The Medical Letter®

on Drugs and Therapeutics

Volume 65 Published online April 17, 2023

Online Article

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IN BRIEF

Olaparib *(Lynparza)* for High-Risk Early Breast Cancer

The oral poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (*Lynparza* – AstraZeneca) has been approved by the FDA for adjuvant treatment of adults with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), human epidermal growth factor receptor 2 (HER2)-negative, high-risk early breast cancer who received prior neoadjuvant or adjuvant chemotherapy. The drug was previously approved for treatment of adults with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who received chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.

OTHER INDICATIONS — Olaparib is also approved for treatment of certain types of epithelial ovarian, fallopian tube, or primary peritoneal, pancreatic, and prostate cancers.[1,2] It was previously approved for treatment of adults with deleterious or suspected deleterious gBRCAm ovarian cancer who had received ≥3 prior lines of chemotherapy, but the manufacturer withdrew the indication in 2022 after a subgroup analysis of the SOLO3 trial found an increase in mortality with olaparib compared to investigator-selected chemotherapy (65.2% vs 52.3%).[3]

MECHANISM OF ACTION — PARPs are involved in many cellular functions, including DNA transcription and repair of single-strand breaks. PARP inhibition leads to double-strand DNA breaks that activate homologous recombination (HR) repair, but when HR is defective, as it is in patients with BRCA mutations, an error-prone repair mechanism is activated that is unable to accurately repair these breaks, leading to DNA damage, apoptosis, and cell death (synthetic lethality). PARP inhibitors are cytotoxic for cancer cells, especially those with a germline or somatic BRCA1/2 mutation or a mutation in another HR gene.

CLINICAL STUDIES — FDA approval of olaparib for the new indication was based on the results of a double-blind trial (OlympiA) in 1836 patients with gBRCAm, HER2-negative, high-risk early breast cancer who previously received local treatment and neoadjuvant or adjuvant chemotherapy. Patients were randomized to receive olaparib 300 mg or placebo twice daily for one year. Patients had to have at least 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or both. Those with hormone receptor positive breast cancer were allowed to continue endocrine therapy. Invasive disease-free survival (IDFS), defined as time to first invasive breast cancer recurrence (locoregional or distant), a second primary cancer, or death from any cause, at 3 years was statistically significantly improved with olaparib compared to placebo (85.9% vs 77.1%). There were 59 deaths in the olaparib group and 86 deaths in the placebo group.[4] Four-year overall survival was 89.8% with olaparib and 86.4% with placebo and four-year IDFS was 82.7% for olaparib and 75.4% with placebo.[5]

ADVERSE EFFECTS — The most common adverse effects (frequency ≥10%) in OlympiA were nausea, fatigue, anemia, vomiting, headache, diarrhea, leukopenia, neutropenia, decreased appetite, dysgeusia, dizziness, and stomatitis.

DRUG INTERACTIONS — Olaparib is metabolized primarily by CYP3A4/5; concomitant use of strong or moderate CYP3A inhibitors or inducers should be avoided.[6]

DOSAGE, ADMINISTRATION, AND COST — *Lynparza* is supplied in 100- and 150-mg tablets. The recommended dosage for all indications is 300 mg

taken twice daily for up to one year. The dosage should be reduced to 200 mg twice daily in patients with moderate renal impairment. A 30-day supply of *Lynparza* costs $15,886.[7] ■

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7. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. April 5, 2023. Reprinted with permission by First Databank, Inc. All rights reserved. ©2023. www.fdbhealth.com/policies/drug-pricing-policy.