Where Science Becomes Hope

LOW-GRADE EPITHELIAL OVARIAN CANCER: OPTIMIZING TARGETED AND HORMONAL AGENT OPTIONS

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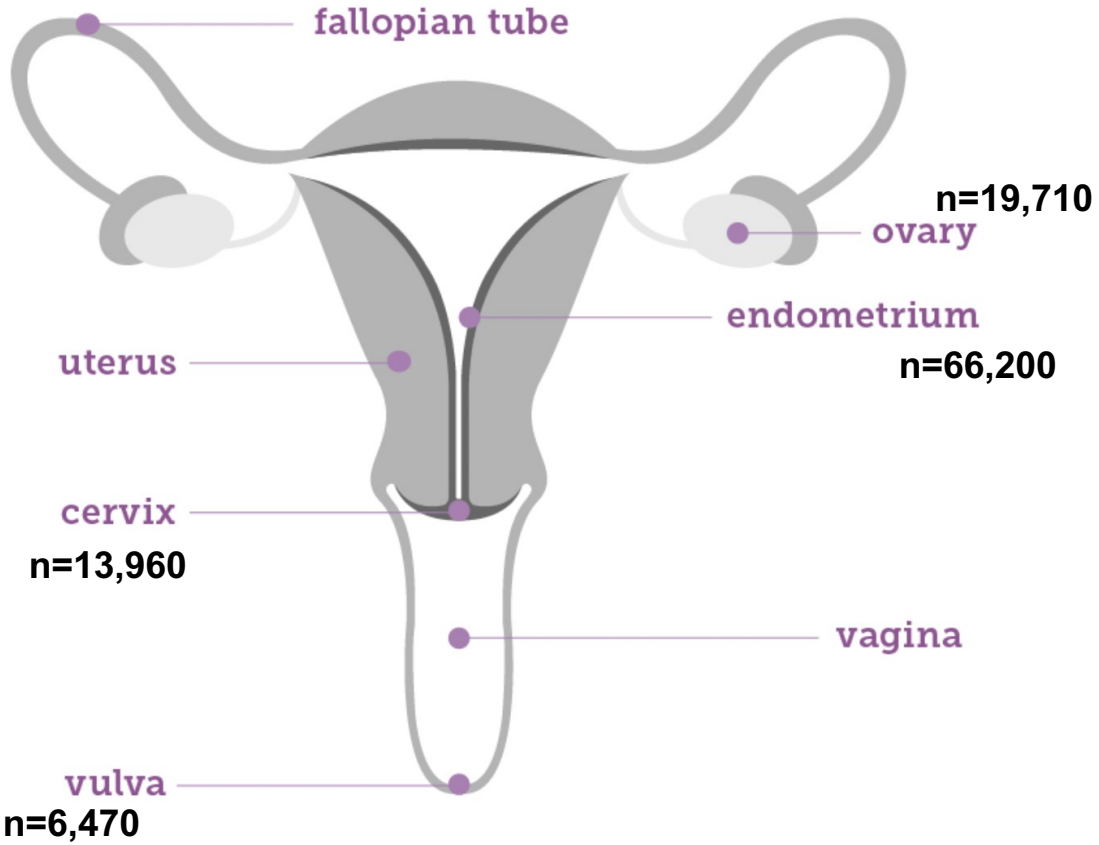
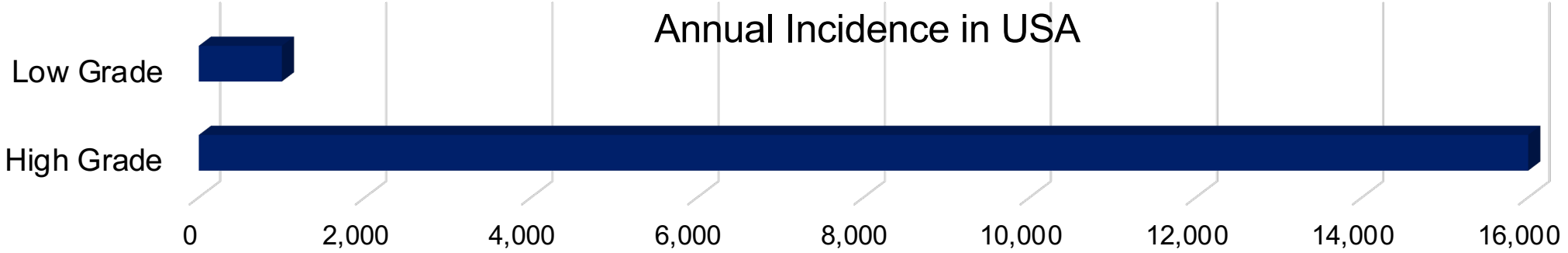
EPITHELIAL OVARIAN CANCER: EPIDEMIOLOGY





Slide courtesy of Dr. Sarah Dilley

BACKGROUND

Ovarian serous carcinoma

Serous carcinomas are classified into low and high-grades

10% of serous ovarian cancer

Low-grade carcinoma

- From borderline tumors
- Low mutational burden: frequent alterations in MAPK pathway genes
- Unclear germline association.
- Bimodal age of onset (20s-30s and 50s-60s)
- Less chemoresponsive
- Indolent or aggressive disease course

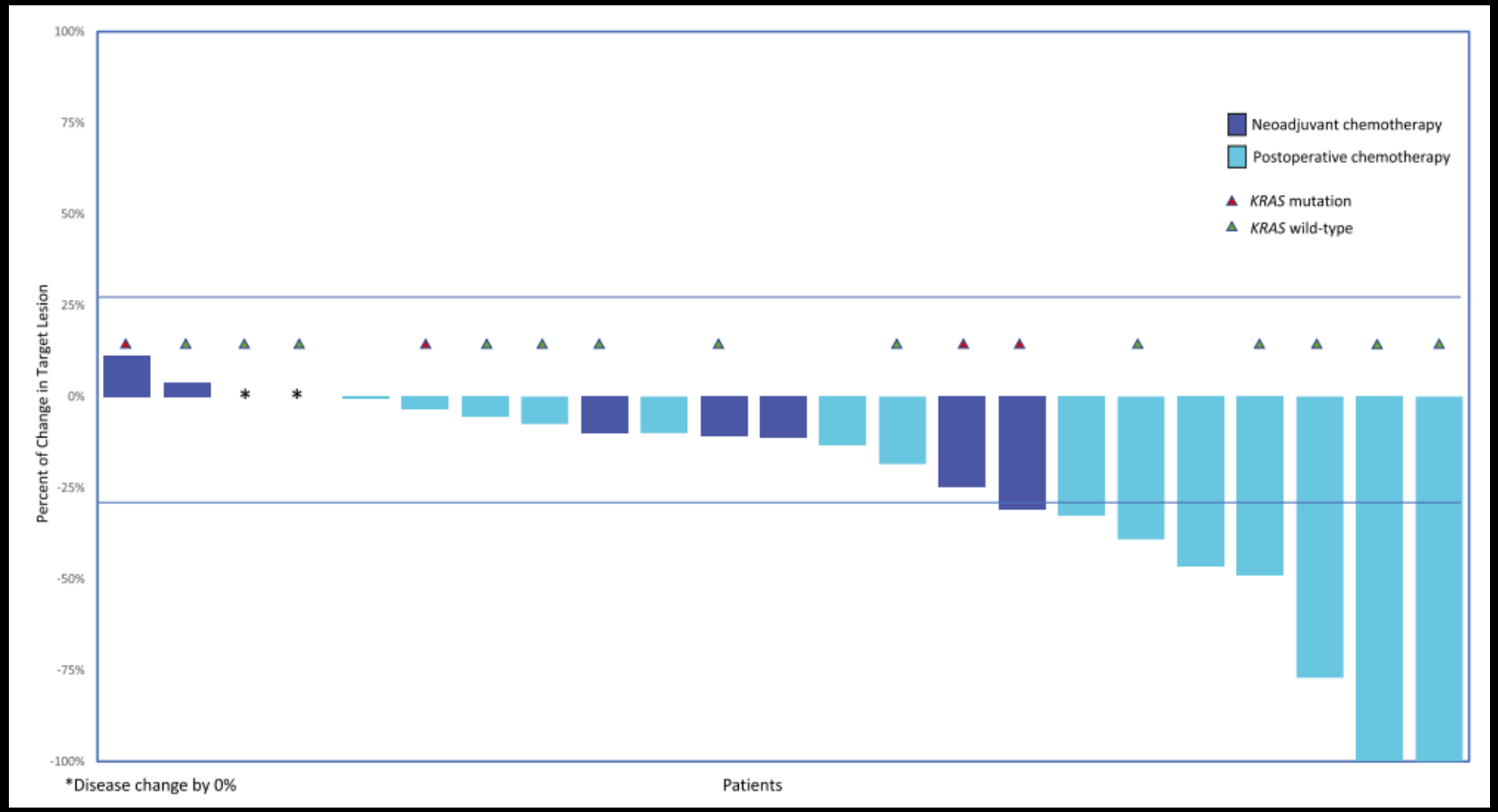
High-grade carcinoma

- Possible STIC precursor lesion
- High levels of chromosomal instability, recurrent TP53 mutations
- Frequent germline association
- Later age of onset (median in 60s)
- Highly chemoresponsive
- Typically aggressive disease course

90% of serous ovarian cancer

CHEMOTHERAPY RESPONSE

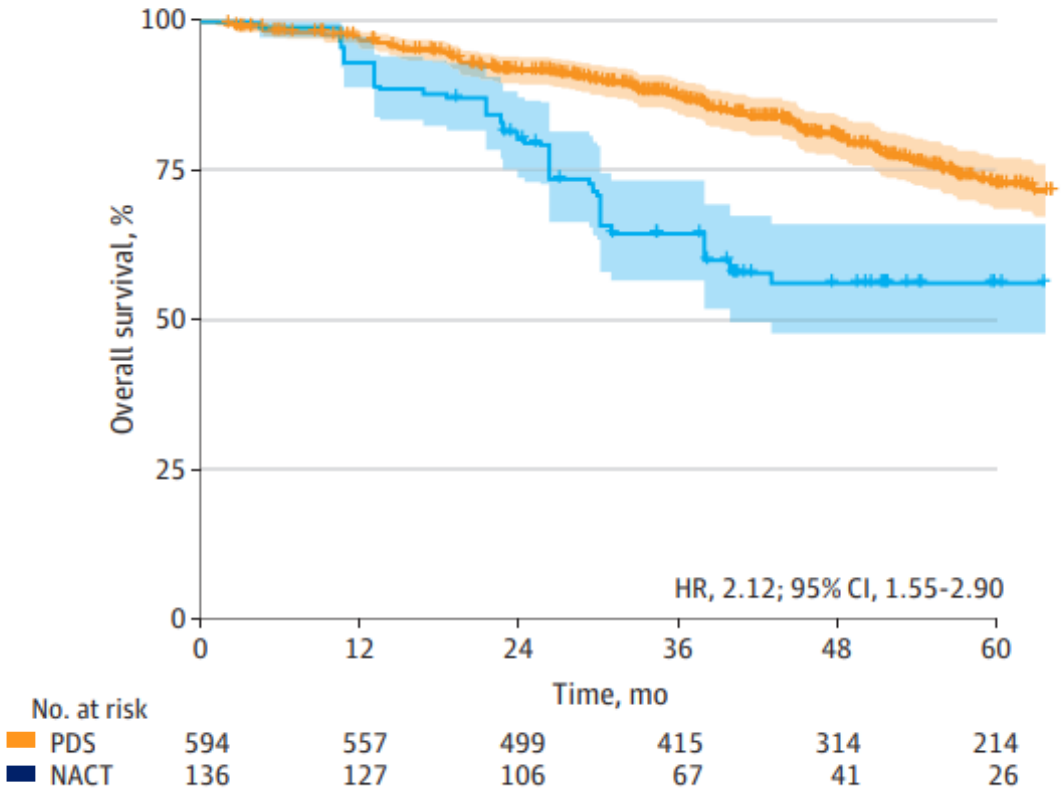
- LGSOC has poor response rates to standard chemotherapy options.
- In our patient population, RECIST-defined response rates to neoadjuvant chemotherapy were 9%.[1] Other studies demonstrated response rates of 4-11%.[2,3]

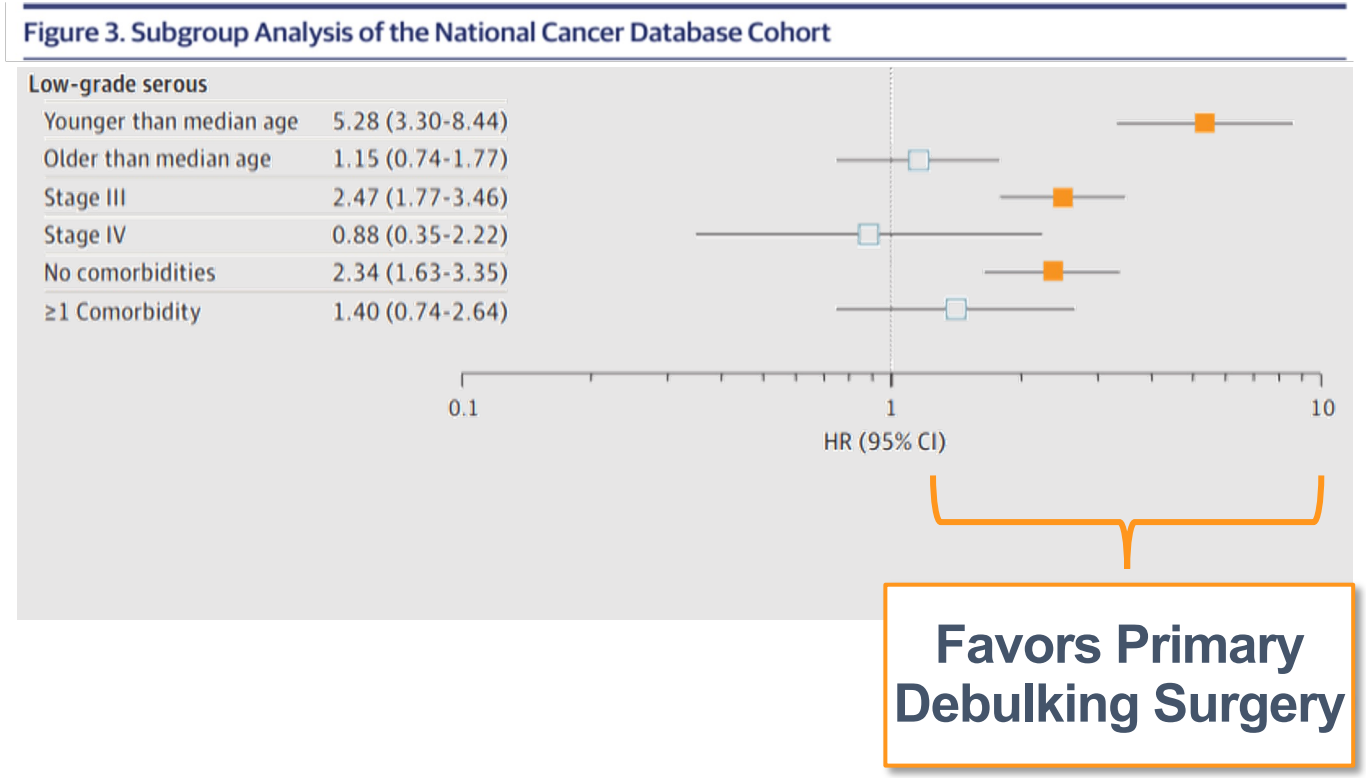


1. Manning-Geist, B, et al. Cancer. 2022. 2. Schmeler et al. Gyn Onc. 2008. 3. Cobb et al Gyn Onc. 2020.

CHEMOTHERAPY RESPONSE

- Use of NACT in LGSOC patients is associated with poor survival outcomes.[1]

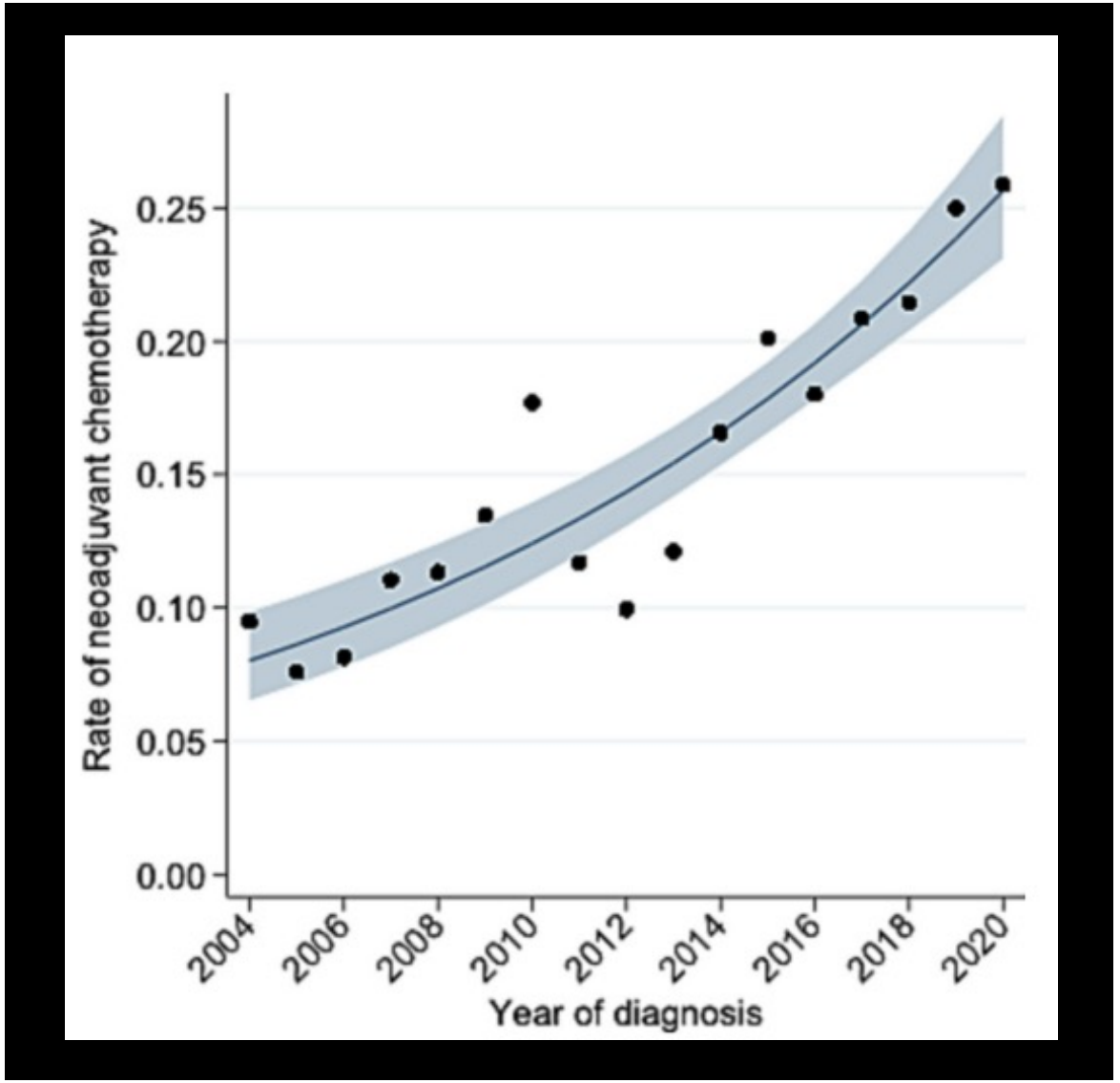




1. Gershenson et al. JAMA Network Open. 2023.

NEOADJUVANT CHEMOTHERAPY TRENDS

- Despite poor response, use of neoadjuvant chemotherapy in LGSOC is increasing
- By NCDB data, 9.5% utilization in 2004 to 25.9% in 2020.[1]



1. Silberman et al. Gyn Onc. 2023

MOLECULAR LANDSCAPE OF LGSOC

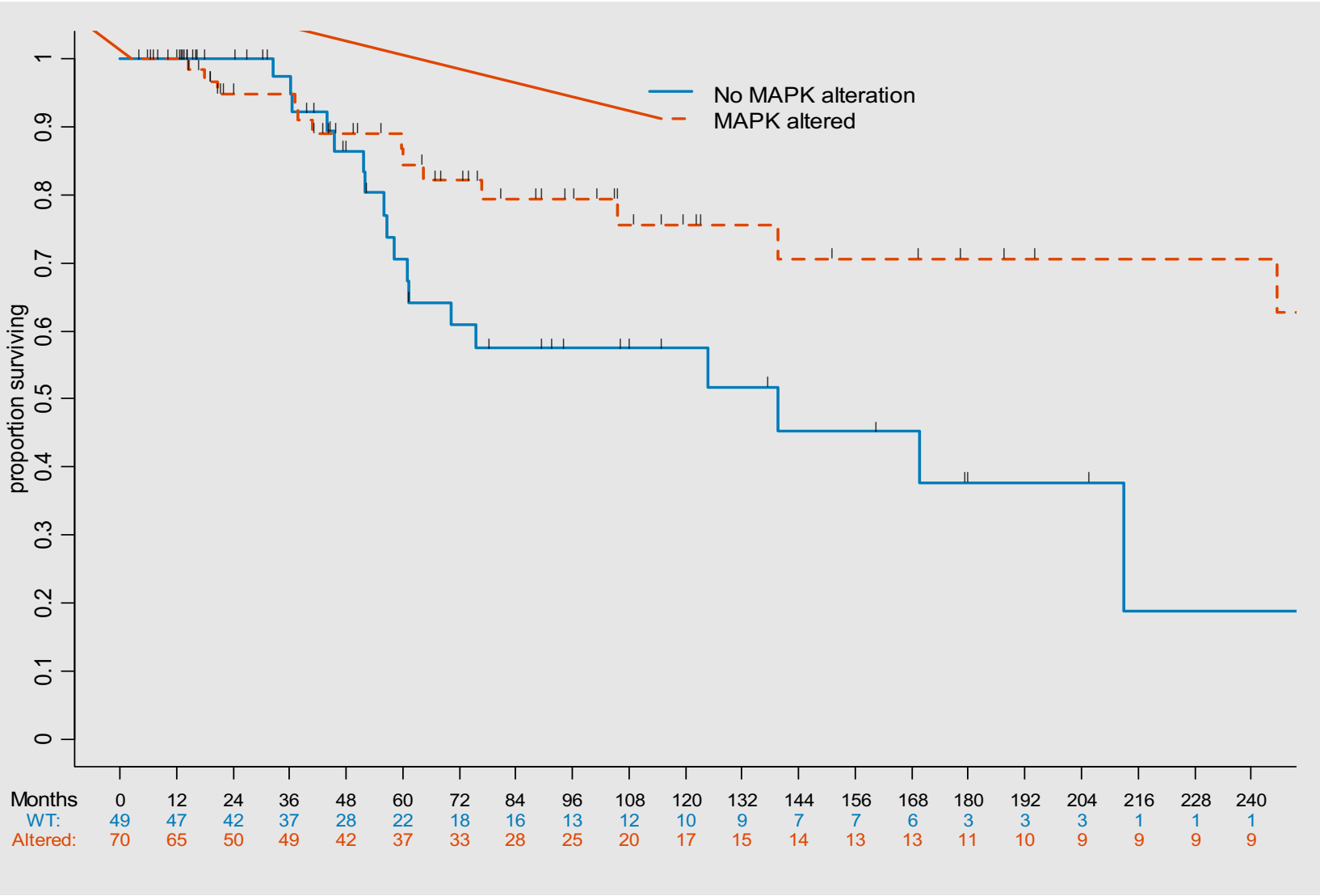
MAPK alteration

1. Manning-Geist B et al. CCR. 2022.

MAPK MUTATION AND OVERALL SURVIVAL

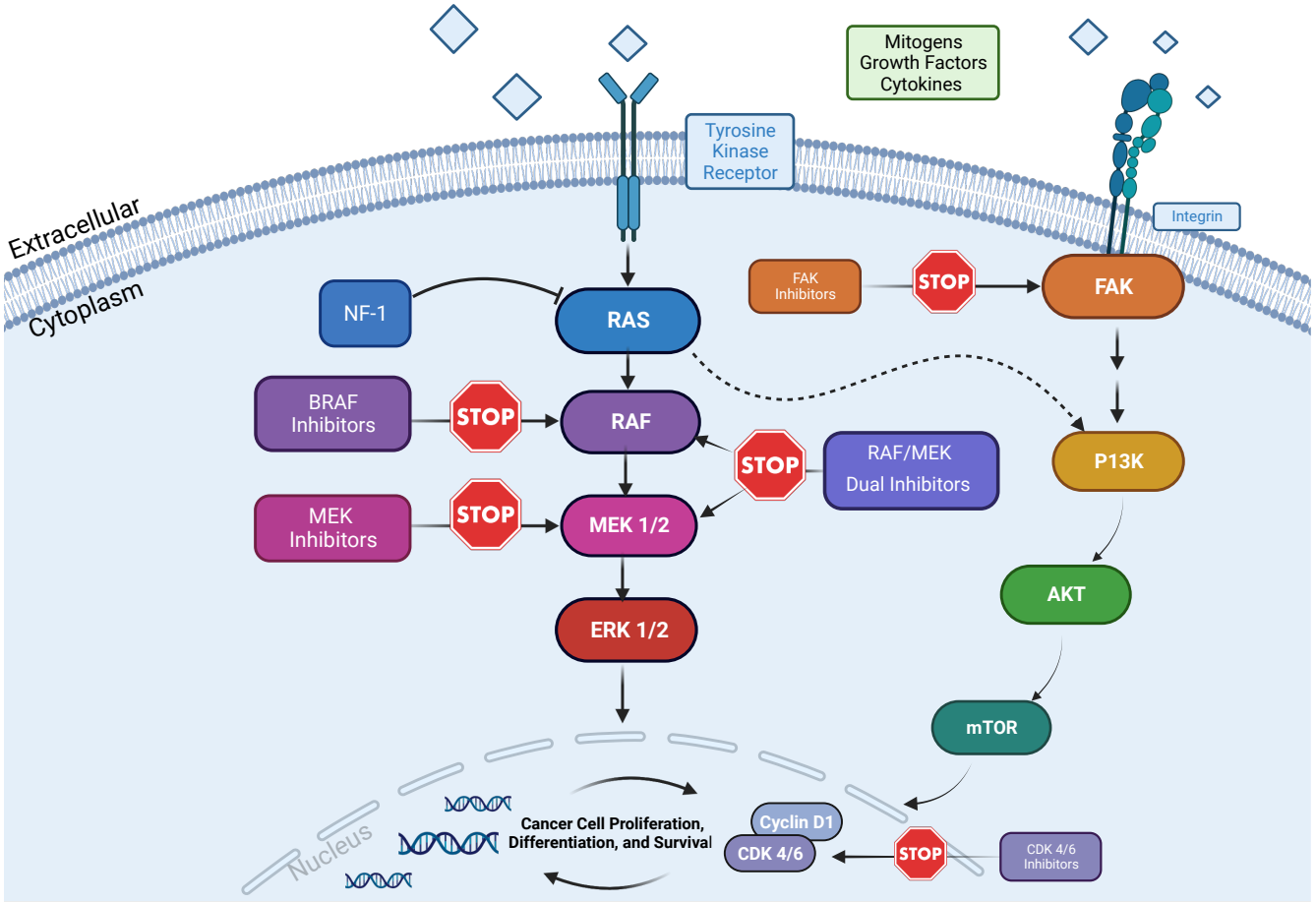
	MAPK Altered *	No MAPK alteration
5-year OS (95% CI)	84.4% (71.1-92.0%)	70.6% (52.1-83.1%)
HR for death	2.3 (1.1-4.7)	
p-value	**0.019**	

*** KRAS, NRAS, HRAS, BRAF, NF1, NF2**



LGSOC—LEVERAGING GENETIC FEATURES

- Most promising "actionable" mutations involve the MAPK pathway: *KRAS*, *NRAS*, and *BRAF* mutations are reported in approximately 50% of LGSC.



Clinical Relevance

- Emerging data on ***KRAS* mutation** as predictive of MEK inhibitor response:
  - MILO/ENGOT-ov11: overall response rates (ORR) of 44% to binimetinib (MEK inhibition) in *KRAS*-mutated patients vs. 19% in *KRAS* wild-type patients to MEK inhibition (p=0.006).
  - No association between *KRAS* mutation and ORR in provider-choice chemotherapy.

1. Manning-Geist et al.Clin Adv Heme Onc. 2023.

STUDIES RECENTLY COMPLETED IN LGSOC

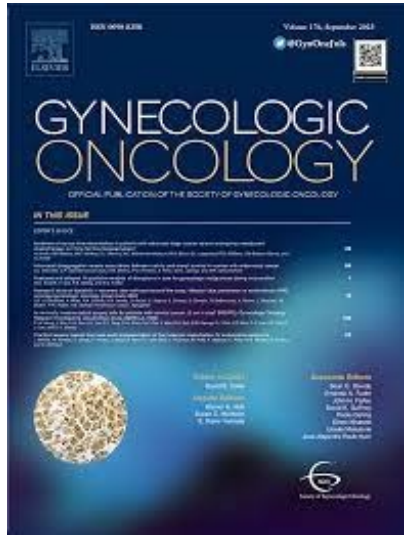
Study	Phase	Treatment	Efficacy Outcome
PARAGON[2]	II	Anastrazole for ER+ LGSOC	14% ORR (5/26)
NCT01974765[1]	II	Enzalutamide for AR+ LGSOC	1/14 unconfirmed PR, 4.6mo mPFS, 38.5% PFS6 mo
NRG-GY019	III	Letrozole vs. Carboplatin/ Paclitaxel +Letrozole	Trial Ongoing:
GOG 3026[3]	II	Ribociclib + Letrozole	23% ORR, 19.1mo mDOR, 19.1mo mPFS
NCT03905148[7]	I	Lifirafenib + Mirdametinib	58.8% ORR (10/17) [BIOMARKER SELECTED]
SOLAR[6]	I/II	Olaparaib + Selumetinib	44% ORR (4/9) [BIOMARKER SELECTED]
FRAME[4]	I	Avutometinib + Defactinib	46% ORR (64% KRAS mt, 44% KRAS wt), 23 mo mPFS
RAMP 201[5]	II	Avutometinib + Defactinib	45% ORR (60% KRAS mt, 29% KRAS wt)

[1] Manning-Geist Gynecol Oncol 2020; [2]Tang Gynecol Oncol 2019; [3]Slomovitz SGO 2023; [4]Banerjee ESMO 2021 #799; [5]Banerjee ASCO 2023 #5515; [6]Westin SGO 2023; [7]Arend Gynecol Oncol 2020

Slide courtesy of Dr. Rachel Grisham

HORMONAL RESPONSE

- Low-grade serous ovarian cancer (LGSOC) is androgen receptor (AR) positive and can respond to hormonal blockade.
- Single-institution phase II trial of enzalutamide in HGSOC and LGSOC patients with AR+ tumors.
- Among 45 HGSOC patients, 6-month PFS 19.8%. Among 14 LGSOC patients, 6-month PFS 38.5%.
- Well-tolerated, but only 1 Partial Response in HGSOC, 1 Partial Response in LGSOC.



Phase II study of enzalutamide in androgen receptor positive, recurrent, high- and low-grade serous ovarian cancer

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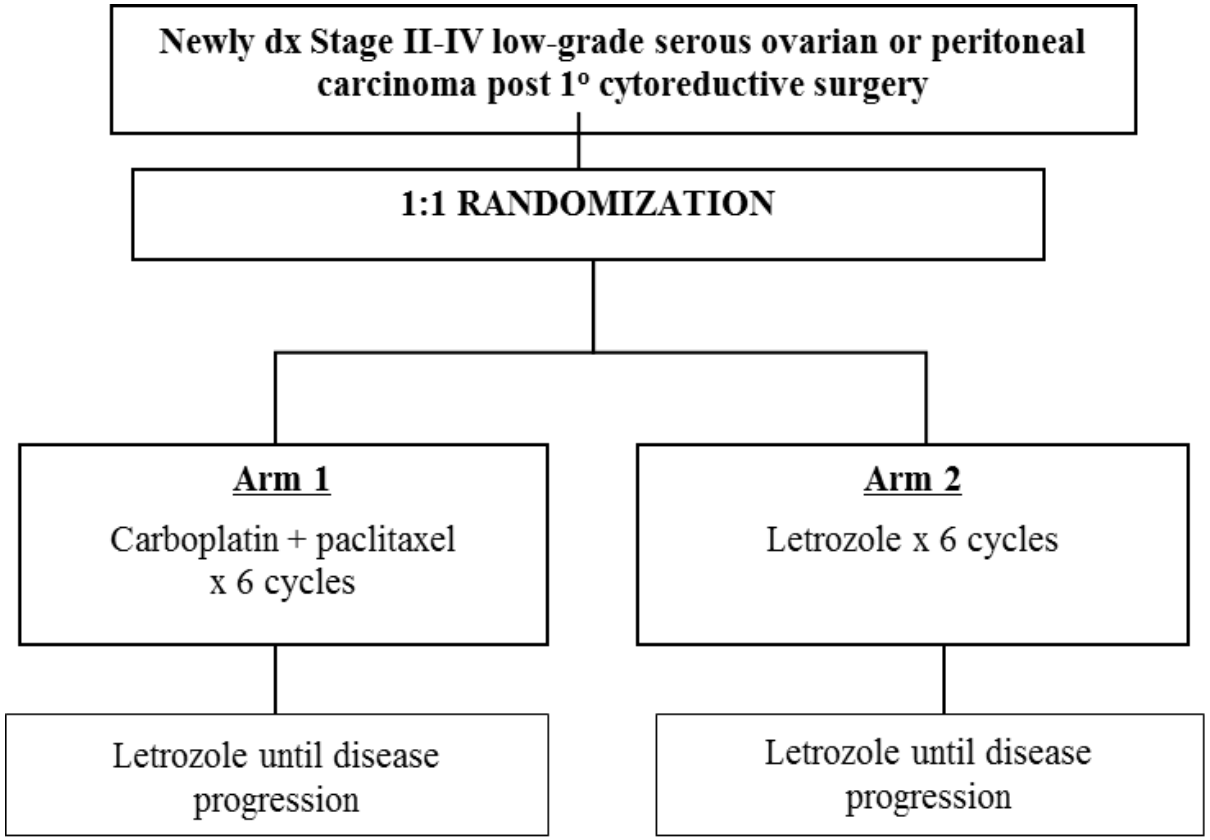
Published: November 08, 2021 • DOI: https://doi.org/10.1016/j.ygyno.2021.10.087 • Check for updates

1. Manning-Geist et al. Gynecol Oncol 2021

ADJUVANT TREATMENT OF LOW GRADE SEROUS OVARIAN CARCINOMA



NRG-GY019

Patients stratified based on:

1) Residual disease following primary cytoreductive surgery
   a) No gross residual disease
   b) Any gross residual disease
2) Country/Region of enrollments
   i. US/Canada
   ii. Asia
   iii. Europe

- Randomization 1:1 ratio
- P53 tumor testing required, no central pathology review

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NCT03909152[8]	II	Onapristone ER + Anastrozole	50% CBR (2/4), 75% PFS3mo
GOG 3026[3]	II	Ribociclib + Letrozole	23% ORR, 19.1mo mDOR, 19.1mo mPFS
NCT03905148[7]	I	Lifirafenib + Mirdametinib	58.8% ORR (10/17) [BIOMARKER SELECTED]
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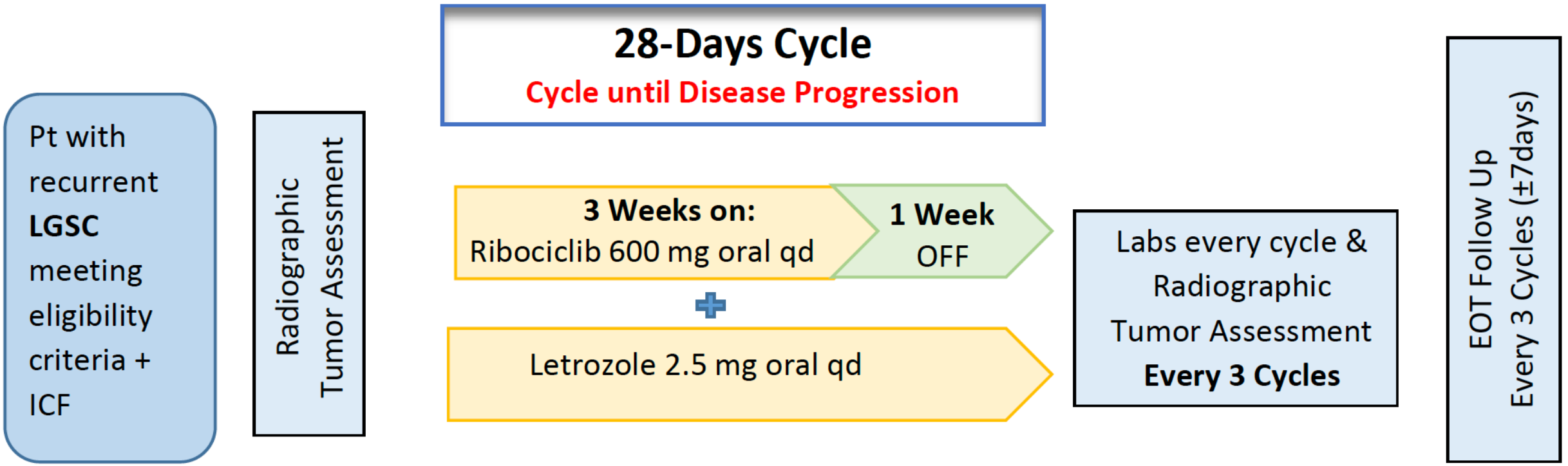
GOG 3026: LETROZOLE+RIBOCICLIB (CDK4/6 INHIBITION) IN RECURRENT LGSOC



Presented by Dr. Brian Slomovitz, SGO 2023

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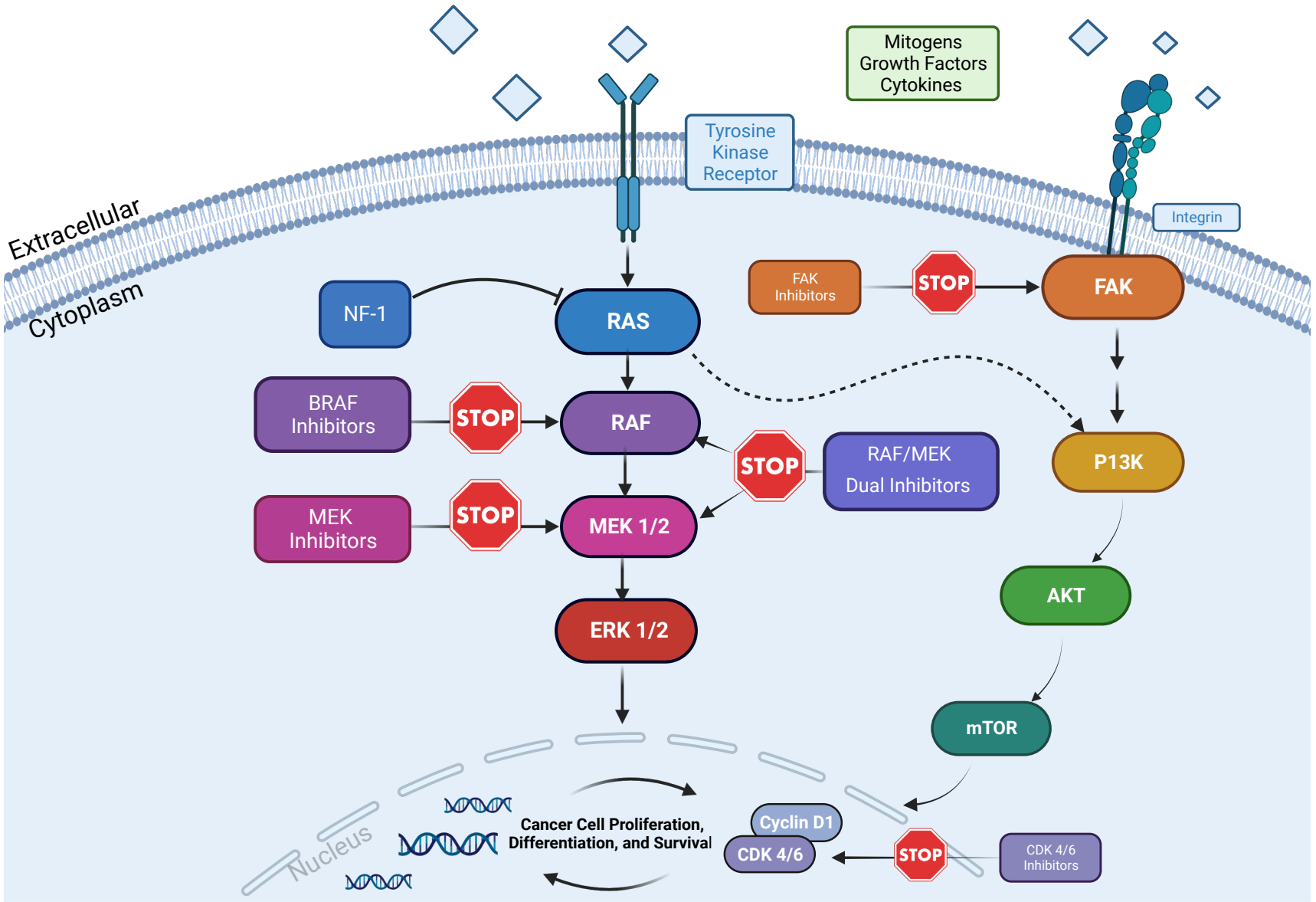
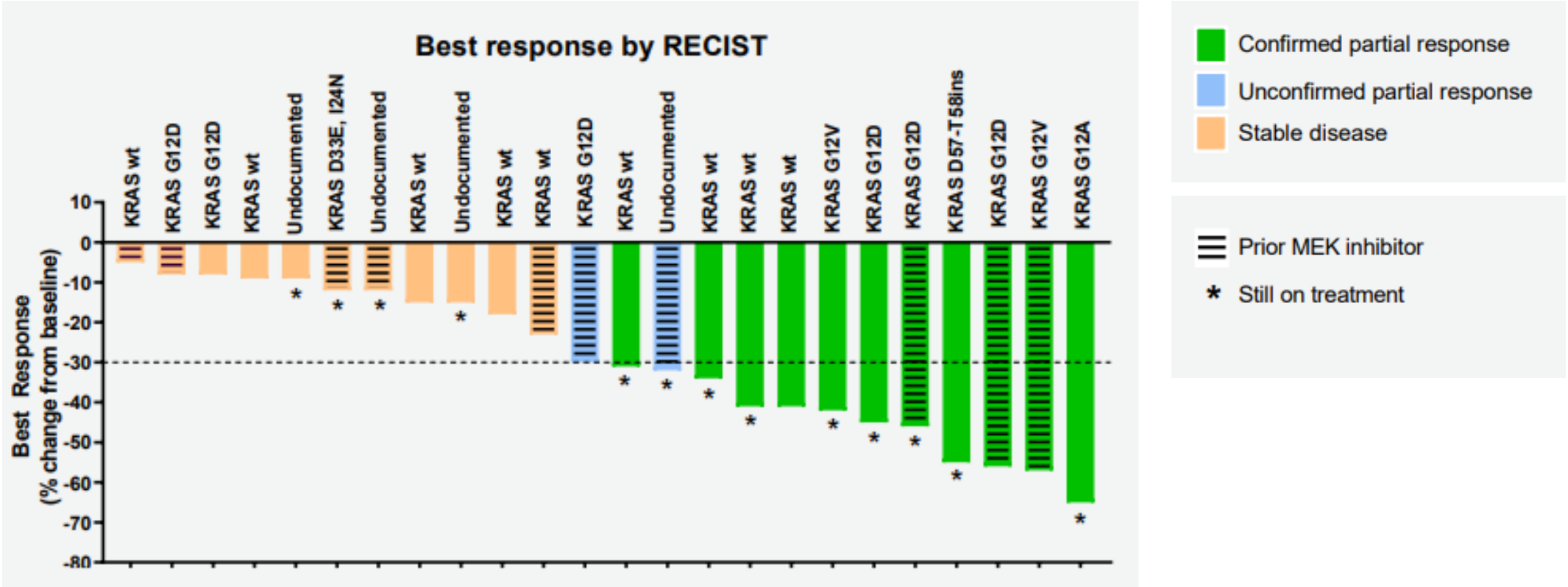


1. Manning-Geist et al.Clin Adv Heme Onc. 2023.

FRAME: MEK/RAF/FAK COMBINATION

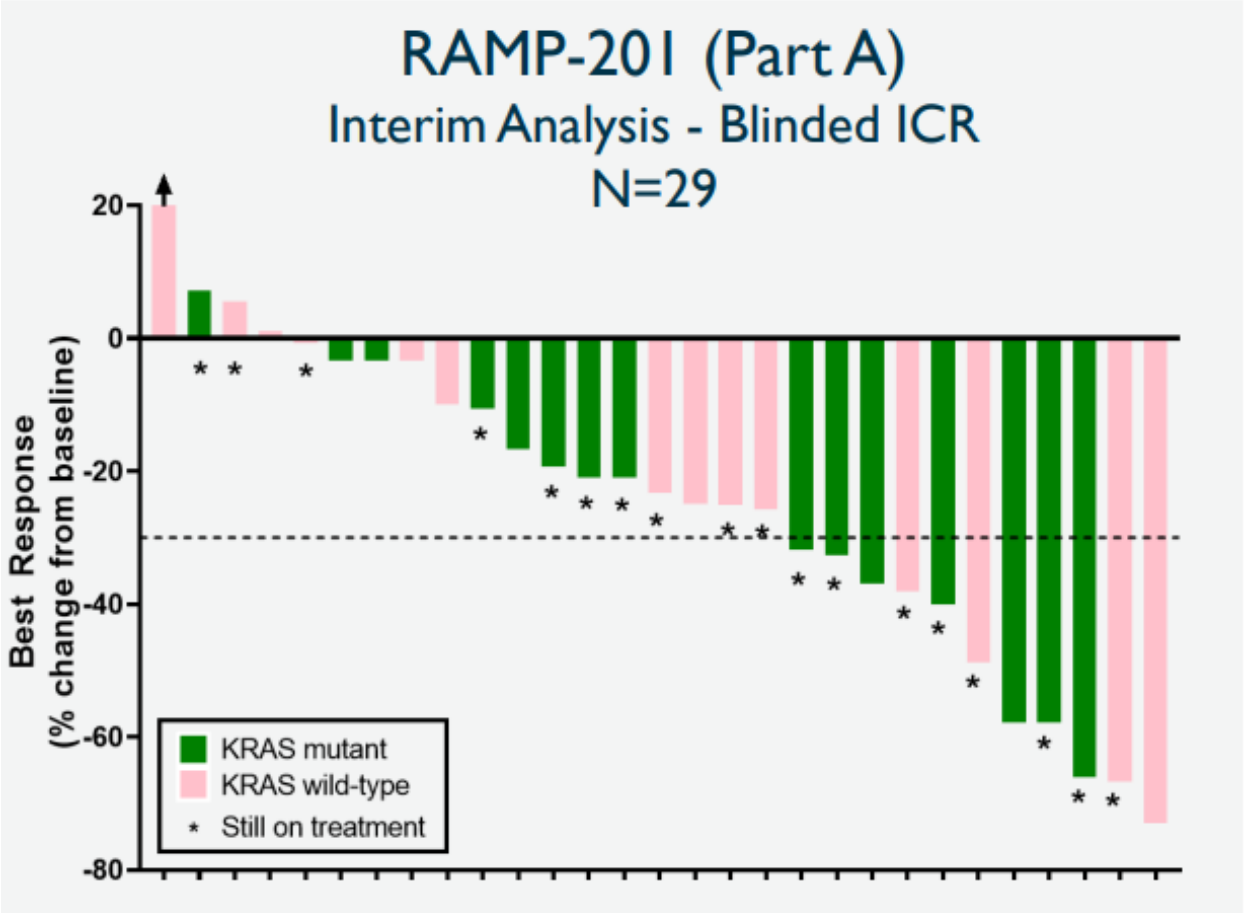
- Phase I trial (FRAME) showed ORR 46% for MEK/RAF inhibition (avutometinib) in combination with FAK inhibition (defactinib) for recurrent LGSOC.



1. Banerjee, ESMO 2021.

PHASE II DATA IN RECURRENT LGSOC: RAMP 201

- ORR 45% (13/29) and tumor shrinkage in 86% (25/29) patients.



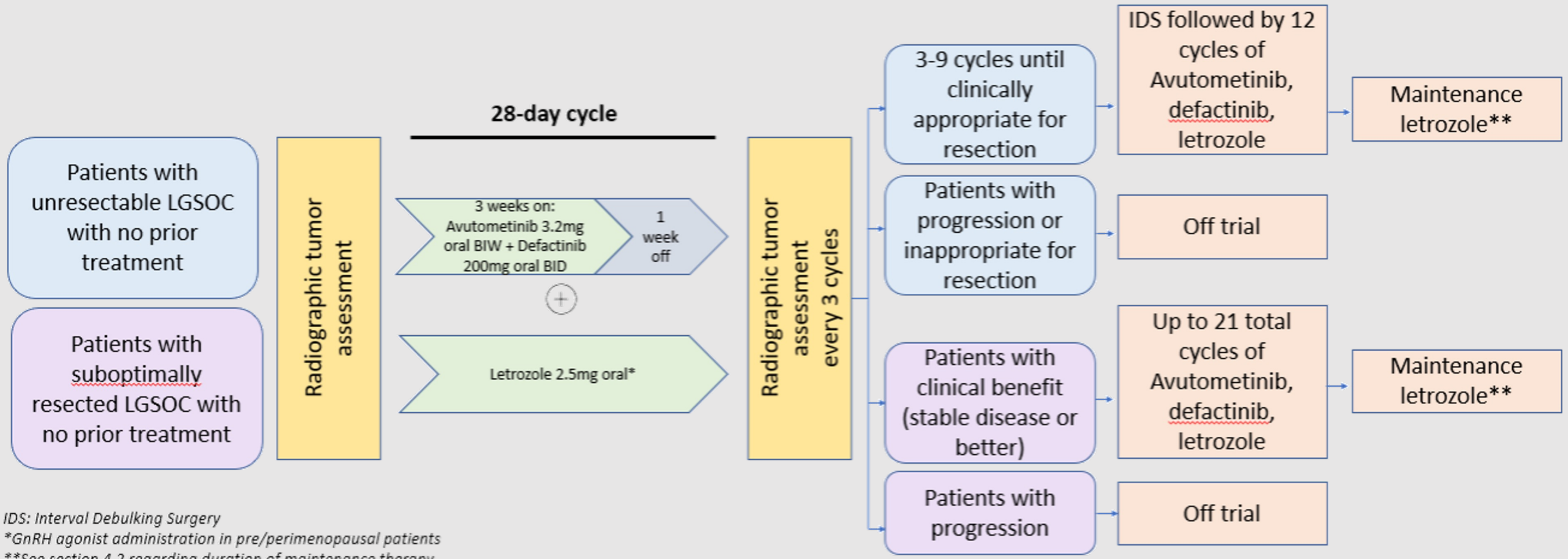
1. Banerjee et al. ASCO 2023.

UPCOMING EMORY TRIALS: Combination targeted and Hormonal treAtMEnt of Low-gradE serous Ovarian cancer in the upfroNt setting (CHAMELEON)

- Phase II, single-arm investigator initiated trial RAF/MEK/FAK inhibition with hormonal blockade in LGSOC patients who are not surgical candidates (NACT) or in those with suboptimal residual disease.

1. **Primary endpoint:** Best overall response (complete or partial response) within 9 months of treatment with avutometinib, defactinib, plus letrozole therapy, as determined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1).
2. **Secondary endpoints:**
   - Characterize the safety and toxicity profile of this combination in the front-line.
   - Evaluate the ability to proceed with attempt at interval cytoreduction, and the number of neoadjuvant cycles of study treatment required prior to attempt at surgical cytoreduction.
   - Describe surgical outcomes (rates of complete gross resection, rates of ostomy formation, blood loss, operative time) at interval cytoreduction.
   - Describe progression free survival (PFS).

CHAMELEON



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

CHAMELEON

Key inclusion criteria:

- Histologically confirmed LGSOC
- Determination by a gynecologic oncologist that patient is not a primary surgical candidate OR patient has undergone primary cytoreduction with RECIST-measurable disease on postoperative imaging.
- Measurable disease according to RECIST v1.1.
- Adequate cardiac function (LVEF≥50%); ECOG≤1

Key exclusion criteria

- Candidates for primary debulking surgery (unless measurable disease exists after PDS).
- Prior systemic anti-cancer therapy for LGSOC.
- Bowel obstruction <3 months from study enrollment, dPEG.

ACKNOWLEDGEMENTS

Rachel Grisham, MD
MSKCC

Joyce Liu, MD
Dana Farber Cancer Institute

Fiona Simpkins, MD
Univ of Pennsylvania

Sarah Adams, MD
Univ of New Mexico

Britta Weigelt, PhD
MSKCC

David Gershenson, MD
MD Anderson Cancer Center

Anil Sood, MD
MD Anderson Cancer Center

Amanda Fader, MD
Johns Hopkins