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Comparative effectiveness and safety of treatment regimens for recurrent advanced ovarian cancer: a systematic review and network meta-analysis

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Abstract

Background The choice of treatment options for recurrent advanced ovarian cancer is very important. However, the most effective treatment options remain unclear.

Methods We searched the PubMed, Web of Science, and Cochrane Library databases and the proceedings of the last 5 years of several meetings on ovarian cancer according to the inclusion and exclusion criteria. Randomized controlled trials (RCTs) of recurrent treatment for advanced ovarian cancer with progression-free survival (PFS) were reticulated network meta-analyzed. RCTs were also analyzed for Grades 3 or higher drug-associated adverse events.

Results We included 24 RCTs involving 6,250 patients with advanced recurrent ovarian cancer and a total of 10 treatment regimens. Our network meta-analysis revealed that the PARP plus anti-angiogenic regimen (Surface Under the Cumulative Ranking Curve, SUCRA 95.26%) outperformed eight other regimens and demonstrated a significant improvement in patient survival. The double immunotherapy plus chemotherapy regimen (SUCRA: 87.24%) showed strong efficacy. Additionally, the anti-angiogenic plus chemotherapy regimens (SUCRA: 60.14%), single anti-angiogenic regimens (SUCRA: 52.3%), and poly ADP-ribose polymerase regimens (SUCRA: 61.82%) demonstrated similar efficacy. Interestingly, immunotherapy plus chemotherapy regimens (SUCRA: 31.61%) showed a significant improvement compared to chemotherapy regimens, and double immunotherapy regimens (SUCRA: 36.49%) also demonstrated strong efficacy. However, single immunotherapy regimens (SUCRA: 8.53%) demonstrated limited efficacy. Finally, we found that the incidence of grade 3 or higher adverse reactions was low and manageable for all treatment options.

Conclusion This meta-analysis showed that the PARP plus anti-angiogenic regimen is superior to the other nine regimens in treating patients with advanced recurrent ovarian cancer and can significantly improve their survival. Our results show that the anti-angiogenic plus CT, single-agent anti-angiogenic, and single-agent PARP regimens have similar efficacies; therefore, clinical treatment plans can be adjusted based on the differences in side effects among the three regimens. The double immunotherapy regimen demonstrated superior efficacy compared to the single

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immunotherapy regimen, particularly in terms of patient survival. These results may offer new therapeutic options for patients with advanced recurrent ovarian cancer, particularly through the use of immunotherapy.

Trial registration PROSPERO (ID CRD420251007476) https://www.crd.york.ac.uk/PROSPERO/view/CRD420251007476.

Keywords Treatment regimens, Advanced recurrent, Ovarian cancer, Network meta-analysis

Background

Ovarian cancer is one of the most lethal and aggressive cancers affecting the female reproductive tract. Globally, 313,959 new cases of ovarian cancer are diagnosed each year, resulting in 207,252 deaths annually [1, 2]. Approximately 75% of patients are diagnosed at stage III/IV, with a 5-year survival rate of only 30% for advanced disease [3]. Platinum/paclitaxel-based chemotherapy, with or without bevacizumab, remains the first-line treatment for advanced ovarian cancer. Although the initial overall response rate (ORR) is 60–80%, 70% of patients experience recurrence within 3 years [3]. Recurrent patients may receive further platinum-based chemotherapy (response rate: 30-70%) and are classified as 'platinum-sensitive' if the platinum-free interval (PFI) exceeds 6 months post-treatment. Those with a PFI < 6 months are deemed 'platinum-resistant' and ineligible for platinum-based therapy [4].

The treatment landscape for advanced ovarian cancer has been reshaped by two major therapeutic advances: anti-angiogenic agents and PARP inhibitors. A review mentions that the combination of "personalized" approaches using antiangiogenic agents and PARP inhibitors affects survival in patients with recurrent disease and will help epithelial ovarian cancer become a chronic disease [5]. Bevacizumab, a VEGF-targeting monoclonal antibody, demonstrates significant efficacy when combined with platinum-based chemotherapy (e.g., paclitaxel/carboplatin), improving progression-free survival (PFS) and overall survival (OS) in recurrent disease [6, 7]. Its mechanism involves tumor vasculature normalization, which enhances chemotherapeutic drug delivery and cytotoxicity [8], particularly in BRCA-mutated patients (~25% of cases) who show heightened sensitivity to this combination therapy [9]. Parallelly, PARP inhibitors exploit homologous recombination repair deficiency (HRD), present in 50% of high-grade serous carcinomas [10, 11], by inducing synthetic lethality in BRCA1/2-mutated tumors through PARP enzyme trapping and DNA repair blockade [12]. While both strategies target molecular vulnerabilities (angiogenesis vs. DNA repair), critical knowledge gaps persist: (1) direct comparisons between anti-angiogenic monotherapy and PARP inhibitors remain limited, despite overlapping target populations (e.g., BRCA-mutated/HRD-positive cases); (2) the optimal integration of these modalities—whether as sequential monotherapies or combined regimens—requires rigorous evaluation, especially in non-BRCA-mutated cohorts where both approaches show heterogeneous responses.

Recurrent ovarian cancer is known as an "immune cold" tumor, owing to a lack of tumor antigens and an immunosuppressive tumor microenvironment [13]. Despite exhibiting a high tumor mutational burden (TMB), this malignancy demonstrates minimal responsiveness to monotherapy with programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors [14], which historically excluded it from immunotherapeutic strategies. Recent advancements reveal that combinatorial approaches integrating anti-PD-1/PD-L1 agents with immunomodulators (e.g., chemotherapy, anti-angiogenic agents, poly ADP-ribose polymerase [PARP] inhibitors, or adoptive cell therapies) may overcome therapeutic resistance. The NINJA trial demonstrated clinical benefits of immune checkpoint inhibitors as later-line therapy in recurrent disease, even when administered as monotherapy compared to conventional chemotherapy [15]. However, pooled evidence from meta-analyses underscores the suboptimal efficacy of single-agent PD-1/PD-L1 blockade in ovarian cancer [16]. Current consensus guidelines cautiously endorse PD-1/PD-L1 inhibitor-chemotherapy combinations as a viable option.

These emerging therapeutic paradigms present both opportunities and challenges. Key unresolved issues include optimization of combination regimens, identification of predictive biomarkers for patient stratification, and management of treatment-related toxicities. While existing agents demonstrate variable efficacy in advanced ovarian cancer, the lack of head-to-head comparisons hinders determination of the optimal therapeutic strategy. To address these uncertainties, we conducted a network meta-analysis evaluating the comparative efficacy and safety profiles of contemporary systemic therapies for advanced ovarian cancer.

Methods

This meta-analysis adhered to the preferred reporting items for systematic reviews and meta-analyses guidelines [17].

Search strategy and selection criteria

We searched PubMed, Web of Science, and Cochrane Library databases for randomized controlled trials (RCTs) on ovarian cancer according to the inclusion and exclusion criteria. We searched for RCTs on multilineage treatment of recurrent metastases in advanced ovarian cancer up to December 2024, as well as articles published in the last 5 years from the American Society of Clinical Oncology and the European Society for Medical Oncology. The search was limited to articles in the English language. We systematically searched the database using the following search terms: "ovarian cancer" or "ovarian plasmacytoma" or "ovarian tumor" and "recurrent" "advanced" or "metastatic," and "anti-angiogenic" or "bevacizumab" or "PDL1/PD1" or "PARP" or "olaparib" or "niraparib" or "immunotherapy" or "avelumab" or "nivolumab" or "durvalumab".

We used the following inclusion criteria: (1) prospective phase II or III RCTs; (2) patients with recurrent metastases after multiple lines of therapy or first-line therapy for advanced ovarian cancer, without differentiating between previous regimens and regimens that included one or more agents in the search; and (3) hazard ratio (HR) values that included patients with progression-free survival (PFS) and their 95% confidence intervals (CIs). The exclusion criteria were as follows: (1) studies with late first-line therapy; (2) single-arm studies; and (3) retrospective studies, meta-analyses, case reports, and reviews.

Data extraction

Data on study features were extracted independently by two researchers (XH and NZ) following a search strategy and then summarized. Disagreements were resolved through discussions. The following information was extracted: study name, study type, trial period, median follow-up time, number of patients included, and drug or regimen used. HRs and 95% confidence intervals (CIs) were extracted for each efficacy metric of PFS and grade 3–5 drug-related adverse events (AEs) when available. The most recently reported data were used when studies with multiple reported outcomes were available.

Statistical analysis

For the network meta-analysis (NMA) of randomized controlled trials (RCTs), we used the "Gemtc" package in R (version 4.4.0, released on 2024-04-24) for network mapping and statistical analysis. The hazard ratio (HR) and its 95% confidence intervals (CI) were used to calculate the log-transformed HR and its log standard errors. Both fixed-effects and random-effects models were considered to assess the robustness of our results, and the final analysis was conducted using the random-effects model, as we anticipated heterogeneity across studies. To evaluate the consistency of the network, we performed consistency testing by comparing direct and indirect estimates using a consistency model, and tested for potential inconsistency using the node-splitting method.

Drug efficacy was assessed by the Surface Under the Cumulative Ranking Curve (SUCRA) values, which range from 0 to 1. Higher SUCRA values indicate better efficacy, with values closer to 1 representing more effective treatments. Additionally, we performed sensitivity analyses by examining the impact of using different models (fixed-effects vs. random-effects) on the SUCRA rankings, which demonstrated the stability of our findings. Adverse effects of the treatment regimens were analyzed using single-regimen rate meta-analysis with the "forest" package in R (version 4.4.0, released on 2024-04-24), and the results were summarized visually through forest plots. This analysis allowed us to assess the comparative safety of the regimens.

The Cochrane Collaboration tool was used to evaluate the quality of included studies. Therefore, each study was categorized as high, low, or unclear risk. Data extraction and quality assessment were performed by two independent investigators, and disagreements were resolved by a third investigator after discussion (Supplement Fig. 1).

Results

Literature search yielded a total of 8,024 relevant studies. After screening the studies according to the inclusion and exclusion criteria, we included 24 RCTs involving 6,250 patients with advanced ovarian cancer who had undergone first-line treatment or in whom ovarian cancer recurred thereafter, and who were treated with 10 different regimens (Fig. 1). The characteristics of the 24 included studies are summarized in Table 1.

Network meta-analysis of RCTs

We conducted a network meta-analysis of the PFS of 24 RCTs, including ten regimens of anti-angiogenic plus CT (chemotherapy), PARP, PARP plus anti-angiogenic, anti-angiogenic, CT, placebo, double immunotherapy, double immunotherapy plus CT, single immunotherapy, and immunotherapy plus CT (Fig. 2).

SUCRA table shows that PARP plus anti-angiogenic regimen has the highest efficacy (95.26%), followed by double immunotherapy plus CT (87.24%), PARP regimen (61.82%), anti-angiogenic plus CT regimen (60.14%) and anti-angiogenic regimen (58.42%) shows similar efficacy; Interestingly, immunotherapy plus CT (52.3%) showed a significant improvement over CT (31.61%), and double immunotherapy (36.49%) also showed stronger results. However, the worst efficacy was found in the single immunotherapy regimen (8.53%). SUCRA of PFS for the different treatment regimens are shown in Table 2.

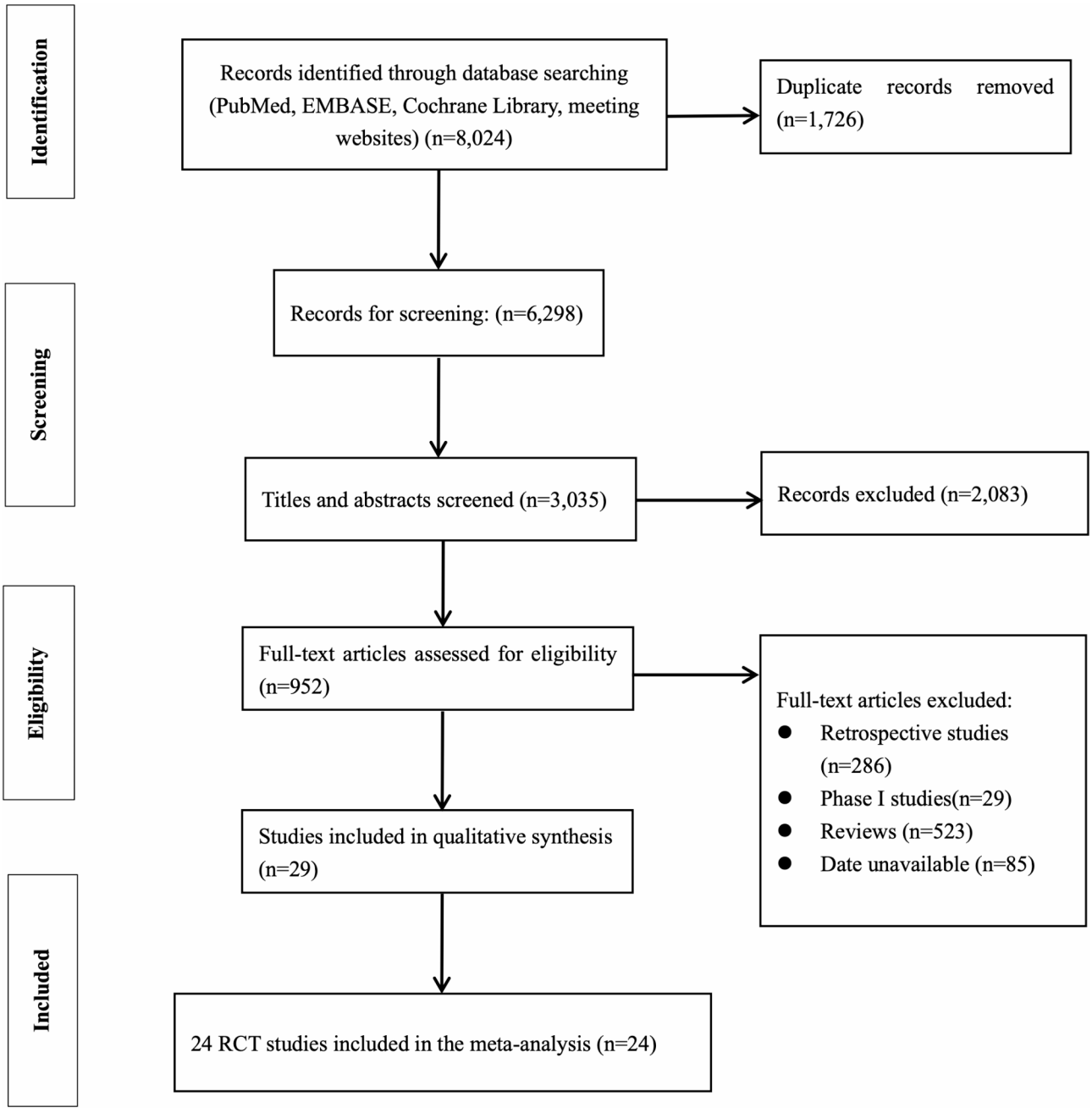


Fig. 1 Search string and flow charts for filtering and research selection

In the rank plots, we found that the PARP plus antiangiogenic regimen had significantly better efficacy than several other regimens or therapeutic strategies, that dual immunotherapy plus CT was very effective. The area under the curve was comparable in the PARP, anti-angiogenic plus CT, and anti-angiogenic regimen. Unfortunately, our results showed little difference between the single immunotherapy and placebo regimens. However, the double immunotherapy plus CT regimen achieved a good therapeutic effect (Fig. 3A). We also compared the differences in PFS between the two regimens (Fig. 3B).

To further determine the optimal treatment regimen, we found from the forest plot that the PARP plus anti-angiogenic regimen was significantly better than several other regimens, except for the double immunotherapy plus CT and immunotherapy plus CT regimens. In the anti-angiogenic regimen, it was significantly better than the placebo (HR = 2.3, 95%CI, 1.1–4.9) and single immunotherapy regimens (HR = 2.1, 95%CI, 1.1–4.0). In the anti-angiogenic plus CT regimen, it was significantly better than the placebo (HR = 2.3, 95%CI, 1.1–4.8) and single immunotherapy regimens (HR = 2.2, 95%CI, 1.2–3.8).

Table 1 Characteristics of the randomized trials included in the meta-analysis

Study	Years	Phase	Regimens	Patients, (*N*)	PFS (HR, 95% CI)		
NINJA	2021	III	Nivolumab	157	1.50	1.20	1.90
			GEM or PLD	159			
AURELIA	2014	III	Bevacizumab plus CT (weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan)	179	0.48	0.38	0.60
			CT alone	182			
JGOG3023	2022	II	CT (PLD, or topotecan, or paclitaxel, or GEM)	51	0.54	0.32	0.90
			Bevacizumab plus CT	52			
GOG-0213	2017	III	Paclitaxel and carboplatin chemotherapy	337	0.63	0.53	0.74
			Paclitaxel and carboplatin chemotherapy plus bevacizumab	337			
JAVELIN Ovarian 200	2021	III	Avelumab plus PLD	188	0.78	0.59	1.24
			PLD	190			
			Avelumab	188	1.68	1.32	2.60
SOLO3	2020	III	Olaparib	178	0.62	0.43	0.91
			CT (PLD or paclitaxel or gemcitabine or topotecan)	88			
ARIEL4	2022	III	Rucaparib	233	0.64	0.49	0.84
			Standard-of-care chemotherapy (single-agent cisplatin or carboplatin, or platinum-doublet chemotherapy [carboplatin plus paclitaxel, carboplatin plus gemcitabine, or cisplatin plus gemcitabine]	116			
SOLO2	2017	III	Olaparib	196	0.30	0.22	0.41
			Placebo	99			
ARIEL3	2020	III	Rucaparib	375	0.66	0.53	0.82
			Placebo	189			
AVANOVA2	2019	II	Niraparib plus bevacizumab	48	0.35	0.21	0.57
			Niraparib	49			
NRG Oncology	2020	II	Nivolumab	49	0.53	0.34	0.82
			Nivolumab plus ipilimumab	51			
MITO 11	2015	II	Weekly Paclitaxel	36	0.42	0.25	0.69
			Paclitaxel plus Pazopanib	37			
TRINOVA-2	2017	III	PLD	109	0.92	0.68	1.24
			PLD plus Trebananib	114			
TRIAS	2018	II	Topotecan and placebo	89	0.60	0.43	0.83
			Topotecan and Sorafenib	83			
Debra L. Richardson	2018	II	Paclitaxel	52	0.84	0.57	1.22
			Paclitaxel plus Pazopanib	54			
TRINOVA-1	2016	III	Weekly Paclitaxel	458	0.70	0.61	0.80
			Trebananib Plus Weekly Paclitaxel	461			
M.R. Hall	2020	II	Oral Cyclophosphamide	55	0.91	0.62	1.32
			Oral Cyclophosphamide plus Nintedanib	59			
SWOG S0904	2014	II	Docetaxel	66	0.99	0.69	1.42
			Vandetanib	63			
Ursula A. Matulonis	2019	II	weekly paclitaxel	54	1.11	0.77	1.61
			Cabozantinib	57			
GOG_3018	2023	III	Ofra-Vec Plus Paclitaxel	204	1.032	0.83	1.29
			Placebo Plus Paclitaxel	205			
OCTOVA	2023	II	Paclitaxel only	46	0.89	0.72	1.09
			Olaparib	46			
KGOG 3045	2024	II	D + T + CT(durvalumab + tremelimumab + single-agent chemotherapy)	35	0.435	0.23	0.82
			D + CT	23			
Emily_M	2023	II	Tremelimumab plus durvalumab, followed by durvalumab	38	0.8	0.47	1.37
			Tremelimumab plus durvalumab, followed by durvalumab	23			

Table 1 (continued)

Study	Years	Phase	Regimens	Patients, (*N*)	PFS (HR, 95% CI)		
Liu et al.	2019	II	Cediranib and olaparib	44	0.5	0.30	0.83
			Olaparib	46			

PLD: Pegylated Liposomal Doxorubicin. GME: Gemcitabine. CT: Chemotherapy

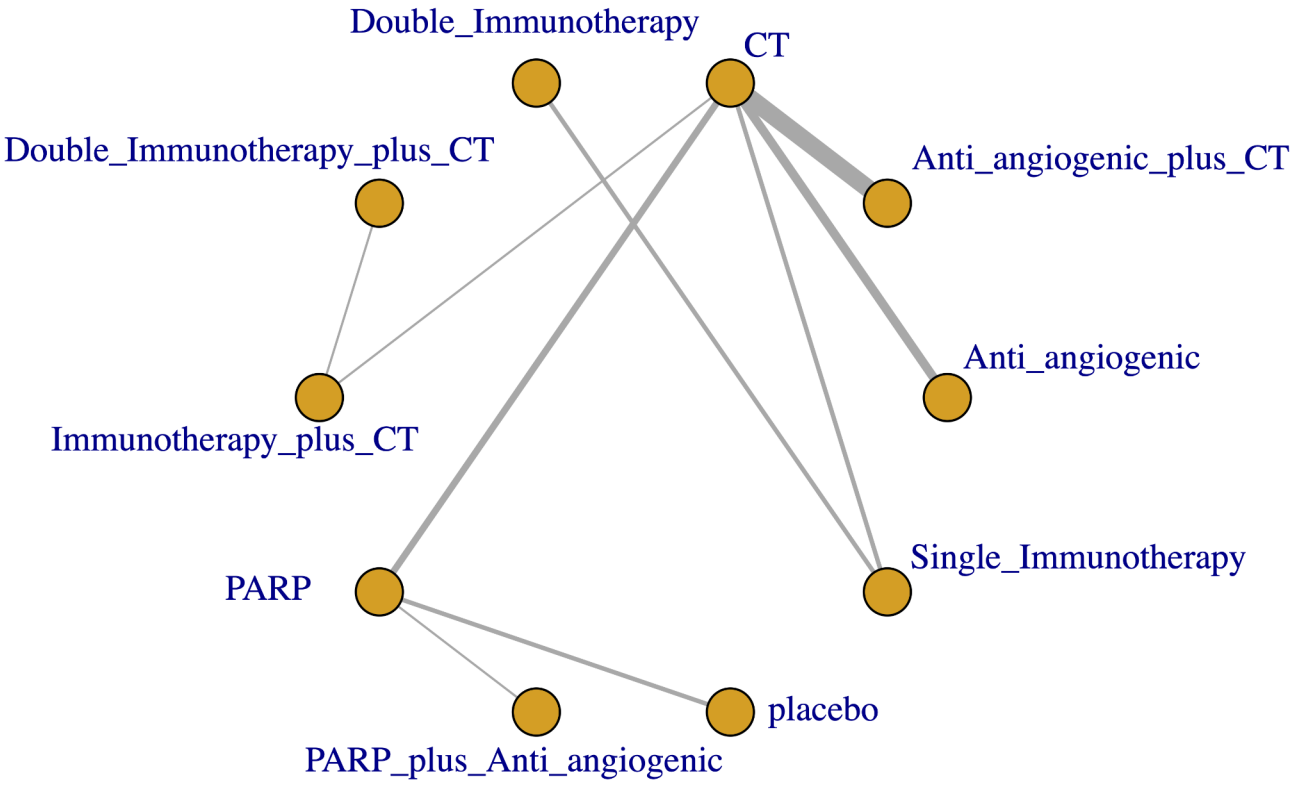


Fig. 2 The network meta-analysis of each intervention for progression-free survival. The width of the line represents the number of studies directly compared. The thicker the line, the greater the number of studies

Table 2 The cumulative ranking curve of each treatment regimens for progression-free survival

Treatment regimens	SUCRA (%)
PARP plus Anti-angiogenic	95.26
Double Immunotherapy_plus_CT	87.24
PARP	61.82
Anti-angiogenic_plus CT	60.14
Anti-angiogenic	58.42
Immunotherapy_plus_CT	52.30
Double Immunotherapy	36.49
CT	31.61
Single Immunotherapy	8.53
Placebo	8.17

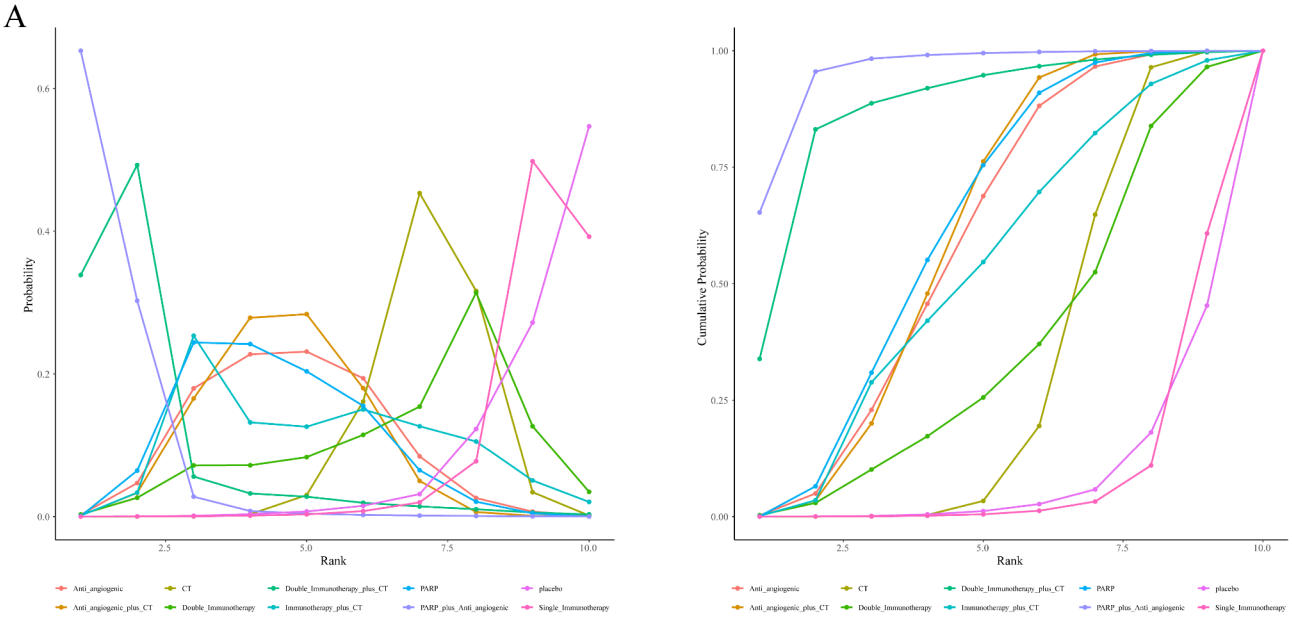
SUCRA: cumulative ranking curve, PARP: Poly ADP-ribosepolymerase inhibitor, CT: chemotherapy

In the double immunotherapy plus CT regimen, it was significantly better than the placebo (HR = 5.0, 95%CI, 1.3–20) and single immunotherapy regimens (HR = 4.7, 95%CI, 1.3–17), respectively. In the PARP regimen, it was significantly better than in the placebo (HR = 2.4, 95%CI, 1.4–4.0) and in single agent immunotherapy regimens (HR = 2.2, 95%CI, 1.2–4.3), it was significantly worse than in the PARP plus Anti angiogenic (HR = 0.15, 95%CI, 0.05–0.39). However, no significant benefits were observed in the CT, immunotherapy plus CT regimens (Fig. 4).

Adverse effects of different treatment regimens

We summarized top 10 Grade 3 or higher adverse reactions of different treatment regimens, which provide a clear picture of the adverse reactions in the lesser regimens of each study (Supplement Figs. 1–10). Immediately following the summary analysis of the adverse reactions to the ten treatment regimens, we found that

A



B

	Anti_angiogenic	Anti_angiogenic_plus_CT	CT	Double_Immunotherapy	Double_Immunotherapy_plus_CT	Immunotherapy_plus_CT	PARP	PARP_plus_Anti_angiogenic	placebo	Single_Immunotherapy
Anti_angiogenic	Anti_angiogenic	0.99 (0.62, 1.58)	1.34 (0.92, 1.99)	1.37 (0.58, 3.3)	0.46 (0.13, 1.62)	1.05 (0.45, 2.46)	0.96 (0.54, 1.7)	0.34 (0.12, 0.92)	2.27 (1.07, 4.97)	2.13 (1.13, 4.08)
Anti_angiogenic_plus_CT	1.01 (0.63, 1.6)	Anti_angiogenic_plus_CT	1.36 (1.05, 1.76)	1.39 (0.62, 3.15)	0.46 (0.14, 1.59)	1.06 (0.47, 2.37)	0.97 (0.59, 1.58)	0.34 (0.13, 0.89)	2.31 (1.14, 4.72)	2.16 (1.22, 3.82)
CT	0.75 (0.5, 1.09)	0.74 (0.57, 0.95)	CT	1.02 (0.47, 2.23)	0.34 (0.1, 1.13)	0.78 (0.36, 1.67)	0.71 (0.47, 1.08)	0.25 (0.1, 0.63)	1.69 (0.88, 3.3)	1.59 (0.95, 2.65)
Double_Immunotherapy	0.73 (0.3, 1.72)	0.72 (0.32, 1.62)	0.98 (0.45, 2.12)	Double_Immunotherapy	0.33 (0.08, 1.39)	0.76 (0.25, 2.25)	0.7 (0.29, 1.68)	0.24 (0.07, 0.81)	1.66 (0.6, 4.6)	1.55 (0.86, 2.77)
Double_Immunotherapy_plus_CT	2.19 (0.62, 7.65)	2.16 (0.63, 7.39)	2.94 (0.88, 9.77)	3.01 (0.72, 12.57)	Double_Immunotherapy_plus_CT	2.29 (0.9, 5.8)	2.1 (0.58, 7.5)	0.73 (0.16, 3.34)	4.98 (1.27, 19.66)	4.67 (1.26, 17.2)
Immunotherapy_plus_CT	0.96 (0.41, 2.23)	0.94 (0.42, 2.11)	1.28 (0.6, 2.75)	1.31 (0.44, 3.92)	0.44 (0.17, 1.11)	Immunotherapy_plus_CT	0.92 (0.38, 2.18)	0.32 (0.1, 1.06)	2.17 (0.8, 6)	2.04 (0.81, 5.12)
PARP	1.04 (0.59, 1.84)	1.03 (0.63, 1.69)	1.4 (0.92, 2.14)	1.43 (0.6, 3.48)	0.48 (0.13, 1.71)	1.09 (0.46, 2.61)	PARP	0.35 (0.15, 0.8)	2.38 (1.43, 4)	2.22 (1.15, 4.32)
PARP_plus_Anti_angiogenic	2.98 (1.09, 8.12)	2.94 (1.13, 7.7)	4 (1.59, 10.12)	4.09 (1.23, 13.74)	1.36 (0.3, 6.22)	3.11 (0.94, 10.35)	2.86 (1.25, 6.54)	PARP_plus_Anti_angiogenic	6.78 (2.59, 17.96)	6.36 (2.2, 18.36)
placebo	0.44 (0.2, 0.94)	0.43 (0.21, 0.88)	0.59 (0.3, 1.14)	0.6 (0.22, 1.66)	0.2 (0.05, 0.79)	0.46 (0.17, 1.25)	0.42 (0.25, 0.7)	0.15 (0.06, 0.39)	placebo	0.94 (0.4, 2.15)
Single_Immunotherapy	0.47 (0.24, 0.89)	0.46 (0.26, 0.82)	0.63 (0.38, 1.05)	0.64 (0.36, 1.16)	0.21 (0.06, 0.8)	0.49 (0.2, 1.23)	0.45 (0.23, 0.87)	0.16 (0.05, 0.45)	1.07 (0.47, 2.48)	Single_Immunotherapy

Fig. 3 The ranking of PFS and a league table of network meta-analysis of the 10 regimens. (**A**) Individual ranking plots of PFS between different regimens (Left). The results of the cumulative ranking curve for PFS between different regimens (Right). (**B**) League table of network analysis of regimens. PFS, progression-free survival. SUCRA, cumulative ranking curve. PARP: Poly ADP-ribose polymerase inhibitor, CT: chemotherapy

adverse reactions such as hypertension (10.86%) and fatigue (16.3%) were more frequent in the PARP plus anti-angiogenic regimen. The anti-angiogenic regimen had more frequent adverse reactions such as neutropenia (33.61%), thrombocytopenia (10.08%), and hypertension (3.06%). The probability of anemia in the PARP regimen was 21.1%, which was significantly higher than that of other side effects in the regimen. Anaemia (11.58%), neutropenia (12.75%), and diarrhoea (11.19%) were observed in the anti-angiogenic plus CT regimen. The CT regimen mostly focused on hematological toxicity, including anemia (11.64%), neutropenia (14.74%). Finally, we found that the single immunotherapy regimen had the lowest incidence of side effects, while the double immunotherapy and immunotherapy plus CT regimen had similar incidence of side effects (Fig. 5).

Discussion

Various approaches are available for treating relapsed ovarian cancer. In addition to secondary cytoreductive surgery, systematic treatment is based on a treatment-free platinum interval. There are currently no molecular biomarkers that can predict the efficacy of platinum rechallenge. Furthermore, several other factors should be evaluated, including tissue type, BRCA1/2-mutation status, previous line of therapy, previous treatment history and response, residual chemotherapy toxicity, and the patient's physical status [18]. Combination therapy may be preferred over single-agent therapy, resulting in a superior objective response rate and PFS, especially in platinum-resistant patients. However, the side effects associated with combination therapies must also be considered. It is not clear which regimen is best suited for patients with advanced recurrent ovarian cancer; therefore, we analyzed 10 regimens from 24 studies and quantified the probability that each regimen would be the best choice using network meta-analysis and SUCRA

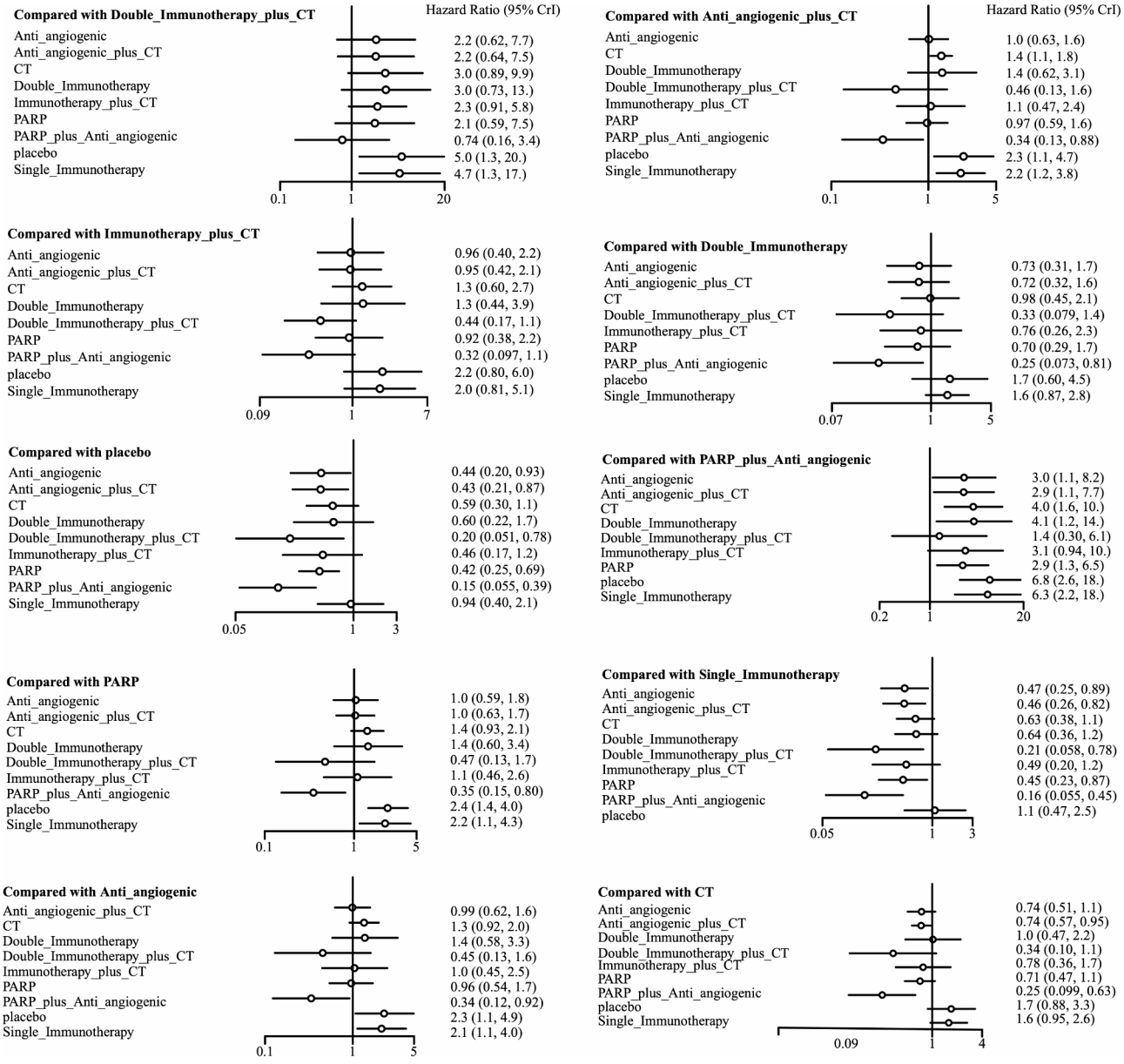


Fig. 4 Forest plot comparing PFS of different regimens

(lower surface of the cumulative ranking curve) values. The PARP inhibitor plus antiangiogenic regimen had the highest SUCRA value for overall survival (95.26%), indicating a 95.26% probability of being ranked first among all compared regimens. Although SUCRA values prioritize interventions based on probability of efficacy, their clinical interpretation requires a combination of toxicity and feasibility. These findings suggest that SUCRA-based grading should be used as a starting point for shared decision making and that clinicians should weigh the statistical superiority of regimens (as reflected by SUCRA) against patient-specific comorbidities, costs, and treatment preferences.

As one of the most attractive and promising targeted therapy reagents studied, both in relapsed ovarian cancer and in advanced settings, PARP inhibitors (PARPi) have changed the clinical management of ovarian cancer ensuring unprecedented advances. To date, three PARPi (olapalil, nilapalil, and lucapalil) have been approved for maintenance therapy in patients with platinum-rechallenged, high-grade fallopian ovarian cancer, regardless of BRCA1/2-mutation or HRD status, and as monotherapy for BRCA1/2 mutated relapsed ovarian cancer. There are several important questions regarding who should be treated, when, and how PARPi should be integrated into the ovarian cancer patient's treatment. For BRCA-mutated ovarian cancer patients, single-agent PARP

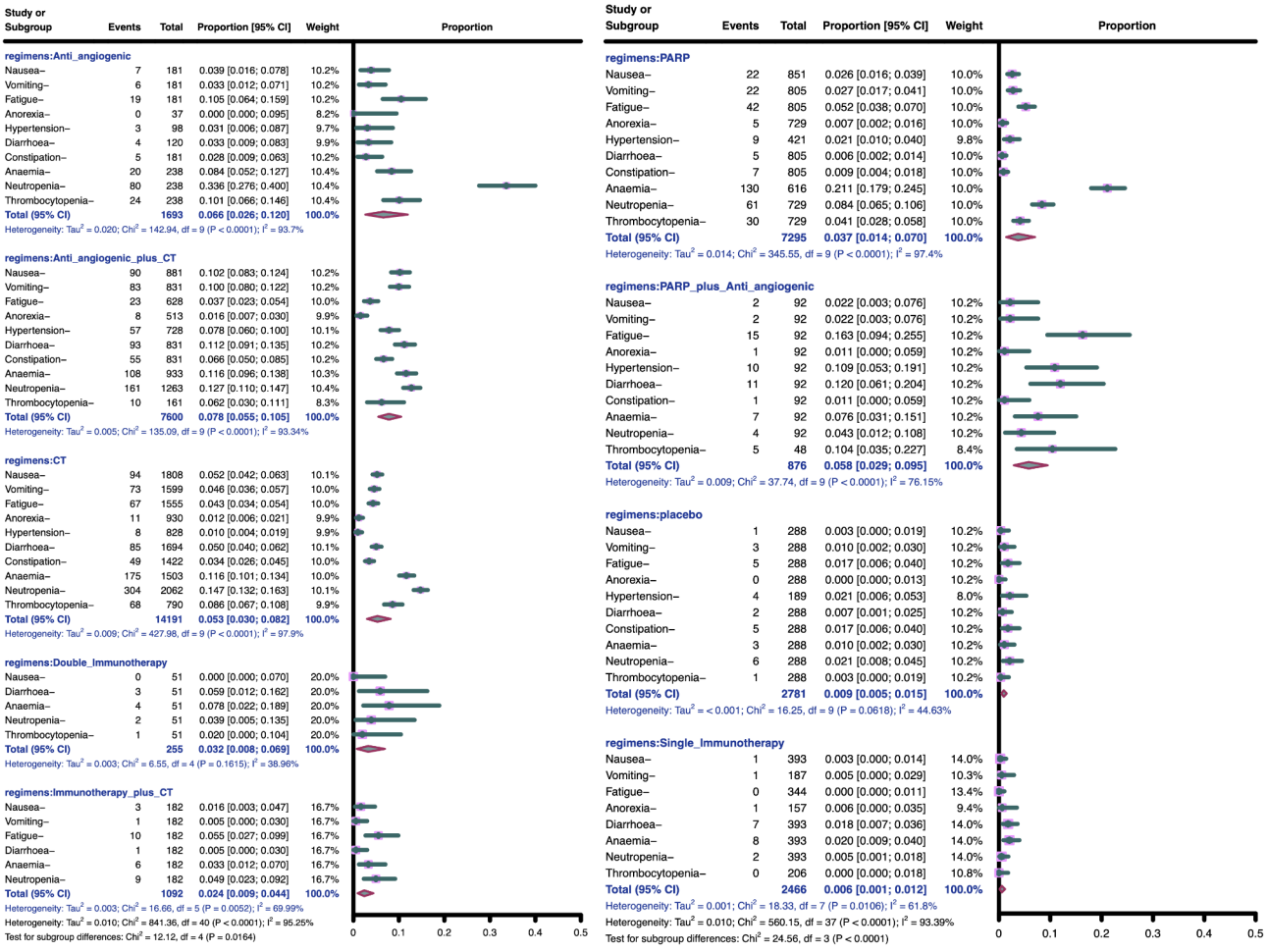


Fig. 5 Adverse effects of different treatment regimens

inhibitors show great antitumor activity and are considered appealing, providing a chemo-free treatment option [19, 20], in particular, the ORR was as high as 53.8% in the Study 10 and ARIEL2 studies. However, for BRCA wild-type replaced ovarian cancer, PARPi monotherapy is not considered a treatment option because of its low response rate [21]. Cumulative myelosuppression, neurotoxicity, and allergies to chemotherapy can be limiting factors in patients receiving multiple lines of platinum-based treatment, especially in patients with platinum-resistant ovarian cancer. To address these issues, combination chemotherapy-free regimens, such as PARPi plus anti-angiogenic agents, may be more effective than PARPi alone. AVANOVA2 study showed niraparib plus bevacizumab significantly improved PFS compared with niraparib alone (median PFS (mPFS) 11.9 vs. 5.5 months) [22]. Similarly, the CONCERTO study for patients with recurrent platinum-sensitive ovarian cancer showed that combination therapy with cediranib and olaparib significantly improved PFS versus olaparib alone (mPFS 16.5 vs. 8.2 months) [23]. The same combination was administered to heavily pretreated patients with recurrent platinum-resistant non-gBRCAm ovarian cancer, representing a particularly difficult-to-treat population. In this trial, the patients received a median of four lines of chemotherapy. The median PFS was 5.1 months, and the median OS was 13.2 months [24]. A large number of phase II/III trials on the combination of different PARPi and anti-angiogenic agents are ongoing when more solid evidence supports our choice. Angiogenesis plays a key role in the pathogenesis of ovarian cancer, with preclinical studies revealing synergistic mechanisms between PARPi iand antiangiogenic agents: (1) PARPi-mediated upregulation of VEGF-A promotes tumor angiogenesis, which PARPi may counteract through antiangiogenic effects; (2) Antiangiogenic therapy induces tumor hypoxia that downregulates homologous recombination repair-related genes (BRCA1/2, RAD51), enhancing PARPi sensitivity; (3) VEGFR3 inhibition directly reduces BRCA1/2 expression in tumor cells, inducing growth arrest; (4) Combined PARPi/antiangiogenic therapy suppresses both tumor cell invasion and microvascular endothelial tubule

formation. Clinically, the AVANOVA2 trial demonstrated superior efficacy of niraparib-bevacizumab combination versus monotherapy in recurrent ovarian cancer, independent of HRD or BRCA status [25, 26]. Our results showed that PARPi combined with antiangiogenic therapy performed best in terms of PFS, and although it is not the best recommendation of current guidelines, this combination strategy may be a viable alternative therapy for patients who are not candidates for or refuse chemotherapy. In addition, it may be a viable option for patients with platinum-resistant recurrent ovarian cancer and for patients who are resistant to PARPi based on the mechanism of resistance [27].

As a classic anti-angiogenic regent, rechallenge with bevacizumab combined with a platinum-based doublet significantly improved mPFS compared to chemotherapy alone in platinum-sensitive patients previously treated with bevacizumab [28]. The addition of bevacizumab to second- or third-line non-platinum chemotherapy in the AURELIA trial was also associated with improvements in the mPFS, tumor response rate, and the quality of life scale [29]. However, the overall survival (OS) benefits and toxicities associated with this combination remain controversial. In addition to antibodies against VEGF, the tyrosine kinase inhibitors pazopanib and sorafenib, administered concurrently with chemotherapy, resulted in significant improvement in the OS of platinum-resistant disease [30]. In our NMA, the efficacy of the anti-angiogenic plus CT and anti-angiogenic regimens ranked second only to that of the PARPi plus anti-angiogenic regimen. Our results show that PARP plus Anti-angiogenic has a cumulative ranking curve of 95.26%, which provides the best option for the treatment of advanced recurrent ovarian cancer. In recent years, novel anti-angiogenic agents have been evaluated in combination with PARPi or immune checkpoint inhibitors (ICIs). Because the majority of this combination is in phase I/II trials, the results are still pending or could not be included in the meta-analysis.

To date, immunotherapy has not been approved for the treatment of ovarian cancer. Despite the promising successes of immunotherapy in some "hot tumors", the efficacy of single-agent ICIs in relapsed ovarian cancer regardless of PD-L1 status has been disappointing [31]. This discrepancy may be attributed to the immunosuppressive tumor microenvironment (TME) unique to ovarian cancer, and these suppressor cells also prevent CD8 T cells from entering the tumor island [32, 33]. Key trials such as NINJA and JAVELIN Ovarian 200 demonstrated that single-agent ICIs (e.g., nivolumab) failed to significantly improve overall survival (OS) or PFS in relapsed ovarian cancer, regardless of PD-L1 status. For instance, in the NINJA trial, the median OS (mOS) of nivolumab was even shorter than that of chemotherapy (10.1 vs. 12.1 months) [13], while JAVELIN Ovarian 200 showed no statistical difference in mPFS (3.7 vs. 3.5 months) or mOS (15.7 vs. 13.1 months) between nivolumab combined with pegylated liposomal doxorubicin (PLD) and PLD alone [15, 34]. To overcome TME-mediated immunosuppression, combination strategies (e.g., immunotherapy + targeted therapy/chemotherapy) may remodel the TME and enhance antitumor immune responses. Bevacizumab plus PD-1 inhibitors achieved an ORR of 40.0% in platinum-sensitive relapsed patients (vs. 16.7% in platinum-resistant cases) [35], suggesting that vascular normalization may promote T-cell infiltration. HRD tumors with high PD-1 expression may respond better to immunotherapy + PARPi combinations. For example, the KEYNOTE-162 trial reported a mPFS of 3.4 months for pembrolizumab plus niraparib [36], while a KGOG 3045 sub-study showed that olaparib combined with durvalumab achieved a mPFS of 5.6 months in HRR-mutated platinum-resistant patients [37, 38]. Camrelizumab plus famitinib demonstrated promising antitumor activity in platinum-resistant patients [39, 40], and a phase Ib trial of anlotinib combined with the PD-L1 inhibitor TQB2450 highlighted synergistic potential [41]. Some studies, such as the KGOG 3045 trial evaluating durvalumab + tremelimumab + chemotherapy, showed a high response rate (87.3%) in reticulation analysis but no significant difference compared to the control group, possibly due to small sample size or population heterogeneity [42]. Most current evidence stems from phase II or small phase III trials (e.g., KGOG 3045), and key studies on dual/triple therapies were not included in this NMA. This result may be biased, but it may be a new direction for the future treatment of advanced recurrent ovarian cancer, which still needs to be confirmed by conducting more clinical trials in the future. The future may benefit from these three areas. First, prioritize populations based on HRD status, TIL density, or TMB (e.g., HRD tumors may benefit more from immunotherapy plus PARPi). Second, explore dosing/sequencing strategies (e.g., metronomic chemotherapy to reduce toxicity) and novel targets (e.g., LAG-3, TIM-3). Third, conduct large-scale studies on promising regimens (e.g., immunotherapy plus anti-angiogenics plus PARPi) to confirm survival benefits and safety.

Our analysis distinct toxicity profiles among treatment regimens, which carry significant clinical implications for patient management and quality of life. Particularly, hypertension (10.86%) and fatigue (16.3%), frequently observed with PARP inhibitor plus anti-angiogenic therapy, are not merely statistical outcomes but critical determinants of treatment tolerability. Hypertension in this context often necessitates aggressive antihypertensive management or dose modifications to prevent cardiovascular complications, while persistent fatigue may

profoundly impair patients' daily functioning and psychological well-being, potentially leading to treatment discontinuation. Similarly, our results demonstrate a high incidence of hematological toxicity, including neutropenia (33.61% with anti-angiogenic monotherapy) and anemia (21.1% with the PARP inhibitor regimen), which necessitate vigilant monitoring and supportive interventions, such as growth factor administration and blood transfusions. These events are associated with an increased risk of infection, hospitalization, and treatment delays. Notably, diarrhea (11.19%) in anti-angiogenic plus chemotherapy regimens may exacerbate malnutrition and electrolyte imbalances, further compromising patients' physical resilience.

This meta-analysis had several limitations. First, it was a meta-analysis based on the results of published trials rather than individual patient data, and there were differences in protocols and adjudication criteria between trials. Second, there are currently no OS data from several trials on the treatment of advanced ovarian cancer after recurrence, and many ongoing phase 2 trials are inconclusive. Finally, there were differences in the use of chemotherapeutic drug regimens, such as paclitaxel and platinum agents, after the recurrence of advanced ovarian cancer; however, the small number of trials did not allow for separate subgroup analyses of these regimens. Finally, the double immunotherapy plus CT regimen was only mentioned in one study, and although the results showed an efficiency rate of 87.3%, this finding may be biased. However, it could represent a new direction for the treatment of advanced ovarian cancer in the future.

Conclusion

This meta-analysis showed that the PARP plus anti-angiogenic regimen is superior to the other 9 regimens in patients with advanced recurrent ovarian cancer and can significantly improve patient survival. Our results show that the anti-angiogenic plus CT, single-agent anti-angiogenic, and single-agent PARP regimen have similar efficacies; therefore, clinical dosing can be adjusted to take into account the differences in side effects of the three regimens. The double immunotherapy regimen showed better efficacy than the single immunotherapy regimen. These results may provide new hope for immunotherapy for advanced recurrent ovarian cancer.

Supplementary Information

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Supplement Figure 1: Risk of bias graph and summary. **Supplement Figure 2–10**: Incidence of different side effects

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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