PARP inhibitors: risk factors for toxicity and matching patients to the proper poly (ADP-ribose) polymerase inhibitor (PARPi) therapy

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ABSTRACT

The past 5 years have seen several fundamental advances in ovarian cancer, with important new insights towards novel therapeutic opportunities within the DNA repair pathway. With the incorporation of poly (ADP-ribose) polymerase inhibitors (PARPi) into maintenance treatment regimens, the management of short- and long-term adverse events are key clinical priorities. Currently, three different PARPi are clinically beneficial and have been approved for primary and recurrent ovarian cancer: olaparib, niraparib, and rucaparib. The duration of treatment with PARPi in patients with ovarian cancer varies; patients can receive treatment for up to 2 or 3 years in first-line setting, or continue treatment until unacceptable toxicity or progression occurs in recurrent disease. Despite their similar mechanisms of action, these three inhibitors have specific toxicity profiles, which may lead to dose interruptions or discontinuation of treatment. This review summarizes the current indications for PARPi, including their role in recurrent and first-line maintenance treatment for advanced ovarian cancer. We also outline dose modifications leading to treatment disruption and potential changes in quality of life after prolonged treatment. Finally, we highlight the patient groups most likely to benefit from each of the three different PARPi.

INTRODUCTION

Over the last 5 years, poly (ADP-ribose) polymerase inhibitors (PARPi) have become the most effective targeted treatment in ovarian cancer, especially in women with mutations in the homologous recombination DNA repair pathway.[1–5] Because patients with ovarian cancer responded so impressively to PARPi, this treatment is now being evaluated in clinical trials enrolling patients with endometrial cancer (NCT02208375, NCT03586661, NCT03162627, NCT03660826, NCT03981796) and cervical cancer,[6 7] as well as several other non-gynecologic solid tumors. Interestingly, alterations in DNA repair also play an important role in endometrial, cervical, breast, and prostate cancer, suggesting that these groups may benefit as well.[8–11] Moreover, results of the phase III OReO/ENGOT Ov-38 trial (NCT03106987) showed a benefit of PARP inhibitor rechallenge in patients with platinum-sensitive relapsed ovarian cancer.[12]

The background to this hypothesis is that inhibiting the DNA repair pathway compensates for defective double-strand break repair and this rationale can be used to treat tumors.[13] In this aim, two groups demonstrated that the absence of the PARP enzyme generates multiple unrepaired single-strand breaks, which subsequently induce double-strand breaks. Bryant et al showed that three of five mice with breast cancer gene 2 (*BRCA2*)-mutated tumors responded to 5 days of PARPi treatment, and one mouse had a complete response.[14] Moreover, Farmer et al showed that cells lacking wild-type *BRCA1* were 133-fold more sensitive to PARPi than control, and *BRCA2*-mutated cells were *in vitro* 1000-fold more sensitive.[15] Taken together, these findings showed that the non-functional DNA repair pathway characteristic of *BRCA1/2*-deficient tumors is susceptible to PARPi treatment.

Clinical biomarkers for ovarian cancer are still an area of active research.[16–19] Approximately 22% of patients with ovarian cancer carry a *BRCA1/2* mutation, with 15% harboring a germline mutation and 7% with a somatic mutation.[20] Furthermore, the same study showed that 50% of ovarian cancer tumors harbor the homologous recombination deficiency signature.[20] In detail, the absence of *BRCA1/2* and other alterations of proteins included in the homologous recombination deficiency signature results in a defective DNA double-strand break repair pathway, which leads to cell death.[21 22] While there is general consensus about the patient selection for PARPi therapy,[23–25] questions remain about the practical management of choosing the best agent from the available three candidates—namely, olaparib, niraparib, or rucaparib.

PARPI THERAPY OPTIONS FOR PATIENTS WITH RECURRENT OVARIAN CANCER

Following the emergence of encouraging PARPi preclinical data, several clinical trials have investigated PARPi for both treatment and maintenance in settings including recurrent and first-line ovarian cancer (Table 1).[24 25]

A series of double-blind, placebo-controlled randomized trials have consistently demonstrated the high efficacy of olaparib in high-grade serous ovarian

Table 1 Summary of efficacy in randomized clinical trials with single-agent PARPi maintenance in primary and recurrent ovarian cancer

Primary setting	**Olaparib[1] Olaparib+bevacizumab[33]**	**Niraparib[2]**	**Rucaparib[6]**
BRCA1/2	HR 0.30 (95% CI 0.23 to 0.41) mPFS 36 months longer HR 0.31 (95% CI 0.20 to 0.47) mPFS 37.2 vs 17.7 months	–	–
HRD/LOH	HR 0.33 (95% CI 0.25 to 0.45) mPFS 28.1 vs 16.6 months	HR 0.43 (95% CI 0.31 to 0.59) mPFS 21.9 vs 10.4 months	HR 0.47 (95% CI 0.31 to 0.72) mPFS 28.7 vs 11.3 months
All non-*gBRCA*	–	HR 0.70 (95% CI 0.44 to 1.11) mPFS 13.8 vs 8.2 months	HR 0.52 (95% CI 0.40 to 0.68) mPFS 20.2 vs 9.2 months
Recurrent setting	**Olaparib[5]**	**Niraparib[4]**	**Rucaparib[3]**
BRCA1/2	HR 0.30 (95% CI 0.22 to 0.41) mPFS 19.1 vs 5.5 months	HR 0.27 (95% CI 0.17 to 0.41) mPFS 21.0 vs 5.5 months	HR 0.23 (95% CI 0.16 to 0.34) mPFS 16.6 vs 5.4 months
HRD/LOH	–	HR 0.38 (95% CI 0.24 to 0.59) mPFS 12.9 vs 3.8 months	HR 0.32 (95% CI 0.24 to 0.42) mPFS 13.6 vs 5.4 months
All non-*gBRCA*	–	HR 0.45 (95% CI 0.34 to 0.61) mPFS 9.3 vs 3.9 months	HR 0.36 (95% CI 0.30 to 0.45) mPFS 10.8 vs 5.4 months

HRD, homologous recombination deficiency; LOH, loss of heterozygosity; mPFS, median progression-free survival.

cancer, with patients with *BRCA*-deficient tumors experiencing the greatest benefit.[5 26 27] The same was observed in a retrospective analysis of phase II Study 19 (NCT00753545), in which a sub-group of patients with germline or somatic *BRCA* mutations showed a median progression-free survival of 11.2 months versus 4.3 months with a hazard ratio (HR) of 0.18 (95% CI 0.10 to 0.31).[27]

Due to the improved progression-free survival regardless of *BRCA* status, with an HR of 0.35 (95% CI 0.25 to 0.49) seen in primary analysis, olaparib use was eventually expanded to maintenance treatment in all patients with platinum-sensitive recurrent high-grade serous ovarian cancer. Following these results, the phase III trial SOLO2 (NCT01874353) was initiated, which enrolled only patients with tumors harboring BRCA mutations after response to platinum.[5] This study showed that maintenance PARPi therapy in these patients improved median progression-free survival from 5.5 months to 19.1 months, with an HR of 0.30 (95% CI 0.22 to 0.41).[5]

After a deeper analysis of ovarian cancer biology, it was found that 50% of ovarian tumors contain defects in homologous recombination DNA repair.[20] This signature, although not universally defined, includes analyses of *BRCA1* hypermethylation, *EMSY* amplifications, *FANCF* hypermethylation, and other mutations in homologous recombination pathway genes such as *RAD51*, *RAD54*, *DSS1*, *RPA1*, *NBS1*, *ATR*, *ATM*, *CHK1*, *CHK2*, *FANCD2*, *FANCA*, *FANCC, PTEN*.[20] Moreover, assessment of genomic loss of heterozygosity using Foundation Medicine's T5 next-generation sequencing assay was performed and added to the mutation analyses.[20 28]

Stratification based on homologous recombination deficiency assay was applied in the phase III ENGOT-OV16/NOVA trial (NCT01847274) in which the efficacy of a second PARPi, niraparib, was explored. In this trial, patients were separated into those with somatic BRCA mutations and those with homologous recombination deficiency evaluated by a commercially available test.[4] The patients with germline *BRCA* mutations showed an HR of 0.27 (95% CI 0.17 to 0.41), while patients with homologous recombination deficiency positive tumors showed an HR of 0.38 (95% CI 0.24 to 0.59).[4] These results are in favor of the use of niraparib as maintenance treatment for patients with platinum-sensitive recurrent high-grade serous ovarian cancer.

Finally, approval of rucaparib, a third PARPi for maintenance therapy in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer, was based on the phase III ARIEL3 trial in which the study population was stratified by their loss of heterozygosity score.[3 29] Median progression-free survival in patients without homologous recombination deficiency or *BRCA* mutations improved from 5.4 to 10.8 months with the use of PARPi, with an HR of 0.36 (95% CI 0.30 to 0.45), whereas the median progression-free survival in patients with homologous recombination deficiency tumors (high loss of heterozygosity score) was 13.6 months with an HR of 0.32 (95% CI 0.24 to 0.42). *BRCA*-mutated patients had a median progression-free survival of 16.6 months (HR 0.23, 95% CI 0.16 to 0.34).[3] The follow-up study of ARIEL3 was ARIEL4, a randomized phase III open-label study assessing rucaparib versus platinum-based and non-platinum-based chemotherapy.[30] The median progression-free survival was 7.4 months (95% CI 6.7 to 7.9) in the rucaparib group versus 5.7 months in the chemotherapy group (HR 0.67 (95% CI 0.52 to 0.86); p=0.0017), which supports rucaparib as an alternative treatment option to chemotherapy. Recent overall survival data in the intention-to-treat population presented at ESMO Meeting 2022 favored chemotherapy while, among patients with platinum-sensitive disease, overall survival was similar between the treatment groups.[31]

In light of the anti-tumor activity demonstrated by olaparib, niraparib, and rucaparib, clinicians can prescribe one of these agents for maintenance therapy in patients with relapsed ovarian cancer, independent of *BRCA1/2* or homologous recombination deficiency status. In addition, rucaparib is Food and Drug (FDA) and European Medicines Agency (EMA) approved for patients with *BRCA* mutated tumors after failure of more than two chemotherapeutics who are not candidates for another platinum-based chemotherapy, and niraparib is FDA approved for patients with homologous recombination deficiency tumors after failure of more than three lines of therapy.[32–35] In addition, investigators of OReO/ENGOT Ov-38

reported for the first time a benefit to PARPi rechallenge in patients with platinum-sensitive relapsed ovarian cancer regardless of *BRCA1/2* mutation status.[12] The median progression-free survival improved from 2.8 months in patients who received placebo to 4.3 months in those randomized to rechallenge with olaparib among the cohort of patients with BRCA-mutant ovarian cancer (HR 0.57 (95% CI 0.37 to 0.87); p=0.022). In the non-BRCA-mutant cohort, the median progression-free survival improved similarly with olaparib rechallenge from 2.8 months in the placebo arm to 5.3 months in the olaparib arm (HR 0.43 (95% CI 0.26 to 0.71); p=0.0023).

PARPI THERAPY OPTIONS FOR PATIENTS WITH PRIMARY OVARIAN CANCER

PARPi are also approved as single agents or in combination with other therapeutics for maintenance treatment of primary tumors.[36–38] This was demonstrated in several phase III clinical trials which showed significant progression-free survival in newly diagnosed advanced-stage epithelial ovarian tumors with *BRCA1/2* mutations or a homologous recombination deficiency signature following platinum-based chemotherapy.[1 2 39] SOLO1, the first trial incorporating PARPi into first-line maintenance therapy for patients with *BRCA1/2* tumors, was started in 2013 and ended in 2018. Analysis of the primary endpoint of this study showed an increase in progression-free survival for the treatment arm compared with the control arm with an HR of 0.3 (95% CI 0.23 to 0.41). In addition, the median progression-free survival was approximately 36 months longer in the olaparib group than in the placebo group. These impressive results led to the approval of olaparib in 2018 as maintenance therapy of 2 years for patients meeting the following criteria: completion of primary or interval debulking surgery and platinum-based chemotherapy, partial or complete response to frontline platinum-based chemotherapy, and proved germline or somatic *BRCA1/2* mutations. Recently, a sub-group analysis in this trial demonstrated patient benefit from olaparib regardless of baseline surgery outcome, response to chemotherapy, or *BRCA1* versus *BRCA2* mutation.[40]

Using the most active agents early in the course of treatment provides maximal opportunities for clinical benefit, which remains fundamental to solid tumor oncology.[37] Moreover, the molecular profile and response to PARPi as active treatment has been shown to be more efficient in earlier lines of therapy. This could be mainly explained by the fact that platinum sensitivity is a strong clinical predictor of PARPi response and several lines of therapy would eventually lead to platinum resistance—and therefore PARPi resistance.[41] Determining the optimal order of targeted therapy such as PARPi or bevacizumab as front-line or maintenance treatment has remained a challenge. To answer this question, the PAOLA-1 phase III clinical trial explored the response of patients receiving bevacizumab and olaparib maintenance treatment following frontline chemotherapy compared with patients who received single bevacizumab maintenance treatment following chemotherapy.[39]

While the main endpoint of this trial was progression-free survival in the overall cohort, the authors performed several exploratory analyses including PARPi efficacy in both *BRCA1/2* and homologous recombination deficiency-positive cohorts. Median progression-free survival was 22.1 months in patients receiving olaparib plus bevacizumab compared with 16.6 months for patients receiving bevacizumab alone, with an HR of 0.59 (95% CI 0.49 to 0.72). The longest progression-free survival was observed in patients with *BRCA1/2*, with an HR of 0.31 (95% CI 0.20 to 0.47) and median progression-free survival of 37.2 versus 17.7 months. Progression-free survival was also longer among patients with homologous recombination deficiency, with an HR of 0.43 (95% CI 0.28 to 0.66) and median progression-free survival of 28.1 versus 16.6 months for the homologous recombination deficiency group without *BRCA1/2* mutations. Although not included as a stratification factor in study design, progression-free survival showed no clinical benefit for the homologous recombination proficient group of patients. On May 8, 2020 the FDA expanded the indication of olaparib to include its combination with bevacizumab for first-line maintenance treatment of adult patients with advanced ovarian cancer, but only for patients with a proven *BRCA1/2* mutation or detection of homologous recombination deficiency.

In contrast, niraparib was approved for maintenance treatment of adult patients with advanced epithelial ovarian cancer regardless of biomarker status. This approval was based on the results of PRIMA/ENGOT-OV26/GOG-3012, a phase III trial which randomized patients in a 2:1 fashion to receive niraparib or placebo. Patients with homologous recombination deficiency tumors who received niraparib showed a significantly longer progression-free survival with an HR of 0.43 (95% CI 0.31 to 0.59). The progression-free survival in the overall population treated with niraparib regardless of biomarker status increased as well (HR 0.70, 95% CI 0.44 to 1.11). Interestingly, progression-free survival in patients with homologous recombination proficient tumors also benefited from niraparib treatment (HR 0.68, 95% CI 0.49 to 0.94).

This situation was seen exclusively in the case of niraparib until, more recently, the phase III ATHENA-MONO trial found that maintenance treatment with rucaparib significantly improved progression-free survival compared with placebo in patients with newly diagnosed advanced ovarian cancer, including those with or without homologous recombination deficiency positive disease.[42] In the intent-to-treat population, median progression-free survival was 20.2 months (95% CI 15.2 to 24.7) in the rucaparib group versus 9.2 months (95% CI 8.3 to 12.2) in the placebo group (HR 0.52 (95% CI 0.40 to 0.68); p<0.0001). In the homologous recombination deficiency negative population, median progression-free survival was 12.1 months (95% CI 11.1 to 17.7) versus 9.1 months (95% CI 4.0 to 12.20) (HR 0.65 (95% CI 0.45 to 0.95)).

Taken together, the indication for maintenance therapy in primary ovarian cancer includes two PARPi, olaparib monotherapy for *BRCA1/2* mutation carriers or olaparib in combination with bevacizumab for patients with homologous recombination deficient tumors. In addition, niraparib can be prescribed for patients regardless of biomarkers. At the moment of writing this review there are no approvals for rucaparib maintenance treatment.

WHICH PATIENT SHOULD RECEIVE WHICH PARPI: OLAPARIB, NIRAPARIB, OR RUCAPARIB?

The three FDA-approved PARPi have broadly similar indications and efficacy for treating primary and recurrent ovarian cancer. More specifically, olaparib is available as first-line maintenance treatment

Table 2 Adverse events grade 3 or 4 in randomized clinical trials with single-agent PARPi maintenance in recurrent and primary ovarian cancer

	Olaparib		Niraparib		Rucaparib	
Adverse events grade 3/4	**SOLO2**	**SOLO1**	**NOVA**	**PRIMA**	**ARIEL3**	**ATHENA**
Blood and lymphatic system disorders						
Anemia	38 (19%)	56 (22%)	93 (25.3%)	150 (31%)	70 (19%)	122 (28.7%)
Neutropenia (neutrophil count decrease)	10 (5%)	22 (9%)	72 (19.6%)	62 (12.8%)	25 (7%)	62 (14.6%)
Thrombocytopenia (platelet count decrease)	2 (1%)	2 (1%)	124 (33.8%)	202 (41.7%)	19 (5%)	30 (7.1%)
Gastrointestinal disorders						
Abdominal pain	5 (3%)	4 (2%)	4 (1.1%)	7 (1.4%)	9 (2%)	2 (0.5%)
Upper abdominal pain	0	0	0		2 (1%)	0
Constipation	0	0	2 (0.5%)	1 (0.2%)	7 (2%)	0
Diarrhea	2 (1%)	8 (3%)	1 (0.3%)		2 (1%)	6 (1.4%)
Dyspepsia	0	0	0		1 (1%)	1 (0.2%)
Nausea	5 (3%)	2 (1%)	11 (3%)	6 (1.2%)	14 (4%)	8 (1.9%)
Vomiting	5 (3%)	1 (<1%)	7 (1.9%)	4 (0.8%)	15 (4%)	6 (1.4%)
General disorders						
Fatigue or asthenia	8 (4%)	10 (4%)	30 (8.2%)	9 (1.9%)	25 (7%)	21 (4.9%)
Investigations						
Increased ALT/AST	0	0	0	0	39 (10%)	45 (10.6%)
Increased creatinine	0	0	0	0	1 (1%)	1 (0.2%)
Metabolism and nutrition disorders						
Decreased appetite	0	0	1 (0.3%)		2 (1%)	2 (0.5%)
Musculoskeletal						
Arthralgia	0	0	1 (0.3%)		2 (1%)	1 (0.2%)
Back pain	0	0	2 (0.5%)		0	1 (0.2%)
Nervous system						
Dizziness	1 (1%)	0	0	4 (0.8%)	0	0
Dysgeusia	0	0	0			1 (0.2%)
Headache	1 (1%)	1 (<1%)	1 (0.3%)	2 (0.4%)	1 (1%)	2 (0.5%)
Respiratory						
Cough	1 (1%)	0	0		0	0
Dyspnea	2 (1%)	0	4 (1.1%)		0	6 (1.4%)

PARPi, poly (ADP-ribose) polymerase inhibitors.

for *BRCA1/2* carriers and patients with homologous recombination deficiency positive tumors in association with bevacizumab, and niraparib is available for all patients regardless of biomarker. Similarly, all patients with recurrent ovarian cancer and response to platinum therapy have the option to receive second-line maintenance treatment with any PARPi, regardless of biomarker. This is often followed by confusion among clinicians as to which patient should receive which PARPi.

While these questions have been extensively discussed in previous reviews which focused mainly on aspects including trial design and clinical benefit depending on biomarkers or molecular assays,[43 44] we propose here a different approach based on analysis of toxicity profiles (Table 2) and present an algorithm (Figure 1) to guide clinicians with PARPi selection, including most frequent toxicities of grade 3 or higher. Furthermore, we briefly highlight aspects of treatment management for each agent, including dose reductions, interruptions, and discontinuation (Tables 3 and 4). While many of the adverse events of PARPi treatment are common effects of the drug class, including hematological complications, fatigue, nausea, and vomiting, other uncommon complications are life-threatening, such as myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) and pneumonitis.

The specific management of hematological side effects has already been described extensively in numerous reviews[43 44]: grade 1 adverse events require monitoring blood counts while continuing treatment; grade 2 adverse events require withholding of treatment for a maximum of 28 days, with the possibility of resuming PARPi at a reduced dose; and grade 3 or 4 adverse events are generally managed by withholding PARPi for a maximum of 28 days, resuming the treatment at a reduced dose or, if already at the lowest dose,

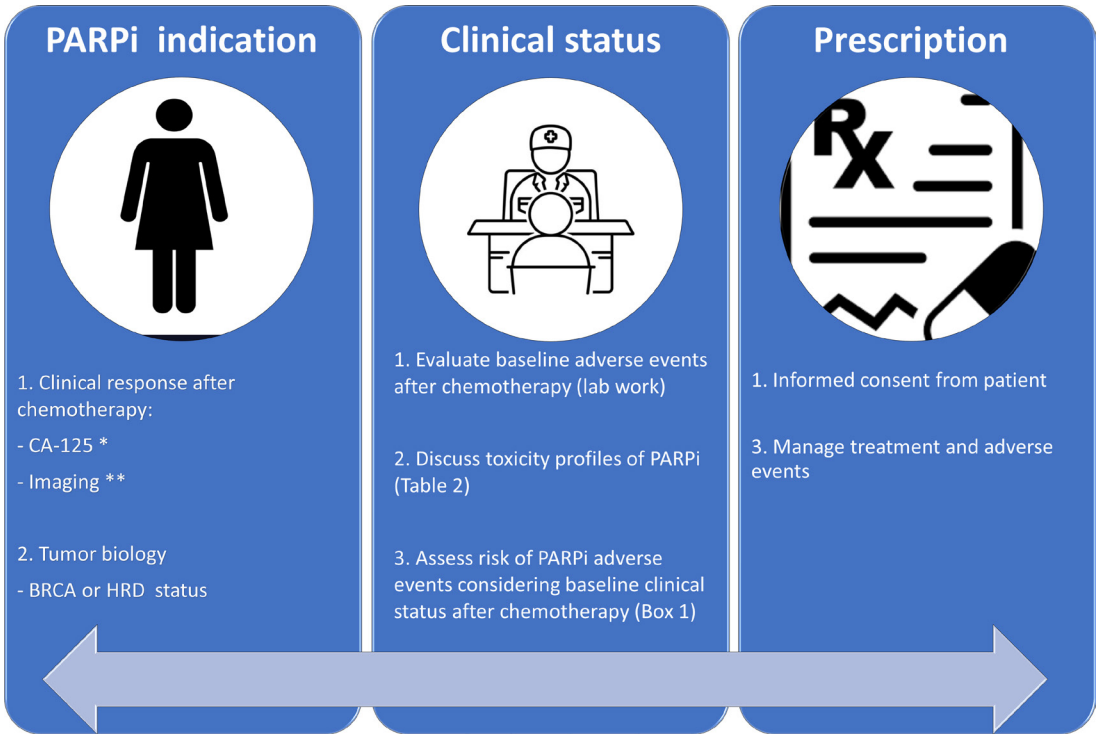

Figure 1 Flow diagram of medical decision on poly (ADP-ribose) polymerase inhibitor (PARPi) treatment for an individual patient based on consideration of PARPi toxicity. *Patients with complete surgical resection. **Patients without complete surgical resection or metastasis.

discontinuing the treatment. Other common adverse events that occur with PARPi are non-hematological complications including gastrointestinal, renal, fatigue, and laboratory toxicities. Common management of grade 1 adverse events includes continuation of PARPi and treatment of symptoms, if necessary. Grade 2 adverse events are managed by continuation of treatment, while stopping the treatment for several days or reducing the dose, the latter of which is discussed with patients if toxicity cannot be controlled with treatment of symptoms. Grade 3 or 4 adverse events require withholding treatment for a maximum of 28 days, then continuing therapy at a reduced dose. The dose should be further reduced if a second withholding period is necessary.

Olaparib

In this review we mainly refer to the safety data of olaparib in two phase III trials, SOLO1 and SOLO2 (Table 2). The median duration of exposure to olaparib was 19.4 months in SOLO2 and 24.6 months in SOLO1. While all patients experienced a side effect of any grade in SOLO2, the most common were grade 1–2 and the overall incidence of grade 3–4 adverse events was low. Grade 1–2 gastrointestinal events such as nausea (73%), fatigue (62%), and vomiting plus diarrhea (35%, 32%) accounted for the most frequent dose reductions. Hematological events of grade 1–2, such as anemia, were less frequent (24%). However, anemia was the most frequent grade 3–4 event (19%). This was followed by neutropenia grade 3–4 (5%). The following dose managements were reported: dose interruptions (45%), reductions (25%), and treatment discontinuations (11%). Furthermore, at least one blood transfusion was administered to 60.4% of patients with anemia in the olaparib group, the prevalence of which peaked at 6 months.[45] In line with the findings from SOLO2, 98% of the patients from SOLO1 experienced a side effect of any grade. Gastrointestinal side effects were mostly grade 1–2, such as nausea (77%), fatigue (63%), vomiting, and diarrhea (40%, 34%). Grade 3–4 hematological events were also consistent with the rates reported by SOLO2, including anemia (22%) and neutropenia (9%). Subsequently, grade 3–4 events led to treatment discontinuation (12%), dose interruptions (52%) and reductions (28%), which were comparable between SOLO2 and SOLO1.

Table 3 Dose modifications and discontinuations of PARPi due to adverse events

	Olaparib		Niraparib		Rucaparib	
	SOLO2	SOLO1	PRIMA	NOVA	ARIEL3	ATHENA
Dose interruptions	88 (45%)	135 (52%)	385 (79.5%)	253 (68.9%)	237 (63.7%)	258 (60.7%)
Dose reductions	49 (25%)	74 (28%)	343 (70.9%)	244 (66.5%)	203 (54.6%)	
Discontinuations	21 (11%)	30 (12%)	58 (12%)	54 (14.7%)	50 (13.4%)	50 (11.8%)

PARPi, poly (ADP-ribose) polymerase inhibitors.

Table 4 Events leading to discontinuation in olaparib, niraparib and rucaparib groups

	Olaparib		Niraparib		Rucaparib	
AEs leading to discontinuation	**SOLO2**	**SOLO1**	**NOVA**	**PRIMA**	**ARIEL3**	**ATHENA**
Blood and lymphatic system disorders						
Anemia	6 (3.1%)	6 (2.3%)	5 (1.4%)	9 (1.9%)	11 (3.0%)	115 (27.1%)
Neutropenia	3 (1.5%)	2 (0.8%)	7 (1.9%)	9 (1.9%)	5 (1.3%)	63 (14.8%)
Leukopenia	1 (0.5%)	1 (0.4%)	7 (1.9%)	10 (2.1%)	1 (0.3%)	16 (3.8%)
Thrombocytopenia	1 (0.5%)	1 (0.4%)	12 (3.3%)	21 (4.3%)	10 (2.7%)	45 (10.6%)
Pancytopenia	0		3 (0.8%)	–	1 (0.3%)	–
Acute myeloid leukemia	1 (0.5%)	0	–	–	1 (0.3%)	–
Myelodysplastic syndrome	1 (0.5%)	0	–	–	2 (0.5%)	–
Gastrointestinal disorders						
Gastric cancer/oral cavity	1 (0.5%)	1 (0.4%)	–	–	0	–
Abdominal pain	1 (0.5%)	1 (0.4%)	–	–	1 (0.3%)	–
Nausea	1 (0.5%)	6 (2.3%)	–	–	9 (2.4%)	38 (8.9%)
Vomiting	0	2 (0.8%)	–	–	5 (1.3%)	19 (4.5%)
Dyspepsia	0	1 (0.4%)	–	–	1 (0.3%)	–
General disorders						
Asthenia/fatigue	0	6 (2.3%)	–	–	6 (1.6%)	41 (9.6%)
Edema peripheral	1 (0.5%)		–	–	0	–
Fever	0	1 (0.4%)	–	–		–
Disturbance in attention	1 (0.5%)	1 (0.4%)	–	–	1 (0.3%)	–
Decreased appetite	0	1 (0.4%)	–	–		7 (1.6%)
Infections						
Pneumonitis	1 (0.5%)	1 (0.4%)	–	–	0	–
Investigations						
Increased ALT/AST	0		–	–	2 (0.5%)	49 (11.5%)
Acute kidney injury	0		–	–	2 (0.5%)	–
Musculoskeletal						
Muscular weakness	1 (0.5%)	2 (0.8%)	–	–	0	–
Pain in extremity	1 (0.5%)	1 (0.4%)	–	–	0	–
Nervous system						
Depression	1 (0.5%)	1 (0.4%)	–	–	0	–
Skin						
Dermatitis (allergic)	1 (0.5%)	0	–	–	0	–
Respiratory						
Dyspnea	0	1 (0.4%)	–	–	1 (0.3%)	8 (1.9%)
Others						
Invasive breast carcinoma	0	1 (0.4%)	–	–	0	–
Cardiac arrest	0		–	–	1 (0.3%)	–

AEs, adverse events.

Other grade 3 adverse effects such as thrombocytopenia, tachycardia, and liver enzyme elevation were found in 1% of patients treated with olaparib, although these toxicities were found in a larger percentage of patients in other PARPi trials (>10%).[5] Given the low frequency of liver toxicities, Pujade-Lauraine et al suggest that olaparib may be best for patients with a history of liver or cardiovascular problems, or platinum chemotherapy-induced liver and cardiac toxicity. Apart from the abovementioned rare toxicities, concern was raised about the presence of the severe adverse events MDS and AML. Recently, a systematic review including 5693 patients in PARPi groups and 3406 patients in control groups from randomized controlled trials reported that PARPi significantly increased the risk of MDS and AML compared with placebo treatment (OR 2.63 (95% CI 1.13 to 6.14); p=0.026).[46] An age group

analysis of SOLO2 recently reported a difference in the rate of AML/MDS in older compared with younger patients (15% vs 6%, respectively).[47]

Researchers have investigated the relationship between olaparib dose and tumor response.[48 49] A phase I study assessed the efficacy and safety of olaparib in 58 patients with recurrent ovarian cancer and confirmed *BRCA*1/2 mutations at different doses: single agent olaparib at a maximum dose of 400 mg and a lower dose of 100 mg. Despite a clinical benefit in both cohorts, the authors suggest that the 100 mg dose might be less efficacious than the 400 mg dose. Limitations of the study, however, included lack of randomization and imbalances regarding poorer prognostic features in the 100 mg cohort.[49] Another phase II study investigated the efficacy and safety of pegylated liposomal doxorubicin (PLD) versus olaparib monotherapy in recurrent ovarian cancer at two different doses of olaparib (200 mg or 400 mg) in separate study arms. Interestingly, there was no significant difference in progression-free survival between the different doses of olaparib or the PLD cohort.[48]

Hypertension (19%), anemia (17%), lymphopenia (7%), neutropenia (6%), fatigue and asthenia were the most common grade 3–4 toxicities reported by the PAOLA-1 study for olaparib plus bevacizumab.[39] While the hypertension rate in the PAOLA-1 study cannot be compared head-to-head with toxicities reported by investigators in GOG-218 and ICON7, 23% (grade 2 or greater) and 1% (grade 3), respectively, grade 3–4 hematological toxicities recorded in the experimental arm (olaparib plus bevacizumab) are in line with those reported for single agent olaparib by SOLO1 and SOLO2. Nevertheless, since PAOLA-1 did not include a third bevacizumab single-agent arm, it is difficult to make assumptions as to whether toxicities reported for the combination of olaparib plus bevacizumab can be considered for a single agent or the combination.

Niraparib

Despite the additional clinical benefit of niraparib in patients without homologous recombination deficiency, which supports the hypothesis that the mechanism of action of niraparib is beyond DNA damage repair, patients experienced a high rate of toxicity (Tables 2 and 3). The median follow-up of the niraparib group was 16.9 months in the ENGOT-OV16/NOVA trial and 13.8 months in the PRIMA/ENGOT-OV26/GOG-3012 trial. All patients experienced at least one adverse event of any grade. While neither trial assessed grade 1–2 adverse events in the niraparib group, a high rate of nausea, fatigue, constipation, and vomiting was reported. Hematological events accounted for toxicities higher than grade 3 and were more frequent in relapse than the primary setting, including anemia (25.3% ENGOT-OV16/NOVA, 31% PRIMA/ENGOT-OV26/GOG-3012), thrombocytopenia (33.8% ENGOT-OV16/NOVA, 28.7% PRIMA/ENGOT-OV26/GOG-3012), and neutropenia (19.6% ENGOT-OV16/NOVA, 12.8% PRIMA/ENGOT-OV26/GOG-3012). A possible cause for the higher toxicity in the relapse setting could be the presence of residual toxicity due to previous chemotherapy lines. This high frequency of hematological events led to dose interruptions (79.5%) or reductions (70.9%) and discontinuation (12%) in the PRIMA/ENGOT-OV26/GOG-3012 trial. Similar data were reported from the ENGOT-OV16/NOVA trial, including dose interruptions (68.9%) or reductions (66.5%) and discontinuations (14.7%). Dose reductions tended to occur early, with most patients reaching their individual-adjusted dose level at the end of treatment month 3.

While discontinuation rates of niraparib were comparable to those reported in trials with olaparib and rucaparib, dose modifications in the niraparib-treated patients were significantly higher. This was an interesting finding given that niraparib efficacy at lower doses was comparable with the other two PARPi: two-thirds of patients received lower doses or interrupted niraparib therapy compared with only half of patients who had dose interruption and a quarter of patients who had dose reduction on olaparib treatment.

The impact of dose modifications on the efficacy of niraparib was subsequently investigated, along with other potential niraparib doses. Mirza et al evaluated the impact of dose modification on microscopic hematologic abnormalities reported after cycle 3 to the end of treatment.[4] Grade 3 or 4 adverse events were assessed in sub-groups of patients who received 300 mg (n=82), 200 mg (n=138), and 100 mg (n=77). Adverse events decreased from 23.2% in patients receiving 300 mg to 7.8% in those who received 100 mg. Additionally, the prevalence of anemia improved with lower doses, as did neutropenia and fatigue at 100 mg. Furthermore, Berek et al carried out a retrospective analysis of the ENGOT-OV16/NOVA trial to identify clinical parameters predictive of the requirement of dose reductions with niraparib treatment.[50] This analysis found that reductions tended to occur during the first 3 months of therapy. The results showed that two risk factors increased the frequency of grade 3 adverse events—namely, baseline platelet count and baseline body weight. Interestingly, progression-free survival remained the same regardless of the niraparib dose level, and the authors concluded that patients were not underexposed at a lower dose of drug. In an effort to improve tolerability of niraparib, the PRIMA/ENGOT-OV26/GOG-3012 protocol was amended during the course of the trial to account for these individualized doses with body weight (cut-off <77 kg) and platelet count (cut-off 150×10^3/mL).[2]

Individualized dosing was further studied in the NORA trial, a randomized, double-blind, placebo-controlled phase III trial investigating treatment with 200 mg/day or 300 mg/day.[51] Notably, in this study niraparib showed an improved safety profile with individualized dosing, and treatment outcomes were unaffected. Another study included patients from the ENGOT-OV16/NOVA trial who were grouped according to age of study entry, with a cut-off of 70 years.[52] After evaluating efficacy and safety according to age, patients >70 years showed a comparable tolerability to niraparib as those aged <70 years.

Rucaparib

Approval of a third PARPi, rucaparib, is currently limited to recurrent ovarian cancer maintenance and monotherapy. The efficacy and safety of rucaparib was validated in the ARIEL3 trial, in which the median treatment duration was 8.3 months. Like the other two PARPi, all 372 patients in the trial experienced an adverse event of any grade. The prevalence of grade 1–2 and grade 3–4 adverse events was approximately the same (44% and 52%, respectively). Gastrointestinal complications were the most common among grade 1–2 adverse events: nausea (72%), constipation (35%), and diarrhea (31%) followed by fatigue (63%). While hematological events such as grade 3 anemia (18%) were in line with rates reported for olaparib and niraparib, laboratory investigations such as increased alanine aminotransferase or aspartate aminotransferase (10%) and creatinine were specific to patients receiving

rucaparib (Table 2). However, the authors interpreted this toxicity as transient, self-limiting, and not associated with other signs of liver toxicity. Dose interruptions occurred in 64% of patients, dose reductions in 55%, and treatment discontinuation in 13%.

An exploratory exposure–efficacy study examined the risk factors for toxicity after rucaparib treatment in patients with recurrent ovarian cancer enrolled in Study 10 and ARIEL2.[53] While previous studies showed a direct relationship between niraparib toxicity and risk factors such as weight and platelet counts, none of these had an impact on the pharmacokinetics of rucaparib. Another group showed that increased creatinine largely overlapped between the sub-groups of patients with normal, mildly impaired, and moderately impaired renal function at baseline, suggesting that no starting dose adjustment of rucaparib is required in patients with mild or moderate renal impairment.[54] This was also the case in a study investigating baseline hepatic impairment during treatment with rucaparib.[55] Similarly, the results of this study suggested that no starting dose adjustment is necessary for patients with moderate hepatic impairment.

A meta-analysis presented at ASCO 2020 assessed the incidence of AML and MDS across multiple randomized trials.[56] The authors investigated the number of patients who experienced AML or MDS while on olaparib, niraparib, and rucaparib from 2017 to 2019. The following rates were reported for MDS/AML: olaparib, 173 adverse events (6.8%); niraparib, 41 adverse events (0.7%); rucaparib, 4 adverse events (2.6%). While treatment with olaparib showed the highest rate of MDS/AML, rucaparib had the second highest rate. However, limitations of cross-trial comparison have to be taken into account with different patient cohorts and inclusion and exclusion criteria impairing the ability to generalize these rates.

Taken together, almost all patients exposed to PARPi experienced adverse events of any grade. In detail, toxicities of grade 1–2 were common in approximately two-thirds of patients and their frequency was similar across all three PARPi. Toxicities of grade 1–2 mostly require monitoring while continuing treatment or withholding treatment for a maximum of 28 days, but toxicities of grade 3 or greater should be extensively discussed and are important parameters when counseling for PARPi therapy. Figure 2 shows an overview of adverse events detected during or after chemotherapy which might be risk factors for toxicities of grade 3 or greater on PARPi maintenance treatment.

Interestingly, a meta-analysis which included results from clinical trials investigating PARPi given as monotherapy or combined with chemotherapy and/or anti-angiogenic drugs compared PARPi with placebo in an elderly cohort aged ≥65 years and in younger patients aged <65 years.[57] In this study, safety information was limited to hematologic toxicity and a lower risk of severe anemia was reported in older patients (p=0.04).[57] However, real-world studies should include more geriatric assessment. This is especially important, given the fact that most patients diagnosed with ovarian cancer are >65 years of age and clinical trials limit the enrollment of patients with concomitant co-morbidities and those with a high frailty risk or geriatric impairments.

Considering that patients with ovarian cancer in both the primary and recurrent setting would mostly be treated with a platinum-based therapy, changes in hematological events such as anemia, neutropenia,

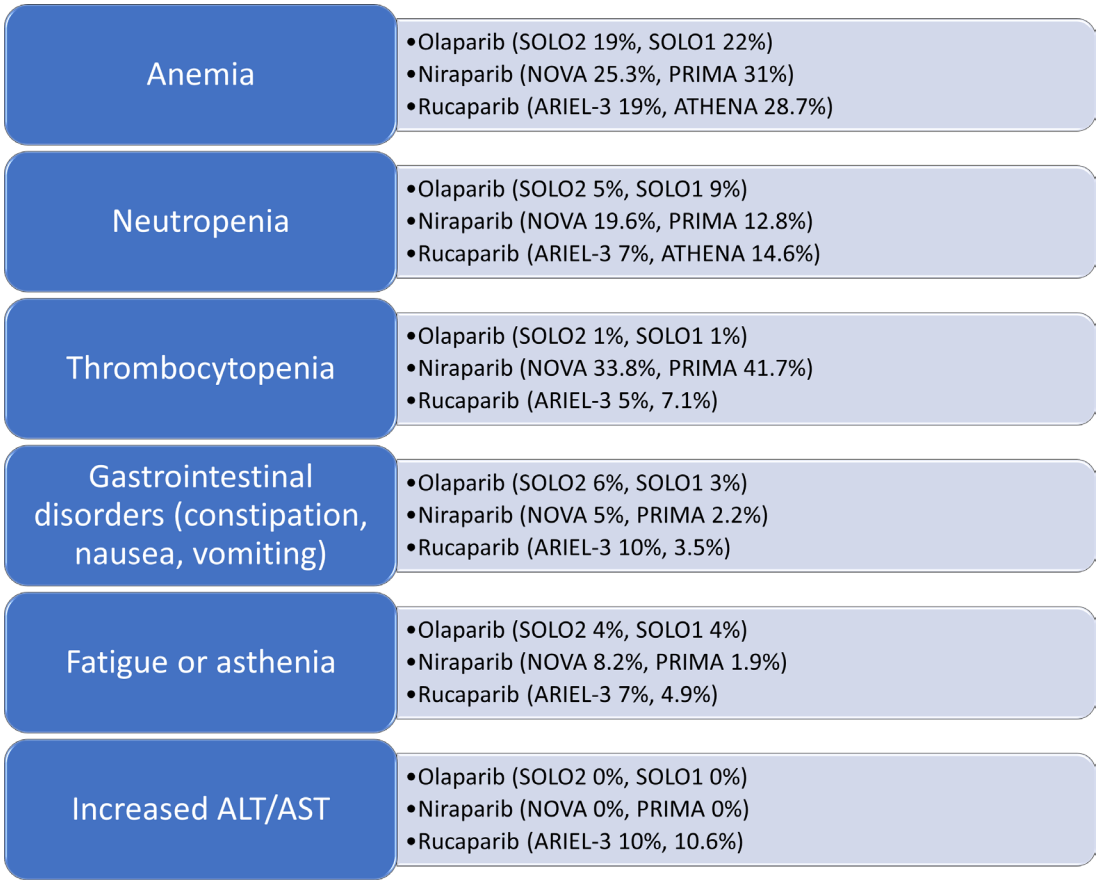

Figure 2 Grade 3 or 4 adverse events after chemotherapy in clinical trials of poly (ADP-ribose) polymerase inhibitors (PARPi).

and low platelet count under platinum-based therapy should be further considered during maintenance. This is especially important, considering that anemia and neutropenia events were lower on olaparib (19–22% and 5–9%, respectively) than on niraparib (25.3–31% and 12.8–19.6%, respectively). With regard to rucaparib, there were differences in hematological toxicities reported by the two trials, 19% for anemia and 7% for neutropenia in ARIEL3 and 28% for anemia and 14.6% for neutropenia in ATHENA. Furthermore, a greater difference between the three PARPi was the platelet count. More specifically, the rate of thrombocytopenia with niraparib was much higher than with olaparib or rucaparib (33.8–41.7% vs 1% and 5%, respectively).

Gastrointestinal disorders, fatigue, or asthenia are frequently side effects in cancer patients receiving chemotherapy. However, clinical trials in the primary and recurrent setting failed to show major differences across the three PARPi and their toxicity profiles, including gastrointestinal disorders, fatigue or asthenia of grade 3 or higher. Last, patients receiving rucaparib more frequently showed laboratory changes in ALT/AST of grade 3 or higher (10%), which was not the case for patients on olaparib or niraparib regimens.

Another aspect to consider are the toxicities which influence everyday activities such as headache and insomnia. These symptoms are usually mild but can have an important impact on quality of life. Headache was reported in 26% of patients on niraparib in the ENGOT-OV16/NOVA trial, 25% on olaparib in the SOL02 trial, and 18% of patients on rucaparib in the ARIEL3 trial. The occurrence of insomnia was highest in patients on niraparib (24%), followed by 14% of patients receiving rucaparib and 5% of patients receiving olaparib.

Finally, the effect of PARPi on other drugs should also be considered in PARPi management, given the fact that patients with ovarian cancer are older women with associated co-morbidities.[58] Furthermore, the cancer burden frequently leads to supportive therapies for depression or anxiety.[59] Both olaparib and rucaparib inhibit CYP3A, which increases total drug exposure over time of caffeine, midazolam, warfarin, omeprazole, and digoxin.[60] In addition, rucaparib reversibly inhibits CYP1A2, CYP2C19, and CYP2C9. In contrast, niraparib has a negligible effect on CYP450 enzymes and no formal drug interaction studies have been performed with niraparib.

QUALITY OF LIFE IN PATIENTS ON PARPI TREATMENT

The assessment of patient-reported outcomes was evaluated in all recurrent maintenance trials using questionnaires including the Functional Assessment of Cancer Therapy (FACT-O), European Quality of Life-5 Dimensions (EQ-5D-3/5 L), and the European Organization for Research and Treatment of Cancer core questionnaire (EORTC-QLQ-C30). Along with cancer site-related symptoms, these tools also evaluated physical, social/family, emotional and functional well/being like self-care, usual activities, pain/discomfort, anxiety, and depression. The high frequency of grade 3–4 adverse events may affect patients with either no active disease or few adverse events at baseline receiving maintenance. A detailed description of the assessment of the abovementioned health-related questionnaires was given in a previous review.[44]

Interestingly, a health-related QoL assessment in patients with platinum-sensitive recurrent disease treated with niraparib maintenance therapy showed increased patient-perceived lack of energy and nausea at the time of treatment initiation, but steadily declined over time to near baseline levels.[61] Similarly, resolution of nausea or vomiting occurred in 90% of these patients.[45] Importantly, health-related QoL was assessed in all recurrent maintenance trials and the results indicate no significant limitations of any PARPi on the well-being of patients.[26 61 62] Moreover, all PARPi were associated with significant patient-centered benefits on quality of life despite the toxicity experienced in the experimental arms versus placebo.[26 61 62]

While the questionnaires mainly analyzed the QoL of patients on PARPi treatment, another tool, Time Without Symptoms or Toxicity (TWiST), aimed to integrate both quantity and quality of treatment. TWiST is defined as the period without any clinically significant symptoms of toxicity after randomization and before protocol-defined disease progression. The adverse events included in the first study evaluating this endpoint for PARPi by Friedlander et al were nausea, vomiting, and fatigue at grade 2 or higher, which were considered most likely to affect the QoL.[26] Despite the fact that the same three adverse events were included in the TWiST model for evaluation of all PARPi, these results are not comparable between different PARPi since the authors used different methodology and their analysis was limited to patients with *BRCA1/2* tumors[5] or all patients regardless of biomarkers.[3 4]

In SOLO2, the authors reported an 8-month longer TWiST duration in patients receiving olaparib compared with placebo.[26] Furthermore, when patients were categorized according to age cut-off at 65 years, the results indicated a median duration of good QoL of 13.5 months in patients aged ≥65 years compared with a median duration of 18.4 months in those aged <65 years on olaparib.[47] Matulonis et al took another approach for calculating TWiST duration by extrapolation of progression-free survival to 20 years, based on expert clinical opinion that patients on niraparib could be disease-free for up to 20 years.[63] Using sophisticated statistical methods, the study showed an increased TWiST duration in patients with both *BRCA1/2* and non-*BRCA1/2*-mutated tumors who received niraparib (2.95 years and 1.34 years, respectively). Finally, Oza et al evaluated TWiST in the ARIEL3 trial investigating rucaparib.[62] Here, the mean TWiST duration remained significantly longer with rucaparib, a difference of 6.40 months compared with placebo. Furthermore, quality-adjusted analysis showed a mean increase of 6.88 months with rucaparib.

Taken together, QoL assessment using questionnaires and TWiST findings suggest that second-line maintenance with the PARPi olaparib, niraparib, and rucaparib is clinically beneficial and well tolerated. Furthermore, despite the impact of toxicities on patients' health status and the longest periods without clinically relevant symptoms, the greatest benefit was observed in patients with *BRCA1/2* tumors. However, TWiST analysis in patients without *BRCA1/2* tumors on rucaparib or niraparib treatment showed a clinical benefit as well.

CONCLUSIONS

Given the convincing clinical data on PARPi efficacy, every patient with high-grade ovarian cancer will receive PARPi during her treatment in the primary or recurrent setting. In this review we discuss the perspective of choosing a PARPi based on its efficacy and biomarker indication, and also from a toxicity point of view. Since there is no major difference in their mechanism of action, clinicians mostly indicate PARPi according to availability and their experience in the management of one or other PARPi adverse events.

However, maintenance treatment has a long-term perspective and most patients will have already experienced several hematological or non-hematological side effects of platinum-based therapy. Additionally, individual PARPi have specific toxicity profiles that should be considered on an individual basis when counseling patients before the start of treatment. As a result, inappropriate management with supportive care and dose reduction can lead to treatment discontinuation and should be avoided. Currently, there are no head-to-head trials of PARPi in recurrent or primary high-grade recurrent platinum-sensitive ovarian cancer. Given the results of the OReO/ENGOT Ov-38 trial showing a slight difference in clinical benefit of approximately 2.5 months in both patients with *BRCA* mutant tumors and those with non-*BRCA* mutant tumors after PARPi rechallenge, evaluating a strategy for a possible PARPi sequence will be necessary. However, some aspects of this trial need further discussion and interpretation, including the heavily pre-treated cohort (more than three previous lines), limitation in the rechallenge to only one PARPi (olaparib), and the modest progression-free survival of 2.5 months. Certainly, the biomarker status and history of toxicity at baseline after chemotherapy will be important determinants to be taken into consideration. Finally, an open question is whether there is a link between the choice of PARPi and surgical resection in the relapse setting, in particular if, from a surgical point of view, the three PARPi correlate with a different disease pattern of relapse such as peritoneal disease, lymph node invasion, or distant metastasis.

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