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NCCN Guidelines Panel: Prostate Cancer (Request A: recurrent *BRCA*-mutated mCRPC)
On behalf of Clovis Oncology, Inc., I respectfully request that the NCCN Prostrate Cancer Panel review the enclosed data and consider the inclusion of RUBRACA® (rucaparib) for the treatment of recurrent *BRCA*-mutated metastatic castration-resistant prostate cancer (mCRPC).

Specific Changes (Guideline page **PROS-16):**
We request the inclusion of rucaparib for patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated mCRPC as Systemic Therapy for M1 CRPC: Adenocarcinoma under "**Useful under Certain Circumstances**" category.

FDA Approval: Rucaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. 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. Please see enclosed prescribing information for other FDA-approved indications.[1]

Rationale: The safety and efficacy of rucaparib was investigated in TRITON2 (NCT02952534), an ongoing multicenter, single arm clinical trial in patients with HRD-positive mCRPC. There were 115 patients with either germline or somatic *BRCA* mutations enrolled in TRITON2, of whom 62 patients had measurable disease at baseline by independent radiology review (IRR). Patients received rucaparib 600 mg orally twice daily until disease progression or unacceptable toxicity. Patients also received concomitant GnRH analog or had prior bilateral orchiectomy. The major efficacy outcomes of the study were confirmed objective response rate (ORR) and duration of response (DOR), assessed in patients with measurable disease by blinded IRR according to modified RECIST version 1.1/Prostate Cancer Working Group 3 (PCWG3) criteria.[1]

The efficacy of rucaparib was evaluated in 62 patients with measurable disease at baseline. Eighteen percent of patients had lung metastases, 21% had liver metastases, 24% had metastases to lymph nodes alone, and 40% had 10 or more bone lesions at baseline. All 62 IRR-evaluable patients had a deleterious somatic (66%) or germline (34%) *BRCA* mutation detected from either central plasma (26%), central tissue (32%), or local (42%) testing. [1]

Efficacy Results in Patients with *BRCA*-mutated mCRPC - TRITON2 (IRR-assessed)[1]

	Rucaparib N= 62
Confirmed Objective Response Rate (95% CI)[a]	44% (31,57)
Median DOR in months (95% CI)[b]	NE (6.4, NE)

IRR, independent radiology review; NE = not evaluable

[a] Defined per modified RECIST v1.1 criteria and with no confirmed bone progression per PCWG3.

[b] The range for the DOR was 1.7-24+ months. Fifteen of the 27 (56%) patients with a confirmed objective response had a DOR of ≥ 6 months.

The ORR by IRR was similar in patients with a germline versus somatic *BRCA*-mutation.[1]

The safety of rucaparib 600 mg twice daily was evaluated in TRITON2 which enrolled 209 patients with HRD-positive mCRPC, including 115 with *BRCA*-mutated mCRPC. Among the patients with *BRCA*-mutated mCRPC, the median duration of rucaparib treatment was 6.5 months (range 0.5 to 26.7).[1]

There were 2 (1.7%) patients with adverse reactions leading to death, one each attributed to acute respiratory distress syndrome and pneumonia. Treatment-emergent myelodysplastic syndrome or acute myeloid leukemia was not reported. Dose interruptions due to an adverse reaction of any grade occurred in 57% of patients receiving rucaparib. Adverse reactions requiring dose interruption in >3% of patients included anemia, thrombocytopenia, asthenia/fatigue, nausea, vomiting, neutropenia, ALT/AST increased, creatinine increased, decreased appetite, acute kidney injury, and hypophosphatemia. Dose reductions due to an adverse reaction occurred in 41% of patients receiving rucaparib. Adverse reactions requiring dose reduction in >3% of patients were anemia (14%), asthenia/fatigue (10%), thrombocytopenia (7%), nausea (6%), decreased appetite (4%), and rash (3%). Discontinuation due to adverse reactions occurred in 8% of patients receiving rucaparib. None of the adverse reactions leading to discontinuation of rucaparib (ECG QT prolonged, acute respiratory distress syndrome, anemia, balance disorder, cardiac failure, decreased appetite/fatigue/weight decreased, leukopenia/neutropenia, ALT/AST increased, and pneumonia) occurred in more than one patient (<1%).[1]

The most common grade 3/4 adverse reactions identified in ≥5% of 115 patients with *BRCA*-mutated mCRPC in TRITON2 included anemia (25%), thrombocytopenia (10%), asthenia/fatigue (9%), and ALT/AST increased (5%).[1]

Although the TRITON2 trial included only third line or later mCRPC patients, the applicant believes that it would be appropriate to recommend use in patients who had received a single line of prior therapy (i.e., second line) for the following reasons:

- Although taxanes are standard of care in second line disease, not all patients with recurrent mCRPC are suitable for taxane-based chemotherapy (e.g., presence of comorbidities, risk of unacceptable toxicities, patient preference, or risk associated with IV therapy in the COVID-19 era). Current NCCN guidelines include a second line of androgen receptor modulating therapy or best supportive care as treatment options in this setting. Given that these options have low activity,[2,3] there is significant unmet need in patients for whom taxane-based chemotherapy is not indicated.
- Regarding COVID-19, it is likely that the new care delivery models necessitated by the pandemic will be in effect for the foreseeable future. Intravenous docetaxel must be administered at a health care facility equipped to manage anaphylaxis. This requirement may limit access for some patients, as it is not a curative therapy and may therefore not be readily available.[4] As an oral, targeted therapy, where presence of a tumor BRCA mutation predicts sensitivity to rucaparib more strongly than line of therapy, it would be appropriate to recommend rucaparib for second line disease where taxane-based chemotherapy is not an option.

The following documents are submitted in support of this proposed change:

1. Rubraca®. Prescribing Information, May 2020. https://clovisoncology.com/pdfs/RubracaUSPI.pdf
2. Attard G, Borre M, Gurney H, et al. Abiraterone alone or in combination with enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific antigen during enzalutamide treatment. *J Clin Oncol.* 2018 Sep 1;36(25):2639-2646.
3. de Bono JS, Chowdhury S, Feveraband S, et al. Antitumour activity and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate plus prednisone for ≥24 weeks in Europe. *Eur Urol*. 2018 Jul;74(1):37-45.
4. Schrag D, Hershman DL, Basch E. Oncology practice during the COVID-19 pandemic. *JAMA*. 2020 Apr 13. doi: 10.1001/jama.2020.6236. [Epub ahead of print].

Thank you for your time and consideration for the inclusion of rucaparib in the management of BRCA-mutant, recurrent mCRPC.

Sincerely,

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