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The impact of PARP inhibitors in the whole scenario of ovarian cancer management: A systematic review and network meta-analysis

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ABSTRACT

Background: Carboplatin is still the cornerstone of the first-line treatment in advanced Epithelial Ovarian Cancer (aEOC) management and the clinical response to platinum-derived agents remains the major predictor of long-term outcomes.

Patient and methods: We aimed to identify the best treatment of the aEOC in terms of efficacy and safety, considering all treatment phases. A systematic literature search has been done to compare all treatments in aEOC population. Randomized trials with available survival and safety data published in the 2011–2022 timeframe were enclosed. Only trials reporting the BRCA or HRD (Homologous Recombination Deficiency) status were considered.

Data extraction and synthesis: A ranking of treatment schedules on the progression-free survival (PFS) endpoint was performed. The random-effect model was used to elaborate and extract data. The Network Meta-Analysis (NMA) by Bayesian model was performed by STATA v17. Data on PFS were extracted in terms of Hazard ratio with relative confidence intervals.

Results: This NMA involved 18 trials for a total of 9105 patients. Within 12 treatment groups, we performed 3 different sensitivity analyses including "all comers" Intention to Treat (ITT) population, BRCA-mutated (BRCAm), and HRD subgroups, respectively. Considering the SUCRA-reported cumulative PFS probabilities, we showed that in the ITT population, the inferred best treatment was niraparib *plus* bevacizumab with a SUCRA of 96.7. In the BRCAm subgroup, the best SUCRA was for olaparib *plus* chemotherapy (96,9). The HRD population showed an inferred best treatment for niraparib *plus* bevacizumab (SUCRA 98,4). Moreover, we reported a cumulative summary of PARPi toxicity, in which different 3–4 grade toxicity profiles were observed, despite the PARPi "class effect" in terms of efficacy.

Conclusions: Considering all aEOC subgroups, the best therapeutical option was identified as PARPi *plus* chemotherapy and/or antiangiogenetic agents, suggesting the relevance of combinatory approaches based on molecular profile. This work underlines the potential value of "chemo-free" regimens to prolong the platinum-free interval (PFI).

1. Introduction

Germ-line BRCA1/2 mutations are the main genetic background of the hereditary breast and ovarian cancer (HBOC) syndrome (Jonsson et al., 2019). BRCA1/2 mutations are considered to underly 5–10% of breast cancers, 20% of ovarian cancers, and approximately 40% of

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platinum-sensitive ovarian cancers (Slavin et al., 2017). However, in some cases, independently of the BRCA status, epithelial ovarian cancer (EOC) is associated with long-lasting platinum sensitivity, while patients with refractory disease represent about 20% of the total Matulonis et al., 2016. The response to platinum-derived agents still represents the major predictor of survival and carboplatin/paclitaxel combination remains the backbone of first-line treatment (Jayson et al., 2014; du Bois et al., 1997). Until 2011, chemotherapy was the only therapeutic option for advanced EOC (aEOC) patients. Despite several attempts to improve treatment efficacy with different cytotoxic and/or biological drugs, for about 10 years bevacizumab represented the only advancement in different settings. Indeed, several guidelines suggested the addition of bevacizumab to the standard treatment (Burger et al., 2011; Hall et al., 2020; Perren et al., 2011; Collinson et al., 2013). To improve patient survival, maintaining or optimizing the platinum-sensitivity is still a major challenge. At the same time, understanding the mechanisms of platinum resistance could modify the "pain in the neck" of this cancer: the dismissal outcome of platinum-refractory patients (Yang et al., 2022).

The heterogeneity of the clinical outcome may reflect the different molecular profiles, involving somatic and germ-line mutations (Bowtell, 2010; Nik et al., 2014; Kurman and Shih Ie, 2011). Moreover, BRCA1/2-mutation carriers were significantly associated with a better prognosis and a significantly longer OS than non-carriers, independently from the stage at diagnosis and histology. BRCA mutations or any other homologous recombination DNA repair (HRD) alteration can predict a better platinum response, as described in experimental in vitro and in vivo models (Cancer Genome Atlas Research, 2011; Tassone et al., 2009, 2005, 2003). PARPi - HRD mechanism is involved in the repair of DNA double-strand breaks, particularly in the G2/S phase of the cell cycle, and is required for genomic integrity (Branco and Paredes, 2022); on this rationale, several trials investigated PARP inhibitors (PARPi) in aEOC (Morgan et al., 2018).

At present, PARPi can be used as the first line of treatment, after carboplatin/paclitaxel treatment in platinum-responsive patients, in subsequent lines of treatment, in the recurring setting, and platinum-sensitive patients. These indications include “all comers” aEOC patients for niraparib, and BRCA-mutated EOC patients for olaparib due to different designs of the pivotal studies (Washington and Moore, 2021; Kaneko, 2022; Lee, 2022; DiSilvestro et al., 2023). In previous work, we evaluated the overall role of PARPi in the aEOC strategies demonstrating that it was possible to report a “class effect” for PARPi efficacy in the predefined endpoints (Staropoli et al., 2018).

Considering this background, the objective of this systematic literature review and network meta-analysis was to rank the available therapeutic strategies to infer the best therapeutic approach, declining the current scientific evidence in the several EOC subgroups, considering, therefore, the overall impact of PARPi in the management of EOC patients.

2. Patients and methods

2.1. Study design

We performed a systematic literature search to compare all treatments, combination or monotherapy in aEOC patients, in terms of progression-free survival (PFS), comparing the PARPi-based experimental arm with a control arm represented by carboplatin containing schedules and bevacizumab. Analyses were intended for “all comers” ITT population and BRCAm/HRD subgroups. This systematic review was submitted on international PROSPERO platform and was registered with Prospero ID 24583.

2.2. Searching

Considering the time frame 2011–2022, as previously performed, bibliographic research included PubMed, Embase, and the Central Registry of Controlled Trials of the Cochrane Library, major meeting proceeding databases (ASCO and ESMO). To avoid selection or information bias, only prospective studies were evaluated (Stewart et al., 1998; Parmar et al., 1998), using the following key-words: “ovarian”, “ovary”, “tumor”, “cancer”, “advanced”, “metastatic”, “therapy”, “PARPi”, “prospective”, and “randomized”, “BRCA status”, in different combinations: i.e. “epithelial ovarian cancer, PARPi”. The ’related articles’ function and references retrieved from articles were used to search for all related studies, abstracts, and citations. Only articles written in English were considered for this research.

2.3. Selection

Table 1 reported the characteristics of trials selected and included in the present review (Burger et al., 2011; Mirza et al., 2016; Gonzalez-Martin et al., 2019; Banerjee et al., 2021; Ray-Coquard et al., 2019; Aghajanian et al., 2021, 2022; Swisher et al., 2022; Monk et al., 2021, 2022; Ledermann et al., 2014, 2012; Poveda et al., 2021; Pujade-Lauraine et al., 2017; Mirza et al., 2019; Wu et al., 2021; Del Campo et al., 2019; Coleman et al., 2017; Liu et al., 2022; Kristeleit et al., 2022; Oza et al., 2015; Aghajanian et al., 2015, 2012; Tewari et al., 2019; Mirza et al., 2020; Yin et al., 2022; Gonzalez Martin et al., 2022; Ledermann et al., 2016; Ray-Coquard et al., 2022; Li et al., 2022).

2.4. Inclusion criteria

The studies were required to include patients with a diagnosis of platinum-sensitive EOC with or without BRCA mutation or HRD. RCTs, with or without blinding were included. We considered abstracts or unpublished data if sufficient information on study design, characteristics of participants, interventions, and outcomes were available.

2.5. Exclusion criteria

Non-comparative studies; non-prospective studies; studies with non-comparable endpoints were excluded. Studies focused on refractory/resistant- platinum patients were excluded.

2.6. Data extraction

Two investigators (N.S. and F.L.) examined the studies, independently. All variables which could be extracted from selected trials were reported and evaluated: number of patients enrolled, year of publication, treatment schedule, and efficacy results. Two arbiters (P.T. and D. C.) evaluated and resolved any discrepancies. PFS represents the primary endpoint evaluated for all patients. Data were retrieved according to the PRISMA statement (Stewart et al., 2015; Shamseer et al., 2015).

2.7. Methods for NMA

We performed our NMA using STATA software implemented by a graphical tool and the “mvmeta” package to simultaneously compare the different therapeutic schedules as described elsewhere (Chaimani et al., 2014, 2013; Ciliberto et al., 2018). Briefly, our NMA synthesizes data from a network of trials involving multiple interventions and therefore has the potential to rank the treatments according to the selected outcome (Rouse et al., 2017). We performed a Bayesian NMA with a random-effects model by a Markov-Chain Monte Carlo simulation technique with up to 30,000 iterations. Loop inconsistency and heterogeneity were assessed by evaluating the logarithm of the ratio of 2 odds ratios (RoR) from direct and indirect evidence in the loop with the ifplot command in STATA (Chaimani et al., 2014, 2013). RoR values close to 0 indicate that both direct and indirect evidence agrees. Heterogeneity of the loop was then assessed through the restricted maximum likelihood (reml) method (Rouse et al., 2017; Higgins et al.,

Table 1
Main characteristics of the randomized trials included in the NMA. Abbreviations: progression-free survival, PFS; hazard ratio, HR.

AUTHOR FIRST LINE	YEAR	N.PTS	TREATMENT	PHASE	OS (HR)	PFS (HR)
Banerjee (SOLO-1)	2022	391	olaparib vs placebo	III	0.55 (0.40–0.76)	0.33 (0.25–0.43)
González-Martín (PRIMA)	2021	733	niraparib vs placebo	III		0.66 (0.56–0.79)
Yin (PRIME)	2022	384	niraparib vs placebo	III		0.45 (0.32–0.61)
Ray-Coquard (PAOLA-1)	2022	806	olaparib + bevacizumab vs placebo + bevacizumab	III	0.92 (0.76–1.12)	0.59 (0.49–0.72)
Aghajanian (VELIA/ GOG-3005)	2021	1140	carboplatin/paclitaxel/ veliparib → veliparib vs carboplatin/paclitaxel → placebo	III		0.64 (0.50–0.80)
Monk (ATHENA-MONO)	2022	538	rucaparib vs placebo	III		0.52 (0.40–0.68)
Tewari (GOG-0218)	2019	1248	Bevacizumab + carboplatin/paclitaxel vs carboplatin/paclitaxel	III	0.96 (0.85–1.09)	
SECOND OR FURTHER LINE OF TREATMENT						
Ledermann (Study 19)	2014	265	olaparib vs placebo	II	0.73 (0.55–0.95)	0.35 (0.25–0.49)
Lauraine (SOLO-2)	2021	295	olaparib vs placebo	III	0.74 (0.54–1.00)	0.30 (0.22–0.41)
Mirza (ENGOT-OV16/ NOVA)	2019	553	niraparib vs placebo	III		0.24 (0.13–0.44)
Wu (NORA)	2020	265	niraparib vs placebo	III		0.32 (0.23–0.45)
Mirza (AVANOVA2/ENGOT-OV24)	2020	97	niraparib + bevacizumab vs niraparib	II	0.77 (0.42–1.41)	0.34 (0.21–0.55)
Coleman (ARIEL-3)	2017	564	rucaparib vs placebo	III		0.36 (0.30–0.45)
Penson (SOLO-3)	2020	266	olaparib vs non-platinum chemotherapy	III	1.07 (0.76–1.49)	0.62 (0.43–0.91)
Liu (NRG-GY004)	2020	565	olaparib + cediranib vs platinum-based chemotherapy	III		0.86 (0.66–1.11)
Kristeleit (ARIEL-4)	2022	349	rucaparib vs chemotherapy	III	1.31	0.69 (0.37–1.29)
Oza	2014	162	olaparib + carboplatin/paclitaxel vs carboplatin/paclitaxel	II	1.17 (0.79–1.73)	0.51 (0.34–0.77)
(OCEANS)	2015	484	Bevacizumab + carboplatin/gemcitabine vs carboplatin/gemcitabine	III	0.95 (0.77–1.17)	

2014). Relative effects of treatments are reported as HR for survival outcomes (PFS), with corresponding 95% credible intervals (CrIs), the Bayesian equivalent of 95% CIs which provides an estimated interval within the results of future studies are expected to fall. The surface under the cumulative ranking curve (SUCRA), which provides a numerical summary of the rank distribution of each treatment schedule on the different endpoints, provided hierarchy of probabilities (Higgins et al., 2014). The larger SUCRA value (i.e. closer to 1), the highest is the rank of the intervention. The NMA results are graphically represented in a forest plot with the mean HRs, with their 95% CIs and CrIs. We ranked the evaluated schedules based on the PFS. Significance is denoted by a $p \leq 0.05$.

2.8. Validity assessment

The quality assessment of selected studies was performed according to the Cochrane reviewers' handbook for six requirements: method of randomization, allocation/concealment, blindness, withdrawal/ dropout, sequence generation, and adequacy of follow-up (Armijo-Olivo et al., 2012; Detsky et al., 1992). All 18 trials involved, were scored A (low risk of bias). (Table 2).

All the statistical analyses were performed by using STATA SE v. 17 (STATA_Corporation, Texas, USA) (Boston and Sumner, 2003). The indirect comparison procedures of PARPi groups were conducted using the STATA-Indirect program. All tests were two-sided with $p \leq 0.05$ considered statistically significant.

3. Results

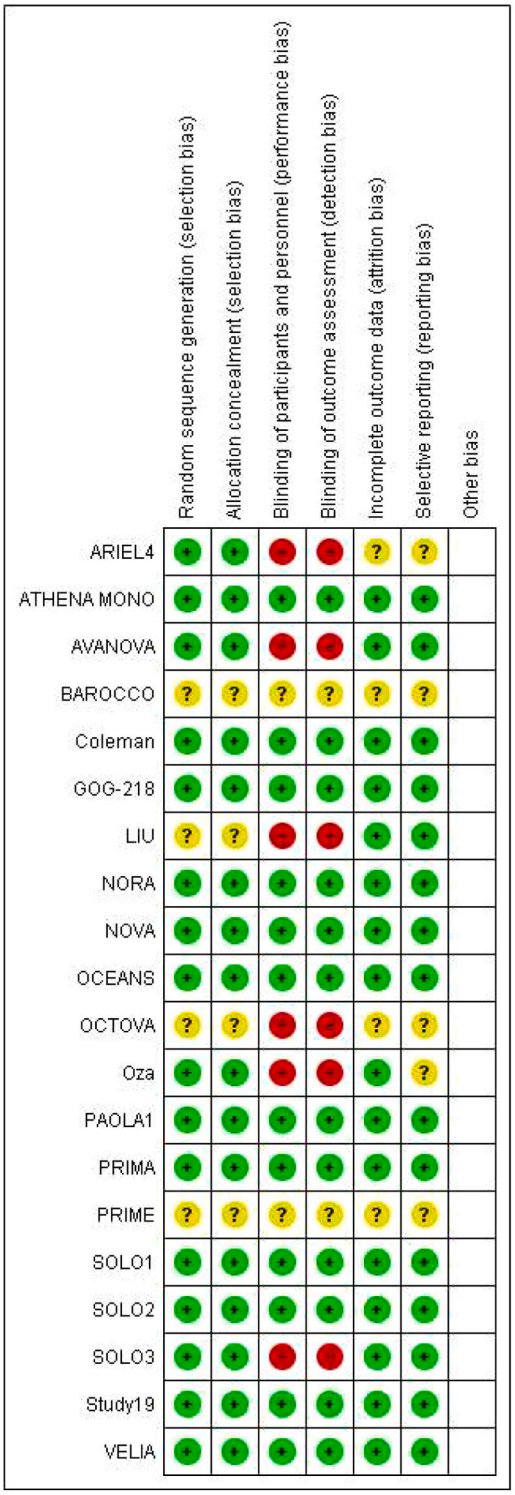
3.1. Studies selection and characteristics

Fig. 1 shows the graphic representation of selection and bibliographic search in the PRISMA chart related to RCTs for the total time frame covered by the present systematic review (2011–2022).

Considering keywords previously reported, a total of 1701 works were identified from a first selection, involving both "in extenso" reports and abstracts. Of these, 849 were excluded as reviews. Of the 852 remaining potentially detected studies, 832 were excluded due to study design, ongoing or overlapping to similar studies. Finally, 20 studies were selected, and two further studies (OCTOVA and BAROCCO), which were potentially evaluable in terms of primary endpoint, were excluded because specifically oriented to platinum-resistant patients, thus not meeting our inclusion criteria (Colombo et al., 2022; Mansouri et al., 2021). Moreover, the ARIEL-4 study, which enrolled both partially platinum-sensitive and platinum-resistant patients, was considered only for data of the platinum-sensitive subgroup, to compare homogeneous populations. Finally, network meta-analysis involved 18 trials for a total of 9105 patients, all evaluable for BRCA/HRD status. All trials were analyzed for PFS as primary endpoint of this work.

OS data were not available for all studies examined, therefore the sensitivity analysis was conducted on the PFS endpoint, as surrogate efficacy endpoint.

Table 2
The quality assessment of selected studies was evaluated according to the Cochrane reviewers' handbook. This table reports for each involved trial, the global risk of bias (selection bias, performance bias, detection bias, attrition bias, reporting bias, and others).



3.2. Study characteristics

Based on the results of the previous 2018 pair-wise meta-analysis, we proceeded to update some Literature data according to PRISMA CHART. Two different update periods were considered for ASCO 2022 (June 2022) and ESMO 2022 (November 2022).

First, a pooled assessment was performed for "all comers" ITT population of 18 reported studies. Subsequently, exploratory analyses were performed according to the genetic background in several subgroups: BRCAm and HRD+ . All studies enrolled platinum-sensitive patients.

3.3. Network meta-analysis

3.3.1. PFS results for all comers ITT population analysis

All treatments were distributed into 12 groups, according to the drug or therapeutic regimens, and were independently analyzed. The groups are represented by: "bevacizumab, chemotherapy, chemotherapy *plus* bevacizumab, niraparib, niraparib *plus* bevacizumab, olaparib, olaparib *plus* bevacizumab, olaparib *plus* cediranib, olaparib *plus* chemotherapy, placebo, rucaparib, veliparib".

Network plots (Fig. 2a-c) showed a graphical representation of possible "networks" between the treatments. Range plots and SUCRA scores for the ITT population showed that the niraparib *plus* bevacizumab demonstrated improved PFS outcome with higher SUCRA (96.7) compared to the other treatments. Olaparib *plus* chemotherapy regimens ranked second (82.0), and the standard combination of chemotherapy *plus* bevacizumab ranked third (64.7).

3.3.2. PFS results for BRCAm subgroup analysis

The analysis revealed that there is an adequate number of indirect comparisons. According to the Bayesian methodology, we were able to rank as the most effective schedule in this subgroup olaparib *plus* chemotherapy (SUCRA 96.9). Fig. 2(d-f) highlights the Network plot for the BRCA mutated population and the related SUCRAs with credible intervals. This result was based on data reported in phase study II by Oza et al., which evaluated the efficacy and tolerability of the combination of olaparib *plus* paclitaxel and carboplatin, followed by olaparib monotherapy until progression or unacceptable toxicity versus a doublet of paclitaxel and carboplatin (Oza et al., 2015). However, this study is just a proof of concept because, at present, it does not represent current clinical practice. The second most effective treatment in survival was niraparib *plus* bevacizumab (SUCRA 89.2), as reported in the phase II study AVANOVA2/ENGOT-OV24, which evaluated the combination of niraparib *plus* bevacizumab versus niraparib alone, as maintenance in platinum-sensitive recurrence of EOC. This combination regimen improved PFS compared with niraparib alone in the subgroup of patients with BRCAm HR 0.49 (95% CI 0.21–1.15) (Mirza et al., 2019).

3.3.3. PFS results for HRD+ subgroup analyses

The Network plot, reported in Fig. 2(g-h), showed that the HRD+ population and the related SUCRAs with credible intervals. Regarding this subgroup of patients, the most effective schedule is niraparib *plus* bevacizumab (SUCRA 98.4), as reported in the phase II study AVANOVA2/ENGOT-OV24, which evaluated niraparib *plus* bevacizumab versus niraparib alone and, therefore, a chemotherapy-free regimen in platinum-sensitive recurrence of EOC. This combination regimen improved PFS compared to niraparib alone with a particularly clear benefit in the subgroup of patients with HRD+ tumors HR 0.41 (95% CI 0.23–0.76).

3.3.4. Descriptive analysis of the main toxicities reported in selected studies

It was not possible to aggregate the toxicity data reported in the individual studies examined in our analysis, because missing data on BRCA/HRD subgroups. However, we reported a cumulative description obtained from an analytical observation that is presented in Table 3.

4. Discussion

Our NMA of 18 randomized clinical trials involved a total of 9105 patients and compared all PARPi-based treatment regimens with any other systemic conventional treatment stratified on BRCA status, in

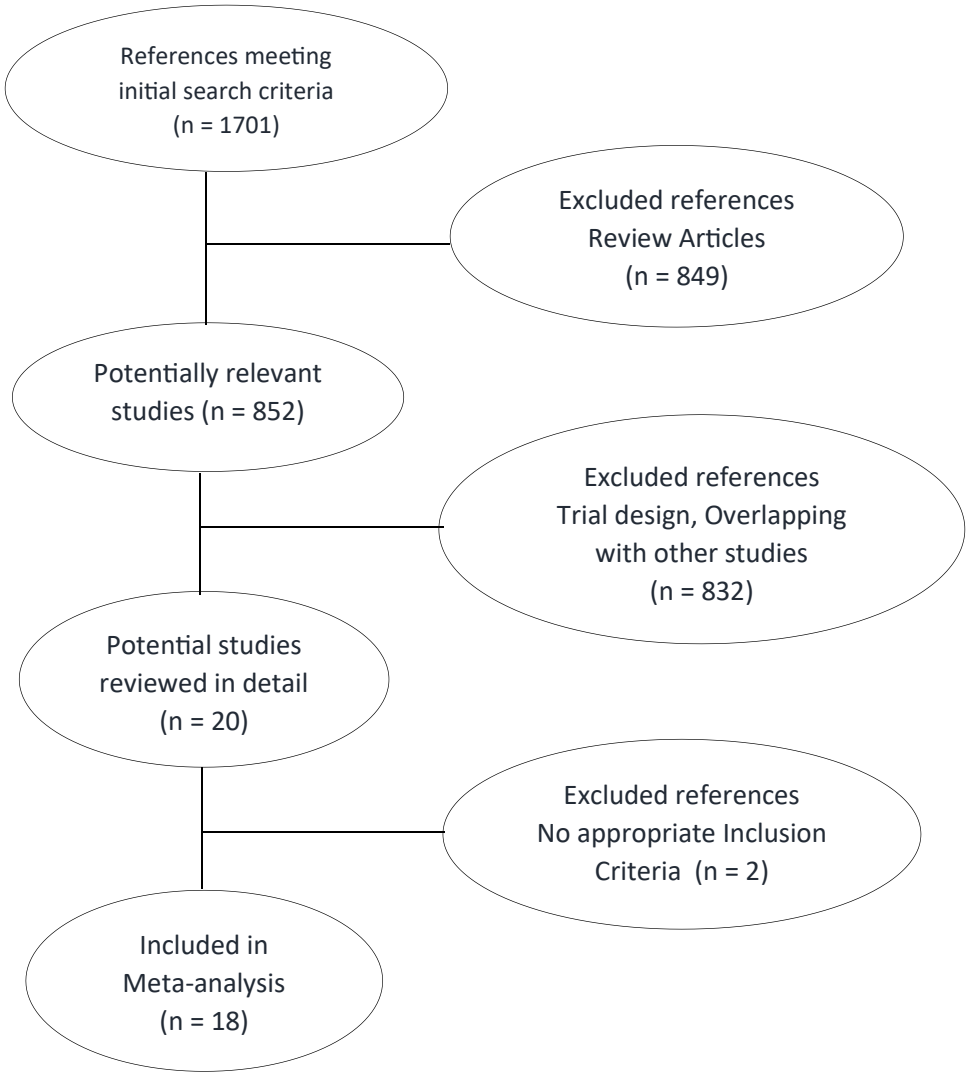


Fig. 1. PRISMA chart showing the graphic explication of bibliographic research describing trial exclusion and inclusion process. SEER, Surveillance, Epidemiology, and End Results.

terms of PFS based on current Literature evidence.

The rationale of this work relies on our previous findings (Staropoli et al., 2018). Furthermore, we demonstrated a "class effect" of PARPis in EOC management in terms of PFS. Moreover, we highlighted the strong limitation due to the evaluation of only the maintenance setting in the absence of direct comparison among treatment arms.

Considering all available data, we performed the main analysis on platinum-sensitive status stratified on BRCA background, the most relevant prognostic/predictive factor in EOC management. Statistical analysis was performed on the PFS endpoint because OS analysis was not available for all reviewed studies.

A ranking of the efficacy of treatments was performed by the SUCRA method. We showed that in all ITT populations, the inferred best treatment was niraparib *plus* bevacizumab with a SUCRA of 96.7. Regarding the BRCA subgroup, olaparib *plus* chemotherapy followed by chemotherapy alone ranked the best SUCRA (96,9). Finally, in the HRD population, the best-inferred treatment was niraparib *plus* bevacizumab, coherently with the ITT population (SUCRA 98,4).

On these findings, we can make some considerations. First, our analyses showed that the highest-ranking position for each subgroup was achieved by a combinatory approach as compared to monotherapy alone.

Considering the BRCA status and related subgroups, the advantage of niraparib *plus* bevacizumab was confirmed in both subgroups, coherently to this hypothesis. On the other hand, the single PARPi (olaparib, niraparib, rucaparib) did not show any difference in terms of efficacy when used as monotherapy, confirming the class effect we previously described. Moreover, it must be considered that, at present, the combination of niraparib *plus* bevacizumab lacks evaluation in phase 3 trials and needs therefore further validation for clinical translation with an adequate sample size.

Interestingly, our results are coherent with the indirect comparison, recently published (Vergote et al., 2021), in which the authors compared the SOLO1 population (BRCAm patients treated with olaparib maintenance after chemotherapy) versus the PAOLA1 population (all patients despite BRCA status, treated with olaparib *plus* bevacizumab after chemotherapy *plus* bevacizumab) demonstrating that the combinatory treatment improved PFS (Vergote et al., 2021). Together these findings highlight the combination of PARPi with bevacizumab as the highest rank treatment in BRCA or HRD populations.

From a biological point of view, this evidence allows us to hypothesize that a potential synergic interaction between PARPi and anti-angiogenics drugs might rely on the modulation of tumor microenvironment (Alvarez Secord et al., 2021; Eckert et al., 2021).

Neoangiogenesis plays an important role in the progression of EOC. Considering the cross-activity of antiangiogenic agents and PARPi in

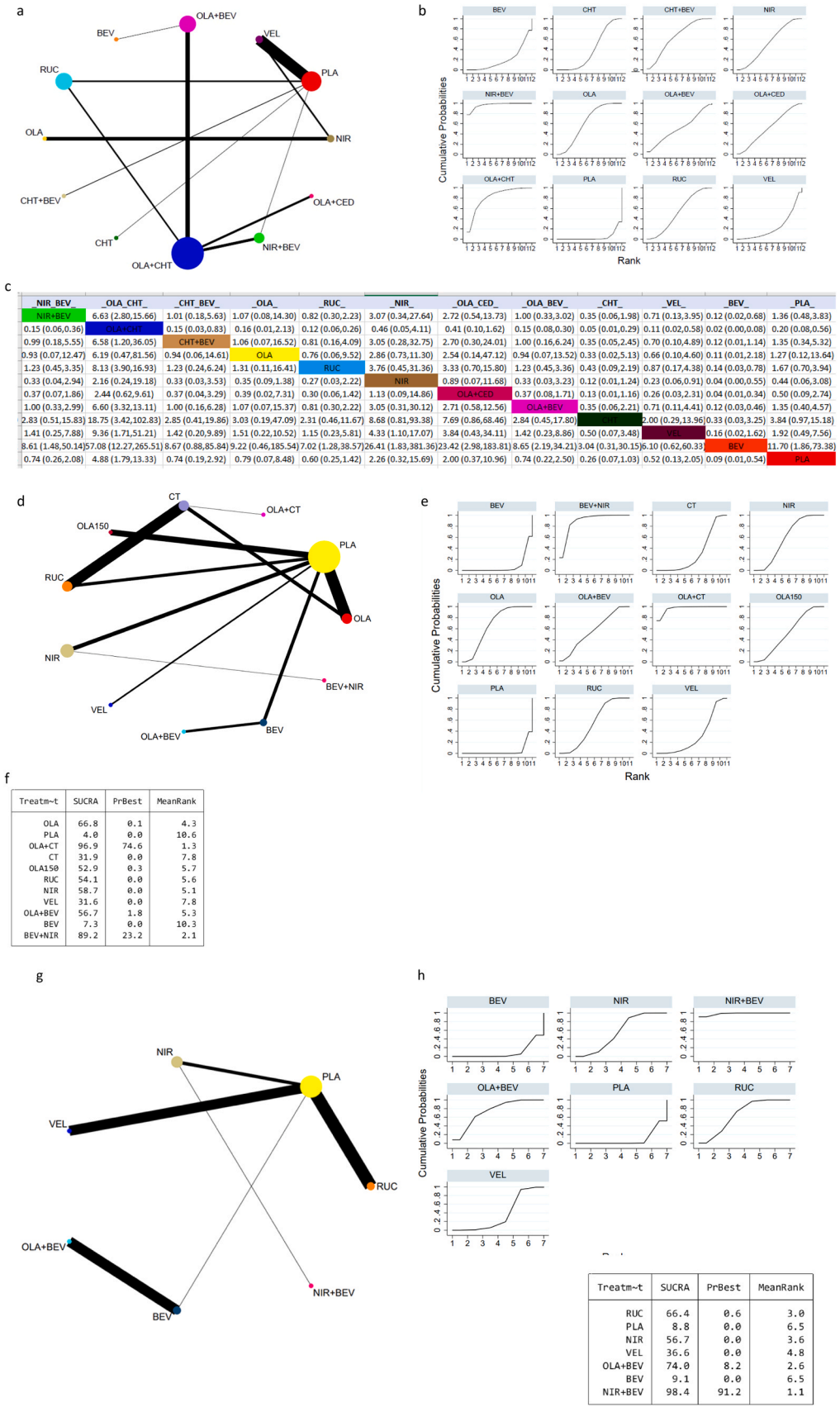


Fig. 2. Analyses of NMA for ITT population and subgroups. This figure describes NMA in all comers/ITT population: Fig. 2a reports the network plot; b-c reports the interval plot and SUCRA with a better outcome for the combination niraparib plus bevacizumab. d-f: report the NMA in BRCAm with network plot and interval plot. SUCRA showed a better outcome with olaparib plus chemotherapy combination. g-h: report the NMA in HRD with network plot and interval plot respectively. SUCRA showed a better outcome with olaparib plus chemotherapy combination.

Table 3
Toxicity cumulative profile in selected trials.

OLAPARIB						
AUTHORS	ANEMIA		THROMBOCYTOPENIA		NEUTROPENIA	
	ALL GRADE	G3-G4	ALL GRADE	G3-G4	ALL GRADE	G3-G4
Banerjee (SOLO-1)	39%	22%	11%	1%	23%	9%
Ledermann (Study 19)	17%	5%	nd	nd	nd	nd
Lauraine (SOLO-2)	25%	21%	14%	3%	16%	8%
Ray-Coquard (PAOLA-1)	41%	17%	8%	2%	18%	6%
Penson (SOLO-3)	51%	21%	12%	4%	23%	10%
Oza	12%	8%	8%	0%	11%	5%
Liu (NRG-GY004)	nd	nd	nd	nd	nd	nd
NIRAPARIB						
González-Martín (PRIMA)	63%	31%	26%	13%	26%	13%
Yin (PRIME)		18%		14%		17%
Mirza (ENGOT-OV16/ NOVA)	nd	25%	nd	28%	nd	11%
Wu (NORA)	53%	15%	55%	11%	59%	20%
Mirza (AVANOVA2/ENGOT-OV24)	nd	15%	nd	10%	nd	nd
VELIPARIB						
Aghajanian (VELIA/ GOG-3005)	65%	41%	60%	31%	75%	62%
RUCAPARIB						
Monk (ATHENA-MONO)	47%	29%	24%	7%	28%	15%
Coleman (ARIEL-3)	37%	19%	28%	5%	18%	7%
Kristeleit (ARIEL-4)	22%	8%	nd	3%	10%	nd
BEVACIZUMAB						
Burger (GOG-218)	nd	nd	nd	nd	nd	63.3%
Aghajanian (OCEANS)	nd	nd	nd	nd	nd	20.6%

delaying EOC recurrences, it was indeed interesting to evaluate the combination of these agents, especially given different toxicity (mostly mild) and considering a chemo-free potential strategy to prolong platinum-free interval (PFI) and bypass platinum-resistance (Flynn and Ledermann, 2022).

On the same basis, it was previously demonstrated that trabectedin *plus* pegylated liposomal doxorubicin (PLD) in platinum-partially-sensitive patients could restore platinum-sensitivity of the subsequent EOC recurrence, as hypothesized in OVA 301 phase III study (Staropoli et al., 2014; Mignogna et al., 2016; Monk et al., 2015; Colombo, 2011).

Although further studies are needed to confirm the hypothesis of a synergistic (more than additive) action of these two drug classes, preclinical findings suggest that antiangiogenic agents can influence homologous recombination DNA repair through several mechanisms. Indeed, by inhibiting VEGFR3, these drugs induce hypoxia in the tumor microenvironment, through down-regulation of BRCA1/2 and RAD51, genes that play a key role in HR, leading to tumor growth arrest (Kaplan et al., 2019; Bindra et al., 2004).

PARP1 might also play a role in angiogenesis induced by EOC cells, through upregulation of VEGF-A secretion. Experiments in PARP1 knockout mice suggest potential antiangiogenic effects of PARPi (Wei et al., 2016).

Our work presents some limitations. Firstly, many trials were excluded because retrospective data or data were not extractable and non-comparable. Indeed, it was not possible to perform “data mining” on the endpoints of OS, ORR, and safety and the latter was presented as a descriptive analysis, confirming previously described findings. Conversely, in terms of PFS, we were able to evaluate all selected studies. Among the limitations of our NMA emerges the hardness in identifying the best strategy for each therapeutic line, probably due to the small number of comparable studies. On this basis, the efficacy data in PFS were evaluated overall, regardless of the treatment line.

The sustainability of the analyzed treatments will have to be evaluated therefore in the long term with a longer follow-up and OS analysis. Moreover, the major question mark is to assess if PFS represents an OS surrogate in aEOC. Furthermore, in terms of the "cost-benefit ratio" the use of PARPi is evaluated with acceptable effectiveness considering a clear improvement in terms of efficacy and with a reasonable safety profile. Moreover, it will be interesting, to evaluate the potential cross-resistance of different PARPis confirming the potential "class effect” or highlighting a substantial difference between these which might justify a possible switch in the therapeutic sequence. Another important limitation of this NMA method regards the inferential approach and the absence of individual patient data.

In conclusion, we focused on the interesting emerging maintenance scenario based on drugs combination with the special emerging activity of PARPi/bevacizumab. PARPi monotherapy in overall maintenance strategy confirms the previously hypothesized efficacy “class effect”. The current work provides therefore a whole scenario analysis where next-generation approaches might be challenged.

CRediT authorship contribution statement

NS, PT, and PT designed the study. NS, FC e CN did the literature search. DC, NS, FC extracted data. DC realized the figures. MC, GR and CN performed the tables. All authors collected data. DC, NS, PT, and PT interpreted and analyzed the data, and wrote the manuscript. All authors readed and approved final version of the manuscript.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2023.104229.

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