Submitted By:

Danielle Schenck, PharmD, RPh
Manager, Global Medical Information
GSK
1000 Winter St
Waltham, MA 02451
danielle.n.schenck@gsk.com

Date of Request: 30 September 2019

NCCN Guidelines Panel: Ovarian Cancer

On behalf of GSK, this letter is a formal request to the NCCN Ovarian Cancer Guidelines Panel to review the enclosed data for inclusion of Zejula® (niraparib) as a preferred targeted monotherapy for treatment of patients who have recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more lines of chemotherapy, regardless of platinum status or molecular biomarker. This request is based on the QUADRA trial which was recently published in *The Lancet Oncology*.

Specific Changes Requested in the Guidelines:

We respectfully request your consideration of the following change:

- Page OV-C 6-7 of 9: Addition of niraparib as targeted therapy (single agent) for patients who have been treated with 3 or more lines of chemotherapy, for platinum-sensitive and platinum-resistant disease, regardless of molecular biomarker status.

FDA Clearance: Zejula® (niraparib) is not FDA approved for the use stated above.

Zejula® is currently 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.

A supplemental New Drug Application (sNDA) was submitted to the U.S. Food and Drug Administration (FDA) to support the use noted above as a new indication for the treatment of advanced ovarian, fallopian tube, or primary peritoneal cancer patients who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with either: a deleterious or suspected deleterious *BRCA* mutation OR a homologous recombination deficiency (HRD) (without *BRCA* mutation) and who have progressed more than six months after the last dose of platinum-based chemotherapy. This submission was granted priority review and has an action date of 24 October 2019.

Rationale:

Our recommendation for this proposed change is based on the QUADRA trial which demonstrated clinical activity amongst all patient subgroups (Tables 1-3).

In the heavily-pretreated patient population, disease stabilization with preserved quality of life is a meaningful clinical outcome for patients and health care providers.[2] In this context, disease stabilization is an important surrogate of treatment efficacy as manifested by disease control rate (DCR)[a] or clinical benefit (CB)[b]. In this later-line treatment setting, the currently approved use of PARP inhibitors is restricted to patients with *BRCA* mutations; however, only ~20% of ovarian cancer patients are carriers of a *BRCA* mutation, and durable treatment responses for patients without this mutation remain a significant unmet need.[3]

[a] Disease control rate (DCR): the proportion of patients achieving a complete response (CR), partial response (PR) or stable disease (SD).
[b] Clinical benefit (CB): the proportion of patients with a complete or partial response or patients with stable disease with a duration of at least 16 and 24 weeks.

QUADRA was an open-label, single arm, phase 2 clinical study that evaluated the safety and efficacy of single-agent niraparib, given 300 mg once daily, in women with advanced, relapsed, high-grade ovarian cancer following 3 or more lines of previous chemotherapy. The primary endpoint was to evaluate the objective response rate (ORR) per RECIST v1.1 in HRD-positive (HRDpos), platinum-sensitive, PARPi naïve patients who received 3 or 4 lines of previous chemotherapy. Prespecified secondary objectives of ORR, duration of response (DoR), DCR, progression-free survival (PFS), and overall survival (OS) were assessed in all treated patients, regardless of prior lines of chemotherapy, platinum status, prior PARPi use, and molecular biomarker status.[1]

The proposed indication for women with *BRCA*mut tumors, regardless of platinum-sensitivity status (n = 63) and patients with non-*BRCA*mut HRDpos platinum-sensitive disease (n = 35), comprised a biomarker-driven population (n = 98). The ORR and mDoR are presented in Table 1. In this biomarker-driven population, the following additional efficacy points were observed: mPFS 5.5 months, mOS 23.3 months, CB at 16 weeks 48.0%, and CB at 24 weeks 35.7%.[4]

Table 1. Investigator-Assessed Overall Response and Duration of Response in Proposed Indication Population (n = 98)[1,4,6]

	***BRCA*mut or HRDpos, platinum-sensitive (n = 98)**	***BRCA*mut (n=63)**	**Non-*BRCA*mut, HRDpos, platinum sensitive (n=35)**
ORR, (95% CI)	26%, (17 – 35)	29%, (18 – 41)	20%, (8 – 37)
mDOR, (95% CI)	8.3 months, (6.6 – NE)	9.2 months, (7.4 – NE)	6.6 months, (3.5 – 15.2)

ORR = objective response rate; mDOR = median duration of response; NE = not estimable

The modified per-protocol population, women who had at least 3 previous lines of chemotherapy (n = 456), showed a mDoR of 9.4 months and an mOS of 17.2 months, regardless of molecular biomarker status The mDoR was similar across all molecular biomarker subgroups and the mOS of these subgroups exceeded the expected OS of this patient population (Table 2). Additionally, patients who had stable disease for at least 24 weeks had a mOS similar to that of patients achieving a partial or complete response (28.0 months for both), regardless of clinical or molecular biomarker status.[1]

Table 2. Median Duration of Response and Median Overall Survival by Molecular Biomarker Status in the Modified Per-Protocol Population[1]

	***BRCA*mut (n = 63)**	**HRDpos* (n = 189)**	**HRDneg/unknown (n = 230)**
mDOR, (95% CI)	9.2 months, (7.4 – NE)	9.2 months, (6.6 – 15.2)	10.1 months, (6.3 – NE)
mOS, (95% CI)	26.0 months, (18.1 – NE)	19.0 months, (14.5 – 24.6)	15.5 months, (11.6 – 19.0)

*Includes patients with BRCA-mutated and non-*BRCA*-mutated tumors. mDOR = median duration of response; mOS = median overall survival; NE = not estimable

The majority of women enrolled in QUADRA were platinum-resistant or -refractory (68%). As seen in Table 3, these difficult-to-treat women achieved a CB at 24 weeks of > 10%, regardless of biomarker status.

Table 3. Proportion of Patients with a Confirmed Overall Response and CB24 by Molecular Biomarker and Platinum Status[1]

	*BRCA*mut (n = 63)		HRDpos* (n = 189)		HRDneg/unknown (n = 230)	
	ORR, %, n/N	CB24, %, n/N	ORR, %, n/N	CB24, %, n/N	ORR, %, n/N	CB24, %, n/N
Platinum-sensitive	39% (7/18)	56% (10/18)	26% (14/53)	40% (21/53)	4% (2/52)	19% (10/52)
Platinum-resistant or -refractory	27% (10/37)	32% (12/37)	10% (12/120)	20% (24/120)	3% (5/169)	11% (18/169)
Platinum status unknown	13% (1/8)	25% (2/8)	19% (3/16)	31% (5/16)	11% (1/9)	56% (5/9)
All	29% (18/63)	38% (24/63)	15% (29/189)	26% (50/189)	3% (8/230)	14% (33/230)

*Includes patients with *BRCA*-mutated and non-*BRCA*-mutated tumors. ORR = objective response rate; CB24 = clinical benefit (CR+PR+SD) at 24 weeks

At a starting dose of 300 mg of niraparib, the most commonly observed treatment-emergent adverse events (TEAEs) were consistent with prior clinical experience and no new safety signals were reported. The percentage of patients in the safety population (n = 463) who experienced a TEAE resulting in dose interruption, reduction, or withdrawal was 62%, 47%, and 21%, respectively. The most common grades ≥ 3 TEAEs observed were thrombocytopenia (28%), anemia (24%), and neutropenia (6%). The most common serious TEAEs were small intestinal obstruction (7%), thrombocytopenia (7%), and vomiting (6%). One death due to gastric hemorrhage was considered treatment related.[1,5]

QUADRA is the largest clinical trial of women with ovarian cancer undergoing later-line treatment, a population where there currently is no standard of care. The findings from QUADRA are consistent with prior niraparib studies (PN001[7], NOVA[8], and AVANOVA[9]) showing clinical activity across clinical and molecular biomarker subgroups. QUADRA demonstrated that patients outside of the primary efficacy population derived benefit from niraparib treatment as defined by ORR and CB24. Clinical benefit correlated with a mOS that exceeds expectations for this later-line, heavily-pretreated population based on historical controls.

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,

Karen Ann Cherkis, PhD

US Medical Affairs Lead- Niraparib

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

1. Moore KN, Alvarez Secord A, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicenter, open-label, single-arm phase 2 trial. *Lancet Oncol*. April 1, 2019. DOI: https://doi.org/10.1016/S1470-2045(19)30029-4.
2. Hanker LC, Loibl S, Burchardi N, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. *Ann Oncol* 2012. Aug 21, 2012. DOI: https://doi.org/10.1093/annonc/mds203.
3. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, et al. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. *Cancer Discov*. October 13, 2015. DOI: https://doi.org/10.1158/2159-8290.CD-15-0714
4. Moore KN, Alvarez Secord A, Geller M, et al. QUADRA: A phase 2, open-label, single-arm study to evaluate niraparib in patients with relapsed ovarian cancer in 4th line or later line of therapy; results from the *BRCA*mut subset. Presented at the European Society of Medical Oncology Meeting. October 19-23, 2018; Munich, Germany. Poster 944P.
5. Matulonis UA, Monk BJ, Alvarez Secord A, et al. Baseline platelet count and body weight as predictors of early dose modification in the QUADRA trial of niraparib monotherapy for the treatment of heavily pretreated (≥4th line), advanced, recurrent high-grade serous ovarian cancer. Presented at the Society of Gynecologic Oncology Annual Meeting. March 16-19, 2019; Honolulu, HI. Scientific Plenary 2.
6. TESARO. Data on File.
7. Sandhu SK, Schelman WR, Wilding G, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. Lancet Oncol 2013; 14:882-92. DOI: http://dx.doi.org/10.1016/S1470-2045(13)70240-7
8. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016;375(22):2154-2164. DOI: http://doi.org/10.1056/NEJMoa1611310
9. Mirza MR, Åvall Lundqvist E, Birrer MJ, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. *Lancet Oncol*. 2019 Aug 29. pii: S1470-2045(19)30515-7. DOI: http://doi.org/10.1016/S1470-2045(19)30515-7. [Epub ahead of print]