Bevacizumab and Chemotherapeutic Agents for the Treatment of Epithelial Ovarian Cancer: A Systematic Review of the Literature, Best Evidence Synthesis and Meta-Analysis

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ABP	albumin-bound paclitaxel
AC	active control
AE	adverse event
AUC	area under the concentration-time curve
BEV	bevacizumab
BRCA1	breast cancer type 1 susceptibility protein
BRCA2	breast cancer type 2 susceptibility protein
BSO	bilateral salpingo-oophorectomy
CA	cancer antigen
CA	contrôle actif
CCNE1	Cyclin E1
CEO	cancer épithélial de l'ovaire
CGIC	Gynecologic Cancer Intergroup
CI	confidence interval
CIC	cortical inclusion cysts
CP	cisplatin
CR	complete response
CT	carboplatin
CX	chemotherapy
CO	cancer de l'ovaire
DM	différence moyenne
ECOG	Eastern Cooperative Group Oncology
ECR	essais contrôlés randomisés
EI	événement indésirable
EIG	évènement indésirable grave
EOC	epithelial ovarian carcinoma
FCEV	facteur de croissance endothélial vasculaire
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
GCTB	gemcitabine
HGSC	high-grade serous carcinoma
HR	hazard ratio
HRD	homologous recombinant deficient
I^2	heterogeneity
IDS	interval debulking surgery
IP	intraperitoneal
IV	intravenous
IXA	ixabepilone
Max	maximum

MD	mean difference
Min	minimum
MRI	magnetic resonance imaging
n	number
N/AP or NA	not applicable
N/AV	not available
NACT	neoadjuvant chemotherapy
NDS	norme des soins
NF1	neurofibromatosis type 1
NR	not reportable
OC	ovarian cancer
OS	overall survival
OSE	ovarian surface epithelium
OR	odds ratio
ORR	objective response rate
PARP	poly-ADP ribose polymerase
PBO	placebo
PDS	primary debulking surgery
PET	positron emission tomography
PFI	platinum-free interval
PFS	progression free survival
PLD	pegylated-doxorubicin liposomal hydrochloride
po	by mouth
PR	partial response
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PS	performance status
PT	paclitaxel
PTEN	Phosphatase and TENsin homolog deleted on chromosome 10
Q2W	repeated every 2 weeks
Q3W	repeated every 3 weeks
Q4W	repeated every 4 weeks
RAC	Research Advisory Committee
RB1	retinoblastoma protein
RC	réponse complète
RCT	randomized controlled trials
RECIST	Response Evaluation Criteria in Solid Tumors
ROB2	Cochrane Risk of Bias tool for randomized trials version 2
RP	réponse partielle
SAE	serious adverse event
SC	subcutaneous
SG	survie globale

SSP	survie sans progression
STIC	serous tubal intraepithelial carcinoma
SOC	Standard of care
TNM	Tumor, nodes, metastasis
TP53	tumor protein 53
TRO	taux de réponse objective
VEGF	vascular endothelial growth factor
wk	week

3 Abstract

Background: Ovarian Cancer (OC) is the eighth most commonly diagnosed cancer among Canadian women, reporting the highest mortality rates among these to date[1]. The lack of reliable and specific signs results in the vast majority (70%) of patients diagnosed at regional and distal metastases (Stage III-IV)[2]. The standard of care (SOC) for OC is debulking surgery and chemotherapy [3-5]. Although initial response to SOC is met with favorable outcomes, long term clinical outcomes such as overall and progression free survival (OS; PFS) have demonstrated modest improvements[6]. Poor prognosis has been associated with platinum-resistant associated relapse, with emphasis on recurrent patients that are treated with singular use platinum-based chemotherapy [7-11]. There is an unmet need to further investigate other treatment modalities in addition to conventional chemotherapy for OC patients.

Bevacizumab (BEV) is an anti-angiogenesis medication that was approved by the FDA in 2018 as a first line of maintenance therapy in OC patients[12]. Anti-angiogenesis therapy inhibits vascular endothelial growth factor (VEGF) impacting tumor blood vessels, cell proliferation and disease progression[12]. BEV may be beneficial alongside other SOC however, the magnitude of the benefit of BEV in OC has not been well documented.

Objective: The objective of this study was to conduct a systematic literature review, best evidence synthesis, and a meta-analysis of randomized controlled trials (RCTs) evaluating PFS, OS, objective response rate (ORR), as well as safety and tolerability in epithelial ovarian carcinoma (EOC) patients treated with BEV compared to an active control (AC).

Hypothesis: We anticipated that the addition of BEV compared to conventional chemotherapy regimens may improve clinical outcome measures such as PFS, OS, ORR as well safety and tolerability in patients diagnosed with EOC.

Methods: This review was conducted according to PRISMA guidelines. PubMed, MEDLINE, and EMBASE were searched (via OVID) for studies published after 2018 that evaluated the addition of BEV for the treatment of EOC. Articles were selected for trial review and included in the study based on the following criteria: clinical trial, original research, full publication, meanwhile abstracts, case reports, and posters were excluded. Furthermore, data available for clinical outcomes, adverse events (AEs), patient characteristics and disease parameters were retained. A total of 7 meta-analyses were performed comparing the PFS, OS, ORR, Complete

Response (CR), Partial Response (PR), incidence of serious adverse events (SAEs) and grade ≥3 AEs between BEV and AC groups. The quality of the evidence was evaluated using the Cochrane Risk of Bias tool for randomized trials (ROB 2). The inverse variance of mean differences (MD), odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated using random-effects models.

Results: Of the 2869 database results screened, 106 full-text articles were assessed for eligibility and 13 were considered for the qualitative analysis. Out of 2316 patients, 1159 received BEV and 1157 received an AC. Between 5 and 8 articles were included in the meta-analyses evaluating PFS, OS, ORR, CR, PR, SAEs, and grade ≥3 AEs, respectively. Significantly longer mean PFS was observed in the BEV group (n = 1125; 10.7 months) compared to patients treated with an AC (n = 1123; 7.9 months; MD: 2.91; 95% CI [2.14, 3.68], $p < 0.00001$; $I^2 = 87\%$). Significantly longer mean OS was observed in the BEV group (n = 1076; 21.6 months) compared to patients treated with an AC (n = 1075; 17.4 months; MD: 3.92; 95% CI [2.11, 5.73], $p < 0.0001$; $I^2 = 90\%$). An objective response was reported for 64.2% (274/427) of patients in the BEV group and 39.3% (172/438) of patients in the AC group (OR: 3.29, 95%CI [2.42, 4.45], $p < 0.00001$, $I^2 = 0\%$). Significantly more patients experienced a SAE (59.8% [370/944]) in the BEV group compared to the AC group (31.7% [299/942]; OR:1.41; 95%CI [1.16, 1.71], $p = 0.0005$, $I^2 = 0\%$). The proportion of patients that experienced grade ≥3 AEs following BEV administration was 49.3% (201/408) compared to the AC group (39.7% [160/403]; OR: 1.68; 95%CI [0.83, 3.37]; $p = 0.15$; $I^2 = 76\%$).

Conclusion: The results of the study demonstrated that BEV administration resulted in improved clinical outcomes such as longer PFS, OS and ORR. Safety with respect to the proportion of SAEs and grade ≥3 AEs were more frequently experienced among patients in the BEV group compared to the AC group.

Résumé

Contexte: Le cancer de l'ovaire (CO) est le huitième cancer le plus fréquemment diagnostiqué chez les femmes canadiennes, y compris le taux de mortalités le plus élevés[1]. La majorité (70%) des patients sont diagnostiqués au niveau de métastases régionales et distales (stade III-IV)[2]. La norme des soins (NDS) pour le CO est la chirurgie suivie par la chimiothérapie [3-5]. Bien que la réponse initiale au NDS mène à des résultats favorables, les résultats cliniques à long terme tels que la survie globale et sans progression (SG; SSP) ont subi des améliorations modestes[6]. Les mauvais pronostics sont souvent associés à la résistance au platine et en particulier, les patients récurrents traités par la chimiothérapie à base de platine à usage unique[7-11]. Il existe un besoin d'étudier d'autres modalités de traitement hors de la chimiothérapie conventionnelle pour le CO.

Le bevacizumab (BEV) est un médicament anti-angiogenèse qui a été approuvé par la FDA en 2018 comme traitement de premier usager pour le CO[12]. Le traitement anti-angiogenèse inhibine le facteur de croissance endothélial vasculaire (FCEV) ayant un impact sur les vaisseaux sanguins tumoraux, la prolifération cellulaire et la progression de la maladie[12]. Le BEV peut être bénéfique en combinaison avec autres NDS, cependant, l'ampleur du bénéfice du BEV pour le traitement de OC n'a pas été bien documentée.

Objectif: L'objectif de cette étude était de mener une revue systématique de la littérature, une synthèse des meilleures preuves et une méta-analyse d'essais contrôlés randomisés (ECRs) évaluant la SSP, la SG, le taux de réponse objective (TRO), ainsi que l'innocuité et la tolérabilité chez les patientes de cancer épithélial de l'ovaire (CEO) qui ont reçus le BEV par rapport à un contrôle actif (CA).

Résultats: Parmi les 2869 résultats de la base de données examinés, 106 articles ont été évalués pour leur éligibilité et 13 ont été pris en compte pour l'analyse qualitative. Sur 2316 patients, 1159 ont reçu le BEV et 1157 ont reçu un CA. Entre 5 et 8 articles ont été inclus dans les méta-analyses évaluant respectivement la SSP, la SG, le TRO, la réponse complète (RC), la réponse partielle (RP), les évènements indésirables grave (EIG) et les événement indésirable (EI) de grade ≥3. Une SSP moyenne significativement plus longue a été observée dans le groupe BEV (n = 1125; 10,7 mois) par rapport aux patients traités avec un CA (n = 1123; 7,9 mois; différence moyenne [DM]: 2,91; IC à 95% [2,14-3,68], $p < 0,00001$; $I^2 = 87\%$). Une SG moyenne significativement plus longue a été observée dans le groupe BEV (n = 1076; 21,6 mois)

par rapport aux patients traités avec un CA (n = 1075; 17.4 mois; DM: 3.92; IC à 95% [2,11-5,73], p < 0,0001; I^2 = 90%). Une réponse objective a été rapportée chez 64.2 % (274/427) des patients du groupe BEV et 39,3 % (172/438) des patients du groupe CA (OR: 3,29, IC à 95% [2,42-4,45]; p < 0,00001); I^2 = 0%). Un nombre significativement plus élevé de patients ont présenté un EIG (59,8 % [370/944]) dans le groupe BEV par rapport au groupe CA (31,7% [299/942]; OR: 1,41; IC à 95% [1,16-1,71], p = 0,0005, I^2 = 0%). La proportion de patients présentant des EIs de grade ≥3 après l'administration de BEV était de 49,3% (201/408) par rapport au groupe CA (39,7% [160/403]; OR: 1,68; IC à 95 % [0,83-3,37], p = 0,15; I^2 = 76%).

Conclusion: Les résultats de l'étude ont démontré que l'administration de BEV a entraînée de meilleurs résultats cliniques, tels qu'une SSP, une SG et un TWO plus longs. L'innocuité en ce qui concerne la proportion d'EIGs et les EIs de grade ≥ 3 ont été plus fréquemment observés chez les patients du groupe BEV par rapport aux patients du groupe CA.

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5 Contribution of Authors

Catherine Silotch (Thesis Candidate):

I provided the thesis topic and research question for my supervisors' review and approval. Thereafter, I was responsible for performing the appropriate database searches, selection of articles, data collection, analysis, and completion of the written thesis.

Dr. John S. Sampalis (Supervisor):

Dr. Sampalis provided insight on the hypothesis, database search methods, and statistical methodology to adequately answer the research question. He was responsible for reviewing and commenting on the quality of the articles that were retained from the database search and for ensuring the extracted data were complete and consistent with the proposed methods.

Conflict of interest statement: There is no conflict of interest.

6 Introduction

Epithelial Ovarian Carcinoma (EOC) is one of the most common gynecologic malignancies diagnosed in women, consistently ranking among the top 5 leading causes of cancer death, worldwide [13-15]. Ovarian malignancies, including EOCs, are often referred to as the "silent killer"[16-19], due to a lack of reliable and specific signs that are often mistaken for other pathogeneses [20 21]. When common symptoms such as abdominal bloating or pelvic discomfort are overlooked, they remain unaddressed, resulting in delayed diagnosis. This is further supported by that fact that 70% of OC patients are diagnosed during regional and distal metastases (Stage III-IV) and almost all (90%) EOC patients are similarly diagnosed at advanced stages[2].

The current SOC for OC is one of primary or interval debulking surgery (PDS; IDS) followed by platinum-based chemotherapy in combination with taxanes [3-5 22 23] . For patients with resectable tumor lesions, debulking surgery is typically performed first and involves a complete hysterectomy/bilateral salpingo-oophorectomy (BSO). Among patients with poor to un-resectable tumor lesions, treatment typically first consists of neoadjuvant chemotherapy (NACT) to decompress the tumor burden and improve the patient's odds of maximal cytoreduction. Maximal cytoreduction as well as stage at diagnosis and baseline performance status (PS) are regarded as independent predictors of improved long-term clinical outcomes. Despite this, five-year survival rates have staggered, reporting a modest increase of roughly 5 percent over the last 3 decades[6].

Possible explanations include the platinum-free interval (PFI), or the period between the last cycle of platinum-based chemotherapy and tumor progression. Platinum-resistant associated relapse and specifically, recurrent patients that are treated with singular use of platinum-based chemotherapy have been shown to be significantly associated with poor long-term clinical outcomes[7-11 24]. It seems the overwhelming majority (80%) of patients that experience recurrence are also diagnosed

with advanced stage at disease onset however, the window of progression among these patients typically occurs after the 6-month cut-off relative to their first cycle of chemotherapy[25]. This would suggest that PFS in EOC is dependent on several parameters including the patient's baseline disease characteristics, response to conventional chemotherapy (platinum-sensitive vs. resistant), residual disease following PDS, number of cytoreductive surgeries (IDS), and whether a combination of therapies outside of conventional chemotherapy have been used. Survival gaps are also highly dependent on baseline demographic data, with differences observed across races and socioeconomic status[6 26]. Chemo-sensitivity[7 8] and the associated cost-effectiveness[27-29] of continuing treatment demonstrates a need to investigate other treatment modalities in addition to conventional chemotherapy.

Bevacizumab is an anti-angiogenesis medication that was approved by the FDA in 2018[12] as a first line treatment and maintenance therapy for OC. Anti-angiogenesis therapy inhibits VEGF impacting tumor blood vessels, and as such cell proliferation and disease progression[30-32]. The approval was justified following the PFS results from study GOG-0218 (NCT000262847), a placebo-controlled, three-arm study evaluating the addition of BEV to carboplatin (CT) and paclitaxel (PT) for patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following surgical resection. The estimated median PFS was 18.2 months for patients receiving BEV with chemotherapy followed by single-agent BEV as maintenance therapy compared to 12.0 months in the cohort which received standard chemotherapy alone (HR = 0.62; 95%CI: 0.52, 0.75; $p<0.0001$)[33].

The objective of this thesis was to determine whether a sustained improvement in clinical outcomes was observed following the FDA's approval in 2018 for EOC patients treated with BEV compared to the SOC. The primary endpoints were to compare the PFS, OS, ORR, CR, PR, SAEs, and grade ≥3

AEs in EOC patients treated with BEV versus an AC. To detect a sustained effect, we conducted a systemic literature review; a best-evidence synthesis, and a meta-analysis of RCTs published after 2018 comparing BEV - in combination with platinum-based chemotherapy as a first-line treatment or as a single agent (maintenance therapy) - versus an AC in the management of EOC.

The aim of this study is to provide oncologists novel insight regarding the management of OC and to provide essential information for the comparative effectiveness of the two treatment modalities. Given the diverse nature of EOC, casting a wider net on the spectrum of therapies beyond conventional chemotherapy remains a pressing need to address both the long-term clinical outcomes and the economic burden of this illness. This includes consideration of EOC's healthcare resource utilization costs with the current SOC, and importantly, assessing the quality of life for patients that are presently undergoing treatment. Until there is a consensus regarding early screening methods, the current SOC is not meeting the needs of the various forms and characteristics of EOC patients, resulting in the demand to supplement current treatments with other, non-chemotherapeutic agents.

7 Epithelial Ovarian Cancer – Background and Review of the Literature

7.1 Anatomy

7.1.1 The Ovaries, Fallopian Tubes, and Peritoneum

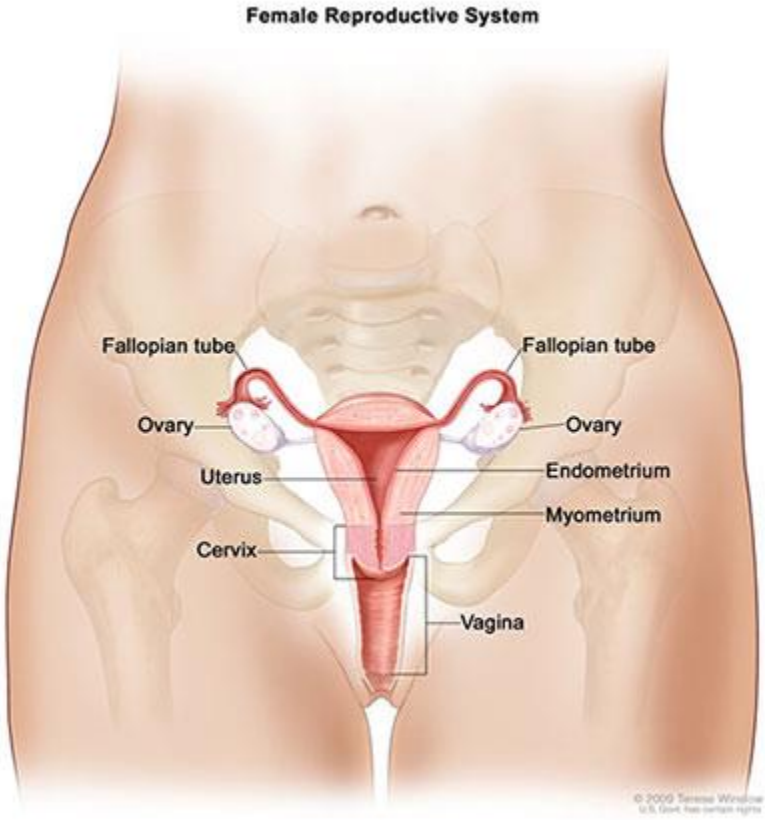
The ovaries are an endocrine organ responsible for several key functions including hormone production and fertility. The ovaries develop from the gonadal ridge during the sixth week of gestation. Around this time, the ovarian epithelium and the endoderm of the yolk sac, responsible for the formation of germ cells, produce immature ova[34].

The ovaries are located in the lower abdomen, in a shallow depression known as the ovarian fossa near the fallopian tubes (refer to **Figure 1**) [34]. The central-most zone of the ovary is the medulla, a highly vascularized region of loose connective tissues, followed by the cortex, which houses the ovarian follicles, the hilum, a layer of collagen rich tissues, and lastly, the outer epithelium. A normal ovary is 2.0 cm in width, 3.5 cm in length and 1.0 cm in thickness; the volume of the ovary has been shown to change over time, reaching its peak volume of 7.7 mL at 20 years of age and slowly declining to an average volume of 2.8 mL at menopause[35].

In close proximity, the fallopian tubes are a muscular set of 4- to 5-inch-long oviducts, extending laterally from the uterus into the abdominal cavity[36]. Its main function is to form a passage between the ovary and the uterus, where the ovum will be implanted following successful fertilization. The fallopian tube is made up of 4 parts, the fimbriae, finger-like projections responsible for capturing the ovum from the surface of the ovary; the infundibulum, a funnel shaped opening adjacent to the fimbriae; the ampulla, where fertilization typically occurs, and finally the isthmus, connecting the ampulla to the uterine cavity. [37]

The fallopian tubes and ovaries receive oxygenated blood from the ovarian and uterine arteries. Lymph drainage of the fallopian tubes and ovaries flow to both the para-aortic and pelvic lymph nodes, respectively. [37]

Figure 1 Female Reproductive System

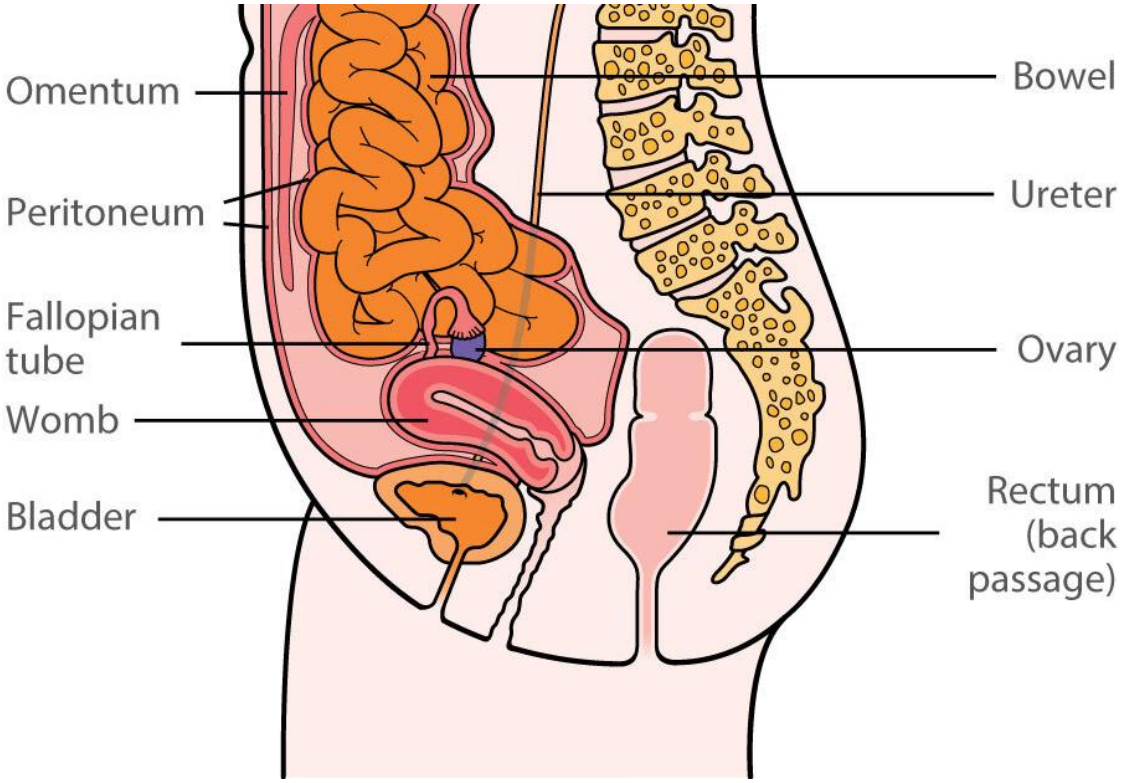


Source: Teresa Winslow (Illustrator), *National Cancer Institute*

The peritoneum is a membrane that lines the abdominal cavity (see **Figure 2**) and consists of mesothelial cells derived from the mesoderm. These cells support the development of the primitive gut during early stages of development. In terms of function, the peritoneum provides support to the organs in the abdomen and acts as a pathway for nerves, blood vessels and lymphatics. [38]

The outer layer of the peritoneum is referred to as the parietal peritoneum. It is firmly attached to the walls of the abdomen and pelvis, receiving its blood supply from arteries originating in this wall as well as those from the iliac, lumbar, epigastric, and intercostal regions. The venous drainage from the peritoneum converges into the vena cava. [38]

Figure 2. Female reproductive system – Sagittal view



Source: (The ovaries and surrounding structures.) MacMillan Support Group., 2021[39]

7.2 Epidemiology

Ovarian cancer is a widespread disease that primarily affects women after menopause and simultaneously reports the highest mortality rates of all gynecological cancers to date[40]. The global estimate of OC diagnoses is approximately 300,000 new cases per year, leading to 180,000 deaths[41]. In 2023, approximately 3,000 Canadian women were diagnosed with OC resulting in the loss of roughly 2000 lives[42]. The majority of OCs (90%) are formed by the epithelial cells of the ovary, with germ cell tumors accounting for 2% and stromal cell tumors making up only 1% of cases [43].

The prevalence of OC varies across different regions around the globe. Western Europe and Northern America have reported the highest rates, followed by Eastern and Southern Europe as

well as South America. In contrast, lower rates are consistently reported in the Middle East and Asia. Several factors contributing to these disparities include racial and reproductive factors, socioeconomic status, and cultural differences.[44-46]

In developed countries, higher rates of OC diagnoses have been associated with specific characteristics. These include longer life expectancy, reduced breastfeeding (which has been found to protect against OC for 30 years after stopping)[47] and consumption of high dietary fat and caloric meals[52]. Another study indicated that white, American women have a 60% increased risk of developing OC compared to African American women[48]. This difference may be related to the presence or absence of mutations (breast cancer type 1 and 2 susceptibility protein [BRCA1 and BRCA2]) among racial and ethnic groups[49 50]. Other risk factors include age, with 75% of OC diagnoses occurring after menopause (corresponding to a median age range of 60 to 65 years)[48 51]; having first degree relatives with OC increases the risk three- to four- fold[52], meanwhile, 24% of women with a history of breast cancer are at an increased risk of developing OC[53]. Additionally, women with a history of other cancer types also face an increased risk[53].

Certain factors like late onset of menopause (after the age of 55)[54], not having given birth[55], and smoking are associated with elevated risk of developing OC although associations with smoking status depend on the subtype of OC[56]. Furthermore, it has been observed that women who experience infertility, defined "as the inability to conceive after a year of unprotected sexual intercourse", are at a 60% increased likelihood of developing OC compared to women who are otherwise able to conceive under similar conditions [57]. Additionally, obesity's role on increased risk of diagnosis remains inconsistent across studies, showing both positive and non-significant correlations[58].

7.3 Histopathology of Epithelial Ovarian Carcinoma

The most frequently diagnosed OC is EOC. Epithelial ovarian carcinomas have several proposed origins depending on the histological subtype. Due to the diverse histology and genomic features of EOCs, precursor lesions of EOCs cannot be traced back to a single origin[59]. They are grouped under one of the following 5 histological subtypes: high grade serous carcinoma (HGSC [68% of cases]) clear cell carcinoma (12%) endometrioid carcinoma (11%) mucinous carcinoma (3%) and low-grade serous carcinoma (3%)[60]. The origins of clear cell, endometrioid, mucinous and low grade serous carcinomas are usually located in the ovarian parenchyma, are intracystic, and do not involve the ovarian surface[61]. The remaining histological subtype referred to as HGSC have several proposed origins including the ovarian surface epithelium (OSE), fallopian tube mucosa, and the peritoneum.

7.3.1 High-Grade Serous Carcinomas – Pathogenesis

The spectrum of lesions that make up HGSCs are diverse with different molecular and microenvironmental attributes[62]. These factors collectively influence the response to treatment and eventual outcomes[62 63]. As with other subtypes of EOCs, several origins leading to the development of the precursor lesions of HGSCs have been proposed, the first of which was the OSE[64 65].

7.3.2 Ovarian surface epithelium (OSE)

The OSE is formed from the mesothelium of the embryonic gonad (the mullerian epithelium)[66]. Some of the earliest theories proposed that the epithelium lesions leading to HGSCs evolve at the OSE and are related to ovulatory cycles. The “incessant ovulation” hypothesis by Fathalla et al., states that increased frequency of ovulatory cycles elevates a woman’s risk of developing HGSC[67]. Ovulation can lead to damage of the OSE cells which undergo repair by post-ovulation mitosis and proliferation. This increase in proliferation was proposed to elevate the chance of age- or toxin-related weakness in homologous recombination, making them susceptible to genetic damage

and eventual neoplastic growth[68]. The ovulation hypothesis would also indirectly suggest that women who ovulate infrequently are at a decreased risk of OC. However, increased risk of OC has been observed among infertile women in previous studies[55 57]. These contrasts would suggest there may be other pathways associated with epithelial ovarian neoplastic origins.

Fathalla et al., hypothesis is rooted in risk factors and their impact on OSE repair during ovulation. Since then, other etiologies have been proposed which focus on the tumor microenvironment. Cortical inclusion cysts (CICs) derived from the OSE were previously thought to be the origin of all EOCs [64 65 69]. During ovulation, the ovarian follicle ruptures, creating a temporary tear to the OSE where the epithelial cells reside. During the repair process, the OSE folds inward, towards the ovarian stroma which can lead to the development of CICs featuring an epithelial lining[69 70]. These events, along with proliferation of the OSE, have been thought to promote metaplastic changes leading to tumor lesion development[71].

In addition to this theory, discussions on whether CICs can develop in the absence of ovulation were postulated. Kindelbergher et al., hypothesized that tumor lesions on the fimbriae of the fallopian tube break off and land on the surface of the ovary where they become trapped, incurring CICs that then produce ovarian or primary peritoneal carcinomas[72]. Their findings were supported by evaluating biopsies from women with breast cancer gene (BRCA) mutations, revealing another important factor of consideration in determining the pathogenesis of EOCs.

7.3.3 Genetic factors

In addition to the role of OSE and CICs, about 25% of women diagnosed with HGSC have a hereditary predisposition[73]. This is often marked by mutations in genes such as BRCA1 and BRCA2[74]. Under normal circumstances, the proteins produced by BRCA1/BRCA2 act as tumor suppressors by maintaining stability and aiding in homologous recombination. Early etiological

studies focused on OC patients with a family history of OC to determine whether certain mutations could be identified at the OSE site. In these studies, increased tumor protein (TP)-53 mutations were identified in the epithelium of ovaries from patients with a family history of the disease compared to controls, confirming the origin of some HGSCs[75 76].

In addition to BRCA1/BRCA2 mutations, other genes and pathways have been shown to be associated with HGSCs and prognosis. In less than 10% of HGSC patients, mutations of tumor suppressing genes such as phosphatase and TENsin homolog deleted on chromosome 10 (PTEN), retinoblastoma protein (RB1), and neurofibromatosis type 1 (NF1) were reported[77]. Homologous recombination deficiency (HRD), or the inability to repair double strand breaks in DNA, was identified in about 50% of women with HGSC[78]. In contrast, women with Cyclin E1 (CCNE1) amplification, which results in genetic instability and tumor proliferation, is present in approximately 20% of all HGSCs[78 79]. Interestingly, CCNE1 amplification is associated with homologous recombination *proficiency* via CDK2 regulation[80], and this proficiency in combination with CCNE1 amplification is believed to be the cause of platinum-resistance in HGSC by some researchers [81].

7.3.4 Fallopian tube involvement

Other origins for precursor lesions of HGSCs were proposed by researchers who examined tissues obtained during risk reducing salpingo oophorectomies[82 83]. On the fimbriae of the fallopian tubes, they discovered serous tubal intraepithelial carcinoma (STIC) lesions[82 83]. These precursor STIC lesions exhibited TP53 mutations which have been previously demonstrated to be associated with development of several high-grade carcinomas[84], including 96% of HGSCs[85]. In these studies, increased TP53 mutations were predominantly concentrated in the fimbriae region of the fallopian tubes and were not identified in other nearby structures. This led researchers to propose that the

fallopian tubes are the origin of a subset of HGSCs, estimated to represent approximately half (45%) of all HGSCs[59].

7.3.5 Other origins

The remaining cases resulting in the development of EOCs are categorized as either primary ovarian or peritoneal origin. Low-grade serous, endometrioid and clear cell or mucinous carcinomas fall under the umbrella of primary ovarian carcinomas which are less frequently diagnosed, and have a more gradual disease progression compared to HGSCs[86]. The peritoneum is the last known site where lesions resulting in HGSCs may develop and are usually determined when all other origins, such as primary ovarian and fallopian tube, have been ruled out.

7.4 Clinical Presentation and Diagnostic Tests

7.4.1 Symptoms

Early signs and symptoms are not a common indicator of ovarian, fallopian tube, or peritoneal carcinomas. Overall, patients presenting with symptoms are already at an advanced stage of disease when diagnosed. The most frequently reported symptoms are abdominal pain, abdominal swelling, gastrointestinal symptoms, and pelvic pain[87 88]. Other symptoms indicated in large observational studies include urinary (urge to urinate), back and systemic (feeling full) events[87-89].

Where many of the signs and symptoms are not exclusive to OC, other diagnostic assessments in combination with the patient's baseline characteristics are used to confirm stage of diagnosis and tumor presentations.

7.4.2 Diagnostics

The subsequent examinations and methods have been employed in diagnosing and determining the stage of ovarian epithelial, fallopian tube, or primary peritoneal cancers:

- “Physical exam and history;
- Pelvic exam;
- Cancer Antigen (CA)-125 assay;
- Ultrasonography (pelvic or transvaginal);
- Computed tomography scan;
- Positron emission tomography (PET) scan;
- Magnetic resonance imaging (MRI);
- Chest x-ray;
- Biopsy.”[90]

Of the methods listed, CA-125 assay, biopsy, and the imaging scans are the main assessments used by oncologists to evaluate a patient’s tumor characteristics such as stage of diagnosis, PS, and importantly, tumor resectability[91].

Another system oncologists use to track tumor lesion response is the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Assessments of tumor lesions typically include computed tomography scan imaging at minimum, and are generally determined at study screening to categorize tumor lesions as either measurable (≥10 mm longest diameter) or non-measurable (longest diameter <10 mm) for the patient’s baseline assessment[92]. Compared to baseline, progression is typically defined as a 20% increase in the sum of diameters of target lesions, whereas PR refers to a minimum 30% decrease in the sum of diameters of target lesions, and finally CR is a disappearance of all target lesions[92].

The International Federation of Gynecology and Obstetrics (FIGO)[93] and the Tumor, extent of spread to the lymph nodes, and presence of metastasis (TNM)[94] are standardized staging classifications systems used to further classify tumor characteristics of ovarian epithelial, fallopian tube, and primary peritoneal carcinomas (refer to **Table 1**)[95].

Table 1. Definitions of FIGO and Equivalent TNM Stage[a]

FIGO	Definition	TNM
IA	Tumor limited to one ovary (capsule intact) or fallopian tube. No tumor on ovarian or fallopian tube surface. No malignant cells in the ascites or peritoneal washings	**T1a**
IB	Tumor is limited to both ovaries and fallopian tubes. No tumor on ovarian or fallopian tube surface. No malignant cells in the ascites or peritoneal washings	**T1b**
IC	Tumor limited to one or both ovaries or fallopian tubes, where surgical spill occurred intra-operatively (IC1), capsule ruptured before surgery, tumor on ovarian or fallopian tube surface (IC2), or malignant cells were present in the ascites or peritoneal washings (IC3)	**T1c**
II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer (Tp)	**T2**
IIA	Extension and/or implants on the uterus and/or fallopian tubes and/or ovaries	**T2a**
IIB	Extension to other pelvic intraperitoneal tissues	**T2b**
III	Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside of the pelvis and/or metastasis to the retroperitoneal lymph nodes	**T3**
IIIA	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis	**T3a N0/1**
IIIB	Macroscopic, extra pelvic, peritoneal metastasis $\leq$ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.	**T3b N01**
IIIC	Macroscopic, extra pelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	**T3c N01**
IV	Distant metastasis excluding peritoneal metastasis	**TX NX M1**
IVA	Pleural effusion with positive cytology	**TX NX M1a**
IVB	Metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity) or parenchymal metastasis	**TX NX M1b**

[a] Adapted from FIGO Committee for Gynecologic Oncology[93] and corresponding TNM by Jaime Prat[94]

Another classification system commonly used to determine the extent of disease from the perspective of the patient (in terms of their function and daily habits) is the Eastern Cooperative Oncology Group (ECOG)-PS scale, as shown in **Table 2**[96]. Lower grades indicate improved function, whereas higher grades indicate significantly reduced function and disability.

Table 2. Eastern Cooperative Oncology Group Performance Status Scale[a]

Grade	ECOG-PS Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory, and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair

[a] Adapted from Oken MM et al. 1982[96]

Patients with EOC can present either resectable or non-resectable tumor lesions at diagnosis. Tumor resectability refers to the likelihood of a complete cytoreduction with little to no residual disease left at the affected sites (R0). Resectability is usually determined by evaluating the abdominal sites critical for cytoreduction (disease location), tumor size and FIGO stage[97]. However, recent studies have included other factors associated with resectability, including those of a retrospective study where poor PS and presence of peritoneal carcinomatosis on the hilum or on the stomach were covariates associated with non-resectability in patients with HGSCs[98]. As evidenced by the literature, consideration of all existing diagnostics, including novel methods, should be deliberated when managing EOC patient prognosis.

7.5 Management and Treatment

Historically, treating OC has heavily relied on opportunistic interventions. Notably, the role of debulking surgery, the introduction of platinum-based chemotherapy and whole-abdomen radiation were explored without proper randomization against a control[99 100]. Over the past five decades, the management of OC has evolved. Treatment decisions now consider factors such as disease stage, precursor lesion pathology, prior therapy, and comorbidities, while other

evidence-based approaches combine complete cytoreductive surgery with systemic therapy tailored to the specific subtype of OC and disease onset.

The primary window for achieving optimal clinical outcomes is considered during initial treatment, with efficacy contingent on the stage and histology of the disease. Early-stage OC has a 90% cure rate, even with more aggressive histologic subtypes[101 102], emphasizing the role of early detection strategies. Despite this, most women are still at greater odds of receiving a late-stage diagnosis, suggesting new innovations are presently required for existing therapies such as cytoreductive surgeries, chemotherapy, and targeted therapies.

7.5.1 Surgery

7.5.1.1 Primary debulking surgery

Primary debulking surgery refers to the surgical resection of tumor lesions at disease onset, before administering other therapeutic agents. Cytoreductive surgery is a fundamental pillar in the treatment of cancer, although its long-term benefit remains an area of debate among OC patients. Some clinical trials have suggested that optimally resected patients (R0) had worse long-term clinical outcomes compared to patients with >1 cm of residual disease following PDS [63].

To further illustrate this, in the recent LION study (Lymphadenectomy in Ovarian Neoplasms), EOC patients who had undergone complete macroscopic resection with normal lymph nodes at baseline were randomly assigned to either undergo or not undergo a lymphadenectomy. The results from this study suggested that subjects randomized to the lymphadenectomy group had a higher HR of death, and an increased risk of experiencing postoperative complications and mortality within 60 days of surgery compared to the group that did not undergo lymphadenectomy[103]. In post-hoc analyses conducted by Du Bois et al., OS was significantly

reduced in EOC patients with optimal debulking at baseline compared to subjects with residual disease exceeding 1 cm in diameter[104]. As proposed by Riester et al., controlling for other factors such as migration/invasion, angiogenesis, metastasis, and the activation of tumor-associated fibroblasts, may be beneficial in determining the independent effect of complete versus incomplete cytoreduction on EOC clinical outcomes[105].

7.5.1.2 Interval debulking surgery

Interval debulking surgery (IDS) refers to surgical resection of the tumor lesions after NACT has been administered to subjects, due to poor resectability and chances of optimal cytoreduction at disease onset. The therapeutic intent is the complete resection of residual disease and is generally considered after 3 cycles of NACT[117]. Two prospective RCTs evaluating PDS compared to IDS demonstrated no significant increase in OS for patients randomized to PDS[106 107]. Although results of these studies suggest PDS provide not added benefit over IDS, it is important to consider other factors that might be influencing these results, such as the type of treatment regimen administered and whether a complete macroscopic resection (R0) was actually achieved in patients randomized to either cohort. In Vergote et al study, a complete cytoreduction resulting in no gross or microscopic lesions (R0) was the strongest independent variable predictive of OS, irrespective of surgical sequence (IDS or PDS)[107]. Altogether, both PDS and IDS have been used interchangeably as viable responses for the treatment of EOC but require further evaluation to confirm their long-term impact.

7.5.1.3 Surgery for recurrent EOC

For patients experiencing platinum-sensitive recurrence, secondary debulking surgery is recommended since tumor status in platinum-sensitive patients is generally well defined and therefore at greater odds of achieving little to no residual disease (R0 status), post-operatively. Recurrence refers to tumor progression and platinum-sensitivity is defined as disease progression

occurring 6 months or more after the last chemotherapy cycle[108]. Therefore, EOC patients exposed to either of these conditions might benefit from additional cytoreductive surgery.

The DESKTOP III/ENGOT-ov20 study was an RCT that enrolled patients with recurrent, platinum-sensitive EOC, where 5-month improvement in PFS was observed for women undergoing secondary debulking surgery compared to those without surgery (HR: 0.66; 95% CI, 0.52-0.83)[109]. This improvement extended up to the subsequent chemotherapy cycle, and a more substantial advantage was observed in patients who achieved R0 status after secondary debulking[109]. In contrast, results from the GOG-0213 study, a double-randomized clinical trial assessing surgery and the addition of BEV in patients experiencing platinum-sensitive recurrence, indicated that secondary cytoreduction did not correlate with improved OS compared to the group who did not proceed with a secondary cytoreductive surgery[110]. Discrepancies in findings may be explained by differences in patient inclusion criteria between DESKTOP III and GOG-0213 (owing to the use of the German Gynecological Oncology Group [AGO] score as inclusion criteria in the DESKTOP III trial). Post-hoc analyses of either study such that one would be controlled to the staging standards of the other may help to confirm whether the staging system at screening is in fact correlated with this discrepancy. Additionally, details on the treatment(s) performed following either cohorts, such as additional chemotherapy cycles or their specific regimens, would further delineate the effect of these systemic therapies on long-term, clinical outcome measures.

7.5.2 Chemotherapy

Systemic therapy in the treatment of EOC consists of both single- and combination-based agents. In the initial phases of OC systemic therapy, alkylating agents or what we commonly refer to as chemotherapy, were explored. With the introduction of platinum in 1976[100], cisplatin (CP)-based

combination therapy in 1984[111], and paclitaxel (PT) in 1993[112], outcomes were thought to significantly improve for women with EOC.

Patients with EOC, and more specifically 80% of patients with HGSCs, initially experience positive responses to traditional chemotherapy[113]. Numerous RCTs have addressed critical questions regarding dose, dose density, platinum and/or taxane selection, administration mode (intravenous [IV], intraperitoneal [IP]), and additional non-chemotherapeutic agents.

Choosing an appropriate chemotherapeutic agent is dependent on several factors including safety and tolerability. Both CT and CP are effective chemotherapies however, CT has been associated with fewer AEs and as such, is thought to be more tolerable compared to CP [113]. The optimal target dose for CT is an area under the concentration-time curve (AUC) of 5 to 6 and 75 mg/m^2 for CP among EOC patients undergoing their first cycle of chemotherapy[114]. Studies have demonstrated that exceeding these target doses with either CP or CT does not necessarily lead to improved long-term outcomes but rather increases the proportion of AEs experienced by patients [114 115].

Varying results have also been observed with respect to frequency of chemotherapy administration. Once weekly administration of CT demonstrated similar progression and overall survival rates, but increased proportion of AEs compared to administration every 3 weeks[116]. Dose-dense chemotherapy, defined as providing chemotherapy more frequently, with less time between doses, has also been evaluated in several RCTs. In a Japanese study where EOC patients were randomized to PT 180 mg/m^2 plus CT AUC6 on day 1 of a 21-day cycle versus PT 80 mg/m^2 on days 1, 8, and 15 plus CT AUC6 on day 1 of the same 21-day cycle resulted in significantly longer PFS and OS for patients randomized to the dose-dense regimen, but also reported a greater number of AEs compared to the conventional regimen group [117].

Furthermore, IP chemotherapy was introduced as a treatment for EOC to improve distribution of treatment by direct exposure to the peritoneal cavity, one of the possible locations of tumor lesion development in HGSC. Several Phase III studies dating back to the early 1990s have shown significant improvements in PFS and OS with IP therapy[118-121]. Among these Phase III trials and 1 recent Phase II study, an added improvement in OS and PFS was demonstrated for patients treated with IP chemotherapy *vs*. IV infusion, and similar effect size among those treated with CT compared to CP as the chemotherapeutic agent[119 122]. Regimen frequencies across studies have varied however, the consensus suggests to the substitution of CP with CT, administered as either IP injection, or IV infusion, to improve tolerability and reduce toxicity[123].

Overall, the chemotherapy standard for EOC is either "CT and PT administered by IV infusion every 3 weeks, or IV infusion of CT every 3 weeks and PT weekly, in a dose-dense manner"[99]. If optimal debulking is feasible, then consideration of IP chemotherapy may provide an added benefit to patients. An example of such a chemotherapy regimen would include "6 cycles of PT administered by IV infusion and CP administered by IP injection on a 3-week cycle"[124]. The main limitation of IP chemotherapy is that it is usually associated with increased toxicity compared to IV chemotherapy[119 122]. For this reason, antiemetics such as granisetron, may be administered prior to chemotherapy (especially for IP administration but not exclusive to IV infusion) to reduce common side effects like nausea and vomiting. Administration methods, such as IV infusion or IP administration in combination with antiemetics, can improve the toxicity associated with these chemotherapeutic agents, with the goal of maintaining improved clinical outcomes.

Apart from initial treatments, disease progression is common in EOC, affecting upwards of 70% of patients following first-line chemotherapy[125]. Decisions on subsequent therapy may be

influenced by the PFI, or the time to relapse following the last cycle of chemotherapy or surgical cytoreduction. According to the fifth Gynecologic Cancer Intergroup (CGIG) definition, disease progression after a PFI of over 6 months indicates platinum sensitivity while progression within 6 months of treatment indicates platinum resistance[126]. The GCIG's categorizations of the PFI provides a straightforward guideline, although it has limitations, not accounting for how progression itself is defined or the impact of maintenance therapy on subsequent PFI and disease pathology. For this reason, supplementing this information with other systems such as RECIST v1.1 may help to objectively assess progression in response to treatment exposure or surgery.

Despite these limitations, both guidelines offer useful frameworks, likely to evolve over time as our perception shifts toward viewing OC as a chronic disease, requiring individualized management for each relapse with other non-platinum chemotherapeutic options.

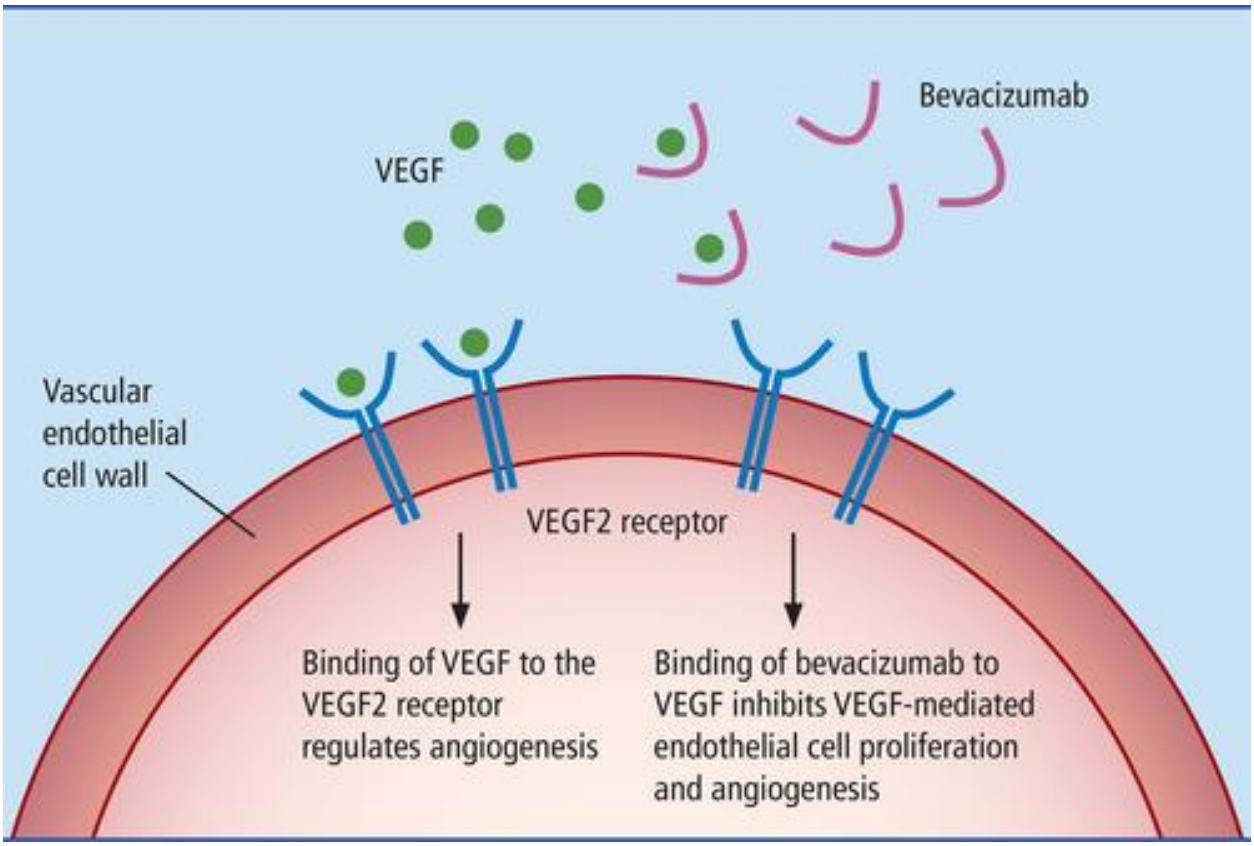
7.5.3 Targeted Therapy

The integration of targeted non-platinum agents into OC treatment has progressed through clinical trials. Notably, concurrent BEV—a humanized monoclonal antibody targeting VEGF- and sequential BEV and poly-ADP ribose polymerase (PARP) inhibitors- have shown improved efficacy and nonoverlapping toxicity in the past decade [139-141]. Bevacizumab, by inhibiting VEGF, disrupts the angiogenesis pathway, a process closely related to tumor growth.

Rapid proliferation of tumor lesions in HGSCs necessitates an increased blood supply to meet the growing demands. Without vascular support, the tumor lesions become hypoxic, resulting in the release of hypoxia inducible factors, such as VEGF. Matrix metalloproteinases (MMPs) triggered by macrophage/mast cells cleave away at the extracellular matrix (ECM), allowing a clear path for VEGF to bind to the VEGF receptors on the endothelial wall of a nearby capillary. This promotes angiogenesis of the capillary, the formation of new blood vessels, which

vascularize the tumor cells, promoting metaplastic growth. Anti-angiogenic agents such as BEV, have a high affinity for VEGF receptors, resulting in the inhibition of VEGF and VEGF-mediated endothelial cell proliferation and angiogenesis (**Figure 3**).

Figure 3. Bevacizumab Mechanism of Action



Source: The pharmacological action of bevacizumab. (*Bevacizumab*)[127]

Bevacizumab and other anti-angiogenic agents have demonstrated enhanced PFS and OS benefit in several large scale RCTs, particularly in high-risk groups such as HGSCs[24 128 129]. The GOG-0218 and a recent real-world evidence study demonstrated that patients with residual or even unresectable disease at baseline can benefit from first-line therapy with BEV, while also resulting in fewer AEs compared to single-agent chemotherapy[130]. Epithelial ovarian cancer patients with platinum-resistance can also benefit from maintenance therapy with BEV. As

demonstrated by the results published from the AURELIA trial, platinum-resistant EOC patients reported significantly longer PFS and OS rates compared to conventional chemotherapy ($p < 0.001$)[128]. Furthermore, recurrence, irrespective of the PFI, was shown to be improved with addition of anti-angiogenic agents, either alone or in combination with PARP-inhibitors[128]. The combination of anti-angiogenics and PARP-inhibitors are especially promising direction for recurrent EOC patients with BRCA mutation, where PARP-inhibitors show additional benefit[131]. Other trials where addition of BEV indicated improved PFS in relapsed patients are the OCEANS[24] trial and the recent MEDIOLA study[132]. Despite associated toxicities, patient selection and careful management have established BEV as a standard in EOC care.

Additional studies continue to investigate anti-angiogenics such as BEV in combination with PARP inhibitors in various contexts, aiming to identify biomarkers for response or toxicities. In one study, presence of BRCA mutations in EOC patients were met with improved outcomes in PFS and OS and reduced number of AEs and toxicity related to treatment with BEV and Olaparib compared to non-BRCA mutated patients. While other antiangiogenics like pazopanib and sorafenib have shown modest activity by interfering with angiogenesis-related pathways, BEV remains one of the only novel agents to be approved by the FDA as a first line and maintenance treatment of EOC in the last 30 years. Other novel drug classes such as epothilones, have also been studied in combination with BEV for maintenance therapy over an extended period equaling a follow-up duration of 829.5 months with a controlled number of AEs[133]. The continuous exploration of combination therapies reflects the dynamic landscape of EOC treatment, pushing the boundaries in pursuit of improved outcomes.

7.6 Comparative Effectives of BEV and Conventional Treatments for EOC

When comparing the value of BEV and conventional treatments for EOC on clinical outcomes, it may be worthwhile to consider the vast array of treatments that can be compared to BEV. As noted previously, chemotherapy options for EOC mainly consist of CT or CP as a single format or in combination with PT. The method of administration and frequency can also differ between IV, or IP, and dose-dense regimens. In addition to chemotherapy, non-chemotherapeutic agents cast an even wider net of potential therapies, ranging from anti-angiogenics, PARP-inhibitors, and even epothilones.

Apart from this, the comparative effectiveness of BEV and conventional EOC treatments in clinical trials has not been recently reviewed or evaluated. Early studies leading up to the FDA's approval in 2018 included the GOG-0170D, and gENETECH avf 2949g which were single cohort studies evaluating BEV for EOC patients to establish preliminary improvement in clinical outcomes and toxicity profile. In these studies, significantly improved ORR, PFS and OS were indicated while the main AEs observed were hypertension and GI events[134 135]. One of the first pioneering RCTs, GOG-0218, demonstrated a median PFS of 12.0 months in the AC group versus 18.2 months in the BEV group[33 129]. Overall survival was premature and could not be identified at the time of the preliminary results publication. In addition to GOG-0218, the following RCTS: AURELIA[128], ICON7[136], OCEANS[24] and GOG-0213[110], were also considered for the FDA's approval in 2018 of BEV for first line and maintenance treatment of advanced stage EOC.

Following this, other RCTs evaluating BEV compared to an AC on clinical outcomes were performed, with one meta-analysis published in 2021 comprising all studies leading up to the FDA's decision in 2018. In contrast, this thesis only retained RCTs following the FDA's

decision in 2018 to evaluate the sustained effect of BEV compared to an AC on clinical outcomes of patients with EOC.

8 Methods

8.1 Systematic Review

For the systematic review, articles were selected according to the inclusion criteria which were determined at the stage of study design by the authors (refer to **Table 3**). PubMed, MEDLINE, and EMBASE were searched via OVID for studies published after 2018, according to the list of pre-defined search terms (**Table 3**). Articles were selected for review based on the following criteria: clinical trial, original research, full publication, while abstract, case reports, and posters were excluded. An amendment to the exclusion criteria was made following the database search to omit non-randomized controlled trials, such as observational studies. To optimize the quality of the data included in the meta-analyses, RCTs were included due to their ability to directly compare two (or more) groups, while also ensuring balance of both known and unknown confounders between groups. In contrast, observational studies have been shown to dilute the observed effect. The full texts of all eligible studies were retrieved and assessed independently. Differences in article selection were discussed and finalized before a final set was determined for the qualitative synthesis. To aid in this process, the PRISMA guidance from Cochrane's Handbook on Systematic Reviews and risk of bias were followed. Among the RCTs selected, data available for clinical outcomes (PFS, OS, ORR, CR, PR), incidence of AEs, patient characteristics and disease parameters were retained.

Table 3. Eligibility Criteria for inclusion in the Systematic Review

Article Selection Criteria	Definition
Language	English
Date	After 2018
Subject	Human studies
Study type	Randomized-controlled Trials
Excluded	Case-control
	Case reports
	Letters
	Editorials
	Abstracts
	Prospective
	Single Cohort
	Retrospective
Keywords (including MeSH terms)	Ovarian Cancer
	Bevacizumab

8.2 Methods of Review

Each study included in the qualitative synthesis was independently reviewed based on the inclusion criteria and later assessed for bias. For studies included in quantitative synthesis, the Cochrane Collaboration's tool for assessing risk of bias in randomized trials version 2 (ROB2)[137] was utilized to conduct the assessment for each publication. The ROB2 evaluation criteria covers randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Using a macro-enabled ROB2 tool and a crib sheet available on Cochrane's website, signaling questions for each article were answered, resulting in either a "low", "some concerns", or "high" risk of bias judgment for the respective domain. The scores for each domain and article were then color graphed into a traffic light plot, as shown in **Figure 5**.

8.3 Quantitative Analysis

In total, 7 meta-analyses were performed evaluating the effect of BEV administration versus an AC on the PFS, OS, ORR, CR, PR, proportion of SAEs, and grade ≥3 AEs in EOC patients. All meta-analyses were performed using the inverse variance random effects models with Revman Manager (RevMan) version 5.4. Source data results for PFS and OS outcomes were provided in months as means ± their standard deviations (SD) while results for ORR, CR, PR, SAEs, and grade ≥3 AEs outcomes were presented in terms of events and total counts. The first two meta-analyses evaluating the overall effect of BEV versus an AC on PFS and OS are presented as mean differences (MDs) and their 95% CIs. For the remaining 5 meta-analyses evaluating the overall effect of BEV versus an AC on ORR, CR, PR, SAEs, and grade ≥3 AEs, odd ratios (ORs) and their 95% CIs are presented. Heterogeneity (I^2) for each meta-analysis was calculated by assessing the variation between studies (between study variance) and transformed into a percentage, where decreased percentages represent variability in effect size due to sampling error within studies. Funnel plots for each meta-analysis are also presented to demonstrate the presence of publication bias.

9 Results

A total of 2869 results from the database search were screened and 106 full-text articles were assessed for eligibility (**Figure 4**). Of these, 13 were considered for the qualitative review and nine studies were included in the quantitative analysis. Out of nine eligible studies, eight were included in the first meta-analysis comparing BEV vs. AC on PFS, seven for meta-analyses 2 through 5 comprising OS, ORR, CR and PR, respectively, six studies for meta-analysis 7 comprising grade ≥3 AEs, and five studies for meta-analysis 6 evaluating SAEs. Out of 2690 patients in the qualitative review, 1299 patients received BEV and 1301 received an AC (**Table 4**). With the exception of Ray-Coquard et al. [138] whose study evaluated patients with sex-cord stromal tumor, Drew et al.[132] who performed post-hoc analyses on patients with HGSC with non-BRCA1/2 mutations from their basket trial (MEDIOLA), and Krasner et al., who performed a sequential clinical trial (Trial A; Trial B), all other studies included in the qualitative analysis were original research, RCTs and evaluated patients with HGSCs, including fallopian tube and/or primary peritoneal carcinomas. The RCT published by Tao et al. which explored serum levels of CA125 and common AEs among BEV vs. AC-treated EOC patients, was included in the qualitative synthesis and excluded from the quantitative synthesis as the proportions of patients that experienced AEs were not available for extraction[139].

The results of the systematic review explored a novel perspective by including articles published after 2018, the year of the FDA's decision to include BEV as a first line and maintenance therapy for OC, and particularly HGSCs. As such, the year of publication for included studies ranged from 2018 to 2023. Out of 2316 patients from the studies included in the quantitative analysis, 1159 patients received BEV and 1157 patients received an AC (**Table 4**). The types of ACs included CP, CT, PT, gemcitabine (GCTB), pegylated doxorubicin liposomal hydrochloride (PLD), ixabepilone (IXA), concurrent cimetidine or dexamethasone with chemotherapy,

durvalumab, and olaparib. Four studies were conducted at single centers in China, two studies each were conducted at single centers in the USA and Japan, and one study was conducted at a single center in Spain. In addition to these locations, the remaining studies were multi-center, conducted in Canada, the Republic of Korea, the UK, Israel, Monaco, as well as several other countries in the European Union.

A total of eight studies evaluating treatment with BEV (n = 1125) compared to an AC (n = 1123) on PFS were included in meta-analysis 1 (**Table 5**). Patients with EOC that were randomized to BEV experienced significantly longer mean PFS (10.7 months) compared to patients in the AC group (7.9 months; MD: 2.91, 95%CI [2.14, 3.68]; $p < 0.00001$; **Figure 6**). Heterogeneity between studies was also significant, corresponding to $I^2 = 87\%$ ($p < 0.00001$). The funnel plot for PFS demonstrated publication bias with 2 studies outside the 95% CI boundaries and overall asymmetry (**Figure 7**).

Seven articles evaluating the comparative effectiveness of BEV (n = 1076) and AC (n = 1075) on OS were included in meta-analysis 2 (**Table 6**). Epithelial ovarian carcinoma patients randomized to BEV experienced significantly longer mean OS (21.6 months) compared to patients in the AC group (17.4 months; MD: 3.92, 95%CI [2.11, 5.73]; $p < 0.0001$; **Figure 8**). Heterogeneity between the studies was significantly increased, corresponding to $I^2 = 90\%$; $p < 0.00001$. Four out of seven studies were observed outside the 95% CI boundaries for the funnel plot, suggesting publication bias (**Figure 9**).

For meta-analyses 3 through 5, seven studies evaluating the effect of BEV (n = 427) on ORR, CR, and PR compared to patients randomized to an AC (n = 438) were included (**Table 7)**. The proportion of patients that experienced an ORR was significantly higher for EOC patients randomized to BEV (64.7%; 274/427) compared to patients in the AC group (39.3% [172/438];

OR: 3.29, 95%CI [2.42, 4.45]; p < 0.00001; **Figure 10**). A similar trend was observed for CR (**Figure 12**) and PR (**Figure 14**), where 22.4% (96/427) of patients in the BEV group achieved CR compared to 12.6% (55/438) of patients in the AC group (OR: 2.18, 95% CI [1.49, 3.20]; p < 0.0001), and 41.7% (178/427) of patients in the BEV group achieved PR compared to 26.7% (117/438) of patients in the AC group (OR: 2.16, 95% CI [1.46, 3.18]; p = 0.0001). Heterogeneity for meta-analyses 3 through 5 were low and none were statistically significant, with I^2 ranging between 0% (for ORR and CR) and 33% for (PR). Given that ORR is calculated as the addition of CR rate to the PR rate, this supports the consistency in overall effect size and heterogeneity between each meta-analysis. Symmetry in the funnel plot for ORR was observed (**Figure 11**), with the majority of studies clustered within the 95% CI boundaries, and some minor skewing for five of the seven studies trending beyond the overall effect size line, suggesting some publication bias. Comparatively few patients achieved CR irrespective of study or treatment however, all study points for CR remained within the 95% CI boundaries and clustered around the overall effect size line in the funnel plot (**Figure 13)**. A similar shape was observed for PR rate (**Figure 15**).

In terms of safety and tolerability, five studies were included in meta-analysis 6, evaluating the effect of treatment with BEV (n = 944) compared to an AC (n = 942) on the proportion of SAEs experienced by EOC subjects (**Table 8**). Significantly more patients in the BEV group experienced SAEs (59.8% [370/944]) compared to patients in the AC group (31.7% [299/942]; OR: 1.41, 95%CI [1.16, 1.71]; p = 0.0005; **Figure 16**). Between-study variance was low (I^2 = 0%; p = 0.85) suggesting that the variability in the overall effect size for SAEs was most likely due to sampling error within the studies. This meta-analysis included only 5 studies with available data for extraction however, the resulting funnel plot was symmetric overall, with only

two studies trending towards an increased OR, and potentially emphasizing BEVs toxicity (**Figure 17**).

Six studies were included in meta-analysis 7, which evaluated the proportion of patients that experienced grade ≥3 AEs following BEV treatment (n = 408) compared to the AC group (n = 403; **Table 8**). Although an increased number of patients experienced grade ≥3 AEs following administration with BEV (49.3% [201/408]) compared to patients in the AC group (39.7% [160/403]), this was not statistically significant (OR: 1.68, 95%CI [0.83, 3.37]; p = 0.15; **Figure 18**). In contrast, heterogeneity was elevated, corresponding to I^2 = 76% (p = 0.0008). Overall, the funnel plot for this outcome was asymmetrical, with two studies venturing outside the 95% CI boundaries and four studies skewing left, suggesting publication bias (**Figure 19**).

Figure 4. PRISMA Flow Diagram - Systematic Review and Meta-Analysis

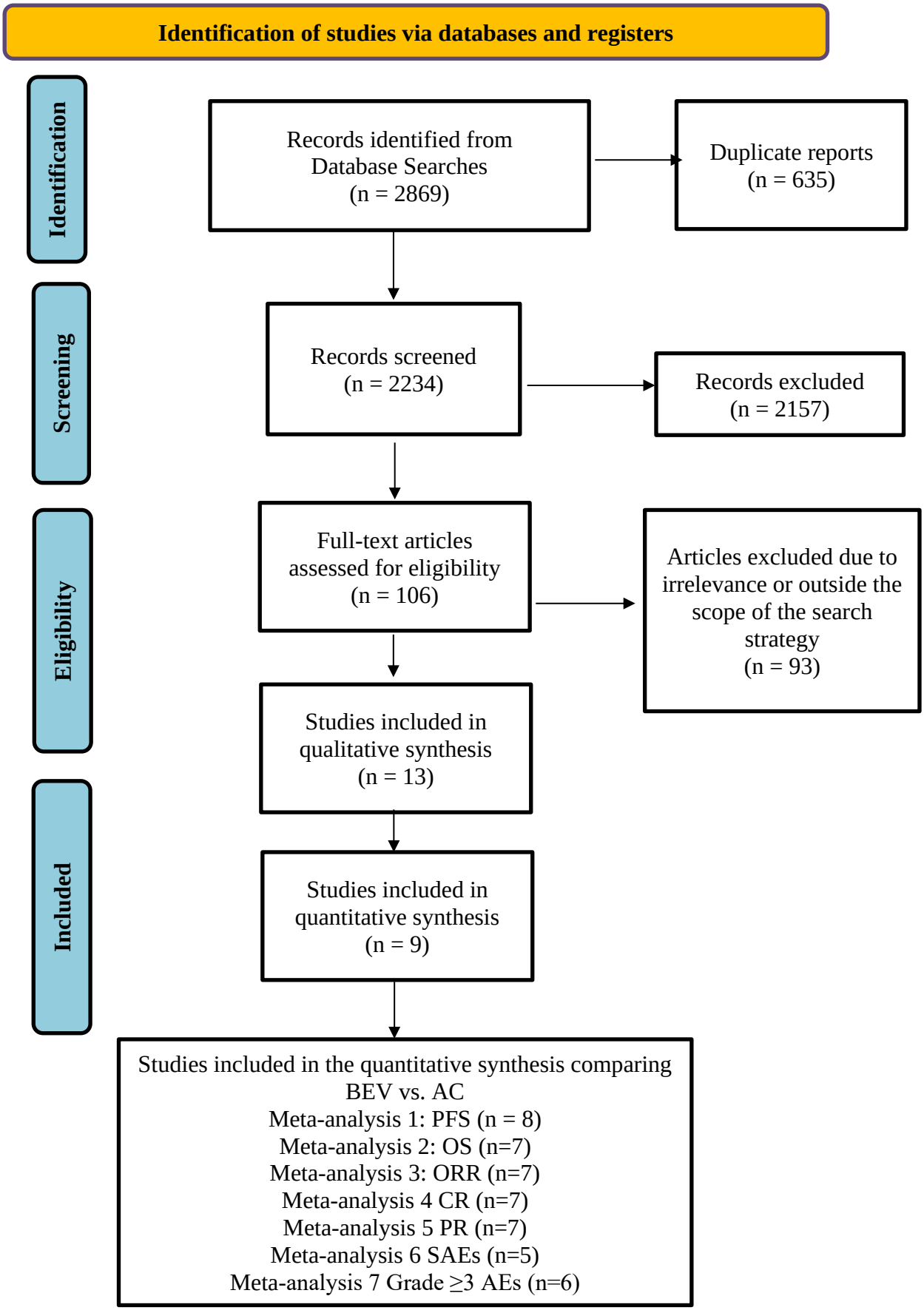


Table 4. Quantitative Result Summaries of Ovarian Cancer Patients treated with Bevacizumab compared to an Active Control

Author	Year	Country	Subject Characteristics	Agent(s), Dose(s)/Strength(s), and Administration Method	BEV *n*	AC *n*
Tewari et al.[130]	2019	Canada, Japan, Korea, USA	• FIGO Stage III/IV epithelial ovarian, primary peritoneal, or fallopian-tube carcinoma, with gross residual disease within 12 weeks after surgery maximal cytoreductive surgery. • ECOG PS 0-2	**AC Group:** Cycles 1-6: IV PT (175 mg/m^2) + CT AUC6 + PBO (starting in cycle 2) Q3W Cycles 7-22: PBO Q3W	623	625
				Experimental Group (BEV): Cycles 1-6: IV PT (175 mg/m^2) + CT AUC6 + BEV (15mg/kg; starting in cycle 2) Q3W Cycles 7-22: BEV Q3W		
Garcia et al.[140]	2019	Spain	• Newly diagnosed, FIGO Stage III/IV, epithelial ovarian, primary peritoneal, or fallopian-tube carcinoma considered unresectable requiring NACT. • ECOG PS 0-2	**AC Group:** 4 cycles: IV PT (175 mg/m^2) + CT AUC6 on Day 1, Q3W.	35	33
				Experimental Group (BEV): 4 cycles: IV PT (175 mg/m^2) + CT AUC6 + BEV 15 mg/kg on Day 1, Q3W		
Chunyan Ma[141]	2022	China	• FIGO Stage III/IV, high-grade serous/endometrioid epithelial ovarian, primary peritoneal, or fallopian-tube carcinoma considered unresectable. • Platinum-sensitive	**AC Group:** IV PT (175 mg/m^2) over 3 h and IV CT (AUC 5-6) mg*min/mL over 1 h on Day 1, Q3W for 6 cycles.	34	34
				Experimental Group (BEV): IV PT (175 mg/m^2) over 3 h and IV CT (AUC 5-6) mg*min/mL over1 h on Day 1, Q3W for 6 cycles. On Day 1: IP perfusion BEV 15mg/kg over 30-90 min, Q3W for up to 2 cycles.		

Author	Year	Country	Subject Characteristics	Agent(s), Dose(s)/Strength(s), and Administration Method	BEV *n*	AC *n*
Mirza et al.[142]	2019	USA, Denmark, Finland, Sweden, Norway.	• Platinum-sensitive recurrent ovarian cancer with high-grade serous or endometrioid histology. • Previous BEV was permitted unless disease had progressed during/within 3 months of BEV treatment. • ECOG PS: 0-2	**AC Group:** 100-300 mg capsules of Niraparib QD po, on Days 1 through 21 until progression or toxicity **Experimental Group (BEV):** 100-300 mg capsules of Niraparib QD po, on Days 1 through 21 until progression or toxicity + BEV 15 mg/kg on Day 1, Q3W	48	49
Pignata et al.[143]	2021	France, Greece, Italy, Monaco, Switzerland	• FIGO >IIIB/IV EOC at first recurrence or progression at least 6 months after first-line PT-based CX, including BEV. • ECOG PS: 0-2	**AC Group:** One of the 3 IV regimens (6 cycles): CT AUC5 + PT 175 mg/m^2 on Day 1 Q3W; CT AUC4 on Day 1+ GCTB 1000 mg/m^2 on Days 1 and 8, Q3W CT AUC5 + PLD 30 mg/m^2 on Day 1, Q4W **Experimental Group (BEV):** One of the 2 IV regimens (6 cycles): BEV 10 mg/kg Q2W (with PLD as above) or BEV 15 mg/kg Q3W + GCTB/CP	203	203
Tao et al.[139]	2022	China	• FIGO >IIIC/IV EOC patients, unresected, undergoing NACT. • ECOG PS: 0-2	**AC Group:** 2 cycles: IV PT (175 mg/m^2) and CT (AUC5) on Day 1, Q3W **Experimental Group (BEV):** 2 cycles: IV PT (175 mg/m^2) and CT (AUC5) plus IP perfusion of 7.5 mg/m ^{2} of BEV over 6 h, on Day 1, Q3W	40	40
Liu, et al.[144]	2019	China	• Platinum-resistant OC • ECOG score ≤1 • Recurrence within 6 months after CR was achieved with platinum based CX and cytoreductive surgery	**AC Group:** 6 cycles (3 wks each): ABP (135-175 mg/m^2 IV infusion/30 min) QD **Experimental Group (BEV):** 6 cycles (3 wks each): ABP (135-175 mg/m^2 IV infusion/30 min) + BEV (7.5 mg/kg IV infusion/90 min) QD	43	43

Author	Year	Country	Subject Characteristics	Agent(s), Dose(s)/Strength(s), and Administration Method	BEV *n*	AC *n*
Shoji et al.[145]	2022	Japan	• Platinum-resistant, epithelial ovarian, fallopian tube, or primary peritoneal carcinoma • ECOG PS score 0-2 • Recurrence after BEV + CX	**AC Group:** One of 4 single-agent CX regimens IV PLD 40 or 50 mg/m^2, 1 mg/min on Day 1 Q4W; IV topotecan 1.25 mg/m^2 for 60 min on Days 1, 2, 3, 4, and 5 Q3W IV PT 80 mg/m^2 for 60 min on Days 1, 8, and 15 Q3W IV GCTB1000 mg/m^2 for 30 min on Days 1 and 8 Q3W.	52	51
				Experimental Group (BEV): One of the single-agent CX regimens above + BEV 15 mg/m^2 given concomitantly		
Roque et al.[133]	2022	USA	• Platinum-resistant, or refractory, epithelial ovarian, fallopian tube, or primary peritoneal carcinoma • ECOG PS score 0-2 • Prior debulking status, CX and BEV treatment permitted.	**AC Group:** IXA 20 mg/m^2 on Days 1, 8, 15, Q4W	39	37
				Experimental Group (BEV): IXA 20 mg/m^2 on Days 1, 8, 15 + BEV 10 mg/kg on Days 1 and 15, Q4W		
Cong et al.[146]	2019	China	• Platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal carcinoma • ECOG PS score 0-2 • Prior debulking status, CX and BEV treatment permitted.	**AC Group:** IV PT 100 mg/m^2 + CT AUC5, 3×wk; 21-day cycle	82	82
				Experimental Group (BEV): IV PT 100 mg/m^2 + CT AUC5 + BEV 15 mg/kg 3×wk; 21-day cycle		
Drew et al.[132]	2023	USA, Republic of Korea, Netherlands, UK, Israel, France,	• PARP inhibitor-naïve, relapsed HGSC, (including primary peritoneal and/or fallopian tube carcinoma), platinum-sensitive, • ECOG PS score 0-1. • Subjects allocated based on germline BRCA1/2 mutation	**AC Group**: Olaparib 300 mg po BID + Durvalumab 1.5 g IV Q4W	31	32
				Experimental Group (BEV): Olaparib 300 mg po BID + Durvalumab 1.5 g IV Q4W + BEV 10 mg/kg IV Q2W		

Author	Year	Country	Subject Characteristics	Agent(s), Dose(s)/Strength(s), and Administration Method	BEV *n*	AC *n*
Krasner et al.[147]	2019	USA	• Advanced epithelial, peritoneal, or fallopian tube carcinoma • Optimal cytoreduction (RO) • ECOG PS score ≤2. • Subjects randomized based on germline BRCA1/2 mutation. • FIGO stage ≤III.	**AC Group (Trial A):** IV (cycle 1), IP (remaining cycles) of CT AUC6 on Day 1 + PT 60 mg/m^2 + on Days 1, 8, 15 of a 21-day cycle.	41	40
				Experimental Group (Trial B; BEV): IV (cycle 1)/IP (remaining cycles) of CT AUC6 on Day 1 + PT 60 mg/m^2 + on Days 1, 8, 15 + IV BEV 15 mg/kg per cycle, starting cycle 2 of a 21-day cycle		
Ray-Coquard et al.[138]	2020	France, Germany, Italy, Japan, Belgium	• Sex-cord stromal tumor (granulosa tumors) • Minimum 1 recorded relapse following platinum based CX. • ECOG PS score ≤2. • BEV-naive	**AC Group:** IV PT (80 mg/m^2) on Days 1, 8, and 15, Q4W, for 6 cycles.	28	32
				Experimental Group (BEV): IV PT (80 mg/m^2) on Days 1, 8, and 15, Q4W + BEV 10mg/kg Q2W, for 6 cycles.		
TOTALS					1299	1301

Abbreviations: ABP = albumin-bound paclitaxel; AC = active control; AUC = area under the concentration-time curve; BEV = bevacizumab; CT = carboplatin; CP = cisplatin; CX = chemotherapy; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; FIGO = International Federation of Gynecology and Obstetrics; GCTB = gemcitabine; h = hours; IP = intraperitoneal; IXA = ixabepilone; min = minute; PBO = placebo; PLD = pegylated liposomal doxorubicin hydrochloride; po = by mouth; PS = performance status; PT = paclitaxel; QD = once daily; Q2W = repeated every 2 weeks; Q3W = repeated every 3 weeks; Q4W = repeated every 4 weeks; wk = week

Figure 5. Traffic-light plot of Studies included in Quantitative Analysis

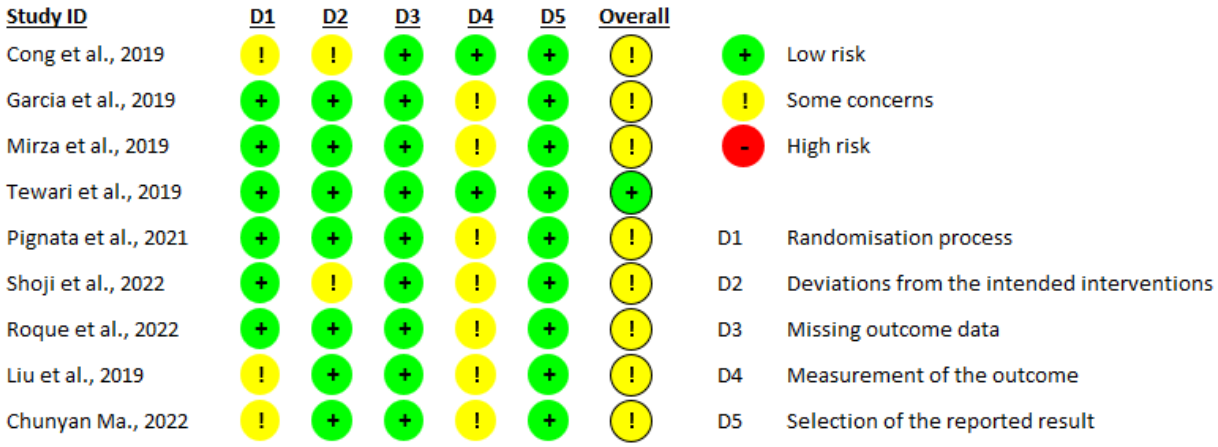


Table 5. Studies comparing Bevacizumab *vs* Active Control on Progression Free Survival

Author	Year	Eligible Patients, *n*		Mean PFS (months)	
		BEV	AC	BEV	AC
Cong et al.	2019	82	82	9.3±1.7	6.6±1.2
Mirza et al.	2019	48	49	11.9 (8.5-16.7)	5.5 (3.8-6.3)
Pignata et al.	2021	203	203	11.8 (10.8-12.9)	8.8 (8.4-9.3)
Tewari et al.[a]	2019	623	625	14.1 (NR)	10.3 (NR)
Garcia et al.	2019	35	33	20.4 (14.4-26.3)	20.1 (14.7-25.6)
Roque et al.	2022	39	37	5.5 (4.6-10.0)	2.2 (1.8-3.8)
Shoji et al.	2022	52	51	4.0 (3.0-5.7)	3.1 (2.5-4.6)
Liu et al.	2019	43	43	8.9 (range: 1-18)	6.7 (range: 1-14)
TOTALS		1125	1123	Mean:10.7	Mean: 7.9

Abbreviations: AC = active control; BEV = bevacizumab; IQR = interquartile range; NR = not reported.
[a] The median PFS survival results were updated to 15.3 (14.2-16.1) for the BEV concurrent group and 11.0 (10.2-12.0) for the AC group on clinicaltrials.gov following the end of the study however, only the published results as cited from Tewari et al., were used for meta-analysis 1.
Note: values that were reported as a median and IQR were converted to a mean (mean = median) and the SD was calculated as IQR/1.35. For studies reporting a range for mean PFS, the SD was calculated as max-min/4. For studies that did not report the SD or IQR, the highest reported SD for the corresponding outcome was used for the meta-analysis.

Figure 6. Meta-Analysis 1: Forest Plot Comparison between Bevacizumab and an Active Control on Progression Free Survival in Patients with Epithelial Ovarian Carcinoma

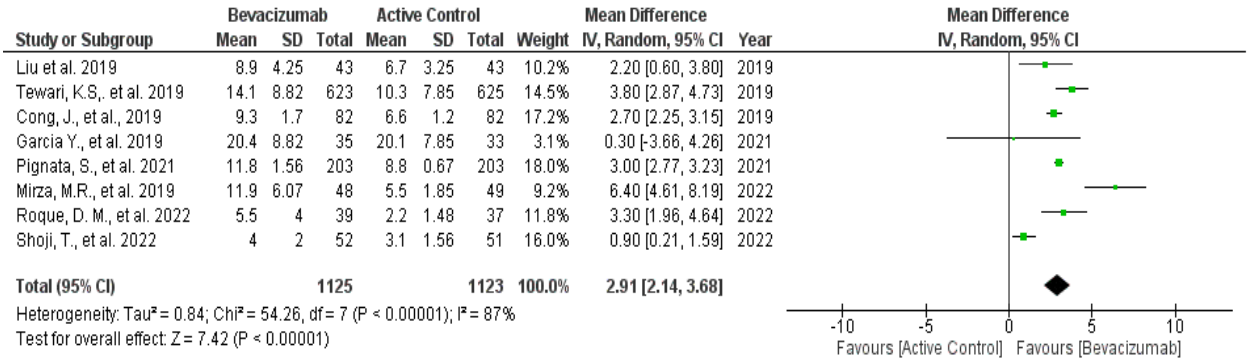


Figure 7. Funnel Plot of Studies included in Meta-Analysis 1 (Progression Free Survival)

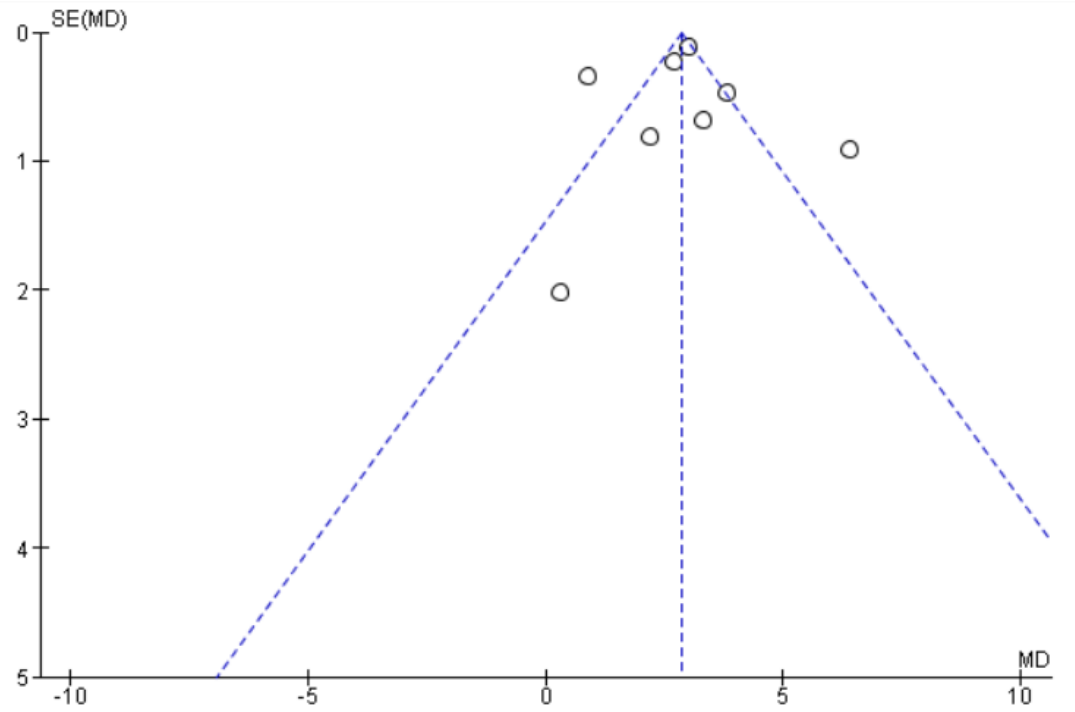


Table 6. Studies comparing Bevacizumab *vs* Active Control on Overall Survival

Author	Year	Eligible Patients, *n*		Mean OS (months)	
		BEV	AC	BEV	AC
Cong et al.	2019	82	82	18.5±3.4	12.8±2.6
Pignata et al.	2021	203	203	27.1 (22.0-NR)	26.7 (22.7-30.5)
Tewari et al.	2019	623	625	43.4 (39.7-49.0)	41.1 (37.1-45.5)
Roque et al.	2022	39	37	10.0 (9.1-20.2)	6.0 (4.1-12.1)
Shoji et al.	2022	52	51	15.3 (10.0-17.4)	11.3 (8.8-12.6)
Chunyan Ma	2021	34	34	20.50 (NR)	11.50 (NR)
Liu et al.	2019	43	43	16.3 (range:1-29)	12.6 (range: 1-26)
TOTALS		1076	1075	Mean: 21.6	Mean: 17.4

Abbreviations: AC = active control; BEV = bevacizumab; IQR = interquartile range; NR = not reported.
Note: values that were reported as a median and IQR were converted to a mean (mean = median) and the SD was calculated as IQR/1.35. For studies reporting a range for mean PFS, the SD was calculated as max-min/4. For studies that did not report the SD or IQR, the highest reported SD for the corresponding outcome was used for the meta-analysis.

Figure 8. Meta-Analysis 2: Forest Plot Comparison between Bevacizumab and an Active Control on Overall Survival in Patients with Epithelial Ovarian Carcinoma

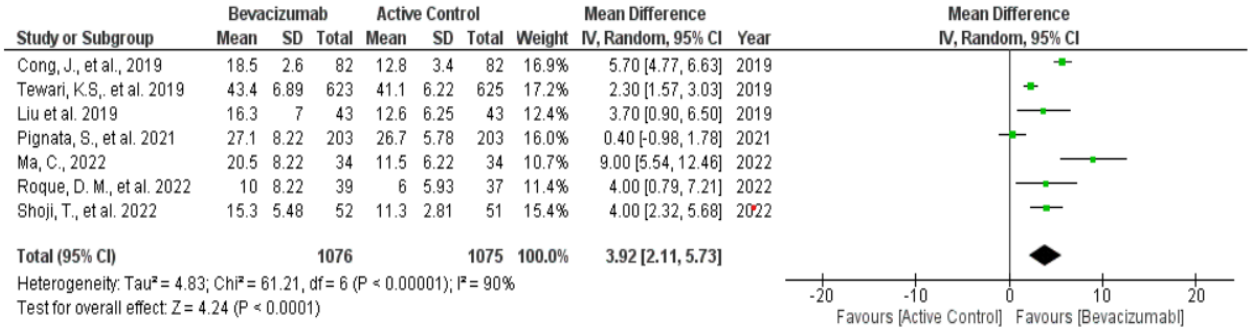


Figure 9. Funnel Plot of Studies included in Meta-Analysis 2 (Overall Survival)

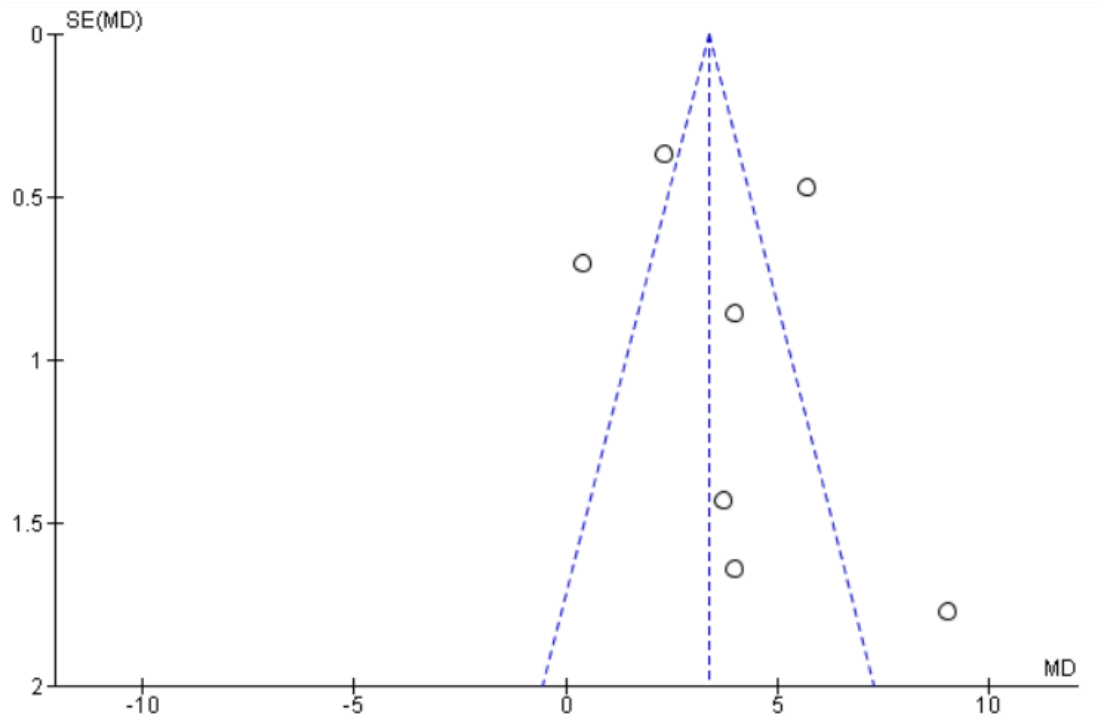


Table 7. Studies comparing Bevacizumab *vs* Active Control on Objective Response Rate, Complete Response, and Partial Response

Author Year	Eligible Patients n		CR n		PR n (%)		ORR n (%)	
	BEV	AC	BEV	AC	BEV	AC	BEV	AC
Cong et al. 2019	82	82	23	13	42	23	65	36
Mirza et al. 2019	48	49	7	5	22	8	29	13
Pignata et al. 2021	130	143	31	16	59	55	90	71
Roque et al. 2022	39	37	0	0	13	3	13	3
Shoji et al. 2022	51	50	1	0	12	7	13	7
Chunyan Ma.2021	34	34	11	5	16	10	27	15
Liu et al. 2019	43	43	23	16	14	11	37	27
TOTALS	427	438	96	55	178	117	274	172

Abbreviations: AC = active control; BEV = bevacizumab; CR = complete response; PR = partial response; ORR = objective response rate.

Figure 10. Meta-analysis 3: Forest Plot Comparison between Bevacizumab and an Active Control on Objective Response Rate in Patients with Epithelial Ovarian Carcinoma

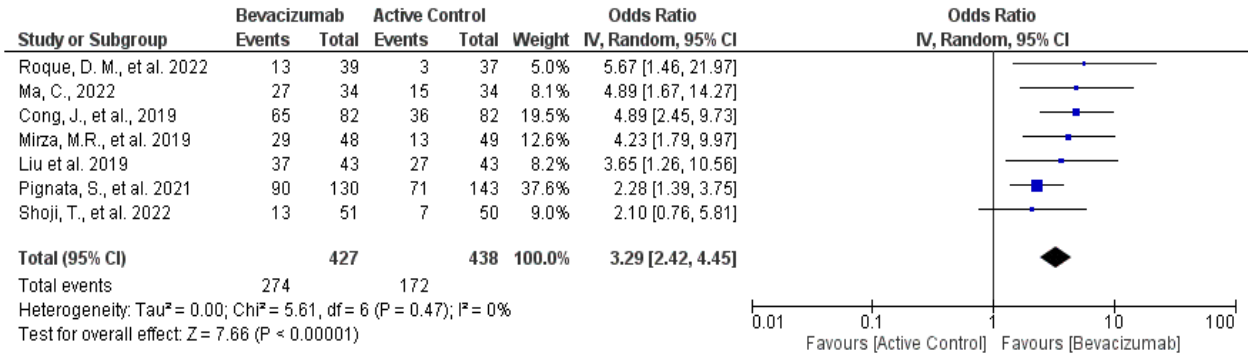


Figure 11. Funnel Plot of Studies included in Meta-Analysis 3 (Objective Response Rate)

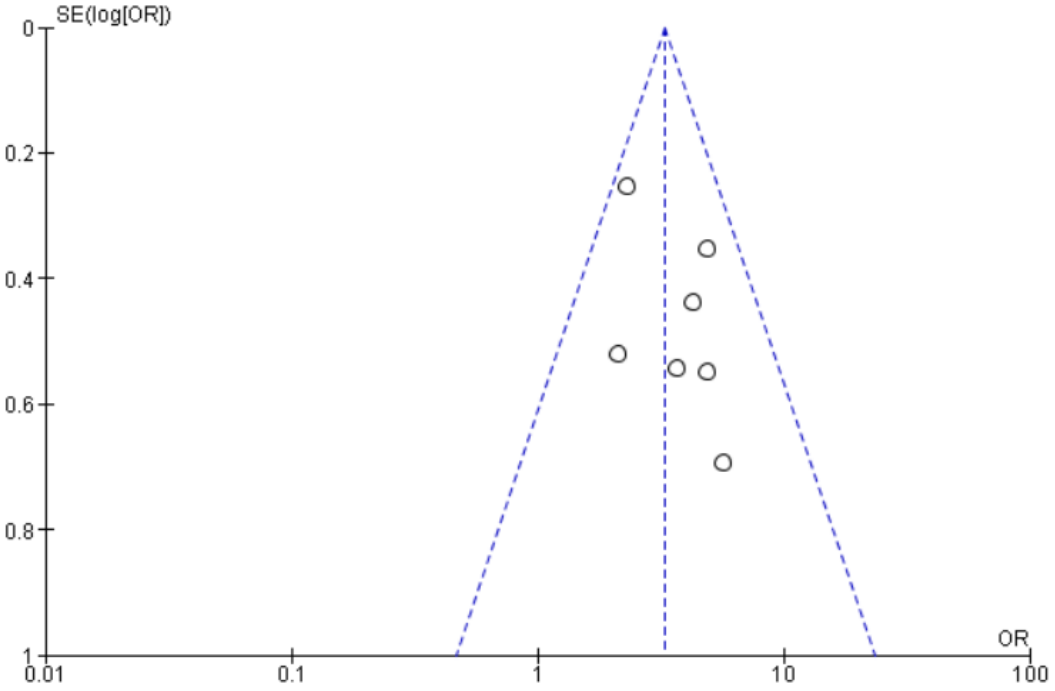


Figure 12. Meta-analysis 4: Forest plot Comparison between Bevacizumab and an Active Control on Complete Response Rate in Patients with Epithelial Ovarian Carcinoma

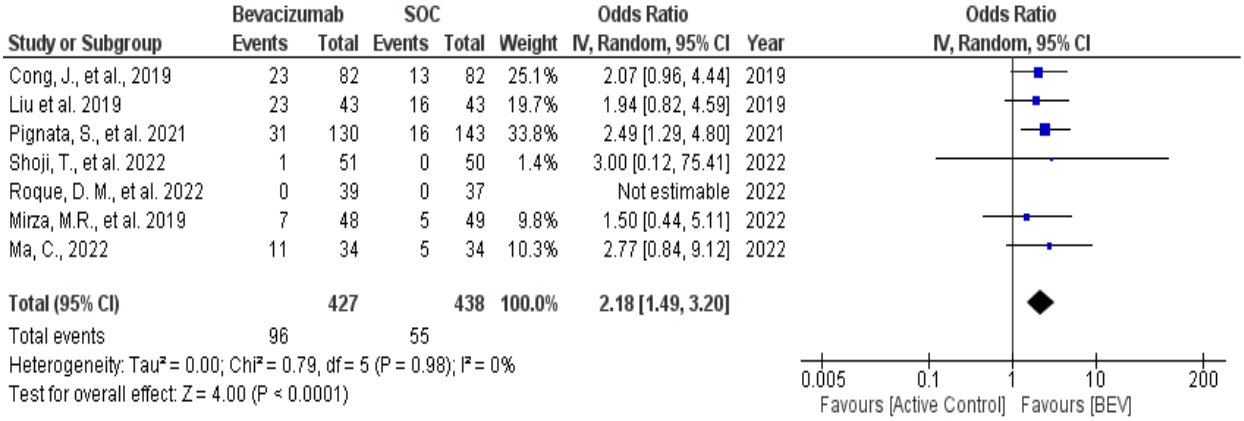


Figure 13. Funnel Plot of Studies included in Meta-Analysis 4 (Complete Response Rate)

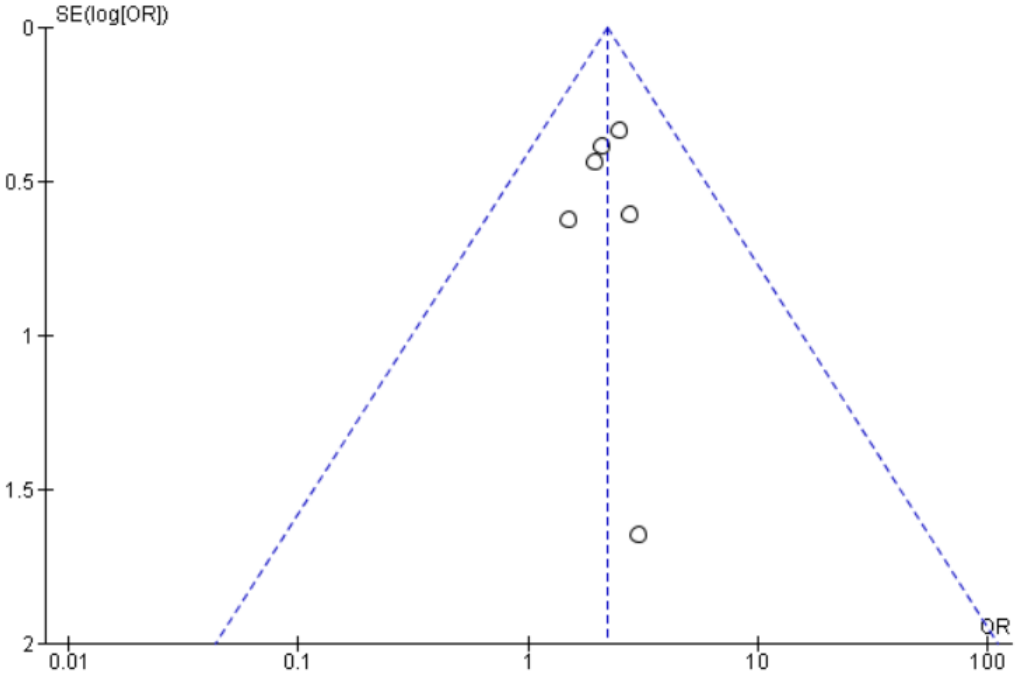


Figure 14. Meta-analysis 5: Forest Plot Comparison between Bevacizumab and an Active Control on Partial Response Rate in Patients with Epithelial Ovarian Carcinoma

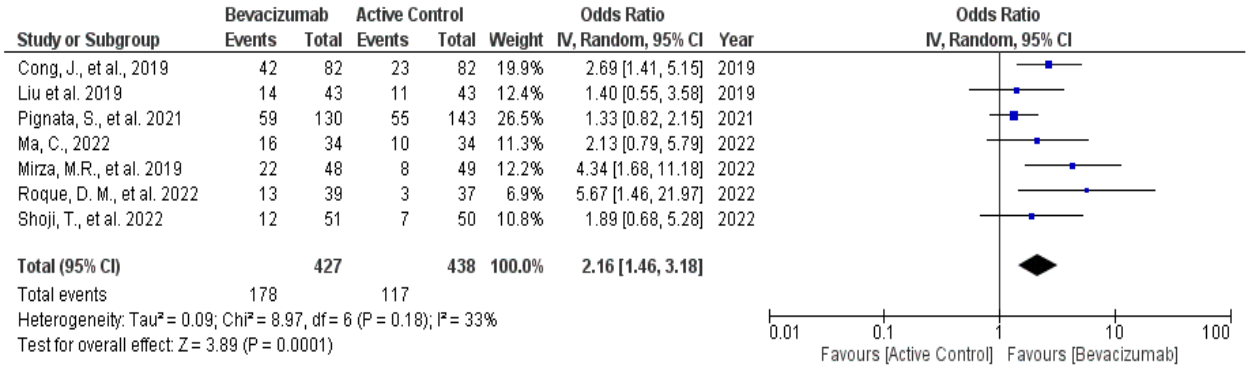


Figure 15. Funnel Plot of Studies included in Meta-Analysis 5 (Partial Response Rate)

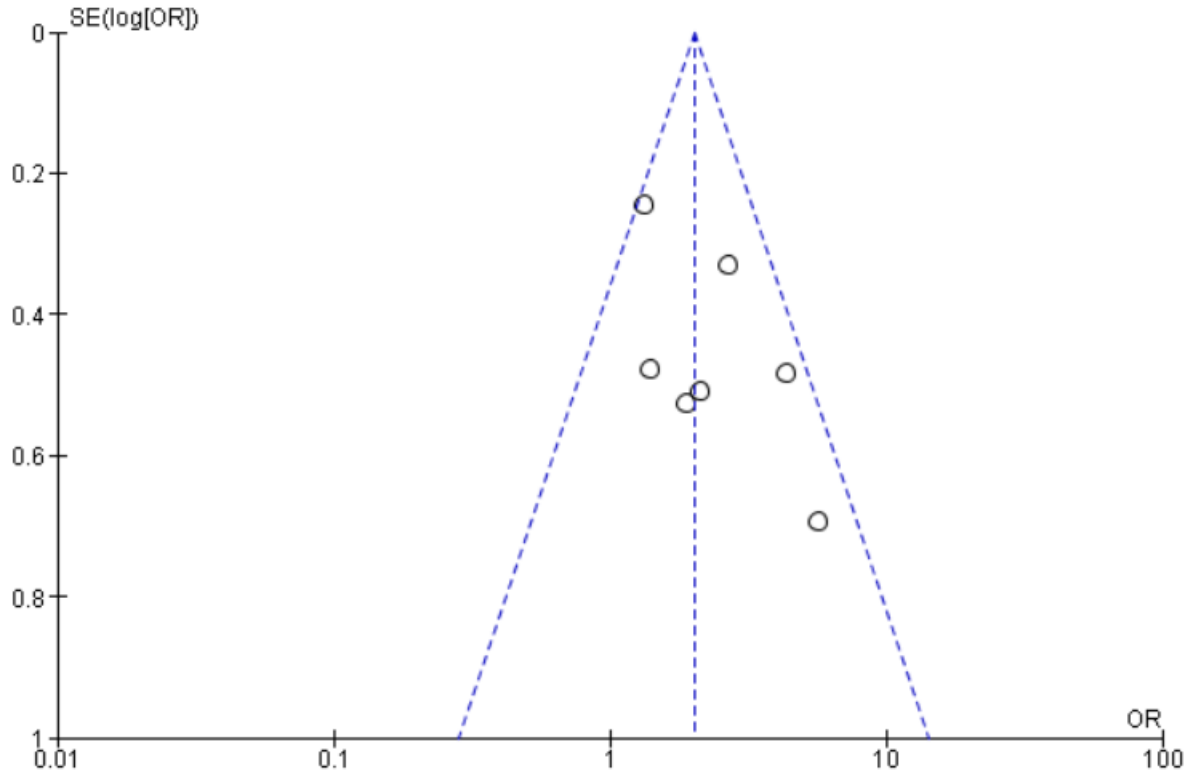


Table 8. Studies Comparing Bevacizumab *vs* Active Control on Serious Adverse Events and Grade ≥ 3 Adverse Events

Author Year	Eligible Patients, n		SAE, n (%)		Grade ≥3 AEs, n (%)	
	BEV	**AC**	**BEV**	**AC**	**BEV**	**AC**
Mirza et al. 2019	48	49	NR	NR	22	8
Pignata et al. 2021	201	200	52	41	110	96
Roque et al. 2022	39	37	8	6	13	3
Shoji et al., 2022	51	50	12	8	30	23
Chunyan Ma., 2021	34	34	11	5	16	10
Tewari et al., 2019	619	621	287	239	NR	NR
Garcia et al., 2019	35	33	NR	NR	10	20
TOTALS	1027	1024	370	299	201	160

Abbreviations: AC = active control; AE = adverse event; BEV = bevacizumab; NR = not reported; SAE = serious adverse event.

Figure 16. Meta-Analysis 6: Forest Plot Comparison of Patients that experienced SAEs following Bevacizumab administration compared to an Active Control

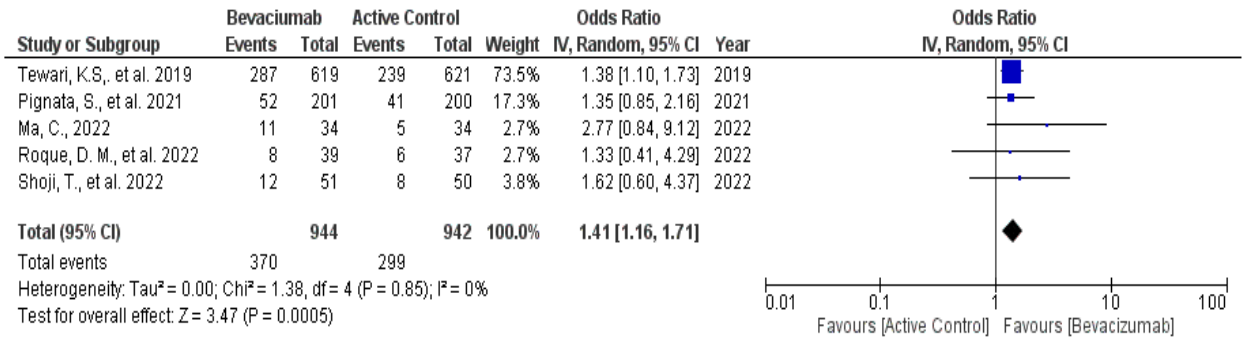


Figure 17. Funnel Plot of Studies included in Meta-Analysis 6 (SAEs)

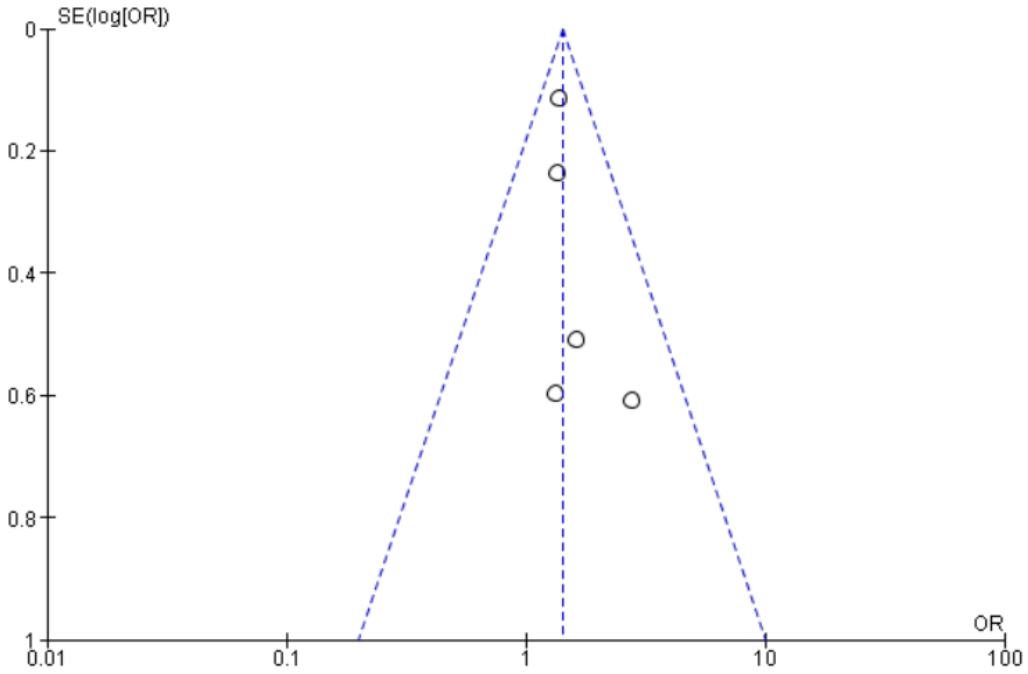


Figure 18. Meta-Analysis 7: Forest Plot of the Proportion of Patients that experienced Grade ≥3 AEs following Bevacizumab administration compared to an Active Control

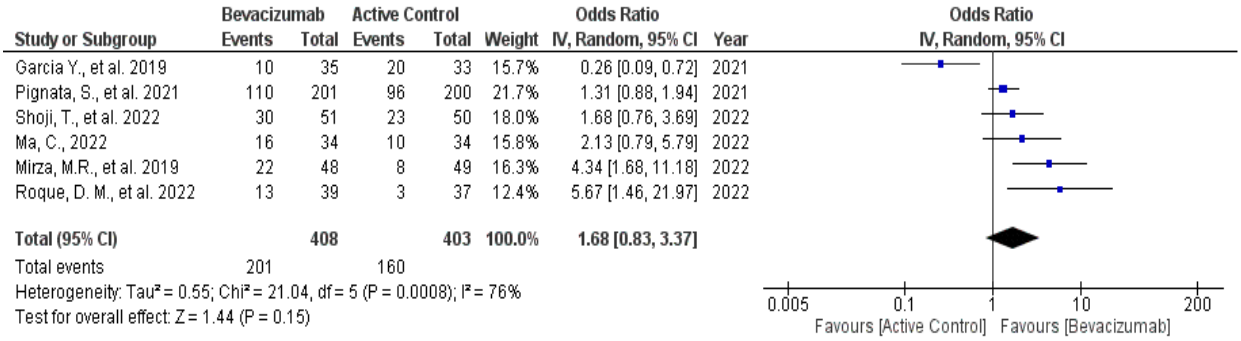
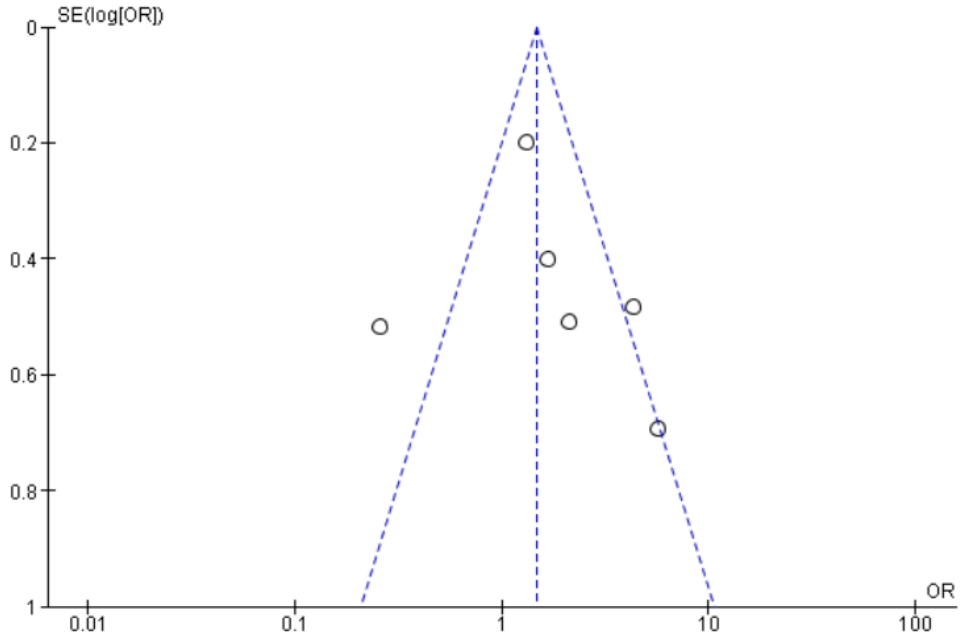


Figure 19. Funnel Plot of Studies included in Meta-Analysis 7 (Grade ≥3 AEs)



10 Discussion

The objective of this study was to determine whether a sustained effect on PFS, OS, ORR, CR, PR, SAEs, and grade ≥3 AEs in patients with EOC treated with BEV was observed in comparison to an AC, for RCTs published after 2018. The systematic review and each respective meta-analysis demonstrated that treatment with BEV was significantly associated with improved PFS, OS, ORR, CR, and PR compared to the AC. Serious adverse events and grade ≥3 AEs were more frequently experienced in BEV-treated patients compared to AC-treated patients and were only statistically significant for the pooled OR of SAEs.

In analyzing the PFS results according to each study's inclusion criteria, it can be observed that key characteristics in patient population may be driving (or inhibiting) the pooled effect and heterogeneity. Several consistencies were noted among the studies included in the PFS meta-analysis. Specifically, three of the eight studies in meta-analysis 1 recruited platinum-resistant patients. Liu et al., included subjects with optimal cytoreductive surgery following disease onset, and disease progression within 6 months of platinum-based chemotherapy[144]. In Shoji et al., subjects were included if demonstrating platinum-resistance with recurrence following PDS and were naïve to BEV in combination with chemotherapy treatment[145]. Finally, Roque et al., included subjects with platinum-resistance, and allowed subjects with previous exposure to BEV in combination with chemotherapy[133]. The magnitude of improvement in PFS increased by 0.9 to 3.3 months for patients randomized to BEV compared to the AC in these studies and is consistent with PFS results from the AURELIA trial which also recruited platinum-resistant EOC patients[128].

Additionally, one of Liu et al., primary endpoints was to measure the CA125 levels over the course of the study for patients randomized to BEV and the AC groups. As cited previously,

increased levels of CA125 are often used as a biomarker to confirm the presence and extent of tumor lesions. Of note, 4 weeks after treatment, CA125 levels decreased to 22.76 kU/L and 28.54 KU/L from a baseline value of 673 kU/L and 654 kU/L, for the BEV with AC arm compared to the single-agent AC arm, respectively[144]. Irrespective of the study treatment received, CA125 values significantly decreased at the 4-week assessment compared to baseline. Despite the similarities in CA125 values following treatment with BEV or the AC, only a sustained effect on the PFI was observed following treatment with BEV, resulting in a significantly longer PFS compared to patients randomized to the AC group.

Other differences were noted among studies included in the PFS meta-analysis, notably the GEICO 1205 trial. In this study, treatment with BEV compared to the AC did not result in significant improvements in PFS (20.4 vs. 20.1 months; $p = 0.66$)[140]. The trial enrolled platinum-sensitive patients with unresectable disease at baseline, requiring NACT. In this setting, addition of BEV with chemotherapy compared to single-agent chemotherapy as a first-line treatment has been shown to improve PFS. In ICON7, subjects randomized to first-line BEV with chemotherapy had a median PFS of 24.1 months compared to 22.4 months in the conventional chemotherapy group ($p=0.04$) but also experienced more grade 2 or higher AEs[136]. In contrast, BEV treatment in GEICO 1205 was associated with fewer grade ≥3 AEs compared to the conventional chemotherapy group. Notably, the ICON7 trial had a higher proportion of patients who had undergone PDS in contrast to the non-resectable patients which were solely recruited in GEICO 1205 for IDS. This could suggest differences in patients' residual disease at baseline were also predictive of clinical outcomes despite similarities in cancer histotypes, stage of disease, and treatment.

The results of the meta-analysis evaluating OS indicated a longer pooled median OS of 21.6 months for BEV patients compared to 17.4 months among AC patients. On the other hand, individual study median OS varied, most likely due to varying data cut-off points and protocol-specified inclusion criteria. A recent observational study reported a significant increase in the 5-year survival rate for platinum-resistant patients treated with BEV (44%) compared to the standard chemotherapy group (36%, $p = 0.001$) and no significant effect for platinum-sensitive patients (64% vs 68%, $p = 0.28$)[148]. In contrast, the final median OS endpoint for the ICON7 trial reported no OS benefit among BEV-treated patients with platinum-resistance (44.6 months) compared to standard chemotherapy (45.5 months, $p = 0.85$) at a median follow up of 48.9 months, or the equivalent of approximately 4 years[136].

Studies with shorter durations of follow-up or which report premature data on PFS and OS may initially result in larger PFS benefit, and in contrast smaller OS benefit. Shorter durations of follow-up may exaggerate the treatment's effect (or lack thereof) on PFS, given that frequency of tumor progression assessments is not necessarily consistent for all studies. This was evidenced by a cross-sectional analysis of RCTs evaluating patients with unresectable or metastatic solid tumors that were randomized to an intervention and control, whereby RCTs with less frequent tumor progression assessments were associated with higher median PFS values for both the intervention and the control groups[149]. Another point of discernment when interpreting pooled OS is the pre-specified cutoff date to initiate the final analysis for the respective study. In the GOG-0240 trial, the pre-specified cutoff date for final analysis was on March 7, 2014, roughly 5 years after the first subject, first screening visit, at which point 348 deaths had occurred[150]. For the GOG-0218 trial included in meta-analysis 2, the database was locked at a median follow-up of 102.9 months (roughly 8 years after the first subject, first screening visit), at which point

493 deaths had occurred in the control arm[130]. In GOG-0218, relative to the AC (41.1 months), there was no significant OS benefit among patients treated with BEV (43.4 months, p = 0.53)[130]. Therefore, additional caution should be taken when interpreting pooled PFS and OS results in meta-analyses, to consider both the impact of frequency of tumor progression assessment and duration of follow-up on effect size.

In addition to study conduct variability, such as discrepancies in frequency of tumor progression assessment and study duration, the estimation of ORR, CR, and PR are highly dependent on definitions of progression. Most studies included in the meta-analyses evaluating ORR, CR, and PR referred to RECIST v1.1 guidelines to properly track patient's progress and tumor status following exposure to treatment. In line with this, the pooled ORs for ORR, CR, and PR were similar to the ORs of the individual studies in each meta-analysis. This resulted in a pooled OR with little to no heterogeneity and overall symmetry in the corresponding funnel plots. Bevacizumab-treated patients had 3.29, 2.18, and 2.16 greater odds of achieving an ORR, CR, and PR compared to AC-treated patients. These results are consistent with prior studies, including AURELIA which reported a 48% ORR in a standard-chemotherapy group compared to 67% in the BEV-treated arm ($p<0.001$) [128]. Similarly, in meta-analysis 3, 64.1% of patients (274/427) achieved an ORR in the BEV group compared to 39.3% of patients (172/438) in the AC group. This emphasizes the importance of reproducible evaluation criteria to objectively rate tumor progression, especially in clinical settings where novel agents are frequently assessed and compared to SOC.

Results of the safety and tolerability meta-analyses indicated increased toxicity for BEV-treated patients compared to the AC group. Specifically, the proportion of patients that experienced a SAEs or a grade ≥3 AEs was 39.2% (370/944 patients) and 49.3% (201/408 patients) for

BEV-treated patients compared to 31.7% (299/942) and 39.7% (160/403) of AC-treated patients. Of note, grade 3 hypertension was more frequently experienced by BEV-treated patients compared to the AC (29% [58/201] vs. 10% [20/200]) in Pignata et al. study, which administered BEV with dose-dense CP compared to CT-based doublet alone[143]. This is consistent with other trials citing hypertension as a common AE following BEV administration but may be influenced by additional factors, including mode of administration. The toxicity of BEV in the presence or absence of PARP inhibitors was previously evaluated and demonstrated that BEV administration in combination with Olaparib and another monoclonal antibody (durvolumab) in EOC patients without BRCA mutation resulted in fewer AEs experienced compared to PARP-inhibitor doublet without BEV (55% vs. 65%)[132]. Further research is required to confirm the independent effect of patient BRCA mutation, administration of VEGF inhibitors, and concurrent therapy with other PARP inhibitors, on safety and tolerability.

10.1 Limitations and Future Directions

This systematic review and meta-analysis aimed to bridge the gap between policy and patient healthcare for a disease with devastating consequences and diverse origins. The FDA's decision to bring BEV at the forefront of EOC treatment emphasizes the need to continually evaluate the evolving characteristics of EOC, its many relationships with genetic predispositions, balance of treatment frequency, surgical cytoreductions, and improvement of novel targeted therapies to reduce toxicity.

This updated meta-analysis provided an insight by focusing on studies published after the FDA's decision to determine the sustained effect of BEV on clinical outcomes for EOC. Despite the many applications of systematic reviews and meta-analyses, it is important to acknowledge certain limitations of this research. The inherent heterogeneity in study designs, patient

populations, and methodologies among the included trials can pose challenges in synthesizing conclusive results. Ovarian cancers intricate molecular diversity and clinical presentations raise important questions that may not be fully resolved in a standardized meta-analysis. Additionally, the potential for publication bias necessitates cautious interpretation, as positive outcomes may be more prominently featured.

Nearly all studies included in the meta-analyses had at least one domain with a moderate risk of bias, defined as "some concern" according to the ROB2. This was predominantly the bias in the measurement of the outcome domain. For studies where progression and response were evaluated, an investigator was responsible for assessing the radiographic images, CA125 levels, ascites, or pleural effusions of each patient. All the studies included in the meta-analyses were randomized however, only the study by Tewari et al., was a double-blinded and placebo-controlled trial, and therefore, the assessor responsible for evaluating progression was blinded from the treatment allocation. For the remaining studies, the investigators that performed the outcome assessment were also aware of the subject treatment allocation, giving rise to potential observer bias. All studies utilized a pre-defined framework to determine disease progression or response to therapy, such as the RECIST v1.1. According to the FDA's guidance for industry in clinical trials where imaging is used to evaluate an endpoint, a blinded independent centralized review is recommended[151]. An application of this recommendation would require the involvement of an additional radiologist, that is independent of study conduct, to perform a second, blinded review of the evaluation. In the case of incongruous assessments, an adjudicator would be assigned to evaluate and resolve the discrepancy[151]. Some studies included in the meta-analyses evaluating PFS, ORR, CR, and PR as primary or secondary endpoints, had an independent radiologist review the subject's tumor radiographic images, and laboratory

assessments, where applicable, to verify the principal investigators evaluation. In other instances, a lack of information in the manuscript and supplementary documentation led to the assignment of “missing information” on the ROB2. Considering this, some concern for observer bias was assumed for this particular outcome.

For the meta-analysis evaluating OS, Cochrane’s guidelines on the risk of bias in outcome measurements specifies that assessments of outcomes, such as all-cause mortality, does not involve subjective judgement and are therefore unlikely to be influenced by knowledge of the intervention received. Overall survival is an extension of all-cause mortality, reporting time to death from study start. Therefore, the studies which were not double-blinded and included in the OS meta-analysis were considered to have a low impact on this domain of the ROB2.

Upwards of 10 different treatments were administered in the studies included in the meta-analyses. Although some overlap in selection of study treatment for the AC occurred, method of administration and dosage were variable across studies. This, in addition to the asymmetry of the funnel plots for PFS and OS, would seem to suggest that the results for these outcomes may be exaggerated in favor of BEV. To have a better understanding of the true impact of BEV on clinical outcomes, it would prove helpful to stratify studies according to the type of AC administered.

As we navigate the era of novel targeted therapies for EOC, it becomes imperative to establish robust protocols for network meta-analysis. This systematic approach is essential for a more comprehensive evaluation of specific classes of novel agents for EOC by methodically integrating and comparing data from diverse sources. To facilitate this process, drug classes may be grouped for a more coherent analysis. For instance, one might categorize therapies based on their mechanisms of action or biological pathways, allowing a coherent evaluation of different

drug classes, in combination with BEV, and their impact on clinical outcomes. Network meta-analysis can be used as a discerning tool, to explore the synergies and interactions of these innovative therapies and their impact on patient outcomes.

11 Conclusion

Beyond the immediate clinical implications, these findings also prompt a broader reflection on the evolving landscape of EOC treatment. The observed enhancements in PFS, OS, and ORR with BEV administration emphasize its potential as a valuable addition to the armamentarium against EOC. However, the heightened incidence of SAEs and grade ≥3 AEs necessitates a meticulous risk-benefit evaluation. This highlights the ongoing challenge in achieving an optimal balance between treatment efficacy and safety. Moreover, the study's revelations also point to the need for continued research and the exploration of alternative therapeutic avenues that could potentially mitigate AEs while maintaining or improving clinical outcomes. As the field progresses, these insights contribute to shaping future strategies and refining the SOC for patients with EOC.

In summary, this study not only provides valuable data for immediate clinical decision-making but also fuels a broader conversation within the oncology community. The delicate interplay between efficacy and safety considerations accentuates the complexity of managing EOC, demanding a nuanced and individualized approach. As researchers and clinicians delve deeper into these findings, the hope is to continually refine treatment strategies, minimize risks, and optimize outcomes for those affected by EOC.

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151. GUIDANCE D. Clinical Trial Imaging Endpoint Process Standards. *Center for Biologics Evaluation and Research (CBER)* 2015

13 Appendix

Table 9. Search Strategy and MeSH Terms

PubMed, MEDLINE, and EMBASE [via OVID]
1. (Ovarian Cancer or Ovarian Neoplasms or Ovarian Epithelial Carcinoma or Carcinoma, Ovarian Epithelial).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
2. (Bevacizumab or Avastin or Mvasi or Bevacizumab-awwb or Bevacizumab awwb).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]
3. 1 AND 2

MeSH terms:

1. Ovarian Cancer

- Neoplasm, Ovarian
- Ovarian Neoplasm
- Ovary Neoplasms
- Neoplasm, Ovary
- Neoplasms, Ovary
- Ovary Neoplasm
- Ovary Cancer
- Cancer, Ovary
- Cancers, Ovary
- Ovary Cancers
- Ovarian Cancer
- Cancer, Ovarian
- Cancers, Ovarian
- Ovarian Cancers
- Cancer of Ovary
- Cancers of the Ovary

2. Epithelial Ovarian Carcinoma

- Epithelial Carcinoma, Ovarian
- Ovarian Epithelial Carcinomas
- Epithelial Ovarian Cancer
- Ovarian Epithelial Cancer
- Cancer, Ovarian Epithelial
- Epithelial Cancer, Ovarian
- Ovarian Epithelial Cancers
- Ovarian Cancer, Epithelial
- Cancer, Epithelial Ovarian
- Epithelial Ovarian Cancers
- Ovarian Epithelial Carcinoma
- Epithelial Ovarian Carcinoma
- Carcinoma, Epithelial Ovarian
- Epithelial Ovarian Carcinomas
- Ovarian Carcinoma, Epithelial

3. Bevacizumab

- Mvasi
- Avastin
- Bevacizumab-awwb
- Bevacizumab awwb

Table 10. ROB2 domain assessments for studies included in the quantitative analysis

Study	Domain	Risk of Bias Judgment	Comments
Cong et al., 2019	Bias arising from the randomization process	Some concerns	"A total of 164 patients with recurrent ovarian cancer who were diagnosed and treated in our hospital from March 2013 to March 2015 were selected and randomly divided into two groups: experimental group and control group."
	Bias due to deviations from intended interventions	Some concern	As there was no use of a placebo in the control group, it is possible that the investigator or patients were not masked to treatment assignment.
	Bias due to missing outcome data	Low	All randomized patients completed the study per protocol and had reportable data relating to the outcome.
	Bias in measurement of the outcome	Low	Progression of disease was determined by independent oncologists.
	Bias in selection of the reported result	Low	RECIST v1.1 guidelines were used to determine progression of disease.
Garcia et al., 2019	Bias arising from the randomization process	Low	The study was described both in the article and on clinicaltrials.gov as an open-labelled, randomized clinical trial. Treatment allocation was controlled by separate study personnel until the first study treatment administration.
	Bias due to deviations from intended interventions	Low	As this was an open-label RCT, patients and investigators were aware of the intervention. All subjects in the ITT population were evaluated.
	Bias due to missing outcome data	Low	All subjects in the ITT population had evaluable data. None were lost to follow-up.
	Bias in measurement of the outcome	Some concern	The study investigators were unblinded to the interventions provided to subjects and were also required to assess the study outcomes therefore, some degree of observer bias may be assumed. However, due to the nature of some assessments (ie,

Study	Domain	Risk of Bias Judgment	Comments
			OS) which do not rely on subjective judgement, this is unlikely.
	Bias in selection of the reported result	Low	RECIST v1.1 guidelines used for tumor progression assessment
Mirza et al., 2019	Bias arising from the randomization process	Low	Patients were randomized in a 1:1 ratio using random permuted block randomization implemented by Sealed Envelope Ltd. Per protocol section 7.2, the study treatment was stored in a suitable container which were held in a securely locked area, accessible to authorized personnel only.
	Bias due to deviations from intended interventions	Low	The full analysis set, or modified intention-to-treat population consisted of all patients that received at least one dose of the study treatment irrespective of further compliance to the planned course of treatment. The population was used for the analysis of the outcomes of interest. Study treatment discontinuation was consistent with the trial protocol rules as defined in the article "Procedures" section and Protocol section 7.1.2 "Dose Modification" and 7.6.6 "Dosing and Toxicity".
	Bias due to missing outcome data	Low	Almost all randomized subjects were included in the modified ITT populations for the analyses.
	Bias in measurement of the outcome	Some concern	The outcome-assessors (Investigators) were aware of the treatment assigned to subjects due to the open-labelled nature of the study. Absence of blinded assessors could have led to observer bias however, assessments such as OS, are unlikely to be influenced by knowledge of the intervention, while some concern for observer bias must be assumed for PFS and ORR.
	Bias in selection of the reported result	Low	RECIST v1.1 guidelines used.

Study	Domain	Risk of Bias Judgment	Comments
Tewari et al., 2019	Bias arising from the randomization process	Low	This was a double-blind, placebo-controlled study. Randomization was performed by the GOG Statistical and Data Center per section 4.2.7."Blinded, patient-specific supplies for Phase A/B will be sent to the registering investigator at the time of randomization."
	Bias due to deviations from intended interventions	Low	As defined in section 2.6 of the clinical study protocol "Rationale for Clinical Trial Design", the present study was a double-blind, placebo-controlled phase III trial whereby investigators, patients, and research personnel did not know whether patients had received BEV or placebo.
	Bias due to missing outcome data	Low	Per section 6.7 of the protocol, the intent-to-treat analysis was necessary to avoid introducing biases that could have resulted from eliminating patients who dropped-out due to toxicity, noncompliance, illnesses, or other factors. Therefore, all randomized patients were included in the analysis regardless of whether they were able to receive the study-directed therapy.
	Bias in measurement of the outcome	Low	Per section 8.5.2 of the protocol: "The time to progression will be determined by the clinical investigator and separately by an independent review of radiology studies. The independent review will occur at the Independent Review Facility (IRF) and will consist of the blinded review of radiology studies and other relevant clinical information by radiologists and oncologists. Details are provided in a separate charter. (10/14/08)"
	Bias in selection of the reported result	Low	RECIST v1.1 guidelines used.
Pignata et al., 2021	Bias arising from the randomization process	Low	Although this was an open-label clinical trial, the allocation sequence was done by computerized minimization using center, time of relapse, performance status and type

Study	Domain	Risk of Bias Judgment	Comments
			of second-line chemotherapy as stratification variables.
	Bias due to deviations from intended interventions	Low	"All randomized patients will be analyzed according to the randomization arm irrespective of the actual treatment they received."
	Bias due to missing outcome data	Low	"All efficacy analyses will be performed on an intention-to-treat (ITT) basis."
	Bias in measurement of the outcome	Some concern	Tumor response was assessed by a non-independent Investigator. Absence of blinded assessors could have led to observer bias however, assessments such as OS, are unlikely to be influenced by knowledge of the intervention, while some concern for observer bias must be assumed for PFS.
	Bias in selection of the reported result	Low	RECIST v1.1 guidelines followed for disease progression as part of the pre-defined statistical analysis plan for the efficacy endpoints.
Shoji et al., 2022	Bias arising from the randomization process	Low	A dynamic randomization (minimization method) with the following stratification factors were implemented: number of regimens received in previous treatment (1, 2, vs. 3), the time to recurrence/disease progression from the last day of platinum-drug administration (during treatment vs. < 3 months vs. >/= 3), and the chemotherapy drug (doxorubicin vs. topotecan vs. paclitaxel vs. gemcitabine).
	Bias due to deviations from intended interventions	Some concerns	The article states that 2 subjects were misallocated to the chemotherapy group and received bevacizumab. These patients were included in the chemotherapy group for the efficacy analyses and in the chemotherapy + bevacizumab group for safety analyses. One patient allocated to the chemotherapy + bevacizumab group received chemotherapy alone (without bevacizumab). This patient was

Study	Domain	Risk of Bias Judgment	Comments
			included in the chemotherapy + bevacizumab group for efficacy analysis and the chemotherapy group for safety analysis.
	Bias due to missing outcome data	Low	The efficacy analysis was performed according to the intention-to-treat population.
	Bias in measurement of the outcome	Some concern	This was an open-labelled, clinical trial, tumor response was assessed by non-independent Investigators. As such, there is a possibility of observer bias however, assessments such as OS, are unlikely to be influenced by knowledge of the intervention, while some concern for observer bias must be assumed for PFS and ORR.
	Bias in selection of the reported result	Low	The statistical analysis plan was developed prior to clinical conduct. Furthermore, for the main outcome measures, the RECIST v1.1 guidelines were followed.
Roque et al., 2022	Bias arising from the randomization process	Low	Per Section 14 of the protocol, patients were randomized 1:1 using a dynamic procedure which minimized stratification-factor imbalance between the treatment arms. Stratification factors were study site and previous receipt of bevacizumab prior to randomization. Per sections 4.1.3 and 4.2.3, study treatments were kept in a secure, limited access storage area and dispensed according to the allocation sequence by an independent designated study personnel which maintained records of the product delivery, use by each patient, and return of any unused product.
	Bias due to deviations from intended interventions	Low	Although dose reductions were reported, these were within the protocol defined scheme (section 7.1.1 of the protocol) which specified the amount of reduction that was used for each specific treatment-related AE type and severity grade observed.

Study	Domain	Risk of Bias Judgment	Comments
	Bias due to missing outcome data	Low	All efficacy analyses were performed on the ITT population.
	Bias in measurement of the outcome	Some concerns	Given that this study was an open-label clinical trial, tumor response to treatment was assessed by an unblinded Investigator. Absence of blinded assessors could have led to observer bias however, assessments such as OS, are unlikely to be influenced by knowledge of the intervention, while some concern for observer bias must be assumed for PFS and ORR.
	Bias in selection of the reported result	Low	The proposed statistical analyses were described in Section 14 of the protocol, prior to clinical conduct. Furthermore, the numerical results for PFS, OS and ORR were determined using a published set of guidelines (RECIST v1.1)
Liu et al., 2019	Bias arising from the randomization process	Some concerns	The article specifies the use of a random number table to allocate the study treatments. Per the exclusion criteria section of the article: no statistically significant differences were detected in basic data of patients including age, menopausal status, histological type, tumor stage, ECOG score, and first-line treatment between the two groups ($p>0.05$).
	Bias due to deviations from intended interventions	Low	The article does not list any deviations from the intended interventions provided to subjects assigned to either treatment group. Furthermore, all 43 subjects (per treatment group respectively) were included in the efficacy analyses.
	Bias due to missing outcome data	Low	The efficacy analyses were performed using the ITT population.
	Bias in measurement of the outcome	Some concerns	The Investigators were not masked to the treatment assigned to patients. Absence of blinded assessors could have led to observer bias however, assessments such as OS, are unlikely to be influenced by knowledge of the

Study	Domain	Risk of Bias Judgment	Comments
			intervention, while some concern for observer bias must be assumed for PFS and ORR.
	Bias in selection of the reported result	Low	Statistical analysis for the efficacy endpoints were predefined. Furthermore, the RECIST v1.1 guidelines were used to determine disease progression.
Chunyan Ma., 2022	Bias arising from the randomization process	Some concerns	Patients were "grouped" according to admission order, 1:1 to each treatment group (A or B). According to baseline data on age, smoking history, differentiation, lymph node metastasis, and staging of epithelial ovarian cancer, no statistically significant differences between the two groups were observed. Four more patients in the control group (A) had a family history of epithelial ovarian cancer and this was statistically significantly different compared to the experimental group (B).
	Bias due to deviations from intended interventions	Low	The article describes the study as an "open-labelled and controlled clinical trial". There were no deviations from the intended intervention that are described in the study. All subjects assigned to Group A or B were included in the ITT population.
	Bias due to missing outcome data	Low	The efficacy analyses were performed using the ITT population.
	Bias in measurement of the outcome	Some concerns	Given that the study was open-labelled, and that the clinical outcomes for tumor response were Investigator-assessed, there is some concern for observer bias as it relates to ORR however, assessments such as OS, are unlikely to be influenced by knowledge of the intervention.
	Bias in selection of the reported result	Low	The statistical analyses were predefined and referred to the RECIST v1.1 guidelines to determine disease progression.

Table 11. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	8-11
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	14-15
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	15-16
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Table 3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	39
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Table 9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	39
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	39
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	39
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	41
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	42
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each	42

Section/topic	#	Checklist item	Reported on page #
		meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	42
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	43 Figure 4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	48-52, 54, 56, 58 Tables 4-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	52
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	43-46, Figures 6-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	53-63
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	85-91, Table 9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	64-68
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	68-71
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	71-72
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data), role of funders for the systematic review.	N/A