

Management of ovarian cancer recurrence in the era of PARPi treatment

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- Groupe GINECO
- France

DECLARATION OF INTERESTS

- Personal honoraria for advisory boards from Adaptimmune, Agenus, Amgen, AstraZeneca, BMS, Clovis, Daiichi Sankyo, Deciphera, Eisai, EQRX, GSK, Merck Serono, MacroGenics, Mersana, Novartis, Onxeo, Roche, Sutro Biopharma, BioNtech, PharmaAnd, Scorpions, MSD, Pharmamar, Abbvie, Immunogen, Genmab, Transgene, Corcept
- Honorarium to institution for advisory boards from MSD (translational research)
- Funding to institution for translational research from BMS, AMGEN, GSK
- Principal investigator of PAOLA-1 trial (unrecompensed)
- President of GINECO (unrecompensed)
- Chair of ENGOT (unrecompensed)

ESMO 2023 guidelines

ARTICLE IN PRESS



ANNALS OF
ONCOLOGY
driving innovation in oncology

SPECIAL ARTICLE

Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[☆]

A. González-Martín¹, P. Harter², A. Leary³, D. Lorusso^{4,5}, R. E. Miller^{6,7}, B. Pothuri⁸, I. Ray-Coquard⁹, D. S. P. Tan^{10,11,12,13}, E. Bellet¹⁴, A. Oaknin¹⁵ & J. A. Ledermann¹⁶, on behalf of the ESMO Guidelines Committee^{*}

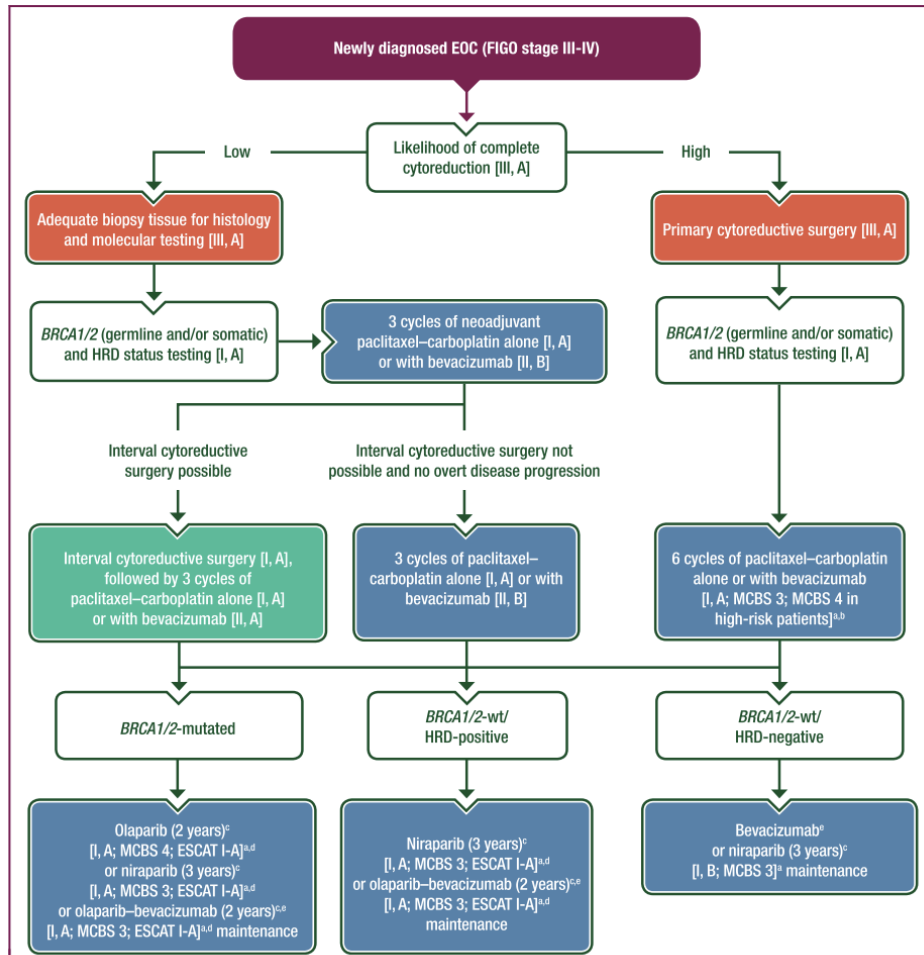


Figure 2. Management of advanced EOC (FIGO stage III-IV).

Ovarian 1L maintenance efficacy

| | SOLO-1 ¹ (Olaparib) | PAOLA-1 ² (Olaparib+Bev) | PRIMA ³ (Niraparib) | ATHENA ⁴ (Rucaparib) |
|------------------|-----------------------------------|---|-----------------------------------|------------------------------------|
| ITT | | 22.1 vs. 16.6 (HR 0.59) | 13.8 vs. 8.2 (HR 0.66)** | 20.2 vs. 9.2 (HR 0.52) |
| BRCAm | 56.0 vs. 13.8 (HR 0.33) | 37.2[§] vs. 21.7 (HR 0.31) | 22.1 vs. 10.9 (HR 0.40) | NR vs. 14.7 (HR 0.40) |
| HRD+ | | 46,8 vs. 17.6 (HR 0.41)** | 24,5 vs. 11,2 (HR 0.52)** | 28.7 vs. 11.3 (HR 0.47) |
| HRD+/Non-BRCA | | 28.1[§] vs. 16.6 (HR 0.43) | 19.6 vs. 8.2 (HR 0.50) | Not Reported |
| HRD Negative | | 16.6 vs. 16.2 (HR 1.0) | 8.1 vs. 5.4 (HR 0.68) | 12.1 vs. 9.1 (HR 0.65) |
| Median Follow-Up | 4.8 years | 5 years | 3,5 years | 26 months |

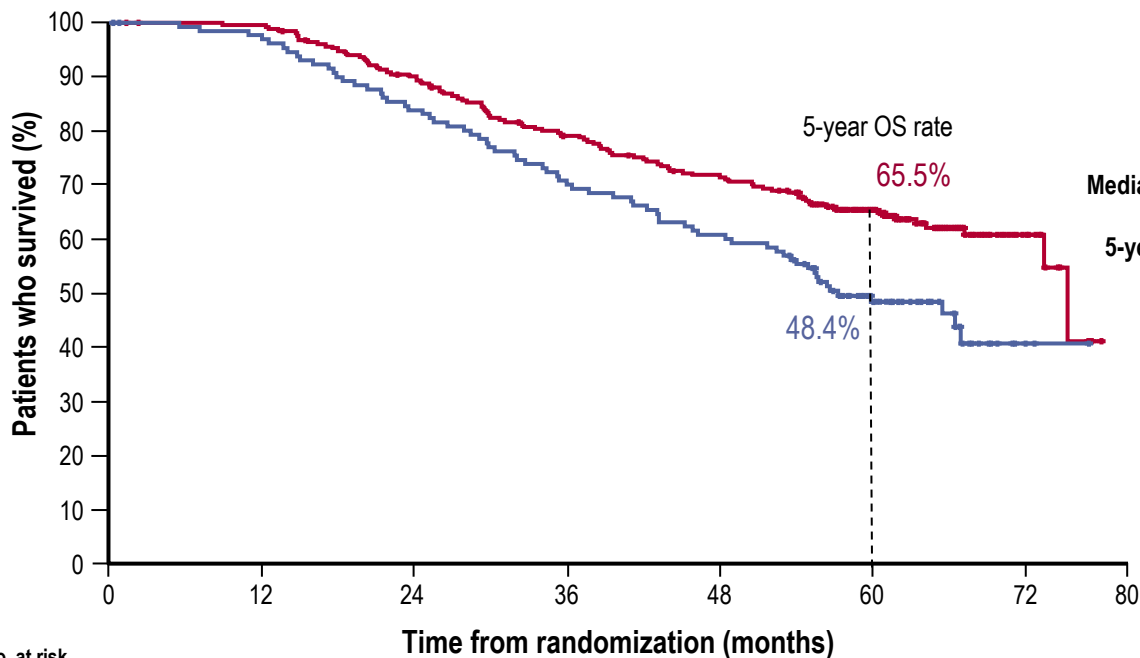
Safety specific to ATHENA not released in press-release.

- Based on 5-Year follow-up data; Primary analysis mPFS was not reached (HR 0.30) at 41 months follow-up
- [§] **instable median**
- **** updated PFS ESMO 2022**

1. Moore K, et al. N Engl J Med. 2018;379:2495–2505/Barnejee ESMO 2020. 2. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 3. Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391–2402 4. Monk B, et al. J Clin Oncol 2022; Jun 6;JCO2201003. doi: 10.1200/JCO.22.01003

OS WAS PROLONGED IN THE HRD-POSITIVE SUBGROUP

PAOLA-1 study (ESMO, Paris 2022)



Events, n (%)

Median OS, months

5-year OS rate, %

| Olaparib + bevacizumab (N=255) | Placebo + bevacizumab (N=132) |
|-----------------------------------|-------------------------------|
| 93 (36.5) | 69 (52.3) |
| 75.2 (unstable)* | 57.3 |
| 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)

No. at risk

| | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 80 | | | | | | | | | | | | | | | | | | | |
|------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|---|---|
| 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 |

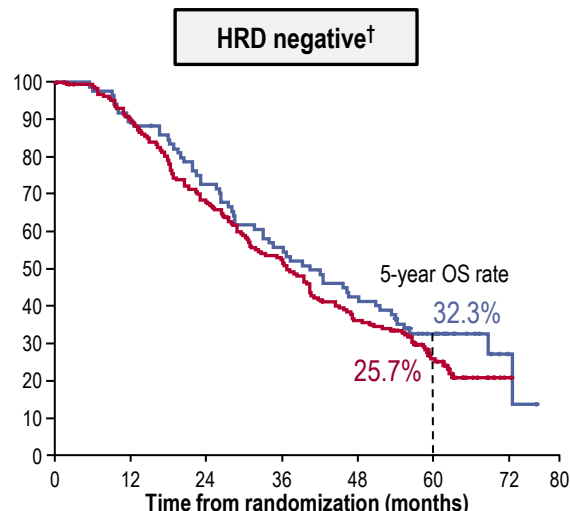
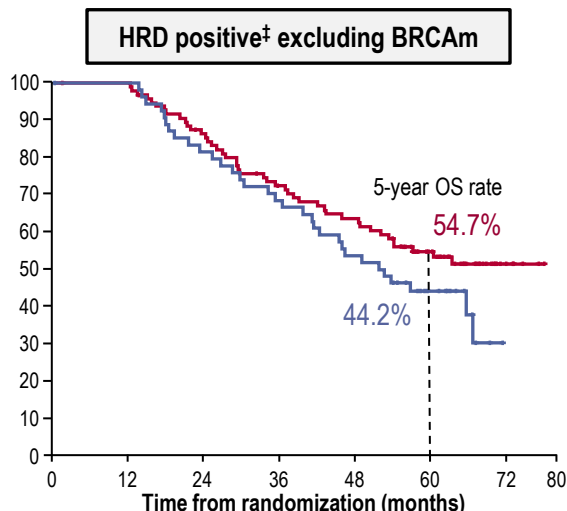
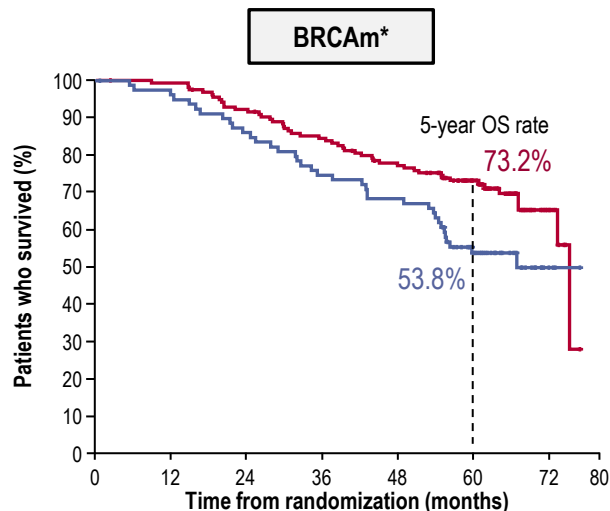
Isabelle Ray-Coquard

HRD positive defined as a tBRCAm and/or genomic instability score of ≥ 42 on the Myriad myChoice HRD Plus assay.



*Median unstable; <50% data maturity.

OS SUBGROUP ANALYSIS BY BRCAm AND HRD STATUS



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

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

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

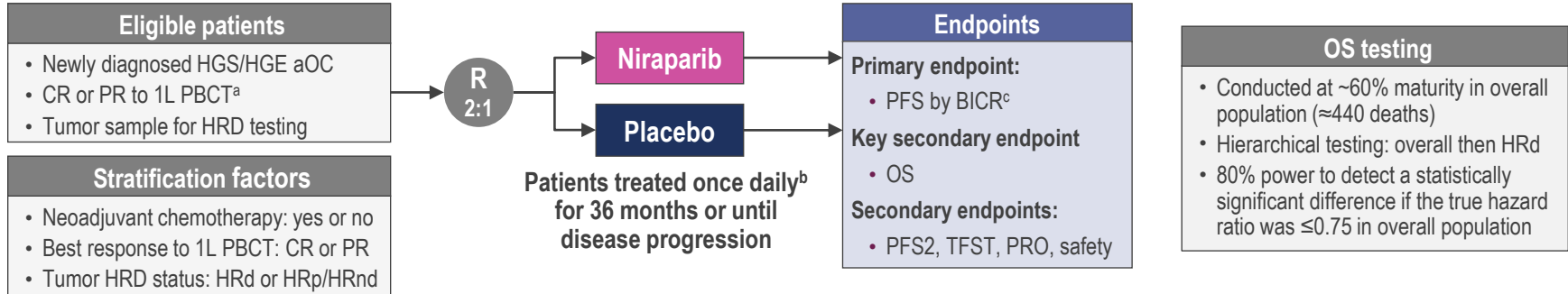
| | Olaparib + bevacizumab (N=157) | Placebo + bevacizumab (N=80) |
|--------------------------------------|--------------------------------|------------------------------|
| Events, n (%) | 48 (30.6) | 37 (46.3) |
| Median OS, months | 75.2 (unstable) [†] | 66.9 |
| 5-year OS rate, % | 73.2 | 53.8 |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

| | Olaparib + bevacizumab (N=97) | Placebo + bevacizumab (N=55) |
|--------------------------------------|-------------------------------|------------------------------|
| Events, n (%) | 44 (45.4) | 32 (58.2) |
| Median OS, months | NR | 52.0 |
| 5-year OS rate, % | 54.7 | 44.2 |
| PARPi as subsequent treatment, n (%) | 9 (9.3) | 23 (41.8) |
| HR 0.71 (95% CI 0.45–1.13) | | |

| | Olaparib + bevacizumab (N=192) | Placebo + bevacizumab (N=85) |
|--------------------------------------|--------------------------------|------------------------------|
| Events, n (%) | 140 (72.9) | 58 (68.2) |
| Median OS, months | 36.8 | 40.4 |
| 5-year OS rate, % | 25.7 | 32.3 |
| PARPi as subsequent treatment, n (%) | 46 (24.0) | 34 (40.0) |
| HR 1.19 (95% CI 0.88–1.63) | | |

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

Role of PARPI in 1st line, including *tBRCA* and beyond PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib 1L maintenance



Key risk characteristics of PRIMA population^{1,2}

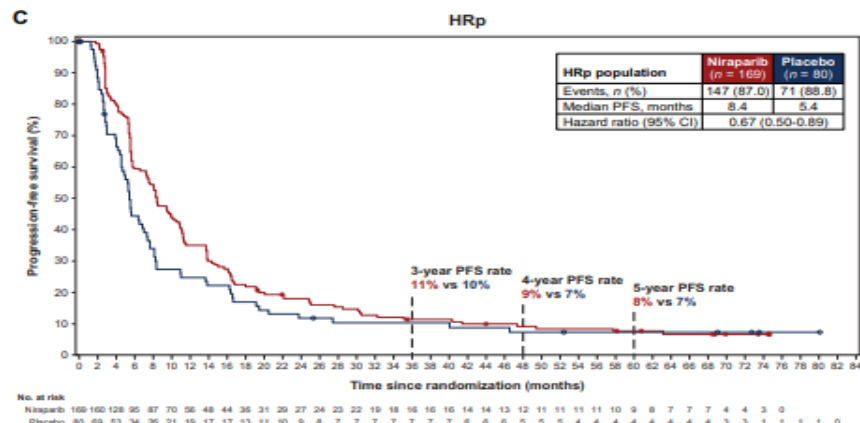
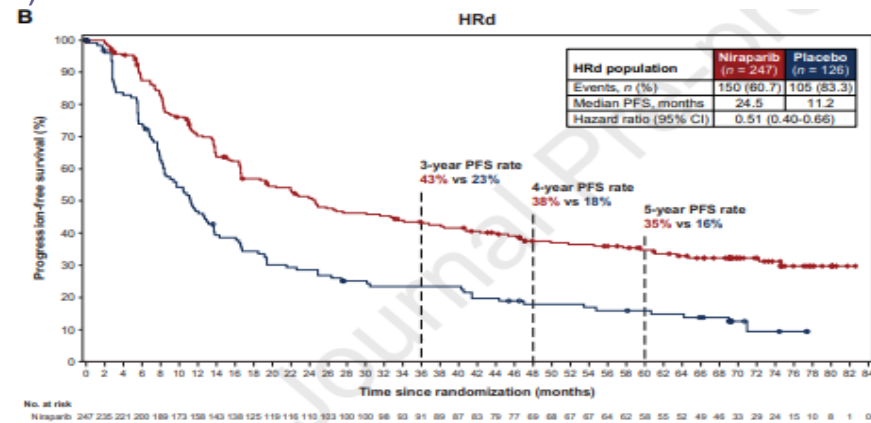
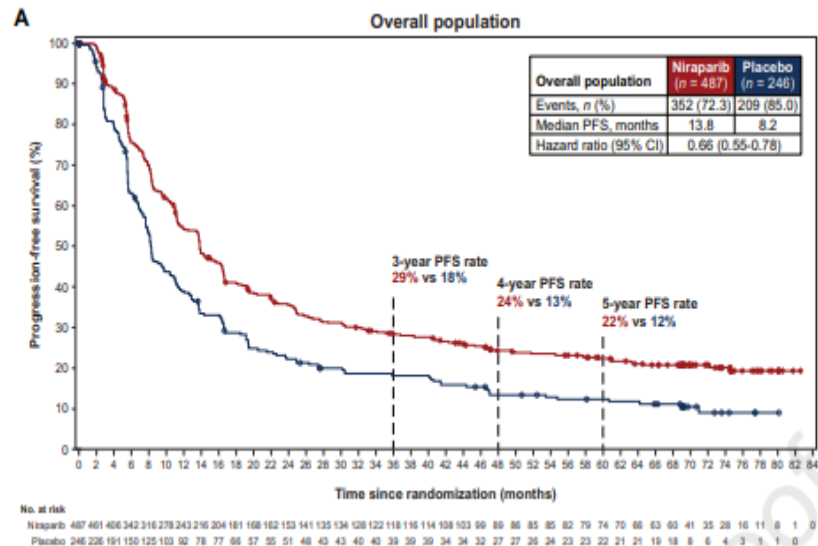
| Disease stage | Residual disease | Tumor HRD/ <i>BRCA</i> status |
|--|---|-------------------------------|
| 35.1% stage IV disease at diagnosis | >99% stage III disease at diagnosis with residual disease after primary debulking surgery | 50.9% HRd |
| 66.7% received neoadjuvant chemotherapy | 47.5% postoperative visible residual disease or no debulking surgery | 30.4% HRd/ <i>BRC</i> Am |
| 30.6% achieved partial response to 1L PBCT | | 34.0% HRp |

PRIMA/ENGOT-OV26/GOG-3012 trial (NCT02655016). ^aPatients must have either had CA-125 in the normal range or a ≥90% decrease in CA-125 during 1L treatment that was stable for at least 7 days. At baseline, 7.1% of the overall population had CA-125 above the upper limit of normal. ^bAt study start, all patients received a fixed starting dose of 300 mg once daily. Subsequently, the protocol was updated to use an individualized starting dose adjusted according to baseline body weight/platelet count. ^cPrimary endpoint of PFS by BICR assessed by hierarchical testing, first in patients with HRd tumors and then in the overall population. 1L, first-line; aOC, advanced ovarian cancer; BICR, blinded independent central review; *BRC*Am, *BRCA*-mutated; CA-125, cancer antigen 125; CR, complete response; HGE, high-grade endometrioid; HGS, high-grade serous; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRnd, homologous recombination status not determined; HRp, homologous recombination proficient; OS, overall survival; PBCT, platinum-based chemotherapy; PFS, progression-free survival; PFS2, progression-free survival 2; PR, partial response; PRO, patient-reported outcomes; TFST, time to first subsequent therapy.

1. González-Martín A, et al. *N Engl J Med*. 2019;381(25):2391–2402. 2. O’Cearbhaill RE, et al. *Gynecol Oncol*. 2022;166(1):36–43.

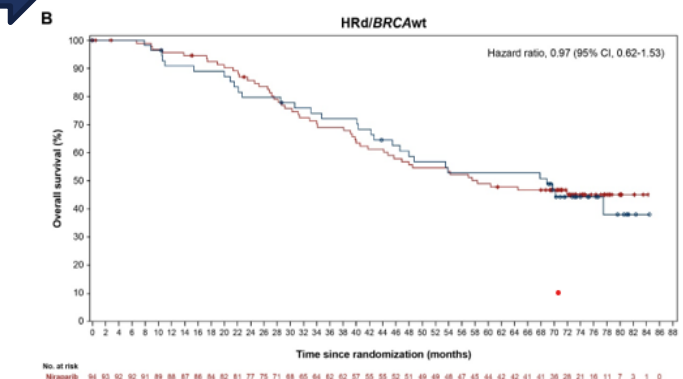
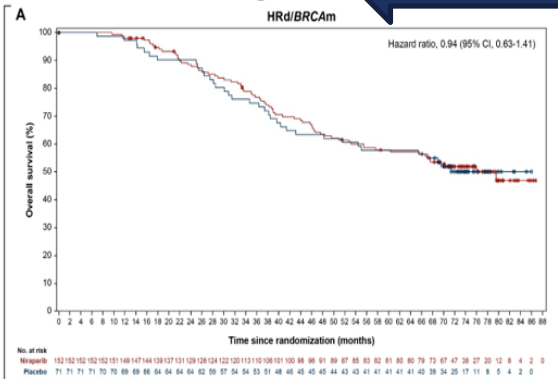
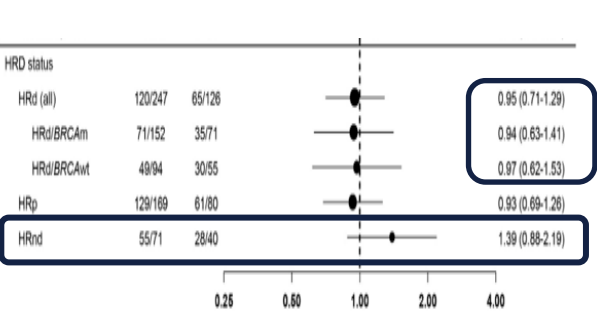
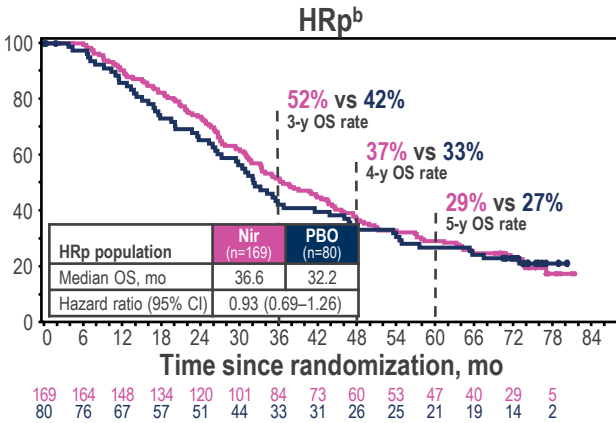
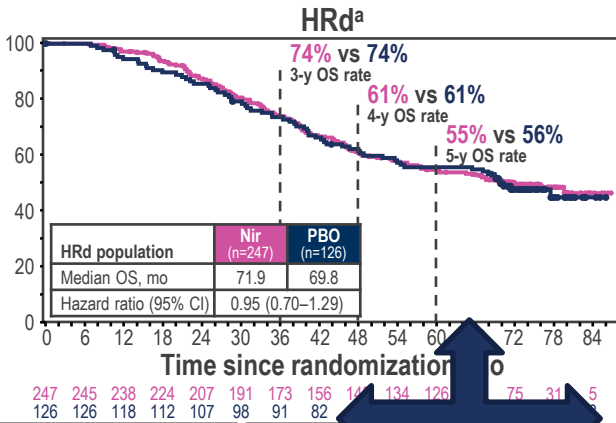
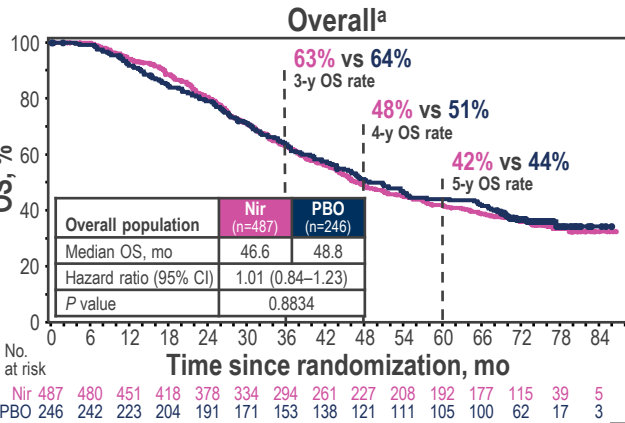
PRIMA/ENGOT-OV26/GOG-3012 trial

Updated long-term PFS (ad hoc, investigator-assessed)

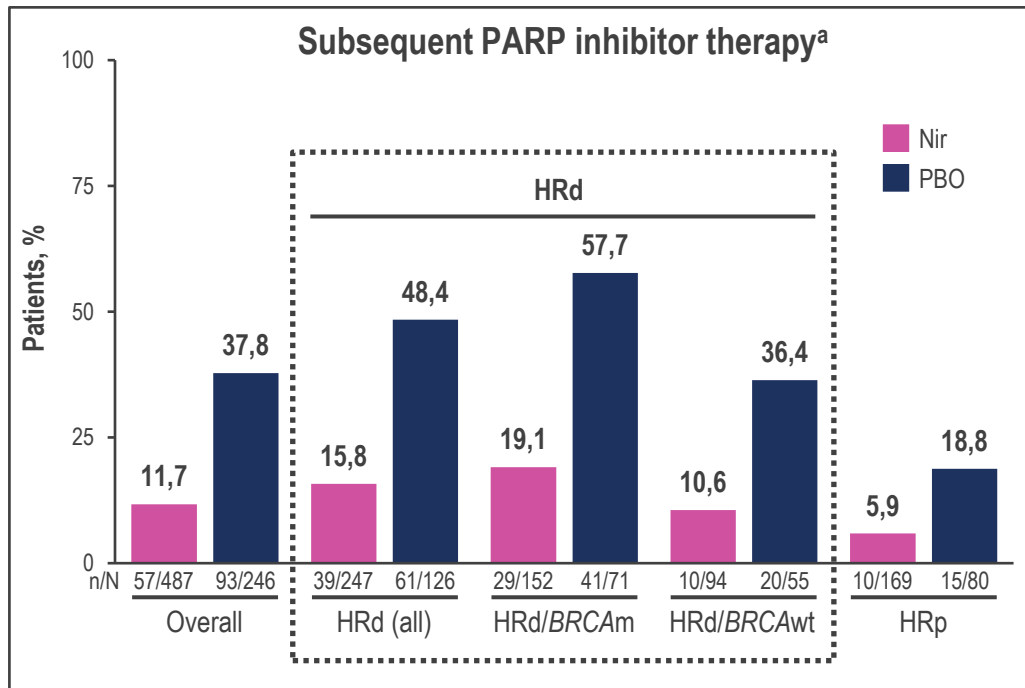


Final OS (62.5% maturity in overall population)

No difference in OS between niraparib and placebo arms in the overall, HRd, and HRp populations



Subsequent PARP inhibitor therapy



Subsequent PARP inhibitor use

- Most predominant in HRd population, with highest use in HRd/*BRCAm* population
- Most patients initiated in the 2L setting

| Any subsequent PARP inhibitor by treatment line, % ^a | Overall | | HRd | |
|---|-------------|-------------|-------------|-------------|
| | Nir (n=487) | PBO (n=246) | Nir (n=247) | PBO (n=126) |
| Any treatment line | 11.7 | 37.8 | 15.8 | 48.4 |
| 2L | 8.2 | 30.5 | 13.0 | 37.3 |
| 3L+ | 3.5 | 7.3 | 2.8 | 11.1 |

^aPercentages calculated out of the total number of patients in each population, not the number of patients who experienced disease progression. 2L, second-line; 3L+, third-line and beyond; *BRCAm*, *BRCA*-mutated; *BRCAw*, *BRCA* wild-type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; Nir, niraparib; PARP, poly(ADP-ribose) polymerase; PBO, placebo.

Why PRIMA did not show overall survival benefice for Ovarian cancer patients in 1st line?



- **Hypotheses to explore**

- Different clinical trial (population, sensitivity to platinum based CT, and no direct comparison)
- Combination with bevacizumab (before randomisation and during maintenance Parpi) versus monotherapy
- Safety and dose intensity
- Role of upfront surgery & no residual disease
- Progression during parpi maintenance alone (more than 90% during parpi versus in combination with Bevacizumab (35% in PAOLA-1))
- Role of subsequent therapies
 - Surgery post progression 15.8% in PRIMA
 - Bevacizumab 35.8% PRIMA and 14.8% PAOLA-1

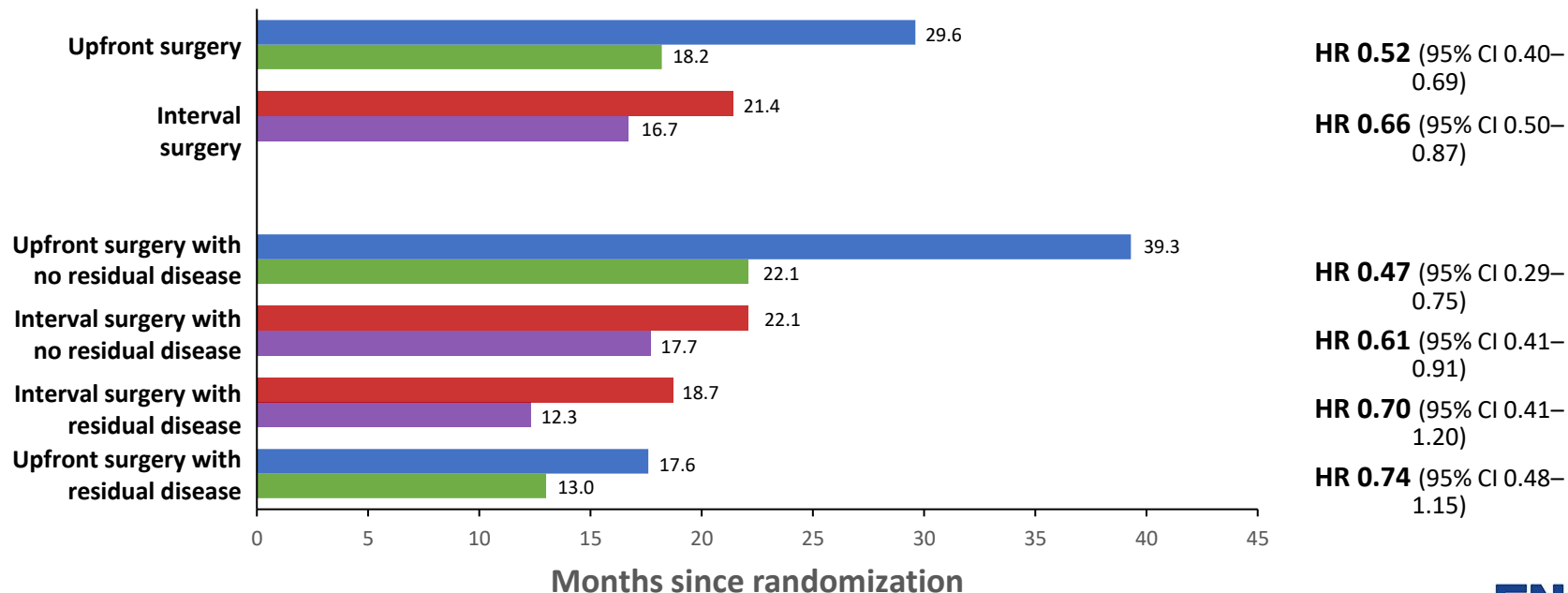
Safety profile across first-line maintenance trials: Summary

| | SOLO1 ¹ | | PRIMA ² | | ATHENA-MONO ³ | | PAOLA-1 ⁴ | |
|--------------------------|--------------------|---------|--------------------|---------|--------------------------|---------|------------------------|-----------------------|
| | Olaparib | Placebo | Niraparib | Placebo | Rucaparib | Placebo | Bevacizumab + olaparib | Bevacizumab + placebo |
| n | 260 | 130 | 484 | 244 | 185 | 49 | 535 | 267 |
| AE leading to | | | | | | | | |
| Dose reduction | 28.8% | 3.1% | 71.7% | 10.2% | 49.4% | 8.2% | 41% | 7% |
| Dose interruption | 52.7% | 16.9% | 80.8% | 23.0% | 60.7% | 20.0% | 54% | 24% |
| Discontinuation | 11.9% | 3.1% | 16.0% | 3.7% | 11.8% | 5.5% | 20% | 6% |
| Grade ≥3 AEs | 39.6% | 20% | 70.5% | 18.9% | 60.5% | 22.7% | 57% | 51% |

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended. **Please note: Rucaparib is not licensed for first-line maintenance treatment in patients with newly-diagnosed ovarian cancer.** AE, adverse event

1. Di Silvestro P, et al. *J Clin Oncol* 2022. doi: <https://ascopubs.org/doi/full/10.1200/JCO.22.01549> [Epub ahead of print]; 2. Gonzalez-Martin A, et al. *N Engl J Med* 2019;381:2391–2402; 3. Monk JM, et al. *J Clin Oncol* 2022. doi: <http://ascopubs.org/doi/full/10.1200/JCO.22.01003> [Epub ahead of print]; 4. Ray-Coquard IL, et al. Presented at European Society for Medical Oncology Congress; 27th September – 1st October 2019; Barcelona, Spain; abstract LBA2

PAOLA-1 substudy: Timing of surgery and residual disease status



Grimm C *et al*, SGO 2020

■ Olaparib plus bev: Upfront surgery

■ Olaparib plus bev: Interval surgery

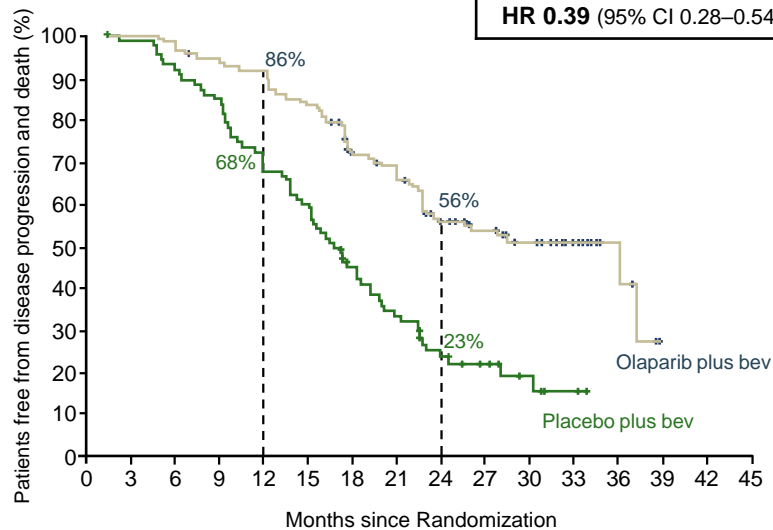
■ Placebo plus bev: Upfront surgery

■ Placebo plus bev: Interval surgery

Residual disease to decide in HRD+ pop ?

**Higher risk*,
HRD positive**

| | Olaparib + bev (n=177) | Placebo + bev (n=89) |
|--------------------|-----------------------------------|----------------------|
| Events, n (%) | 77 (44) | 67 (75) |
| Median PFS, months | 36.0* | 16.0 |
| | HR 0.39 (95% CI 0.28–0.54) | |



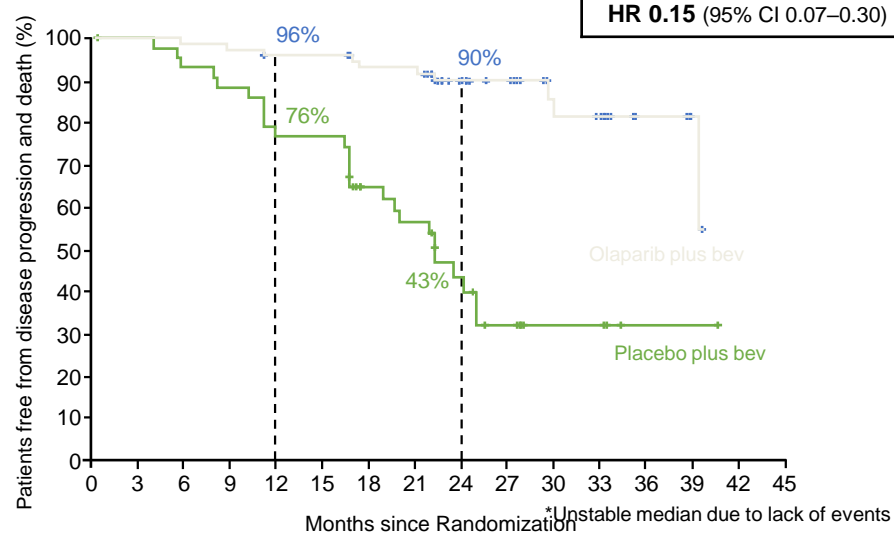
Number of patients at risk:

| | | | | | | | | | | | | | | | |
|-------------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|---|---|---|
| Olaparib plus bev | 177 | 175 | 166 | 161 | 150 | 140 | 109 | 95 | 63 | 50 | 27 | 15 | 5 | 0 | 0 |
| Placebo plus bev | 89 | 86 | 78 | 66 | 59 | 47 | 31 | 24 | 16 | 11 | 5 | 2 | 0 | 0 | 0 |

*higher-risk patients: FIGO stage III disease with upfront surgery and residual disease / - NACT, OR FIGO stage IV disease

**Lower risk*,
HRD positive**

| | Olaparib + bev (n=78) | Placebo + bev (n=43) |
|--------------------|-----------------------------------|----------------------|
| Events, n (%) | 10 (13) | 25 (58) |
| Median PFS, months | NR | 22.1 |
| | HR 0.15 (95% CI 0.07–0.30) | |



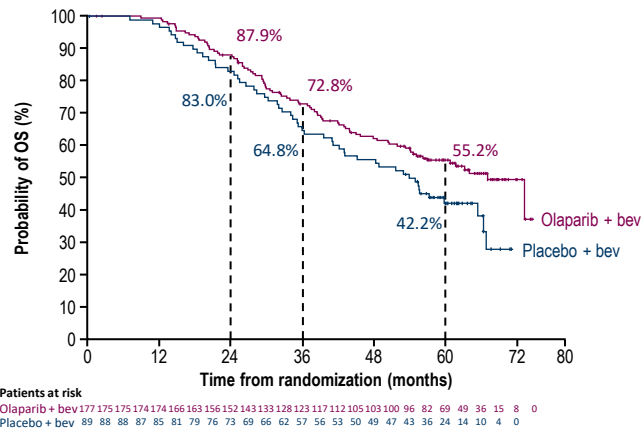
Number of patients at risk:

| | | | | | | | | | | | | | | | |
|-------------------|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|
| Olaparib plus bev | 78 | 77 | 76 | 75 | 73 | 73 | 60 | 60 | 40 | 35 | 19 | 14 | 6 | 3 | 0 |
| Placebo plus bev | 43 | 42 | 39 | 37 | 32 | 32 | 23 | 20 | 12 | 7 | 3 | 3 | 1 | 1 | 0 |

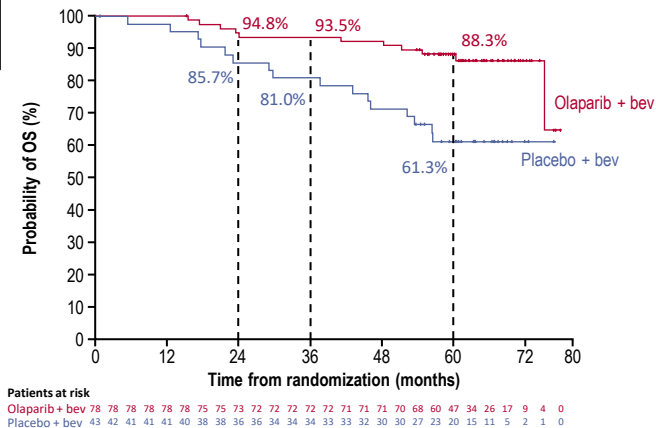
*lower-risk patients: FIGO stage III disease with upfront surgery and complete resection)

5-year OS by clinical risk in HRD-positive patients

Higher risk



Lower risk



| | Olaparib + bevacizumab (n=177) | Placebo + bevacizumab (n=89) |
|--|-----------------------------------|------------------------------|
| Events, n (%) | 82 (46.3) | 53 (59.6) |
| Median OS, months | 67.0* | 54.0 |
| 5-year OS rate, % | 55.2 | 42.2 |
| | HR 0.70 (95% CI 0.50–1.00) | |
| Patients receiving a PARP inhibitor during any subsequent treatment, % | 18.6 | 56.2 |

| | Olaparib + bevacizumab (n=78) | Placebo + bevacizumab (n=43) |
|--|-----------------------------------|------------------------------|
| Events, n (%) | 11 (14.1) | 16 (37.2) |
| Median OS, months | NE | NE |
| 5-year OS rate, % | 88.3 | 61.3 |
| | HR 0.31 (95% CI 0.14–0.66) | |
| Patients receiving a PARP inhibitor during any subsequent treatment, % | 14.1 | 39.5 |

Patients receiving a PARP inhibitor during any subsequent treatment, %

Patients receiving a PARP inhibitor during any subsequent treatment, %

In the relapse setting

In the most recent phase III as PAOLA1, DUO-O or IMAGYN050

Less than 10% of patients progressed in the 1st 6 months during chemotherapy period

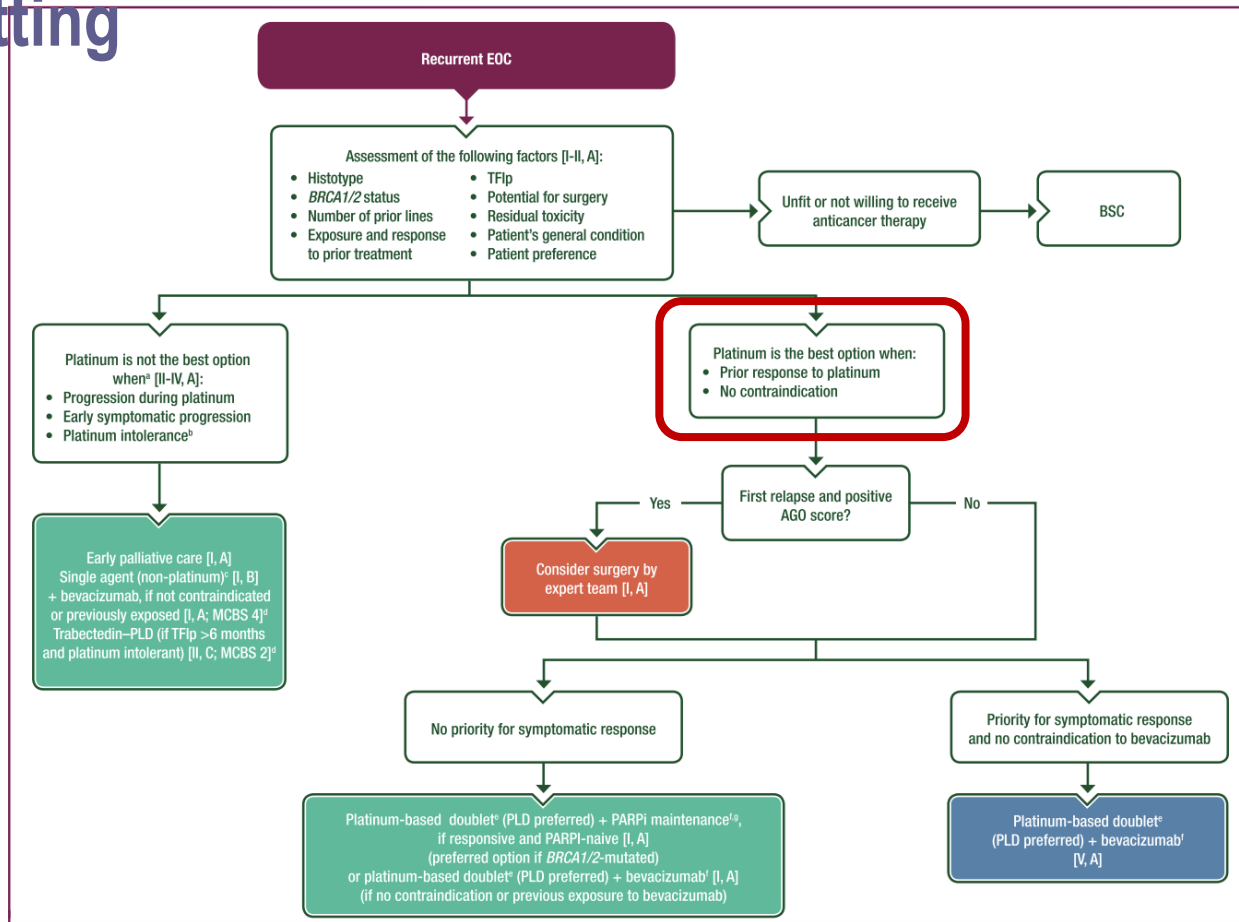
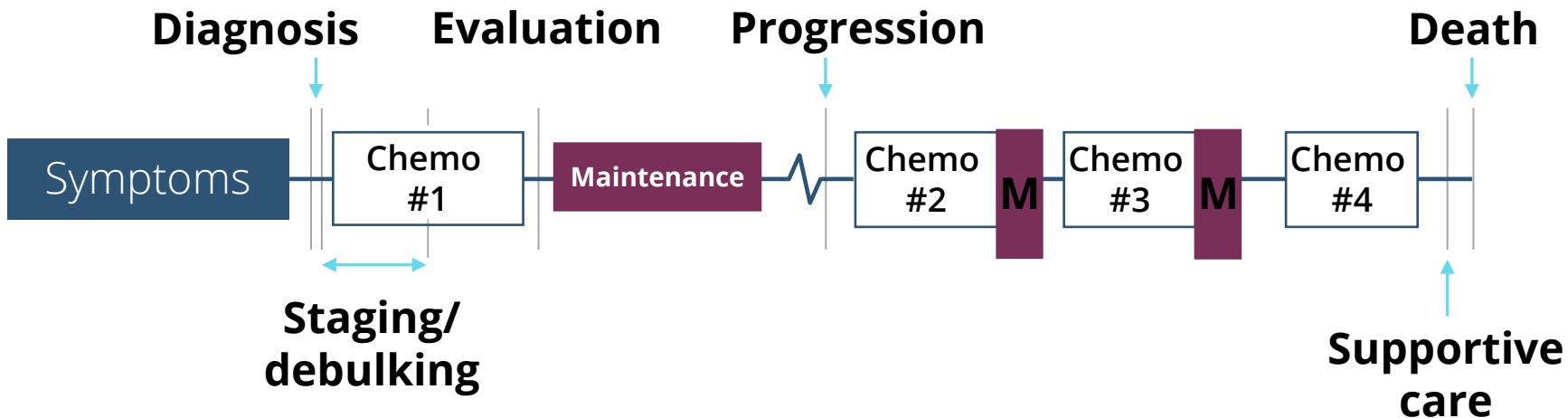


Figure 3. Management of recurrent EOC.

Treatment Landscape in Ovarian Cancer (2024)



1. Pre treated by PARPi alone → relapse → CT + Bev followed by Bev
2. Pre treated by BEV alone → relapse → CT followed by parpi if CR/PR to CT
3. Pre treated by PARPi & BEV → relapse → **Place for re challenge?**

Bevacizumab rechallenge

EVIDENCE

Carboplatin-based doublet plus bevacizumab beyond progression versus carboplatin-based doublet alone in patients with platinum-sensitive ovarian cancer: a randomised, phase 3 trial

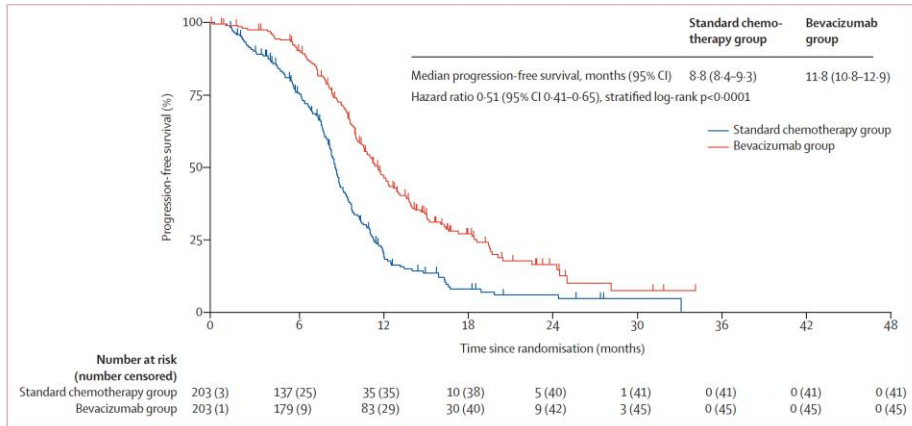


Figure 2: Kaplan-Meier estimated curves of progression-free survival

Sandro Pignata et al. *Lancet Oncol* 2021; 22: 267–76

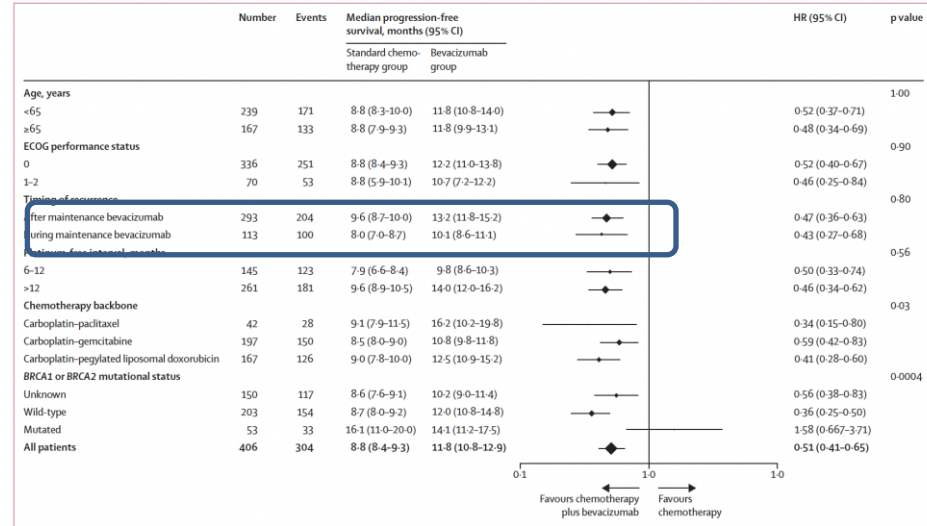


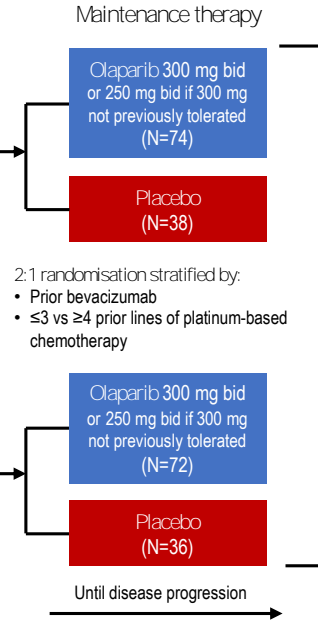
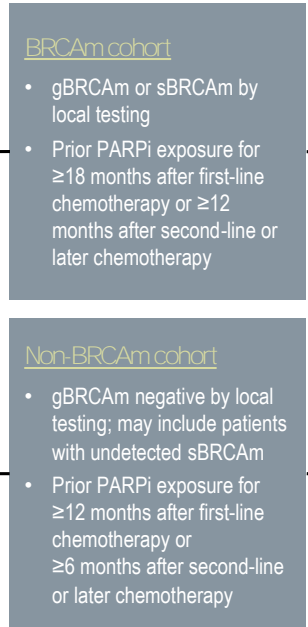
Figure 3: Forest plot of subgroup analysis of progression-free survival

PARPi rechallenge: OREO study / ENGOT-ov38

EVIDENCE

Study design

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



- Primary endpoint**
- Investigator-assessed PFS (modified RECIST 1.1)
- Secondary endpoints**
- Time to RECIST/CA-125 progression or death
 - Time to first subsequent therapy or death
 - Time to second subsequent therapy or death
 - Time to treatment discontinuation or death
 - Overall survival
 - HRQoL
 - Safety

2.5 years for recruiting 112 patients BRCAm

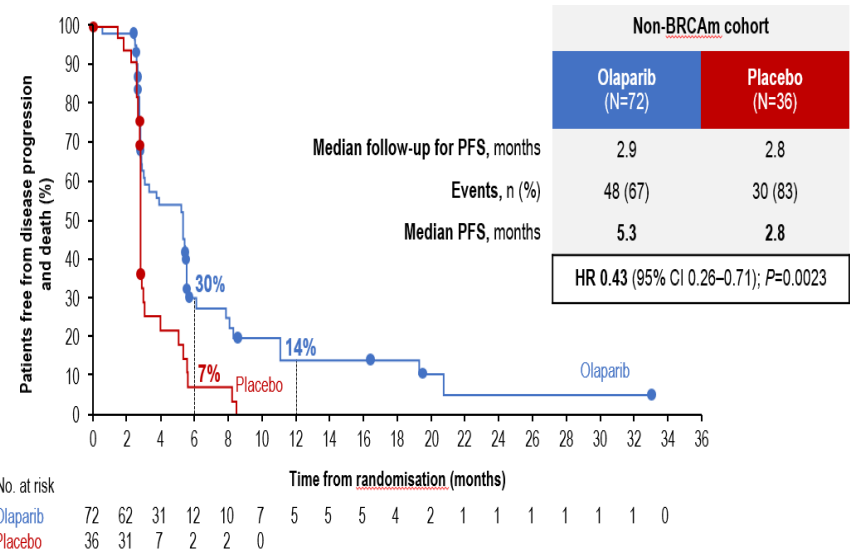
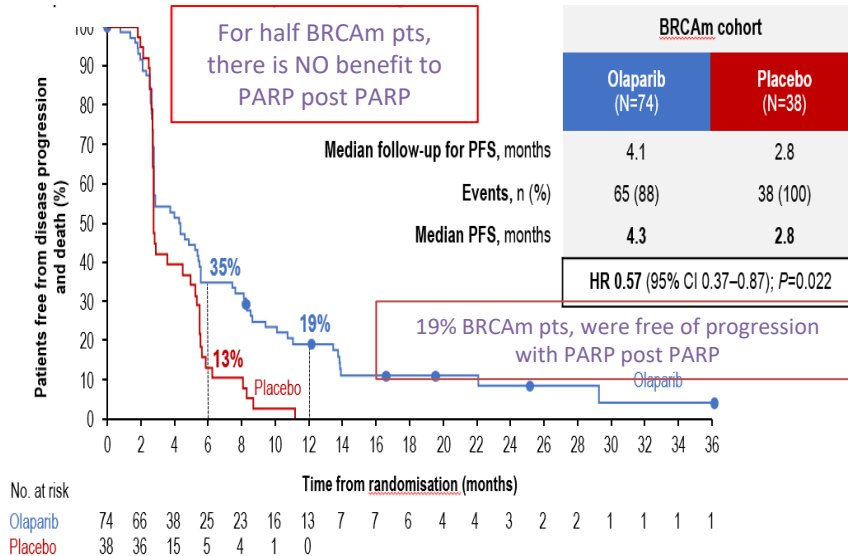
3.5 years for recruiting 108 patients non-BRCAm

How was the response to platinum after iPARP exposition?

*NED was permitted if optimal cytoreductive surgery conducted prior to chemotherapy
 bid, twice daily; CA-125, cancer antigen 125; CR, complete response; gBRCAm, germline BRCA mutation; HRQoL, health-related quality of life; NED, no evidence of disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; sBRCAm, somatic BRCA mutation

ROLE OF PARPi RECHALLENGE

- Re-challenge with olaparib significantly prolonged PFS in patients with and without BRCA mutations.¹ However, these results were not clinically relevant, as the median PFS increase was only 1.5 months in patients with BRCA mutation and 2.5 months in BRCAwt patients:²



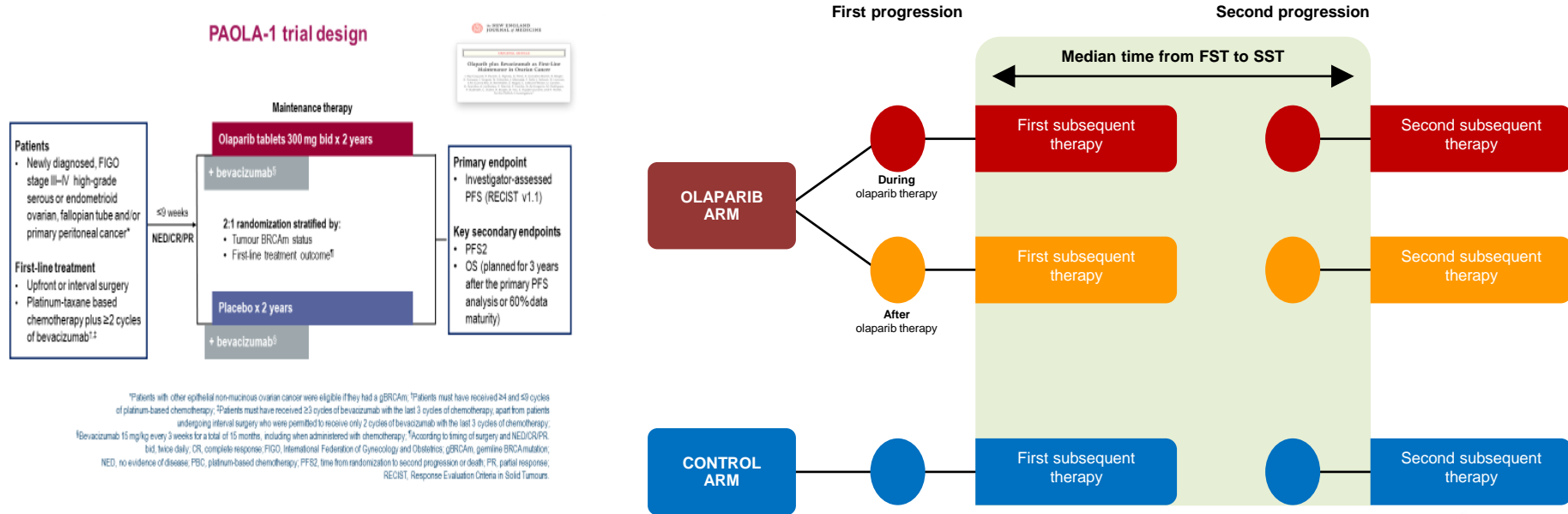
The evidence for PARPi rechallenge is still limited and warrants further validation³

WHAT IS NEW IN THE RELAPSE SETTING

- **PARPI in the 1st line setting for at least 50% of patients with HGSC and advanced FIGO stage**
- **Potential overlap of platinum resistance and parpi resistance**
- **efficacy of subsequent chemotherapy at first relapse may be impact by the time of the progression compared to disease progression during vs after olaparib plus bevacizumab maintenance**
- **A Need to integrate parpi interval free survival in our algorithms?**
- **Alternative coming soon**

New data from PAOLA-1/ENGOTov25 trial

- Post hoc exploratory analysis: time from first subsequent therapy to second subsequent therapy**

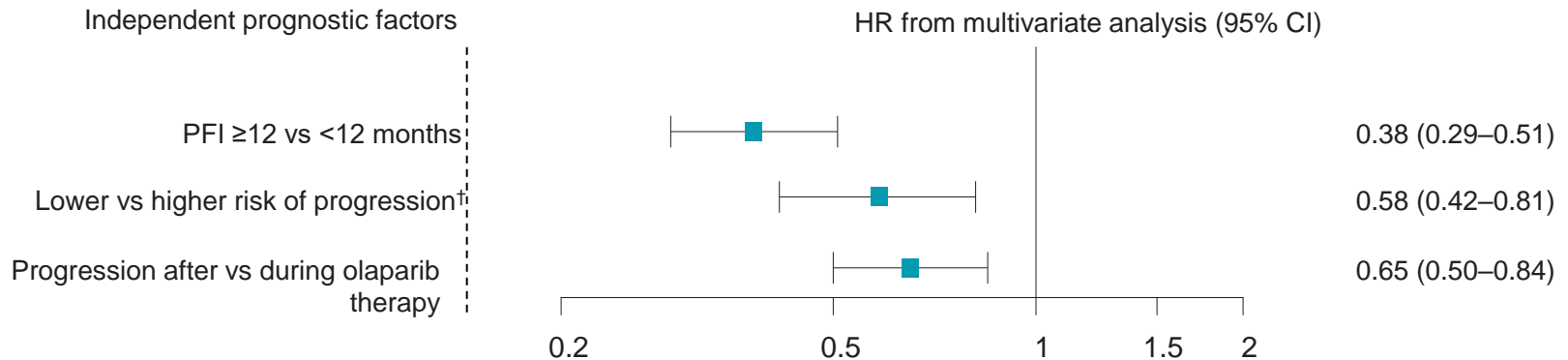


Ray Coquard et al NEJM 2019 & Harter, Ray Coquard et al Ann Oncol 2024

New factors to be integrated in our decision making process?

- A multivariate analysis showed that progression after vs during olaparib was a significant prognostic factor for time from FST to SST, together with platinum-free interval and initial risk of disease progression:

Prognostic factors influencing median time from FST to SST (olaparib arm)*

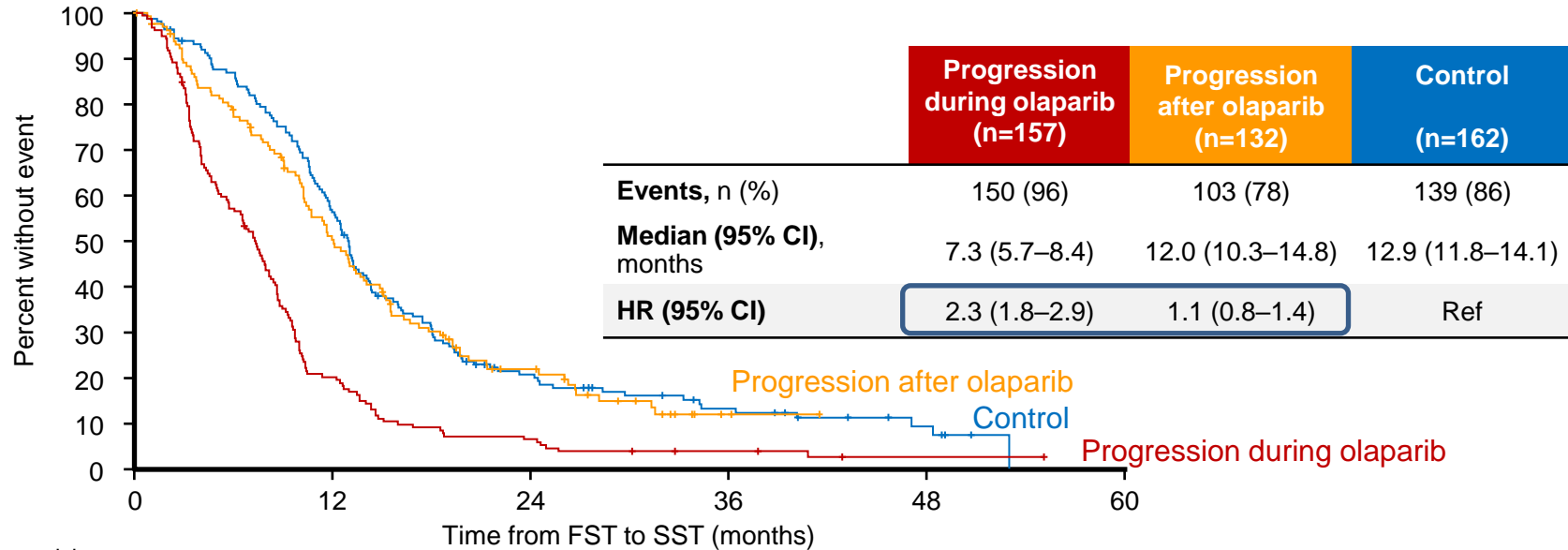


This analysis should be interpreted with caution as the subgroup analyses conducted meant the factors used in the initial randomization of patients for PAOLA-1 were lost

*337 patients treated in the olaparib arm received any chemotherapy as first subsequent therapy and were included in the multivariate analysis; †Lower risk of progression: FIGO stage III, no residual disease at upfront surgery. Higher risk of progression: all other settings for FIGO stage III; FIGO stage IV. FST, first subsequent therapy; PFS, platinum-free interval; SST, second subsequent therapy.
1. Harter P *et al. J Clin Oncol* 2023;41(Suppl. 16):abstr 5550.

2nd Progression free survival (Patients receiving PBC as 1st therapy)

A *post hoc* exploratory PAOLA-1 analysis suggested the efficacy of subsequent chemotherapy at first relapse was reduced in patients with disease progression during vs after olaparib plus bevacizumab maintenance¹



Patients at risk

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | 57 | 60 | |
|-----------------------------|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--|
| Progression after olaparib | 132 | 113 | 97 | 83 | 60 | 46 | 35 | 25 | 21 | 14 | 11 | 5 | 2 | 1 | 0 | | | | | | | |
| Progression during olaparib | 157 | 130 | 88 | 54 | 31 | 17 | 14 | 11 | 10 | 6 | 6 | 4 | 4 | 3 | 2 | 1 | 1 | 1 | 1 | | | |
| Control | 162 | 150 | 139 | 120 | 90 | 58 | 45 | 33 | 28 | 24 | 19 | 18 | 14 | 12 | 9 | 8 | 5 | 1 | 0 | | | |

One patient in the olaparib arm did not receive study treatment and is not included in this analysis.

Response rate to CT after PAOLA-1 regimen

Supplementary Table S2. Best response to any chemotherapy or to combination therapy with PBC as FST

| Best overall response, n (%) | Progression during first-line olaparib maintenance therapy | Progression after first-line olaparib maintenance therapy | Placebo plus bevacizumab arm |
|------------------------------|--|---|------------------------------|
| Any chemotherapy as FST | n = 192 | n = 145 | n = 206 |
| Complete response | 11 (5.7) | 33 (22.8) | 38 (18.4) |
| Partial response | 37 (19.3) | 39 (26.9) | 75 (36.4) |
| Progressive disease | 88 (45.8) | 26 (17.9) | 38 (18.4) |
| Stable disease | 43 (22.4) | 30 (20.7) | 43 (20.9) |
| Not evaluable | 13 (6.8) | 17 (11.7) | 12 (5.8) |
| Combination PBC as FST | n = 157 | n = 132 | n = 162 |
| Complete response | 11 (7.0) | 32 (24.4) | 35 (21.6) |
| Partial response | 36 (22.9) | 37 (28.0) | 68 (42.0) |
| Progressive disease | 64 (40.8) | 22 (16.7) | 18 (11.1) |
| Stable disease | 39 (24.8) | 29 (22.0) | 32 (19.8) |
| Not evaluable | 7 (4.5) | 12 (9.1) | 9 (5.6) |

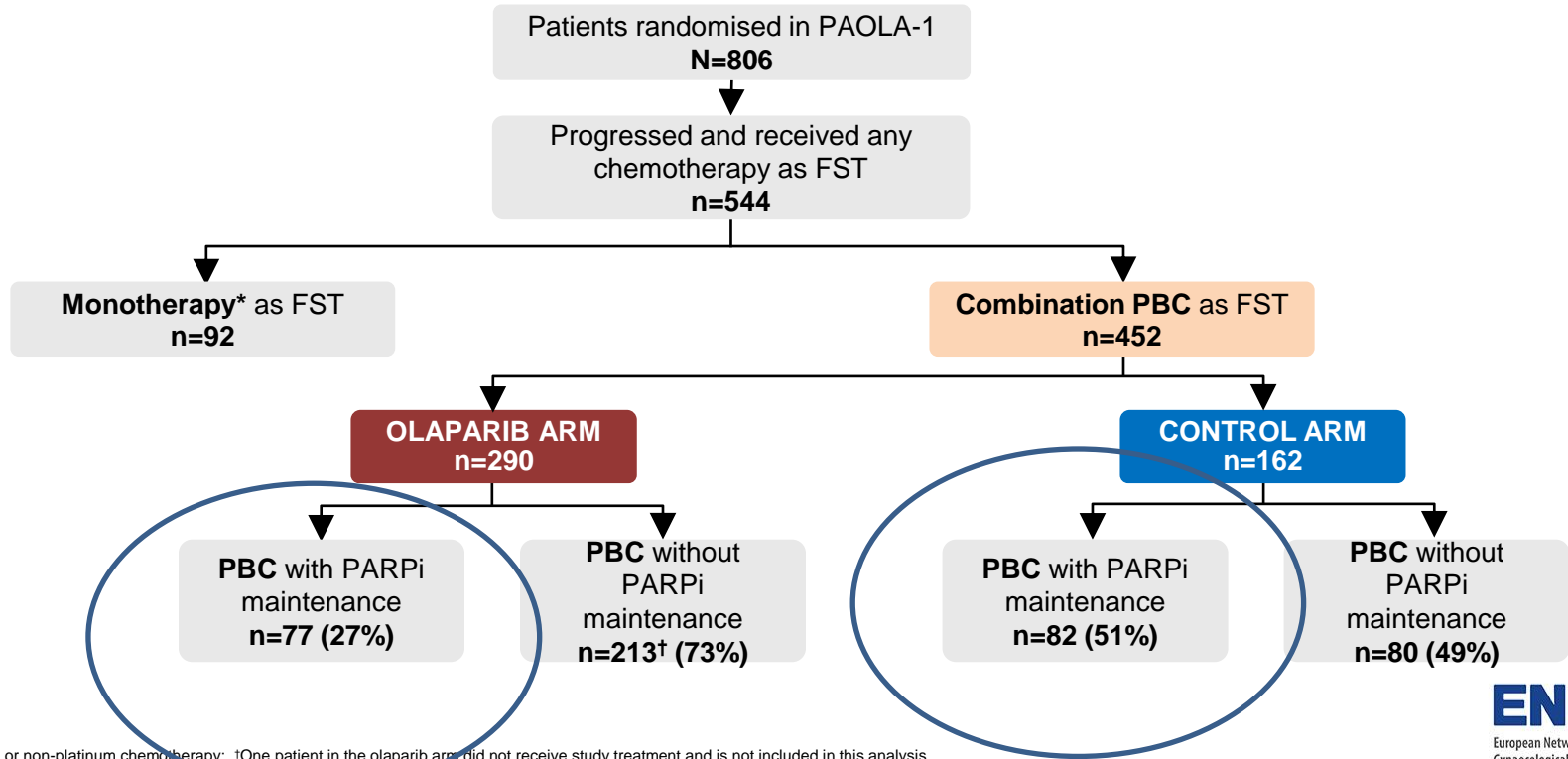
One patient in the olaparib plus bevacizumab arm did not receive treatment and was not included in this analysis.

FST, first subsequent therapy; PBC, platinum-based chemotherapy.

Harter P, Ray-Coquard I et al Ann Oncol 2024

Re challenge with parpi after response to PBC regimen in 1st relapse?

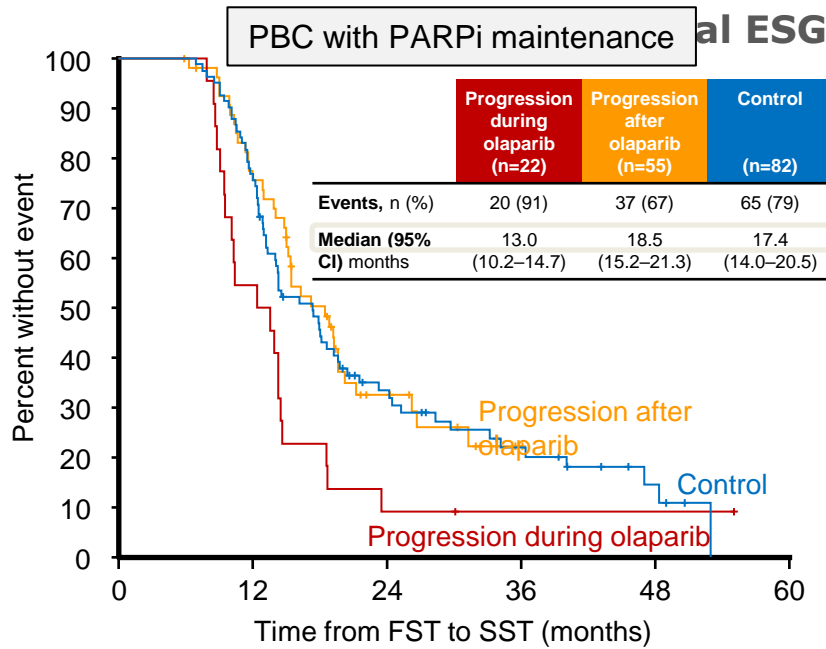
- Patients distribution in PAOLA-1



*Platinum or non-platinum chemotherapy; †One patient in the olaparib arm did not receive study treatment and is not included in this analysis.

Impact of the PARPi free interval on the rechallenge

- Time from FST to SST was longer in patients who received PBC with PARPi maintenance in the control arm or if they progressed after parpi 1st line



- Very promising results
- But need to be confirmed by a large prospective randomized clinical trial
- Integrating the benefic risk for patients and myeloid toxicity
- Time to consider a “fixed period maintenance duration also in the relapse setting

Patients at risk

| | 0 | 12 | 24 | 36 | 48 | 60 |
|-----------------------------|----|----|----|----|----|----|
| Progression after olaparib | 55 | 55 | 54 | 51 | 40 | 33 |
| Progression during olaparib | 22 | 22 | 22 | 18 | 12 | 5 |
| Control | 82 | 82 | 82 | 78 | 63 | 40 |

*One patient in the olaparib arm did not receive study treatment and is not included in this analysis.

| | | | | | | | | | | | | | | |
|-----|-----|----|----|----|----|----|----|---|---|---|---|---|---|---|
| 77 | 58 | 43 | 32 | 20 | 13 | 10 | 10 | 9 | 6 | 3 | 1 | 1 | 1 | 0 |
| 135 | 108 | 66 | 36 | 19 | 12 | 9 | 8 | 8 | 4 | 4 | 3 | 3 | 2 | 1 |
| 80 | 68 | 57 | 42 | 27 | 18 | 10 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 1 |

CONCLUSION AND FUTURE

- **Both re challenge maintenance bevacizumab and olaparib reported statistically significant benefice for relapsed EOC**
- **However, magnitude of benefice & access not identical**
 - **BEV after BEV: large benefice for PFS BUT local regulatory authorization not largely accepted and MITO16 did not included patients pre treated by PARPi**
 - **PARPi post PARPi :**
 - **OREO trial (progression during parpi): in BRCAm pts, outcomes are poor post-PARPi regardless of treatment arm! Also good response to Platine, only 14 to 19% received olaparib > 1year**
 - **PAOLA-1 retrospective data encouraging to re introduce parpi after parpi for those who progressed after maintenance therapy**

Next steps:

1. **To introduce a parpiTFI for clinical trial including Platine**
2. **To explore the re challenge parpi for those who did not progressed during parpi maintenance**
3. **To develop/re inforce alternatives for patients progressing during parpi (ADC regimen, wee1 inhibitors, surgery, local therapies....)**