

Updates in Ovarian Cancer

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Division of Gynecologic Oncology

2025 Multidisciplinary Cancer Update

October 9, 2025

Disclosures

None

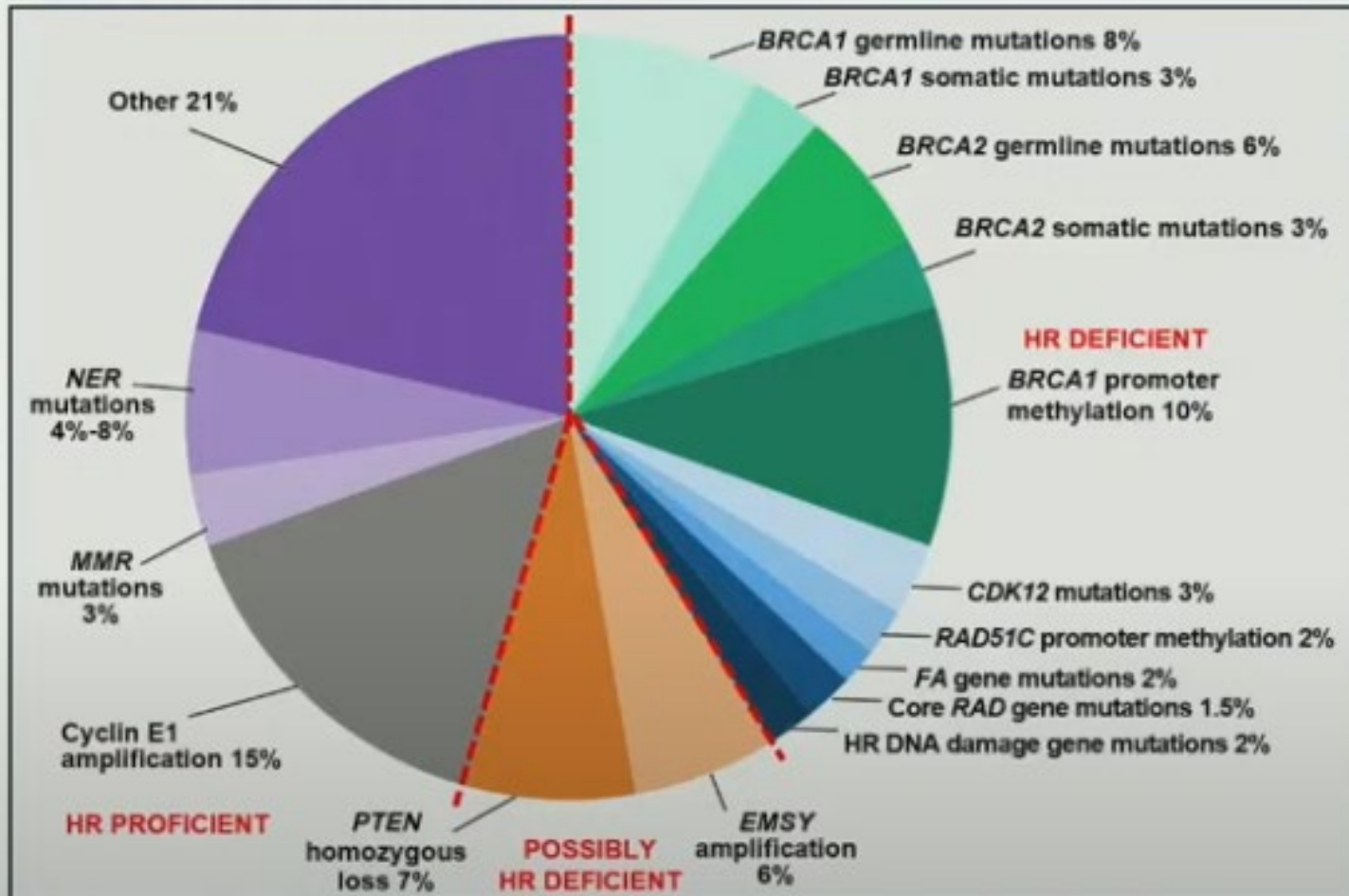
Agenda for Today:

1. Navigating Frontline Maintenance Options in Advanced Ovarian Cancer

2. The Evolving Landscape of ADCs in Ovarian Cancer

Navigating Frontline Maintenance Options in Advanced Ovarian Cancer

BRCA and Beyond in Advanced High-Grade Ovarian Cancer



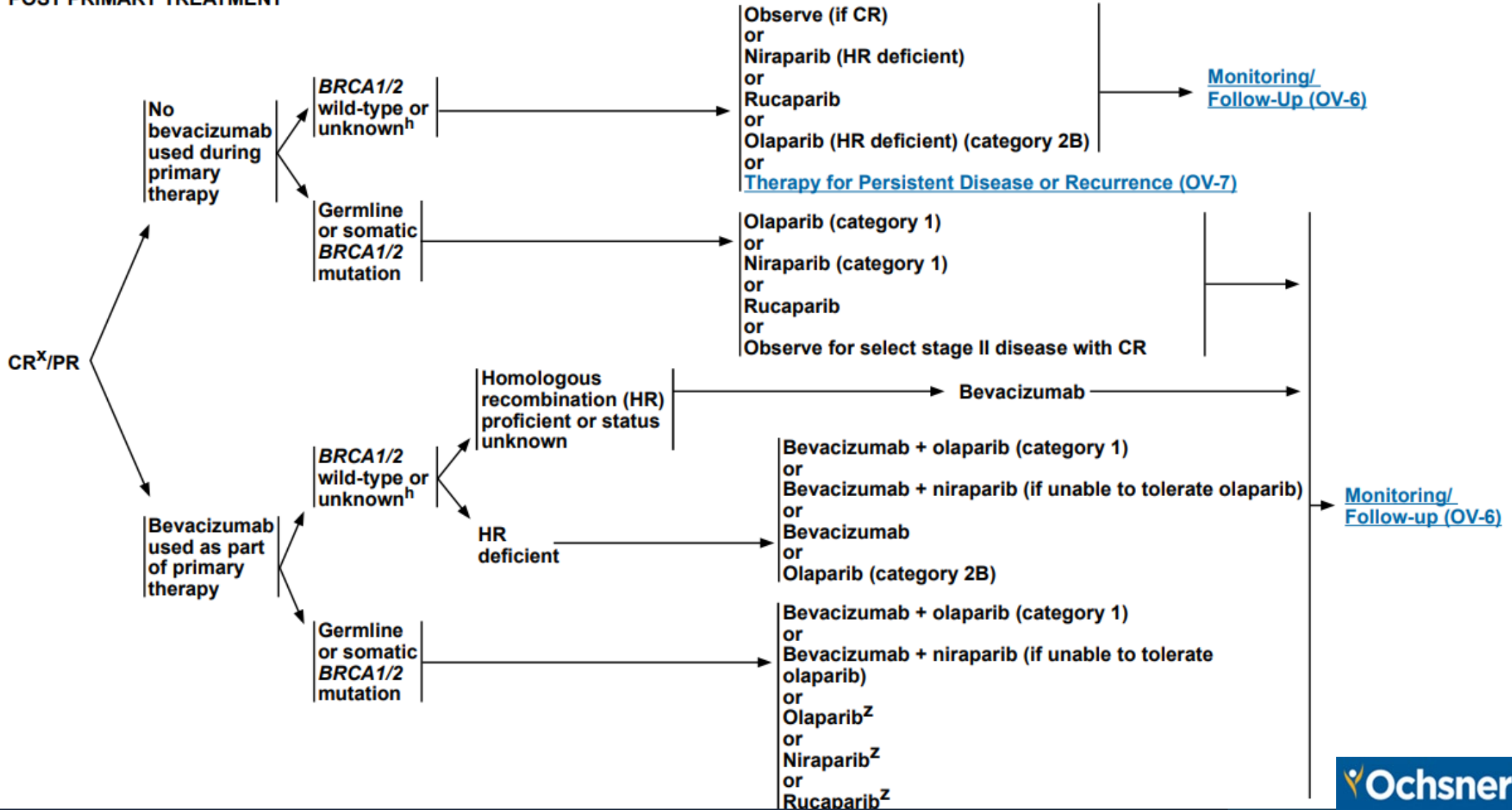
- Approximately 50% of patients with high-grade serous EOC are HRD¹
- *BRCA1* and *BRCA2* mutations are the most common alterations among those who are HRD
- Around 16% have a germline *BRCA* mutation²; 4% to 7% have a somatic *BRCA* mutation³
- *BRCA* mutation testing is essential in routine clinical practice^{4,5}

PARP inhibitors have clinical activity beyond *BRCAm* ovarian cancer

1. Konstantinopoulos PA et al. *Cancer Discov.* 2015;5:1137-1154. 2. George A et al. *Sci Rep.* 2016;6:29506. 3. Moschetta M et al. *Ann Oncol.* 2016;27:1449-1455. 4. Percival N et al. *Br J Nurs.* 2016;25:690-694. 5. George A et al. *Nat Rev Clin Oncol.* 2017;14:284-296.

STAGE II, III, IV^w
POST PRIMARY TREATMENT

MAINTENANCE THERAPY^{h,n,y}



What About Including a Checkpoint Inhibitor?

Future Directions in the Front Line: What is Potentially Exciting?

Trial	Size	Anti-angiogenic	PARPi	ICI	Start	Estimated Primary Completion
FIRST ^[a] ENGOT OV-44	1405	± Bevacizumab	Niraparib	Dostarlimab	Oct 2018	Jan 2023
DUO-O ^[b] ENGOT OV-46	~1254	Bevacizumab	Olaparib	Durvalumab	Jan 2019	June 2023
ATHENA ^[c] GOG-3020 ENGOT OV-45	~1000	-	Rucaparib	Nivolumab	May 2018	Dec 2024
ENGOT OV-43 ^[d] KEYLYNK 001	~1086	± Bevacizumab	Olaparib	Pembrolizuma b	Dec 2018	Aug 2025

- a. ClinicalTrials.gov. NCT03602859; b. ClinicalTrials.gov. NCT03737643; c. ClinicalTrials.gov. NCT03522246;

Combinations as Maintenance Therapy in the Frontline Setting

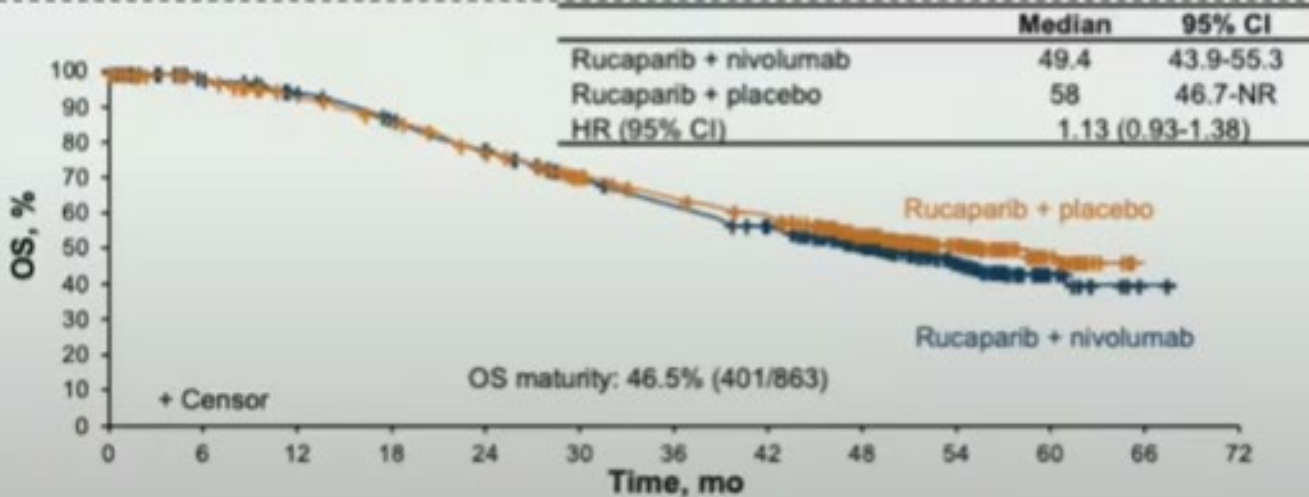
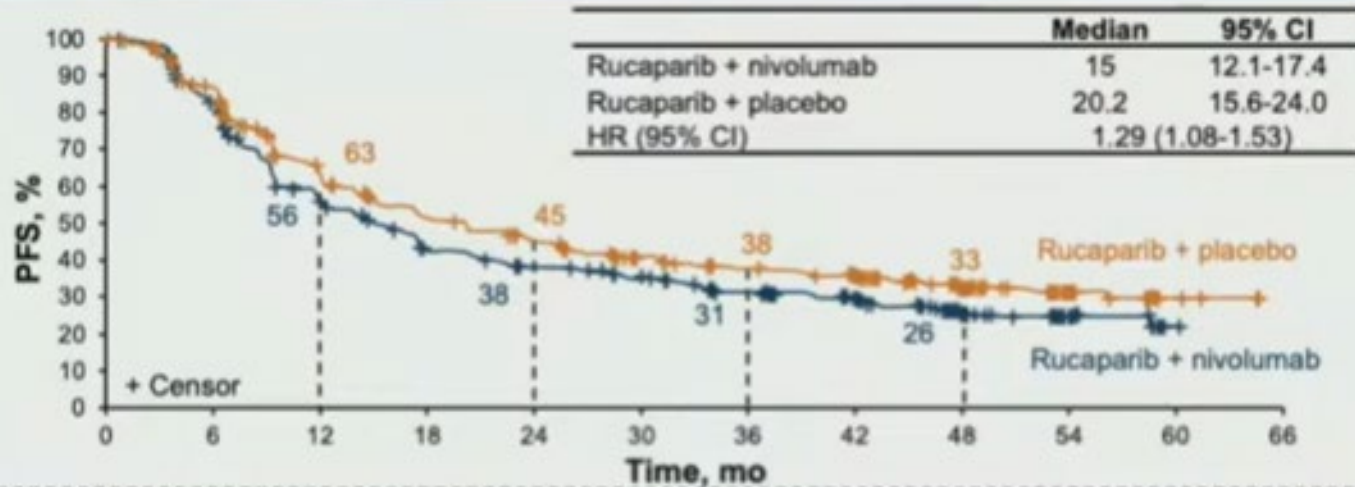
1L Maintenance Phase 3 Trial	Agent/Regimen	Status
ATHENA-COMBO ^{1,2}	Rucaparib + nivolumab	(N = 863) No improvement in PFS or OS
DUO-O ^{3,4}	Olaparib + durvalumab + chemotherapy + bevacizumab	(N = 1,130) Improved PFS
KEYLYNK-001 ^{5,6}	Olaparib + pembrolizumab + chemotherapy	(N = 1,367) Improved PFS No improvement in OS
FIRST ^{7,8}	Niraparib + dostarlimab + chemotherapy	(N = 1,402) Improved PFS No improvement in OS

1. <https://www.clinicaltrials.gov/study/NCT03522246>. 2. Monk BJ et al. ESMO 2024. LBA30.

3. <https://clinicaltrials.gov/study/NCT03737643>. 4. Harter P et al. ASCO 2023. LBA5506. 5. <https://www.clinicaltrials.gov/study/NCT03740165>.

6. Vergote I et al. *Int J Gynecol Cancer*. 2025;35:101704. 7. <https://clinicaltrials.gov/study/NCT03602859>. 8. <https://firstwordpharma.com/story/5922977>.

Phase 3 ATHENA-COMBO: PARPi + CPI as Switch Maintenance¹



- No difference in PFS or OS between treatment arms
 - Inclusion of CPI appears to have worsened outcomes
- Not a single subgroup favored the addition of CPI
 - Regardless of PD-L1 expression level, *BRCA* mutation status

Which takes us to optimization questions...

1. Monk BJ et al. ESMO 2024. LBA30.

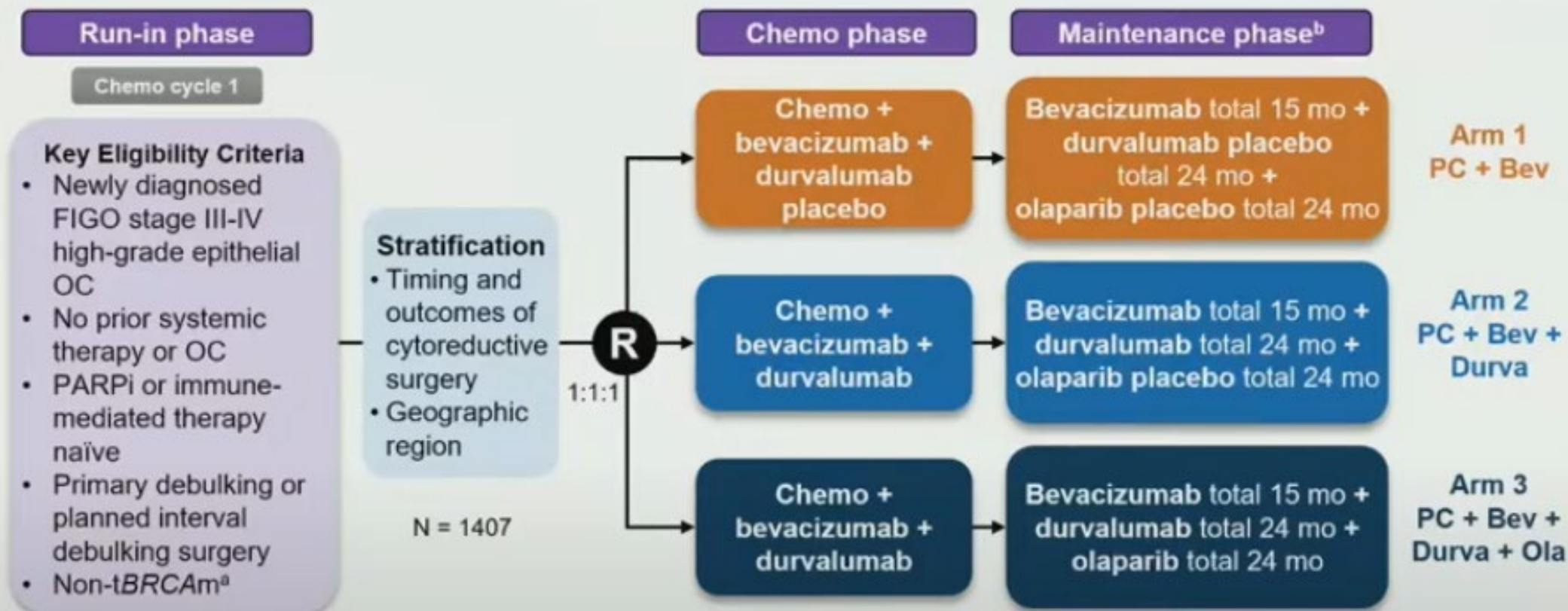
Was This Combination Optimized?

PARPi + CPI as Switch Maintenance: ATHENA COMBO¹

	Rucaparib + Nivolumab (n = 436)	Rucaparib + Placebo (n = 427)
Treatment received, n (%)		
Yes	410 (94)	425 (99.5)
No	26 (6)	2 (0.5)
Reason for discontinuation, n (%)		
Disease progression	180 (43.9)	182 (42.8)
AE	86 (21)	54 (12.7)
Completed protocol durations of study drug	103 (25.1)	147 (34.6)
Other	41 (10)	42 (9.9)

1. Monk BJ et al. ESMO 2024. LBA30.

Phase 3 DUO-O: Combination of Chemotherapy + Bevacizumab + Durvalumab ± Olaparib¹



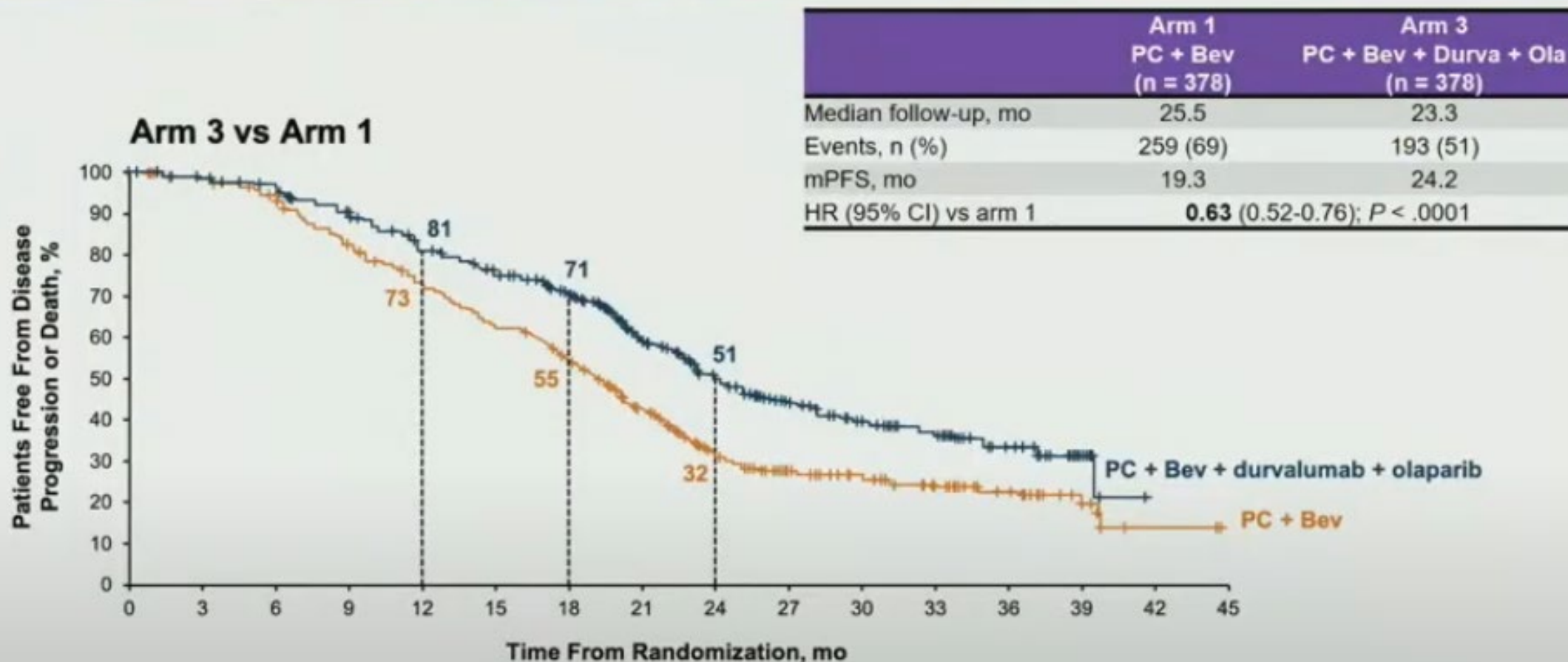
- Primary endpoint:** INV PFS: arm 3 vs arm 1 (non-tBRCA^a HRD+; ITT)
- Key secondary endpoints:** INV PFS: arm 2 vs arm 1 (ITT), OS, safety

^a DUO-O also included an independent, single-arm, open-label tBRCA^a cohort—results are not presented.

^b Treatment continued until disease progression, study treatment was complete, or other discontinuation criteria were met.

1. <https://www.clinicaltrials.gov/study/NCT03737643>.

DUO-O: PFS Primary Endpoint Met in the ITT Population¹



1. Harter P et al. ASCO 2023. Abstract LBA5506.

Phase 3 KEYLYNK-001: Combination of Chemotherapy + Pembrolizumab ± Olaparib^{1,2}

PARPi + CPI as switch and continuous maintenance respectively: *BRCAwt* only

SGO 2025 Update
Powell M et al.
3/15/25

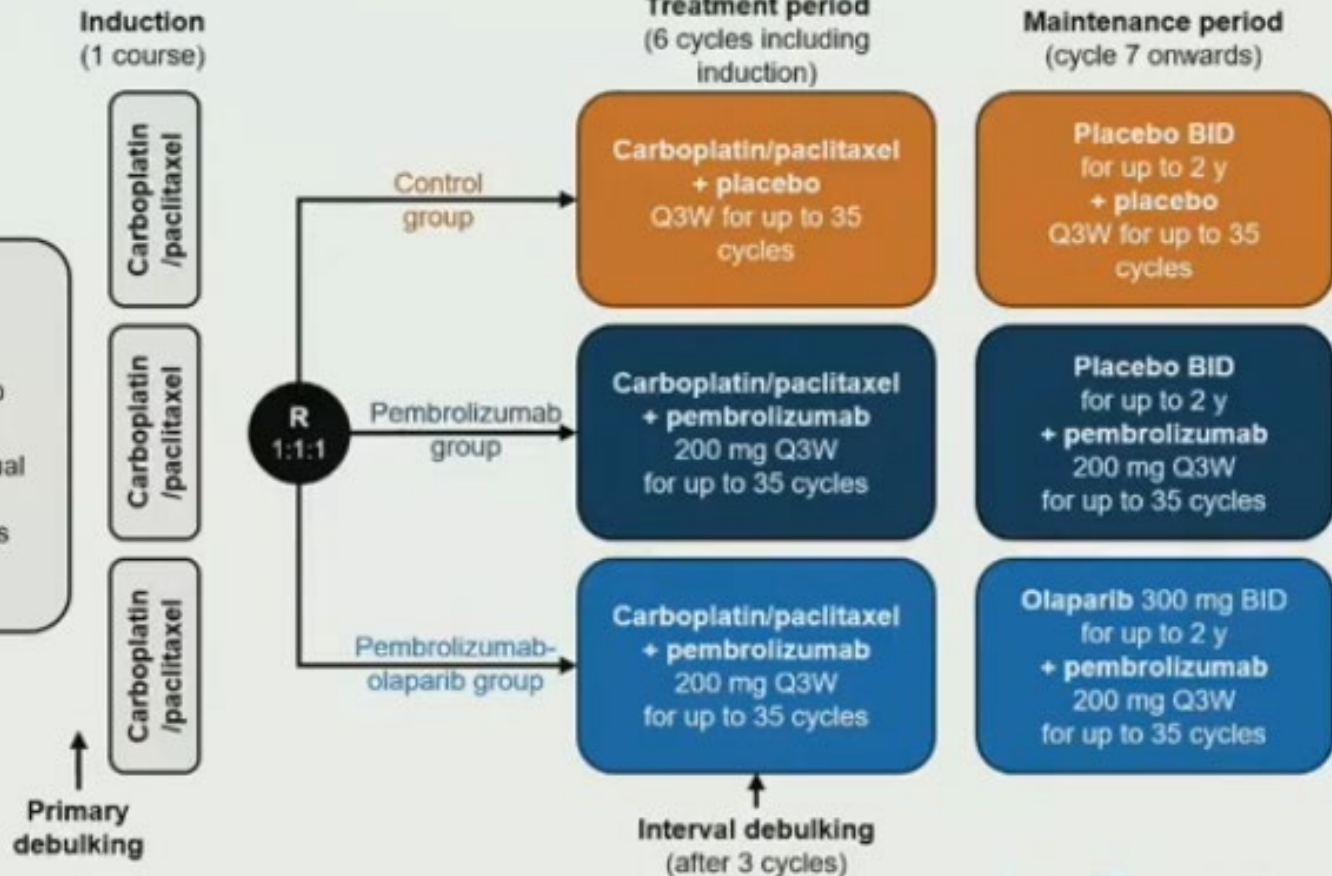
Key Eligibility Criteria

- Advanced (FIGO stage ≥III) epithelial ovarian cancer
- *BRCA1/2*-nonmutated
- No prior systemic therapy
- Candidate for carboplatin + paclitaxel as adjuvant or neoadjuvant therapy
- Bevacizumab permitted per investigator discretion

N = 1,367

Stratification

- PD-L1 expression (CPS ≥10 vs <10)
- Planned bevacizumab use (yes vs no)
- Surgery status (residual tumor after primary debulking surgery [yes vs no] or planned interval debulking)



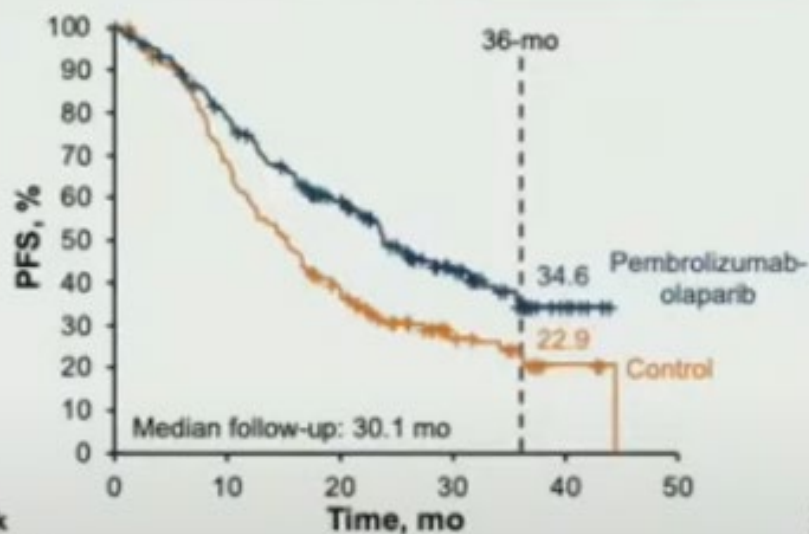
1. <https://www.clinicaltrials.gov/study/NCT03740185>. 2. Vergote I et al. *Int J Gynecol Cancer*. 2025;35:101704.

Phase 3 KEYLYNK-001: Combination of Chemotherapy + Pembrolizumab ± Olaparib¹

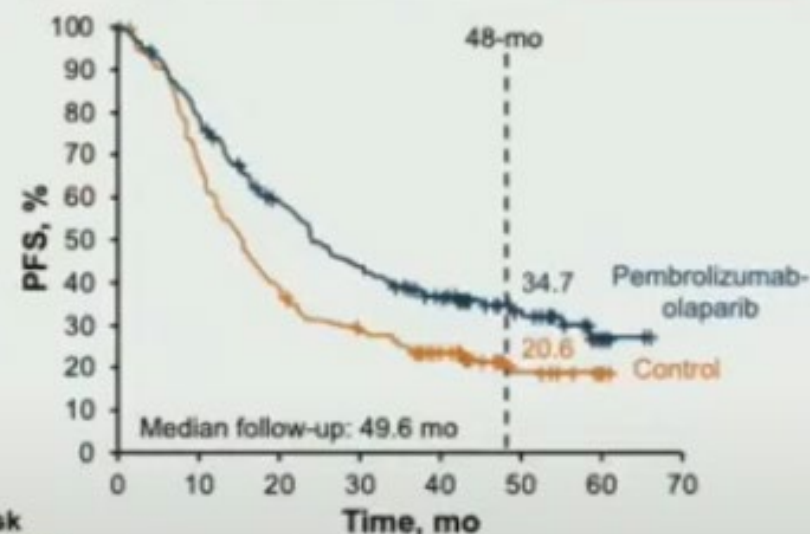
PFS Pembrolizumab-Olaparib vs Control, CPS ≥10 Population

IA1	Median, mo	Events, %	HR (95% CI)	P
Pembrolizumab -olaparib	23.7	48.9	0.63 (0.49-0.80)	<.0001
Control	15.2	66.2		

FA	Median, mo	Events, %	HR (95% CI)
Pembrolizumab -olaparib	23.9	58.5	0.66 (0.53-0.83)
Control	15.2	72.4	



No. at Risk	Time, mo					
Pembrolizumab -olaparib	229	161	103	40	9	0
Control	228	142	70	24	3	0



No. at Risk	Time, mo							
Pembrolizumab -olaparib	229	161	115	84	59	26	5	0
Control	228	142	81	58	37	14	2	0

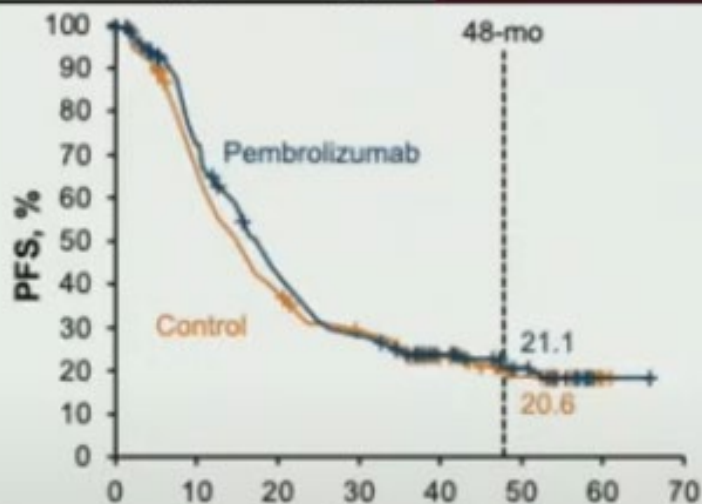
PFS is better, but what does this mean with no monotherapy PARPi arm?

1. Vergote I et al. *Int J Gynecol Cancer*. 2025;35:101704.

Phase 3 KEYLYNK-001: Combination of Chemotherapy + Pembrolizumab ± Olaparib¹

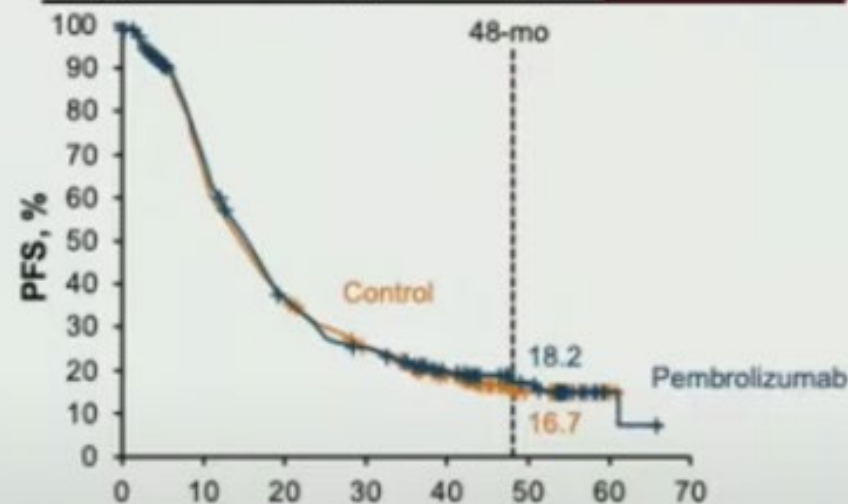
PFS Pembrolizumab vs Control at FA

CPS ≥10 Population	Median, mo	Events, %	HR (95% CI)	P
Pembrolizumab	17.3	69.6	0.95 (0.77-1.19)	.3339
Control	15.2	72.4		



No. at Risk	Time, mo							
	0	10	20	30	40	50	60	70
Pembrolizumab	230	150	85	56	33	17	1	0
Control	228	142	81	58	37	14	2	0

Total ITT Population	Median, mo	Events, %	HR (95% CI)
Pembrolizumab	15.2	73.8	1.01 (0.87-1.18)
Control	14.6	77.5	



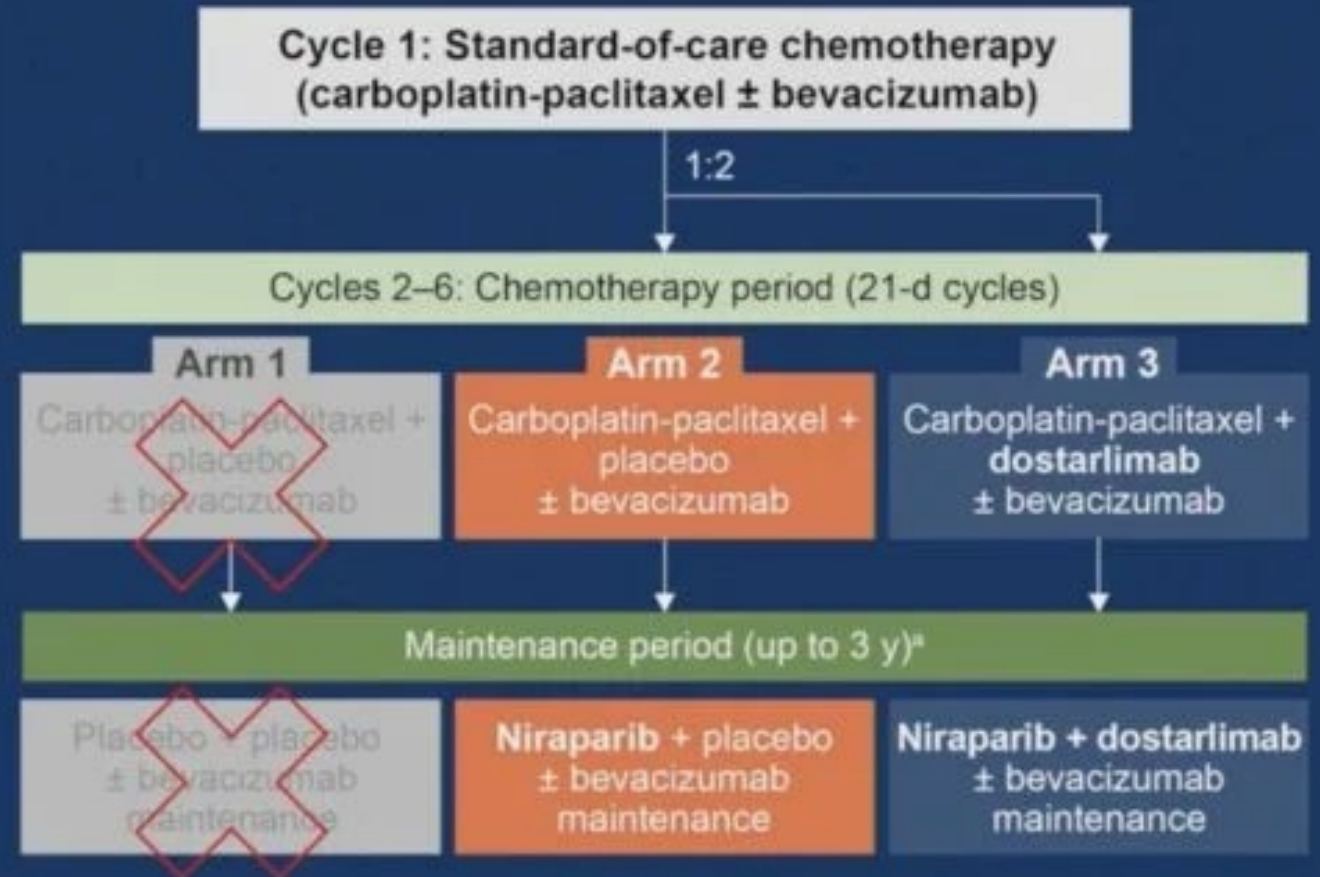
No. at Risk	Time, mo							
	0	10	20	30	40	50	60	70
Pembrolizumab	458	279	144	99	61	32	2	0
Control	454	285	157	106	64	26	3	0

No benefit of adding pembrolizumab vs placebo

1. Vergote I et al. *Int J Gynecol Cancer*. 2025;35:101704.

FIRST Trial Design

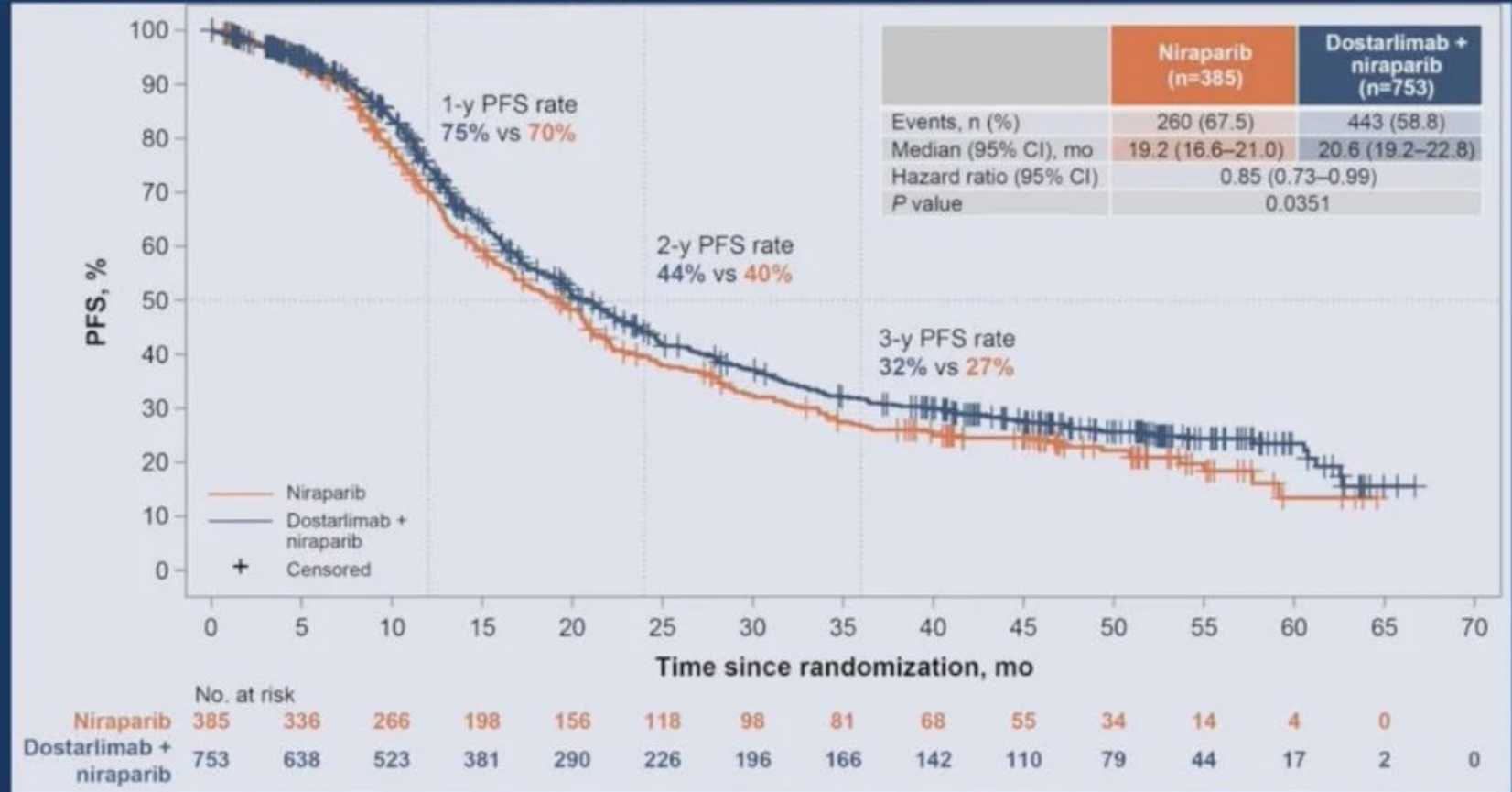
- Given ongoing PARPi maintenance clinical trials during the design of FIRST, it was an *a priori* intention to amend the protocol to redefine the control arm if emerging evidence supported the incorporation of PARPis during the maintenance period
- Following approvals of olaparib and niraparib as first-line maintenance therapy,^{1,2} enrollment into arm 1 was terminated



^aMay continue treatment beyond 3 years in consultation with the medical monitor. PARPi, poly(ADP-ribose) polymerase inhibitor. 1. González-Martín A, et al. *N Engl J Med* 2019;381(25):2391–2402. 2. Ray-Coquard I, et al. *N Engl J Med* 2019;381(25):2416–2428.

PFS per RECIST v1.1 in the ITT Population

Median duration of follow-up was 53.1 mo (IQR, 47.5–59.7 mo).

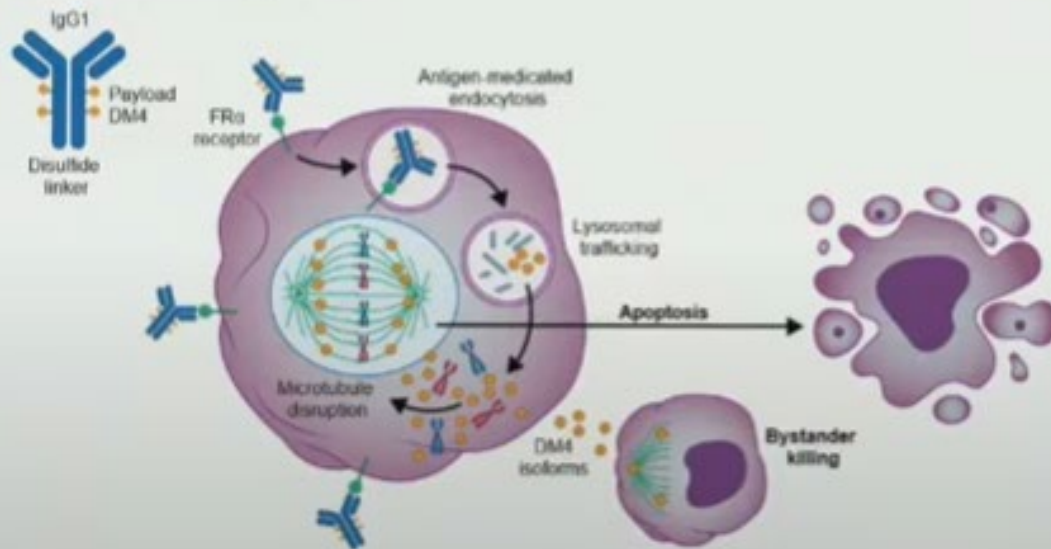


Data cutoff date: October 31, 2024. Curves estimated with Kaplan–Meier analyses. Hazard ratio and P value are from a stratified Cox proportional hazards model and log-rank test (2-sided), with treatment as only covariate, adjusted for randomization stratification factors. Reasons for nonadministrative censoring included no baseline/postbaseline tumor assessments, early study discontinuation without event, initiation of subsequent anticancer therapy before or without event, or 2 consecutive missed tumor assessments before event. The main contributor to nonadministrative censoring was initiation of subsequent anticancer therapy before or without event. CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

The Evolving Landscape of ADCs in Ovarian Cancer

Targeting FR α in Ovarian Cancer¹

- Folate receptor alpha (FR α): membrane protein that binds to and transports folate into cells and is highly overexpressed on ovarian cancer cells
- In high-grade serous ovarian cancer, approximately 80% of cells are positive for some expression of FR α
- FR α is most highly expressed on the surface of serous EOC, as assessed by IHC



Mirvetuximab Soravtansine (MIRV)

The antibody portion of MIRV binds to FR α found on the surface of epithelial ovarian cancer cells

MIRV is internalized via endocytosis

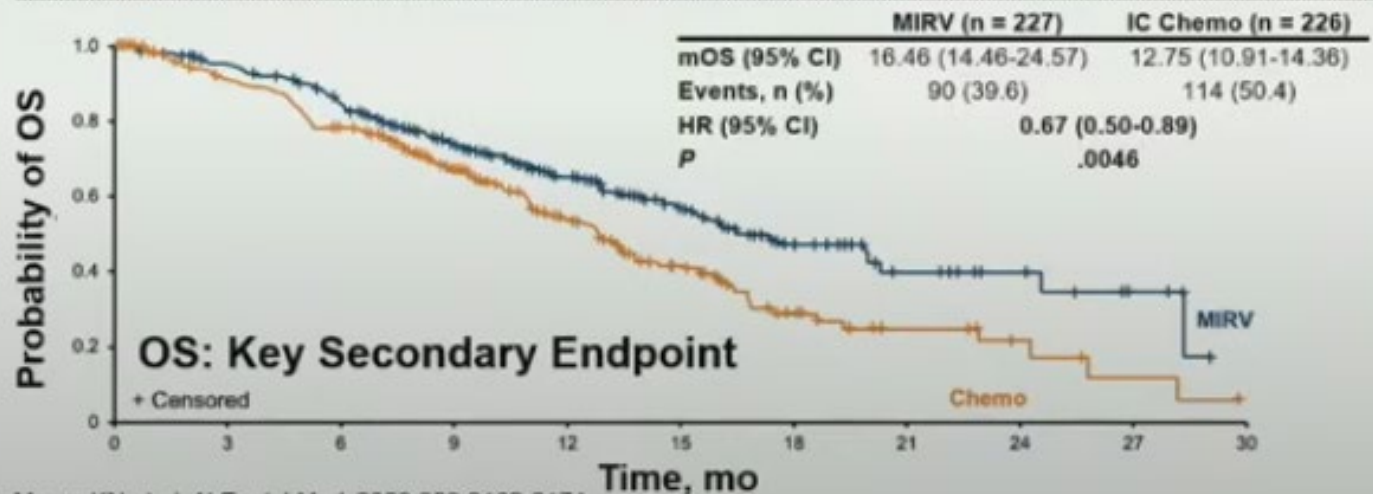
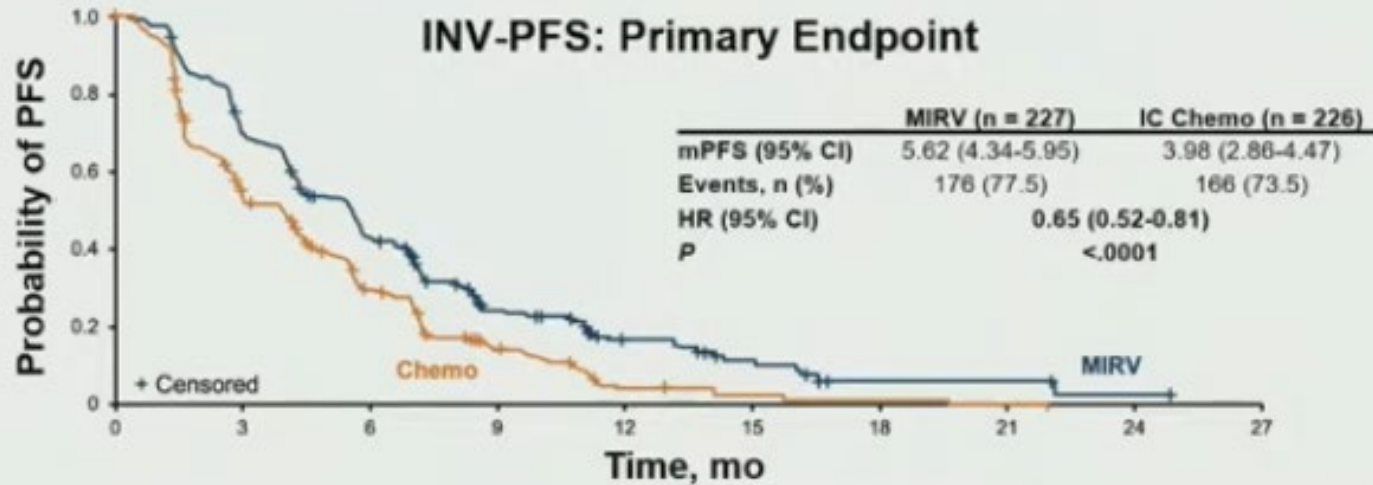
MIRV is degraded within the lysosome to release its cytotoxic payload (DM4)

DM4 disrupts tubulin resulting in mitotic arrest and apoptosis

DM4 also diffuses through the lipophilic cell membrane allowing bystander killing on adjacent tumor cells

1. Bax HJ et al. *Br J Cancer*. 2023;128:342-353.

Mirvetuximab Soravtansine Improved Outcomes in Platinum-Resistant Ovarian Cancer¹

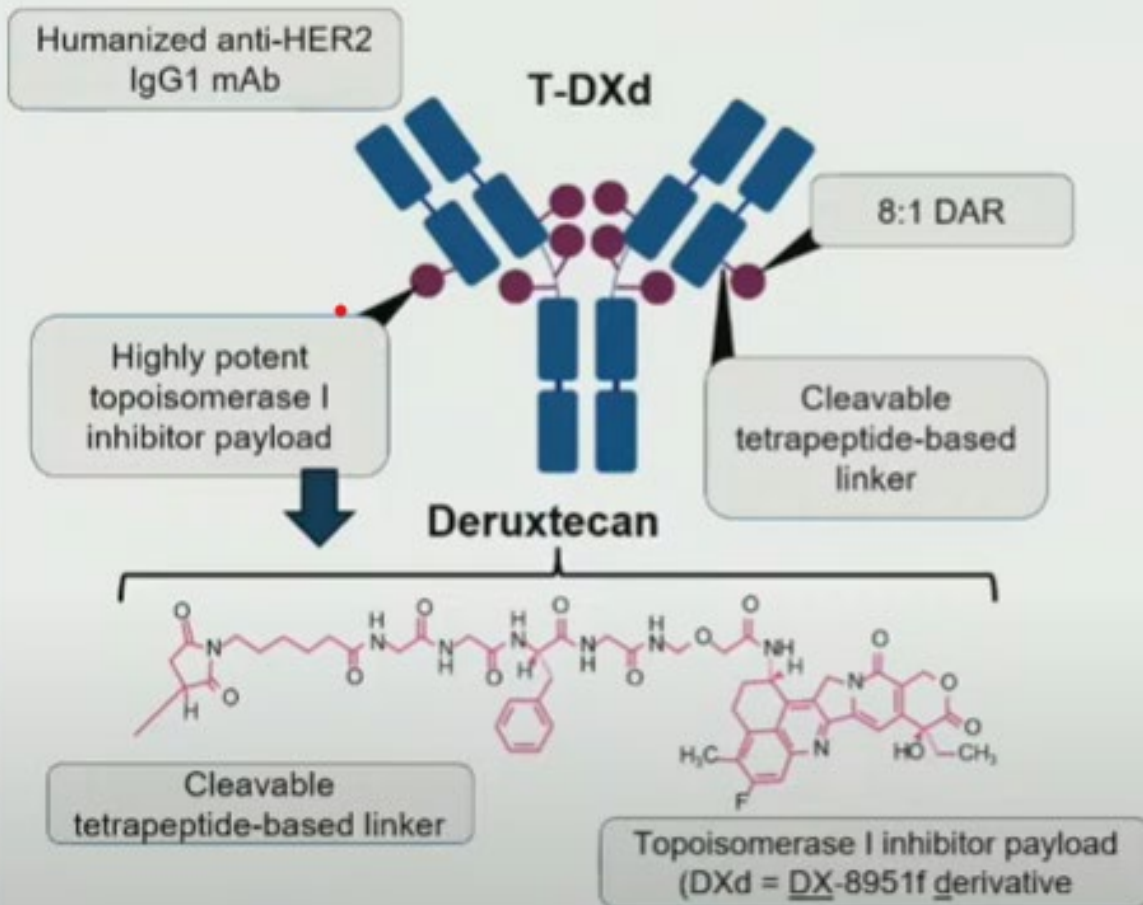


Phase 3 MIRASOL

- 35% improvement in PFS with MIRV vs chemotherapy
- 33% improvement in OS with MIRV vs chemotherapy
- ORR more than doubled: 42% vs 16% with MIRV vs chemotherapy ($P < .0001$; 12 CRs vs 0 CRs)

1. Moore KN et al. *N Engl J Med*. 2023;389:2162-2174.

Targeting HER2 in Ovarian Cancer¹⁻⁵



Trastuzumab Deruxtecan (T-DXd)

Payload MOA: topoisomerase I inhibitor
High potency of payload

High drug-to-antibody ratio ~8
Payload with short systemic half-life

Tumor-selective cleavable linker
Bystander antitumor effect

1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185. 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-5108.
3. Trail PA et al. *Pharmacol Ther*. 2018;181:126-142. 4. Okamoto H et al. *Xenobiotica*. 2020;50:1242-1250. 5. Nagi Y et al. *Xenobiotica*. 2019;49:1086-1096.

DESTINY-PanTumor02: T-DXd in HER2-Expressing Solid Tumors¹⁻⁴

An open-label, multicenter study (NCT04482309)

Key Eligibility Criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
 - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring)^b
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0-1

T-DXd
5.4 mg/kg
Q3W
40 per cohort^c



- **Primary endpoint:** confirmed ORR (investigator)
- **Secondary endpoints:** DOR, DCR, PFS, OS, safety
- **Exploratory analysis:** subgroup analysis by HER2 status

Baseline Characteristics

- 267 patients received treatment; 202 (75.7%) based on local HER2 testing
 - 111 (41.6%) patients were IHC 3+ based on HER2 test (local or central) at enrollment; primary efficacy analysis (all patients)
 - 75 (28.1%) patients were IHC 3+ on central testing; sensitivity analysis on efficacy endpoints (subgroup analyses)
- Median age was 62 years (23-85), and 109 (40.8%) patients had received ≥3 lines of therapy

^a Primary analysis data cutoff: June 8, 2023; median follow-up: 12.75 mo. ^b Patients were eligible for either test. All patients were centrally confirmed.

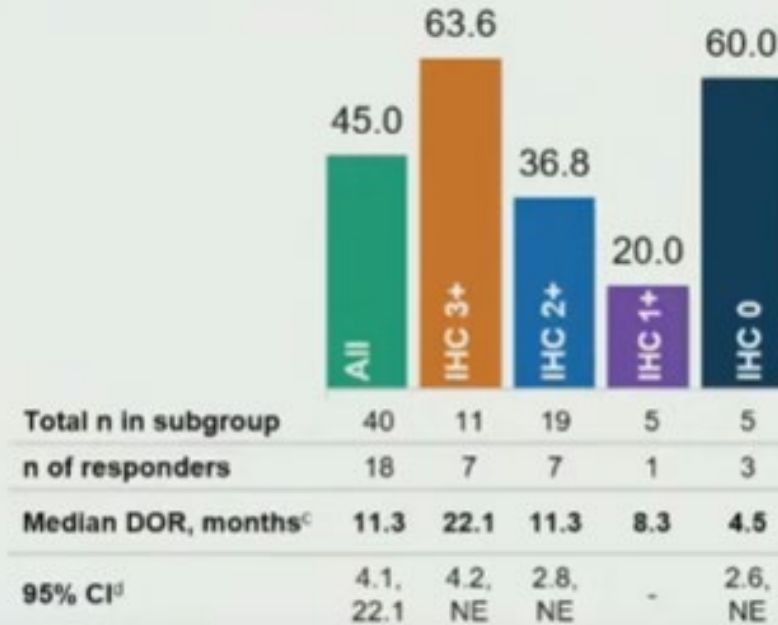
^c Planned recruitment, cohorts with no objective responses in the first 15 patients were to be closed. ^d Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, NSCLC, gastric cancer, and CRC.

1. <https://clinicaltrials.gov/study/NCT04482309>. 2. Hofmann M et al. *Histopathology*. 2008;52:797-805. 3. Meric-Bernstam F et al. ESMO 2023. Abstract LBA34.

4. Meric-Bernstam F et al. *J Clin Oncol*. 2024;42:47-58.

Responses With T-DXd in Ovarian Cancer by HER2 Status¹⁻³

Confirmed ORR by Investigator
(95% CI), %



Updated NCCN Guidelines for Ovarian Cancer⁴
Second- or subsequent-line therapy:
T-DXd for HER2-positive tumors (IHC 3+ or 2+)
Useful in certain circumstances

April 2024:
Accelerated Tumor-agnostic FDA Approval⁵
For adult patients with unresectable or metastatic
HER2-positive (IHC3+) solid tumors who have received
prior systemic treatment and have no satisfactory
alternative treatment options

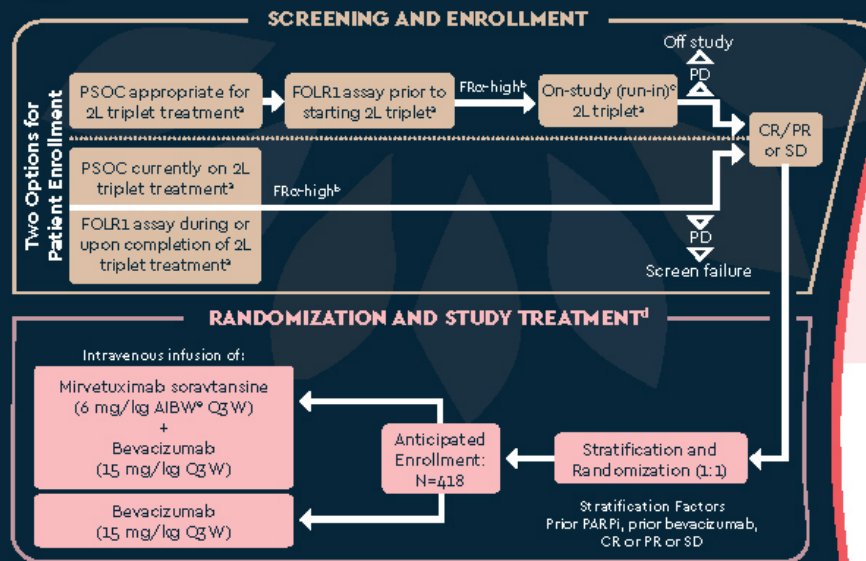
1. Meric-Bernstam F et al. *J Clin Oncol*. 2024;42:47-58. 2. Oaknin A et al. *Adv Ther*. 2024;41:4125-4139. 3. Lee J et al. *Int J Gynecol Cancer*. 2023;33:A6-A7.
4. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer. Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
5. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761139s032s035lbl.pdf.

Maintenance with Mirvetuximab Soravtansine plus Bevacizumab vs Bevacizumab in FR α -High Platinum-Sensitive Ovarian Cancer

David M. O'Malley, MD, Tashanna Myers, MD, Pauline Wimberger, MD, PhD, Toon Van Gorp, MD, PhD, Andrej Redondb, MD, PhD, David Cibula, MD, PhD, Shihani Nicum, PhD, Manuel Rodrigues, MD, PhD, Floor J. Baales, MD, Joyce N. Barlin, MD, Sharyn N. Lewin, MD, Peter Lim, MD, Bhavana Pothuri, MD, Elisabeth Diver, MD, Susana Banerjee, MBBS, PhD, Domenica Lorusso, MD, PhD

Rationale:

- FR α :** In ovarian cancer, 72% to 97% of patients have tumors that express FR α .
- MIRV** Mirvetuximab soravtansine-gynx (MIRV) is an FR α -targeting antibody-drug conjugate that received accelerated US FDA approval in November 2022 for the treatment of FR α -positive platinum-resistant ovarian cancer.
- MIRV + BEV** MIRV+bevacizumab demonstrated clinically meaningful activity in patients with platinum-sensitive and platinum-resistant ovarian cancer in the phase 1b/2 FORWARD II trial.



^aTriplet treatment consists of platinum plus chemotherapy plus bevacizumab for planned 6 cycles (minimum 4 and maximum 8 cycles), including at least 3 cycles of bevacizumab.

^bFR α -high is defined by FR α positivity of $\geq 75\%$ of tumor membrane staining at $\geq 2+$ intensity (PS $2+$).

^cFR α -high participants who desire to be treated and followed while on their run-in triplet therapy must sign a run-in consent as part of the main consent form if they meet eligibility criteria as assessed by the investigator.

^dMaintenance treatment must begin ≤ 12 weeks from last dose of triplet therapy and within 30 days of randomization. Treatment continues until PD, unacceptable toxicity, withdrawal of consent, death, or study sponsor termination.

*AIBW, also known as AdjBW, is calculated as IBW (kg) + 0.4 (actual weight - IBW). IBW for females is calculated as 0.9 \times height (cm) - 92.

GLORIOSA



Key Eligibility Criteria

- ✓ High-grade serous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
- ✓ Platinum-sensitive disease (defined as progression > 6 months from last dose of primary platinum therapy)
- ✓ Patients ≥ 18 years old
- ✓ FR α positivity detected by IHC with PS $2+$ intensity among $\geq 75\%$ of viable tumor cells
- ✓ 1 prior systemic treatment
- ✓ Prior PARPi required if BRCA+
- ✓ CR, PR, or SD after treatment with platinum-based doublet + bevacizumab



Outcomes Assessed

Primary Endpoint: Investigator-assessed PFS

Key Secondary Endpoint: OS

Other Secondary Endpoints: Safety and tolerability, PFS 2 , ORR, DOR, DFS, CA-125 response, patient-reported outcomes

Abbreviations: 2L, second-line; AdjBW, adjusted body weight; 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; FDA, US Food and Drug Administration; FOLR1, folate receptor 1; FR α , folate receptor alpha; IBW, ideal body weight; IHC, immunohistochemistry; MIRV, mirvetuximab soravtansine gynx; ORR, objective response rate; OS, overall survival; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor; PD, progressive disease; PFS, progression-free survival; PFS 2 , time from date of randomization until second disease progression or death, whichever occurs first; PR, partial response; PS $2+$, positive staining $2+$; PSOC, platinum-sensitive ovarian cancer; Q3W, 3 times per week; SD, stable disease.

Funding: This clinical trial is funded by ImmunoGen, Inc.

Additional Information

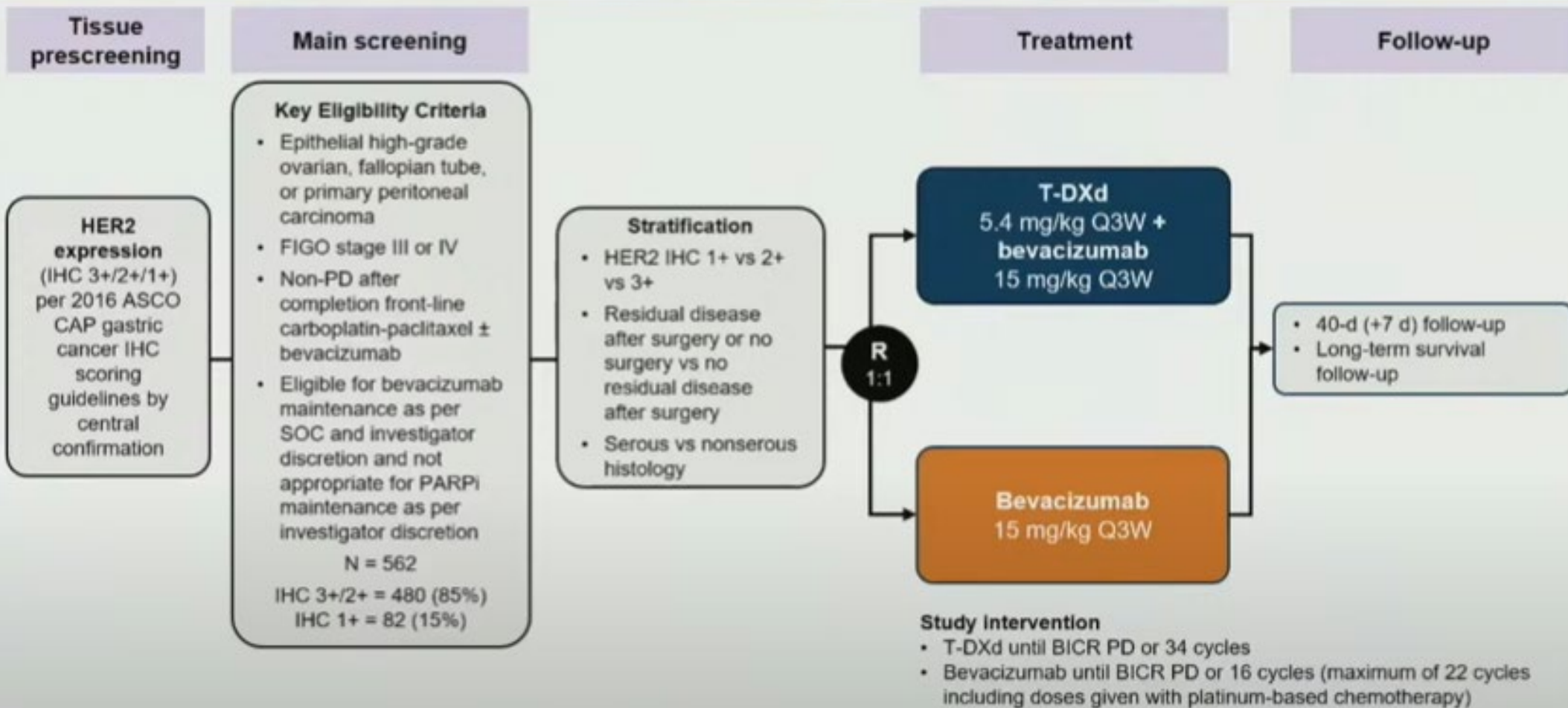
- This trial will be performed according to the principles of the Joint ENGOT and GOG Foundation requirements for trials with industry partners. A model C design will be utilized.

Trial Tracking Information

- ClinicalTrials.gov ID: NCT05445778
- ENGOT.ESGO.org ID: ENGOT-ov76
- GOG.org ID: GOG-3078



Phase 3 DESTINY-Ovarian01: T-DXd + Bevacizumab as 1L Maintenance Therapy in HER2-Expressing Ovarian Cancer¹



1. <https://clinicaltrials.gov/study/NCT06819007>; [ENGOT-ov89/GOG 3112].

Trial/Drug	Target	Payload
REFRaME-O1: Efficacy of Luveltamab Tazevibulin for FR α -Expressing Relapsed PROC	FR α	Microtubulin inhibitor, hemiasterlin
RainFol: Efficacy of Rina-S (Rinatabart Sesutecan) for Relapsed PROC	FR α	Topoisomerase 1 inhibitor
REJOICE-Ovarian01: Efficacy of R-DXd (Raludotatug deruxtecan) in PROC	Cadherin 6	Topoisomerase 1 inhibitor
TROPION-PanTumor03: Dato-DXd (Datopotamab Deruxtecan) in Ovarian Cancer Cohort	TROP2	Topoisomerase 1 inhibitor
TroFuse-005: Sac-TMT (Sacituzumab Tirumotecan) Efficacy in Ovarian Cancer	TROP2	Topoisomerase 1 inhibitor
DB-1305	TROP2	Topoisomerase 1 inhibitor

A 70-Year-Old Patient

Presentation	<ul style="list-style-type: none">• Recurrent, platinum resistant ovarian cancer referred for treatment options
PMH	<ul style="list-style-type: none">• Grade 2 HTN related to bevacizumab in her last line of therapy with PLD• 3 prior lines of cytotoxic chemotherapy
Testing	<ul style="list-style-type: none">• FR-alpha 2+ 80%• CDH6 present• Trop2 present• HER2 2+

- She is eligible for MIRV— would you start with this vs start with a camptothecin?
- Do you think sequencing will matter MIRV → Rina-S?
- How would you pick between TDXd, RDXd, DatoDXd?

Thank You
