VERASTEM ONCOLOGY

Corporate Presentation

April 2023

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, as well as Verastem Oncology's potential income under its asset purchase agreement with Secura Bio. Inc. and borrowings under its credit facility, 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, 2022, as filed with the Securities and Exchange Commission (SEC) on March 14, 2023, 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.

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

Verastem Oncology
Well Positioned to Capitalize on Growth Opportunities

Lead clinical program has best-in-class potential	Avutometinib (VS-6766; RAF/MEK clamp) and defactinib (FAK inhibitor) are clinically active against RAS pathway-driven cancers
Rapid development path to market in LGSOC	**FDA Breakthrough Therapy Designation;** Interim analysis of Part A of registration-directed RAMP 201 trial: avutometinib + defactinib confirmed response rates and safety profile support continued development in all recurrent LGSOC; timing of accelerated approval filing to be based on data maturity and finalization of confirmatory study plans
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 studies in progress** evaluating avutometinib combinations across RAS pathway-driven cancers
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	Cash balance of $87.9 million as of December 31, 2022 Pro-forma cash balance of $132.9 million including Q1 2023 financing activities ($30 million from Series B Preferred Stock issuance and $15 million from Oxford Term B Loan draw) Up to $150 million of non-dilutive funding available from credit facility Company ended Q4 2022 with $15.6 million non-GAAP operating expenses*

* Q4 2022 GAAP operating expenses - $16.85M minus Q4 2022 stock compensation of $1.29M = $15.56M Q4 2022 non-GAAP operating expenses

Key VSTM Achievements 2022 & Anticipated Milestones 2023

	1H2022	2H2022	1Q2023	2Q2023	2H2023
LGSOC	✓ RAMP 201 Selection Phase Complete; Initiated enrollment of Expansion Phase	✓ RAMP 201 Second Interim Update	✓ RAMP 201 Complete target enrollment of Expansion Phase	Present updated results of Part A RAMP 201	Initiate confirmatory study of avutometinib + defactinib in recurrent LGSOC
	✓ RAMP 201 Selection Phase Update**	✓ RAMP 201 FDA Meeting - Avuto + defactinib selected as Go-Forward	✓ Launch LGSOC patient education campaign	Discuss confirmatory trial study design for recurrent LGSOC program	
	✓ Translational data from FRAME LGSOC cohort presented				
NSCLC	✓ RAMP 202 Complete enrollment of Selection Phase	✓ Initiate RAMP 204 (avuto + adagrasib) G12C		RAMP 203: Determine recommended phase 2 dose	RAMP 203: Report initial read-out of safety and preliminary efficacy
	✓ Initiate RAMP 203 (avuto + sotorasib) G12C	✓ Top-Line Data from RAMP 202 Selection Phase		Present updated results of IST avutometinib + everolimus in KRAS mt NSCLC	RAMP 204: Initial read-out of safety and recommended dose
	✓ Top-Line Data from avutometinib + everolimus in KRAS mt	✓ RAMP 203 advanced to final dose level			
	✓ RAMP 202 Amended to include BRAF mt cohorts				
Additional Indications	✓ PanCAN Agreement Executed	✓ Initiate combo study of avutometinib + cetuximab in KRAS mt CRC *	Initiate combo study of avutometinib + pembrolizumab in BRAF mt melanoma *	Pediatric Cancer *	RAMP 205: determine recommended phase 2 dose and complete enrollment of initial phase 2 expansion cohort
		✓ Initiate RAMP 205 combo avutometinib + gemcitabine/nab-paclitaxel + defactinib in metastatic pancreatic cancer	Initiate thyroid cancer *	Early safety data of avutometinib + cetuximab in KRAS mt CRC *	Initial results of Gynecological basket trial *
				AACR: Everolimus NSCLC presentation Preclinical-combinations presentations *	Early efficacy results of thyroid cancer *
					Early safety results of avutometinib + pembrolizumab in BRAF melanoma *

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*Investigator-sponsored research

**RAMP 201 update expected to be provided once go-forward treatment regimen determined, timing of which will be driven by data maturity

- - - Indicate anticipated milestones

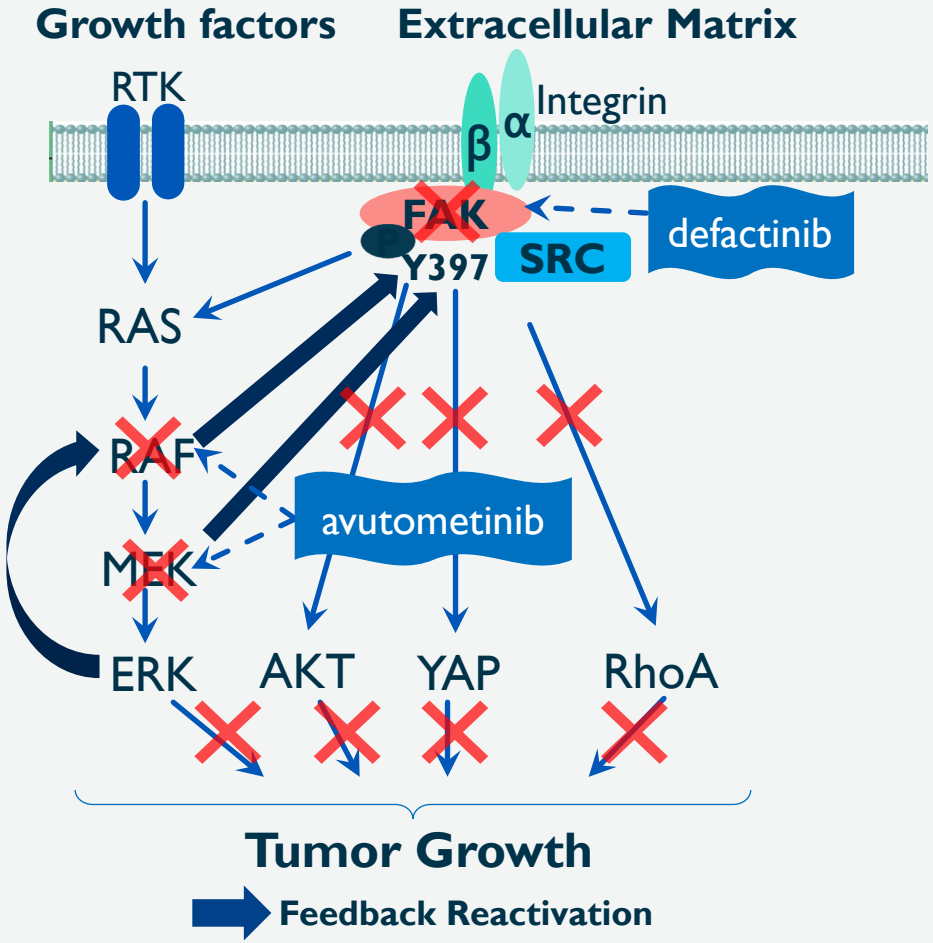
Avutometinib is a Differentiated Agent with the Potential to Serve as the Backbone for Combinations Across RAS Pathway-Driven Cancers

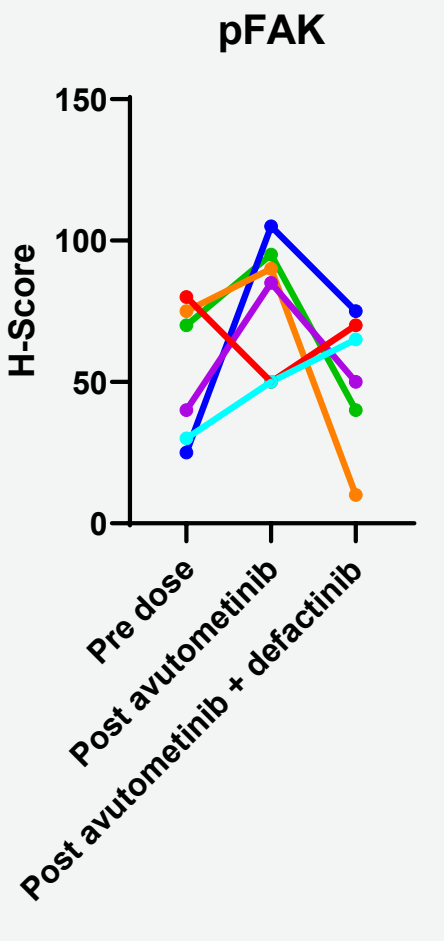
- Unique RAF/MEK clamp mechanism of action
- Novel intermittent dosing schedule; convenient oral regimen
- Breakthrough Therapy Designation in recurrent low-grade serous ovarian cancer(LGSOC) regardless of KRAS status
- Potential best-in-class safety & tolerability profile relative to marketed MEK inhibitors, with potential for combinability with agents from multiple target classes
- Promising signals of clinical activity in various RAS pathway-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 (e.g. KRAS G12C inhibitors) and parallel pathways (e.g. FAK inhibitors)

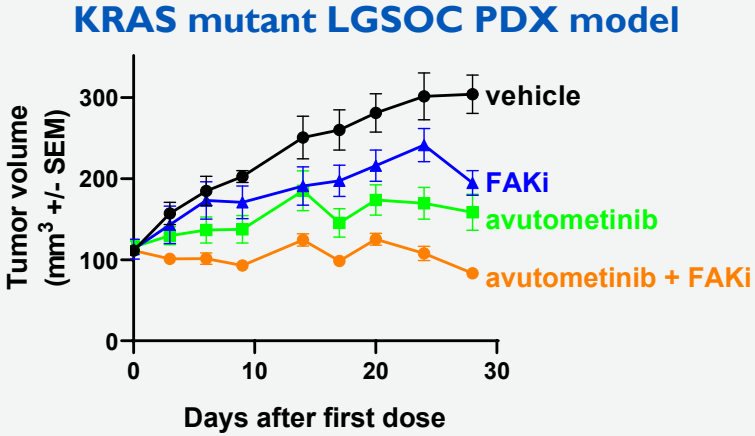
RAF-Rapidly accelerated fibrosarcoma
MEK-Mitogen-activated protein kinase kinase
RAS-Rat sarcoma virus
MAPK-Mitogen-activated protein kinase
KRAS-Kirsten rat sarcoma virus
NRAS-Neuroblastoma RAS viral oncogene homolog
BRAF-v-raf murine sarcoma viral oncogene homolog B1
NF1-Neurofibromatosis type 1

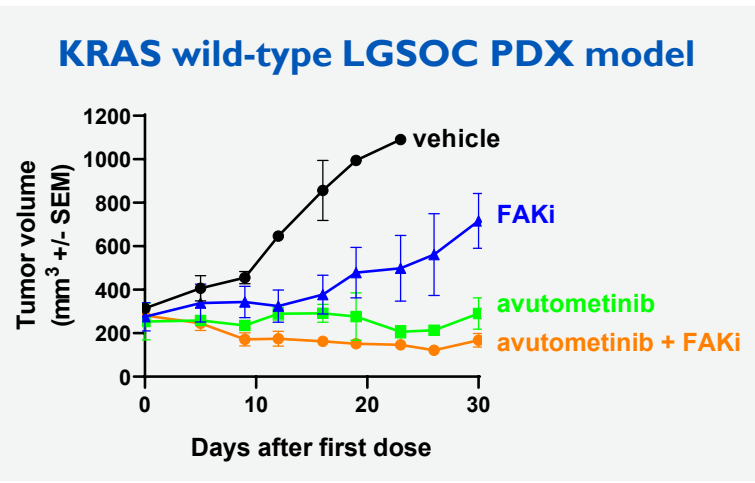
Strong Scientific Rationale for Avutometinib and FAK Inhibitor Combination

Anti-Tumor Efficacy in KRAS Mutant and Wild-Type LGSOC models









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

LGSOC Unmet Need & Opportunity

- LGSOC is a less common type of ovarian cancer that is often diagnosed in younger women
  - LGSOC is a unique disease that is distinct from high-grade serous ovarian cancer (HGSOC) in its pathology, protracted clinical course and low response to chemotherapy and thus requires a more tailored therapeutic approach
  - An estimated 1,000-2,000 patients are diagnosed with LGSOC per year in the U.S., with prevalence of ~6,000
- There are currently no approved therapies specifically indicated for recurrent LGSOC
  - Recent clinical trials in recurrent LGSOC showed that standard-of-care chemo and endocrine therapy are relatively ineffective (6-13% ORR).
  - Currently available therapies have a poor benefit/risk profile and NCCN guidelines include clinical trials and observation highlighting the lack of approved & effective therapies
- LGSOC is known to be driven by the MAPK (RAS) pathway in ≥70% of patients
- A phase I/II study in the UK (FRAME) evaluated the combination of avutometinib and defactinib
  - Results in recurrent LGSOC showed a 46% confirmed ORR with durable responses and favorable safety/tolerability

- ➢ Breakthrough Therapy Designation was granted for avutometinib and defactinib in recurrent LGSOC
- ➢ RAMP 201: A registration-directed Phase 2 trial of avutometinib + defactinib in recurrent LGSOC is ongoing

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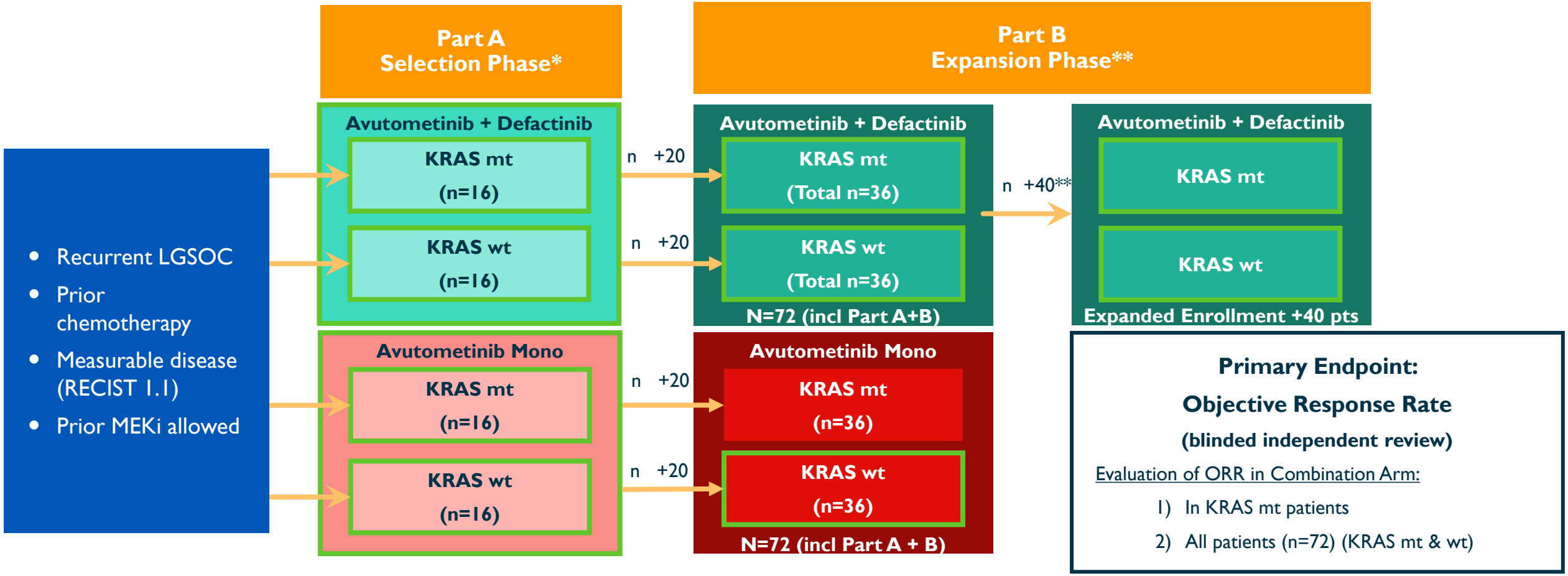
References: Monk et al., The Evolving Landscape of Chemotherapy in Newly Diagnosed Advanced Epithelial Ovarian Cancer, 2019; Slomovitz et al., Low-Grade serous ovarian cancer: State of the Science, 2020; Grisham et al., Low-Grade Serous Ovarian Cancer: Current Treatment Paradigms and Future Directions, 2018; AACR Project GENIE Cohort v9.0-public and Verastem unpublished analysis; Banerjee et al., Phase I study of the combination of the dual RAF/MEK inhibitor VS-6766 and the FAK inhibitor defactinib: Results of efficacy in low grade serous ovarian cancer, ESMO 2021; Malpica et al., Interobserver and intraobserver variability of a two-tier system for grading ovarian serous carcinoma, 2007; NCCN guidelines v1.2023

RAMP 201 (ENGOTov60/GOG3052): Registration-Directed Phase 2 Trial of Avutometinib ± Defactinib in Patients with Recurrent LGSOC



*Dosing: Avutometinib + Defactinib combo: Avutometinib 3.2 mg PO 2x/wk 21/28 days + Defactinib 200 mg 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

Combination Arm:
- ❖ **Expanded Enrollment Ongoing**
- ✓ **Target Enrollment Reached (N=72)**

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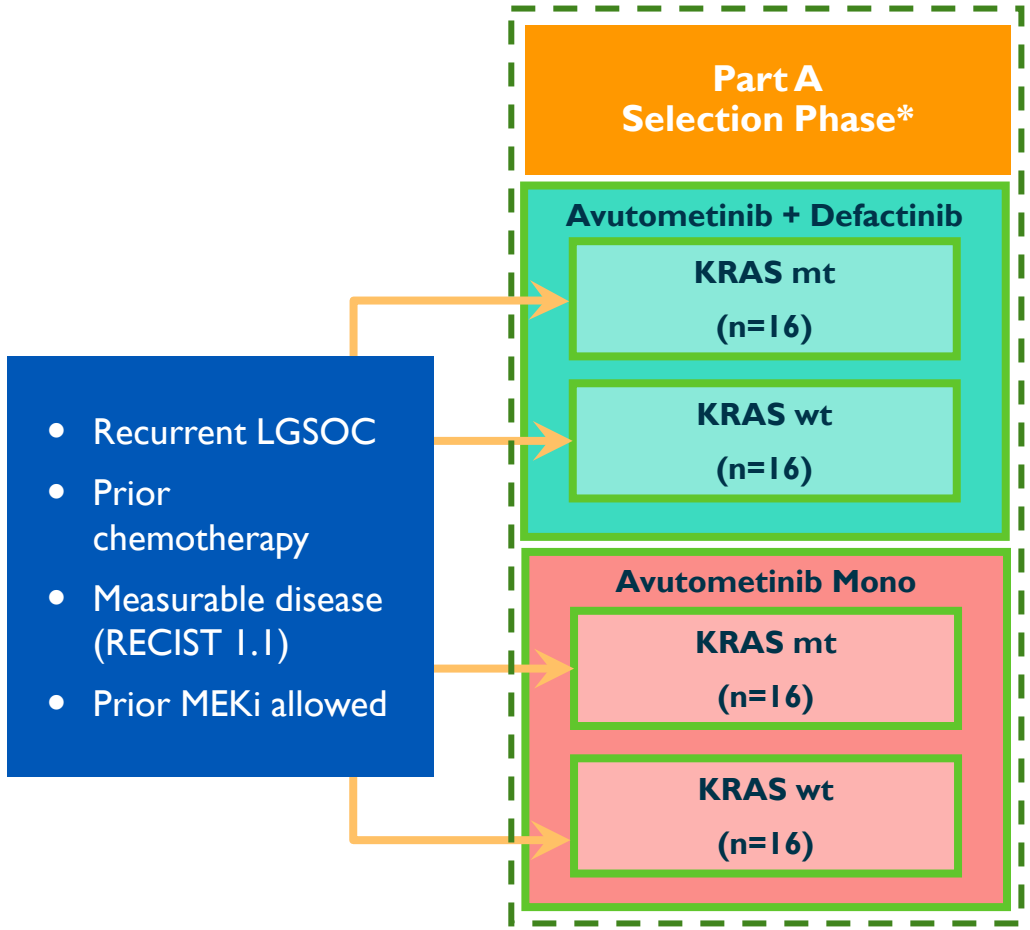
RAMP 201 (ENGOTov60/GOG3052): Registration-Directed Phase 2 Trial of Avutometinib ± Defactinib in Patients with Recurrent LGSOC



Planned Interim Analysis:

- ***Initial Efficacy Data: Part A (Evaluable Patients)***
- ***Safety Data: All Treated Patients***

- **Heavily** pretreated population;
  - Median of **4** prior lines of systemic therapy
- Clinical development continues in **all recurrent LGSOC**, regardless of KRAS status
- **Combination of avutometinib and defactinib** selected as "Go Forward" treatment regimen
  - **ORR 28%** independently confirmed
    - KRAS mt: 27%; KRAS wt: 29%
  - Tolerable safety profile - No new safety signals;
  - Majority of evaluable patients remain on treatment (62%)

*Dosing: Avutometinib + defactinib combo: Avutometinib 3.2 mg PO 2x/wk 21/28 days + Defactinib 200 mg PO BID: 21/28 days
Avutometinib monotherapy: Avutometinib 4.0 mg PO 2x/wk 21/28 days

Efficacy and Tolerability of Avutometinib and Defactinib in LGSOC

A Head-to-Head Study Has Not Been Performed

Trial	Median Number of Prior lines of Therapy	Prior MEK Allowed	Prior Bevacizumab	Therapy	Response Rate ORR	Image Assessment	Median PFS Months (95% CI)	Discontinuation Rate Due to AEs
GOG 281[1]	**3** (1-10)	No	* Low %	**Standard of Care**	**6% ^**	INV	7.2 (5.6-9.9)	13%
				Trametinib	26%^	INV	13.0 (9.9-15.0)	**36%**
MILO[2]	**2** (1-8)	No	* Low %	**Standard of Care**	**13%**	**BICR**	10.6 (9.2 to 14.5)	17%
				Binimetinib	**16%**	**BICR**	9.1 (7.3-11.3)	**31%**
FRAME[3]	3	Yes	12 %	Avutometinib + Defactinib	**46%^** *95% CI: (26%, 67%)*	INV	**23** (11 - NR)	4%
RAMP 201 Part A[3]	4	Yes	65%	**Avutometinib + Defactinib**	**28%** **95% CI: (13%, 47%)** **38%****	**BICR**	Not Yet Available	9%

** Low historical use of bevacizumab during trial conduct.*
*** Confirmed + Unconfirmed Objectives responses*
^ Investigator Assessment only (No independent Central Review of Imaging)

Standard of Care = letrozole, tamoxifen, chemotherapy
INV = Investigator
BICR = Blinded independent central review
PFS = Progression free survival

[1] Study GOG 281 trial Gershenson et al., Lancet 2022
[2] MILO Study Monk et al., J Clin Oncol 2020.
[3] Avutometinib + Defactinib combination evaluable population

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RAMP 201: Safety and Tolerability Profile of Avutometinib + Defactinib
No New Safety Signals; Few Discontinuations Due to Adverse Events

Most Common Treatment-Related Adverse Events (>20%) in All Treated Patients

- Majority of adverse events are mild to moderate
- Adverse events are monitorable, manageable and reversible
- Few discontinuations due to adverse events (9% in combo n=5 – includes 3 pts for elevated blood CPK laboratory values*)
  * No association to date with clinically significant toxicities, including rhabdomyolysis

Avutometinib + Defactinib						
	Any Grade			Grade ≥3		
	KRAS mt (n=22) %	KRAS wt (n=35) %	Total (n=57) %	KRAS mt (n=22) %	KRAS wt (n=35) %	**Total (n=57) %**
Nausea	45.5	65.7	57.9	0	0	**0**
Diarrhea	54.5	51.4	52.6	4.5	2.9	**3.5**
Edema peripheral	36.4	48.6	43.9	0	0	**0**
Fatigue	40.9	40.0	40.4	9.1	2.9	**5.3**
Vision blurred	31.8	42.9	38.6	0	0	**0**
Vomiting	40.9	37.1	38.6	0	0	**0**
Blood creatine phosphokinase increased	40.9	37.1	38.6	18.2	14.3	**15.8**
Dermatitis acneiform	27.3	45.7	38.6	4.5	0	**1.8**
Rash	31.8	37.1	35.1	0	2.9	**1.8**
Dry skin	13.6	31.4	24.6	0	0	**0**

RAMP 201 Part A Results and FDA Feedback Establish Path to Filing for Accelerated Approval

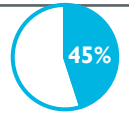
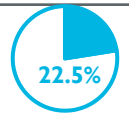
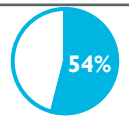
Update

- Combination of avutometinib with defactinib selected as go forward treatment regimen
- Combination development continues in all recurrent LGSOC, regardless of KRAS status
- Encouraging efficacy results include independently confirmed responses
- No new safety signals; few discontinuations due to adverse events
- Majority of patients remain on treatment

Next Steps

- Target enrollment for primary analysis (n=72) in combination has been achieved
- Plan to file for accelerated approval based on the totality of the data from the RAMP 201 and FRAME studies
- Continued enrollment in RAMP 201 combination arm only is planned to expand clinical experience in anticipation of initiation of a confirmatory study
- The Company will provide an update after agreement with the FDA on the confirmatory study
- The Company is planning a RAMP 201 presentation at a scientific conference in mid-2023

Comprehensive approach to establish more complete blockade of RAS pathway & resistance pathways

	Indication	Incidence/ Prevalence	Regimen	Setting
Gynecologic Cancers	LGSOC	Prevalence[1]: 6K	Avutometinib + defactinib	Relapsed Refractory molecularly profiled LGSOC
	Gynecologic Basket*	Incidence[6-10]: 85K	Avutometinib + defactinib	Recurrent RAS Pathway-driven (RAS/RAF/NF1) endometrioid cancer, mucinous ovarian cancer, high-grade serous ovarian cancer or cervical cancer
NSCLC Adenocarcinoma	KRAS G12C	Incidence[2,3]: 114K	Avutometinib + sotorasib (AMGEN)	Recurrent KRAS G12C with prior KRAS G12C inhibitor(i) treatment or KRAS G12Ci naïve
			Avutometinib + adagrasib (MIRATI THERAPEUTICS)	Recurrent KRAS G12C with prior KRAS G12Ci treatment that progressed
	BRAF mt	Incidence[2,3]: 114K	Avutometinib + defactinib	Recurrent BRAF V600E & non-V600E mutant NSCLC
Pancreatic	PDAC	Incidence[4]: 58K	Avutometinib + defactinib + gemcitabine/nab-paclitaxel (PANCREATIC CANCER ACTION NETWORK)	Previously untreated (front-line) metastatic pancreatic ductal adenocarcinoma (PDAC)
CRC	KRAS mt*	Incidence[5]: 148K 	Avutometinib + cetuximab	Recurrent metastatic KRAS mt
Breast Cancer	ER+*	Incidence[5]: 279K 	Avutometinib + abemaciclib + fulvestrant	Recurrent ER+/HER2- breast cancer following progression on CDK4/6i + aromatase inhibitor
Melanoma	BRAF V600E*	Incidence[4]: 108K 	Avutometinib + pembrolizumab	Recurrent BRAF V600E/K or NRAS (Phase 1 only) mutant Melanoma following progression on prior anti-PD1 therapy

*IST

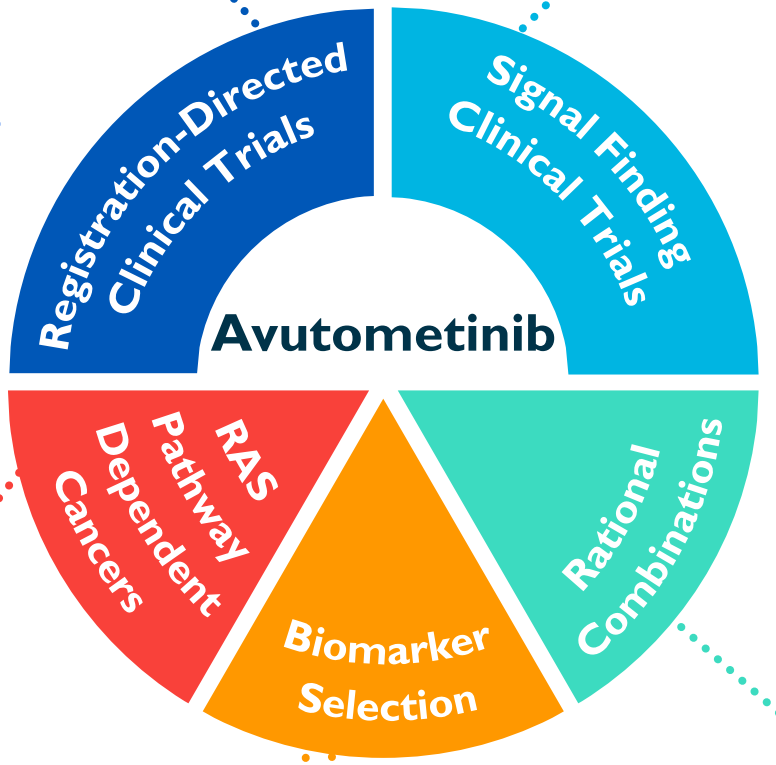
[1] References: Monk, Randall, Grisham, The Evolving Landscape of Chemotherapy in Newly Diagnosed Advanced Epithelial Ovarian Cancer, Am Soc Clin Oncol Educ Book; 2019; Slomovitz, Gourley, Carey, Malpica, Shih, Huntsman, Fader., Grisham et al, Low-Grade serous ovarian cancer: State of the Science; Gynecol Oncol; 2020. Grisham, Iyer, Low-Grade Serous Ovarian Cancer: Current Treatment Paradigms and Future Directions; Curr Treat Options Oncology; 2018; Globocan 2020; [2]Pakkala and Ramalingam JCI Insight 2018); [3]Cancer Statistics 2020, Siegel et. al. *CA Cancer J Clin* 2020;70:7-30; [4]Cancer Statistics 2020, Siegel et. al. *CA Cancer J Clin* 2020;70:7-30 [5]CbioPortal; [6]Uterine cancer is one of the leading gynecologic neoplastic disorders in the US, of which over 80% are endometrioid adenocarcinomas (EA); [7]Endometrioid OC (EnOC) accounts for approximately 10% of all OC, with the majority of cases diagnosed as low grade, early stage disease with excellent clinical; [8]Mucinous ovarian cancer: 3-11% of ovarian cancer (Hada et al., 2021); [9]90% of Ovarian Cancer is Epithelial Ovarian Cancer (https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf); [10]HGSOC the most common type of ovarian cancer, accounting for approximately 75% of epithelial ovarian cancers. (https://ocrahope.org/news/high-grade-serous-carcinoma/#:~:text=High%2Dgrade%20serous%20carcinoma%20is,unless%20another%20type%20is%20specified.)

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)-Target enrollment reached



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/NF1 mt gynecological cancers[1,2]
- Avutometinib + cetuximab in KRAS mt CRC[2]
- Avutometinib + abemaciclib and fulvestrant in ER+ breast cancer[2]
- Avutometinib + pembrolizumab in BRAFV600E melanoma[2]

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

- KRAS inhibitors[2] (G12Ci & G12Di)
- 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

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]	Avutometinib + defactinib	RAMP 201	Registration-directed trial: accelerated approval cohort fully enrolled	
R/R LGSOC	Avutometinib + defactinib	IST-FRAME		
Gynecological Cancers (RAS Pathway-driven)[2]	Avutometinib + defactinib	IST		
Mesonephric[2]	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	Avutometinib + gemcitabine/nab-paclitaxel + defactinib	RAMP 205		PANCREATIC CANCER ACTION NETWORK
R/R NSCLC (KRAS mt)	Avutometinib + everolimus (mTORi)	IST		
R/R Colorectal Cancer (KRAS mt)	Avutometinib + cetuximab (EGFRi)	IST		
ER+ Breast Cancer	Avutometinib + abemaciclib + fulvestrant	IST		
BRAF V600E Melanoma[2]	Avutometinib + pembrolizumab	IST		

[1] FDA Breakthrough Therapy Designation
[2] Imminent initiation

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Key Financial Statistics

As of and for the quarter ended December 31, 2022

Cash, cash equivalents & investments	$87.9M
Pro-forma cash, cash equivalents, & investments	$132.9M^
Non-GAAP Operating Expenses*	$15.6M
Shares Outstanding	200.5M

^ Pro-forma cash, cash equivalents & investments includes Q1 2023 financing activities ($30M from Series B Preferred Stock issuance and $15M from Oxford Term B Loan draw).

Sources of Non-Dilutive Capital

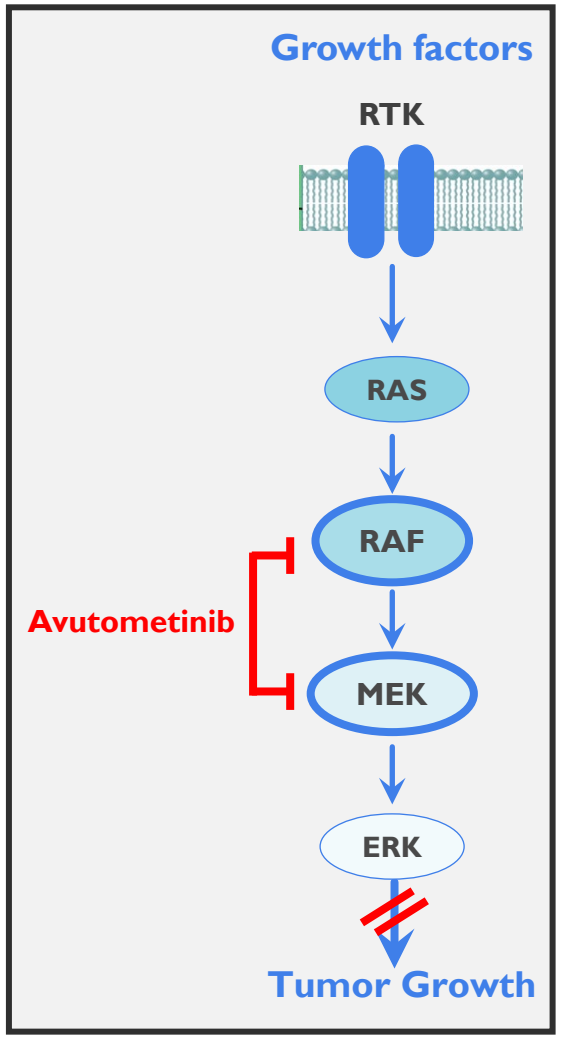
- **Oxford Finance LLC Credit Facility**
  - Up to $150M available in a series of term loans
    - $40M term loans outstanding as of March 2023.
    - Remaining $110M available upon achievement of pre-defined milestones or at lender's discretion
  - Floating interest rate, subject to a floor and a cap; 5% final payment charge, and loan subject to 1-3% early payment fee
  - Interest only payments through April 2025
  - No financial covenants

- **Secura Bio, Inc. (Secura) Asset Purchase Agreement – COPIKTRA**
  - Regulatory and commercial milestone payments up to $95M
  - Entitled to receive 50% of royalties, milestones, and sublicensee revenue payments made to Secura related to COPIKTRA
  - Low double-digit royalties on annual net sales over $100M in US, EU, and UK

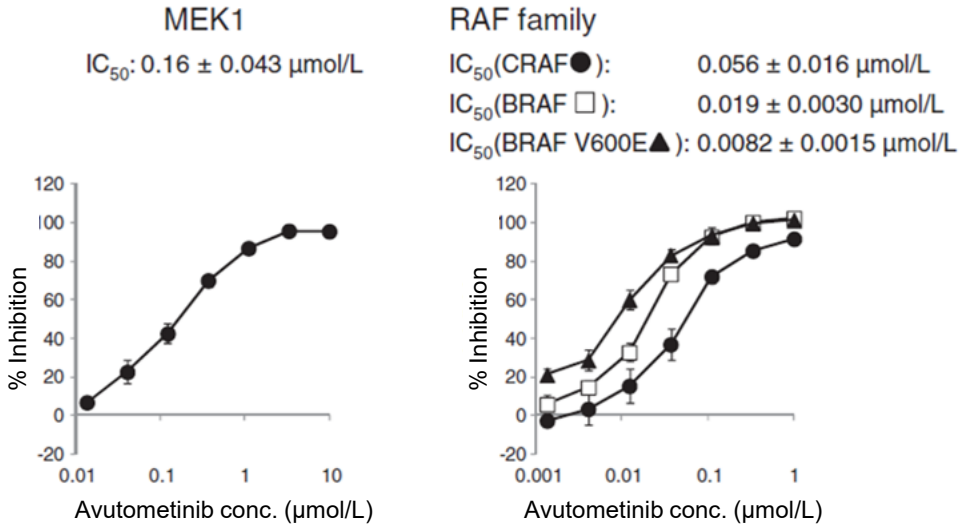
* Q4 2022 GAAP operating expenses - $16.85M minus Q4 2022 stock compensation of $1.29M = $15.56M Q4 2022 non-GAAP operating expenses

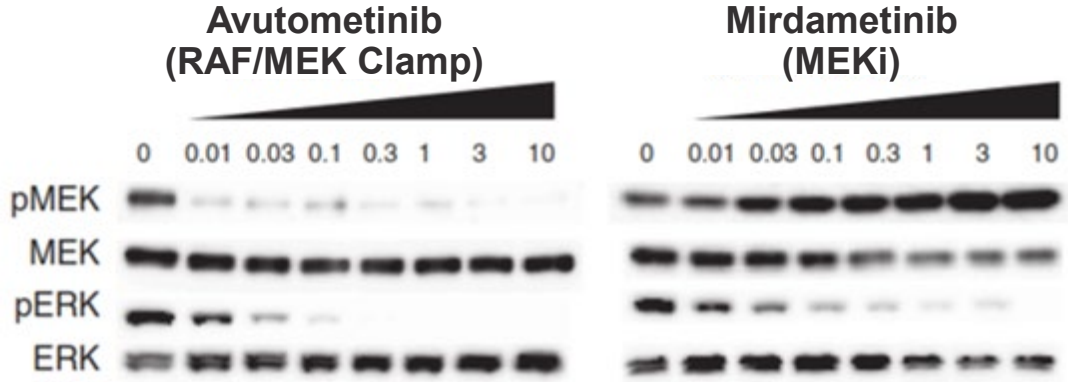
Avutometinib RAF/MEK Clamp Program Overview

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

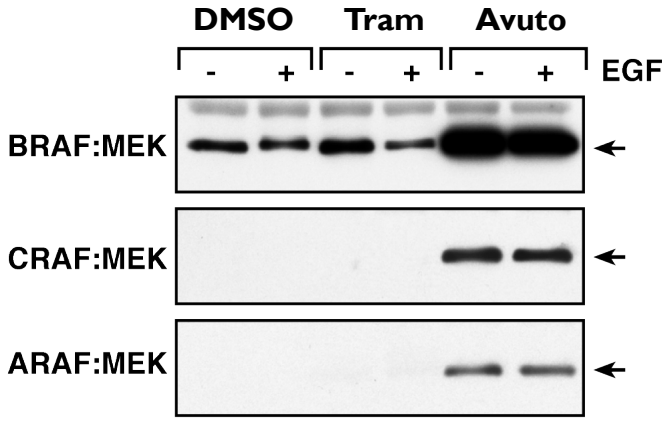


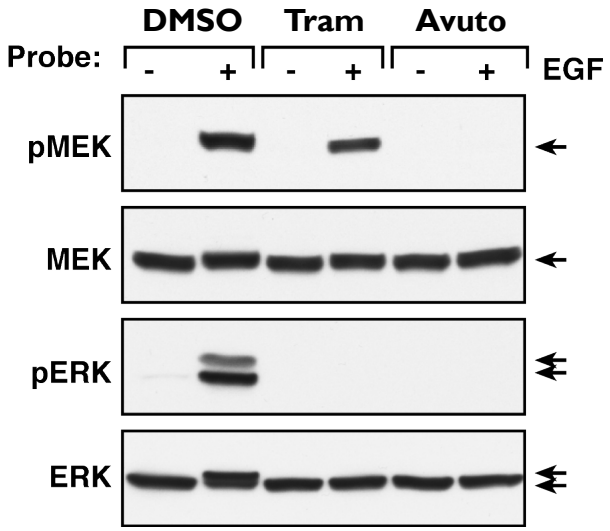


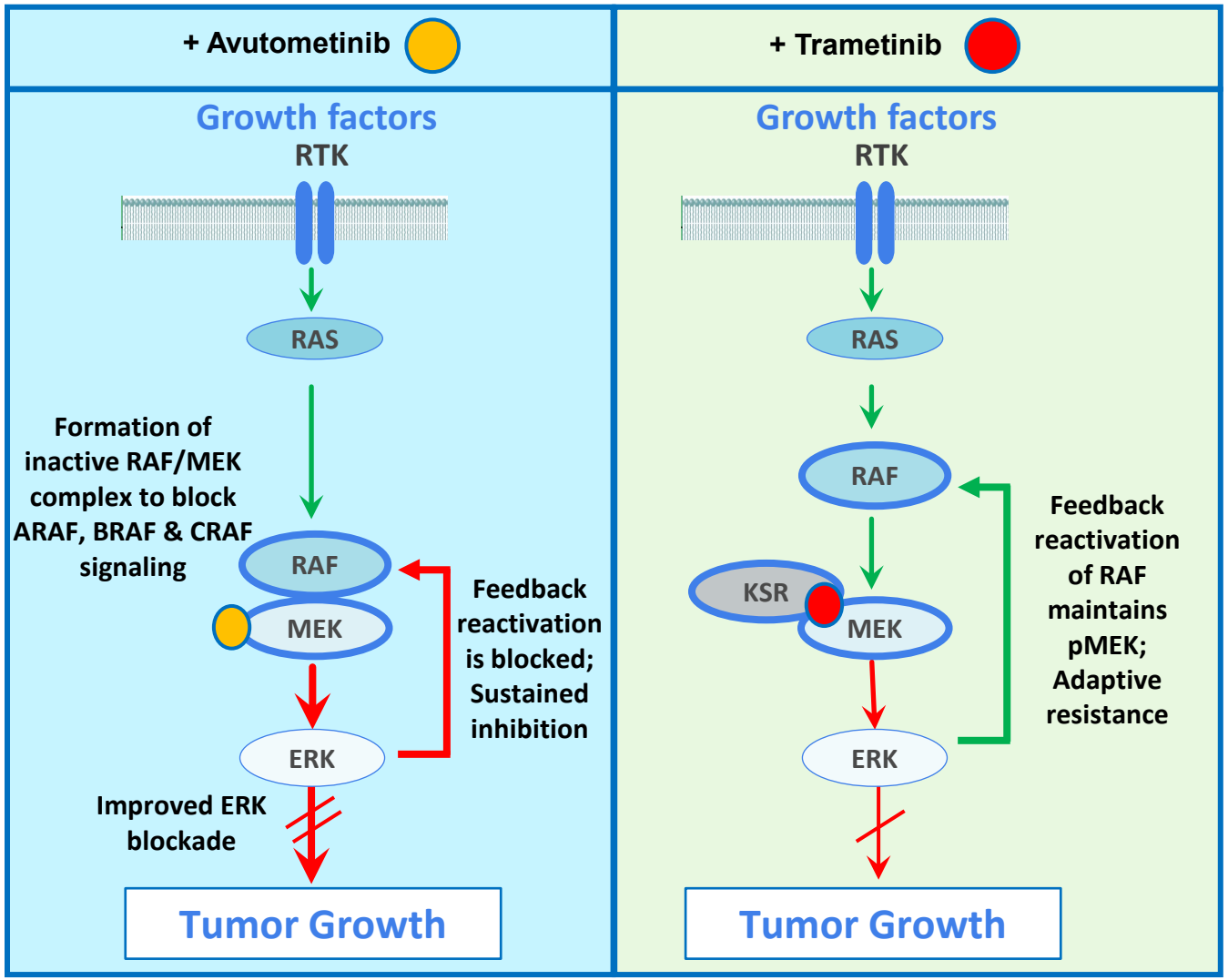
References: Ishii et al., *Cancer Res*, 2013; Lito et al., *Cancer Cell*, 2014

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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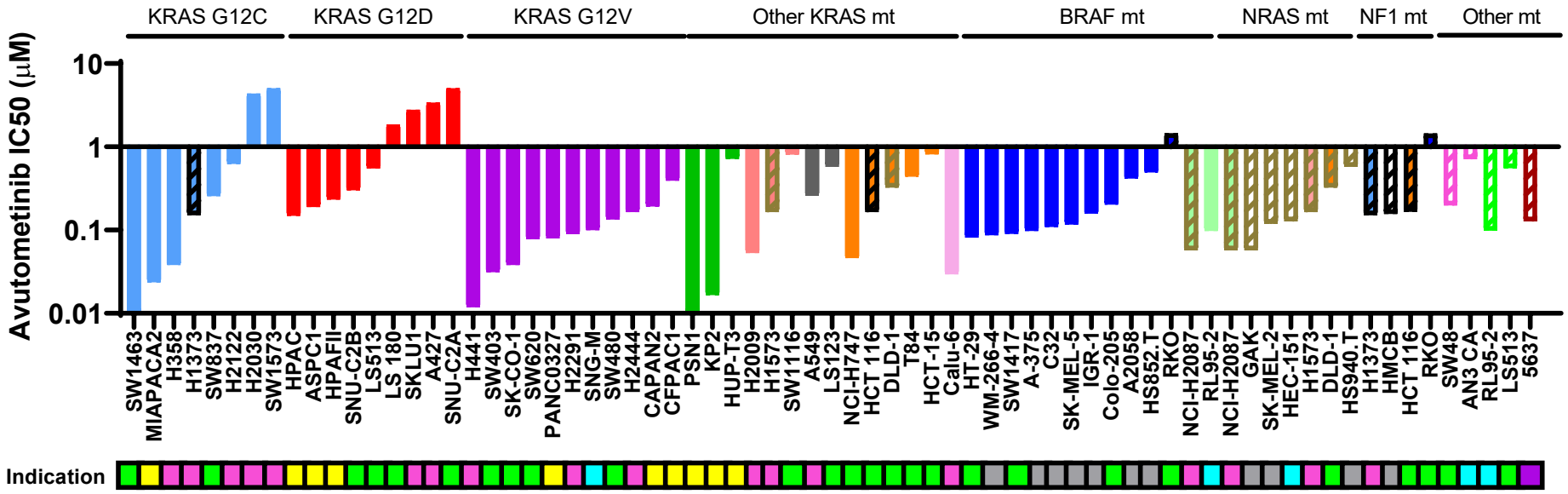
Deborah Morrison unpublished

Reference: Coma et al., AACR 2022

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



Reference: Pachter *RAS-Targeted Drug Development Summit 2022;* 3D proliferation assay

Optimized Dosing Schedule Defined: 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%)

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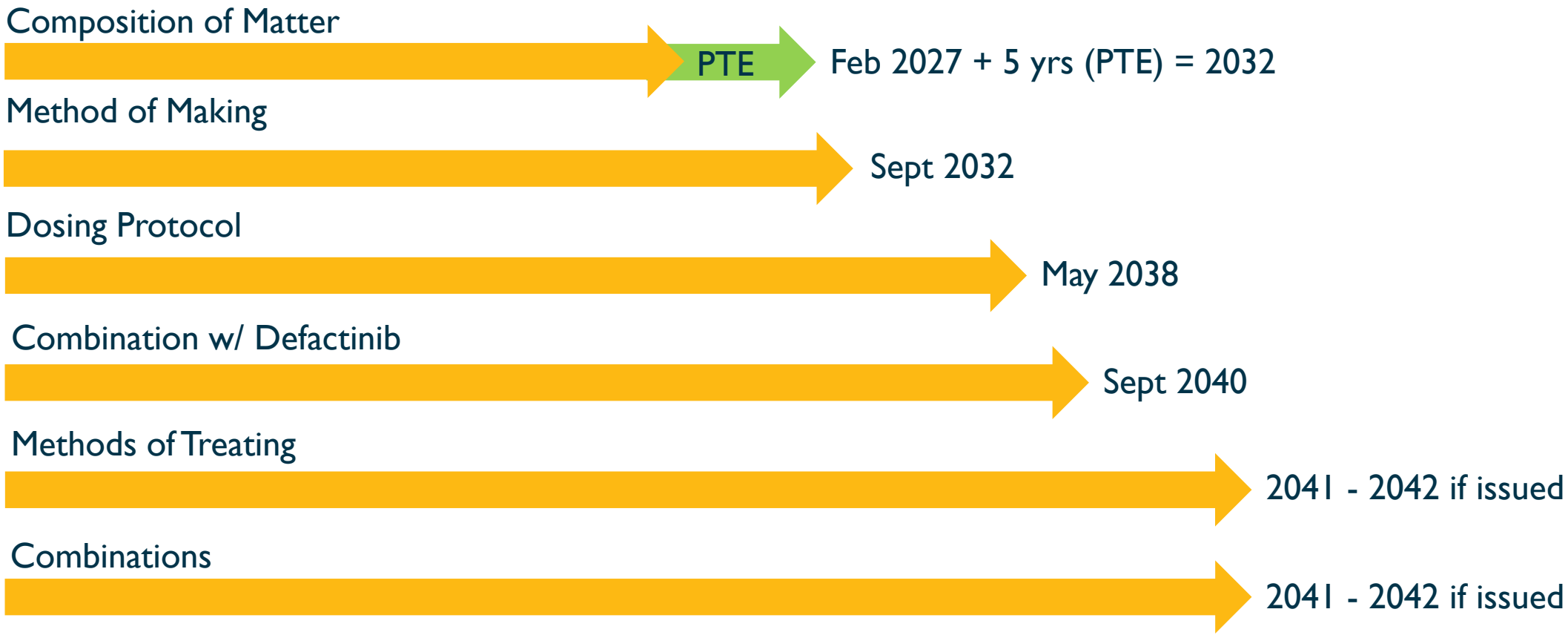
[1] Chenard-Poirier, *et al.* ASCO 2017

References: Banerji, Q4 2020 report; Data on file

RP2D: recommended phase 2 dosing

Avutometinib Patent Exclusivity

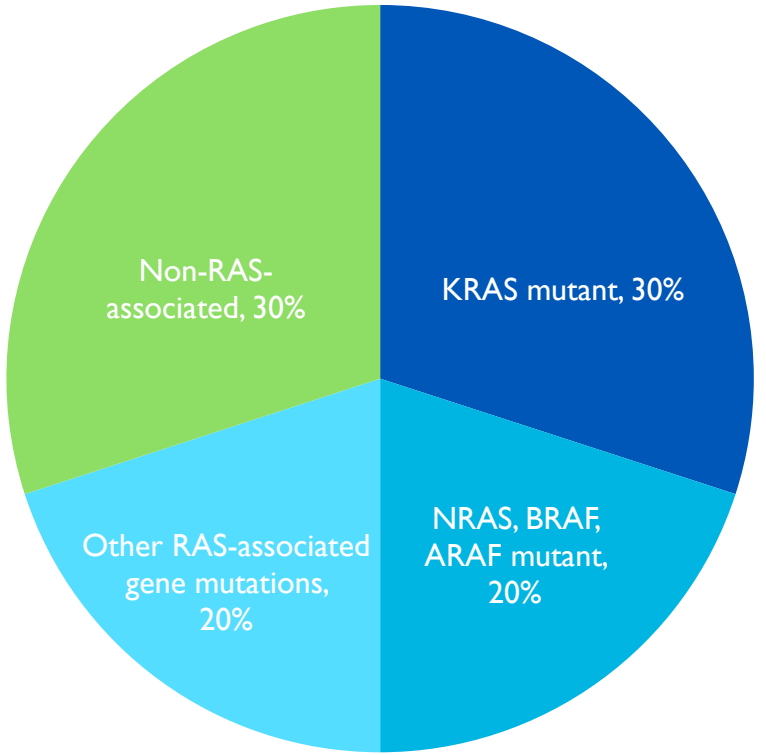


Avutometinib ± Defactinib in Low-Grade Serous Ovarian Cancer

LGSOC is a Unique RAS Pathway-Driven Cancer with a High Unmet Need

- 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

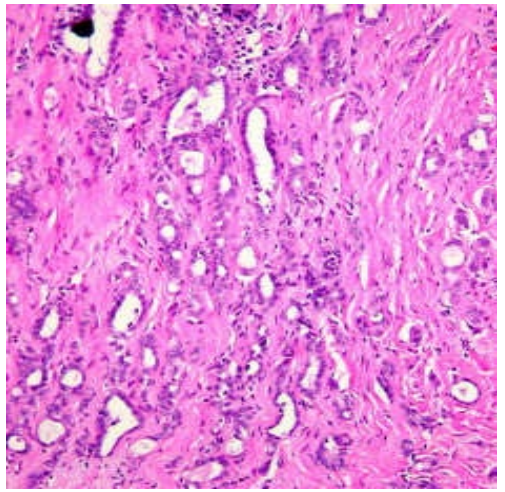


References: AACR Project GENIE Cohort v9.0-public and Verastem unpublished analysis

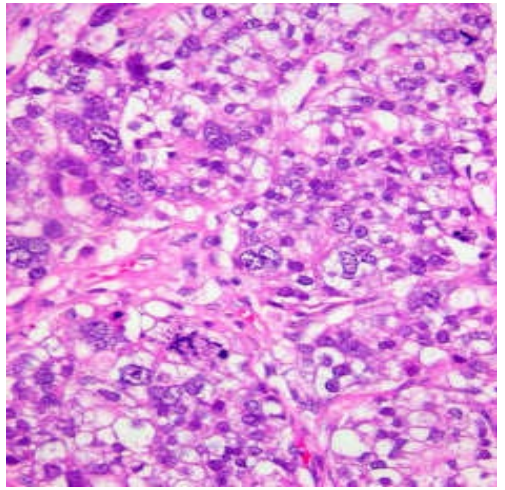
References: Monk, Randall, Grisham, The Evolving Landscape of Chemotherapy in Newly Diagnosed Advanced Epithelial Ovarian Cancer, Am Soc Clin Oncol Educ Book; 2019; Slomovitz, Gourley, Carey, Malpica, Shih, Huntsman, Fader., Grisham et al, Low-Grade serous ovarian cancer: State of the Science; Gynecol Oncol; 2020. Grisham, Iyer, Low-Grade Serous Ovarian Cancer: Current Treatment Paradigms and Future Directions; Curr Treat Options Oncology; 2018; Malpica et al., Am J. Surg Pathol 2007

Low-Grade and High-Grade Serous Ovarian Cancer Are Different Diseases

Variable	LGSOC	HGSOC
Nuclear atypia	Uniform round to oval with little variation	+++ Marked variation
Mitotic Index	<12 mitoses per 10 hpf	>12 mitoses per 10 hpf
Chromatin and variation in size of nucleus	Little	Marked (nuclear size ratio ≥3)
Mutation	KRAS ++ BRAF + ER/PR +++	P53 +++ BRCA1/2 +
Precursor	Serous borderline tumor	Tubal intraepithelial neoplasia



LGSOC



HGSOC

Reference: Malpica et al., Am J. Surg Pathol 2007

Recurrent LGSOC: High Medical Need
No Approved Treatment Options – Limited Benefit from Available Therapies

Recurrent Low-Grade Ovarian Cancer – Treatment Guidelines [1]

RECURRENCE THERAPY[r]

Recurrent disease[s] →

Clinical trial
or
Trametinib[f]
or
Binimetinib (category 2B)[f]
or
Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[f]
or
Hormonal therapy[t]
or
Chemotherapy (if not previously used), see OV-C (6 of 11)
or
Other systemic therapy[f,u]
- **For platinum-sensitive disease, see OV-C (8 of 11)**
- **For platinum-resistant disease, see OV-C (9 of 11)**

or
Observation

Preferred Regimens
- Paclitaxel/carboplatin q3weeks[f,g] ± maintenance letrozole (category 2B) or other hormonal therapy (category 2B)[h]
- Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[f,i] (ICON-7 & GOG-218)
- Hormone therapy (aromatase inhibitors: anastrozole, letrozole, exemestane) (category 2B)

No Category 1 recommendations (high-level evidence).
Category 2a (lower-level evidence with uniform NCCN consensus) unless otherwise indicated
f: There is no standard sequencing of drugs for recurrent disease. Considerations include prior therapies, disease burden, relative efficacy, and relative toxicity profile.
t: An aromatase inhibitor (i.e., letrozole, anastrozole, exemestane) is preferred if not used previously. Fulvestrant, tamoxifen, or leuprolide acetate is recommended if an aromatase inhibitor was given previously.

References:
[1] NCCN guidelines v1.2023

Recent LGSOC Trials Highlight High Unmet Need

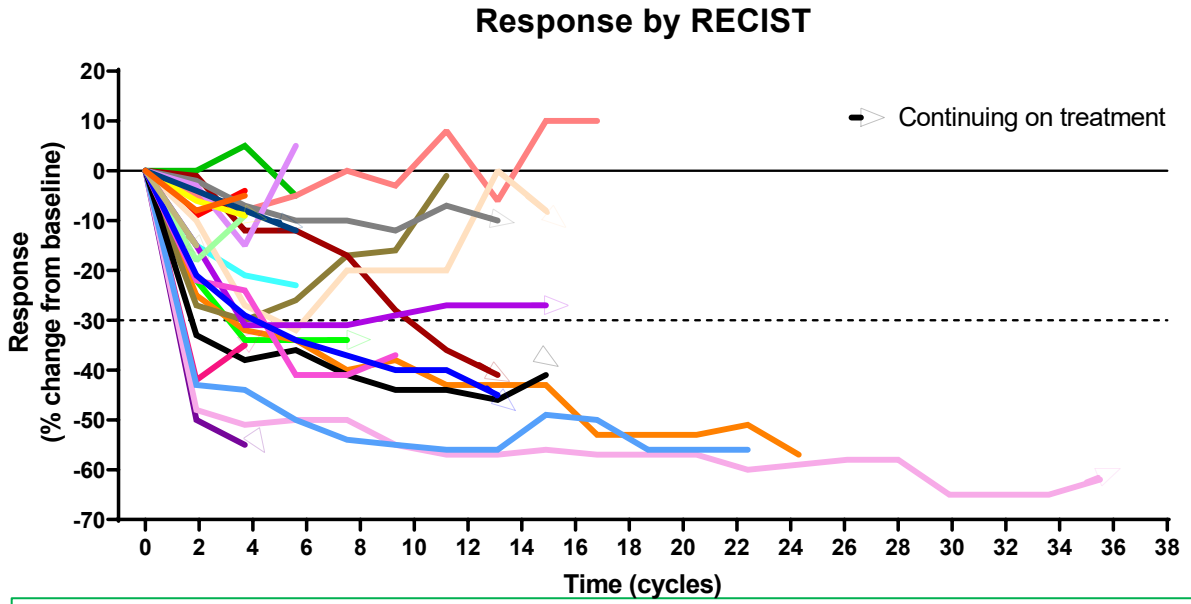
Trial	Number of Prior Systemic Therapies Median (range)	Prior MEK allowed	Prior Bevacizumab	Therapy	Response Rate ORR	Image Assessment	Median PFS Months (95% CI)	Discontinuation Rate due to AEs
GOG 281[1]	**3** (1-10)	No	* Low %	**SoC**	**6%**	INV	7.2 (5.6-9.9)	13%
				Trametinib	**26%**	INV	13.0 (9.9-15.0)	**36%**
MILO[2]	**2** (1-8)	No	* Low %	**SoC**	**13%**	BICR	10.6 (9.2 - 14.5)	17%
				Binimetinib[2]	**16%**	BICR	9.1 (7.3-11.3)	**31%**

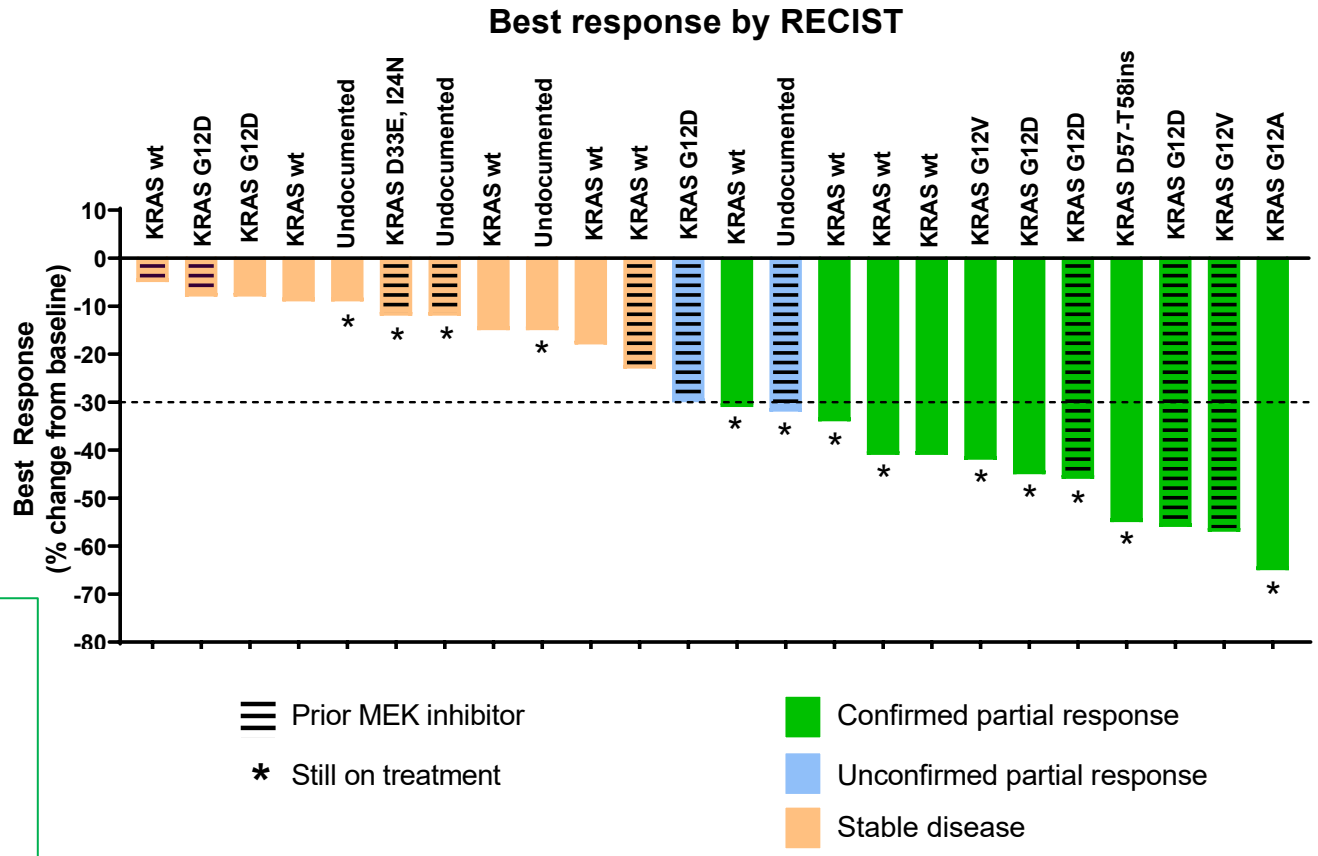
[1] Study GOG 281 trial Gershenson et al., Lancet 2022
[2] MILO Study Monk et al., J Clin Oncol 2020.

** Low historical use of bevacizumab during trial conduct. % not reported*
MILO: no more than 3 lines of prior chemotherapy

SoC = Standard of Care (endocrine / chemotherapy)
INV = Investigator
BICR = Blinded independent central review
PFS = Progression free survival
CI = confidence interval
NR = Not reached

FRAME Study: Solid Foundation for the Development of Avutometinib in Combination with Defactinib in Recurrent LGSOC (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
- Median 3 lines of Prior Treatment (Prior MEKi 10 pts, Prior Bev 4 pts)
- 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
MEKi: MEK inhibitor
Bev: Bevacizumab
PFS: Progression free survival
NR: Not reached

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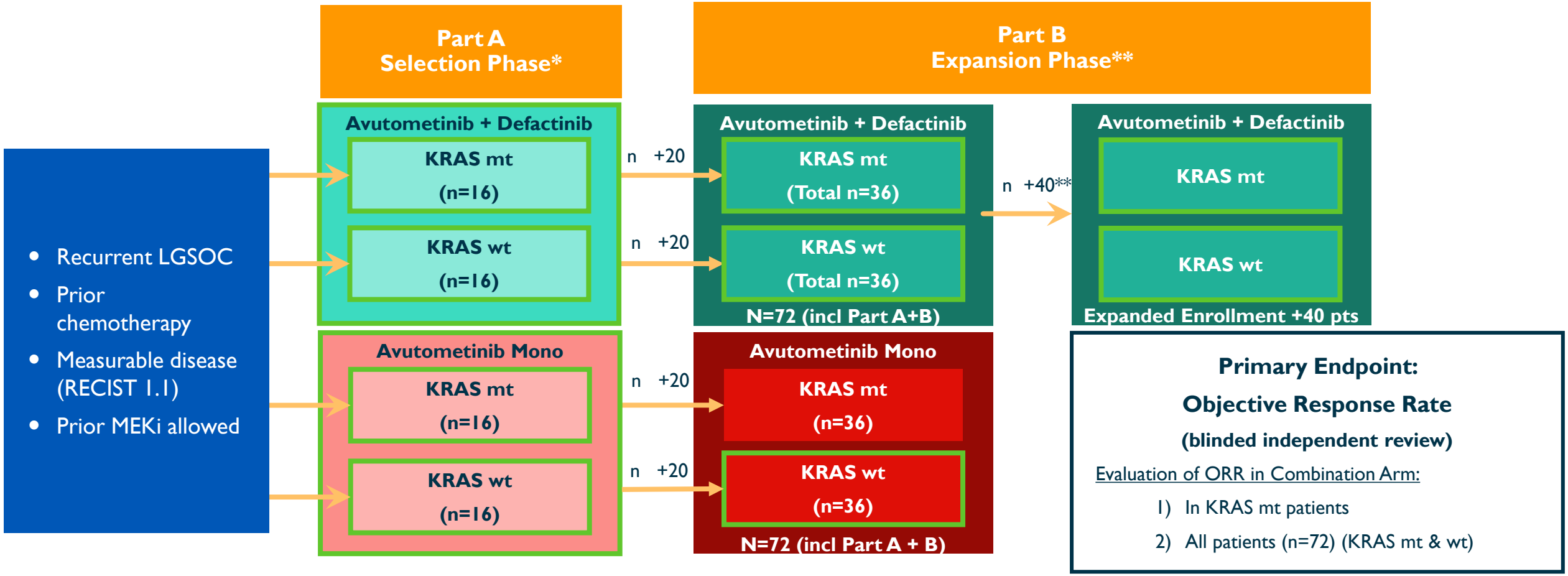
Reference: Banerjee et al., ESMO Sept 2021

RAMP 201 (ENGOTov60/GOG3052): Registration-Directed Phase 2 Trial of Avutometinib ± Defactinib in Patients with Recurrent LGSOC



*Dosing: Avutometinib + Defactinib combo: Avutometinib 3.2 mg PO 2x/wk 21/28 days + Defactinib 200 mg 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

Combination Arm:
- ❖ **Expanded Enrollment Ongoing**
- ✓ **Target Enrollment Reached (N=72)**

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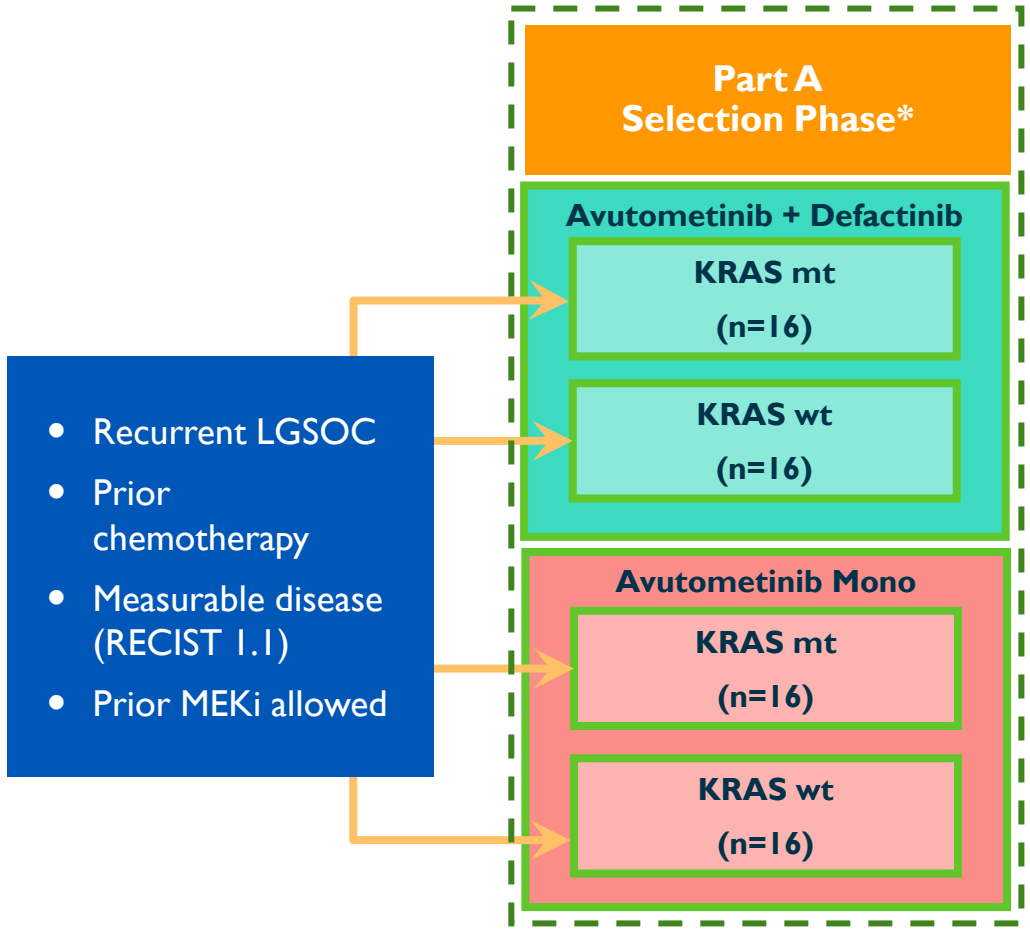
RAMP 201 (ENGOTov60/GOG3052): Registration-Directed Phase 2 Trial of Avutometinib ± Defactinib in Patients with Recurrent LGSOC



Planned Interim Analysis:

- ***Initial Efficacy Data: Part A (Evaluable Patients)***
- ***Safety Data: All Treated Patients***

- **Heavily** pretreated population;
  - Median of **4** prior lines of systemic therapy
- Clinical development continues in **all recurrent LGSOC**, regardless of KRAS status
- **Combination of avutometinib and defactinib** selected as "Go Forward" treatment regimen
  - **ORR 28%** by blinded independent central review
    - KRAS mt: 27%; KRAS wt: 29%
  - Tolerable safety profile - No new safety signals;
  - Majority of evaluable patients remain on treatment (62%)

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

RAMP 201 Part A: Heavily Pre-Treated Patient Population

Prior Platinum-Based Chemotherapy, Endocrine Therapy, Bevacizumab in Most Patients; Prior MEK Inhibitor Therapy was Permitted

	Avutometinib Monotherapy			Avutometinib + Defactinib		
	KRAS mt (n=16)	KRAS wt (n=17)	Total (n=33)	KRAS mt (n=16)	KRAS wt (n=15)	Total (n=31)
Age (yrs), median (min, max)	58 (27, 72)	48 (27, 74)	**51 (27, 74)**	61 (29, 71)	50 (30, 74)	**55 (29, 74)**
ECOG, n (%)						
0	8 (50)	15 (88)	23 (70)	11 (69)	9 (60)	20 (65)
1	8 (50)	2 (12)	10 (30)	5 (31)	6 (40)	11 (35)
Number of Prior Systemic Regimens, median (min, max)	3.0 (1, 10)	3.0 (1, 9)	3.0 (1, 10)	4.0 (1, 9)	4.0 (1, 11)	**4.0 (1, 11)**
Prior platinum-based chemotherapy, n (%)	15 (93.8)	17 (100)	32 (97.0)	16 (100)	15 (100)	**31 (100)**
Prior MEK inhibitor therapy, n (%)	5 (31.3)	5 (29.4)	10 (30.3)	2 (12.5)	2 (13.3)	**4 (12.9)**
Prior Bevacizumab, n (%)	8 (50.0)	8 (47.1)	16 (48.5)	7 (43.8)	13 (86.7)	**20 (64.5)**
Prior Hormonal therapy, n (%)	11 (68.8)	12 (70.6)	23 (69.7)	15 (93.8)	13 (86.7)	**28 (90.3)**

RAMP 201 Part A: Evaluable Patient Population*
Positive ORR Confirmed by Blinded Independent Central Review (BICR) Support Avutometinib + Defactinib as Go Forward Regimen in LGSOC - Regardless of KRAS Status

	Avutometinib			Avutometinib + Defactinib		
	KRAS mt (n=15)	KRAS wt (n=15)	Total (n=30)	KRAS mt (n=15)	KRAS wt (n=14)	Total (n=29)
ORR, n(%)						
Confirmed PR	2 (13)	0	2 (7)	**4 (27)**	**4 (29)**	**8 (28)** 95% CI: (13%, 47%)
Confirmed + Unconfirmed PR**	2 (13)	0	2 (7)	7 (47)	4 (29)	**11 (38)**
SD**	12 (80)	13 (87)	25 (83)	11 (73)	8 (57)	**19 (66)**
Disease Control Rate	14 (93)	13 (87)	27 (90)	15 (100)	12 (86)	**27 (93%)**
PD	1 (7)	2 (13)	3 (10)	0	2 (14)	2 (7)

* Evaluable for Efficacy: At least one blinded imaging assessment in 30 of 33 and 29 of 31 patients enrolled in respective treatment arms

** Includes patients with unconfirmed PR who have a chance to be confirmed at their next assessment

Go Forward Regimen: Combination of Avutometinib and Defactinib

High Disease Control Rate + Tumor Reduction in Recurrent LGSOC

Part A (Evaluable for Efficacy *)

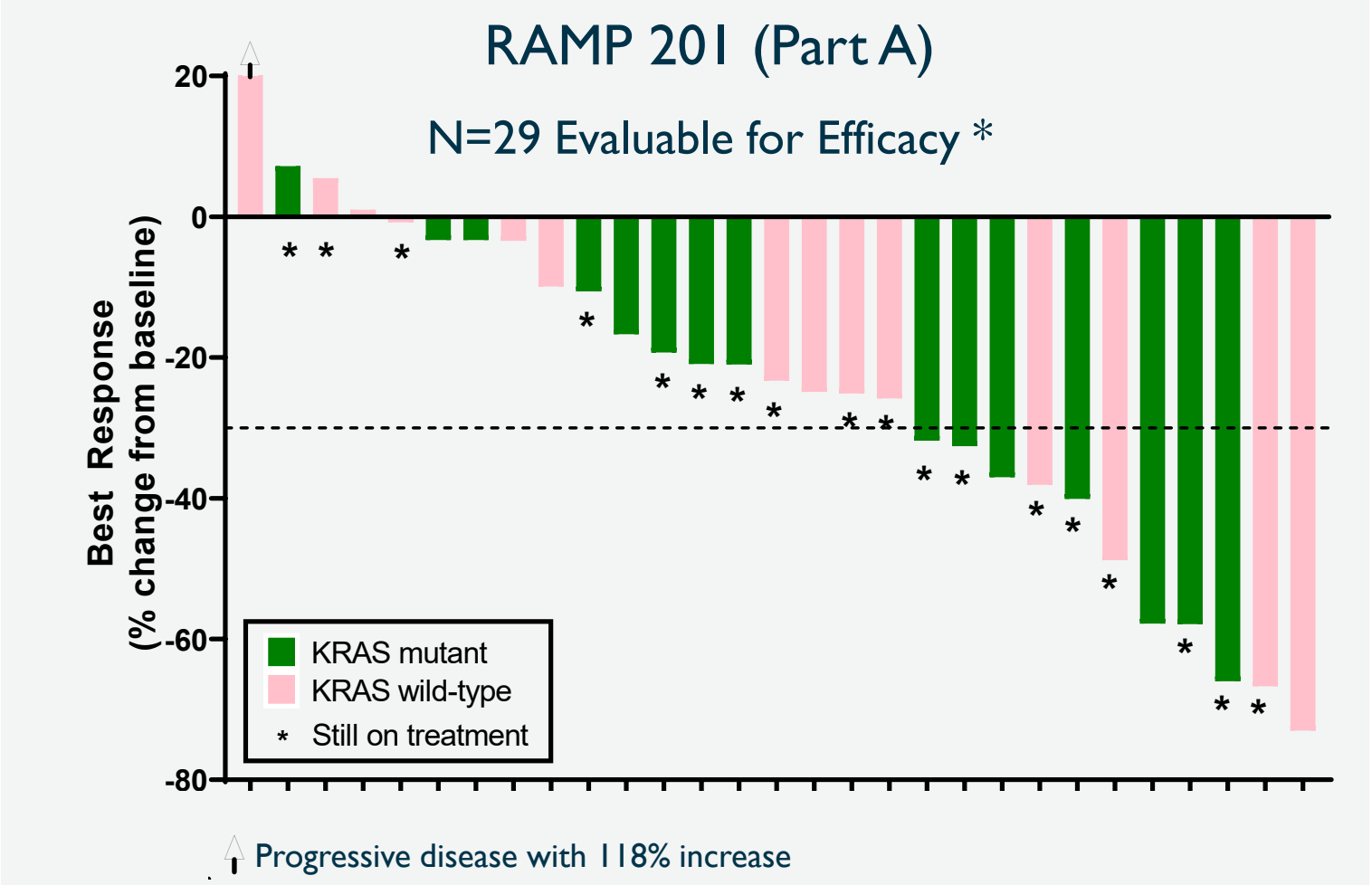
Confirmed ORR: **28%**

Confirmed/Unconfirmed ORR: **38%**

Disease Control Rate (SD+PR): **93%**

Patients still on study treatment: 62%

Shortest follow up: 5 months



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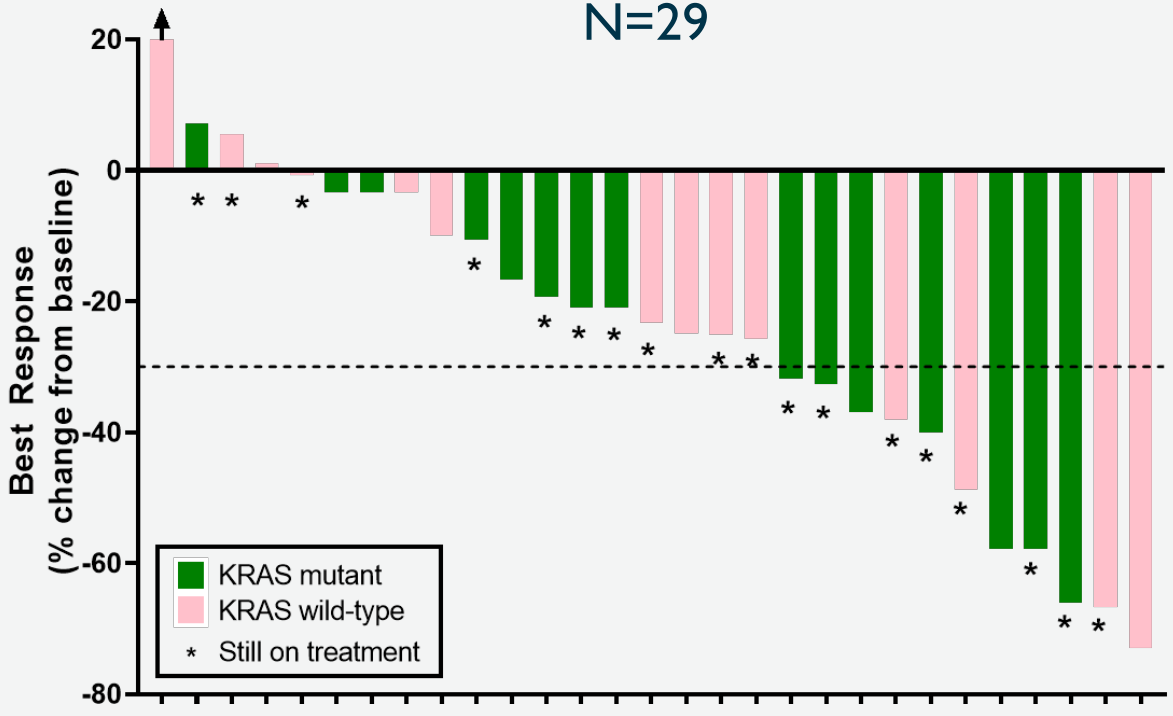
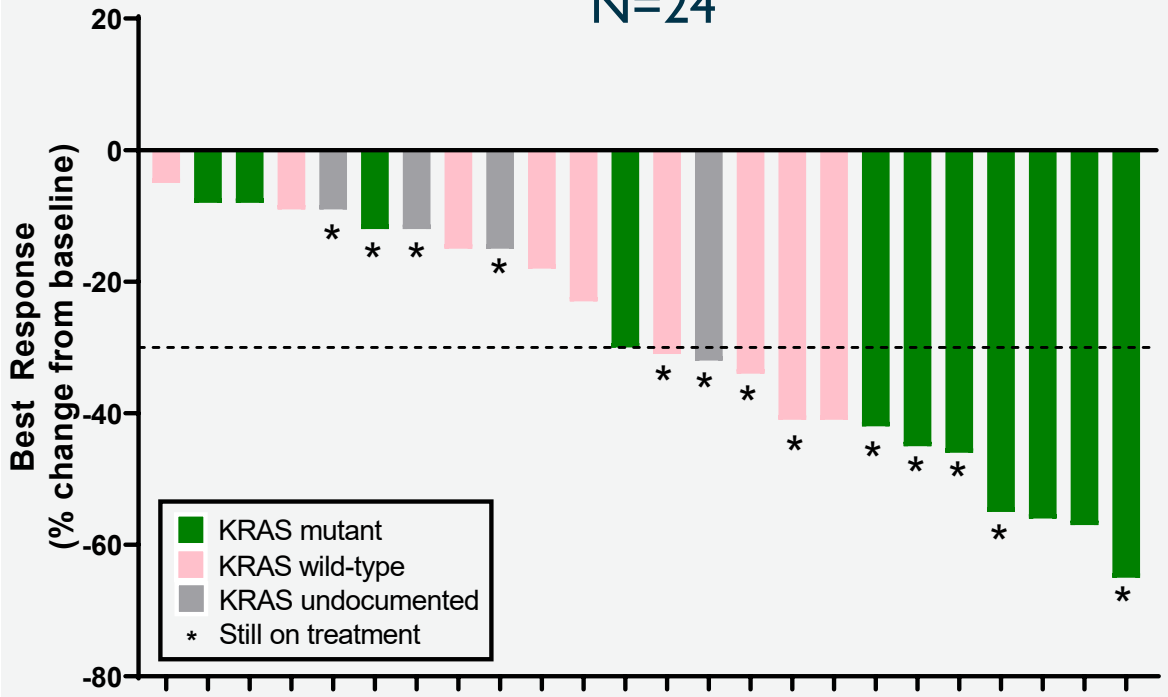
* Evaluable for Efficacy: At least one blinded imaging assessment

Go Forward Regimen: Combination of Avutometinib and Defactinib
Initial Data from RAMP 201 Trial Reinforce Findings from FRAME Trial

RAMP 201 (Part A)
Interim Analysis - Blinded ICR
N=29



FRAME
Investigator Assessment
N=24



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Progressive disease with 118% increase

RAMP 201: Safety and Tolerability Profile of Avutometinib + Defactinib
No New Safety Signals; Few Discontinuations Due to Adverse Events

Most Common Treatment-Related Adverse Events (>20%) in All Treated Patients

- Majority of adverse events are mild to moderate
- Adverse events are monitorable, manageable and reversible
- Few discontinuations due to adverse events (9% in combo n=5 – includes 3 pts for elevated blood CPK laboratory values*)
  * No association to date with clinically significant toxicities, including rhabdomyolysis

Avutometinib + Defactinib						
	Any Grade			Grade ≥3		
	KRAS mt (n=22) %	KRAS wt (n=35) %	Total (n=57) %	KRAS mt (n=22) %	KRAS wt (n=35) %	**Total (n=57) %**
Nausea	45.5	65.7	57.9	0	0	**0**
Diarrhea	54.5	51.4	52.6	4.5	2.9	**3.5**
Edema peripheral	36.4	48.6	43.9	0	0	**0**
Fatigue	40.9	40.0	40.4	9.1	2.9	**5.3**
Vision blurred	31.8	42.9	38.6	0	0	**0**
Vomiting	40.9	37.1	38.6	0	0	**0**
Blood creatine phosphokinase increased	40.9	37.1	38.6	18.2	14.3	**15.8**
Dermatitis acneiform	27.3	45.7	38.6	4.5	0	**1.8**
Rash	31.8	37.1	35.1	0	2.9	**1.8**
Dry skin	13.6	31.4	24.6	0	0	**0**

RAMP 201 Part A Results and FDA Feedback Establish Path to Filing for Accelerated Approval

Update

- Combination of avutometinib with defactinib selected as go forward treatment regimen
- Combination development continues in all recurrent LGSOC, regardless of KRAS status
- Encouraging efficacy results include independently confirmed responses
- No new safety signals; few discontinuations due to adverse events
- Majority of patients remain on treatment

Next Steps

- Target enrollment for primary analysis (n=72) in combination has been achieved
- Plan to file for accelerated approval based on the totality of the data from the RAMP 201 and FRAME studies
- Continued enrollment in RAMP 201 combination arm only is planned to expand clinical experience in anticipation of initiation of a confirmatory study
- The Company will provide an update after agreement with the FDA on the confirmatory study
- The Company is planning a RAMP 201 presentation at a scientific conference in mid-2023

Efficacy and Tolerability of Avutometinib and Defactinib in LGSOC

A Head-to-Head Study Has Not Been Performed

Trial	Median Number of Prior lines of Therapy	Prior MEK Allowed	Prior Bevacizumab	Therapy	Response Rate ORR	Image Assessment	Median PFS Months (95% CI)	Discontinuation Rate Due to AEs
GOG 281[1]	**3** (1-10)	No	* Low %	**Standard of Care**	**6% ^**	INV	7.2 (5.6-9.9)	13%
				Trametinib	26%^	INV	13.0 (9.9-15.0)	**36%**
MILO[2]	**2** (1-8)	No	* Low %	**Standard of Care**	**13%**	**BICR**	10.6 (9.2 to 14.5)	17%
				Binimetinib	**16%**	**BICR**	9.1 (7.3-11.3)	**31%**
FRAME[3]	3	Yes	12 %	Avutometinib + defactinib	**46%^** *95% CI: (26%, 67%)*	INV	**23** (11 - NR)	4%
RAMP 201 Part A[3]	4	Yes	65%	**Avutometinib + defactinib**	**28%** **95% CI: (13%, 47%)** **38%****	**BICR**	Not Yet Available	9%

** Low historical use of bevacizumab during trial conduct.*
*** Confirmed + Unconfirmed Objectives responses*
^ Investigator Assessment only (No independent Central Review of Imaging)

Standard of Care = letrozole, tamoxifen, chemotherapy
INV = Investigator
BICR = Blinded independent central review
PFS = Progression free survival
CI = confidence interval
NR = Not reached

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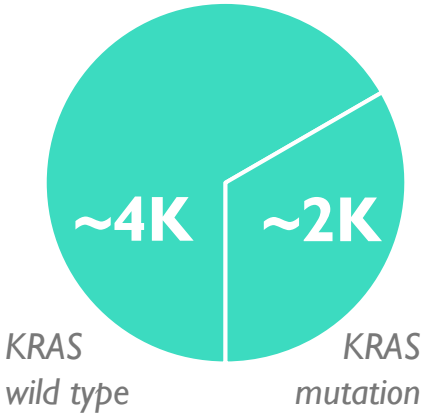
[1] Study GOG 281 trial Gershenson et al., Lancet 2022
[2] MILO Study Monk et al., J Clin Oncol 2020.
[3] Avutometinib + Defactinib combination evaluable population

RAMP 201 Part A Interim Data Support Meaningful Market Potential for All Recurrent LGSOC Regardless of KRAS Status with Long Duration of Therapy

Prevalence

~6K

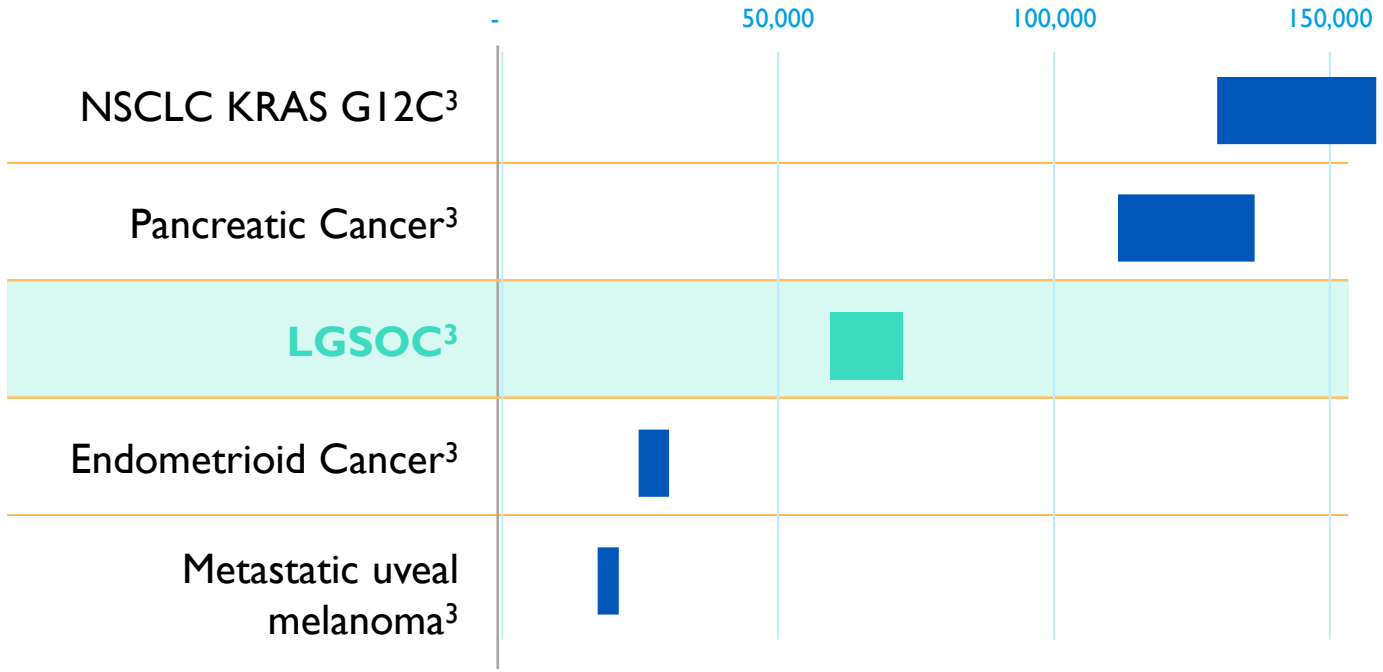
patients US[1]



~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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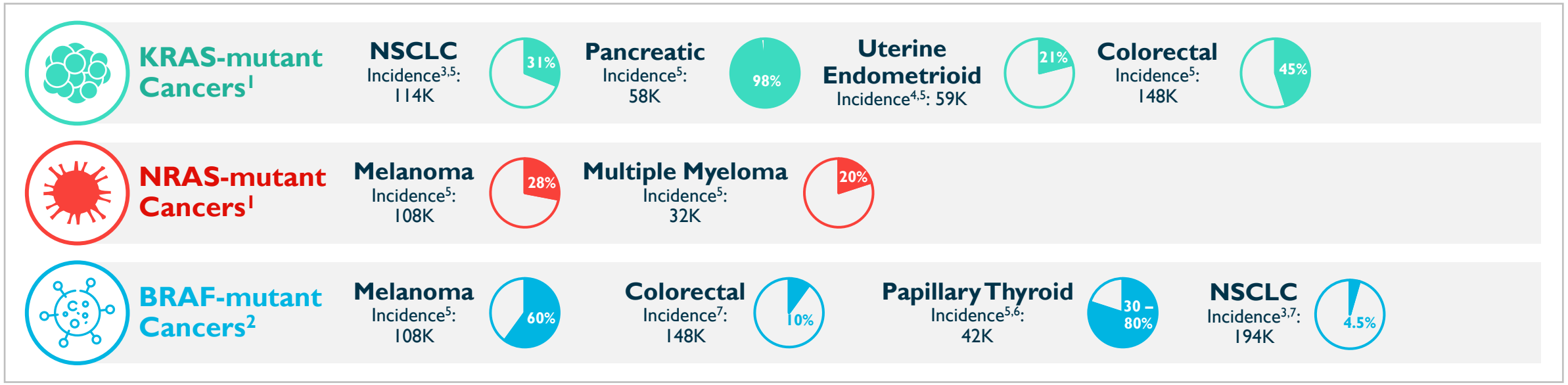
RAS Pathway-Driven Cancers and Rational Avutometinib Combinations

High Unmet Needs in Additional 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
- Approved RAS inhibitors address only a minority of all RAS mutated cancers (KRAS G12C)

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]50% of NSCLC is adenocarcinoma (Pakkala and Ramalingam JCI Insight 2018); [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

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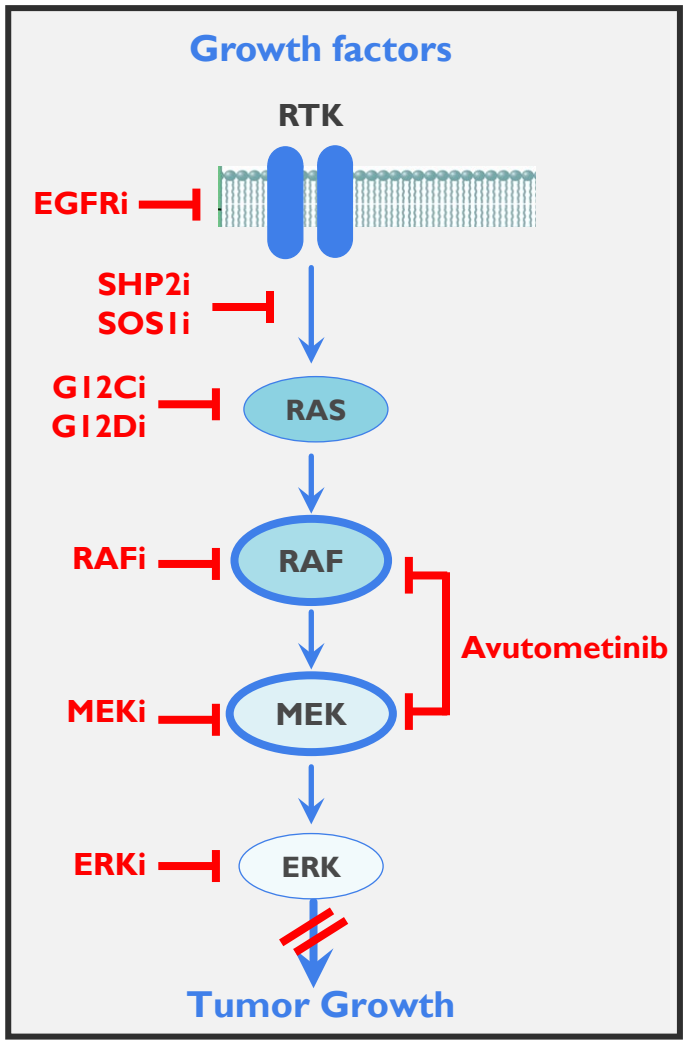
Vertical Blockade: Establishing Avutometinib as the Backbone of Therapy for RAS/MAPK Pathway-Driven Tumors



- **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
  - Ongoing clinical combination studies with G12Ci (sotorasib, adagrasib), anti-EGFR (cetuximab)

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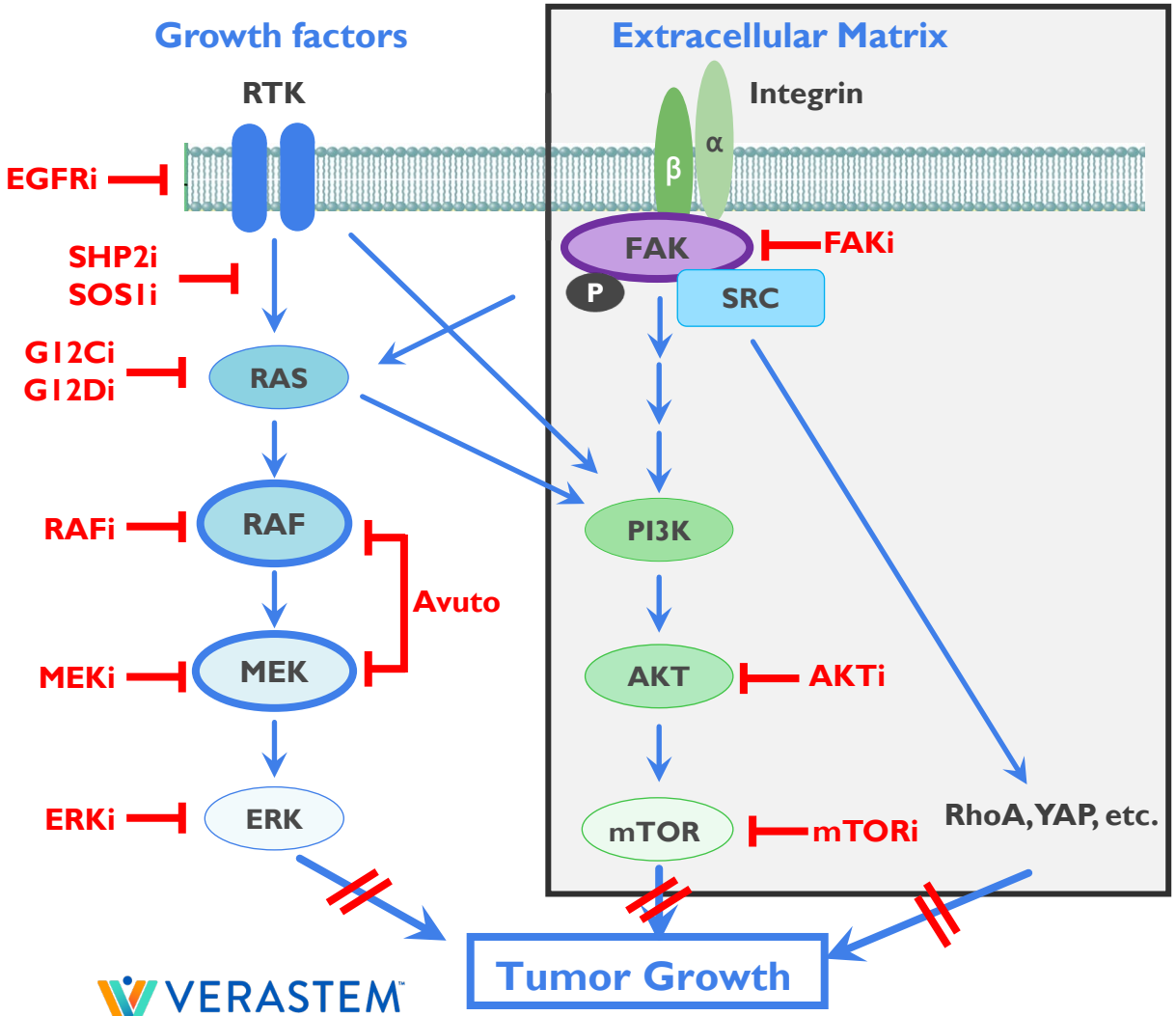
References: [1] Chen, *Mol Cancer Res* 2018; [2] Banerji, BTOG Dublin, Jan 23, 2019

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 and early clinical data 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 (e.g. FAKi, mTORi)
  - RP2D established for avutometinib + FAKi (defactinib) and for avutometinib + mTORi (everolimus) with twice weekly regimen

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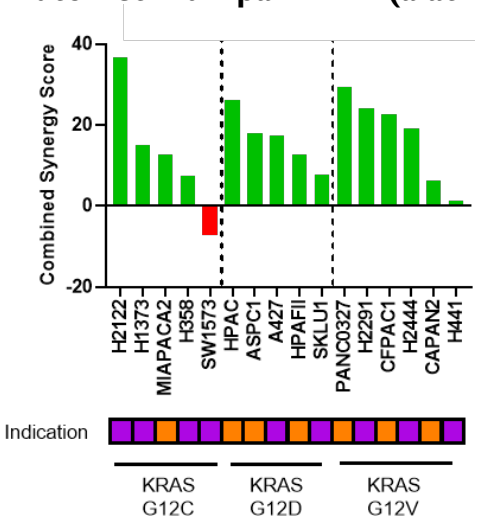
References: [1] Chen, *Mol Cancer Res* 2018; [2] Banerji, BTOG Dublin, Jan 23, 2019

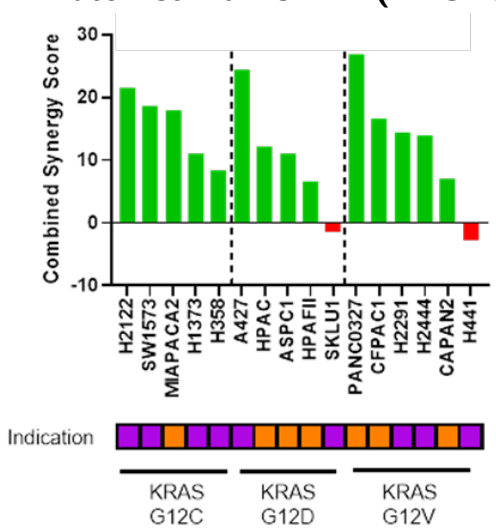
Preclinical Synergy of Avutometinib in Combination with Promising Agents for Clinical Investigation

Vertical RAS/MAPK Pathway Inhibition

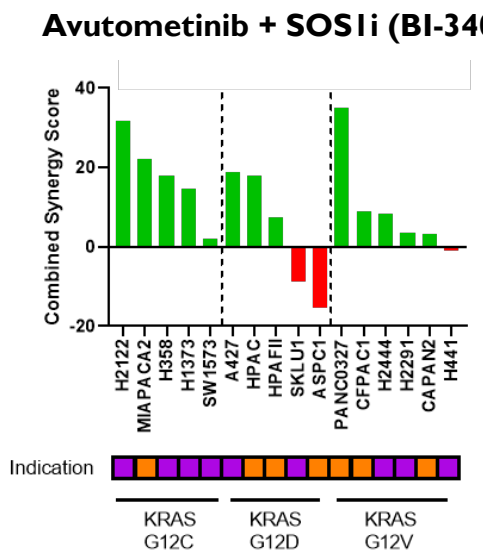
Avutometinib + pan-HERi (afatinib)



Avutometinib + SHP2i (RMC-4550)

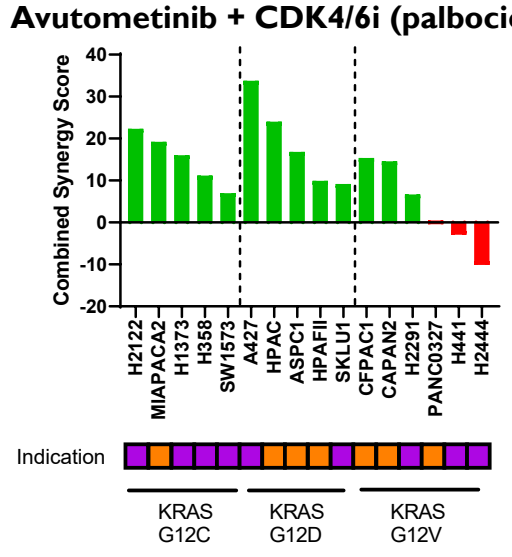


Avutometinib + SOS1i (BI-3406)

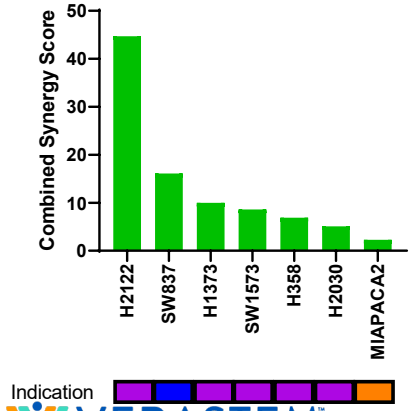


Parallel Pathway Inhibition

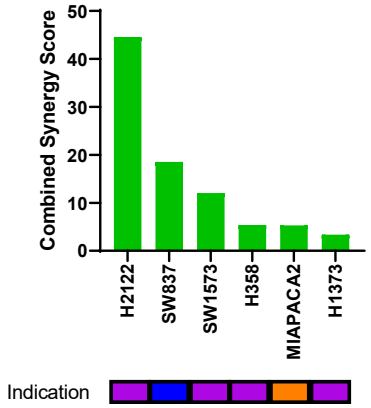
Avutometinib + CDK4/6i (palbociclib)



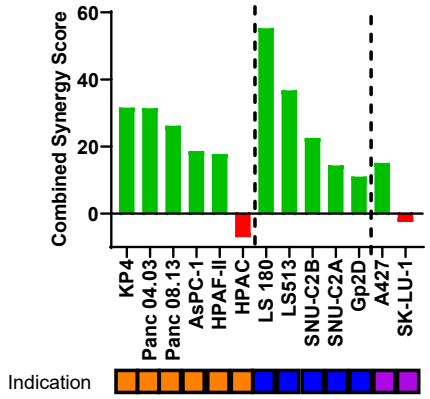
Avutometinib + G12Ci (sotorasib)

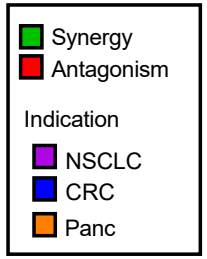


Avutometinib + G12Ci (adagrasib)

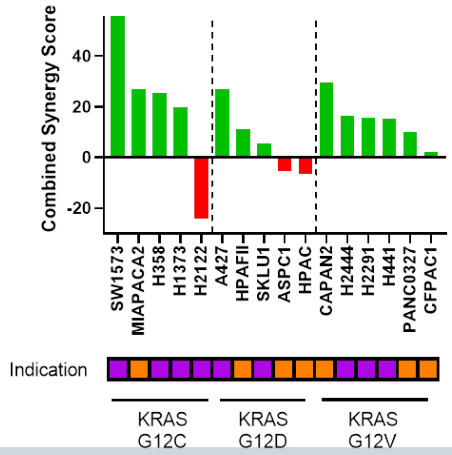


Avutometinib + G12Di (MRTX1133)





Avutometinib + mTORi (everolimus)



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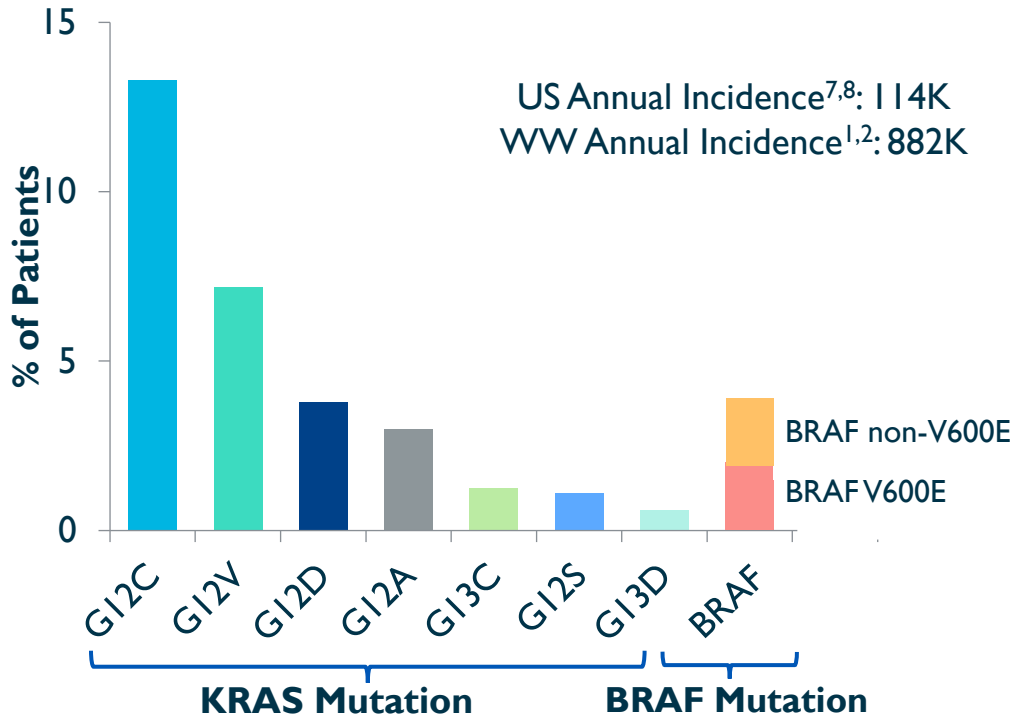
Avutometinib Combinations in Non-Small Cell Lung Cancer

High Unmet Need in Refractory KRAS & BRAF mt NSCLC Adenocarcinoma

NSCLC Adenocarcinoma[3]



KRAS Mutations Represent 25% of Lung Cancer Adenocarcinoma & BRAF Mutations Represent ~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%

Verastem Clinical Trials:

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

References:
[1] Globocan, 2020
[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
[7] 50% of NSCLC is adenocarcinoma (Pakkala and Ramalingam JCI Insight 2018)
[8] Cancer Statistics 2020, Siegel et. al. *CA Cancer J Clin* 2020;70:7-30

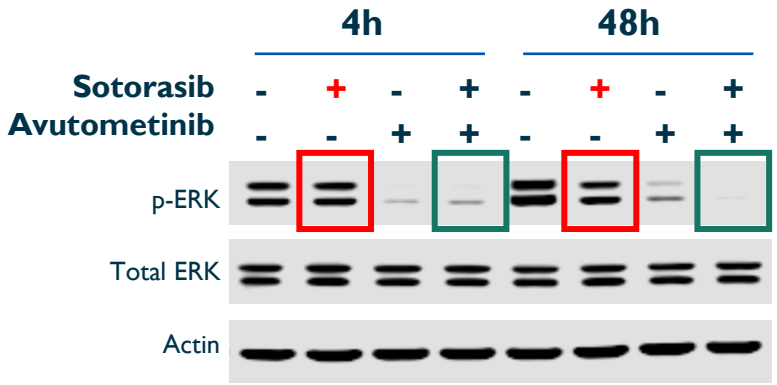
Preclinical Synergy of Avutometinib + G12C Inhibitors in KRAS G12C Models

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

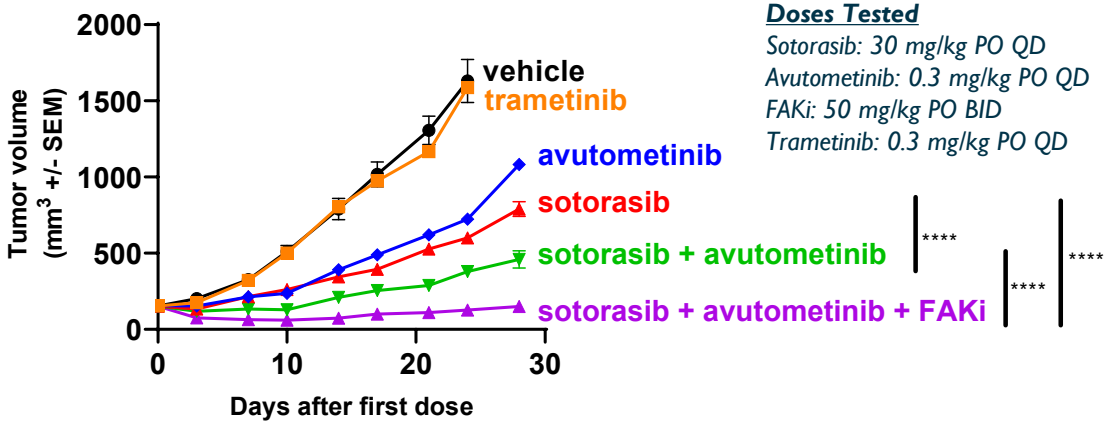
Avutometinib + sotorasib yields deeper and more sustained inhibition of ERK signaling pathway



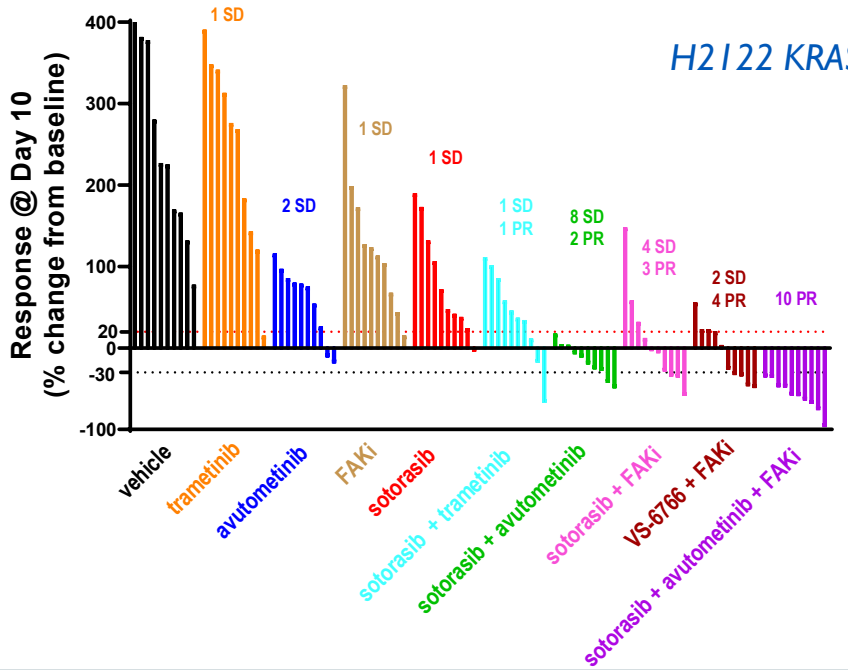
H2122 KRAS G12C NSCLC

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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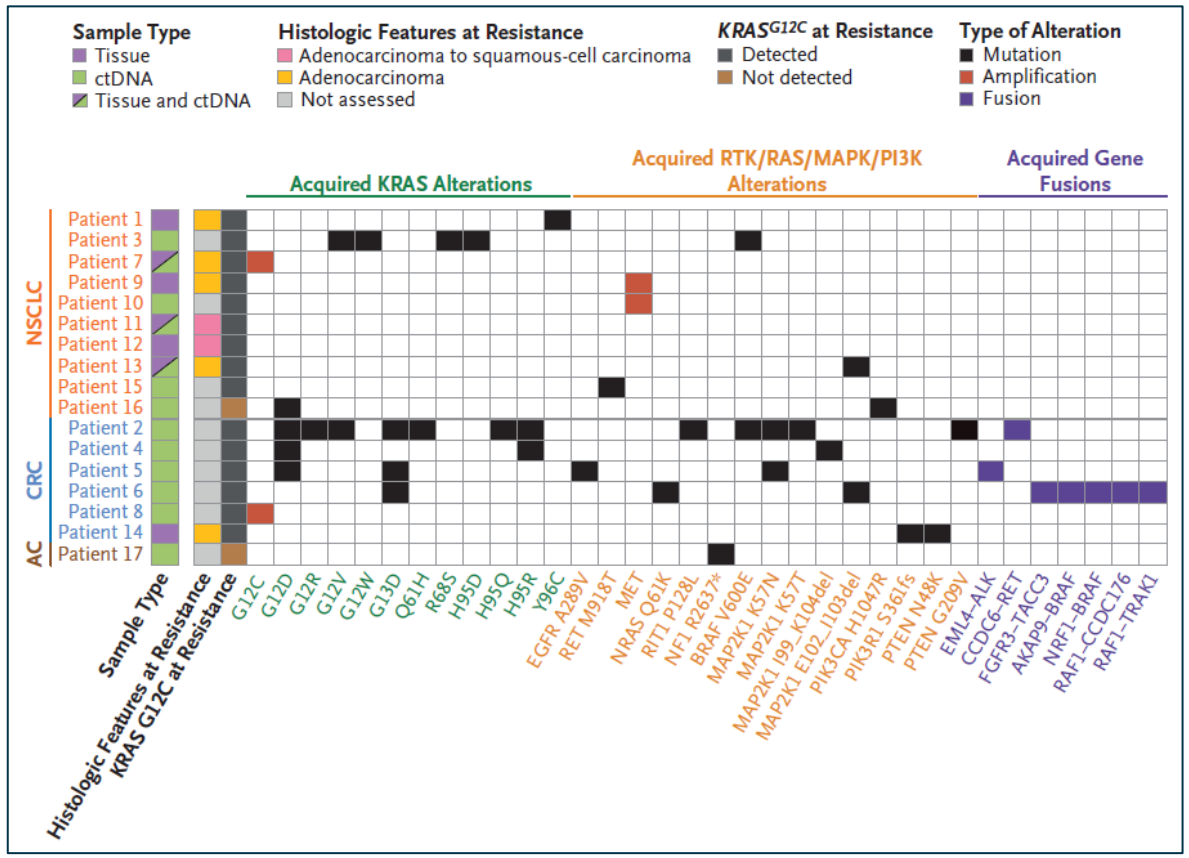
Reference: Coma et al., AACR 2021

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

References: [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

NCT05074810

Abbreviations: DLT = dose-limiting toxicity; n = number of patients; ORR = overall response rate; RP2D = recommended phase 2 dose

RAMP 204: Phase 1/2 Trial of Avutometinib + KRAZATI™ (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)

Part B: Dose Expansion (Primary endpoint ORR)

Avutometinib + Adagrasib

Dose Finding Cohorts (n=3-6)

→

RP2D Selection

→

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

Stage 2: expand to 55 patients

NCT05375994

Abbreviations: DLT = dose-limiting toxicity; n = number of patients; ORR = overall response rate; RP2D = recommended phase 2 dose

RAMP 202: Phase 2 Trial of Avutometinib + Defactinib in BRAF mt NSCLC

- Patients with 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

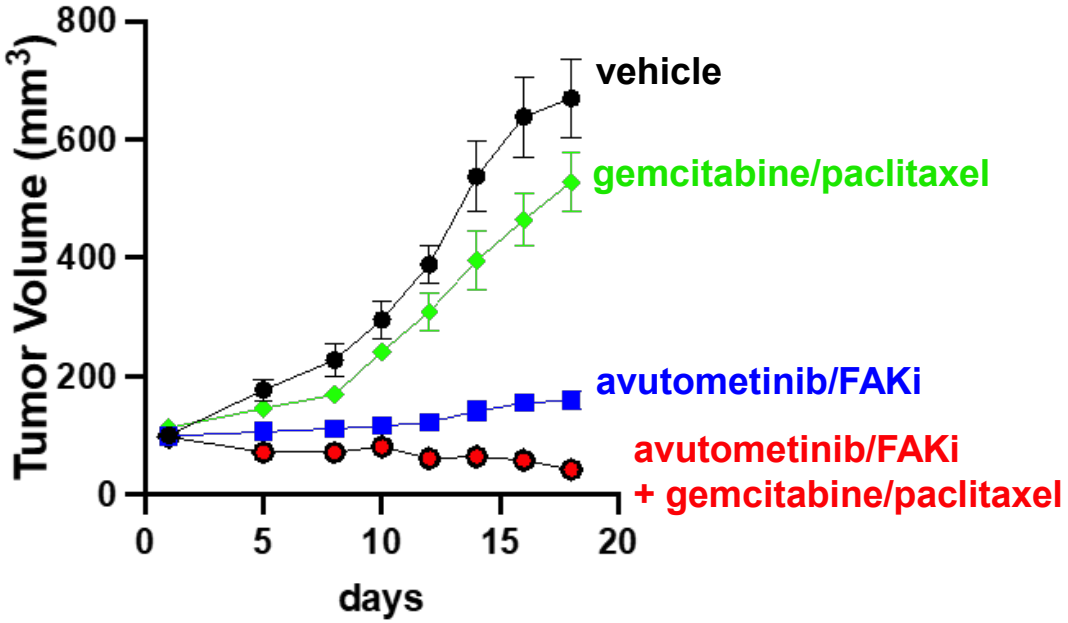
Expansion TBD based on results of analysis

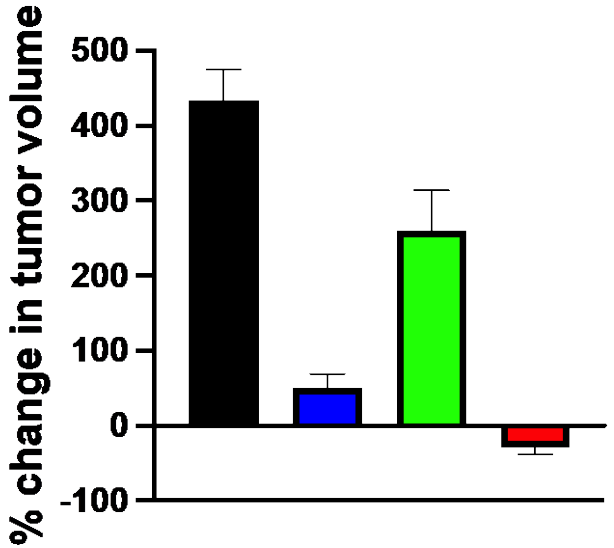
References:[1] Avutometinib 3.2 mg PO 2x/wk (21/28 days) + Defactinib 200 mg PO BID (21/28 days)

NCT04620330

Additional Avutometinib Combinations for Pancreatic, Colorectal and Melanoma

Preclinical Synergy of Avutometinib/FAK Inhibition + Chemotherapy in a KRAS/p53 pancreatic cancer mouse model





- ✓ The combination of avutometinib + FAKi induces tumor growth inhibition and increases survival but does not induce tumor regression
- ✓ Addition of chemo (gemcitabine + paclitaxel) to avutometinib/FAKi induces tumor regression

Collaboration with David DeNardo, Washington University; unpublished

RAMP 205: Phase 1/2 Trial of Avutometinib/Defactinib + GEMZAR™ (Gemcitabine)/ABRAXANE™ (Nab-paclitaxel) in Front Line Metastatic Pancreatic Cancer

- Patients with confirmed metastatic pancreatic ductal adenocarcinoma
- Eligible for treatment in the first-line setting with standard gemcitabine and nab-paclitaxel
- Prior adjuvant or neoadjuvant chemotherapy, radiotherapy or surgery is permitted if the last intervention/ dose was ≥ 12 months prior to the diagnosis of metastatic disease
- Measurable disease according to RECIST 1.1
- ECOG performance status ≤ 1

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

Avutometinib + Defactinib + Gemcitabine + Nab-paclitaxel

Dose Finding Cohorts (n=3-6)

→ RP2D Selection →

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

Patients with PDAC
KRAS G12D
KRAS G12V
KRAS G12R
Others

Treated with RP2D

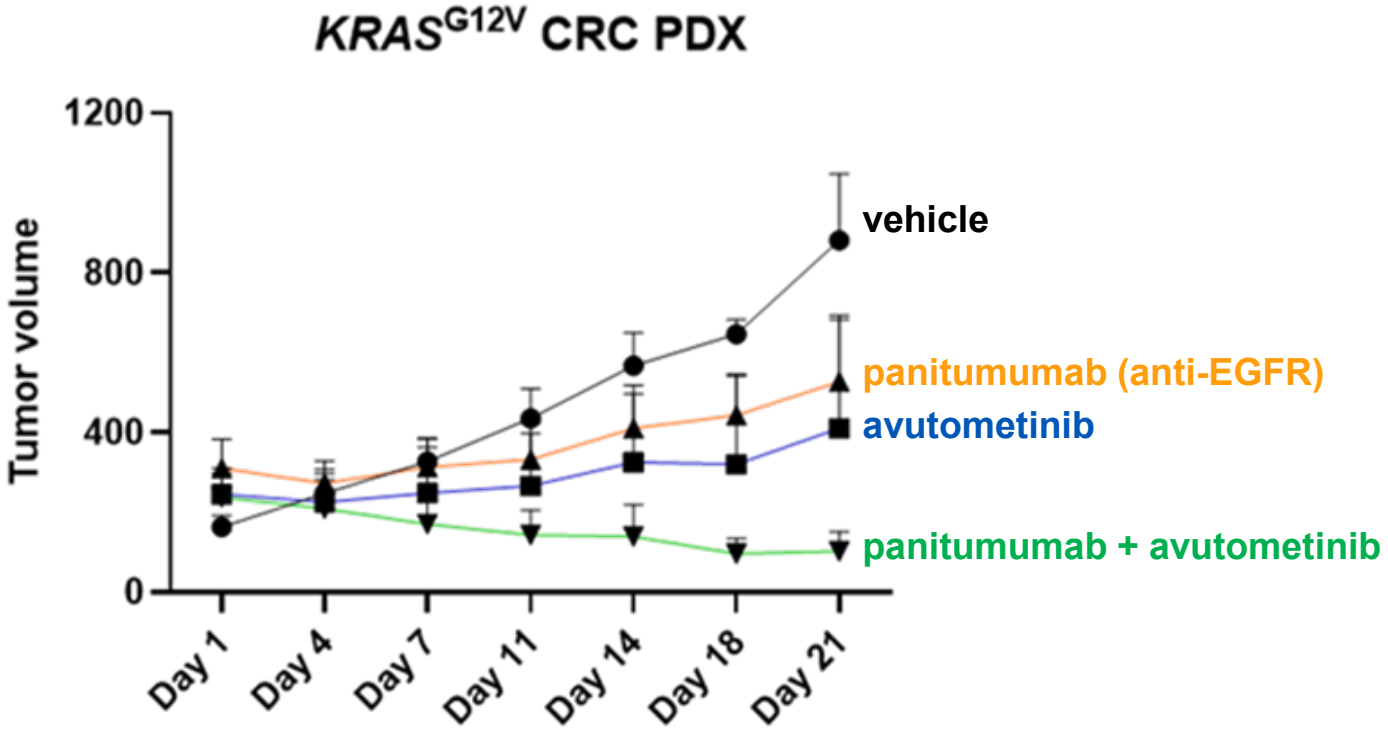
Stage 1: 17 patients
If ≥4 responders, then

Stage 2: expand to 29 patients

NCT05669482

Abbreviations: DLT = dose-limiting toxicity; n = number of patients; ORR = overall response rate; RP2D = recommended phase 2 dose

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

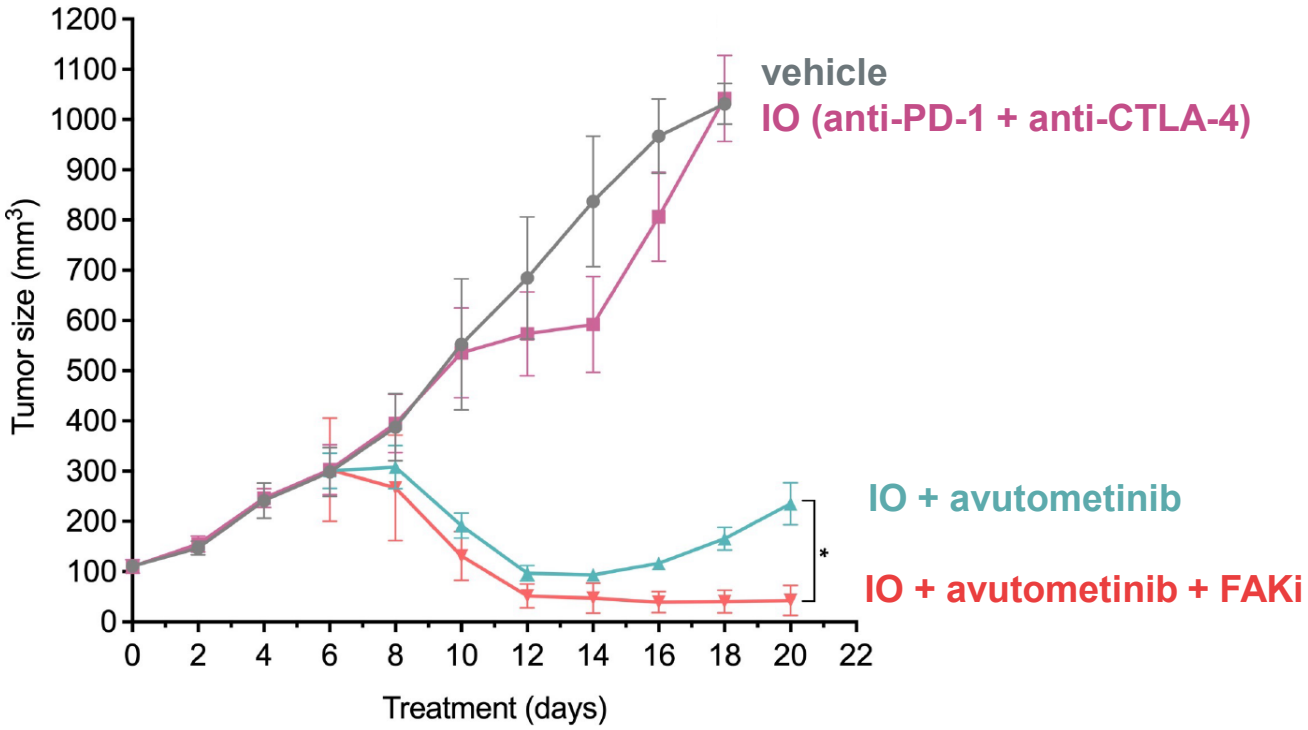


- Avutometinib + anti-EGFR (panitumumab) induces tumor regression in a KRAS mutant CRC patient-derived xenograft model
- G12Ci + anti-EGFR (sotorasib + panitumumab and adagrasib + cetuximab) have shown partial responses in KRAS G12C CRC (Fakih et al. ESMO 2021; Weiss et al. ESMO 2021)
- **These data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

Collaboration with Marwan Fakih, City of Hope

Pachter, RAS Development Summit, 2021

Combination of Avutometinib + FAK Inhibition with Checkpoint Inhibitor Induces Tumor Regression in an IO-resistant BRAF V600E melanoma model



- Avutometinib + IO (anti-PD-1 + anti-CTLA-4) induces tumor regression in an IO-resistant syngeneic BRAF V600E melanoma model (YUMM 1.7)
- FAK inhibition deepens and sustains avutometinib-induced tumor regression
- **These data support the imminent clinical evaluation of avutometinib + pembrolizumab (anti-PD-1) for treatment of BRAF V600E melanoma**

Collaboration with Silvio Gutkind, UCSD; unpublished

Avutometinib Development in Multiple Combinations Across RAS Pathway-Driven Tumors with Potential Early Read-Outs in 2H 2023

Indication	Study
KRAS G12C NSCLC	RAMP 203: Avutometinib/Sotorasib combo
KRAS G12C NSCLC	RAMP 204: Avutometinib/Adagrasib combo
Pancreatic	RAMP 205: Avutometinib/Gem/Abraxane/Defactinib combo
KRAS mt NSCLC	Avutometinib/Everolimus combo*
KRAS mt CRC	Avutometinib/Cetuximab combo*
ER+ Breast	Avutometinib/Abemaciclib/fulvestrant combo*
RAS/RAF/NF1 Gynecological	Avutometinib/Defactinib combo*
BRAF V600E Melanoma	Avutometinib/Pembrolizumab combo*

*Investigator Sponsored Trials

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Cathy Carew
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