Rucaparib and Niraparib in Advanced Ovarian Cancer

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Abstract

Rucaparib and niraparib are two of the newest U.S. Food and Drug Administration–approved PARP inhibitors, joining olaparib with indications in ovarian cancer. Both drugs have led to meaningful responses when used as monotherapy in previously treated ovarian cancers, with niraparib demonstrating activity in both *BRCA*-mutated and *BRCA* wild-type tumors. Both rucaparib and niraparib have remarkably increased progression-free survival as maintenance therapy for patients with relapsed, platinum-sensitive epithelial ovarian cancer who responded to their most recent platinum-based regimen. In this setting, these drugs appear to be similar in efficacy but have distinct pharmacokinetic and adverse effect profiles. This article will guide the advanced practitioner through the efficacy, safety, and pharmacologic profiles of rucaparib and niraparib, while benchmarking them against olaparib for the treatment of ovarian cancer.

Poly(ADP-ribose) polymerases (PARPs) are a family of enzymes, some of which are key components of the base-excision DNA repair pathway (Livraghi & Garber, 2015). There are now four approved PARP inhibitors: olaparib (Lynparza) was approved by the U.S. Food and Drug Administration (FDA) in 2014, followed soon after by rucaparib (Rubraca) in 2016, niraparib (Zejula) in 2017, and talazoparib (Talzenna) in 2018 (AstraZeneca Pharmaceuticals LP, 2018; Clovis Oncology, Inc., 2018; Tesaro, Inc., 2018; Pfizer, Inc., 2018). Indications are summarized in Table 1. Other than the approval of olaparib

and talazoparib in breast cancer, all approved indications thus far have been in gynecologic malignancies.

PARP inhibitors have a proven place in therapy in the management of cancers driven by *BRCA* mutations in multiple disease sites including ovarian and breast, and have an emerging role in others. *BRCA1* and *BRCA2* are tumor suppressor genes involved in DNA repair, and they have an important role in the correction of double-stranded DNA breaks through the homologous recombination pathway. Deleterious, inheritable (germline) mutations (*gBRCA*m) account for at least 5% of breast and 10% of epithelial ovarian

Table 1. U.S. Food and Drug Administration Indications for Currently Approved PARP Inhibitors

Indication	Olaparib	Rucaparib	Niraparib	Talazoparib
*BRCA*m ovarian cancer as monotherapy	Germline, after 3 or more prior chemotherapies	Germline or somatic, after 2 or more prior chemotherapies	–	–
Maintenance for platinum-sensitive recurrent ovarian cancer	Approved	Approved	Approved	–
Maintenance after first-line platinum-based chemotherapy for *BRCA*m ovarian cancer	Approved	–	–	–
g*BRCA*m, HER2-negative breast cancer	Metastatic, previously treated with chemotherapy	–	–	Metastatic or locally advanced

Note. PARP = poly(ADP-ribose) polymerase.

cancers. In other patients who do not have a germline mutation, a cell can develop *BRCA* mutations, leading to malignant transformation. These are referred to as somatic *BRCA* mutations (s*BRCA*m) and only exist in the cancer cells (National Comprehensive Cancer Network, 2019).

This article will focus on rucaparib and niraparib, which are proven for high-grade serous or endometrioid epithelial ovarian cancer. Note that these drugs are also approved in fallopian tube and primary peritoneal cancers, which are managed identically to epithelial ovarian cancer and for the rest of the article will be implicit in the definition of ovarian cancer. When advanced, these cancers are generally treated with platinum doublet regimens and surgery. If a patient relapses within 6 months of completing treatment, they are considered platinum-resistant and will then be treated with nonplatinum chemotherapy. Patients who relapse after 6 months are considered platinum-sensitive and will typically be retreated with a platinum doublet (National Comprehensive Cancer Network, 2018b).

PHARMACOLOGY AND MECHANISM

DNA breaks occur in both normal and cancerous cells, and PARPs are activated in the presence of single-stranded breaks. PARP inhibitors block the catalytic activity of PARPs, and some additionally trap PARPs while they are bound to DNA. In time, these mechanisms lead to double-stranded DNA breaks, which are repaired through alternate mechanisms such as homologous recombination.

In cells that are homologous recombination deficient (HRD), which include but are not limited to cancers driven by *BRCA*m, the accumulation of double-stranded DNA breaks can lead to cell death. Normal cells are spared to some extent, as their functional DNA repair mechanism enables survival in the presence of PARP inhibition. This synergistic effect in cancer cells that are unable to repair PARP inhibitor-facilitated DNA damage is known as synthetic lethality (Livraghi & Garber, 2015).

Rucaparib tablets are 30% to 45% bioavailable after oral administration and can be taken with or without food. It is metabolized primarily by CYP2D6, and to a lesser extent by CYP1A2 and CYP3A4. The mean terminal half-life is 17 to 19 hours, and it is approved with an every-12-hour dosing interval. Dose adjustment is not needed for moderate renal dysfunction nor mild hepatic impairment (Clovis Oncology, Inc., 2018).

Niraparib tablets are approximately 73% bioavailable after ingestion and can also be taken with or without food. Metabolism is primarily through carboxylesterases to inactive metabolites, which are excreted via both urine and feces. Mean terminal half-life is 36 hours, enabling once-daily dosing. Similar to rucaparib, dose adjustment is not needed for moderate renal dysfunction nor mild hepatic impairment (Tesaro, Inc., 2018).

CLINICAL TRIALS
Treatment for Relapsed Ovarian Cancer
Rucaparib was evaluated as monotherapy treatment in two single-arm trials, Study 10 and ARIEL2,

with combined results reported in an integrated analysis (Oza et al., 2017). This analysis included patients with ovarian cancer who received at least two prior platinum-based regimens and had a deleterious germline or somatic *BRCA*m. Patients received the FDA-approved dose of rucaparib at 600 mg by mouth twice daily. Of the 106 patients in this analysis, 57 (53.8%) had a partial or complete response as assessed by the investigator. The median duration of confirmed response was 9.2 months (95% confidence interval [CI] = 6.6–11.6).

Niraparib was also evaluated as monotherapy in the recently published QUADRA trial, which was conducted in patients with relapsed ovarian cancer who received at least three prior lines of chemotherapy (Moore et al., 2019). Patients received niraparib at 300 mg by mouth once daily and were not required to have *BRCA*m. A total of 463 patients were enrolled, 222 (48%) of whom had HRD-positive tumors, and 87 (19%) had a germline or somatic *BRCA* mutation. In the modified per-protocol population who were PARP inhibitor–naive, the overall response rate was 29% (18/63) in *BRCA*m patients, 15% (29/189) in HRD-positive (including *BRCA*m) patients, and 3% (8/230) in patients who were HRD-negative or HRD-unknown. The median duration of response was 9.4 (95% CI = 6.6–18.3) months, and this was similar for responders regardless of *BRCA* or HRD status.

Maintenance After Platinum Response in Relapsed Ovarian Cancer

PARP inhibitors now have proven efficacy in patients with ovarian cancer who have platinum-sensitive disease, including patients who do not have HRD. Both platinum agents and PARP inhibitors affect cancer cells by increasing the amount of misrepaired DNA strand breaks, and tumor platinum sensitivity has been associated with PARP inhibitor efficacy (Basourakos et al., 2017).

The ENGOT-OV16/NOVA trial evaluated niraparib in patients with serous ovarian cancer that was sensitive to their penultimate platinum-based chemotherapy regimen, and had a partial or complete response to their most recent platinum-based treatment (Mirza et al., 2016). Subjects were divided into two cohorts based on the presence of g*BRCA*m and randomized 2:1 to the FDA-

approved dose of niraparib at 300 mg by mouth daily or placebo. The primary endpoint was centrally-assessed progression-free survival (PFS).

The g*BRCA*m cohort included 203 patients, with a median PFS of 21.0 months with niraparib vs. 5.5 months with placebo (hazard ratio [HR], 0.27; 95% CI = 0.17–0.41; *p* < .001). The non-g*BRCA*m cohort included 350 patients, with a median PFS of 9.3 vs. 3.9 months (HR, 0.45; 95% CI = 0.34–0.61; *p* < .001). Of note, the non-g*BRCA*m cohort included patients with s*BRCA*m as well as other causes of HRD such as loss of heterozygosity, large-scale state transitions, and telometric allelic imbalance identified through the Myriad Genetics myChoice HRD assay. Together, these genetic changes in the tumor indicate a *BRCA*m-like phenotype, and in this subgroup of 162 patients, those who received niraparib were also found to have improved PFS vs. placebo, with a median PFS of 12.9 vs. 3.9 months, respectively (HR, 0.38; 95% CI = 0.24–0.59; *p* < .001).

The ARIEL3 trial evaluated rucaparib in a similar patient population, and additionally allowed the enrollment of patients with residual bulky disease (target lesion > 2 cm; Coleman et al., 2017). Subjects were randomized 2:1 to receive rucaparib at 600 mg by mouth twice daily or placebo. The primary endpoint was investigator-assessed PFS, evaluated sequentially in three different subgroups. The first group included patients with germline or somatic *BRCA*m, the second additionally included patients with *BRCA* wild-type cancer with high loss of heterozygosity, and the third was comprised of the entire intention-to-treat (ITT) population. s*BRCA*m and loss of heterozygosity were identified via the Foundation Medicine T5 assay.

The *BRCA*m group included 196 patients, with a median PFS of 16.6 vs. 5.4 months in the rucaparib and placebo arms, respectively (HR, 0.23; 95% CI = 0.16–0.34; *p* < .0001). Group 2 included an additional 158 patients (354 total) with a median PFS of 13.6 vs. 5.4 months (HR, 0.32; 95% CI = 0.24–0.42; *p* < .0001). The entire ITT population of 564 patients had a median PFS of 10.8 vs. 5.4 months (HR, 0.36; 95% CI = 0.30–0.45; *p* < .0001).

ADVERSE EVENTS

There are a number of adverse events specific to PARP inhibitors, and dose interruptions and re-

ductions due to toxicity are common. The rates of toxicities of olaparib, niraparib, and rucaparib observed during maintenance trials are listed in Table 2. Class toxicities include nausea and vomiting (up to 37% of patients experienced any-grade vomiting with rucaparib), cytopenias (up to 34% of patients experienced grade 3–4 thrombocytopenia and 25% grade 3–4 anemia with niraparib), fatigue (up to 69% of patients experienced any-grade fatigue with rucaparib), and dysgeusia (up to 39% of patients experienced any-grade dysgeusia with rucaparib). This class of medications may be associated with an increased risk for myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML; approximately 1%), possibly related to DNA damage in bone marrow stem cells, although these patients are already at increased risk due to previous treatment with DNA-damaging chemotherapy (Livraghi & Garber, 2015).

In addition to class effects, it is important to monitor for photosensitivity (17% any grade, 1% grade 3) with rucaparib and for insomnia (24% any grade, < 1% grade 3–4), hypertension (19% any grade, 8% grade 3–4), and palpitations (10% grade 1–2) with niraparib.

PLACE IN THERAPY

Rucaparib and niraparib join olaparib as the second and third PARP inhibitors approved in ovarian cancer. For ovarian cancer, PARP inhibitors

Table 2. Adverse Event Rates in the Recurrent Maintenance Setting

	Olaparib 400 mg[a] twice daily[b], % any grade (% grades 3–4)	Niraparib 300 mg daily[c], % any grade (% grades 3–4)	Rucaparib 600 mg twice daily[d], % any grade (% grades 3–4)
Nausea	68% (2%)	74% (3%)	75% (4%)
Vomiting	32% (2%)	34% (2%)	37% (4%)
Fatigue	49% (7%)	59% (8%)	69% (7%)
Anemia	17% (5%)	50% (25%)	37% (19%)
Thrombocytopenia	< 20%	61% (34%)	28% (5%)
Neutropenia	< 20%	30% (20%)	18% (7%)
Diarrhea	23% (2%)	19% (< 1%)	32% (1%)
Constipation	13% (0%)	40% (1%)	37% (2%)
Headache	18% (0%)	26% (< 1%)	18% (< 1%)
Insomnia	Not reported	24% (< 1%)	14% (0%)
Dysgeusia	14% (N/A)	10% (N/A)	39% (N/A)
Dyspepsia	16% (0%)	11% (0%)	15% (< 1%)
Photosensitivity	Not reported	Not reported	17% (1%)
Hypertension	Not reported	19% (8%)	Not reported
Palpitations	Not reported	10% (N/A)	Not reported
Increased ALT or AST	Not reported	36% (1%)	34% (10%)
Increased serum creatinine	< 20%	< 10%	15% (< 1%)
Dose interruption[e]	35%	69%	64%
Dose reduction[e]	26%	67%	55%
Drug discontinuation[e]	4%	15%	13%

Note. ALT = alanine aminotransferase; AST = aspartate aminotransferase; N/A = not available.
[a]This study used olaparib capsules at 400-mg dose. Later studies used tablets at 300-mg dose.
[b]Study 19; Ledermann et al., 2012; N = 136.
[c]NOVA; Mirza et al., 2016; N = 367.
[d]ARIEL3; Coleman et al., 2017; N = 372.
[e]Due to adverse event.

are proven as single-agent therapy for previously treated cancers with *BRCA*m, as well as HRD-positive tumors with niraparib, and as maintenance therapy for platinum-sensitive disease.

The first indication for olaparib was for the treatment of patients with g*BRCA*m ovarian cancer after three or more lines of chemotherapy. This approval is supported by the subgroup of patients in a phase II study who were resistant to or ineligible to receive platinum therapy (Domcheck et al., 2016; Kaufman et al., 2015). Of the 193 patients in this subgroup treated with olaparib capsules twice daily, the overall response rate was 34%. Rucaparib is approved for the treatment of patients with germline or somatic *BRCA*m who were previously treated with two lines of chemotherapy, supported by the aforementioned analysis by Oza and colleagues (2017). Niraparib demonstrated activity in *BRCA*m ovarian cancer, as well as for some patients with HRD-positive and a few patients with HRD-negative or unknown tumors. For these three medications, a randomized trial comparing them to standard-of-care chemotherapy would be ideal, but given the information available, these drugs are good options in the setting of their studied indications.

In the maintenance setting of platinum-sensitive recurrent ovarian cancer, these three PARP inhibitors are FDA-approved and have a proven place in therapy. Olaparib was evaluated in the Study 19 and SOLO2 trials (Ledermann et al., 2012; Pujade-Lauraine et al., 2017) in similar patient populations to those enrolled in ENGOT-OV16/NOVA with niraparib and ARIEL3 with rucaparib, although in Study 19, *BRCA* status was unknown in 60% of patients and tumor HRD was not measured, complicating crosstrial comparisons. Between rucaparib and niraparib, comparing efficacy is possible, but not exact due to different tests for homologous recombination deficiency and small differences in baseline characteristics. Overall, efficacy in the maintenance setting following platinum-sensitive recurrence appears to be practically identical between olaparib, rucaparib, and niraparib; therefore, their safety profiles are the more important deciding factor. Authors of a recently published meta-analysis came to similar conclusions (Staropoli et al., 2018).

Most recently, olaparib has demonstrated a striking improvement in PFS compared to placebo in the maintenance setting for patients with newly diagnosed, *BRCA*m, advanced ovarian cancer that has responded to platinum-based chemotherapy after surgery (Moore et al., 2018). After a median 40.7 months of follow-up, the median investigator-assessed PFS was not reached in the olaparib arm, compared to 13.8 months for placebo (HR, 0.30; 95% CI = 0.23–0.41; $p < .001$). Adverse events were similar to those reported in previous trials. At the time of this writing, this is the only published data on PARP inhibitors in the front-line maintenance setting.

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

PARP inhibitors are an effective class of drugs with both an established role in ovarian cancer and an evolving place in therapy. It is now clear that these medications are particularly effective in patients with *BRCA*m (including *BRCA1*, *BRCA2*, germline, and somatic mutations), as well as those with HRD-positive tumors. Additionally, PARP inhibitors have activity in patients without these genetic mutations who have relapsed, platinum-sensitive disease.

There are a number of class toxicities, including nausea, vomiting, anemia, fatigue, and dysgeusia, which each drug causes to a varying extent. The adverse effect profiles and dosing schedules are the most important differentiating factors when choosing between these agents. Rucaparib is dosed twice daily and is associated with higher rates of fatigue, dysgeusia, and photosensitivity. Niraparib is dosed once daily and is associated with higher rates of cytopenias, insomnia, and hypertension.

Dose interruptions and reductions are common with this class, with reductions occurring in 67% of patients on niraparib, 55% of patients on rucaparib, and 26% of patients on olaparib in the maintenance setting. Niraparib is easiest to dose reduce since the reductions are in increments of 100 mg tablets, with a starting dose of three tablets once daily. Of note, a retrospective analysis of the ENGOT-OV16/NOVA trial reported that patients with a body weight less than 77 kg or baseline platelets less than 150,000/μL had frequent dose

reductions, so starting these patients on niraparib at 200 mg daily may be more appropriate (Berek, et al., 2018). Both olaparib and rucaparib require new prescriptions for different tablet sizes when dose reducing. In general, these drugs are withheld for toxicities of grade 3 or greater, and restarted at a lower dose level upon resolution. The package insert (niraparib) or published literature (olaparib, rucaparib) should be consulted for detailed information. Despite the common need for dose reductions, only 4% to 15% of patients discontinued treatment with a PARP inhibitor due to toxicity.

Nausea and vomiting are common with these drugs, and are fortunately often low grade. Patients should be prescribed antiemetics such as ondansetron or prochlorperazine to take as needed. A trial of scheduled antiemetics prior to each dose can be considered in patients with persistent emesis, while dose reductions can be considered in refractory cases. Fatigue is best managed according to established guidelines. The National Comprehensive Cancer Network lists physical activity, yoga, and psychosocial interventions such as cognitive behavioral therapy as Category 1 recommendations (National Comprehensive Cancer Network, 2018a).

The rucaparib package insert recommends monitoring complete blood counts at baseline and monthly thereafter. For niraparib, the package insert advises checking complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter, while monitoring blood pressure and heart rate monthly for the first year and then periodically. I would additionally monitor complete metabolic panels monthly for both drugs because of the risk for liver test and creatinine abnormalities. It should be noted that PARP inhibitors may be associated with an increased risk for MDS/AML, so patients with persistent cytopenias should be closely followed.

Rucaparib can interact with other drugs by inhibiting metabolism of CYP1A2, CYP3A, CYP2C9, and CYP2C19 substrates. Pharmacokinetic studies have demonstrated increased exposure with caffeine, midazolam, warfarin, omeprazole, and digoxin. Each patient's medication list should be checked for any CYP substrates, and patients should be counseled to reduce caffeine intake, as exposure is more than doubled. Since rucaparib is primarily metabolized through CYP2D6, it is possible that it can interact with inhibitors such as fluoxetine and paroxetine, although the extent of which is not clear. Niraparib does not have any CYP drug interactions. Olaparib is a CYP3A4 substrate, and must be dose reduced when given with moderate or strong inhibitors.

These are all oral medications, which come with logistical challenges. They are expensive: as of February 2019, the average wholesale price of a 30-day supply of rucaparib is $19,108, while that for niraparib is $23,703. Of note, the monthly cost for niraparib decreases proportionally with dose reductions, while the price of rucaparib does not. Coordination with manufacturer patient and copay assistance programs, as well as foundation support, are key to facilitate access for uninsured patients or those with unaffordable copays. From what my patient-access colleagues tell me, the foundation support for gynecologic malignancies is sometimes inadequate, especially relative to support for other tumor types. Patient adherence must also be assessed with these oral therapies, although the impact of missed doses is yet to be published for this class of medications.

SUMMARY

PARP inhibitors now have an established place in therapy for epithelial ovarian, fallopian tube, and primary peritoneal cancers in both *BRCA*m and platinum-sensitive disease. These medications continue to be studied in patients with ovarian cancer, as well as those with breast, prostate, pancreatic, and others. In relapsed, platinum-sensitive ovarian cancer, the efficacy appears to be similar between olaparib, rucaparib, and niraparib for maintenance therapy, while each agent has a distinct adverse event profile and dosing considerations. These medications are expected to have an expanding place in therapy as precision medicine continues to advance and additional trials are conducted. ●

Disclosure

Dr. Redelico has served on the speakers bureau and advisory board for AstraZeneca and the advisory board for Tesaro.

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