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Avutometinib + Defactinib in Recurrent Low-Grade Serous Ovarian Cancer (ENGOT-ov60/GOG-3052/RAMP 201): Dose Intensity and Subgroup Analysis

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Financial Disclosure for:
Rachel N. Grisham

I have the following financial relationships with ACCME defined ineligible companies to report over the past 24 months:

- AZ (ended), GSK (ended), Verastem (ended), Cardinal Health (ended), Genmab (ended), Incyte (ended), Incyclix (ended)

Unlabeled/Investigational Uses

Avutometinib and defactinib are investigational drugs and have not been approved for use by the FDA or any other regulatory health authority. Safety and efficacy have not been established.

This presentation includes data from a phase 2 trial (ENGOT-ov60/GOG-3052/RAMP 201; NCT04625270) assessing the efficacy and safety of avutometinib with and without defactinib in patients with recurrent low-grade serous ovarian cancer.

New Treatment Options are Needed for Patients With LGSOC

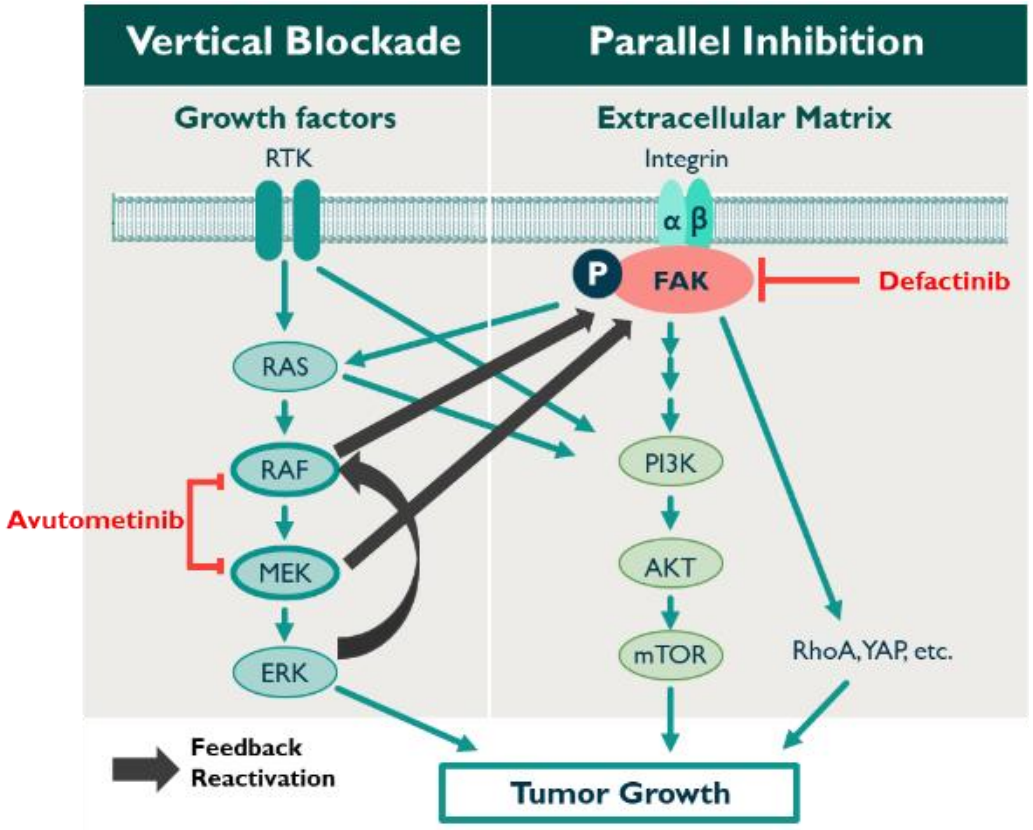
- LGSOC is a rare, histopathologically, molecularly, and clinically distinct cancer accounting for <10% of new epithelial ovarian cancers[1,2]
- LGSOC is commonly driven by alterations in the RAS/MAPK pathway, including *KRAS* mutations, which occur in approximately 30% of patients[3,4]
- Molecular alterations may influence patient outcomes[5]
- *KRAS* mutations/MAPK alterations are associated with improved prognosis[1,3,6]
- Chemotherapy options have shown limited efficacy in LGSOC ORR (0%-13%)[6,7]
- Response rates of 26% and 16% were observed with trametinib and binimetinib, respectively, but with discontinuation rates of 36% and 31% due to toxicity[6,7]

KRAS, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MAPK, mitogen-activated protein kinase; ORR, objective response rate; RAS, rat sarcoma virus.

1. Grisham RN, et al. *Int J Gynecol Cancer*. 2023;33(9):1331-1344. **2**. Matsuo K, et al. *J Gynecol Oncol*. 2018;29(1a):e15. **3.** Manning-Geist B, et al. *Clin Cancer Res*. 2022;28(20)4456-4465. **4**. ElNaggar A, et al. *Gynecol Oncol*. 2022;167(2):306-313. **5**. Manning-Geist BL, et al. *Clin Adv Hematol Oncol*. 2024:22(5):205-226. **6.** Gershenson DM, et al. *Lancet*. 2022;399(10324):541-553. **7.** Monk BJ, et al. *J Clin Oncol*. 2020;38(32):3753-3762.

Avutometinib and Defactinib Mechanism of Action

- **Avutometinib** is a first-in-class oral RAF/MEK clamp that potently inhibits MEK while also blocking the compensatory reactivation of MEK by upstream RAF[1,2]
- **Defactinib** is a selective inhibitor of FAK, a key adaptive resistance mechanism to the RAS/MAPK pathway[3-5]
- The clinical activity of avutometinib + defactinib demonstrated in the phase 1 FRAME study (NCT03875820) led to US FDA Breakthrough Therapy Designation and rationale for the phase 2 ENGOT-ov60/GOG-3052/RAMP 201 (NCT04625270) study[6,7]



AKT, protein kinase B; ERK; extracellular signal-regulated kinase; FAK, focal adhesion kinase; FDA, Food and Drug Administration; *KRAS*, Kirsten rat sarcoma virus; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase Gynecology; mTOR, mammalian target of rapamycin; NRAS, neuroblastoma RAS viral oncogene homolog; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RhoA, Ras homolog family member A; RTK, receptor tyrosine kinase; US, United States; YAP, Yes-associated protein.

1. Lito P, et al. *Cancer Cell*. 2014;25(5):697-710. **2**. Gonzalez-Del Pino GL, et al. *Proc Natl Acad Sci U S A*. 2021;118(36):e2107207118. **3**. Dawson JC, et al. *Nat Rev Cancer*. 2021;21:313-324. **4**. Shinde R, et al. *Cancer Res*. 2020;80(suppl 16):CT143. **5**. Kang Y, et al. *J Natl Cancer Inst*. 2013;105(19):1485-1495. **6**. Banerjee S, et al. *Ann Oncol*. 2021;32(suppl 5):S728. **7**. Verastem Oncology. 2021. https://investor.verastem.com/node/12421/pdf. Accessed January 24, 2025.

ENGOT-ov60/GOG-3052/RAMP 201: Registration-Directed Phase 2 Trial of Avutometinib ± Defactinib in Patients With Recurrent LGSOC

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Go Forward Regimen

Key Inclusion Criteria
- Recurrent LGSOC
- Prior platinum chemotherapy
- Measurable disease (RECIST v1.1)
- Prior MEKi allowed

Oral dosing for monotherapy and combination therapy: 3 weeks on/1 week off

Part A Selection Phase	Part B Expansion Phase	Part C Expansion Phase Combination	Part D Lower Dose in Combination
Avutometinib + Defactinib 3.2 mg BIW 200 mg BID	Avutometinib + Defactinib 3.2 mg BIW 200 mg BID	Avutometinib + Defactinib 3.2 mg BIW 200 mg BID	Avutometinib + Defactinib 1.6 mg BIW 200 mg BID
KRAS mt (n=16)	*KRAS* mt (n=20)	*KRAS* mt (n=22)	*KRAS* mt (n=11)
KRAS wt (n=15)	*KRAS* wt (n=22)	*KRAS* wt (n=20)	*KRAS* wt (n=16)
Avutometinib 4.0 mg BIW	Avutometinib 4.0 mg BIW		
KRAS mt (n=16)	*KRAS* mt (total n=15)		
KRAS wt (n=17)	*KRAS* wt (total n=22)		

Primary Endpoint: ORR (BICR per RECIST v1.1)

Evaluation of ORR in Combination Arm
1. In *KRAS* mt patients
2. All patients (*KRAS* mt & wt)

Go Forward Regimen Selection Criteria (Selection Phase):
1. Observed ORR is comparatively greater than the other regimen
2. Observed ORR of the leading regimen is ≥15%

N-values represent patients who were treated in the study.
BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MEK, mitogen-activated protein kinase kinase; MEKi, mitogen-activated protein kinase kinase inhibitor; mt, mutant; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; wt, wild type.

Baseline Characteristics

Avutometinib 3.2 mg BIW and Defactinib 200 mg BID

Baseline characteristic	All patients (N=115)	*KRAS* mt (n=58)	*KRAS* wt (n=57)
Age, median (min, max), y	54 (21, 87)	60 (29, 87)	45 (21, 80)
ECOG PS, n (%) 0 1	78 (68) 37 (32)	42 (72) 16 (28)	36 (63) 21 (37)
Number of prior systemic regimens, median (min, max)	3 (1, 9)	3 (1, 9)	3 (1, 9)
Prior platinum-based chemotherapy, n (%)[a]	114 (99)	58 (100)	56 (98)
Prior hormonal therapy, n (%)	99 (86)	49 (85)	50 (88)
Prior bevacizumab, n (%)	59 (51)	23 (40)	36 (63)
Prior MEKi therapy, n (%)	25 (22)	12 (21)	13 (23)

- Overall, 53% and 47% of patients were from the United States and European Union, respectively
- The majority of patients were White (White, 77%; not reported, 11%; Asian, 4%; Black or African American, 4%; other, 4%)

Avutometinib and defactinib dosing was 3 weeks on and 1 week off.
[a]One patient without prior platinum received anastrozole only.
BID, twice daily; BIW, twice weekly; ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS*, Kirsten rat sarcoma virus; MEKi, mitogen-activated protein kinase kinase inhibitor; mt, mutant; wt, wild type.

Patient Disposition

Avutometinib 3.2 mg BIW and Defactinib 200 mg BID

Median follow-up was **13.6 months** (range, 1.4-39.5)

All patients treated (N=115)	*KRAS* mt treated (n=58)	*KRAS* wt treated (n=57)
Discontinued treatment (n=83; 72%)	**Discontinued treatment (n=34; 59%)**	**Discontinued treatment (n=49; 86%)**
Primary reason	Primary reason	Primary reason
RECIST v1.1 disease progression 46 (40%)	RECIST v1.1 disease progression 18 (31%)	RECIST v1.1 disease progression 28 (49%)
AE/unacceptable toxicity 12 (10%)	AE/unacceptable toxicity 4 (7%)	AE/unacceptable toxicity 8 (14%)
Withdrawal of consent 10 (9%)	Withdrawal of consent 4 (7%)	Withdrawal of consent 6 (11%)
Other[a] 10 (9%)	Other[a] 5 (9%)	Other[a] 5 (9%)
Clinical deterioration 5 (4%)	Clinical deterioration 3 (5%)	Clinical deterioration 2 (4%)
Death 0	Death 0	Death 0
Continuing on treatment (n=32; 28%)	**Continuing on treatment (n=24; 41%)**	**Continuing on treatment (n=8; 14%)**

Avutometinib and defactinib dosing was 3 weeks on and 1 week off. Visit cutoff date of June 30, 2024.

[a]Other includes clinical progression (n=6) and progression confirmed by biopsy/pathology report, patient noncompliance, patient withdrawal with agreement to follow-up, physician decision (1 each).

AE, adverse event; BID, twice daily; BIW, twice weekly; *KRAS*, Kirsten rat sarcoma virus; mt, mutant; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; wt, wild type.

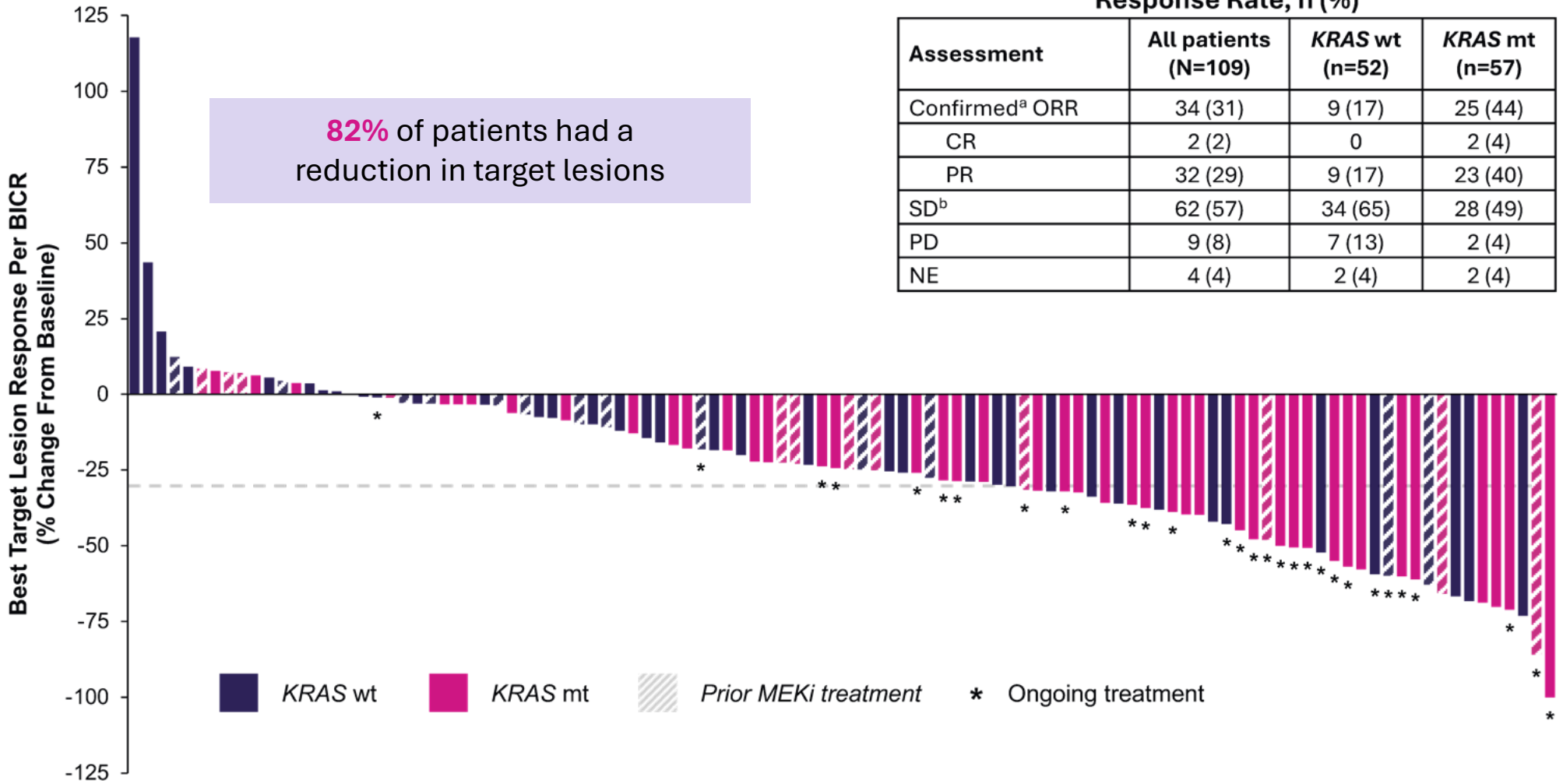
Best Percentage Change From Baseline in Target Lesions

Avutometinib 3.2 mg BIW and Defactinib 200 mg BID

82% of patients had a reduction in target lesions

Response Rate, n (%)

Assessment	All patients (N=109)	*KRAS* wt (n=52)	*KRAS* mt (n=57)
Confirmed[a] ORR	34 (31)	9 (17)	25 (44)
CR	2 (2)	0	2 (4)
PR	32 (29)	9 (17)	23 (40)
SD[b]	62 (57)	34 (65)	28 (49)
PD	9 (8)	7 (13)	2 (4)
NE	4 (4)	2 (4)	2 (4)

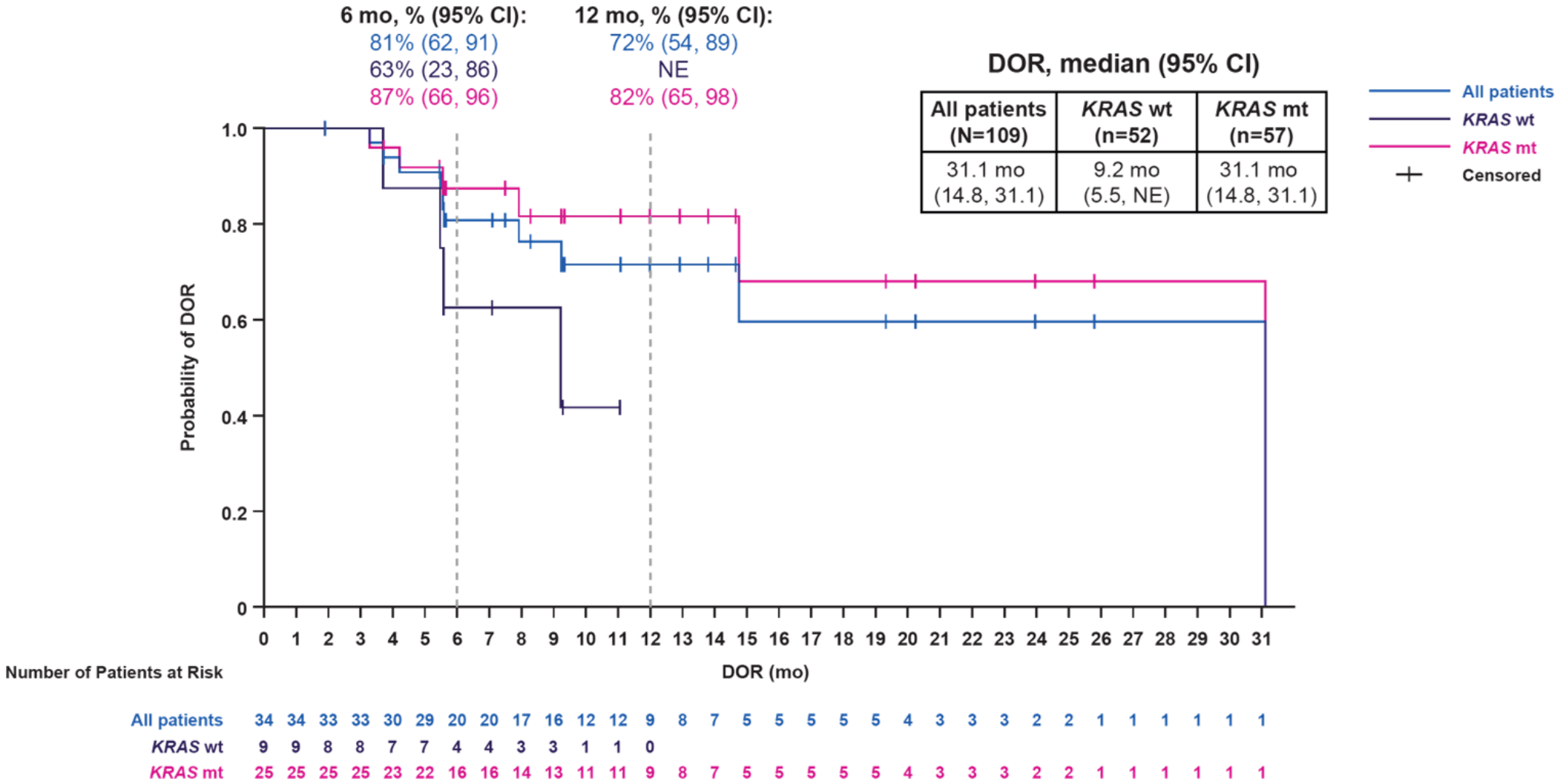


[a]According to RECIST v1.1 as assessed by BICR. [b]Includes unconfirmed partial response; stable disease (or unconfirmed partial response) must occur ≥53 days after first dose date.

Avutometinib and defactinib dosing was 3 weeks on and 1 week off. BID, twice daily; BIW, twice weekly; CR, complete response; *KRAS*, Kirsten rat sarcoma virus; MEK, mitogen-activated protein kinase kinase; mt, mutant; NE, not evaluable or unknown; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; wt, wild type.

Duration of Response:

Avutometinib 3.2 mg BIW and Defactinib 200 mg BID



Avutometinib and defactinib dosing was 3 weeks on and 1 week off. DOR as assessed by the BICR was calculated for patients with a complete response or partial response from the time of first response to progressive disease using Kaplan-Meier methods.
BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; CI, confidence interval; DOR, duration of response; *KRAS*, Kirsten rat sarcoma virus; mo, months; mt, mutant; NE, not evaluable or unknown; No, number; wt, wild type.

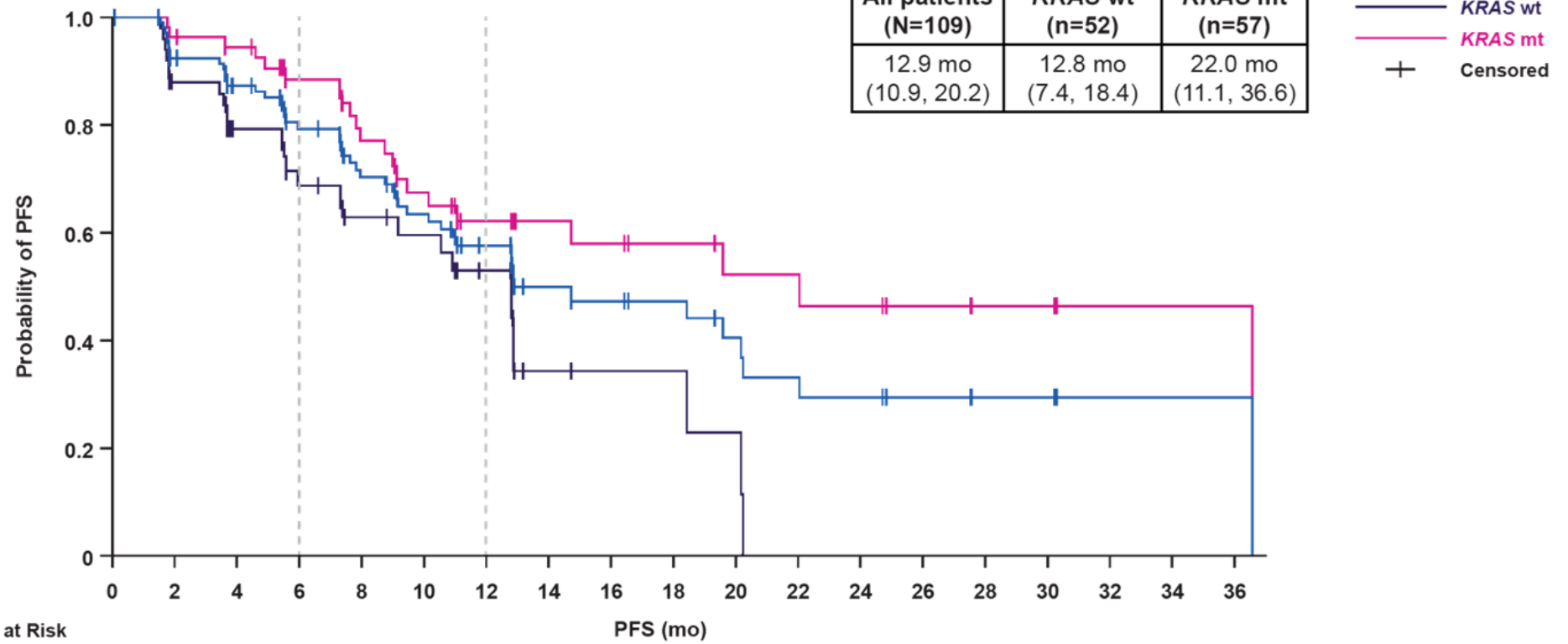
Progression-Free Survival

Avutometinib 3.2 mg BIW and Defactinib 200 mg BID

	6 mo, % (95% CI):	12 mo, % (95% CI):
All patients	79% (70, 86)	58% (47, 68)
KRAS wt	69% (53, 80)	53% (37, 69)
KRAS mt	88% (76, 95)	62% (48, 77)

PFS, median (95% CI)

All patients (N=109)	*KRAS* wt (n=52)	*KRAS* mt (n=57)
12.9 mo (10.9, 20.2)	12.8 mo (7.4, 18.4)	22.0 mo (11.1, 36.6)



Number of Patients at Risk

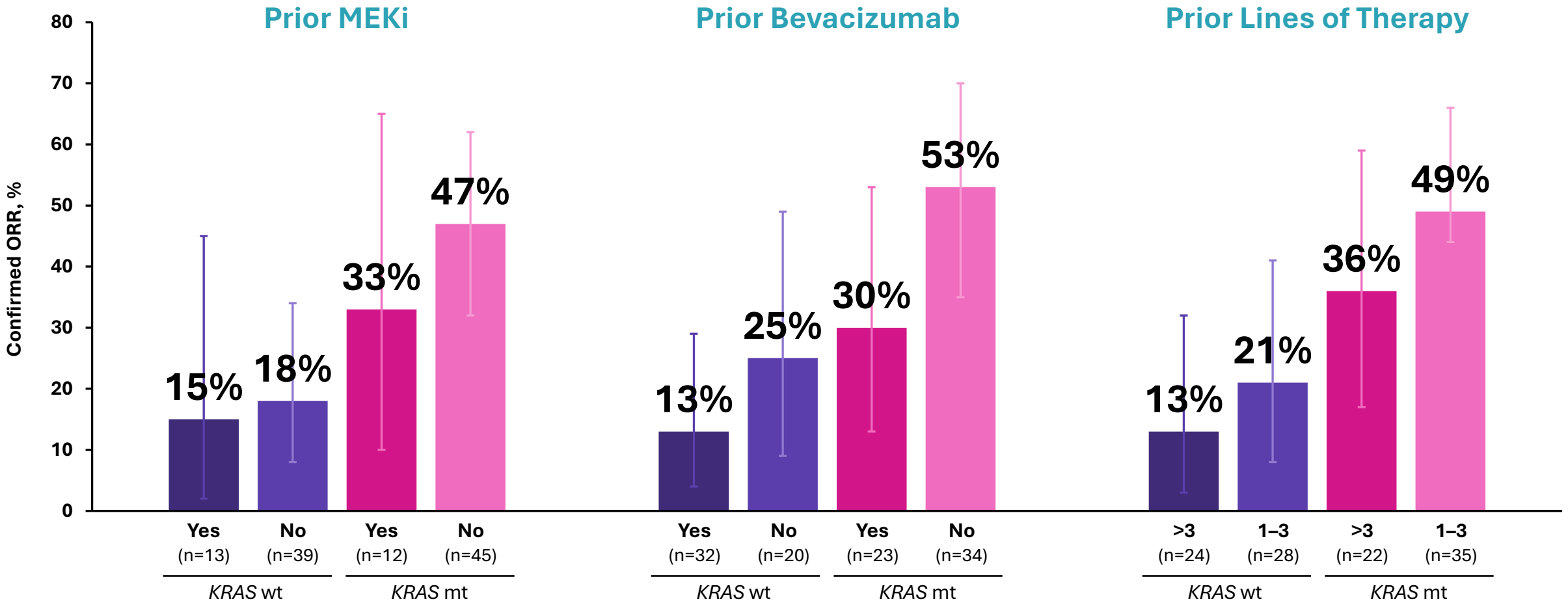
All patients	109	94	81	66	53	45	32	19	17	15	11	9	8	6	3	3	1	1	1
KRAS wt	52	41	32	25	20	18	13	4	3	3	2	0							
KRAS mt	57	53	49	41	33	27	19	15	14	12	9	9	8	6	3	3	1	1	1

Avutometinib and defactinib dosing was 3 weeks on and 1 week off.

BID, twice daily; BIW, twice weekly; CI, confidence interval; *KRAS*, Kirsten rat sarcoma virus; mo, months; mt, mutant; No, number; PFS, progression-free survival; wt, wild type.

Confirmed ORR in Subgroups by Prior Therapies and *KRAS* Status

Avutometinib 3.2 mg BIW and Defactinib 200 mg BID



Avutometinib and defactinib dosing was 3 weeks on and 1 week off. Error bars represent 95% CI.

BID, twice daily; BIW, twice weekly; *KRAS*, Kirsten rat sarcoma virus; MEKi, mitogen-activated protein kinase kinase inhibitor; mt, mutant; ORR, objective response rate; wt, wild type.

Adverse Event Profile

Avutometinib 3.2 mg BIW and Defactinib 200 mg BID

Mean relative dose intensity:
0.84 for avutometinib and **0.77** for defactinib

- 80% (92/115) of patients had AEs leading to **dose interruption**
  - 38% (44/115) for elevations in CPK
- 37% (42/115) of patients had AEs leading to **dose reduction**
- 10% (12/115) of patients **discontinued for AEs**; the most common reason was increased CPK (n=4)
- 7% (8/115) of patients had **serious AEs** considered by the investigator to be related to study treatment; the only event occurring in >1 patient was abdominal pain
- **After 3 months of follow-up** after the data cut, there were no additional discontinuations for AEs and no additional serious AEs considered related to treatments or deaths

Treatment-Related AEs (>20% of patients)[a], n (%)	All patients (N=115)	
Preferred term	**All grades**	**Grade ≥3**
Non-laboratory AEs		
Nausea	77 (67)	3 (3)
Diarrhea	67 (58)	9 (8)
Oedema peripheral	61 (53)	1 (1)
Rash[b]	58 (50)	3 (3)
Fatigue	50 (44)	3 (3)
Vomiting	49 (43)	3 (3)
Vision blurred	47 (41)	0
Dermatitis acneiform	39 (34)	5 (4)
Dry skin	30 (26)	0
Anemia	26 (23)	6 (5)
Laboratory-related AEs		
Increased blood CPK	69 (60)	28 (24)
Increased blood bilirubin increased/hyperbilirubinemia	38 (33)	5 (4)
AST increased	36 (31)	2 (2)
ALT increased	25 (22)	2 (2)

Avutometinib and defactinib dosing was 3 weeks on and 1 week off.
[a]Most common AEs (preferred term) considered by the investigator to be related to study drug (either avutometinib or defactinib). [b]Treatment-related AEs for "rash" include the preferred terms butterfly rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic.
AE, adverse event; ALT, alanine aminotransferase; AST; aspartate aminotransferase; BID, twice daily; BIW, twice weekly; CPK, creatine phosphokinase.

Adverse Events of Interest

Avutometinib 3.2 mg BIW and Defactinib 200 mg BID

Ocular AEs – Blurred Vision

- Blurred vision was the most common treatment-related ocular event (41% of patients)
- The majority of events occurred within the first week (median onset 4 days)
- All events of blurred vision were grade 1 or 2
- Often resolved without treatment interruption, and did not lead to treatment discontinuation

Skin and Subcutaneous Tissue AEs

- Treatment-related skin reactions included rash (50%), dermatitis acneiform (34%), and dry skin (26%); most were grade 1 or 2
- Median onset of 15 days; median duration of 35 days
- 6% of patients had a treatment-related skin reaction that resulted in a dose interruption or dose reduction
- One patient discontinued due to dermatitis acneiform; no grade 4 or serious skin reactions were observed

Avutometinib and defactinib dosing was 3 weeks on and 1 week off.
AE, adverse event; BID, twice daily; BIW, twice weekly; CPK, creatine phosphokinase.

Low Starting Dose of Avutometinib

Avutometinib 1.6 mg BIW and Defactinib 200 mg BID

Efficacy

- Low-dose regimen was suboptimal[a] based on the predefined analysis (**83%** difference in PD within 4 months)

BICR Assessment, n (%)	Parts A, B, and C	Part D
	Avutometinib 3.2 mg BIW and Defactinib 200 mg BID (N=109)	Avutometinib 1.6 mg BIW and Defactinib 200 mg BID (N=23)
PD[b] within 4 months	13 (12)	5 (22)
Confirmed ORR	34 (31)	1 (4)
SD	62 (57)	17 (74)

Safety

- The most common treatment-related AEs in Part D were nausea (56%), fatigue (44%), and increased CPK (33%)
- Five patients had ≥grade 3 treatment-related AEs, most commonly increased CPK (n=2); AEs leading to discontinuation occurred in 15% of patients

Avutometinib 1.6 mg BID in combination with defactinib 200 mg BID will not be pursued as a starting dose in the treatment of recurrent LGSOC

Avutometinib and defactinib dosing was 3 weeks on and 1 week off.
[a]Suboptimal threshold was defined as disease progression by second scheduled assessment (Cycle 5 Day 1) >50% higher than that observed with avutometinib 3.2 mg BIW + defactinib. [b]According to RECIST v1.1 as assessed by BICR.
AE, adverse event; BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; CPK, creatine phosphokinase; LGSOC, low-grade serous ovarian cancer; ORR, objective response rate; PD, progressive disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease;.

Summary and Conclusions

- In women with recurrent LGSOC with few available treatment options, the combination of avutometinib 3.2 mg BIW and defactinib 200 mg BID resulted in clinically meaningful ORR, DOR, and PFS
  - **Confirmed[a] ORR:** 31% overall; 44% in *KRAS* mt and 17% in *KRAS* wt
  - **Median DOR:** 31 months overall; 31 months in *KRAS* mt and 9 months in *KRAS* wt
  - **Median PFS**: 12.9 months overall; 22.0 months in *KRAS* mt and 12.8 months in *KRAS* wt
- The safety profile of this combination therapy was consistent with previous reports
  - The majority of AEs were grade 1 or 2
  - The majority of AEs were managed with dose interruptions and reductions
  - The discontinuation rate for AEs was 10%

These data support the potential for avutometinib and defactinib as a new standard of care for recurrent LGSOC

A phase 3 trial (GOG-3097/ENGOT-OV81/NCRI/RAMP 301) comparing the combination of avutometinib and defactinib to investigator's choice of therapy in recurrent LGSOC is enrolling

[a]According to RECIST v1.1 as assessed by BICR.
AE, adverse event; BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; DOR, duration of response; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; mt, mutant; ORR, objective response rate; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; wt, wild type.

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