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Date of Request: October 22, 2018
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 to consider updating the guidelines based on the enclosed SOLO-1 data for LYNPARZA® (olaparib) that was presented at the European Society for Medical Oncology (ESMO) meeting in Munich, Germany, October 21, 2018, as well as published online in the *New England Journal of Medicine* on October 21, 2018.

Specific Changes:

We respectfully request your consideration of the following changes:

- Page OV-4, include olaparib in the Maintenance Therapy category following Complete clinical remission, Partial remission or progression (olaparib, if partial remission), and Partial or complete remission; three insertions in total
- Page OV-6, include olaparib for DISEASE STATUS “stable or persistent disease on primary chemotherapy” and “Stage II-IV with partial response”
- Page OV-B, 9 of 10, expand the Recommended Use category for olaparib to include “Maintenance therapy after first line platinum-based chemotherapy for those in a complete or partial response,” prior to your current guidelines which state, “Single-agent maintenance therapy if platinum-sensitive disease with partial or complete response following two or more lines of platinum-based therapy”
- Page MS-10, or placed within the debulking/surgery section, add “consider sending tissue for genetic evaluation”
- Page MS-16, after the Anti-Angiogenesis Agents section, consider adding PARP Inhibitor section, “Phase III randomized trial (SOLO-1) assessed olaparib maintenance therapy for women in a complete or partial response following front-line platinum-based chemotherapy...”
- Page OV-1, consider inserting “Tissue testing” under Primary Treatment category following Clinical Stages IB (fertility desired) and IA-IV, surgical candidate (fertility not desired) and Bulky stage III-IV or poor surgical candidate
 - Note: The current guidelines do not specify time for testing, e.g. at diagnosis
- Page OV-1, consider moving “All patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer should be referred for genetic risk evaluation^{c,d}” and place in between Workup and Clinical Stage, so that HCPs consider testing earlier
- Page OV-3, consider adding a third bullet for “Tissue testing” under Primary Chemotherapy/Primary Adjuvant Therapy following Stage II, Stage III, Stage IV under - Completion Surgery
- Page OV-3, consider adding olaparib as an additional bullet under Primary Chemotherapy/Primary Adjuvant Therapy following Stage II, Stage III, Stage IV

FDA Status: The use of olaparib for the maintenance treatment of women with newly diagnosed *BRCA1* and/or *BRCA2* mutated advanced ovarian cancer who are in complete or partial response to first-line platinum-based chemotherapy is not currently FDA-approved.

Rationale:

This request is based on the results of the SOLO-1 trial (Moore K et al). SOLO-1 is a phase III, randomized, double-blind, placebo-controlled, multicenter international trial evaluating olaparib maintenance monotherapy in newly diagnosed patients with *BRCA1* and/or *BRCA2* mutated advanced ovarian cancer who had received platinum-based chemotherapy and were in complete or partial response.

Following completion of platinum-based chemotherapy, patients were randomized to olaparib tablets 300 mg twice daily or placebo. Patients were stratified according to the response to platinum-based chemotherapy (complete or partial response). The primary endpoint was investigator-assessed progression-free survival (PFS) defined as the time from randomization until objective radiological disease progression (modified Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 criteria), provided patients were experiencing benefit and did not meet other discontinuation criteria. Patients with no evidence of disease at 2 years stopped treatment, although patients with partial response at 2 years were permitted to continue blinded study treatment.

In total, 391 patients were randomized 2:1; all 260 patients assigned to the olaparib group and 130 of the 131 patients assigned to the placebo group received the assigned treatment (one patient did not receive placebo due to decision to withdraw before receiving any study treatment). Central germline testing confirmed that 388 of 391 patients had a *BRCA1* and/or *BRCA2* mutation, 1 had a *BRCA* variant of uncertain significance, and two patients were *BRCA* wild-type; testing confirmed that the two patients with wild-type germline *BRCA* had somatic *BRCA* mutations.

Efficacy Results:

- After a median follow-up of 41 months, a statistically significant 70% reduction in the risk of disease progression or death was seen for olaparib versus placebo (PFS at 3 years: 60% vs 27%; hazard ratio [HR], 0.30; 95% CI, 0.23-0.41; $p < 0.001$); median PFS for women treated with olaparib was not reached compared to 13.8 months for women treated with placebo
- Assessment by blinded independent central review (BICR) showed PFS at 3 years was 69% in the olaparib group and 35% in the placebo group (HR, 0.28; 95% CI, 0.20-0.39; $P < 0.001$; 38% maturity)
- Time from study randomization to second progression or death (PFS 2; 31% maturity) at 3 years was 75% in the olaparib group versus 60% in the placebo group (HR, 0.50; 95% CI, 0.35-0.72; $P < 0.001$); median PFS 2 for women treated with olaparib was not reached compared to 41.9 months for women treated with placebo
- Interim overall survival (OS; 21% maturity) at 3 years was 84% in the olaparib group and 80% in the placebo group (HR, 0.95; 95% CI, 0.60-1.53). Median OS has not been reached in either arm.
- Median time to first subsequent therapy or death (TFST) was 51.8 months in the olaparib group and 15.1 months in the placebo group (HR, 0.30, 95% CI, 0.22-0.40)

Safety Results:

- The most common ($\geq 15\%$ of patients who received olaparib) adverse events (all grades) included nausea (77%), fatigue/asthenia (63%), vomiting (40%), anemia (39%), diarrhea (34%), constipation (28%), dysgeusia (26%), abdominal pain (25%) and arthralgia (25%)
- Grade ≥ 3 adverse events ($\geq 2\%$ of patients who received olaparib) included anemia (22%), neutropenia (9%), fatigue/asthenia (4%), diarrhea (3%) and abdominal pain (2%)
- The dose interruption, dose reduction and discontinuation rates for olaparib were 52%, 28% and 12%, and for placebo were 17%, 3%, and 2%, respectively
- Myelodysplastic syndrome or acute myeloid leukemia: occurred in 3 of 260 patients (1%) in the olaparib group and 0 of 130 patients in the placebo group
- Pneumonitis/interstitial lung disease: occurred in 5 of 260 patients (2%) in the olaparib group and no patients in the placebo group.

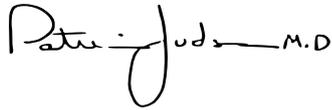
Health Related Quality of Life:

Mean Trial Outcome Index (TOI) score at baseline was 73.6 in the olaparib group and 75.0 in the placebo group. The adjusted mean change from baseline to 2 years in the olaparib group (237 patients), was 0.30 points (95% CI, -0.72 to 1.32), compared with 3.30 points (95% CI, 1.84 to 4.76) in the placebo group (125 patients) The estimated between group difference in change was -3.00 points (95% CI, -4.78 to -1.22); the difference was not considered to be clinically meaningful.

References submitted in support of this proposal:

1. LYNPARZA Prescribing Information.
2. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer [published online October 21, 2018]. *N Engl J Med*. doi: 10.1056/NEJMoa1810858.

Sincerely,

A handwritten signature in black ink that reads "Patricia Judson M.D." The signature is written in a cursive style with a horizontal line extending from the end of the name.

Patricia L. Judson, MD
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