PARP Inhibitors in Gynecologic and Breast Malignancies: Clinical Evolution, Biomarker Selection, and Emerging Combination Strategies

Madison Ambrose[1 2], OSM-II and Guang Peng[1], M.D., Ph.D.

[1]The University of Texas MD Anderson Cancer Center, Department of Experimental Therapeutics, Division of Cancer Medicine, Houston, Texas

[2]UNT Health, Texas College of Osteopathic Medicine, Fort Worth, Texas

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

Introduction

The Breakthrough

PARP inhibitors (PARPi) exploit tumor-specific DNA repair vulnerabilities through synthetic lethality (1,2). In tumors with BRCA1/2 mutations or homologous recombination deficiency (HRD), impaired DNA repair creates a therapeutic vulnerability that can be selectively targeted by PARP inhibition.

The Clinical Evolution

This biologic principle has translated into clinically meaningful advances across ovarian, fallopian tube, primary peritoneal, and breast malignancies, with PARPi treatment expanding from heavily pretreated disease to maintenance and earlier-stage settings (3-5). Increasingly, BRCA1/2 status, HRD, and other biomarkers inform patient selection and therapeutic strategy.

The Remaining Challenge

Despite these advances, heterogeneous treatment response, acquired resistance, and limitations in biomarker selection continue to restrict the full potential of PARPi therapy. Understanding these challenges is essential for developing more effective and durable treatment strategies.

Review Objective

This review examines the clinical evolution of PARPi in gynecologic and breast malignancies, emphasizing biomarker selection, landmark clinical outcomes, mechanisms of resistance, and emerging therapeutic strategies.

Methods

A focused literature review was conducted to evaluate the clinical development and therapeutic applications of PARPi in gynecologic and breast malignancies. Landmark clinical trials evaluating olaparib, rucaparib, niraparib, talazoparib, and veliparib were reviewed, with emphasis on ovarian, fallopian tube, primary peritoneal, and breast cancers. Studies were examined for treatment setting, biomarker status, therapeutic regimen, and clinical outcomes, including progression-free survival (PFS), hazard ratio (HR), overall survival (OS), and objective response rate (ORR). Key regulatory approvals and emerging combination strategies were also evaluated to characterize the evolution of PARPi therapy and identify remaining challenges and opportunities for clinical advancement.

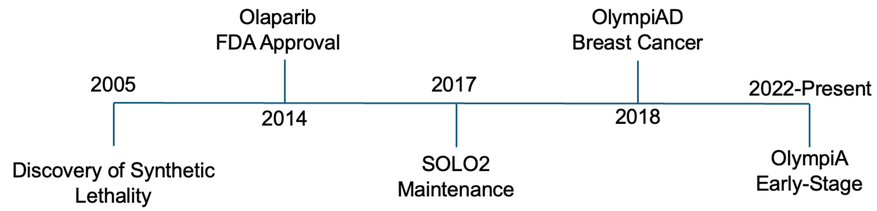
References

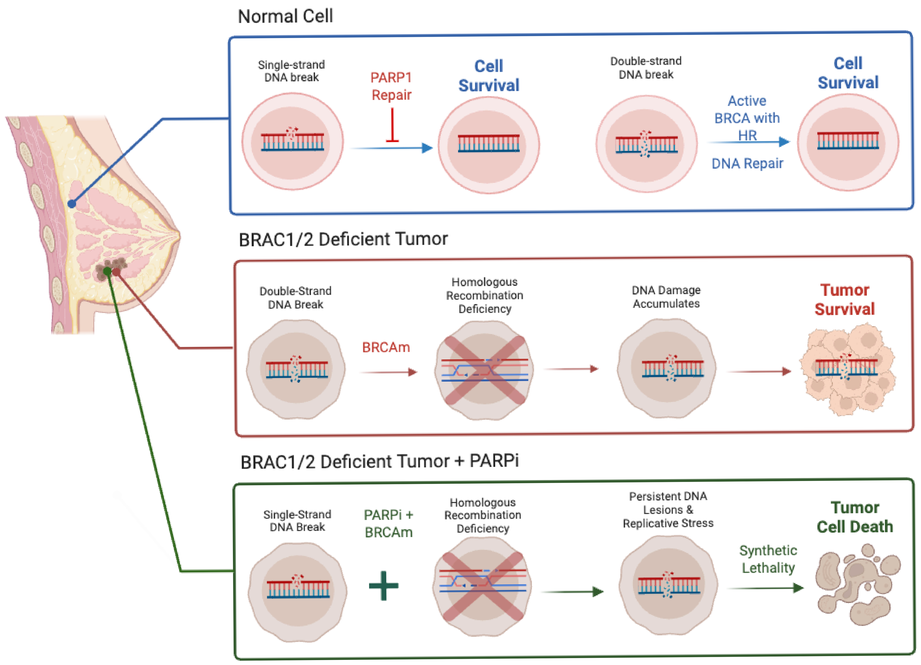
1. Herencia-Ropero A, Llop-Guevara A, Staniszewska AD, Domenech-Vivo J, Garcia-Galea E, Moles-Fernandez A, et al. The PARP1 selective inhibitor saruparib (AZD5305) elicits potent and durable antitumor activity in patient-derived BRCA1/2-associated cancer models. Genome Med. 2024;16(1):107.
2. McMullen M, Karakasis K, Madariaga A, Oza AM. Overcoming Platinum and PARP-Inhibitor Resistance in Ovarian Cancer. Cancers (Basel). 2020;12(6).
3. Liu J, Matulonis UA. Update on PARP inhibitors for the treatment of ovarian cancer. Clin Adv Hematol Oncol. 2025;23(2):100–10.
4. Banerjee S, Moore KN, Colombo N, Scambia G, Kim BG, Oaknin A, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2021;22(12):1721–31.
5. Arora S, Balasubramaniam S, Zhang H, Berman T, Narayan P, Suzman D, et al. FDA Approval Summary: Olaparib Monotherapy or in Combination with Bevacizumab for the Maintenance Treatment of Patients with Advanced Ovarian Cancer. Oncologist. 2021;26(1):e164–e72.
6. JLitton JK, Rugo HS, Ettl J, Hurvitz SA, Goncalves A, Lee KH, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018;379(8):753–63.
7. Shu Y, Liu Y, He X, Ding Y, Zhang Q. Cost-effectiveness analysis of olaparib as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation in china. Front Pharmacol. 2022;13:818579.
8. FDA Approves Niraparib for First-Line Maintenance of Advanced Ovarian Cancer: Oncology Nursing Society; 2020 [Available from: https://www.ons.org/publications-research/voice/news-views/04-2020/fda-approves-niraparib-first-line-maintenance.
9. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10106):1949–61.
10. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523–33.
11. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394–405.

Results

PARP inhibitor therapy has undergone a substantial clinical evolution, progressing from treatment of heavily pretreated BRCA-mutated disease to maintenance and earlier-line therapy across gynecologic and breast malignancies. In ovarian cancer, landmark trials established PARPi maintenance as an effective strategy following response to platinum-based chemotherapy, with subsequent studies expanding investigation into first-line treatment and broader biomarker-defined populations (5). In breast cancer, trials of olaparib and talazoparib demonstrated the clinical utility of PARP inhibition in patients with germline BRCA mutations, extending the application of synthetic lethality beyond ovarian cancer (5,6). Collectively, these studies established PARP inhibition as an important component of biomarker-directed cancer therapy while highlighting the continued need for improved patient selection and strategies to overcome therapeutic resistance.

Clinical Evolution





Created in BioRender.com

Take-Home Message

From exploiting a DNA-repair vulnerability to reshaping precision oncology, PARP inhibition continues to redefine the treatment landscape for women's cancers.

Clinical Evidence

Gynecologic Malignancies

SOLO1: Olaparib (5)
- First-line maintenance
- BRCAm ovarian cancer
- PFS: NR vs 13.8 months
- HR: 0.30

SOLO2: Olaparib (7)
- Recurrent maintenance
- BRCAm ovarian/fallopian tube/primary peritoneal cancer
- PFS: 19.1 vs 5.5 months
- HR: 0.30

PAOLA-1: Olaparib (5)
- First-line maintenance + bevacizumab
- HRD-positive
- PFS: 37.2 vs 17.7 months
- HR: 0.33

PRIMA: Niraparib (8)
- Demonstrated activity in broader populations, highlighting the evolving role of HRD-based selection beyond BRCAm alone
- PFS: 21.9 vs 10.4 months
- HR: 0.43

ARIEL3: Rucaparib (9)
- Recurrent platinum-sensitive ovarian cancer
- PFS: 16.6 vs 5.4 months in BRCAm population

Breast Cancer

OlympiAD: Olaparib (10)
- Metastatic breast cancer
- gBRCAm
- HER2-negative
- PFS: 7.0 vs 4.2 months
- HR: 0.58

OlympiA (11)
- High-risk early breast cancer
- gBRCAm
- HER2-negative
- 4-year IDFS: 82.7% vs 75.4%
- IDFS HR: 0.58

EMBRACA: Talazoparib (6)
- Metastatic
- gBRNCAm
- HER2-negtaive
- PFS: 8.6 vs 5.6 months
- HR: 0.54

Clinical Impact & Future Directions

Clinical Impact

PARP inhibitors have transformed precision treatment for BRCA-mutated and HRD-associated malignancies. In ovarian cancer, their role has expanded from recurrent disease to maintenance following platinum response and first-line therapy. In breast cancer, PARPi have demonstrated benefit in both metastatic and high-risk early disease, illustrating a broader shift toward biomarker-directed treatment and earlier therapeutic intervention.

Remaining Challenges

The next phase of PARP inhibitor development is defined by selectivity rather than simply expansion. Not all patients with HRD derive the same degree of benefit, and acquired resistance remains a major limitation. Restoration of homologous recombination, replication-fork stabilization, and other mechanisms can allow tumor cells to escape PARP-mediated cytotoxicity.

Future Directions

Future development will focus on expanding the therapeutic window of PARP inhibition while overcoming resistance and improving patient selection. Combination strategies—including PARPi with antiangiogenic therapy and immune checkpoint blockade—seek to exploit complementary vulnerabilities within the tumor microenvironment. At the same time, selective PARP1 inhibitors represent a next-generation approach designed to preserve antitumor activity while potentially reducing effects associated with broader PARP inhibition. Together, these strategies may move PARP-directed therapy beyond its current biomarker-defined boundaries.