An Industry Supported Symposium at the 2026 SGO Allied Health Professionals Meeting

Optimizing Management of *KRAS*-Mutated Malignancies

Practical Approaches to Dosing, Monitoring, and Adverse Event Management



Chicago, Illinois

Saturday, October 17, 2026

11:30 am – 12:30 pm CT

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

GOG Faculty Disclosure Information

Optimizing Management of *KRAS*-Mutated Malignancies:
Practical Approaches to Dosing, Monitoring, and Adverse Event Management Industry Supported Symposium
Saturday, October 17, 2026 | Chicago, Illinois

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Faculty Disclosure Information

LAST NAME		FIRST NAME	Individual's Role(s) in Activity	Name of Ineligible Company(s)	Nature of Relevant Financial Relationship(s)
Planning Disclosures					
Slomovitz, MD		Brian	**Moderator**	Novocure; AstraZeneca; Aasi; Regeneron; Immunocore; Merck; Gilead; Eisai; Incyte	Consultant
Speaker Disclosures					
Flint, NP		Michelle	**Speaker**	Corcept Therapeutics Verastem	Speaker Bureau Advisory Board
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Rush		Heather	**Staff**	Nothing to disclose	
Shumaker		Kara	**Reviewer/Staff**	Nothing to disclose	
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Duska, MD		Linda	**Edu-Co-Chair/ Reviewer**	Merck; Corcept	Honoraria (Merck) Speakers Bureau (Corcept) Research Funding (Merck)
Blank, MD		Stephanie	**Reviewer**	American Board of Obstetrics and Gynecology; Merck; AstraZeneca; GlaxoSmithKline; Pfizer; Seattle Genetics/Astellas; Acrivon; Zentalis; NX Development Corp.	Leadership (American Board of Obstetrics and Gynecology) Research Funding (Merck; AstraZeneca; GlaxoSmithKline; Pfizer; Seattle Genetics/Astellas; Acrivon; Zentalis; NX Development Corp.)
Gien, MD		Lilian	**Reviewer**	Glaxo Smith Kline; Merck; Abbvie; AstraZeneca	Speaker Honoraria (Glaxo Smith Kline; Merck) Advisory Board (Abbvie; AstraZeneca)
Mutch, MD		David	**Reviewer**	Nothing to disclose	
Zweizig, MD		Susan	**Reviewer**	Nothing to disclose	

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Faculty



Brian Slomovitz, MD
Mount Sinai Medical Center



Michelle Flint, NP
Mount Sinai Medical Center

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Learning Objectives

At the conclusion of this activity, participants should be able to:

1. **Recognize and understand prevention and management options of common adverse events** associated with targeted therapies, including rash, edema, and visual disturbances, using evidence-based approaches.

2. **Apply biomarker-driven strategies** to identify appropriate patients for targeted therapies, including understanding *KRAS* mutations and available testing methodologies.

3. **Implement effective dosing strategies** that optimize treatment adherence while minimizing toxicity.

4. **Develop monitoring plans** to assess treatment safety and efficacy in patients receiving targeted therapies.

5. **Translate clinical evidence into practice** through case-based application of adverse event management and therapeutic decision-making.

Agenda

5 minutes	**Welcome, Introduction and Program Overview**	Brian Slomovitz, MD
15 minutes	**Didactic Presentation: Biomarkers & Patient Identification**	Michelle Flint, NP
15 minutes	**Treatment Considerations & Mechanism of Action**	Brian Slomovitz, MD
20 minutes	**Case Based Scenarios with Audience Interaction**	All Faculty
5 minutes	**Key Takeaways & Audience Q&A**	All Faculty



Didactic Presentation: Biomarkers & Patient Identification

Michelle Flint, NP
Mount Sinai Medical Center

Agenda

1. Overview of *KRAS* mutations and clinical significance
2. Testing methods and interpretation
3. Patient selection considerations
4. Integrating biomarker testing into clinical workflow

History of *KRAS*

KRAS is one of the most frequently mutated oncogenes in human cancer[1]

1967

Kirsten and Mayer identified the Kirsten murine sarcoma virus after passage of murine leukemia virus in rats.[2]

1981-82 → **1982-83**

Viral *RAS* genes were sequenced in 1981–1982. In 1982–1983, researchers identified mutated human *HRAS* and *KRAS* genes in cancer-cell DNA, establishing *RAS* genes among the first human oncogenes and helping launch molecular oncology.[3]

1. Rosen N. et al. N Engl J Med. 2021;384(25):2447–2449; 2. Kirsten WH, et al. J Natl Cancer Inst. 1967;39(2):311–335; 3. Tsuchida N, et al. Oncotarget. 2016;7(29):46717–46733.
DNA, deoxyribonucleic acid; KRAS, Kirsten rat sarcoma viral oncogene homologue

KRAS: From proto-oncogene to oncogene



An oncogene is an altered or overactive gene that can promote the transformation of a normal cell into a cancer cell[1]



The normal, healthy version is called a proto-oncogene, and it helps control cell growth and division



The ***KRAS*** proto-oncogene encodes the *KRAS* signaling protein. Activating mutations can keep *KRAS* switched on, driving persistent proliferative signaling.[2]

1. Kontomanolis EN, et al. Anticancer Res. 2020;40(11):6009–6015; 2. Son J, et al. Clin Cancer Res. 2024;30(14):2986–2995.

Clinical significance of *KRAS* mutations

Diagnostic and histotype significance

3,328

patients

A retrospective, single-institution next-generation sequencing cohort study from MD Anderson used tumor profiling from 3,328 patients to define how often RAS mutations occur across gynecologic cancer types and which histologies they cluster in.[1]

***KRAS* mutation is seen mostly in lower-grade histotypes, supporting histologic classification**

1. Son et al., Clinical Cancer Research, 2024 · https://pmc.ncbi.nlm.nih.gov/articles/PMC11250057/#R16

Histologic distribution of *KRAS* mutations in gynecologic cancers

Distribution across uterine and ovarian histologies

Uterine (n=1140)

Histology	Total	RAS mut, n (%)	KRAS mut, n (%)	G12D, n (%)	G12V, n (%)	G12C, n (%)
All Uterine	**1140**	**230 (20.2)**	**209 (18.3)**	**67 (5.9)**	**60 (5.3)**	**14 (1.2)**
Mesonephric-like	**9**	**9 (100)**	**9 (100)**	**3 (33.3)**	**3 (33.3)**	**1 (11.1)**
Endometrioid	**418**	**139 (33.3)**	**130 (31.1)**	**48 (11.5)**	**31 (7.4)**	**8 (1.9)**
Undiff/Dediff	41	10 (24.4)	8 (19.5)	3 (7.3)	4 (9.8)	0
Carcinosarcoma	144	22 (15.3)	20 (13.9)	4 (2.8)	4 (2.8)	2 (1.4)
Clear cell	77	11 (14.3)	8 (10.4)	2 (2.6)	4 (5.2)	1 (1.3)
Adenocarcinoma NOS	45	5 (11.1)	5 (11.1)	1 (2.2)	0	0
Serous	265	25 (9.4)	21 (7.9)	5 (1.9)	10 (3.8)	2 (0.8)
Sarcoma	117	6 (5.1)	5 (4.3)	1 (0.9)	2 (1.7)	0
Other	24	3 (12.5)	3 (12.5)	0	0	0

Ovarian (n=1724)

Histology	Total	RAS mut, n (%)	KRAS mut, n (%)	G12D, n (%)	G12V, n (%)	G12C, n (%)
All Ovarian	**1724**	**229 (13.3)**	**192 (11.1)**	**71 (4.1)**	**72 (4.2)**	**11 (0.6)**
Mesonephric-like	**6**	**6 (100)**	**5 (83.3)**	**3 (50.0)**	**1 (16.7)**	**0**
Mucinous	**48**	**29 (60.4)**	**29 (60.4)**	**10 (20.8)**	**9 (18.8)**	**3 (6.3)**
Low-grade serous	**133**	**78 (58.6)**	**59 (44.4)**	**26 (19.5)**	**27 (20.3)**	**1 (0.8)**
Endometrioid	**72**	**31 (43.1)**	**28 (38.9)**	**11 (15.3)**	**11 (15.3)**	**2 (2.8)**
Adenocarcinoma NOS	31	7 (22.6)	7 (22.6)	3 (9.7)	2 (6.5)	0
Clear cell	139	26 (18.7)	25 (18)	5 (3.6)	10 (7.2)	1 (0.7)
Carcinosarcoma	49	5 (10.2)	4 (8.2)	1 (2)	2 (4.1)	0
Granulosa	56	2 (3.6)	0	0	0	0
High-grade serous	1135	39 (3.4)	29 (2.6)	9 (0.8)	7 (0.6)	4 (0.4)
Other	55	6 (10.9)	6 (10.9)	3 (5.5)	3 (5.5)	0

1. ***Son J, et al. Clin Cancer Res. 2024;30(14):2986–2995.***

G12C, glycine-to-cysteine substitution at codon 12; G12D, glycine-to-aspartic acid substitution at codon 12; G12V, glycine-to-valine substitution at codon 12; n, number of tumors; NOS, not otherwise specified, mut, mutated; Undiff/Dediff, undifferentiated/dedifferentiated.

Histologic distribution of *KRAS* mutations in gynecologic cancers

Distribution across cervical and vulvovaginal histologies

Cervical (n=339)

Histology	Total	RAS mut, n (%)	KRAS mut, n (%)	G12D, n (%)	G12V, n (%)	G12C, n (%)
All Cervical	**339**	**49 (14.5)**	**44 (13.0)**	**15 (4.4)**	**10 (2.9)**	**0**
Adenosquamous	13	4 (30.8)	4 (30.8)	2 (15.4)	0	0
Adenocarcinoma	109	29 (26.6)	27 (24.8)	10 (9.2)	6 (5.5)	0
Neuroendocrine	44	7 (15.9)	6 (13.6)	2 (4.5)	3 (6.8)	0
Squamous	158	8 (5.1)	6 (3.8)	0	1 (0.6)	0
Other	15	1 (6.7)	1 (6.7)	1 (6.7)	0	0

Vulvovaginal (n=125)

Histology	Total	RAS mut, n (%)	KRAS mut, n (%)	G12D, n (%)	G12V, n (%)	G12C, n (%)
All Vulvovaginal	**125**	**15 (12.0)**	**4 (3.2)**	**2 (1.6)**	**1 (0.8)**	**0**
Melanoma	59	10 (16.9)	0	0	0	0
Squamous	36	1 (2.8)	0	0	0	0
Other	30	4 (13.3)	4 (13.3)	2 (6.7)	1 (3.3)	0

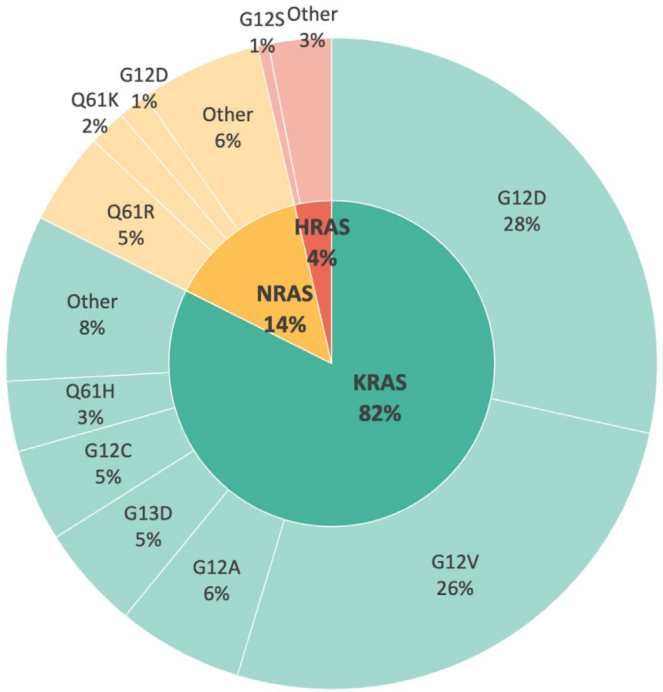
1. ***Son J, et al. Clin Cancer Res. 2024;30(14):2986–2995.***

G12C, glycine-to-cysteine substitution at codon 12; G12D, glycine-to-aspartic acid substitution at codon 12; G12V, glycine-to-valine substitution at codon 12; n, number of tumors.

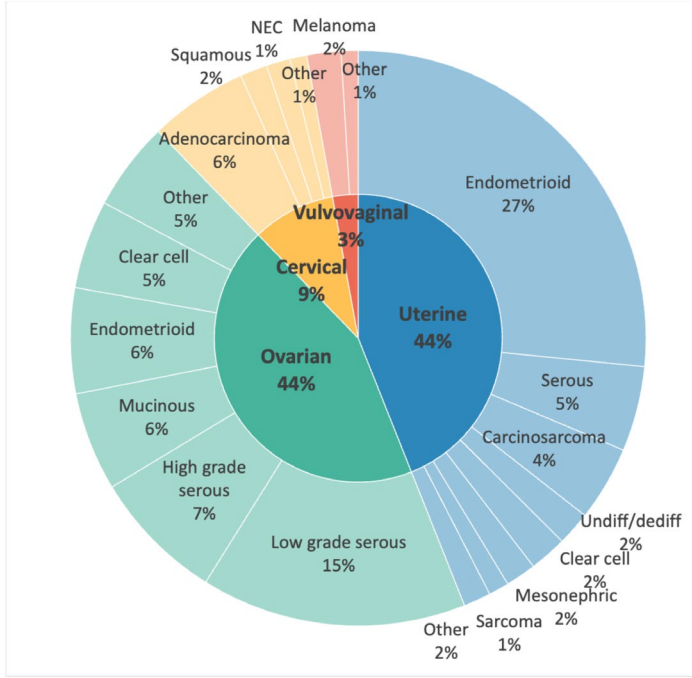
Distribution of RAS mutations in gynecologic cancers

Allelic and histologic distribution

Allelic Distribution of *RAS* Mutations in Gynecologic Cancers (n=545)



Histologic Distribution of *RAS*-Mutated Gynecologic Cancers (n=523)



NEC, neuroendocrine carcinoma; undiff/dediff, undifferentiated/dedifferentiated

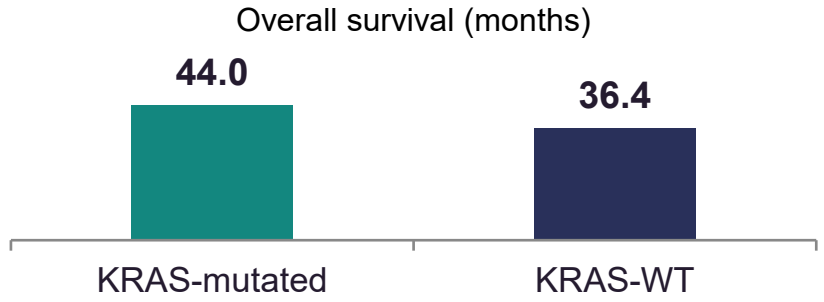
1. Son J, et al. Clin Cancer Res. 2024;30(14):2986–2995.

Prognostic associations of RAS mutations

HR=1.3

p=0.001

RAS mutation was associated with worse overall survival (HR=1.3, p=0.001) in the MD Anderson retrospective analysis [1]



In a separate claims-based analysis of 9,836 patients with endometrial cancer, ***KRAS*-mutated** disease was associated with longer mean survival than ***KRAS* wild-type** disease ($P < .001$).[2]

Improved survival outcomes are seen in *KRAS* mutant LGSOC

1.Son J, et al. Clin Cancer Res. 2024;30(14):2986–2995; 2. Kilowski KA, et al. Gynecol Oncol. 2024;191:299-306.

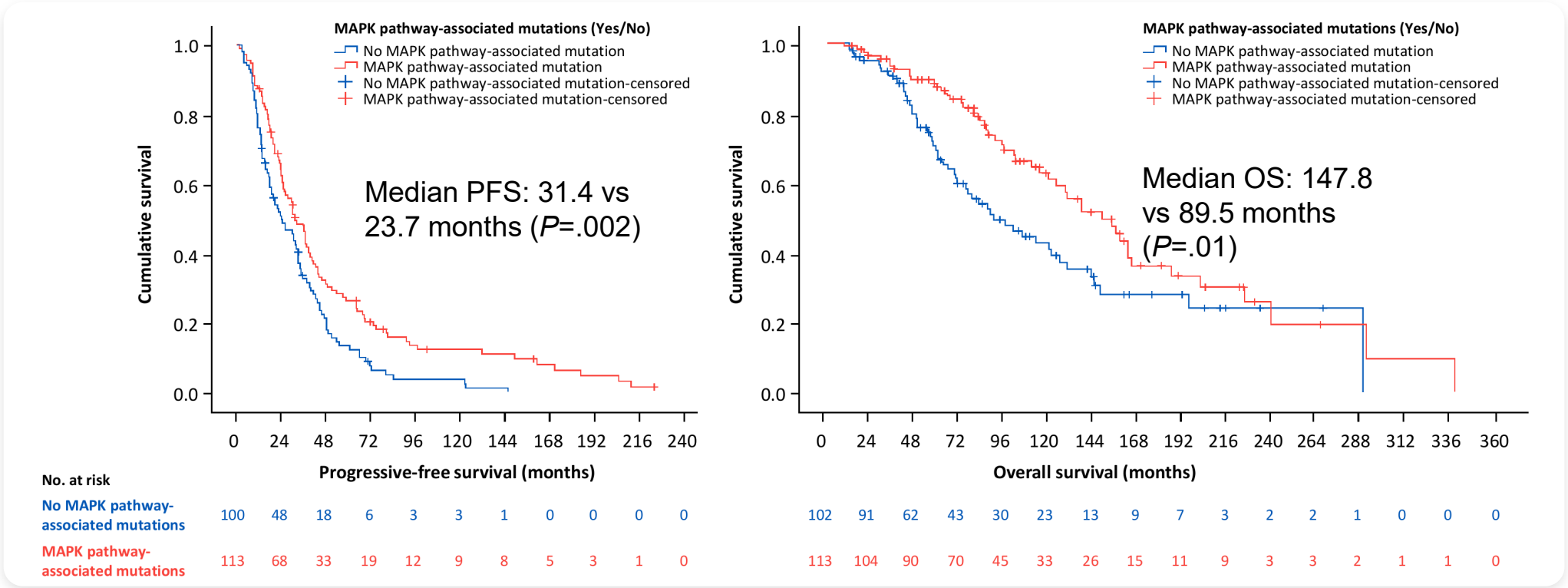
Features of *LGSOC* by *KRAS* mutation status

Clinical presentation and prognosis of LGSOC can vary based on *KRAS* status[1–5]

	KRAS mt	*KRAS* wt
Presentation[1,2]	• Early-stage disease, advanced age	• Advanced stage disease, younger age
Prognosis[1–5]	• Improved survival outcomes, longer median PFS and median OS	• Higher recurrence rates, more rapid disease progression
Treatment response[2,4,5]	• Higher sensitivity to platinum-based chemotherapy • Higher sensitivity to targeted therapy with MEK-only inhibitors	• Lower sensitivity to platinum-based chemotherapy • Lower sensitivity to targeted therapy with MEK-only inhibitors

1. Gershenson DM, et al. Br J Cancer. 2015;113(9):1254-1258. 2. Manning-Geist B, et al. Clin Cancer Res. 2022;28(20):4456-4465. 3. Gershenson DM, et al. Gynecol Oncol. 2022;165(3):560-567.
4. Gershenson DM, et al. Lancet. 2022;399(10324):541-553. 5. Monk BJ, et al. J Clin Oncol. 2020;38(32):3753-3762.
KRAS, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MEK, mitogen-activated protein kinase; mt, mutant; OS, overall survival; PFS, progression-free survival; wt, wild-type.

Progression-Free Survival and overall survival in *LGSOC* patients with and without MAPK Pathway-associated mutations



MAPK pathway–mutated tumors (n=113); most common alterations: *KRAS* (n=71), *NRAS* (n=24), *BRAF* (n=18)

Gershenson DM, et al. Gynecol Oncol. 2022;165(3):560-567. Figure reproduced with permission from Gershenson et al. 2022.
LGSOC, low-grade serous ovarian carcinoma; MAPK, mitogen-activated protein kinase; OS, overall survival; PFS, progression-free survival.

What is ctDNA?

ctDNA is the portion of the cell-free DNA in the blood of cancer patients released from tumor cells via apoptosis, necrosis, or active release

In blood circulation, ctDNA has a half-life of <2 hours and consists of short DNA fragments

From 10 mL of blood, the 4–5 mL of plasma obtained from a cancer patient contains 5–10 ng/mL of ctDNA

- ctDNA may help address the need for optimizing biomarkers that can serve as potential targets for novel therapies in ovarian cancer

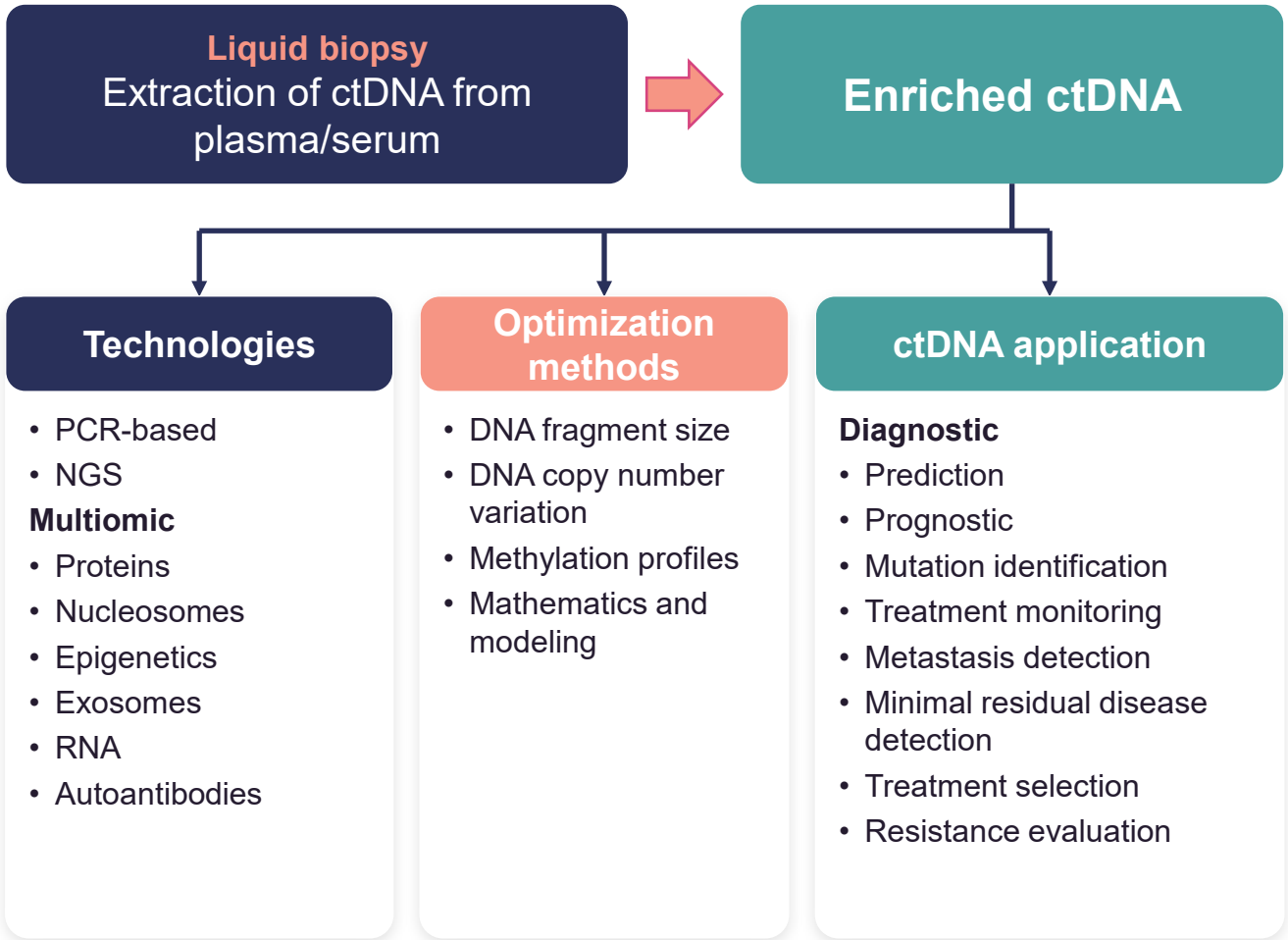


Figure from Yang F, et al. Reprod Biol Endocrinol. 2021;19:178.
cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; NGS, next-generation sequencing; PCR, polymerase chain reaction.

ctDNA Testing: Clinical value and limitations

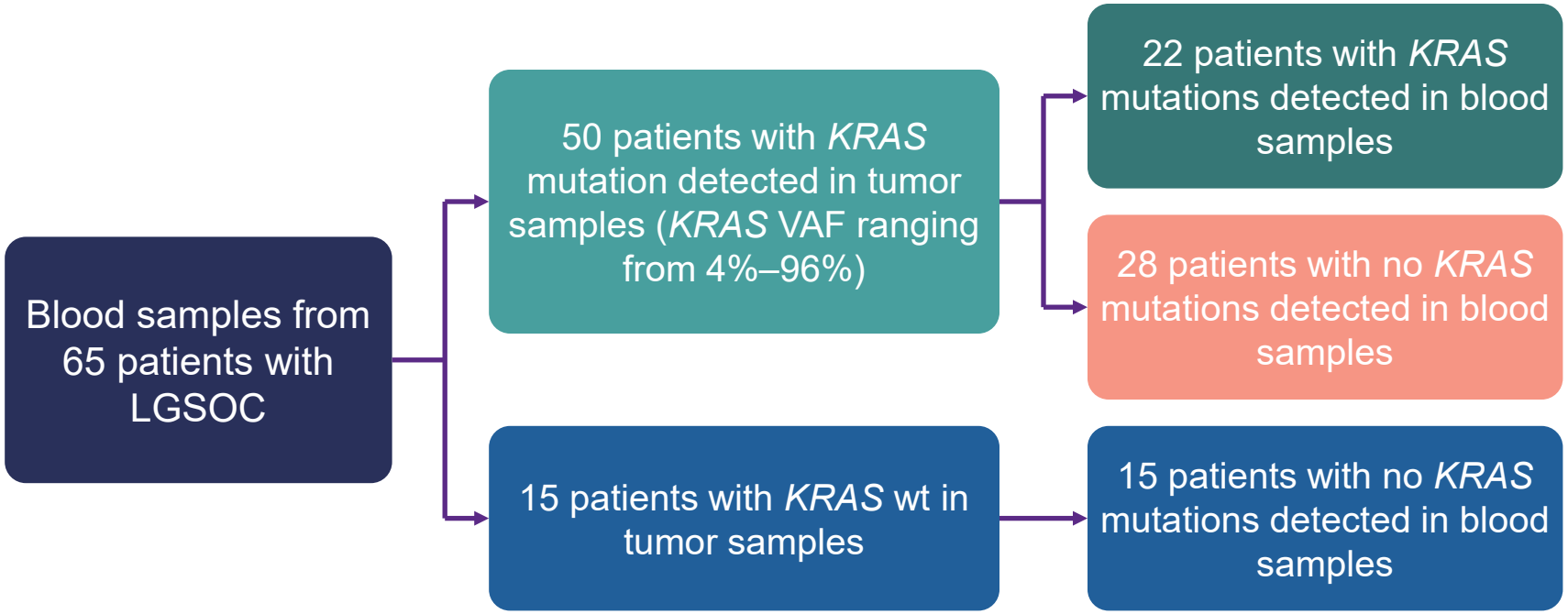
ctDNA supports longitudinal monitoring and early relapse detection in high-risk or recurrent disease.

ctDNA has limited sensitivity in early-stage, low-volume, and low-shedding tumors, meaning that it should not replace tissue-based molecular classification.

Giordano WG, et al. Biomolecules. 2026;16(6):911.

Detection of *KRAS* Mutations in tumor tissue vs blood

PATIENTS WITH *LGSOC* IN ENGOT-OV60/GOG-3052/RAMP 201[1]



44% (22/50) concordance between tumor vs blood samples

For these 22 patients, 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* wt in tumor samples

A negative blood ctDNA result does not exclude a tumor *KRAS* mutation; tissue testing remains necessary when feasible.

1. Van Nieuwenhuysen E, et al. Presented at: ESMO Gynaecological Cancers Congress 2025; June 19–21, 2025; Vienna, Austria.

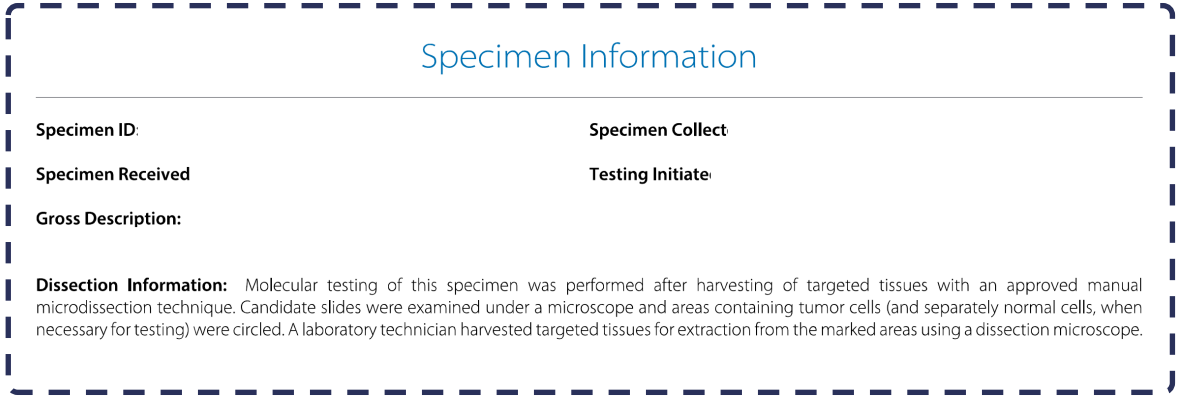
ctDNA, circulating tumor DNA; KRAS, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; VAF, variant allele frequency; wt, wild-type.

In summary, *KRAS* is best profiled within a broad multigene NGS panel on tissue at diagnosis, with plasma ctDNA reserved for insufficient/unobtainable tissue, or serial monitoring and early relapse detection in high-shedding tumors.

Interpreting NGS *KRAS* results

1 Is the result informative or limited by the specimen?

- "No mutation detected" is only valid on an adequate sample
- Interpret a "wild-type"/negative result against tumor content and stated limit of detection
- A negative result from a low-purity, non-enriched specimen may be a false negative[1,2]



Specimen Information

Specimen ID: **Specimen Collect**

Specimen Received **Testing Initiate**

Gross Description:

Dissection Information: Molecular testing of this specimen was performed after harvesting of targeted tissues with an approved manual microdissection technique. Candidate slides were examined under a microscope and areas containing tumor cells (and separately normal cells, when necessary for testing) were circled. A laboratory technician harvested targeted tissues for extraction from the marked areas using a dissection microscope.

1. Sepulveda AR, et al. Am J Clin Pathol. 2017;147(3):221–260. 2. Zarabi SK, et al. Biomolecules. 2024;14(2):168.

Interpreting NGS *KRAS* results

2 What is the exact variant?

Review the specific codon/substitution

The MD Anderson retrospective analysis showed that G12D and G12V predominated, whereas G12C was uncommon.[1]

Knowing the exact *KRAS* variant is important for clinical trial eligibility because many trials enroll patients by specific variant.

G12D	G12V	G12C
~28%	~26%	~5%

Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
KRAS	DNA-Tumor	Pathogenic Variant	p.G12V	2	c.35G>T	10	NM_004985.4

Interpretation: A pathogenic codon 12 mutation was detected in KRAS.

KRAS or V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog encodes a signaling intermediate involved in many signaling cascades including the EGFR pathway. KRAS somatic mutations have been found in pancreatic (57%), colon (35%), lung (16%), biliary tract (28%), and endometrial (15%) cancers. Several germline mutations of KRAS (V14I, T58I, and D153V amino acid substitutions) are associated with Noonan syndrome.

1. Son J, et al. Clin Cancer Res. 2024;30(14):2986-2995.

Interpreting NGS *KRAS* results

3 What does the VAF mean?

Variant allele frequency (VAF) is the fraction of sequencing reads at a given genomic position that carry the mutant allele rather than the reference (wild-type) allele.[1]

A report reading "*KRAS* p.G12V, VAF 10%" means that 10% of reads at that position contained the variant.

A tumor VAF near 50% or 100% may suggest germline origin but requires confirmatory germline testing.[2]

Mutational Analysis by Next-Generation Sequencing (NGS)

Gene	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
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1. Boscolo Bielo L, et al. Trends Cancer. 2023;9(12):1058–1068.. 2. Li MM, et al. J Mol Diagn. 2017;19(1):4–23.

Interpreting NGS KRAS results

4 VUS?

A variant of uncertain significance (VUS) is a genetic variant for which available evidence is insufficient to classify it as pathogenic or benign.[1]

VUS must not guide treatment decisions.[1]

Cancer-Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
PIK3CA	Seq	DNA-Tumor	**Likely Pathogenic Variant Exon 14 | p.E674Q**
		DNA-Tumor	**Pathogenic Variant Exon 10 | p.E545K**
		DNA-Tumor	Variant of Uncertain Significance Exon 14 | p.E722K

Li MM, et al. J Mol Diagn. 2017;19(1):4–23.

Patient selection considerations

Timing for tissue testing

Test early

- *KRAS* mutations are generally seen as early carcinogenic events in gynecologic cancers [1]
- Early testing preserves results for future treatment selection.
- The MD Anderson cohort found *KRAS* mutations enriched in endometrioid and low-grade serous gynecologic cancers.[1]

Re-testing after POD

- Heterogeneity in tumor tissue [2]
- Possibility of acquired *KRAS* mutation [2]
- *KRAS* should be part of a broad NGS panel rather than a single-gene test to conserve tissue and capture co-alterations

1. Son J, et al. Clin Cancer Res. 2024;30(14):2986–2995. 2. Dong J, et al. J Ovarian Res. 2024;17:133.

Integrating biomarker testing into clinical workflow

1. **Build testing into the workflow so an adequate specimen routes to comprehensive NGS at the decision point**

   Best used at diagnosis of advanced/recurrent disease

2. **Route complex or actionable results to a molecular tumor board**

   Helpful for review of NGS with clinical data and form a documented consensus recommendation

3. **Close the loop on turnaround by tracking when testing is ordered and resulted**

   One failure point in biomarker testing is unreviewed PDFs sitting in the chart

4. **Incorporate the report into the office note to make the results findable and actionable**

   Include the specific variant (ex: *KRAS* G12V) as this is often important in treatment planning and clinical trial eligibility



Treatment Considerations & Mechanism of Action

Brian Slomovitz, MD
Mount Sinai Medical Center

LGSOC vs HGSOC

Two different diseases that share a name

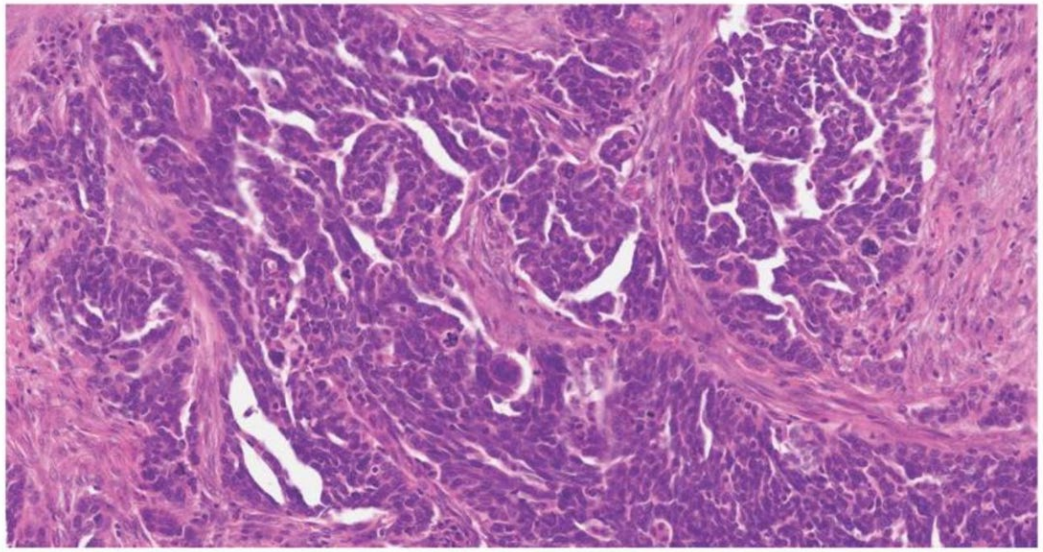
	LGSOC	HGSOC
Share of epithelial ovarian cancers	**5–10%**	The large majority
Median age at diagnosis	**Mid-40s to mid-50s**	62
Growth rate	Indolent, over years	Rapid
Chemosensitivity at recurrence	**Poor**	Usually good initially
Hormone receptors	ER-positive in most; endocrine therapy active	Often ER-positive; limited treatment role
Principal molecular driver(s)	**MAPK pathway alterations: *KRAS, BRAF, NRAS***	DNA repair defects: **HRD including *BRCA1/2*; *TP53* mutation**

LGSOC and HGSOC are biologically distinct diseases; evidence from HGSOC should not be directly extrapolated to LGSOC.

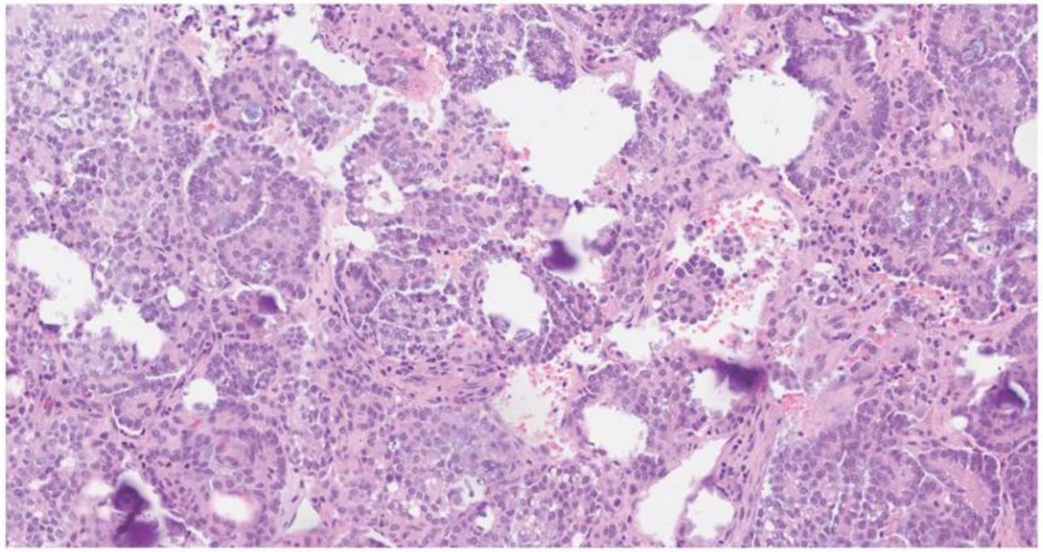
Grisham RN, et al. Int J Gynecol Cancer. 2023;33(9):1331–1344.
ER, estrogen receptor; HGSOC, high-grade serous ovarian carcinoma; HRD, homologous recombination deficiency; LGSOC, low-grade serous ovarian carcinoma; MAPK, mitogen-activated protein kinase

Pathologic distinction between HGSOC and LGSOC

HGSOC



LGSOC



Clinicopathological Characteristics of Serous Ovarian Carcinoma		
	HGSOC	**LGSOC**
Presumed precursor	STIC of the fallopian tube	Serous borderline
Clinical course	Rapid	Slow
Grading[a]	Severe nuclear atypia; >12 mitoses/10 HPFs	Mild-to-moderate nuclear atypia; ≤12 mitoses/10 HPFs

- [a] *Grading two-tiered pathology grading system based on nuclear atypia and mitotic index as a secondary feature is used to distinguish subtypes.*
- *Zwimpfer TA, et al. Cancer Treat Rev. 2023:112:102497.*
- *HGSOC, high-grade serous ovarian carcinoma; HPF, high-power field; LGSOC, low-grade serous ovarian carcinoma; STIC, serous tubal intraepithelial carcinoma.*

Recurrence and survival in advanced LGSOC

Outcomes from a retrospective study of 92 patients treated at two high-volume centers.

80.4%
Experienced recurrence

25 mo
Median PFS

86 mo
Median OS

142 mo
Median OS with no gross residual disease

Natural history

- Recurrence is common in advanced LGSOC.
- Prolonged survival remains possible despite recurrence.
- Treatment often focuses on durable disease control and quality of life.

Residual disease after primary cytoreductive surgery

- No gross residual disease: **142 months**
- Residual disease 1–10 mm: **86 months**
- Residual disease >10 mm: **35 months**

- The strongest modifiable variable in the whole disease. Reasonable to ask a surgeon directly how many of these they do a year

Di Lorenzo P, et al. Front Oncol. 2022;12:970918.

Why chemotherapy has limited activity in recurrent LGSOC

Key therapeutic vulnerabilities in LGSOC

Chemotherapy in recurrent disease

- Chemotherapy has limited activity after recurrence.
- Historical recurrent disease ORR: 3.7%
- Platinum-based ORR: **22% (2/9) in second line; 10% (1/10) in third line**

Key therapeutic vulnerabilities

- ER is expressed in most LGSOCs, supporting endocrine therapy.
- **MAPK-pathway mutations occur in approximately 53%**
- ***KRAS* 33%; *NRAS* 11%; *BRAF* 8%**

In one retrospective series, MAPK pathway mutations were associated with longer median OS (148 vs 90 months)

Gershenson DM, et al. Gynecol Oncol. 2009;114:48–52; Manning-Geist BL, et al. Cancer. 2023;129:2004–2012; Gershenson DM, et al. Gynecol Oncol. 2022;165:560–567.
ER, estrogen receptor; LGSOC, low-grade serous ovarian carcinoma; MAPK, mitogen-activated protein kinase; ORR, objective response rate; OS, overall survival.

Systemic treatment options for recurrent LGSOC

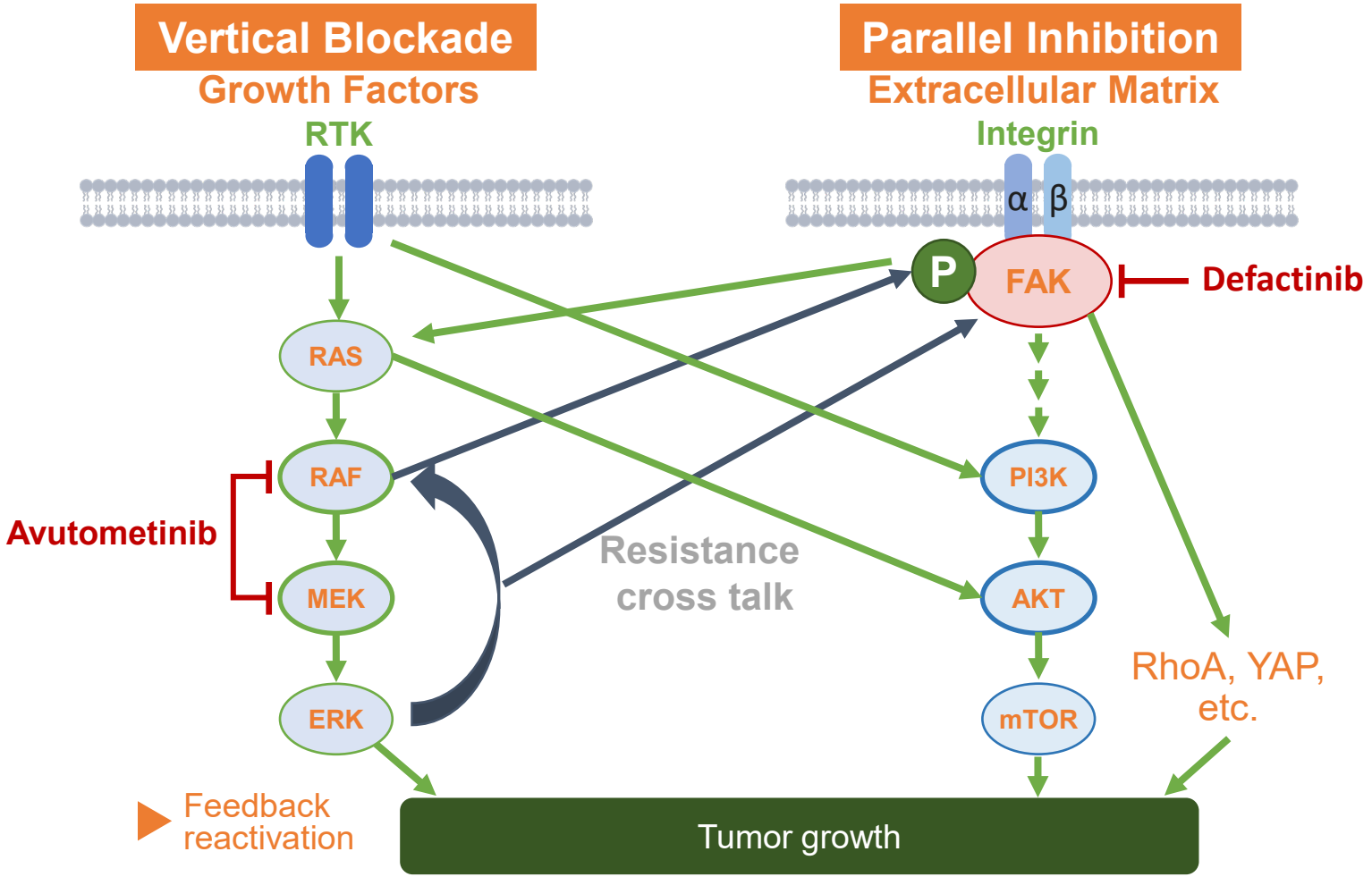
Regimen	Study/design	ORR (%)	mPFS (mo)	mOS (mo)	CBR
Trametinib	Phase 2/3; GOG-281/LOGS[1]	26%	13.0 vs 7.2	37.6 vs 29.2	NR
Anastrozole	Phase 2; PARAGON	14%	11.1	NR	61% at 6 mo
Letrozole+Ribociclib	Single-arm, Phase 2; GOG-3026[3]	30.6%	14.5	44.5	84%
Bevacizumab-containing therapy	Retrospective[4]	47.5%	10.2	NR	77.5%
Chemotherapy	Retrospective[5]	25%	NR	NR	NR

1. Gershenson DM, et al. Lancet. 2022;399(10324):541–553. NCT02101788. 2. Tang M, et al. Gynecol Oncol. 2019;154(3):531–538. ACTRN12610000796088. 3. Slomovitz BM, et al. J Clin Oncol. 2026;44(3):153–163. NCT03673124. 4. Dalton HJ, et al. Gynecol Oncol. 2017;145(1):37–40. 5. Manning-Geist BL, et al. Cancer. 2023;129(13):2004–2012.
CBR, clinical benefit rate; DOR, duration of response; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Avutometinib + Defactinib in Recurrent LGSOC

avutometinib + defactinib targets 3 kinases across the 2 pathways (MEK1/2 + FAK [resistance pathway]) vs MEK inhibitors targeting only 1 pathway (MEK1/2)

Avutometinib: RAF/MEK clamp may be more effective than MEK inhibition alone in inhibiting MAPK-mediated tumor growth



Defactinib: FAK inhibitor may act as an intrinsic adaptive resistance response

Banerjee SN, et al. Presented at IGCS 2024; Abstract LB007/1548. Banerjee SN, et al. J Clin Oncol. 2025;43(25):2782–2792. NCT04625270. Grisham RN, et al. Presented at SGO 2025; Abstract 814288. Grisham RN, et al. Presented at SGO 2025; Abstract 814605. US Food and Drug Administration. Avmapki and Fakzynja Prescribing Information. 2025.

AKT, protein kinase B; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; LGSOC, low-grade serous ovarian cancer; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; mTOR, mechanistic target of rapamycin; PI3K, phosphoinositide 3-kinase; PYK2, proline-rich tyrosine kinase 2; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RhoA, Ras homolog family member A; RTK, receptor tyrosine kinase; YAP, Yes-associated protein.

RAMP 201: Avutometinib ± defactinib in recurrent LGSOC[1,2] registration-directed phase 2 study

Key Eligibility Criteria

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

Avutometinib + Defactinib
Avutometinib 3.2 mg PO biw
Defactinib 200 mg PO bid
(N=115)

Primary Endpoint

ORR (BICR per RECIST v1.1)

Secondary Endpoints

DOR, ORR by INV, PFS, OS, safety, PK

Patient Characteristics		Avutometinib + Defactinib		
		All (N=115)	*KRAS*mut (n=58)	*KRAS*wt (n=57)
Median age (range), years		54 (21-87)	60 (29-87)	45 (21-80)
ECOG PS, %	**0**	78 (68)	42 (72)	36 (63)
	1	37 (32)	16 (28)	21 (37)
Median number of prior systemic regimens (range), n		3 (1-9)	3 (1-9)	3 (1-9)
Prior platinum-based chemotherapy, n (%)		114 (99)	58 (100)	56 (98)
Prior hormonal therapy, n (%)		99 (86)	49 (85)	50 (88)
Prior bevacizumab, n (%)		59 (51)	23 (40)	36 (63)
Prior MEKi therapy, n (%)		25 (22)	12 (21)	13 (23)

1. Banerjee SN, et al. J Clin Oncol. 2025;43(25):2782-2792. *2.* Grisham RN, et al. SGO 2026.

BICR, blinded independent central review; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; LGSOC, low-grade serous ovarian cancer; MEKi, MEK inhibitor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; wt, wild-type.

KRASwt

Efficacy outcomes of RAMP 201 for recurrent *KRAS*wt LGSOC[1,2]

RAMP 201 has not received a NCCN® Compendium Listing or FDA Approval in the *KRAS*wt cohort

	Avutometinib + Defactinib[1,2,a]	
	All (n=109)	*KRAS*wt (n=52)
Median PFS (95% CI), mo	12.9 (10.9-19.6)	12.7 (7.4-12.9)
Median DOR (95% CI), mo	31.1 (14.8-NE)	12.0 (5.5-NE)
Confirmed ORR (BICR), n (%)	34 (31%)	9 (17%)

[a] *Data cutoff date: August 12, 2025. Median follow-up: 24.9 months (range, 22.4-52.5).*

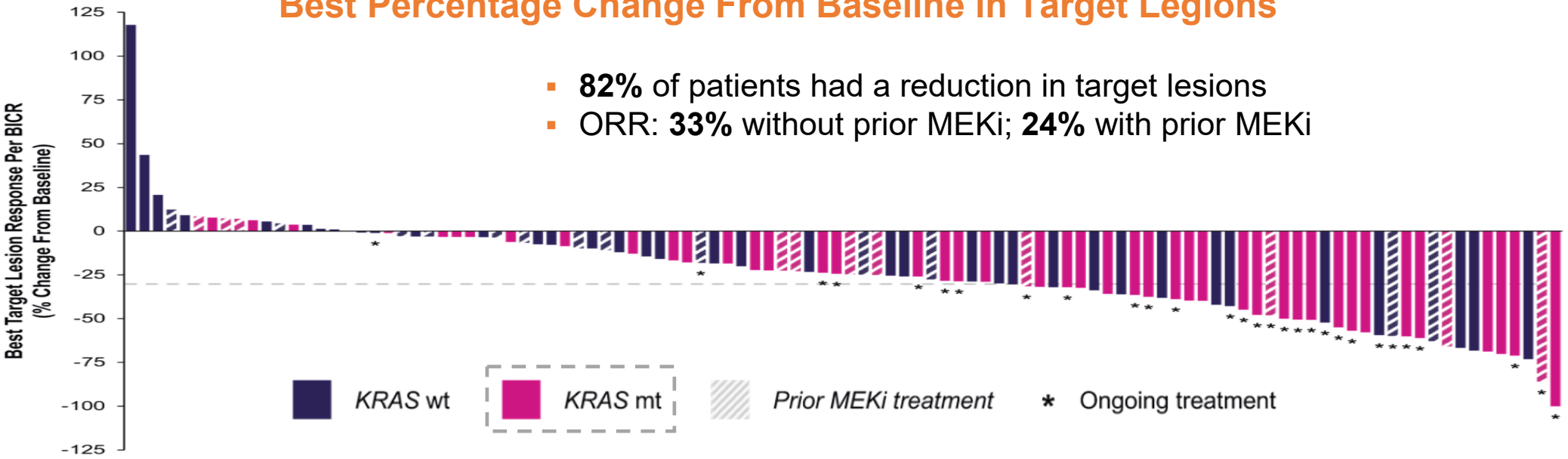
1. *Banerjee SN, et al. J Clin Oncol. 2025;43(25):2782-2792. NCT04625270. 2. Grisham RN, et al. Gynecol Oncol. 2026;213:59–67. 3. Grisham RN, et al. SGO 2026. US Food and Drug Administration. Avmapki and Fakzynja Prescribing Information. 2025.*

BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; FDA, US Food and Drug Administration; NCCN Guidelines®. Ovarian Cancer. Version 4.2026. Accessed October 7, 2026. LGSOC, low-grade serous ovarian cancer; NCCN, National Comprehensive Cancer Network; NE, not evaluable; ORR, objective response rate; PFS, progression-free survival; wt, wild-type.

KRASmut

RAMP 201:
Tumor response overall and by KRAS status[1,2]

Best Percentage Change From Baseline in Target Legions



- **82%** of patients had a reduction in target lesions
- ORR: **33%** without prior MEKi; **24%** with prior MEKi

Response	Avutometinib + Defactinib	
	All (n=109)	*KRAS*mut (n=57)
Confirmed ORR (BICR), n (%)	**34 (31)**	**25 (44)**
CR	2 (2)	2 (4)
PR	32 (29)	23 (40)
SD	62 (57)	28 (49)
PD	9 (8)	2 (4)

- Subgroup analyses showed high response rates in heavily pretreated patients, regardless of previous line of therapy

Data cutoff date: June 30, 2024. Median follow-up: 13.6 months (range, 1.4-39.5).
Efficacy-evaluable population includes patients who received at least 1 dose of study drug and had measurable disease at baseline by BICR.

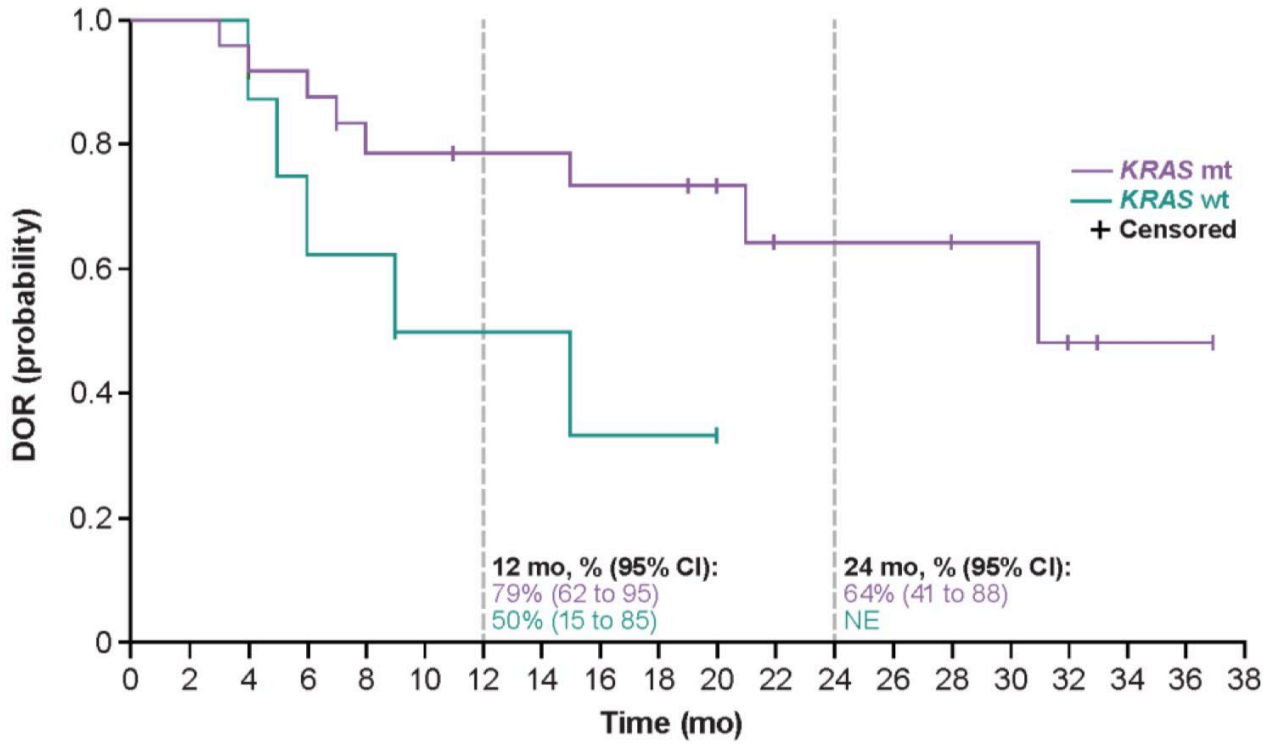
1. Banerjee SN, et al. J Clin Oncol. 2025;43(25):2782-2792. 2. Grisham RN, et al. SGO 2025. Abstract 814288.Grisham RN, et al. SGO 2025. Abstract 814288.

BICR, blinded independent central review; CR, complete response; MEKi, MEK inhibitor; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

RAMP 201:
Duration of response 1 year post primary analysis (Avutometinib + Defactinib)[1,2]

*KRAS*mut

DOR by *KRAS* Mutational Status

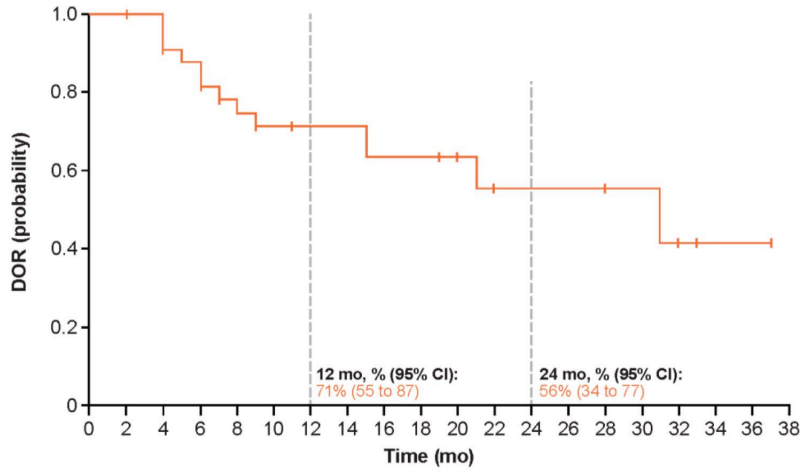


Number at risk:

KRAS mt	25	22	16	14	5	4	1
KRAS wt	9	6	3	2	0		

Median DOR (95% CI), mo	
Avutometinib + Defactinib	
All (n=109)	*KRAS*mut (n=57)
31.1 (14.8-NE)	31.1 (21.2-NE)

DOR in ITT



Number at risk:

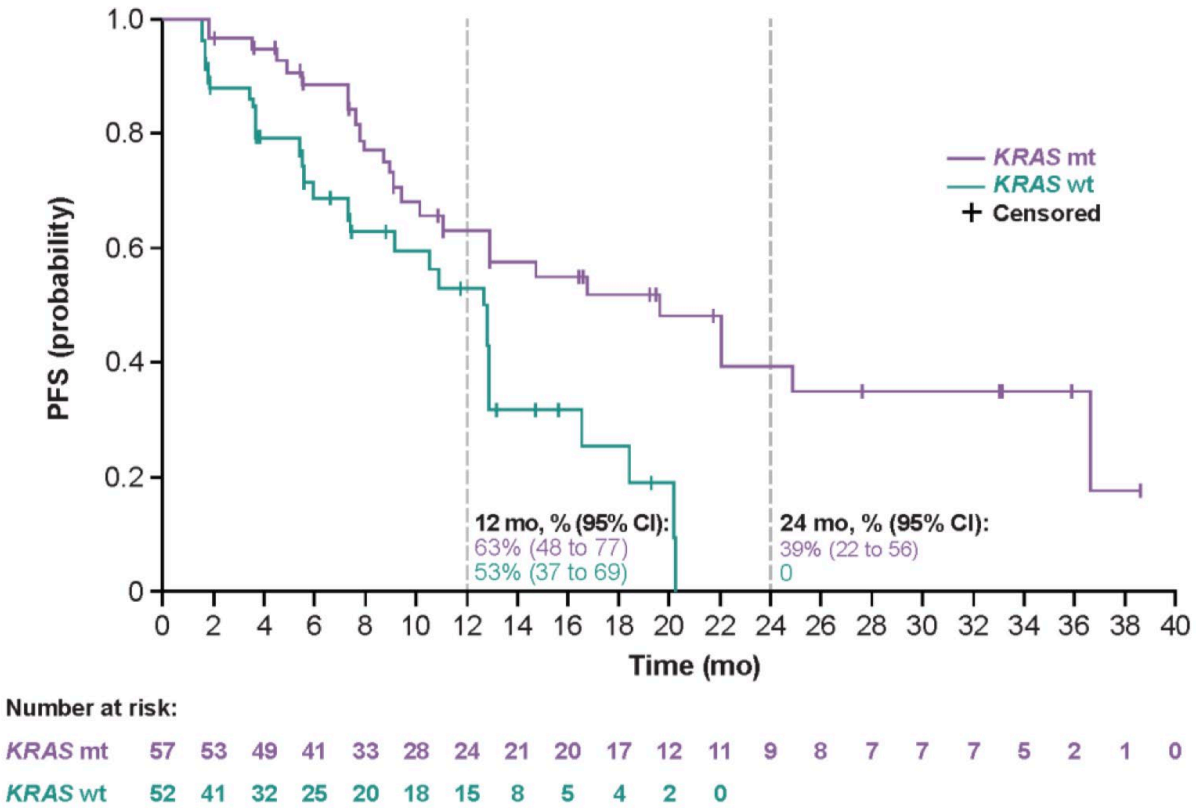
All patients	34	28	19	16	5	4	1

Data cutoff date: August 12, 2025. Median follow-up: 24.9 months (range, 22.4-52.5).
BICR-assessed DOR was calculated for patients with a CR or PR from the time of first response to PD using Kaplan-Meier methods.
1. Banerjee SN, et al. J Clin Oncol. 2025;43(25):2782-2792. 2. Grisham RN, et al. SGO 2026. 3. Grisham RN, et al. Gynecol Oncol. 2026;213:59–67.
BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; NE, not evaluable; PR, partial response.

KRASmut

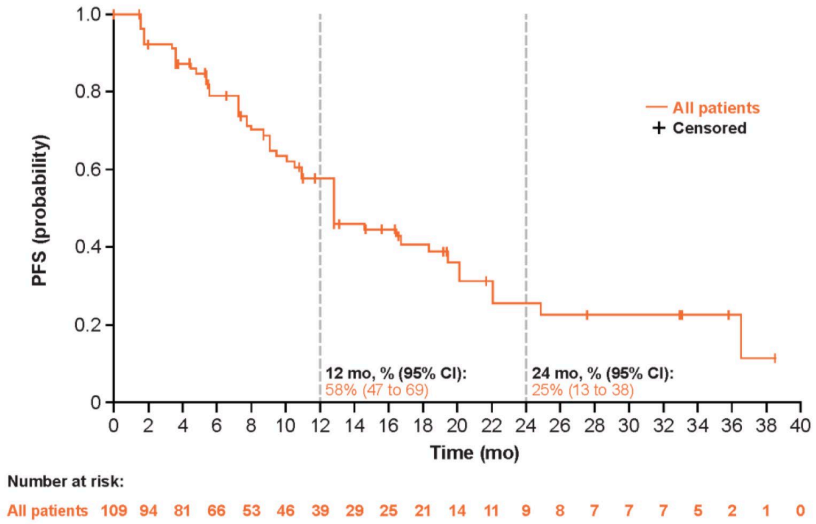
RAMP 201:
PFS by BICR (Avutometinib + Defactinib)[1,2]

PFS by *KRAS* Mutational Status



Median PFS (95% CI), mo	
Avutometinib + Defactinib	
All (n=109)	*KRAS*mut (n=57)
12.9 (10.9-19.6)	19.6 (11.1-36.6)

PFS in ITT



Data cutoff date: August 12, 2025. Median follow-up: 24.9 months (range, 22.4-52.5).

1. Banerjee SN, et al. J Clin Oncol. 2025;43(25):2782-2792. 2. Grisham RN, et al. Gynecol Oncol. 2026;213:59–67.

BICR, blinded independent central review; CI, confidence interval; PFS, progression-free survival.

RAMP 201:
Safety (Avutometinib + Defactinib)[1,2]

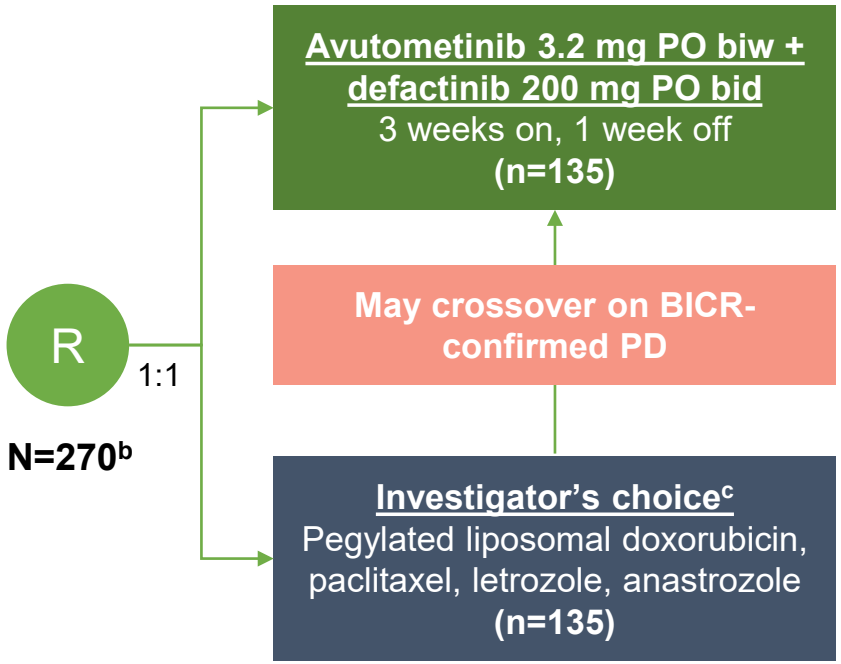
TRAEs[c] (All grades >20%), n (%)		Primary analysis[a] N=115		Updated analysis[b] N=115	
		All grades	Grade ≥3	All grades	Grade ≥3
Nonlaboratory	Nausea	77 (67)	3 (3)	78 (68)	3 (3)
	Diarrhea	67 (58)	9 (8)	68 (59)	9 (8)
	Peripheral edema	61 (53)	1 (1)	61 (53)	1 (1)
	Rash[d]	58 (50)	3 (3)	59 (51)	5 (4)
	Fatigue	50 (44)	3 (3)	51 (44)	3 (3)
	Vomiting	49 (43)	3 (3)	50 (44)	3 (3)
	Vision blurred	47 (41)	0	48 (42)	0
	Dermatitis acneiform	39 (34)	5 (4)	39 (34)	5 (4)
	Dry skin	30 (26)	0	31 (27)	0
	Anemia	26 (23)	6 (5)	27 (24)	8 (7)
Laboratory related	Increased blood CPK	69 (60)	28 (24)	69 (60)	30 (26)
	Hyperbilirubinemia	38 (33)	5 (4)	38 (33)	5 (4)
	AST increased	36 (31)	2 (2)	36 (31)	2 (2)
	ALT increased	25 (22)	2 (2)	26 (23)	2 (2)

[a] Data cutoff date: June 30, 2024. [b] Data cutoff date: August 12, 2025.
[c] Most common AEs (preferred term) considered by the investigator to be related to study drug (either avutometinib or defactinib).
[d] Treatment-related AEs for rash include preferred terms: butterfly rash, rash, rash erythematous, rash macular, rash maculopapular, rash papular, and rash pruritic.
1. *Banerjee SN, et al. J Clin Oncol. 2025;43(25):2782-2792.* ***2.*** *Grisham RN, et al. Gynecol Oncol. 2026;213:59–67.*
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; TRAE, treatment-related adverse event.

RAMP 301:
Phase 3 trial of avutometinib + defactinib in recurrent LGSOC[1,2]

Key Eligibility Criteria

- Confirmed LGSOC diagnosis
- Recurrent disease after prior platinum therapy
- Documented *KRAS* mutation status (wt or mut)
- Measurable disease per RECIST v1.1
- Prior MEKi allowed[a]
- Prior bevacizumab allowed



Primary Endpoint

PFS (BICR); sequential evaluation of PFS in (1) *KRAS*mut LGSOC; (2) all recurrent LGSOC

Key Secondary Endpoints

OS, PFS per INV assessment, ORR, DOR, DCR, safety, PK, PROs

Stratification Factors

- *KRAS* mutation status (wt vs mut)
- Number of prior lines of therapy (1-3 vs ≥4)
- Geography (North America/Europe vs ROW)

[a] Previous line of treatment with a MEK and/or RAF inhibitor is permitted. [b] RAMP-301 is expected to enroll 270 patients across 96 sites globally in Australia, United States, Canada, United Kingdom, Europe, and Korea. [c] Pegylated liposomal doxorubicin 40 mg/m² intravenously on day 1 of each 28-day (4-week) cycle; paclitaxel 80 mg/m² intravenously on days 1, 8, and 15 of each 28-day (4-week) cycle; anastrozole 1 mg orally once daily of each 28-day (4-week) cycle; letrozole 2.5 mg orally once daily of each 28-day (4-week) cycle.

1. Grisham R, et al. Int J Gynecol Cancer. 2025:ijgc-2024-005919. 2. ClinicalTrials.gov. NCT06072781. Accessed February 18, 2026.

BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; INV, investigator; IV, intravenous; LGSOC, low-grade serous ovarian cancer; MEKi, MEK inhibitor; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcome; RAF, rapidly accelerated fibrosarcoma kinase; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world.

GOG-3026: Ribociclib and Letrozole in Recurrent Low-Grade Serous Carcinoma

Phase 2 Study

Key Eligibility Criteria[1]

- Histological confirmation of diagnosis
- Recurrent, measurable disease by RECIST v1.1
- No restrictions on number of prior therapies
- No prior CDKi, those treated with letrozole or another AI for other indications must have ≥6 mo AI-free interval prior to initiating this trial
- ECOG PS 0-2

Ribociclib 600 mg orally once daily, 3 weeks on/1 week off + letrozole 2.5 mg orally once daily

(n=49[a])

Primary Endpoint

ORR

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)
Median cycles (range)	12 (1-61)
Discontinuation due to AE	2 (4.1)

As of December 23, 2024, 18.4% of patients remained on treatment

[a] *51 enrolled, 49 eligible and treated were included in the safety and efficacy analysis.*

Active, accrual closed (Est. completion Dec 2026)

1. *ClinicalTrials.gov. NCT03673124. Accessed October 07 2026.* ***2.*** *Slomovitz BM, et al. J Clin Oncol. 2026;44:153-163.*

AE, adverse event; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4/6; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

GOG-3026: Post hoc exploratory subgroup analyses

Exploratory Subgroups

- Prior endocrine, PARP, MEK, bevacizumab exposure
- <3 vs ≥3 prior lines
- Age <60 vs ≥60

Subgroup	Ribociclib and Letrozole			
	Outcomes by Prior Therapy, Chemotherapy Intensity, and Age (n=47[a])			
	Exposed ORR, %	Exposed CBR, %	Naive ORR, %	Naive CBR, %
Endocrine therapy	40.0	93.3	28.1	84.4
MEK inhibitor	16.7	83.3	34.1	87.8
PARP inhibitor	40.0	100	31.0	85.7
Bevacizumab	14.3	85.7	35.0	87.5

	ORR, %	CBR, % (n)
<3 prior lines	32.4	89.2
≥3 prior lines	30.0	80.0
<60 years	36.0	92.0
≥60 years	27.3	81.8

[a] 49 were treated; 47 were response-evaluable.
ORR = CR + PR
CBR = CR + PR + SD lasting ≥6 months.
Podder V, et al. Presented at the SGO Annual Meeting for Women's Cancer 2026. ClinicalTrials.gov. NCT03673124. ssed October 07 2026.
CBR, clinical benefit rate; CR, complete response; MEK, mitogen-activated protein kinase kinase; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase; PR, partial response; SD, stable disease.

FRα–Targeted ADC Landscape in HGSOC

	Mirv[1] (N=453)	Rina-S[2] (N=42)	LY4170156[3] (N=95)	BAT-8006[4] (N=54)	AZD5335[5] (N=28)
Payload	DM4	Exatecan	Exatecan	Exatecan	Topoisomerase I inhibitor
DAR	~4	~8	~8	~7-8	~8
Trial	MIRASOL[1]	RAINFOL-01[2]	NCT06400472[3]	NCT05378737[4]	FONTANA[5]
ORR	42.3% vs 15.9%	50% (n=18 at 120 mg/m^2)	55% (n=20 at 4 mg/kg)	41% all FRα 43% ≥50% FRα 48% ≥75% FRα	34% (all patients, all doses) 56% FRα-high at ≥1.6 mg/kg
mPFS, mo	5.62 vs 3.98 HR=0.65	NR	NR	7.47 (4.27-7.93) (n=43 at 84 mg/m^2) 7.67 (4.07-NE) (n=39 at 93 mg/m^2)	NR
mOS, mo	16.46 vs 12.75 HR=0.67	NR	NR	NR	NR

- Approximately 40% of LGSOC tumors are FRα-high (≥75%)[6]
  - LGSOC lacking MAPK pathway genetic alterations are more likely to be FRα-high

1. Moore KN, et al. N Engl J Med. 2023;389(23):2162-2174. *2.* Lee E, et al. SGO 2025. Abstract 809034. *3.* Ray-Coquard IL, et al. ASCO 2025. Abstract 3023. *4.* Zhang S, et al. ASCO 2025. Abstract 5517. *5.* Shapira-Frommer R, et al. ESMO 2024. Abstract 754P. *6.* Manning-Gelst BL, et al. Gynecol Oncol. 2024;188:52-57.

ADC, antibody–drug conjugate; CI, confidence interval; DAR, drug-to-antibody ratio; DM4, maytansinoid DM4; FRα, folate receptor alpha; HGSOC, high-grade serous ovarian cancer; HR, hazard ratio; LGSOC, low-grade serous ovarian cancer; MAPK, mitogen-activated protein kinase; mirv, mirvetuximab soravtansine-gynx; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; ORR, objective response rate; Rina-S, rinatabart sesutecan.

Systemic treatment options for Recurrent LGSOC

Regimen	Study/design	ORR (%)	mPFS (mo)	mOS (mo)	CBR
Avutometinib + defactinib	Phase 2; RAMP 201; FDA accelerated approval, May 8, 2025	**44%**	NR	NR	NR
Trametinib	Phase 2/3; GOG-281/LOGS[1]	26%	13.0 vs 7.2	37.6 vs 29.2	NR
Anastrozole	Phase 2; PARAGON	14%	11.1	NR	61% at 6 mo
Letrozole + Ribociclib	Single-arm, Phase 2; GOG-3026[3]	30.6%	14.5	44.5	84%
Bevacizumab-containing therapy	Retrospective[4]	47.5%	10.2	NR	77.5%
Chemotherapy	Retrospective[5]	25%	NR	NR	NR

1. Gershenson DM, et al. Lancet. 2022;399(10324):541–553. NCT02101788. 2. Tang M, et al. Gynecol Oncol. 2019;154(3):531–538. ACTRN12610000796088. 3. Slomovitz BM, et al. J Clin Oncol. 2026;44(3):153–163. NCT03673124. 4. Dalton HJ, et al. Gynecol Oncol. 2017;145(1):37–40. 5. Manning-Geist BL, et al. Cancer. 2023;129(13):2004–2012.
CBR, clinical benefit rate; DOR, duration of response; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival;

Key toxicities of avutometinib + defactinib

Dermatologic	Ocular	Systemic/Laboratory
Acneiform or maculopapular rash	Visual impairment or blurred vision	CPK elevation; potential rhabdomyolysis
Dry skin, pruritus, and photosensitivity	MEK inhibitor–associated retinopathy/subretinal fluid	AST/ALT and bilirubin elevations
Paronychia	Vitreoretinal disorders, including retinal detachment	Edema, fatigue, nausea, diarrhea, and vomiting
Rare serious cutaneous reactions	Retinal vein occlusion (rare)	Musculoskeletal pain

Banerjee SN, et al. J Clin Oncol. 2025;43:2782–2792; Jeng-Miller KW, et al. The Oncologist. 2024;29:e616–e621. avutometinib + defactinib Prescribing Information. Verastem, Inc.; 2025.

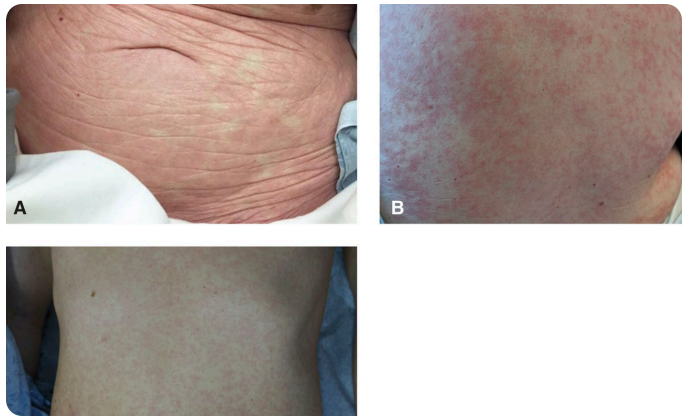
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; FAK, focal adhesion kinase; MEK, mitogen-activated extracellular signal-regulated kinase; RAF, rapidly accelerated fibrosarcoma kinase.

Recognizing common treatment-related skin toxicities



ACNEIFORM ERUPTION

- Early papules and pustules on the face, scalp, chest, or back
- Monomorphic eruption without comedones



MACULOPAPULAR ERUPTION

- Erythematous patches or plaques on the trunk and extremities
- Often accompanied by pruritus or xerosis

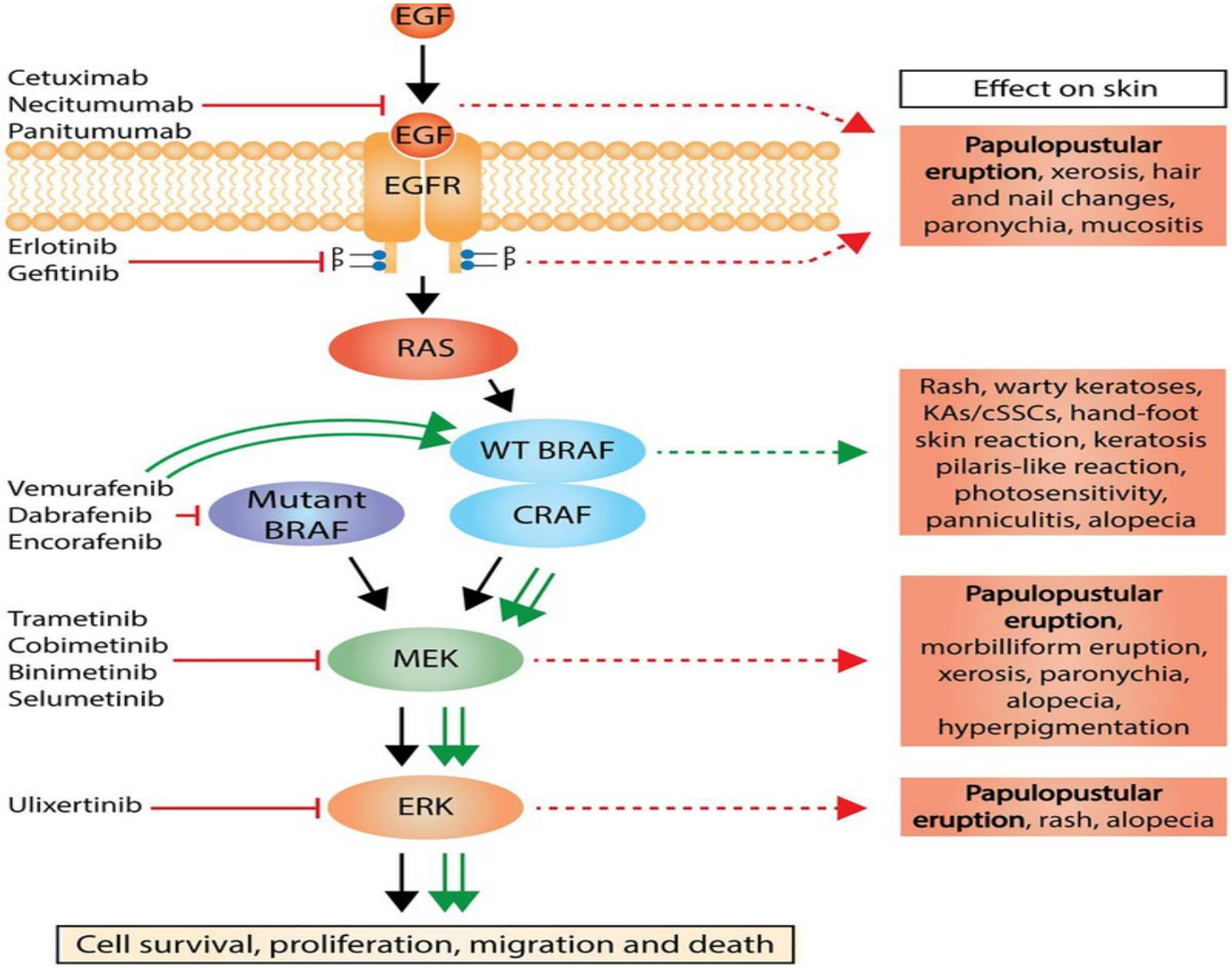


PARONYCHIA

- Tender nail-fold edema, fissuring, or granulation tissue
- Assess for secondary infection

Acneiform images: Lacouture ME, et al. Clin Colorectal Cancer. 2018;17(2):85-96. Alloo A, LeBoeuf NR, eds. Cutaneous Toxicities from Anti-Cancer Therapies. Wolters Kluwer; 2023. avutometinib + defactinib Prescribing Information. Verastem, Inc.; 2025.

Mechanisms of MAPK inhibitor–associated skin toxicity



Wang CJ, Brownell I. Am J Clin Dermatol. 2020;21(6):759–764.

BRAF, B-Raf proto-oncogene; CRAF, RAF-1 proto-oncogene; cSCC, cutaneous squamous-cell carcinoma; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; KA, keratoacanthoma; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; RAS, rat sarcoma; WT, wild-type.

Recognizing common treatment-related skin toxicities

Phenotype	Initial Management
Maculopapular eruption	Moisturizer, topical corticosteroid, oral antihistamine for pruritus; assess severity and exclude infection or severe cutaneous reaction
Paronychia	Antiseptic soaks, bland emollient, topical anti-inflammatory/antimicrobial care; treat secondary infection and obtain dermatology input when persistent or severe
Papulopustular (acneiform) eruption	Continue prophylactic topical corticosteroid and oral antibiotic; assess severity and secondary infection; escalate treatment or obtain dermatology input if persistent or severe

Lacouture ME, et al. Ann Oncol. 2021;32:157–170; avutometinib + defactinib Prescribing Information.

Preventing and managing common toxicities

Skin, muscle, edema, and gastrointestinal events: when to call

Skin

Start prophylaxis with the first dose

Rash 72%; acneiform dermatitis 37%; photosensitivity 16%. Start topical corticosteroid and oral antibiotic prophylaxis with the first dose and continue for at least 2 cycles. Limit sun exposure and use Sroad-spectrum sunscreen (SPF ≥30). Urgently assess blistering, peeling, mucosal involvement, or facial swelling.

Muscle

Monitor CPK and promptly evaluate muscle symptoms

CPK elevation occurred in 82% and was often asymptomatic. Check CPK before each cycle, on day 15 of the first 4 cycles, and as clinically indicated. Immediately report muscle pain or weakness, difficulty moving, dark/red urine, or reduced urine output.

Edema

Monitor swelling, weight, and respiratory symptoms

Edema occurred in 67%. Monitor swelling and weight. Promptly assess for rapid weight gain, unilateral swelling, rapidly worsening edema, or new shortness of breath.

GI

Take with food and establish a symptom-management plan

Nausea occurred in 74% and diarrhea in 68%. Establish antiemetic and antidiarrheal plans before treatment. Urgently assess for severe abdominal pain, persistent vomiting, or inability to pass stool or gas. Intestinal obstruction may be fatal.

Rates are all-grade adverse reactions or laboratory abnormalities reported in the indicated KRAS-mutated RAMP-201 population (N=57).
avutometinib + defactinib [prescribing information]. Verastem, Inc.; revised May 2025.
CPK, creatine phosphokinase; GI, gastrointestinal.

Ocular toxicity: Monitoring and red flags

INCIDENCE

68% experienced an ocular adverse reaction

38%
Visual impairment

26%
Vitreoretinal disorders

13%
Dry eye

9%
Retinal detachment

Median onset of symptomatic events **5 days**

REQUIRED MONITORING

1. **Baseline**
   Comprehensive ophthalmic examination
2. **Before cycle 2**
   Repeat the comprehensive examination
3. **Every 3 cycles**
   Continue regardless of baseline findings

Additional examination as clinically indicated

PROMPT OPHTHALMIC ASSESSMENT

- New or worsening blurred vision
- New floaters or flashes
- Curtain or shadow across the visual field
- Sudden vision loss
- Eye pain, redness, swelling, or marked light sensitivity

Prompt referral may lead to treatment interruption, dose reduction, or permanent discontinuation.

avutometinib + defactinib [prescribing information]. Verastem, Inc.; revised May 2025. Rates are from the pooled safety population with recurrent LGSOC (N=136).

Laboratory and pretreatment monitoring

Test	Frequency	Purpose
Comprehensive ophthalmic examination	Baseline; before cycle 2; every 3 cycles thereafter; and as clinically indicated	Detect subretinal fluid before vision is affected; Monitor for visual impairment and vitreoretinal disorders
CPK	Before each cycle; day 15 of the first 4 cycles; and as clinically indicated	Detect CPK elevation and evaluate for rhabdomyolysis
Liver tests	Before each cycle; day 15 of the first 4 cycles; and as clinically indicated	Monitor for hepatotoxicity; bilirubin elevation may reflect UGT1A1 and OATP1B1/1B3 inhibition
Pregnancy test	Before treatment in females of reproductive potential	Confirm pregnancy status because of embryo-fetal toxicity

Questions to bring to the first visit

- Has my tumor been tested for a *KRAS* mutation, and can I have a copy of the report?
- Who is my eye doctor for this, and is the first appointment booked?
- What is my skin prophylaxis prescription, and does it start on day 1?
- Who do I call after hours, and for which symptoms?

avutometinib + defactinib US prescribing information, revised May 2025
CPK, creatine phosphokinase; OATP, organic anion transporting polypeptide; UGT1A1, uridine diphosphate glucuronosyltransferase 1A1.

Accelerated approval and the confirmatory trial

What the FDA decision established, and what RAMP 301 still needs to show

RAMP 201 Response Rate

44% confirmed ORR

88% of responses lasted ≥ 6 months

Single-arm, phase 2 (n=57) in *KRAS*-mutated recurrent LGSOC

ACCELERATED APPROVAL

FDA approval

Adult patients with *KRAS*-mutated recurrent LGSOC

Continued approval may depend on confirmation of clinical benefit.

RAMP 301 CONFIRMATION

Randomized phase 3 trial

Avutometinib plus defactinib versus investigator's choice

Primary endpoint: PFS

FDA-required analysis: Final OS

Population: *KRAS*-mutated and *KRAS* wild-type LGSOC

Enrollment completed: Topline primary-endpoint results expected mid-2027

The regimen has not yet demonstrated clinical benefit in a completed phase 3 trial. Patients should consider the 44% confirmed response rate alongside the overall safety profile, including ocular adverse reactions reported in 68% of the pooled safety population.

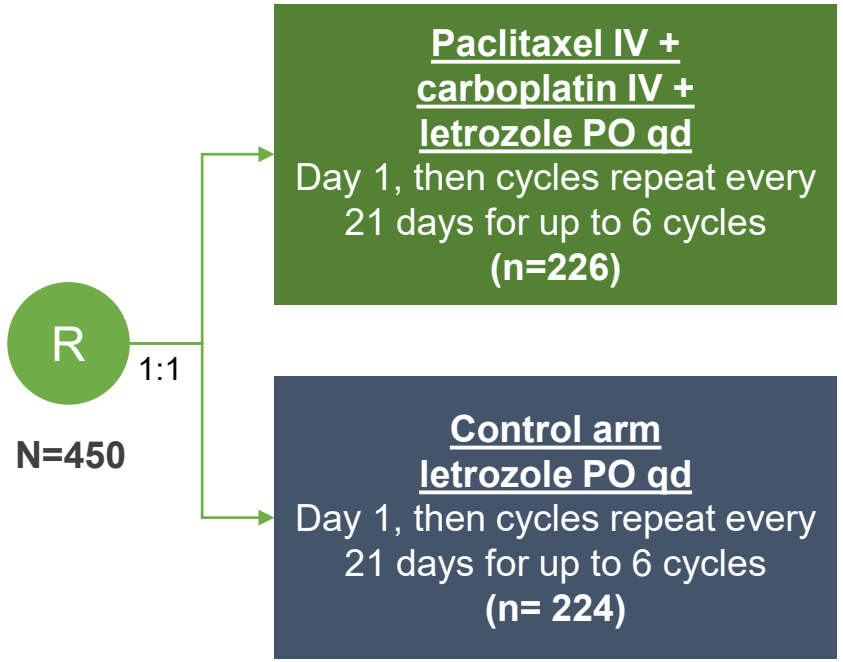
FDA, US Food and Drug Administration; LGSOC, low-grade serous ovarian cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival. 1. avutometinib + defactinib [prescribing information]. Verastem, Inc.; 2025. 2. FDA. Ongoing Cancer Accelerated Approvals. Accessed October 8, 2026. 3. ClinicalTrials.gov. NCT06072781. Accessed October 8, 2026. 4. Verastem Oncology. Second-quarter 2026 financial results. 2026.

NRG GY019: Paclitaxel/carboplatin followed by letrozole vs letrozole alone in newly diagnosed stage II–IV LGSOC

*Randomized Phase 3 trial | Frontline setting

Key Eligibility Criteria

- Stage II-IV low-grade serous carcinoma of the ovary, fallopian tube, or peritoneum
- Nonaberrant p53 IHC
- Prior attempt at maximal up-front cytoreductive surgery
- ECOG PS 0-2



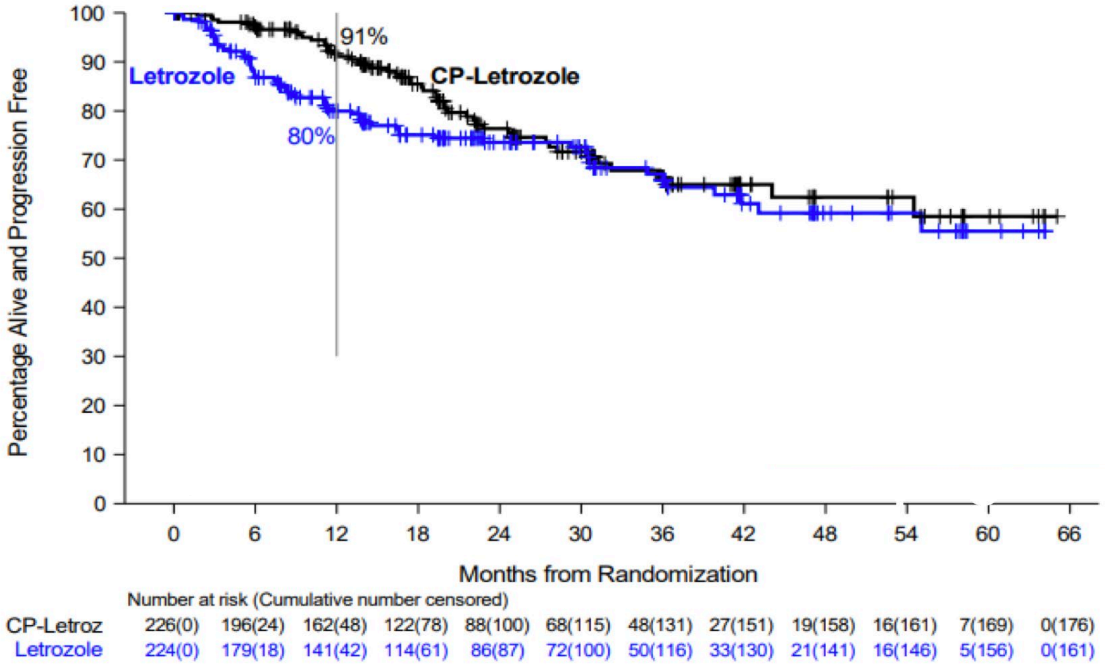
Primary Endpoint
PFS by INV

Key Secondary Endpoints ORR/DOR per RECIST v1.1, OS, safety

1. Fader AN, et al. SGO 2026. *2.* ClinicalTrials.gov, NCT04095364. Accessed October 7, 2026.
ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; LGSOC, low-grade serous ovarian carcinoma; OS, overall survival; PFS, progression-free survival.

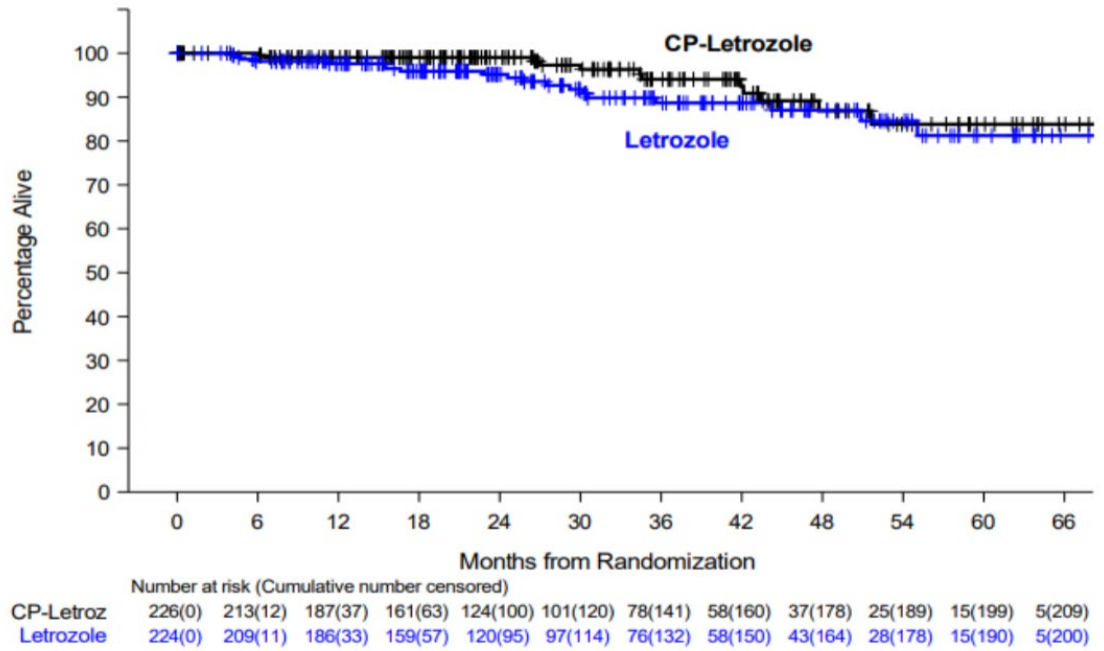
NRG GY019: Efficacy Endpoints

PFS by INV



	PFS (95% CI)	
	Letrozole (N=224)	Letrozole + CarboTaxol (N=226)
N/Events	63	50
HR (95% CI)	1.30 (0.90, 1.89)	-
Non-inferiority *P* (1-sided)	0.6977	

Interim OS



	OS (95% CI)	
	Letrozole (N=224)	Letrozole + CarboTaxol (N=226)
N/Events	19	12
HR (95% CI)	1.52 (0.73, 3.13)	-

Data cutoff: January 5, 2026; median follow-up: 27.3 months.

1. *Fader AN, et al. SGO 2026.* ***2.*** *ClinicalTrials.gov, NCT04095364. Accessed October 7, 2026.*

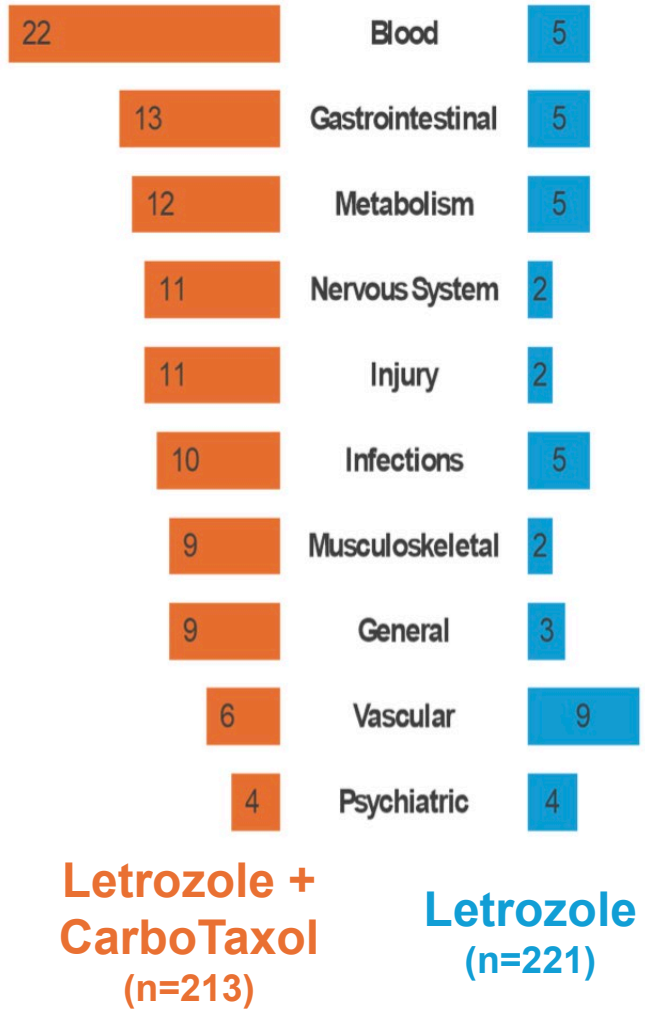
CI, confidence interval; HR, hazard ratio; INV, investigator; OS, overall survival; CP, paclitaxel/carboplatin; PFS, progression-free survival.

NRG GY019: Adverse events by treatment period

Adverse Event	Cycle 1-6		Cycle 7+	
	Letrozole + CarboTaxol (n=213)	Letrozole (n=221)	Letrozole + CarboTaxol (n=191)	Letrozole (n=189)
Any grade AE	**213 (100)**	**214 (96.8)**	**191 (100)**	**189 (100)**
Grade 3-5 AE	100 (46.9)	39 (17.6)	79 (41.4)	66 (34.9)
Leading to death	0 (0)	1 (0.5)	0 (0)	1 (0.5)

During cycles 1-6, the odds of observing a Grade 3/4 AE was **3.99 (95% CI: 2.57, 6.18; *P* <0.001)** higher in the patients treated with the letrozole + CarboTaxol than the patients treated with letrozole monotherapy

Grade 3– 5 AEs by Organ Type



1. Fader AN, et al. SGO 2026. 2. ClinicalTrials.gov, NCT04095364. Accessed October 7, 2026.
AE, adverse event; CI, confidence interval; OR, odds ratio; CarboTaxol, paclitaxel/carboplatin

NRG-GY019

Can newly diagnosed women skip chemotherapy?

Design and primary result

- 450 patients with newly diagnosed stage II–IV LGSOC
- Paclitaxel/carboplatin followed by letrozole vs letrozole alone
- Non-inferiority design: could letrozole alone match the combination?
- Letrozole alone did not demonstrate noninferiority: HR, 1.30 (95% CI, 0.90–1.89)
- The prespecified futility boundary was crossed; CarboTaxol followed by letrozole remains the standard first-line treatment

Efficacy–toxicity trade-off

- Grade 3–4 AEs were more frequent with PC/L: OR, 4.26 (95% CI, 2.74–6.62
- Interim OS rates were 95% with PC/L and 92% with letrozole alone
- OS remains immature; no definitive survival difference has been established
- Investigators noted that deferring chemotherapy may be reasonable to discuss in selected women with complete gross resection. Exploratory, not an established option

A well-designed negative trial. It did not deliver the easier answer everyone wanted, but it measured the size of the trade: a modest survival advantage bought with a fourfold increase in serious toxicity. That is the information a woman needs to make her own decision.

Data cutoff: January 5, 2026; median follow-up: 27.3 months.
Fader AN, et al. NRG-GY019 (NCT04095364). SGO Annual Meeting Opening Plenary; April 10, 2026.
AE, adverse event; CI, confidence interval; HR, hazard ratio; LGSOC, low-grade serous ovarian carcinoma; OS, overall survival; PC/L, paclitaxel/carboplatin followed by letrozole; PFS, progression-free survival.

Selected safety outcomes across LGSOC trials

Descriptive cross-trial summary; study populations, exposure and adverse-event reporting differed

Safety outcome (Any grade / grade ≥3, %)	Avutometinib + defactinib[1] RAMP 201; phase 2; n=115	Ribociclib + letrozole[2] GOG-3026; phase 2; n=49	Trametinib[3] GOG-281/LOGS; phase 2/3; n=128	Binimetinib[4] MILO/ENGOT-ov11; phase 3; n=200
Discontinuation due to AEs	10%	4%	36%	31%
Diarrhea	58% / 8%	45% / 2%	73% / 10%	70% / 6%
Nausea	67% / 3%	57% / 2%	61% / 9%	55% / 4%
Anemia	23% / 5%	51% / 4%	52% / 13%	NR
Neutropenia	NR	69% / 47%	NR	NR
Selected cutaneous AEs	Rash 50% / 3% Dermatitis acneiform 34% / 4%	Maculopapular rash 22% / 2%	Dermatitis acneiform 63% / 6% Maculopapular rash 42% / 7%	Dermatitis acneiform 46% / 6%
CPK increased	60% / 24%	NR	NR	50% / 26%
Selected ocular events	Blurred vision 41% / 0% Grade ≥3 ocular events: 2 patients	NR	Retinal vascular disorder 2% Retinal tear 1%	Retinal vein occlusion 3%
Decreased ejection fraction	1 patient; resolved	NR	8%	28% / 4%

Individual-event values are treatment-related AEs in RAMP 201 and GOG-3026; GOG-281/LOGS and MILO primarily report treatment-emergent AEs regardless of causality.

Cross-trial comparisons are descriptive. NR means not reported in the selected source, not absence of the event. Values are any grade / grade ≥3 unless otherwise stated. AE, adverse event; CPK, creatine phosphokinase; EF, ejection fraction.

1. Banerjee SN, et al. J Clin Oncol. 2025;43:2782–2792. 2. Slomovitz BM, et al. J Clin Oncol. 2026;44:153–163. 3. Gershenson DM, et al. Lancet. 2022;399:541–553. 4. Monk BJ, et al. J Clin Oncol. 2020;38:3753–3762.

Low-Grade Serous Carcinoma

Clinical Takeaways

1. **Obtain tumor molecular testing early**
   KRAS mutation status determines eligibility for the FDA-approved avutometinib–defactinib combination. Testing uses tumor tissue and can often use an archived specimen.

2. **Individualize treatment at recurrence**
   Endocrine therapy, trametinib and avutometinib–defactinib are established options. Selection should consider molecular findings, prior therapy, disease tempo and expected toxicity.

3. **Avutometinib–defactinib is approved for *KRAS*-mutated recurrent LGSOC**
   The FDA granted accelerated approval for adults who have received prior systemic therapy. RAMP 301 is evaluating confirmatory clinical benefit.

4. **Proactive toxicity management supports treatment continuity**
   Start skin prophylaxis, scheduled ophthalmic examinations and laboratory monitoring with treatment. Early recognition and dose modification can prevent serious complications.

5. **Paclitaxel/carboplatin followed by letrozole remains the reference frontline approach**
   In NRG-GY019, letrozole alone did not demonstrate noninferiority. The greater toxicity of chemotherapy remains relevant to individualized treatment discussions.

Sources: FDA avutometinib + defactinib prescribing information, revised May 2025; NRG-GY019, SGO Annual Meeting 2026; ClinicalTrials.gov NCT06072781.

FDA, US Food and Drug Administration; LGSOC, low-grade serous ovarian carcinoma.

Case Based Scenarios with Audience Interaction

Early-onset rash and visual symptoms in recurrent LGSOC



All Faculty

Case 1: Early-onset rash and treatment continuation

Patient and Treatment

- 52-year-old with *KRAS* G12D-mutated recurrent LGSOC after two prior systemic regimens
- ECOG 1; no active dermatologic disease and no baseline edema
- Starts avutometinib 3.2 mg twice weekly plus defactinib 200 mg twice daily, days 1–21 of a 28-day cycle, with food
- Begins topical corticosteroid and systemic oral antibiotic prophylaxis; uses daily SPF 30 sunscreen

Cycle 1, Day 13: She calls the clinic

- Papules and pustules on face, scalp, and upper chest; ~12% BSA
- Moderate pruritus; sleep interrupted, but self-care and usual activities intact
- No fever, skin pain, blisters, mucosal lesions, or purulent drainage
- New 1+ bilateral ankle edema and 1.8-kg weight gain; no dyspnea or calf pain



Case 1: Continue treatment or hold?

Assume the eruption is tolerable Grade 2, and the patient has no red flags.

a) Permanently discontinue both drugs

b) Continue treatment, intensify supportive care, and reassess within 48–72 hours

c) Hold both drugs until the rash completely resolves

d) Treat empirically as bacterial cellulitis

Before deciding

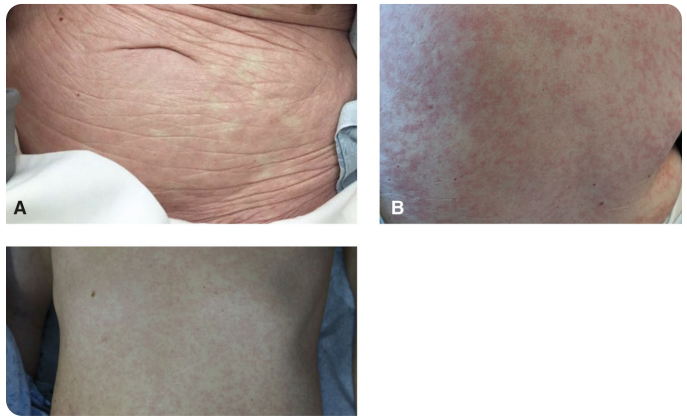
Confirm grade and functional impact; examine mucosa; assess infection and SCAR features; document distribution with photographs; evaluate edema for cardiopulmonary, renal, hepatic, or thrombotic clues.

Case 1: Acneiform, maculopapular, and nail-fold toxicities



ACNEIFORM ERUPTION

- Early papules and pustules on the face, scalp, chest, or back
- Monomorphic eruption without comedones



MACULOPAPULAR ERUPTION

- Erythematous patches or plaques on the trunk and extremities
- Often accompanied by pruritus or xerosis



PARONYCHIA

- Tender nail-fold edema, fissuring, or granulation tissue
- Assess for secondary infection

Case 1 fits an acneiform eruption: early onset, papules and pustules, and no mucosal or systemic red flags.

Managing rash and edema

RASH

1. Continue both agents while the Grade 2 eruption remains tolerable
2. Confirm use of the prescribed topical corticosteroid and oral antibiotic. Add a gentle cleanser and bland moisturizer
3. Reinforce sun protection and avoid unnecessary exposure
4. Send photographs today. Arrange dermatology review if the eruption is atypical, infected or not improving promptly

EDEMA AND FOLLOW-UP

1. Record weight, edema distribution, vital signs, oxygen saturation and cardiopulmonary symptoms
2. Review medications and available renal and hepatic laboratory results. Investigate an atypical pattern
3. For mild uncomplicated edema, consider leg elevation, compression when appropriate, salt moderation and daily weights
4. Follow up in 48–72 hours. Escalate the same day for rapid progression, dyspnea, fever, blisters or mucosal lesions

SCAR concern: stop treatment and arrange urgent evaluation for blistering, mucosal involvement, skin pain, facial edema with systemic illness or a rapidly spreading eruption.

Preventing early skin toxicity

START WITH THE FIRST DOSE

- Apply the prescribed topical corticosteroid to the face, scalp, neck, upper chest and upper back
- Start the prescribed systemic oral antibiotic
- Continue both prophylactic medications through at least the first 2 cycles
- Limit unnecessary sun exposure and use broad-spectrum sunscreen with SPF 30 or higher

ASSESS AT EACH CONTACT

- Confirm that prophylaxis is being used as prescribed
- Ask about fever, skin pain, blistering, mucosal lesions and drainage
- Document distribution, body-surface area, functional impact and photographs
- Reassess promptly when symptoms worsen or supportive care is ineffective

Begin prophylaxis with treatment. Escalate promptly for infection or a suspected severe cutaneous reaction.

Source: avutometinib + defactinib US prescribing information, revised May 2025.

Rash-related dose modification

Grade ≤2	Supportive care. Consider withholding the co-pack if rash does not respond or recurs after resolution to Grade ≤1. Reduce the co-pack dose for intolerable Grade 2.
Grade 3	Withhold the co-pack. If rash resolves to Grade 2, resume at the reduced dose. If it resolves to Grade ≤1, resume at the same dose.
Recurrent Grade 3	Permanently discontinue the co-pack if Grade 3 rash recurs despite dose reduction.
Grade 4	Permanently discontinue the co-pack.

Single labeled dose reduction: avutometinib 2.4 mg twice weekly plus defactinib 200 mg once daily, both during the first 3 weeks of each 4-week cycle.

Permanently discontinue both products if the patient cannot tolerate treatment after this dose reduction.

Source: avutometinib + defactinib US prescribing information, Tables 1 and 2, revised May 2025.

Rash improves and treatment continues

DAY 16 **Rash has improved to Grade 1, pruritus no longer interrupts sleep, edema remains mild, weight is stable and laboratory results are reassuring.**

WHY CONTINUATION IS REASONABLE

- No SCAR, infection or systemic warning signs
- Symptoms improved promptly with supportive care
- Close follow-up allows rapid escalation if the course changes

PATIENT EDUCATION

“Send photos early. Call the same day for blistering, mouth sores, fever, skin pain, rapidly worsening swelling or shortness of breath. Do not wait for the next visit.”

In the pooled safety population, the median onset of the first skin toxicity was 14 days. Early reporting supports timely treatment modification.

Source: avutometinib + defactinib US prescribing information, revised May 2025. SCAR, severe cutaneous adverse reaction.

Cutaneous toxicity across RAF and MEK inhibitors

Agent / regimen	Target	Selected all-grade events	Selected Grade ≥3 events	Predominant cutaneous pattern	Median onset
Vemurafenib[1] **BRIM-3, n=336**	BRAF inhibitor	Rash 37% Photosensitivity 33%	Rash 8% Photosensitivity 3%	Photosensitivity, rash, pruritus, hyperkeratosis, KA/cuSCC	Rash: NR KA/cuSCC: 7–8 weeks
Dabrafenib[2] **BREAK-3, n=187**	BRAF inhibitor	Rash 17% Hyperkeratosis 37%	Rash 0% Hyperkeratosis 1%	Hyperkeratosis, rash, PPES, papilloma, KA/cuSCC	Rash: NR KA/cuSCC: NR in cited table
Trametinib[3] **METRIC, n=211**	MEK inhibitor	Rash 57% Acneiform dermatitis 19%	Rash 8% Acneiform dermatitis <1%	Rash, acneiform dermatitis, dry skin, pruritus, paronychia	NR in cited label
Avutometinib + defactinib[4] **Pooled recurrent LGSOC, n=136**	RAF/MEK clamp + FAK inhibitor	Any skin toxicity 94% Rash 67% Acneiform dermatitis 43%	Any skin toxicity 12% Rash 7% Acneiform dermatitis 7%	Rash, acneiform dermatitis, dry skin, pruritus, photosensitivity	First skin toxicity: 14 days

Cross-trial comparisons are descriptive. Populations, event definitions, grading systems and prophylaxis differed among studies.

[1] ZELBORAF US prescribing information, Table 1. [2] TAFINLAR US prescribing information, BREAK-3 table. [3] MEKINIST US prescribing information, METRIC table. [4] avutometinib + defactinib US prescribing information, §5.2. All accessed October 8, 2026.

BRAF, B-Raf proto-oncogene; FAK, focal adhesion kinase; KA, keratoacanthoma; LGSOC, low-grade serous ovarian cancer; MEK, mitogen-activated protein kinase kinase; NR, not reported; PPES, palmar-plantar erythrodysesthesia syndrome; cuSCC, cutaneous squamous-cell carcinoma.



Case 2: Visual symptoms and therapy adjustment

Before Treatment

- 58-year-old with KRAS G12V-mutated recurrent LGSOC; prior platinum chemotherapy and letrozole; ECOG 1
- No diabetes or pre-existing retinal or macular disease; baseline eye examination normal; BCVA 20/20 in both eyes
- Starts avutometinib 3.2 mg twice weekly plus defactinib 200 mg twice daily, days 1–21 of a 28-day cycle

Before treatment, counsel patients to report any new or worsening visual symptom immediately.

Cycle 1, Day 5: She reports a sudden change

- Bilateral blurred vision and wavy lines while reading
- No flashes, new floaters, or curtain-like visual-field defect
- No eye pain, redness, headache, or focal neurologic symptoms
- Clinic screening: BCVA approximately 20/60 in both eyes



Case 2:
New visual symptoms: What should happen today?

Cycle 1, Day 5: sudden bilateral blurred vision and distortion; BCVA is approximately 20/60 in both eyes.

a) Continue treatment and reassess at the next clinic visit

b) Hold both drugs and arrange prompt ophthalmology assessment with OCT

c) Hold avutometinib only and continue defactinib

d) Permanently discontinue both drugs

Urgency check

Would new flashes, floaters, or a curtain or shadow in the visual field change the urgency of the evaluation? 1. Yes 2. No

MEK-associated retinopathy or a vision-threatening event?

Any new or worsening ocular symptom warrants prompt evaluation by a qualified eye-care professional.

MEK-ASSOCIATED RETINOPATHY

- Often bilateral blurred or distorted vision
- Multifocal RPE detachments or subretinal fluid on OCT
- Frequently early and reversible; document BCVA and OCT

RETINAL VEIN OCCLUSION

- Sudden, painless—usually monocular—vision loss
- Visual-field defect or marked acuity loss
- Emergency retinal assessment; permanently discontinue the co-pack if RVO is confirmed

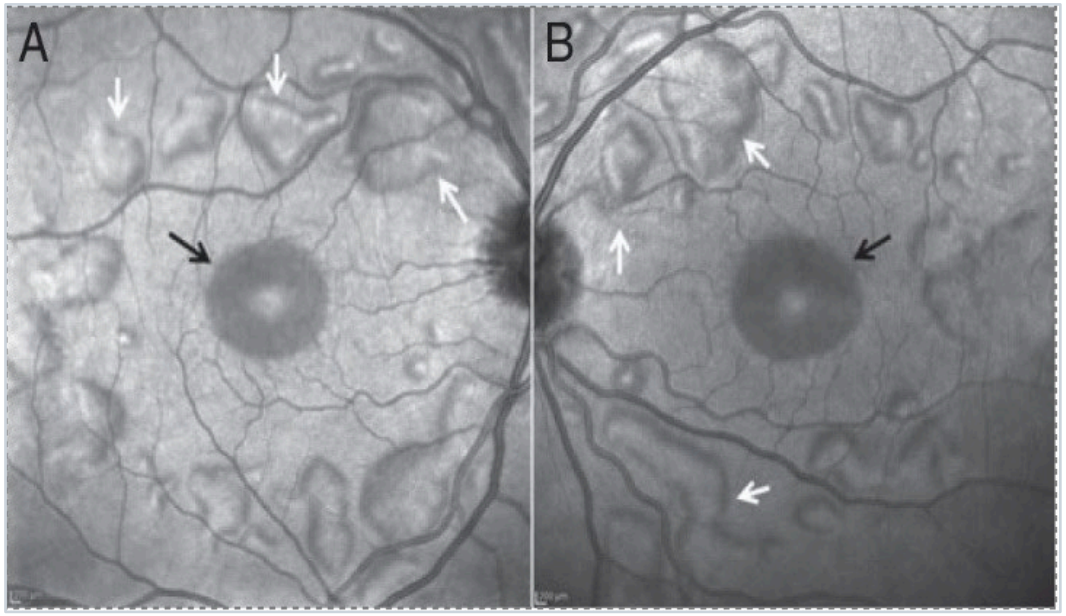
RETINAL TEAR / DETACHMENT

- New flashes, floaters or a curtain-like shadow
- Retinal tear/detachment on dilated examination or OCT
- Same-day retinal specialist management; use the co-pack label's event-specific dose pathway

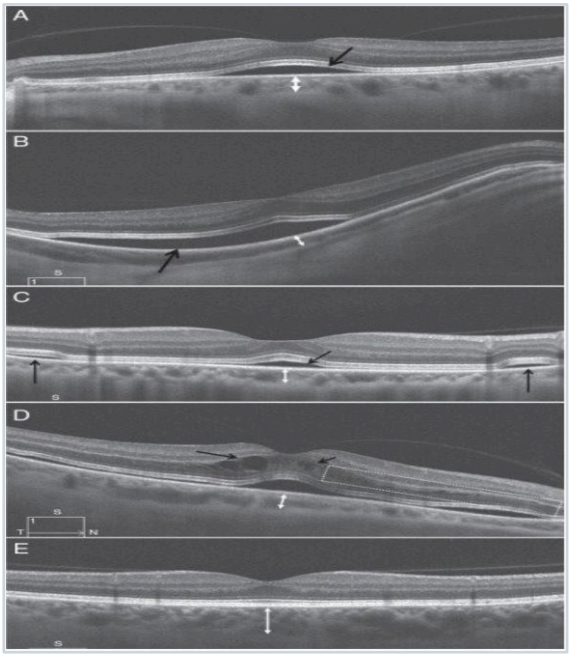
Pooled label population: ocular reactions 68%; visual impairment 38%; vitreoretinal disorders 26%; retinal detachment 9%; RVO 0.7%.

Source: avutometinib + defactinib US prescribing information (USPI), May 2025. BCVA, best-corrected visual acuity; OCT, optical coherence tomography; RPE, retinal pigment epithelium; RVO, retinal vein occlusion.

Characteristic OCT findings in MEK-associated retinopathy



En face / infrared imaging: bilateral multifocal lesions surrounding the macula.



OCT B-scans: multifocal subretinal fluid and shallow RPE detachments, with interval resolution after treatment interruption.

Pattern recognition matters: bilateral multifocal fluid favors MEK-associated retinopathy; it does not exclude other urgent retinal disease.

Images reproduced from Stjepanovic N, et al. Ann Oncol. 2016;27(6):998–1005. MEK, mitogen-activated protein kinase kinase; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

Ocular adverse-event management across MEK inhibitors

Product	Ophthalmic monitoring	Retinopathy / RPED	Confirmed RVO
Trametinib	Evaluate new or worsening visual symptoms; periodic examination	Withhold up to 3 weeks; resume same/lower dose if improved; discontinue if not improved	Permanently discontinue
Cobimetinib	Regular ophthalmic examinations and for new/worsening symptoms	Withhold, reduce or discontinue according to severity and persistence	Permanently discontinue
Binimetinib	Assess symptoms at each visit; regular examinations and as clinically indicated	Symptomatic RPED: withhold up to 10 days; resume same dose if improved, otherwise reduce/discontinue	Permanently discontinue
Selumetinib	Baseline and regular comprehensive examinations; assess new/worsening symptoms	Withhold for RPED until resolution; resume at reduced dose	Permanently discontinue

Sources: Han J, et al. Oncology (Williston Park). 2023;37(3):130-141. US prescribing information for MEKINIST (trametinib), COTELLIC (cobimetinib), MEKTOVI (binimetinib), and KOSELUGO (selumetinib), accessed October 2026. RPED, retinal pigment epithelial detachment; RVO, retinal vein occlusion.

Same-day ophthalmology findings

SAME-DAY EXAM

BCVA 20/60 in both eyes. OCT shows bilateral multifocal RPE detachments with subretinal fluid. No retinal tear, rhegmatogenous detachment or RVO.

MOST LIKELY DIAGNOSIS

MEK-associated retinopathy with RPE detachment

Bilateral multifocal fluid and lack of RVO or retinal tear support this diagnosis.

CO-PACK BLURRED-VISION PATHWAY

- BCVA worse than baseline but better than 20/200: withhold until recovery to baseline or 20/40, whichever is worse; then resume at the same dose
- BCVA 20/200 or worse: withhold to the same recovery threshold; then resume at reduced doses

Also follow the separate RPE-detachment algorithm with repeat OCT; persistent findings can trigger dose reduction or discontinuation.

Source: avutometinib + defactinib USPI, Table 2, May 2025. BCVA, best-corrected visual acuity; OCT, optical coherence tomography; RPE, retinal pigment epithelium; RVO, retinal vein occlusion.



Case 2:
Vision recovers and treatment resumes

Day 12: Symptoms resolve. BCVA returns to 20/20 in both eyes and repeat OCT shows resolution of the retinal findings.

What should happen now?

a) Resume both drugs at the same doses

b) Resume both drugs at reduced doses

c) Continue holding until the next scheduled eye examination

d) Permanently discontinue both drugs

If BCVA had been 20/200 or worse

a) Hold both drugs until recovery to baseline or 20/40, whichever is worse

b) Resume both drugs at reduced doses after recovery

c) Continue ophthalmic monitoring after treatment resumes

Key Takeaways and Audience Q&A



All Faculty

Mount Sinai Medical Center

Key Takeaways: Monitoring and treatment continuity

BEFORE THE FIRST DOSE

- Comprehensive ophthalmic examination at baseline
- Book the cycle 2 examination and subsequent examination every 3 cycles
- Start labeled skin prophylaxis and teach dosing/urgent-contact rules

DURING EARLY CYCLES

- Complete the eye examination before cycle 2
- Monitor CPK and liver tests on the label schedule
- Encourage early symptom calls; document severity and trajectory

WHEN TOXICITY APPEARS

- Promptly refer every new or worsening ocular symptom
- Exclude RVO and retinal tear/detachment before assuming MEKAR
- Use the event-specific label threshold for hold, reduction or discontinuation

CORE PRINCIPLE **Early recognition, specialist confirmation and documented recovery can preserve treatment without compromising ocular safety.**

Source: avutometinib + defactinib USPI, May 2025. CPK, creatine phosphokinase; MEKAR, MEK inhibitor-associated retinopathy; RVO, retinal vein occlusion.

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