Poly(ADP-Ribose) Polymerase Inhibitors in the Management of Ovarian Cancer: ASCO Guideline Rapid Recommendation Update

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ASCO Rapid Recommendations Updates highlight revisions to select ASCO guideline recommendations as a response to the emergence of new and practice-changing data. The rapid updates are supported by an evidence review and follow the guideline development processes outlined in the ASCO Guideline Methodology Manual. The goal of these articles is to disseminate updated recommendations, in a timely manner, to better inform health practitioners and the public on the best available cancer care options.

BACKGROUND

In 2020, ASCO published a guideline on poly(ADP-ribose) polymerase inhibitor (PARPi) therapy in the management of ovarian cancer.[1] In June 2022, the ATHENA-MONO[2] phase III multinational, double-blind, randomized controlled trial (RCT) evaluating rucaparib monotherapy reported on the efficacy of rucaparib maintenance therapy compared with placebo in patients with stage III-IV epithelial ovarian cancer (EOC) who are in complete or partial response to first-line platinum-based chemotherapy. A significant improvement in progression-free survival (PFS) constituted a strong signal for an update of the 2020 ASCO guideline recommendation for first-line maintenance therapy. Furthermore, reports of detrimental overall survival (OS) from the ARIEL4 trial[3] (rucaparib), SOLO3 trial (olaparib),[4] and ENGOT-OV16/NOVA trial[5] (niraparib) constituted safety signals for recommendation updates for treatment in recurrent platinum-sensitive EOC (*BRCA* mutation or homologous recombination deficiency [HRD] positive status) and in unselected patient population second-line maintenance treatment, respectively.

METHODS

A targeted literature search was conducted to identify any additional phase III RCTs of PARPi in this patient population. No additional randomized trials were found, although three Dear Health Care Provider letters,[4-6] one abstract,[3] and changes in US Food and Drug Administration (FDA) labeling were identified. The original Expert Panel was reconvened to review the evidence from ATHENA-MONO[2] and reports of ARIEL4,[3] SOLO3,[4] ENGOT-OV16/NOVA[5] OS outcomes, and new GSK prescribing information[6] to approve the updated recommendation (see Appendix Figs A1 and A2, online only, for summary).

EVIDENCE REVIEW

Monk et al[2] reported that, compared with placebo, rucaparib maintenance in patients with newly diagnosed advanced ovarian cancer was associated with significantly longer PFS. The median PFS was 28.7 months (95% CI, 23.0 to not reached) with rucaparib versus 11.3 months (95% CI, 9.1 to 22.1) with placebo in the *BRCA*-mutant and homologous recombination deficiency (HRD) population, determined using FoundationOne CDx (log rank $P = .0004$; HR, 0.47; 95% CI, 0.31 to 0.72); 20.2 months (95% CI, 15.2 to 24.7) versus 9.2 months (95% CI, 8.3 to 12.2) in the intent-to-treat population (log-rank $P < .0001$; HR, 0.52; 95% CI, 0.40 to 0.68); and 12.1 months (95% CI, 11.1 to 17.7) versus 9.1 months (95% CI, 4.0 to 12.2) in the HRD-negative population (HR, 0.65; 95% CI, 0.45 to 0.95).

ARIEL4, a phase III RCT, evaluated rucaparib versus chemotherapy in patients with relapsed, *BRCA*-mutated, high-grade EOC who received two or more prior lines of chemotherapy. The final analysis of the secondary OS end point[3] (70% of death events reported) found an OS detriment for patients randomly assigned to rucaparib. In the intent-to-treat population, the median OS was 19.4 months in the rucaparib group compared with 25.4 months in the chemotherapy group, resulting in a HR of 1.31 (95% CI, 1.00 to 1.73), $P = .0507$. A withdrawal of FDA approval in the United States of rucaparib as a treatment for patients with *BRCA*-mutated EOC after two or more chemotherapies became effective on June 10, 2022.[7]

SOLO3 is a phase III trial comparing olaparib versus nonplatinum chemotherapy in patients with germline *BRCA*-mutated (g*BRCA*mut) platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum-based chemotherapy. At the final analysis (data cutoff: April 16, 2021),[4] there was no significant difference in OS, a secondary end point,

ASSOCIATED CONTENT

The companion to this article was published in the October 20, 2020 issue of *Journal of Clinical Oncology*. See accompanying article on page 3468

Appendix

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

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between the treatment arms. The median OS was 34.9 months in the olaparib arm and 32.9 months in the chemotherapy arm (HR, 1.07; $P = .71$). A subgroup analysis[4] of patients treated with three or more prior lines of chemotherapy found a potential survival detriment, with a median OS of 29.9 months in the olaparib arm compared with 39.4 months in the chemotherapy arm (HR, 1.33; 95% CI, 0.84 to 2.18). AstraZeneca electively withdrew on August 26, 2022 the indication for olaparib in the treatment of adult patients with deleterious or suspected deleterious g*BRCA*mut advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy as a monotherapy line of treatment at the time of disease recurrence.[4]

Given the withdrawal of rucaparib and olaparib in the late line treatment setting in EOC, a voluntary withdrawal of niraparib and FDA label changes became effective on September 14, 2022 for the treatment of adult patients with advanced platinum-sensitive EOC who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD positive status.[6]

Lastly, ENGOT-OV16/NOVA is a phase III RCT evaluating the efficacy of niraparib as maintenance treatment for patients with platinum-sensitive recurrent EOC. On the basis of the updated analysis[5] (data cutoff: October 1, 2020), the median OS (a secondary end point) in the non-g*BRCA*mut cohort was 31.1 months for patients treated with niraparib compared with 36.5 months for patients on placebo (HR, 1.10; 95% CI, 0.83 to 1.46). In the non-g*BRCA*mut, HRDpos subgroup, with HRD status determined using Myriad myChoice CDx, the median OS was 37.3 months compared with 41.4 months, respectively (HR, 1.32; 95% CI, 0.84 to 2.06). Although the study was not powered for OS, was performed at a one-sided α-level of 0.025, and interpretation of OS is confounded by a high rate of crossover and missing data, these results warrant caution in the overall non-g*BRCA*mut cohort and to patients in the non-g*BRCA*mut/HRDpos subgroup who received niraparib maintenance in this setting. No change in regulatory labeling occurred as of date in this publication.

UPDATED RECOMMENDATIONS

Newly Diagnosed Ovarian Cancer

Recommendation 2.1. Patients with newly diagnosed stage III-IV EOC who are in complete or partial response to first-line platinum-based chemotherapy should be offered PARPi maintenance therapy in high-grade serous or endometrioid ovarian cancer. For those with germline or somatic pathogenic or likely pathogenic variants in *BRCA*1 or *BRCA*2 genes, options should include olaparib (300 mg orally every 12 hours for 2 years), niraparib (200-300 mg orally daily for 3 years) or rucaparib (600 mg twice a day for 2 years). Longer duration could be considered in selected individuals after discussion of risks. For those who are HRD positive, determined using FDA-approved companion diagnostic tests, rucaparib and niraparib are options. Niraparib or rucaparib may be offered for non-*BRCA*mut/HRDneg patients. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.)

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 or niraparib 200-300 mg once daily. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.) Maintenance treatment with niraparib for patients without germline or somatic *BRCA* mutation should weigh potential PFS benefit against possible OS decrement. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Moderate.)

Recommendations 3.1/3.2. PARPi monotherapy should not be routinely offered to patients for the treatment of recurrent platinum sensitive EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate.) *Evidence on PARPi use in this setting is evolving and data are continuing to emerge. Any decision to proceed with PARPi treatment in select populations* (BRCA *mutation, No prior PARPi use, Platinum Sensitive, Advanced Lines of Treatment) should be based on individualized patient and provider assessment of risks, benefits, and preferences.*

Recommendation 3.3. PARPi monotherapy is not recommended for treatment for patients with either *BRCA* wild-type or platinum-resistant recurrent EOC. (Type: Evidence-based, benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong.)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Recommendation Update provides a recommendation update, with review and analysis of the relevant literature for the recommendation. Additional information, including links to patient information at www.cancer.net, is available at www.asco.org/vanity.

EQUAL CONTRIBUTION

W.P.T. and E.C.K. were Expert Panel cochairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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REFERENCES

1. Tew WP, Lacchetti C, Ellis A, et al: PARP inhibitors in the management of ovarian cancer: ASCO guideline. J Clin Oncol 38:3468-3493, 2020
2. Monk BJ, Parkinson C, Lim MC, et al: A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). J Clin Oncol 10.1200/JCO.22.01003 [epub ahead of print on June 6, 2022]
3. Oza AM, Lisyanskaya AS, Fedenko AA, et al: Overall survival results from ARIEL4: A phase III study assessing rucaparib vs chemotherapy in patients with advanced, relapsed ovarian carcinoma and a deleterious BRCA1/2 mutation. Presented at ESMO 2022, Paris, France, September 9-13, 2022 (abstr 5180)

4. AstraZeneca: Dear healthcare professional letter. 2022. https://www.accc-cancer.org/docs/ossn-network/industry-news-announcements/solo3-dhcp.pdf?sfvrsn=b70b4ab8_2
5. GSK: Dear health care provider letter (niraparib). Important drug warning. 2022. https://www.zejulahcp.com/content/dam/cf-pharma/hcp-zejulahcp-v2/en_US/pdf/ZEJULA%Q:6 20(niraparib)%20Dear%20HCP%20Letter.pdf
6. GSK: Dear health care provider letter (niraparib): Important prescribing information. 2022. https://www.zejulahcp.com/content/dam/cf-pharma/hcp-zejulahcp-v2/en_US/pdf/ZEJULA%20(niraparib)%20Dear%20HCP%20Letter%20September%202022.pdf
7. Clovis Oncology: Dear health care provider letter. 2022. https://clovisoncology.com/pdfs/US_DHCPL_final_signed.pdf

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No potential conflicts of interest were reported.

APPENDIX

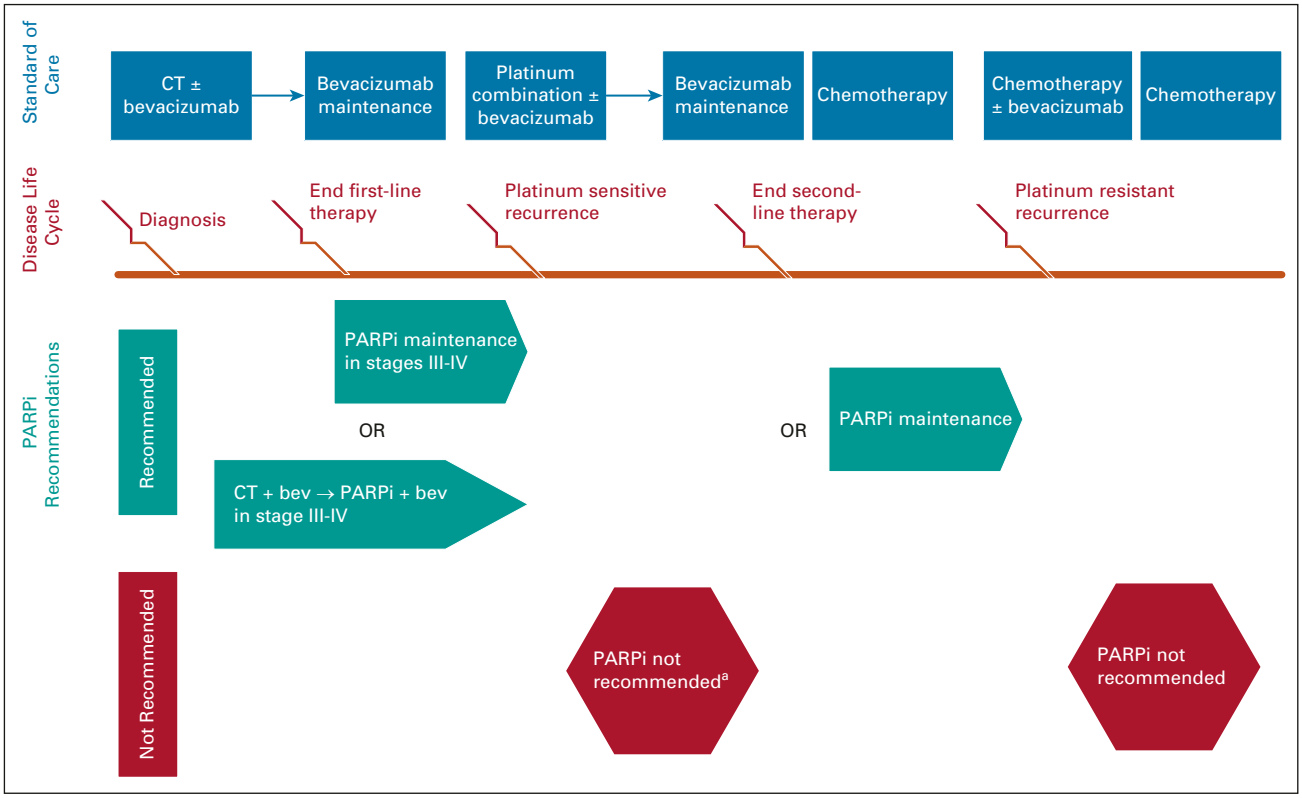

FIG A1. PARPi use opportunities in PARPi-naive women. This figure should not be interpreted as justification for PARPi use in more than one of these settings. [a]Evidence on PARPi use as treatment in platinum-sensitive recurrence is evolving and data are continuing to emerge. Any decision to proceed with PARPi treatment in select populations should be based on individualized patient and provider assessment of risks, benefits, and preferences. CT, carboplatin and paclitaxel; PARPi, poly(ADP-ribose) polymerase inhibitor.

PARPi	First remission: maintenance	Second or greater remission: maintenance[b]
Olaparib	g/s*BRCA*	g/s*BRCA*
Olaparib combined with bevacizumab	g/s*BRCA*[a]	No
Niraparib	g/s*BRCA*; HRD; wt	g/s*BRCA*; HRD; wt
Rucaparib	g/s*BRCA*; HRD; wt	g/s*BRCA*; HRD; wt

Abbreviations. g/s*BRCA*, germline or somatic *BRCA*1/2 mutation; HRD, homologous recombination deficiency; wt, *BRCA*1/2 wild-type.

FIG A2. ASCO recommendations for PARPi use: should (blue), may (red), caution (green). Of note: (1) PARPis are not recommended for use in combination with chemotherapy, nor is it recommended for monotherapy treatment. (2) HRD score companion diagnostic (Myriad MyChoice for niraparib; FoundationOne CDx for rucaparib). (3) Olaparib has not been studied in the HRD population. Olaparib may be considered an option in the HRD population in settings where any PARPi is recommended. [a]After completion of up-front chemotherapy, continue bevacizumab (1 year) and olaparib (2 years). [b]PARPi-naive. g/s*BRCA*, germline or somatic *BRCA*1/2; HRD, homologous recombination deficiency; PARPi, poly(ADP-ribose) polymerase inhibitor; wt, *BRCA*1/2 wildtype.