TESARO, Inc. | 1000 Winter Street | Waltham, MA 02451

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

Specific Changes Requested in the Guidelines:

- We recommend that niraparib be included as a monotherapy recurrence treatment for patients who have been treated with 3 or more lines of chemotherapy, regardless of platinum status or molecular biomarker on page OV-B, 5 of 10.

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

Rationale: Our recommendation is based on the recent data from the QUADRA trial, which was presented at the 2018 annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago, Illinois. The trial is completed, and TESARO plans to submit results of the QUADRA trial to regulatory agencies for inclusion of these data in the Zejula label. The manuscript has been recently submitted to *Lancet Oncology* under accelerated review. The unpublished manuscript is enclosed for consideration.

Late-line ovarian cancer represents a particularly challenging patient population to treat, with limited effective treatment options. Historically, the expected OS has been described to be <1 year for patients treated in 4th or later line. Survivorship including palliation of both treatment and disease-related symptoms in this setting is prioritized, and as such, there is an increasing focus on minimizing toxicity and spending more time outside of the hospital or clinic. Therefore, disease stabilization with preserved quality of life and the ability to take their treatment at home are likely very meaningful for the patient. In this context, capturing clinically meaningful disease stabilization is an important descriptor of treatment efficacy. In this late-line treatment setting, the approved use of PARP inhibitors is restricted to patients with *BRCA* mutations; however, only ≈20% of ovarian cancer patients have cancers with a *BRCA* mutation, and treatments for patients without this mutation remain an unmet need.

QUADRA was a large open-label, single-arm, multicenter, phase 2 study (n=463) evaluating the safety and efficacy of single-agent niraparib, given 300 mg once daily, in patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, who must have received 3 or more lines of chemotherapy. The primary endpoint was objective response rate (ORR) per RECIST v1.1 in homologous recombination deficiency (HRD) positive, PARPi-naïve patients who have been treated with 3 or 4 prior lines of chemotherapy and were considered platinum-sensitive to the last platinum-based chemotherapy. Prespecified secondary objectives of ORR, duration of response (DOR), disease control rate (DCR), progression-free survival, and overall survival (OS) were assessed in all treated patients regardless of prior lines of chemotherapy, platinum status, prior PARPi use, and molecular biomarker. The clinical benefit rate at 24 weeks (CBR24) was also determined as post hoc exploratory analyses.

QUADRA is the largest ovarian cancer treatment study to date with 463 patients enrolled and treated. The intent-to-treat (ITT) population was comprised of 461 patients, and 391 patients were response-evaluable. After enrollment, it was determined that 5 patients had only 2 prior lines of therapy, a modified ITT (mITT) population excluding these patients was used for further analyses (n=456). Patients were enrolled without regard to *BRCA* mutation (*BRCA*mut) or HRD biomarker status, platinum sensitivity, or prior PARPi use. The study population was heavily pretreated with patients receiving a median of 4 (range 2–16) prior lines of therapy and a significant portion of patients received 5 or more lines of therapy (27%). Biomarker status was consistent with mutation rates in the overall ovarian cancer population with 48% HRD-positive patients (including *BRCA* wild type, germline *BRCA*mut and somatic *BRCA*mut); 19% of enrolled patients had a germline or somatic *BRCA* mutation. All patients had at least 1 previous line of platinum-based therapy, with 235 (51%) having received 2 prior lines and 147 (32%) having received 3 prior lines of platinum-based therapy. The trial population was predominately made of patients with platinum-resistant (33%) or -refractory (35%) disease; 26% of patients were platinum-sensitive to the last line of administered platinum therapy, with the remaining 7% with unknown platinum status. Eighty-three (18%) of the patients were primary platinum-resistant or -refractory (42 and 41 patients, respectively). The median time from last dose of last treatment to first dose on study was 2 months (range 1–73).

Niraparib clinical benefit was observed across the entire study population with a median OS across the mITT population of 17.2 months (95% CI, 14.9-19.8). Among the biomarker populations, *BRCA*mut patients demonstrated the greatest magnitude of benefit: median OS was 26.0 months (95% CI, 18.1–NE) in the *BRCA*mut population, 19.0 months (95% CI, 14.5-24.6) in the HRD-positive population, and 15.5 months (95% CI, 11.6–19.0) in the HRD-negative population. These data compare favorably to the expected median overall survival of < 1 year in a late-line recurrent ovarian cancer population. Additional clinical benefit was seen across the spectrum of biomarker and platinum status, as reviewed in Table 1. Responses were durable with a mDOR of 9.4 months (95% CI, 6.6-18.3) CBR24 with CR, PR and/or stable disease for at least 24 weeks was clinically meaningful in a population in which the natural history is rapid progression of disease. Note that it has been previously reported that CBR is associated with increased OS.

Table 1. Clinical Response by Molecular Biomarker and Platinum Status in All PARPi-naive Patients Treated with 3 or More Prior Lines of Therapy

		*BRCA*mut	HRDpos	HRDneg/unknown
Platinum-sensitive to last line of platinum therapy	**ORR**	39% (7/18)	26% (14/53)	4% (2/52)
	CBR24	56% (10/18)	40% (21/53)	19% (10/52)
Platinum-resistant or -refractory	**ORR**	27% (10/37)	10% (12/120)	3% (5/169)
	CBR24	32% (12/37)	20% (24/120)	11% (18/169)
All*	**ORR**	31% (17/55)	15% (26/173)	3% (7/221)
	CBR24	40% (22/55)	26% (45/173)	13% (28/221)

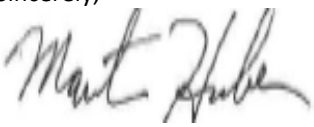
* The platinum response "All" group includes patients who were platinum-sensitive, -resistant, or -refractory. An additional 16 HRDpos (8 of which were BRCAmut) patients had unknown platinum status; of these, 3 had PR and 5 had CR+PR+SD (CBR) for at least 24 weeks.

No new safety signals were reported, and safety was consisted with previous clinical experience (e.g., the NOVA study); these involved gastrointestinal disorders, including nausea (67%), vomiting (44%), and constipation (34%); hematological toxicities, including anemia (49%), thrombocytopenia (34%), and decreased platelet count (22%); and general disorders, including fatigue (51%).

QUADRA is the largest clinical trial ever conducted to evaluate the activity of a single agent PARPi in the late-line treatment setting and is notable for its comparability to a real-world patient population. Consistent with prior niraparib studies (PN001 and NOVA), QUADRA demonstrated a continuum of clinical benefit in subgroups defined by clinical and molecular biomarkers. Notably, QUADRA demonstrated that patients across the continuum derive clinical benefit from niraparib treatment as defined by ORR and CBR24. Clinical benefit rates correlated with a median OS that exceeds expectations for this late-line, heavily pretreated population based on historic controls. No new safety signals were identified, and hematologic toxicity was well managed by dose modification. Niraparib represents a meaningful treatment option and alternative to established chemotherapy regimens for late-line treatment of patients with ovarian cancer.

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,



Martin Huber, MD
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