



Virginia Spadoni, PharmD, BCOP  
Senior Director, Medical Communications  
[gspadoni@clovisoncology.com](mailto:gspadoni@clovisoncology.com)  
415-409-5440

December 20, 2016

**NCCN Guidelines Panel: Ovarian Cancer**

On behalf of Clovis Oncology, Inc., I respectfully request that the NCCN Ovarian Cancer Guidelines Panel review the enclosed data and consider the inclusion of rucaparib in the Ovarian Cancer treatment guidelines.

**Specific Changes:** We recommend the addition of rucaparib as a single agent for recurrence therapy for patients with either platinum-sensitive or platinum-resistant epithelial ovarian/fallopian tube/primary peritoneal cancer associated with a tumor BRCA mutation.

**FDA Clearance:** Rucaparib (Rubraca™) is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated 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. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca™.<sup>1</sup>

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.<sup>1</sup>

**Rationale:** The efficacy and safety of rucaparib were evaluated in two open-label, multicenter, single-arm studies, Study 10 (Study 1; NCT01482715)<sup>2</sup> and ARIEL2 (Study 2; NCT01891344). The efficacy data to support FDA approval was based on the pooled subset of patients in Study 1 and 2 with either a germline or somatic *BRCA1* or *BRCA2* mutation who had received two or more prior lines of therapy (N=106).<sup>1,3-4</sup> All 106 patients received rucaparib 600 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator and independent radiology review (IRR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

The median age of the patients in the efficacy population was 59 years (range 33 to 84), the majority were Caucasian (78%), and 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. All patients had received at least two prior platinum-based chemotherapies and 43% had received 3 or more prior lines of chemotherapy. There were 18/106 patients (17%) who had deleterious *BRCA* mutations detected in tumor tissue and not in whole blood specimens.

**Overall Response and Duration of Response in Patients with *BRCA*-mutant Ovarian Cancer Who Received 2 or More Chemotherapies in Study 1 and Study 2**

	<b>Overall<sup>8</sup> N=106</b>
Objective Response Rate (95% CI)	54% (44, 64)
Complete Response	9%
Partial Response	45%
Median DOR in months (95% CI)	9.2 (6.6 ,11.6)

\*Pooled analysis of Study 1 and Study 2; DOR, duration of response

Response assessment by independent radiology review was 42% (95% CI [32, 52]), with a median DOR of 6.7 months (95% CI [5.5, 11.1]). 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. ORR was similar for patients with a *BRCA1* gene mutation or *BRCA2* gene mutation.

The overall safety evaluation of rucaparib is based on data from 377 patients with ovarian cancer who received rucaparib 600 mg twice daily as monotherapy. In these patients the median age was 62 years (range 31 to 86), 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 38% had *BRCA*-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range 6 to 197).

Adverse reactions led to dose reduction or interruption in 62% of patients, most frequently from anemia (27%), and fatigue/asthenia (22%). Adverse reactions led to dose discontinuation in 10% of patients, most frequently from fatigue/asthenia (2%). The median duration of treatment was 5.5 months (range 0.1 to 28.0).

The most common grade 1 through 4 (NCI CTCAE version 4.03) adverse reactions included: nausea (77%), asthenia/fatigue (77%), vomiting (46%), anemia (44%), and constipation (40%). The most common grade 3/4 adverse reactions included anemia (25%), asthenia/fatigue (11%), nausea (5%), thrombocytopenia (5%) and vomiting (4%).

Most common laboratory abnormalities ( $\geq 35\%$ ; all grades) were increase in creatinine, increase in alanine aminotransferase (ALT), increase in aspartate aminotransferase (AST), decrease in hemoglobin, decrease in lymphocytes, increase in cholesterol, decrease in platelets, and decrease in absolute neutrophil count.

Rucaparib demonstrated activity in patients with advanced ovarian cancer with deleterious *BRCA*-mutated tumors, inclusive of both germline and/or somatic *BRCA* mutations, and who have previously been treated with two or more chemotherapies.

The following articles and presentations are submitted in support of this proposed change. We would like to acknowledge the contributions of the NCCN panel members who are also co-authors or co-contributors to many of these publications.

1. Rubraca™. Prescribing Information, December 2016.  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/209115s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209115s000lbl.pdf)
2. Shapira-Fromer R, *et al.* A phase 2 open-label, multicentre study of single-agent Rucaparib in the treatment of patients with relapsed ovarian cancer and a deleterious *BRCA* mutation. Paper presented at: 18<sup>th</sup> ECCO-40<sup>th</sup> ESMO European Cancer Congress 2015; September 25-29, 2015; Vienna, Austria. <http://www.poster-submission.com/ecc2015/authors/poster/download/30194>
3. Swisher EM, Lin KK, Oza AM, *et al.* Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2016, epub ahead of print November 28, 2016. DOI: [http://dx.doi.org/10.1016/S1470-2045\(16\)30559-9](http://dx.doi.org/10.1016/S1470-2045(16)30559-9)
4. Kristeleit RS, Shapira-Frommer R, *et al.* Clinical Activity of the Poly (ADP-Ribose) polymerase (PARP) inhibitor Rucaparib in patients with high-grade ovarian carcinoma and *BRCA* mutation: Analysis of pooled data from Study 10 (Parts 1, 2a, and 3) and ARIEL2 (Parts 1 and 2). Paper presented at: the European Society of Medical Oncology 2016, October 7-11, 2016; Copenhagen, DK. [http://clovisoncology.com/files/Rucaparib\\_RKristeleit\\_ESMO2016.pdf](http://clovisoncology.com/files/Rucaparib_RKristeleit_ESMO2016.pdf)

Regards,



Virginia Spadoni, PharmD, BCOP  
Senior Director, Global Medical Communications