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NCCN Guidelines Panel: Breast Cancer

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Breast Cancer to consider updating the guidelines based on the enclosed OlympiAD data for LYNPARZA® (olaparib) which was presented at the American Society of Clinical Oncology (ASCO) meeting in Chicago, IL as well as published online in the New England Journal of Medicine on June 4, 2017.

Specific Changes:
We respectfully request the following changes:

- Place Olaparib in a *PARP inhibitor* category on page BINV-O 1 and remove it from the *Microtubule Inhibitor* category

FDA Status: The use of olaparib for the treatment of metastatic breast cancer is not currently FDA-approved.

Rationale:
LYNPARZA is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular functions, such as DNA transcription and DNA repair. Olaparib has been shown to inhibit growth of select tumor cell lines *in vitro* and decrease tumor growth in mouse xenograft models of human cancer, both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with olaparib were noted in cell lines and mouse tumor models with deficiencies in BRCA and non-BRCA proteins involved in the homologous recombination repair (HRR) of DNA damage and correlated with platinum response. *In vitro* studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and cancer cell death.[1]

OlympiAD was a Phase III, randomized, open-label study that evaluated olaparib monotherapy versus standard of care in patients with germline *BRCA* mutations and human epidermal growth factor receptor-2 (HER2)-negative metastatic breast cancer, who had received ≤2 lines of chemotherapy in the metastatic setting.[2] Patients were randomized 2:1 to olaparib tablets (300 mg twice daily) or single-agent chemotherapy treatment of physician's choice (TPC; 21-day cycles of either capecitabine, eribulin or vinorelbine). Of 302 randomized patients, 205 were allocated to olaparib and 97 to TPC. Six patients randomized to TPC refused treatment due to treatment allocation. Progression-free survival (PFS) by blinded independent central review (BICR) was significantly longer with olaparib versus TPC (hazard ratio 0.58; 95% CI 0.43 to 0.80; P<0.001; 7.0 vs. 4.2 months, respectively). Investigator-assessed time to second progression or death (PFS2) was also extended in the olaparib arm (hazard ratio 0.57; 95% CI 0.40 to 0.83; P=0.003; 13.2 vs 9.3 months, respectively). Objective response was reported in 59.9% of olaparib patients and 28.8% of TPC patients. Complete response was reported in 9.0% of olaparib patients and 1.5% of TPC patients. Overall survival (OS) data are currently immature. The most common AEs (all grades) reported with olaparib included nausea, anemia, vomiting, fatigue, neutropenia, diarrhea, and headache. Grade ≥3 adverse events occurred in 36.6% and 50.5% of olaparib and TPC patients, respectively. The treatment discontinuation rate due to AEs was 4.9% in the olaparib arm and 7.7% in the TPC arm.

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.

Reference(s):

1. LYNPARZA Prescribing Information.
2. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377:523-533.

Sincerely,

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