Data + Perspectives: Clinical Investigators Discuss the Current and Future Management of Ovarian Cancer

Saturday, March 19, 2022

2:30 PM – 4:00 PM ET

Faculty

Mansoor Raza Mirza, MD
Kathleen N Moore, MD, MS
David M O'Malley, MD

Moderator

Robert L Coleman, MD

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Faculty

Mansoor Raza Mirza, MD
Chief Oncologist
Copenhagen University Hospital
Medical Director
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Chairman, European Network of Gynaecological Trial Groups
Vice President, European Society of Gynaecological Oncology
Copenhagen, Denmark

Kathleen N Moore, MD, MS
Virginia Kerley Cade Chair in Developmental Therapeutics
Associate Director for Clinical Research
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Professor, Section of Gynecologic Oncology
Associate Program Director, Gynecologic Oncology Fellowship
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David M O'Malley, MD
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Division Director, Gynecologic Oncology
The Ohio State University and The James Cancer Center
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Moderator

Robert L Coleman, MD
Chief Scientific Officer
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Gynecologic Oncology
The Woodlands, Texas

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Commercial Support

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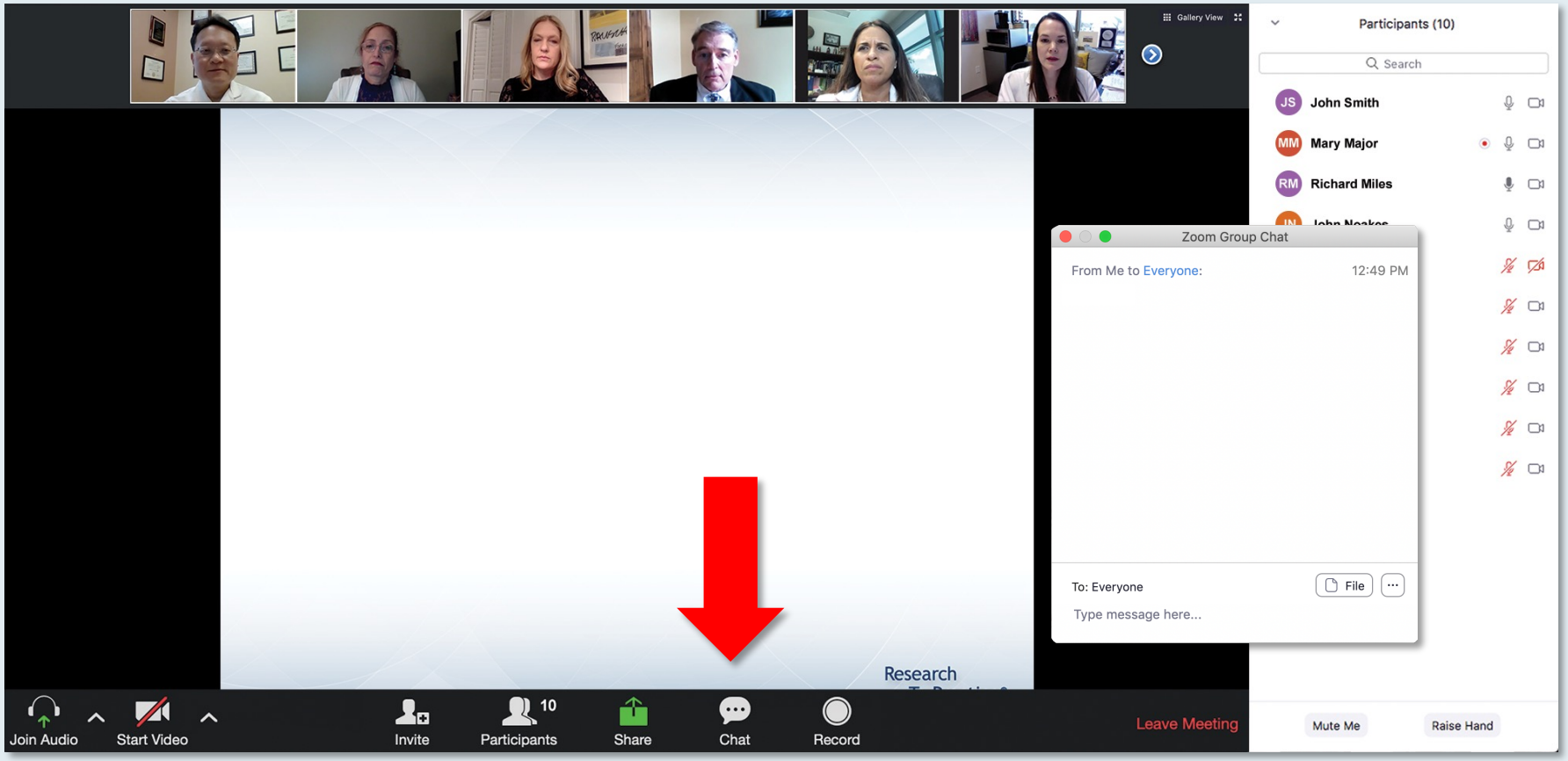
We Encourage Clinicians in Practice to Submit Questions



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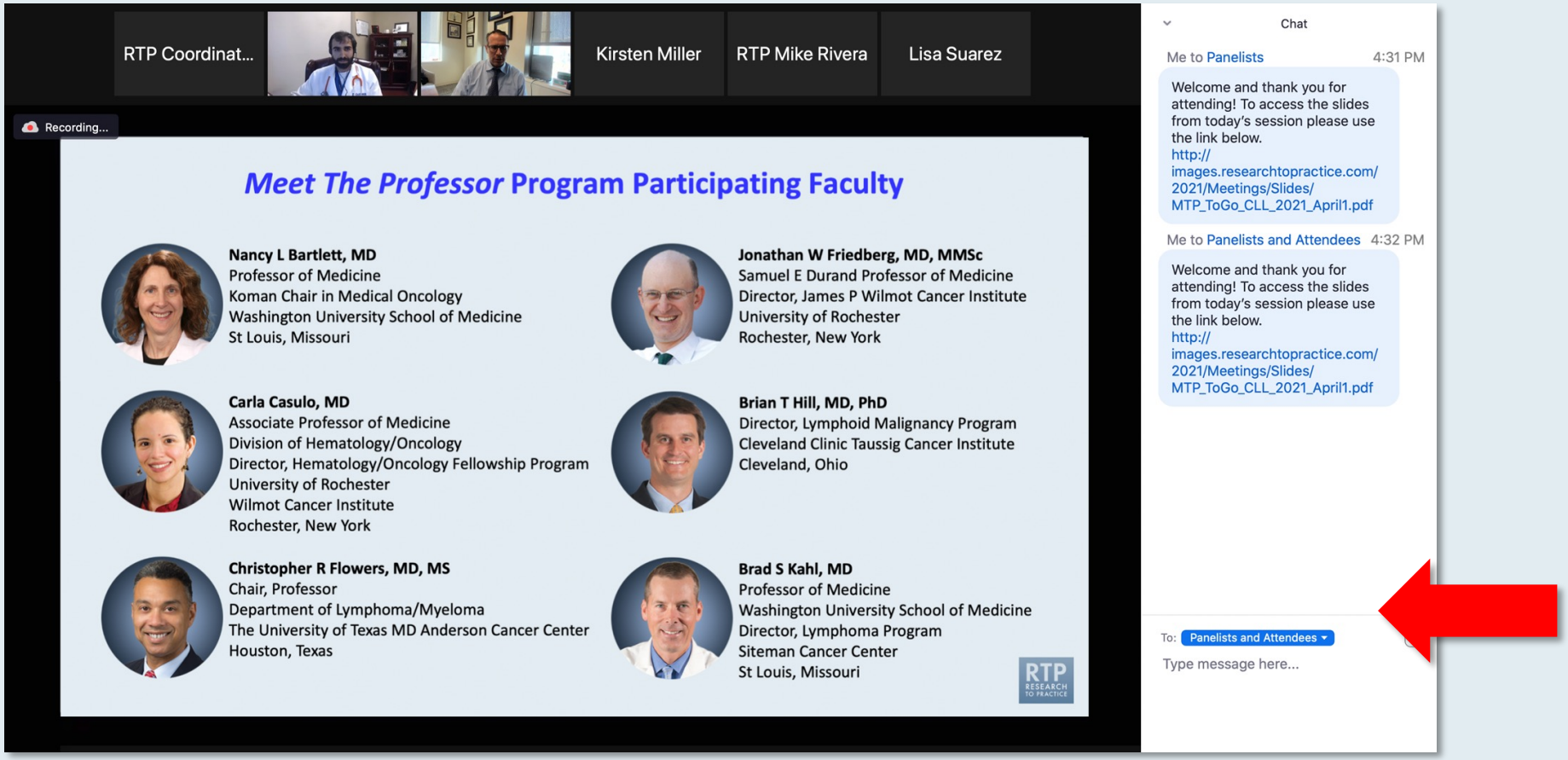

Drag the white line above the submission box up to create more space for your message.

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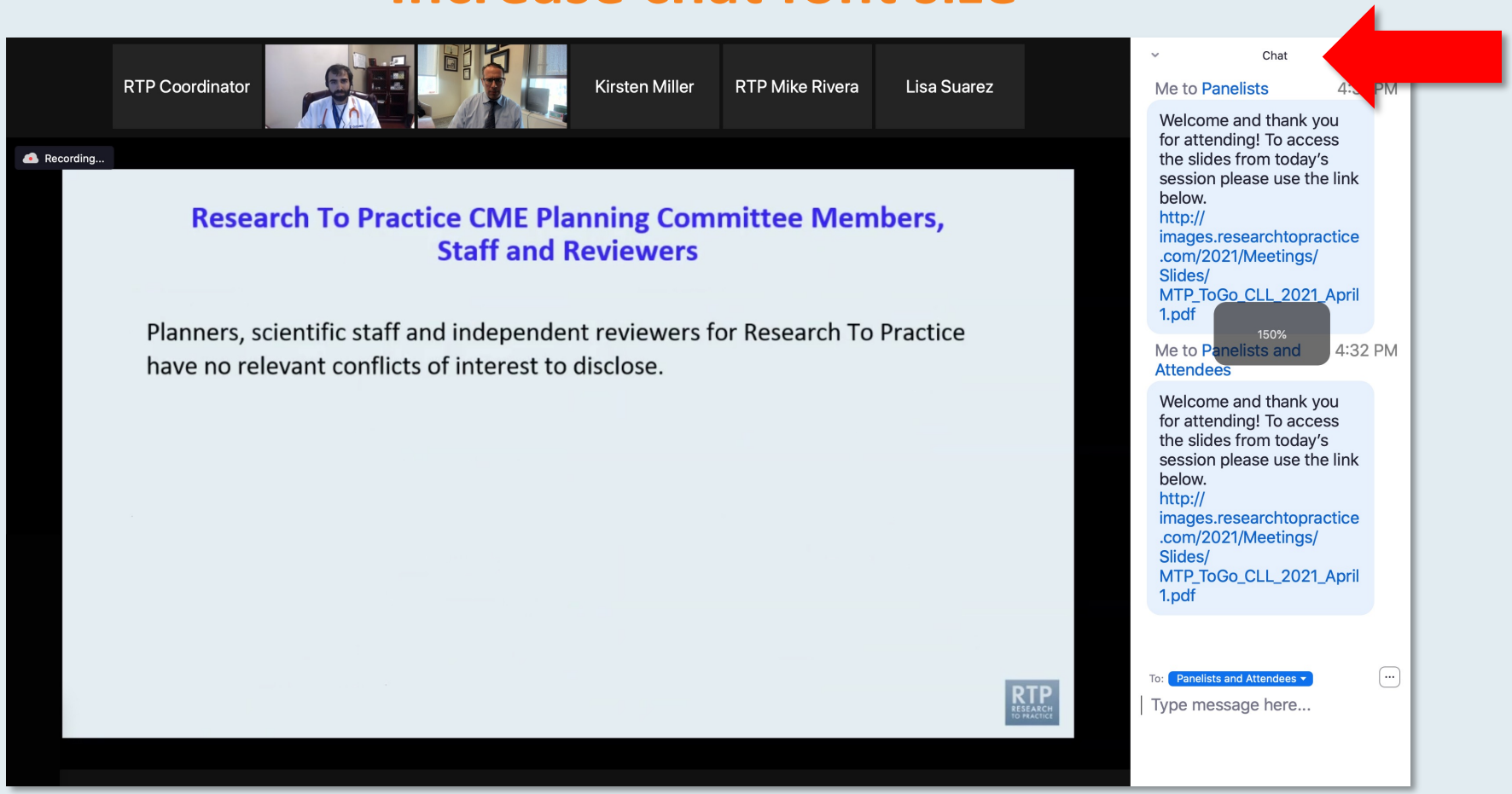
Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Ovarian Cancer

DR BRADLEY MONK

UNIVERSITY OF ARIZONA COLLEGE OF MEDICINE

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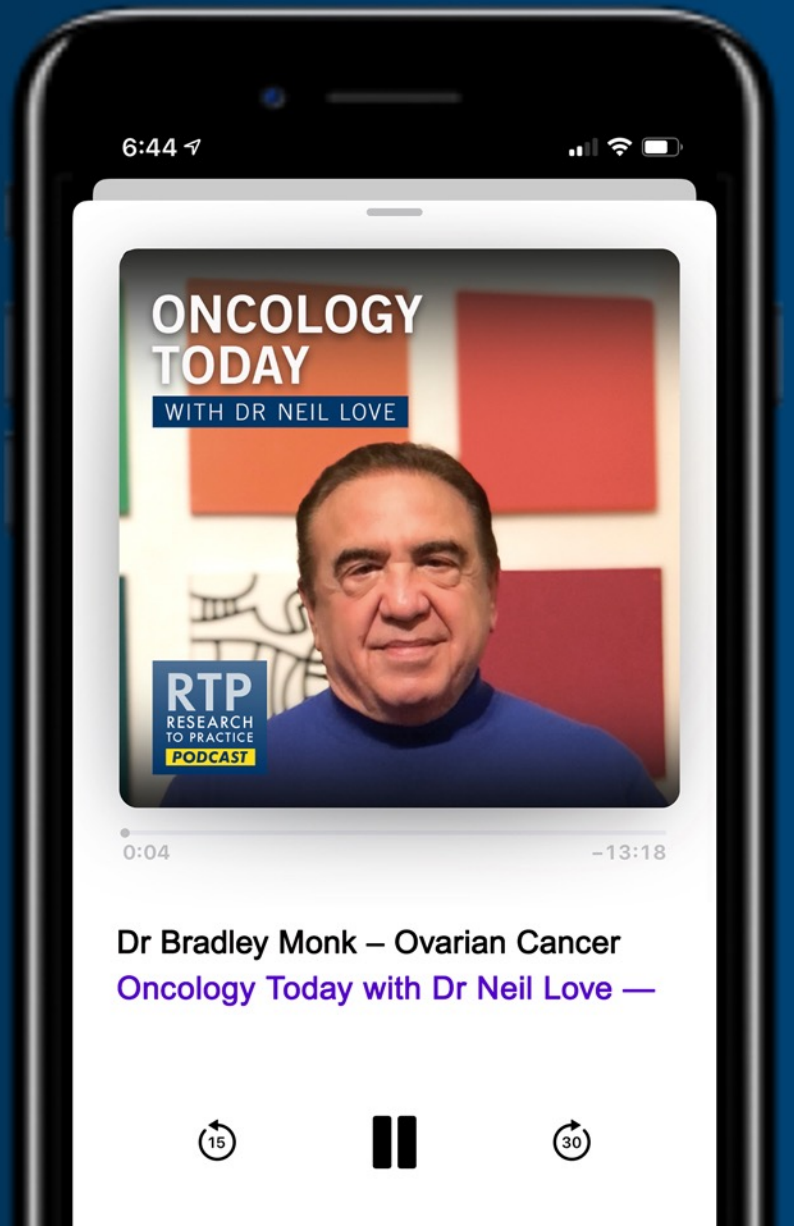

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Meet The Professor

Current and Future Role of Immunotherapy in the Management of Lung Cancer

Wednesday, March 30, 2022
5:00 PM – 6:00 PM ET

Faculty

Sarah B Goldberg, MD, MPH

Moderator

Neil Love, MD

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Meet The Professor

Current and Future Management of Chronic Lymphocytic Leukemia

Thursday, March 31, 2022
5:00 PM – 6:00 PM ET

Faculty

Kerry Rogers, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Myelodysplastic Syndromes

Tuesday, April 5, 2022
5:00 PM – 6:00 PM ET

Faculty

Rami Komrokji, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Wednesday, April 6, 2022
5:00 PM – 6:00 PM ET

Faculty

Andrew M Evens, DO, MSc

Moderator

Neil Love, MD

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RESEARCH
TO PRACTICE

Meet The Professor

Current and Future Management of Myelofibrosis

Thursday, April 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Professor Claire Harrison

Moderator

Neil Love, MD

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"What I Tell My Patients"
16th Annual RTP/ONS CE Seminar Series
ONS Congress, Anaheim, California — April 27 - May 1, 2022

Thursday April 28	**Prostate Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Ovarian Cancer 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)
	Non-Small Cell Lung Cancer 6:00 PM – 7:30 PM PT (9:00 PM – 10:30 PM ET)
Friday April 29	**Small Cell Lung Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Chronic Lymphocytic Leukemia 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)
	Breast Cancer 6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)
Saturday April 30	**Cervical and Endometrial Cancer** 6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)
	Bladder Cancer 12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

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Thank you for attending!

CME Credit Information

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Chairman, European Network of Gynaecological Trial Groups
Vice President, European Society of Gynaecological Oncology
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Virginia Kerley Cade Chair in Developmental Therapeutics
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Director, Early Phase Drug Development
Stephenson Cancer Center at the University of Oklahoma HSC
Professor, Section of Gynecologic Oncology
Associate Program Director, Gynecologic Oncology Fellowship
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

David M O'Malley, MD
Professor
Division Director, Gynecologic Oncology
The Ohio State University and The James Cancer Center
Columbus, Ohio

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Networked iPads are available.

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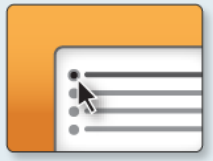

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

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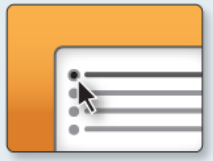

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Agenda

Module 1: Optimal Biomarker Evaluation and Management of Treatment-Naïve Advanced Ovarian Cancer (OC) — Dr Moore

Module 2: Treatment of Recurrent OC; Ongoing Research Efforts with PARP Inhibitors for Newly Diagnosed and Relapsed Disease — Dr O'Malley

Module 3: Recognition and Management of Side Effects Associated with PARP Inhibitor Therapy for OC — Dr Mirza

Module 4: Novel Investigational Agents and Strategies in OC — Dr Coleman

MODULE 1: Optimal Biomarker Evaluation and Management of Treatment-Naïve Advanced Ovarian Cancer (OC) — Dr Moore

Decision Making in Ovarian Cancer

Kathleen Moore, MD

Dr Moore — Disclosures

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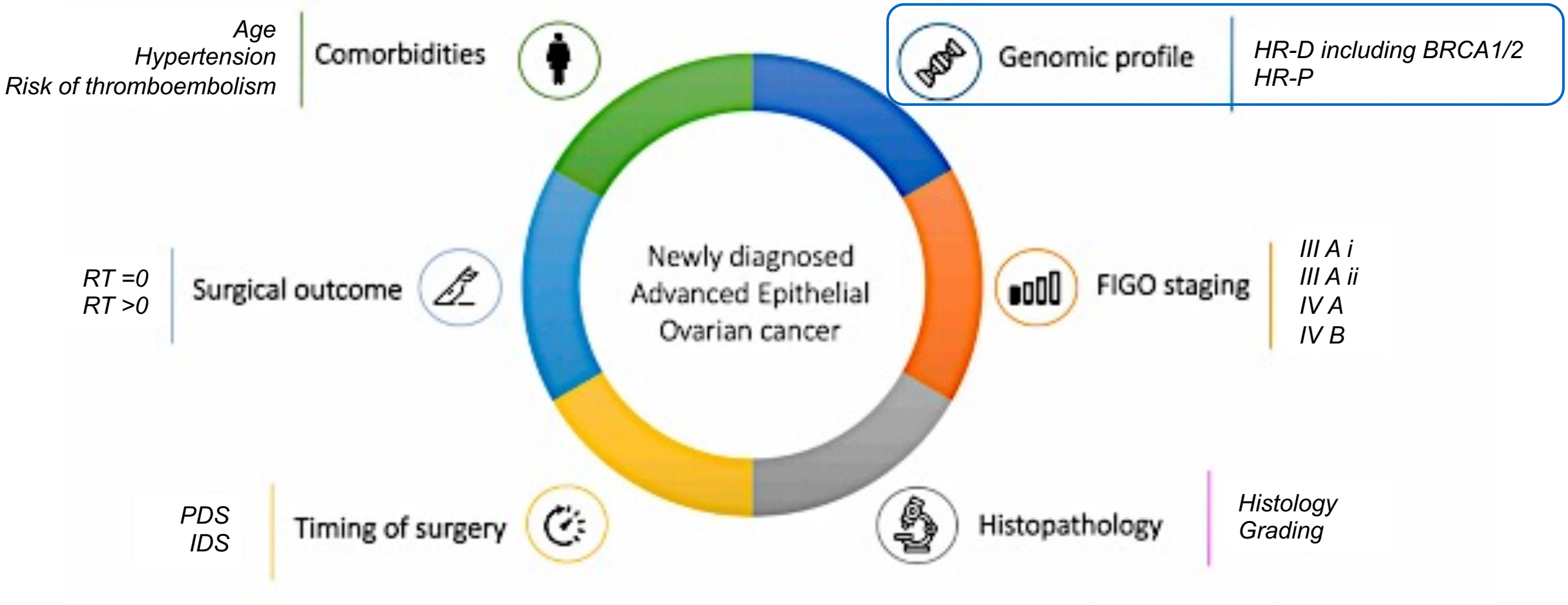
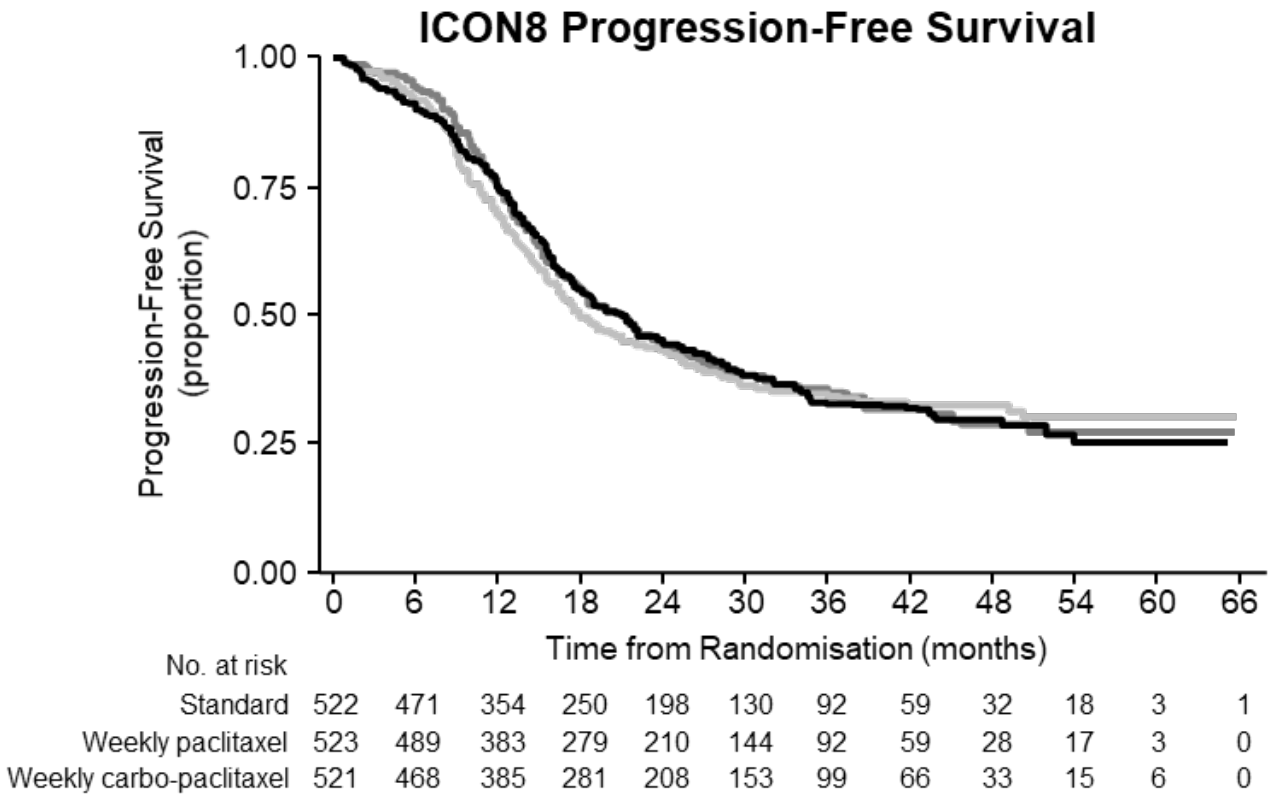
Considerations for Selection of Therapy in Front Line Ovarian Cancer



Nero et al. Cancers 2021, 13; 1298

What Can We Expect with Platinum Based Chemo Alone?

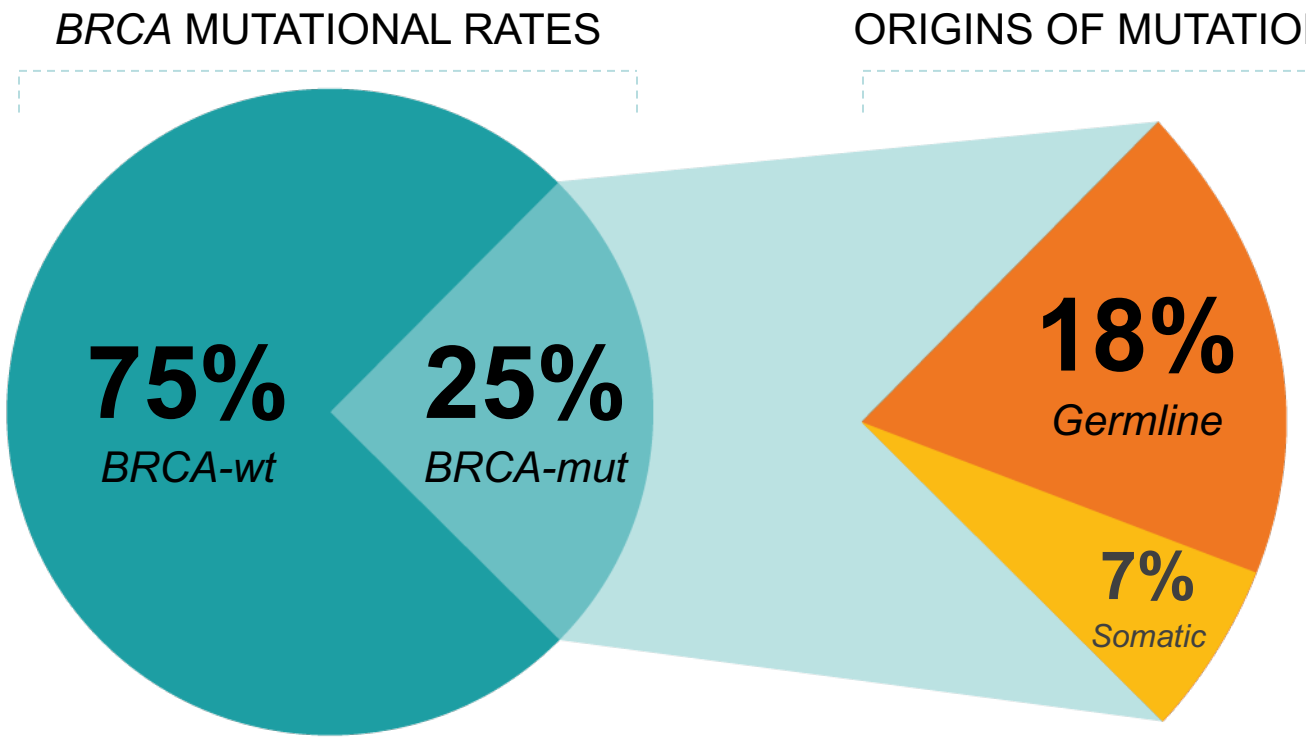


	Standard (n=522)	Weekly paclitaxel (n=523)	Weekly carbo-paclitaxel (n=521)
Progressions	330 (63%)	335 (64%)	338 (65%)
Median PFS, mo	17.9	20.6	21.1
Log rank (vs standard)		P=0.45	P=0.56
HR vs Standard (97.5% CI)		0.92 (0.77–1.09)	0.94 (0.79–1.12)
Restricted means	24.4 mos	24.9 mo	25.3 mo

Weekly dose-dense chemotherapy can be delivered successfully as first-line epithelial ovarian cancer treatment without substantial toxicity increase; it does not significantly improve PFS compared to standard 3-weekly chemotherapy

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
Clamp AR, et al. ESMO 2017. Abstract 4427.

An estimated 25% of Newly Diagnosed Ovarian Cancers Harbor *BRCA 1/2* Mutations



An estimated 1 in 4 women with EOC will have a *BRCA*-positive tumor result
Tumor testing detects more patients with *BRCA* mutations than blood/saliva tests that do not look at tumor DNA

EOC, epithelial ovarian cancer; mut, mutation; wt, wild type
Pennington et al. Clin Cancer Res. 2014;20(3):764-75.

Clinical Utility of Multigene Panel Testing

- Additional mutations (besides *BRCA1/2*) create risk for ovarian cancer[1]
  - *PALB2, BARD1, BRIP1, RAD51C, RAD51D, MSH2, MLH1, PMS2,* and *MSH6*
- Traditional test: targeted sequencing of each candidate gene[2]
- Multigene cancer panels use next-generation sequencing (NGS) to assess multiple genes simultaneously[2]

Advantages

Decreases:

- Resource use (efficient use of funds and time)
- Number of patient visits
- Number of tests sent

Limitations

Increases:

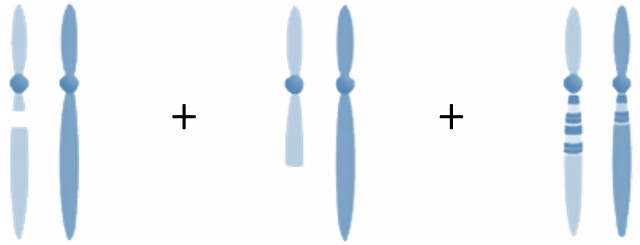
- Complexity of results
- Likelihood of identifying results of uncertain clinical significance
- Potential for misinterpretation of results

1. Norquist et al. JAMA Oncol. 2016;2(4):482-490
2. SGO Clinical Practice Statement: SGO Clinical Practice Statement: Next Generation Cancer Gene Panels Versus Gene by Gene Testing. Available at: https://www.sgo.org/clinical-practice/guidelines/next-generation-cancer-gene-panels-versus-gene-by-gene-testing/. Accessed August 1, 2016.

Direct HRD/LOH Assays[a]

myChoice®

(CDx olaparib, niraparib, veliparib)



Loss of Heterozygosity (LOH) + Telomeric Allelic Imbalance (TAI) + Large-Scale State Transitions (LST) = myChoice "GIS" Score

Homologous recombination status is determined by Genomic Instability Score:

- **HR-deficient tumors:** tissue GIS ≥42 ***or*** a *BRCA* mutation
- **HR-proficient tumors:** tissue GIS <42
- HR not determined

FoundationOne® LOH

(CDx rucaparib)

Loss of Heterozygosity (LOH)

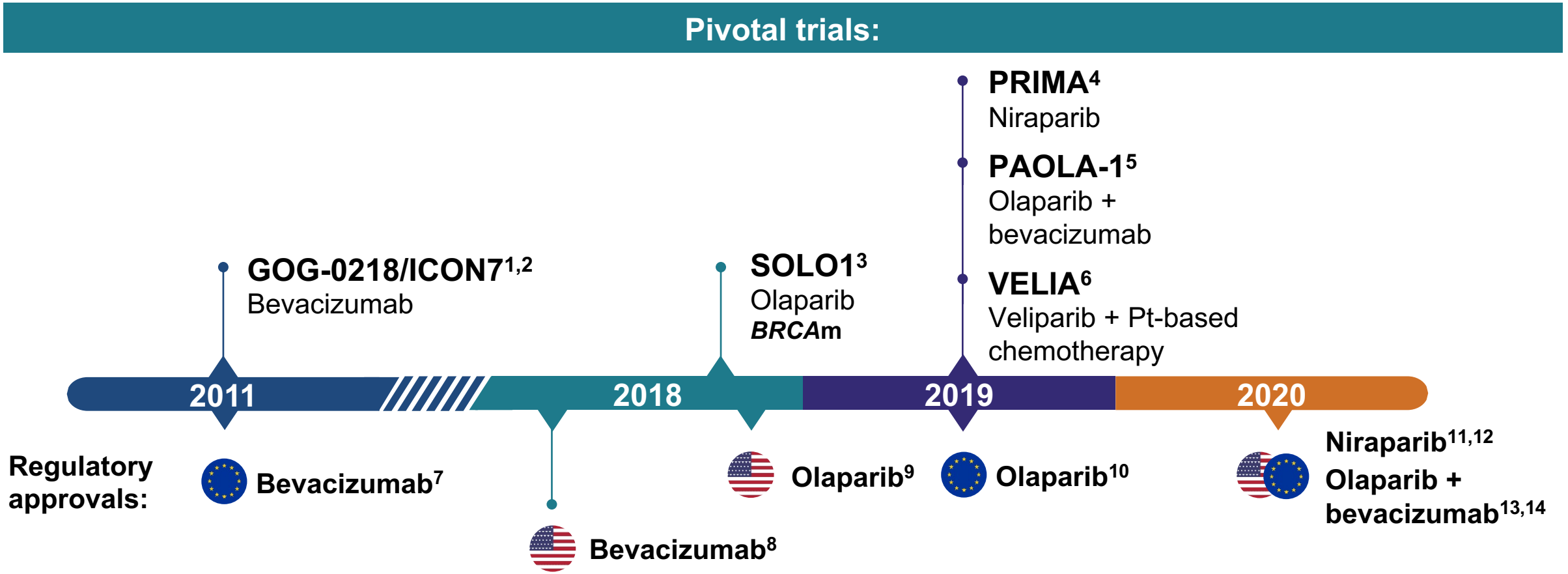
Indirect HRD/LOH

Deleterious alteration in HRD genes

- Germline or somatic (eg, *BRCA*mut by definition is HRD)

[a] Test have not been compared head to head. Paired with development of respective drugs.

Pivotal trials and regulatory milestones in 1L maintenance therapy of advanced ovarian cancer



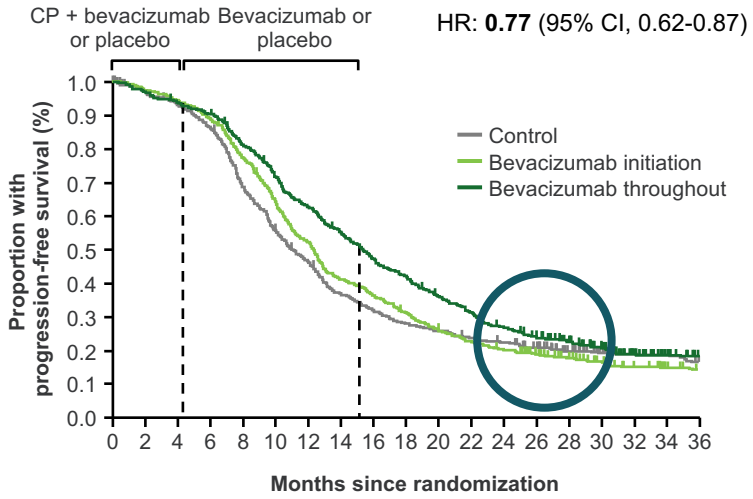
Dates shown indicate the year of the publication of the pivotal studies and regulatory approvals for these compounds.

1L, first line; *BRCA*m, breast cancer gene mutant; GOG, Gynecologic Oncology Group; Pt, platinum.

1. Burger RA et al. *N Engl J Med*. 2011;365(26):2473-2483. **2.** Perren TJ et al. *N Engl J Med*. 2011;365(26):2484-2496. **3.** Moore K et al. *N Engl J Med*. 2018;379(26):2495-2505. **4.** González-Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. **5.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416-2428. **6.** Coleman RL et al. *N Engl J Med*. 2019;381(25):2403-2415. **7.** European Medicines Agency. Published September 22, 2011. Accessed June 7, 2021. **8.** F. Hoffmann-La Roche Ltd. Published June 13, 2018. Accessed June 7, 2021. **9.** US Food and Drug Administration. Published December 26, 2018. Accessed June 7, 2021. **10.** European Medicines Agency. Published April 26, 2019. Accessed June 7, 2021. **11.** GlaxoSmithKline. Published April 29, 2020. Accessed June 7, 2021. **12.** GlaxoSmithKline. Published October 29, 2020. Accessed June 7, 2021. **13.** US Food and Drug Administration. Published May 11, 2020. Accessed June 7, 2021. **14.** European Medicines Agency. Published September 17, 2020. Accessed June 7, 2021.

PARP inhibitors are changing the course of disease progression in patients with advanced ovarian cancer

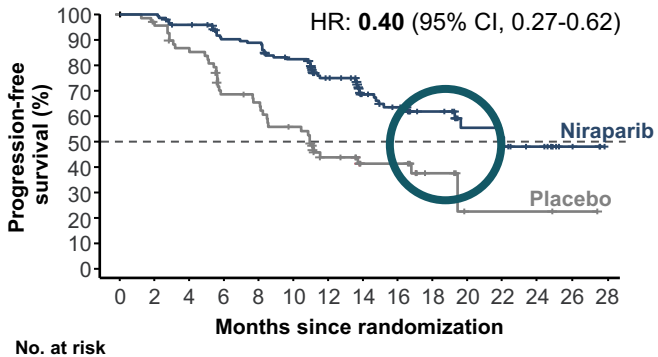
GOG-0218[1]



No. at risk							
Control	625	535	283	169	133	78	49
Bevacizumab initiation	625	552	319	190	121	67	40
Bevacizumab throughout	623	559	386	256	162	97	56

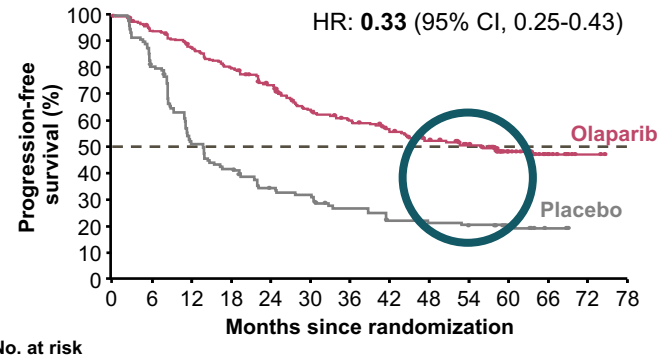
PARP inhibitors

PRIMA: HRd *BRCA*m[2]



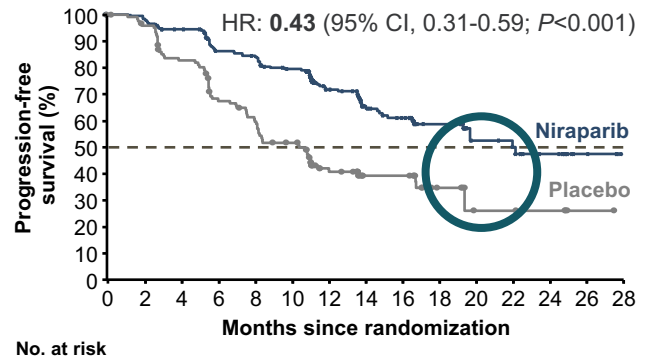
No. at risk														
Niraparib	152	148	140	127	125	113	77	55	48	29	15	14	10	4
Placebo	71	65	57	44	41	34	21	14	14	7	2	2	2	1

SOLO1: *BRCA*m[4]



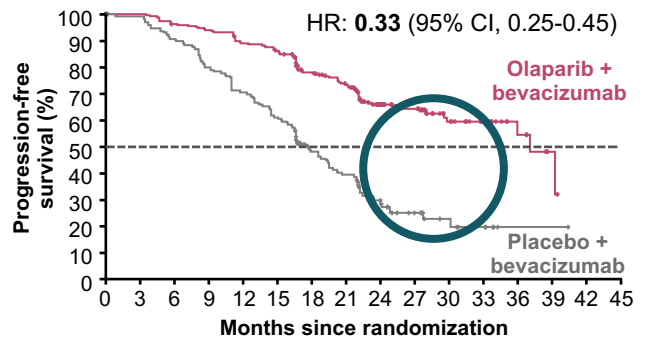
No. at risk														
Olaparib	260	229	212	194	173	140	129	115	101	91	58	30	2	0
Placebo	131	103	65	53	41	38	30	24	23	22	16	3	0	0

PRIMA: HRd[3]



No. at risk														
Niraparib	247	231	215	189	184	168	111	76	66	42	22	19	13	4	0
Placebo	126	117	99	79	70	57	34	21	21	11	5	5	4	1	0

PAOLA-1: HRd[5]



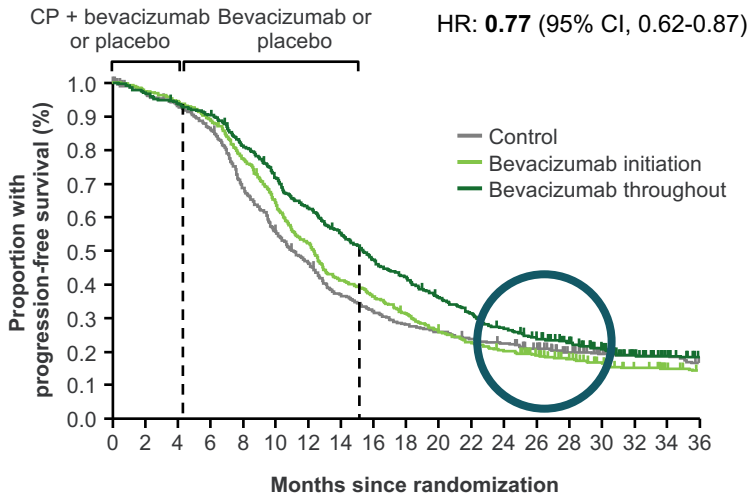
No. at risk														
Olaparib + bevacizumab	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo + bevacizumab	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

1. Burger RA et al. *N Engl J Med.* 2011;365(26):2473-2483. **2.** Monk BJ et al. Presented at: SGO Annual Meeting; March 29, 2020. Presentation 31. **3.** González Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. **4.** Banerjee S et al. Presented at: ESMO Virtual Congress; September 19-21, 2020. Presentation 811MO. **5.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416-2428.

PARP inhibitors are changing the course of disease progression in patients with advanced ovarian cancer : HRp

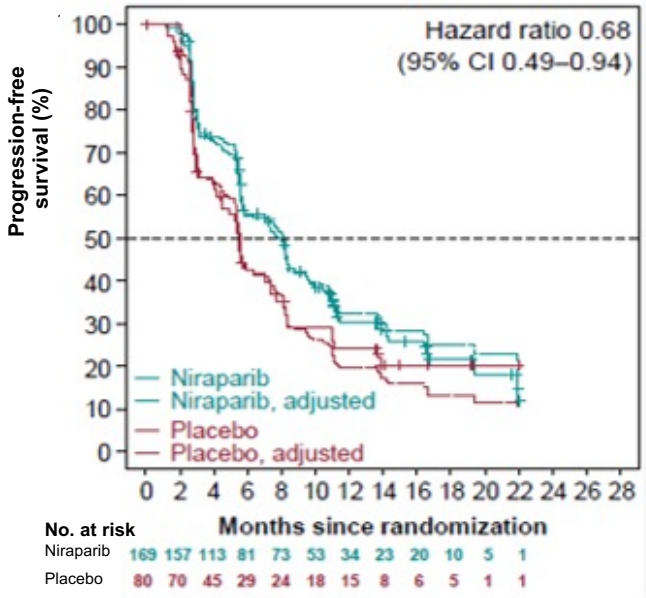
PARP inhibitors

GOG-0218[1]

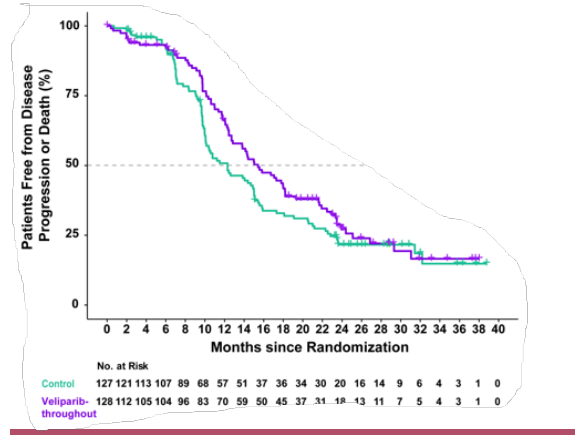


No. at risk							
Control	625	535	283	169	133	78	49
Bevacizumab initiation	625	552	319	190	121	67	40
Bevacizumab throughout	623	559	386	256	162	97	56

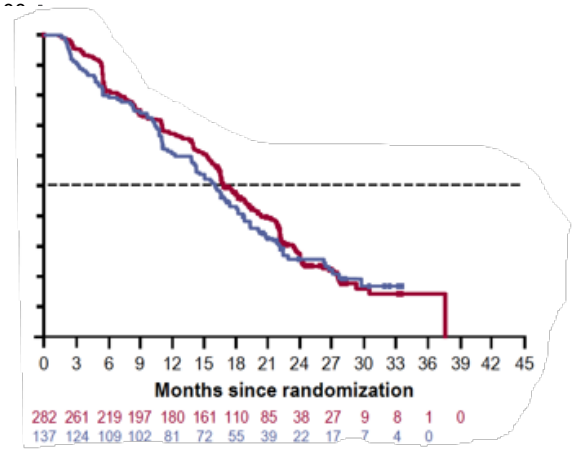
PRIMA: HRp [2]



VELIA: *HRp*[4]



PAOLA-1: HRp[5]



1. Burger RA et al. *N Engl J Med.* 2011;365(26):2473-2483. **2.** Monk BJ et al. Presented at: SGO Annual Meeting; March 29, 2020. Presentation 31. **3.** González Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. **4.** Coleman et al. N Engl J Med. 2019: 381(25): 2403. **5.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416-2428.

Niraparib and bevacizumab in high-risk patients has comparable efficacy with other 1L maintenance treatment trials

OVARIO: PFS rate at 6, 12, and 18 months				
Parameter	**Overall N=105**	**HRd n=49**	**HRp n=38**	**HRnd n=18**
Events at 6 months, n	11	1	7	3
6-month PFS rate, % (95% CI)	90 (82-95)	98 (89-100)	82 (66-92)	83 (59-96)
Events at 12 months, n	26	6	13	7
12-month PFS rate, % (95% CI)	75 (66-83)	88 (75-95)	66 (49-80)	61 (36-83)
Events at 18 months, n	40	12	20	8
18-month PFS rate, % (95% CI)	62 (52-71)	76 (61-87)	47 (31-64)	56 (31-78)

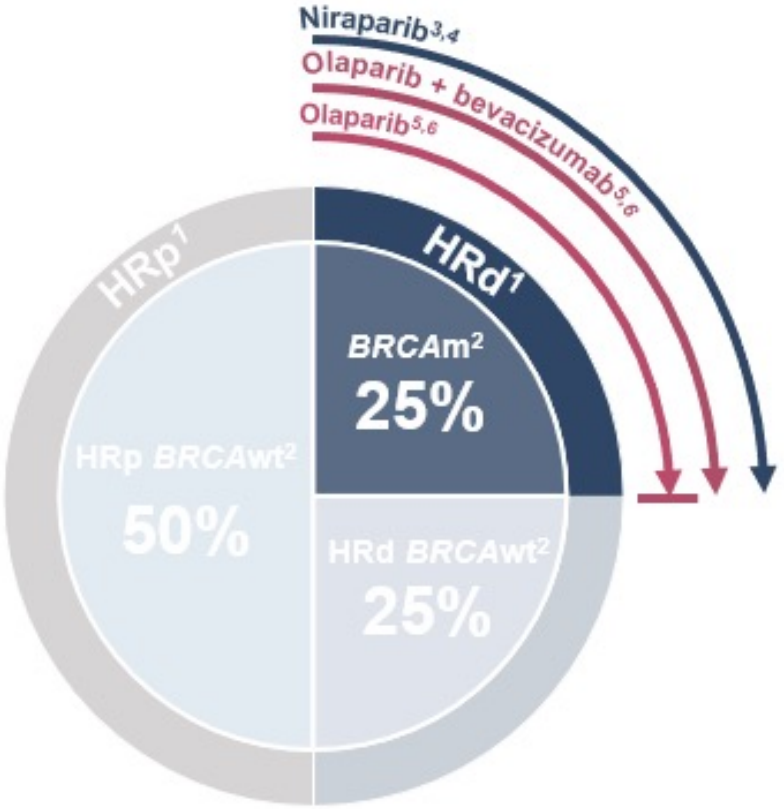
- OVARIO is a phase II single-arm study of niraparib + bevacizumab therapy in advanced ovarian cancer following frontline platinum-based chemotherapy with bevacizumab
- The study enrolled a high-risk population of patients with OC (N=105); despite the high-risk population, results were favorable compared with other upfront maintenance treatment trials
- At the 18-month analysis, 62% of patients in the overall population remained progression free
- The safety of niraparib + bevacizumab was consistent with the known side effects of each drug as monotherapy; **no new safety signals were observed**

Dosing: Niraparib (200 or 300 mg QD) + bevacizumab (15 mg/kg Q3W).
The 6-,12-, and 18-month PFS efficacy population (N=105) includes all OVARIO patients dosed ≥6, ≥12, and ≥18 months, from the data cutoff dates of August 14, 2019; February 14, 2020; and August 14, 2020 (last patient enrolled February 14, 2019). Median follow-up was 8.6, 12.8, and 16.0 months.

CI, confidence interval; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; n, number of patients; OC, ovarian cancer; PARPi, poly(ADP-ribose polymerase) inhibitor; PFS, progression-free survival.

Hardesty MM et al. Poster presented at: SGO Virtual Congress; March 19-25, 2021. Poster 22.

PARP inhibitors are available for 1L maintenance therapy across biomarker subgroups



*BRCA*m/HRd

Niraparib (PRIMA)[3,4,7]

HR: 0.40 (95% CI, 0.27-0.62)

Olaparib + bevacizumab (PAOLA-1)[5,6,8]

HR: 0.31 (95% CI, 0.20-0.47)

Olaparib (SOLO1)[5,6,9]

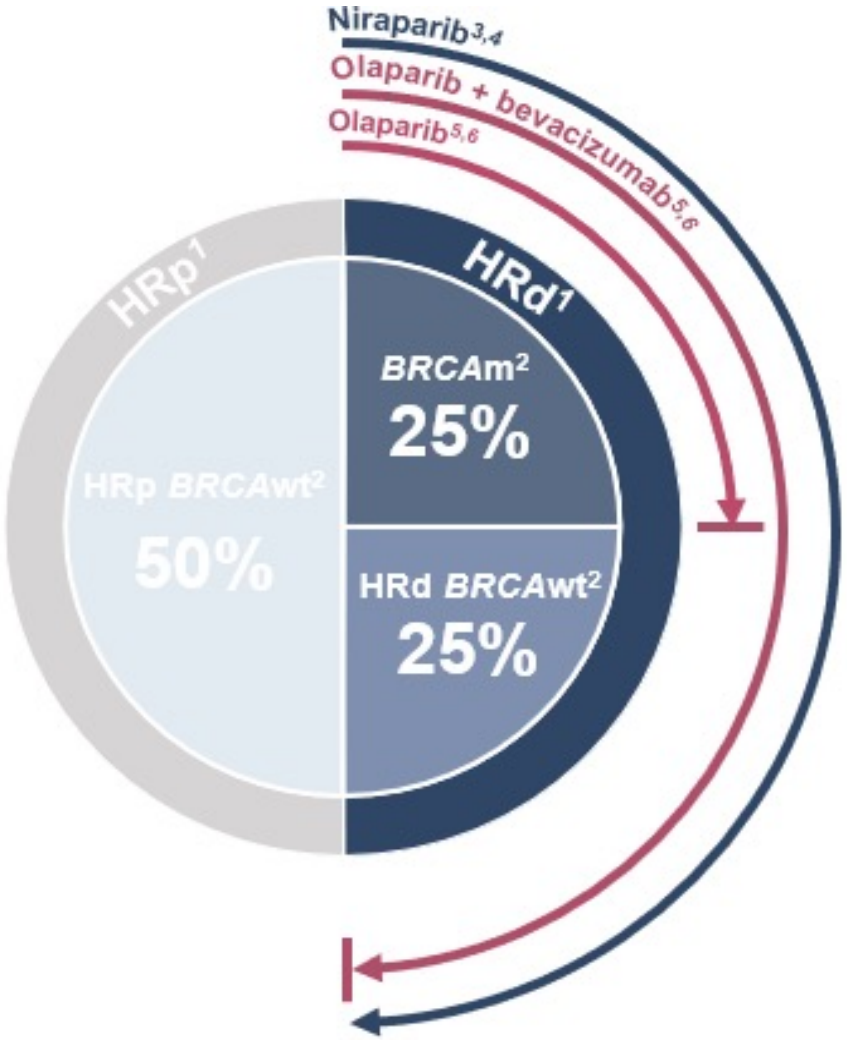
HR: 0.33 (95% CI, 0.25-0.43)

Percentages denote proportion of patients with genomic mutations in ovarian cancer.[2]

1L, first line; *BRCA*m, breast cancer gene mutant; *BRCA*wt, breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PARP, poly (ADP-ribose) polymerase.

1. The Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-615. **2.** Pennington KP et al. *Clin Cancer Res*. 2014;20(3):764-775. **3.** ZEJULA. Summary of Product Characteristics. GlaxoSmithKline (Ireland) Ltd; 2021. **4.** ZEJULA. Prescribing Information. GlaxoSmithKline; 2021. **5.** Lynparza. Prescribing Information. AstraZeneca Pharmaceuticals LP; 2021. **6.** Lynparza. Summary of Product Characteristics. AstraZeneca AB; 2021. **7.** González-Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. **8.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(5):2416-2428. **9.** Banerjee S et al. Presented at: ESMO Virtual Congress; September 19-21, 2020. Presentation 811MO.

PARP inhibitors are available for 1L maintenance therapy across biomarker subgroups



HRd

Niraparib (PRIMA)[3,4,7]

HR: 0.43 (95% CI, 0.31-0.59; *P*<0.001)

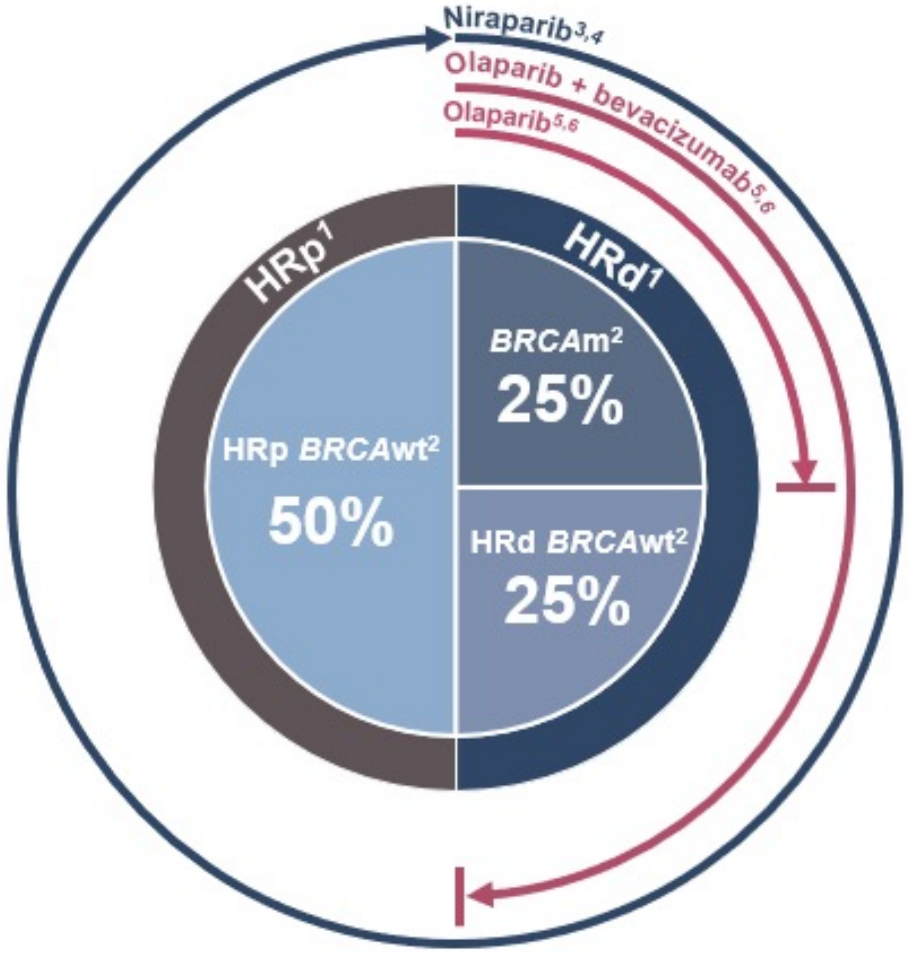
Olaparib + bevacizumab (PAOLA-1)[5,6,8]

HR: 0.33 (95% CI, 0.25-0.45)

1L, first line; *BRCA*m, breast cancer gene mutant; *BRCA*wt, breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PARP, poly (ADP-ribose) polymerase.

1. The Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-615. **2.** Pennington KP et al. *Clin Cancer Res*. 2014;20(3):764-775. **3.** ZEJULA. Summary of Product Characteristics. GlaxoSmithKline (Ireland) Ltd; 2021. **4.** ZEJULA. Prescribing Information. GlaxoSmithKline; 2021. **5.** Lynparza. Prescribing Information. AstraZeneca Pharmaceuticals LP; 2021. **6.** Lynparza. Summary of Product Characteristics. AstraZeneca AB; 2021. **7.** González-Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. **8.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(5):2416-2428.

PARP inhibitors are available for 1L maintenance therapy across biomarker subgroups



All biomarker subgroups

Niraparib (PRIMA)[3,4,7]

HR: 0.62 (95% CI, 0.50-0.76; *P*<0.001)

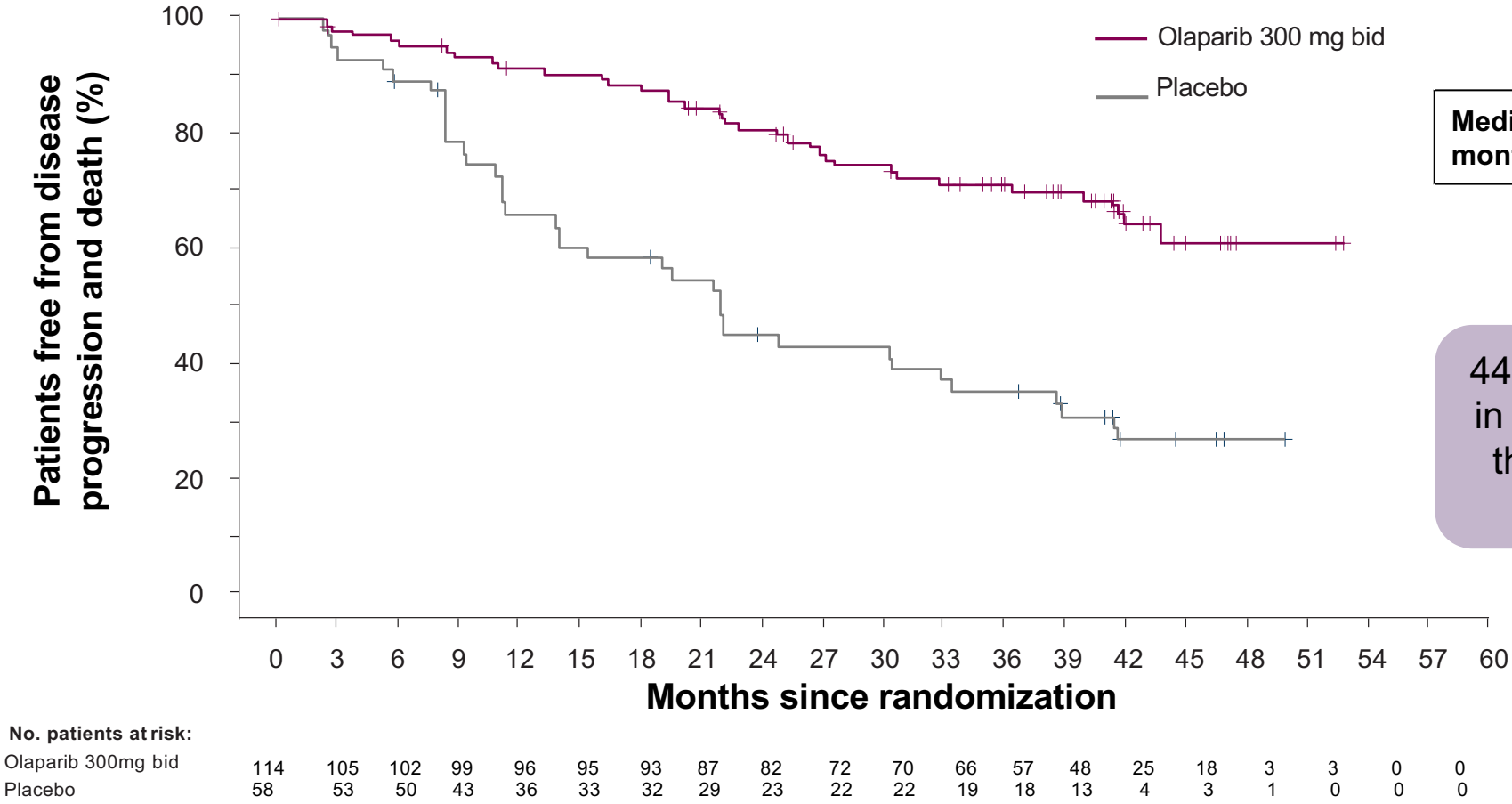
Percentages denote proportion of patients with genomic mutations in ovarian cancer.[2]

1L, first line; *BRCA*m, breast cancer gene mutant; *BRCA*wt, breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PARP, poly (ADP-ribose) polymerase.

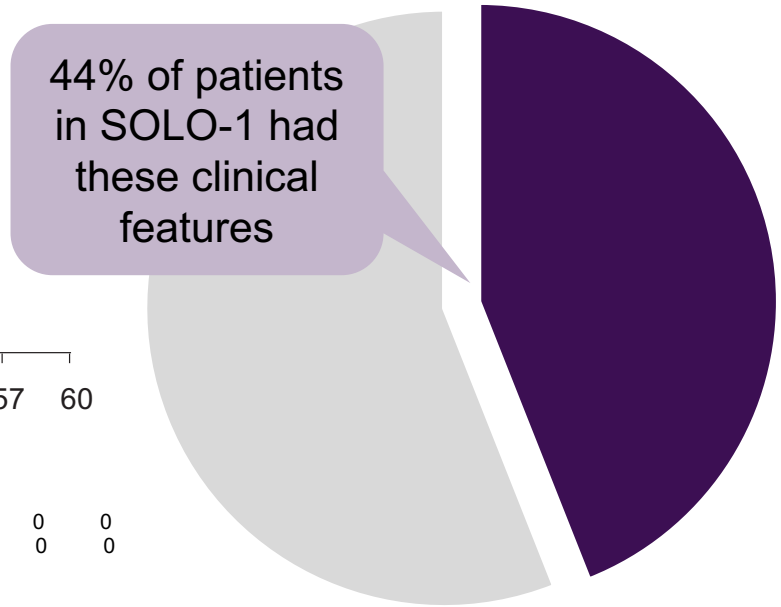
1. The Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-615. **2.** Pennington KP et al. *Clin Cancer Res*. 2014;20(3):764-775. **3.** ZEJULA. Summary of Product Characteristics. GlaxoSmithKline (Ireland) Ltd; 2021. **4.** ZEJULA. Prescribing Information. GlaxoSmithKline; 2021. **5.** Lynparza. Prescribing Information. AstraZeneca Pharmaceuticals LP; 2021. **6.** Lynparza. Summary of Product Characteristics. AstraZeneca AB; 2021. **7.** González-Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402.

SOLO1: PFS was improved with olaparib in stage III patients who underwent upfront surgery and had no residual disease

This population has been excluded from a number of contemporary first line trials[2,3]



	Olaparib (N=114)	Placebo (N=58)
Median PFS, months	NR	21.9
	HR = 0.32 95% CI: 0.20–0.51	



bid=twice daily; CI=confidence interval; HR=hazard ratio; NR=not reached; PFS=progression-free survival.

1. Mathews C et al. Poster presented at: 2019 ASCO Annual Meeting; May 31-Jun 4, 2019; Chicago, IL. Poster 5541; 2. Gonzalez-Martin, A. et al. *Ann Oncol.* 2017;28(Suppl_5);
3. Gonzalez-Martin A et al. *Ann Oncol.* 2018;29 viii332-viii358.

Magnitude of Benefit for PARPi Maintenance By Clinical Prognostic Factors

Front Line Ovarian Trials				
Parameter	**SOLO1[3]**	**PAOLA[2]**	**PRIMA**	**VELIA[4]**
Timing of Surgery **pCRS** **iCRS**	HR 0.31 HR 0.37	HR 0.52 HR 0.66	HR 0.66 HR 0.59	HR 0.72 HR 0.64
Residual Disease **NGR** **Residual Dz**	HR 0.33 HR 0.44	HR 0.47-0.61 HR 0.74-0.70	NR	HR 0.60-0.72 HR 0.64-0.77
CR or PR on entry **NED** **CR** **PR**	NR HR 0.34 HR 0.31	HR 0.53 HR 0.44 HR 0.86	NR HR 0.60 HR 0.60	NR
Age **<75** **≥75**		Ref 5 HRD is main independent predictive factor	HR 0.62[1] HR 0.37	HR 0.65 HR 0.77 (< 65)

- Subset analyses from all 4 trials have not shown any subgroups who benefit less from PARPi than others
- Clinical High Risk features (stage, residual disease, timing of surgery) which may identify patients who benefit more from bevacizumab – do not identify patients more likely to benefit from PARPI
- Even patients in the “best” clinical prognostic group (stage III, BRCA, pCRS to NGR) have unprecedented benefit from PARPI. % Cure remains to be seen

1. Valabrega et al. ESMO Virtual Congress 2020. Grimm et al. SGO 2020. 3. Mathews et al. ASCO Poster 5541 2019 4. Coleman et al. NEJM 2019 5. Sabatier et al. ESMO 2021 poster 1990

Case Discussions

A woman in her 50s with Stage IIIB ovarian cancer and a germline BRCA1 mutation is s/p hysterectomy/bilateral salpingo-oophorectomy/omentectomy and 6 cycles of carboplatin/paclitaxel. What would you most likely recommend as maintenance therapy?

1. None
2. Bevacizumab
3. Olaparib
4. Niraparib
5. Olaparib/bevacizumab
6. Other

Dr O' Malley – BRCA1+

- 50s referred for consideration of RRBSO for BRCA1 mutation with personal history of breast cancer (17 years prior). No genetic counseling until 2018
- Converted risk reducing bilateral salpingo-oophorectomy to tumor reduction, hyst/BSO/omentectomy (stage IIIB)
- Completed 6 cycles of Paclitaxel 175 mg/m2 and Carboplatin AUC 5
- 8/2018-8/2020: maintenance Olaparib 300 mg BID (delayed start due to mastectomy)
  - Cycle 4 reduced Olaparib to 250 mg BID (fatigue, nausea, constipation)
  - Cycle 7 reduced Olaparib to 200 mg BID given persistent and worsening fatigue
- NED currently

A 73-year-old woman with ascites and a fixed pelvic mass that are confirmed to be BRCA wild-type, high-grade serous ovarian cancer receives neoadjuvant carboplatin/paclitaxel/bevacizumab and undergoes near-complete gross resection. Tumor testing for HRD is 19%. What would you most likely recommend as maintenance therapy?

1. None
2. Bevacizumab
3. Olaparib
4. Niraparib
5. Olaparib/bevacizumab
6. Other

Dr Coleman: 73-Yr-Old With Primary Ovarian Cancer

- 73-yr-old woman presents with chief complaint of abdominal distension, cough, and pain for >1 mo
- Patient has history of mild hypertension but negative for diabetes, coronary heart disease, depression
- Family history: sister with AML
- Exam significant for decreased breath sounds in right side of chest
- Abdominal distension with fluid wave and ballotable mass; pelvic exam shows nodularity in cul-de-sac and fixed pelvic mass
- Labs: CA-125, 231 U/mL; albumin, 3.3 g/dL

Imaging

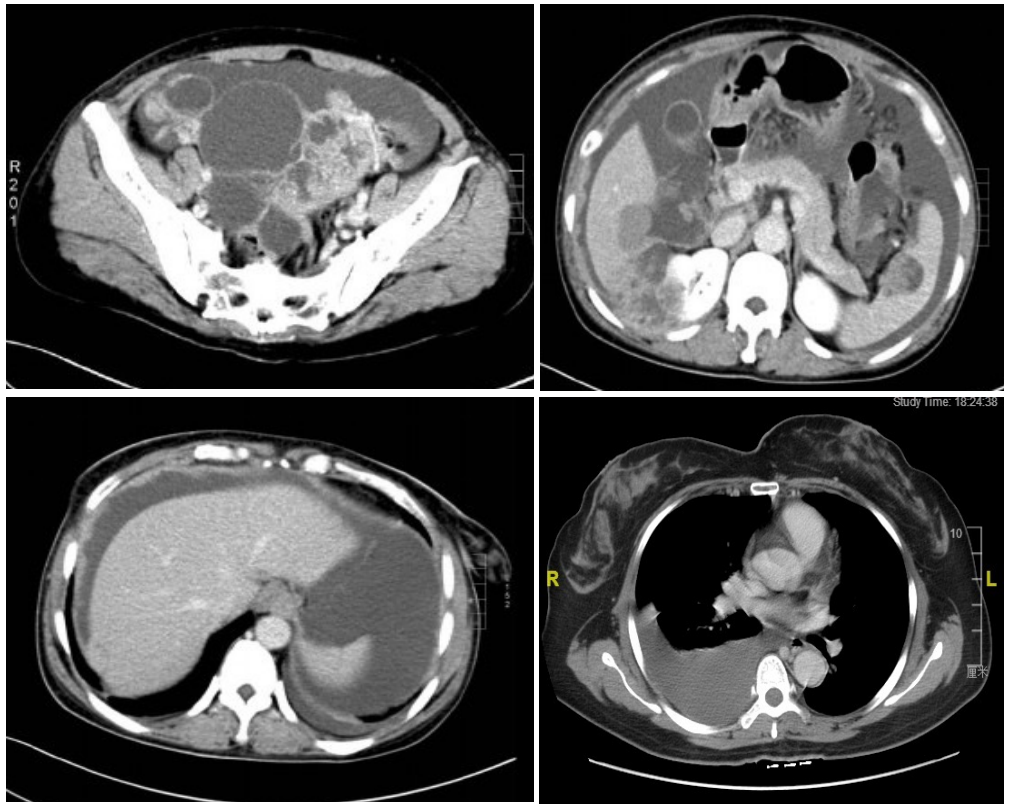


Image courtesy of Dr. Robert L. Coleman, MD, FACOG, FACS, at US Oncology Research, The Woodlands, Texas.

Dr Coleman: Follow-up: 73-Yr-Old With Primary Ovarian Cancer

- Tissue biopsy of omentum confirmed high-grade serous cancer
- Patient started on neoadjuvant paclitaxel/carboplatin + bevacizumab (15 mg/kg)
- During first cycle of therapy, germline panel showed no deleterious mutations in *BRCA1/2*
- Bevacizumab given with cycles 1-2 with good response to fluid collection and tumor volume, but significant disease still present after cycle 3 (no bevacizumab)
- IDS had near-complete gross resection with MRD
- FoundationOne tumor testing for HRD test was 19%, and no somatic *BRCA*mt

Dr Coleman: Follow-up: 73-Yr-Old With Primary Ovarian Cancer

- Add olaparib 300 mg BID to bevacizumab (15mg/kg)
- Cycles 3 and 5 develops Grade 3 anemia supported first by transfusion and second by marrow assessment for dysplasia, transfusion, delay and dose reduction
- All treatment suspended at 12 months with rising CA-125 (256 U/mL) and new disease on imaging
- Initiated PLD/Carboplatin (2^{nd} line)

Module 2: Treatment of Recurrent OC; Ongoing Research Efforts with PARP Inhibitors for Newly Diagnosed and Relapsed Disease — Dr O'Malley

Treatment of Recurrent OC - Ongoing Research Efforts with PARP Inhibitors for Newly Diagnosed and Relapsed Disease

David O'Malley, MD
Professor
Division Director, Gynecologic Oncology
Co-Director, Gyn Oncology Phase I Program

The James

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Creating a cancer-free world. One person, one discovery at a time.




Dr O'Malley — Disclosures

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Personal Fees	Agenus Inc, Myriad Genetic Laboratories Inc, Rubis, Tarveda Therapeutics

RTP
RESEARCH TO PRACTICE

The Era of Targeted Therapy in Ovarian Cancer

Drug	Maintenance	Later-line Treatment
Olaparib [1]	**SOLO-2 (*BRCA* mut)** **Study 19** *(Aug 17, 2017)* **SOLO-1 (*BRCA* mut)** *(Dec 19, 2018)* **With Bev** **PAOLA-1 (*HRD*)** *(May 8, 2020)*	**Study 42 (*BRCA* mut)** *(Dec 19, 2014)*
Rucaparib [2,3]	**ARIEL3** *(April 6, 2018)*	**Study 10 (*BRCA* mut)** **ARIEL2 (*BRCA* mut)** *(Dec 19, 2016)*
Niraparib [4]	**NOVA** *(Mar 27, 2017)* **PRIMA** *(April 29, 2020)*	**QUADRA** (Oct 23, 2019)
Bevacizumab[5]	**GOG218** *(June 13, 2018)* **OCEANS – GOG213** *(Dec 6, 2016)*	**AURELIA** *(Nov 14, 2014)*

1. Olaparib package insert. AstraZeneca Pharmaceuticals LP; 2020.
2. FDA. Summary Review for Regulatory Action: Olaparib. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000SumR.pdf. Approval date December 19, 2014. Accessed April 10, 2018.
3. Rucaparib package insert. Clovis Oncology, Inc; April 2018.
4. Niraparib package insert. TESARO, Inc; August 2020.
5. https://www.drugs.com/history/avastin.html

Platinum Sensitive – Maintenance

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Maintenance PFS in PSOC

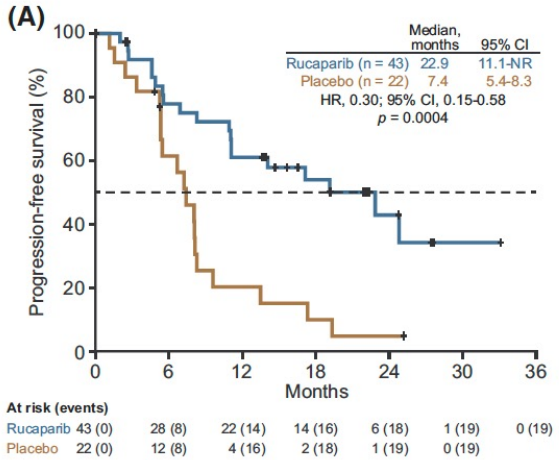
PFS (inv Review – Primary)	Rucaparib	Placebo	HR	P
tBRCA	16.8	5.4	**0.23**	P<0.0001
tBRCA + HRD	13.6	5.4	**0.32**	P<0.0001
ITT	10.8	5.4	**0.37**	P<0.0001
HRD (LOH-H) BRCAwt	11.1	5.6	**0.55**	p=0.0135
HRP (LOH-L) BRCAwt	8.2	5.3	**0.47**	p=0.0002
PFS (BICR – Primary)	**Niraparib**	**Placebo**	**HR**	**P**
tBRCA	21.0	5.5	**0.26**	P<0.0001
tBRCA + HRD	-	-	**-**	
All non-gBRCA (*sBRCA*+ HRD + HRP)	9.3	3.9	**0.45**	P<0.001
ITT (FDA analysis)	11.3	4.7	**0.42**	Not Given
HRD gBRCAwt	12.9	3.9	**0.38**	P<0.001
HRP gBRCAwt	6.9	3.8	**0.58**	p=0.02
PFS (Inv Review - Primary)	**Olaparib**	**Placebo**	**HR**	**P**
gBRCA	19.1	5.5	**0.30**	P<0.0001
PFS (Inv Review)	**Bev**	**Placebo**		
ITT (chemo + maintenance)	13.8	10.4	**0.63**	P<0.0001

1. Coleman RL, Lancet Oncol. 2017 Jun;18(6):779-791. 2. Burger RA, et al. *N Engl J Med.* 2011;365(26):2473-2483. 3. González-Martín A, et al. *N Engl J Med.* 2019;381:2391-2402. 4. Ray-Coquard IL, et al. *N Engl J Med*. 2019: doi: 10.1056/NEJMoa1911361. 5. Banerjee S, et al. Presented at: ESMO Congress; September 19-20, 2020; virtual meeting. Abstract 811MO.

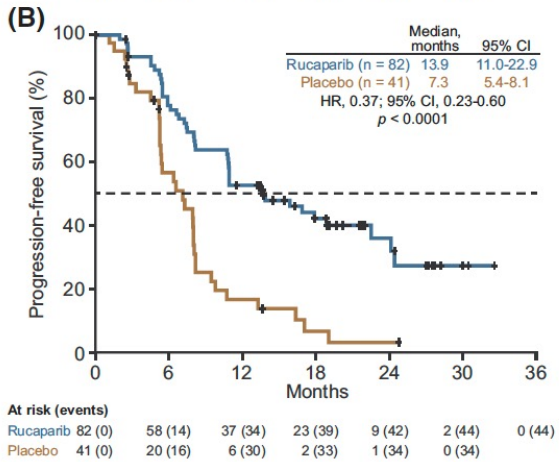
Which PSOC patients should be treated with PARPi maintenance?

- Exploratory Analysis of ARIEL3
- Effects of Best Response to last platinum-based therapy

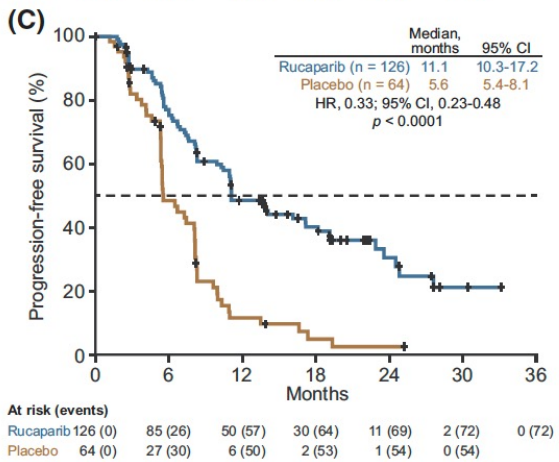
CR - BRCA



CR - HRD



CR - ITT

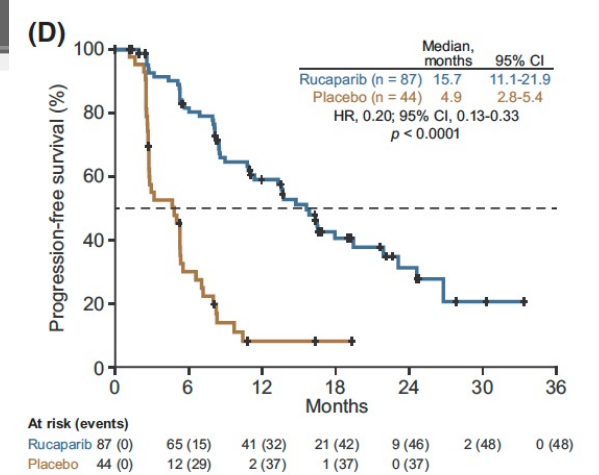


Oaknin et al. Cancer Med. 2021 Oct;10(20):7162-7173

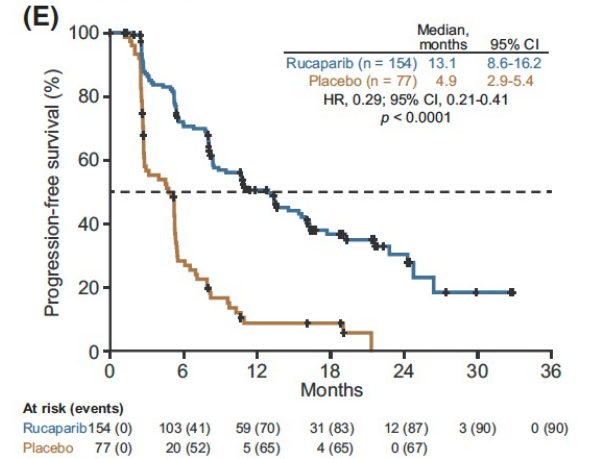
Which PSOC patients should be treated with PARPi maintenance?

- Exploratory Analysis of ARIEL3
- Effects of Best Response to last platinum-based therapy

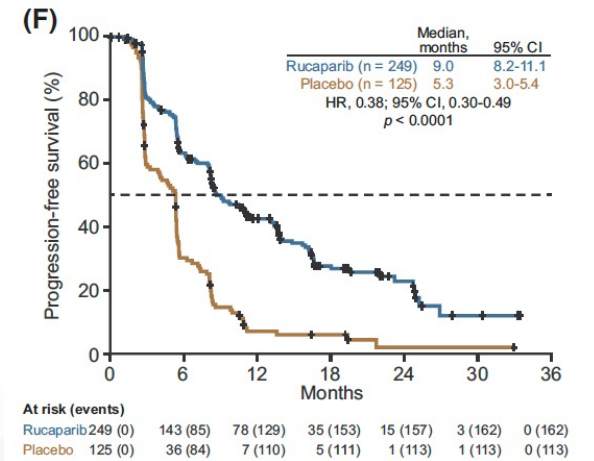
PR - BRCA



PR - HRD

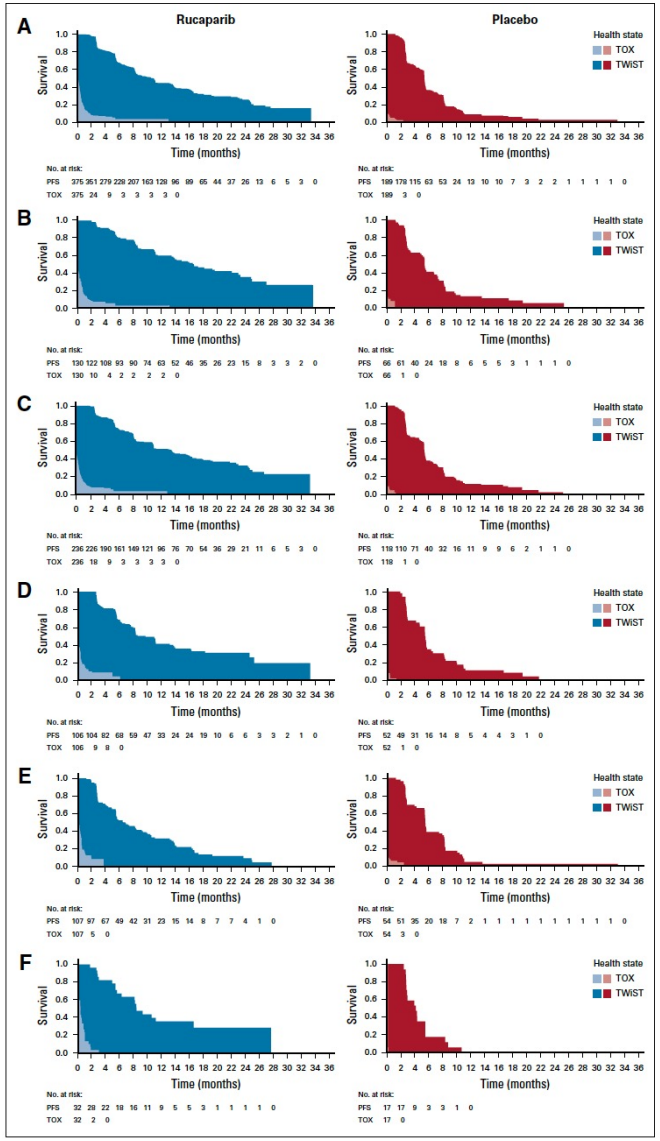


PR - ITT



Oaknin et al. Cancer Med. 2021 Oct;10(20):7162-7173

PARPi Maintenance Therapy in PSOC – Patient Reported Outcomes



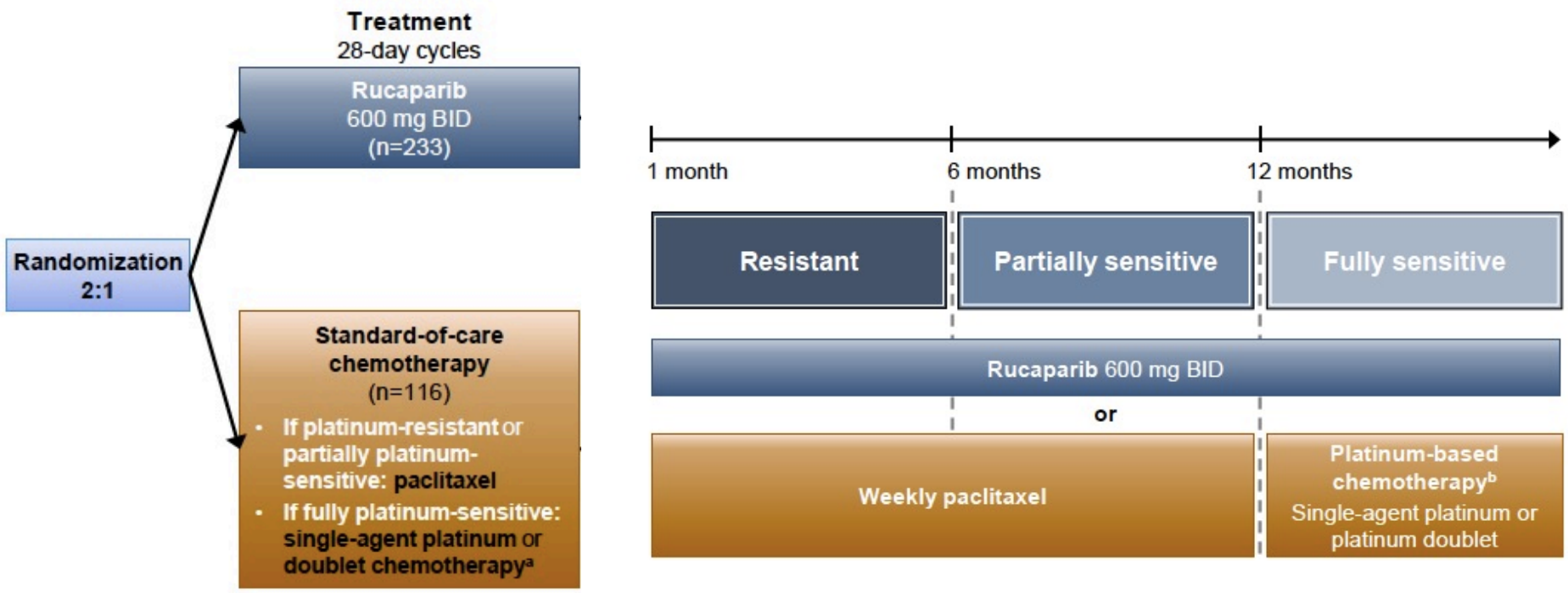
- BRCA
- HRD
- ITT
- LOH-H/BRCAwt
- LOH-L/BRCAwt
- LOH indeterminate/BRCAwt

Oza et al; J Clin Oncol. 2020 Oct 20;38(30):3494-3505

PSOC Recurrent Ovarian Cancer – Treatment Considerations

- Consideration for all PSOC patients who have not previously been exposed to PARPi
  - Clinical Factors versus Molecular Findings
    - BRCA/RAD51 mutated
    - Markedly Platinum Sensitive
      - CR>>>PR>>>>>>>stable disease
    - HRD/GIS
- Curative intent is no longer the goal – Prevention of symptoms and improved PROs
- Management of Toxicity is essential

ARIEL4: Trial eligibility and Design

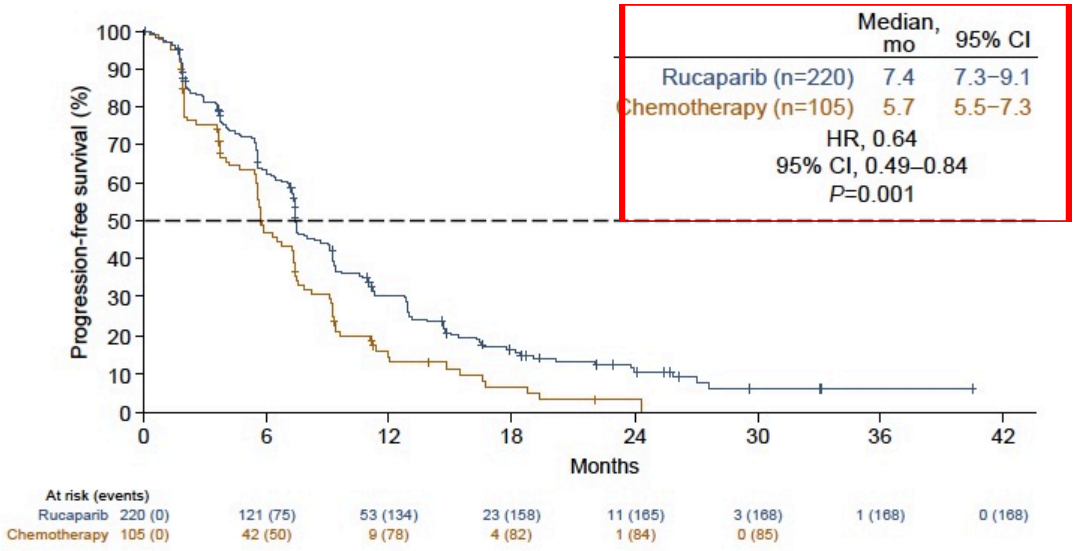


ARIEL4 Eligibility:
Recurrent *BRCA* mutated ovarian cancer
No prior PARP inhibitor or single agent paclitaxel treatment
≥ 2 prior chemotherapy regimens and ≥ 1 platinum regimen

Kristeleit et al SGO 2021

Primary Endpoint – Investigator-assessed PFS: Efficacy Population

PFS better in rucaparib arm



ORR: Rucaparib comparable to Chemotherapy

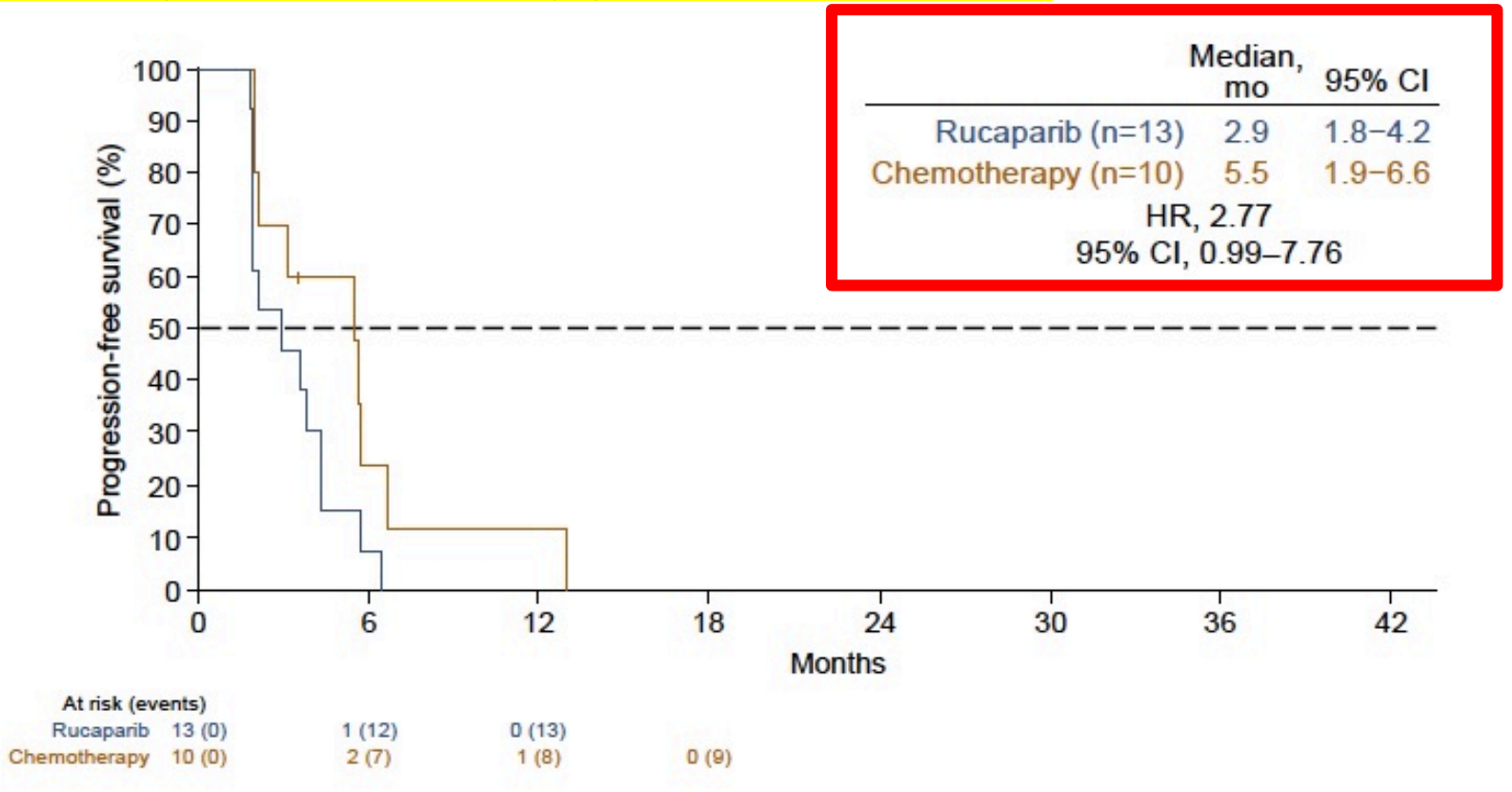
	Rucaparib	Chemotherapy
RECIST ORR, n/N (%) [95% CI][a]	85/211 (40.3) [33.6–47.2]	31/96 (32.3) [23.1–42.6]
	P=0.13[b]	

Kristeleit et al SGO 2021

ARIEL4

BRCA Reversion Mutation Subgroup

PFS longer in chemotherapy group versus rucaparib



Kristeleit et al SGO 2021

PARP Inhibitors in Ovarian Cancer

Parameter	Niraparib	Rucaparib	Olaparib
First line Maintenance after CR/PR on platinum-based chemotherapy	✓	✗	BRCAm (germline or somatic) with BEV in HRD ✓
Platinum Sensitive Maintenance after CR/PR on platinum-based chemotherapy	✓	✓	✓
3rd line **Treatment**	✗	BRCAm (germline or somatic) ✓	✗
4th + line **Treatment**	*BRCA*m, or genomic instability **and** progression >6 mo after response to the last platinum-based chemotherapy ✓	*BRCA*m (germline or somatic) ✓	*BRCA*m (germline or somatic) ✓
Blood labs	• Weekly for the first month • Monthly for the next 11 months	• Monthly during treatment	• Monthly during treatment

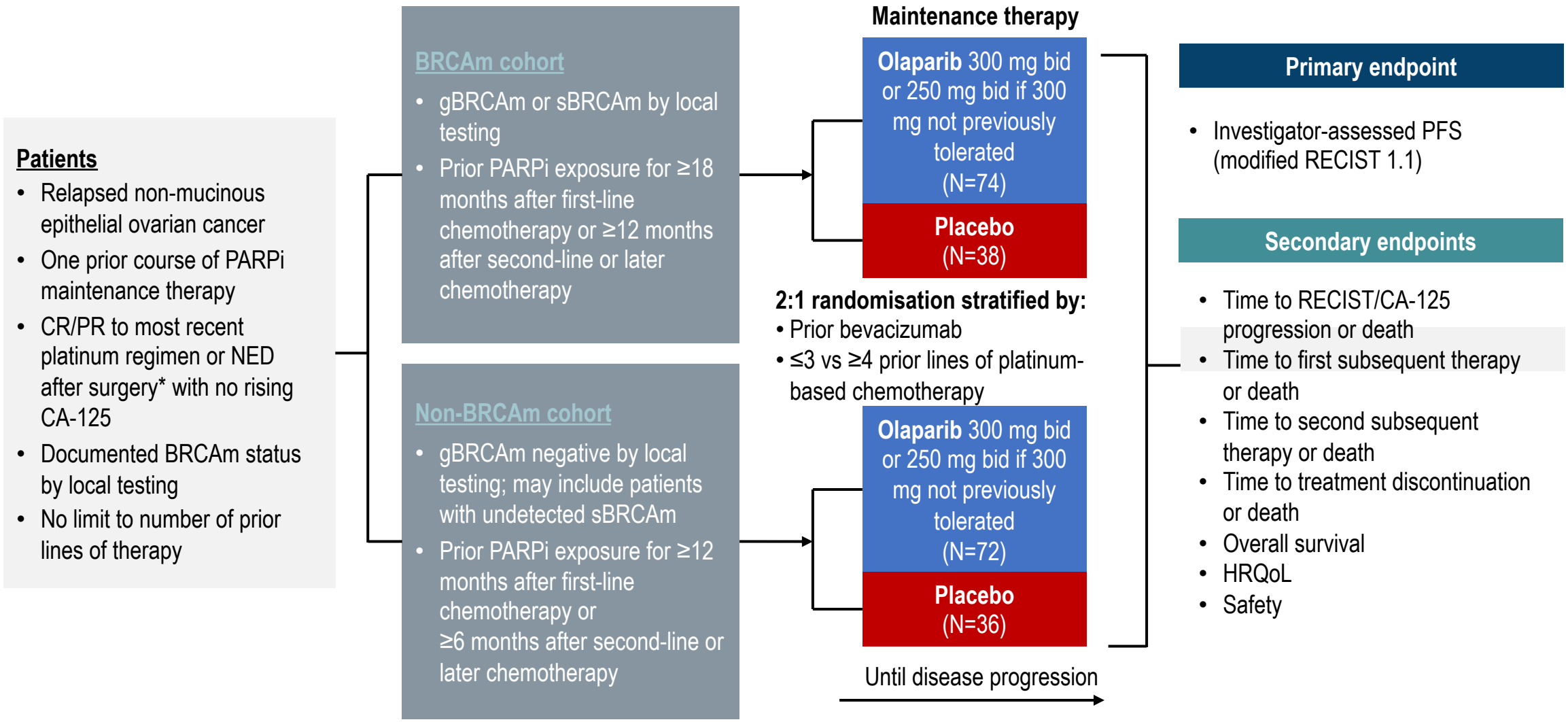
USPI for ZEJULA®. GlaxoSmithKline. Research Triangle Park, NC. USA. 2020; USPI for RUBRACA®. Clovis Oncology. Boulder, CO, USA. 2018; USPI for LYNPARZA®. AstraZeneca. Wilmington, DL, USA. 2019.

PARPi after PARPi

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

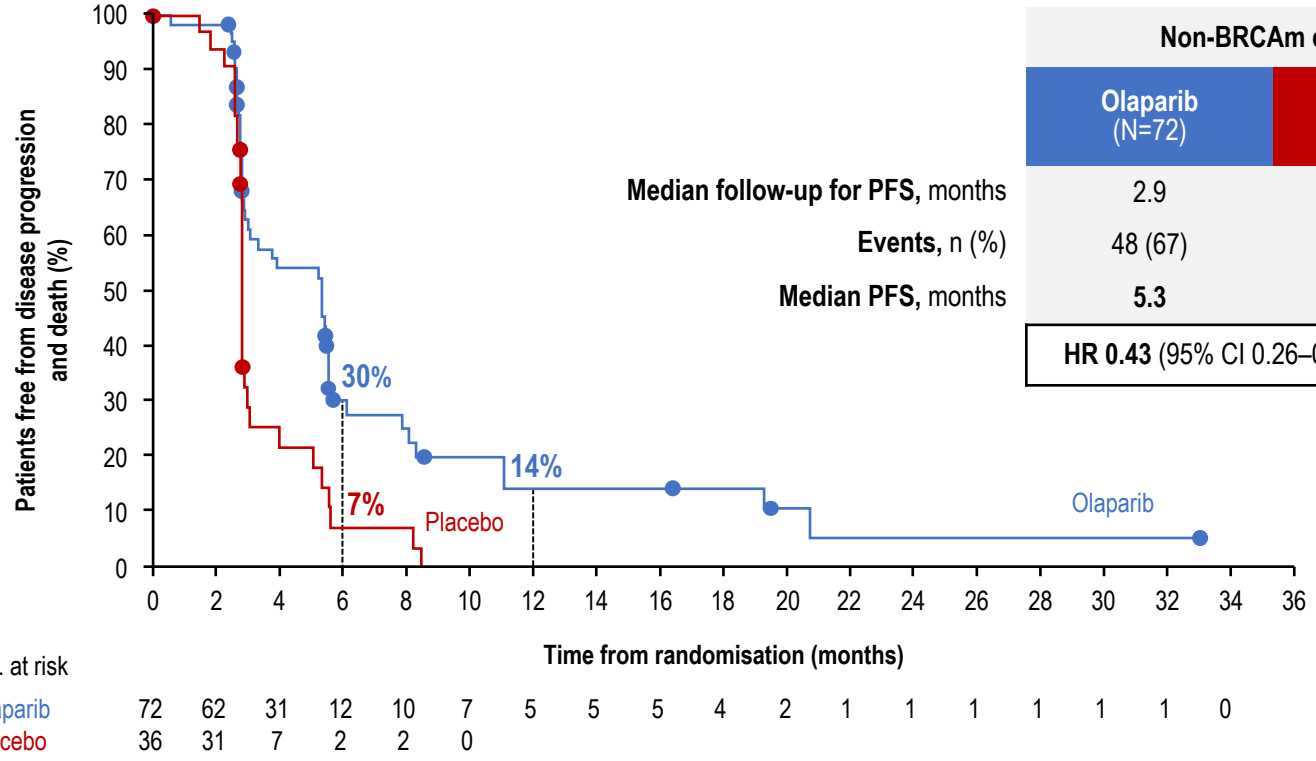
OREO Study design



Eric Pujade-Lauraine, et al ESMO 2021

A statistically significant PFS benefit was observed with olaparib in the non-BRCAm cohort

A proportion of patients derived clinically relevant long-term benefit

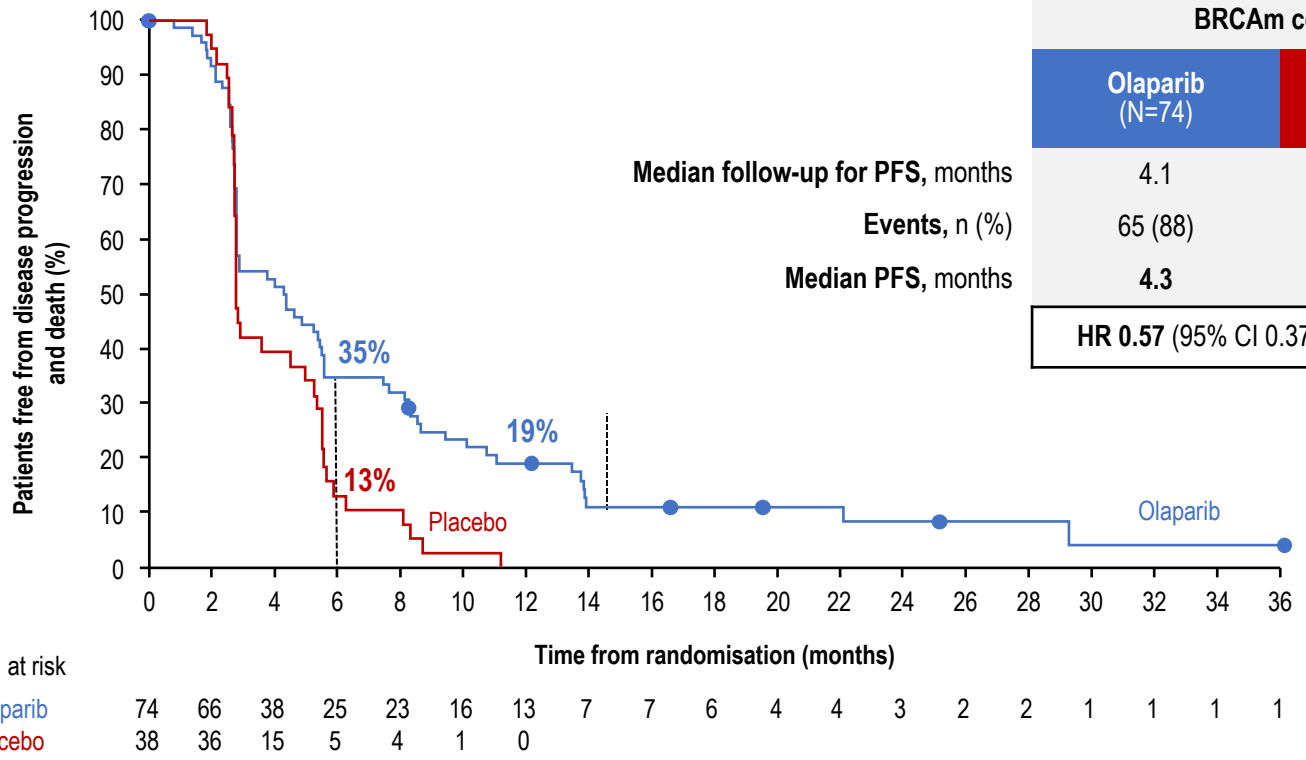


Non-BRCAm cohort	Olaparib (N=72)	Placebo (N=36)
Median follow-up for PFS, months	2.9	2.8
Events, n (%)	48 (67)	30 (83)
Median PFS, months	**5.3**	**2.8**
HR 0.43 (95% CI 0.26–0.71); *P*=0.0023		

Eric Pujade-Lauraine, et al ESMO 2021

A statistically significant PFS benefit was observed with olaparib in the BRCAm cohort

A proportion of patients derived clinically relevant long-term benefit



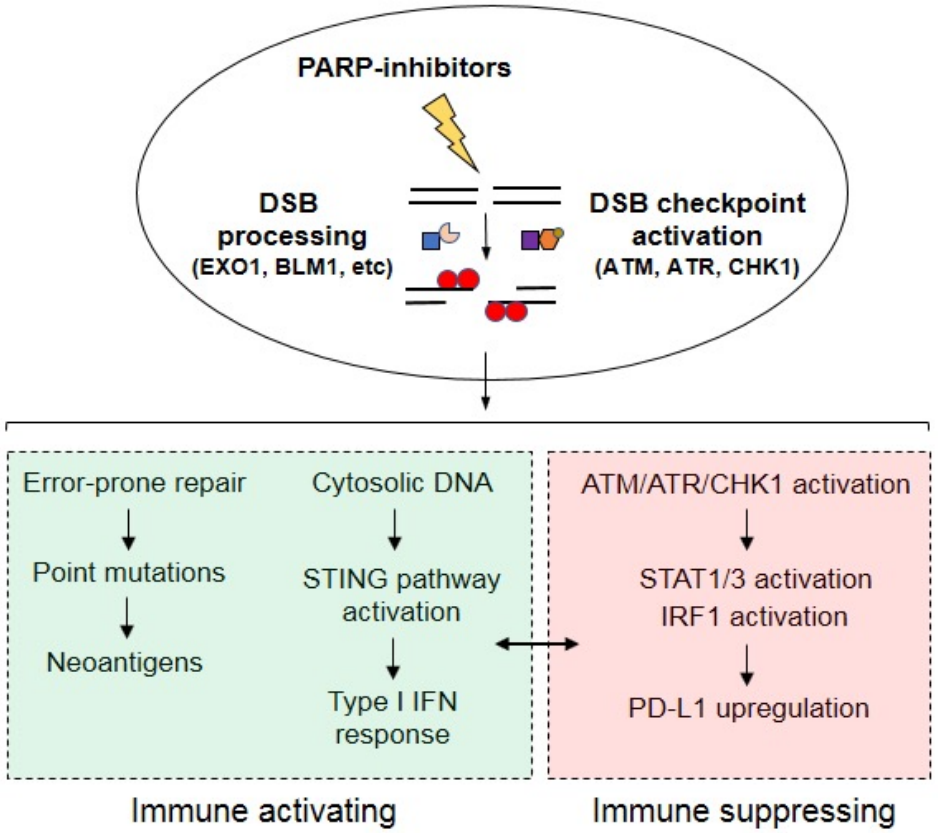
BRCAm cohort	Olaparib (N=74)	Placebo (N=38)
Median follow-up for PFS, months	4.1	2.8
Events, n (%)	65 (88)	38 (100)
Median PFS, months	**4.3**	**2.8**
HR 0.57 (95% CI 0.37–0.87); *P*=0.022		

Eric Pujade-Lauraine, et al ESMO 2021

Rationale for Combination Treatment: Immune Checkpoint Inhibitors and PARP Inhibitors

- BRCA1/2 and other HRD mutations lead to an increased antigenic load
  - Mutations create tumor-specific antigens or “neoepitopes” targeted by the immune response
  - Increased mutational load correlated with increased benefit from immune checkpoint blockade
- Patient population that responds to a PARPi and a PD-(L)1 antibody may significantly overlap, ie, PARPi responsive may = PD-(L)1 responsive
  - Supported by preclinical data to date
  - Mutational load may be used as a specific biomarker of LOH
- Cell death induced by a PARPi is considered immunogenic
  - Stimulates STING pathway
- **Thus, it is hypothesized that increased DNA damage by PARP inhibition will increase the number of tumor neoantigens, creating a more antigenic environment in which to stimulate the immune microenvironment**

Preclinical and Scientific Rationale for Combination of PARP Inhibition and PD1/PDL1 Blockade

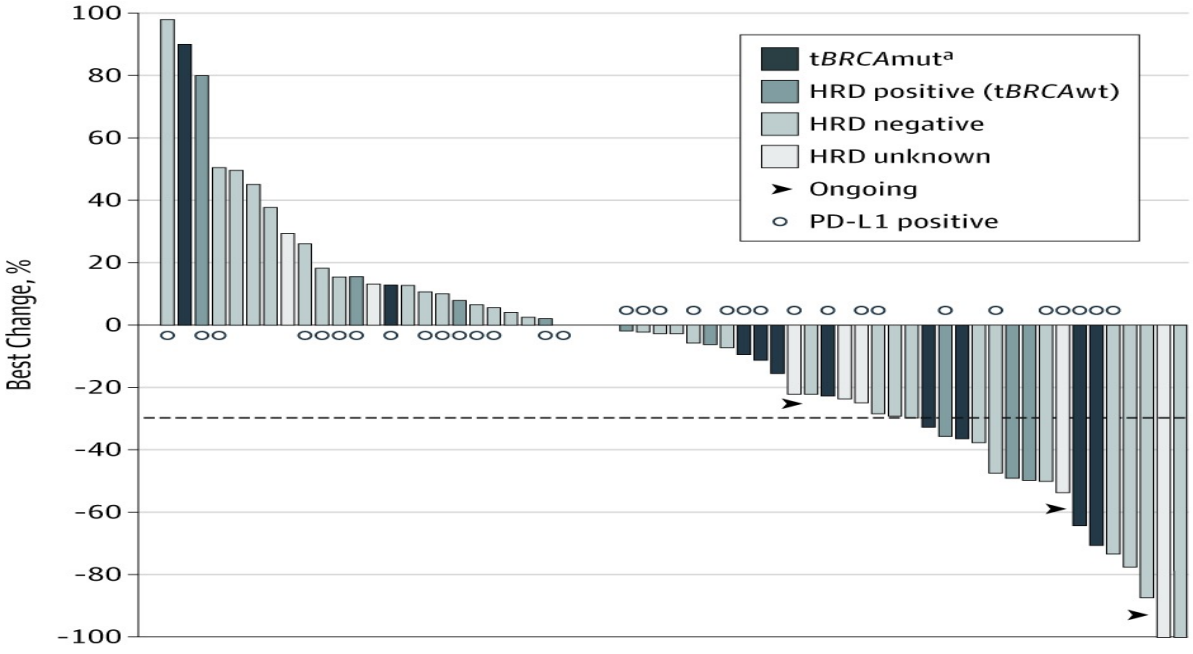


Preclinical models of ovarian cancer have demonstrated synergy between PARP inhibition and PD1/PDL1 checkpoint blockade.[1,2]

Mouw KW, et al. *Br J Cancer.* 2018;118(7):933-935. [1]Ding L, et al. *Cell Reports*, 2018;25(11):2972-2980. [2]Shen J et al. *Cancer Research*. 2019;79(2):311-319.

Immunotherapy + PARP inhibitors: TOPACIO and MEDIOLA

TOPACIO: Pembrolizumab/niraparib in PROC



ORR 18%, including 19% in tBRCAwt, and 19% in HRP tumors

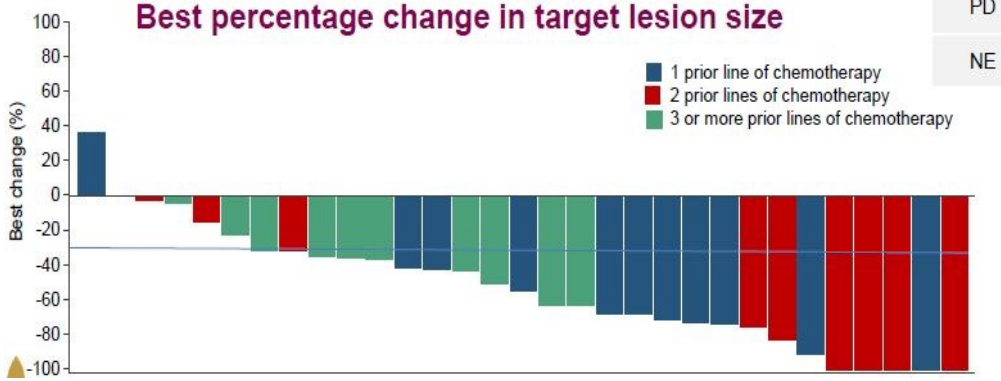
Konstantinopoulos et al., *JAMA Oncol* 2019

MEDIOLA: Durvalumab/olaparib in **BRCAmt PSOC**

Tumor responses

	1 prior (2L)	2 prior (3L)	3+ prior (4L)	All lines
ORR	10/13=77%	6/9=67%	7/10=70%	23/32=72%
95% CI	(46%, 95%)	(30%, 93%)	(35%, 93%)	(53%, 86%)

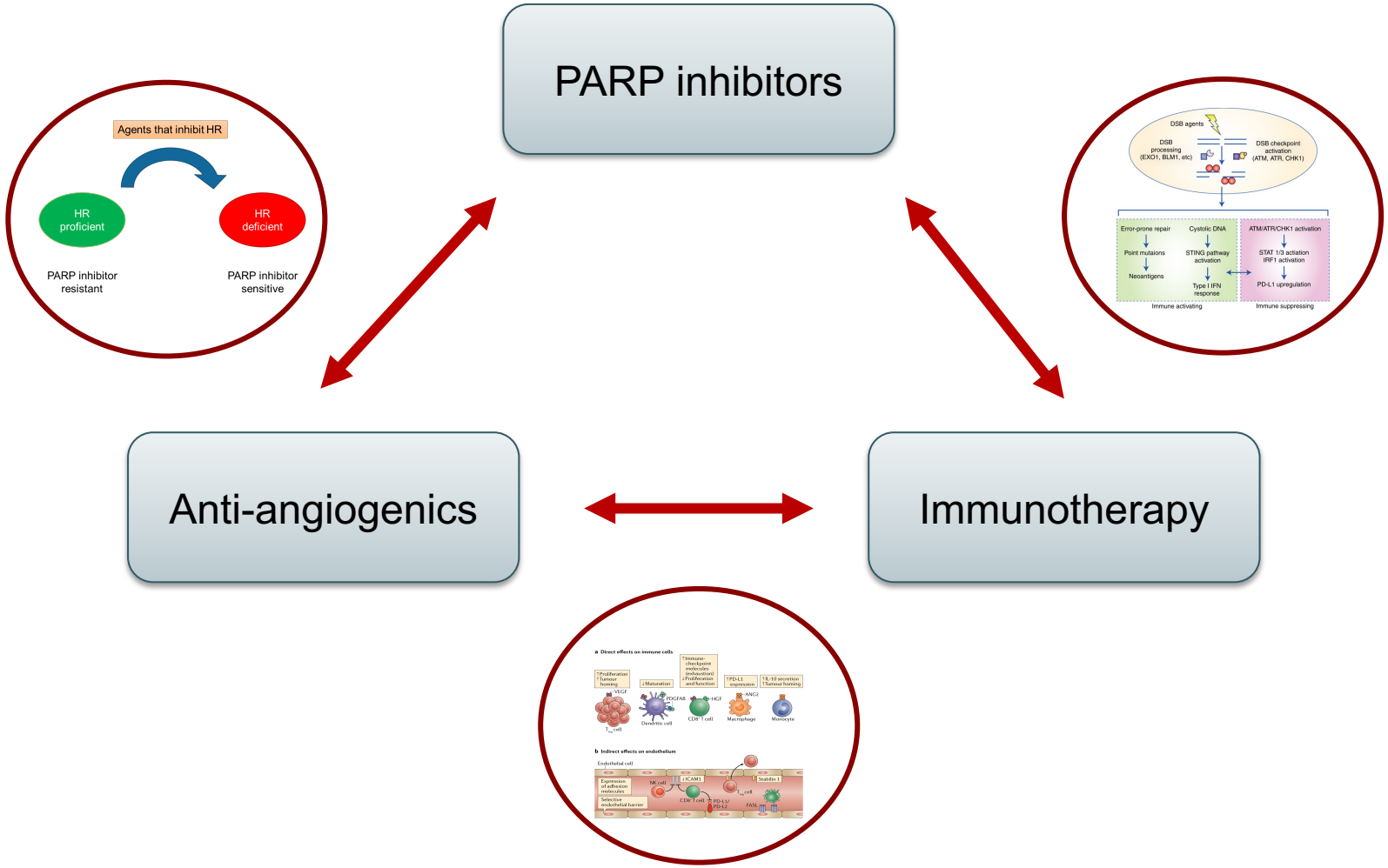
Best Response	N (%)
CR	6 (19)
PR	17 (53)
SD	3 (9)
PD	3 (9)
NE	3 (9)



ORR 72%

Drew et al., SGO 2018 Annual Meeting

“Triplet” therapy: IO + anti-angiogenic + PARPi

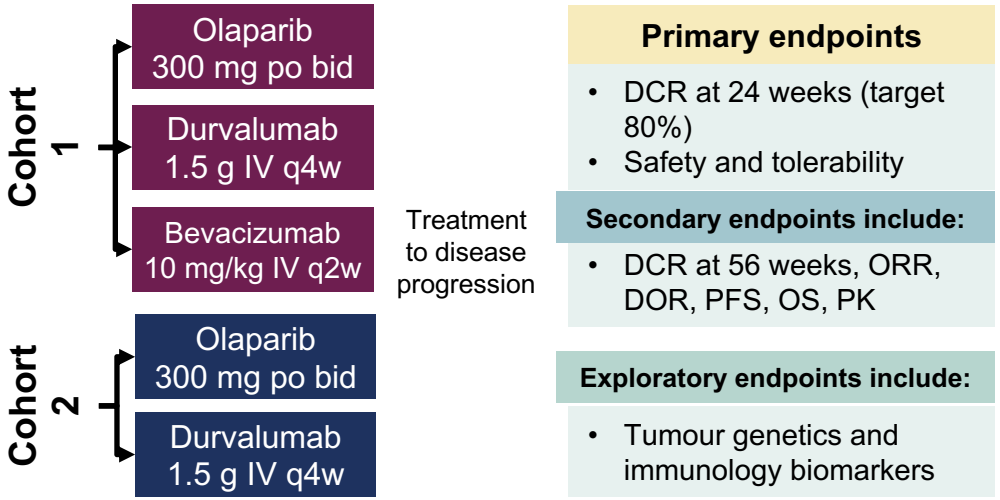


Adopted from Joyce Liu

MEDIOLA: non-germline BRCA-mutated platinum sensitive relapsed ovarian cancer

Patient population

- gBRCAwt
- PSR ovarian cancer
- ≤2 prior lines of chemotherapy
- PARP inhibitor and IO agent naïve



Primary endpoints

- DCR at 24 weeks (target 80%)
- Safety and tolerability

Secondary endpoints include:

- DCR at 56 weeks, ORR, DOR, PFS, OS, PK

Exploratory endpoints include:

- Tumour genetics and immunology biomarkers

Sequential enrolment

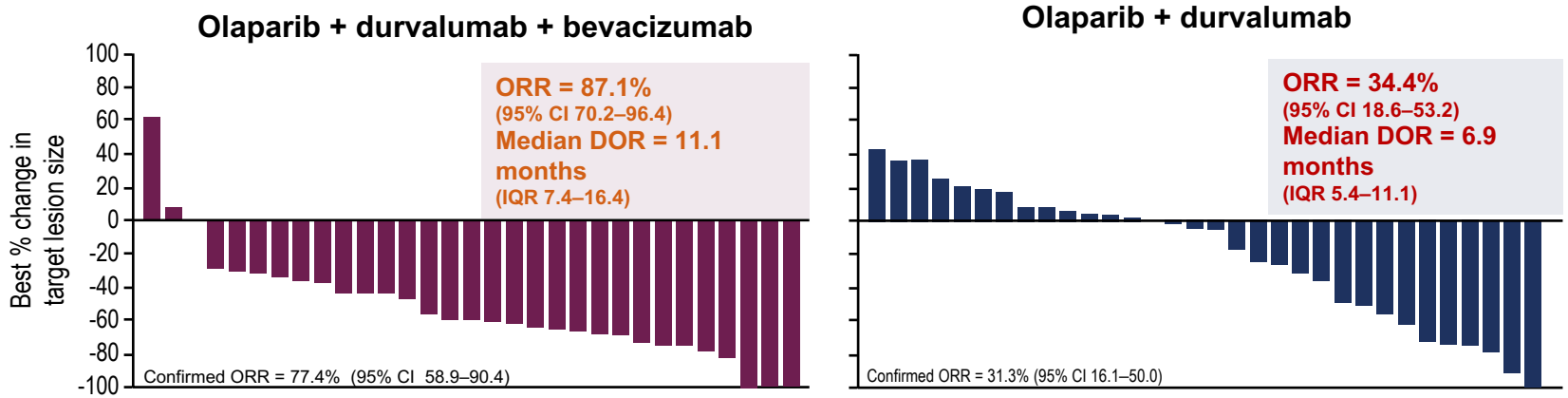
Tumour assessments every 8 weeks

	Olap + durva + bev (N=31)	Olap + durva (N=32)
Median age, years	64.0	68.5
Age group (years), n (%)		
<50	3 (9.7)	4 (12.5)
≥50–<65	14 (45.2)	8 (25.0)
≥65	14 (45.2)	20 (62.5)
Race, n (%)		
White	20 (64.5)	24 (75.0)
Asian	10 (32.3)	3 (9.4)
Other	1 (3.2)	5 (15.6)
Platinum sensitivity, n (%)		
>6–12 months	18 (58.1)	14 (43.8)
>12 months	13 (41.9)	18 (56.3)
Number of prior lines of chemotherapy, n (%)		
1 prior line	20 (64.5)	23 (71.9)
2 prior lines	11 (35.5)	9 (28.1)
Enrolment completed	January 2019	February 2019
Patients on study treatment at DCO, n (%) (13 February 2020)		
Olap; durva; bev	13 (41.9); 13 (41.9); 12 (38.7)	7 (21.9); 6 (18.8); NA

Drew et al ESMO 2020

Bev, bevacizumab; bid, twice daily, DCO, data cut-off; DCR, disease control rate; DOR, duration of response; durva, durvalumab; IO, immuno-oncology; IV, intravenous; olap; olaparib; NA, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; po, by mouth; PSR, platinum-sensitive relapsed; q2w, every 2 weeks; q4w, every 4 weeks

Triplet cohort demonstrates high ORR
Exploratory analysis suggests triplet cohort ORR is not GIS-dependent

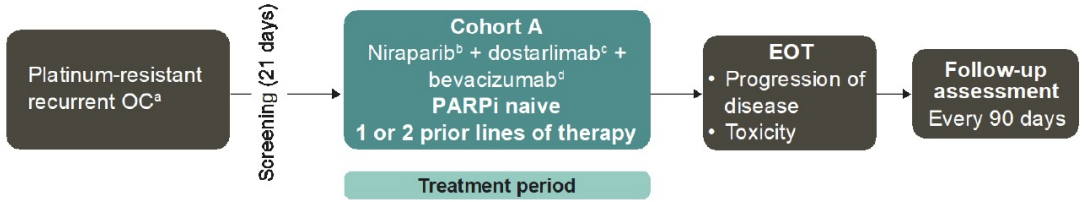


Genomic instability status* subgroup	Olaparib + durvalumab + bevacizumab		Olaparib + durvalumab	
	ORR (95% CI), %	n/N patients	ORR (95% CI), %	n/N patients
GIS-positive	100.0 (69.2–100.0)	10/10	50.0 (18.7–81.3)	5/10
GIS-negative	75.0 (34.9–96.8)	6/8	16.7 (0.4–64.1)	1/6
GIS-unknown	84.6 (54.6–98.1)	11/13	31.3 (11.0–58.7)	5/16

*GIS, as determined by Foundation Medicine tumour analysis; must have genome-wide LOH ≥14, a somatic *BRCA1* and/or *BRCA2* mutation, or a mutation in *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D* or *RAD54L* to be considered positive. At the time of the DCO, the prespecified cut-off for genome-wide LOH of 14% was used[1]; GIS, genomic instability status; IQR, interquartile range; LOH, loss of heterozygosity. [1]Swisher *et al. Lancet Oncol* 2017;18:75–87

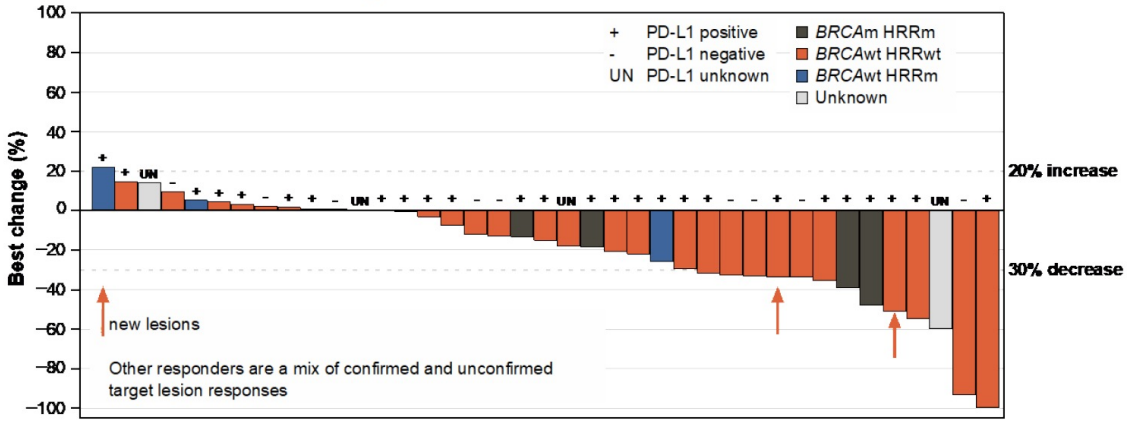
Drew et al ESMO 2020

OPAL: Niraparib, Dostarlimab, and Bev in PROC



Antitumor Activity per RECIST v1.1	
Variable, n (%)	**Response-evaluable population (n=39)**
Complete response	0
Partial response	7 (17.9)
Stable disease	23 (59.0)
Progressive disease	8 (20.5)
Inconclusive	1 (2.6)
ORR (90% CI), %	17.9 (8.7–31.1)
DCR (90% CI), %	76.9 (63.2–87.4)

Best Percent Change from Baseline Sum of Target Lesions by HRR and PD-L1 Status



J Liu et al, SGO 2021

Ongoing Trials
-First Line
-PROC

The James

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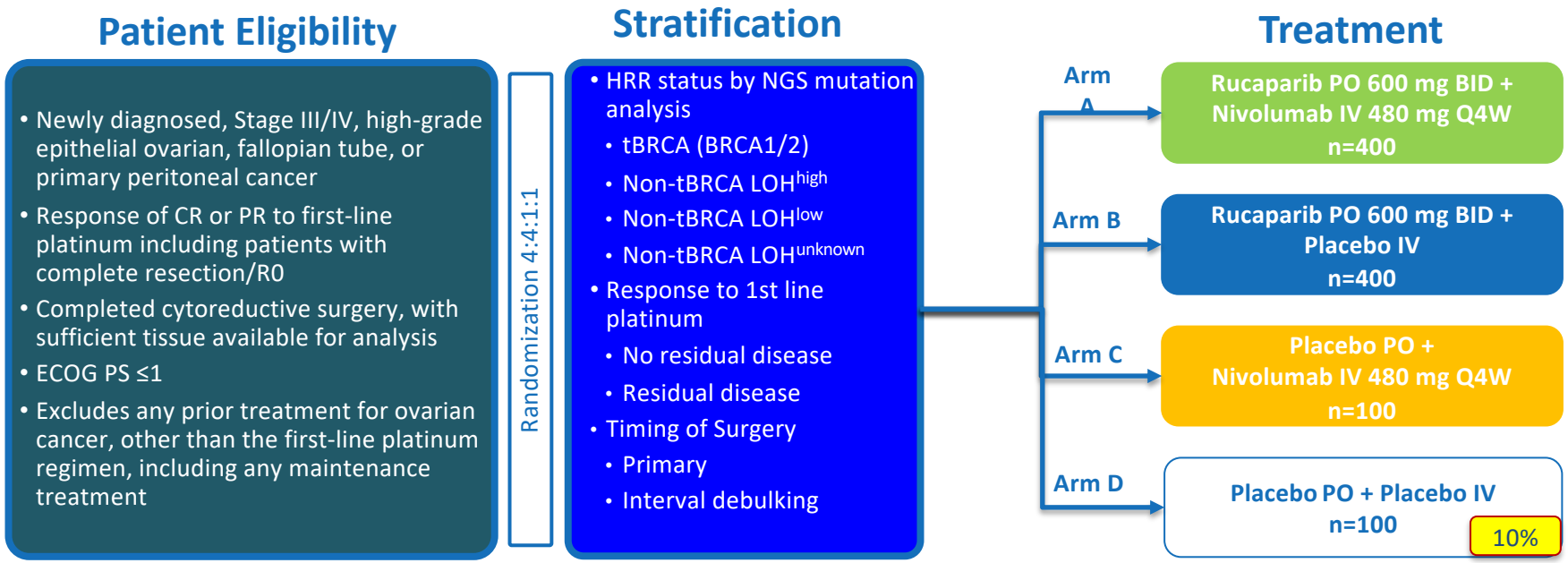
ATHENA Study Design



Primary Endpoint

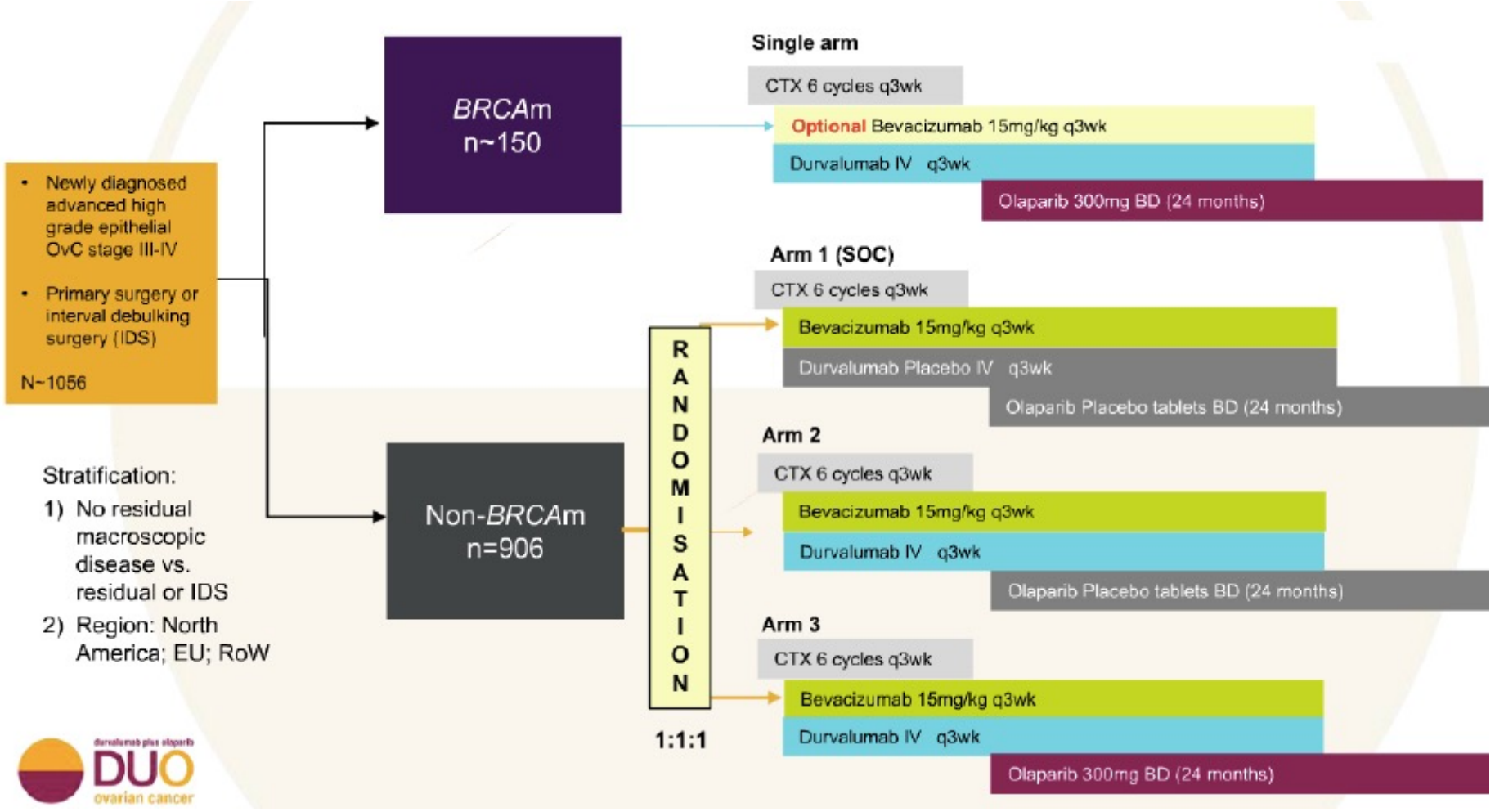
- PFS by Investigator in molecularly-defined HRD subgroups

Secondary Endpoints

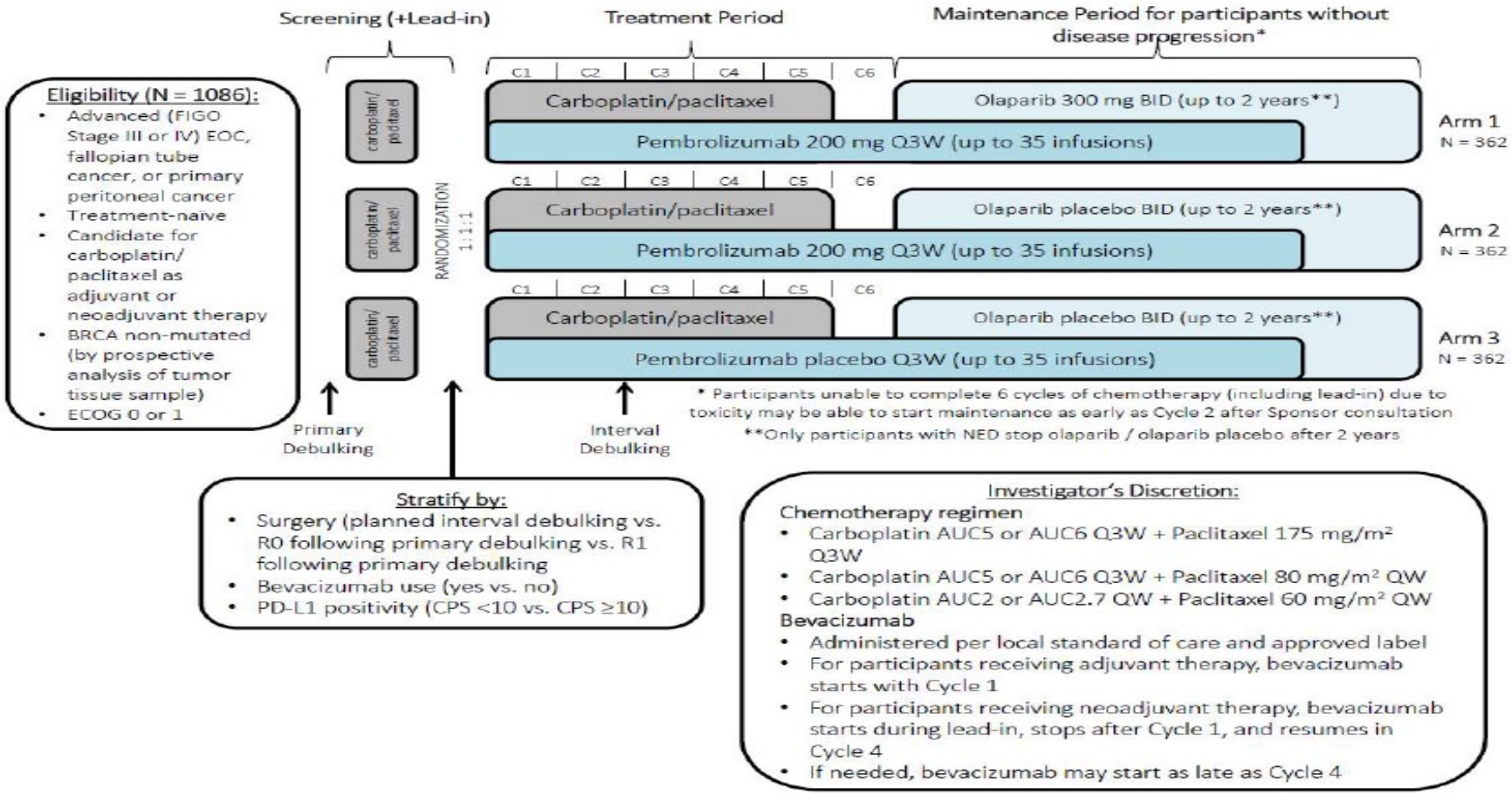
- PFS by BICR in molecularly-defined HRD subgroups
- ORR and DOR in patients with measurable disease
- OS and Safety

ClinicalTrials.gov Identifier: NCT03522246

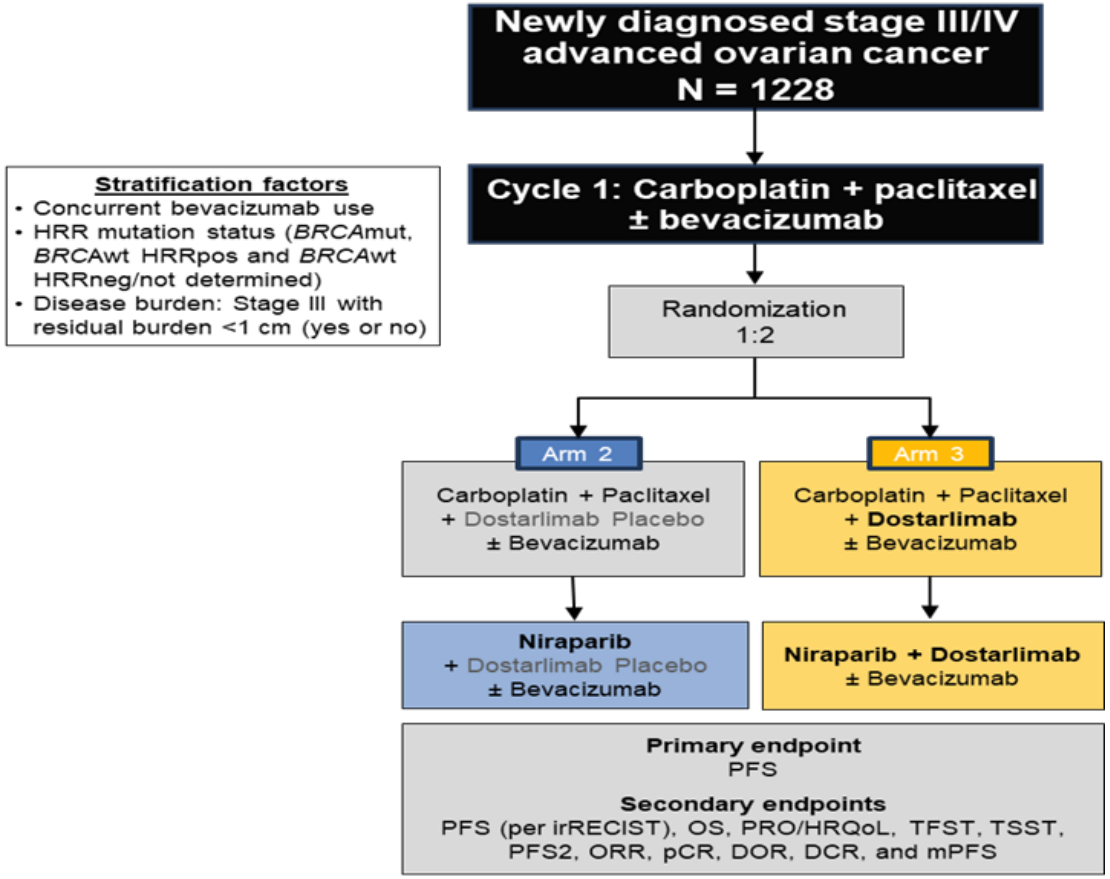
GOG 3025 DUO-O : C/T/Bev +/- Durva +/- Olaparib



KEYLYNK-001: **GOG-3036/ENGOT-ov43: C/T (choice Bev) +/- Pembro +/- Olaparib**



FIRST: Niraparib + Dostarlimab (± Bev) in 1L OC

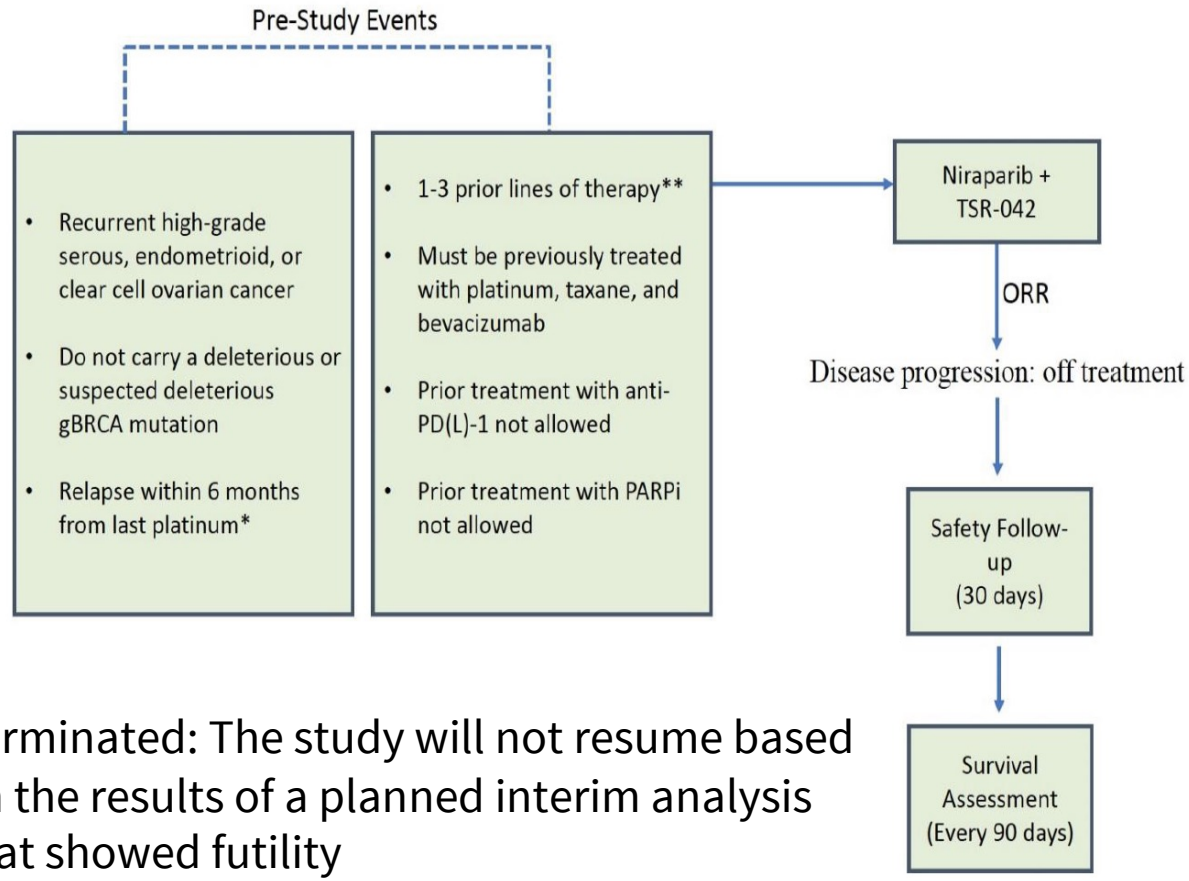


- Adaptive study design was selected to enable modifications
  - 2018: Arm 1 closed for *BRCA*mut patients post SOLO-1
  - 2019: Based on PRIMA data, amendment approved to drop Arm 1 (placebo) for *BRCA*wt patients

* As of 13th Dec 2019

NCT03602859

MOONSTONE: A PHASE 2 OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFICACY AND SAFETY OF THE COMBINATION OF NIRAPARIB AND TSR-042 IN PATIENTS WITH PLATINUM RESISTANT OVARIAN CANCER



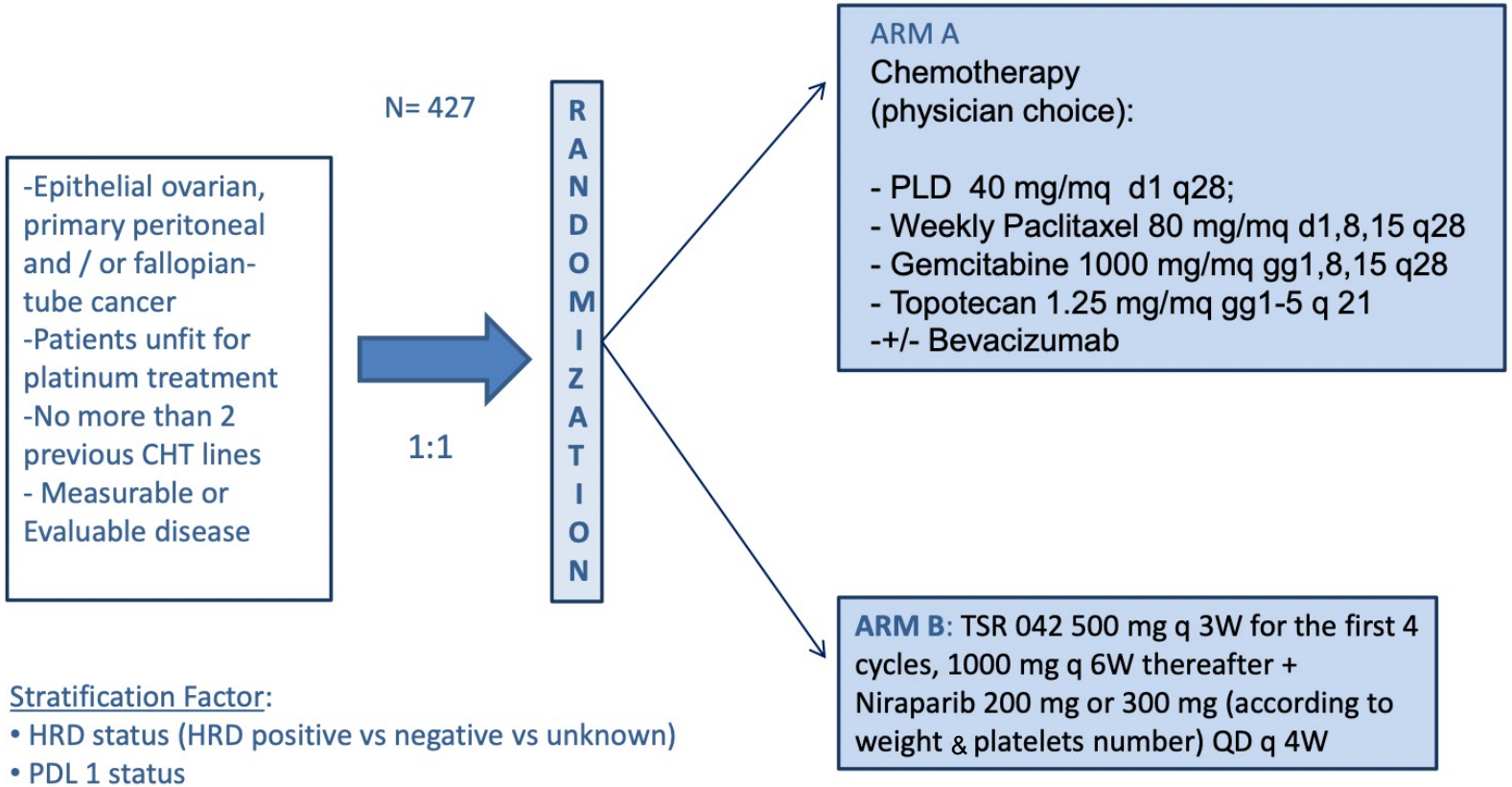
Study Design

Population: Patients with platinum-resistant ovarian (+tubal/peritoneal) cancer
Treatment: Niraparib + Dostarlimab
N Patients: 150 patients
N Sites: 40 Sites in the US
Primary Endpoint: Investigator-assessed ORR per RECIST v1.1

Terminated: The study will not resume based on the results of a planned interim analysis that showed futility

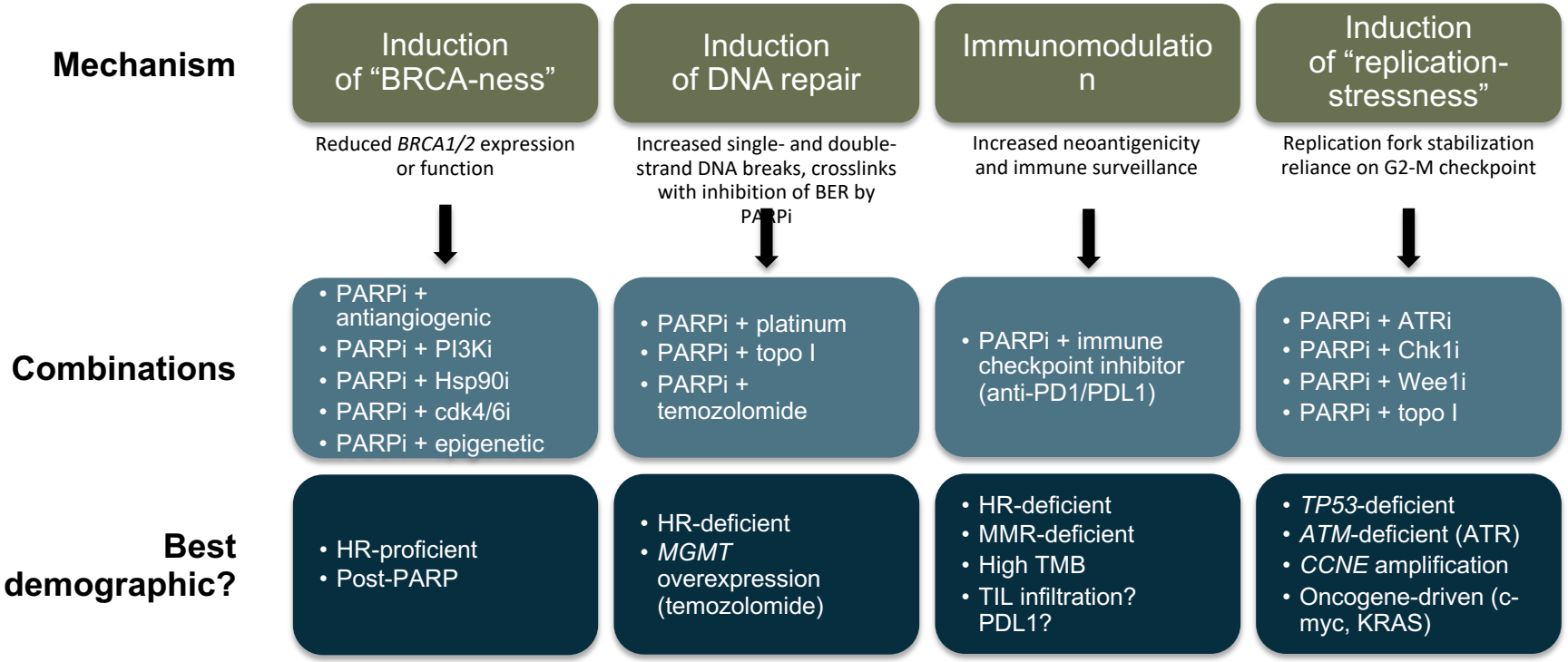
NCT03955471

NItCHE-MITO33: Trial on NIraparib-Dostarlimab vs Physician's Choice CHEmotherapy in Recurrent, Ovarian, Fallopian Tube or Primary Peritoneal Cancer Patients **Not Candidate for Platinum Retreatment**



NCT04679064

PARP Inhibitor Combinations



Veneris JT, et al. *Gynecol Oncol.* 2020

Case Discussions

A 58-year-old woman with Stage IIIC ovarian cancer (BRCA wild type, HRD positive score 38) is s/p debulking surgery and 6 cycles of carboplatin/paclitaxel with no evidence of disease. What would you most likely recommend as maintenance therapy?

1. None
2. Bevacizumab
3. Olaparib
4. Niraparib
5. Olaparib/bevacizumab
6. Other

Dr Mirza - First-Line Maintenance PARP Inhibitor

58 yrs old
No comorbidity
Ovarian cancer diagnosed:
January 2021: HGSOC, FIGO IIIC, Complete upfront cytoreduction
carboplatin-paclitaxel x 6 with no evidence of disease at the end of 6 cycles

sBRCAwt, non-gBRCAmut
Myriad MyChoice HRD: positive score 48

July 2021: Four weeks post chemotherapy, perf status 0; grade 1 neurotoxicity; normal blood counts, body weight 71kg

Patient starts on niraparib 200mg daily
Weekly haematology for first four weeks – results acceptable

After that blood counts and CA125 every 4 weeks; CT scan every 12 weeks
Patient is tolerating treatment well without any other toxicities

A 77-year-old with BRCA wild-type, HRD-positive ovarian cancer receives carboplatin/gemcitabine and 12 months of niraparib maintenance for platinum-sensitive recurrent disease. She subsequently experiences response followed by disease progression on 2 subsequent lines of therapy. Would you consider rechallenge with a PARP inhibitor at this time?

1. Yes
2. No

Dr Moore

Currently 77 years old, AA woman, BRCAwt, HRD
Diagnosed with Stage III High Grade Serous Ovarian Cancer in June, 2012

1. Dispositioned to NACT with carboplatin and paclitaxel x 3 with good response.

Interval CRS Sept, 2012 with disease present but resected to NGR
She received 3 more cycles of carboplatin and paclitaxel completed Nov 2012.

2. Recurred by imaging April 2014 – PFI 1 = 16 months. Treated with Gemcitabine and carboplatin x 6 cycles completed Aug 2014 with PR. She was treated in the NOVA trial with **niraparib** until recurrence by imaging in Aug of 2015. PFI 2 = 12 months
3. Treated with carboplatin and novel antibody drug conjugate x 6 cycles completed Jan 2016. Maintenance ADC started but discontinued due to neuropathy and patient opted for close monitoring.
4. Recurred January 2017, PFI 3 = 12 months and treated with carboplatin/PLD/bev x 6 as of July, 2017 with PR – bevacizumab continued x 17 cycles at which time she had growth of an oligo-met in pelvis which was radiated and bevacizumab continued for a total of 22 cycles. Disease progression noted by imaging January 2019, PFI 4 = 17 months
5. Treated with paclitaxel and carboplatin x 8 cycles completed July 2019 with PR. Started on **olaparib** maintenance and continues currently with PFI 5 = ongoing but currently 31 months. CT with SD but small growth in one lesion, CA-125 is 16 (up from 10).

Module 3: Recognition and Management of Side Effects Associated with PARP Inhibitor Therapy for OC — Dr Mirza

RTP
RESEARCH
TO PRACTICE

PARP inhibitors
Recognition and Management of Adverse Events

Mansoor Raza Mirza

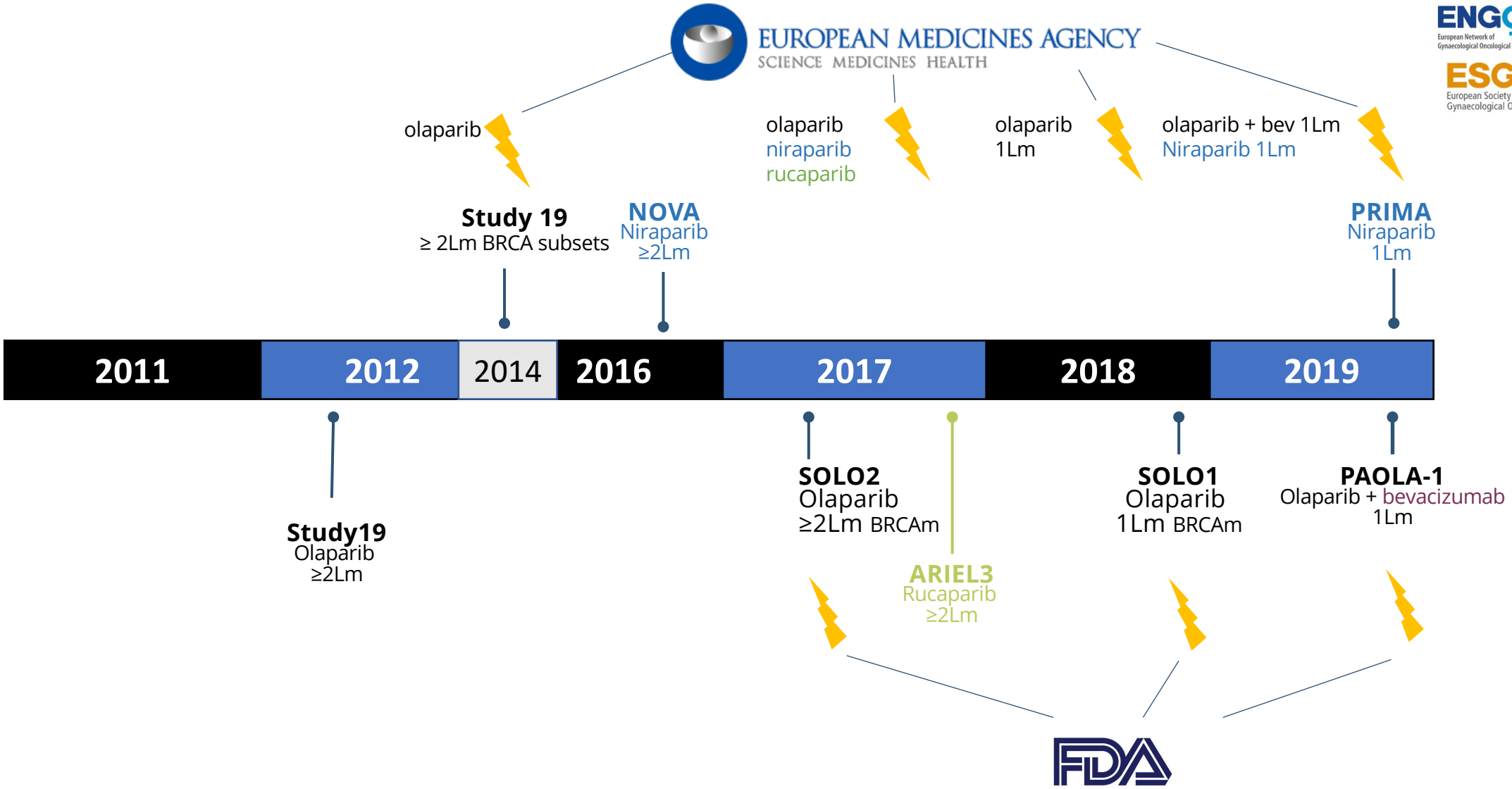
Medical Director: **NSGO** (Nordic Society of Gynaecological Oncology)
Chief Oncologist: **Rigshospitalet** (Copenhagen University Hospital)
Chairman: **ENGOT** (European Network of Gynaecological Oncology Trials group)
Vice-President: **ESGO** (European Society of Gynaecological Oncology)

Dr Mirza — Disclosures

Advisory Board (Invited Speaker, Personal)	AstraZeneca Pharmaceuticals LP, GlaxoSmithKline
Advisory Board (Personal)	Allarity Therapeutics, AstraZeneca Pharmaceuticals LP, BIOCAD, Boehringer Ingelheim Pharmaceuticals Inc, GlaxoSmithKline, Karyopharm Therapeutics, Merck, Roche Laboratories Inc, Zai Lab
Ownership Interest (Member of Board of Directors)	Karyopharm Therapeutics, Sera Prognostics

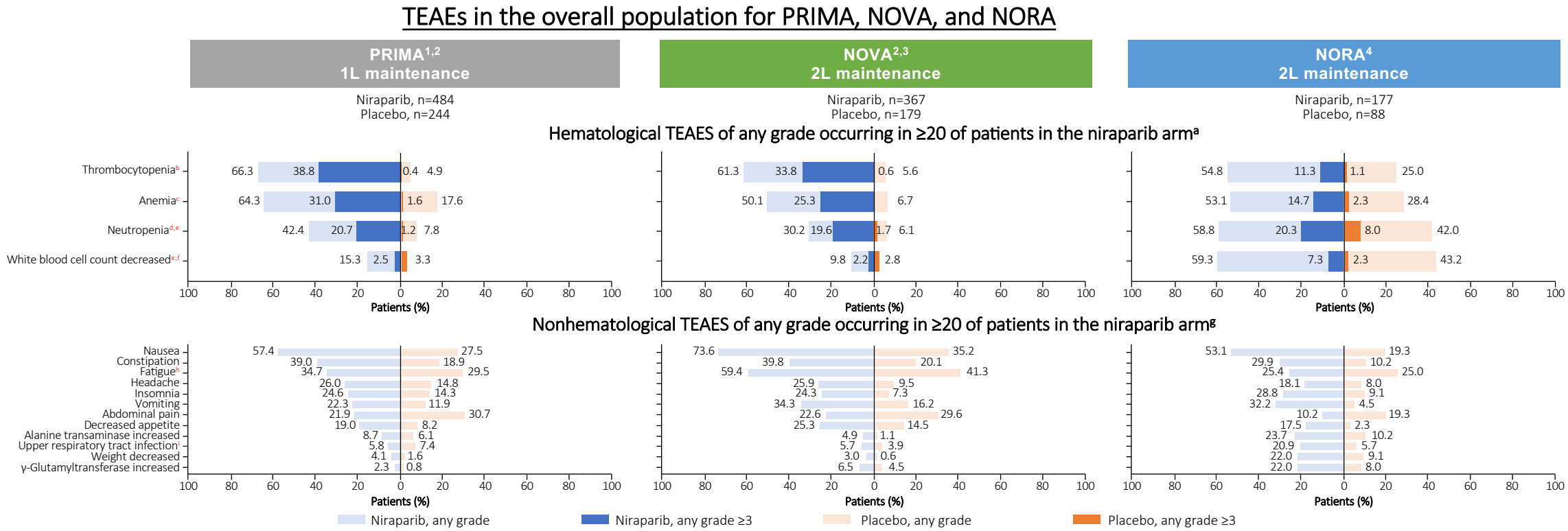
RTP
RESEARCH
TO PRACTICE

PARP Inhibitor therapy in advanced ovarian cancer



Niraparib safety in patients with *BRCA*-mutated ovarian cancer: results from three phase 3 niraparib trials

Summary of the safety of niraparib in patients with *BRCA*m ovarian cancer across three phase 3 trials: no new safety signals were identified



[a]Hematologic TEAEs of any grade occurring in ≥20% of patients in the niraparib arm of PRIMA, NOVA, or NORA. Grade ≥3 TEAEs are also reported for each event; [b]Thrombocytopenia: PRIMA, NOVA, and NORA: thrombocytopenia and platelet count decreased; [c]Anemia: PRIMA, anemia; Nova, anemia and decreased hemoglobin count; NORA, anemia; [d]Neutropenia: PRIMA, neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis; NOVA, neutropenia, neutrophil count decreased, and febrile neutropenia; NORA, neutropenia and neutrophil count decreased; [e]NORA: In the niraparib group, among 105 patients who experienced white blood cell count decreased and 104 patients who experienced neutrophil count decreased, 94 patients had both events reported with overlapping duration, and among 13 patients who experienced grade 3 white blood cell count decreased, 11 patients also had grade 3 neutrophil count decreased reported with overlapping duration. In the placebo group, among the 38 patients who experienced white blood cell count decreased of any grade and 37 patients who experienced neutrophil count decreased, 32 patients reported both events with overlapping duration, and 2 patients who experienced grade 3 white blood cell count decreased also reported grade 3 neutrophil count decreased with overlapping duration; [f]White blood cell decreased: PRIMA and NOVA, white blood cell decreased; NORA, white blood cell decreased and leukopenia; [g]Nonhematologic TEAEs of any grade occurring in ≥20 of patients in the niraparib arm of PRIMA, NOVA, or NORA; [h]Fatigue: PRIMA, fatigue; NOVA, fatigue, asthenia, malaise, and lethargy; NORA, asthenia; [i]Did not include viral upper respiratory tract infection for PRIMA or NOVA.

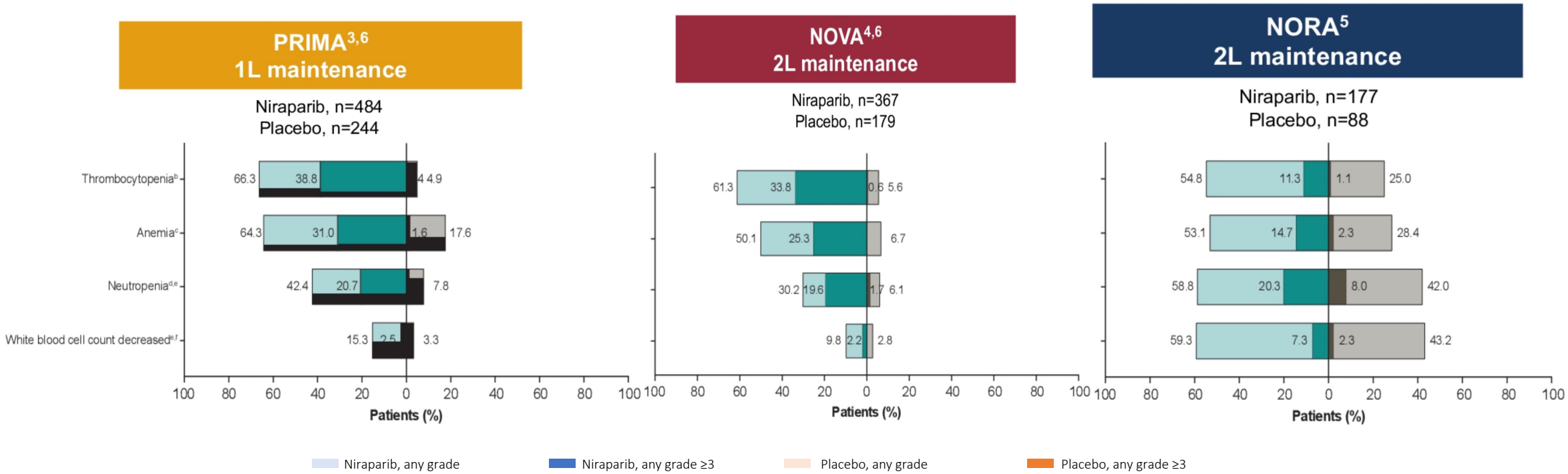
González-Martin A et al. ASCO Annual Meeting 2021; Abstract 5518.

Niraparib safety in patients with *BRCA*-mutated ovarian cancer: results from three phase 3 niraparib trials

Summary of the safety of niraparib in patients with *BRCA*m ovarian cancer across three phase 3 trials: no new safety signals were identified

TEAEs in the overall population for PRIMA, NOVA, and NORA

Hematological TEAES of any grade occurring in ≥20 of patients in the niraparib arm[a]

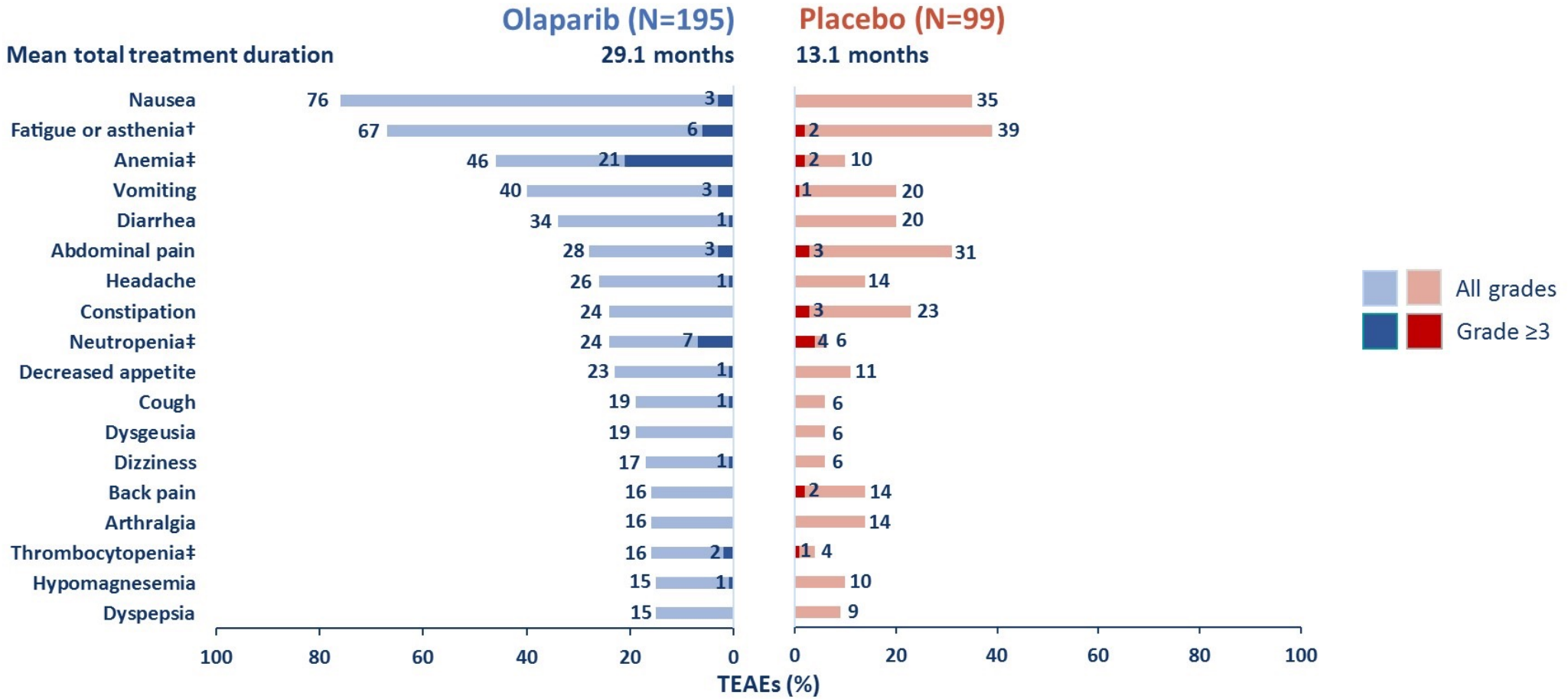


[a]Hematologic TEAEs of any grade occurring in ≥20% of patients in the niraparib arm of PRIMA, NOVA, or NORA. Grade ≥3 TEAEs are also reported for each event; [b]Thrombocytopenia: PRIMA, NOVA, and NORA: thrombocytopenia and platelet count decreased; [c]Anemia: PRIMA, anemia; Nova, anemia and decreased hemoglobin count; NORA, anemia; [d]Neutropenia: PRIMA, neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis; NOVA, neutropenia, neutrophil count decreased, and febrile neutropenia; NORA, neutropenia and neutrophil count decreased; [e]NORA: In the niraparib group, among 105 patients who experienced white blood cell count decreased and 104 patients who experienced neutrophil count decreased, 94 patients had both events reported with overlapping duration, and among 13 patients who experienced grade 3 white blood cell count decreased, 11 patients also had grade 3 neutrophil count decreased reported with overlapping duration. In the placebo group, among the 38 patients who experienced white blood cell count decreased of any grade and 37 patients who experienced neutrophil count decreased, 32 patients reported both events with overlapping duration, and 2 patients who experienced grade 3 white blood cell count decreased also reported grade 3 neutrophil count decreased with overlapping duration; [f]White blood cell decreased: PRIMA and NOVA, white blood cell decreased; NORA, white blood cell decreased and leukopenia; [g]Nonhematologic TEAEs of any grade occurring in ≥20 of patients in the niraparib arm of PRIMA, NOVA, or NORA; [h]Fatigue: PRIMA, fatigue; NOVA, fatigue, asthenia, malaise, and lethargy; NORA, asthenia; [i]Did not include viral upper respiratory tract infection for PRIMA or NOVA.

González-Martin, A. ASCO Annual Meeting. 2021.

SOLO2: most common TEAEs – final analysis*

Small increase in TEAEs in the olaparib group, compared with the primary analysis, despite longer treatment duration



*Frequency ≥15%; †Includes patients with fatigue and patients with asthenia; ‡Grouped terms

Poveda A et al. ASCO 2020; Abstract 6002.

Summary of toxicity of maintenance PARPi trials (first-line)

	GOG-218	SOLO-1	PAOLA-1	PRIMA
Administration	IV q3weeks 15 months	Oral BID 2 years	Oral BID 2y + IV q3w 15m	Oral QD 3 years
% dose reduction	-	28.5	41	70.9
% dose interruption	-	51.9	54	79.5
% discontinuation	**17**	**11.5**	**20**	**12**
Most frequent Grade ≥ 3 AE	Neut G4 (64%) HT G ≥2 (23%)	Anaemia (22%) Neut. (9%) Asthenia (4%)	HT (19%) Anaemia (17%) Lymph (7%)	Anaemia (31%) Plates. (28%) Neut. (12.8%)

Burger. NEJM 2011; Moore. NEJM 2018;Ray-Coquard. NEJM 2019; Gonzalez-Martin. NEJM 2019

Summary of toxicity of maintenance PARPi trials (relapsed disease)

Treatment Related Dose Discontinuations

Rucaparib	Olaparib	Niraparib
13.4%	17%	14.7%

Coleman RL et al. *Lancet 2017*

Poveda et al. *ASCO 2020*

Mirza MR et al. *N Engl J Med 2016*

SOLO2: AEs of special interest – primary and final analyses*,†

	Olaparib (N=195)		Placebo (N=99)	
	Primary	Final	Primary	Final
Mean total treatment duration (SD), months	17.4 (9.8)	**29.1 (24.7)**	9.0 (8.1)	**13.1 (18.6)**
MDS/AML, n (%)	4 (2)	**16 (8)**	4 (4)	**4 (4)**
During the safety follow-up period (TEAE)		**7 (4)**		**0**
After the safety follow-up period (non-TEAE)		**9 (5)**		**4 (4)**
Pneumonitis, n (%)	3 (2)	**3 (2)**	0	**0**

MDS/AML

- **Actively solicited throughout study treatment and follow-up**
- **Incidences should be interpreted in the context of their late onset‡ and the longer OS observed with olaparib vs placebo**
- **Association with the number of prior platinum regimens, olaparib treatment and other potential risk factors is being explored**

In patients with newly diagnosed ovarian cancer and a BRCAm, at median follow-up of 65 months, MDS/AML occurred in 1% of olaparib patients and no placebo patients[1]

*Includes AEs that occurred outside safety follow-up period (during treatment and up to 30 days after discontinuation); †New primary malignancies (excluding hematologic malignancies) occurred in one olaparib patient (1%) and one placebo patient (1%) in the primary analysis, and in eight olaparib patients (4%) and two placebo patients (2%) in the final analysis; ‡After the safety follow-up period
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome

1. AstraZeneca data on file for the SOLO1 trial (NCT01844986)

Poveda et al. ASCO 2020; Abstract 6002.

NOVA: Summary of MDS/AML

- At the time of the primary analysis, incidence of MDS/AML was 1.4% (5/367) in the niraparib arm vs. 1.1% (2/179) in the placebo arm[1]
- With long-term follow-up and administration of subsequent therapies, 3.5% (13/367) of patients in the niraparib arm vs. 1.7% (3/179) in the placebo arm developed MDS/AML[2]

	Niraparib arm			Placebo arm		
Adverse event, n (%)	**All (N=367)**	**g*BRCA*m (n=136)**	**Non-g*BRCA*m (n=231)**	**All (N=179)**	**g*BRCA*m (n=65)**	**Non-g*BRCA*m (n=114)**
MDS/AML all	**13[a] (3.5)**	9 (6.6)	4 (1.7)	**3 (1.7)**	2 (3.1)	1 (0.9)
TEAE (treatment)	9 (2.5)	7 (5.1)	2 (0.9)	0	0	0
TEAE (follow-up)	4 (1.1)	2 (1.5)	2 (0.9)	3 (1.7)	2 (3.1)	1 (0.9)

AML, acute myeloid leukemia; MDS, myelodysplastic syndromes.
Final data cutoff date was October 1, 2020 (average duration of follow-up for OS was 67 months).
[a]A total of 16 events of MDS/AML were reported in 13 patients treated with niraparib: 1 patient had MDS then AML; 1 patient had MDS grade 1, then MDS grade 4, then AML.

1. Mirza MR, et al. *N Engl J Med* 2016;375:2154–2164.
2. Matulonis U et al. SGO 2021;Abstract 11139.

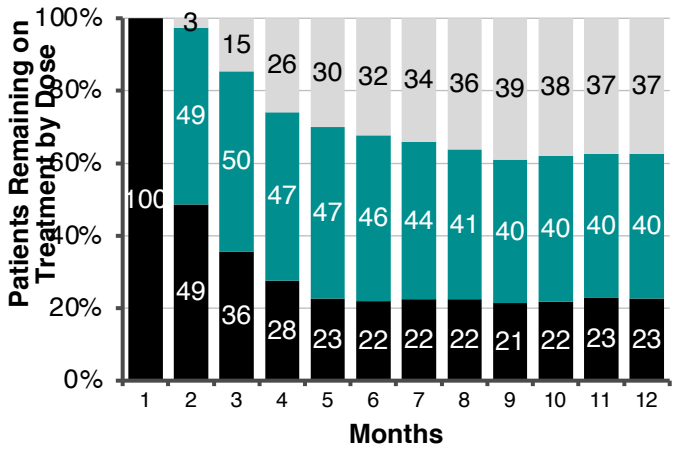
Approved dose & modification due to adverse effects
Example: niraparib – *ENGOTOV16/NOVA*

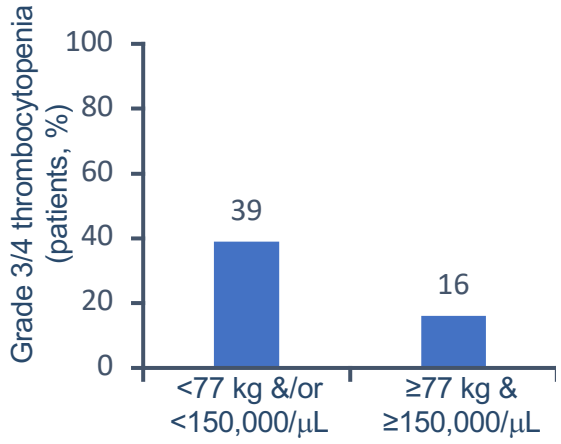
This exploratory analysis of the NOVA data was conducted to identify patients most likely to require an early dose modification

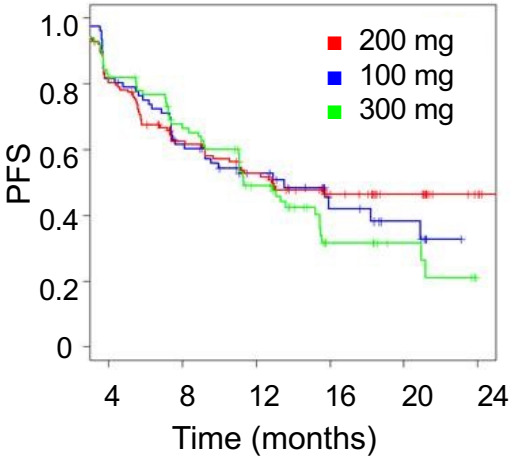
The only 2 identified predictors of early dose modification were:

- 17% patients with baseline weight <77 kg and/or platelet count <150,000/uL remained at the 300 mg dose
- Mean daily dose 206 mg in the first 2 months
- No impact on efficacy with dose reductions
- Grade 3/4 thrombocytopenia 6% in PRIMA and 9% in TOPACIO with 200mg starting dose per W&P

Baseline Weight: <170 lbs (77 kg) **OR** **Baseline Platelets:** <150,000/µL







From Month 4: HR (300 vs 200): 1.01 (95%CI: 0.69, 1.48)

From Month 4: HR (300 vs 100): 1.05 (95%CI: 0.84, 1.31)

PRIMA and NORA studies have prospectively validated these data!

W&P: "Weights and plates"

Mirza MR, et al. *SGO, 2018*.
Wang J, et al. *ESMO 2017. Abstract #933PD*.
Berek J…. Mirza MR. *Annals Oncol 2018*

Evidence for Optimal duration of maintenance PARPi therapy

	First Line	Relapsed disease
Olaparib	BID for 2 years	BID until progression
Niraparib	OD for 3 years	OD until progression
Rucaparib	-	BID until progression

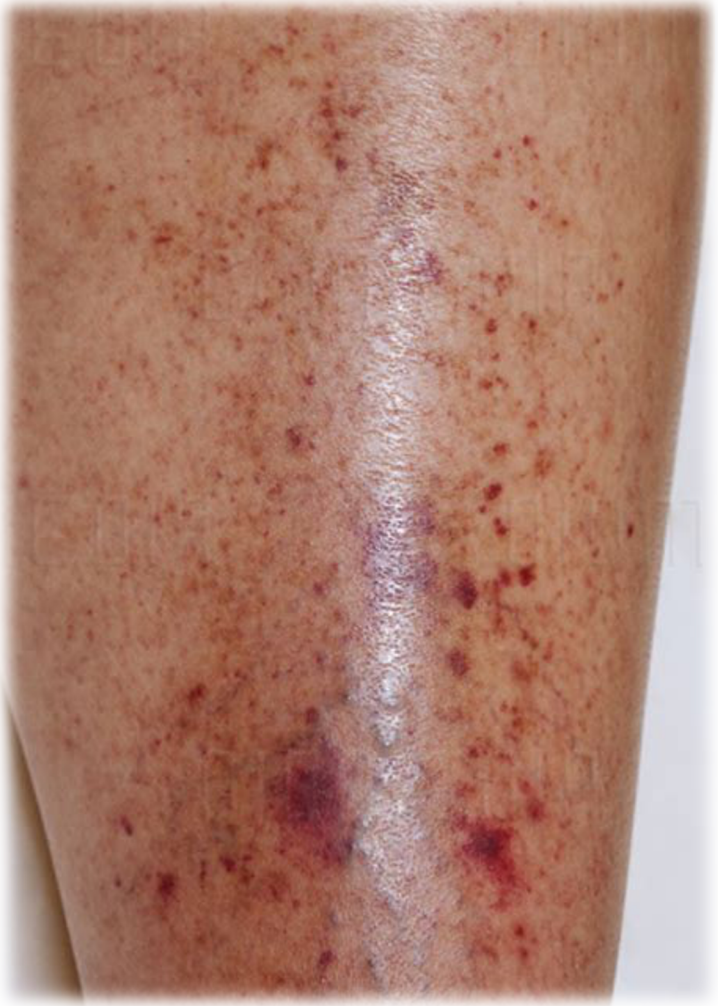
Case Discussions

What starting dose would you use for a 51-year-old patient with advanced platinum-sensitive recurrent ovarian cancer with a body weight of 163 pounds and a platelet count of 388,000 for whom you are about to initiate maintenance niraparib?

1. 300 mg daily
2. 200 mg daily
3. 100 mg daily
4. I don’t know

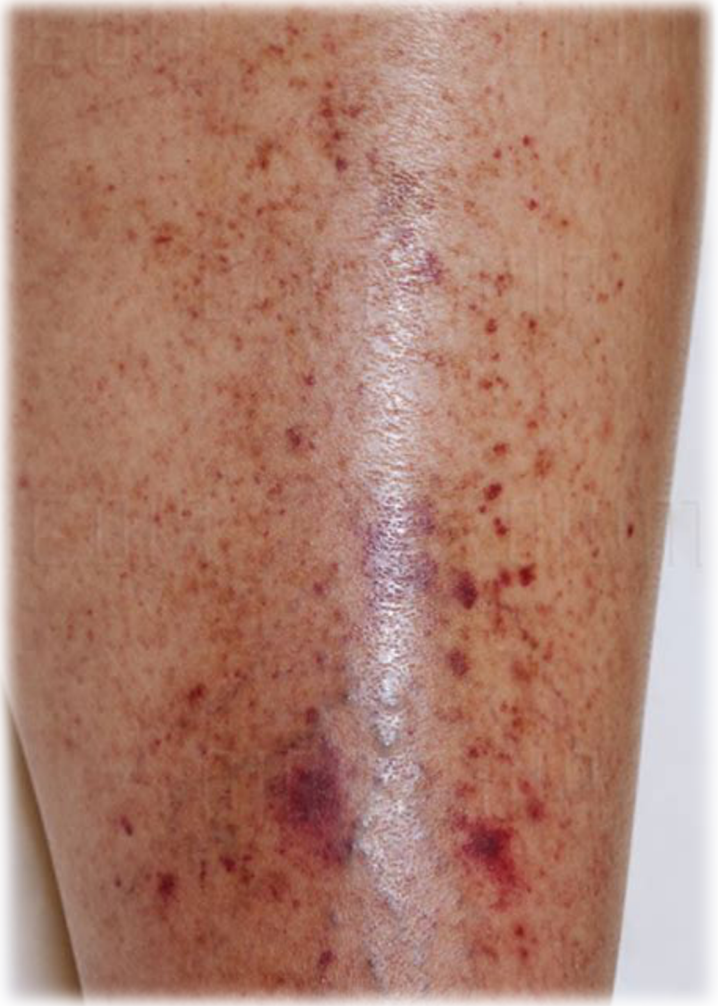
Dr Coleman – PARPi Switch due to Toxicity

- 51 y.o. woman with history of platinum-sensitive recurrent ovarian cancer (BRCAwt)
- Treated with PLD/carboplatin with significant PR x 5 cycles but stomatitis causing delay for cycle 6
- Niraparib 300mg maintenance started
- Wt: 74kg, Platelets: 388,000
- Returns for follow up 14 days in cycle 1 complaining of “rash”



Dr Coleman- PARPi Switch due to Toxicity

- Platelet count 4K
- Given platelets and dose delay
- Platelets normalized and stable 7 days later
- Dose reduced to 200 mg q day
- Tolerated cycles 2-4
- Cycle 5 severe fatigue and malaise – requested discontinuation
- Imaging demonstrates near CR



Dr Coleman

PARPi Switch due to Toxicity

Imaging demonstrates near CR

Long discussion of her treatment effect and the adverse effects seen with PARPi's as a class

Alternative to discontinuation was delay to recovery and trial of rucaparib dose reduced to 400mg BID to start

Tolerated first month without AE's; did not tolerate attempt at dose escalation to 500mg BID (anxiety)

In general, what is your approach to antiemetic therapy for a patient with ovarian cancer who is starting treatment with a PARP inhibitor?

1. Prophylactic antiemetic therapy prior to administration of the PARP inhibitor
2. Prophylactic antiemetic therapy prior to PARP inhibitor administration and for the first 2 months
3. Recommend antiemetic if the patient experiences nausea
4. Reduce the dose of the PARP inhibitor if the patient experiences nausea
5. Other

Dr Mirza - Switching to another PARP Inhibitor

50 yrs old: BRCA1mut
No comorbidity, dentist, three children

Prophylactic bilateral mastectomy in November 2014

Ovarian cancer diagnosed:
August 2015: HGSOC, FIGO IIIC, evaluated non-operable
Neo-Adjuvant carboplatin-paclitaxel x 3 with radiological partial response
CT scan and laparoscopy: R=0 not possible
Patient continues with carboplatin-paclitaxel (total 8 cycles with CR) and bevacizumab from cycle 5 then maintenance.

May 2017: Radiologic progression of disease while on maintenance bevacizumab.
Evaluated for relapse surgery: Radical, R=0
24 July 2017: Post-op carboplatin-PLD x4: No evidence of disease

Dr Mirza - Switching to another PARP Inhibitor

20 November 2017: starts capsule olaparib 400mg BID
Severe nausea & fatigue from day 2

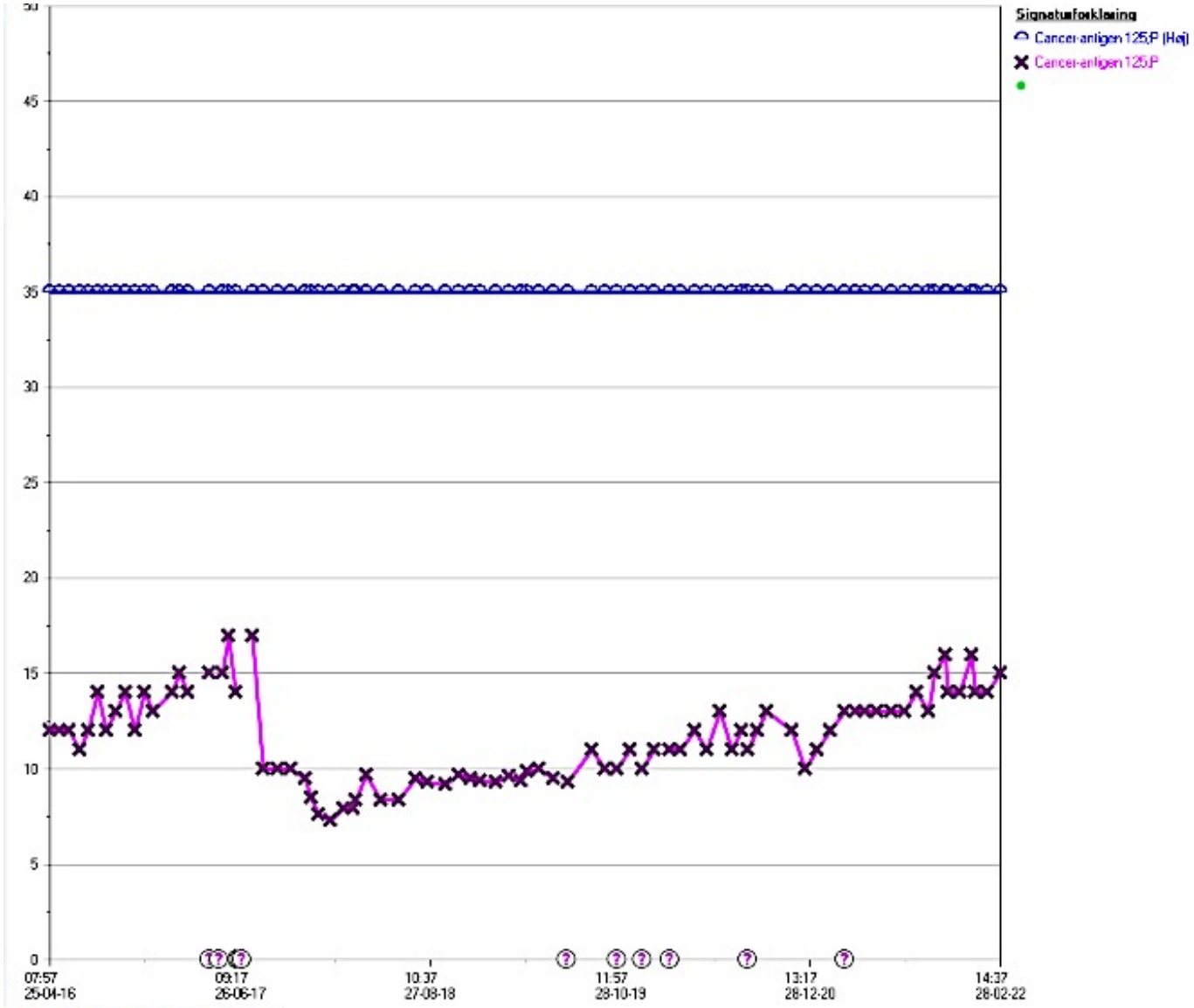
27 November 2017: Olaparib dose reduced to 300mg BID
Continuous unacceptable nausea & fatigue

18 December 2017: Olaparib dose reduced to 200mg BID
Continuous unacceptable nausea & fatigue
Patient felt it unacceptable to have daily antiemetics

5 February 2018: patient switched to Niraparib 200 mg daily (weight 58Kg, height 180, normal platelets count)
No side effects

March 2022: relapse-free on niraparib 200mg daily

Dr Mirza - Switching to another PARP Inhibitor



Module 4: Novel Investigational Agents and Strategies in OC — Dr Coleman

RTP
RESEARCH
TO PRACTICE

Novel Investigational Agents and Strategies in Recurrent Ovarian Cancer

Robert L. Coleman, MD, FACOG, FACS

Co-Director, GOG-Partners

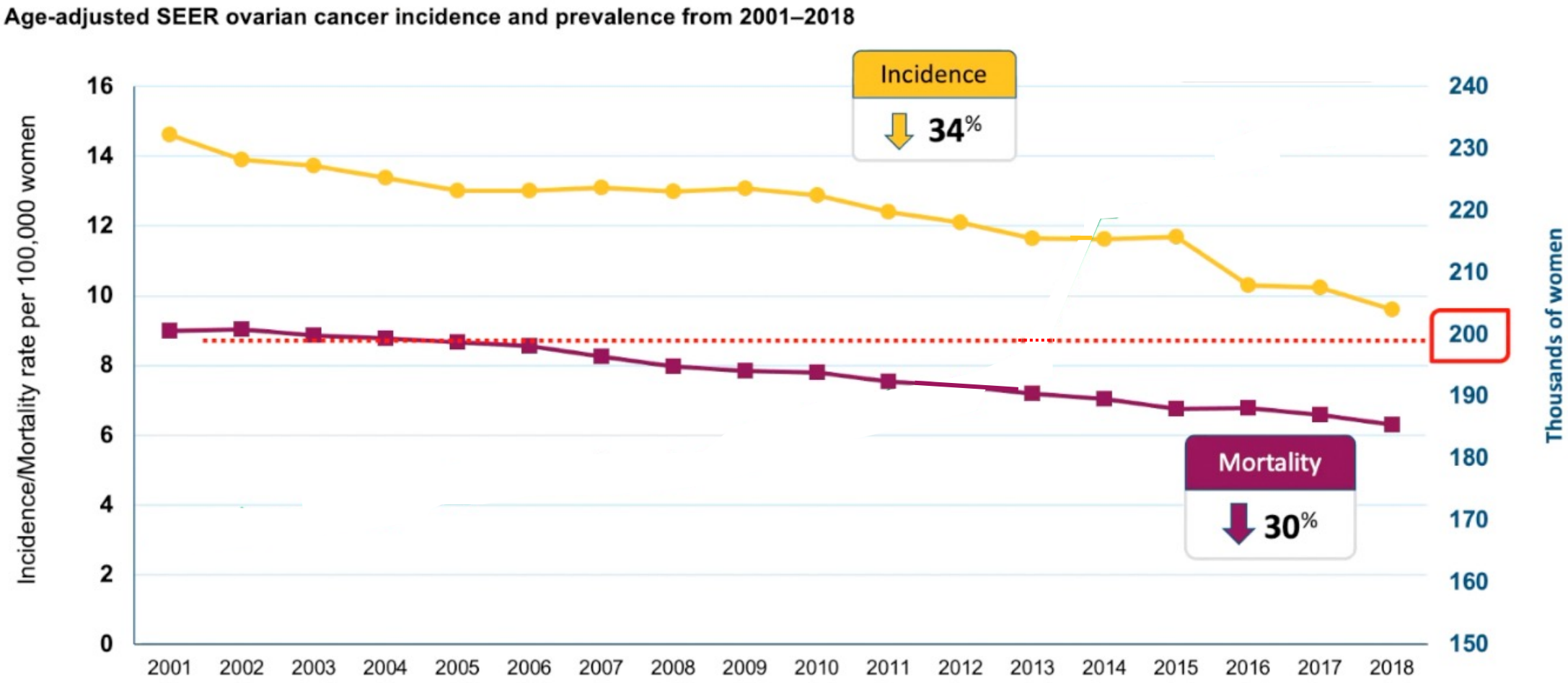
Chief Scientific Officer, US Oncology Research

The Woodlands, TX, USA

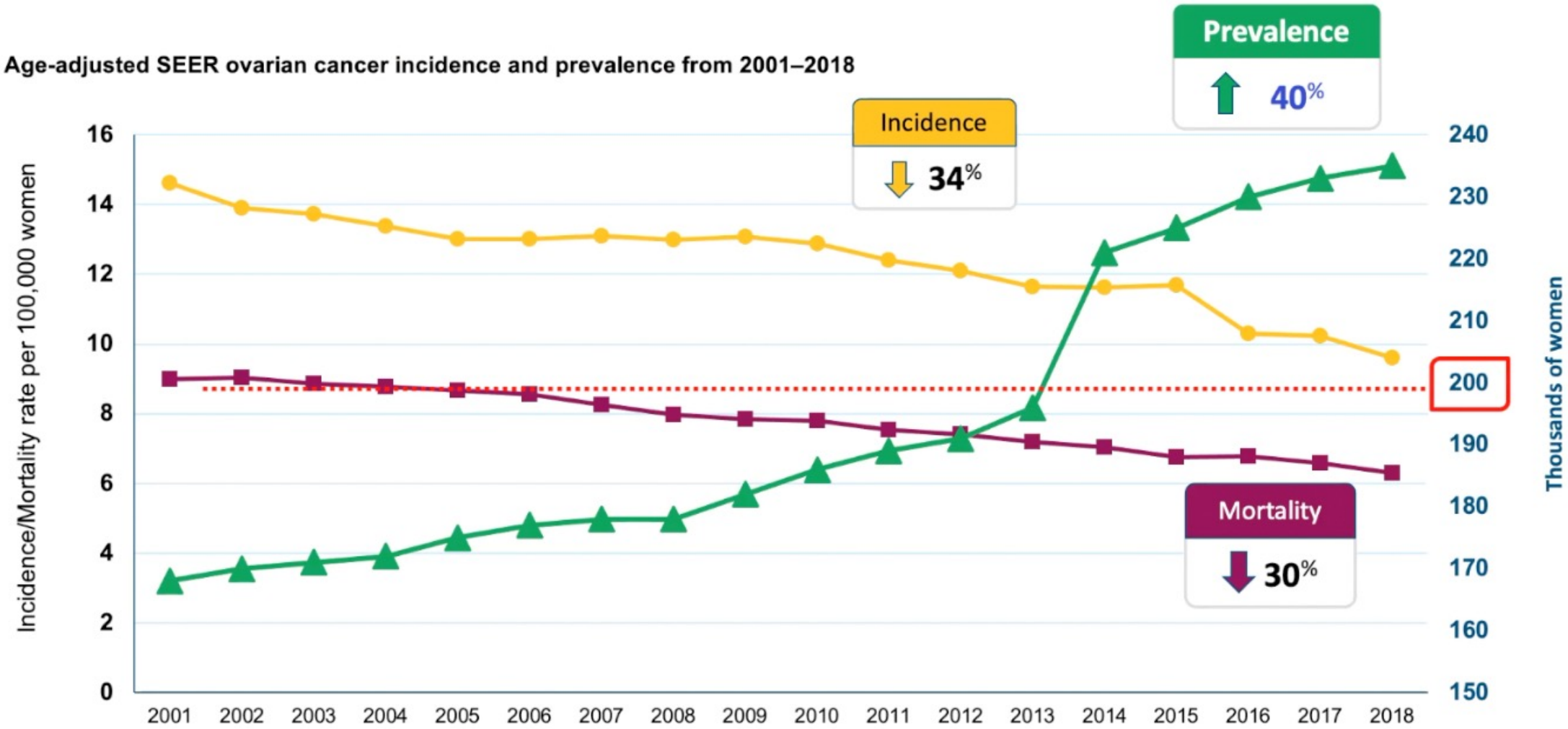
Dr Coleman — Disclosures

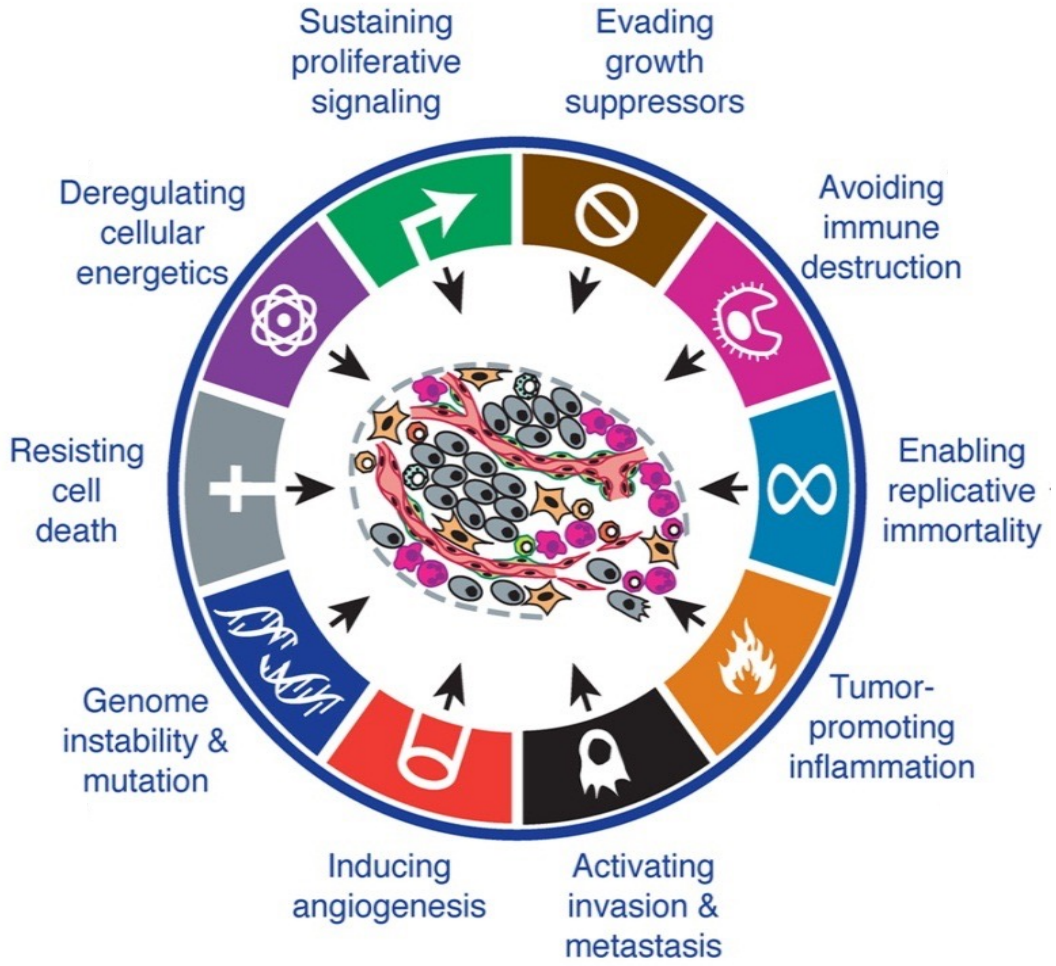
Advisory Committee	Agenus Inc, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Janssen Biotech Inc, Merck, Novartis, OncXernaTherapeutics Inc, Onxeo
Consulting Agreements	AbbVie Inc, Agenus Inc, Alkermes, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, Genentech, a member of the Roche Group, Genmab, GlaxoSmithKline, Gradalis Inc, ImmunoGen Inc, Incyte Corporation, Janssen Biotech Inc, Merck, Myriad Genetic Laboratories Inc, Novartis, OncXerna Therapeutics Inc, Onxeo, Seagen Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Clovis Oncology, Genentech, a member of the Roche Group, ImmunoGen Inc, Merck, Novartis
Data and Safety Monitoring Board/Committee	GOG Foundation Inc, VBL Therapeutics
Employment	Texas Oncology

Ovarian Cancer: Epidemiologic Trends



Ovarian Cancer: Epidemiologic Trends



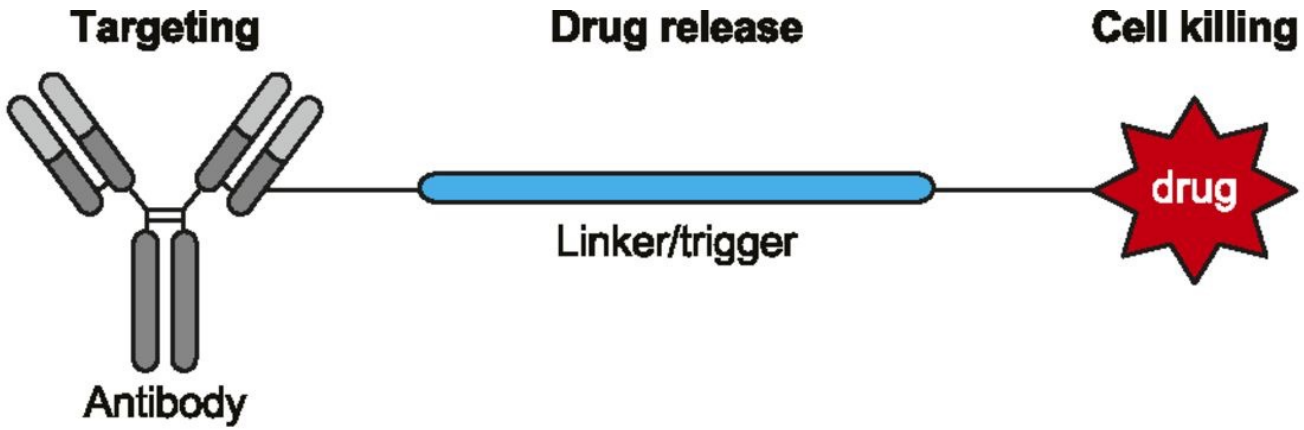


Hanahan, Cell (2011)

Other Modalities Under Development

- ADC's
  - Mirvetuximab Soravtansine: Fr-α
  - Tisotumab vedotin: tissue factor
  - Upifitamab Rilsodotin: NaPi2b
  - Others (B7H4, FRB, Trop-2, Her2, etc)
- Oncolytic Virus
  - VB-111
- Vaccines
  - WT-1
- Tumor Treatment Fields
  - INNOVATE3
- Pathway inhibitors
  - DDR: PARPi, ATR, CHK1/2, CDK
  - Cell Cycle inhibitors: WEE-1, CDK
  - MAPK and PI3K/AKT/mTOR/S6
  - Angiogenesis
  - Metabolomics
- Immunotherapy
  - PD-1/…
- Bi-specific antibodies and conjugates

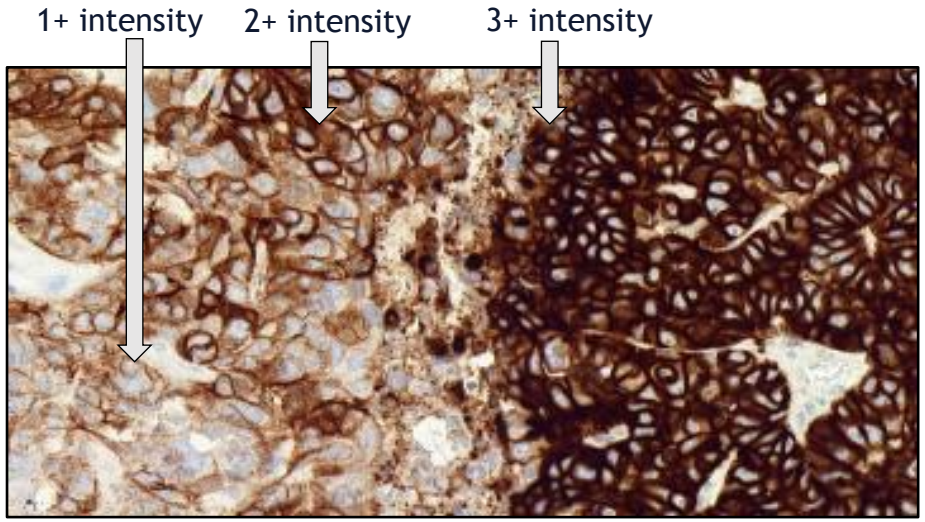
Antibody Drug Conjugates: Targeted Cytotoxicity



Targeted antigen	Release mechanism	MOA
Tumor Specific	Cleaved by reduction	Microtubule disruption DM1, DM4, MMAE, MMAF
Minimal Normal Expression	Cleaved by low pH	DNA damage calicheamicin, duocarmicin, SN-38, D6.5, PDB dimers
Internalizing	Cleaved by proteases	Transcriptional Inhibitor amanitin
Prevalent in cancers	Non-cleavable	
Abundant in cancers		

Folate Receptor Alpha (FRα)

- FRα is a cell surface folate receptor which mediates folate transport into epithelial cells
- FRα expression is limited on normal cells, but is upregulated on cancers, primarily ovarian, but also endometrial, and triple negative breast
- It is most highly expressed on the surface of serous epithelial ovarian cancers (EOC) – As assessed by immunohistochemistry (IHC)



STUDY DESIGN

FORWARD I

- Platinum-resistant ovarian cancer
- FRα-positive tumor expression
  - Medium (50-74% cells positive)
  - High (≥75% cells positive)
- ECOG performance status 0 or 1
- 1-3 prior therapies

Statistical Assumptions

- Hochberg procedure
- α=0.05 (two-sided), power = 90%
  HR=0.58; control arm mPFS 3.5 mos

Mirvetuximab Soravtansine (n=248)

6 mg/kg (adjusted ideal body weight) once every 3 weeks

2:1 Randomization

Stratification Factors:
FRα expression (medium or high)
Prior therapies (1 and 2, or 3)
Choice of chemotherapy

Investigator's Choice Chemotherapy
Paclitaxel, PLD†, or Topotecan (n=118)

***Paclitaxel**: 80 mg/m^2 weekly*
***PLD**: 40 mg/m^2 once every 4 weeks*
***Topotecan**: 4 mg/m^2 on Days 1, 8, and 15 every 4 weeks; or 1.25 mg/m^2 on Days 1-5 every 3 weeks*

Primary Endpoint

Progression-free survival (PFS; by BIRC*) for ITT and high FRα populations

*BIRC = Blinded Independent Review Committee; analyzed by Hochberg procedure

Secondary Endpoints

Overall response rate (ORR)
Overall survival (OS)
Patient reported outcomes (PRO)

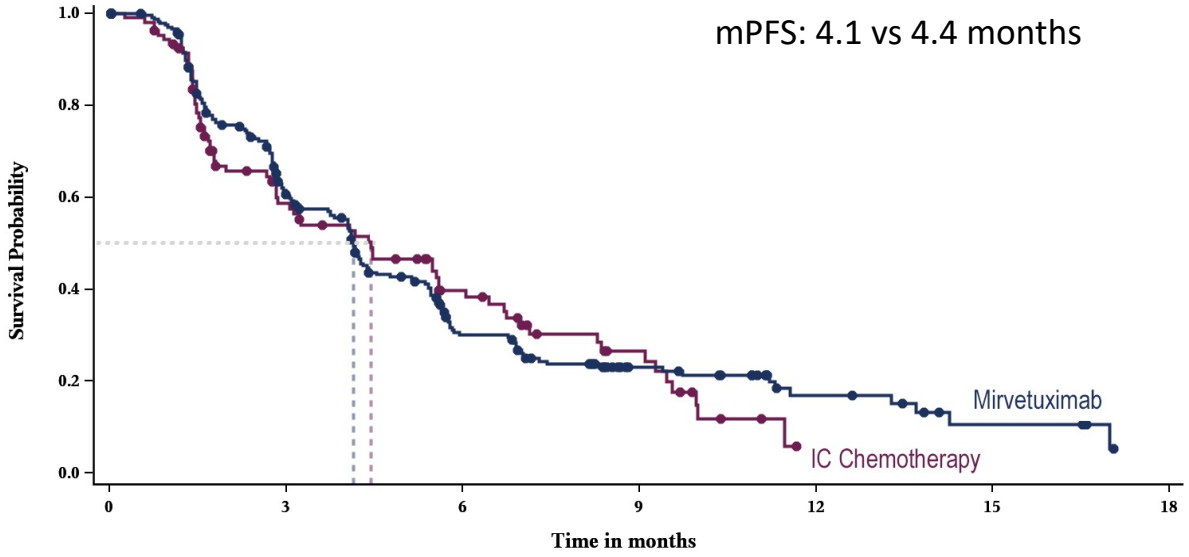
BARCELONA 2019 ESMO congress

†Pegylated liposomal doxorubicin
ClinicalTrials.gov Identifier: NCT02631876

Primary Endpoint: Progression-Free Survival (By BIRC)

ITT

HR: 0.981 P=0.897
mPFS: 4.1 vs 4.4 months



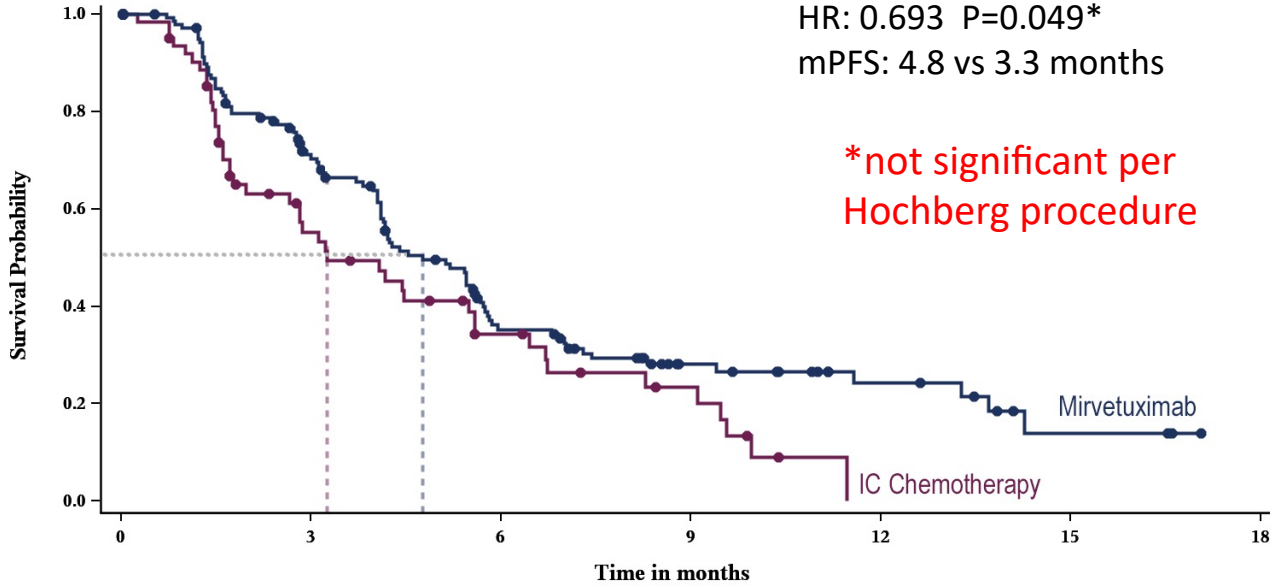
No. at risk

Mirvetuximab	248	132	54	26	11	4	0
IC Chemo	118	50	27	12	0		

FRα High^

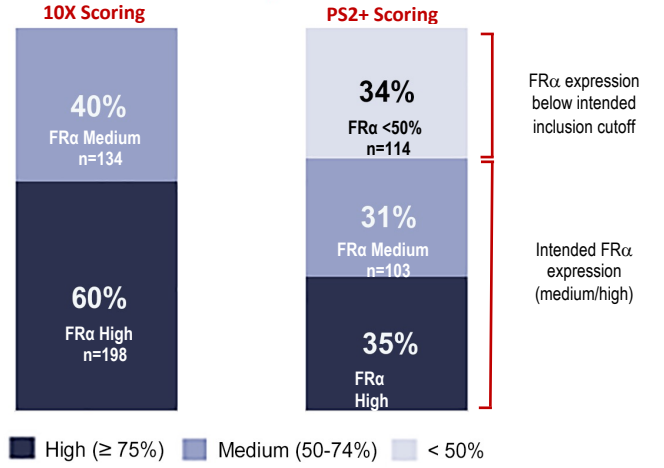
HR: 0.693 P=0.049*
mPFS: 4.8 vs 3.3 months

*not significant per Hochberg procedure



No. at risk

Mirvetuximab	147	88	38	19	10	3	0
IC Chemo	71	28	14	7	0		



Moore, Ann Oncol 2021

Mirvetuximab Soravtansine: SORAYA Trial

INCLUSION CRITERIA

- Platinum-resistant disease (PFI < 6 months)
- **FRα-high only PS2+ scoring**
- Prior bevacizumab required
- Prior PARPi allowed
- 1 to 3 prior lines allowed
- Patients with BRCA mutations allowed

PRIOR TREATMENT

51%
3 prior lines of therapy

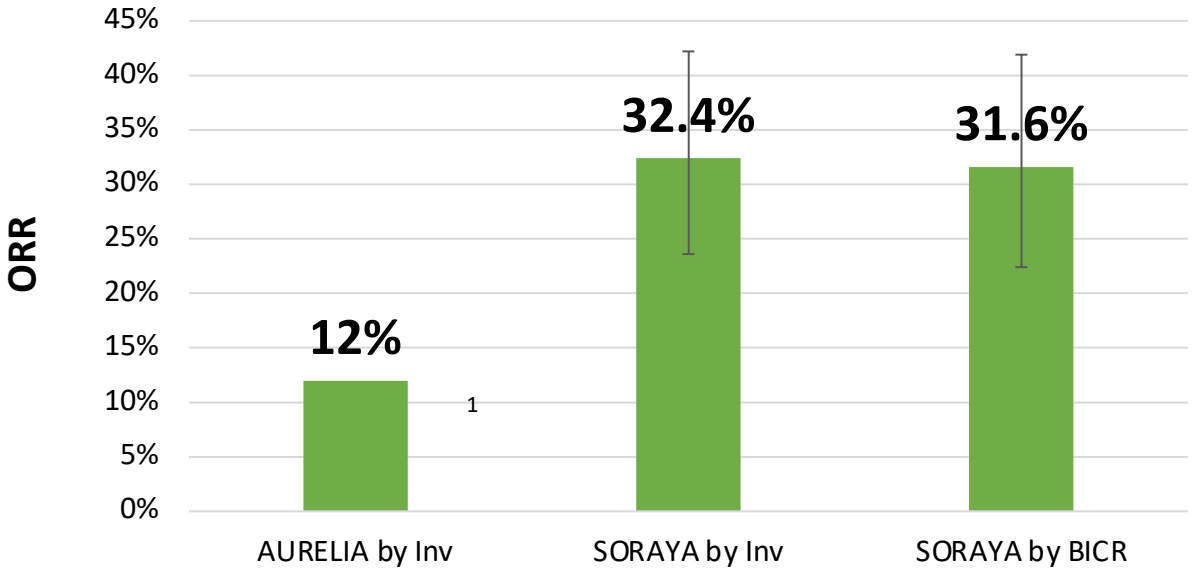
100%
Received prior bevacizumab

48%
Received prior PARPi

SAFETY AND TOLERABILITY

- The most common AEs were low-grade gastrointestinal and ocular events, including blurred vision, keratopathy, and nausea;
- 7% of patients discontinued due to treatment-related AEs, including one patient due to ocular AE

PRIMARY ENDPOINT[2]



[1]

KEY SECONDARY ENDPOINT

6.9 months mDOR

By Investigator at Data Cutoff *(95% CI: 5.6, 8.1)*

[1]AURELIA Study, JCO 2014, Pujade-Lauraine, E., et al.; [2]Matalonis, SGO 2022 annual meeting

GOG 3045

MIRASOL

PHASE 3 RANDOMIZED TRIAL FOR MIRVETUXIMAB USING PS2+ SCORING IN FRα-HIGH, PLATINUM-RESISTANT OVARIAN CANCER

ENROLLMENT AND KEY ELIGIBILITY

- 430 patients/330 events for PFS by Investigator
- Platinum-resistant disease (primary PFI >3 mos)
- Prior bevacizumab allowed*
- Prior PARPi allowed
- Patients with BRCA mutations allowed

1:1 RANDOMIZATION

Mirvetuximab Soravtansine

STRATIFICATION FACTORS
IC Chemotherapy (Paclitaxel, PLD, Topotecan)
Prior Therapies (1 vs 2 vs 3)

Investigator's Choice Chemotherapy Paclitaxel, PLD, or Topotecan

PRIMARY ENDPOINT

PFS by Investigator
BICR for Sensitivity Analysis

SECONDARY ENDPOINTS

ORR by Investigator, OS, and PRO

ClinicalTrials.gov Identifier: NCT04209855

GOG FOUNDATION®
Transforming the standard of care™

Mirvetuximab Development and Combinations

MIRVETUXIMAB PSOC MONOTHERAPY

PHASE 1 EFFICACY DATA[1]

64% ORR

FRα-HIGH RECURRENT OVARIAN CANCER
n= 11

- Potential for a clinically meaningful benefit in FRα-high recurrent platinum-sensitive ovarian cancer
  - 64% ORR (7/11); 2 CRs and 5 PRs

PICCOLO

- Single-arm Phase 2 trial for mirvetuximab in FRα-high patients with platinum-sensitive ovarian cancer
- Now enrolling
- Potential for label expansion in 2024

MIRVETUXIMAB IN COMBINATION

MIRVETUXIMAB + BEVACIZUMAB[2,3]

64% ORR

FRα-HIGH RECURRENT OVARIAN CANCER
n= 33

- Compelling activity in FRα-high recurrent ovarian cancer, regardless of platinum status
  - 59% ORR (10/17), 9.4 month mDOR, 9.7 month mPFS in the platinum-resistant subgroup
  - 69% ORR (11/16), 12.7 month mDOR, 13.3 month mPFS in the platinum-sensitive subgroup

GLORIOSA

- Randomized Phase 3 trial for mirvetuximab + bevacizumab maintenance in FRα-high platinum-sensitive ovarian cancer
- Aligned with FDA on trial design

MIRVETUXIMAB + CARBOPLATIN[4]

80% ORR

15 MOS mPFS
FRα-MED and -HIGH
n= 10

- Highly active in recurrent platinum-sensitive ovarian cancer with mDOR of 24 months
- Supporting ongoing ISTs in recurrent platinum-sensitive ovarian cancer: ~70 patient neo-adjuvant study initiated in H1 2021; and a randomized Phase 2 ~140 patient study

TRIAL 420

- Single-arm Phase 2 trial for mirvetuximab + carboplatin followed by mirvetuximab continuation in FRα-low, medium, and high patients with platinum-sensitive ovarian cancer

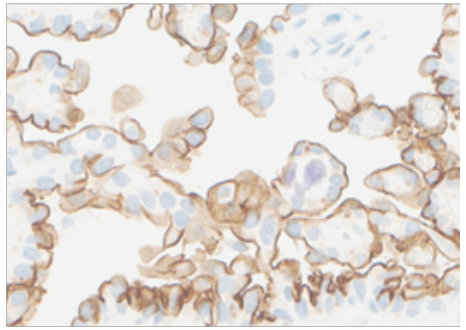
[1]Immunogen internal data on file. [2]ASCO 2020 Oral Presentation; Gilbert, L., et al. [3]ASCO 2021 Oral Presentation; O'Malley, D., et al. [4]Gynecologic Oncology 151 (2018) 46-52.

NaPi2b is an Ideal Antibody-Drug Conjugate (ADC) Target

- ADC internalizing sodium phosphate transporter; not an oncogene
- Broadly expressed in ovarian cancer and NSCLC adenocarcinoma
- Limited expression in normal tissues
- IHC assay calibrated to distinguish wide range of expression

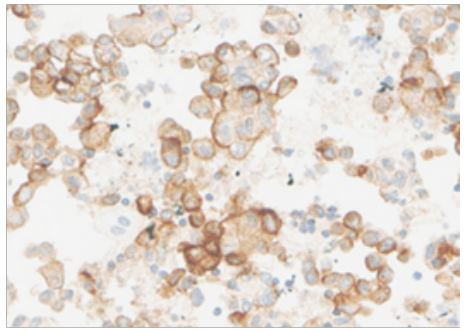
Epithelial ovarian cancer

H score = 293



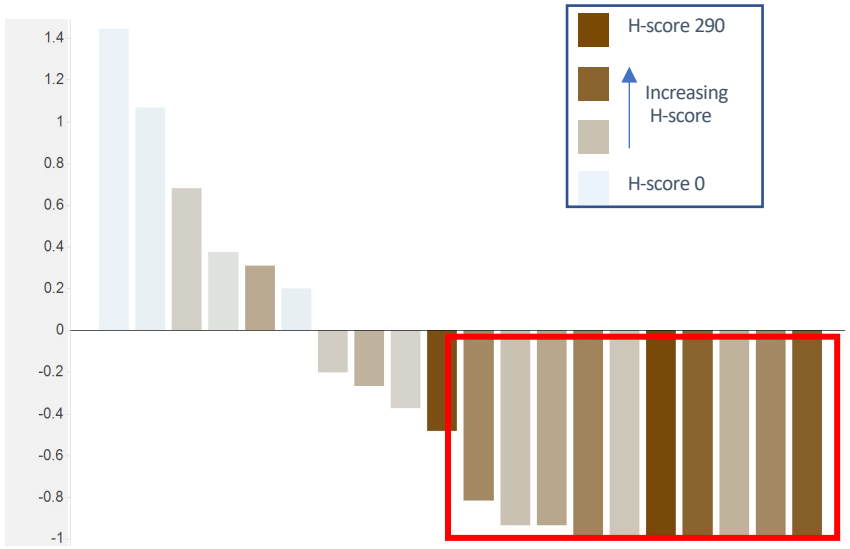
Lung adenocarcinoma

H score = 265



Ovarian Cancer Patient-Derived Xenograft Models

Response correlated with NaPi2b Expression



H-score measures the percentage of cells staining multiplied by their intensity (0, 1+, 2+, 3+) for a range of 0 - 300

Phase I Expansion Study of Upifitamab Rilsodotin: Efficacy Results

Outcome Response for Evaluable Patients with OC

- Response observed within 2 cycles in 70 % of patients (7 of 10)
- Response observed within 4 cycles in 100% of patients (10 of 10)

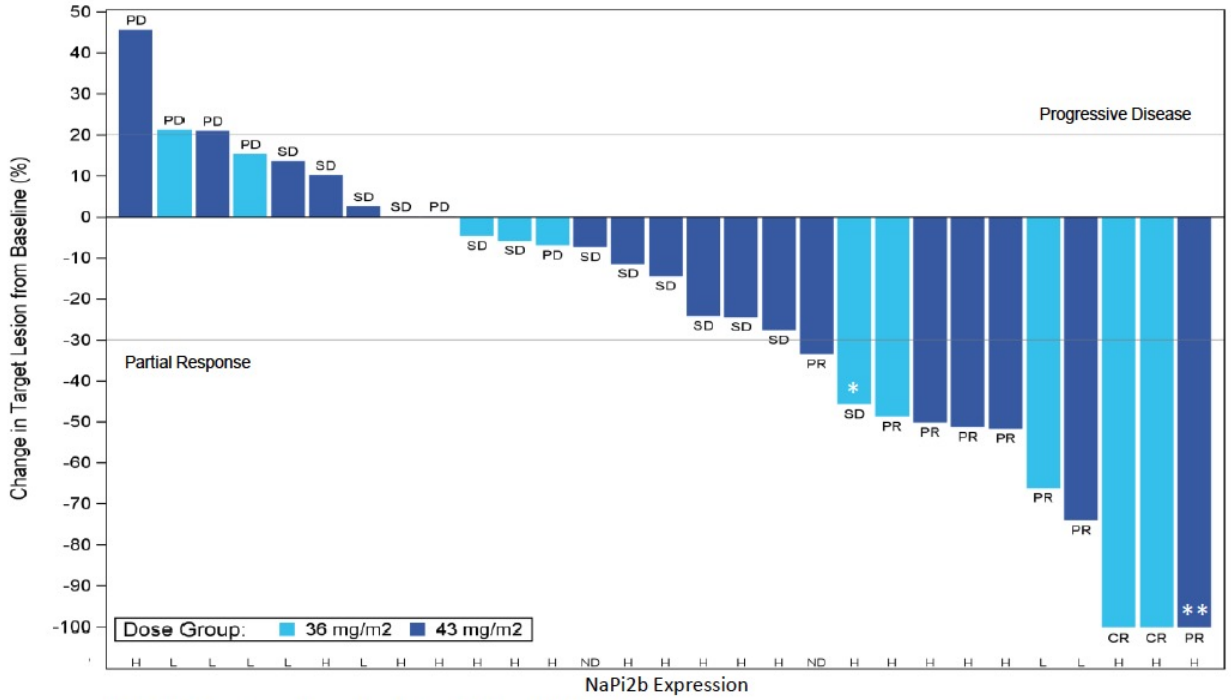
Table 2. Efficacy Results in Evaluable Patients with OC (n=29)

Endpoint	All Patients (n = 29)	Higher NaPi2b (n = 20)	Lower NaPi2b (n = 7)	NaPi2b ND (n = 2)
CR; n(%)	2 (7)	2 (10)	0	0
PR; n (%)	8 (28)	5 (25)	2 (29)	1 (50)
SD; n (%)	13 (45)	10 (50)	2 (29)	1 (50)
PD; n (%)	6 (21)	3 (15)	3 (43)	0
ORR [CR + PR]; n (%)	10 (34)	7 (35)	2 (29)	1 (50)
DCR [CR + PR + SD]; n (%)	23 (79)	17 (85)	4 (57)	2 (100)

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ORR = objective response rate; DCR = disease control rate; ND = not determined (i.e., Hypocellular specimen/indeterminate for H-score or not determined yet)

- Of the 47 patients with OC, 29 were evaluable at the time of data cut
- 18 patients were not evaluable for RECIST response
  - 15 patients did not have RECIST assessment as of data cut
  - 3 patients discontinued prior to receiving the first scan (1 clinical progression [lower NaPi2b expression]; 1 withdrew consent [lower NaPi2b expression]; 1 unrelated Grade 5 SAE [lower NaPi2b expression])

Figure 4. Maximum % Change from Baseline in Target Lesions in Patients with OC

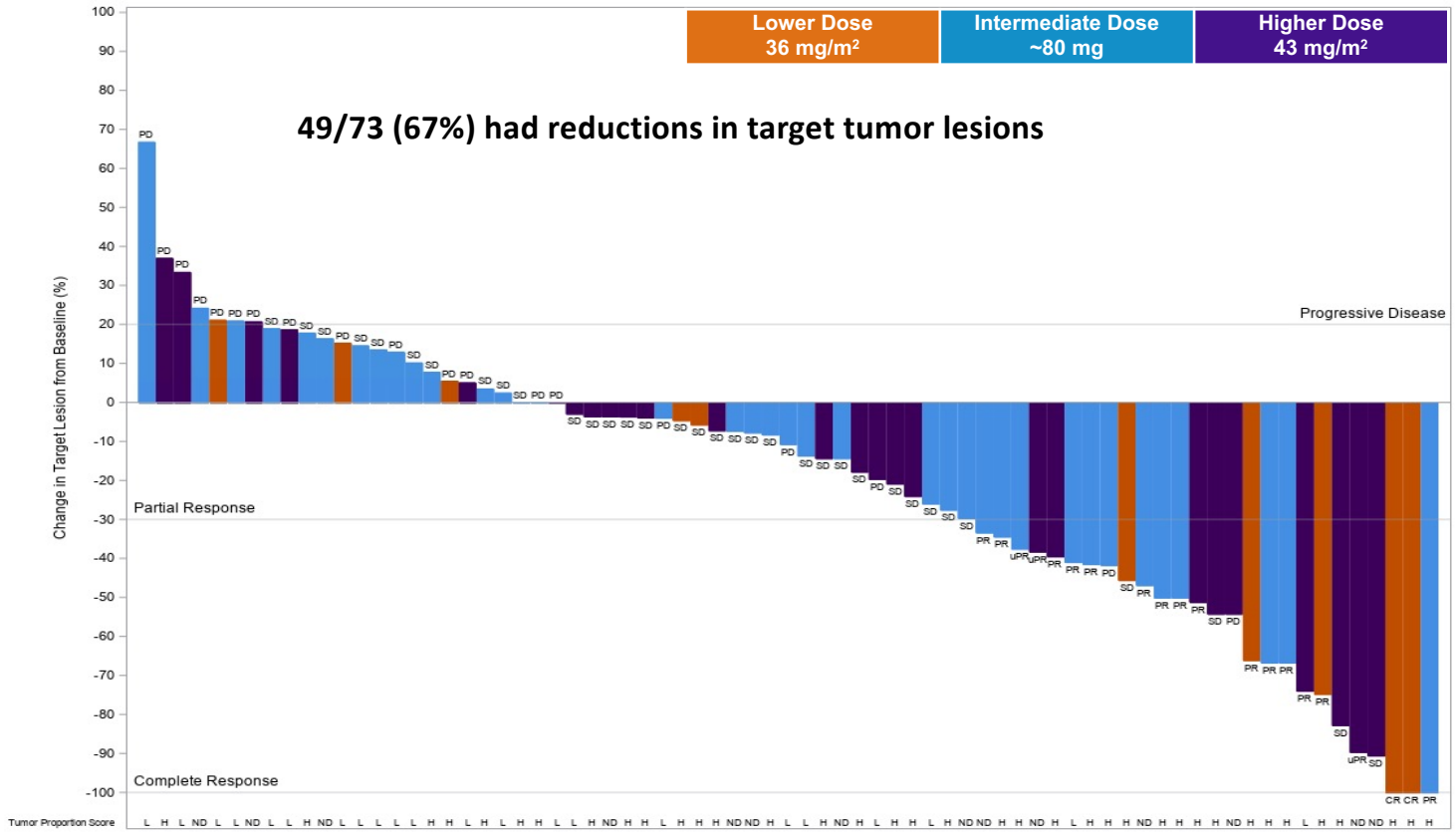


* Following PR next scan showed new lesions, BOR per RECIST v1.1 is SD
** CR of target lesions and non-CR/non-PD of non-target lesions, BOR per RECIST v1.1 is PR
Abbreviations: PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response; H = Higher NaPi2b Expression; L = Lower NaPi2b Expression; ND = not determined (i.e., Hypocellular specimen/indeterminate for H-score or not determined yet)

Hamilton E et al, ESMO 2020; Abstract 836P

Antibody Drug Conjugates: Upifitamab in PROC – UPLIFT Cohort

Maximum % Change from Baseline in Target Lesions in Evaluable Patients with Ovarian Cancer (n=73*)



Best Response in Evaluable Patients with Ovarian Cancer (n=75**)

	NaPi2b High (TPS≥75)	NaPi2b Low (TPS<75)	Not Yet Determined NaPi2b	All Patients
N	**38**	**23**	**14**	**75**
CR	2 (5)	0	0	2 (3)
PR	11 (29)	2 (9)	2 (14)	15 (20)
uPR	1 (3)	0	2 (14)	3 (4)
SD	19 (50)	8 (35)	7 (50)	34 (45)
PD	5 (13)	13 (57)	3 (21)	21 (28)
Confirmed ORR	**13 (34)**	**2 (9)**	**2 (14)**	**17 (23)**
DCR	**33 (87)**	**10 (43)**	**11 (79)**	**54 (72)**

Median Duration of Response in NaPi2b High: ~5 months

CR, complete response; DCR, disease control rate; PR, partial response; H, high NaPi2b expression; L, low NaPi2b expression; ND, NaPi2b expression not yet determined or tissue not available; ORR, overall response rate; uPR, unconfirmed PR.
*2 pts in waterfall plot excluded as post-baseline tumor measurement shows "Not Measurable", yet "PD" was assigned by Investigator in the response dataset. **22 patients were not evaluable by RECIST 1.1: 10 deaths (4 disease progression, 2 pneumonitis, 2 sepsis, 1 viral pneumonia, 1 unknown); 5 patient withdrawals; 1 enrolled in hospice; 1 clinical progression; 4 discontinued treatment; 1 had not yet reached first scan.
Data cut June 10, 2021.

UPLIFT: Single Arm Study/GOG 3048

XMT-1536: Upifitamab rilsodotin - “Up-Ri”

Patient Population:

No Pre-Selection for NaPi2b

Inclusion Criteria:
Platinum Resistant Ovarian Cancer
1 – 4 Prior Lines

Exclusion Criteria:
1 – 2 Prior Lines Bev-naïve
Primary Platinum Refractory Disease

Global:
US, Europe,
Australia, Canada

Dose:
43 mg/m^2 q4w

N:
~180 Patients

36 mg/m^2 q4w

Primary Endpoint:
Confirmed ORR in higher NaPi2b

Key Secondary Endpoint:
Confirmed ORR in overall population

Other Secondary Endpoints:

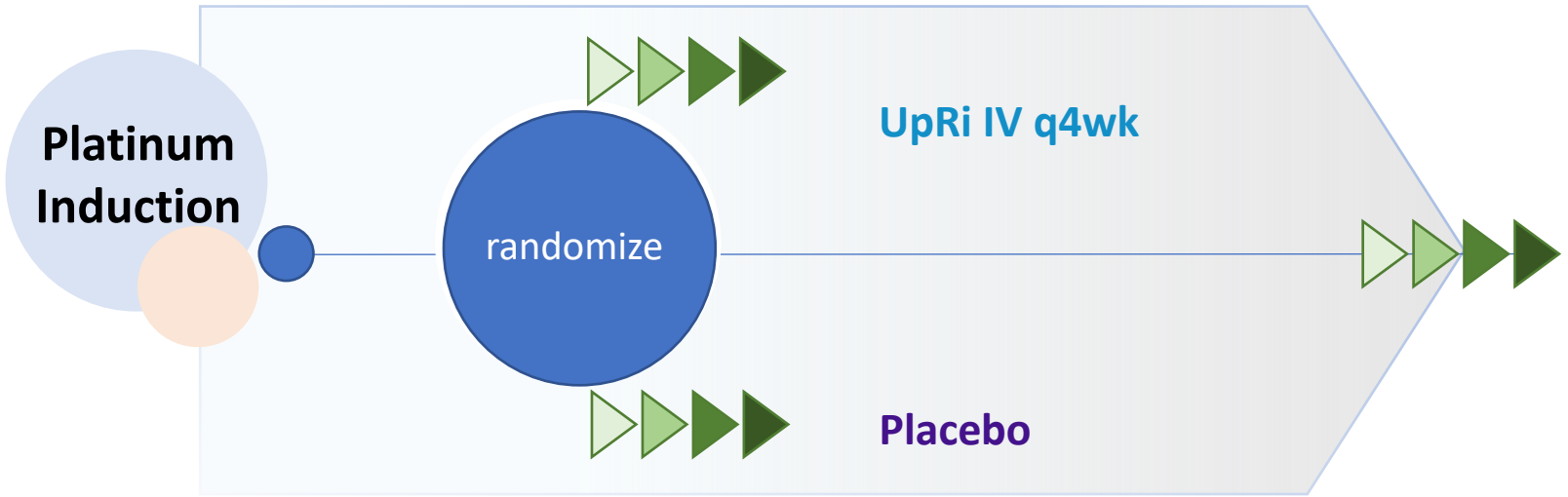
- Duration of Response
- Safety

ClinicalTrials.gov Identifier: NCT03319628

UP-NEXT/GOG-3049: Phase 3 Study of UpRi Monotherapy Maintenance vs Placebo in Platinum-Sensitive Recurrent OC

Key Enrollment Criteria:

- Platinum-sensitive recurrence, following platinum induction
- NaPi2b high biomarker selection by TPS≥75
- 2–4 prior platinum-based regimes (including induction)
- Prior PARPi therapy allowed, but only required for BRCAmut
- SD in addition to CR/PR as best response following platinum induction



Primary Endpoint:

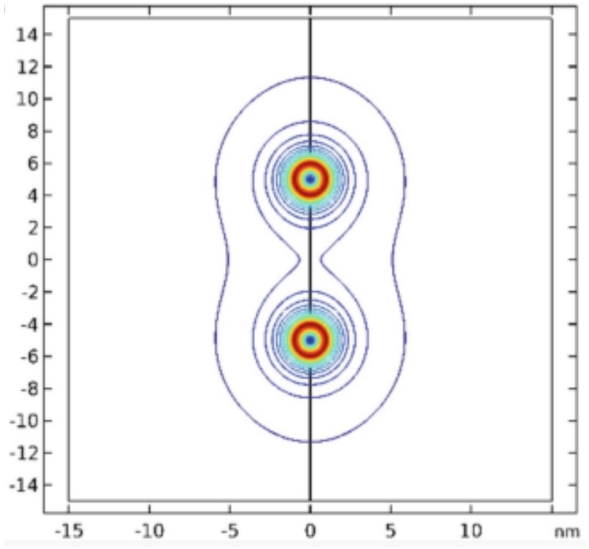
- PFS

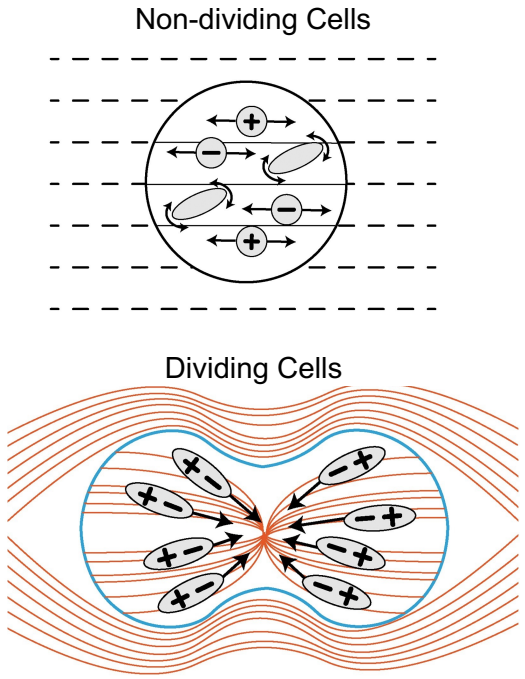
BRCAmut, breast cancer gene mutated; CR, complete response; OC, ovarian cancer; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PR, partial response; SD, stable disease.

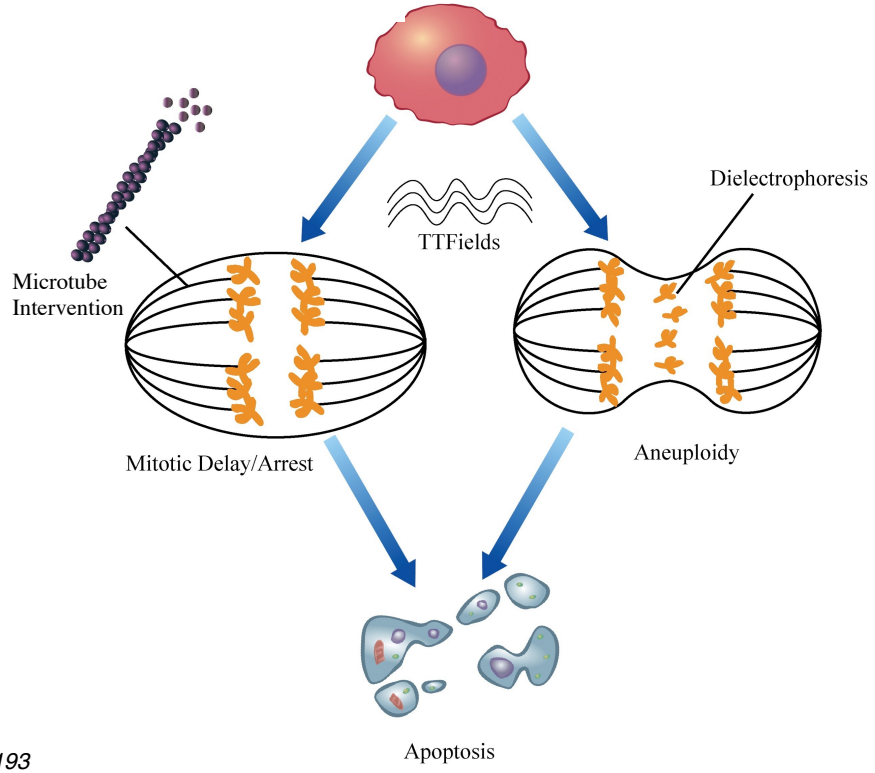
Upifitamab rilsodotin is an investigational agent not approved for use in any country.

Tumor Treatment Fields

Dividing Cell under TTF
Selective Electric Field Sensitivity







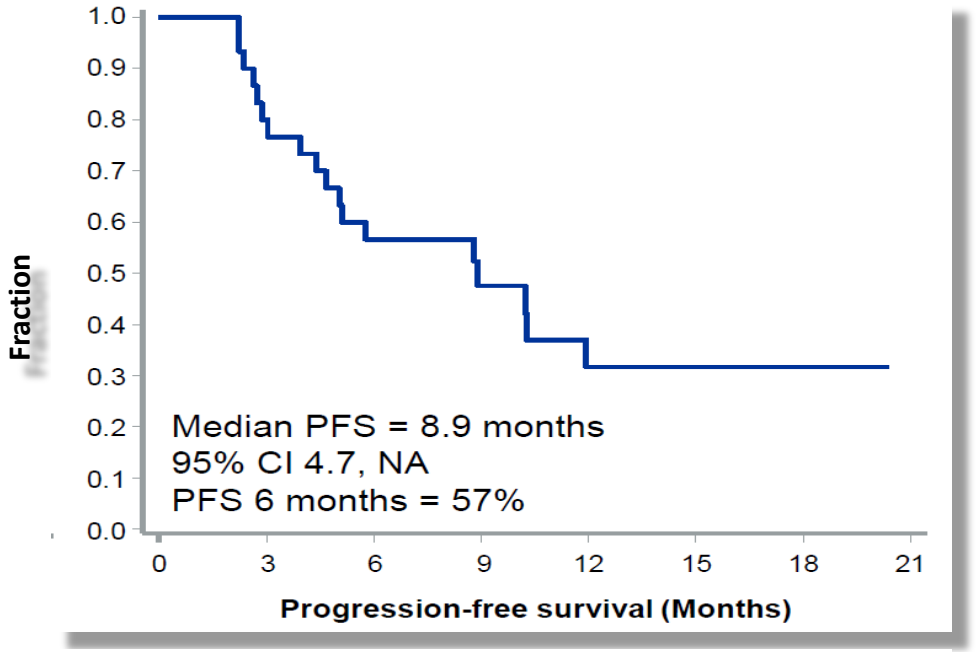
Luo et al. *Biomedicine and Pharmocotherapy 2020; 127:110193*

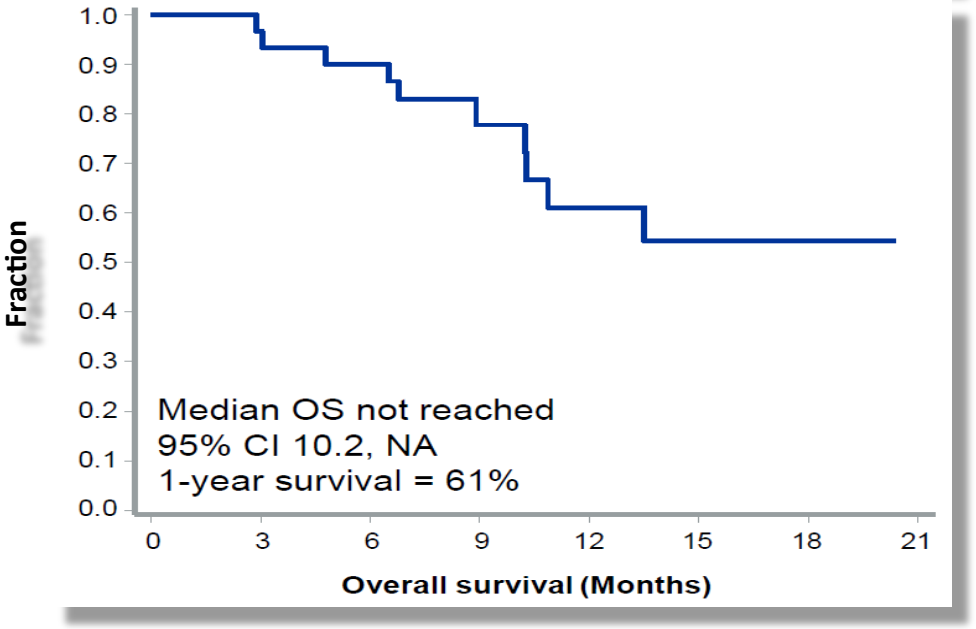
Luo et al. Biomedicine and Pharmacotherapy 2020;127:11013

Tumor Treatment Fields

Outcomes (PROC)	TTFields + Paclitaxel (n=31)
Median OS in months (95% CI)	NR
Survival Rates, % (95% CI) 6 months 12 months	 90 (72-97) 61 (37-78)
Median PFS in months (95% CI)	8.9 (4.7-NA)
PFS Rates, % (95% CI) 6 months	 57 (37-72)
Best Response in Patients w/Available Radiologic Data*, n (%) CR PR SD PD CBR	28 (90%) 0 (0) 7 (25%) 13 (46%) 8 (29%) 20 (71%)

*CT scans were performed every 2 months and stable disease was defined as at least for 2 months





Vergote I, et al., Gynecologic Oncology. 150: 471-477, 2018

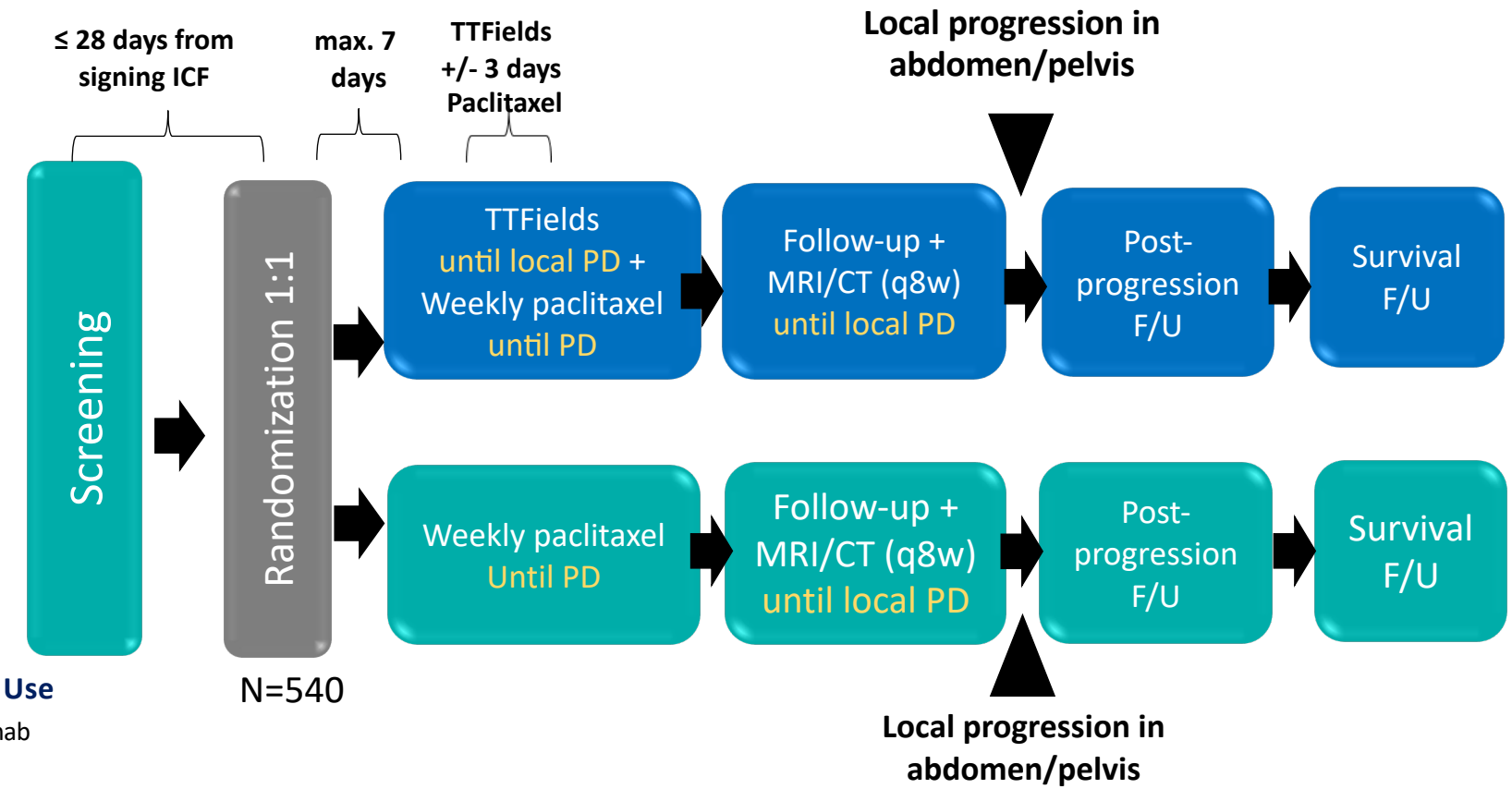
INNOVATE-3 (ENGOT-ov50 / GOG-3029) (TTFields, 200 kHz)

Enrolment target (n=540)

Number of sites (n=110)

- ENGOT enrollment began March 2019
- GOG enrollment began February 2020

Enrollment Closed October 2020



Stratification

- **Prior therapy**
  - no prior systemic therapy following PROC
  - one prior line
  - two prior lines
- **Prior Bevacizumab Use**
  - prior bevacizumab use
  - no prior bevacizumab
- **BRCA Status**
  - mutated BRCA
  - wild type BRCA/ unknown

https://clinicaltrials.gov/ct2/show/NCT03940196

VBL-111: Ofranergene Obadenovec

Gynecologic Oncology 157 (2020) 578–584

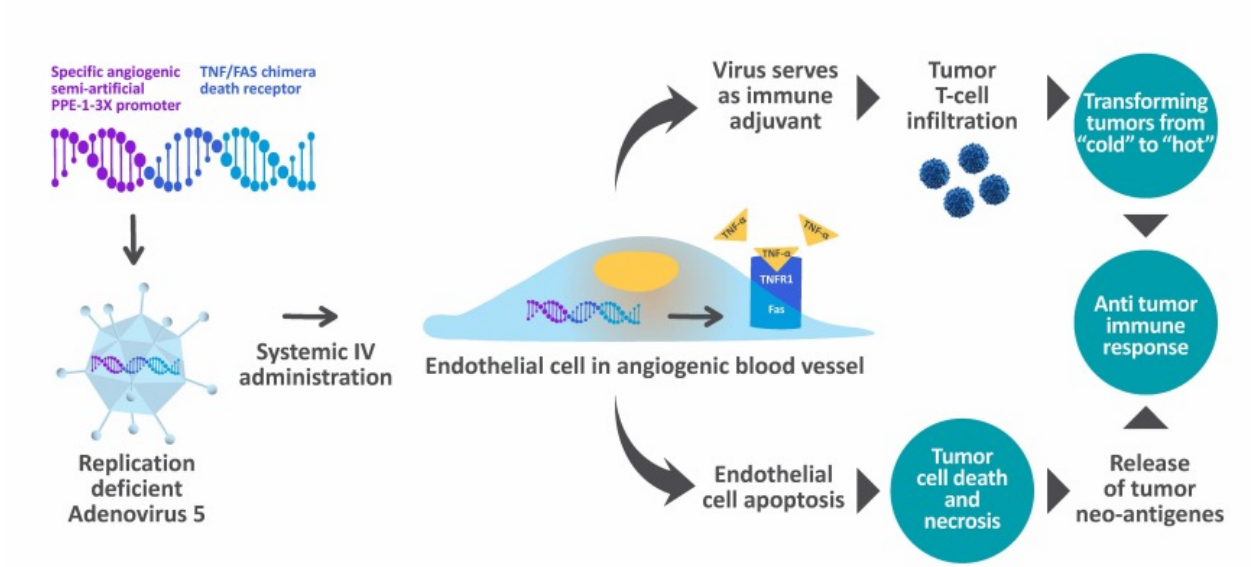
Contents lists available at ScienceDirect

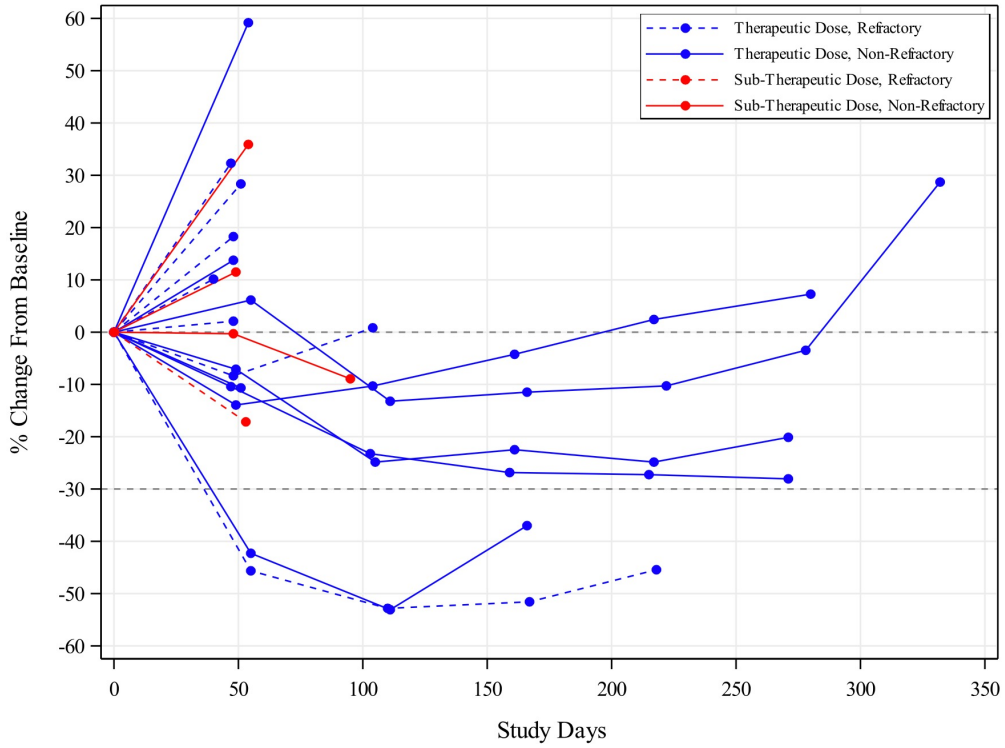
Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Ofranergene obadenovec (VB-111) in platinum-resistant ovarian cancer; favorable response rates in a phase I/II study are associated with an immunotherapeutic effect

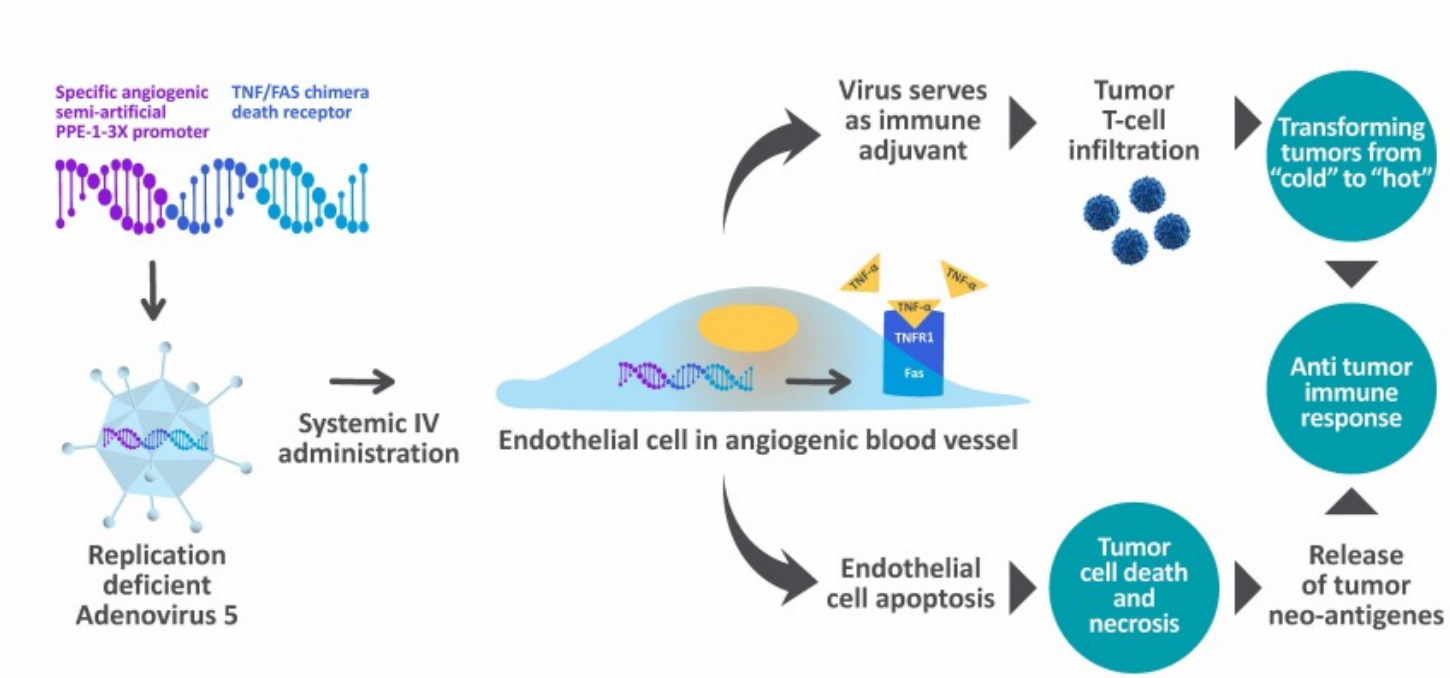
Rebecca C. Arend [a], Hannah M. Beer [a], Yael C. Cohen [d], Suzanne Berlin [c], Michael J. Birrer [e], Susana M. Campos [c], Tamar Rachmilewitz Minei [d], Dror Harats [d], Jaclyn A. Wall [a], McKenzie E. Foxall [a], Richard T. Penson [b,*]





GOG 3018: Phase III Weekly Paclitaxel +/- VBL-111

- PROC (PFI < 6 mos)
- EOC 1-5 prior lines
- Measurable disease
- Primary endpoints: **PFS/OS**



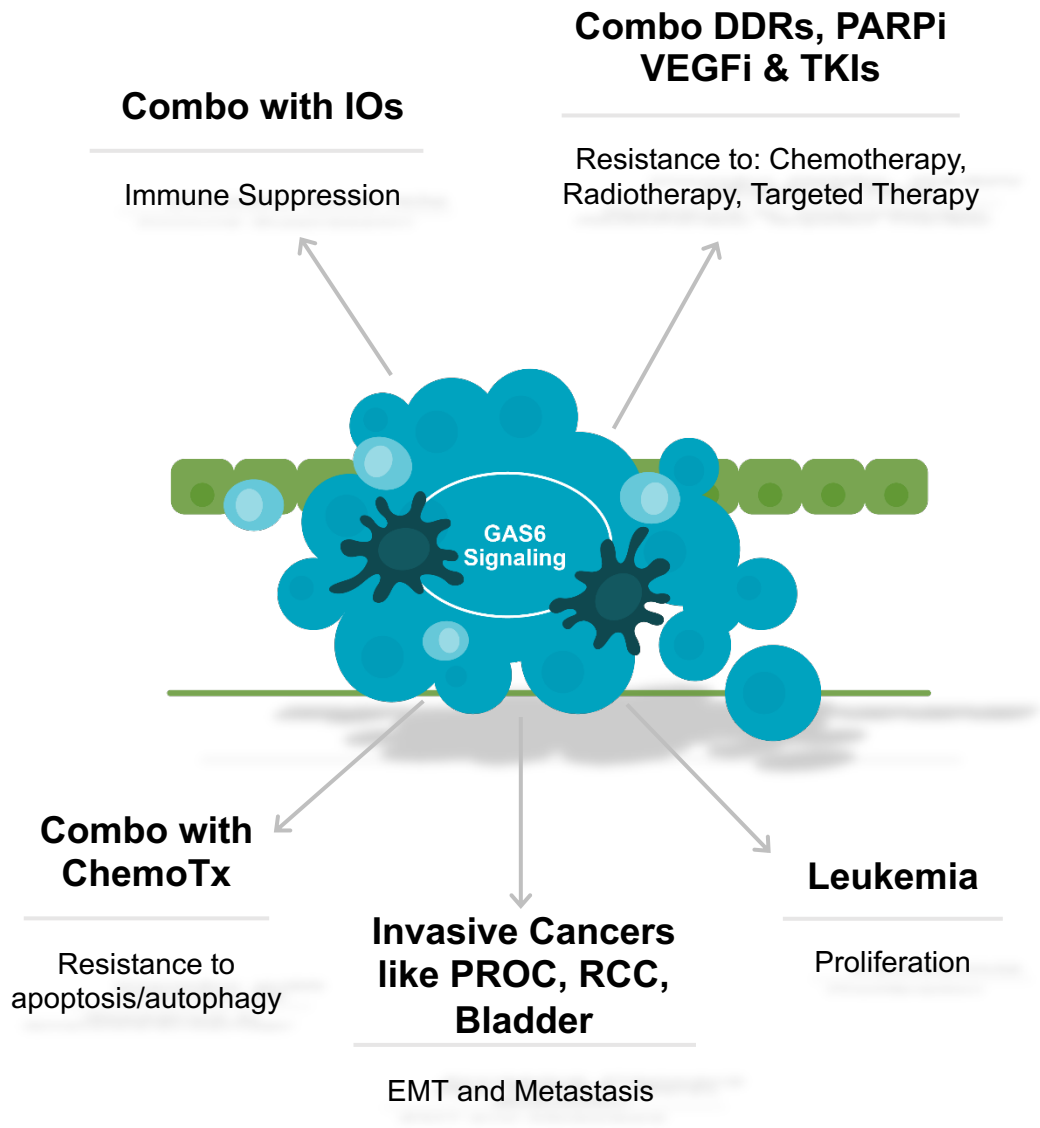
Open: Jan 2019
Status: open and accruing

ClinicalTrials.gov Identifier: NCT03398655

GAS6/AXL Signaling Pathway

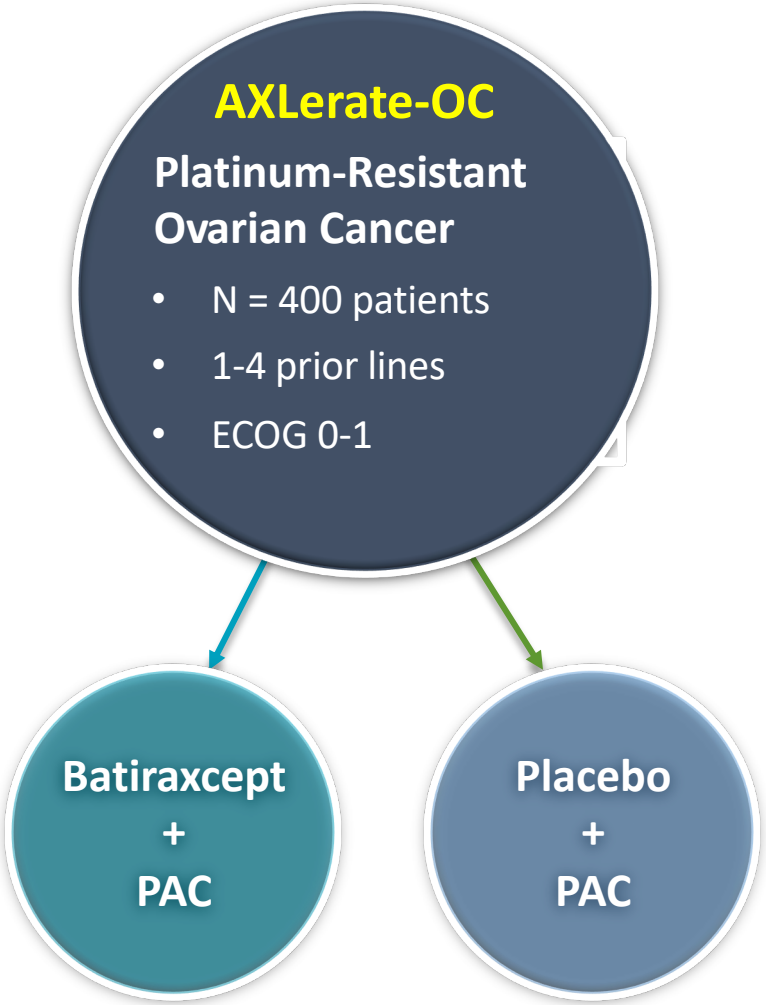
GAS6 and AXL are overexpressed in many cancers and associated with tumor growth, metastasis, drug resistance, and poor overall survival

- GAS6 is a growth factor that regulates several biologic processes in cells through interaction with its receptors, including AXL, Tyro3, and Mer
- GAS6 is the sole activating ligand of AXL
- Associated with acquired resistance to chemotherapy, platinum-containing therapy, and targeted agents
- Inhibition of GAS6 & AXL has no toxicity to normal tissues



GOG-3059: Batiraxcept (AVB-S6-500) Phase 3 Adaptive Trial Design

- Batiraxcept is a “GAS6-Trap” IgG fusion protein
- Patients with high-grade serous ovarian cancer
  - Strata: prior bevacizumab use, prior lines, and platinum-free interval
- Primary objective: **PFS**
  - Secondary endpoints: OS, ORR based on RECIST 1.1, DOR, QoL, CBR, PK/PD
- Design Element:
  - Interim analyses exploring potential biomarkers and prior bevacizumab treatment with ability to adapt and enrich patient population
- Exploratory biomarkers:
  - Serum GAS6, batiraxcept drug levels, *serum sAXL/GAS6 ratio* (Renal CC 3/22)*



ClinicalTrials.gov Identifier: NCT04729608

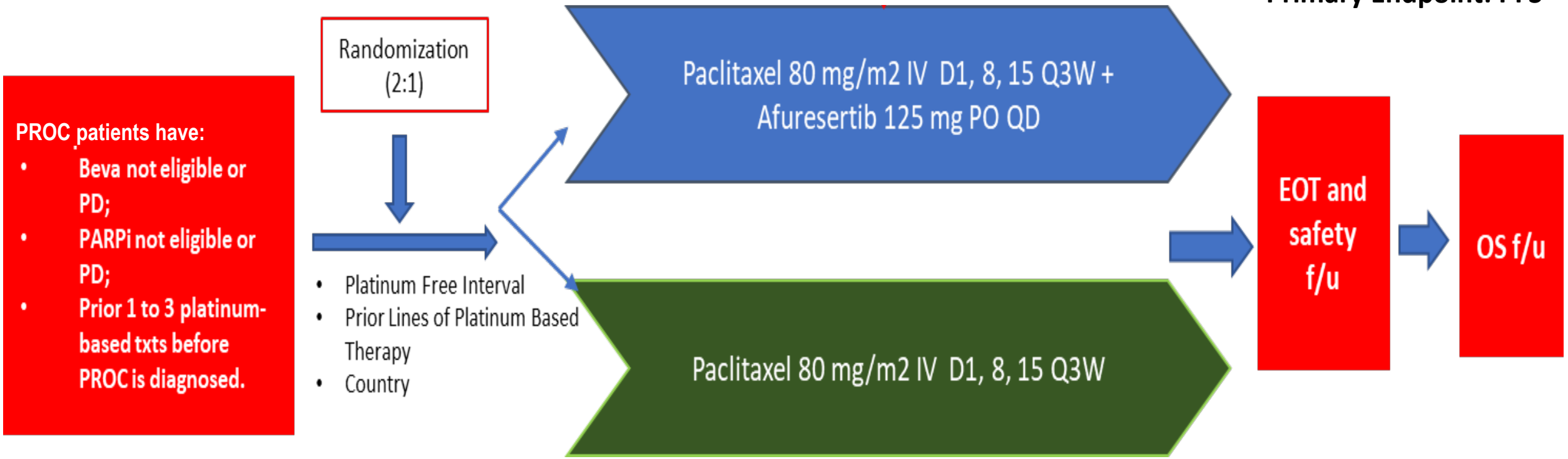
GOG FOUNDATION® Transforming the standard of care™

GOG-3044/PROFECTA-II: MOA and Rationale

- **Afuresertib** - MOA is a Pan AKT (Akt 1/2/3) inhibitor
- AKT inhibition thought to restore chemo sensitivity
- Platinum resistant disease is a rational therapeutic target
- Can be combined with chemotherapy backbone
    - Phase IB data with paclitaxel and platinum + paclitaxel

GOG-3044/PROFECTA-II: Schema

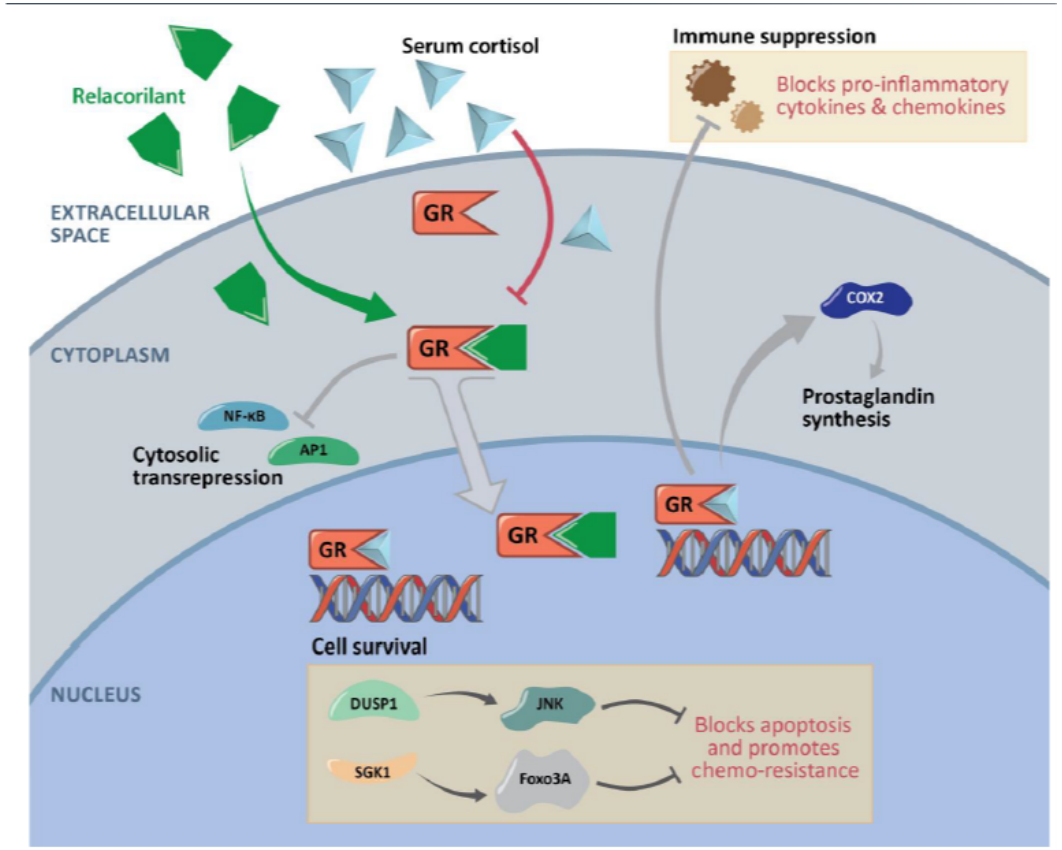
N=210
Primary Endpoint: PFS

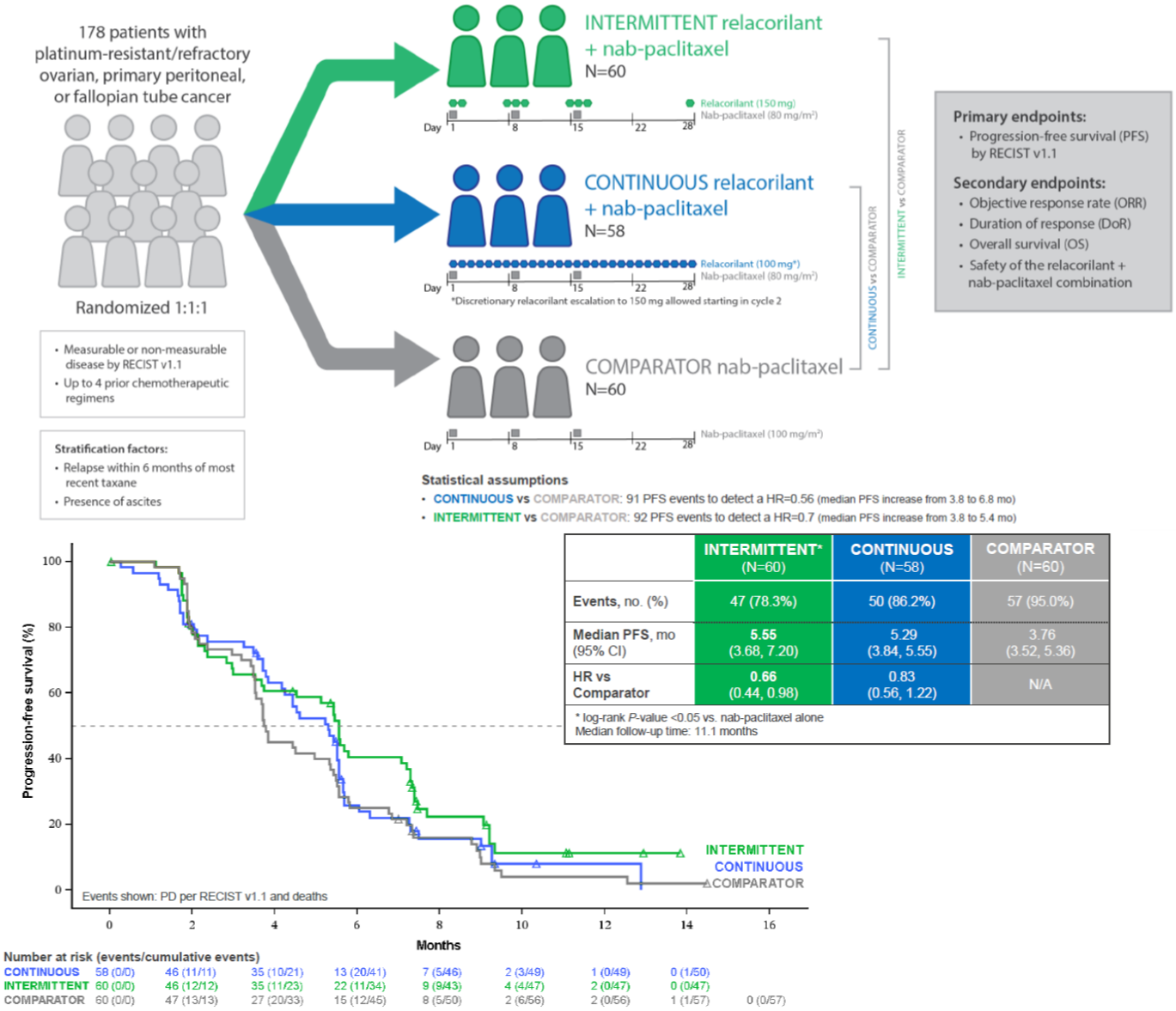


ClinicalTrials.gov Identifier: NCT04374630

GOG FOUNDATION

Synergy with Taxanes: Relacorilant + Abraxane



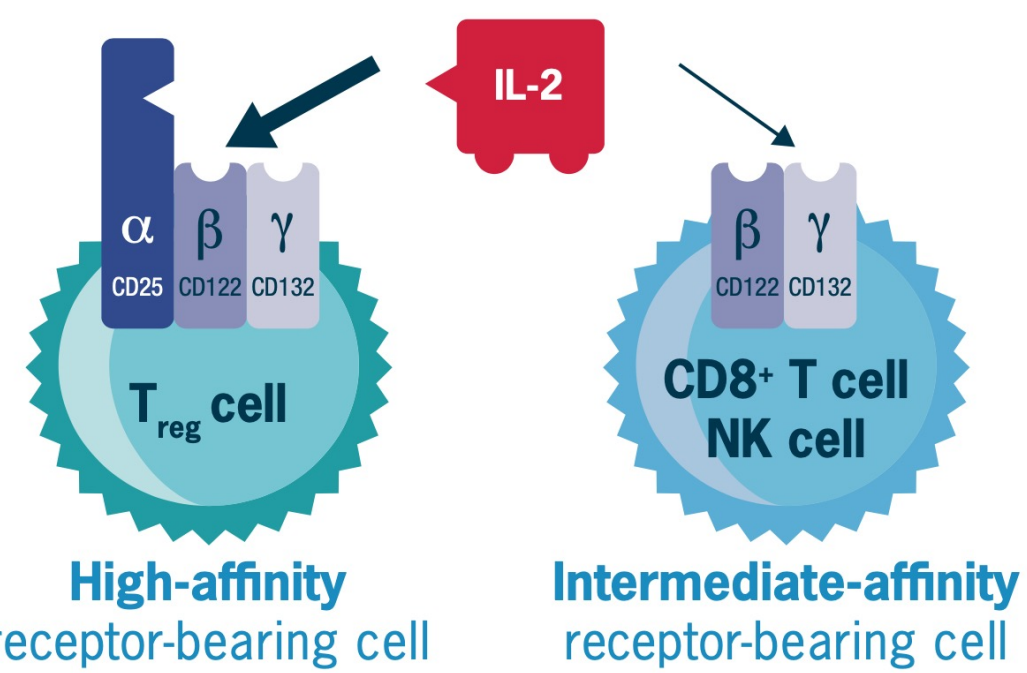


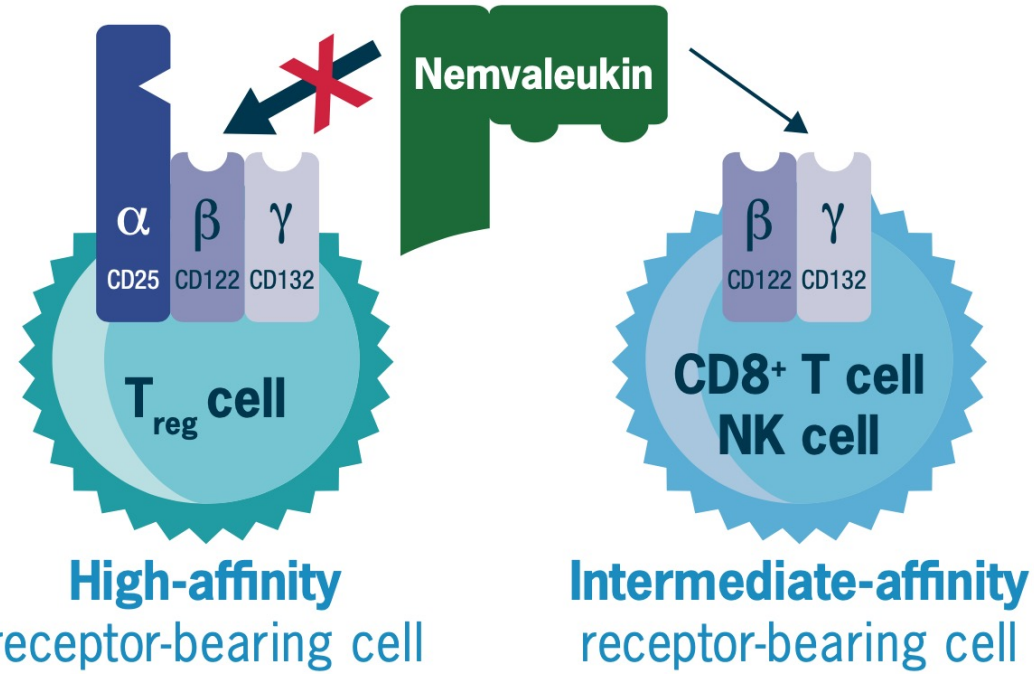
	INTERMITTENT* (N=60)	CONTINUOUS (N=58)	COMPARATOR (N=60)
Events, no. (%)	47 (78.3%)	50 (86.2%)	57 (95.0%)
Median PFS, mo (95% CI)	5.55 (3.68, 7.20)	5.29 (3.84, 5.55)	3.76 (3.52, 5.36)
HR vs Comparator	0.66 (0.44, 0.98)	0.83 (0.56, 1.22)	N/A

* log-rank *P*-value <0.05 vs. nab-paclitaxel alone
Median follow-up time: 11.1 months

Lorusso et al. ESMO 2021

Novel Immunotherapy: Artistry-7



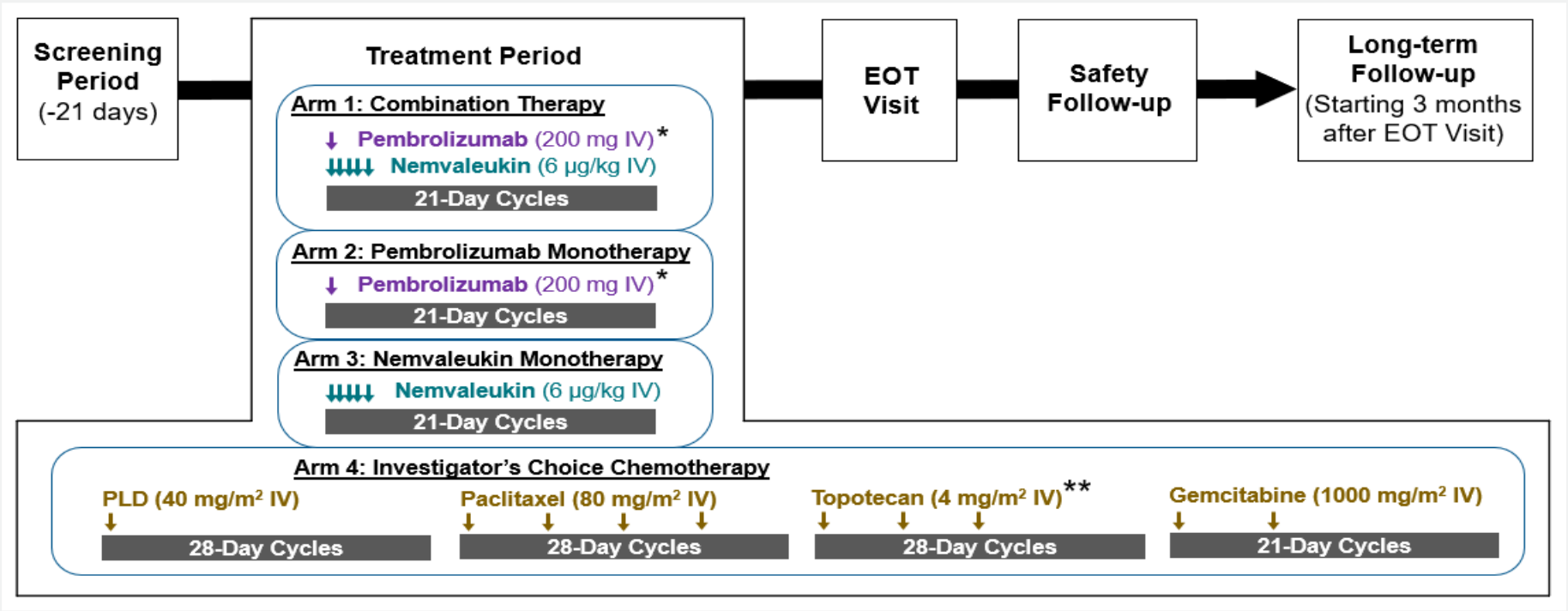


NCT: 05092360

ALKS 4230-007/GOG-3063/ENGOT-OV68
ARTISTRY-7

A Phase 3, Multicenter, Open Label, Randomized Trial of Nemvaleukin Alfa in Combination with Pembrolizumab Versus Investigator's Choice Chemotherapy in Patients with Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

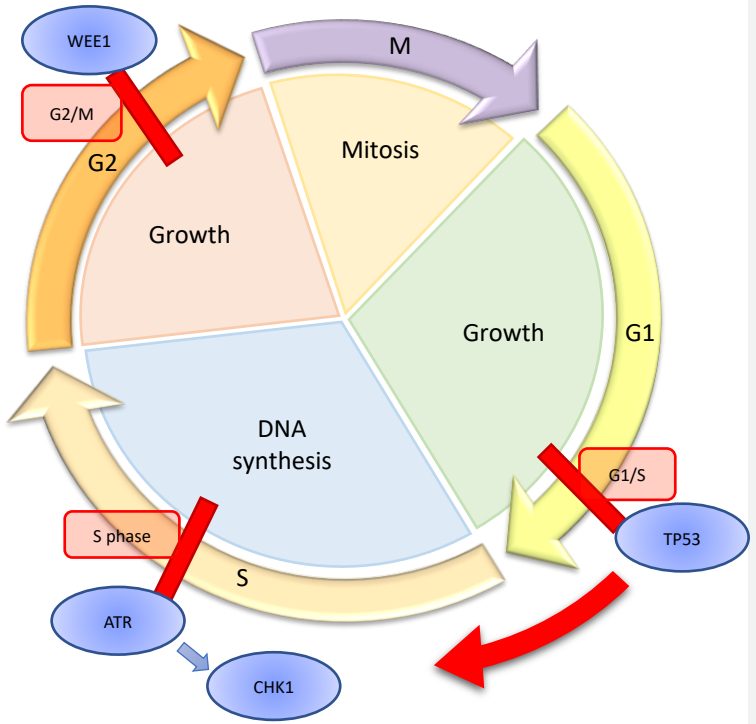
Stratification:
- **PD-L1 status**
- **Histologic subtype (high-grade serous vs non-high-grade serous)**
- **IC Chemotherapy (paclitaxel vs other chemotherapies)**



NCT: 05092360

GOG FOUNDATION

Cell Cycle Checkpoints



GOG-3072 (ZN-c3-002) - Study Design

Subjects with:
- High-grade Serous Ovarian Cancer
- Platinum-resistant or refractory
- 1 or 2 prior chemotherapies
- Measurable disease

Combination Dose Escalation
ZN-c3 + PLD
N = ~ 22

→ **Combination MTD/RP2D** → **Expansion**
N = 15 total at RP2D
ZN-c3 + PLD
Total N = ~ 50

CRM Bayesian Design with borrowing between cohorts

Combination Dose Escalation
ZN-c3 + Carboplatin
N = ~ 22

→ **Combination MTD/RP2D** → **Expansion**
N = 15 total at RP2D
ZN-c3 + Carboplatin
Total N = ~ 50

3+3 Design Safety lead-in, based on MTD from PLD/Carbo cohorts

Combination Dose Escalation
ZN-c3 + Paclitaxel
N = ~ 22

→ **Combination MTD/RP2D** → **Expansion**
N = 15 total at RP2D
ZN-c3 + Paclitaxel
Total N = ~ 20

NCT04516447

Novel Strategies: Summary

		Phase	Regimen	Prior total Therapies	Prior therapies for PROC	Tumor testing/ Prevalence
Taxanes	**GOG-3018 (OVAL)**	**3**	VB-111/placebo D1 (56 day cycle) +weekly paclitaxel vs. weekly Paclitaxel	≤ 5	<3	no
	GOG-3029 (INNOVATE-3)	**3**	TTFields >18 hr/day + weekly paclitaxel vs. weekly Paclitaxel	≤ 5	<3	no
	GOG-3044 (PROFECTA)	**2**	Afuresertib PO QD + Paclitaxel D1,8,15 Q3W vs. weekly Paclitaxel	1-3 prior platinum	0	yes
	GOG-3059 (AXLerate)	**3**	AVB-S6-500 (D1 & 15) +Weekly paclitaxel (D 1, 8, 15 on a 28d cycle) vs. weekly Paclitaxel	1-4	not defined (no prior taxanes for recurrence	no
Antibody Drug Conjugates	**GOG-3045 (MIRASOL)**	**3**	Mirvetuximab vs Investigator Choice chemotherapy	1-3	Not defined	yes
	GOG-3048 (UPLIFT)	**1b**	XMT-1536 every 4 weeks	1-3 permis. Can be granted for 4 prior)	not defined (only 2 prior taxanes allowed)	no
Immunotherapy	**NRG-GY009**	**2/3**	PLD/Atezo (D1&15) vs. PLD/Bev(D1&15)/ Atezo (D1&15) vs. PLD/Bev (D1&15)	1-2	Not defined	no
	GOG 3063 (ARTISTRY-7)	3	Nemvaleukin & Pembro vs. Pembro vs. Nemvaleukin vs. IC	unlimited (prior bev req.)	<6	no
Targeting Replication Stress/PARPi Resistance	**NRG-GY029**	**2**	IC vs olaparib and copanlisib (PARPI resistant)	Unlimited PSOC ≤ 2 PROC, bev req	≤ 2	no
	NRG-GY030	**2/3**	Gemcitabine vs. Gemcitabine + Berzosertib	Unlimited PSOC, 1 PROC, prior bev req	1	no

Summary

- Recurrent ovarian cancer, particularly platinum-resistant disease continues as a high unmet medical need
- Prolific investigation into new options but track record of success has been dismal
- Best opportunity for success is to follow tumor biology and the dynamic changes that occur under selective pressure

Case Discussions

The ocular side effects observed in trials evaluating mirvetuximab soravtansine are generally reversible.

1. Yes
2. No

RTP
RESEARCH
TO PRACTICE

Dr O'Malley – Recurrent high grade serous ovarian cancer

- 09/2013: TAH, BSO, pelvic and paraaortic lymphadenectomy, omentectomy and resection of abdominal wall nodule High grade serous carcinoma of the ovary - stage IIIB
- Completed 6 cycles of Carbo/Taxol (dose dense)
- 10/2017 CT C/A/P with significant increase in size of right paracolic gutter soft tissue mass, mild free fluid, thickening of the urinary bladder wall, enlarged lymph node within the upper abdomen
- 12/2017: CT biopsy of right paracolic gutter mass- High grade serous carcinoma
- 2018: Completed 7 cycles of Carbo/Gemzar
- Progressed within 3 months of completing therapy

Dr O'Malley – Tissue Testing

- Caris Testing 1/2014: VUS MLH1, no clinically actionable mutations
- Foundation Testing of Recurrence 12/2017: EGFR D314N, NF1 exon 1 loss, MYC amplications, TP53 D281E, MLH1 R325Q.
- **Microsatellite STABLE**. TMB-intermediate.

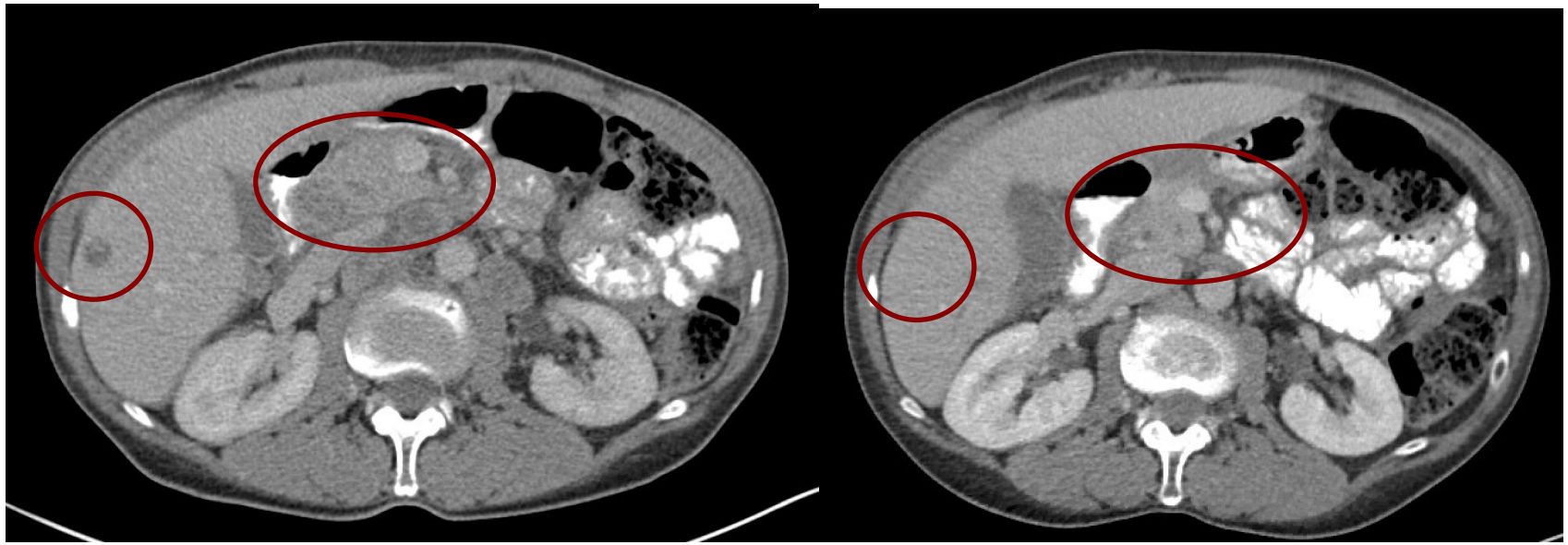
Dr O'Malley – Clinical Trials

- 2018: Clinical trial Olaparib and AZD6738 (WEE1i) x 3 cycles - progressed
- Transfer of Care to the James/OSU
- 1/2019: C1D1 OSU-15186 (IMGN853 6 mg/kg & Bevacizumab 15 mg/kg)
- 8/2020: C27 delayed 2 weeks due to Grade 2 neuropathy, Imgn reduced to 5 mg/kg
- 2/2021: Received 35 cycles of IMGN853+ Bev on OSU 15186; clinical trial closed
- 3/2021: Started treatment on Compassionate Use IMGN853 and Bev (commercial supply) on single patient compassionate use trial.
- Continues on therapy

Dr O'Malley – Response

Pre Cycle 1 – multi-focal disease

Cycle 33 – near CR



CA 125 Results	Notes
272	C1 Imgn/Bev
170	C2
96	C3
34	C4
12	C5
7	C6
5	C7

Have you or would you administer trastuzumab deruxtecan to a patient with HER2-amplified advanced ovarian cancer?

1. I have not and would not
2. I have not, but I would for the right patient
3. I have, and I've seen clinically significant response
4. I have, but I haven't seen clinically significant response

Dr Moore

Currently 68 year old, white female with recurrent ovarian cancer, BRCAwt
Diagnosed with Stage IV, high grade serous ovarian cancer July 2016

1. Dispositioned to NACT with paclitaxel, carboplatin and a novel intraperitoneal immune agent x 3 cycles. She underwent interval CRS OCT 2016 with disease present but debulked to NGR and received 5 more cycles of paclitaxel and carboplatin (total of 8) completed Feb 2017
2. Recurred Aug of 2018. PFI 1 = 17 months. Treated with docetaxel, carboplatin and pevonedistat (Neddylation agent) x 11 cycles (completed June 2019) followed by pevonedistat maintenance until recurrence Feb 2020. PFI 2= 8 months
3. Foundation 1 with ERBB2 amplification. Treated on a novel combination containing margetuximab and an immune agent with excellent response but immune related hepatitis that was steroid refractory and necessitated use of mycophenylate to resolve

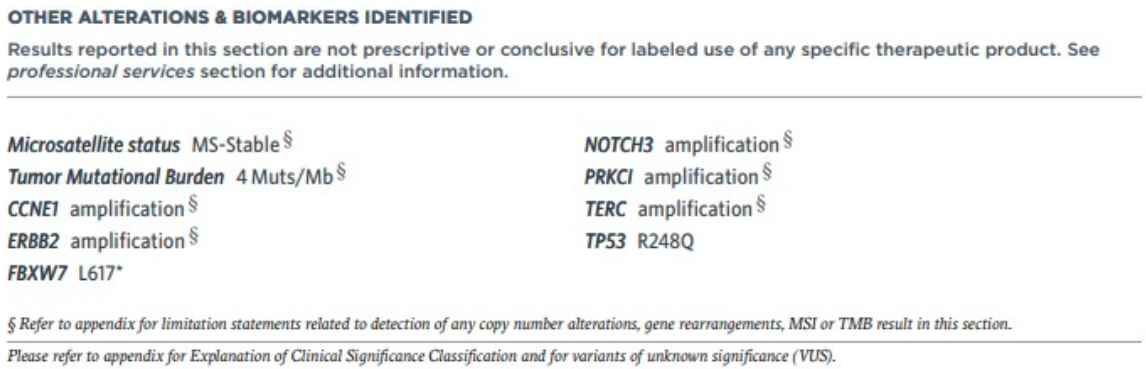
3/12 – C1D1 IV tx
4/1 - Gr 2 -> Mercy lab -> repeat at SCC
4/2 – repeat lab at SCC: Gr 2 -> C2D1 Held, start steroids 20mg
4/4 – Gr 2 (Saturday) -> 4/6 – steroids increased to 60mg
4/7 – Gr 1 -> no changes
4/10 – Gr 1 -> taper steroid to 40mg; 4/13 taper to 30mg; 4/14 taper to 20mg
4/15 – Gr 2 -> C2D1 Held, steroids increased to 60mg
4/17 – Gr 1 -> unable to contact patient; 4/20 - start steroid taper to 50mg
4/21 – Gr 1 -> no changes
4/23 – Gr 1, IV tx C2D1, continue taper, decrease to 40mg on 4/27
4/28 – Gr 2 – steroids 80mg (1mg/kg)
Has remained a Gr 2 since this time
5/11 – Gr 2, unable to contact patient. 5/13 – increased steroids to 160mg (2mg/kg)
5/18 - G3 - d/w medical monitor
<All steroids listed are total daily dose>

Dr Moore

Steroids eventually tapered as was mycophenylate and participation in the clinical trial was stopped.
Given her ERBB2 amplification, we counseled her for trastuzumab and pertuzumab.
When she stopped in to sign consent and was standing chatting with her team she laughingly told us that her nephew had tossed a ball to her and when it got close to her left side she "lost view of it" – which = an immediate brain MRI which showed a 5.5 x 4.2 x 5.9 temporo-occipital brain met.

She was admitted, started on steroids and had a resection within 24 hours and recovered great. Brain lesion also + for ERBB2 amp.

Pertuzumab and Trastuzumab started with PD after 2 cycles.



OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

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Microsatellite status MS-Stable §
Tumor Mutational Burden 4 Muts/Mb §
CCNE1 amplification §
ERBB2 amplification §
FBXW7 L617*
NOTCH3 amplification §
PRKCI amplification §
TERC amplification §
TP53 R248Q

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, MSI or TMB result in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

Dr Moore

Carbo/PLD started x 8 (completed Sept 2021) with PR. Olaparib maintenance started with PD Feb 2022.
PFI 3 = 5 months

Patient is HLA020 + and about to start a clinical trial of CAR-T.

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Appendix: Additional Cases

Dr O'Malley – Recurrent Endometrioid Adenocarcinoma of the Ovary, Stage IC, endometrioid, FIGO grade 3

- 2006: TAH/BSO/Nodes/Omentectomy/Appy
  - Taxol/Carbo x 6 cycles
- 2011: CT consistent with recurrence; CA-125 = 17 (up from 5). Secondary debulking/Liver wedge resection/Splenectomy/Distal pancreatectomy
- Completion of chemotherapy (6 cycles of carboplatin and dose-dense paclitaxel)
- 2015: CT- Increase in size of mass in the left lobe of the liver, increase in area of kidney and lung nodules
- Completed 6 cycles of Taxol/Carbo
- 2016: Completed 7 cycles of Gem, Cisplatin and Bev with PR

Dr O'Malley

- 36 cycles of Niraparib 2016-2019
  - Reduced niraparib to 200 mg due to thrombocytopenia
  - Reduced Niraparib to 100 mg daily, due to persistent anemia
- 2018: CT A/P: interval increase in size of left psoas muscle mass, now measuring 2.9 x 2.1 cm
  - 5 fractions SBRT left psoas muscle
- 2019: progression in chest – removed from Niraparib

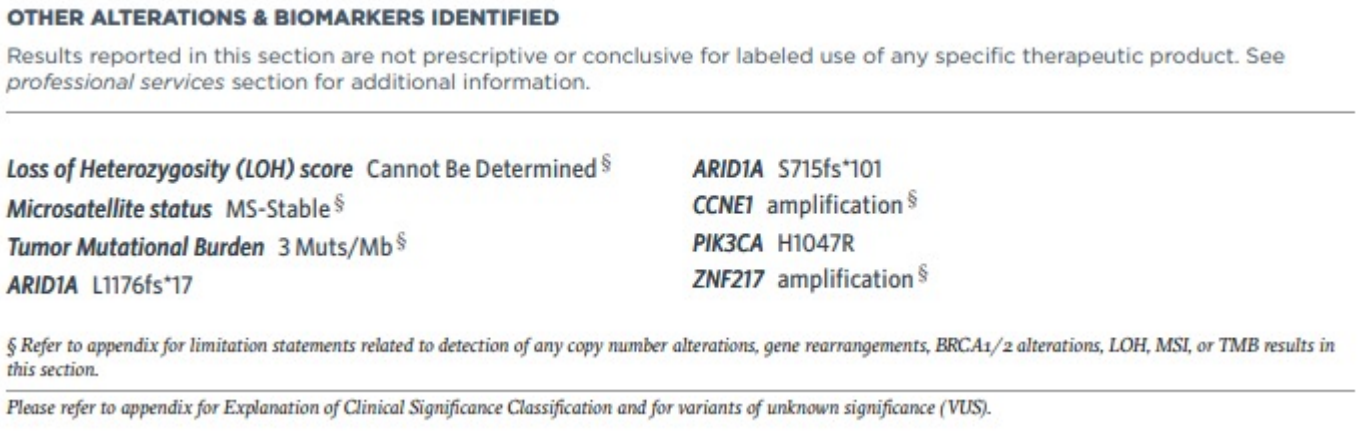
Dr O'Malley – Testing

- 2012: Genetic testing- No mutation in BRCA1/2 by sequencing or checking 5 most common rearrangements
- 2019: Foundation Medicine- MS-Stable, TMB-Low (4 Muts/Mb), HRD+
  - Alterations identified: APC, ESR1, MRE11A, MYC, PTEN (mTOR inhibitors), TP53

Dr Moore

Patient is currently 52 y/o, Hispanic woman with recurrent clear cell ovarian cancer

1. Diagnosed Feb 2018 and s/p total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic LND, omentectomy for stage IC clear cell cancer. She was treated with paclitaxel and carboplatin x 3 completed Aug 2018
2. Presented Dec 2019 with a large GI bleed and was found to have a small bowel mass and multiple other sites of recurrence confirmed pathologically. PFI 1 = 16 months. Patient became transfusion dependent because of erosion of her tumor into bowel. Also developed pulmonary emboli and a CVA requiring anticoagulation which could not be done given ongoing GI Bleed. She underwent exlap and resection of tumor (focused on small bowel mass), mass around superior mesenteric artery was considered non resectable. GI bleed resolved, patient recovered really well and was restarted on anti-coagulation and started on carboplatin and PLD x 4 with PD during treatment.
3. Enrolled on a clinical trial of a targeted beta emitter with PD as best response.
4. Enrolled on a clinical trial of a novel TKI plus an immune checkpoint inhibitor and has an ongoing, deep PR x 20 cycles. Sept 2020 – ongoing.



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Loss of Heterozygosity (LOH) score Cannot Be Determined §
Microsatellite status MS-Stable §
Tumor Mutational Burden 3 Muts/Mb §
ARID1A L1176fs*17
ARID1A S715fs*101
CCNE1 amplification §
PIK3CA H1047R
ZNF217 amplification §

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Dr Moore

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3. Enrolled on a clinical trial of a targeted beta emitter with PD as best response.
4. Enrolled on a clinical trial of a novel TKI plus an immune checkpoint inhibitor and has an ongoing, deep PR x 20 cycles. Sept 2020 – ongoing.

If/when PD: can consider screening for NRG GY014: Tazemetostat (EZH2 inhibitor) for ARID1A mut clear cell

Also BRD4/BET inhibitors would be of interest

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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