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IN BRIEF

A New Prostate Cancer Indication for Olaparib *(Lynparza)*

The oral poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (*Lynparza* – AstraZeneca) has now been approved by the FDA for use in combination with abiraterone (*Zytiga*, and others) and either prednisone or prednisolone for treatment of adults with deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer (mCRPC). Olaparib was previously approved by the FDA for treatment of adults with deleterious or suspected deleterious germline or somatic homologous recombinant repair (HRR) gene-mutated mCRPC who progressed on prior treatment with enzalutamide *(Xtandi)* or abiraterone.

OTHER SOLID TUMOR INDICATIONS — Olaparib was recently 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.[1] It had previously been 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.

Olaparib is also approved for certain types of **epithelial ovarian, fallopian tube, or primary peritoneal and pancreatic cancers**.[2,3] It was previously approved for treatment of adults with deleterious or suspected deleterious gBRCAm ovarian cancer who 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%).[4]

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 the new indication was based on the results of a double-blind trial (PROpel) in 796 patients with mCRPC who were randomized to receive first-line treatment with olaparib 300 mg or placebo twice daily in addition to abiraterone and either prednisone or prednisolone. All patients had a prior orchiectomy or were receiving gonadotropin-releasing hormone (GnRH) analogs. Image-based progression-free survival, the primary endpoint, was statistically significantly longer in the olaparib arm than in the placebo arm (24.8 vs 16.6 months).[5]

ADVERSE EFFECTS – The most common adverse effects of olaparib in the PROpel trial were anemia, fatigue/asthenia, and nausea. Diarrhea, decreased appetite, lymphopenia, dizziness, and abdominal pain were also reported.

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 as 100- and 150-mg tablets. The recommended dosage for all indications is 300 mg twice daily. The dosage of olaparib should be reduced

to 200 mg twice daily in patients with moderate renal impairment. Patients should also receive a GnRH analog concurrently or have had a prior bilateral orchiectomy. The wholesale aquisition cost of a 30-day supply of *Lynparza* is $15,886.[7] ■

1. In brief: Olaparib (Lynparza) for high-risk early breast cancer. Med Lett Drugs Ther 2023; 65:e77.
2. PARP inhibitors for ovarian cancer. Med Lett Drugs Ther 2017; 59:200.
3. Olaparib (Lynparza) for advanced ovarian cancer. Med Lett Drugs Ther 2016; 58:e32.
4. RT Penson et al. Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial. J Clin Oncol 2020; 28:1164.
5. NW Clarke et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. NEJM Evid 2022; 1:(9).
6. Inhibitors and inducers of CYP enzymes, P-glycoprotein, and other transporters. Med Lett Drugs Ther 2023 January 25 (epub). Available at: medicalletter.org/downloads/CYP_PGP_Tables.pdf.
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. June 5, 2023. Reprinted with permission by First Databank, Inc. All rights reserved. ©2023. www.fdbhealth.com/policies/drug-pricing-policy.