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CCR Drug Updates

Clinical Cancer Research

# FDA Approval Summary: Niraparib for the Maintenance Treatment of Patients with Recurrent Ovarian Cancer in Response to Platinum-Based Chemotherapy

Gwynn Ison, Lynn J. Howie, Laleh Amiri-Kordestani, Lijun Zhang, Shenghui Tang, Rajeshwari Sridhara, Vadryn Pierre, Rosane Charlab, Anuradha Ramamoorthy, Pengfei Song, Fang Li, Jingyu Yu, Wimolnut Manheng, Todd R. Palmby, Soma Ghosh, Hisani N. Horne, Eunice Y. Lee, Reena Philip, Kaushalkumar Dave, Xiao Hong Chen, Sharon L. Kelly, Kumar G. Janoria, Anamitro Banerjee, Okponanabofa Eradiri, Jeannette Dinin, Kirsten B. Goldberg, William F. Pierce, Amna Ibrahim, Paul G. Kluetz, Gideon M. Blumenthal, Julia A. Beaver, and Richard Pazdur

## Abstract

The FDA approved niraparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, on March 27, 2017, for maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy. Approval was based on data from the NOVA trial comparing niraparib with placebo in two independent cohorts, based on germline *BRCA* mutation status (g*BRCA*m vs. non-g*BRCA*m). Progression-free survival (PFS) in each cohort was the primary endpoint. In the g*BRCA*m cohort, estimated median PFS on niraparib was 21 months versus 5.5 months on placebo [HR, 0.26; 95% confidence interval (CI), 0.17–0.41; $P < 0.0001$]. In the non-g*BRCA*m cohort, estimated median PFS for niraparib and placebo was 9.3 and 3.9 months, respectively (HR, 0.45; 95% CI, 0.34–0.61; $P < 0.0001$). Common adverse reactions (>20% and higher incidence in the niraparib arm) with niraparib included thrombocytopenia, anemia, neutropenia, nausea, constipation, vomiting, mucositis, fatigue, decreased appetite, headache, insomnia, nasopharyngitis, dyspnea, rash, and hypertension. There were five cases of myelodysplastic syndrome and acute myeloid leukemia (1.4%) in patients treated with niraparib compared with two cases (1.1%) on placebo. Niraparib is the first PARP inhibitor approved as maintenance therapy for patients with ovarian, fallopian tube, or primary peritoneal cancer, with improvement in PFS, regardless of g*BRCA*m status. *Clin Cancer Res; 24(17); 4066–71. ©2018 AACR.*

*See related commentary by Konstantinopoulos and Matulonis, p. 4062*

## Introduction

Ovarian cancer is the ninth most common cancer and the fifth most common cause of cancer death for women in the United States (1, 2). The primary treatment for ovarian cancer includes surgery and platinum-based chemotherapy. Women whose disease recurs 6 months or more after platinum therapy are considered to have platinum-sensitive disease, and re-treatment with a platinum-based regimen is typical. However, continued therapy is associated with cumulative toxicity and the development of resistance. Platinum resistance is associated with low response rates to subsequent chemotherapies and worsened progression-free survival (PFA) and overall survival (OS; ref. 3). Increasing progression-free interval with a maintenance therapy may increase the interval between treatments.

The *BRCA1* and *BRCA2* genes encode proteins involved in repair of DNA damage. Deleterious mutations of the *BRCA1* and *BRCA2* genes are associated with increased risk of developing ovarian cancer (4, 5). The homologous recombination (HRD) pathway is known to be disrupted in patients with underlying *BRCA* mutations, resulting in reliance upon other pathways, such as the poly(ADP-ribose) polymerase (PARP) pathway, to initiate DNA repair (6). PARP inhibitors target cells with impaired DNA repair through the HRD pathway, leading to cell death through a process called "synthetic lethality." In this article, we present the FDA rationale for approval of niraparib for maintenance therapy for patients with relapsed ovarian, fallopian tube, or primary peritoneal cancer in response to platinum-based chemotherapy (7).

## Chemistry

The chemical name for niraparib tosylate monohydrate is 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole 7-carboxamide 4-methylbenzenesulfonate hydrate (1:1:1). Niraparib tosylate monohydrate is a white to off-white, non-hygroscopic crystalline

Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland.



G. Ison and L.J. Howie contributed equally to this article.

**Corresponding Author:** Gwynn Ison, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993. Phone 301-796-4057; Fax: 301-796-9849; E-mail: Gwynn.Ison@fda.hhs.gov

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solid. Niraparib is poorly soluble in aqueous media, with an aqueous free-base solubility of 0.7 to 1.1 mg/mL across the physiologic pH range of 1.0 to 6.8 at 37°C (niraparib tosylate pKa = 9.95). Niraparib is approved as 100-mg capsules for oral administration, which is equivalent to 159.4 mg of niraparib tosylate monohydrate. The approved dose is three capsules once daily, for a total dose of 300 mg.

## Nonclinical Pharmacology and Toxicology

*In vitro*, niraparib inhibited isoforms of PARP, including PARP-1 and PARP-2, and proliferation of *BRCA1*- and *BRCA2*-deficient cell lines. Niraparib decreased tumor growth in mouse xenograft models of human cancers with deficiencies in *BRCA1* and *BRCA2* or with homologous recombination deficiency (HRD) that had either mutated or wild-type *BRCA1/2*. Published reports provide evidence that niraparib can form PARP–DNA complexes resulting in DNA damage, apoptosis, and cell death (8).

Based on an *in vitro* secondary pharmacology screen, niraparib has off-target pharmacologic activity on dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT) at concentrations similar to those achieved in patients receiving the recommended dose.

In repeat-dose toxicology studies of oral niraparib in rats and dogs, a major target organ of toxicity was the hematopoietic system, consistent with the frequent adverse events observed in clinical trials (i.e., anemia, neutropenia, and lymphopenia).

Niraparib targets rapidly dividing cells (e.g., adverse effects on the hematopoietic system in nonclinical studies and clinical trials) and is genotoxic. Therefore, it is expected to cause teratogenicity and/or embryo-fetal death if administered to a pregnant woman, so no developmental and reproductive toxicology studies were conducted based on recommendations of the International Council for Harmonization (ICH) Guidance for Industry, "S9 Nonclinical Evaluation for Anticancer Pharmaceuticals" (9).

## Clinical Pharmacology

Niraparib demonstrated linear pharmacokinetics (PK) at daily oral doses ranging from 30 to 400 mg. After approximately 7 once-daily doses, the exposure of niraparib reached steady state with a 2-fold accumulation ratio. Niraparib can be administered without regard to food.

The primary metabolism of niraparib involves hydrolysis and subsequent glucuronidation via carboxylesterases and UDP-glucuronosyltransferases. No dose adjustment is necessary in patients with mild [60 mL/min ≥ creatinine clearance (CLcr) > 90 mL/min, $n = 221$] or moderate (30 mL/min ≥ CLcr > 60 mL/min, $n = 81$) renal impairment, or those with mild [total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin > ULN to ≤ 1.5× ULN, $n = 27$] hepatic impairment. The safety of niraparib is unknown in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease undergoing hemodialysis, or moderate to severe hepatic impairment.

The proposed once-daily oral dose of niraparib 300 mg is acceptable based on the effectiveness and clinically manageable safety profile demonstrated in the NOVA trial. Due to hematologic adverse events, most patients who started on the proposed 300-mg daily dose were switched to lower doses after the first month. Those events were effectively mitigated with clinical interventions along with frequent dose modifications. At the fifth treatment cycle, most patients remained on a stable dose (e.g., roughly 30% on 100 mg, 47% on 200 mg, and 23% on 300 mg).

## Clinical Trial Design

FDA approval of niraparib was based on a double-blind, randomized, placebo-controlled trial (NOVA) in 553 patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who were randomized 2:1 to receive niraparib 300 mg orally daily or matched placebo. Patients were enrolled within 8 weeks of completing their last therapy. All patients had received at least two prior platinum regimens and were in complete or partial response to their most recent platinum regimen, as assessed by their treating physician.

Eligible patients were assigned to one of two cohorts based on whether BRACAnalysis CDx testing revealed a germline *BRCA* mutation (10). Patients with a deleterious or suspected deleterious germline *BRCA* mutation were assigned to the g*BRCA*m cohort ($n = 203$), and those without germline mutations were assigned to the non-g*BRCA*m cohort ($n = 350$; Fig. 1).

Randomization was stratified by time to progression after the penultimate platinum regimen (6–<12 months vs. ≥12 months); use of bevacizumab with the penultimate or last platinum regimen (yes vs. no); and best response to the most recent platinum regimen (complete response vs. partial response). Patients were treated with niraparib capsules at a dose of 300 mg daily until disease progression or unacceptable toxicity.

Within the non-g*BRCA*m cohort, patients were further stratified by HRD status (positive vs. negative) with evaluation of patients'

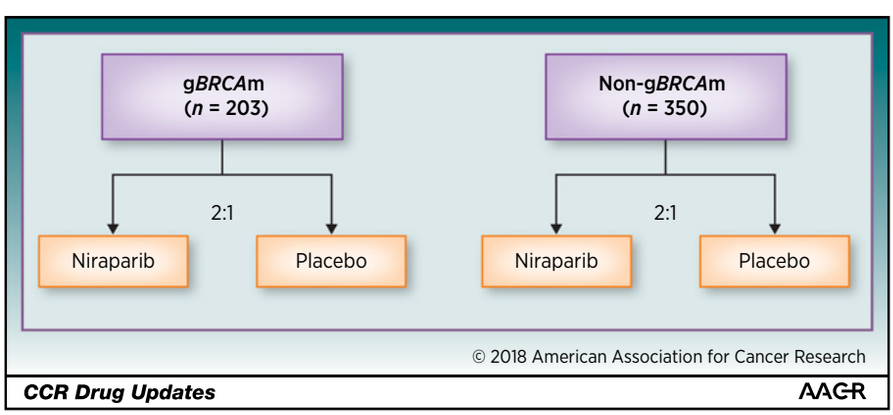


**Figure 1.**
NOVA study design.

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tumor specimens for deleterious somatic *BRCA* mutations and HRD status. The statistical analysis plan for this cohort specified that the primary endpoint would be evaluated hierarchically, first evaluating PFS in patients determined to be HRD positive and then in the overall non-g*BRCA*m cohort.

The majority of patients were Caucasian (87%) and had a baseline Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 (68%); the median age at enrollment was 60 years. The median number of prior chemotherapy regimens was two (range, 2–12). The median number of prior platinum regimens was two. Half of patients were in complete response to their most recent platinum regimen. Twenty-seven percent had received prior bevacizumab therapy.

## Efficacy Results

The primary study endpoint was independent review committee (IRC)–assessed PFS, and the primary analyses were performed in the g*BRCA*m and non-g*BRCA*m cohorts independently. Tumor response assessment was according to RECIST 1.1.

In the g*BRCA*m cohort, the estimated median PFS in patients randomized to the niraparib arm was 21 months [95% confidence

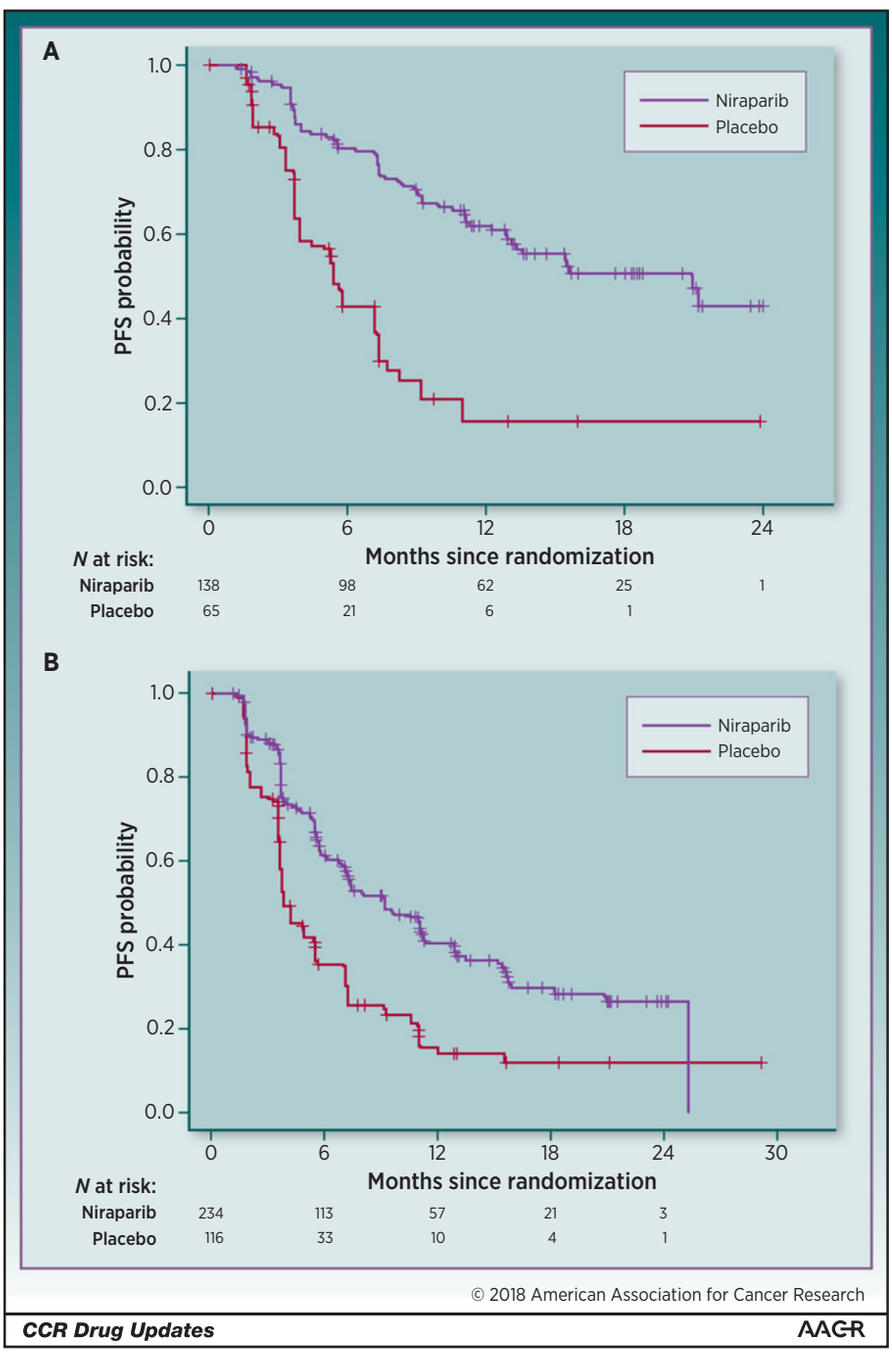


**Figure 2.**
**A,** Kaplain–Meier (K–M) curve of PFS per IRC assessment for the g*BRCA*m cohort. **B,** K–M curve of PFS per IRC assessment for the non-g*BRCA*m cohort.

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interval (CI), 12.9–not reached) and 5.5 months in patients randomized to the placebo arm (95% CI, 3.8–7.2), (HR, 0.26; 95% CI, 0.17–0.41; $P < 0.0001$; Fig. 2A). In the non-g*BRCA*m cohort, the estimated median PFS in patients randomized to the niraparib arm was 9.3 months (95% CI, 7.2–11.2) and 3.9 months in patients randomized to the placebo arm (95% CI, 3.7–5.5), (HR, 0.45; 95% CI, 0.34–0.61; $P < 0.0001$; Fig. 2B). An exploratory analysis of the intent-to-treat (ITT) population pooled from both cohorts revealed an estimated median PFS of 11.3 months for patients randomized to the niraparib arm and 4.7 months for placebo (HR, 0.42; 95% CI, 0.34–0.53).

OS was a secondary endpoint. No specific hypothesis testing plan was prespecified for OS. At the time of data analysis, at a median follow-up of 17 months, OS was immature, with approximately 17% of patients having died.

## Safety Results

The primary safety population included 367 patients exposed to niraparib. The median exposure to niraparib was 250 days. No deaths within 30 days of ending study treatment were associated with study therapy. Dose interruptions due to adverse events were reported in 66%, and dose reductions were reported in 69% of patients treated with niraparib compared with 15% and 5% of patients on placebo, respectively. Treatment discontinuation due to adverse events occurred in 15% of patients treated with niraparib compared with 2% of patients on placebo. The most common adverse events leading to discontinuation included thrombocytopenia, fatigue, and neutropenia. The most common adverse reactions ($\geq$20% and higher incidence in the niraparib arm) in patients treated with niraparib were thrombocytopenia, anemia, neutropenia, nausea, constipation, vomiting, mucositis, fatigue, decreased appetite, headache, insomnia, nasopharyngitis, dyspnea, rash, and hypertension.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been reported in patients who received niraparib. In the NOVA trial, MDS/AML occurred in five patients treated with niraparib (1.4%) and two patients on placebo (1.1%). The overall incidence of MDS/AML was 0.9% (seven of 751). Based on the mechanism of action of niraparib, the known risk associated with other PARP inhibitors, and the rate of MDS/AML seen in the safety population, niraparib may increase the risk of developing MDS/AML (11).

Cardiovascular effects, including hypertension, hypertensive crisis, tachycardia, and palpitations, were safety signals identified during review of the niraparib clinical studies, which are unique to this PARP inhibitor. Hypertension of any grade was reported in 20% of patients treated with niraparib (9% grades 3–4) compared with 6% of those on placebo (2% grades 3–4). Hypertensive crisis occurred in two patients treated with niraparib. These events did not seem to be associated with prior bevacizumab exposure, as only 4% of the niraparib-treated patients experiencing hypertension of any grade had previously been treated with bevacizumab.

## Patient-Reported Outcomes Results

Tolerability is important for a maintenance therapy, as the therapeutic alternative is typically observation in this setting. To better understand the patient experience while on niraparib or placebo, patient-reported outcomes (PRO) data were collected as part of the NOVA trial. The FDA focused its analysis on results from the Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index (FOSI), an eight-item subset of the FACT-Ovarian instrument that combines several common symptoms with more global impacts of quality of life and worry about prognosis, and the EuroQol five dimensions, five-level version questionnaire (EQ-5D-5L), an instrument used to assess generic health status and outcomes.

Exploratory analysis of the PRO data demonstrated reasonable quality data were collected, with over 80% completion rates at each assessment. Analysis of the mean change in total score for the FOSI and the EQ-5D-5L visual analogue score (VAS) did not identify notable differences between treatment groups over time. Results from a composite total score such as the FOSI may obscure important changes in individual-level symptoms or functional measures. To address this, we analyzed responses to individual symptom items to better understand the patient experience. Analysis of individual item data showed that patients receiving niraparib reported an increase in nausea and vomiting compared with baseline that was greatest at cycle 2 and decreased in incidence for those patients who received subsequent cycles (12). These analyses provided information on the trajectory of symptoms and complemented findings from the Common Terminology Criteria for Adverse Events (CTCAE) clinician-reported safety data.

## Regulatory Insights

Niraparib is the first PARP inhibitor to receive FDA approval for the maintenance treatment of patients with recurrent ovarian cancer who are in response to platinum-based chemotherapy and may represent a new treatment paradigm for patients in first relapse after first-line therapy. Prior to this approval, the only approved maintenance therapy was bevacizumab, based on results from the OCEANS trial in which bevacizumab was administered in conjunction with chemotherapy and continued as a single agent in patients who are in response at the end of six to eight cycles of combination chemotherapy (13, 14). The addition of niraparib as a treatment option in this therapeutic setting may have certain advantages, including the convenience of once-daily oral administration and a different mechanism of action.

For the niraparib application, the prospectively defined plan to analyze patients with and without a deleterious g*BRCA* mutation allowed for the independent evaluation of two groups who have different magnitudes of benefit from niraparib, based upon mutation status. Although the study results show a more robust benefit for patients carrying a g*BRCA* mutation, there is evidence that patients without a g*BRCA* mutation also benefit from therapy with niraparib. This is likely because, although *BRCA* mutations account for the most common deficit in the HRD pathway, aberrations in other homologous recombination genes may also result in sensitivity to niraparib.

No diagnostic device accurately distinguishes those specific patients in the non-g*BRCA*m group who benefit from niraparib compared with those who do not. In addition, the magnitude of benefit in the non-g*BRCA*m group is similar to that observed with bevacizumab in a similar setting. Therefore, current evidence supports the hypothesis that patients who are in response to platinum-based chemotherapy may benefit from maintenance therapy with niraparib regardless of the presence or absence of g*BRCA* mutation. As a result, a broad indication for niraparib use, without a companion diagnostic for *BRCA* status, was granted such that all patients with recurrent epithelial ovarian, fallopian

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tube, or primary peritoneal cancers who are in response to platinum-based therapy may receive maintenance therapy with niraparib. The BRACAnalysis CDx was designated as a complementary diagnostic device for niraparib. Complementary diagnostics are not required for the safe and effective use of their corresponding therapeutic product but rather provide information about a drug's effect on a subpopulation, thereby potentially informing the risk and benefit assessment for an individual patient.

The overall safety profile was similar to other currently available PARP inhibitors, including the common adverse events of cytopenias, nausea, and fatigue. Given the risk of bone marrow suppression and cytopenias, it is recommended that patients have a complete blood count performed weekly for the first month of therapy, monthly for the next 11 months, and periodically thereafter. Unlike other agents in this class, niraparib also demonstrated an increased risk of hypertension and cardiac arrhythmias. Insomnia and anxiety were also reported in >10% of patients receiving therapy with niraparib. Both sets of events are possibly related to the inhibitory effect of niraparib on DAT, NET, and SERTs given that niraparib has a relatively higher CNS penetration than other PARP inhibitors. At this time, it is not clear whether the increased CNS penetration is associated with clinical activity in patients with brain metastases. Although the cardiovascular events were mostly manageable with dose modifications and antihypertensive medications, patients with underlying cardiovascular disorders, including coronary artery disease or prior history of cardiac arrhythmias, should be monitored closely for worsening symptoms and managed appropriately.

Analysis of the PRO data did not identify notable differences between niraparib and placebo in total score for the FOSI and the EQ-5D-5L VAS. Well-defined symptom and functional measures can be more sensitive to therapeutic effects, and item-level analyses of symptom-related events did demonstrate an increase in nausea and vomiting for patients on niraparib that improved with time for those who remained on treatment. Sponsors and applicants are encouraged to continue to discuss the use of appropriate instruments to assess patient outcomes in trials. PRO data can be descriptive or support claims of treatment benefit. In both cases, development of standard analyses and visualization is needed to maximize the utility of longitudinal patient-reported symptom and function data in the evaluation of new therapies. As with any trial endpoint, a prespecified statistical analysis plan that controls for multiple comparisons is necessary if seeking a marketing claim of treatment benefit.

## Conclusions

Niraparib is the first PARP inhibitor approved for maintenance therapy of patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. Results from the NOVA study demonstrated patient benefit without regard to g*BRCA*m status (Table 1); however, the magnitude of benefit differed among these subgroups. The most common adverse events associated with this therapy were hematologic events, nausea, vomiting, abdominal pain, and diarrhea. As with other PARP inhibitors, MDS and AML were rare events associated with treatment. A new safety signal of hypertension, tachycardia, and palpitations was identified with this agent. Niraparib offers patients an oral therapy that can lengthen the interval between chemotherapy regimens for patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer. The safe use of niraparib can be managed through accurate labeling and routine oncology care.

**Table 1.** FDA risk–benefit assessment

| Dimension | Evidence and uncertainties | Conclusions and reasons |
|---|---|---|
| Analysis of condition | • Ovarian cancer is the fifth cause of cancer death in women and represents 5% of all cancer deaths.<br>• In 2018, it is estimated that there will be 22,240 new cases of ovarian cancer and that 14,070 women will die in the United States. | • Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers are serious, life-threatening, and incurable. |
| Current treatment options | • Most patients with ovarian cancer receive primary debulking surgery followed by chemotherapy with platinum plus taxanes with or without bevacizumab. Response rates in the first-line setting are high, but most patients will develop a recurrence within 2 years and die within 3 to 4 years of diagnosis. | • Prior to the current approval, bevacizumab was the only FDA-approved maintenance therapy for the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. |
| Benefit | • Niraparib demonstrated statistically significant and clinically meaningful improvement in PFS over placebo in both the g*BRCA*m cohort (HR, 0.26; 95% CI, 0.17–0.41; $P < 0.0001$) and the non-g*BRCA*m cohort (HR, 0.45; 95% CI, 0.34–0.61; $P < 0.0001$). | • Evidence of effectiveness was supported by a statistically significant and clinically meaningful PFS improvement. |
| Risk | • The most common adverse reactions (AR) experienced (≥20%) were thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, nausea, constipation, vomiting, abdominal pain/distention, mucositis/stomatitis, diarrhea, fatigue/asthenia, decreased appetite, headache, insomnia, nasopharyngitis, dyspnea, rash, and hypertension. AML/MDS, bone marrow suppression, and cardiovascular effects are the AR described in the warnings and precautions section of labeling. | • The observed PFS benefits outweigh the risks in this patient population, which represents an unmet medical need. |
| Risk management | • Niraparib is intended to be prescribed by oncologists who are well versed in the identification and management of the toxicities associated with niraparib.<br>• Labeling details dose interruption, reduction, or discontinuation.<br>• AML/MDS, bone marrow suppression, and cardiovascular effects are the AR being described in the warnings and precautions section of labeling.<br>• Laboratory and vital sign monitoring are recommended before and during treatment. | • The safe use of niraparib can be managed through accurate labeling and routine oncology care. |

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## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Disclaimer

The Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose. Vadryn Pierre and Todd R. Palmby contributed to this manuscript while working at the FDA but have since become employees of MedImmune (Dr. Pierre) and AstraZeneca (Dr. Palmby). Any views expressed in this article do not reflect the views of these companies.

## Authors' Contributions

**Conception and design:** L.J. Howie, J.A. Beaver, R. Pazdur
**Development of methodology:** W.F. Pierce, J.A. Beaver, R. Pazdur
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** W. Manheng, O. Eradiri, R. Pazdur
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** G. Ison, L.J. Howie, L. Amiri-Kordestani, L. Zhang, S. Tang, R. Sridhara, V. Pierre, R. Charlab, A. Ramamoorthy, P. Song, F. Li, W. Manheng, H.N. Horne, R. Philip, A. Banerjee, W.F. Pierce, P.G. Kluetz, J.A. Beaver, R. Pazdur
**Writing, review, and/or revision of the manuscript:** G. Ison, L.J. Howie, L. Amiri-Kordestani, L. Zhang, S. Tang, R. Sridhara, V. Pierre, R. Charlab, A. Ramamoorthy, P. Song, F. Li, J. Yu, W. Manheng, T.R. Palmby, S. Ghosh, H.N. Horne, E.Y. Lee, R. Philip, K. Dave, X.H. Chen, K.G. Janoria, A. Banerjee, O. Eradiri, K.B. Goldberg, W.F. Pierce, P.G. Kluetz, G.M. Blumenthal, J.A. Beaver, R. Pazdur
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** L.J. Howie, V. Pierre, J. Dinin, K.B. Goldberg, G.M. Blumenthal, J.A. Beaver, R. Pazdur
**Study supervision:** G.M. Blumenthal, J.A. Beaver, R. Pazdur
**Other (chemistry manufacturing and controls of test articles):** S.L. Kelly
**Other (co-supervision of review by FDA team):** A. Ibrahim

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