Submitted By:
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NCCN Guidelines Panel: Ovarian Cancer

On behalf of TESARO, I respectfully request the NCCN Ovarian Cancer Guidelines Panel to review the enclosed information for the inclusion in the Guidelines of ZEJULA (niraparib) for the treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Specific Changes Requested to the guidelines:

- We recommend that niraparib be included for the maintenance treatment of patients with platinum sensitive recurrent ovarian cancer following a Complete Response (CR) to their most recent platinum-based chemotherapy
- We also recommend that niraparib be included for the treatment of patients with recurrent ovarian cancer following a Partial Response (PR) to their most recent platinum based regimen

FDA Clearance: Zejula is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Rationale: Our recommendations are primarily based on the ENGOT-OV16/NOVA study, a large, global, multi-center, randomized, double-blinded, placebo-controlled study of patients with recurrent ovarian cancer who had responded (CR or PR) to a previous (penultimate) platinum based therapy and progressed >6 months after the last dose of chemotherapy (n= 553) and then went on to receive another platinum based chemotherapy regimen upon recurrence. Following a response (CR or PR) to their most recent platinum based regimen, patients were assigned to one of two cohorts based on their germline *BRCA* mutation status (g*BRCA* mutant [n= 203] or non-g*BRCA* mutant [n= 350]), and were then randomized within each cohort 2:1 to receive niraparib or placebo. The study was published in *The New England Journal of Medicine* in 2016.

A clinically meaningful benefit was observed in all populations studied in ENGOT-OV16/NOVA. Therefore, niraparib does not require any diagnostic test for patient selection and can be used irrespective of *BRCA* mutation or HRD status. This is reflected in the indication statement of the US Package Insert.

1. Maintenance treatment of patients with platinum sensitive recurrent ovarian cancer following a Complete Response (CR) to their most recent platinum-based chemotherapy

In the ENGOT-OV16/NOVA study, Progression Free Survival (PFS) was significantly longer for niraparib versus placebo in the g*BRCA*mut cohort, (HR 0.27; 95% CI, 0.173-0.410; p<0.0001) with a median PFS of 21 months for patients in the niraparib arm versus 5.5 months for patients in the placebo arm, a difference of 15.5 months. The estimated probability of patients remaining progression free at 18 months (approximately 24 months from initiation of platinum based chemotherapy) was 50% for niraparib and 16% for placebo. In the non-g*BRCA*mut cohort, PFS was also significantly longer for niraparib versus placebo (0.45; 95% CI, 0.338-0.607; p<0.0001) with a median PFS of 9.3 months for niraparib versus 3.9 months for patients in the placebo arm. The estimated probability of patients remaining progression free at 18 months was 30% for niraparib and 12% for placebo.

Best overall response on the most recent chemotherapy (CR or PR) was a stratification factor. Approximately 50% of the patients had a CR following the most recent chemotherapy in both cohorts. For patients with a CR, PFS hazard ratios for g*BRCA*mut (HR=0.30; 95% CI, 0.160-0.546; p <0.0001) and non-g*BRCA* mut (HR=0.58; 95% CI, 0.383-0.868; p=0.0089) cohorts were statistically significant and substantially below 1 *(Mirza et al. NEJM 2016)* (data on file enclosed).

2. Treatment of patients with recurrent ovarian cancer following a Partial Response (PR) to their most recent platinum based regimen

Treatment after a PR:
In the ENGOT-OV16/NOVA study approximately 50% of patients had a PR to their last platinum based chemotherapy (equally proportioned in both cohorts and arms). Of note, 42 patients had residual lesions of more than 2 cm per IRC (15.4% of PR patients) at baseline. Niraparib treatment was effective in patients following a PR to their most recent platinum based chemotherapy. For these patients, PFS hazard ratios for g*BRCA*mut (HR=0.24; 95% CI 0.131-0.441; p< 0.0001) and non-g*BRCA*mut (HR=0.35; 95% CI 0.230-0.532; p<0.001) cohorts. These results were comparable to the results in the overall study population *(NEJM 2016 & data accepted for publication at the 2017 Annual ASCO meeting enclosed)*.

Additional note on the definition of platinum sensitivity used in NOVA:
The definition of "platinum sensitivity" adopted differs from the one currently used by NCCN and is more aligned with European guidance. Patients were deemed "platinum sensitive" if tumors had responded (CR or PR) to a previous (penultimate) platinum based therapy and progressed >6 months after the last dose of the penultimate chemotherapy regimen. Twenty eight percent of patients in the NOVA study achieved only a PR to their penultimate platinum based chemotherapy regimen. The efficacy observed in these patients was substantial in both cohorts (g*BRCA*mut HR=0.16; 95% CI 0.056-0.443; p<0.0001 and non-g*BRCA*mut HR=0.51; 95% CI 0.293-0.900; p=0.0208). These results were comparable to the results in the overall study population *(data on file enclosed)*.

Niraparib treatment was tolerated by the majority of women in the NOVA study. The incidence of grade 3/4 treatment emergent AEs was 74.1% with niraparib versus 22.9% with placebo. The majority of these events were hematological laboratory abnormalities. The most common hematological AEs related to niraparib were thrombocytopenia (29%), anemia (25%), and neutropenia (20%). Most hematologic abnormalities, irrespective of grade, occurred within the first three treatment cycles and resolved by cycle 4 with per protocol dose adjustments based on individual tolerability. Importantly, only 3%, 2% and 1% of patients discontinued treatment due to thrombocytopenia, anemia or neutropenia, respectively. Other Grade 3/4 AEs of note were fatigue (8%) and hypertension (9%) – per PI. Patients' quality of life was maintained in the niraparib arm and no different from the placebo arm as assessed by the FOSI and EQ-5D-5L, validated PRO instruments *(Mirza et al. NEJM 2016 – supplemental appendix)*.

While no direct comparisons of PARP inhibitors have been conducted in a clinical setting, pre-clinical experiments have shown that PARP inhibitors have clinical pharmacology and chemical property differences. Important variations have been noted in anti-PARP activity, as well as tissue penetration *(Mikule et al. ECCO 2017 abstract #716)*. This may help explain why some currently approved PARP inhibitors require companion diagnostics, while niraparib does not. Based on the findings of the ENGOT-OV16/NOVA study, and in the context of these pre-clinical findings, we believe that clinical activity of each PARP inhibitor should be assessed in the context of its own data, and that PARP inhibitors are not considered interchangeable.

Please find attached enclosures in support of the proposed changes. We sincerely appreciate the opportunity to provide this information for consideration by the NCCN Ovarian Cancer Panel. If any questions arise or if you require any additional information, please don't hesitate to contact me by phone at 781-257-2536, or email me at mhuber@tesarobio.com.

Sincerely,

Martin Huber, MD