Clinics in Oncology

Research Article
Published: 03 Jun, 2025

Maintenance Therapy with Poly (Adp-Ribose) Polymerase Inhibitors (Parpi) in Patients with Newly Diagnosed Ovarian Cancer: A Systematic Review and Meta-Analysis

Al-Alam O[1], Stecca C[2], Michelon I[3], Vilbert M[4,5], Castro C[6], Dacoregio MI[7], Da Costa AABA[8], Gaillard S[1] and Nogueira-Rodrigues A[9,10,11,12]*

[1]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore

[2]Department of Medicine, Division of Medical Oncology, Evangelical Mackenzie University Hospital, Brazil

[3]Department of Medicine, Catholic University of Pelotas, Brazil

[4]Department of Medicine, Division of Hematology/Oncology, Mass General Cancer Center, Massachusetts General Hospital, USA

[5]Harvard Medical School, Boston, USA

[6]Department of Medicine, University of Brasilia, Brazil

[7]Department of Medicine, University of Centro-oeste, Brazil

[8]Department of Medicine, Division of Medical Oncology, AC Camargo Cancer Center, Brazil

[9]Federal University of Minas Gerais (UFMG), Brazil

[10]Oncoclínicas&Co, Brazil

[11]Brazilian Group of Gynecologic Oncology (EVA)

[12]DOM Oncologia, Brazil

OPEN ACCESS

Correspondence:
Otávio Al-Alam, Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Skip Viragh Outpatient Cancer Building, 201 N. Broadway, Baltimore, 21287, USA,
E-mail: oalalam1@jh.edu

Received Date: *13 May 2025*
Accepted Date: *02 Jun 2025*
Published Date: *03 Jun 2025*

Citation:
Al-Alam O, Stecca C, Michelon I, Vilbert M, Castro C, Dacoregio MI, et al. Maintenance Therapy with Poly (Adp-Ribose) Polymerase Inhibitors (Parpi) in Patients with Newly Diagnosed Ovarian Cancer: A Systematic Review and Meta-Analysis. Clin Oncol. 2025; 10: 2123.

ISSN: 2474-1663

Abstract

Background: PARP inhibitors (PARPi) have demonstrated efficacy in maintenance therapy for newly diagnosed ovarian cancer, particularly in patients with BRCA pathogenic variants and Homologous Recombination Deficiency (HRD). However, in recent updates from the PRIMA trial, no overall survival benefit was observed across all subgroups. This systematic review and meta-analysis evaluate the efficacy and safety of PARPi based on this clinical context.

Methods: A systematic search of PubMed, Cochrane, and Embase was conducted for randomized controlled trials comparing PARPi with placebo in newly diagnosed ovarian cancer. Outcomes included Overall Survival (OS) and Progression-Free Survival (PFS), by BRCA and HRD status, Adverse Events (AEs), and rates of Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML). This meta-analysis followed PRISMA guidelines (PROSPERO: CRD42024603696) and used random-effects models across all analyses.

Results: Seven Randomized Clinical Trials (RCTs) with 4,013 patients were included. In patients with BRCA pathogenic variants, PARPi significantly improved OS [HR 0.67, 95% CI 0.48–0.93, p=0.02] and PFS [HR 0.38, 95% CI 0.32-0.44, p<0.01]. No OS benefit was observed in HRD test-positive [HR 0.77, 95% CI 0.51-1.17, p=0.22] or HRD test-negative [HR 1.05, 95% CI 0.85-1.30, p=0.66] groups. PFS was significantly improved in HRD test-positive patients [HR 0.45, 95% CI 0.38-0.55, p<0.01] and HRD test-negative patients [HR 0.73, 95% CI 0.61-0.88, p<0.01]. Grade ≥ 3 AEs were more common in the PARPi group (p<0.01), with non-significant increases in MDS or AML rates.

Conclusion: PARPi maintenance therapy improves OS in ovarian cancer patients with BRCA pathogenic variants, and PFS across all subgroups regardless of HRD test.

Keywords: Ovarian Cancer; PARP inhibitor; Maintenance

Key Messages

What is already known on this topic

PARP inhibitors (PARPi) improve progression-free survival in newly diagnosed ovarian

cancer, particularly in patients with BRCA pathogenic variants or HRD test-positive status. However, their overall survival benefit has been inconsistent, and recent data have questioned their efficacy in broader populations.

What this study adds

This meta-analysis demonstrates that PARPi significantly improve OS in patients with BRCA pathogenic variants and PFS in all subgroups. It also highlights the lack of OS benefit in HRD test-positive and HRD test-negative patients, emphasizing the need for careful patient selection and standardized HRD tests.

How this study might affect research, practice or policy

These findings support the robust activity of PARPi, especially in patients with BRCA pathogenic variants and HRD test-positive status. Yet, we highlight the heterogeneity in currently available HRD assays.

Introduction

Ovarian cancer remains one of the leading causes of cancer-related mortality among women worldwide.1 Most patients are diagnosed at advanced stages (III and IV) and have a poor prognosis [1] Standard treatment involves cytoreductive surgery followed by platinum-based chemotherapy. Despite notable initial responses, a great percentage of patients still face disease relapse within three years [2].

The introduction of targeted therapies has reshaped the treatment landscape of ovarian cancer. Bevacizumab, an antiangiogenic agent, was the first targeted therapy approved for both platinum-sensitive and resistant relapsed ovarian cancer [3,4]. Following this, poly (ADP-ribose) Polymerase Inhibitors (PARPi) emerged. Targeting PARP proteins on DNA, PARPi have exhibited great efficacy in ovarian cancer, particularly in the subgroup with BRCA pathogenic variants and Homologous Recombination Deficiency (HRD) test-positive. These agents have been shown to significantly prolong remission and improve long-term outcomes of ovarian cancer patients [5-11]. Nowadays, it is approved as maintenance therapy following first-line platinum-based chemotherapy [3].

While the phase III PRIMA trial (NCT02655016) confirmed an extended Progression-Free Survival (PFS) in favor of niraparib compared to placebo across multiple subgroups, updated results showed no Overall Survival (OS) advantage in any of the subgroups, including patients with BRCA pathogenic variants [12]. These findings contrast with evidence brought by other trials and underscore the need for a deeper understanding of the long-term impact of PARPi [12]. In light of the latest evidence, this systematic review and meta-analysis aims to evaluate the efficacy and safety of PARPi in newly diagnosed ovarian cancer across various subgroups, focusing on both OS and PFS endpoints.

Methods

Overview

This systematic review and meta-analysis followed the guidelines from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the protocol number CRD42024603696. The PRISMA checklist for the abstract and the manuscript can be found in Supplementary Table S1.

Search Strategy

A systematic search was conducted in PubMed, Cochrane, and Embase on September 27th, 2024, using the following combination of Medical Subject Headings (MeSH) terms and Boolean connectors: 'Ovarian Neoplasms' AND PARP inhibitor OR Olaparib OR rucaparib OR niraparib OR veliparib OR talazoparib OR pamiparib OR fluzoparib OR senaparib AND 'first-line therapy' OR 'primary intervention' OR maintenance AND 'randomized clinical trial'. A full description of the search strategy used on each database can be found in Supplementary Table S2. We also searched the references of all included studies and relevant reviews about this topic.

Eligibility Criteria

In this meta-analysis, inclusion criteria were restricted to phase III Randomized Clinical Trials (RCT) comparing maintenance PARPi to placebo in patients with newly diagnosed ovarian cancer (stage III and IV) who had a partial or complete response to first-line platinum-based chemotherapy. Presentations or abstracts from conference proceedings were considered for inclusion. Only English-written studies were considered for inclusion. No restrictions were made as to the sample size.

While most included studies fully met the eligibility criteria, some trials analyzed subgroups that did not fit the intervention and control groups of interest. For instance, we only considered the ATHENA-MONO arm (rucaparib as monotherapy maintenance without immunotherapy) from ATHENA study (NCT03522246). Similarly, in the VELIA study (NCT02470585), we considered only data on the subgroups of maintenance therapy with veliparib versus placebo following initial chemotherapy with carboplatin and paclitaxel.

The following exclusion criteria were applied: (A) retrospective or prospective observational studies; (B) phase I, II, or non-randomized clinical trials; (C) overlapping populations - in case of a study with multiple publications, the most updated one was preferred.

Study selection and data extraction

Two authors (O.A. and C.S.) independently validated the search strategy and screened reports by title and abstract. Subsequently, the authors performed a comprehensive review of all studies that potentially met the eligibility criteria and selected studies for inclusion. One additional author (I.M.) was consulted in case of disagreements.

Data extraction was also performed independently by two authors (O.A. and C.S.). Data were collected from individual studies on study design; study location; number of patients; median age; BRCA status; HRD test status; disease stage; and the outcomes of interest as described below.

Primary outcomes

Outcomes of interest were OS and PFS as follows: (A) OS and PFS in the group carrying BRCA pathogenic variants; (B) OS and PFS in the HRD test-positive group; (C) OS and PFS in the HRD test-negative group; (D) OS and PFS in the HRD test-positive population without BRCA pathogenic variants; (E) OS in the Intention-To-Treat (ITT) population. Some outcomes are not yet available for some trials. All-grade and grade 3 or higher Adverse Events (AEs) were collected, including the occurrence of myelodysplastic syndrome/myeloid acute leukemia.

The studies included in each analysis are as follows: (1) PAOLA-1(NCT01874353), PRIMA, and SOLO-1(NCT01844986) trials for OS in the group carrying BRCA pathogenic variants; (2) PAOLA-1,

PRIMA, SOLO-1, ATHENA, FLAMES (NCT04169997), PRIME (NCT03709316) and VELIA trials for PFS; (3) PAOLA-1 and PRIMA for OS in the HRD test-positive population; (4) ATHENA, FLAMES, PAOLA-1, PRIMA, PRIME and VELIA for PFS in HRD test-positive population; (5) PAOLA-1, PRIMA, PRIME and VELIA for OS in the HRD test-negative population; (6) PAOLA-1 and PRIMA for OS in the HRD test-positive population without BRCA pathogenic variants; (7) ATHENA, PAOLA-1 and PRIMA for PFS in the HRD test-positive population without BRCA pathogenic variants; and (8) PAOLA-1, PRIMA and PRIME for OS in the ITT population.

AEs were consistently assessed across all seven studies. We reported main AEs according to PARPi used in each study in table format (Table S3). We also explored health-related quality of life (HRQoL, Table S4).

Quality assessment

The Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess the quality of included studies. Publication bias was explored, including the higher number of patients (i.e., PFS analysis for patients with BRCA pathogenic variants) using the funnel plot of individual study weights against point estimates, along with the Egger test.

Exploring heterogeneity

The Baujat plot and a leave-one-out sensitivity analysis were used to further assess the heterogeneity seen in the analyses. The first shows the contribution of each study on the overall effect and their influence on the heterogeneity. The latter estimates the effect size and heterogeneity when leaving each study out at a time. For both, we used the PFS in patients with BRCA pathogenic variants as the outcome of reference.

Most studies included a large population of patients with stage III disease, which may present differently compared to stage IV patients. However, survival analyses according to staging in the subgroups of interest were not provided in our included studies. Since we did not have access to individual patient data, we performed a sensitivity analysis of the overall PFS including only stage III patients receiving PARPi compared to placebo (Figure S2).

Statistical analysis

Analyses were carried out using R software (version 4.2.2, R Foundation, Vienna, Austria). The packages 'meta' and 'metafor' were used. OS and PFS were pooled for analyses using Hazard Ratios (HR) with 95% Confidence Intervals (CIs). For dichotomous outcomes (i.e. AEs), Odds Ratio (OR) with 95% CI were used. In all analyses, inverse variance or Mantel Haenszel methods were used. We applied random-effects models for all analyses. Between-study variance was assessed using restricted maximum likelihood (REML) estimation. Heterogeneity was explored using Cochran's Q test and the I^2 statistic (p-values <0.10 and I^2>0.25 were considered appreciable for heterogeneity). Statistical significance was set at $p<0.05$.

Data sharing

In accordance with the journal's guidelines, data for independent analysis will be provided to a selected team from the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers, if such is requested.

Results

Systematic review

Initially, 832 reports were identified. After the deduplication process and exclusion by title and abstract, 45 studies were fully assessed. Finally, seven RCTs with ten related publications met the eligibility criteria [5-14] (Figure 1).

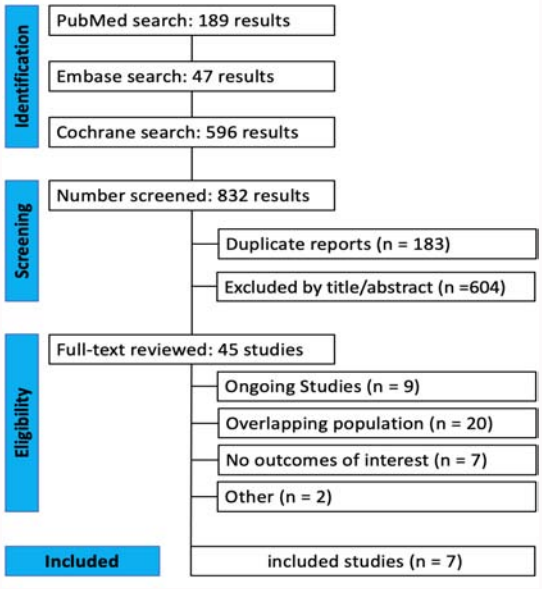

Figure 1: PRISMA flow diagram of study screening and selection. Blue vertical boxes indicate each stage of the screening, and the horizontal boxes present more detailed information about the process, including the steps performed in each stage.

Study characteristics and patient population

Overall, 4,013 patients with ovarian cancer who had not progressed after platinum-based chemotherapy were included, of whom 2,619 received PARPi, while 1,394 patients were assigned to the placebo group. Most patients had stage III (72.58%) according to FIGO staging. Study characteristics, including the follow-up duration and patient demographics, are summarized in Table S1.

Overall survival

Overall survival data were available for PRIMA, PRIME, PAOLA-1 and SOLO-1 studies. In the ITT population, OS analysis across PRIMA, PRIME and PAOLA-1 showed an HR of 0.94 (95% CI 0.82-1.07, p=0.33) (Figure 2A). For patients with HRD test-positive, as assessed in PRIMA and PAOLA-1, the HR was 0.77 (95% CI 0.51-1.17, p=0.22). Similarly, HRD test-positive excluding patients with BRCA pathogenic variants, analyzed in PRIMA and PAOLA-1, had an HR of 0.83 (95% CI 0.60-1.15, p=0.26), and those with HRD test-negative, also assessed in PRIMA and PAOLA-1, showed an HR of 1.05 (95% CI 0.85-1.30, p=0.66), not demonstrating a statistically significant benefit in these populations (Figure 2B, 2C and 2D). On the other hand, the pooled OS analysis of SOLO-1, PRIMA and PAOLA-1 studies revealed a significantly better OS for the PARPi group compared to placebo in the population with BRCA pathogenic variants (HR, 0.67, 95% CI 0.48-0.93, p=0.02) (Figure 2E).

Progression-Free survival

Progression free survival data was available for the following trials: ATHENA, FLAMES, PAOLA-1, PRIMA, PRIME, VELIA AND SOLO-1. The pooled analyses showed a significant benefit in PFS across multiple subgroups. In both HRD test-negative and HRD test-positive patients, which were assessed in ATHENA, FLAMES, PAOLA-1, PRIMA, PRIME and VELIA, significant benefits were observed in

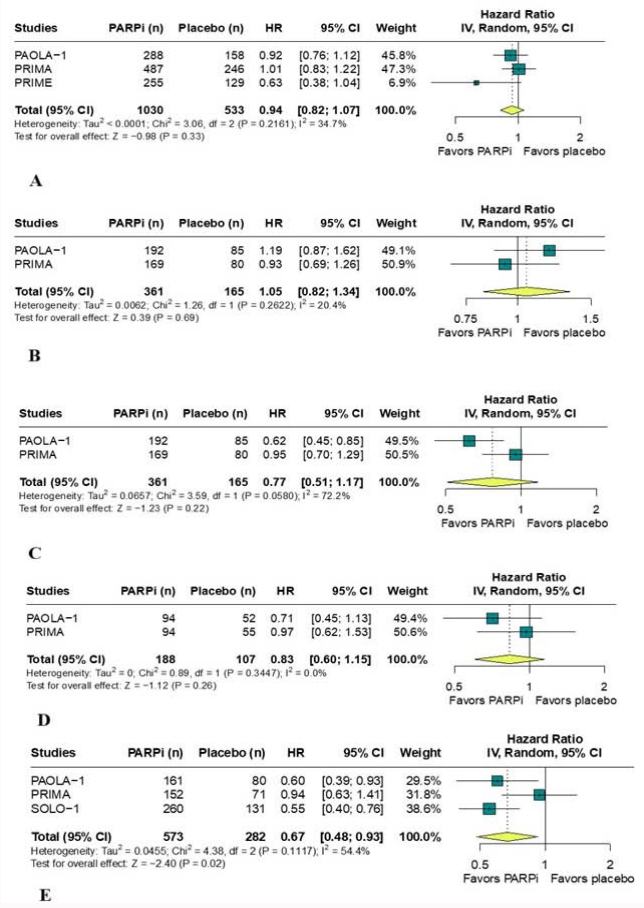

Figure 2: Overall survival in patients receiving PARPi compared to placebo across subgroups.
(A). OS in the ITT population. **(B).** OS in patients with HRD test-negative. **(C).** OS in patients with HRD test-positive. **(D).** OS in patients with HRD test-positive and without BRCA pathogenic variants. **(E).** OS in patients with BRCA pathogenic variants.
Overall effect of each trial is represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects.
CI: Confidence Interval; HR: Hazard Ratio; HRD: Homologous Recombination Proficient; HRP: Homologous Recombination Proficient; IV: Inverse Variance; ITT: Intention-to-Treat; n: Number of patients; PARPI: Poly(ADP-ribose) Polymerase Inhibitors; OS: Overall Survival.

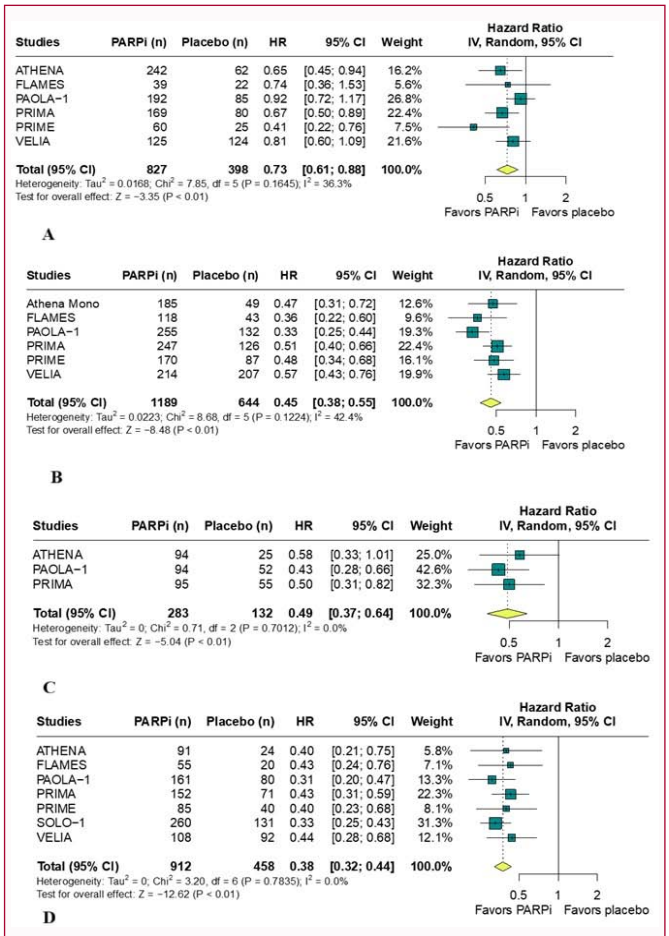

Figure 3: PFS in patients receiving PARPi compared to placebo across subgroups.
(A). PFS in patients with HRD test-negative. **(B).** PFS in patients with HRD test-positive. **(C)**. PFS in patients with HRD test-positive and without BRCA pathogenic variants. **(D).** PFS in patients with BRCA pathogenic variants.
Overall effect of each trial is represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects.
CI: Confidence Interval; HR: Hazard Ratio; HRD: Homologous Recombination Proficient; HRP: Homologous Recombination Proficient; IV: Inverse Variance; ITT: Intention-to-Treat; N: Number of Patients; PARPI: Poly(ADP-Ribose) Polymerase Inhibitors; PFS: Progression-Free Survival.

the PARPi arm. For HRD test-negative patients, a 28% reduction in the risk of disease progression or death was observed (HR 0.73, 95% CI 0.61-0.88, p<0.01) (Figure 3A), while for HRD test-positive patients, PFS was notably longer with PARPi compared to placebo (HR 0.45, 95% CI 0.38-0.55, p<0.01) (Figure 3B). Consistently, the group with HRD test-positive and lacking BRCA pathogenic variants, analyzed in ATHENA, PAOLA-1 and PRIMA, demonstrated a 51% lower risk of disease progression or death with PARPi compared to placebo (HR 0.49, 95% CI 0.37-0.64, p< 0.01) (Figure 3C). Among patients with BRCA pathogenic variants, evaluated in ATHENA, FLAMES, PAOLA-1, PRIMA, PRIME, VELIA and SOLO-1, PARPi significantly improved PFS rates compared to placebo (HR 0.38, 95% CI 0.32-0.44, p<0.01) (Figure 3D).

Adverse events and HRQoL

Adverse events data were available for all seven trials: ATHENA [9], FLAMES [11], PAOLA-1 [7], PRIMA [6], PRIME [10], VELIA [8] and SOLO-1 [5]. Toxicity analyses are shown in Figure 4. The incidence of AEs of any grade was higher in the PARPi-treated patients (OR 4.62, 95% CI 2.83-7.57, p<0.01) (Figure 4A). Grade 3 or higher AEs were significantly more common in the PARPi group (OR 4.39, 95% CI 2.28-8.42, p<0.01) (Figure 4B). Frequencies of Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) were not significantly different between PARPi and placebo (OR 1.19, 95% CI 0.61-2.31, p=0.60) (Figure 4C).

Most commonly reported AEs among PARPi include nausea and hematological toxicity. Table S3 displays detailed information about toxicity data from included studies. Concerning quality of life, PARPi were generally well tolerated and did not significantly affect patients´ HRQoL (Table S4).

Quality assessment

Overall, the seven randomized trials included in this analysis were considered to have a low risk of bias (Supplementary Table S5). The

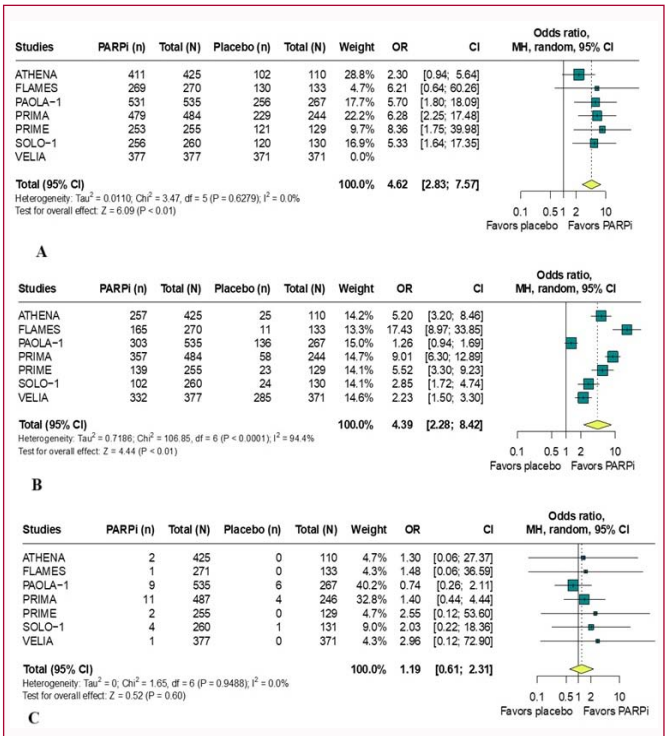

Figure 4: (A). Incidence of AEs of any grade (B). AEs grade ≥ 3 (C). MDS/AML.

Overall effect of each trial is represented by a square and the horizontal line crossing the squares indicates the 95% confidence interval. The diamonds represent the estimated overall effect of the meta-analysis based on random effects.

Aes: Adverse Events; CI: Confidence Interval; N: Number Of Cases; MH: Mantel-Haenszel; N: Total Number of Patients; OR: Odds Ratio.

funnel plot revealed a symmetrical distribution of studies, suggesting no publication bias. This was further confirmed by the Egger test (t=0.97, p=0.37).

Exploring heterogeneity

The leave-one-out analysis showed consistent results with the overall PFS analysis in patients carrying BRCA pathogenic variants. In the Baujat plot, it was observed that three studies remarkably contributed to the overall heterogeneity: SOLO-1, PRIMA and PAOLA-1. This likely reflects different PARPi used and different inclusion criteria. The sensitivity analysis including only stage III patients revealed a similar benefit compared to the overall PFS analysis (Figure S2).

Discussion

Summary of main results

This meta-analysis including over 4,000 advanced ovarian patients supports the benefit of PARPi in PFS across multiple subgroups. In regard to OS, the subset of 573 patients with BRCA pathogenic variants experienced a substantial OS benefit (HR 0.67, 95% CI 0.48-0.93). OS benefit was not statistically significant in the other subgroups.

Results in the context of published literature

Initially, PARPi were studied in the scenario of a more heavily pretreated ovarian cancer population [18-36]. The phase III SOLO-1 trial was the first to demonstrate the benefit of PARPi in an earlier setting for patients with BRCA pathogenic variant tumors. This study demonstrated a significant improvement in PFS associated with olaparib after platinum-based chemotherapy, even at a 7-year follow-up period. Therefore, it established PARPi as the standard of care in this patient population [5,13].

Following this, other studies such as PAOLA-1, PRIMA, VELIA, ATHENA, PRIME, and FLAMES expanded the scope of investigation to allow inclusion of patients without BRCA pathogenic variants or with mutations in other homologous recombination genes. Each of these trials had distinct inclusion criteria, contributing to heterogeneity in their populations. Beyond the differences in disease stage, the populations in the studies also varied in terms of stratification risk. For instance, PRIMA included higher-risk patients, excluding those with stage III disease who had no residual disease after upfront surgery whereas the PAOLA-1, PRIME, and ATHENA included patients regardless of postoperative residual disease status, encompassing a broader spectrum of clinical risk. Additionally, factors such as response to initial platinum-based chemotherapy and extent of residual disease after surgery played a critical role in defining patient prognosis across these trials. The inclusion of patients with varied responses to prior treatment adds another layer of complexity when comparing outcomes. These variations in inclusion criteria likely contributed to differences in PFS outcomes across studies, with significant benefits observed in HRD test-positive and BRCA pathogenic variant subgroups, while benefits for HRD test-negative patients were less pronounced [6-12,14, 37-46].

Another key consideration is the distinct control arms among studies. PAOLA-1 utilized bevacizumab as an active control, whereas other studies used placebo, which may have contributed to differences in OS outcomes. This discrepancy is particularly relevant when interpreting the added benefit of PARPi in different treatment landscapes, as bevacizumab itself has been shown to improve PFS in previous trials [4,47]. However, its impact on OS remains uncertain, with potential benefits suggested in high-risk subgroups [48]. The inclusion of bevacizumab in PAOLA-1 as an active control may have contributed to the heterogeneity seen in survival analyses and influenced our findings.

Although HRD is a widely used predictive and prognostic biomarker, currently used HRD assays are known for their analytical variability [37]. At present, there are two genomic HRD tests approved by the Food and Drug Administration: Myriad MyChoice CDx and Foundation One CDx [38]. Both define HRD based on BRCA1/2 mutations and genomic instability. The first, however, scores genomic instability based on Loss of Heterozygosity (LOH), telomeric allelic imbalance, and large-scale state transitions. A test score ≥ 42 is considered HRD-positive. On the other hand, the latter analyzes an extensive gene panel plus the percentage of LOH - a threshold of 16% is used to define HRD-positive [38]. The two tests have been validated as response predictors across clinical trials exploring PARPi on ovarian cancer [5-14]. While both are FDA-approved, additional non-FDA validated assays, such as the BGI HRD assay and TruSight Oncology 500 HRD, are also utilized in clinical research. These tests evaluate genomic instability through LOH and analyze a broader gene panel for HRD scoring, respectively. The use of non-validated tests may have contributed to the heterogeneity observed across studies. Moreover, the European Network of Gynecological Oncology Trial HRD Initiative and other upcoming studies are exploring alternative assays and may expand the HRD test availability for patients with ovarian cancer [39]. A head-to-head comparison among all available

assays is urgently needed to clarify their differences in clinical practice.

Another key aspect when considering between-study variability and treatment response consists of ethnic factors. Evidence suggests that patients of East Asian descent have a higher prevalence of HRD test-positive tumors, which may translate into better response to PARPi. In this meta-analysis, one trial (PRIME) included exclusively Chinese patients, whereas others such as ATHENA and VELIA included a broader population and several ethnic backgrounds. Although the benefit of PARPi was fairly consistent among studies, genetic and ethnic factors should always be considered in clinical decision-making scenarios.

Final overall survival results from PRIMA and PAOLA-1 trials have added evidence against the use of PARPi for an unselected patient population. While both studies have met their primary endpoints of PFS, the PRIMA trial failed to document an OS advantage in any of the pre-specified subgroups, and PAOLA-1 only showed an OS benefit in patients with a BRCA pathogenic variants or HRD test-positive. A potential explanation is the impact of subsequent PARPi use. In PRIMA, 12% of patients in the niraparib arm and 38% in the placebo arm subsequently received PARPi, with most receiving it in second-line. In PAOLA-1, 45.7% of patients in the placebo group and 19.5% in the olaparib group received subsequent PARPi and importantly, 24.4% of placebo patients received a PARPi as first subsequent therapy and 13.0% as second subsequent therapy. These numbers indicate that a significant proportion of patients in both trials received a PARPi early in later-line treatment, potentially confounding OS outcomes. Differences in patient populations and study design may have also influenced the results as previously discussed. Additionally, variations in PARPi maintenance duration could have affected responses to subsequent treatments [12,14].

The disparity between PFS and OS across different subgroups highlights the need for caution when interpreting PFS as a surrogate for OS, particularly in HRD test-positive and test-negative patients. Additionally, the role of bevacizumab in combination with PARPi, especially in HRD test-positive patients without BRCA pathogenic variants and in HRD test-negative populations, remains inconclusive and requires further investigation. It is also worth mentioning that although PARPi share common adverse events, there are particularities in toxicity profile among the studied agents that may influence patient adherence and treatment outcomes. Niraparib was associated with the highest rates of thrombocytopenia, but less fatigue when compared to olaparib, veliparib and rucaparib for example. Nausea is a common PARPi side effect, but rucaparib was the only to report ≥ G3 elevations in ALT/AST. AEs leading to treatment discontinuation ranged from 4% to 12%, with the lowest rate for senaparib. Therefore, understanding the toxicity landscape is crucial for interpreting the efficacy data and ensuring a balanced approach to patient management in clinical practice.

Strengths and weaknesses

A key strength of this meta-analysis is the large sample size of more than 4,000 patients, which provides a robust and diverse dataset, improving the reliability of findings and allowing for broad generalizability across various patient demographics. Subgroup analyses further enriched the study, offering insights into how PARPi affects specific populations, such as patients with either BRCA pathogenic variants or HRD test-positive status. Lastly, the analysis of adverse events, including rare but significant risks, such MDS and AML, highlights both the benefits and potential harms of PARPi, supporting a balanced risk-benefit evaluation.

Despite these strengths, several limitations may affect the interpretation and applicability of the findings. Among them, the lack of long-term OS data in most studies should be highlighted, which may limit conclusions about the extended survival benefits of PARPi across different subgroups. Additionally, a high heterogeneity was seen across the analyses. This likely reflects the between-HRD test heterogeneity among studies, as well as different patient characteristics, such as BRCA statuses. Furthermore, the impact of subsequent therapies on OS, where many patients received PARPi in post-trial lines of treatment, may dilute the true effect of PARPi, hindering difficulties in assessing the long-term survival benefit. Another key limitation is the lack of a stratified analysis within stage III. While we performed an additional analysis of PFS for stage III patients, a more detailed subgroup analysis was not feasible due to the lack of individual patient-level data in the included trials. Together, these limitations underscore the need for caution in applying these findings broadly and highlight areas where future research could enhance our understanding of PARPi's role in treating newly diagnosed ovarian cancer.

Implications for practice and future research

These results have direct implications for clinical practice, particularly regarding the tailored use of PARPi in treating ovarian cancer. The OS benefit in patients with BRCA pathogenic variants underscores the importance of early genetic and molecular testing to identify patients most likely to benefit from PARPi. Notably, the PFS benefit observed in our analysis was present in both HRD test-positive and HRD test-negative patients, demonstrating that PARPi provide progression-free survival advantage across these subgroups. However, no overall survival benefit was identified in either HRD test-positive or HRD test-negative populations. These findings suggest that while PARPi improve PFS, their impact on long-term survival remains uncertain. This highlights the need for longer follow-up to better identify subpopulations that derive the most significant benefit from PARPi, particularly in the context of optimizing resource allocation and therapeutic strategies.

Despite great initial benefit of PARPi following platinum-based chemotherapy, up to 85% of ovarian cancer patients face disease progression under PARPi treatment [13,24]. Limited options are available in the scenario of PARPi resistance. Evidence suggests an association between relapse on platinum-based chemotherapy and PARPi.40 The loss of BRCA1 methylation appears to be the leading cross-resistance mechanism between them [41]. Additionally, reversion mutations in BRCA1/2, which restore homologous recombination proficiency, are among the most well-documented mechanisms of resistance to both PARPi and platinum-based chemotherapy [42,43]. Furthermore, RAD51 overexpression and a shift toward error-prone repair pathways like Non-Homologous End Joining (NHEJ) have also been identified as contributors to chemoresistance. This combination of resistance mechanisms may explain the reduced benefit of subsequent chemotherapy following PARPi resistance [44]. A retrospective cohort evaluated the effectiveness of chemotherapy (platinum-based and non-platinum-based) following progression under PARPi on 291 ovarian cancer patients [45]. The subgroup of patients with a platinum-free interval of at least six months who received platinum-based regimens after progression on PARPi had numerically better survival rates than those who received non-platinum-based chemotherapy. Yet,

the median PFS was only 5.6 months in the overall population. Additionally, post-progression data from the PAOLA-1 trial suggest that disease progression during PARPi treatment may negatively impact responses to subsequent chemotherapy [7,14].

Another treatment alternative currently being studied for those experiencing PARPi resistance consists of treatment rechallenge. The phase IIIb OReO/ENGOT-ov38 trial investigated olaparib compared to placebo in ovarian cancer patients previously treated with PARPi after first-line platinum-based chemotherapy. Slightly better survival rates were seen for the olaparib arm, regardless of BRCA status [46], with a manageable safety profile. Despite encouraging data, subsequent treatment options for patients progressing under or after PARPi treatment still pose a major challenge. Future studies exploring novel prognostic biomarkers and other agents in this patient population are urgently needed.

Conclusion

The current systematic review and meta-analysis supports a significant survival benefit of PARPi in patients with BRCA pathogenic variants. However, the absence of a clear OS benefit in HRD test-positive and test-negative patients suggests a need for more selective use of these agents across ovarian cancer populations. Further research should focus on identifying patients who may benefit from alternative or combination therapies. Such efforts could pave the way for more personalized approaches that maximize therapeutic efficacy across all patient subgroups.

Declaration of Conflicting Interest

The authors O.A., C.S., I.M., M.V., C.E.R.C., M.I.D. declare no conflicts of interest. S.G. has received institutional support from AstraZeneca, Compugen, Genentech/Roche, Clovis Pharma, Iovance, Tempest, Tesaro/GSK, Blueprint, Immunogen, Volastra, Beigene, and the GOG Foundation, though this support was unrelated to the PARP inhibitor meta-analysis. She has served as a consultant for Immunogen, Novartis, Verastem, and Compugen (compensated personally). S.G. is a co-inventor of U.S. Patents No. 10,258,604 and No. 10,905,659 related to the use of Lasofoxifene in breast cancer treatment, licensed by Duke University. She serves on the Data Safety Monitoring Board of Sign Path Pharma without compensation and is the Chair of the Phase I Subcommittee of NRG Oncology, with support provided to her institution. A.N.G - Consultant: ANVISA (Brazil), Roche, AstraZeneca, MSD, EISAI, Pfizer, GSK, Agenus, Daiichi, Eurofarma; Research Funding: CNPq, FAPEMIG (public research organizations in Brazil); Educational training: Roche, AstraZeneca, MSD, GSK, Pfizer, Novartis, Daiichi, Gilead, EISAI.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12-49.
2. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol. 2002;20(5):1248-59.
3. Baradács I, Teutsch B, Váradi A, Bilá A, Vincze A, Hegyi P, et al. PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis of randomized controlled trials. J Ovarian Res. 2024;17(1):53.
4. Colomban O, Tod M, Peron J, Perren TJ, Leary A, Cook AD, et al. Bevacizumab for newly diagnosed ovarian cancers: best candidates among high-risk disease patients (ICON-7). JNCI Cancer Spectr. 2020;4(3):pkaa026.
5. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379(26):2495-505.
6. González-Martín A, Pothuri B, Vergote I, Christensen RD, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019;381(25):2391-402.
7. Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med. 2019;381(25):2416-28.
8. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019;381(25):2403-15.
9. Monk BJ, Parkinson C, Lim MC. ATHENA trial: rucaparib in newly diagnosed ovarian cancer (ENGOT-ov45). J Clin Oncol. 2022;40(36_suppl):3870.
10. Li N, Zhu J, Yin R, Wang J, Pan L, Kong B, et al. Treatment with niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer: a phase 3 randomized clinical trial. JAMA Oncol. 2023;9(9):1230-7.
11. Wu X, Liu J, Wang J, Wang L, Lin Z, Wang X, et al. Senaparib as first-line maintenance therapy in advanced ovarian cancer: a randomized phase 3 trial. Nat Med. 2024;30(6):1612-21.
12. Monk BJ, Barretina-Ginesta MP, Pothuri B, Vergote I, Graybill W, Mirza MR, et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Ann Oncol. 2024; 35(11):981-992.
13. DiSilvestro P, Banerjee S, Colombo N, Scambia G, Kim BG, Oaknin A, et al. Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients with Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. J Clin Oncol. 2023;41(3):609-17.
14. Ray-Coquard I, Leary A, Pignata S, Cropet C, González-Martín A, Marth C, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. Ann Oncol. 2023;34(8):681-92.
15. 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.
16. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
18. Sun G, Liu Y. Efficacy and safety of PARP inhibitor maintenance therapy for ovarian cancer: a meta-analysis and trial sequential analysis of randomized controlled trials. Front Pharmacol. 2024;15:1460285.
19. Higgins JPT. Cochrane handbook for systematic reviews of interventions version 5.0.1. The Cochrane Collaboration; 2008.
20. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016;375(22):2154-64.
21. 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.
22. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et

al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366(15):1382-92.

23. Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol. 2016;17(11):1579-89.

24. Mirza MR, Benigno B, Dørum A, Mahner S, Bessette P, Barceló IB, et al. Long-term safety in patients with recurrent ovarian cancer treated with niraparib versus placebo: results from the phase III ENGOT-OV16/NOVA trial. Gynecol Oncol. 2020;159(2):442-8.

25. Oza AM, Cibula D, Benzaquen AO, Poole C, Mathijssen RHJ, Sonke GS, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol. 2015;16(1):87-97.

26. Penson RT, Valencia RV, Cibula D, Colombo N, Leath 3rd CA, Mariusz Bidziński, 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;38(11):1164-74.

27. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(9):1274-84.

28. Poveda A, Floquet A, Ledermann JA, Asher R, Penson RT, Oza AM, 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. Obstet Gynecol Surv. 2021;76(9):535-6.

29. Li XH, Wu XH, Zhu JQ, Yin RT, Yang JX, Liu JH, Wang J, et al. Niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer using an individualized starting dose (NORA): a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol. 2021;32(4):512-21.

30. Wu L, Zhu J, Yin R, Wu X, Lou G, Wang J, et al. Olaparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer and a BRCA1 and/or BRCA2 mutation: SOLO1 China cohort. Gynecol Oncol. 2021;160(1):175-81.

31. Paoletti X, Lewsley LA, Daniele G, Cook A, Yanaihara N, Tinker A, et al. Assessment of progression-free survival as a surrogate end point of overall survival in first-line treatment of ovarian cancer: a systematic review and meta-analysis. JAMA Netw Open. 2020;3(1):e1918939.

32. Pommier Y, O'Connor MJ, Bono JD. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med. 2016;8(362):362ps17.

33. Morice PM, Leary A, Dolladille C, Chrétien B, Poulain L, González-Martín A, et al. Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database. Lancet Haematol. 2021;8(2):e122-e134.

34. LaFargue CJ, Molin GZD, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. Lancet Oncol. 2019;20(1):e15-28.

35. Bitler BG, Watson ZL, Wheeler LJ, Behbakht K. PARP inhibitors: clinical utility and possibilities of overcoming resistance. Gynecol Oncol. 2017;147(3):695-704.

36. D'Andrea AD. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst). 2018;71:172-6.

37. Mangogna A, Munari G, Pepe F, Maffii E, Giampaolino P, Ricci G, et al. Homologous Recombination Deficiency in Ovarian Cancer: from the Biological Rationale to Current Diagnostic Approaches. J Pers Med. 2023;13(2):284.

38. Ngoi NYL, Tan DSP. The role of homologous recombination deficiency testing in ovarian cancer and its clinical implications: do we need it? ESMO Open. 2021;6(3):100144.

39. Loverix L, Vergote I, Busschaert P, Vanderstichele A, Venken T, Boeckx B, et al. PARP inhibitor predictive value of the Leuven HRD test compared with Myriad MyChoice CDx PLUS HRD on 468 ovarian cancer patients from the PAOLA-1/ENGOT-ov25 trial. Eur J Cancer. 2023;188:131-9.

40. McMullen M, Karakasis K, Madariaga A, Oza AM. Overcoming Platinum and PARP-Inhibitor Resistance in Ovarian Cancer. Cancers (Basel). 2020;12(6):1607.

41. Fu X, Li P, Zhou Q, He R, Wang G, Zhu S, et al. Mechanism of PARP inhibitor resistance and potential overcoming strategies. Genes Dis. 2024;11(1):306-20.

42. Norquist B, Wurz KA, Pennil CC, Garcia R, Gross J, Sakai W, et al. Secondary somatic mutations restoring BRCA1/2 predict chemotherapy resistance in hereditary ovarian carcinomas. J Clin Oncol. 2011;29(22):3008-15.

43. Patch AM, Christie EL, Etemadmoghadam D, Garsed DW, George J, Fereday S, et al. Whole-genome characterization of chemoresistant ovarian cancer. Nature. 2015;521(7553):489-94.

44. Frenel JS, Kim JW, Aryal N, Asher R, Berton D, Vidal L, et al. Efficacy of subsequent chemotherapy for patients with BRCA1/2-mutated recurrent epithelial ovarian cancer progressing on olaparib versus placebo maintenance: post-hoc analyses of the SOLO2/ENGOT Ov-21 trial. Ann Oncol. 2022;33(10):1021-28.

45. Xu-Vuillard A, Guerin-Charbonnel C, Bocquet F, Cheeseman S, Kubelac PM, Zenatri M, et al. Efficacy of chemotherapy after progression during or following PARPi exposure in ovarian cancer. ESMO Open. 2024;9(9):103694.

46. Pujade-Lauraine E, Selle F, Scambia G, Asselain B, Marmé F, Lindemann K, et al. Maintenance olaparib rechallenge in patients with platinum-sensitive relapsed ovarian cancer previously treated with a PARP inhibitor (OReO/ENGOT-ov38): a phase IIIb trial. Ann Oncol. 2023;34(12):1152-64.

47. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365(26):2473-83.

48. Ferriss JS, Java JJ, Bookman MA, Fleming GF, Monk BJ, Walker JL, et al. Ascites predicts treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian, fallopian tube and peritoneal cancers: an NRG Oncology/GOG study. Gynecol Oncol. 2015;139(1):17-22.