AmerisourceBergen

# Deb Armstong, MD

Dr. Armstrong is a medical oncologist at the Johns Hopkins Kimmel Cancer Center who works in the area of women's malignancies, with a particular emphasis on breast cancer, ovarian cancer and other gynecologic malignancies, and the genetics of breast and ovarian cancer.  Dr. Armstrong's clinical focus is on the development of new therapeutic approaches to the treatment of breast cancer and gynecologic malignancies. Dr. Armstrong is active in NRG/GOG, serving on Developmental Therapeutics and Phase I committees and as co-chair of the Medical Oncology Committee.  She is co-chair of the Ovarian Cancer Task Force for the Gynecologic Cancer Steering Committee of the National Cancer Institute and chair of the Ovarian Committee for the National Comprehensive Cancer Network (NCCN).  She is a former member and chair of the Oncology Drugs Advisory Committee (ODAC) to the FDA. She has been an Integration Panel Member of the DOD Ovarian Cancer Research Program since 2007 and currently chairs the Panel.

KIMMEL CANCER CENTER

# PARP Inhibitors in Ovarian Cancer:

## Most Important Advances in Gynecologic Cancers

**CME Virtual Event**

**October 15, 2022**

**Deborah K. Armstrong, M.D.**

**Johns Hopkins Kimmel Cancer Center**

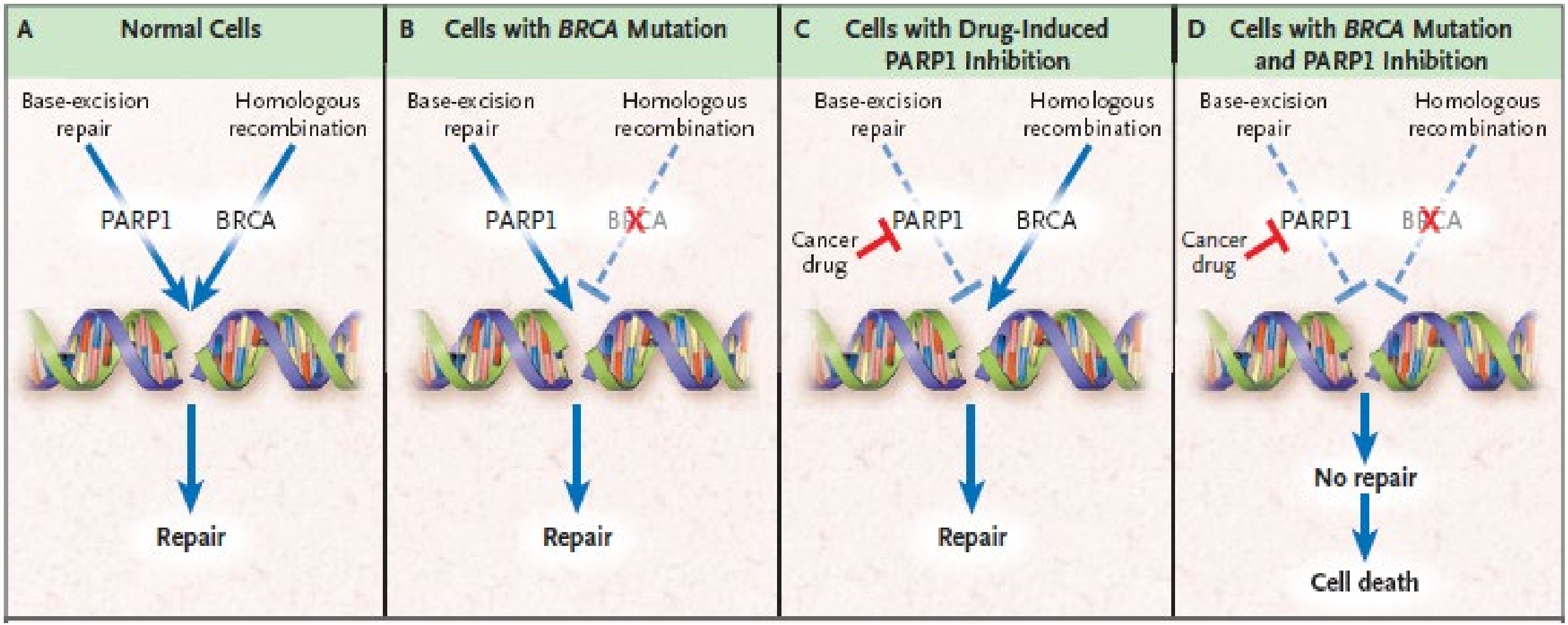
**Baltimore, MD**

JOHNS HOPKINS MEDICINE

# Learning Objectives

- Describe data from PARP inhibitor trials in patients with newly-diagnosed advanced ovarian cancer, and discuss how it may inform treatment and molecular testing in this setting
- Review factors that may impact the extent of clinical benefit from PARP inhibitor therapy
- Understand recent changes in recommendations for primary PARP inhibitor treatment in recurrent ovarian cancer

# PARP inhibitors exploit defects in DNA repair




Silver and Iglehart, NEJM, 2009

# The “Landscape” of PARP Inhibition in Ovarian Cancer

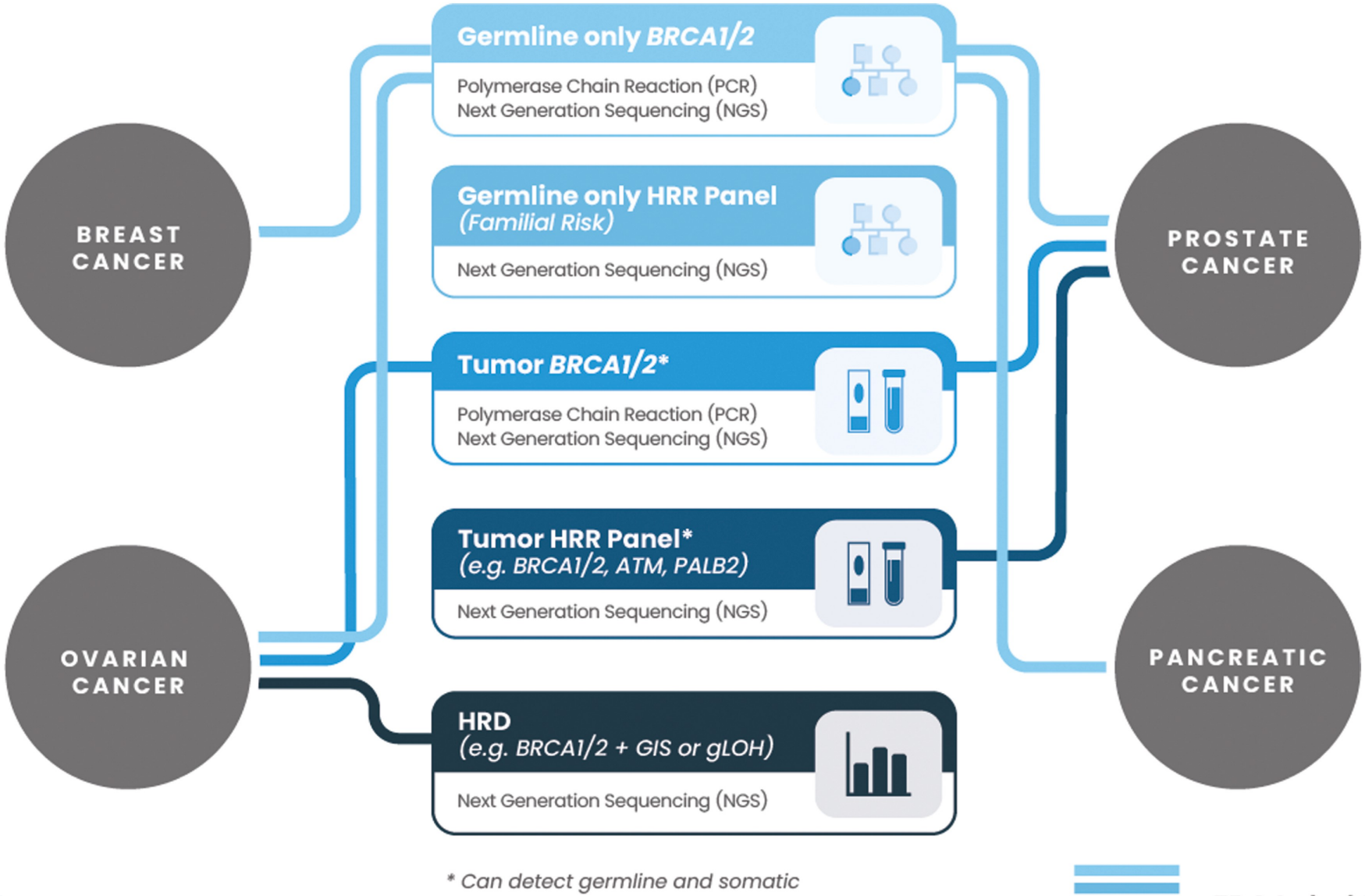
## Clinical Setting

- Newly diagnosed disease-maintenance
- Platinum-sensitive maintenance
- ~~Active relapsed disease~~

## Molecular Features

- BRCA mutated (somatic or germline)
- BRCA wild-type
  - HR deficient
  - HR proficient

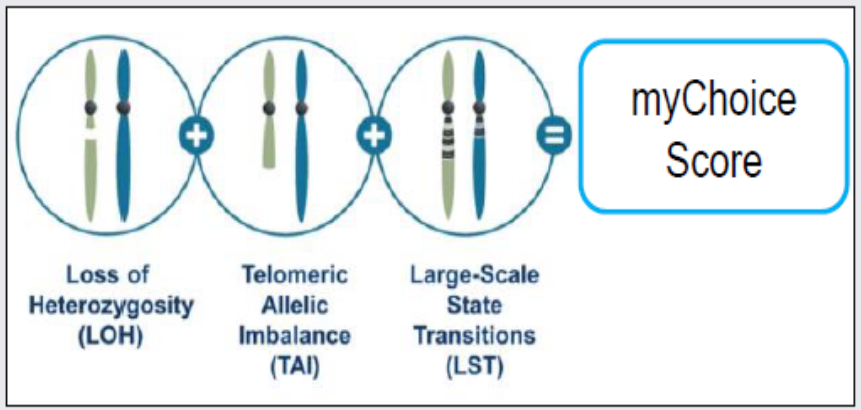
# Diagnostic tools for PARPi treatment




Stewart MD et al. *Oncologist*, Volume 27, Issue 3, March 2022, Pages 167–174

# Testing for Homologous Recombination Deficiency (HRd) and Proficiency (HRp)

- Next generation sequencing of DNA from tumor tissue (Myriad Genetics myChoice® Test)
  - Provides a score based on algorithmic measurement of 3 tumor factors:
    - Loss of heterozygosity (LOH)
    - Telomeric allelic imbalance (TAI)
    - Large-scale state transitions (LST)

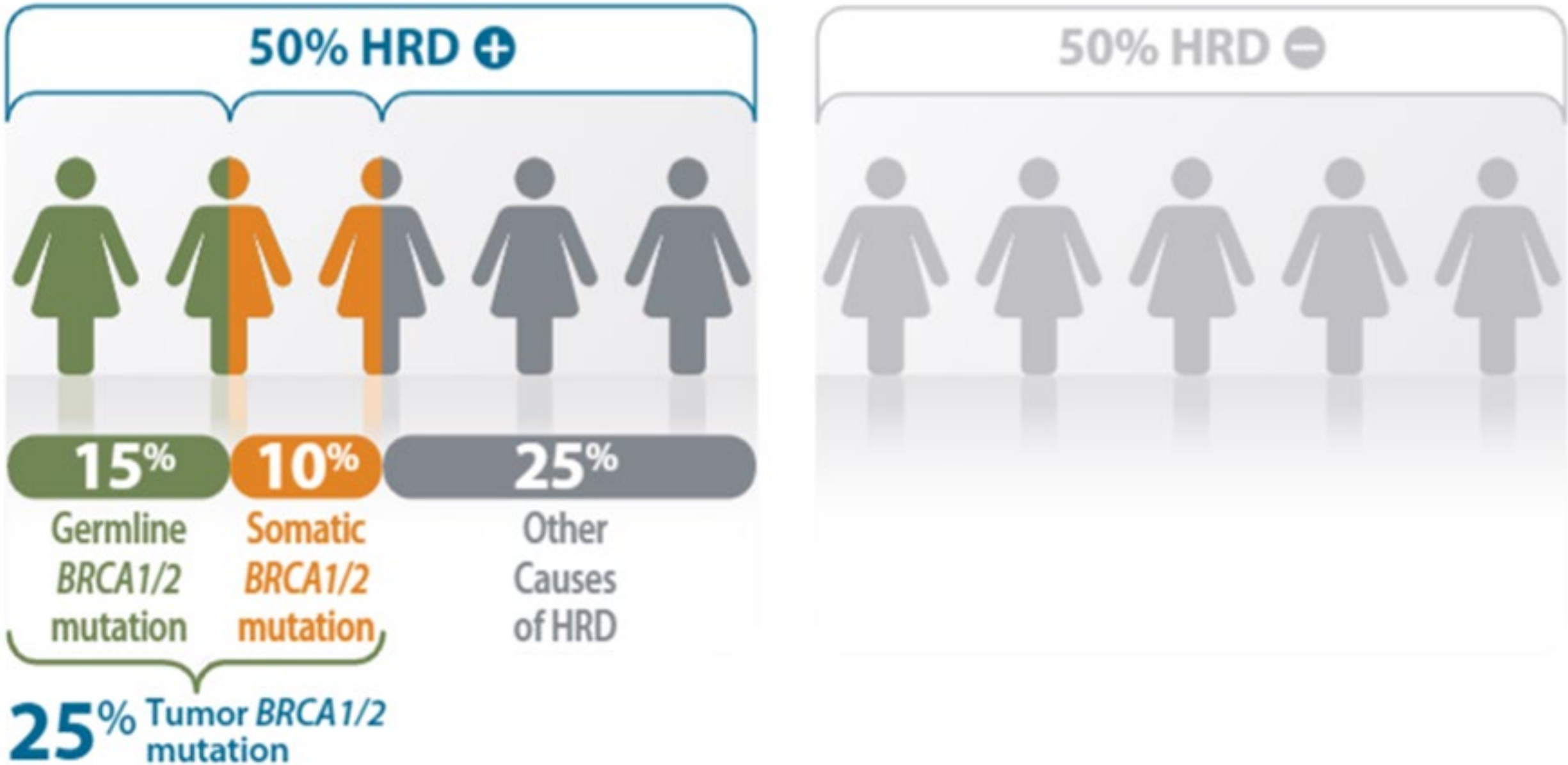



- Homologous recombination status is determined by the following:
  - HR-deficient tumors: Tissue test score ≥42 **OR** a *BRCA* mutation
  - HR-proficient tumors: Tissue test score <42
  - HR-not-determined

# Foundation Medicine LOH

Genomic Instability Score (GIS), as determined by Foundation Medicine tumor analysis; must have genome-wide LOH ≥14, a somatic *BRCA1* and/or *BRCA2* mutation, or a mutation in *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D* or *RAD54L* to be considered positive.

Swisher *et al. Lancet Oncol* 2017;18:75–87


50% HRD ⊕
50% HRD ⊖
15%
Germline BRCA1/2 mutation
10%
Somatic BRCA1/2 mutation
25%
Other Causes of HRD
25% Tumor BRCA1/2 mutation

# Study design SOLO-1

**BRCA mutation carriers only**

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCA*m
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy

Olaparib 300 mg bd (N=260)

2:1 randomization

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease

**Primary endpoint**

- Investigator-assessed PFS (modified RECIST 1.1)

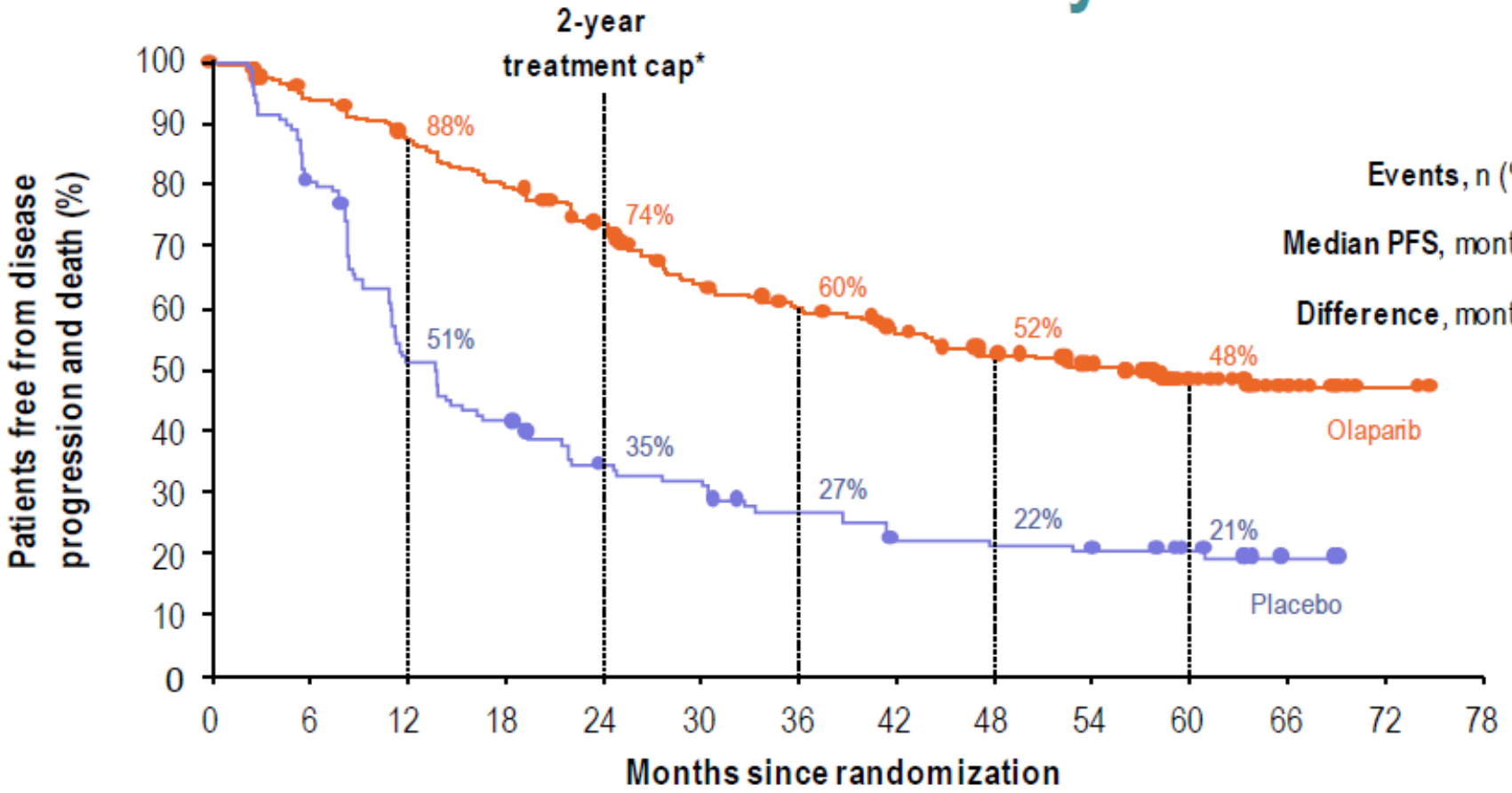
**Secondary endpoints**

- PFS using BICR
- PFS2
- Overall survival
- Time from randomization to first subsequent therapy or death
- Time from randomization to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO, International Federation of Gynecology and Obstetrics; HRQoL, health-related quality of life; PFS, progression-free survival; PFS2, time to second progression or death; RECIST, response evaluation criteria in solid tumours; TOI, Trial Outcome Index

Moore K, et al. N Engl J Med 2018;379:2495-2505.

# PFS benefit of maintenance olaparib was sustained beyond the end of treatment




| | Olaparib (N=260) | Placebo (N=131) |
|---|---|---|
| **Events**, n (%) | 118 (45) | 100 (76) |
| **Median PFS**, months | **56.0** | **13.8** |
| **Difference**, months | 42.2 | |
| | **HR 0.33** (95% CI 0.25–0.43) | |

**Median treatment duration:**
**Olaparib**, 24.6 months
**Placebo**†, 13.9 months

No. at risk

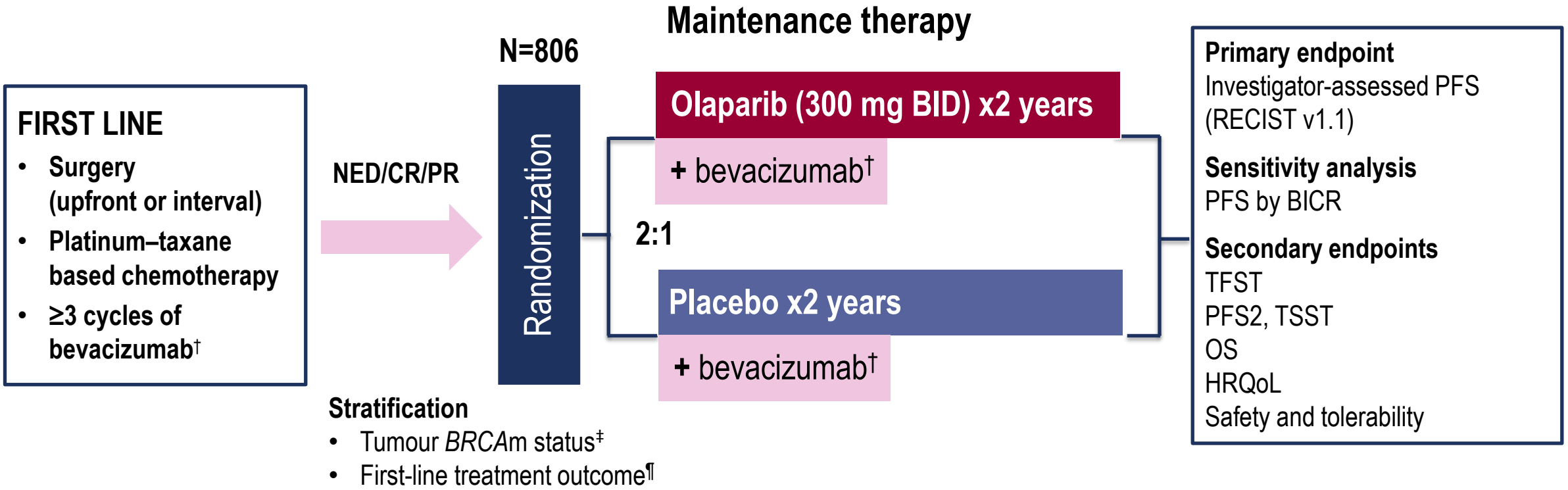
| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib | 260 | 229 | 212 | 194 | 173 | 140 | 129 | 115 | 101 | 91 | 58 | 30 | 2 | 0 |
| Placebo | 131 | 103 | 65 | 53 | 41 | 38 | 30 | 24 | 23 | 22 | 16 | 3 | 0 | |

*13 patients, all in the olaparib arm, continued study treatment past 2 years; †n=130 (safety analysis set)
Investigator-assessed by modified RECIST v1.1. DCO: 5 March 2020

Friedlander ML, et al. ESMO Asia Virtual Congress 2020 (20–22 November).
Banerjee S, et al. Annals of Oncology 2020;31:S613.

# Study design PAOLA-1

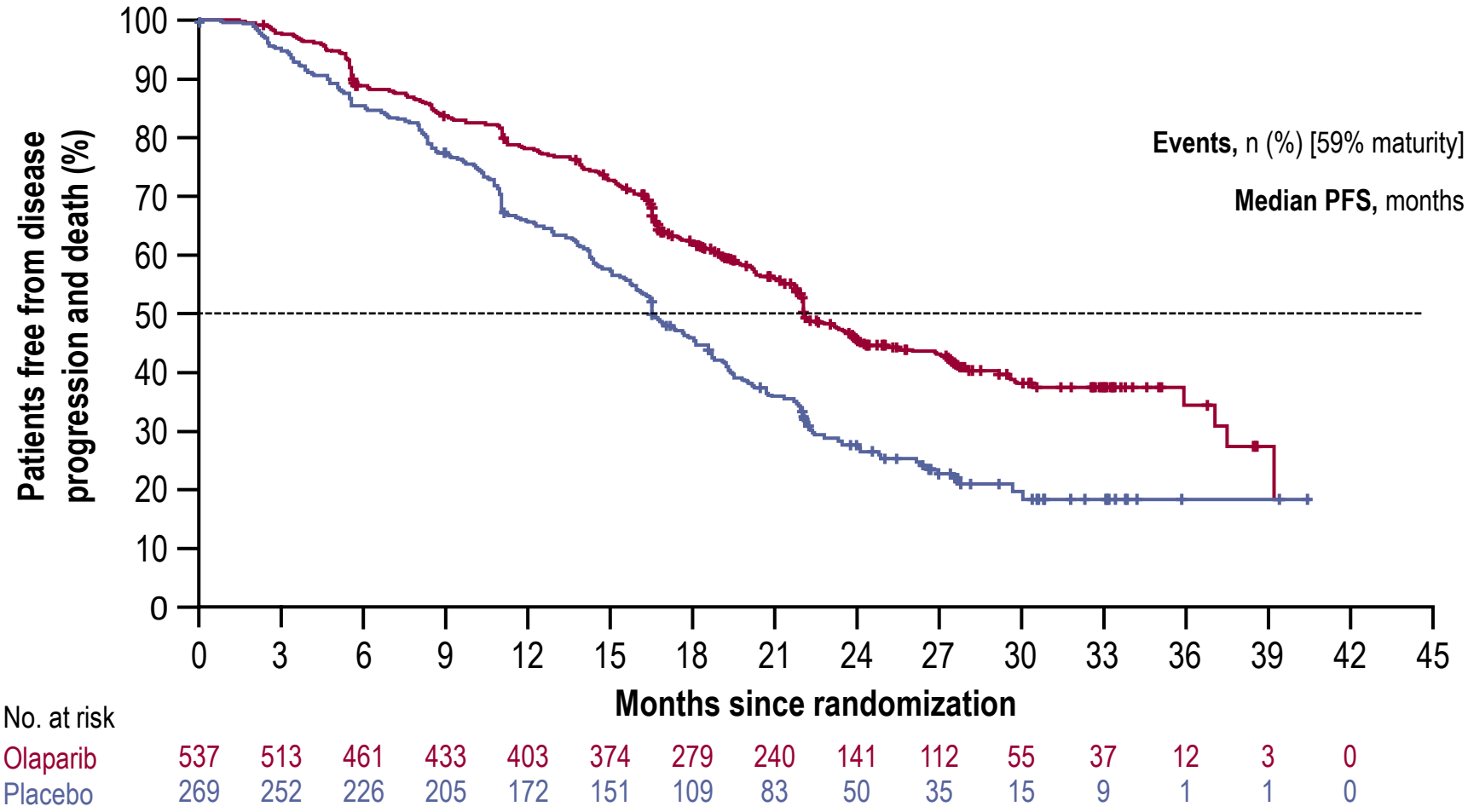
**Newly diagnosed FIGO stage III–IV high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer***




*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation
†Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; ‡By central labs; ¶According to timing of surgery and NED/CR/PR
BICR, blinded independent central review; HRQoL, health-related quality of life; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

Ray-Coquard I, et al. N Engl J Med 2019;381:2416-2428.
Ray-Coquard IL, et al. Annals of Oncology 2019;30:v894-v895.

# PAOLA: PFS by investigator assessment: ITT




| | Olaparib + bevacizumab (N=537) | Placebo + bevacizumab (N=269) |
|---|---|---|
| **Events,** n (%) [59% maturity] | 280 (52) | 194 (72) |
| **Median PFS,** months | **22.1** | **16.6** |

**HR 0.59** (95% CI 0.49–0.72; *P*<0.0001)

**Median time from first cycle of chemotherapy to randomization = 7 months**

ITT, intent-to-treat population


Ray-Coquard I, et al. N Engl J Med 2019;381:2416-2428.
Ray-Coquard IL, et al. Annals of Oncology 2019;30:v894-v895.

# PRIMA: STUDY DESIGN

- Newly diagnosed, FIGO stage III-IV high-grade serous or endometrioid*
- **Stage III with visible residual disease post-surgery**
- **Inoperable stage III disease**
- Any stage IV disease
- Had received NACT
- CR or PR after platinum-based chemotherapy

**HRD testing prior to randomization**

**Randomize 2:1**
N=733

**Stratification:**
- NACT
- CR/PR
- HRD-positive or HRD-negative/unknown

**Maintenance therapy**

**Niraparib**
200/300 mg PO QD†

**Placebo**

**Primary endpoint**

- PFS (BICR) in **HRD population** and step down to all-comers (RECIST 1.1)

**Secondary endpoints**

- OS
- PFS2
- TFST
- Safety
- PRO/HRQoL

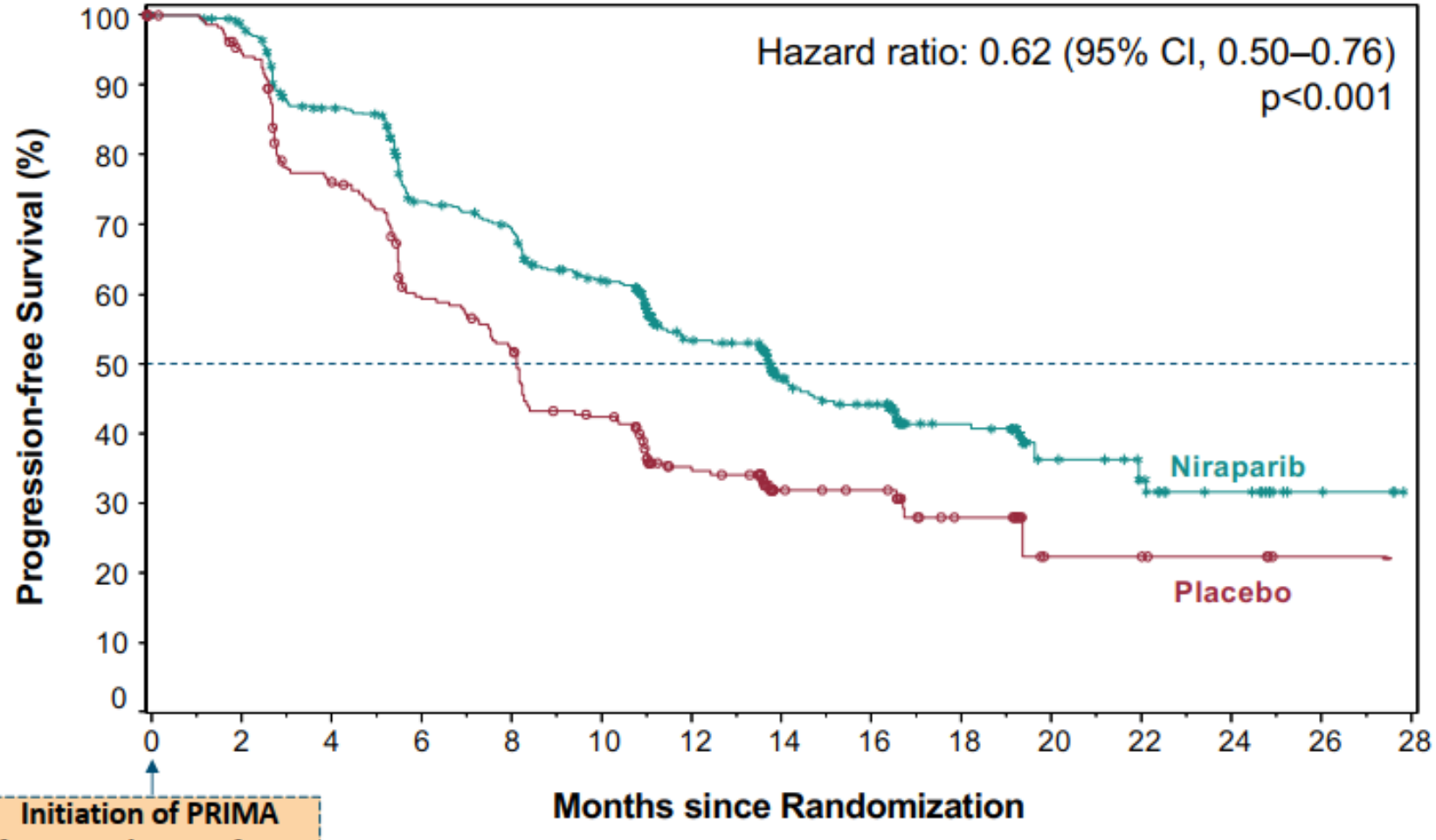
- Patients with stage III disease with no visible residual disease (ie, complete cytoreduction) post-surgery were excluded
- In clinical practice, some physicians would treat PRIMA candidates with chemotherapy + bevacizumab as standard of care

Niraparib is not approved for use outside the platinum-sensitive relapsed ovarian cancer setting.
*Includes patients with primary peritoneal and/or fallopian tube cancer. †Modified starting dose permitted to mitigate for hematological toxicity following protocol amendment.
BICR = blinded independent central review; CA-125 = cancer antigen-125; CR = complete response; FIGO = International Federation of Gynecology and Obstetrics; HRD = homologous recombination deficiency; HRQoL= health-related quality of life; NACT = neoadjuvant chemotherapy; OS = overall survival; PFS = progression-free survival; PFS2 = time to second progression; PR = partial response; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumours; TFST = time to first subsequent therapy.

1. Gonzalez-Martin A, et al. N Engl J Med. 2019;381(25):2391-2402; 2. Gonzalez-Martin A, et al. Presented at: ESMO; 27 September–1 October 2019; Barcelona, Spain. Abstract LBA1.

Courtesy of Robert L Coleman, MD

# PRIMA PRIMARY ENDPOINT: PFS OVERALL POPULATION




| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Niraparib | 487 | 454 | 385 | 312 | 295 | 253 | 167 | 111 | 94 | 58 | 29 | 21 | 13 | 4 | 0 |
| Placebo | 246 | 226 | 177 | 133 | 117 | 90 | 60 | 32 | 29 | 17 | 6 | 6 | 4 | 1 | 0 |

38% reduction in hazard of relapse or death with niraparib

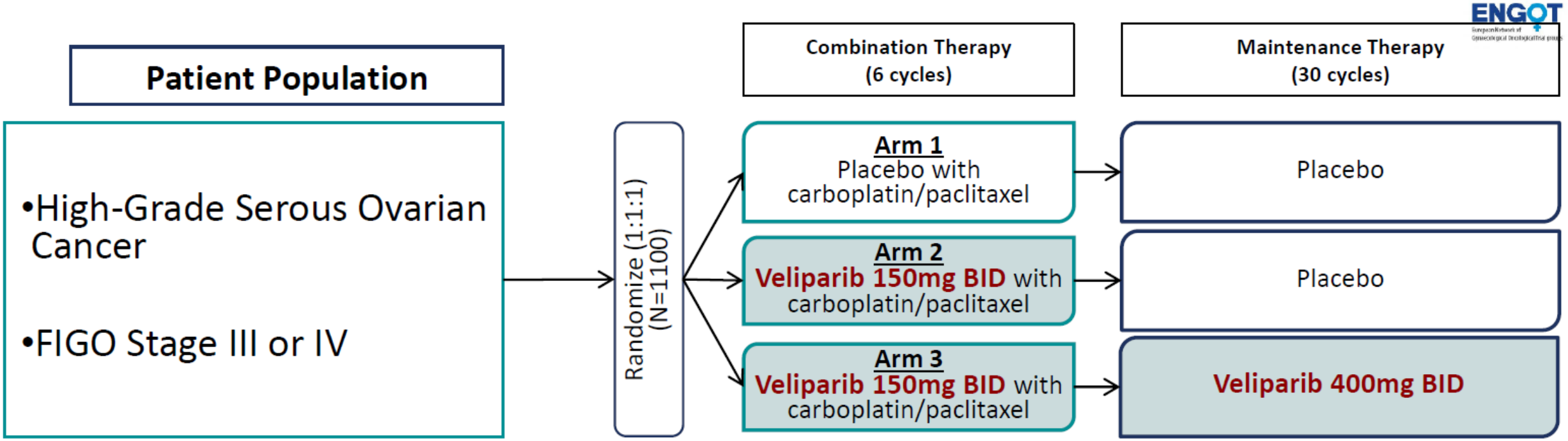
| | Niraparib (n=487) | Placebo (n=246) |
|---|---|---|
| **Median PFS** | | |
| months (95% CI) | 13.8 (11.5–14.9) | 8.2 (7.3–8.5) |
| **Patients without PD or death (%)** | | |
| 6 months | 73% | 60% |
| 12 months | 53% | 35% |
| 18 months | 42% | 28% |

1L, first-line; CI, confidence interval; CT, chemotherapy; PD, progressive disease; PFS, progression-free survival.
Discordance in PFS event between investigator assessment vs BICR ≈12%.
González-Martin, NEJM 2019

Courtesy of Robert L Coleman, MD

# VELIA: Study Design

**Only trial to include PARPi with chemotherapy before maintenance**




**Stratification Factors:**

- Stage III vs Stage IV
- ***gBRCA*-pos vs. *gBRCA*-neg**
- Region

**Primary Endpoints:**

- PFS of Arm 1 versus Arm 3 in ***BRCAmut*** *and in* ***ITT populations***

*In contrast to PRIMA and PAOLA,* ***PFS is measured from time of initiating chemotherapy*** *rather than from completion of chemotherapy*

BARCELONA 2019 ESMO congress

Subjects who complete the Combination Therapy Phase **and have not progressed** received single-agent veliparib/placebo

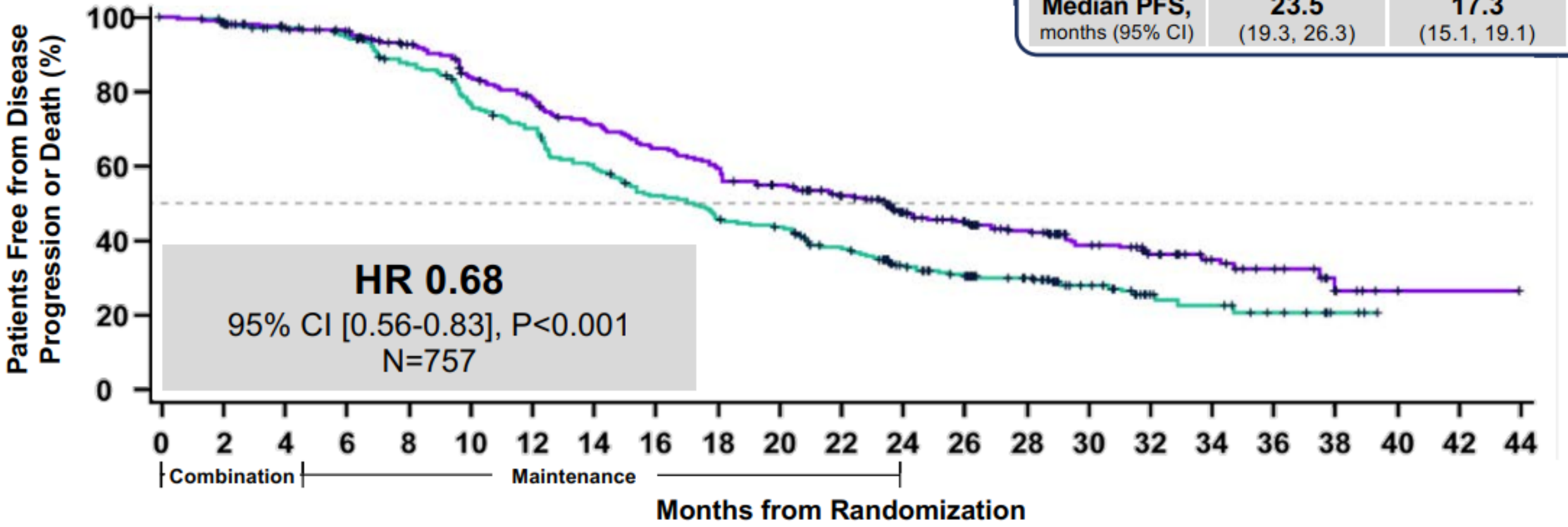

Coleman RL, et al. N Engl J Med 2019;381:1929-1939.
Coleman RL, et al. Annals of Oncology 2019;30:v895-v896.

# VELIA: PFS by Investigator Assessment

## ITT Population

*BRCAm* HRD | Non-HRD

| ITT | Veliparib-throughout | Control |
|---|---|---|
| Events (%) | 191/382 (50.0) | 237/375 (63.2) |
| **Median PFS,** months (95% CI) | **23.5** (19.3, 26.3) | **17.3** (15.1, 19.1) |




No. at Risk

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 375 | 356 | 340 | 328 | 297 | 260 | 236 | 202 | 172 | 153 | 143 | 119 | 84 | 70 | 55 | 36 | 21 | 16 | 10 | 3 | 0 |
| Veliparib-throughout | 382 | 352 | 337 | 329 | 308 | 275 | 253 | 228 | 208 | 192 | 172 | 153 | 111 | 95 | 76 | 55 | 38 | 26 | 19 | 7 | 2 | 1 | 0 |


Coleman RL, et al. N Engl J Med 2019;381:1929-1939.
Coleman RL, et al. Annals of Oncology 2019;30:v895-v896.


BARCELONA 2019 ESMO congress

Median duration of follow-up was 28 months at the time of database lock.

Courtesy of Robert L Coleman, MD

# ATHENA–MONO Study Schema

Athena
RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF NIVOLUMAB AND RUCAPARIB

## 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

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

### Randomization Stratification Factors

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

## 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.



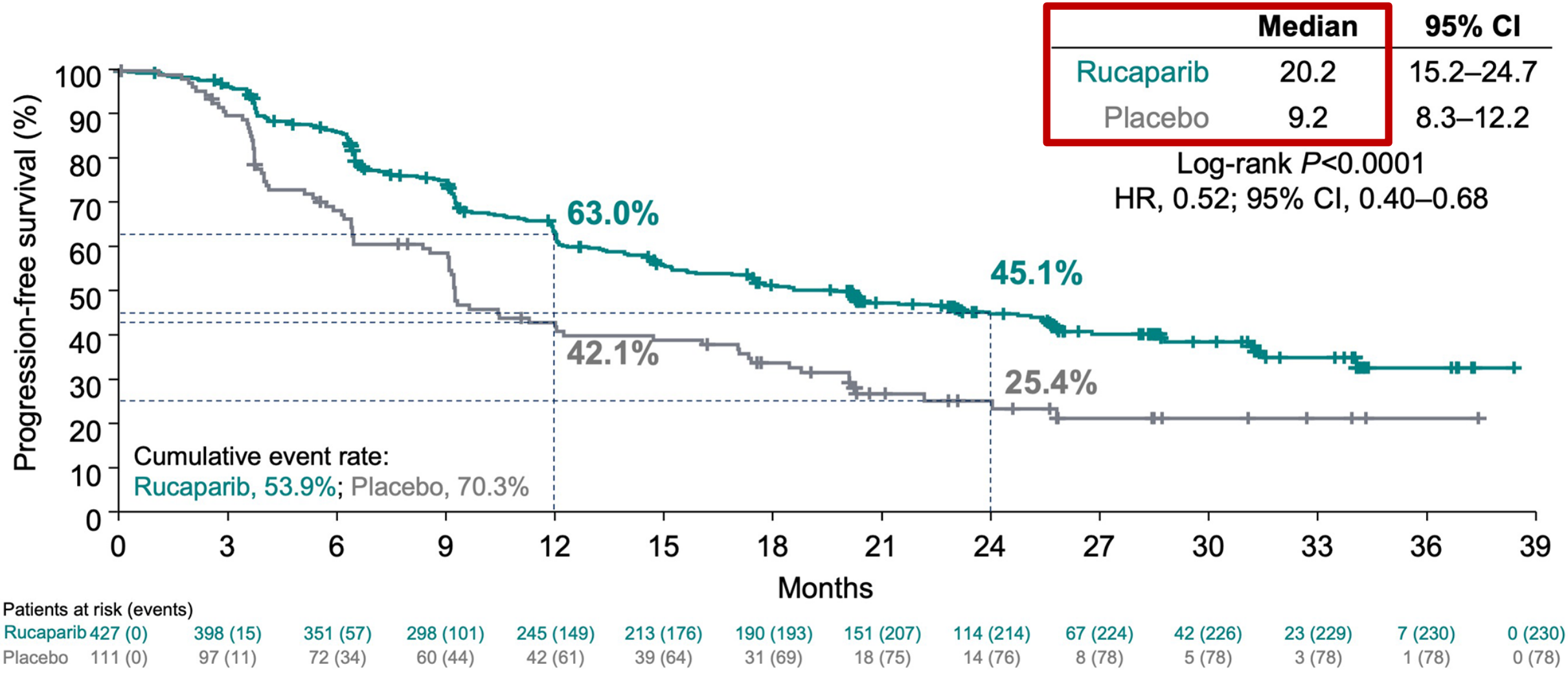
PRESENTED BY:
Bradley J. Monk, MD, FACS, FACOG (LBA5500)



***About half had NACT with interval debulking surgery**

# ATHENA MONO: RP3 trial of rucaparib vs placebo maintenance in first line responsive ovarian cancer

## Monk B et al. ASCO 2022

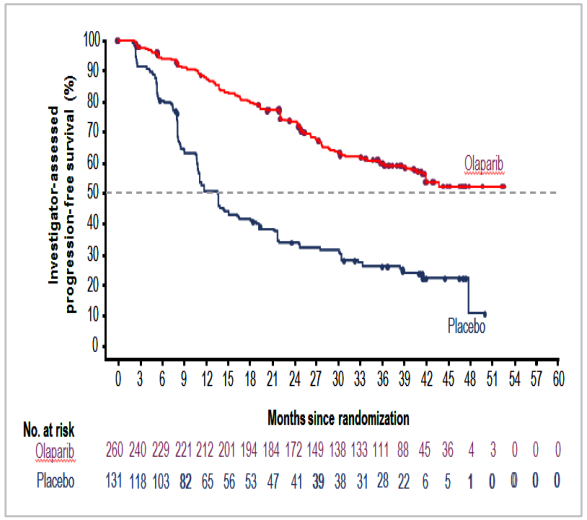
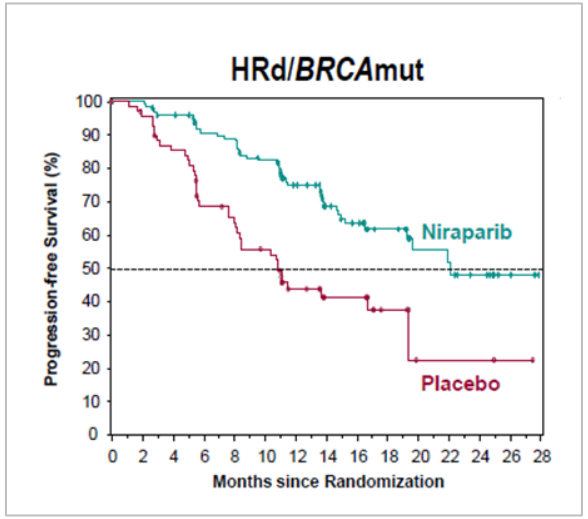
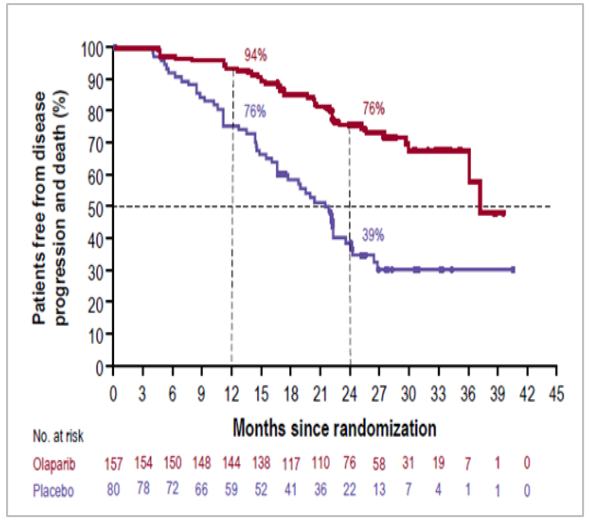
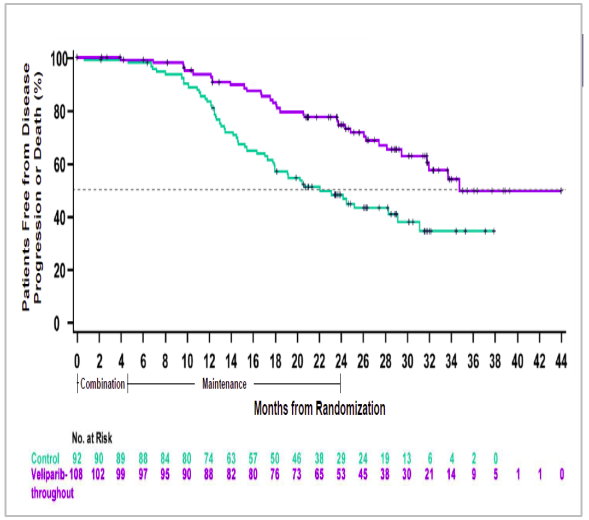



Data cutoff date: March 23, 2022.

# PFS Subgroups:

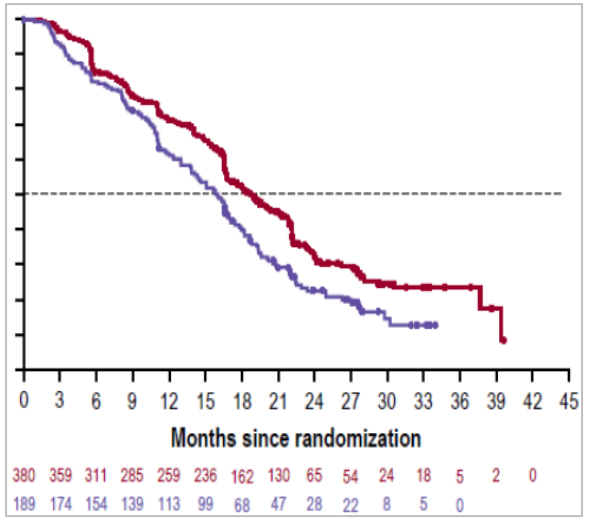
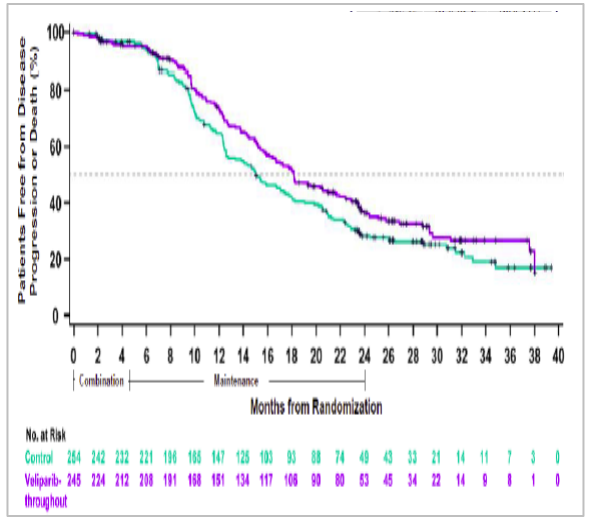
# First Line PARP Inhibitor Maintenance

# Newly diagnosed ovarian cancer: **BRCAmt**

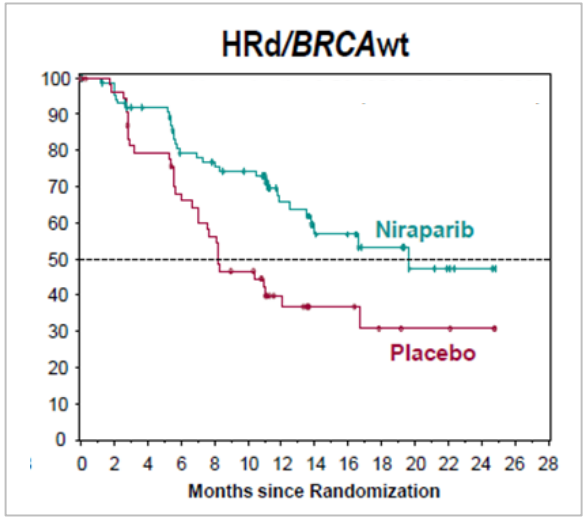
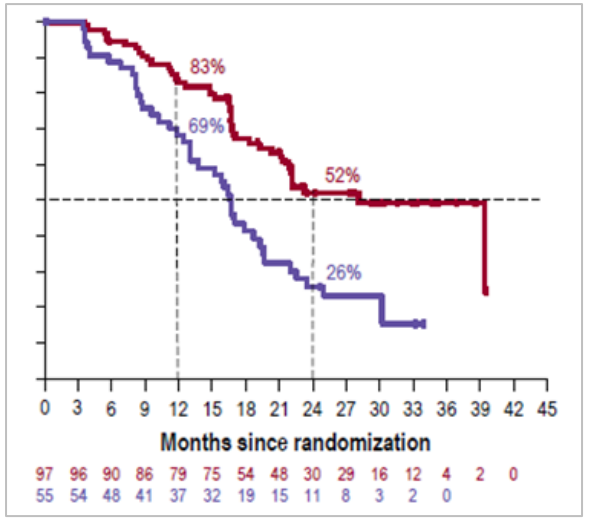
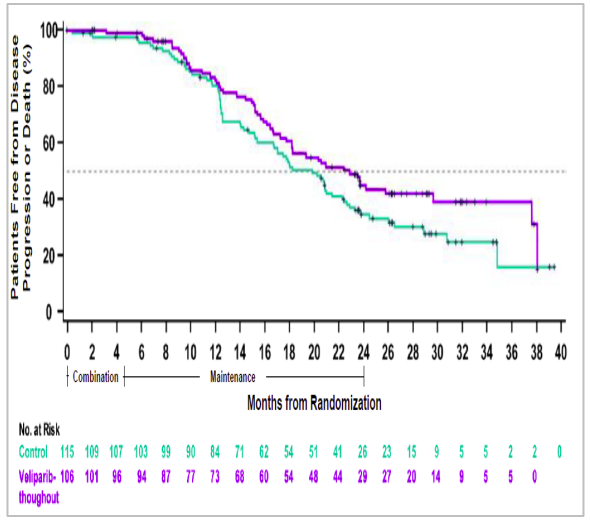
| SOLO1 | PRIMA | PAOLA1 | VELIA |
|---|---|---|---|
|  |  |  |  |
| **N = 391** | **N = 223** | **N = 235** | **N = 200** |
| **HR 0.30**<br>95% CI 0.23-0.41 | **HR 0.40**<br>95% CI 0.27-0.62 | **HR 0.31**<br>95% CI 0.20-0.47 | **HR 0.44**<br>95% CI 0.28-0.68 |
| 13.8 mos vs NR | 10.9 vs 22.1 mos | 21.7 vs 37.2 mos | 22.0 vs 34.7 mos |
| Moore NEJM 2018 | Gonzalez-Martin NEJM 2019 | Ray-Coquard NEJM 2019 | Coleman NEJM 2019 |

# Newly diagnosed ovarian cancer:

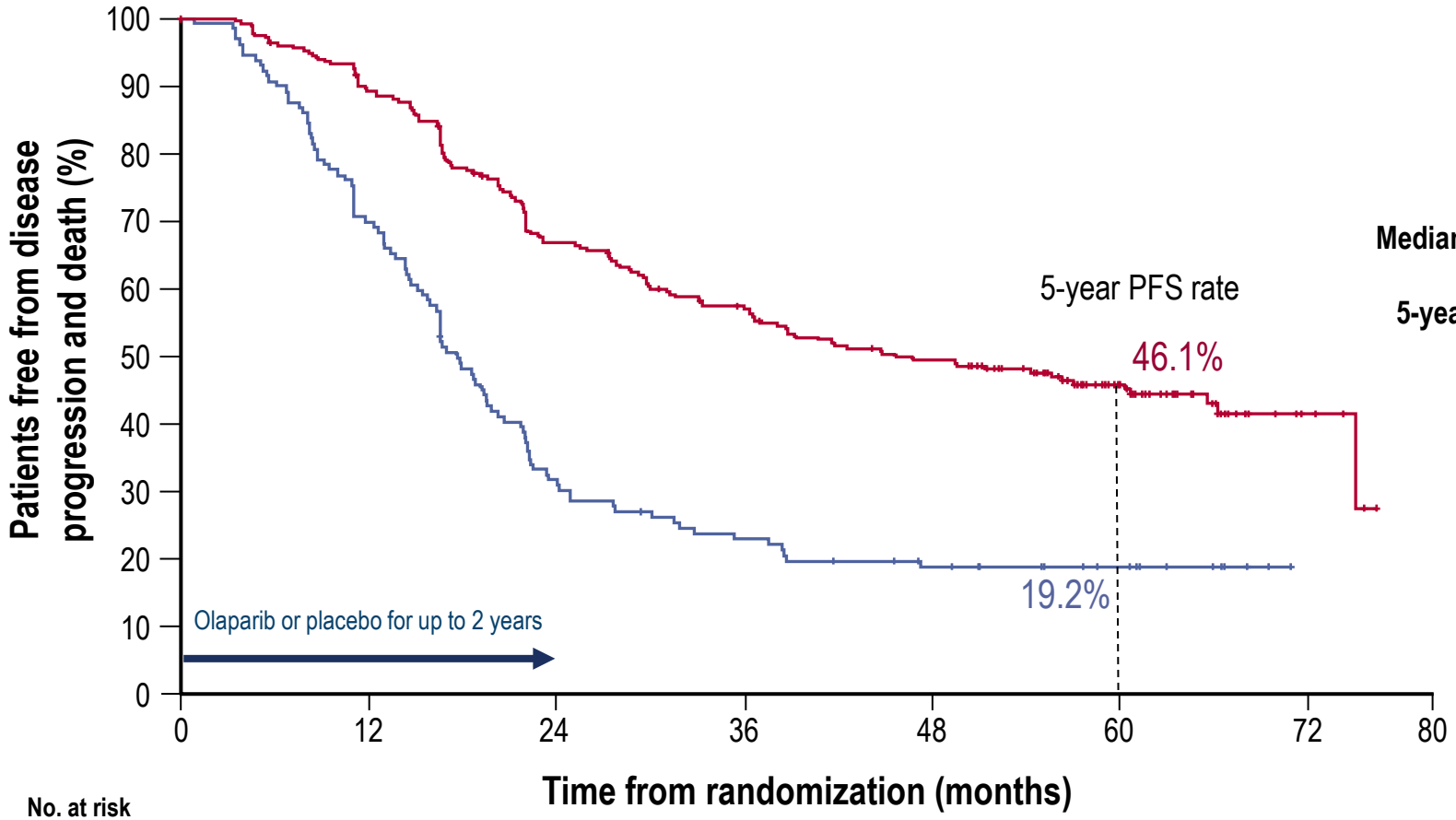
# BRCA wild-type (BRCAwt)

| PRIMA | PAOLA1 | VELIA |
|---|---|---|
| |  |  |
| **N = 510** | **N = 571** | **N = 557** |
| **N/A**<br>HR 0.50 (HRD; N=150)<br>HR 0.68 (HRP; N=249)<br>HR 0.85 (unknown; N=111) | **HR 0.71**<br>95% CI 0.58-0.88 | **HR 0.80**<br>95% CI 0.64-0.997 |
| N/A | 16.0 vs 18.9 mos | 15.1 vs 18.2 mos |
| Gonzalez-Martin NEJM 2019 | Ray-Coquard NEJM 2019 | Coleman NEJM 2019 |

# Newly diagnosed ovarian cancer:
# BRCAwt/HR deficient (HRD)

| PRIMA | PAOLA1 | VELIA |
|---|---|---|
|  |  |  |
| **N = 150** | **N = 152** | **N = 221** |
| **HR 0.50**<br>95% CI 0.31-0.83 | **HR 0.43**<br>95% CI 0.28-0.66 | **HR 0.74**<br>95% CI 0.52-1.06 |
| 8.2 vs 19.6 mos | 16.6 vs 28.1 mos | 11.5 vs 15.0 mos |
| MyChoice HRD ≥42 | MyChoice HRD ≥42 | MyChoice HRD ≥33 |
| Gonzalez-Martin NEJM 2019 | Ray-Coquard ESMO 2019 | Coleman NEJM 2019 |

# 2022 PAOLA Updated PFS: HRD-positive population*




| | Olaparib + bevacizumab (N=255) | Placebo + bevacizumab (N=132) |
|---|---|---|
| **Events,** n (%) | 136 (53.3) | 104 (78.8) |
| **Median PFS,** months | **46.8** | **17.6** |
| **5-year PFS rate**, % | **46.1** | **19.2** |

**HR 0.41** (95% CI 0.32–0.54)

59% reduction in risk of disease progression or death for olaparib + bevacizumab vs bevacizumab alone

**No. at risk**

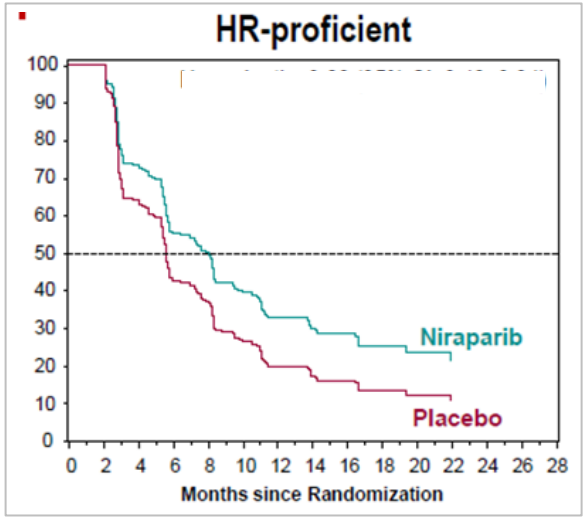
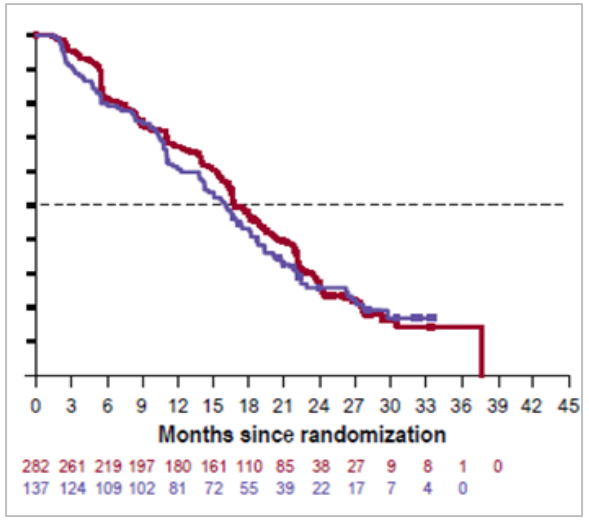
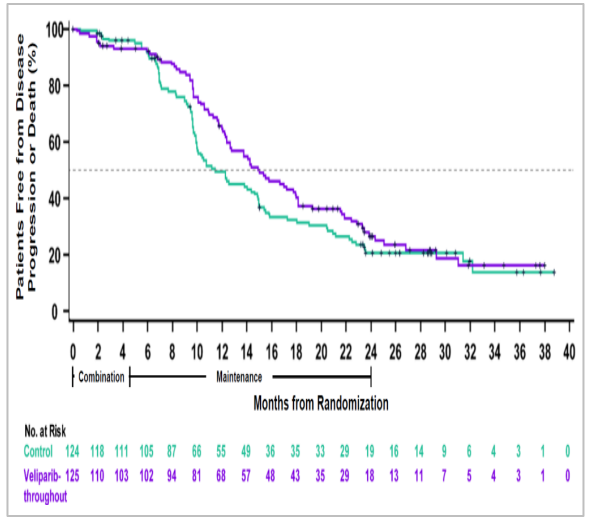
| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib + bevacizumab | 255 | 252 | 242 | 236 | 223 | 214 | 194 | 183 | 165 | 162 | 147 | 143 | 138 | 127 | 123 | 119 | 117 | 112 | 103 | 79 | 63 | 40 | 31 | 8 | 5 | 3 | 0 |
| Placebo + bevacizumab | 132 | 129 | 118 | 103 | 91 | 79 | 62 | 52 | 41 | 37 | 34 | 30 | 29 | 25 | 24 | 24 | 21 | 20 | 19 | 15 | 13 | 8 | 6 | 2 | 0 | | |



*Descriptive analysis; PFS by investigator-assessment (modified RECIST v1.1).

# Newly diagnosed ovarian cancer:

# BRCAwt/HR proficient (HRP)

| PRIMA | PAOLA1 | VELIA |
|---|---|---|
|  |  |  |
| N = 249 | N = 277 | N = 249 |
| **HR 0.68**<br>95% CI 0.49-0.94 | **HR 0.92**<br>95% CI 0.72-1.17 | **HR 0.81**<br>95% CI 0.60-1.09 |
| 5.4 vs 8.1 mos | 16.0 vs 18.9 mos | 15.1 vs 18.2 mos |
| MyChoice HRD <42 | MyChoice HRD <42 | MyChoice HRD <33 |
| Gonzalez-Martin NEJM 2019 | Ray-Coquard ESMO 2019 | Coleman NEJM 2019 |

# Investigator-Assessed PFS: Exploratory Subgroups

ATHENA-MONO

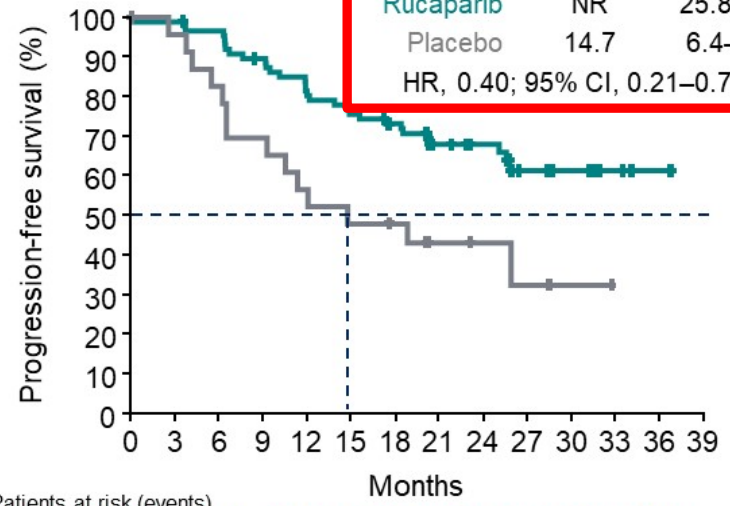


## HRD positive

### 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



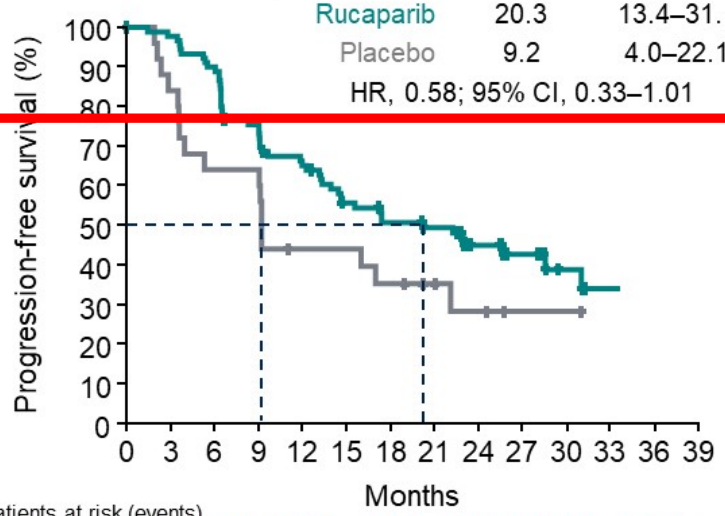

Patients at risk (events)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 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)

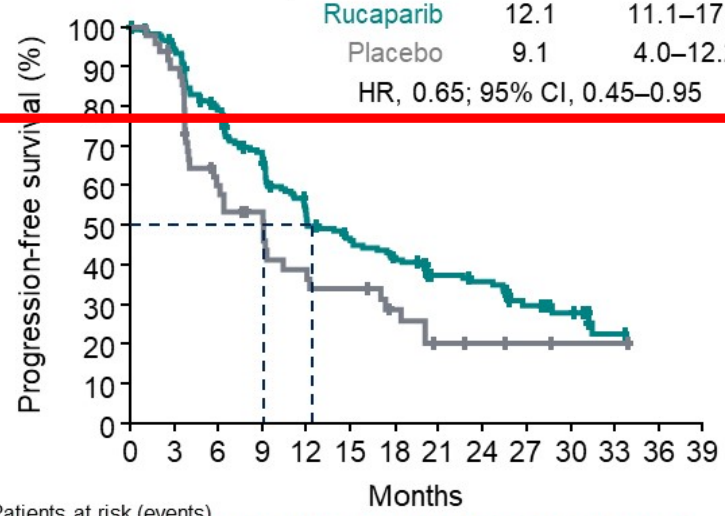
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rucaparib | 94 (0) | 81 (9) | 57 (30) | 41 (43) | 25 (47) | 8 (49) | 4 (50) |
| Placebo | 25 (0) | 16 (9) | 10 (14) | 8 (16) | 4 (17) | 1 (17) | 0 (17) |

## 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) |

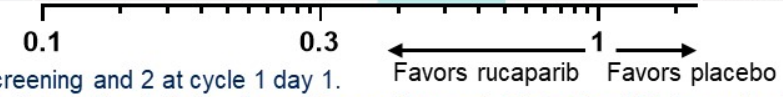
- Rucaparib demonstrated treatment benefit vs placebo regardless of BRCA mutation and HRD status

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.

# Investigator-Assessed PFS: Exploratory Subgroups

| | Rucaparib (n/N) | Placebo (n/N) | HR (95% CI) |
|---|---|---|---|
| **ITT population** | 230/427 | 78/111 | 0.52 (0.40–0.68) |
| **HRD population** | 80/185 | 31/49 | 0.47 (0.31–0.72) |
| **Randomization stratification factors** | | | |
| **HRD test status** | | | |
| HRD positive: BRCA$^{mut}$ | 30/91 | 14/24 | 0.40 (0.21–0.75) |
| HRD positive: BRCA$^{wt}$/LOH$^{high}$ | 50/94 | 17/25 | 0.58 (0.33–1.01) |
| HRD negative: BRCA$^{wt}$/LOH$^{low}$ | 120/189 | 35/49 | 0.65 (0.45–0.95) |
| HRD unknown: BRCA$^{wt}$/LOH$^{indeterminate}$ | 30/53 | 12/13 | 0.39 (0.20–0.78) |
| **Disease status post chemotherapy** | | | |
| No residual disease | 164/322 | 56/82 | 0.59 (0.43–0.80) |
| Residual disease | 66/105 | 22/29 | 0.44 (0.27–0.73) |
| **Timing of surgery** | | | |
| Primary surgery | 94/209 | 33/54 | 0.64 (0.43–0.95) |
| Interval debulking | 136/218 | 45/57 | 0.44 (0.31–0.62) |
| **ECOG performance status** | | | |
| 0 | 153/295 | 55/76 | 0.51 (0.37–0.69) |
| ≥1[a] | 77/132 | 23/35 | 0.68 (0.43–1.09) |
| **FIGO stage at diagnosis** | | | |
| III | 171/323 | 51/78 | 0.64 (0.46–0.87) |
| IV | 59/104 | 27/33 | 0.40 (0.25–0.64) |
| **CA-125 at baseline** | | | |
| Normal | 187/371 | 68/100 | 0.55 (0.42–0.72) |
| Above normal | 43/56 | 10/11 | 0.26 (0.13–0.55) |




Data cutoff date: March 23, 2022. [a]One rucaparib-treated patient had an ECOG performance status of 1 at screening and 2 at cycle 1 day 1.
BRCA, *BRCA1* or *BRCA2*; CA-125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; LOH, loss of heterozygosity; mut, mutant, PFS, progression-free survival; wt, wild type.

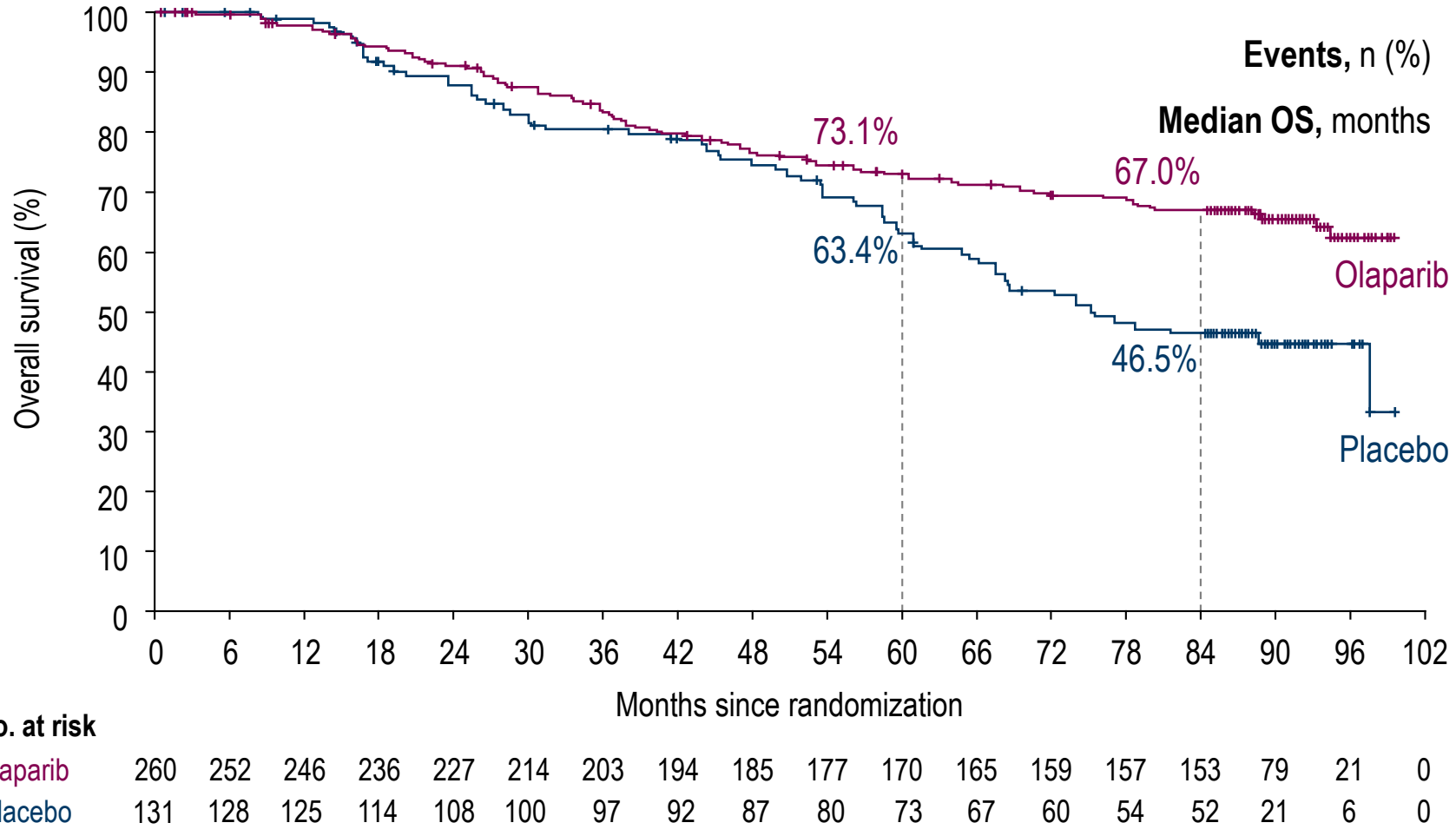



ATHENA-MONO

# Overall Survival First Line PARP Inhibitor Maintenance

# 2022 SOLO1 7-year Survival Analysis

## (ESMO 2022, JCO 9/2022)




| | Olaparib (N=260) | Placebo (N=131) |
|---|---|---|
| **Events,** n (%) | 84 (32.3) | 65 (49.6) |
| **Median OS,** months | **NR** | **75.2** |

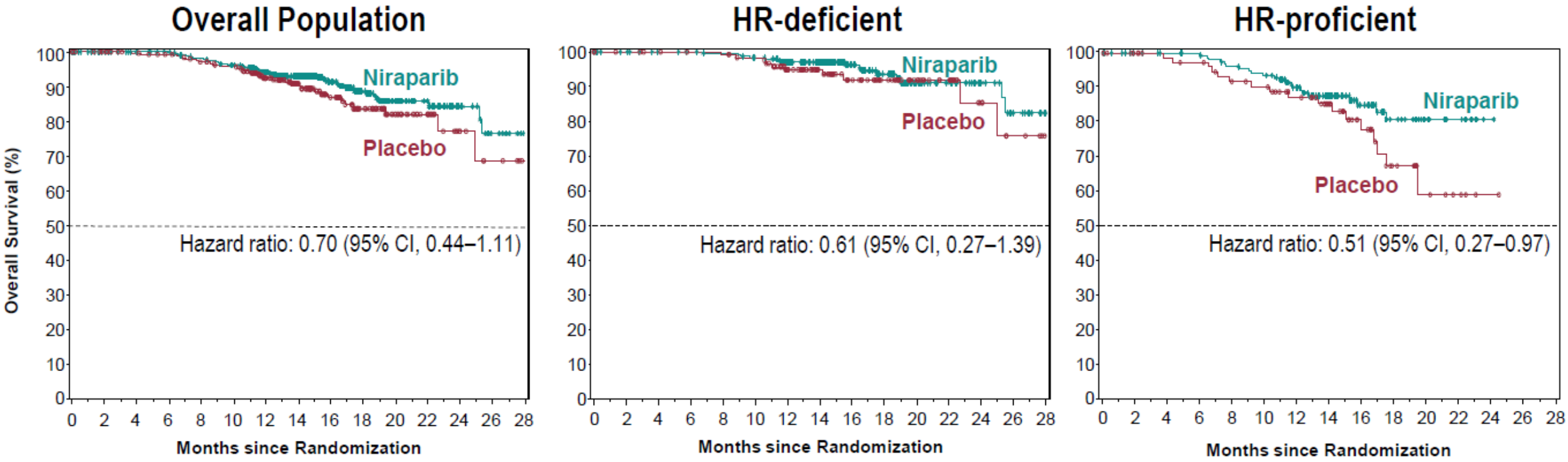
**HR 0.55** (95% CI 0.40–0.76); *P*=0.0004*

44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

**P*<0.0001 required to declare statistical significance

SOLO1 7-year OS: DiSilvestro P. et al. J Clin Oncol. 2022 Sep 9;JCO2201549. Online ahead of print. PMID: 36082969

# PRIMA Key Secondary Endpoint, Overall Survival (11% data maturity)



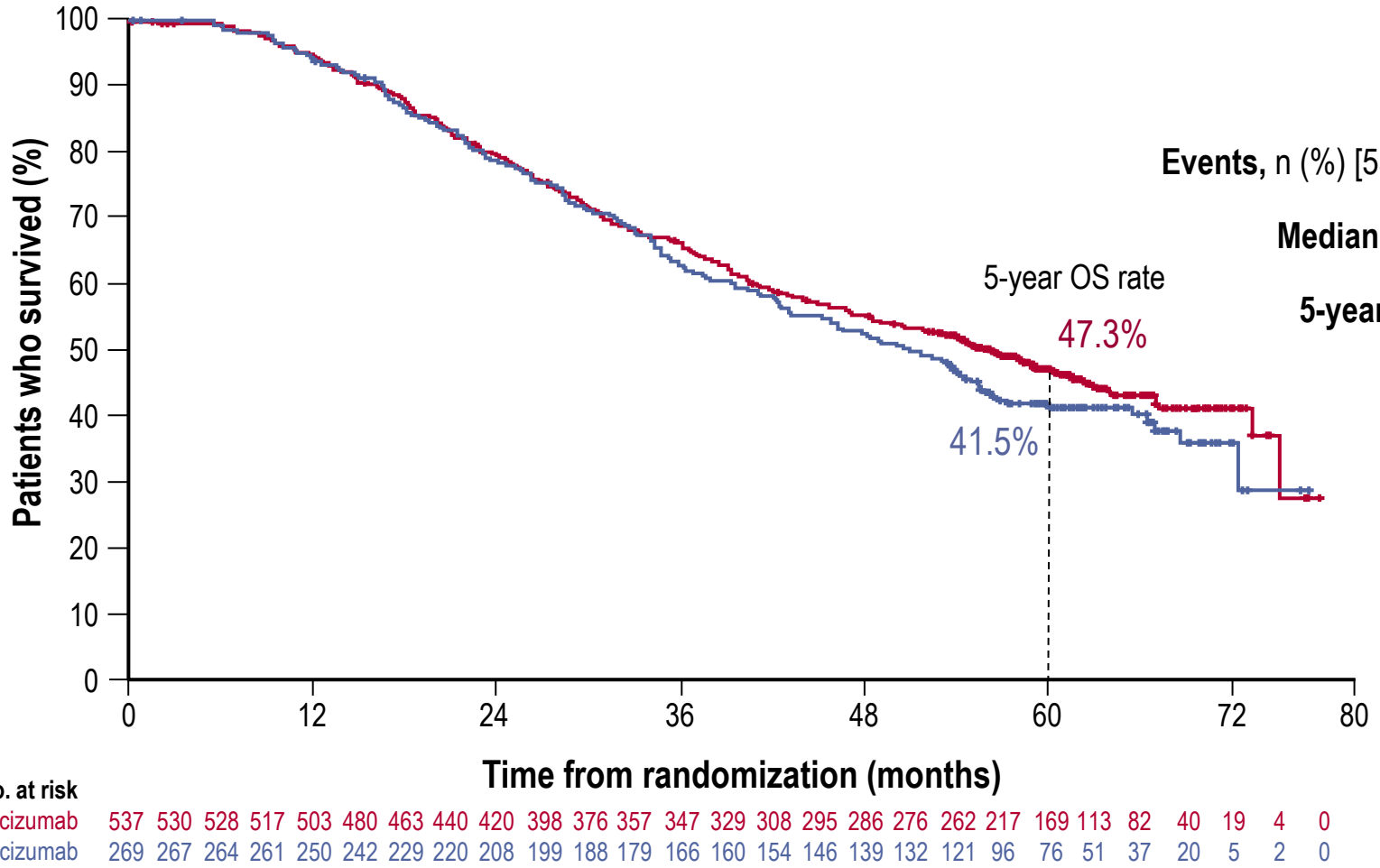

- **Pre-planned** interim analysis of overall survival numerically favors niraparib over placebo
  - Overall population 84% vs 77% alive at 2 years
  - HR-deficient 91% vs 85% alive at 2 years
  - HR-proficient 81% vs 59% alive at 2 years

**Overall survival data are not yet mature based on the prespecified analysis plan – GSK press release 9/2022**



CI, confidence interval; HR, homologous recombination.

# 2022 PAOLA OS analysis: 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**

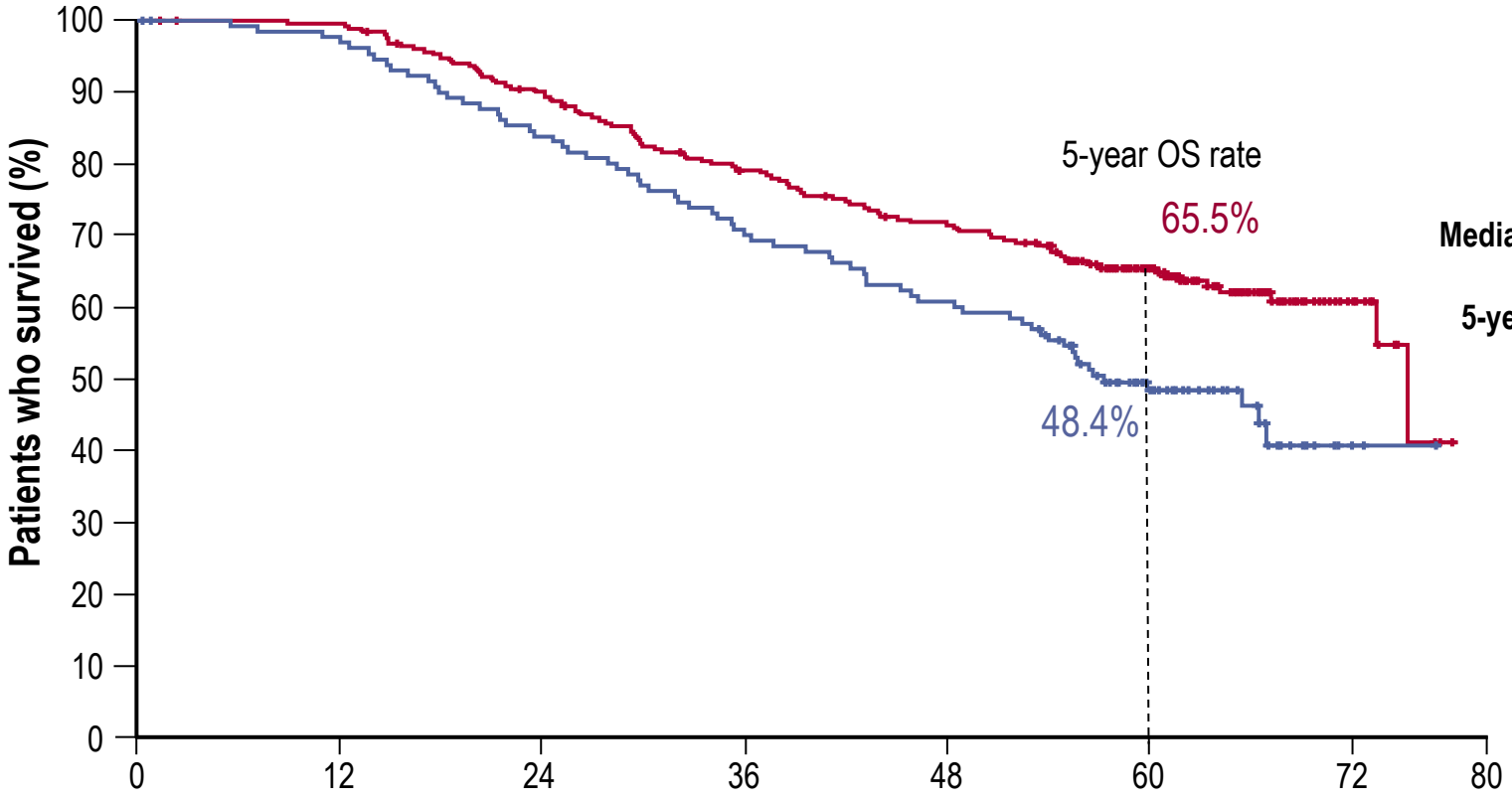
**Patients receiving a PARP inhibitor during any subsequent treatment**
Olaparib + bevacizumab: **19.6%** (105/537)
Placebo + bevacizumab: **45.7%** (123/269)

| No. at risk | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib + bevacizumab | 537 | 530 | 528 | 517 | 503 | 480 | 463 | 440 | 420 | 398 | 376 | 357 | 347 | 329 | 308 | 295 | 286 | 276 | 262 | 217 | 169 | 113 | 82 | 40 | 19 | 4 | 0 |
| Placebo + bevacizumab | 269 | 267 | 264 | 261 | 250 | 242 | 229 | 220 | 208 | 199 | 188 | 179 | 166 | 160 | 154 | 146 | 139 | 132 | 121 | 96 | 76 | 51 | 37 | 20 | 5 | 2 | 0 |

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

PARP, poly(ADP-ribose) polymerase.

# 2022 PAOLA: OS prolonged in the HRD+ subgroup




| No. at risk | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib + bevacizumab | 255 | 253 | 253 | 252 | 252 | 244 | 238 | 231 | 225 | 215 | 205 | 200 | 195 | 189 | 183 | 176 | 174 | 170 | 164 | 142 | 116 | 83 | 62 | 32 | 17 | 4 | 0 |
| Placebo + bevacizumab | 132 | 130 | 129 | 128 | 126 | 121 | 117 | 114 | 109 | 105 | 100 | 96 | 91 | 89 | 86 | 82 | 79 | 77 | 70 | 59 | 44 | 29 | 21 | 9 | 2 | 1 | 0 |

| | Olaparib + bevacizumab (N=255) | Placebo + bevacizumab (N=132) |
|---|---|---|
| **Events,** n (%) | 93 (36.5) | 69 (52.3) |
| **Median OS,** months | **75.2** (unstable)* | **57.3** |
| **5-year OS rate**, % | **65.5** | **48.4** |

**HR 0.62** (95% CI 0.45–0.85)

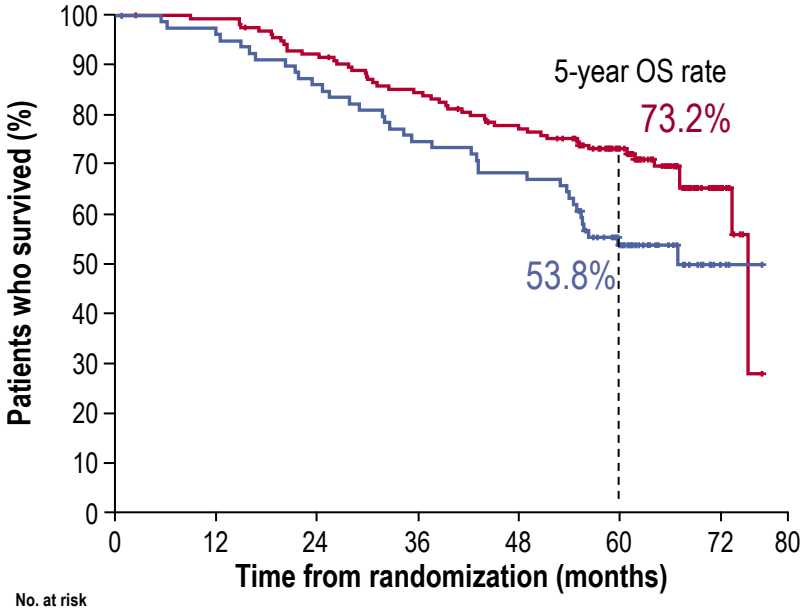
38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

**Patients receiving a PARP inhibitor during any subsequent treatment**
Olaparib + bevacizumab: **17.3%** (44/255)
Placebo + bevacizumab: **50.8%** (67/132)

*Median unstable; <50% data maturity.
HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay.

# 2022 PAOLA OS: BRCAm and HRD subgroups

**BRCAm***



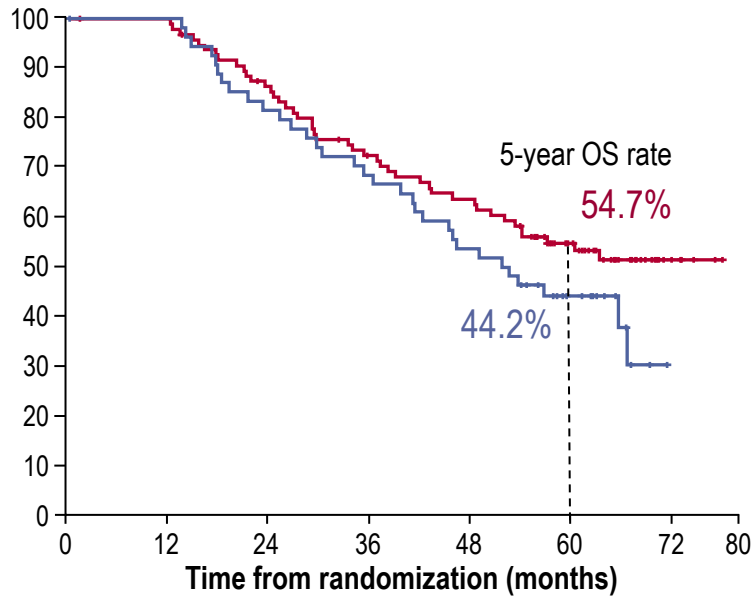

No. at risk

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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) | |

**36% mature**

**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) | |

**50% mature**

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

# Newly diagnosed ovarian cancer

| | SOLO-1[1] (N=391) | PRIMA[2] (N=733) | PAOLA-1[3] (N=806) | VELIA[4] (N=1140) | ATHENA-MONO[5] (N=538) |
|---|---|---|---|---|---|
| **PARP inhibitor** | Olaparib | Niraparib | Olaparib | Veliparib | Rucaparib |
| **Arms** | 1. Olaparib<br>2. Placebo | 1. Niraparib<br>2. Placebo | 1. Bev/olaparib<br>2. Bev/placebo | 1. Chemo/veliparib⇨veliparib<br>2. Chemo/veliparib⇨placebo<br>3. Chemo/placebo⇨placebo | 1. Rucaparib<br>2. Placebo |
| **Population** | HGS/endometrioid and BRCAmt | HGS/endometrioid | HGS/endometrioid or BRCAmt | HGS | HG Ovarian |
| **Primary endpoint** | **PFS** (investigator) | **PFS** (BICR)<br><br>Hierarchical:<br>HRD⇨ITT | **PFS** (investigator)<br><br>Predefined subgroups:<br>tBRCA status and HRD | **PFS** (investigator)<br><br>Hierarchical:<br>BRCAmt⇨HRD⇨ITT | **PFS** (investigator)<br><br>Predefined subgroups:<br>ITT, HRD positive |
| **PFS Outcome** | **HR 0.30**<br>(13.8mos vs NR) | **HR 0.62**<br>(8.2 vs 13.8 mos) | **HR 0.59**<br>(16.6 vs 22.1 mos) | **HR 0.68**[8] (Arm 1 vs 3)<br>(17.3 vs 23.5 mos) | **HR 0.52**<br>(9.2 vs 20.2 mos) |
| **OS Outcome** | **HR 0.55**[6] (NS)<br>(75.2mos vs NR)<br>p=0.0004 | **HR 0.70** (NS)<br>(24m 77% vs 84%) | **HR 0.92**[7] (NS)<br>(51.6 vs 56.5mos) | | |

[1]Moore NEJM 2018
[2]Gonzalez-Martin NEJM 2019
[3]Ray-Coquard NEJM 2019
[4]Coleman NEJM 2019
[5]Monk B ASCO 2022 3/31/22
[6]DiSIlvestro JCO 2022
[7]Ray-Coquard ESMO 2022
[8]Conf by BICR

# Newly diagnosed disease

- All trials of PARPi maintenance in newly diagnosed ovarian cancer are positive for prolonged PFS
- Patients with BRCA mutations consistently derive the greatest PFS benefit in these trials
- HRD testing does not consistently identify a subpopulation of patients with no PFS benefit from PARPi maintenance
  - May provide information regarding degree of PFS benefit
  - ~12-18% of patients had indeterminate results on testing
- Clinically meaningful 7-year OS for *BRCAm* pts treated with olaparib (SOLO1) and HRD positive pts treated with olaparib and bevacizumab (PAOLA)

# PARPi: Approved Indications in Ovarian Cancer

| Primary Therapy | Front-Line Maintenance | Maintenance post-Recurrence | Recurrent Disease |
|---|---|---|---|
| Veliparib: Pending, data from VELIA | Olaparib [FDA]: gBRCAm or sBRCAm, (SOLO-1) 12/2018 | | |
| | Niraparib [FDA]: maintenance in pts with CR or PR after initial therapy (PRIMA) 4/2020 | | |
| | Olaparib + Bev [FDA]: Chemo with bev and olaparib with bev maintenance: HRD positive (PAOLA) 5/2020 | | |
| | Rucaparib: maintenance in responding pts (ATHENA-MONO) ASCO 2022 | | |

# FDA Advises Manufacturer Not to Submit First-Line Maintenance sNDA for Rucaparib Until OS Survival Data from the ATHENA-MONO Trial Are More Mature

## June 17, 2022

"In consultation with the FDA, [the manufacturer of rucaparib] recently was advised not to file a supplemental new drug application based on data from a cohort of the Phase III ATHENA study until the study's overall survival data mature.

In the 8-K, [the manufacturer] said the FDA has accepted a request for a pre-NDA meeting and noted that the ATHENA-MONO portion of the Phase III study has met its primary endpoint of progression-free survival compared to placebo. OS is a secondary endpoint for ATHENA-MONO and the data are approximately 25% mature at present. [The manufacturer] said the FDA urged it to hold off filing for supplemental approval until the OS data reach 50% maturity, and indicated an advisory committee review would likely be necessary if the data were filed earlier than that point.

In a statement to *Scrip*, the firm said that although it cannot anticipate the outcome of the pre-NDA meeting, 'we are encouraged that the FDA is willing to have a dialogue.' [They] estimate the ATHENA-MONO OS data will reach 50% maturity in approximately two years."

https://scrip.pharmaintelligence.informa.com/SC146575/Clovis-Withdraws-Rubraca-Ovarian-Cancer-Indication-Due-To-Survival-Imbalance?vid=Pharma

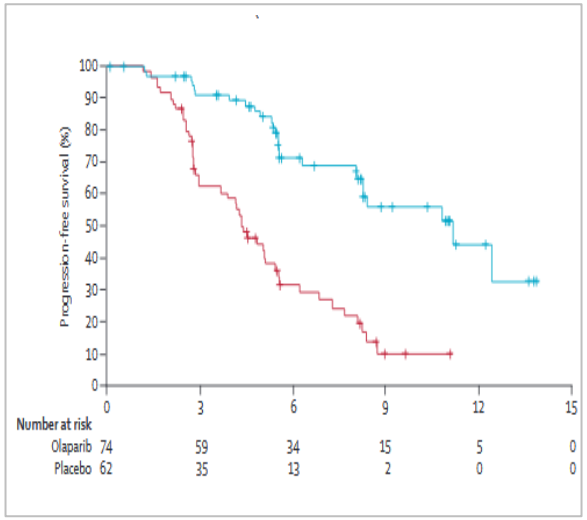
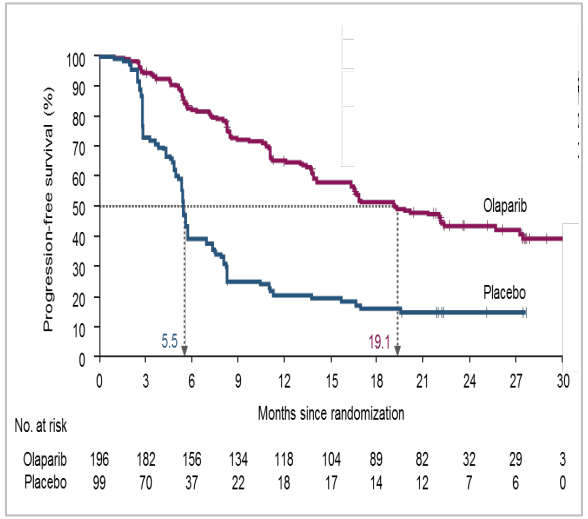
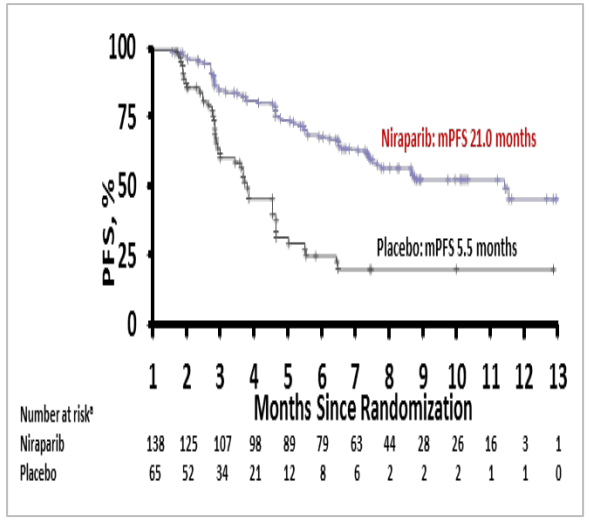
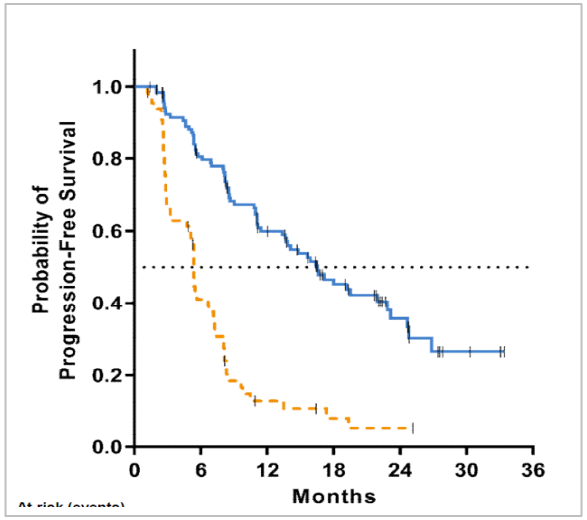
RTP RESEARCH TO PRACTICE

# Platinum-sensitive maintenance

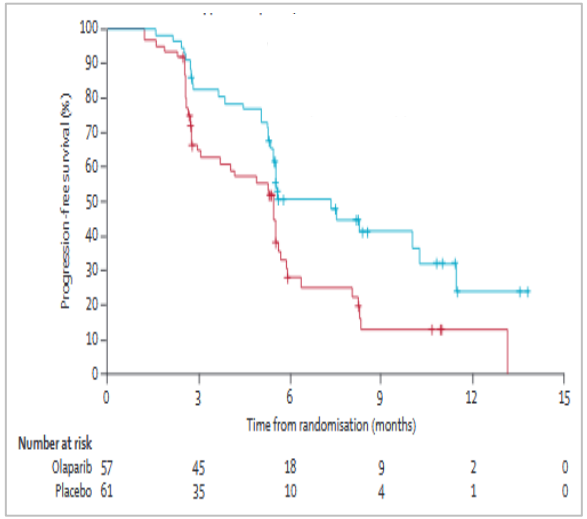
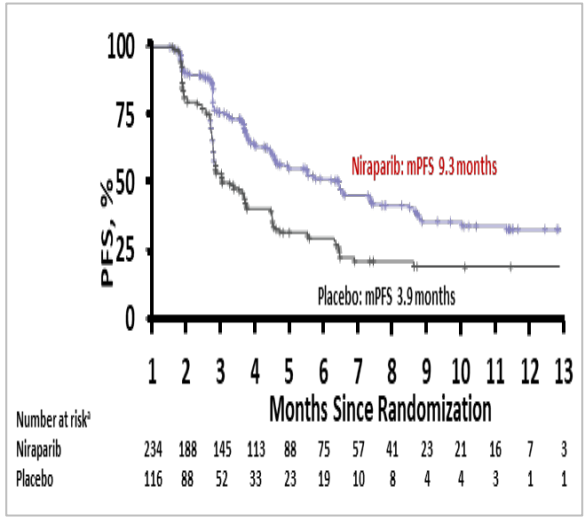
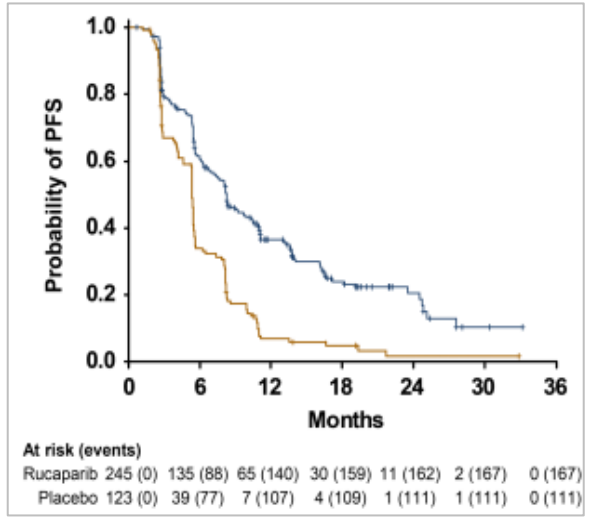
| | Study 19[1] (N=265) | SOLO-2[2] (N=295) | NOVA[3] (N=553; 203 gBRCA, 350 non-gBRCA) | ARIEL3[4] (N=564) |
|---|---|---|---|---|
| **PARP inhibitor** | Olaparib | Olaparib | Niraparib | Rucaparib |
| **Arms** | 1. Olaparib<br>2. Placebo | 1. Olaparib<br>2. Placebo | 1. Niraparib<br>2. Placebo | 1. Rucaparib<br>2. Placebo |
| **Population** | HGS | HGS/endometrioid and BRCAmt | HGS | HGS/endometrioid |
| **Primary endpoint** | **PFS** (investigator) | **PFS** (investigator) | **PFS** (BICR)<br><br>Independent cohorts:<br>gBRCAmt<br>gBRCAwt<br>Hierarchical HRD⇨ITT | **PFS** (investigator)<br><br>Hierarchical<br>BRCAmt⇨HRD⇨ITT |
| **Outcome** | **HR 0.35**<br>(4.8 vs 8.4 mos) | **HR 0.30**<br>(5.5 vs 19.1 mos) | gBRCAmt: **HR 0.27**<br>(5.5 vs 21.0 mos)<br>gBRCAwt: **HR 0.45**<br>(3.9 vs 9.3 mos) | **HR 0.36**<br>(5.4 vs 10.8 mos) |

[1]Ledermann NEJM 2012; [2]Pujade-Lauraine Lancet Oncol 2017; [3]Mirza NEJM 2016; [4]Coleman Lancet 2017

# Platinum sensitive maintenance: BRCAmt

| Study 19 | SOLO2 | NOVA | ARIEL3 |
|---|---|---|---|
|  |  |  |  |
| **N = 136** | **N = 294** | **N = 203** | **N = 196** |
| **HR 0.18**<br>95% CI 0.10-0.31 | **HR 0.30**<br>95% CI 0.22-0.41 | **HR 0.27**<br>95% CI 0.17-0.41 | **HR 0.23**<br>95% CI 0.16-0.34 |
| 4.3 vs 11.2 mos | 5.5 vs 19.1 mos | 5.5 vs 21.0 mos | 5.4 vs 16.6 mos |
| Ledermann NEJM 2012 | Pujade-Lauraine Lancet Oncol 2017 | Mirza NEJM 2016 | Coleman Lancet 2017 |

# Platinum sensitive maintenance: BRCAwt

| Study 19 | NOVA | ARIEL3 |
|---|---|---|
|  |  |  |
| **N=118** | **N = 350** | **N = 368** |
| **HR 0.54**<br>95% CI 0.34-0.85 | **HR 0.45**<br>95% CI 0.34-0.61 | **HR 0.44**<br>95% CI 0.34-0.56 |
| 5.5 vs 7.4 mos | 3.9 vs 9.3 mos | 5.4 vs 8.2 mos |





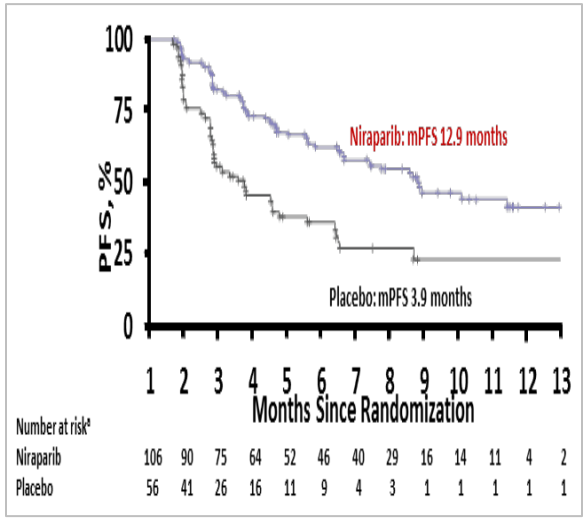


Ledermann Lancet Oncol 2014; Mirza NEJM 2016; Coleman Lancet Oncol 2017; Coleman SGO 2019

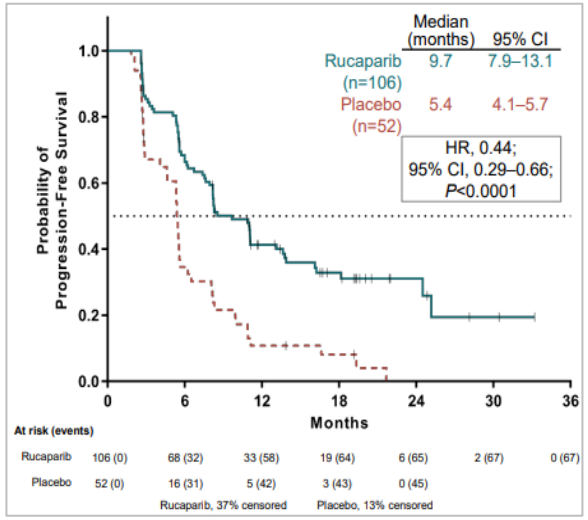
# Platinum sensitive maintenance: BRCAwt

## HR Deficient

### NOVA



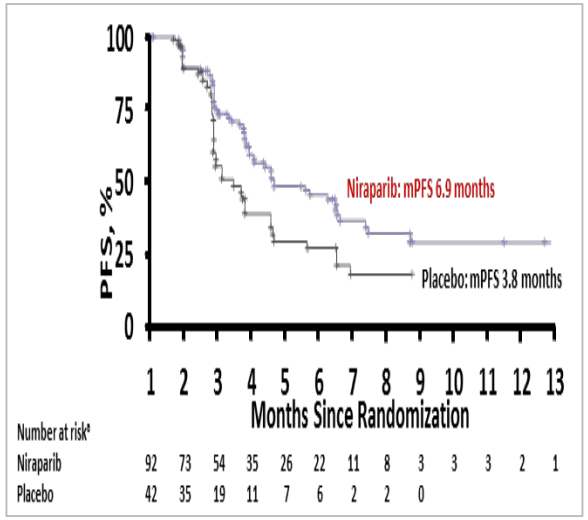

### ARIEL3



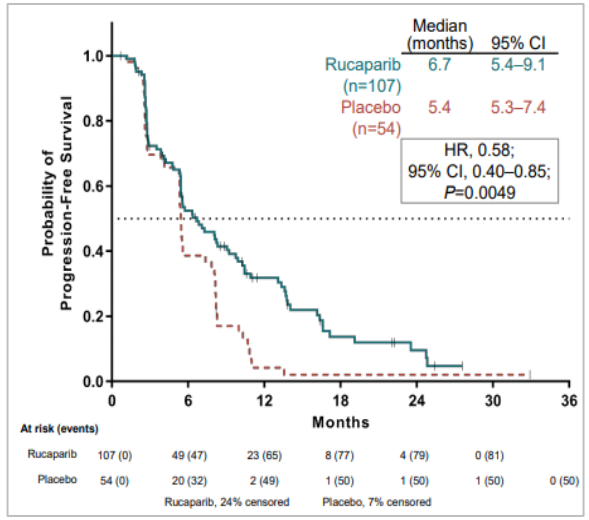

| N = 162 | N = 158 |
|---|---|
| **HR 0.38**<br>95% CI 0.24-0.59 | **HR 0.44**<br>95% CI 0.29-0.66 |
| 3.9 vs 12.9 mos | 5.4 vs 9.7 mos |
| MyChoice HRD ≥42 | Foundation LOH ≥16 |

## HR Proficient

### NOVA




### ARIEL3

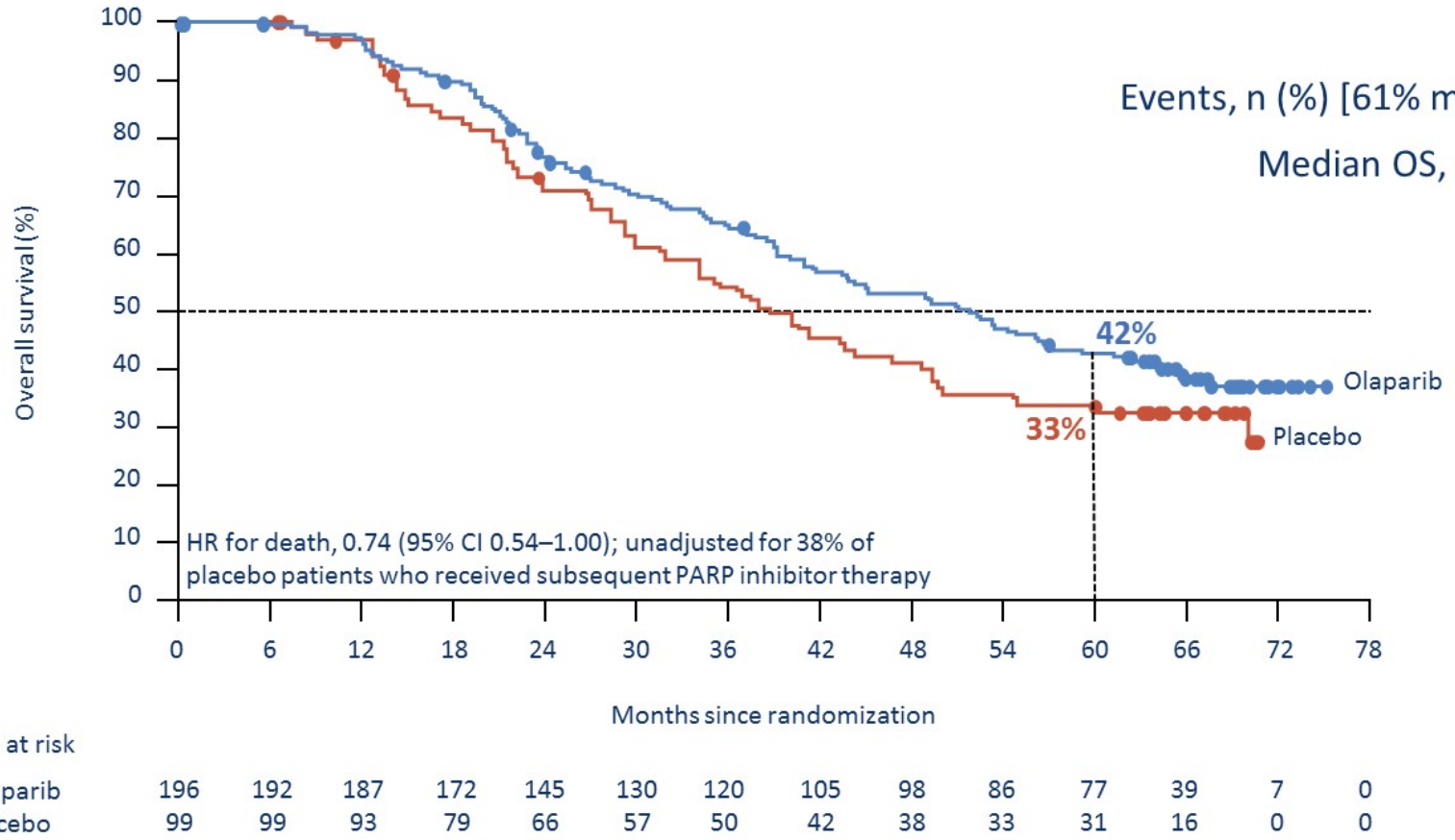



| N = 134 | N = 161 |
|---|---|
| **HR 0.58**<br>95% CI 0.36-0.92 | **HR 0.58**<br>95% CI 0.40-0.85 |
| 3.8 vs 6.9 mos | 5.4 vs 6.7 mos |
| MyChoice HRD <42 | Foundation LOH <16 |

Mirza NEJM 2016; Coleman Lancet Oncol 2017; Ledermann Lancet 2017

# 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)

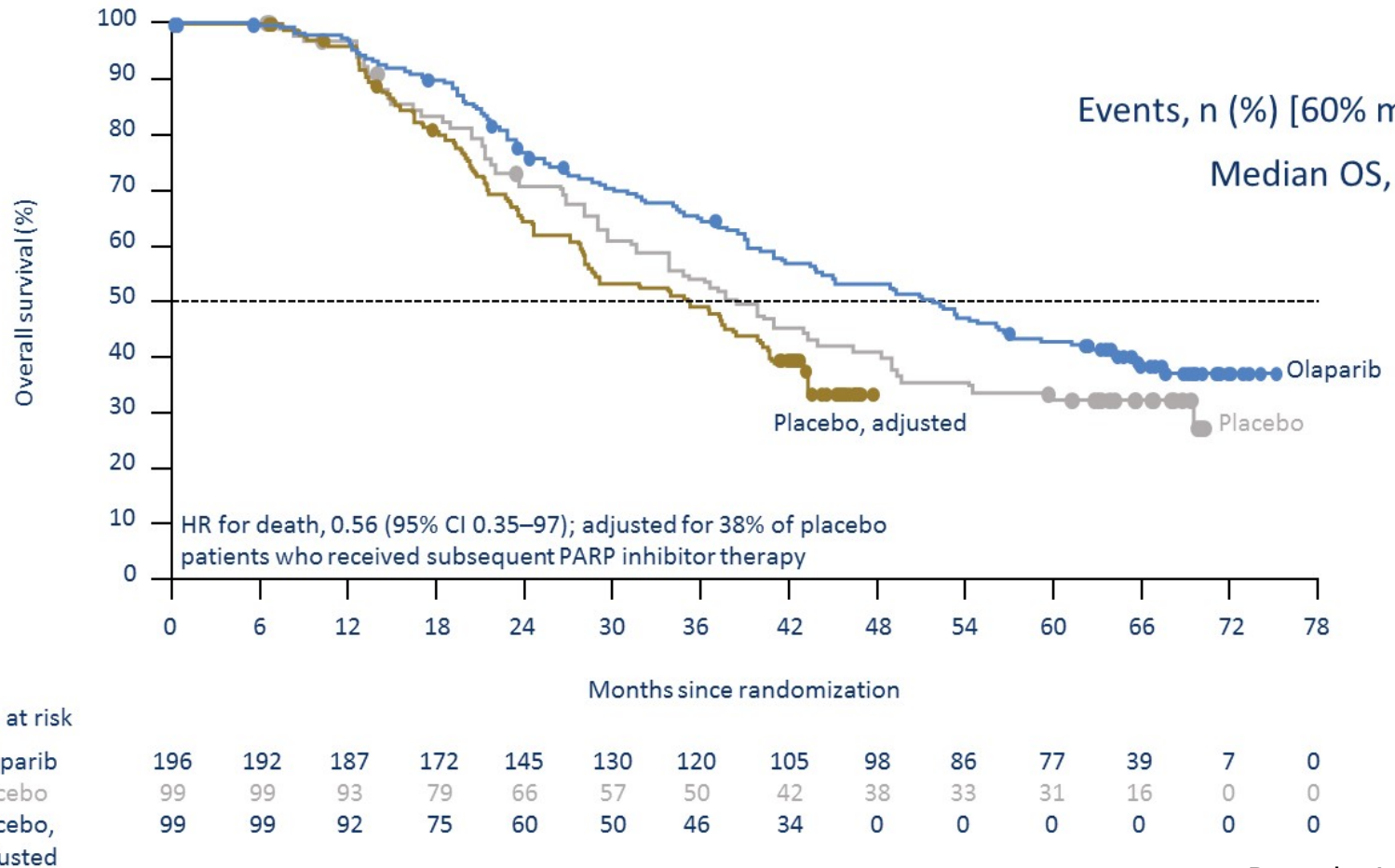
**OS analysis in the Myriad gBRCAm subgroup†**
HR 0.71 (95% CI 0.52–0.97)

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

Poveda A, et al. J Clin Oncol 2020;38(15_suppl):abstract 6002.

# SOLO2: final analysis of OS, adjusted for subsequent PARP inhibitor therapy in the placebo group

## Median OS improved by 16.3 months with maintenance olaparib over placebo, after adjusting for subsequent PARP inhibitor therapy in placebo patients




No. at risk

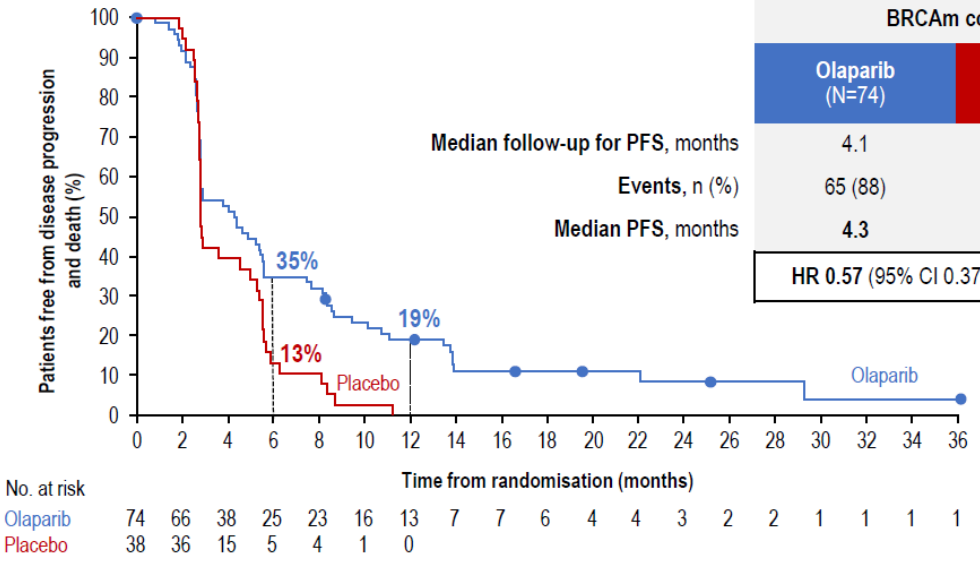
| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib | 196 | 192 | 187 | 172 | 145 | 130 | 120 | 105 | 98 | 86 | 77 | 39 | 7 | 0 |
| Placebo | 99 | 99 | 93 | 79 | 66 | 57 | 50 | 42 | 38 | 33 | 31 | 16 | 0 | 0 |
| Placebo, adjusted | 99 | 99 | 92 | 75 | 60 | 50 | 46 | 34 | 0 | 0 | 0 | 0 | 0 | 0 |

| | Olaparib (N=196) | Placebo (N=99) |
|---|---|---|
| Events, n (%) [60% maturity] | 116 (59) | 61 (62) |
| Median OS, months | 51.7 | 35.4 |
| **HR 0.56** | | |
| 95% CI 0.35–0.97 | | |

**The RPSFT model (re-censored) adjusts for the 38% of placebo patients who received subsequent PARP inhibitor therapy**

Poveda A, et al. J Clin Oncol 2020;38(15_suppl):abstract 6002.

# PFS BRCAm Cohort




| | 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 | | |

# OReO study

## Olaparib Re-treatment in platinum sensitive recurrent Ovarian cancer

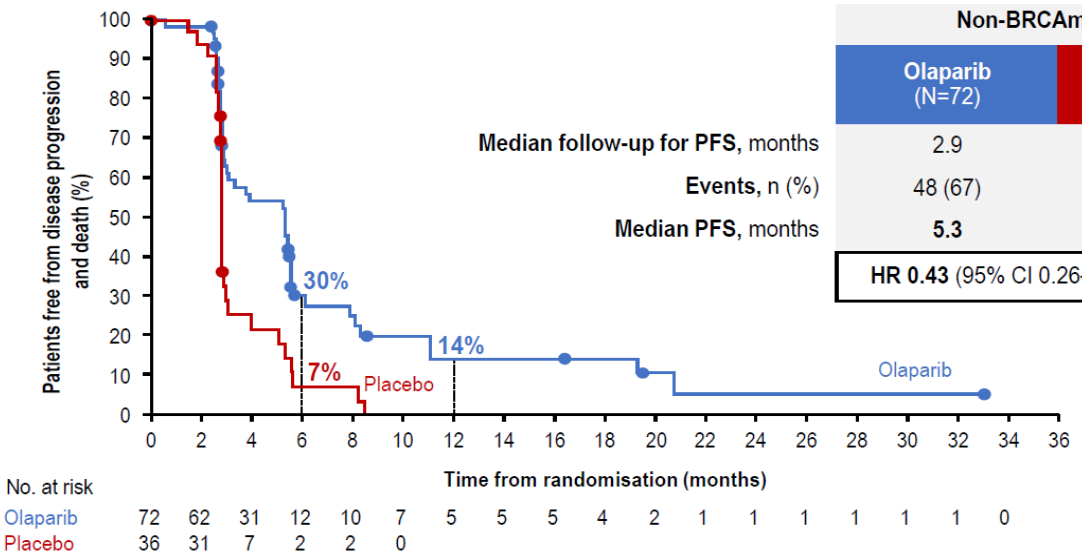
2021 ESMO congress

CI, confidence interval.

## Baseline characteristics

| | BRCAm cohort (N=112) | | Non-BRCAm cohort (N=108) | |
|---|---|---|---|---|
| | Olaparib (N=74) | Placebo (N=38) | Olaparib (N=72) | Placebo (N=36) |
| Median (range) patient age, years | 58.5 (37–80) | 61.5 (44–87) | 66.5 (29–81) | 62.5 (43–77) |
| **No. of prior lines of any chemotherapy, n (%)** | | | | |
| 2 | 5 (7) | 3 (8) | 10 (14) | 5 (14) |
| 3 | 31 (42) | 16 (42) | 31 (43) | 17 (47) |
| 4 | 21 (28) | 11 (29) | 11 (15) | 6 (17) |
| >4 | 17 (23) | 8 (21) | 20 (28) | 8 (22) |
| **No. of prior lines of PBC, n (%)** | | | | |
| 2 | 12 (16) | 3 (8) | 17 (24) | 5 (14) |
| 3 | 36 (49) | 19 (50) | 32 (44) | 20 (56) |
| ≥4 | 26 (35) | 16 (42) | 23 (32) | 11 (31) |
| **Response to PBC prior to study entry, n (%)** | | | | |
| Complete | 15 (20) | 13 (34) | 19 (26) | 11 (31) |
| Partial | 58 (78) | 25 (66) | 53 (74) | 25 (69) |
| Missing | 1 (1) | 0 | 0 | 0 |

# PFS non-BRCAm Cohort




| | 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

# MDS/AML in Randomized Ovarian Cancer PARP Inhibitor Maintenance Trials

JOHNS HOPKINS MEDICINE

| Trial | Setting | Agent | PARPi Duration | MDS/AML Events by arm PARPi, n (%) | Comparator, n (%) |
|---|---|---|---|---|---|
| SOLO1[4] | 1L maint | Olaparib | 2 years | 3/260 (1.5) | 1/130 (0.8) |
| PRIMA[6] | 1L maint | Niraparib | 3 years | 1/484 (<1) | 0/244 |
| PAOLA1[5] | 1L maint | Olaparib | 2 years | 6/535 (1) | 1/267 (<1) |
| ATHENA MONO[9] | 1L maint | Rucaparib | 2 years | 2/425 (0.5) | 0/110 |
| Study19[8] | PS maint | Olaparib | UDP, 18% >3yrs | 2/136 (1.5) | 1/129 (<1) |
| SOLO2[2] | PS maint | Olaparib | UDP, mean 29.1 mos | 16/195 (8) | 4/99 (4) |
| NOVA[3] | PS maint | Niraparib | UDP | 13/367 (3.5) | 3/179 (1.7) |
| g*BRCA*m | | | | 9/136 (6.6) | 6/56 (3.1) |
| non-g*BRCA*m | | | | 4/231 (1.7) | 1/114 (0.9) |
| ARIEL3[7] | PS maint | Rucaparib | UDP, median 8.3 mos | 3/375 (1) | 0/189 |

Median time to onset of MDS/AML 17.8 months[1]

[1]Morice P-M, et al. Lancet Haematol 2021;8:e122-e134, [2]Poveda A, et al. J Clin Oncol 2020;38(15_suppl):abstract 6002, [3]Matulonis U. et al. SGO 2021, [4]DiSilvestro P, et al. J Clin Oncol 2022, [5]Ray-Coquard I et al. NEJM Dec 2019, [6]Gonzalez-Martin A et al. NEJM 2019, [7]Coleman RL et al. Lancet 2017 390: 1949-61, [8]Lederman J et al. Lancet 2016 17: 1579-89, [9]Monk B et al. J Clin Oncol 2022

# Platinum sensitive maintenance

- For platinum-sensitive PARP-naïve patients responding to platinum, PARPi maintenance prolongs PFS
- As in the upfront setting, patients with BRCA mutations consistently derive the most PFS benefit in these trials
- Like in the upfront setting, testing for HRD does not identify a subpopulation of patients who have no PFS benefit from PARPi maintenance
  - Does provide information regarding degree of PFS benefit
- Repeat PARP inhibitor maintenance provides some benefit
- SOLO2 show an adjusted OS benefit of PARP inhibitor maintenance in BRCA mutation ovarian cancer
- Increasing concerns about secondary hematologic malignancies
  - In BRCA mutation carriers
  - In more heavily treated patients
  - Possibly with longer duration of PARP inhibitor treatment

# PARPi: Approved Indications in Ovarian Cancer

| Primary Therapy | Front-Line Maintenance | Maintenance post-Recurrence | Recurrent Disease |
|---|---|---|---|
| Veliparib: Pending, data from VELIA | Olaparib [FDA]: gBRCAm or sBRCAm, (SOLO-1) 12/2018 | Olaparib [FDA]: Maintenance in patients with CR or PR after platinum-based chemotherapy (SOLO 2) 8/2017 | |
| | Niraparib [FDA]: maintenance in pts with CR or PR after initial therapy (PRIMA) 4/2020 | Niraparib [FDA]: Maintenance in patients with CR or PR following platinum-based chemotherapy (NOVA) 3/2017 | |
| | Olaparib + Bev [FDA]: Chemo with bev and olaparib with bev maintenance: HRD positive (PAOLA) 5/2020 | Rucaparib [FDA]: Maintenance in patients with CR or PR following platinum-based chemotherapy (ARIEL 3) 4/2018 | |
| | Rucaparib: maintenance in responding pts (ATHENA-MONO) ASCO 2022 | | |

# PARP Inhibitor Primary Treatment: Recurrent Ovarian Cancer

# Study 42:Olaparib *BRCAm*

Domchek SM et al. Gynecol Oncol 2016

| Platinum sensitivity | ORR | Median DoR |
|---|---|---|
| Total (N = 137) | 34% | 7.9 mo |
| Platinum sensitive (n = 39) | 46% | 8.2 mo |
| Platinum resistant (n = 81) | 30% | 8.0 mo |
| Platinum refractory (n = 14) | 14% | 6.4 mo |
| Unknown (n = 3) | 67% | 6.3 mo |

FDA approval 12/19/14 for germline *BRCA* mutated advanced ovarian cancer who have had three or more prior lines of chemotherapy

# Active Treatment-Relapsed Disease: ARIEL2 (rucaparib) and QUADRA (niraparib)

| | ARIEL2 (N=204) plat-sens | | QUADRA (N=419) plat-agnostic | | QUADRA plat-sens (N=105) | | QUADRA plat-res (N=326) | |
|---|---|---|---|---|---|---|---|---|
| | ORR | PFS | ORR | CBR at 24wks | ORR | CBR at 24wks | ORR | CBR at 24wks |
| **BRCAmt** | 80% | 12.8 mos | 29% | 38% | 39% | 56% | 27% | 32% |
| **HRD (incl BRCAmt)** | -- | -- | 15% | 26% | 26% | 40% | 10% | 20% |
| **BRCAwt/ HRD*** | 29% | 5.7 mos | 9% | 21% | 20% | 31% | 2% | 14% |
| **BRCAwt/ HRP** | 10% | 5.2 mos | 3% | 14% | 4% | 19% | 3% | 11% |

*HRD by Foundation LOH in ARIEL2 and Myriad MyChoice HRD in QUADRA

Swisher Lancet Oncol 2017

Moore Lancet Oncol 2019

# PARPi: Approved Indications in Ovarian Cancer

| Primary Therapy | Front-Line Maintenance | Maintenance post-Recurrence | Recurrent Disease |
|---|---|---|---|
| Veliparib: Pending, data from VELIA | Olaparib [FDA]: gBRCAm or sBRCAm, (SOLO-1) 12/2018 | Olaparib [FDA]: Maintenance in patients with CR or PR after platinum-based chemotherapy (SOLO 2) 8/2017 | Olaparib [FDA]: Treatment in patients with gBRCAm and ≥ 3 prior lines of chemotherapy 12/2014 |
| | Niraparib [FDA]: maintenance in pts with CR or PR after initial therapy (PRIMA) 4/2020 | Niraparib [FDA]: Maintenance in patients with CR or PR following platinum-based chemotherapy (NOVA) 3/2017 | Rucaparib [FDA]: Treatment in patients with gBRCAm or sBRCAm and ≥ 2 prior lines of chemotherapy (ARIEL 2) 12/2016 |
| | Olaparib + Bev [FDA]: Chemo with bev and olaparib with bev maintenance: HRD positive (PAOLA) 5/2020 | Rucaparib [FDA]: Maintenance in patients with CR or PR following platinum-based chemotherapy (ARIEL 3) 4/2018 | Niraparib [FDA]: Recurrent BRCAm or genomic instability and plat sens, 3 or more therapies (QUADRA) 10/2019 |
| | Rucaparib: maintenance in responding pts (ATHENA-MONO) ASCO 2022 | | |

# GSK Health Care Provider Letter, May 2022
# ENGOT- OV16/NOVA

## IMPORTANT DRUG WARNING

**Subject: Zejula (Niraparib) Important Drug Warning For The Maintenance Treatment In Recurrent Ovarian Cancer (2L+)**

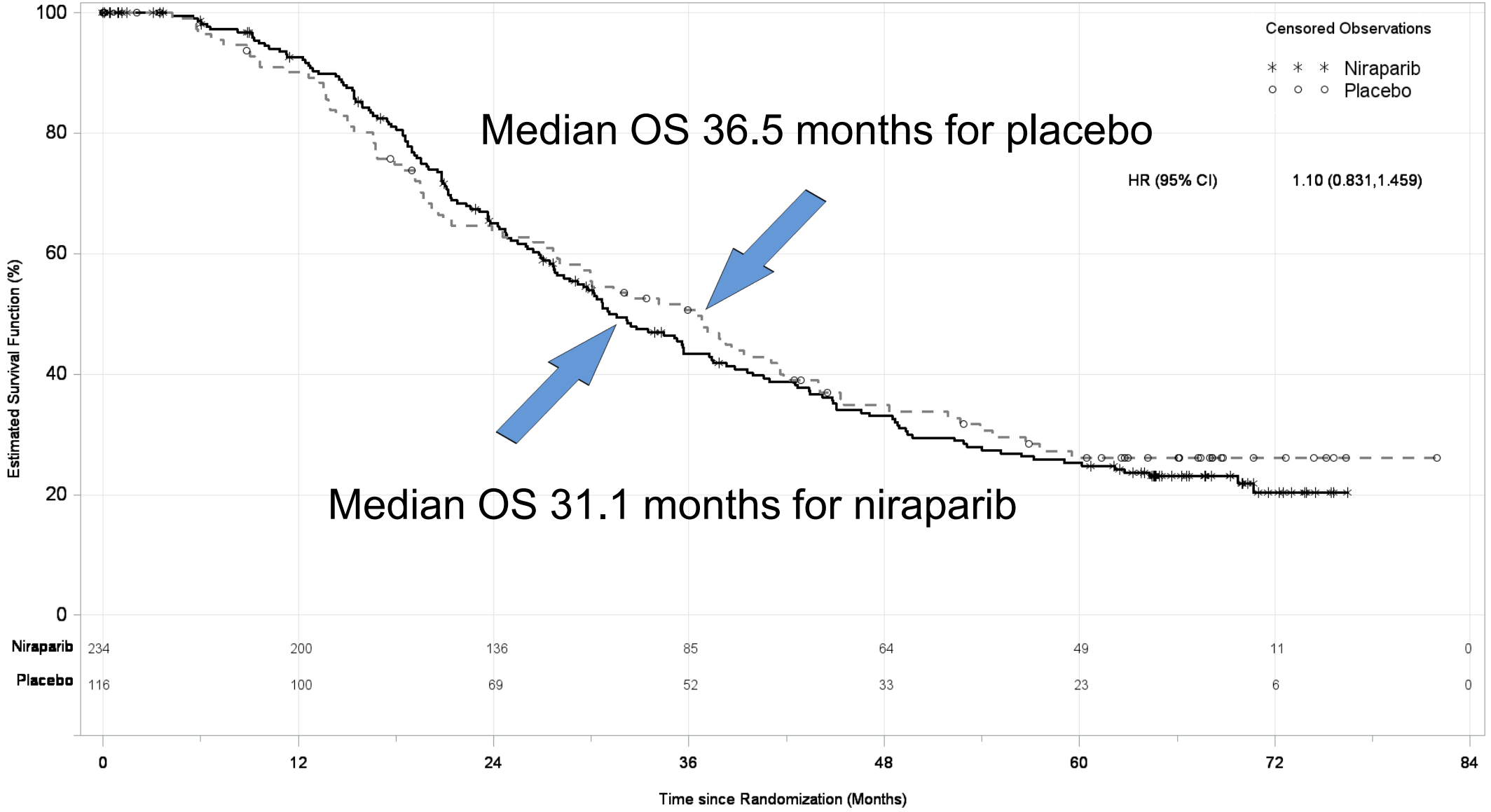
Dear Health Care Provider:

The purpose of this letter is to inform you of important information for Zejula® (niraparib) a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy received in the 2nd line or higher settings. GlaxoSmithKline (GSK) would like to inform you of updated overall survival (OS) data from the ENGOT- OV16/NOVA study.

**Updated OS Data from the ENGOT-OV16/NOVA study, a Phase III trial which evaluated the efficacy and safety of niraparib as maintenance treatment for patients with platinum-sensitive recurrent ovarian cancer**

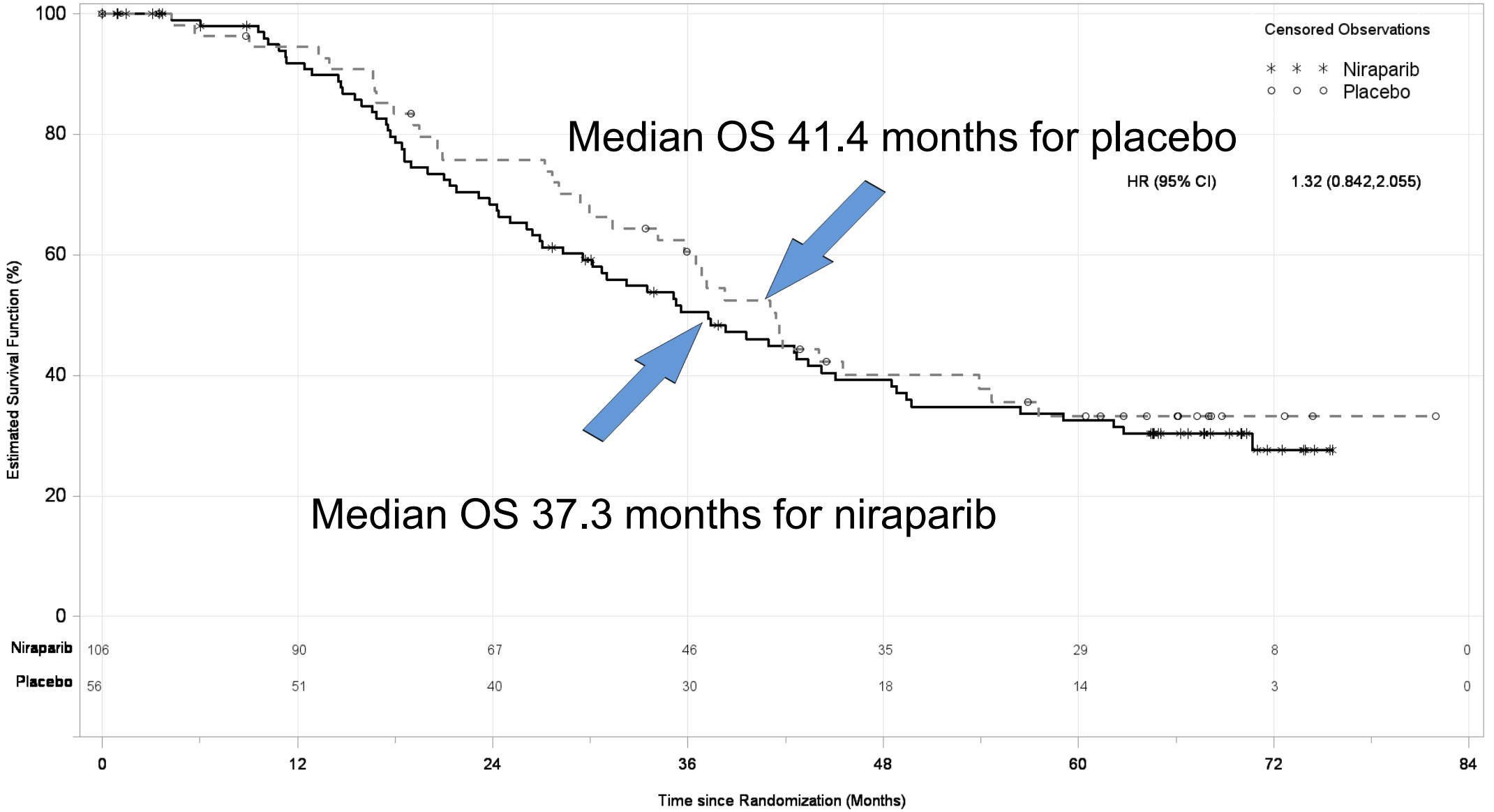
# ENGOT- OV16/NOVA May 2022

## OS Kaplan Meier curve for the non-g*BRCA*mut cohort



# ENGOT- OV16/NOVA May 2022

# OS Kaplan Meier curve for the non-g*BRCA*mut HRD positive subgroup



# Rucaparib (Rubraca®▼): interim data from Study CO-338-043 (ARIEL4) show a decrease in overall survival compared to standard of care

## Dear Healthcare Professional,

Clovis Oncology Ireland Ltd, in agreement with the European Medicines Agency (EMA) and the <National Competent Authority> would like to inform you of the following:

## *Summary*


- A detrimental effect in terms of overall survival (OS) has been observed for rucaparib compared to the chemotherapy-containing control arm (19.6 months and 27.1 months respectively with a Hazard Ratio (HR) of 1.550 (95% CI: 1.085, 2.214), p=0.0161) following a planned interim analysis (IA) in the post-approval randomized controlled study CO-338-043 (ARIEL4).
- The European Medicines Agency (EMA) is performing a review of all available information to assess the impact of this information on the use of rucaparib as monotherapy for the treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.

**Rucaparib (Rubraca®▼): interim data from Study CO-338-043 (ARIEL4) show a decrease in overall survival comp**

June 2022

"Based on further discussions with the FDA following submission of ARIEL4 OS data…Clovis Oncology elected to voluntarily withdraw the approval for rucaparib in the U.S. as treatment of BRCA-mutated ovarian cancer after two or more chemotherapies"

…other rucaparib indications remain in place

…Clovis has also requested a withdrawal of the rucaparib indication in Europe

**Dear H**

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somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy.

# AZ Dear Investigator Letter August 8, 2022

- SOLO3 Final OS, 60.9% maturity (data cut-off 16 Apr 2021): Full Analysis Set and OS subgroup analysis in patients who had received 3 or more prior lines of chemotherapy

**Table 1.** SOLO3 Final OS, 60.9% maturity (data cut-off 16 Apr 2021): OS for Full Analysis Set and OS subgroup analysis in patients who had received 3 or more prior lines of chemotherapy

| | Full Analysis Set 2 or more prior lines of chemotherapy | | 3 or more prior lines of chemotherapy (Indicated population) | |
|---|---|---|---|---|
| | Olaparib 300 mg bd (N=178) | Chemo (N=88) | Olaparib 300 mg bd (N=90) | Chemo (N=42) |
| Deaths, n (%) | 116 (65.2) | 46 (52.3) | 63 (70.0) | 23 (54.8) |
| Median (months) | 34.9 | 32.9 | 29.9 | 39.4 |
| | OS HR = 1.07<br>95% CI = 0.76, 1.49<br>P value = 0.714 | | OS HR = 1.33<br>95% CI = 0.84, 2.18 | |

- AstraZeneca is planning to voluntarily withdraw this indication
- NCCN: Olaparib for treatment of platinum sensitive, recurrent disease in gBRCAm ovarian cancer with ≥2 lines of chemo
  - Change from Category 2A to Category 3

September 2022

# IMPORTANT PRESCRIBING INFORMATION

**Subject: ZEJULA® (niraparib) Important Prescribing Information for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens**

Dear Health Care Provider,

This letter is to inform you that GSK is planning to voluntarily withdraw the indication of ZEJULA (niraparib) for **treatment** of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status.

- The voluntary withdrawal of this indication is based on a totality of information from PARP inhibitors in the late line **treatment** setting in ovarian cancer. A potential detrimental effect on overall survival was observed with other (non-GSK) PARP inhibitors in two independent randomized, active-controlled clinical trials conducted in a *BRCA* mutant 3L+ advanced ovarian cancer population.

- The approval for ZEJULA for this indication was based on the QUADRA Study (NCT02354586), a single-arm study which evaluated the safety and efficacy of niraparib for the **treatment** of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a deleterious or suspected deleterious *BRCA* mutation, or genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy. Given the setting of the QUADRA trial (single arm, uncontrolled nature), no comparative overall survival information can be obtained from the study, and it is difficult to assess any potential effect of ZEJULA on time to event endpoints. There were no new safety findings observed.

# PARP Inhibitors in Ovarian Cancer

FDA Approval

10/13/22

## Ovarian Cancer Clinical Setting

| Population | Phase | Upfront maintenance | Plat Sens Rec (maintenance post chemo) | Plat Sens Rec (treatment) | Plat Res Rec (treatment) |
|---|---|---|---|---|---|
| BRCA mutated (*BRCAm or HRD) | III | SOLO-1 (olaparib) | SOLO-2 (olaparib) | ARIEL 4 (rucaparib v chemo)<br>SOLO-3 (olaparib vs chemo) | |
| | II | | | Study 42 (olaparib[¥]) XXX<br>ARIEL 2 (rucaparib[#]) XXX<br>QUADRA (niraparib*[¤]) XXX | QUADRA (niraparib*) |
| All Comers | III | PAOLA-1 (olaparib/bev*)<br>VELIA (veliparib)<br>PRIMA (niraparib)<br>ATHENA-MONO (rucaparib) | Study 19 (olaparib)<br>NOVA (niraparib[@]) ???<br>ARIEL3 (rucaparib) | AVANOVA2 (niraparib+/-bev)<br>GY-004 (olaparib +/- cedirinib) | |
| | II | OVARIO (niraparib/bev) | MEDIOLA (olaparib/durva or olaparib/durva/bev) | LIGHT study (olaparib)<br>ARIEL2/Study 10 (rucaparib)<br>CLIO (olaparib vs. chemo) | |

[@]Notice of Inferior OS from NOVA trial (5/2022)
XXX Withdrawal of FDA approval:
[#]Inferior OS in ARIEL 4, rucaparib withdrawal by Clovis (6/10/22)
[¥]SOLO3 Inferior OS, olaparib withdrawal by Astra Zeneca (8/26/22)
-AZ requiring reconsent for SOLO-3, Study 42 and LIGHT
[¤]QUADRA single arm w/o comparator, niraparib withdrawal by GSK: (9/6/22)
??? To be reviewed at ODAC (FDA) 11/22/22

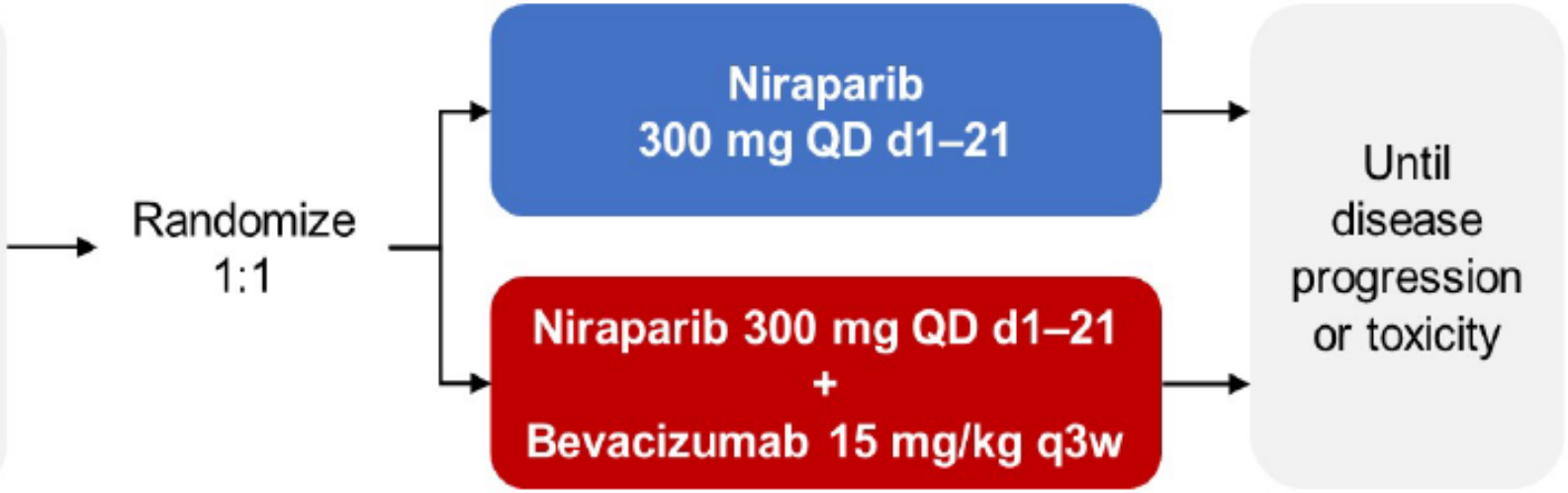
XXX NCCN Change from Category 2A to Category 3
8/25/2022 ASCO Guidelines Update: PARPi monoRx should not routinely be offered

# OvCa: Future Directions in PARP Inhibitor Therapy

- PARP inhibitor combination with anti-vascular therapy
  - PAOLA – olaparib with bevacizumab, upfront
  - Avanova – niraparib with bevacizumab, recurrent

# ENGOT-OV24 / NSGO-AVANOVA2 trial design

- High-grade serous/endometrioid PSROC
- Any number of previous lines of therapies
- Measurable/evaluable disease
- Prior bevacizumab permitted



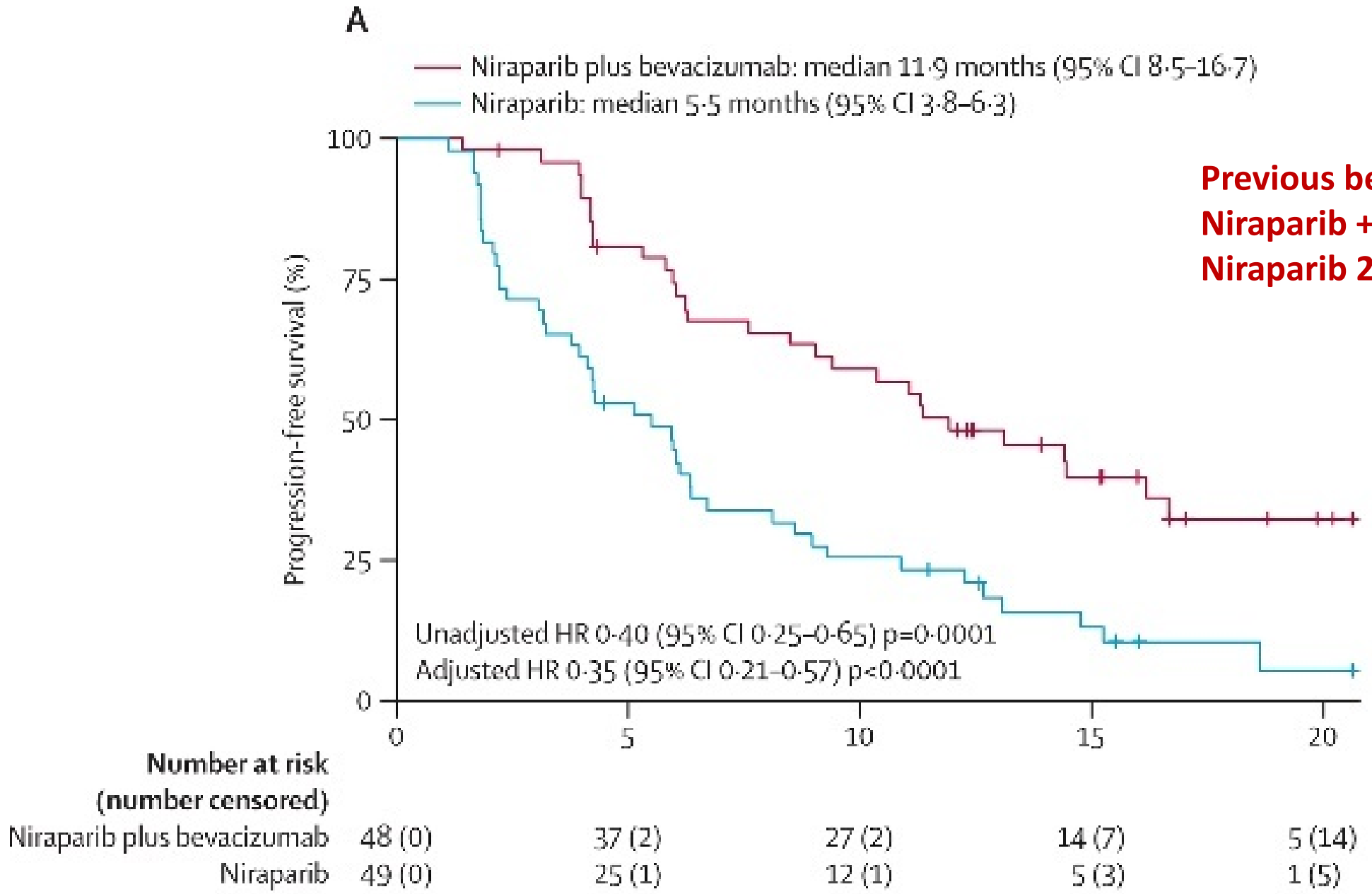

**Previous treatment with bevacizumab or first-line maintenance PARP inhibitors permitted**

**Stratification factors**

- HRD status (positive vs negative) Myriad MyChoice HRD Assay
- Chemotherapy-free interval (6–12 vs >12 months)

**Primary endpoint: Investigator-assessed PFS in the ITT population**

Mirza et.al. Lancet Oncology 2019




**Previous bevacizumab:**
**Niraparib + Bev 21%**
**Niraparib 27%**

**NCCN Compendia listed for PSROC**

Mirza et.al. Lancet Oncology 2019

# PSROC: Niraparib vs. Niraparib plus Bevacizumab

Mirza et.al. Lancet Oncology 2019

| Group | Num | PFS Comb | PFS Niraparib | HR | P-value |
|---|---|---|---|---|---|
| ITT | 97 | 11.9 | 5.5 | 0.35 | <0.0001 |
| BRCA-neg | 64 | 11.3 | 4.2 | 0.32 | |
| BRCA-pos | 33 | 14.4 | 9.0 | 0.49 | |
| HRD-pos | 58 | 11.9 | 6.1 | 0.38 | |
| BRCA-neg | 25 | 11.9 | 4.1 | 0.19 | |
| HRD-neg | 49 | 11.3 | 4.2 | 0.40 | |
| 6-12 months | 64 | 11.3 | 2.2 | 0.29 | |
| >12 months | 33 | 13.1 | 6.1 | 0.42 | |

# OvCa: Future Directions in PARP Inhibitor Therapy

- PARP inhibitor combination with anti-vascular therapy
- PARP inhibitors with Immune checkpoint inhibitors +/- bevacizumab
  - MEDIOLA

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# Phase II study of olaparib plus durvalumab and bevacizumab (MEDIOLA): initial results in patients with non-germline BRCA-mutated platinum sensitive relapsed ovarian cancer

Yvette Drew,[1] Richard Penson,[2] David M O'Malley,[3] Jae-Weon Kim,[4] Stefan Zimmermann,[5] Patricia Roxburgh,[6] Joohyuk Sohn,[7] Salomon M Stemmer,[8] Sara Bastian,[9] Michelle Ferguson,[10] Benoit You,[11] Susan Domchek,[12] Haiyan Gao,[13] Helen K Angell,[13] Kassondra Meyer,[14] Laura Opincar,[14] Lone Ottesen,[13] Susana Banerjee[15]

*[1]Northern Centre for Cancer Care, Newcastle upon Tyne Hospitals NHS Foundation Trust, and Newcastle University, Newcastle upon Tyne, UK; [2]Massachusetts General Hospital, Boston, MA, USA; [3]The Ohio State University – James Comprehensive Cancer Center, Columbus, OH, USA; [4]Seoul National University Hospital, Seoul, Republic of Korea; [5]Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland; [6]Beatson West of Scotland Cancer Centre, and Institute of Cancer Sciences, University of Glasgow, Glasgow, UK, [7]Yonsei Cancer Centre, Yonsei University, Sinchon-dong, Republic of Korea; [8]Rabin Medical Center-Beilinson Campus, Petach Tikva and Tel-Aviv University, Tel-Aviv, Israel; [9]Kantonsspital Graubuenden, Chur, Switzerland; [10]NHS Tayside, Dundee, UK; [11]Institut de Cancérologie des Hospices Civils de Lyon, CITOHL, GINECO, Université Claude Bernard Lyon 1, Lyon, France; [12]Basser Center for BRCA University of Pennsylvania, Philadelphia, PA, USA; [13]Pharmaceutical Company Sponsor, Cambridge, UK; [14]Pharmaceutical Company Sponsor, Gaithersburg, MD, USA; [15]The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK*

ClinicalTrials.gov identifier: NCT02734004

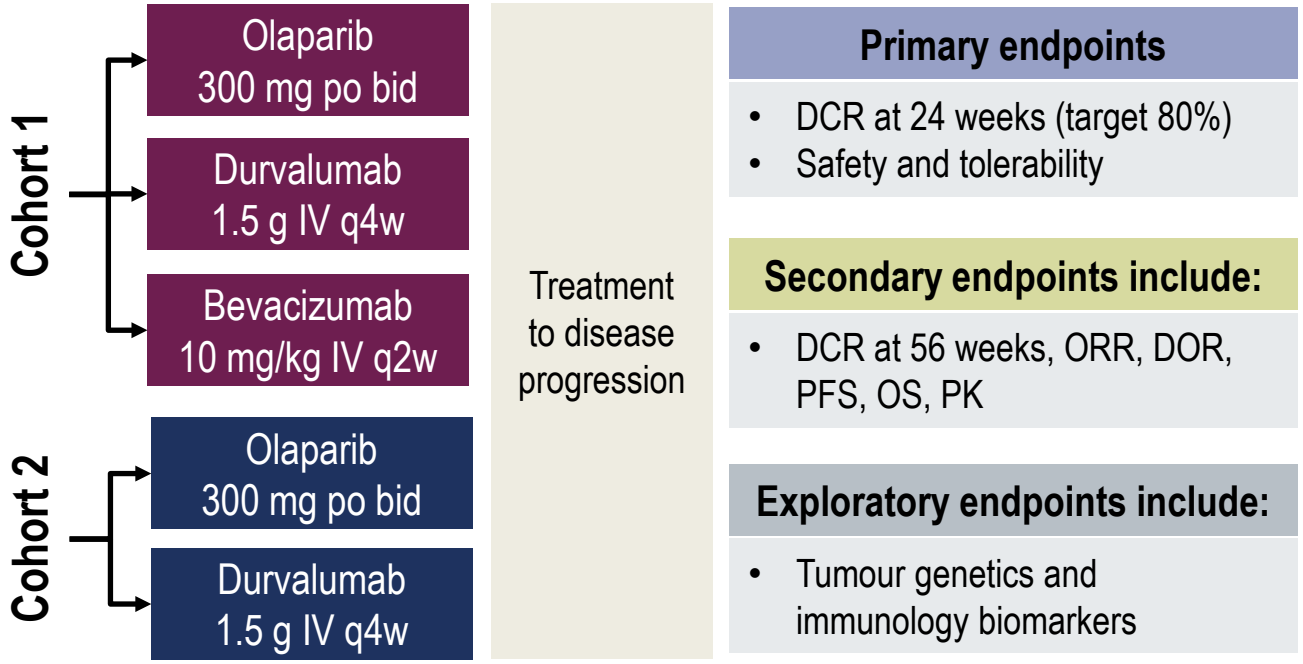
esmo.org

Drew Y, et al. Annals of Oncology 2020;31:S615-S616.

# MEDIOLA: gBRCAwt cohorts
## Study schema and patient demographics

**Patient population**

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




**Primary endpoints**

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

**Secondary endpoints include:**

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

**Exploratory endpoints include:**

- Tumour genetics and immunology biomarkers

**Sequential enrolment**

**Tumour assessments every 8 weeks**

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

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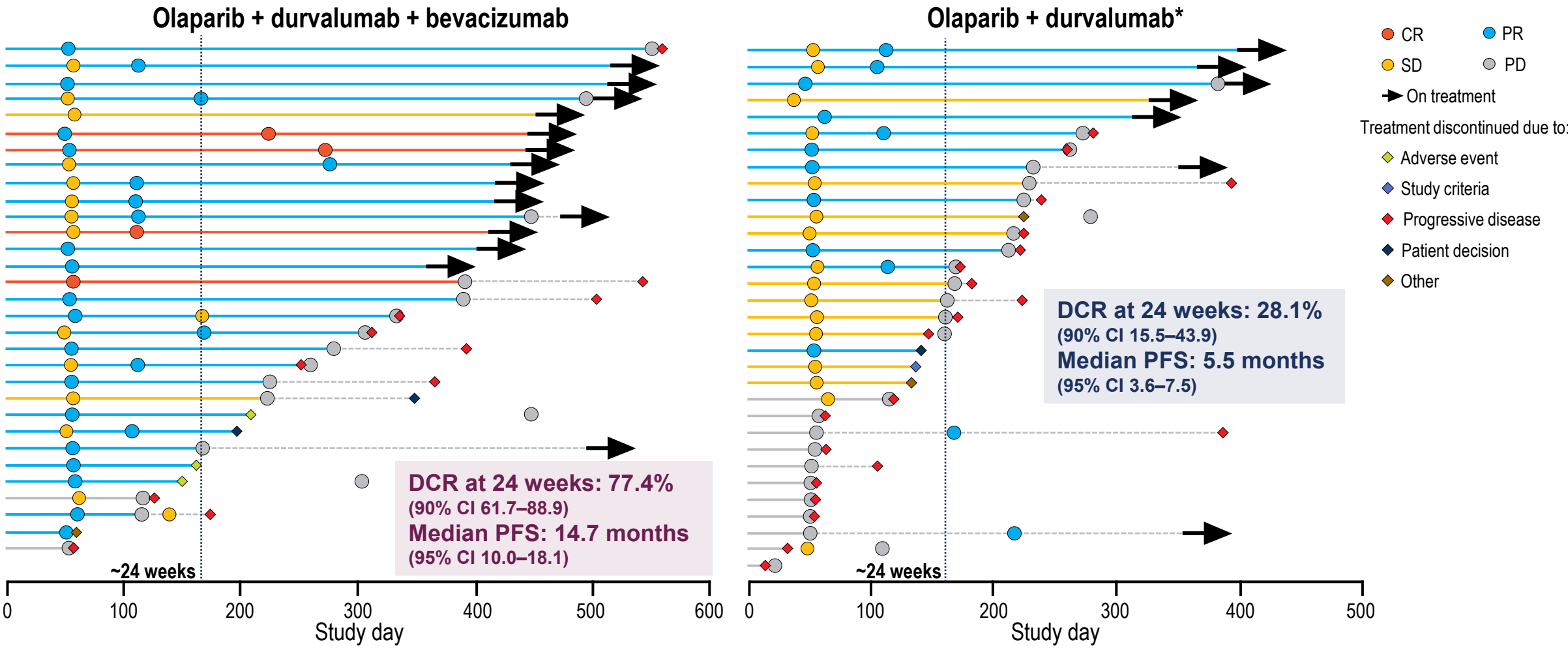
Bev, bevacizumab; bid, twice daily, DCO, data cut-off; DCR, disease control rate; DOR, duration of response; durva, durvalumab; IO, immuno-oncology; IV, intravenous; olap; olaparib; NA, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics;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

Drew Y, et al. Annals of Oncology 2020;31:S615-S616.

# Time to progression or treatment discontinuation
## Triplet cohort showed high DCR at 24 weeks and long median PFS




Colours represent best objective response.

*Four patients had out of window (±1 week) scans at week 24, and were counted as not evaluable for DCR, despite having SD or PR before and after week 24

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

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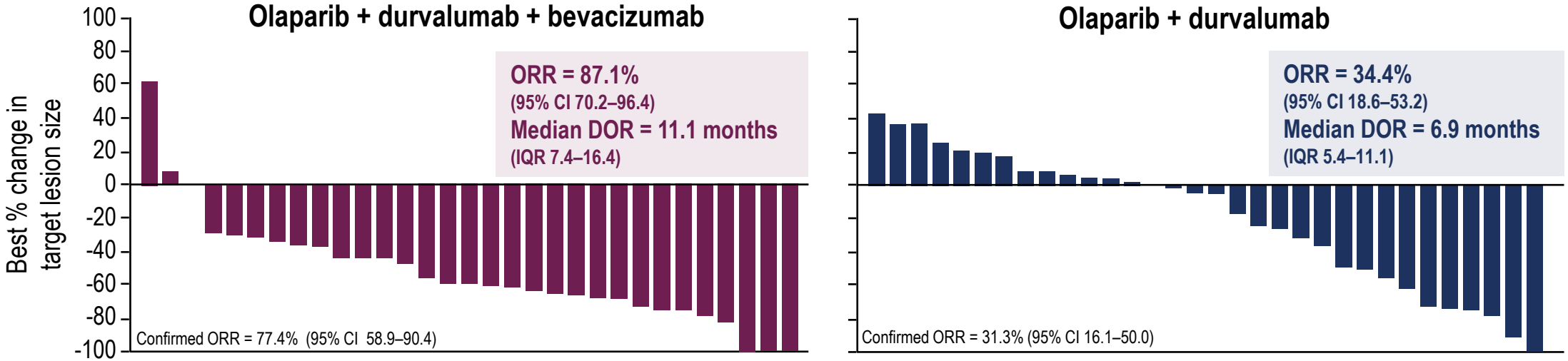
# Triplet cohort demonstrates high ORR

## Exploratory analysis suggests triplet cohort ORR is not GIS-dependent

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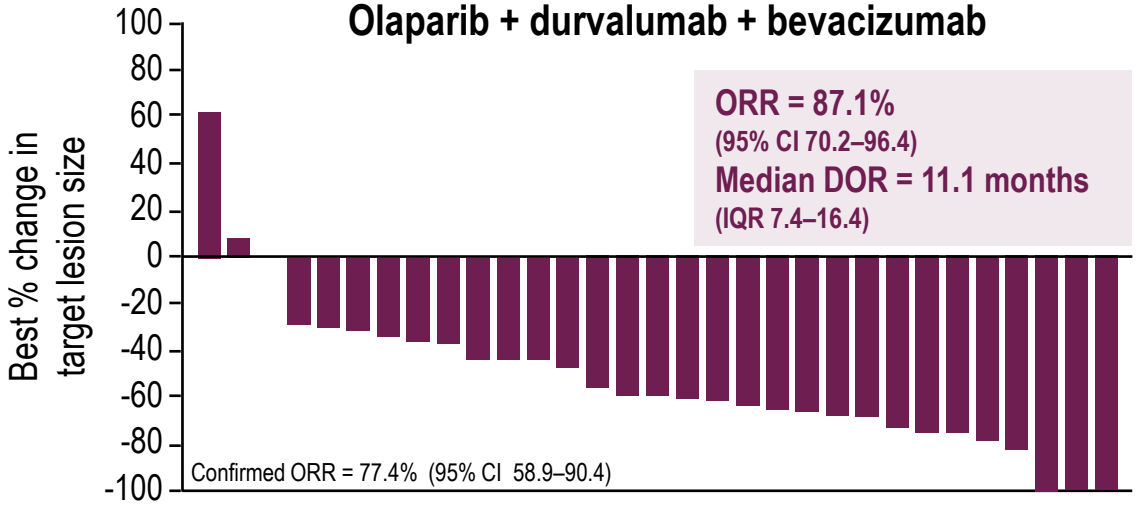
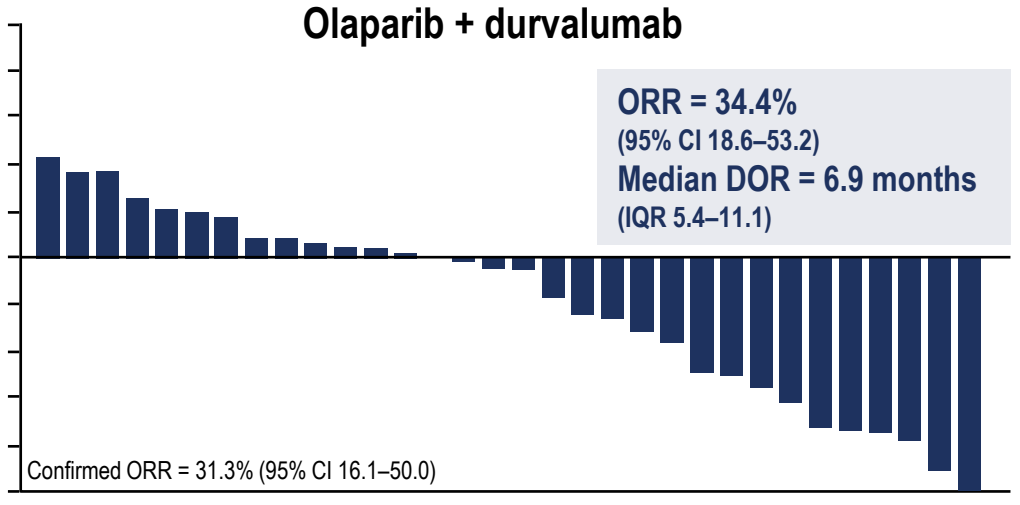
GIS, genomic instability status; IQR, interquartile range

Drew Y, et al. Annals of Oncology 2020;31:S615-S616.

# Triplet cohort demonstrates high ORR

## Exploratory analysis suggests triplet cohort ORR is not GIS-dependent




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

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

Drew Y, et al. Annals of Oncology 2020;31:S615-S616.

# Conclusions

- The triplet combination of olaparib, durvalumab and bevacizumab showed promising efficacy as treatment in the absence of chemotherapy for women with germline BRCA wildtype, platinum-sensitive relapsed advanced ovarian cancer, with 77% DCR at 24 weeks and median PFS of 15 months
- Exploratory analysis suggests the high ORR in the triplet cohort was **NOT** driven by differences in genomic instability status; ORR was ≥75% in the GIS+, GIS− and GIS unknown subgroups
- The safety profile of the combination of olaparib plus durvalumab with or without bevacizumab was consistent with the known safety profiles expected for the single agents
- The combination of olaparib, durvalumab and bevacizumab is now being tested as part of first-line **maintenance** treatment in the Phase III study, DUO-O (NCT03737643)

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ClinicalTrials.gov identifier: NCT02734004

Drew Y, et al. Annals of Oncology 2020;31:S615-S616.

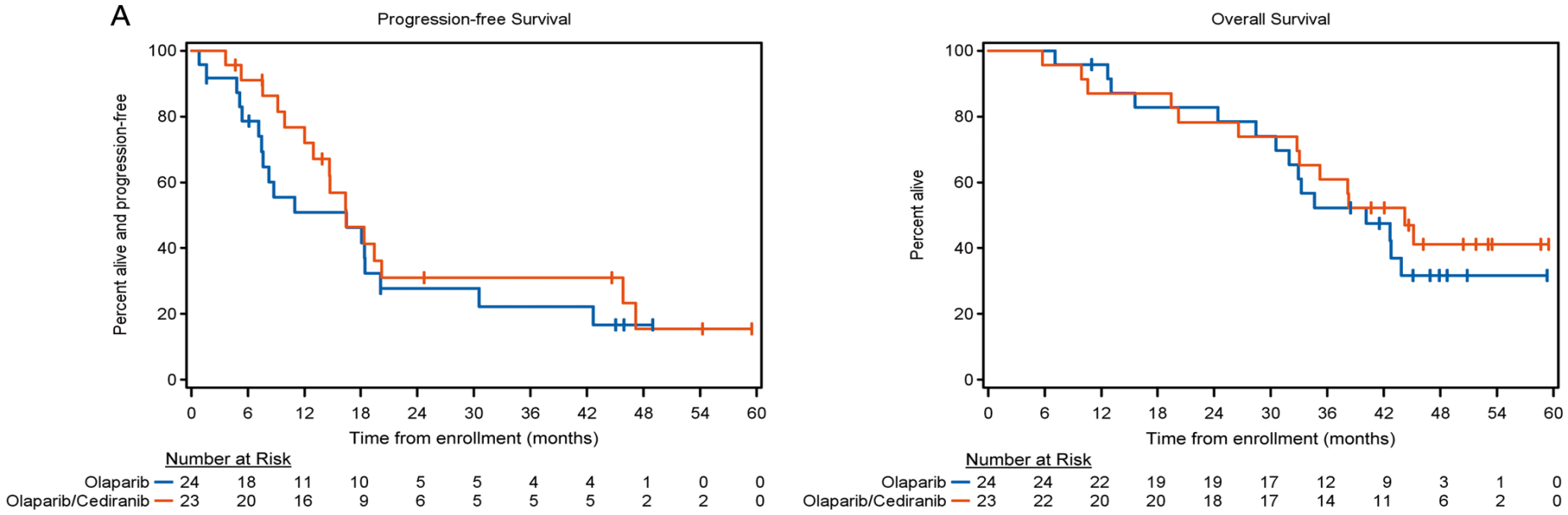
# OvCa: Future Directions in PARP Inhibitor Therapy

- PARP inhibitor combination with anti-vascular therapy
- PARP inhibitors with Immune checkpoint inhibitors +/- bevacizumab
  - MEDIOLA
  - Cedirinib olaparib trials

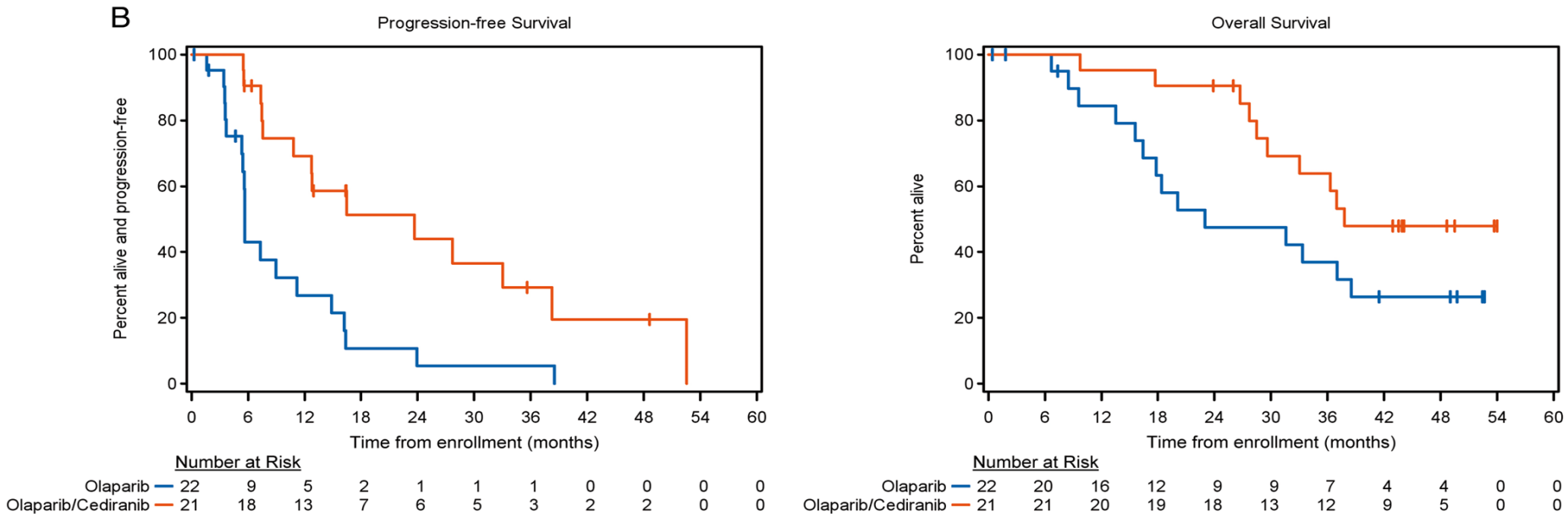
**Figure 3. Randomized Phase II trial of Olaparib +/- Cedirinib in PSROC**

Updated PFS and OS in (A) germline BRCA-mutated and (B) germline *BRCA* wild-type/unknown

Liu JF et al. *Annals of Oncology*, Volume 30, Issue 4, April 2019, Pages 551–557




gBRCA-pos benefit from olaparib alone, no additional benefit with addition of cedirinib




BRCA-wt/unk get little benefit from olaparib alone, significant improvement with addition of cedirinib to olaparib

# RP2 Olaparib vs. Cedirinib plus Olaparib in PSROC

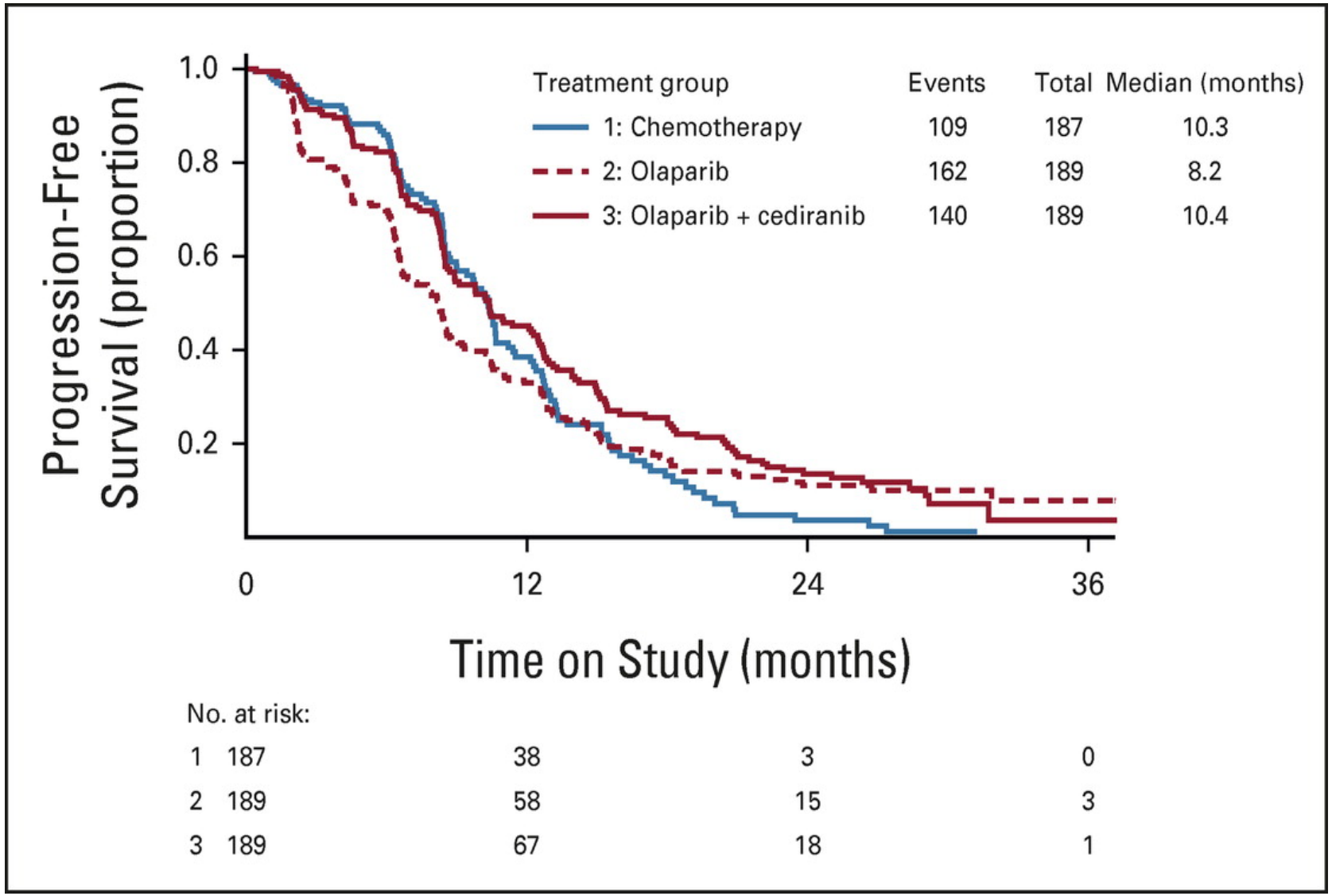
Liu JF et.al. Annals of Oncology April 2019

| Group | Num | PFS Comb | PFS Olaparib | HR | P-value |
|---|---|---|---|---|---|
| ITT | 90 | 16.5 | 8.2 | 0.35 | <0.0001 |
| gBRCA-pos | 47 | 16.4 | 16.5 | 0.76 | 0.42 |
| gBRCA-wt/unk | 43 | 23.7 | 5.7 | 0.31 | 0.0013 |

| Group | Num | OS Comb | OS Olaparib | HR | P-value |
|---|---|---|---|---|---|
| ITT | 90 | 44.2 | 33.3 | 0.64 | 0.11 |
| gBRCA-pos | 47 | 44.2 | 40.1 | 0.86 | 0.70 |
| gBRCA-wt/unk | 43 | 37.8 | 23.0 | 0.44 | 0.047 |

**Olaparib With or Without Cediranib Versus Platinum-Based Chemotherapy in Recurrent Platinum-Sensitive Ovarian Cancer (NRG-GY004): A Randomized, Open-Label, Phase III Trial**

Liu JF et al. Journal of Clinical Oncology 2022 40:19, 2138-2147

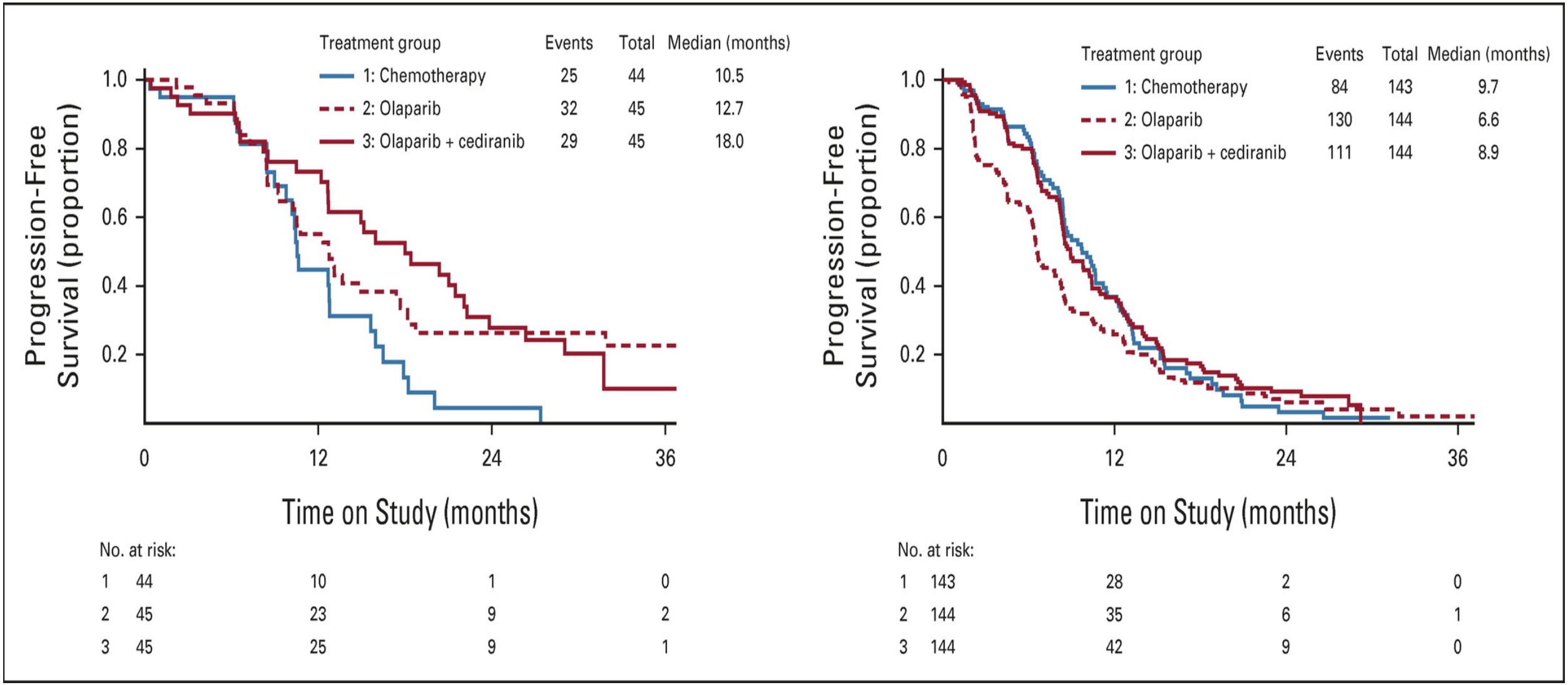



Combination olaparib/cediranib did not improve PFS c/w chemotherapy and resulted in reduced PROs

*FIG 2. Progression-free survival by randomized treatment.*

# Olaparib With or Without Cediranib Versus Platinum-Based Chemotherapy in Recurrent Platinum-Sensitive Ovarian Cancer (NRG-GY004): A Randomized, Open-Label, Phase III Trial

Liu JF et al. Journal of Clinical Oncology 2022 40:19, 2138-2147

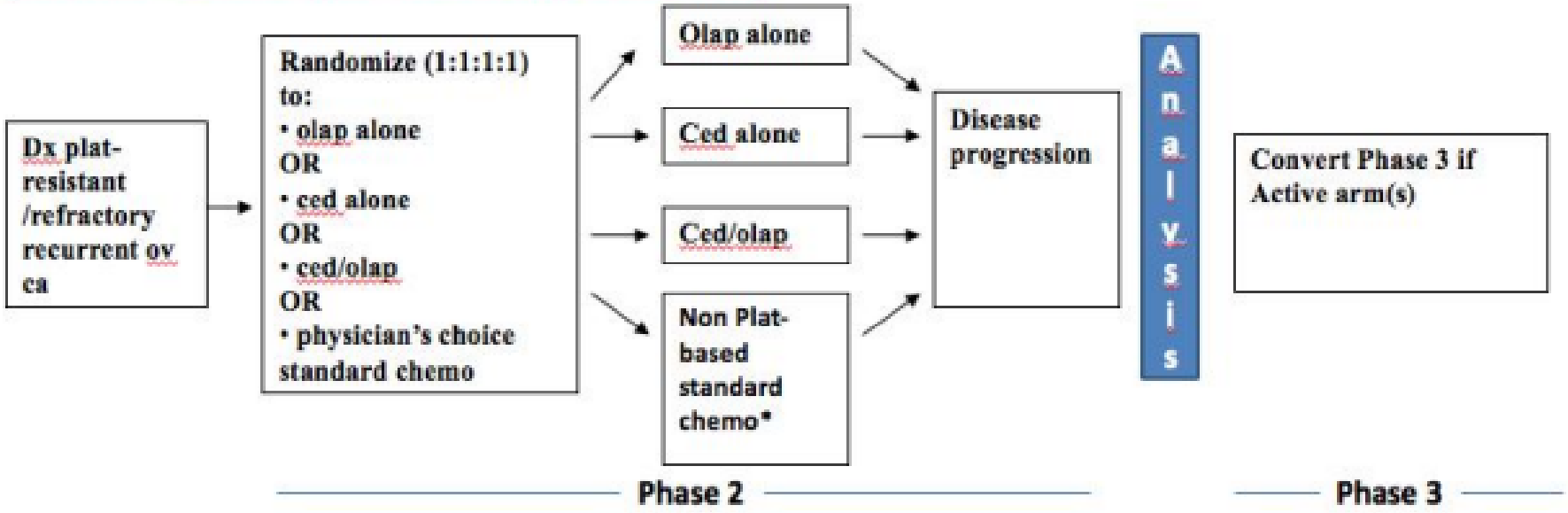



PFS for (A) participants with a deleterious germline *BRCA1/2* mutation and (B) participants without a deleterious germline *BRCA1/2* mutation

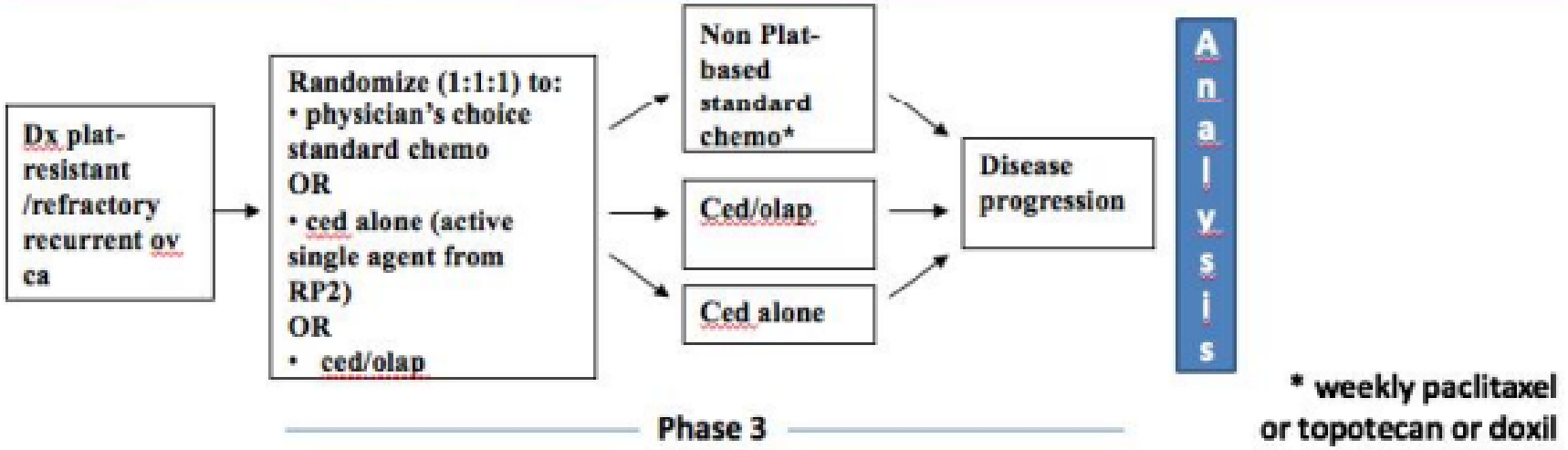
# NRG-GY005

## SCHEMA

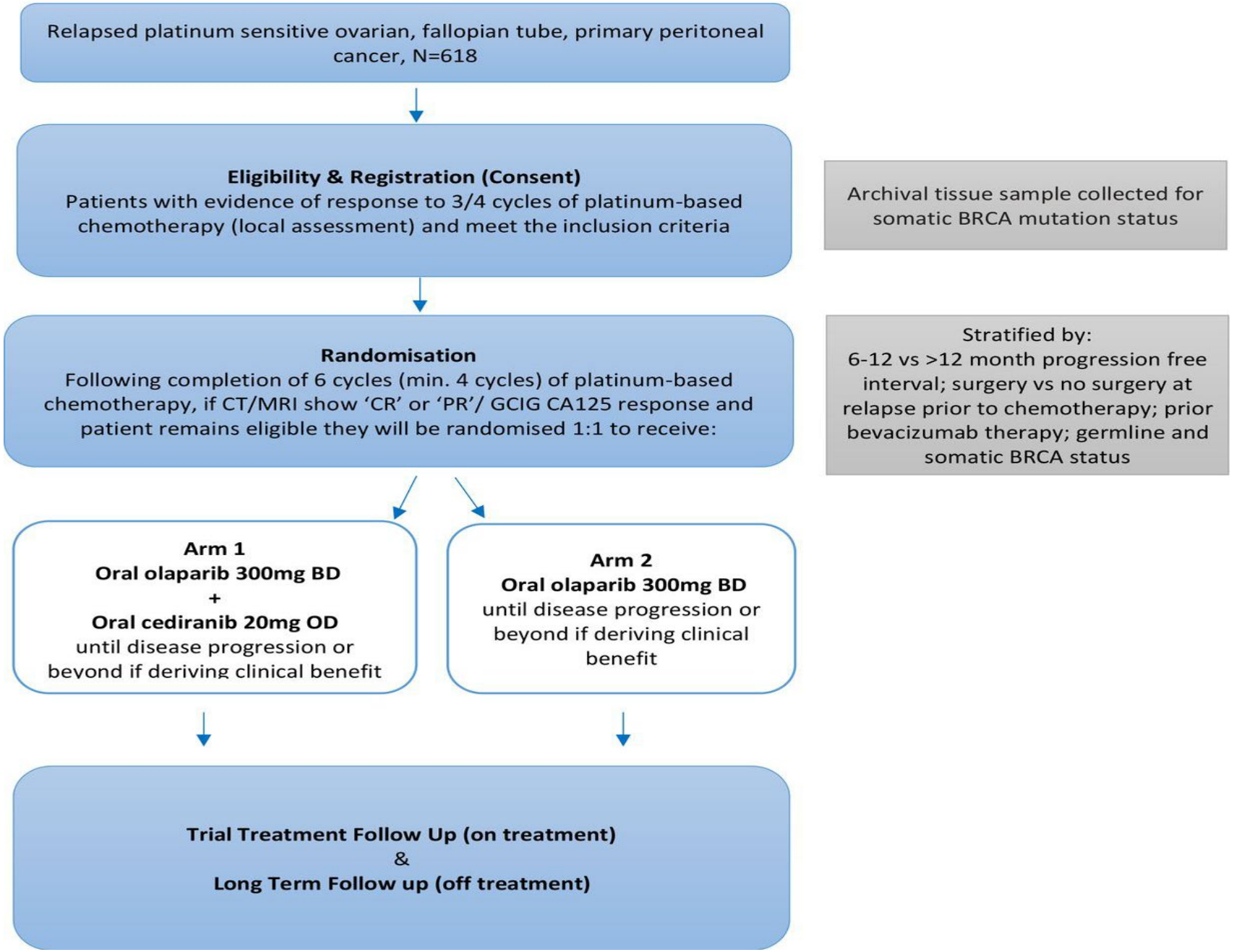
### RPII: Cediranib/olaparib vs. cediranib vs. olaparib vs. physician's choice standard chemo -> drop inactive arm(s) to Ph III




### RPIII: Cediranib/olaparib vs. cediranib vs. physician's choice standard chemo



# ICON9: PSROC - Maintenance olaparib vs cedirinib/olaparib



# OvCa: Future Directions in PARP Inhibitor Therapy

- PARP inhibitor combination with anti-vascular therapy
- PARP inhibitors with Immune checkpoint inhibitors +/- bevacizumab
- Initial Therapy: PARP inhibitor/Immune checkpoint inhibitors /bevacizumab
  - –ATHENA, DUO-O, FIRST

# ATHENA: maintenance trial after initial chemotherapy

## 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 without disease progression or rise in CA-125 at any time during frontline platinum-doublet chemotherapy
  - Received cytoreductive surgery (R0 permitted), either prior to chemotherapy or following neoadjuvant chemotherapy, with sufficient tissue available for analysis
- 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 PO + nivolumab IV

**Arm B (n≈400)**
rucaparib PO + placebo IV

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

**Arm D (n≈100)**
placebo PO + placebo IV

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

### Stratification Factors

- Centrally assessed tumor status (BRCA mutation, BRCA wild-type/high LOH, BRCA wild-type/low LOH, BRCA wild-type/LOH indeterminate)
- Response to frontline platinum doublet (no residual disease vs residual disease)
- Timing of surgery (primary vs interval debulking)

## Study Analyses

**ATHENA–MONO**
**(Arm B vs Arm D)**

**Arm B (n≈400)**
rucaparib PO + placebo IV

**Arm D (n≈100)**
placebo PO + placebo IV

**ATHENA–COMBO**
**(Arm A vs Arm B)**

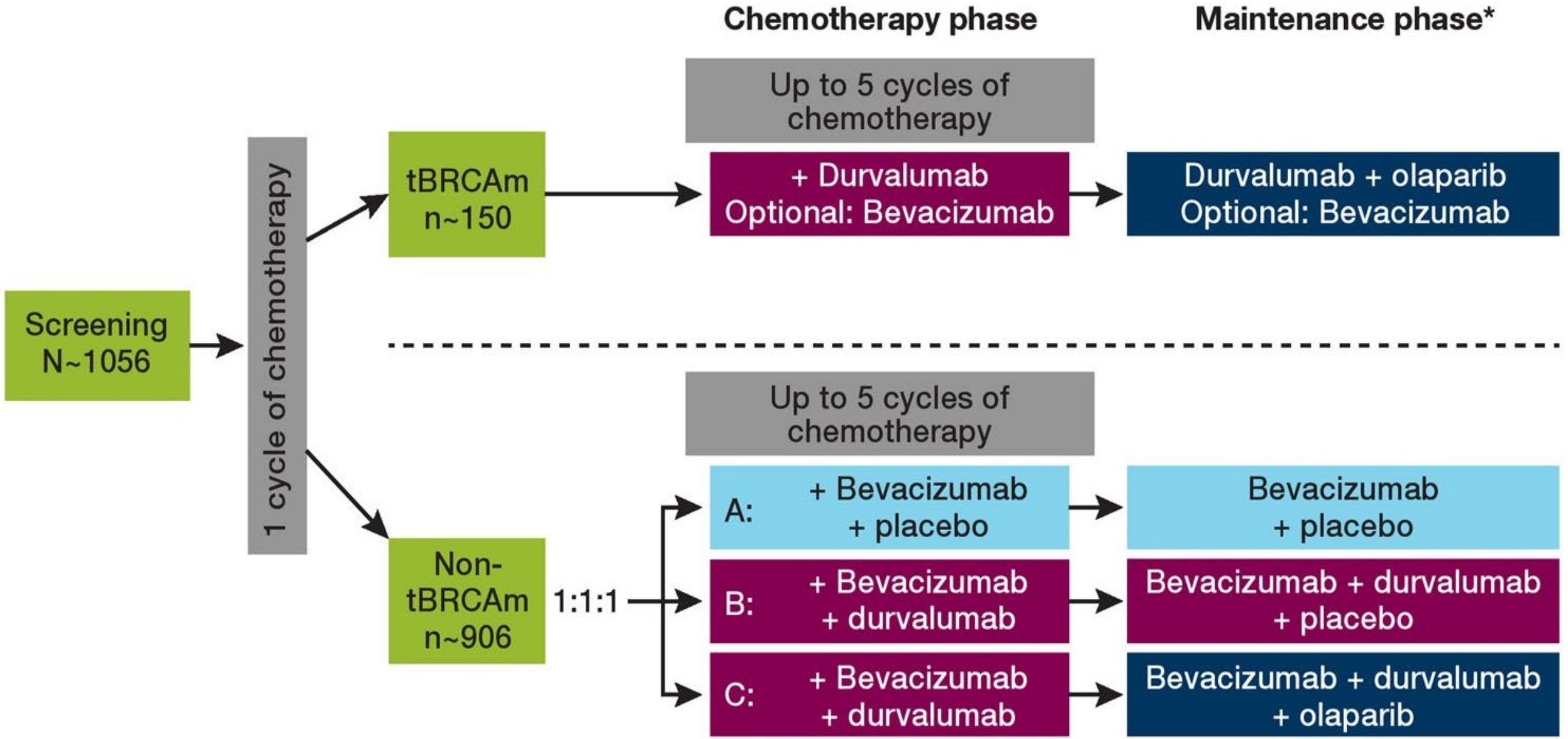
**Arm A (n≈400)**
rucaparib PO + nivolumab IV

**Arm B (n≈400)**
rucaparib PO + placebo IV

### Primary Endpoint

Investigator-assessed PFS per RECIST v1.

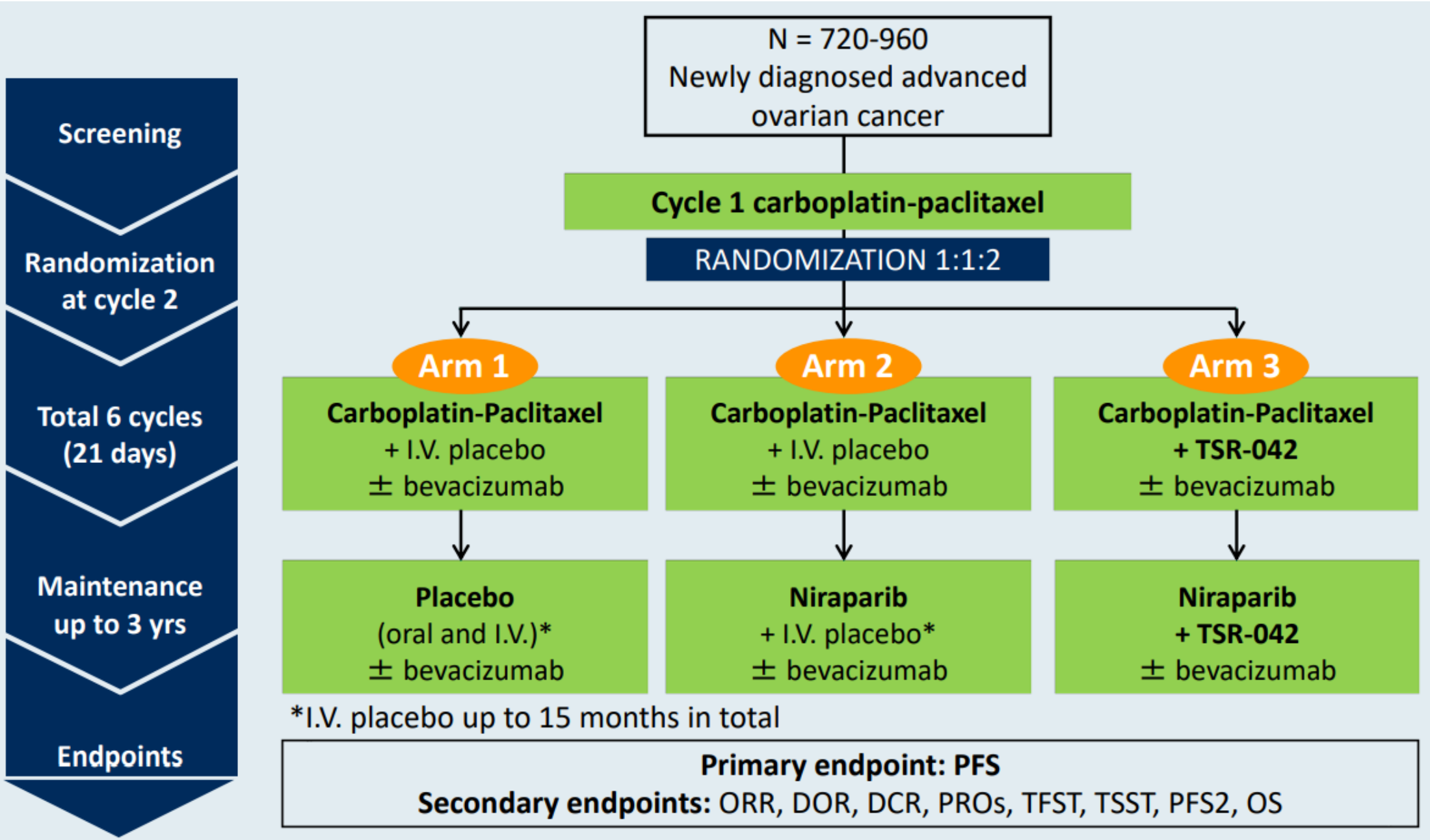
# Figure 1. Overall study design of DUO-O




Harter P, et al. Journal of Clinical Oncology 2019;37:TPS5598

# ENGOT-OV44/FIRST – Trial Design

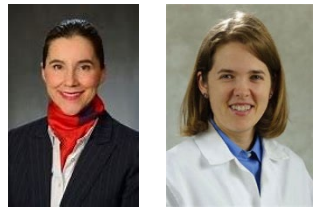
TSR-042 = Dostarlimab

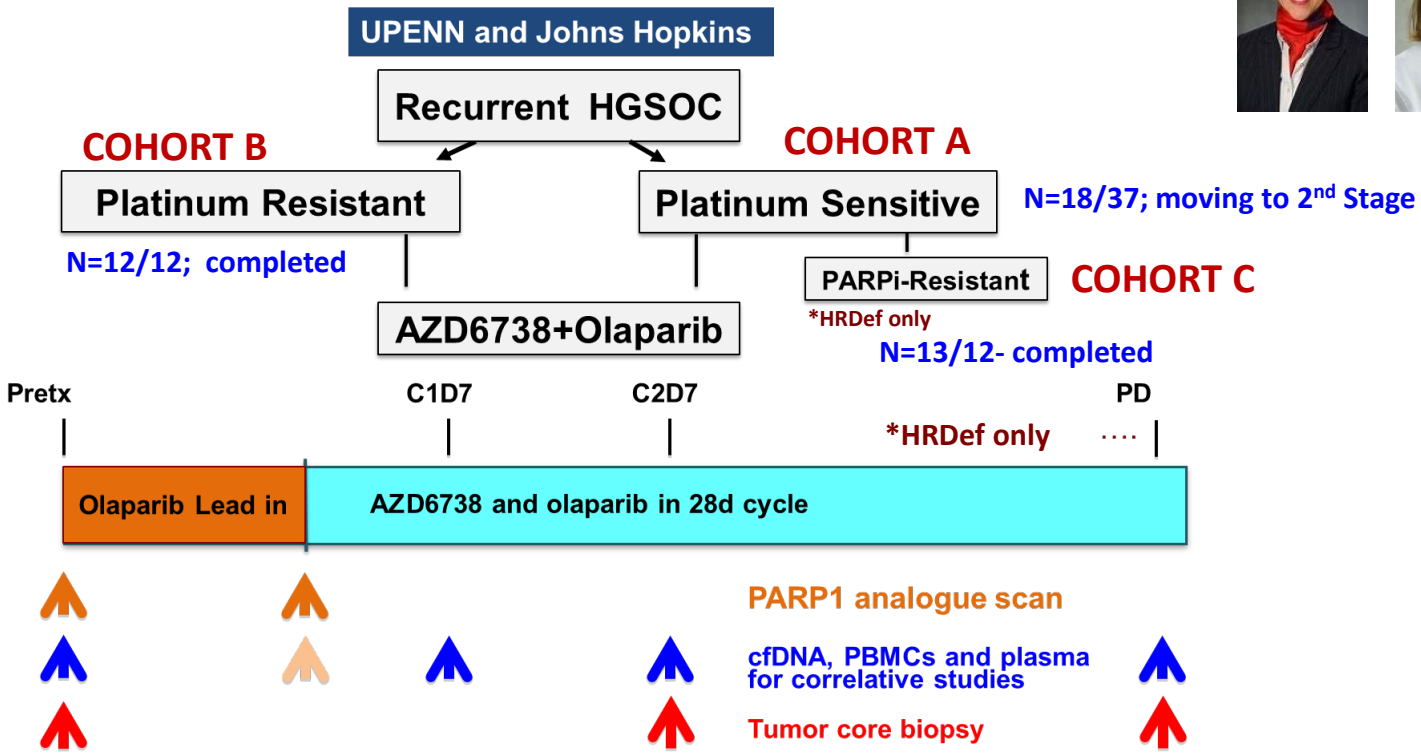


# OvCa: Future Directions in PARP Inhibitor Therapy

- PARP inhibitor combination with anti-vascular therapy
- PARP inhibitors with Immune checkpoint inhibitors +/- bevacizumab
- Initial Therapy: PARP inhibitor/Immune checkpoint inhibitors /bevacizumab
- With other molecular targeted agents to overcome PARP inhibitor resistance

# Phase IB/II clinical trial to examine the efficacy of Combination ATR (AZD-6738) and PARP Inhibition (olaparib) in ovarian cancer (AIM1)

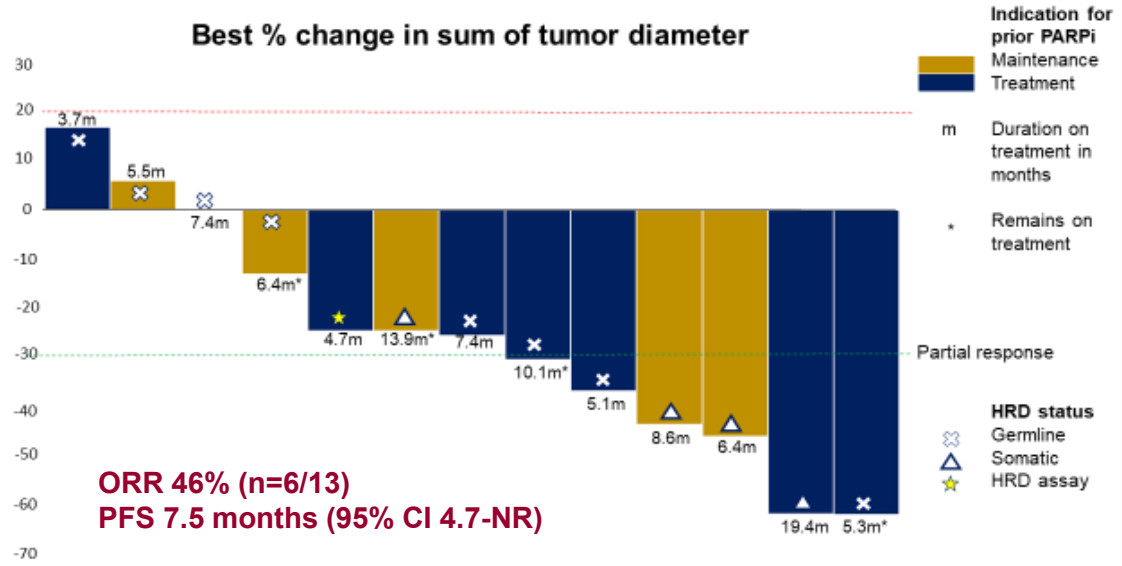





Total enrolled =52 patients

# Clinical evidence demonstrating activity and tolerability in acquired PARPi-resistance HGSOC (CAPRI)

**unpublished**




| | Any Grade n (%) | Grade 3 or 4 n (%) |
|---|---|---|
| **Hematologic** | | |
| Anemia | 6 (46.2) | 1 ( 7.7) |
| Thrombocytopenia | 7 (53.8) | 3 (23.1) |
| Leukopenia | 1 ( 7.7) | 1 ( 7.7) |
| Neutropenia | 2 (15.4) | 1 ( 7.7) |
| **Non-hematologic** | | |
| Fatigue | 10 (76.9) | 0 ( 0.0) |
| Dizziness | 3 (23.1) | 0 ( 0.0) |
| Generalized Muscle Weakness | 1 ( 7.7) | 0 ( 0.0) |
| Flu-like symptoms | 1 ( 7.7) | 0 ( 0.0) |
| Headache | 2 (15.4) | 0 ( 0.0) |
| Anorexia | 3 (23.1) | 0 ( 0.0) |
| Dyspnea | 1 ( 7.7) | 0 ( 0.0) |
| Abdominal pain | 2 (15.4) | 0 ( 0.0) |
| Mucositis | 3 (23.1) | 0 ( 0.0) |
| Nausea | 9 (69.2) | 0 ( 0.0) |
| Vomitting | 4 (30.8) | 0 ( 0.0) |
| Diarrhea | 5 (38.5) | 0 ( 0.0) |
| Constipation | 1 ( 7.7) | 0 ( 0.0) |
| Dyspepsia | 3 (23.1) | 0 ( 0.0) |
| Dysgeusia | 5 (38.5) | 0 ( 0.0) |
| Dehydration | 1 ( 7.7) | 0 ( 0.0) |
| Elevated Creatinine | 3 (23.1) | 0 ( 0.0) |
| Hypomagnesemia | 1 ( 7.7) | 0 ( 0.0) |
| Hematuria | 1 ( 7.7) | 0 ( 0.0) |

# Q&A