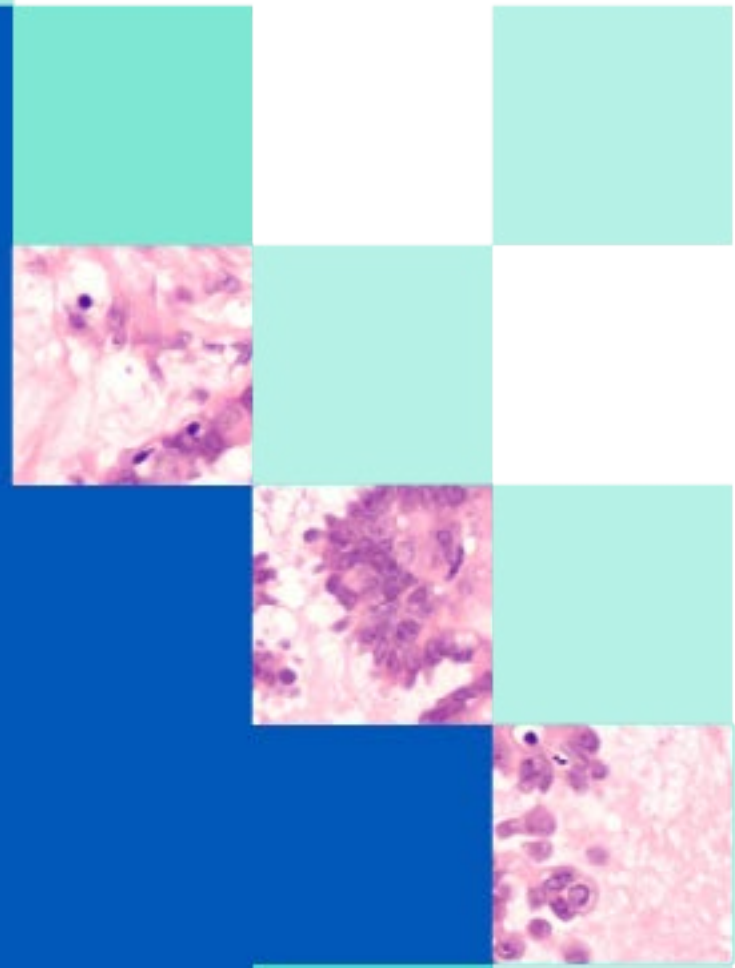
An Industry Supported Symposium at the
2025 SGO Annual Meeting on Women's Cancer

Advancing Care in Recurrent Low-Grade Serous Ovarian Cancer: *A Case Based Approach*

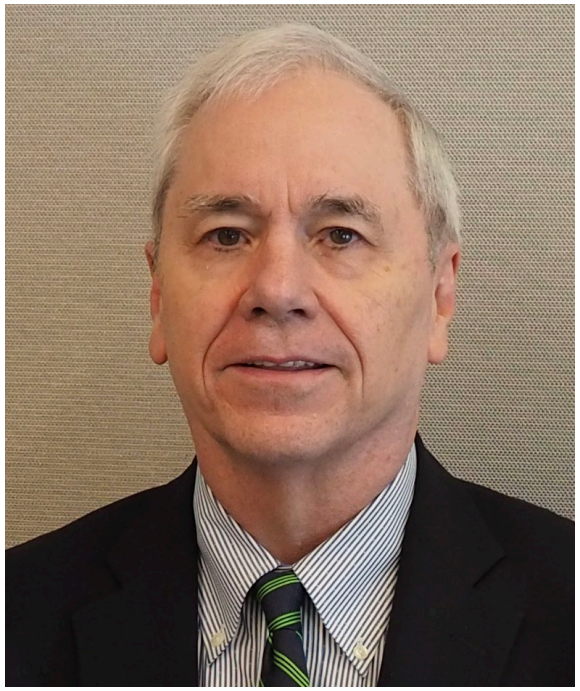


Monday, March 17, 2025 | 7:00 am – 8:15 am PDT

Seattle, Washington, USA

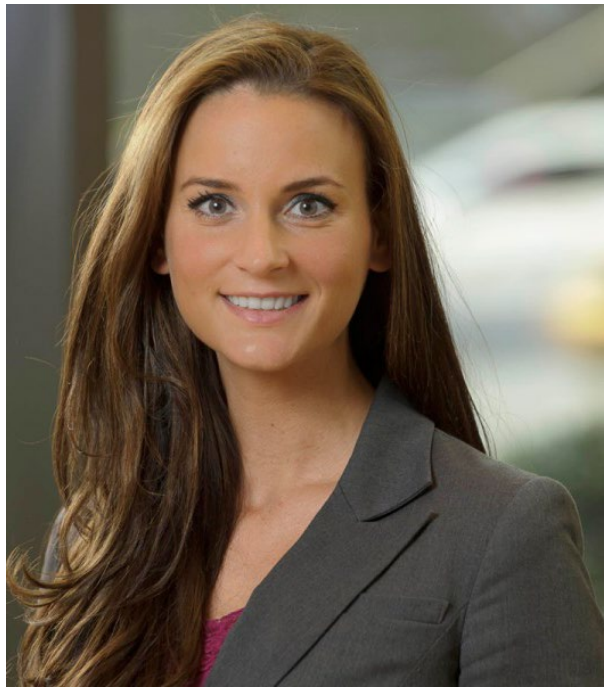
Moderator | Faculty

Brian Slomovitz, MD, FACOG
Mount Sinai Medical Center
Miami Beach, FL, USA



David M. Gershenson, MD
University of Texas
MD Anderson Cancer Center
Houston, TX, USA

Isabelle Ray-Coquard, MD, PhD
Centre Léon Bérard
Lyon, France



Rachel N. Grisham, MD
Memorial Sloan Kettering Cancer Center
New York, New York, USA

Disclosures

Speaker Name	Role in Activity	Name of Ineligible Company(ies) and Nature of Financial Relationships
Dr. Brian Slomovitz	Moderator	**Consultant:** Aadi; AstraZeneca Eisai; Gilead; Immunocore; Incyte; Merck; Novocure; Regeneron; Seagen
Dr. David Gershenson	Speaker	**Advisor** *(no compensation):* Genetech **Author (Royalties):** UpToDate **Author(Royalties)/Editor:** Elsevier **Consultant, Steering Committee:** Verastem **Equity Interest:** Bristol Myers Squibb; Johnson & Johnson; Procter and Gamble
Dr. Isabelle Ray-Coquard	Speaker	**Consultant/Speaker:** Abbvie; Adaptimmune; Agenus; Amgen; AstraZeneca; BMS; Clovis; Corsett; Daiichi Sankyo; Deciphera; Eisai; EQRX; GSK; Immunogen; Immunocore; Loxo Lilly; Merck Serono; MacroGenics; MSD; Mersana; Novartis; Onxeo; Pharmamar; Roche; Sutro Biopharma; Verastem; Zentalis
Dr. Rachel N. Grisham	Speaker	**Consultant:** AstraZeneca; Genmab; GSK; Incyte; Myriad; SpringWorks; Verastem

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Participants who complete the educational activity, pre-/post-tests, and evaluation, will receive certificate of credit.

Complete our Pre-Test!

Agenda

7:00 – 7:05 am: **Welcome and Introductions**
Brian Slomovitz, MD, FACOG; Mount Sinai Medical Center; Miami Beach, Florida, USA

7:05 – 7:25 am: **Current Clinical Landscape of First-Line Therapy for Newly Diagnosed LGSOC**
David M. Gershenson, MD; University of Texas MD Anderson Cancer Center, Houston, TX, USA

7:25 – 7:45 am: **Case 1: Incorporating Best Available Approaches in the Management of LGSOC**
Isabelle Ray-Coquard, MD, PhD; Centre Léon Bérard, Lyon, France

7:45 – 8:05 am: **Case 2: Incorporating Best Investigational Strategies in the Management of LGSOC**
Rachel N. Grisham, MD; MSK Cancer Center; West Harrison, New York, USA

8:05 – 8:15 am: **Closing Remarks**
Brian Slomovitz, MD, FACOG; Mount Sinai Medical Center; Miami, Florida, USA

Learning Objectives

- Describe the challenges in managing recurrent low-grade serous ovarian cancer (LGSOC) and understand the clinical complexities associated with this disease
- Summarize the most recent clinical trial data and treatment options for recurrent LGSOC, with a focus on novel therapies and combination treatment strategies
- Discuss best practices for clinical management and outline potential future directions in the treatment of recurrent LGSOC

Current Clinical Landscape of First-Line Therapy for Newly Diagnosed LGSOC

David M. Gershenson, MD

University of Texas MD Anderson Cancer Center
Houston, Texas, USA

Primary Treatment for LGSOC

- Primary surgery is preferred initial treatment
- If US reveals complex ovarian mass, CA 125 is elevated, or CT reveals possible metastatic disease, referral to gyn onc
- Surgical Procedure:
  - If tumor apparently confined to ovary(ies), TAH + BSO, and comprehensive surgical staging (omentectomy, multiple biopsies, cytology, etc.) in patients who have completed childbearing
  - Fertility-sparing surgery (FSS) in young patients
  - Oocyte retrieval (IVF) may be considered after FSS
  - If tumor is obviously metastatic, then cytoreductive surgery to achieve no gross residual disease: TAH + BSO, omentectomy, resection of all tumor

Primary Surgery: Stages II-IV LGSOC

Study	No. Pts	Stages	Median PFS (mos)			Median OS (mos)		
			0	≤ 1 cm	> 1 cm	0	≤ 1 cm	> 1 cm
Fader AN, et al. *Obstet Gynecol.* (2013). **GOG-0182**	189	III, IV	33.2	14.7	14.1	96.9	44.5	42.0
Grabowski JP, et al. *Gynecol Oncol.* (2016).	145	III, IV	92	32	15	97	60	35
Di Lorenzo P, et al. *Front Oncol.* (2022).	92	III, IV	38.3	23.3	14.8	142.3	86.4	35.2
May et al.	381	I-IV	Ref.	HR = 2.42		Ref.	HR = 2.53	
Gershenson DM, et al. *Gynecol Oncol.* (2022).	99	II, III	Ref.	HR = 2.78		Ref.	HR = 2.75	
Vatansever D, et al. *J Surg Oncol.* (2021).	191	I-IV	Ref.	HR = 2.46		Ref.	HR = 3.61	

Important Considerations Following Surgery for LGSOC?

- Request a second opinion on the pathology?
  - SBT vs LGSOC
  - HGSOC vs LGSOC
  - Rare LGSOC/HGSOC cases
- Seek a second opinion regarding postoperative management?
- Postoperative baseline CT chest/abdomen/pelvis
- Genetic testing is recommended
- Genomic profiling is recommended
- Regardless of postoperative treatment, monitoring in Year 1 is CA 125 and CT every 3 months, then less frequently

First-Line Systemic Therapy for Stage II-IV LGSOC

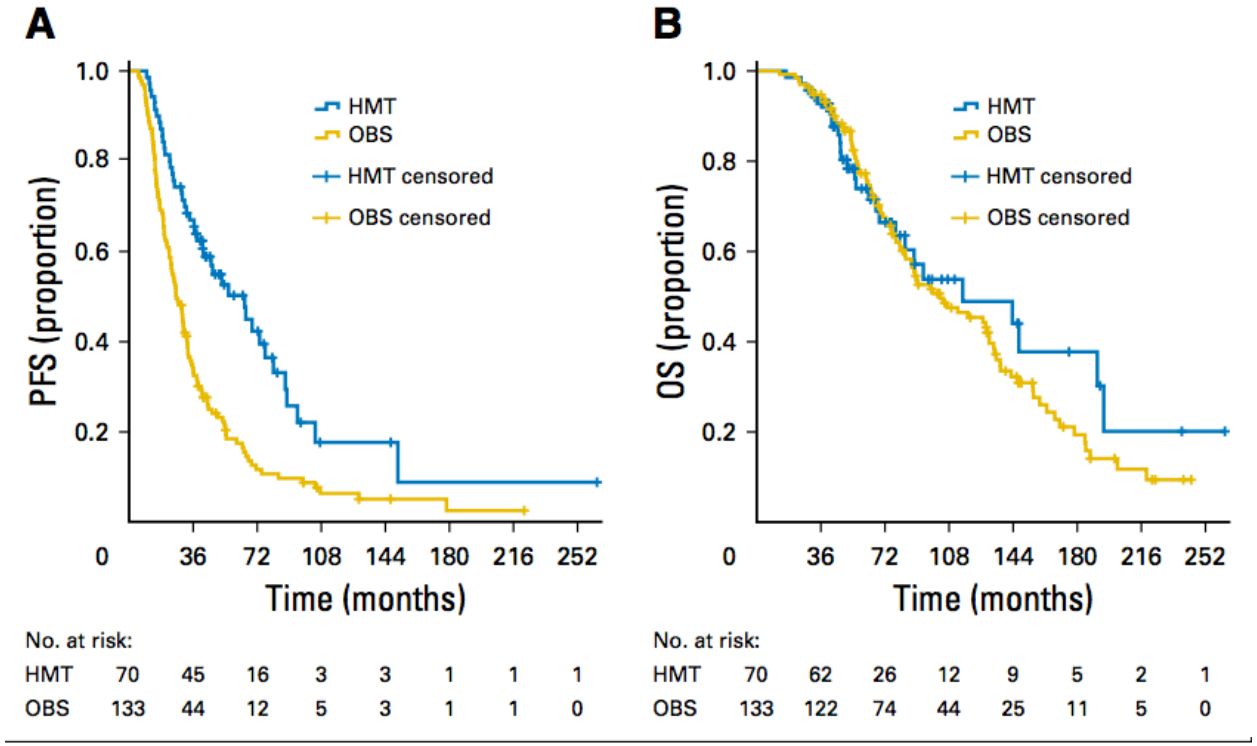
Stage II-IV LGSOC: Platinum-Based Chemotherapy Alone

Study	Period	No. Pts.	ORR (%)	Median PFS (mo)	Median OS (mo)
Gershenson DM, et al. *Obstet Gynecol. (*2006)	1978-2003	112	8/10 (80%)	19.5	81.8
Grabowski JP, et al. *Gynecol Oncol.* (2016).	2003-2010	145	9/39 (23.1%)	35	97
Gockley A, et al. *Obstet Gynecol.* (2017).	2003-2011	755	---	---	90.8
Manning-Geist BL, et al. *Cancer.* (2023).	1998-2021	124	7/12 (58%)	---	---
Gershenson DM, et al. *J Clin Oncol.* (2017)	1981-2013	133	---	26.4	102.7

Endocrine Therapy: Maintenance or Adjuvant

MD Anderson Study[1]

- 203 pts (133 OBS, 70 HMT)



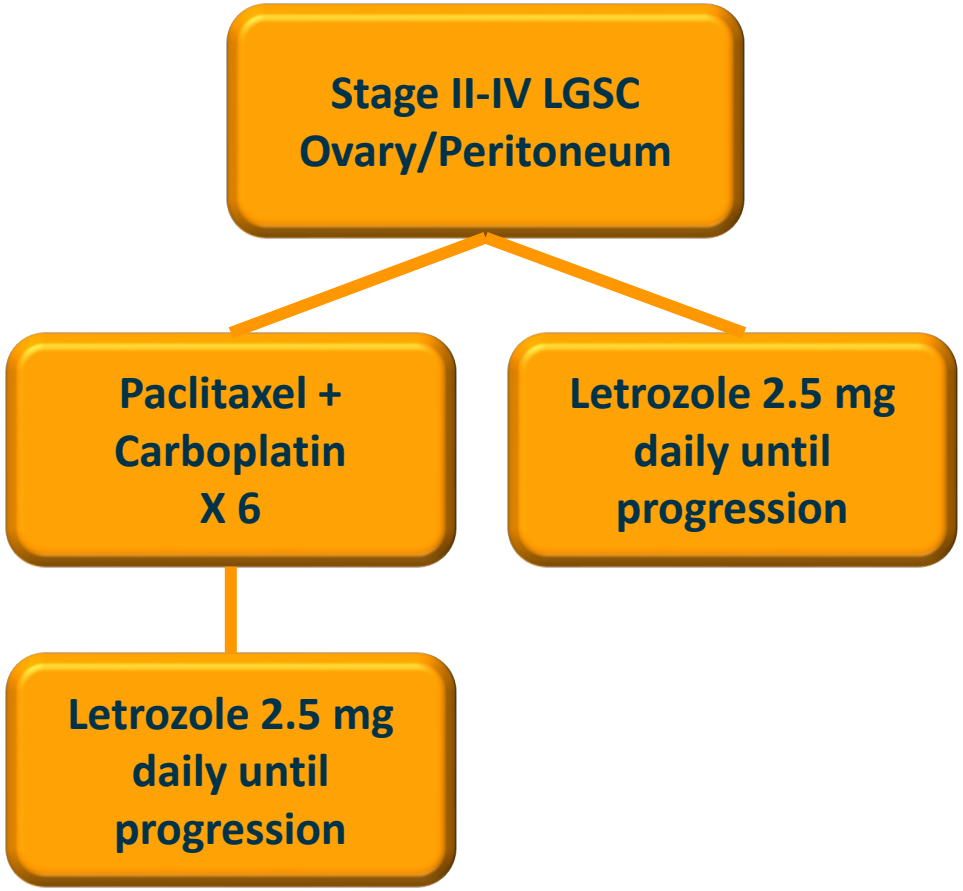
Johns Hopkins Study[2]

- 27 pts with stage II-IV LGSC
- Primary CRS + HT
- Median duration HT = 18 mo
- After median FU = 41 mo, 6 (22%) pts relapsed
- Median PFS and OS not reached
- 3-yr PFS = 79.0%
- 3-yr OS = 93.1%

1. Gershenson DM et al. *J Clin Oncol*. 2017;35:1103.; 2. Fader AN et al. *Gynecol Oncol.* 2017;147:85.

NRG-GY019: Randomized Phase III Trial of Paclitaxel/Carboplatin Followed by Maintenance Letrozole versus Letrozole Monotherapy in Stage II-IV Low-Grade Serous Carcinoma

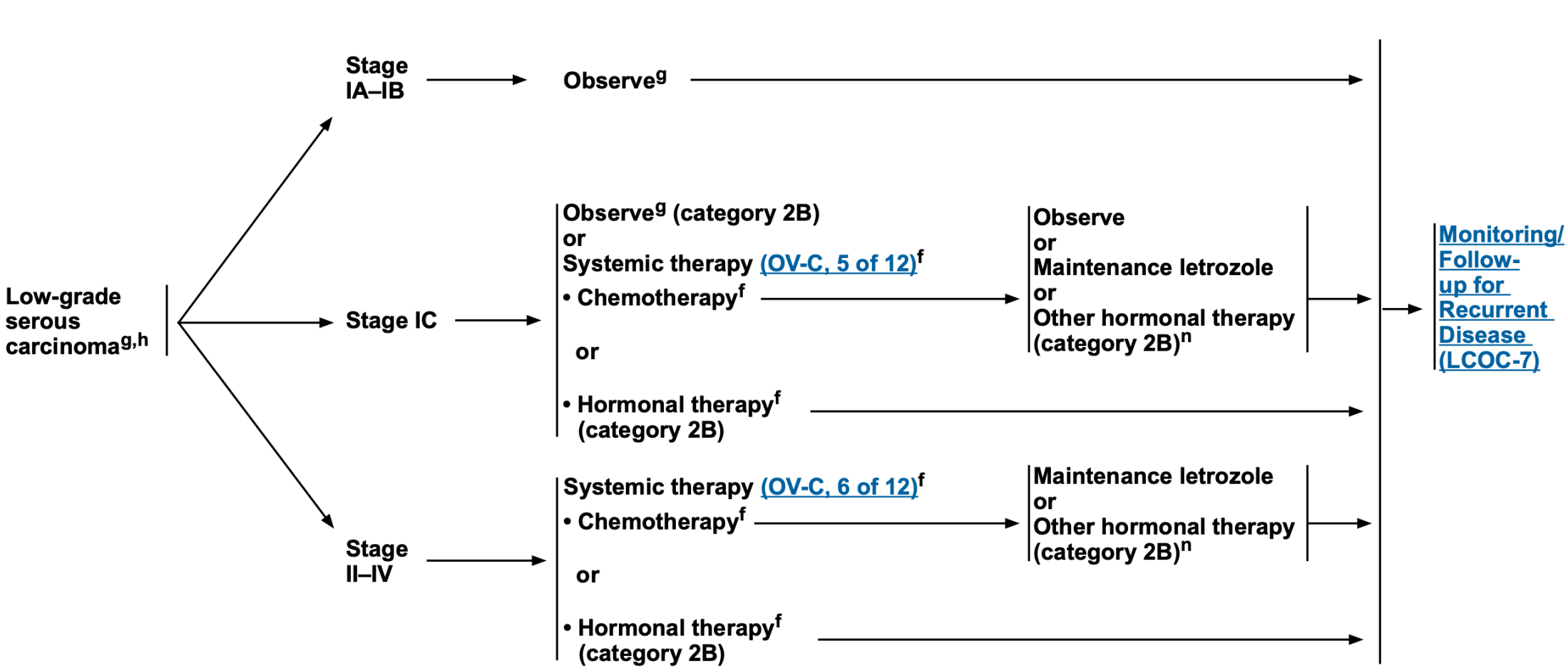
PI: Amanda Fader, MD
NCT04095364



- Sponsor: NCI (NRG Oncology)
- International phase III trial
- Primary Objective: PFS
- Target: 450 pts
- *Accrual will be complete in 2025*

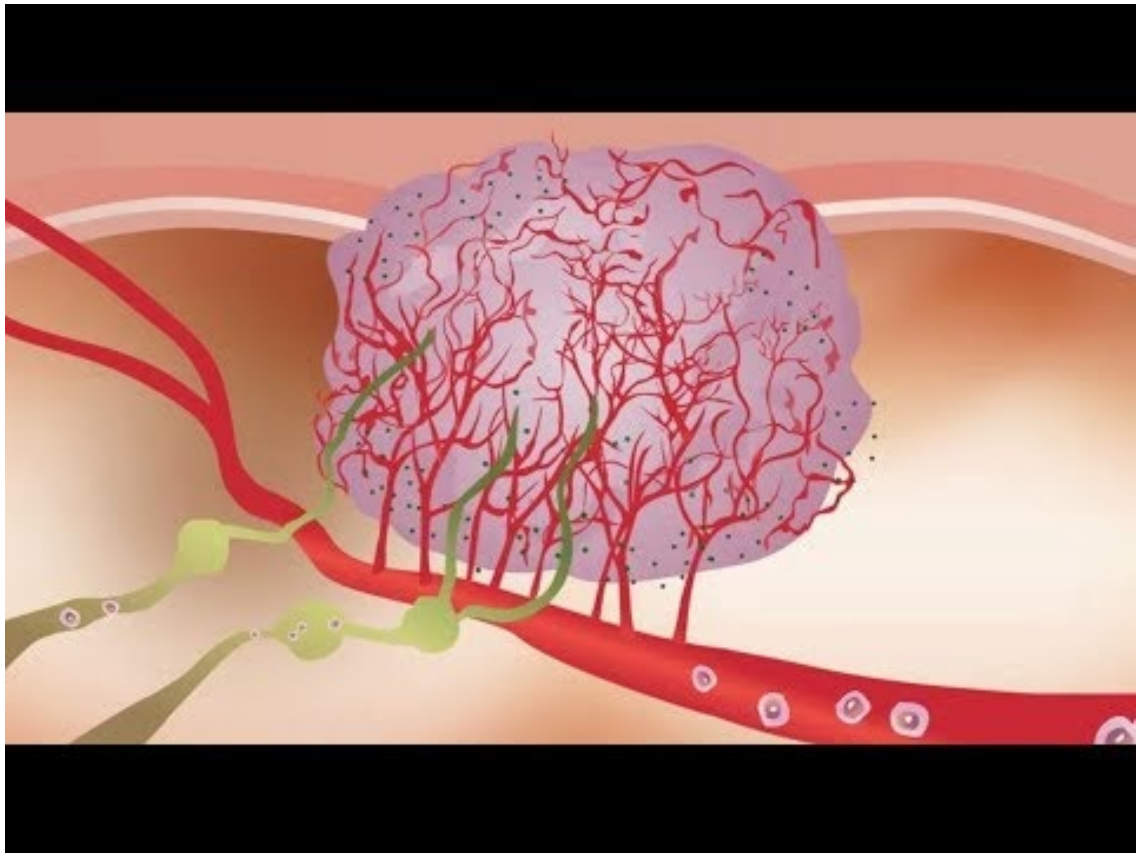
https://clinicaltrials.gov/study/NCT04095364.

NCCN Guidelines Version 3.2024
Low-Grade Serous Carcinoma



Is There a Role for Bevacizumab in First-Line Therapy for LGSOC?

Study	No. Patients	Outcome
Grisham RN, et al. *Int J Gynecol Cancer.* 2014.	17	CR = 0 PR = 40% SD = 33%
Dalton HJ, et al. *Gynecol Oncol.* 2017.	40 *(45 separate regimens)*	CR = 7.5% PR = 40% SD = 30%



MITO 22: Chemotherapy + Bev in First-Line Treatment of LGSOC

Cohort	No. Pts.	ORR (%)	Median PFS (mo)
CT alone	59	19/30 (63)	22.6
CT + Bev	29	8/8 (100)	47.9

Musacchio L, et al. *Gynecol Oncol.* (2023).

Role for Neoadjuvant Chemotherapy in LGSOC?

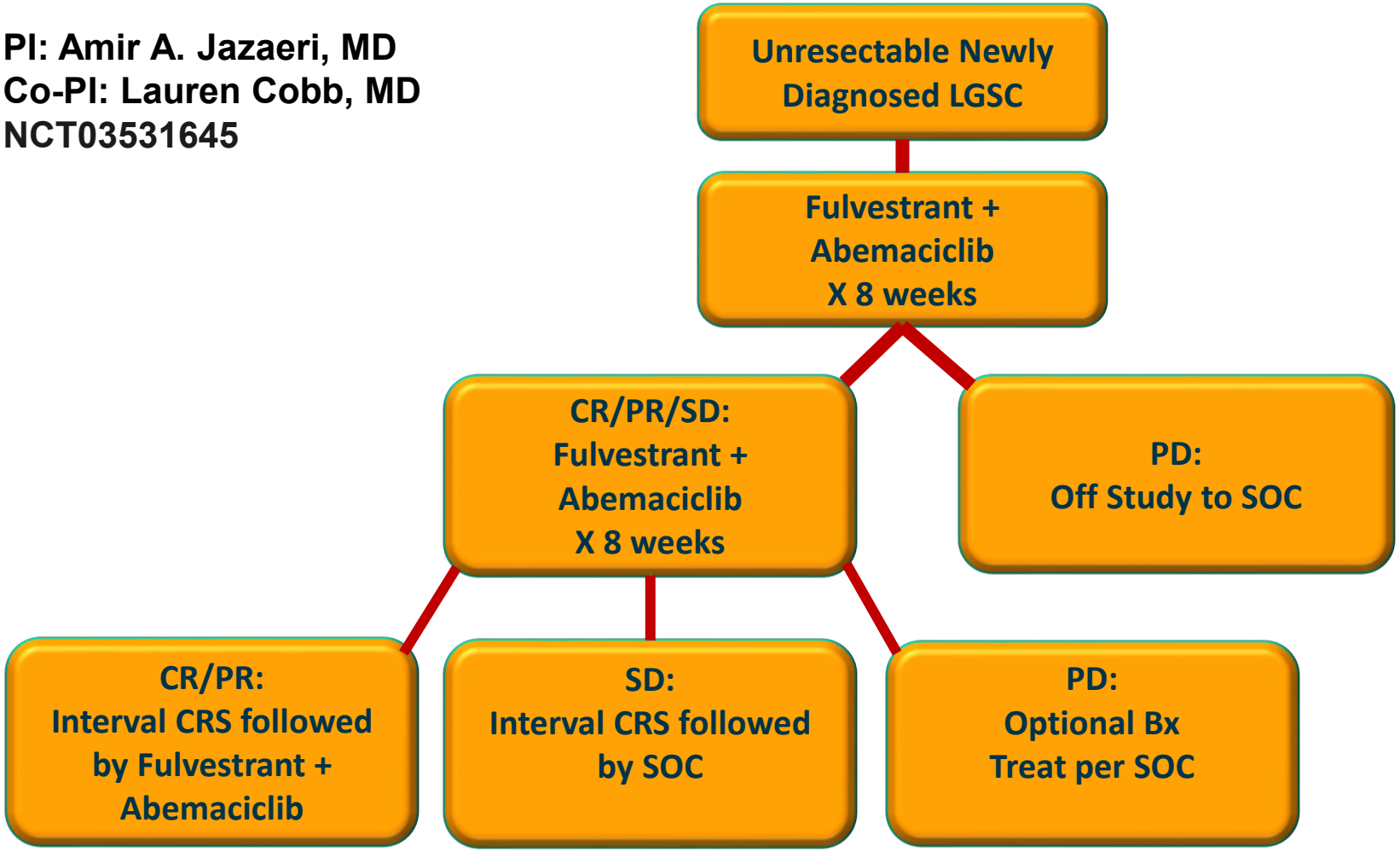
- Neoadjuvant chemotherapy is not preferred approach in LGSOC
- However, small proportion of pts may be candidates based on presence of extensive tumor or comorbidities
- Decision should be made by gynecologic oncologist
- There are no absolute criteria for selection of NACT
  - Imaging
  - Laparoscopic assessment
- Consists of systemic treatment (3-6 cycles) followed by interval cytoreductive surgery and further systemic therapy
- Two studies documented increase in NACT for LGSOC in US

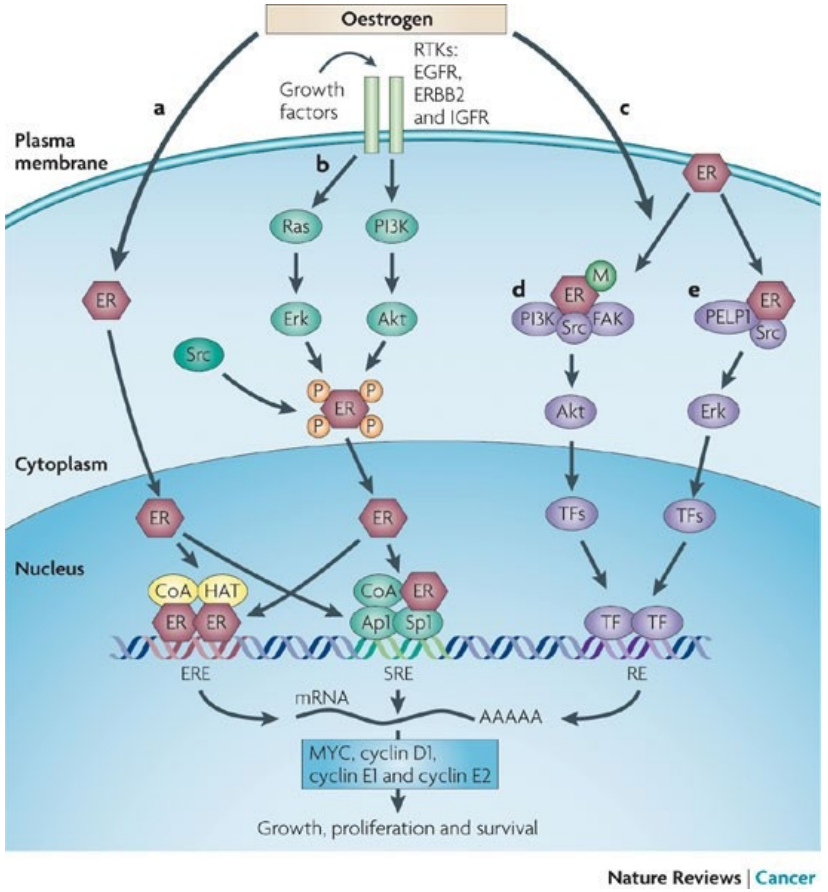
Neoadjuvant Chemotherapy in LGSOC

Study	No. Pts	ORR (%)	SD (%)	PD (%)	Interval CRS	Median PFS (mos)	Median OS (mos)
LGSOC Cobb LP, et al. *Gynecol Oncol* (2020).	36	11%	83%	6%	29 (80.6%)	18.5	47.4
HGSOC Cobb LP, et al. *Gynecol Oncol* (2020).	36	75%	25%	0%	32 (88.9%)	16.4	48.2
LGSOC Manning-Geist BL, et al. *Cancer.* (2023).	11	9%	91%	0%	---	---	---

Pilot Study of Neoadjuvant Fulvestrant + Abemaciclib in Low-Grade Serous Ovarian Cancer

PI: Amir A. Jazaeri, MD
Co-PI: Lauren Cobb, MD
NCT03531645





https://clinicaltrials.gov/study/NCT03531645#study-overview

Neoadjuvant Therapy for LGSOC

NACT Carboplatin/Paclitaxel Chemotherapy[1]

RECIST 1.1	# of Subjects	
Partial Response	4	11.1%
Complete response	0	0%
SD	30	83.3%
ORR	4	11.1%
PD	2	5.5%
Total	36	100%

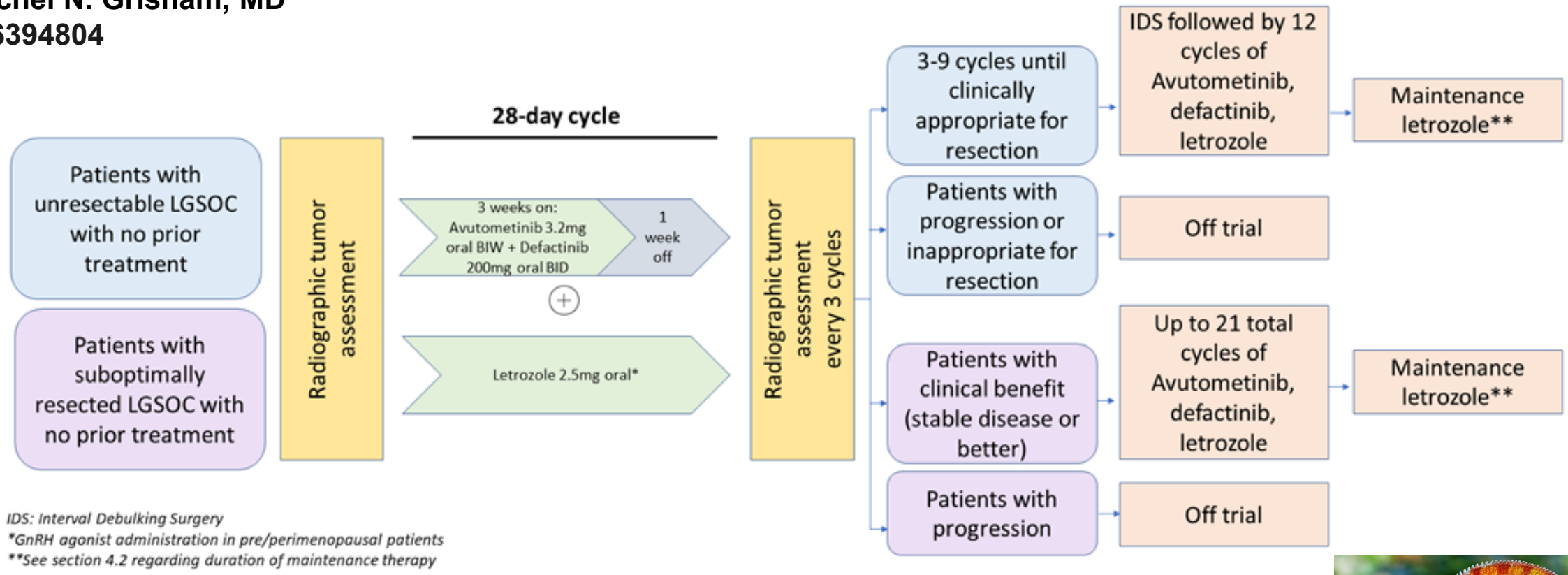
2017-0405: Neoadjuvant Fulvestrant + Abemaciclib[2]

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%

1. Cobb LP, et al. *Gynecol Oncol.* (2020).; 2. Cobb LP, et al. ASCO 2022.

Combination targeted and Hormonal treAtMEnt of Low-gradE serous Ovarian cancer in the upfroNt setting (CHAMELEON) Study Schema

PI: Rachel N. Grisham, MD
NCT06394804



IDS: Interval Debulking Surgery
**GnRH agonist administration in pre/perimenopausal patients*
***See section 4.2 regarding duration of maintenance therapy*

https://clinicaltrials.gov/study/NCT06394804#study-overview

Case: Lilian

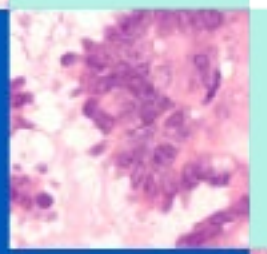
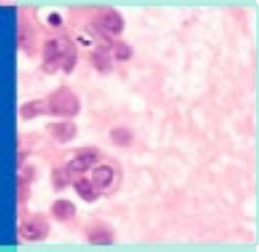
- 28 y/o woman who presented with pelvic pain. US revealed 8 cm complex left ovarian mass suspicious for endometriosis. Preoperative evaluation did not include CA 125 or CT
  - Her obstetrician-gynecologist performed laparoscopic LSO and biopsy of cul-de-sac mass, both of which revealed high-grade serous carcinoma
  - Referred to GYN ONC, who performed CA 125 = 306 and CT that revealed omental mass and mass posterior to the uterus. She underwent second surgery consisting of Xlap, TAH + RSO, omentectomy, pelvic and paraaortic lymphadenectomy. Pathology again revealed stage IIIC high-grade serous carcinoma
  - Lilian sought second opinion at an academic center. **Pathology review revealed low-grade serous carcinoma, not high-grade serous carcinoma.** Genetic testing was negative, and genomic profiling revealed no mutations

What is the Preferred Postoperative Therapy for Lilian?

- Carboplatin/paclitaxel X 6 cycles
- Carboplatin/paclitaxel/bevacizumab X 6 cycles followed by bevacizumab maintenance therapy
- Carboplatin/paclitaxel X 6 cycles followed by letrozole maintenance therapy
- Letrozole monotherapy
- Clinical trial

Case 1: Incorporating Best Available Approaches in the Management of LGSOC

Isabelle Ray-Coquard, MD, PhD
Centre Léon Bérard
Lyon, France

Acknowledgements

Thank you to Dr Antonella De Palma of
Centre Léon BÉRARD in
Lyon, France for his contributions to the case studies.

Dr. Ray-Coquard, Case 1 | 61-year-old patient

1° case

- Diagnosis of low-grade serous adenocarcinoma since 2002
- No comorbidities
- No concomitant medications

History of the Disease

- **2002 diagnosis:** Low-grade serous adenocarcinoma of the ovary, FIGO stage III (ER 100%, PR 0%)
  - ➔ Cytoreductive surgery CCO, followed by 6 cycles of adjuvant CARBOPLATIN-TAXOL

History of the Disease *cont.*

- **2002 diagnosis:** Low-grade serous adenocarcinoma of the ovary, FIGO stage III (ER 100%, PR 0%)
  - ➔ Cytoreductive surgery CCO, followed by 6 cycles of adjuvant CARBOPLATIN-TAXOL
- **2011:** Supradiaphragmatic and infradiaphragmatic nodal recurrence → 6 cycles of CARBOPLATIN, GEMCITABINE, and BEVACIZUMAB; followed by BEVACIZUMAB maintenance for 18 months

LGSC |Treatment for Recurrence: Chemotherapy

- **N: 58 evaluable patients** with recurrent LGSC received **108** separate chemotherapy regimens **("patient-regimens")**:
  - **ORR: 4 responses (1 CR+ 3 PR)= 3.7%**
    - ✓ **platinum-sensitive cohort** (61 patient- regimens):
      - 1CR+2PR= ORR: 4.9%,
    - ✓ **platinum-resistant cohort** (47 patient-regimens):
      - 1PR=ORR 2.1%
    - ✓ **Differences in response by platinum status did not reach statistical significance (P=0.63)**
  - **Stable disease(SD)** observed in 65 **(60.2%)** of 108 patient-regimens
  - Median OS 87.1 months
  - **Median time to progression was 7.2 months**

- Despite its limitations (retrospective and descriptive) study findings indicate: **LGSC is less chemosensitive than its HGSC counterpart**
- Remains unclear whether high rate of SD is due to tumor biology or effects of therapy
- **All the above supports exploration of novel targeted agents for this disease**

Response to chemotherapy by regimen and platinum status

Regimen	CR		PR		SD		PD		Total
	PSe	PRe	PSe	Pre	PSe	PRe	PSe	PRe	
Carboplatin	1	0	2	0	14	1	7	0	25
Liposomal doxorubicin	0	0	0	0	2	9	4	6	21
Paclitaxel	0	0	0	1	6	3	2	2	14
Paclitaxel/carboplatin	0	0	0	0	7	0	3	0	10
Topotecan	0	0	0	0	3	2	1	4	10
Oral etoposide	0	0	0	0	1	4	0	1	6
Gemcitabine	0	0	0	0	1	2	1	1	5
Capecitabine	0	0	0	0	1	3	0	1	5
Weekly paclitaxel	0	0	0	0	0	2	0	2	4
Hexamethyl-melamine	0	0	0	0	0	0	0	2	2
Carboplatin/gemcitabine	0	0	0	0	1	0	0	0	1
Cisplatin/5 fluorouracil	0	0	0	0	0	0	0	1	1
Cisplatin/etoposide	0	0	0	0	1	0	0	0	1
Irinotecan	0	0	0	0	1	0	0	0	1
Docetaxel	0	0	0	0	0	0	1	0	1
Docetaxel/carboplatin	0	0	0	0	1	0	0	0	1
Total	1	0	2	1	39	26	19	20	108

PSe = Platinum-sensitive; PRe = Platinum-resistant CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease.

Gershenson DM, et al. *Gynecol Oncol.* 2009;114:48–52.

LGSC | Targeting Angiogenesis: Bevacizumab

Recurrent LGSC

Grisham RN, et al. *Int J Gynecol Cancer.* 2014;24:1010–1014.

- **Retrospective Study**
  - **N= 17 pts (15 evaluable)**
    - 10 pts with ovarian LGSC
    - 3 pts with Peritoneal LGSC
    - 4 pts with STLMP
- **Treatment:**
  - Bevacizumab/Chemo: N=15pts
  - Bevacizumab alone: N= 2pts
- **Outcomes:**
  - RR: 40%
  - RR in the LGSC group: 55%

Recurrent LGSC

Schmeler KM, et al. *J Clin Oncol.* 2010;j.28.15_suppl.e15503.

- **Retrospective Study**
  - **N=21 pts (**13 patients evaluable)
  - **All previously treated** w chemotherapy and/or hormonal agents: **median of 4 regimens (range 1-11)**
- **Treatment:**
  - Bevacizumab/Chemo: N=20pts
  - Bevacizumab alone: N= 1pts
- **Outcomes:**
  - RR: 41%
  - SD: 18%

Further study is warranted to develop anti-VEGF therapy in this group of patients.

History of the Disease *cont.*

- **2002 diagnosis:** Low-grade serous adenocarcinoma of the ovary, FIGO stage III (ER 100%, PR 0%)
  - ➔ Cytoreductive surgery CCO, followed by 6 cycles of adjuvant CARBOPLATIN-TAXOL
- **2011:** Supradiaphragmatic and infradiaphragmatic nodal recurrence → 6 cycles of CARBOPLATIN, GEMCITABINE, and BEVACIZUMAB; followed by BEVACIZUMAB maintenance for 18 months
- **2014:** Locoregional relapse → cervical lymphadenectomy

Role of Surgery in Relapse *(retrospective data)*

Patient characteristics (N = 41).

Variable	Median (range)
Age at diagnosis (years)	41.3 (21.0, 73.7)
	n (%)
Ethnicity	
White	31 (75.6)
Black	4 (9.8)
Hispanic	3 (7.3)
Other	3 (7.3)
FIGO stage at initial diagnosis	
I or II	3 (7.3)
III or IV	35 (85.4)
Unknown	3 (7.3)
Disease status at end of primary cytoreductive surgery	
No gross residual	7 (17.0)
Gross residual	24 (58.5)
Unknown	10 (24.4)
Adjuvant therapy	
Surveillance	4 (9.8)
Chemotherapy	
Platinum + taxane	26 (63.4)
Platinum, single agent	5 (12.2)
Platinum + cyclophosphamide	3 (7.3)
Platinum + taxane + bevacizumab	1 (2.4)
Platinum + hormonal agent	1 (2.4)
Hormonal therapy	
Letrozole	1 (2.4)
Maintenance therapy	
Chemotherapy	
Platinum	2 (4.9)
Hormonal therapy	
Letrozole	4 (9.8)
Tamoxifen	5 (12.2)
Leuprolide acetate	1 (2.4)

Characteristics of patients undergoing secondary cytoreductive surgery (SCRS) (N = 41).

Variable	n (%)
Initial treatment at time of first progression/recurrence	
Chemotherapy	16 (39.0)
Surgery	25 (61.0)
Platinum status at the time of SCRS	
Resistant	17 (41.5)
Sensitive	19 (46.3)
Did not receive any platinum-based chemotherapy	5 (12.2)
Disease status at end of SCRS	
No gross residual	9 (22.0)
Gross residual	32 (78.0)
Complications	
Hemorrhage requiring transfusion	11 (26.8)
Pneumonia	2 (4.9)
Abscess	1 (2.4)
Anastomotic leak	1 (2.4)
Bacteremia	1 (2.4)
Cystotomy	2 (4.9)
Enterotomy	1 (2.4)
ICU admission	2 (2.4)
Pancreatitis	1 (2.4)
Urinary tract infection	1 (2.4)
Wound infection	1 (2.4)
Readmission for small bowel obstruction	1 (2.4)

Crane EK. *Gynecol Oncol.* 2015.

OS Post-Surgery in Relapse

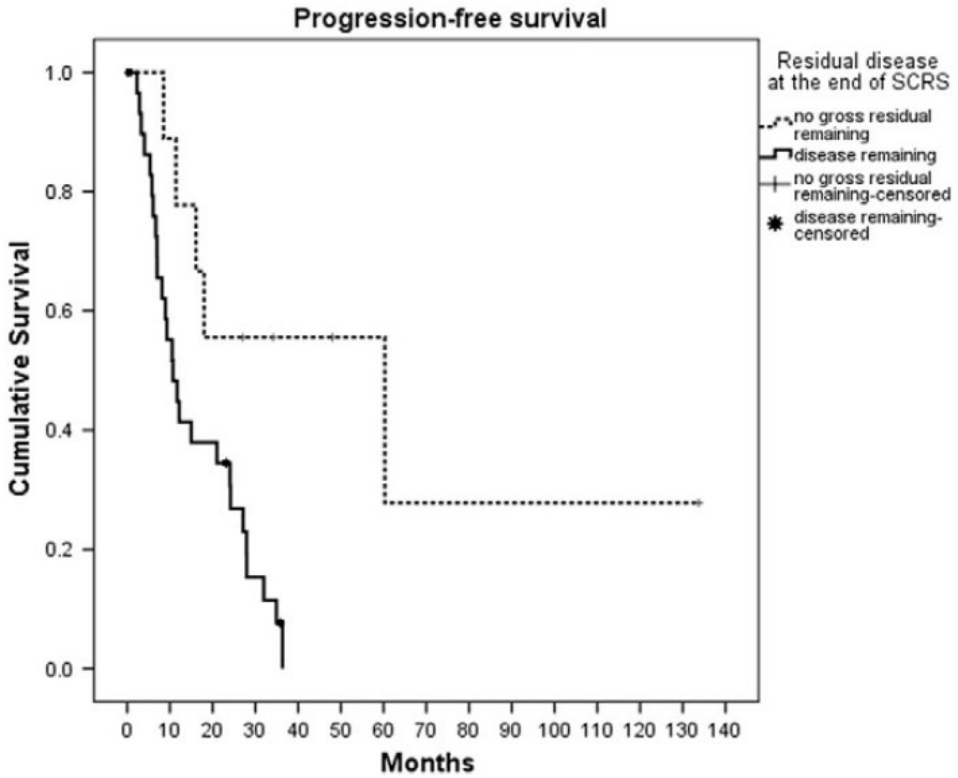


Fig. 1. Progression-free survival from the time of secondary cytoreductive surgery ($p = 0.008$).

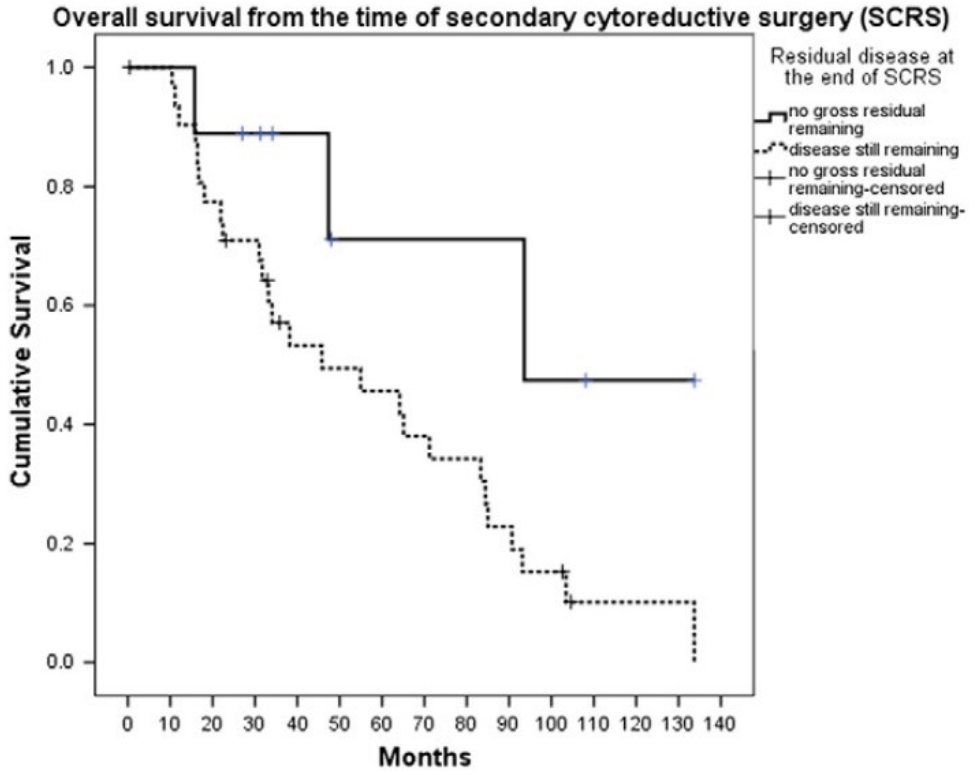


Fig. 2. Overall survival from the time of secondary cytoreductive surgery ($p = 0.04$).

	CCO	Residual Disease	p
PFS (months)	30.3	10.7	0.008
OS post surgery	93.6	45.8	0.04

Crane EK. *Gynecol Oncol.* 2015.

Multivariate Analysis

Univariate and multivariate results for progression-free survival (N = 41).

Variable	N	Univariate		Multivariate	
		HR [95% CI]	p	HR; [95% CI]	p
Ascites[a]					
No (reference)	37	–			
Yes	3	0.91 [0.28, 3.02]	0.88		
Residual disease					
No gross residual (reference)	9	–			
Gross residual	32	3.83 [1.32, 11.19]	0.01		
Treatment strategy at recurrence					
Systemic therapy (reference)	16	–		–	
Secondary cytoreductive surgery	25	0.36 [0.17, 0.77]	0.009	0.43 [0.20, 0.93]	0.03
CA125 at time of progression/recurrence[b]					
< median,(57 U/mL) (reference)	18	–			
≥ median,(57 U/mL)	16	1.71 [0.77, 3.82]	0.19		
Age at progression/recurrence					
< median,(45.6 years) (reference)	20	–			
≥ median,(45.6 years)	21	0.58 [0.28, 1.22]	0.16		
Number of tumor nodules at progression/recurrence[c]					
<3 (reference)	4	–		–	
≥3	36	6.20 [0.84, 45.7]	0.07	5.29 [0.71, 39.35]	0.10

*Ascites information missing for 1 patient

Crane EK. *Gynecol Oncol.* 2015.

History of the Disease *cont.*

- **2002 diagnosis:** Low-grade serous adenocarcinoma of the ovary, FIGO stage III (ER 100%, PR 0%)
  - ➔ Cytoreductive surgery CCO, followed by 6 cycles of adjuvant CARBOPLATIN-TAXOL
- **2011:** Supradiaphragmatic and infradiaphragmatic nodal recurrence -> 6 cycles of CARBOPLATIN, GEMCITABINE, and BEVACIZUMAB; followed by BEVACIZUMAB maintenance for 18 months
- **2014:** Locoregional relapse → cervical lymphadenectomy
- **2017:** Lymph node recurrence → mediastinal and cervical radiotherapy
- **2019:** New cervical lymph node relapse confirmed by biopsy → LETROZOLE

Single Agent Aromatase Inhibitors and SERMs

- Anastrozole
- Letrozole
- Tamoxifen

PARAGON: Phase II Study of Anastrozole in Low Grade Ovarian Tumors

- Patients with ER and or PR + tumor > 10% by IHC
- Measurable disease by RECIST 1.1 or GCIG CA125 criteria
- Patients treated with anastrozole 1mg daily until POD

Results:

- 23/36 (64%) of patients had clinical benefit at 3 months
- **12-month CBR of 34%** (95% CI , 19-50%)
- **Response rate of 14%**
- **Median PFS 11.1 months** (95% CI, 3.2-11.9)

Patient characteristics at baseline ($n = 36$).

Characteristic	n (%)
Age [years, mean (range)]	57 (22–77)[a]
ECOG performance status	
0	23 (64)
1	13 (36)
Hormone receptor status	
ER+/PR-	16 (44)
ER+/PR+	20 (56)
Histology	
Low-grade serous carcinoma	34 (94)[b,c,d]
Low-grade endometrioid carcinoma	2 (6)
Lines of prior chemotherapy	
0	1 (3)
1	22 (61)
≥2	13 (36)
Prior chemotherapy	35 (97)
Prior radiotherapy	3 (8)
Treatment-free interval	
<6 months	11 (31)
6–12 months	8 (22)
>12 months	16 (44)
No prior chemotherapy	1 (3)
Method of response measurement	
RECIST V1.1	32 (89)
CA125 by GCIG criteria	4 (11)

ER, estrogen receptor; PR, progesterone receptor; GCIG, Gynecologic Cancer InterGroup;

Tang, et al. *Gynecol Oncol.* 2019:531-538.

History of the Disease *cont.*

- **2002 diagnosis:** Low-grade serous adenocarcinoma of the ovary, FIGO stage III (ER 100%, PR 0%)
  - ➔ Cytoreductive surgery CCO, followed by 6 cycles of adjuvant CARBOPLATIN-TAXOL
- **2011:** Supradiaphragmatic and infradiaphragmatic nodal recurrence -> 6 cycles of CARBOPLATIN, GEMCITABINE, and BEVACIZUMAB; followed by BEVACIZUMAB maintenance for 18 months
- **2014:** Locoregional relapse → cervical linfadenectomy
- **2017:** Nodal recurrence → mediastinal and cervical radiotherapy
- **2019:** New cervical lymph node relapse confirmed by biopsy → LETROZOLE
- **2020:** Supradiaphragmatic and pulmonary nodal progression → 6 cycles CARBOPLATIN PLD from **December 2020 – August 2021**
  - ➔June 2021 surgical removal of supraclavicular mass, as well as mediastinal and jugular lymph node groups

History of the Disease *cont.*

- **December 2021:** Low-Pulmonary and nodal progression and cauda equina syndrome (very low symptoms)

- Molecular analysis: BRAF V600E mutation, MSS

Molecular & 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.

GOG-239 | Selumetinib (AZD6244) for LGSOC

Eligibility:

- Prospective Central Pathology
- Recurrent Disease
- Measurable Disease
- No Restrictions on Prior Therapy

Selumetinib 50 mg oral BID

- **ORR = 15% (8/52 patients)**
- 1 Complete Response and 7 Partial Responses
- 35 patients had archival FFPE tissue available for direct sequencing of KRAS and BRAF, ***no association found between mutation and response to treatment***

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Farley, et al. *Lancet Oncology*. 2013.

MILO: Phase III Study of Binimetinib vs PCC in LGSOC

Patients with Recurrent/Persistent LGS Carcinoma of the Ovary, Fallopian Tube or Primary Peritoneum

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

Randomization 2:1

- Study initiation: June 2013
- Interim analysis cutoff date: January 2016 (N=303)*
- Updated analysis cutoff date: January 2019 (N=341)

*Study enrollment discontinued after this planned interim PFS analysis crossed the predefined futility boundary (observed hazard ratio of 1.21).

Binimetinib (N=228)

(45mg PO BID)

Physicians' Choice of Chemotherapy (N=113)

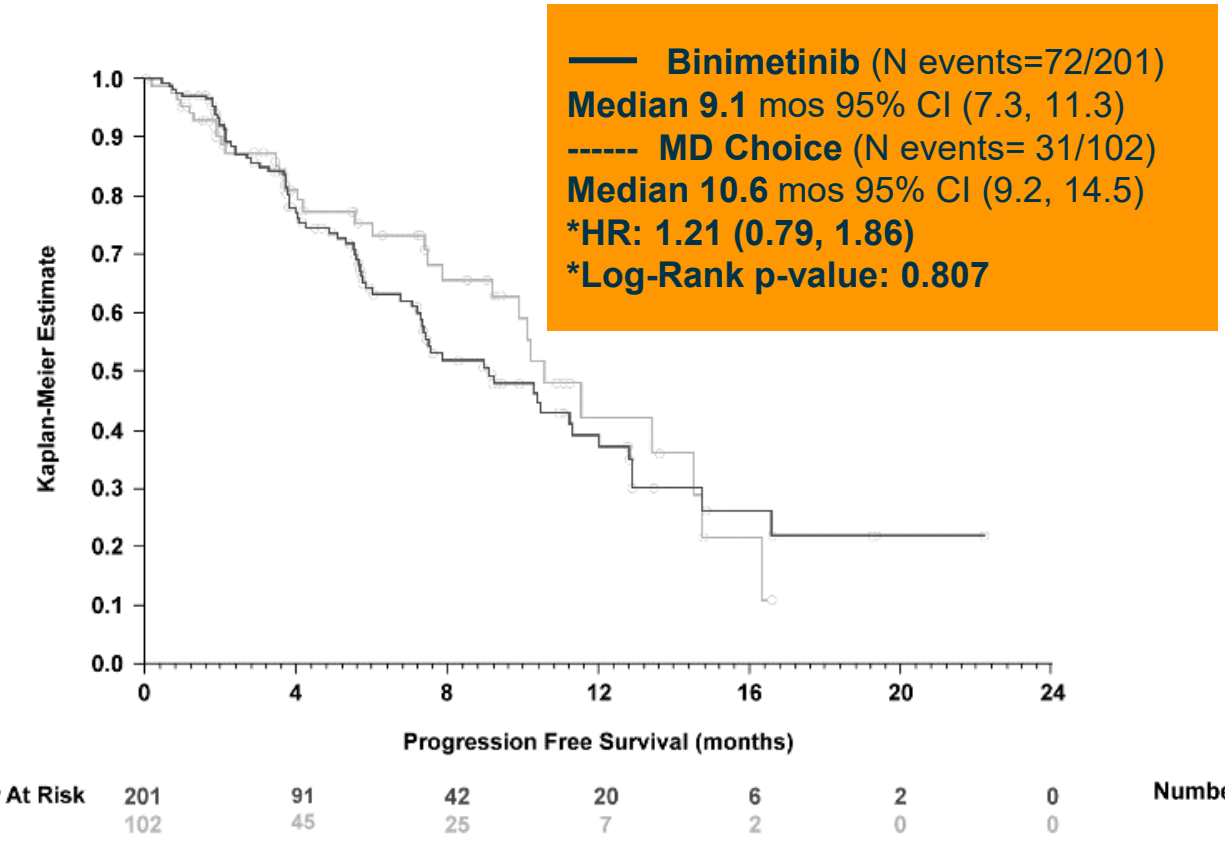
Pegylated Liposomal Doxorubicin	Paclitaxel	Topotecan
(40mg/m2 IV, day 1 of 28 day cycle)	(80mg/m2 IV on days 1,8,15 of 28 day cycle)	1.25 mg/m2 IV on Days 1-5 of 21 day cycle)

Grisham RN, et al. IGCS 2019.; Monk BJ, et al. *J Clin Oncol. 2020.*

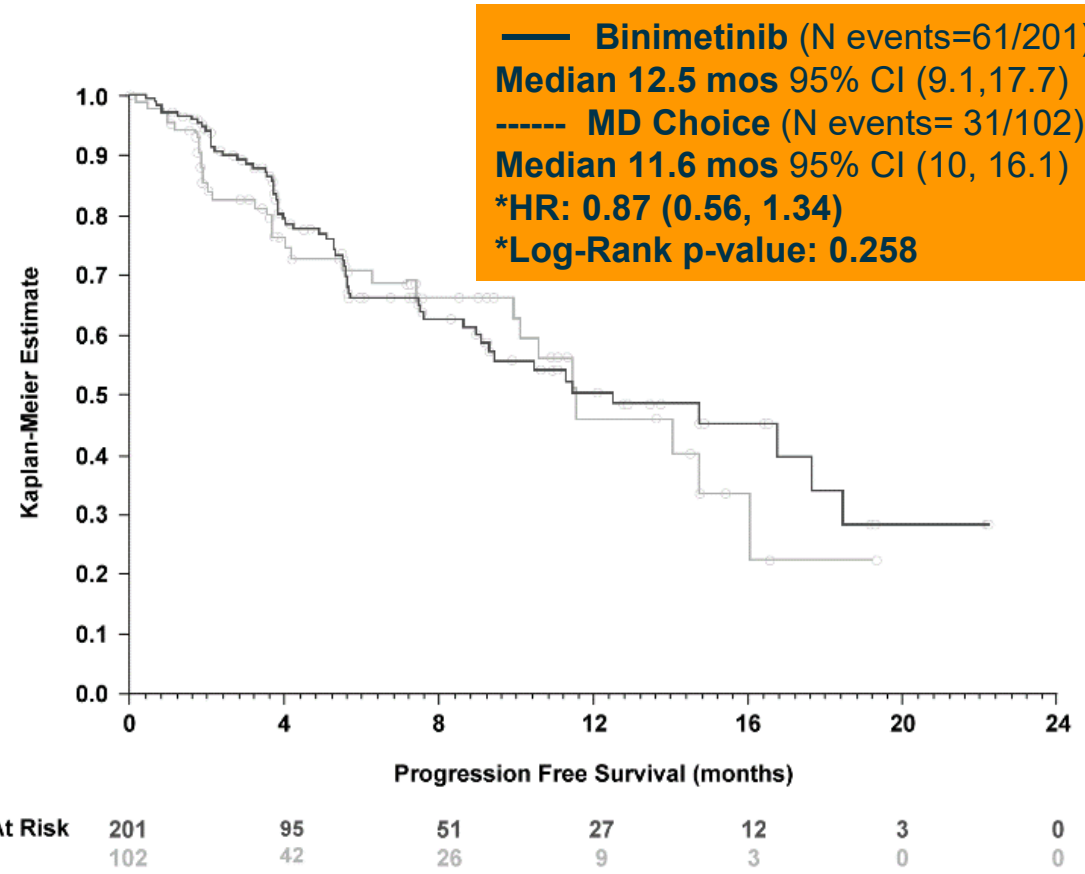
MILO: Interim Analysis

Progression Free Survival BICR and Local

BICR



Local

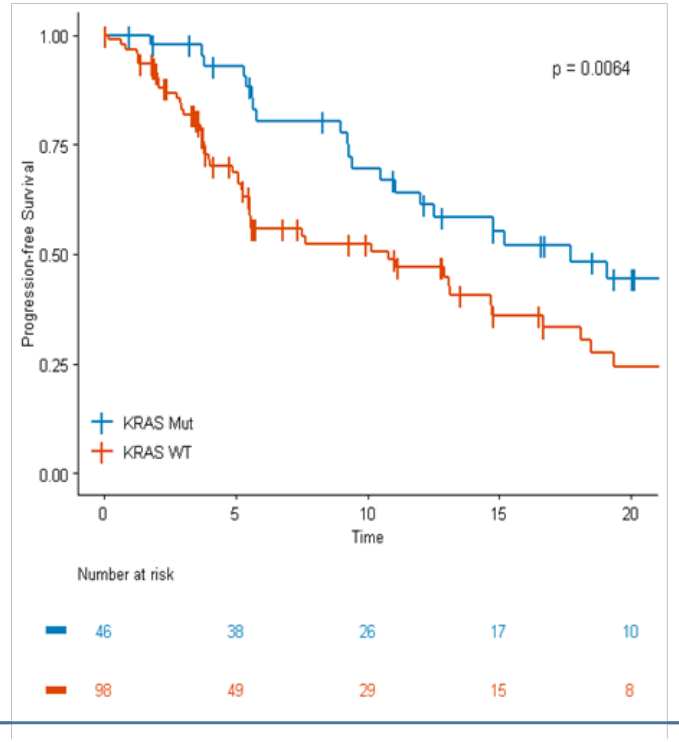


Grisham RN, et al. IGCS 2019.; Monk BJ, et al. *J Clin Oncol. 2020.*

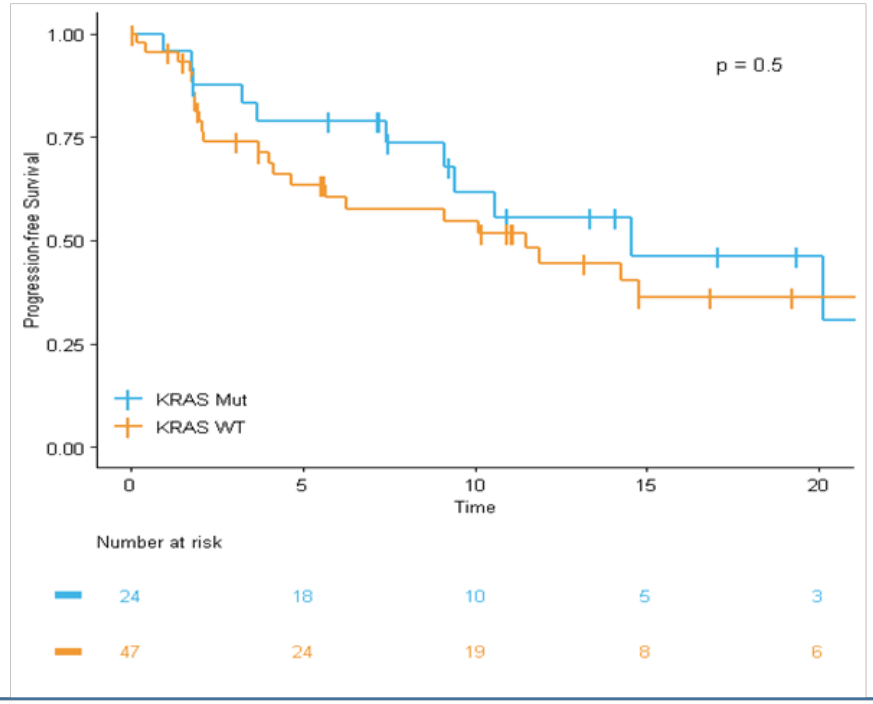
KRASm Predicted Prolonged PFS with Binimetinob

Median PFS for Binimetinib treated patients: KRAS Mutant: 17.7 months (12, NA)

KRAS WT: 10.8 months (5.5, 16.7) P= 0.006



Median PFS for PC treated patients:
KRAS Mutant: 14.6 months (9.4, NA)
KRAS WT: 11.5 months (5.7, 26.6) P=0.502



R Grisham, et al Ann Oncol 2023

GOG-0281 Study

N=260
Primary Endpoint: PFS (investigator-assessed)

Key Eligibility Criteria

- Recurrent LGSOC
- Prospective digital path review
- Measurable disease by RECIST 1.1
- At least 1 prior platinum regimen
- Unlimited no. prior therapies
- No prior MEKi, BRAFi
- Cannot have received all 5 SOC

Trametinib 2 mg daily continuously until progression

Crossover Allowed

Standard of Care
1. Letrozole 2.5 mg daily
2. PLD 40-50 mg IV Q. 28d
3. Weekly Paclitaxel 80 mg/m2 3/4 weeks
4. Tamoxifen 20 mg bid daily
5. Topotecan 4.0 mg/m2 on days 1, 8, 15 Q. 28d

Until progression

Trametinib 2 mg daily continuously until progression

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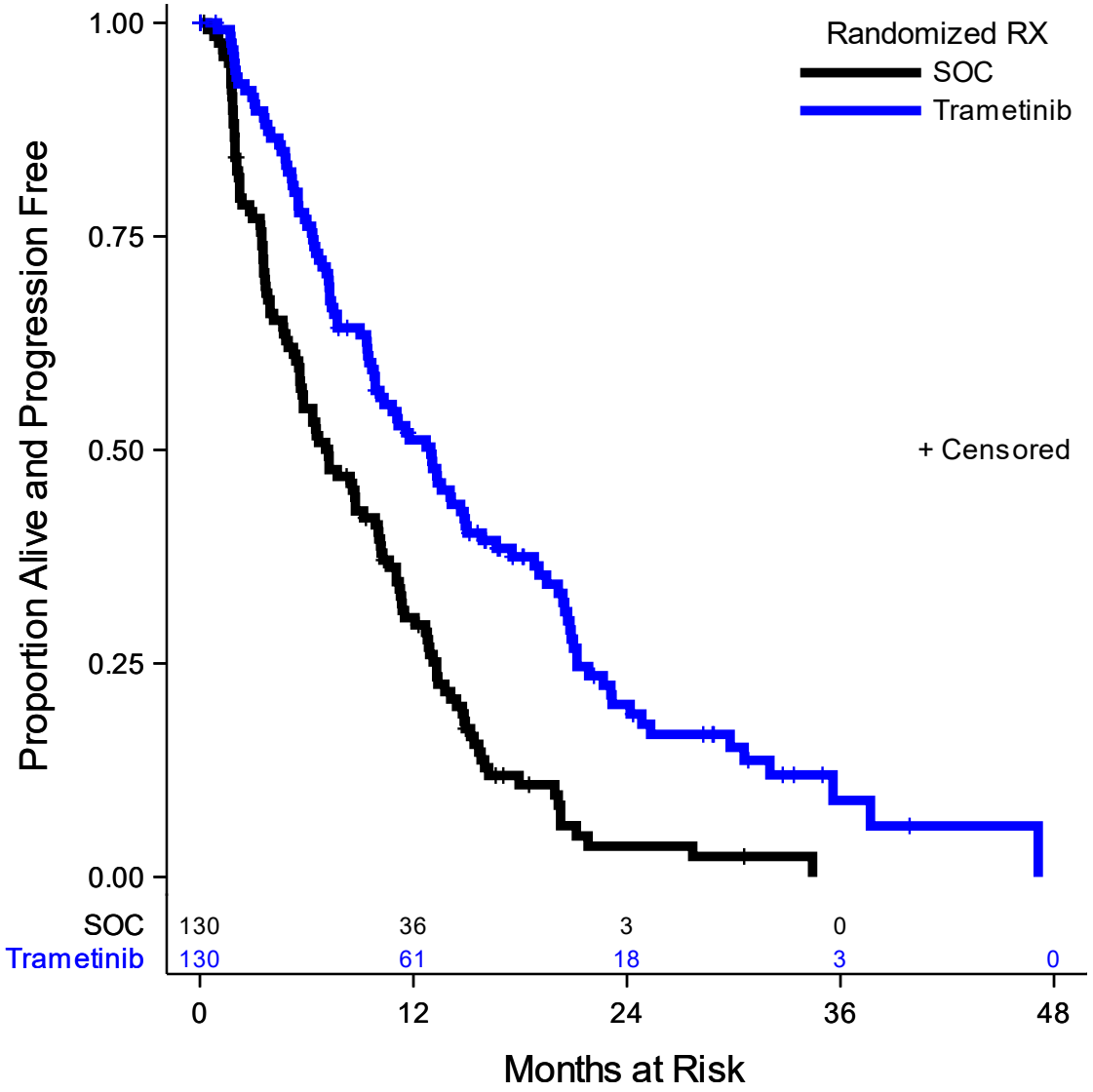
Gershenson DM, et al. ESMO 2019.; Gershenson DM, et al. *Lancet.* 2022.

GOG-0281 | PFS by Local Assessment



	Trametinib	Control (SOC)
Median (Months) 95% CI	13.0 (9.9 – 15.0)	7.2 (5.6 - 9.9)
Hazard Ratio 95% CI	0.48 (0.36 – 0.64)	
One-sided p-value	< 0.0001	

Overall survival secondary endpoint

	Trametinib	Control (SOC)
Median (Months) 95% CI	37.0 (30.3 to NE)	29.2 (23.5 to 51.6)
Hazard Ratio 95% CI	0.75 (0.51 – 1.11)	
One-sided p-value	0.054	

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Gershenson DM, et al. ESMO 2019.; Gershenson DM, et al. *Lancet.* 2022.

GOG-0281 | Response by RECIST 1.1 by Local Assessment

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%			

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Gershenson DM, et al. *Lancet*. 2022.

LOW GRADE SEROUS CARCINOMA OPTIONS

BOUQUET | ENGOT-GYN2 | GOG-3051

- **Persistent or recurrent rare EOC, FTC, PPC**
- **1–4 priors**
  - **≥1 prior platinum**
- **ECOG 0 or 1**
- **Measurable disease**
- **Submission of tumor specimen**

Central NGS + Pathology

Prescreening

General & Arm-Specific Screening

Screening

PTEN LOF alt. and/or *PIK3CA- or AKT1*-act. mut.	ipatasertib + paclitaxel
BRAF/KRAS/NRAS-act. mut. and/or *NF1* LOF alt.	cobimetinib
ERBB2-amp. and/or mut.	trastuzumab emtansine
PIK3CA-act. mut. (w/o *PTEN* LOF alt., *AKT1*-act. mut.)	inavolisib + palbo
ER+ [a] and *PIK3CA*-act. mut. (w/o *PTEN* LOF alt., *AKT1*-act. mut.)	inavolisib+palbo+letrozole
Non-matched [b] (w/o *BRCA* mut.)	inavolisib + olaparib
ER+[a]	giredestrant + abemaciclib
Non-matched [b]	atezolizumab + bevacizumab

Efficacy Gate

Preliminary n=20 pts/arm

Potential Expansion +30 pts/arm

LOF=loss of function.

[a] ER+ defined as ER-positive, defined as detection of ERα in ≥10% of tumor cells as assessed by central ER IHC (HistoGeneX; Ventana SP1 IHC assay).

[b] The Atezo+Bev and Inavo+Ola arms are for eligible patients who do not have a biomarker profile matching them to an open and enrolling biomarker-driven treatment arm, or do not meet the arm-specific eligibility criteria for an arm they are matched to based on their biomarker profile, or withdraw from another arm.

PI: David Gershenson, MD
Co-PI: Jubilee Brown, MD
NCT04931342

GOG FOUNDATION® Transforming the standard of care™ GCIG GYNECOLOGIC CANCER INTERGROUP ENGOT European Network of Gynaecological Oncological Trial groups

History of the Disease *cont.*

- **December 2021:** Low-Pulmonary and nodal progression and cauda equina syndrome (very low symptoms)

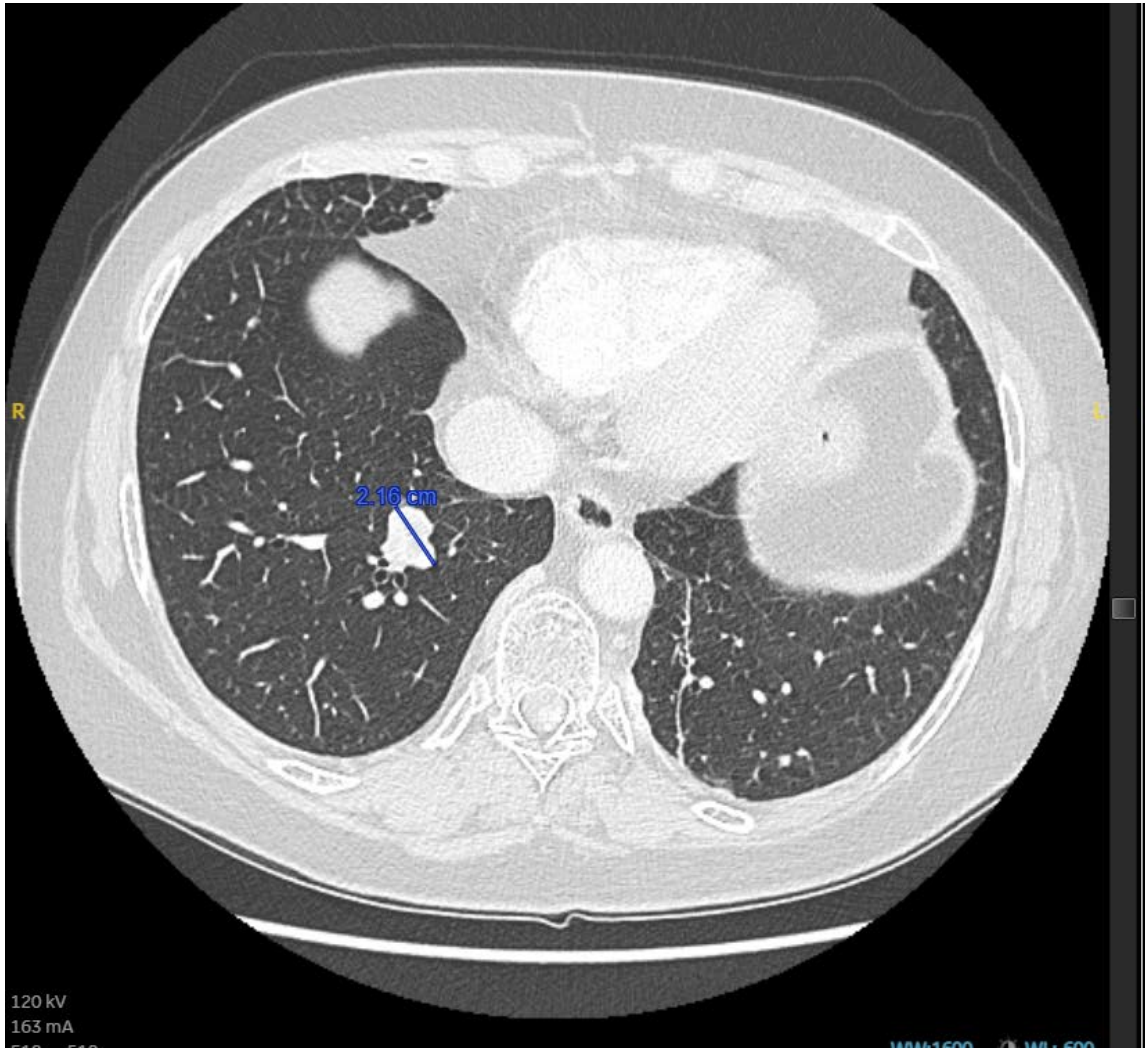
- Molecular analysis: BRAF V600E mutation, MSS

- **COBIMETINIB:** 60 mg/day: 3 weeks on/1 week off

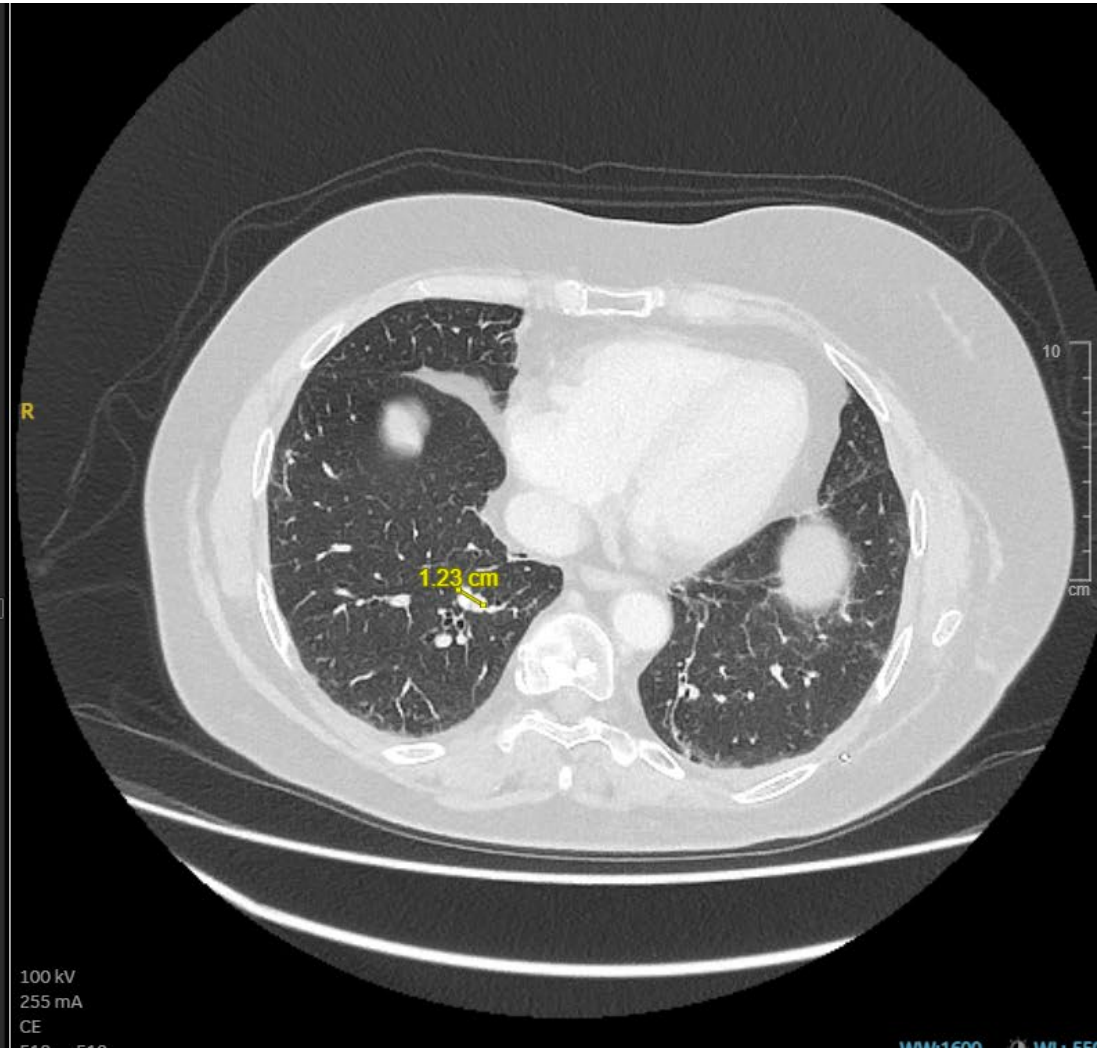
- **C1D1 06/01/2022**

Target Lesions

DECEMBER 2021

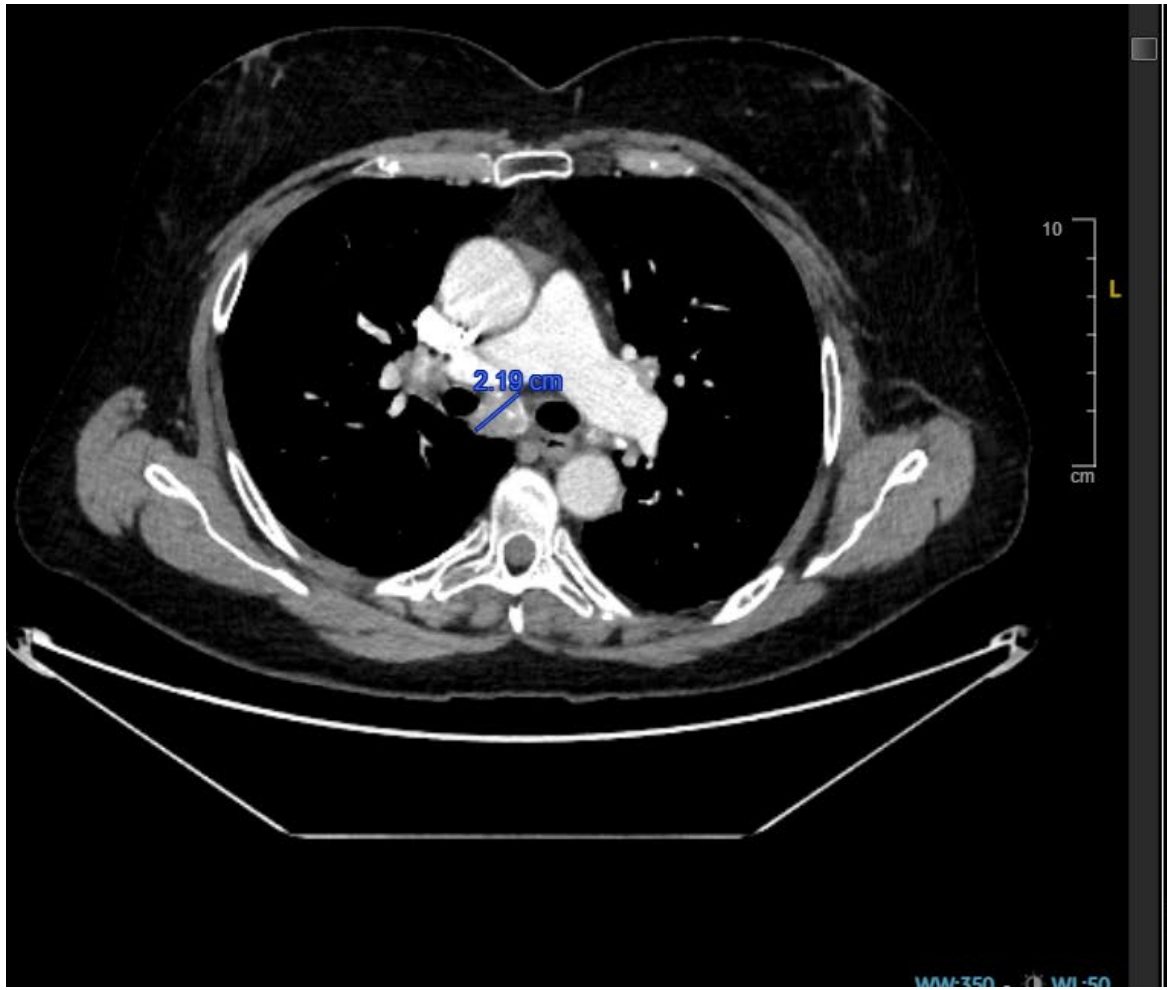


FEBRUARY 2022

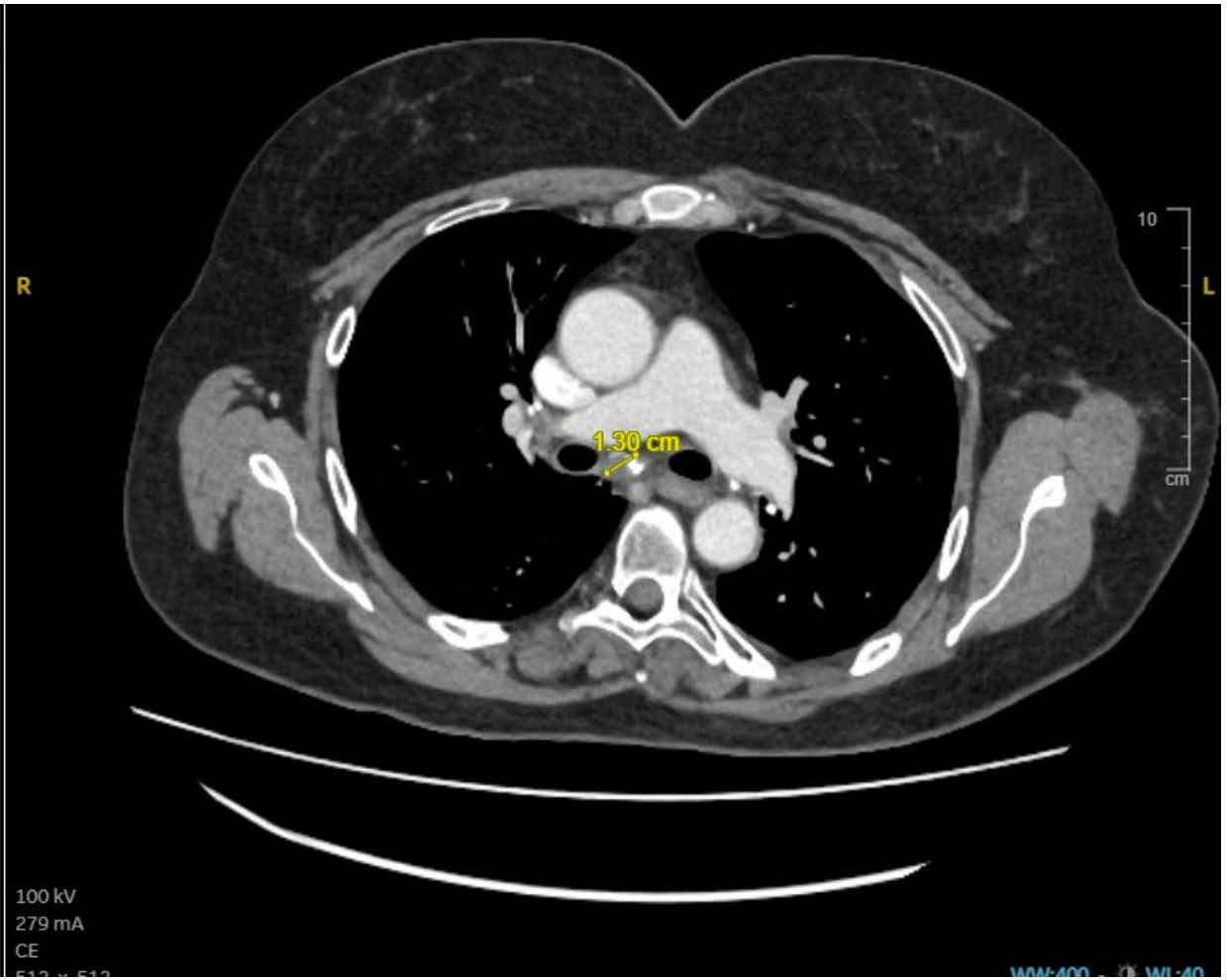


Target Lesions *cont.*

DECEMBER 2021



FEBRUARY 2022



History of the Disease *cont.*

COMPLETE REPONSE on CT scan ACHIEVED IN JUNE 2022

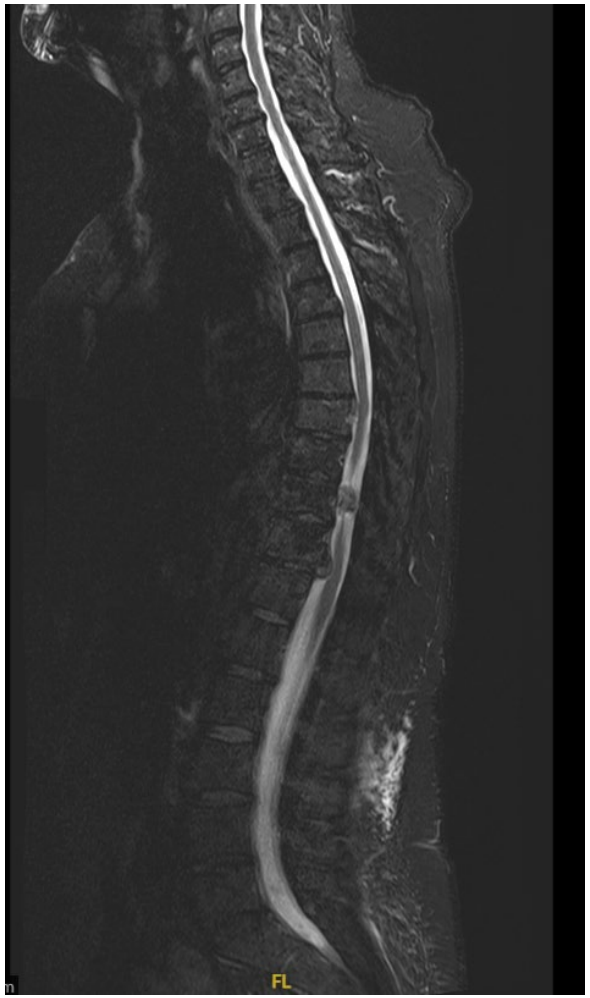
History of the Disease *cont.*

- **April 2024:** Sensory deficits in gluteal region and urinary incontenence
  - Slight deficits in left lower limb when standing on tiptpoes
    - No other deficits + preservation bilateral patellar DTRs

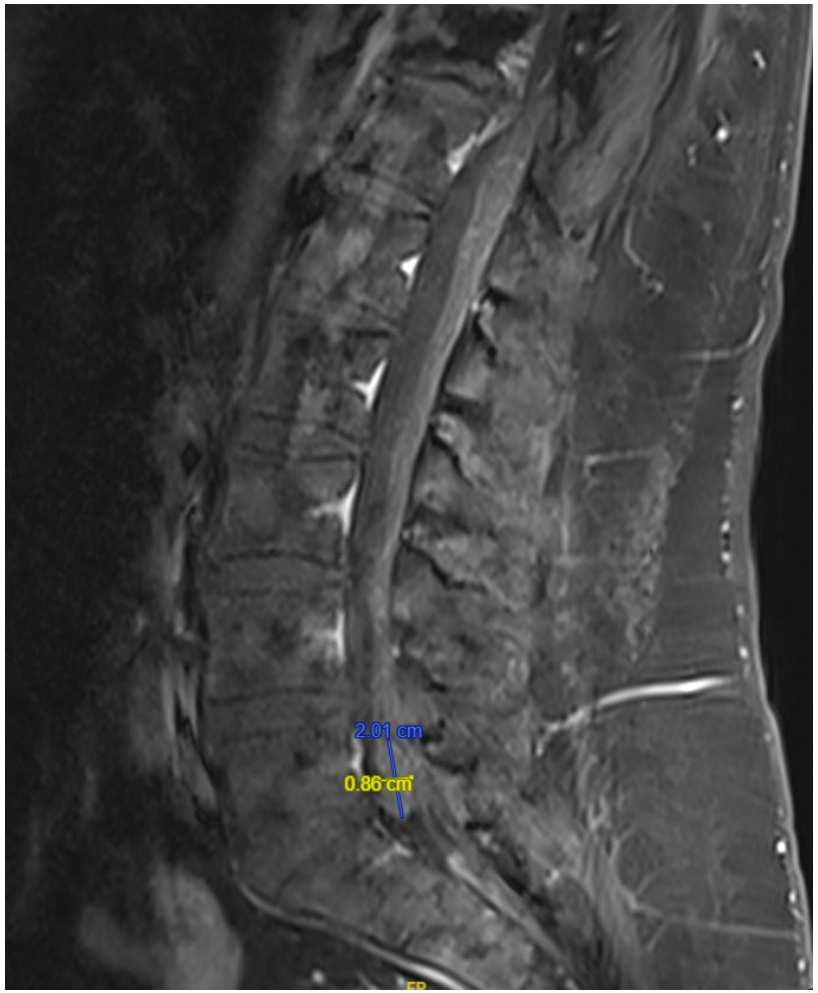
- **May 2024:** Lumbar puncture: +tumor cells; however, no prior examination available to assess duration of this finding
  - **MRI performed**

MRI Showed Leptomeningeal Disease

T10



L5



A review of imaging studies suggested the pathology was present before inclusion in the trial

History of the Disease *cont.*

We discovered at the same time that for comfort reasons the patient had independently reduced her dose to 2 tablets per day for roughly one year. However, when she realised symptoms were coming back, she immediately restarted oral therapy, and saw symptoms disappearing in 2 weeks *(just after to receive the LP)*

We considered that this subtherapeutic dosing led to the recent reappearance of symptoms, which completely resolved when she resumed the effective dose of 3 tablets per day. Furthermore, CT scan was in favor of non-progressive disease

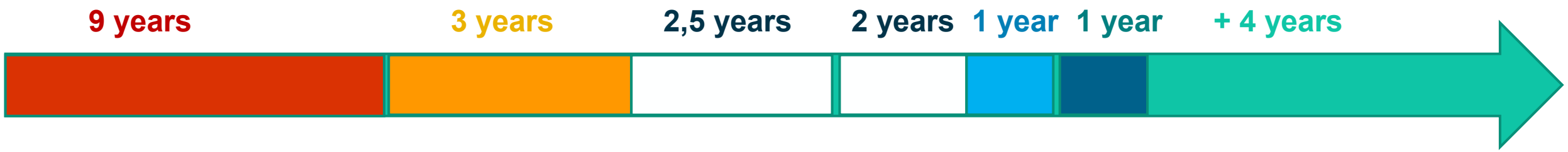
History of the Disease *cont.*

Good tolerance of treatment; only observed SE diarrhea, which was controlled by administration of antidiarrheal agents

From May 2024, patient confirmed good adherence to treatment according to therapeutic regimen per protocol

Disease confirmed to be in complete remission at thoraco-abdominal level and stable at the level of leptomeningeal carcinomatosis

Chronologic History



2002
Surgery
Adjuvant CT x6

2011
2nd Surgery
Adj CT x6 +
Bev 15
mths

2014
3rd Surgery

2017
4th Surgery

2019
5th Surgery
Letrozol

2020
CT PBC
6th Surgery (IDS)

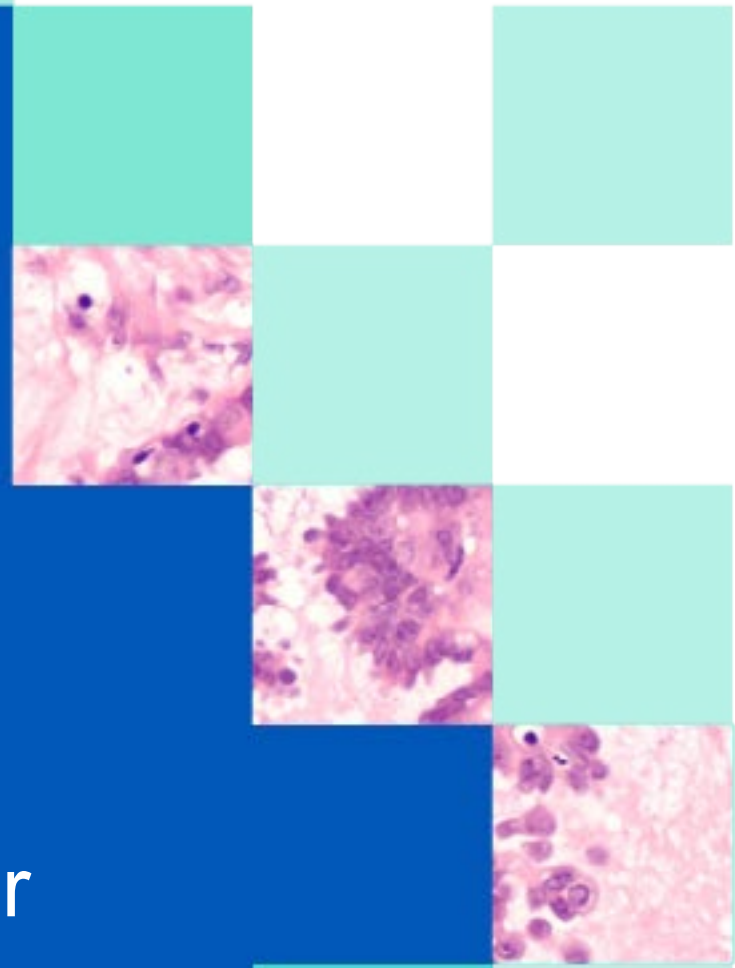
Dec 2021
Cobimetinib

2025

Take Home Message

- Molecularly distinct disease (MAPK alterations) with low incidence, but higher prevalence, due to younger age at diagnosis and extended course of disease
- Standard of care is chemotherapy (RR of 4-24%)
- Single agent endocrine therapy is currently widely used and well tolerated, but with low response rates
- Promising results with bevacizumab used for LGSOC
- Promising results seen with single agent MEK inhibitors
- Potential to enhance activity by combination?

Case 2: Incorporating Best Investigational Strategies in the Management of LGSOC



Rachel N. Grisham, MD

Memorial Sloan Kettering Cancer Center
West Harrison, New York, USA

How can we build on these promising initial results with single-agent MEK inhibitors and improve tolerability?

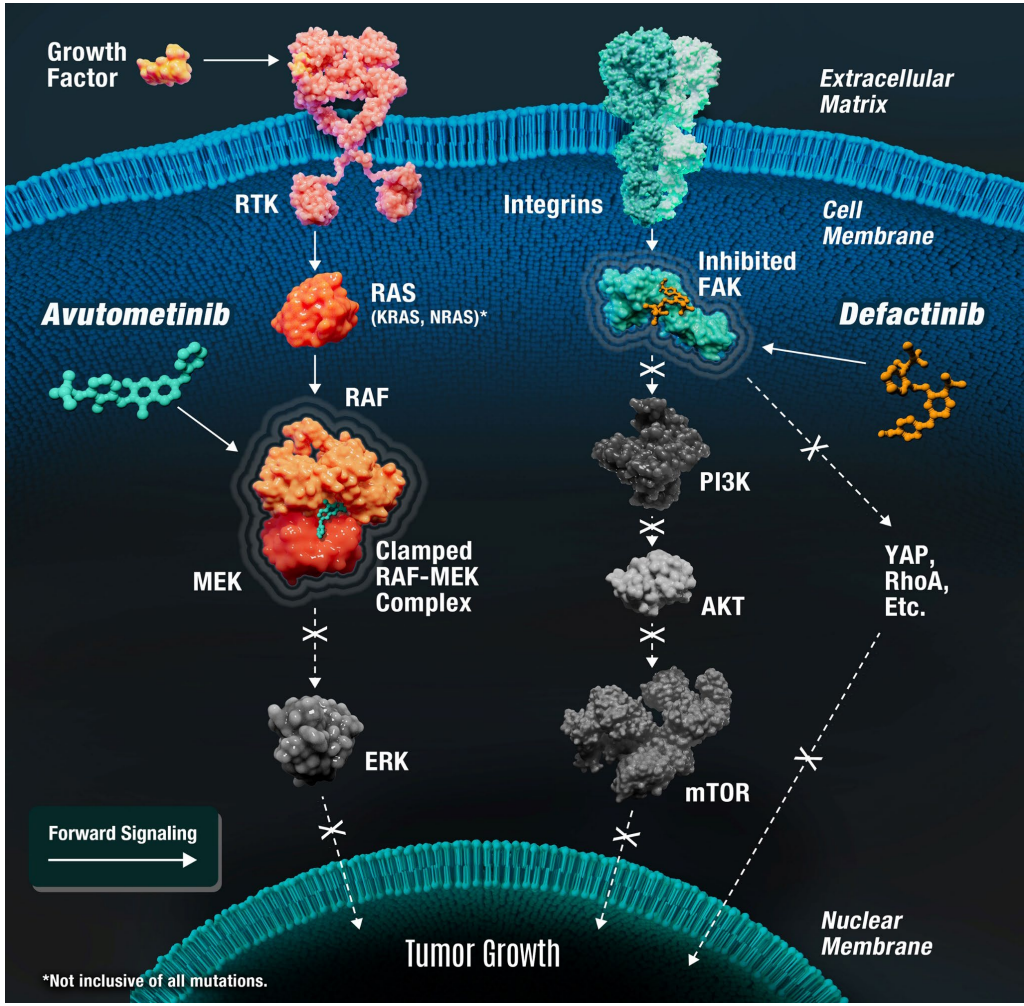
Single Agent MEK Inhibitors:

- ❑Response Rate 16-26%
- ❑Median PFS 11-13 months
- ❑Greatest efficacy in patients with MAPK alterations
- ❑Cumulative toxicity with continuous dosing schedule
- ❑31-36% discontinuation rate due to toxicity

Oral Combination Therapy with Intermittent Dosing Schedule

- **Avutometinib** is a first-in-class oral RAF/MEK clamp that potently inhibits MEK kinase activity, while also blocking the compensatory reactivation of MEK by upstream RAF[1-4]
- **Defactinib** is a selective inhibitor of FAK, a signaling target that has been shown to mediate resistance to multiple anticancer agents[5-7]
- **Avutometinib + defactinib** demonstrated an ORR of 42% (n/N=11/26), a mDOR of 26.9 months (95% CI, 8.5-47.3), and a mPFS of 20.0 months (95% CI, 11.1-31.2) in recurrent LGSOC in the FRAME study (NCT03875820)[8-10]
- Results of **FRAME study** led to **FDA Breakthrough Therapy Designation** and rationale for the phase 2 **ENGOT-ov60/GOG-3052/RAMP 201** (NCT04625270)[11-12]

Avutometinib + Defactinib MOA



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1. Martinez-Garcia C, et al. *Clin Cancer Res.* 2012;18:4806-4819; 2. Ishii N, et al. *Cancer Res.* 2013;73:4050-4060; 3. Lito P, et al. *Cancer Cell.* 2014;25:697-710; 4. Gonzalez-Del Pino GL, et al. *PNAS.* 2021;118:e2107207118; 5. Dawson JC, et al. *Nat Rev Cancer.* 2021;21:313-324; 6. Shinde R, et al. *Cancer Res.* 2020;80(suppl 16):CT143; 7. Kang Y, et al. *J Natl Cancer Inst.* 2013;105(19):1485-1495; 8. Banerjee S, et al. *Ann Oncol.* 2021;32(suppl_5):S725-S772; 9. Banerji Udai. Targeting RAS 2023 SYMPOSIUM. Proteomic profiling of KRAS signaling; Context, CAFs and Combinations; 10. Denis Louis. 5th RAS- Targeted Drug Development Summit. Introducing Rational Combinations of RAF/MEK Clamp Avutometinib: Breakthrough Designation & Beyond; 11. Banerjee SN, et al. *J Clin Oncol.* 2023;41(16 suppl):5515; 12. Verastem Oncology Receives Breakthrough Therapy Designation for VS-6766 with Defactinib in Recurrent Low-Grade Serous Ovarian Cancer. Press Release. Verastem Oncology. May 24, 2021. Accessed September 28, 2023. https://investor.verastem.com/node/12421/pdf.

ENGOT-ov60/GOG-3052/RAMP 201: Registration-Directed Ph2 Trial of Avutometinib ± Defactinib in Patients with Recurrent LGSOC

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%

Enrolled >200 patients in <2 years

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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: Parts A, B, & 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

***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.

ClinicalTrials.gov identifier: NCT04625270

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

In the avutometinib + defactinib combination group:

- RECIST 1.1 ORR 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)

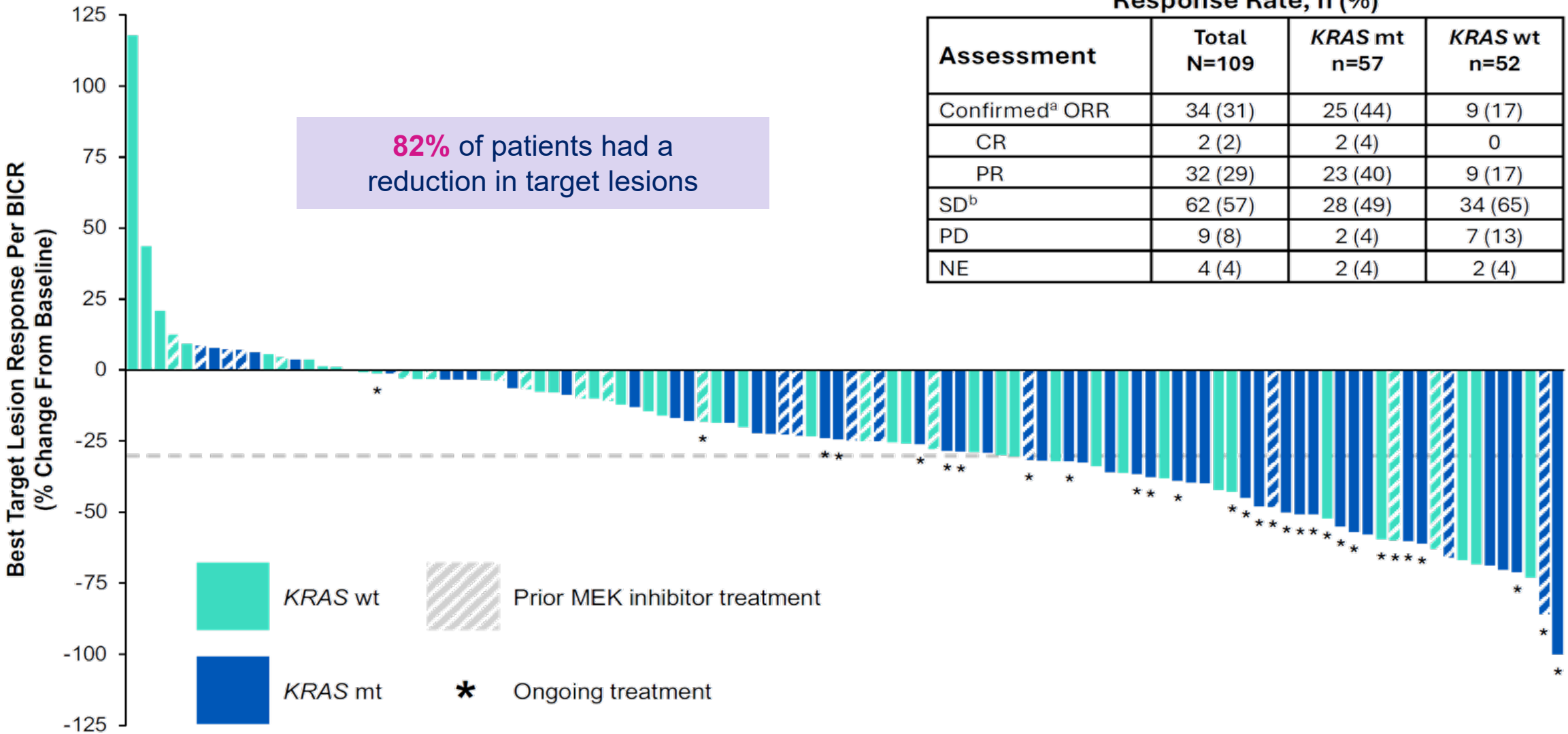
Efficacy evaluable population includes patients who received at least one dose of study drug and had measurable disease at baseline by BICR.
Patients not evaluable for response did not have a postbaseline assessment but are included in the denominator for the efficacy evaluable population.
***By BICR. †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 3.2 mg BIW + Defactinib 200 mg BID

82% of patients had a reduction in target lesions

Response Rate, n (%)

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

AE Profile: Avutometinib 3.2 mg BIW + Defactinib 200 mg BID

- 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
- 4 **deaths** (within 30 days of discontinuation): gastrointestinal hemorrhage, large intestine perforation, clinical progression, clinical deterioration; none were considered related to study treatment

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 + 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.

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
  - 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.

Watch This Space!

Verastem Oncology Announces FDA Acceptance and Priority Review of New Drug Application for Avutometinib in Combination with Defactinib for the Treatment of Recurrent KRAS Mutant Low-Grade Serous Ovarian Cancer

December 30, 2024 at 4:30 PM EST

PDUFA target action date is June 30, 2025

If approved, avutometinib in combination with defactinib would be the first-ever FDA-approved treatment specifically for adults with recurrent KRAS mutant LGSOC

BOSTON--(BUSINESS WIRE)--Dec. 30, 2024-- Verastem Oncology (Nasdaq: VSTM), a biopharmaceutical company committed to advancing new medicines for patients with cancer, today announced that the U.S. Food and Drug Administration (FDA) has accepted for review the New Drug Application (NDA) under the accelerated approval pathway for avutometinib, an oral RAF/MEK clamp, in combination with defactinib, an oral FAK inhibitor, for the treatment of adult patients with recurrent low-grade serous ovarian cancer (LGSOC), who received at least one prior systemic therapy and have a KRAS mutation. The NDA, which was completed in October 2024, has been granted Priority Review with a Prescription Drug User Fee Act (PDUFA) action date of June 30, 2025. In addition, the FDA has stated that it is not currently planning to hold an advisory committee meeting to discuss the application.

GOG-3097/ENGOT-ov81/NCRI/RAMP 301:

A Phase 3, Randomized, Open-Label Study of Combination Therapy with Avutometinib plus Defactinib Versus Investigator's Choice of Treatment in Patients with Recurrent Low-Grade Serous Ovarian Cancer (LGSOC)

Key Inclusion Criteria

- Confirmed LGSOC diagnosis
- Recurrent disease after prior platinum therapy
- Documented *KRAS* mutation status
- Measurable disease per RECIST v1.1
- Prior MEKi allowed
- Prior Bev allowed

PI: Rachel Grisham, MD
NCT06072781

1:1 Randomization
N = 270

Stratification Factors
KRAS mutation status: wt vs mt
Number of prior therapies: 1-3 vs ≥4
Geography: North America/Europe vs ROW

Avutometinib + Defactinib
N = 135

Avutometinib 3.2 mg PO BIW
Defactinib 200 mg PO BID
3 weeks on, 1 week off

May crossover upon BICR confirmed PD

Investigator's Choice
N = 135

Pegylated Liposomal Doxorubicin
Paclitaxel
Letrozole
Anastrozole

Primary Endpoint

PFS via RECIST v1.1 per BICR

Secondary Endpoints

OS
PFS via RECIST v1.1 per INV Assessment
ORR
DoR
DCR
Safety
Pharmacokinetics
PROs

Summary of Analyses

Interim analysis at 50% of planned PFS events for possible sample-size adjustment to maintain power

Hierarchical Evaluation of Primary PFS Endp.:
- KRAS mutant LGSOC only
- All recurrent LGSOC

RECIST, response evaluation criteria in solid tumors; BICR, blinded independent central review; BID: twice a day; BIW: twice a week; DCR: disease control rate; DoR: duration of response; INV: investigator; mt: mutant; wt, wild type; PFS: progression free survival; ORR: objective response rate; OS: overall survival; PD: progressive disease; PROs: patient reported outcomes; ROW: rest of world

Case 1: Doreen

- **Doreen is a 42-year-old woman with recurrent low grade serous ovarian cancer**
  - **First diagnosed 2020**, underwent primary debulking therapy, followed by IV Carbo/Taxol x 6 cycles, then letrozole maintenance
  - Foundation NGS tumor testing: **KRAS G12V mutation**, no other actionable alterations
  - Progressed after 5 months of letrozole maintenance and was treated second-line with IV liposomal doxorubicin
  - Progressed after 4 cycles of liposomal doxorubicin and was changed to IV bevacizumab in combination with oral cyclophosphamide
  - Progressed after 5 months of treatment and was changed to trametinib
  - Treated with trametinib 2mg daily. After 2 months underwent dose reduction due to rash and continued 1.5mg po daily, experiencing partial response at 4 months
  - After 12 months of treatment, she experienced progression of disease
  - She was next treated with single-agent carboplatin x 3 cycles, and again experienced progression with measurable disease

Is Doreen Potentially Eligible for GOG-3097/ENGOT-ov81/NCRI/RAMP 301:

- Recurrent measurable low grade serous ovarian cancer
- Five prior lines of therapy
- Somatic KRAS mutation
- Prior trametinib

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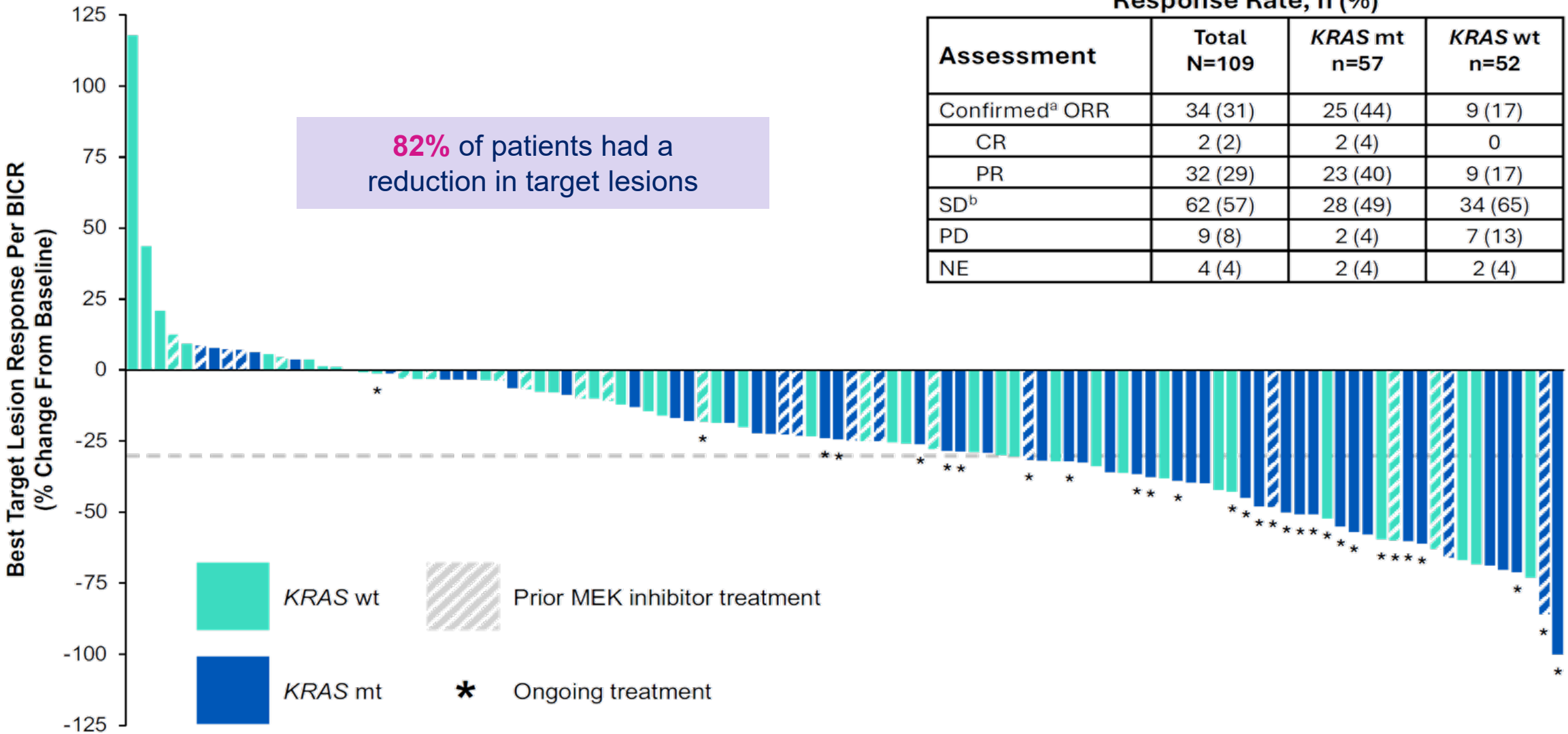

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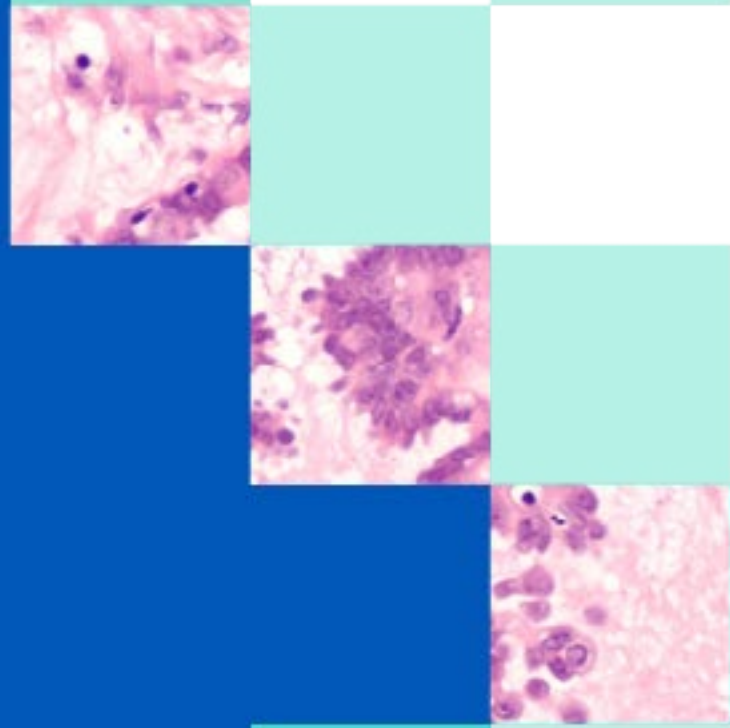
Closing Remarks

Brian Slomovitz, MD, FACOG
Mount Sinai Medical Center
Miami Beach, Florida, USA



The GOG Foundation, Inc. Continuing Education

In support of improving patient care, this activity has been planned and implemented by The GOG Foundation, Inc.

Accreditation Statement

The GOG Foundation, Inc. is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide Continuing Medical Education for physicians.

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Participants who complete the educational activity, pre-/post-tests, and evaluation, will receive certificate of credit.

Complete our Pre-Test!

THANK YOU!