IGCS 2024
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Efficacy and Safety of Avutometinib ± Defactinib in Recurrent Low-Grade Serous Ovarian Cancer: Primary Analysis of ENGOT-OV60/GOG-3052/RAMP 201

ENGOT
European Network of Gynaecological Oncological Trial groups

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GTG-UK

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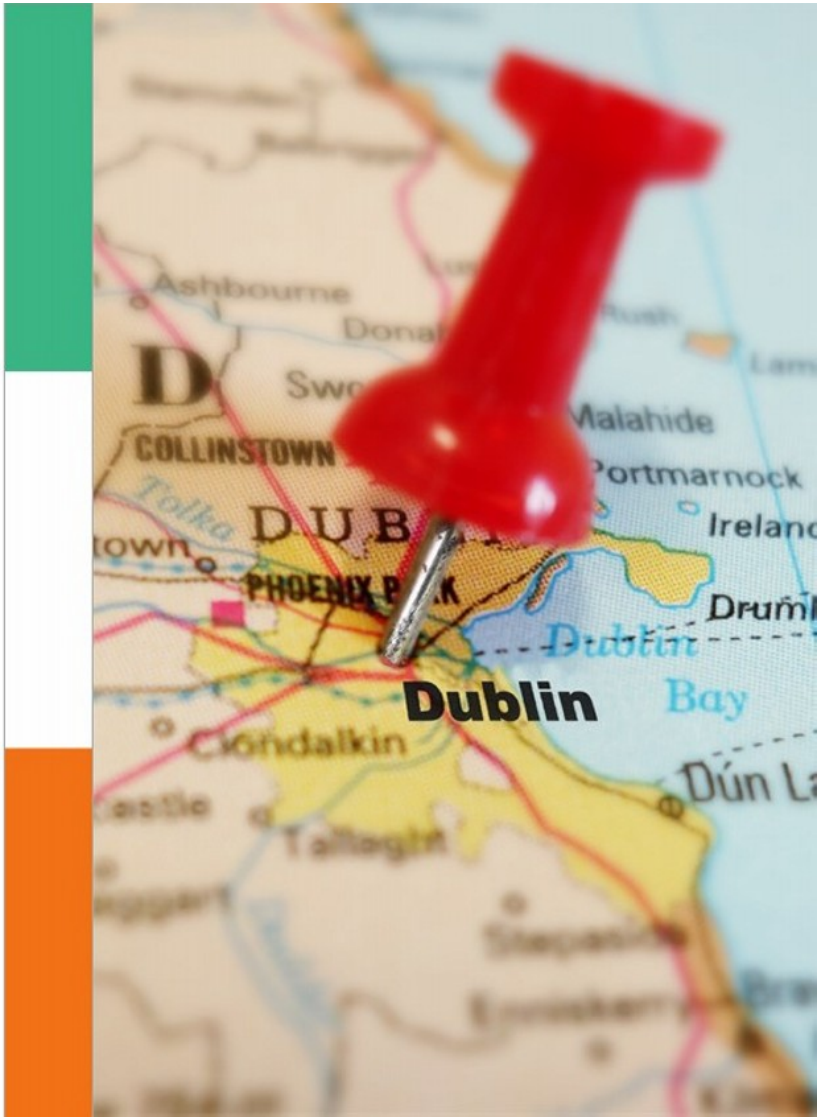

Disclosure

	No, nothing to disclose
x	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
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Institution AstraZeneca, GlaxoSmithKline, Verastem (PI)			X					

New Treatment Options Are Needed for Patients With LGSOC

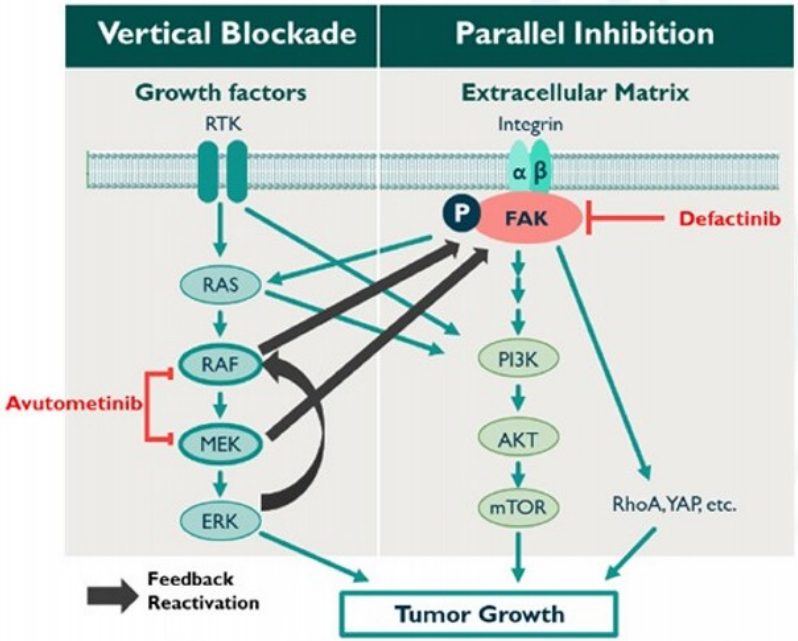
- LGSOC is a rare, histopathologically, molecularly, and clinically distinct cancer accounting for <10% of new epithelial ovarian cancers[1,2]
- LGSOC is commonly driven by alterations in the RAS/MAPK pathway, including KRAS mutations, which occur in approximately 30% of patients[3,4]
- Molecular alterations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

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

1. Grisham RN, et al. *Int J Gynecol Cancer*. 2023;33(9):1331-1344; **2**. Matsuo K, et al. *J Gynecol Oncol*. 2018;29(1ə):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**. Gershenson DM, et al. *Lancet*. 2022;399(10324):541-553; **6**. Manning-Geist BL, et al. *Clin Adv Hematol Oncol*. 2024:22(5):205-226; **7**. Monk BJ, et al. *J Clin Oncol*. 2020;38(32):3753-3762.

Avutometinib and Defactinib Mechanism of Action

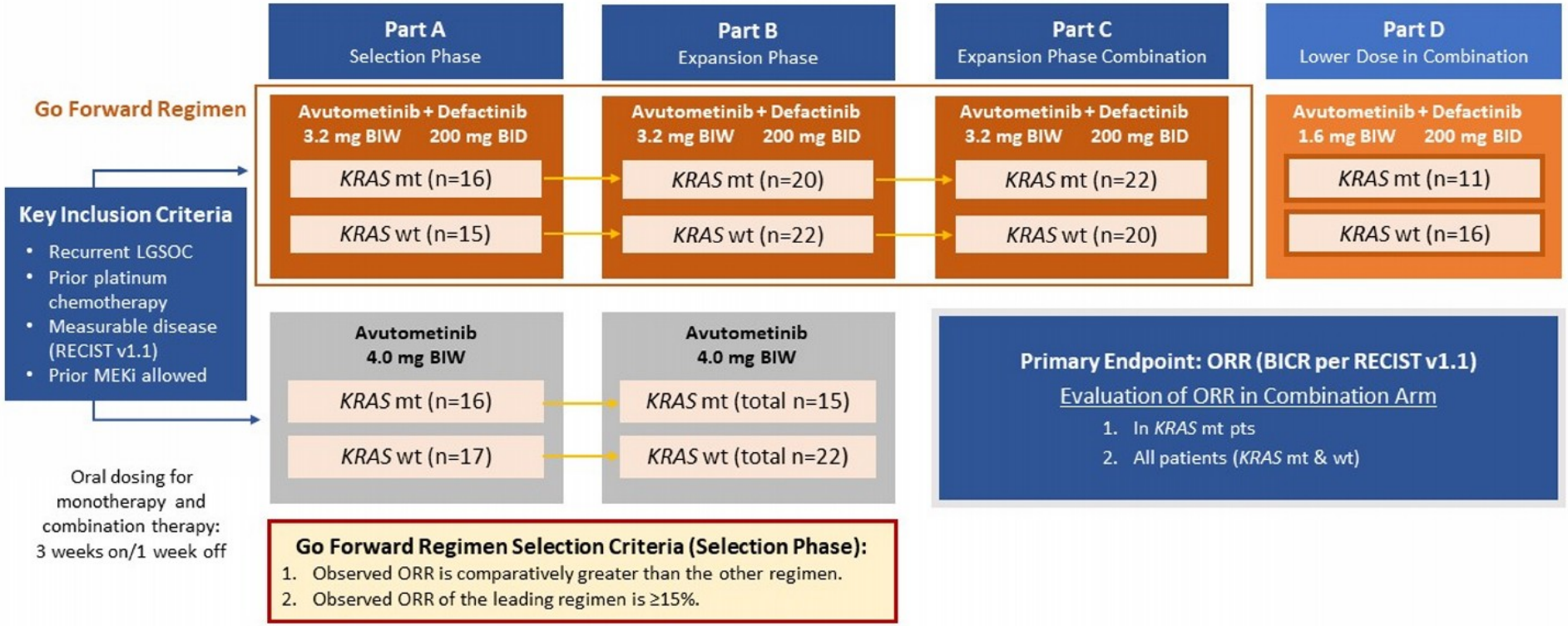
- **Avutometinib** is a first-in-class oral RAF/MEK clamp that potently inhibits MEK while also blocking the compensatory reactivation of MEK by upstream RAF[1,2]
- **Defactinib** is a selective inhibitor of FAK, a key adaptive resistance mechanism to the RAS/MAPK pathway[3-5]
- The clinical activity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



ERK; extracellular signal-regulated kinase; FAK, focal adhesion kinase; KRAS, kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer. MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; P, phosphate; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RhoA, Ras homolog family member A; RTK, receptor tyrosine kinase; 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. Press Release: Verastem Oncology Receives Breakthrough Therapy Designation for VS-6766 with Defactinib in Recurrent Low-Grade Serous Ovarian Cancer. May 24, 2021. Accessed September 28, 2023. https://investor.verastem.com/node/12421/pdf.

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



Numbers represent patients treated on study.

BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; KRAS, kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MEKi, mitogen-activated protein kinase kinase inhibitor; mt, mutant; pts, patients; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; wt, wild type.

ClinicalTrials.gov identifier: NCT04625270

Baseline Characteristics: Parts A, B, and C

	Avutometinib + Defactinib 3.2 mg BIW + 200 mg BID 3 weeks on/1 week off			Avutometinib Monotherapy 4.0 mg BIW 3 weeks on/1 week off		
	All patients N=115	**KRAS mt N=58**	**KRAS wt N=57**	**All patients N=70**	**KRAS mt N=31**	**KRAS wt N=39**
Age, median (min, max), y	54 (21, 87)	60 (29, 87)	45 (21, 80)	54 (21, 77)	57 (27, 74)	48 (21, 77)
ECOG PS, n (%) 0	78 (68)	42 (72)	36 (63)	50 (71)	19 (61)	31 (80)
1	37 (32)	16 (28)	21 (37)	20 (29)	12 (39)	9 (20)
# of prior systemic regimens, median (min, max)	3 (1, 9)	3 (1, 9)	3 (1, 9)	3 (1, 10)	3 (1, 10)	3 (1, 9)
Prior platinum-based chemotherapy, n (%)*	114 (99)	58 (100)	56 (98)	69 (99)	30 (97)	39 (100)
Prior hormonal therapy, n (%)	99 (86)	49 (84)	50 (88)	58 (83)	25 (81)	33 (85)
Prior bevacizumab, n (%)	59 (51)	23 (40)	36 (63)	34 (49)	17 (55)	17 (44)
Prior MEK inhibitor therapy, n (%)	25 (22)	12 (21)	13 (23)	18 (26)	8 (26)	10 (26)

Avutometinib + defactinib group: 77% of patients were White; 4% Asian; 4% Black or African American; 4% other; 11% not reported
Avutometinib monotherapy group: 85% of patients were White; 3% Asian; 3% Black or African American; 2% other; 1% unknown; 7% not reported

EU / US patients: 47% / 53% in the avutometinib + defactinib group, and 39% / 61% in the avutometinib monotherapy group

*2 pts without prior platinum received anastrazole only (1 in the monotherapy and 1 in combination arm)
BID, twice daily; BIW, twice weekly; ECOG PS, Eastern Cooperative Oncology Group performance status; KRAS, kirsten rat sarcoma virus; MEK, mitogen-activated protein kinase kinase; mt, mutant; wt, wild type.

Patient Disposition: Parts A, B, and C

- Median follow-up in the combination group = 13.6 months (range, 1.4–39.5)
- In the combination group, mean relative dose intensity of 0.84 for avutometinib and 0.77 for defactinib

	Avutometinib + Defactinib 3.2 mg BIW + 200 mg BID 3 weeks on/1 week off			Avutometinib Monotherapy 4.0 mg BIW 3 weeks on/1 week off		
	All patients	**KRAS mt**	**KRAS wt**	**All patients**	**KRAS mt**	**KRAS wt**
Patients treated	115	58	57	70	31	39
Patients on treatment, n (%)	32 (28)	24 (41)	8 (14)	10 (14)	8 (26)	2 (5)
Patients discontinued treatment, n (%)	83 (72)	34 (59)	49 (86)	60 (86)	23 (74)	37 (95)
Primary reason for discontinuation						
RECIST v1.1 disease progression	46 (40)	18 (31)	28 (49)	33 (47)	14 (45)	19 (49)
Adverse event/unacceptable toxicity	12 (10)	4 (7)	8 (14)	11 (16)	4 (13)	7 (18)
Withdrawal of informed consent	10 (9)	4 (7)	6 (11)	6 (9)	3 (10)	3 (8)
Other*	10 (9)	5 (9)	5 (9)	4 (6)	2 (6)	2 (5)
Clinical deterioration	5 (4)	3 (5)	2 (4)	5 (7)	0	5 (13)
Death	0	0	0	1 (1)	0	1 (3)

Discontinuations due to AEs/unacceptable toxicity were reported in 10% of patients in the avutometinib + defactinib group

Visit cutoff date: 30 June 2024

*Other includes: clinical progression (n=8) and progression confirmed by biopsy/pathology report, progression by confirmation of cytology from pleural effusion showing malignant etiology, debulking surgery, 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.

Response Rate and Duration of Response: Parts A, B, and C

In the avutometinib + defactinib combination group

- **RECIST 1.1 Objective Response Rate by BICR (primary endpoint):**
  - **31% overall; 44% KRAS mt, 17% KRAS wt**
  - **33% without prior MEKi, 24% with prior MEKi**
- **Median time to response: 3.7 months (range, 1.7 – 19.2)**
- **Median duration of response: 31.1 months (95% CI, 14.8, 31.1)**

	Avutometinib + Defactinib 3.2 mg BIW + 200 mg BID 3 weeks on/1 week off			Avutometinib Monotherapy 4.0 mg BIW 3 weeks on/1 week off		
	All patients N=109	**KRAS mt N=57**	**KRAS wt N=52**	**All patients N=69**	**KRAS mt N=30**	**KRAS wt N=39**
Confirmed* ORR, n (%)	**34 (31)**	**25 (44)**	**9 (17)**	12 (17)	7 (23)	5 (13)
CR	2 (2)	2 (4)	0	1 (1)	1 (3)	0
PR	32 (29)	23 (40)	9 (17)	11 (16)	6 (20)	5 (13)
DOR, median (95% CI), mo	31.1 (14.8, 31.1)	31.1 (14.8, 31.1)	9.2 (5.5, NE)	NE‡	NE‡	NE‡
SD,† n (%)	62 (57)	28 (49)	34 (65)	43 (62)	17 (57)	26 (67)
PD, n (%)	9 (8)	2 (4)	7 (13)	7 (10)	3 (10)	4 (10)
Not evaluable, n (%)	4 (4)	2 (4)	2 (4)	7 (10)	3 (10)	4 (10)

Efficacy evaluable population includes patients who received at least one dose of study drug and had measurable disease at baseline by BICR.
Patients not evaluable for response did not have a postbaseline assessment but are included in the denominator for the efficacy evaluable population.

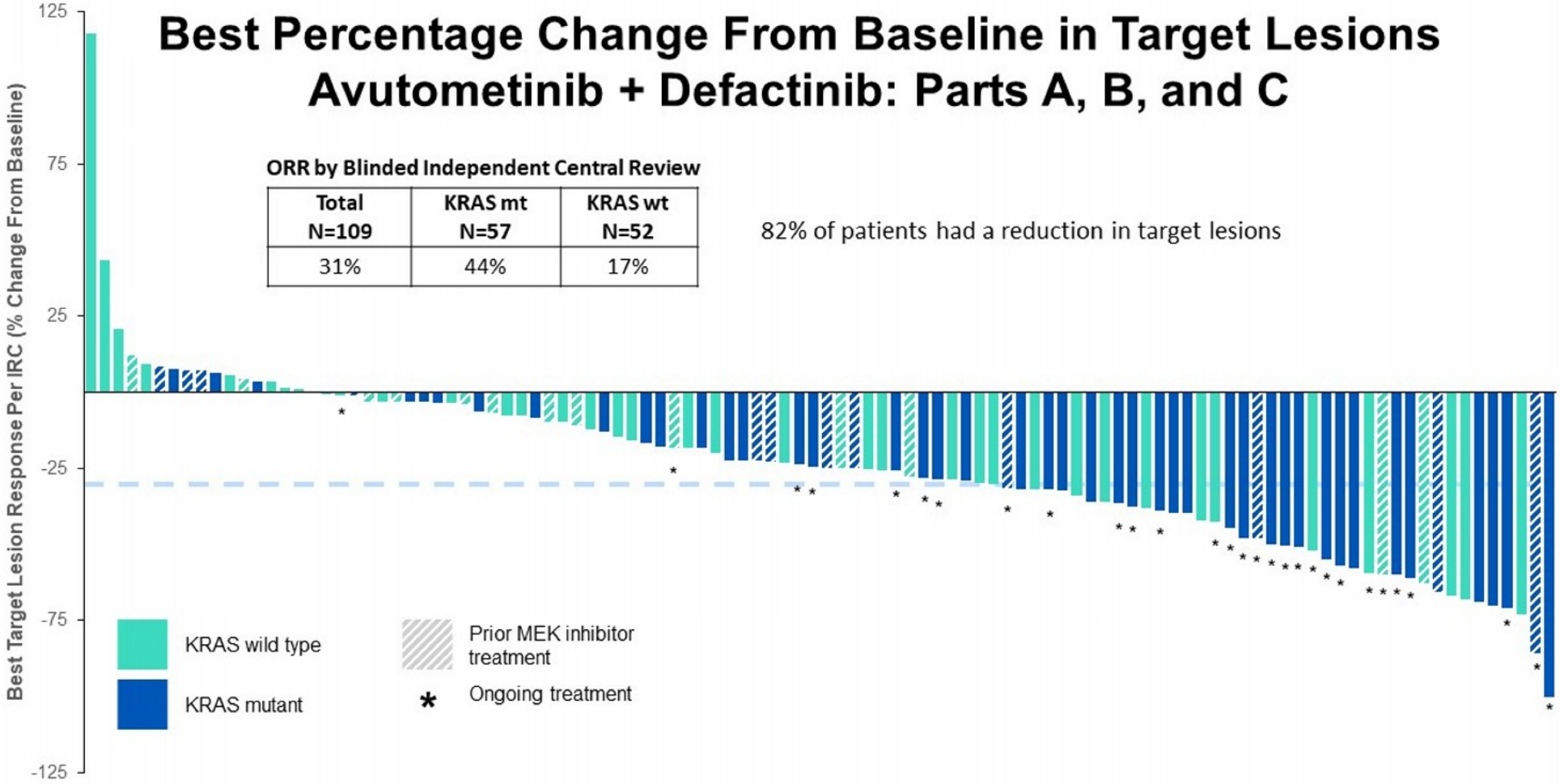
*By BICR. †Includes unconfirmed PR; SD (or unconfirmed PR) must occur ≥53 days after first dose date. ‡NE = Could not be estimated based on number of patients with loss of response.
BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; CR, complete response; DOR, duration of response; KRAS, kirsten rat sarcoma virus; MEK, mitogen-activated protein kinase kinase; mt, mutant; 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.

Best Percentage Change From Baseline in Target Lesions
Avutometinib + Defactinib: Parts A, B, and C

ORR by Blinded Independent Central Review

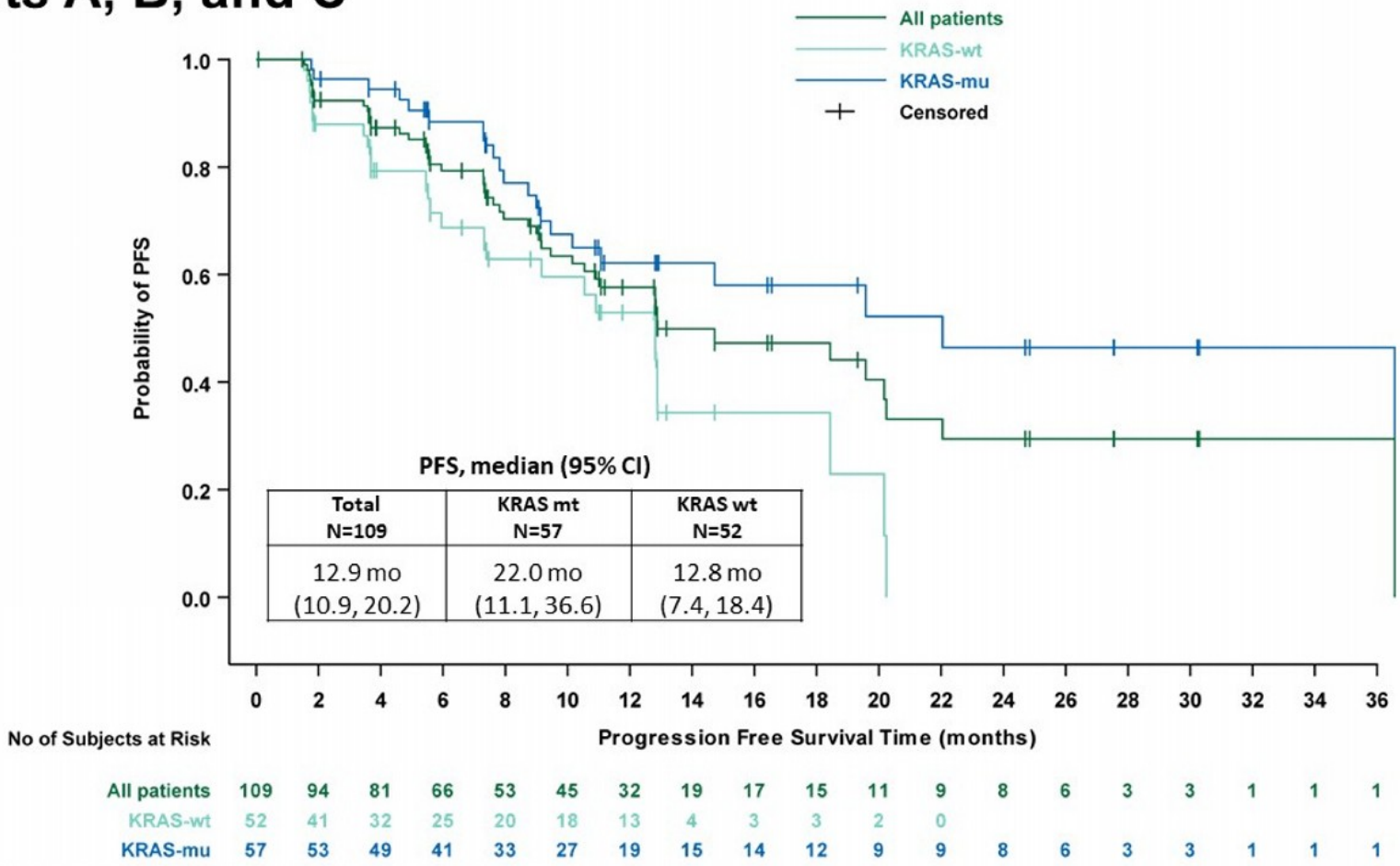
Total N=109	KRAS mt N=57	KRAS wt N=52
31%	44%	17%

82% of patients had a reduction in target lesions



IRC, independent review committee; KRAS, kirsten rat sarcoma virus; MEK, mitogen-activated protein kinase kinase.

Progression-Free Survival: Avutometinib + Defactinib: Parts A, B, and C



KRAS, kirsten rat sarcoma virus; mt, mutant; PFS, progression-free survival; wt, wild type.

Adverse Events Profile for Avutometinib + Defactinib: Parts A, B, and C

- 80% (92/115) of patients had AEs leading to **dose interruption**
  - 38% (44/115) for elevations in CPK
- 36.5% (42/115) of patients had AEs leading to **dose reduction**
- 10% (12/115) of patients **discontinued for AEs**; most common 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 more than 1 patient was abdominal pain
- 4 **deaths** (within 30 days of discontinuation): GI hemorrhage, large intestine perforation, clinical progression, clinical deterioration (none considered related to study treatment)

Treatment-Related Adverse Events (>20% of patients)* n (%)	Avutometinib + Defactinib 3.2 mg BIW + 200 mg BID 3 weeks on/1 week off N= 115	
Preferred term	**All Grades**	**Grade ≥3**
Non-laboratory AEs		
Nausea	77 (67.0)	3 (2.6)
Diarrhea	67 (58.3)	9 (7.8)
Oedema peripheral	61 (53.0)	1 (0.9)
Fatigue	50 (43.5)	3 (2.6)
Vomiting	49 (42.6)	3 (2.6)
Vision blurred	47 (40.9)	0
Rash	41 (35.7)	2 (1.7)
Dermatitis acneiform	39 (33.9)	5 (4.3)
Dry skin	30 (26.1)	0
Anemia	26 (22.6)	6 (5.2)
Laboratory-related AEs		
Increased blood CPK	69 (60.0)	28 (24.3)
Increased blood bilirubin increased/ hyperbilirubinemia	38 (33.0)	5 (4.3)
AST increased	36 (31.3)	2 (1.7)

*Most common adverse events (preferred term) considered by the investigator to be related to study drug (either avutometinib or defactinib).

AE, adverse event; AST; aspartate aminotransferase; BID, twice daily; BIW, twice weekly; CPK, creatine phosphokinase; GI, gastrointestinal.

Adverse Events Profile for Avutometinib + Defactinib: Parts A, B, and C

Adverse events of interest that have been associated with MEK inhibitors

Treatment-Related Adverse Events, n (%)*	Avutometinib + Defactinib 3.2 mg BIW + 200 mg BID 3 weeks on/1 week off N=115	
Preferred term	**All Grades**	**Grade ≥3**
Ocular events		
Blurred vision	47 (40.9)	0
Visual impairment	7 (6.1)	0
Retinal pigment epithelial detachment	6 (5.2)	0
Retinal detachment	4 (3.5)	0
Serous retinal detachment	2 (1.7)	0
Serous retinopathy	2 (1.7)	0
Retinopathy	2 (1.7)	0
Retinal vein occlusion	1 (0.9)	0
Pneumonitis	1 (0.9)	0
Hypertension	4 (3.5)	1 (0.9)
Ejection fraction decreased	1 (0.9)	0
Congestive heart failure	0	0

*Adverse events (preferred term) considered by the investigator to be related to study drug (either avutometinib or defactinib).

BID, twice daily; BIW, twice weekly; MEK, mitogen-activated protein kinase kinase.

Low-Dose Avutometinib Evaluation: Part D

- The **low-dose regimen** of avutometinib (1.6 mg BIW) + defactinib (200 mg BID) evaluated in Part D was determined to be **suboptimal** based on the predefined analysis
  - Suboptimal threshold: disease progression by second scheduled assessment (Cycle 5 Day 1) >50% higher than that observed with avutometinib 3.2 mg BIW + defactinib

IRC Assessment	Avutometinib 3.2 mg + 200 mg Defactinib 3 weeks on/1 week off N=109	Avutometinib 1.6 mg + 200 mg Defactinib 3 weeks on/1 week off N=23	% Difference
RECIST v1.1 progressive disease within 4 months	13 (12%)	5 (22%)	**+83%**

- Therefore, the low-dose regimen will not be pursued as a starting dose in the treatment of recurrent LGSOC

BID, twice daily; BIW, twice weekly; IRC, independent review committee; LGSOC, low-grade serous ovarian cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

Summary and Conclusions

- In women with recurrent LGSOC with few available treatment options, the combination of avutometinib 3.2 mg BIW + defactinib 200 mg BID resulted in clinically meaningful responses, duration of response, and progression-free survival
  - **ORR:** 31% overall; 44% in KRAS mt and 17% in KRAS wt
  - **Median DOR:** 31 months overall
  - **Median PFS**: 12.9 months overall; 22.0 months in KRAS mt and 12.8 months in KRAS wt
- The safety profile of the combination was consistent with previous reports
  - The majority of adverse events were grade 1 and 2
  - The majority of adverse events were managed with dose interruptions and reductions
  - Discontinuation rate of 10% for adverse events
- These data support the potential for avutometinib + defactinib as a new standard of care for recurrent LGSOC, regardless of KRAS status

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

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; wt, wild type.

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