





# Poly (ADP-ribose) polymerase inhibitors (PARPi) in ovarian cancer: lessons learned and future directions

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## ABSTRACT

Poly (ADP-ribose) polymerase inhibitors (PARPi) represent a new standard of care in the upfront treatment of advanced epithelial ovarian cancer to the point that the vast majority of patients now receive a PARPi, alone or in combination with the anti-angiogenic bevacizumab, as part of their first-line maintenance therapy. The clinical benefit of PARPi is well established; however, much has changed since their introduction and several relevant questions have been raised and remain unresolved in the post-PARPi era. The decision-making process regarding the most appropriate first-line maintenance therapy could be challenging in clinical practice, especially in the homologous recombination-proficient setting, and several other factors need to be considered apart from the mutational status. Concerns regarding post-PARPi progression treatment have emerged, highlighting an unmet need to define a valid algorithm strategy. PARPi may not only compromise the response to further platinum due to cross-resistance mechanisms but the impact on subsequent non-platinum chemotherapy and surgery also remains unclear. Definitive results on the role of PARPi rechallenge are awaited, especially in the case of oligoprogression managed with locoregional treatment. Moreover, the updated overall survival data from the recurrent setting warrant caution in using PARPi as single agents for unselected patients. Several PARPi combination regimens are emerging for overcoming PARPi resistance and may become our new therapeutic armamentarium. This review discusses a set of clinically relevant issues in the PARPi era and provides a glimpse of future challenges and opportunities in ovarian cancer treatment.

## WHAT IS THE STATE OF THE ART OF FIRST-LINE POLY (ADP-RIBOSE) POLYMERASE INHIBITORS (PARPi)?

The advent of poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) as first-line maintenance therapy is likely the most impacting practice change since the carboplatin-paclitaxel milestone and has marked a new PARPi era in the natural history of advanced epithelial ovarian cancer.<sup>1</sup> Following the results of the SOLO1,<sup>2</sup> PRIMA,<sup>3</sup> and PAOLA1<sup>4</sup> trials, the vast majority of patients have been receiving a PARPi as part of their upfront treatment algorithm. Indeed, the main prerequisites, namely advanced International Federation of Gynecology and Obstetrics (FIGO) stage

III-IV, high-grade serous or high-grade endometrioid histology, and (complete or partial) response to platinum-based chemotherapy, are met in most cases. Epithelial ovarian cancer presents at an advanced (FIGO III-IV) stage in 60–70% of cases and high-grade serous ovarian cancer is seen in 70–80% of patients. Approximately 70–80% of patients will respond to first-line platinum with a complete response in more than half of cases, and very rarely patients are platinum unsuitable due to hypersensitivity reactions during first-line chemotherapy.<sup>5</sup>

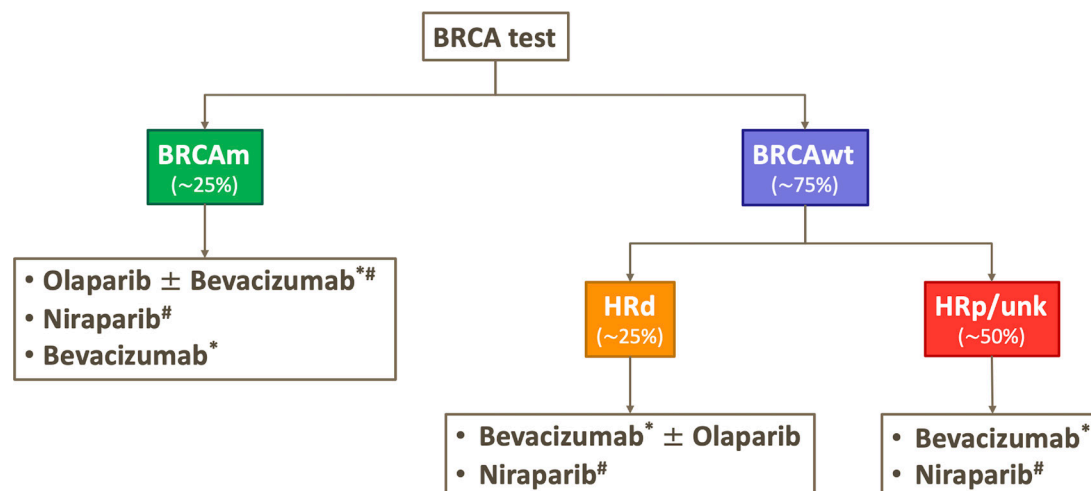
Before the advent of PARPi, 70% of patients with advanced ovarian cancer relapsed within 3 years from the initial diagnosis and the 5-year overall survival was extremely poor (5–20%) with a median time to progression of 10–20 months.<sup>5</sup> The updated long-term data from the SOLO1,<sup>6</sup> PAOLA1,<sup>7</sup> and PRIMA<sup>8</sup> trials showed unprecedented survival rates in ovarian cancer, reinforcing the role of PARPi as a practice-changing treatment (Table 1). In the updated analysis of the SOLO1 trial after 7 years of follow-up—although the data were still immature—nearly 70% of patients treated with olaparib were alive and half of them did not receive any subsequent treatment.<sup>6</sup> Notably, PAOLA1 is the first trial showing a statistically significant increase in the 5-year overall survival, an extraordinary result in the history of ovarian cancer.<sup>7</sup> Moreover, the updated progression-free survival data from the PRIMA trial confirmed the clinical benefit of PARPi also in homologous recombination-proficient patients, although the magnitude of this benefit was less prominent and further effort is required to improve the outcomes in this cohort.<sup>8</sup>

Figure 1 illustrates an algorithm with the currently approved first-line maintenance options in advanced epithelial ovarian cancer. The BRCA/homologous recombination deficiency mutational status is the main driver for choosing the most appropriate strategy. All women with non-mucinous epithelial ovarian cancer should be tested for BRCA at diagnosis, and a homologous recombination deficiency test should be performed in case of BRCA-wild type (BRCAwt) status. The PARPi olaparib is indicated for BRCA-mutated (BRCAm) patients, olaparib plus bevacizumab for homologous recombination deficiency-positive patients (including BRCAm), while

## Review

**Table 1** Overview of the pivotal phase III randomized controlled trials with poly (ADP-ribose) polymerase inhibitors (PARPi) in the first-line setting.

Parameter	SOLO1	PAOLA1	PRIMA	PRIME	ATHENA-MONO
Drug	Olaparib	Olaparib+bevacizumab	Niraparib	Niraparib	Rucaparib
Histotype	HGSOC and HGEOC	HGSOC and HGEOC	HGSOC and HGEOC	HGSOC and HGEOC	HGSOC and HGEOC
Eligibility	<ul style="list-style-type: none"> <li>▶ Stage III-IV</li> <li>▶ BRCAm</li> <li>▶ Response to platinum</li> </ul>	<ul style="list-style-type: none"> <li>▶ Stage III-IV</li> <li>▶ HRD-positive</li> <li>▶ Response to platinum</li> <li>▶ At least two cycles of bevacizumab with chemotherapy</li> </ul>	<ul style="list-style-type: none"> <li>▶ Stage III with RT&gt;0, NACT, or inoperable</li> <li>▶ Stage IV</li> <li>▶ Response to platinum</li> </ul>	<ul style="list-style-type: none"> <li>▶ Stage III-IV</li> <li>▶ Response to platinum</li> </ul>	<ul style="list-style-type: none"> <li>▶ Stage III-IV undergoing surgical cytoreduction (complete resection was permitted)</li> <li>▶ Response to platinum</li> </ul>
Starting dose	300 mg twice daily	300 mg twice daily + 15 mg/kg every 3 weeks	Initially fixed dose of 300 mg, then individualized dose: 300 mg (if weight >77 kg and platelet count >150 000/ $\mu$ l) or 200 mg	Individualized dose: 300 mg (if weight >77 kg and platelet count >150 000/ $\mu$ l) or 200 mg	600 mg twice daily
Duration	Up to 2 years (in the absence of unacceptable toxicity or PD)	<ul style="list-style-type: none"> <li>▶ Olaparib: up to 2 years (in the absence of unacceptable toxicity or PD)</li> <li>▶ Bevacizumab: up to 15 months/22 cycles (in the absence of toxicity or PD)</li> </ul>	Up to 3 years (in the absence of unacceptable toxicity or PD)	Up to 3 years (in the absence of unacceptable toxicity or PD)	Up to 2 years (in the absence of unacceptable toxicity or PD)
Mutational status	BRCAm	HRD-positive	All-comers	All-comers	All-comers
HRD test	–	Myriad MyChoice	Myriad MyChoice	BGI	FoundationOne
Benefit across biomarkers					
ITT	7-year OS: 67.0% vs 46.5% (HR: 0.55; 95% CI 0.40 to 0.76; p=0.004)	5-year OS: 47.3% vs 41.5% (HR: 0.92; 95% CI 0.76 to 1.12)	3.5-year PFS: 13.8 vs 8.2 months (HR: 0.66; 95% CI 0.56 to 0.79; p<0.0001)	PFS: 24.8 vs 8.3 months (HR: 0.45; 95% CI 0.34 to 0.60; p<0.001)	PFS: 20.2 vs 9.2 months (HR: 0.52; 95% CI 0.40 to 0.68; p<0.0001)
BRCAm	–	5-year OS: 73.2% vs 53.8% (HR: 0.60; 95% CI 0.39 to 0.93; p<0.001)	1.2-year PFS: HR 0.40; 95% CI 0.27 to 0.62	PFS: NR vs 10.8 months (HR: 0.40; 95% CI 0.23 to 0.68; p<0.001)	PFS: NR vs 14.7 months (HR: 0.40; 95% CI 0.21 to 0.75)
HRD+ (including BRCAm)	–	5-year OS 65.5% vs 48.4% (HR: 0.62; 95% CI 0.45 to 0.85; p<0.001)	3.5-year PFS: 24.5 vs 11.2 months (HR: 0.52; 95% CI 0.40 to 0.68; p<0.0001)	PFS: HR 0.48	PFS: 28.7 vs 11.3 months (HR: 0.47; 95% CI 0.31 to 0.72; p=0.0004)
HRD+/BRCAwt	–	5-year OS: 54.7% vs 44.2% (HR: 0.71; 95% CI 0.45 to 1.13; p<0.001)	1.2-year PFS: HR 0.50; 95% CI 0.31 to 0.83	PFS: 24.8 vs 11.1 months (HR: 0.58; 95% CI 0.36 to 0.93; p=0.022)	PFS: 20.3 vs 9.2 months (HR: 0.58; 95% CI 0.33 to 1.01)
HRD–	–	5-year OS: 25.7% vs 32.3% (HR: 1.19; 95% CI 0.88 to 1.63)	3.5-year PFS: HR 0.65; 95% CI 0.49 to 0.87; p<0.00038	PFS: HR 0.41; 95% CI 0.25 to 0.65; p<0.001	PFS: 12.1 vs 9.1 months (HR: 0.65; 95% CI 0.45 to 0.95)
Limitations	Lack of bevacizumab arm	Lack of PARPi alone arm	<ul style="list-style-type: none"> <li>▶ Lack of bevacizumab arm</li> <li>▶ Low-risk patients (stage III with no residual disease after primary debulking surgery) were excluded</li> </ul>	Lack of bevacizumab arm	Lack of bevacizumab arm
BRCAm, BRCA-mutated; BRCAwt, BRCA-wild type; CI, confidence interval; HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; HR, hazard ratio; HRD, homologous recombination (DNA repair) deficiency; ITT, intention-to-treat population; NACT, neoadjuvant chemotherapy; NR, not reached; OS, overall survival; PD, progressive disease; PFS, median progression-free survival; RCT, randomized clinical trial; RT, residual tumor.					



**Figure 1** Sum-up algorithm with currently approved first-line maintenance options in advanced epithelial ovarian cancer based on mutational status. \*Bevacizumab should be considered in high-risk disease (stage IV, residual disease after surgery, neoadjuvant chemotherapy, inoperable disease, and/or “wet disease”), suboptimal response to platinum, platinum intolerance, other histotypes than high-grade serous or high-grade endometrioid, and (in some countries) homologous recombination deficiency-negative patients with stage III and no residual disease after primary cytoreductive surgery. #Note that reimbursement policies may differ from approval indications and vary across countries. Niraparib for stage III disease with no residual disease after primary cytoreductive surgery as well as the combination of bevacizumab with olaparib in BRCA-mutated patients are not reimbursed in some countries. BRCA, breast cancer gene; BRCAm, BRCA-mutated; BRCAwt, BRCA-wild type; HRd, homologous recombination (DNA repair) deficiency; HRp, homologous recombination (DNA repair) proficiency, unk, unknown.

niraparib for all-comers, regardless of biomarker status. The benefit of PARPi maintenance is higher in the BRCAm cohort, followed by BRCAwt/homologous recombination deficiency-positive, and then homologous recombination deficiency-negative patients. The type and location of mutations in the BRCA1/2 and homologous recombination repair genes are also prognostic in ovarian cancer patients but their predictive role in the maintenance decision-making needs to be further explored.<sup>9 10</sup>

It should be noted that reimbursement policies may differ from approval indications and vary across countries. In some countries that strictly followed the PRIMA inclusion criteria for niraparib reimbursement, homologous recombination deficiency-negative low-risk patients (stage III disease with no residual tumor after primary debulking surgery) currently do not have the opportunity to receive upfront PARPi. Moreover, the combination of bevacizumab with olaparib is only reimbursed for BRCAwt/homologous recombination deficiency-positive patients and not for those with BRCA mutations in some countries.

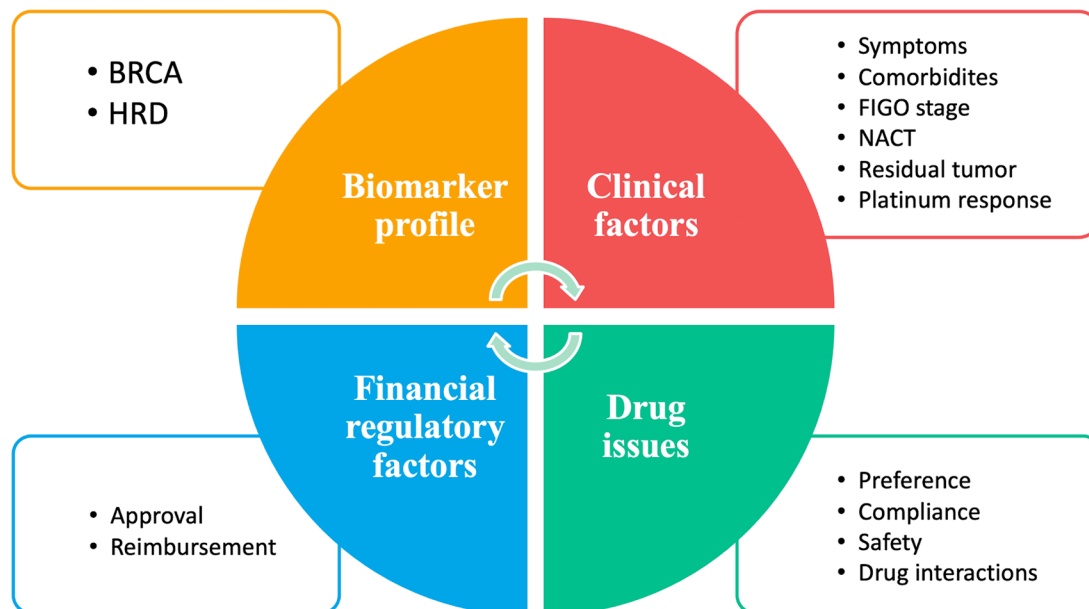
However, this therapeutic landscape is constantly evolving. The latest results from the ATHENA-MONO<sup>11</sup> and PRIME trials<sup>12</sup> were presented at the 2022 American Society of Clinical Oncology (ASCO) meeting and confirmed the benefit of PARPi in the homologous recombination-proficient subset previously observed in PRIMA<sup>3</sup> (Table 1). In the ATHENA-MONO trial, the PARPi rucaparib, which for now is approved only in the recurrence setting, has been demonstrated to be effective also as first-line maintenance. Compared with olaparib and niraparib, the benefit was demonstrated in a broader population, with no restrictions on BRCA/homologous recombination deficiency status or surgical outcome, thus also including patients with no residual disease after primary debulking surgery. The PRIME trial confirmed the survival advantage of niraparib compared with placebo in patients with newly diagnosed advanced ovarian cancer,

regardless of surgical residual disease and biomarker status. Notably, this trial differs from the PRIMA trial for four main reasons: (a) it was performed in an Asian (Chinese) population; (b) it also included low-risk patients (stage III disease with no residual disease after primary debulking surgery); (c) it used an individualized starting dose of niraparib, according to baseline bodyweight and platelet count; and (d) it used another homologous recombination deficiency test rather than the Myriad MyChoice, namely the BGI kit.

#### HOW CAN WE CHOOSE THE BEST MAINTENANCE THERAPY IN PRACTICE?

Not only the mutational status but also several other factors are essential for personalizing the maintenance treatment, especially in the homologous recombination deficiency-negative setting. Figure 2 outlines all the key factors that should be considered for guiding the decision-making process.

Platinum sensitivity represents a pivotal predictive marker of PARPi sensitivity, and it can be assessed in different not mutually exclusive ways: radiologically (RECIST, the Response Evaluation Criteria in Solid Tumors), biochemically (KELIM score, CA-125 ELIMination rate constant K), and/or pathologically (CRS, chemotherapy response score, also known as Böhm’s score). The homologous recombination deficiency test has a central role, but it is not perfect and has several limitations with potentially false-positive and false-negative results, thus there is still room for improvement (for example, through the RAD51 functional assay). Different homologous recombination deficiency assays have been used across clinical trials and the results are not comparable. The cut-off for homologous recombination deficiency positivity is conventional and there is a gray zone with borderline scores where the clinical



**Figure 2** Key factors for guiding the decision-making process in practice. BRCA, breast cancer gene; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination (DNA repair) deficiency; NACT, neoadjuvant chemotherapy.

response to platinum can help decide whether or not the patient is an ideal candidate for PARPi. Nevertheless, the homologous recombination deficiency test remains a useful and practical test and the only guide available when the response to platinum is not evaluable, such as in cases with no residual tumor after primary cytoreductive surgery or when bevacizumab is added to neoadjuvant platinum chemotherapy. All BRCAwt patients with advanced high-grade non-mucinous epithelial ovarian cancer should be tested for homologous recombination deficiency status at diagnosis and ideally before the end of first-line chemotherapy to properly plan the first-line maintenance strategy, especially in patients undergoing neoadjuvant chemotherapy where one needs to decide whether or not to add bevacizumab.

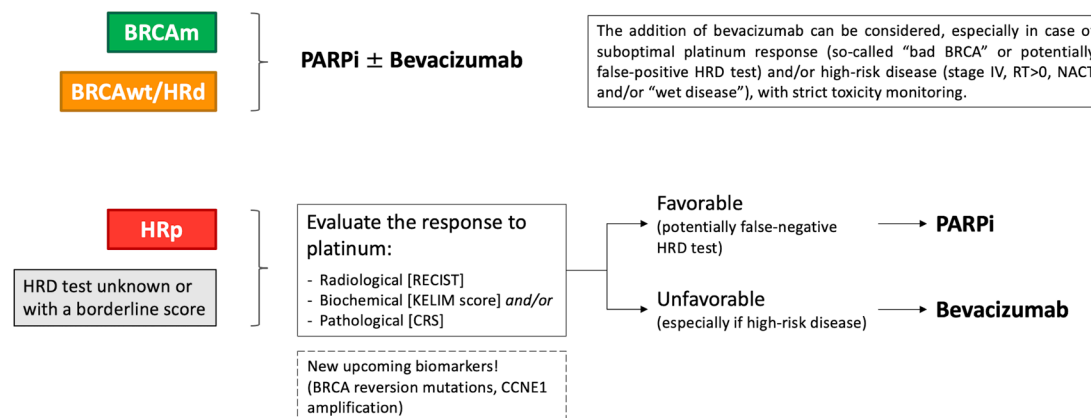
Among the other factors, not only the residual tumor after surgery is important but, in the case of no macroscopic residual disease, also the surgical effort and the number of cycles of neoadjuvant chemotherapy. The decision should also consider the financial regulatory factors (reimbursement), which vary across countries, contraindications and/or drug interactions, and the patient's preference and compliance concerning the route of administration and the duration of treatment. Indeed, PARPi are administered orally once (niraparib) or twice (olaparib and rucaparib) daily for a duration of 2 (olaparib and rucaparib) or 3 years (niraparib), in the absence of unacceptable toxicity or progressive disease. Longer PARPi duration might be considered in selected individuals with evidence of disease and after an accurate discussion of the risks. Conversely, bevacizumab is administered intravenously every 3 weeks for a total of 22 cycles (15 months). The longer treatment with bevacizumab for up to 30 months did not demonstrate an improvement in survival rates, thus the duration of 15 months remains the standard of care.<sup>13</sup> Finally, there are new potentially predictive biomarkers of platinum/PARPi sensitivity on the horizon (reversion mutations in BRCA1/2 or RAD51C/D genes, loss of BRCA1 promoter methylation, CCNE1 amplification, ABCB1 upregulation), which are currently

being investigated and could be integrated into clinical practice in the near future.

### **BRCAm and Homologous Recombination-deficient Patients**

Figure 3 illustrates a proposed algorithm for choosing the most efficient first-line maintenance option. There is no doubt that BRCAm and BRCAwt/homologous recombination deficiency-positive patients should receive a PARPi, either alone or in combination with bevacizumab. Indeed, a subgroup analysis of the GOG-0218 trial showed no advantage in progression-free survival when bevacizumab alone was added to standard chemotherapy in the subset of BRCAm patients. The addition of bevacizumab to PARPi can be considered in the case of suboptimal response to platinum (the so-called “bad BRCA” or potentially false-positive homologous recombination deficiency test) and/or high-risk disease (FIGO stage IV, macroscopic residual disease after surgery, neoadjuvant chemotherapy, inoperable disease, and/or “wet disease” presenting with ascites/pleural effusion). However, when considering the combination of PARPi and bevacizumab, several issues need to be addressed:

1. The true benefit of adding bevacizumab to PARPi remains unclear. As the PAOLA1 trial did not include a PARPi alone arm, comparisons between PARPi and bevacizumab can currently be drawn only indirectly by crossing the results of pivotal trials. In a population-adjusted indirect comparison of the SOLO1 and PAOLA1 trials, the benefit appeared to be additive rather than synergistic, raising the question of whether it is better to use these agents contemporaneously in the upfront setting or in sequence.<sup>14</sup> This uncertainty is even stronger for BRCAm carriers, while there are some positive signals for the combination of PARPi and anti-angiogenics in BRCAwt/homologous recombination deficiency-positive patients.<sup>15 16</sup> The magnitude of benefit from olaparib and bevacizumab according to the location of BRCA1/2 mutations remains unclear. Interesting data from



**Figure 3** Proposed algorithm for choosing the most effective first-line maintenance option. BRCA, breast cancer gene; BRCAm, BRCA-mutated; BRCAwt, BRCA-wild type; CCNE1, cyclin E1 gene; CRS, chemotherapy response score (Böhms score); HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; HRd, homologous recombination (DNA repair) deficiency; HRp homologous recombination (DNA repair) proficiency, KELIM, CA-125 ELIMination rate constant K; NACT, neoadjuvant chemotherapy; PARPi, poly (ADP-ribose) polymerase inhibitors; RT, residual tumor.

a subgroup exploratory analysis of the PAOLA1 trial showed a higher benefit in patients with mutations in the DNA-binding domain of BRCA1/2 genes. Several ongoing studies (NIRVANA-1,<sup>17</sup> AGO-OVAR 28/ENGOT-ov57,<sup>18</sup> MITO 25 [NCT03462212]) are currently exploring the contribution of bevacizumab added to PARPi maintenance and will provide further evidence on this subject.

2. If both PARPi and bevacizumab are used in combination as first-line maintenance, there are no options available in the recurrent setting since the rechallenge is not currently approved.
3. Since the response to platinum after PARPi might be reduced due to cross-resistance mechanisms, it may be reasonable to reserve bevacizumab for the relapse to enhance the efficacy of subsequent chemotherapy.
4. The combination regimen results in additive toxicity and cannot be easily prescribed to all patients. The proportion of patients discontinuing olaparib due to an adverse event in the PAOLA1 trial<sup>4</sup> was higher than in olaparib monotherapy trials (20% vs 12%).<sup>2</sup>

### Homologous Recombination-proficient Patients

The decision between PARPi and bevacizumab becomes even more challenging in the homologous recombination deficiency-negative setting, where the benefit of PARPi is less striking. The available homologous recombination deficiency tests are useful for selecting homologous recombination-deficient patients who are ideal candidates for PARPi maintenance but are not sufficient for ruling out the benefit of PARPi in homologous recombination-proficient patients. Indeed, homologous recombination-proficient patients treated with niraparib in the PRIMA trial showed a 35% reduction in the risk of progression or death and around 10–15% derived sustained long-term benefit.<sup>3</sup> Moreover, homologous recombination deficiency testing is still not easily available in clinical practice and, even if available, in some cases could be inconclusive (12–18% of cases) or give borderline scores. In all these scenarios, pending further evidence, the evaluation of the quality of the response to platinum (when possible) is the key. PARPi monotherapy should be offered in the case of optimal response to platinum, even

in the case of high-risk disease, as the homologous recombination deficiency test may have given a false-negative result. Conversely, bevacizumab should be prioritized in cases of unfavorable platinum response (assessed after the first three cycles of neoadjuvant/adjunct chemotherapy), especially in high-risk patients.

However, since there are no randomized clinical trials directly comparing the use of PARPi with bevacizumab in the first-line setting, the question is still open. Moreover, no maintenance treatment might also be an option in homologous recombination-proficient patients. It is clear that homologous recombination-proficient patients represent a molecularly heterogeneous cohort and further prospective research is needed to better identify the subset of patients who would benefit most from PARPi rather than bevacizumab and vice versa. A “one-size-fits-all” strategy when using the homologous recombination deficiency status to predict PARPi sensitivity should be avoided. Interestingly, long-term data from the PRIMA,<sup>3</sup> PRIME,<sup>12</sup> and ATHENA-MONO<sup>11</sup> trials will provide further evidence on this specific subpopulation.

Ultimately, in the post-PARPi scenario, bevacizumab as maintenance should be considered in cases of suboptimal response to platinum and/or high-risk disease. The high-risk factors are FIGO stage IV, FIGO stage III with residual disease after primary debulking surgery, neoadjuvant chemotherapy/interval debulking surgery, inoperable disease, and the so-called “wet disease” (ascites, pleural effusion) where the priority is to relieve symptoms. In particular, the use of bevacizumab is recommended independently of any biomarker and it is a valid option in the case of homologous recombination deficiency-negative patients where the clinical benefit of PARPi is expected to be modest. Furthermore, it remains the only strategy available in those cases where PARPi is not an option: other histotypes than high-grade serous or high-grade endometrioid, platinum intolerance, absence of response to platinum, and (at least in some countries) patients with homologous recombination deficiency-negative stage III disease and no residual disease after primary debulking surgery.

## Review

### WHY SHOULD PARPi BE USED UPFRONT?

Currently, there is no doubt that PARPi (either alone or in combination) should be preferred in the first-line maintenance treatment, at least in the BRCAm and homologous recombination deficiency-positive settings, and this is due to five reasons.

1. The clinical efficacy of first-line PARPi maintenance is well established. The updated results from the SOLO1<sup>6,8</sup> and PAOLA1<sup>7</sup> trials showed a long-term overall survival benefit suggesting hope for cure.
2. First-line maintenance aims to prevent recurrence by targeting and helping eradicate the minimal residual disease following surgery and/or response to chemotherapy. The earlier introduction of PARPi may prevent resistance to subsequent treatments by targeting a smaller disease burden with less tumor heterogeneity and less chance of de novo or acquired resistance.
3. The frontline decision-making process affects the treatment algorithm at the time of recurrence. For approximately 40% of patients, the first line may represent the only opportunity to receive a PARPi given the current indications and reimbursement policies, thus earlier introduction is highly recommended. The Kaplan–Meier progression-free survival curve of the SOLO1 placebo arm shows that approximately 20% of BRCAm patients recur within 6 months from the last platinum dose (platinum-resistant), 55% relapse after 6 months (platinum-eligible), and 25% are long-term responders.<sup>2</sup> However, of the 55% platinum-eligible patients, around 40% (ie, ~22%) fail to respond to subsequent platinum and become unsuitable to receive PARPi in the second line. Hence, approximately 42% of patients will never benefit from PARPi activity if they miss their opportunity in the first line. The risk of missing the PARPi benefit in the treatment algorithm is even higher in the subgroup of BRCAwt/homologous recombination deficiency-positive and homologous recombination deficiency-negative patients (online supplemental table S1).
4. New overall survival data from the recurrent setting warranted caution in using PARPi maintenance in second and further lines for unselected (BRCAwt) patients.<sup>19,20</sup>
5. The paradigm shift of PARPi in the upfront setting reduces the risk of developing secondary myeloid neoplasms.<sup>21</sup> Indeed, patients receiving PARPi after only one line of chemotherapy have been less exposed to prior cytotoxic treatments and thus are at lower risk of accumulating DNA damage and leukemogenic progression. Moreover, the duration of PARPi treatment in the first-line setting is limited, from 2 to 3 years, compared with until progression or unacceptable toxicity in the recurrent disease, thus further reducing the risk of developing secondary neoplasms.

### WILL FIRST-LINE PARPi ENABLE CHEMOTHERAPY DE-ESCALATION?

Continuous advances in our understanding of ovarian cancer heterogeneity may offer an opportunity for treatment de-escalation and more personalized targeted therapy based on the mutational status, molecular subtypes, and predictive/prognostic biomarkers. The benefit of PARPi in the BRCAm and homologous recombination deficiency-positive cohorts is so evident that several clinical trials are currently exploring the feasibility of chemotherapy de-escalation

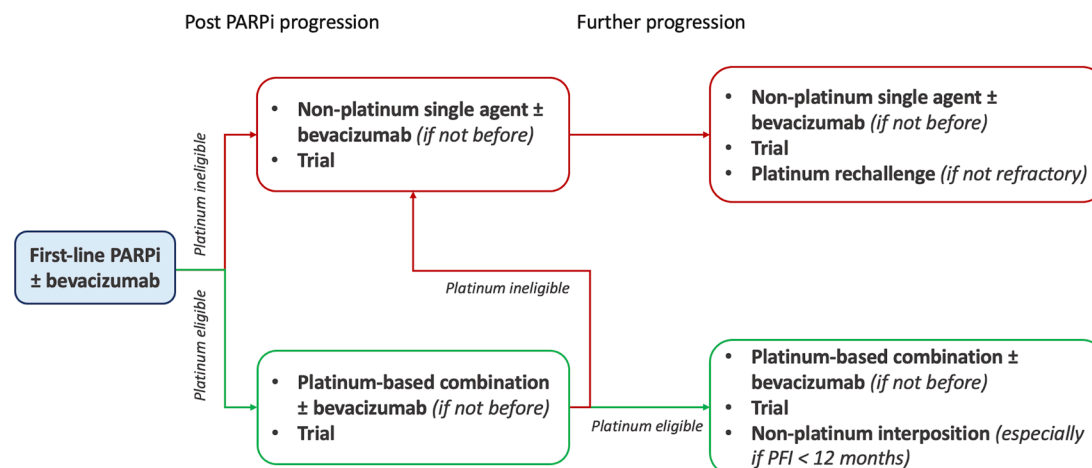
approaches in combination with PARPi in the first-line treatment of ovarian cancer.

Ongoing phase I/II trials are evaluating the efficacy and safety of PARPi in the neoadjuvant setting. The phase I NOW trial [NCT03943173] is studying how well olaparib works in treating BRCAm patients before surgery. Patients will receive olaparib for two 28-day cycles followed by surgery and chemotherapy for up to four cycles or vice versa, at the discretion of the treating physician. The phase II OPAL-C trial [NCT03574779] is investigating the role of niraparib as a neoadjuvant treatment before surgery in homologous recombination deficiency-positive patients. Patients will receive either three cycles of chemotherapy or niraparib before surgery, followed by three cycles of chemotherapy with or without bevacizumab, and then maintenance with niraparib with or without bevacizumab. Other ongoing studies focused on neoadjuvant setting include the phase II NUVOLA [NCT04261465] and OLAPem [NCT04417192] trials with olaparib and the phase II NANT [NCT04507841] and NEOPRIMA [NCT04284852] trials with niraparib. The phase III N-PLUS trial, on the other hand, aims at assessing whether niraparib maintenance after chemotherapy in homologous recombination deficiency-positive patients optimally debulked during primary surgery might allow a reduction in the number of adjuvant chemotherapy cycles from six to three cycles. Effective de-escalation strategies might help to personalize patient care, reduce toxicity, improve the quality of life, and optimize treatment outcomes in specific patient subpopulations.

### WHAT ARE THE TREATMENT STRATEGIES IN A PLATINUM/PARPi-RESISTANT SETTING?

Progression to first-line PARPi poses a huge clinical challenge in daily practice and the best treatment algorithm after PARPi progression needs to be prospectively validated. Despite the unquestionable benefit, there is still a relevant percentage (5–25%) of patients who will progress shortly after starting PARPi maintenance. Although the concept of platinum-free interval has been gradually converted into treatment-free interval in clinical trials since the introduction of non-platinum and targeted therapies, its use in clinical practice has never been abandoned and still guides the treatment of relapses. During the 4th Ovarian Cancer Consensus Conference (OCCC) in Vancouver in 2010, the Gynecologic Cancer InterGroup first criticized the use of a temporal cut-off as an absolute predictor of the response to subsequent platinum, underlining how response rates to platinum fall on a continuum.<sup>22</sup> Patients who relapse within 6 months still have a reasonable chance of responding to further platinum. Indeed, platinum resistance is certain only if there is progression during the treatment; otherwise, it can only be suspected in those cases that relapse within 6 months. Conversely, a platinum-free interval of more than 6 months does not guarantee platinum sensitivity and these patients should be regarded as “platinum-eligible” and not “platinum-sensitive”, to be precise. Moreover, we should remember that these temporal cutoffs (<6 months, 6–12 months, >12 months) were arbitrarily defined when there were no other options than platinum and, certainly, no targeted therapies.

Waiting for further predictors of platinum sensitivity, the medical treatment outside clinical trials for patients on PARPi maintenance who relapse within 6 months from the last dose of platinum remains



**Figure 4** Overview of the current treatment algorithm after poly (ADP-ribose) polymerase inhibitor (PARPi) progression in ovarian cancer. PFI, platinum-free interval.

non-platinum monotherapy (Figure 4). The most commonly used agents are pegylated liposomal doxorubicin, gemcitabine, paclitaxel, trabectedin, and topotecan. The response rates vary between 16.3% and 35%, but these should probably be reassessed in the post-PARPi era as there are still no data available on how maintenance therapies might affect the efficacy of subsequent treatments.<sup>23</sup> The addition of bevacizumab, if not previously used, is highly recommended in this setting. The AURELIA trial demonstrated that combining bevacizumab with non-platinum agents (paclitaxel, pegylated liposomal doxorubicin, topotecan) in platinum-resistant ovarian cancer enhances the progression-free survival and the tumor response to chemotherapy, and this treatment option should be further explored in the PARPi-resistant setting.<sup>24</sup> Furthermore, platinum rechallenge following treatment with a non-platinum regimen could be considered for later relapses if a patient had not progressed during platinum therapy (platinum-refractory), especially in the post-PARPi era.

Due to the poor outcomes and the cumulative toxicity associated with multiple subsequent chemotherapy lines, enrollment in clinical trials is strongly encouraged for platinum-resistant patients (online supplemental table S2) and particular attention should be paid to biomarker-driven treatments. Although chemotherapy remains the cornerstone of recurrent ovarian cancer treatment, new and promising data are emerging in favor of chemotherapy-free alternatives, which can be equally effective, less toxic, easier to administer, and could delay the time to the next chemotherapy. Recently, the US Food and Drug Administration (FDA) granted mirvetuximab soravtansine accelerated approval for patients with folate receptor  $\alpha$  (FR $\alpha$ )-positive, platinum-resistant ovarian cancer who had received one to three prior lines of chemotherapy. This new therapy was approved based on results from the single-arm phase III SORAYA trial, which showed an overall response rate of 31.7% (95% CI: 22.9% to 41.6%) and a median duration of response of 6.9 months (95% CI: 5.6 to 9.7), without significant adverse events.<sup>25</sup> Confirmatory results are awaited from the randomized phase III MIRASOL trial evaluating the safety and efficacy of mirvetuximab soravtansine versus the investigator's choice of non-platinum agent (paclitaxel, topotecan, or pegylated liposomal doxorubicin).<sup>26</sup> Moreover, the combination of mirvetuximab soravtansine and bevacizumab has been recently tested in the phase Ib/II FORWARD II trial and

showed encouraging activity in recurrent ovarian cancer with high FR $\alpha$  expression warranting later-phase investigation.<sup>27</sup> All these findings make mirvetuximab soravtansine a leading agent in the platinum-resistant scenario, as it could become a practice-changing, biomarker-driven standard of care. Its promising role acquires even more importance in the post-PARPi era as this novel agent has a completely different mechanism of action from PARPi, thus potentially escaping PARPi cross-resistance. Indeed, mirvetuximab soravtansine is the first antibody–drug conjugate approved in ovarian cancer and it specifically acts on FR $\alpha$ -positive ovarian tumor cells by combining the targeting properties of monoclonal antibodies with the anticancer activity of a microtubule inhibitor payload. Another antibody–drug conjugate, namely upifitamab rilsodotin, is currently being investigated in the phase Ib/II UPLIFT/ENGOT-ov67 trial for platinum-resistant ovarian cancer patients.<sup>28</sup> Upifitamab rilsodotin (XMT-1536) targets NaPi2b, a sodium-dependent phosphate transport protein, broadly expressed in solid tumors such as serous epithelial ovarian cancers, and delivers ari-statin cytotoxic drug payload.

#### WHAT ARE THE TREATMENT STRATEGIES IN PLATINUM-ELIGIBLE PATIENTS?

Patients who received PARPi maintenance and relapse with a platinum-free interval of more than 6 months are regarded as platinum-eligible. For these patients, re-treatment with a platinum-based doublet (mainly carboplatin plus pegylated liposomal doxorubicin, gemcitabine, or paclitaxel) with or without bevacizumab currently represents the standard treatment strategy.<sup>23 29 30</sup> (Figure 4). Notably, the benefit of adding an anti-angiogenic agent could be further reinforced after PARPi as bevacizumab may help overcome the potential cross-resistance between PARPi and platinum.

The concept of platinum-free interval as a surrogate of platinum sensitivity should be further questioned since the advent of PARPi. PARPi and platinum agents share several mechanisms of resistance,<sup>31</sup> thus upfront PARPi may affect the response to further platinum-based chemotherapy in those cases where platinum sensitivity is potentially expected merely based on the platinum-free

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interval. Not only the response to further platinum but also the influence on subsequent non-platinum chemotherapy remains unclear. Recent clinical evidence suggested an altered sensitivity towards subsequent chemotherapy after prior PARPi treatment. A post hoc analysis of the SOLO2 trial showed a longer time to second progression in the placebo compared with olaparib arm (12.1 vs 6.9 months): 14.3 versus 7.0 months in patients who received subsequent platinum-based chemotherapy and 8.3 versus 6.0 months in case of non-platinum chemotherapy.<sup>32</sup> Similar real-life data came from a retrospective study of the Italian MITO group, which evaluated 66 BRCAm patients who received olaparib for relapsed ovarian cancer and then further treatment.<sup>33</sup> The objective response rate in patients with platinum-free interval >12 months was only 22.2% and thus lower than the expected rate of 50–60% in recurrence. More recently, Romeo et al published the largest real-life data series of ovarian cancer patients treated with platinum rechallenge after progression to PARPi maintenance in a relapse setting.<sup>34</sup> Although the overall outcomes appeared similar to the pre-PARPi era, this analysis raised concerns regarding the use of platinum after PARPi in the cohort of BRCAm patients, especially if the progression was earlier than expected. The overall response rate and the median progression-free survival were 40% and 3.5 months, respectively, among BRCAm patients, and 43.5%, and 7.5 months, respectively, in the BRCAwt cohort. Although all these retrospective data derive from a recurrence setting, it seems reasonable to think that the same applies to the first line. Prospective studies are needed to further assess the efficacy of platinum-based chemotherapy after PARPi.

The role of non-platinum chemotherapy in patients relapsing with a platinum-free interval >6 months, especially when this is between 6 and 12 months, should be reassessed in the post-introduction of PARPi era, as the available data regarding the better efficacy of platinum-based chemotherapy refer to the pre-introduction of PARPi era. The MITO-8 trial demonstrated that treating patients with a platinum-free interval of 6–12 months with a non-platinum-based regimen before re-introducing platinum did not improve survival,<sup>35</sup> but this scenario could change in the post-introduction of PARPi era. Moreover, the pegylated liposomal doxorubicin–trabectedin doublet should be further evaluated in the subgroup of patients with a platinum-free interval of 6–12 months as the results from the INOVATYON trial could be reversed after the advent of PARPi in the first-line setting.<sup>36,37</sup> At least theoretically, not only non-platinum agents could be more effective than expected as second-line treatment in patients who progress after PARPi, but the interposition of non-platinum-based chemotherapy may help overcome cross-resistance and possibly improve the response to subsequent platinum-based therapy. The 6th OCCO suggests that a trabectedin/pegylated liposomal doxorubicin regimen could be considered in those patients who are intolerant to platinum and who have relapsed after 6 months from the last dose of platinum.<sup>38</sup> Interestingly, the LUPPA-1/ENGOT-ov73 trial will assess the efficacy of lurbinectedin plus paclitaxel compared with later-line standard chemotherapy (platinum-based combination or weekly paclitaxel) in patients with platinum-sensitive recurrent ovarian cancer who already received two to three prior lines of chemotherapy. Pending more data on this issue, we could speculate that platinum rechallenge should remain the preferred option in the first platinum-eligible relapse, including when the platinum-free interval

is between 6 and 12 months, while non-platinum agents could be considered in cases of further relapses.

Enrollment in clinical trials can also be considered in patients with platinum-eligible recurrent ovarian cancer. Notably, the phase II PICCOLO trial [NCT05041257] is currently evaluating the safety and efficacy of mirvetuximab soravtansine in patients with platinum-sensitive recurrent ovarian cancer with high folate receptor- $\alpha$  (FR $\alpha$ ) expression who received at least 2 prior lines of platinum therapy. The phase I UPGRADE-A trial [NCT04907968] is assessing the combination of upifitamab rilsodotin and carboplatin in patients with platinum-sensitive ovarian cancer after 1–3 prior lines of treatment.

## IS THERE STILL A ROLE FOR PARPi IN THE RECURRENT SETTING?

### Maintenance Therapy Setting

It is now well-recognized that PARP inhibitors should be used in the first-line setting, at least in the BRCAm and homologous recombination deficiency-positive settings. However, there is still room for PARPi maintenance in the recurrent setting in at least four different scenarios:

1. Platinum-sensitive patients who did not receive first-line maintenance, either because it was not still approved, or the disease was at an early stage at diagnosis;
2. Platinum-sensitive patients who received bevacizumab alone as first-line maintenance setting;
3. Clinical trials investigating PARPi combined therapies; and
4. PARPi rechallenge (within an experimental setting/clinical trial), especially in the case of oligoprogression managed with locoregional treatment (either surgery, radiotherapy, or thermal ablation).

New regulatory actions have been recently taken by the FDA regarding the approval of PARPi in the recurrent maintenance setting. The updated overall survival data from the NOVA trial<sup>19</sup> prompted the voluntary withdrawal of the FDA approval of niraparib as maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer without germline BRCA mutation. These detrimental results, however, were not confirmed in the NORA trial, which showed a potentially favorable overall survival trend in Chinese patients irrespective of germline BRCA status.<sup>39</sup> Similarly, the withdrawal of rucaparib has been recently anticipated for BRCAwt patients, according to the updated analysis of ARIEL3.<sup>20</sup> PARPi indications will continue to be updated as new evidence progressively emerges and further revisions are expected.

There are several potential explanations for the lack of impact on overall survival with PARPi in the second line. Data coming from studies in the recurrent setting (SOLO2,<sup>40</sup> ARIEL3,<sup>41</sup> NOVA<sup>42</sup>) were not powered to detect overall survival; therefore, these results are hypothesis-generating only and probably should not be used to influence practice. A relevant percentage of patients in the placebo arms had received subsequent PARPi in these studies, either through crossover<sup>41</sup> or on disease progression or withdrawal from the study,<sup>42</sup> and this could have confounded the overall survival outcomes. Moreover, other confounding factors might have influenced the overall survival data, such as the subsequent lines of



treatment after PARPi, patient loss to follow-up, and the potential induction of cross-resistance to subsequent therapies.

### Single-agent Treatment Setting

Regarding the use of PARPi as monotherapy in the late-line platinum-sensitive recurrence, the overall survival results from ARIEL4 (rucaparib as monotherapy for somatic or germline BRCAm patients treated with two or more prior lines of chemotherapy)<sup>43</sup> and SOLO3 (olaparib as monotherapy in germline BRCAm patients treated with three or more prior lines of chemotherapy)<sup>44</sup> trials were detrimental. Therefore, the FDA approval of rucaparib and olaparib for heavily pre-treated BRCAm ovarian cancer patients has been voluntarily withdrawn. These new data also led to the spontaneous withdrawal of the FDA approval of niraparib for homologous recombination deficiency-positive patients who had received three or more previous lines of chemotherapy.<sup>45</sup> Ultimately, there is no role for PARPi as single-agent treatment (instead of chemotherapy) in the recurrent setting. Nevertheless, several ongoing clinical trials are investigating PARPi activity in combination with other agents.

### IS THERE A PLACE FOR PARPi RECHALLENGE?

PARPi, as well as bevacizumab, are currently approved as maintenance treatment for ovarian cancer, either in first-line setting or in relapsed patients not previously treated with the same drug. Given the high efficacy in terms of survival of using these drugs regardless of the treatment line, strong interest has been raised in whether rechallenging these agents could be effective and safe. The phase III MITO16b/MANGO-ov2/ENGOT-ov17 trial first showed the effectiveness of continuing bevacizumab beyond progression combined with second-line platinum therapy compared with standard chemotherapy alone (median progression-free survival: 11.8 vs 8.8 months; HR: 0.51 [95% CI 0.41 to 0.65];  $p < 0.0001$ ).<sup>46</sup> The 6th OCCO supports the re-treatment with bevacizumab in the recurrent maintenance setting; thus, pending regulatory approval, it might be considered in clinical practice through an expanded access program. The preferred chemotherapy partner for bevacizumab rechallenge is carboplatin/pegylated liposomal doxorubicin.<sup>38</sup>

Conversely, the evidence for PARPi rechallenge is still limited and warrants further validation.<sup>38</sup> The phase IIIb OREO/ENGOT-ov38 trial is the first to investigate the potential role of PARPi rechallenge in patients with platinum-sensitive recurrent ovarian cancer. Patients previously treated with PARPi derived a benefit when rechallenged with olaparib maintenance, irrespective of their BRCA/homologous recombination deficiency status.<sup>47</sup> Indeed, a statistically significant benefit in terms of progression-free survival was observed not only in the BRCAm cohort (HR: 0.57 [95% CI 0.37 to 0.87];  $p = 0.022$ ) but also in the BRCAwt/homologous recombination deficiency-positive (HR: 0.52 [95% CI 0.26 to 1.10]) and BRCA/homologous recombination deficiency-negative (HR: 0.49 [95% CI 0.21 to 1.23]) cohorts. The progression-free survival rates at 12 months after randomization were 19% in the olaparib arm versus 0% in the placebo arm among BRCAm patients and 14% versus 0%, respectively, in the BRCAwt patients, regardless of the homologous recombination deficiency status. Therefore, a clinically relevant proportion of patients were long-term responders in the olaparib arm.

Two retrospective studies suggested that patients with oligometastatic progression under PARPi may continue to benefit from PARPi maintenance if managed with locoregional treatment, either surgery or stereotactic body radiotherapy.<sup>48,49</sup> The rationale behind this is that locoregional treatment may remove those neoplastic clones that developed PARPi resistance while the rest of the disease remains stable under PARPi influence. Preliminary data on the role of radiotherapy alone as a valid option in the treatment of first oligometastatic platinum-sensitive recurrent ovarian cancer have been presented at the 2022 ESGO meeting.<sup>50</sup> If confirmed, these findings will allow prolongation of the therapeutic effect of PARPi beyond oligoprogression and also extend the platinum-free interval. PARPi rechallenge appeared to be also safe; however, more long-term data are required to properly assess the safety of re-treating patients with PARPi, especially when considering the risk of myeloid neoplasms.<sup>21</sup> The 6th OCCO suggests that PARPi rechallenge may be considered in cases of prior PARPi exposure of 18 months in the first line and 12 months (or, in more detail, 12 months in BRCAm and 6 months in BRCAwt patients) in further lines.<sup>38</sup>

Larger-scale prospective research is warranted to shed more light on the role of PARPi rechallenge, which might change the treatment algorithm of ovarian cancer in the future. The phase III randomized MITO 35b trial is currently investigating the use of olaparib beyond progression compared with platinum chemotherapy after secondary cytoreductive surgery in recurrent ovarian cancer patients.<sup>51</sup> Since PARPi are not all the same but display different chemical structures, targets, and trapping potency, it would also be worth exploring the clinical impact of rechallenging with a different PARPi agent than the one used previously.

Contextually, novel agents are currently under investigation as alternative maintenance options to PARPi and bevacizumab in platinum-sensitive recurrent ovarian cancer, such as upifitamab rilsodotin (UP-NEXT trial [NCT05329545]) and mirvetuximab soravtansine (GLORIOSA trial [NCT05445778]). These two agents represent two examples of antibody–drug conjugates, a new promising class of therapeutic agents composed of a targeting monoclonal antibody linked to a classic cytotoxic payload.

### HOW MIGHT PARPi IMPACT SURGICAL TREATMENT?

First-line PARPi have demonstrated to be effective regardless of the timing of surgery (upfront or interval surgery) and the disease status after surgery (residual or no gross residual disease).<sup>52–53</sup> Nevertheless, primary cytoreductive surgery with no macroscopic residual disease remains the gold standard treatment for ovarian cancer patients even in the post-PARPi era. The absence of residual tumor is still the most important prognostic factor, even in the most chemosensitive/PARPi-responsive population of BRCAm patients.

On the other hand, the impact of PARPi on secondary cytoreductive surgery needs prospective validation as the currently available studies have all been conducted in the pre-PARPi era.<sup>54–57</sup> The DESKTOP III trial confirmed the survival benefit of secondary cytoreductive surgery followed by chemotherapy compared with chemotherapy alone in patients with first platinum-sensitive recurrence and a positive AGO (Arbeitsgemeinschaft Gynaekologische Onkologie) score.<sup>54</sup> A positive AGO score identifies those patients who are more likely to obtain a complete resection and is defined

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as an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 (on a five-point scale, with higher scores indicating greater disability), ascites <500 ml, and complete cytoreduction at primary surgery (or, alternatively, stage I-II disease at diagnosis). However, new targeted agents have changed and will further change the landscape of recurrent ovarian cancer. The traditional concept of platinum sensitivity based on the platinum-free interval is not fully applicable in the post-PARPi era and as a consequence new validated and personalized criteria are required for secondary cytoreductive surgery.

The logical question is whether the introduction of PARPi in the first-line setting would mitigate the role of secondary cytoreductive surgery or, on the contrary, further reinforce it. A retrospective MITO group study confirmed the positive role of secondary cytoreductive surgery before platinum therapy and olaparib maintenance in BRCAm patients.<sup>58</sup> In this study, the PARPi was used in a relapsed setting rather than in the first line and so there are still some issues on surgery secondary to PARPi. Nevertheless, the pattern of first recurrence under or after PARPi is frequently oligometastatic<sup>59</sup> and secondary cytoreductive surgery might play even a greater role in the post-PARPi era. Indeed, it could be speculated that surgery may reduce the tumor burden and the number of resistant clones, in particular those which became cross-resistant to platinum under the influence of PARPi, thus increasing the likelihood to respond to subsequent platinum and eventually PARPi rechallenge. Moreover, there is an increasing interest in assessing whether patients with oligoprogression under PARPi may still benefit from PARPi maintenance after secondary cytoreductive surgery instead of stopping the PARPi and undergoing second-line chemotherapy, especially in the BRCAm and homologous recombination deficiency-positive settings.

### HOW CAN WE OVERCOME PARPi RESISTANCE?

PARPi resistance can be divided into primary (intrinsic) if the disease progression occurs under PARPi maintenance and secondary (acquired) if the disease relapses once the PARPi maintenance has ended. Understanding the underlying mechanisms of PARPi resistance is crucial to identify short-term responders who would probably benefit earlier from combined regimens. In the future we will hopefully be able to identify novel predictive biomarkers of long-term PARPi sensitivity, a sort of PARPi version of platinum sensitivity. Combined strategies might also play a key role in the homologous recombination deficiency-negative setting where only modest benefit is seen with single-agent PARPi.

Several trials are currently investigating the safety and efficacy of combining PARPi with agents that target additional pathways outside of DNA damage repair to overcome PARPi resistance. PARPi-resistant cells exhibit enhanced dependency on other DNA repair pathways and cell cycle mechanisms. The rationale behind combined regimens is that synergy exploits different cell cycle vulnerabilities, thus potentially leading to PARPi re-sensitization. The cellular mechanisms of PARPi resistance can be classified into four main groups:<sup>31</sup>

1. PARP enzyme alterations, either mutations or post-translational modifications, such as phosphorylation, reducing PARPi trapping;

2. Restoration (at least partial) of the homologous recombination system, either through reversion mutations (BRCA1/2, RAD51C/D), BRCA1 promoter demethylation leading to protein re-expression, amplification of the wild-type BRCA allele, generation of hypomorphic BRCA with residual function, decreased proteasomal degradation of mutant BRCA/RAD51, CCNE1 amplification, or inactivation of inhibitory proteins (RB1, NF1, RAD51B, PTEN, 53BP1, REV7, DYNLL1);
3. Stabilization of stalled replication forks (depletion of chromatin remodelers, such as SMARCAL1, ZRANB3, and HTLF); and
4. Upregulation of PARPi efflux pumps (MDR1).

The reversion of BRCA mutations seems to be the most frequent mechanism of PARPi resistance. Data coming from four phase II/III clinical trials (OLYMPIAD,<sup>60</sup> SOLO3,<sup>44</sup> LIGHT,<sup>61</sup> EVOLVE<sup>62</sup>) showed that approximately 20–25% of ovarian cancer patients had BRCA reversion mutations after olaparib treatment.<sup>63</sup>

All these molecules involved in the multiple mechanisms described for PARPi resistance represent potential targets for post-progression PARPi combination regimens. Promising molecular agents include anti-angiogenics (cediranib [EVOLVE, ICON-9]<sup>62,64</sup>), inhibitors of PI3K (alpelisib [EPIK-O/ENGOT-ov61]<sup>65</sup>), Hsp90, MEK, ALK, ATR (ceralaserib [CAPRI]<sup>66</sup>), CHK1, WEE1 (adavosertib [EFFORT]<sup>67</sup>), BET/BRD4, CDK12, and immune checkpoint inhibitors (pembrolizumab [ENGOT-ov43/KEYLYNK-001],<sup>68</sup> dostarlimab [FIRST, NitCHE/MITO 33],<sup>69,70</sup> nivolumab [ATHENA-COMBO],<sup>71</sup> durvalumab [DUO-O],<sup>72</sup> atezolizumab [ANITA]<sup>73</sup>).

Despite the progressive knowledge, data regarding PARPi resistance currently derive only from pre-clinical and early-phase trials and require clinical validation; hence, the question of how best to treat patients who progress to PARPi remains open. Enrollment in dedicated clinical trials with a strong translational research component is urgently needed. The AMBITION umbrella study provided preliminary evidence on the clinical benefit of biomarker-driven targeted therapy in platinum-resistant ovarian cancer: olaparib plus cediranib or durvalumab for homologous recombination deficiency-positive patients, while for homologous recombination deficiency-negative patients, durvalumab plus non-platinum-single agent in cases of high PD-L1 expression, and durvalumab plus tremelimumab and non-platinum single agent if low PD-L1 expression.<sup>74</sup> The most promising partner, for now, is the WEE1 inhibitor adavosertib, which in the recent phase II EFFORT trial was demonstrated to be effective both alone and in combination with olaparib in patients with recurrent PARPi-resistant ovarian cancer.<sup>67</sup> Cediranib–olaparib combination therapy also showed some activity after PARPi progression in the phase II EVOLVE trial, which underlined the importance of translational research for selecting treatment based on the specific mechanisms of resistance.<sup>62</sup>

Multiple resistance mechanisms may develop in each patient and a great effort is being made to establish the most accurate assay for determining these events. Given the unstable nature of tumor biology, the molecular profile should be reassessed at each relapse or progression, either through repeated tumor biopsies or, probably better, through liquid biopsy (evaluating cell-free DNA), whose application in ovarian cancer is still under investigation. With the diversity of molecular signatures, not only between patients but also during the course of the disease in the same patient, molecularly driven clinical trials using a translational approach are the key to unraveling tumor heterogeneity and personalizing treatment. The

ultimate goal is to address the dynamic nature of ovarian cancer in a timely manner and find the right combination treatment for that specific relapse in that single patient while minimizing possible overlapping toxicities.

## SUMMARY

- ▶ PARPi should be preferred upfront for both efficacy and safety reasons.
- ▶ Not only the mutational status, but several factors are essential for personalizing the maintenance strategy, first and foremost the response to platinum.
- ▶ Identifying better predictive biomarkers of resistance to platinum and PARPi is an unmet need.
- ▶ Progression after first-line PARPi poses a large clinical challenge and the best treatment algorithm needs prospective validation in clinical and translational studies.
- ▶ PARPi may compromise the response to subsequent platinum due to cross-resistance mechanisms.
- ▶ The potential benefit of PARPi rechallenge needs further investigation.
- ▶ The role and criteria of secondary cytoreductive surgery could change in the post-PARPi scenario.
- ▶ PARPi combinations may become our future armamentarium for homologous recombination deficiency-negative and PARPi-resistant patients.
- ▶ The future challenge is to address in a timely manner the tumor biology both at diagnosis and each relapse and provide the right personalized therapy for each patient.

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**Table S1.** Comparing the relapse timing between placebo (a) and PARPi (b) arms from SOLO1, PRIMA, and ATHENA-MONO trials.

	SOLO1		PRIMA		ATHENA-MONO		
	Placebo		Placebo		Placebo		
	BRCAm	HRd	Overall	BRCAm	HRd	Overall	HRp
<b>Platinum-resistant recurrent ovarian cancer (&lt; 6 months)</b>	~20%	~30%	~40%	~15%	~25%	~30%	~40%
<b>Platinum-eligible recurrent ovarian cancer (&gt; 6 months)</b>	~55%	~40%	~35%	~55%	~45%	~45%	~40%
<b>Long-term responders (&gt; 2 years)</b>	~25%	~30%	~25%	~30%	~30%	~25%	~20%

	SOLO1		PRIMA		ATHENA-MONO		
	Olaparib		Niraparib		Rucaparib		
	BRCAm	HRd	Overall	BRCAm	HRd	Overall	HRp
<b>Platinum-resistant recurrent ovarian cancer (&lt; 6 months)</b>	~5%	~15%	~25%	< 5%	~5%	~15%	~20%
<b>Platinum-eligible recurrent ovarian cancer (&gt; 6 months)</b>	~45%	~35%	~40%	~35%	~45%	~55%	~55%
<b>Long-term responders (&gt; 2 years)</b>	~50%	~50%	~35%	~60%	~50%	~30%	~25%

Abbreviations: BRCAm, BRCA gene-mutated; HRd, homologous recombination-deficient; HRp, homologous recombination-proficient.

**Table S2.** Ongoing, registered phase III RCTs for PRROC (as of November 2022).

Trial	NCT identifier	Design	Setting	Treatment arms	Primary endpoints	Estimated enrollment	ECD	Sponsor / Collaborator
A Phase 3 Study of Relacorilant in Combination With Nab-Paclitaxel Versus Nab-Paclitaxel Monotherapy in Advanced, Platinum-Resistant, High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian-Tube Cancer	NCT05257408 GOG-3073 (ROSELLA)	Open-label, multicenter, phase III RCT	PRROC, ≤ 3 CHT lines. One prior treatment with bevacizumab is required.	<b>Experimental:</b> Nab-paclitaxel 80 mg/mq d1,8,15 Q4W + Relacorilant (SGRM) 150 mg PO OD (on the day before, the day of, and the day after nab-paclitaxel). Relacorilant will not be administered on cycle 1 day -1.  <b>Comparator:</b> Nab-paclitaxel 100 mg/mq d1,8,15 Q4W.	PFS	360	June 2025	Corcept Therapeutics / GOG
A Multicenter, Randomized, Open, Parallel Controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of TQB2450 Injection Combined With Anlotinib Hydrochloride Capsules Versus Paclitaxel as Weekly Treatment in the Treatment of Recurrent Platinum-resistant Ovarian Cancer	NCT05145218	Open-label, multicenter, phase III RCT	PRROC, ≤ 4 CHT lines (no more than 1 CHT is accepted after platinum resistance)	<b>Experimental:</b> TQB2450 (anti-PD-1 mAb) 1200 mg IV Q3W (maximum 24 months) + Anlotinib Hydrochloride (TKI) 12 mg PO OD for 2 weeks Q3W  <b>Comparator:</b> PTX 80 mg/mq IV QW	PFS OS	405	December 2024	Chia Tai Tianqing Pharmaceutical Group Co., Ltd.
A Randomized, Open-label, Phase 3 Study of Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers With High Folate Receptor-Alpha Expression	NCT04209855 (MIRASOL/ENGOT-ov55)	Open-label, multicenter, phase III RCT	PRROC with IHC confirmation of FR $\alpha$ positivity, ≤ 3 CHT lines	<b>Experimental:</b> MIRV (anti-FRa mAb) 6 mg/kg IV Q3W.  <b>Comparator (IC):</b> PTX 80 mg/mq IV d1,8,15 Q4W; PLD 40 mg/mq IV Q4W; Topo either 4	PFS	430	April 2024	ImmunoGen, Inc. GOG ENGOT

				mg/mq QW or 1.25 mg/mq d1-5 Q3W				
A Multi-center, Double-blind, Randomized Phase III Clinical Trial of Chiauranib Plus Weekly Paclitaxel in Patients With Platinum-refractory or Platinum-resistant Recurrent Ovarian Cancer	NCT04921527 (CHIPRO)	Double-blind, multicenter, phase III RCT	PRROC, $\leq 2$ CHT lines	<b>Experimental:</b> Chiauranib (TKI) 50 mg PO OD + PTX 60-80 mg/mq IV d1,8,15 Q3W, for 6 cycles.  <b>Comparator:</b> Placebo + PTX 60-80 mg/mq IV d1,8,15 Q3W, for 6 cycles.	PFS OS	376	July 31, 2025	Chipscreen Biosciences, Ltd.
A Phase 3, Randomized, Double-Blind Study of Pembrolizumab Versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer	NCT05116189 (MK-3475-B96/KEYNOTE-B96/ENGOT-ov65)	Double-blind, multicenter, phase III RCT	PRROC, $\leq 2$ CHT lines	<b>Experimental:</b> Pembrolizumab 400 mg IV Q6W for 18 cycles (~2 years) + PTX 80 mg/mq IV d1,8,15 Q3W, until PD or intolerance $\pm$ Bevacizumab 10 mg/kg IV Q2W until PD, intolerance or at the investigator's discretion.  <b>Comparator:</b> Placebo + PTX 80 mg/mq IV d1,8,15 Q3W, until PD or intolerance $\pm$ Bevacizumab 10 mg/kg IV Q2W until PD, intolerance or at the Investigator's discretion.	PFS	616	August 31, 2027	Merck Sharp & Dohme LLC
A Phase III, Multi-center, Randomized (1:1), Open-label, Active-controlled, Study to Assess the Efficacy and Safety of Alpelisib (BYL719) in	NCT04729387 (EPIK-O/ENGOT-ov61)	Open-label, multicenter, phase III RCT	PRROC, gBRCAwt, $\leq 3$ CHT lines	<b>Experimental:</b> Alpelisib 200 mg PO OD + Olaparib 200 mg PO BID.	PFS	358	January 31, 2025	Novartis Pharmaceuticals



Combination With Olaparib as Compared to Single Agent Cytotoxic Chemotherapy, in Participants With no Germline BRCA Mutation Detected, Platinum-resistant or Refractory, High-grade Serous Ovarian Cancer				<b>Comparator (IC):</b> PTX 80 mg/mq IV QW or PLD 40-50 mg/mq IV Q4W.				
A Phase 3, Randomized, Double-Blind, Placebo/Paclitaxel-Controlled Study of Batiraxcept (AVB-S6-500) in Combination With Paclitaxel in Patients With Platinum-Resistant Recurrent Ovarian Cancer	NCT04729608 (AXLerate-OC/ENGOT-ov66)	Double-blind, multicenter, phase III RCT	PRROC, ≤ 4 CHT lines	<b>Experimental:</b> Batiraxcept (soluble AXL-IgG1 Fc fusion protein, that inhibits GAS6) + PTX  <b>Comparator:</b> Placebo + PTX	PFS	350	July 2024	Aravive GOG ENGOT
A Phase 3, Multicenter, Open-Label, Randomized Study of Nemvaleukin Alfa in Combination With Pembrolizumab Versus Investigator's Choice Chemotherapy in Patients With Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	NCT05092360 (ARTISTRY-7)	Open-label, multicenter, phase III RCT	PRROC, ≤ 5 CHT lines. One prior treatment with bevacizumab is required.	<b>Experimental:</b> Nemvaleukin (IL-2R agonist) 6 µg/kg IV d1-5 Q3W + Pembrolizumab: 200 mg IV Q3W <b>Experimental:</b> Nemvaleukin <b>Experimental:</b> Pembrolizumab  <b>Comparator (IC):</b> PLD 40 mg/mq IV Q4W, PTX 80 mg/mq IV QW, Topo 4 mg/mq IV d1,8,15 Q4W (or 1.25 mg/mq d1-5 Q3W) or Gemcitabine 1000 mg/mq d1,8 Q3W	PFS	376	December 2026	Alkermes, Inc. Merck Sharp & Dohme LLC
A Randomized, Double-blind, Phase III Study of BD0801 Injection Combined With Chemotherapy Versus Placebo Combined With Chemotherapy in Patients With Recurrent, Platinum-	NCT04908787	Double-blind, multicenter, phase III RCT	PRROC, ≤ 2 CHT lines	<b>Experimental:</b> BD0801 (anti-VEGF mAb) 1.5 mg/kg IV d1,15 Q4W + PLD, PTX or Topo	PFS	357	December 2023	Jiangsu Simcere Pharmaceutical Co., Ltd.

resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer				<b>Comparator:</b> PLD 40 mg/mq IV Q4W, PTX 80 mg/mq IV QW, Topo 4 mg/mq IV d1,8,15 Q4W				
A Randomized Phase 3 Study Assessing the Efficacy and Safety of Olvi-Vec Followed by Platinum-doublet Chemotherapy and Bevacizumab Compared With Platinum-doublet Chemotherapy and Bevacizumab in Women With Platinum-Resistant/Refractory Ovarian Cancer	NCT05281471 GOG-3076 (OnPrime)	Open-label, multicenter, phase III RCT	PRROC, minimum 3 prior CHT lines with no maximal limit. One prior treatment with bevacizumab is required.	<b>Experimental:</b> Olvi-Vec (oncolytic vaccinia virus) IP 2 consecutive days at week 0 + Platinum-doublet + bevacizumab starting from week 4  <b>Comparator:</b> Platinum-doublet + bevacizumab starting from week 0	PFS	186	October 2026	Genelux Corporation GOG
An Open Label Randomized Study of Navicixizumab Plus Paclitaxel and Navicixizumab Monotherapy in Comparison to Paclitaxel Monotherapy in Patients With Platinum-Resistant Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	NCT05043402	Open-label, multicenter, phase III RCT	PRROC, $\geq 2$ and $\leq 5$ prior CHT lines. One prior treatment with bevacizumab is required.	<b>Experimental:</b> Navicixizumab 3 mg/kg IV d1,15 Q4W + PTX 80 mg/mq IV d1,8,15 Q4W  <b>Experimental:</b> Navicixizumab  <b>Comparator:</b> PTX	ORR PFS	400	August 15, 2024 (not yet recruiting)	OncXerna Therapeutics, Inc.
Randomized Phase III Trial on Niraparib-TSR-042 (Dostarlimab) vs Physician's Choice CHEmotherapy in Recurrent, Ovarian, Fallopian Tube or Primary Peritoneal Cancer Patients Not Candidate for Platinum Retreatment: NITCHE Trial (MITO 33)	NCT04679064 (NITCHE/MITO33)	Open-label, multicenter, phase III RCT	PRROC, $\leq 2$ prior CHT lines.	<b>Experimental:</b> Niraparib 200-300 mg OD + Dostarlimab 500 mg Q3W for the first 4 cycles and then 1000 mg Q6W  <b>Comparator (IC):</b> PLD 40 mg/mq IV Q4W, PTX 80 mg/mq IV QW, Gemcitabine 1000 mg/mq d1,8,15 Q4W, or Topotecan 1.25 mg d1-5 Q3W. Bevacizumab can be added.	OS	427	January 1, 2025	Fondazione Policlinico Universitario Agostino Gemelli IRCCS GSK

Abbreviations: AXL, gene encoding for the tyrosine-protein kinase receptor UFO; ENGOT, European Network of Gynaecological Oncological Trial Groups; FR, folate receptor; GAS6, growth arrest-specific 6; gBRCAwt, germline BRCA wild type; GOG, Gynecologic Oncology Group; IC, investigator's choice; IgG, immunoglobulin G; IHC, immunohistochemical; IL-2R, interleukin-2 receptor; IP, intraperitoneal; IV, intravenous; MIRV, mirvetuximab soravtansine; mAb, monoclonal antibody; Nab, Nanoparticle albumin-bound; OD, once daily; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PO, per os; PRROC, platinum-resistant recurrent ovarian cancer; PTX, paclitaxel; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; QW, once a week; RCT, randomized clinical trial; SGRM, selective glucocorticoid receptor modulator, TKI, tyrosine kinase inhibitor; Topo, topotecan; VEGF, vascular endothelial growth factor.