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LGSOC Program Update

January 24, 2023

Today's Speakers

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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, in the Company's Quarterly Reports on Form 10-Q for the quarters ended June 30, 2022 and September 30, 2022, as filed with the SEC on August 8, 2022 and November 3, 2022, respectively, 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.

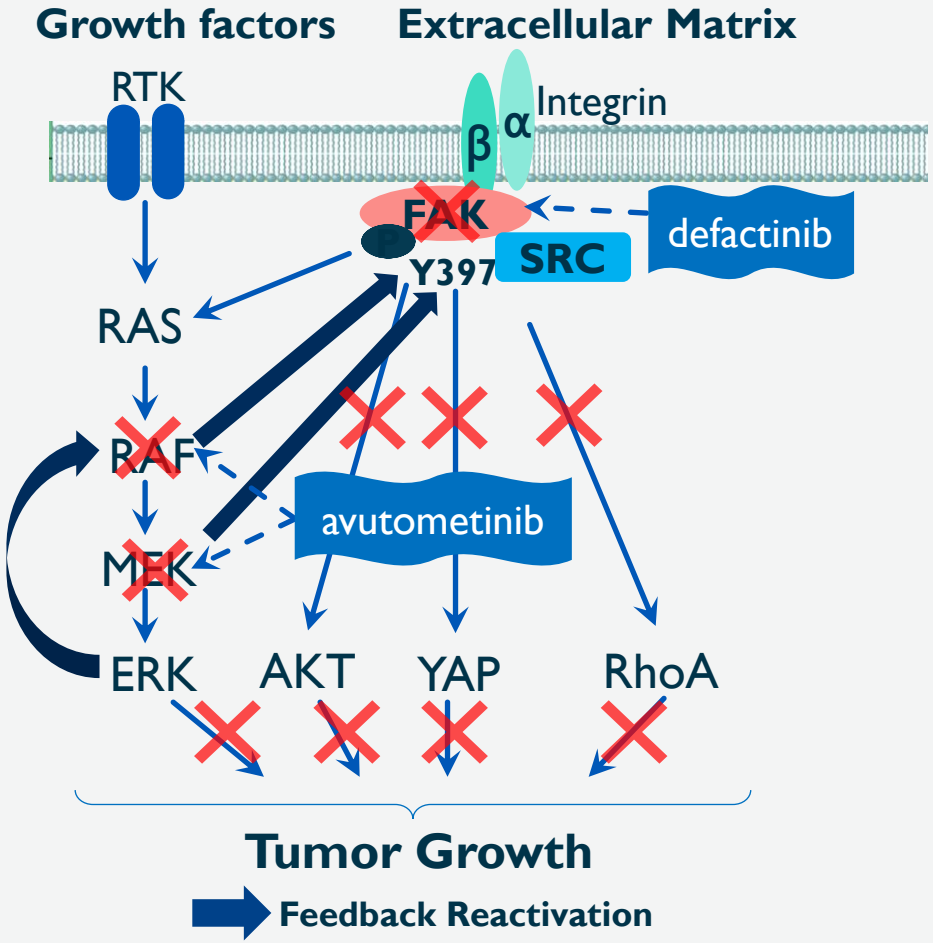
Brian Stuglik

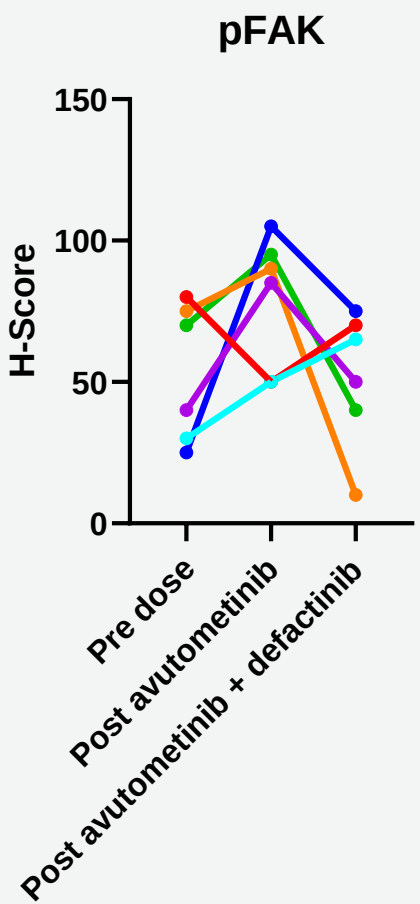
Avutometinib is a Differentiated Agent with the Potential to Serve as the Backbone for Combinations Across RAS Pathway-Driven Cancers

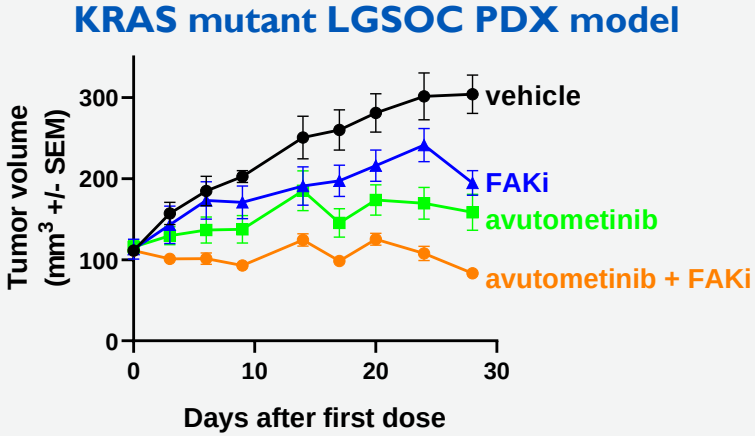
- Unique RAF/MEK clamp mechanism of action
- Novel intermittent dosing schedule; convenient oral regimen
- Breakthrough Therapy Designation in recurrent low-grade serous ovarian cancer
- Potential best-in-class safety & tolerability profile relative to marketed MEK inhibitors, with potential for combinability 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 and parallel pathways

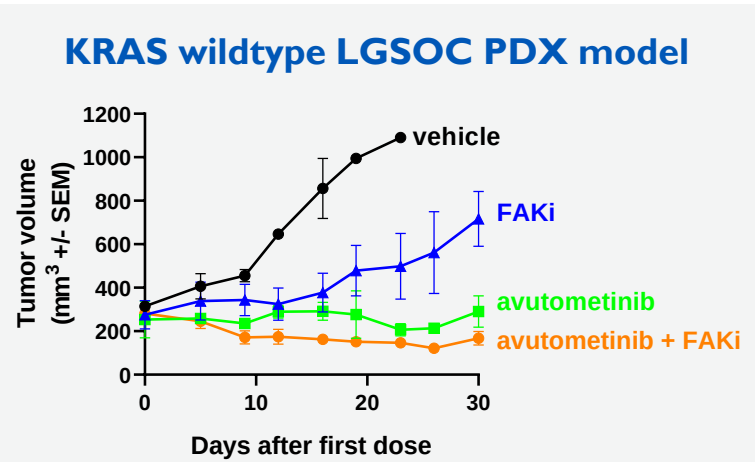
Strong Scientific Rationale for Avutometinib and FAK Inhibitor Combination

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









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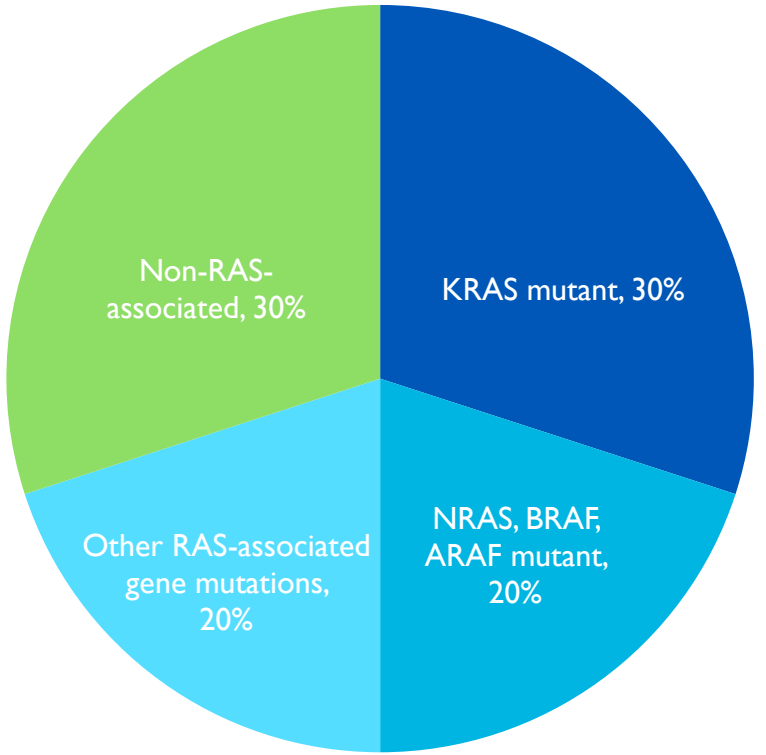
References: Banerji, BTOG Dublin, Jan 23, 2019; Banerji, AACR VM 1, April 27, 2020, CT143; Banerji, unpublished; Santin, unpublished

Kathleen Moore, MD

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

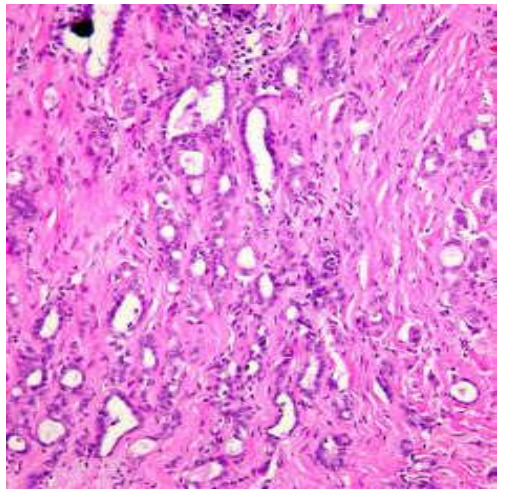


References: AACR Project GENIE Cohort v9.0-public and Verastem unpublished analysis

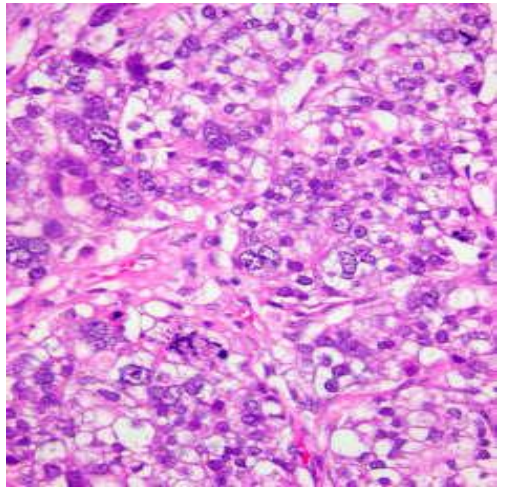
Reference: Monk, Randall, Grisham, The Evolving Landscape of Chemotherapy in Newly Diagnosed Advanced Epithelial Ovarian Cancer, Am Soc Clin Oncol Educ Book; 2019; Slomovitz, Gourley, Carey, Malpica, Shih, Huntsman, Fader., Grisham et al, Low-Grade serous ovarian cancer: State of the Science; Gynecol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

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

Variable	LGSOC (Grade 1)	HGSOC (Grade 2/3)
Nuclear atypia	Uniform round to oval with little variation	+++ Marked variation
Mitotic Index	<12 mitosis 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. 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

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 (ie, letrozole, anastrozole, exemestane) is preferred if not used previously. Fulvestrant, tamoxifen, or leuprolide acetate is recommended if an aromatase inhibitor was given previously.

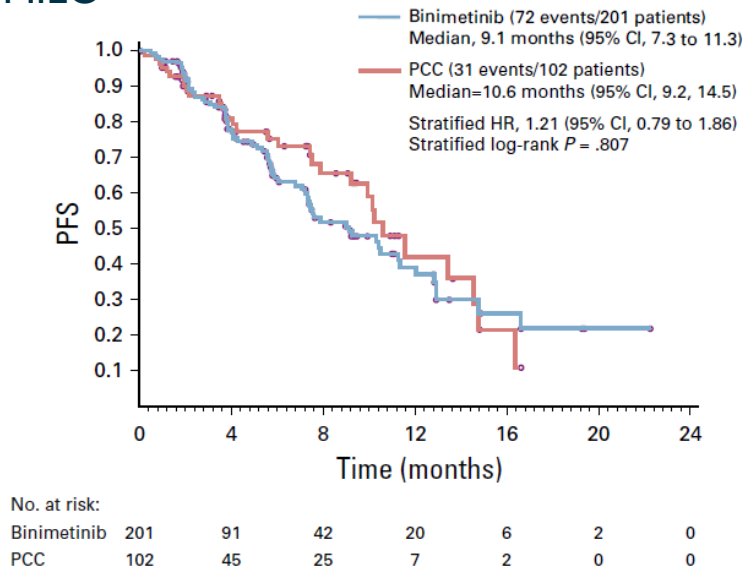
Preferred Regimens
- Paclitaxel/carboplatin q3weeks[f,g] ± maintenance letrozole (category 2B) or other hormonal therapy (category 2B)[ff]
- Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[f,l] (ICON-7 & GOG-218)
- Hormone therapy (aromatase inhibitors: anastrozole, letrozole, exemestane)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

References:
[1] NCCN guidelines v1.2023

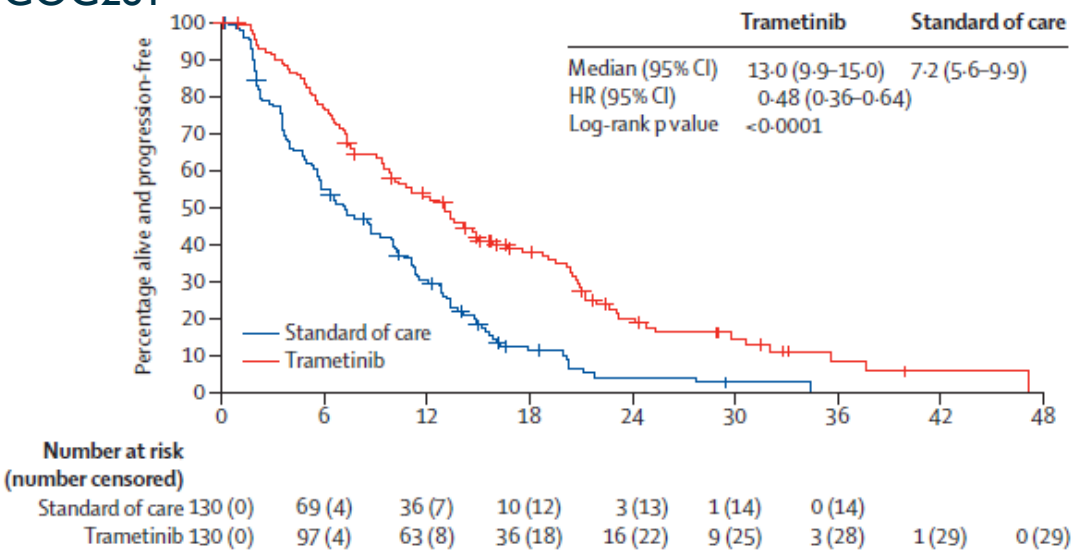
Recent LGSOC Trials Highlight High Unmet Need

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)	12 %
				Trametinib	**26%**	INV	13.0 (9.9-15.0)	**35%**
MILO[2]	**2** (1-8)	No	* Low %	**SoC**	**13%**	BICR	10.6 (9.2 to 14.5)	17%
				Binimetinib[2]	**16%**	BICR	9.1 (7.3-11.3)	**31%**

MILO



GOG281



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

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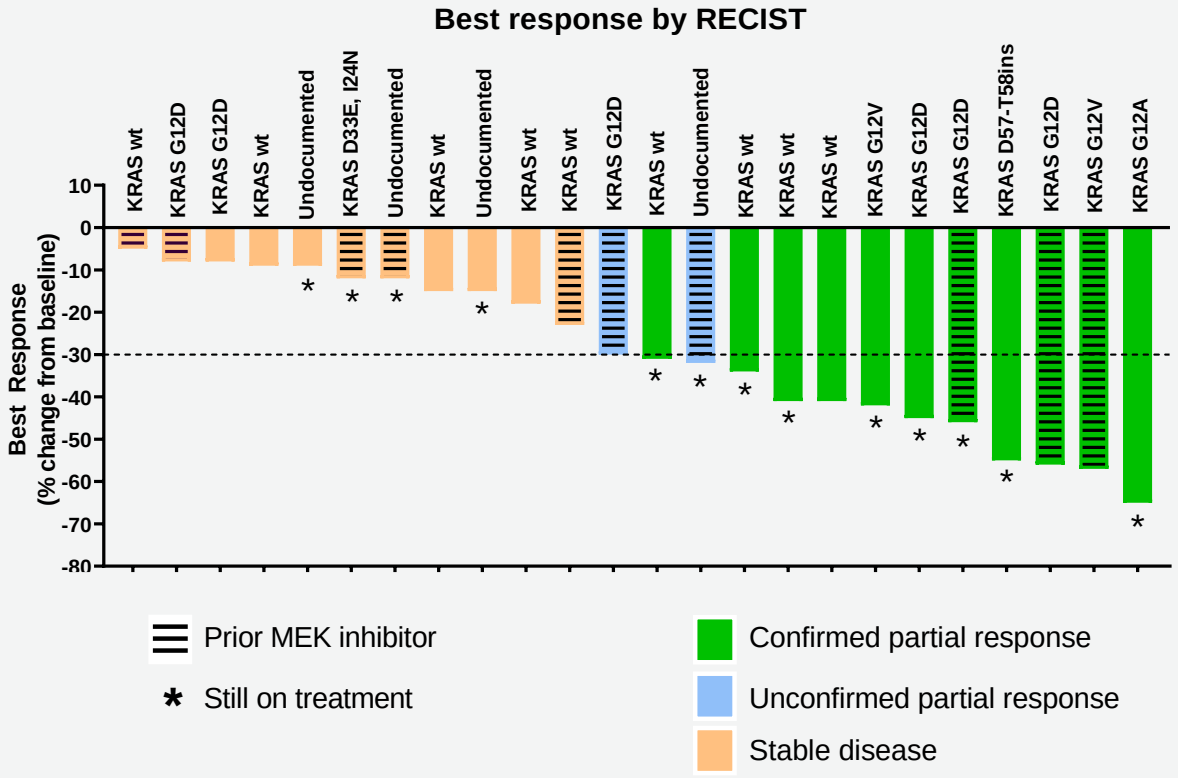
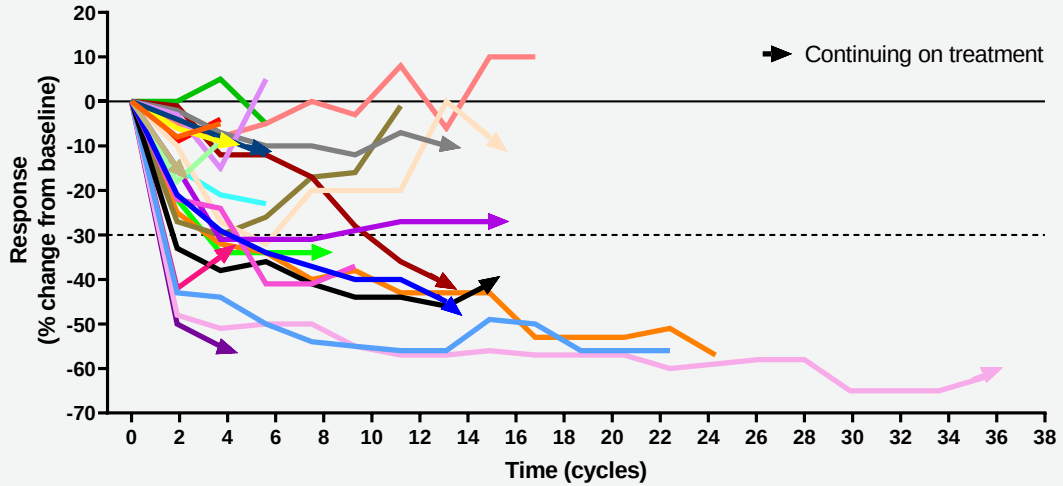
[1] Study GOG 281 trial Gershenson et al., Lancet 2022
[2] MILO Study Monk et al., J Clin Oncol 2020.

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

FRAME Study: Solid Foundation for the Development of Avutometinib in Combination with Defactinib in Recurrent LGSOC (n=24)





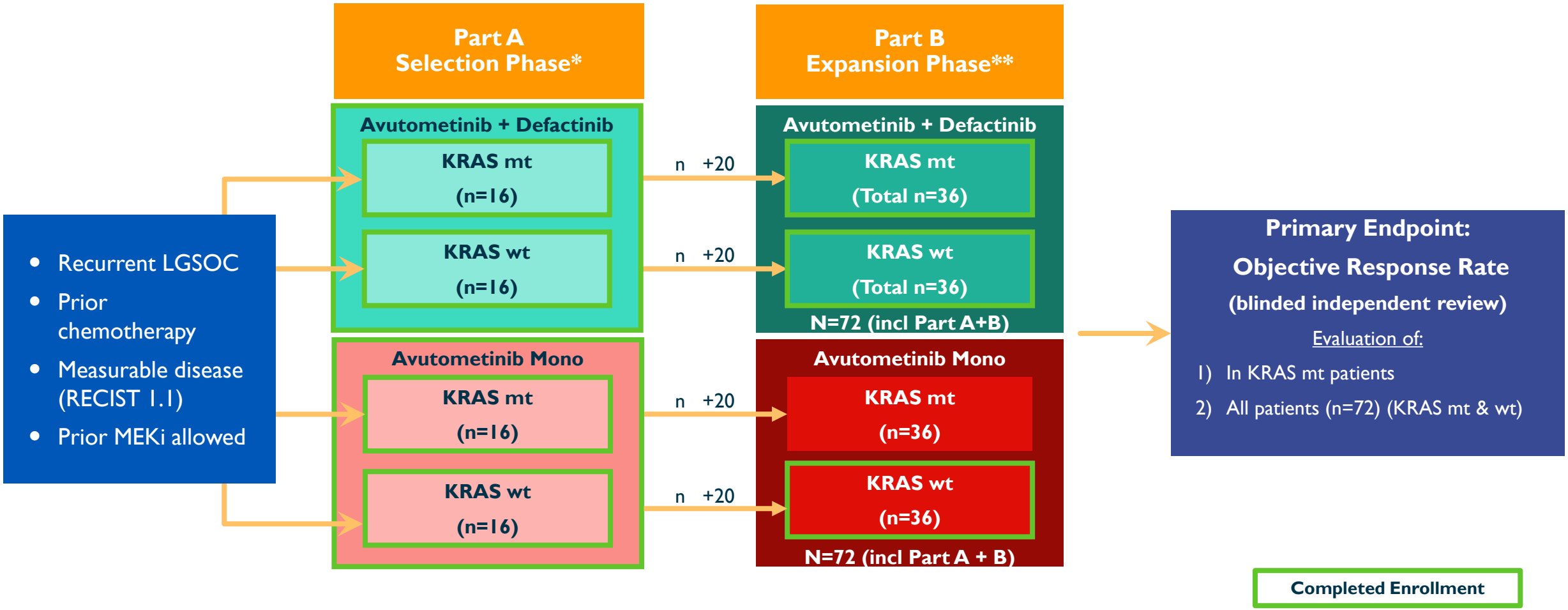
- Median 3 lines of Prior Treatment (Prior MEKi 10 pts, Prior Bev 3 pts)
- Overall response rate (ORR) = 46% (11 confirmed PRs/24)
  - KRAS mutant ORR = 64% (7 confirmed PRs/11)
  - KRAS wild-type ORR = 44% (4 confirmed PRs/9)
  - KRAS status undetermined (1 unconfirmed PR/4)
- DCR rate = 100% (24/24 achieved SD or better)
- Responses in patients previously treated with MEKi
- Median PFS 23 months (95% CI 10.6-NR) across all LGSOC

MEKi: MEK inhibitor, Bev: bevacizumab
PFS: Progression free survival, NR: Not reached

Reference: Banerjee et al., ESMO Sept 2021

Louis Denis, MD

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

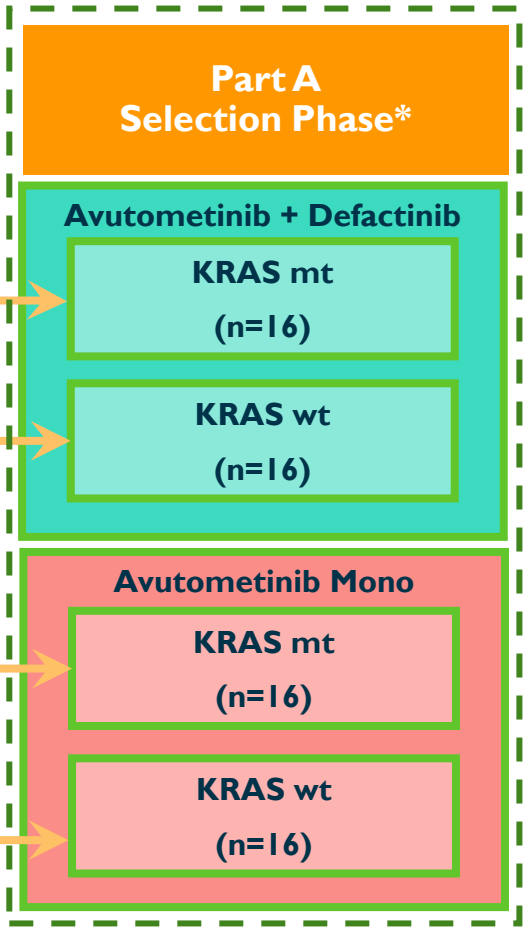


*Dosing: Defactinib + VS-6766 combo: Defactinib 200mg PO BID: 21/28 days + VS-6766 3.2mg PO 2x/wk 21/28 days; VS-6766 monotherapy: VS6766 4.0 mg PO 2x/wk 21/28 days

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

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

- Recurrent LGSOC
- Prior chemotherapy
- Measurable disease (RECIST 1.1)
- Prior MEKi allowed



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: Defactinib + VS-6766 combo: Defactinib 200mg PO BID: 21/28 days + VS-6766 3.2mg PO 2x/wk 21/28 days; VS-6766 monotherapy: VS6766 4.0 mg PO 2x/wk 21/28 days

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

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

<u>Part A (Evaluable for Efficacy *)</u>

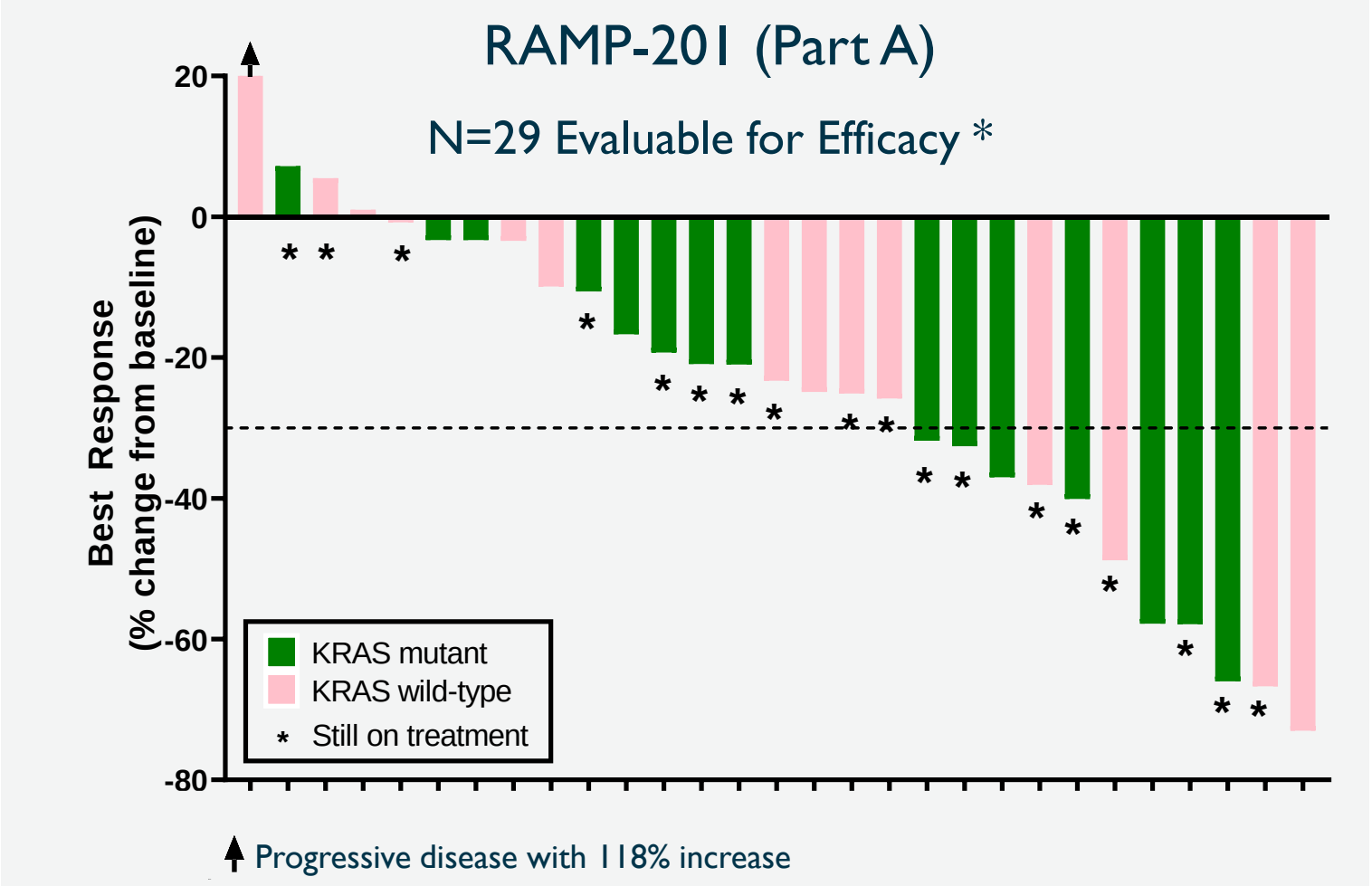
Confirmed ORR: **28%**

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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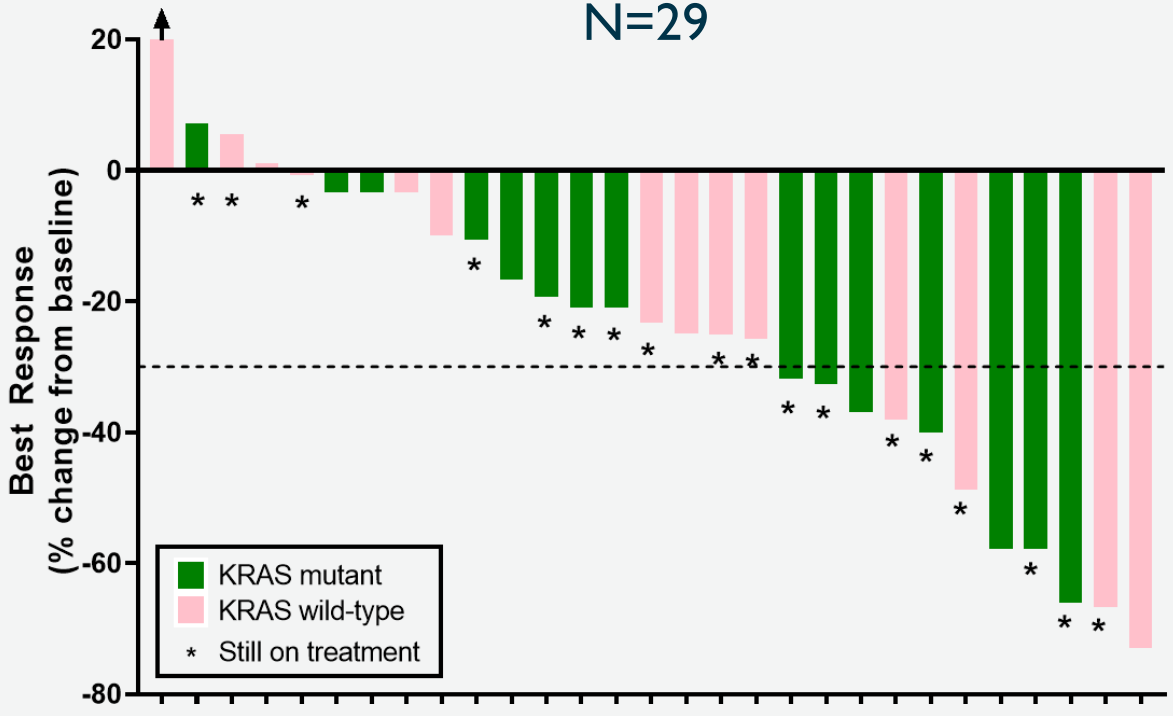
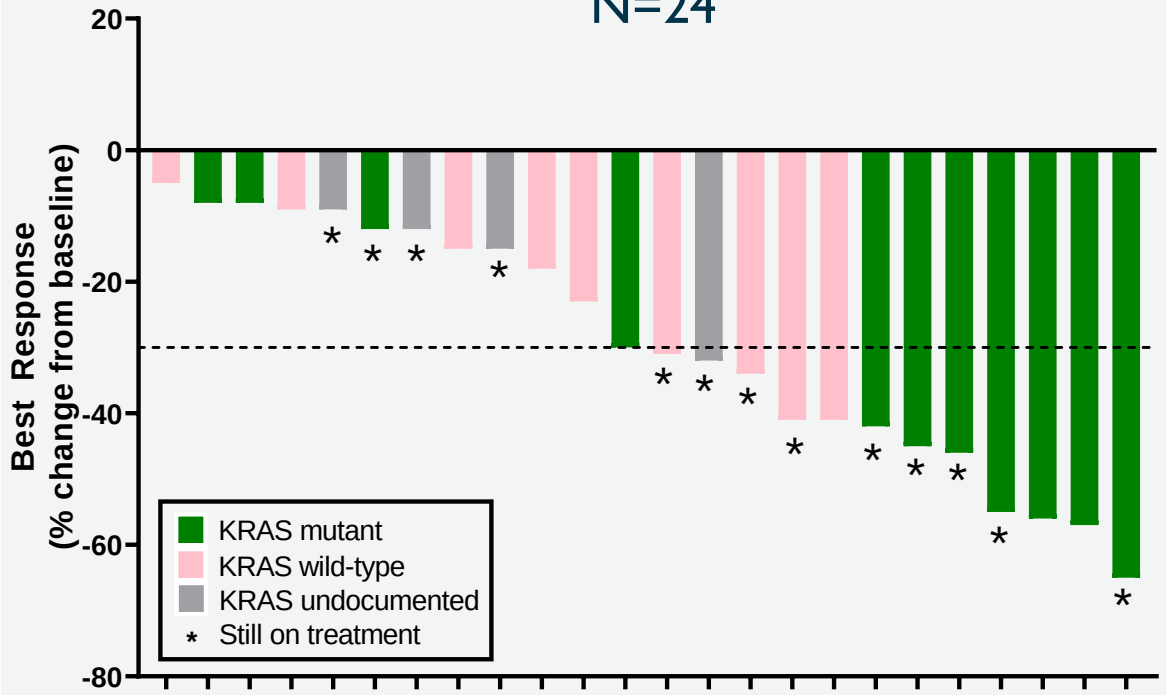
* Evaluable for Efficacy: At least one blinded imaging assessment

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

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)

	Any Grade (%)						Grade ≥ 3 (%)					
	Avutometinib Monotherapy			Avutometinib + Defactinib			Avutometinib Monotherapy			Avutometinib + Defactinib		
	KRAS mt (n=26) %	KRAS wt (n=38) %	Total (n=64) %	KRAS mt (n=22) %	KRAS wt (n=35) %	Total (n=57) %	KRAS mt (n=26) %	KRAS wt (n=38) %	Total (n=64) %	KRAS mt (n=22) %	KRAS wt (n=35) %	**Total (n=57) %**
Nausea	23.1	39.5	32.8	45.5	65.7	57.9	0	5.3	3.1	0	0	**0**
Diarrhea	57.7	55.3	56.3	54.5	51.4	52.6	3.8	0	1.6	4.5	2.9	**3.5**
Edema peripheral	26.9	28.9	28.1	36.4	48.6	43.9	0	0	0	0	0	**0**
Fatigue	30.8	31.6	31.3	40.9	40.0	40.4	3.8	0	1.6	9.1	2.9	**5.3**
Vision blurred	23.1	44.7	35.9	31.8	42.9	38.6	0	2.6	1.6	0	0	**0**
Vomiting	19.2	26.3	23.4	40.9	37.1	38.6	0	2.6	1.6	0	0	**0**
Blood creatine phosphokinase increased	26.9	50.0	40.6	40.9	37.1	38.6	7.7	18.4	14.1	18.2	14.3	**15.8**
Dermatitis acneiform	30.8	36.8	34.4	27.3	45.7	38.6	0	10.5	6.3	4.5	0	**1.8**
Rash	34.6	28.9	31.3	31.8	37.1	35.1	0	5.3	3.1	0	2.9	**1.8**
Dry skin	26.9	31.6	29.7	13.6	31.4	24.6	0	0	0	0	0	**0**

Positive Interim Data Supports Selection of Combination of Avutometinib + Defactinib for Continued Development in Recurrent LGSOC – Regardless of KRAS Status

Planned Interim Analysis of RAMP-201 (ENGOTov60/GOG3052) trial

- Registration-directed Phase 2 trial of avutometinib +/- defactinib in recurrent LGSOC

Objectives of Part A ("Selection Phase") achieved

- Combination of avutometinib + defactinib declared as 'Go Forward Treatment Regimen'
- Objective response rate by blinded independent review supports continued development in both KRAS mt and KRAS wt LGSOC

Positive interim data of the Go Forward Regimen in heavily pretreated recurrent LGSOC

- Evidence of disease control and tumor regression in the vast majority of patients
- No new safety signals; few discontinuations due to adverse events

Initial combination data from RAMP 201 reinforce findings from earlier clinical trial (FRAME)

- Majority of patients still on study; mature data with longer follow up to characterize final ORR and duration of response
- Enrollment continues for the combination of avutometinib and defactinib

Dan Paterson

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

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

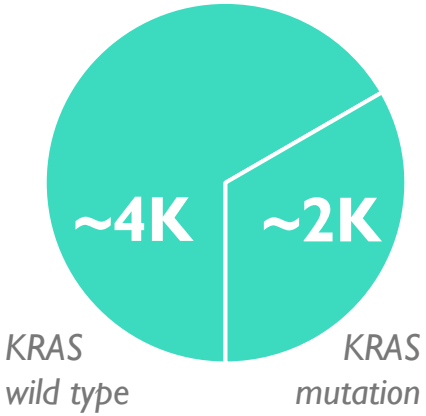
- Target enrollment for primary analysis (n=72) in combination has been achieved
- Plan to file for accelerated approval based on the totality of the data from the RAMP 201 and FRAME studies
- Continued enrollment in RAMP 201 combination arm only is planned to expand clinical experience in anticipation 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

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

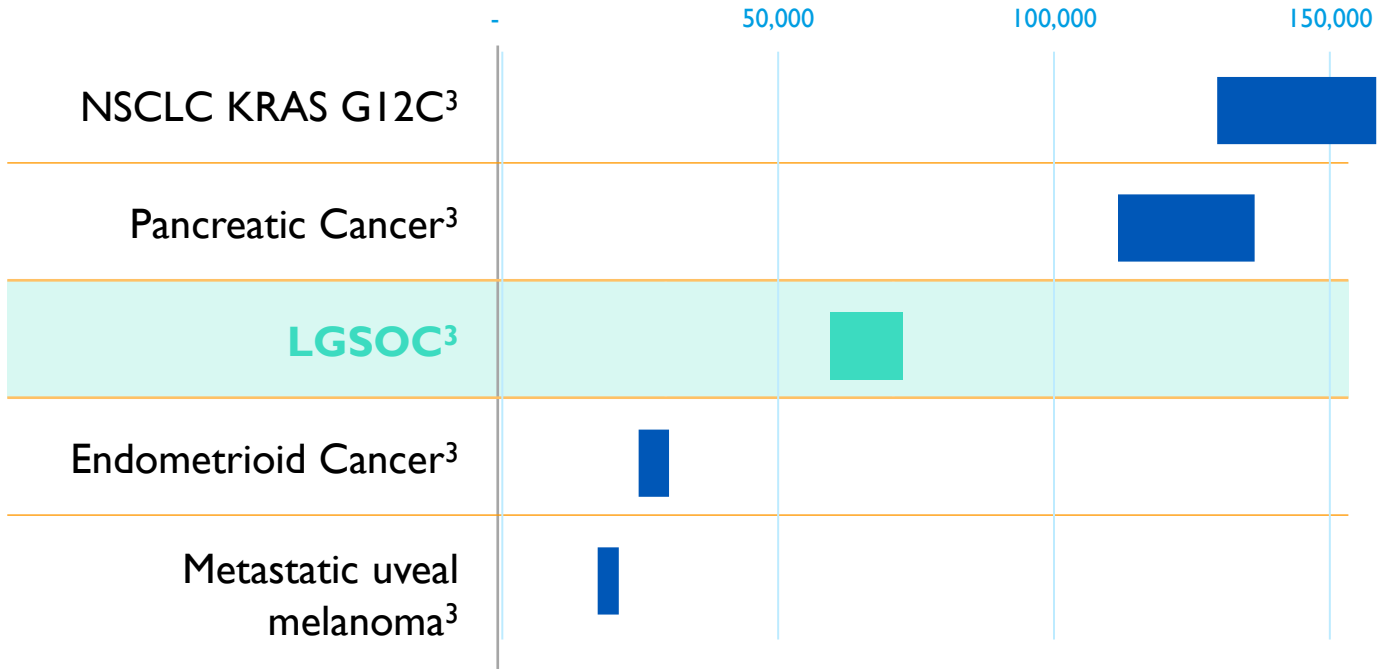
patients US[1]



~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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RAMP 201 Part A Update Advancing Path to Accelerated Filing

- LGSOC is a unique RAS pathway-driven cancer with an unacceptably high unmet need
- The unique RAF/MEK clamp mechanism of action and novel intermittent dosing schedule of avutometinib make it an attractive combination partner in RAS pathway driven cancers, including LGSOC
- Combination of avutometinib with defactinib declared as go forward treatment regimen in LGSOC program
- Independently confirmed response rates in both KRAS mutant and KRAS wild-type tumors and favorable safety and tolerability profile in heavily pretreated patient population of RAMP 201 supports continued development in all recurrent LGSOC
- Building on Breakthrough Therapy Designation, the Company intends to file for accelerated approval; timing based on mature data from RAMP 201 study and finalization of confirmatory study plans

Q&A

THANK YOU

VERASTEM ONCOLOGY

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

[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

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

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

*Investigator Sponsored Trials

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