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PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline

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abstract

PURPOSE To provide recommendations on the use of poly(ADP-ribose) polymerase inhibitors (PARPis) for management of epithelial ovarian, tubal, or primary peritoneal cancer (EOC).

METHODS Randomized, controlled, and open-labeled trials published from 2011 through 2020 were identified in a literature search. Guideline recommendations were based on the review of the evidence, US Food and Drug Administration approvals, and consensus when evidence was lacking.

RESULTS The systematic review identified 17 eligible trials.

RECOMMENDATIONS The guideline pertains to patients who are PARPi naïve. All patients with newly diagnosed, stage III-IV EOC whose disease is in complete or partial response to first-line, platinum-based chemotherapy with high-grade serous or endometrioid EOC should be offered PARPi maintenance therapy with niraparib. For patients with germline or somatic pathogenic or likely pathogenic variants in *BRCA1* (g/s*BRCA*1) or *BRCA2* (g/s*BRCA*2) genes should be treated with olaparib. The addition of olaparib to bevacizumab may be offered to patients with stage III-IV EOC with g/s*BRCA1/2* and/or genomic instability and a partial or complete response to chemotherapy plus bevacizumab combination. Maintenance therapy (second line or more) with single-agent PARPi may be offered for patients with EOC who have not received a PARPi and have responded to platinum-based therapy regardless of *BRCA* mutation status. Treatment with a PARPi should be offered to patients with recurrent EOC that has not recurred within 6 months of platinum-based therapy, who have not received a PARPi and have a g/s*BRCA1/2*, or whose tumor demonstrates genomic instability. PARPis are not recommended for use in combination with chemotherapy, other targeted agents, or immune-oncology agents in the recurrent setting outside the context of a clinical trial. Recommendations for managing specific adverse events are presented. Data to support reuse of PARPis in any setting are needed.

Additional information is available at www.asco.org/gynecologic-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

In 2020, it is estimated that there will be 21,750 new cases of ovarian cancers diagnosed in the United States, and despite advances in treatment, an estimated 13,940 women will die of the disease.[1] A woman's risk of getting ovarian cancer during her lifetime is approximately 1 in 78 and her lifetime chance of dying of ovarian cancer is about 1 in 108.[1] Approximately 85%-90% of all ovarian cancers are epithelial in origin, and approximately 70% of all epithelial ovarian cancers are high-grade serous (HGS) adenocarcinoma.[2] Despite initial therapy, usually consisting of surgical cytoreduction and platinum-taxane combination therapy, the majority of women with advanced-stage epithelial ovarian, tubal, or primary peritoneal cancer (hereinafter referred to as EOC), will have a relapse of their disease and require additional treatment.[3]

Germline alterations in breast cancer 1 (g*BRCA1*) and breast cancer 2 (g*BRCA2*) genes have been identified in up to 17% of women diagnosed with EOC, and somatic mutations are found in an additional 7%.[4-7] Approximately 41%-50% of EOCs are estimated to exhibit homologous recombination deficiency (HRD) involved in repair of DNA damage and replication.[8] The introduction of poly(ADP-ribose) polymerase

THE BOTTOM LINE

PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline

Guideline Questions

1. Should PARPi therapy for EOC be repeated over the course of treatment?
2. In which patients with newly diagnosed EOC are PARPis recommended?
   a. What are the histologic types of EOC for which PARPis are recommended?
   b. What are the biomarker subsets for which PARPis are recommended?
3. Is PARPi monotherapy recommended for recurrent EOC? If so,
   a. In which settings (eg, second-line maintenance or treatment of recurrent disease)?
   b. At what dose and duration?
4. Are there settings where PARPis in combination with chemotherapy or other targeted therapy are recommended?
5. How should clinicians manage the specific toxicities of the various PARPis?

Target Population

Patients diagnosed with epithelial ovarian, tubal, or primary peritoneal cancer (EOC) who have not previously received a poly(ADP-ribose) polymerase inhibitor (PARPi).

Target Audience

Medical, radiation, and surgical oncologists; gynecologic oncologists; gynecologists; advanced practice and other health professionals; women with ovarian cancer and their families.

METHODS

An Expert Panel was convened to develop clinical practice guideline recommendations on the basis of a systematic review of the medical literature and Food and Drug Administration (FDA) regulatory approvals.

Recommendations

Note: These recommendations pertain only to patients with EOC who have not previously received a PARPi. The recommendations are based on clinical trial results and FDA approvals and do not necessarily capture regulatory approvals in other jurisdictions.

Repeating PARPi

Recommendation 1.0. Repeating PARPi therapy in the treatment of EOC is not recommended at this time. Consideration should be made as to the best time in the life cycle of an individual patient's EOC in which to use PARPi; clinical trial participation is encouraged (Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong).

Newly Diagnosed Ovarian Cancer

Recommendation 2.0. PARPis are not recommended for use in initial treatment of early stage (stage I-II) EOC because there is insufficient evidence to support use in this population (Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong).

Recommendation 2.1. Women with newly diagnosed stage III-IV EOC that is in complete or partial response to first-line platinum-based chemotherapy should be offered PARPi maintenance therapy with olaparib (for those with germline or somatic pathogenic or likely pathogenic variants in *BRCA*1 or *BRCA*2 genes) or niraparib (all women) in high-grade serous (HGS) or endometrioid ovarian cancer.

- PARPi maintenance therapy should consist of olaparib (300 mg orally every 12 hours for 2 years) or niraparib (200-300 mg orally daily for 3 years). Longer duration could be considered in selected individuals. (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 2.2. The addition of olaparib to bevacizumab maintenance may be offered to patients who have stage III-IV HGS or endometrioid ovarian cancer and germline or somatic pathogenic or likely pathogenic variants in *BRCA*1 or *BRCA*2 genes and/or genomic instability, as determined by Myriad myChoice CDx, and who have had a partial or complete response to chemotherapy plus bevacizumab combination (Type: evidence based, benefits outweigh harms; Evidence quality: strong; Strength of recommendation: strong).

Recommendation 2.3. Inclusion of the PARPi veliparib with combination chemotherapy followed by veliparib maintenance therapy cannot be recommended at this time. There are no data that this approach is superior, equal, or less toxic than a switch maintenance (Type: evidence based; benefit/harms ratio unknown; Evidence quality: intermediate; Strength of recommendation: strong).

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THE BOTTOM LINE (CONTINUED)

Note: As of this writing, veliparib is not commercially available.

Recurrent Ovarian Cancer: Second-Line or Greater Maintenance and Treatment

Recommendation 3.0. PARPi monotherapy maintenance (second-line or more) may be offered to patients with EOC who have not already received a PARPi and who have responded to platinum-based therapy regardless of *BRCA* mutation status; treatment is continued until progression of disease or toxicity despite dose reductions and best supportive care.

- Options include: olaparib 300 mg every 12 hours; rucaparib 600 mg every 12 hours; niraparib 200-300 mg once daily. (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.1. Treatment with a PARPi should be offered to patients with recurrent EOC who have not already received a PARPi and have a germline or somatic pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* genes.

- Options include: olaparib 300 mg every 12 hours; rucaparib 600 mg every 12 hours; niraparib 200-300 mg once daily (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.2. Treatment with a PARPi monotherapy should be offered to patients with recurrent EOC who have not already received a PARPi and whose tumor demonstrates genomic instability, as determined by Myriad myChoice CDx, and has not recurred within 6 months of platinum-based therapy (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.3. PARPis are not recommended for treatment of *BRCA* wild-type or platinum-resistant recurrent EOC (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

PARPis in Combination

Recommendation 4.0. PARPi are not recommended for use in combination with chemotherapy, other targeted agents, or immune-oncology agents in the recurrent setting outside the context of a clinical trial. Clinical trial participation is encouraged (Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong).

Management of Adverse Events

Recommendation 5.0 Anemia:

a. Patients requiring a blood transfusion for symptom relief and/or hemoglobin level < 8 g/dL should be monitored. PARPi dose should be reduced with evidence of repeated anemia to avoid multiple transfusions.
b. Patients with progressive anemia may be offered growth factor per ASCO guidelines and physician and patient comfort.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 5.1 Neutropenia:

a. Growth factor is not indicated for use in patients receiving daily PARPi.
b. Neutropenia (grade 4 lasting at least 5-7 days or associated with fever) should result in dose hold until recovery of infection and granulocyte count, followed by dose reduction. Growth factor support may be used in this setting to support patient safety during the drug hold.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 5.2 Platelets:

a. Thrombocytopenia is most common with niraparib. Niraparib dosing guidelines should be used to lower starting dose (200 mg) based on weight and platelet count.
b. Discontinue PARPi for persistent thrombocytopenia or significant bleeding despite dose reduction.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate)

Recommendation 5.3 Persistent cytopenia:

a. Evaluation for treatment-related myelodysplastic syndrome/acute myeloid leukemia should be initiated in patients with persistent cytopenia that occurs despite drug hold.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 5.4 Nausea:

a. Many patients will have tachyphylaxis of nausea symptoms over the first cycle of therapy.
b. Persistent nausea requiring daily antiemetic intervention, causing a reduction in performance status, and/or resulting in $> 5\%$ weight loss should result in dose reduction.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

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ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, as well as a companion guideline on Germline and Somatic Tumor Testing in EOC,[9] is available at www.asco.org/gynecologic-cancer-guidelines. The *ASCO Guidelines Methodology Manual* (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

inhibitors (PARPis) has led to major change in the approaches to EOC management across the treatment life cycle. In 2014, the US Food and Drug Administration (FDA) approved the first PARPi, olaparib, as a treatment of g*BRCA* EOC for patients who had received ≥ 3 prior lines of chemotherapy. Rucaparib received FDA approval for treatment of g/s*BRCA* recurrent disease in 2016. Approval for niraparib and, subsequently, olaparib as maintenance therapy for women with complete or partial response to platinum-based chemotherapy was granted in 2017. Since then, the FDA has expanded the regulatory approval of PARPis, thereby allowing more patients to benefit from these agents and access the drugs earlier in treatment. Recent studies have confirmed that the efficacy of PARPis is enhanced not only in g/s*BRCA* EOC but also in cancers in which HRD is caused by other underlying etiologies. The applications of PARPis in the management of EOC are complex and all approvals to date are predicated on the absence of prior exposure to PARPis.

The purpose of this guideline is to provide clinicians, other health care practitioners, patients, and caregivers with recommendations regarding the role of PARPis in the management of EOC based on the best available evidence.

GUIDELINE QUESTIONS

This clinical practice guideline addresses five overarching clinical questions:

1. Should PARPi therapy for EOC be repeated over the course of treatment?
2. In which patients with newly diagnosed EOC are PARPis recommended?
   - 2a. What are the histologic types of EOC for which PARPis are recommended?
   - 2b. What are the biomarker subsets for which PARPis are recommended?
3. Is PARPi monotherapy recommended for recurrent EOC? If so:
   - 3a. In which settings (eg, second-line maintenance or treatment of recurrent disease)?
   - 3b. At what dose and duration?
4. Are there settings where PARPis in combination with chemotherapy or other targeted therapy are recommended?
5. How should clinicians manage the specific toxicities of the various PARPis?

METHODS

Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included two patient representatives and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met in person, via teleconference, and/or webinar, and corresponded through e-mail. Based on the consideration of the evidence and FDA regulatory approval, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to *Journal of Clinical Oncology (JCO)* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of the literature conducted in PubMed for randomized controlled trials (RCTs) published from January 1, 2009, to May 3, 2019. The search was then updated on April 20, 2020, and relevant trials released at ESMO (European Society for Medical Oncology) 2019 and ASCO 2020 were also identified. The FDA's Center for Drug Evaluation and Research database was also searched for regulatory information. Articles were selected for inclusion in the systematic review of the evidence on the basis of the following criteria:

- Population: Adult women with EOC
- Intervention: PARPi, including olaparib, niraparib, rucaparib, and veliparib
- Comparator: Standard-of-care options or placebo
- Outcomes: Therapeutic efficacy (eg, survival, response rate), health-related quality of life, adverse events
- Fully published or recent meeting presentations of English-language reports of phase II-III RCTs
- For special circumstances, prospective, single-arm trials were accepted.

Articles were excluded from the systematic review if they were (1) editorials, commentaries, letters, news articles, case reports, narrative reviews; or (2) published in a non-English language. The guideline recommendations were crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[9] In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The *ASCO Guidelines Methodology Manual* (hereafter, Methodology Manual; available at www.asco.org/guidelines-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 17 trials[10-27] met eligibility criteria and form the evidentiary basis for the guideline recommendations (Table 1). Outcomes are summarized in Tables 2-5. The identified trials were published between 2011 and 2020 and compared, when comparators were part of the study design, PARPis to standard-of-care options or placebo. The primary outcome for all trials was therapeutic efficacy, expressed as progression-free survival (PFS). Secondary and exploratory outcomes included overall survival (OS), objective response rate, progression-free survival 2, time to discontinuation of treatment or death, time to first subsequent therapy or death (TFST), adverse events (AEs) and health-related quality of life (HRQoL). Characteristics of the studies' participants are outlined in Table 1. Figure 1 outlines the current approval of PARPis in ovarian cancer.

Study Quality

Study design aspects related to individual study quality, strength of evidence, strength of recommendations, and risk of bias were assessed. Refer to the Methodology

Manual for more information and for definitions of ratings for overall potential risk of bias.

Study quality was formally assessed for the fully published trials identified but not for the study only available in abstract form.[26] Design aspects related to the individual study quality were assessed by one reviewer, including factors such as blinding, allocation concealment, placebo control, intention to treat (ITT), funding sources, and so forth, and generally indicated a low to intermediate potential risk of bias for most of the identified evidence. In general, the quality of the included studies ranged from intermediate to high. Quality assessment ratings are found in the Data Supplement. Please refer to Methodology Manual for definitions of ratings for overall potential risk of bias.

KEY OUTCOMES OF INTEREST

Efficacy

Newly diagnosed (frontline) maintenance setting. In the upfront setting, a total of four trials investigated PARPis for maintenance therapy, two as monotherapy[13,20] one as combination therapy,[24] and one as combination therapy followed by monotherapy.[10]

The SOLO1 trial[20] investigated olaparib as first-line maintenance therapy in patients with g*BRCA*1/2 International Federation of Obstetrics and Gynecology (FIGO) stage III-IV, HGS or endometrioid EOC after a complete response (CR) or partial response (PR) to initial first-line, platinum-based chemotherapy. The trial showed that maintenance with olaparib improved PFS compared with placebo (hazard ratio [HR], 0.30; 95% CI, 0.23 to 0.41). Although the data from secondary outcomes are still immature, they suggest olaparib delays TFST (median, 51.8 months) compared with placebo (median, 15.1 months; TFST HR, 0.30; 95% CI, 0.22 to 0.40).

The PRIMA trial[13] investigated the efficacy of niraparib maintenance therapy after a response to platinum-based chemotherapy in patients with newly diagnosed, advanced (FIGO stage III-IV), HGS or endometrioid EOC at high risk for relapse. The trial confirmed that the clinical benefit of first-line treatment with niraparib could be extended to all patients with advanced EOC regardless of HRD status, which was used as a stratification factor. In the overall population, a significant benefit in median duration of PFS was seen with niraparib over placebo (13.8 months *v* 8.2 months; HR, 0.62; 95% CI, 0.50 to 0.76; $P < .001$). PFS was also significantly improved in those with HRD tumors (21.9 months *v* 10.4 months; HR, 0.43; 95% CI, 0.31 to 0.59; $P < .001$). The extended median duration of PFS was also observed in the niraparib group compared with the placebo group (8.1 months *v* 5.4 months; HR, 0.68) in the subgroup of patients with homologous recombination–proficient tumors.

The PAOLA-1[24] trial is the first phase III trial to examine the efficacy of a PARPi with bevacizumab as first-line maintenance therapy in patients with advanced (FIGO stage III-IV), HGS and endometrioid EOC (other histologies if g*BRCA*m) with CR or PR (CR/PR) to standard platinum-based chemotherapy given with bevacizumab. Patients, who were not restricted by surgical outcome or g*BRCA* status, were randomly assigned to receive olaparib for up to 24 months and bevacizumab for 15 months in total, or placebo. A statistically significant improvement in PFS was demonstrated in the ITT population compared with placebo (median PFS, 22.1 months *v* 16.6 months; HR, 0.59; 95% CI, 0.49 to 0.72; $P < .0001$). Prespecified subgroup analyses showed that patients with s*BRCA* mutations (HR, 0.31; 95% CI, 0.20 to 0.47) and patients with positive HRD status (including g/s*BRCA*-mutated tumors; HR, 0.33; 95% CI, 0.25 to 0.45) had the greatest PFS benefits. No benefit was observed in patients with negative HRD status (16.6 *v* 16.2 months; HR, 1.00; 95% CI, 0.75 to 1.35). The recent approval was limited to women with g/sBRCA and and/or genomic instability by Myriad myChoice CDx (Myriad Genetics, Salt Lake City, UT) and who have had a CR/PR to chemotherapy plus bevacizumab combination.

The VELIA trial[10] assessed the efficacy of veliparib added to first-line chemotherapy with carboplatin and paclitaxel and continued as maintenance monotherapy in patients with previously untreated, advanced, FIGO stage III-IV, HGS EOC. In the overall population, the median PFS was 23.5 months in the induction and maintenance veliparib group compared with 17.3 months in those receiving placebo (HR, 0.68; 95% CI, 0.56 to 0.83; $P < .001$). In patients with g*BRCA* mutation, the median PFS was 34.7 versus 22.0 months, respectively, in the veliparib compared with the control group (HR, 0.44; 95% CI, 0.28 to 0.68; $P < .001$). In the HRD cohort, the corresponding duration was 31.9 months and 20.5 months, respectively (HR, 0.57; 95% CI, 0.43 to 0.76; $P < .001$). In the ITT population, median PFS was 23.5 months versus 17.3 months, respectively (HR, 0.68; 95% CI, 0.56 to 0.83; $P < .001$). Stratification was based on g*BRCA* status and was added 14 months after initiation of the study, at which time the study was more than half accrued. No benefit was seen in patients with homologous-recombination–deficient *BRCA* wild-type (*BRCA*wt) disease (HR, 0.74; 95% CI, 0.52 to 1.06) or those with homologous-recombination–proficient disease (HR, 0.81; 95% CI, 0.60 to 1.09). Veliparib is not approved in this setting and is not commercially available at this writing.

Treatment of Recurrence Setting. Eight studies[12,14,16,18,21,22,25,26] were identified that investigated PARPis as treatment for recurrence. Four open-label, phase II studies[12,14,18,26] examined olaparib for patients with g*BRCA*m advanced EOC. Each study found improved clinical benefit with olaparib. Two single-arm studies of rucaparib, ARIEL 2[25] and Study 10,[16], also both demonstrated improved PFS in measurable g*BRCA*m ovarian cancer.

TABLE 1. Clinical Trials Evaluating PARPis in EOC

Study (ClinicalTrials.gov identifier)	Patient Population	PARPi	FDA Approval Date	Treatment Dosing	Indication
Front-line maintenance					
SOLO1[20] (NCT01844986). Phase III, randomized, double-blind, placebo controlled, multicenter study	Female patients with newly diagnosed, histologically confirmed, high-risk advanced (FIGO stage III-IV) *BRCA*m, HGS or high-grade endometrioid ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer who have completed first-line platinum-based chemotherapy	Olaparib	12/2018	300 mg BID (150 mg, 100 mg tablets)	Deleterious germline OR somatic *BRCA*m and CR/PR to first-line platinum-based chemotherapy
	Patients must have clinical CR/PR and have no clinical evidence of disease progression				
	Patients must be randomly assigned within 8 weeks of their last dose of chemotherapy				
PRIMA (Gonzalez-Martin, 2019[13] NCT02655016). Phase III, randomized, double-blind, placebo controlled, multicenter study	Newly diagnosed advanced ovarian cancer, regardless of *BRCA*m status	Niraparib	4/2020	300 mg (3 × 100-mg capsules) for patients with a baseline body weight ≥ 77 kg and baseline platelet count ≥ 150,000 μL	CR/PR to first-line platinum-based chemotherapy, regardless of *BRCA*m or HRD status
	Histologically confirmed, advanced (FIGO stage III or IV), high-grade, predominantly serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have completed first-line platinum-based chemotherapy (neoadjuvant or adjuvant)			200 mg (2 × 100-mg capsules) for patients with a baseline body weight < 77 kg or baseline platelet count < 150,000 μL	
	Patient must have clinical CR/PR after completing chemotherapy course				
	Patient must be randomly assigned within 12 weeks of the first day of the last cycle of chemotherapy				
PAOLA-1[24] (NCT02477644). Phase III, randomized, double-blind, placebo controlled, multicenter study	Newly diagnosed ovarian cancer, primary peritoneal cancer, and/or fallopian tube cancer	Olaparib + bevacizumab	5/2020	300 mg BID (2 × 150-mg or 3 × 100-mg tablets)	CR/PR to first-line chemotherapy and bevacizumab combination and g/sBRCA and/or genomic instability by Myriad myChoice CDx
	Histologically confirmed HGS, high-grade endometrioid or other epithelial nonmucinous ovarian cancer in a patient with deleterious germline *BRCA*1/2 at an advanced stage (FIGO stage IIIB, IIIC, or IV)				
	Non-*BRCA*m patients allowed if HGS				
	Completed first-line platinum-taxane chemotherapy with bevacizumab prior to randomization				
	Platinum-taxane–based regimen must have consisted of a minimum of four treatment cycles, including platinum, and a maximum of nine				
	Bevacizumab dose 15 mg/kg every 3 weeks up to a total of 15 months				
	Prior to randomization, patient's disease must be NED or in CR/PR from her first-line treatment				

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TABLE 1. Clinical Trials Evaluating PARPis in EOC (continued)

Study (ClinicalTrials.gov identifier)	Patient Population	PARPi	FDA Approval Date	Treatment Dosing	Indication
VELIA[10] (NCT02470585). Phase III, randomized, double-blind, placebo controlled, multicenter study	Histologic diagnosis of FIGO stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, with the appropriate tissue available for histologic evaluation	Veliparib	None to date	150 mg BID for 2 weeks then (transition period) 400 mg BID	Stage III or IV HGS EOC
	HGS adenocarcinoma				
	Willing to undergo testing for g*BRCA*				
Treatment of recurrent ovarian cancer					
Study 42[14] (NCT01078662). Phase II, open label, nonrandomized, noncomparative, multicenter study	Confirmed germline loss-of-function *BRCA1* or *BRCA2* mutation deemed deleterious or suspected	Olaparib	12/2014	400 mg BID (50-mg capsules)	Deleterious germline *BRCA* mutation, ≥ 3 prior systemic therapies
	Platinum-resistant (relapse within 6 months of platinum therapy) epithelial ovarian, primary peritoneal, or fallopian tube cancer (or unsuitable for additional platinum therapy)				
	Select patients with breast, pancreatic, and hormone-refractory prostate cancer were also eligible to participate	Olaparib	12/2014	400 mg BID (50-mg capsules)	Deleterious germline *BRCA* mutation, ≥ 3 prior systemic therapies
Gelmon et al[12] (NCT00679783). Phase II, open label, nonrandomized, noncomparative, multicenter study	Histologically confirmed HGS and/or undifferentiated carcinoma of ovary, fallopian tube, or peritoneum				
	Estrogen, progesterone, and HER2-negative advanced adenocarcinoma of the breast	Olaparib	12/2014	400 mg BID (50-mg capsules)	Deleterious germline *BRCA* mutation, ≥ 3 prior systemic therapies
	Known *BRCA*-positive breast cancer or ovarian cancer that is not HGS or undifferentiated tubo-ovarian carcinoma				
CLIO Study[26] (NCT02822157). Phase II, open label, randomized, crossover study	Recurrent epithelial carcinoma of the ovary, fallopian tube, or primary peritoneum	Olaparib	12/2014	400 mg BID (50-mg capsules)	Deleterious germline *BRCA* mutation, ≥ 3 prior systemic therapies
	At least one previous line of chemotherapy				
Liu et al[18] (NCT01116648). Phase II, open label, randomized study	Histologically or cytologically grade 2 or 3 (high-grade) papillary-serous or endometrioid epithelial ovarian cancer, primary peritoneal serous cancer, or fallopian tube cancer;	Olaparib	12/2014	400 mg BID (50-mg capsules)	Deleterious germline *BRCA* mutation, ≥ 3 prior systemic therapies
	Participants with epithelial ovarian, primary peritoneal, or fallopian tube cancers of other high-grade histologies who carry a known deleterious *BRCA* germline mutation				
Kaye et al[15] (NCT 00628251). Phase II, open label, randomized study	Histologically or cytologically confirmed recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma and ≥ 1 measurable lesions according to RECIST	Olaparib	12/2014	400 mg BID (50-mg capsules)	Deleterious germline *BRCA* mutation, ≥ 3 prior systemic therapies
	Confirmed germline *BRCA1/2* mutation, disease that recurred or progressed within 12 months of the most recent platinum-based chemotherapy regimen				

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TABLE 1. Clinical Trials Evaluating PARPis in EOC (continued)

Study (ClinicalTrials.gov identifier)	Patient Population	PARPi	FDA Approval Date	Treatment Dosing	Indication
SOLO 3[22] (NCT02282020). Phase III, open label, randomized, controlled, study	Histologically diagnosed relapsed HGS ovarian cancer (including primary peritoneal and/or fallopian tube cancer) or high-grade endometrioid cancer. Patients are eligible to undergo *BRCA* testing even if they have not yet had recurrence or progression of disease > 6 months (≥ 183 d) after completion of their last platinum therapy	Olaparib	12/2014	300 mg BID (150-mg tablets)	Deleterious germline *BRCA* mutation, ≥ 3 prior systemic therapies
	Documented germline mutation in *BRCA1* and/or *BRCA2* predicted to be deleterious or suspected deleterious				
	Patients must have received ≥ 2 prior platinum-based lines of chemotherapy				
	Patients must be partially platinum sensitive or platinum sensitive				
Study 10[16] (NCT01482715). Phase I/II, open-label, safety, pharmacokinetic, and preliminary efficacy study	Known deleterious *BRCA* mutation (g*BRCA* or s*BRCA*)	Rucaparib	12/2016	600 mg BID (200-mg, 300-mg capsules)	Deleterious germline OR somatic *BRCA*m and ≥ 2 priors
	Evidence of measurable disease				
	Histologically confirmed diagnosis of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer				
	Received ≥ 3 prior chemotherapy regimens and had disease relapse				
ARIEL 2[25] (NCT01891344). Phase II, open-label, multicenter study	Histologically confirmed diagnosis of HGS or grade 2 or grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer. If mixed histology, > 50% of the primary tumor had to be confirmed to be HGS or endometrioid upon rereview by local pathology	Rucaparib	12/2016	600 mg BID (200-mg, 300-mg capsules)	Deleterious germline OR somatic *BRCA*m and ≥ 2 priors
	Relapsed/progressive disease				
	Received prior platinum-based therapy and had platinum-sensitive disease				
	Disease had progressed ≥ 6 months after their most recent platinum-based treatment				

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TABLE 1. Clinical Trials Evaluating PARPis in EOC (continued)

Study (ClinicalTrials.gov identifier)	Patient Population	PARPi	FDA Approval Date	Treatment Dosing	Indication
QUADRA[21] (NCT02354586). Phase II, multicenter, open-label, single arm study	Tumor HRD testing and blood g*BRCA*m status testing	Niraparib	10/2019	300 mg daily	Recurrent ovarian cancer treated with ≥ 3 prior chemotherapy regimens and cancer is associated with HRD positivity
	Patients must have histologically diagnosed high-grade (grade 2 or 3) serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with recurrent disease and must have been previously treated with chemotherapy and experienced a response lasting ≥ 6 months to first-line platinum-based therapy				
	Patients must have completed three or four previous chemotherapy regimens, with the last chemotherapy regimen > 4 weeks before treatment initiation				
	Patients must have measurable disease according to RECIST				
	Patients must have formalin-fixed, paraffin-embedded tumor samples available from the primary or recurrent cancer or agree to undergo fresh biopsy before study treatment initiation				
Maintenance therapy, second-line and beyond					
Study 19[17,28] (NCT00753545). A phase II, randomized, double-blind, placebo controlled, multicenter study	Female patients with histologically diagnosed recurrent ovarian or fallopian tube cancer or primary peritoneal cancer with HGS (grade 2 or 3) features	Olaparib	8/2017	400 mg BID (50-mg capsules)[a]	Recurrent ovarian cancer and CR/PR to platinum-based chemotherapy
	Completed ≥ 2 courses of platinum-based chemotherapy and patient's most recent regimen induced an objective response				
	*BRCA*m status was not required (preplanned retrospective analysis was conducted and published based on *BRCA*m status)				
	Patients must be treated in the study within 8 weeks of completion of their final dose of the platinum-containing regimen				
SOLO 2[23,27] (NCT01874353). A phase III, randomized, double-blind, placebo-controlled, multicenter study	Recurrent ovarian or fallopian tube or peritoneal cancer	Olaparib	8/2017	300 mg BID (150-mg tablets)[a]	Recurrent ovarian cancer and CR/PR to platinum-based chemotherapy
	Platinum-sensitive disease				
	Patients had completed ≥ 2 courses of platinum-based chemotherapy with objective response				
	Required to have a predicted deleterious, or suspected deleterious, *BRCA*m based on blood or tumor testing				

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TABLE 1. Clinical Trials Evaluating PARPis in EOC (continued)

Study (ClinicalTrials.gov identifier)	Patient Population	PARPi	FDA Approval Date	Treatment Dosing	Indication
NOVA[19] (NCT01847274). A phase III, randomized, double-blind, placebo controlled, multicenter study	Histologically diagnosed ovarian cancer, fallopian tube cancer or primary peritoneal cancer	Niraparib	3/2017	300 mg daily (100-mg capsules)	Recurrent ovarian cancer and CR/PR to platinum-based chemotherapy
	HGS (or grade 3) histology or known to have g*BRCA*m				
	Received ≥ 2 previous courses of platinum-containing therapy and had disease that was considered platinum sensitive (> 6 months between penultimate platinum regimen and progression of disease)				
	Responded to last the platinum regimen and enrolled within 8 weeks of the last platinum regimen				
ARIEL 3[11] (NCT01968213). A phase III, randomized, double-blind, parallel assignment, multicenter study	Confirmed diagnosis of HGS or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer	Rucaparib	4/2018	600 mg BID (200-mg, 300-mg capsules)	Recurrent ovarian cancer and CR/PR to platinum-based chemotherapy
	Received ≥ 2 prior platinum-based treatments; last platinum-based regimen must have been administered immediately before maintenance therapy				
	Received ≤ 1 nonplatinum chemotherapy regimen. Prior hormonal therapy will not be counted as a nonplatinum regimen				
	At least a 6-month disease-free period after prior treatment with the penultimate platinum-based chemotherapy and achieved a response				
	For the last chemotherapy course before study entry, patients must have received a platinum-based doublet chemotherapy regimen and have achieved a CR/PR and/or a GCIG CA-125 response				

Abbreviations: BID, twice daily; *BRCA*m, *BRCA* mutation; CGIC, Clinical Global Impression of Change; CR, complete response; EOC, epithelial ovarian, tubal, or primary peritoneal cancer; FDA, Food and Drug Administration; FIGO, International Federation of Obstetrics and Gynecology; g*BRCA*m, germline *BRCA* mutation; g*BRCA*wt, germline *BRCA* wild-type; g/s*BRCA*m, germline and/or somatic *BRCA* mutation; HGS, high-grade serous; HRD, homologous recombination deficiency; NED, without evidence of disease; PARPi, PARP inhibitor; PR, partial response; s*BRCA*m, somatic *BRCA* mutation.

[a]In an attempt to improve dosing constraints of the capsule formulation, an alternative tablet formulation with improved bioavailability was developed to facilitate olaparib administration to patients. Comparisons of the bioavailability of these two different oral formulations was investigated.[29] Study 24 demonstrated that patients' exposure after tablet doses ≥ 300 mg BID matched or exceeded that of the approved 400-mg BID capsule formulation (8 × 5-mg capsules BID). The 300-mg tablet dose BID was better tolerated than higher doses and it showed similar effectiveness in tumor shrinkage.

TABLE 2. Newly Diagnosed Maintenance Setting

	SOLO1[20]		PRIMA[13]		PRIMA[13]		VELIA[10]		VELIA[10]		PAOLA-1[24]	
	ITT Set (n = 391)		ITT Set (n = 733)		HRD Population Subset (n = 373)		ITT Set (n = 757)		*BRCA*m Subset (n = 200)		ITT Set (n = 806)	
Outcome	Olaparib (n = 260)	Placebo (n = 131)	Niraparib (n = 487	Placebo (n = 246)	Niraparib (n = 247	Placebo (n = 126)	Veliparib (n = 382)	Control (n = 375)	Veliparib (n = 108)	Control (n = 92)	Olaparib + Bev (n = 537)	Placebo + Bev (n = 269)
PFS	Data maturity: 51%										Data maturity: 59%	
Rate, %	60	27	—	—	—	—	48	34	—	—	52	72
Median PFS, months	NR	13.8	13.8	8.2	21.9	10.4	23.5	17.3	34.7	22.0	22.1	16.6
HR (95% CI)	0.30 (0.23 to 0.41)		0.62 (0.50 to 0.76)		0.43 (0.31 to 0.59)		0.68 (0.56 to 0.83)		0.44 (0.2 8to 0.68)		0.59 (0.49 to 0.72)	
Two-sided *P*	< .001		< .001		< .001		< .001		< .001		< .0001	
PFS2	Data maturity: 31%										Data maturity: 39%	
Rate, %	75	60	NR		NR		NR		NR		—	—
Median PFS2 (months)	NR	41.9									32.3	30.1
HR (95% CI)	0.50 (0.35 to 0.72)										0.86 (0.69 to 1.09)	
Two-sided *P*	.0002										—	
OS	Data maturity: 21%		Interim analysis only								Data maturity 26%	
Rate, %	84	80	84	77%	91	85	NR		NR		NR	
Median OS (months)	—	—				—						
HR (95% CI)	0.95 (0.60 to 1.53)		0.70 (0.44 to 1.11)		0.61 (0.27 to 1.39)							
Two-sided *P*	—		—									
TFST											Data maturity: 59%	
Rate, %	—	—	NR		NR		NR		NR		—	—
Median time (months)	51.8	15.1									24.8	18.5
HR (95% CI)	0.30 (0.22 to 0.40)										0.59 (0.49 to 0.71)	
Two-sided *P*	—										< .0001	

Abbreviations: —, not available; Bev, bevacizumab; *BRCA*m: breast cancer susceptibility gene mutation; HR, hazard ratio; HRD, homologous recombinant deficiency; ITT, intention to treat; NR, not reported; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; TDT, time to study treatment discontinuation or death; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

TABLE 3. Treatment of Recurrent Ovarian Cancer

Study	Dose and Formulation	Data Cutoff	No. of Patients	Treatment and Comparator	Efficacy Outcomes				
					PFS Rate and HR (95% CI) *P*	Median PFS (months) and HR (95% CI) *P*	OS Rate and HR (95% CI)	Median OS (months)	ORR% and ORR (95% CI) *P*
Study 42[14]	400 mg BID, capsule	July 2012	Ovarian cancer subset: 193	Olaparib (no comparator)	54.6%	7.0	64.4%	16.6	31.1 (24.6 to 38.1)
CLIO[26]	300 mg BID, tablet	Dec 2018	100	Olaparib *v* CT[a]	NA	Olaparib: 2.9 CT: 3.4	NA	NA	Olaparib: 18%[b] CT: 6%
Liu et al[18]	400 mg BID, capsule	Mar 2014	90	Olaparib + cediranib *v* olaparib	NA	Olaparib + cediranib: 17.7 Olaparib: 9.0 0.42 (0.23 to 0.76) *P* = .005	NA	NA	NA
Gelmon et al[12]	400 mg BID, capsule	Mar 2010	Ovarian cancer subset: 65	Olaparib (no comparator)	NA	*BRCA*m nonserous: 11.4[c] *BRCA*m serous: 7.2[c] *BRCA*wt nonserous: 2.6[c] *BRCA*wt serous: 6.3[c]	NA	NA	*BRCA*m nonserous: 75% *BRCA*m serous: 30.8% *BRCA*wt nonserous: 0% *BRCA*wt serous: 25.6%
Kaye et al[15]	200 or 400 mg BID, capsules	PFS: Sep 15, 2009 OS: April 30, 2010	97	Olaparib *v* PLD	0.88 (0.51 to 1.56) .66	Olaparib 200 mg: 6.5 (5.5 to 10.1) Olaparib 400 mg: 8.8 (5.4 to 9.2) PLD: 7.1 (3.7 to 10.7)	PLD *v* 200: 0.66 (0.27 to 1.55) PLD *v* 40: 1.01 (0.44 to 2.27)	NA	Olaparib 200 mg: 25% Olaparib 400 mg: 31% PLD: 18%
SOLO3[22]	300 mg BID, tablets	Oct 2018	266	Olaparib *v* chemotherapy treatment of physician's choice	0.62 (0.43 to 0.91) .013	Olaparib: 13.4 TPC: 9.2	NA	NA	Olaparib: 72.2% TPC: 51.4% 2.53 (1.40 to 4.58) .002
Study 10[16]	600 mg BID, capsule	Nov 2015	42	Rucaparib (no comparator)	59.5%	7.8	NA	NA	—
ARIEL 2[25]	600 mg BID, capsule	Jan 2016	206	Rucaparib (no comparator)	*BRCA*m: 50% LOH low: 10% 0.27 (0.16 to 0.44) < .0001 LOH high: 28% LOH low: 10% 0.62 (0.42 to 0.90) .011	*BRCA*m: 12.8 LOH low: 5.2 LOH high: 5.7 LOH low: 5.2	NA	NA	*BRCA*m: 32% LOH low: 7% *P* < .0001 LOH high: 24% LOH low: 7% *P* = .0033
QUADRA[21]	300 mg, daily	Apr 2018	463	Niraparib (no comparator)	NA	5.5	NA	17.2	28% Median duration of response: 9.2 months

Abbreviations: BID, twice daily; CT, chemotherapy; HR, hazard ratio; LOH, loss of heterozygosity; NA, not available; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; TPC, treatment of physician's choice.

[a]Physician's choice chemotherapy that includes carboplatin + gemcitabine or carboplatin + paclitaxel or carboplatin + liposomal doxorubicin or liposomal doxorubicin every 4 weeks or topotecan or paclitaxel weekly.

[b]ORR for olaparib was 38% (n = 5 of 13) in patients with g*BRCA*m and 13% (n = 7 of 54) in patients with g*BRCA*wt.

[c]Median PFS was reported in days and converted to months for the table.

TABLE 4. Maintenance Therapy for Recurrent Platinum-Sensitive Disease

	SOLO2[23,27] (tablet formulation, 300 mg BID)		STUDY 19[17,28] (capsule formulation, 400 mg BID)		NOVA[19] (capsule formulation, 300 mg daily)		NOVA[19] capsule formulation, 300 mg daily)		ARIEL 3[11] (capsule formulation, 600 mg BID)		ARIEL 3[11] (capsule formulation, 600 mg BID)	
	DCO Sept 2016/Feb 2020 for OS Full Analysis Set (N = 295)		DCO 2012/2015 *BRCA*m Subset (n = 136)		DCO June 2016 g*BRCA*m Subset (n = 203)		DCO June 2016 Non-g*BRCA*m Subset (n = 350)		DCO April 2017 *BRCA*m Subset (n = 196)		DCO April 2017 ITT (n = 207)	
Outcome	**Olaparib (n = 196)**	**Placebo (n = 99)**	**Olaparib (n = 74)**	**Placebo (n = 62)**	**Niraparib (n = 138)**	**Placebo (n = 65)**	**Niraparib (n = 234)**	**Placebo (n = 116)**	**Rucaparib (n = 130)**	**Placebo (n = 66)**	**Rucaparib (n = 141)**	**Placebo (n = 66)**
PFS												
Median PFS (months)	19.1	5.5	11.2	4.3	21.0	5.5	9.3	3.9	16.6	5.4	10.8	5.4
HR (95% CI)	0.30 (0.22 to 0.41)		0.18 (0.10 to 0.31)		0.27 (0.17 to 0.41)		0.45 (0.34 to 0.61)		0.23 (0.16 to 0.34)		0.37 (0.30 to 0.45)	
Two-sided *P*	< .0001		< .00001		< .0001		< .001		< .001		< .0001	
PFS2												
Median PFS2 (months)	NR	18.4	NA	NA	25.8	19.5	18.6	15.6	NA	NA	NA	NA
HR (95% CI)	0.50 (0.34 to 0.72)		NA		0.48 (0.28 to 0.82)		0.69 (0.49 to 0.96)		NA		NA	
Two-sided *P*	.0002		NA		.006		.03		NA		NA	
OS												
Median OS (months)	51.7	38.8	34.9	30.2	NA	NA	NA	NA	NA	NA	NA	NA
HR (95% CI)	0.74 (0.54 to 1.00)		0.62 (0.41 to 0.94)		NA		NA		NA		NA	
Two-sided *P*	.054		.02480		NA		NA		NA		NA	
ORR (CR+PR)												
No. of events: total no. of patients (%)	NA	NA	7:57 (12)	2:48 (4)	NA	NA	NA	NA	15:40 (37.5)	2:23 (8.7)	26:141 (18.4)	5:66 (7.6)
HR (95% CI)	NA		3.36 (0.75 to 23.72)		NA		NA		NR		NR	
Two-sided *P*	NA		.12		NA		NA					
TDT												
Median time (months)	19.4	5.6	11.0	4.6	NA	NA	NA	NA	NA	NA	NA	NA
HR (95% CI)	0.31 (0.23 to 0.42)		0.36 (0.25 to 0.52)		NA		NA		NA		NA	
Two-sided *P*	< .0001 (nominal *P* value)		< .00001		NA		NA		NA		NA	
TFST												
Median time (months)	27.9	7.1	15.6	6.2	21.0	8.4	11.8	7.2	NA	NA	NA	NA
HR (95% CI)	0.28 (0.21 to 0.38)		0.32 (0.22 to 0.48)		0.31 (0.21 to 0.48)		0.55 (0.41 to 0.72)		NA		NA	
Two-sided *P*)	< .0001		< .00001		< .001		< .001		NA		NA	
TSST												
Median time (months)	NR	18.2	22.0	15.3	NA	NA	NA	NA	NA	NA	NA	NA
HR (95% CI)	0.37 (0.26 to 0.53)		0.41 (0.28 to 0.62)		NA		NA		NA		NA	
Two-sided *P*	< .0001		.00001		NA		NA		NA		NA	

Abbreviations: BID, twice daily; *BRCA*m, breast cancer susceptibility gene mutation; CR, complete response; DCO, data cutoff; g*BRCA*m, germline breast cancer susceptibility gene mutation; HR, hazard ratio; ITT, intention to treat; NA, not available; NR, not reached; PFS, progression-free survival; PFS2, progression-free survival 2; OS, overall survival; ORR, objective response rate; PR, partial response; TDT, time to study treatment discontinuation or death; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

TABLE 5. Grade 3/4 Adverse Events in Randomized Controlled Trials

Reference	Intervention	No. of Patients	Grade 3/4 Adverse Events (%)				
			Fatigue[a]	Nausea/Vomiting	Anemia[b]	Neutropenia[c]	Thrombocytopenia
Study 19[17]	Olaparib	136	7.3	4.4	5.1	4	NR
	Placebo	129	3.0	< 1	< 1	< 1	
SOLO2[23]	Olaparib	195	4.1	5.2	19.5	5.1	1
	Placebo	99	2.0	1.0	2.0	4.0	NR
SOLO1[20]	Olaparib	260	4	1.1	22	9	1
	Placebo	130	2	1	2	5	2
SOLO3[22]	Olaparib	178	4.5	2.2	21.3	9.6	3.9
	Nonplatinum-based chemotherapy	88	1.3	3.9	0	15.8	2.6
Study 10[16]	Rucaparib	42	26.2	14.3	38.1	16.7	2.4
ARIEL 2[25]	Rucaparib	204	9	6	22	8	2
ARIEL 3[11]	Rucaparib	372	7	8	19	7	5
	Placebo	189	3	2	1	2	0
NOVA[19]	Niraparib	367	8.2	4.9	25.3	19.6	33.8
	Placebo	179	0.6	1.7	0	1.7	0.6
PRIMA[13]	Niraparib	484	1.9	2.0	31	12.8	28.7
	Placebo	244	0.4	1.6	1.6	1.2	0.4
VELIA[10]	Veliparib combination	376	5	8	41	62	31
	Veliparib throughout	377	8	12	38	58	28
	Control	371	3	5	26	49	8
PAOLA-1[24]	Olaparib + bev	535	5	4	17	6	2
	Placebo + bev	267	1	3	< 1	3	< 1

Abbreviations: bev, bevacizumab; NR, not reported.

[a]Includes patients with fatigue and patients with asthenia.

[b]Includes patients with anemia, decreased hemoglobin, hematocrit, and red blood cell count.

[c]Includes patients with neutropenia; febrile neutropenia; neutropenic sepsis; decreased neutrophil and granulocytes; granulocytopenia.

The SOLO3 trial[22] assessed the efficacy of olaparib compared with chemotherapy of physician's choice in patients with platinum-sensitive, relapsed, HGS or endometrioid EOC with g*BRCA*m. Patients were stratified by type of chemotherapy received, prior lines of chemotherapy (2-3 $v \geq 4$), and platinum-free interval (6-12 $v > 12$ months). The objective response rate (ORR) by independent central review was 72% with olaparib versus 51% with treatment of physician's choice (odds ratio, 2.53; 95% CI, 1.40 to 4.58; $P = .002$). The HR for PFS independent central review was 0.62 (95% CI, 0.43 to 0.91; $P = .013$), with a median of 13.4 months with olaparib versus 9.2 months with chemotherapy. The PFS by investigator assessment was 0.49 (95% CI, 0.35 to 0.70; $P < .001$), with a median of 13.2 versus 8.5 months, respectively.

The QUADRA trial,[21] a single-arm nonrandomized trial, evaluated niraparib in adult patients with relapsed, HGS epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with ≥ 3 previous chemotherapy regimens. The trial met its primary end point of overall response, with 13 of 47 patients (28%; 95% CI, 15.6% to 42.6%; one-sided $P = .00053$) with HRD-positive tumors who received three to four previous anticancer therapies and were sensitive to the most recent platinum-based therapy. The median duration of PFS in this population was 5.5 months (95% CI, 3.5 to 8.2 months), and median duration of response was 9.2 months (95% CI, 5.9–not estimable months). A total of 38 of 456 patients (8%) in the modified per-protocol population achieved an overall response. The observed median OS in the modified per-protocol population was 17.2 months (95% CI, 14.9 to 19.8 months).

Second-line and beyond maintenance setting. Four trials investigated the efficacy of PARPis in maintenance therapy in recurrent disease.[11,17,19,23,28]

Study 19[17] accrued patients with platinum-sensitive, recurrent, high-grade EOC who had received ≥ 2 prior lines of platinum-based chemotherapy and had a CR/PR to the most recent treatment, demonstrating olaparib maintenance significantly improved PFS (median 8.4 *v* 4.8 months; HR, 0.35; 95% CI, 0.25 to 0.49; $P < .001$).

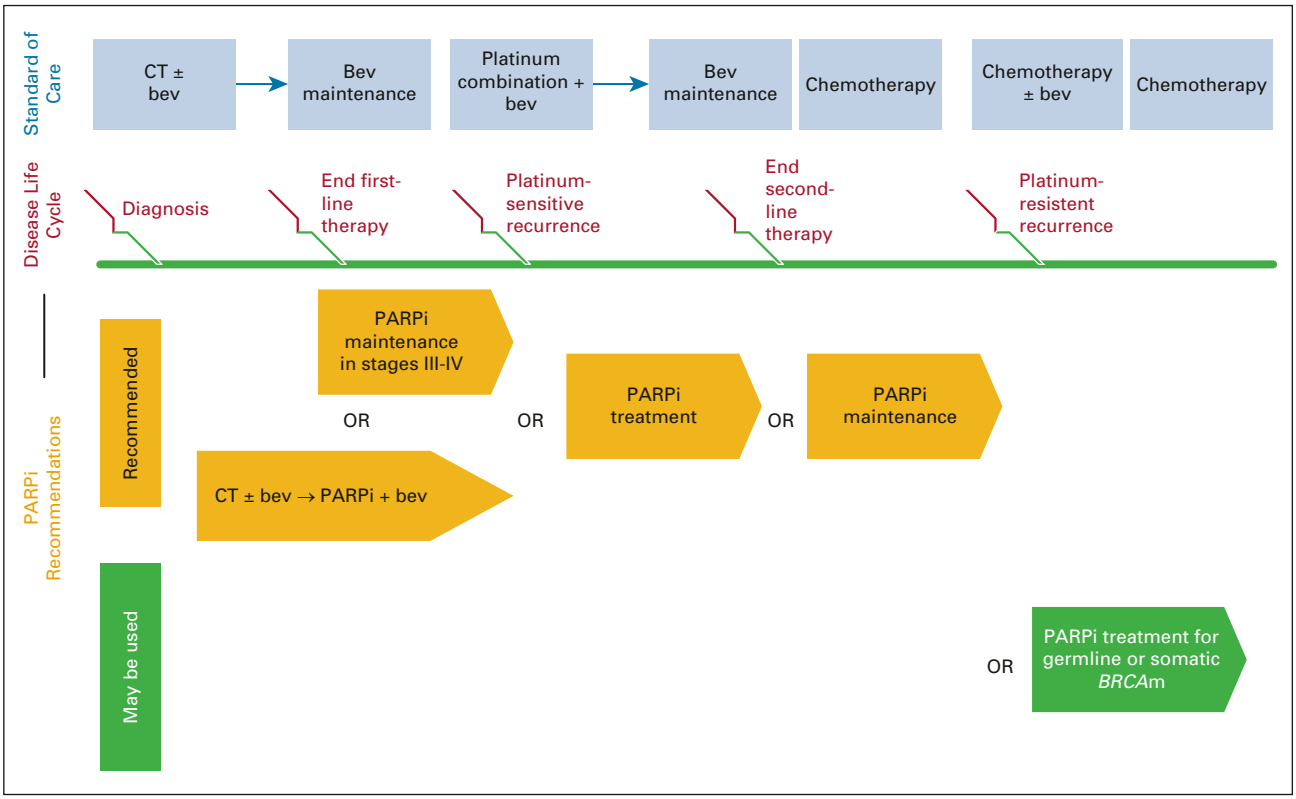

FIG 1. PARP inhibitor (PARPi) use opportunities in women who are PARPi naïve. Recommendations are color coded: Orange indicates recommendations; green indicates considerations for use. Figure 1 should not be interpreted as justification for PARPi use in > 1 of these settings. Bev, bevacixumab; CT, carboplatin and paclitaxel; *BRCA*m: *BRCA1/2* mutation.

Retrospective testing for g/s*BRCA* mutations was performed for all patients, and it was determined that 51% of participants had g/s*BRCA*m. Patients with g*BRCA*m tumors were reported to have a 6.9-month prolongation of median PFS (11.2 compared with 4.3 months in the olaparib and placebo arms, respectively). Additional analyses in the *BRCA*wt population also demonstrated a statistically significant difference in favor of the olaparib maintenance treatment arm. However, the magnitude of difference was lower when compared with the population of patients with g*BRCA*m (7.4 months *v* 5.5 months; HR, 0.54; 95% CI, 0.34 to 0.85; $P = .0075$). Analyses for OS[28] showed a slight survival advantage with olaparib over placebo in the ITT population (media OS, 29.8 *v* 27.8 months, respectively; HR, 0.73; 95% CI, 0.55 to 0.95; $P = .02$) after a median follow-up of 78 months. In the g*BRCA*m population, OS was 34.9 months versus 30.2 months in the olaparib-treated patients compared with those receiving placebo, respectively. The median improvement in OS was 4.7 months longer for olaparib versus placebo (HR, 0.62; 95% CI, 0.42 to 0.93). It is notable that the threshold was not set to determine statistical significance for OS in the *BRCA*m subgroup; therefore, the reported *P* values are nominal.

The SOLO2 trial[23] investigated olaparib monotherapy in patients with platinum-sensitive, recurrent, g/s*BRCA*1/2m EOC who had received ≥ 2 lines of chemotherapy and demonstrated a CR/PR to the most recent line of treatment. Results showed a statistically significant improvement in the median PFS for olaparib over placebo of 13.6 months (median PFS, 19.1 *v* 5.5 months), translating to a 70% reduction in risk of disease progression or death with olaparib versus placebo (HR, 0.30; 95% CI, 0.22 to 0.41; $P < .0001$). The proportion of patients who had not experienced disease progression at 12 months was 3.1 times greater in the olaparib group than in the placebo group (65.1% *v* 20.9%, respectively). Moreover, the proportion of patients who remained progression free at the 2-year mark was 2.8 times greater in the olaparib group than in the placebo group (43.0% *v* 15.1%, respectively). A preplanned, final, OS analysis with data maturity of 61% demonstrated that olaparib extended OS by approximately 13 months compared with placebo (38.8 *v* 51.7 months; HR, 0.74; 95% CI, 0.54 to 1.00; $P = .054$) in the full analysis set.[27] In the prespecified sensitivity analysis of patients with germline *BRCA* mutation, OS was extended by 15 months with olaparib compared with placebo (37.4 *v* 52.4 months; HR, 0.71; 95% CI, 0.52 to 0.97; $P = .031$).[27]

The NOVA trial[19] evaluated niraparib in patients with platinum-sensitive, recurrent EOC who had a CR/PR after ≥ 2 prior lines of platinum-based chemotherapy. Niraparib maintenance significantly improved PFS, compared with placebo, irrespective of the g*BRCA*m (21.0 *v* 5.5 months; HR, 0.27; 95% CI, 0.17 to 0.41; $P < .001$) or HRD status (HRD plus *BRCA*wt: 12.9 *v* 3.8 months; HR, 0.38; 95% CI, 0.24 to 0.59; $P < .001$) and in the overall *BRCA*wt group (9.3 *v* 3.9 months; HR, 0.45; 95% CI, 0.34 to 0.61; $P < .001$).

The ARIEL 3 trial[11] for rucaparib included three populations for step-down analysis of the primary end point, PFS: tumor *BRCA*-mutant (germline or somatic); HRD-positive, which included the g*BRCA*m group along with those with a positive HRD score (including *BRCA*wt with high [≥ 16%] genomic loss of heterozygosity; and the ITT [all-comer] population), which, again, included the g*BRCA*m and HRD-positive groups.[11] PFS was significantly improved with rucaparib versus placebo in all three populations, although the most robust clinical outcomes were seen in the g*BRCA*m subgroup.

Quality of Life

Seven RCTs[10,13,17,19,20,23,24] reported quality-of-life (QOL) end points with high completion rates. Analyses of these patient-reported outcomes found, in general, the majority of QOL scores numerically favored treatment with PARPis. However, few significant differences were observed between the treatment groups. In the absence of disease-related symptoms for trials occurring in the maintenance setting, that comparable scores were observed over time across and between treatment groups suggests that women maintain QOL during their PARPi treatment when compared with placebo. PARPis did not appear to incur additional burden or negatively impact HRQoL either during treatment or long-term follow up.

Adverse Events

The proportion of patients who experienced any AEs was higher in patients receiving PARPis than those in the comparator groups (Table 5). Anemia was the most common grade ≥ 3 AE in the PARPi group, reported to range from 5% to 22% with olaparib,[17,20,22,23] 19% to 38% with rucaparib,[11,16,25] 25% to 31% with niraparib,[13,19] 38% to 41% with veliparib combination therapy,[10] and 17% with olaparib plus bevacizumab.[24] The incidence of other AEs such as fatigue/asthenia, nausea, and vomiting were much lower (Table 5). Hematologic toxicities were more frequent with veliparib combination and niraparib monotherapy than with treatment with other PARPis. Grade 3 or higher neutropenia occurred in up to 62% of patients receiving veliparib combination treatment[10] and in 19.6% of patient treated with niraparib.[19] Similarly, thrombocytopenia was reported in up to 31% of patients receiving veliparib combination treatment and in 34% of those treated with niraparib. However, in the NOVA trial, thrombocytopenia was transient and treatment discontinuations were not attributed to these hematologic events.[19] The most prominent grade 3/4 AEs with rucaparib included fatigue (26.2%) and nausea and vomiting (14%).[16] Overall, management of AEs, for the majority of cases, were handled with appropriate dose reductions and delays.

RECOMMENDATIONS

NOTE: These recommendations pertain only to patients with EOC who have not previously received a PARPi. The recommendations are based on clinical trial results and FDA approvals and do not necessarily capture regulatory approval in other jurisdictions.

CLINICAL QUESTION 1

Repeating PARPi

Should PARPi therapy for EOC be repeated over the course of treatment?

Recommendation 1.0

Repeating PARPi therapy in the treatment of EOC is not recommended at this time. Consideration should be made as to the best time in the life cycle of an individual patient's EOC in which to use PARPi; clinical trial participation is encouraged (Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong).

Literature review and analysis. Trials investigating the redeployment of PARPis are currently underway. Enrollment began in 2017 for the OReO/ENGOT Ov-38 trial (ClinicalTrials.gov identifier: NCT03106987), a randomized, placebo-controlled, multicenter trial of olaparib maintenance retreatment in patients with nonmucinous EOC, and a CR/PR to their most recent platinum-based chemotherapy. Eligibility requires prior receipt of maintenance PARPi therapy. Random assignment to olaparib or matching placebo is split across two cohorts (approximately 416 patients): patients with a known *BRCA*m in cohort 1; patients with *BRCA*wt in cohort 2. The primary end point is investigator-assessed PFS and the study is expected to be completed in 2021.

CLINICAL QUESTION 2

Newly Diagnosed Ovarian Cancer

For which patients with newly diagnosed EOC are PARPi recommended?

a. What are the histologic types of EOC for which PARPis are recommended?
b. What are the biomarker subsets for which PARPis are recommended?

Recommendation 2.0

PARPis are not recommended for use in initial treatment of early-stage (ie, stage I-II) EOC, because there is insufficient evidence to support use in this population. (Type: informal

consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 2.1

Women with newly diagnosed stage III-IV EOC whose disease is in CR/PR to first-line, platinum-based chemotherapy should be offered PARPi maintenance therapy with olaparib (for those with germline or somatic pathogenic or likely pathogenic variants in *BRCA*1 and *BRCA*2 genes) or niraparib (all women) for treatment of high-grade serous or endometrioid ovarian cancer.

- PARPi maintenance therapy should consist of olaparib (300 mg orally every 12 hours for 2 years) or niraparib (200-300 mg orally daily for 3 years). Longer duration could be considered in selected individuals.

(Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 2.2

The addition of olaparib to bevacizumab maintenance may be offered to patients who have stage III-IV, high-grade serous or endometrioid ovarian cancer and germline or somatic pathogenic or likely pathogenic variants in *BRCA*1 or *BRCA*2 genes and/or genomic instability, as determined by Myriad myChoice CDx, and who have a CR/PR to chemotherapy plus bevacizumab combination (Type: evidence based, benefits outweigh harms; Evidence quality: strong; Strength of recommendation: strong).

Recommendation 2.3

Inclusion of the PARPi veliparib with combination chemotherapy followed by veliparib maintenance therapy cannot be recommended at this time. There are no data that this approach is superior, equal, or less toxic than a switch maintenance (Type: evidence based; benefits/harms ratio unknown; Evidence quality: intermediate; Strength of recommendation: strong).

Note: As of this writing, veliparib is not commercially available.

Literature review and analysis. The efficacy of PARPi as front-line maintenance therapy has been demonstrated in four randomized trials identified by the systematic review: SOLO1,[20] PRIMA,[13] PAOLA-1,[24] and VELIA.[10] Maintenance therapy with PARPi achieved substantial PFS benefit among patients with platinum-sensitive, recurrent ovarian cancer after a CR/PR to the most recent regimen. SOLO1[20] demonstrated that, after a CR/PR to first-line platinum-based chemotherapy, olaparib maintenance therapy confers PFS benefits to patients with advanced primary *BRCA*1/2-mutated ovarian cancer (Table 2). The PRIMA trial,[13] in which patients newly diagnosed with advanced ovarian cancer were enrolled regardless of their *BRCA* status, found a significant improvement in PFS compared with placebo in the overall population (Table 2). The PFS benefit was even more pronounced in the HRD-positive patient subgroup. Notably, maintenance with niraparib also demonstrated a significant reduction in the risk of disease progression or death in the HRD-negative subgroup.

Two trials were identified that considered PARPi combination therapy. The PAOLA-1 trial[24] investigated the efficacy of maintenance therapy with a PARPi in patients with advanced ovarian cancer regardless of *BRCA* mutation status who are receiving first-line standard-of-care treatment including bevacizumab. Results demonstrate olaparib added to bevacizumab maintenance treatment significantly improved PFS in the overall population. The benefit was even more pronounced in the *BRCA*-mutated and HRD-positive subgroups. No statistically significant benefit was seen in patients with HRD-negative tumors (HR, 1.00; 95% CI, 0.75 to 1.35). VELIA[10] evaluated a PARPi, veliparib, in combination with chemotherapy (carboplatin and paclitaxel), followed by PARPi maintenance treatment in the first-line setting. The primary analysis demonstrated a significantly extended PFS in all women, regardless of biomarker status. However, it remains unclear if the addition of veliparib is necessary for the overall benefit, because no chemotherapy-plus-placebo comparator arm was included in the study design.

Clinical interpretation. All trials reported to date present results for women who were PARPi naïve at the time of initiation of PARPi therapy. The rapid progression of studies examining PARPi for therapy of recurrent disease to second-line maintenance to front-line maintenance limited having a re-exposure scenario. This is an important area of unmet need for investigation. Retreatment off study is strongly discouraged because it is unsupported by data and prevents the capture of data that may be useful to the community. The lack of OS benefit from any of the treatment or maintenance studies to date should be balanced against factors such as the unknown short-term and late risks (eg, acute myeloid leukemia [AML]/myelodysplastic syndromes [MDS]) and development of collateral resistance to other agents (eg, platinum).

Physicians and patients are strongly encouraged to consider the full life cycle of advanced ovarian cancer against current data in determining when to use PARPi for individual care (Fig 1). The evolution of knowledge regarding mechanisms of resistance to PARPi makes clear that parameters defining resistance (eg, minimum treatment-free interval, biomarker selection) may need to be taken into account in clinical testing of PARPi retreatment. This should be done in the context of well-defined clinical trials. The recommendations herein are focused on the use of PARPi for women with ovarian cancer who have not received prior treatment with a PARPi.

Data are strong from all studies indicating that women with g*BRCA*m (or the rare s*BRCA*m) have improved PFS with PARPi maintenance therapy with either olaparib or niraparib. The recently published ASCO guideline on germline and somatic tumor testing in epithelial ovarian cancer[30]

recommends early germline testing. This recommendation recognizes that the identification of a deleterious germline or somatic mutation in *BRCA*1 or *BRCA*2 would inform PARPi treatment decisions for women with newly diagnosed disease. The PRIMA study demonstrates progression-free benefit for all women with high-grade serous or endometrioid ovarian cancer. Together, these results support consideration of primary maintenance therapy for all women with high-grade serous or endometrioid disease. However, no OS results are available from these studies nor data to address conservation of platinum-sensitivity in women whose disease progressed while they received PARPi maintenance or after completion of PARPi maintenance. Those results should inform future treatment decision-making. Given the expectation that early treatment may confer the best outcome, maintenance therapy with PARPi should be offered, with these caveats.

Doses recommended are the standard dose used for either maintenance or treatment of existing disease and are shown in Recommendation 2.0 with a qualification in the discussion for Recommendation 5.2. Eligibility for maintenance therapy includes women with CR/PR to initial platinum-based therapy, to continue for up to 2 years (olaparib) or 3 years (niraparib) in women with CRs who are tolerating the drug. Longer treatment duration can be considered for women initiating maintenance therapy with a PR to platinum-based therapy and demonstrating clinical improvement with PARPi treatment. The patient and her physician should consider risk-benefit balance for prolonged therapy. Switching PARPis to address tolerance is acceptable; however, it is not acceptable to switch to a different PARPi at the time of disease progression while being treated with a PARPi.

Inclusion of bevacizumab with primary chemotherapy and as maintenance has been evaluated for women with advanced stage III-IV, newly diagnosed EOC.[31] It is recognized that not all women with newly diagnosed EOC may have results of a germline test at the initiation or even during primary chemotherapy and may have been initiated on a bevacizumab-containing therapy. Moving to a PARPi maintenance per the FDA approval would then be difficult. The PAOLA-1 trial examined the role of olaparib maintenance added on top of a regimen including bevacizumab with primary chemotherapy and as maintenance. This phase III trial demonstrated benefit with addition of olaparib for women with g/s*BRCA* and women with HRD score ≥ 42; there was a 0.9-month difference for women with wild-type disease and no evidence of HRD.[24] Thus, addition of a PARPi in the setting of a bevacizumab combination primary therapy is a reasonable option for those women who have attained a CR/PR to primary therapy. This recommendation is of moderate strength, because the added value for women with wild-type disease is questionable and may be informed further by the outcome of the ongoing FDA review.

Only the VELIA study included a PARPi with chemotherapy in initial treatment of ovarian cancer.[10] Inclusion of veliparib with chemotherapy and continued into maintenance therapy for 30 cycles may be offered if veliparib becomes commercially available.[10] There are no data, to our knowledge, to demonstrate inclusion during chemotherapy followed by maintenance provides equal to or greater benefit, or reduced toxicity, compared with switch maintenance approaches. Furthermore, long-term safety data for inclusion of veliparib with chemotherapy followed by maintenance are needed, especially to address risk of AML/MDS. Substitution of another PARPi in the VELIA regimen is strongly discouraged, because safety, dose, and duration of niraparib and rucaparib have not been defined. Use of olaparib requires a carboplatin dose modification and attenuation of the olaparib exposure per cycle.[32-34] There are also limited long-term safety data for the olaparib/carboplatin/paclitaxel regimen.[34]

CLINICAL QUESTION 3

Recurrent Ovarian Cancer: Second-Line or Greater Maintenance and Treatment

Is PARPi monotherapy recommended for recurrent EOC? If so:

a. In which settings (eg, second-line maintenance or treatment of recurrent disease)?
b. At what dose and duration?

Recommendation 3.0

PARPi monotherapy maintenance (second-line or more) may be offered to patients with EOC who have not already received a PARPi and who have responded to platinum-based therapy regardless of *BRCA* mutation status; treatment is continued until progression of disease or toxicity despite dose reductions and best supportive care.

- Options include: olaparib 300 mg every 12 hours; rucaparib 600 mg every 12 hours; niraparib 200-300 mg once daily.

(Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)

Recommendation 3.1

Treatment with a PARPi should be offered to patients with recurrent EOC who have not already received a PARPi and have a germline or somatic pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2* genes.

- Options include: olaparib 300 mg every 12 hours; rucaparib 600 mg every 12 hours; niraparib 200-300 mg once daily.

(Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)

Recommendation 3.2

Treatment with a PARPi monotherapy should be offered to patients with recurrent EOC who have not already received

a PARPi and whose tumor demonstrates genomic instability, as determined by Myriad myChoice CDx, and has not recurred within 6 months of platinum-based therapy (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.3

PARPis are not recommended for treatment of *BRCA*wt or platinum-resistant, recurrent EOC (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Literature review and analysis. The systematic review identified 13 trials in total, nine of which were open label, phase II studies[12,14-16,18,21,22,25,26] and four of which were phase II or III controlled trials.[11,17,19,23] In maintenance therapy for the second-line or greater setting, Study 19,[17,28] SOLO2,[23] NOVA,[19] and ARIEL3[11] all demonstrated significant efficacy of PARPis compared with placebo (Table 3). For recurrent disease, Study 42,[14] SOLO3,[22] Study 10[16], ARIEL2,[25] and QUADRA[21] all reported a significant improvement in response and PFS in patients with *BRCA* mutations (Table 4).

Clinical interpretation:

- **Maintenance:** Four trials investigated the efficacy of PARPi maintenance therapy in platinum-sensitive recurrent disease, and all showed an improvement in PFS.[11,17,19,23] Across all studies, women with a g/sBRCA mutation had the most robust clinical improvements. OS results just reported on the SOLO2 trial, which investigated olaparib monotherapy in patients with platinum-sensitive, recurrent, g/s*BRCA*1/2m EOC who had received ≥ 2 lines of chemotherapy. The preplanned, final, OS analysis with data maturity of 61% demonstrated that olaparib extended OS by approximately 13 months compared with placebo (38.8 *v* 51.7 months; HR, 0.74, 95% CI, 0.54 to 1.00; $P = .054$) in the full analysis set and extended OS by 15 months with olaparib compared with placebo (37.4 *v* 52.4 months; HR, 0.71; 95% CI, 0.52 to 0.97; $P = .031$) in the prespecified sensitivity analysis of patients with germline *BRCA* mutation.
- **Recurrent disease:** The first approval for PARPis was for use in the treatment setting for recurrent ovarian cancer for PARPi-naïve women. Olaparib is FDA approved for the treatment of patients with gBRCAm ovarian, fallopian, or primary peritoneal cancer who have received ≥ 3 prior lines of chemotherapy. Rucaparib is approved for the treatment of patients with gBRCAm–associated ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥ 2 chemotherapy regimens. Rucaparib yielded benefit in ARIEL2 in a small cohort (n = 5) of ovarian cancers with RAD51C or RAD51D mutations, with three PRs and two patients with prolonged stable disease for 8.3 and 11.0 months.[25]

The recently reported, single-arm QUADRA trial of niraparib treatment in recurrent ovarian cancer met its primary end point demonstrating activity in fourth- and fifth-line treatment of patients with g*BRCA* and positive for HRD who were PARPi naïve and platinum sensitive to their last platinum therapy (n = 47). The study had an ORR of 28% and a median duration of response of 9.2 months. It was approved in 2019 for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with ≥ 3 prior chemotherapy regimens who are PARPi naïve and whose cancer is associated with HRD-positive status determined using the myChoice CDx as either tumor *BRCA* mutated and/or with a genomic instability score ≥ 42. Patients with HRD-positive cancers but without *BRCA* mutations must have experienced progression at least 6 months after the last dose of platinum-based therapy (ie, must have platinum-sensitive disease).

Dosing recommendations for treatment with all three agents are the same as defined previously for use in maintenance therapy. PARPi treatment is not generally recommended for treatment of platinum-resistant cancer. It has < 5% activity for treatment of *BRCA*wt, platinum-resistant, recurrent EOC. Any use of PARPi in the platinum-resistant setting is recommended to occur in the setting of a clinical trial, whether as a single agent or in chemotherapy, antiangiogenesis, or immunotherapy combinations. Nor should PARPis be readministered after prior exposure and progression on PARPi therapy, because there are no data to support that re-exposure in this setting is beneficial, and agent approval does not specify this option. Clinical trial participation is encouraged.

CLINICAL QUESTION 4

PARPi in Combination

Are there settings where a PARPi in combination with chemotherapy or other targeted therapy are recommended?

Recommendation 4.0

PARPis are not recommended for use in combination with chemotherapy, other targeted agents, or immune-oncology agents outside the context of a clinical trial. Clinical trial participation is encouraged (Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

Clinical interpretation. There are limited data and numerous clinical trials now investigating the roles of PARPis in combination with chemotherapy, antiangiogenesis, or immunotherapies as treatment and in maintenance. The addition of PARPi is safe given no significant overlapping toxicity for women receiving hormonal blockade (ie, aromatase inhibitor) for synchronous breast cancer. However, there are no outcome data specific to this approach, to our knowledge. There is an increasing need to understand when and how to retreat with a PARPi, especially when

there has been progression while receiving a prior PARPi. These unmet needs can only be clarified with well-designed randomized trials stratified for confounding elements such as g/s*BRCA* status, prior exposure to platinum agents, prior exposure to a PARPi, and accounting for AE risks. At this time, it is not recommended to re-treat with PARPi, even for patients with g/s*BRCA* platinum-sensitive disease, nor to use combination therapy not in a clinical trial.

CLINICAL QUESTION 5

Adverse Events

How should clinicians manage the specific toxicities of the various PARPis?

Recommendation 5.0 Anemia

a. Patients requiring a blood transfusion for symptom relief and/or hemoglobin level < 8 g/dL should be monitored. PARPi dose should be reduced with evidence of repeated anemia to avoid multiple transfusions.
b. Patients with progressive anemia may be offered growth factor per ASCO guidelines and physician and patient comfort.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 5.1 Neutropenia

a. Growth factor is not indicated for use in patients receiving daily PARPi.
b. Neutropenia (grade 4 lasting ≥ 5-7 days or associated with fever) should result in dose hold until recovery of infection and granulocyte count, then dose may be reduced. Growth factor support may be used in this setting to support patient safety during the drug hold.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate),

Recommendation 5.2 Platelets

a. Thrombocytopenia is most common with niraparib. Niraparib dosing guidelines should be used to lower starting dose (200 mg) based on weight and platelet count.
b. Discontinue PARPi for persistent thrombocytopenia or significant bleeding despite dose reduction.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 5.3 Persistent cytopenia

a. Evaluation for treatment-related MDS/AML should be initiated in patients with persistent cytopenia that occurs despite drug hold.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 5.4 Nausea

a. Many patients will have tachyphylaxis of nausea symptoms over the first cycle of therapy.
b. Persistent nausea requiring daily antiemetic intervention, causing a reduction in performance status, and/or resulting in > 5% weight loss should result in dose reduction.

(Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

Clinical interpretation. PARPis, while generally well tolerated, have class- and agent-specific AEs, some of which may lead to requirements for dose modification (Table 6). The most common of those include fatigue, anemia, neutropenia, thrombocytopenia, persistent cytopenias, and nausea. Other, less common, class-effect AEs include vomiting and diarrhea, headache, elevation in levels of liver function enzymes or creatinine, and the rarer, but also more serious, pneumonitis and leukemia risks. Fatigue maybe multifactorial, due to and/or representing cytopenias, stress of nausea, and other elements, and may also be a consequence of persistent grade 1 and/or grade 2 events. Thus, because these are daily, continuously administered agents, special attention should be paid to low-grade AEs, and any grade 2 AE requiring a dose hold should be accompanied

TABLE 6. Dose Modification for PARPi

PARPi	Starting Dose	Initial Dose Reduction	Second Dose Reduction	Third Dose Reduction	Final Reduction
Olaparib	300 mg every 12 hours	200 mg[a] every 12 hours	150 mg[a] every 12 hours	Discontinue	–
Rucaparib	600 mg every 12 hours	500 mg every 12 hours	400 mg every 12 hours	300 mg every 12 hours	Discontinue
Niraparib	300 mg once daily	200 mg once daily	100 mg once daily	Discontinue	–
Niraparib if weight < 77 kg and/or platelet counts < 150,000/μL (UK based on weight < 58 kg)	200 mg once daily	100 mg once daily	Discontinue	–	–

Abbreviations: –, not applicable; PARPi, PARP inhibitor; UK, United Kingdom.
[a]Dose reductions are based on general practice standard and deviate slightly from AstraZeneca's Prescribing Information

by a dose reduction to minimize risk of a second dose hold and further or persistent events or injury. Re-escalation or resumption of initial dose is never recommended.

Anemia. Anemia is found across all PARPi use and is characterized by a macrocytic phenotype with mean corpuscular volumes that can reach > 105 (units) but is not a vitamin B_{12}–dependent pernicious anemia functionally. The anemia may present early or slowly progressively; have the commonly associated effects of fatigue, decreased exercise tolerance, and shortness of breath; and come on at different levels of anemia across patients depending on their underlying tolerance. Interventions include drug hold, dose reduction, transfusion, and consideration of growth factor support. The latter is recommended to follow existing ASCO guidelines and appears to be used less commonly. Ample experience demonstrates that drug holding without associated other change will result in recurrence of the anemia upon reinstitution of the agent. Thus, dose modification with or without transfusion to acutely ameliorate effects of anemia is recommended.

Neutropenia. More variable across agents is the presence and depth of neutropenia. All PARPis have the potential for trilineage suppression; however, the severity of neutropenia appears to vary across agents and patients. The degree of prior marrow suppressive treatment(s) and bone marrow reserve may also contribute to the tolerance of PARPi by the bone marrow. The degree of myelosuppression has not been shown to reach the levels defined in the ASCO 2015 Guideline Update for prophylactic use of growth factor support recommended for use with a > 20% risk of neutropenia with fever.[35] Thus, growth factor support is not recommended for prophylactic use during PARPi therapy.

The 2015 guidelines also reinforce that growth factors should be administered 24-72 hours after completion of the chemotherapy, making consistent use of such agents not feasible when administering a daily treatment regimen such as a PARPi. Grade 4 neutropenia of ≥ 5-7 days or grade 3 with fever are indications for holding PARPi. Severe circumstances warrant consideration of short-acting growth factor support, such as 3 days of neupogen, to mitigate further decline. If that is done, PARPi should not be restarted until resolution of fever, a granulocyte count of ≥ 1,000/dL, and adequate time (ie, 48-72 hours) have elapsed since the last dose of growth factor.

Thrombocytopenia. Thrombocytopenia has been reported with all commercially available PARPis, with variability in frequency and depth across agents. Of the three approved PARPis for ovarian cancer, niraparib had the greatest impact on platelet counts, and the risk of thrombocytopenia was greatest with initial exposures. Recommendations have been proposed in the United States (pending FDA approval) and the United Kingdom (recommended in drug insert) to modify doses as a function of age and/or weight. United Kingdom recommendations are based on the finding from the NOVA trial that there was a greater proportion grade 3/4 adverse reactions including thrombocytopenia in women in the lowest quartile of weight (≤ 58 kg) and state that a starting dose of 200 mg is recommended for women weighing < 58 kg.[19] Pending US dosing recommendations indicate that 200 mg be the starting dose for women weighing < 77 kg and/or with a starting platelet count < 150,000/μL. Dose hold followed by reduction is the recommended approach to grade 3/4 thrombocytopenia to avoid the requirement for platelet transfusions. Patients who develop persistent or recurrent thrombocytopenia while receiving a reduced dose or dose hold of PARPi should be evaluated per the following section on persistent cytopenias.

Persistent cytopenia, AML, MDS. As with all DNA-damaging agents, there is a risk for inducing injury, with the bone marrow the most common site for such injury. It is unclear the extent to which the PARPis contribute to underlying injury that may have occurred from prior exposures such as platinums, topoisomerase 1 and 2 inhibitors, and antimetabolites, all of which have some reported risks. In addition, women are living longer and thus having more overall treatment exposures, which may contribute to accumulated injury. The most common first sign is development of a single or multiple persistent cytopenias. Such a finding should trigger drug discontinuation and evaluation for common underlying causes, such as evaluation of iron stores, vitamin B_{12} level, and folate status, in the case of persistent anemia. A low threshold should be used for moving to bone marrow evaluation to rule out development of MDS or AML, especially with persistent multilinear cytopenia. Where appropriate, early hematology consultation is recommended.

Nausea. Nausea occurs in various frequency and severity across patients and PARPis. Many patients will have tachyphylaxis of nausea symptoms during the first cycle of therapy, often without institution of antiemetic therapy or dose reduction. Some patients may find a light meal or snack before taking a PARPi improves their symptoms. Persistent nausea associated with vomiting, weight loss > 5%, and/or reduction in performance status should be evaluated to rule out other causes, such as bowel obstruction. Absent other causes, any situation with a requirement for daily antiemetic intervention, causing a reduction in performance status, and/or resulting in > 5% weight loss should result in dose hold and then dose reduction upon improvement and reinstitution.

PATIENT AND CLINICIAN COMMUNICATION

Women with advanced ovarian cancer considering treatment or maintenance with a PARPi do so during a time of rapidly emerging new data and complex regulatory approvals. It is important to recognize that patients no longer rely solely on their medical team for information and often access other sources online, in print, or through social

media and support groups. Shared decision-making is essential, and patients should be informed that the evidence-based options for treatment (or maintenance), as well as the potential benefits and risks communicated by the physician, are based on knowledge that continues to evolve. Consideration of the patient's preferences should be supported in deciding the best course of treatment.

For patients faced with a decision to undergo potentially years of treatment or maintenance with a PARPi, it is essential that providers thoroughly explain the potential impact on QoL during the initial 30- to 60-day adjustment period and provide a plan for aggressive management of AEs during this phase and beyond. Patients should also be informed that a potential dose reduction may be reasonable to manage AEs. Connection with other patients who have already navigated adjustment to PARPis, through local or on-line support networks, may increase tolerability and adherence.

For recommendations and strategies to optimize patient-clinician communication, see "Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline."[36]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care, and access to drugs can vary between countries. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. A recent, large, population-based study of multigene testing in patients with breast or ovarian cancer observed racial disparities in genetic testing.[37] While approximately 34% of White women were tested, only about 22% of Black women and 24% of Hispanic women received testing. Furthermore, racial/ethnic differences in pathogenic variants observed in patients with ovarian cancer include *BRCA1,* which is reported to be 1% in individuals of African descent, 7% in Whites and 16% in Hispanics.[37] Patients with cancer who are members of racial/ethnic minorities also suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[38-41] It is also recognized and unfortunate that there are disparities in adherence to treatment guidelines.[42] As such, it is important for clinicians to offer appropriate testing and to address patients' questions, concerns, and/or misconceptions. Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have ≥ 2 such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

Because many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision-making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of the aforementioned considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[43,44] Higher patient out-of-pocket costs are a barrier to initiating and adhering to recommended cancer treatments.[45,46] PARPis are costlier than other available therapies, 18.8, 6.9, and 2.2-2.7 times costlier than paclitaxel, pembrolizumab, and bevacizumab, respectively. Patients' out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. While most insurance carriers will provide some coverage for PARPis, the patient's copayment can remain prohibitive, nonetheless. Medicare, which is used by many patients with ovarian cancer, given that the

disease largely affects older women, does cover most PARPis. The amount of coverage and the size of copay, however, vary from state to state. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[47]

Discussion of cost can be an important part of shared decision-making.[47] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and when there are ≥ 2 treatment options that are comparable in terms of benefits and harms.[47]

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from February 11, 2020, through February 25, 2020. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation, with 58 written comments received. A total of 12 respondents, who had not previously reviewed the recommendations, either agreed or agreed with slight modifications to the vast majority of the recommendations. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to Clinical Practice Guideline Committee review and approval.

The draft was submitted to two external reviewers with content expertise. It was rated as high quality, and it was agreed it would be useful in practice. Specific comments were reviewed by the Expert Panel and integrated into the final manuscript before submission to *JCO*.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting and also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in *JCO*.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

A major limitation of these guidelines is their focus on women who are PARPi naïve. The physician and patient need to consider the full lifetime of the patient and disease and weigh the data benefits and risks, especially given the lack of an OS benefit to date. A critical unmet need is to understand the opportunities and where the benefits may be for re-exposure to a PARPi after an initial good response and in combinations after a progression outcome. Preclinical development is moving rapidly and some empirical and some data-driven clinical trials have begun. Reuse of a PARPi should only be considered in such a trial situation until data develop to guide evidence-based clinical care. Future clinical trials that examine PARPi timing within the treatment life cycle and optimal duration of treatment could help establish the best risk-benefit balance practice pattern for PARPi use in the management of EOC.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/gynecologic-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline[30] (https://ascopubs.org/doi/full/10.1200/JCO.19.02960)
- Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline[36] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/gynecologic-cancer-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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APPENDICES

All Appendices and Acknowledgment material (including the table of Expert Panel members) are online only. It will appear on JCO website online but not in the print version.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX

TABLE A1. PARP Inhibitor Expert Panel Membership

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Abbreviations: NHS, National Health Service; PGIN, Practice Guideline Implementation Network.