CME CAST EPISODE 4

Who, What, and Why of Biomarker Testing in Ovarian Cancer

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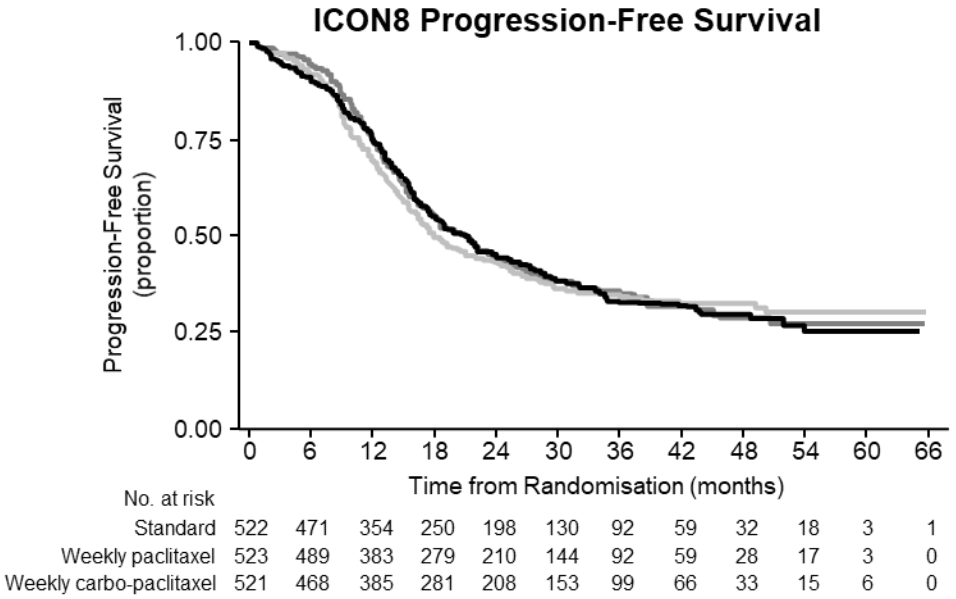
Richard T. Penson, MD, MRCP
Physician, Mass General Brigham
Associate Professor, Harvard Medical School
Institutional Review Board (IRB) Chair
Dana Farber Harvard Cancer Center
Boston, MA

Antonio González-Martín, MD, PhD
Director
Cancer Center Clinica
Universidad de Navarra
Madrid, Spain

Learning Objective

Assess the significance of homologous recombination deficiency (HRD) positivity in the first-line treatment of ovarian cancer (OC)

Platinum Therapy Can't Get Much Better



	Standard (n = 522)	Weekly paclitaxel (n = 523)	Weekly carbo-paclitaxel (n = 521)
Progressions	330 (63%)	335 (64%)	338 (65%)
Median PFS, mo	17.9	20.6	21.1
Log rank (vs standard)		*p* = .45	*p* = .56
HR vs Standard (97.5% CI)		.92 (.77–1.09)	.94 (.79–1.12)
Restricted means	24.4 mos	24.9 mos	25.3 mos

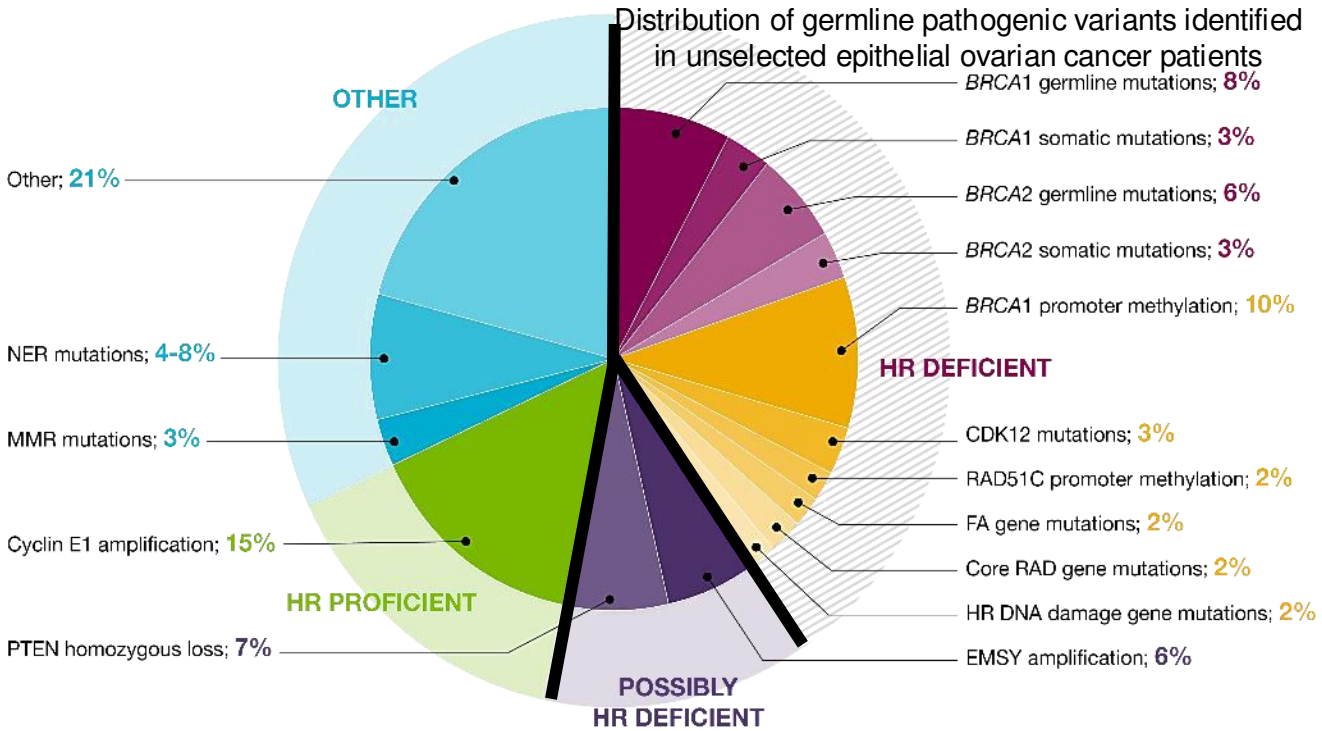
Weekly dose-dense chemotherapy can be delivered successfully as first-line epithelial ovarian cancer treatment without substantial toxicity increase; it does not significantly improve PFS compared to standard 3-weekly chemotherapy

CI = confidence interval; HR = hazard ratio; Mos = months; PFS = progression-free survival.
Clamp AR, et al. *Ann Oncol*. 2017;28(suppl_5):v627.

Tumor Molecular Analyses in the Upfront Setting

NCCN recommendation

- Somatic testing to identify molecular alterations that point to use of interventions that have demonstrated benefit in this setting
  - e.g., BRCA1/2, loss of heterozygosity (LOH), or homologous recombination deficiency (HRD) status in the absence of a germline BRCA mutation



NCCN = National Comprehensive Cancer Network.

NCCN Guidelines. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (Version 3.2024). https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Konstantinopoulos PA, et al. *Cancer Discov.* 2015;5(11):1137-1154.

Which Patients Should Receive Genetic Testing?

Leading oncology societies recommend testing all women with ovarian cancer

NCCN
Genetic counseling and testing should be considered in women with a history of ovarian carcinoma, fallopian tube cancer, or primary peritoneal cancer

SGO
Women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should receive genetic counseling and be offered genetic testing, even in the absence of family history

ASCO
Genetic counseling and testing should be considered in women with epithelial ovarian, fallopian tube, or primary peritoneal cancer, even in the absence of family history

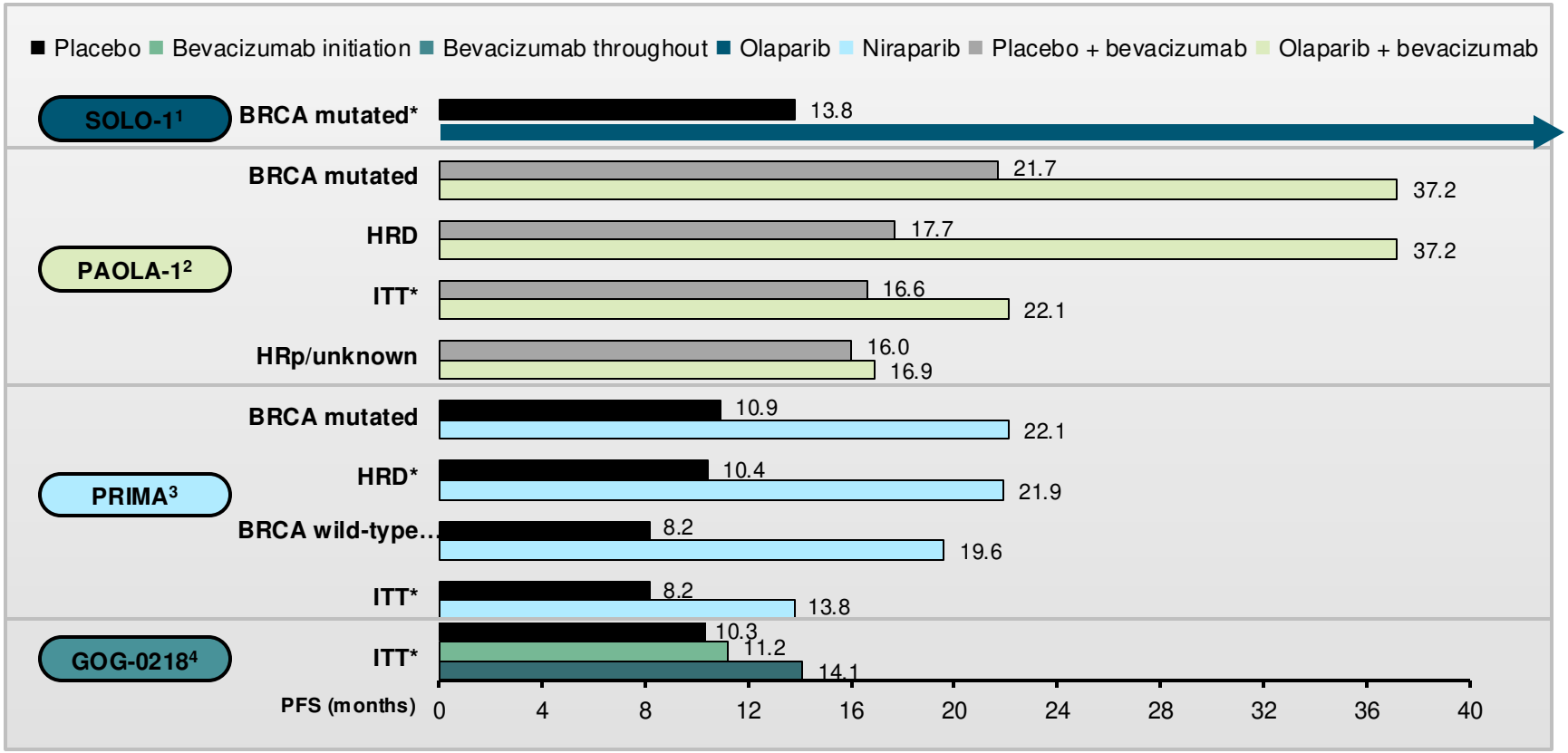
ESMO
Patients with high-grade tumours should be tested for a germline BRCA mutation. Consideration should be given to testing tumours for a somatic *BRCA* mutation

Recommended testing sequence

First: Tumor *BRCA* Second: Germline testing

ASCO = American Society of Clinical Oncology; ESMO = European Society of Medical Oncology; SGO = Society of Gynecologic Oncology.
Ledermann JA, et al. *Ann Oncol.* 2013;24(S6):vi24–vi32. Lu KH, et al. *J Clin Oncol.* 2014;32(8):833-840. NCCN Guidelines. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (Version 3.2024). https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Society of Gynecologic Oncology [SGO]. SGO Website. 2014. https://www.sgo.org/resources/genetic-testing-for-ovarian-cancer/.

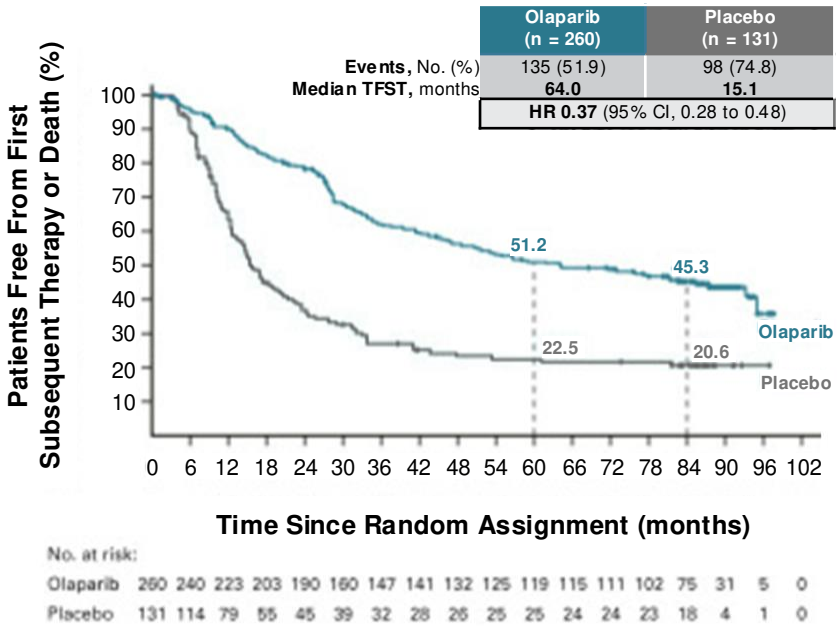
Summary of First-line Maintenance Studies

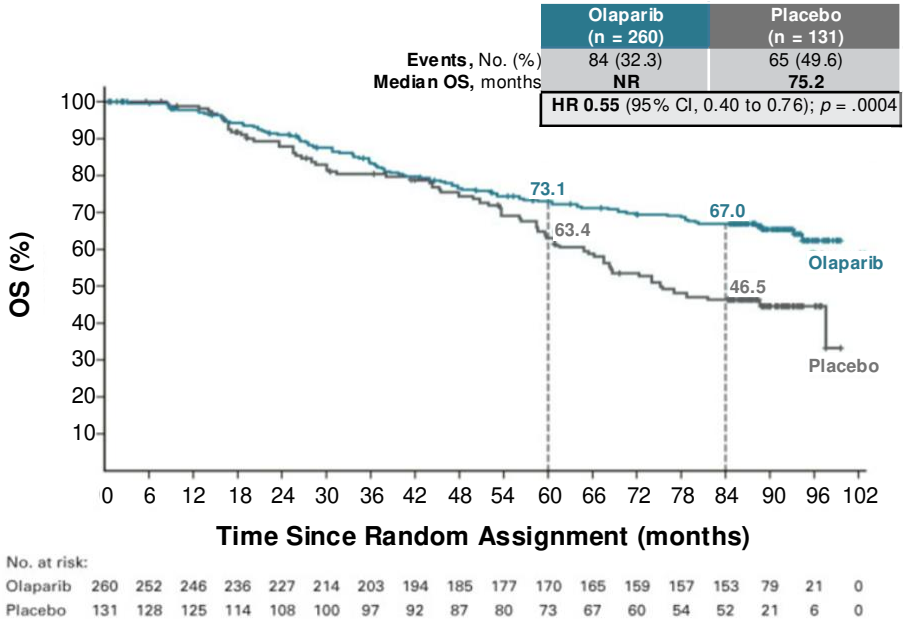


ITT = Intention to treat.

1. Moore K, et al. *N Engl J Med.* 2018;379(26):2495-2505. 2. González-Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402. 3. Ray-Coquard I, et al. *N Engl J Med.* 2019:381(25):2416-2428.

SOLO-1: Olaparib vs Placebo Maintenance

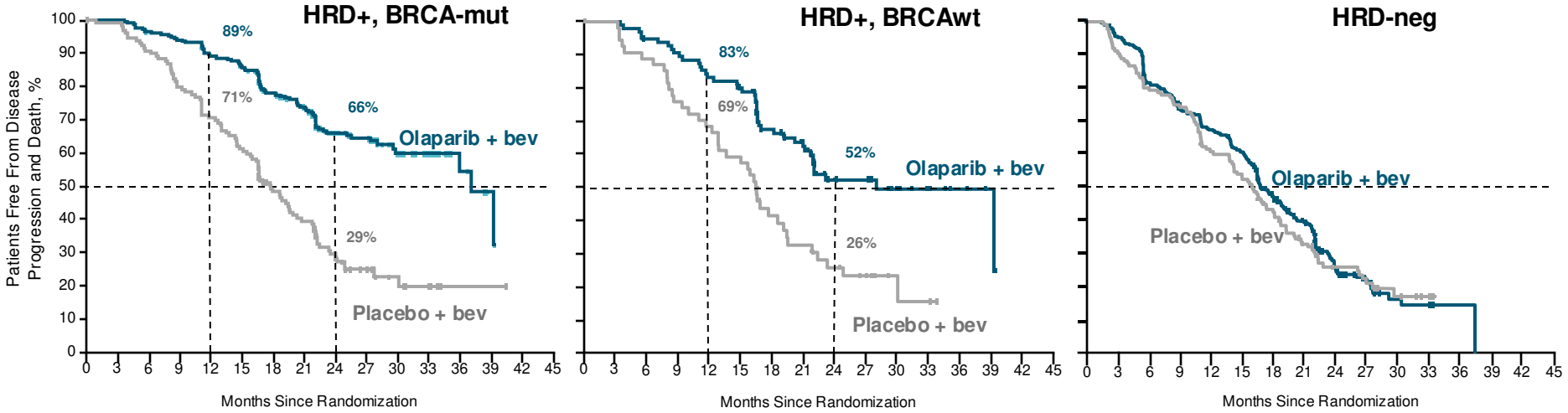




TFST = time to first subsequent therapy.

DiSilvestro P, et al. *J Clin Oncol.* 2023;41(3):609-617.

PAOLA-1: Bevacizumab ± Olaparib



HRD+, BRCA-mut	Median PFS (months)
Olaparib + bev	37.2
Placebo + bev	17.7

HRD+, BRCA-wt	Median PFS (months)
Olaparib + bev	28.1
Placebo + bev	16.6

HRD-negative	Median PFS (months)
Olaparib + bev	16.9
Placebo + bev	16.0

Ray-Coquard I, et al. *N Engl J Med*. 2019:381(25):2416-2428.

Occurrence of PARPi Therapy-induced BRCA1/2 Reversion Mutation

- Real-word evidence suggests ovarian cancer becomes resistant to prolonged PARPi therapy with a median time to progression of 10-16 months
- In the EVOLVE study, among 34 heavily pretreated patients, patients with reversion mutations in homologous recombination genes had poor outcomes
  - 19% of patients had reversion mutations in BRCA1, BRCA2, or RAD51B at PARPi progression
- In a meta-analysis of 234 patients with ovarian cancer, 23.5% of tumors in patients with a germline BRCA1/2 mutation experienced a reversion mutation upon progression on a PARPi

PARPi = poly (ADP-ribose) polymerase inhibitors.

Lheureux S, et al. *Clin Cancer Res.* 2020;26(16):4206-4215. Pan YE, et al. *Ann Pharmacother.* 2023;57(10):1162-1171. Tobalina L, et al. Ann Oncol. 2021;32(1):103-112. Vilming B, et al. *Int J Gynecol Cancer.* 2023;33(12):1898-1905.

Molecular Testing Recommendations

- Retest BRCA1/2 and HRD status at progression on a PARPi
- Consider laproscopic biopsy, if the patient is going to receive neoadjuvant therapy, in order to have sufficient tissue for complete testing

"We are dividing patients at presentation into ever increasingly small groups of ever increasingly important determinants of outcome."

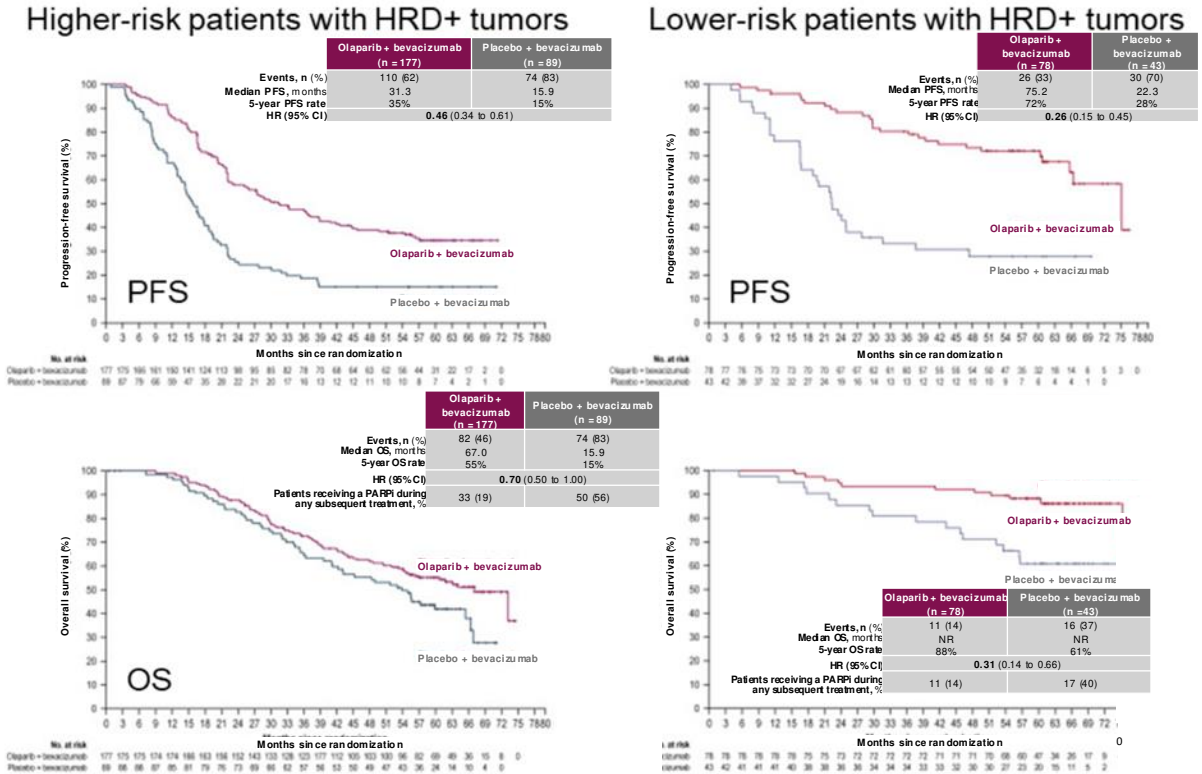
Length of PARPi Therapy

- Wide variation in PARPi maintenance therapy duration
  - In the absence of institutional guidelines (73% of surveyed world-wide respondents), 76% recommended ≥ 5 yrs, with 48% recommending indefinite treatment
  - In the presence of institutional guidelines (27% of respondents), most (40%) recommended indefinite treatment; 5% = 1 yr, 25% = 2 yrs, 10% = 3 yrs
- Optimal length of PARPi maintenance therapy in 1st-line appears to be ~ 2 yrs
  - Based on SOLO-1, PRIMA, and PAOLA-1

Coleman RL, et al. *N Engl J Med.* 2019;381(25):2403-2415. González-Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402. Haggstrom L, et al. *Int J Gynecol Cancer.* 2024;ijgc-2024-005976. Moore K, et al. *N Engl J Med.* 2018;379(26):2495-2505. NCCN Guidelines. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (Version 3.2024). https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Ray-Coquard I, et al. *N Engl J Med.* 2019;381(25):2416-2428.

PAOLA-1 High-risk, HRD+ Patient Subgroup

- PRIMA: only enrolled high-risk, HRD+ patients; maintenance was niraparib or placebo (no bev)
- PAOLA-1: 74% high-risk, HRD+ patients; maintenance was bev + olaparib or placebo, 2 yrs
  - In the high-risk, HRD+ population (i.e., PRIMA-like), median PFS was 31.3 months with olaparib + bev and 15.9 months with placebo + bev
- Both studies at 5 yrs:
  - ~ 35% PFS
  - ~ 50% OS



Lorusso D, et al. *Int J Gynecol Cancer.* 2024;34(4):550-558.

Biomarker Testing After PARPi Therapy

- At first relapse:
  - HER2
    - FDA indication: IHC3+
    - NCCN recommendation: IHC ≥ 2+
    - HER2-zero/ultra-low?
  - FRα

Summary

- According to the NCCN guidelines, in the front-line setting, somatic testing should be used to identify molecular alterations that point to use of interventions that have demonstrated benefit.
- Low-risk, HRD+ tumors are very sensitive to PARP inhibitor maintenance therapy and may offer cures with very long follow up.
  - High-risk HRD+ tumors are sensitive to PARP inhibitor maintenance therapy, but cures are less likely.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Record tumor molecular testing receipt and results in EHR system for all ovarian cancers:
  - Early tumor molecular testing to determine BRCA and HRD status
  - At relapse testing to verify BRCA and HRD status has not changed

EHR = electronic health record.

EPISODE 1	The When and How of Maintenance Therapy in Endometrial Cancer
EPISODE 2	Confusion on the Horizon: Novel Therapies Emerging for the Treatment of Endometrial Cancer
EPISODE 3	Expanding Options for Immune Checkpoint Inhibitors in Front-Line Advanced/Recurrent Endometrial Cancer
EPISODE 4	Who, What, and Why of Biomarker Testing in Ovarian Cancer

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