Systematic Literature Review of Clinical Data from First-line Treatment or First-line Maintenance Therapy for Advanced or Metastatic Ovarian Cancer (2010–2023)

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Poster #CO133

Background

- Advanced ovarian cancer (aOC) has a high mortality rate despite treatment[1,2]
- First-line (1L) treatment typically consists of a combination of surgery and platinum-based chemotherapy with or without bevacizumab[3]
- More recently, the treatment landscape has evolved to include first-line maintenance (1LM) therapy with poly(ADP-ribose) polymerase (PARP) inhibitors, alone or in combination with bevacizumab, after patients achieved a complete or partial response to an initial fixed number of cycles of platinum-based chemotherapy[3,4]

Conclusions

- Maintenance strategies dominated the focus of recent research efforts, per our analysis of RCTs that evaluated approved or recommended treatments for aOC. Limited treatment options are available in the 1L setting except for platinum-based chemotherapy and bevacizumab
- Direct comparability of results from RCTs in the 1L and 1LM aOC landscape would be hindered by substantial differences in study design and patient population

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Objective

- To design and perform a systematic literature review (SLR) to identify RCTs that evaluated 1L and/or 1LM treatments currently in use or under evaluation to gain a better understanding of clinical outcomes, trial heterogeneity, and the underlying unmet need for improved treatment options for patients with aOC

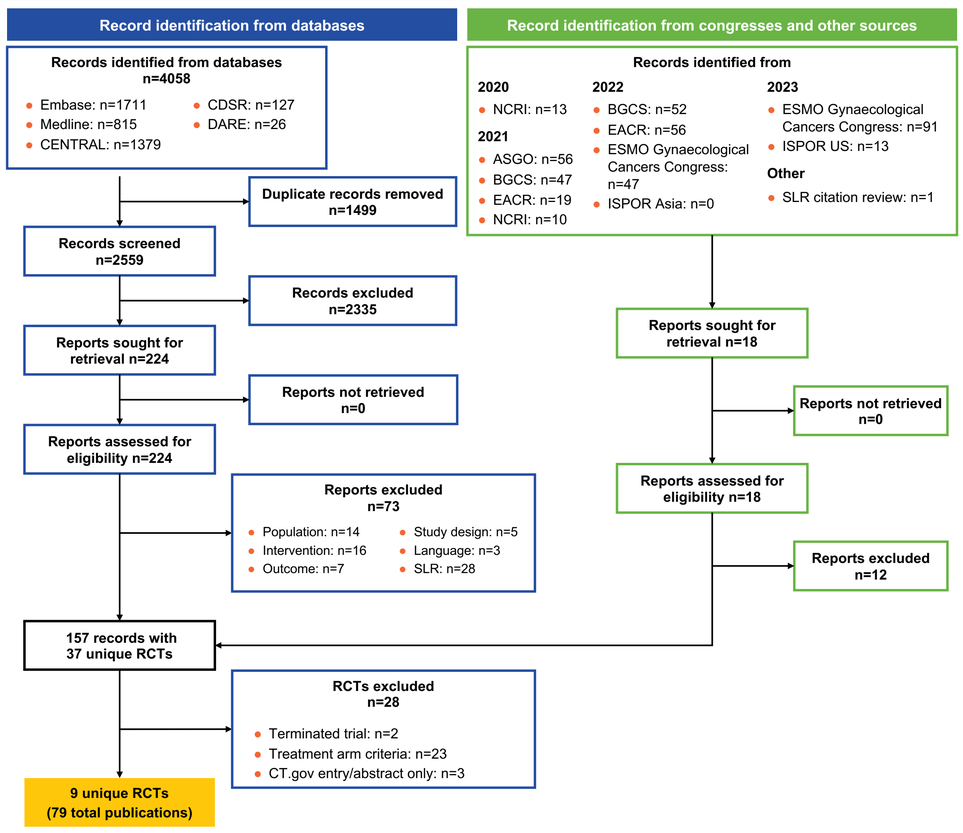
Methods

- The Embase, Medline, CENTRAL, CDSR, and DARE databases were searched between 1 January 2010 and 24 March 2023 for full-text English-language publications reporting efficacy and safety results for patients with aOC who received 1L and/or 1LM treatment
  - The search strategy included a combination of free-text and controlled vocabulary terms for ovarian cancer (OC) combined with 1L and maintenance terms; additional study design terms were added to increase search sensitivity and limit irrelevant articles
  - Search terms were customised for each database (eg, Emtree terms for Embase or Medical Subject Headings in MEDLINE)
- A supplementary congress search from 1 January 2020 to 24 March 2023 was conducted. The Embase database was searched for indexed congresses, and the proceedings of additional prespecified congresses of interest were hand searched
- Health technology assessment submissions from prespecified countries and bibliographies of relevant SLRs and meta-analyses were also hand searched for eligible studies
- Study eligibility was assessed using population, intervention, comparison, outcome, and study design criteria (PICOS)
  - Population: adult women with stage III/IV OC who received 1L and/or 1LM treatment
  - Intervention: systemic pharmacological therapies approved, recommended, or frequently used in clinical practice
  - Comparator: at least 1 systemic pharmacological therapy approved, recommended, or used in clinical practice
  - Outcomes: clinical efficacy (eg, progression-free survival [PFS], overall survival) and safety (eg, total adverse events, treatment discontinuation) outcomes
  - Study design: RCTs
- Terminated trials were not considered for inclusion
- Because the SLR was designed to support future effectiveness and safety comparative analyses, additional restrictions and considerations were applied to the evidence base to comply with the National Institute for Health and Clinical Excellence Decision Support Unit Technical Support Document 1 (NICE DSU TSD1)[5,6] recommendations. In particular, only RCTs with ≥2 relevant treatment arms or those needed to form a connected network were considered. Application of the NICE DSU TSD1 criteria resulted in the inclusion of the DoCaCel trial because of the relevance of the carboplatin + docetaxel arm. In addition, RCTs must have had ≥1 full-text publication for data completeness
- Dual data screening and extraction were conducted using predefined templates to capture publication, study, patient, treatment characteristics, and outcome data of interest; data extraction was conducted by 1 individual and validated by a second
- Quality assessment, including risk of bias, was performed using Cochrane Risk of Bias Assessment Tool 2.0

Results

- The SLR identified a total of 9 RCTs from 79 publications (**Figure 1**; see QR code for the full list of included publications)

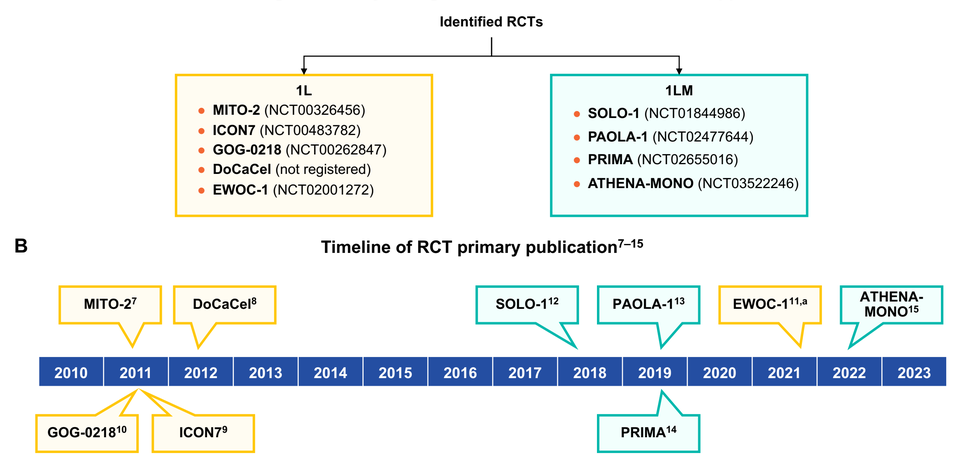
Figure 1 . PRISMA Study Selection (Search Date 24 March 2023)



ASGO, Asian Society of Gynaecologic Oncology; BGCS, British Gynaecological Cancer Society; CDSR, Cochrane Database of Systematic Reviews; CT.gov, ClinicalTrials.gov; DARE, Database of Abstracts of Reviews of Effectiveness; EACR, European Association for Cancer Research; ESMO, European Society of Medical Oncology; ISPOR, The Professional Society for Health Economics and Outcomes Research; NCRI, National Cancer Research Institute; RCT, randomised clinical trial; SLR, systematic literature review.

- The 9 RCTs were categorised into 2 groups by timing of randomisation and treatment approach (**Figure 2A**)
- The primary publications for the 1L RCTs predominately occurred in 2011 and 2012; for 1LM RCTs, primary publications occurred from 2018 to 2022 (**Figure 2B**)

Figure 2 . PRISMA Study Categorisation and Timeline of Primary Publication



[a]No new therapeutic agents investigated; trial evaluated alternative dosing schedules for carboplatin and paclitaxel.
1L, first-line; 1LM, first-line maintenance; RCT, randomised clinical trial.

Results *(cont'd)*

- An overview of study characteristics for 1L trials is provided in **Table 1**
- 1L RCTs were predominately multicountry-based open-label and focused on chemotherapy, with carboplatin + paclitaxel as the most common comparator
- Study populations varied in terms of age and disease stage at diagnosis; no 1L trial had biomarker-related inclusion criteria

Table 1 . Study Characteristics for 1L Trials

Study	Blinding	Study phase	Country	Age	FIGO stage at diagnosis	Biomarker-related inclusion criteria	Evaluated interventions
MITO-2[7]	Open-label	3	Multiple (3 countries)	≤75 y	IC–IV	None	• Carboplatin + paclitaxel (Q3W for 6 cycles) • Carboplatin + pegylated liposomal doxorubicin (Q3W for 6 cycles)
DoCaCel[8]	Open-label	2	Single	Not specified	IC–IV	None	• Carboplatin + docetaxel (Q3W for 6–9 cycles) • Carboplatin + docetaxel + celecoxib (Q3W for 6–9 cycles)
ICON7[9]	Open-label	3	Multiple (11 countries)	≥18 y	High-risk I or IIA[a] IIB–IV[b]	None	• Carboplatin + paclitaxel (Q3W for 6 cycles) • Carboplatin + paclitaxel + bevacizumab (Q3W for 6–9 cycles) + bevacizumab 1LM (Q3W for 12 cycles)[c]
GOG-0218[10]	Double-blind	3	Multiple (4 countries)	≥18 y	III (gross residual disease) IV	None	• Carboplatin + paclitaxel (Q3W cycles 1–6) + placebo (Q3W cycles 2–6) + placebo 1LM (Q3W cycles 7–22) • Carboplatin + paclitaxel (Q3W cycles 1–6) + bevacizumab (Q3W cycles 2–6) + placebo 1LM (Q3W cycles 7–22) • Carboplatin + paclitaxel (Q3W cycles 1–6) + bevacizumab (Q3W cycles 2–6) + bevacizumab 1LM (Q3W cycles 7–22)
EWOC-1[11]	Open-label	2	Multiple (6 countries)	≥70 y	III–IV	None	• Carboplatin (Q3W for 6 cycles) • Carboplatin + paclitaxel (Q3W for 6 cycles) • Carboplatin + paclitaxel (day 1, day 8, day 15, every 4 weeks)

[a]High-risk stage I or IIA disease (grade 3 disease or clear cell carcinoma only). [b]Stage IIB–IV disease (all grades and all histological types). [c]Bevacizumab omitted at cycle 1 if chemotherapy was started within 4 weeks of surgery. Cycles of bevacizumab that were omitted were not replaced.
1L, first-line; 1LM, first-line maintenance; FIGO, International Federation of Gynecologic Oncology; Q3W, every 3 weeks.

- An overview of study characteristics for 1LM trials is provided in **Table 2**
- All 1LM RCTs were phase 3 double-blinded trials that evaluated PARP inhibitor maintenance therapy
- Only 1 trial, PAOLA-1, investigated PARP inhibitor + bevacizumab combination therapy
- 1LM RCT patient populations varied by 1L treatment, *BRCA* mutation status, and homologous recombination–deficiency (HRD) status
- SOLO-1 was the only 1LM RCT that excluded patients based on *BRCA* mutation status; all other 1LM RCTs used *BRCA* and/or HRD status as a stratification factor for randomization

Table 2. Study Characteristics for 1LM Trials

Study	Blinding	Study phase	Country	Age	FIGO stage at diagnosis	Biomarker-related inclusion criteria	1L treatment	Evaluated interventions
SOLO-1[12]	Double-blind	3	Multiple (15 countries)	≥18 y	III–IV	Deleterious or suspected deleterious germline or somatic *BRCA1/2* mutation	Platinum-based chemotherapy without bevacizumab	• Olaparib (orally BID) • Placebo (orally BID)
PAOLA-1[13]	Double-blind	3	Multiple (11 countries)	≥18 y	III–IV	Tumour sample for *BRCA* mutation status testing (stratification factor)	Platinum-taxane chemotherapy + bevacizumab	• Olaparib (BID) + bevacizumab (Q3W for up to 15 mo, including 1L treatment) • Bevacizumab (Q3W for up to 15 mo, including 1L treatment)
PRIMA[14]	Double-blind	3	Multiple (20 countries)	≥18 y	III (inoperable or gross residual disease) IV	Tumour sample for HRD status testing (stratification factor)	Platinum-based chemotherapy	• Niraparib (orally QD) • Placebo (orally QD)
ATHENA-MONO[15]	Double-blind	3	Multiple (24 countries)	≥18 y (≥20 y in South Korea, Taiwan, and Japan)	III–IV	Known *BRCA* mutation result (stratification factor)	Platinum-doublet treatment[a] ± bevacizumab	• Rucaparib (orally BID) + placebo (IV Q4W) for up to 24 mo • Placebo (orally BID) + placebo (IV Q4W) for up to 24 mo

[a]Including a minimum of 4 cycles of a platinum-taxane combination treatment. 1L, first-line; 1LM, first-line maintenance; BID, twice daily; FIGO, International Federation of Gynecologic Oncology; HRD, homologous recombination deficiency; Q3W, every 3 weeks; Q4W, every 4 weeks; QD, once daily.

- The most commonly reported clinical efficacy outcome was PFS
- How PFS was defined, who assessed disease progression, and the tumour response criteria used to assess disease progression varied across trials
- For all 1L RCTs, PFS (primary endpoint) was investigator assessed (**Table 3**)
- Median duration of follow-up for 1L RCTs ranged from almost 1 year (12.7 months) to over 4 years (48.9 months), and significant variations in PFS outcomes were observed across the identified RCTs
- The median investigator-assessed PFS for the overall population varied across 1L RCTs (most mature data available, 1L treatment only/no maintenance):
  - Carboplatin + paclitaxel every 3 weeks: range, 10.3–17.5 months[7,11,16,17]
  - Carboplatin + paclitaxel + bevacizumab every 3 weeks: range, 12.8–19.9 months[16,17]

Table 3. PFS Outcome Assessment Across 1L Studies

Study	Number of patients	Longest median follow-up for PFS[a]	PFS definition[b]	PFS assessor	Tumour response criteria
MITO-2[7]	Randomised, N=820 • Carboplatin + paclitaxel, n=410 • Carboplatin + pegylated liposomal doxorubicin, n=410	40.0 mo	Time interval between random assignment and progression or death, whichever occurred first, or last follow-up for patients alive without progression	Investigator	RECIST 1.0
DoCaCel[8]	Randomised, N=202 • Carboplatin + docetaxel, n=99[c] • Carboplatin + docetaxel + celecoxib, n=97[d]	26.0 mo	Definition not provided	Investigator	CA-125 response (using the Rustin criteria) and RECIST 1.0 criteria
ICON7[9,16]	Randomised, N=1528 • Carboplatin + paclitaxel, n=764 • Carboplatin + paclitaxel + bevacizumab, n=764	48.9 mo	The date of randomisation to the date of the first indication of disease progression or death, whichever occurred first	Investigator	RECIST 1.0
GOG-0218[10,17]	Randomised, N=1873 • Carboplatin + paclitaxel + placebo 1LM, n=625 • Carboplatin + paclitaxel + bevacizumab + placebo 1LM, n=623 • Carboplatin + paclitaxel + bevacizumab + bevacizumab 1LM, n=625	17.4 mo	Considered to have ended at the time of cancer progression according to RECIST; an increase in the CA-125 level according to Gynecologic Cancer InterGroup criteria, global deterioration of health, or death from any cause. Censored for nonprotocol therapy	Investigator	RECIST 1.0
EWOC-1[11]	Randomised, N=120 • Carboplatin (Q3W), n=40 • Carboplatin + paclitaxel (Q3W), n=40 • Carboplatin + paclitaxel (weekly), n=40	12.7 mo	The period from the date of randomisation to the date of disease progression or death, whichever occurs first	Investigator	RECIST 1.1

[a]Per literature published within SLR search period (1 January 2010 and 24 March 2023) for PFS measured per primary endpoint. [b]Definition for primary endpoint per primary analysis publication. [c]Two patients from the carboplatin + docetaxel arm were excluded from PFS analysis because they did not have ovarian cancer. [d]Three patients from the carboplatin + docetaxel + celecoxib arm were excluded from PFS analysis because they did not have ovarian cancer. 1L, first-line; 1LM, first-line maintenance; CA-125, cancer antigen 125; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SLR, systematic literature review.

- For 1LM RCTs, PFS (primary endpoint) was predominately investigator assessed (**Table 4**)
- The longest available median duration of follow-up for 1LM RCTs ranged from 13.8 months to 5 years, and PFS outcomes varied across trials for patients treated with placebo
- The median PFS for the overall population varied across 1LM RCTs (most mature data available, definition per primary endpoint):
  - Placebo: range, 8.2–13.8 months[14,15,18]
  - PARP inhibitor monotherapy: range, 13.8–56.0 months[14,15,18]

Table 4. PFS Outcome Assessment Across 1LM Studies

Study	Number of patients	Longest median follow-up for PFS[a]	PFS definition[b]	PFS assessor	Tumour response criteria
SOLO-1[12,18]	Randomised, N=390 • Olaparib, n=260 • Placebo, n=130	Olaparib: 4.8 y Placebo: 5.0 y	Time from randomisation to objective disease progression on imaging (according to modified RECIST, version 1.1) or death from any cause	Investigator	RECIST 1.1
PAOLA-1[13,19]	Randomised, N=806 • Olaparib + bevacizumab, n=537 • Bevacizumab, n=269	Olaparib + bevacizumab: 56.7 mo Bevacizumab: 57.8 mo	Clinical progression or progression according to the serum level of CA-125	Investigator	RECIST 1.1
PRIMA[14]	Randomised, N=733 • Niraparib, n=487 • Placebo, n=246	13.8 mo	Time from randomisation after completion of platinum-based chemotherapy to the earliest date of objective disease progression on imaging or death from any cause	BICR	RECIST 1.1
ATHENA-MONO[15]	Randomised, N=538 • Rucaparib, n=427 • Placebo, n=111	Rucaparib: 26.1 mo Placebo: 26.2 mo	Definition not provided	Investigator	RECIST 1.1

[a]Per literature published within SLR search period (1 January 2010 and 24 March 2023) for PFS measured per primary endpoint. [b]Definition for primary endpoint per primary analysis publication. 1LM, first-line maintenance; BICR, blinded independent central review; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SLR, systematic literature review.

- Available PFS data varied widely both in data maturity and follow-up duration
- Clinical heterogeneity precluded cross-trial comparisons

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Conflicts of Interest

Soham Shukla and **Zsofia Kiss** are employees of and hold stock in GSK.
Katherine Appiah, Andreas Freitag, Rachel Van Dusen, and **Grammati Sarri** are employees of Cytel, a consulting company that has provided paid consulting services to GSK, which funded the development and conduct of this study and poster. **Grammati Sarri** also reports an unremunerated leadership position with the International Society of Pharmacoepidemiology (chair of the Comparative Effectiveness Research Special Interest Group).