

From Promise to Practice: Implementing Precision Therapy in Low-Grade Serous Ovarian Cancer

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Disclosures

- **Jubilee Brown, MD:** Advisory Board – AbbVie, AstraZeneca, Caris, GSK/Tesaro, Natera, Verastem; Principal Investigator/Steering Committee – Genentech/Roche, GSK/Tesaro

Learning Objectives

- Interpret the molecular features of LGSOC and the significance of comprehensive genomic profiling, including KRAS testing, to guide precision treatment strategies in recurrent disease
- Describe considerations for integrating FDA-approved and emerging targeted therapies into LGSOC treatment algorithms, including patient selection criteria, sequencing considerations, and adverse event management strategies
- Evaluate interdisciplinary care strategies to align molecular findings, evolving evidence, and individualized treatment planning for patients with LGSOC

Challenges in Studying Rare Tumors

- Important: 35% of deaths occur from the rarest 20% of tumors
- Limited number of patients over a wide geographic area
- Limited access to experienced oncologists
- Natural history is poorly defined: Statistical difficulty
- Similar tumors are “lumped together” – phenotypic heterogeneity, so clinically distinct tumors are combined to meet accrual goals
- Limited funding
- Prolonged accrual
- Restrictions on international data sharing

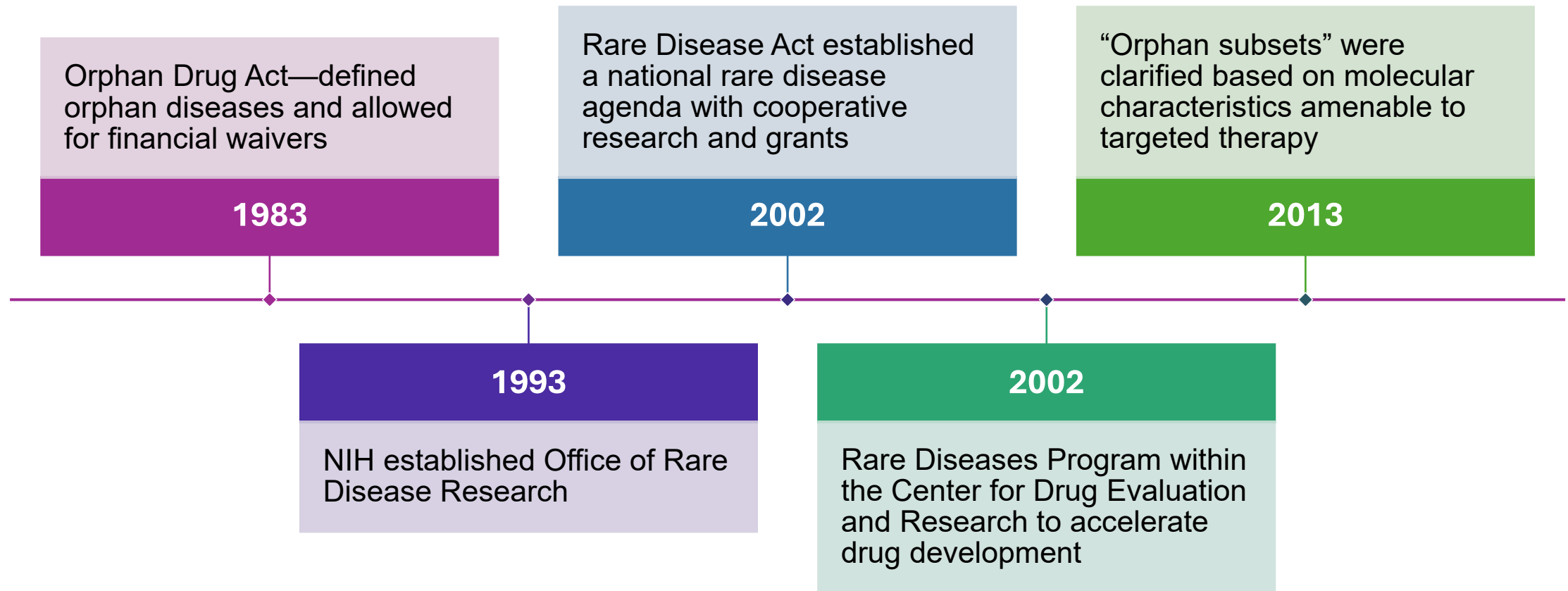


Challenges in Rare Tumor Trials

- Limited number of eligible patients
- Reluctance of sites to (keep) open trials with potential for poor and prolonged accrual
- Incentive for pharma to invest in rare tumor trials: Return on investment, protracted approval
- Rapidly changing landscape
- Statistical design limitations



Progress in Studying Rare Tumors



NIH = National Institutes of Health.

Brown J, et al. *Gynecol Oncol*. 2018;149(3):605-611. Gaddipati H, et al. *Clin Cancer Res*. 2012;18(19):5172-5178.

The Solution

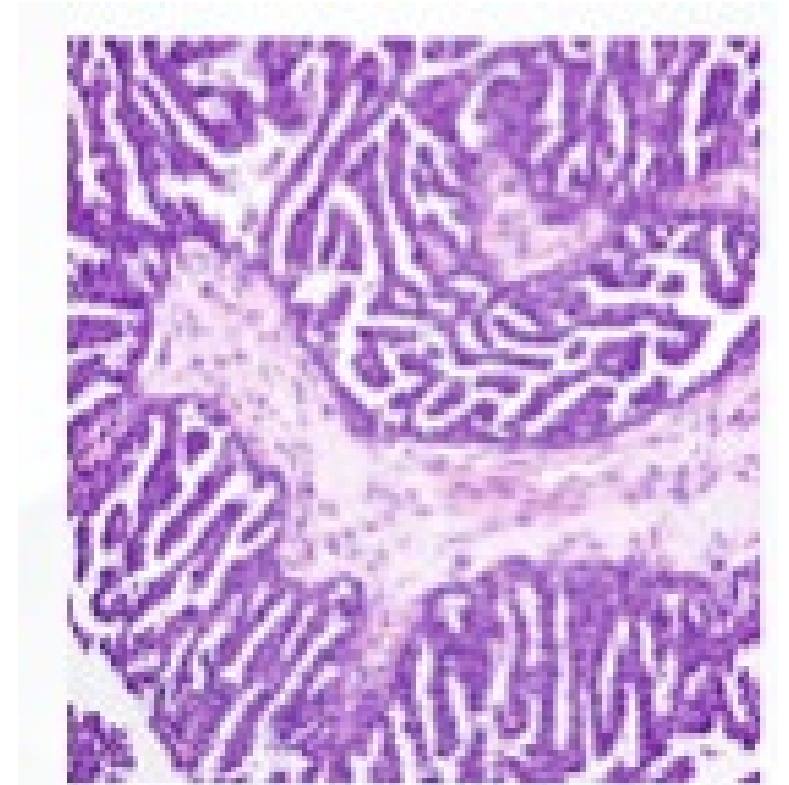
- NGS and precision medicine: improved speed and precision of diagnosis—but greater uptake/equity needed
- Clinical trial designs: adaptive—platform—basket
- Tumor-agnostic approvals
- Need international cooperative group collaboration
- AI integration: screening, matching patients to trials

Examples of Rare Gynecologic Cancer with Prevalent Driver Alterations

Disease	Alteration
Granulosa cell tumor	FOXL2
Mesonephric cancer	KRAS
Mesonephric-like cancer	KRAS
Small cell carcinoma of the ovary, hypercalcemic type	SMARCA4 pathogenic variant
Low-grade serous ovarian cancer	MAPK alterations
NTRK-fusion positive uterine spindle cell sarcomas	NTRK gene fusions

Scope of Rare Tumors

- GOG (now NRG) established the Rare Tumor Committee in 2005
 - Ovarian sex cord-stromal tumors
 - Malignant ovarian germ cell tumors
 - Mucinous ovarian cancers
 - Clear cell ovarian cancers
 - **Low-grade serous ovarian cancers (LGSOC)**
 - Carcinosarcoma of the ovary
 - Small cell carcinomas of the ovary and cervix
 - Mucosal melanoma of the lower genital tract



GOG = Gynecologic Oncology Group.

Covens A, Brown J. Rare Tumor Committee. In: *The GOG Foundation, Inc.: A Half Century of Transforming the Standard of Care*. GOG Foundation, Inc.; 2023.

Statistical Design Options (Prior to Profiling)

Phase III randomized controlled trials—not feasible

2011: Oncologic Drugs Advisory Committee—recommended single-arm trials in rare tumors

FDA allows for drug approval with this approach

Modified phase II trials can be considered equivalent to phase III trials if the aim is to affect clinical practice

Phase II Trials Have Been Successful in the GOG

Rare Tumor Committee has been involved in >24 clinical trials

Table 2

Phase II trials in rare gynecologic cancers.

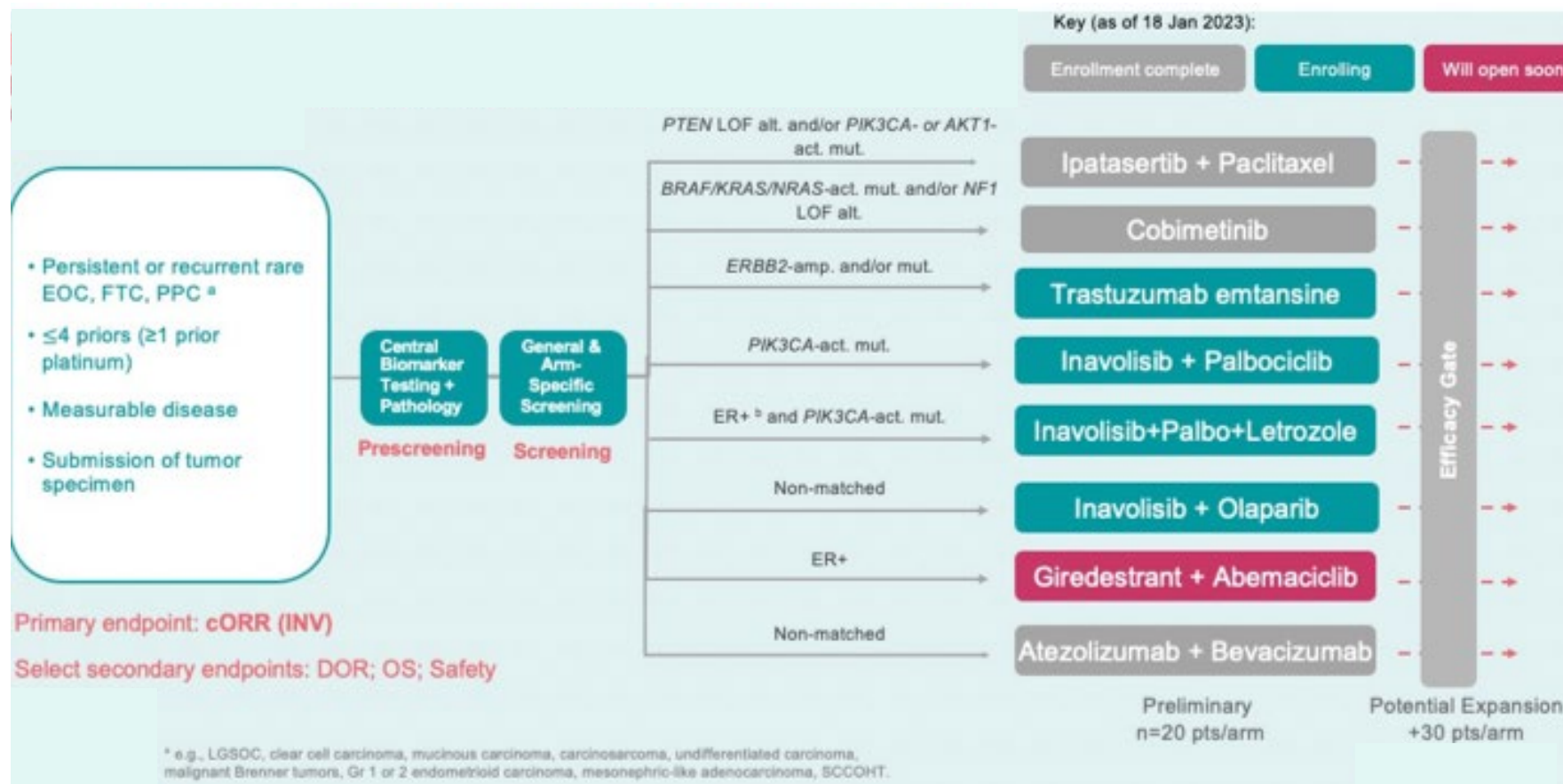
GOG Number [Reference]	Histology	Site	Drugs studied
Single arm phase II trials			
254 [12]	Clear cell carcinoma	Ovary	Sunitinib
268 [13]	Clear cell carcinoma	Ovary	Paclitaxel, carboplatin, temsirolimus
251 [14]	Sex cord-stromal tumor	Ovary	Bevacizumab
187 [15]	Sex cord-stromal tumor	Ovary	Paclitaxel
239 [16]	Low-grade serous	Ovary	Selumetinib
GY-001 [18]	Clear cell carcinoma	Ovary	Cabozantinib-s-malate
283 [19]	Clear cell carcinoma	Ovary	Dasatinib
Multi-arm phase II trials			
241 [17]	Mucinous	Ovary	Paclitaxel/carboplatin vs. oxaliplatin/capecitabine ± bevacizumab



Molecular Profiling and Platform Testing

BOUQUET (WO42178 / ENGOT-GYN2 / GOG-3051)

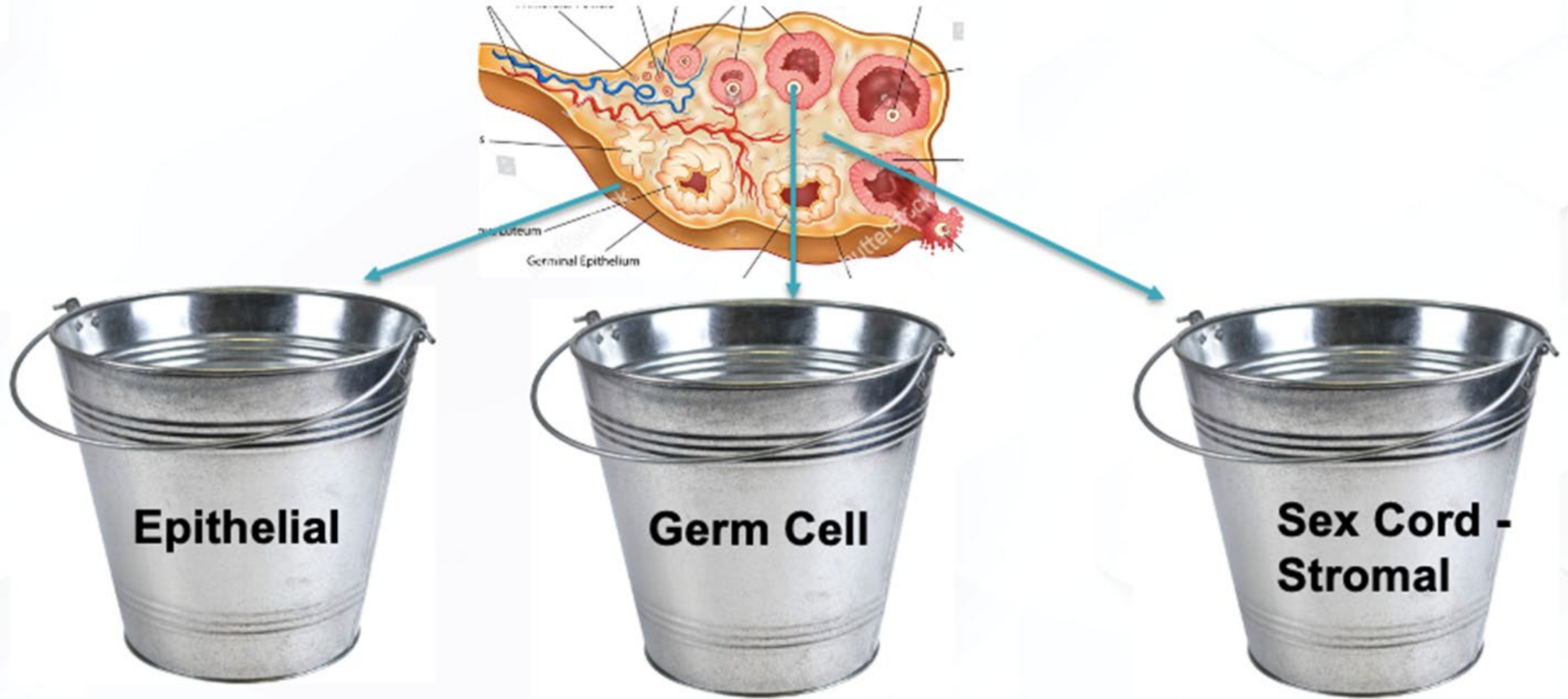
Phase II platform study evaluating biomarker-driven therapies in patients with persistent or recurrent rare EOC



Lessons in Rare Tumor Trial Conduct

- Plan ahead: Trials take a long time to develop
- Low-grade tumors are rare, but common enough that they will accrue if planned
- Working groups inform best trial design: translational work
- Partner with industry early—they have the assets
- Share information
- Make eligibility broad
- Obtain support from key institutions early so that opening can be streamlined
 - Contrast 264 with 033
- Patient-friendly media and social media presence

3 Major Groups of Ovarian Cancer

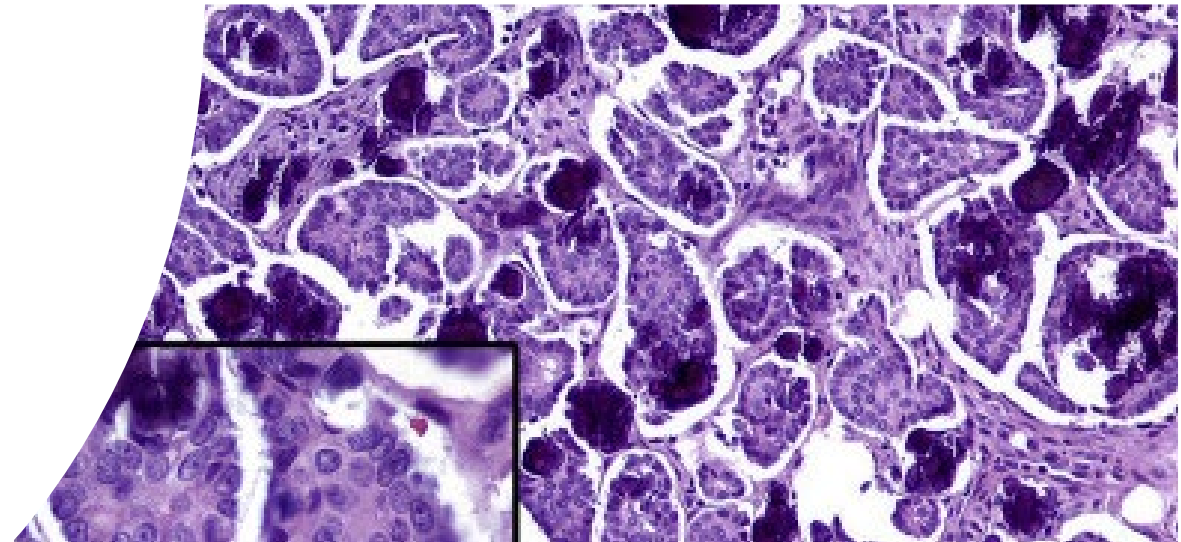
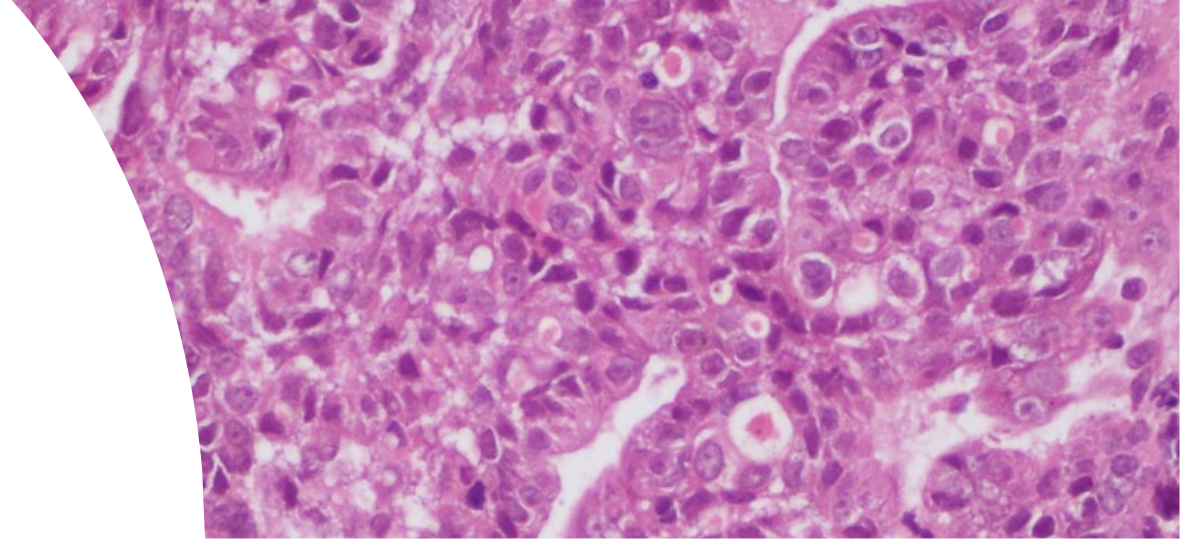


HGSOC

Low-Grade Serous

- 5% of all epithelial ovarian cancers
- 70% of advanced-stage patients eventually relapse

LGSOC



HG = high-grade.

Historically Poor Response in LGSOC



- Paclitaxel and carboplatin
 - 52% of 112 pts were disease-free after primary cytoreductive surgery and platinum-based chemotherapy
 - 4% of 25 pts with stage III/IV disease responded to NACT
 - In 4 randomized phase III trials (AGO) of over 5000 pts, women with LGSOC were much less likely to respond

NACT = neoadjuvant chemotherapy; AGO = Arbeitsgemeinschaft Gynaekologische Onkologie.

Gershenson DM, et al. *Obstet Gynecol*. 2009;114(1):48-52. Schmeler KM, et al. *Gynecol Oncol*. 2008;108(3):510-514.

Grabowski JP, et al. *Gynecol Oncol*. 2016;140(3):457-462.

Comprehensive molecular profiles of low-grade serous ovarian carcinoma

[A.C. ElNaggar](#) ^a · [D.B. Robins](#)^a · [D. Arguello](#)^b · ... · [V. Galvan-Turner](#)^h · [T.J. Herzog](#)ⁱ · [J. Brown](#)^j ... [Show more](#)

- 185 cases of LGSOC
- Hot-spot and whole-exon NGS
- Histologic confirmation

Comprehensive molecular profiles of low-grade serous ovarian carcinoma

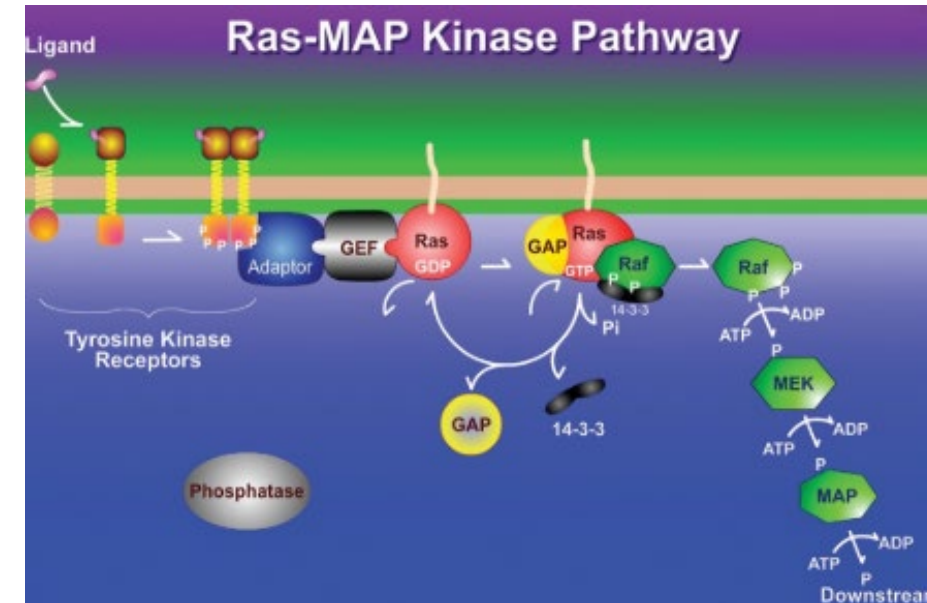
[A.C. ElNaggar](#) ^a · [D.B. Robins](#) ^a · [D. Arguello](#) ^b · ... · [V. Galvan-Turner](#) ^h · [T.J. Herzog](#) ⁱ · [J. Brown](#) ^j ... [Show more](#)

- KRAS 27.2%, 50/184
- NRAS 10.3%, 19/184
- PIK3CA 2.2%, 4/184
- AR 41.5%, 35/82
- ER 81.5%, 150/184 ($\geq 2+$)
- PR 31.5%, 58/184
- PD-L1 3.7%, 6/163

Low-Grade Serous Ovarian Cancer

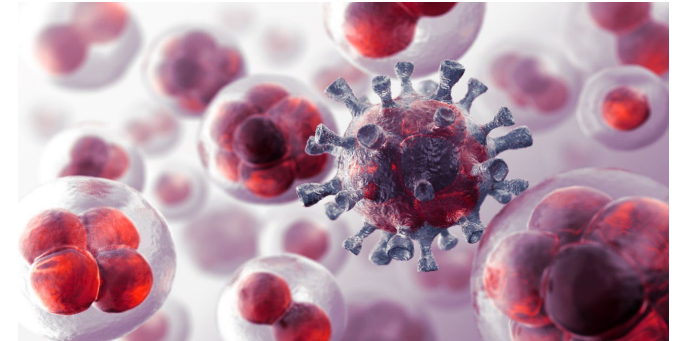


- MAP kinase pathway is active in 52%
 - 30% KRAS+; 13% BRAF+; 9% NRAS+
 - MEK inhibitors
- Hormonally active (97% ER+)
 - 60% stable disease with hormonal therapy
- 55% of patients have actionable mutations



Low-Grade Serous Ovarian Cancer

- Bevacizumab has some "special" support
- ORR 40% (Grisham, et al.)
- Systematic review 2023: ORR 47.5%
- Median PFS: 48 m (prolonged disease stabilization)
- Other small case series: stable disease/PR when added to chemo or letrozole
- Ongoing trial: trametinib +/- bev



ORR = objective response rate; PFS = progression-free survival; PR = partial response.

Grisham RN, et al. *Int J Gynecol Cancer*. 2014;24(6):1010-1014. Lazurko C, et al. *Curr Oncol*. 2023;30(9):8159-8171. Rose PG, et al. *Int J Gynecol Cancer*. 2016;26(6):1048-1052.

Historically Poor Response in LGSOC

- Paclitaxel and carboplatin are standard of care
 - Neoadjuvant: 4% response, 88% stable disease (Schmeler)
 - Recurrent: 3.7% response rate to chemotherapy (Gershenson, et al.)
- Hormonally active (97% ER+)
- Being replaced by letrozole
 - Maintenance therapy: mPFS 64.9 m (letrozole) vs 26.4 m (observation), $P < 0.001$ (Gershenson, et al)
- Trial is important!

mPFS = median PFS.

Barakzai SK, et al. *Gynecol Oncol.* 2024;190:119-123. Grisham RN, et al. *Int J Gynecol Cancer.* 2023;33(9):1331-1344.

Brown J. *Gynecol Oncol.* 2024;190:A1-A2. Gershenson DM, et al. *J Clin Oncol.* 2017;35(10):1103-1111. Gershenson DM, et al. *Gynecol Oncol.* 2009;114(1):48-52. Schmeler KM, et al. *Gynecol Oncol.* 2008;108(3):510-514.

The association of maintenance hormone therapy with overall survival in advanced-stage low-grade serous ovarian carcinoma: A risk-set matched retrospective study

Syem K Barakzai¹, Amy J Bregar¹, Marcela G Del Carmen¹, Eric L Eisenhauer¹, Annekathryn Goodman¹, Jose A Rauh-Hain², Allison A Gockley¹, Alexander Melamed³

Hormonal maintenance therapy for advance low grade serous ovarian carcinoma appears to be of benefit – That's a relief!

Jubilee Brown¹

- Multi-institutional observational study, N=296 pts
- All stage III/IV LGSOC 2004-19 in CoC cancer programs
- HT matched to non-HT patients by risk-set propensity score
- Primary outcome: risk of death from any cause within 5 years
- HT: academics (55 vs 44%), later in study period (62 vs 23%)
- 45% vs 17% received NO chemotherapy (45% had HT alone!)
- HT: reduction in risk of death (HR 0.60; 95% CI 0.38-0.94)
- HT: 60 m survival of 75% vs 65%

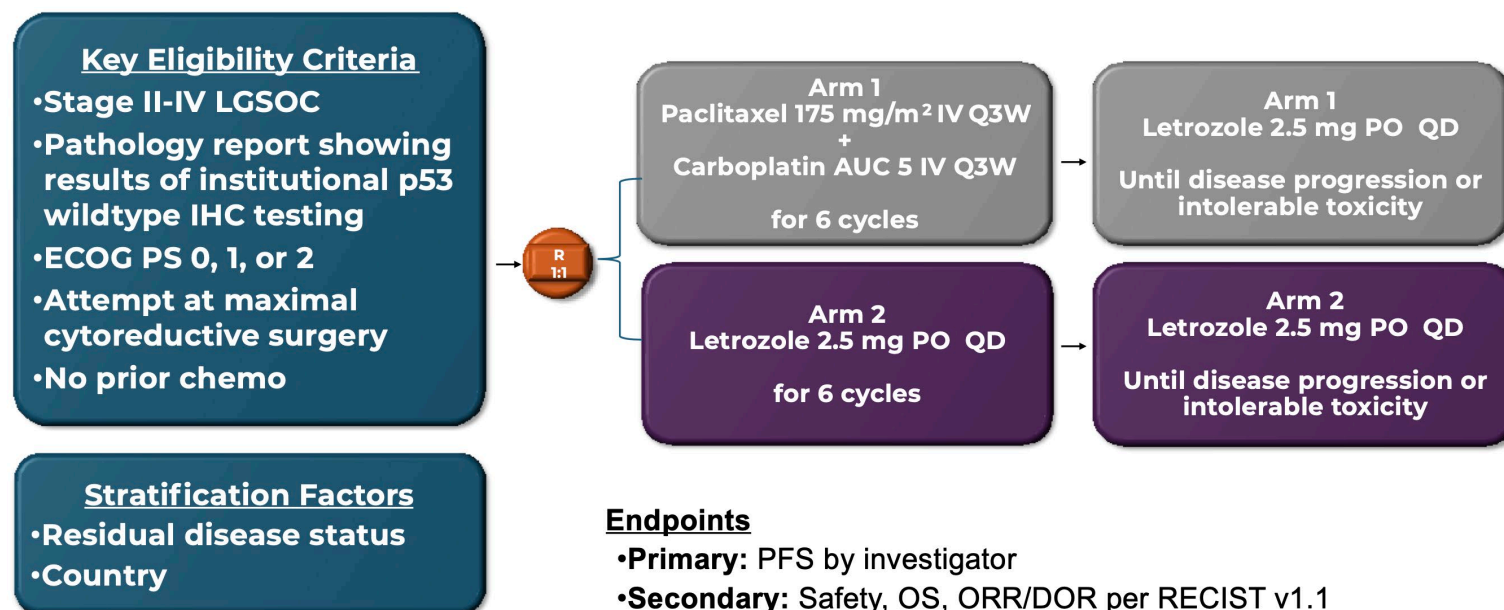
CoC = Commission on Cancer; HT = hormone therapy; HR = hazard ratio; CI = confidence interval.
Barakzai SK, et al. *Gynecol Oncol.* 2024;190:119-123. Brown J. *Gynecol Oncol.* 2024;190:A1-A2.

ER/PR Are Biomarkers

- **Upfront: GY-019**—A randomized, phase III 2-arm trial of **P/C/maintenance letrozole vs letrozole monotherapy**

NRG-GY019 (NCT04095364)

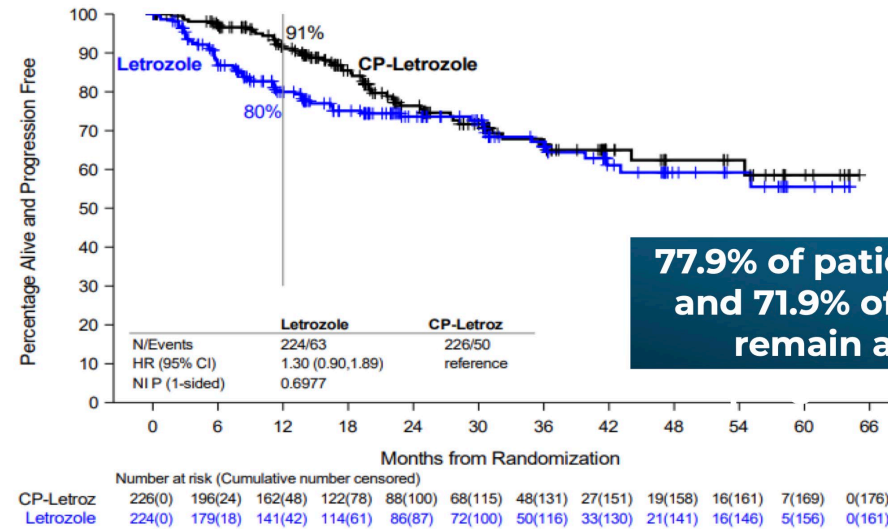
- 1 endpoint: PFS
- Open 8/2019
- N=450 pts



ER = estrogen receptor; PR = progesterone receptor; ECOG PS = Eastern Cooperative Oncology Group performance status; AUC = area under the curve; DOR = duration of response; RECIST = response evaluation criteria in solid tumors; IHC = immunohistochemistry.
ClinicalTrials.gov. Accessed March 13, 2026. <https://clinicaltrials.gov/ct2/show/NCT04095364>.

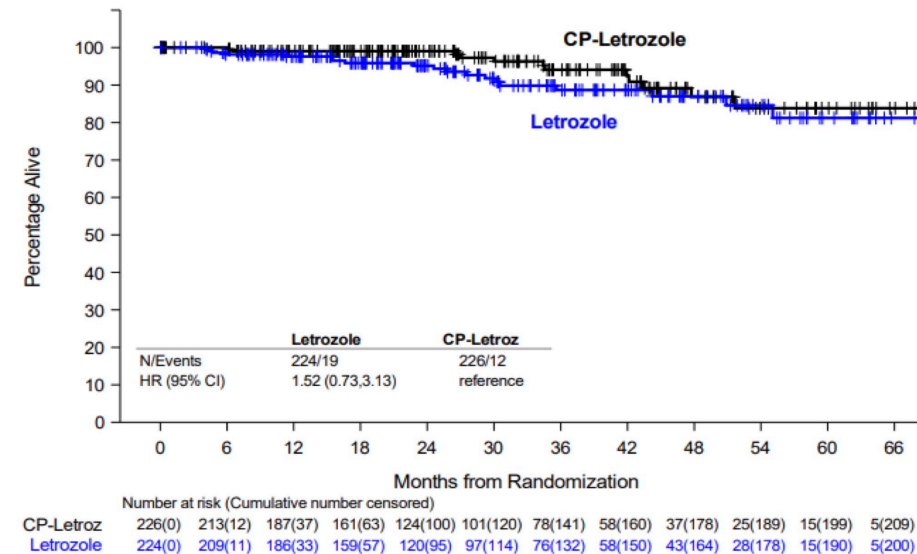
GY-019: PFS and OS

Progression-Free Survival (PFS)



HR 1.30 P=NS

Overall Survival (OS)

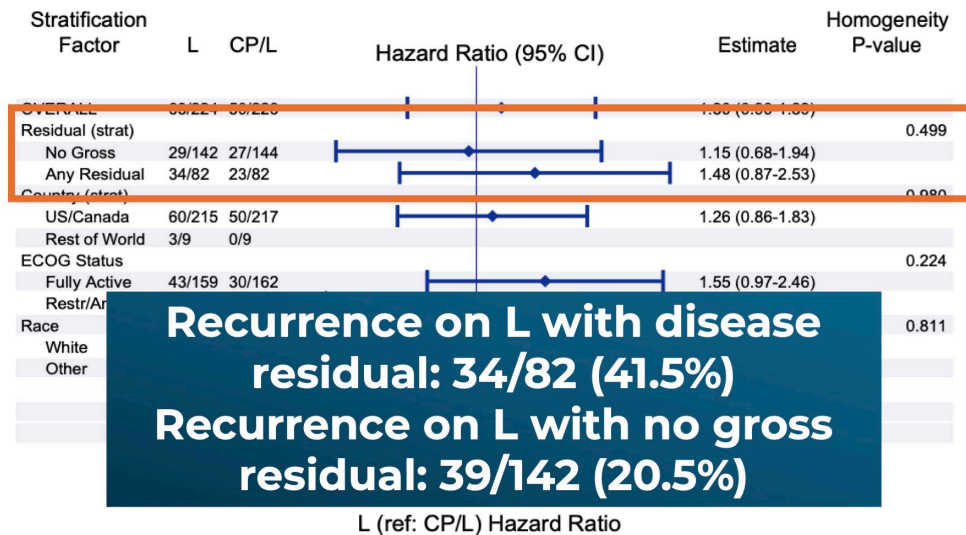


HR 1.52

Abbreviations: CP/L = carboplatin/paclitaxel followed by letrozole maintenance;
L = letrozole; NS = not significant; OS = overall survival.
Fader AN, et al. Presented at SGO Annual Meeting 2026 (LBA02); Fader AN, et al.
Gynecol Oncol. 2023;176(Suppl 1):S195. ClinicalTrials.gov identifier: NCT04095364.

NRG-GY019: Subgroup Efficacy and Safety Outcomes

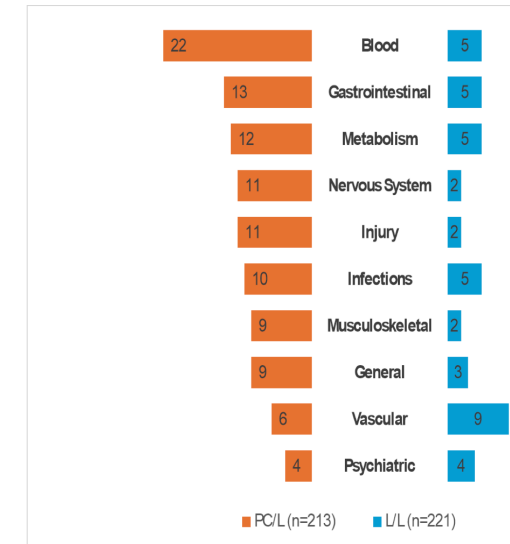
PFS: Subgroup Analysis



Adverse Event Summary

Adverse Event	Cycle 1-6		Cycle 7+	
	PC/L (n=213)	L/L (n=221)	PC/L (n=191)	L/L (n=189)
Any Adverse Event	213 (100)	214 (96.8)	191 (100)	189 (100)
Grade 3-5	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 at least 1 grade 3/4 adverse event was **3.99 (95%CI: 2.57, 6.18 p<0.001)** higher in the patients on the CP/L than the patients on the L arm.



Low-Grade Serous— Recurrent

- Hormonally active (97% ER+)
- MEK inhibitors (trametinib)

GOG 239	Selumetinib	II	Selumetinib	Objective tumor response, toxicity	52	2007-2009	ORR 15%, CBR 80%	POSITIVE TRIAL
GOG 281	Trametinib	II/III	SOC vs trametinib	PFS translational	250	2014-2019	PFS 13 vs 7 m ORR 26 vs 6%	POSITIVE TRIAL
CLEE011-XUS5IT	Letrozole + ribociclib	II	Letrozole + ribociclib	Response rate	51	2018	Pending	Ongoing
MILO - ENGOT-ov11	Binimetinib	III	Binimetinib vs Physician's Choice	PFS, OS, safety, toxicity	341	2013-2022	10.4 m vs 11.5 m	Negative—but details important

CBR = clinical benefit rate.

Farley J, et al. *Lancet Oncol*. 2013;14(2):134-140. Monk BJ, et al. *J Clin Oncol*. 2020;38(32):3753-3762.

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

Recurrent LGSOC

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GOG 3026	Letrozole + Ribociclib	II	Letrozole + Ribociclib	ORR CBR, PFS, OS, safety	51	2018-2026	ORR 30.6% CBR 84% PFS 14m, OS 44m	POSITIVE TRIAL

Farley J et al. Lancet Oncol 2013; 14: 134–40; Monk BJ et al. J Clin Oncol 2020; 38: 3753–62.
Gershenson DM et al. Lancet 2022; 399: 541.

Recurrent LGSOC

Phase II Trial of Ribociclib Plus Letrozole in Women With Recurrent Low-Grade Serous Carcinoma of the Ovary, Fallopian Tube, or Peritoneum: A GOG Partners Trial (GOG 3026)

Methods: This open-label, single-arm, multicenter phase II study enrolled women with measurable, recurrent LGSOC. Patients received ribociclib (600 mg orally, once daily, days 1-21 of a 28-day cycle) and letrozole (2.5 mg orally, once daily). The primary end point was investigator-assessed objective response rate (ORR) per RECIST 1.1. Secondary end points included clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and safety.

Results: Of 74 patients screened, 51 were enrolled and 49 treated. The confirmed ORR was 30.6% (90% CI, 19.9 to 43.2), including one complete and 14 partial responses. Among responders, the median duration of response was 21.2 months. The CBR was 84% (90% CI, 72.5 to 91.6). The median PFS was 14.5 months (90% CI, 10.1 to 28.8), and the median OS was 44.5 months (90% CI, 31.8 to not reached). The most common grade ≥ 3 adverse event (AE) was neutropenia (47%), managed with dose modifications. Three grade 5 events (6%) occurred but were unrelated to treatment. Treatment discontinuation because of AEs occurred in 4%. No dose-limiting toxicities were observed.

Recurrent LGSOC

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Gershenson DM et al. Lancet 2022; 399: 541.

Recurrent LGSOC

- GOG 239: phase II trial of selumetinib (oral)
 - 15% RR
 - 65% stable disease
 - PFS 11 m
 - OS NR
 - No correlation with KRAS

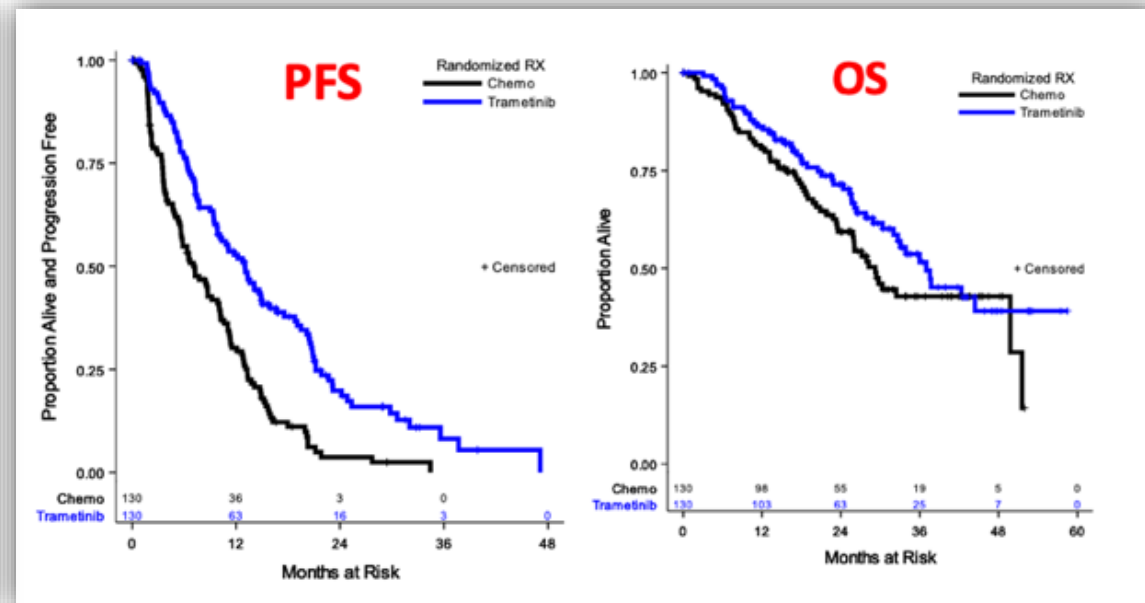
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Gershenson DM et al. Lancet 2022; 399: 541.

GOG281/LOGS: Trametinib vs Standard of Care

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



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

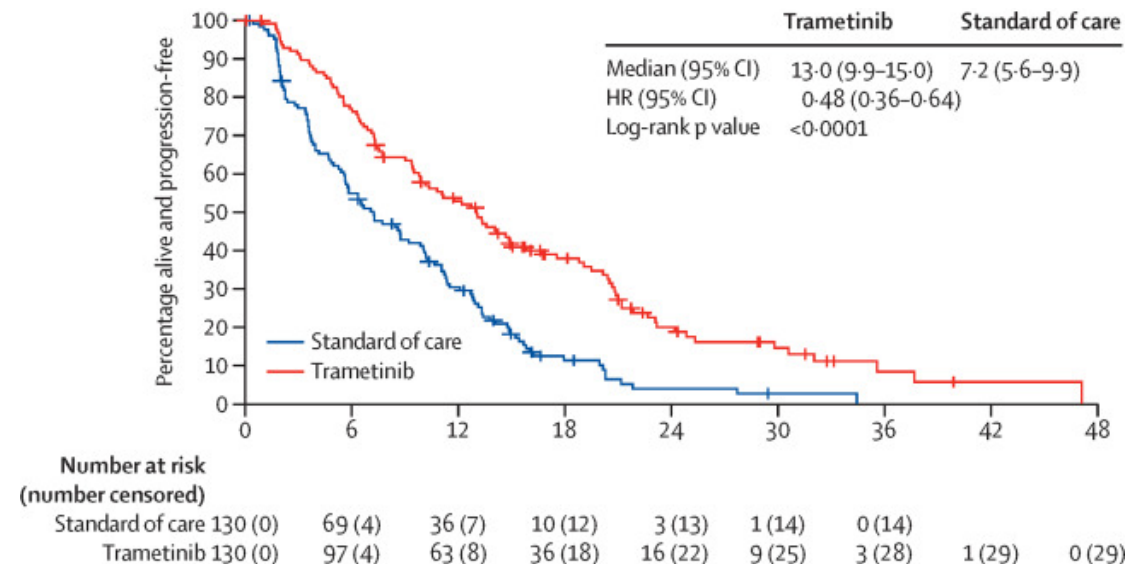
Final Overall Survival (IGCS 2025)

PLD = pegylated liposomal doxorubicin; SOC = standard of care; IGCS = International Gynecology Cancer Society. Gershenson DM, et al. *Lancet*. 2022;399(10324):541-553. ClinicalTrials.gov identifier: NCT02101788.

Recurrent LGSOC

- GOG 281: Trametinib vs chemo/hormonal therapy
 - PFS: 13.0 vs 7.2 m ($P < 0.0001$); HR 0.48 (CI 0.36-0.64)
 - Improved over both chemo and letrozole
 - 36% discontinued therapy

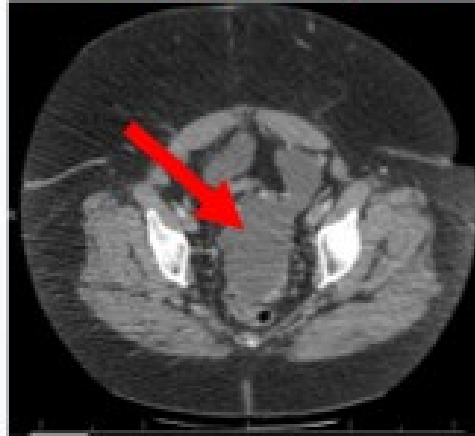
“...trametinib should be considered a new standard-of-care option for... progressive or relapsed low-grade serous carcinoma.”



Recurrent Low-Grade Serous Ovarian Carcinoma

55 y.o. with Stage IIIC LGSOC recurred after TRS/paclitaxel/carboplatin;
progressed after letrozole; KRAS+ on molecular profiling

- Pre-trametinib:
paracentesis q2weeks
(10/21)



- Post-trametinib:
dry (9/22)



TRS = tumor response score.

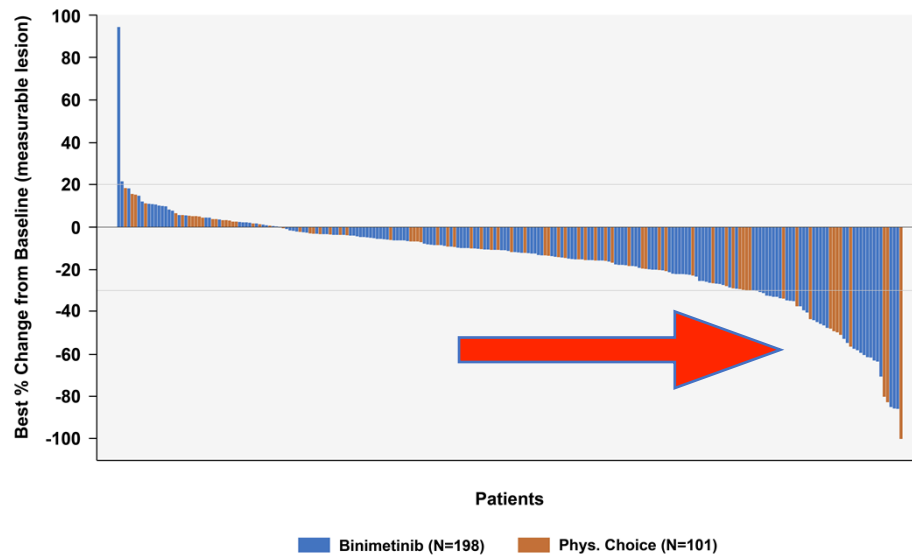
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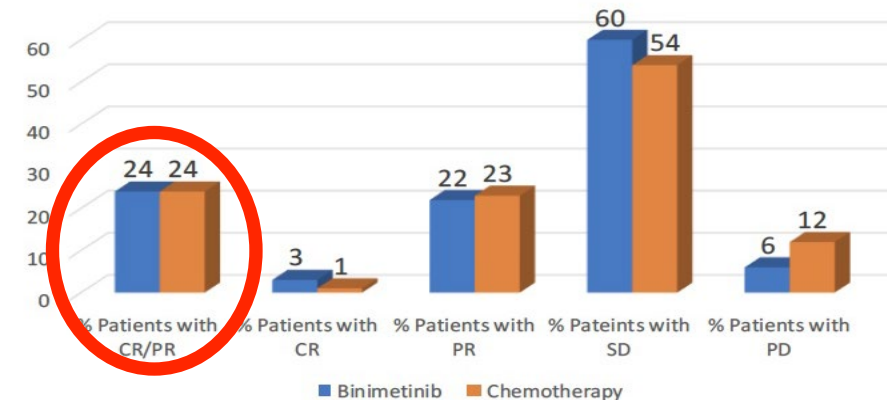
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Gershenson DM et al. Lancet 2022; 399: 541.

Recurrent LGSOC

- MILO/ENGOT-ov11: Binimetinib vs physician's choice chemo
 - PFS: 10.4 vs 11.5 m ($P=0.748$); HR 1.15 (CI 0.76-1.74)



Best RECIST Response (local)

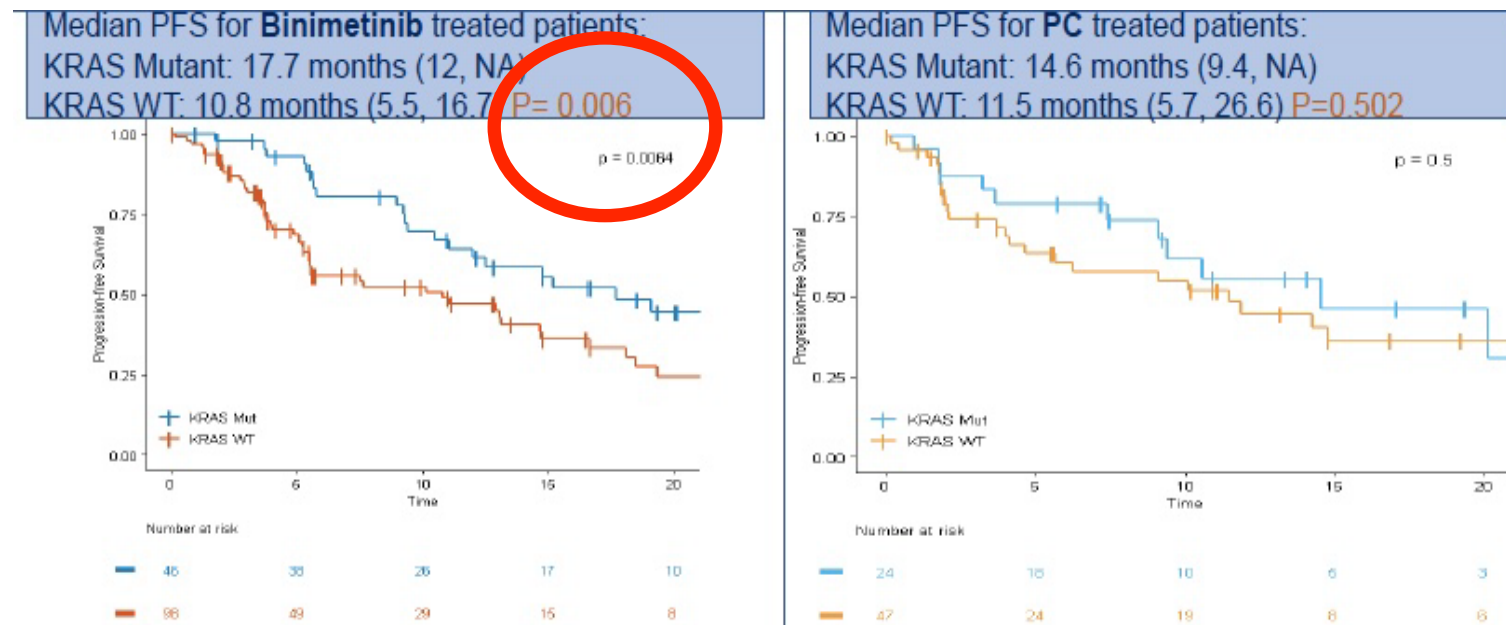


CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
Monk BJ, et al. *J Clin Oncol.* 2020;38(32):3753-3762.

Recurrent LGSOC

- MILO/ENGOT-ov11: Binimetinib vs physician's choice chemo
 - PFS: 10.4 vs 11.5 m ($P=0.748$); HR 1.15 (CI 0.76-1.74)
 - Efficacy may be related to KRAS status (post-hoc analysis)

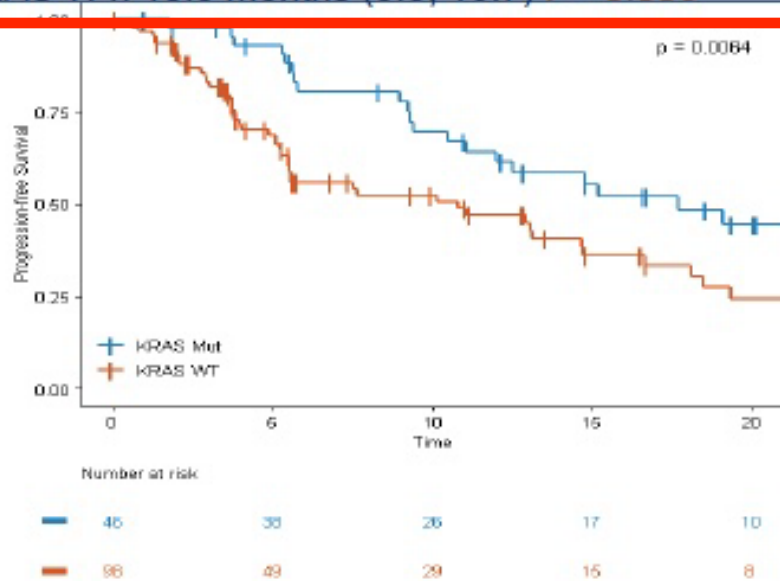
KRAS+: 17.7 m
KRAS-: 10.8 m
 $P=0.006$



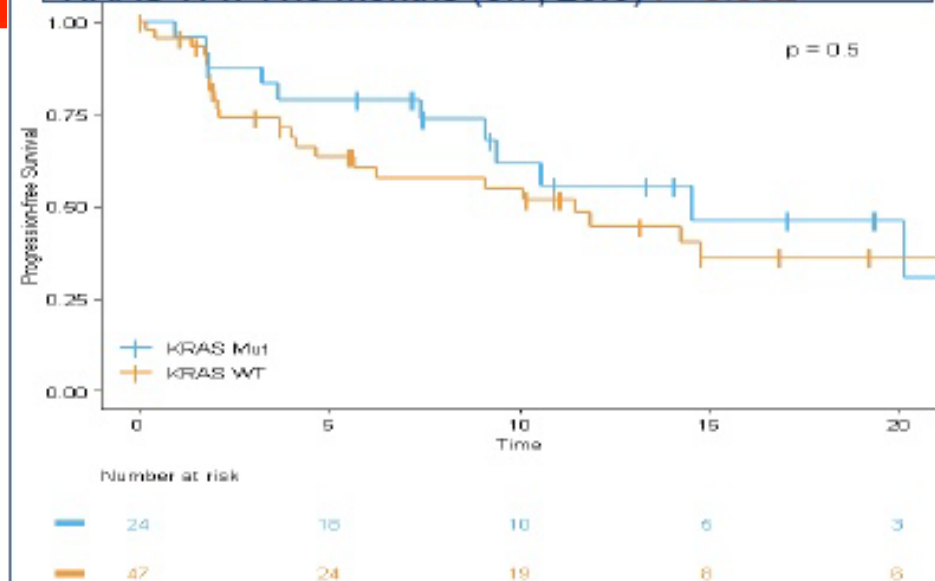
KRAS Mutation Status and PFS in Patients Treated with Binimetinib or Chemotherapy



Median PFS for **Binimetinib** treated patients:
KRAS Mutant: 17.7 months (12, NA)
KRAS WT: 10.8 months (5.5, 16.7) $P=0.006$



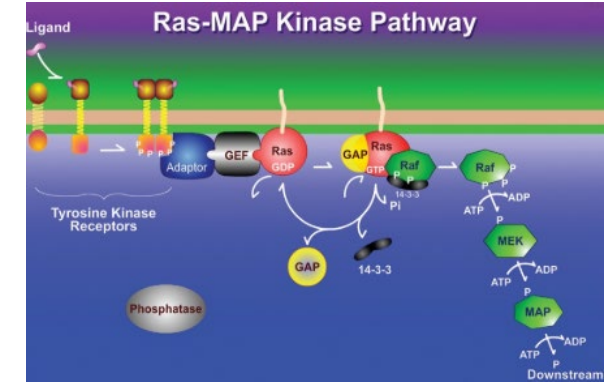
Median PFS for **PC** treated patients:
KRAS Mutant: 14.6 months (9.4, NA)
KRAS WT: 11.5 months (5.7, 26.6) $P=0.502$



- Mutation status may impact interpretation of the trial
- Does not mean you should ignore the histology...

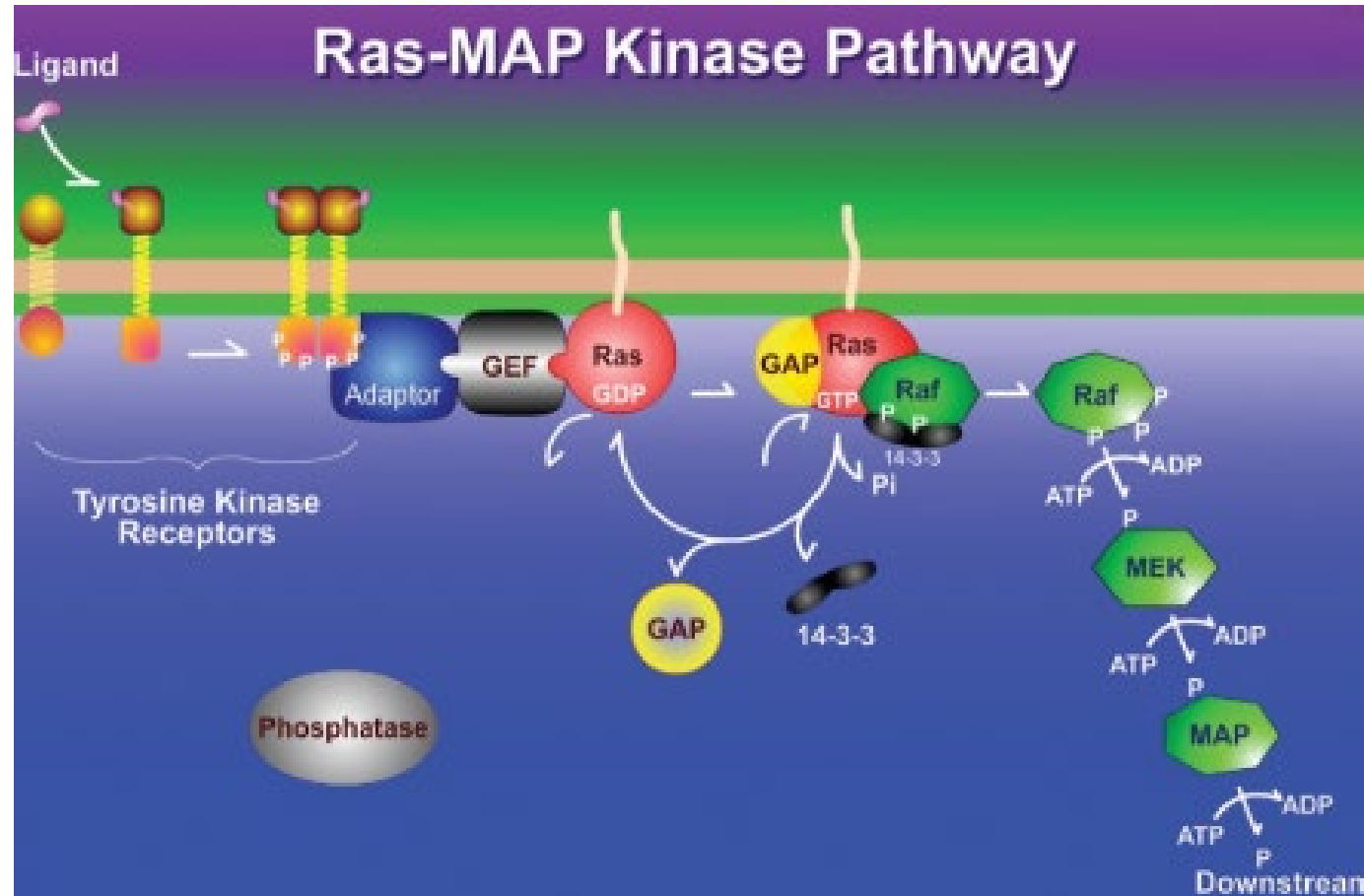
Recurrent LGSOC

- Hormonal therapy
- Ribociclib/letrozole
- GOG 239: phase II trial of selumetinib (oral)
 - 15% RR, 65% stable disease
 - PFS 11 m; OS NR; no correlation with KRAS
- GOG 281: Trametinib vs chemo/hormonal therapy
 - PFS: 13.0 vs 7.2 m ($P<0.0001$)
 - HR 0.48 (0.36-0.64) improved over both chemo and letrozole
- MILO/ENGOT-ov11: binimetinib vs physician's choice CT
 - PFS: 10.4 vs 11.5 m ($P=0.748$)
 - HR 1.15 (CR 0.76-1.74)
 - Efficacy ? associated with KRAS (post-hoc analysis)



Farley J et al. Lancet Oncol 2013; 14: 134–40; Monk BJ et al. J Clin Oncol 2020; 38: 3753–62.
Gershenson DM et al. Lancet 2022; 399: 541.

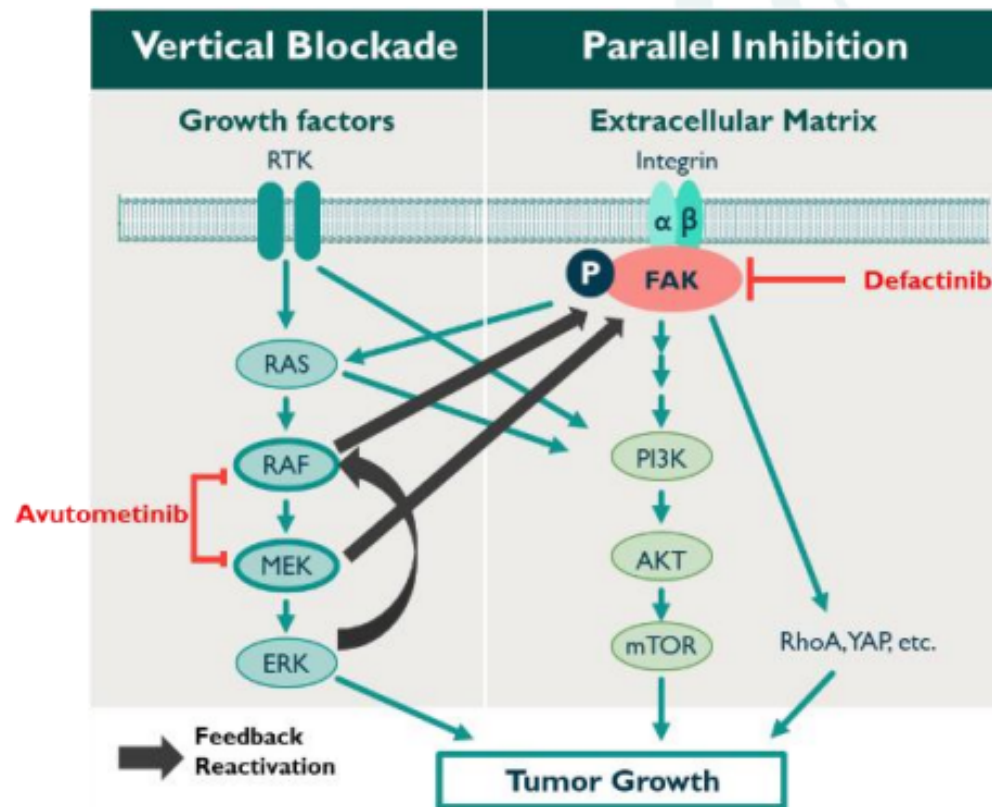
Recurrent Low-Grade Serous Ovarian Carcinoma



Future: Combination RAF/MEK and FAK inhibitors

Avutometinib and Defactinib Mechanism of Action

- **Avutometinib** is a first-in-class oral RAF/MEK clamp that potently inhibits MEK while also blocking the compensatory reactivation of MEK by upstream RAF^{1,2}
- **Defactinib** is a selective inhibitor of FAK, a key adaptive resistance mechanism to the RAS/MAPK pathway³⁻⁵
- The clinical activity of avutometinib + defactinib demonstrated in the phase 1 FRAME study (NCT03875820) led to FDA Breakthrough Therapy Designation and rationale for the phase 2 ENGOT-ov60/GOG-3052/RAMP 201 (NCT04625270) study^{6,7}

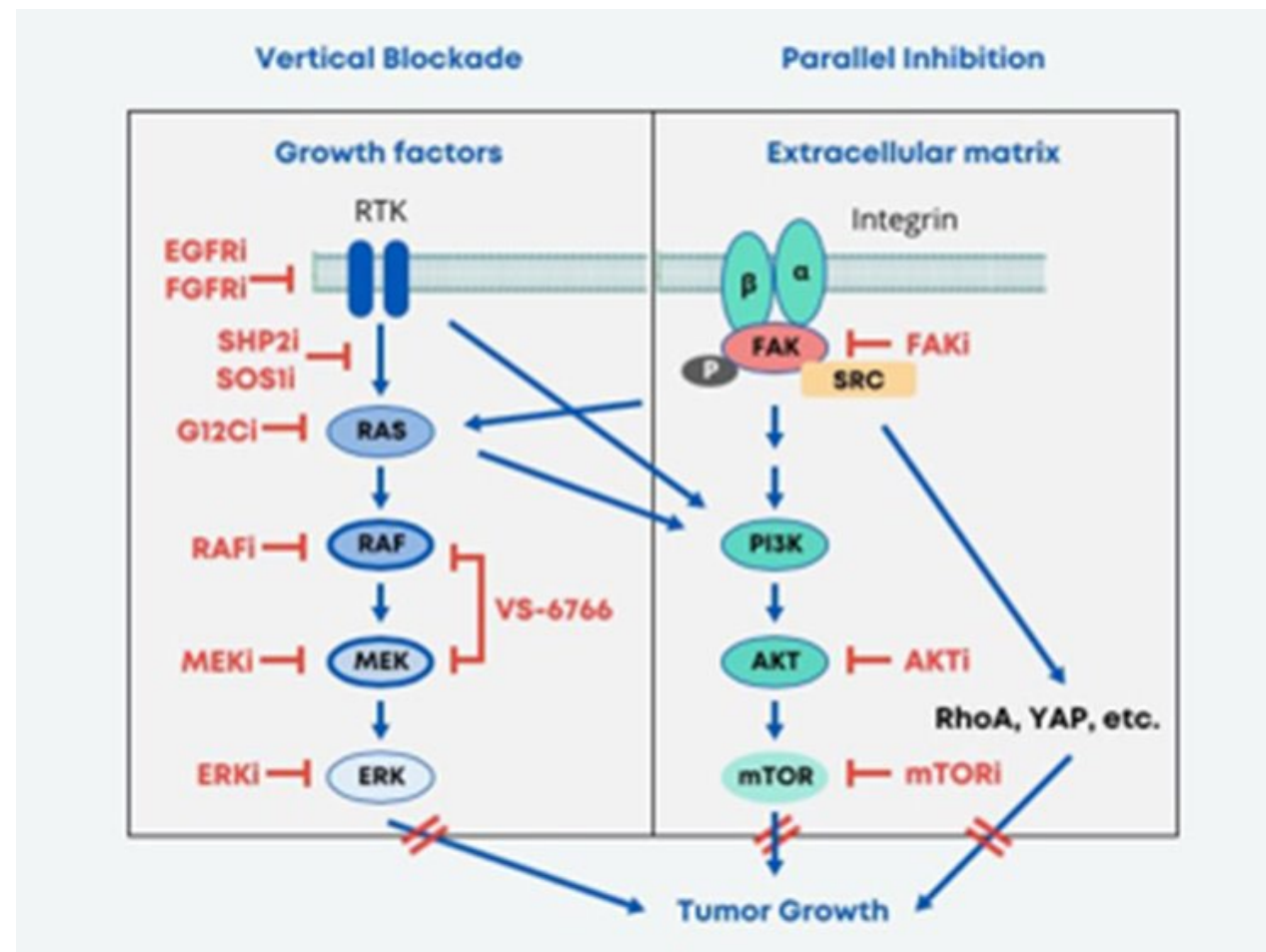


ERK; extracellular signal-regulated kinase; FAK, focal adhesion kinase; KRAS, kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer. MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; P, phosphate; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RhoA, Ras homolog family member A; RTK, receptor tyrosine kinase; YAP, Yes-associated protein.

1. Lito P, et al. *Cancer Cell*. 2014;25(5):697-710; 2. Gonzalez-Del Pino GL, et al. *Proc Natl Acad Sci U S A*. 2021;118(36):e2107207118; 3. Dawson JC, et al. *Nat Rev Cancer*. 2021;21:313-324; 4. Shinde R, et al. *Cancer Res*. 2020;80(suppl 16):CT143; 5. Kang Y, et al. *J Natl Cancer Inst*. 2013;105(19):1485-1495; 6. Banerjee S, et al. *Ann Oncol*. 2021;32(suppl 5):S728; 7. Verastem Oncology. Press Release: Verastem Oncology Receives Breakthrough Therapy Designation for VS-6766 with Defactinib in Recurrent Low-Grade Serous Ovarian Cancer. May 24, 2021. Accessed September 28, 2023. <https://investor.verastem.com/node/12421/pdf>.

Avutometinib and Defactinib Mechanism of Action

- FRAME: phase I/II avutometinib +defactinib
 - 52% ORR in LGSOC cohort (24 pts)
 - 44% KRAS mutated pts
- RAMP 201: VS-6766 vs combination
 - 45% vs 10% ORR, tolerable
 - Median DOR: 3.3-31.1 m
- RAMP 301
 - Combination vs IC, 270 pts

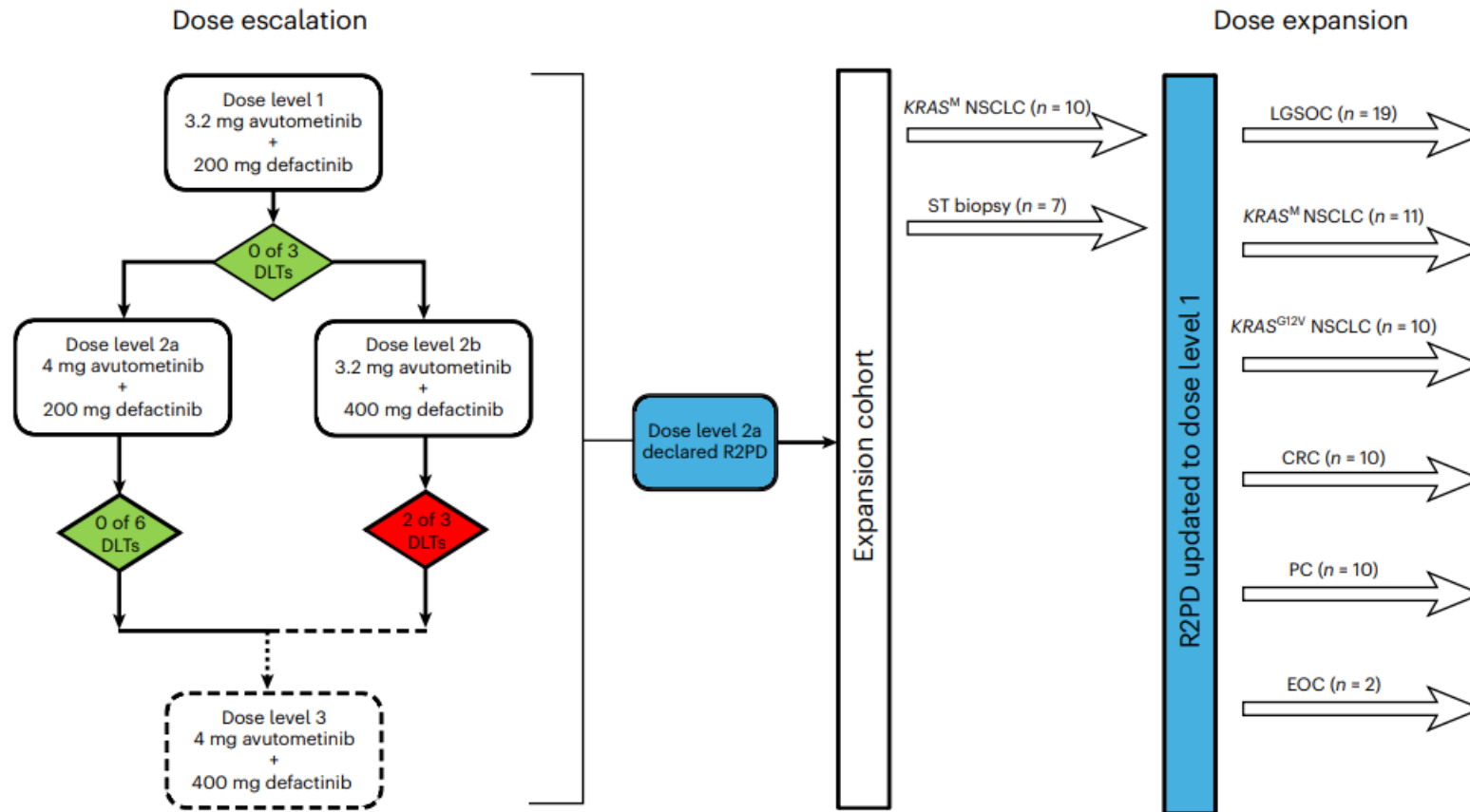


IC = induction chemotherapy.

Banerjee SN, et al. Presented at: IGCS Annual Global Meeting; October 16-18, 2024; Dublin, Ireland.

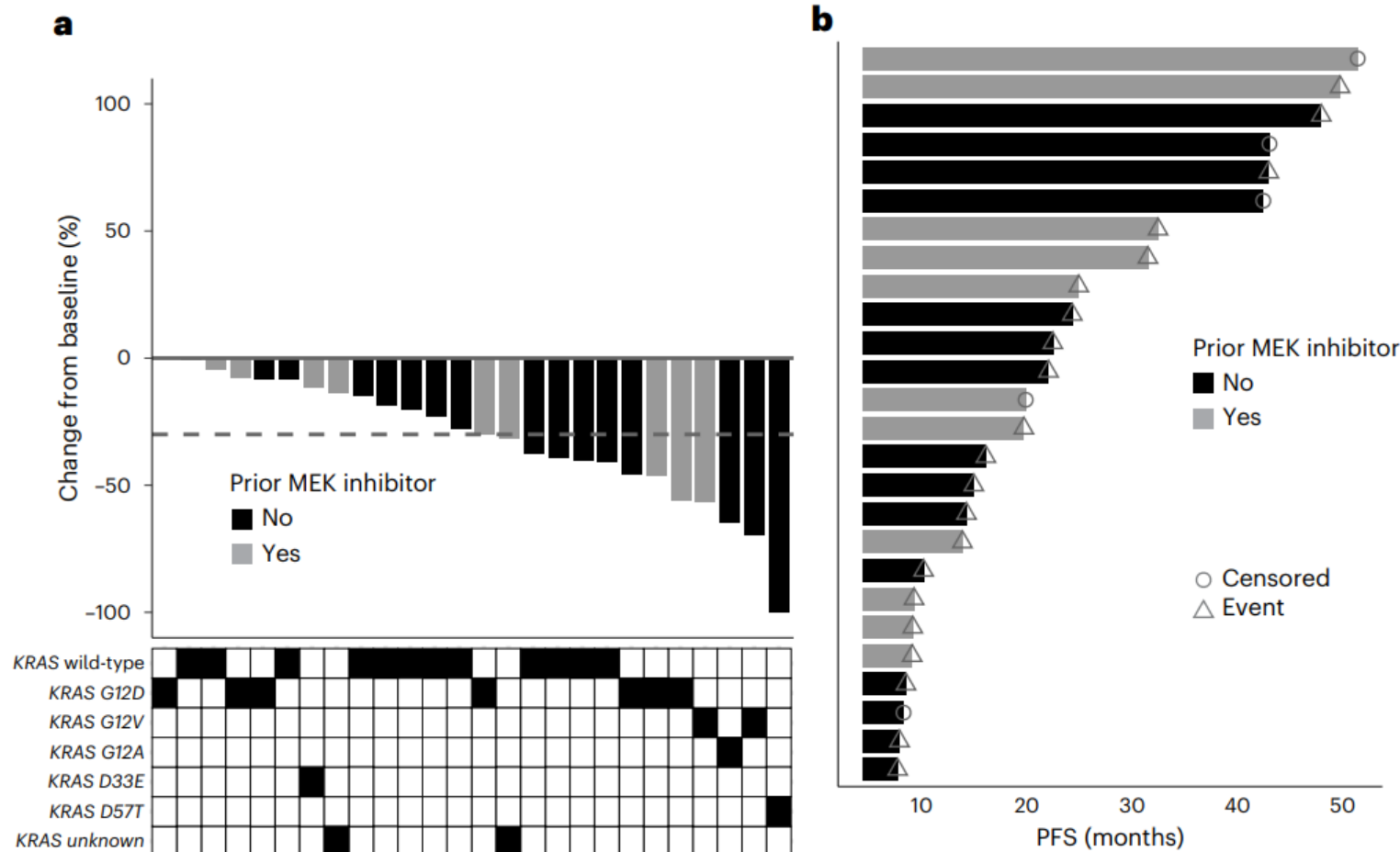
Defactinib with avutometinib in patients with solid tumors: the phase 1 FRAME trial

Received: 12 December 2024

Susana Banerjee¹, Matthew G. Krebs², Alastair Greystoke³,

Defactinib with avutometinib in patients with solid tumors: the phase 1 FRAME trial

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- Phase I/II
- Avutometinib + defactinib
- 52% ORR in LGSOC cohort (24 pts)
- 44% were pts with KRAS mutation

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

Susana N. Banerjee, PhD, MBBS, MA, FRCP¹ ; Els Van Nieuwenhuysen, MD²; Carol Aghajanian, MD^{3,4}; Véronique D'Hondt, MD, PhD⁵ ; Bradley J. Monk, MD, FACS, FACOG⁶ ; Andrew Clamp, PhD, MSc, BMBCh, MRCP⁷; Emily Prendergast, MD⁸ ; Ana Oaknin, MD, PhD⁹ ; Kari Ring, MD¹⁰; Nicoletta Colombo, MD, PhD^{11,12} ; Robert W. Holloway, MD¹³ ; Manuel Rodrigues, MD^{14,15} ; Hye Sook Chon, MD¹⁶; Charlie Gourley, PhD, FRCP¹⁷ ; Alessandro D. Santin, MD¹⁸ ; Premal H. Thaker, MD¹⁹ ; Christine Gennigens, MD, PhD²⁰ ; Gregg Newman, MD²¹; Erin Salinas, MD²²; Hagop Youssoufian, MD²³; Kathleen N. Moore, MD, MS, FASCO²⁴ ; Stephanie Lustgarten, PhD²³; David M. O'Malley, MD²⁵ ; Toon Van Gorp, MD, PhD² ; and Rachel N. Grisham, MD^{3,4}

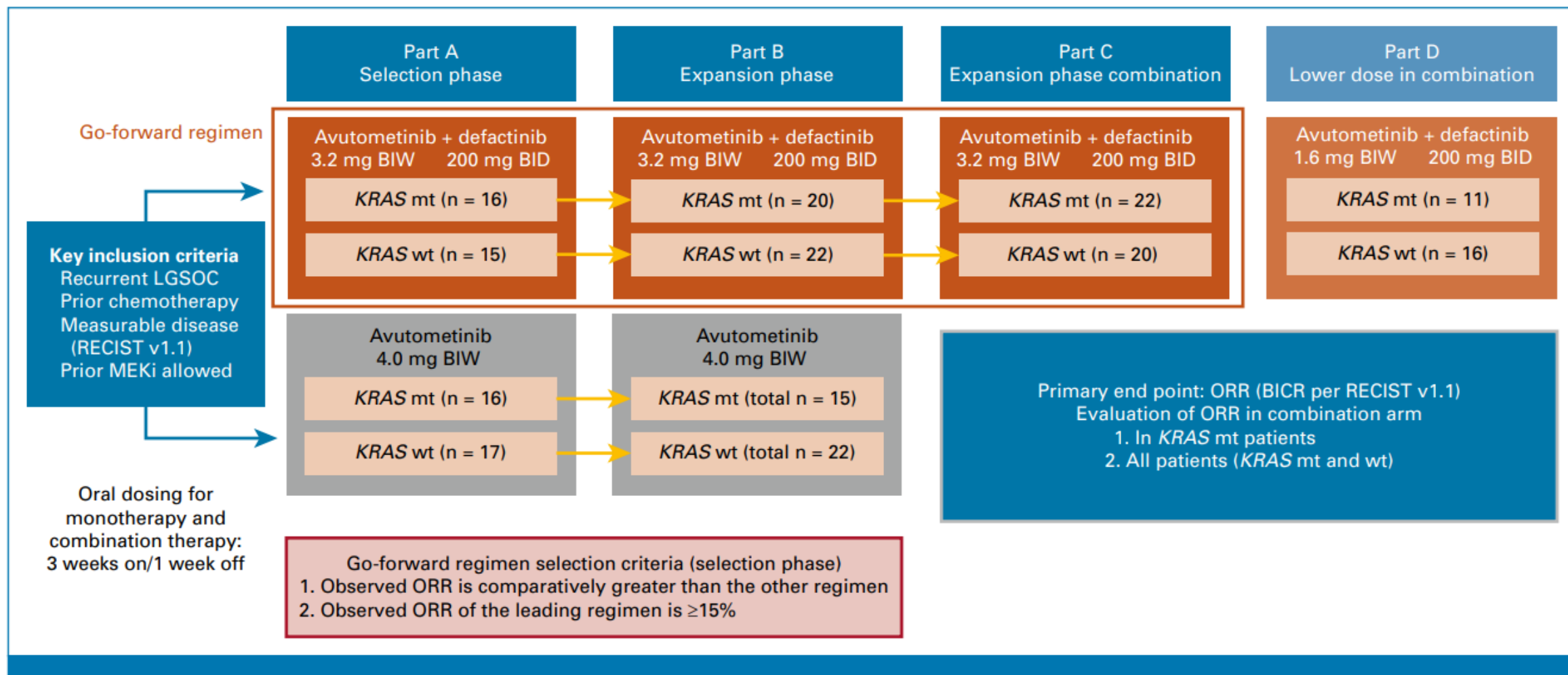


FIG 1. Study design. n values represent patients treated in the study. BICR, blinded independent central review; BID, two times per day; BIW, two times per week; LGSOC, low-grade serous ovarian cancer; *KRAS*, Kirsten rat sarcoma virus; MEKi, mitogen-activated extracellular signal-regulated kinase inhibitor; mt, mutant; ORR, objective response rate; wt, wild-type.

RAMP 201

TABLE 1. Baseline Characteristics in the Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day) Group and the Avutometinib (4.0 mg two times per week) Group

Characteristic	Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day)			Avutometinib (4.0 mg two times per week)		
	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 (years), median (min, max)	54 (21, 87)	60 (29, 87)	45 (21, 80)	54 (21, 77)	57 (27, 74)	48 (21, 77)
Race, ^a No. (%)						
White	88 (77)	43 (74)	45 (80)	59 (84)	24 (77)	35 (90)
Asian	4 (3)	2 (3)	2 (4)	1 (3)	1 (3)	0
Black or African American	5 (4)	3 (5)	2 (4)	1 (3)	1 (3)	0
Other	5 (4)	0	5 (9)	2 (3)	2 (6)	0
Not reported	13 (11)	10 (17)	3 (5)	6 (9)	3 (10)	3 (8)
Unknown	0	0	0	1 (1)	0	1 (3)
ECOG PS, No. (%)						
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)
Prior systemic regimens, No., 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, No. (%)	114 (99)	58 (100)	56 (98)	69 (99)	30 (97)	39 (100)
Prior hormonal therapy, No. (%)	99 (86)	49 (85)	50 (88)	58 (83)	25 (81)	33 (85)
Prior bevacizumab, No. (%)	59 (51)	23 (40)	36 (63)	34 (49)	17 (55)	17 (44)
Prior MEK inhibitor therapy, No. (%)	25 (22)	12 (21)	13 (23)	18 (26)	8 (26)	10 (26)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; KRAS, Kirsten rat sarcoma virus homolog; MEK, mitogen-activated extracellular signal-regulated kinase; mt, mutant; wt, wild type.

^aSelf-reported.

RAMP 201—Update

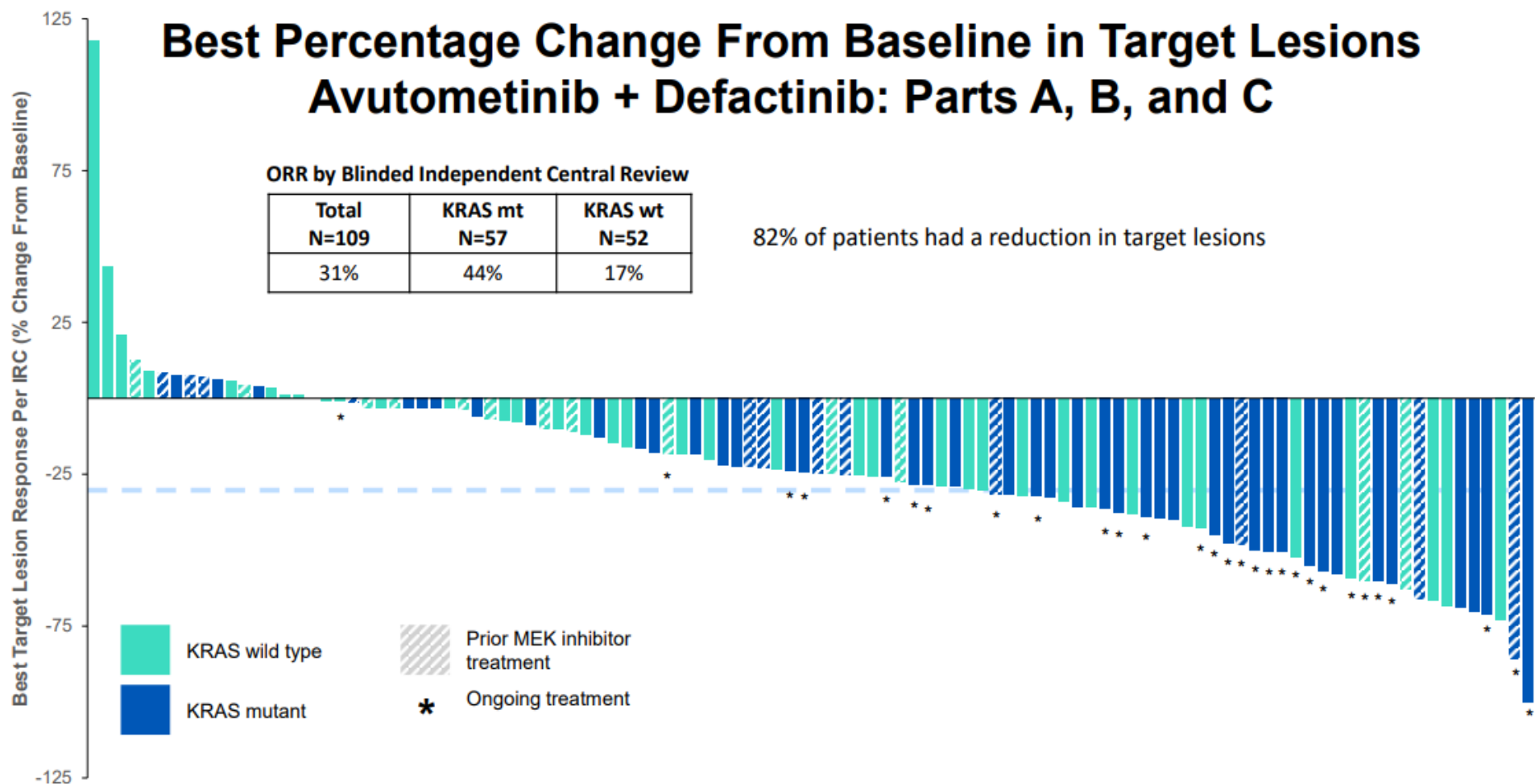
TABLE 2. ORR (RECIST v1.1) by BICR in the Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day) Group and the Avutometinib (4.0 mg two times per week) Monotherapy Group

Clinical Outcome	Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day)			Avutometinib (4.0 mg two times per week)		
	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 ^a ORR, No. (%)	34 (31)	25 (44)	9 (17)	12 (17)	7 (23)	5 (13)
Complete response	2 (2)	2 (4)	0	1 (1)	1 (3)	0
Partial response	32 (29)	23 (40)	9 (17)	11 (16)	6 (20)	5 (13)
Stable disease, ^b No. (%)	62 (57)	28 (49)	34 (65)	43 (62)	17 (57)	26 (67)
Progressive disease, No. (%)	9 (8)	2 (4)	7 (14)	7 (10)	3 (10)	4 (10)
Not evaluable, No. (%)	4 (4)	2 (4)	2 (4)	7 (10)	3 (10)	4 (10)

RAMP 201

RAMP 201 trial

- 31% ORR total
- 44% ORR KRAS+



IRC = independent review committee.

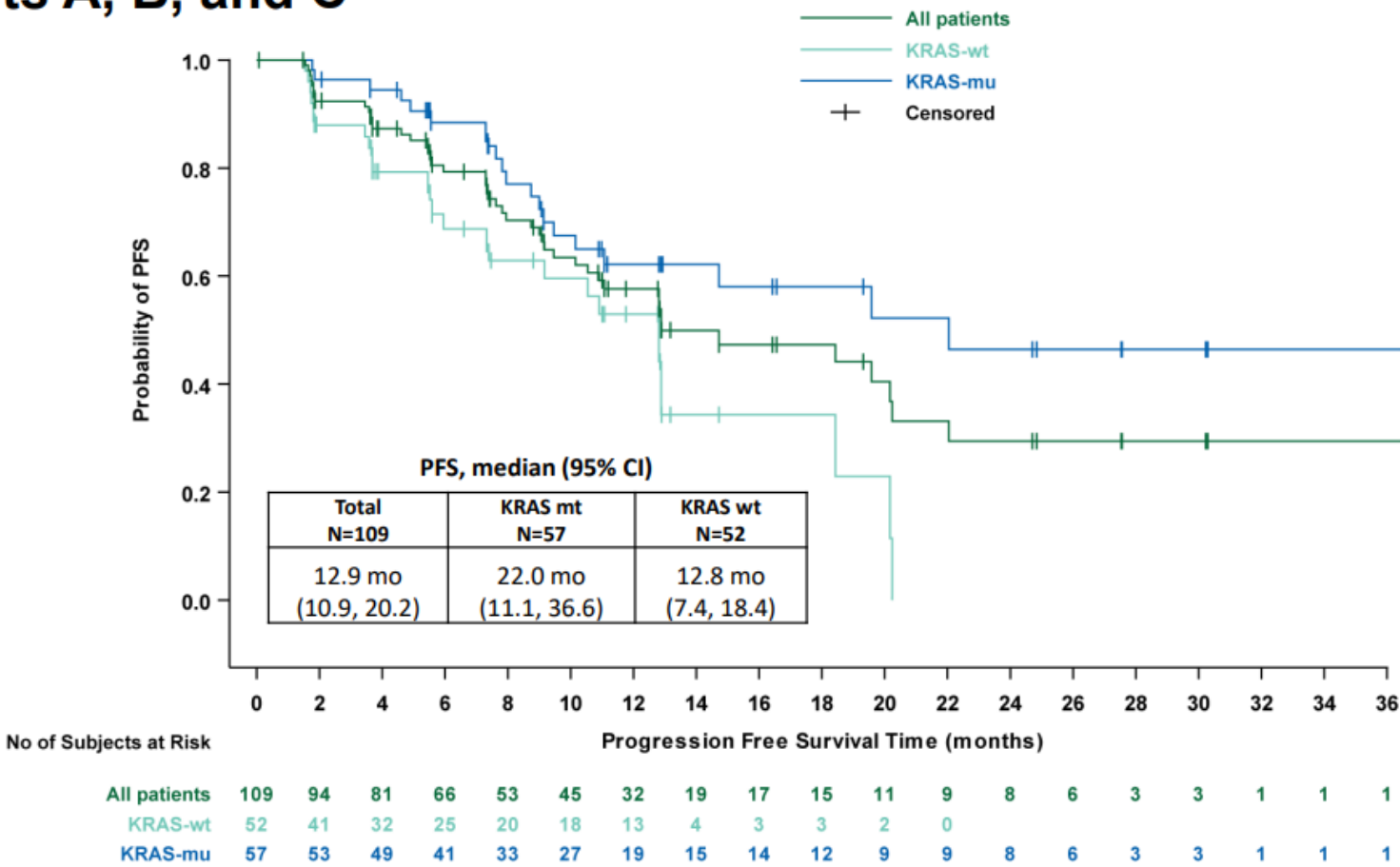
Banerjee SN, et al. *J Clin Oncol.* 2025;43(25):2782-2792.

RAMP 201

- RAMP 201 trial**
- 12.9 m PFS total
 - 22 m PFS KRAS+

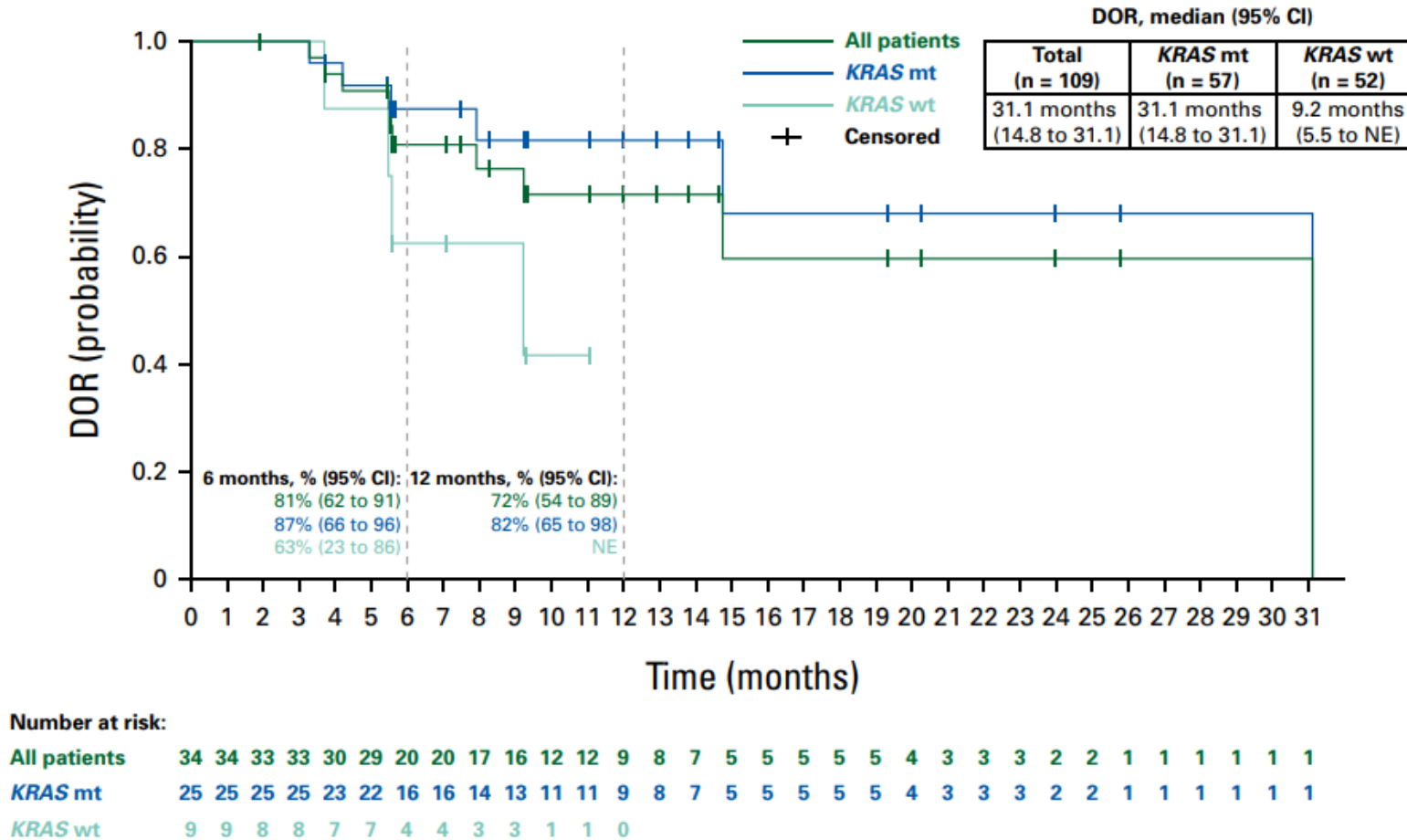


Progression-Free Survival: Avutometinib + Defactinib: Parts A, B, and C



RAMP 201—Update

A



RAMP 201

TABLE 2. ORR (RECIST v1.1) by BICR in the Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day) Group and the Avutometinib (4.0 mg two times per week) Monotherapy Group

Clinical Outcome	Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day)			Avutometinib (4.0 mg two times per week)		
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Abbreviations: BICR, blinded independent central review; *KRAS*, Kirsten rat sarcoma virus homolog; mt, mutant; ORR, objective response rate; wt, wild type.

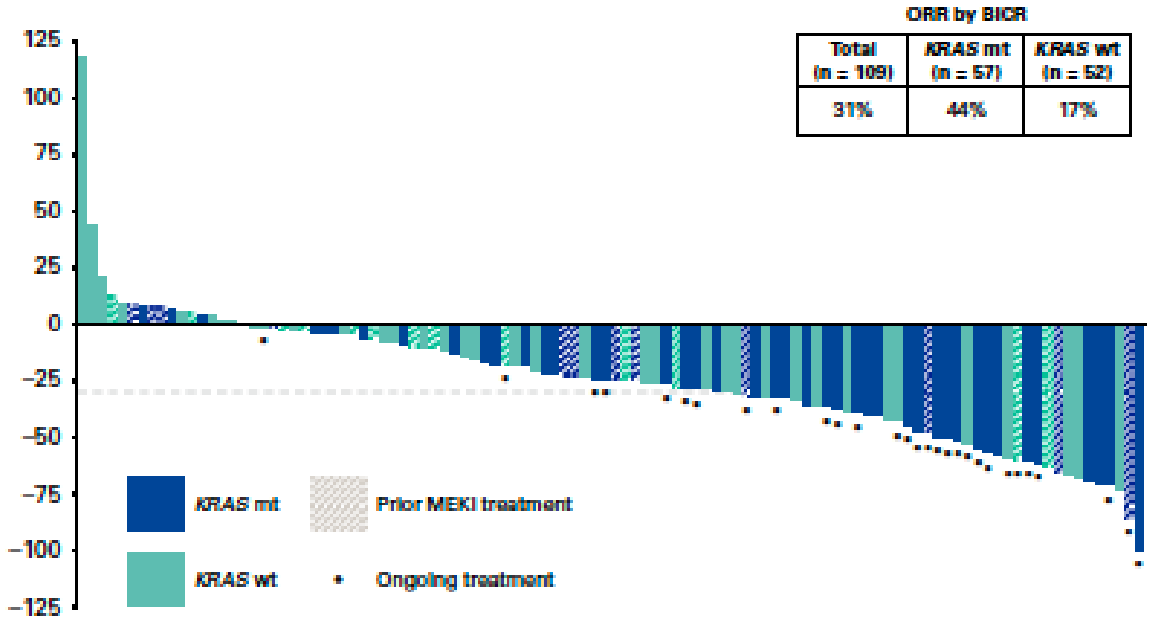
^aBy BICR.

^bIncludes unconfirmed partial response; stable disease (or unconfirmed partial response) must occur ≥53 days after first dose date.

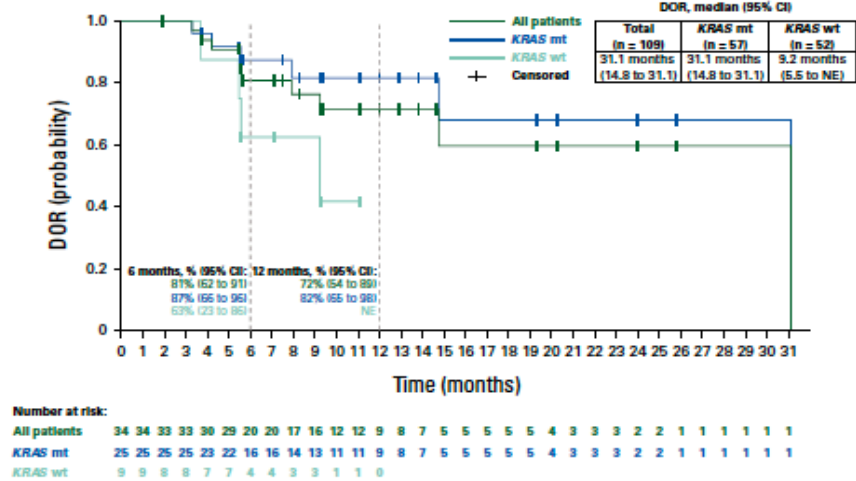
RAMP 201

C

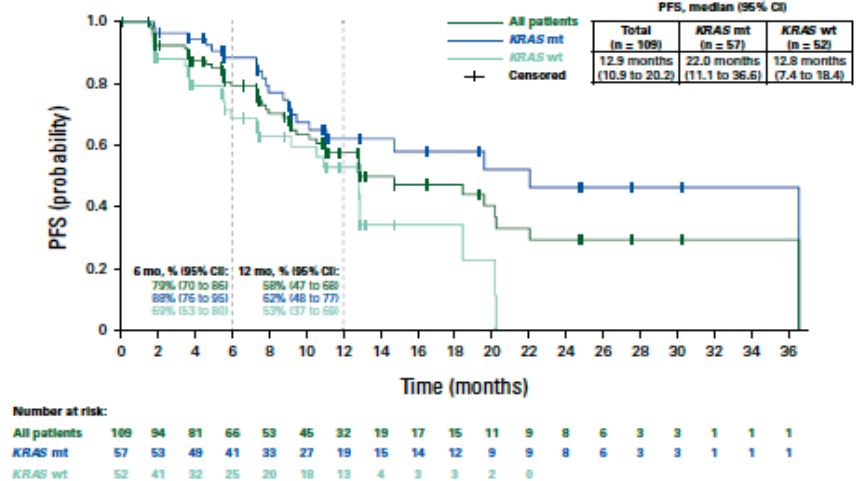
Best Target Lesion Response per BICR
(% change from baseline)



A



B



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

FDA Accelerated Approval

May 8, 2025

Avutometinib 3.2 mg BIW +
Defactinib 200 mg BID

KRAS mutated recurrent LGSOC

RAMP 201

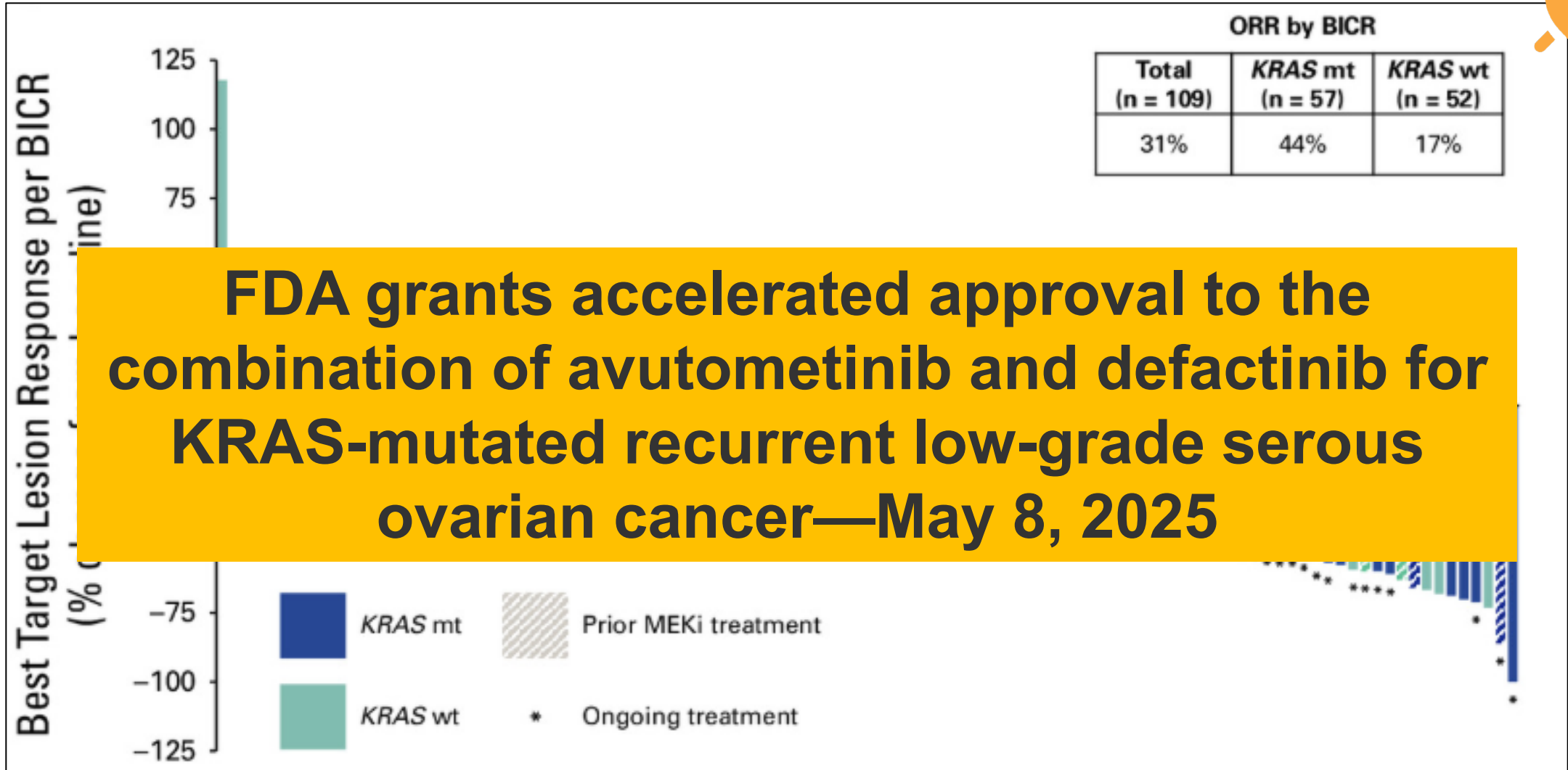


Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day),
n = 115

Preferred Term, No. (%)	All Grades	Grade ≥3 ^a
Nonlaboratory AEs		
Nausea	77 (67)	3 (3)
Diarrhea	67 (58)	9 (8)
Edema 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)
Stomatitis	18 (16)	3 (3)
Laboratory-related AEs		
Increased blood CPK	69 (60)	28 (24)
Increased blood bilirubin/hyperbilirubinemia	38 (33)	5 (4)
AST increased	36 (31)	2 (2)
ALT increased	25 (22)	2 (2)

- 80% (92/115) of patients had AEs leading to **dose interruption**
 - 38% (44/115) for elevations in CPK
- 36.5% (42/115) of patients had AEs leading to **dose reduction**
- 10% (12/115) of patients **discontinued for AEs**; most common increased CPK (n=4)
- 7% (8/115) of patients had **serious AEs** considered by the investigator to be related to study treatment: the only event occurring in more than 1 patient was abdominal pain
- 4 **deaths** (within 30 days of discontinuation): GI hemorrhage, large intestine perforation, clinical progression, clinical deterioration (none considered related to study treatment)

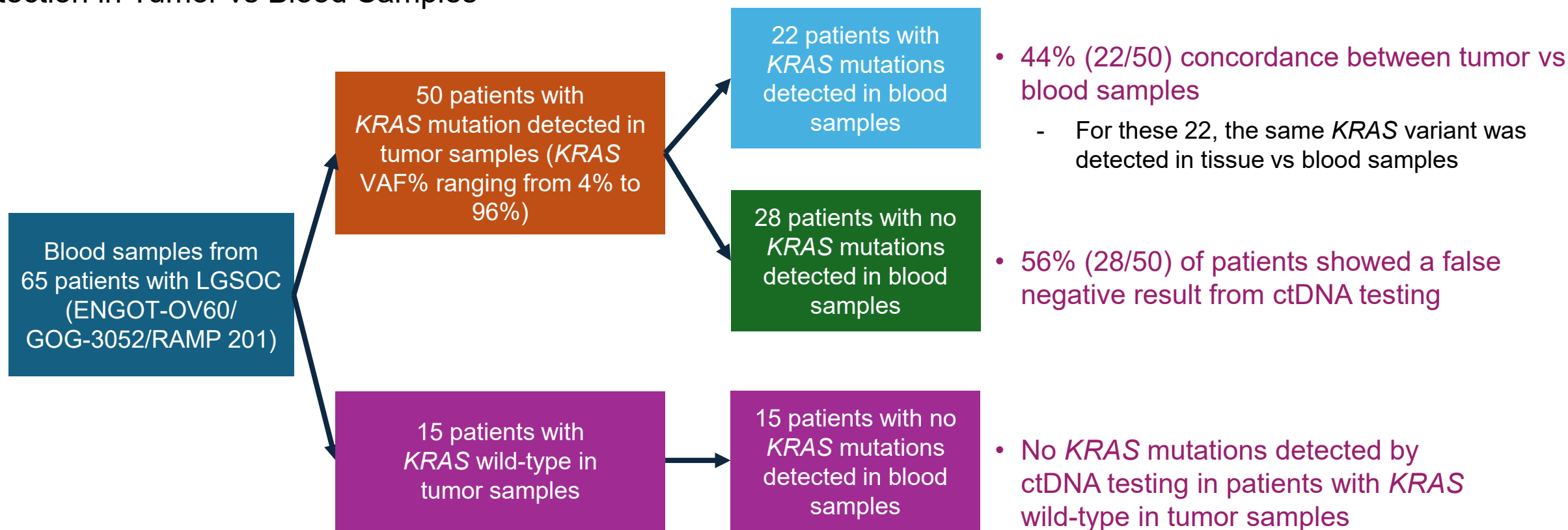
RAMP 201 Update



Banerjee SN, et al. *J Clin Oncol*. 2025;43(25):2782-2792. FDA. May 8, 2025. Accessed March 13, 2026.
<https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-combination-avutometinib-and-defactinib-kras-mutated-recurrent-low>.

ctDNA in LGSOC: Results from RAMP201 Samples

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



ctDNA = circulating tumor DNA; VAF = variant allele frequency.

Van Nieuwenhuysen, et al. Presented at: European Society for Medical Oncology (ESMO) Gynaecological Cancers Congress; 2025. Banerjee SN, et al. Presented at IGCS 2024.

Key Learning Points



- Upfront: Paclitaxel/carboplatin followed by letrozole is standard
 - Possible letrozole only in subset of R-zero patients
- Recurrent
 - MEK inhibitors approved
 - Hormonal therapy (letrozole) approved
 - Avutometinib and defactinib approved in KRASSm LGSOC
 - RAMP 301 ongoing
 - Importance of precision medicine in LGSOC

Key Recommendations for Integration

- Benefit of interdisciplinary care—tumor board
- Send every specimen for paired genetic/genomic testing
- Consider ER/PR status for letrozole maintenance
- If ER/PR+, as most will be, consider emerging evidence
 - Consider letrozole maintenance in stage III/IV disease

Key Recommendations for Integration

- Recurrent disease: essential to send molecular profiling
 - MEK inhibitors approved
 - Hormonal therapy (letrozole) approved
 - Avutometinib and defactinib approved in KRASSm LGSOC
 - RAMP 301 ongoing (will determine KRAS wt activity)
- Importance of precision medicine in LGSOC
 - If ER/PR+, consider letrozole
 - If KRAS+, consider avutometinib/defactinib
 - If KRAS wt, avutometinib/defactinib not yet approved
 - If KRAS+, other MEK inhibitors (eg, trametinib)
 - Other mutations may guide therapy with additional options