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Date of Request:	September 13, 2016
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 a monotherapy option for the maintenance treatment of patients with *BRCA*-mutated (*BRCA*m), platinum-sensitive, relapsed ovarian cancer. This request is primarily based on an updated overall survival (OS) analysis of olaparib in this patient population.

These materials include information that is not found in the currently approved Food and Drug Administration (FDA) prescribing information for olaparib.

FDA Status: Olaparib was approved by the FDA in December 2014 as monotherapy in patients with deleterious or suspected deleterious germline *BRCA*m (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

European Medicines Agency (EMA) Status: Olaparib was approved by the EMA in October 2014 as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Specific Changes: We recommend inclusion of olaparib as an acceptable targeted single-agent maintenance therapy after at least two prior courses of platinum-based chemotherapy in platinum-sensitive, germline and somatic *BRCA*m patients.

Rationale: This request is based on an updated OS analysis (at 77% OS data maturity) of a Phase 2, randomized, double-blind, placebo-controlled trial (Study 19) that evaluated olaparib versus placebo following response after platinum-based chemotherapy in patients with relapsed high-grade serous ovarian cancer. After a median follow-up of 5.9 years, the median OS was 34.9 months with olaparib versus 30.2 months with placebo in *BRCA*m patients (nominal *P*=0.025).[1] PFS data and OS data for the small subgroup of patients with somatic *BRCA*m (n=20) were consistent with those from other subgroups.[1,2] This observation is aligned with Study 19 translational analysis data that demonstrate similarities between tumors with somatic or germline *BRCA*m, both biologically and in sensitivity to olaparib.

Additionally, 15% of patients with *BRCA*m, continued on olaparib therapy for ≥5 years, compared with 2% of patients continuing on study drug in the placebo arm.[1] There were no new safety signals observed.[1]

Previously reported results from this study are also included within this submission.[3,4]

The following articles and poster 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. 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 phase II, randomised, double-blind, placebo-controlled trial [published online ahead of print September 8, 2016]. *Lancet Oncol*. 2016. http://dx.doi.org/10.1016/S1470-2045(16)30376-X.. Accessed September 8, 2016.
2. Dougherty B, Lai Z, Ledermann JA, et al. Exploratory analyses suggest ovarian tumors with somatic or germline loss-of-function mutations in *BRCA*1 or *BRCA*2 are biologically similar and sensitive to PARP inhibition. Presented at: AACR Annual Meeting; April 18-22, 2015; Philadelphia, PA. Poster 611.
3. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med.* 2012;366(15):1382–1392.
4. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer: a preplanned retrospective analysis of outcomes by *BRCA* status in a randomised phase 2 trial. *Lancet Oncol*. 2014;15:852–861.

Sincerely,

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