Systematic Literature Review of Efficacy and Safety of First-Line Maintenance Therapy Trials in Advanced Ovarian Cancer

Poster number: 373

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Background

- OC remains a leading cause of cancer-related death in women[1]
- The majority of cases are diagnosed in an advanced stage and, in general, approximately 85% of advanced OC will recur within 3 years of 1L treatment (surgery and CT)[2]
- The 5-year overall survival rate is around 25%[3]
- Maintenance treatment with PARP inhibitors and anti-angiogenic agents (e.g. bevacizumab) have changed the treatment landscape in OC in recent years[3]
- This approach aims to sustain the disease-free interval and survival in patients whose tumour has responded to 1L CT[1,3]

Objective

To review efficacy and safety outcomes in clinical trials of 1L maintenance therapies for advanced OC

Methods

A SLR was performed to identify clinical outcomes associated with 1L maintenance therapies and therapies initiated alongside 1L CT, which were extended into maintenance for advanced OC

Databases and grey literature were searched on 27 February 2020, with no restriction imposed on publication date (other than per database as detailed below)

Databases included EMBASE, Medline and Medline (R) In-Process (EMBASE interface 1947 to present), Cochrane Central Register of Controlled Trials Centre (Cochrane library), Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database (1989 to present), CRD National Health Service (NHS) Economic Evaluation Database (EED), ScHARRHUD (2006 to present) and EuroQol database (1970 to present)

Grey literature searches (from April 2017) included Google Scholar, clinicaltrials.gov, searches of manufacturer's repository of evidence, websites of manufacturers of comparator products, bibliographic searching of any SLRs identified during screening, and relevant congresses over the last 3 years

RCTs, non-RCTs and observational studies were eligible

Selection criteria followed the PICOS principle as specified in **Table 1**

Key outcomes of interest were PFS, OS and TEAEs

During the first pass stage, studies were reviewed based on title and abstract. A full-text review was completed during the second pass stage, after which selected studies were extracted. All stages were completed by two reviewers with disagreements arbitrated by a third reviewer when required

Table 1. PICOS criteria used for SLR

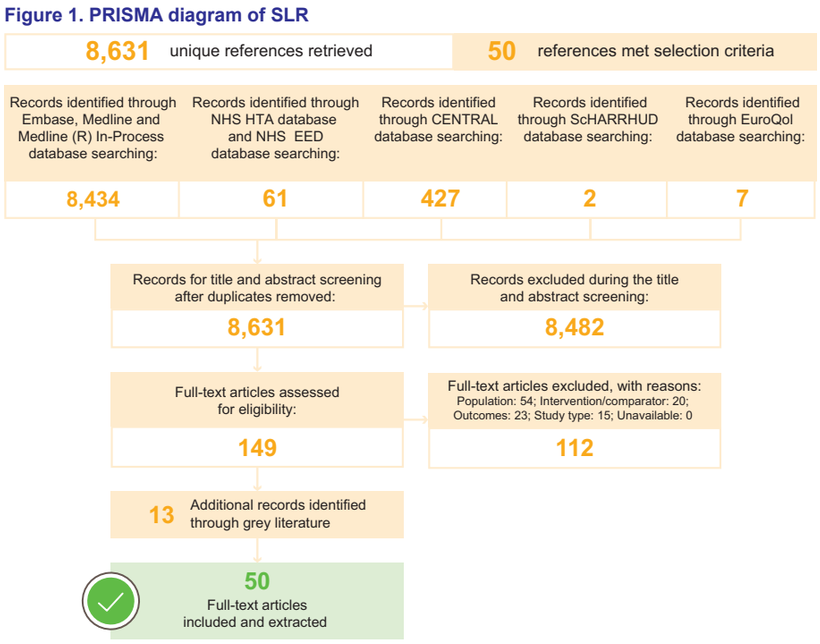
Selection criteria	Inclusion criteria	Exclusion criteria
Population	Patients with OC who have received one line of previous chemotherapy treatment	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest Patients who have received more than one line of previous chemotherapy treatment
Interventions/ comparators	Any maintenance therapy for OC	No intervention/comparators of interest
Outcomes	Efficacy (e.g. PFS, OS, TTD, duration of treatment, TTNT, TFST, TSST, SD, PD, RFS, PFS2, platinum-free interval, RR, HRQoL) Safety (e.g. adverse events)	No reported outcomes of interest (i.e. only reporting pharmacodynamics, pharmacokinetics, genetic, cellular, or molecular outcomes)
Study type	RCTs, non-RCTs, observational studies (including patient registries)	Individual case study reports, reviews, letters, comment articles
Publication type	Article, conference abstract, conference paper, article in press	Short survey, letter, editorial, review

HRQoL, health-related quality of life; OC, ovarian cancer; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PFS2, second PFS; PICOS, population, interventions, comparators, outcomes and study type; RFS, recurrence-free survival; RCT, randomised controlled trial; RR, response rate; SD, stable disease; SLR, systematic literature review; TFST, time to first subsequent treatment; TSST, time to second subsequent treatment; TTD, time to treatment discontinuation, TTNT, time to next treatment

Results

Study selection

Figure 1. PRISMA diagram of SLR



CENTRAL, Cochrane Central Register of Controlled Trials; EED, Economic Evaluation Database; HTA, Health Technology Assessment; NHS, National Health Service; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ScHARRHUD, School of Health and Related Research Health Utilities Database; SLR, systematic literature review

The 50 references covered 18 clinical trials, 12 of which were RCTs and 6 non-RCTs (**Table 2**)

Table 2. Summary of the 18 trials included in the SLR

Study type	Drug class	Trial	Key paper	Treatment arms*
RCT	PARP inhibitors	SOLO-1 (NCT01844986)	Moore 2018[4]	Olaparib vs PBO†
		PAOLA-1 (NCT02477644)	Ray-Coquard 2019[5]	[CT + bevacizumab], followed by olaparib + bevacizumab vs bevacizumab alone in maintenance
		PRIMA (NCT02655015)	González-Martín 2019[6]	Niraparib vs PBO
		VELIA/GOG-3005 (NCT02470585)	Coleman 2020[7]	CT + veliparib in active treatment, followed by veliparib maintenance CT + veliparib in active treatment, followed by PBO maintenance CT + PBO in active treatment, followed by PBO maintenance
	Anti-angiogenic therapies	AGO-OVAR16 (NCT00866697); plus East Asian substudy (NCT01227928)	Du Bois 2014[8] Vergote 2018[9] Kim 2018[10]	Pazopanib vs PBO
		NCT01227928	Zang 2013[11]	Pazopanib vs PBO
		ICON-7 (NCT00483782)	Oza 2015[12]	CT in active treatment, followed by surveillance vs CT + bevacizumab in active treatment, followed by bevacizumab maintenance
		GOG-0218 (NCT00262847)	Burger 2011[13]	CT ± bevacizumab in active treatment, followed by PBO maintenance vs CT + bevacizumab in active treatment, followed by bevacizumab maintenance
		TRINOVA-3 (NCT01493505)	Vergote 2019[14]	CT + trebananib in active treatment, followed by trebananib maintenance vs CT in active treatment, followed by PBO maintenance
	Anti-idiopathic therapies	MIMOSA (NCT00418574)	Sabbatini 2013[15]	Abagovomab vs PBO
	Tyrosine protein kinase inhibitors	AGO-OVAR12 (NCT01015118)	Ray-Coquard 2017[16]	CT + nintendanib in active treatment, followed by nintendanib maintenance vs CT in active treatment, followed by PBO maintenance
		CHIVA/GINECO (NCT01583322)	Feron 2019[17]	NACT + nintendanib in active treatment, followed by nintendanib maintenance vs NACT in active treatment, followed by PBO maintenance
Observational study	Aromatase inhibitor	—	Knipprath-Meszaros 2017[18]	Letrozole vs "do nothing"
	Hormone therapy	—	Goel 2017[19]	Tamoxifen vs surveillance
	CT + VEGF inhibitor	OSCAR (NCT01863693)	Hall 2018[20]	CT + bevacizumab in active treatment, followed by bevacizumab maintenance
	CT + VEGF inhibitor	JGOG3022 (NCT00951496)	Komiyama 2019[21]	CT + bevacizumab
Dose-escalation study	Anti-idiopathic therapy	NCT00058435	Sabbatini 2006[22]	Abagovomab
Retrospective chart review	CT ± VEGF inhibitor	ESME (NCT03275298)	Romeo 2019[23]	Platinum-based CT in active treatment, followed by maintenance treatment (included patients with bevacizumab maintenance)

*Treatments were in the maintenance phase following 1L CT unless otherwise specified; †trial performed in *BRCA*m patients only.
1L, first line; *BRCA*m, breast cancer gene mutated; CT, chemotherapy; NACT, neoadjuvant chemotherapy; PARP, poly(ADP-ribose) polymerase; PBO, placebo; VEGF, vascular endothelial growth factor

Efficacy

PFS

16/18 trials, (all but 2, NCT00058435 and MIMOSA[15,22]) assessed PFS as an efficacy endpoint

Overall, PARP inhibitors reported a more favourable (lower) PFS HR than the other OC maintenance therapies analysed here (**Figure 2**)

The lowest HR (0.59) for all patients regardless of *BRCA* status (included *BRCA*wt and *BRCA*m) was olaparib + bevacizumab vs PBO + bevacizumab (*P*-value not reported; PAOLA-1[5]); the second lowest HR was niraparib vs PBO (0.62, *P*<0.001; PRIMA[6]); CT + veliparib followed by veliparib maintenance vs CT + PBO followed by PBO maintenance had the third lowest HR (0.68, *P*<0.001; VELIA/GOG-3005[7])

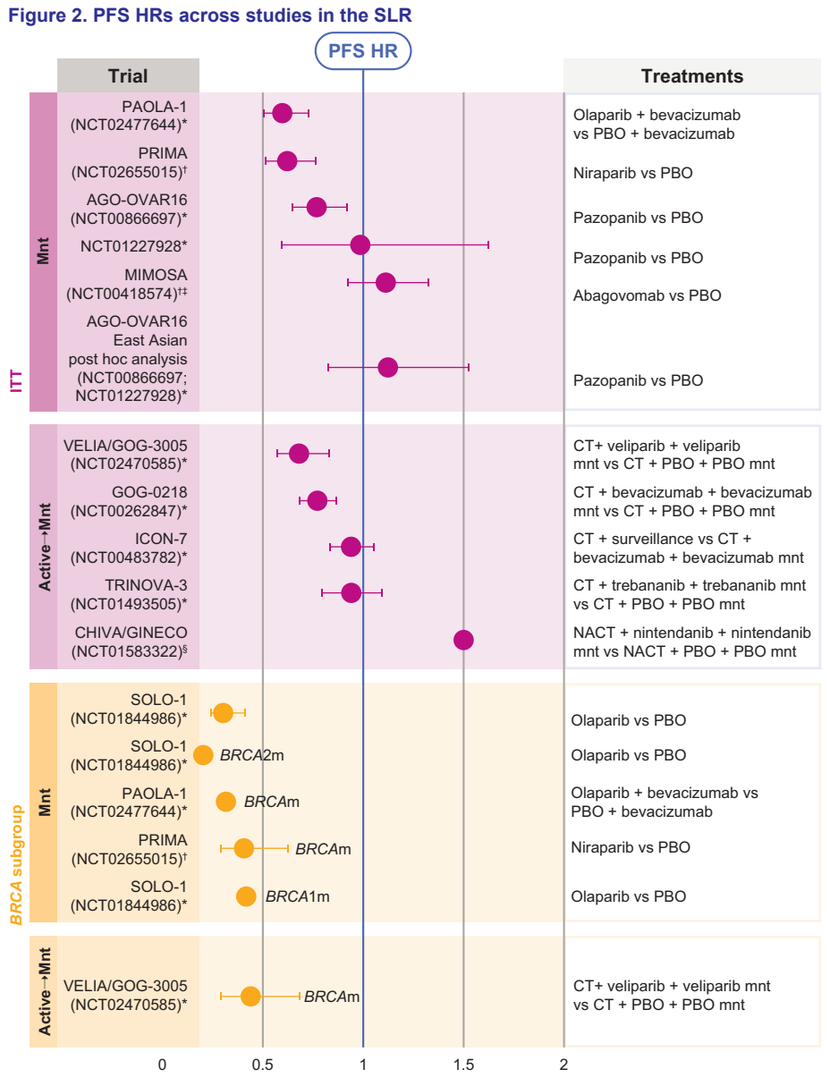
The highest HR (1.5; *P*=0.02) was for NACT + nintedanib followed by nintedanib maintenance vs NACT + PBO followed by PBO maintenance (CHIVA/GINECO; only NACT trial analysed), indicating that treatment with nintedanib resulted in worse PFS than with PBO[17]

No pattern was identified in relation to PFS in patients treated with a maintenance therapy following 1L CT (mnt in **Figure 2**) vs those who concurrently received a maintenance drug and 1L CT then continued with the maintenance treatment (active→mnt in **Figure 2**)

Four studies reported PFS data specifically in *BRCA*m patients

1. SOLO-1: Patients with *BRCA*2m treated with olaparib had a lower PFS HR than those with *BRCA*1m (HR 0.20 vs 0.41; *P*-values not reported), both compared with PBO[4]
2. PAOLA-1: PFS HR was lower in *BRCA*m patients than in *BRCA*wt patients treated with olaparib + bevacizumab (HR 0.31 [*P*<0.0001] vs 0.71 [*P*-value not reported]) compared with PBO + bevacizumab[5]
3. PRIMA: PFS HR was 0.40 (95% CI: 0.27–0.62; *P*-value not reported) in *BRCA*m patients treated with niraparib compared with PBO[6]
4. VELIA/GOG-3005: *BRCA*m patients treated with CT + veliparib followed by veliparib maintenance had a lower PFS HR than patients in the intention-to-treat population (HR 0.44 vs 0.68; both *P*<0.001) when compared with CT + PBO followed by PBO[7]

Figure 2. PFS HRs across studies in the SLR



PFS HR data only included for studies with reported values; error bars indicate 95% CI; missing error bars indicate 95% CI not reported. *PFS investigator-assessed; †PFS assessed by independent central review; ‡reported data were recurrence-free survival; §method of assessment not specified/reported. Active→Mnt, patients given active treatment followed by maintenance treatment; *BRCA*, breast cancer gene; *BRCA*m, *BRCA* mutated; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, intention-to-treat; mnt, maintenance; NACT, neoadjuvant chemotherapy; PBO, placebo; PFS, progression-free survival

OS

OS was included as a secondary endpoint in 12 trials; MIMOSA,[15] SOLO-1,[4] CHIVA/GINECO,[17] and PRIMA[6] reported interim, immature OS data; VELIA/GOG-3005[7] and PAOLA-1[5] OS data were not available due to lack of OS event maturity and ESME[23] data were only descriptive

Across all trial populations, only PARP inhibitor-containing maintenance therapies reported OS HRs below 1; however, the 95% CI all included the null hypothesis (HR=1) (**Figure 3**)

OS data revealed that:

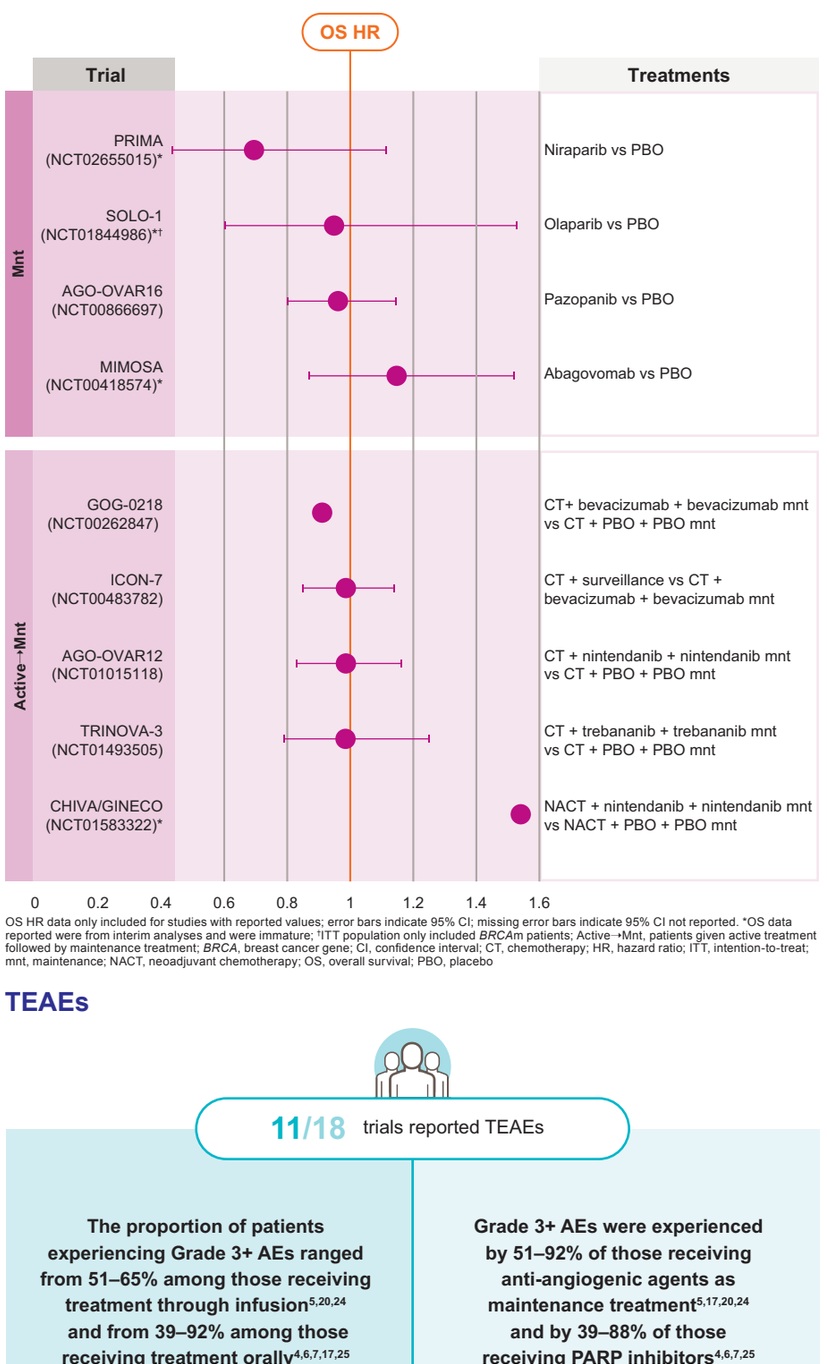
The lowest OS HR was for niraparib vs PBO (HR 0.7 [0.44–1.11], PRIMA[6])

The highest OS HR was for NACT + nintedanib followed by nintedanib maintenance vs NACT + PBO followed by PBO maintenance (HR 1.54; CHIVA/GINECO[17])

These results were interim and immature such that final conclusions on long-term OS results could not be drawn

Niraparib (regardless of *BRCA*m status) and olaparib (*BRCA*m subgroup) resulted in improved OS vs PBO (PRIMA[6]: HR 0.7 [0.44–1.11]; SOLO-1[4]: HR 0.95 [0.60–1.53])

Figure 3. OS HRs across studies in the SLR



OS HR data only included for studies with reported values; error bars indicate 95% CI; missing error bars indicate 95% CI not reported. *OS data reported were from interim analyses and were immature; †ITT population only included *BRCA*m patients; Active→Mnt, patients given active treatment followed by maintenance treatment; *BRCA*, breast cancer gene; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, intention-to-treat; mnt, maintenance; NACT, neoadjuvant chemotherapy; OS, overall survival; PBO, placebo

TEAEs

11/18 trials reported TEAEs

The proportion of patients experiencing Grade 3+ AEs ranged from 51–65% among those receiving treatment through infusion[5,20,24] and from 39–92% among those receiving treatment orally[4,6,7,17,25]

Grade 3+ AEs were experienced by 51–92% of those receiving anti-angiogenic agents as maintenance treatment[5,17,20,24] and by 39–88% of those receiving PARP inhibitors[4,6,7,25]

Conclusions

- **Frontline OC maintenance treatments with PARP inhibitors conferred greater clinical benefit than other types of maintenance therapies, as reported by lower PFS HRs**
- **Niraparib was the only PARP inhibitor monotherapy with which statistically significant clinical benefit in 1L OC maintenance was demonstrated, regardless of biomarker status**
- **OS data largely remained immature for the studies analysed; therefore, the impact of PARP inhibitor maintenance therapy on OS is unclear**

Implications for Field of OC

This SLR generated evidence to inform an indirect treatment comparison feasibility assessment, of maintenance therapies following 1L CT in advanced OC – see Poster 366 (Lorusso et al.) at this meeting

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Abbreviations

1L, first line; AE, adverse event; *BRCA*, breast cancer gene; CT, chemotherapy; HR, hazard ratio; mnt, maintenance; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PBO, placebo; PICOS, population, interventions, comparators, outcomes and study type; PFS, progression-free survival; RCT, randomised controlled trial; SLR, systematic literature review; TEAE, treatment-emergent adverse event

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