

SYSTEMATIC REVIEW

Efficacy and safety of PARP inhibitors in advanced or recurrent endometrial cancer patients: a systematic review and single arm meta-analysis

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Abstract

Background: Patients diagnosed with advanced or recurrent endometrial cancer have a poor prognosis, with few available treatment options. Poly (ADP-ribose) polymerase inhibitors (PARPi) have gained interest as a potential therapy for gynecological cancers. This single-arm meta-analysis aimed to evaluate the efficacy and safety of PARPi therapy in patients with advanced or recurrent endometrial cancer. **Methods:** The search strategy included PubMed, Cochrane, and Embase databases. Statistical analysis was performed using R software, applying the DerSimonian/Laird random-effects model for all analyses. Heterogeneity was evaluated using the I^2 statistic. **Results:** Our analysis included ten clinical trials comprising 345 patients with advanced or recurrent endometrial cancer. 81.2% (280/345) of patients received PARPi in combination with immune checkpoint inhibitors (ICI), angiogenesis inhibitors, and other drugs. Our pooled analysis demonstrated an overall objective response rate (ORR) of 20.59% (95% Confidence Interval (CI): 13.88–29.45) and a disease control rate (DCR) of 60.7% (95% CI: 46.53–74.87). ORR and DCR were better in combination treatment compared with monotherapy. The 6-month progression-free survival (PFS) and 12-month overall survival (OS) rates were, respectively, 27.51% (95% CI: 21.12–33.9) and 45.77% (95% CI: 38.21–53.33). The prevalence of adverse events of grades 3–5 were 44.24% (95% CI: 25.91–62.58). **Conclusions:** These findings suggest that PARPi may have potential in combination therapy for progressive endometrial cancer, but the current evidence is limited. Additional well-designed randomized studies are necessary to confirm these results and to develop more effective treatment strategies. **The PROSPERO Registration:** CRD42024535632.

Keywords

PARP inhibitor therapy; Advanced or recurrent endometrial cancer; Immune checkpoint inhibitors; Angiogenesis inhibitors

1. Introduction

Endometrial cancer is the most prevalent gynecological malignancy, with incidence rates rising across the world. Early-stage endometrial cancer generally has a favorable outcome; however, for advanced-stage or recurrent disease, treatment options become limited, and prognosis remains poor. Recent developments in treatment options involve the use of immune-checkpoint inhibitors (ICI) either as monotherapy or in combination with other treatments. Studies have demonstrated that ICI monotherapy has been beneficial in patients with mismatch repair deficiency (MMRd), which is present in approximately 25–30% cases [1, 2]. Combining ICI with chemotherapy in trials like RUBY part 1 and NRG-GY018 has proven effective as first-line treatment for primary advanced or recurrent endometrial cancer [3, 4]. In the Keynote 775 trial, the combination of

ICI with angiogenesis inhibitors was explored. Results have shown that combining lenvatinib and pembrolizumab yields significantly longer progression-free survival (PFS) and overall survival (OS) rates compared with chemotherapy, leading to US Food and Drug Administration approval [5].

Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as a groundbreaking therapeutic option and have shown significant effectiveness in cancers such as ovarian and breast cancer, resulting in their approval for use in treating these malignancies. They are particularly beneficial in cancers with defective homologous recombination repair (HRR) pathways, such as those with *BRCA1* or *BRCA2* mutations [6]. DNA double-strand break repair by HRR pathway is vital for cell function but can be impaired in cancers like breast, ovarian, prostate, pancreas, and endometrial cancer. Key genes involved include *BRCA1*, *BRCA2*, *MRE11A*, *NBN*,

RAD50, *ATM*, *PALB2*, and *RAD51*, and mutations in any of these genes can lead to homologous recombination deficiency (HRD). Cancer cells with HRD are particularly sensitive to PARP inhibition [7].

Heeke *et al.* [8] showed that, among the tumors tested with NGS600, the overall frequency of HRD mutations detected in endometrial cancer (EC) was 34.4% and is largely restricted to non-endometrioid cancer. Moreover, the The Cancer Genome Atlas (TCGA) analysis revealed genomic features in EC suggesting susceptibility to DNA-damaging agents, including high mutational loads, *TP53* mutations, *PTEN* loss, and *ARID1A* mutations [9].

In recent decades, there has been growing interest in evaluating the efficacy of PARPi treatment in EC patients. Clinical trials, often focusing on specific molecular subgroups, have investigated the effectiveness of PARPi as monotherapy and in combination with other treatments to explore potential synergistic effects. Our objective is to perform a systematic review and meta-analysis of these studies to comprehensively evaluate the overall effectiveness and safety of PARPi in managing EC.

2. Material and methods

2.1 Protocol and registration

This systematic review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42024535632). The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10], and the completed checklist has been included as **Supplementary material 1**.

2.2 Eligibility criteria

Eligible studies were required to meet the following criteria: (1) participants aged 18 years and older with advanced, recurrent, or metastatic primary endometrial cancer; (2) Eastern Cooperative Oncology Group (ECOG) performance status scores of 0, 1, or 2; (3) prior chemotherapy failure, unwilling to undergo chemotherapy, or chemo-naïve not suitable for chemotherapy (4) measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [11]; (5) evaluation of PARPi in the primary treatment setting; and (6) could have received prior surgery, radiotherapy, or hormone therapy. We excluded studies with overlapping populations, no outcomes of interest, unpublished studies, and studies that used PARPi as maintenance treatments. For homogeneous analysis, we excluded three major studies-DUOE, RUBY part 2, and UTOLA, due to their use of PARPi in a maintenance treatment setting.

2.3 Search strategy and data extraction

A systematic search of PubMed, the Cochrane Library, Scopus, and Web of Science was conducted on 07 January 2024, using structured search strategies that incorporated MeSH terms related to “Endometrial Neoplasms”, “Poly (ADP-ribose) Polymerase Inhibitors”, and specific PARP inhibitors (olaparib, niraparib, rucaparib, talazoparib). All

identified studies were managed using reference management software (Zotero), and duplicated records were removed. Titles and abstracts were independently reviewed by two reviewers (TA and GMS), with disagreements resolved by consensus among the authors. This comprehensive approach ensured the inclusion of relevant literature in the analysis.

Pre-specified baseline characteristics and outcome data were collected by two authors (TA and GMS). The following baseline characteristics were extracted: (1) study design; (2) regimen details; (3) number of patients; and (4) main patient characteristics. The ensuing outcomes of interest were extracted: (1) objective response rate (ORR); (2) disease control rate (DCR); (3) progression-free survival (PFS), defined as the time from patient randomization to disease progression or death from any cause; (4) overall survival (OS), defined as the period of time that patients are still alive from the start of treatment; and (5) adverse events.

2.4 Endpoints and subanalysis

The efficacy outcomes included ORR, DCR, six-month PFS, and twelve-month OS. Safety outcomes comprised adverse events related to the intervention. ORR consisted of patients with partial or complete response, while DCR included those with stable disease, partial, or complete response. Response assessment was performed either by the investigator through clinical evaluation or based on RECIST criteria version 1.1, following each study’s specific criteria [11]. We performed a subgroup analysis to assess ORR and six-month PFS in patients with different MMR, TP53, and HRR profiles.

2.5 Risk of bias assessment

Two researchers (TA and GMS) independently assessed the risk of bias, with a third reviewer (HS) resolving any disagreements. The risk of bias assessment utilized the Cochrane RoB2 tool for randomized controlled trials and the risk of bias in non-randomized studies of Interventions (ROBINS-I) tool for observational studies [12, 13]. Publication bias was investigated using Egger’s linear regression test.

2.6 Statistical analysis

The systematic review and meta-analysis followed the guidelines outlined by the Cochrane Collaboration and the PRISMA statement [10]. Statistical analysis was performed using R Studio 4.3.2 (R Foundation for Statistical Computing). To evaluate efficacy outcomes, proportional meta-analysis was conducted using the “metaprop” and “pool.median” functions available in the “meta”, “metaphor”, and “metamedian” packages in R. Proportional meta-analyses were utilized for dichotomous outcomes and presented as percentages with 95% confidence intervals (CIs). Logit-transformation was applied when the proportion in an individual study was below 0.2 or above 0.8. For studies with zero events, we used the double-arcsine transformation. A Der Simonian and Laird random-effects model was applied to all analyses. Heterogeneity was assessed using Cochran’s Q test and I^2 statistics, with significance set at p -values less than 0.10 and I^2 values exceeding 25%.

3. Results

3.1 Study selection and characteristics

The search strategy initially identified 986 records, as detailed in Fig. 1. After removing duplicates and excluding ineligible studies, 29 studies remained and were thoroughly reviewed according to the inclusion criteria. Of these, ten studies were selected for inclusion in the analysis, with a total of 345 patients. All patients had an ECOG performance status scale score of 0 to 2, with 72.3% (141/195) identifying themselves as belonging to the white race. The median age of patients ranged from 60 to 69 years, and the median follow-up time

was from 2.5 to 27 months. The most prevalent histological type was endometrioid, accounting for 42.5% (135/318) of the cases. Almost all patients received at least one line of standard therapy, with the median number of previous therapies ranging from one to six lines. Out of 345 patients, 31% (107/345) received treatment with the combination of PARPi/ICI, 24.9% (86/345) with PARPi/angiogenesis inhibitors, 18.8% (65/345) with PARPi alone, 16.5% (57/345) treated with PARPi/other drugs, and 8.8% (30/345) with PARPi/ICI/angiogenesis inhibitors. Baseline characteristics of the studies are described in Table 1 (Ref. [14–23]).

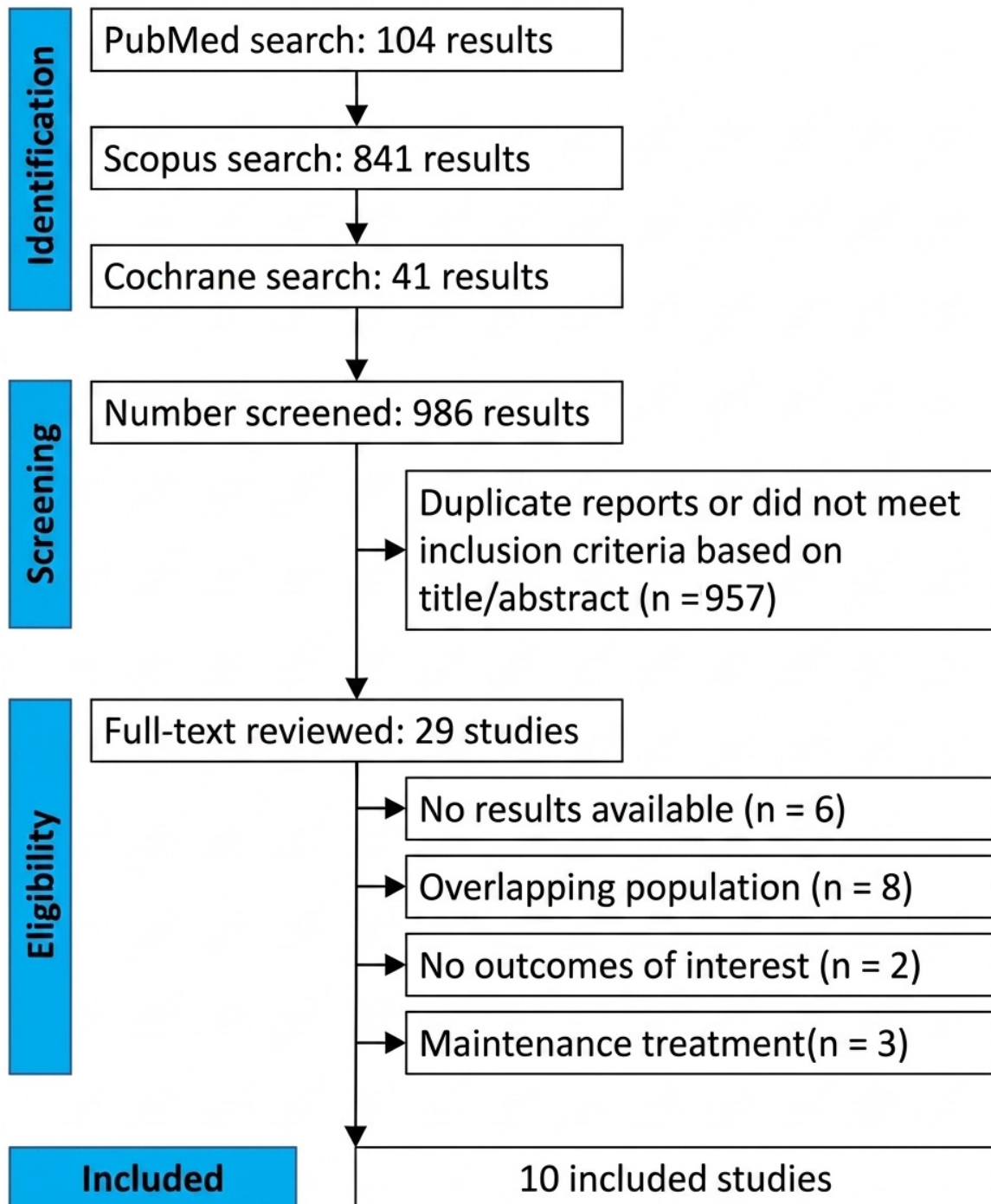


FIGURE 1. PRISMA flow diagram of study screening and selection.

TABLE 1. Design and characteristics of studies included in the meta-analysis.

Study	Design	Follow-up (mon)	No. of Patients	Age [†]	ECOG, No. (%)	Race, No. (%)	Histology, No. (%)	Intervention	Dosage of PARPi	Molecular Characteristics, No. (%)	Number of prior chemotherapy lines, No. (%)
Aghajanian <i>et al.</i> [14] 2012	Non-RCT, phase 2	N/A	17	N/A	0: 9 (52.9) I–II: 8 (48.1)	White: 14 (82.4) Black: 2 (11.8) Others: 1 (5.9)	Carcinosarcoma: 17 (100)	Iniparib + C/P	4 mg/kg IV twice weekly	N/A	0
Bradley <i>et al.</i> [15] 2022	Non-RCT, phase 2	14.9	30	N/A	N/A	White: 19 (63.3) Black: 8 (26.7) Others: 3 (10)	Serous: 15 (50) Endometrioid: 6 (20) Carsinosarcoma: 4 (13)	Bevacizumab + Atezolizumab + Rucaparib	N/A	N/A	1/2 lines
DOMEC 2022 [16]	Non-RCT, phase 2	17	50	69	0: 13 (27.7) I: 34 (72.3)	N/A	Serous: 11 (36) Endometrioid: 18 (51) Carsinosarcoma: 2 (7)	Olaparib + Durvalumab	300 mg BID	MMRd: 10 (20.4) P53: 29 (59.2) POLE: 0	1–29 (69.0) 2–11 (26.2) 3–2 (4.8)
ENDOLA 2022 [17]	Non-RCT, Phase 2	2.5	14	69	N/A	N/A	N/A	Olaparib + m.Cp + Metformin	300 mg BID	N/A	N/A
Jackson <i>et al.</i> [18] 2022	Non-RCT, phase 2	25	33*	64	N/A	White: 27 (81.8) Black: 4 (12.1) Others: 2 (6.1)	Serous: 6 (18) Endometrioid: 15 (46) Carsinosarcoma: 3 (9) Mixed: 2 (6) Other: 1 (3)	Rucaparib + Bevacizumab	600 mg BID	RID1A: 5 (31.25) PTEN: 5 (31.25)	N/A
Konstantinopoulos <i>et al.</i> [19] 2022	Non-RCT, phase 2	12.9	35	N/A	0: 14 (40) I: 21 (60)	White: 18 (51.4) Black: 5 (14.3) Others: 12 (34.3)	Serous: 12 (34) Endometrioid: 11 (31) Clear cell: 3 (9) Carsinosarcoma: 4 (11) Mixed: 5 (14)	Talozaparib + Avelumab	1 mg daily	MMRp: 35 (100)	N/A

TABLE 1. Continued.

Study	Design	Follow-up (mon)	No. of Patients	Age [†]	ECOG, No. (%)	Race, No. (%)	Histology, No. (%)	Intervention	Dosage of PARPi	Molecular Characteristics, No. (%)	Number of prior chemotherapy lines, No. (%)
POLA 2022 [20]	Non-RCT, phase 2	N/A	26	N/A	N/A	N/A	Endometrioid: 23 (88) Carsinosarcoma: 3 (12)	Olaparib + Lurbinectedin	250 mg BID	N/A	N/A
Ren <i>et al.</i> [21] 2022	Non-RCT, phase 2	7.8	13	60	N/A	N/A	N/A	Niraparib + Anlotinib	200 mg daily	N/A	N/A
Madariaga <i>et al.</i> [22] 2023	Non-RCT, phase 2 Cohort 1	27	25	69	0: 5 (20) I–II: 20 (80)	N/A	Serous: 15 (60) Endometrioid: 9 (36) Mixed: 1 (4)	Niraparib	200/300 mg daily	MMRd: 4 (16) mTP53: 3 (14) POLE: 0	1–8 (32) 2–9 (36) 3–2 (8) 4–6 (24)
Madariaga <i>et al.</i> [22] 2023	Non-RCT, phase 2 Cohort 2	27	22	64.5	0: 2 (9) I–II: 20 (91)	N/A	Serous: 9 (41) Endometrioid: 12 (55) Mixed: 1 (4)	Niraparib + Dostarlumab	200/300 mg daily	MMRd: 3 (14) mTP53: 12 (55) POLE: 1 (5)	1–6 (27) 2–6 (27) 3–5 (23) 4–3 (14) 5–1 (5) 6–1 (5)
NRG-GY012 2023 [23]	RCT, phase 2 Arm 1	18.3	40	69	0: 23 (57.5) I–II: 17 (42.5)	White: 31 (77.5) Black: 5 (12.5) Others: 4 (10)	Serous: 16 (40) Endometrioid: 20 (50) Other: 4 (10)	Olaparib	300 mg BID	mTP53: 25 (67) wtTP53: 13 (32.5) ukTP53: 2 (5)	1–27 (67.5) 2–13 (32.5)

[†], median; No, number; N/A, not available; uk, unknown; C/P, carboplatin and paclitaxel; m.Cp, metronomic cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; MMRd, mismatch repair-deficient; MMR, Mismatch repair; MMRp, mismatch repair-proficient; Others: American indian or native, unknown, latin or hispanic, caribbean, asian, multiracial; *, six patients had cervical cancer; the pooled analysis only included endometrial cancer patients; BID, Bis in die (Twice a day); IV, intravenous; wt, wild-type; PARPi, Poly (ADP-ribose) Polymerase/inhibitor; RID1A, AT-Rich Interaction Domain 1A; PTEN, Phosphatase and Tensin Homolog; POLE, DNA Polymerase Epsilon, Catalytic Subunit; TP53, Tumor Protein p53.

3.2 Objective response rate

In a pooled analysis, the ORR was 20.59% (95% CI: 13.88 to 29.45) with a total of 63 events out of 317 patients. The analysis revealed a high level of heterogeneity among the studies ($I^2 = 59\%$, $p < 0.01$), as shown in Fig. 2A. In the subgroup analysis of tumor response according to the treatment administered, including PARPi monotherapy, PARPi combined with ICI, PARPi combined with angiogenesis inhibitors, PARPi combined with other therapies, and PARPi combined with ICI and angiogenesis inhibitors, we found a significant difference between subgroups ($p = 0.03$). Combination treatment showed better response rates. Patients receiving PARPi plus angiogenesis inhibitors had an ORR of 33.94% (95% CI: 11.35–67.34), PARPi in combination with other therapies and PARPi in combination with ICIs showed ORRs of 19.57% (95% CI: 11.17–32.03) and 14.14% (95% CI: 8.71–22.15), respectively. For PARPi monotherapy, the ORR was the lowest at 9.49% (95% CI: 3.55–23).

3.3 Disease control rate

The overall population's DCR was 60.7% (95% CI: 46.53–74.87) with 153 events out of 260 patients. Fig. 2B (Ref. [14–22]) shows a high level of heterogeneity, with an I^2 value of 87%, $p < 0.01$. This analysis also showed a significant difference among subgroups, with combination treatment demonstrating better DCR. PARPi plus angiogenesis inhibitors, PARPi plus ICI, and PARPi plus other therapies demonstrated DCR rates of 74.77% (95% CI: 41.37–100), 52.22% (95% CI: 32.1–72.33), and 65.16% (95% CI: 52.84–77.47), respectively. PARPi monotherapy had the lowest DCR at 20% (95% CI: 6.83–40.7).

3.4 Progression-free survival rate

Pooled PFS rate at 6 months was 27.51% (95% CI: 21.12–33.9), with 82 events out of 282 patients included in the analyses, with no significant difference seen among the treatment strategies ($p = 0.20$), described in Fig. 3A. The pooled PFS results had a modest level of heterogeneity, with an I^2 of 34%.

3.5 Overall survival rate

In a pooled analysis of OS, patients alive at 12 months were 45.77% (95% CI: 38.21–53.33) with 101 out of 220 events, with no significant difference seen among the treatment strategies and monotherapy ($p = 0.97$), described in Fig. 3B (Ref. [14, 16, 18–20, 22, 23]). The analysis indicated low heterogeneity, with an I^2 of 28%.

3.6 Adverse events

Regarding adverse events (AEs), a significant proportion of patients, 93.6% (95% CI: 66.23–99.09), experienced an AE of any grade, as illustrated in Fig. 4A. Additionally, 44.24% (95% CI: 25.91–62.58) of patients reported grade 3–5 AEs, indicating severe adverse events in a considerable portion of the population (Fig. 4B, Ref. [15–18, 21, 23]). A random effects model was applied for any AE grade, with a total of 77 AE events in a population of 83 patients included in the study.

The analysis demonstrated high heterogeneity, with an I^2 value of 55%. Analyzing grade 3–5 AEs in the overall population, there were 99 AEs out of 214 patients, with a high level of heterogeneity ($I^2 = 92\%$).

3.7 Quality assessment

One Randomized Controlled Trial (RCT), NRG-GY012 [23] had some concerns due to open-label randomization. Among the non-RCT clinical trials, Bradley *et al.* [15], ENDOLA [17], and Ren *et al.* [21] were assessed as having a serious overall risk of bias due to incomplete information, as they were available only as abstracts and not fully published studies. The risk of bias for the remaining non-RCT studies was considered moderate. Tables using RoB2 and ROBINS-I tools are available in **Supplementary Tables 1 and 2**.

We conducted leave-one-out sensitivity analyses, systematically removing each study from the pooled estimates for the prevalence of ORR, DCR, 6-month PFS, and 1-year OS rate (**Supplementary Fig. 1**, Ref. [14–22], respectively). These tests showed that removing any single study did not substantially alter the results. During the visual inspection of the funnel plots for ORR, DCR, 6-month PFS, and 12-month OS rate outcomes, we observed a predominantly symmetrical pattern in the distribution of studies around the central axis, as illustrated in **Supplementary Fig. 2** respectively. However, some studies were positioned slightly outside the plot in each analysis, suggesting potential differences in patient selection and intervention. Therefore, we conducted Egger's regression test to explore it further. However, we did not find any significant evidence of publication bias in any of these outcomes.

4. Discussion

In this systematic review and single-arm meta-analysis of twelve studies, including 345 patients, we evaluated the efficacy and safety of PARP inhibitors in advanced/recurrent EC. The main findings from pooled analysis related to this therapeutic strategy include the following: (1) 60.7% of patients achieved DCR, mainly attributed to partial response and stable disease; (2) ORR was observed in 20.59% of patients; (3) DCR and ORR were better in combination treatment compared with monotherapy; (4) with 45.77% of patients alive at 1 year; (5) grade 3–5 AEs were higher across treatment groups. However, substantial heterogeneity across studies and the non-randomized design of most included trials limit the robustness of these pooled estimates and warrant cautious interpretation of the efficacy and safety findings.

Given the poor prognosis of advanced EC, new treatment strategies are being investigated, including exploring the combination of chemotherapy and immunotherapy for potential synergistic effects. In RUBY Part 1, dostarlimab combined with carboplatin and paclitaxel significantly improved PFS in primary advanced or recurrent EC, particularly in the MMRd–MSI-H (Microsatellite Instability-High) group (Hazard Ratio (HR): 0.28; 95% CI, 0.16–0.50; $p < 0.001$) [4]. Moreover, in the NRG-GY018 trial, pembrolizumab combined with chemotherapy showed promising results in both MMRd and Mismatch Repair Proficient (pMMR) settings [3]. Despite

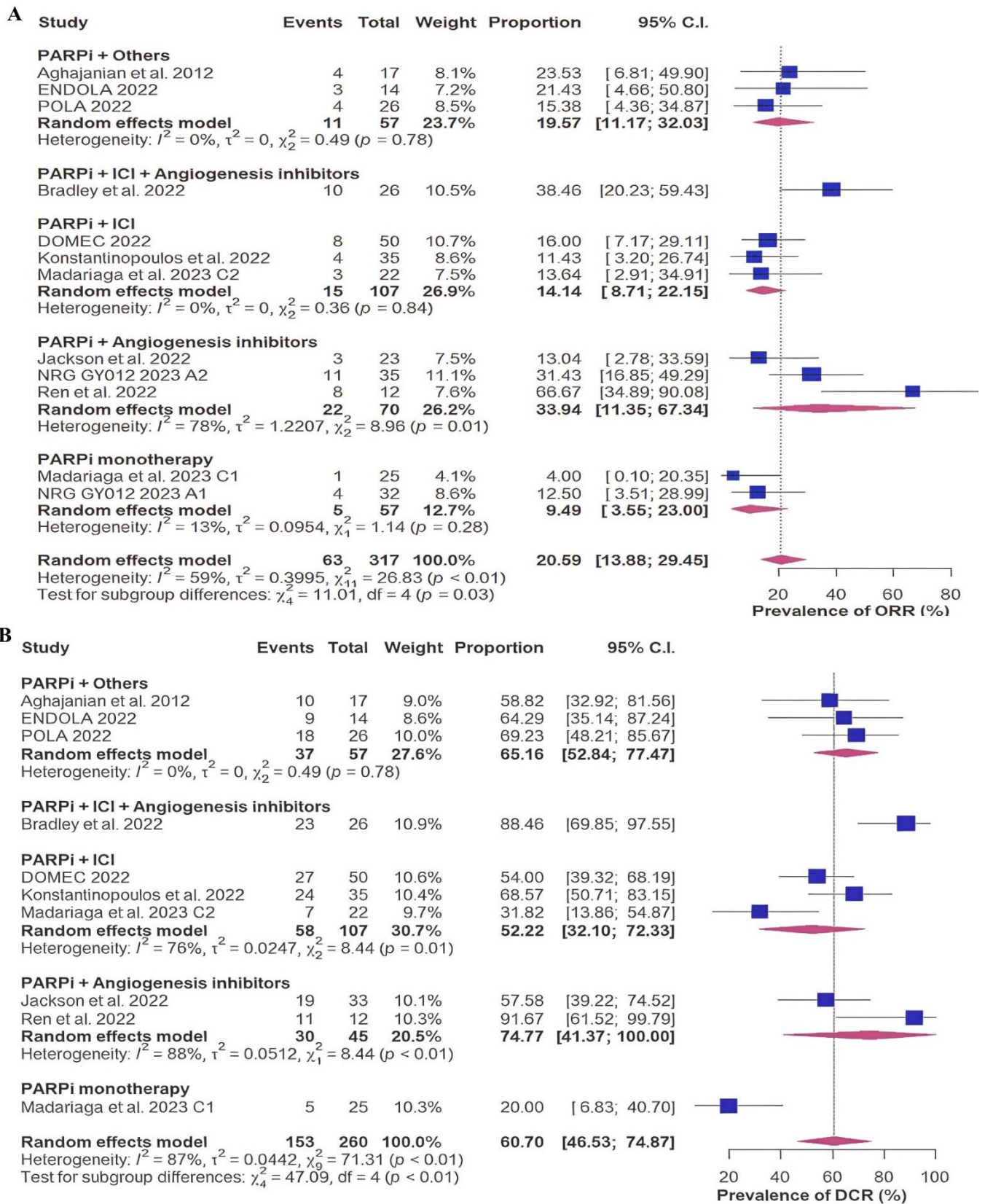
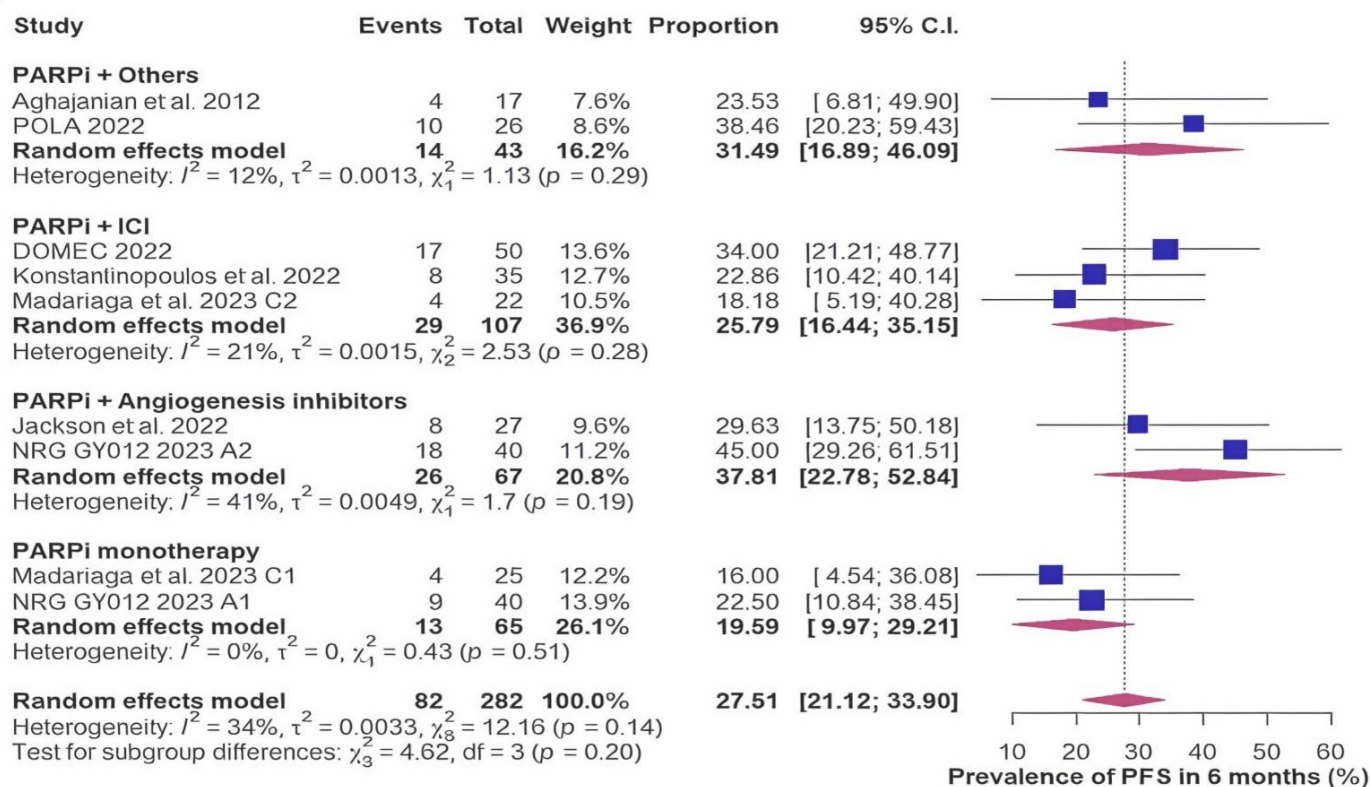


FIGURE 2. Treatment efficacy and response rates in the study population [14–22]. (A) Objective response rate (ORR) in the overall population, ORR stratified by administered treatment. (B) Disease control rate (DCR) in the overall population, DCR stratified by administered treatment. PARPi, Poly (ADP-ribose) polymerase inhibitors; ICI, immune-checkpoint inhibitors; CI, Confidence Interval; df , degrees of freedom.

A



B

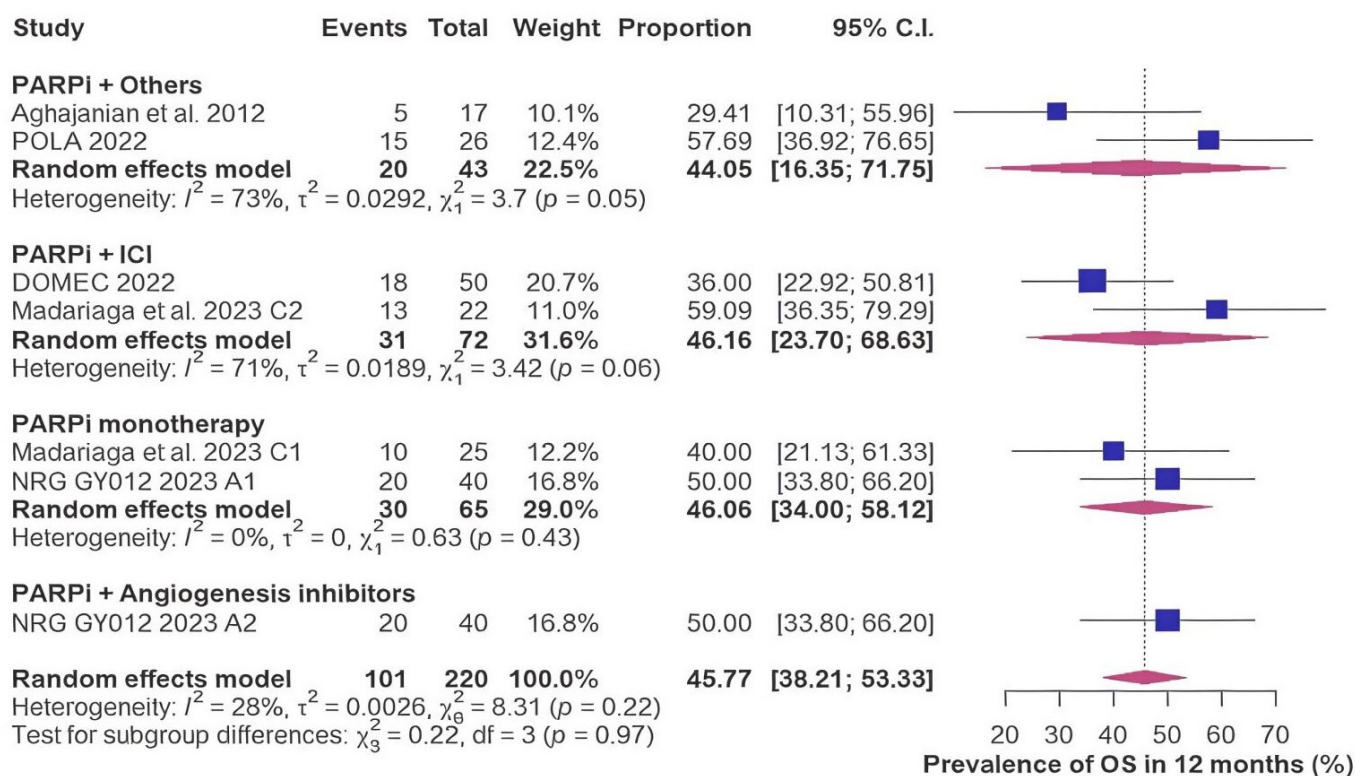


FIGURE 3. Survival outcomes [14, 16, 18–20, 22, 23]. (A) Progression-free survival (PFS) at 6 months in the overall population. (B) Overall survival (OS) rate at 12 months in the overall population. PARPi, Poly (ADP-ribose) polymerase inhibitors; ICI, immune-checkpoint inhibitors; CI, Confidence Interval; OS, overall survival; df , degrees of freedom.

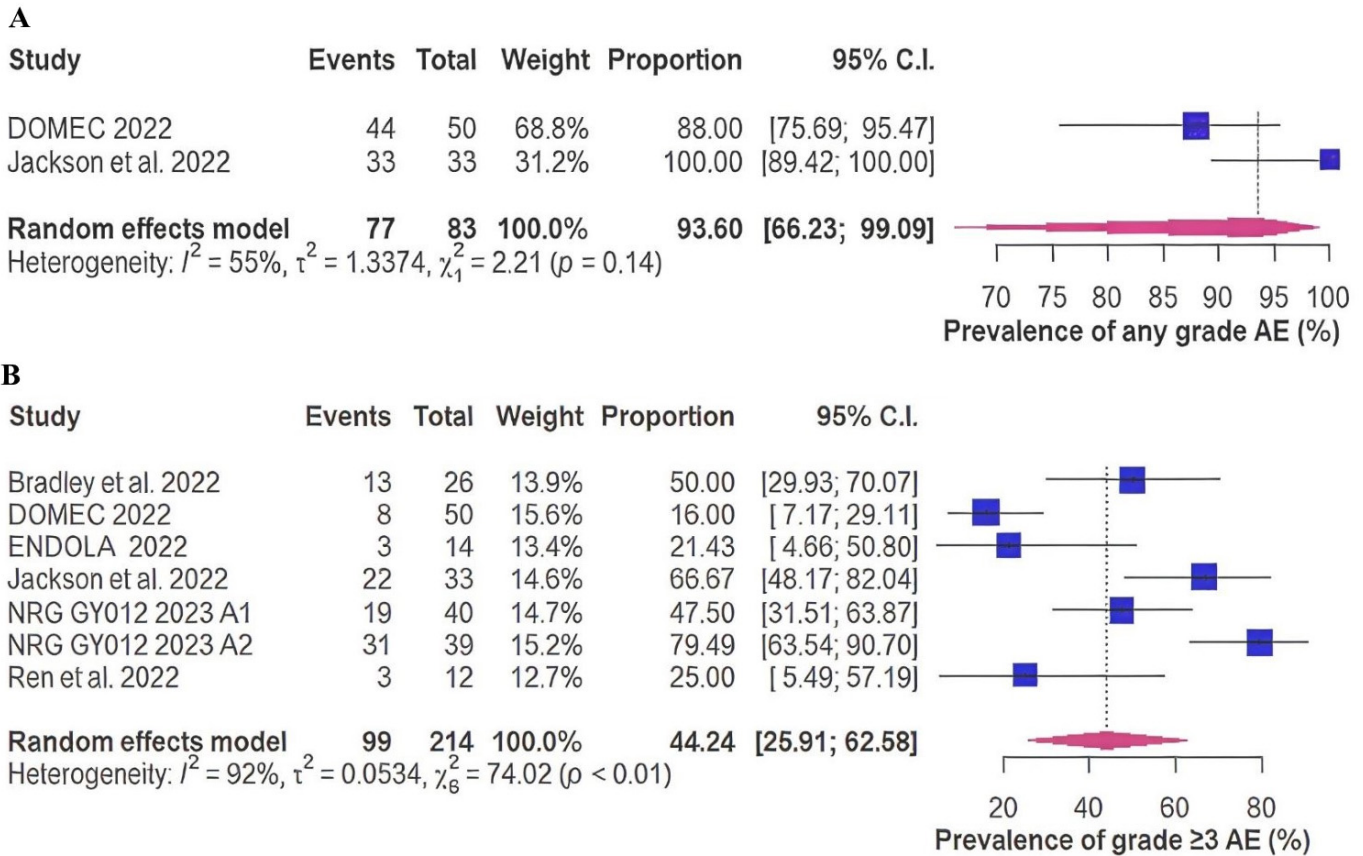


FIGURE 4. Safety profile and adverse events [15–18, 21, 23]. (A) Adverse events (any grade) in the overall population. (B) Adverse events (grade ≥ 3) in the overall population. AE, adverse events; CI, Confidence Interval.

significant advances, ICIs are the most effective in tumors that are MMRd/MSI-H, or a TMB-H. There is a need for therapeutic options for other molecular patterns.

PARPi represent a significant advancement in the treatment of OC, particularly for patients with BRCA mutations and HRR deficiencies [24]. BRCA-mutated OC patients showed significant PFS and OS benefits with PARPi maintenance in the first-line setting [25]. After this promising result in OC, their efficacy in other gynecological cancers has been explored. In the UTOLA trial, which assessed PARPi monotherapy maintenance in advanced/metastatic EC patients after first-line platinum-based chemotherapy, olaparib didn't enhance overall PFS compared with placebo. However, in tumors with HRD, olaparib showed a statistically significant improvement in median PFS: 5.4 vs. 3.6 months (HR: 0.59; 90% CI, 1.8–4.9; $p = 0.02$). There were no significant differences in OS across all subgroups [26]. However, in a recent randomized phase II trial by Corr *et al.* [27] maintenance rucaparib significantly prolonged median PFS compared with placebo (28.1 vs. 8.7 months; HR: 0.45, 95% CI, 0.24–0.87; $p = 0.02$). Furthermore, median OS was not reached in the rucaparib cohort compared with the 28.4 months in the placebo arm (HR: 0.43, 95% CI, 0.18–1.05).

There is growing interest in combining PARPi with other therapeutic modalities to enhance their efficacy. Combinations of ICI, angiogenesis inhibitors, and other targeted therapies are being explored to address resistance mechanisms and improve clinical outcomes. Preclinical studies have indicated that com-

binning angiogenesis inhibitors with PARPi shows synergistic activity, possibly due to the reduction of HRR gene activity in response to hypoxia [28–30]. Kaplan *et al.* [28] showed that cediranib also directly affects DNA repair pathways in cancer cells. This makes the cells more responsive to PARPi, suggesting a targeted treatment approach. Our meta-analysis revealed that the combination of PARPi with angiogenesis inhibitors yielded the highest ORR (33.94%) and DCR (74.77%) compared with other combination treatments. However, it's worth noting that most of the studies included were single-arm analyses with small sample sizes [18, 21]. The only RCT was NRG-GY012 trial, where patients were assigned to receive cediranib alone, olaparib, or a combination of olaparib and cediranib. The cediranib and olaparib combination exhibited moderate clinical efficacy but did not reach statistical significance. The median PFS was 3.8 months for the cediranib group, 2.0 months for the olaparib group (HR: 1.45; 95% CI, 0.91–2.3; $p = 0.935$), and 5.5 months for the combination of olaparib and cediranib (HR: 0.7; 95% CI, 0.43–1.14; $p = 0.064$). Molecular patterns did not correlate with treatment response [23].

Furthermore, the combination of PARPi with ICI may have the potential to overcome several immune evasion strategies [31]. In our analysis, the combination treatment with ICI and PARPi showed an ORR of 14.14% and DCR of 55.08%. DUO-E, the first trial to combine durvalumab and olaparib as maintenance treatment in EC, demonstrated significantly improved PFS compared with chemotherapy

plus placebo (HR: 0.55; 95% CI, 0.43–0.69; $p < 0.0001$). Regardless of MMR status, the durvalumab arm showed a PFS benefit over the control, with the greatest benefit observed in the MMRd subgroups. However, combining chemotherapy with durvalumab and olaparib doesn't seem to enhance outcomes compared with chemotherapy plus durvalumab alone, although the study wasn't designed for direct comparison [32]. In an update on Part 2 of the RUBY trial, the addition of niraparib to dostarlimab in the maintenance setting significantly improved PFS in first-line advanced or recurrent EC, compared with chemotherapy alone. In the overall population and the mismatch repair-proficient/Microsatellite Stable (MMRp/MSS) population, dostarlimab plus chemotherapy followed by dostarlimab plus niraparib significantly reduced the risk of disease progression or death by 40% (HR = 0.60, 95% CI = 0.43–0.82) and 37% (HR = 0.63, 95% CI = 0.44–0.91), respectively, and improved median PFS by 6.2 months (14.5 vs. 8.3 months) and 6.0 months (14.3 vs. 8.3 months), respectively.

Despite increasing interest in combination strategies involving PARP inhibitors, the available clinical evidence remains limited and is predominantly derived from small, early-phase, and non-randomized studies. Consequently, these findings should be interpreted with caution, and definitive conclusions regarding optimal combination regimens, appropriate patient selection, and long-term safety cannot yet be established. Well-designed, large-scale randomized controlled trials are therefore essential to validate these preliminary results and to clarify the role of PARP inhibitor-based combination therapies in the treatment landscape of EC.

In our analysis of subgroups, we observed no statistically significant difference in treatment response across different molecular profiles (Supplementary Figs. 1,2). This can be attributed to the heterogeneous patient populations in the studies, small sample sizes, inconsistencies in evaluating molecular profiles across studies and diverse tumor characteristics. To overcome these challenges, future research should focus on standardized methodologies and larger datasets to better understand the relationship between molecular profiles and treatment outcomes.

Compared with ovarian cancer, where PARP inhibitors have demonstrated robust and well-established clinical efficacy, the activity of PARP inhibitors in EC appears to be more limited. The response rates observed in the included studies are modest, and this difference may reflect underlying biological heterogeneity, differences in homologous recombination deficiency prevalence, and prior treatment exposure. Therefore, the efficacy outcomes reported in this analysis should be interpreted with caution, and direct extrapolation from ovarian cancer to EC is not appropriate.

5. Limitations

The primary limitation of our meta-analysis was the limited number of available RCTs, which reduced the statistical power of our findings. Additionally, the heterogeneity in patient populations, including variations in disease characteristics and prior treatments, along with the diverse treatment regimens,

particularly the different PARPi combinations, presented significant challenges in ensuring consistent comparisons. Another limiting factor in the non-RCT studies was the small sample size, which could introduce bias. These methodological constraints increase the risk of bias and make it difficult to draw definitive conclusions regarding the efficacy and safety of PARP inhibitors in this setting. Moreover, our analysis mainly involved white participants, so caution is needed when applying these results to other populations. In addition, hazard ratios for PFS and OS could not be pooled because these outcomes were not consistently reported across the included studies, most of which were single-arm or early-phase trials.

6. Conclusions

Although our results suggest that PARP inhibitor-based combination treatments may offer improved efficacy over monotherapy in patients with advanced or recurrent EC, the response rates remain modest, and the frequency of grade 3–5 adverse events indicates that the clinical benefit of PARP inhibitors in this setting is still uncertain. However, given the limitations of the available data, these findings should be interpreted with caution, and thus these findings should be considered hypothesis-generating rather than definitive. Further well-designed clinical trials are necessary to validate the efficacy of these combinations. Larger studies in EC patients are required to identify the most effective treatment regimens. Additionally, efforts to identify predictive biomarkers for patient selection and to better understand the molecular characteristics and resistance mechanisms are essential to fully explore the therapeutic potential of PARPi in this setting.

ABBREVIATIONS

ARID1A, AT-Rich Interaction Domain 1A; ATM, ATM Serine/Threonine Kinase; *BRCA1/2*, BRCA1/2 DNA Repair Associated; HR, Hazard Ratio; HRD, Homologous Recombination Deficiency; HRR, Homologous Recombination Repair; ICIs, Immune-checkpoint inhibitors; MMRd, Mismatch Repair Deficient; *MRE11*, MRE11 Double Strand Break Repair Nuclease; MSI-H, Microsatellite Instability-High; MSS, Microsatellite Stable; *NBN*, Nibrin; NGS, Next-Generation Sequencing; PALB2, Partner and Localizer of BRCA2; PARP/PARPi, Poly (ADP-ribose) Polymerase/inhibitor; MMRp, Mismatch Repair Proficient; POLE, DNA Polymerase Epsilon, Catalytic Subunit; *PTEN*, Phosphatase and Tensin Homolog; *RAD50*, RAD50 Double Strand Break Repair Protein; *RAD51*, RAD51 Recombinase; TCGA, The Cancer Genome Atlas; TMB-H, Tumor Mutational Burden-High; *TP53*, Tumor Protein p53; ORR, objective response rate; CI, Confidence Interval; DCR, disease control rate; OS, overall survival; PFS, progression-free survival; EC, endometrial cancer; PROSPERO, International Prospective Register of Systematic Reviews; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; AEs, adverse events; RCT, Randomized Controlled Trial.

AVAILABILITY OF DATA AND MATERIALS

The data for this study were systematically collected and organized into a comprehensive database. The data that support the findings of this study are not publicly available due to participant confidentiality but can be made accessible from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

TA and GMS—conceptualization; methodology. TA, GMS and HS—provision of study materials. TA and YAW—collection and congregation of data, data analysis and interpretation. FMH—writing original draft preparation, writing review and editing. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable. An ethics statement is not applicable because this study is based exclusively on published literature.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at <https://oss.ejgo.net/files/article/2110253924382326784/attachment/Supplementary%20material.zip>.

REFERENCES

- [1] Antill Y, Kok PS, Robledo K, Yip S, Cummins M, Smith D, *et al.*; Australia New Zealand Gynaecological Oncology Group (ANZGOG). Clinical activity of durvalumab for patients with advanced mismatch repair-deficient and repair-proficient endometrial cancer. A nonrandomized phase 2 clinical trial. *Journal for ImmunoTherapy of Cancer*. 2021; 9: e002255.
- [2] Konstantinopoulos PA, Luo W, Liu JF, Gulhan DC, Krasner C, Ishizuka JJ, *et al.* Phase II study of avelumab in patients with mismatch repair deficient and mismatch repair proficient recurrent/persistent endometrial cancer. *Journal of Clinical Oncology*. 2019; 37: 2786–2794.
- [3] Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, *et al.* Pembrolizumab plus chemotherapy in advanced endometrial cancer. *The New England Journal of Medicine*. 2023; 388: 2159–2170.
- [4] Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novák Z, Black D, *et al.*; RUBY Investigators. Dostarlimab for primary advanced or recurrent endometrial cancer. *The New England Journal of Medicine*. 2023; 388: 2145–2158.
- [5] Makker V, Colombo N, Casado Herráez A, Santin AD, Colomba E, Miller DS, *et al.*; Study 309—KEYNOTE-775 Investigators. Lenvatinib plus pembrolizumab for advanced endometrial cancer. *The New England Journal of Medicine*. 2022; 386: 437–448.
- [6] O'Malley DM, Krivak TC, Kabil N, Munley J, Moore KN. PARP inhibitors in ovarian cancer: a review. *Targeted Oncology*. 2023; 18: 471–503.
- [7] Yamamoto H, Hirasawa A. Homologous recombination deficiencies and hereditary tumors. *International Journal of Molecular Sciences*. 2021; 23: 348.
- [8] Heeke AL, Pishvaian MJ, Lynce F, Xiu J, Brody JR, Chen WJ, *et al.* Prevalence of homologous recombination-related gene mutations across multiple cancer types. *JCO Precision Oncology*. 2018; 2: 1–13.
- [9] MacKay HJ, Levine DA, Bae-Jump VL, Bell DW, McAlpine JN, Santin A, *et al.* Moving forward with actionable therapeutic targets and opportunities in endometrial cancer: NCI clinical trials planning meeting report on identifying key genes and molecular pathways for targeted endometrial cancer trials. *Oncotarget*. 2017; 8: 84579–84594.
- [10] 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. *The BMJ*. 2021; 372: n71.
- [11] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European Journal of Cancer*. 2009; 45: 228–247.
- [12] 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. *The BMJ*. 2019; 366: 14898.
- [13] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *The BMJ*. 2016; 355: i4919.
- [14] Aghajanian C, Sill MW, Secord AA, Powell MA, Steinhoff M. Iniparib plus paclitaxel and carboplatin as initial treatment of advanced or recurrent uterine carcinosarcoma: a Gynecologic Oncology Group Study. *Gynecologic Oncology*. 2012; 126: 424–427.
- [15] Bradley WH, Hayes MP, Taylor N, Rader JS, Bishop E, Hopp E, *et al.* An open label, nonrandomized, multisite phase II trial combining bevacizumab, atezolizumab, and rucaparib for the treatment of previously treated recurrent and progressive endometrial cancer. *Journal of Clinical Oncology*. 2022; 40: 5510.
- [16] Post CCB, Westermann AM, Boere IA, Witteveen PO, Ottevanger PB, Sonke GS, *et al.* Efficacy and safety of durvalumab with olaparib in metastatic or recurrent endometrial cancer (phase II DOME trial). *Gynecologic Oncology*. 2022; 165: 223–229.
- [17] You B, Leary A, Rodrigues M, Follana P, Abdeddaim C, Joly F, *et al.* Safety and efficacy of olaparib combined to metronomic cyclophosphamide and metformin in recurrent advanced/metastatic endometrial cancer patients: ENDOLA trial. *Cancer Research*. 2022; 82: CT005.
- [18] Jackson CG, Moore KN, Cantrell L, Erickson BK, Duska LR, Richardson DL, *et al.* A phase II trial of bevacizumab and rucaparib in recurrent carcinoma of the cervix or endometrium. *Gynecologic Oncology*. 2022; 166: 44–49.
- [19] Konstantinopoulos PA, Gockley AA, Xiong N, Krasner C, Horowitz N, Campos S, *et al.* Evaluation of treatment with talazoparib and avelumab in patients with recurrent mismatch repair proficient endometrial cancer. *JAMA Oncology*. 2022; 8: 1317–1322.
- [20] Poveda A, Lopez-Reig R, Oaknin A, Redondo A, Rubio MJ, Guerra E, *et al.* Phase 2 trial (POLA Study) of lurbinectedin plus olaparib in patients with advanced solid tumors: results of efficacy, tolerability, and the translational study. *Cancers*. 2022; 14: 915.
- [21] Ren YL, Lu J, Tian WJ, Li H, Wang H. Combination of niraparib and anlotinib in patients with recurrent or metastatic endometrial cancer: an open-label, single-arm, two-stage, phase II study. *International Journal of Gynecological Cancer*. 2022; 32: A107.
- [22] Madariaga A, Garg S, Tchakian N, Dhani NC, Jimenez W, Welch S, *et al.* Clinical outcome and biomarker assessments of a multi-centre phase II trial assessing niraparib with or without dostarlimab in recurrent endometrial carcinoma. *Nature Communications*. 2023; 14: 1452.
- [23] Rimel BJ, Enserro D, Bender DP, Jackson CG, Tan A, Alluri N, *et al.* NRG-GY012: randomized phase 2 study comparing olaparib, cediranib, and the combination of cediranib/olaparib in women with recurrent,

- persistent, or metastatic endometrial cancer. *Cancer*. 2024; 130: 1234–1245.
- [24] 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 Oncology*. 2023; 9: 1230–1237.
- [25] 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. *The Lancet Oncology*. 2021; 22: 1721–1731.
- [26] Lobbedez FJ, Leary A, Ray-Coquard IL, Asselain B, Rodrigues MJ, Gladiéff L, *et al.* LBA42 Olaparib vs placebo as maintenance therapy after platinum-based chemotherapy in advanced/metastatic endometrial cancer patients: the GINECO randomized phase IIb UTOLA trial. *Annals of Oncology*. 2023; 34: S1283–S1284.
- [27] Corr BR, Haggerty A, Gysler SM, Taylor S, Behbakht K, Alldredge J, *et al.* A phase II, randomized, double-blind study of the use of rucaparib vs. placebo maintenance therapy in metastatic and recurrent endometrial cancer. *Gynecologic Oncology*. 2025; 200: 58–67.
- [28] Kaplan AR, Gueble SE, Liu Y, Oeck S, Kim H, Yun Z, *et al.* Cediranib suppresses homology-directed DNA repair through down-regulation of BRCA1/2 and RAD51. *Science Translational Medicine*. 2019; 11: eaav4508.
- [29] Bindra RS, Schaffer PJ, Meng A, Woo J, Måseide K, Roth ME, *et al.* Down-regulation of Rad51 and decreased homologous recombination in hypoxic cancer cells. *Molecular and Cellular Biology*. 2004; 24: 8504–8518.
- [30] Liu JF, Brady MF, Matulonis UA, Miller A, Kohn EC, Swisher EM, *et al.* Olaparib with or without cediranib versus platinum-based chemotherapy in recurrent platinum-sensitive ovarian cancer (NRG-GY004): a randomized, open-label, phase III trial. *Journal of Clinical Oncology*. 2022; 40: 2138–2147.
- [31] Lee EK, Konstantinopoulos PA. PARP inhibition and immune modulation: scientific rationale and perspectives for the treatment of gynecologic cancers. *Therapeutic Advances in Medical Oncology*. 2020; 12: 1758835920944116.
- [32] Westin SN, Moore K, Chon HS, Lee JY, Thomes Pepin J, Sundborg M, *et al.*; DUO-E Investigators. Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: the phase III DUO-E trial. *Journal of Clinical Oncology*. 2024; 42: 283–299.

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