Rational Combinations of RAF/MEK Clamp Avutometinib; *Breakthrough Therapy Designation and Beyond*

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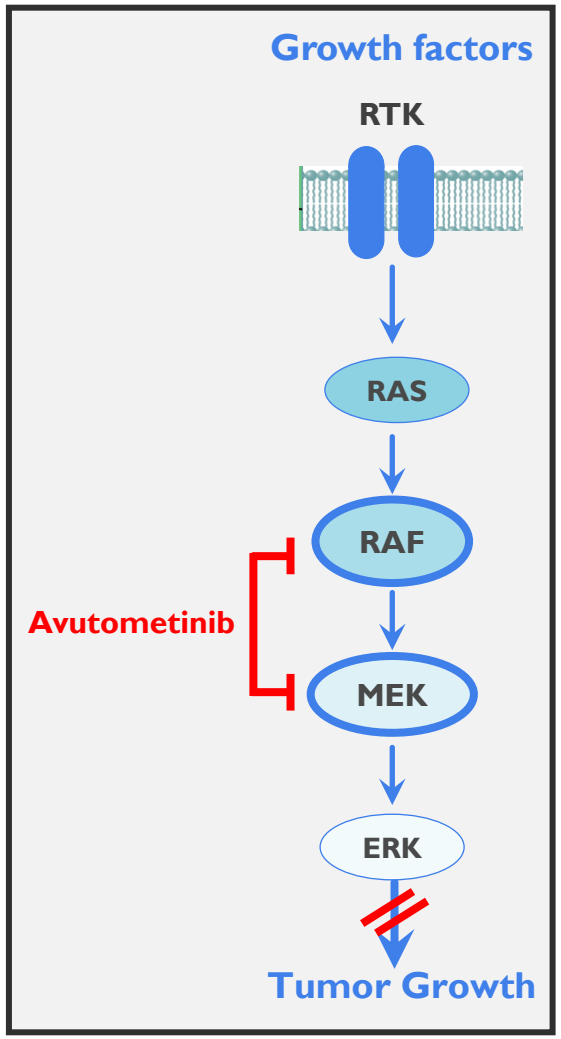
5th Annual RAS-Targeted Drug Development Summit
September 27, 2023

Avutometinib + Defactinib

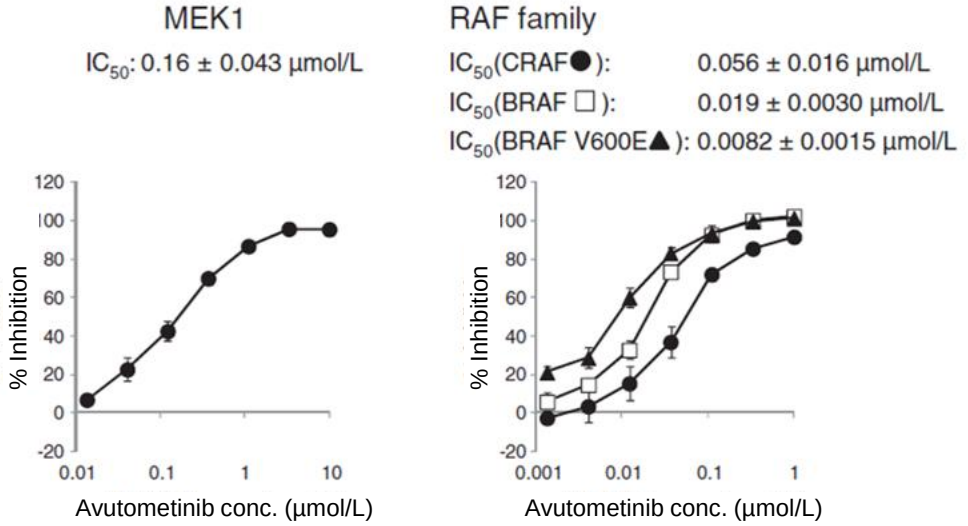
Avutometinib is a Unique Small Molecule RAF/MEK Clamp

Differentiated Mechanism of Action versus Selective MEK Inhibitors

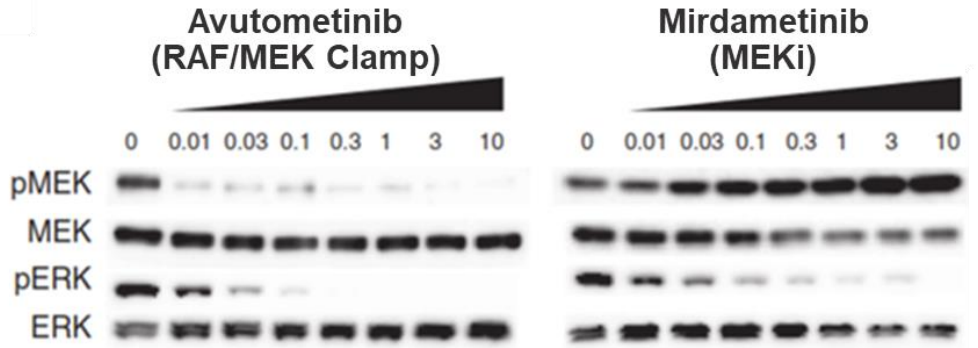


- Avutometinib inhibits MEK, BRAF & CRAF by trapping these molecules in dominant negative RAF/MEK complexes
- MEK inhibitors induce MEK phosphorylation (pMEK) by relieving ERK-dependent feedback inhibition of RAF (ie paradoxical activation)
  - ➢ By inhibiting RAF phosphorylation of MEK, avutometinib has advantage of **not** inducing pMEK
  - ➢ Avutometinib inhibits ERK signaling more completely; may confer enhanced therapeutic activity

Avutometinib inhibits both RAF and MEK activities

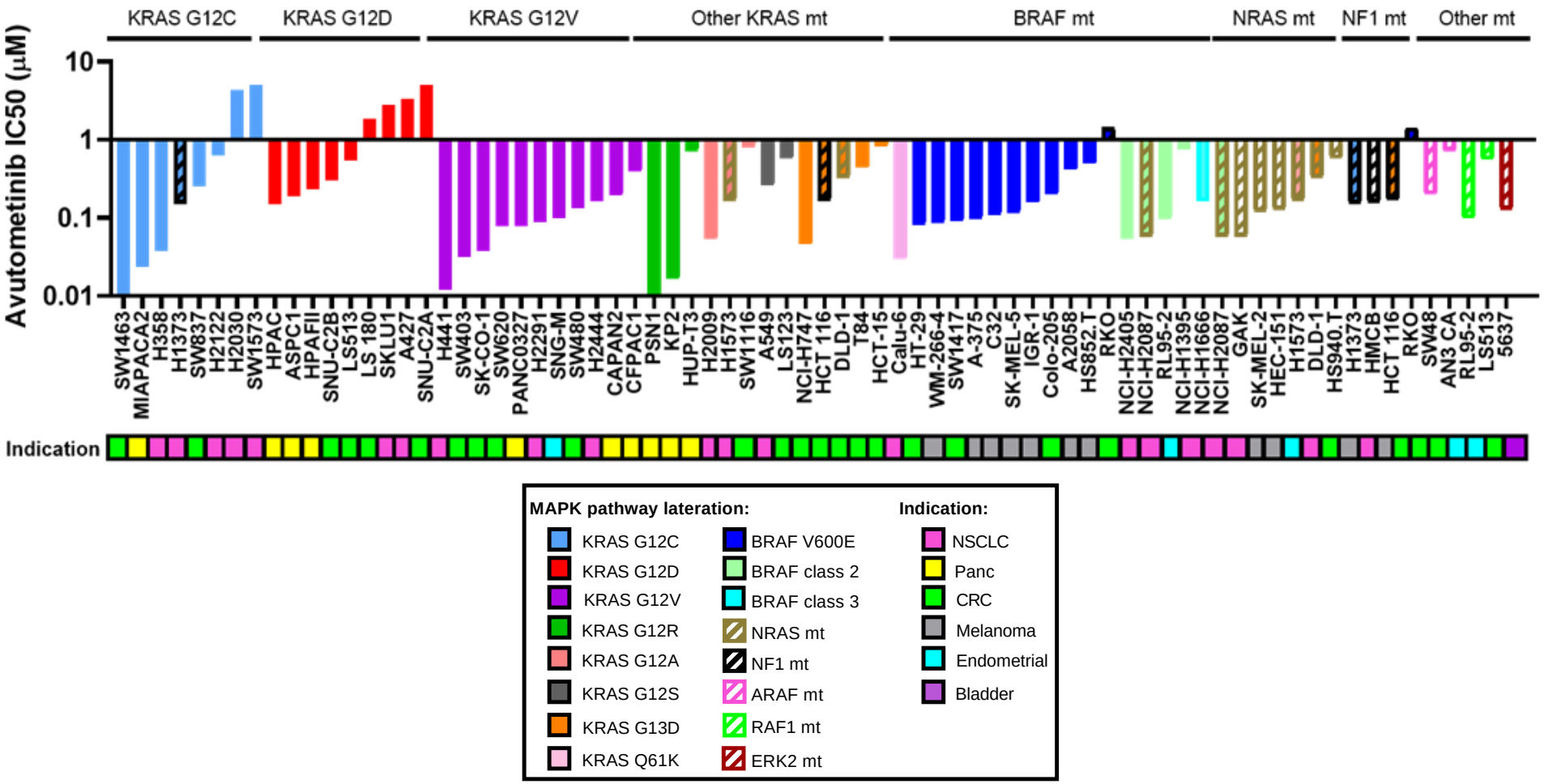


The RAF/MEK clamp mechanism avoids the compensatory activation of pMEK enabling more complete pERK inhibition



References: Coma et al., AACR 2022; Ishii et al., *Cancer Res*, 2013; Lito et al., *Cancer Cell*, 2014

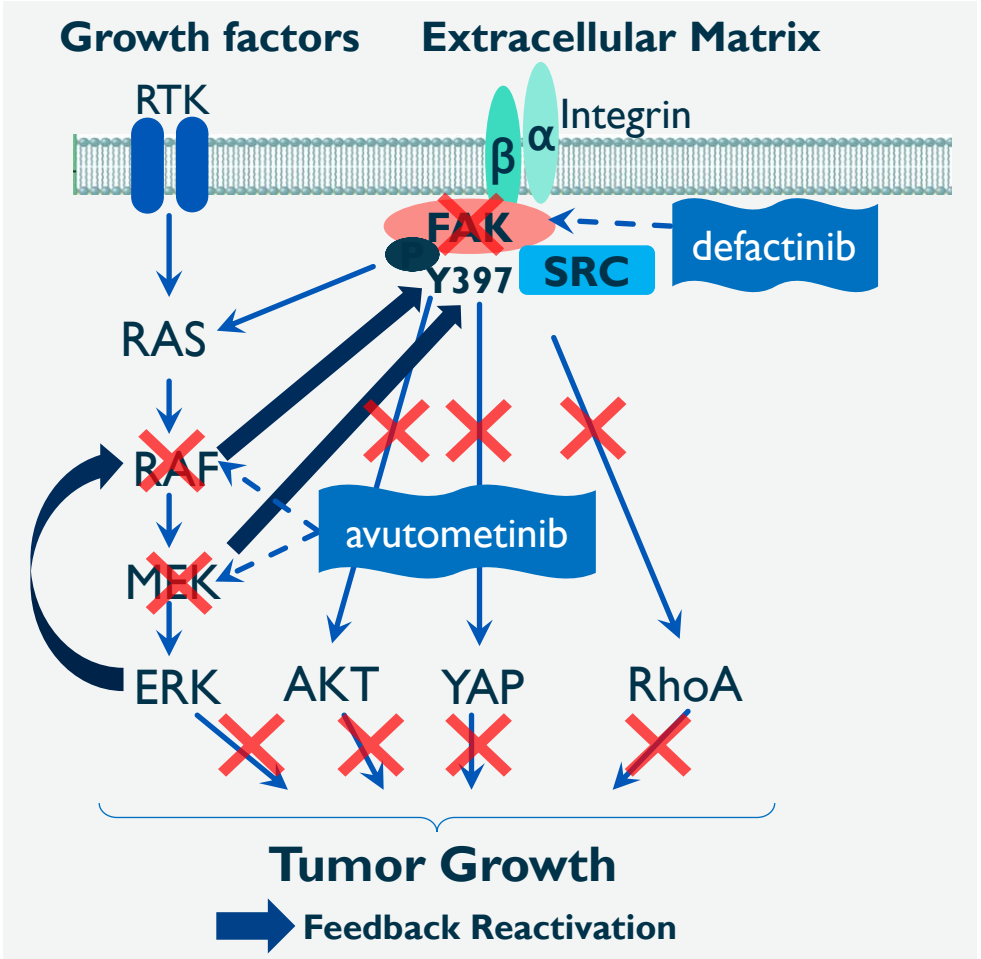
Avutometinib Inhibits Cell Proliferation Across Multiple RAS/MAPK Pathway Alterations and Multiple Solid Tumor Histologies

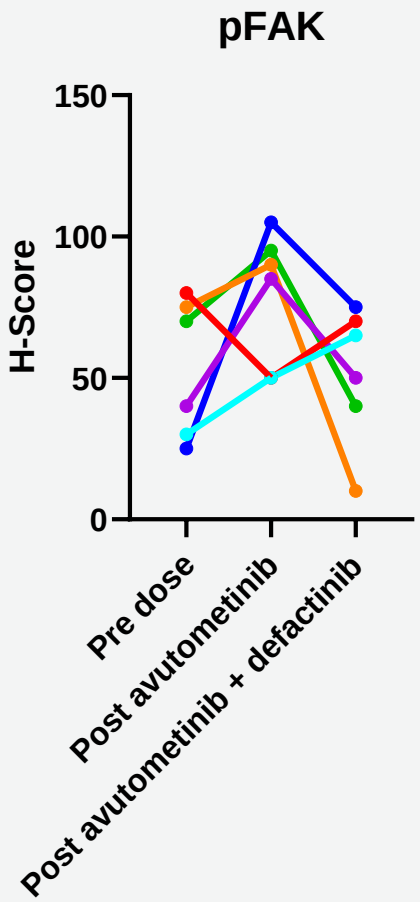


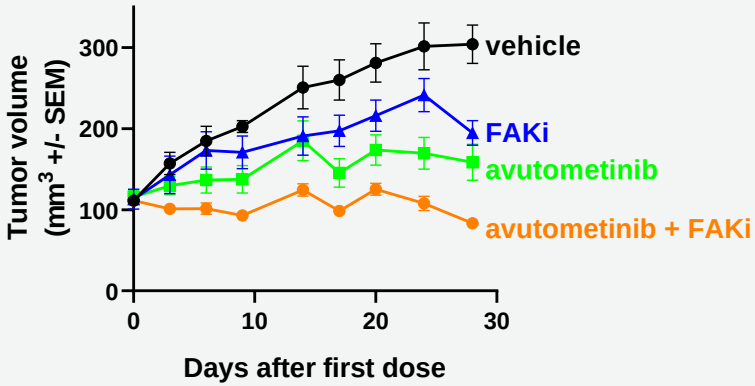
Reference: Pachter *RAS-Targeted Drug Development Summit 2022;* 3D proliferation assay

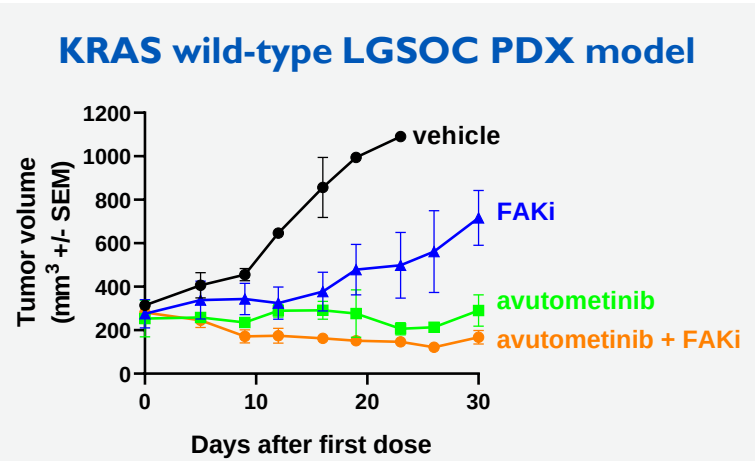
Strong Scientific Rationale for Avutometinib and FAK Inhibitor Combination

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

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%)

RP2D

- **Avutometinib 3.2 mg** oral BIW (3 of every 4 wks)
- **Defactinib 200 mg** oral BID (3 of every 4 wks)

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

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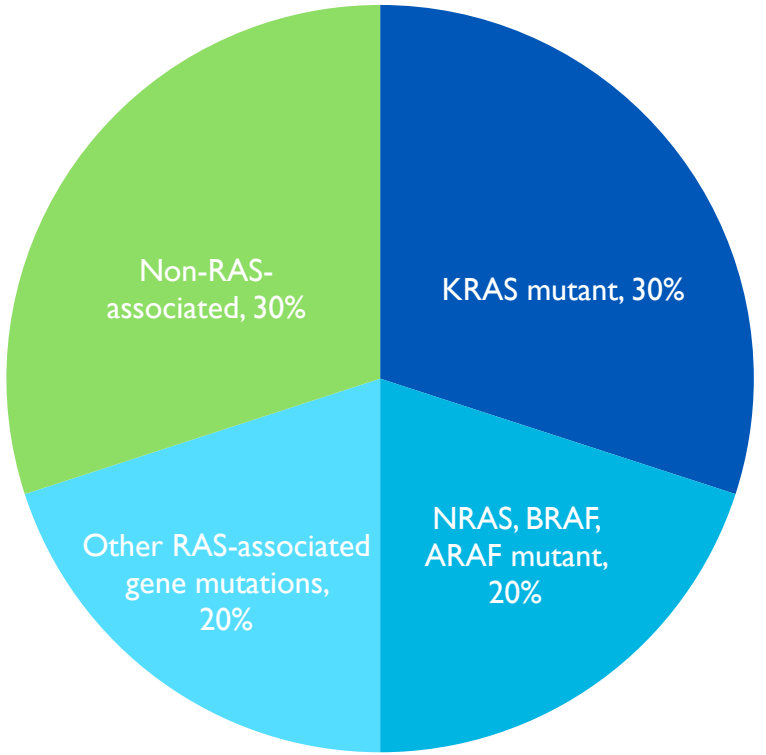
Low Grade Serous Ovarian Cancer (LGSOC)

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

- LGSOC is a type of ovarian cancer that disproportionately affects younger women (median 43-47 years)[1-2]
- LGSOC accounts for approximately1-4% of epithelial ovarian carcinoma and <10% of serous ovarian carcinoma worldwide diagnosed with LGSOC each year[3-4]
- LGSOC features relatively low proliferative activity that has a mOS of almost 10 years, so patients remain in treatment for an extended period of time[1-2, 5]
- 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[6-7]

~30% of LGSOC Patients Have KRAS mt
~70% of LGSOC Shows RAS Pathway-Associated mts[8-11]



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[1]Slomovitz *Gynecol Oncol* 2020; [2]Gershenson *Ann Oncol* 2016; [3]Matsuo *J Gynecol Oncol* 2018; [4]Grisham *Curr Treat Options Oncol* 2018; [5]Gockley *Obstet Gynecol* 2017; NCCN Guidelines: Ovarian Cancer v1.2022; [7]WHO Classification of Tumours 5th Ed.; [8]Gershenson *Gynecol Oncol* 2022; [9]Manning-Geist *Clin Cancer Res* 2022; [10]ElNaggar *Gynecol Oncol* 2022; [11]AACR GENIE v9.0 VSTM unpublished analysis (data on file); mOS = median overall survival ; mts = mutations

Recent LGSOC Trials with Standard of Care Highlight High Unmet Need in Recurrent LGSOC

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]	**2** (1-10)	No	* Low %	**Standard of Care**	**6% ^ *95% CI: (3%, 12%)***	INV	7.2 (5.6-9.9)	13%
				Trametinib	26%^ 95% CI: (19%, 35%)	INV	13.0 (9.9-15.0)	**36%**
MILO[2]	**2** (1-8)	No	* Low %	**Standard of Care**	**13% 95% CI: (7%, 21%)**	**BICR**	10.6 (9.2 to 14.5)	17%
				Binimetinib	16% 95% CI: (11%, 22%)	**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

GOG 281: *(chemotherapy / endocrine therapy)*
PLD (liposomal doxorubicin), paclitaxel, topotecan, letrozole or tamoxifen

MILO: *(chemotherapy only)*
PLD (liposomal doxorubicin), paclitaxel or topotecan

INV = Investigator
BICR = Blinded independent central review
PFS = Progression free survival
CI = confidence interval

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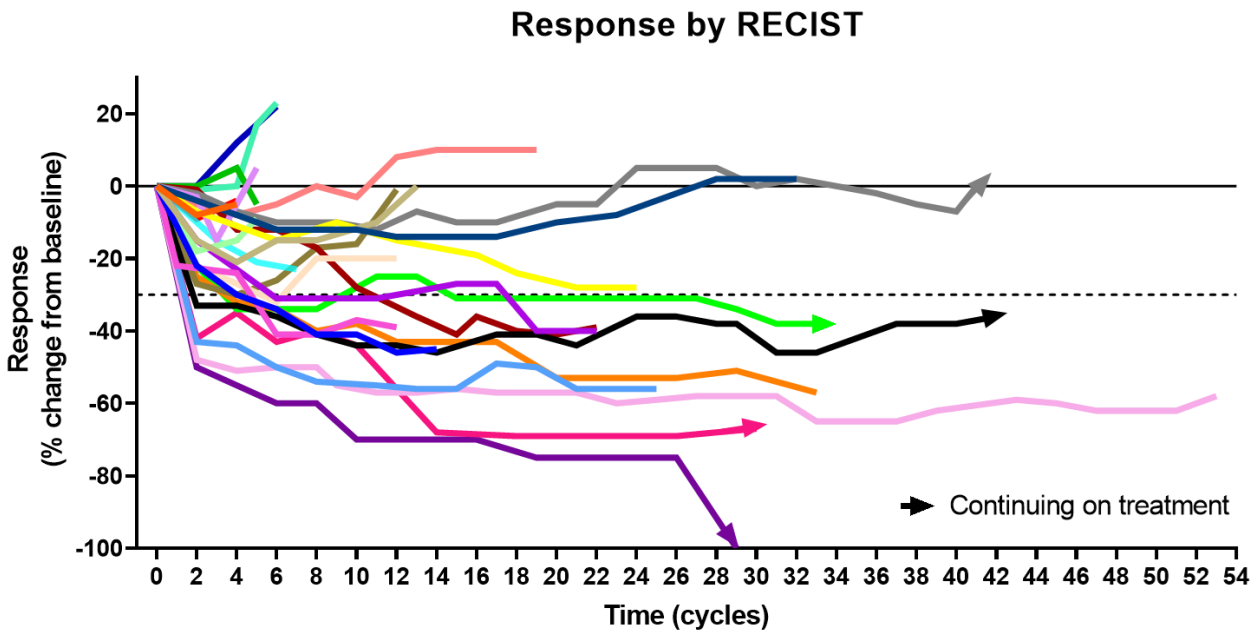
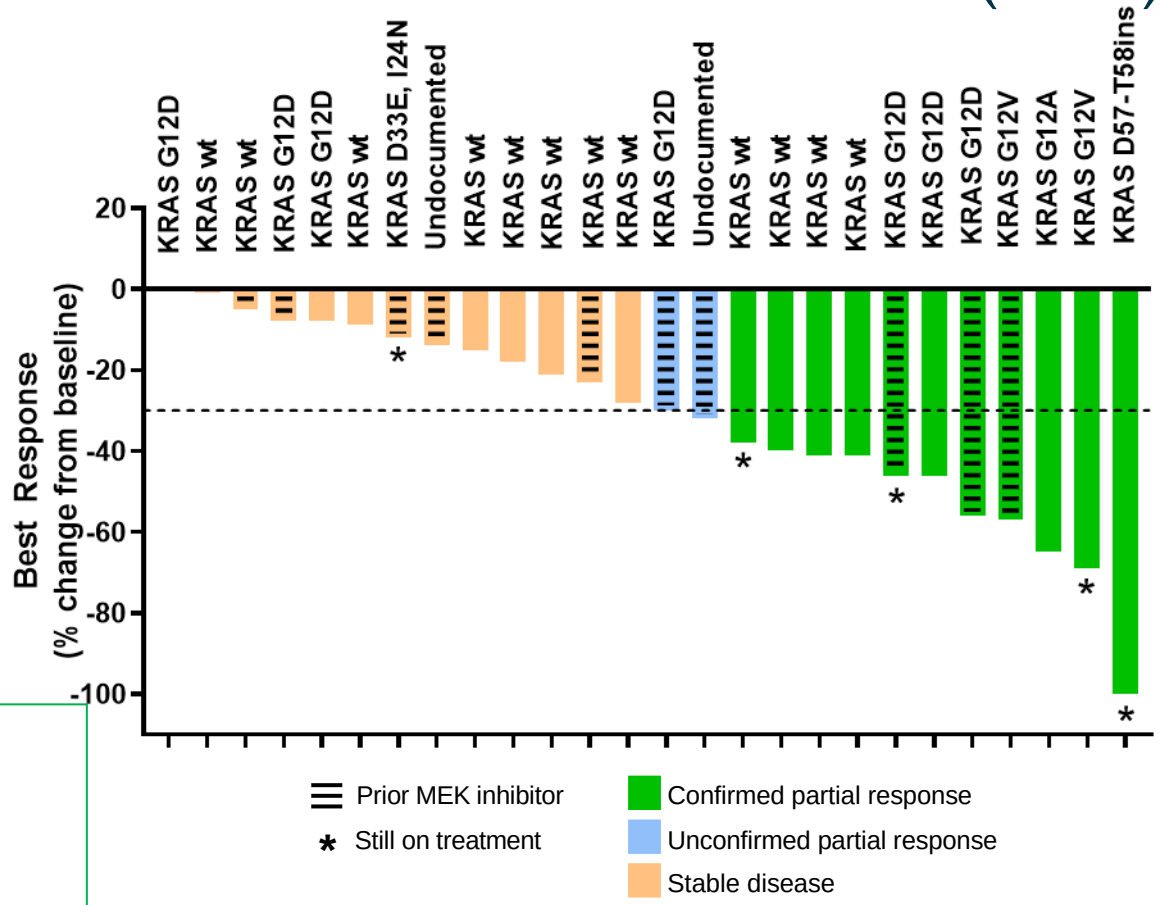
FRAME Study: High Rate of Durable Responses with the Combination of Avutometinib and Defactinib in Recurrent Low Grade Serous Ovarian Cancer (n=26)



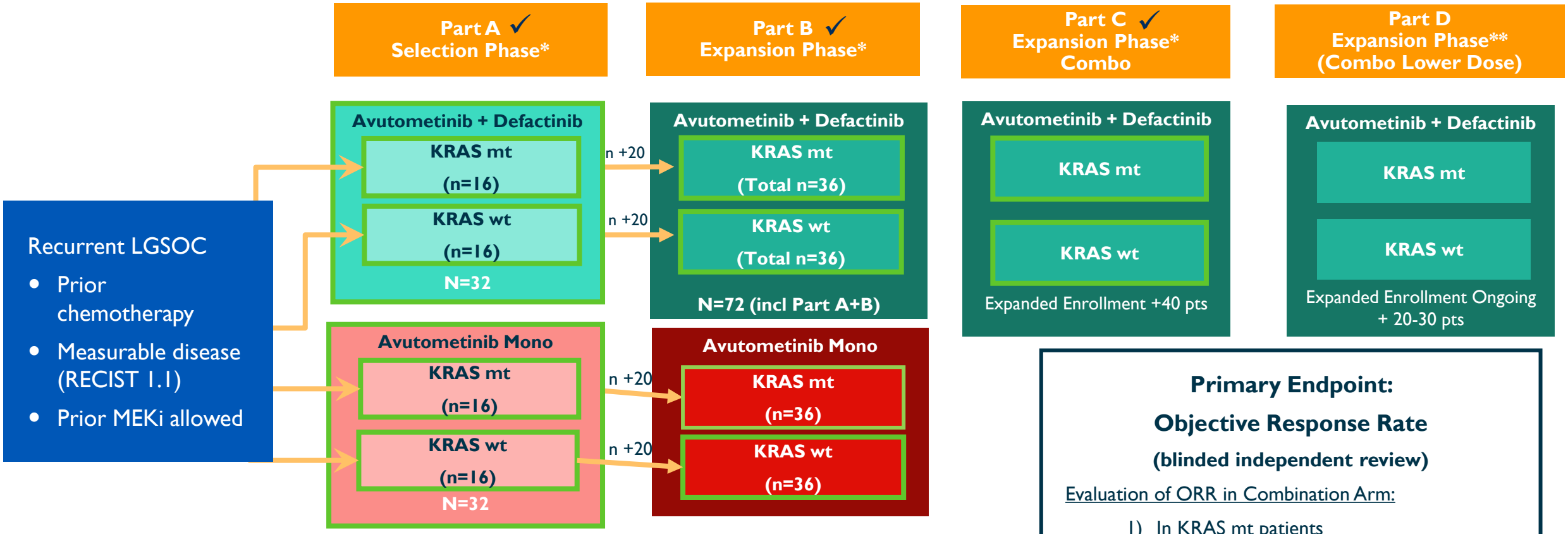


- Overall response rate (ORR) = 42% (11 confirmed PRs/26)
  - KRAS mutant ORR = 58% (7 confirmed PRs/12)
  - KRAS wild-type ORR = 33% (4 confirmed PRs/12)
- Median DoR 26.9 months (95% CI 8.5-47.3) across all LGSOC patients
- Median PFS 20.0 months (95% CI 11.1 – 31.2) across all LGSOC per RECIST 1.1
- Median 3.5 prior lines of treatment (n=26)
- Responses observed in patients previously treated with MEK inhibitor
- 19% (5/26) patients still on treatment as of July 2023 (minimum follow up: ~17 months)
- No new safety findings with continued follow-up
- 1 patient discontinued for adverse events as of July 2023 (skin AE)

28-day cycles
DoR: Duration of Response
PFS: Progression free survival
NR: Not reached

Banerjee et al., ESMO Sept 2021. Banerji U Targeting RAS Symposium Sept 2023
(Data Cut Off July 2023: Data on File)

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



Primary Endpoint:

Objective Response Rate

(blinded independent review)

Evaluation of ORR in Combination Arm:

1) In KRAS mt patients
2) All patients (KRAS mt & wt)

Combination Arm:

✓ **Target Enrollment Reached (N=72)**

❖ **Expanded Enrollment Ongoing (Lower Dose)**

* 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

** Lower Dose: Avutometinib + Defactinib combo: Avutometinib 1.6 mg PO 2x/wk 21/28 days + Defactinib 200 mg PO BID: 21/28 days;

✓ Completed Enrollment

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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 PS, 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)	4 (1, 10)	3 (1, 9)	3 (1, 10)	4 (1, 8)	5 (2, 11)	**4 (1, 11)**
Prior platinum-based chemotherapy, n (%)	15 (94)	17 (100)	32 (97)	16 (100)	15 (100)	31 (100)
Prior MEK inhibitor therapy, n (%)	5 (31)	5 (29)	10 (30)	2 (13)	2 (13)	4 (13)
Prior Bevacizumab, n (%)	8 (50)	8 (47)	16 (48)	7 (44)	13 (87)	20 (64)
Prior Hormonal therapy, n (%)	11 (69)	13 (76)	24 (73)	15 (94)	13 (87)	28 (90)

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)
Confirmed ORR, n (%)	2 (13)	1 (6)	3 (10) 95% CI (2%, 24%)	9 (60)	4 (29)	13 (45) 95% CI (26%, 64%)
CR, n (%)	1 (7)	0	1 (3)	0	0	0
PR, n (%)	1 (7)	1 (6)	2 (7)	9** (60)	4 (29)	13 (45)
SD, n (%)	12 (80)	13 (81)	25 (83)	6 (40)	7 (50)	13 (45)
Disease control rate*, n (%)**	14 (93)	14 (88)	28 (93)	15 (100)	11 (79)	26 (90)
PD, n (%)	1 (7)	2 (13)	3 (10)	0	3 (21)	3 (10)
Confirmed + unconfirmed ORR, n (%)	2 (13)	1 (6)	3 (10)	11 (73)	4 (29)	15 (52)

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

** Includes patient deepened to CR at last assessment; CR not yet confirmed

***Disease control rate (SD + PR + CR) at 8 weeks.

BICR, blinded independent central review; mt, mutant; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; wt, wild type

ASCO 2023 data

Combination of Avutometinib and Defactinib

High Disease Control Rate + Tumor Reduction in Recurrent LGSOC

Part A (Evaluable for Efficacy *)

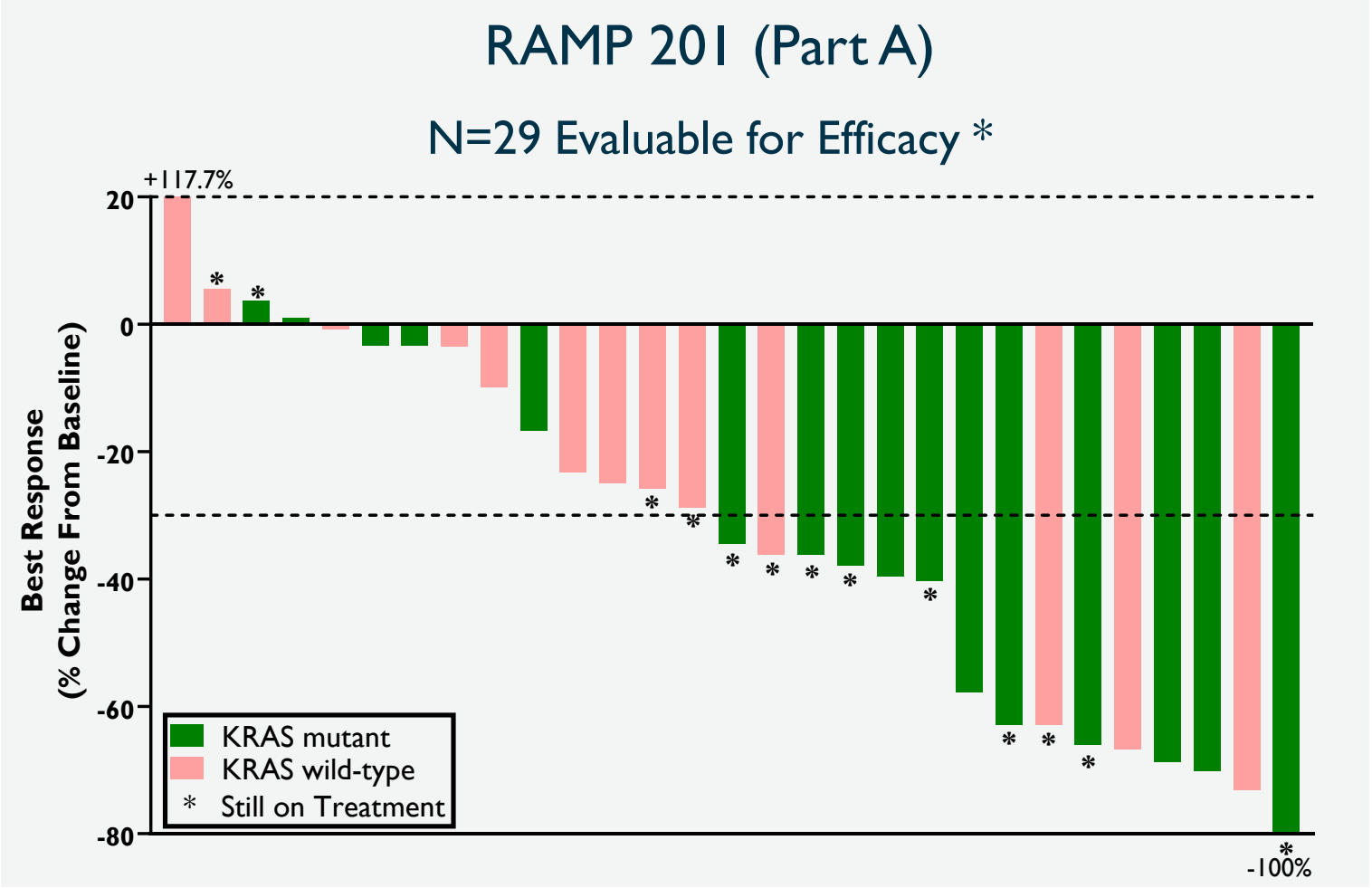
Confirmed ORR: **45%**

Confirmed/Unconfirmed ORR: **52%**

Disease Control Rate (SD+PR): **90%**

Patients still on study treatment: 45%

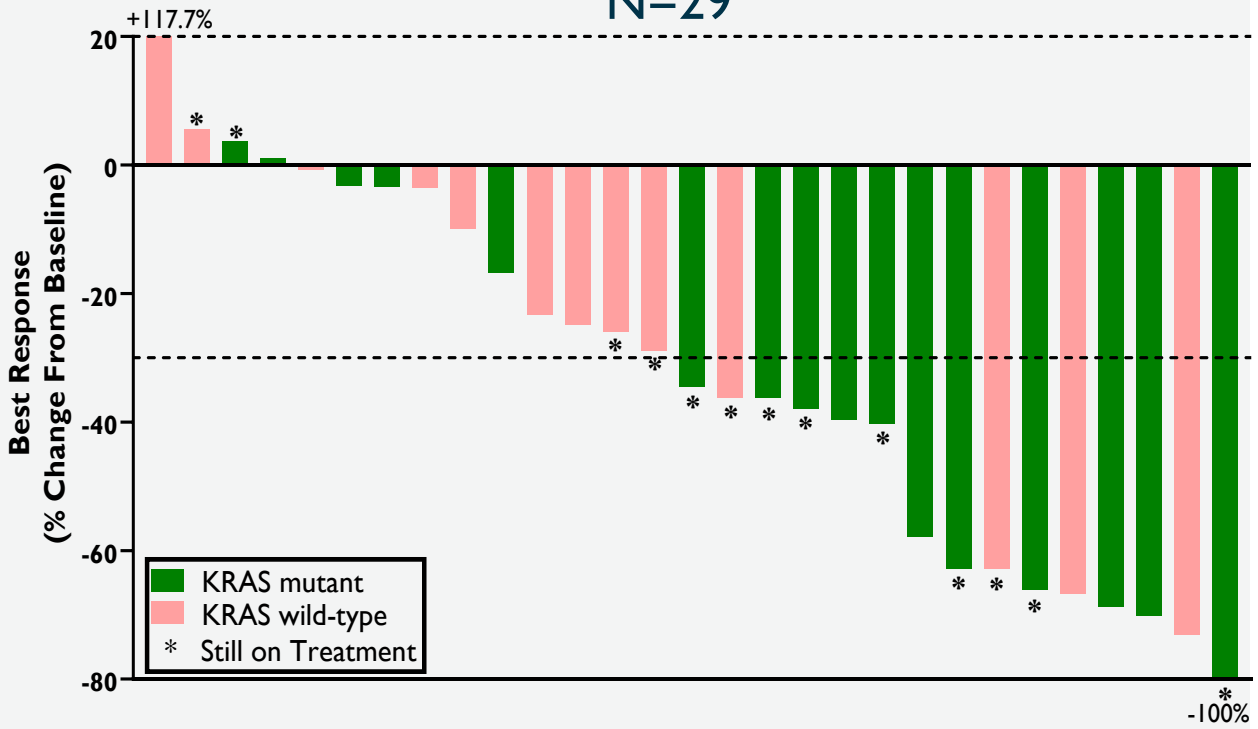
Minimum follow-up: 12 months



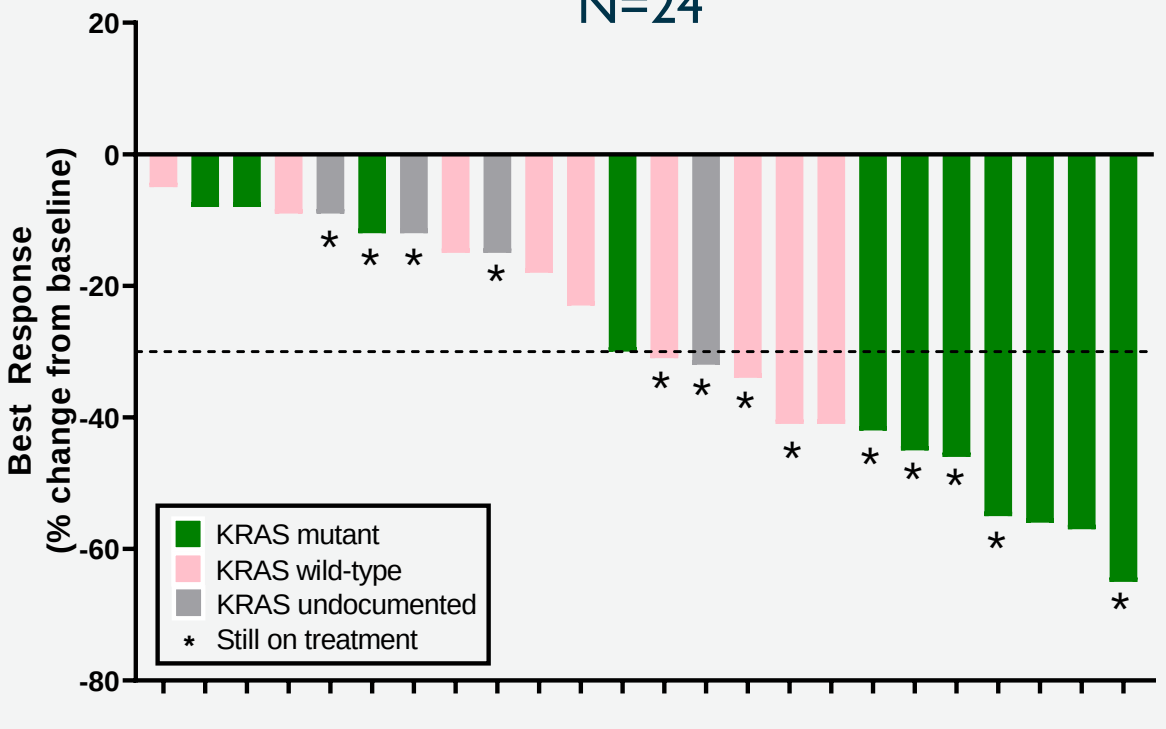
* Evaluable for Efficacy: At least one blinded imaging assessment

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



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 and manageable/reversible[1]
- Few discontinuations due to adverse events (12.3% in combo due to ≥ 1 TEAE 4.9% due to elevated blood CPK*)
  * No association to date with clinically significant toxicities, including rhabdomyolysis

Avutometinib + Defactinib (n=81)		
	Any Grade	Grade ≥3
Nausea, n (%)	50 (61.7)	0
Diarrhea, n (%)	40 (49.4)	3 (3.7)
Blood CPK increased, n (%)	39 (48.1)	15 (18.5)
Oedema peripheral, n (%)	34 (42.0)	1 (1.2)
Vomiting, n (%)	30 (37.0)	0
Vision blurred, n (%)	29 (35.8)	0
Dermatitis acneiform, n (%)	28 (34.6)	2 (2.5)
Fatigue, n (%)	27 (33.3)	3 (3.7)
Rash, n (%)	25 (30.9)	2 (2.5)
Dry skin, n (%)	18 (22.2)	0
Anemia, n (%)	14 (17.3)	3 (3.7)

Reference: Banerjee et al., ASCO June 2023;
[1] J Clin Oncol 41, 2023 (suppl 16; abstr 5515)

Forward Plan: **Confirmatory Trial** – Randomized Controlled Trial (RCT)

- Recurrent LGSOC
  - KRAS mt+wt
- Prior platinum chemotherapy
- Prior MEKi allowed
- Prior Bev allowed
- Measurable disease (RECIST 1.1)

Randomized 1:1

Strat Factors include:

KRAS Mut Status (KRAS mt vs wt)

Avutometinib + Defactinib*

Recurrent LGSOC

(N=135)

Avutometinib + Defactinib*

Crossover upon PD

Investigator's Choice Treatment (ICT)*

Recurrent LGSOC

(N=135)

ICT*

Primary Endpoint:

Progression-Free Survival (PFS) by **BICR****

Secondary Endpoints include:

- **Objective Response Rate (ORR)**
- **Duration of Response (DoR)**
- **Disease Control Rate (DCR)**
- **Safety / Tolerability**
- **Patient Reported Outcomes**
- **Overall Survival**

Primary Analysis: Hierarchical Evaluation

1) KRAS mutant LGSOC only

2) All recurrent LGSOC

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

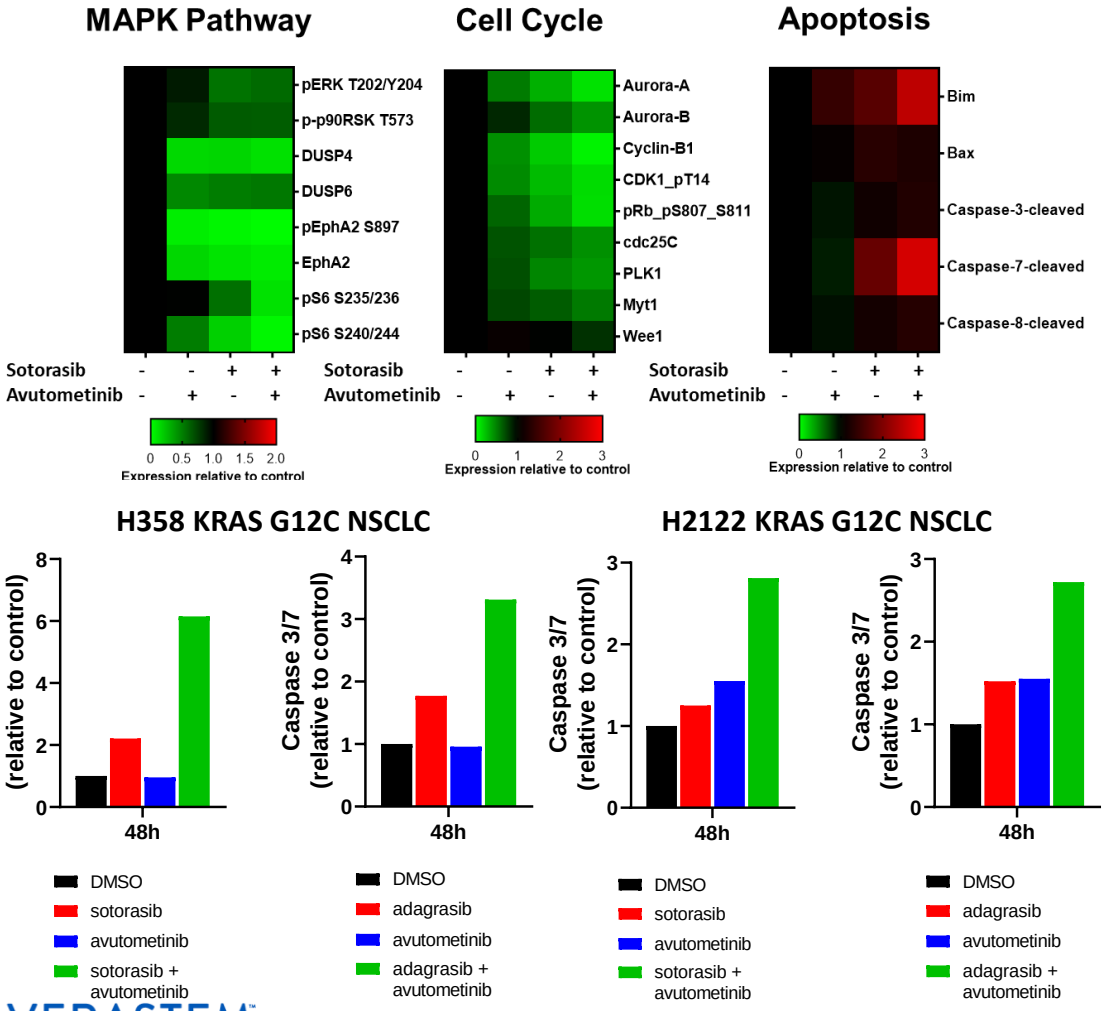
***Chemo Hormonal ICT: Liposomal doxorubicin (PLD), Paclitaxel, Topotecan, Letrozole, Anastrozole**

**** BICR: Blinded Independent Central Review**

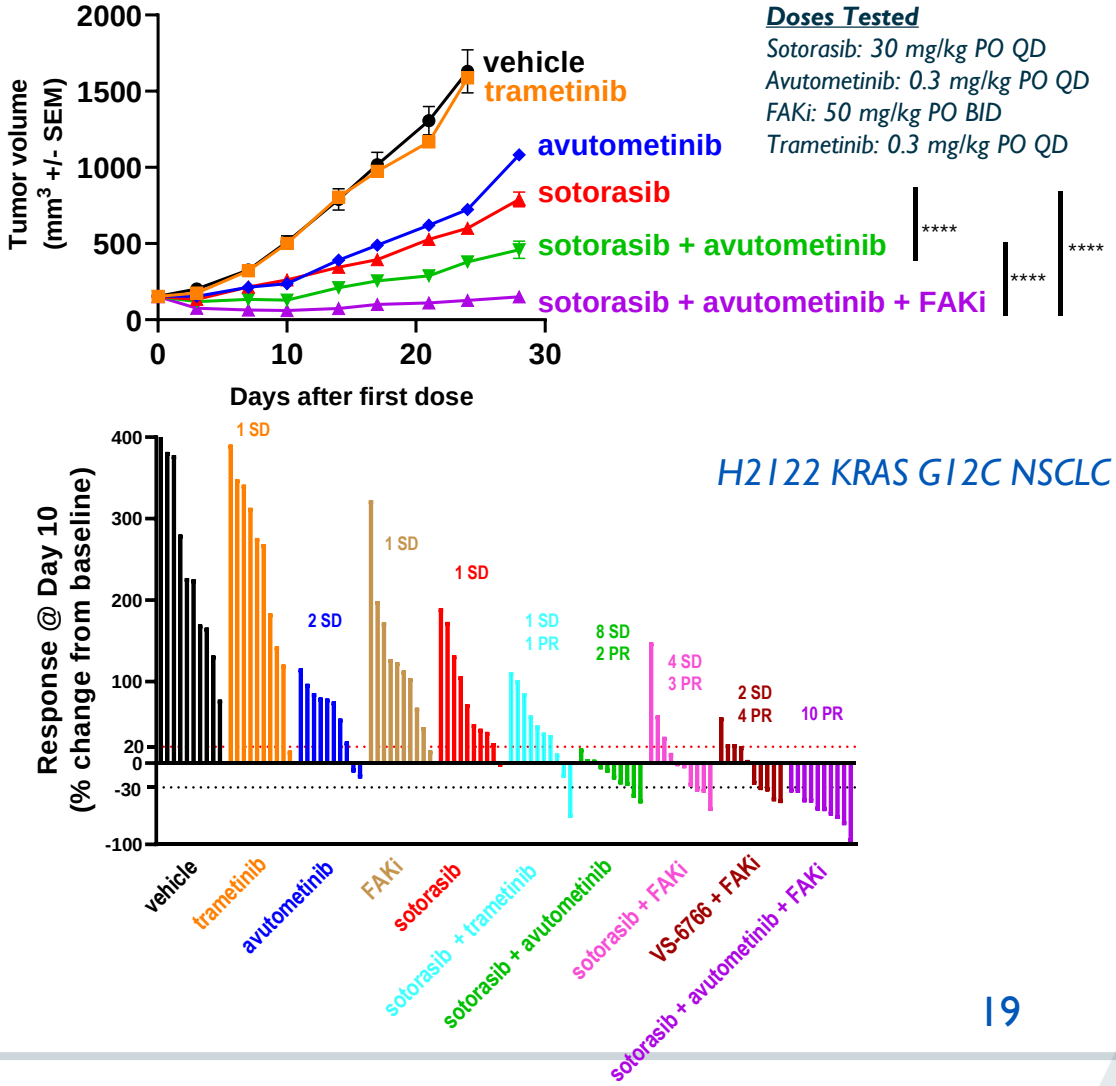
Rational Combinations
Clinical Development Program

Avutometinib ± FAKi Potentiates Anti-Tumor Efficacy of G12Ci in G12Ci-Naïve KRAS G12C NSCLC Models

RAS, RAF & MEK blockade with avutometinib + G12C inhibitor confers anti-proliferative & pro-apoptotic signaling



Avutometinib & FAKi potentiate sotorasib-induced anti-tumor efficacy in KRAS G12C NSCLC models



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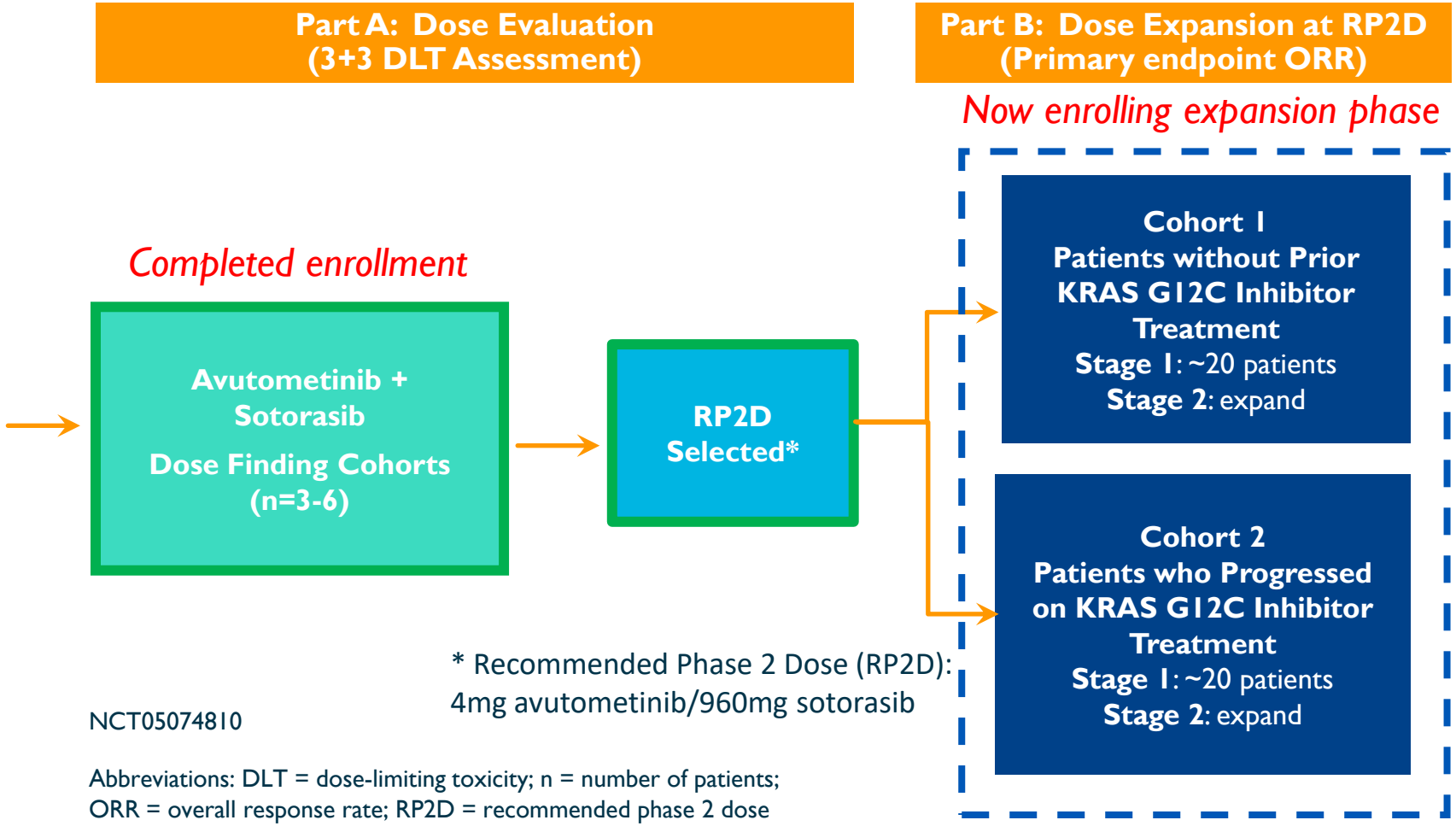
Reference: Coma et al., AACR 2021

RAMP 203: Phase 1/2 Trial of Avutometinib + Sotorasib in G12Ci-naïve and G12Ci-progressing KRAS G12C 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



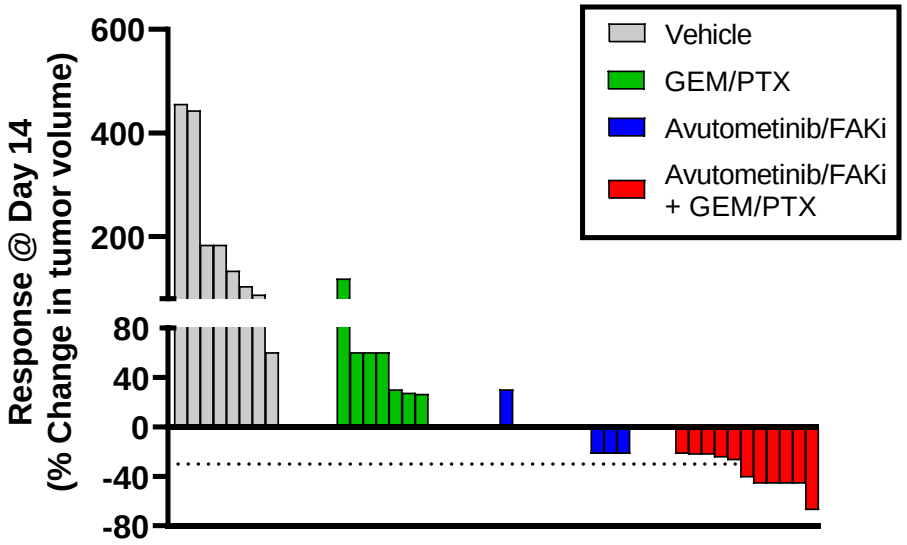
* Recommended Phase 2 Dose (RP2D): 4mg avutometinib/960mg sotorasib

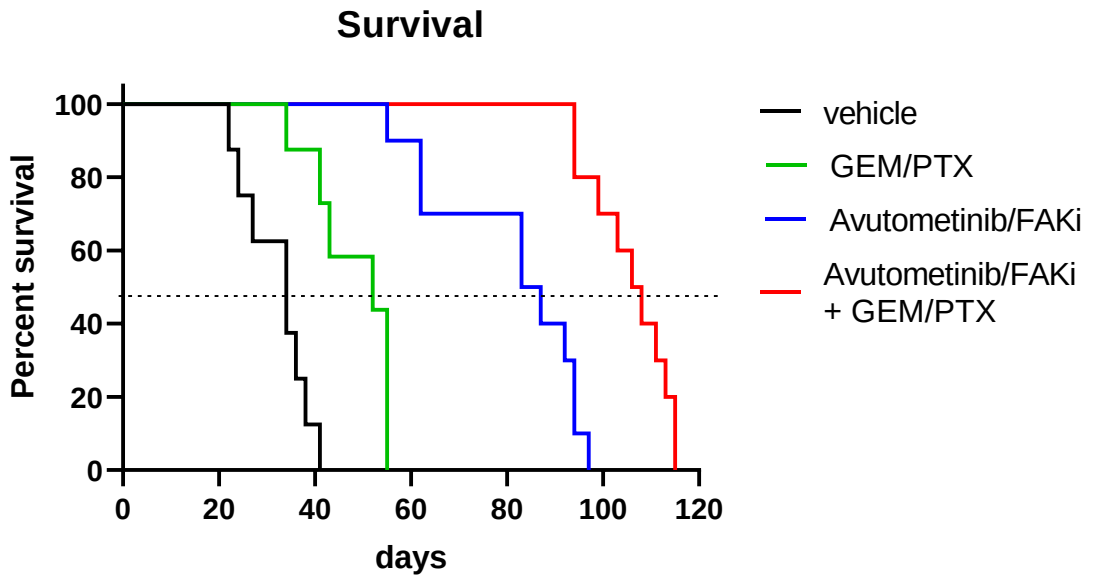
NCT05074810

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

Clinical trial also ongoing with avutometinib + adagrasib in KRAS G12C NSCLC (RAMP 204; NCT05375994)

Addition of Avutometinib + FAKi to Chemotherapy Induces Tumor Regression and Increases Survival in a KRAS/p53 Pancreatic Cancer Mouse Model





- The combination of avutometinib + FAKi induces tumor growth inhibition and increases survival but induces tumor regression only in some mice
- Addition of chemo (gemcitabine + paclitaxel) to avutometinib/FAKi induces tumor regression in all mice and further increases survival

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

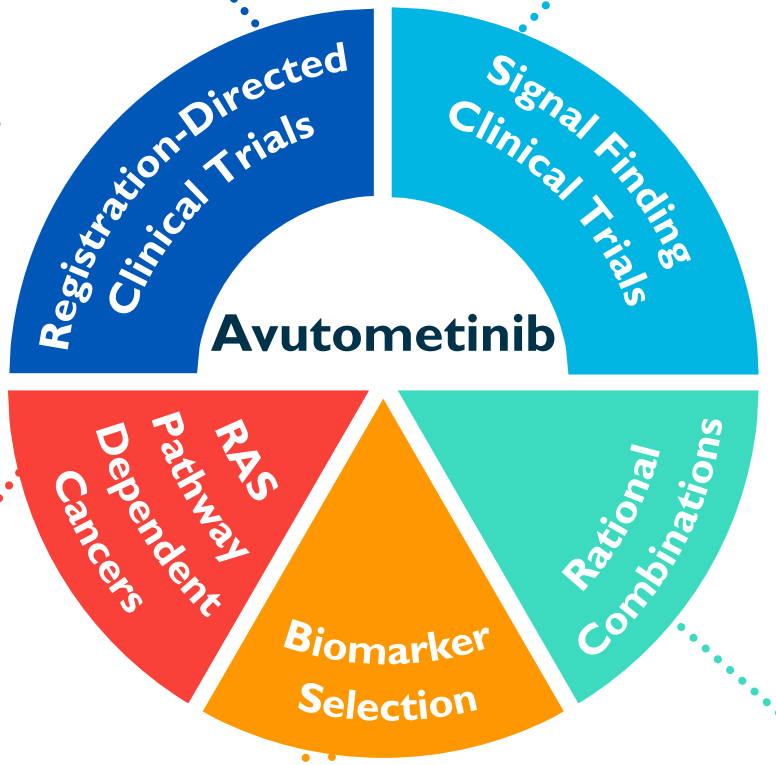
Abbreviations: DLT = dose-limiting toxicity; n = number of patients; ORR = overall response rate; RP2D = recommended phase 2 dose

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]

VERASTEM ONCOLOGY

[1] Supported by clinical data

[2] Supported by preclinical data

Conclusions: Avutometinib and Defactinib in Clinical Development for Patients with RAS/MAPK Pathway-Driven Cancers

- **Avutometinib** is a differentiated RAF/MEK clamp with activity across multiple MAPK pathway alterations and multiple cancer indications
  - Intermittent oral dosing schedule confers manageable clinical safety profile with potential for combinability with multiple target classes

- Combination of avutometinib with **defactinib** (FAKi) has shown consistent clinical efficacy and safety/tolerability and has received Breakthrough Therapy Designation in low-grade serous ovarian cancer
  - **High rate** of **durable responses** in recurrent KRAS mutant and KRAS wt **LGSOC**
  - Target enrollment in **Registration-directed trial** reached**. Confirmatory Trial** initiation 2H2023
  - Combination with defactinib also being evaluated in other gynecological cancers

- Additional **rational** combinations shown tolerable and in clinical development in RAS/MAPK driven cancers
  - Combinations with **sotorasib** or **adagrasib** (G12Ci) in KRAS G12C **NSCLC** - G12Ci-naïve / pretreated
  - Combination with **chemotherapy (gemcitabine/Nab-paclitaxel) and defactinib** being evaluated in 1st line metastatic pancreatic cancer