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REVIEW ARTICLE

PARP Inhibitors in Ovarian Cancer: A Review

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Abstract
Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPis) have transformed the ovarian cancer (OC) treatment landscape. This narrative review provides a comprehensive overview of data for the PARPis olaparib, niraparib, and rucaparib in patients with OC and discusses their role in disease management, with a focus on the use of PARPis as maintenance therapy in the United States (US). Olaparib was the first PARPi to be approved as first-line maintenance monotherapy in the US, with maintenance niraparib subsequently approved in the first-line setting. Data also support the efficacy of rucaparib as first-line maintenance monotherapy. PARPi maintenance combination therapy (olaparib plus bevacizumab) also provides benefit in patients with newly diagnosed advanced OC whose tumors tested positive for homologous recombination deficiency (HRD). Biomarker testing is critical in the newly diagnosed setting to identify patients most likely to benefit from PARPi maintenance therapy and guide treatment decisions. Clinical trial data support the use of PARPis (olaparib, niraparib, rucaparib) as second-line or later maintenance therapy in patients with platinum-sensitive relapsed OC. Although distinct differences in tolerability profile were observed between PARPis, they were generally well tolerated, with the majority of adverse events managed by dose modification. PARPis had no detrimental effect on patients' health-related quality of life. Real-world data support the use of PARPis in OC, although some differences between PARPis are apparent. Data from trials investigating novel combination strategies, such as PARPis plus immune checkpoint inhibitors, are awaited with interest; the optimal sequencing of novel therapies in OC remains to be established.

1 Introduction

Ovarian cancer (OC) is often diagnosed at an advanced stage and is associated with poor prognosis. Until recently, first-line treatment for advanced (International Federation of Gynecology and Obstetrics [FIGO] stage II–IV) OC included debulking surgery combined with platinum-based chemotherapy [1]. Despite exquisite sensitivity to platinum-based therapy in the front line, most patients relapse within 3 years despite treatment [2] and are often retreated with

Key Points

We provide a comprehensive overview of data for the poly(ADP-ribose) polymerase (PARP) inhibitors olaparib, niraparib, and rucaparib in patients with ovarian cancer (OC) and discuss their role in disease management.

In the newly diagnosed OC setting, PARP inhibitors provide the greatest clinical benefit in patients with a *BRCA1* and/or *BRCA2* mutation (BRCAm) or whose tumors test positive for homologous recombination deficiency, meaning biomarker testing is critical to identify those patients most likely to benefit from PARP inhibitor maintenance therapy and guide treatment decisions.

Although there are distinct differences in tolerability profile between PARP inhibitors, they are generally well tolerated, with the majority of adverse events managed by dose modification.

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multiple courses of therapy, including further cytoreductive surgery and chemotherapy [1].

The OC treatment landscape has evolved with the development of targeted therapies, such as anti-angiogenic agents and poly(ADP-ribose) polymerase (PARP) inhibitors (PARPis). The anti-angiogenic agent bevacizumab was the first targeted therapy to be approved in the United States (US) for use in OC [3]. Bevacizumab has demonstrated efficacy in patients with newly diagnosed [4–7], platinum-sensitive relapsed (PSR) [8–10], and platinum-resistant relapsed [11] OC. Given its efficacy in these settings, treatment guidelines include bevacizumab-containing regimens as options in first-line and later-line settings, with maintenance bevacizumab recommended in patients in response to platinum-based regimens incorporating bevacizumab [1, 2, 12].

More recently, PARPis have emerged as important new therapies in OC, with three PARPis, olaparib, niraparib, and rucaparib, currently approved by the US FDA as maintenance therapy for patients with OC (Fig. 1 and Table 1) [13–15]. As more treatment options become available, determining the best therapy for patients can be challenging. The authors undertook a comprehensive narrative review of evidence supporting the use of PARPis in OC,

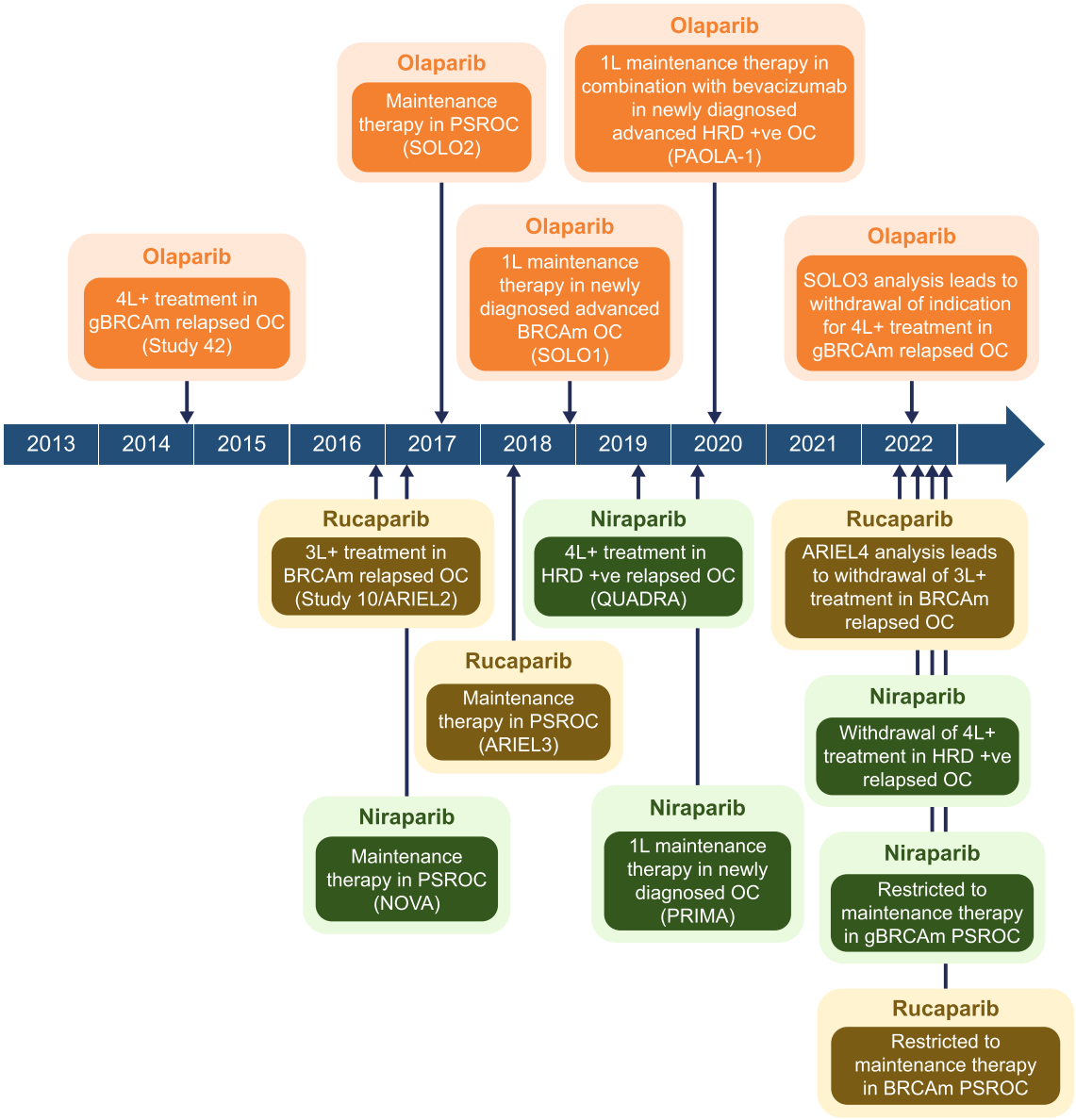

Fig. 1 US approval of PARP inhibitors for use in patients with OC*. *The trial(s) on which approval was based is shown in parentheses. *1L* first-line, *3L+* third-line or later, *4L+* fourth-line or later, *BRCAm* *BRCA1* and/or *BRCA2* mutation, *g* germline, *HRD* homologous recombination deficiency, *OC* ovarian cancer, *PARP* poly(ADP-ribose) polymerase, *PSR* platinum-sensitive relapsed, *+ve* positive

Table 1 PARP inhibitors approved for OC in the US[a]

PARP inhibitor	Year of approval	Use as monotherapy or combination therapy	Line of treatment or maintenance therapy	OC population	Pivotal study	Updated indication (year)
Olaparib [13]	2014	Monotherapy	4L+ treatment	gBRCAm relapsed	Study 42 [62]	SOLO3 analysis leads to voluntary withdrawal of indication (2022) [66]
	2017	Monotherapy	2L+ maintenance therapy	PSR	SOLO2 [37] and Study 19 [36]	
	2018	Monotherapy	1L maintenance therapy	Newly diagnosed advanced BRCAm	SOLO1 [16]	
	2020	In combination with bevacizumab	1L maintenance therapy	Newly diagnosed advanced HRD-positive (defined as BRCAm and/or genomic instability)	PAOLA-1 [31]	
Rucaparib [15]	2016	Monotherapy	3L+ treatment	BRCAm relapsed	Study10/ARIEL2 [57]	ARIEL4 analysis leads to voluntary withdrawal of indication (2022) [61]
	2018	Monotherapy	2L+ maintenance therapy	PSR	ARIEL3 [39]	Indication restricted to patients with BRCAm PSROC (2022) [15]
Niraparib [14]	2017	Monotherapy	2L+ maintenance therapy	PSR	NOVA [38]	Indication restricted to patients with gBRCAm PSROC (2022) [52]
	2019	Monotherapy	4L+ treatment	Relapsed HRD-positive (defined as BRCAm and/or genomic instability)	QUADRA [69]	Voluntary withdrawal of indication (2022) [70]
	2020	Monotherapy	1L maintenance therapy	Newly diagnosed	PRIMA [17]	

1L first-line, *2L+* second-line or later, *3L+* third-line or later, *4L+* fourth-line or later, *BRCAm BRCA1* and/or *BRCA2* mutation, *g* germline, *HRD* homologous recombination deficiency, *OC* ovarian cancer, *PARP* poly(ADP-ribose) polymerase, *PSR* platinum-sensitive relapsed, *PSROC* platinum-sensitive relapsed ovarian cancer

[a]PARP inhibitors are also approved in the US for cancers other than OC. US prescribing information should be consulted for further information [13–15]

including topics not easily captured by systematic reviews. This review focuses on data from Phase III trials and trials that led to the approval of PARPis in OC, highlighting the current and future treatment landscape in OC, including the role of biomarker testing and adverse event (AE) management strategies.

2 Methods

Literature searches for the narrative review were initially conducted in PubMed for papers published up to 6 September 2021, using the following search terms: '(PARP inhibitor OR olaparib OR veliparib OR niraparib OR rucaparib) AND (ovarian cancer)'. A search alert in PubMed was used to capture additional articles published between 6 September 2021 and 9 January 2023. Searches were restricted to 'Humans', 'Clinical Trial', 'Clinical Study', and 'Research support, non-U.S. Gov't'.

Databases of the American Society of Clinical Oncology, European Society of Gynaecological Oncology, European Society for Medical Oncology, International Gynecologic Cancer Society, and Society of Gynaecological Oncology were also searched for congress abstracts from 2019 to 2022.

Articles retrieved from the above searches were included if they were Phase III clinical trials or trials that led to the approval of PARPis in OC and key trials conducted thereafter. Clinical studies of PARPis not approved for use in the US or novel treatments, preclinical studies, *in vitro* studies, and review articles were excluded.

In addition, reference lists of retrieved papers were hand-searched for relevant studies, and key papers were included based on the authors' clinical experience and knowledge of the field.

3 Efficacy in Ovarian Cancer

3.1 First-Line Maintenance Monotherapy

Olaparib was the first PARPi to be approved as first-line maintenance monotherapy in the US based on the results of the Phase III SOLO1 trial [16], with niraparib subsequently approved in the first-line setting based on the results of the Phase III PRIMA trial [17]. Results of the Phase III ATHENA-MONO trial evaluating rucaparib as first-line maintenance monotherapy are also included for completeness [18]. All three studies included patients with stage III–IV, high-grade serous or endometrioid OC, primary peritoneal cancer, and/or fallopian tube cancer who had clinical complete response (CR) or partial response (PR) after platinum-based chemotherapy. SOLO1 enrolled patients with tumors with a *BRCA1* and/or *BRCA2* mutation (BRCAm) [16], whereas PRIMA [17] and ATHENA-MONO [18] enrolled patients regardless of tumor biomarker status. Although all patients with newly diagnosed advanced OC are at high risk of disease progression, PRIMA only enrolled patients considered at higher clinical risk (patients with FIGO stage III disease and no residual macroscopic disease after upfront surgery were excluded from the study) [17], whereas SOLO1 [16] and ATHENA-MONO [18] included patients irrespective of their clinical risk.

SOLO1 randomized 391 patients to receive maintenance olaparib tablets or placebo for up to 2 years or until disease progression (Table 2); patients with ongoing evidence of disease at 2 years could continue to receive study treatment at the investigators' discretion (at the time of the primary analysis, 10% of patients randomized to olaparib and 2% of those randomized to placebo had continued treatment beyond 2 years) [16, 19]. After a median follow-up of ≈41 months, a statistically significant improvement in the primary endpoint of investigator-assessed progression-free survival (PFS) was observed with olaparib versus placebo (median not reached vs. 13.8 months), with a hazard ratio (HR) of 0.30 (95% confidence interval [CI] 0.23–0.41; $P < 0.001$) [Table 2]. At 3 years, 60% of patients in the olaparib group versus 27% in the placebo group were free of PFS events [16]. Exploratory subgroup analyses showed that the risk of disease progression or death was significantly reduced with olaparib versus placebo in patients with both higher-risk disease (FIGO stage III with upfront surgery and residual disease or neoadjuvant chemotherapy, or FIGO stage IV; HR 0.34, 95% CI 0.24–0.48) and lower-risk disease (FIGO stage III with upfront surgery and no residual disease; HR 0.33, 95% CI 0.20–0.52) [20].

An updated, *post hoc* analysis showed that the PFS benefit derived from 2 years' maintenance therapy with olaparib was sustained beyond the end of treatment [21]. After a median follow-up of ≈5 years, median PFS was 56.0 months with maintenance olaparib compared with 13.8 months with placebo (HR 0.33, 95% CI 0.25–0.43). Consistent PFS benefit was observed in both the higher-risk (median PFS 40.6 vs. 11.1 months; HR 0.34, 95% CI 0.24–0.49) and lower-risk (median PFS not reached vs. 21.9 months; HR 0.38, 95% CI 0.25–0.59) subgroups in an exploratory analysis (Table 2) [21].

A prespecified descriptive analysis conducted after 7 years of follow-up showed a clinically meaningful improvement in overall survival (OS) with olaparib versus placebo (median OS not reached vs. 75.2 months; HR 0.55, 95% CI 0.40–0.76; $P = 0.0004$ [$P < 0.0001$ required to declare statistical significance]) in SOLO1 (Table 2) [22]. At 7 years, 67% of patients in the olaparib group versus 46.5% of patients in the placebo group were alive, and 45.3% versus 20.6% were alive and had not received a first subsequent treatment [22].

In PRIMA, 733 patients were randomized to receive maintenance niraparib or placebo for 36 months or until disease progression (Table 2); patients were eligible regardless of biomarker status. A subsequent protocol amendment permitted the use of an individualized starting dose (ISD) of niraparib based on baseline weight and platelet levels, because of increased risk of thrombocytopenia [17]. The primary endpoint was PFS as assessed by real-time blinded independent central review (BICR) in patients with homologous recombination deficiency (HRD)-positive tumors (defined as a BRCAm and/or genomic instability [genomic instability score ≥ 42]; MyChoice® CDx test [Myriad Genetic Laboratories, Inc., Salt Lake City, UT, US]) and in the overall population. After a median follow-up of 13.8 months, median PFS was significantly longer with maintenance niraparib than with placebo, both in patients whose tumors tested positive for HRD (21.9 vs. 10.4 months; HR 0.43; 95% CI 0.31–0.59; $P < 0.001$) and in the

Table 2 Efficacy results for PARP inhibitors approved in the US (unless specified otherwise) as first-line maintenance monotherapy

Study and study design	Pt population	Treatment (no. of pts)	Key efficacy outcomes
Olaparib			
SOLO1 [16, 20–22, 90] Phase III, randomized, double-blind, multicenter (NCT01844986)	Newly diagnosed, stage III–IV, BRCAm, CR/PR after platinum-based chemotherapy, regardless of clinical risk	Olaparib tablets 300 mg bid[a] ($n = 260$) vs. placebo ($n = 131$)	**Primary PFS analysis (DCO 17 May 2018; median follow-up ≈41 months)** Primary endpoint [16] Median inv-assessed PFS NR vs. 13.8 months (HR 0.30, 95% CI 0.23–0.41, $P < 0.001$) PFS subgroup analyses [20] Higher-risk[b] pts: HR for inv-assessed PFS 0.34 (95% CI 0.24–0.48) Lower-risk[b] pts: HR for inv-assessed PFS 0.33 (95% CI 0.20–0.52) HRQoL outcomes [16, 90] Adjusted mean change in FACT-O TOI score over 24 months: 0.30 vs. 3.30 points (between-group difference −3.00, 95% CI −4.78 to −1.22) Mean QA-PFS 29.75 vs. 17.58 months ($P < 0.0001$) Mean TWiST 33.15 vs. 20.24 months ($P < 0.0001$) **Updated PFS analysis (DCO 5 March 2020; median follow-up ≈5 years)** [21] Median inv-assessed PFS 56.0 vs. 13.8 months (HR 0.33, 95% CI 0.25–0.43) Higher-risk[b] pts: median inv-assessed PFS 40.6 vs. 11.1 months (HR 0.34, 95% CI 0.24–0.49) Lower-risk[b] pts: median inv-assessed PFS NR vs. 21.9 months (HR 0.38, 95% CI 0.25–0.59) **Descriptive OS analysis (DCO 7 March 2022; median follow-up ≈7 years)** [22] Median OS NR vs. 75.2 months (HR 0.55, 95% CI 0.40–0.76, $P = 0.0004$)[c] Median TFST 64.0 vs. 15.1 months (HR 0.37, 95% CI 0.28–0.48)
Niraparib			
PRIMA [17, 23–25, 27, 92] Phase III, randomized, double-blind, multicenter (NCT02655016)	Newly diagnosed, stage III–IV, CR/PR after platinum-based chemotherapy, regardless of biomarker status, higher clinical risk[d]	Niraparib 300 mg od FSD, or 200 or 300 mg od ISD ($n = 487$) vs. placebo ($n = 246$)[e,f]	**Primary PFS analysis (DCO 17 May 2019)** Primary endpoint (median follow-up 13.8 months) [17] HRD-positive: median BICR-assessed PFS 21.9 vs. 10.4 months (HR 0.43, 95% CI 0.31–0.59, $P < 0.001$) Overall population: median BICR-assessed PFS 13.8 vs. 8.2 months (HR 0.62, 95% CI 0.50–0.76, $P < 0.001$) PFS subgroup analyses (exploratory) [17, 23] BRCAm: median BICR-assessed PFS 22.1 vs. 10.9 months (HR 0.40, 95% CI 0.27–0.62, $P < 0.001$) Non-BRCAm: median BICR-assessed PFS 10.9 vs. 7.4 months (HR 0.69, 95% CI 0.54–0.88) HRD-positive without BRCAm: median BICR-assessed PFS 19.6 vs. 8.2 months (HR 0.50, 95% CI 0.31–0.83, $P = 0.006$) HRD-negative: median BICR-assessed PFS 8.1 vs. 5.4 months (HR 0.68, 95% CI 0.49–0.94, $P = 0.02$) PFS in FSD and ISD groups (median follow-up 17.1 and 11.2 months, respectively) [24, 25] BICR-assessed PFS: FSD group HR 0.59 (95% CI 0.46–0.76) and ISD group HR 0.69 (95% CI 0.48–0.98) (P interaction = 0.30) PFS in ISD 200 mg (based on platelet count and bodyweight) group [26] Overall population: BICR-assessed PFS HR 0.68, 95% CI 0.435–1.056, $P = 0.0858$) HRD-positive: BICR-assessed PFS HR 0.35 (95% CI 0.169–0.720, $P = 0.0030$) HRD-negative: BICR-assessed PFS HR 0.75 (95% CI 0.356–1.586, $P = 0.4761$) HRQoL outcomes [92] ITT: mean QA-PFS 14.0 vs. 9.9 months (between-group difference 4.1 [95% CI 2.2−5.8] months) HRD-positive: mean QA-PFS 17.7 vs. 11.2 months (between-group difference 6.5 [95% CI 3.9−8.9] months) ITT: mean Q-TWiST 15.4 vs. 11.8 months (between-group difference 3.5 [95% CI 1.7−5.6] months) HRD-positive: mean Q-TWiST 19.1 vs. 13.3 months (between-group difference 5.9 [95% CI 3.5−8.6] months) **Updated PFS analysis (DCO 17 November 2019)** [25] PFS in FSD and ISD groups (additional 6 months of follow-up) Inv-assessed PFS: FSD group HR 0.62 (95% CI 0.49–0.78) and ISD group HR 0.68 (95% CI 0.49–0.94) **Updated PFS analysis (DCO 17 November 2021; median follow-up 3.5 years)** [27] Overall population: median inv-assessed PFS 13.8 vs. 8.2 months (HR 0.66, 95% CI 0.56–0.79, $P < 0.0001$) HRD-positive: median inv-assessed PFS 24.5 vs. 11.2 months (HR 0.52, 95% CI 0.40–0.68, $P < 0.0001$) HRD-negative: median inv-assessed PFS 8.4 vs. 5.4 months (HR 0.65, 95% CI 0.49–0.87, $P = 0.0038$)
PRIME [28] Phase III, randomized, double-blind, multicenter (NCT0370931)	Newly diagnosed, stage III–IV, CR/PR after platinum-based chemotherapy, regardless of biomarker status and postoperative residual disease status	Niraparib 200 or 300 mg ISD ($n = 255$) vs. placebo ($n = 129$)[e]	**Primary PFS analysis (DCO 30 September 2021)** Primary endpoint (median follow-up 27.5 months) ITT: Median BICR-assessed PFS 24.8 vs. 8.3 months (HR 0.45, 95% CI 0.34–0.60, $P < 0.001$) Preplanned PFS subgroup analyses gBRCAm: BICR-assessed PFS HR 0.40 (95% CI 0.23–0.68) Non-gBRCAm: BICR-assessed PFS HR 0.48 (95% CI 0.34–0.67) HRD-positive: BICR-assessed PFS HR 0.48 (95% CI 0.34–0.68) HRD-negative: PFS HR 0.41 (95% CI 0.25–0.65) Presence of residual disease/missing status: BICR-assessed PFS HR 0.43 (95% CI 0.21–0.87) Absence of residual disease: BICR-assessed PFS HR 0.44 (95% CI 0.32–0.61)

Table 2 (continued)

Study and study design	Pt population	Treatment (no. of pts)	Key efficacy outcomes
Rucaparib[g]			
ATHENA-MONO [29, 119] Phase III, randomized, double-blind, multicenter (NCT03522246)	Newly diagnosed, stage III–IV, CR/PR after platinum-based chemotherapy, regardless of biomarker status and postoperative residual disease status	Rucaparib tablets 600 mg bid[h] ($n = 427$) vs. placebo ($n = 111$)	**Primary PFS analysis (DCO 23 March 2022)** [18] Primary endpoint (median follow-up ≈26 months) HRD-positive: Median inv-assessed PFS 28.7 vs. 11.3 months (HR 0.47, 95% CI 0.31–0.72, $P = 0.0004$) ITT: Median inv-assessed PFS 20.2 vs. 9.2 months (HR 0.52, 95% CI 0.40–0.68, $P < 0.0001$) Preplanned exploratory PFS subgroup analyses BRCAm: Median inv-assessed PFS NR vs. 14.7 months (HR 0.40, 95% CI 0.21–0.75) nonBRCAm/LOH high: Median inv-assessed PFS 20.3 vs. 9.2 months (HR 0.58, 95% CI 0.33–1.01) HRD-negative: Median inv-assessed PFS 12.1 vs. 9.1 months (HR 0.65, 95% CI 0.45–0.95) PFS subgroup analysis by clinical risk (ITT) [29] FIGO stage III: inv-assessed PFS HR 0.64 (95% CI 0.46–0.87) FIGO stage IV: inv-assessed PFS HR 0.40 (95% CI 0.25–0.64) Upfront surgery: inv-assessed PFS HR 0.64 (95% CI 0.43–0.95) Interval surgery: inv-assessed PFS HR 0.44 (95% CI 0.31–0.62) Residual disease: inv-assessed PFS HR 0.44 (95% CI 0.27–0.73) No residual disease: inv-assessed PFS HR 0.59 (95% CI 0.43–0.80)

BICR blinded independent central review, *bid* twice daily, *BRCAm BRCA1* and/or *BRCA2* mutation, *CI* confidence interval, *CR* complete response, *DCO* data cut-off, *FACT-O* Functional Assessment of Cancer Therapy–Ovarian Cancer, *FIGO* International Federation of Gynecology and Obstetrics, *FSD* fixed starting dose, *gBRCAm* germline BRCAm, *HR* hazard ratio, *HRD* homologous recombination deficiency, *HRQoL* health-related quality of life, *inv* investigator, *ISD* individualized starting dose, *ITT* intent-to-treat, *LOH* loss of heterozygosity, *NR* not reached, *od* once daily, *OS* overall survival, *PARP* poly(ADP-ribose) polymerase, *PFS* progression-free survival, *PR* partial response, *pt(s)* patient(s), *QA-PFS* quality-adjusted PFS, *Q-TWiST* quality-adjusted TWiST, *TFST* time to first subsequent therapy, *TOI* Trial Outcome Index, *TWiST* time without significant symptoms of toxicity

[a]Olaparib maintenance therapy capped at 2 years

[b]Higher risk defined as stage IV disease, stage III disease with residual disease following upfront surgery, inoperable stage III disease, or had stage III disease and underwent interval surgery. Lower risk defined as stage III disease without residual disease following upfront surgery

[c]$P < 0.0001$ required to declare statistical significance due to administrative alpha spend (Haybittle-Peto alpha = 0.0001)

[d]Pts with stage III disease and no residual macroscopic disease after upfront surgery were excluded

[e]Niraparib maintenance therapy capped at 3 years

[f]Protocol amended to incorporate an ISD of 200 mg od for pts with a baseline body weight <77 kg, a platelet count of <150,000/mm^3, or both

[g]Rucaparib not approved as first-line maintenance therapy in the US

[h]Rucaparib maintenance therapy capped at 2 years

overall population (13.8 vs, 8.2 months; HR 0.62; 95% CI 0.50–0.76; $P < 0.001$) (Table 2) [17]. In prespecified exploratory analyses, a PFS benefit was seen with maintenance niraparib versus placebo in patients with a BRCAm, as well as patients without a BRCAm, patients whose tumors tested positive for HRD without BRCAm, and patients whose tumors tested negative for HRD (Table 2) [17, 23]. At the time of the primary analysis, no difference was observed between the fixed starting dose (HR 0.59; 95% CI 0.46–0.76) and ISD (HR 0.69; 95% CI 0.48–0.98) groups in terms of PFS benefit with niraparib versus placebo [24] (Table 2; an updated analysis of investigator-assessed PFS [25] is also shown in Table 2). However, in a non-analytical analysis reported in the European Medicines Agency (EMA) assessment report in patients receiving an ISD of niraparib 200 mg based on bodyweight and platelet count, while a significant PFS benefit was observed with niraparib in patients whose tumors tested positive for HRD, there was no significant difference between niraparib and placebo in the overall population or in patients whose tumors tested negative for HRD (Table 2) [26]. OS data were immature at the time of the primary analysis [17].

An updated analysis showed that the PFS benefit was maintained after a median 3.5 years of follow-up [27]. HRs for investigator-assessed PFS with niraparib versus placebo were 0.66 (95% CI 0.56–0.79) in the intent-to-treat (ITT) population, 0.52 (95% CI 0.40–0.68) in patients whose tumors tested positive for HRD, and 0.65 (95% CI 0.49–0.87) in patients whose tumors tested negative for HRD (Table 2).

Additionally, the Phase III PRIME study evaluated niraparib (ISD) versus placebo as first-line maintenance therapy in 384 Chinese patients with newly diagnosed advanced OC. Treatment continued for up to 3 years or until disease progression or unacceptable toxicity. Like PRIMA, PRIME enrolled patients regardless of biomarker status, but included patients with or without residual disease after primary debulking surgery, and the assay used to test tumor HRD

status differed between PRIME (BGI assay; BGI Genomics, Shenzhen, China) and PRIMA (MyChoice® CDx). After a median follow-up of 27.5 months, a statistically significant PFS benefit was observed with the niraparib ISD regimen versus placebo in the ITT population (HR 0.45; 95% CI 0.34–0.60; $P < 0.001$) and across prespecified subgroups, including groups based on biomarker or postoperative residual disease status (Table 2) [28].

ATHENA-MONO randomized 538 patients to receive maintenance rucaparib or placebo for up to 2 years or until disease progression, death, or unacceptable toxicity (Table 2) [18]. Patients were eligible regardless of biomarker status and were stratified according to HRD status using the FoundationOne CDx™ next-generation sequencing assay (Foundation Medicine, Inc., Cambridge, MA, US). The primary endpoint was investigator-assessed PFS in patients with HRD-positive tumors (defined as a BRCAm and/or a high genomic loss of heterozygosity [LOH] score [≥ 16%]) and in the overall population. After a median follow-up of ≈26 months, median PFS was significantly longer with maintenance rucaparib than with placebo both in patients whose tumors tested positive for HRD (28.7 vs. 11.3 months; HR 0.47; 95% CI 0.31–0.72; $P = 0.0004$) and in the overall population (20.2 vs. 9.2 months; HR 0.52; 95% CI 0.40–0.68; $P < 0.0001$) (Table 2). In prespecified exploratory analyses, a PFS benefit was seen with maintenance rucaparib versus placebo in patients with a BRCAm, patients with non-BRCAm/LOH high tumors, and patients whose tumors tested negative for HRD (Table 2) [18]. PFS benefit was seen with rucaparib over placebo regardless of clinical risk (Table 2) [29]. OS data were immature at the time of the primary analysis [18].

Taken together, findings from SOLO1 [16], PRIMA [17], and ATHENA-MONO [18] indicate that PARPi maintenance therapy provides the greatest benefit in the first-line setting in patients with a BRCAm [16–18] (prespecified exploratory analyses in PRIMA [17] and ATHENA-MONO [18]) or whose tumors test positive for HRD [17, 18]. A PFS benefit was also seen in the overall PRIMA and ATHENA-MONO populations regardless of biomarker status. The limited benefit seen with niraparib or rucaparib in patients whose tumors tested negative for HRD highlights the importance of testing for HRD status. Benefit in SOLO1 and ATHENA-MONO was seen regardless of clinical risk. Longer-term follow-up in SOLO1 indicated an OS benefit with olaparib versus placebo and that maintenance olaparib provides long-term remission in some patients; factors predicting which patients will experience long-term benefit from PARPi maintenance therapy remain to be identified. Maintenance therapy with a PARPi should be considered in all patients with newly diagnosed advanced OC regardless of their clinical risk. Data strongly support the first-line use of maintenance PARPi therapy in patients with a BRCAm or whose tumors test positive for HRD, with maintenance therapy with bevacizumab alone remaining an option for some patients, including some patients whose tumors test negative for HRD, a population with high unmet need [30].

3.2 First-Line Maintenance Combination Therapy

Results of the Phase III PAOLA-1 study led to the US approval of olaparib in combination with bevacizumab for the maintenance treatment of patients with advanced OC who are in response to first-line platinum-based chemotherapy and whose tumors tested positive for HRD [31]. Results of the Phase II OVARIO trial evaluating niraparib plus bevacizumab as first-line maintenance combination therapy in patients with newly diagnosed advanced OC are also included for completeness [32].

PAOLA-1 randomized 806 patients with newly diagnosed, stage III–IV, high-grade serous or endometrioid OC, primary peritoneal cancer, and/or fallopian tube cancer who had no evidence of disease or a clinical CR or PR after platinum-based chemotherapy plus bevacizumab. Patients were eligible irrespective of biomarker status or clinical risk. Following randomization, patients received maintenance olaparib tablets or placebo for up to 24 months or until disease progression or unacceptable toxicity; all patients received bevacizumab for up to 15 months in total (Table 3).

After a median follow-up of 22.9 months, the primary endpoint of investigator-assessed PFS was significantly longer with olaparib plus bevacizumab than with placebo plus bevacizumab (median 22.1 vs. 16.6 months; HR 0.59; 95% CI 0.49–0.72; $P < 0.001$) [31]. Results of subgroup analyses showed a substantial PFS benefit with maintenance olaparib plus bevacizumab versus bevacizumab alone in patients with a tumor BRCAm (tBRCAm) (HR 0.31; 95% CI 0.20–0.47) and in patients whose tumors tested positive for HRD (HR 0.33; 95% CI 0.25–0.45; (MyChoice® CDx test) (Table 3). Patients whose tumors tested negative for HRD did not show a PFS benefit with olaparib plus bevacizumab maintenance versus bevacizumab alone (HR 1.00; 95% CI 0.75–1.35) [31]. An exploratory analysis showed that PFS was substantially improved with olaparib plus bevacizumab versus bevacizumab alone in both higher-risk patients (FIGO stage III with upfront surgery and residual disease or neoadjuvant chemotherapy, or FIGO stage IV; HR 0.60; 95% CI 0.49–0.74) and lower-risk patients (FIGO stage III with upfront surgery and no residual disease; HR 0.46; 95% CI 0.30–0.72), with the greatest PFS benefit observed in the tBRCAm and HRD-positive subgroups [33] (Table 3). Results of the main time to second progression or death (PFS2) analysis are also shown in Table 3 [34].

Final OS analysis after approximately 5 years of follow-up showed a median OS of 56.5 months with olaparib plus bevacizumab versus 51.6 months with placebo

plus bevacizumab in the ITT population (HR 0.92; 95% CI 0.76–1.12; $P=0.4118$) (Table 3) [35]. Clinically meaningful OS improvements were seen with maintenance olaparib plus bevacizumab versus bevacizumab alone in patients with a tBRCAm (HR 0.60; 95% CI 0.39–0.93; 73% of patients in the olaparib plus bevacizumab group vs. 54% of patients in the placebo plus bevacizumab group were alive at 5 years) and in patients whose tumors tested positive for HRD (HR 0.62; 95% CI 0.45–0.85; 66% of patients in the olaparib plus bevacizumab group versus 48% of patients in the placebo plus bevacizumab group were alive at 5 years) (Table 3). No survival benefit was seen in patients whose tumors tested negative for HRD (HR 1.19; 95% CI 0.88–1.63) [35].

OVARIO enrolled 105 patients with newly diagnosed, stage III–IV, high-grade serous or endometrioid OC, primary peritoneal cancer and/or fallopian tube cancer who had no

Table 3 Efficacy results for PARP inhibitors approved in the US (unless specified otherwise) as first-line maintenance combination therapy

Study and phase	Pt population	Treatment (no. of pts)	Key efficacy outcomes
Olaparib plus bev			
PAOLA-1 [31, 33–35, 93] Phase III, randomized, double-blind, multicenter (NCT02477644)	Newly diagnosed, stage III–IV, NED/CR/PR after platinum-based chemotherapy plus bev, regardless of biomarker status or clinical risk	Olaparib tablets 300 mg bid[a] + bev[b] ($n=537$) vs. placebo + bev[b] ($n=269$)	**Primary PFS analysis (DCO 22 March 2019; median follow-up 22.9 months)** Primary endpoint [31] Median inv-assessed PFS 22.1 vs. 16.6 months (HR 0.59; 95% CI 0.49–0.72; $P<0.001$) PFS subgroup analyses [31, 33] Tumor BRCAm: median inv-assessed PFS 37.2 vs. 21.7 months (HR 0.31; 95% CI 0.20–0.47) HRD-positive: median PFS inv-assessed 37.2 vs. 17.7 months (HR 0.33; 95% CI 0.25–0.45) HRD-negative: median inv-assessed PFS 16.6 vs. 16.2 months (HR 1.00; 95% CI 0.75–1.35) *Higher-risk pts*[c] ITT: median inv-assessed PFS 20.3 vs. 14.7 months (HR 0.60; 95% CI 0.49–0.74) Tumor BRCAm: median inv-assessed PFS 36.0 vs. 19.4 months (HR 0.37; 95% CI 0.23–0.59) HRD-positive: median inv-assessed PFS 36.0 vs. 16.0 months (HR 0.39; 95% CI 0.28–0.54) *Lower-risk pts*[c] ITT: median inv-assessed PFS 39.3 vs. 22.9 months (HR 0.46; 95% CI 0.30–0.72) Tumor BRCAm: median inv-assessed PFS NR vs. 22.2 months (HR 0.11; 95% CI 0.03–0.31) HRD-positive: median inv-assessed PFS NR vs. 22.1 months (HR 0.15; 95% CI 0.07–0.30) HRQoL outcomes [31, 93] Adjusted mean change in GHS-QOL score: −1.33 vs. −2.89 points (between-group difference 1.56; 95% CI −0.42 to 3.55) ITT: Median TWiST 14.1 vs. 7.7 months HRD-positive: Median TWiST 24.1 vs. 7.4 months **Final PFS2 analysis (DCO 22 March 2020; median follow-up ≈36 months)** [34] ITT: median PFS2 36.5 vs. 32.6 months (HR 0.78; 95% CI 0.64–0.95) Tumor BRCAm: median PFS2 NR vs. 45.0 months (HR 0.53; 95% CI 0.34–0.83) HRD-positive: median PFS 50.3 vs. 35.3 months (HR 0.56; 95% CI 0.41–0.77) **Final OS analysis (median follow-up ≈62 months)** [35] ITT: median OS 56.5 vs. 51.6 months (HR 0.92; 95% CI 0.76–1.12; $P=0.4118$) Tumor BRCAm: OS HR 0.60 (95% CI 0.39–0.93) HRD-positive: OS HR 0.62 (95% CI 0.45–0.85) HRD-negative: OS HR 1.19 (95% CI 0.88–1.63)

Table 3 (continued)

Study and phase	Pt population	Treatment (no. of pts)	Key efficacy outcomes
Niraparib plus bev[d]			
OVARIO [32] Phase II, single-arm, open-label, multicenter (NCT03326193)	Newly diagnosed, stage III–IV, NED/CR/PR after platinum-based chemotherapy plus bev, irrespective of biomarker status (high-grade serous or endometrioid) or gBRCAm (non-mucinous epithelial)	Niraparib 200 or 300 mg ISD[e] + bev[b] ($n = 105$)	**Primary analysis (DCO 24 December 2020; median follow-up 23.9 months)** [32] Primary endpoint ITT: 18-month inv-assessed PFS rate 62% HRD-positive: 18-month inv-assessed PFS rate 76% HRD-negative: 18-month inv-assessed PFS rate 47% HRD status unknown: 18-month inv-assessed PFS rate 56% BRCAm: 18-month inv-assessed PFS rate 76% **Updated analysis (DCO 16 June 2021; median follow-up 28.7 months)** [32] ITT: median inv-assessed PFS 19.6 months (95% CI 16.5–25.1) HRD-positive: median inv-assessed PFS 28.3 months (95% CI 19.9–NC) HRD-negative: median inv-assessed PFS 14.2 months (95% CI 8.6–16.8) HRD unknown: median inv-assessed PFS 12.1 months (95% CI 8.0–NC) BRCAm: median inv-assessed PFS NR

bev bevacizumab, *bid* twice daily, *BRCAm BRCA1* and/or *BRCA2* mutation, *CI* confidence interval, *CR* complete response, *DCO* data cut-off, *gBRCAm* germline BRCAm, *GHS-QOL* global health status quality of life, *HR* hazard ratio, *HRD* homologous recombination deficiency, *HRQoL* health-related quality of life, *inv* investigator, *ISD* individualized starting dose, *ITT* intent-to-treat, *NC* not calculable, *NED* no evidence of disease, *NR* not reached, *OS* overall survival, *PARP* poly(ADP-ribose) polymerase, *PFS* progression-free survival, *PFS2* time to second progression or death, *PR* partial response, *pt(s)* patient(s), *q3w* every 3 weeks, *TOI* Trial Outcome Index, *TWiST* time without significant symptoms of toxicity

[a]Olaparib maintenance therapy capped at 2 years

[b]15 mg/kg q3w for up to 15 months in total

[c]Higher risk defined as stage IV disease, stage III disease with residual disease following upfront surgery, inoperable stage III disease, or had stage III disease and underwent interval surgery. Lower risk defined as stage III disease without residual disease following upfront surgery

[d]Niraparib plus bev not approved as first-line maintenance therapy in the US

[e]Niraparib maintenance therapy capped at 3 years

evidence of disease or a clinical CR or PR after platinum-based chemotherapy plus bevacizumab [32]. Patients with high-grade serous or endometrioid histology were enrolled irrespective of biomarker status; additionally, other epithelial non-mucinous OC patients were allowed to enroll if they had a germline BRCAm (gBRCAm). With maintenance niraparib plus bevacizumab, the 18-month PFS rate (primary endpoint) in the ITT population was 62%, with a median PFS of 19.6 months (95% CI 16.5–25.1) (Table 3). Subgroup analysis found that 18-month PFS rates were highest (and median PFS was longest) in patients whose tumors tested positive for HRD or who had a BRCAm (Table 3) [32].

Based on the results of PAOLA-1, maintenance combination therapy with olaparib plus bevacizumab should be considered in patients with newly diagnosed advanced OC whose tumors test positive for HRD, regardless of their clinical risk. Interestingly, the greatest impact may be in patients who have historically been defined to have "lower-risk" advanced stage disease (stage III, upfront surgery with no residual disease).

3.3 Second-Line or Later Maintenance Monotherapy

Olaparib, niraparib, and rucaparib are approved in the US as second-line or later maintenance monotherapy in patients in response to platinum-based chemotherapy. The approval of olaparib was based on the results of the Phase II Study 19 [36] and Phase III SOLO2 [37] studies and the approvals of niraparib and rucaparib were based on the Phase III NOVA [38] and ARIEL3 [39] studies, respectively. Subsequent studies included two olaparib studies, Phase IIIb OPINION [40] and Phase IV ORZORA [41], as well as the Phase III NORA study of niraparib [42]. All studies included patients with PSR OC (PSROC) who were in response to platinum-based chemotherapy and had received two or more prior platinum-based regimens (Table 4).

Table 4 Efficacy results for PARP inhibitors approved in the US as second-line or later maintenance monotherapy

Study and phase	Pt population	Treatment (no. of pts)	Key efficacy outcomes
Olaparib			
Study 19 [36, 43, 44] Phase II, randomized, double-blind, multicenter (NCT00753545)	PSROC, two or more prior platinum-based chemotherapy regimens, regardless of BRCAm status	Olaparib 400 mg bid ($n = 136$) vs. placebo ($n = 129$)	**Primary PFS analysis (DCO 30 June 2010; median follow-up 5.6 months)** [43] Primary endpoint [36] Median inv-assessed PFS 8.4 vs. 4.8 months (HR 0.35; 95% CI 0.25–0.49; $P < 0.001$) Preplanned, retrospective analysis by BRCAm status [43] BRCAm: median inv-assessed PFS 11.2 vs. 4.3 months (HR 0.18; 95% CI 0.10–0.31); $P < 0.0001$) Non-BRCAm: median inv-assessed PFS 7.4 vs. 5.5 months (HR 0.54; 95% CI 0.34–0.85; $P = 0.0075$) **Final OS analysis (DCO 9 May 2016; median follow-up 78 months)** [44] Overall: median OS 29.8 vs. 27.8 months (HR 0.73; 95% CI 0.55–0.95; $P = 0.02138$)[a] BRCAm: median OS 34.9 vs. 30.2 months (HR 0.62; 95% CI 0.42–0.93; $P = 0.02140$) Non-BRCAm: median OS 24.5 vs. 26.6 months (HR 0.84; 95% CI 0.57–1.25; $P = 0.3975$)
SOLO2 [37, 46, 94] Phase III, randomized, double-blind, multicenter (NCT01874353)	PSROC, BRCAm, CR/PR after two or more prior platinum-based chemotherapy regimens	Olaparib tablets 300 mg bid ($n = 196$) vs. placebo ($n = 99$)	**Primary PFS analysis (DCO 19 September 2016)** Primary endpoint (median follow-up ≈22 months) [37] Median inv-assessed PFS 19.1 vs. 5.5 months (HR 0.30; 95% CI 0.22–0.41; $P < 0.0001$) HRQoL outcomes [37, 94] Adjusted mean change in FACT-O TOI score over 12 months: −2.90 vs. −2.87 points (between-group difference −0.03; 95% CI −2.19 to 2.13) Mean QA-PFS 13.96 vs. 7.28 months ($P < 0.0001$) Mean TWiST 15.03 vs. 7.70 months ($P < 0.0001$) **Final OS analysis (DCO 3 February 2020; median follow-up ≈65 months)** [46] Median OS 51.7 vs. 38.8 months (HR 0.74; 95% CI 0.54–1.00; $P = 0.054$) Preplanned exploratory OS analysis adjusted for subsequent PARP therapy in the placebo group Median OS 51.7 vs. 35.4 months (HR 0.56; 95% CI 0.35–0.97)
OPINION [40, 47] Phase IIIb, single-arm, open-label, multicenter (NCT03402841)	PSROC, non-gBRCAm, NED/CR/PR after two or more prior platinum-based chemotherapy regimens	Olaparib tablets 300 mg bid ($n = 279$)	**Primary PFS analysis (DCO 2 October 2020; median follow-up 19.2 months)** [40] Primary endpoint ITT: median inv-assessed PFS 9.2 months (95% CI 7.6–10.9) Preplanned subgroup analyses by sBRCAm and HRD status sBRCAm: median inv-assessed PFS 16.4[b] months (95% CI 12.8–NC) HRD-positive including sBRCAm: median inv-assessed PFS 11.1 months (95% CI 9.2–14.6) HRD-positive excluding sBRCAm pts: median inv-assessed PFS 9.7 months (95% CI 8.1–13.6) HRD-negative: median inv-assessed PFS 7.3 months (95% CI 5.5–9.0) **Final OS analysis (DCO 17 September 2021; median follow-up 33.1 months)** [47] ITT: median OS 32.7 months (95% CI 29.5–35.3) HRD-positive including sBRCAm: 30-month OS rate 66.7% (95% CI 57.5–74.3) HRD-positive excluding sBRCAm: 30-month OS rate 65.6% (95% CI 55.0–74.3) sBRCAm: 30-month OS rate 70.4% (95% CI 49.4–83.9) HRD-negative: 30-month OS rate 38.9% (95% CI 29.9–47.8) Partially platinum sensitive: 30-month OS rate 40.2% (95% CI 29.9–50.3) Platinum sensitive: 30-month OS rate 62.6% (95% CI 55.1–69.2)
ORZORA [41, 48] Phase IV single-arm, open-label, multicenter (NCT02476968)	PSROC, BRCAm or non-BRCA HRRm (exploratory cohort), CR/PR after two or more prior platinum-based chemotherapy regimens	Olaparib capsules 400 mg bid ($n = 181$)	**Primary analysis (DCO 17 April 2020; median follow-up 22.3 months)** [41] Primary endpoint BRCAm: median inv-assessed PFS 18.0 months (95% CI 14.3–22.1) sBRCAm: median inv-assessed PFS 16.6 months (95% CI 12.4–22.2) gBRCAm: median inv-assessed PFS 19.3 months (95% CI 14.3–27.6) Non-BRCA HRRm: median inv-assessed PFS 16.4 months (95% CI 10.9–19.3) **Final OS analysis (DCO 25 June 2021; median follow-up 42.6 months in BRCAm and 39.3 months in non-BRCA HRRm)** [48] BRCAm: median OS 46.8 months (95% CI 37.9–54.4) sBRCAm: median OS 43.2 months (95% CI 31.7–NC) gBRCAm: median OS 47.4 months (95% CI 37.9–NC) Non-BRCA HRRm: median OS 44.9 months (95% CI 28.9–NC)

Table 4 (continued)

Study and phase	Pt population	Treatment (no. of pts)	Key efficacy outcomes
Niraparib			
NOVA [38, 49–51, 95, 97] Phase III, randomized, double-blind, multi-center (NCT01847274)	PSROC, gBRCAm ($n = 203$) or non-gBRCAm ($n = 350$) CR/PR after two or more prior platinum-based chemotherapy regimens	Niraparib 300 mg od ($n = 372$) vs. placebo ($n = 181$)	**Primary PFS analysis (database lock 20 June 2016; median follow-up 16.9 months)** Primary endpoint [38] gBRCAm: median BICR-assessed PFS 21.0 vs. 5.5. months (HR 0.27; 95% CI 0.17–0.41; $P < 0.001$) Non-gBRCAm: median BICR-assessed PFS 9.3 vs. 3.9 months; HR 0.45; 95% CI 0.34–0.61; $P < 0.001$) Non-gBRCAm, HRD-positive: median BICR-assessed PFS 12.9 vs. 3.8 months (HR 0.38; 95% CI 0.24–0.59) Preplanned exploratory subgroup analyses [38] HRD-positive with sBRCAm: median BICR-assessed PFS 20.9 vs. 11.0 months (HR 0.27; 95% CI 0.08–0.90; $P = 0.02$) HRD-positive, non-BRCAm: median BICR-assessed PFS 9.3 vs. 3.7 months (HR 0.38; 95% CI 0.23–0.63; $P < 0.001$) HRD-negative: median BICR-assessed PFS 6.9 vs. 3.8 months (HR 0.58; 95% CI 0.36–0.92; $P = 0.02$) Retrospective exploratory subgroup analyses [49] sBRCAm: HR for PFS 0.27 Non-BRCAm: HR for PFS 0.47 Non-BRCA HRRm: HR for PFS 0.31 Non-HRRm, non-BRCAm: HR for PFS 0.49 HRQoL outcomes [95, 97] gBRCAm: mean EQ-5D-5L score: 0.838 vs. 0.834 Non-gBRCAm: mean EQ-5D-5L score: 0.833 vs. 0.815 gBRCAm: mean TWiST: 3.83 vs. 0.88 years (between-group difference 2.95 years) Non-gBRCAm: mean TWiST: 2.46 vs. 1.12 years (between-group difference 1.34 years) **OS analysis (DCO 1 October 2020; average follow-up 5.5 years)** [50, 51] gBRCAm: median OS 43.6 vs. 41.6 months (HR 0.93; 95% CI 0.63–1.36) Non-gBRCAm: median OS 31.1 vs. 36.5 months (HR 1.10; 95% CI 0.83–1.46) Non-gBRCAm, HRD-positive: median OS 37.3 vs. 41.4 months (HR 1.32; 95% CI 0.84–2.06) **Updated OS analysis (DCO 31 March 2021)** [52] gBRCAm: median OS 40.9 vs. 38.1 months (HR 0.85; 95% CI 0.61–1.20) Non-gBRCAm: median OS 31.0 vs. 34.8 months (HR 1.06; 95% CI 0.81–1.37) Non-gBRCAm, HRD-positive: median OS 35.6 vs. 41.4 months (HR 1.29; 95% CI 0.85–1.95)
NORA [42] Phase III, randomized, double-blind, multi-center (NCT03705156)	PSROC, CR/PR after two or more prior platinum-based chemotherapy regimens	Niraparib 300 mg od FSD, or 200 or 300 mg od ISD ($n = 177$) vs. placebo ($n = 88$)[b]	**Primary PFS analysis (DCO 1 February 2020; median follow-up 15.8 months)** [42] Primary endpoint ITT: median BICR-assessed PFS 18.3 vs. 5.4 months (HR 0.32; 95% CI 0.23–0.45; $P < 0.0001$) gBRCAm: median BICR-assessed PFS NR vs. 5.5 months (HR 0.22; 95% CI 0.12–0.39) Non-gBRCAm: median BICR-assessed PFS 11.1 vs. 3.9 months (HR 0.40; 95% CI 0.26–0.61) Subgroup analysis Pts receiving ISD: median BICR-assessed PFS 18.3 vs. 5.4 months (HR 0.30; 95% CI 0.21–0.43) OS analysis Median OS: NR vs. NR (HR 0.64; 95% CI 0.29–1.42; $P = 0.0267$)

Table 4 (continued)

Study and phase	Pt population	Treatment (no. of pts)	Key efficacy outcomes
Rucaparib			
ARIEL3 [39, 53, 54, 96] Phase III, randomized, double-blind, multicenter (NCT01968213)	PSROC, CR/PR after two or more prior platinum-based chemotherapy regimens	Rucaparib 600 mg bid ($n = 375$) vs. placebo ($n = 189$)	**Primary PFS analysis (DCO 15 April 2017)** Primary endpoint [39] BRCAm: median inv-assessed PFS 16.6 vs. 5.4 months (HR 0.23; 95% CI 0.16–0.34; $P < 0.0001$) HRD-positive: median inv-assessed PFS 13.6 vs. 5.4 months (HR 0.32; 95% CI 0.24–0.42; $P < 0.0001$) ITT: median inv-assessed PFS 10.8 vs. 5.4 months (HR 0.36; 95% CI 0.30–0.45; $P < 0.0001$) HRQoL outcomes [39, 96] BRCAm: time to worsening in FOSI-18 DRS-P subscale score: HR 1.24 (95% CI 0.82–1.86; $P = 0.30$) ITT: mean QA-PFS: 12.02 vs. 5.74 months (difference 6.28 [95% CI 4.85–7.47] months) BRCAm: mean QA-PFS: 15.28 vs. 5.92 months (difference 9.37 [95% CI 6.65–11.85] months) HRD-positive: mean QA-PFS: 13.83 vs. 5.90 months (difference 7.93 [95% CI 5.93–9.53] months) ITT: mean Q-TWiST: 13.32 vs. 6.44 months (difference 6.88 [95% CI 5.71–8.23] months) BRCAm: mean Q-TWiST: 16.42 vs. 6.70 months (difference 9.73 [95% CI 7.10–11.94] months) HRD-positive: mean Q-TWiST: 14.91 vs. 6.80 months (difference 8.11 [95% CI 6.36–9.49] months) **Exploratory PFS analysis (31 December 2019; median follow-up 51.4 months)** [53] Proportion of pts with exceptional PFS benefit:[c] 21.1% vs. 2.1% Median PFS in pts with exceptional PFS benefit:[c] NR vs. 37.1 months **Final OS analysis (DCO 4 April 2022; median follow-up 6.4 years)** [54] BRCAm: median OS 45.9 vs. 47.8 months (HR 0.83; 95% CI 0.58–1.19; $P = 0.32$) HRD-positive: median OS 40.5 vs. 47.8 months (HR 1.01; 95% CI 0.77–1.32; $P = 0.97$) ITT: median OS 36.0 vs. 43.2 months (HR 1.00; 95% CI 0.81–1.22; $P = 0.96$)

BICR blinded independent central review, *bid* twice daily, *BRCAm BRCA1* and/or *BRCA2* mutation, *CI* confidence interval, *CR* complete response, *DCO* data cut-off, *EQ-5D-5L* 5-level EQ-5D, *FACT-O* Functional Assessment of Cancer Therapy–Ovarian Cancer, *FOSI-18 DRS-P* Functional Assessment of Cancer Therapy–Ovarian Symptom Index-18 disease-related symptoms–physical, *FSD* fixed starting dose, *gBRCAm* germline BRCAm, *HR* hazard ratio, *HRD* homologous recombination deficiency, *HRQoL* health-related quality of life, *HRRm* homologous recombination repair mutation, *inv* investigator, *ISD* individualized starting dose, *ITT* intent-to-treat, *NC* not calculable, *NED* no evidence of disease, *NR* not reached, *OC* ovarian cancer, *od* once daily, *OS* overall survival, *PARP* poly(ADP-ribose) polymerase, *PFS* progression-free survival, *PR* partial response, *PSROC* platinum-sensitive relapsed ovarian cancer, *pt(s)* patient(s), *QA-PFS* quality-adjusted PFS, *Q-TWiST* quality-adjusted TWiST, *sBRCAm* somatic BRCAm, *TOI* Trial Outcome Index, *TWiST* time without significant symptoms of toxicity

[a]Nominal $P = 0.02138$; did not meet the threshold defined for statistical significance ($P < 0.0095$)

[b]Protocol amended to incorporate an ISD of 200 mg od for patients with a baseline body weight <77 kg, a platelet count of <150,000/mm^3, or both

[c]Exceptional benefit was defined as double the median PFS in the ITT population

In Study 19, 265 patients were randomized to receive maintenance olaparib capsules or placebo until disease progression (Table 4) [36]. After a median follow-up of 5.6 months, the primary endpoint of PFS in the overall population was significantly longer with maintenance olaparib than with placebo (median PFS 8.4 vs. 4.8 months; HR 0.35; 95% CI 0.25–0.49; $P < 0.001$; Table 4) [36, 43]. A retrospective, preplanned, subgroup analysis demonstrated a PFS benefit with maintenance olaparib versus placebo in both patients with a BRCAm (HR 0.18; 95% CI 0.10–0.31) and patients without a BRCAm (HR 0.54; 95% CI 0.34–0.85), with a greater PFS benefit seen in patients with a BRCAm (Table 4) [43]. At the time of final analysis (79% data maturity), although the predefined threshold ($P < 0.0095$) for statistical significance was not met, an apparent OS advantage was observed with olaparib versus placebo in the overall population (HR 0.73; 95% CI 0.55−0.95; nominal $P = 0.02138$) with the greatest benefit seen in patients with a BRCAm (HR 0.62; 95% CI 0.42–0.93; nominal $P = 0.02140$) and an HR favoring olaparib also seen in patients without a BRCAm (HR 0.84; 95% CI 0.57–1.25) [44]. Crossover of placebo patients (12% of ITT placebo patients and 23% of BRCAm placebo patients crossed over) to a PARPi following disease progression may have confounded the OS results [45]. Fifteen patients (11%) were taking olaparib for >6 years, suggesting a durable response [44].

In SOLO2, 295 patients with a gBRCAm were randomized to receive maintenance olaparib tablets or placebo until disease progression (Table 4) [37]. After a median follow-up of ≈22 months, the primary endpoint of investigator-assessed PFS was significantly longer with olaparib than with placebo (median 19.1 vs. 5.5 months; HR 0.30; 95% CI 0.22–0.41; $P < 0.0001$). PFS rates at 24 months were 43% and 15%, respectively [37]. Maintenance olaparib provided a clinically meaningful OS benefit of 12.9 months over placebo at final OS analysis. After a median-follow-up of ≈65 months, median OS was 51.7 months with olaparib compared with 38.8 months with placebo (HR 0.74; 95% CI 0.54–1.00; $P = 0.054$), unadjusted for the 38% of patients in the placebo group who received subsequent PARPi therapy [46]. The OS benefit was also apparent in a prespecified exploratory OS analysis adjusted for subsequent PARP therapy in the placebo group (HR 0.56; 95% CI 0.35–0.97) (Table 4). Cumulative exposure of ≥5 years was seen in 22% of patients in the olaparib group (vs. 9% of patients in the placebo group), indicating a durable response to maintenance olaparib in this subgroup of patients [46].

Subsequent studies support the use of maintenance olaparib in patients without a gBRCAm (OPINION [40, 47]; Table 4) and in patients with a tBRCAm of somatic and/or germline origin as well as in an exploratory non-BRCA homologous recombination repair (HRR) mutation (HRRm) cohort (ORZORA [41, 48]; Table 4).

In the NOVA study, 553 patients with ($n = 203$) and without ($n = 350$) a gBRCAm were randomized to receive maintenance niraparib or placebo until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up (Table 4) [38]. After a median follow-up of 16.9 months, PFS (primary endpoint) was significantly longer with maintenance niraparib than with placebo in the three efficacy populations, patients with a gBRCAm (median 21.0 vs. 5.5. months; HR 0.27; 95% CI 0.17–0.41; $P < 0.001$), patients without a gBRCAm (median 9.3 vs. 3.9 months; HR 0.45; 95% CI 0.34–0.61; $P < 0.001$), and patients whose tumors tested HRD-positive without a gBRCAm (median 12.9 vs. 3.8 months; HR 0.38; 95% CI 0.24–0.59; $P < 0.001$) [38]. Preplanned exploratory analyses found consistent PFS benefit with niraparib versus placebo in patients whose tumors tested HRD-positive with a somatic BRCAm (sBRCAm) (HR 0.27; 95% CI 0.08–0.90), patients whose tumors tested HRD-positive without a BRCAm (HR 0.38; 95% CI 0.23–0.63), and patients whose tumors tested HRD-negative (HR 0.58; 95% CI 0.36–0.92) (Table 4) [38]. Additionally, a retrospective exploratory analysis showed that in addition to patients with BRCAm and other HRRm, clinical benefit with niraparib was also observed in patients whose tumors tested HRD-negative without HRRm (Table 4) [49]. After a median follow-up of 5.5 years (data cut-off [DCO] 1 October 2020), median OS with maintenance niraparib versus placebo was 43.6 versus 41.6 months in the gBRCAm cohort (HR 0.93; 95% CI 0.63–1.36), 31.1 versus 36.5 months in the non-gBRCAm cohort (HR 1.10; 95% CI 0.83–1.46), and 37.3 versus 41.4 months in the non-gBRCAm, HRD-positive cohort (HR 1.32; 95% CI 0.84–2.06) (Table 4) [50, 51]. Although NOVA was not powered to evaluate between-group differences in OS, these results bring into question whether there could be an OS detriment to patients in the non-gBRCAm and the non-gBRCAm, HRD-positive subgroups who received maintenance niraparib compared with placebo [50, 51]. It should be noted that results may be confounded by crossover (46% of placebo patients in the gBRCAm cohort and 13% in the non-gBRCAm cohort received subsequent PARPi therapy) and missing data (OS data missing in 14% of patients in both the gBRCAm and non-gBRCAm cohorts) [50, 51]. In an updated OS analysis (DCO 31 March 2021), which accounted for missing survival data, median OS with maintenance niraparib versus placebo was 40.9 versus 38.1 months in the gBRCAm cohort (HR 0.85; 95% CI 0.61–1.20), 31.0 versus 34.8 months in the non-gBRCAm cohort (HR 1.06; 95% CI 0.81–1.37), and 35.6 versus 41.4 months in the non-gBRCAm, HRD-positive cohort (HR 1.29; 95% CI 0.85–1.95) (Table 4) [52]. Based on these results, maintenance therapy with niraparib has

Table 5 Efficacy results for PARP inhibitors in later-line treatment

Study and phase	Pt population	Treatment (no. of pts)	Key efficacy outcomes
Olaparib			
Study 42 [62] Phase II, non-randomized, multicenter (NCT00494442)	gBRCAm advanced OC with measurable disease and three or more prior lines of chemotherapy	Olaparib capsules 400 mg bid ($n = 137$)	Overall ORR 34% (95% CI 26–42) PR 32%; CR: 2%; SD: 23% Median DOR 7.9 (95% CI 5.6–9.6) months Platinum sensitive ORR 46% (95% CI 30–63) Median DOR 8.2 (95% CI 5.6–13.5) months Platinum resistant ORR 30% (95% CI 20–41) Median DOR 8.0 (95% CI 4.8–14.8) months Platinum refractory ORR 14% (95% CI 2–43) Median DOR 6.4 (95% CI 5.4–7.4) months
SOLO3 [63–65] Phase III, randomized, open-label, multi-center (NCT00628251)	PSROC, gBRCAm, two or more prior platinum-based chemotherapy regimens	Olaparib tablets 300 mg bid ($n = 178$) vs. physician's choice of single-agent non-platinum chemotherapy (PLD, paclitaxel, gemcitabine or topotecan; $n = 88$)	**Primary analysis[a] (10 October 2018)** Primary endpoint (primary analysis population) [63] Median BICR-assessed ORR 72.2% vs. 51.4% (OR 2.53; 95% CI 1.40–4.58; $P = 0.002$) PR: 62.9% vs. 48.6% CR: 9.3% vs. 2.8% SD: 16.6% vs. 26.4% PFS analysis (ITT; median follow-up 13.8 vs. 3.9 months) [63] Median BICR-assessed PFS 13.4 vs. 9.2 months (HR 0.62; 95% CI 0.43–0.91; $P = 0.013$) Median inv-assessed PFS 13.2 vs. 8.5 months (HR 0.49; 95% CI 0.35–0.70; $P < 0.001$) HRQoL outcomes Overall LSM change in TOI score: −2.3 vs. −4.8 (between-group difference 2.5; 95% CI −0.5 to 5.5; $P = 0.108$) **Final OS analysis (DCO 16 April 2021)** [64] Median OS 34.9 vs. 32.9 months (HR 1.07; 95% CI 0.76−1.49; $P = 0.714$) Median PFS2 23.6 vs. 19.6 months (HR 0.80; 95% CI 0.56−1.15; $P = 0.229$) *Post hoc* subgroup analysis [65] Two prior lines of chemotherapy: median OS 37.9 vs. 28.8 months (HR 0.83; 95% CI 0.51–1.38) Three or more prior lines of chemotherapy: median OS 29.9 vs. 39.4 months (HR 1.33; 95% CI 0.84–2.18)

Table 5 (continued)

Study and phase	Pt population	Treatment (no. of pts)	Key efficacy outcomes
LIGHT [67, 68] Phase II, non-randomized, open-label, multi-center (NCT02983799)	PSROC, ≥1 prior platinum-based chemotherapy regimens	Olaparib tablets 300 mg bid ($n = 270$[b])	**Primary analysis (DCO 27 August 2019)** Primary endpoint [67] gBRCAm: ORR 69.3% (95% CI 57.6–79.5) sBRCAm: ORR 64.0% (95% CI 42.5–82.0) HRD-positive without BRCAm: ORR 29.4% (95% CI 19.0–41.7) HRD-negative: ORR 10.1% (95% CI 4.7–18.3) PFS analysis [67] gBRCAm: median inv-assessed PFS 11.0 months (95% CI 8.3–12.2) sBRCAm: median inv-assessed PFS 10.8 months (95% CI 7.3–NE) HRD-positive without BRCAm: median inv-assessed PFS 7.2 months (95% CI 5.3–7.6) HRD-negative: median inv-assessed PFS 5.4 months (95% CI 3.7–5.6) PFS subgroup analysis [67] *One prior line of chemotherapy* gBRCAm: ORR 70.0% sBRCAm: ORR 63.6% HRD-positive without BRCAm: ORR 29.0% HRD-negative: ORR 3.4% *Two or more prior lines of chemotherapy* gBRCAm: ORR 68.6% sBRCAm: ORR 64.3% HRD-positive without BRCAm: ORR 29.7% HRD-negative: ORR 13.3% **Final OS analysis (DCO 27 August 2020; median follow-up 26.3 months)** 18-month OS rate [68] Overall: 74.3% (95% CI 68.5–79.1) gBRCAm: 86.4% (95% CI 76.2–92.4) sBRCAm: 88.0% (95% CI 67.3–96.0) HRD-positive without BRCAm: 78.6% (95% CI 66.6–86.8) HRD-negative: 59.6% (95% CI 48.6–68.9)

Table 5 (continued)

Study and phase	Pt population	Treatment (no. of pts)	Key efficacy outcomes
Niraparib			
QUADRA [14, 69, 120] Phase II, single-arm, open-label, multicenter (NCT02354586)	Relapsed OC, three or more prior chemotherapy regimens	Niraparib 300 mg od ($n = 463$)	**Primary PFS analysis (DCO 11 April 2018)** Primary endpoint [69] HRD-positive platinum sensitive: inv-assessed ORR 28% (95% CI 15.6–42.6; $P = 0.00053$) PFS analysis HRD-positive platinum sensitive: median PFS 5.5 months (95% CI 3.5–8.2) OS analysis (median follow-up 12.2 months)[c] Median OS 17.2 months (95% CI 14.9–19.8) Additional analysis[d] [14] HRD-positive: inv-assessed ORR 24% (95% CI 16–34) PR 24%; CR 0% ***Post hoc* analyses** [120] Pts with PC <150,000/μL or BW <77 kg Mean starting dose ≤200 mg od: ORR 8%; DCR: 58%; 24-week CBR 19% Mean starting dose >200 mg od: ORR 7%; DCR: 39%; 24-week CBR 15% Pts with PC ≥150,000/μL or BW ≥77 kg Mean starting dose ≤200 mg od: ORR 9%; DCR: 59%; 24-week CBR 21% Mean starting dose >200 mg od: ORR 11%; DCR: 57%; 24-week CBR 23%
Rucaparib			
Study 10 [56] Phase I/II, open-label, multicenter (NCT01482715)	Part 2A: PSROC, gBRCAm, two to four prior chemotherapy regimens	Part 2A: Rucaparib 600 mg bid ($n = 42$)	Part 2A [56] ORR 59.5% (95% CI 43.3–74.4) PR 50.0%; CR: 9.5%; SD: 28.6%

Table 5 (continued)

Study and phase	Pt population	Treatment (no. of pts)	Key efficacy outcomes
ARIEL2 [58, 78] Phase II, open-label, multi-center (NCT01891344)	Part 1: PSROC Part 2: Relapsed high-grade OC, three to four chemotherapy regimens and CFI >6 months after first-line chemotherapy	Parts 1 and 2: Rucaparib 600 mg bid (n = 204 and 287)	**Part 1 (DCO 18 January 2016)** Primary endpoint [58] BRCAm: median inv-assessed PFS 12.8 months (95% CI 9.0–14.7) [HR vs. LOH low 0.27; 95% CI 0.16–0.44, $P < 0.0001$] LOH high[e] without BRCAm: median inv-assessed PFS 5.7 months (95% CI 5.3–7.6) [HR vs. LOH low 0.62; 95% CI 0.42–0.90, $P = 0.011$] LOH low without BRCAm: median inv-assessed PFS 5.2 months (95% CI 3.6–5.5) **Part 2** Primary endpoint [78] BRCAm: inv-assessed ORR 31.0% (95% CI 21.3–42.0) LOH high[e] without BRCAm: inv-assessed ORR 6.8% (95% CI 2.3–15.3) LOH low without BRCAm: inv-assessed ORR 5.6% (95% CI 2.1–11.8) PFS and OS analysis [78] BRCAm: median inv-assessed PFS 7.3 months (95% CI 6.2–9.0) LOH high[e] without BRCAm: median inv-assessed PFS 1.9 months (95% CI 1.8–3.7) LOH low without BRCAm: median inv-assessed PFS 3.7 months (95% CI 2.1–5.4) BRCAm: median OS 22.7 months (95% CI 16.7–28.6) LOH high[e] without BRCAm: median OS 14.7 months (95% CI 10.8–19.8) LOH low without BRCAm: median OS 13.3 months (95% CI 9.1–16.0) **Integrated Parts 1 and 2** [78] ORR analysis BRCAm: inv-assessed ORR 45.7% (95% CI 37.2–54.3) LOH high[e] without BRCAm: inv-assessed ORR 16.7% (95% CI 11.2–23.5) LOH low without BRCAm: inv-assessed ORR 7.7% (95% CI 4.2–12.9) gBRCAm: inv-assessed ORR 48.2% (95% CI 37.3–59.3) sBRCAm: inv-assessed ORR 45.5% (95% CI 30.4–61.2) Non-BRCAm with del HRRm: inv-assessed ORR 16.7% (95% CI 6.4–32.8) Non-BRCAm without HRRm: inv-assessed ORR 11.7% (95% CI 8.4–15.7) *RAD51C/D*-mutated: 71.4% (95% CI 29.0–96.3) PFS analysis BRCAm: median inv-assessed PFS 7.8 months (95% CI 7.3–9.2) LOH high[e] without BRCAm: median inv-assessed PFS 4.3 months (95% CI 3.5–5.7) LOH low without BRCAm: median inv-assessed PFS 4.0 months (95% CI 3.5–5.3) Non-BRCAm with del HRRm: median inv-assessed PFS 5.7 months Non-BRCAm without HRRm: median inv-assessed PFS 3.7 months *RAD51C/D*-mutated: median inv-assessed PFS 11.0 months Non BRCAm with high methylation: median PFS inv-assessed 7.8 months Non BRCAm with low methylation: median inv-assessed PFS 2.7 months Non BRCAm unmethylated: median inv-assessed PFS 4.3 months

Table 5 (continued)

Study and phase	Pt population	Treatment (no. of pts)	Key efficacy outcomes
Integrated analysis of Study 10/ARIEL2 [57, 82]	Advanced OC, gBRCAm or sBRCAm, two or more prior chemotherapy regimens	Rucaparib 600 mg bid ($n = 106$[f])	**Efficacy analysis** Primary outcome [57] Overall: inv-assessed ORR 53.8% (95% CI 43.8–63.5) PR: 45.3%; CR: 8.5%; SD: 34.0% PFS analysis Overall: median inv-assessed PFS 10.0 months (95% CI 7.3–12.5) **Updated analysis** [82] ORR analysis Overall: inv-assessed ORR 54.7% Platinum-sensitive: inv-assessed ORR 64.6% (95% CI 53.0–75.0) Platinum-resistant: inv-assessed ORR 35.0% Platinum-refractory: inv-assessed ORR 0% PFS analysis Platinum-sensitive: median inv-assessed PFS 10.9 months (95% CI 8.4–12.8)
ARIEL4 [59, 60] Phase III, randomized, open-label, multi-center (NCT02855944)	Relapsed high-grade OC, gBRCAm or sBRCAm, two or more prior chemotherapy regimens	Rucaparib 600 mg bid ($n = 233$) vs. chemotherapy (paclitaxel for platinum-resistant or partially platinum-sensitive disease, or investigator's choice of platinum-based chemotherapy for platinum-sensitive disease; $n = 116$)	**Primary analysis (DCO 30 September 2020)** Primary endpoint (median follow-up 25 months) [59] BRCAm:[g] median inv-assessed PFS 7.4 vs. 5.7 months (HR 0.64; 95% CI 0.49–0.84; $P = 0.0010$) ITT: median inv-assessed PFS 7.4 vs. 5.7 months (HR 0.67; 95% CI 0.52–0.86; $P = 0.0017$) Prespecified exploratory analysis Pts with BRCA reversion mutations: median inv-assessed PFS 2.9 vs. 5.5 months (HR 2.77; 95% CI 0.99–7.76) ORR analysis BRCAm:[g] inv-assessed ORR 40% vs. 32% ($P = 0.13$) ITT: inv-assessed ORR 38% vs. 30% ($P = 0.13$) Final OS analysis [60, 61] ITT: Median OS 19.4 vs. 25.4 months (HR 1.31; 95% CI 1.00–1.73; $P = 0.0507$) Platinum sensitive: median OS 29.4 vs. 27.6 months (HR 1.07; 95% CI 0.71–1.62) Platinum resistant: median OS 14.2 vs. 22.2 months (HR 1.51; 95% CI 1.05–2.17)

BICR blinded independent central review, *bid* twice daily, *BRCAm BRCA1* and/or *BRCA2* mutation, *BW* body weight, *CBR* clinical benefit rate, *CFI* chemotherapy-free interval, *CI* confidence interval, *CR* complete response, *DCO* data cut-off, *DCR* disease control rate, *del* deleterious, *DOR* duration of response, *gBRCAm* germline BRCAm, *HR* hazard ratio, *HRD* homologous repair deficiency, *HRQoL* health-related quality of life, *HRRm* homologous recombination repair mutation, *inv* investigator, *ITT* intent-to-treat, *LOH* loss of heterozygosity quantified with a next-generation sequencing assay, *LSM* least squares mean, *NE* not estimable, *OC* ovarian cancer, *od* once daily, *OR* odds ratio, *ORR* objective response rate, *OS* overall survival, *PARP* poly(ADP-ribose) polymerase, *PC* platelet count, *PFS* progression-free survival, *PFS2* time to second progression or death, *PLD* pegylated liposomal doxorubicin, *PR* partial response, *PSROC* platinum-sensitive relapsed ovarian cancer, *pt(s)* patient(s), *sBRCAm* somatic BRCAm, *SD* stable disease, *TOI* Trial Outcome Index

[a]Primary analysis population comprising 151 pts in the olaparib group and 72 pts in the chemotherapy group with measurable disease as assessed by BICR

[b]Efficacy analysis population comprising 270 pts with measurable disease

[c]Assessed in the modified per-protocol population which included 456 pts with measurable disease who had received only two previous lines of therapy

[d]HRD pts with a tumor BRCAm ($n = 63$) or a genomic instability score of ≥42 and who had progressed ≥6 months after their last dose of platinum-based chemotherapy ($n = 35$)

[e]In Part 2, LOH high was a cut-off of ≥18%, and in pooled Parts 1and 2, LOH high was a cut-off of ≥16%[121]

[f]The efficacy analysis population included 42 pts from Study 10 Part 2A and 64 pts from ARIEL2 Parts 1 and 2

[g]Excluding pts with BRCA reversion mutations

been restricted to patients with PSROC who have a gBRCAm in the US [14].

The Phase III NORA study in 265 Chinese patients demonstrated the efficacy of a niraparib ISD regimen as maintenance therapy, as evidenced by a significant reduction in the risk of disease progression and death with niraparib versus placebo after a median follow-up of 15.8 months (HR 0.32; 95% CI 0.23–0.45; $P < 0.0001$; Table 4) [42].

In ARIEL3, 564 patients were randomized to receive maintenance rucaparib or placebo until disease progression, death, or other reason for discontinuation [39]. The study met its primary endpoint with significantly longer investigator-assessed PFS seen with maintenance rucaparib than with placebo in patients with a BRCAm (median 16.6. vs. 5.4 months; HR 0.23; 95% CI 0.16–0.34; $P < 0.0001$), in patients whose tumors tested HRD-positive (median 13.6 vs. 5.4 months; HR 0.32; 95% CI 0.24–0.42; $P < 0.0001$), and in the ITT population (median 10.8 vs. 5.4 months; HR 0.36; 95% CI 0.30–0.45; $P < 0.0001$) (Table 4) [39]. A *post hoc* exploratory analysis assessed the clinical and molecular characteristics of patients with exceptional PFS benefit, where exceptional benefit was defined as double the median PFS (≥2 years) in the ITT population [53]. Overall, 21.1% of patients in the rucaparib group and 2.1% of patients in the placebo group showed exceptional benefit, with PFS of ≥2 years (Table 4); 13.9% and 6.9% of patients in the rucaparib group had PFS of ≥3 and ≥4 years, respectively. Results showed that exceptional benefit was more common in, but not exclusive to, patients with favorable clinical characteristics (including no measurable disease at baseline, longer penultimate platinum-free interval and CR to last platinum therapy) and known mechanisms of PARPi sensitivity (including *BRCA1*, *BRCA2*, *RAD51C*, and *RAD51D* alterations and genome-wide LOH) [53]. In the final OS analysis of ARIEL3, (median follow-up of 6.4 years), median OS with maintenance rucaparib versus placebo was 45.9 versus 47.8 months in the BRCAm cohort (HR 0.83; 95% CI 0.58–1.19), 40.5 versus 47.8 months in the HRD-positive cohort (HR 1.01; 95% CI 0.77–1.32), and 36.0 versus 43.2 months in the ITT population (HR 1.00; 95% CI 0.81–1.22) (Table 4). [54] Approximately 45% of patients in the placebo group received subsequent PARPi therapy [54]. ARIEL3 was not powered to evaluate between-group differences in OS; however, based on these results, maintenance rucaparib has been restricted to patients with PSROC who have a BRCAm in the US [15].

To summarize, PFS data from olaparib, niraparib, and rucaparib studies support the use of PARPi maintenance therapy in patients with PSROC, regardless of biomarker status. OS data from SOLO2 also support the use of maintenance olaparib in the relapsed disease setting in patients with BRCAm and Study 19 demonstrated an apparent OS advantage for olaparib over placebo in the overall population of patients with or without a BRCAm. In patients with PSROC, as requested by the FDA, maintenance niraparib is restricted to those with a gBRCAm, based on final OS data from NOVA, and maintenance rucaparib is restricted to those with a BRCAm, based on final OS data from ARIEL3, in the US; it should be noted that neither study was powered to assess between-group differences in OS. It is clear that the outcomes in platinum-sensitive patients who respond to a platinum doublet are quite poor without maintenance therapy with PFS of ≤5.5 months. A subset of patients will derive exceptional benefit from PARPi maintenance therapy in the relapsed disease setting; as well as HRD status, clinical factors such as platinum sensitivity seem to be important predictors of response to PARPi maintenance therapy.

3.4 Later-Line Treatment

In patients with relapsed advanced OC, olaparib was approved in the US as later-line treatment in patients with a gBRCAm, niraparib in patients whose tumors tested HRD-positive and rucaparib in patients with a BRCAm; however, these treatment indications have been voluntarily withdrawn (Fig. 1 and Table 1). The studies leading to the approval of these PARPis and subsequent studies are discussed briefly below and are shown in Table 5.

An early Phase II study (NCT00664781) [55], the three-part Phase I/II Study 10 [56, 57], and the two-part Phase II ARIEL2 study [57, 58] evaluated rucaparib treatment in OC. The approval of rucaparib treatment for patients with relapsed OC and a BRCAm who had received two or more prior chemotherapies was based on an integrated analysis of data from Study 10 Part 2A ($n = 42$) and ARIEL2 Parts 1 and 2 ($n = 64$) [57] (Table 5).

The Phase III ARIEL4 study subsequently evaluated rucaparib in patients with relapsed high-grade OC who had a gBRCAm or sBRCAm and had received two or more prior platinum or non-platinum chemotherapy regimens (Table 5) with a planned crossover to rucaparib for those who progressed on the chemotherapy arm (72% underwent crossover to a PARPi as first subsequent therapy) [59]. At the final OS analysis, a possible detriment in OS was observed with rucaparib versus chemotherapy (median OS 19.4 vs. 25.4 months; HR 1.31; 95% CI 1.00–1.73; $P = 0.0507$), driven by results in the subgroup of patients with platinum resistance (Table 5) [60]. It is important to note that an unusually high number of patients in the rucaparib arm did not receive any subsequent therapy after progressing on rucaparib compared with those who received chemotherapy (43% vs. 24% in the platinum-resistant subgroup; 38% vs.

16% in the partially platinum-sensitive subgroup; and 46% vs. 15% in the fully platinum-sensitive subgroup) [60, 61]. Based on these results, rucaparib has been voluntarily withdrawn in the US for the treatment of patients with BRCAm OC who have received two or more prior lines of chemotherapy [61].

The approval of olaparib in the treatment of patients with PSROC and a gBRCAm who have received three or more prior lines of chemotherapy was based on the results of the Phase II Study 42 trial (Table 5) [62].

The Phase III SOLO3 study in patients with gBRCAm PSROC who had received two or more prior lines of platinum-based chemotherapy confirmed and extended the results of Study 42 in the treatment setting (Table 5) [63]. At final analysis, OS (HR 1.07; 95% CI 0.76–1.49) and PFS2 (HR 0.80; 95% CI 0.56–1.15) did not significantly differ between the olaparib and chemotherapy groups (Table 5) [64]. A subsequent *post hoc* analysis found favorable OS for olaparib versus chemotherapy in the subgroup of patients who had received two prior lines of chemotherapy and a potential detrimental effect in patients who had received three or more prior lines of chemotherapy (Table 5) [65]. Based on these results, olaparib has been voluntarily withdrawn in the US for the treatment of patients with gBRCAm OC who have received three or more prior lines of chemotherapy [66].

The Phase II LIGHT study evaluated olaparib treatment in patients with PSROC and known BRCAm and HRD status who had received one or more prior lines of platinum-based chemotherapy (Table 5) [67]. Subgroup analyses found that ORR and median PFS were generally similar in patients with one or two or more prior lines of chemotherapy in the BRCAm cohorts and the HRD-positive non-BRCAm cohort (Table 5) [67]. At final OS analysis, the 18-month OS rate was 60–88% (Table 5) [68].

The approval of niraparib in the later-line treatment of patients with HRD-positive advanced OC who had been treated with three or more previous chemotherapy regimens was based on the results of the Phase II QUADRA study (Table 5) [69]. After a median follow-up of 12.2 months, the median OS was 17.2 months in 456 patients with measurable disease who had received three or more previous therapies (modified per-protocol population) (Table 5) [69]. A decision was made to voluntarily withdraw niraparib in the US for the treatment of patients with advanced OC whose tumors are associated with an HRD-positive status and who have received three or more prior lines of chemotherapy based on a totality of information from PARPis in the later-line treatment setting in OC [70].

In summary, olaparib, niraparib, and rucaparib are no longer indicated in the US for later-line treatment in patients with relapsed OC. It should be noted that neither SOLO3 nor ARIEL4 were powered to assess between-group differences in OS.

4 Role of Biomarker Testing in Optimal Therapeutic Decisions

Regardless of the PARPi administered, HRD testing is critical in the newly diagnosed setting to identify which patients may experience the greatest benefit from PARPi maintenance therapy and guide treatment decisions [1, 71]. As discussed previously, PARPi maintenance therapy showed the greatest benefit in newly diagnosed OC patients with a BRCAm or who tested positive for HRD in clinical trials.

Myriad MyChoice® CDx and FoundationOne CDx™ are US-approved companion diagnostics in OC. Clinical trials in the newly diagnosed setting have used MyChoice® CDx, which tests for the presence of a BRCAm and/or genomic instability (LOH, telomeric allelic imbalance, and large-scale state transitions) [17, 31], and FoundationOne CDx™, which tests for the presence of a BRCAm and LOH [18].

Laboratory-developed tests (e.g. the Geneva HRD test [72]) that can be deployed in a clinical laboratory may provide a viable alternative to commercial assays for determining HRD status.

In terms of testing for BRCAm, both germline and tumor testing are warranted [1]. Current guidelines recommend germline testing of all patients with epithelial OC at diagnosis, and tumor testing for sBRCAm for patients in whom a gBRCAm is not detected [73, 74].

Notably, tumor testing reliably identified BRCAm that are germline in origin in clinical trial settings [75, 76]. The availability of a reliable tumor test for use in clinical practice may permit more flexibility in the approach to testing, with initial tumor testing followed by genetic testing of patients in whom a tBRCAm is detected.

Germline testing remains essential if a tBRCAm is identified so the patient is aware of their personal risk of other cancers (e.g. breast cancer) and first- or second-degree blood relatives can be offered genetic risk evaluation, counseling, and testing [73].

Interestingly, as compared with the newly diagnosed setting, results of Phase III trials [38, 39] suggest that the benefit of HRD testing is impactful but not as profound in PSROC. The dominant factors are clinical, with platinum sensitivity being the dominant predictor of response in this setting.

The predictive potential of non-BRCA HRRm (e.g. mutations in *RAD51B*, *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *NBN*, *ATM*, *CHK1*, *CHK2*, *CDK12*) has been evaluated in an exploratory fashion. In PAOLA-1, HRRm gene panels (excluding BRCA) did not predict the efficacy of maintenance olaparib plus bevacizumab in the newly diagnosed setting [77]. Using

Table 6 Dose modifications and discontinuations because of AEs in key PARP inhibitor trials

Study	Treatment (no. of patients)	Median[a] treatment duration, months	Patients with AEs leading to		
			Dose interruption	Dose reduction	Discontinuation
First-line maintenance monotherapy					
SOLO1 [22]	Olaparib ($n = 260$) vs. placebo ($n = 130$)[b]	24.6 vs. 13.9	53% vs. 17%	29% vs. 3%	12% vs. 3%
PRIMA [17]	Niraparib ($n = 484$) vs. placebo ($n = 244$)[b]	11.1[c]	80% vs. 18%	71% vs. 8%	12% vs. 2%
ATHENA-MONO [18]	Rucaparib ($n = 425$) vs. placebo ($n = 110$)[b]	14.7 vs. 9.9	61% vs. 20%	49% vs. 8%	12% vs. 5%
First-line maintenance combination therapy					
PAOLA-1 [34]	Olaparib + bev ($n = 535$) vs. placebo + bev ($n = 267$)[b]	17.3 vs. 15.6	54% vs. 24%	42% vs. 8%	21% vs. 6%
Second-line or later maintenance monotherapy					
SOLO2 [46]	Olaparib ($n = 195$) vs. placebo ($n = 99$)	Mean 29.1 vs. 13.1	50% vs. 19%	28% vs. 3%	17% vs. 3%
NOVA [38]	Niraparib ($n = 367$) vs. placebo ($n = 179$)	8.2[c]	69% vs. 5%	66% vs. 15%	15% vs. 2%
ARIEL3 [83]	Rucaparib ($n = 372$) vs. placebo ($n = 189$)	8.3 vs. 5.5	65% vs. 10%	55% vs. 4%	15% vs. 2%
Later-line treatment					
SOLO3 [63]	Olaparib tablets ($n = 178$) vs. non-platinum chemotherapy ($n = 76$)	11.3 vs. 6.0 for PLD, 5.1 for paclitaxel, 3.3 for gemcitabine, and 6.2 for topotecan	48% vs. 42%[d]	27% vs. 33%	7% vs. 20%
QUADRA [69]	Niraparib ($n = 463$)	3[c]	62%	47%	21%
ARIEL4 [59]	Rucaparib ($n = 232$) vs. chemotherapy ($n = 113$)	7.3 vs. 3.6	50% vs. 44%[e]		8% vs. 12%

AE adverse event, *bev* bevacizumab, *PARP* poly(ADP-ribose) polymerase, *PLD* pegylated liposomal doxorubicin

Comparisons across trials should be made with caution because of differences in patient populations and trial methods between the studies

[a]Median values unless stated otherwise

[b]Maintenance olaparib and maintenance rucaparib capped at 2 years and maintenance niraparib capped at 3 years

[c]Median duration of treatment in niraparib patients[14]

[d]Dose interruptions or delays due to AEs

[e]Treatment interruption, dose reduction, or both

a 13-gene panel, the HR for PFS in patients with HRRm excluding tBRCAm ($n = 54$), was 0.95 (95% CI 0.49–1.94); on expansion of this panel to include five additional genes ($n = 72$), the HR for PFS was 1.01 (95% CI 0.55–1.95). Consistent results were also observed in patients with HRRm excluding tBRCAm using three other HRR gene panels [77]. However, in a *post hoc* analysis of ARIEL2 in patients with relapsed OC, *RAD51C* and *RAD51D* mutations predicted response to treatment with rucaparib, similar to BRCAm; the median PFS in patients with *RAD51C/RAD51D*-mutated OC ($n = 7$) was similar to that in patients with BRCAm ($n = 138$) (11.0 vs. 7.8 months; HR 1.52; 95% CI 0.67–3.44; $P = 0.32$) [78].

5 Safety and Tolerability of Poly(ADP-Ribose) Polymerase (PARP) Inhibitors

Although similarities are evident in the tolerability profiles of the different PARPis (with AEs such as anemia, neutropenia, nausea, vomiting, and fatigue considered class effects), distinct differences are also observed, requiring customization of monitoring and/or dosing regimens. When considered individually, the AE profile of each PARPi was generally consistent when administered as monotherapy in maintenance or treatment settings.

The safety profile of combination therapy with olaparib plus bevacizumab in PAOLA-1 was generally consistent with that observed with olaparib monotherapy [16, 37], with the exception of hypertension, which is commonly associated with bevacizumab [31]. Adding maintenance olaparib to bevacizumab did not increase bevacizumab-associated AEs, with a numerically lower incidence of

hypertension with olaparib plus bevacizumab than with bevacizumab alone [31].

The most commonly reported hematologic and non-hematologic AEs generally occurred early in patients receiving PARPis. For olaparib, the median time to first onset was 1.94 months for anemia, 1.77 months for neutropenia, 2.83 months for thrombocytopenia, 0.13 months for nausea, 0.72 months for fatigue/asthenia, and 1.46 months for vomiting in SOLO1 [19, 79]. For niraparib, the incidence of thrombocytopenia, nausea, vomiting, diarrhea, fatigue, insomnia, and hypertension was highest during the first month of therapy and declined thereafter, whereas the incidence of anemia and neutropenia peaked in months 3 and 2, respectively, of maintenance niraparib therapy in NOVA [38, 80]. For rucaparib, the median time to first onset was 56 days for anemia, 52 days for thrombocytopenia, 5–15 days for nausea, vomiting, fatigue/asthenia, dysgeusia, and increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels, 22–29 days for decrease appetite, constipation, and diarrhea, and 45 days for abdominal pain in an integrated analysis of trial data [81].

When considering the safety and tolerability profiles of the PARPis, it is important to note that the duration of maintenance therapy was capped in newly diagnosed OC (2 years for olaparib [16, 31] and rucaparib [18] and 3 years for niraparib [17]), whereas olaparib [36, 37, 63, 79], niraparib [17, 38, 69], and rucaparib [39, 82] were continued until disease progression in the second-line or later maintenance and later-line treatment settings. For example, the median duration of maintenance olaparib therapy was 24.6 months in SOLO1 [22], whereas cumulative exposure of ≥5 years was seen in 22% of olaparib patients in the final analysis of SOLO2 [46]. The duration of study treatment in the key PARPi trials is shown in Table 6. Other factors, such as prior treatment and the duration of follow-up (shown in Tables 2–5), should also be considered when interpreting safety findings. Importantly, no new safety signals were identified with olaparib [22, 34, 46], niraparib [27, 50, 80], or rucaparib [82, 83] during longer-term follow-up.

Comparisons across trials should be made with caution because of differences in patient populations and trial methods between the studies. It should also be noted that only studies in which patients received the tablet formulation of olaparib are discussed in this section, given it is the only formulation currently marketed in the US for all olaparib indications [13].

5.1 Hematologic Adverse Events

Anemia and neutropenia are class effects of PARPis, with anemia being one of the most commonly reported treatment-emergent AEs reported with olaparib, niraparib, or rucaparib in randomized, placebo-controlled maintenance therapy studies, and randomized, controlled later-line treatment trials (Online Resource Table S1) [14, 17, 18, 22, 34, 38, 46, 59, 63, 83].

Grade ≥3 anemia was the most common grade ≥3 treatment-emergent AE reported in olaparib patients in SOLO1 [22], SOLO2 [46], and SOLO3 [63], and in rucaparib patients in ATHENA-MONO [18], ARIEL3 [83], and ARIEL4 [59] (Online Resource Table S1).

Although thrombocytopenia is seen with all PARPis [14, 17, 22, 34, 38, 46, 59, 63, 83], there is an increased risk of thrombocytopenia with niraparib (66% of niraparib patients vs. 5% of placebo patients in PRIMA [14] and 61% vs. 6%, respectively, in NOVA [38]), including grade ≥3 thrombocytopenia (39% vs. <1%, respectively, in PRIMA [14], and 34% vs. 1%, respectively, in NOVA [38]) (Online Resource Table S1).

The PRIMA protocol was amended to incorporate an ISD [17] because of the safety benefit observed with the lower starting dose in a retrospective analysis of NOVA [84]. In NOVA, the study protocol mandated an interruption of treatment for patients with specific hematologic and non-hematologic AEs, with resumption of treatment at a lower dose. The subsequent retrospective analysis suggested that patients with baseline body weight of <77 kg or baseline platelets of <150,000/μL may benefit from a lower starting dose of 200 mg/day [84], which is now the recommended dose for patients with a baseline body weight of <77 kg or baseline platelets of <150,000/μL who are receiving maintenance niraparib in the newly diagnosed setting [14]. The lower starting dose approved for use in patients receiving first-line maintenance therapy who have a lower bodyweight or baseline platelet count helps ameliorate thrombocytopenia [14]. In PRIMA, the incidence of grade ≥3 thrombocytopenia was 22% in patients whose starting dose of niraparib was based on baseline body weight or platelet count [14], which is closer to the rates of grade ≥3 thrombocytopenia reported in SOLO1 (1%) [22] and ATHENA-MONO (7%) [18].

The incidence of hematologic AEs reported in patients receiving niraparib also decreased over time [50, 80]. In NOVA, the incidence of grade ≥3 thrombocytopenia in niraparib patients decreased from 34% at year 1 to 3% at years 2–3 [50].

In terms of managing bone marrow suppression, US prescribing information recommends that PARPi therapy should not commence until hematologic toxicity caused by prior chemotherapy has recovered to grade ≤1 [13–15].

In patients receiving olaparib [13] or rucaparib [15], the complete blood count (CBC) should be monitored at baseline and monthly thereafter. Dose modification of olaparib [13] or rucaparib [15] may be required to manage prolonged hematologic toxicities. If blood counts do not recover, the

patient should be referred to a hematologist for further investigation [13, 15].

In patients receiving niraparib, the CBC should be monitored weekly for the first month, and with dosage changes related to hematologic toxicity, monthly for the next 11 months and then periodically thereafter [14]. If prolonged hematologic toxicities persist despite dose interruption of niraparib, discontinue niraparib and refer the patient to a hematologist for further investigation [14].

Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) have been reported in patients receiving olaparib, niraparib and rucaparib and are included in the warnings and precautions section of the US prescribing information for all three PARPis [13–15]. Collection of data pertaining to these AEs differed across trials.

A low incidence of MDS/AML was reported in patients receiving first-line maintenance olaparib with or without bevacizumab. In SOLO1, MDS/AML was reported in 1% of patients receiving maintenance olaparib (vs. 0% of placebo patients) at the primary PFS analysis [16] and in 2% of olaparib patients (vs. 1% of placebo patients) with longer-term follow-up [22]. In PAOLA-1, MDS/AML/aplastic anemia was reported in 1% of patients receiving maintenance olaparib plus bevacizumab (vs. 0.4% of placebo plus bevacizumab patients) at the time of the primary PFS analysis [31] and in 2% of olaparib patients (vs. 2% of placebo patients) at the final OS analysis [35].

In the relapsed disease setting in SOLO2, MDS/AML was reported in 2% of patients receiving maintenance olaparib (vs. 4% of placebo patients) at the primary PFS analysis [37] and in 8% of olaparib patients (vs. 4% of placebo patients) at the final OS analysis [46]. The imbalance in MDS/AML seen between olaparib and placebo patients with longer-term follow-up should be considered in the context of potential baseline risk factors (e.g. prior chemotherapy with DNA-damaging agents), the late onset of these events, and the survival benefit seen with olaparib in SOLO2 (patients with longer survival may have more time to develop late-onset toxicities).

During third-line or later treatment with olaparib in SOLO3, MDS/AML was reported in 2% of patients receiving olaparib treatment (vs. 4% of non-platinum chemotherapy patients) at the primary analysis [63].

In PRIMA, one case of MDS was reported in patients receiving first-line maintenance niraparib (0.3%; no cases of MDS/AML were reported in placebo patients) at the primary PFS analysis [17], and in 1.2% of niraparib patients (vs. 1.2% of placebo patients) with longer-term follow-up [27]. In the relapsed disease setting in the NOVA trial, the incidence of MDS/AML was 1% in maintenance niraparib patients and 1% in placebo patients at the primary PFS analysis [38] and 4% versus 2% at the final OS analysis [50].

At the primary PFS analysis in ATHENA-MONO, MDS/AML was reported in two patients in the rucaparib group (0.5%) and no patients in the placebo group [18]. In the relapsed disease setting in the ARIEL3 trial, the incidence of MDS/AML was 1% in patients receiving maintenance rucaparib, with no cases reported in the placebo group at the primary PFS analysis [39], and 4% versus 3% at the final OS analysis [54].

PARPi therapy should be discontinued in any patient in whom MDS/AML is confirmed [13–15], and the risk should be discussed with each patient prescribed a PARPi.

5.2 Non-Hematologic Adverse Events

Gastrointestinal AEs (e.g. nausea, vomiting, diarrhea, constipation, abdominal pain, dysgeusia, decreased appetite) are among the most common treatment-emergent AEs reported with PARPis in randomized, placebo-controlled maintenance therapy studies and randomized, controlled later-line treatment trials (Online Resource Table S2) [14, 17, 18, 22, 34, 38, 46, 59, 63, 83]. The vast majority of these AEs were mild to moderate.

Patients receiving rucaparib in ATHENA-MONO [18], ARIEL3 [83], and ARIEL4 [59] also experienced increased ALT/AST levels (Online Resource Table S2). Elevations in ALT/AST occurred within the first few weeks of rucaparib therapy and were reversible, rarely associated with increases in bilirubin, and not felt to be clinically meaningful [39, 82].

Gastrointestinal AEs are usually manageable with supportive therapy (e.g. antinausea/antiemetic therapy, antidiarrheal medication, laxatives, and dietary modification as appropriate) and/or dose modification [85–87].

Fatigue was commonly reported in patients receiving olaparib, niraparib, or rucaparib in randomized, placebo-controlled maintenance therapy studies and randomized, controlled later-line treatment trials (Online Resource Table S2) [14, 17, 18, 22, 34, 38, 46, 59, 63, 83]. Most fatigue events were mild to moderate. Fatigue/asthenia can usually be managed using supportive care (e.g. strategies to conserve energy) and dose modification [85–87].

Pneumonitis/interstitial lung disease (ILD) has rarely been reported with PARPis in clinical trials. Various confounding factors may contribute to development of pneumonitis (e.g. pneumonitis is a recognized adverse effect of many anticancer therapies [88]). Pneumonitis is included in the warnings and precautions section of the US prescribing information for olaparib, with 0.8% of 2901 olaparib patients reported as developing pneumonitis across various tumor types [13]. In placebo-controlled maintenance therapy studies, pneumonitis/ILD was reported in 2% of olaparib patients versus 0% of placebo patients in SOLO1 [16], pneumonitis/ILD/bronchiolitis was reported in 1% of olaparib plus bevacizumab patients versus 0% of placebo plus bevacizumab

patients in PAOLA-1 [34], and pneumonitis was reported in 2% of olaparib patients versus 0% of placebo patients in SOLO2 [46]. Olaparib should be interrupted in patients presenting with new or worsening respiratory symptoms (e.g. dyspnea, cough, fever) [13], signs (e.g. hypoxia), or radiological abnormalities [13] and the source of the symptoms assessed [13]. Olaparib should be discontinued and appropriate treatment initiated if pneumonitis is confirmed. Pneumonitis has also been reported with niraparib during post-marketing experience [14, 88].

Hypertension is included in the warnings and precautions section of the US prescribing information for niraparib, as both hypertension and hypertensive crisis have been reported in patients receiving this PARPi [14]. In placebo-controlled maintenance therapy studies, hypertension was reported in 17% of niraparib patients versus 7% of placebo patients in PRIMA [17] and in 19% versus 4% of patients, in NOVA [38], with grade ≥3 hypertension reported in 6% versus 1% of patients, in PRIMA [17] and in 8% versus 2% of patients, in NOVA [38]. In patients receiving niraparib, blood pressure (BP) and heart rate should be monitored regularly and patients with cardiovascular disorders should be monitored closely [14]. Hypertension should be managed with antihypertensives and the niraparib dose should be adjusted, if necessary [14].

As mentioned previously, hypertension is commonly associated with bevacizumab. In PAOLA-1, the incidence of hypertension was numerically lower in patients receiving olaparib plus bevacizumab than in those receiving bevacizumab alone (46% vs. 60% of patients) [34]. In patients receiving a PARPi in combination with bevacizumab, BP should be monitored every 2−3 weeks and appropriate antihypertensive therapy should be initiated in patients who develop hypertension. For severe hypertension, bevacizumab should be withheld until BP is controlled, and bevacizumab should be discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy [3].

5.3 Dose Modifications and Discontinuations

AEs associated with PARPis can usually be managed with dose modifications, including dose interruption and dose reduction. The rates of dose modification and treatment discontinuation and the durations of treatment in key trials of PARPis approved in the US are shown in Table 6.

In patients receiving olaparib, most AEs were managed with dose interruptions or reductions, with ≤21% of patients requiring treatment discontinuation across trials (Table 6) [22, 34, 46, 63]. Rates of dose modification or treatment discontinuation in patients receiving olaparib were generally consistent across treatment settings; the higher rate of olaparib discontinuation in PAOLA-1 [31] versus SOLO1 [16] may partly reflect differences between the studies (e.g. combination therapy) and differences between the populations (patients with a BRCAm vs. all comers) [89]. In SOLO1, of the 162 patients still receiving olaparib at month 24, the majority (64%) were receiving the recommended starting dose of olaparib 300 mg twice daily without requiring a dose reduction, with 17% receiving a reduced olaparib dose of 250 mg twice daily [19].

In patients receiving niraparib, although most AEs were managed by niraparib dose modification, with ≤21% of patients requiring treatment discontinuation, a high proportion of patients required niraparib dose interruptions (≤80% of patients) or dose reductions (≤71%; Table 6) [17, 38, 69]. The rate of niraparib dose modification appeared higher in the first-line maintenance setting [17] than in the later-line maintenance [38] or treatment [69] settings, although comparisons across trials should be made with caution given the protocol amendment permitting use of an ISD in PRIMA [17].

AEs occurring in patients receiving rucaparib as maintenance or treatment were also usually managed with dose reductions or interruptions, and few (≤15%; Table 6) patients required treatment discontinuation of rucaparib [18, 59]. Rates of dose modification or treatment discontinuation in patients receiving rucaparib were generally consistent across treatment settings.

5.4 Impact on Health-Related Quality of Life

The PFS benefit seen with PARPi maintenance monotherapy and combination therapy in patients with newly diagnosed advanced OC was achieved with no detrimental effect on health-related quality of life (HRQoL) and was supported by patient-centered outcomes such as quality-adjusted PFS (QA-PFS) and time without significant symptoms of toxicity (TWiST) or quality-adjusted TWiST (Q-TWiST); these outcomes take into account the adverse effects of PARPis.

In SOLO1, there was no clinically meaningful difference in the mean change from baseline in the Functional Assessment of Cancer Therapy–Ovarian Cancer (FACT-O) Trial Outcome Index (TOI) score over 24 months between maintenance olaparib and placebo (Table 2) [16, 90]. In PRIMA, mean Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI), European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), and EORTC-QLQ-ovarian cancer module (EORTC-QLQ-OV28) scores did not indicate a difference in HRQoL between maintenance niraparib and placebo [17, 91, 92]. In ATHENA-MONO, changes from baseline in the FACT-O TOI score were similar in the rucaparib and placebo groups [18]. In SOLO1 and PRIMA, PARPi maintenance monotherapy was associated with significant gains in QA-PFS [17, 90–92] and TWiST [90] or Q-TWiST [17, 91, 92] (Table 2). In PAOLA-1, no clinically

meaningful difference in the global health status quality of life (GHS-QOL) score was observed between maintenance olaparib plus bevacizumab and placebo plus bevacizumab [31]; olaparib plus bevacizumab was associated with significant gains in TWiST over placebo plus bevacizumab [93] (Table 3).

Similarly, maintenance monotherapy had no detrimental effect on HRQoL in the relapsed disease setting. In SOLO2, the mean change from baseline in FACT-O TOI score did not significantly differ between maintenance olaparib and placebo [37, 94], in NOVA, the adjusted mean FOSI and 5-level EQ-5D (EQ-5D-5L) scores were generally similar between maintenance niraparib and placebo [38, 95], and in ARIEL3, there was no significant difference between maintenance rucaparib and placebo in the time to worsening in the FOSI-18 disease-related symptoms–physical (DRS-P) subscale score [39] (Table 4). Patient-centered benefits were seen in QA-PFS [94, 96] and TWiST [94, 97] or Q-TWIST [96] (Table 4).

Later-line olaparib treatment did not adversely affect HRQoL in SOLO3, with no clinically or statistically significant difference in the mean change from baseline in the FACT-O TOI score with olaparib treatment versus non-platinum chemotherapy [63] (Table 5).

6 Evidence From Real-World Studies

Real-world data support the use of PARPis in OC, although differences between olaparib, niraparib, and rucaparib are apparent in real-world settings.

In a US real-world evidence study, differences between olaparib, niraparib, and rucaparib were seen in the maintenance and treatment settings [98]. For example, the risk of a clinical event of interest was significantly higher with niraparib than with either olaparib (odds ratio [OR] 3.36; 95% CI 2.00–5.65) or rucaparib (OR 2.09; 95% CI 1.10–3.95); dose reductions were seen in significantly ($P < 0.05$) fewer olaparib patients (21%) than in rucaparib (30%) or niraparib (35%) patients; persistence and adherence were significantly ($P < 0.05$) higher with olaparib than with niraparib or rucaparib; and healthcare resource utilization was higher with niraparib and rucaparib than with olaparib [98].

In support of clinical trial findings, a PFS benefit was seen in newly diagnosed OC patients who did, compared with those who did not, receive PARPi maintenance therapy in a real-world setting [99]. Prolonging the time to disease progression also has the potential to delay the high costs associated with progression in newly diagnosed patients [100]. Despite this, utilization of PARPi maintenance therapy in the first-line setting is currently suboptimal; this is especially noticeable in those patients who will benefit the most, with PARPi maintenance therapy administered to 56% of patients with BRCAm tumors and 57% of patients whose tumors tested HRD positive [99].

The low utilization raises the question: if those patients whose tumors are found to have a sBRCAm or gBRCAm are not strongly encouraged to receive PARPi maintenance therapy, are they not being recommended the standard of care given the overwhelming evidence supports PARPi maintenance therapy in this population? If patients with BRCAm tumors are not encouraged to be treated with PARPi maintenance therapy, then the potential to markedly increase the curative intent is lost [22]. A similar question could be asked of those patients whose tumors are found to be HRD-positive.

Although utilization of PARPi maintenance therapy in the relapsed disease setting has improved over time, real-world data show that a proportion of eligible patients with OC are still not receiving PARPi maintenance therapy [101, 102].

Optimizing adherence to PARPi therapy is critical. Real-world data found that as many as one-quarter of OC patients may have suboptimal adherence to PARPi therapy, with non-adherent patients more likely to receive niraparib and have a longer duration of therapy [103]. Appropriate management of AEs such as nausea and vomiting is also key to maintaining adherence to the recommended PARPi dosage [86, 87]. Patient preference data indicate that patients with OC would be willing to accept a shorter PFS to avoid severe AEs, particularly nausea and vomiting [104].

Although rates of BRCAm and HRD testing in OC patients are improving [102], a proportion of patients are still not being tested [105]. Universal biomarker testing of all patients with newly diagnosed OC remains the goal [102].

7 Challenges and Future Directions

The optimal sequencing of therapies in OC (including the potential impact of PARPi therapy on the efficacy of subsequent platinum-based chemotherapy [106]), mechanism of PARPi resistance, and use of novel combination therapies remain areas of interest.

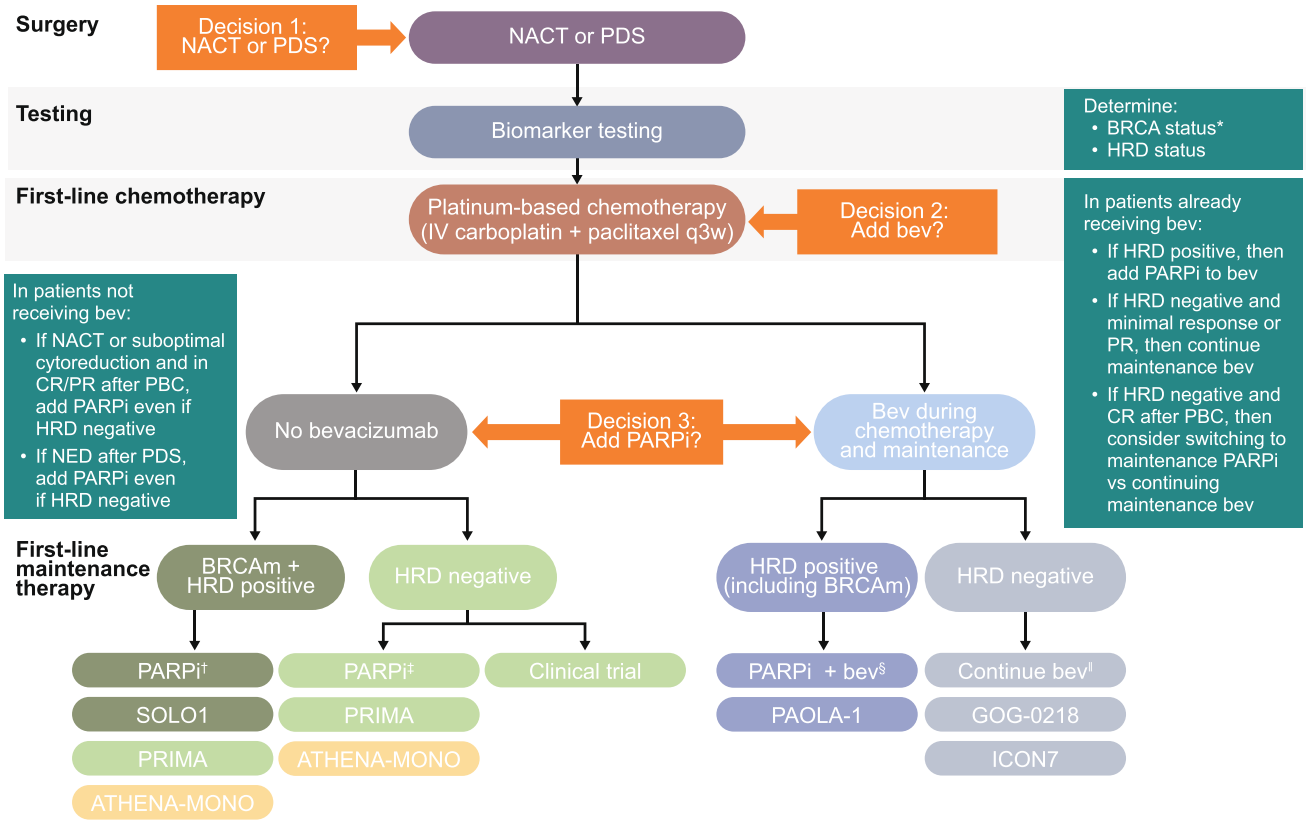

Fig. 2 Proposed treatment algorithm for newly diagnosed ovarian cancer. Adapted from DiSilvestro *et al.* Maintenance treatment of newly diagnosed advanced ovarian cancer: time for a paradigm shift? *Cancers* 2021;13(22):5756 [118] (https://doi.org/10.3390/cancers13225756), an open access article distributed under the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/). *Germline BRCAm testing should be offered to all patients with epithelial ovarian cancer at diagnosis, with tumor testing for somatic BRCAm for patients in whom a germline BRCAm is not detected; †Olaparib and niraparib approved in the US; ‡Niraparib approved in the US; §Olaparib + bev approved in the US; ‖Bev approved in the US. *bev* bevacizumab, *BRCAm BRCA1* and/or *BRCA2* mutation, *CR* complete response, *HRD* homologous recombination deficiency, *IV* intravenous, *NACT* neoadjuvant therapy, *NED* no evidence of disease, *PARPi* poly(ADP-ribose) polymerase inhibitor, *PBC* platinum-based chemotherapy, *PDS* primary debulking surgery, *PR* partial response, *q3w* every 3 weeks

In terms of maintenance combination therapy in the newly diagnosed setting, the Phase III ATHENA-COMBO (GOG-3020/ENGOT-ov45) trial (NCT03522246) is comparing rucaparib plus nivolumab with rucaparib alone. A non-analytical arm (nivolumab alone) will be analyzed as an exploratory endpoint to assess the relative contribution of nivolumab alone [107].

A number of other studies are investigating PARPi (with or without anti-angiogenic agents) in combination with immune checkpoint inhibitors and novel targeted agents, including inhibitors of WEE-1, ATR, MEK, AKT, and mTORC1/2, in OC. Key Phase III trials currently underway investigating triplet therapy in patients with newly diagnosed advanced OC include: DUO-O/ENGOT-ov46/GOG-3025, evaluating combinations of platinum-based chemotherapy, bevacizumab, and the anti-programmed death-ligand 1 (PD-L1) antibody durvalumab, followed by maintenance bevacizumab, durvalumab, and olaparib in patients without BRCAm [108]; KEYLYNK-001/MK-7339-001/ENGOT-ov43/

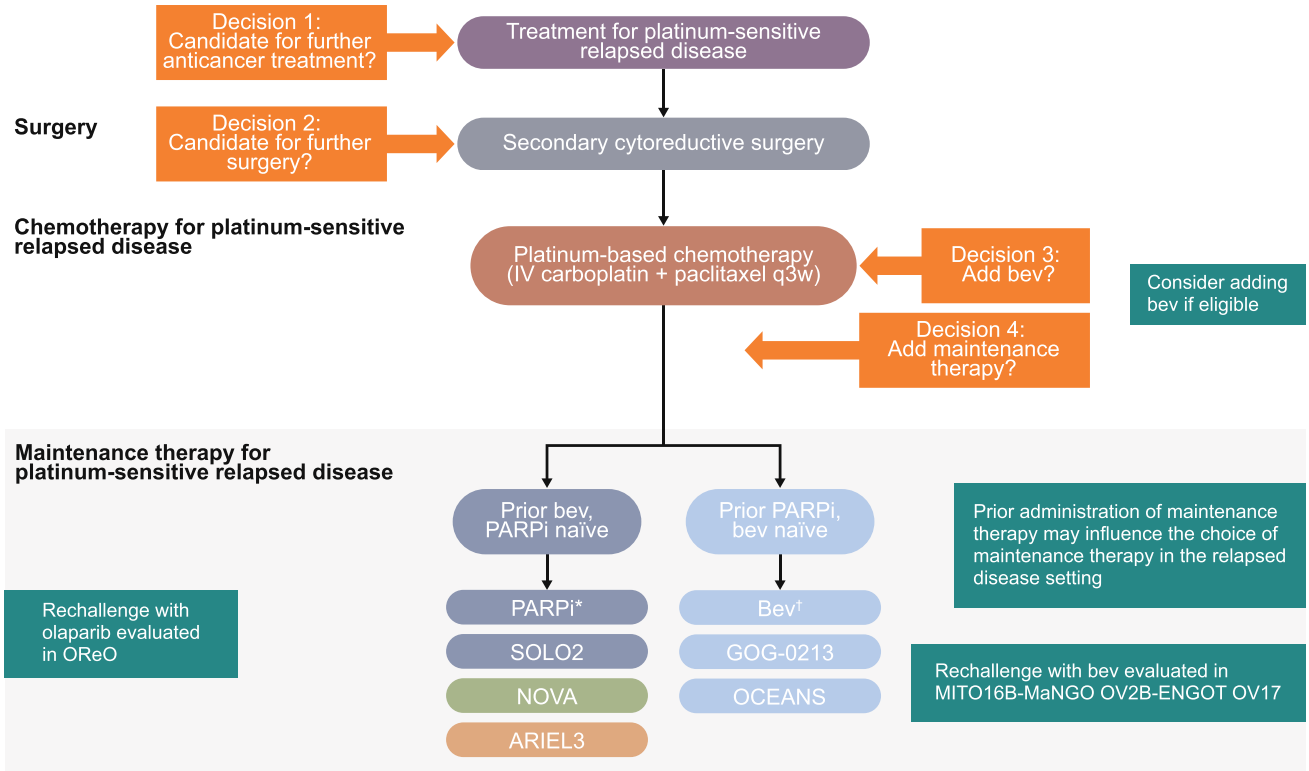

Fig. 3 Proposed treatment algorithm for platinum-sensitive relapsed ovarian cancer. *Olaparib, niraparib, and rucaparib approved in the US (niraparib approved in patients with a germline BRCAm and rucaparib approved in patients with a BRCAm); †Bev approved in the US. *bev* bevacizumab, *BRCAm BRCA1* and/or *BRCA2* mutation, *IV* intravenous, *PARPi* poly(ADP-ribose) polymerase inhibitor, *PBC* platinum-based chemotherapy, *q3w* every 3 weeks

GOG-3036, evaluating the anti-programmed cell death protein 1 (PD-1) agent pembrolizumab combined with carboplatin/paclitaxel followed by maintenance olaparib in non-BRCAm patients (concurrent, maintenance bevacizumab is optional) [109]; and FIRST/ENGOT-ov44, evaluating the anti-PD-L1 agent dostarlimab in combination with first-line paclitaxel/carboplatin, followed by maintenance dostarlimab plus niraparib (concurrent, maintenance bevacizumab is optional) [110].

Although some patients exhibit primary resistance to PARPi, various acquired resistance mechanisms (e.g. BRCA reversion mutations, restoration of HRR function, replication fork stabilization, epigenetic changes) can lead to disease progression during PARPi therapy [111–113]. Combining PARPis with novel targeted agents (e.g. WEE-1 or ATR inhibitors) may help achieve PARPi resensitization in patients who develop PARPi resistance and progress during PARPi therapy [114–116]. The potential benefit and limitations of PARPi rechallenge were shown in OReO/ENGOT Ov-38 (NCT03106987), the first Phase IIIb study to provide data on PARPi maintenance rechallenge [117]. Patients in OReO had PSROC and were heavily pretreated; maintenance olaparib rechallenge provided a statistically significant improvement in PFS over placebo in patients with a BRCAm (HR 0.57; 95% CI 0.37–0.87; $P = 0.022$) or without a BRCAm (HR 0.43; 95% CI 0.26–0.71; $P = 0.002$) [117]. Although OReO selected patients who had previously demonstrated sensitivity to a PARPi, some olaparib patients most likely progressed during OReO because PARPi resistance had developed during their prior PARPi therapy. Currently, there are limited clinical data on rechallenging patients with a single-agent PARPi as maintenance therapy; rechallenge may be an option for some patients, such as those patients who have not progressed on a prior PARPi followed by response to platinum-based chemotherapy.

8 Conclusions

To our knowledge, this narrative review provides the most comprehensive and up-to-date review of PARPi as maintenance therapy and treatment in OC.

Strong evidence supports the use of PARPis in OC. Over time, the treatment landscape has shifted from use

of PARPis in the relapsed disease setting to the first-line maintenance therapy setting. Indeed, data support the early introduction of PARPis as they appear to provide the most benefit in the newly diagnosed setting, rather than reserving their use for the relapsed setting. Our proposed treatment algorithms for both newly diagnosed and PSROC are shown in Figs. 2 and 3.

Within the newly diagnosed setting, PARPis provide the greatest clinical benefit in patients with BRCAm or who test positive for HRD, meaning biomarker testing is critical to identify patients most likely to benefit from PARPi maintenance therapy and guide treatment decisions. For this reason, biomarker testing, including evaluation of HRD and genomic instability, should be conducted in all newly diagnosed OC patients.

It is becoming clear that curative intent is an achievable outcome in advanced OC. In the first-line setting, 7-year results from SOLO1 showed a clinically meaningful improvement in OS in patients with a BRCAm who received maintenance olaparib, and 5-year results from PAOLA-1 showed a clinically meaningful improvement in OS in patients whose tumors tested positive for HRD who received maintenance olaparib plus bevacizumab. Identifying which factors predict the patients who will experience long-term remission with PARPi maintenance therapy remains critical.

Although similarities are evident in the tolerability profiles of the different PARPis, distinct differences are also observed, requiring customization of monitoring recommendations and/or dosing regimens (e.g. use of a lower starting dose of niraparib in the first-line setting in patients with a lower bodyweight or baseline platelet count to help ameliorate thrombocytopenia). Importantly, new safety signals have not been observed with longer-term follow-up. The risk of MDS/AML with PARPis remained low in the newly diagnosed setting with longer-term follow-up. The risk of MDS/AML appears higher when PARPis are utilized in the recurrent setting, although multiple factors may potentially impact the imbalance in MDS/AML seen with PARPi usage versus placebo in the relapsed disease setting. Long-term follow-up of patients receiving PARPis for MDS/AML remains important.

Data from trials investigating novel combination strategies including PARPis are awaited with interest; the optimal sequencing of novel therapies in OC remains to be established.

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