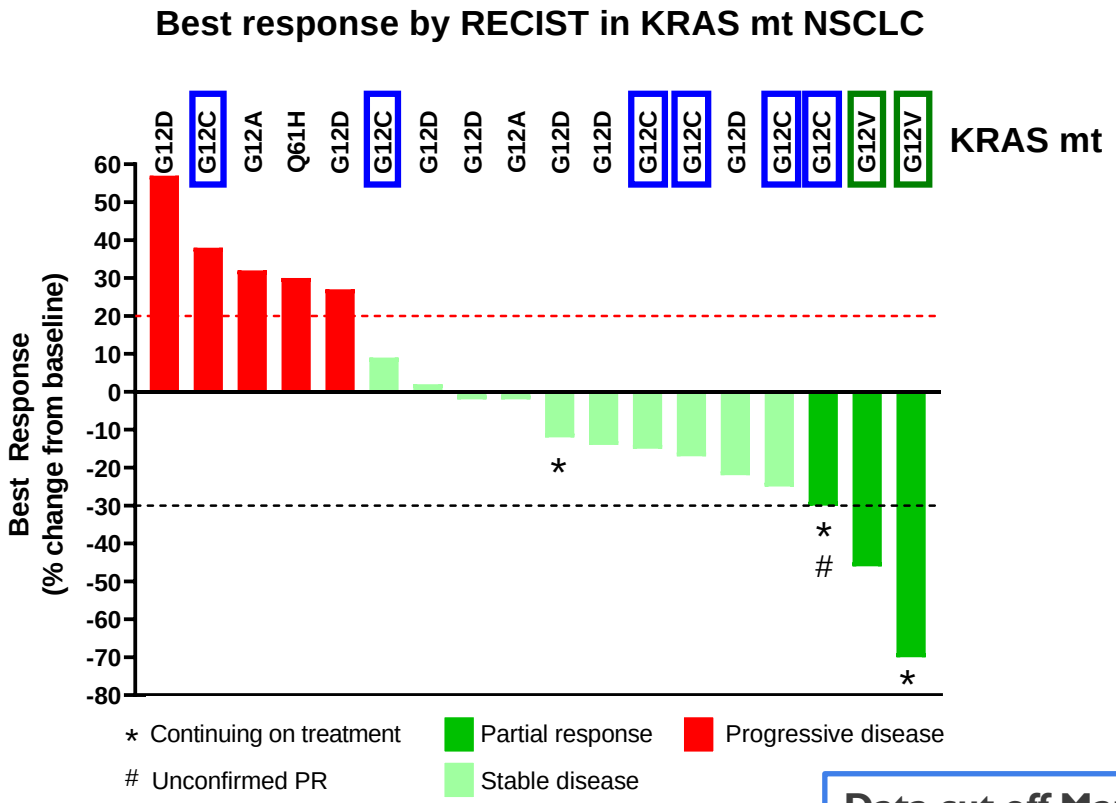
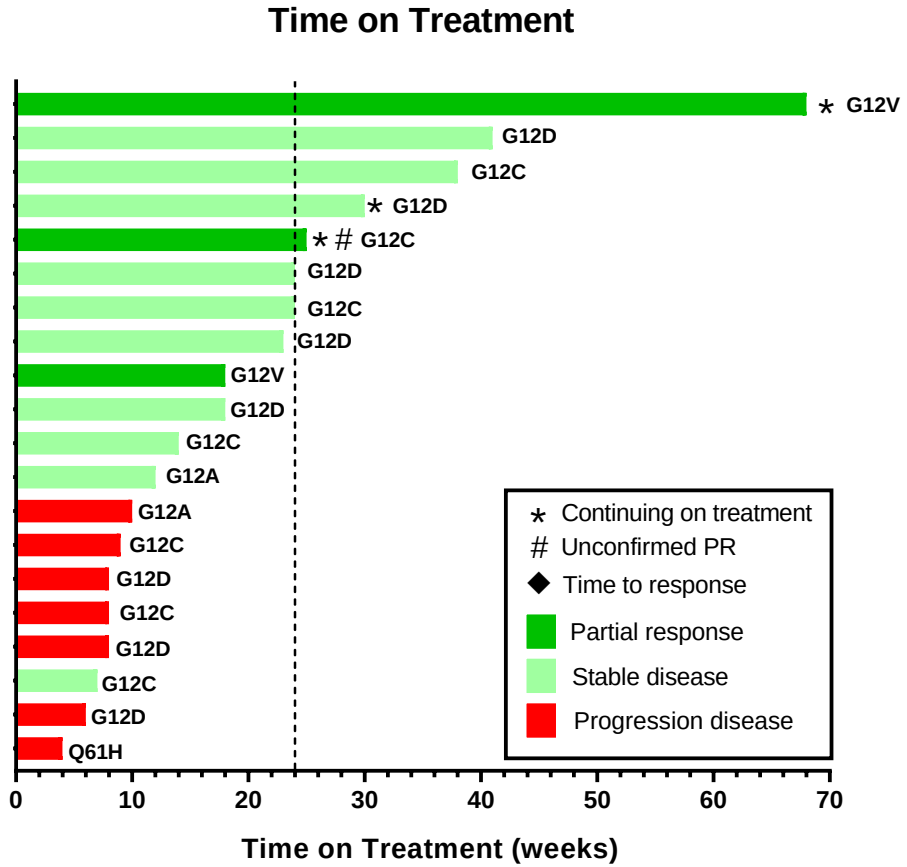
References: [1] Coma AACR 2021; [2] Krebs AACR 2021

NSCLC Responses with Avutometinib + Defactinib Combination (FRAME) (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 = 100% (2/2)
- DCR =65% (13/20)
- 3/20 (15%) still on study
- 7 pts on treatment ≥ 24 weeks

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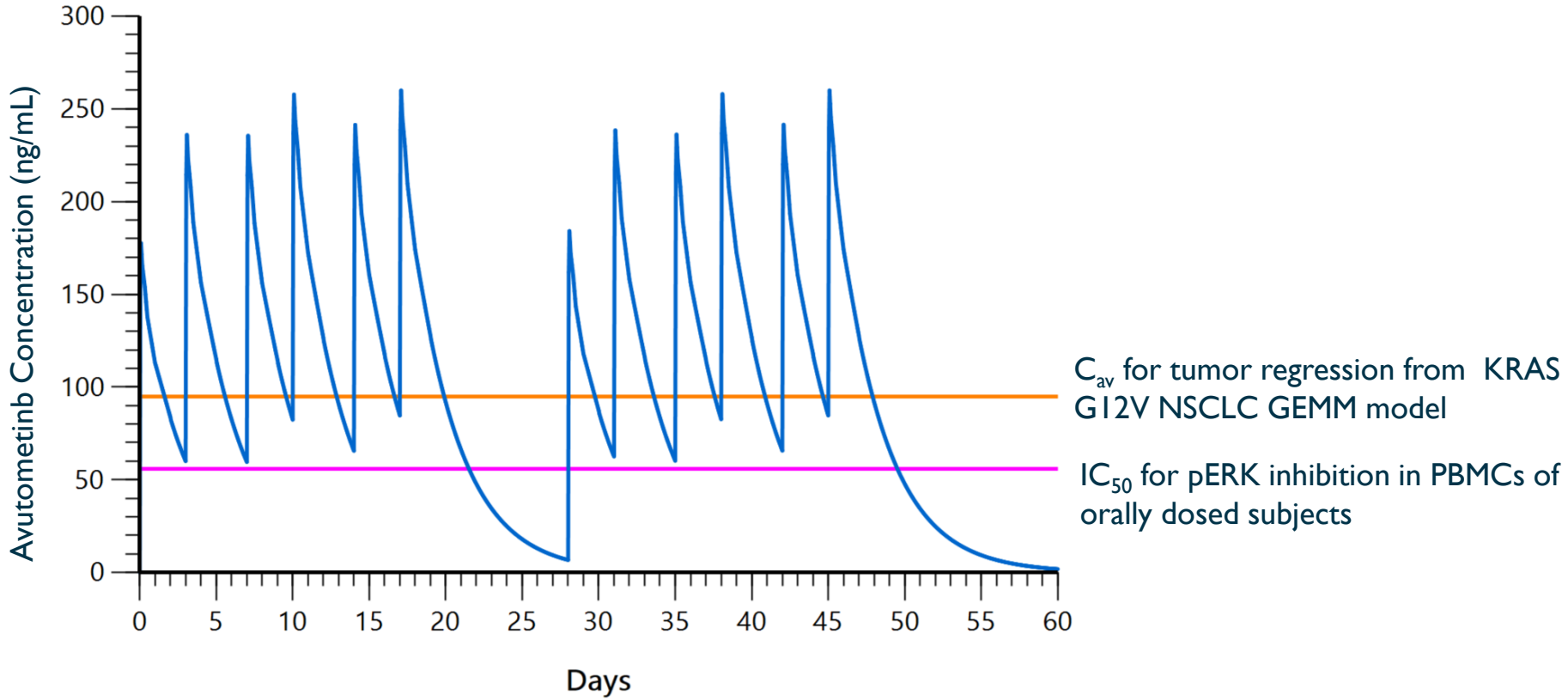
Reference: Krebs et al. AACR 2021

Target exposures for preclinical tumor regression & pERK inhibition in human subjects are covered by twice weekly dosing of 3.2 mg avutometinib, 3 wks on/1 wk off



- Modeling of PK for 3.2 mg avutometinib 2/wk, 3 wks on/1 wk off, based on 3.2 mg single dose PK data (study CCR3808)
- Relationship to average exposure for tumor regression in KRAS G12V NSCLC mouse model and IC_{50} against human PBMC pERK activity

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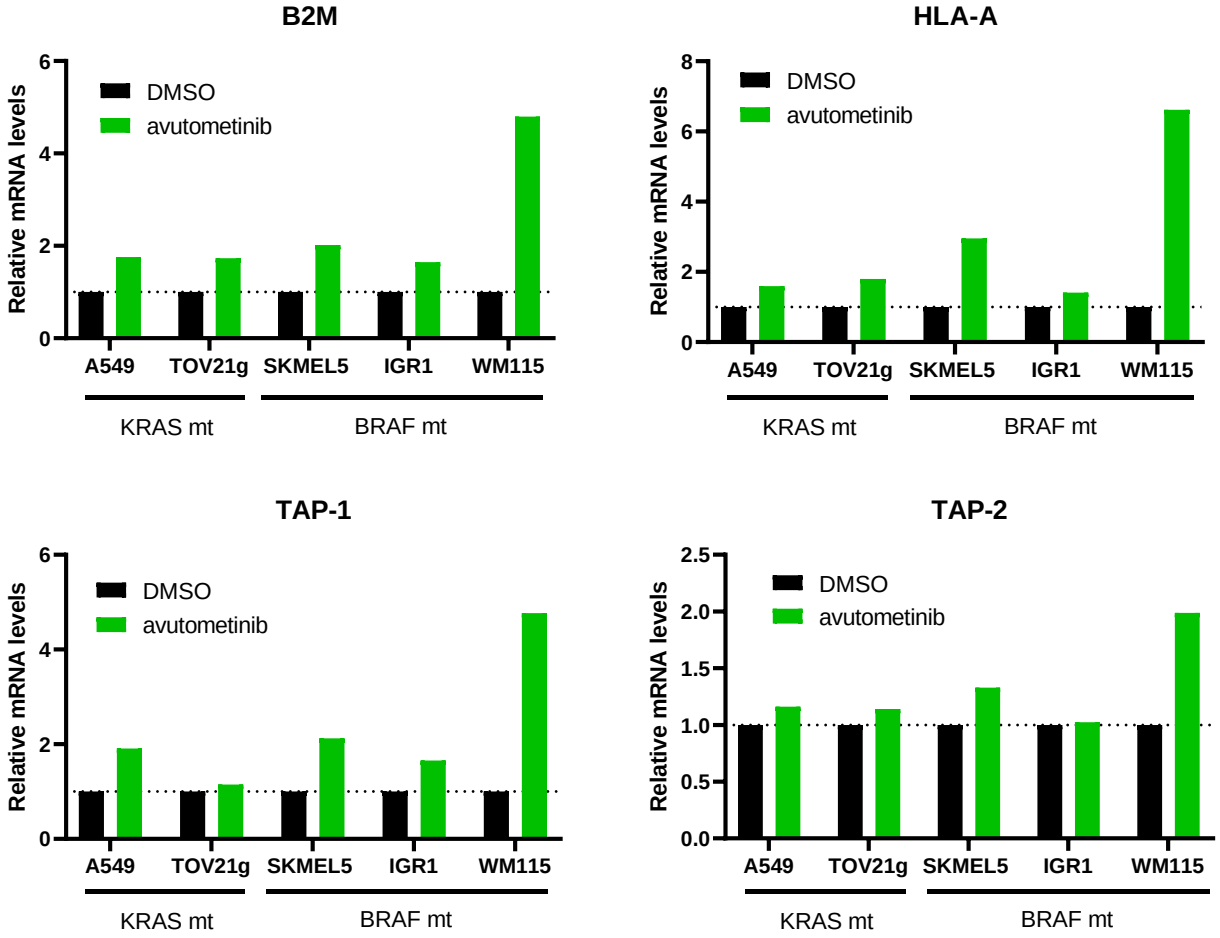
References: Martinez-Garcia et al., Clin Cancer Res 2012; Coma et al. AACR 2021

Avutometinib 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	KRAS G12S
TOV21g	Ovarian	KRAS G13C
SKMEL5	Melanoma	BRAF V600E
IGR-1	Melanoma	BRAF V600E
WM115	Melanoma	BRAF V600E

Avutometinib @ 1 μM (except SKMEL5 and IGR-1, 300 nM)

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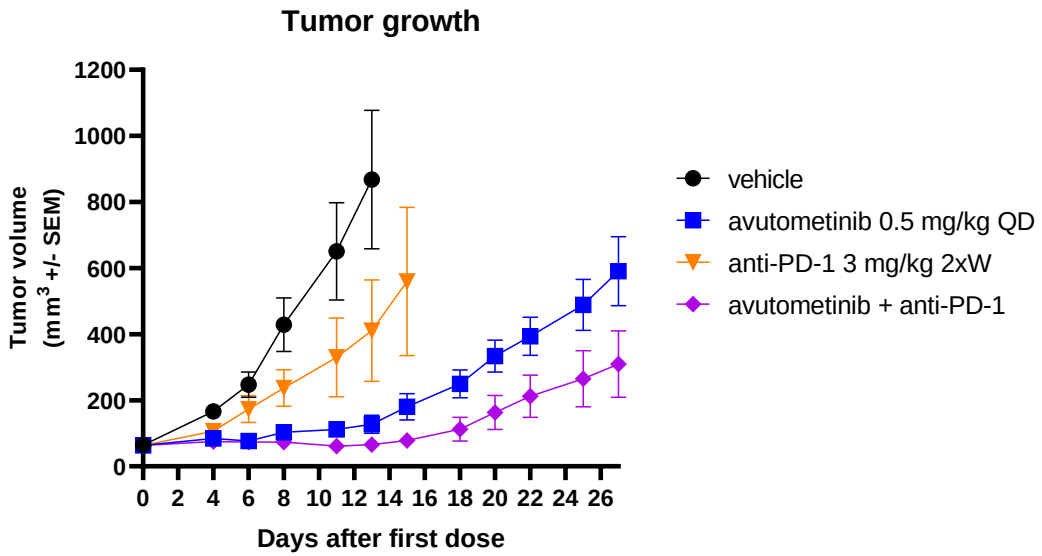
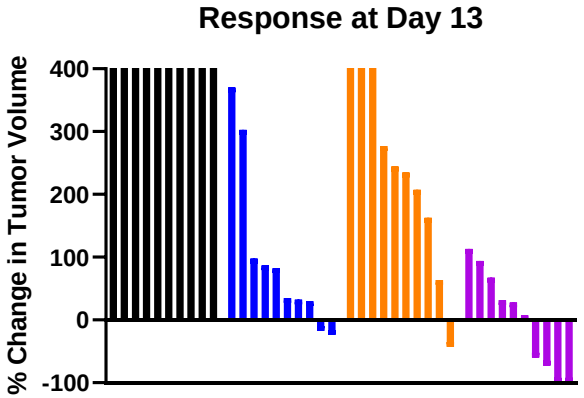
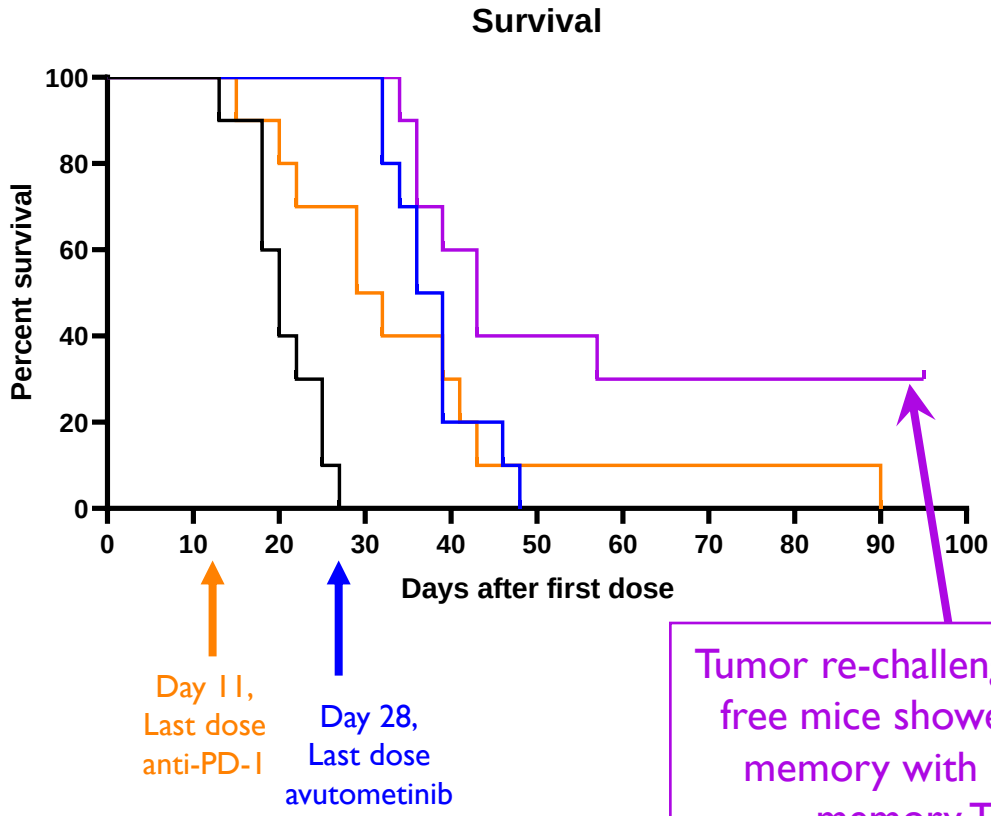
Reference: Pachter, RAS-Targeted Drug Development, Sept 2020

Avutometinib Enhances Tumor Growth Inhibition when Combined with Anti-PD-1 in the CT26 KRAS G12D Syngeneic Model







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

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Reference: Pachter, RAS-Targeted Drug Development, Sept 2020

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

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

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