An Industry Supported Symposium at the IGCS 2025 Annual Global Meeting

A New Era in Recurrent LGSOC: Incorporating Approved Therapies, Biomarkers, and Clinical Strategies

This session is not included in the main event CME/CPD credit.

Cape Town, South Africa

Thursday, November 6, 2025

11:55 - 13:25 (GMT+2)

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Welcome and Introductions

Brian Slomovitz, MD

Mount Sinai Medical Center

Miami Beach, Florida, USA

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MODERATOR

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Mount Sinai Medical Center
Miami Beach, Florida, USA

FACULTY

Saketh Guntupalli, MD

University of Colorado
School of Medicine
Aurora, Colorado, USA

Susana Banerjee, MBBS, MA, PhD, FRCP

The Royal Marsden NHS Foundation Trust
London, United Kingdom

Faculty Disclosures

Name	Role in Activity	Disclosures
Brian Slomovitz, MD	Moderator	**Consultant:** Seagen, Novocure; AstraZeneca; Aadi; Regeneron; Immunocore; Merck; Gilead, Eisai; Incyte
Saketh Guntupalli, MD	Speaker	**Advisory Board:** Pfizer | Genmab
Susana Banerjee, MBBS, MA, PhD, FRCP	Speaker	**Consultant/advisory board for:** Abbvie, Astrazeneca, Beigene, Biontech, Eisai, Epsilogen, Gilead, GlaxoSmithKline, Grey Wolf Therapeutics, Immunogen, Incyte, ITM Oncologics, Lilly, Merck Sharpe Dohme, Myriad, Pharmaand, TORL BioTherapeutics, Verastem, Zymeworks **Honoraria/expenses from:** Abbvie, Astrazeneca, GlaxoSmithKline, Immunogen, Merck Sharpe Dohme, Takeda, Verastem, Zymeworks **Grant/Research support from:** Astrazeneca, GSK, Verastem (PI) **Non-compensated roles:** ESMO Executive Board Member (2020-2022); President Royal Society of Medicine Oncology Section; GCIG Rare Cancers Committee Chair; BGCS Research Group Co-chair

Learning Objectives

Upon completion of the activities in this series, learners will demonstrate increased knowledge regarding:

1. Describe the challenges in managing recurrent low-grade serous ovarian cancer (LGSOC) and understand the clinical complexities associated with this disease.

2. Summarize the most recent clinical trial data and treatment options for recurrent LGSOC, including novel and FDA-approved therapies, FDA-approved therapies and investigational strategies, MEK Inhibitors, CDK4/6 Inhibitors, hormonal treatments and other opportunities in the competitive landscape.

3. Understand the role and importance of biomarker testing and sequencing in informing treatment decisions.

4. Discuss strategies for accessing newly approved treatments and managing associated side effects in clinical practice.

5. Highlight future directions for integrating precision medicine and emerging investigational strategies in the care of patients with recurrent LGSOC.

Agenda

11:55 - 12:05: **Welcome and Introductions**
Brian Slomovitz, MD, Mount Sinai Medical Center; Miami Beach, Florida, USA

12:05 – 12:25: **Evolving Clinical Landscape and New Treatment Options in LGSOC**
Susana Banerjee, MBBS, MA, PhD, FRCP; The Royal Marsden and the Institute of Cancer Research London, United Kingdom

12:25 – 12:45: **The Role of Biomarker Testing and Sequencing in Treatment Selection**
Saketh Guntupalli, MD; University of Colorado School of Medicine; Aurora, Colorado, USA

12:45 - 13:05: **Panel Discussion: Managing Side Effects, Optimizing Quality of Life, and Access to Treatment**
All Faculty

13:05 - 13:10: **Closing Remarks and Key Takeaways**
Brian Slomovitz, MD, Mount Sinai Medical Center; Miami Beach, Florida, USA

Case 1: 34-year-old nulliparous woman with an unexpected ovarian mass

Initial Complaint:
34-year-old nulliparous woman presented with vague, persistent bloating and mild pelvic heaviness for 4 months. Her menstrual cycles were regular, and she denied weight loss or systemic symptoms.

Laboratory Work-Up:
Serum CA-125 was mildly elevated (62 U/mL). HE4 and ROMA scores were inconclusive. No radiologic evidence of ascites or lymphadenopathy was noted.

Imaging Impression:
MRI shows a unilocular cyst with mural nodules and enhancing solid foci. The radiologist commented: “Findings suggest a borderline epithelial tumor; early low-grade serous carcinoma cannot be excluded.”

Surgical Event:
A planned laparoscopic cystectomy was escalated intraoperatively when the ovarian surface appeared irregular with fine excrescences. Frozen section was equivocal: Serous borderline tumor vs. low-grade serous carcinoma.

Case 1: 34-year-old nulliparous woman with an unexpected ovarian mass

Final Pathology:
Permanent sections confirmed low-grade serous carcinoma (LGSOC) with classic papillary structures, psammoma bodies, and low mitotic activity. No invasive implants were identified**.**

Molecular Profile:
NGS detected a pathogenic **KRAS G12D** mutation and **TP53 wild-type** status. Tumor was **ER/PR-positive, HER2-negative,** consistent with the molecular profile of LGSOC.

Staging & Surgical Outcome:
Comprehensive staging with peritoneal washings, omentectomy, and biopsies showed **no metastatic disease (FIGO stage IA).**

Multidisciplinary Tumor Board:
The consensus favored **observation without adjuvant therapy**, balancing excellent prognosis with the patient's fertility goals.

Follow-Up:
She entered a structured surveillance program with imaging and CA-125 every six months. At **16 months**, she remains disease-free and is pursuing fertility counseling.

Case 2: 49-year-old woman with recurrent LGSOC

Initial History:
A 49-year-old woman was diagnosed five years ago with stage IIIC LGSOC after presenting with abdominal distension and omental caking. She underwent optimal cytoreductive surgery followed by six cycles of carboplatin–paclitaxel, achieving complete remission. She remained disease-free for nearly four years while on **letrozole maintenance therapy.**

Relapse:
The patient re-presented with progressive abdominal fullness and early satiety. Serum CA-125 increased to 158 U/mL (previously 20).

Imaging and Biopsy:
CT abdomen and pelvis revealed multiple peritoneal implants, the largest measuring 3 cm, without ascites. CT-guided biopsy confirmed recurrent LGSOC with papillary features and psammoma bodies.

Molecular Profile:
NGS detected a **KRAS G12V mutation** and **NF2 loss,** indicating activation of both the **MAPK** and **FAK** signaling pathways.

Case 2: 49-year-old woman with recurrent LGSOC

Treatment Course:
She was re-treated with carboplatin–paclitaxel (6 cycles), achieving stable disease. Subsequent therapy with letrozole plus bevacizumab produced a transient response before disease progression.

Targeted Therapy:
Given her platinum-resistant, ER/PR-positive, KRAS-mutated recurrence, she was initiated on **avutometinib (dual RAF/MEK inhibitor)** in combination with **defactinib (FAK inhibitor),** now an **FDA-approved regimen** for *KRAS-mutated* recurrent LGSOC.

Clinical Course and Tolerability:
At 8 weeks, she reported improved abdominal comfort and appetite. CT at 3 months demonstrated a ~40% reduction in measurable disease (partial response by RECIST).

Tolerability:
Mild rash, diarrhea, and transient transaminitis, managed with supportive care and dose adjustments.

Current Status:
She remains on treatment with sustained disease control at 4.5 months, ECOG 0, and preserved quality of life.

Evolving Clinical Landscape and New Treatment Options in LGSOC

Susana Banerjee, MBBS, MA, PhD, FRCP

The Royal Marsden and
the Institute of Cancer Research
United Kingdom

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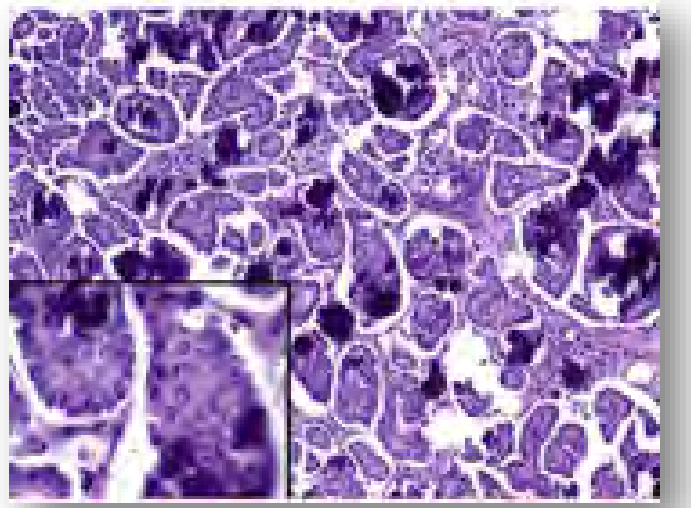
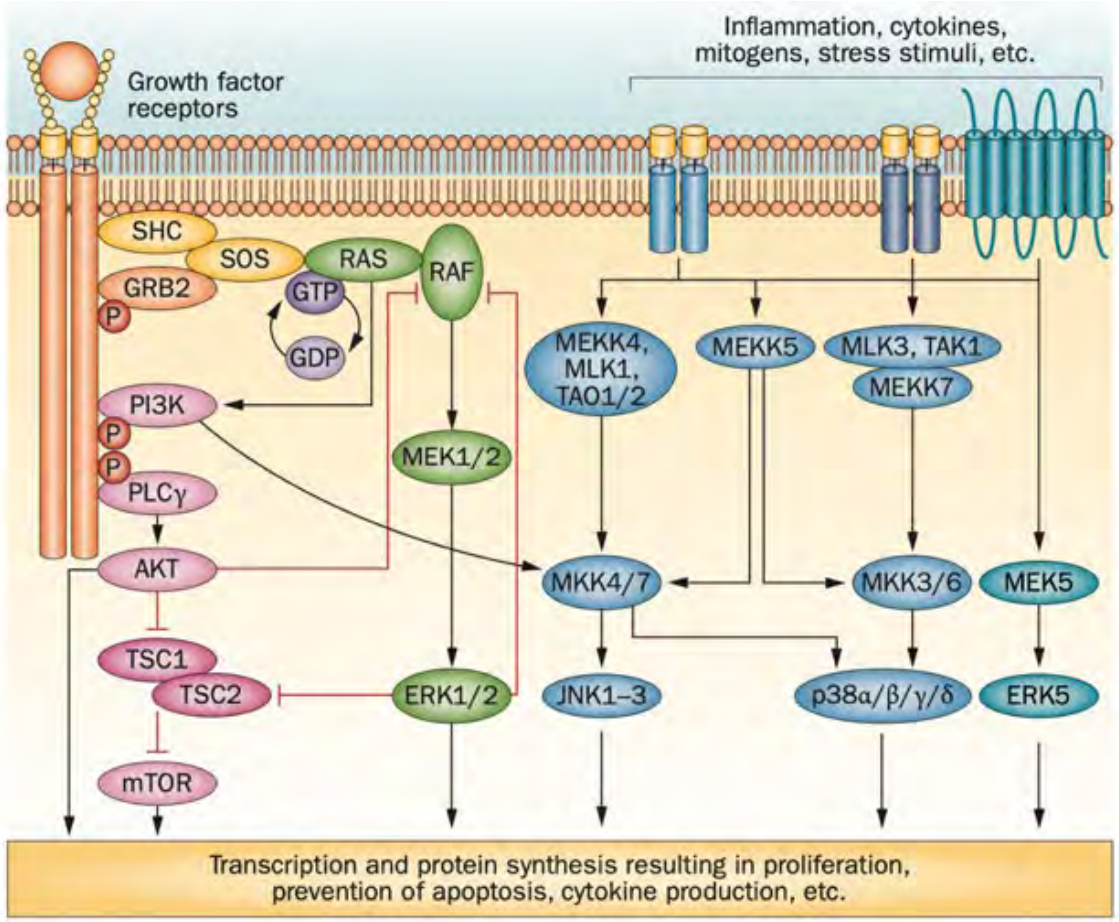
Low Grade Serous Carcinoma

- Pathology: mild to moderate atypia, low proliferative activity
- Median age 43-47 years, less chemo-responsive, generally longer survival than HGSOC (median OS 90.9 vs 40.7 months)
- LGSOC is noted to harbour alterations (KRAS, BRAF, NRAS, ERBB2) in the MAP kinase signaling pathway; ER/PgR expression. (BRCA1/2 mutations rare/not present)
- High FOLR1 expression 30%, associated with fewer MAPK pathway alterations, low PR expression, and p16 loss

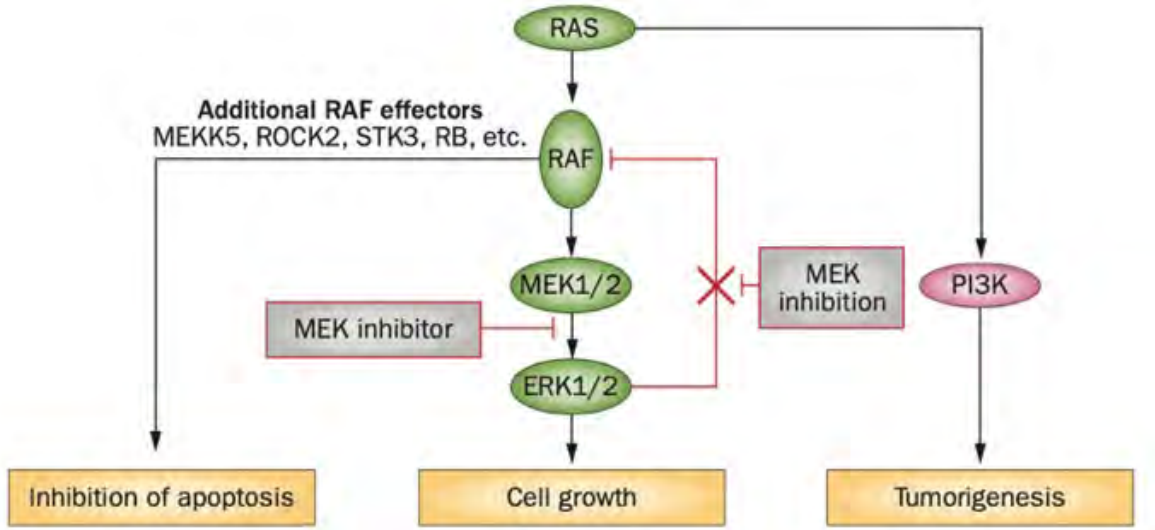


Chui et al JCO Precision Oncology 2021
Slomovitz et al Gyn Onc 2020; Gockley et al Obstet Gynae 2017
Leung et al J Gynaecol Oncol 2025

MAPK pathway: MEK1/2 mediates cellular signals transduced from RAS–RAF



- ***LGSOC MAPK pathway mutations***
- *KRAS 20-40%, NRAS 7-26%, BRAF 5-33%*



Zhao Y et al. Nat Rev Clin Oncol. 2014;11:385–400. Cheasley D et al. J Pathol. 2021;253(1):41-54. McLachlan J et al. Pharmacogenomics. 2016;17(12):1353-1363.

Clinical Trials Targeting MEK/MAPK pathway

Selumetinib: First phase II report MEK inhibitor activity[1]

Open-label phase II recurrent LGSOC:

- 52 patients
- Selumetinib 50mg bd orally
- Response rate 15%
- Activity not restricted by presence of BRAF/KRAS mutation

Dabrafenib + Trametinib for BRAFV600E Tumors2

- 5 patients with LGSOC:4/5 LGSOC patients had PR; 1 patient had SD
- 3 of 4 PRs lasted 25.1, 24.4, and 13.8 months

Farley, et al. Lancet Oncology. 2013 2. Salama et al. J Clin Oncol 2020

MILO/ENGOT-ov60: Binimetinib

Patients with Recurrent/Persistent LGS Carcinoma of the Ovary, Fallopian Tube or Primary Peritoneum
≥1 prior platinum based regimen but ≤ 3 prior lines of chemo
Unlimited prior hormonal therapies (ENGOT Model C)

↓

Stratification:
Platinum-Free Interval (≤ 182 days vs > 182 days)
# of Prior Systemic Chemo Regimens (1 or 2 vs. >2)

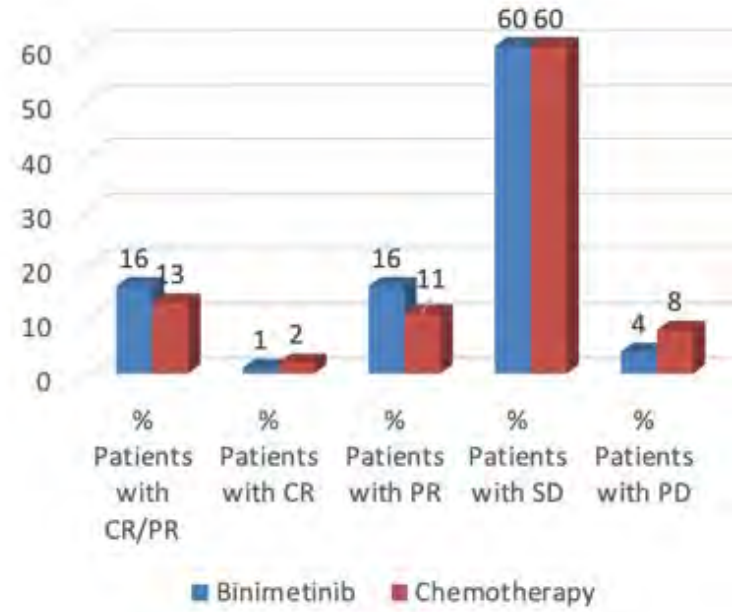
↓

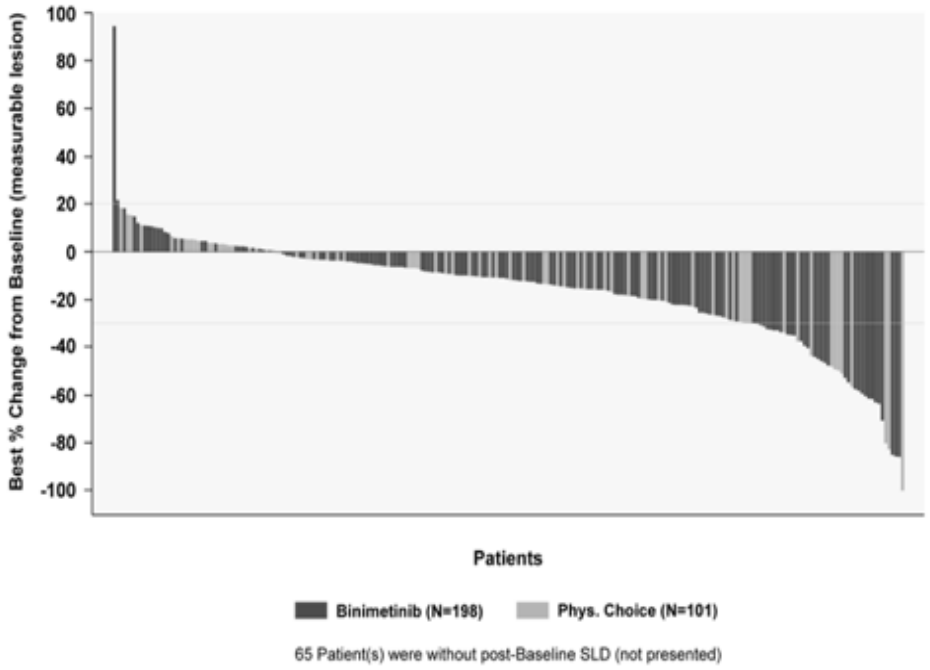
Randomization 2:1

Binimetinib (N=228)
(45mg PO BID)

Physicians' Choice of Chemotherapy (N=113)**

Pegylated Liposomal Doxorubicin	Paclitaxel	Topotecan
(40mg/m2 IV, day 1 of 28 day cycle)	(80mg/m2 IV on days 1,8,15 of 28 day cycle)	1.25 mg/m2 IV on Days 1-5 of 21 day cycle)





Updated analysis DOC Jan 2019 (n=341)

- ORR local 24% binimetinib and PCC
- Median PFS 11.2 binimetinib vs 14.1 months PCC
- OS 34.6 vs 34.2 months

Monk et al J Clin Oncol. 2020 Nov 10;38(32):3753-3762

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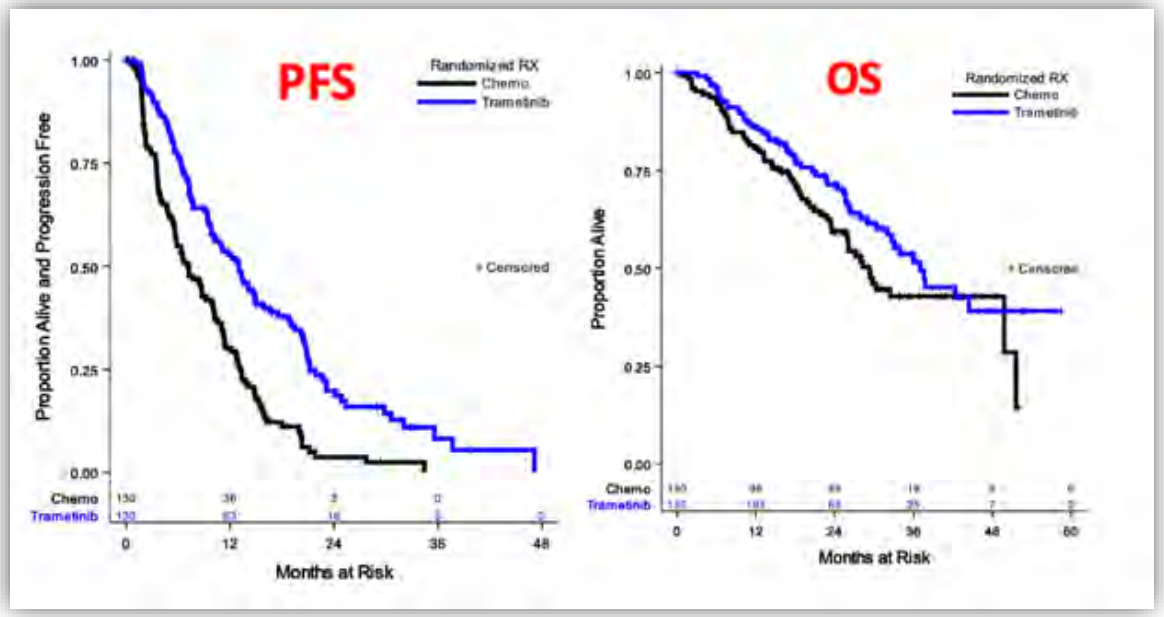
GOG218/LOGS: Trametinib vs standard of care

Arm	No. Pts CR + PR /Treated	Objective Response Rate (95% CI)	Stable Disease Rate	Response Duration Months (95% CI)	Odds Ratio For ORR (95% CI)	P-Value
Trametinib	**34/130**	**26.2% (19.0-34.0)**	**59.2%**	**13.6 (8.1-18.8)**		
					5.4 (2.4-12.2)	**< 0.0001**
Control (SOC)	**8/130**	**6.2% (2.0-10.0)**	**70.8%**	**5.9 (2.8-12.2)**		
Letrozole	6/44	13.6%	70.5%			
Tamoxifen	0/27	0%	66.7%			
Paclitaxel	1/11	9.1%	63.6%			
PLD	1/40	2.5%	80.0%			
Topotecan	0/8	0%	50.0%			



- Median PFS: 13.0 vs 7.2 months (HR = 0.48; p < 0.0001)
- Median OS: 37.0 vs 29.2 months (HR = 0.75; p = 0.054)

Gershenson DM, et al. Lancet. 2022;399(10324):541-553.

Final Overall Survival IGCS 2025

NRG ONCOLOGY

NCRI National Cancer Research Institute

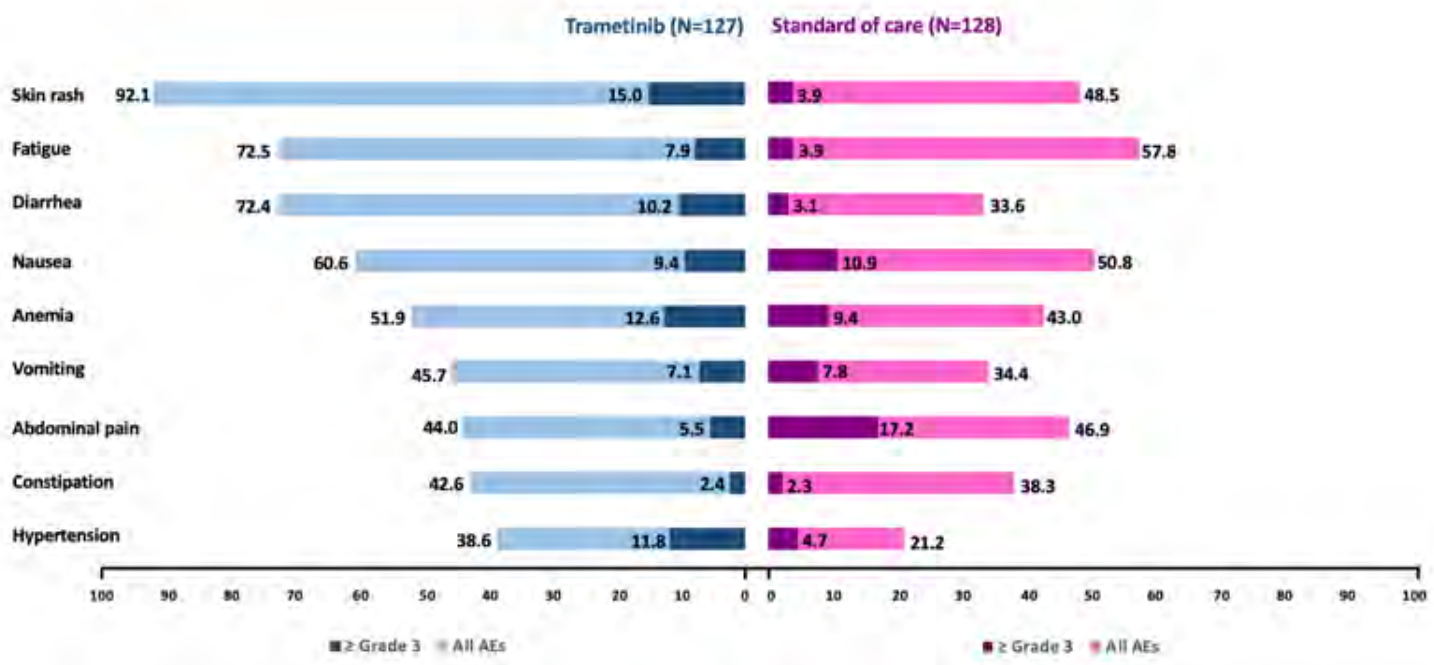
GOG218/LOGS: outcomes according to mutation status

134 patients sequencing data available: 33% KRAS, BRAF or NRAS mutation present

- There was no evidence that KRAS mutation status was predictive for progression-free survival
- ORR was numerically better for trametinib than SOC in
  - mutation-present patients (50% (11/22) vs 9% (2/22)) than in
  - mutation-absent patients (8% (4/48) vs 7% (3/42))

GOG218/LOGS: Treatment-emergent Adverse Events

Adverse Event of Special Interest	Trametinib (N = 130)	Standard of Care (N = 130)
Retinal tear	1 (0.8%)	0
Retinal vascular disorder	2 (1.6%)	0
LV systolic dysfunction	2 (1.6%)	1 (0.8%)
Decreased ejection fraction	10 (7.9%)	1 (0.8%)
QTc prolongation	2 (1.6%)	0
Pneumonitis	3 (2.4%)	0



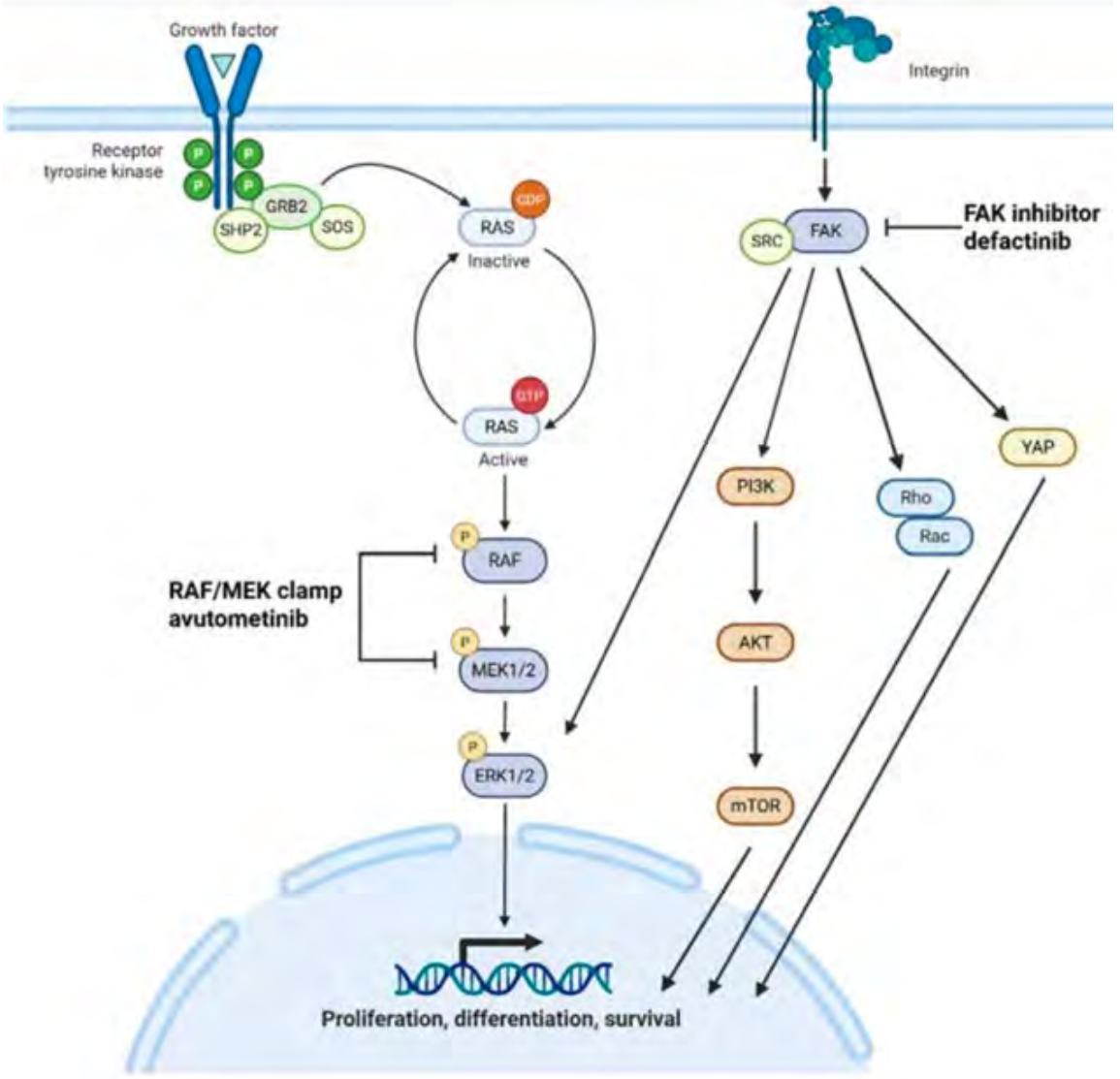
Discontinuation due to toxicity:
36% trametinib; 30% standard of care

Gershenson et al ESMO 2019

Mechanism of Action

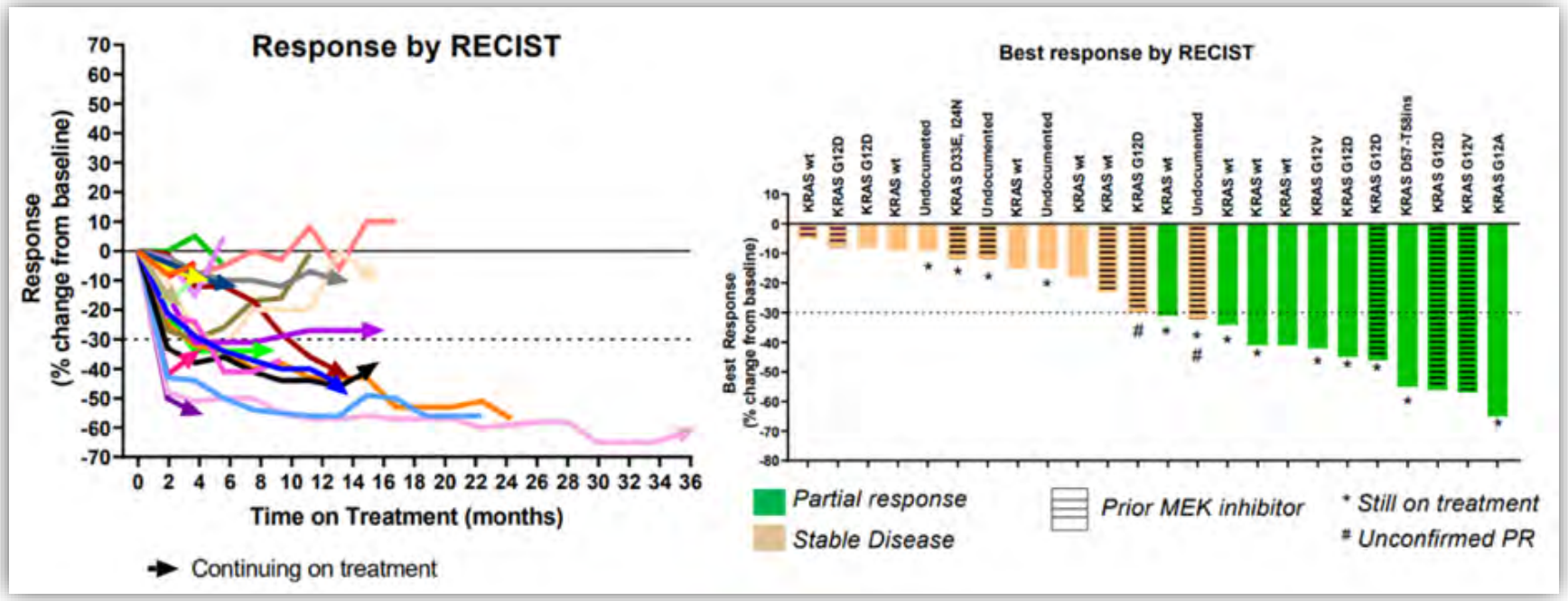
- **Avutometinib** inhibits MEK and RAF by stabilising the MEK-RAF complex, blocking both MEK activity and the feedback reactivation of MEK by RAF

- **Defactinib** inhibits FAK kinase, a mechanism of adaptive resistance to MEK inhibition, and an activator of a variety of oncogenic signaling pathways



Strover et al Gyn Onc 2025, figure adapted from Banerjee et al IGCS 2024

Phase 1 FRAME trial Avetumetinib (VS-6766) + Defactinib LGSOC cohort




nature medicine
Article
Defactinib with avutometinib in patients with solid tumors: the phase 1 FRAME trial
Received: 12 December 2024
Accepted: 7 May 2025
Check for updates

Overall response rate (ORR) = 46% (11/24)
KRAS mutant ORR = 64% (7/11)
KRAS wild-type ORR = 44% (4/9)
KRAS status undetermined (3 SD; 1 unconfirmed PR)
Responses in patients previously treated with MEKi
Median PFS 23 months (95% CI 10.6-NR) across all LGSOC

G3/G4 AE 32%
12% CK elevation
8% rash
4% mucositis
4% hyperbilirubinemia

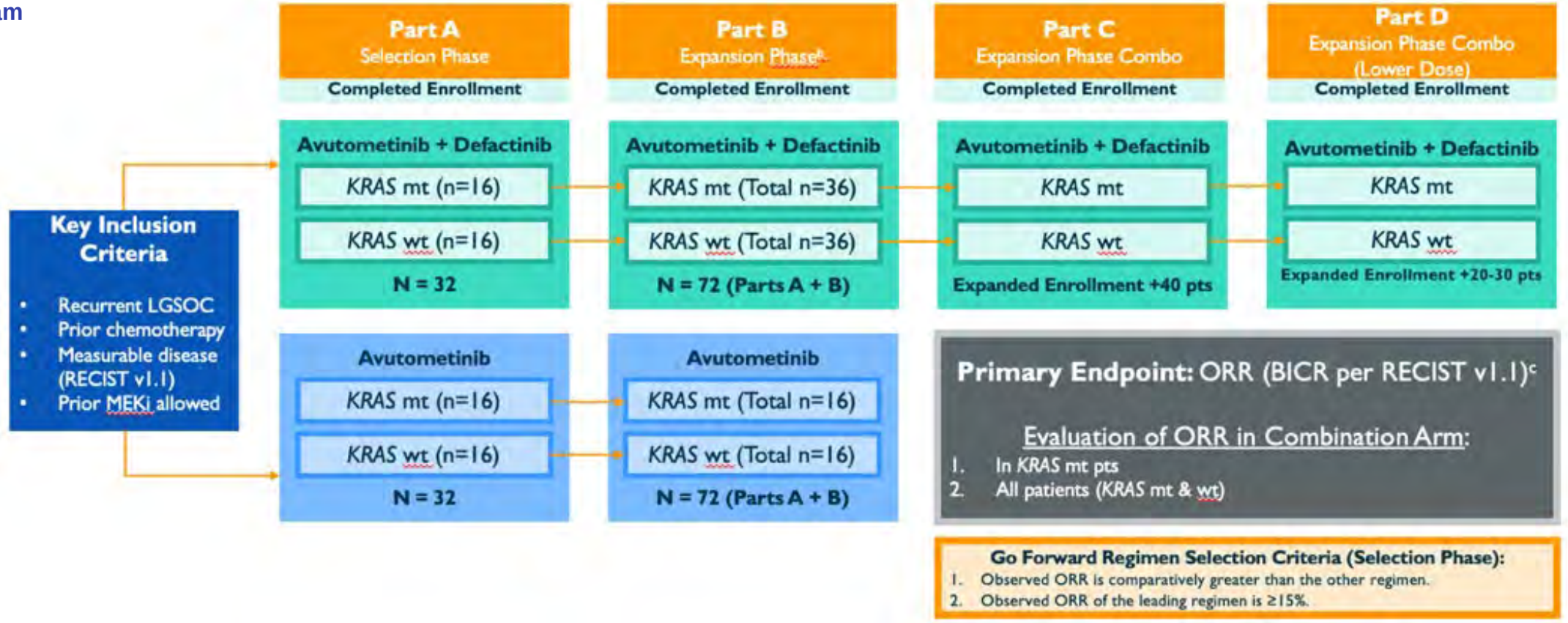
PK-PD driven unique intermittent dosing schedule
Recommended phase II dose
Avutometinib 3.2 mg PO BIW 3/4 wks +
Defactinib 200 mg PO BID: 3/4 wks

Banerjee et al, ESMO 2021; Nature Medicine 2025

ENGOT-ov60/NCRI/GOG-3052/RAMP 201

Phase 2 Study of VS-6766 (Dual RAF/MEK Inhibitor) Alone and In Combination with Defactinib (FAK Inhibitor) in Recurrent Low- Grade Serous Ovarian Cancer (LGSOC)

ENGOT/Global Lead: S Banerjee
GOG Lead: R Grisham



Avutometinib Monotherapy Dosing: Avutometinib 4.0 mg PO BIW 3/4 wks.
Avutometinib + Defactinib Dosing: Avutometinib 3.2 mg PO BIW 3/4 wks + Defactinib 200 mg PO BID: 3/4 wks.
Avutometinib + Defactinib Part D Dosing: Avutometinib 1.6 mg PO BIW 3/4 wks + Defactinib 200 mg PO BID 3/4 wks.

RAMP201: Baseline Characteristics

	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.

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Response Rate and Duration of Response: 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=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 mo.; 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.

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ENGOT-OV60/GOG-3052/RAMP201: Primary endpoint combination

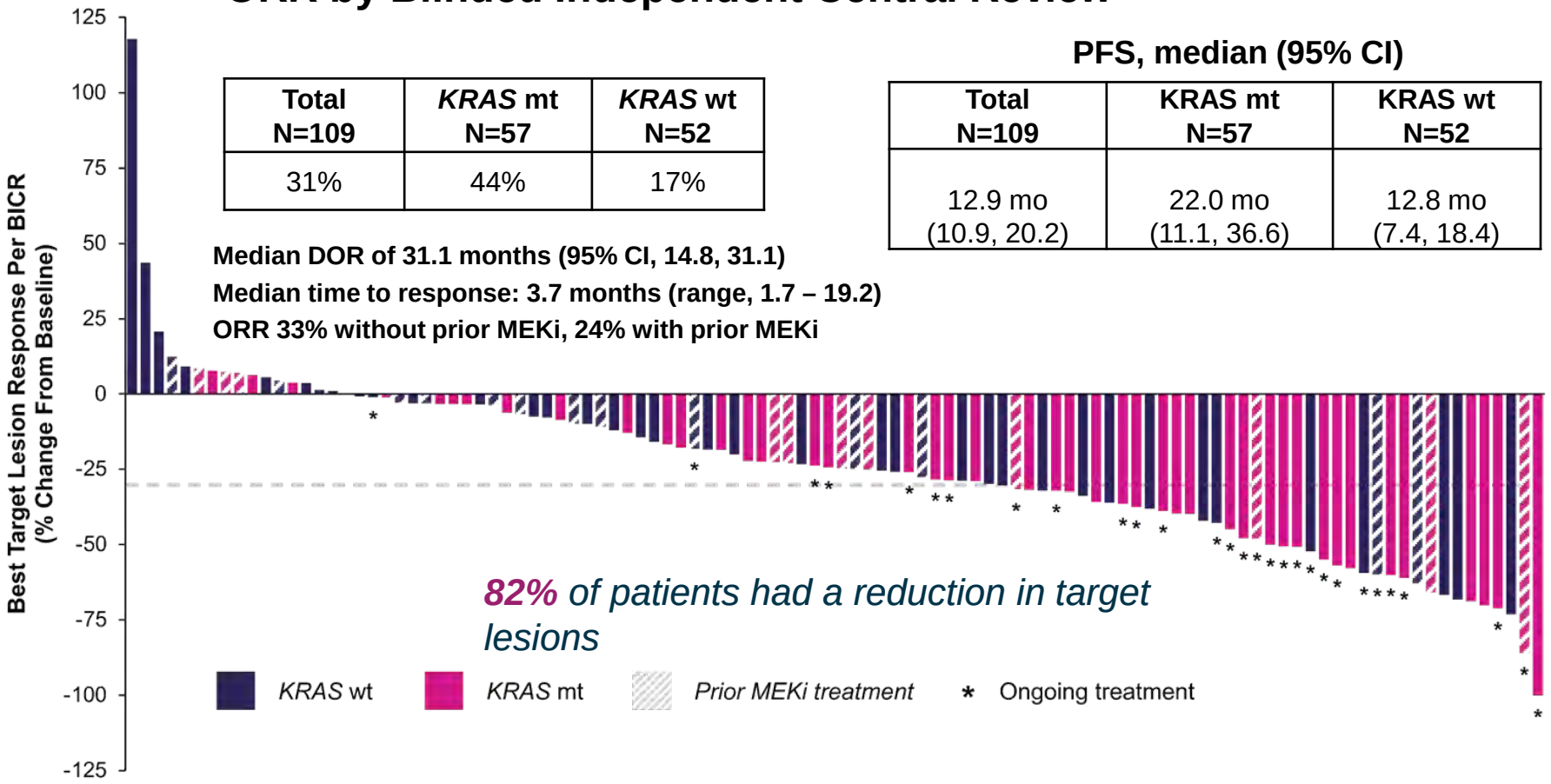
ORR by Blinded Independent Central Review

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

Median DOR of 31.1 months (95% CI, 14.8, 31.1)
Median time to response: 3.7 months (range, 1.7 – 19.2)
ORR 33% without prior MEKi, 24% with prior MEKi

PFS, median (95% CI)

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




Journal of Clinical Oncology

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

Responses Observed in both KRAS Mutant and KRAS Wild-Type Recurrent LGSOC

FDA Accelerated Approval

May 8, 2025

Avutometinib 3.2 mg BIW + Defactinib 200 mg BID

KRAS mutated recurrent LGSOC

Banerjee et al IGCS 2024; Journal Clinical Oncology 2025

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Adverse Events Profile for Avutometinib + Defactinib (parts A-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)

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

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)

Banerjee et al IGCS 2024; Journal Clinical Oncology 2025

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RAMP201: Adverse events of interest 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

Banerjee et al IGCS 2024; Journal Clinical Oncology 2025

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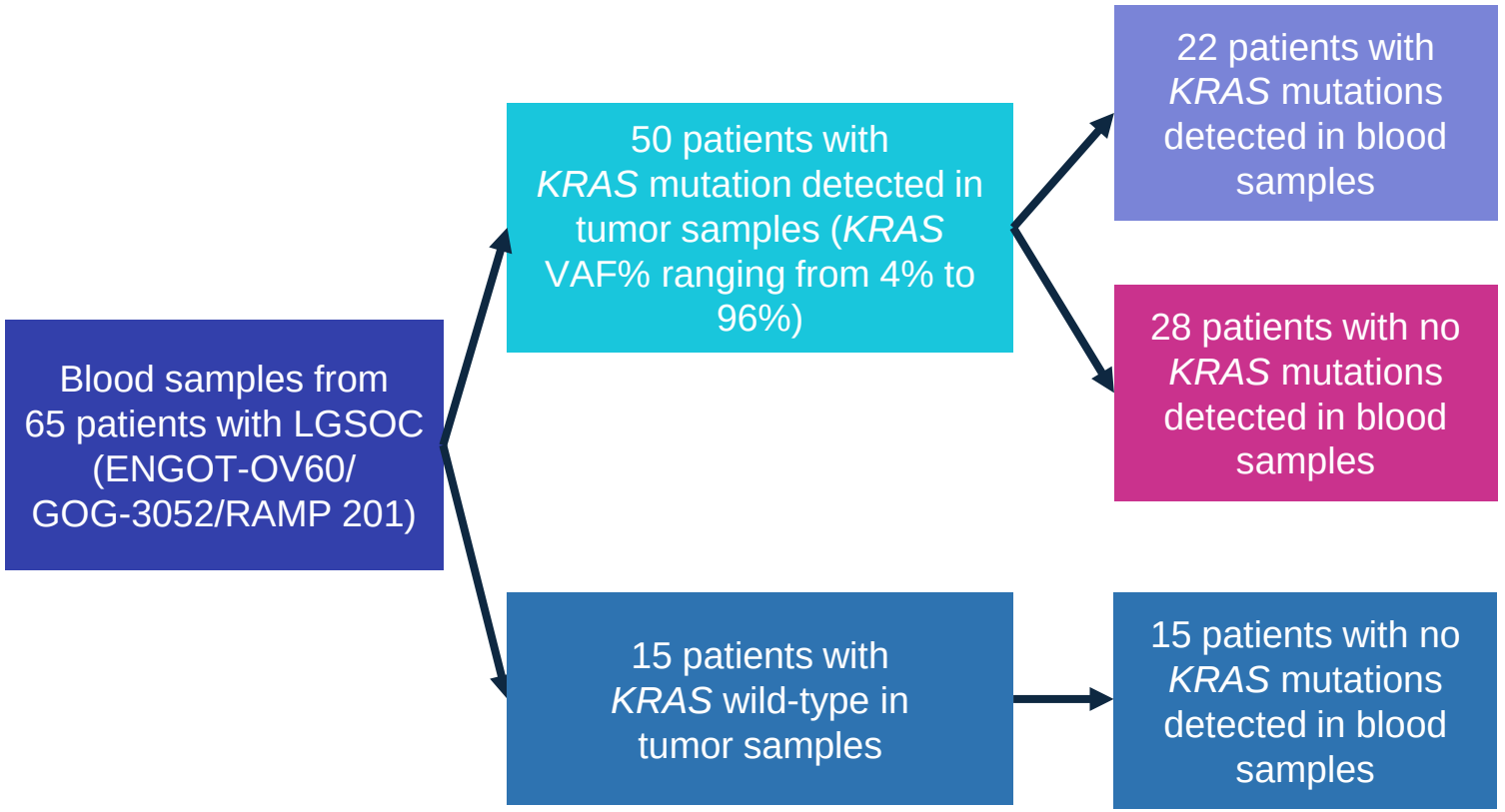
ctDNA in LGSOC: results from RAMP201 samples

In Patients With KRAS Mutations Detectable in Tumor Samples, 44% (22/50) Concordance Between KRAS Detection in Tumor vs Blood Samples



- 44% (22/50) concordance between tumor vs blood samples
  - For these 22, the same *KRAS* variant was detected in tissue vs blood samples
- 56% (28/50) of patients showed a false negative result from ctDNA testing
- No *KRAS* mutations detected by ctDNA testing in patients with *KRAS* wild-type in tumor samples

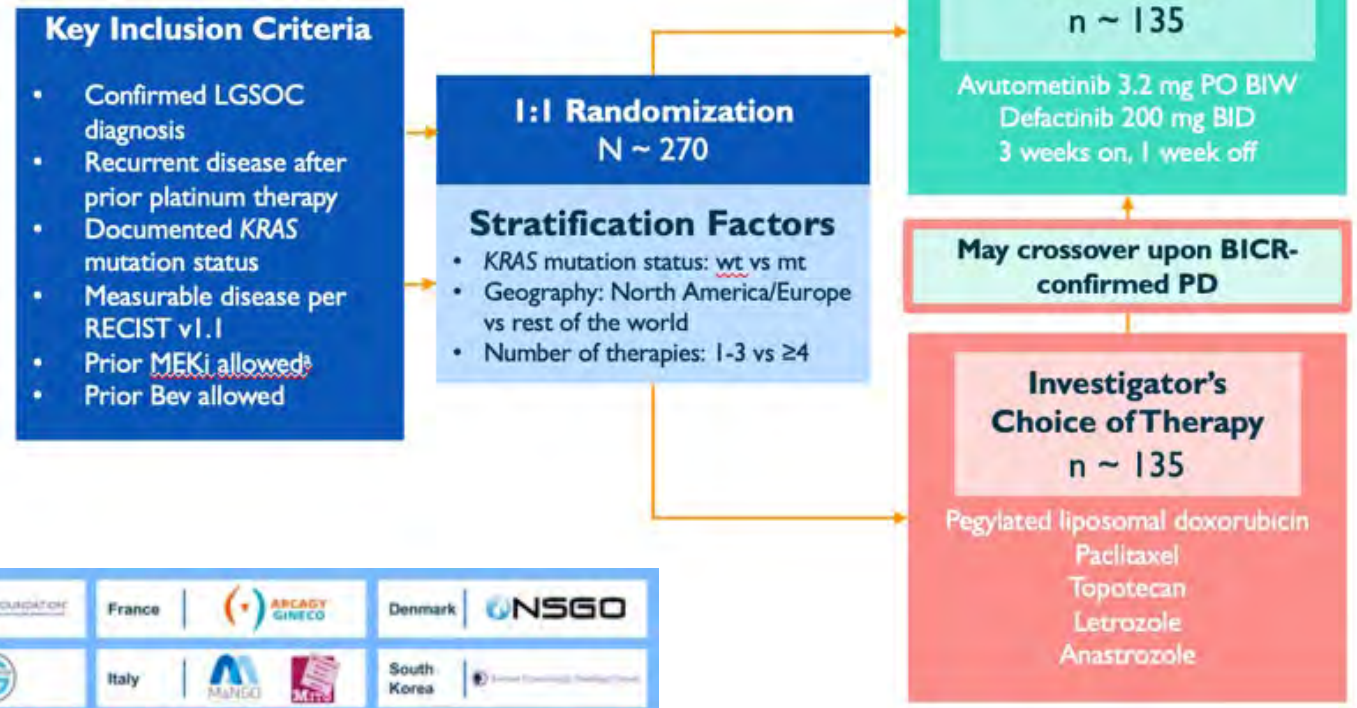
ctDNA, circulating tumor DNA; KRAS, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; VAF, variant allele frequency.

Van Nieuwenhuysen et al ESMO Gyn 2025
Banerjee et al IGCS 2025 (encore)

RAMP301: GOG-3097/ENGOTov81-GTG-UK

A Global Phase 3, Randomized, Open-Label Study of Avutometinib + Defactinib vs Investigator's Choice of Treatment in Recurrent Low-Grade Serous Ovarian Cancer

ENGOT/Global Lead: S Banerjee
GOG Lead: R Grisham



Primary Endpoint: PFS
per BICR by RECIST v1.1

Secondary Endpoints[b]
- OS
- PFS via RECIST v1.1 by investigator assessment
- ORR
- DOR
- DCR
- Safety
- Pharmacokinetics
- PROs

Primary Analysis: Hierarchical Evaluation
1. *KRAS* mutant LGSOC only
2. All recurrent LGSOC

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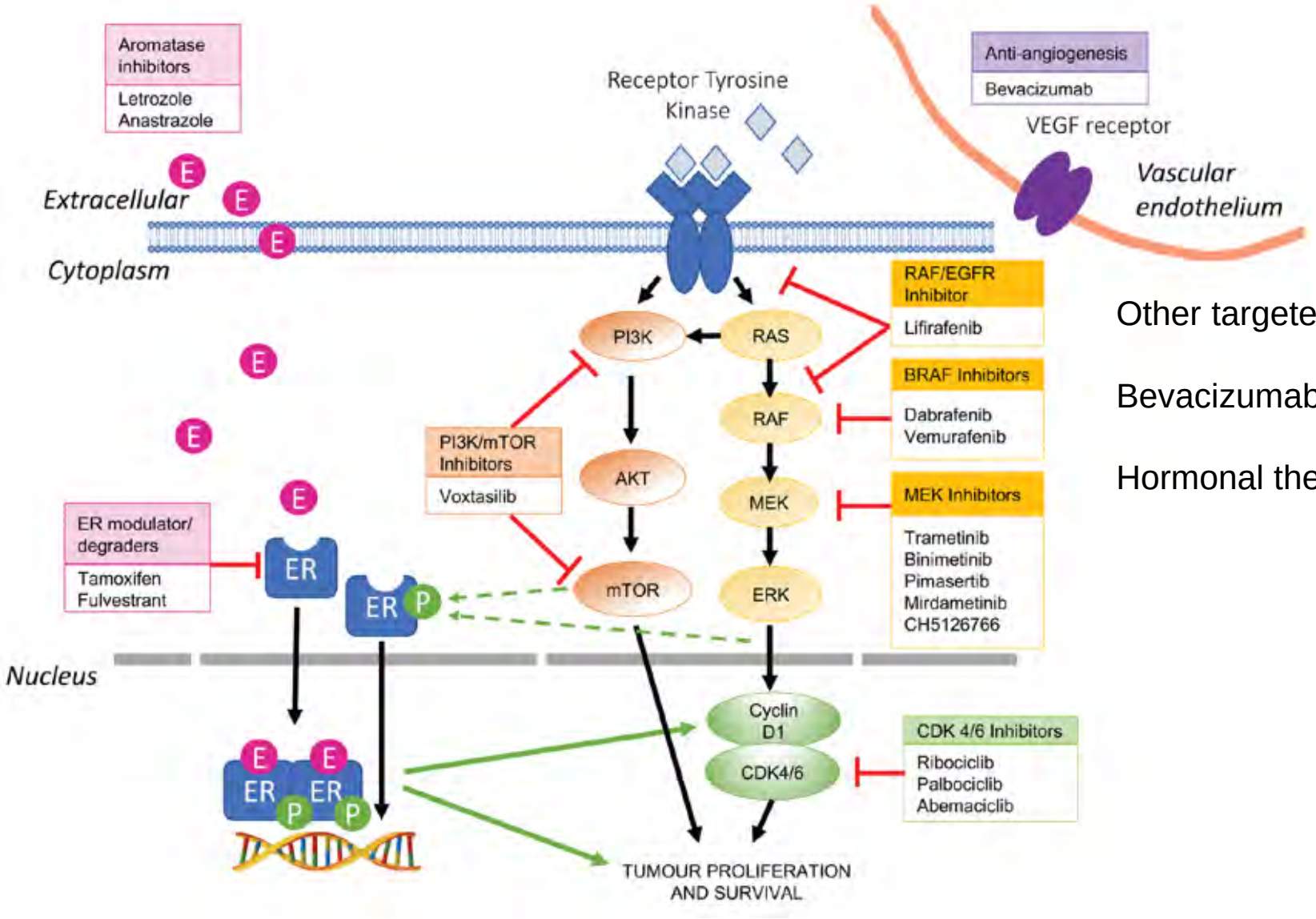
United States | France | Denmark
UK | Italy | South Korea
Spain | Canada | Australia
Belgium | Germany

NCT06072781

LGSOC- Pathways and potential drug targets



Other targeted therapies

Bevacizumab[1,2] (retrospective series RR ~ 40-55%)

Hormonal therapies

Moujaber T et al. Endocr Relat Cancer. 2021;29(1):R1-R16.

1. Grisham RN, et al. Int J Gynecol Cancer. 2014; 2. Dalton HJ, et al. Gynecol Oncol. 2017.

GOG 3026: Ribociclib and Letrozole in Patients With Low Grade Serous Cancer of the Ovary, Fallopian Tube, or Peritoneum

Ribociclib 600mg oral daily for 3 weeks then 1 week off

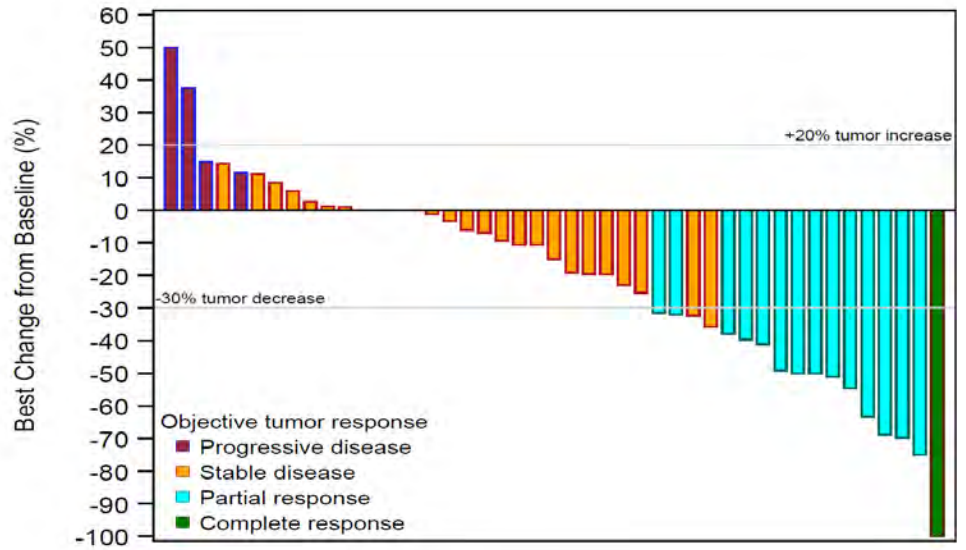
Letrozole 2.5 mg oral daily

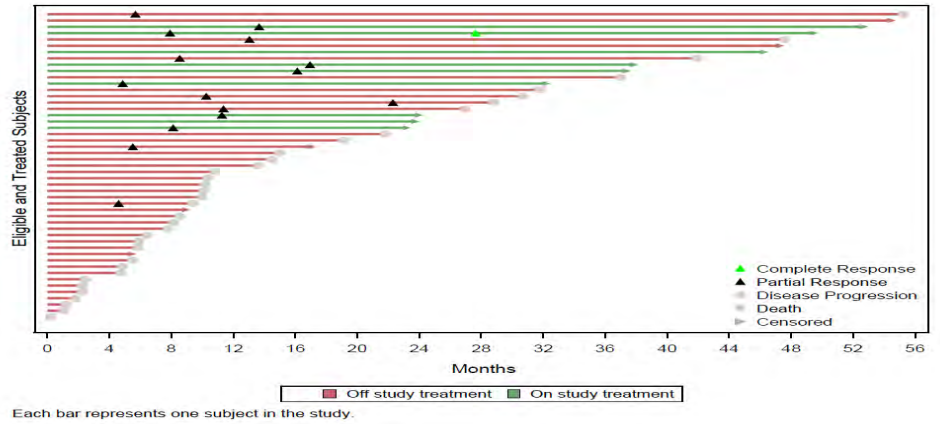
(N=49[a])

Primary Endpoint
Objective response rate

Key Secondary Endpoints
PFS, CBR, OS, Safety

Response[2]	Ribociclib and Letrozole N=49
Confirmed ORR, n (%)	**15 (30.6)**
CR	1 (2.0)
PR	14 (28.6)
CBR	41 (83.7)
Cycles, median (range)	12 (1–61)
Discontinuation due to AE	2 (4.1)



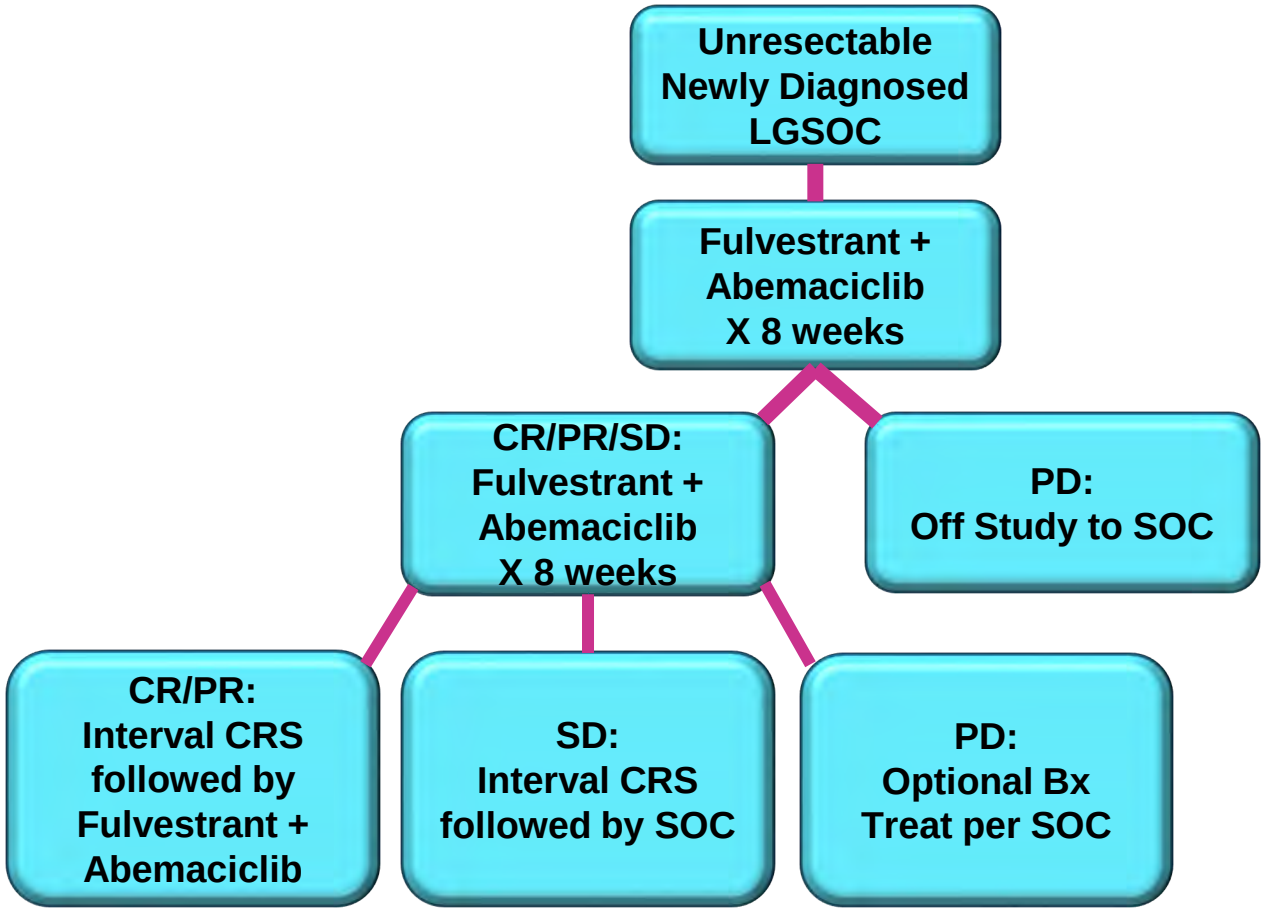


As of December 23, 2024, 18.4% of patients were still on treatment

- *[a]51 enrolled, 49 eligible and treated were included in the safety and efficacy analysis.*
- *ClinicalTrials.gov website. https://www.clinicaltrials.gov/study/NCT03673124*
- *Slomovitz et al, JCO, in press*

Endocrine Combination Therapy: Neoadjuvant Fulvestrant + Abemaciclib

NCT03531645



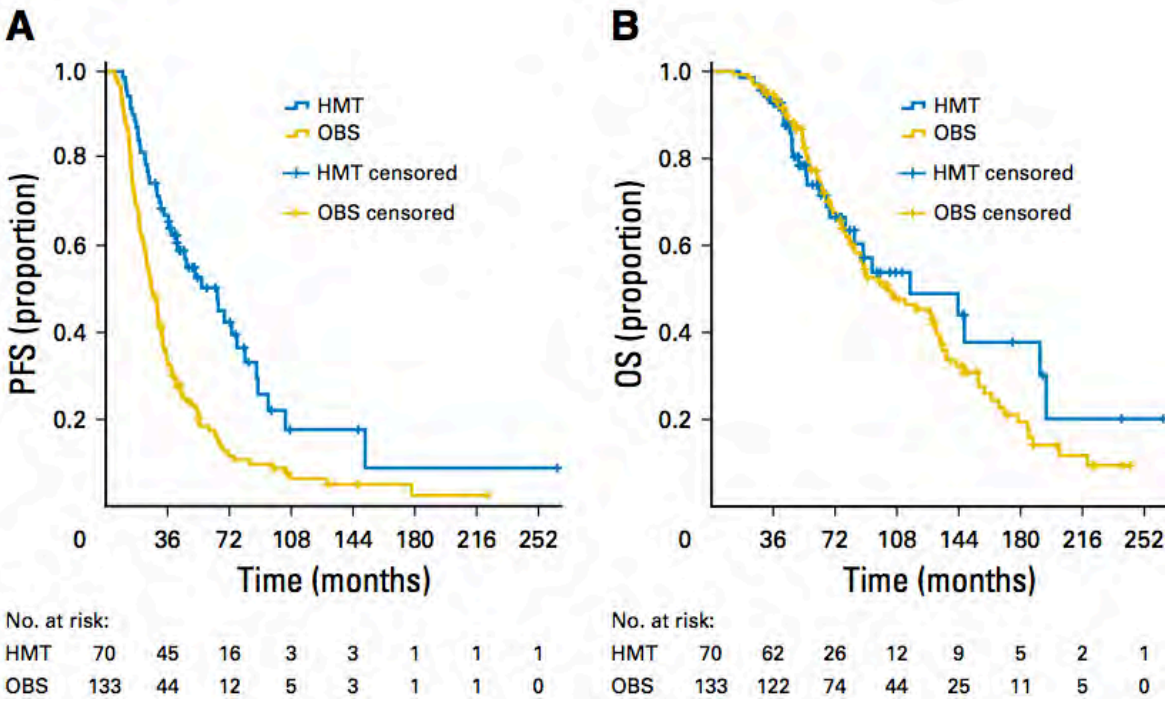
RECIST 1.1	# of Subjects	
Partial Response	8	53.3%
Complete response	1	6.7%
SD	6	40%
ORR	**9**	**60%**
PD	0	0%
Total with at least one scan	15	100%

Cobb LP, et al. ASCO 2022.

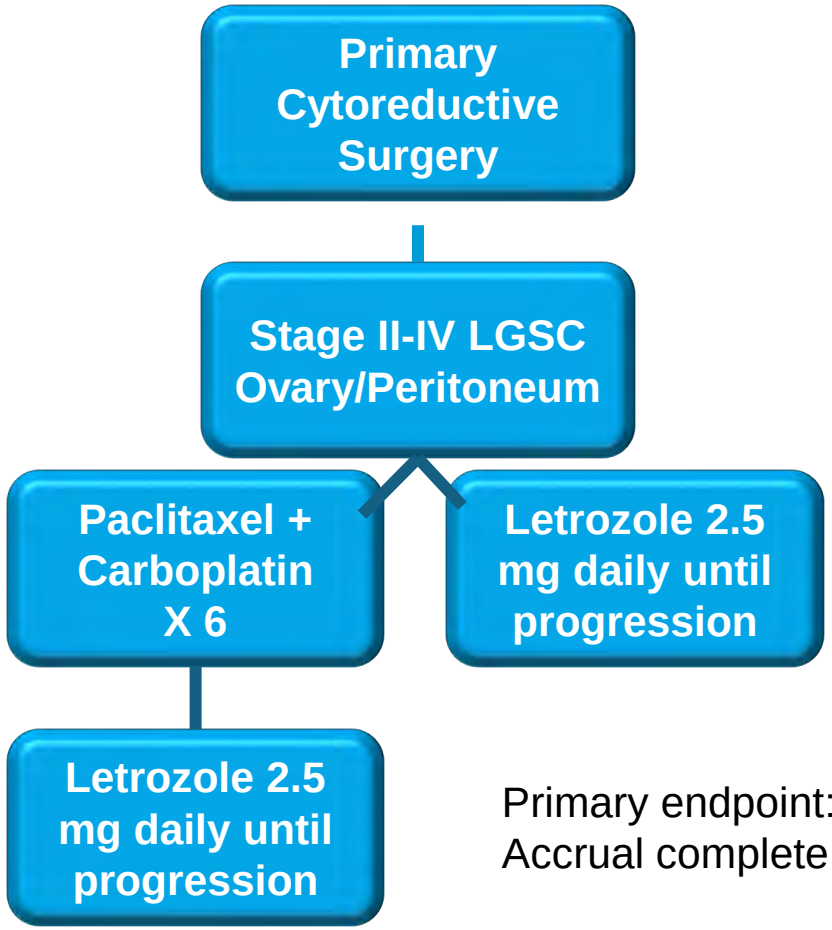
Endocrine Therapy: First line (Maintenance or Adjuvant?)

Retrospective series 203 patients:

- Primary surgery, platinum-based chemotherapy
- Followed by observation of maintenance hormonal treatment
- No OS difference
- PFS: 26.4 months vs 64.9 months



NRG-GY-019:
Randomized Phase III Trial of Paclitaxel/Carboplatin Followed by Maintenance Letrozole versus Letrozole Monotherapy in Stage II-IV Low-Grade Serous Carcinoma



Primary endpoint: PFS
Accrual complete

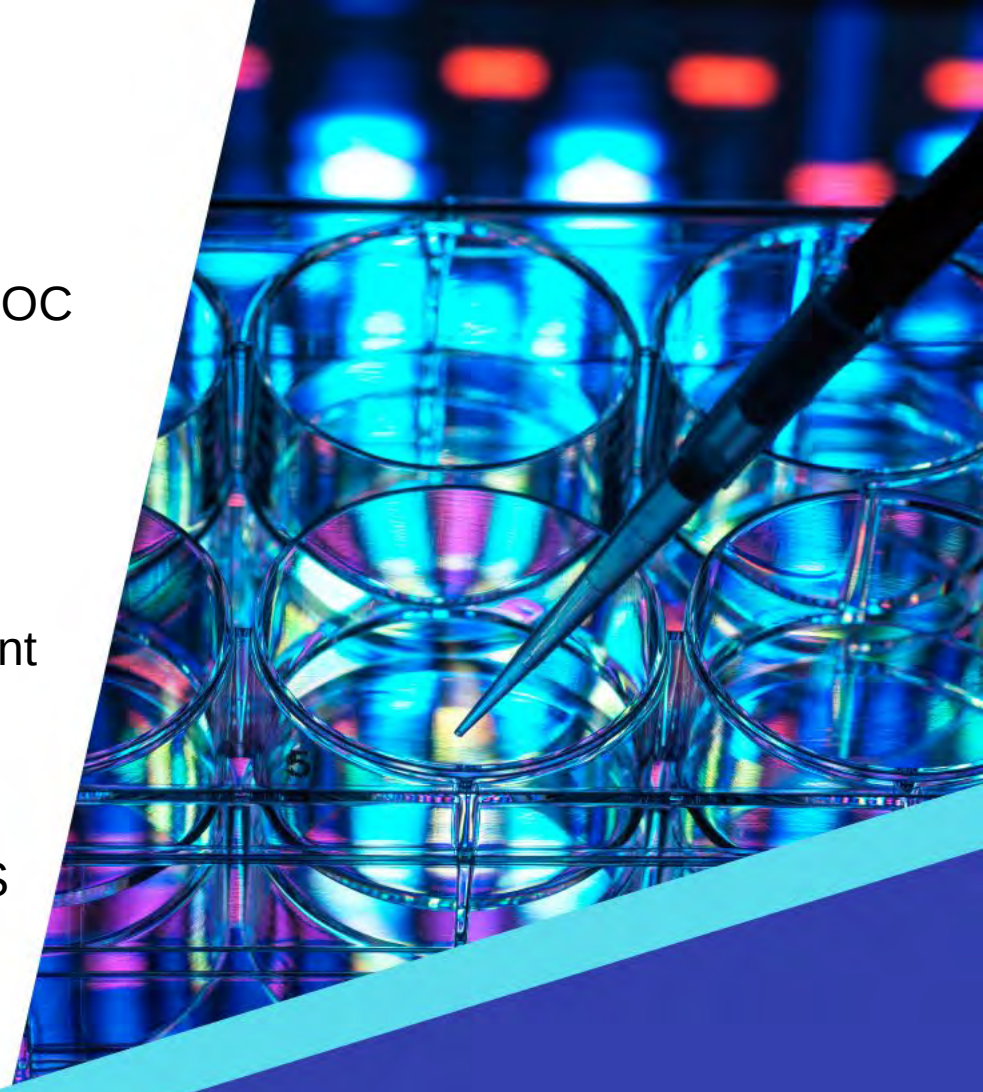
Conclusions

- Clinical Trials changing the treatment landscape for advanced LGSOC

- Systemic treatment options improving for LGSOC
  - MEK inhibitors
  - Endocrine therapy combinations (CDK 4/6 inhibitors)

- Avetumetinib and Defactinib combination in KRAS mutated recurrent disease is the first approved
  (FDA accelerated approval) therapy in LGSOC

- Phase 3 RAMP301 results awaited (confirmatory trial, role in KRAS mutated and wildtype)



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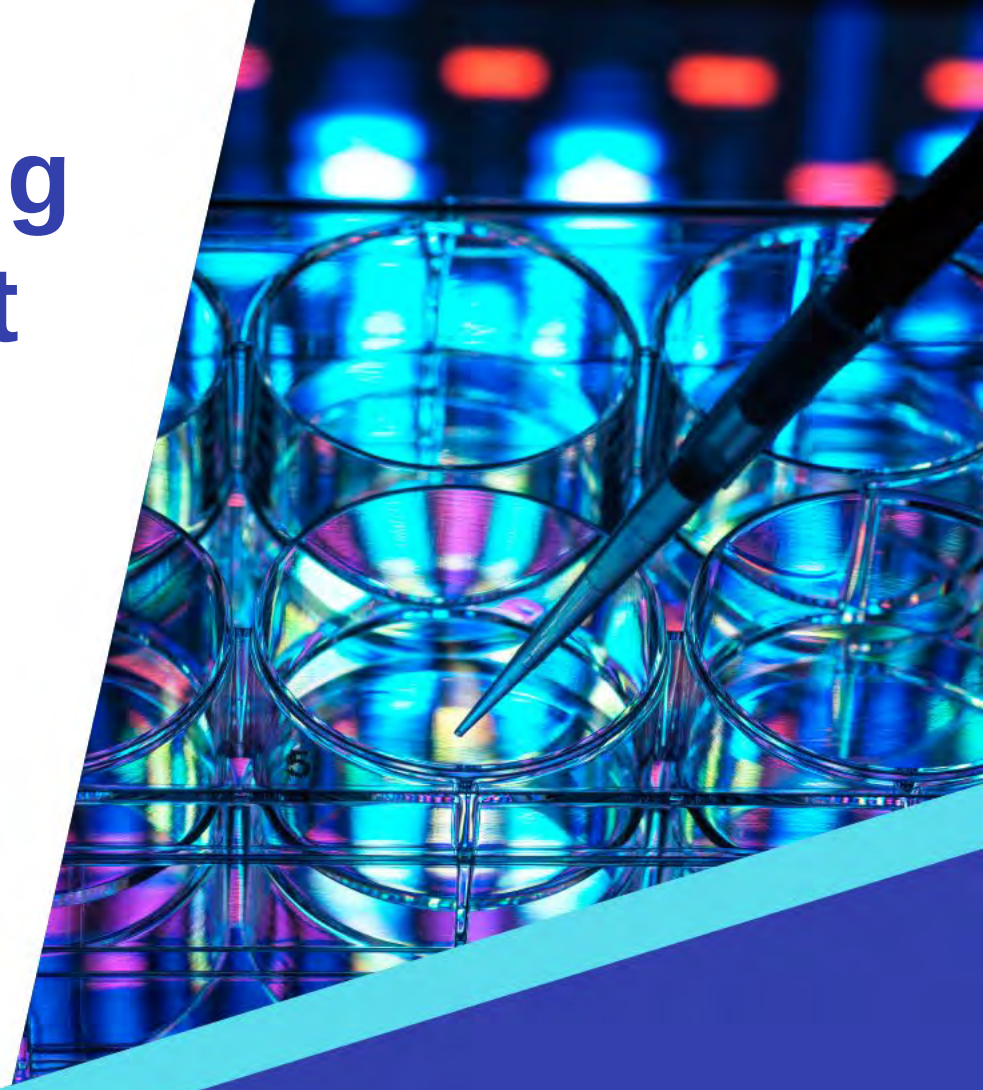
The Role of Biomarker Testing and Sequencing in Treatment Selection



Saketh Guntupalli, MD

University of Colorado
School of Medicine
Aurora, Colorado, USA

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Sequencing Treatment in Low Grade Ovarian Cancer

Surgical Debulking

- Mainstay of treatment
- Goal is R0 resection with removal of all visible disease
- Most predictive of survival
- Consultation with other services vital
- Peritonectomy

Adjuvant Therapy

- Molecular and targeted therapy testing
- *KRAS* testing is vital
- Other genetic testing
- Treatment with chemotherapy
  - Carbo/Taxol
- Additional of anti-estrogen therapy/hormonal
  - Aromatase Inhibitors
- Maintenance therapy

Recurrent disease

- Surgical resection for oligometastatic disease
- MEK Inhibitors
- Trametinib
- Retreatment with AI
- Avutometinib/Defactinib
- Clinical Trial
- Palliative Care

Molecular and Clinical Features of LGSOC and HGSOC

LGSOC accounts for <10% of new epithelial ovarian cancers

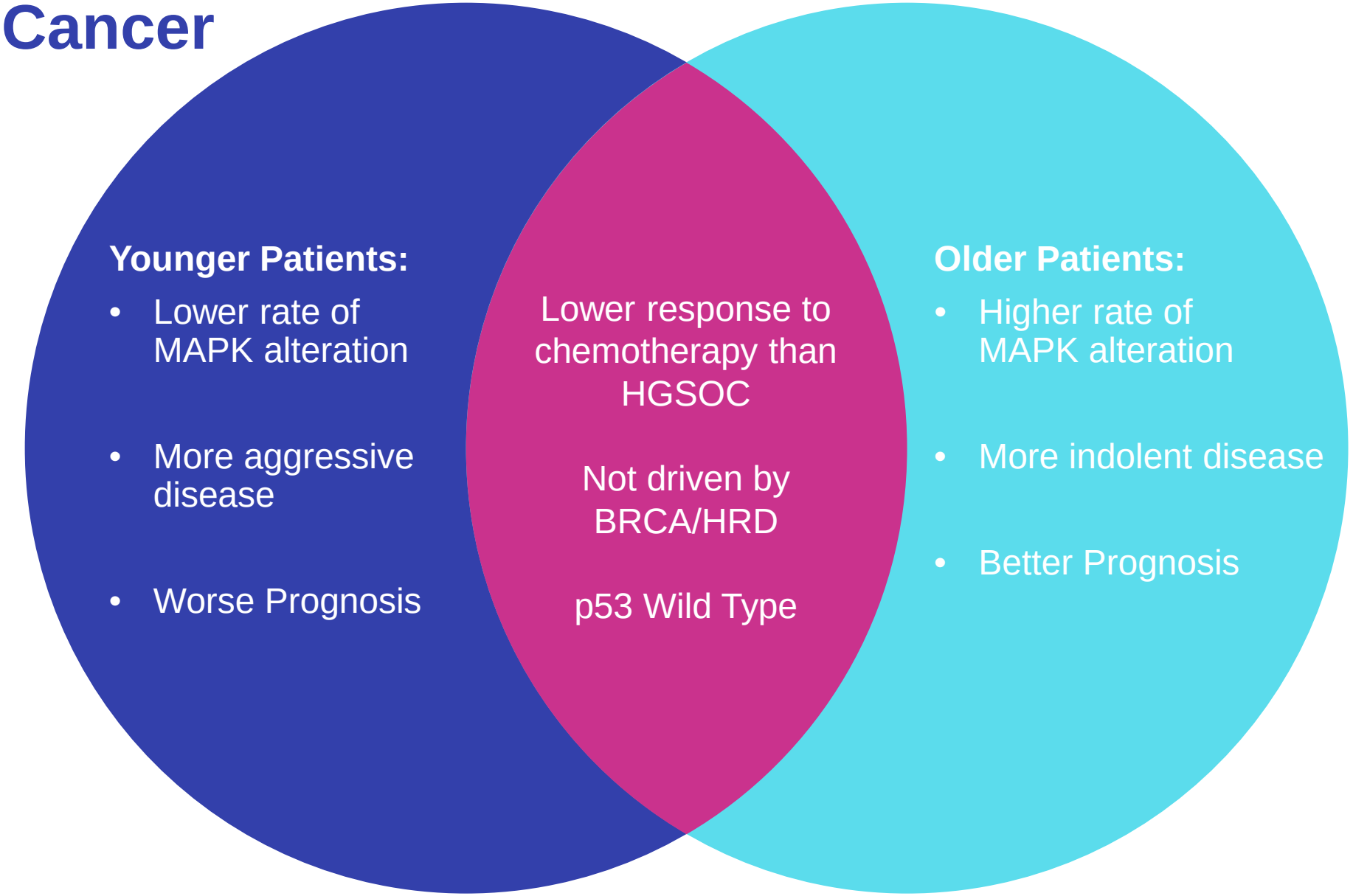
LGSOC | **HGSOC**

Clinical/Molecular Features	LGSOC	HGSOC
Median age at diagnosis[2,3]	40-50 years	50-60 years
Molecular genetics[4-6]	Mutant: *BRAF*, *RAS* Wild type: *p53*	Mutant: *p53*, *BRCA*, *HRD* Wild type: *BRAF*, *RAS*
GOG158 (stage III, optimal) upfront chemotherapy; BICR (paclitaxel + carboplatin)[3]	n=21 PFS: 45.0 months OS: 126.2 months	n=220 PFS: 19.8 months OS: 53.8 months
Response rate to neoadjuvant chemotherapy[7-9]	4%-23%	80%-90%
Response to chemotherapy in the recurrent setting (weekly paclitaxel, topotecan, or PLD)[10-13]	0%-15%	0%-30%
Rate of hormone receptor positivity[14-16]	ER: 58%-96% PR: 32%-76%	ER: 81%-86% PR: 31%-55%

BICR, blinded independent central review; BRAF, B-Raf proto-oncogene; BRCA, breast cancer gene; ER, estrogen receptor; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; LGSOC, low-grade serous ovarian cancer; OS, overall survival; p53, tumor protein p53 gene; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PR, progesterone receptor; RAS, rat sarcoma gene.

1. Grisham RN, et al, Int J Gyn Can. 2023;33(9):1331-1344; 2. Grisham RN. Oncology. 2016;30(7):650-652; 3. Bodurka DC, et al. Cancer. 2012;118(12):3087-3094; 4. Bookman MA, et al. J Natl Cancer Inst. 2014;106(4):1-8; 5. Mullany LK, et al. Endocrinology. 2012;153(4):1638-1648; 6. Vang R, et al. Adv Anat Path. 2009;16(5):267-282; 7. du Bois A, et al. J Clin Oncol. 2019;37(27):2398-2405; 8. Schmeler KM, et al. Gynecol Oncol. 2008;108(3):510-514; 9. Grabowski JP, et al. Gynecol Oncol. 2016;140(3):457-462; 10. Poveda AM, et al. J Clin Oncol. 2015;33(32):3836-3838; 11. Monk BJ, et al. J Clin Oncol. 2020;38(32):3753-3762; 12. Gershenson DM, et al. Gynecol Oncol. 2009;114(1):48-52; 13. Pujade-Lauraine E, et al. J Clin Oncol. 2014;32(13):1302-1308; 14. Chen S, et al. Sci Rep. 2017;7(1):16922; 15. Sieh et al, Lancet Oncol, 2013;14(9):853-862; 16. Gadducci A, Cosio S. Cancers. 2020;12(5):1336.

Clinical Characteristics of Low Grade Serous Ovarian Cancer



FOLR1+ Inversely Associated with MAPK Alteration

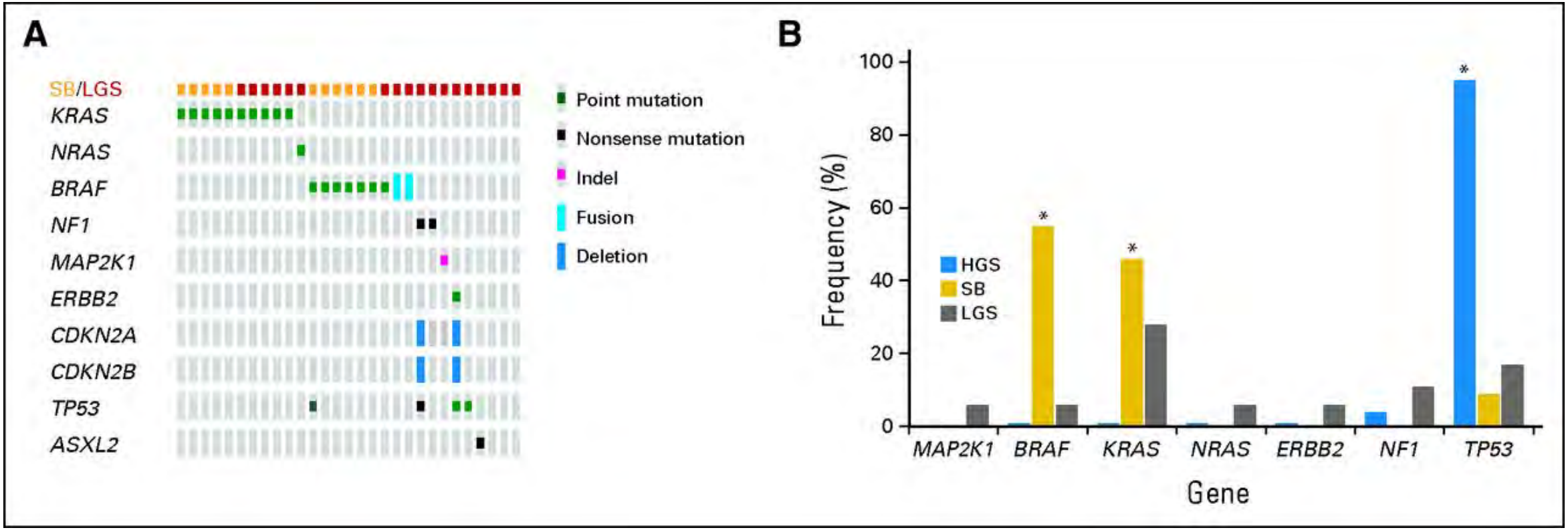
- Overall, 45 of 78 sequenced tumors (58%) had MAPK alteration.

- Negative association between FRa positivity and MAPK pathway alteration ($p<0.001$):
  - **20%** (9 of 45) of LGSOC **with MAPK** alteration were **FRa positive**.
  - **61%** (20 of 33) of LGSOC **without MAPK** alteration were **FRa positive**

***Manning-Geist**, Sullivan, Zhou, Iasonos, Selenica, Stallworth, Liu, Roche, Gordhandas, Aghajanian, Chi, O'Cearbhaill, **Grisham,** Chui; Gyn Onc, 2024.*

Frequent MAPK Pathway Alterations

Serous Borderline Tumors (n=11)
Low Grade Serous Cancer (n=18)



***Grisham**, Sylvester, Won, McDermott, DeLair, Ramirez, Yao, Shen, Dao, Bogomolniy, Makker, Sala, Soumerai, Hyman, Socci, Viale, Gershenson, Farley, Levine, Rosen, Berger, Spriggs, Aghajanian, Solit, **Iyer;** J Clin Oncol, 2015.*

Diagnosis of LGSOC: Key Biomarkers[1–4]

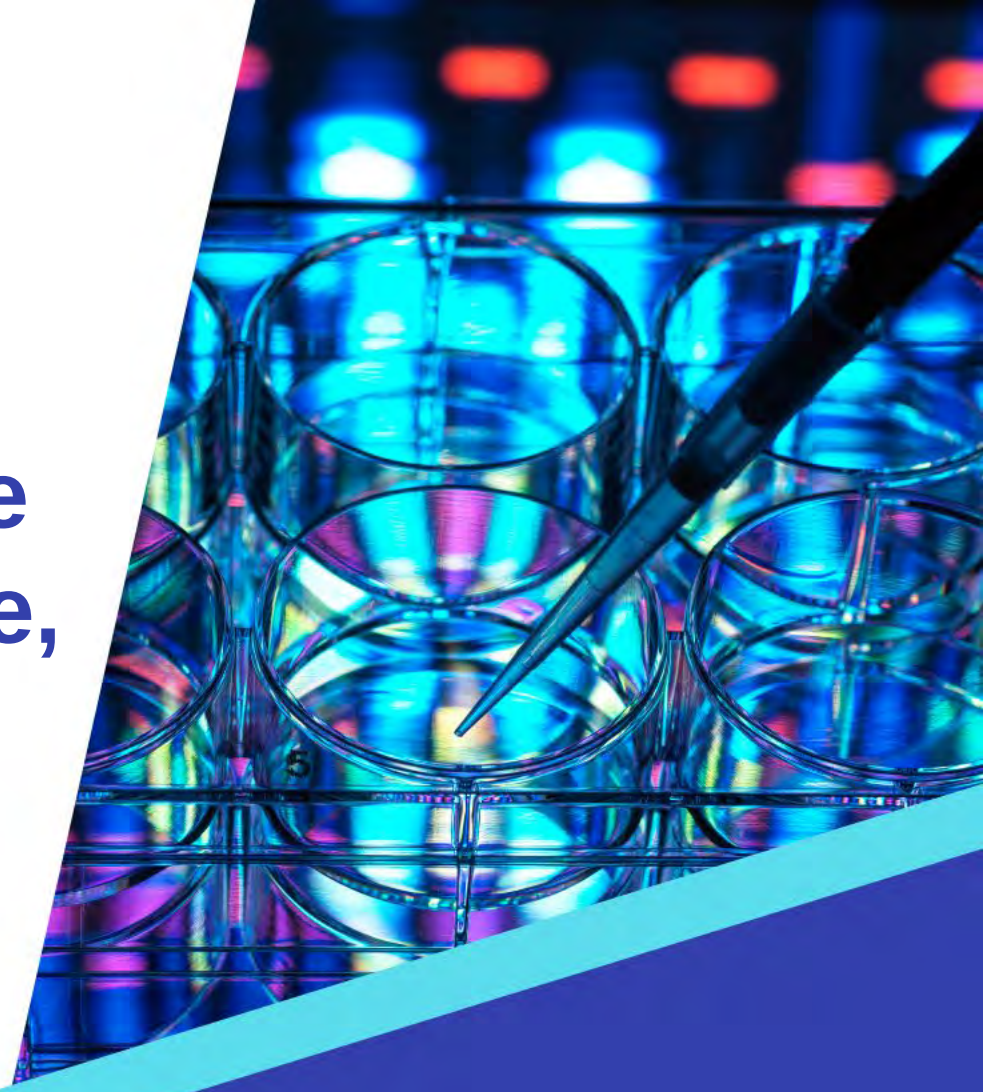
~80% of patients are diagnosed in an advanced stage, highlighting the need for an early and accurate diagnosis.

Predictive Biomarker Testing in Ovarian Cancer: NGS vs IHC

KRAS Mutation Testing: Concordance in Tumor vs Blood Samples

Panel Discussion: Managing Side Effects, Optimizing Quality of Life, and Access to Treatment

All Faculty



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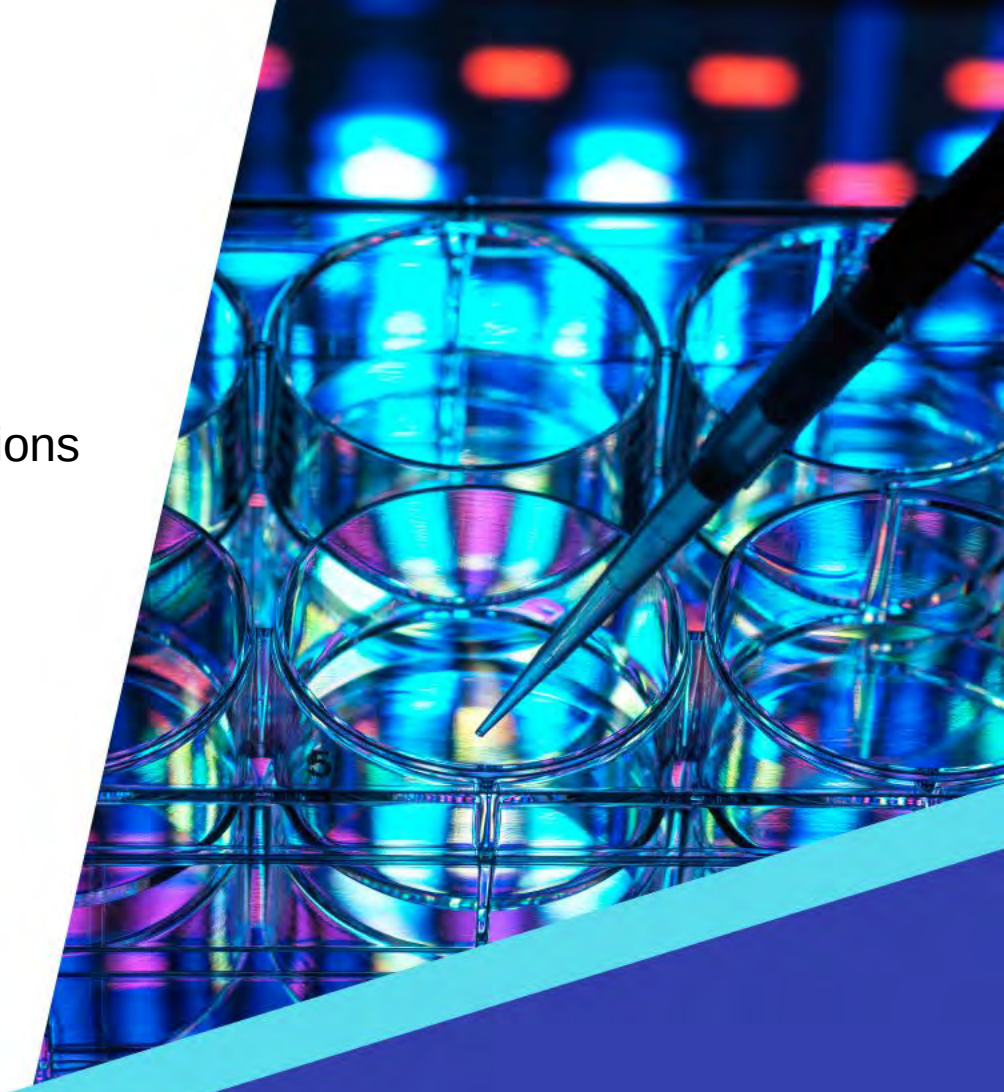
Case Studies:
Audience Engagement

Please scan the QR Code below to participate in the audience questions



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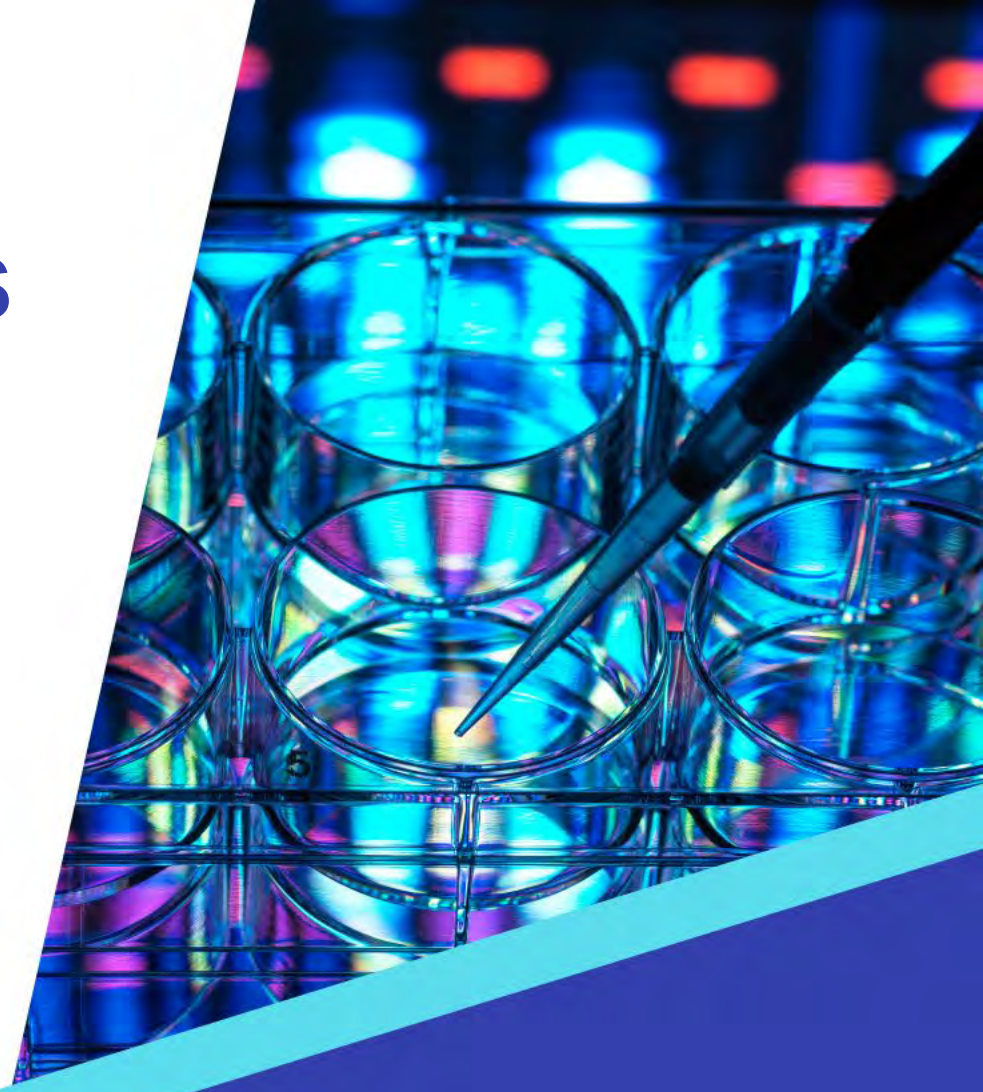
Case 1
Key Discussion Questions

- Should we be testing early?
- How does uncovering a *KRAS* or *BRAF* mutation at diagnosis reshape our counseling, surveillance, or fertility discussions?
- In a young woman with Stage IA disease and strong ER/PR positivity, is observation truly enough, or could there ever be a role for adjuvant hormonal therapy?



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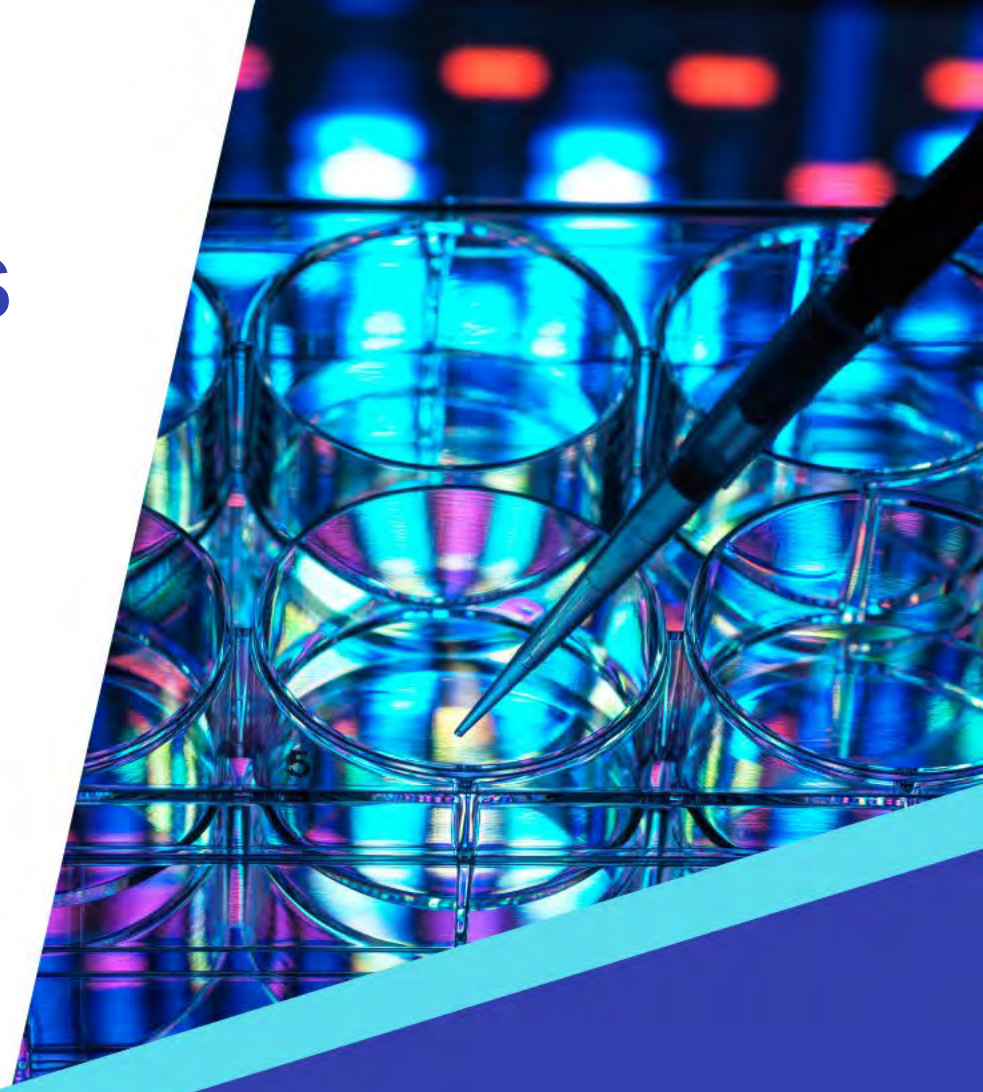
Case 2
Key Discussion Questions

- How do we define *treatment resistance* in low-grade serous ovarian carcinoma, and when should we pivot from hormonal to targeted therapy?
- At what point do we stop thinking of LGSOC as “chemoresistant” and start managing it as a chronic, pathway-driven disease?
- How should we think about sequencing? Should targeted combinations come earlier, before cumulative platinum exposure blunts biology?
- If progression occurs on avutometinib + defactinib, what biological space do we explore next?
- Could lessons from hormone-driven breast cancer help reshape treatment for these rare ovarian tumors?



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Closing Remarks and Key Takeaways

Brian Slomovitz, MD

Mount Sinai Medical Center

Miami Beach, Florida, USA

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Thank You

View this symposium as part of the IGCS on-demand program following the meeting

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