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**Date of Request:** 22 March 2021
**NCCN Guidelines Panel:** Ovarian Cancer

On behalf of GSK, this letter is in response to the NCCN Guidelines Panels submission request. We request the NCCN Ovarian Cancer Guidelines Panel review the enclosed data for inclusion of niraparib + bevacizumab as a combination therapy for patients diagnosed with advanced ovarian cancer following response to front-line platinum-based chemotherapy + bevacizumab, in all biomarker subgroups. This request is based on the OVARIO (NCT03326193) primary efficacy and safety analyses, which were presented at the Annual Meeting of the Society of Gynecologic Oncology on March 20, 2021. Previously, results of interim efficacy and safety analyses were submitted 19 May 2020.

**Specific Update Requested in the Guidelines:**

We respectfully request your consideration of the following change:

- Page OV-5: Addition of niraparib + bevacizumab as targeted combination for patients who had a complete or partial response to front-line platinum-based chemotherapy + bevacizumab, and who have either germline or somatic *BRCA1/2* mutations or are *BRCA1/2* wild-type or unknown, regardless of homologous recombination (HR) status.

**FDA Clearance:** *Zejula* (niraparib) is a poly(ADP-ribose) polymerase (PARP) inhibitor (PARPi) currently approved as monotherapy for first-line maintenance therapy for adult patients with advanced epithelial ovarian cancer who are in a complete or partial response to platinum-based chemotherapy and as maintenance therapy for adult patients with recurrent ovarian cancer who are in a complete or partial response to platinum-based chemotherapy, as well as treatment of patients with late-line ovarian cancer and have homologous recombination deficiency (HRD) positive status as defined by deleterious or suspected *BRCA* mutation regardless of platinum sensitivity, or genomic instability and who have progressed more than 6 months after response to their last platinum therapy.

**Rationale:**

Our submission is based on the OVARIO (NCT03326193) trial which had results demonstrating that 62% of patients were progression free at 18 months. The safety profile observed in OVARIO of the combination of niraparib + bevacizumab was consistent with the known safety profiles for the individual agents. No new safety signals were identified.[1]

The majority of women with ovarian cancer are diagnosed with advanced, stage III or IV disease with a 5 year survival rate of ~30%.[2] Until recently, front-line treatment of ovarian cancer consisted of surgery and platinum-based chemotherapy (with or without bevacizumab) followed by active surveillance.[3] PARP inhibitor monotherapy maintenance treatments have been approved for first-line use, however, both trials leading to monotherapy approvals (PRIMA and SOLO-1) excluded patients who were to receive bevacizumab as maintenance as part of their 1L treatment approach.[4,5] In May 2020, approval was granted for use of a maintenance PARP inhibitor as combination with bevacizumab in women with HRD selected through use of an FDA-approved companion diagnostic.[6]

OVARIO (NCT03326193) is a phase 2, single-arm, open-label study to evaluate niraparib + bevacizumab as maintenance treatment in patients with newly diagnosed, advanced (stage IIIB-IV) epithelial ovarian, fallopian tube, or peritoneal cancer, regardless of HRD or germline *BRCA* status, who have complete response (CR), partial response (PR), or no evidence

of disease (NED) following front-line, platinum-based chemotherapy with bevacizumab. Patients with a baseline body weight < 77 kg and/or a screening platelet count < 150,000/μL receive 200 mg niraparib daily. All other patients, or those with a baseline body weight ≥ 77 kg and a screening platelet count ≥ 150,000/μL, receive 300 mg niraparib daily. The dose of bevacizumab is 15 mg/kg intravenous every 3 weeks for a total of 15 months. Patients must receive their first dose of study treatment within 12 weeks of the first day of the last cycle of chemotherapy. The primary endpoint is a landmark analysis of 18-month progression-free survival (PFS18) rate with niraparib + bevacizumab maintenance therapy in patients who have achieved CR, PR, or NED following front-line, platinum-based chemotherapy + bevacizumab. The PFS rate is defined as the proportion of patients who have not progressed or died within a defined period after niraparib + bevacizumab treatment initiation.[1]

A total of 105 patients were enrolled; 82 patients received 200 mg and 23 patients received 300 mg, based on their baseline weight and platelet count. Patients enrolled were considered high risk, with 63% of patients receiving interval debulking surgery and neoadjuvant chemotherapy and 42% of patients having a partial response to first-line surgery and chemotherapy with bevacizumab. At the data cut-off date for PFS18 (August 14, 2020), the median follow-up was 16 months. [1]

**Table 1. Progression-Free Survival Rates at 6, 12, and 18 Months[1]**

| Parameter | Overall (N=105) | HR-deficient (n=49) | HR-proficient (n=38) | HR-not determined (n=18) |
|---|---|---|---|---|
| Events at 6 months, n | 11 | 1 | 7 | 3 |
| 6-month PFS rate, % (95% CI) | 90 (82-95) | 98 (89-100) | 82 (66-92) | 83 (59-96) |
| Events at 12 months, n | 26 | 6 | 13 | 7 |
| 12-month PFS rate, % (95% CI) | 75 (66-83) | 88 (75-95) | 66 (49-80) | 61 (36-83) |
| Events at 18 months, n | 40 | 12 | 20 | 8 |
| 18-month PFS rate, % (95% CI) | 62 (52-71) | 76 (61-87) | 47 (31-64) | 56 (31-78) |

At the data cut-off date for PFS6 (August 14, 2019), the median follow-up was 8.6 months. At the data cut-off date for PFS12 (February 14, 2020), the median follow-up was 12.8 months.

The safety profile in OVARIO of the combination of niraparib + bevacizumab was consistent with the known safety profiles for each drug as monotherapy. At the 18-month data cut off, 99% of patients experienced at least one treatment-related treatment-emergent adverse event (TEAE). Treatment-related TEAEs leading to treatment interruption occurred in 89 patients (85%) and treatment discontinuation occurred in 28 patients (27%). The rate of discontinuation is higher for combination therapy than for monotherapy alone, consistent with other PARPi and bevacizumab combination studies in the first-line setting. The most common any grade treatment-related TEAEs were thrombocytopenia (70%), fatigue (57%), anemia (52%), nausea (52%), and hypertension (50%). The most common grade ≥ 3 treatment-related TEAEs were thrombocytopenia (39%), anemia (34%), hypertension (27%), neutropenia (12%), and fatigue (10%).[1]

OVARIO is a phase 2, single-arm, open label study evaluating niraparib + bevacizumab as maintenance treatment in patients with advanced ovarian cancer following response to front-line platinum-based chemotherapy + bevacizumab with a CR, PR or NED. The findings from OVARIO demonstrate consistency with prior niraparib studies showing clinical activity and safety across clinical and molecular biomarker subgroups (PN001[7], NOVA[8], PRIMA[4], AVANOVA[9], and QUADRA[10]). The PFS rate observed in patients at 18 months with niraparib + bevacizumab maintenance therapy was noted across all biomarker subgroups, and with an acceptable safety profile.[1]

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 Danielle Schenck, PharmD, RPh at danielle.n.schenck@gsk.com.

Sincerely,

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The following data disclosures are submitted in support of this proposed change.

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2. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.
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