

## SYSTEMATIC REVIEW AND META-ANALYSIS

### Efficacy and safety of angiogenesis inhibitor in platinum-resistant ovarian cancer: meta-analysis on randomized controlled trial

*Meta-Analysis: Angiogenesis in PROC*

Made Favian Budi **Gunawan**<sup>1,\*</sup>, Cindy Thiovany **Soetomo**<sup>1</sup>, Bryan Gervais de **Liyis**<sup>1</sup>, I Nyoman Gede **Budiana**<sup>2</sup>

<sup>1</sup> Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia

<sup>2</sup> Department of Obstetrics and Gynecology, Udayana University, Denpasar, Bali, Indonesia

**\*Corresponding author:** Made Favian Budi **Gunawan**, Faculty of Medicine, Udayana University, Jl. PB Sudirman 80234, Denpasar, Bali, Indonesia.

Email: favian262@gmail.com.

ORCID: 0009-0005-2549-374X.

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## ABSTRACT

**Objective.** Treatment options for platinum-resistant ovarian cancer (PROC) remain scarce, necessitating the exploration of novel therapeutic approaches, such as angiogenesis inhibitors. This study aimed to assess the effectiveness and safety of combining angiogenesis inhibitors with chemotherapy in patients diagnosed with PROC.

**Materials and Methods.** Systematic review and meta-analysis conducted based on PRISMA guidelines. Randomized trials comparing angiogenesis inhibitors against chemotherapy alone as treatment of PROC were identified from several electronic databases including PubMed, Cochrane, and Science Direct up to November 2023. The data were combined across trials and assessed using RevMan. The efficacy determined from progression-free survival (PFS) and overall survival (OS), and the safety assessment calculated based on the odd ratios of the adverse events (AE).

**Results.** Seven trials with 1,085 patients were included. Angiogenesis inhibitors significantly improved OS (HR = 0.70, 95% CI [0.58, 0.84]) and PFS (HR = 0.50, 95% CI [0.43, 0.57]). Among 15 grade  $\geq 3$  AEs analyzed, several were significantly increased with angiogenesis inhibitors, including hand-foot syndrome (OR = 3.13, 95% CI [1.40, 6.98]), hypertension (OR = 8.15, 95% CI [3.67, 18.09]), leukopenia (OR = 1.60, 95% CI [1.00, 2.57]), neutropenia (OR = 1.42, 95% CI [1.06, 1.91]), proteinuria (OR = 6.48, 95% CI [1.15, 36.62]), sensory neuropathy (OR = 3.12, 95% CI [1.51, 6.47]), and vomiting (OR = 0.36, 95% CI [0.13, 1.00]).

**Conclusions.** Angiogenesis inhibitors combined with chemotherapy significantly improved survival in PROC but were associated with higher rates of specific toxicities. These findings support their clinical value with attention to adverse event profiles.

### **Key words**

Angiogenesis inhibitor; meta-analysis; platinum-resistant ovarian cancer.

### **Introduction**

Ovarian cancer (OC) is one of the most common gynecologic malignancies globally and is associated with the lowest survival rates among them, with epithelial ovarian cancer (EOC) accounting for the majority of cases [1–3]. By 2040, the global incidence of OC is projected to increase by 36.6%, with a 47.6% rise in mortality [4]. Despite the initial effectiveness of first-line platinum-based chemotherapy and cytoreductive surgery in managing advanced OC, most patients eventually experience relapse and develop platinum resistance, which markedly worsens survival outcomes [5]. Based on that, The Fifth Gynecologic Cancer InterGroup (GCIG) has recommended a revised classification of platinum sensitivity based on the platinum-free interval (PFI), dividing it into the following categories: <1 month, 1–6 months, 6–12 months, and >12 months [6]. Among these categories, platinum-resistant ovarian cancer (PROC) specifically refers to cases where disease progression occurs within six months after completing at least three cycles of platinum-based chemotherapy, including bevacizumab. This subgroup of patients is associated with particularly poor outcomes, with a median overall survival (OS) of approximately 12 months [7–9].

At present, treatment with systemic chemotherapy, including polyethylene glycol liposome doxorubicin (PLD), paclitaxel, topotecan, gemcitabine, and etoposide with varying efficacy rates, is the primary approach for PROC and were tailored based on the patient's characteristics [10]. In comparison to chemotherapy alone, the addition of anti-angiogenic agents, targeted therapies, and immunotherapies has shown improved survival outcomes in patients with recurrent PROC [11,12]. However, despite the availability of multiple therapeutic options, there is still no global consensus on standardized treatment guidelines for this patient population. Therefore, to support broader and more effective treatment strategies, it is crucial to simultaneously assess both the efficacy and tolerability of emerging therapies [13].

Among the various therapeutic approaches under investigation for PROC, targeting angiogenesis has emerged as a particularly promising strategy due to its essential role in tumor progression by supplying nutrients and removing metabolic waste [14]. Although the underlying mechanisms are not yet fully elucidated, tumor vascularization is known to be regulated by multiple factors, with the vascular endothelial growth factor (VEGF) and its receptor (VEGFR) pathway being the primary target of early anti-angiogenic therapies [15]. Anti-angiogenic agents approved for use in ovarian cancer function by disrupting tumor vascularization, both through the destruction of existing blood vessels and the inhibition of new vessel formation [16].

Considering their molecular benefits, the therapeutic effectiveness of angiogenesis inhibitors in PROC remains contentious. Some studies have shown enhanced progression-free survival (PFS) and OS, while others have shown either negligible advantages or heightened toxicity. The AURELIA trial, a pivotal phase III research, demonstrated that the incorporation of bevacizumab into chemotherapy markedly enhanced PFS relative to chemotherapy alone, while overall survival benefits were limited [5]. Conversely, trials like MITO-11 and TRIAS have shown inconclusive findings for angiogenesis inhibitors in PROC, raising concerns about treatment-associated toxicities, including hypertension, proteinuria, thromboembolic events, and gastrointestinal perforations [7,17].

Given the urgent need for improved therapeutic options and the ongoing uncertainty surrounding the role of angiogenesis inhibitors, a comprehensive evaluation of their efficacy and safety in PROC is warranted. Although previous meta-analyses have assessed these agents in recurrent or platinum-sensitive ovarian cancer, few have focused exclusively on PROC, a category with unique biological traits and therapeutic difficulties. This meta-analysis seeks to address this significant gap by synthesizing high-quality information from randomized controlled trials (RCTs), the benchmark of clinical research, to ascertain the actual effects of angiogenesis inhibitors on survival outcomes and treatment-related toxicities in PROC. This project aims to enhance clinical decision-making and eventually improve therapeutic methods for patients with this very aggressive illness by combining current data.

## **Materials and Methods**

### **Study design and registration**

Systematic review and meta-analysis carried out in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. The protocol was filed in PROSPERO (ID: CRD42024525072) before data extraction to guarantee methodological openness and reduce the likelihood of reporting bias. The analysis only included RCTs to provide the most robust information about the effectiveness and safety of angiogenesis inhibitors in PROC.

### **Inclusion criteria**

The inclusion criteria based on the PICOS framework were as follows: (1) patients with PROC, defined as those who experience recurrence during six months of completion of platinum-based treatment; (2) direct comparison of an angiogenesis inhibitor with chemotherapy versus chemotherapy alone; (3) outcome measures including OS, PFS based on RECIST, and adverse events (AE); (4) inclusion of RCTs. Studies with unavailable full-text articles or incomplete data were excluded.

### **Search strategy and study selection**

Trials were sourced from PubMed, Cochrane Library, and ScienceDirect up to November 2023 without language restrictions. The literature search was conducted by two independent reviewers. Titles and abstracts were screened, followed by full-text review to determine eligibility. Discrepancies during study selection were resolved through discussion and consensus with the remaining authors. The search strategy included combinations of Medical Subject Headings (MeSH) and free-text terms: (((Angiogenesis Inhibitor) AND (Chemotherapy)) AND ((Platinum Resistant Ovarian Cancer) OR (PROC) OR (Platinum Resistant Recurrent Ovarian Cancer)) AND (Randomized Controlled Trial) OR (RCT)). Additionally, the reference lists of included articles were reviewed to identify further eligible studies.

### **Data extraction and quality assessment**

Demographic and baseline clinical characteristics, along with outcome variables, were extracted independently by two reviewers using a standardized form. Extracted data included the study period, inclusion and exclusion criteria, trial registration status, participating countries, patient age, tumor histology, FIGO stage, and prior treatments. Information regarding angiogenesis inhibitor regimens and chemotherapy comparators was collected. Disagreements in data extraction were

resolved through discussion and, if needed, arbitration by a third author. Outcome measures such as overall survival (OS) and progression-free survival (PFS) were analyzed, while adverse events (AEs) were assessed when reported in more than two studies. The risk of bias for each RCT was evaluated using the RoB 2.0 tool. Sensitivity analyses were performed in RevMan 5.4 by sequentially omitting individual studies to test the robustness of the pooled results.

### Data synthesis and statistical analysis

Outcomes for OS and PFS were estimated using the restricted maximum likelihood method, and data synthesis was performed using RevMan version 5.4. Odds ratios (ORs) were calculated using the Mantel-Haenszel method. To account for variability in study design and population characteristics, both random-effects and fixed-effects models were applied. Heterogeneity was assessed using the chi-square test and the  $I^2$  statistic. Significant heterogeneity was defined as a chi-square  $p$ -value  $< 0.10$ , an  $I^2$  value  $> 50\%$ , and a  $\tau^2$  value  $> 1$ . All statistical analyses were two-tailed, with a  $p$ -value  $< 0.05$  considered statistically significant.

## Results

### Study selection and risk of bias of study

A total of 45,349 articles were initially identified, from which seven published RCTs were ultimately included in the meta-analysis in accordance with PRISMA guidelines (**Figure 1**). The selected trials included: the AURELIA trial on bevacizumab; weekly paclitaxel with or without pazopanib (MITO-11, Italy); the efficacy and safety study of sorafenib (TRIAS, Germany); weekly gemcitabine plus pazopanib versus gemcitabine alone (NCT01610206, USA); a bevacizumab trial (JGOG3023, Japan); bevacizumab and ixabepilone (NCT03093155, USA); and apatinib combined with pegylated liposomal doxorubicin (PLD) versus PLD alone (APPROVE, China). The methodological quality of the included studies was assessed using the RoB 2.0 tool (**Figure 2**) and summarized (**Figure 3**). Most trials were rated as having a low risk of bias across domains such as selection, detection, attrition, and reporting. However, the studies by Duska and Shoji presented some concerns and were rated as having a high risk of bias related to the randomization process.

### Characteristics of included studies

The relevant initial data and population characteristics were extracted and summarized (**Table 1**). A total of seven trials were included, comprising 543 patients who received chemotherapy in combination with angiogenesis inhibitors: apatinib [18], 14%; bevacizumab [5,19,20], 50%; pazopanib [7,21], 21%; sorafenib [17], 15%. Additionally, 542 patients who received chemotherapy alone were included for comparison in this study. All included studies were conducted across various multicenter health institutions located in Europe, Italy, Germany, the USA, Japan, and China. The median age of patients was comparable between the intervention and control groups, and the predominant histological subtype of ovarian cancer was serous. Three studies did not report the cancer stage of the enrolled patients. However, most trials stratified randomization based on cancer stage, with over 80% of the study population comprising patients diagnosed with Stage III or IV disease.

Two studies raised some concerns regarding the population, as they included a mix of other patient groups. In the study by Pignata et al., 25 patients (65%) in the control group and 23 patients (62%) in the intervention group had primary resistant or refractory disease [7]. Similarly, in the study by Roque et al., 33 patients (89%) in the control group and 29 patients (74%) in the

intervention group were classified as platinum-resistant, while the remainder were platinum-refractory patients [19]. Despite these deviations, we included both studies in our analysis as the majority of participants had PROC, whereas all other included trials exclusively enrolled patients with PROC. The therapeutic regimens given to the intervention and comparator groups were also summarized (**Table 2**).

### Clinical outcomes of intervention in PROC patients

Our meta-analysis showed that angiogenesis inhibitors significantly improve the overall survival (HR 0.70, 95% CI [0.58,0.84],  $p=0.00$ ) based on the forest plot (**Figure 4**) and progression-free survival (HR 0.50, 95% CI [0.43,0.57]),  $p=0.00$ ) which is supported by the  $p$ -value lower than 0.05 (**Figure 5**). Of the 7 trials used in this meta-analysis, Duska's study did not display a PFS value. Furthermore, this association were homogenous, with an  $I^2$  value of 14.93% in OS of six trials and  $I^2$  value of 0% in PFS of seven trials. A sensitivity analysis was performed by methodically excluding individual research. The aggregated impact size was stable throughout all exclusions, indicating that no one research substantially affected the overall findings. Additional analysis contrasting fixed and random-effects models revealed no variance, hence reinforcing the robustness of the results.

### Adverse event post-angiogenesis inhibitors therapy

A total of 15 grade  $\geq 3$  adverse events were identified and analyzed, grouped according to physiological systems for improved interpretation (**Table 3**). Common adverse events were classified as those reported in at least four of the seven included studies, and some common AE were found to be statistically significant based on this analysis, such as hand foot syndrome (HFS) (OR=3.13, 95% CI [1.40, 6.98],  $p=0.005$ ), hypertension (OR=8.15, 95% CI [3.67, 18.09],  $p<0.00001$ ), leukopenia (OR=1.60, 95% CI [1.00, 2.57],  $p=0.05$ ), neutropenia (OR=1.42, 95% CI [1.06, 1.91],  $p=0.02$ ), and vomiting (OR=0.36, 95% CI [0.13, 1.00],  $p=0.05$ ). Proteinuria (OR=6.48, 95% CI [1.15, 36.62],  $p=0.03$ ) and sensory neuropathy (OR=3.12, 95% CI [1.51, 6.47],  $p=0.002$ ) were considered rare events, as they were reported in fewer trials, but also reached statistical significance. The remaining adverse events, including thrombocytopenia, anemia, diarrhea, fatigue, and gastrointestinal perforation, showed no statistically significant differences between groups, with  $p$ -values greater than 0.05.

## **Discussion**

### Main findings

The findings of this meta-analysis demonstrate that angiogenesis inhibitors significantly improve OS and PFS compared to chemotherapy alone in patients with PROC. This aligns with two of the included studies, which showed that adding sorafenib to topotecan improved OS (HR 0.65) [17], and that combining ixabepilone with bevacizumab (IXA + BEV) yielded a significantly longer OS compared to ixabepilone monotherapy (HR 0.52) [19]. In contrast, four other studies reported no statistically significant survival benefit from the addition of angiogenesis inhibitors to chemotherapy [5,7,18,20]. For example, while the AURELIA trial found no OS improvement with the addition of bevacizumab to topotecan, the TRIAS trial demonstrated a clear benefit with sorafenib. This discrepancy may be due to differences in study design, particularly regarding crossover policies and treatment duration. Crossover to the experimental arm was permitted in AURELIA, whereas it was prohibited in TRIAS. Additionally, chemotherapy in AURELIA continued until disease progression, while in TRIAS, it was limited to six cycles to minimize cumulative toxicity and

treatment fatigue, favoring a transition to non-chemotherapeutic strategies. Such variations likely contributed to differences in median OS between the trials [5,17]. Nevertheless, the improvement in PFS observed in this meta-analysis was consistently reported across all included studies.

### Mechanism of action and toxicity

In cancer, dysregulated angiogenic signals from malignant cells trigger abnormal blood vessel growth by releasing growth factors and cytokines, leading to expansion of tumor endothelial cells and the emergence of irregular and immature vasculature. This chaotic vascular environment hinders nutrient and drug delivery, perpetuating a cycle of abnormal angiogenesis and tumor growth [22,23]. In ovarian cancer, VEGF signaling plays a particularly pivotal role, driving angiogenesis, metastasis, higher tumor grade, and poor clinical outcomes. VEGF ligands interact with VEGFR, initiating pathways that stimulate endothelial cell growth and the formation of aberrant vasculature, often exacerbated by hypoxia-inducible factors. Anti-VEGF therapies aim to normalize this vasculature and enhance therapeutic efficacy; however, the complexity of VEGF signaling and its involvement in resistance mechanisms remain significant clinical challenges [24,25].

The anti-angiogenic agents included in this study are apatinib, bevacizumab, pazopanib, and sorafenib. Bevacizumab, a monoclonal antibody targeting VEGF-A, was first approved in 2014 for use in combination with non-platinum-based chemotherapy in the treatment of platinum-resistant ovarian cancer [26,27]. In 2018, its indication expanded to include adjuvant therapy and maintenance monotherapy in advanced ovarian cancer, supported by findings from the GOG-0218 trial, which demonstrated a significant improvement in PFS [28,29]. In contrast to bevacizumab, apatinib, sorafenib, and pazopanib are oral tyrosine kinase inhibitors (TKIs) that inhibit multiple kinases involved in angiogenesis and tumor proliferation. Apatinib selectively inhibits VEGFR-2, thereby blocking a key signaling pathway responsible for tumor vascularization [30]. Sorafenib targets multiple kinases, disrupting several critical pathways required for tumor cell growth and survival [31]. Pazopanib acts on VEGFRs as well as platelet-derived growth factor receptors (PDGFR- $\alpha$  and - $\beta$ ), interfering with various processes essential for tumor angiogenesis and progression [32].

The most commonly reported adverse event was hypertension, primarily due to inhibition of VEGF-mediated nitric oxide synthesis. Nitric oxide is a key vasodilator involved in maintaining vascular tone, and its suppression leads to increased vascular resistance and elevated blood pressure [33]. Another notable toxicity is proteinuria, which arises from direct injury to glomerular endothelial cells. Inhibition of VEGF compromises the integrity of the glomerular filtration barrier, increasing permeability and resulting in protein leakage into the urine, with potential progression to renal dysfunction [34]. Hematologic toxicities, including neutropenia and leukopenia, are attributed to VEGF inhibition impairing the bone marrow microvascular environment, leading to bone marrow suppression and heightened infection risk, an especially critical concern in PROC patients [35,36]. Sensory neuropathy is also frequently observed, likely due to microvascular damage to peripheral nerves causing ischemic injury and axonal degeneration. Clinically, this manifests as tingling, numbness, or pain, and may necessitate dose reduction or discontinuation of therapy [37].

By rigorously studying these mechanisms and conducting comprehensive research, it was evident that anti-angiogenic therapies can significantly enhance PFS and OS outcomes. This meta-analysis supports the idea that these therapies were beneficial, consistent with the current body of evidence, albeit side effects need attention. Such findings underscore the potential of anti-angiogenics in improving clinical outcomes for ovarian cancer patients.

### Role of biomarkers, genetic testing, and tailored management

The evolving role of molecular biomarkers such as BRCA1/2, homologous recombination deficiency (HRD), and mismatch repair deficiency (MMR) underscores the increasing importance of personalized approaches in the treatment of ovarian cancer [38]. HRD, often driven by BRCA1/2 mutations, impairs the DNA damage repair process, making tumors more susceptible to platinum agents and PARP inhibitors (PARPi). MMR deficiency, though less frequent, is associated with microsatellite instability and has emerged as a key predictor of response to immune checkpoint inhibitors [39].

Emerging evidence suggests that HRD-positive tumors exhibit increased angiogenic signaling, particularly via the VEGF pathway, which may influence their sensitivity to anti-angiogenic therapies [39,40]. Tumors with HRD or BRCA mutations often show higher VEGF-A expression and abnormal vasculature, potentially enhancing the effectiveness of VEGF-targeted agents such as bevacizumab. Similarly, MMR deficiency may also affect the tumor immune microenvironment and angiogenesis, although its role in modulating the response to angiogenesis inhibitors remains under investigation [38,39].

Beyond these genomic markers, several circulating biomarkers have shown promise in predicting benefit from angiogenesis inhibitors. Elevated baseline levels of VEGF-A and placental growth factor (PIGF) have been linked to poorer response to VEGF-targeted therapies [41,42]. Additionally, the angiopoietin-Tie2 axis may serve as a predictive tool, as patients with high Ang1 and low Tie2 levels reportedly demonstrate better PFS with bevacizumab-based regimens [43,44]. Despite their potential, these biomarkers are not yet validated for routine clinical use, and none were incorporated in the RCTs included in our meta-analysis.

Another molecular target of growing relevance is the RAS-RAF-MEK-ERK (MAPK) pathway, particularly in low-grade serous ovarian carcinoma [45]. Mutations in this cascade, such as KRAS, NRAS, and BRAF, are associated with chemoresistance and poorer outcomes [46]. MEK inhibitors like trametinib and binimetinib have demonstrated promising results in tumors harboring these mutations [46,47]. While their role in PROC remains to be defined, preclinical studies suggest crosstalk between MAPK and VEGF signaling, raising the possibility of future combinatory therapies [45,48]. Incorporating MAPK pathway profiling in PROC trials may improve patient stratification and inform more effective therapeutic approaches. Taken together, these findings underscore the expanding potential of biomarker-driven strategies to personalize treatment in PROC. Future research should focus on integrating genomic and angiogenic profiles into clinical decision-making to enhance outcomes and guide tailored management.

### Combination therapies and surgical consideration

While this meta-analysis focuses on angiogenesis inhibitors as monotherapy or in combination with chemotherapy for PROC, recent advancements suggest that dual-targeted approaches, particularly the combination of PARPi and anti-angiogenic agents, may offer synergistic benefits in selected patient populations [49]. Preclinical studies and early-phase trials have shown that anti-VEGF therapy may enhance the efficacy of PARPi by promoting a hypoxic environment and impairing homologous recombination repair mechanisms, thereby sensitizing tumors to DNA damage-induced cell death [50,51]. This is especially relevant in patients with HRD, including those with BRCA1/2 mutations, where PARPi have demonstrated substantial survival benefits [52]. The consolidated use of PARPi and anti-VEGF therapies is gaining traction in both maintenance and treatment settings for recurrent ovarian cancer, highlighting a shift toward biomarker-driven combination strategies [49].

In parallel, optimal surgical cytoreduction remains a cornerstone of ovarian cancer treatment and a key prognostic factor. Numerous predictive models, such as the Peritoneal Cancer Index (PCI) and laparoscopic scoring systems, have been developed to assess the likelihood of achieving complete gross resection (R0) [53,54]. Furthermore, emerging evidence suggests that even minimal residual disease, such as microscopic residual tumor following neoadjuvant chemotherapy and interval debulking surgery, can significantly affect survival outcomes in advanced epithelial ovarian cancer [55,56]. As treatment strategies evolve, integrating surgical predictors with molecular profiling may help refine patient selection for combination regimens and improve the overall likelihood of achieving long-term disease control [57].

### **Strengths and limitations of the study**

This meta-analysis exclusively includes RCTs, the gold standard for clinical research, ensuring the highest level of evidence in evaluating the efficacy and safety of angiogenesis inhibitors in PROC. Unlike previous reviews that focused on recurrent or platinum-sensitive ovarian cancer, this study specifically examines PROC, addressing a critical gap in the literature. By systematically analyzing data from multiple high-quality RCTs, the study provides robust conclusions on the significant improvements in PFS and OS with angiogenesis inhibitors.

Several limitations should be noted. First, potential biases may arise due to heterogeneity in patient characteristics and treatment regimens across studies. These variations include differences in age, disease burden, types and duration of angiogenesis inhibitors used, and chemotherapy protocols in the comparator arms. Some studies also included a small proportion of patients who may still have been platinum-sensitive, although these were limited in number and did not dominate the overall findings.

Moreover, while BRCA1/2 mutation status and other molecular biomarkers are increasingly recognized as critical factors in guiding treatment decisions in ovarian cancer, none of the included RCTs provided subgroup analyses or stratification based on these genomic features. This limits the ability to assess whether angiogenesis inhibitors offer differential benefits among genetically defined subgroups. Finally, a formal assessment of reporting bias such as a funnel plot was not performed, as the number of included studies was insufficient to support a reliable analysis. Future trials should incorporate molecular profiling to better tailor therapeutic strategies and optimize outcomes in PROC.

### **Conclusions**

This meta-analysis demonstrates that angiogenesis inhibitors significantly improve PFS and OS in patients with PROC, albeit with a higher incidence of adverse events compared to chemotherapy alone. However, as current trials suggest that overall survival outcomes may remain comparable between treatment arms, further research is warranted to validate these findings and clarify the long-term clinical benefit of angiogenesis inhibitors in this population.

## Compliance with Ethical Standards

**Authors contribution:** F.B.G. contributed to the conceptualization, methodology, formal analysis, data curation, investigation and writing – original draft. C.T.S. was responsible for data curation, investigation, data extraction, validation, and writing – review & editing. B.G.L. conducted the literature search, data extraction, visualization, and contributed to writing – review & editing. I.N.G.B. was responsible for project administration, formal analysis, resource management, and supervision. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work. No funding acquisition was involved in this study and no software development in this study.

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**Disclosure of Interests:** The authors declare the absence of any financial, personal, or professional conflicts of interest that may have impacted the study content.

**Ethical Approval:** Ethical approval were not required for this study, as it is a meta-analysis of previously published data.

**Informed consent:** This research did not include direct human participants; hence, informed consent was not relevant.

**Data sharing:** The data supporting the findings of this meta-analysis are available within the cited studies.

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**Table 1.** Demographic and baseline information of included studies.

Trials	Location	Number of cases		Age (years)		Histology (no./%)		Stadium in FIGO stage (no./%)		Previous Treatment Lines (no./%)	
		I	C	I	C	I	C	I	C	I	C
Pujade Lauraine, 2014 (AURELIA)	Europe	179	182	61 5-8 0	62 5-8 4	Serous/adenocarcinoma (156/87%); endometrioid (8/5%); clear cell (4/2%)	Serous/adenocarcinoma (152/84%); endometrioid (9/5%); clear cell (12/7%)	I (10/6%); II (53/30%); III (94/53%); MD (22/12%)	I (9/5%); II (48/26%); III (105/58%); MD (20/11%)	NR	NR
Pignata, 2015 (MITO-11)	Italy	37	36	56 5-6 5	58 5-6 8	Serous (26/70%); mucinous (1/3%); endometrioid (4/11%); undifferentiated (3/8%); clear cell (1/3%); mixed serous and endometrioid (0/0%); transitional cells (1/3%); mixed Mullerian (1/3%)	Serous (24/67%); mucinous (0/0%); endometrioid (2/6%); undifferentiated (1/3%); clear cell (3/8%); mixed serous and endometrioid (3/8%); transitional cells (2/6%); mixed Mullerian (1/3%)	Patients with stage IC-IV were randomized	Patients with stage IC-IV were randomized	1 (17/46%); 2 (17/46%); 3 (3/8%)	1 (15/42%); 2 (18/50%); 3 (3/8%)
Chekero v, 2018 (TRIAS)	Germany	83	89	59 3-7 8	58 2-7 9	Serous (69/83%); other (14/17%)	Serous (67/75%); other (22/25%)	I (0/0%); II (7/8%);	I (4/4%); II (3/3%);	1 (32/39%); 2 (38/46%);	1 (40/45%); 2 (37/42%);

									III (49/59%); IV (18/22%); MD (9/11%)	III (54/61%); IV (20/22%); MD (8/9%)	3 (13/16%)	3 (12/13%)
Duska, 2020 (NCT01610206)	USA	75	73	63 (30-82)		Serous (91%); other (9%)		NR	NR	1 (19/25%); ≥2 (56/75%)	1 (18/25%); ≥2 (55/75%)	
Shoji, 2021 (JGOG3023)	Japan	52	51	603	607	Serous (29/55.8%); clear cell (7/13.5%); endometrioid (5/9.6%); mucinous (3/5.8%); other (8/15.4%)	Serous (35/68.6%); clear cell (9/17.6%); endometrioid (3/5.9%); mucinous (1/2.0%); other (3/5.9%)	I (3/5.9%); II (3/5.9%); III (37/71.2%); IV (9/17.3%)	I (3/5.9%); II (3/5.9%); III (27/52.9%); IV (18/35.3%)	<3 (45/86%); ≥3 (7/14%)	<3 (43/84%); ≥3 (8/16%)	
Roque, 2022 (NCT3093155)	USA	39	37	6748	6788	Serous (34/87%); carcinosarcoma (1/3%); other (4/10%)	Serous (29/78%); carcinosarcoma (2/6%); other (6/16%)	NR	NR	≤3 (21/54%); >3 (18/46%)	≤3 (18/49%); >3 (19/51%)	
Wang, 2022 (APPROVE)	China	78	74	54276	53622	Serous (78/100%)	Serous (70/94.6%); endometrioid (2/2.7%); clear cell (2/2.7%)	I (3/3.8%); II (3/3.8%); III (54/69.2%); IV	I (5/6.8%); II (3/4.1%); III (55/71.1%)	1 (44/56%); 2 (18/23%); ≥3 (16/21%)	1 (38/50%); 2 (26/35%); 3 (10/14%)	

								(11/1 4.1%) ; MD (7/9.0 %)	4.3%) ; IV (10/1 3.5%) ; MD (1/1.4 %)		
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\*Data are mean (SD), number/total (n/%), or median (IQR); I: intervention arm (angiogenesis inhibitor with chemotherapy); C: controlled arm (chemotherapy alone); FIGO: International Federation of Gynecology and Obstetrics; MD: missing data; NR: not reported.

**Table 2.** Angiogenesis inhibitors and chemotherapy regiment of included studies.

Trials	Regiment	
	Control	Intervention
Pujade Lauraine, 2014 (AURELIA)	Paclitaxel 80 mg/m <sup>2</sup> intravenously on days 1, 8, 15, and 22 every 4 weeks; polyethylene glycol liposome doxorubicin 40 mg/m <sup>2</sup> IV on day 1 every 4 weeks; or topotecan 4 mg/m <sup>2</sup> IV on days 1, 8, and 15 every 4 weeks, or 1.25 mg/m <sup>2</sup> IV on days 1 to 5 every 3 weeks.	Additional bevacizumab 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks in patients receiving topotecan.
Pignata, 2015 (MITO-11)	Patients in the paclitaxel only group received paclitaxel 80 mg/m <sup>2</sup> on days 1, 8, and 15 in a 28-day cycle.	Additional pazopanib 800 mg was administered daily, with patients required to fast for at least 2 hours before and up to 1 hour after taking the medication.
Chekerov, 2018 (TRIAS)	Topotecan 1.25 mg/m <sup>2</sup> IV infusion over 30 minutes on days 1–5, followed by placebo administered twice daily on days 6–15 repeated every 21 days for up to six cycles.	Additional oral sorafenib 400 mg twice daily on days 6–15, repeated every 21 days for up to six cycles.
Duska, 2020 (NCT01610206)	Gemcitabine 1000 mg/m <sup>2</sup> weekly on days 1 and 8 (30-60 min intravenous infusion) every 21 days.	Additional pazopanib 800 mg orally daily.
Shoji, 2021 (JGOG3023)	Polyethylene glycol liposome doxorubicin 40 or 50 mg/m <sup>2</sup> intravenously or topotecan 1.25 mg/m <sup>2</sup> IV, paclitaxel 80 mg/m <sup>2</sup> IV, or gemcitabine 1000 mg/m <sup>2</sup> intravenously.	Additional bevacizumab 15 mg/m <sup>2</sup> intravenously.

Roque, 2022 (NCT3093155)	Ixabepilone 20 mg/ m <sup>2</sup> days 1, 8, and 15.	Additional bevacizumab 10mg/kg days 1,15 every 28 days.
Wang, 2022 (APPROVE)	Polyethylene glycol liposome doxorubicin 40 mg/m <sup>2</sup> intravenously every 4 weeks up to 6 cycles	Additional apatinib 250mg oral daily

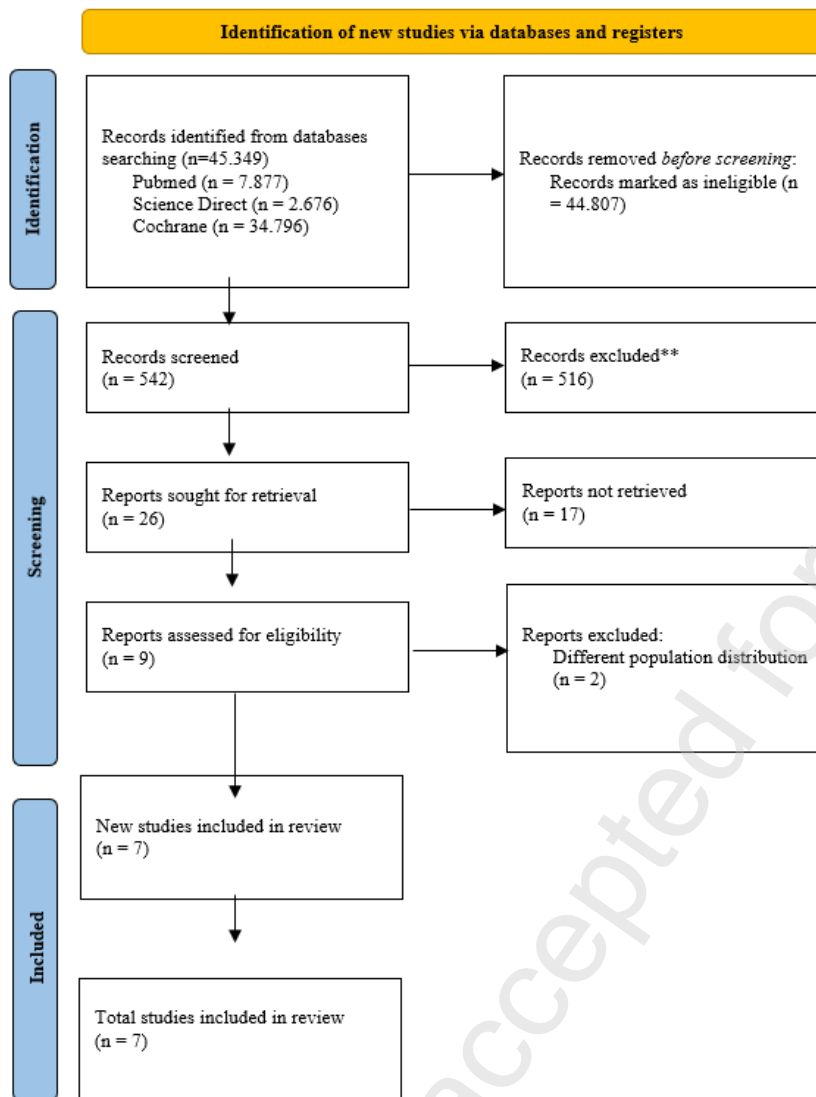
**Table 3.** Summary pooled odds ratio of adverse events.

Adverse Event	Number of Included Study	Odds Ratio	95% CI	p-value	Heterogeneity		
					Chi <sup>2</sup>	τ <sup>2</sup>	I <sup>2</sup>
<b>Cardiovascular and renal system</b>							
Hypertension	6	8.15	[3.67, 18.09]	<0.00001	0.65	0.99	0%
Proteinuria	3	6.48	[1.15, 36.62]	0.03	0.04	0.98	0%
Thromboembolic	4	0.94	[0.43, 2.06]	0.88	1.96	0.58	0%
<b>Dermatologic system</b>							
Hand Foot Syndrome	4	3.13	[1.40, 6.98]	0.005	5.83	0.12	49%
<b>Gastrointestinal system</b>							
Diarrhea	3	1.26	[0.52, 3.01]	0.61	0.97	0.62	0%
Vomiting	4	0.36	[0.13, 1.00]	0.05	0.75	0.69	0%
Gastrointestinal Perforation	4	4.03	[0.85, 19.14]	0.08	0.25	0.97	0%
<b>Hematologic system</b>							
Anemia	7	0.77	[0.46, 1.30]	0.33	3.04	0.80	0%
Leukopenia	4	1.60	[1.00, 2.57]	0.05	3.17	0.37	5%
Neutropenia	7	1.42	[1.06, 1.91]	0.02	10.93	0.09	45%
Febrile Neutropenia	3	1.16	[0.45, 3.01]	0.75	2.19	0.34	9%
Thrombocytopenia	6	1.46	[0.89, 2.39]	0.13	6.31	0.18	37%

<b>Neurologic system</b>							
Sensory Neuropathy	3	3.12	[1.51, 6.47]	0.002	2.06	0.36	3%
<b>General side effect</b>							
Fatigue	5	1.84	[0.43, 7.88]	0.41	1.62	0.0005	77%
Infection	4	0.84	[0.43, 1.64]	0.61	2.82	0.42	0%

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**Figure 1.** Flow diagram of the study in accordance with PRISMA guidelines.



**Figure 2.** Quality of trials evaluated using the RoB 2.0 tool for each included study based on reviewers' assessments.

Study	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Chekerov 2018	+	+	+	+	+	!
Duska 2020	!	+	+	+	+	+
Pignata 2015	+	+	+	+	+	+
Pujade-Lauraine 2014	+	+	+	+	+	+
Roque 2022	+	+	+	+	+	+
Shoji 2021	-	+	+	+	+	-
Wang 2022	+	+	+	+	+	+

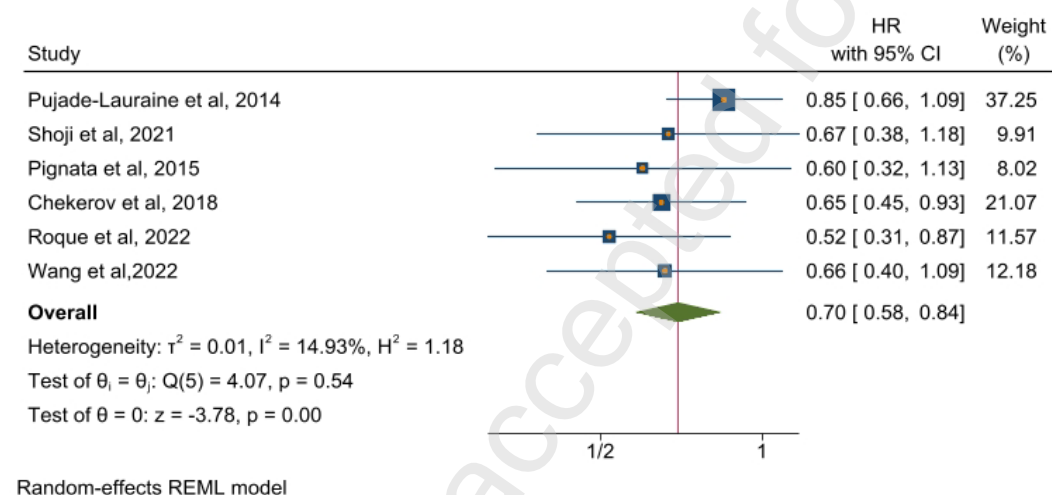
**Interpretation**

- Low risk (+)
- Some concerns (!)
- High risk (-)

**Figure 3.** Summary of bias from the included studies based on reviewers' assessments.



**Figure 4.** Forest plot hazard ratio of overall survival.



**Figure 5.** Forest plot hazard ratio of progression-free survival.

