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On behalf of TESARO, I respectfully request the NCCN Ovarian Cancer Guidelines Panel to review the enclosed information for the inclusion of a recommendation to start ZEJULA[®] (niraparib) in patients with a baseline weight of <77kg or baseline platelet count of <150,000 cell/µL at 200 mg, orally, once daily.

Specific Changes Requested in the Guidelines:

- We recommend that the following language be added as a footnote for niraparib on page 9 of section OV-B, and page OV-6: "Consider starting niraparib at 200 mg, once daily, for patients with baseline body weight of <77 kg or baseline platelet counts of <150,000 cell/μL to reduce the incidence of thrombocytopenic events."
- We recommend the following paragraph be added to the paragraph summarizing niraparib on page MS-25: "During the first 3 months of niraparib administration, the starting dose of 300 mg resulted in grade ≥3 hematologic laboratory events of thrombocytopenia in 33% of patients, however this decreased to 0.7% after 3 months following dose modification to 200 or 100 mg. Predictive modeling identified that the characteristics that were significantly associated with the likelihood of requiring dose interruption and reduction within the first 30 days were baseline body weight <77kg or baseline platelet counts of <150,000 cell/µL. Dose reductions did not appear to affect efficacy. Therefore, a starting dose of 200 mg once daily should be considered in patients <77kg or with a baseline platelet count <150,000 cell/µL to minimize the incidence of thrombocytopenia."</p>

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 or partial response to platinum-based chemotherapy.

Rationale: Our recommendations are based on a recent multivariate analysis of the phase 3 ENGOT-OV16/NOVA (NOVA) trial, which was published online in *Annals of Oncology* in May 2018.

NOVA was a large, global, multi-center, randomized, double-blinded, placebo-controlled study of patients with recurrent ovarian cancer who had responded (complete or partial) to the penultimate platinum-based therapy (n= 553), and remains the only study of a PARPi for maintenance in the recurrent setting that prospectively evaluated both gBRCA and non-gBRCA cohorts independently as primary endpoints. The study was fully published in *The New England Journal of Medicine* in 2016.

Dose reductions due to hematological adverse events are described in detail in the NOVA primary publication and U.S. package insert (PI). In brief, all patients in the NOVA trial started at niraparib 300 mg, based on the recommended phase 2 dose identified in Sandhu *et al*. Patients experiencing an adverse event (AE) had their dose withheld up to 28 days until the AE resolved, and then resumed at 200 mg (first incidence of platelet count <100,000 cell/ μ L, but >75,000 cell/ μ L, could resume at 300 mg). If unacceptable toxicity persisted, the dose was withheld again, and reduced to 100 mg. During the first 3 months of niraparib administration, the starting dose of 300 mg resulted in grade ≥3 hematologic laboratory events of thrombocytopenia (33% of patients), anemia (13%), and neutropenia (18%). Incidences of these grade ≥3 events decreased to 0.7% for thrombocytopenia and 1.6% for neutropenia after month 3, when most patients reached their optimal individually-adjusted dose. Anemia events remained at 15%. Of note, there was only a 1.2% incidence of grade ≥3 thrombocytopenia in patients who did not require a dose reduction due to thrombocytopenia by month 3. Delayed thrombocytopenia, occurring after cycle 3, was extremely rare (approximately 1% incidence of



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thrombocytopenia any grade). Overall, few patients taking niraparib discontinued due to hematologic treatmentemergent AEs (TEAE) (thrombocytopenia 3.3%, neutropenia 1.9%, and anemia 1.4%). Many non-hematological adverse events also showed a decrease over time. Two-hundred milligrams remained the most common dose after cycle 3; after 12 months 22.7% of patients were at 300 mg, 39.9% at 200 mg and 37.4% at 100 mg.

A multivariate predictive modeling analysis was done to identify patient characteristics that may predict likelihood to need dose reduction for thrombocytopenia within the first 30 days of starting niraparib. The baseline covariate factors that were evaluated included: age, race, Eastern Cooperative Oncology Group (ECOG) status at screening, region, neutrophil counts, hemoglobin counts, albumin, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, platelet nadir (overall, across all study visits), duration of prior chemotherapy, lines of prior chemotherapy, time from last chemotherapy, and prior history of myelosuppression. Only baseline weight of <77 kg or baseline platelet count <150,000 cell/ μ L were predictive of requiring a dose reduction due to thrombocytopenia in the first 30 days.

Importantly, progression-free survival (evaluated from cycle 4 onward to account for the period of time when most dose reductions were completed) remained consistent across all dose levels, suggesting that each patient's individualized dose improves tolerability and maintains efficacy. Furthermore, the median daily dose taken within the first two months (where most dose reductions and interruptions occurred) was only 207 mg for patients with baseline body weight <77 kg or baseline platelet count <150,000 cell/µL compared with a median of 295 mg for patients with baseline body weight \geq 77 kg and baseline platelet count \geq 150,000 cell/µL. Thus, the actual delivered dose approximated a starting dose of 200 mg for patients with baseline body weight <77 kg or baseline platelets with baseline body weight <77 kg or baseline platelet count \geq 150,000 cell/µL. Thus, the actual delivered dose approximated a starting dose of 200 mg for patients with baseline body weight <77 kg or baseline platelet count <150,000 cell/µL. Thus, the actual delivered dose approximated a starting dose of 200 mg for patients with baseline body weight <77 kg or baseline platelet count <150,000 cell/µL. Therefore, NOVA ultimately measured efficacy in the lower weight or lower baseline platelet count patients at a dose of essentially 200 mg, rather than the planned 300 mg.

Of note, the double-blind, placebo-controlled, phase 3 PRIMA trial of niraparib maintenance therapy following frontline platinum-based chemotherapy was amended to initiate niraparib treatment at a dose of 200 mg/day in patients who had a baseline weight <77 kg or baseline platelet count <150,000 cell/µL. A blinded analysis was conducted to assess the impact of this amended dosing recommendation. At the time of analysis there were 630 patients enrolled, including 159 who were enrolled after the dosing amendment. The rates of adverse events were reported for the pooled patient population (combined niraparib and control arms) who were enrolled prior to the amendment and after the amendment. The rate of grade ≥3 thrombocytopenia was 30.7% in the pre-amendment group versus 5.6% in the postamendment group. Details of this analysis were submitted to the 2018 annual meeting of the European Society of Medical Oncology (ESMO) and are currently under review. The PRIMA trial remains blinded.

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

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