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Comparative efficacy and safety of low-dose versus high-dose bevacizumab in ovarian cancer: An indirect treatment comparison

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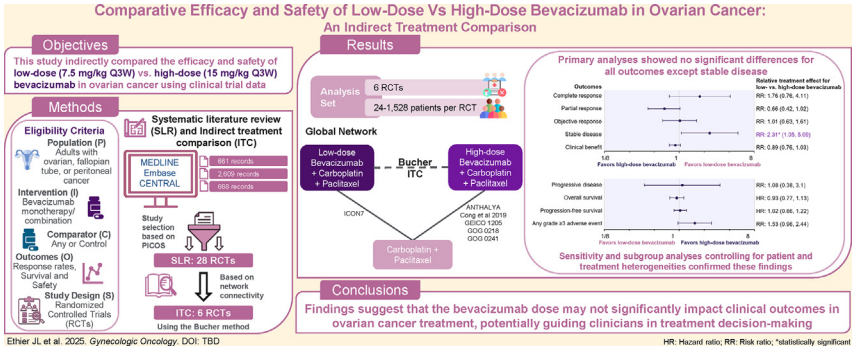
HIGHLIGHTS

- First review and analysis comparing the efficacy and safety of low-dose vs. high-dose bevacizumab in ovarian cancer.
- Indirect comparison showed no significant difference in low-dose vs. high-dose bevacizumab with carboplatin + paclitaxel.
- Sensitivity and subgroup analyses confirmed consistent findings for response rates, survival, and safety outcomes.
- Overall findings suggest that bevacizumab dose may not significantly impact clinical outcomes in ovarian cancer.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. First-line therapy for ovarian cancer involves cytoreductive surgery and platinum-based chemotherapy, with or without bevacizumab. Bevacizumab can be administered at low (7.5 mg/kg every three weeks [Q3W]) or high dose (15 mg/kg Q3W). This study compared the efficacy and safety of these dosing strategies.

Methods. Systematic literature review of Embase, MEDLINE®, and CENTRAL (18/09/2023) identified randomized controlled trials (RCTs) evaluating bevacizumab versus any therapy or control in ovarian, fallopian tube, or primary peritoneal cancer. Indirect treatment comparisons (ITC) of response, survival, and safety outcomes were performed, including sensitivity/subgroup analyses adjusting for heterogeneity.

Results. Six RCTs (sample size: 24–1528 patients) were included for ITC. Five evaluated high-dose bevacizumab with chemotherapy. The common comparator was carboplatin + paclitaxel. Trials mainly included stage III ($n = 4$) or stage II-III ($n = 1$) ovarian cancer patients; one did not report cancer stage. Primary analyses showed no significant differences between low- versus high-dose bevacizumab for partial response (risk ratio [95 % confidence interval]: 0.66 [0.42, 1.02]), complete response (1.76 [0.76, 4.11]), objective response rate (1.01 [0.63, 1.61]), progressive disease (1.08 [0.38, 3.10]), clinical benefit (0.89 [0.76, 1.03]), any grade ≥ 3 adverse event (1.53 [0.96, 2.44]), specific grade ≥ 3 adverse events, overall survival (hazard ratio: 0.93 [0.77, 1.13]), or progression-free survival (1.02 [0.86, 1.22]). Sensitivity and subgroup analyses confirmed findings.

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Conclusions. This ITC found no significant difference in clinical outcomes between low- and high-dose bevacizumab combination therapy. Despite limitations of small sample size and heterogeneities, findings suggest that bevacizumab dose may not significantly impact ovarian cancer outcomes.

Contents

1. Introduction

Ovarian cancer ranks as the third most prevalent and the deadliest gynecological cancer among women worldwide [1,2]. Due in part to a lack of a definitive screening tool, vague signs and symptoms that can mimic other non-malignant conditions, and the aggressive tendency of ovarian cancer to progress, more than 70 % of patients are diagnosed at an advanced stage [3]. The current first-line (1 L) therapy for advanced ovarian cancer involves a combination of cytoreductive surgery and platinum-based chemotherapy to achieve no residual disease [4]. Despite the effectiveness of 1 L therapy, recurrence is common, with more than 50 % of patients experiencing disease recurrence within two years [5]. This high recurrence rate highlights the need for additional treatments and maintenance strategies to extend the period of remission and improve long-term outcomes.

To treat ovarian cancer recurrence and improve outcomes, targeted therapies, including anti-vascular endothelial growth factor (VEGF) antibodies, have become an essential component of treatment [6,7]. Bevacizumab (BEV) is a monoclonal antibody that targets and inhibits VEGF-A and is used at different dosages of 7.5 mg/kg every three weeks (Q3W), 10 mg/kg Q2W, or 15 mg/kg Q3W depending on the clinical scenario. For platinum-sensitive recurrent epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC), BEV is administered at 15 mg/kg Q3W in combination with carboplatin and gemcitabine, followed by continued use as a single agent until disease progression, consistent with dosing used in the OCEANS clinical trial [8]. For platinum-resistant recurrent cases, BEV is given at 10 mg/kg Q2W with paclitaxel, topotecan, or pegylated doxorubicin, or 15 mg/kg Q3W with topotecan administered on days 1–5 Q3W based on the AURELIA clinical trial [8]. The lowest dosage of BEV at 7.5 mg/kg, although less commonly used, has been evaluated in a clinical trial on high-risk, early-stage or advanced EOC, PPC, or FTC [9].

In the front-line setting, the ICON7 trial [9] compared low-dose BEV (7.5 mg/kg Q3W) + carboplatin + paclitaxel to carboplatin + paclitaxel, while the GOG 0218 trial [10] compared high-dose BEV (15 mg/kg Q3W) + carboplatin + paclitaxel to carboplatin + paclitaxel. Based on the results of these trials, low-dose BEV is funded in all Canadian provinces except for Prince Edward Island, where it is currently under provincial consideration [11,12], and Québec, where it is not covered under the Public Prescription Drug Insurance Plan [12,13].

Recent advancements in treatment strategies include combining BEV with other novel agents. The PAOLA-1 trial (NCT02477644) investigated the efficacy and safety of adding the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib to BEV (15 mg/kg Q3W) as a 1 L maintenance therapy for newly diagnosed advanced ovarian cancer patients who responded to initial platinum-taxane chemotherapy and BEV. Findings demonstrated a significant benefit for patients with homologous recombination deficiency (HRD+), including those with genome instability and/or *BRCA1*/*BRCA2* mutations. In this group, maintenance therapy with olaparib and BEV reduced the risk of disease progression or death by 67 % compared to BEV with a placebo [14]. Five-year overall survival rates in HRD+ patients were 66 % for patients receiving olaparib + BEV compared to 48 % for patients receiving BEV. Five-year progression-free survival rates were 46 % for patients receiving olaparib + BEV compared with 19 % for patients receiving BEV [15].

A previous narrative review of BEV dosing in solid tumor malignancies [16] described studies that led to the approval of BEV in clinical practice, including ICON7 [9], GOG 0218 [10], AURELIA [17], and OCEANS [18]. Direct clinical trials comparing the efficacy and safety of high-dose versus low-dose BEV are limited [19,20] and not available for ovarian cancer. Here, we aim to undertake a systematic review and indirect treatment comparison (ITC) to compare the efficacy and safety of low-dose versus high-dose BEV, as a standalone treatment or in combination with other therapies, in patients diagnosed with ovarian cancer.

2. Methods

2.1. Data sources and search strategies

Standard methodologies outlined in the Cochrane Collaboration's Handbook for Systematic Reviews of Interventions were followed [21]. The findings were presented in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22].

Relevant publications were identified by searching Embase, MEDLINE®, and Cochrane Central Register of Controlled Trials (CENTRAL) via OvidSP from database inception to September 18, 2023, using predefined search strategies (**Supplementary Table S1-S3**). Abstracts published between 2020 and 2023 from the following conferences were also searched: American Association for Cancer Research, American Society of Clinical Oncology, American Society of Clinical Oncology Genitourinary, Canadian Cancer Research Alliance, European Society of Gynecological Oncology, European Society for Medical Oncology, International Gynecologic Cancer Society, International Society for Pharmacoeconomics and Outcomes Research, Ovarian Cancer Canada, and Society of Gynecologic Oncology. Additionally, searches for gray literature included clinical trials registry databases for clinical trials that have reported results but were not published in peer-reviewed journals (http://clinicaltrials.gov, https://www.clinicaltrialsregister.eu). Finally, searches of bibliographies of included literature reviews were conducted.

2.2. Study selection

For inclusion into the SLR, study identification and eligibility criteria were developed using the Population, Intervention, Comparator, and Outcome (PICO) framework. Randomized controlled trials (RCTs) evaluating the efficacy or safety of BEV monotherapy or in combination with other therapies compared to any other therapy or control in adult patients with ovarian cancer were included. The efficacy outcomes of interest were survival outcomes, including overall survival and progression-free survival, and response outcomes, including objective response rate, complete response, partial response, and stable disease. Safety outcomes of interest were serious adverse events, treatment-emergent serious adverse events, discontinuation, and mortality. Studies including pediatric or adolescent patients were excluded. Publications in languages other than English were also excluded. For the ITC, only studies that allowed the comparison between low-dose and high-dose BEV indirectly through a common comparator treatment were included.

Two independent reviewers (EK and MMP) performed abstract selection and full-text selection. Any unresolved discrepancies occurring between the two reviewers were resolved through arbitration by a third senior reviewer (MSF) to reach a consensus.

2.3. Data extraction and quality assessment

The same two independent reviewers (EK and MMP) performed data extraction of included studies, and a third reviewer (MSF) resolved

Table 1
Analysis sets.

Analysis set	Definition	Rationale
Primary analysis A	Included all trials with the comparator arm C + P	The primary analysis was conducted with and without the addition of a placebo in addition to treatment as the common comparator to consider the potential influence of receiving placebo. This only included one trial (GOG 0218 [10]) that administered placebo in addition to C + P.
Primary analysis B	Allowed trials with placebo in addition to treatment	
Sensitivity analysis 1 A	Restricted to trials with six cycles of C + P and front-line treatment	Sensitivity analysis 1 was conducted to adjust for heterogeneity in treatment administered (i.e., line of treatment, number of treatment cycles) across the included trials.
Sensitivity analysis 1B	Restricted to trials with six cycles of C + P and front-line treatment, and allowed trials with placebo in addition to treatment	
Sensitivity analysis 2*	Restricted to trials that included a majority of stage IIIC patients (outcomes in included trials were reported regardless of disease stage)	Sensitivity analysis 2 was conducted to adjust for heterogeneity in disease stage across trials. In three trials, ICON7 [9], ANTHALYA [27], and GEICO 1205 [28], the majority of patients had stage IIIC ovarian cancer. GOG 0218 [10] included mainly patients with stage III (any substage) ovarian cancer, and GOG 0241 [29] included mostly stage II-III ovarian cancer patients. Cong 2019 [30] did not report cancer stage.
Subgroup analysis 1*	Included only patients with stage III ovarian cancer.	Subgroup analyses were conducted to adjust for heterogeneity in the disease stage of patients across the included trials.
Subgroup analysis 1.1*	Included only patients with stage III (tumor ≤1 cm) ovarian cancer	
Subgroup analysis 1.2*	Included only patients with stage III (tumor >1 cm) ovarian cancer	
Subgroup analysis 2*	Included only patients with stage IV ovarian cancer	
Sensitivity analysis 3 A	Restricted to trials with similar types of ovarian cancer (i.e., excluding mucinous ovarian cancer)	Sensitivity analysis 3 was conducted to adjust for heterogeneity in cancer type, as GOG 0241 [29] only included patients with mucinous ovarian cancer, while other trials did not include patients with mucinous ovarian cancer, or inclusion of such patients was limited (<5 %).
Sensitivity analysis 3B	Restricted to trials with similar types of ovarian cancer (i.e., excluding mucinous ovarian cancer), and allowed trials with placebo in addition to treatment	
Sensitivity analysis 4 A	Excluded trials where all patients received BEV maintenance therapy after surgery (comparison only in pre-operative setting)	Sensitivity analysis 4 was conducted to adjust for heterogeneity in subsequent treatment. In ANTHALYA [27] and GEICO 1205 [28], both treatment arms, one of which originally did not receive BEV, received BEV after undergoing interval debulking surgery.
Sensitivity analysis 4B	Excluded trials where all patients received BEV maintenance therapy after surgery and allowed trials with placebo in addition to treatment (comparison only in pre-operative setting)	

BEV, bevacizumab; C, carboplatin; OS, overall survival; P, paclitaxel; PFS, progression-free survival.
* No separate analyses (i.e., analysis A/analysis B allowing/not allowing trials with placebo in addition to treatment) were conducted for this analysis, as these analysis sets would include the same trials based on reported outcomes and lead to equivalent results.

any discrepancies between the two reviewers. Data extraction included study, intervention, patient characteristics, and outcomes. Baseline patient characteristics of interest were age, sex, race/ethnicity, disease stage, performance status, mutational status, genomic instability markers, tumor homologous recombination deficiency status, histology, prior treatment experience, and comorbidities.

Study quality was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [23].

2.4. Statistical analysis

Before conducting the ITC, a comprehensive feasibility assessment was performed to evaluate if a quantitative analysis was possible and feasible [24]. Based on the feasibility assessment, heterogeneities were observed across trials for treatment (e.g., the number of treatment cycles, line of treatment, maintenance therapy) and disease characteristics (e.g., disease stage, ovarian cancer type). To address such heterogeneities, various sensitivity analyses were conducted to validate the reliability of the primary analysis, and subgroup analyses were conducted to identify differences in treatment effects among subgroups based on cancer stage, resulting in 13 sets of analyses in total (Table 1).

In the absence of direct comparisons, ITCs were conducted using the Bucher method, which applies to the "simple star" pattern of the network of the available evidence base, involving only three treatment nodes [25]. If a direct treatment comparison had multiple studies or multiple subpopulations of the same studies, the estimates from those studies/subpopulations were combined using random-effects (RE) pairwise meta-analysis to derive a single estimate of the relative treatment effect. Risk ratios (RRs) were calculated for binary event outcomes and hazard ratios (HRs) were calculated for survival outcomes.

All analyses were conducted using the 'metafor' package for R version 4.3.1 (http://www.r-project.org/) [26], implementing the RE (restricted maximum likelihood estimator for tau) models. For presentation, log-transformed RRs and HRs and their 95 % CIs were

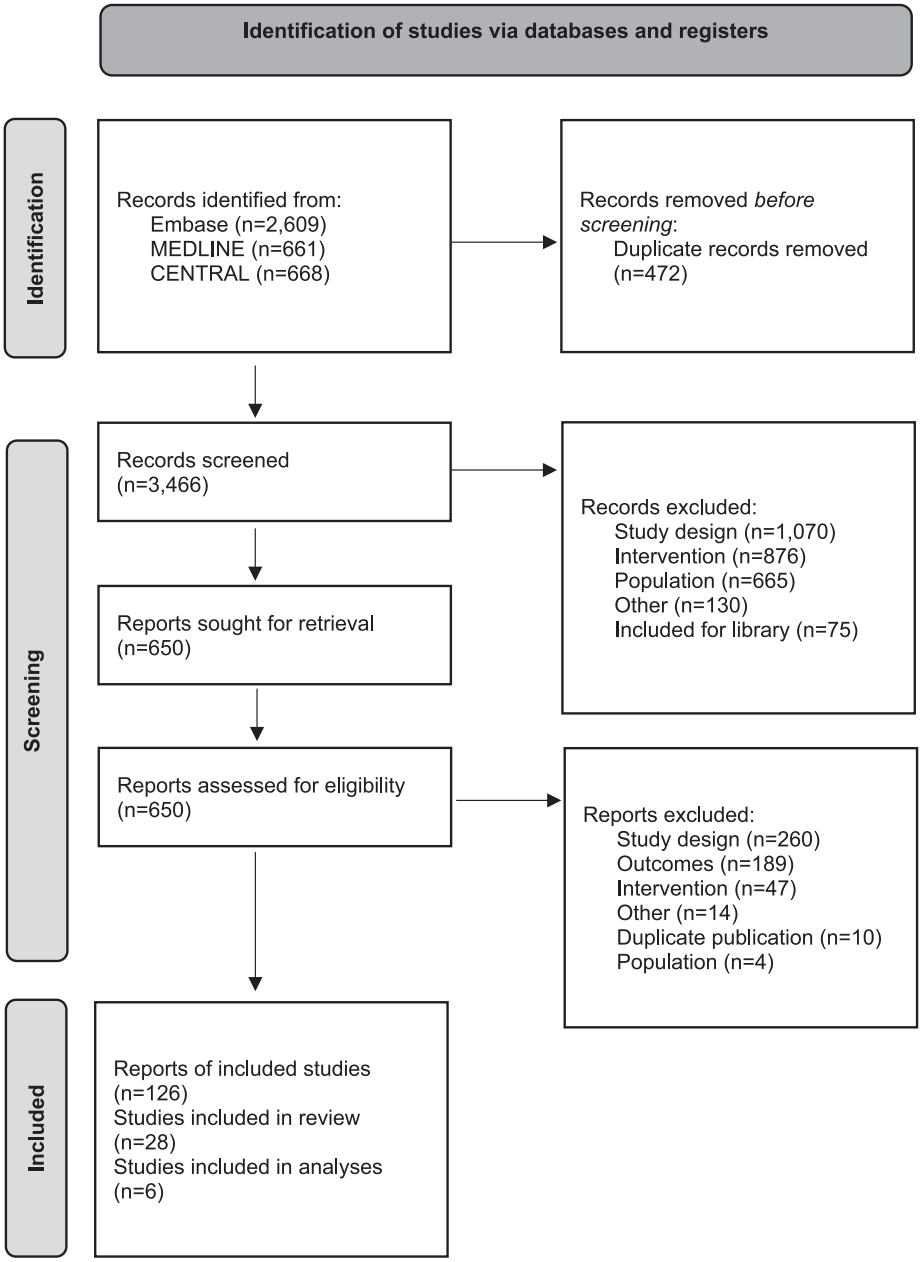

Fig. 1. Study selection process.

converted back to RRs and HRs using the exponential function. The null hypothesis of equality between treatments was evaluated for each analysis. A type I error rate of 5 % was used to evaluate statistical significance.

3. Results

3.1. Study selection

The SLR search identified a total of 3938 records. Following screening, 126 publications representing 28 unique RCTs were included in the SLR. The most common reasons for the exclusion of studies were based on study design (i.e., the study was not an RCT), outcomes (i.e., the study did not report efficacy or safety outcomes of interest), and intervention (i.e., the study did not include BEV). Data were extracted for all studies. Finally, six RCTs were included in the ITC based on network connectivity through a common comparator. A list of all included 28 RCTs is provided in **Supplementary Table S4**. The study selection process is summarized in Fig. 1.

3.2. Study characteristics

The SLR identified six RCTs that formed a connected network to allow the comparison between low-dose and high-dose BEV indirectly through a common comparator treatment. ICON7 was the only RCT that studied low-dose BEV while all other trials studied high-dose BEV. The common comparator was carboplatin + paclitaxel in all studies except for GOG 0218 [10], which included placebo in addition to carboplatin + paclitaxel. Notably, the comparator arm of the studies ANTHALYA [27] and GEICO 1205 [28] included BEV in addition to carboplatin + paclitaxel in the post-operative setting. As a result, only outcomes reported for the pre-operative setting in these trials were included in the analyses. The global network based on all outcomes is presented in Fig. 2.

Study and intervention characteristics are summarized in Table 2. Sample size across the six trials ranged from 24 [29] to 1528 [9] with a median of 130 patients. Two trials were phase II [27,28], three were phase III [9,10,29], and one did not report the study phase [30]. Most studies were multi-center [9,10,27–29], while one trial was a single-center trial [30]. Four trials were open-label [9,27–29], one was double-blind [10], and blinding was not reported in the remaining trial [30]. Three trials were multinational [9,10,29], while one trial each was conducted in Spain, France, and China, respectively [27,28,30].

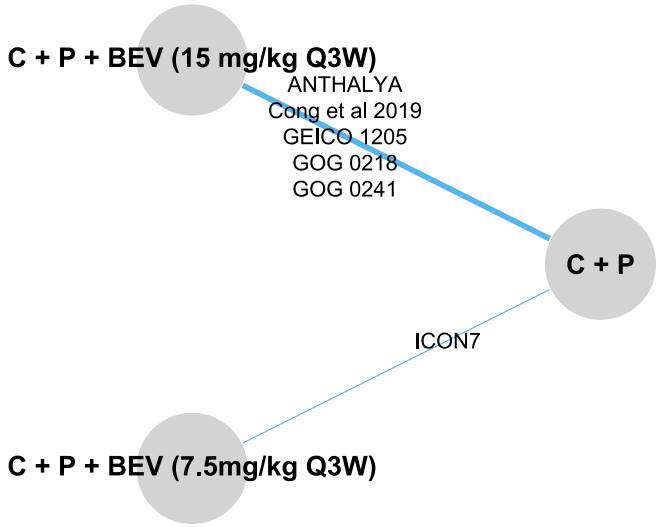

Fig. 2. Global network of included studies.

Baseline patient characteristics are summarized in Table 3. The median age was reported by five studies [9,10,27–29] and ranged from 51 [29] to 63 [27] years (median of medians across studies: 60). Race/ethnicity was reported by two studies [9,10], in which most patients were white (83.6 %; 96.0 %). Disease stage as measured by the International Federation of Gynecology and Obstetrics (FIGO) criteria was reported in five trials. ICON7 [9], GEICO 1205 [28], and ANTHALYA [27] included mostly stage IIIC ovarian cancer (56.9 %–69.5 %) patients, GOG 0218 [10] included mostly stage III (73.8 %) patients, and GOG 0241 [29] mostly included stage III (45.9 %) or stage II (33.6 %) patients. Performance status as measured by Eastern Cooperative Oncology Group (ECOG) criteria was reported in four studies [9,27–29], and as measured by Gynecologic Oncology Group (GOG) criteria in one study [10]. All trials included patients with ECOG/GOG 0, 1, or 2, with a median proportion of patients with ECOG/GOG 0 of 45.3 %, with ECOG/GOG 1 of 47.1 %, and with ECOG/GOG 2 of 5.8 %. Histology was reported in five trials [9,10,27–29]. ICON7 [9], GEICO 1205 [28], ANTHALYA [27], and GOG 0218 [10] mostly included patients with serous ovarian cancer (69.0 %–95.2 %). In GOG 0218 [10], more than 80 % of patients had high-grade serous histology, while in the ANTHALYA [27] and GEICO 1205 [28] trials, 90 % and 100 % of cases of serous histology were high-grade, respectively. GOG 0241 [29] included patients with mucinous ovarian cancer only, of which 40.6 % of patients had confirmed mucinous histology after a central pathology review and 59.4 % had unconfirmed mucinous histology. Finally, tumor grade was reported in three trials. GEICO 1205 [28], ANTHALYA [27], and GOG 0218 [10] included mostly patients with poorly differentiated tumors.

3.3. Study quality assessment and risk of bias

The Cochrane RoB 2 tool for randomized trials was used for study quality assessment (**Supplementary Table S5**). The included studies were of generally moderate quality; however, there were some biases based on the absence of blinding of the participants and study personnel to the treatment being administered.

3.4. Indirect treatment comparison

Six RCTs were included in the ITCs. In the primary analyses, no significant differences were observed between low- and high-dose BEV treatment in combination with carboplatin + paclitaxel for partial response (RR [95 % confidence interval for low versus high-dose BEV]: 0.66 [0.42, 1.02]), complete response (RR: 1.76 [0.76, 4.11]), objective response rate (RR: 1.01 [0.63, 1.61]), progressive disease (RR: 1.08 [0.38, 3.10]), clinical benefit, defined as the proportion of patients who achieved complete response, partial response, or stable disease (RR: 0.89 [0.76, 1.03]), overall survival (HR: 0.93 [0.77, 1.13]), progression-free survival (HR: 1.02 [0.86, 1.22]), any grade ≥ 3 adverse event (RR: 1.53 [0.96, 2.44]), grade ≥ 3 bleeding (RR: 5.31 [0.08, 332.01]), grade ≥ 3 gastrointestinal perforation (RR: 3.93 [0.07, 226.26]), grade ≥ 3 hypertension (RR: 3.87 [0.16, 94.16]), grade ≥ 3 neutropenia (RR: 1.00 [0.77, 1.28]), or grade ≥ 3 proteinuria (RR: 4.08 [0.31, 54.34]). A summary of the results of the primary analyses is depicted in Table 4.

Similarly, in both the sensitivity analyses (**Supplementary Table S6**) and subgroup analyses (**Supplementary Table S7**), no significant differences were observed between low-dose BEV + carboplatin + paclitaxel and high-dose BEV + carboplatin + paclitaxel for partial response, complete response, objective response rate, progressive disease, clinical benefit, overall survival, progression-free survival, any grade ≥ 3 adverse event, or specific grade ≥ 3 adverse events such as bleeding, gastrointestinal perforation, hypertension, neutropenia, and proteinuria. The forest plots for all primary, sensitivity, and subgroup analyses can be found in **Supplementary Fig. S1-S34**.

The only significant difference was observed for stable disease in the primary analysis and sensitivity analysis 3 A, which was restricted to trials with similar types of ovarian cancer (i.e., excluding trials that

Table 2
Study and intervention characteristics of included studies.

Trial	Phase	Blinding	Country	Setting	Sample Size	Intervention	Comparator	Line of Treatment
ANTHALYA [27]	II	Open-label	France	Multi-center	95	High-dose BEV + carboplatin + paclitaxel	Carboplatin + paclitaxel (post-operative: + BEV)	1 L
Cong 2019 [30]	NR	NR	China	Single center	164	High-dose BEV + carboplatin + paclitaxel	Carboplatin + paclitaxel	≥2 L
GEICO 1205 [28]	II	Open-label	Spain	Multi-center	68	High-dose BEV + carboplatin + paclitaxel	Carboplatin + paclitaxel (post-operative: + BEV)	1 L
GOG 0218 [10]	III	Double-blind	Multi-national	Multi-center	1248	High-dose BEV + carboplatin + paclitaxel + placebo	Carboplatin + paclitaxel + placebo	1 L
GOG 0241 [29]	III	Open-label	Multi-national	Multi-center	24	High-dose BEV + carboplatin + paclitaxel	Carboplatin + paclitaxel	1 L
ICON7 [9]	III	Open-label	Multi-national	Multi-center	1528	Low-dose BEV + carboplatin + paclitaxel	Carboplatin + paclitaxel	1 L

1 L, first line; 2 L, second line; BEV, bevacizumab; NR, not reported.

included patients with mucinous ovarian cancer only). Patients receiving low-dose BEV in combination with carboplatin + paclitaxel were 2.31 times and 2.38 times more likely, respectively, to achieve stable disease than patients receiving high-dose BEV + carboplatin + paclitaxel. Although the direction of the effect was equivalent, no significant differences in stable disease were observed between low-dose and high-dose BEV combined with carboplatin + paclitaxel in sensitivity analysis 1, which was restricted to trials with six treatment cycles and front-line treatment.

4. Discussion

This study assessed the relative efficacy and safety of low-dose (7.5 mg/kg Q3W) versus high-dose (15 mg/kg Q3W) BEV in combination with other therapies in patients with ovarian cancer within RCTs. Six RCTs formed a connected network allowing indirect comparisons between the two doses via the common comparator treatment carboplatin + paclitaxel. The outcomes evaluated included response rates, survival, and safety. The primary analyses showed no significant differences between low-dose and high-dose BEV when combined with carboplatin + paclitaxel for complete response, partial response, objective response, overall survival, progression-free survival, or safety outcomes (any grade ≥ 3 adverse event and specific grade ≥ 3 adverse events like bleeding, gastrointestinal perforation, hypertension, neutropenia, and proteinuria). To address patient and treatment heterogeneities in the primary analysis, multiple sensitivity and subgroup analyses were conducted to analyze more homogeneous populations, which yielded comparable results to the primary analyses, demonstrating consistency.

The only significant difference between low-dose and high-dose BEV combined with carboplatin + paclitaxel was observed in stable disease rates; patients on low-dose BEV were more likely to achieve stable disease compared to those on high-dose BEV. Notably, stable disease may be difficult to interpret as it can be considered positive in scenarios where the treatment goal is to maintain the current condition but is less favorable compared to achieving a partial or complete response. Additionally, while there was a notable difference between low- and high-dose BEV in terms of stable disease alone, this difference did not translate into a significant difference when stable disease was considered as part of the broader composite outcome of clinical benefit, which also includes partial response and complete response. Therefore, the impact of the observed difference in stable disease alone may be less

Table 3
Baseline patient characteristics of included studies.

Trial	Age (Median)	Race/Ethnicity (%)	Disease Stage (%)	Performance Status (%)	Histology	Tumor Grade
ANTHALYA [27]	63 years	NR	IIIC: 69.5 % IV: 30.5 %	ECOG 0: 38.4 % ECOG 1: 54.5 % ECOG 2: 5.8 % Missing: 1.3 %	Serous: 95.2 % Other: 3.1 % Endometrioid: 0.9 % Serous/Endometrioid: 0.9 %	Poorly differentiated: 87.6 % Well-differentiated: 6.8 % Missing: 5.6 %
Cong 2019 [30]	Range: 38 to 74 years	NR	NR	NR	NR	NR
GEICO 1205 [28]	60 years	NR	IIIC: 66.2 % IV: 33.8 %	ECOG 0: 19.1 % ECOG 1: 66.1 % ECOG 2: 14.9 %	Serous: 78.0 % Adenocarcinoma: 17.6 % Endometrioid: 4.5 %	Poorly differentiated: 98.5 % Missing: 1.5 %
GOG 0218 [10]	60 years	White: 83.6 % Asian/Black/Other: 16.4 %	III: 74.3 % IV: 25.7 %	GOG 0: 49.7 % GOG 1: 43.2 % GOG 2: 7.1 %	Serous: 84.8 % Other: 8.7 % Clear cell: 2.8 % Endometrioid: 2.8 % Mucinous: 0.9 %	Poorly differentiated: 72.8 % Moderately differentiated: 15.1 % Missing: 7.1 % Well-differentiated: 5.2 %
GOG 0241 [29]	51 years	NR	Recurrence after stage I: 12.3 % II: 33.6 % III: 45.9 % IV: 8.4 %	ECOG 0: 53.5 % ECOG 1: 42.0 % ECOG 2: 4.6 %	Mucinous (unconfirmed): 59.4 % Mucinous (confirmed): 40.6 %	NR
ICON7 [9]	57 years	White: 96.0 % Asian/Black/Other: 4.0 %	I/IIA: 9.3 % II: 9.2 % III: 2.1 % IIIA: 3.6 % IIIB: 5.9 % IIIC: 56.9 % IV: 13.2 %	ECOG 0: 46.0 % ECOG 1: 48.0 % ECOG 2: 6.0 %	Serous: 69.0 % Clear cell: 8.4 % Endometrioid: 7.7 % Other: 7.1 % Mixed: 5.8 % Mucinous: 2.3 %	NR

ECOG, Eastern Cooperative Oncology Group; GOG, Gynecologic Oncology Group; NR, not reported.

Table 4
Summary table of the primary analysis results.

Outcome	Primary analysis			
	A		B	
	Included trials	Estimate (95 % CI) for low vs. high-dose BEV	Included trials	Estimate (95 % CI) for low vs. high-dose BEV
Complete response	ICON7, Cong et al. 2019, GOG 0241	RR: 1.76 (0.76, 4.11)	ICON7, Cong et al. 2019, GOG 0241	Equivalent to primary analysis A
Partial response	ICON7, Cong et al. 2019, GOG 0241	RR: 0.66 (0.42, 1.02)	ICON7, Cong et al. 2019, GOG 0241	Equivalent to primary analysis A
Stable disease	ICON7, Cong et al. 2019, GOG 0241	RR: *2.31 (1.05, 5.09)	ICON7, Cong et al. 2019, GOG 0241	Equivalent to primary analysis A
Progressive disease	ICON7, Cong et al. 2019	RR: 1.08 (0.38, 3.10)	ICON7, Cong et al. 2019	Equivalent to primary analysis A
Clinical benefit	ICON7, Cong et al. 2019, GOG 0241	RR: 0.89 (0.76, 1.03)	ICON7, Cong et al. 2019, GOG 0241	Equivalent to primary analysis A
Objective response	ICON7, ANTHALYA, Cong et al. 2019, GOG 0241	RR: 1.01 (0.63, 1.61)	ICON7, ANTHALYA, Cong et al. 2019, GOG 0241	Equivalent to primary analysis A
OS hazard ratio	–	–	ICON7, GOG 0218	HR: 0.93 (0.77, 1.13)
PFS hazard ratio	–	–	ICON7, GOG 0218	HR: 1.02 (0.86, 1.22)
Any grade ≥ 3 adverse event	ICON7, ANTHALYA, GEICO 1205, GOG 0241	RR: 1.53 (0.96, 2.44)	ICON7, ANTHALYA, GEICO 1205, GOG 0241	Equivalent to primary analysis A
Grade ≥ 3 bleeding	ICON7, GOG 0241	RR: 5.31 (0.08, 332.01)	ICON7, GOG 0241	Equivalent to primary analysis A
Grade ≥ 3 gastrointestinal perforation	ICON7, GOG 0241	RR: 3.93 (0.07, 226.26)	ICON7, GOG 0241	Equivalent to primary analysis A
Grade ≥ 3 hypertension	ICON7, GOG 0241	RR: 3.87 (0.16, 94.16)	ICON7, GOG 0241	Equivalent to primary analysis A
Grade ≥ 3 neutropenia	–	–	ICON7, GOG 0218	RR: 1.00 (0.77, 1.28)
Grade ≥ 3 proteinuria	–	–	ICON7, GOG 0218	RR: 4.08 (0.31, 54.34)

Note: Clinical benefit was a composite outcome of complete response, partial response, and stable disease.
Note: Objective response was a composite outcome of complete response and partial response.
Note: Primary analysis A included all trials with the comparator arm C + P; primary analysis B allowed trials with placebo in addition to treatment.
* , statistical significance; CI, confidence interval; HR, hazard ratio; n, number of included trials; OS, overall survival; PFS, progression-free survival; RR, risk ratio.

substantial or influential when viewed within the context of overall treatment efficacy.

To our knowledge, no studies directly compare response and survival outcomes between low-dose and high-dose BEV in ovarian cancer. While previous reviews have explored treatment options for ovarian cancer [31–36], none specifically compared low-dose versus high-dose BEV. Falk et al. [16] conducted a narrative review discussing BEV dosing in pivotal studies that led to its approval for various advanced cancers. For ovarian cancer, the authors summarized findings from four RCTs (ICON7 [9], GOG 0218 [10], AURELIA [17], and OCEANS [18]), all included in this current study. They concluded that low-dose BEV should be prioritized in 1 L ovarian cancer treatment, particularly based on findings from the ICON7 trial [16]. However, no comparative analysis was undertaken. In contrast, the current study found no clear evidence favoring one BEV dose over the other.

Another finding of our study was the observation that studies evaluating low-dose BEV are limited (<10 % of the evidence base), suggesting an evidence gap. Most included studies focused on high-dose BEV, limiting the scope for indirect comparisons between the two doses. This scarcity of studies reporting on low-dose BEV reflects the generally accepted treatment standards internationally for high-dose BEV [37–39]. Similarly, high-dose BEV is approved by health authorities, including the FDA, EMA, and Health Canada [40], across various therapeutic areas.

A limitation of our study was the limited number of studies included in the analyses, with only six trials involving sample sizes ranging from 24 to 1528 patients. Among the 34 analyses conducted, 25 were based on only two trials each, while none of the remaining nine analyses included more than four trials. Secondly, heterogeneities were noted in both intervention and patient characteristics, such as variations in the number of treatment cycles, line of treatment, distribution of disease stage, and histologic subtype. Notably, the trial by Cong et al. [30] was performed in second- rather than front-line setting, where response rates are typically lower compared to first-line treatment. Additionally, the GOG 0241 [29] trial included patients with mucinous ovarian cancer, a histological subtype associated with a poorer response to chemotherapy compared to other ovarian cancer subtypes, which may have affected the ITC results for response rates. Moreover, some trials included BEV maintenance therapy in the comparator arm post-operatively [27,28]. However, multiple sensitivity and subgroup analyses were conducted to address these heterogeneities and the results did not significantly differ from the results of the primary analyses. Notably, the limited number of trials did not allow for all sources of heterogeneity to be addressed simultaneously. Thirdly, the ITC results for certain adverse events, such as bleeding, should be interpreted with caution. The low event rates for these outcomes limited the precision of the relative treatment effect estimates, resulting in wide CIs and increased uncertainty in the findings. Finally, as the evidence base was limited to BEV combinations with platinum-based chemotherapy, the results of the comparison between low-dose and high-dose BEV in combination with these treatments may or may not be generalizable to other treatment combinations. It was not possible to compare BEV dosages with PARP inhibitors, such as olaparib since this combination was only used for studies with high-dose BEV. Nevertheless, these treatments' mechanisms of action suggest an additive effect, potentially inhibiting ovarian cancer cell invasion and microvascular endothelial cell tube formation [41]. Phase III trials, such as PAOLA-1 [42], have shown significant improvements in PFS with this combination, especially in patients with HRD-positive tumors.

The strengths of this study included adherence to the standard recommendations for conducting and reporting systematic reviews as recommended by the Cochrane Handbook for Systematic Reviews of Interventions [21] and PRISMA guidelines [22] for all review stages.

Additionally, the literature search was thorough, encompassing all major databases and conference proceedings. Finally, the inclusion of only RCTs was intentional to ensure the most robust evidence for the ITC. This approach aligned with the model assumption for ITCs that treatment effects are estimated from RCTs. Individual RCTs included in the SLR showed variability in response rates, survival outcomes, and safety profiles, with no consistent pattern favoring one BEV dose, thus corroborating the ITC results.

While acknowledging the need for future studies with a larger evidence base, the findings of this ITC provide insight into the comparative efficacy and safety of low- and high-dose BEV combination therapy. They underscore the lack of a difference between low- and high-dose BEV in managing ovarian cancer, potentially guiding clinicians in treatment decision-making as currently only low-dose BEV is approved in the front-line setting within Canada, while high-dose BEV is predominantly used internationally and in combination with olaparib. Ultimately, this study can support patient access to effective treatments. Furthermore, the findings can inform the design of future clinical trials, particularly in selecting appropriate comparator arms, addressing the heterogeneity of the dosing of BEV in the standard of care for ovarian cancer.

5. Conclusions

This ITC evaluated the comparative efficacy and safety of low- and high-dose BEV in combination with other therapies for patients with ovarian cancer. The study found no significant difference in response, survival, or safety outcomes between the two doses except for stable disease. Notably, while patients receiving low-dose BEV were more likely to achieve stable disease compared to those receiving high-dose BEV, this difference did not significantly impact the overall clinical benefit, suggesting the observed difference alone may have limited clinical relevance. Despite limited data comparing low- and high-dose BEV, no consistent superiority of either dose was observed, suggesting that the choice of BEV dose may not significantly impact clinical outcomes.

CRediT authorship contribution statement

Josée-Lyne Ethier: Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Cal Shephard:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Diana P. Granados:** Writing – review & editing, Writing – original draft, Methodology. **Nikkita Dutta:** Writing – review & editing, Writing – original draft, Methodology. **Rana Qadeer:** Writing – review & editing, Writing – original draft, Methodology. **Saima Ahmad:** Writing – review & editing, Writing – original draft, Conceptualization. **Ellen Kasireddy:** Project administration, Methodology, Investigation, Formal analysis. **Mir-Masoud Pourrahmat:** Methodology, Investigation, Formal analysis. **Mir Sohail Fazeli:** Methodology, Investigation, Formal analysis, Conceptualization.

Disclosure

This study was funded by AstraZeneca Canada.

Declaration of competing interest

Josée-Lyne Ethier reports consultant work with AstraZeneca, participation in Advisory Boards with AstraZeneca, Merck, Esai, and GSK, and speaker engagements with AstraZeneca, Merck, and GSK.

Cal Shephard, Diana P. Granados, Nikkita Dutta, Rana Qadeer, and Saima Ahmad report employment with AstraZeneca Canada (Mississauga, ON, Canada). Cal Shephard, Diana P. Granados, and Rana Qadeer hold shares in AstraZeneca.

Ellen Kasireddy, Mir-Masoud Pourrahmat, and Mir Sohail Fazeli are employed by Evidinno Outcomes Research Inc. (Vancouver, BC, Canada), which was contracted by AstraZeneca Canada to conduct this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2025.03.022.

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