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Submitted By:

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Date of Request: October 10, 2018 NCCN Guidelines Panel: Ovarian Cancer

TESARO respectfully requests the NCCN Ovarian Cancer Guidelines Panel to review the enclosed information to update the recommendations on OV6 to recommend PARP inhibitors (PARPis) maintenance (niraparib, olaparib, or rucaparib) over observation following a complete or partial response to platinum-based chemotherapy, based on the current body of evidence regarding these PARP inhibitors in this setting.

Specific Changes Requested in the Guidelines:

- We recommend that “observe” on page OV6 be downgraded from category 2A to 2B
- Add a footnote for “observe” on page OV6 that this option should be considered for individuals who cannot be treated with PARPis
- We recommend that there is now sufficient evidence to elevate PARPi maintenance in this setting to category 1

FDA Clearance:

- Lynparza® (olaparib) is indicated for 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. Additionally, for treatment of adult patients with deleterious or suspected deleterious germline *BRCA* mutation (*gBRCA*mut) advanced ovarian cancer who have been treated with ≥3 lines of chemotherapy.
- Rubraca® (rucaparib) is indicated for 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. Additionally, for the treatment of adult patients with deleterious *BRCA* mutation (*gBRCA*mut and/or somatic) associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥2 chemotherapies.
- Zejula® (niraparib) is 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:

The prognosis for women with recurrent ovarian cancer remains poor, with shorter chemotherapy-free intervals with each subsequent recurrence as shown by the progression-free survival (PFS) and overall survival (OS). Following the first, second, third, fourth and fifth relapse, median PFS was 10.2 (95% CI, 9.6–10.7], 6.4 (5.9–7.0), 5.6 (4.8–6.2), 4.4 (3.7–4.9) and 4.1 (3.0–5.1) months and median OS was 17.6 (95% CI, 16.4–18.6), 11.3 (10.4–12.9), 8.9 (7.8–9.9), 6.2 (5.1–7.7) and 5.0 (3.8–10.4) months, respectively. Secondly, effectiveness of platinum-based chemotherapy lessens, and cumulative toxicity increases over time. Thirdly, approximately 80% of women with ovarian cancer express worry about recurrence after remission and indicate that ending active treatment triggers new fears and anxieties because they are no longer actively fighting the disease or under the “protection” of treatment. Most (87%) women who experience a recurrence report that the thought of cancer returning can be overwhelming and 58% report that no longer receiving therapy is sometimes worse than going through treatment. Finally, with an average duration of the watchful waiting period of 253.1 days (standard deviation [SD] 270.9 days), 30% of patients had an inpatient admission; 395 patients were hospitalized for 650 inpatient admissions; and the mean cost per hospitalization was \$44,396 (SD \$61,022) with a mean length of stay of 10 days (median 5 days). Additionally, 359 patients had 726 ER visits and the mean cost per visit was \$2,261 (SD \$8,666).



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Three large, phase 3, placebo-controlled, double-blinded studies (SOLO-2, ARIEL3 and NOVA) and a retrospective analysis of a randomized, double-blind, phase 2 study (Study 19) showed similar outcomes of 4.0 to 6.0 months median PFS (analogous to observation) with placebo compared to 11.2-21.0 months in *gBRCA*mut patients and 6.7-9.7 months in non-*gBRCA*mut patients following chemotherapy. While the larger effect is seen, on average, in the *BRCA*mut populations, hazard ratios (HR) in non-*gBRCA*mut, including the *BRCA* wild type (*BRCA*wt) populations, are 0.44-0.58, which still translates into a 42% mean reduction of risk of death or progression. Additionally, PARPi maintenance is very tolerable, and numerous publications have found that maintenance treatment with a PARPi maintains quality of life (QoL) compared to placebo and may even improve it. Moreover, women receiving maintenance treatment following chemotherapy report experiencing less anxiety and fear of recurrence. Despite PARPis having demonstrated efficacy, less than 40% of eligible women with recurrent ovarian cancer currently receive PARPi maintenance therapy.

For rucaparib, maintenance therapy resulted in a median PFS equal to 10.8 months (95% CI, 8.3–11.4) in the overall population (n=375) vs 5.4 months with placebo (n=189) [95% CI, 5.3-5.5; HR, 0.36 [95% CI, 0.30-0.45], $P<0.0001$). Similarly, maintenance olaparib therapy for patients with platinum-sensitive high-grade serous ovarian cancer (OC) and *BRCA*mut who received ≥ 2 lines of chemotherapy (n=295) resulted in a longer median PFS (19.1 months [95% CI, 16.3-25.7]) than in patients receiving placebo (n=99) (5.5 months, 95% CI, 5.2-5.8; HR, 0.30 [95% CI, 0.22-0.41], $P<0.0001$). Median PFS for niraparib maintenance therapy for *gBRCA*mut patients (n=138) was 21.0 months (95% CI, 12.9-NR) vs placebo (n=65) 5.5 months (95% CI, 3.8-7.2; HR 0.27 [95% CI, 0.17-0.41], $P<0.0001$). Importantly, the clinical benefit was robust in non-*gBRCA*mut patients (n=234) as the median PFS was 9.3 months (95% CI, 7.2-11.2) for niraparib vs placebo (n=116) 3.9 months (95% CI, 3.7-5.5; HR 0.45 [95% CI, 0.34-0.61], $P<0.0001$). Moreover, for *gBRCA*mut patients, maintenance therapy was prolonged by 15.5 months (vs placebo), risk of progression or death was reduced by 73% (vs placebo); for the non-*gBRCA*mut patients, maintenance treatment was prolonged by 5.4 months (vs placebo), risk of progression or death was reduced by 55% (vs placebo). In the *gBRCA*mut population, it is estimated that long-term PFS of 24 months would be achieved by 42% of niraparib-treated patients compared to 16% of patients on placebo.

The common adverse events (AEs) for rucaparib, most of which were of grade 1/2 severity, include gastrointestinal (GI)-related events, fatigue, rash, elevated aspartate aminotransferase/alanine aminotransferase, dysgeusia and anemia. The most common AEs for olaparib are GI-related events, fatigue, anemia, infections and arthralgia/myalgia. For niraparib, AEs included GI-related events, fatigue, thrombocytopenia, anemia and neutropenia; the incidence of AEs was reduced by dose modification and relatively rare after cycle 3. The proportion of patients who discontinued treatment due to AEs was 13% for rucaparib, 11% for olaparib, and 14.7% for niraparib.

For rucaparib vs placebo, there was no significant differences in time to worsening of disease-related physical symptoms (disease-related symptoms—physical subscale of the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI-18). Health-related QoL based on the European QoL 5-Dimension 5-Level questionnaire (EQ-5D-5L) and FOSI was similar for olaparib or niraparib vs placebo throughout the studies and was maintained at pre-treatment levels. Olaparib showed clinically meaningful patient-centered benefits with longer quality-adjusted progression-free survival (QAPFS) and time without significant symptoms of toxicity (TWiST).

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 do not hesitate to contact me by phone at 781-257-2536 or email me at mhuber@tesarobio.com.

Sincerely,

A handwritten signature in black ink that reads "Martin Huber".

Martin Huber, MD



TESARO, INC. | 1000 WINTER STREET | WALTHAM, MA 02451

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