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May 15, 2020

NCCN Guidelines Panel: Prostate Cancer (Request B: Non-*BRCA* HRRm 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 non-*BRCA* homologous recombination repair-mutant (HRRm) metastatic castration-resistant prostate cancer (mCRPC).

Specific Changes (Guideline page **PROS-16)**
We request the inclusion of rucaparib for select patients with non-*BRCA* HRRm (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 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 refer to the prescribing information for approved indications in other cancers.[1]

Rationale for Rucaparib for Non-*BRCA* HRRm: Rucaparib is the first PARP inhibitor to receive FDA approval for patients with *BRCA*-mutation associated mCRPC for whom few effective options exist.[1] In addition to the registrational *BRCA*-mutated patients, the phase 2, multicenter, open-label, single-arm TRITON2 trial of rucaparib (NCT02952534) also included 78 patients with mCRPC with non-*BRCA* HRR mutations. Please refer to the enclosed manuscript for details about the study design and full results. In brief, rucaparib in previously treated patients with non-*BRCA* HRR-mutated mCRPC reported 0-28.6% objective response, 47%-67% stable disease, and 4.1%-35.7% PSA response.[2] Key results from the study are summarized in the table below.

Response to Rucaparib in Patients with non-*BRCA* HRR-mutated previously treated mCRPC in TRITON2.

	***ATM* (N=49)**	***CDK12* (N=15)**	***CHEK2* (N=12)**	**Other[a] (N=14)**
Confirmed Objective Response Rate	10.5%	0	11.1%	28.6%
Complete Response	0	0	0	7.1%
Partial Response	10.5%	0	11.1%	21.4%
Stable Disease	47.4%	60.0%	66.7%	57.1%
Clinical Benefit Rate at 6 months	28.6%	20.0%	37.5%	54.5%
Clinical Benefit Rate at 12 months	16.7%	7.1%	0%	37.5%
Confirmed PSA response	4.1%	6.7%	16.7%	35.7%
Median Duration of Response in months	3.1	3.2	7.4	11.1

[a]Patients with alterations in other HRR genes, including *FANCA* (n = 4), *NBN* (n = 4), *BRIP1* (n = 2), *PALB2* (n = 2), *RAD51* (n = 1), *RAD51B* (n = 1), and/or *RAD54L* (n = 1).

Among the 78 patients, 50% experienced grade 3 or higher treatment-emergent adverse events (TEAE), the most frequent being anemia, asthenia or fatigue, and thrombocytopenia. Treatment-emergent myelodysplastic syndrome or acute myeloid leukemia was not reported. Treatment interruption due to TEAE was reported in 43.6% of patients. Dose reduction due to TEAE occurred in 26.9% of patients. Four patients (5.1%) discontinued rucaparib due to TEAE (one each of asthenia or fatigue, decreased appetite, hematuria, and postoperative respiratory failure). One death was reported due to intestinal ischemia, which was considered unrelated to rucaparib.

The following articles and presentations are submitted in support of this proposed change:

1. Rubraca®. Prescribing Information, May 2020. https://clovisoncology.com/pdfs/RubracaUSPI.pdf
2. Abida W, Campbell D, Patnaik A, et al: Non-*BRCA* DNA damage repair gene alterations and response to the PARP Inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase 2 TRITON2 study. Clin Cancer Res, 2020 [EPub ahead of print.]

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

Sincerely,

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