

Submitted by: Donna Zarzuela, PharmD, BCPS
Company/Organization: AstraZeneca/Medical Affairs
Address: One MedImmune Way, Gaithersburg, MD 20878
Phone: 1-877-212-6597
E-mail: MedinfoUS@astrazeneca.com
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NCCN Guidelines Panel: Ovarian Cancer

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for “Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer” to review the enclosed data for inclusion of LYNPARZA® (olaparib) as an option for use in platinum-sensitive, relapsed (PSR) ovarian cancer patients in the maintenance setting. This request is based on the recent Food and Drug Administration (FDA) approval of olaparib for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. This new indication is based on data from the SOLO-2 trial which was recently published in *Lancet Oncology*, as well as data from Study 19.¹⁻⁴

Specific Changes:

We respectfully request the following changes:

- Removal of the sentence on page MS-20 of the guidelines stating “However, the NCCN Panel decided not to recommend olaparib as maintenance therapy for patients with platinum-sensitive disease, because panel members feel that current data are not sufficient for recommending olaparib in this setting.”
- Inclusion of olaparib as a treatment option in the guidelines for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.

FDA Status:

Olaparib was recently approved by the FDA for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.

Rationale:

SOLO-2 is a Phase III, randomized, double-blind, placebo-controlled, multicenter trial which evaluated olaparib maintenance monotherapy in 295 patients with PSR *BRCAm* high-grade serous ovarian or high-grade endometrioid cancer who were in complete or partial response following ≥ 2 prior lines of platinum-based chemotherapy.¹ Patients were randomized to olaparib tablets 300 mg BID or matching placebo. There was a statistically significant improvement in investigator-assessed progression-free survival (PFS) with olaparib compared to placebo (19.1 months vs 5.5 months; HR 0.30 [95% CI: 0.22-0.41]; $p < 0.0001$). Overall survival (OS) data are currently immature. The most common Grade 1-2 adverse events (AEs) were nausea, fatigue/asthenia, vomiting, abdominal pain, diarrhea, and anemia. The most common Grade ≥ 3 AEs were anemia, fatigue/asthenia, and neutropenia.

Study 19 is a Phase II, randomized, double-blind, placebo-controlled trial which evaluated maintenance treatment with olaparib 400 mg (8 x 50 mg capsules) BID in 265 patients with PSR high-grade serous ovarian cancer who responded to their most recent platinum-based chemotherapy.² In the overall patient population, median PFS (investigator-assessed) was 8.4 months with olaparib and 4.8 months with placebo (HR 0.35 [95% CI: 0.25-0.49]; $p < 0.001$). In *BRCAm* patients, median PFS was 11.2 months with olaparib and 4.3 months with placebo (HR 0.18 [95% CI: 0.10-0.31]; $p < 0.0001$). OS did not significantly differ between the olaparib and placebo groups (29.8 versus 27.8 months; HR

0.73 [95% CI: 0.55–0.95]; nominal $p=0.021$).³ At the final data cut-off on May 9, 2016 (79% data maturity), 15 patients (11.0%) in the olaparib arm continued to have a durable response to olaparib maintenance monotherapy for ≥ 6 years (median follow-up of 6.5 years).⁴ Of these 15 patients, 9 were *BRCAm* (3 were *sBRCAm*) and 6 were *BRCaWt* (1 had a RAD51Bm). Adverse events with an incidence at least 10% higher in the olaparib group than in the placebo group were nausea, fatigue, vomiting, and anemia.² Grade ≥ 3 events, which were reported in 35.3% of patients, included nausea, fatigue, vomiting, diarrhea, abdominal pain, anemia, asthenia, and back pain.

Background on the Olaparib Tablet Formulation: The capsule formulation of olaparib was approved for use by the FDA in December 2014, and the recommended monotherapy dose was 400 mg (eight 50 mg capsules) twice daily, for a total daily dose of 800 mg.⁶

On August 17, 2017, the FDA approved the tablet formulation of olaparib.⁵ The tablet formulation has improved bioavailability. The recommended dose of olaparib tablets is 300 mg (two 150 mg tablets) taken orally twice daily for a total daily dose of 600 mg. This dose was selected based on results from a pharmacokinetic study which showed that olaparib tablets dosed as 300 mg (two 150 mg tablets) twice daily had similar safety and efficacy as olaparib capsules dosed as 400 mg (eight 50 mg capsules) twice daily.⁷ DO NOT substitute olaparib tablets (100 mg and 150 mg) with olaparib capsules (50 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation.⁵

In order to reduce the risk of dosing errors due to two different olaparib formulations (capsules and tablets) on the market, AstraZeneca with support from the FDA, has implemented measures to shorten the duration of the co-existence of the two formulations on the market. Specifically, the olaparib tablet formulation is now available to institutions and oncology practices through the current LYNPARZA Specialty Pharmacy Distribution Network. All patients new to olaparib treatment should receive the tablet formulation. Patients already receiving olaparib capsules who wish to remain on this formulation will need to have their medication dispensed from one of the two designated Specialty Pharmacies (Accredo and Biologics).

Reference(s): The following references are submitted in support of this proposal. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial [published online ahead of print July 25, 2017]. *Lancet Oncol*. 2017. [http://dx.doi.org/10.1016/S1470-2045\(17\)30469-2](http://dx.doi.org/10.1016/S1470-2045(17)30469-2). Accessed July 25, 2017.
2. Ledermann JA, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366:1382-1392.
3. Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomized, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol*. 2016;17:1579-1589.
4. Gourley C, Friedlander M, Matulonis U, et al. Clinically significant long-term maintenance treatment with olaparib in patients with platinum-sensitive relapsed serous ovarian cancer [abstract and poster]. *J Clin Oncol*. 2017;35(suppl; abstr 5533). Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL.
5. LYNPARZA Tablets Prescribing Information.
6. LYNPARZA Capsules Prescribing Information.
7. Mateo J, Moreno V, Gupta A, et al. An adaptive study to determine the optimal dose of the tablet formulation of the PARP inhibitor olaparib. *Targ Oncol*. 2016;11(3):401-415.

Sincerely,

Josefa Briceno

Josefa Briceno, MD
Medical Director, Women's Cancer
US Medical Affairs
AstraZeneca Pharmaceuticals
1-301-398-6654
josefa.briceno@astrazeneca.com