Written By: Katie Carter, PharmD, BCPS
Indiana University Health

Positive Quality Intervention: Olaparib (Lynparza®) Clinical Management

Description: This PQI will highlight its place in therapy in these disease states, safety profiles, and clinical pearls regarding dose adjustment.

Background: Olaparib is a poly ADP-ribose polymerase (PARP) enzyme inhibitor and is FDA approved for[1]

- First-line maintenance BRCAm advanced ovarian cancer
- First-line maintenance HRD-Positive advanced ovarian cancer in combination with bevacizumab
- Maintenance BRCA-mutated recurrent ovarian cancer
- Adjuvant treatment of gBRCAm, HER2 negative, high-risk early breast cancer
- gBRCA, HER2 negative metastatic breast cancer
- First-line maintenance gBRCAm metastatic pancreatic cancer
- HRR gene-mutated metastatic castration-resistant prostate cancer
- BRCAm metastatic castration-resistant prostate cancer in combination with abiraterone and prednisone or prednisolone

A summary of the clinical trials that led to the approval of the above indications can be found in the Supplemental Information.

PQI Process:

- Verify correct dose
  - Typical starting dose for all FDA-approved indications: 300 mg orally twice daily
    - Available as 100 mg and 150 mg tablets
  - The dose of olaparib must be adjusted to 200 mg twice daily for renal dysfunction when creatinine clearance is $\leq$ 50 mL/minute; olaparib has not been studied in patients with creatinine clearance $\leq$ 30 mL/minute
- Dose adjustments for adverse reactions
  - Consider holding treatment or dose reductions if patients experience adverse reactions

Dose reduction	Recommended Dose	How to Supply
1st dose reduction	250 mg BID	One 150 mg tablet + one 100 mg tablet BID
2nd dose reduction	200 mg BID	Two 100 mg tablets BID

- Drug interactions
  - Avoid concomitant use with moderate and/or strong CYP3A4 inhibitors
    - If a strong CYP3A4 inhibitor must be used concomitantly, the olaparib dose should be reduced to 100 mg twice daily
    - If a moderate CYP3A4 inhibitor must be used concomitantly, the olaparib dose should be reduced to 150 mg twice daily
  - Avoid concomitant strong CYP3A inducers; if a moderate CYP3A inducer must be used, there is the potential for reduced efficacy of olaparib
- Laboratory monitoring
  - Complete blood counts should be performed at baseline and monthly thereafter
  - Renal function should be verified at baseline and periodically thereafter
  - Taking other anticancer agents may cause a potentiation/prolongation of myelosuppression

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) sheet

- Counsel patient on side effect profile (see supplemental information and Olaparib (Lynparza®) Adverse Event Management PQI)
- Instruct patient to avoid grapefruit, grapefruit juice, Seville oranges, and/or Seville orange juice
- Advise effective contraception during treatment and for 3 months (males) or 6 months (females of reproductive potential) after the last dose
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Lynparza® (olaparib) [package insert].
2. Paik J. Olaparib: A Review as First-Line Maintenance Therapy in Advanced Ovarian Cancer. Targeted Oncology. 2021;16(6):847-856. doi:https://doi.org/10.1007/s11523-021-00842-1.
3. Grimm C, et. al. Maintenance olaparib plus bevacizumab (bev) after platinum based chemotherapy plus bev in patients (pts) with newly diagnosed advanced high-grade ovarian cancer (HGOC): Efficacy by timing of surgery and residual tumor status in the Phase III PAOLA-1 trial. Gynecologic Oncology. 2020;159:19-19.
4. Poveda A, et al. Olaparib Tablets as Maintenance Therapy in Patients With Platinum-Sensitive Relapsed Ovarian Cancer and a BRCA1/2 Mutation (SOLO2/ENGOT-Ov21): A Final Analysis of a Double-Blind, Randomised, Placebo-Controlled, Phase 3 Trial. Obstetrical & Gynecological Survey. 2021;76(9):535-536. doi:https://doi.org/10.1097/ogx.0000000000000962.
5. Lheureux S, et al. Long-Term Responders on Olaparib Maintenance in High-Grade Serous Ovarian Cancer: Clinical and Molecular Characterization. Clinical Cancer Research. 2017;23(15):4086-4094. doi:https://doi.org/10.1158/1078-0432.ccr-16-2615.
6. Kim G, et al. FDA Approval Summary: Olaparib Monotherapy in Patients with Deleterious Germline BRCA-Mutated Advanced Ovarian Cancer Treated with Three or More Lines of Chemotherapy. Clinical Cancer Research. 2015;21(19):4257-4261. doi:https://doi.org/10.1158/1078-0432.ccr-15-0887.
7. Senkus E, et al. Olaparib efficacy in patients with germline BRCA-mutated, HER2-negative metastatic breast cancer: Subgroup analyses from the phase III OlympiAD trial. International Journal of Cancer. 2023;153(4):803-814. doi:https://doi.org/10.1002/ijc.34525.
8. Golan T, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. New England Journal of Medicine. 2019;381(4):317-327. doi:https://doi.org/10.1056/nejmoa1903387.
9. Hussain M, Corcoran C, Sibilla C, et al. Tumor Genomic Testing for >4,000 Men with Metastatic Castration-resistant Prostate Cancer in the Phase III Trial PROfound (Olaparib). Clinical Cancer Research. 2022;28(8):1518-1530. doi:https://doi.org/10.1158/1078-0432.ccr-21-3940.
10. Oya M, et al. 157O Biomarker analysis and updated results from the phase III PROpel trial of abiraterone (abi) and olaparib (ola) vs abi and placebo (pbo) as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). Annals of Oncology. 2022;33:S1495. doi:https://doi.org/10.1016/j.annonc.2022.10.194.

Supplemental Information:

Current FDA-approved indications: Starting dose is 300 mg twice daily for all indications

Indication	Efficacy	Safety
Ovarian cancer		
First-line maintenance treatment for deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer for patients who are in a complete or partial response to first-line platinum-based chemotherapy (SOLO-1)[2]	mPFS results: olaparib 56 months vs placebo 13.8 months 5-Year PFS: olaparib 48% vs placebo 21%	Most common AEs with olaparib: nausea, vomiting, fatigue, anemia, diarrhea Serious AEs occurred in 21% of olaparib patients vs 12% of placebo patients, most commonly anemia
In combination with bevacizumab for maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer for patients who are in a complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either deleterious or suspected deleterious *BRCA* mutation and/or genomic instability PAOLA-1 trial[3]	Reduced the risk of disease progression or death by 67% (equal to HR of 0.33) and improved progression-free survival to a median of 37.2 months vs 17.7 months with bevacizumab alone Higher Risk: mPFS olaparib 36.0 vs. 16.0 bevacizumab Lower Risk: mPFS olaparib Not Reached vs. 22.1 bevacizumab	Adverse reactions (Grade 1-4) occurring in ≥10% of patients treated with olaparib/bevacizumab in PAOLA-1 compared with the placebo/bevacizumab arm were nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia (24%), vomiting (22%), and leukopenia (18%), diarrhea (18%), neutropenia (18%), urinary tract infection (15%), and headache (14%)
Maintenance treatment for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer for patients who are in a complete or partial response to platinum-based chemotherapy – 2 randomized trails completed SOLO-2 trial[4]	SOLO-2: PFS: olaparib 19.1 months vs placebo 5.5 months OS: olaparib 51.7 months vs placebo 38.8 months Study 19: PFS: olaparib 8.4 months vs placebo 4.8 months;	SOLO-2: Most common Grade 1/2 AEs in both groups: nausea, fatigue, vomiting, abdominal pain, and diarrhea Most common ≥ Grade 3 AE: anemia Study 19: Most common AEs of all grads in olaparib arm included nausea (71%), fatigue

Study 19[5]	OS: olaparib 29.8 months vs placebo 27.8 months	(63%), vomiting (35%), diarrhea (28%), anemia (23%), constipation (22%), respiratory tract infection (22%), decreased appetite (21%), and headache (21%)
Deleterious or suspected deleterious gBRCAm advanced ovarian cancer after ≥3 prior lines of chemotherapy[6]	Single arm trial PFS results: ORR: 34%; Median DoR: 7.9 months	Serious AEs reported in 30% of patients, most frequently anemia, abdominal pain
Breast Cancer		
Deleterious or suspected deleterious g*BRCA*m, HER2-negative metastatic breast cancer after treatment with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting OlympiAD trial[7]	PFS: olaparib 7 months vs chemotherapy 4.2 months; ORR: olaparib 52% vs chemotherapy 23%; OS: olaparib 19.3 months vs chemotherapy 17.2 months	Rate of ≥ Grade 3 AEs olaparib (36.6%) vs chemotherapy (50.5%) AEs that occurred more frequently with olaparib: anemia, nausea, vomiting, fatigue, headache, and cough
Pancreatic Cancer		
Maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen POLO trial[8]	PFS: olaparib vs. placebo: median 7.4 months vs 3.8 months ORR: 23% in olaparib vs 12% in placebo OS: olaparib 19.3 months vs placebo 17.1 months	Most common AE at grades 3-4 for olaparib: anemia (11%) All grades AE >30% for olaparib: Fatigue (60%), nausea (45%), abdominal pain (34%) All grade diarrhea occurred at a rate of 29%
Prostate Cancer		
Treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone PROfound trial[9]	Reduced risk of disease progression or death by 66% (HR 0.34) Radiographic PFS median of 7.4 months vs 3.6 months with enzalutamide or abiraterone in men with *BRCA1/2* or *ATM* gene-mutated mCRPC OS: olaparib 19.1 months vs placebo 14.7 months	PROfound: Most common AE (Grade 1-4) occurring in ≥10% in the olaparib arm were anemia (46%), nausea (41%), fatigue including asthenia (41%), decreased appetite (30%), diarrhea (21%), vomiting (18%), thrombocytopenia (12%), cough (11%) and dyspnea (10%) Venous thromboembolic events, including pulmonary embolism occurred in 7% of patients with mCRPC who received olaparib plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT
Treatment of adult patients in combination with abiraterone and prednisone (or prednisolone) for adult patients with deleterious or suspected deleterious BRCAm mCRPC PROpel trial[10]	Radiographic PFS: olaparib + abiraterone 30% vs placebo + abiraterone 74%; OS: olaparib + abiraterone 28% vs placebo + abiraterone 66%	Most common AE (≥10%) in patients receiving olaparib plus abiraterone were anemia (48%), fatigue (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), and abdominal pain (13%). Seventy-two patients (18%) required at least one blood transfusion and 46 (12%) required multiple transfusions.

PFS: progression free survival; AEs: adverse events; ORR: objective response rates; DoR: duration of response

Olaparib was previously available as both a tablet and a capsule, and the two dosage forms had different bioavailability therefore are not interchangeable on a milligram-per-milligram basis

- Capsules were discontinued August 2018; only the tablets are currently available in the United States