Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Ovarian Cancer

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2023 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Sunday, March 26, 2023

11:45 AM – 1:15 PM ET

Faculty

Mansoor Raza Mirza, MD

Amit M Oza, MD

Richard T Penson, MD, MRCP

Moderator

Joyce F Liu, MD, MPH

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Faculty

Mansoor Raza Mirza, MD
Chief Oncologist
Copenhagen University Hospital
Medical Director
Nordic Society of Gynaecological Oncology – Clinical Trial Unit
Vice President
European Society of Gynaecological Oncology
Copenhagen, Denmark

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Professor of Medicine
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Moderator

Joyce F Liu, MD, MPH
Associate Chief and Director of Clinical Research
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Boston, Massachusetts

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Dr Mirza — Disclosures
Faculty

Advisory Committee	Boehringer Ingelheim Pharmaceuticals Inc, Clovis Oncology, GSK, Karyopharm Therapeutics, Merck, Roche Laboratories Inc, Zai Lab
Consulting Agreements	Boehringer Ingelheim Pharmaceuticals Inc, Clovis Oncology, GSK, Karyopharm Therapeutics, Merck, Novartis, Roche Laboratories Inc, Zai Lab
Nonrelevant Financial Relationship	Chairman 2020-2022, European Network of Gynaecological Trial Groups

Dr Oza — Disclosures
Faculty

No relevant conflicts of interest to disclose.

Dr Penson — Disclosures
Faculty

Advisory Committee	AstraZeneca Pharmaceuticals LP, Eisai Inc, GSK, ImmunoGen Inc, Merck, Mersana Therapeutics Inc, Novocure Inc, Roche Laboratories Inc, Sutro Biopharma, VBL Therapeutics
Contracted Research	Array BioPharma Inc, a subsidiary of Pfizer Inc, AstraZeneca Pharmaceuticals LP, Eisai Inc, Genentech, a member of the Roche Group, Regeneron Pharmaceuticals Inc, Sanofi, Tesaro, A GSK Company, VBL Therapeutics
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP, Roche Laboratories Inc
Nonrelevant Financial Relationship	BMJ Publishing Group Ltd, Elsevier, UptoDate, Wiley-Blackwell, Wolters Kluwer Health

Dr Liu — Disclosures
Moderator

Advisory Committee	AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, Genentech, a member of the Roche Group, GSK, Regeneron Pharmaceuticals Inc
Consulting Agreement	Bristol-Myers Squibb Company
Trial Support (to Institution for Study Conduct)	2X Oncology Inc, Aravive Inc, Arch Oncology, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Clovis Oncology, CytomX Therapeutics, GSK, Impact Therapeutics, Regeneron Pharmaceuticals Inc, Vigeo Therapeutics, Zentalis Pharmaceuticals

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.

Answer Survey Questions: Complete the pre- and post-meeting surveys.

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.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.

Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Endometrial Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2023 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Monday, March 27, 2023

11:45 AM – 1:15 PM ET

Faculty

Robert L Coleman, MD

Matthew A Powell, MD

Brian M Slomovitz, MD

Moderator

Shannon N Westin, MD, MPH

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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Ovarian Cancer

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2023 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Sunday, March 26, 2023

11:45 AM – 1:15 PM ET

Faculty

Mansoor Raza Mirza, MD

Amit M Oza, MD

Richard T Penson, MD, MRCP

Moderator

Joyce F Liu, MD, MPH

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Agenda

MODULE 1: Optimal Genomic Evaluation of and Targeted Therapies for Newly Diagnosed Advanced Ovarian Cancer — *Dr Mirza*

MODULE 2: PARP Inhibitors for Relapsed/Refractory Ovarian Cancer — *Dr Oza*

MODULE 3: Rationale for and Available Data with PARP Inhibitors in Combination with Other Anticancer Therapies for Advanced Ovarian Cancer — *Dr Liu*

MODULE 4: Novel Agents for the Treatment of Ovarian Cancer — *Dr Penson*

John K Chan, MD
Sutter Cancer Research Consortium
San Francisco, California

Kellie E Schneider, MD
Novant Health Cancer Institute
Charlotte, North Carolina

Dana M Chase, MD
David Geffen School of
Medicine at UCLA
Los Angeles, California

Lyndsay J Willmott, MD
Virginia G Piper Cancer
Care Network
Phoenix, Arizona

Thomas P Morrissey, MD
Lynn Cancer Institute
Boca Raton, Florida

Neil Love, MD
Research To Practice
Miami, Florida

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Module 1: Optimal Genomic Evaluation of and Targeted Therapies for Newly Diagnosed Advanced Ovarian Cancer — Dr Mirza

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Case Presentation: 44-year-old morbidly obese woman who is a Jehovah's Witness with gBRCA2-mutant ovarian cancer

Dr Lyndsay Willmott (Phoenix, Arizona)

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QUESTIONS FOR THE FACULTY

Dr Lyndsay Willmott

How do you determine whether a patient is a candidate for surgery, and what is your treatment approach for patients who are not surgical candidates?

What is the optimal PARP inhibitor to use as primary maintenance therapy for patients with germline BRCA and somatic mutations? Duration? Role of bevacizumab?

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Case Presentation: 53-year-old woman with BRCA WT, HRD-negative Stage IV ovarian cancer and large pleural effusion and ascites

Dr Kellie Schneider (Charlotte, North Carolina)

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QUESTIONS FOR THE FACULTY

Dr Kellie Schneider

What is your approach to patients with HR-proficient ovarian cancer with extensive intra-abdominal disease and pleural effusions?

How, if at all, do you use PARP inhibitors in patients with non-BRCA alterations such as PALB2, CHEK2 and ATM?

Optimal Genomic Evaluation of and Targeted Therapies for Newly Diagnosed Advanced Ovarian Cancer

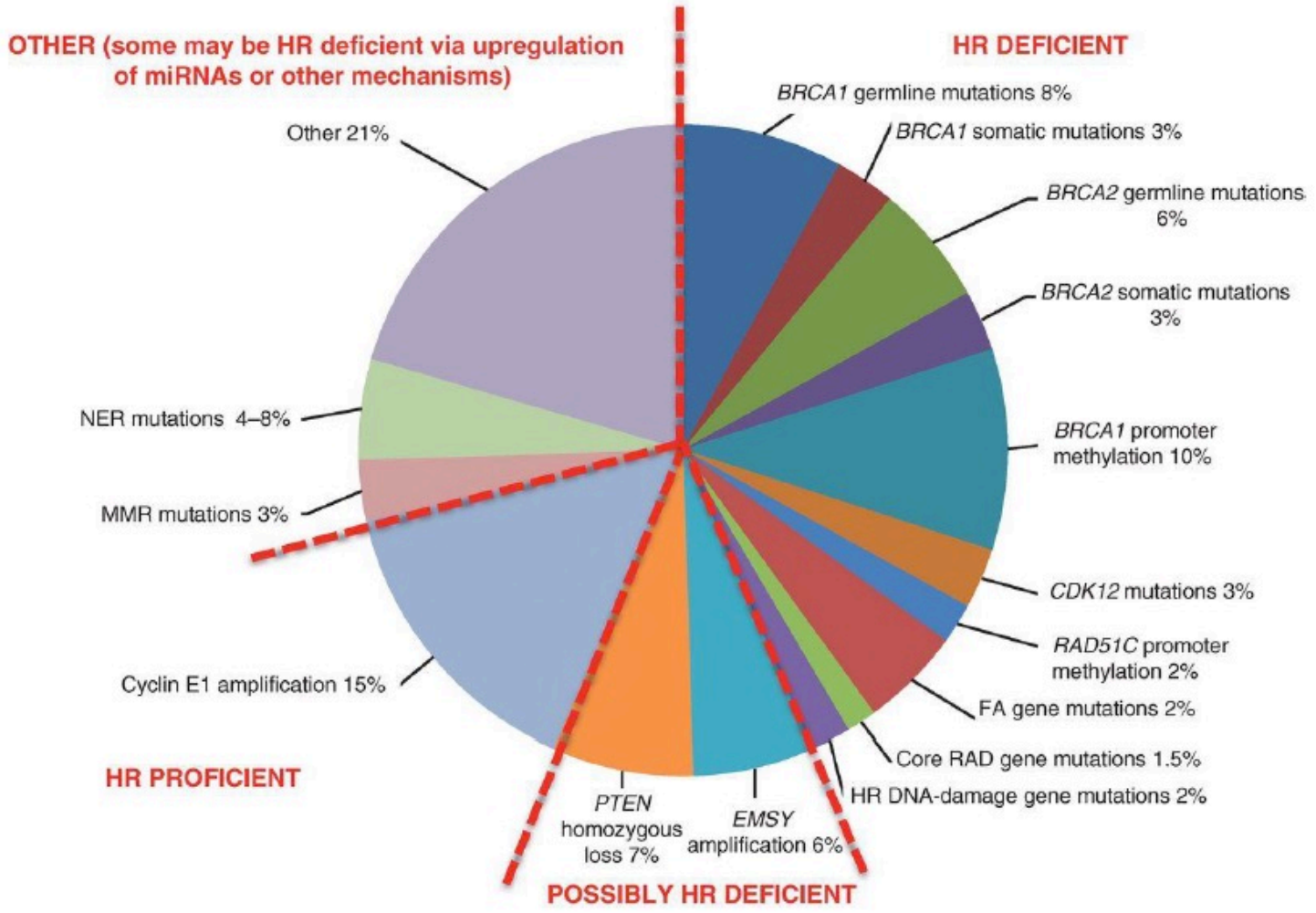
Mansoor Raza Mirza

Medical Director: **NSGO-CTU** (Nordic Society of Gynaecological Oncology)
Chief Oncologist: **Rigshospitalet** (Copenhagen University Hospital)
Chairman$_{2020\text{-}2022}$: **ENGOT** (European Network of Gynaecological Oncology Trials group)
Vice-President: **ESGO** (European Society of Gynaecological Oncology)

Homologous Recombination Defects in High-Grade Serous Ovarian Cancer

- Ovarian Cancer is a genetically heterogeneous disease

- *BRCA*1/2 deleterious mutations or chromosomal damage result in similar biology



Levine D. *The Cancer Genome Atlas, 2011*
Konstantinopoulos et al. *Cancer Discov 2015*

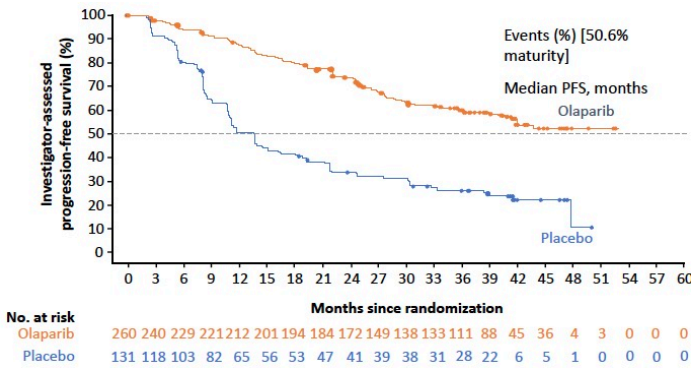
PARP INHIBITORS IN PATIENTS WITH PRIMARY ADVANCED OVARIAN CANCER

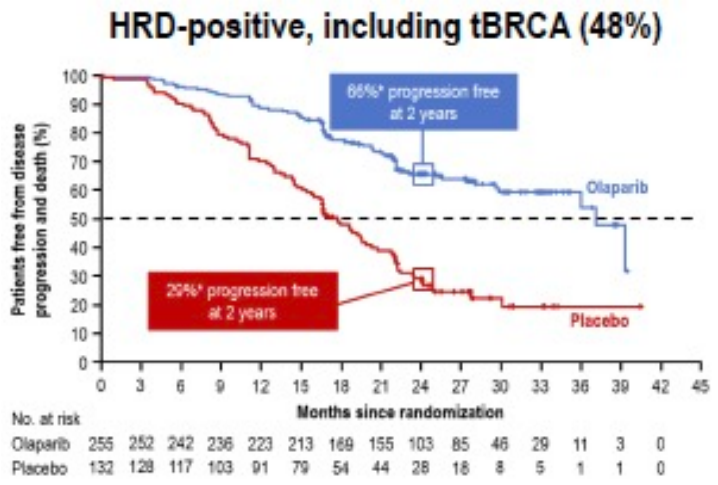
SOLO1[1] *BRCA*mut	ENGOT-OV25 PAOLA1[2]	ENGOT-OV26 PRIMA[3]	PRIME[4]	ENGOT-OV45 ATHENA$_{mono}$[5]
Olaparib	Olaparib + bevacizumab	Niraparib	Niraparib	Rucaparib*

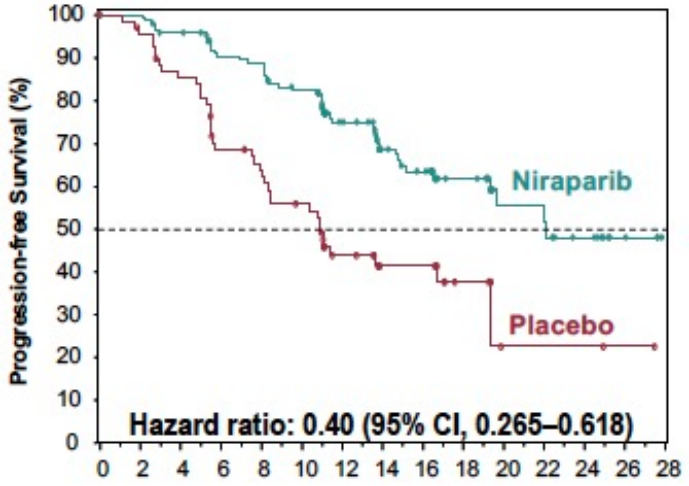
1. Moore K, et al. NEJM 2018 2. Ray-Coquard I, et al. NEJM 2019 3. Gonzales-Martin A…Mirza MR, et al. NEJM 2019 **4**. Li N, et al. SGO2022. 5. Monk et al. ASCO2022

BRCAmut, HR deficient population

Study	SOLO1[1]	PAOLA1[2]	PRIMA[3]
Agent	Olaparib	Olaparib + bevacizumab	Niraparib
PFS Hazard Ratio	**0.30** (95% CI 0.23-0.41)	**0.33** (95% CI 0.25-0.45)	**0.40** (95% CI 0.265-0.618)





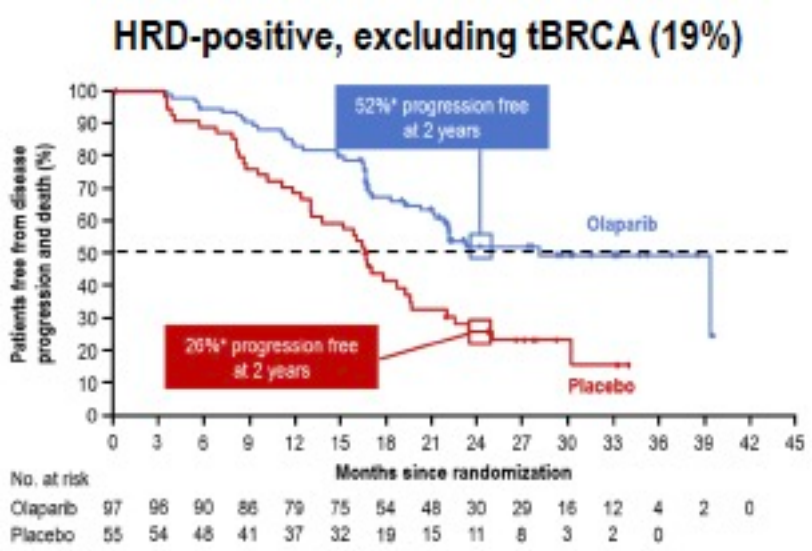


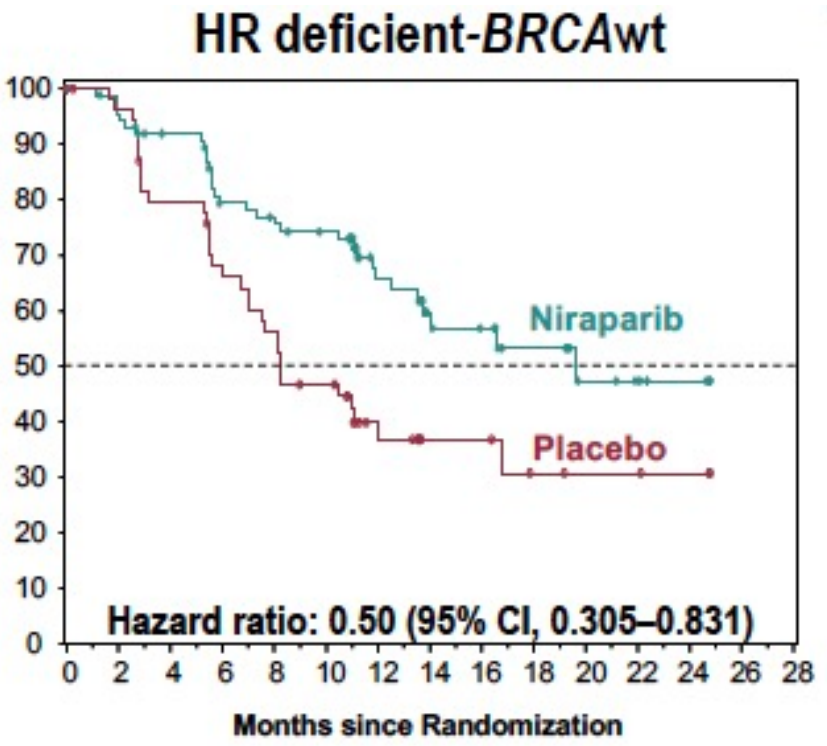
Note: In the absence of head-to-head data between PARPi efficacy and safety comparisons between PARPi are not to be made.

1. Moore K, et al. NEJM 2018 2. Ray-Coquard !, et al. NEJM 2019 3. Gonzales-Martin A…Mirza MR, et al. NEJM 2019

BRCAwt, HR deficient population

Study	SOLO1[1]	PAOLA1[2]	PRIMA[3]
Agent	**Olaparib**	**Olaparib + bevacizumab**	**Niraparib**
PFS Hazard Ratio	-	**0.43** (95% CI 0.29-0.66)	**0.50** (95% CI 0.305-0.831)



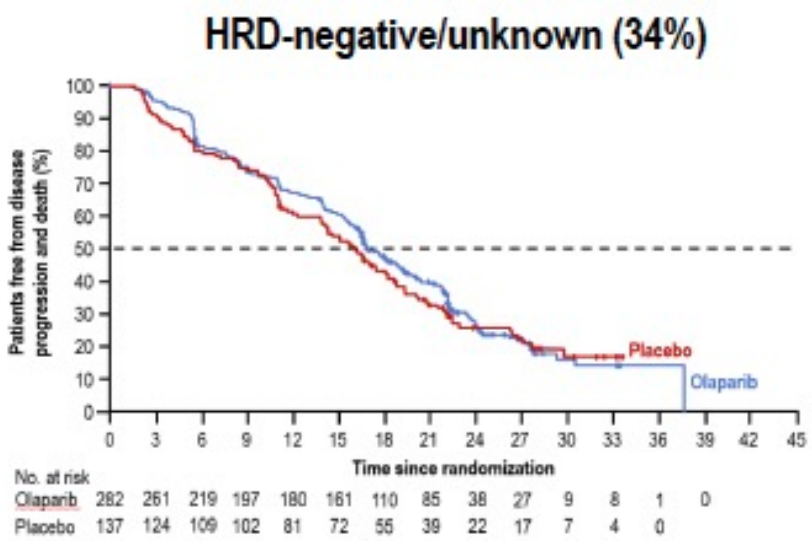


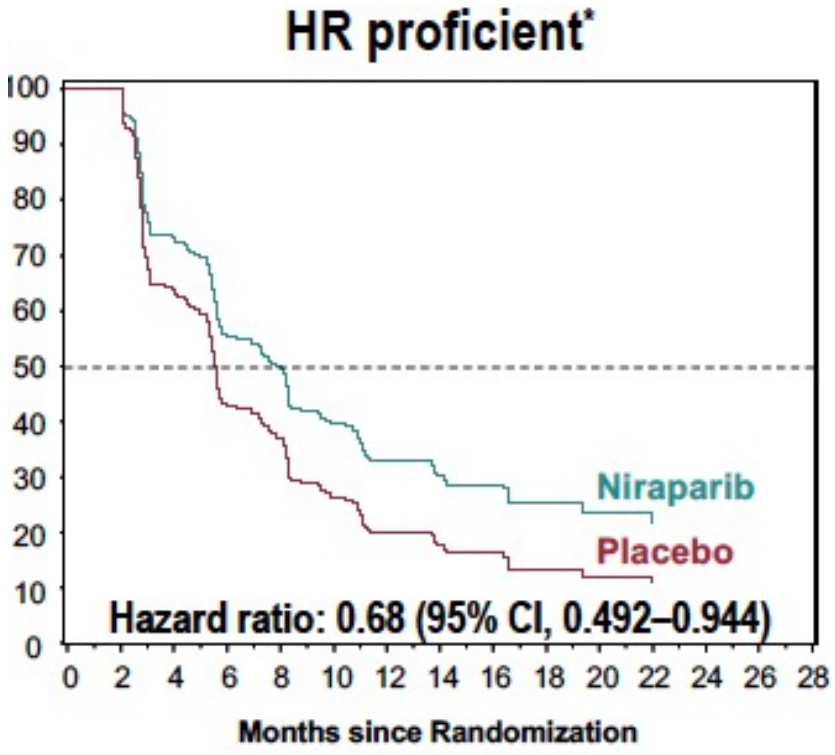
Note: In the absence of head-to-head data between PARPi efficacy and safety comparisons between PARPi are not to be made.

1. Moore K, et al. NEJM 2018 2. Ray-Coquard !, et al. NEJM 2019 3. Gonzales-Martin A…Mirza MR, et al. NEJM 2019

BRCAwt, HR proficient population

Study	SOLO1[1]	PAOLA1[2]	PRIMA[3]
Agent	Olaparib	Olaparib + bevacizumab	Niraparib
PFS Hazard Ratio	-	0.92 NS (95% CI 0.72-1.17)	0.68 (95% CI 0.492-0.944)

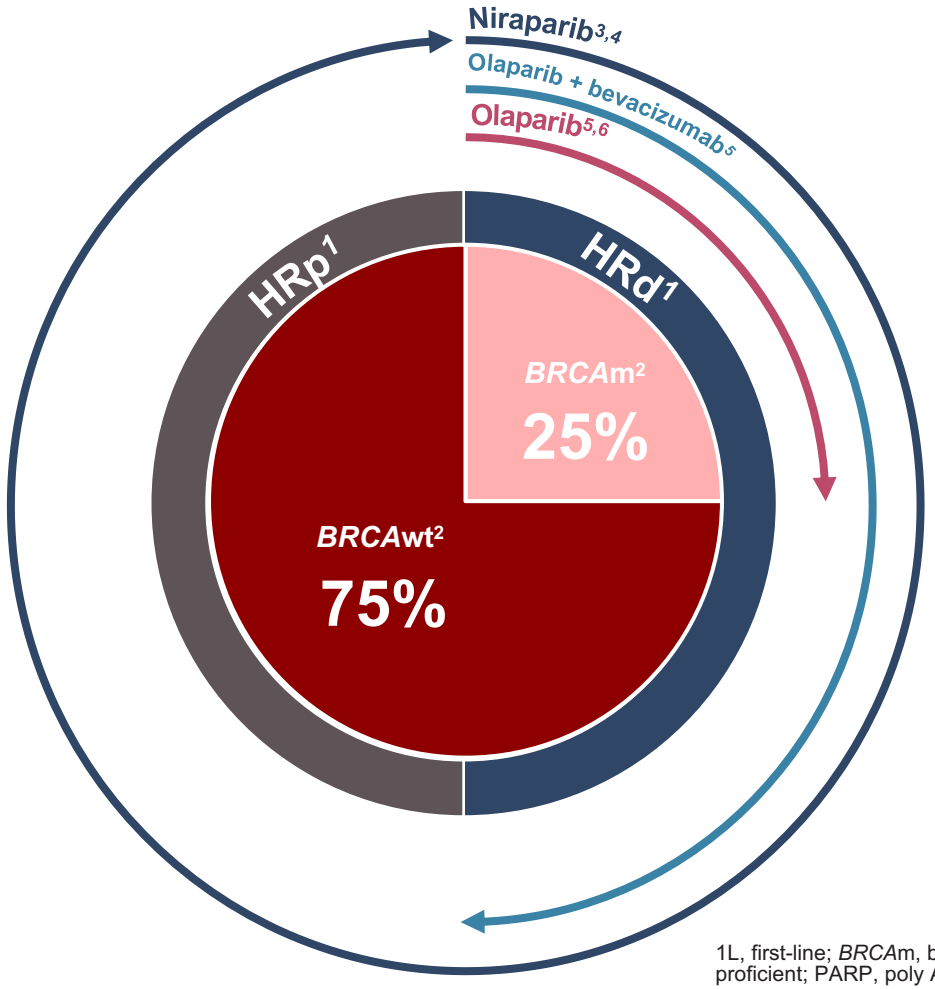




Note: In the absence of head-to-head data between PARPi efficacy and safety comparisons between PARPi are not to be made.

1. Moore K, et al. NEJM 2018 2. Ray-Coquard !, et al. NEJM 2019 3. Gonzales-Martin A…Mirza MR, et al. NEJM 2019

PARP inhibitor 1L maintenance treatments showed clinical benefit across biomarker subgroups

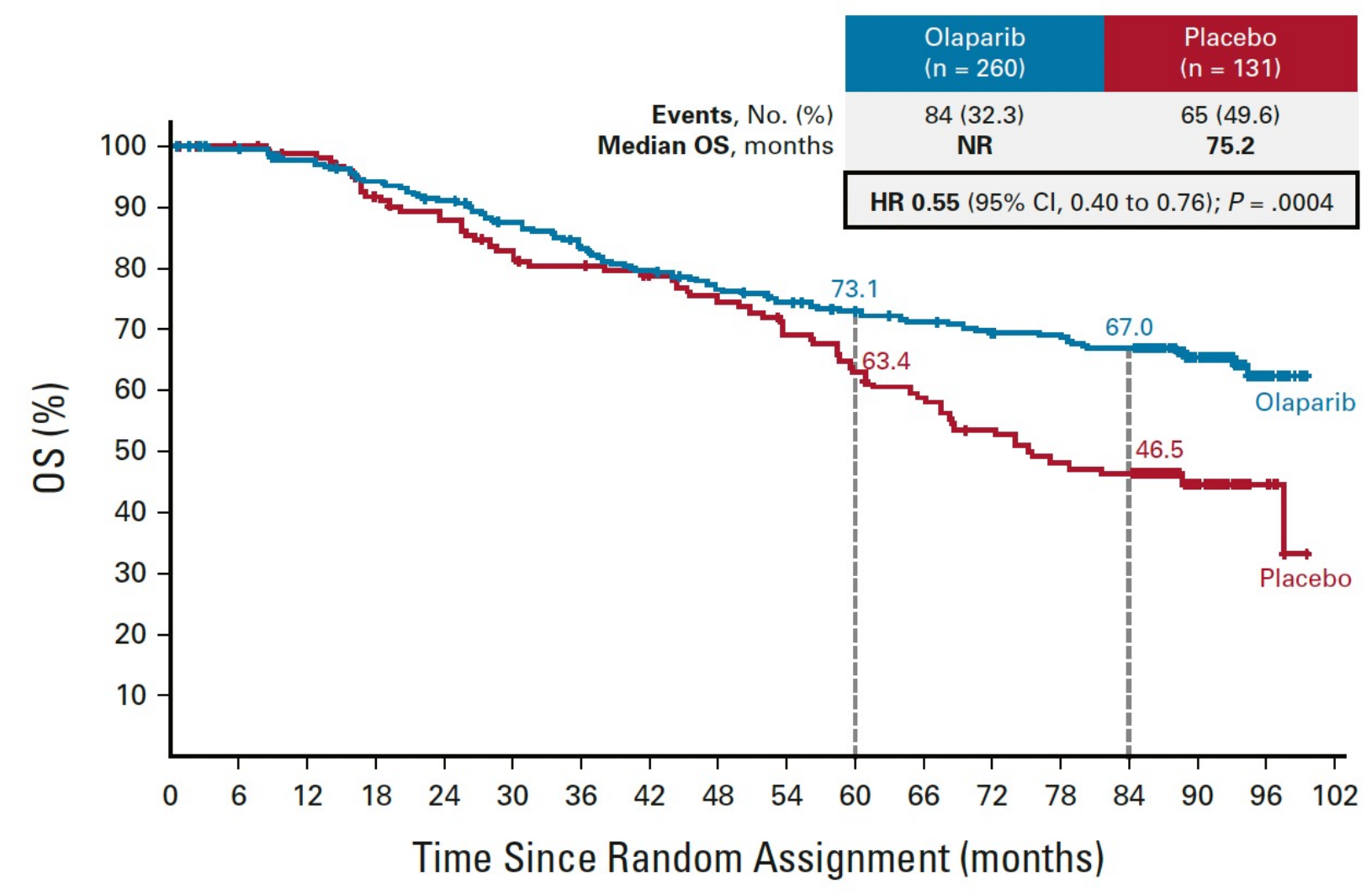


Niraparib[3,4]	Olaparib[5,6]	Olaparib + bevacizumab[5]
All comers	*BRCA*m	*BRCA*m or HRd

1L, first-line; *BRCA*m, breast cancer gene mutation; *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. European commission approves Zejula (niraparib) as first-line monotherapy maintenance treatment in advanced ovarian cancer. Press release. GlaxoSmithKline. October 29, 2020. Accessed November 4, 2020. https://www.gsk.com/en-gb/media/press-releases/european-commission-approves-zejula-niraparib-as-first-line-monotherapy-maintenance-treatment-in-advanced-ovarian-cancer/. 4. ZEJULA. Prescribing information. GlaxoSmithKline; 2020. 5. LYNPARZA. Prescribing information. AstraZeneca Pharmaceuticals LP; 2020. 6. LYNPARZA. Summary of product characteristics. AstraZeneca AB; 2020.

SOLO-1: Maintenance Olaparib Provided a Clinically Meaningful OS Benefit – 7-Year Follow-Up



DiSilvestro P et al. *J Clin Oncol* 2023 Jan 20;41(3):609-17.

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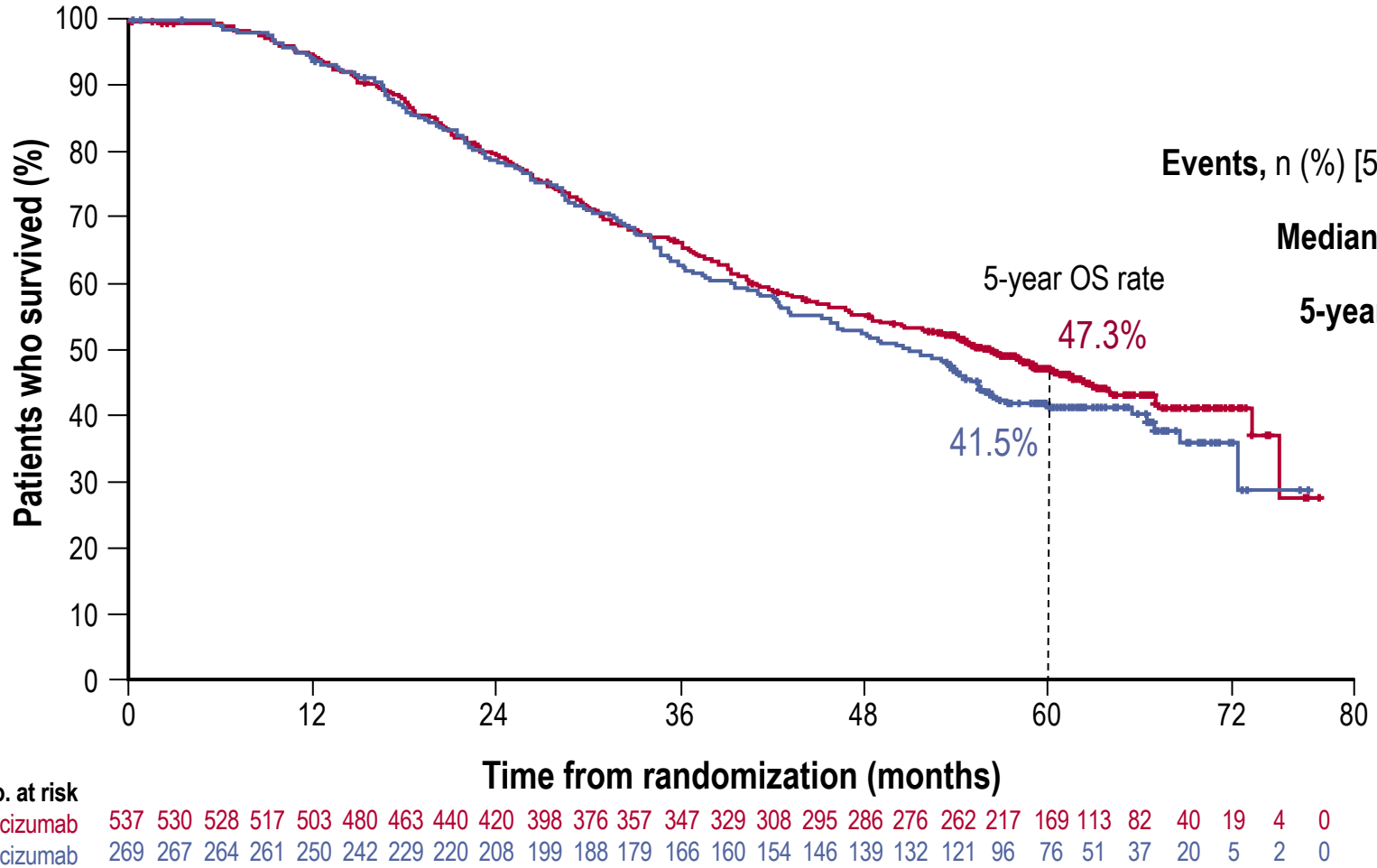
ENGOT-OV25 / PAOLA1: OS analysis in ITT population



	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [55% maturity]	288 (53.6)	158 (58.7)
Median OS, months	**56.5**	**51.6**
5-year OS rate, %	**47.3**	**41.5**

HR 0.92 (95% CI 0.76–1.12);
***P*=0.4118**

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **19.6%** (105/537)
Placebo + bevacizumab: **45.7%** (123/269)

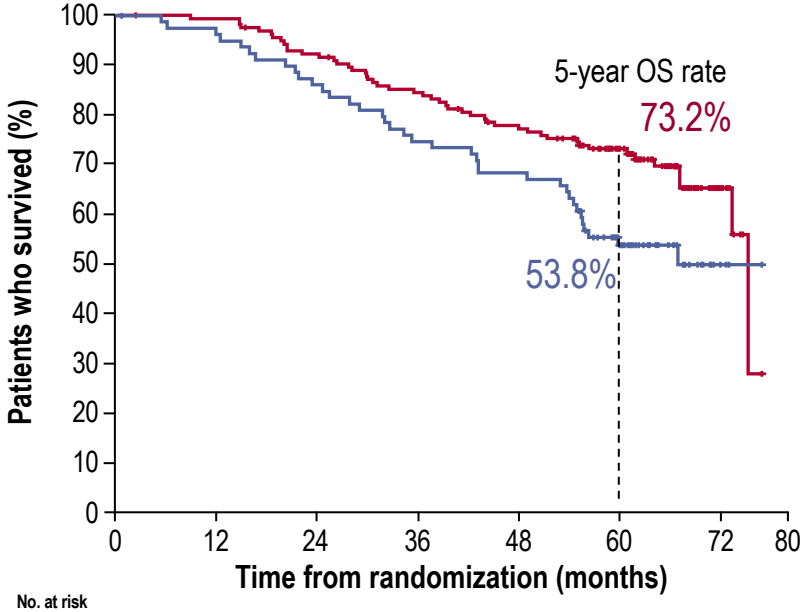
Median time from first cycle of chemotherapy to randomization = 6 months

PARP, poly(ADP-ribose) polymerase.

Ray-Coquard I et al. ESMO 2022; Abstract LBA29.

ENGOT-OV25 / PAOLA1: OS subgroup analysis by BRCAm & HRD status

BRCAm*

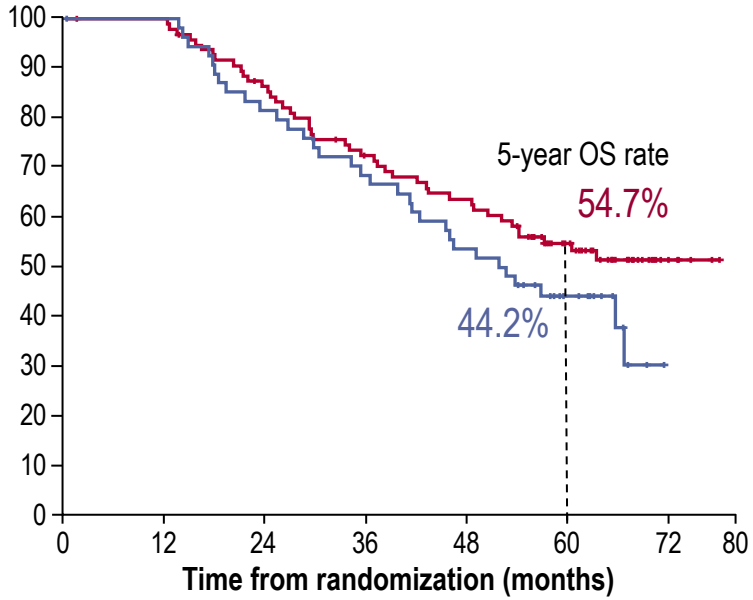


No. at risk

Olaparib + bevacizumab	157	156	156	155	155	152	150	144	143	139	134	131	130	127	123	118	117	115	112	99	80	55	42	21	11	2	0
Placebo + bevacizumab	80	79	78	77	76	74	72	71	68	66	64	61	59	58	58	54	54	53	50	40	33	22	17	10	3	1	0

	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)
	HR 0.60 (95% CI 0.39–0.93)	

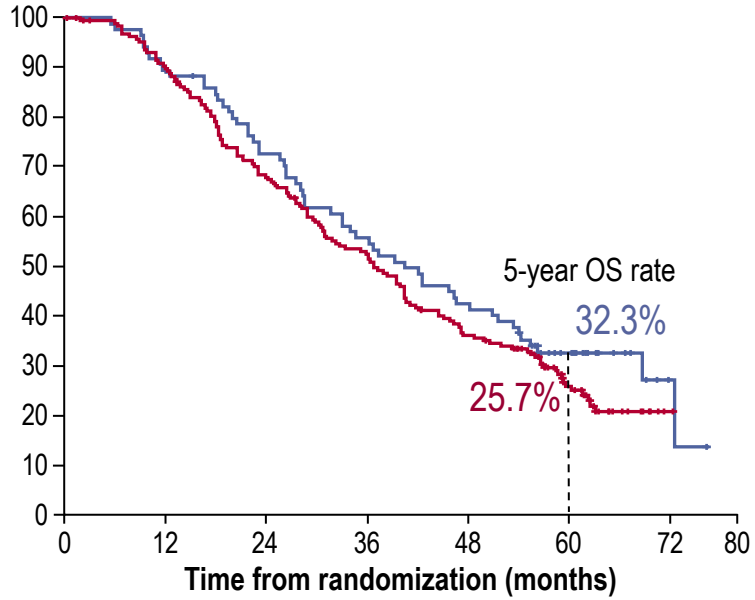
HRD positive‡ excluding BRCAm



	97	96	96	96	96	91	87	86	81	76	71	70	66	63	61	59	58	55	52	45	37	29	22	12	5	2	0
	55	54	54	54	54	51	48	46	44	42	40	39	37	36	33	32	29	28	24	21	15	9	6	2	0		

	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
	44 (45.4)	32 (58.2)
	NR	52.0
	54.7	**44.2**
	9 (9.3)	23 (41.8)
	HR 0.71 (95% CI 0.45–1.13)	

HRD negative†



	192	187	186	179	169	157	146	135	126	119	109	100	97	89	77	72	66	62	57	43	30	16	11	5	1	0	
	85	85	84	83	76	74	71	65	60	56	51	48	46	43	41	38	35	33	31	21	17	11	8	5	2	1	0

	Olaparib + bevacizumab (N=192)	Placebo + bevacizumab (N=85)
	140 (72.9)	58 (68.2)
	36.8	40.4
	25.7	**32.3**
	46 (24.0)	34 (40.0)
	HR 1.19 (95% CI 0.88–1.63)	

*By central labs; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported.

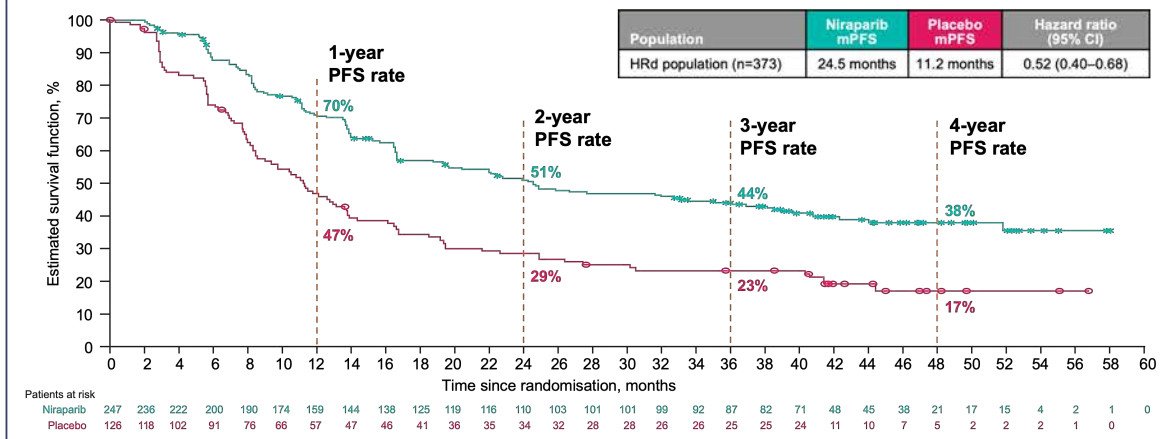
Ray-Coquard I et al. ESMO 2022; Abstract LBA29.

ENGOT-OV26 / PRIMA: Investigator-Assessed PFS in the HRd and Overall Populations

17 November 2021 Clinical Cutoff Date

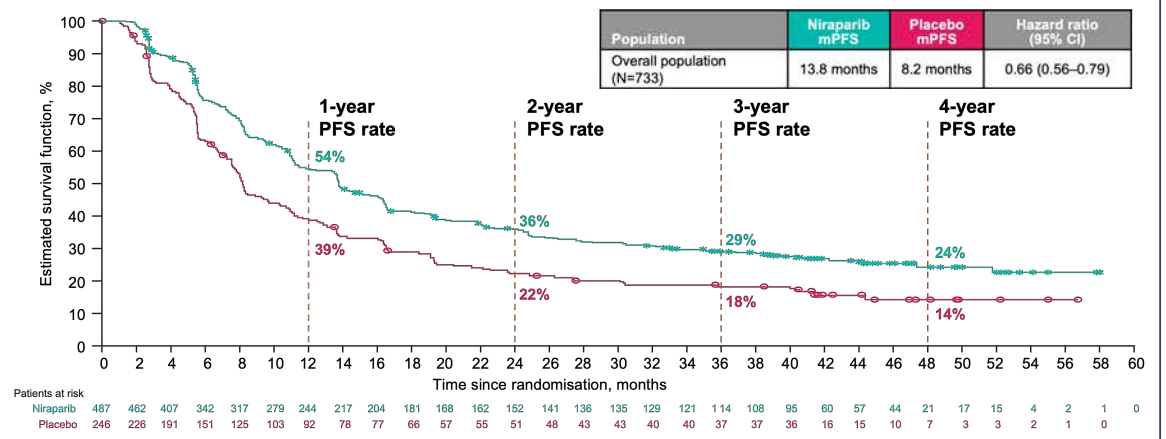
- As of the 17 November 2021 clinical cutoff date, the median PFS in the HRd population was 24.5 months in the niraparib arm compared with 11.2 months in the placebo arm (hazard ratio, 0.52; 95% CI, 0.40–0.68; *P*<0.001; **Figure 2**)
- As of the 17 November 2021 clinical cutoff date, the median PFS in the overall population was 13.8 months in the niraparib arm compared with 8.2 months in the placebo arm (hazard ratio, 0.66; 95% CI, 0.56–0.79; *P*<0.001; **Figure 3**)

Figure 2. Kaplan-Meier Plot of Progression-Free Survival by Investigator Assessment in the HRd Population, 17 November 2021 Clinical Cutoff Date



HRd, homologous recombination–deficient; mPFS, median progression-free survival; PFS, progression-free survival.

Figure 3. Kaplan-Meier Plot of Progression-Free Survival by Investigator Assessment in the Overall Population, 17 November 2021 Clinical Cutoff Date



mPFS, median progression-free survival; PFS, progression-free survival.

PARIS 2022 ESMO congress

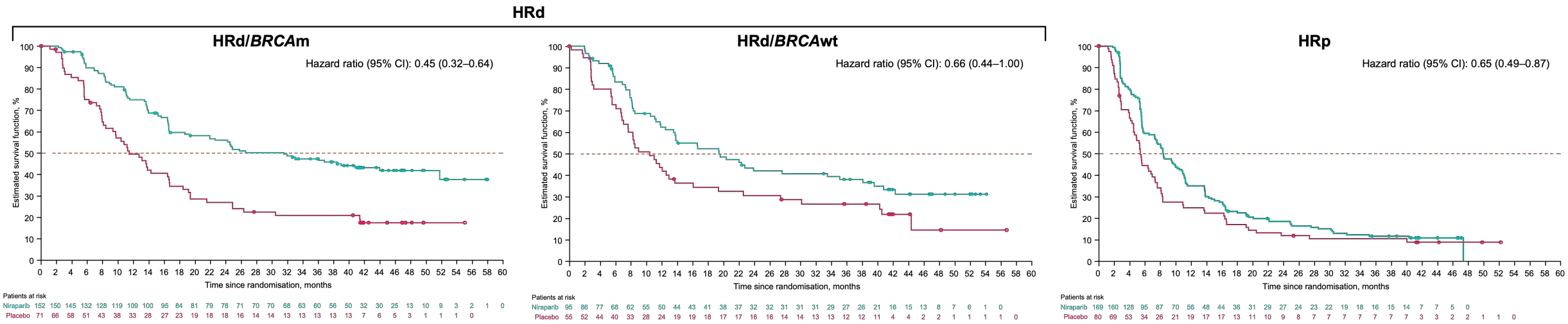
Gonzales-Martin A…Mirza MR et al. ESMO 2022; Abstract 530P.

ENGOT-OV26 / PRIMA: Investigator-Assessed PFS across Biomarker Subgroups

17 November 2021 Clinical Cutoff Date

- Niraparib treatment increased PFS duration compared with placebo treatment across biomarker subgroups
- The greatest treatment benefit was seen in patients with HRd tumours that were *BRCA* mutated (hazard ratio, 0.45; 95% CI, 0.32–0.64)

Figure 4. Kaplan-Meier Plot of Progression-Free Survival by Investigator Assessment Across Biomarker Subgroups, 17 November 2021 Clinical Cutoff Date



*BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild-type; HRd, homologous recombination–deficient; HRp, homologous recombination–proficient.

PARIS 2022 ESMO congress

Gonzales-Martin A…Mirza MR et al. ESMO 2022; Abstract 530P.

PRIME study

Efficacy and Safety of Niraparib as Maintenance Treatment in Patients with Newly Diagnosed Advanced Ovarian Cancer Using an Individualized Starting Dose (PRIME Study): A Randomized, Double-blind, Placebo-controlled, Phase 3 Trial

Ning Li*, Jianqing Zhu, Rutie Yin, Jing Wang, Lingya Pan, Beihua Kong, Hong Zheng, Jihong Liu, Xiaohua Wu, Li Wang, Yi Huang, Ke Wang, Dongling Zou, Hongqin Zhao, Chunyan Wang, Weiguo Lu, An Lin, Ge Lou, Guiling Li, Pengpeng Qu, Hongying Yang, Xiaoa Zhen, Wenzhao Hang, Jianmei Hou, Lingying Wu*

* National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

- PRIME is a randomized, double-blind, placebo-controlled phase III trial (NCT03709316).

Schema

Eligible Patients
- Age ≥18 years
- FIGO stage III/IV ovarian cancer
- High-grade serous or endometroid tumor[a]
- Receipt of primary or interval cytoreductive surgery, irrespective of postoperative residual disease status
- CR/PR to 1L Pt-based chemotherapy

Stratified randomization
- Status of g*BRCA* mutations (g*BRCA*mut/non-g*BRCA*mut)
- Tumor HRD status[b] (positive/negative)
- Receipt of neoadjuvant chemotherapy (Y/N)
- Response to 1L Pt-based chemotherapy (CR/PR)

2:1 Randomization

→ **Niraparib*** / **Placebo***

→ 36 months or until disease progression or unacceptable toxicity

*Individualised starting dose (ISD) was adopted in **ALL** patients: *starting dose of 200 mg administered orally, once daily, but 300 mg for patients with body weight ≥77 kg AND platelet count ≥150,000/μL*

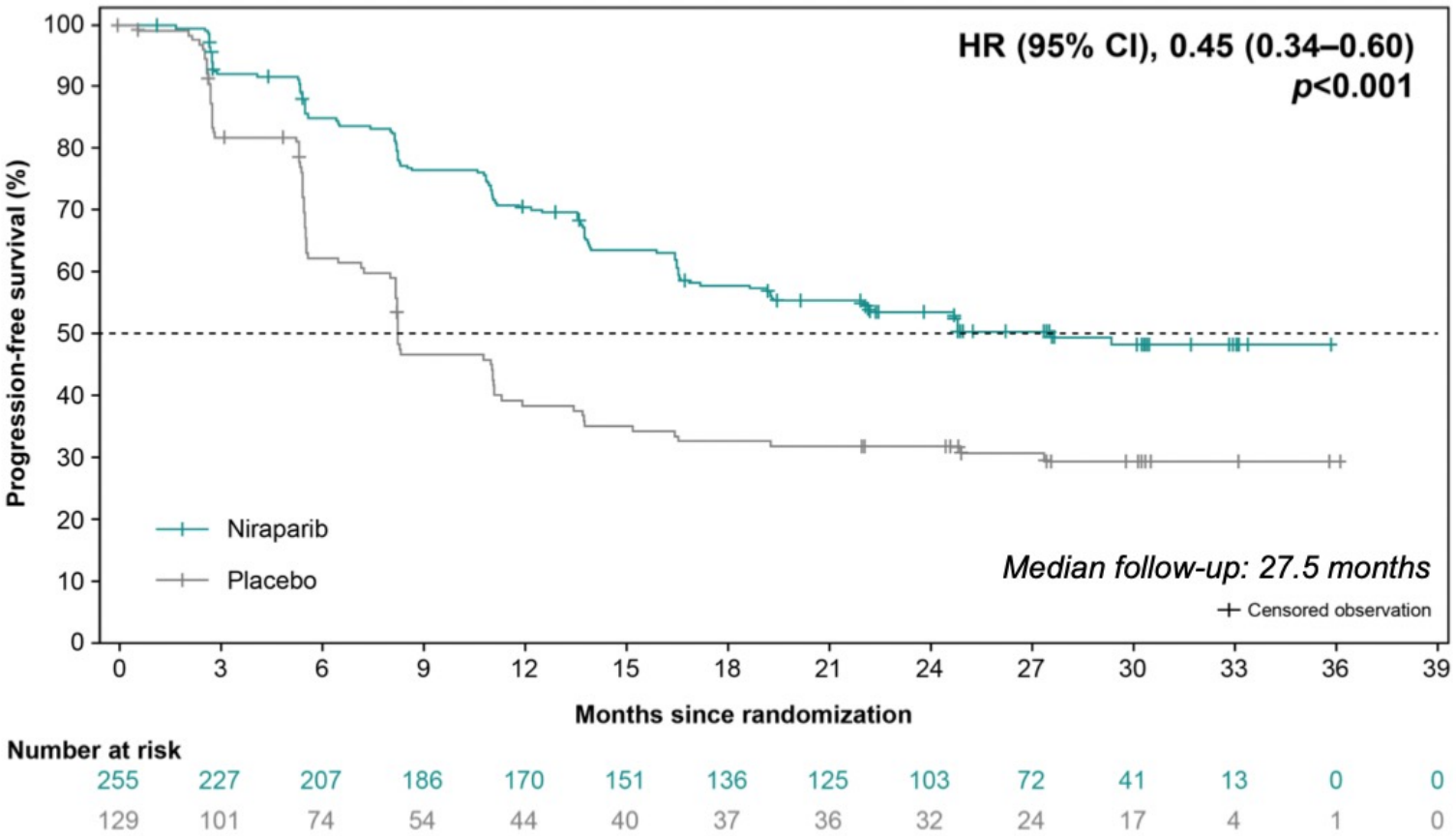
Primary Endpoint
- **PFS by BICR in the ITT population**

Secondary Endpoints
- OS and TFST in the ITT population
- PFS and OS in the HRD subgroup[c]
- Safety

Li N et al. SGO 2022; Abstract 244.

PRIME Primary Endpoint: PFS (by BICR) in the ITT population

PFS (by BICR) in the ITT Population
PRIME Study Primary Endpoint



16.5 months longer median PFS with niraparib versus placebo

	Niraparib (N=255)	Placebo (N=129)
PFS (54.4% data maturity)		
Events, n (%)	123 (48.2)	86 (66.7)
mPFS (95% CI), months	24.8 (19.2–NE)	8.3 (7.3–11.1)
Patients without PD or death (%)		
24 months	52.6	30.4

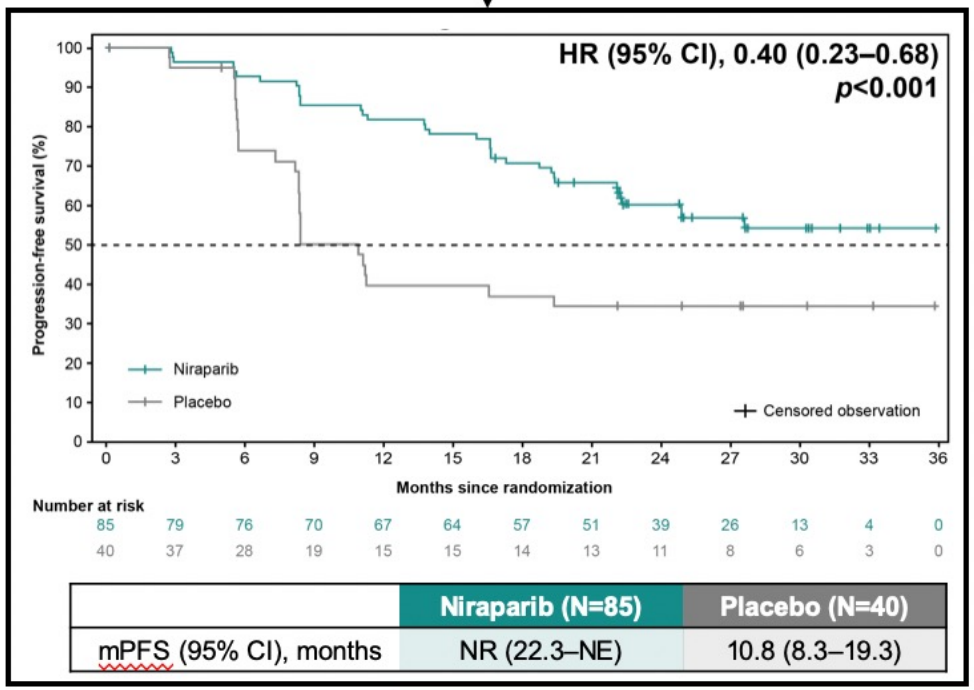
Li N et al. SGO 2022; Abstract 244.

PRIME: gBRCAmut subgroup - PFS (by BICR)

PFS Benefit by g*BRCA*mut Status

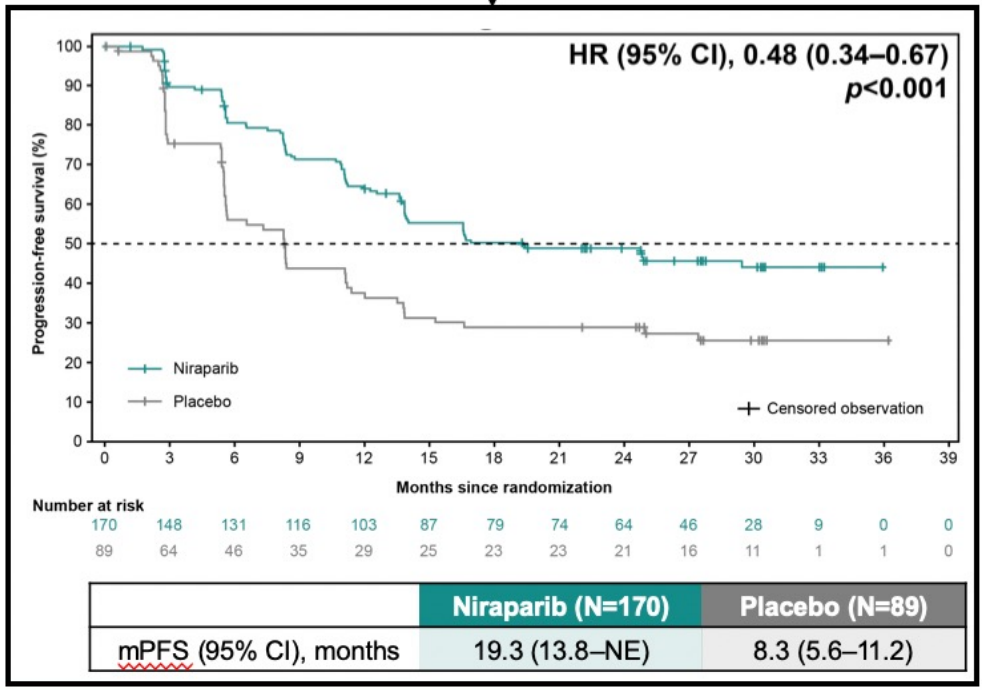
PRIME Study: Prespecified Subgroup Analysis

g*BRCA*mut



	Niraparib (N=85)	Placebo (N=40)
mPFS (95% CI), months	NR (22.3–NE)	10.8 (8.3–19.3)

Non-g*BRCA*mut



	Niraparib (N=170)	Placebo (N=89)
mPFS (95% CI), months	19.3 (13.8–NE)	8.3 (5.6–11.2)

- Median PFS has not been yet reached for the g*BRCA*mut population.
- The benefit of niraparib in the non-g*BRCA*mut population is confirmed.

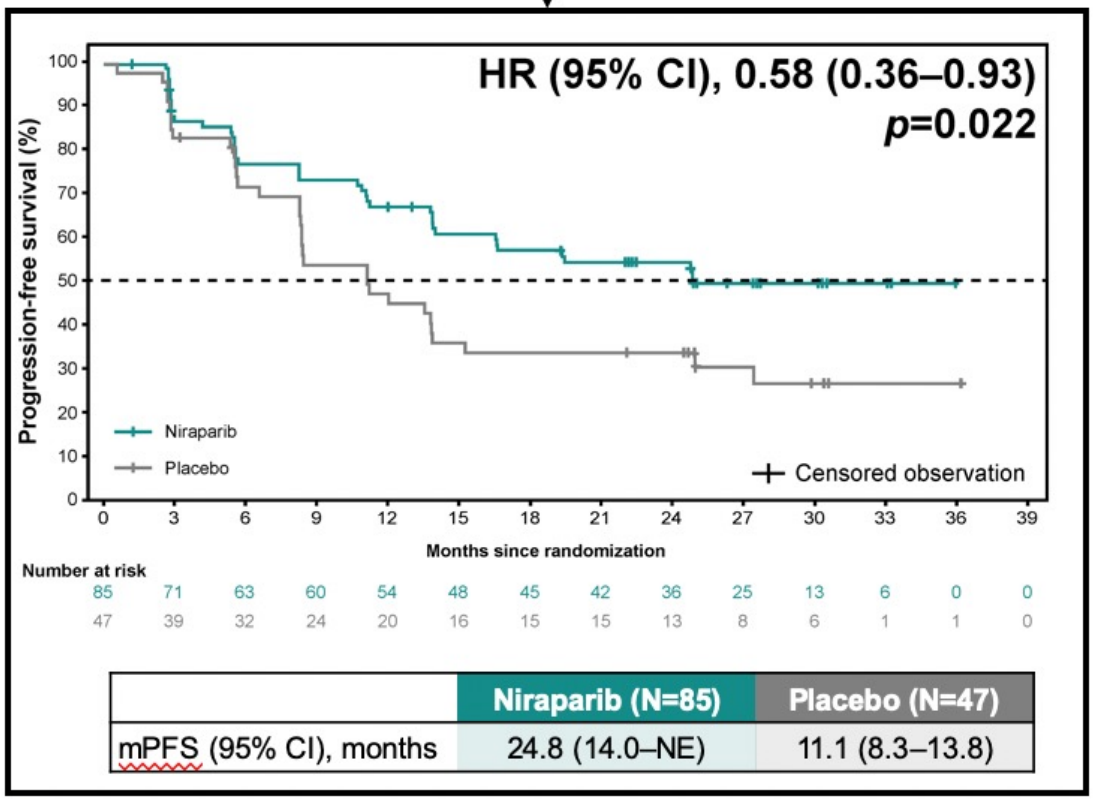
ANNUAL MEETING ON WOMENS' CANCER®

Li N et al. SGO 2022; Abstract 244.

PRIME: Non-gBRCAmut subgroup - PFS (by BICR)

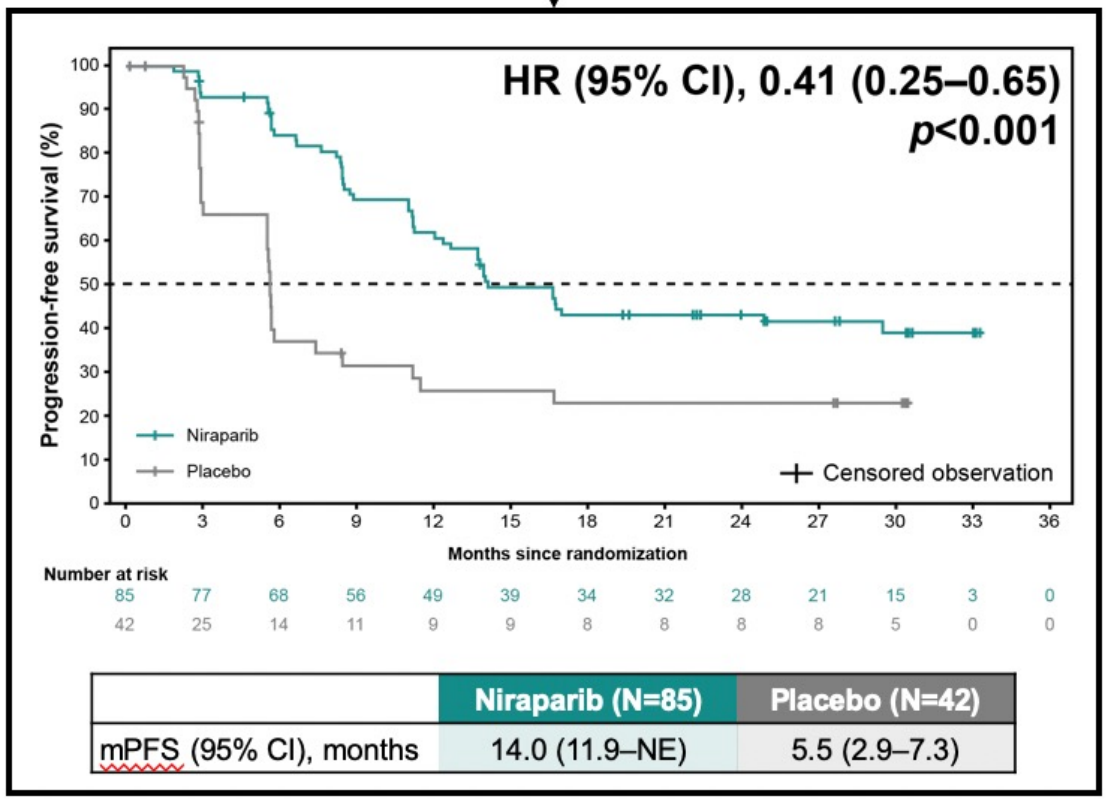
PFS Benefit in Non-g*BRCA*mut Subgroups

Non-g*BRCA*mut/HRd



	Niraparib (N=85)	Placebo (N=47)
mPFS (95% CI), months	24.8 (14.0–NE)	11.1 (8.3–13.8)

Non-g*BRCA*mut/HRp



	Niraparib (N=85)	Placebo (N=42)
mPFS (95% CI), months	14.0 (11.9–NE)	5.5 (2.9–7.3)

Li N et al. SGO 2022; Abstract 244.

ENGOT-OV45 / ATHENA$_{mono}$ study

Key Patient Eligibility

- Newly diagnosed, stage III–IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Completed frontline platinum-doublet chemotherapy and surgery
  - Achieved investigator-assessed CR or PR
  - Received cytoreductive surgery (primary or interval; R0/complete resection permitted)
- ECOG PS 0 or 1
- No prior treatment for ovarian cancer, including any maintenance treatment, other than frontline platinum regimen

Randomization 4:4:1:1

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm C (n≈100)
placebo PO + nivolumab 480 mg IV

Arm D (n≈100)
placebo PO + placebo IV

Randomization Stratification Factors

- Tumor HRD test status†
- Disease status post-chemotherapy
- Timing of surgery

Treatment for 24 months*, or until radiographic progression, unacceptable toxicity, or other reason for discontinuation

Study Analyses

ATHENA–MONO

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm D (n≈100)
placebo PO + placebo IV

ATHENA–COMBO

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

*After initiation of oral/IV combination study treatment (IV drug was initiated cycle 2 day 1; 28-day cycles). †Centrally assessed, determined by FoundationOne CDx (BRCA^{mut}, BRCA^{wt}/LOH^{high} [LOH ≥16%], BRCA^{wt}/LOH^{low} [LOH <16%], BRCA^{wt}/LOH^{indeterminate}). BID, twice daily; BRCA, *BRCA1* or *BRCA2*; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; IV, intravenous; LOH, loss of heterozygosity; mut, mutant; PO, by mouth; PR, partial response; wt, wild type.

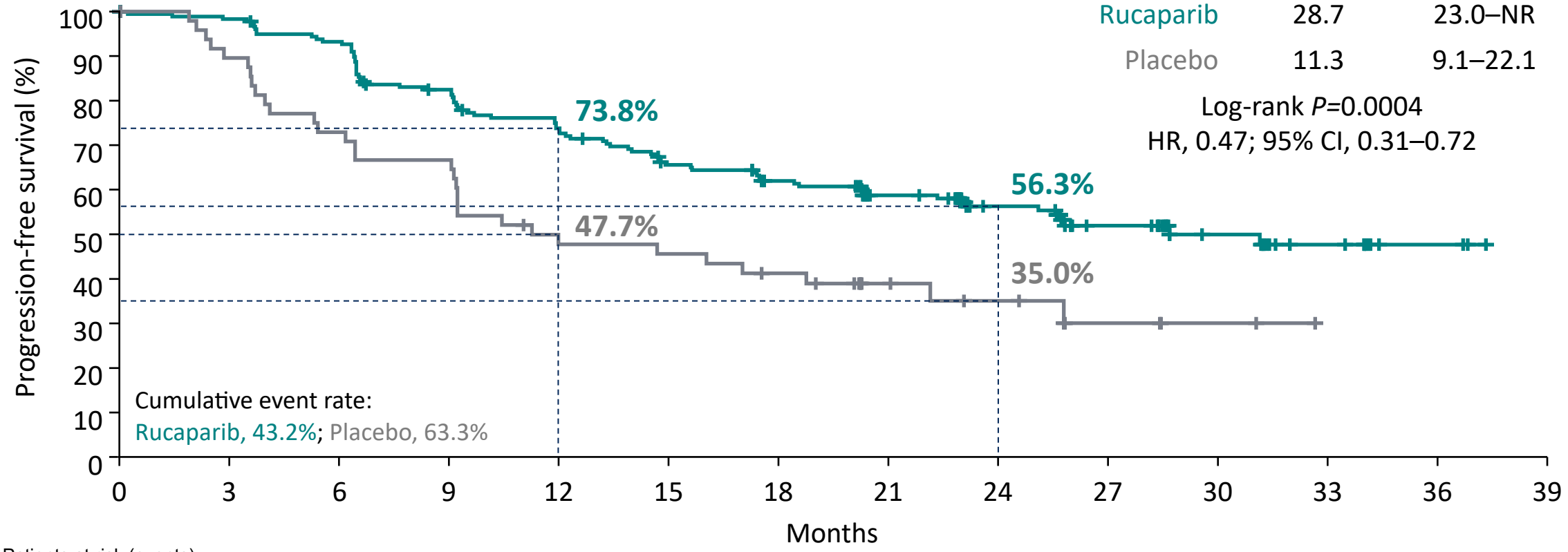
Monk B et al. JCO 2022 Dec 1;40(34):3952-3964.

ENGOT-OV45 / ATHENA$_{mono}$

Primary Endpoint – Investigator Assessed PFS in HRD Population

	Median	95% CI
Rucaparib	28.7	23.0–NR
Placebo	11.3	9.1–22.1

Log-rank *P*=0.0004
HR, 0.47; 95% CI, 0.31–0.72



Patients at risk (events)

Rucaparib	185(0)	175(3)	165(12)	143(31)	127(46)	110(60)	100(66)	82(71)	59(74)	36(78)	22(79)	12(80)	3(80)	0(80)
Placebo	49(0)	43(5)	35(13)	32(16)	22(25)	21(26)	18(28)	11(29)	8(30)	4(31)	2(31)	0(31)		

Data cutoff date: March 23, 2022.
HR, hazard ratio; HRD, homologous recombination deficiency; NR, not reached; PFS, progression-free survival.

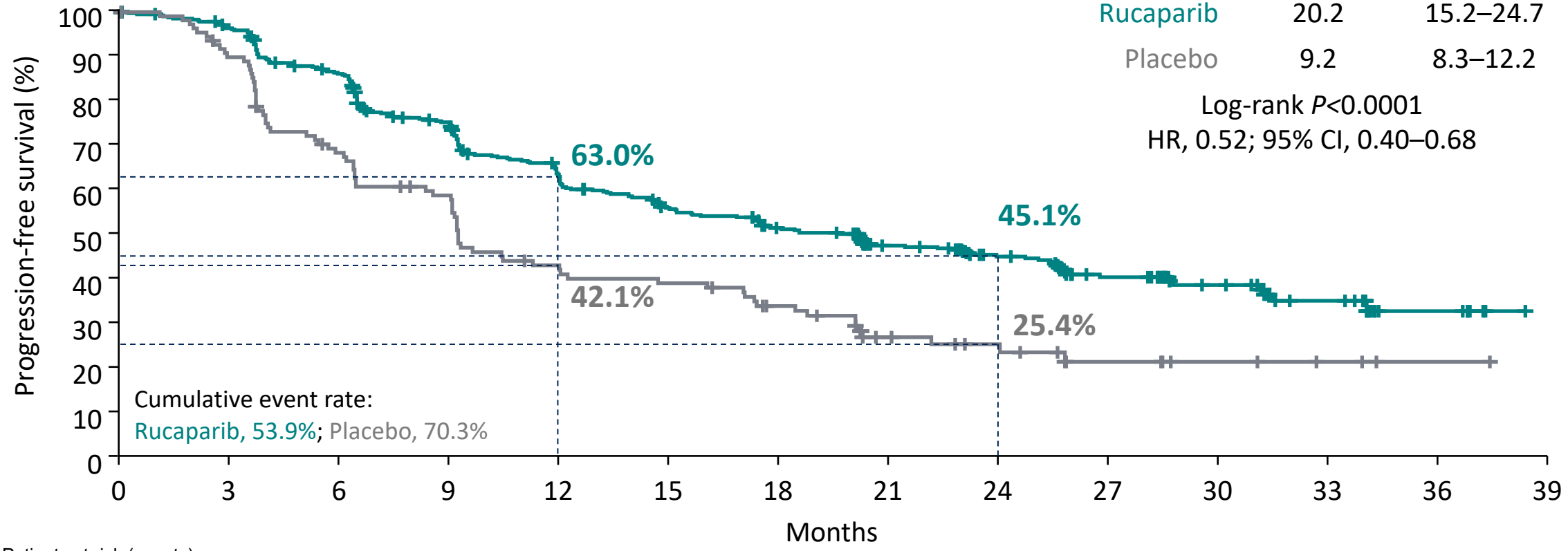
Monk B et al. ASCO 2022; Abstract LBA5500; Monk B et al. JCO 2022 Dec 1;40(34):3952-3964.

ENGOT-OV45 / ATHENA$_{mono}$

Primary Endpoint – Investigator Assessed PFS in ITT Population

	Median	95% CI
Rucaparib	20.2	15.2–24.7
Placebo	9.2	8.3–12.2

Log-rank $P<0.0001$
HR, 0.52; 95% CI, 0.40–0.68



Patients at risk (events)

Rucaparib	427 (0)	398 (15)	351 (57)	298 (101)	245 (149)	213 (176)	190 (193)	151 (207)	114 (214)	67 (224)	42 (226)	23 (229)	7 (230)	0 (230)
Placebo	111 (0)	97 (11)	72 (34)	60 (44)	42 (61)	39 (64)	31 (69)	18 (75)	14 (76)	8 (78)	5 (78)	3 (78)	1 (78)	0 (78)

Data cutoff date: March 23, 2022.
HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

Monk B et al. ASCO 2022; Abstract LBA5500; Monk B et al. JCO 2022 Dec 1;40(34):3952-3964.

ENGOT-OV45 / ATHENA$_{mono}$

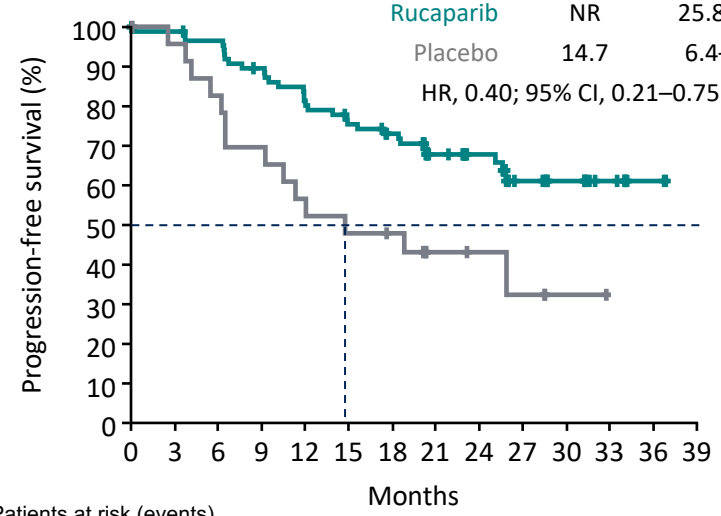
Investigator Assessed in Exploratory Subgroups

HRD positive

BRCA^{mut}

	Median	95% CI
Rucaparib	NR	25.8–NR
Placebo	14.7	6.4–NR

HR, 0.40; 95% CI, 0.21–0.75



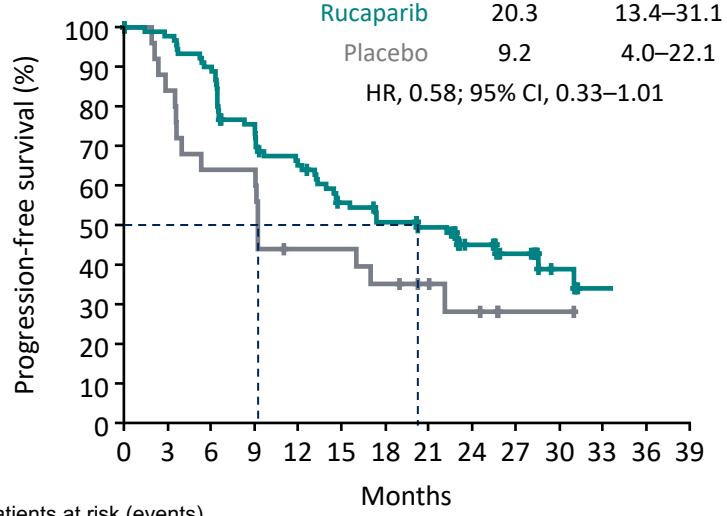
Patients at risk (events)

Rucaparib	91 (0)	84 (3)	70 (16)	59 (23)	34 (27)	14 (30)	2 (30)
Placebo	24 (0)	19 (4)	12 (11)	10 (12)	4 (13)	1 (14)	0 (14)

BRCA^{wt}/LOH^{high}

	Median	95% CI
Rucaparib	20.3	13.4–31.1
Placebo	9.2	4.0–22.1

HR, 0.58; 95% CI, 0.33–1.01



Patients at risk (events)

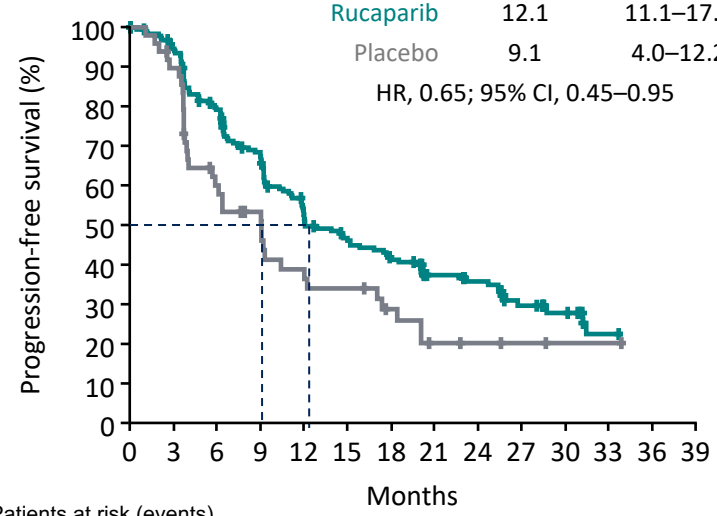
Rucaparib	94 (0)	81 (9)	57 (30)	41 (43)	25 (47)	8 (49)	4 (50)
Placebo	25 (0)	16 (9)	10 (14)	8 (16)	4 (17)	1 (17)	0 (17)

HRD negative

BRCA^{wt}/LOH^{low}

	Median	95% CI
Rucaparib	12.1	11.1–17.7
Placebo	9.1	4.0–12.2

HR, 0.65; 95% CI, 0.45–0.95



Patients at risk (events)

Rucaparib	189 (0)	142 (38)	89 (84)	68 (102)	42 (111)	15 (118)	8 (120)
Placebo	49 (0)	27 (19)	16 (28)	10 (32)	5 (35)	3 (35)	3 (35)

- Rucaparib demonstrated treatment benefit vs placebo regardless of BRCA mutation and HRD status

Data cutoff date: March 23, 2022.

BRCA, *BRCA1* or *BRCA2*; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; mut, mutant; NR, not reached; PFS, progression-free survival; wt, wild type.

Monk B et al. ASCO 2022; Abstract LBA5500; Monk B et al. JCO 2022 Dec 1;40(34):3952-3964.

SOME UNANSWERED QUESTIONS IN THE PREVIOUS THREE TRIALS ARE ANSWERED *BY PRIME OR ATHENA-MONO*

- Is addition of bevacizumab to PARP inhibitor beneficial? **?**
  - olaparib arm is missing in PAOLA1
  - bevacizumab arm is missing in PRIMA, SOLO1, PRIME & ATHENA$_{mono}$
- In BRCA $_{WT}$:Efficacy of PARPi (as single agent) in lower risk patients: R0, stage III disease? **+**
  - Demonstrated in PRIME & ATHENA$_{mono}$
- Efficacy of PARPi in HR proficient disease **+**
  - Three randomised trials have established the efficacy of PARP inhibitors (PRIMA, PRIME & ATHENA$_{mono}$)

Is HRD test Predictive of Response to PARPi therapy ?

Test	Trial	Predictive
MyChoice	PAOLA-1	Yes
MyChoice	PRIMA	**Partially**
BGI	PRIME	**No**
FoundationOne	ATHENA	**Partially**

REVIEW

European experts consensus: BRCA/homologous recombination deficiency testing in first-line ovarian cancer

I. Vergote[1*], A. González-Martín[2,3], I. Ray-Coquard[4], P. Harter[5], N. Colombo[6], P. Pujol[7], D. Lorusso[8], M. R. Mirza[9], B. Brasiuniene[10], R. Madry[11], J. D. Brenton[12], M. G. E. M. Ausems[13], R. Büttner[14] & D. Lambrechts[15], on behalf of the European experts' consensus group[†]

Lancet Oncol. 2022 Aug;23(8):e374-e384.

Safety

	SOLO-1	PRIMA	PRIME	ATHENA-MONO	PAOLA-1
Discontinuation (%)	11.5	12	6.7	11.8	**20**
Dose interruption (%)	51.9	79.5	62	60.7	54
Dose reduction (%)	28.5	70.9	40.4	49.4	41
MDS/AML (%)	1	0.2	0.7	0.4	1.1

The aim of the table is not the cross-trial comparison

Key Takeaways

- Integration of PARPi has an unprecedented improvement for our patients.
- Use of PARP inhibitors in front line therapy leads to a significant benefit in progression-free survival, especially in BRCA mutated tumours and those with high GIS scores
- Testing for BRCA mutations and HRD should be part of standard management of ovarian cancer
- Most/all patients should be considered for maintenance therapy with PARP inhibitor, bevacizumab or both

Module 2: PARP Inhibitors for Relapsed/Refractory Ovarian Cancer — Dr Oza

RTP
RESEARCH
TO PRACTICE

Case Presentation: 65-year-old woman with recurrent BRCA WT ovarian cancer in ongoing and durable remission with paclitaxel/carboplatin → maintenance niraparib

Dr John Chan (San Francisco, California)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Dr John Chan

What is the rationale behind the FDA retraction of approvals for PARP inhibitors in the metastatic and recurrent settings?

How should clinicians approach the use of PARP inhibitors in these settings?

RTP
RESEARCH
TO PRACTICE

Case Presentation: 51-year-old woman with recurrent platinum-sensitive, gBRCA2-mutant ovarian cancer treated with paclitaxel/carboplatin/bevacizumab and maintenance olaparib/bevacizumab

Dr Thomas Morrissey (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Dr Thomas Morrissey

How long do you generally continue maintenance with PARP inhibitor/bevacizumab in the recurrent platinum-sensitive setting?

What is the risk of long-term toxicity with extended duration of PARP inhibitor use?

What is the role, if any, of using ctDNA in determining how long to continue treatment for patients with ovarian cancer?

RTP
RESEARCH
TO PRACTICE

PARP Inhibitors for Relapsed/Refractory Ovarian Cancer

Amit M. Oza MD (Lon), FRCP, FRCPC

Head, Division of Medical Oncology & Hematology, University Health Network/Mount Sinai

Director, Clinical Research and Clinical Cancer Research Unit, Princess Margaret

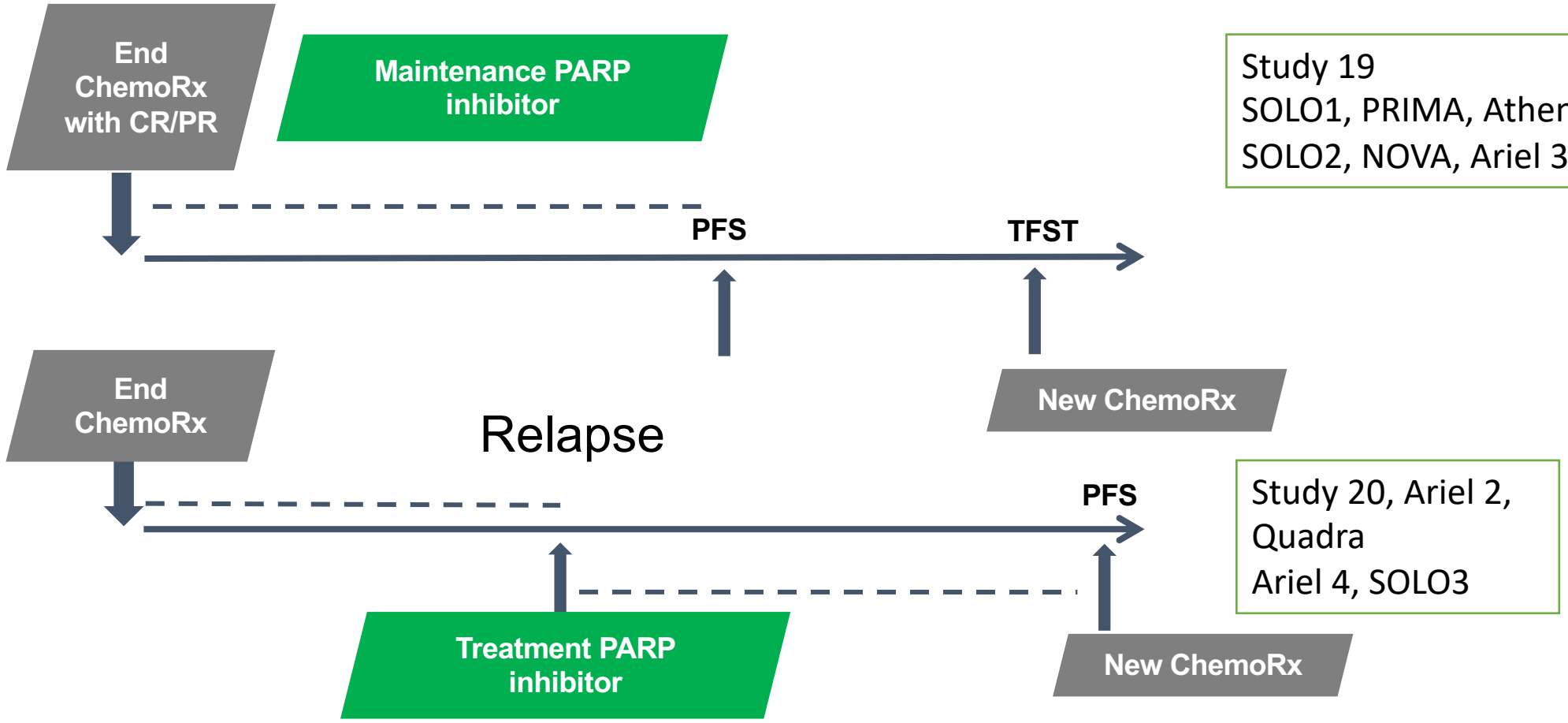
Professor, Faculty of Medicine, University of Toronto

Ovarian Cancer: Parp inhibitors: 14 years – the story evolves

- Impressive Activity in HGS OC
- Active as a single agent
- Sequential, maintenance strategies effective
- Earlier use is better—and can be given for a shorter duration
- Improvement in Survival
- Synergy with anti-angiogenics
- ? Retreatment in some circumstances

- Predictive, validated biomarkers (context specific)
  - mBRCA, LOH, HRD
  - Platinum Sensitivity
- Activity goes beyond mBRCA
  - Maintenance single agent
  - In combination with bevacizumab
- Clinical Trial Outcomes need careful evaluation in context-regulatory endpoints

Treatment Versus Maintenance in Ovarian Cancer

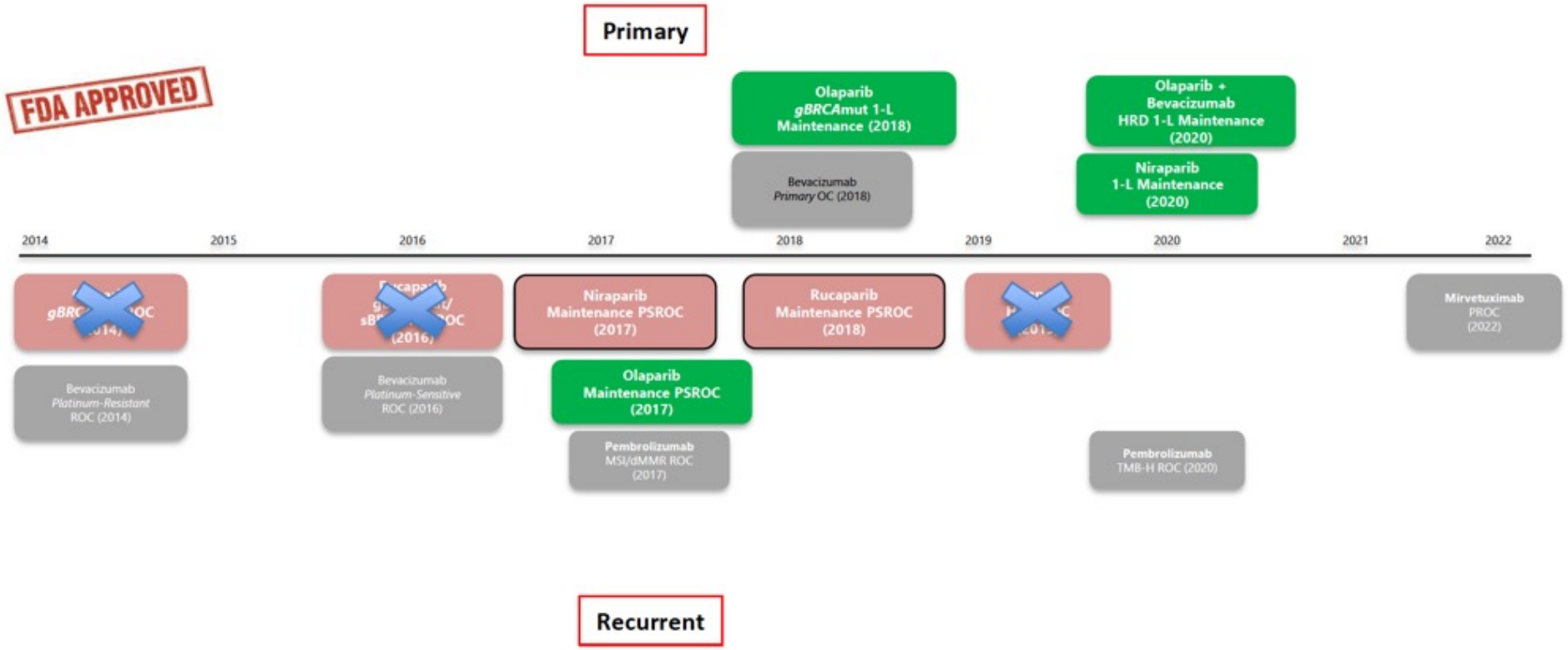


Study 19
SOLO1, PRIMA, Athena M
SOLO2, NOVA, Ariel 3

Study 20, Ariel 2, Quadra
Ariel 4, SOLO3

So why the anxiety

Fifteen Ovarian Cancer Approvals in the Last 9 Years!
(2023…So Far)



Coleman ESMO 2023

ASCO guidelines 2022

Recommendation 3.0.

PARPi monotherapy maintenance (second-line or more) may be offered to patients with EOC who have not already received a PARPi and who have responded to platinum-based therapy regardless of BRCA mutation status; treatment is continued until progression of disease or toxicity despite dose reductions and best supportive care. Options include olaparib 300 mg every 12 hours, rucaparib 600 mg every 12 hours or niraparib 200-300 mg once daily. (Type: Evidence-based, benefits outweigh harms; **Evidence quality: High; Strength of recommendation: Strong.)**

Maintenance treatment with niraparib for patients without germline or somatic BRCA mutation should weigh potential PFS benefit against possible OS decrement. (Type: Evidence-based, benefits outweigh harms; **Evidence quality: Low; Strength of recommendation: Moderate**.)

Tew WP et al. *J Clin Oncol* 2022 Nov 20; 40(33):3878-3881.

ASCO Guidelines 2022

Recommendations 3.1/3.2.

PARPi monotherapy should not be routinely offered to patients for the treatment of recurrent platinum sensitive EOC.

Type: Evidence-based, benefits outweigh harms; **Evidence quality: Intermediate; Strength of recommendation: Moderate.)**

Evidence on PARPi use in this setting is evolving and data are continuing to emerge. Any decision to proceed with PARPi treatment in select populations (BRCA mutation, No prior PARPi use, Platinum Sensitive, Advanced Lines of Treatment) should be based on individualized patient and provider assessment of risks, benefits, and preferences.

Tew WP et al. *J Clin Oncol* 2022 Nov 20; 40(33):3878-3881.

ASCO Guidelines

Recommendation 3.3.

PARPi monotherapy is not recommended for treatment for patients with either BRCA wildtype or platinum-resistant recurrent EOC.

(Type: Evidencebased, benefits outweigh harms**; Evidence quality: High; Strength of recommendation: Strong.)**

Tew WP et al. *J Clin Oncol* 2022 Nov 20; 40(33):3878-3881.

Development of Parpi: 2009-2023

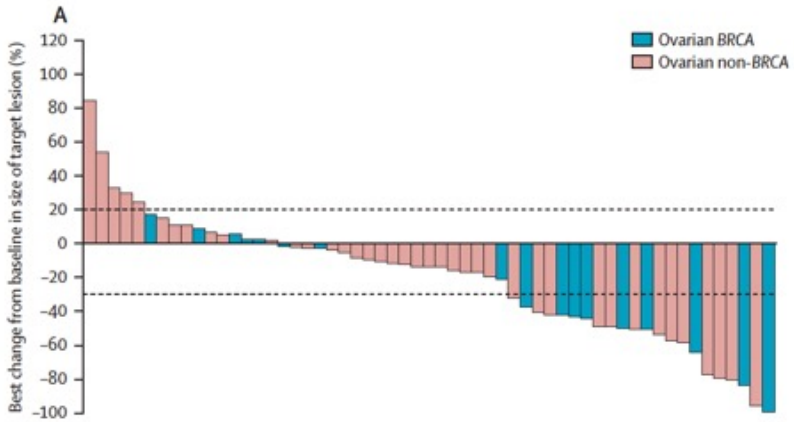
Single Agent Activity –gBRCA
Activity in PS>PR
PS activity– mBRCA>LOH/HRD>HRP

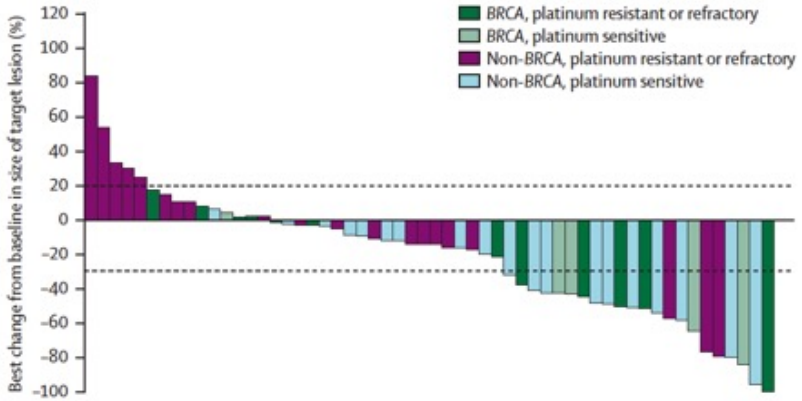
Active in Maintenance
Activity mBRCA>HRD>HRP
PFS primary endpoint met
OS? - non regulatory endpoint

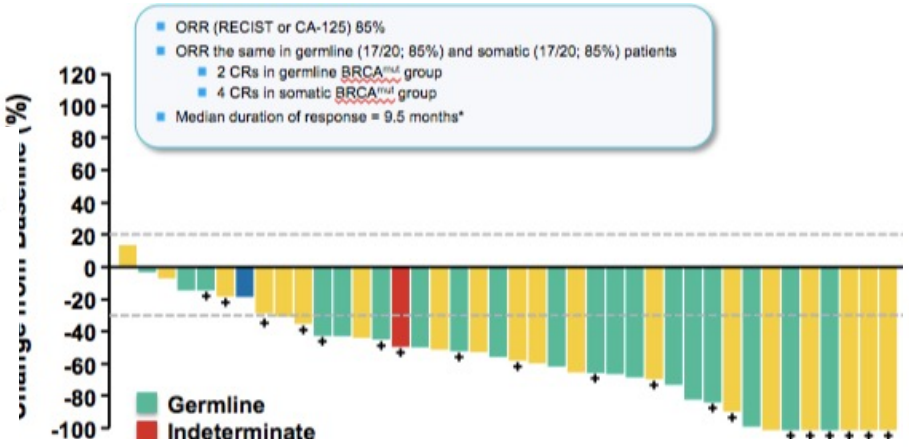
Active in maintenance
Activity mBRCA>HRD>HRP
PFS endpoint met mBRCA>HRD>HRP
OS: 7yr OS mBRCA

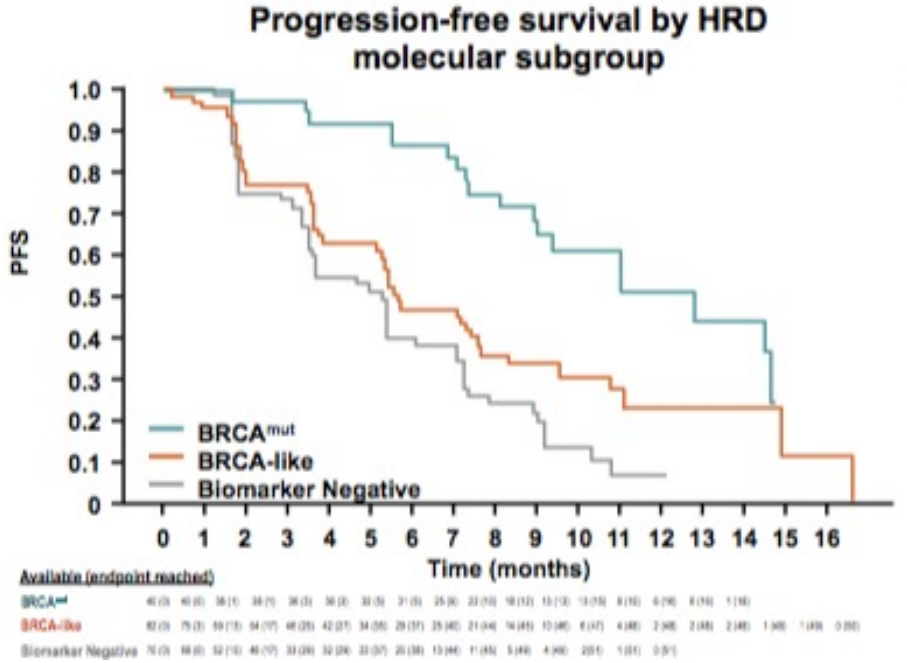
Single agent PARPi in recurrence

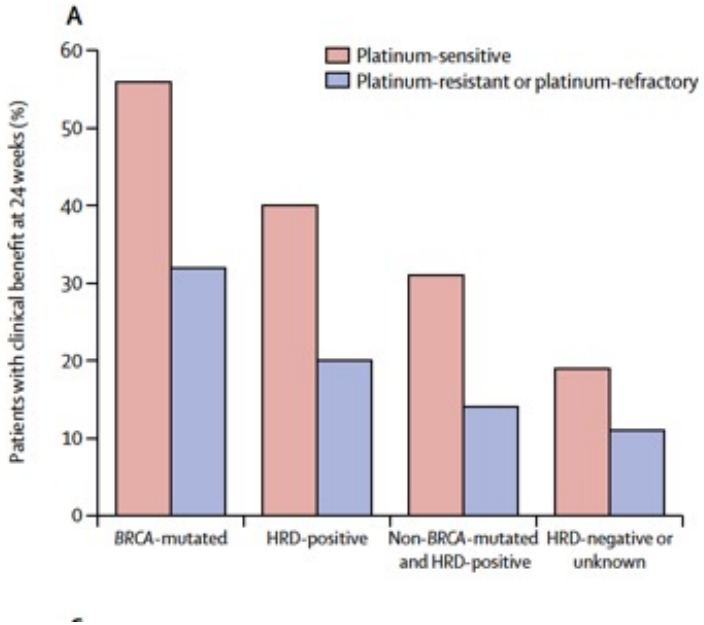
What did we learn from single agent studies – in non mBRCA patients: Study 20, Ariel 2, Quadra?





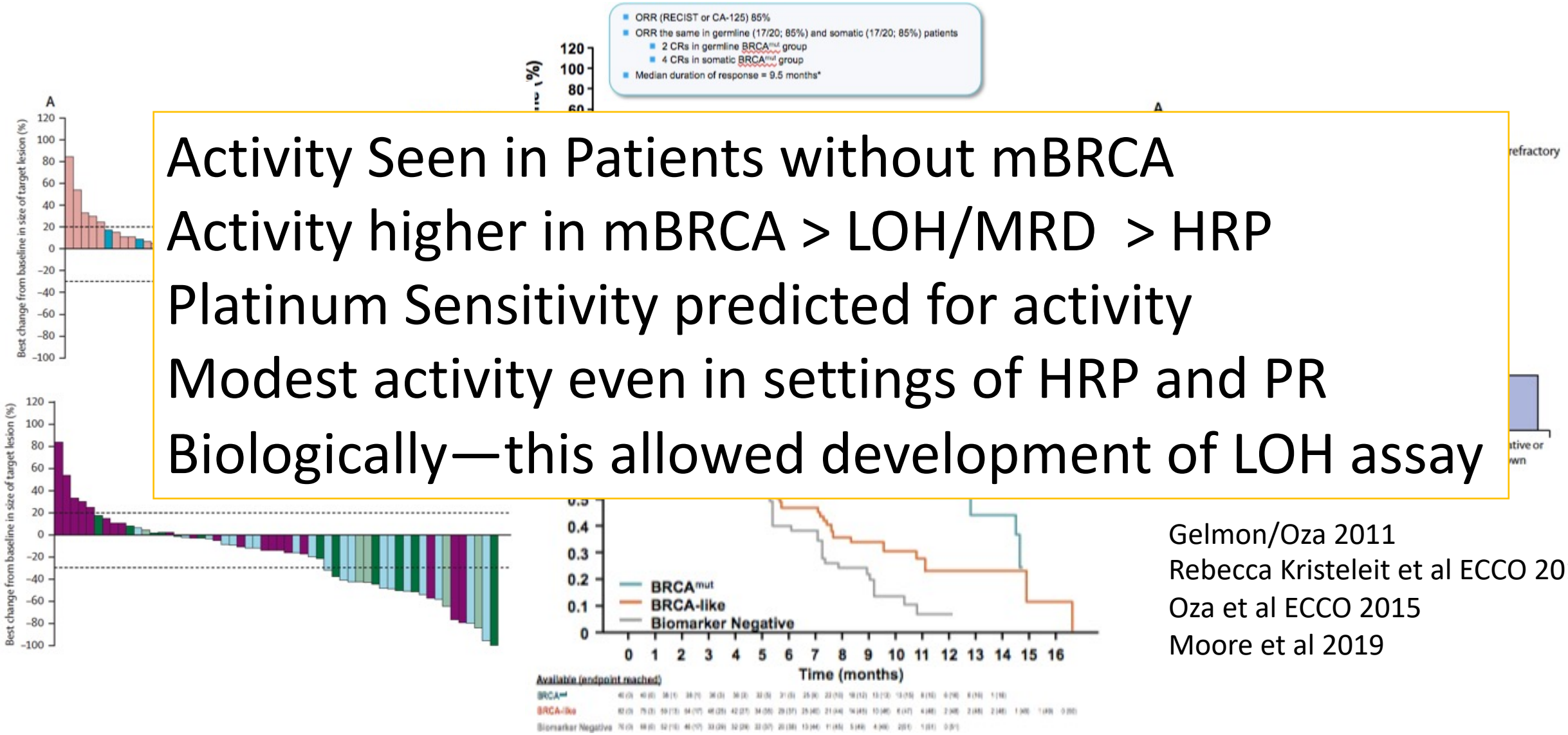






Gelmon/Oza 2011
Rebecca Kristeleit et al ECCO 2015
Oza et al ECCO 2015
Moore et al 2019

What did we learn from single agent studies – in non mBRCA patients: Study 20, Ariel 2, Quadra?



Activity Seen in Patients without mBRCA

Activity higher in mBRCA > LOH/MRD > HRP

Platinum Sensitivity predicted for activity

Modest activity even in settings of HRP and PR

Biologically—this allowed development of LOH assay

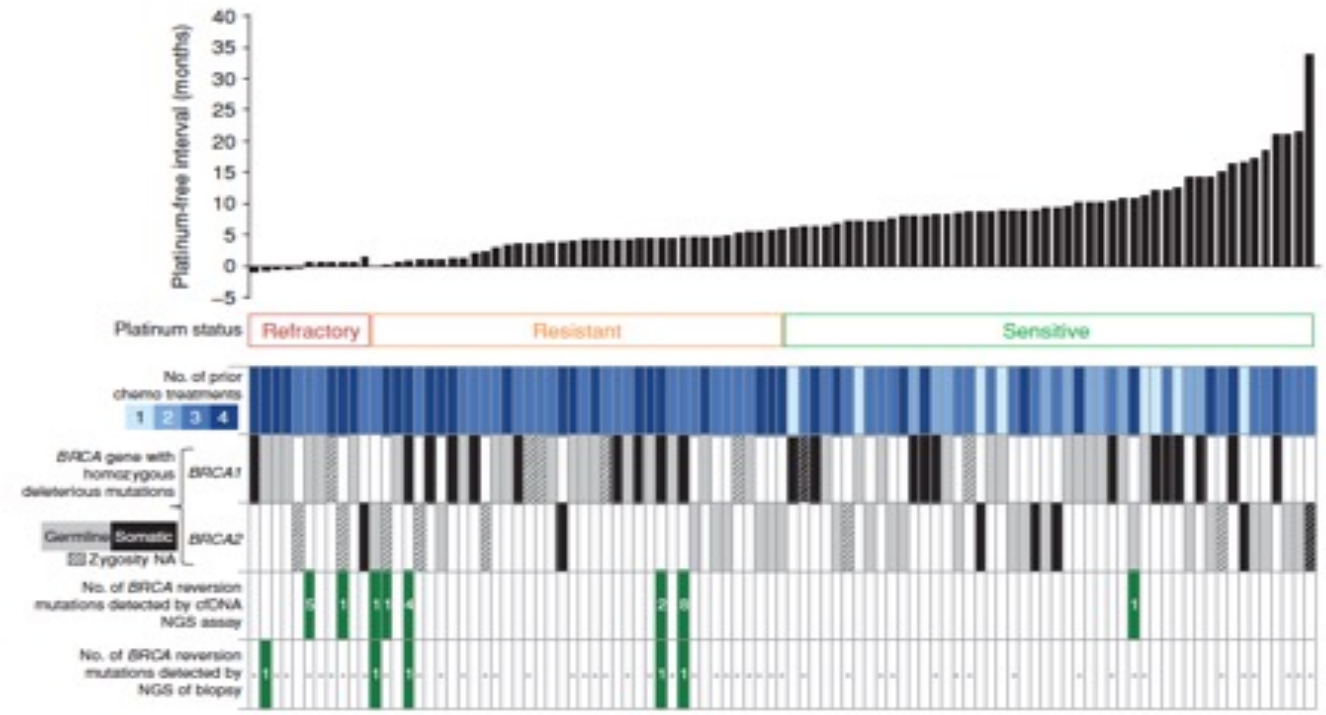
Gelmon/Oza 2011

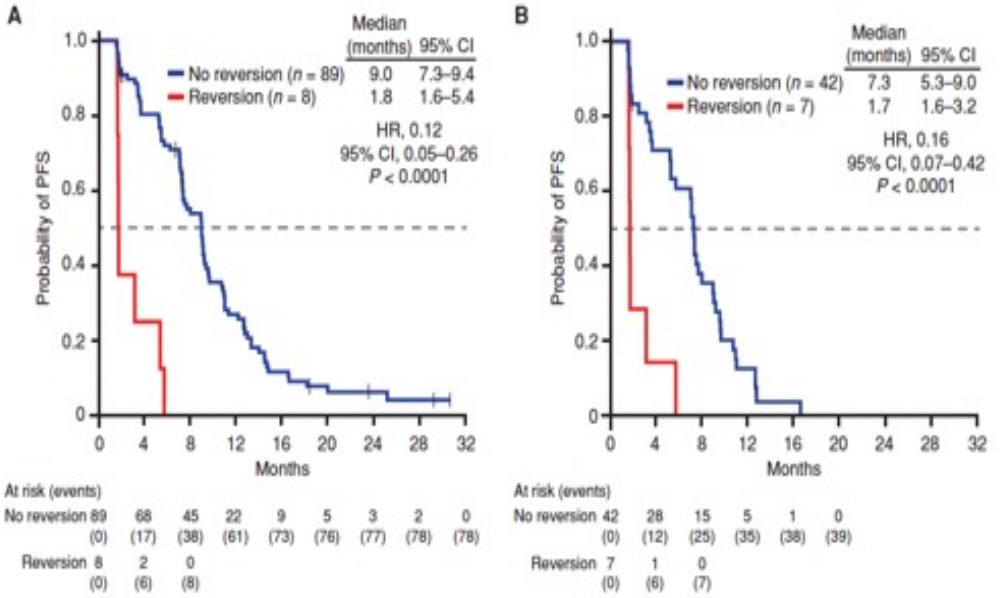
Rebecca Kristeleit et al ECCO 2015

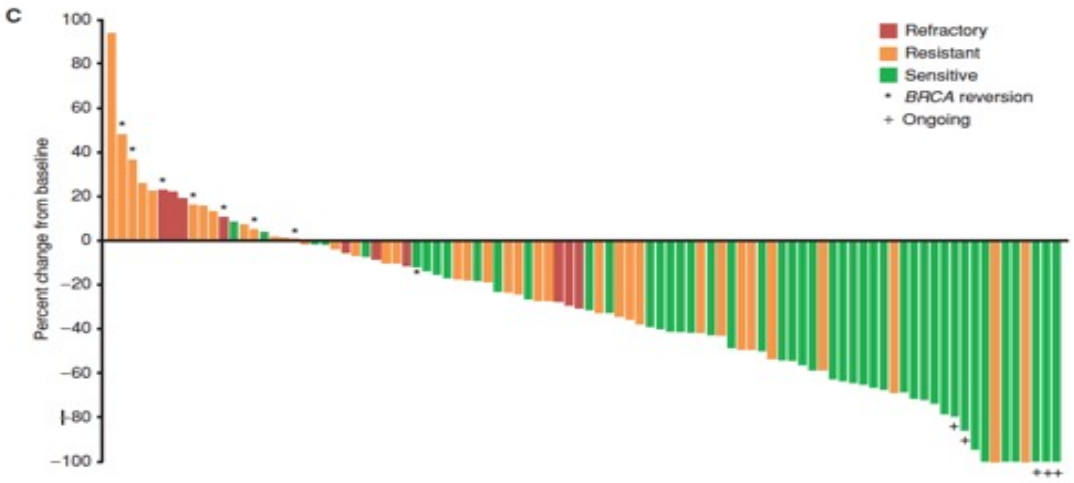
Oza et al ECCO 2015

Moore et al 2019

BRCA1/2 Reversions & Influence on Response – ARIEL 2 Findings



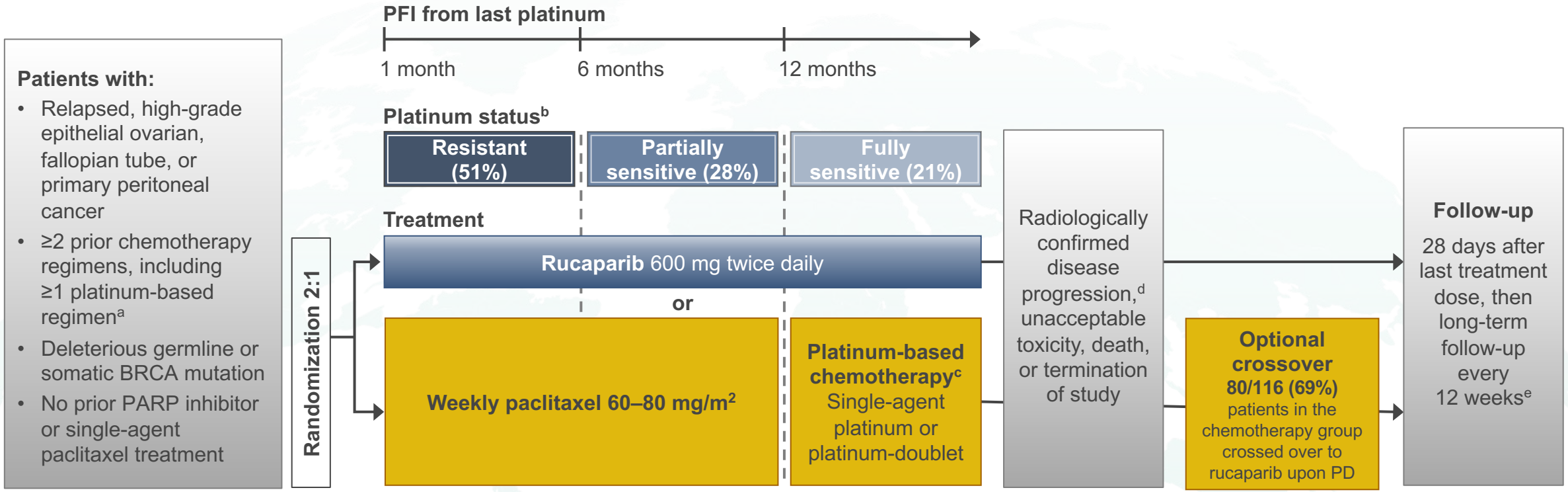




Reversions more prevalent in resistant and refractory patients.
Multiple Reversions can be present in an individual patient

Lin et al. 2018

ARIEL4 Study Design



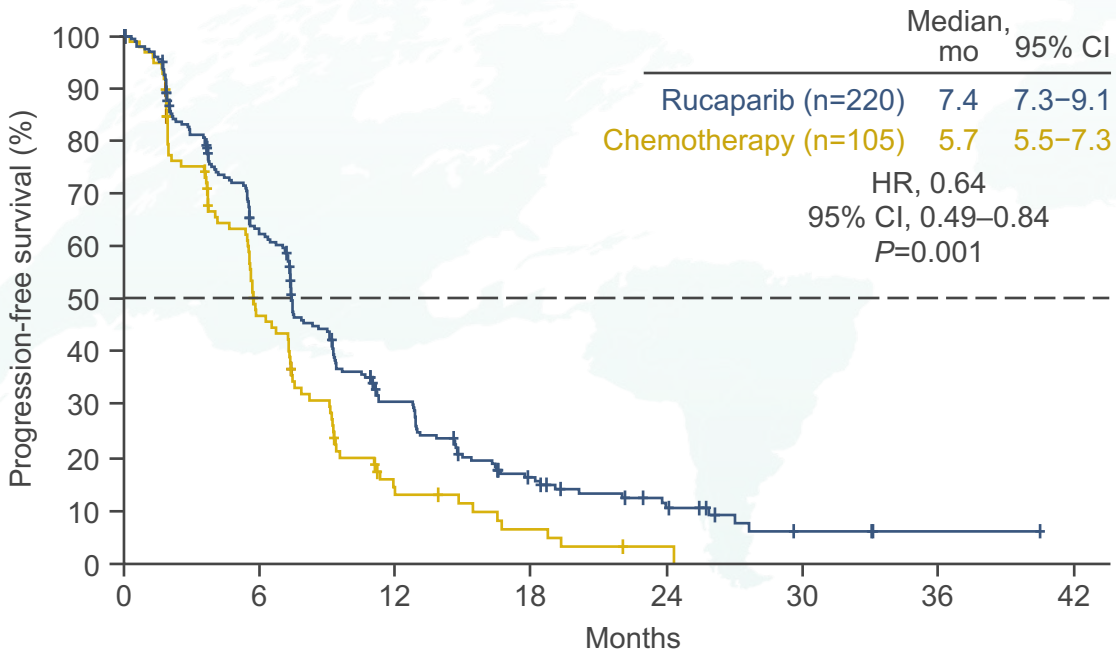
- Efficacy endpoints
  - Prespecified secondary endpoint: OS in the ITT population (OS maturity is at 70%)
  - Exploratory endpoints: OS in platinum-status subgroups; PFS2 in the ITT population and in platinum-status subgroups

[a]With treatment-free interval ≥6 months following first chemotherapy received. [b]Randomization stratification factor. [c]At investigator's discretion. [d]Per RECIST. [e]Patients who discontinued for reasons other than PD were followed every 8 weeks. BRCA, *BRCA1* or *BRCA2*; ITT, intent-to-treat; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFI, progression-free interval; PFS, progression-free survival; PFS2, PFS from randomization to progression on the subsequent line of therapy; RECIST, Response Evaluation Criteria in Solid Tumors, version 1.1.

Presented by: Amit M. Oza

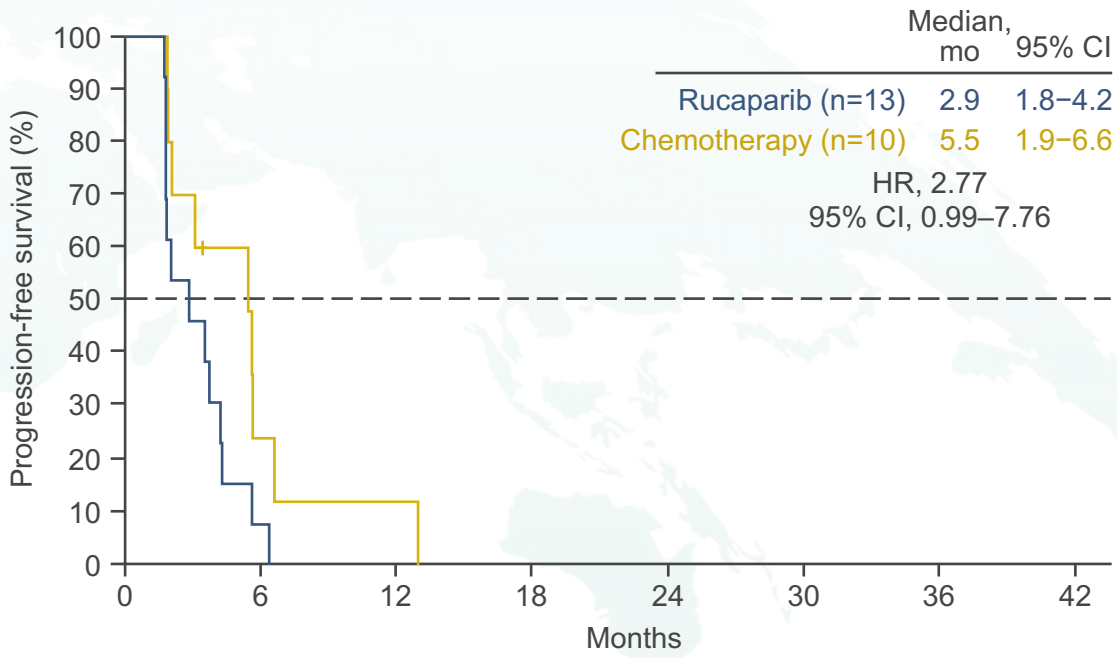
Investigator-assessed PFS

Efficacy Population[1,*]



At risk (events)							
Rucaparib 220 (0)	121 (75)	53 (134)	23 (158)	11 (165)	3 (168)	1 (168)	0 (168)
Chemotherapy 105 (0)	42 (50)	9 (78)	4 (82)	1 (84)	0 (85)		

BRCA Reversion Mutation Subgroup[1]



At risk (events)				
Rucaparib 13 (0)	1 (12)	0 (13)		
Chemotherapy 10 (0)	2 (7)	1 (8)	0 (9)	

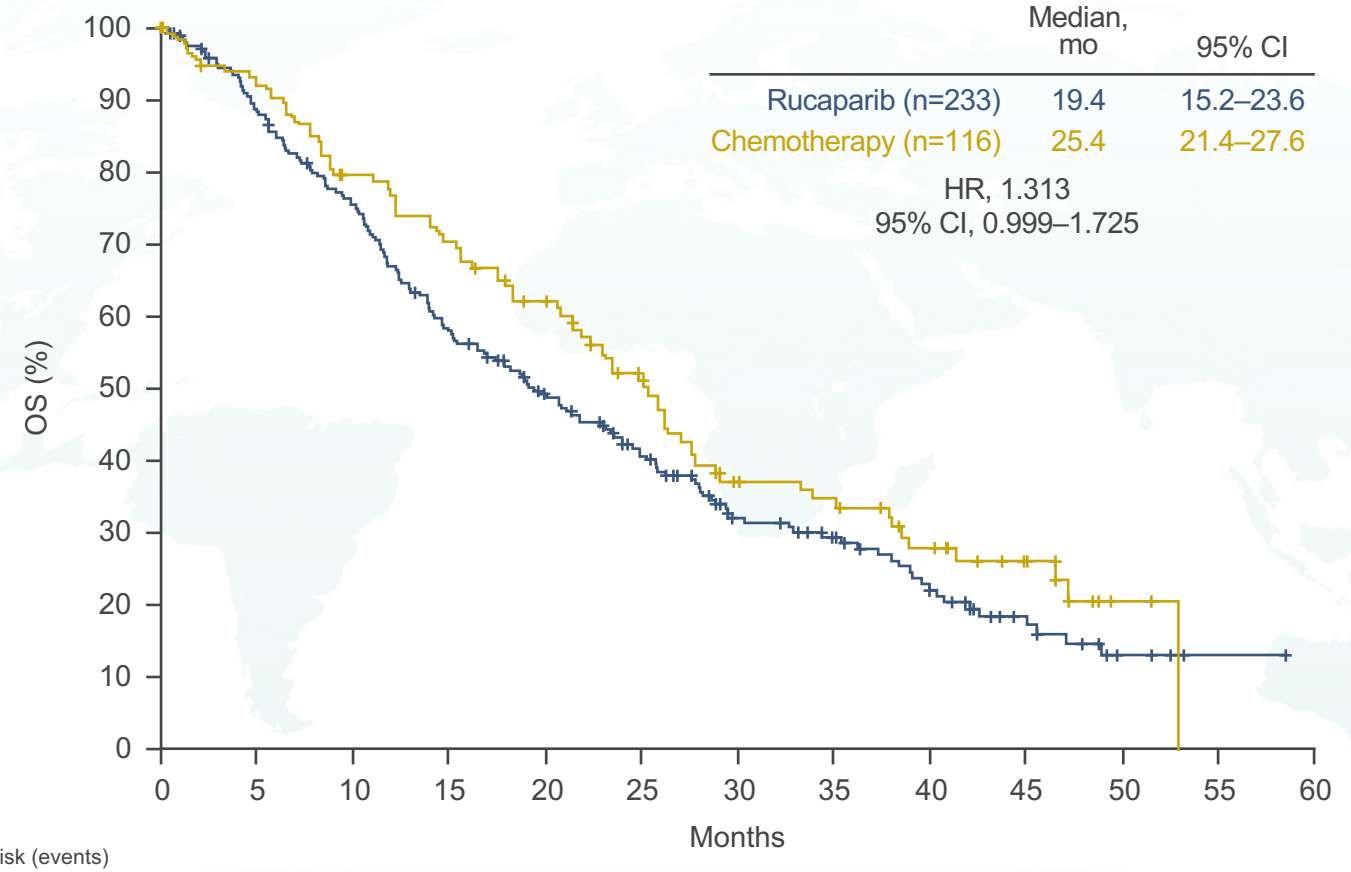
Visit cutoff September 30, 2020.

*Patients with deleterious BRCA mutations, excluding those with BRCA reversion mutations. HR and associated *P* value calculated using a stratified Cox proportional hazards model. *P* value was significant for treatment by BRCA reversion mutation (yes vs no) interaction test (*P*=0.0097).

BRCA, *BRCA1* or *BRCA2*; HR, hazard ratio; PFS, progression-free survival.

1. Kristeleit et al. *Lancet Oncol*. 2022;23(4):465-478.

OS: ITT Population

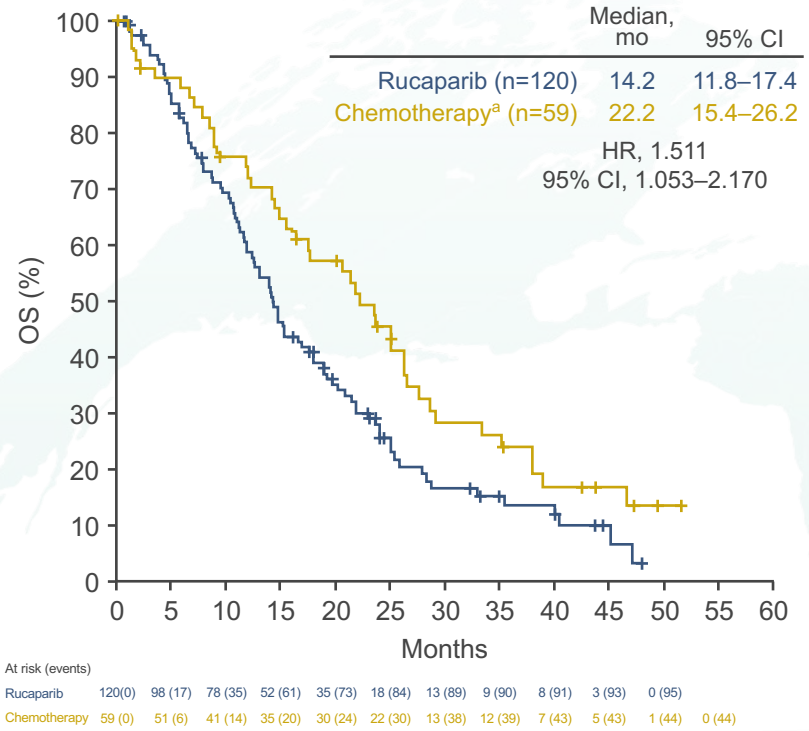


Data cutoff: April 10, 2022. HRs estimated with a Cox proportional hazards model.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival.

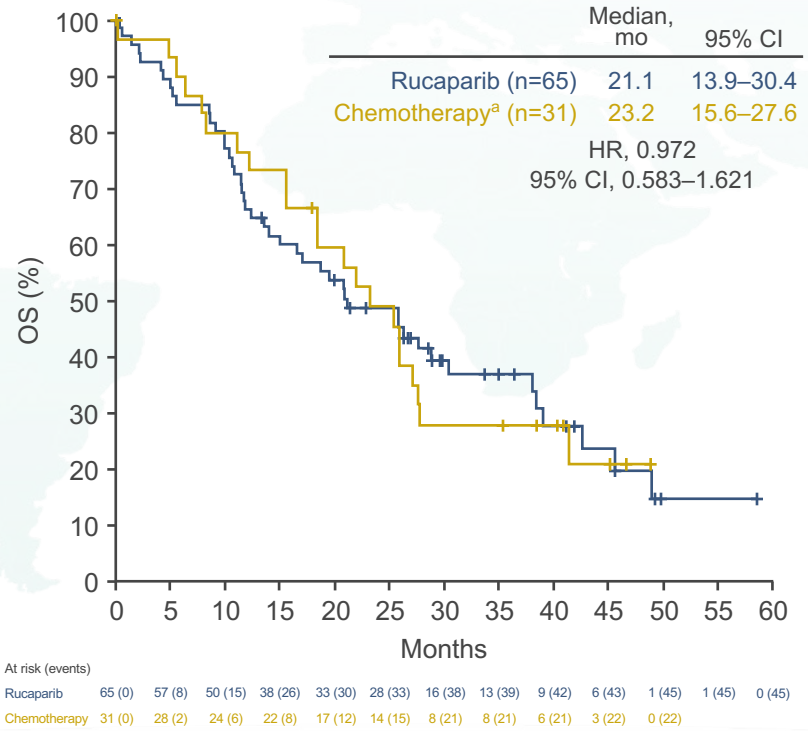
Presented by: Amit M. Oza

OS: Platinum Status Subgroups

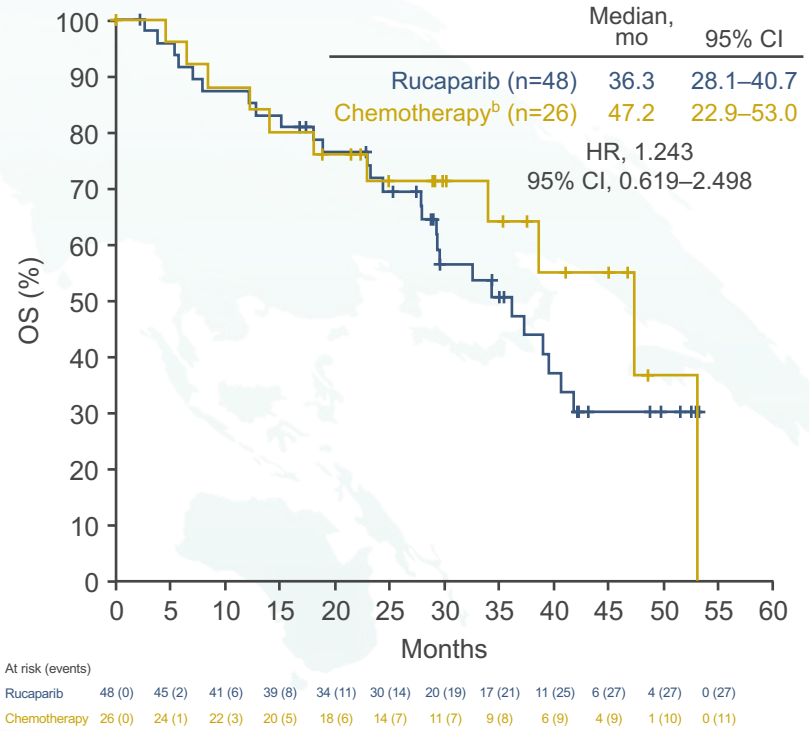
Platinum Resistant



Partially Platinum Sensitive



Fully Platinum Sensitive



- Simple and more complex methods of adjustment for crossover yielded results that were not consistent with OS results in the ITT population

Data cutoff: April 10, 2022. HRs estimated with a Cox proportional hazards model. [a]Weekly paclitaxel. [b]Single-agent platinum or platinum doublet.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; OS, overall survival.

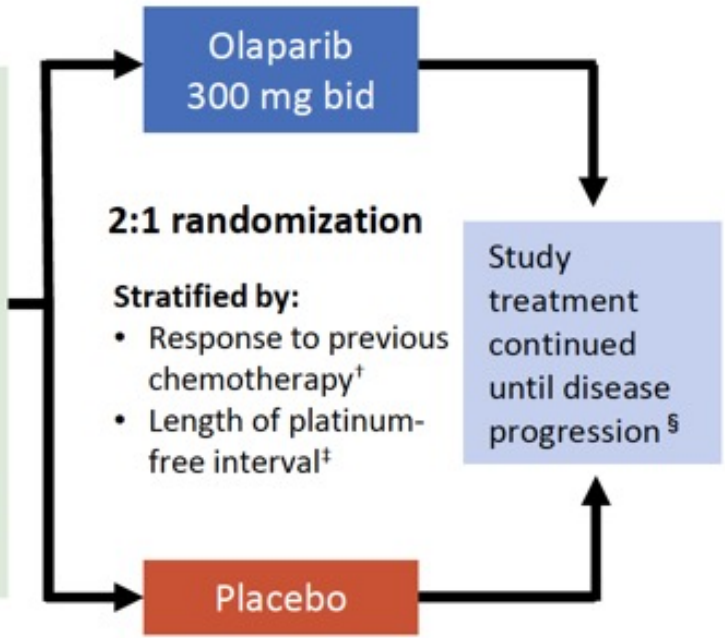
Presented by: Amit M. Oza

Maintenance Therapy following Recurrence

SOLO2, NOVO, Ariel 3

SOLO2: study design

Eligible patients had:
- Relapsed, high-grade serous or endometrioid ovarian cancer*
- BRCAm
- Received ≥2 previous lines of platinum-based chemotherapy
- Responded to most recent platinum regimen



Primary endpoint
- Investigator-assessed PFS

Time-dependent secondary endpoints
- **Overall survival**
- PFS2
- TFST
- TSST
- TDT
- HRQoL¶

Final analysis

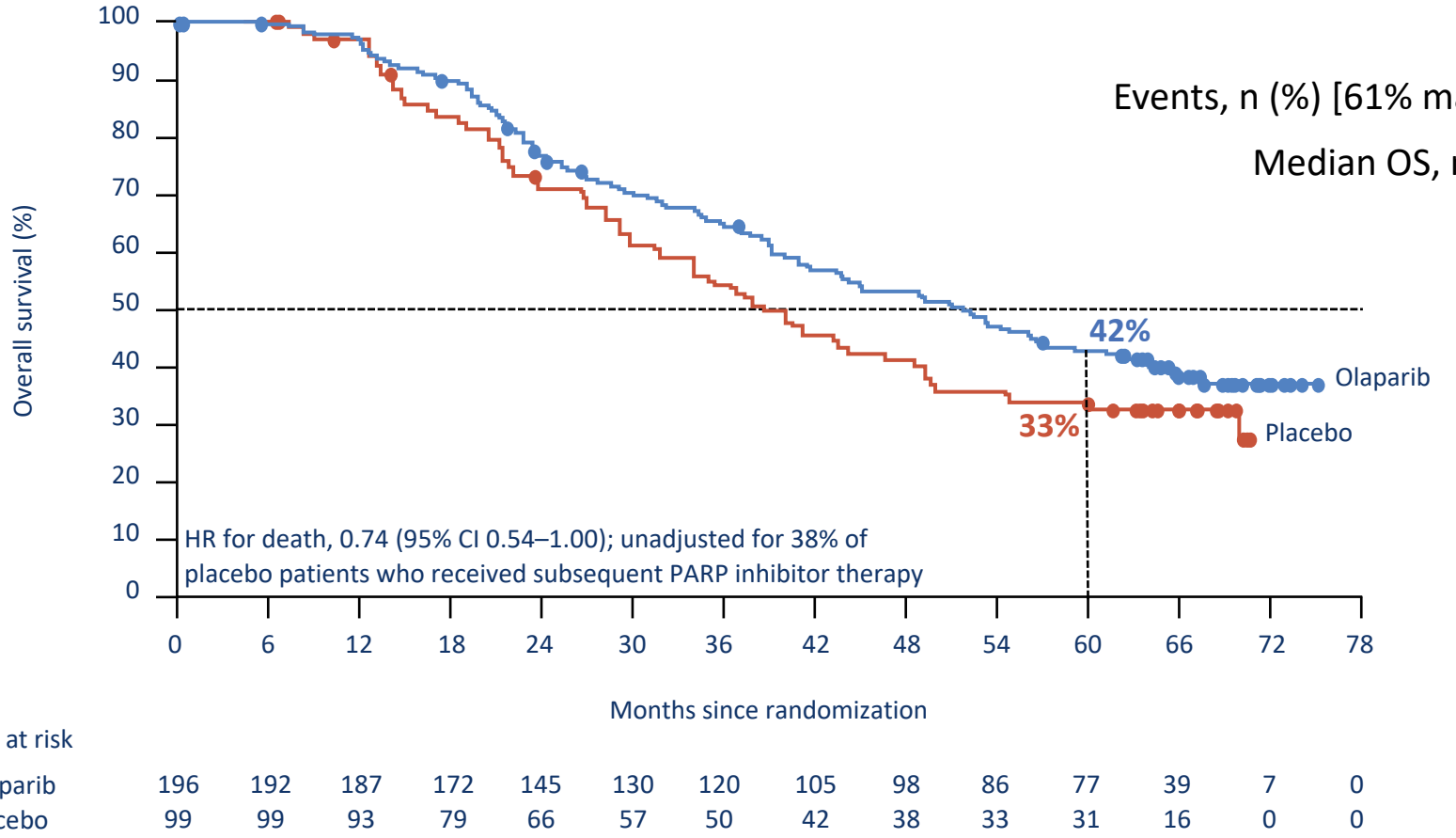
DCO: Feb 3, 2020

- Planned for **60% data maturity** (~177 events)
- **Prespecified adjusted OS analysis (RPSFT model, re-censored):** to adjust for subsequent PARP inhibitor therapy in placebo group
- ***Post hoc* OS sensitivity analysis (eCRF)**: to correct for patients mis-stratified at randomization
- **Prespecified OS sensitivity analysis**: Myriad gBRCAm subgroup

*Includes primary peritoneal of fallopian tube cancer; †Complete or partial response; ‡>6–12 or >12 months; § Or until discontinuation criteria were met, and treatment could continue beyond progression if the investigator deemed the patient be experiencing benefit; ¶Assessed by the TOI of the FACT-O
eCRF, electronic case report form; gBRCAm, germline BRCA mutation; FACT-O, Functional Assessment of Cancer Therapy – Ovarian; HRQoL, health-related quality of life; PFS2, time to second progression; RPSFT, rank preserving structural failure time model; TDT, time to study treatment discontinuation or death; TFST, time to first subsequent therapy or death; TOI, trial outcome index; TSST, time to second subsequent therapy or death

SOLO2: final analysis of OS

Median OS improved by 12.9 months with maintenance olaparib over placebo, despite 38% of placebo patients receiving subsequent PARP inhibitor therapy



No. at risk

Olaparib	196	192	187	172	145	130	120	105	98	86	77	39	7	0
Placebo	99	99	93	79	66	57	50	42	38	33	31	16	0	0

	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [61% maturity]	116 (59)	65 (66)
Median OS, months	51.7	38.8
HR 0.74		
95% CI 0.54–1.00; *P*=0.0537		

38% of placebo patients and 10% of olaparib patients received subsequent PARP inhibitor therapy*

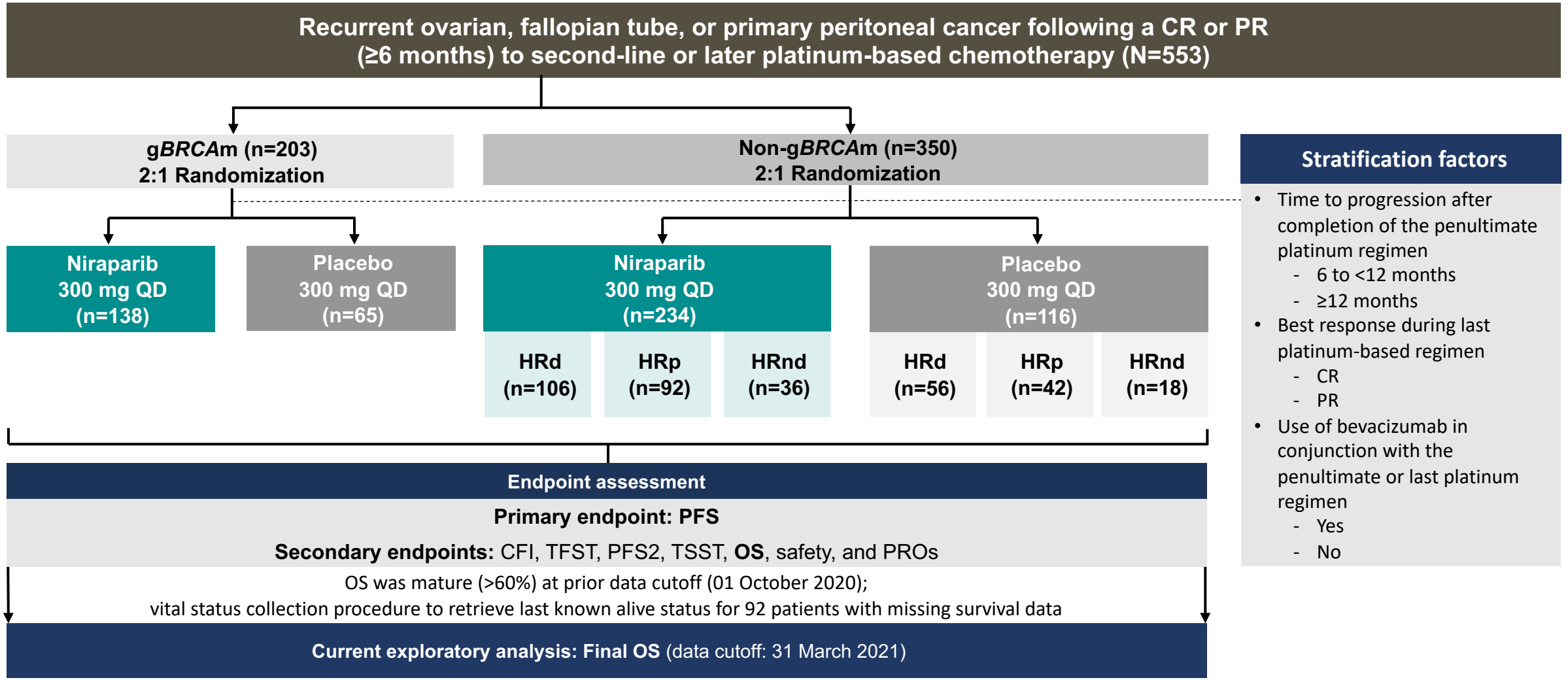
OS analysis per eCRF in the full analysis set†
HR 0.70 (95% CI 0.52–0.96)

OS analysis in the Myriad gBRCAm subgroup†
HR 0.71 (95% CI 0.52–0.97)

*According to medical review of PARP inhibitor use; †Not adjusted for multiplicity
CI, confidence interval

Background: ENGOT-OV16/NOVA Study Design

Scan for slides



CFI, chemotherapy-free interval; CR, complete response; g*BRCA*m, germline *BRCA*-mutated; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; OS, overall survival; PFS, progression-free survival; PFS2, time to second progression or death; PR, partial response; PRO, patient-reported outcome; QD, once daily; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.

Presented by Dr. Ursula A. Matulonis

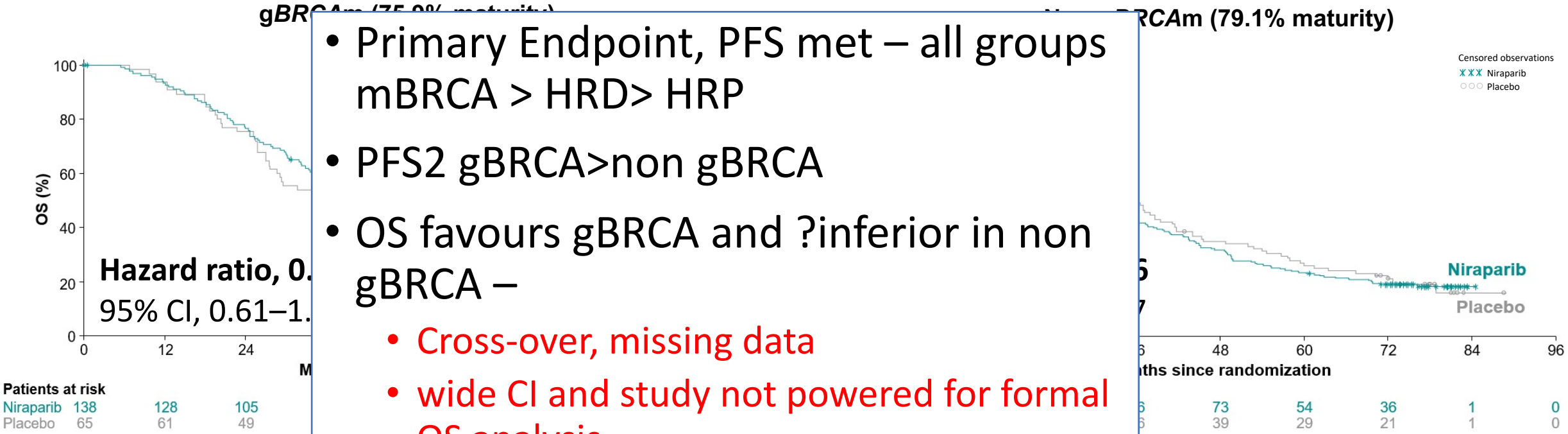
NSGO-CTU Nordic Society of Gynaecological Oncology - Clinical Trial Unit

ENGOT European Network of Gynaecological Oncological Trial groups

NOVA Trial: Final OS for the g*BRCA*m and Non-g*BRCA*m Cohorts

Scan for slides

- Overall OS maturity was 77.9%



- Primary Endpoint, PFS met – all groups mBRCA > HRD> HRP
- PFS2 gBRCA>non gBRCA
- OS favours gBRCA and ?inferior in non gBRCA –
  - Cross-over, missing data
  - wide CI and study not powered for formal OS analysis

Data cutoff: 31 March 2021.

Hazard ratios presented in figures were based on stratified Cox proportional hazards model using randomization stratification factors.

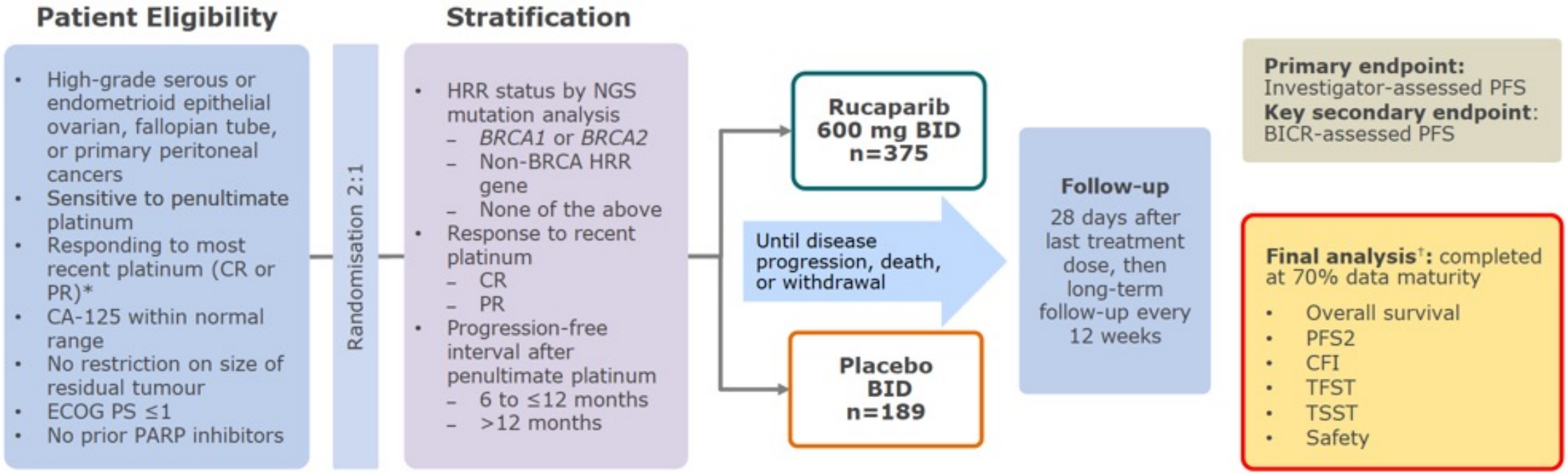
CI: confidence interval; g*BRCA*m, germline *BRCA*-mutated; OS, overall survival.

Presented by Dr. Ursula A. Matulonis

NSGO-CTU Nordic Society of Gynaecological Oncology - Clinical Trial Unit

ENGOT European Network of Gynaecological Oncological Trial groups

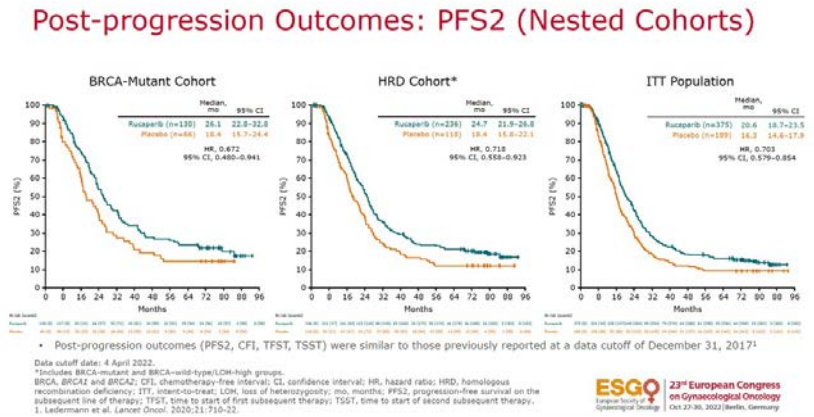
ARIEL3 Study Design

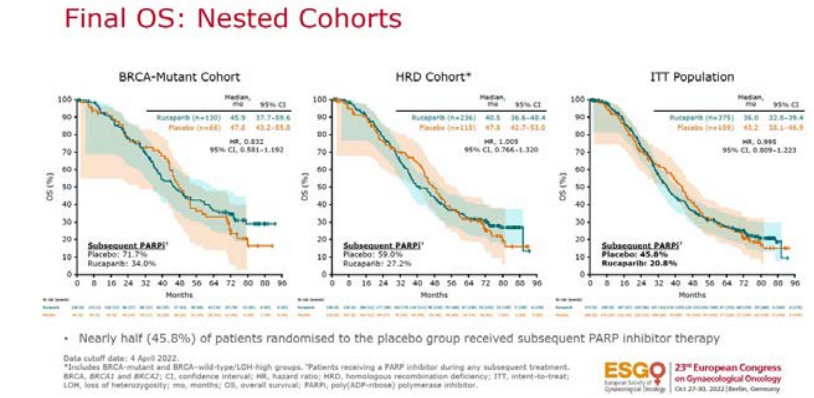


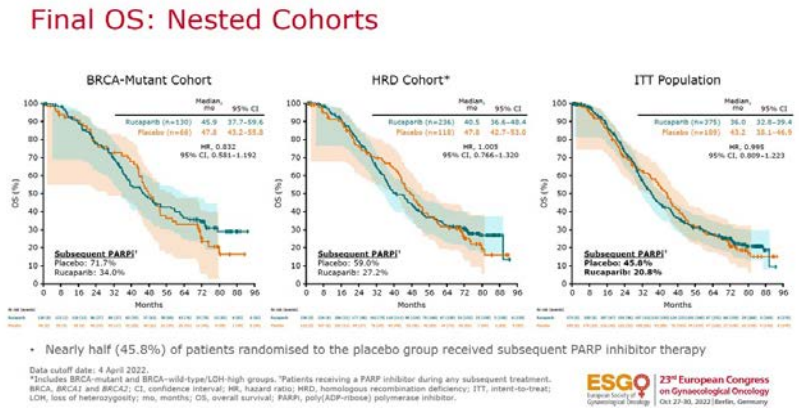
A hypothesis of superiority in overall survival was not prespecified in the protocol/study design.
*CR (defined by RECIST) or PR (defined by RECIST and/or a GCIG CA-125 response [CA-125 within normal range]) maintained until entry to ARIEL3 (≤8 weeks from last dose of chemotherapy). †Analyses were done for the molecularly defined nested cohorts (BRCA mutant, HRD, and ITT), and exploratory analyses were done in the non-nested subgroups of patients with BRCA wild-type carcinoma.
BICR, blinded independent central review; BID, twice daily; BRCA, *BRCA1* and *BRCA2;* CA-125, cancer antigen 125; CFI, chemotherapy-free interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; GCIG, Gynecological Cancer InterGroup; HRD, homologous recombination deficiency; HRR, homologous recombination repair; NGS, next-generation sequencing; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFS, progression-free survival; PFS2, PFS on the subsequent line of therapy; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours version 1.1; TFST, time to start of first subsequent therapy; TSST, time to start of second subsequent therapy.

What this study showed

- Progression Free Survival was improved with rucaparib maintenance
  - Benefit greatest in mBRCA>LOH-H>LOH-L – all > placebo
- Cross over to chemo and parpi post progression
  - PFS2 higher for rucaparib in all cohorts
  - PFS to post progression chemo (+/-parpi) higher post placebo
- HR for OS did not show benefit, and median OS inferior in non BRCA
  - But contaminated by cross over







Coleman ESGO 2022

Exploratory Analysis of PFS During First Subsequent Platinum-Based Chemotherapy

	ITT Population			PFI <6 months			PFI 6–≤12 months			PFI >12 months		
	Event rate	Median, mo (95% CI)	Log-rank *P* value	Event rate	Median, mo (95% CI)	Log-rank *P* value	Event rate	Median, mo (95% CI)	Log-rank *P* value	Event rate	Median, mo (95% CI)	Log-rank *P* value
Rucaparib	163/174	7.0 (6.2–7.8)	<0.0001	30/30	5.4 (2.8–7.7)	0.2139	58/61	7.4 (6.1–8.6)	0.0056	75/83	7.1 (6.2–9.7)	0.0017
Placebo	61/76	11.3 (9.9–14.1)		14/16	8.3 (3.3–10.9)		38/46	11.3 (9.4–14.4)		9/14	18.5 (10.3–NA)	

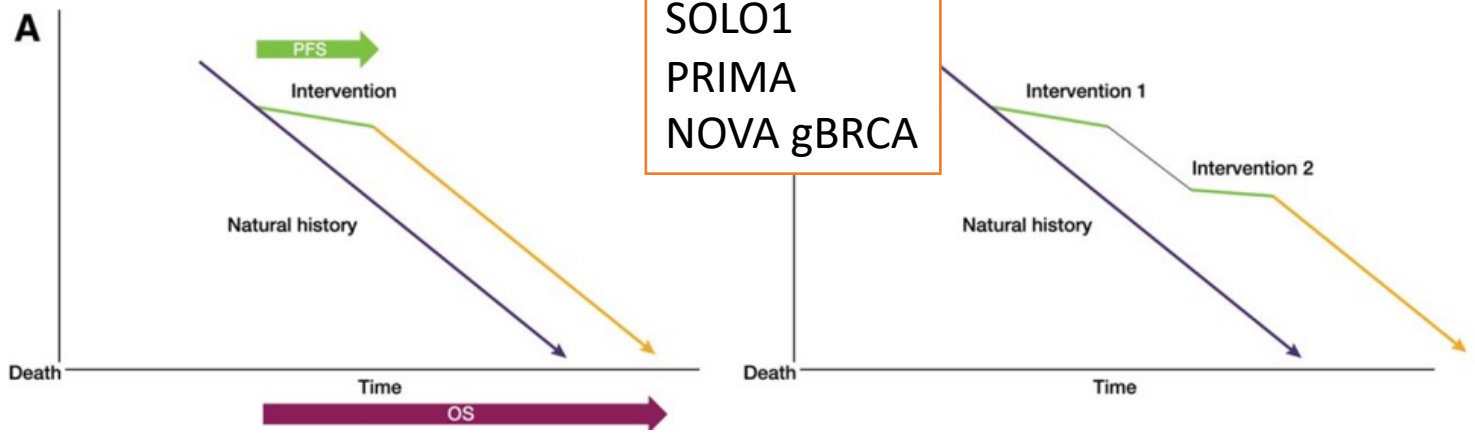
- In the ITT population, 9.2% of patients in the rucaparib group and 25.0% in the placebo group received a PARP inhibitor maintenance therapy following their first subsequent platinum-based chemotherapy

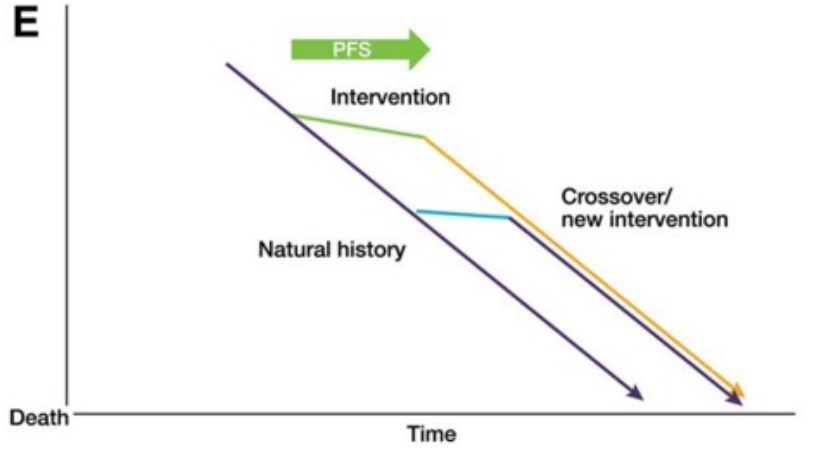
Data cutoff date: 4 April 2022.
*Progression free survival from the start of first subsequent therapy to disease progression. †From date of last chemotherapy prior to randomisation to date of PD on ARIEL3 treatment. CI, confidence interval; ITT, intent-to-treat; mo, months; NA, not applicable; PD, disease progression; PFI, progression-free interval; PFS, progression-free survival; R, randomisation.

PFS and OS in Ovarian Cancer-

mBRCA
SOLO1
SOLO1
PRIMA
NOVA gBRCA

mBRCA – ARIEL 4





PFS, progression-free survival; OS, overall survival

Platinum sensitive ??

Platinum Resistant?

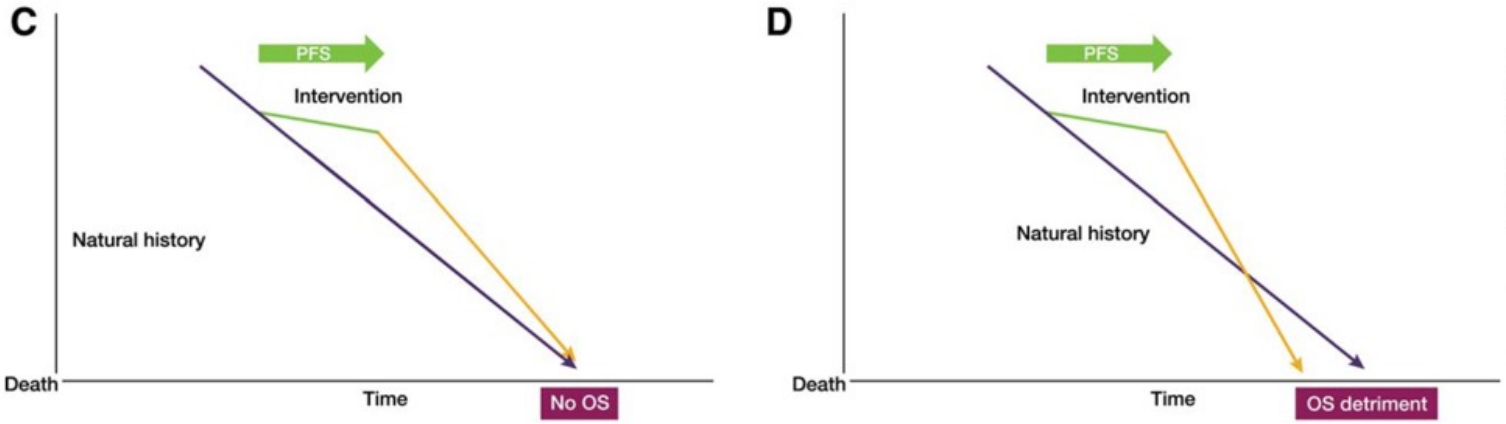


Table 1. Summary of hazard ratios for overall survival (OS)*

Median SPP, mo	Median OS, HR (95% interval)
2	0.687 (0.514–0.909)
4	0.710 (0.517–0.966)
6	0.727 (0.511–1.023)
8	0.736 (0.502–1.068)
10	0.746 (0.491–1.100)
12	0.749 (0.479–1.140)
14	0.752 (0.470–1.174)
16	0.758 (0.462–1.207)
18	0.759 (0.448–1.241)
20	0.762 (0.440–1.277)
22	0.763 (0.428–1.304)
24	0.763 (0.416–1.333)

* The 95% interval of the OS hazard ratio values extends from the 2.5 percentile to the 97.5 percentile for 50 000 simulations. HR = hazard ratio; SPP = survival postprogression.

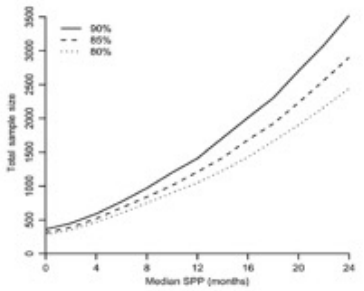


Figure 3. Sample sizes required for detecting a statistically significant difference in overall survival by median survival postprogression (SPP). The three curves were indexed by the power for overall survival (ie, powers of 90%, 85%, and 80%).

OS is a reasonable primary endpoint median survival post progression is short, but is too high a bar when median SPP is long (>12 months

Matulonis, Oza, Ho and Ledermann, 2014

Broglio and Berry 2009

PARPi after PARPi?

OREO

Study design

Patients
- Relapsed non-mucinous epithelial ovarian cancer
- One prior course of PARPi maintenance therapy
- CR/PR to most recent platinum regimen or NED after surgery* with no rising CA-125
- Documented BRCAm status by local testing
- No limit to number of prior lines of therapy

BRCAm cohort
- gBRCAm or sBRCAm by local testing
- Prior PARPi exposure for ≥18 months after first-line chemotherapy or ≥12 months after second-line or later chemotherapy

Non-BRCAm cohort
- gBRCAm negative by local testing; may include patients with undetected sBRCAm
- Prior PARPi exposure for ≥12 months after first-line chemotherapy or ≥6 months after second-line or later chemotherapy

Maintenance therapy

2:1 randomisation stratified by:
- Prior bevacizumab
- ≤3 vs ≥4 prior lines of platinum-based chemotherapy

BRCAm cohort	non-BRCAm cohort
Olaparib 300 mg bid or 250 mg bid if 300 mg not previously tolerated (N=74)	Olaparib 300 mg bid or 250 mg bid if 300 mg not previously tolerated (N=72)
Placebo (N=38)	Placebo (N=36)

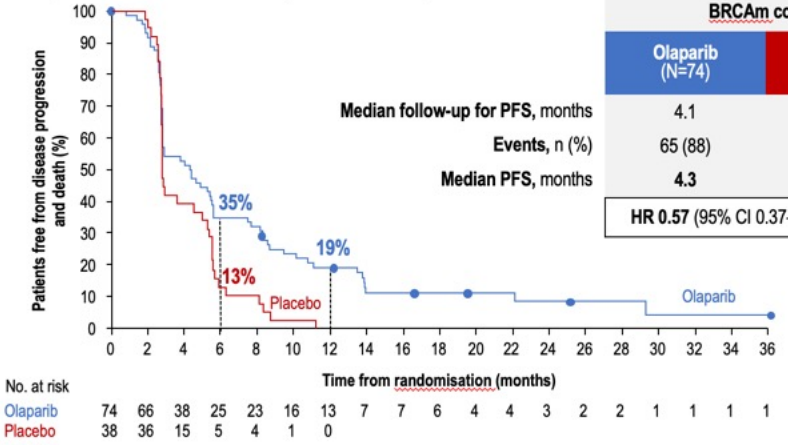
Until disease progression

Primary endpoint
- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints
- Time to RECIST/CA-125 progression or death
- Time to first subsequent therapy or death
- Time to second subsequent therapy or death
- Time to treatment discontinuation or death
- Overall survival
- HRQoL
- Safety

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

A proportion of patients derived clinically relevant long-term benefit



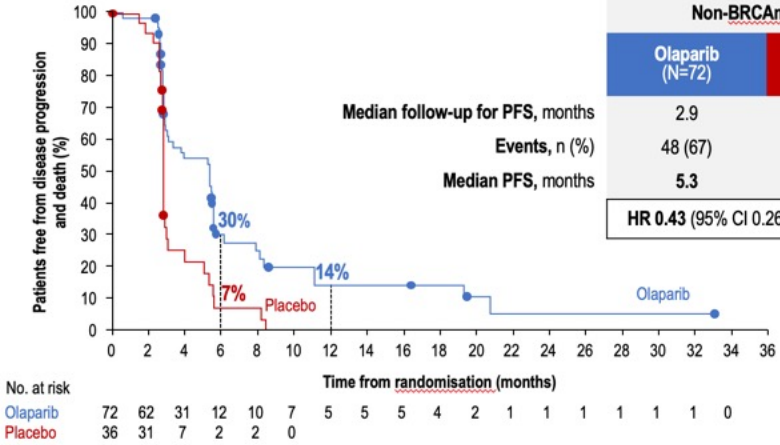
BRCAm cohort	Olaparib (N=74)	Placebo (N=38)
Median follow-up for PFS, months	4.1	2.8
Events, n (%)	65 (88)	38 (100)
Median PFS, months	**4.3**	**2.8**
HR 0.57 (95% CI 0.37–0.87); *P*=0.022		

CI, confidence interval.

2021 ESMO congress

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		

2021 ESMO congress

EVOLVE Trial: Beyond BRCA1/2 Restoration

- Prior to PARPi Resistance - Archival

- DNA Damage Response Pathway
  - HRR
    - TCGA data shows
      - 50% serous ovarian cancers have compromised HRR
      - Sporadic Breast
        - Histopathological features, promoter methylation, reduced RNA expression or DNA
- PARPi
  - Trapping PARP1 at sites of DNA Damage
  - Reduced efficacy of Base Excision Repair (BER)
  - Defective recruitment of BRCA1 to DNA damage sites
  - Activation of NHEJ

Lheureux, Oza

- Post PARPi Resistance – Bx post PARP-i

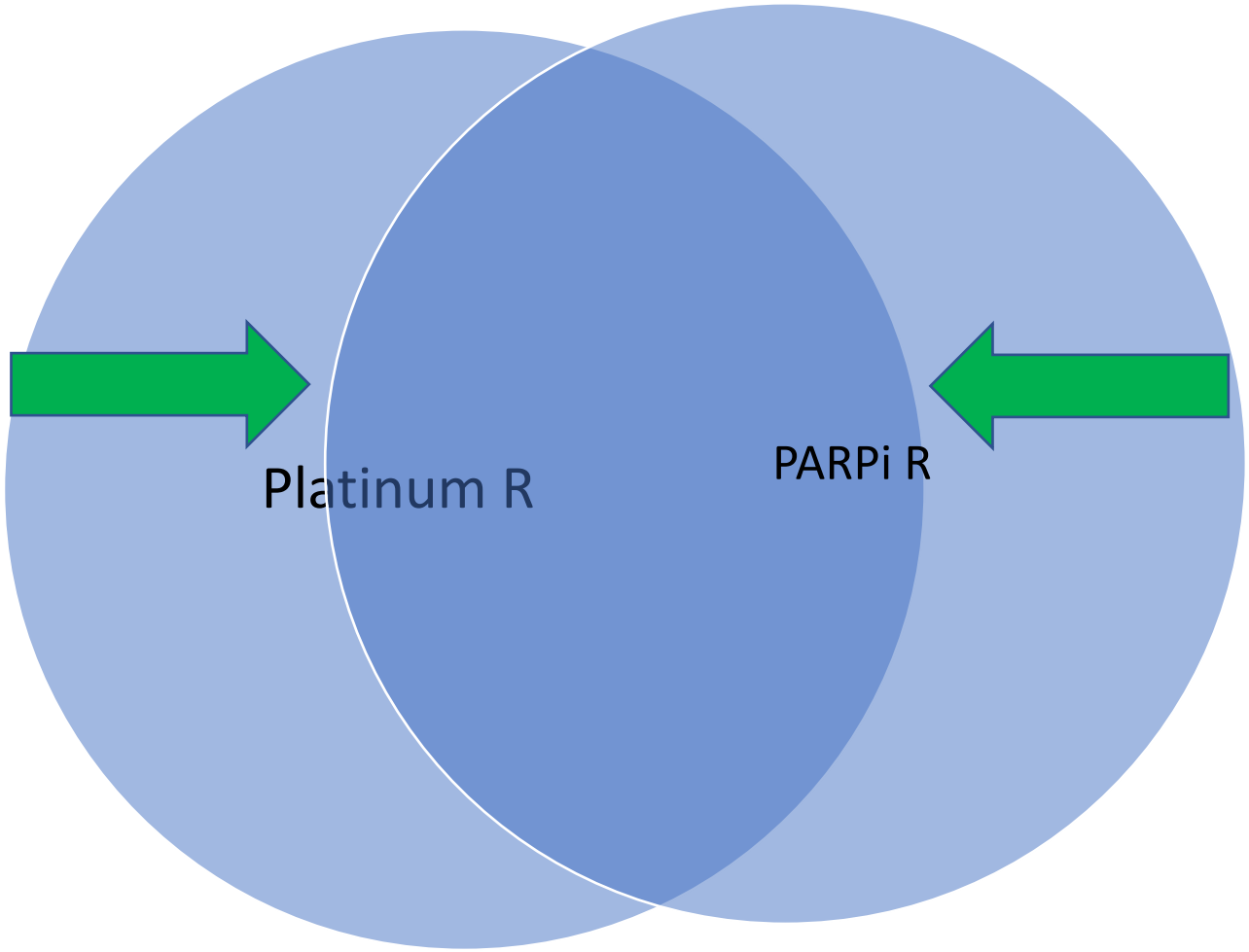
- PARPi do not reach their target
- BRCA1/2 Alterations
  - Secondary mutations
  - Promoter methylation
  - Differing functional defects
- Reduced PARP1 levels
- Alternative DNA Repair Mechanisms
  - Cell signaling cascade changes
  - Alterations in SSB repair

Overcoming Resistance

How much overlap?

Overlap changes over time

Evolution of resistance mechanisms

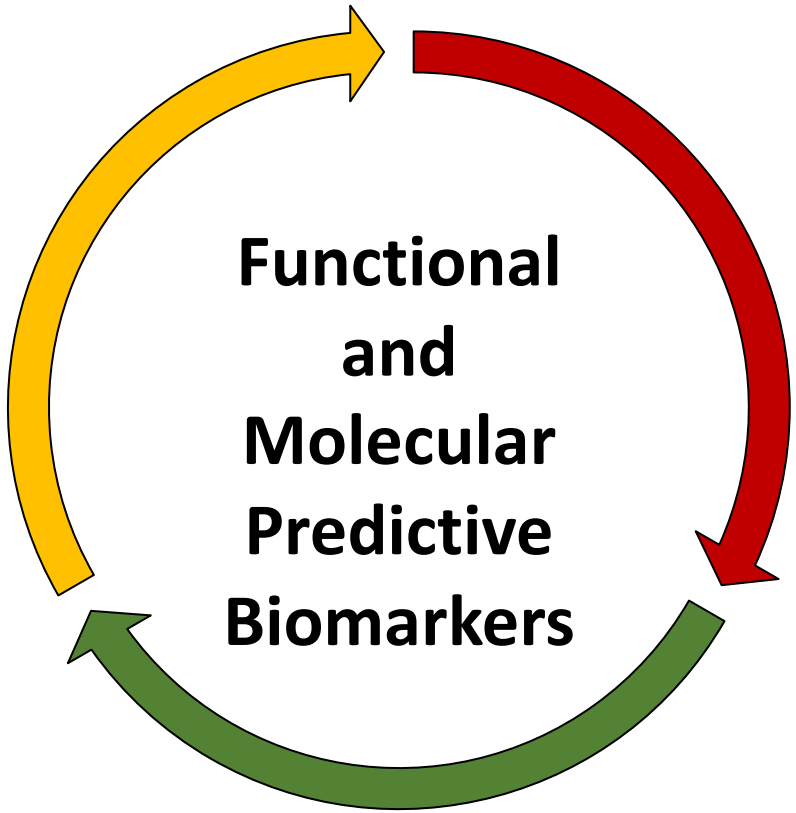


Ariel 2,3,4 and Evolve trials

A. Oza

Therapeutic Strategies for the Post PARPi Space

Overcoming Resistance
Combination PARPi studies



Bypassing Resistance
Non-cross resistant agents

Chemotherapy and or
Parpi rechallenge

Oza 2020

So what are these studies telling us?

- Biomarkers: mBRCA, HRD, reversion m - also predict for platinum response
- Plat sensitivity –predicts for future platinum and parpi response
- Platinum resistance – predicts for parp resistance
- Parp exposure and resistance –may confer resistance to platinum, parpi
- **Assess risk and benefit for treatment**
  - First line maintenance therapy ideal – mBRCA>HRD>HRP
  - Recurrent disease – if patient has not had first line Parpi
    - P sensitive- mBRCA –**Yes**.
    - P resistant – **No**
    - Psensitive, HRD and HRP: weigh up risk benefit: platinum chemo +/- Maint parpi
    - Chemo free options – consider on trial or assess risk benefit.
- Understanding and monitoring clinical and molecular resistance is essential

- To rigorously measure OS, it should to be a primary endpoint
- If secondary or non-analytic, need caution
  - patients throughout the period?
  - Loss of f/u
  - Post progression therapy and cross over effects to be accounted for
- Assess risk benefit for patients who have recurrent disease

Module 3: Rationale for and Available Data with PARP Inhibitors in Combination with Other Anticancer Therapies for Advanced Ovarian Cancer — Dr Liu

Case Presentation: 23-year-old woman with newly diagnosed Stage IV, low-grade serous carcinoma of the ovary with pleural effusions

Dr Dana Chase (Phoenix, Arizona)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Dr Dana Chase

Should this patient receive neoadjuvant treatment or undergo debulking surgery?

What is the optimal chemotherapy/maintenance regimen for patients with Stage IV, low-grade serous ovarian cancer?

In general, what is your approach to fertility preservation in young patients with ovarian cancer?

RTP
RESEARCH
TO PRACTICE

Case Presentation: 48-year-old woman with HGSOC s/p neoadjuvant chemotherapy and R0 debulking surgery enrolled on the Phase III FIRST trial

Dr Kellie Schneider (Charlotte, North Carolina)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Dr Kellie Schneider

What would be your treatment approach to a patient with an HRD-positive tumor whose disease progresses with an isolated recurrence on maintenance therapy with a PARP inhibitor?

RTP
RESEARCH
TO PRACTICE

Dana-Farber Cancer Institute

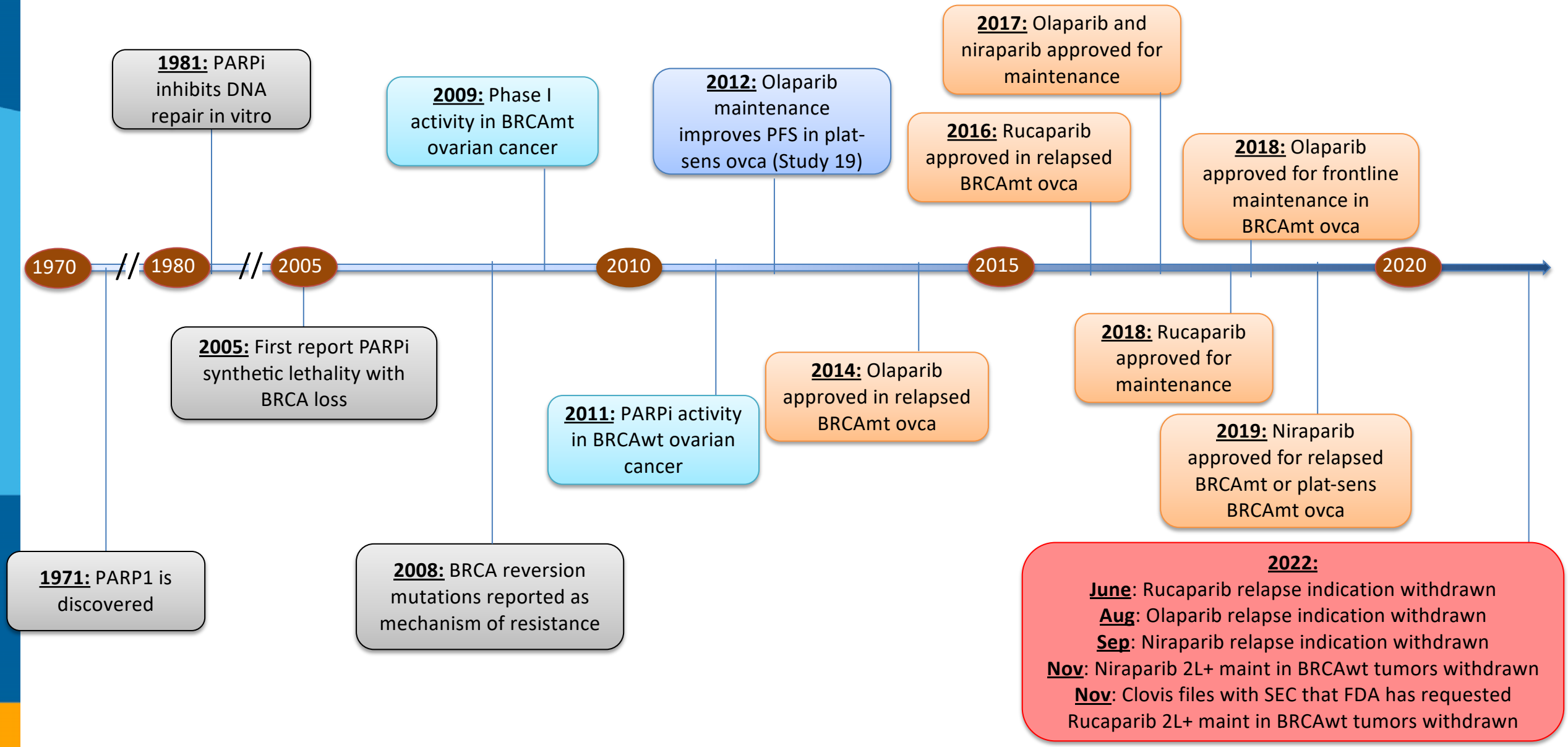
Rationale for and Available Data with PARP Inhibitors in Combination with Other Anticancer Therapies for Advanced Ovarian Cancer

Joyce Liu, MD, MPH

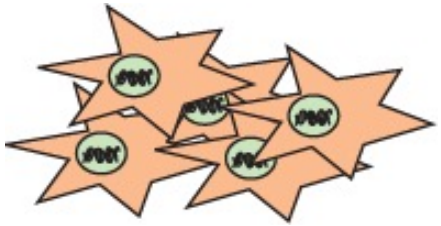
Associate Chief and Director of Clinical Research, Department of Gynecologic Oncology, Dana-Farber Cancer Institute

March 26, 2023

PARP inhibitor development in ovarian cancer

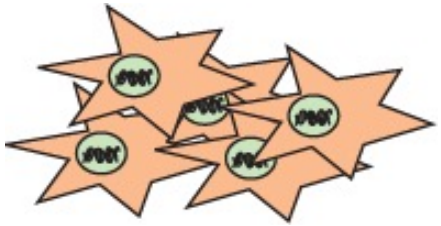


Selected PARP inhibitor combinatorial strategies



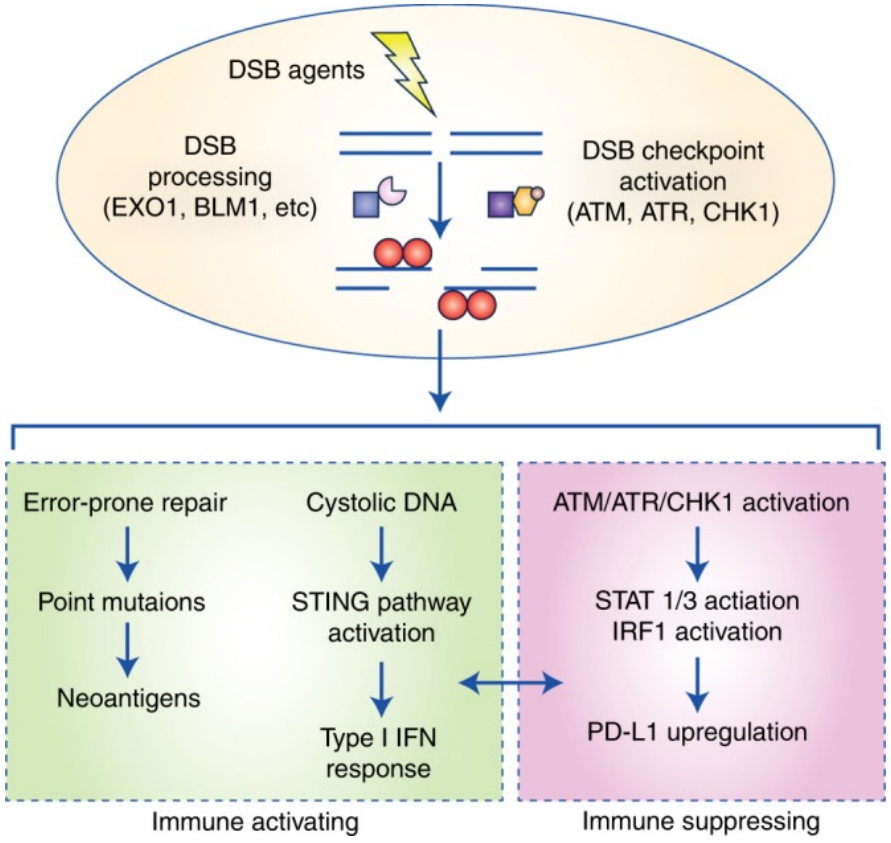
- **IO-based combinations**
  - **Doublet combos**
    - PD1/PD-L1
    - CTLA4
  - **Triplet combos**
    - PD1/PD-L1 + anti-angiogenics
- **Combo with other DDR agents**
  - **DDR kinases / regulators**
    - ATR
    - CHK1
    - WEE1
    - USP1
  - **DNA repair proteins**
    - POLθ
    - DNA-PK
- **Induction of HR deficiency**
  - **Anti-angiogenics**
  - **Oncogenic pathways**
    - PI3K inhibition
    - MEK inhibition
  - **Epigenetic modulation**
    - BET inhibition
    - HDAC inhibition
    - HSP90 inhibition
    - DNMT inhibition

Selected PARP inhibitor combinatorial strategies

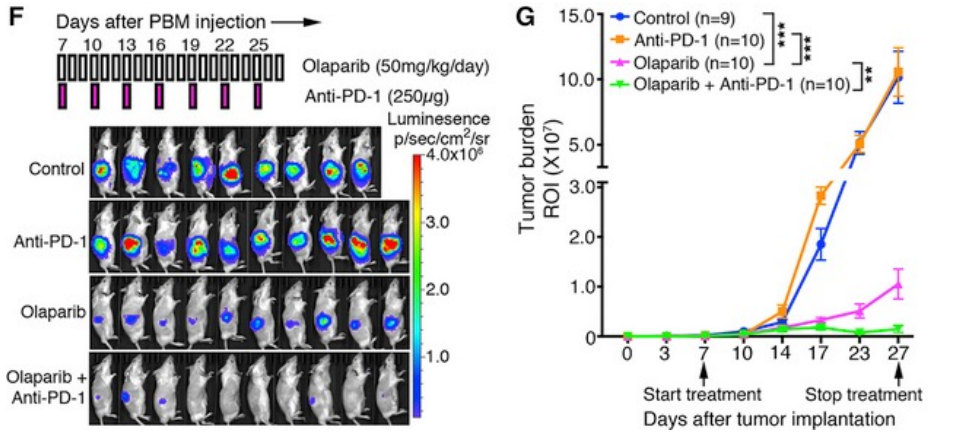


- **IO-based combinations**
  - **Doublet combos**
    - PD1/PD-L1
    - CTLA4
  - **Triplet combos**
    - PD1/PD-L1 + anti-angiogenics
- **Combo with other DDR agents**
  - **DDR kinases / regulators**
    - ATR
    - CHK1
    - WEE1
    - USP1
  - **DNA repair proteins**
    - POLθ
    - DNA-PK
- **Induction of HR deficiency**
  - **Anti-angiogenics**
  - **Oncogenic pathways**
    - PI3K inhibition
    - MEK inhibition
  - **Epigenetic modulation**
    - BET inhibition
    - HDAC inhibition
    - HSP90 inhibition
    - DNMT inhibition

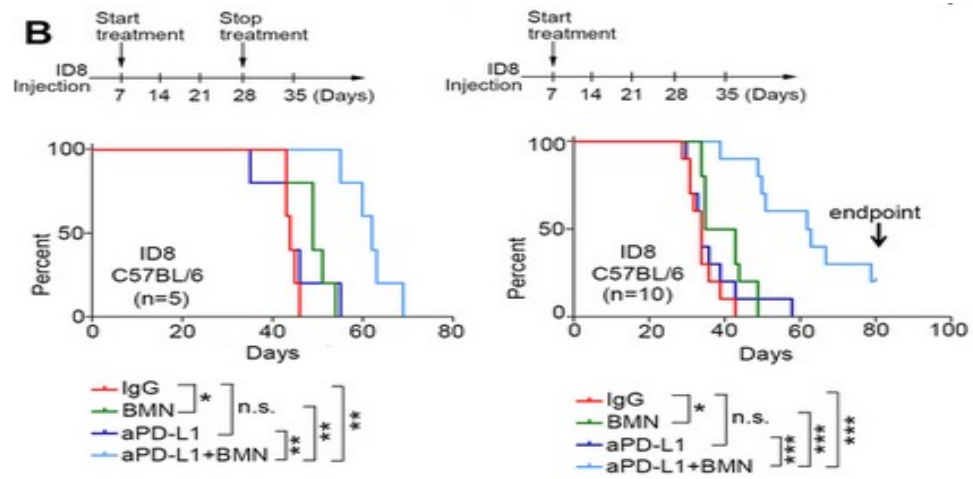
Immunotherapy + PARP inhibitors



Mouw and Konstantinopoulos, *Brit J Cancer* 2018



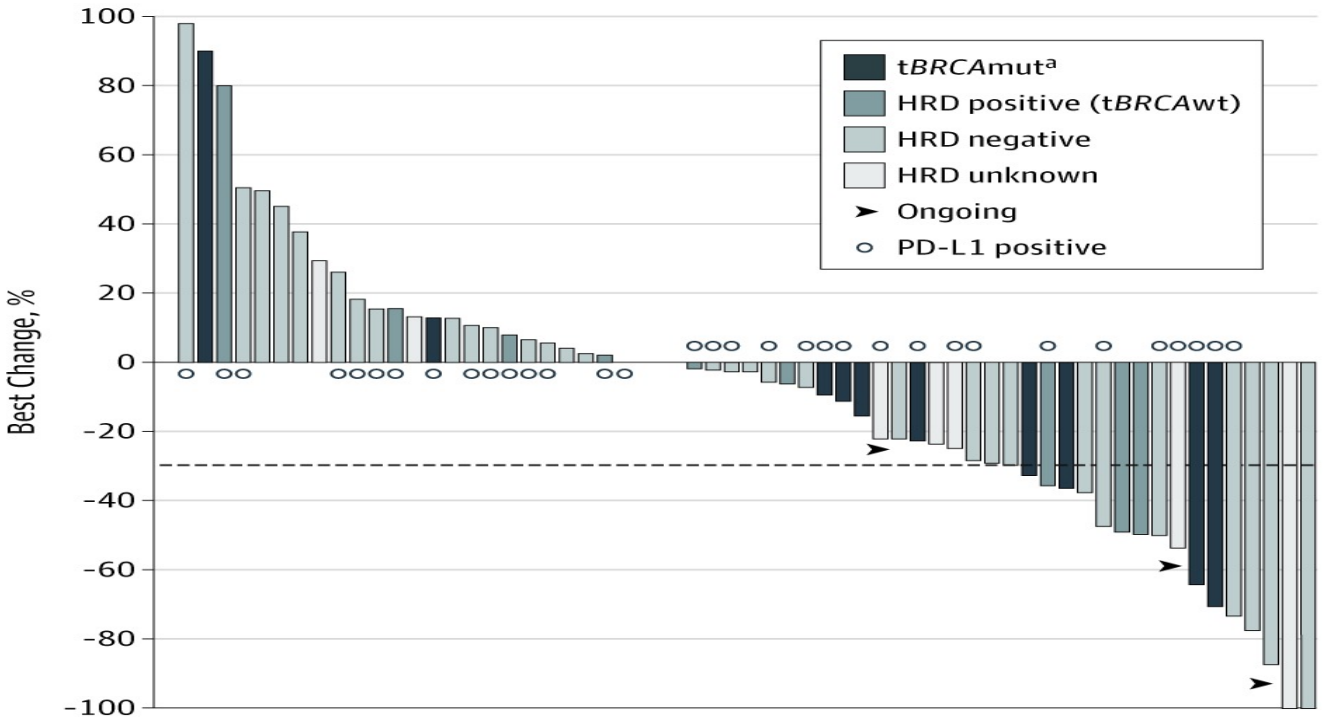
Ding et al., *Cell Reports* 2018



Shen et al., *Cancer Res* 2019

Initial studies of ICB + PARP inhibitor in platinum-resistant ovarian cancer: TOPACIO

- Phase 1/2 study
- Niraparib + pembrolizumab
- 62 patients with ovarian cancer enrolled
  - 9 Phase 1, 53 Phase 2
- Patients with “acquired” platinum-resistance
  - Initial PFI ≥ 6 months
- Up to 5 (Ph1) or 4 (Ph2) prior lines of cytotoxic therapy

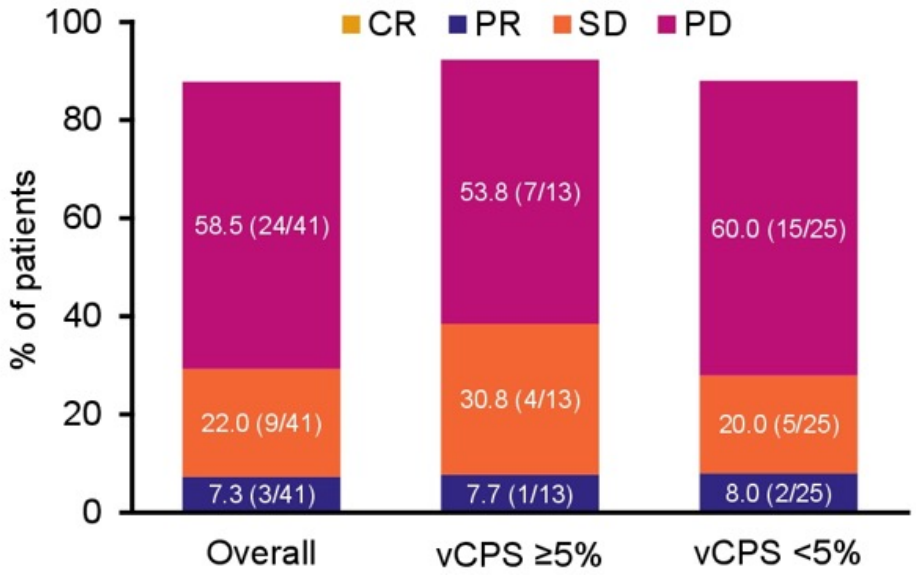


ORR 18%, PFS 3.4 months
(ORR 19% in tBRCAwt and 19% in HRP tumors)

Konstantinopoulos et al., *JAMA Oncol* 2019

Initial studies of ICB + PARP inhibitor in platinum-resistant ovarian cancer: MOONSTONE

- Phase 2 study
- Niraparib + dostarlimab
- 41 patients with platinum-resistant ovarian cancer (PROC) enrolled
- Could not have known g*BRCA*mt
- Could have progressed within 3-6 months of first platinum therapy
- 1-3 prior lines
  - Prior platinum, taxane, and bevacizumab required



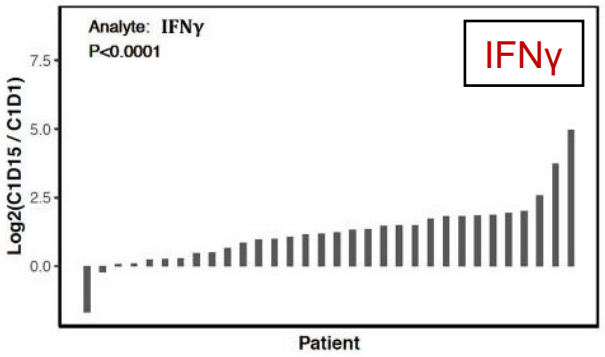
ORR 7.3%; PD-L1 status non-predictive
Median PFS: 2.1 months

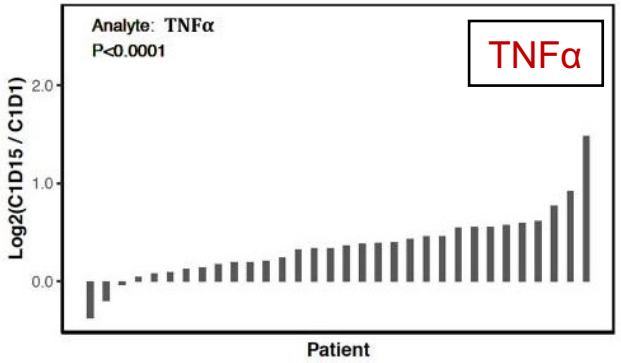
Randall et al., ASCO Annual Meeting 2022

Can we improve activity of IO+PARPi in ovarian cancer with a “triplet” combination?

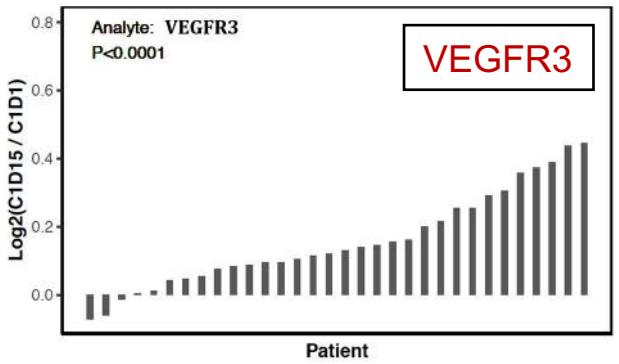
- Proof of concept study of olaparib + durvalumab
- 35 evaluable patients
  - 30 (86%) platinum-resistant
  - 6 (17%) *BRCA*mt
- Pre-treatment biopsies and paired blood samples
- ORR 15% (3 plat-res; 2 plat-sens); median PFS 3.9 months

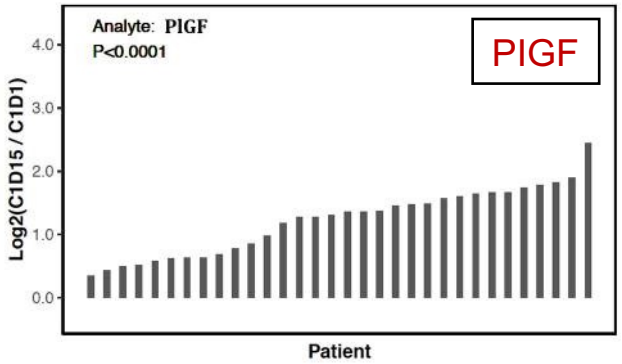
Immunostimulatory cytokines





Circulating angiogenic factors

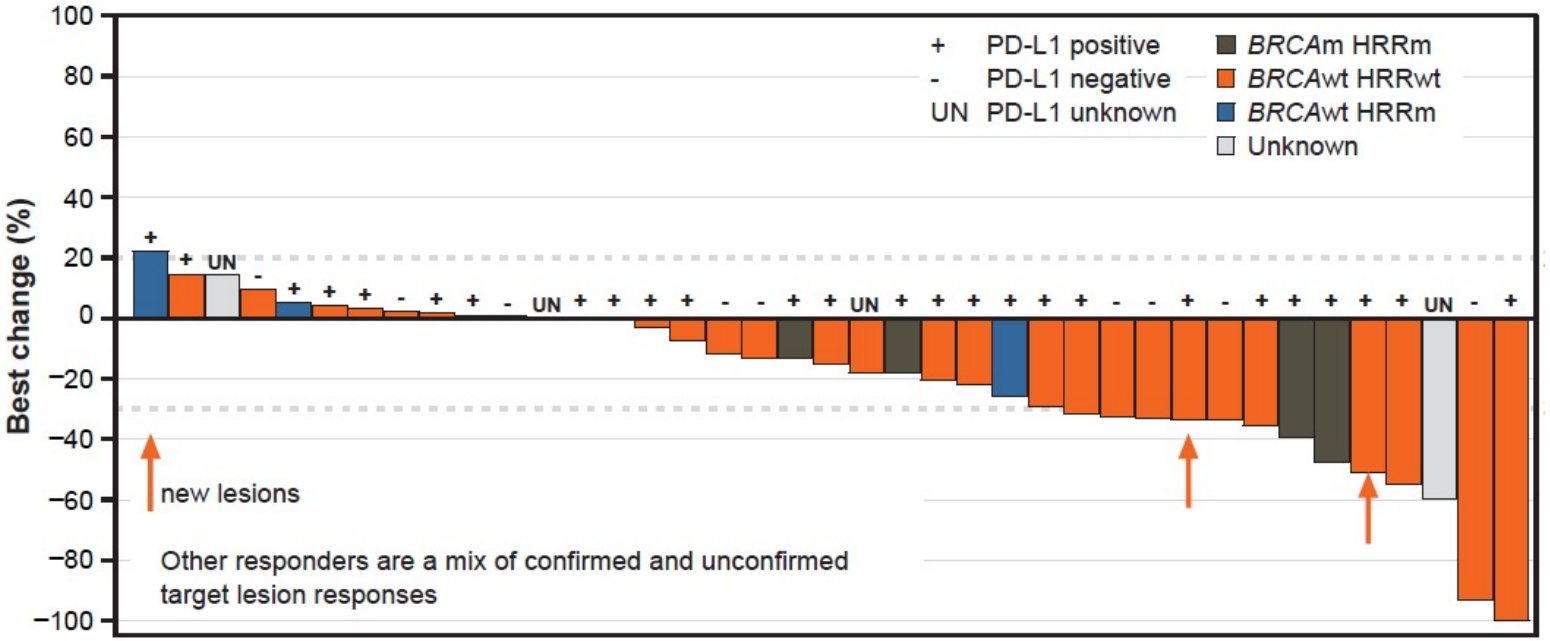




Lampert et al., *Clin Can Res* 2020

OPAL: Niraparib + dostarlimab + bevacizumab in platinum-resistant ovarian cancer

- Phase 2 study
- 41 patients with platinum-resistant ovarian cancer
- 1-2 prior lines of therapy
  - 44% 1 prior line
  - 56% 2 prior lines
- 44% prior bev

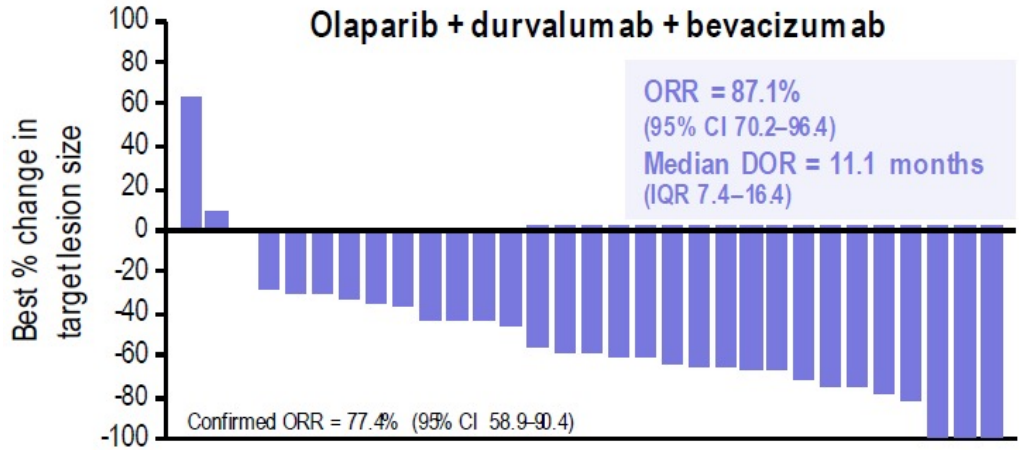


ORR 17.9%, PFS 7.6 months
ORR consistent across subgroups

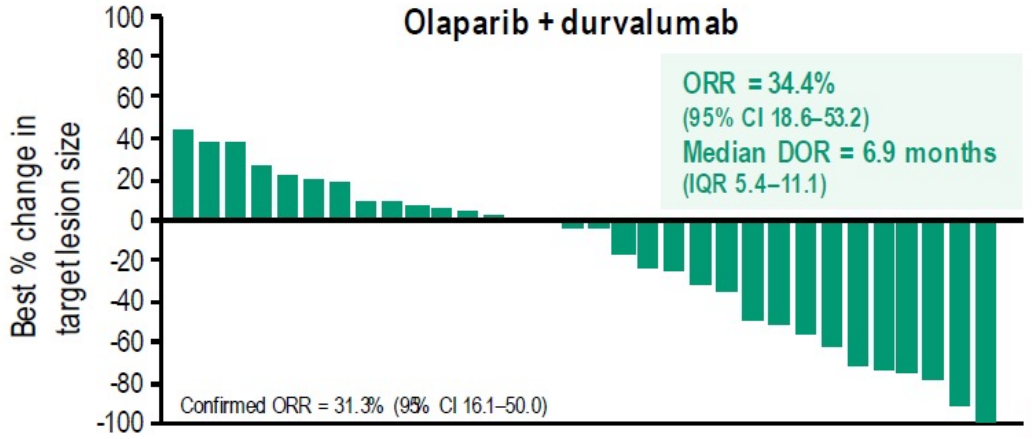
Liu et al., SGO 2021 Annual Meeting

MEDIOLA: Olaparib + durvalumab + bevacizumab in gBRCAwt plat-sens ovarian cancer

- Phase 2 study
- Confirmed non-gBRCAmt high-grade serous plat-sens ovarian cancer
- 1-2 prior lines of plat-based chemotherapy
- Sequentially enrolled cohorts of triplet and doublet therapy



Confirmed ORR 77.4%
PFS 14.7 months
OS 31.9 months



Confirmed ORR 31.3%
PFS 5.5 months
26.1 months

Drew et al., ESMO 2020 Virtual Congress
Banerjee et al., ESMO 2022 Annual Congress

Side effect profile of IO + PARPi combinations consistent with known side effects of single agents

Doublet therapy

	MOONSTONE	MEDIOLA (doublet)
Grade ≥3 TEAE (%)	75.6	65.6
Any TEAE leading to study drug interruption/ reduction/delay	70.7	NR
% patients discontinuing at least one drug	NR	3.1
Most common AEs	Nausea (56%) Fatigue (34%) Vomiting (32%) Anemia (32%) Plt count decr (27%)	Nausea (88%) Fatigue (50%) Diarrhea (44%) Anemia (41%) Decr appetite (28%) Arthralgia (25%) Constipation (22%) Headache (22%) Myalgia (22%) Asthenia (22%)

Triplet therapy

	OPAL	MEDIOLA (triplet)
Grade ≥3 TEAE (%)	78.0	61.3
Any TEAE leading to study drug interruption/ reduction/delay	NR	NR
% patients discontinuing at least one drug	34.1	32.3
Most common AEs	Fatigue (61%) Plt count decr (49%) Hypertension (44%) Nausea (42%) Anemia (34%) Vomiting (32%) Neutropenia (29%) Decr appetite (22%)	Nausea (71%) Fatigue (52%) Anemia (48%) Vomiting (48%) Diarrhea (39%) Decr appetite (35%) Headache (35%) Constipation (29%) UTI (29%) Hypertension (26%)

Drew et al., ESMO 2020 Virtual Congress
Banerjee et al., ESMO 2022 Annual Congress

The future of PARPi + IO combos…?

Trial	Setting	Arms
ATHENA-COMBO (NCT03522246)	Maintenance CR or PR to 1L surgery + chemo	1. Rucaparib + Nivolumab 2. Rucaparib
FIRST (NCT03602859)	Treatment	1. (Carbo/Pac) 2. Carbo/Pac→Nirap maint 3. Carbo/Pac/Dostar→Nirap/Dostar maint Inv choice bevacizumab
DUO-O (NCT03737643)	Treatment BRCAwt (non-randomized arm of tBRCAm with Arm 3 regimen, Bev optional)	1. Carbo/Pac/Bev→Bev maint 2. Carbo/Pac/Bev/Durva→Bev/Durva maint 3. Carbo/Pac/Bev/Durva→Bev/Durva/Olap maint
KEYLYNK-001 (NCT03740165)	Treatment BRCAwt	1. Carbo/Pac 2. Carbo/Pac/Pembro→Pembro maint 3. Carbo/Pac/Pembro→Pembro/Olap maint Inv choice bevacizumab

Summary

- PARP inhibitor combinations have the potential to build upon the activity of PARP inhibitors in ovarian cancer
- PARPi + IO combinations with signals of activity in phase 2 trials
  - Four Phase 3 1L trials pending results
- Other PARPi combinations in development
  - DDR kinases (ATR, WEE1)
  - Novel DNA repair/DDR targets (POLθ, USP1)
  - Pathway inhibitors (MEK, PI3K)
  - DNA damaging agents (e.g, ADCs)

Module 4: Novel Agents for the Treatment of Ovarian Cancer — Dr Penson

RTP
RESEARCH
TO PRACTICE

Case Presentation: 66-year-old woman with multiregimen-refractory metastatic ovarian cancer who receives paclitaxel/tumor treating fields on the INNOVATE-3 trial and develops dermatologic toxicity

Dr John Chan (San Francisco, California)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Dr John Chan

What is the future of tumor treating fields in ovarian cancer?

Are there any novel biomarkers that can help identify a subset of patients that might derive a greater benefit from tumor treating fields?

RTP
RESEARCH
TO PRACTICE

Dr Dana Chase
(Phoenix, Arizona)

Case Presentation: 73-year-old woman with multiple comorbidities and extensively treated recurrent, platinum-resistant, BRCA WT, HRD-negative, PD-L1-positive, FR-alpha-positive ovarian cancer

Dr Lyndsay Willmott
(Phoenix, Arizona)

Case Presentation: 46-year-old woman with multiregimen-recurrent gBRCA1-mutant, FR-alpha-positive carcinomatosis

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Dr Dana Chase

Dr Lyndsay Willmott

How do you counsel patients regarding fourth-line therapy versus hospice?

Do you use immunotherapy in patients with PD-L1-positive MSS ovarian cancer?

What is your personal clinical experience with mirvetuximab soravtansine in terms of efficacy and tolerability?

What is your strategy for partnering with eye care professionals when using mirvetuximab soravtansine?

What is your clinical trial experience with the ADC upifitamab rilsodotin, and how do you see this agent potentially being integrated initially into ovarian cancer management?

RTP RESEARCH TO PRACTICE

A Teaching Affiliate
of Harvard Medical School

Novel Agents for the Treatment of Ovarian Cancer

Richard T Penson MD MRCP
Associate Professor of Medicine HMS
Clinical Director Medical Gynecologic Oncology
IRB Chair DF/HCC

MASSACHUSETTS
GENERAL HOSPITAL

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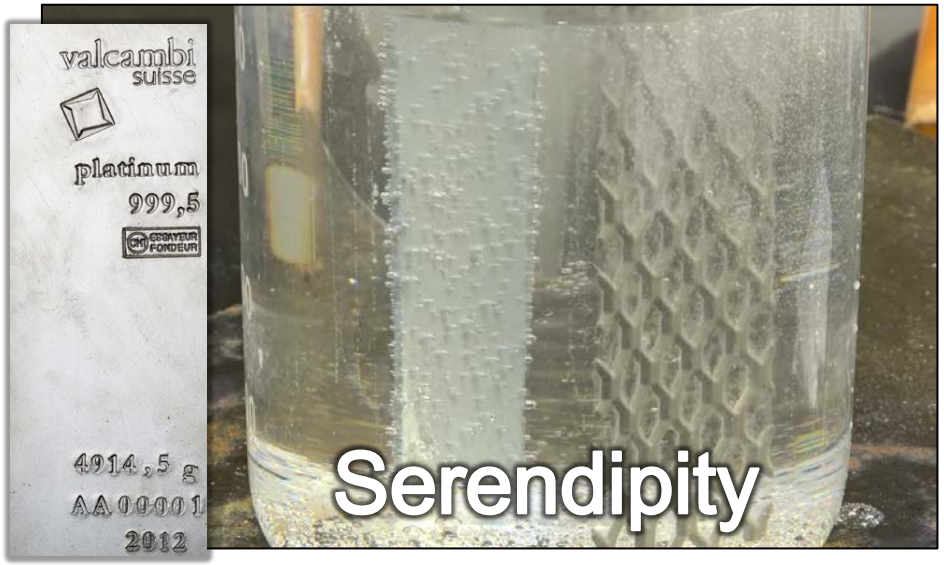
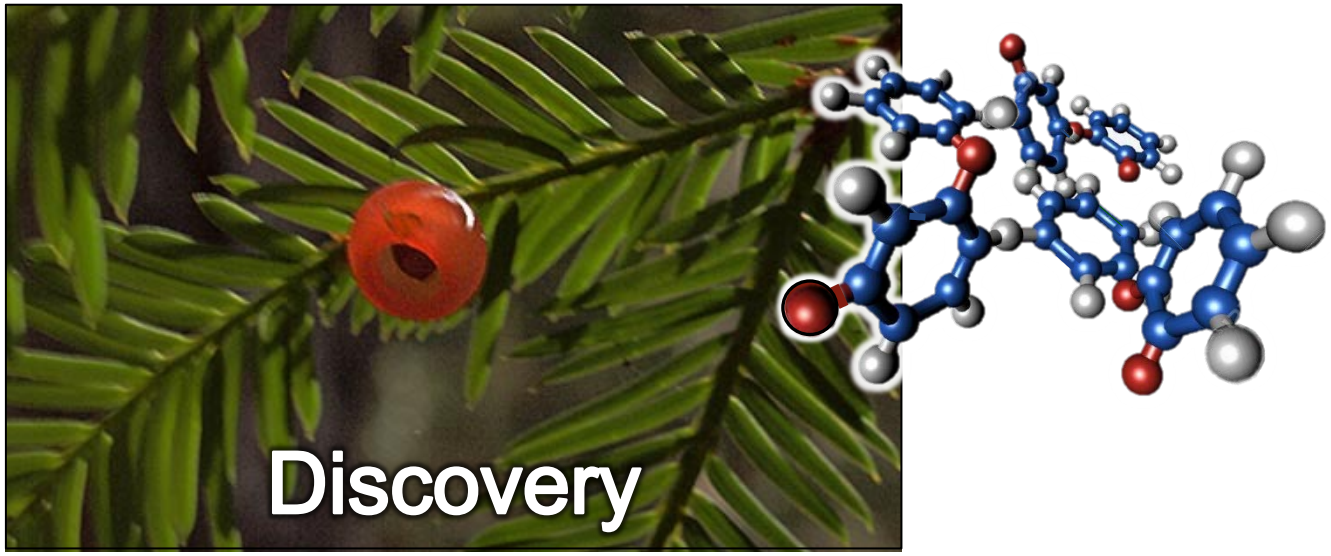
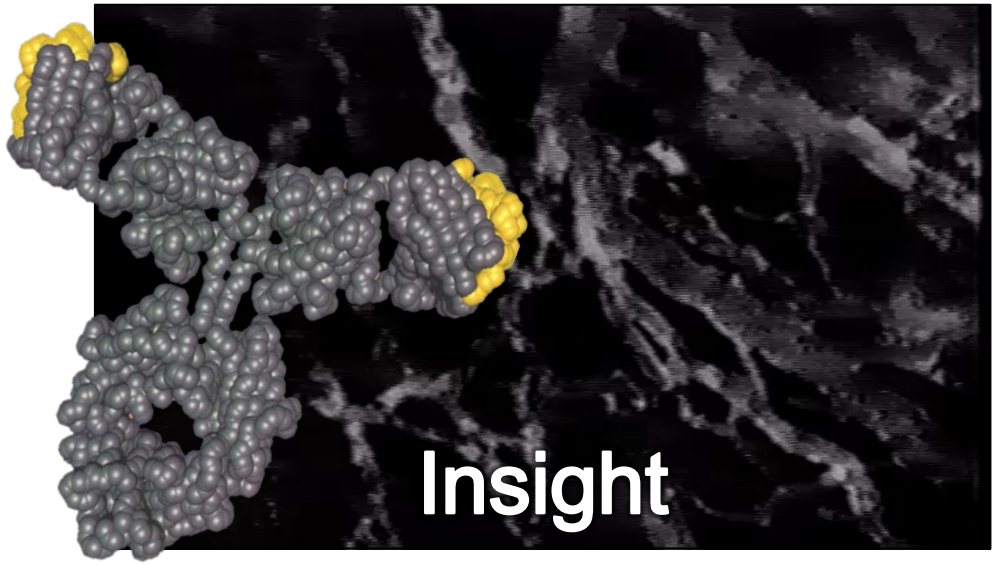
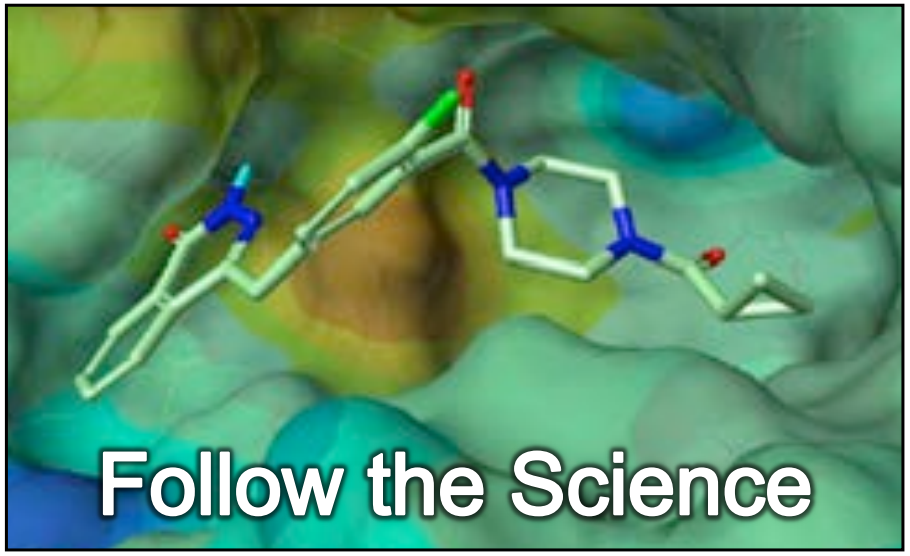
Great Stories









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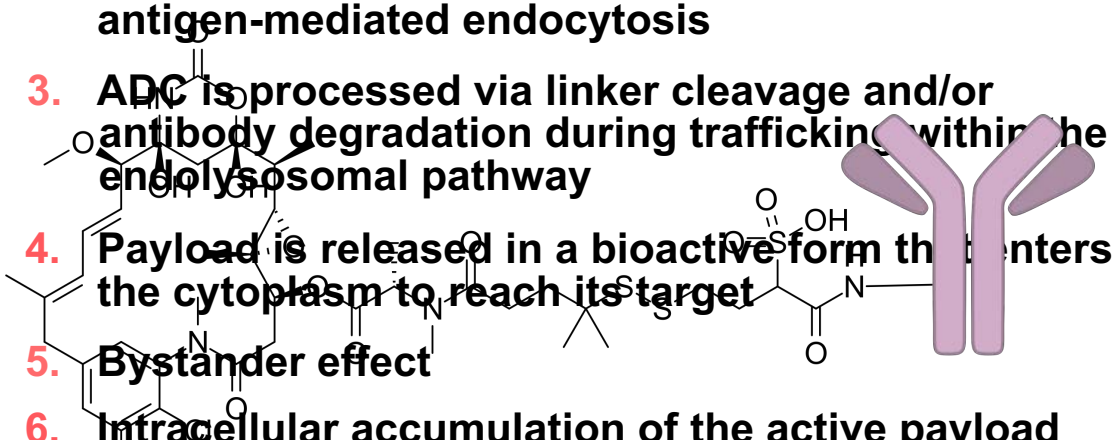
Novel Agents & New Targets

- Mirvetuximab soravtansine
  - SORAYA & ongoing trials
- Upifitamab rilsodotin
  - New ADCs
- Tumor treating fields
- Other promising novel agents and strategies

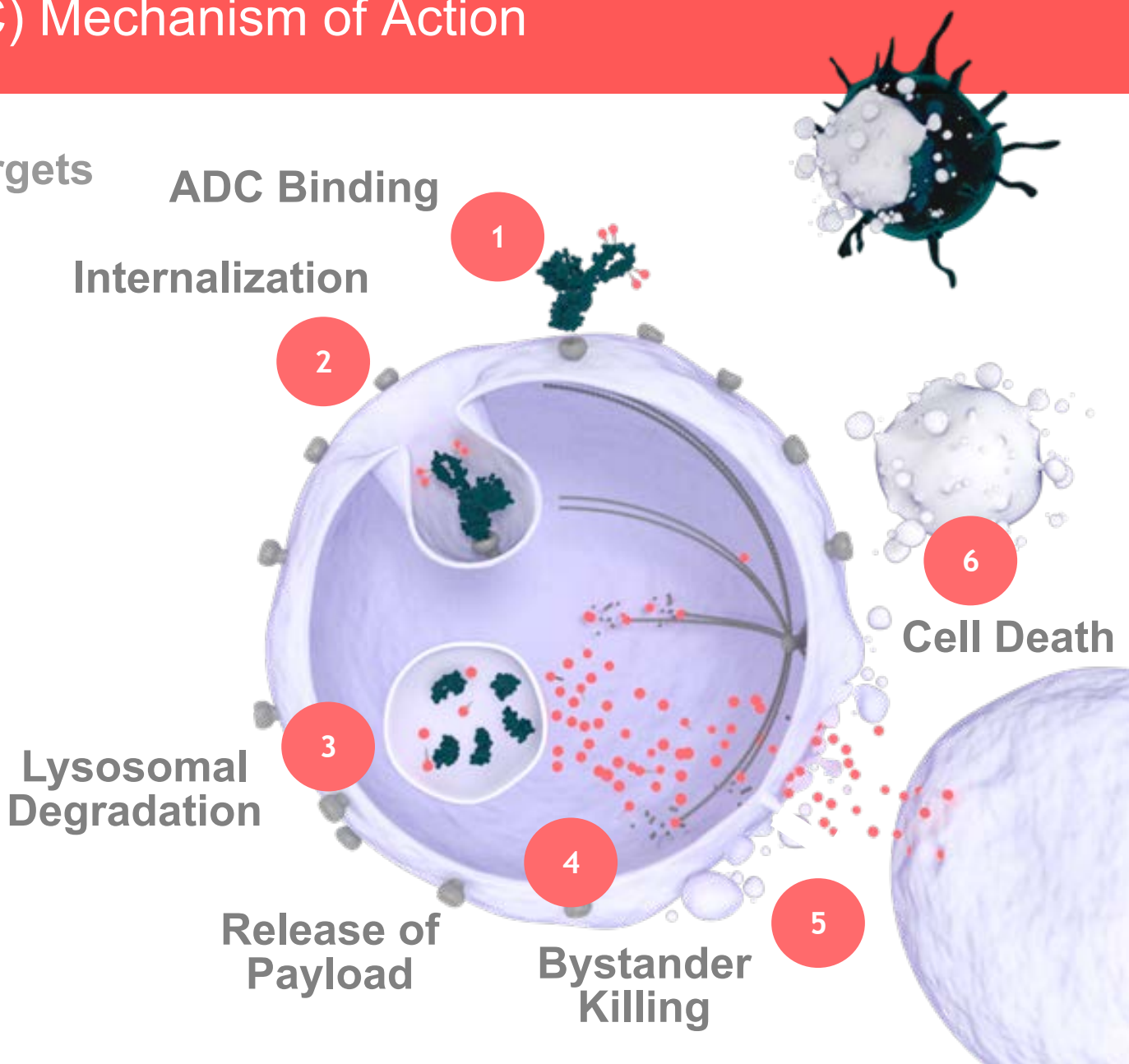
A Targeted Approach:
Antibody Drug Conjugate (ADC) Mechanism of Action

A tailored approach to unique molecular targets

Humanized monoclonal antibody
Cleavable linker
Cytotoxic drug payload



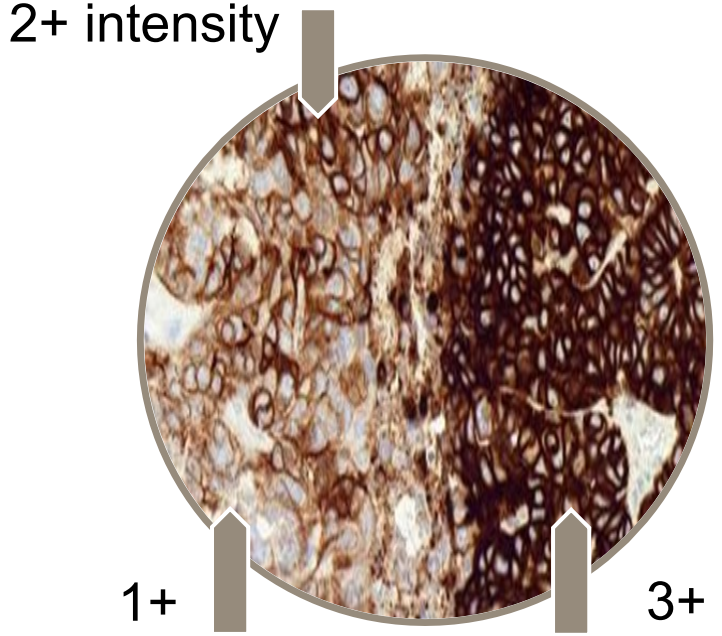
1. **ADC binds to its cell surface target**
2. **ADC-receptor complex becomes internalized via antigen-mediated endocytosis**
3. **ADC is processed via linker cleavage and/or antibody degradation during trafficking within the endolysosomal pathway**
4. **Payload is released in a bioactive form that enters the cytoplasm to reach its target**
5. **Bystander effect**
6. **Intracellular accumulation of the active payload results in cell death. The cytotoxic metabolites may, depending on the payload and linker, enter neighboring cells to effect bystander killing**



A Targeted Approach: Targeting Folate Receptor Alpha (FRα)

- FRα mediates folate transport into epithelial cells
- Expression is limited on normal cells, but upregulated on ovarian, endometrial, and TNBC
- In ovarian cancer, the majority of patients have tumors that express FRα,[1-6] and high levels of FRα expression have been observed in approximately 36% of patients[7*]
- FRα has limited expression in normal tissues[8-10]
- FRα expression can be assessed in archival tumor tissue or a fresh biopsy using immunohistochemical (IHC) staining[6,9-11]
- FRα expression is quantified using the positive staining (PS) methodology,[6,11-13] which evaluates intensity (0,1+,2+,3+) and percentage (0-100%) of viable tumor cells staining

FRα Staining Intensities



1. Parker N, et al. Anal Biochem. 2005;338(2):284-293. 2. Kalli KR, et al. Gynecol Oncol. 2008;108(3):619-626. 3. Markert S, et al. Anticancer Res. 2008;28(6A);3567-3572. 4. Brown Jones M, et al. Int J Cancer. 2008; 123(7):1699-1703. 5. Crane LM, et al. Cell Oncol(Dordr). 2012;35(1):9-18. 6. Martin LP, et al. Gynecol Oncol. 2017;147(2):402-407. 7. Matulonis UA et al. J. Clin Oncol. Published online January 30, 2023, doi:10.1200/JCO.22.01900. 8. Ledermann JA, et al. Ann Oncol. 2015;26(10):2034-2043. 9. Despierre E, et al. Gynecol Oncol. 2013;130(1):192-199. 10. O'Shannessy DJ, et al. Int J Gynecol Pathol. 2013;32(3):258-268. 11. Zhao J, et al. Presented at: 2015 American Association for Cancer Research Annual Meeting; April 18-22, 2015; Philadelphia, PA. Abstract 3400A. 12. Dolled-Filhart M, et al. Arch Pathol Lab Med. 2016;140(11):1243-1249. 13. Moore KN, et al. Presented at: 2019 European Society for Medical Oncology Congress; September 27-October 1, 2019; Barcelona, Spain. Abstract 4093.

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A Targeted Approach: SORAYA

Design

Enrollment and Key Eligibility

- Enrolled 106 patients 38% Stage IV
- Platinum-resistant disease (PFI ≤6 mo)[a] 37% 0-3m
  - 1° platinum refractory disease excluded (primary PFI <3 mo)
- Prior bevacizumab required, prior PARPi allowed 48%
- 1-3 prior lines of therapy 51% 3 Priors
- Patients with *BRCA* mutations allowed
- FRα-high (≥75% PS2+ scoring shown by membrane stain intensity)[b]

Primary Objective

Confirmed objective response rate (ORR) by investigator assessment

Secondary Objectives

- Duration of response (DOR)
- Safety and tolerability
- Progression-free survival (PFS)
- Overall survival (OS)
- ORR, DOR, and PFS by BICR as sensitivity analyses
- CA-125 response by GCIG criteria

Dosing

MIRV 6 mg/kg adjusted ideal body weight Q3W until disease progression or unaccepted toxicity

Statistical Assumptions

- α=0.025 (one-sided)
- Power=91% to detect a difference in ORR of 12% (historical benchmark)

1°, primary; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; FRα, folate receptor alpha; GCIG, Gynecological Cancer Intergroup; MIRV, mirvetuximab soravtansine; PARPi, poly ADP-ribose polymerase inhibitor; PFI, platinum-free interval; Q3W, every 3 weeks. [a]PFI is calculated from the last cycle of platinum-containing treatment to the time of disease progression. [b]The PS2+ scoring method required the pathologist (at the central laboratory) to assess the percentage of tumor cells with moderate (2) and/or strong (3) membrane staining compared with the total number of viable tumor cells. To be considered positive for FRα expression and eligibility for the study, ≥75% of viable tumor cells must have exhibited level 2 and/or 3 membrane staining intensity. Matulonis U, et al. *J Clin Oncol.* 2023. doi: 10.1200/JCO.22.01900.

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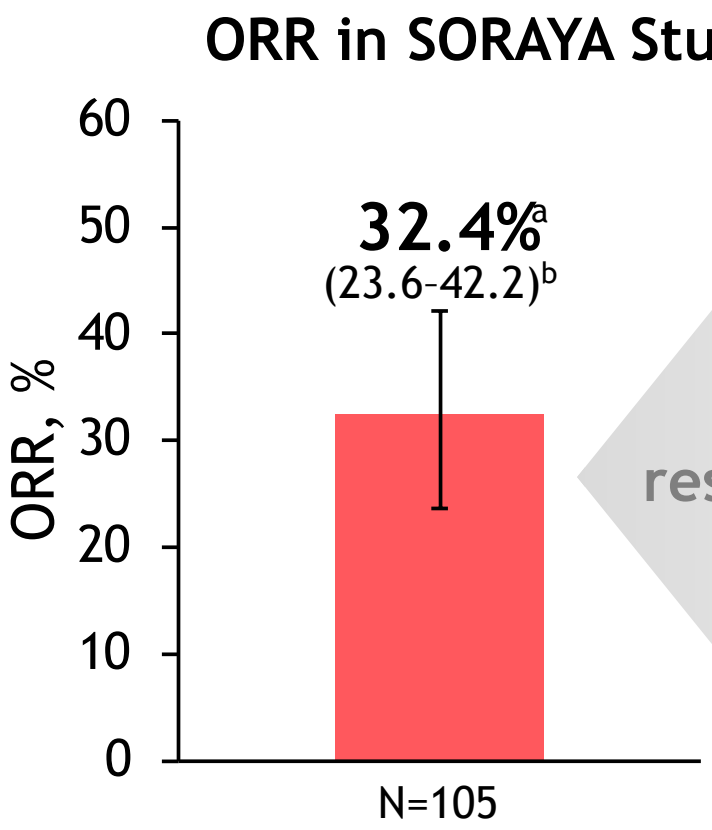
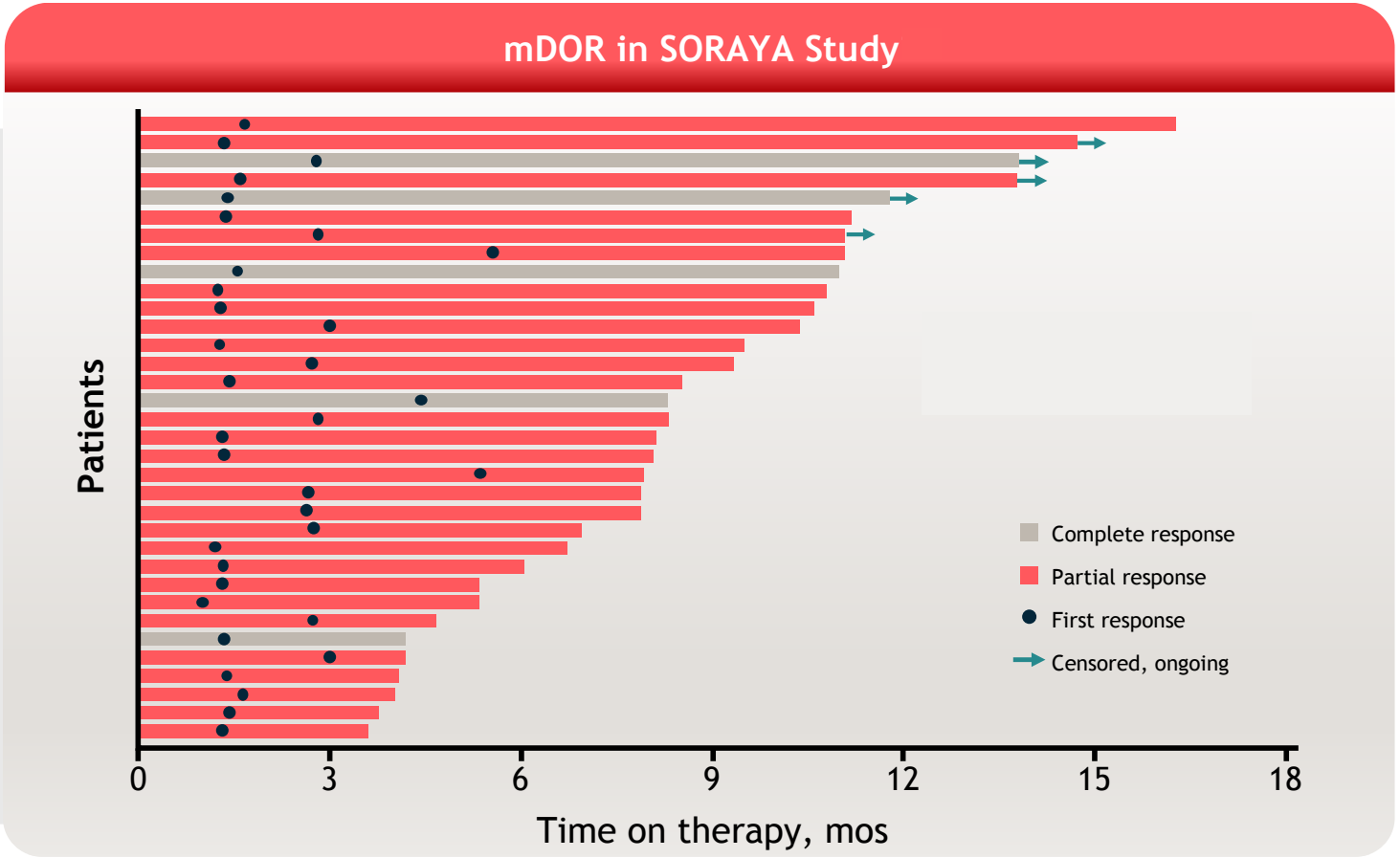
A Targeted Approach: SORAYA Investigator-Assessed ORR in Overall Efficacy-Evaluable Patients



34 responders



ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors. [a]The denominator for the percentage is the number of patients in the investigator-assessed efficacy evaluable population. Patients without at least 1 postbaseline RECIST assessment were treated as not evaluable. [b]95% exact confidence interval is estimated by Clopper-Pearson method (Clopper-Pearson exact CI). Matulonis U, et al. *J Clin Oncol.* 2023. doi: 10.1200/JCO.22.01900.

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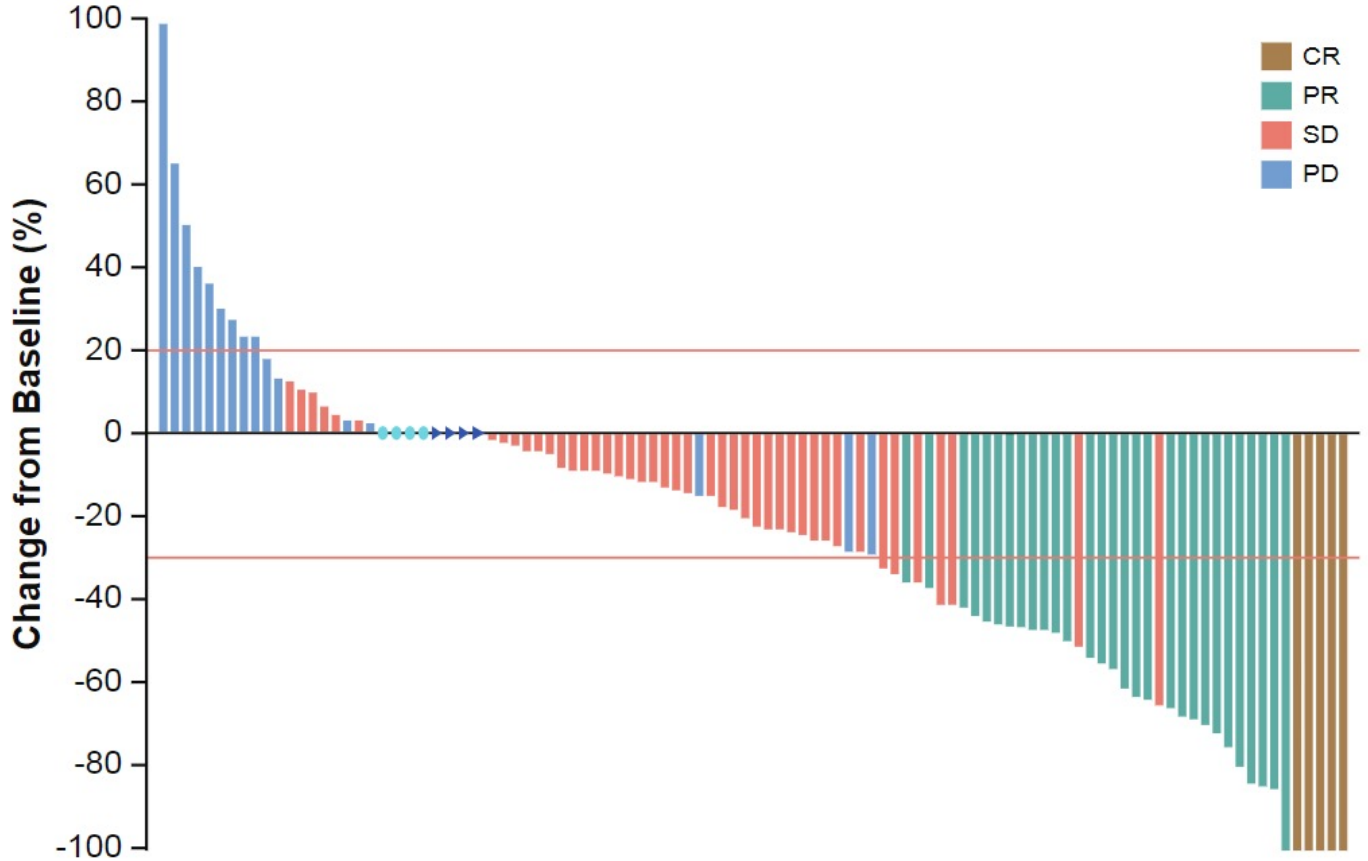
A Targeted Approach:
SORAYA Investigator-Assessed ORR in Overall Efficacy-Evaluable Patients



Disease Control Rate 51%

Tumor Reduction 71%

mPFS 4.3 mo

mOS 13.8 mo

ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors. [a]The denominator for the percentage is the number of patients in the investigator-assessed efficacy evaluable population. Patients without at least 1 postbaseline RECIST assessment were treated as not evaluable. [b]95% exact confidence interval is estimated by Clopper-Pearson method (Clopper-Pearson exact CI). Matulonis U, et al. *J Clin Oncol.* 2023. doi: 10.1200/JCO.22.01900.

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A Targeted Approach:
SORAYA TRAEs Reported in ≥10% of Patients (N=106)

TRAEs, n (%)	All Grades	Grade 3	Grade 4
Patients with any event	91 (86)	30 (28)	1 (1)
Blurred vision	43 (41)	6 (6)	0 (0)
Keratopathy*†	31 (29)	8 (8)	1 (1)
Nausea	31 (29)	0 (0)	0 (0)
Dry eye	26 (25)	2 (2)	0 (0)
Fatigue	25 (24)	1 (1)	0 (0)
Diarrhea	23 (22)	2 (2)	0 (0)
Asthenia	16 (15)	1 (1)	0 (0)
Photophobia	14 (13)	0 (0)	0 (0)
Peripheral neuropathy	14 (13)	0 (0)	0 (0)
Decreased appetite	14 (13)	1 (1)	0 (0)
Neutropenia	14 (13)	2 (2)	0 (0)
Vomiting	12 (11)	0 (0)	0 (0)

Predictable
- Median onset #2

Proactive Supportive Care
- Ophthalmic exam Qalt# to #8
- Topical steroids 6x a day from D-1
- Lubricating drops 4x a day 10 mins after steroid

Manageable & Reversible
- >80% Gr 2-3 resolved to Gr 1
- DR or DD 22%

<1% DCed (n=1)
- Resolved within 15 days

Data cutoff: April 29, 2022. AE, adverse event; GI, gastrointestinal; TRAEs, treatment-related adverse events. *The grouped preferred term "Keratopathy" includes the following preferred terms: "corneal cyst," "corneal disorder," "corneal epithelial microcysts," "keratitis," "keratopathy," "limbal stem cell deficiency," "corneal opacity," "corneal erosion," "corneal pigmentation," "corneal deposits," "keratitis interstitial," "punctate keratitis," and "corneal epithelial defect." †One patient experiencing a grade 4 event recorded as keratopathy was based upon the visual acuity evaluation of one eye (20/200). This patient had confirmed grade 2 corneal changes, and both the visual acuity and these corneal changes resolved completely (grade 0) in 15 days by ophthalmic exam. Matulonis U, et al. *J Clin Oncol.* 2023. doi: 10.1200/JCO.22.01900.

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A Targeted Approach: MIRASOL (NCT04209855)

Enrollment Complete

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer

MIRASOL Patient Population (N≈430)

Enrollment and Key Eligibility

Platinum-resistant disease (PFI ≤6 mo)

FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells

1^0 platinum-refractory disease excluded (primary PFI <3 mo)

Prior BEV and PARPi allowed

1-3 prior lines of therapy

Patients with BRCA mutations allowed

1:1 Randomization

Treatment Regimen-Experimental

MIRV
(6 mg/kg AIBW Q3W)

Treatment Regimen-Control

Investigator's Choice Chemotherapy
(Paclitaxel, PLD, Topotecan)

Stratification Factors

IC CTX: paclitaxel, PLD, topotecan
Prior lines of therapy: 1 vs 2 vs 3

Primary Endpoint

PFS by INV
(BICR for sensitivity analysis)

Secondary Endpoints

ORR by INV
OS
PROs[a]
Safety and tolerability
DOR
CA-125 response GCIG criteria
PFS2

AIBW, adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; CTX, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; GCIG, Gynecological Cancer InterGroup; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.aPROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855 2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

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A Targeted Approach: PICCOLO (NCT05041257)

Enrollment Complete

A single-arm, open-label, phase 2 trial for MIRV using PS2+ scoring in FRα-high 3L+ platinum-sensitive ovarian cancer

PICCOLO Patient Population (N≈75)

Enrollment and Key Eligibility

Platinum-sensitive disease
(defined as radiographic progression >6 months from last dose of most recent platinum therapy)

FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells

At least 2 prior platinum-containing regimens[a]

Prior PARPi required if BRCA+

Prior BEV not required

Appropriate for single-agent therapy

Treatment Regimen

MIRV
(6 mg/kg AIBW Q3W)

Primary Endpoint

ORR by INV

Key Secondary Endpoint

DOR by INV

Other Secondary Endpoints

Safety and tolerability
CA-125 response by GCIG criteria
PFS
OS
Sensitivity analysis[b]

3L, third line; AIBW; adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; DOR, duration of response; FRα, folate receptor alpha; GCIG, Gynecological Cancer InterGroup; IHC, immunohistochemistry; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFS, progression-free survival; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks. [a]1 prior line if documented platinum allergy. bORR, DOR, and PFS by BICR will be summarized as sensitivity analysis.

1. ClinicalTrials.gov identifier: NCT05041257. Updated July 27, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT05041257 2. Alvarez Secord A, et al. Presented at: 2022 Annual Global Meeting of the International Gynecologic Cancer Society; Sept 29-Oct 1, 2022; New York City, NY. Abstract 1556. 3. Alvarez Secord A, et al. Presented at: 2022 Society of Gynecologic Oncology Annual Meeting on Women's Cancer; March 18-21, 2022; Phoenix, AZ. Abstract 300.

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

A Targeted Approach: IMGN853-0420 (NCT05456685)

Actively Enrolling

An open-label, phase 2 trial of MIRV + carboplatin followed by MIRV continuation in FRα-low, -medium, and -high patients with platinum-sensitive ovarian cancer

420 Patient Population (N≈114)

Enrollment and Key Eligibility

Platinum-sensitive disease
(defined as radiographic progression >6 months from last dose of most recent platinum therapy)

FRα detected by IHC with PS2+ intensity among ≥25% of viable tumor cells

1 prior platinum treatment

Prior PARPi required if BRCA+

Treatment Regimen

MIRV
(6 mg/kg AIBW Q3W)
+
Carboplatin
(AUC 5 Q3W)

6 cycles[a]

CR, PR, SD

Treatment Regimen: Continuation[b]

MIRV
(6 mg/kg AIBW Q3W)

Primary Endpoint

ORR by INV

Secondary Endpoints

DOR
Safety and tolerability
PFS
OS
CA-125 response by GCIG criteria
Sensitivity analysis[c]

AIBW, adjusted ideal body weight; AUC, area under the concentration-time curve; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; CR, complete response; DOR, duration of response; FRα, folate receptor alpha; GCIG, Gynecological Cancer InterGroup; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks; SD, stable disease. [a]May be increased to 8 cycles at discretion of INV. [b]Patients will continue to receive MIRV Q3W until PD, unacceptable toxicity, withdrawal of consent, death, or the sponsor terminates the study (whichever comes first). [c]ORR, DOR, and PFS by BICR will be summarized as sensitivity analysis. ClinicalTrials.gov identifier: NCT05456685. Updated July 13, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT05456685

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

A Targeted Approach: GLORIOSA (NCT05445778)

Actively Enrolling

An open-label, phase 3 trial for MIRV + BEV maintenance in FRα-high patients with platinum-sensitive ovarian cancer

GLORIOSA Patient Population (N≈418)

Enrollment and Key Eligibility

Platinum-sensitive disease
(defined as progression >6 months from last dose of primary platinum therapy)

FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells

1 prior systemic treatment

CR, PR, or SD after treatment with platinum-based doublet + BEV

Prior PARPi required if BRCA+

2L Treatment
Platinum-based doublet + BEV

CR, PR, or SD

1:1 Randomization

Treatment Regimen[a] Experimental
MIRV
(6 mg/kg AIBW Q3W)
+
BEV
(15 mg/kg Q3W)

Treatment Regimen[a] Control
BEV
(15 mg/kg Q3W)

Stratification Factors
Prior PARPi,
Prior BEV, CR or PR or SD

Primary Endpoint
PFS

Key Secondary Endpoint
OS

Other Secondary Endpoints
Safety and tolerability
PFS2
ORR
DOR
DFS
CA-125 response by GCIG criteria
PROs[b]

2L, second line; AIBW; adjusted ideal body weight; BEV, bevacizumab; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; CR, complete response; DFS, disease-free survival; DOR, duration of response; FRα, folate receptor alpha; GCIG, Gynecological Cancer InterGroup; IHC, immunohistochemistry; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PR, partial response; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks; SD, stable disease. [a]Treatment in both study arms will continue until disease progression or unacceptable toxicity. [b]PROs will be measured using the EuroQol-5 Dimension 5-level (EQ-5D-5L) and NCCN-FACT Ovarian Symptom Index (NFOSI-18) study instruments.

1. ClinicalTrials.gov identifier: NCT05445778. Updated July 13, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT05445778 2. Data on file. ImmunoGen, Inc.

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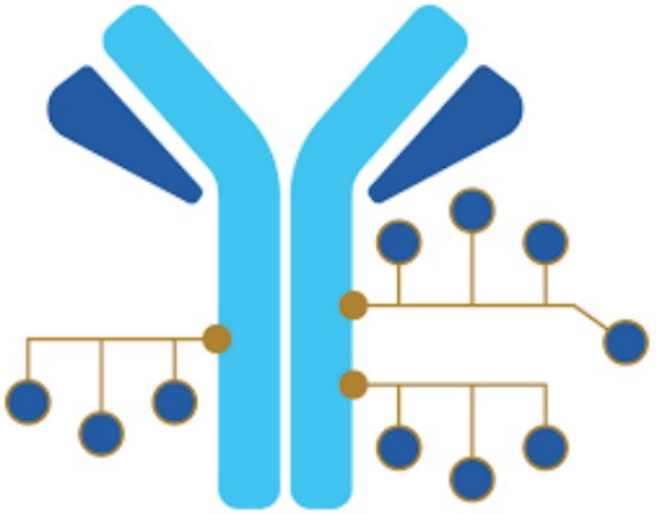
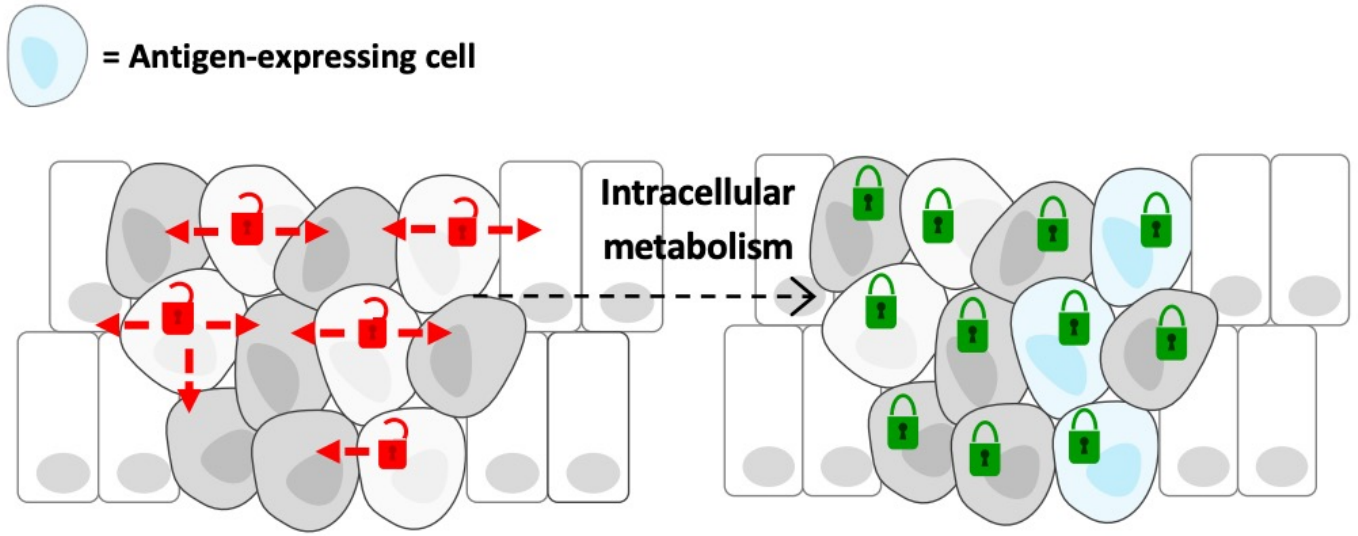
A Targeted Approach: Upifitamab Rilsodotin



Dolaflexin ADC
Antibody: Humanized anti-NaPi2b
Linker: Polymer scaffold
Cleavable ester linker
Payload: Auristatin F-HPA
DAR: Approx. 10-15
DolaLock: controlled bystander

AF-HPA auristatin F-hydroxypropylamide



Tolcher AW, et al. J Clin Oncol 2019;37(15):3010

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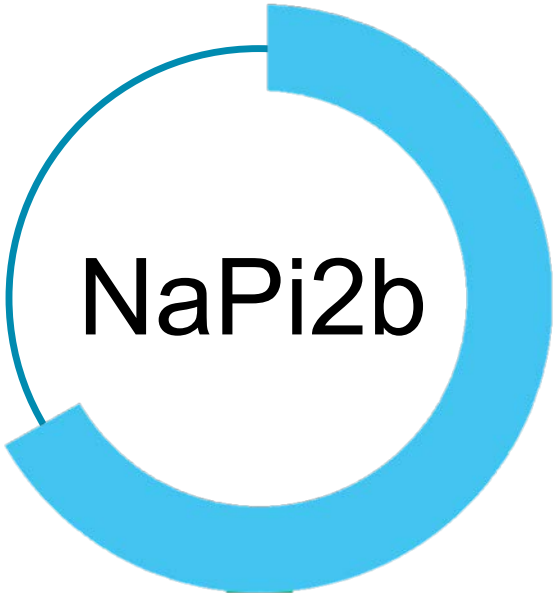
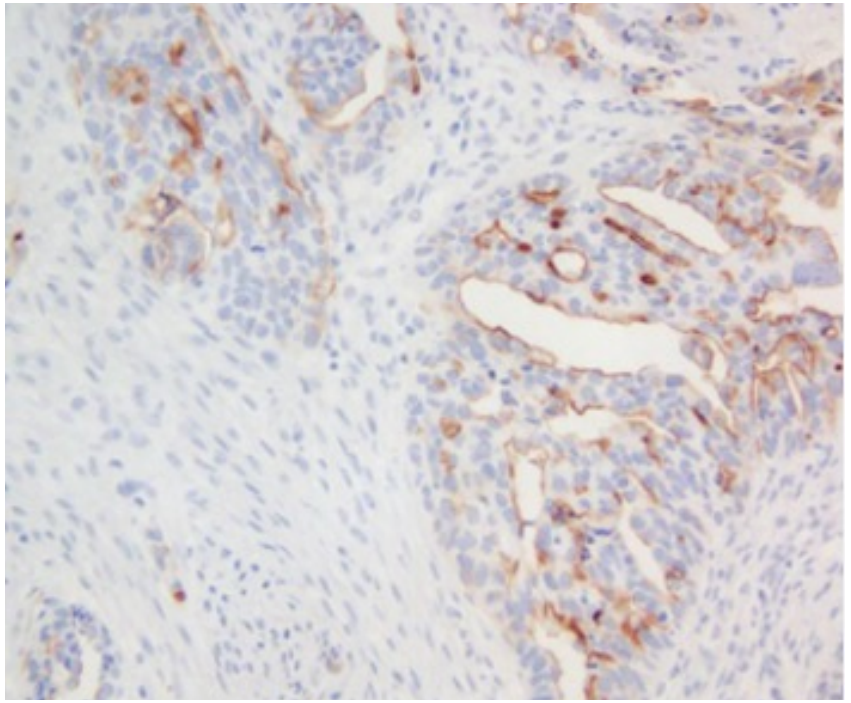
A Targeted Approach:
Upifitamab Rilsodotin



Sodium-dependent phosphate transporter

Expressed in 2/3 HGSOC



IHC TPS Tumor Proportion Score
0 1+ 2+ 3+ & 0-100%

Bodyak ND, et al. Mol Cancer Ther 2021;20(5):885-95
Lin K, et al. Clin Cancer Res 2015;21(22):5139-50

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

A Targeted Approach: Upifitamab Rilsodotin: Phase I Design

Patient Population: HGSOC[a] progressing after standard treatments; measurable disease per RECIST v1.1; ECOG PS 0 or 1

Ovarian Cancer Cohort
- 1–3 prior lines in platinum-resistant
- 4 prior lines regardless of platinum status
- High-grade serous histology
- Archived tumor and fresh biopsy (if medically feasible) for NaPi2b
- Exclusion: Primary platinum-refractory disease

UpRi IV Q4W until disease progression or unacceptable toxicity

36 mg/m² cohort initiated in August 2019

43 mg/m² to a max of ~80 mg cohort initiated in December 2019

Primary Objectives
- Evaluate safety and tolerability of MTD or RP2D
- Assess preliminary efficacy (ORR, DCR)

Secondary Objectives
- Association of tumor NaPi2b expression and objective tumor response using an IHC assay with a broad dynamic range to distinguish tumors with high and low NaPi2b expression
- Further assessment of preliminary anti-neoplastic activity (DoR)

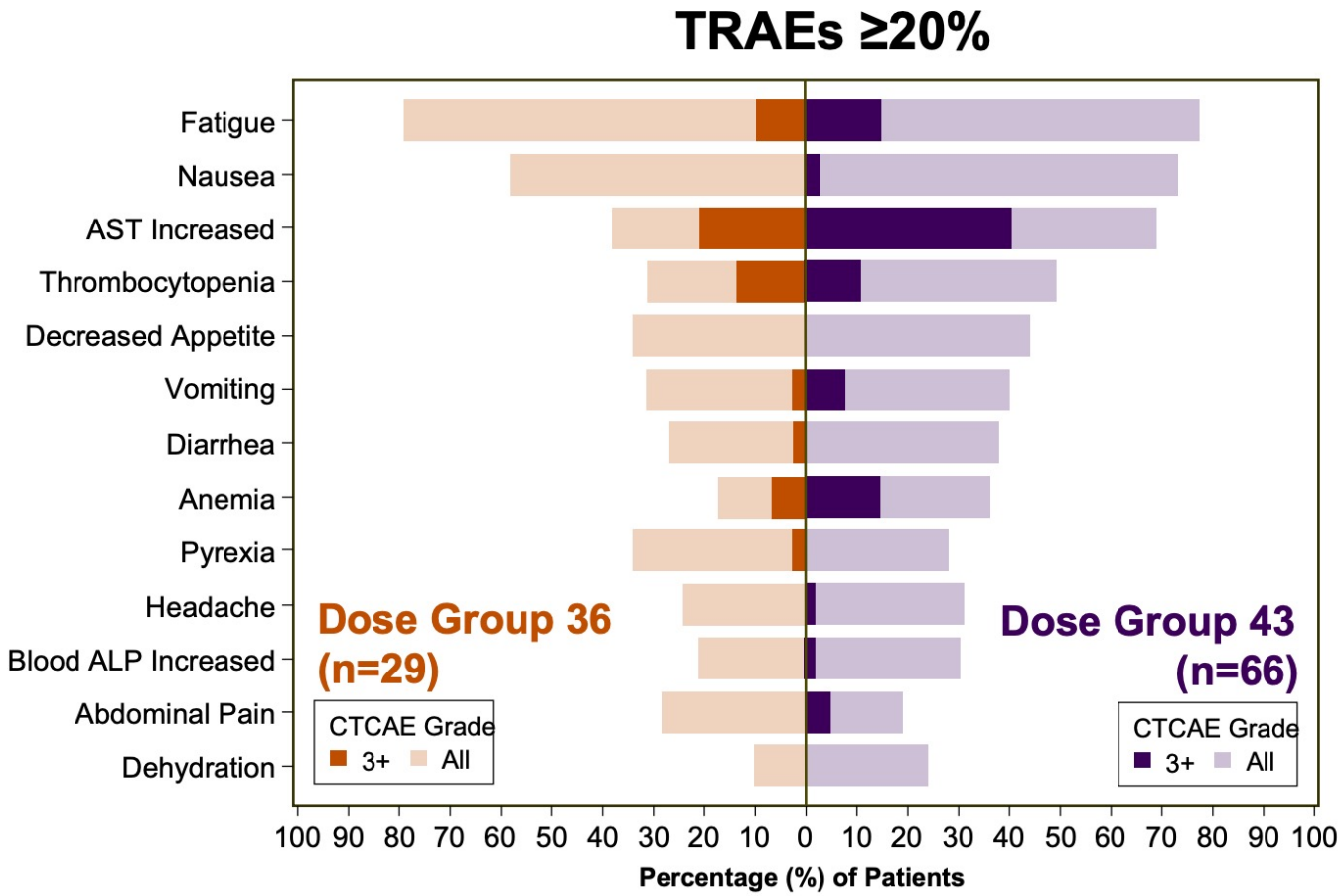
Assessment: Tumor imaging (MRI or CT) at baseline and every 2nd # Response per RECIST 1.1

Richardson DL, et al. Upifitamab Ph 1b Expansion SGO 2022 Abs 76

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

A Targeted Approach: Upifitamab Rilsodotin: TRAEs

Upifitamab 36 mg/m2 more favorable toxicity profile



- No severe ocular toxicity, neutropenia, or peripheral neuropathy in either dose group
- 4 (14%) patients had treatment-related SAEs in Dose Group 36 vs 18 (27%) in Dose Group 43
- Lower frequencies and lower grade pneumonitis occurred in Dose Group 36 (with no Grade 3+) vs Dose Group 43

Richardson DL, et al. Upifitamab Ph 1b Expansion SGO 2022 Abs 76

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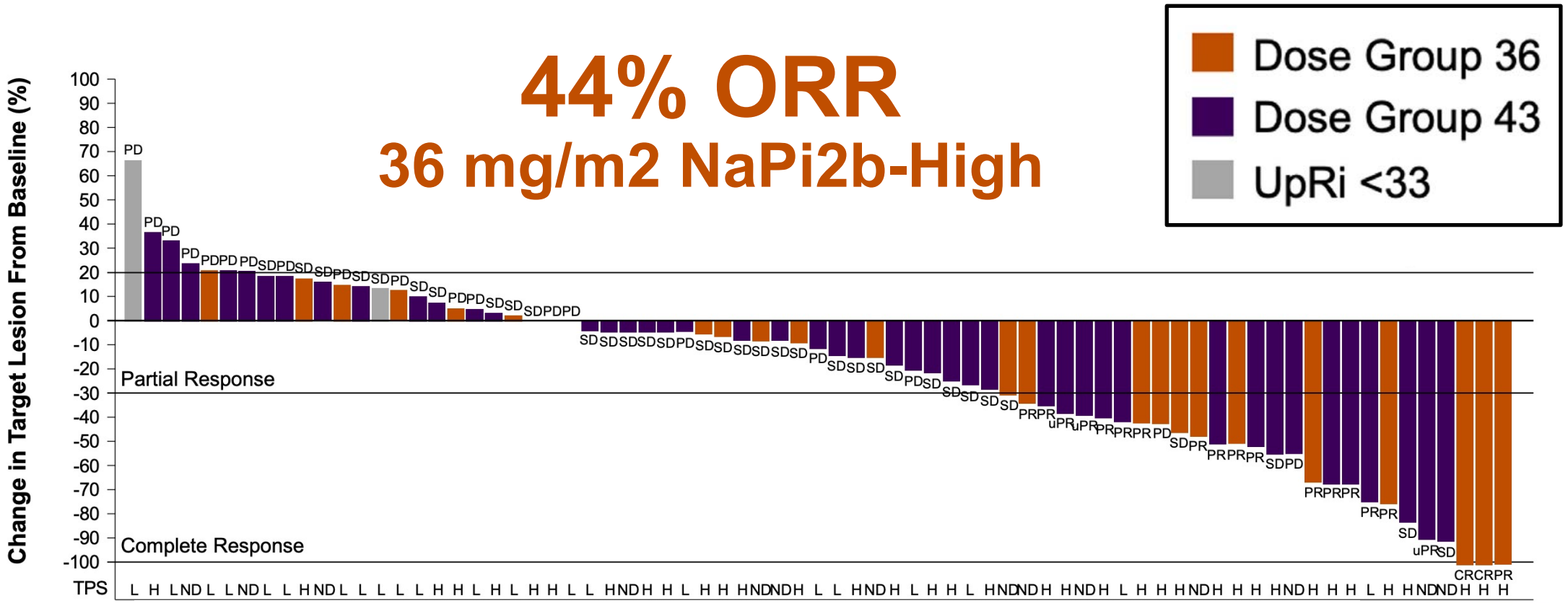
A Targeted Approach:
Upifitamab Rilsodotin: Best Response

Upifitamab 36 & 43 mg/m2 similar efficacy with 2/3 tumor reductions

44% ORR

36 mg/m2 NaPi2b-High



Richardson DL, et al. Upifitamab Ph 1b Expansion SGO 2022 Abs 76

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

ENGOT-ov67/GOG-3048

Phase 2 UpRi single-arm registrational trial in platinum-resistant ovarian cancer

Patient population: HGSOC[a] progressing after standard treatments; measurable disease per RECIST v1.1; ECOG PS 0 or 1; enrolling regardless of NaPi2b expression

Global
US, Europe, Australia, Canada

Key inclusion criteria

- Platinum-resistant[b] HGSOC
- 1–4 prior lines of therapy
- Prior bevacizumab required if patient received only 1–2 prior lines of therapy
- ECOG PS 0–1
- Available archived or fresh tissue for retrospective NaPi2b evaluation
- Grade ≤2 peripheral neuropathy

Key exclusion criteria

- 1–2 prior lines AND bevacizumab-naive
- Primary platinum-refractory disease

UpRi 36 mg/m^2 up to max 80 mg; IV q4w

Primary endpoint

- Investigator-assessed confirmed ORR in NaPi2b-positive (N=~100)

Secondary endpoint

- Investigator-assessed confirmed ORR in overall population (N=~180–240, including 100 NaPi2b-positive)

Other secondary endpoints

- DOR
- Safety

Prospectively defined retrospective analysis to validate NaPi2b biomarker cutoff

Completed Enrollment – Topline data mid-year 2023

[a] HGSOC, including fallopian tube and primary peritoneal cancer. [b] Platinum-resistant is defined as disease that has progressed within 6 months of the last dose of platinum.

DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HGSOC, high-grade serous ovarian cancer; IV, intravenous; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab rilsodotin.

1. Richardson DL et al. IGCS Annual Meeting 2022; Abstract 426. 2. ClinicalTrials.gov. NCT03319628. Accessed September 9, 2022.

UpRi is an investigational drug not currently approved for use by any health authority in any indication.

GOG-3049 / ENGOT-ov71-NSGO-CTU

Phase 3 Study of UpRi Monotherapy Maintenance vs Placebo in Platinum-Sensitive Recurrent Ovarian Cancer

UP-NEXT

Key Enrollment Criteria

- Platinum-sensitive recurrent HGSOC[a]
- 4–8 cycles of platinum-based therapy in 2nd to 4th line setting (not all lines need to include platinum-based therapy)
- Best response to last line of treatment: NED, CR, PR, or SD[b]
- ECOG PS 0–1
- NaPi2b-positive (TPS ≥75%) tumor (archival or fresh biopsy)
- Prior PARPi required for patients with known deleterious *BRCA* mutations
- Patients who received bevacizumab in combination with their last platinum-containing regimen are excluded

Randomized 2:1 N=350

UpRi 30 mg/m² (capped at 66 mg) **IV q4w**

Placebo q4w

All patients continue until PD or unacceptable AE, or up to 18 months

Primary Endpoint

- PFS by BICR

Secondary Endpoints

- PFS by Investigator
- ORR
- OS
- PROs

NCT05329545: Trial Currently Enrolling Patients

[a] HGSOC, including fallopian tube and primary peritoneal cancer. [b] For SD, no increase in disease confirmed by central review of imaging and absence of CA-125 rise >15% in 7 days prior to first dose.

AE, adverse event; BICR, blinded independent central review; *BRCA*, BRCA DNA repair associated gene; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HGSOC, high-grade serous ovarian cancer; IV, intravenous; NaPi2b, sodium-dependent phosphate transport protein 2B; NED, no evidence of disease; ORR, overall response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRO, patient reported outcomes; q4w, every 4 weeks; SD, stable disease; TPS, tumor proportion score; UpRi, upifitamab rilsodotin.

ENGOT European Network of Gynaecological Oncological Trial groups

GOG FOUNDATION Transforming the standard of care

UPGRADE-A

Phase 1 UpRi + Carboplatin Combination in Platinum-Sensitive Ovarian Cancer

Key Enrollment Criteria

- Recurrent, platinum-sensitive,[a] high-grade serous ovarian cancer, including fallopian tube or primary peritoneal cancer
- Participant has received 1 to 3 prior lines of therapy for their ovarian cancer; a non-platinum-based chemotherapy regimen is permitted provided it is not the most recent line of therapy
- Participants not selected for NaPi2b expression
- Tissue (fresh or archival) for retrospective assessment of NaPi2b expression
- RECIST v1.1 measurable disease
- ECOG PS = 0–1

Dose Escalation (BOIN design)

UpRi IV q4w
+ carbo AUC 5 q4w × 6[b]

→ **UpRi** until PD or unacceptable AE

Primary Endpoint
- MTD for UpRi with carboplatin AUC 5

Secondary Endpoints
- AEs, PK for UpRi, PK for carboplatin, immunogenicity for UpRi, ORR, PFS, OS

Expansion (N=30)

UpRi 30 mg/m² (capped at BSA 2.2 m²) **IV q4w**
+ carbo AUC 5 q4w × 6[b]

→ **UpRi** until PD or unacceptable AE

Primary Endpoint
- Feasibility at 30mg/m² (≥60% of participants complete at least 4 cycles of the combination)

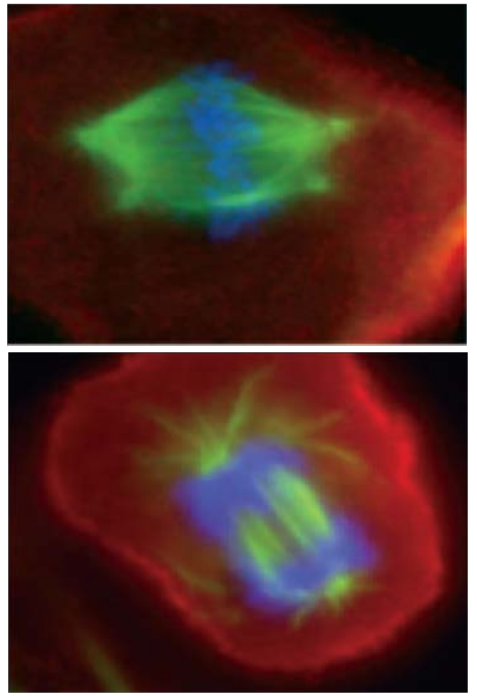
Secondary Endpoints
- AEs, PK for UpRi, PK for carboplatin, immunogenicity for UpRi, ORR, PFS, OS, efficacy by NaPi2b expression

NCT04907968: Currently Enrolling Patients to Dose Expansion Portion of Trial

[a] Platinum-sensitive is defined as having achieved either a partial or complete response to 4 or more cycles in their last platinum-containing regimen and their disease progressing more than 6 months after completion of the last dose of platinum-containing therapy. [b] Up to 6 cycles.

AE, adverse event; AUC, area under the curve; BOIN, Bayesian Optimal Interval; carbo, carboplatin; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; MTD, maximum tolerated dose; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PS, performance score; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab rilsodotin.

Tumor Treating Fields (TTFields)



Disrupted Microtubule and Chromosomal Assembly
IHC: Microtubules Actin DNA

Kirson ED, et al. Cancer Res. 2004;64(9):3288-95
Mun EJ, et al. Clin Cancer Res 2018;24(2):266–275

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CANCER CENTER

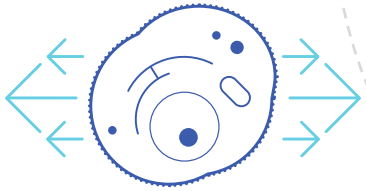
TTFields Mechanism of Action

TTFields therapy mechanism of action

1 DDR DOWNREGULATION

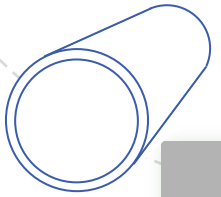
R-loop formation disruption
Red. replication fork speed
Chromatid aberrations
Downregulation of the FA-BRCA pathway

2 INTERFERENCE IN CELL MOBILITY AND MIGRATION



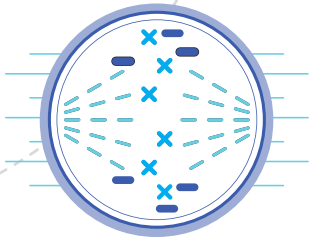
Actin bundling and formation of focal adhesions
Loss of cytoskeletal directionality

3 PERMEABILITY



Tight junction protein delocalisation in endothelial cells

4 DISRUPTION OF MITOSIS



Diminished microtubule abundance
Red. mitotic spindle assembly
Septin disruption and cytoplasmic blebbing
Organelle migration to cleavage furrow

5 ENHANCEMENT OF ANTITUMOR IMMUNITY

Activation of immunogenic cell death
Recruitment and infiltration of tumor leukocytes
Activation of downstream adaptive immunity

Kirson ED, et al. Cancer Res. 2004;64(9):3288-95
Mun EJ, et al. Clin Cancer Res 2018;24(2):266–275

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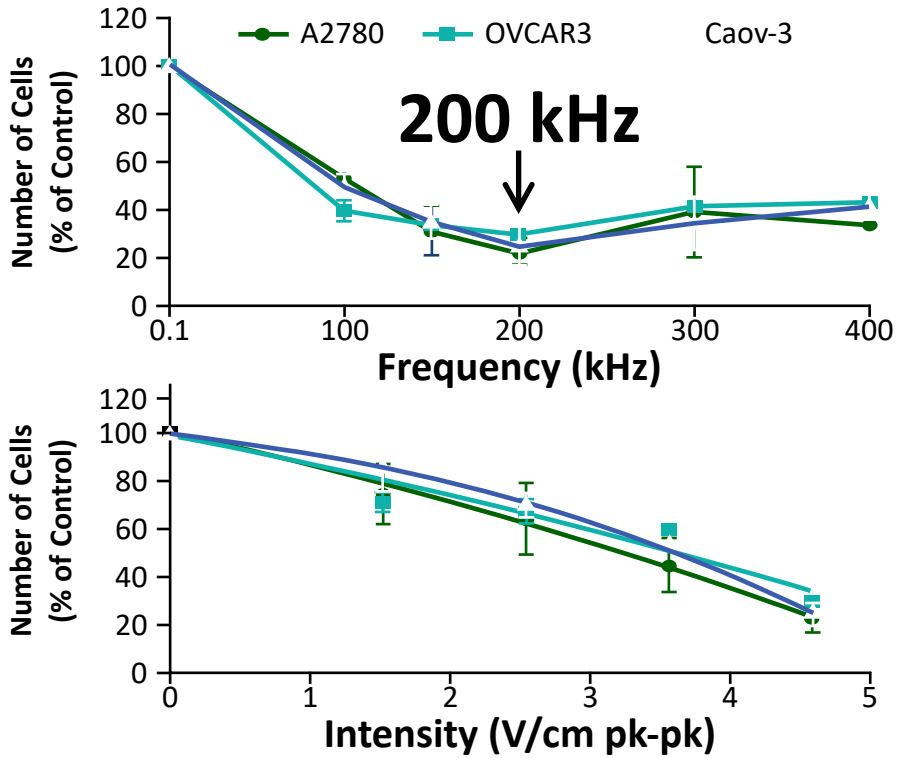
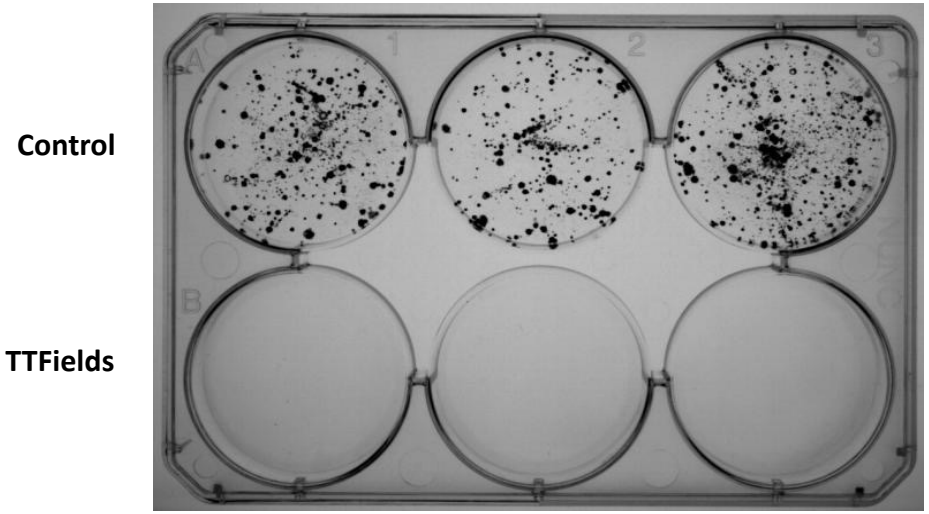
CANCER CENTER

TTFields Mechanism of Action

***In Vitro* Efficacy of TTFields in Human Ovarian Cancer Cell Lines**



TTFields Significantly Impair the Ability of Ovarian Cancer Cells to Form Colonies Demonstrating Reduced Clonogenic Potential



Voloshin T, et al. Int J Cancer. 2016;139(12):2850-8
Schneiderman RS, et al. Cancer Res. 2014;74(suppl 19): Abstract 5521

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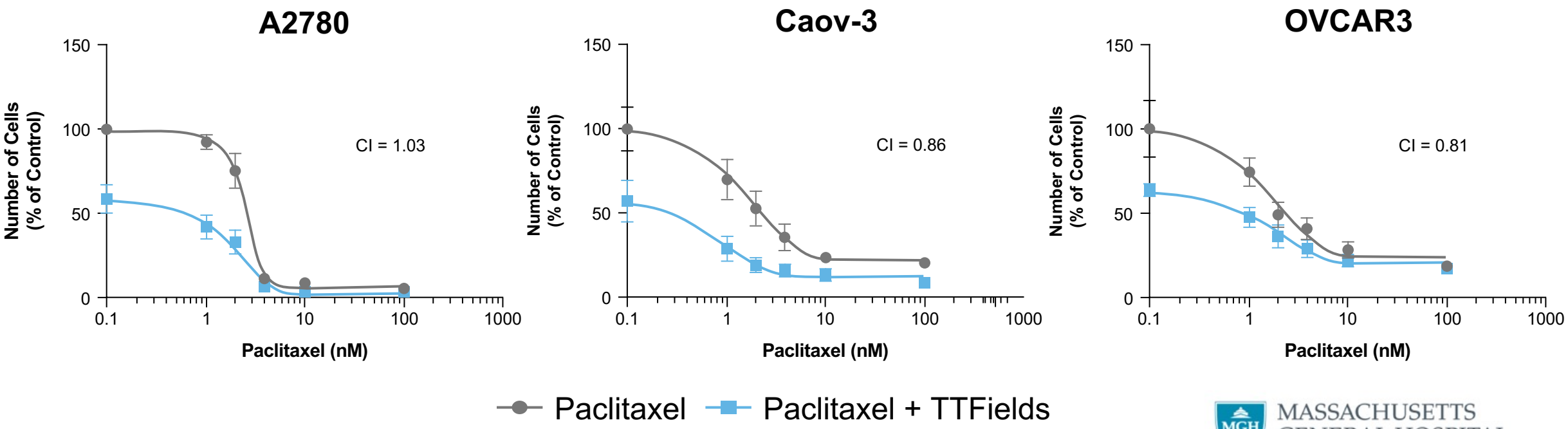
TTFields Mechanism of Action

Antiproliferative effects in ovarian cancer cells *in vitro* paclitaxel +/- TTFields 72h

Combination Index >1 suggests synergistic effect of TTFields and paclitaxel



Voloshin T et al. Int J Cancer. 2016;139(12):2850-8

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INNOVATE

Phase 2 Trial Design

- Histologically or cytologically confirmed recurrent ovarian, fallopian tube, or primary peritoneal carcinoma
- ECOG PS 0–1

Paclitaxel 80 mg/m^2 weekly for #2 then on days 1, 8, 15 of each subsequent 28-day cycle + TTFields (200 kHz 18 h/day)

N = 31

CT scan Q2mo

Radiological/clinical disease progression/ unacceptable toxicity

Survival follow-up

ORR 25% mPFS 8.9mo

Clinical benefit 71% OS_{1yr} 61%

84% TTFields-related dermatitis

Start date: September 2014
Primary completion date: December 2016
Study sites: 5 (Europe)

Primary endpoints:
- AE severity and frequency, No. prematurely DCing TTFields due to skin toxicity

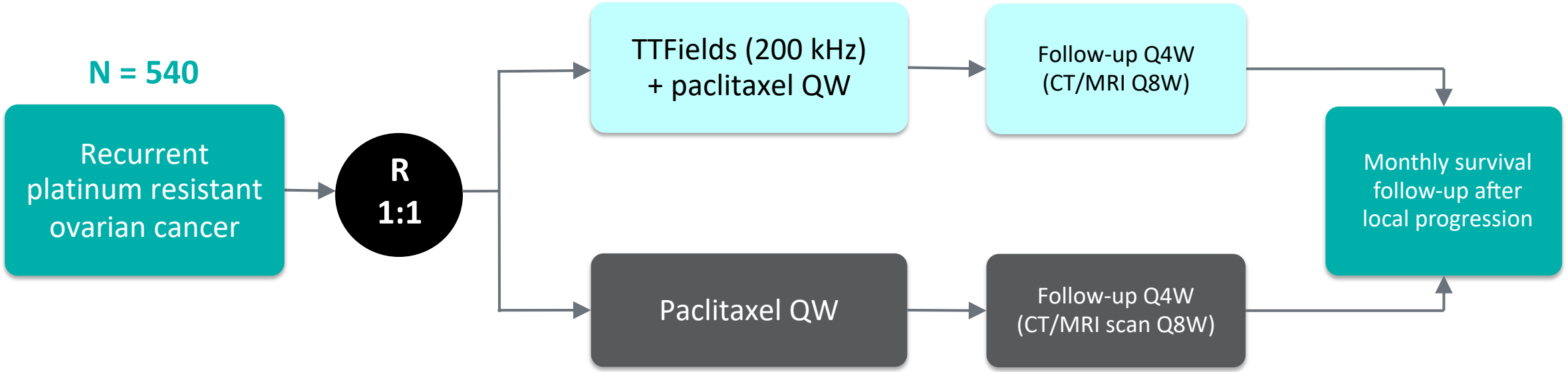
Secondary endpoints:
- PFS, OS, OS_{1yr}, ORR and DOR, CA-125 response and DOR, TTFields usage

Vergote I, et al. Gynecol Oncol. 2018;150(3):471-477

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

INNOVATE-3 (ENGOT-ov50)

Phase 3 Trial Design



Start date: March 2019
Primary completion: September 2023
Study sites: 119 (North America, EU, Israel)

Stratification:
- Prior lines of therapy
- Prior use of bevacizumab
- BRCA status

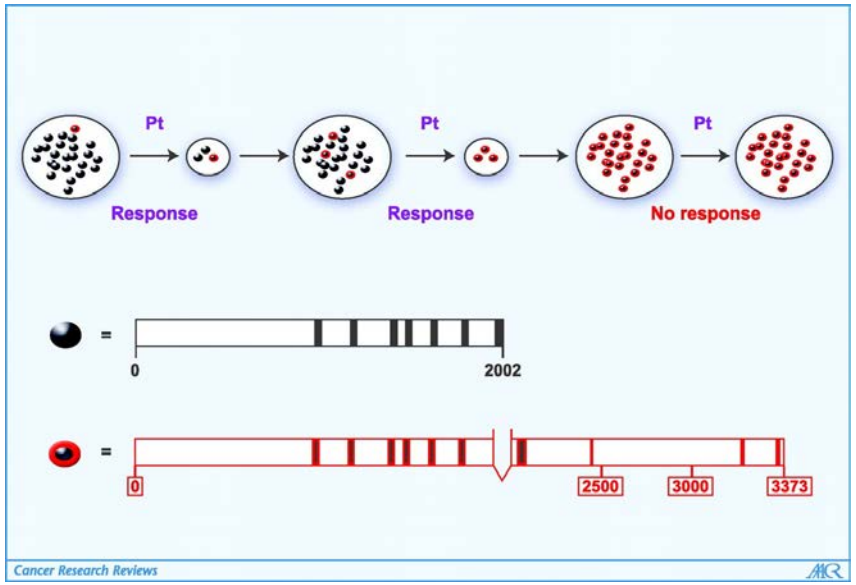
Primary endpoint:
- OS

Key Secondary endpoints:
- PFS, ORR, Safety, HRQoL

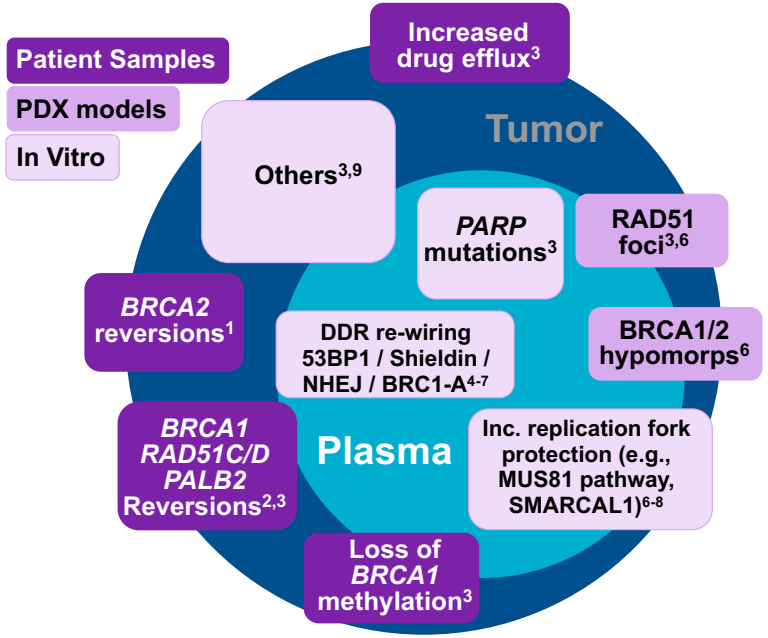
MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Kirson ED et al. J Clin Oncol. 2018;36(suppl 15):AbsTPS5614

Ovarian Cancer: Emerging Paradigms



Ashworth A Cancer Res 2008;68:10021-10023



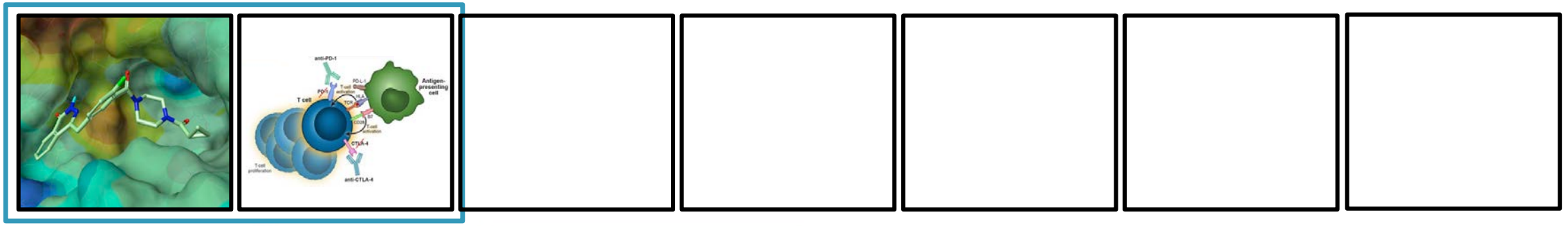
Courtesy of Jess Brown MD PhD

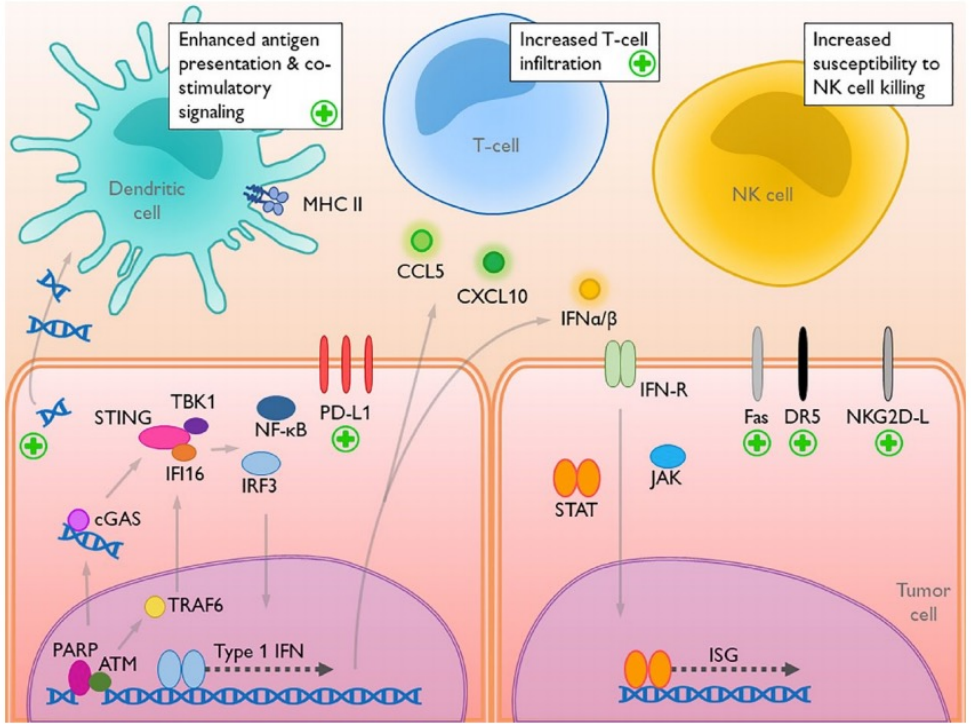
1. Restoration of *BRCA* / HRR gene function / protein expression [1-3]
2. DDR re-wiring: restoration of homologous recombination [4-7]
3. PARP mutations and red. in trapped PARP [3]
4. Replication fork protection [6-8]
5. Others: Drug Efflux, Cyclin E1 SLFN11 loss, PARG loss [3,9]

1. Norquist JCO 2011;29(22):3008; 2. Lin Cancer Discov 2018;9(2):210; 3. Patch Nature 2015;521(7553):489; 4. Pettitt Nature Comm 2018;9(1849):1849; 5. Bunting Cell 2010;141(2):243-54; 6. Cruz Annals Oncol 2018;29(5):1203; 7. Gupta Cell 2018; ;173(4):972; 8. Taglialatela Mol Cell 2017;68(2):414; 9. Yeung Clin Cancer Res 2017;23:7

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Ovarian Cancer: Emerging Paradigms





Error Prone Repair ⟶ Neoantigens

CD80 & 86, MHC II ⟶ Ag presentation

PD-L1 upregulation ⟶ 'Warmer' Tumors

NKG2D Ligands ⟶ 'Warmer' Tumors

STING Pathway ⟶ Type I IFN response

Lee LK & Konstantinopoulos PA. Trends Cancer. 2019;5(9):524-8

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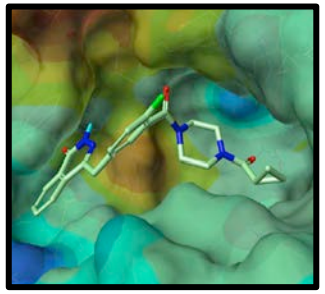
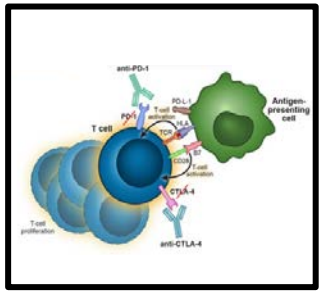
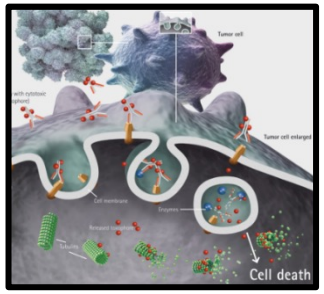
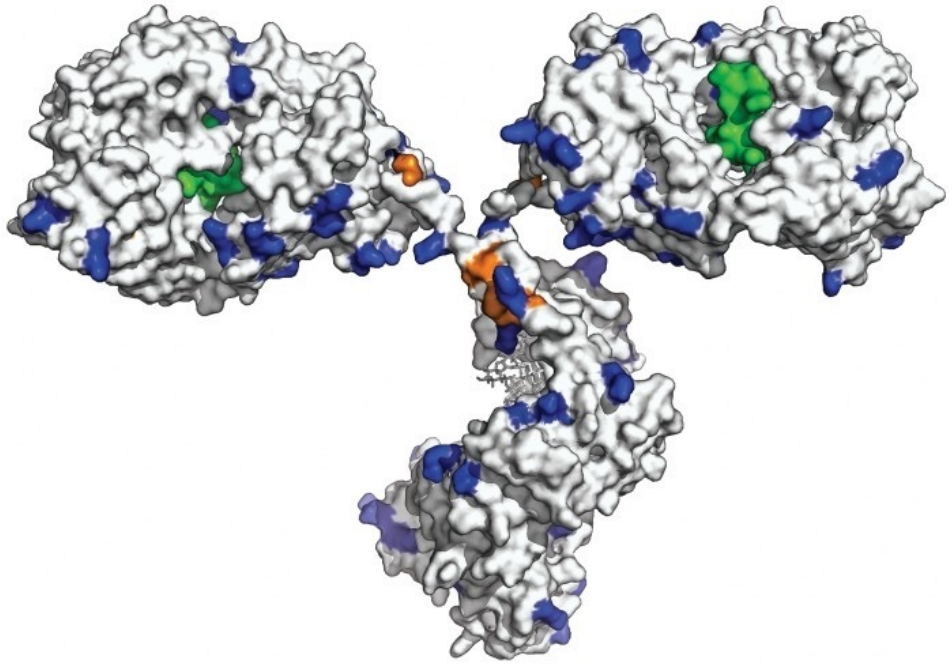
Ovarian Cancer: Emerging Paradigms





AXL	Enapotamab
CA-125	Sofituzumab; DMU4C064A
CD166	Praluzatamab
FRα	Mirvetuximab; Luveltamab; MORAb-202
Mesothelin	Anetumab; DMOT4039A
NaPi2B	Upifitamab; Lifastuzumab
NOTCH-3	PF-06650808
PTK7	Cofituzumab
TIM1	CDX-014
Tissue factor	Tisotumab
TROP-2	Sacituzumab

Manzano A & Ocaña A. Cancers (Basel). 2020;12(8):2223

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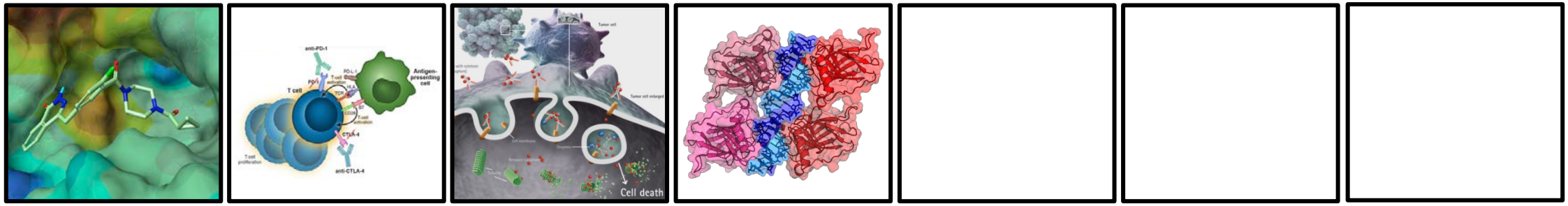
Ovarian Cancer: Emerging Paradigms

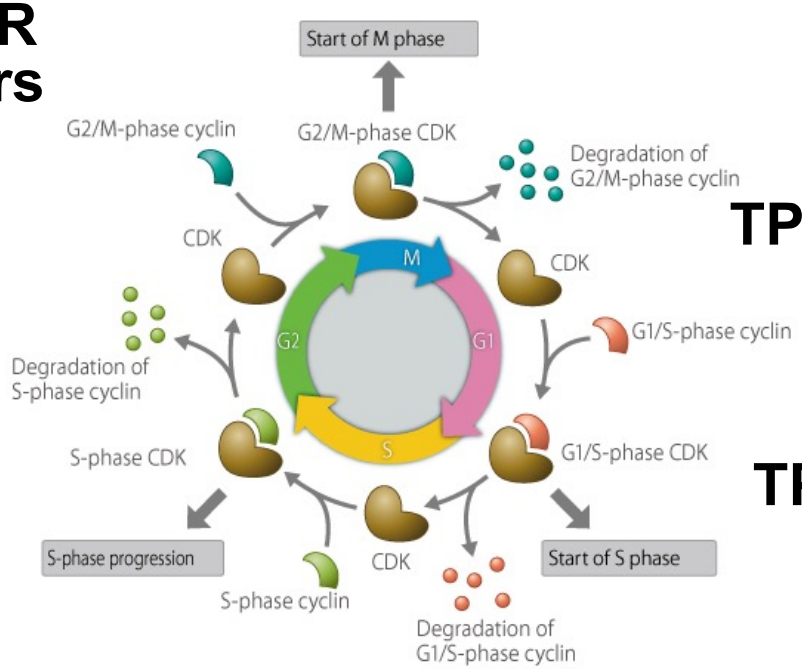


ATM ATR inhibitors

Wee1 Inhibitors

POLQ DNA pol-theta

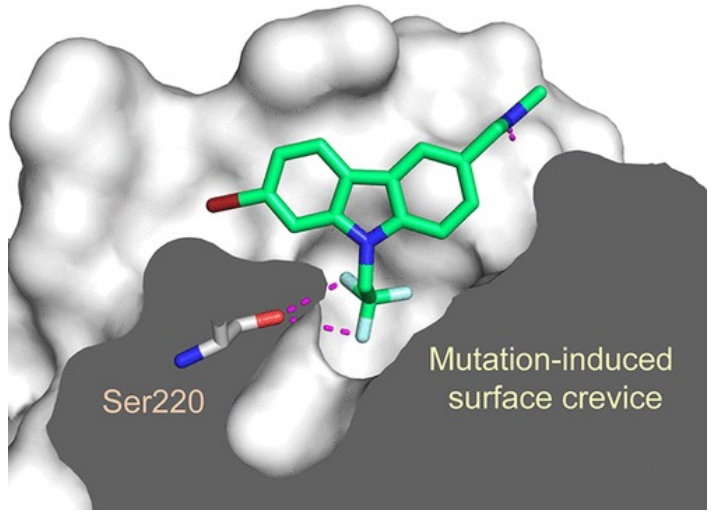
CHK1 inhibitors



Small Molecule TP53 stabilization

APR-246 TP53 activation

Rescue of p53-Y220X cancer mutants with small-molecule stabilizers



Pilié PG, et al. Nat Rev Clin Oncol 2019;16(2):81–104
Bauer MR et al. ACS Chem Biol 2020;15(3)657–68

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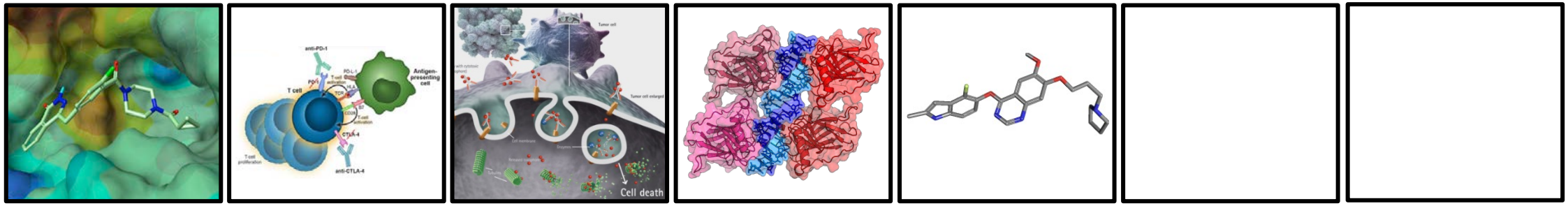
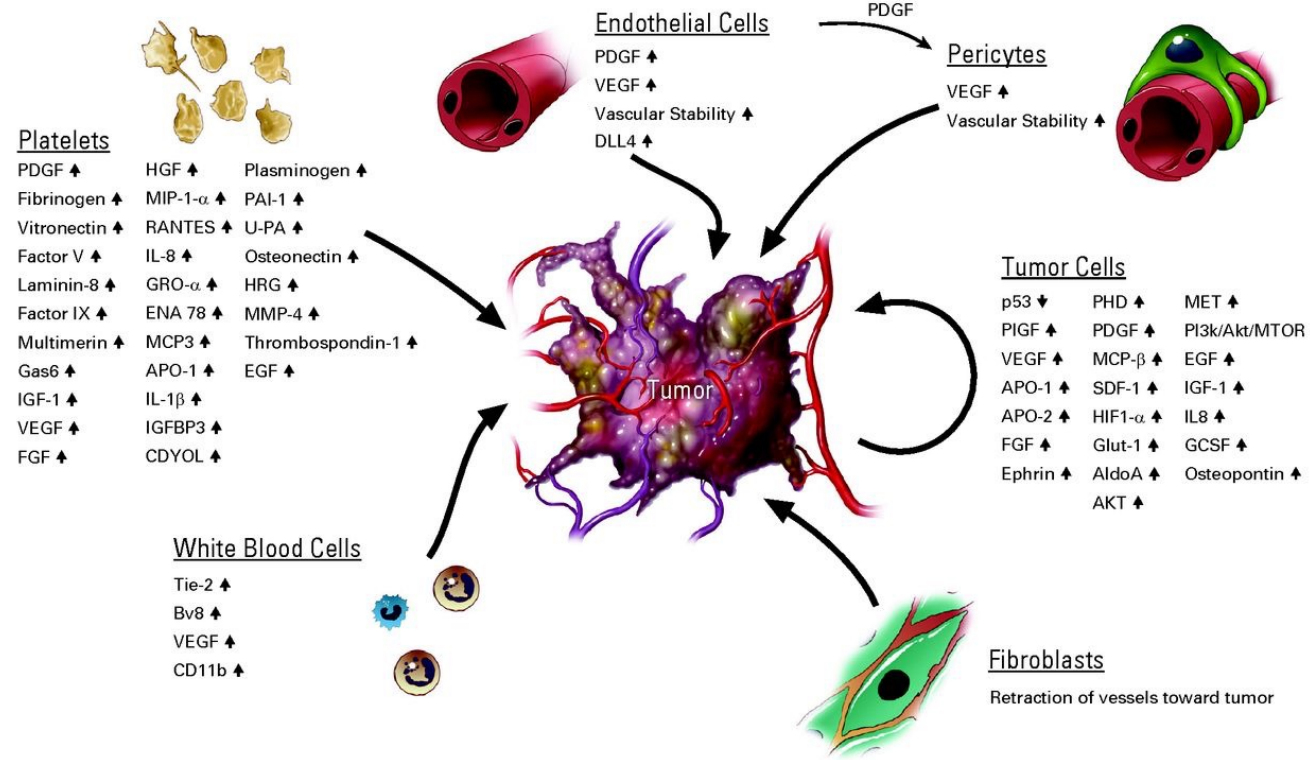
Ovarian Cancer: Emerging Paradigms





Courtesy Anil Sood MD

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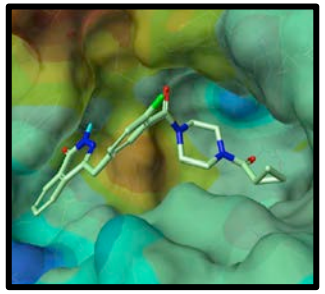
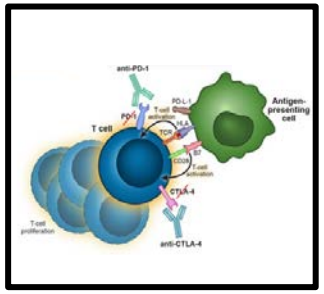
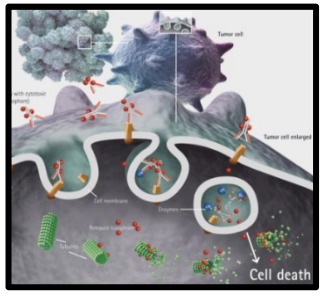
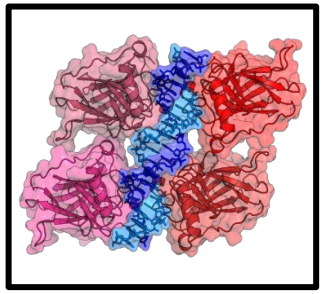
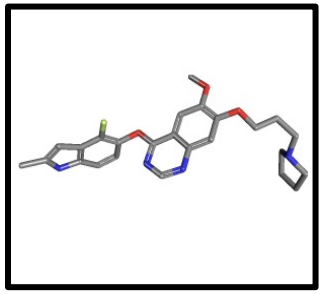
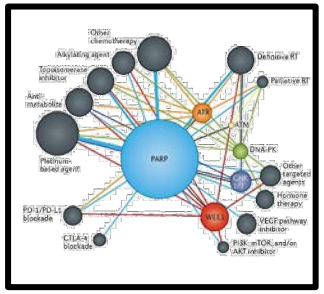
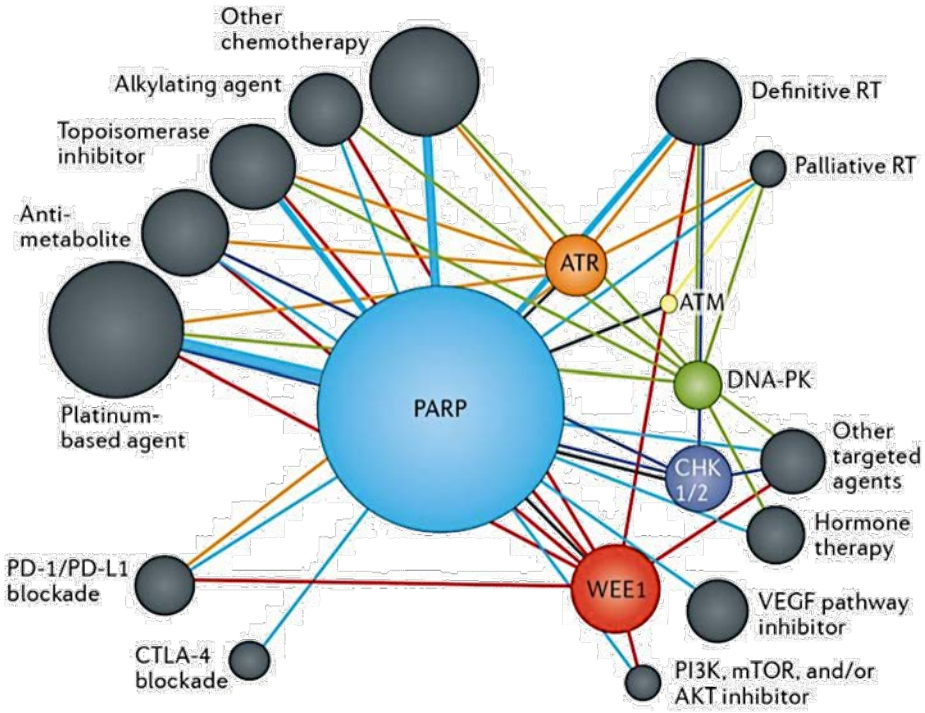
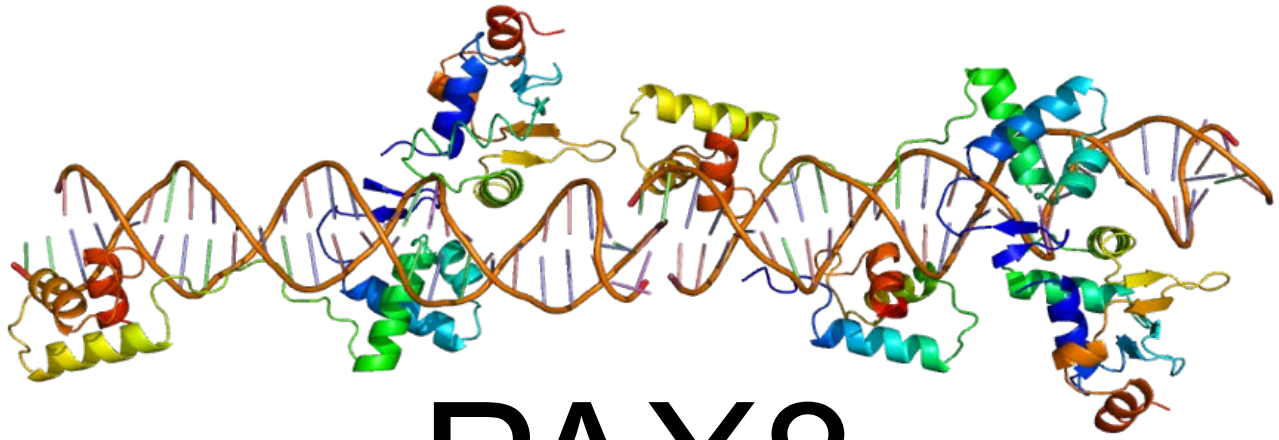
Ovarian Cancer: Emerging Paradigms




CA-125





PAX8

Pilie PG, et al. State-of-the-art strategies targeting DDR. Nat Rev Clin Oncol. 201916(2):81

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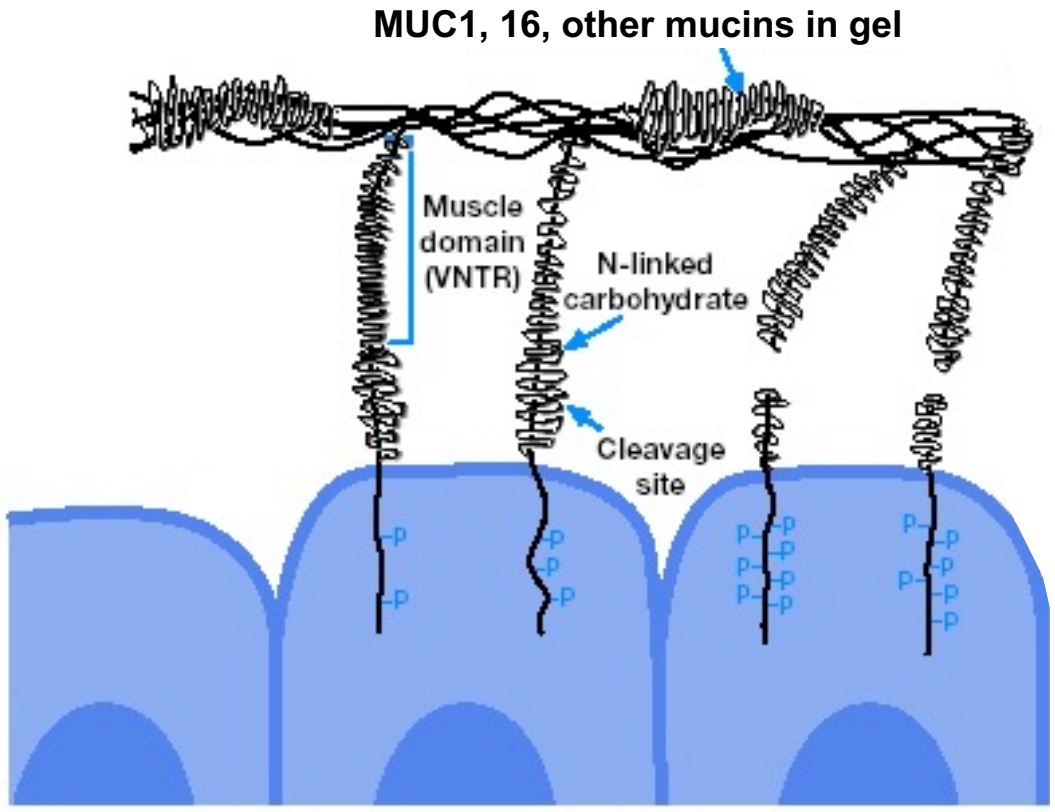
CA-125: Four Seasons

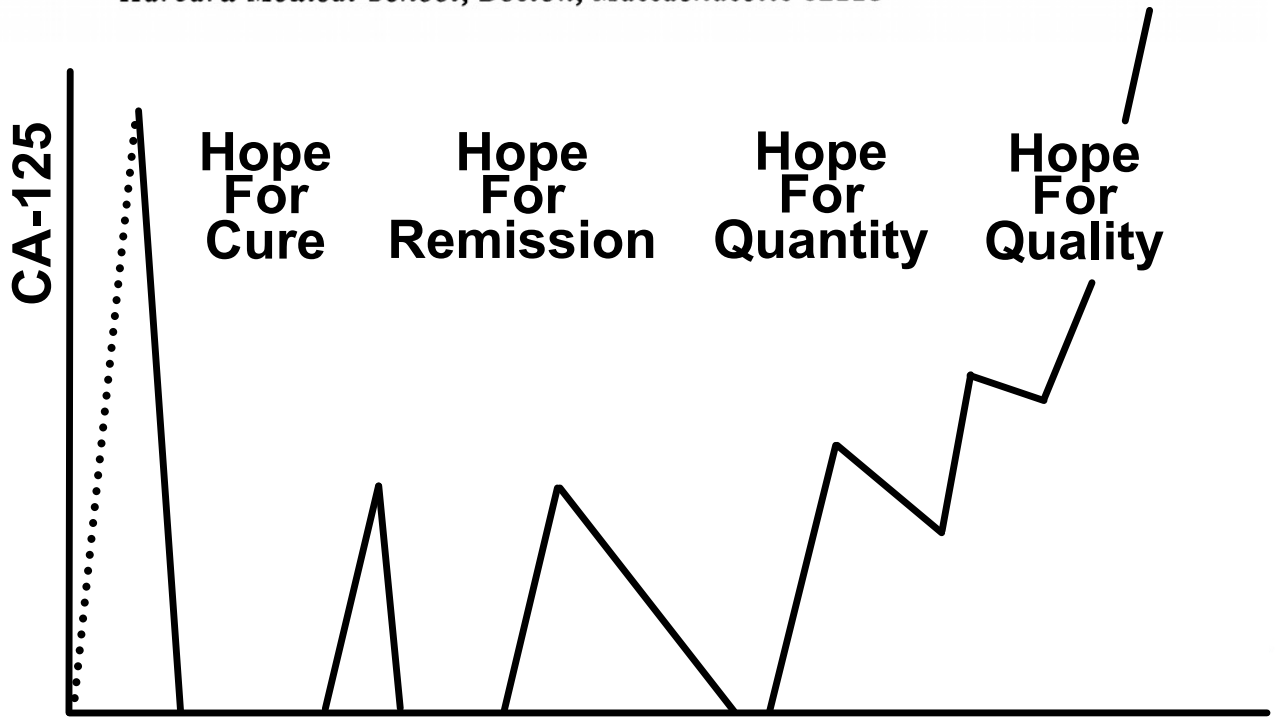


Mukherjee P, et al. Clin Cancer Res. 2001;7(3):848-55
Courtesy: Sandra Gendler PhD

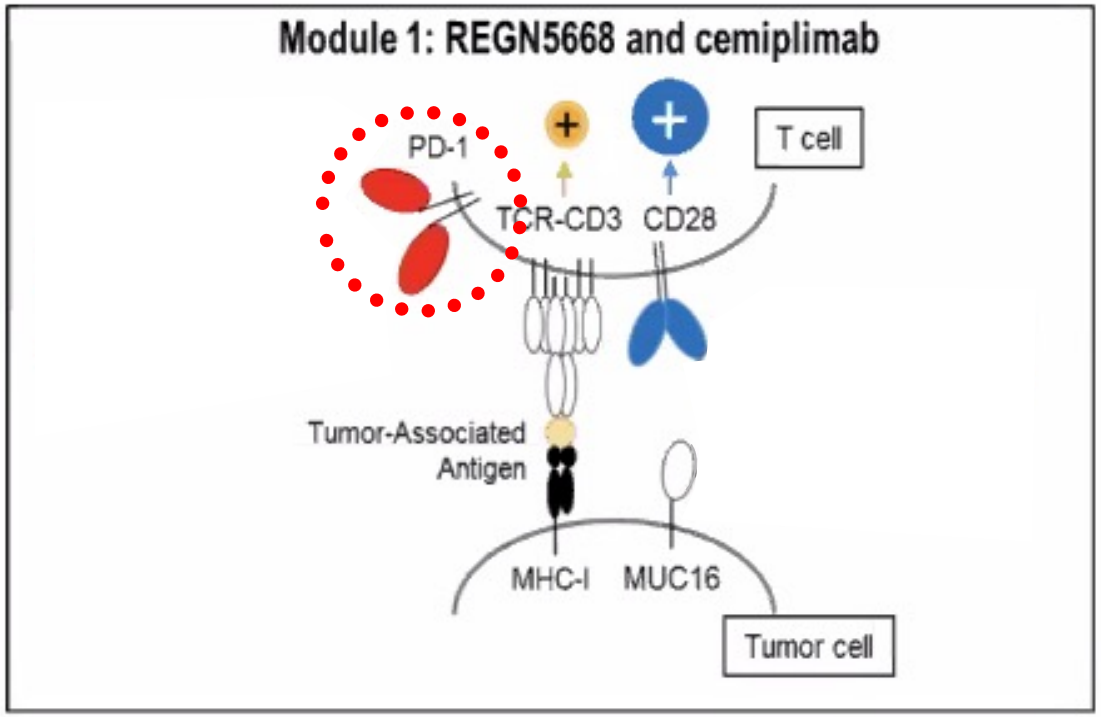
Bast RC, et al. J Clin Invest. 1981;68(5):1331–7

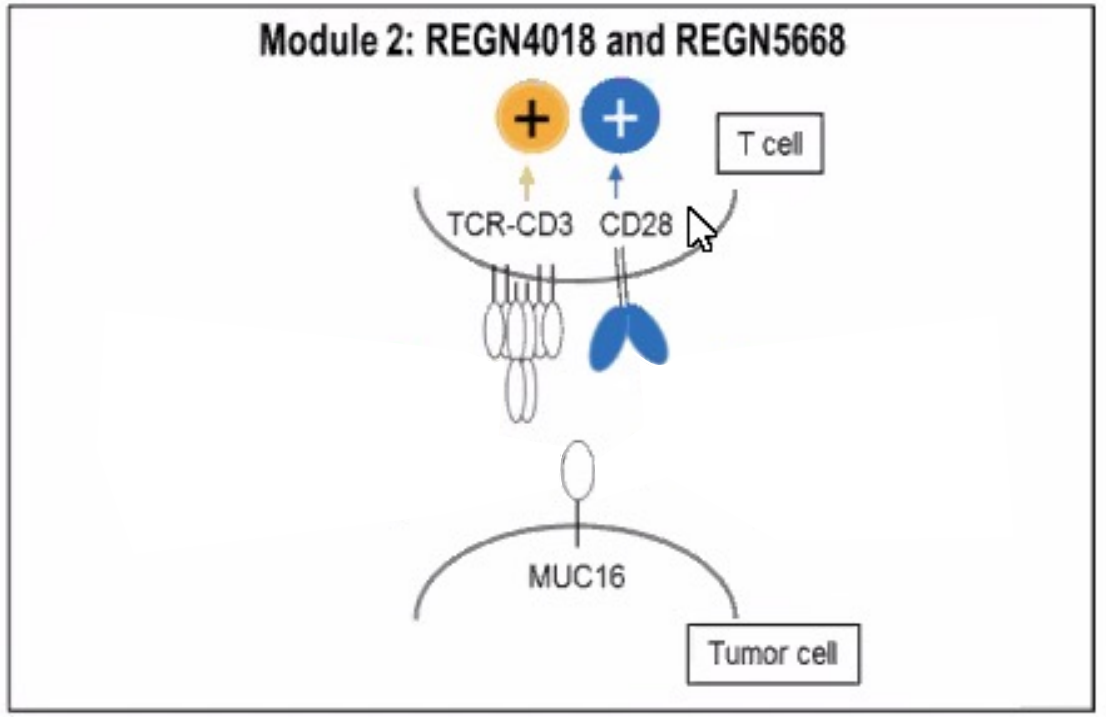
Reactivity of a Monoclonal Antibody with Human Ovarian Carcinoma

ROBERT C. BAST, JR., MARYELLEN FEENEY, HERBERT LAZARUS, LEE M. NADLER, ROBERT B. COLVIN, and ROBERT C. KNAPP, *Sidney Farber Cancer Institute, Brigham and Women's Hospital, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts 02115*



CA-125: Look How Far It's Come!





Gear Gas Gas Gear Gas

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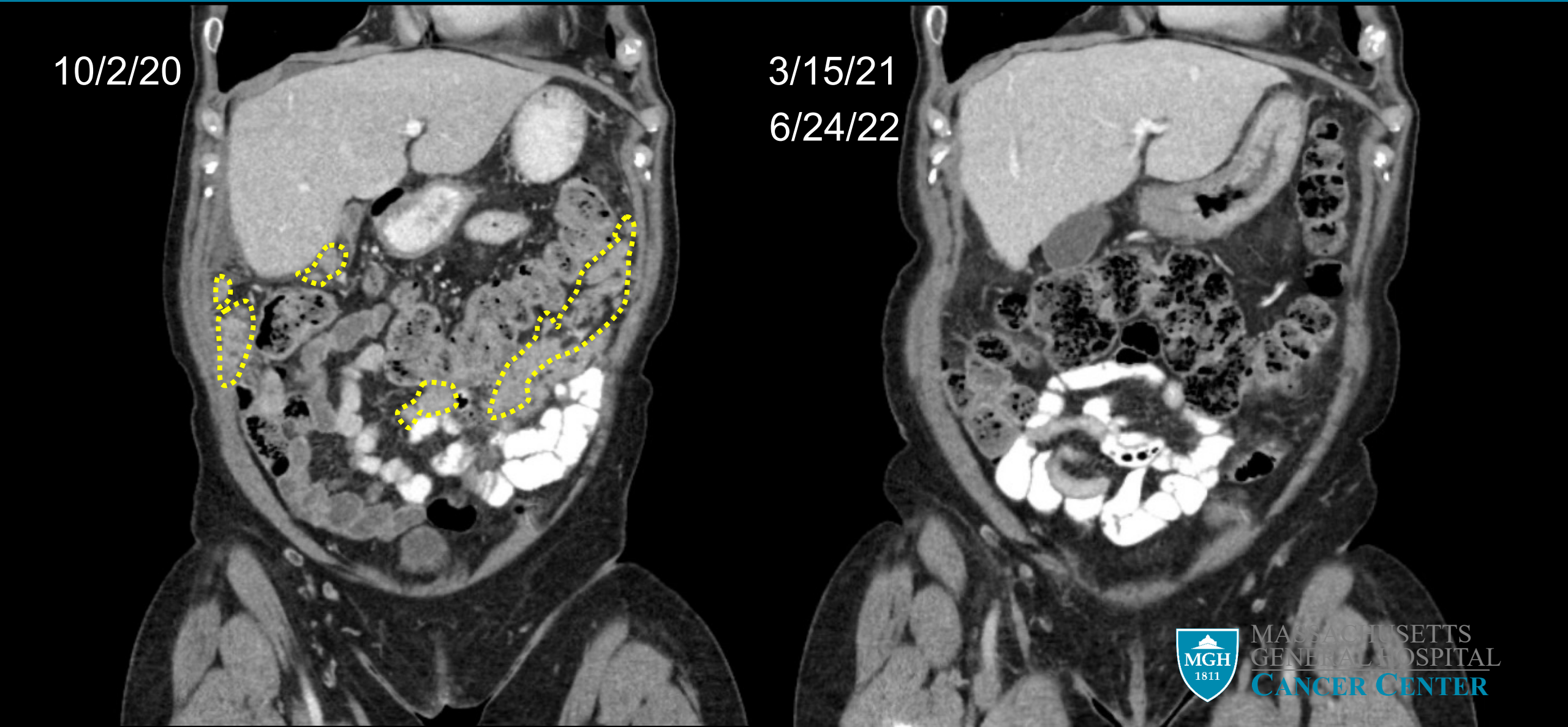
CA-125: Look How Far It's Come!



Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Ovarian Cancer

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2023 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Sunday, March 26, 2023

11:45 AM – 1:15 PM ET

Faculty

Mansoor Raza Mirza, MD

Amit M Oza, MD

Richard T Penson, MD, MRCP

Moderator

Joyce F Liu, MD, MPH

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John K Chan, MD
Sutter Cancer Research Consortium
San Francisco, California

Kellie E Schneider, MD
Novant Health Cancer Institute
Charlotte, North Carolina

Dana M Chase, MD
David Geffen School of
Medicine at UCLA
Los Angeles, California

Lyndsay J Willmott, MD
Virginia G Piper Cancer
Care Network
Phoenix, Arizona

Thomas P Morrissey, MD
Lynn Cancer Institute
Boca Raton, Florida

Neil Love, MD
Research To Practice
Miami, Florida

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Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Endometrial Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2023 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer®

Monday, March 27, 2023

11:45 AM – 1:15 PM ET

Faculty

Robert L Coleman, MD

Matthew A Powell, MD

Brian M Slomovitz, MD

Moderator

Shannon N Westin, MD, MPH

RTP RESEARCH TO PRACTICE

Thank you for joining us!

Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

In-person attendees can use the networked iPads® to claim CME credit.

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