IGCS 2024
Annual Global Meeting
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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 Gynae-oncology Trials Group UK

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IGCS INTERNATIONAL GYNECOLOGIC CANCER SOCIETY

In Collaboration With

Fáilte Ireland

Disclosure

	No, nothing to disclose
x	Yes, please specify:

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Institution AstraZeneca, GlaxoSmithKline, Verastem (PI)			X					

New Treatment Options Are Needed for Patients With LGSOC

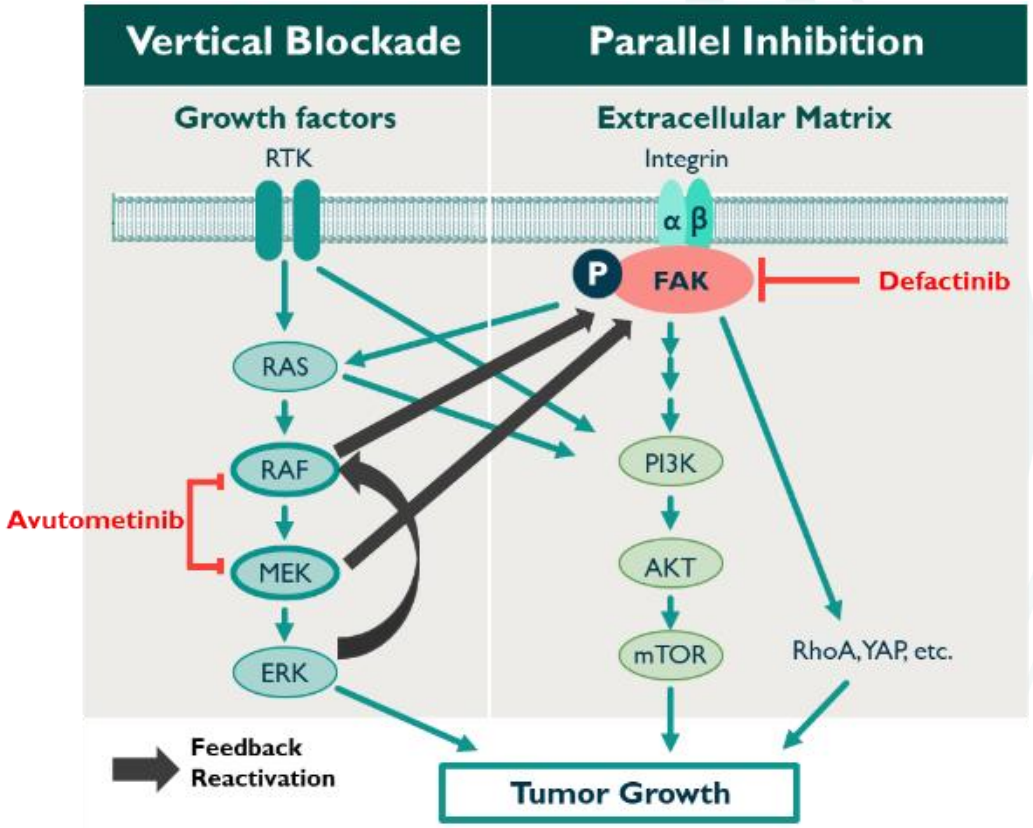
- LGSOC is a rare, histopathologically, molecularly, and clinically distinct cancer accounting for <10% of new epithelial ovarian cancers[1,2]
- LGSOC is commonly driven by alterations in the RAS/MAPK pathway, including KRAS mutations, which occur in approximately 30% of patients[3,4]
- Molecular alterations 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(1~~a~~):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

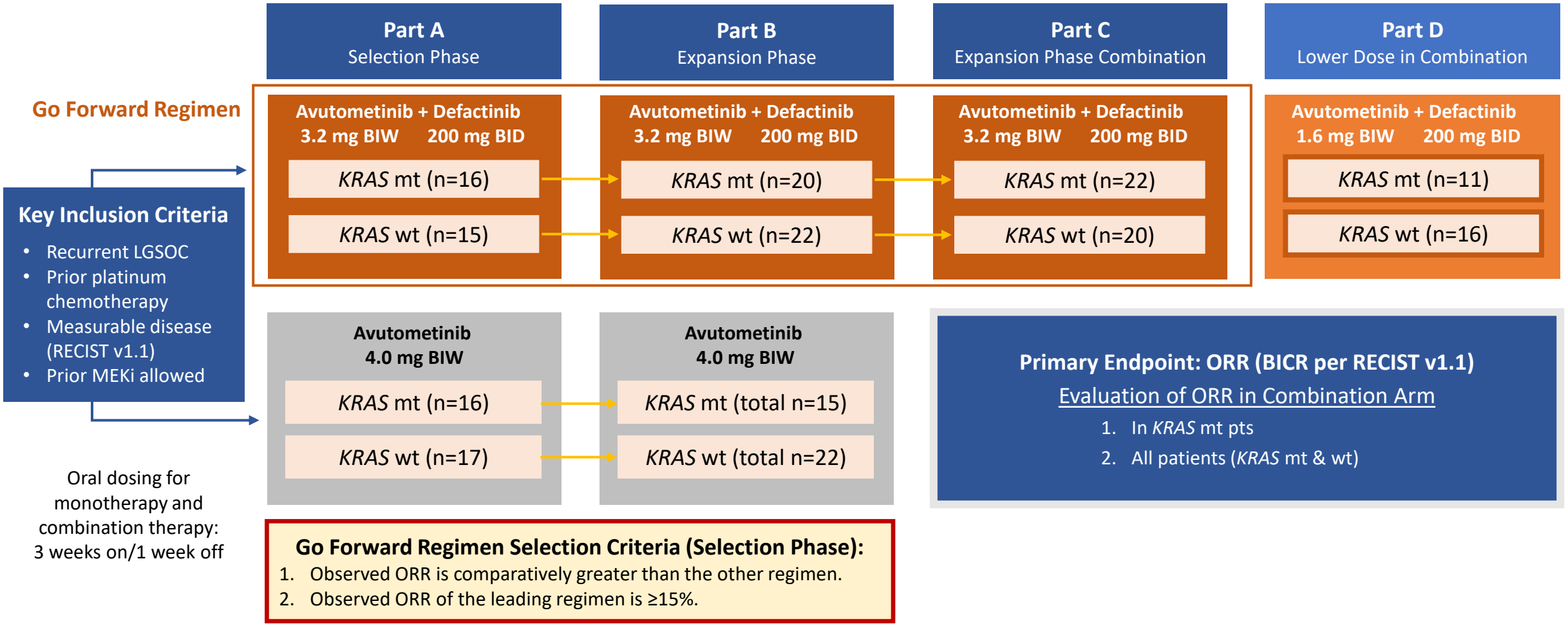
- **Avutometinib** is a first-in-class oral RAF/MEK clamp that potently inhibits MEK while also blocking the compensatory reactivation of MEK by upstream RAF[1,2]
- **Defactinib** is a selective inhibitor of FAK, a key adaptive resistance mechanism to the RAS/MAPK pathway[3-5]
- The clinical activity 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.

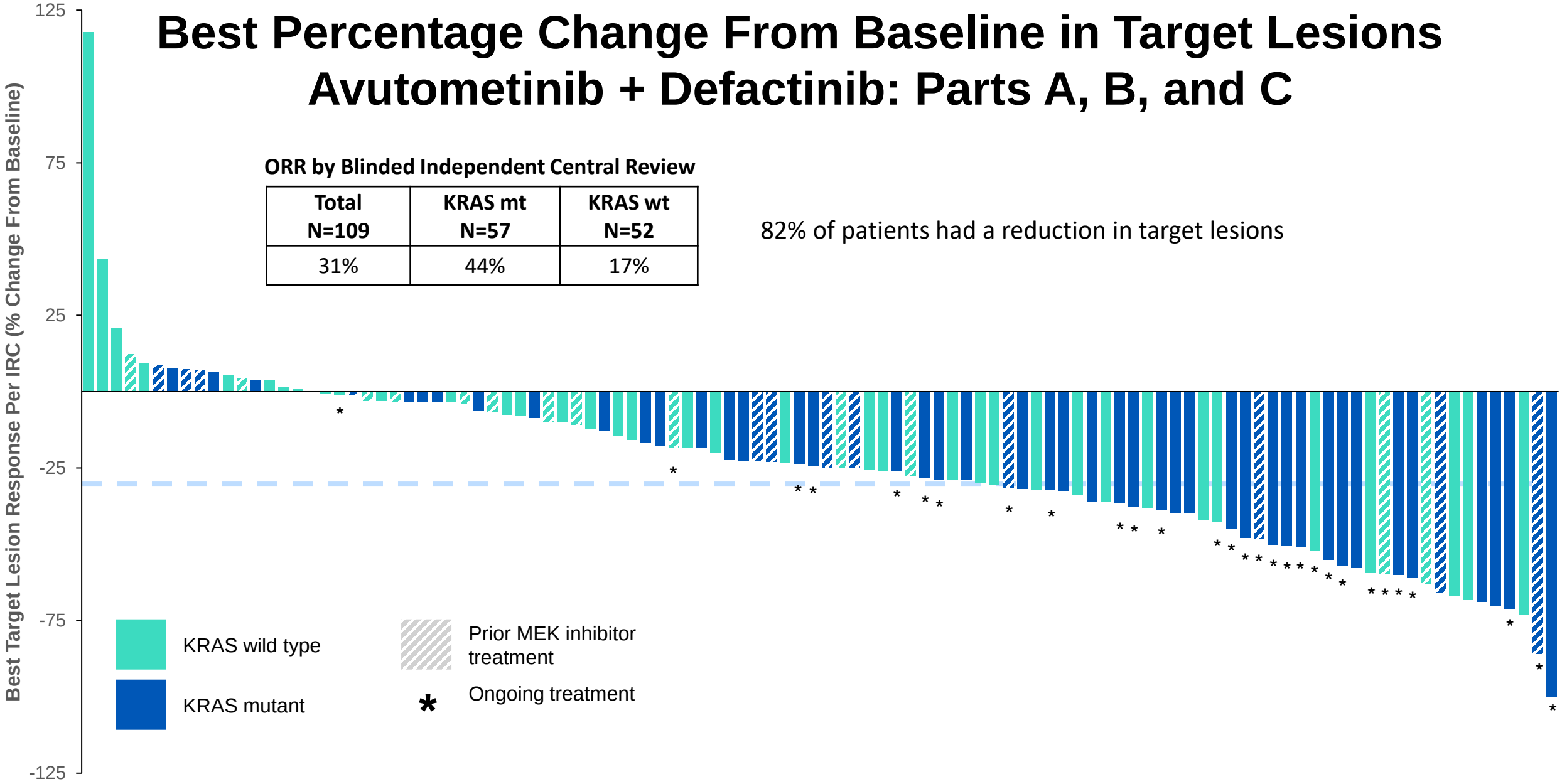
*By BICR. †Includes unconfirmed PR; SD (or unconfirmed PR) must occur ≥53 days after first dose date. ‡NE = Could not be estimated based on number of patients with loss of response.
BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; CR, complete response; DOR, duration of 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

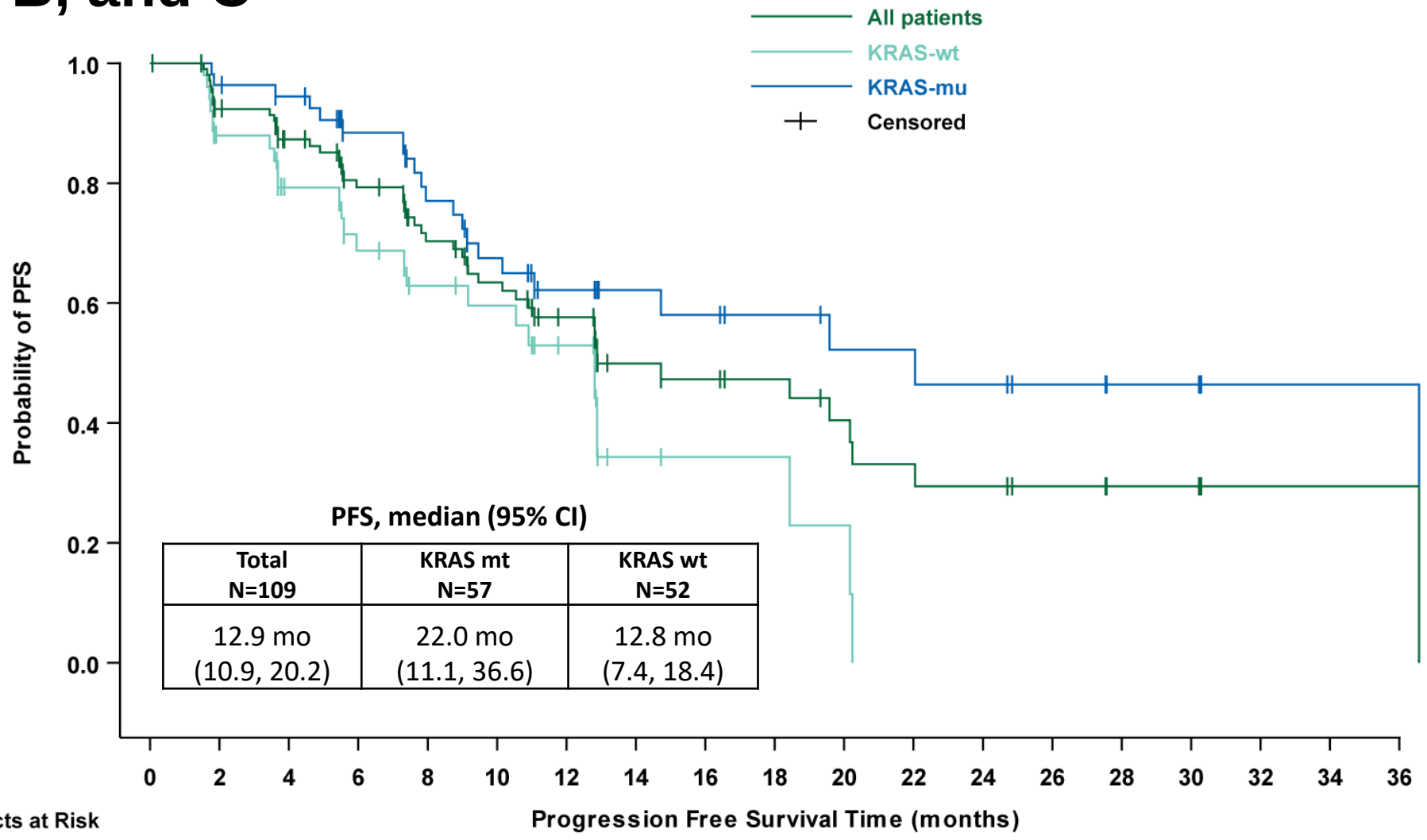
Total N=109	KRAS mt N=57	KRAS wt N=52
31%	44%	17%

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.

We thank the patients and their families, the trial teams at the participating centers, ENGOT, and GOG for supporting this study

United Kingdom (GTG-UK)
Royal Marsden NHS Foundation Trust (Susana Banerjee)
Beatson West of Scotland Cancer Centre (Rosalind Glasspool)
The Christie NHS Foundation Trust (Andrew Clamp)
UCLH Cancer Clinical Trials Unit (Rowan Miller)
Western General Hospital (Charlie Gourley)
Belgium (BGOG)
CHU de Liège (Christine Gennigens)
UZ Gent Medische Oncologie (Hannelorre Denys)
UZ Leuven (Els Van Nieuwenhuysen and Toon Van Gorp)
France (GINECO)
Centre Leon Berard (Isabelle Ray-Coquard)
Hospital Jean Minjoz (Elsa Kalbacher)
ICM Vall d'Aurelle (Michel Fabbro)
Institut Curie (Manuel Rodrigues)
Italy (MaNGO)
Instituto Europeo di Oncologia IRCCS (Nicoletta Colombo)
UOC Oncologia 2, Istituto Oncologico Veneto IRCCS (Valentina Guarneri)

Spain (GEICO)
Hospital Clínico Universitario de Valencia (Jose Alejandro Perez Fidalgo)
Hospital Universitario Ramon y Cajal (Alfonso Cortés-Salgado)
Hospital Universitario Reina Sofia (Maria Jesus Rubio)
Hospital Universitario Vall D'Hebron (Ana Oaknin)
Canada (ENGOT)
Centre de recherche di Centre Hospitalier de i'Universite de Montreal (Diane Provencher)
Princess Margaret Cancer Centre (Amit Oza)
United States (GOG)
Memorial Sloan Kettering Cancer Center (Rachel Grisham)
Advent Health (Robert Holloway)
Florida Cancer Specialists and Research Institute (Bradley J. Monk)
Cleveland Clinic Women's Health Institute (Peter Rose)
Comprehensive Cancer Centers of Nevada (Anu Thummala)
H. Lee Moffitt Cancer Center and Research Institute (Hye Sook Chon)
Maryland Oncology and Hematology (Carol Tweed)
Minnesota Oncology Hematology (Lauren Bollinger)
Northwest Cancer Specialists (Erin Salinas)

United States (GOG, continued)
Sansum Clinic (Gregg Newman)
Sarah Cannon Research Institute (Erika Hamilton)
The Ohio State University Wexner Medical Center & James Cancer Hospital (David O'Malley)
Texas Oncology Austin (Lynne Knowles)
Texas Oncology Dallas (Kristi McIntyre)
Texas Oncology Longview (Anna M. Priebe)
Texas Oncology McAllen (Suresh Ratnam)
Texas Oncology San Antonio (Antonio Santillian-Gomez)
Texas Oncology The Woodlands (Christine Lee)
University of Chicago (John Maroney)
University of New Mexico Comprehensive Cancer Center (Carolyn Muller)
University of Oklahoma Medical Center (Kathleen Moore)
University of Virginia (Kari Ring)
UT Southwestern Medical Center (David S. Miller)
Washington University School of Medicine (Premal Thaker)
Willamette Valley Cancer Institute and Research Center (Charles Anderson)
Yale School of Medicine (Alessandro Santin)
Virginia Cancer Specialists (Mitul Gandhi)

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ENGOT-ov60/GOG-3052/RAMP 201 was sponsored by Verastem Oncology