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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

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Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer, Version 3.2024

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer provide multidisciplinary diagnostic workup, staging, and treatment recommendations for this disease. These NCCN Guidelines Insights detail how the evolution of the use of PARP inhibitors as maintenance and single-agent regimens for the treatment of ovarian cancer informed panel recommendations in the guidelines.

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Overview

Epithelial ovarian cancer is the sixth most common cause of cancer mortality in females in the United States.[1] Germline or somatic *BRCA1/2* mutations are identified in 6% to 15% of patients with ovarian cancer.[2,3] *BRCA1* and *BRCA2* are important components of the homologous recombination repair (HRR) pathway that can be triggered upon accumulation of DNA damage–mediated double-stranded breaks (DSBs).[4,5] Loss of *BRCA* function causes HRR deficiency (HRD), resulting in dependence on other less efficient mechanisms of DNA repair and leading to accumulation of unrepaired DNA, genomic instability, and cell death.[4,5]

Poly-ADP ribose polymerase (PARP) enzymes have a multifaceted role in the sequence of events after DNA damage, one of which is to act as a scaffold to assemble components of HRR at the site of DSBs.[6] PARP1 is the best characterized enzyme of the PARP enzyme family. Inhibiting PARP activity prevents assembly of repair components, including BRCA proteins, leading to accumulation of unrepaired DSBs that ultimately lead to cell death.[6] Cells with germline or somatic *BRCA* mutations will already have inefficient repair processes due to HRD and are dependent on PARP-mediated repair, making these cells susceptible to death via inhibition of PARP activity. This sets the stage for exploiting synthetic lethality by using PARP inhibitors to cause cell death and therefore curtail tumor growth in a subset of patients with deleterious germline or somatic *BRCA* mutations.

PARP inhibitors, including olaparib, rucaparib, and niraparib, were widely studied in ovarian cancer and became established as maintenance treatment after frontline and recurrent platinum-based therapies and as monotherapy for *BRCA*-mutated or HRD disease. Long-term clinical data raised questions about the prolonged efficacy and safety of these agents in the recurrent setting. This resulted in company/FDA-initiated withdrawals for the monotherapy indications and restriction of PARP inhibitor maintenance in the recurrent setting to those patients with *BRCA*-mutated disease. These NCCN Guidelines Insights address the changing treatment landscape and provide a summary of current recommended PARP inhibitor use in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer.

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The full and most current version of these NCCN Guidelines is available at NCCN.org.

PARP Inhibitors as Maintenance Therapy in First-Line Setting

Several clinical trials have examined the efficacy of PARP inhibitors as maintenance regimens post primary therapy, including the SOLO-1 trial that investigated 2 years maintenance olaparib (vs placebo) in patients with newly diagnosed advanced ovarian cancer harboring germline or somatic *BRCA1/2* mutations.[7,8] Patients with complete response (CR) or partial response (PR) after first-line platinum-based chemotherapy were included, whereas those who received bevacizumab as part of primary systemic therapy were excluded.[7,8] After a median follow-up of approximately 41 months, patients receiving olaparib demonstrated a remarkable improvement in progression-free survival (PFS). The rate of freedom from disease progression and death at 3 years was 69% in those receiving olaparib compared with 35% in those receiving placebo ($P<.001$).[7,8] Longer follow-up at 7 years showed that 67% of patients treated with olaparib compared with 46% of patients treated with placebo were still alive.[9] Additionally, the time to first subsequent therapy was delayed in the olaparib arm compared with the placebo arm.[9] Unlike SOLO-1, PAOLA-1 included patients with newly diagnosed high-grade serous ovarian cancer regardless of *BRCA1/2* status and compared the combination of olaparib (up to 24 months)/bevacizumab with bevacizumab monotherapy in the maintenance setting.[10] Although there was no statistically significant improvement in overall survival (OS) in the intent-to-treat (ITT) population, a clinically meaningful OS benefit was observed for those with HRD tumors; 5-year OS was 65.5% versus 48.4% and median OS was 75.2 versus 57.3 months with olaparib/bevacizumab treatment versus bevacizumab alone, respectively (hazard ratio [HR], 0.62; 95% CI, 0.45–0.85).[10] Survival benefit was greatest in the *BRCA*-mutated subgroup (HR, 0.60; 95% CI, 0.39–0.93) but was also observed in the HRD-positive subgroup in the absence of somatic *BRCA* mutations (HR, 0.71; 95% CI, 0.45–1.13). The trial did not include an olaparib single-agent arm.

Other PARP inhibitors, niraparib and rucaparib, were investigated in different clinical trials around the same time. The PRIMA trial examined single-agent niraparib, for 3 years or until disease progression, as maintenance therapy for patients with advanced-stage disease who were in CR/PR after first-line platinum-based chemotherapy, and demonstrated a significant improvement in PFS with niraparib compared with placebo in the patients with HRD, with or without a *BRCA1/2* mutation (21.9 vs 10.4 months; $P<.001$).[11] In the ITT population, which included patients who had homologous recombination proficient (HRP) tumors, median PFS was 13.8 versus 8.2 months.[11] In the HRD group, median PFS was 24.5 months for those receiving niraparib versus 11.2 months for the placebo arm. In the HRP population, median PFS was 8.4 months for those receiving niraparib versus 5.4 months for the placebo arm. The final OS analysis from PRIMA confirmed the PFS benefit reported in the initial analysis, but no difference in OS was observed between the niraparib maintenance or placebo arms in either the overall population or by HRD/BRCA status.[12] In the PRIMA study about half of the patients in the placebo group received a PARP inhibitor in subsequent lines of therapy, which could compromise the ability to demonstrate improved OS. Similarly, single-agent maintenance rucaparib for up to 2 years demonstrated significant clinical benefit in those with HRD as well as the overall ITT population when compared with placebo in the ATHENA-MONO trial, which included patients regardless of *BRCA* or HRD status.[13] In ARIEL3, 21% of patients in the rucaparib arm had a PFS of ≥2 years compared with 2% in the placebo arm. There was an association between the presence of *BRCA* or certain HRR mutations (*RAD51C*, *RAD51D*) and long-term PFS benefit from rucaparib.[14] Niraparib in combination with bevacizumab for up to 3 years has also been studied in a single-arm phase II study, OVARIO, which reported that 62% of all patients, 76% of patients with HRD, 47% of patients with HRP tumors, and 56% of those with unknown homologous recombination status remained progression-free at 18 months.[15]

Results from these trials led to FDA approval of olaparib as monotherapy (for patients with a *BRCA* mutation) or in combination with bevacizumab (for patients with a *BRCA* mutation and/or HRD tumors) and of niraparib monotherapy as maintenance therapy for patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who have CR/PR following first-line platinum-based chemotherapy.[16,17] Following FDA

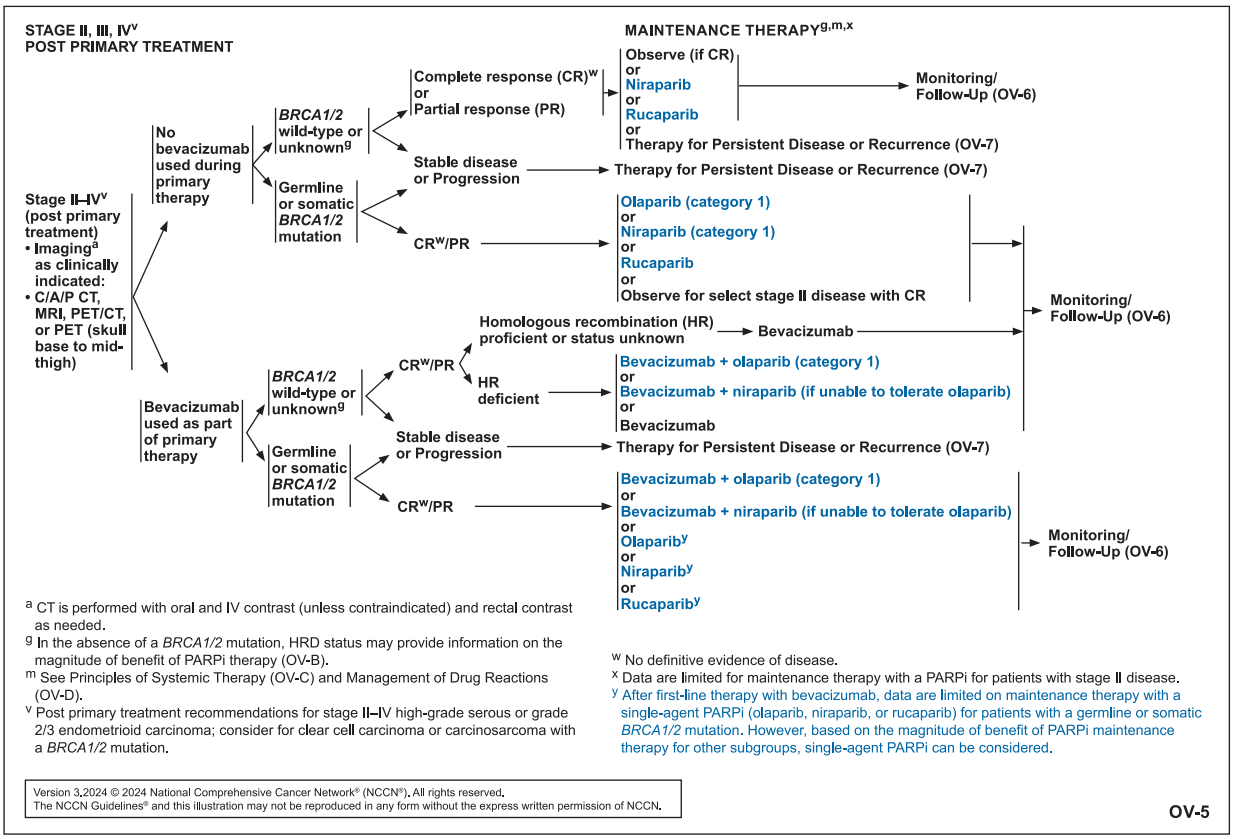


Figure 1. OV-5. NCCN Clinical Practice Guidelines in Oncology for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer, Version 3.2024.

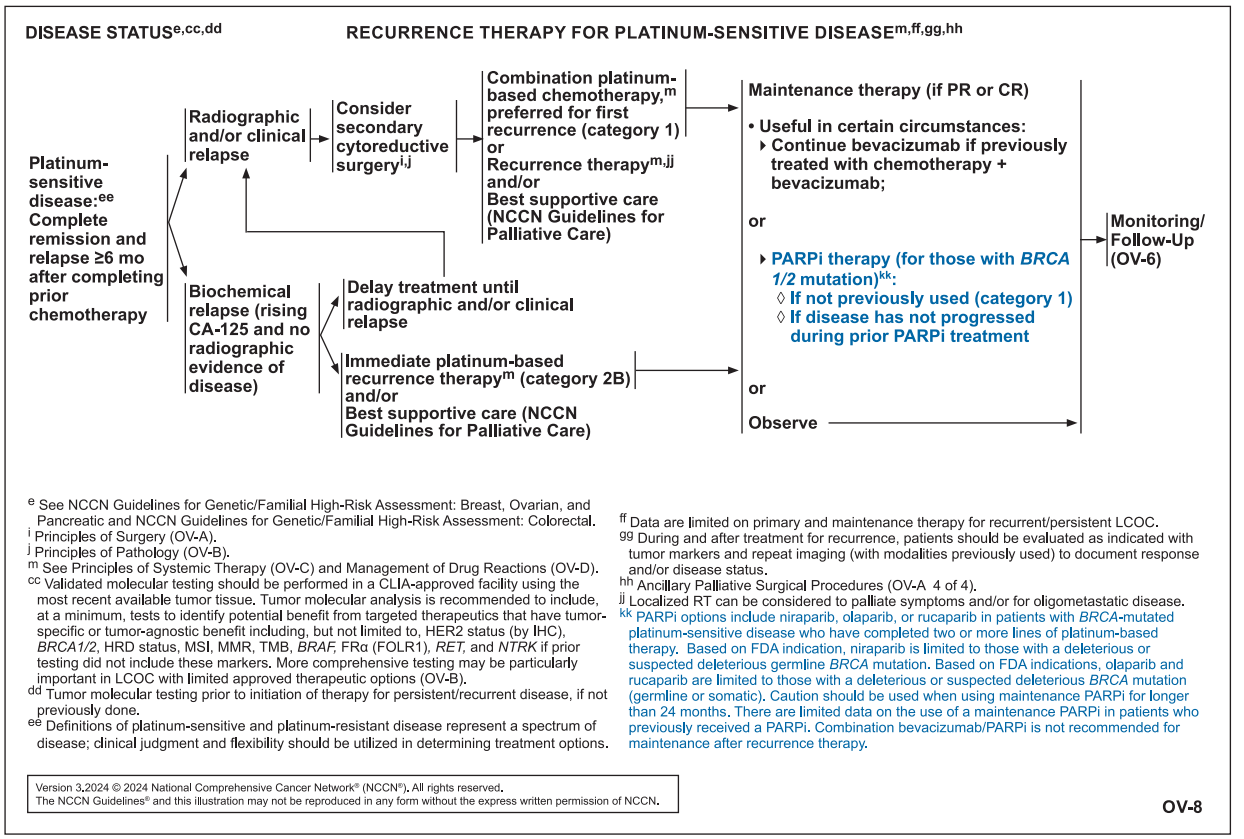
approvals, olaparib, olaparib/bevacizumab, and niraparib were initially added as first-line maintenance therapy options to the guidelines between 2019 and 2020. In 2023, rucaparib (which was previously FDA-approved for maintenance therapy in recurrent disease) was added as a monotherapy first-line maintenance option based on panel consensus. In 2024, niraparib/bevacizumab was added as a first-line maintenance therapy option for patients unable to tolerate olaparib. Neither of the latter 2 indications are currently FDA-approved.

The current recommendations for PARP inhibitors as first-line maintenance therapy post primary treatment of stage II–IV tumors (Figure 1) are based on (1) prior use of bevacizumab, (2) presence of germline or somatic *BRCA1/2* mutations, and (3) CR/PR status after first-line treatment. The panel recognizes that the current clinical HRD tests are proxy measures of HRD and lack accuracy in fully predicting functional HRD. Nonetheless, the panel members recommend HRD testing for those patients without germline *BRCA1/2* mutations, because HRD status may provide information on the magnitude of benefit of PARP inhibitor maintenance therapy in these patients. The median survival benefit is approximately 3 months in patients with HRP status, which comprise approximately half of all cases. Therefore, the panel considered the use of PARP inhibitors in patients who have HRP tumors to be of minimal benefit at present. Maintenance with bevacizumab + olaparib is a Category 1 option for patients with HRD tumors who have achieved CR/PR after completing bevacizumab-containing first-line therapy. Olaparib and niraparib monotherapy are Category 1 recommendations for those with germline or somatic *BRCA1/2* mutations and who received first-line platinum-based chemotherapy without bevacizumab, whereas olaparib and niraparib monotherapy are Category 2A options for those who received bevacizumab as part of primary therapy.

Data regarding PARP inhibitor use in patients with stage II ovarian cancer is limited and it is unlikely that future trials of PARP inhibitors as maintenance therapy post primary treatment will address this question. Furthermore, diagnosis of stage II disease is rare, especially among patients who have undergone complete surgical staging. For these reasons, the NCCN panel decided that PARP inhibitor maintenance therapy options that are recommended for patients with stage III–IV disease (Figure 1) and who have completed first-line chemotherapy should also be considered for patients who have stage II disease. The NCCN Guidelines recommendations for maintenance options specifically apply to patients with high-grade serous or grade 2/3 endometrioid cancer types. Whether these maintenance therapies are appropriate for patients with less common epithelial ovarian cancer types (ie, carcinosarcoma, clear cell carcinoma, mucinous carcinoma, grade 1 endometrioid, and low-grade serous) has not been studied.

PARP Inhibitors as Maintenance Therapy for Recurrent Disease

The recommendations for PARP inhibitors as second-line maintenance therapy options have been updated based on the following studies and FDA indications. In 2017, the FDA approved niraparib and olaparib for maintenance therapy after response to platinum-based therapy for recurrent platinum-sensitive disease based on the results of 3 phase III randomized controlled



[e] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[i] Principles of Surgery (OV-A).
[j] Principles of Pathology (OV-B).
[m] See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).
[cc] Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), *BRCA1/2*, HRD status, MSI, MMR, TMB, *BRAF*, FRα (FOLR1), *RET*, and *NTRK* if prior testing did not include these markers. More comprehensive testing may be particularly important in LCOC with limited approved therapeutic options (OV-B).
[dd] Tumor molecular testing prior to initiation of therapy for persistent/recurrent disease, if not previously done.
[ee] Definitions of platinum-sensitive and platinum-resistant disease represent a spectrum of disease; clinical judgment and flexibility should be utilized in determining treatment options.
[ff] Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.
[gg] During and after treatment for recurrence, patients should be evaluated as indicated with tumor markers and repeat imaging (with modalities previously used) to document response and/or disease status.
[hh] Ancillary Palliative Surgical Procedures (OV-A 4 of 4).
[jj] Localized RT can be considered to palliate symptoms and/or for oligometastatic disease.
[kk] PARPi options include niraparib, olaparib, or rucaparib in patients with *BRCA*-mutated platinum-sensitive disease who have completed two or more lines of platinum-based therapy. Based on FDA indication, niraparib is limited to those with a deleterious or suspected deleterious germline *BRCA* mutation. Based on FDA indications, olaparib and rucaparib are limited to those with a deleterious or suspected deleterious *BRCA* mutation (germline or somatic). Caution should be used when using maintenance PARPi for longer than 24 months. There are limited data on the use of a maintenance PARPi in patients who previously received a PARPi. Combination bevacizumab/PARPi is not recommended for maintenance after recurrence therapy.

OV-8

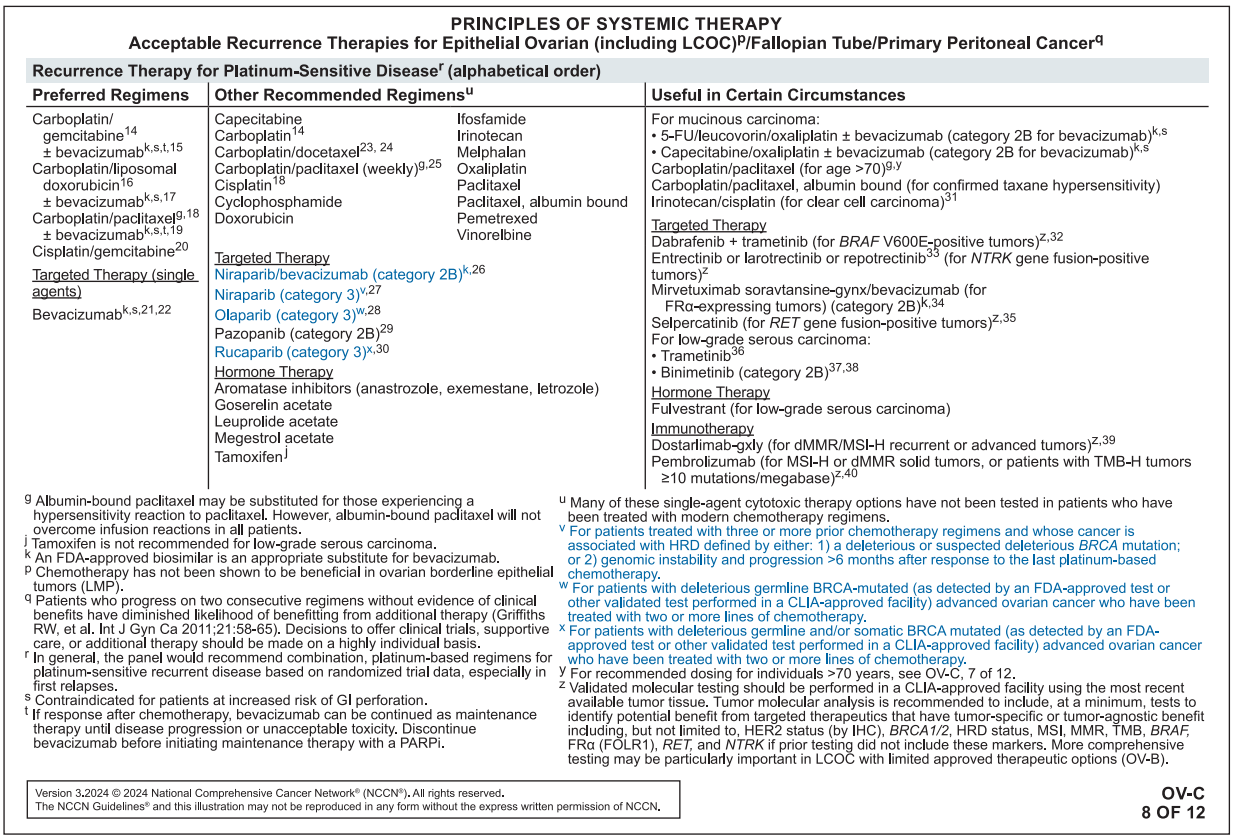
Figure 2. OV-8. NCCN Clinical Practice Guidelines in Oncology for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer, Version 3.2024.

trials: NOVA, SOLO-2, and Study 19. In 2018, the FDA approved rucaparib as maintenance therapy in recurrent disease.[18] Subset retrospective nonanalytical analyses of several studies in recurrent disease for OS did not demonstrate a statistically significant improvement in OS with the use of PARP inhibitors as second-line maintenance therapy, and further raised the question whether there could be a negative impact in patients with wild-type *BRCA*. Therefore, the FDA approached manufacturers and requested that they voluntarily revise PARP inhibitor indications in the second-line maintenance therapy to restrict use to patients with germline/somatic *BRCA*-mutated cancers only. Following the FDA's request, second-line maintenance indications were modified for all 3 PARP inhibitors: rucaparib is now limited to patients with germline or somatic *BRCA* mutations, niraparib is now limited to patients with germline *BRCA* mutations, and olaparib is now limited to patients with germline or somatic *BRCA* mutations.

The panel does not recommend bevacizumab and PARP inhibitor combination as a maintenance option in the recurrent disease setting. PARP inhibitor use is limited to those with *BRCA1/2* mutations if not previously used (Category 1) or if disease did not progress during prior PARP inhibitor treatment (Category 2A) (Figure 2). The panel notes that these regimens significantly improve outcomes in patients with *BRCA*-mutated tumors and who are PARP inhibitor–naïve, suggesting that patients who most likely benefit from PARP inhibitors are those who receive them in the frontline setting. However, patients who have *BRCA*-mutated tumors who are PARP inhibitor–naïve and respond to platinum in the recurrent setting should still be offered a maintenance PARP inhibitor. For patients who have received prior PARP inhibitors, the panel recognizes that there are limited data in those who receive repeat PARP inhibitors as second-line maintenance therapy.

PARP Inhibitor Monotherapy for Recurrent Platinum-Sensitive/Resistant Disease

Initial results from trials utilizing PARP inhibitors in platinum-sensitive/resistant disease showed promising results. Early phase I/II trials demonstrated that olaparib is active in select patients with *BRCA1/2* mutations and recurrent disease.[19–21] The FDA approved olaparib in 2014 for patients with advanced ovarian cancer who have received ≥3 lines of chemotherapy and who carry a germline deleterious *BRCA* mutation.[22,23] Based on early trial results and FDA approval, during the 2015 annual update the NCCN panel recommended single-agent olaparib as a recurrence therapy option for patients with advanced ovarian cancer (platinum-sensitive or platinum-resistant) who had received ≥3 lines of chemotherapy and a germline *BRCA* mutation. Trials assessing rucaparib and niraparib showed similar antitumor activity and rates of adverse events, which led to all the PARP inhibitors incorporated in the guidelines over the next 5 years as targeted therapy options for recurrent platinum-sensitive and resistant disease.[24–26] During short-term follow-up, the common adverse events observed in those treated with PARP inhibitors included thrombocytopenia, neutropenia, and anemia.[24,26] Until this point, there were no major concerns regarding the use of single-agent PARP inhibitors when given in the third or even fourth line of therapy in patients with recurrent disease.



PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[p]/Fallopian Tube/Primary Peritoneal Cancer[q]

Recurrence Therapy for Platinum-Sensitive Disease[r] (alphabetical order)

Preferred Regimens	Other Recommended Regimens[u]	Useful in Certain Circumstances
Carboplatin/gemcitabine[14] ± bevacizumab[k,s,t,15] Carboplatin/liposomal doxorubicin[16] ± bevacizumab[k,s,17] Carboplatin/paclitaxel[g,18] ± bevacizumab[k,s,t,19] Cisplatin/gemcitabine[20] Targeted Therapy (single agents) Bevacizumab[k,s,21,22]	Capecitabine Carboplatin[14] Carboplatin/docetaxel[23, 24] Carboplatin/paclitaxel (weekly)[g,25] Cisplatin[18] Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Vinorelbine Targeted Therapy Niraparib/bevacizumab (category 2B)[k,26] Niraparib (category 3)[v,27] Olaparib (category 3)[w,28] Pazopanib (category 2B)[29] Rucaparib (category 3)[x,30] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Goserelin acetate Leuprolide acetate Megestrol acetate Tamoxifen[j]	For mucinous carcinoma: • 5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[k,s] • Capecitabine/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[k,s] Carboplatin/paclitaxel (for age >70)[g,y] Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity) Irinotecan/cisplatin (for clear cell carcinoma)[31] Targeted Therapy Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[z,32] Entrectinib or larotrectinib or repotrectinib[33] (for *NTRK* gene fusion-positive tumors)[z] Mirvetuximab soravtansine-gynx/bevacizumab (for FRα-expressing tumors) (category 2B)[k,34] Selpercatinib (for *RET* gene fusion-positive tumors)[z,35] For low-grade serous carcinoma: • Trametinib[36] • Binimetinib (category 2B)[37,38] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Immunotherapy Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[z,39] Pembrolizumab (for MSI-H or dMMR solid tumors, or patients with TMB-H tumors ≥10 mutations/megabase)[z,40]

[g] Albumin-bound paclitaxel may be substituted for those experiencing a hypersensitivity reaction to paclitaxel. However, albumin-bound paclitaxel will not overcome infusion reactions in all patients.
[j] Tamoxifen is not recommended for low-grade serous carcinoma.
[k] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[p] Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[q] Patients who progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy (Griffiths RW, et al. Int J Gyn Ca 2011;21:58-65). Decisions to offer clinical trials, supportive care, or additional therapy should be made on a highly individual basis.
[r] In general, the panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.
[s] Contraindicated for patients at increased risk of GI perforation.
[t] If response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity. Discontinue bevacizumab before initiating maintenance therapy with a PARPi.
[u] Many of these single-agent cytotoxic therapy options have not been tested in patients who have been treated with modern chemotherapy regimens.
[v] For patients treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD defined by either: 1) a deleterious or suspected deleterious *BRCA* mutation; or 2) genomic instability and progression >6 months after response to the last platinum-based chemotherapy.
[w] For patients with deleterious germline BRCA-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.
[x] For patients with deleterious germline and/or somatic BRCA mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.
[y] For recommended dosing for individuals >70 years, see OV-C, 7 of 12.
[z] Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), *BRCA1/2*, HRD status, MSI, MMR, TMB, *BRAF*, FRα (FOLR1), *RET*, and *NTRK* if prior testing did not include these markers. More comprehensive testing may be particularly important in LCOC with limited approved therapeutic options (OV-B).

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Figure 3. OV-C 8 of 12. NCCN Clinical Practice Guidelines in Oncology for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer, Version 3.2024.

However, the long-term efficacy and safety data on the use of PARP inhibitors as therapy for recurrent disease were not as complimentary as the initial data. At 70% data maturity in the ARIEL-4 trial, which compared rucaparib with chemotherapy, rucaparib treatment was not associated with improved OS in the ITT population.[27,28] Although nonsignificant OS differences were observed in the recurrent platinum-sensitive disease, rucaparib use was associated with significantly worse OS in those with platinum-resistant disease.[27,28] It is thought that the OS analysis was confounded due to >60% of patients from the control group crossing over to receive rucaparib. There were no additional safety concerns with regard to adverse events in patients treated with rucaparib at this point during the analysis. However, in June 2022, the company voluntarily withdrew rucaparib for treating patients with *BRCA1/2*-mutated ovarian cancer after ≥2 prior lines of chemotherapy, because no OS benefit was observed.[29]

Phase II studies of olaparib as monotherapy in advanced cancers with germline *BRCA* mutations showed initial promising results, with approximately 31% tumor response rates (CR/PR) in those with heavily pretreated ovarian cancer.[30] SOLO-3 compared olaparib to physician's choice single-agent nonplatinum chemotherapy in patients with germline *BRCA* mutations and recurrent high-grade platinum-sensitive ovarian cancer who had been treated with ≥2 lines of platinum-based chemotherapy.[31] The initial study that conducted blinded independent central review showed that olaparib treatment resulted in statistically significant improvements in overall response rates and PFS.[31] However, at final data cutoff analysis, there was no statistical difference in clinical responses, and OS was similar between the olaparib and chemotherapy groups.[32] In August 2022, following the final analysis, the company voluntarily withdrew olaparib indication for the treatment of patients with germline *BRCA1/2*-mutated advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy.[33] Subsequently, in September 2022, niraparib, which was approved for treatment of patients with HRD-positive advanced ovarian cancer who had been treated with ≥3 prior lines of chemotherapy, was also voluntarily withdrawn by the company for this indication.[34]

Based on these data and the FDA withdrawal announcements, the NCCN panel met and revised the recommendations for PARP inhibitor monotherapy for recurrent ovarian cancer. In a series of interim updates in 2022, the category of evidence and preference for rucaparib, niraparib, and olaparib was changed from Category 2A, Preferred regimen to Category 3, Other Recommended regimens for both platinum-sensitive and platinum-resistant disease (Figures 3 and 4).

Evolving Landscape of PARP Inhibitors

In a meta-analysis of 28 randomized control trials, the risk of hematologic malignancies, including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), were higher in patients treated with long-term PARP inhibitors.[35] Analysis of the PAOLA-1 trial at 5 years, showed that the rates of MDS, AML, aplastic anemia, and new primary malignancy incidence remained low and at a similar rate between the olaparib/

PRINCIPLES OF SYSTEMIC THERAPY

Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[p]/Fallopian Tube/Primary Peritoneal Cancer[q]

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Cytotoxic Therapy Cyclophosphamide (oral)/ bevacizumab[k,41] Docetaxel[42] Etoposide (oral)[43] Gemcitabine[44,45] Liposomal doxorubicin[44,45] Liposomal doxorubicin/ bevacizumab[k,s,46] Paclitaxel (weekly)[g,47] Paclitaxel (weekly)/ bevacizumab[g,k,s,46] Topotecan[48,49] Topotecan/bevacizumab[k,s,46] Targeted Therapy (single agents) Bevacizumab[k,s,21,22] Mirvetuximab soravtansine-gynx (for FRα-expressing tumors [≥75% positive tumor cells])(category 1)[z,50,51]	Cytotoxic Therapy[u] Capecitabine Carboplatin[*] Carboplatin/docetaxel[*] Carboplatin/paclitaxel (weekly)[g,*] Carboplatin/gemcitabine[14] ± bevacizumab[k,s,t,15,*] Carboplatin/liposomal doxorubicin[16] ± bevacizumab[k,s,17,*] Carboplatin/paclitaxel[g,18] ± bevacizumab[k,s,t,19,*] Cyclophosphamide Cyclophosphamide (oral)/pembrolizumab/bevacizumab[k,53,54] Doxorubicin Gemcitabine/bevacizumab[k,55] Gemcitabine/cisplatin[20,*] Ifosfamide Irinotecan Ixabepilone/bevacizumab (category 2B)[k,aa,56] Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Sorafenib/topotecan[51] Vinorelbine Targeted Therapy (single agents) Niraparib (category 3)[v,27] Olaparib (category 3)[w,28] Pazopanib (category 2B)[29] Rucaparib (category 3)[x,30] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Goserelin acetate Leuprolide acetate Megestrol acetate Tamoxifen[j]	Carboplatin/paclitaxel (for age >70)[g,y,*] Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity)[*] Immunotherapy Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[z,39] Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/megabase)[z,40] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Targeted Therapy Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[z,32] Entrectinib or larotrectinib or repotrectinib[33] (for *NTRK* gene fusion-positive tumors)[z] Fam-trastuzumab deruxtecan-nxki (for HER2-positive tumors [IHC 3+ or 2+])[57] Mirvetuximab soravtansine-gynx/bevacizumab (for FRα-expressing tumors)[k,z,34,58,59] Selpercatinib (for *RET* gene fusion-positive tumors)[z,35] For low-grade serous carcinoma: • Trametinib[36] • Binimetinib (category 2B)[37,38]

* Platinum agents have limited activity when the disease has demonstrated growth through a platinum-based regimen, and platinum rechallenge is generally not recommended in this setting.

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Figure 4. OV-C 9 of 12. NCCN Clinical Practice Guidelines in Oncology for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer, Version 3.2024.

bevacizumab and placebo/bevacizumab arms.[10] The authors note that a higher proportion of patients in the placebo arm received subsequent PARP inhibitor therapy and could be a reason similar rates were observed between the 2 arms.[10] Patients with *BRCA* mutation and prolonged PARP exposure (≥2 years) show increased risk of developing MDS and AML.[14,36,37] Therefore, the panel urges caution when using PARP inhibitors as maintenance therapy for longer than 24 months, especially in the recurrence setting (Figure 2), and emphasizes the need for careful evaluation of risks and benefits when considering PARP inhibitor use in subsequent lines of therapy.

Summary and Conclusions

The panel recognizes that data relevant to subsequent lines of therapy cannot be extrapolated to the frontline setting. The NCCN panel recommendations for PARP inhibitors have been updated to align with the evolution of efficacy and safety profiles of these treatments as maintenance and single-agent regimens in select patients in both frontline and subsequent therapies.

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