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# Patient Selection for the Use of Niraparib in Advanced Ovarian Cancer: A Review

Anna Gonzalez[1], Quinn Kistenfeger[2], Casey M Cosgrove[1]

[1]Division of Gynecologic Oncology; The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute, Columbus, OH, USA; [2]Division of Obstetrics & Gynecology; The Ohio State University, Columbus, OH, USA

Correspondence: Anna Gonzalez, Email anna.gonzalez@osumc.edu

**Abstract:** The advent of poly(ADP-ribose) polymerase (PARP) inhibitors has resulted in a significant paradigm shift in ovarian cancer treatment. Niraparib, a potent PARP inhibitor, has demonstrated substantial efficacy in both first-line and recurrent disease settings. By targeting homologous recombination DNA repair, a pathway frequently disrupted in ovarian cancer, particularly in the context of BRCA mutations, niraparib induces synthetic lethality. Pivotal clinical trials, including PRIMA, ENGOT-OV16/NOVA, and QUADRA, have solidified niraparib's role in the treatment paradigm. While sharing a common mechanism of action with other PARP inhibitors, niraparib exhibits a distinct toxicity profile. Notably, hematologic toxicities, particularly thrombocytopenia, and hypertension have been observed at Grade 3–4 levels. A comprehensive understanding of niraparib's efficacy and safety is essential for optimal patient selection and management.

**Keywords:** Niraparib, ovarian cancer, maintenance therapy, recurrent

## Introduction

Epithelial ovarian cancer (EOC) represents a significant public health burden, ranking as the second most common gynecologic malignancy in the United States. Unfortunately, the insidious nature of EOC, often presenting asymptomatically until advanced stages, contributes to 75% of patients being diagnosed with metastatic disease. Consequently, it remains the leading cause of gynecologic cancer mortality (Torre,1).[1] Historically, management has relied primarily on cytoreductive surgery and platinum-based chemotherapy, and in more recent years, with the addition of bevacizumab in some settings.[2–4] The therapeutic landscape for EOC has evolved significantly with the advent of targeted therapies, including poly(ADP-ribose) polymerase (PARP) inhibitors such as niraparib, olaparib, and rucaparib (NCCN version 3.2024).[4] This review delves into the clinical utility of niraparib, with a particular emphasis on patient selection criteria and its role in both first-line and recurrent advanced ovarian cancer.

## Niraparib: Mechanism of Action

Niraparib is a PARP inhibitor that interrupts DNA repair after damage occurs during the cell cycle. While DNA replication is a highly accurate process, single (SSB) and double strand breaks (DSB) occur by intrinsic and extrinsic insults.[5] DNA repair occurs by five pathways: base excision repair (BER), nucleotide excision repair, or mismatch mediated repair for SSBs and homologous recombination repair (HRR) or non-homologous end joining (NHEJ) for DSBs.[5,6]

PARP is part of an important family of proteins that contributes to multiple cellular functions. While there are several PARP proteins thought to be associated with DNA repair, PARP-1 is instrumental in this function, making it a primary target of PARP inhibitors.[5] PARP-1 consists of 3 domains, a DNA binding domain, an auto-modification domain, and a catalytic domain, that work together for effective repair of SSBs through BER. The catalytic domain contains binding sites for NAD+ that facilitate polymerization of ADP-ribose units, creating the poly(ADP-ribose) (PAR) chain. The PAR chain initiates recruitment of multiple enzymes that result in DNA replication and repair.[5,7]

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PARP inhibitors, like niraparib, bind in the catalytic domain of the protein to inhibit binding of nicotinamide adenine dinucleotide (NAD+) and formation of PAR polymers, ultimately preventing PARP-1 from dissociating from the SSB.[5] This action causes disruption of BER and persistent SSBs in DNA by collapse of the replication fork. The resulting unrepaired SSB becomes a DSB and relies on HRR or NHEJ for recovery.[5,6]

When DSBs occur, either HRR or NEJH are initiated.[6] HRR is a high-fidelity process that requires intact homologous recombination proteins (HRP) to successfully complete DSB repair. While there are many proteins involved in HRR, breast cancer susceptibility genes (BRCA) 1 and 2 are two of the most critical. HRR is initiated by the MRN complex, which activates a cascade of downstream targets including BRCA1 (Rose 2020).[8] BRCA1 mitigates excision of nucleotides in a 5' to 3' direction on one chromatid to produce 3' overhangs of single stranded DNA.[5] BRCA2 then binds with RAD51 to repair the DNA using the overhangs to prime homologous repair which reproduces the exact replica of the initial, undamaged DNA.[8]

In patients with homologous recombination deficient (HRD) tumors, especially BRCA1 and 2, this process is not successful, leading to persistent DNA damage. Disruption in both BER by PARP inhibitors and HRR in HRD tumors leads to synthetic lethality resulting in cellular death, making patients with HRD particularly susceptible to PARP inhibitors.[9]

## Niraparib: Efficacy in the Treatment of Advanced Ovarian Cancer in the Frontline Setting

Niraparib has received the US Food and Drug Administration (FDA) approval for first-line maintenance therapy in patients with advanced EOC following platinum-based chemotherapy, regardless of their molecular profile (Kurnit).[10] This approval rests on the results of the PRIMA/ENGOT-OV26 trial.

PRIMA/ENGOT-OV26 was a Phase 3, randomized, double-blind clinical trial designed to assess the efficacy and safety of niraparib in the first-line maintenance setting for patients with newly diagnosed advanced EOC. The trial population comprised individuals diagnosed with high-grade serous or endometrioid histology and achieving complete or partial response to platinum-based chemotherapy. Patients were then randomized 2:1 to receive daily niraparib (300mg) or placebo for 36 months (about 3 years) or until disease progression. Progression-free survival (PFS) was the primary endpoint, evaluated in the overall patient population and the HRD-positive subgroup. Patients harboring HRD-positive tumors exhibited a significant 57% reduction in disease progression or death compared to the placebo arm. Notably, even patients lacking HRD status demonstrated a substantial 38% reduction in disease progression or death. Both findings achieved statistical significance. At the same time, preliminary data from the interim analysis hint at a potential improvement in overall survival; further data maturation is necessary to confirm this observation. These findings from PRIMA/ENGOT-OV26 have paved the way for niraparib's incorporation as a first-line maintenance therapy option for a broader population of patients with advanced EOC.[11]

## Niraparib: Efficacy in the Treatment of Advanced Ovarian Cancer in the Recurrent Setting

Despite initial treatment response, recurrence rates remain high among patients with advanced EOC, reaching 70%.[12] Two fundamental randomized control trials, ENGOT-OV16/NOVA (Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer) and QUADRA (Niraparib monotherapy for late-line treatment of ovarian cancer), support the efficacy of niraparib for treatment of EOC in the recurrent setting. Table 1 summarizes the trial design, study population, treatment arms, primary endpoints, results, and conclusions of these trials.

ENGOT-OV16/NOVA was a randomized, double-blind, international, phase 3 trial comparing Niraparib to placebo daily in the maintenance therapy of patients with platinum-sensitive recurrent EOC. Patients were eligible if they had predominantly high-grade serous histology and had demonstrated sensitivity to platinum-based chemotherapy in two prior lines. Participants were stratified based on germline BRCA mutation status and randomly assigned (2:1) to receive either niraparib (300 mg daily) or placebo for 28-day cycles until disease progression. 533 patients were enrolled with a median follow-up of 16.9 months. The cohort was predominantly characterized by advanced-stage disease and

**Table 1** Key Randomized Control Trials of Niraparib

| Study | Patient Population | Molecular Testing | Inclusion Criteria | Treatment Arm(s) | Primary Endpoint | Key Findings | Conclusion |
|---|---|---|---|---|---|---|---|
| **ENGOT-OV26/ PRIMA**[11] | Primary EOC | Myriad Genetics – HRD (MyChoice HRD test) | - stage III–IV^ disease<br>- HGS or endometrioid histology<br>- PR/CR to platinum-based chemotherapy | 1) Niraparib 300 mg daily x 28 day cycle for 36 months<br>2) Placebo daily x 28 day cycle for 36 months | Median PFS (months):<br>- overall population-HRD+ | Median PFS:<br>overall population<br>13.8 vs 8.2 (HR 0.62)<br>HRD+<br>21.9 vs 10.4 (HRD 0.43) | Patients with advanced primary EOC had a PFS benefit, regardless of molecular status, with the addition of Niraparib. |
| **QUADRA**[16] | Recurrent EOC | Myriad Genetics – HRD (MyChoice HRD test)<br>Blood germline BRCA-mutated status testing | - HGS histology<br>- 3+ prior lines<br>- measurable disease | 1) Niraparib 300 mg daily x 28 day cycle | OR | OR:<br>gBRCA+<br>29%<br>HRD+<br>15%<br>HRD-<br>3% | Niraparib provides OR, which greatest clinical benefit demonstrated in gBRCA+ and HRD+ patients. *Of note, they further subdivided patients by platinum-response with graduated response based on platinum-sensitivity.* |
| **ENGOT-OV16/ NOVA**[15] | Recurrent EOC<br>- stratification by BRCA germline mutation | Myriad Genetics – HRD (MyChoice HRD test), BRCA (BRACAnalysis testing) | - HGS histology<br>- platinum sensitive+<br>- 2+ prior lines | 1) Niraparib 300 mg daily x 28 day cycle<br>2) Placebo daily x 28 day cycle | PFS | Median PFS:<br>gBRCA+<br>21 mo vs 5.5 mo (HR 0.27)<br>HRD+/gBRCA-<br>12.9 mo vs 3.8 mo, (HR 0.38)<br>HRD-/gBRCA-<br>9.3 mo vs 3.9 mo (HR 0.45) | Niraparib provides significant improvement in PFS, regardless of BRCA or HRD status. |

**Notes**: ^included: stage III with visible residual tumor after primary debulking surgery, inoperable stage III, any stage IV disease, stage III–IV receiving NACT. +Platinum sensitive defined as having complete or partial response and disease progression >6 months after last round of platinum-based therapy.

**Abbreviations**: gBRCA, germline BRCA mutation; HGS, high grade serous; OR, overall response; CR, complete response; PR, partial response.



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a median age range of 57 to 63 years. The primary outcome, progression-free survival (PFS), was significantly extended in the niraparib arm compared to placebo regardless of BRCA germline mutation status. In those with a germline BRCA mutation, PFS was prolonged by over 15 months (HR 0.27) and in those without a germline BRCA mutation, PFS was prolonged by over 5 months (HR 0.45). Additionally, patients with HRD-positive tumors demonstrated a significant benefit with PFS prolonged by 9 months (HR 0.38). Irrespective of BRCA mutation or HRD status, niraparib significantly extended PFS. However, patients with a germline BRCA mutations or HRD-positive tumors derived the greatest clinical benefit.[15] Notably, the PFS advantage observed in HRD/BRCA-negative patients was comparable to the efficacy previously demonstrated by bevacizumab.[16] Subsequent to the ENGOT-OV16/NOVA trial, the FDA granted approval for niraparib as maintenance therapy in March 2017. This indication was designated for patients with recurrent EOC, regardless of their BRCA or HRD status, who achieved complete or partial response to their most recent platinum-based chemotherapy regimen (Kurnit).[10] An updated survival analysis conducted by Matulonis et al failed to demonstrate a significant overall survival advantage for niraparib over placebo (Matulonis).[14] Consequently, the initial FDA approval for niraparib in the maintenance setting for patients with recurrent epithelial ovarian cancer was rescinded. Currently, niraparib is approved for second-line maintenance therapy exclusively in patients harboring germline BRCA mutations (Kurnit).[10]

The QUADRA study, conducted in the US and Canada, was a multicenter, open-label, single-arm, Phase 2 trial evaluating the safety and efficacy of niraparib (300 mg daily) in patients with recurrent EOC. Patients met inclusion criteria if they had high-grade serous EOC, had received three or more prior lines of systemic chemotherapy, and had measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Similar to ENGOT-OV16 /NOVA, all patients had to undergo germline BRCA mutation testing as well as HRD testing. Of note, the initial study protocol included platinum-resistant and -refractory patients; however, after the enrollment of 292 patients, the study was amended to include only patients who had a response to platinum-based therapy of at least 6 months. Additionally, the upper limit of treatment was adjusted to four prior lines, and a second amendment closed the study for patients with HRD-negative tumors. All patients received niraparib daily and continued until disease progression. Four-hundred and sixty-three patients were enrolled with a median age of 65 years old. Forty-eight percent of patients had HRD-positive tumors, and 19% had a BRCA mutation (6% somatic, 13% germline). Prior treatment lines were as expected for the study's inclusion criteria, with 41% of patients having received three, 31% having received four, and 27% having received five or more prior lines of therapy. Notably, only 26% of patients were platinum-sensitive, while 33% and 35% were platinum-resistant and -refractory, respectively. The highest overall response was seen in BRCA-mutated and HRD-positive tumors with 28% of patients with HRD-positive tumors achieving an overall response.[13]

Niraparib demonstrated clinical utility as a maintenance therapy in a patient population with advanced EOC and limited treatment options. While niraparib prolonged PFS across all patient subgroups in ENGOT-OV16/NOVA, irrespective of biomarker status, its greatest impact was observed in those with BRCA mutations or homologous recombination deficiency. Additionally, there remains a need to demonstrate an OS benefit, and this has yet to be demonstrated by either QUADRA or ENGOT-OV16/NOVA.

## Niraparib: Consideration of Niraparib Following Prior PARP Inhibitor Exposure

The use of niraparib in patients who have previously received niraparib or another PARP inhibitor is not yet established. A phase IIIB trial, OReO/ENGOT Ov-38, is currently investigating the effectiveness of re-administering olaparib for maintenance therapy in patients with recurrent platinum-sensitive EOC. Initial findings from this trial suggest that re-treatment with olaparib, compared to a placebo, extends PFS for patients with relapsed ovarian cancer, regardless of their BRCA mutation status (median PFS 2.8 vs 4.3 mo; HR 0.57, p=0.022). The final survival data from this trial is not yet available (OReO/ENGOT Ov-38).[17] These findings are important because they raise the possibility that niraparib might also be effective in this setting. Further research is needed to explore this potential application of niraparib.

# Niraparib: Guidelines

## Frontline Maintenance Therapy

Niraparib stands out among PARP inhibitors for its broad frontline maintenance therapy approval in EOC. Niraparib is recommended for use by the National Comprehensive Cancer Network (NCCN) guidelines and is approved by the FDA as first-line maintenance therapy in stage II–IV EOC patients, regardless of BRCA mutation or HRD-positive status, after complete (CR) or partial response (PR) to platinum-based chemotherapy.[4] After primary chemotherapy, niraparib can be given up to 36-months or until disease progression or toxicity is appreciated. For patients who achieve a CR or PR to first-line platinum-based chemotherapy with bevacizumab, if they cannot tolerate olaparib, another option for first-line maintenance therapy is niraparib combined with bevacizumab, but only if they have a HRD-mutation.[4]

The decision to incorporate bevacizumab, a VEGF inhibitor, into maintenance therapy in combination with a parp inhibitor is primarily informed by the PAOLO-1 trial.[18] This Phase III randomized controlled trial compared olaparib plus bevacizumab to placebo in patients with stage III–IV EOC who had completed primary adjuvant therapy with carboplatin, paclitaxel, and bevacizumab. While the trial demonstrated a significant prolongation of progression-free survival (PFS) in patients harboring BRCA mutations or HRD-positive tumors, no such benefit was observed in those without these genetic alterations.[18] A notable limitation of the PAOLO-1 trial is the absence of a maintenance therapy arm with a parp inhibitor alone, hindering a direct assessment of the incremental benefit conferred by the combination regimen. The rationale for combining bevacizumab with a PARP inhibitor is often grounded in the established efficacy of bevacizumab in stage III disease with suboptimal debulking or in stage IV disease.[19] Additionally, the potential for increased toxicity with this combination needs careful consideration.

Niraparib as a first-line maintenance therapy option is supported by the European Society for Medical Oncology (ESMO) for patients with EOC. ESMO's recommendation applies regardless of a patient's BRCA mutation status or a positive/unknown genomic instability score (GIS). This applies to patients who initially received platinum-based treatments for up to three years. Additionally, ESMO recommendations for the consideration of bevacizumab overall mirror that of NCCN guidelines (Ledermann).[20]

## Recurrent Maintenance Therapy

Niraparib's use in recurrent EOC has seen a significant shift. Initially, based on encouraging phase 3 trials showing extended PFS, the NCCN included niraparib for maintenance therapy following platinum-sensitive recurrence, irrespective of HRD or BRCA mutation status. However, the landscape has recently changed. Updated analyses from the NOVA trial failed to demonstrate a statistically significant improvement in overall survival compared to placebo. Consequently, the FDA approval for niraparib has narrowed, excluding patients without a germline BRCA mutation. NCCN guidelines have adapted to reflect this new data (NCCN version 3.2024).[4] While niraparib might still be considered for specific recurrent scenarios, its role in this setting is now more limited compared to its wider application in frontline maintenance therapy. When used as maintenance after additional lines of therapy, it can be given until disease progression or toxicity, without definitive duration. (NCCN version 3.2024).[4]

## Safety

The adverse event profiles across the PRIMA, NOVA, and QUADRA trials were generally consistent. The most common adverse events, affecting more than 10% of patients, included hematologic toxicities (anemia, neutropenia, thrombocytopenia), gastrointestinal disturbances (nausea, vomiting, diarrhea, constipation), and fatigue. Other frequently reported adverse events encompassed headache, insomnia, abdominal pain, decreased appetite, dyspnea, dizziness, cough, back pain, arthralgia, dyspepsia, nasopharyngitis, urinary tract infection, and palpitations. Notably, hematologic toxicities predominated among grade 3–4 adverse events, with thrombocytopenia (21–33.8%), anemia (24–31%), and neutropenia (11–19.6%) occurring in at least 10% of patients receiving niraparib across all three trials.[11,13,15]

### Thrombocytopenia

Thrombocytopenia is a distinct adverse event associated with niraparib treatment. A post-hoc analysis of the NOVA trial by Berek et al revealed a trend towards a 200mg/day dose being more commonly used in practice compared to the

standard dose of 300mg/day. Notably, the analysis suggests that patients with lower body weight (<77kg) or baseline platelet count (<150,000/uL) might benefit from initiating therapy with a reduced dose without compromising efficacy compared to those receiving the full dose (Berek 2018).[21] These findings informed the design of the PRIMA trial, which incorporated weight and platelet count into a strategy for individualized niraparib dosing.

### Hypertension

New-onset hypertension has been reported in patients receiving niraparib. The PRIMA trial demonstrated a significantly increased risk of grade 3–4 hypertension in patients receiving niraparib compared to placebo (6% vs 1%, respectively) with a median onset of 50 days.[11] Similarly, the NOVA trial reported a prevalence of 8.2% for grade 3–4 hypertension in the niraparib arm.[15] The QUADRA trial observed a relatively low prevalence (around 2%), potentially attributable to dose reductions implemented in 47% of the enrolled patients.[13] While specific guidelines for managing niraparib-induced hypertension are lacking, established treatment protocols for hypertension should be followed, aiming to maintain blood pressure below 120/80 mmHg.[22]

### Myelodysplastic Syndrome/Acute Myeloid Leukemia

Niraparib treatment, like all PARP inhibitors, carries a risk of developing myelodysplastic syndrome or acute myeloid leukemia (MDS/AML). This rare but specific and severe toxicity was observed in approximately 1% of patients receiving niraparib across the three trials. Notably, three patients in the NOVA trial succumbed to MDS/AML (one in the niraparib arm and two in the placebo arm).[15] While the incidence is low, it is crucial for patients to be informed of this potential risk.

## Cost Considerations

The economic implications of treatment selection in EOC are substantial for both patients and healthcare systems. While niraparib has demonstrated clinical efficacy, its cost-effectiveness has been the subject of ongoing evaluation. In the frontline setting, the cost-effectiveness of niraparib as maintenance therapy has yielded mixed results. While one study found it cost-effective when administered to all patients regardless of biomarker status, other analyses, particularly those stratifying patients by molecular characteristics, indicated less favorable cost-effectiveness profiles compared to alternative maintenance strategies.[23,24] The cost-effectiveness landscape becomes more complex in the recurrent setting. Niraparib has demonstrated potential cost savings compared to other PARP inhibitors. In comparison to other PARP inhibitors, Guy et al found that niraparib was superior and demonstrated cost savings of up to $22,000 and $198,000 in comparison to olaparib and rucaparib, respectively, for the patient.[25] However, its overall cost-effectiveness relative to surveillance remains controversial, with studies reporting varying incremental cost-effectiveness ratios. Notably, the cost per treatment month required for niraparib to be considered cost-effective in comparison to observation was substantial.[26,27] These findings underscore the importance of considering both clinical and economic factors when making treatment decisions for patients with EOC.

# Summary

Niraparib has emerged as a powerful tool in the fight against EOC. Its ability to target DNA repair deficiencies and prolong progression-free survival, particularly in the frontline setting, offers a significant improvement for patients. This is most notably demonstrated in patients with a BRCA-mutation or HRD-positive tumors. Ongoing research is crucial to further refine its use in recurrent disease and optimize patient selection based on BRCA/HRD status and cost-effectiveness analyses. Additionally, exploring the potential for re-administration of niraparib or its efficacy in combination with other therapies holds promise for further enhancing treatment outcomes for women with EOC.

# Abbreviations

PARP, poly(ADP-ribose) polymerase; EOC, epithelial ovarian cancer; SSB, single strand break; DSB, double strand break; BER, base excision repair; HRR, Homologous recombination repair; NHEJ, non-homologous end joining; NAD+, nicotinamide adenine dinucleotide; HRP, homologous recombination proteins; HRD, homologous recombination deficiency; RECIST, Response Evaluation Criteria in Solid Tumors; FDA, the US Food and Drug Administration; PFS,

Progression-free survival; NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology; GIS, genomic instability score; PR, partial response; CR, complete response.

## Disclosure

The authors report no conflicts of interest in this work.

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