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First-line PARP inhibitors in ovarian cancer: summary of an *ESMO Open - Cancer Horizons* round-table discussion

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ABSTRACT

Poly(ADP-ribose) polymerase (PARP) inhibitor maintenance therapy is the latest breakthrough in the management of newly diagnosed advanced ovarian cancer. The results of the SOLO-1 trial in 2018 led to European Medicines Agency and Food and Drug Administration approval of olaparib as first-line maintenance therapy in patients with *BRCA1/2* mutation, establishing a new standard of care. Subsequently, the results of three phase III trials (PRIMA, PAOLA-1, VELIA) evaluating the use of first-line PARP inhibitors beyond patients with *BRCA1/2* mutations and as combination strategies were presented in 2019, leading to the recent approval of maintenance niraparib irrespective of biomarker status and olaparib in combination with bevacizumab in homologous recombination deficiency-positive-associated advanced ovarian cancer. An *ESMO Open - Cancer Horizons* round-table expert panel discussed the four phase III trials of first-line PARP inhibitor therapy and how they are changing the clinical management of advanced ovarian cancer.

INTRODUCTION

For women with newly diagnosed advanced ovarian cancer (AOC), first-line therapy with a combination of debulking surgery and platinum-based chemotherapy has been the standard of care for decades. In 2011, the GOG-0218 and ICON7 trial results of the addition of the antiangiogenic agent bevacizumab to first-line chemotherapy and continuation as maintenance therapy was a step forward leading to the European Medicines Agency (EMA) approval of the first targeted therapy in AOC.[1 2] However, despite high responses to first-line systemic therapy, around 70% of women diagnosed with AOC relapsed within 3 years from completion of treatment.[3] Since 2018, there has been a paradigm shift in the management of newly diagnosed AOC as a result of the substantial benefit with poly(ADP-ribose) polymerase (PARP) inhibitors,[4] demonstrated in four randomised phase III trials (SOLO-1, PAOLA-1, PRIMA, VELIA) in the first-line setting.[5–8]

In 2018, the SOLO-1 trial[5] was the first, randomised, phase III trial to report the effects of a first-line maintenance therapy in newly diagnosed AOC. First-line maintenance therapy with olaparib for 2 years substantially extended progression-free survival (PFS) in women with newly diagnosed *BRCA1/2*-mutated AOC, leading to US Food and Drug Administration (FDA) (December 2018) and EMA (May 2019) approval and setting a new standard of care. In 2019, three further phase III trials showed a significant improvement in PFS with the addition of a PARP inhibitor to first-line therapy beyond patients with *BRCA1/2* mutation: PRIMA (niraparib),[7] PAOLA-1 (olaparib plus bevacizumab) and[6] VELIA (veliparib concurrently with chemotherapy and followed by maintenance).[8] The three trials presented at the European Society of Medical Oncology (ESMO) conference in 2019 assessed molecular subgroups according to *BRCA1/2* mutation status and homologous recombination deficiency (HRD) status.

The key results of the four trials are shown in table 1.

In Spring 2020, based on the results of the PAOLA-1 and PRIMA trials, the FDA approved first-line maintenance olaparib in combination with bevacizumab for HRD-positive (tested with companion diagnostic Myriad MyChoice CDx) AOC and niraparib first-line monotherapy maintenance therapy for women with advanced AOC regardless of their biomarker status.[9 10] In November 2020, EMA approval was granted recommending niraparib in first-line monotherapy maintenance therapy for women with advanced AOC regardless of their biomarker status and olaparib in combination with bevacizumab for patients with HRD-positive AOC.[11] The approval for first-line maintenance PARP inhibitors was in patients who have had a response (complete or partial) following completion of first-line platinum-based chemotherapy. The results of the VELIA trial have not been submitted for regulatory approval.

Table 1 Results of phase III trials of first-line PARP inhibitors

Trial name	Patients (n) and randomisation	Median PFS duration (primary endpoint and biomarker subgroups)
SOLO-1[5]	391 (olaparib vs placebo maintenance)	NR vs 13.8 months; HR 0.30, 95% CI 0.23 to 0.41; p<0.001 (all patients *BRCA1/2*-mutated)
PAOLA-1[6]	806 (olaparib plus bevacizumab vs placebo vs bevacizumab)	ITT: 22.1 months vs 16.6 months; HR 0.59, 95% CI 0.49 to 0.72; p<0.0001 HRD-positive: 37.2 months vs 17.7 months; HR 0.33, 95% CI 0.25 to 0.45; p<0.0001 HRD-negative: 16.6 months vs 16.2 months; HR 1.00, 95% CI 0.75 to 1.35; p<0.0001
PRIMA[7]	733 (niraparib vs placebo maintenance)	HRD-positive:21.9 months vs 10.4 months; HR 0.43, 95% CI 0.31 to 0.59; p<0.001 ITT: 13.8 months vs 8.2 months; HR 0.62, 95% CI 0.50 to 0.76; p<0.001 HRD-negative: 8.1 months vs 5.4 months; HR 0.68, 95% CI 0.49 to 0.94; p=0.02
VELIA[8]	1140 (veliparib combination only vs veliparib throughout vs chemotherapy)	Veliparib throughout vs chemotherapy: *BRCA1/2*-mutated: 34.7 months and 22.0 months; HR 0.44, 95% CI 0.28 to 0.68; p<0.001 HRD-positive: 31.9 months and 20.5 months; HR 0.57, 95% CI 0.43 to 0.76; p<0.001 ITT: 23.5 months and 17.3 months; HR 0.68, 95% CI 0.56 to 0.83; p<0.001 HRD-negative: 15.0 months vs 11.5 months; HR 0.81, 95% CI 0.60 to 1.09

SOLO-1 5-year follow up post-hoc analysis 56.0 months vs 13.8 months HR 0.33 95% CI 0.25-0.43[13]
HRD, homologous recombination deficiency (including t*BRCA*); ITT, intention to treat; PFS, progression-free survival.

Even with the consistent demonstration of PARP inhibitors' efficacy in this setting, the three trials and the subsequent FDA and EMA approval raise several questions regarding the optimal treatment strategy for women with newly diagnosed AOC.[12] In order to shed light on some of the clinically relevant questions surrounding the integration of first-line PARP inhibitors in clinical practice, a round table of experts was convened by *ESMO Open - Cancer Horizons* online in June 2020. The expert panel discussed selection of patients for PARP inhibitor maintenance therapy, monitoring and toxicity management, and how to treat patients in recurrence following first-line PARP inhibitor maintenance therapy.

SELECTING PATIENTS FOR FIRST-LINE MAINTENANCE PARP INHIBITOR THERAPY

Following the results from first-line PARP inhibitor trials and regulatory approvals, the oncology community is reviewing best practice in first-line treatment of patients with newly diagnosed AOC and discussing which patients should be offered a maintenance PARP inhibitor. The round table reviewed the results from the four first-line trials with regard to the molecular characteristics of patients and discussed best treatment approaches in each defined subgroup, that is, *BRCA*-mutated, HR-deficient ('HRD-positive') and HR-proficient ('HRD-negative'). The terms HRD-positive and HRD-negative refer to the results of a molecular diagnostic test.

BRCA-mutated AOC

The SOLO-1 trial enrolled women with *BRCA1/2*-associated high-grade serous ovarian cancer (HGSOC) or high-grade endometrioid ovarian cancer (HGEOC) who had partial response (PR) or complete response (CR) to front-line platinum-based chemotherapy. Patients were randomised in a 2:1 ratio to receive olaparib 300 mg tablets orally two times per day or to placebo until disease progression or toxicity for a maximum of 2 years in women with no evidence of disease. The primary endpoint presented in 2018 revealed a substantial reduction in the hazard for progression (HR 0.30, 95% CI 0.23 to 0.41; p<0.0001). At a median follow-up of 41 months, the PFS for placebo was 13.1 months as compared with 'not reached' for olaparib.[5] Long-term follow-up after 5 years since randomisation of the last patient in SOLO-1 reported an HR for PFS of 0.33 (95% CI 0.25 to 0.43), with a median PFS of 56 months in the olaparib arm compared with 13.8 months in the placebo arm. The median olaparib treatment duration was 24.6 months, indicating a sustained benefit of olaparib beyond cessation of treatment.[13] These results led to the new standard of care of 2 years of maintenance olaparib for patients with newly diagnosed *BRCA1/2* mutation-associated AOC. This study highlights the importance of timely germline and tumour testing to identify *BRCA*-associated ovarian cancers so women can be offered maintenance olaparib therapy and established it as the standard of care for this population.

A year after the initial presentation of the SOLO-1 trial at ESMO, the results of the PAOLA-1, PRIMA and VELIA trials were presented at ESMO 2019; all these trials evaluated the use of PARP inhibitor in the first-line setting of HGSOC and HGEOC (HGSOC only in VELIA) in patients with and without *BRCA1/2* mutations.

PAOLA-1/ENGOT-ov25 is a randomised phase III study that built its rationale on prior studies reporting the efficacy of bevacizumab given during platinum and taxane chemotherapy and after as maintenance. Therefore, the PAOLA trial addressed the activity of adding olaparib or placebo as maintenance therapy alongside bevacizumab, and included patients with and without *BRCA1/2* mutation. Women with stage III or IV HGSOC or HGEOC who received chemotherapy with at least two cycles of bevacizumab as part of their front-line regimen and achieved CR or PR were randomised in a 2:1 ratio to olaparib 300 mg orally two times per day for 2 years plus bevacizumab 15 mg/kg intravenously every 21 days for 15 months or to placebo plus bevacizumab. With a median follow-up

of 24.0 months in the olaparib plus bevacizumab arm and 22.7 months in the placebo plus bevacizumab arm, the median PFS for the *BRCA*-mutated group was 37.2 months vs 21.7 months, respectively (HR 0.31, 95% CI 0.20 to 0.47; p<0.001).[6]

PRIMA/ENGOT-OV26/GOG-3012 enrolled women with clinically high-risk advanced HGSOC or HGEOC with and without *BRCA1/2* mutation who were in CR or PR following platinum-based chemotherapy. Women were randomised in a 2:1 ratio to niraparib once daily or to placebo for 3 years. With a median follow-up of 13.8 months, the HR for progression or death in the subgroup of patients with *BRCA*-associated tumours was 0.40 (95% CI 0.27 to 0.62). The median PFS was 22 months vs 10.9 months in the experimental and control arm, respectively.[7]

The VELIA/GOG 3005 randomised phase III trial is the only front-line study to incorporate a PARP inhibitor (veliparib) both during and to follow front-line chemotherapy. This study enrolled women at the beginning of chemotherapy (in contrast to SOLO-1, PRIMA and PAOLA-1, which all enrolled women who had responded to chemotherapy at the time of randomisation). Eligible women with HGSOC, stage III or IV and good performance status were randomised 1:1:1 to veliparib throughout, versus veliparib with chemotherapy followed by placebo, versus placebo throughout. The veliparib dosing with chemotherapy was 150 mg orally two times per day; once maintenance was reached, it was increased to 300 mg and then 400 mg orally two times per day by cycle 7. Maintenance cycles were 21 days and continued until disease progression or toxicity for a maximum of 30 cycles. Among women with *BRCA* mutation-associated AOC, the median PFS was 34.7 months vs 22 months (HR 0.44, 95% CI 0.28 to 0.68; p<0.001).[8]

The results of the subset analysis for women with *BRCA*-associated AOC enrolled into the PAOLA-1, PRIMA and VELIA trials are consistent with those seen in the SOLO-1 trial and provide further evidence of the benefit of maintenance PARP inhibitors in the first-line setting for patients with *BRCA1/2* mutation-associated AOC.

Based on these results, the incorporation of PARP inhibitor maintenance therapy should be the standard of care for patients with *BRCA* mutation-associated newly diagnosed AOC given the consistent and unprecedented improvement in PFS. Overall survival (OS) data remain immature for all presented studies. To date, veliparib does not have regulatory approval in the first-line setting.

A key question is whether women with *BRCA* mutation-associated AOC should be treated with PARP inhibitor monotherapy or added to bevacizumab.

An exploratory, population-adjusted, indirect treatment comparison suggested an increased benefit of the bevacizumab and olaparib combination compared with olaparib alone in patients with *BRCA1/2* mutation, which was at most additive.[14] It is important to note that this conclusion is limited, based on an indirect comparison of trials, and is not a substitute for prospective, well-designed and powered clinical trials. Furthermore, a subanalysis of the GOG-0218 trial showed that the benefit of adding bevacizumab in the first-line setting was not significantly modified by homologous recombination repair gene mutation status.[15] Decisions regarding the additional use of bevacizumab should currently be individualised and based on physicians' choice, local guidelines, availability and clinical contraindications to bevacizumab.

Key message for *BRCA*-mutated AOC

- The incorporation of PARP inhibitor switch maintenance in the first-line setting should be the standard of care for all patients with *BRCA1/2* mutation-associated newly diagnosed AOC.

HR-deficient ('HRD-positive') AOC

In the PAOLA-1/ENGOT-ov25 trial,[6] patients with newly diagnosed stage III–IV high-grade serous/endometrioid AOC treated with platinum–taxane chemotherapy in combination with at least two cycles of bevacizumab were randomised following response to receive the addition of maintenance olaparib or placebo (up to 2 years) to bevacizumab (total 15 months). PAOLA-1 met its primary endpoint with a reduction in the hazard of progression or death in the intention-to-treat (ITT) population (HR 0.59, 95% CI 0.49 to 0.72; p<0.0001).

A preplanned biomarker analysis according to the Myriad MyChoice HR testing showed a significant effect in the HRD-positive population, both when including t*BRCA*-mutated (tBRCAm) tumours (HR 0.33, 95% CI 0.25 to 0.45) and excluding t*BRCA*-mutated tumours (BRCAwt) (HR 0.43, 95% CI 0.28 to 0.66). The median PFS was 37.2 months vs 17.7 months in the olaparib and placebo group, respectively, for HRD-positive/f t*BRCA*m and 28.1 months vs 16.6 months, respectively, for HRD-positive/*BRCA*wt.

A post-hoc exploratory analysis demonstrated that in a clinical 'lower' risk subgroup (defined as FIGO (International Federation of Gynecology and Obstetrics) stage III, primary debulking surgery and complete resection), the 2-year PFS rates in the *BRCA*-mutated and HRD-positive populations were 94% and 90%, respectively, with the addition of olaparib to bevacizumab maintenance therapy.[16]

In the PRIMA/ENGOT-ov26 trial,[7] patients with newly diagnosed high-grade serous/endometrioid AOC at high risk for recurrence after response to first-line platinum-based chemotherapy were randomised to maintenance niraparib or to placebo. The primary endpoint was PFS determined by a blinded independent central review (BICR) following hierarchical testing, first in patients with HRD-positive tumours, followed by the overall population if the first analysis detected a significant difference. PRIMA met its primary endpoint with a significant reduction in hazard of progression or death in the HRD-positive population (HR 0.43, 95% CI 0.31 to 0.59; p<0.001) and in the overall population (HR 0.62, 95% CI 0.50 to 0.76; p<0.001). The median PFS in the HRD-positive

subgroup was 21.9 months vs 10.4 months (inclusive of *BRCA*-mutated) and 19.6 months vs 8.2 months in HRD-positive/*BRCA*wt, respectively. In the preplanned biomarker analysis, niraparib provided similar clinical benefit in the HRD-positive subgroups, s*BRCA*-mutated (HR 0.40, 95% CI 0.27 to 0.62) and s*BRCA*wt (HR 0.50, 95% CI 0.31 to 0.83).

In the VELIA/GOG 3005 trial,[8] patients with newly diagnosed high-grade serous AOC at the time of diagnosis were randomised to receive paclitaxel/carboplatin/veliparib and veliparib maintenance (arm 1), paclitaxel/carboplatin/veliparib and placebo maintenance (arm 2), or paclitaxel/carboplatin/placebo throughout (arm 3). The primary analysis compared arm 1 versus arm 3 in the *BRCA*, HRD-positive and ITT subgroups. In the HRD-positive subgroup (inclusive of *BRCA*), there was a significant reduction in HR for progression or death (HR 0.57, 95% CI 0.43 to 0.76; p<0.001). The median PFS was 20.5 months vs 18.1 months. In the group of patients who were HRD-positive/*BRCA*wt, the HR for reduction of progression or death was 0.8 (95% CI 0.64 to 0.997), with a median PFS of 22.9 months vs 19.8 months.

In summary, these clinical trials have demonstrated a statistically significant and clinically meaningful benefit of PARP inhibitor maintenance therapy (alone or in combination with bevacizumab) after platinum-based front-line chemotherapy in HRD-positive. Maintenance PARP inhibitor (alone or in combination with bevacizumab) in newly diagnosed AOC should be offered as standard of care in this group. Therefore, HRD testing needs to be implemented in clinical practice.

Outstanding questions that need to be addressed include the following:

- What is the role of traditional clinical factors, that is, primary debulking surgery (PDS) or interval debulking surgery (IDS) and residual tumour, in the decision-making process?
- In which patients with HRD-positive tumours should bevacizumab be added to the PARP inhibitor?
- In the first-line setting, response to platinum may not necessarily be considered a valuable surrogate for HRD: all patients in the PRIMA trial and almost half of the patients in the PAOLA-1 trial (54% had No Evidence of Disease at study entry) were randomised after achieving PR (26%) or CR (20%) to platinum to testify their platinum sensitivity. However, about 35% of patients had homologous recombination proficient (HRp, 'HRD-negative') tumours by Myriad HRD testing, comprising a worse prognosis subgroup even though they had responded to platinum. This fact suggests a prognostic role of an HRD test which cannot be addressed simply by platinum responsiveness. Therefore, in a setting where an Homologous Recombination (HR) assay is not available, could the quality of response to platinum-based chemotherapy be a surrogate marker of HRD?
- Patients' clinical characteristics will inform treatment decisions regarding PARP inhibitors alone or in combination with bevacizumab. Residual disease status alone is unlikely to have sufficient precision to inform treatment given the variability in assessment.[17]

Key messages for HR-deficient ('HRD-positive') AOC

- In patients with HRD-positive tumours, there is a significant and clinically meaningful benefit of adding PARP inhibitor maintenance therapy (alone or in combination with bevacizumab) following response to platinum-based chemotherapy.
- Molecular tests for HRD are better to guide the use of PARP inhibitors than traditional clinical factors.

HR-proficient (HRp, 'HRD-negative') AOC

Patients with HR-proficient ovarian cancer have the worst prognosis.[6 7 18] The results for this group of patients were different across the three randomised trials of first-line PARP inhibitors.[6–8] The PAOLA-1 trial did not report any benefit of adding olaparib to bevacizumab compared with bevacizumab alone in the HRD-negative subgroup (HR 1.00, 95% CI 0.75 to 1.35). The median PFS in this population was 16.6 months vs 16.2 months, respectively (Harter P, Personal communication).[6] In the PRIMA trial, the authors reported a statistically significant improvement in PFS with niraparib versus placebo (HR 0.68, CI 95% 0.49 to 0.94) in the HRD-negative subgroup. The median PFS was relatively short in both treatment arms (8.1 months vs 5.4 months, respectively), which could be explained by the high-risk AOC population included in this trial alongside the molecular status of HR proficiency.[7] In the VELIA trial, there was no statistically significant improvement in PFS. The HR for the HRD-negative population was 0.81 (95% CI 0.6 to 1.09), with a median PFS of 15.0 months in veliparib throughout the arm compared with 11.5 months in the control (placebo) arm.

The benefit of maintenance PARP inhibitors in patients with HRD-negative tumours is of less magnitude than in patients with HRD-positive tumours.[7 19 20] Importantly, in the first-line setting, a benefit from maintenance PARP inhibitors was not shown in all the three trials.[18] The difference in inclusion criteria for the three trials (PAOLA-1, PRIMA, VELIA) has been argued as a potential explanation. In the PAOLA-1 trial,[6] 60% of patients have no residual disease after PDS and therefore were not selected based on a documented response to platinum-based therapy. Moreover, bevacizumab's role in increasing response rate to platinum-based chemotherapy could have increased the number of patients in response to platinum. On the other hand, in the PRIMA trial,[7] patients were selected based on high-risk clinical features (neoadjuvant chemotherapy, stage IV or stage III with residual disease after PDS), and despite this experienced a sufficient response to front-line platinum-based chemotherapy such that they were eligible to be randomised to niraparib or placebo. The patients enrolled in the PRIMA trial may be considered profoundly platinum-sensitive having obtained CA125 normalisation or >90% reduction and measurable lesions <2 cm, following platinum-based

chemotherapy alone (ie, no bevacizumab) in the context of those undergoing PDS to have residual disease prior to commencing platinum. The proportion of patients in CR at the time of randomisation was 69% in the PRIMA trial and 20% in the PAOLA-1 trial, which may reflect the selection for platinum sensitivity which is hypothesised to predict benefit from PARP inhibition. Other differences in the design of the trials which need to be considered include duration of maintenance therapy (PRIMA 3 years; PAOLA-1 2 years) and the median duration of follow-up (PRIMA 13 months; PAOLA-1 24 months). Furthermore, HRD status (HRD-positive vs HRD-negative or not determined) was a stratification factor at randomisation in the PRIMA trial, whereas analyses according to HRD status (HRD-positive, HRD-negative or unknown) were prespecified in the PAOLA-1 trial, so HRD-negative subgroup analyses are exploratory in both trials.

Another potential explanation is that an active drug, such as bevacizumab which has confirmed activity in the first-line setting,[1 2] included in the control arm of the PAOLA-1 trial[6] may have made it difficult to reveal an additional treatment effect. Indeed, the median PFS in both arms in the PAOLA-1 trial was substantially longer than that observed in the other placebo maintenance trials (PRIMA[7] and VELIA[8]).

Finally, it cannot be ruled out that molecular or pharmacokinetic differences between the three PARP inhibitors may explain the difference in the results. In this regard, niraparib has shown in preclinical studies higher trapping potency and deeper cell penetration. In addition, recent papers discussed how trapping can play a role to explain efficacy beyond *BRCA* mutation. Notably, Zandarashvili *et al*[21] showed that allostery plays a critical role in cellular PARP-1 trapping and can increase potency towards cancer cell killing (olaparib and talazoparib > rucaparib and niraparib). The results highlight the molecular basis for the fine-tuning of PARP inhibitors to achieve allosteric effects and to influence PARP-1 retention on DNA damage and trapping on chromatin in cells. This can explain differences in terms of allosteric DNA binding and activity.[21 22]

Currently bevacizumab is an option for maintenance therapy in the HRD-negative AOC population. Although a synergy between PARP inhibitors and bevacizumab was anticipated, no clinical signal to support this was reported in the PAOLA-1 exploratory HRD-negative subgroup. As maintenance niraparib alone was shown to improve PFS in the HRD-negative subgroup in the PRIMA trial,[7] it might be a good alternative for patients who are not receiving bevacizumab. However, the potential risks of PARP inhibitor therapy have to be balanced with the relatively modest benefit. Unfortunately, none of the trials reports strong evidence, and as the statistical analyses were exploratory further trials are needed to resolve the question of what should be the best first-line maintenance therapy for HRD-negative tumours.

Key messages for HR-proficient ('HRD-negative') AOC

- Both bevacizumab and niraparib can be considered as maintenance therapy options in patients harbouring HRp tumours. The decision is at the physician's discretion, taking into account patients' clinical characteristics.
- Due to the modest effect of PARP inhibitors in HR-proficient patients and their poorer prognosis, there is an urgent need for new treatment strategies in this patient subgroup.

SITUATIONS WHEN PARP INHIBITORS SHOULD NOT BE USED AS FIRST-LINE MAINTENANCE STRATEGY

It is important to be able to identify those patients who will not benefit (enough) from PARP inhibitors in the first-line setting according to biomarker status and/or clinical characteristics.

Unlike in the *BRCA*-mutated and HRD-positive tumours, adding olaparib to bevacizumab in the HRD-negative tumour does not prolong PFS compared with bevacizumab alone in the PAOLA-1 trial,[6] as mentioned above.

In the PRIMA trial,[7] the addition of niraparib significantly, both statistically and clinically, prolongs the PFS in tumours harbouring a *BRCA* mutation or are HRD-positive. In addition, and in contrast to the PAOLA-1 trial,[8] in the HRD-negative group, niraparib also showed a statistically significant benefit in terms of PFS compared with placebo, with an HR of 0.68. However, the magnitude of benefit is clearly inferior than in other subgroups.

Therefore, based on these results, niraparib maintenance therapy is indicated for all patients with high-grade ovarian cancer in response to first-line therapy supported by the FDA and EMA approval.[10 11] Despite the regulatory approval status, questions for clinical practice arise: Is the benefit of niraparib in the HRD-negative subgroup clinically meaningful enough to justify its use in all patients? How many more patients is niraparib able to keep free of progression at the threshold of 6 months from the last dose of platinum compared with placebo?

Assuming different time-points of randomisation (≤12 weeks), the difference between the arms is about 10% in favour of niraparib. Moreover, numerically, the median PFS was 8.1 months and 5.4 months in the niraparib and placebo arm, respectively.

Looking at clinical characteristics, the PRIMA trial[7] enrolled high-risk patients, that is, 35% of patients had stage IV and 45% any visible disease after PDS or IDS. The ICON7 trial[2] showed that for the high-risk population (ie, suboptimally debulked stage III with residual disease >1 cm and stage IV) bevacizumab in combination with paclitaxel/carboplatin improved the PFS with an HR of 0.73 and a median PFS of 16 months in the experimental arm vs 10.5 months in the control arm. The results are similar to the outcomes of the PRIMA trial in the HRD-negative group. The relevant difference with the ICON7 trial is that patients were randomised before starting chemotherapy. The HR of 0.73

in the bevacizumab arm also includes patients progressing and achieving a stabilisation of disease during platinum treatment, not only patients selected for platinum response as in the PRIMA trial.

As a matter of discussion with these patients, carboplatin in combination with paclitaxel plus bevacizumab as first-line therapy should be considered mainly for patients who also present high-risk clinical characteristics, that is, suboptimally debulked, stage IV and no debulking surgery, as was the population enrolled in the PRIMA trial.

A consideration on the general strategy in ovarian cancer treatment when building a treatment algorithm needs to be addressed: both PARP inhibitors and antiangiogenic agents can be used only once in many countries during the patient's course of disease, in first line or in a subsequent line where both drugs are labelled. Despite clinical trial results reporting the efficacy of bevacizumab beyond progression,[23] in many countries (not in the USA) it is not possible to further use bevacizumab in patients who have previously received bevacizumab. These limitations in prescribing should be taken into account when considering the treatment algorithm. When a clear benefit of the combination of a PARP inhibitor plus bevacizumab is not evident, as in patients with HRD-negative tumours, or for example if bevacizumab is not feasible in the first line, a possible strategy is to consider the sequential use of maintenance therapies, using PARP inhibitors in first line (considering the necessity of platinum response to prescribe PARP inhibitors which decreases over time in later lines), and delay the use of bevacizumab to the time of recurrence, either in the platinum-resistant or platinum-sensitive setting, where a significant benefit has also been reported (HR 0.48 in both settings of disease), or the alternative order depending on disease and patient characteristics.

Key messages on when not to use PARP inhibitors

- Patients with non-*BRCA* mutation-associated histological subtypes other than HGSOC or HGEOC should not routinely be considered for PARP inhibitor maintenance therapy given that these groups of patients were excluded from the first-line phase III trials. However, decisions should be individualised and take into consideration the licensed indication, which may include high-grade histologies.
- Patients deemed to be at potential risk or with a history of haematological disease of acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) should not receive PARP inhibitors.
- For HR-proficient patients receiving bevacizumab, the addition of PARP inhibitors is not recommended.
- There is no effective biomarker for excluding the benefit of PARP inhibitor maintenance therapy in HRD-negative-proficient patients who are not receiving bevacizumab.

BIOMARKER TESTING

Around half of patients with HGSOC have evidence of HRD, and 20%–25% of HRD are related to *BRCA1/2* mutations.[24] The results of the four first-line maintenance PARP inhibitor trials[5–8] highlight the importance of molecular profiling as a biomarker to guide decision-making. Three independent DNA-based measures of genomic scars have been developed by next-generation sequencing: loss of heterozygosity (LOH), telomeric allelic imbalance (TAI) and large-scale state transitions (LST).

Two assays have been developed to measure genomic instability[25]:

- The test by the Foundation Medicine combines tumour *BRCA* status as well as the percentage of genome-wide LOH.
- The test by Myriad MyChoice provides a scoring based on the unweighted sum of the three genomic scarring (LOH, TAI and LST). An HRD-positive test result is determined by a tissue test score >42 or a *BRCA* mutation, and an HRD-negative test result by a tissue test score <42; however, the cut-off is somewhat controversial. The Myriad MyChoice test was used as a stratification factor in the PRIMA trial and in the prespecified biomarker analysis of the PAOLA-1 and VELIA trials (cut-off of 42 in PRIMA and PAOLA-1; cut-off of 33 in VELIA). Nevertheless, uncertainty with HRD testing is observed in 15%–19% of patients with HRD unknown status in three recent trials.[6–8] Limitations and challenges for clinical practice include sample amount and quality (eg, biopsy, post neoadjuvant chemotherapy), access to testing, false negatives, spatial and temporal tumour heterogeneity, and costs. Nevertheless, better identification of patients with HR-proficient tumours is a priority. A more robust HRD test needs to be developed for successful integration in clinical practice.

Several academic initiatives are ongoing at international and national levels aiming to identify the 'best' HRD testing, but the quest is not straightforward. It is a challenge which requires expertise in molecular profiling, bioinformatics and biostatistics in order to address the panel genes of the genomic scars involved in the HRD mechanisms and clinical validation.[26]

Key message on biomarker testing

- A robust, cost-effective and accessible test to identify HRD is needed.

MONITORING PATIENTS ON FIRST-LINE PARP INHIBITOR MAINTENANCE THERAPY

In the industry-sponsored PRIMA trial, the primary endpoint was BICR-assessed PFS, and radiological evaluation (CT scan) in combination with serological evaluation of CA125 was performed every 12 weeks.[7] In the academic-sponsored PAOLA-1 trial, radiological evaluation was performed every 24 weeks and CA125 every

12 weeks, a closer strategy to routine clinical practice in many countries.[6] A recent presentation at the American Society of Clinical Oncology 2020 suggests an incomplete concordance between the Gynecological Cancer Intergroup CA125 criteria and the Response Evaluation Criteria in Solid Tumours for progression in the *BRCA* population. More cases of progression were captured by CT scan than by CA125, concluding that radiological evaluation should be routinely performed to evaluate progression of disease; otherwise up to 50% of cases of progression could potentially be missed.[27]

In the light of the positive results of the DESKTOP III/ENGOT-ov20 trial reporting an OS increase of about 8 months in patients with successful (residual tumour=0) secondary surgery,[28] the timely diagnosis of recurrence may play a role in the possibility of achieving a complete cytoreduction. This opportunity should not be missed.

Key message on monitoring

- There are no data showing a survival benefit by close and intensive follow-up compared with less intensive follow-up. However, regular assessment is recommended to monitor the toxicity and efficacy of maintenance therapy, including evaluation of symptoms suggesting relapsed disease. Further investigations (CA125 and imaging) should be carried out according to national guidelines for follow-up.

DURATION OF FIRST-LINE PARP INHIBITOR MAINTENANCE THERAPY

In patients with AOC, most recurrences occur during the first 3 years after completion of first-line chemotherapy. Therefore, the ideal maintenance treatment should perhaps at least cover the period of maximum risk of relapse. However, the duration of maintenance therapy is another point of discussion: in the SOLO-1, PAOLA-1 and VELIA trials,[5 6 8] PARP inhibitors were given as maintenance treatment for 2 years, while in the PRIMA trial[7] maintenance duration was up to 3 years. Looking at the molecular subgroup analysis, it is clear that there is a gradient in the efficacy of PARP inhibitors, with the *BRCA*-mutated group deriving the largest benefit, followed by HRD-positive, and lastly the HRD-negative population. Moreover, in the best scenario in AOC represented by the optimally debulked *BRCA*-mutated patients enrolled in the SOLO-1 trial,[5] receiving maintenance olaparib for 24 months, 2 years after completion of maintenance therapy, about 50% of patients experienced recurrence of disease. These data raise the question of whether prolonged duration of treatment may play a role in further reducing progression events and impacting on survival. In recurrent ovarian cancer, maintenance PARP inhibitors are continued until disease progression. The SOLO-2 trial is the first trial in recurrent ovarian cancer to report final OS results. The median OS improved by 12.9 months with maintenance olaparib compared with placebo; however, this did not reach statistical significance (HR 0.74, 95% CI 0.54 to 1.00; p=0.054). Of note, 38% of placebo patients received subsequent PARP inhibitor therapy.[29]

The 5-year follow-up results from SOLO-1[13] are encouraging, with almost 50% of patients progression-free at 5 years compared with 21% in the placebo arm following 2 years of maintenance therapy in the first-line setting. It is possible that different molecular subgroups, which gain different magnitudes of benefit from maintenance treatment, may benefit from differential maintenance durations.

Long-term safety data of PARP inhibitors, particularly in terms of severe adverse events (AE) such as acute AML and MDS and quality of life, will further inform the optimal length of duration for a well-balanced risk:benefit ratio.[30]

Key messages on duration of therapy

- After first-line platinum-based chemotherapy, PARP inhibitors should be maintained for at least 2 years (olaparib) or 3 years (niraparib) to cover the period of maximum risk of recurrence.
- The question of whether different molecular subgroups may benefit from different maintenance therapy durations needs to be addressed.

MANAGING TOXICITIES OF PARP INHIBITORS DURING MAINTENANCE THERAPY

Clinicians, nurses and patients need to be aware of class-specific and drug-specific toxicities and how to manage them. Class-specific AEs include anaemia, fatigue and nausea, which are common in all available PARP inhibitors; others are more typical of specific agents, that is, thrombocytopaenia and hypertension for niraparib and transaminases elevation for rucaparib. Most events are grade 1–2 (nausea and asthenia in particular), while grade 3 AEs involve up to 65% of patients (mainly thrombocytopaenia 29% or anaemia 17%–31%). AEs should be managed with dose reductions and interruptions, while definitive discontinuations should be reserved for few severe situations (about 10%) not manageable otherwise.

Individualised niraparib starting dosing according to baseline body weight and platelet count has been reported to decrease toxicity without significantly impacting on treatment efficacy,[31 32] and this strategy should be routinely implemented in clinical practice. Moreover great effort should be made to better understand which patients (<2% in first line, 8% in second line)[6–8 19 20 30] develop AEs of special interest, such as MDS and AML, in order to offer appropriate counselling, individualised treatment and personalised surveillance. MDS and AML, although rare, can be fatal and require careful surveillance. Long-term follow-up within the SOLO-2 trial of patients receiving maintenance olaparib or placebo in recurrent ovarian cancer reported increased rates of MDS and AML (8% olaparib vs 4% placebo).[29] Reassuringly, to date, the longer-term follow-up of patients treated in the

first-line setting within SOLO-1 and PAOLA-1 has shown no new cases of MDS or AML.[13 32]

Key messages on toxicities

- Most PARP inhibitor toxicities are manageable with dose reductions and dose interruptions.
- Permanent discontinuations due to unmanageable toxicity should be considered only when dose reduction or interruptions have failed.
- Active surveillance for AEs of special interest (ie, MDS or AML) is required.

TREATMENT OF PATIENTS IN RECURRENCE FOLLOWING MAINTENANCE PARP INHIBITOR THERAPY

With current approvals for PARP inhibitors in the recurrent disease setting, excluding women who previously received a PARP inhibitor,[33] other postprogression approaches need to be considered for patients in recurrence following maintenance PARP inhibitor therapy.

While there are data that retreatment with bevacizumab is beneficial,[23 34] there are so far no data for retreatment with a PARP inhibitor with regard to efficacy and safety. The ongoing OREO/ENGOT-ov38 trial (NCT03106987) is evaluating retreatment with a maintenance PARP inhibitor (olaparib) in patients with recurrent ovarian cancer who have received one prior PARP inhibitor in either the first-line or recurrent setting.

An important question is whether there is a difference in clinical outcomes between patients who develop disease relapse after planned end of maintenance PARP inhibitor therapy (eg, 2 or 3 years) and patients who develop disease relapse/progression while receiving a PARP inhibitor. It is likely that there are biological differences given the mechanisms of PARP inhibitor resistance, including the development of secondary mutations.[35] To help understand PARP inhibitor resistance further in these settings, tumour biopsies on progression/relapse will be important but a challenge to obtain for most patients given the likely distribution of the disease. The development of liquid biopsies to study PARP inhibitor resistance would be helpful. In light of the DESKTOP III results,[28] which showed a substantial OS benefit following complete resection in selected patients with relapse, surgery is a consideration. Of note, given most patients in DESKTOP III did not receive further maintenance therapy following adjuvant chemotherapy, the benefit of further maintenance therapy is not clear yet. However, as patients who underwent surgery on relapse were also included in the maintenance PARP inhibitor and bevacizumab trials in relapsed disease,[19 20 30 36] there is no evidence to withhold maintenance therapy if this remains an option.

Given the increasing patient population receiving first-line PARP inhibitors, the development of new agents and strategies for treatment post progression following a PARP inhibitor is urgently needed. Strategies under development beyond retreatment with a single-agent PARP inhibitor include treatment or maintenance with other 'next generation' DNA damage repair inhibitors alone or in combination with PARP inhibitors. For example, the DUETTE trial[37] is a randomised phase II trial assessing a second maintenance treatment with olaparib, olaparib in combination with the ataxia telangiectasia and rad3-related (ATR) inhibitor ceralasertib, or placebo following response or disease stabilisation with platinum-based chemotherapy in patients who have received prior maintenance PARP inhibitor therapy.

A critical aspect is related to the efficacy of subsequent chemotherapy, particularly platinum-based, after PARP inhibitor progression. Results from PARP inhibitor maintenance trials in recurrent ovarian cancer[19 20 29] and now first-line trials[11 38] show improvements in PFS2 ('time from randomisation to second disease progression') and time to second subsequent therapy. A retrospective multi-institutional series of patients treated with prior olaparib (median of three prior treatment lines) reported a response rate of 40% with a median PFS of 22 weeks and OS of 45 weeks.[39] More recent real-world experience suggests a reduced efficacy of platinum in patients recurring after treatment with PARP inhibitors, which perhaps is not surprising when considering that one of the identified mechanisms of PARP resistance is the occurrence of *BRCA* reversion mutation, which also impacts on platinum sensitivity.[40] The efficacy of subsequent chemotherapy lines after PARP inhibitor progression needs to be better addressed and additional data need to be collected in ongoing and recently closed trials as well as real-world experience to inform the optimal treatment after a PARP inhibitor.

Key messages on treatment in recurrence following maintenance PARP inhibitor therapy

- At present no data are available on the efficacy of retreatment with PARP inhibitors after progression or relapse following a PARP inhibitor.
- Data on the efficacy of subsequent chemotherapy after PARP inhibitor failure need to be collected in the ongoing and recently closed trials to inform treatment decisions.

NEXT STEPS FOR CLINICAL TRIALS

Ongoing and planned trials are addressing the possibility of reintroducing PARP inhibitors in the treatment strategy of patients who have previously received a PARP inhibitor. The trials include patients who have disease progression and those who develop relapse post planned cessation of a PARP inhibitor. These groups represent two different populations in terms of mechanism of resistance. Clinical trials are supported by robust translational substudies aimed at defining the mechanisms of resistance and how best to overcome them. In the absence of any defined predictive biomarker of sensitivity to PARP inhibitor retreatment, the magnitude of benefit derived during previous PARP inhibitor treatment in terms of duration

of benefit and PARP inhibitor treatment-free interval is likely to be relevant and hence represented in the inclusion criteria of trials such as the OREO (NCT03106987) trial. Future trials should look at these aspects and possibly stratify the populations accordingly.

In the SOLO-2 trial[29] about 20% of *BRCA*-mutated patients are still on treatment with olaparib after 5 years, and in the NOVA trial[19] about 30% of *BRCA* and non-*BRCA* patients remain on niraparib after 3 years, indicating that there are 'long responder' patients in both *BRCA* and non-*BRCA*-mutated categories. The ability to identify these patients early on is a priority of clinical research of the next years. In addition, it is important to identify patients who may develop MDS or AML. Finally, there are four international, randomised ongoing trials involving more than 5000 patients with newly diagnosed AOC investigating the combination of PARP inhibitors with programmed death 1/ligand 1 inhibitors (NCT03602859, NCT03737643, NCT03740165, NCT03522246). The results of these trials will be available in the next 2–3 years and will possibly further change first-line AOC treatment.

Key messages on future clinical trials

- Future clinical trials should include robust translational studies to better characterise the mechanism of resistance to PARP inhibitors and guide therapeutic options, as well as predictors of response to identify 'long responder' patients and those who do not benefit from PARP inhibitors.
- Treatment-free interval from last PARP inhibitor and duration of PARP inhibitor treatment should be considered as stratification criteria in studies enrolling patients who have received a prior PARP inhibitor.

CONCLUSION

PARP inhibitors are changing the course of AOC and represent a significant step forward in the fight against it. There remain questions that need to be addressed in ongoing and completed clinical trials, such as when and how patients should be treated with a PARP inhibitor in first line and/or at the time of recurrence[41]; alone or in combination with other therapies such as antiangiogenic agents or immunotherapy; and the best treatment according to molecular subgroups (ie, HRD status).

As PARP inhibitors are now being used in the first-line setting, careful evaluation of the effect of PARP inhibitors on subsequent treatment efficacy is needed. The mechanism of PARP inhibitor resistance and how to overcome it, as well as the identification of short-term and long-term responders, will be a priority of clinical research in the next few years. Finally, great effort should be made to identify which patients are more prone to develop severe haematological toxicity such as MDS or AML. Ultimately, mature OS results of first-line PARP inhibitor maintenance therapy are key and these are eagerly awaited.

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