

FDA Approval Summary: Rucaparib for the Treatment of Patients with Deleterious *BRCA* Mutation–Associated Advanced Ovarian Cancer



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Abstract

On December 19, 2016, the FDA granted accelerated approval to rucaparib (RUBRACA; Clovis Oncology, Inc.) for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic)–associated advanced ovarian cancer who have been treated with two or more chemotherapies. The FDA also approved the FoundationFocus CDx_{BRCA} test (Foundation Medicine, Inc.), the first next-generation sequencing-based companion diagnostic, for identifying patients with advanced ovarian cancer eligible for treatment with rucaparib based on detection of deleterious *BRCA1* and/or *BRCA2* mutations in tumor tissue. Rucaparib's approval was based primarily on efficacy data from 106 patients with *BRCA* mutation–associated ovarian cancer who had prior treatment with two or more chemotherapies and safety data from

377 patients with ovarian cancer treated with rucaparib 600 mg orally twice daily on two open-label, single-arm trials. Investigator-assessed objective response rate was 54% [57/106; 95% confidence interval (CI), 44–64], and median duration of response was 9.2 months (95% CI, 6.6–11.7). The approved companion diagnostic verified tumor *BRCA* mutation status retrospectively in 96% (64/67) of patients. Common adverse reactions ($\geq 20\%$) to rucaparib were nausea, fatigue, vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea. This article summarizes the FDA review and data supporting rucaparib's accelerated approval. *Clin Cancer Res*; 23(23); 7165–70. ©2017 AACR.

See related commentary by Kohn et al., p. 7155

Introduction

Deleterious germline *BRCA1* and *BRCA2* mutations are known to confer increased risk of breast and ovarian cancer, and an estimated 17% of all U.S. patients with ovarian cancer carry a germline *BRCA* mutation (gBRCAm; ref. 1). Epidemiologic evidence suggests that patients with *BRCA*-associated ovarian cancer may have improved survival, likely due to increased and prolonged chemotherapy sensitivity (2). In 2014, the FDA granted accelerated approval to olaparib for the treatment of women with gBRCAm ovarian cancer after three prior chemotherapy regimens (3). No specific therapy was approved for the treatment of women with *BRCA* mutation–associated (BRCAm) advanced ovarian cancer after two prior chemotherapy regimens, although several chemotherapy agents are commonly used for treatment of women with ovarian cancer regardless of *BRCA* status in this setting, both

on- and off-label. More recently, based on a phase III trial, the FDA approved niraparib for the maintenance treatment of women with relapsed ovarian cancer who are in complete or partial response to platinum-containing therapy.

In accordance with FDA regulations for expedited drug development programs, the FDA granted the rucaparib application breakthrough therapy designation, priority review status, and orphan drug designation, and approved the application 2 months before the goal date for treatment of women with recurrent ovarian cancer who have been treated with two or more prior chemotherapy regimens, representing advancement of PARP inhibition into an earlier line of therapy than that approved for olaparib.

Mechanism of Action

This is the first FDA approval for rucaparib, an inhibitor of the mammalian PARP enzyme. *In vitro*, rucaparib inhibited several enzymes in the PARP family, with strongest effect on PARP-1, PARP-2, and PARP-3. PARP enzymes have been shown to be crucial for specific aspects of cellular homeostasis, including cell-cycle regulation, DNA transcription, and DNA repair. Blocking PARP activity prevents DNA single-strand break repair mechanisms, leading to double-strand breaks that require other DNA repair mechanisms, such as homologous recombination or non-homologous end joining. In patients with deleterious *BRCA* mutations, homologous recombination is defective, preventing the repair of the double-strand break. Thus, the addition of PARP

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inhibition to *BRCA* deficiency is thought to result in cell death and is the main rationale supporting the use of rucaparib in patients with deleterious *BRCA* mutations. On the basis of this mechanism of action, it is postulated that PARP inhibition would be effective in malignant cells whether the *BRCA* mutation is inherited (i.e., germline) or arises in the tumor itself as a *de novo* somatic mutation.

Clinical Pharmacology

Following oral administration of rucaparib 600 mg, the median T_{max} was 1.9 hours. The mean (range) absolute bioavailability of rucaparib 600 mg orally twice daily was 36% (30%–45%), and the mean (coefficient of variation) steady-state rucaparib C_{max} was 1,940 ng/mL (54%) and AUC_{0-12h} was 16,900 h*ng/mL (54%). The volume of distribution at steady state was 113 to 262 L following a single intravenous dose of 12 to 40 mg. *In vitro*, rucaparib protein binding was 70% in human plasma at therapeutic concentrations and displayed a low metabolic turnover rate in human liver microsomes, metabolized primarily by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. The median terminal half-life ($T_{1/2}$) was 17 hours. Apparent clearance ranged from 15.3 to 79.2 L/hour, following 600 mg orally twice-daily dosing.

Exposure–response (E–R) analysis and pharmacometric modeling support the appropriateness of the proposed dosing regimen. The E–R analysis for efficacy showed a trend of a positive relationship between rucaparib exposure and objective response rate (ORR; by independent radiology review) over the exposure range after administration of rucaparib 600 mg orally twice daily, suggesting that a lower starting dose may lead to a loss of efficacy. In addition, the positive E–R relationships for adverse events (AE) suggested that a higher dose may increase the incidence of AEs.

A relatively small food effect with large pharmacokinetic variability was observed in a food effect trial; therefore, it was deemed acceptable for rucaparib to be given with or without food. On the basis of population pharmacokinetic analyses and the clinical safety data in the application, no dose adjustments have been recommended for mild hepatic impairment [total bilirubin less than or equal to the upper limit of normal (ULN) and aspartate

aminotransferase (AST) greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST] or mild-to-moderate renal impairment (creatinine clearance of 30 to 89 mL/minute by Cockcroft–Gault). The results of a study to determine the appropriate starting dose in patients with moderate hepatic impairment (total bilirubin 1.5 to 3 times ULN) will be submitted to the FDA.

Clinical Trial Design

The rucaparib approval was based on data from two open-label, single-arm, multicenter trials: ARIEL2 (4) and Study 10 (Table 1). Study 10 was initially a safety and dose-finding trial; once the recommended phase II dose was established, at 600 mg orally twice daily, an expansion cohort of patients with solid tumors and *gBRCAm* was evaluated. An additional part 2A of Study 10 evaluated the tolerability and efficacy of rucaparib 600 mg twice daily in patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a *gBRCAm* who had progressed after two to four prior regimens, and part 2B enrolled ovarian cancer patients with *gBRCAm* or somatic *BRCA* mutation (*sBRCAm*) who had been treated with three or four prior treatment regimens. Study 10 evaluated efficacy endpoints of ORR and duration of response (DoR).

ARIEL2 was designed to evaluate the efficacy of rucaparib 600 mg orally twice daily in women with relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer after they had been treated with prior platinum-containing chemotherapies. In ARIEL2, 315 patients were treated with rucaparib 600 mg orally twice daily continuously in a 28-day cycle until unacceptable toxicity, patient/investigator request to discontinue, disease progression, or death. Three genomically differentiated subgroups were investigated in this trial: patients with deleterious *BRCAm*, including *gBRCAm* and *sBRCAm*; patients with non-*BRCA*-mutated homologous recombination deficiency genetic signature; and a biomarker-negative subgroup. In the submitted data, part 1 of the trial enrolled patients ($N = 204$) who had been treated with at least one prior platinum-based regimen and had platinum-sensitive disease. To further evaluate efficacy in a more heavily pretreated group irrespective of platinum sensitivity, part 2 ($N = 111$)

Table 1. Sources of efficacy population of women with *BRCAm* ovarian cancer and treatment with ≥ 2 prior platinum-containing regimens

Trial identity	Trial design	Regimen/schedule	Study endpoints	Study population	Patients enrolled in efficacy population (N)
CO-338-010 Study 10	Phase I/II Open-label Single-arm	Phase 1: dose escalation	Primary: Safety, MTD, PK, ORR (INV), DoR by RECIST version 1.1	Part 1: solid tumors	Part 2: 42
		Phase 2: rucaparib 600 mg PO BID; 21-day cycles	Key secondary: OS	Part 2: <i>gBRCAm</i> patients with ovarian cancer after 2–4 prior treatment regimens and <i>tBRCAm</i> patients with ovarian cancer after 3–4 prior treatment regimens	
CO-338-017 ARIEL2	Phase 2 Open-label Single-arm	Rucaparib 600 mg PO BID; 21-day cycles	Primary: PFS (INV), ORR (INV) by RECIST version 1.1	Part 1: <i>tBRCAm</i> platinum-sensitive ovarian cancer after ≥ 1 regimen	Part 1: 24 Part 2: 40
			Key secondary: OS	Part 2: <i>tBRCAm</i> platinum-sensitive ovarian cancer after 3–4 prior regimens	
Efficacy population					Total: 106

Abbreviations: BID, twice daily; INV, investigator-assessed; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PO, by mouth; *tBRCAm*, tumor *BRCA* mutation.

followed a protocol amendment to evaluate rucaparib efficacy in patients with ovarian cancer who had undergone treatment with three or four prior chemotherapy regimens. Thus, in part 2, platinum-resistant and platinum-refractory patients were enrolled along with patients who were platinum sensitive. In addition, resistant/refractory patients who may have had prior non-platinum treatment regimens were permitted.

Following discussion with the FDA, the review of efficacy for this accelerated approval was limited to a combined efficacy population from both trials. This population included 106 patients with deleterious *BRCA*-mutated (either germline or somatic) advanced ovarian cancer who had received at least two prior platinum-based chemotherapy regimens and were treated with rucaparib 600 mg orally twice daily, including 42 patients from Study 10 and 64 patients from ARIEL2. ORR and DoR were assessed by the investigator and independent radiology review according to RECIST version 1.1 (5). The primary safety evaluation was conducted in 377 patients with ovarian cancer who were also treated on ARIEL2 and Study 10 and received at least one dose of rucaparib 600 mg regardless of *BRCA* status and prior lines of chemotherapy.

Results

Demographics and disease characteristics

The clinical trials that provided data for this single-arm efficacy analysis enrolled 106 patients from 50 sites in seven countries. Although a large fraction of patients (24.5%) were from the United States, patients were enrolled in six other countries, making up 75.5% of the efficacy population. The median age of the efficacy population was 59.2 years (range, 33–84); 78% of patients were White, 6.6% Asian, and 3.8% Black, and 100% had an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1. The majority of patients (78.3%) had serous histology epithelial ovarian cancer; 74.5% were considered to have platinum-sensitive disease, 19% were platinum resistant, and 6.5% were platinum refractory. All patients had *BRCAM* ovarian cancer; 83% had *gBRCAM* status, 17% had *sBRCAM* status, 63.2% had a *BRCA1* mutation, and 36.8% had a *BRCA2* mutation. All efficacy population patients were pretreated with at least two lines of prior platinum-based therapy, and 61.4% had received at least three prior treatment regimens.

The safety population analyzed includes 377 patients with ovarian cancer, with a median age of 62 years (range, 31–86); 80.2% patients were White, 5.8% Asian, and 2.1% Black, and 100% had an ECOG score of 0 or 1. A total of 144 patients (38%) had *BRCAM* ovarian cancer, and 45% had received three or more prior lines of chemotherapy.

The companion diagnostic (CDx) device review focused on performance characteristics to ensure that the device was appropriately validated to detect *BRCA1* and *BRCA2* alterations (e.g., SNPs and small insertions/deletions up to 13 nucleotides) in formalin-fixed, paraffin-embedded ovarian tumor tissue. The clinical performance of the FoundationFocus CDx_{BRCA} was established using the same two clinical trials used to establish the safety and efficacy of rucaparib. Of the 106 patients included in the primary efficacy population, specimens from 64 patients identified as positive by the clinical trial assay (CTA) were available for retrospective testing with the FoundationFocus CDx_{BRCA} test in the bridging study for clinical validation of the device. The concordance between the local laboratory tests or clinical trial

assay used to identify patients during the clinical trials and the results from the FoundationFocus CDx_{BRCA} test was 97.9% [95% confidence interval (CI), 92.6–99.7]. Response rates were comparable between patients with a *BRCA* alteration detected by the FoundationFocus CDx_{BRCA} test (confirmed ORR of 53.1%; 95% CI, 40.2–65.7) and the overall population.

Efficacy

The efficacy review included 106 patients from the two ovarian cancer trials who met the indicated clinical characteristics, as described above. Investigator-assessed ORR was 54%, with a median DoR of 9.2 months (Table 1). The median DoR and the distribution of patients having a durable response in 3-month categories are shown in Table 2. Investigator-assessed ORR was 66% (52/79; 95% CI, 54–76) in platinum-sensitive patients, 25% (5/20; 95% CI, 9–49) in platinum-resistant patients, and 0% (0/7; 95% CI, 0–41) in platinum-refractory patients. For patients with *BRCA1* mutations, the ORR was 54% (36/67; 95% CI, 41–66), and for patients with *BRCA2* mutations, the ORR was 54% (21/39; 95% CI, 37–70). Patients with *gBRCAM* had an ORR of 54% (47/88; 95% CI, 43–64), and patients with *sBRCAM* or indeterminate mutation had an ORR of 56% (10/18; 95% CI, 31–79). Tumor *BRCA* mutation status (including germline and/or somatic *BRCA* mutations) was verified retrospectively in 96% (64/67) of the patients for whom a tumor tissue sample was available by the approved CDx FoundationFocus CDx_{BRCA} test.

Safety

The safety review primarily focused on 377 patients with ovarian cancer (including 144 patients with *BRCAM* ovarian cancer) treated with at least one 600 mg dose of rucaparib. Rucaparib exposure was adequate to assess safety with 29% of all ovarian cancer patients and 43% of *BRCAM* patients receiving treatment for 6 to 12 months, and 14% of all ovarian cancer patients and 19% of *BRCAM* ovarian patients receiving treatment past 12 months. The most common adverse reactions (≥20%) were nausea, fatigue (including asthenia), vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea. Adverse reactions led to dose modifications (reductions or interruption) in 62% of patients, most frequently from anemia (27%) and fatigue/asthenia (22%). Adverse reactions resulted in dose discontinuation in 10% of patients, most frequently from fatigue/asthenia (2%). No patient died on or within 28 days of treatment due to causes other

Table 2. Best objective response in the rucaparib efficacy population as per the investigator and IRR based on 106 patients drawn from ARIEL2 and Study 10 with relapsed *BRCA*-positive ovarian cancer who had been treated with two or more platinum-containing regimens

Response	INV N = 106 n (%)	IRR N = 106 n (%)
ORR	57 (54)	44 (42)
CR + PR (95% CI)	(44–64)	(32–52)
CR	9 (8)	5 (5)
PR	48 (45)	39 (37)
PD	9 (8)	17 (16)
SD	36 (34)	40 (38)
NE	4 (4)	5 (5)

Abbreviations: CR, complete response; INV, investigator-assessed; IRR, independent radiology review; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

than disease progression. Other safety concerns include laboratory abnormalities in liver functions [74% increase in alanine aminotransferase (ALT), 73% increase in AST], which were generally low grade (only 13% ALT increase and 5% AST increase grade 3/4 toxicities) and resulted in treatment discontinuation in only one patient, and anemia (67%), which occurred across all grades (23% grade 3/4) and was easily managed with dose modification.

Two of the 377 patients (0.5%) with ovarian cancer treated with rucaparib were diagnosed with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML). These patients developed MDS/AML after 57 and 539 days on rucaparib therapy. In addition, AML was reported in two patients with ovarian cancer enrolled on a blinded, randomized trial of maintenance rucaparib versus placebo following chemotherapy, and one of these cases was fatal. All four of these patients had received prior treatment with platinum and other DNA-damaging agents.

Discussion

Recurrent, advanced ovarian cancer is an incurable disease, and patients routinely undergo successive treatment regimens with a variety of cytotoxic and antiangiogenic combinations. An important goal for drug development in this patient population is to find safe and effective alternatives to the traditional cytotoxics that provide clinical benefit while avoiding the additive toxicities of

the original regimens. Exploiting a molecular defect can provide a meaningful alternative to cytotoxics, as has been the case in lung cancer and other solid tumors.

Few controlled trials are available to benchmark response rates to traditional chemotherapy in the third-line, platinum-sensitive setting. No trials are available that evaluate ORR, or any endpoint, for a population with *BRCAM* cancer in the third-line setting. Traditional chemotherapy trials strictly follow convention in denoting ovarian cancer as platinum sensitive or resistant, and, therefore, comparison of the rucaparib efficacy population as a whole is untenable, as it included women who were considered platinum sensitive as well as platinum resistant/refractory. Response rates to standard treatment for third-line, platinum-sensitive ovarian cancer are reported as 39% to 45% for platinum-sensitive patients who were progression free for 6 to 12 months after platinum to 38% to 42% for patients with platinum-free intervals of >24 months; although the latter are thought to be more chemosensitive, these results demonstrate the generally lower response rates in later-line therapy (6). Given these rates, the rucaparib-treated platinum-sensitive *BRCAM* subpopulation ORR of 66% is a substantial improvement. For platinum-resistant disease, response rates (for patients who had been treated with two or fewer prior lines of therapy) have been reported as 28% (95% CI, 21–36) in chemotherapy plus bevacizumab-treated patients (and higher in the un-prespecified bevacizumab plus paclitaxel subgroup at 53%; ref. 7). However, the

Table 3. FDA benefit-risk analysis

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	<ul style="list-style-type: none"> Approximately 14,000 U.S. deaths annually from advanced ovarian cancer. Poor prognosis for patients with advanced ovarian cancer following two or more chemotherapies. Patients with deleterious <i>BRCAM</i>-associated (germline and/or somatic) ovarian cancer represent a unique population with defects in homologous recombination pathway genes. 	Advanced ovarian cancer is a serious and life-threatening disease with a significant unmet medical need. Certain therapies can exploit defects in the homologous recombination pathway.
Current treatment options	<ul style="list-style-type: none"> No available therapies specifically for patients with <i>BRCAM</i> ovarian cancer who received two or more chemotherapies. Independent of <i>BRCAM</i> status, chemotherapies or chemotherapy plus bevacizumab are standard of care in patients who received two or more chemotherapies. Choice of therapy depends on platinum sensitivity status. Response rates vary from 10% to 50% depending on line of therapy and platinum sensitivity status. Available therapies are toxic regimens. 	Patients with <i>BRCAM</i> advanced ovarian cancer may have a different natural history of disease and could benefit from safe and effective oral monotherapy after two or more chemotherapies.
Benefit	<ul style="list-style-type: none"> Of 106 patients with <i>BRCAM</i> advanced ovarian cancer who received two or more chemotherapies, ORR was 54% (95% CI, 44–64) and DoR was 9.2 months (91% CI, 6.6–11.7). Investigator-assessed ORR was 66% (52/79; 95% CI, 54–76) in platinum-sensitive patients, 25% (5/20; 95% CI, 9–49) in platinum-resistant patients, and 0% (0/7; 95% CI, 0–41) in platinum-refractory patients. Tumor <i>BRCAM</i> mutation status was verified retrospectively by the FoundationFocus CDx_{<i>BRCAM</i>} test in 96% (64/67) of patients for whom a tumor tissue sample was available. 	Evidence of effectiveness was supported by ORR, with supportive DoR reasonable likely to predict clinical benefit. FoundationFocus CDx _{<i>BRCAM</i>} test is recommended for patient selection. Uncertainty about clinical benefit of rucaparib, in context of known safety profile, is acceptable based on the nature of incurable advanced ovarian cancer as a life-threatening disease.
Risk	<ul style="list-style-type: none"> Most common adverse reactions (AR; ≥20%) were nausea, fatigue (including asthenia), vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea. Ten percent dose discontinuation due to ARs, most frequently from fatigue at 2%. AML/MDS risk is clinically significant but was low (0.5%). 	Overall safety profile acceptable for the intended population and is potentially an improvement over other available therapies. AML/MDS is described in the Warnings section of the product label.
Risk management	<ul style="list-style-type: none"> Oncologists are well versed in identification and management of toxicities associated with rucaparib. Labeling for AML/MDS in the Warnings and Precautions section of the product label. Accelerated approval based on ORR and DoR. 	Safe use of rucaparib can be managed through labeling and routine oncology care. Confirmatory trials (ARIEL3 and ARIEL4) ongoing.

rucaparib-treated platinum-resistant *BRCAm* subgroup, which demonstrated an ORR of 25%, included patients with more chemotherapy-resistant disease, as all patients were treated with rucaparib in the fourth- or fifth-line treatment setting where responses would be expected to be considerably less. Therefore, extrapolation for comparison with older benchmark trials is difficult, and no data exist for the specific subset of patients with deleterious *BRCAm* ovarian cancer after two prior chemotherapy regimens. The ORR of 54%, supported by a DoR of 9.2 months, is considered better than currently available therapies and reasonably likely to predict clinical benefit, translating into an effective treatment with oral monotherapy by a targeted agent while avoiding the recurring and cumulative toxicity of repeated platinum-based regimens. Because of the uncertainty regarding the accuracy of ORR to predict clinical benefit, the accelerated approval pathway, which mandates description and/or verification of benefit with additional data, was used for the approval of rucaparib. The clinical benefit is to be established by confirmatory trials ARIEL3 and ARIEL4. ARIEL3 evaluates rucaparib monotherapy versus placebo as maintenance in the *BRCA* mutation-positive platinum-sensitive relapse setting. If positive, this trial will establish rucaparib efficacy in an earlier line of therapy than the current indication, confirming clinical benefit and supporting regular approval. This trial is fully accrued, and preliminary results are expected in late 2017. The second trial, ARIEL4, is a multicenter, open-label, randomized trial of rucaparib versus chemotherapy in patients with *BRCA* mutation-associated relapsed ovarian cancer; interim results are expected in late 2022.

The approved CDx device is the first next-generation sequencing (NGS)-based CDx device approved by FDA. The FDA Center for Devices and Radiological Health approved the Foundation-Focus CDx_{BRCA} device contemporaneously with rucaparib for the detection of deleterious *BRCA1* and *BRCA2* mutations in DNA from tumor specimens. The device is intended to detect *BRCA1* and *BRCA2* alterations in formalin-fixed, paraffin-embedded tumor tissue and, therefore, should detect both germline and somatic alterations. However, the device does not adjudicate whether the source of the mutation is germline or somatic. The applicant agreed to a postmarketing commitment (PMC) to provide clinical and scientific validation of a CDx device capable of distinguishing germline *BRCA* alterations.

The safety profile of rucaparib is acceptable for the intended population and considered tolerable compared with alternative chemotherapy (with or without bevacizumab) options. Although AML and MDS were the most concerning adverse reactions identified, they occurred in only two (0.5%) of the patients in the safety population. In contrast to olaparib, the first PARP inhibitor approved, the approval of rucaparib did not require a postmarketing requirement (PMR) for the evaluation of MDS/AML due to the body of evidence of the PARP inhibitor class and data of rucaparib related to the MDS/AML adverse reaction. The product label adequately describes and conveys the AML/MDS concern in the Warnings and Precautions section.

Regulatory Considerations for Future Applications

The first approval of an NGS-based CDx will inform the evaluation of NGS data for future device approvals. NGS-based companion diagnostics present challenges related to the large number of variants detected by the assay, including sample

Table 4. DoR in patients with objective response (investigator assessment) based on 106 patients drawn from ARIEL2 and Study 10 with relapsed *BRCA*-positive ovarian cancer who had been treated with two or more platinum-containing regimens

Median DoR in months (95% CI)	Rucaparib treated (N = 57) n (%)
Events (PD)	30 (53)
≤3 months	13 (22.8)
3–6 months	17 (29.8)
6–9 months	9 (15.8)
9–12 months	9 (15.8)
>1 year	9 (15.8)

Abbreviations: DoR, duration of response; PD, progressive disease.

representativeness to cover those variants. In prior applications for molecular diagnostics, sponsors have generally been required to validate each variant detected by the assay in the intended-use population. Given the large number of variants detected by the NGS assay (single-nucleotide variants, insertions and deletions up to 13 base pairs, large rearrangements, and homozygous deletions), it would be too burdensome to expect that every variant be directly validated. Instead, a representative approach was employed whereby the intended-use specimens that covered the range of variant types, sizes, and genomic regions (i.e., GC content and homopolymer runs) detected by the assay were evaluated in the validation studies. This provided reasonable assurance that the performance in the representative variants would likely reflect the performance across all variants the assay is designed to detect. Any lack of representativeness in the validation studies was reflected in the Limitations section of the device labeling and patient results report, and requires post-approval studies to supplement the data.

Conclusions

Overall, rucaparib, an oral monotherapy with a biologic and mechanistic rationale for use in the subpopulation of patients with deleterious *BRCAm* ovarian cancer, demonstrated an ORR, with supportive DoR, reasonably likely to predict clinical benefit in a genomically defined subset of patients who are facing a malignancy that is refractory, advanced, and life-threatening and an unmet medical need. The safety profile is acceptable in the population indicated and provides an alternative toxicity profile, and the potential for patients to be treated with an effective monotherapy while delaying the repeated and cumulative toxicity of chemotherapy, chemotherapy combinations, or chemotherapy plus bevacizumab. In addition, the studies demonstrate the validity of sparing additional platinum exposure into the third-line setting, previously only demonstrated in the fourth line. Therefore, the benefit–risk profile (Table 3) is favorable to support accelerated approval of rucaparib as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic)-associated advanced ovarian cancer who have been treated with two or more chemotherapies (Table 4). Continued approval for the indication is contingent upon verification and description of clinical benefit in the confirmatory trials ARIEL3 and ARIEL4.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The Deputy Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose.

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