Ovarian Cancer Treatment in the Post-PARP Inhibitor Era

Evolution, the Biology We Reshape, and What Comes Next in PSOC

Jennifer Scalici MD
Professor and Division Director Gynecologic Oncology
Department of Gynecology and Obstetrics
Emory University School of Medicine

2026 Debates and Didactics in Hematology and Oncology

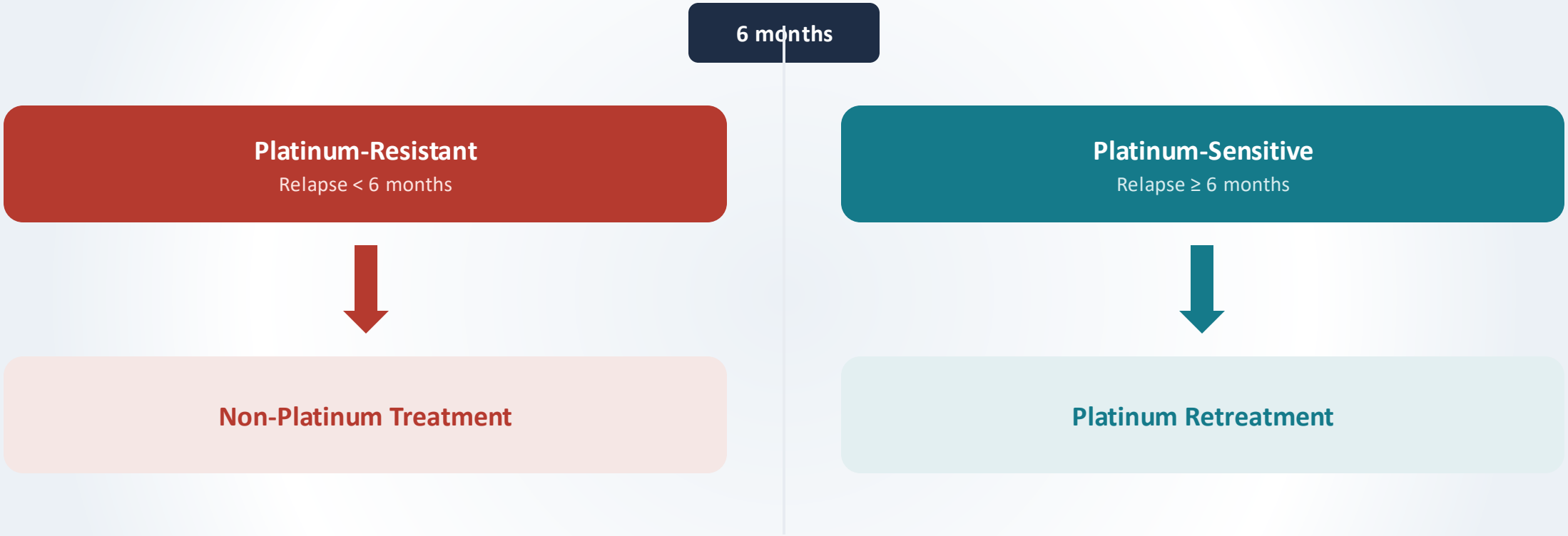
The PARPi Story: How We Got Here

From synthetic lethality to first-line standard of care

1

Recurrent Ovarian Cancer: The Traditional Paradigm

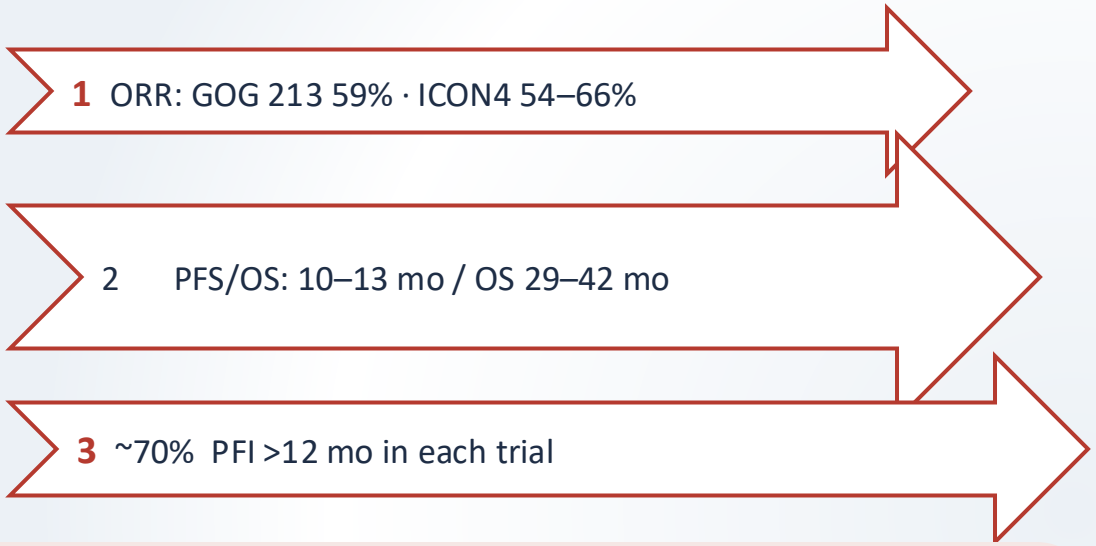
Recurrence is classified by the platinum-free interval — the time off platinum before relapse



Pre-PARP era classification based on the platinum-free interval (GCIG definition).

The Pre-PARPi Baseline: Where We Started

Frontline OS and recurrence benchmarks that shaped the field



Platinum ± Bevacizumab → Maintenance

- Platinum rechallenge response 55–65%
- PFS improved with bevacizumab maintenance
- OS-advantage signal (median OS 29–42 mo)

GOG213/ICON4: Recurrent Platinum sensitive Ovarian Cancer (PSOC)

- Pre-Parp inhibitor benchmark for mPFS/OS
- Highly favorable patient populations

GOG-172: Frontline IP therapy and OS signal

Armstrong et al. 2006: IP cisplatin + paclitaxel vs IV

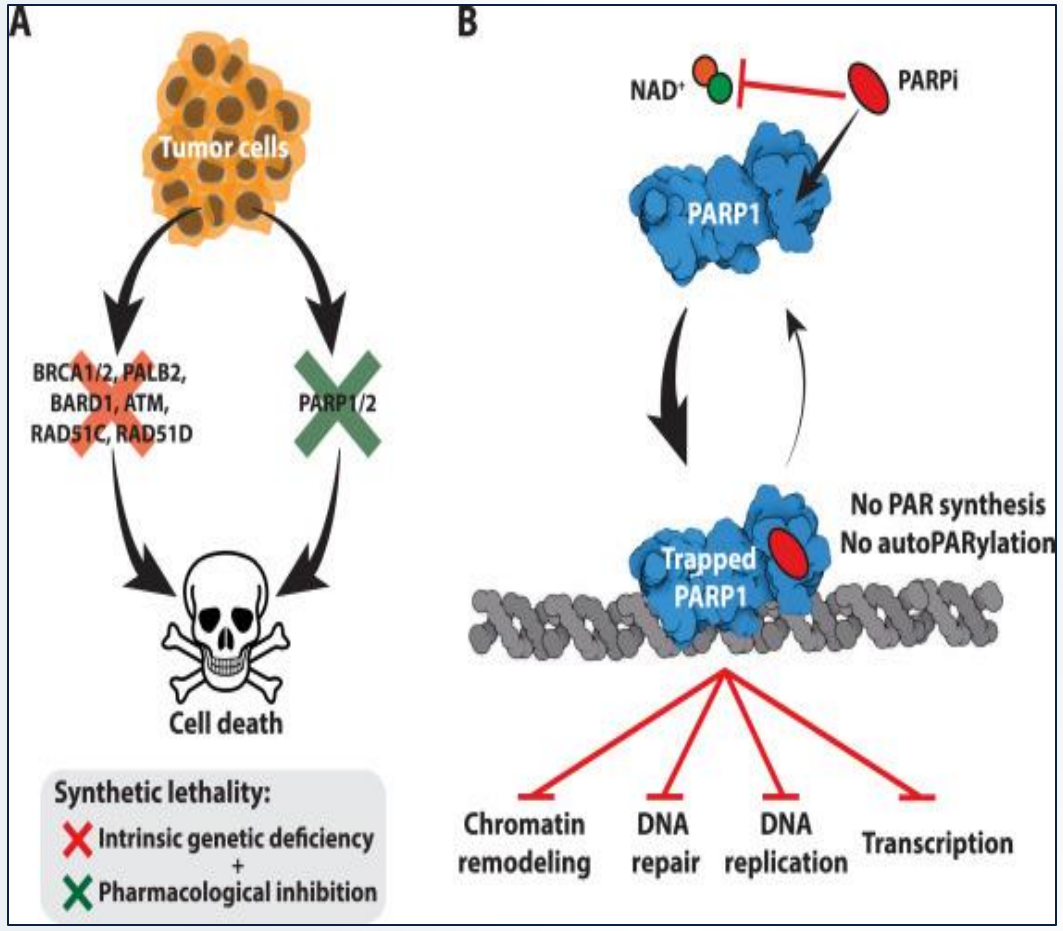
- **OS 65.6 vs 49.7 mo** (HR 0.75, p=0.03)
- Lesnock et al. 2013: in GOG-172, IP benefit was concentrated in **BRCA1-deficient tumors**.
- Frontline decision have shape long-term survival.

Buechel et al. Ann Oncol 2019; GOG 213; ICON4; Armstrong et al. NEJM 2006 (GOG-172); Lesnock et al. Br J Cancer 2013

Platinum after platinum in recurrence (PFI >12 months) works.

PARP Inhibitors: What Are They Actually Doing?

Beyond synthetic lethality — trapping, replication stress, and resistance



PARP Trapping

- PARP1 trapped on DNA; **inhibitor outcompetes NAD+**
- **Trapping does not fully correlate with efficacy**

Replication Speed / Okazaki Processing

- Replication fork processing accelerated
- Replication stress / fork collapse

Resistance

- **Reversion mutations**
- **Polθ (POLQ)** alternative end-joining buffers PARPi damage
- **PARG loss** effects PAR turnover, restores PARP1 function

Kanev PB, Atemin A, Stoynov S, Aleksandrov R. PARP1 roles in DNA repair and DNA replication: the basi(c)s of PARP inhibitor efficacy and resistance. Semin Oncol. 2024;51(1–2):2–18. doi:10.1053/j.seminoncol.2023.08.001

Frontline Maintenance PARPi:

Trial	Population	Active Arm	PFS Benefit	OS Signal
SOLO-1	BRCAm, newly diagnosed	Olaparib ×2 yrs	56.0 vs 13.8 mo (HR 0.30)	**7-yr OS: 67% vs 47%** **Median OS not reached vs 75 mos**
PAOLA-1	All comers after Bev	Olaparib + Bev	37.2 vs 17.7 mo HRD+ (HR 0.33)	HRD+: OS HR 0.62 ITT: no OS benefit
PRIMA	High risk All comer (HRD+/-, mBRCA), Stage IV, residual disease	Niraparib ×36 mos	ITT HR 0.62 · HRD HR 0.43	No OS benefit in any subgroup*

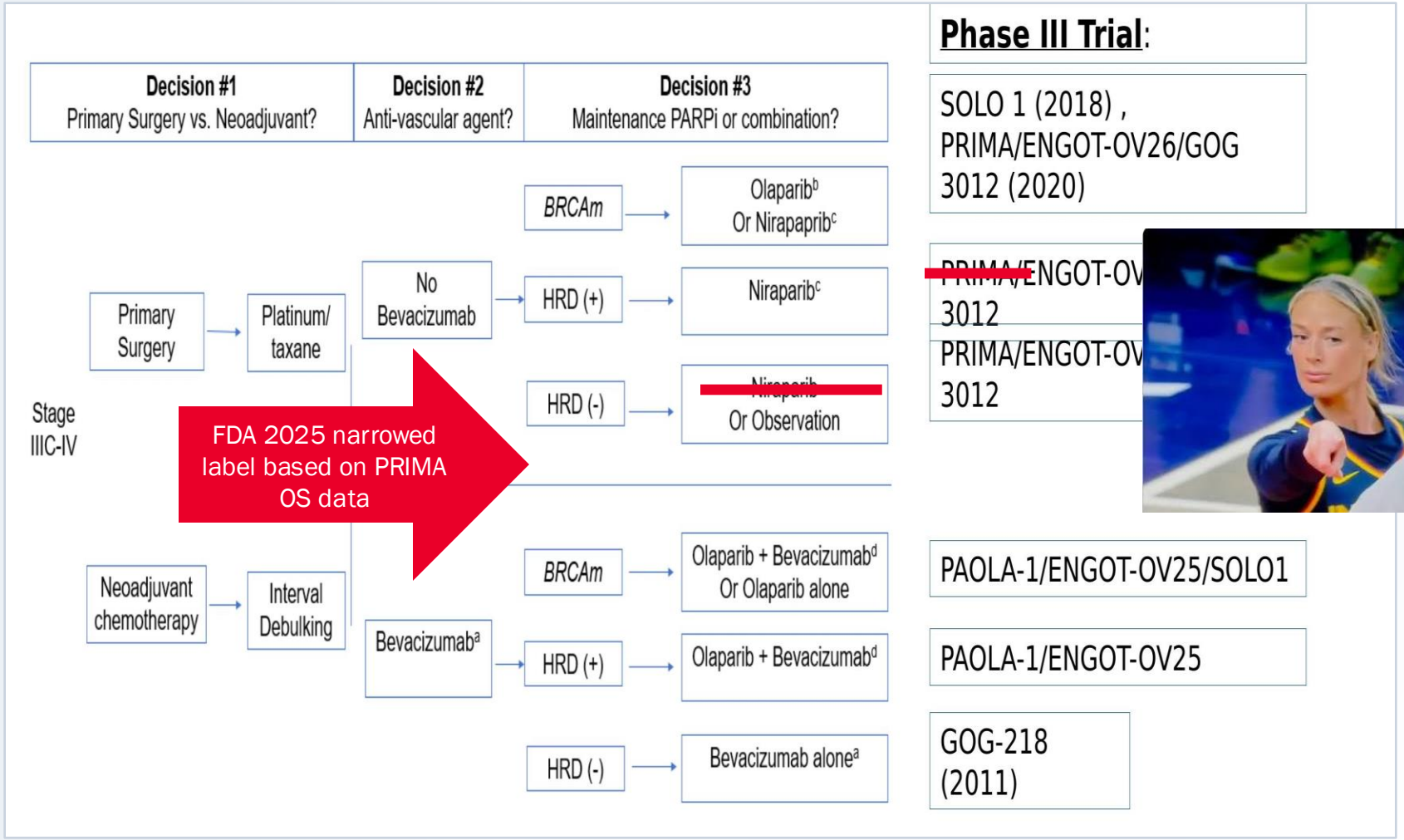
- SOLO-1 placebo (44% received subsequent PARP): **highest OS of any frontline trial** — above GOG-172.
- PRIMA (higher-risk, all-comer, 38% subsequent PARPi in placebo): **no statistically significant OS benefit**.

Population matters: Benefit is likely biomarker dependent.

SOLO-1: Moore et al., N Engl J Med 2018;379:2495–2505. PAOLA-1: Ray-Coquard et al., N Engl J Med 2019;381:2416–2428. PRIMA: González-Martín et al., N Engl J Med 2019;381:2391–2402. ATHENA-MONO: Monk et al., J Clin Oncol 2022;40:3952–3964.

PRIMA final OS (González-Martín et al., Ann Oncol 2024): overall 46.6 vs 48.8 mo (HR 1.01); HRD 71.9 vs 69.8 (HR 0.95); HRP 36.6vs 32.2 (HR 0.93) — no subgroup showed OS benefit.

Biomarker-Directed Frontline Treatment: The Decision Tree



Three decisions at every 1L encounter

1. Primary surgery vs neoadjuvant
2. Add bevacizumab or not?
3. Which maintenance? (biomarker-driven)

SOLO-1 · PRIMA · PAOLA-1
ATHENA-MONO · GOG-218

Chan et al. Gynecologic Oncology, Volume 159, Issue 3, December 2020, Pages 604–606

Partners for Advancing Clinical Education
Bio Ascend

New Rules:
PARPi exposure imprints recurrent disease

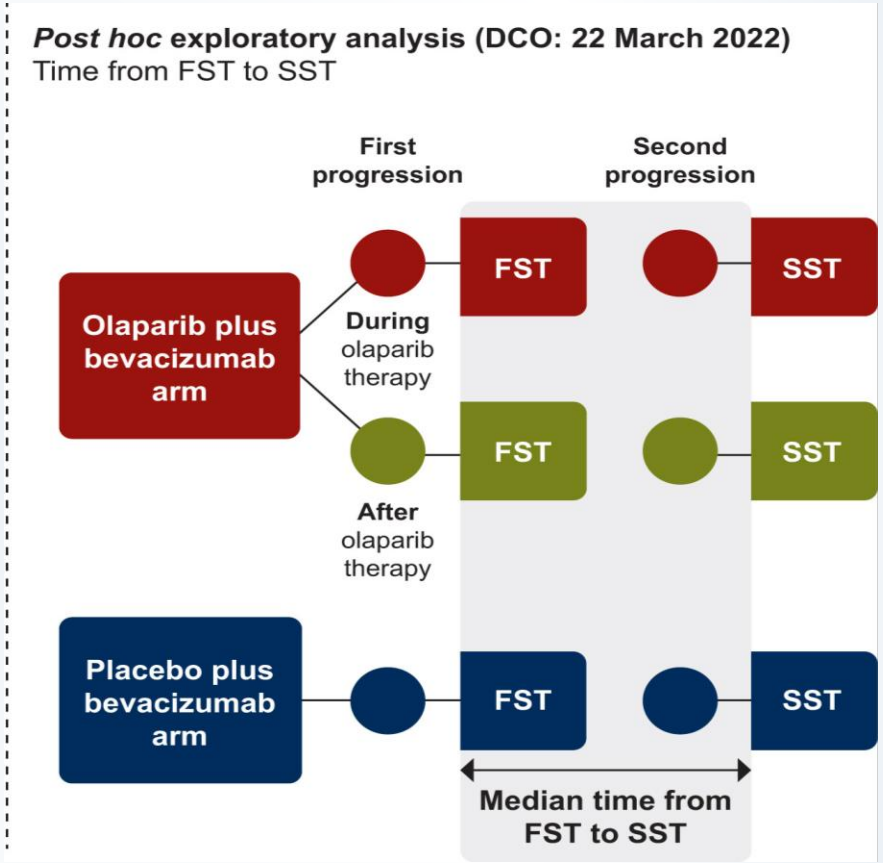
2

Efficacy of Subsequent therapy after progression on 1st line PARP maintenance: The PAOLA experience

Harter et al.

- ALL COMER POPULATION AFTER BEV
  - Post-hoc analysis of ΔPFS (FST-SST)
  - Progression stratified (HRD+/BRCAm)
  - During Olaparib maintenance
  - After Olabarib maintenance

- Platinum Combination as First Subsequent Therapy:
  - 64% Olap+Bev
  - 35% placebo + Bev

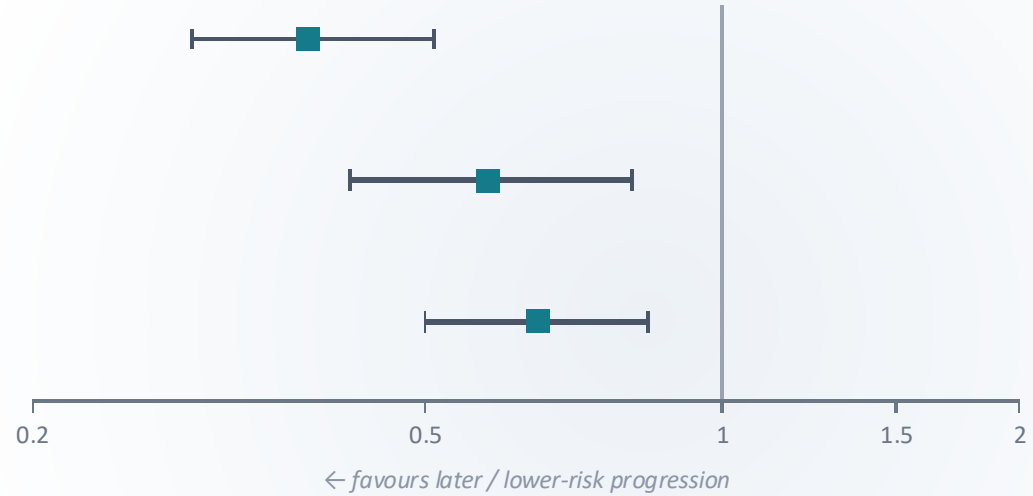


Harter, P.Bogner, Gerhard et al.Efficacy of subsequent therapies in patients with advanced ovarian cancer who relapse after first-line olaparib maintenance: results of the PAOLA-1/ENGOT-ov25 trial Annals of Oncology, Volume 36, Issue 2, 185 - 196

What happens to the Platinum-Free Interval?

PAOLA-1/ENGOT-ov25 · post-hoc exploratory analysis (DCO Mar 2022): subsequent-therapy PFS2 (FST→SST) after progression on 1L olaparib + bevacizumab.

Independent prognostic factor	HR from multivariable analysis (95% CI)	Event rate, n/N (%)	
PFI ≥12 vs <12 months	**0.38 (0.29–0.51)**	≥12 mo: 212/250 (85%) <12 mo: 87/88 (99%)
Lower vs higher risk of progression	**0.58 (0.42–0.81)**	Lower: 44/60 (73%) Higher: 255/278 (92%)
Progression after vs during olaparib	**0.65 (0.50–0.84)**	After: 114/145 (79%) During: 184/192 (96%)

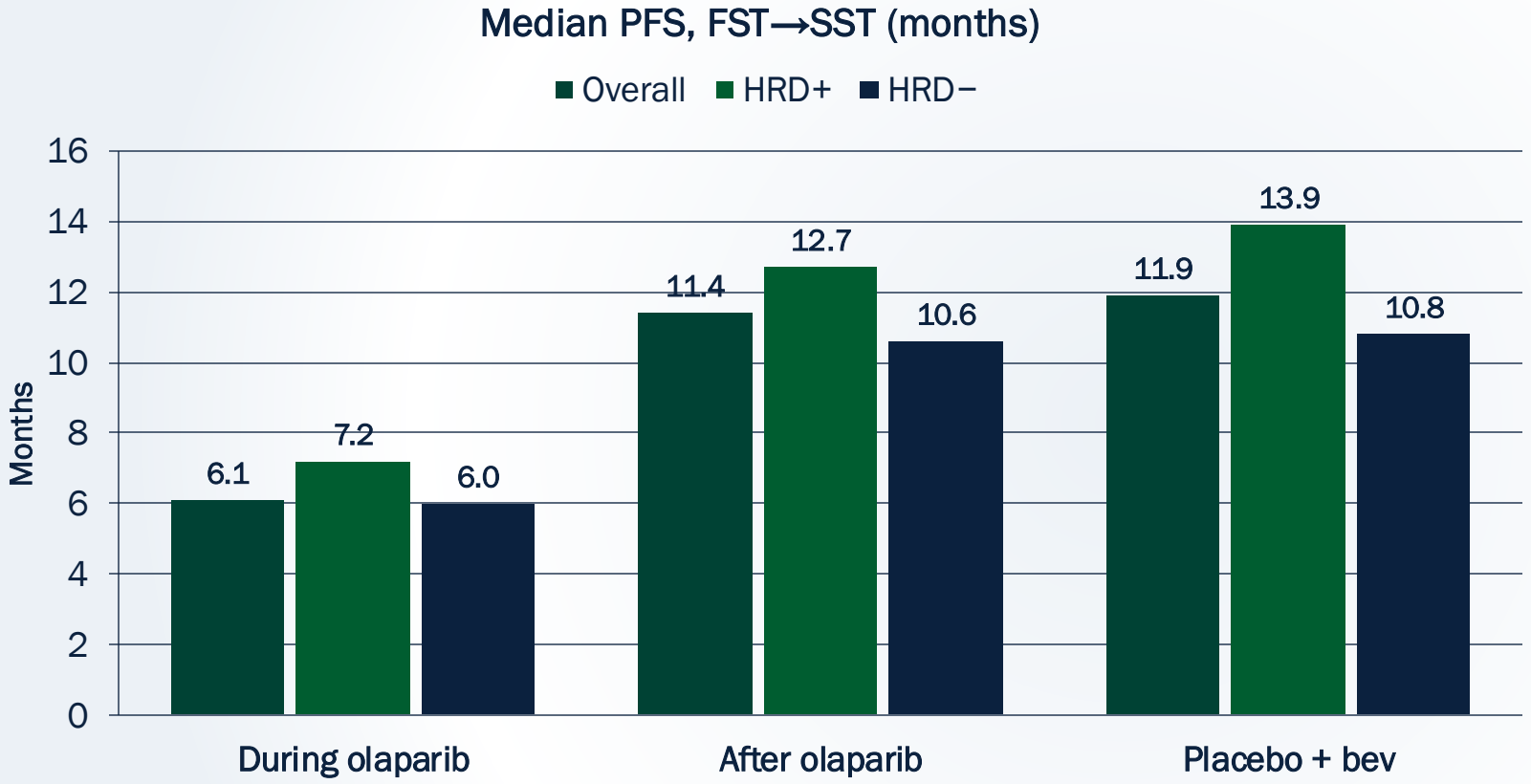


- **PFI ≥12 mo remains strongly prognostic (HR 0.38),**
- **Progression after vs during PARP is independently prognostic (HR 0.65).**

Harter P, et al. Subsequent-therapy efficacy after 1L olaparib maintenance — PAOLA-1/ENGOT-ov25. Ann Oncol. 2024;36(2):185–196.

Platinum Responsiveness following PARPi Exposure: post-hoc PAOLA-1

Median PFS from first to second subsequent therapy (FST→SST), by progression timing and HRD status



Progression DURING olaparib

Behaves platinum-resistant · median ~6–7 mo · HR vs placebo+bev 2.1–2.3

Progression AFTER olaparib

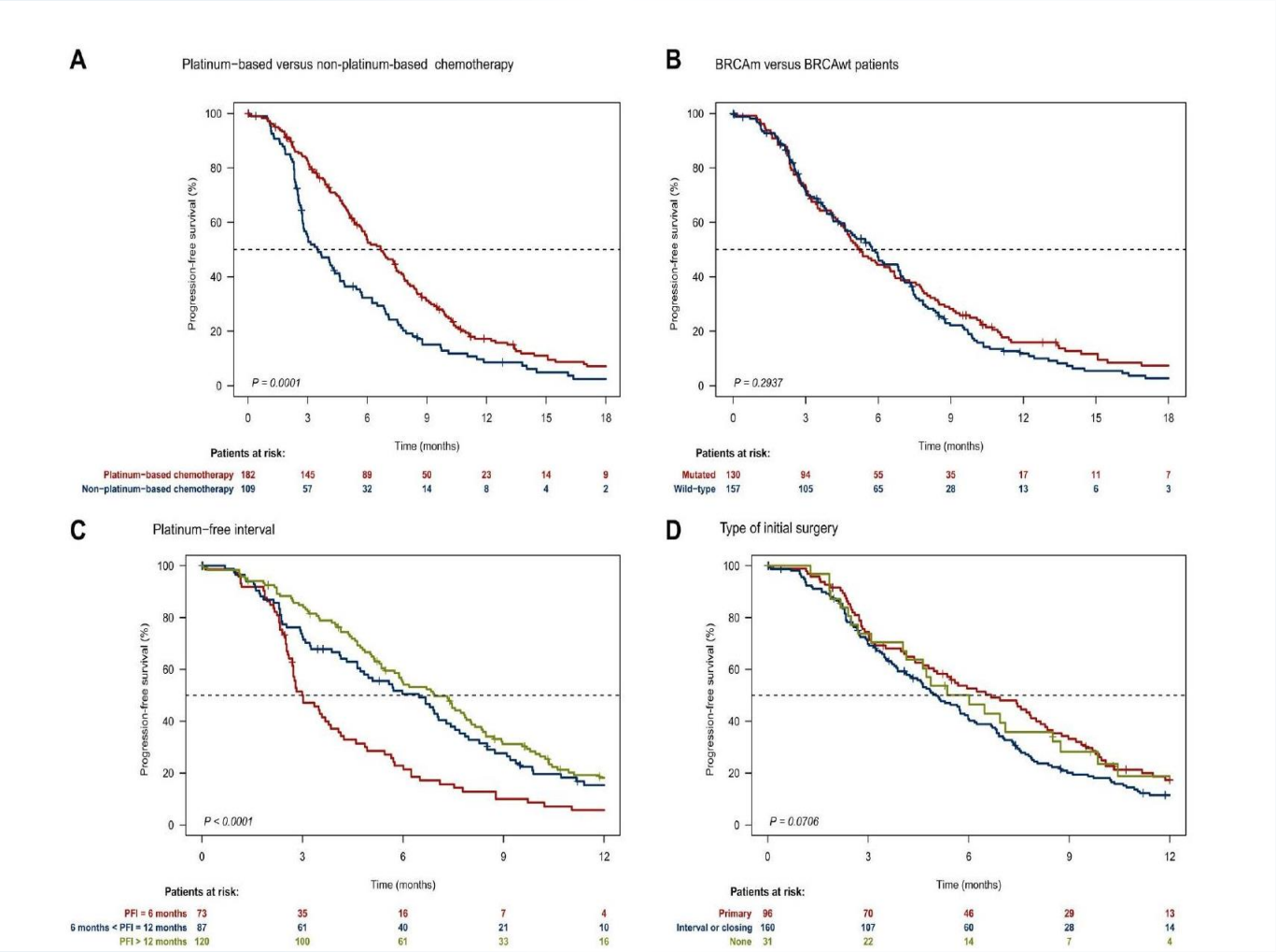
Behaves platinum-sensitive · median ~11–12 mo · HR vs placebo+bev 1.0–1.1

HRD status was not as predictive as timing of progression

Harter P, et al. PAOLA-1/ENGOT-ov25 subsequent-therapy analysis. Ann Oncol. 2024;36(2):185–196.

PFI Remains Prognostic — But the Numbers Have Shifted

Vuillard et al. ESMO Open 2024 · Post-PARPi cohort, N=291



Pre-PARPi (GOG213/ICON4)	
mPFS 10–13 mo	ORR 54–66%
mOS 29–42 mo	Platinum clearly superior

Post-PARPi (Retrospective Cohorts)	
mPFS 7.5 mo (BRCA-WT)	**3.5 mo (BRCAm)**
PFI <6 mo: mPFS ~3 mo	46% primary progression
PFI 6–12 mo: 6.2 mos	drops from ≥12 mo (9.6 mos)

- **Real-world post-PARPi exposure (2002–2021):**
- 90% progressed while ON a PARP inhibitor
- Marked reduction in platinum sensitivity

Vuillard et al. ESMO Open 2024 (Vuillard ESMO Open 2024); Yuan et al. J Ovarian Res 2024; GOG213; ICON4

Can We Predict PARPi Sensitivity?

Looking beyond HRD — timing of progression AND resistance acquisition together predict treatment responsiveness

Progression on 1L PARPi Maintenance

ON PARPi · EARLY	ON PARPi · LATE	AFTER PARPi
Primary progression < 6 mo · ~15%	Some Benefit· ~74%	Relapse off drug · ~11% of progressions
~13–18%	**~26%**	**~5–10%**
reversion mutation (baseline, pre-PARPi)	**reversion mutation at progression (range 10–40%)**	**reversion mutation**
Present before treatment starts —enriched in platinum-resistant/refractory disease	Acquired via clonal selection under treatment pressure	escape more often reflects non-reversion resistance mechanisms
Lin et al., Cancer Discov 2019	*Lukashchuk et al., JCO 2022; Collet et al., Front Oncol 2024*	*Xu-Vuillard et al., ESMO Open 2024*
Platinum-resistant	**Platinum attenuated**	**Platinum-sensitive**
ORR ~0% · PFI < 6 mo	Works if PFI ≥ 12 mo	ORR 42–65%

ctDNA detection: ~60% sensitivity / ~90% specificity for identifying reversion mutations in plasma, with reversions detectable a median of 3.4 months before radiologic progression (ARIEL2 post-hoc analysis).

Emerging framework: BOTH the timing of progression (ON early/late vs. AFTER PARPi) AND the rate of reversion-mutation acquisition dictate next steps

References: Lin KK, et al. Cancer Discov. 2019;9(2):210–219 (baseline reversion rates by platinum sensitivity). • Lukashchuk N, et al. J Clin Oncol. 2022;40(16_suppl):5559 (reversion rate at progression). • Collet L, et al. Front Oncol. 2024;14:1354427 (reversion rate range; ARIEL2 ctDNA sensitivity/specificity and lead time). • Xu-Vuillard A, et al. ESMO Open. 2024;9(9):103694 (N=291; 89.1% progressed during PARPi). • Yuan H, et al. J Ovarian Res. 2024;17:70. • Brann A, et al. ASCO 2025 (UT Southwestern).

**Early/late proportions are approximate subdivisions of the 89.1% of progressions occurring on PARPi (Xu-Vuillard 2024); the prospective early-vs-late split and post-discontinuation reversion rate are not precisely reported and are shown as estimates. Adapted from: 2026 Debates and Didactics in Hematology and Oncology — Partners for Advancing Clinical Education / Bio Ascend.*

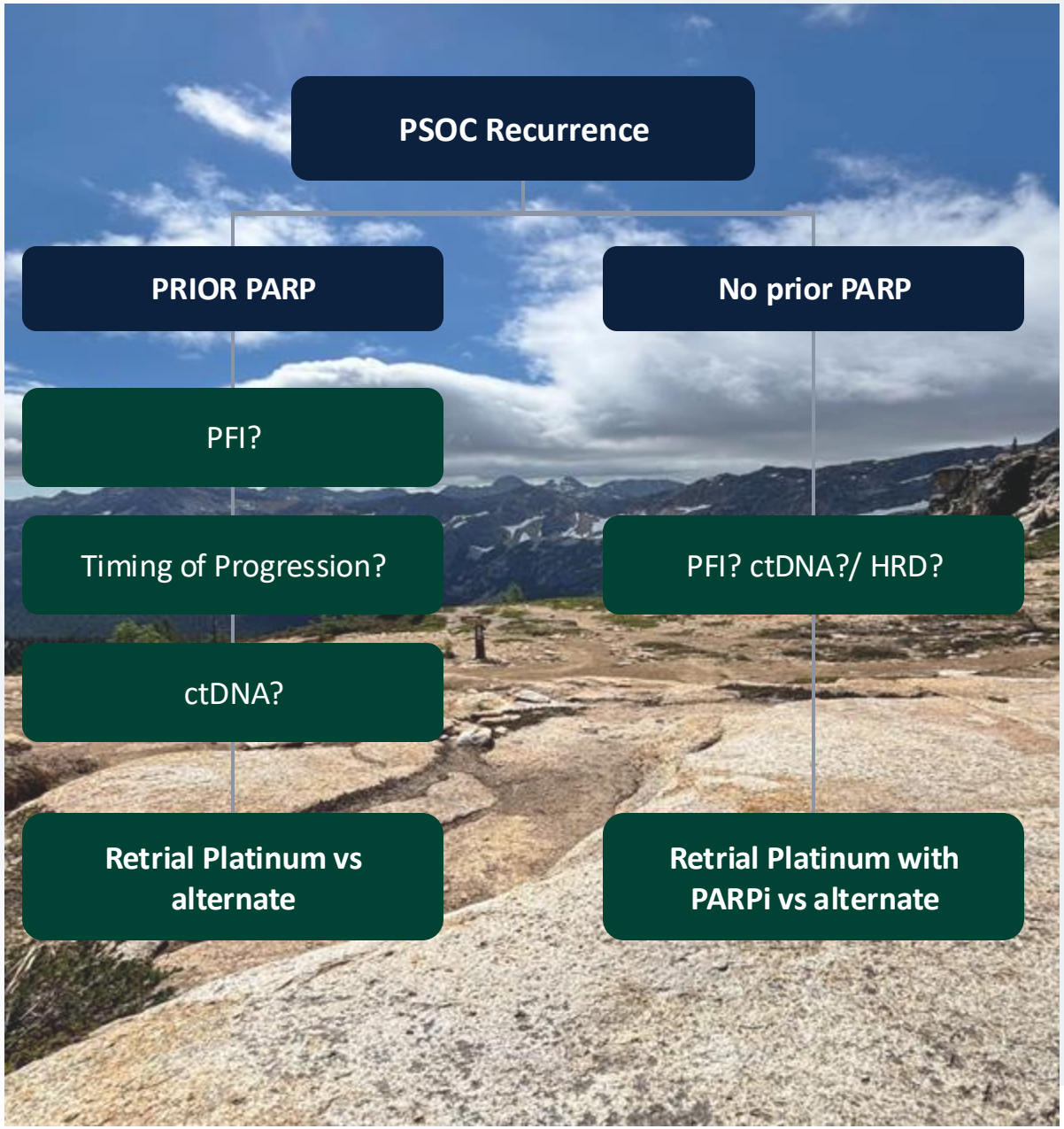
New framework emerging:

Maintenance olaparib rechallenge in patients with PSOC previously treated with a PARP inhibitor (OReO/ENGOT-ov38)

- Significant but **MODEST PFS benefit (2 mo)** in both BRCA mutant and non-mutant population

KGOG NIRVANA-R trial: Niraparib + bevacizumab maintenance following platinum response prior exposure to PARP (Cho et al. ASCO 2025)

- 6-mo PFS 68% median 11.5 mos
- 65% >3 lines of therapy, 85% CR to last platinum
- ctDNA? HRD? PFI?
- **Treatment free interval predictive of response**



Part 3

Treatment After PARPi:Where do we go from here?

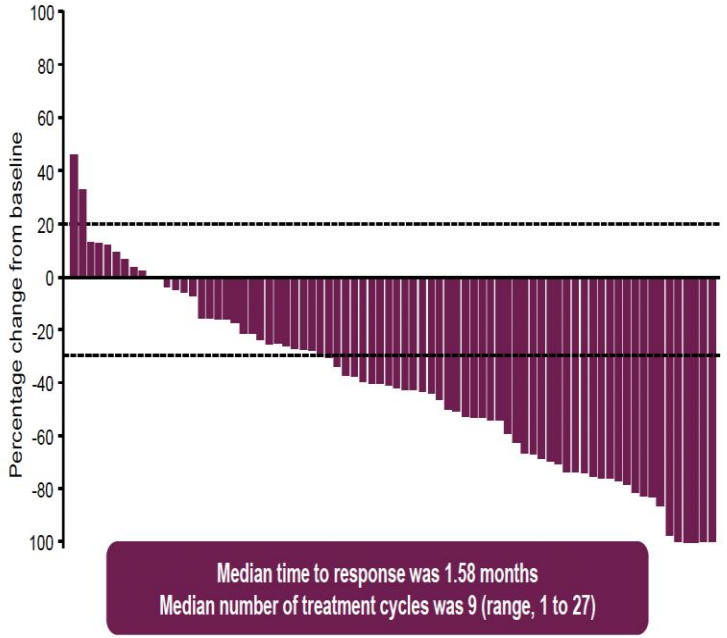
3

PICCOLO: Ph II Mirvetuximab in Plat Sens Ov Cancer: ≥3rd Line

Investigator-Assessed Efficacy Measures

BARCELONA 2024 ESMO congress

Maximum Tumor Percentage Change From Baseline With MIRV



Primary Endpoint	N=79
ORR, n (%) 95% CI	41 (51.9) 40.4-63.3
Best overall response, n (%)	
CR	6 (7.6)
PR	35 (44.3)
SD	29 (36.7)
PD	7 (8.9)
Not evaluable	2 (2.5)

Secondary Endpoints	
Median DOR[a]	n=41
Months (95% CI)	8.25 (5.55-10.78)
Median PFS	N=79
Months (95% CI)	6.93 (5.85-9.59)
CA-125 response[b]	n=47
n (%)	35 (74.5)
95% CI	59.7-86.1

Data cutoff: January 17, 2024.

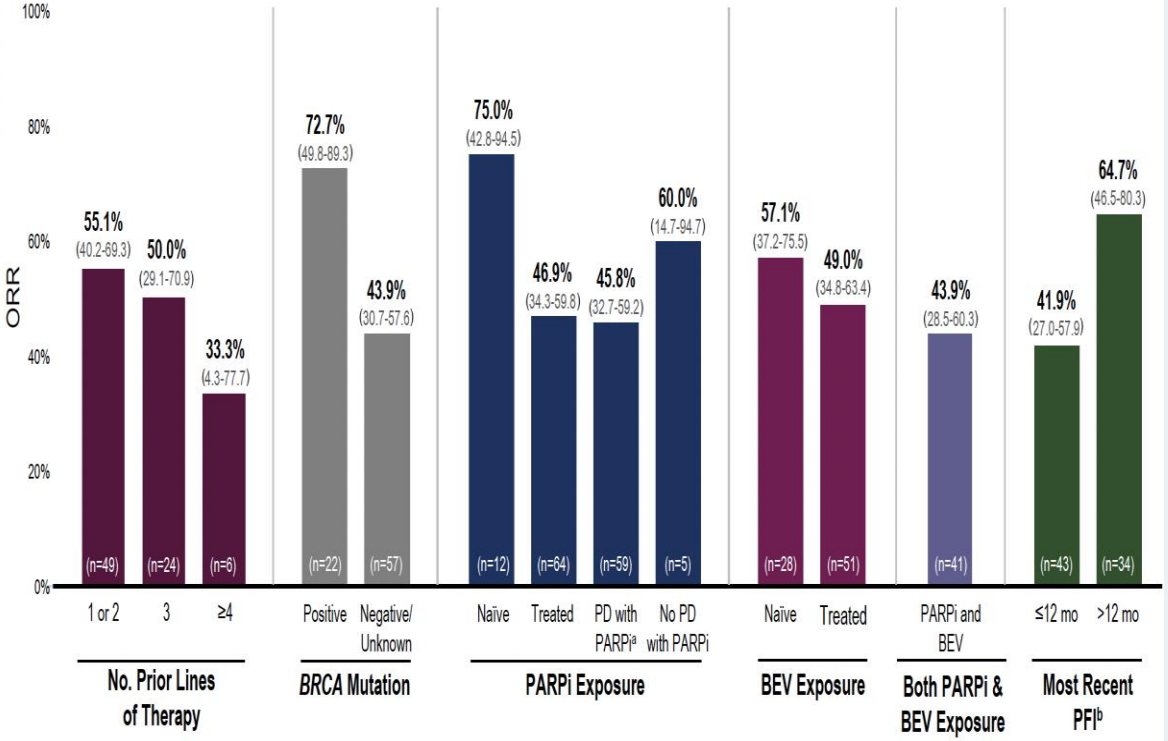
[a]Calculated among participants who had a complete or partial response. [b]Analysis performed on the CA-125–evaluable population.

CA-125, cancer antigen 125; CI, confidence interval; CR, complete response; DOR, duration of response; MIRV, mirvetuximab soravtansine-gynx; ORR, objective response rate; PFS, progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

ORR by Subgroups

BARCELONA 2024 ESMO congress

Total population ORR: 51.9% (95% CI, 40.4-63.3)



Data cutoff: January 17, 2024. ORR presented with 95% CI.

[a]If the participant had progression of disease within 30 days after the last dosing of a PARPi or progression was listed as the reason for treatment discontinuation of a PARPi, the participant was defined as having progressive disease on prior PARPi and was included in this category. [b]Platinum-free interval is defined as time from last dose of the latest line platinum therapy to the date of disease progression and/or relapse following that line of therapy (time rounded to whole number).

BEV, bevacizumab; *BRCA*, Breast Cancer gene; CI, confidence interval; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor; PD, progressive disease; PFI, platinum-free interval; ORR, objective response rate.

Alvarez-Secord, et al ESMO 2024

Next-Generation FRα ADCs in Platinum Sensitive Disease

Mature combination data (IMGN853-0420) and the next randomized trial(FRAmework-01, Part B)

IMGN853-0420 · Phase 2 ·mirvetuximab+ Carboplatin
· mirvetuximab soravtansine → maintenance

62.7%
confirmed ORR (≥50% FRα) · primary endpoint met

Single-arm Phase 2; n=125. FRα⁺ (≥25%), recurrent PSOC, one prior platinum line. Mirvetuximab + carboplatin ×6–8 cycles → mirvetuximab maintenance

SGO 2026:

- ORR 62.4% across the broader ≥25% FRα population **(INCLUDING PARP EXPOSED)**
- ~81% progression-free after the combination phase
- Safety consistent with single-agent mirvetuximab

FRAmework-01 · Part B · Phase 3
· sofetabart mipitecan + bevacizumab

Randomized Phase 3 · ENGOT / GINECO–NOGGO · NCT07213804

PART B

PSOC: sofetabart mipitecan + bevacizumab vs standard of care.

- Next-gen FRα ADC: exatecan (TOPO1) payload
- Active across all FRα levels, incl. mirvetuximab-resistant
- Phase 1 ORR ~55% at RP2D

IMGN853-0420 (NCT05456685): Konecny GE et al., SGO 2026 — AbbVie. · FRAmework-01 (NCT07213804): Eli Lilly / ENGOT — sofetabart mipitecan (LY4170156), Part B.

It’s an ADCs Extravaganza

A wave of antibody–drug conjugates across three targets — FRα, Trop-2, and NaPi2b — PARP alternatives to ovarian cancer maintenance and treatment

Trial	ADC — target · payload	Setting / line	Randomization
GLORIOSA (NCT05445778)	Mirvetuximab soravtansine — FRα · DM4 (anti-tubulin)	FRα-high, PSOC— maintenance	MIRV + bev vs bev
TroFuse-021 (ENGOT-ov85 / GOG-3102)	Sacituzumab tirumotecan — Trop-2 · topo-I	First-line maintenance, HRD-negative (PARPi-ineligible)	sac-TMT ± bev vs standard of care
TroFuse-022 (ENGOT-ov84 / GOG-3103)	Sacituzumab tirumotecan — Trop-2 · topo-I	PSOC— maintenance	sac-TMT ± bev vs standard of care

NAPISTAR · TUB-040, ESMO 2025 (n=46): ORR 59% (50% confirmed) · DCR 96% · no treatment discontinuations for adverse events

GLORIOSA NCT05445778; TroFuse-021/ENGOT-ov85/GOG-3102 NCT07318558; TroFuse-022/ENGOT-ov84/GOG-3103 NCT06824467 (Phase 3, PFS). NAPISTAR 1-01 NCT06303505 — TUB-040, Phase I/IIa, ESMO 2025.

Beyond PARP: PARG and POLθ — the Next Synthetic-Lethality Targets

Emerging DNA-damage-response targets reported at ASCO 2026

PARG inhibition · ETX-19477
858 Therapeutics · first-in-human Ph 1/2

57% ORR
Phase 2–eligible subset (n=7) · durable RECIST responses

POLθ inhibition · GSK4524101, ART4215
GSK · Artios · Ph 1/2, often combined with a PARPi

Emerging — early clinical
Efficacy data still maturing at ASCO 2026

ASCO 2026 · PHASE 1/2

- 53 patients across dose escalation + expansion
- Durable responses in BRCA-mut ovarian & HR+/HER2− breast
- First clinical proof-of-concept for PARG inhibition
- Well tolerated; low hematologic toxicity

Mechanism: blocks PAR breakdown → persistent replication stress, distinct from PARP trapping.

LEADING PROGRAMS

- GSK4524101 ± niraparib — FIH Ph 1/2, advanced solid tumors / gBRCA breast (NCT06077877)
- ART4215 (Artios) + talazoparib — Ph 2 expansion, BRCA-deficient breast

RATIONALE

POLθ drives MMEJ backup repair — synthetic lethal in HRd tumors and active in PARPi-resistant disease;

Two new DDR targets extend synthetic lethality beyond PARP — PARG delivers first clinical proof-of-concept; POLθ advances in PARPi-resistance combinations.

ETX-19477: 858 Therapeutics, ASCO 2026 (Ph 1/2). · GSK4524101: GSK, NCT06077877. · ART4215: Artios, NCT04991480. · All investigational — not approved.

Stenoparib (2X-121)

First-in-Class Dual PARP / Tankyrase Inhibitor — Now in Phase 2 for Platinum-Resistant Ovarian Cancer

NCT03878849 opening at Emory

Novel Mechanism

- Dual-targets PARP1/2 AND Tankyrase ½ (PARP5a/b)
- Impairs DNA damage repair while independently shutting down oncogenic WNT/β-catenin signaling
- Orally bioavailable and brain-penetrant, broadening potential use beyond BRCA-mutant disease alone

Preclinical Evidence

- Significant single-agent antitumor activity in BRCA-deficient xenograft models; potentiates chemotherapy in vivo
- Proprietary DRP® genomic signature (414 genes) retrospectively predicted which patients benefited most — being evaluated concurrentlyp
- Phase 1 dose-escalation showed clinical responses concentrated in PROC motivating the disease-focused Phase 2 program
- >25 mo mOS

Stenoparib (2X-121/E7449), Allarity Therapeutics; originally developed by Eisai. Prior-cohort survival data are from an ongoing, maturing trial and may change. Sources: AACR 2025/2026, ESMO Gynaecological Cancers Congress 2026.

Key Takeaways

PARPi has transformed first-line OC — But Biomarker is important

PARPi isn't for everyone: HRD doesn’t drive all disease, Platinum exposure can lead to accumulation of resistance mechanisms

Timing of recurrence ON or AFTER PARP is predictive of next response

The Platinum Free interval still matters, but real-time biomarkers (ctDNA) are needed

Emerging trials are addressing Post-Parp progression