Systematic Review

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Systematic literature review of efficacy and safety of first-line maintenance therapy trials in advanced ovarian cancer

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Aim: To review safety and efficacy outcomes in studies of first-line maintenance therapies for advanced ovarian cancer. **Methods:** A systematic literature review was performed (27 February 2020) to identify clinical outcomes including progression-free survival (PFS), overall survival (OS) and Grade ≥3 adverse events. **Results:** Overall 50 references met prespecified criteria; 18 studies evaluated 10 different agents, including PARP inhibitors. PFS was an end point in 16 trials and OS in 12 trials. PARP inhibitors reported better PFS hazard ratios (HRs: 0.59–0.68) compared with other classes; no mature OS data were identified. Safety reporting was inconsistent. **Conclusion:** Reported PFS HRs were better for PARP inhibitors than for other ovarian cancer maintenance therapies; overall survival data remain immature.

Plain language summary: This article reports the results from a systematic literature review (SLR), enabling a critical and unbiased comparison of clinical studies, of responses and side effects of first-line maintenance therapies used for advanced ovarian cancer. Overall, this SLR supports the use of PARP inhibitors as maintenance therapy for patients with advanced ovarian cancer as they demonstrated a greater effect on delaying further disease progression than other drug types assessed. However, due to large differences between the clinical studies included (e.g. design of the trial), direct comparisons between first-line maintenance therapies must be made with caution. Healthcare professionals must factor individual patient circumstances when choosing the most appropriate therapy.

Tweetable abstract: Systematic literature review of 18 ovarian cancer trials of first-line maintenance therapy demonstrates PARP inhibitors confer greater clinical benefit than other drug classes; niraparib demonstrated significant improvement in progression-free survival beyond *BRCA* status.

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Keywords: *BRCA* mutation • first-line maintenance • ovarian cancer • PARP inhibitor • progression-free survival • systematic literature review

Ovarian cancer remains one of the leading causes of cancer-related death in women [1]. Most cases are diagnosed in an advanced stage (III/IV) and, despite standard-of-care management with surgery and platinum-based chemotherapy, approximately 85% of women with advanced ovarian cancer experience recurrence within 3 years of first-line treatment; the 5-year overall survival rate is approximately 30–50% [2,3]. Around 15–18% of women with advanced ovarian cancer have a *BRCA1/2* mutation (*BRCA*m) [4].

In women whose tumors respond to chemotherapy, maintenance treatment aims to sustain the disease-free interval and survival, and to maintain quality of life (QoL) [5,6]. Multiple agents, including chemotherapeutic agents, monoclonal antibodies, tyrosine kinase inhibitors, peptide inhibitors, aromatase inhibitors, and hormone therapy have been evaluated as maintenance therapies in clinical trials [7,8,9,10,11,12,13]. Approval of PARP inhibitors (e.g., niraparib, olaparib and rucaparib) and anti-angiogenic agents (e.g., bevacizumab) as maintenance therapies has changed the treatment landscape in ovarian cancer [14]. Maintenance treatment with PARP inhibitors or bevacizumab has been shown to significantly prolong progression-free survival, and their use is endorsed by multiple ovarian cancer treatment guidelines [5,15,16,17]. Additionally, PARP inhibitor treatment has been shown to maintain patients' QoL [6,18,19]. Patients with *BRCA*m tumors historically have a better prognosis compared with

those with *BRCA* wild-type (*BRCA*wt) tumors, and have improved outcomes with PARP inhibitor treatment and chemotherapy [20,21]. PARP inhibitors, including niraparib, have demonstrated improvement in progression-free survival when administered as monotherapy in platinum-responsive patients, irrespective of biomarker status [6].

Several publications have reported the recent clinical advancements in maintenance treatment of advanced ovarian cancer, with substantial investigation of maintenance therapies in the first-line setting [6,18,19]. Multiple stakeholders need to parse this rapidly evolving information to optimize outcomes for women with ovarian cancer. Physicians and healthcare providers must weigh all available data to select the best treatment approach for each individual patient. Policymakers also rely on clinical trial data and health technology assessments, which evaluate treatments and their impact on social, ethical, and economic issues.

A systematic review provides a critical appraisal and an unbiased comparison of all relevant studies. This type of literature review can inform indirect treatment comparisons, such as network meta-analyses, which evaluate the relative efficacy of different treatments against each other. We conducted a systematic literature review to assess efficacy and safety outcomes in clinical trials of first-line maintenance therapies for advanced ovarian cancer.

Methods

Systematic search

An integrated clinical and economic systematic literature review was performed to identify outcomes associated with first-line maintenance therapies. Databases and gray literature were searched on 27 February 2020, with no restriction imposed on publication date (other than per database as detailed below). Databases searched included EMBASE, Medline and Medline (R) In-Process (EMBASE interface 1947 to present), Cochrane Central Register of Controlled Trials (Cochrane library), Centre for Reviews and Dissemination Health Technology Assessment Database (1989 to present), Centre for Reviews and Dissemination National Health Service Economic Evaluation Database, ScHARRHUD (2006 to present), and the EuroQol Group database (1970 to present). Gray literature searches (from April 2017) included Google Scholar; websites for the National Institute for Health and Care Excellence, Pharmaceutical Benefit Scheme, Canadian Agency for Drugs and Technologies in Health, and Scottish Medicines Consortium; ClinicalTrials.gov; searches of manufacturer's evidence repositories; websites of manufacturers of comparator products; bibliographic searching of any systematic literature reviews identified during screening; and relevant congresses over the last 3 years (European Society for Medical Oncology, European Society of Gynaecological Oncology, American Society of Clinical Oncology, Asian Society of Gynaecologic Oncology, Society of Gynaecologic Oncology, National Cancer Research Institute, European Association for Cancer Research, and the International Society for Pharmacoeconomics and Outcomes Research). Search strategies included terms for free text and keywords combined using Boolean techniques and filters to ensure relevance (full details on all clinical and economic search terms used are shown in Supplementary Tables 1–8). The outcomes of the clinical search only are reported here.

Selection criteria

Selection criteria followed the population, intervention, comparator, outcomes and study design principle, based on guidelines endorsed by the Cochrane Handbook, which is designed to appropriately define the scope of the review [22]. The details of the selection criteria are specified in Supplementary Table 1. Randomized controlled trials, non-randomized controlled trials, and observational studies were eligible. Key outcomes of interest were progression-free survival, overall survival, and treatment-emergent adverse events.

Trials evaluating chemotherapeutic agents given as maintenance therapy were excluded because the intent was to evaluate maintenance therapy following active chemotherapy treatment and not continued chemotherapy [23,24,25,26,27].

Quality assessment & data collection

All stages of review were completed by two independent reviewers, with disagreements arbitrated by a third reviewer when required. During the first-pass stage, duplicate records were removed and then each record was reviewed for relevance based on title and abstract. Full texts were obtained and reviewed during the second-pass stage. At each stage, a discussion was held between the two reviewers after 20% of the publications had been reviewed to ensure alignment on the selection criteria. A reason for exclusion was noted for studies not selected during the second-pass stage.

Data were extracted from the selected studies by one reviewer and checked for accuracy by a second reviewer; discrepancies were resolved via discussion. The data were extracted from each study onto an Excel-based data collection form, with tables formatted to align with the National Institute for Health and Care Excellence systematic literature review template and developed in line with the University of York Centre for Reviews and Dissemination and National Institute for Health and Care Excellence reporting requirements [28,29]. Selected studies were classified by study design (randomized controlled trial or observational) and assessed against the National Institute for Health and Care Excellence comprehensive quality assessment checklist for clinical studies and a checklist adapted from Chambers 2009 for observational studies [28,30].

This systematic literature search was used to identify the studies for inclusion in network meta-analysis and population-adjusted indirect treatment comparison feasibility assessments, which were conducted and are being reported separately. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

Results

The details of the literature search review and extraction are presented in Supplementary Figure 1. A total of 8631 publication titles and abstracts were retrieved in the overall search; 8482 were excluded. Full texts of the remaining 149 publications were reviewed at second pass, with 112 excluded (Supplementary Figure 1). Gray literature searching contributed an additional 13 relevant records. The 50 full-text records that met the selection criteria covered 18 clinical studies: 12 randomized controlled trials, 4 observational studies, 1 dose-escalation study and 1 retrospective chart review (Table 1). Drug class and approval status for each agent included in these studies are detailed in Supplementary Table 8. Study designs varied, with some agents being investigated following first-line chemotherapy and others initiated with first-line chemotherapy and continuing into a maintenance phase (Table 1). Patient populations differed between studies and study end points also varied greatly; progression-free survival and overall survival were selected as the two efficacy end points consistently reported in these studies.

Efficacy: progression-free survival

Sixteen of the 18 studies assessed progression-free survival as an efficacy outcome (NCT00058435 [40] and MI-MOSA [34,42] assessed other efficacy outcomes). In 14 studies, progression-free survival was the primary end point [6,8,9,10,12,13,18,19,31,33,35,37,38,43]. Four studies assessed progression-free survival by a blinded independent central review committee [6,18,19,35], 10 used investigator assessment [6,9,18,19,31,33,35,37,39], and 2 did not state the methodology [10,43].

Overall, lower hazard ratios (HRs) for progression-free survival were reported for PARP inhibitors than for other ovarian cancer maintenance therapies assessed (Figure 1); however, there were differences between studies in terms of design and patient populations, which make these data difficult to compare. The lowest HR (0.59) for all patients regardless of *BRCA* status (including *BRCA*wt and *BRCA*m) was for olaparib plus bevacizumab versus placebo plus bevacizumab ($p < 0.001$; PAOLA-1 [19]), followed by niraparib versus placebo (HR 0.62, $p < 0.001$; PRIMA [6]). The highest HR (1.5; $p = 0.02$) was for neoadjuvant chemotherapy plus nintedanib followed by nintedanib maintenance versus neoadjuvant chemotherapy plus placebo followed by placebo maintenance (CHIVA/GINECO [10]; the only neoadjuvant chemotherapy trial analyzed), indicating that treatment with nintedanib resulted in worse progression-free survival than with placebo.

No pattern was identified in relation to progression-free survival in patients treated with a maintenance therapy following first-line chemotherapy or who received a maintenance treatment concurrently with first-line chemotherapy then continued with the maintenance treatment (Figure 1). Of the 16 studies that assessed progression-free survival, 8 [6,12,18,19,31,33,35,43] demonstrated a statistically significant improvement in progression-free survival at a 5% confidence level ($p < 0.05$) and 1 study showed a statistically significant decrease in progression-free survival [10]. It was not possible to conclude significance in seven trials because insufficient data were reported [8,9,13,38,39,41,44].

Four studies reported progression-free survival data specifically in *BRCA*m patients. Progression-free survival HR was lowest (0.30 [95% CI: 0.23–0.41]) in SOLO-1 [18] and was also reported separately according to *BRCA1*m and *BRCA2*m status: patients with *BRCA2*m who received olaparib monotherapy had a lower progression-free survival HR (0.20) than those with *BRCA1*m (0.41) when compared with placebo. In PAOLA-1 [19], progression-free survival HR was 0.31 ($p < 0.0001$) for *BRCA*m patients treated with olaparib plus bevacizumab compared with placebo plus bevacizumab. A higher progression-free survival HR (0.40 [95% CI: 0.27–0.62]) in *BRCA*m patients treated with niraparib monotherapy compared with placebo was reported in PRIMA [6]. The highest HR (0.44;

Table 1. Summary of the trials included in the systematic literature search.

Study type	Drug class	Trial	Key paper	Treatment arms	Disease stage	Prior chemotherapy	Population of patients with *BRCA* mutation	PFS as primary end point (yes/no)	PFS measurement	Mature OS data (yes/no)	Ref.
Randomized controlled trial	PARP inhibitors	SOLO-1 (NCT01844986)	Moore 2018	Olaparib vs placebo	III/IV	≥6 and ≤9 cycles	Only *BRCA*m	Yes	From (randomization) maintenance therapy	No	[18]
		PAOLA-1 (NCT02477644)	Ray-Coquard 2019	Chemotherapy plus bevacizumab in active treatment, followed by olaparib plus bevacizumab vs bevacizumab alone in maintenance	III/IV	≥6 and ≤9 cycles	Patients with or without *BRCA*m	Yes	From (randomization) maintenance therapy	No	[19]
		PRIMA (NCT02655016)	Gonzalez-Martin 2019	Niraparib vs placebo	III/IV	≥6 and ≤9 cycles	Patients with or without *BRCA*m	Yes	From (randomization) maintenance therapy	No	[6]
		VELIA/GOG-3005 (NCT02470585)	Coleman 2019	Chemotherapy plus veliparib in active treatment, followed by veliparib maintenance chemotherapy plus veliparib in active treatment, followed by placebo maintenance chemotherapy plus placebo in active treatment, followed by placebo maintenance	III/IV		Patients with or without *BRCA*m	Yes	From (randomization) first-line therapy and continued throughout maintenance therapy	No	[31]
	Monoclonal Antibodies	ICON-7 (NCT00483782)	Oza 2015	Chemotherapy in active treatment, followed by surveillance vs chemotherapy plus bevacizumab in active treatment, followed by bevacizumab maintenance	I–IIa & IIb–IV	Excluded if received any prior anticancer therapy for OC	NR	Yes	From (randomization) first-line therapy and continued throughout maintenance therapy	Yes	[32]
		GOG-0218 (NCT00262847)	Burger 2011	Chemotherapy with/without bevacizumab in active treatment, followed by placebo maintenance vs chemotherapy plus bevacizumab in active treatment, followed by bevacizumab maintenance	III/IV	Excluded if received neoadjuvant chemotherapy for OC	NR	Yes	From (study entry) first-line therapy and continued throughout maintenance therapy	Yes	[33]
		MIMOSA (NCT00418574)	Sabbatini 2013	Abagovomab vs placebo	III/IV	6–8 cycles	NR	Recurrence-free survival	From (randomization) maintenance therapy	No	[34]
	Tyrosine kinase pathway inhibitors	AGO-OVAR16 (NCT00866697); plus East Asian substudy (NCT01227928)	Du Bois 2014 Vergote 2018 Kim 2018	Pazopanib vs placebo	II–IV	≥5 cycles (platinum-taxane doublet chemotherapy)	NR	Yes	From (randomization) maintenance therapy	No	[8,35,36]
		NCT01227928	Zang 2013	Pazopanib vs placebo	II–IV	≥5 cycles	Patients with or without *BRCA*m†	Yes	From (randomization) maintenance therapy	No	[37]

†Patients from AGO-OVAR16 and the East Asian study who provided informed consent and a blood sample for genotyping (n = 256 East Asian patients from the 2 studies combined).
NA: Not applicable; NR: Not reported; OC: Ovarian cancer; OS: Overall survival; PFS: Progression-free survival.

Table 1. Summary of the trials included in the systematic literature search (cont.).

Study type	Drug class	Trial	Key paper	Treatment arms	Disease stage	Prior chemotherapy	Population of patients with *BRCA* mutation	PFS as primary end point (yes/no)	PFS measurement	Mature OS data (yes/no)	Ref.
		AGO-OVAR12 (NCT01015118)	Ray-Coquard 2017	Chemotherapy plus nintedanib in active treatment, followed by nintedanib maintenance vs chemotherapy in active treatment, followed by placebo maintenance	IIb–IV	Excluded if received any prior anticancer therapy for OC	NR	Yes	From (randomization) first-line therapy	No	[9]
		CHIVA/GINECO (NCT01583322)	Ferron 2019	Neoadjuvant chemotherapy plus nintedanib in active treatment, followed by nintedanib maintenance vs neoadjuvant chemotherapy in active treatment, followed by placebo maintenance	IIIc/IV	Excluded if received any prior anticancer therapy for OC	NR	Yes	From (randomization) for neoadjuvant therapy	No	[10]
	Peptide inhibitor	TRINOVA-3 (NCT01493505)	Vergote 2019	Chemotherapy plus trebananib in active treatment, followed by trebananib maintenance vs chemotherapy in active treatment, followed by placebo maintenance	III/IV	Excluded if received any prior anticancer therapy for OC	NR	Yes	From (randomization) of first-line therapy	No	[11]
Observational study	Aromatase inhibitor	–	Knipprath-Meszaros 2017	Letrozole vs 'do nothing'	III/IV	Number of prior cycles not specified	NR	Yes	From (randomization) start of maintenance therapy	No	[12]
	Hormone therapy	–	Goel 2017	Tamoxifen vs surveillance	III/IV	Number of prior cycles not specified	NR	Yes	From (randomization) start of maintenance therapy	No	[13]
	Monoclonal Antibodies	OSCAR (NCT01863693)	Hall 2018	Chemotherapy plus bevacizumab in active treatment, followed by bevacizumab maintenance	IIIb/c and IV	Excluded if received any prior anticancer therapy for OC	NR	Yes	From (randomization) start of first-line therapy	Yes	[38]
		JGOG3022	Komiyama 2019	Chemotherapy plus bevacizumab	III/IV	Excluded if received neoadjuvant chemotherapy for OC	NR	Yes	From (randomization) start of first-line therapy	No	[39]
Dose-escalation study	Monoclonal Antibodies	NCT00058435	Sabbatini 2006	Abagovomab	II–IV	≥1 cycle	NR	NA	NA	NA	[40]
Retrospective chart review	Monoclonal Antibodies	ESME (NCT03275298)	Romeo 2019	Platinum-based chemotherapy in active treatment, followed by maintenance treatment (included patients with bevacizumab maintenance)	III/IV	NA	Patients with or without *BRCA*m	NA	NA	NA	[41]

[†] Patients from AGO-OVAR16 and the East Asian study who provided informed consent and a blood sample for genotyping (n = 256 East Asian patients from the 2 studies combined).
NA: Not applicable; NR: Not reported; OC: Ovarian cancer; OS: Overall survival; PFS: Progression-free survival.

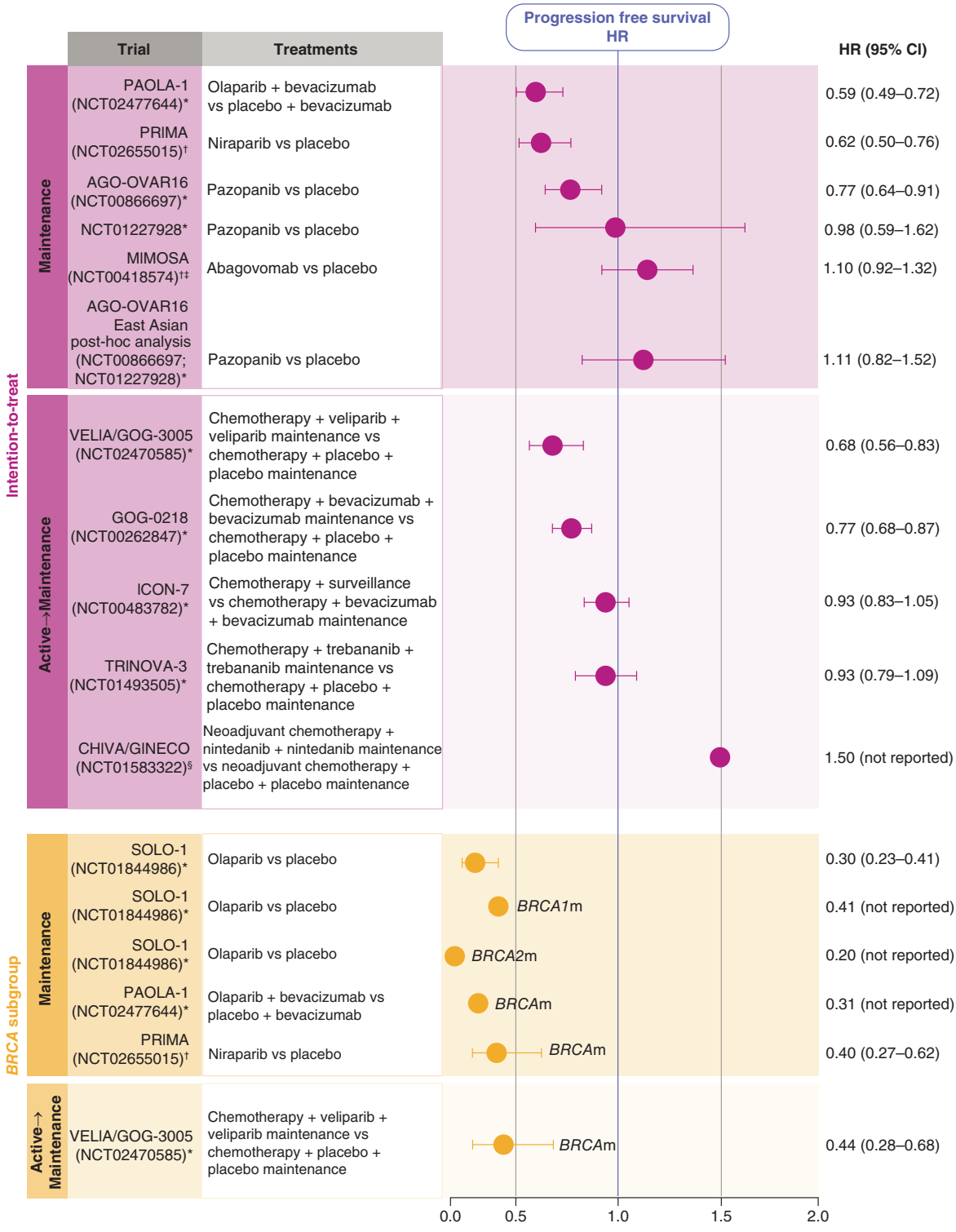

Figure 1. Progression-free survival hazard ratios across studies in systematic literature review. Progression-free survival HR data as reported in trials for overall populations and *BRCA*m subgroups, when available. Progression-free survival HR data only included for studies with reported values; error bars indicate 95% CI; missing error bars indicate 95% CI not reported.

*Progression-free survival investigator-assessed.

†Progression-free survival assessed by independent central review.

‡Reported data were recurrence-free survival.

§Method of assessment not specified/reported.

Active→Maintenance, patients given active treatment followed by maintenance treatment.

*BRCA*m: *BRCA* mutated; CI: Confidence interval; HR: Hazard ratio.

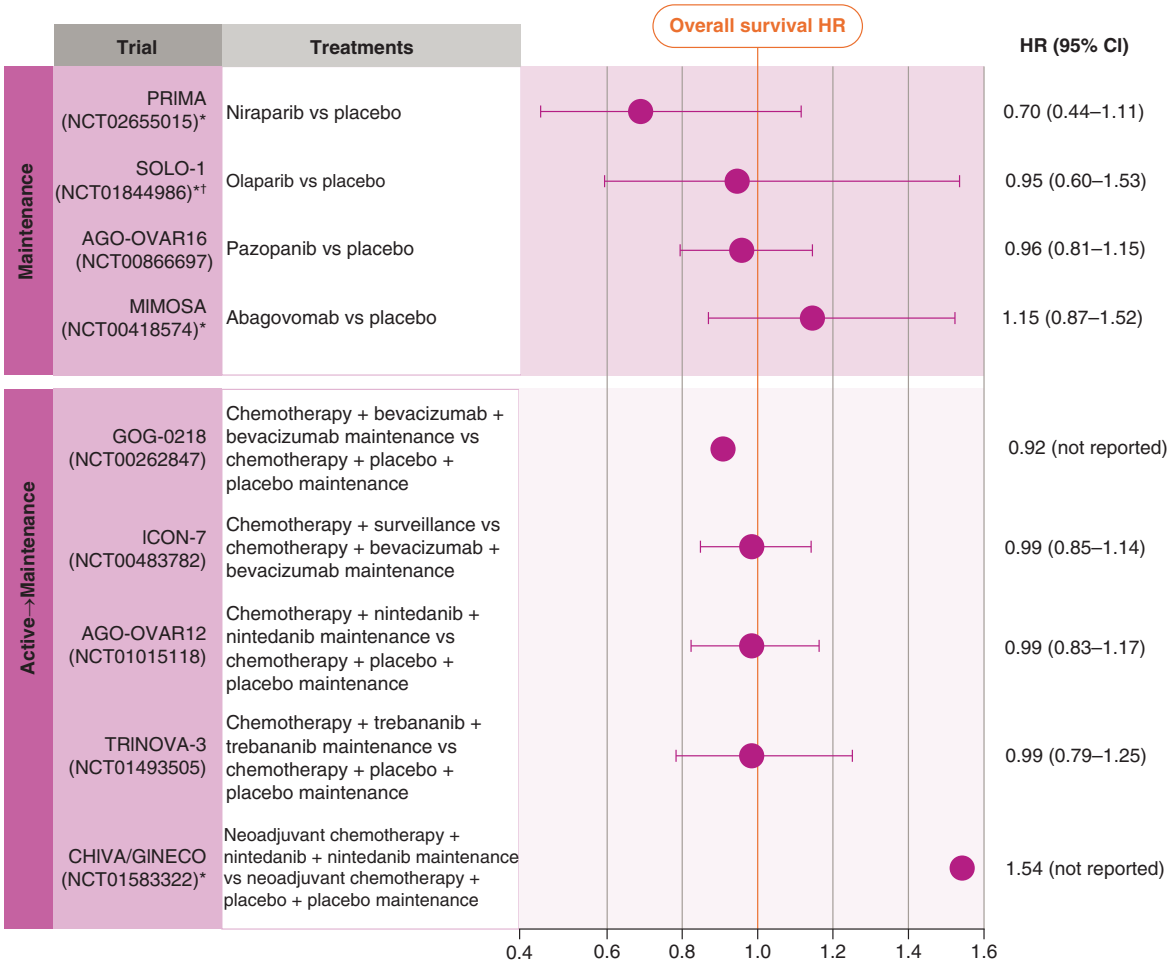

Figure 2. Overall survival HRs across studies in systematic literature review. Overall survival HR data as reported in trials for overall populations. Overall survival HR data only included for studies with reported values; error bars indicate 95% CI; missing error bars indicate 95% CI not reported.
*Overall survival data reported were from interim analyses and were immature.
†ITT population only included *BRCA*m patients.
Active→Maintenance, patients given active treatment followed by maintenance treatment.
CI: Confidence interval; HR: Hazard ratio.

$p < 0.001$) was reported in VELIA/GOG-3005 [31], for *BRCA*m patients treated with chemotherapy plus veliparib followed by veliparib maintenance compared with chemotherapy plus placebo followed by placebo.

Efficacy: overall survival

Overall survival was included as a secondary end point in 12 trials [6,9,10,18,19,31,33,34,35,41,42,43]. MIMOSA [34,42], SOLO-1 [18], CHIVA/GINECO [10] and PRIMA [6] reported interim, immature overall survival data, while overall survival data for VELIA/GOG-3005 [31] and PAOLA-1 [19] were not available due to lack of overall survival event maturity. Overall survival data from the Epidemiological Strategy and Medical Economics (ESME) [41] study, a retrospective cohort study, were only descriptive and therefore not summarized here. Trials with bevacizumab reported mature data. Across all trial populations, PARP inhibitor-containing maintenance therapies (PRIMA [6] and SOLO-1 [18]), one pazopanib maintenance therapy (AGO-OVAR16 [8]), one nintedanib maintenance therapy (AO-OVAR12 [9]), one trebananib maintenance therapy (TRINOVA-3 [11]), and two bevacizumab maintenance therapies (GOG-0218 [33] and ICON-7 [43]) reported overall survival HRs below 1. However, the 95% CIs for the overall survival HRs all included the null hypothesis (HR = 1) for the PARP inhibitor and pazopanib studies; the 95% CI was not reported in the bevacizumab study (Figure 2) [33].

Overall survival data revealed that the lowest HR was for niraparib versus placebo (HR: 0.70 [95% CI: 0.44–1.11], PRIMA [6]) and the highest HR was for neoadjuvant chemotherapy plus nintedanib followed by nintedanib maintenance versus neoadjuvant chemotherapy plus placebo followed by placebo maintenance (HR 1.54; CHIVA/GINECO [10]); regardless of *BRCA* status (including *BRCA*wt and *BRCA*m). These results were interim and immature, so final conclusions on long-term overall survival results could not be drawn.

In both ICON-7 [43] and GOG-0218 [33,45] studies, which evaluated bevacizumab plus chemotherapy followed by bevacizumab maintenance in patients regardless of *BRCA* status, overall survival improvement was not statistically significant versus the respective placebo arms once enough events were recorded and when censored for crossover [32].

Interim analyses showed a numerical overall survival advantage over placebo at 24 months with niraparib monotherapy irrespective of *BRCA* status in PRIMA [6] (HR: 0.70 [95% CI: 0.44–1.11]) and with olaparib monotherapy in the *BRCA*m subgroup at 36 months in SOLO-1 [18] (HR: 0.95 [95% CI: 0.60–1.53]). However, these overall survival improvements were not statistically significant. MIMOSA [34,42] showed that abagovomab treatment resulted in lower overall survival compared with placebo (HR: 1.15 [95% CI: 0.872–1.518]) but this result was not significant at the 5% significance level.

Treatment-emergent adverse events

Eleven out of 18 studies reported aggregate safety data. Treatment-emergent adverse events were reported in nearly all (90–100%) patients in treatment and control arms across studies. The proportion of patients experiencing Grade ≥3 adverse events ranged from 39 to 88% among those receiving PARP inhibitors [6,18,19,31], 51 to 92% among those receiving tyrosine kinase pathway inhibitors [8,10,37], and 21 to 66% for those receiving monoclonal antibodies (Figure 3A) [34,43]. Discontinuation due to treatment-emergent adverse events was reported in 11 trials [6,8,18,19,31,33,34,38,39,40,44] and rates ranged from 8 to 20% for PARP inhibitors [6,18,19,31], and 6 to 16% for monoclonal antibodies (Figure 3B) [34,39].

Discussion

Summary of main results

This systematic literature review identified 18 clinical studies evaluating 10 maintenance therapies with several different mechanisms of action. Of these studies, 8 demonstrated a significant improvement in progression-free survival in women with advanced ovarian cancer [6,12,18,19,31,33,35,43]. Maintenance treatment with PARP inhibitors in the first-line setting appears to confer greater clinical benefit compared with other drug classes, as demonstrated by improved progression-free survival outcomes; however, direct comparisons of HRs between studies cannot be made due to differences in study design and patient populations [6,19,31]. Niraparib was the only PARP inhibitor monotherapy in this review that demonstrated statistically significant progression-free survival improvement as first-line maintenance treatment, irrespective of biomarker status [6,19].

Mature studies for bevacizumab showed a lack of effect on overall survival, despite a statistically significant impact on progression-free survival [32,33,43]. Overall survival data remained immature for most of the studies analyzed; therefore, the impact of PARP inhibitor maintenance therapy on overall survival in the first-line setting is unclear [6,10,18,19,31,34,41,42].

Aggregate safety data were not available for all of the clinical trials identified and, for which we did report these data, the proportion of patients reporting grade ≥3 treatment-emergent adverse events and discontinuations due to adverse events varied widely, with no class of agents appearing to have a more favorable safety profile than other classes [6,8,18,19,31,32,33,34,38,39,40,44].

Results in the context of published literature

The wide ranges in outcomes likely reflect the variability of safety profiles among different classes of agents, combined with distinct differences in pharmacokinetics of the agents, baseline disease burden and study design between these trials. A systematic literature review and meta-analysis of 10 phase II or III randomized control trials assessed efficacy and toxicity profiles of PARP inhibitors in patients with advanced ovarian cancer and also reported a statistically significant improvement in progression-free survival in overall patients (HR: 0.41; 95% CI: 0.35–0.5) treated with PARP inhibitors, and further improvement in *BRCA*m patients (HR: 0.32; 95% CI: 0.26–0.39) compared with control therapies [46]. Further, a meta-analysis of first-line maintenance therapies assessed 7 studies of 7,770 participants, found improved progression-free survival in *BRCA*m patients treated with PARP

inhibitors [47]. Efficacy of PARP inhibitors on overall survival could not be determined due to the incomplete follow-up data in the majority of the trials, similar to our findings [46].

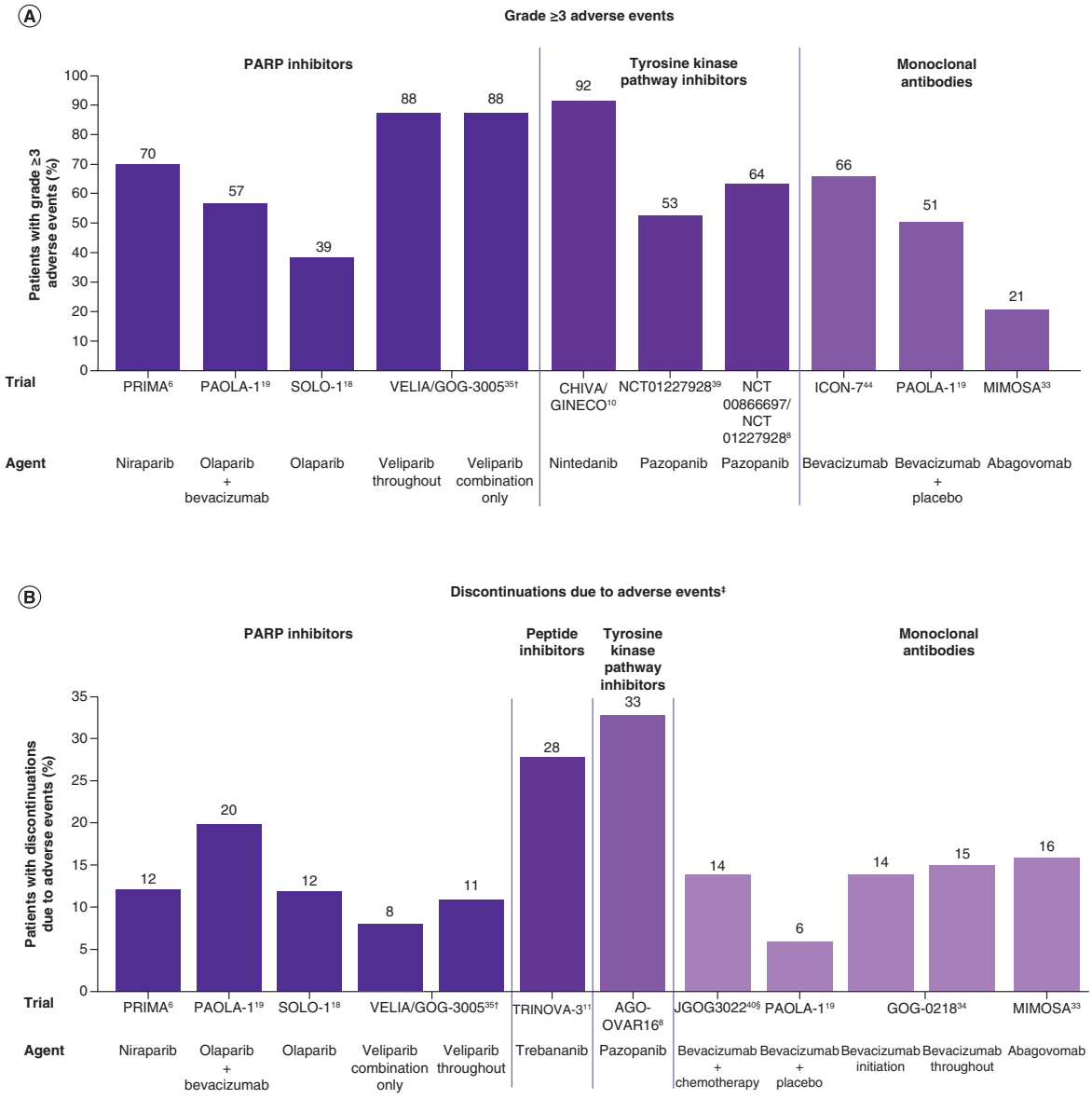

Figure 3. Safety overview across studies in systematic literature search. Rates of grade ≥3 adverse events **(A)** and discontinuation due to adverse events **(B)** from studies that reported total Grade ≥3 adverse events or discontinuations due to adverse events for the overall population. Data are grouped by drug class.
†Patients were randomized to receive chemotherapy plus veliparib followed by placebo maintenance (veliparib combination only), or chemotherapy plus veliparib followed by veliparib maintenance (veliparib throughout).
‡Studies that reported discontinuations due to adverse events reported.
§Discontinuations due to serious AEs. Safety data taken from NCT00058345 [40] was not graphed because Grade ≥3 adverse events were not reported.

Safety analysis of first-line maintenance PARP inhibitors demonstrate the frequency of Grade ≥3 adverse events varies across PARP inhibitors [47]. Additionally, 3 studies investigating the combination of PARP inhibitors with other therapies demonstrated 53/81 (65%) of patients experienced grade 3 or 4 toxicities and 15/81 (19%) patients had treatment discontinuation [46]. They also report a range of adverse events across active therapy arms similar to our study.

Strengths & weaknesses

The strengths of this systematic literature review included the broad search terms not restricted by date or language, resulting in a pool of publications for analysis that included a large patient population. Furthermore, data were extracted in accordance with best practices for systematic literature reviews [28,29,30]. Overall, this review provides collated evidence of first-line maintenance treatment in ovarian cancer that can potentially inform indirect treatment comparison analyses and clinical decision-making in the absence of head-to head clinical trials.

Since clinical trial end points differed between studies (e.g., progression-free survival assessed as either a primary or secondary end point) and long-term survival data are immature for newer agents, there were limited overlapping efficacy and safety end points to include in the analysis, which is a limitation of this study.

Implications for practice & future research

This review highlighted the substantial heterogeneity in clinical trial design in the first-line maintenance therapy setting. Evidence generated in the review was used to inform network meta-analysis and population-adjusted indirect treatment comparison feasibility assessments, which confirmed the magnitude of inter-trial heterogeneity and the infeasibility of network meta-analysis and population-adjusted indirect treatment comparison based on the current body of evidence [48]. Given that trials were conducted at different times and designed to address different hypotheses, the heterogeneity in study designs will limit the ability to compare outcomes systematically. Furthermore, the rapid pace of therapeutic advances in advanced ovarian cancer is likely to complicate assessment of overall survival because of the consequent availability of subsequent effective therapy options. While overall survival is the gold-standard and most objective primary end point in any trial, demonstrating an overall survival benefit in ovarian cancer is challenging [49,50]. Progression-free survival has been shown to be a valid surrogate end point for overall survival in 1L ovarian cancer trials and is considered acceptable for regulatory approvals by US FDA [50,51]. However, the increased observation of prolonged post-progression survival is largely attributed to patients receiving subsequent lines of therapy, and therefore caution must be taken when extrapolating these data [51]. More recently there has been an increased focus on end points that are of clinical relevance to patients such as health related quality of life (HRQoL). In a *post hoc* analysis of the PRIMA trial, HRQoL assessments in patients with advanced ovarian cancer were significantly reduced from pre-progression to post-progression []. Prolonging a patient's time before disease progression and preserving their HRQoL is clinically relevant and achieved by prolonging progression-free survival outcome [49,]. Therefore, any comparisons of the efficacy or safety of first-line maintenance therapies for advanced ovarian cancer must be made with caution. Instead, prescribers must evaluate individual patient factors and preferences when selecting the optimal first-line maintenance therapy.

Conclusion

In conclusion, this systematic literature review of first-line maintenance therapy studies in ovarian cancer supports treatment with maintenance therapy for all patients with advanced ovarian cancer, regardless of biomarker status. Multiple agents, particularly PARP inhibitors, demonstrated improvements in progression-free survival. Although immature, overall survival data for PARP inhibitors in preliminary analyses are encouraging. Safety profiles across agents are difficult to compare. Follow-up analyses and the introduction of novel combinations and therapeutic options will contribute to our growing knowledge of this disease area, with the aim of providing better outcomes for women with advanced ovarian cancer.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0578

Author contributions

H Guy, C Hawkes and L Walder contributed to both data acquisition and data analysis or interpretation. I Malinowska and D Gupta contributed to data analysis or interpretation.

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Financial & competing interests disclosure

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Data availability statement

GlaxoSmithKline (GSK) makes available anonymized individual participant data and associated documents from interventional clinical studies that evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com.

Summary points

- Approximately 85% of women with advanced ovarian cancer (OC) will experience disease recurrence within 3 years of first-line (1L) treatment.
- Around 15–18% of women with advanced OC have mutations in *BRCA1/2*; the remaining 82–85% of patients with no *BRCA* mutation have a considerably worse prognosis.
- Maintenance treatment with PARP inhibitors or bevacizumab has been shown to significantly prolong progression-free survival (PFS); patients with *BRCA1/2*m have improved outcomes with PARP inhibitor treatment.
- We report the results from a systematic literature review which identified 18 OC trials of 1L maintenance therapy.
- Overall, maintenance treatment with PARP inhibitors in the 1L setting appears to confer greater clinical benefit compared with other drug classes.
- For overall survival (OS), results were interim and immature, so final conclusions on long-term OS could not be drawn.
- Niraparib was the only PARP inhibitor monotherapy that demonstrated statistically significant improvement in PFS as 1L maintenance treatment, irrespective of biomarker status.
- Safety was reported inconsistently, and no safety profile trends emerged between drug classes.

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