Expanding the Treatment Landscape for Recurrent Low-Grade Serous Ovarian Cancer

An Industry Supported Symposium at the IGCS 2024 Annual Global Meeting

Friday, October 18, 2024

Dublin, Ireland

This non-promotional symposium is organized and funded by Verastem in collaboration with The GOG Foundation, Inc.
NP-Ex-US--24-0007 October 2024

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

Welcome and Introductions

All Faculty

This non-promotional symposium is organized and funded by Verastem in collaboration with The GOG Foundation, Inc.

Faculty

Pedro T. Ramirez, MD, FACOG
Houston Methodist Hospital
Houston, Texas, USA

Susana Banerjee, MBBS, MA, PhD, FRCP
The Royal Marsden and the Institute of Cancer Research
United Kingdom

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

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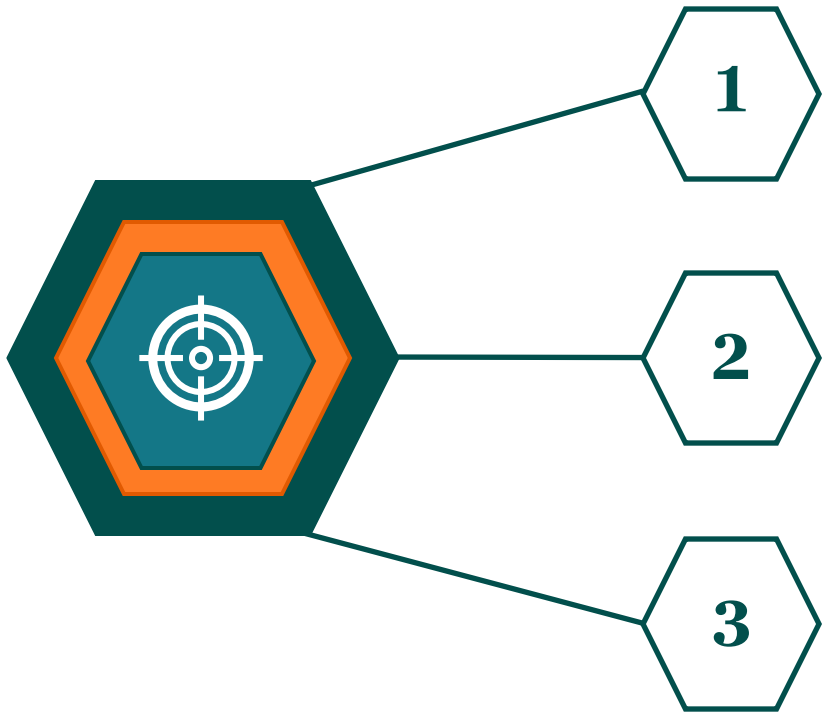
Faculty Disclosures

Name	Role in Activity	Disclosures
Pedro T. Ramirez, MD, FACOG	Moderator	**Nothing to Disclose**
Susana Banerjee, MBBS, MA, PhD, FRCP	Speaker	**Consulting/ Advisory Board:** AbbVie, AstraZeneca, BioNTech, Eisai, Gilead, GlaxoSmithKline, Immunogen, Incyte, ITM Oncologics, Merck Sharpe Dohme, Mersana, Myriad, Oncxerna, Pharma&, Seagen, Verastem, Zymeworks **Honoraria/Expenses:** AbbVie, AstraZeneca, GlaxoSmithKline, Immunogen, Merck Sharpe Dohme, Mersana, Takeda, Verastem **Funded Research:** Institution AstraZeneca, GlaxoSmithKline, Verastem (PI)
Rachel N. Grisham, MD	Speaker	**Consulting/ Advisory Board:** AstraZeneca, GlaxoSmithKline, Incyte, GenMab, Verastem, SpringWorks, Myriad **Funded Research to Institution:** Context, Pfizer, Bayer, Verastem

Learning Objectives



1. Highlight Clinical Landscape and Learn About Challenges as it Pertains to Recurrent LGSOC
2. Understand Most Recent Clinical Trial Data and Treatment Options in Recurrent LGSOC
3. Share Best Practices and Discuss Future Directions in Treatment Landscape

Agenda

7:45 – 7:50: **Welcome and Introductions**
Pedro T. Ramirez, MD, FACOG, Houston Methodist Hospital; Houston, Texas, USA

7:50 – 8:10: **Current Landscape in LGSOC**
Rachel N. Grisham, MD; Memorial Sloan Kettering Cancer Center; West Harrison, New York, USA

8:10 – 8:30: **Latest Data and Future Directions**
Susana Banerjee, MBBS, MA, PhD, FRCP, The Royal Marsden and the Institute of Cancer Research, United Kingdom

8:30 – 8:40: **Question and Answers**
All Faculty

8:40 – 8:45: **Closing Comments**
Pedro T. Ramirez, MD, FACOG, Houston Methodist Hospital; Houston, Texas, USA

Current Landscape in LGSOC

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

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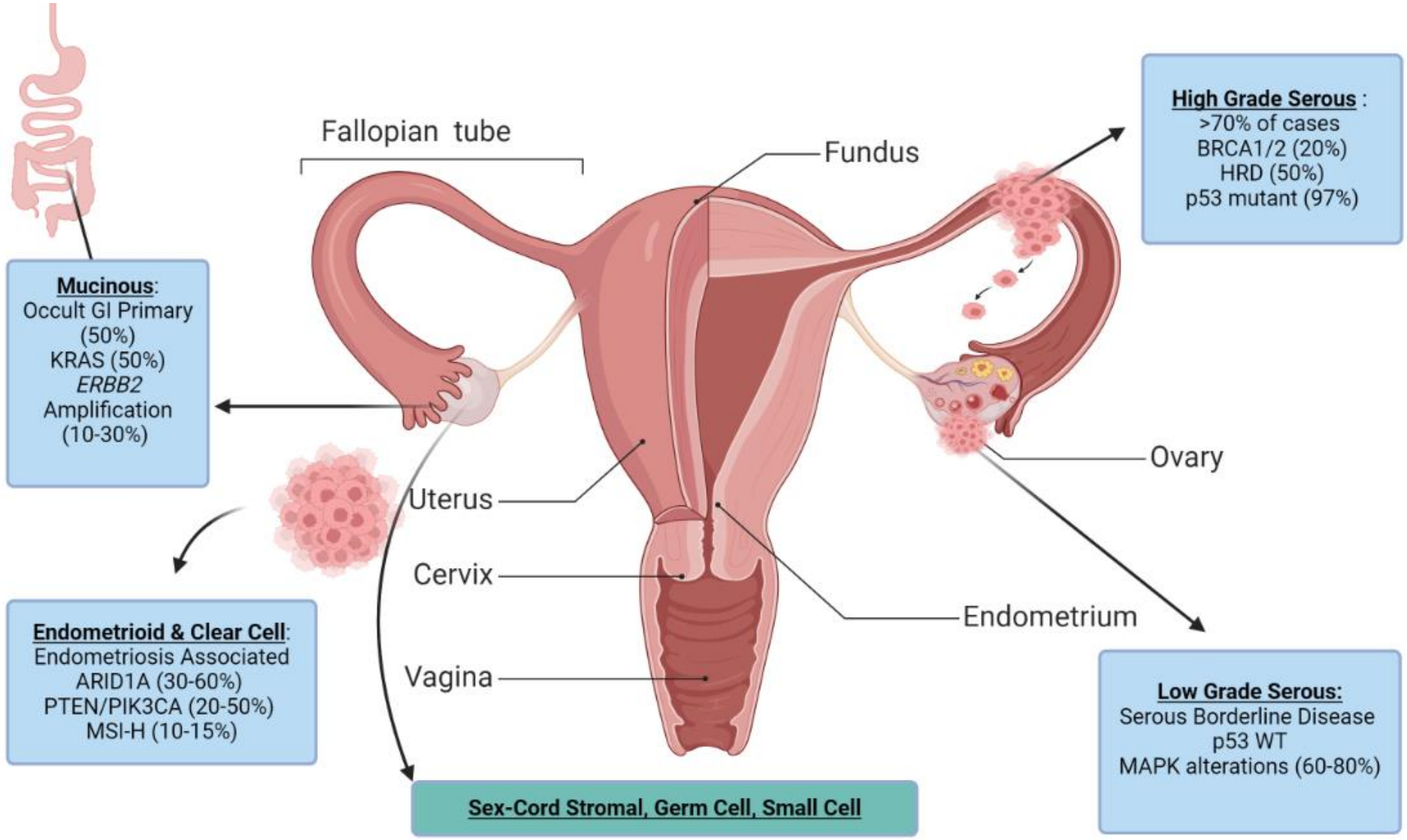
Ovarian, Primary Peritoneal and Fallopian Tube Cancer



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Molecular and Clinical Features of LGSOC and HGSOC

LGSOC accounts for <10% of new epithelial ovarian cancers

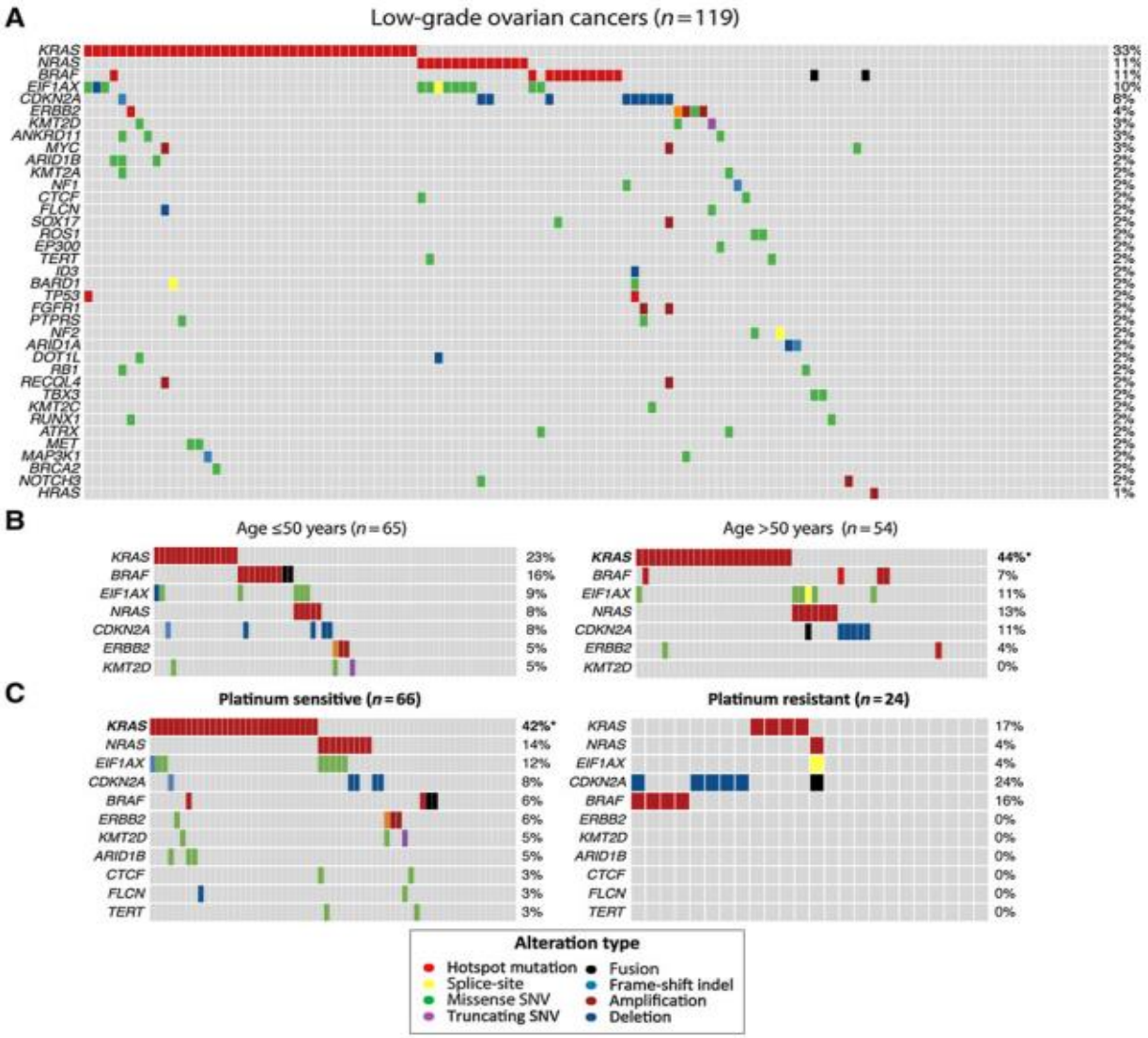
LGSOC | **HGSOC**

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

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

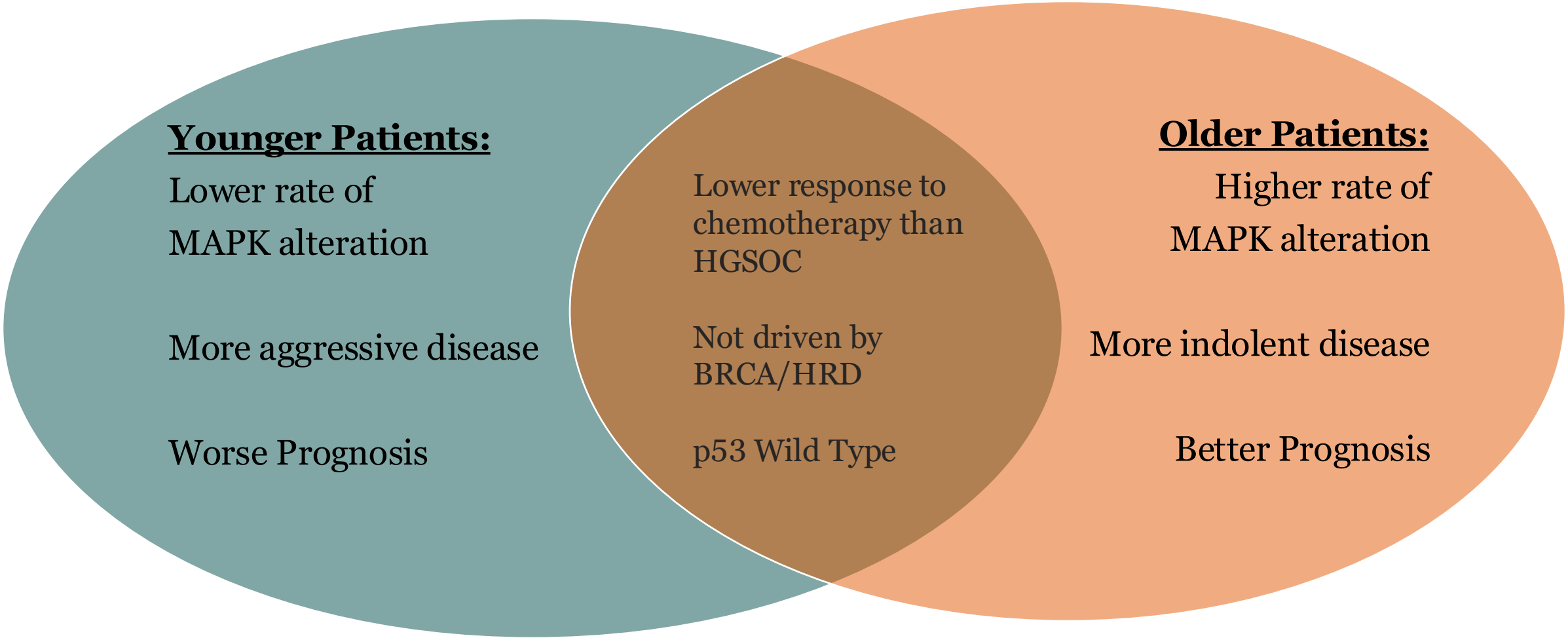
1. Grisham RN, et al, Int J Gyn Can. 2023;33(9):1331-1344; 2. Grisham RN. Oncology. 2016;30(7):650-652; 3. Bodurka DC, et al. Cancer. 2012;118(12):3087-3094; 4. Bookman MA, et al. J Natl Cancer Inst. 2014;106(4):1-8; 5. Mullany LK, et al. Endocrinology. 2012;153(4):1638-1648; 6. Vang R, et al. Adv Anat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

MAPK Alterations Both Prognostic and a Treatment Target

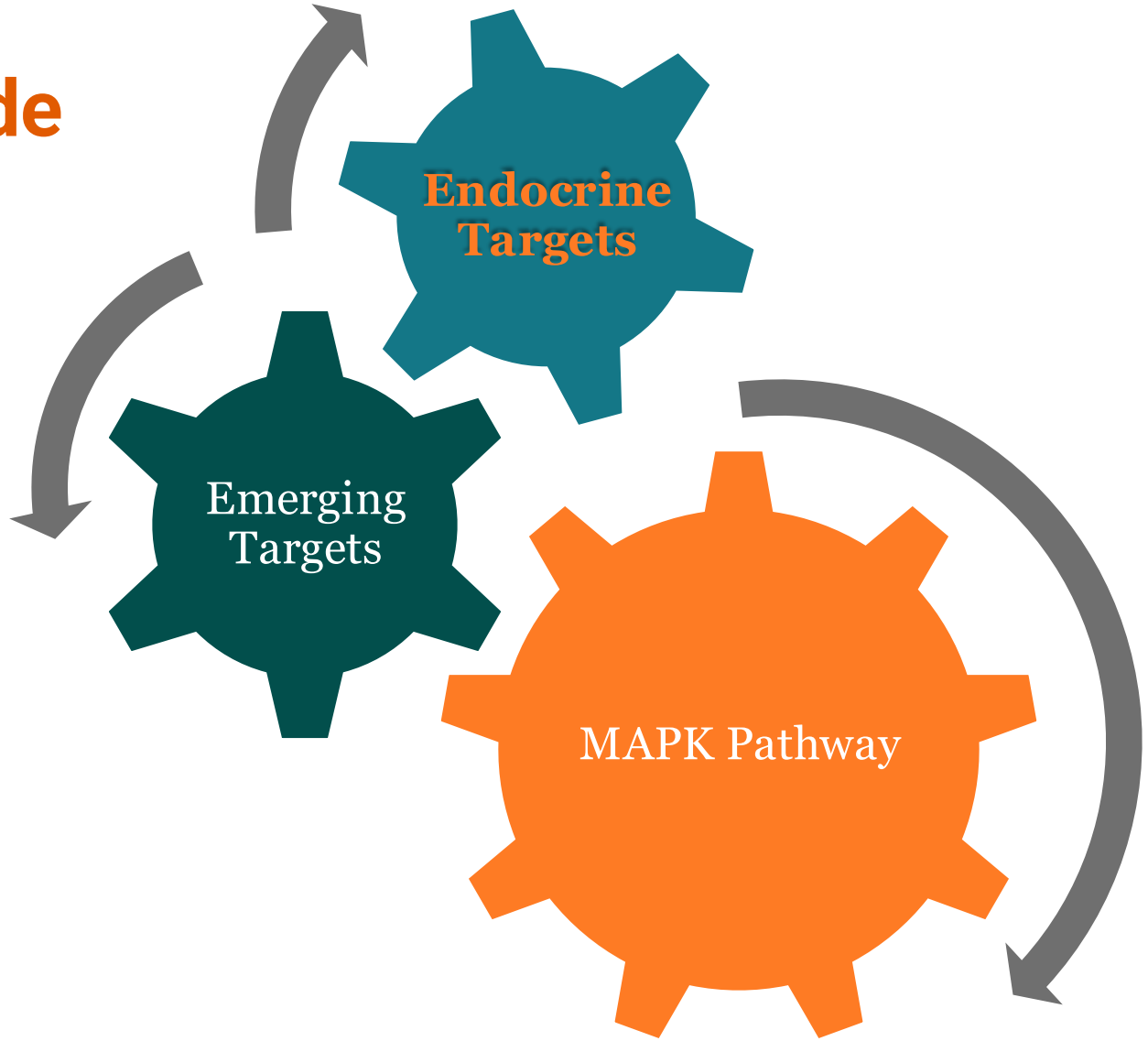


Manning-Geist, Gordhandas, Liu, Zhou, Iasonos, Da Cruz Paula, Mandelker, Roche, Zivanovic, Maio, Kemel, Chi, O'Cearbhaill, Aghajanian, Weigelt, Chui, Grisham; Clin Cancer Res, 2022.

Clinical Characteristics of Low Grade Serous Ovarian Cancer



Beyond Chemotherapy: Targeting Recurrent Low Grade Serous Ovarian Cancer



Single Agent Aromatase Inhibitors and SERMs

- Anastrozole
- Letrozole
- Tamoxifen

Alternative Endocrine Therapies

- Enzalutamide
- Onapristone

Combination Strategies

- Ribociclib with Letrozole

Single Agent Aromatase Inhibitors and SERMs

- Anastrozole
- Letrozole
- Tamoxifen

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

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

Results:

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

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

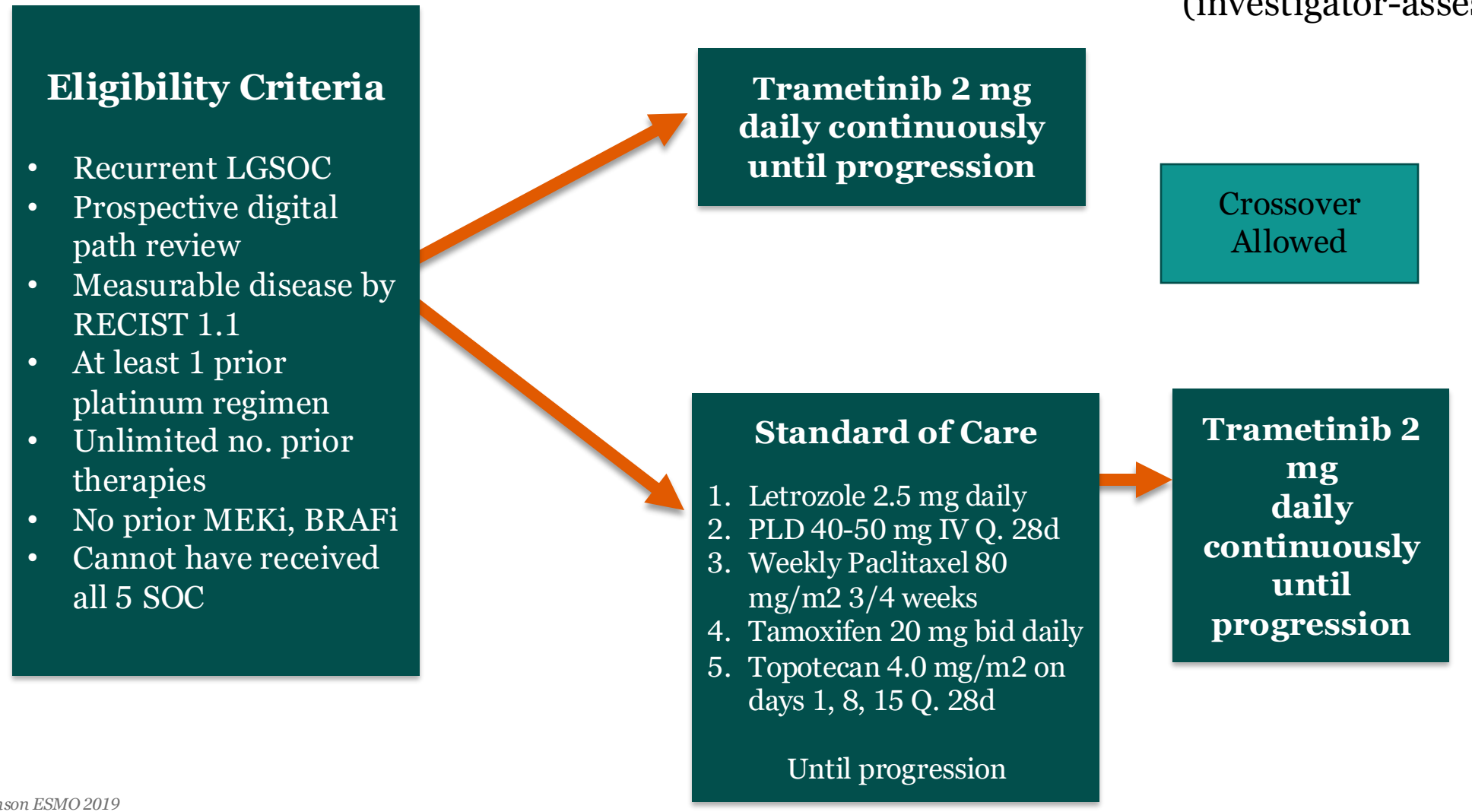
Characteristic	n (%)
Age [years, mean (range)]	57 (22–77)[a]
ECOG performance status	
0	23 (64)
1	13 (36)
Hormone receptor status	
ER+/PR-	16 (44)
ER+/PR+	20 (56)
Histology	
Low-grade serous carcinoma	34 (94)[b,c,d]
Low-grade endometrioid carcinoma	2 (6)
Lines of prior chemotherapy	
0	1 (3)
1	22 (61)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

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

Tang, O'Connell, Amant, Beale, McNally, Sjoquist, Grant, Davis, Sykes, Mileshkin, Moujaber, Kennedy, deFazio, Tan, Antill, Goh, Bonaventura, Scurry, Friedlander, Gynecol Oncol, 2019:531-538

NRG-GOG 0281 Study Design

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



Presented by D. Gershenson ESMO 2019

NRG-GOG 0281 Control Arm Outcomes

Treatment	# of Patients with CR or PR	Objective Response Rate	Response Duration in Months (95% CI)
Control	**8/130**	**6.2% (2-10)**	**5.9 (2.8-12.2)**
Letrozole	6/44	13.6%	
Tamoxifen	0/27	0%	
Paclitaxel	1/11	9.1%	
Liposomal Doxorubicin	1/40	2.5%	
Topotecan	0/8	0%	

Presented by D. Gershenson ESMO 2019

Single Agent Aromatase Inhibitors and SERMs

- Anastrozole
- Letrozole
- Tamoxifen

Alternative Endocrine Therapies

- Enzalutamide
- Onapristone

Phase II Study of Enzalutamide in AR+ Recurrent Ovarian Cancer

- Enzalutamide is a small molecule androgen-receptor antagonist that blocks testosterone binding to the androgen receptor, impedes nuclear translocation of the androgen receptor, and inhibits binding of DNA
- Enzalutamide is FDA approved for multiple indications in prostate cancer
- Enzalutamide has demonstrated clinical activity and was well tolerated in AR+ TNBC patients (CBR 25% at 16 weeks and PFS 2.9 months in ITT population)
- Androgen receptor positivity has been shown to decrease following chemotherapy, indicating that patients with multiple prior lines of chemo may be less responsive to antiandrogen therapy
- Androgen receptors are found in 67% of epithelial ovarian cancer cases

Traina et al, JCO, 2018 36:9,8.84-890

Phase II Study of Enzalutamide in AR+ Recurrent Ovarian Cancer

- Single Institution, all patients enrolled at Memorial Sloan Kettering Cancer Center (MSKCC), USA
- Advanced or Recurrent Ovarian, Primary Peritoneal or Fallopian Tube Cancer
- 1-3 Prior Lines of Chemotherapy
- Measurable Disease

- Screening of Archival Tumor Tissue in MSKCC CLIA Approved Lab for AR by IHC (Ventana)

AR < 5%
Ineligible for Study Screening

AR ≥5%
Eligible for Study Screening

Enzalutamide 160 mg PO QD until POD or Unacceptable Toxicity

Primary Objective: estimate the proportion of women who survive progression free for ≥ 6 months or have objective tumor response by RECIST 1.1

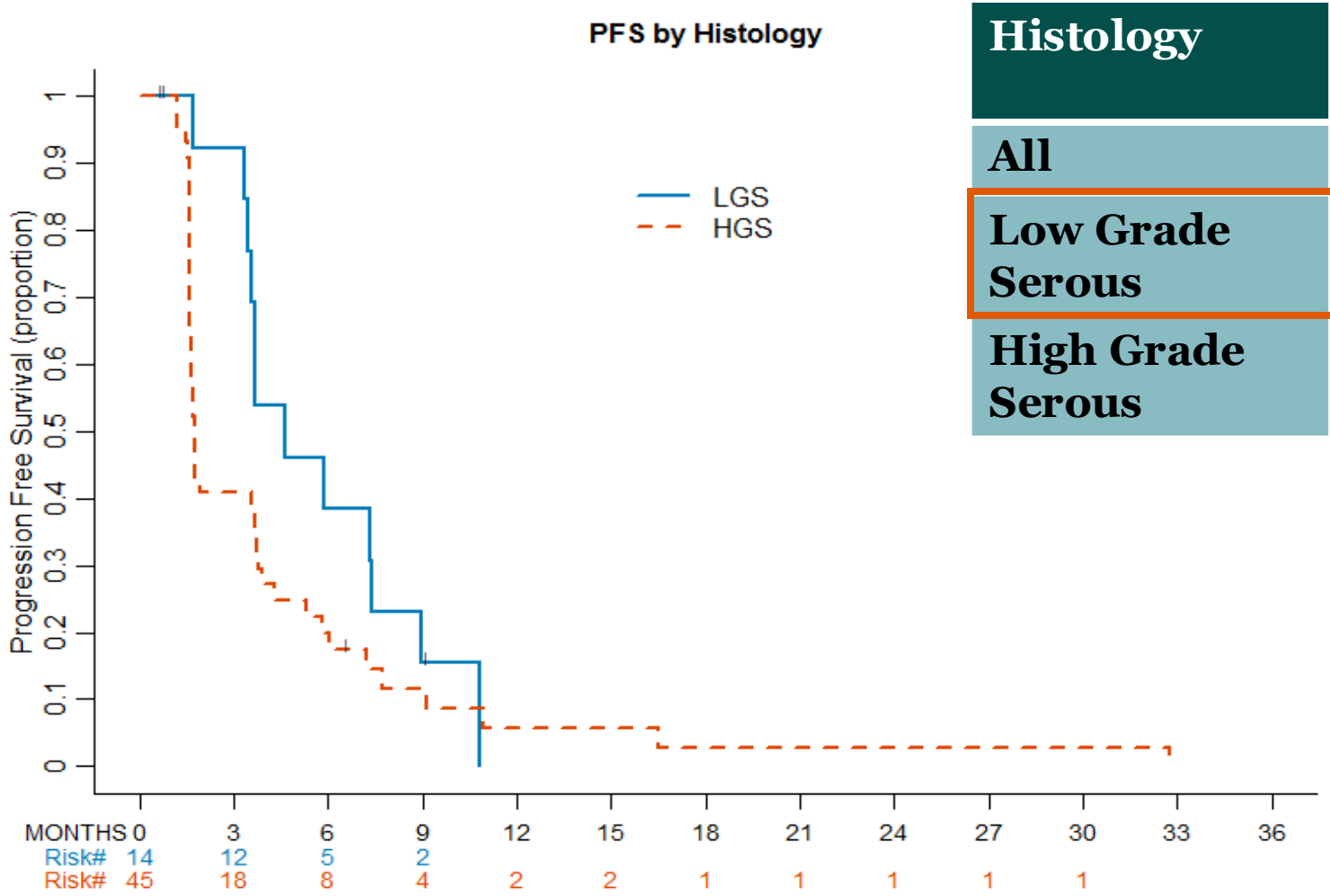
Baseline Characteristics

Age		
	Median	64
	Mean	68
	Range	29-87
BMI		
	Median	26
	Mean	29
	Range	19.8-56.4
# Lines of Prior Chemotherapy		
	1 Line	11 (19%)
	2 Lines	32 (54%)
	3 Lines	16 (27%)

Debulking Surgery		
	Optimal	53 (90%)
	Suboptimal	5 (8%)
	Unknown	1 (2%)
Prior Hormonal therapy		13 (22%)
Prior Radiation Therapy		1 (2%)
Race		
	White	48 (81%)
	African American	2 (3%)
	Asian, Indian, Pakistani	5 (9%)
	Unknown	4 (7%)
Histology		
	High Grade Serous	45 (76%)
	Low Grade Serous	14 (24%)

Manning-Geist, Gordhandas, Giri, Iasonos, Zhou, Grishman, O'Cearbhaill, Zamarin, Lictman, Sabbatini, Tew, Li, McDonnell, Aviki, Chi, Aghajanian, Grisham; Gynecologic Oncology, January 2022.

Progression Free Survival By Histology



Histology	Median PFS	6 month PFS (90% CI)
All	3.5 months	24% (17-100%)
Low Grade Serous	4.6 months	39 % (22-100%)
High Grade Serous	1.7 months	20 % (13%-100%)

- There was 1 confirmed (HGSOC) and 1 unconfirmed (LGSOC) partial response by RECIST 1.1
  2% (1/59) confirmed response rate
- Thirteen patients remained progression free for ≥ 6 months
  - 22% PFS_6 (13/59)
  - 8 with HGSOC
  - 5 with LGSOC

Manning-Geist, Gordhandas, Giri, Iasonos, Zhou, Grishman, O'Cearbhaill, Zamarin, Lictman, Sabbatini, Tew, Li, McDonnell, Aviki, Chi, Aghajanian, Grisham; Gynecologic Oncology, January 2022.

Basket Study of Oral Progesterone Antagonist Onapristone Extended Release in PR+ Granulosa Cell, LGSOC or Endometrioid Endometrial Cancer

- Onapristone extended release (ONA-XR) (Context Therapeutics) is a type I full progesterone antagonist that inhibits progesterone mediated PR activation and stabilizes PR association with corepressors
- ONA-XR has shown activity across multiple preclinical models of hormonally driven cancer
- Two phase I-II studies of breast cancer patients onapristone exhibited a 56% ORR and a 67% CBR in patients with locally advanced hormone therapy naïve MBC [1] and a 10% ORR and 49% CBR in metastatic tamoxifen-resistant patients [2]
- The progesterone receptor is commonly expressed in GCT (98% of cases), LGSOC (58% of cases), and EEC (67% of cases)

1=Robertson JF, Willsher PC, Winterbottom L, Blamey RW, Thorpe S. Onapristone, a progesterone receptor antagonist, as first-line therapy in primary breast cancer. Eur J Cancer. 1999;35(2):214–218. doi: 10.1016/S0959-8049(98)00388-8; 2= Jonat W, Girurescu M, Robertson JFR. The clinical efficacy of progesterone antagonists in breast cancer. In: Robertson JFR, Nicholson RI, Hayes DF, editors. Endocrine therapy of breast cancer, Chapter 8. London: Martin Dunitz Ltd, Taylor and Francis; 2002. pp. 117–124.

Basket Study of Oral Progesterone Antagonist Onapristone Extended Release in PR+ Granulosa Cell, LGSOC or Endometrioid Endometrial Cancer

Table 1: Key Inclusion & Exclusion Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
Histologically confirmed at MSKCC GCT, LGSOC, or EEC with PR expression ≥ 1% by IHC from tissue collected within the past 3 years	Endocrine/hormonal therapy for treatment of cancer within 28 days of starting study drug
Measurable disease by RECIST 1.1	Requirement for chronic corticosteroid therapy
≥ 1 prior line of chemotherapy, unlimited additional lines of therapy are allowed	Another invasive malignancy with evidence of disease within past 3 years
Ability to swallow and absorb tablets	Know brain metastasis without stability for ≥ 6 months

__Andres__, Finch, Iasonos, Zhou, Girshman, Chhetri-Long, Green, Jang, O'Cearbhaill, Kyi, Cohen, Friedman, Makker, Chi, Sonoda, Chiang, Aghajanian, Weigelt, __Grisham__; Gynecologic Oncology, October 2024.

Basket Study of Oral Progesterone Antagonist Onapristone Extended Release in PR+ Granulosa Cell, LGSOC or Endometrioid Endometrial Cancer

Cancer Type	Evaluable Patients	Median PFS, months (2-sided 95% CI)	3 month PFS rate (2-sided 95% CI)	6 month PFS rate (2-sided 95% CI)
Granulosa Cell	14	2.8 (1.6-4.9)	50% (22.9-72.2%)	21.4% (5.2%-44.8%)
LGSOC	4	4.4 (1.8-NE)	75% (12.8%-96.1%)	NR
Endometrial Cancer	1	Progressed at 1.6 months	NR	NR

__Andres__, Finch, Iasonos, Zhou, Girshman, Chhetri-Long, Green, Jang, O'Cearbhaill, Kyi, Cohen, Friedman, Makker, Chi, Sonoda, Chiang, Aghajanian, Weigelt, __Grisham__; Gynecologic Oncology, October 2024.

Single Agent Aromatase Inhibitors and SERMs

- Anastrozole
- Letrozole
- Tamoxifen

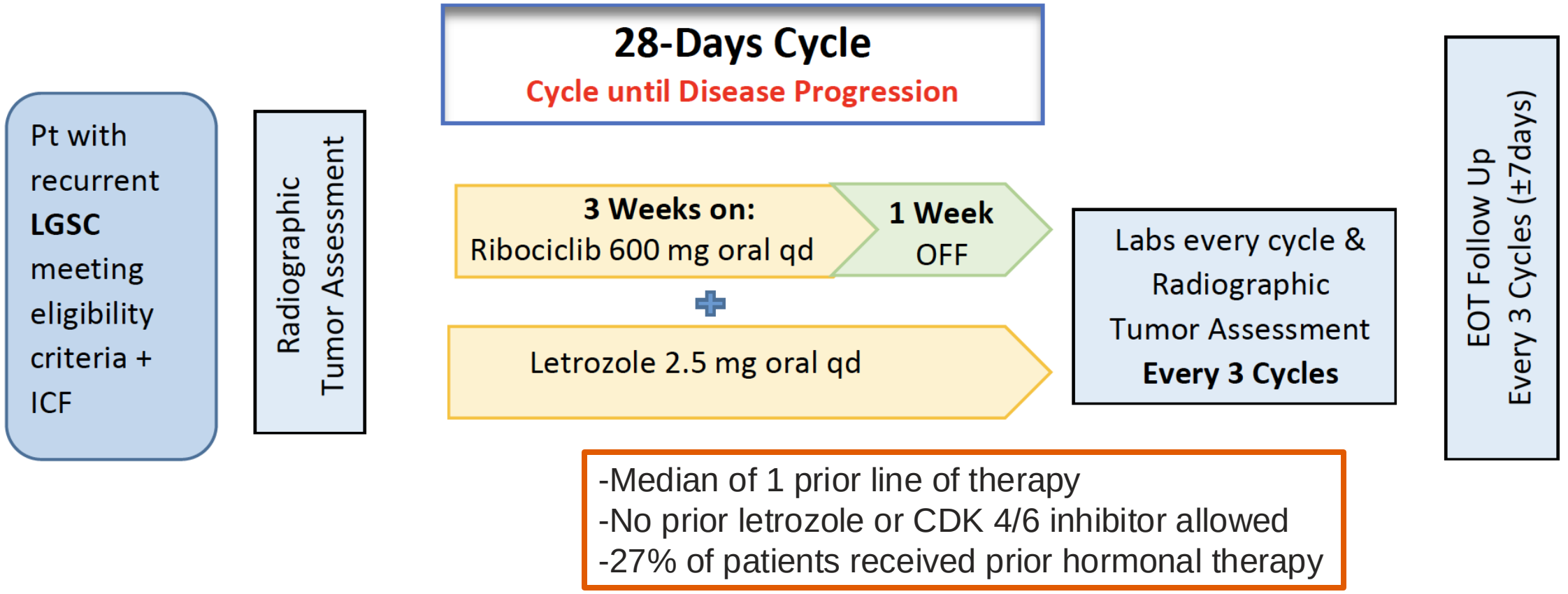
Alternative Endocrine Therapies

- Enzalutamide
- Onapristone

Combination Strategies

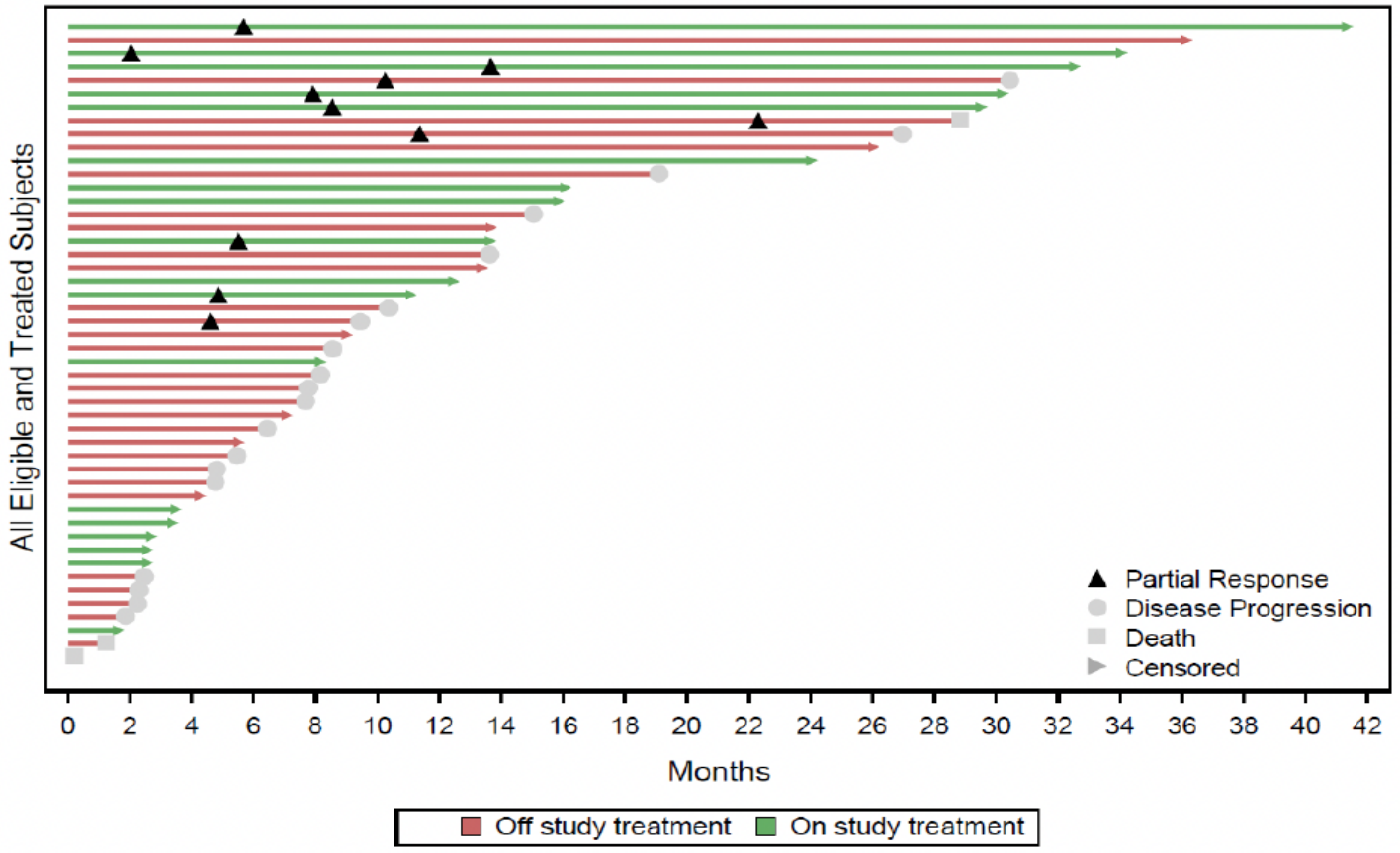
- Ribociclib with Letrozole

GOG 3026: A Phase II Trial of Letrozole + Ribociclib in Women with Recurrent LGSOC



Presented by B. Slomovitz at SGO 2023.

GOG 3026 A Phase II Trial of Letrozole + Ribociclib in Women with Recurrent LGSOC



Each bar represents one subject in the study.

‡: Data for this trial are still accumulating. Patient dispositions and outcomes will change as the data mature.

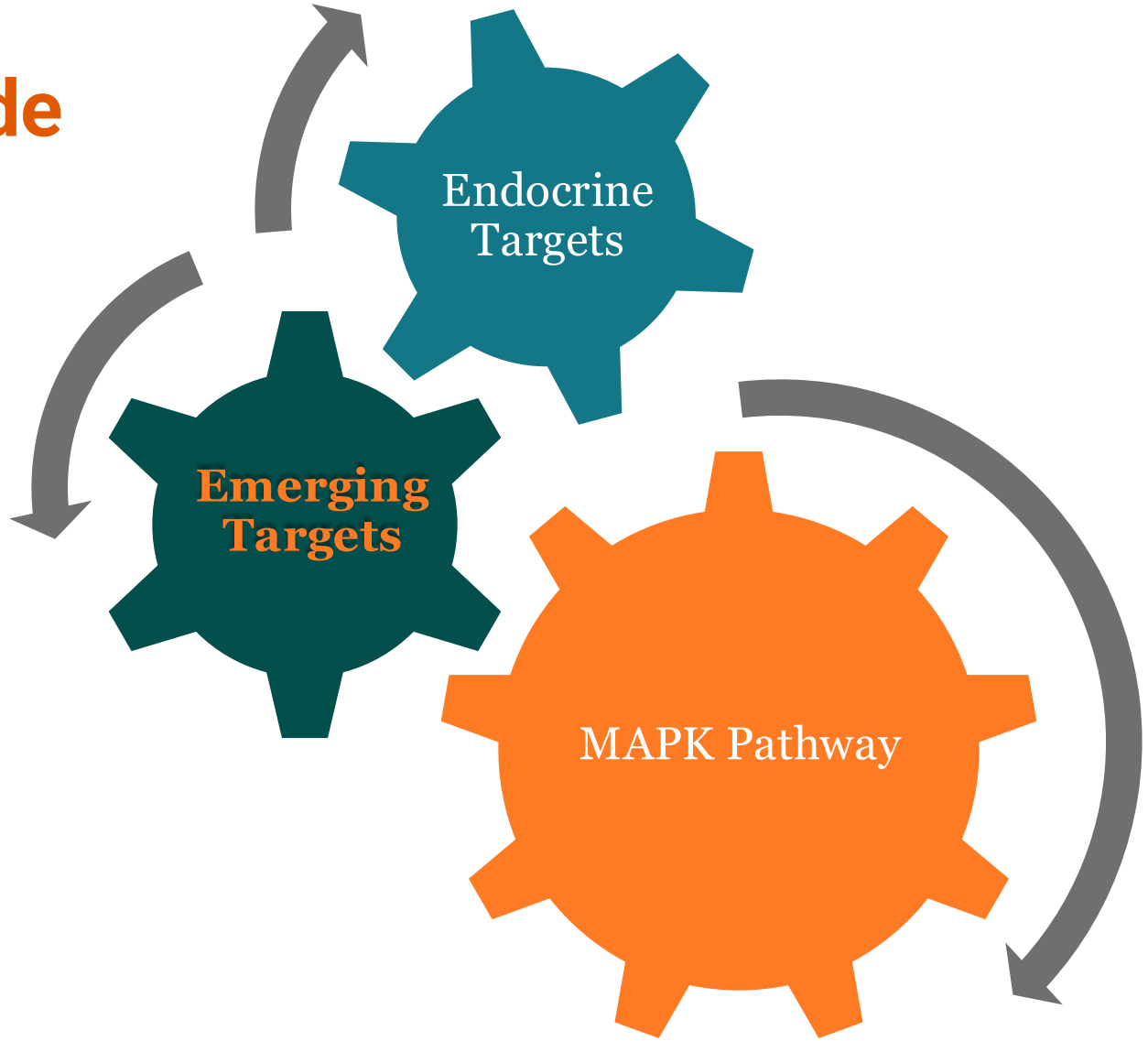
ORR: **23%** (n=11, all PR)

Responders:

DOR (median): **19.1 mos** (4.8 -35.8)

Presented by B. Slomovitz at SGO 2023.

Beyond Chemotherapy: Targeting Recurrent Low Grade Serous Ovarian Cancer



Folate Receptor Alpha in LGSOC

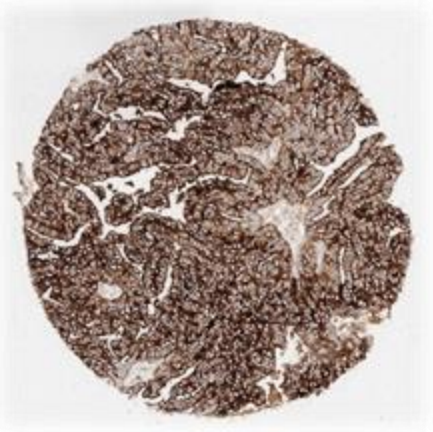
Tissue microarray constructed (archival LGSOC and SBT tissue)

Immunohistochemistry & FRa scoring

Massively parallel sequencing of LGSOC

Associations between FRa & clinical variables/MAPK alterations

FRa positive (≥75% membrane staining)

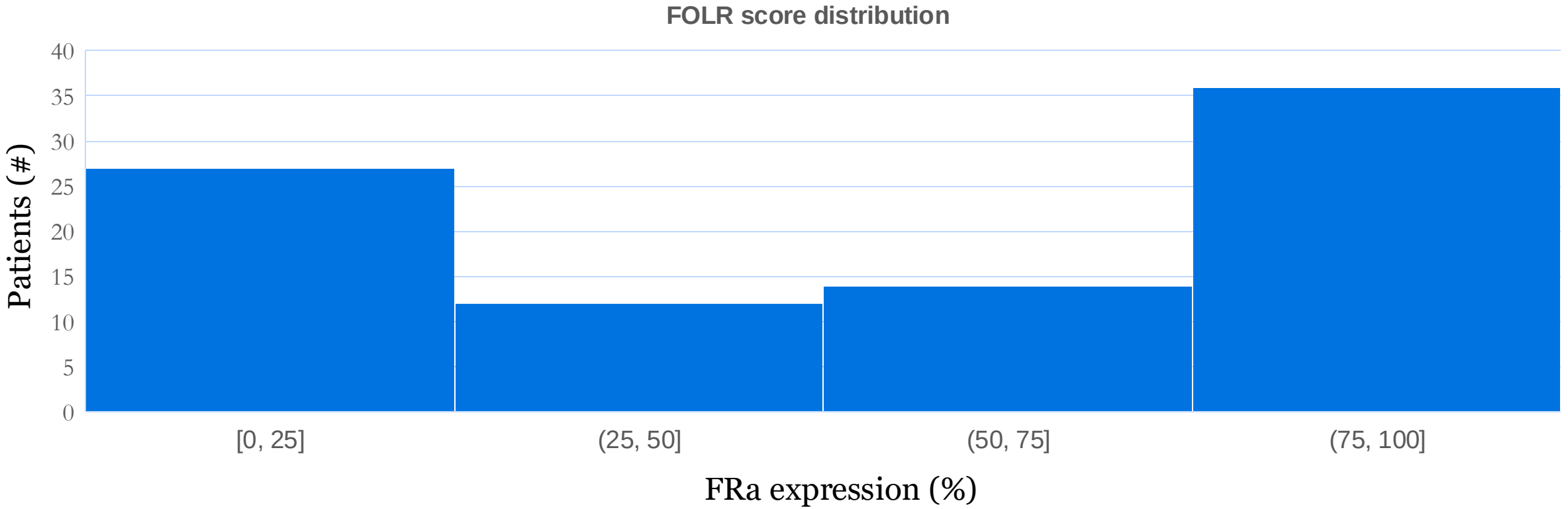


FRa negative (<75% membrane staining)

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

Results: prevalence of FRa positivity

- Of **89** low grade serous ovarian cancer samples
  - FRa positive: 36 (40.4%) (median FR+ expression 85.5%, range 77.5-100.0%)
  - FRa negative: 53 (60.6%) (median FR+ cells 24.1% , range 0.0-72.9%)



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

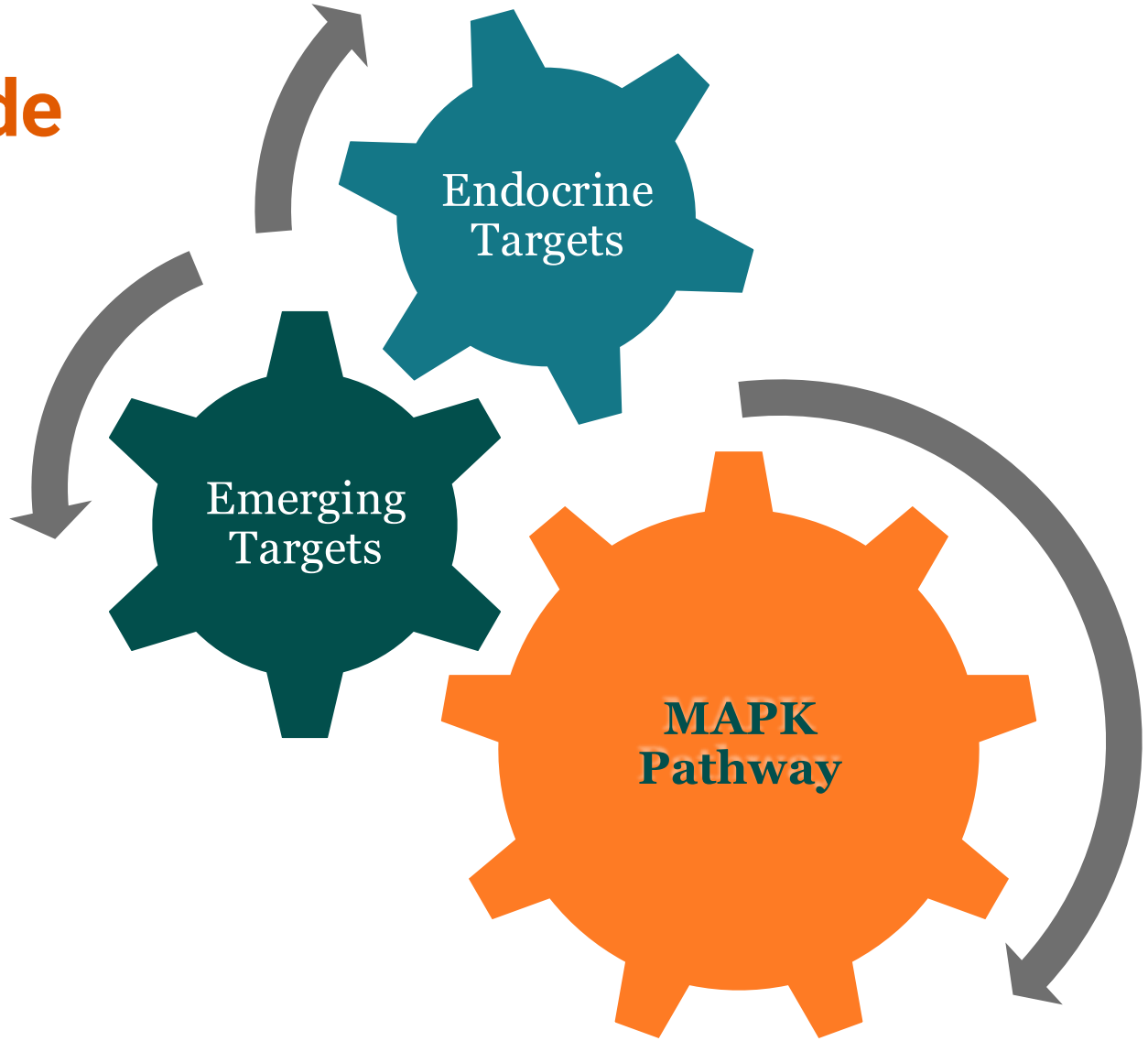
FOLR1+ Inversely Associated with MAPK Alteration

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

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

__Manning-Geist__, Sullivan, Zhou, Iasonos, Selenica, Stallworth, Liu, Roche, Gordhandas, Aghajanian, Chi, O'Cearbhaill, __Grisham__, Chui; Gyn Onc, 2024.

Beyond Chemotherapy: Targeting Recurrent Low Grade Serous Ovarian Cancer



GOG 239 – Selumetinib (AZD6244) For Low Grade Serous Ovarian Cancer

Eligibility:

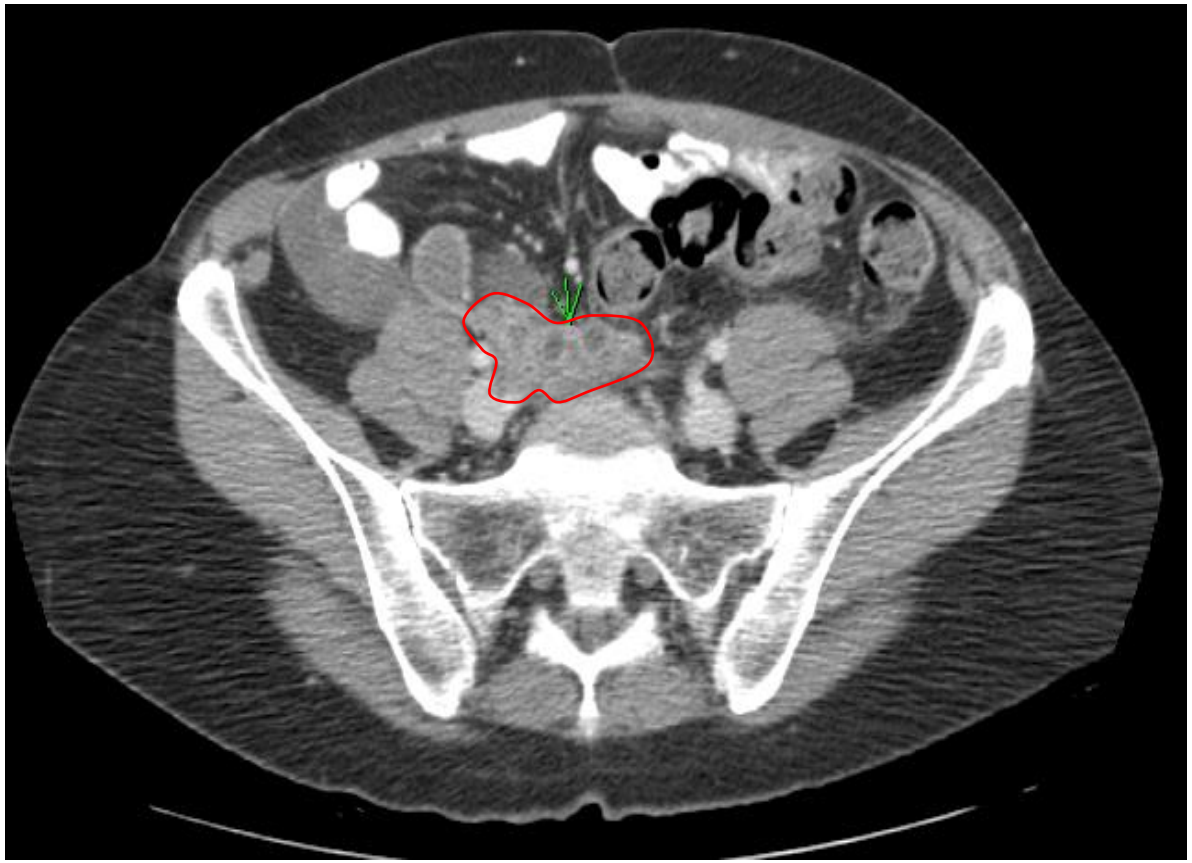
- Prospective Central Pathology
- Recurrent Disease
- Measurable Disease
- No Restrictions on Prior Therapy

Selumetinib 50 mg oral BID

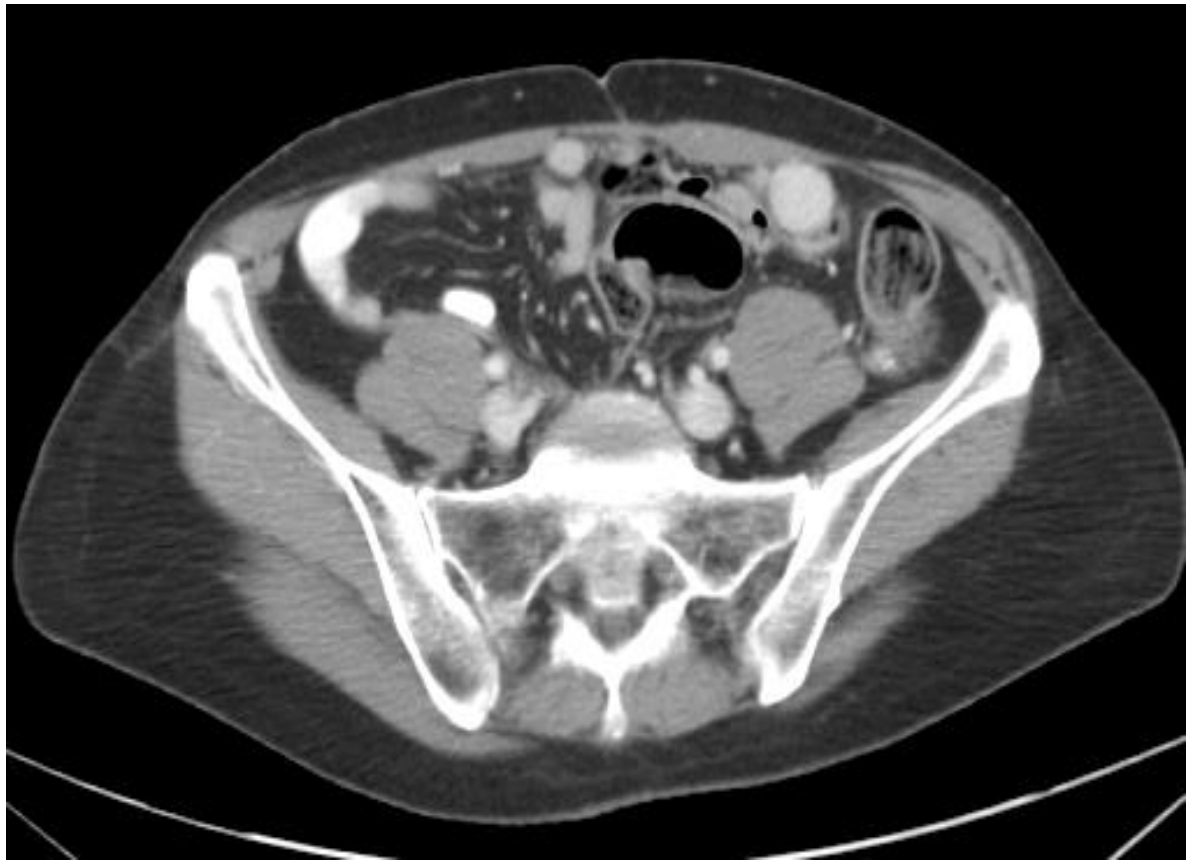
- Objective Response Rate = 15% (8/52 patients)
- 1 Complete Response and 7 Partial Responses
- 35 Patients had archival FFPE tissue available for direct sequencing of KRAS and BRAF, no association found between mutation and response to treatment

Farley et al, Lancet Oncology, 2013.

GOG 239 Complete Responder; WT BRAF/KRAS



9/2009

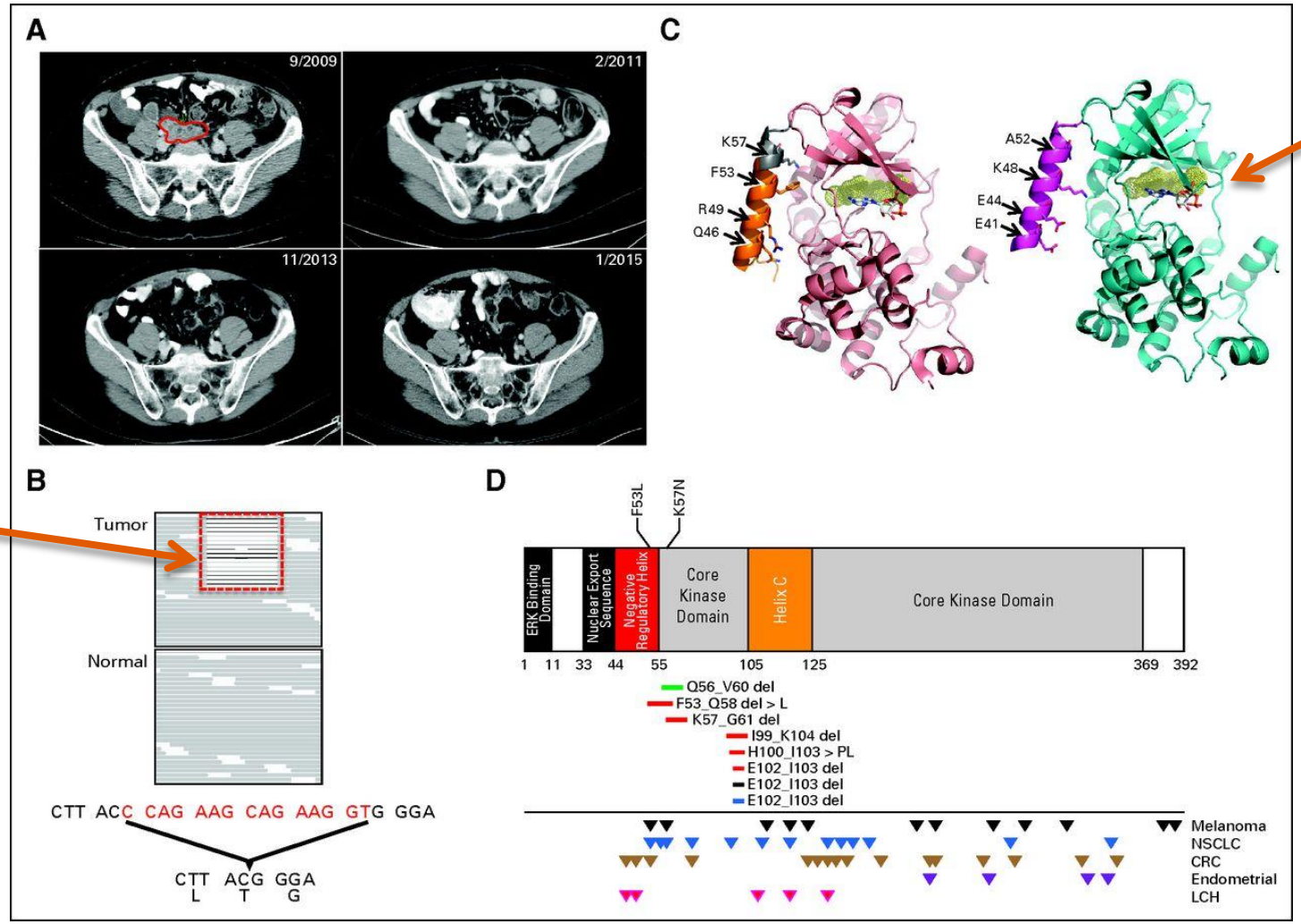


2/2011

Analysis of Extraordinary Responder to Selumetinib Identified 15-Base Pair Deletion in MAP2K1 gene

MAP2K1 (MEK1) Deletion

In frame deletion of 5 amino acids (Q56_V60del)

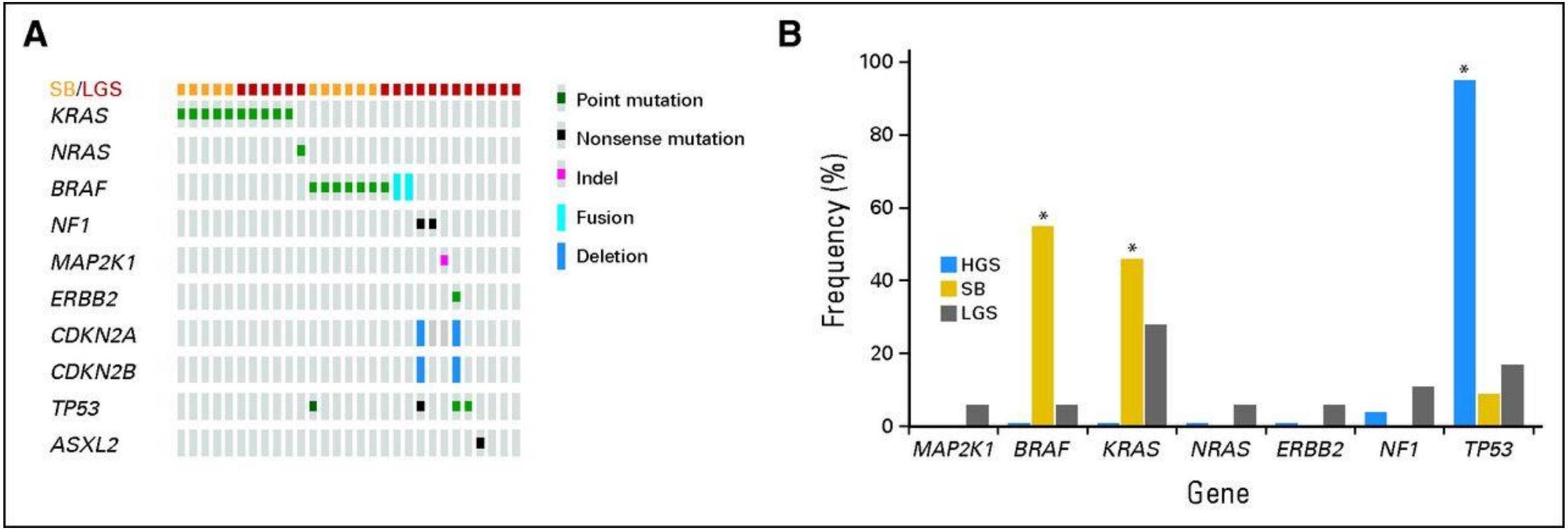


Structural modeling predicts disruption of interaction between negative regulatory helix and core kinase domain -> Constitutive kinase activation

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

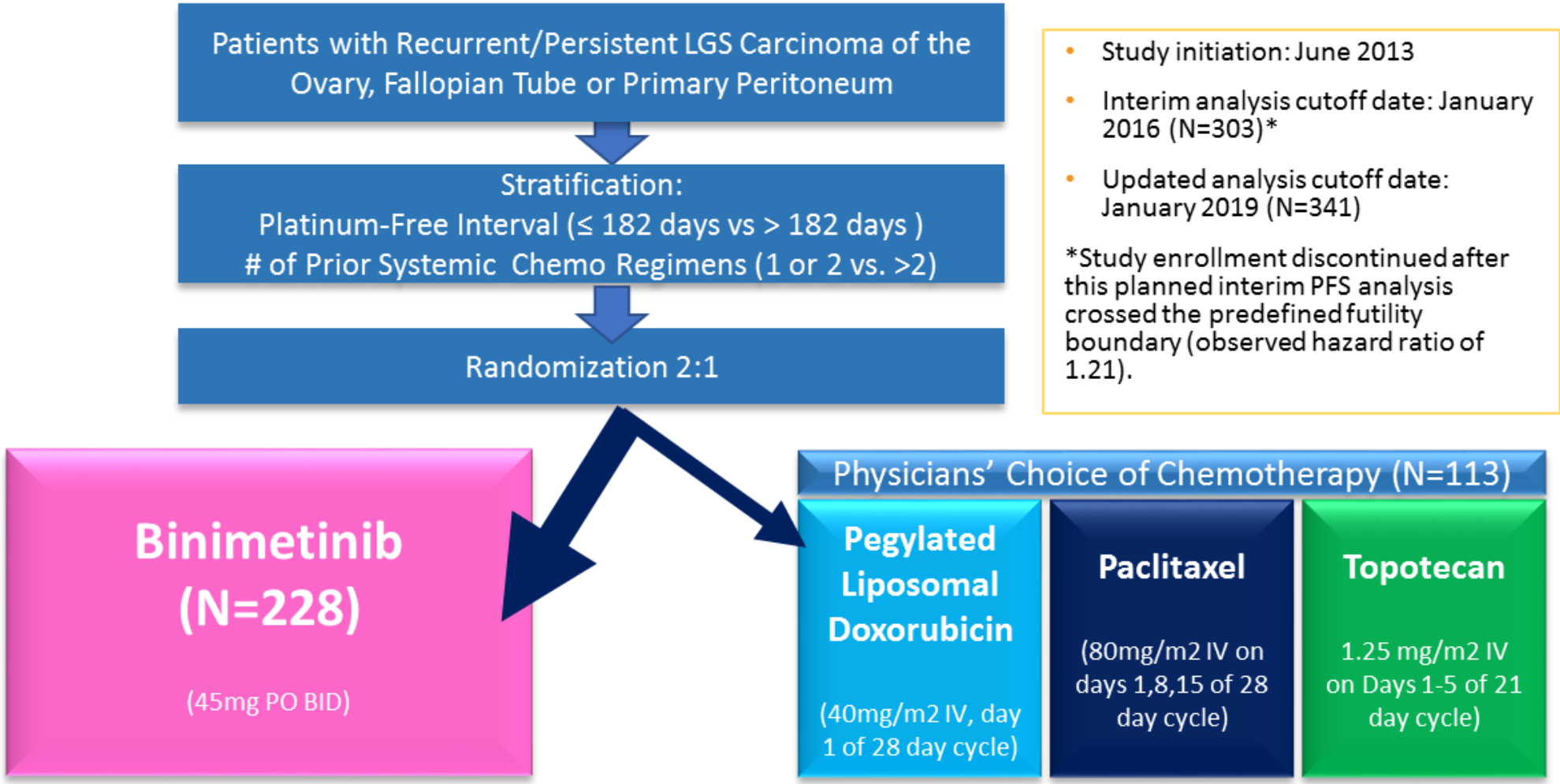
Frequent MAPK Pathway Alterations

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



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

MILO Phase III Study of Binimetinib vs PCC in LGSOC



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

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

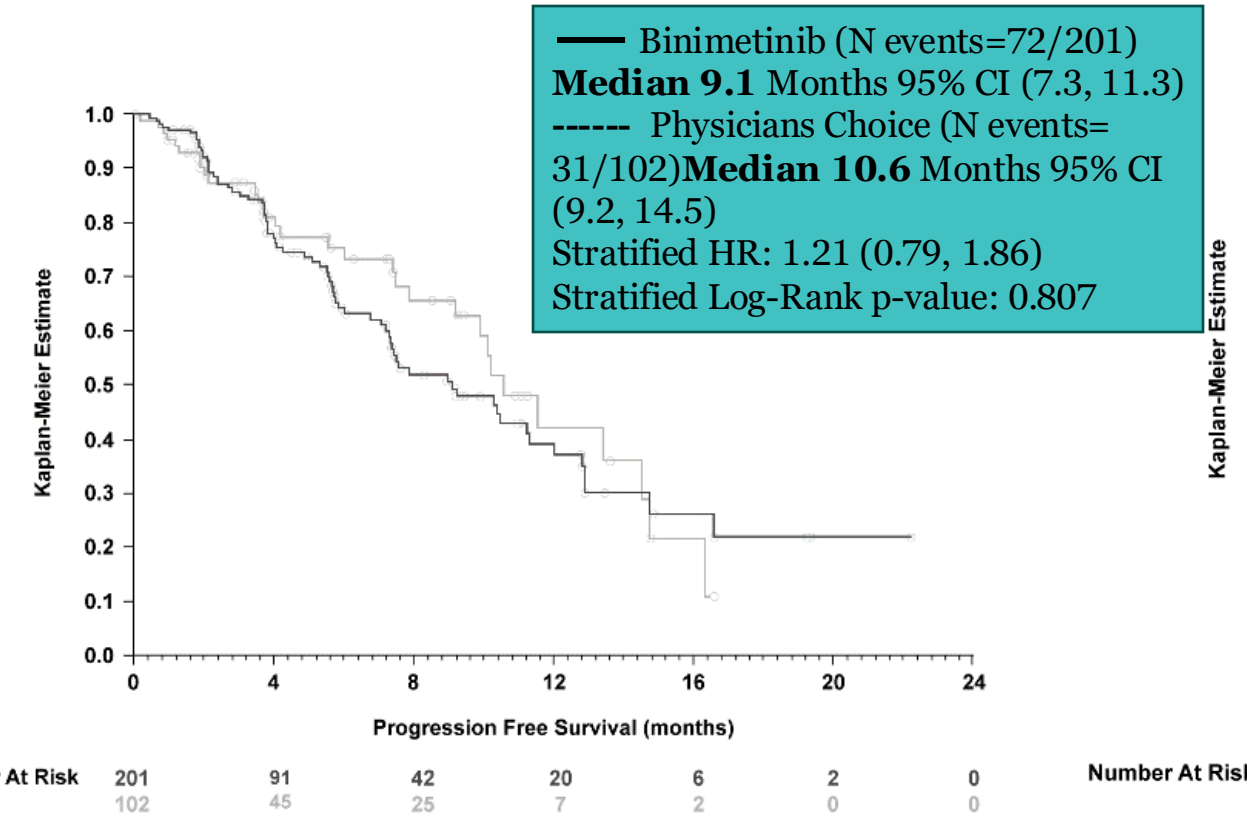
Presented by Rachel Grisham, IGCS Annual Conference, Brazil, 2019

Published: Monk, Grisham, *Banerjee, Kalbacher, Mirza, Romero, Vuylsteke, Coleman, Hilpert, Oza, Westermann, Oehler, Pignata, Aghajanian, Colombo, Drill, Cibula, Moore, Bittel, Campo, Berger, Marth, Sehouli, Omalley, Churruca, Boyd, Kristensen, Clamp, Ray-Coquard,* ***Vergote;*** *J Clin Oncol, 2020.*

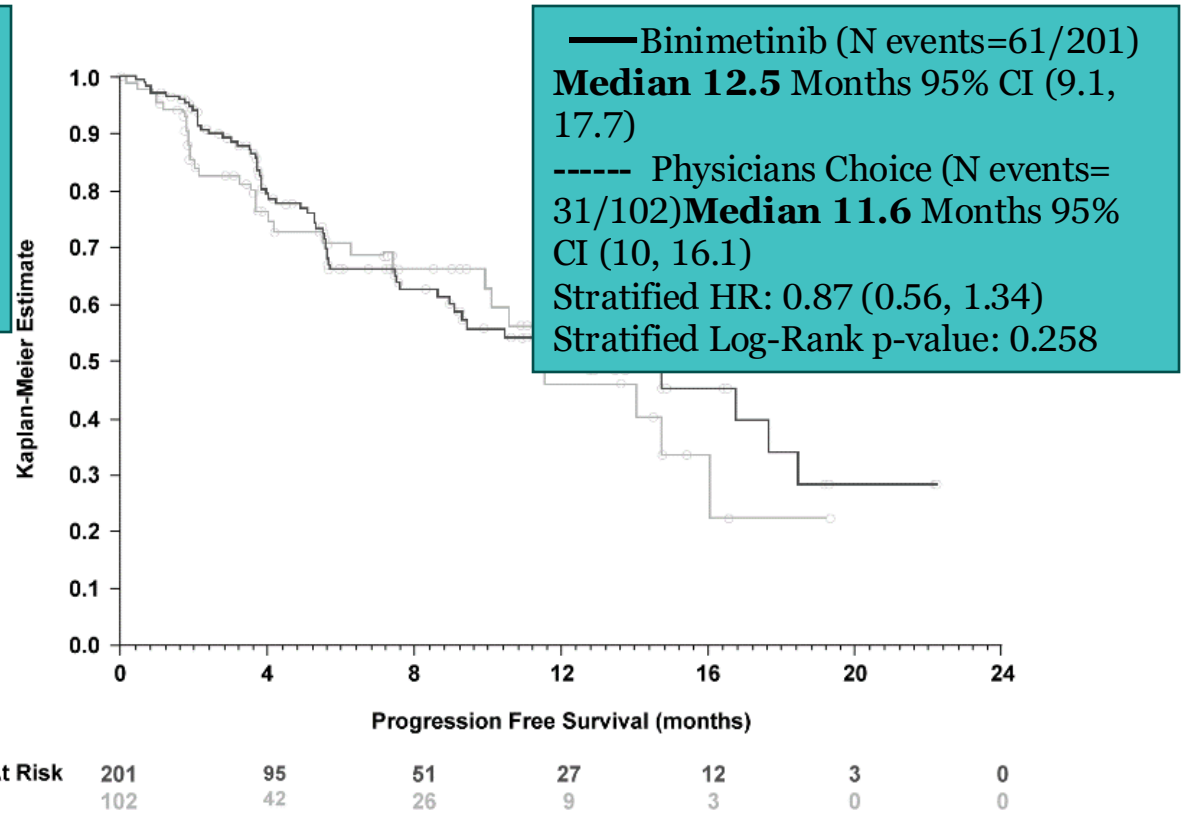
Interim Analysis

Progression Free Survival BICR and Local

BICR



Local



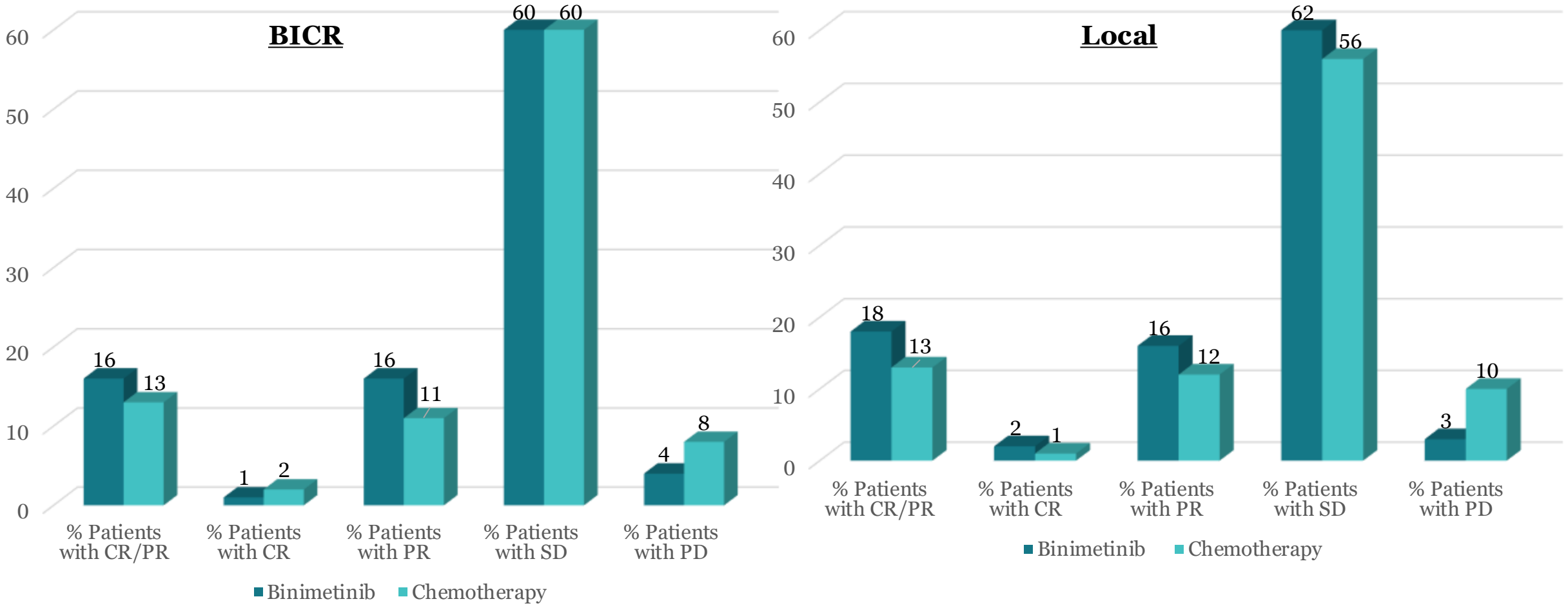
Presented by Rachel Grisham, IGCS Annual Conference, Brazil, 2019

Published: Monk, Grisham, Banerjee, Kalbacher, Mirza, Romero, Vuylsteke, Coleman, Hilpert, Oza, Westermann, Oehler, Pignata, Aghajanian, Colombo, Drill, Cibula, Moore, Bittel, Campo, Berger, Marth, Sehouli, Omalley, Churruca, Boyd, Kristensen, Clamp, Ray-Coquard, Vergote; J Clin Oncol, 2020.

Interim analysis cutoff date: January 2016 (N=303)

Interim Analysis

Best RECIST Response by BICR and Local



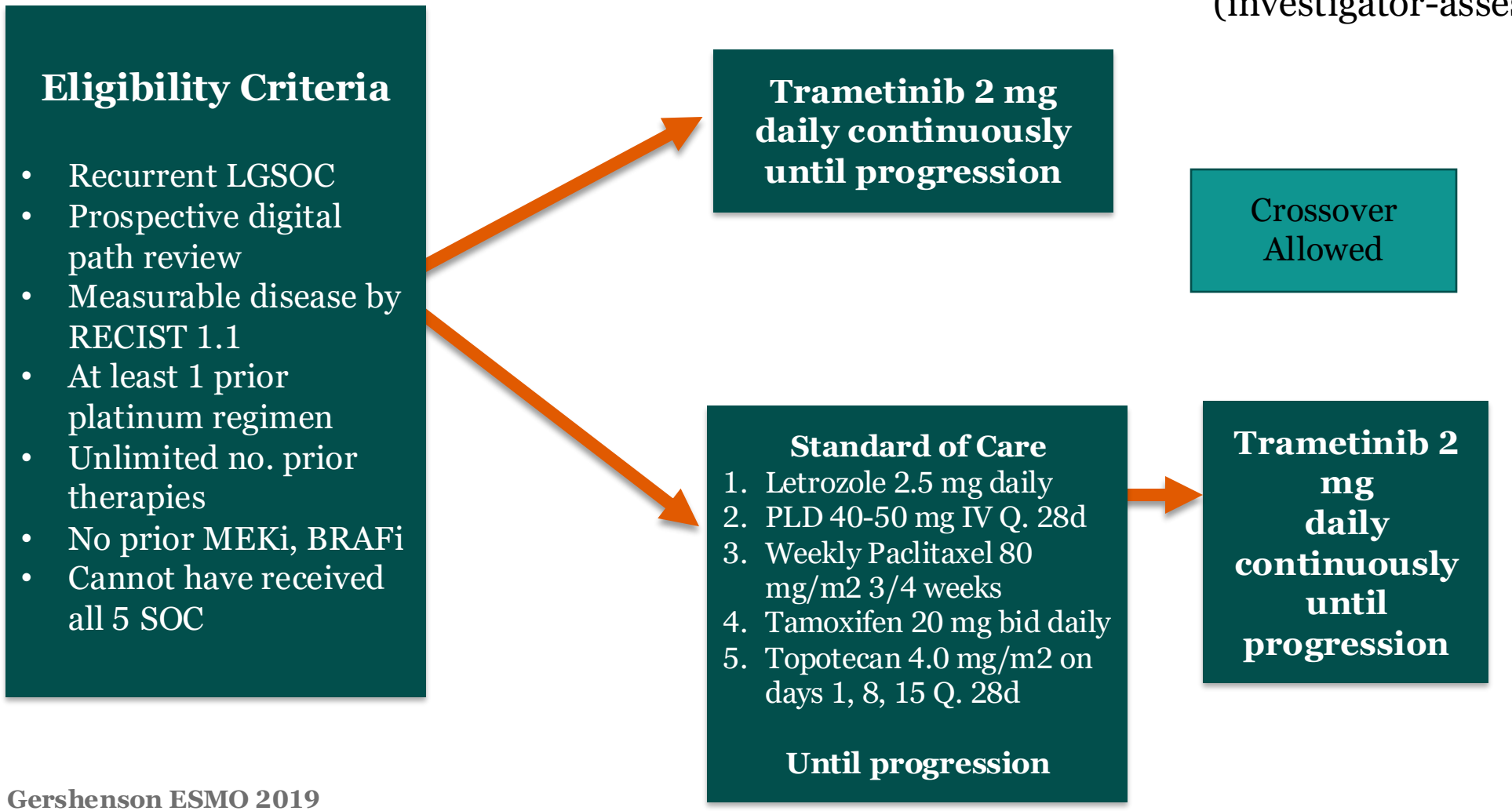
Presented by Rachel Grisham, IGCS Annual Conference, Brazil, 2019

Published: Monk, Grisham, Banerjee, Kalbacher, Mirza, Romero, Vuylsteke, Coleman, Hilpert, Oza, Westermann, Oehler, Pignata, Aghajanian, Colombo, Drill, Cibula, Moore, Bittel, Campo, Berger, Marth, Sehouli, Omalley, Churruca, Boyd, Kristensen, Clamp, Ray-Coquard, Vergote; J Clin Oncol, 2020.

Interim analysis cutoff date: January 2016 (N=303)

NRG-GOG 0281 Study Design

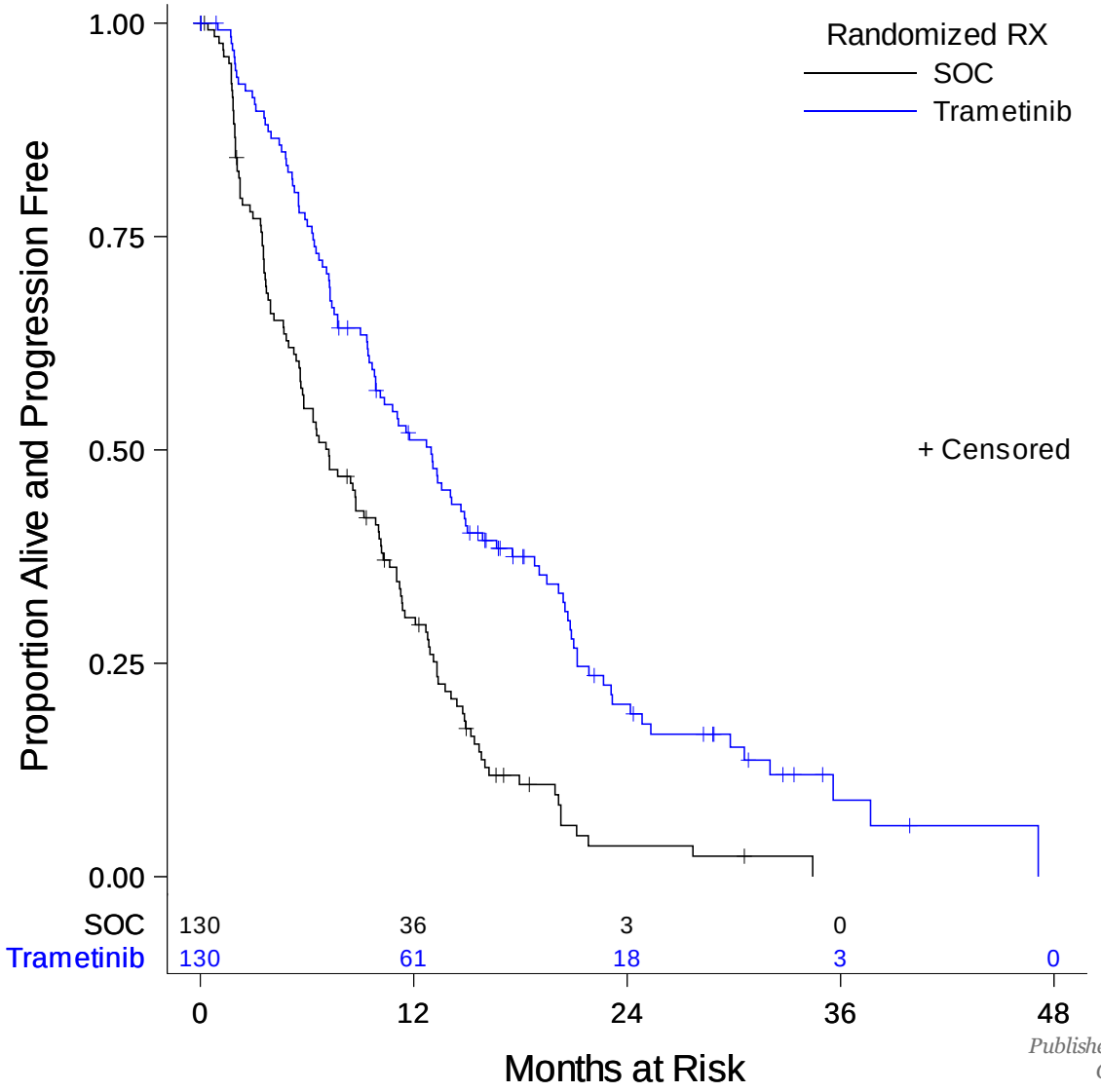
N=260
Primary Endpoint: PFS (investigator-assessed)



Presented by D. Gershenson ESMO 2019

Published: Gershenson, Miller, Brady, Paul, Carty, Rodgers, Millan, Coleman, Moore, Banerjee, Connolly, Secord, O'Malley, Dorigo, Gaillard, Gabra, Slomovitz, Hanjani, Farley, Churchman, Ewing, Hollis, Herrington, Huang, Wenzel, Gourley, Lancet, 2022.

Progression-Free Survival by Local Assessment



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

Presented by D. Gershenson ESMO 2019

Published: Gershenson, Miller, Brady, Paul, Carty, Rodgers, Millan, Coleman, Moore, Banerjee, Connolly, Secord, O'Malley, Dorigo, Gaillard, Gabra, Slomovitz, Hanjani, Farley, Churchman, Ewing, Hollis, Herrington, Huang, Wenzel, Gourley, Lancet, 2022.

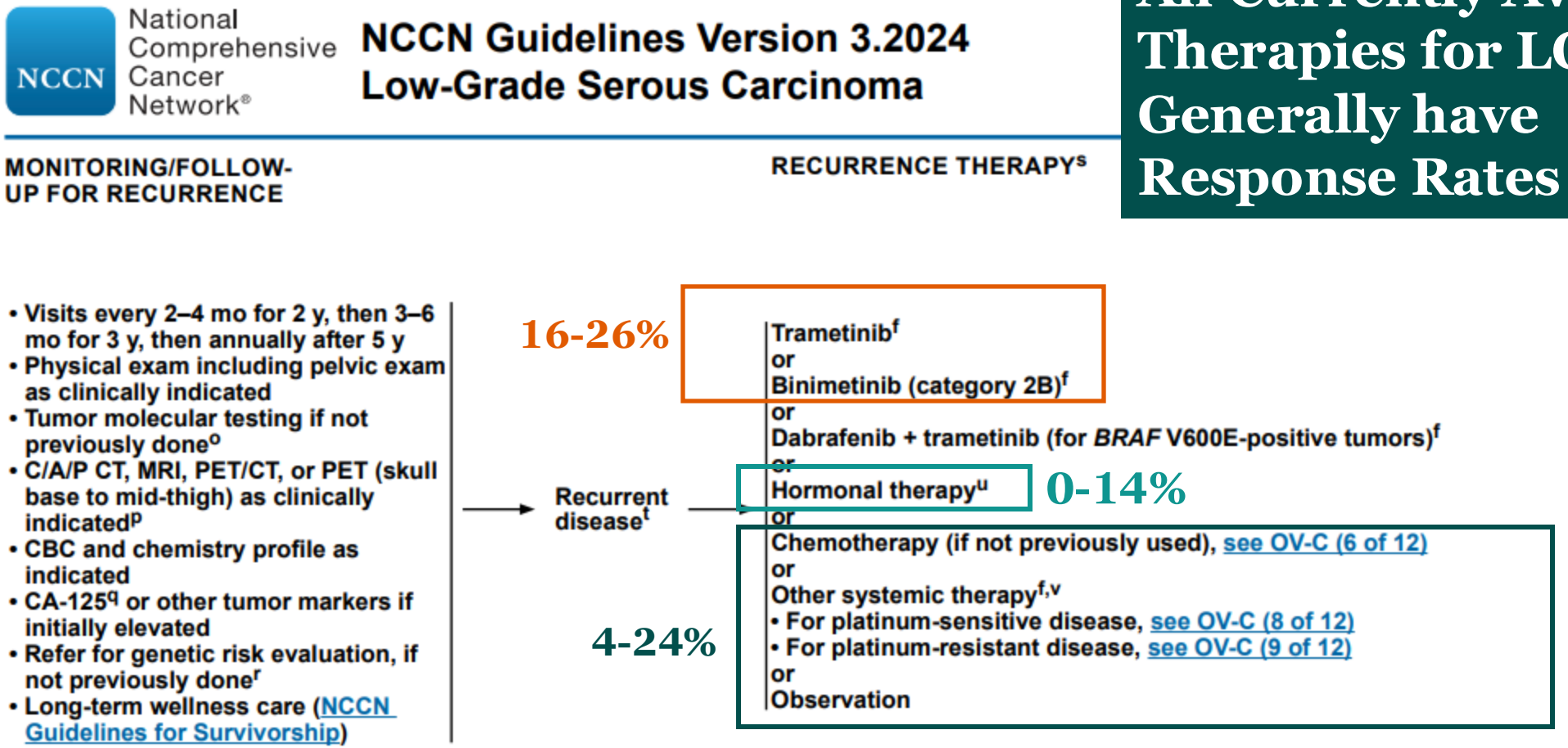
Response by RECIST 1.1 by Local Assessment

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

Published: Gershenson, Miller, Brady, Paul, Carty, Rodgers, Millan, Coleman, Moore, Banerjee, Connolly, Secord, O'Malley, Dorigo, Gaillard, Gabra, Slomovitz, Hanjani, Farley, Churchman, Ewing, Hollis, Herrington, Huang, Wenzel, Gourley, Lancet, 2022.

There Are No FDA Approved Options For Recurrent LGSOC

All Currently Available Therapies for LGSOC Generally have Response Rates ≤ 26%

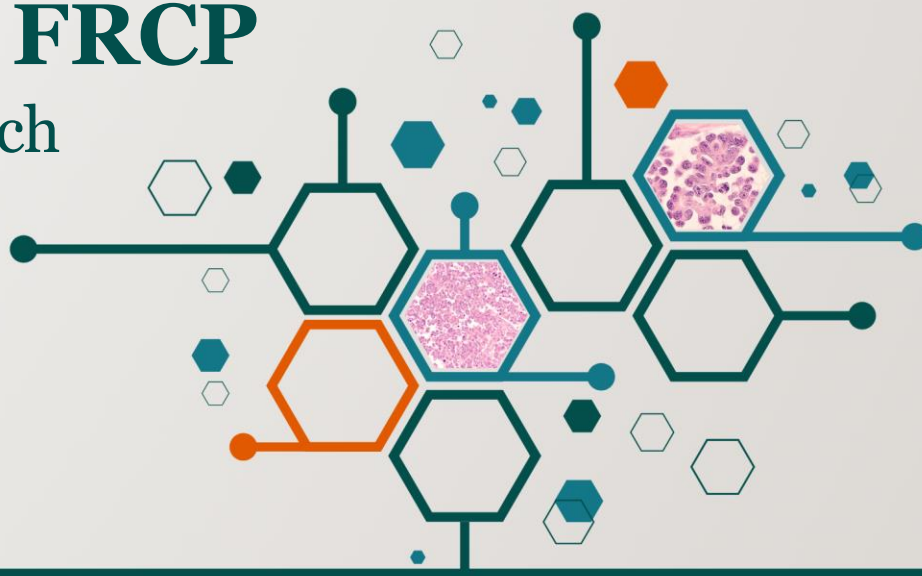


The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.
NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Latest Data and Future Directions

Susana Banerjee, MBBS, MA, PhD, FRCP

The Royal Marsden and the Institute of Cancer Research
United Kingdom



This non-promotional symposium is organized and funded by Verastem in collaboration with The GOG Foundation, Inc.

New Treatment Options Are Needed for Patients With LGSOC

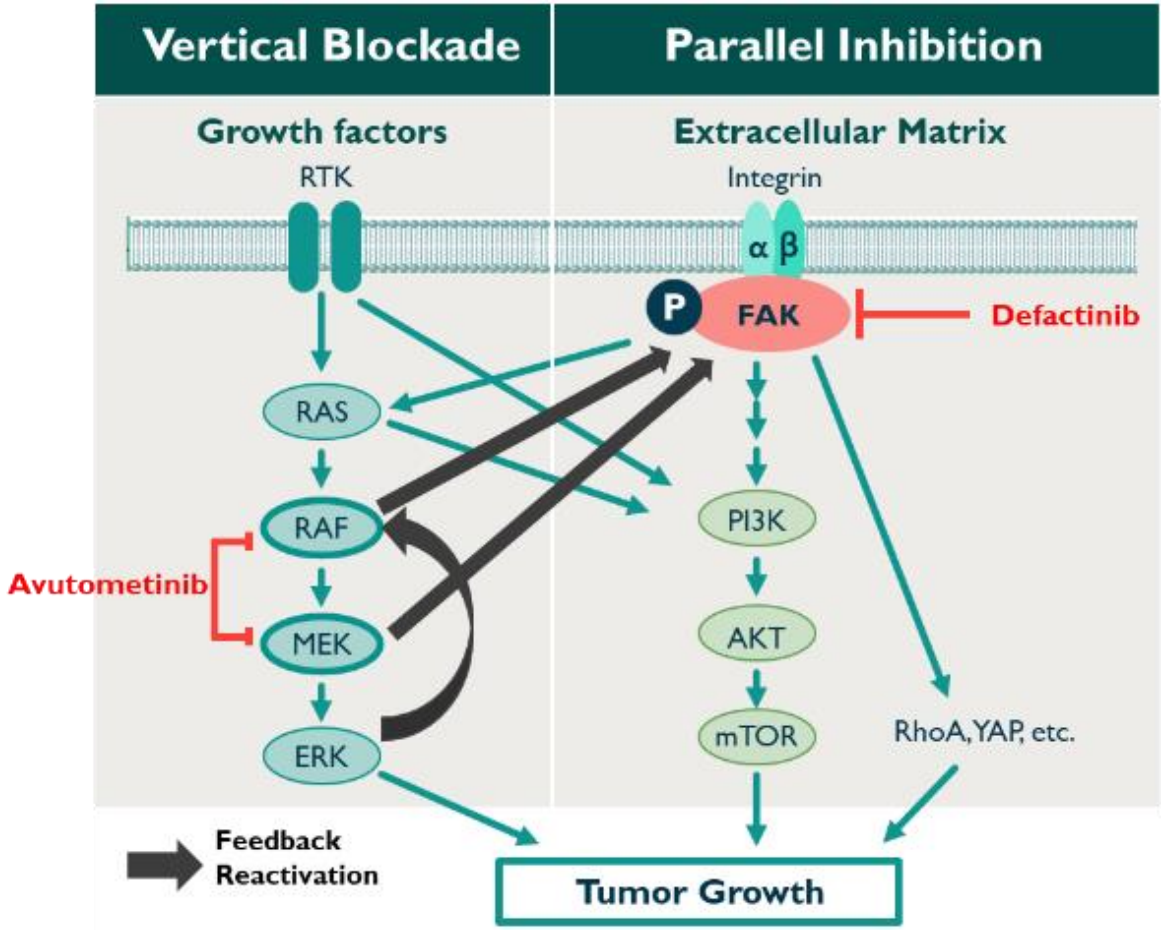
- LGSOC is a rare, histopathologically, molecularly, and clinically distinct cancer accounting for <10% of new epithelial ovarian cancers[1,2]
- LGSOC is commonly driven by alterations in the RAS/MAPK pathway, including KRAS mutations, which occur in approximately 30% of patients[3,4]
- Molecular alterations may influence patient outcomes
  - KRAS mutations/MAPK alterations are associated with improved prognosis[1,5,6]
- Chemotherapy options have shown limited efficacy in LGSOC (ORR 0%–13%)[5,7]
- Response rates of 26% and 16% were observed with trametinib and binimetinib, respectively, but with discontinuation rates of 36% and 31% due to toxicity[5,7]

KRAS, kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MAPK, mitogen-activated protein kinase; ORR, objective response rate.

1. Grisham RN, et al. Int J Gynecol Cancer. 2023;33(9):1331-1344; 2. Matsuo K, et al. J Gynecol Oncol. 2018;29(1e):e15; 3. Manning-Geist B, et al. Clin Cancer Res. 2022;28(20)4456-4465; 4. ElNaggar A, et al. Gynecol Oncol. 2022;167(2):306-313; 5. Gershenson DM, et al. Lancet. 2022;399(10324):541-553; 6. Manning-Geist BL, et al. Clin Adv Hematol Oncol. 2024:22(5):205-226; 7. Monk BJ, et al. J Clin Oncol. 2020;38(32):3753-3762.

Avutometinib and Defactinib Mechanism of Action

- **Avutometinib** is a first-in-class oral RAF/MEK clamp that potently inhibits MEK while also blocking the compensatory reactivation of MEK by upstream RAF[1,2]
- **Defactinib** is a selective inhibitor of FAK, a key adaptive resistance mechanism to the RAS/MAPK pathway[3-5]
- The clinical activity of avutometinib + defactinib demonstrated in the phase 1 FRAME study (NCT03875820) led to FDA Breakthrough Therapy Designation and rationale for the phase 2 ENGOT-ov60/GOG-3052/RAMP 201 (NCT04625270) study[6,7]

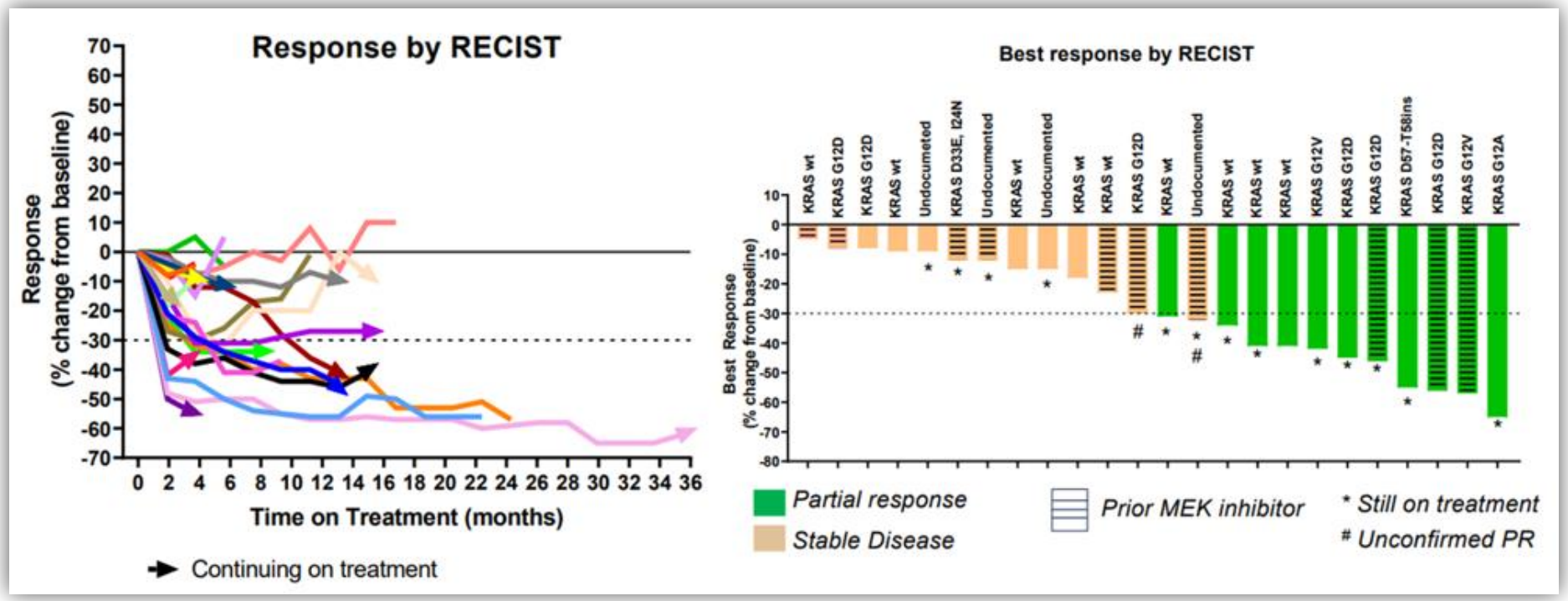


ERK; extracellular signal-regulated kinase; FAK, focal adhesion kinase; KRAS, kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer. MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; P, phosphate; PI3K,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

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

Avutometinib and defactinib are investigational drugs and have not been approved for use by any regulatory health authority. Safety and efficacy have not been established.

Phase 1 FRAME trial VS-6766 + Defactinib LGSC cohort



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

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

Avutometinib and defactinib are investigational drugs and have not been approved for use by any regulatory health authority. Safety and efficacy have notbeen established.

Banerjee et al. ESMO 2021.

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, Carol Aghajanian, Els Van Nieuwenhuysen, Alessandro D. Santin, Kari L. Ring, Nicoletta Colombo, Premal H. Thaker, Emily N. Prendergast, Kathleen N. Moore, Hye Sook Chon, Andrew R. Clamp, David M. O'Malley, Bradley J. Monk, Alfonso Cortés Salgado, Michel Fabbro, Elsa Kalbacher, Toon Van Gorp, Stephanie Lustgarten, Hagop Youssoufian, Rachel N. Grisham

ENGOT European Network of Gynaecological Oncological Trial groups

GOG FOUNDATION® Transforming the standard of care

GTG-UK Gynae-oncology Trials Group UK

Avutometinib and defactinib are investigational drugs and have not been approved for use by any regulatory health authority. Safety and efficacy have not been established.

ENGOT-ov60/GOG-3052/RAMP 201:

Registration-Directed Phase 2 Trial of Avutometinib ± Defactinib in Patients With Recurrent LGSOC

Go Forward Regim

Part A Selection Phase	Part B Expansion Phase	Part C Expansion Phase Combination	Part D Lower Dose in Combination
Avutometinib + Defactinib **3.2 mg BIW 200 mg BID**	**Avutometinib + Defactinib** **3.2 mg BIW 200 mg BID**	**Avutometinib + Defactinib** **3.2 mg BIW 200 mg BID**	**Avutometinib + Defactinib** **1.6 mg BIW 200 mg BID**
KRAS mt (n=16)	*KRAS* mt (n=20)	*KRAS* mt (n=22)	*KRAS* mt (n=11)
KRAS wt (n=15)	*KRAS* wt (n=22)	*KRAS* wt (n=20)	*KRAS* wt (n=16)

Key Inclusion Criteria

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

Avutometinib 4.0 mg BIW	Avutometinib 4.0 mg BIW
KRAS mt (n=16)	*KRAS* mt (total n=15)
KRAS wt (n=17)	*KRAS* wt (total n=22)

Oral dosing for monotherapy and combination therapy: 3 weeks on/1 week off

Primary Endpoint: ORR (BICR per RECIST v1.1)

Evaluation of ORR in Combination Arm

1. In *KRAS* mt pts
2. All patients (*KRAS* mt & wt)

Go Forward Regimen Selection Criteria (Selection Phase):

1. Observed ORR is comparatively greater than the other regimen.
2. Observed ORR of the leading regimen is ≥15%.

Numbers represent patients treated on study.

BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; KRAS, kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MEKi, mitogen-activated protein kinase kinase inhibitor; mt, mutant; pts, patients; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; wt, wild type.

Avutometinib and defactinib are investigational drugs and have not been approved for use by any regulatory health authority. Safety and efficacy have notbeen established.

ClinicalTrials.gov identifier: NCT04625270

Baseline Characteristics: Parts A, B, & C

	Avutometinib + Defactinib 3.2 mg BIW + 200 mg BID 3 weeks on/1 week off			Avutometinib Monotherapy 4.0 mg BIW 3 weeks on/1 week off		
	All patients N=115	**KRAS mt N=58**	**KRAS wt N=57**	**All patients N=70**	**KRAS mt N=31**	**KRAS wt N=39**
Age, median (min, max), y	54 (21, 87)	60 (29, 87)	45 (21, 80)	54 (21, 77)	57 (27, 74)	48 (21, 77)
ECOG PS, n (%) 0	78 (68)	42 (72)	36 (63)	50 (71)	19 (61)	31 (80)
1	37 (32)	16 (28)	21 (37)	20 (29)	12 (39)	9 (20)
# of prior systemic regimens, median (min, max)	3 (1, 9)	3 (1, 9)	3 (1, 9)	3 (1, 10)	3 (1, 10)	3 (1, 9)
Prior platinum-based chemotherapy, n (%)*	114 (99)	58 (100)	56 (98)	69 (99)	30 (97)	39 (100)
Prior hormonal therapy, n (%)	99 (86)	49 (84)	50 (88)	58 (83)	25 (81)	33 (85)
Prior bevacizumab, n (%)	59 (51)	23 (40)	36 (63)	34 (49)	17 (55)	17 (44)
Prior MEK inhibitor therapy, n (%)	25 (22)	12 (21)	13 (23)	18 (26)	8 (26)	10 (26)

Avutometinib + defactinib group: 77% of patients were White; 4% Asian; 4% Black or African American; 4% other; 11% not reported
Avutometinib monotherapy group: 85% of patients were White; 3% Asian; 3% Black or African American; 2% other; 1% unknown; 7% not reported

**2 pts without prior platinum received anastrazole only (1 in the monotherapy and 1 in combination arm)*
BID, twice daily; BIW, twice weekly; ECOG PS, Eastern Cooperative Oncology Group performance status; KRAS, kirsten rat sarcoma virus; MEK, mitogen-activated protein kinase kinase; mt, mutant; wt, wild type.

Avutometinib and defactinib are investigational drugs and have not been approved for use by any regulatory health authority. Safety and efficacy have not been established.

ClinicalTrials.gov identifier: NCT04625270

Patient Disposition: Parts A, B, & C

- Median follow-up in the combination group = 13.6 months (range, 1.4–39.5)
- In the combination group, mean relative dose intensity of 0.84 for avutometinib and 0.77 for defactinib

	Avutometinib + Defactinib 3.2 mg BIW + 200 mg BID 3 weeks on/1 week off			Avutometinib Monotherapy 4.0 mg BIW 3 weeks on/1 week off		
	All patients	**KRAS mt**	**KRAS wt**	**All patients**	**KRAS mt**	**KRAS wt**
Patients treated	115	58	57	70	31	39
Patients on treatment, n (%)	32 (28)	24 (41)	8 (14)	10 (14)	8 (26)	2 (5)
Patients discontinued treatment, n (%)	83 (72)	34 (59)	49 (86)	60 (86)	23 (74)	37 (95)
Primary reason for discontinuation						
RECIST v1.1 disease progression	46 (40)	18 (31)	28 (49)	33 (47)	14 (45)	19 (49)
Adverse event/unacceptable toxicity	12 (10)	4 (7)	8 (14)	11 (16)	4 (13)	7 (18)
Withdrawal of informed consent	10 (9)	4 (7)	6 (11)	6 (9)	3 (10)	3 (8)
Other*	10 (9)	5 (9)	5 (9)	4 (6)	2 (6)	2 (5)
Clinical deterioration	5 (4)	3 (5)	2 (4)	5 (7)	0	5 (13)
Death	0	0	0	1 (1)	0	1 (3)

Discontinuations due to AEs/unacceptable toxicity were reported in 10% of patients in the avutometinib + defactinib group

Visit cutoff date: 30 June 2024

**Other includes: clinical progression (n=8) and progression confirmed by biopsy/pathology report, progression by confirmation of cytology from pleural effusion showing malignant etiology, debulking surgery, patient noncompliance, patient withdrawal with agreement to follow-up, physician decision (1 each).*

AE, adverse event; BID, twice daily; BIW, twice weekly; KRAS, kirsten rat sarcoma virus; mt, mutant; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; wt, wild type.

Avutometinib and defactinib are investigational drugs and have not been approved for use by any regulatory health authority. Safety and efficacy have not been established.

ClinicalTrials.gov identifier: NCT04625270

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

In the avutometinib + defactinib combination group

RECIST 1.1 Objective Response Rate by BICR (primary endpoint):

- **31% overall; 44% KRAS mt, 17% KRAS wt**
- **33% without prior MEKi, 24% with prior MEKi**
- **Median time to response: 3.7 months (range, 1.7 – 19.2)**
- **Median duration of response: 31.1 months (95% CI, 14.8, 31.1)**

	Avutometinib + Defactinib 3.2 mg BIW + 200 mg BID 3 weeks on/1 week off			Avutometinib Monotherapy 4.0 mg BIW 3 weeks on/1 week off		
	All patients N=109	**KRAS mt N=57**	**KRAS wt N=52**	**All patients N=69**	**KRAS mt N=30**	**KRAS wt N=39**
Confirmed* ORR, n (%)	**34 (31)**	**25 (44)**	**9 (17)**	12 (17)	7 (23)	5 (13)
CR	2 (2)	2 (4)	0	1 (1)	1 (3)	0
PR	32 (29)	23 (40)	9 (17)	11 (16)	6 (20)	5 (13)
DOR, median (95% CI), mo	31.1 (14.8, 31.1)	31.1 (14.8, 31.1)	9.2 (5.5, NE)	NE‡	NE‡	NE‡
SD,† n (%)	62 (57)	28 (49)	34 (65)	43 (62)	17 (57)	26 (67)
PD, n (%)	9 (8)	2 (4)	7 (13)	7 (10)	3 (10)	4 (10)
Not evaluable, n (%)	4 (4)	2 (4)	2 (4)	7 (10)	3 (10)	4 (10)

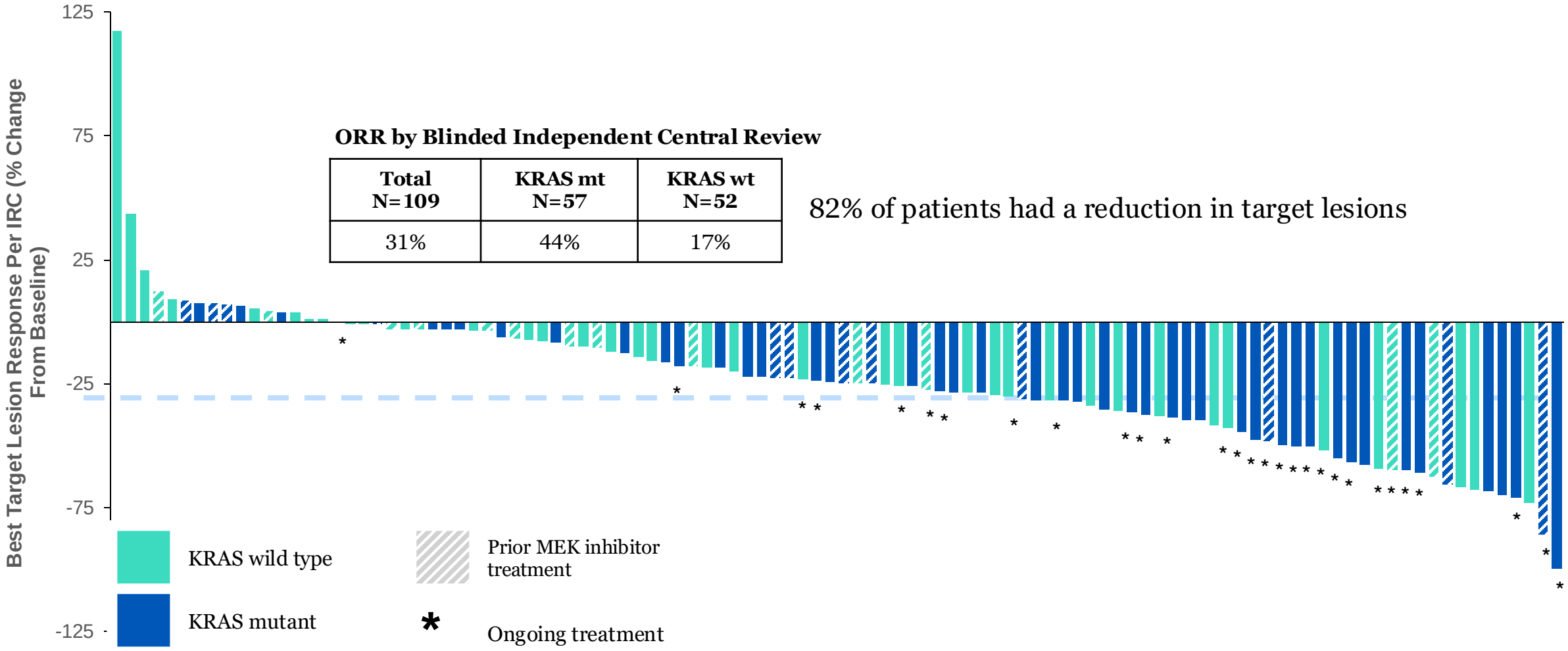
Efficacy evaluable population includes patients who received at least one dose of study drug and had measurable disease at baseline by BICR.
Patients not evaluable for response did not have a postbaseline assessment but are included in the denominator for the efficacy evaluable population.

**By BICR. †Includes unconfirmed PR; SD (or unconfirmed PR) must occur ≥53 days after first dose date. ‡NE = Could not be estimated based on number of patients with loss of response.*
BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; CR, complete response; DOR, duration of response; KRAS, kirsten rat sarcoma virus; MEK, mitogen-activated protein kinase kinase; mt, mutant; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; wt, wild type

Avutometinib and defactinib are investigational drugs and have not been approved for use by any regulatory health authority. Safety and efficacy have not been established.

ClinicalTrials.gov identifier: NCT04625270

Best Percentage Change From Baseline in Target Lesions Avutometinib + Defactinib: Parts A, B, and C



ClinicalTrials.gov identifier: NCT04625270

IRC, independent review committee; KRAS, kirsten rat sarcoma virus; MEK, mitogen-activated protein kinase kinase.

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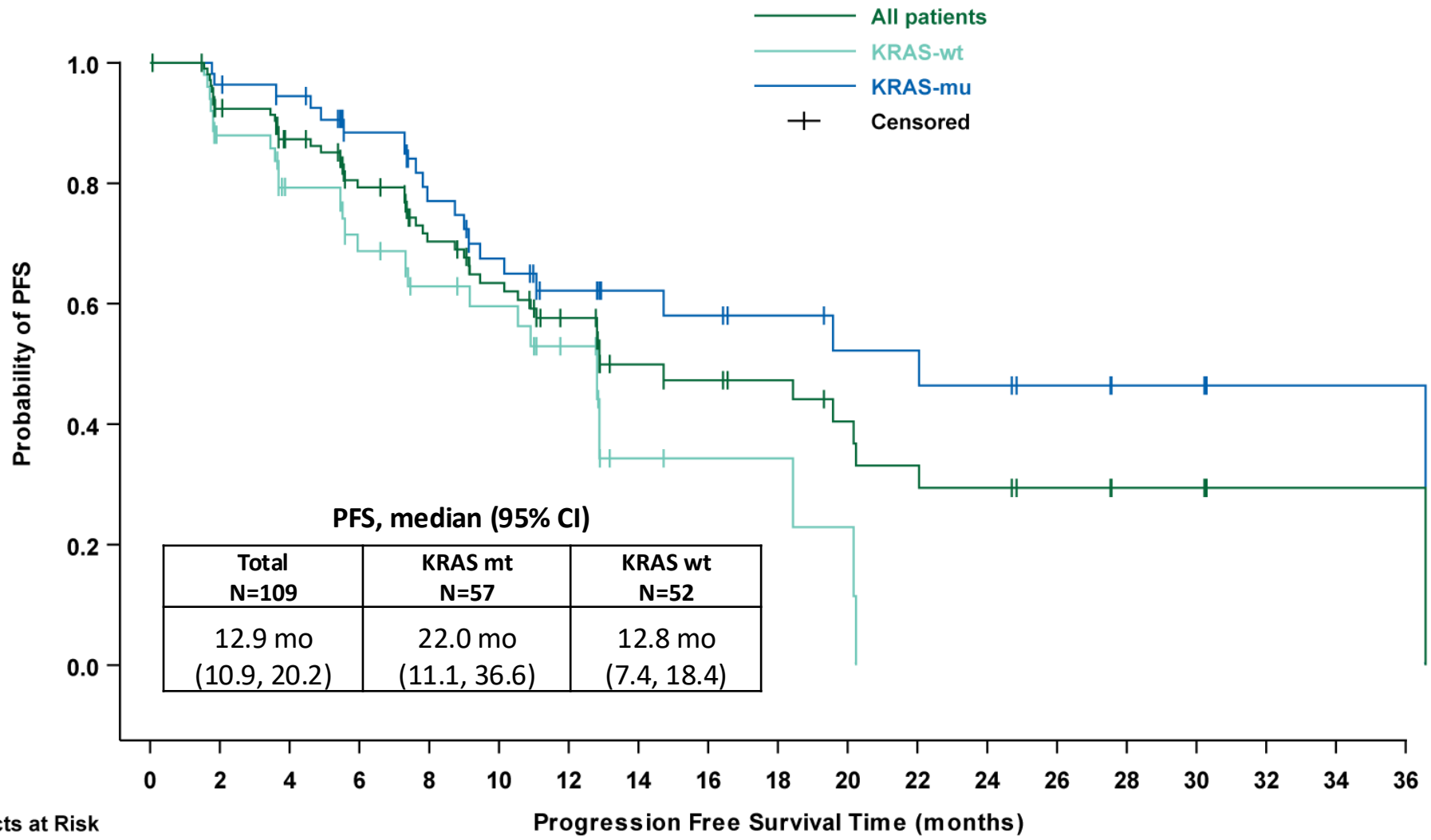
Progression-Free Survival: Avutometinib + Defactinib: Parts A, B, & C



PFS, median (95% CI)

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

No of Subjects at Risk

All patients	109	94	81	66	53	45	32	19	17	15	11	9	8	6	3	3	1	1	1
KRAS-wt	52	41	32	25	20	18	13	4	3	3	2	0							
KRAS-mu	57	53	49	41	33	27	19	15	14	12	9	9	8	6	3	3	1	1	1

ClinicalTrials.gov identifier: NCT04625270

KRAS, kirsten rat sarcoma virus; mt, mutant; PFS, progression-free survival; wt, wild type.

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Adverse Events Profile for Avutometinib + Defactinib: Parts A, B, & C

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

Treatment-Related Adverse Events (>20% of patients)* n (%)	Avutometinib + Defactinib 3.2 mg BIW + 200 mg BID 3 weeks on/1 week off N= 115	
Preferred term	**All Grades**	**Grade ≥3**
Non-laboratory AEs		
Nausea	77 (67.0)	3 (2.6)
Diarrhea	67 (58.3)	9 (7.8)
Oedema peripheral	61 (53.0)	1 (0.9)
Fatigue	50 (43.5)	3 (2.6)
Vomiting	49 (42.6)	3 (2.6)
Vision blurred	47 (40.9)	0
Rash	41 (35.7)	2 (1.7)
Dermatitis acneiform	39 (33.9)	5 (4.3)
Dry skin	30 (26.1)	0
Anemia	26 (22.6)	6 (5.2)
Laboratory-related AEs		
Increased blood CPK	69 (60.0)	28 (24.3)
Increased blood bilirubin increased/ hyperbilirubinemia	38 (33.0)	5 (4.3)
AST increased	36 (31.3)	2 (1.7)

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

AE, adverse event; AST; aspartate aminotransferase; BID, twice daily; BIW, twice weekly; CPK, creatine phosphokinase; GI, gastrointestinal.

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ClinicalTrials.gov identifier: NCT04625270

Adverse Events Profile for Avutometinib + Defactinib: Parts A, B, & C

Adverse events of interest that have been associated with MEK inhibitors

Treatment-Related Adverse Events, n (%)*	Avutometinib + Defactinib 3.2 mg BIW + 200 mg BID 3 weeks on/1 week off N=115	
Preferred term	**All Grades**	**Grade ≥3**
Ocular events		
Blurred vision	47 (40.9)	0
Visual impairment	7 (6.1)	0
Retinal pigment epithelial detachment	6 (5.2)	0
Retinal detachment	4 (3.5)	0
Serous retinal detachment	2 (1.7)	0
Serous retinopathy	2 (1.7)	0
Retinopathy	2 (1.7)	0
Retinal vein occlusion	1 (0.9)	0
Pneumonitis	1 (0.9)	0
Hypertension	4 (3.5)	1 (0.9)
Ejection fraction decreased	1 (0.9)	0
Congestive heart failure	0	0

BID, twice daily; BIW, twice weekly; MEK, mitogen-activated protein kinase kinase.

ClinicalTrials.gov identifier: NCT04625270

Avutometinib and defactinib are investigational drugs and have not been approved for use by any regulatory health authority. Safety and efficacy have not been established.

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

Low-Dose Avutometinib Evaluation: Part D

- The **low-dose regimen** of avutometinib (1.6 mg BIW) + defactinib (200 mg BID) evaluated in Part D was determined to be **suboptimal** based on the predefined analysis
  - Suboptimal threshold: disease progression by second scheduled assessment (Cycle 5 Day 1) >50% higher than that observed with avutometinib 3.2 mg BIW + defactinib

IRC Assessment	Avutometinib 3.2 mg + 200 mg Defactinib 3 weeks on/1 week off N=109	Avutometinib 1.6 mg + 200 mg Defactinib 3 weeks on/1 week off N=23	% Difference
RECIST v1.1 progressive disease within 4 months	13 (12%)	5 (22%)	**+83%**

- Therefore, the low-dose regimen will not be pursued as a starting dose in the treatment of recurrent LGSOC

BID, twice daily; BIW, twice weekly; IRC, independent review committee; LGSOC, low-grade serous ovarian cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

ClinicalTrials.gov identifier: NCT04625270

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Summary and Conclusions

- In women with recurrent LGSOC with few available treatment options, the combination of avutometinib 3.2 mg BIW + defactinib 200 mg BID resulted in clinically meaningful responses, duration of response, and progression-free survival
    - **ORR:** 31% overall; 44% in KRAS mt and 17% in KRAS wt
    - **Median DOR:** 31 months overall
    - **Median PFS**: 12.9 months overall; 22.0 months in KRAS mt and 12.8 months in KRAS wt
- The safety profile of the combination was consistent with previous reports
    - The majority of adverse events were grade 1 and 2
    - The majority of adverse events were managed with dose interruptions and reductions
    - Discontinuation rate of 10% for adverse events
- These data support the potential for avutometinib + defactinib as a new standard of care for recurrent LGSOC, regardless of KRAS status

A phase 3 trial (GOG-3097/ENGOT-OV81/NCRI/RAMP 301) comparing avutometinib + defactinib to investigator's choice of therapy in recurrent LGSOC is enrolling

BID, twice daily; BIW, twice weekly; DOR, duration of response; KRAS, kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; mt, mutant; ORR, objective response rate; PFS, progression-free survival; wt, wild type.

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

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

Key Inclusion Criteria

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

NCT06072781

1:1 Randomization
N = 270

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

Avutometinib + Defactinib
N = 135

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

May crossover upon BICR confirmed PD

Investigator's Choice
N = 135

Pegylated Liposomal Doxorubicin
Paclitaxel
Letrozole
Anastrozole

- Sparse PK samples to be collected only from patients randomized to the avutometinib/defactinib arm

Primary Endpoint

PFS via RECIST v1.1 per BICR

Secondary Endpoints

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

Summary of Analyses

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

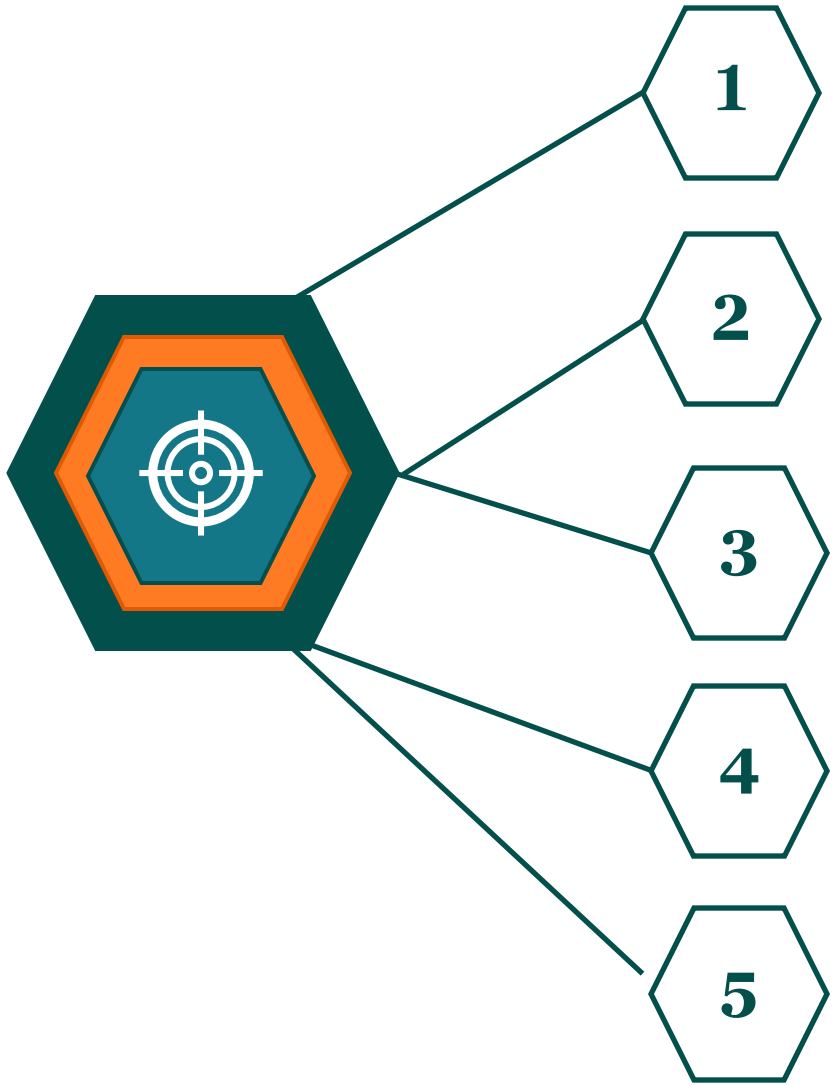
Hierarchical Evaluation of Primary PFS Endp.:
- KRAS mutant LGSOC only
- All recurrent LGSOC

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

Examples of Ongoing Studies in Recurrent LGSOC

Study	Phase	Therapy	Estimated primary completion
RAMP301 (NCT06072781)	3	Avutometinib + defactinib vs Investigators choice SOC	
ALEPRO* (NCT05872204)	2	Abemaciclib + letrozole	Oct 2026
NCT05113368	2	Regorafenib + fulvestrant	Jun 2023
PERCEPTION (NCT04575961)	2	Pembrolizumab + chemotherapy	Nov 2023
FUCHSia (NCT03926936)	2	Fulvestrant	Apr 2022
ComboMATCH* (NCT05554367)	2	Palbociclib + binimetinib	Aug 2026
ComboMATCH* (NCT05554328)	2	Selumetinib + Olaparib	Oct 2028
NCT04092270*	1	Peposertib + chemotherapy	Sep 2023
NCT04739800*	2	Durvalumab + olaparib + cediranib	Dec 2023
NCT02923934*	2	Ipilimumab + nivolumab	Dec 2023
NCT06494150	2	Nab-sirolimus + fulvestrant	Aug 2027

Future Directions



1. New treatments for recurrent LGSOC
2. New treatments for 1st line treatment of LGSOC
3. Maintenance Therapy options
4. Monitoring benefit- response, toxicities, QOL
5. Biomarker testing in LGSOC eg ctDNA (poster Hasson et al IGCS 2024)

Question and Answers

All Faculty

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Closing Comments

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Thank You

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