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Review Article

The use of bevacizumab in the modern era of targeted therapy for ovarian cancer: A systematic review and meta-analysis

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HIGHLIGHTS

- Bevacizumab combination therapy has been extensively studied in advanced and recurrent epithelial ovarian cancer.
- There is significant progression-free survival benefit associated with bevacizumab combination therapies.
- There is significant heterogeneity in the published studies with regards to the choice of bevacizumab combination therapies.

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ABSTRACT

Objectives. The optimal systemic therapy strategy for advanced epithelial ovarian cancer (EOC) remains unclear. We performed a systematic review and meta-analysis to assess oncologic outcomes and toxicity of bevacizumab combination treatment in advanced EOC.

Methods. We conducted an electronic search of all phase 2 and 3 clinical trials involving bevacizumab combination therapy in advanced-stage EOC between 2010 and March 2020, using Embase, Medline, Epub Ahead of Print, Cochrane for clinical trials, Cochrane Database of Systematic Reviews, Web of Science and clinicaltrials.gov databases. Progression-free survival (PFS), overall survival (OS), and their hazard ratios (HR) when available were extracted. Pooled HR were calculated for each efficacy endpoint in the meta-analysis using inverse variance weighted method. Bias was assessed using the Cochrane Collaboration Risk of Bias I (ROB1) tool for randomized controlled trials.

Results. Thirty-five studies were included in the qualitative analysis and eight studies in the quantitative synthesis. In the first-line setting, bevacizumab combined with chemotherapy revealed a significant improvement in PFS (pooled HR = 0.72, 95% CI 0.65–0.81) when compared to chemotherapy alone but no significant OS benefit (pooled HR = 0.88, 95% CI 0.72–1.06). In the recurrent setting, bevacizumab combinations showed significant PFS (pooled HR = 0.52, 95% CI 0.47–0.58) and OS benefits (pooled HR = 0.88, 95% CI 0.79–0.99) compared with non-bevacizumab regimens. Rate of bowel perforation was low at 1.24% (range 0–4.2%).

Conclusions. Bevacizumab-containing regimens are associated with significant PFS benefit in advanced and recurrent epithelial ovarian cancer. While the difference in OS did not reach statistical significance in the first-line setting, bevacizumab was associated with improved survival in the recurrent setting.

Contents

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1. Background

Epithelial ovarian cancer (EOC) is the 5th most common cause of cancer death in women and the most common cause of death in gynecologic malignancies [1]. For many years, standard treatment options consisted of combination chemotherapy with cytoreductive surgery; however over 70% of patients are diagnosed at advanced stage and most recur despite optimal upfront therapy [2]. The estimated 5-year overall survival for EOC is approximately 40%, and prognosis is much worse for those with stage IV disease at presentation or other high-risk features such as residual disease greater than 1 cm following cytoreductive surgery [3].

Systemic therapy has been evolving in the past decade with the emergence of targeted therapy for ovarian cancer, such as bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF) in the angiogenesis pathway, which has shown activity and survival benefit in several large randomized clinical trials [4–7]. A previous systematic review and meta-analysis published in 2016 by Wu et al., which included five landmark phase 3 randomized clinical trials, showed significant improvement in progression-free survival (PFS) and overall survival (OS) in advanced EOC patients at high-risk of progression and in those with recurrent disease receiving combination bevacizumab and chemotherapy compared to those receiving chemotherapy alone. High risk of progression is defined as stage IV disease at presentation or those with suboptimal debulking surgery. However, no significant improvement in overall survival was seen in the front-line setting for all-comers [8]. A subsequent systematic review focusing on safety of bevacizumab in the context of cytoreductive surgery suggested that incorporation of bevacizumab with first-line chemotherapy is not associated with increased morbidity before or after cytoreductive surgery in women with advanced stage EOC [9].

While prior reviews have assessed combination bevacizumab with chemotherapy, the benefit of combining bevacizumab with other targeted therapies is currently unclear. In more recent years, novel targeted therapies have been studied in EOC, with recent clinical trials demonstrating advantage of bevacizumab in combination with other targeted therapies such as PARP inhibitors as maintenance treatment [10]. As ongoing clinical trials continue to integrate bevacizumab into standard treatment algorithms for EOC with therapies beyond platinum-based chemotherapy, it remains crucial to regularly reassess the literature. The objectives of our systematic review were to: [1] define the type of bevacizumab combinations used in advanced EOC; [2] evaluate updated PFS and OS associated with bevacizumab combinations in advanced and recurrent setting; and [3] assess safety of bevacizumab, focusing on rates of bowel perforation across all studies.

2. Methodology

2.1. Eligibility criteria and search strategy

This systematic review with meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO ID 167840) and a comprehensive review protocol was developed. We used the "PICOS" [11] for the selection process. For the study population, we included all adult women with advanced stage (FIGO stage III and IV) and recurrent EOC of any histology. The intervention consisted of any systemic therapy incorporating bevacizumab in either the front-line or recurrent settings, including combinations with other targeted therapy or monotherapy in the maintenance setting. For the study outcome, we focused on clinical efficacy endpoints measured by median PFS and OS, if available, which were stratified based on first-line or recurrent setting. We selected only experimental studies, which include randomized phase 3, randomized phase 2, and single-arm phase 2 studies, with the endpoints of interest reported.

For studies that included patients with all stages, we extracted data of subgroups with stage III and IV. We excluded studies examining other anti-angiogenesis agents and studies with less than 10 patients enrolled. For studies with two arms, we had no restriction regarding the comparison arm, acknowledging that chemotherapy alone may not be the standard control arm in more recent studies. Safety assessment for this analysis focused on rates of common toxicity criteria for adverse events (CTCAE) grade 3 toxicity and serious adverse events associated with bevacizumab combinations, given heterogeneity of potential targeted therapy combinations. We included abstract and conference presentations that had not yet been published in full, but we excluded research-in-progress without mature survival endpoints. We excluded all non-experimental, observational and pre-clinical studies. The meta-analysis excluded trials with bevacizumab in both arms. Only those with two-arms, one of which involved bevacizumab, were included for the quantitative analysis.

The initial literature search was performed on March 5, 2020, which included all studies from January 2010 until March 2020. We searched Medline, Epub Ahead of Print and In-Process & Other Non-Indexed

Citations, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews, all from the OvidSP platform; Web of Science from the Clarivate Analytics. We also searched clinicaltrials.gov and abstract libraries for the following annual conferences: American Society of Clinical Oncology (ASCO) scientific meeting, European Society of Medical Oncology (ESMO) annual congress, and the Society of Gynecology Oncology (SGO) annual meeting. We excluded books, book chapters and thesis dissertations. We subsequently manually excluded scoping reviews during the screening process. We used the search terms "bevacizumab", "Avastin", and "ovarian cancer" along with its derivatives, in various combinations. Where provided, both controlled vocabulary terms and text words were utilized. There were no language restrictions in our initial search strategy, but we limited to studies in English or French when screening titles and abstracts due to translational services available. Where applicable, the search was limited to adults. The full search Medline search strategy is included in the Supplementary material.

2.2. Data extraction and assessment

Data was managed using Covidence software. Two investigators (SLL and LK) independently evaluated the trials for eligibility in two stages: title and abstract screening, and full-text review. Discrepancies were resolved by consensus discussion and involved a third reviewer (GBF) with expertise in gynecology oncology when required. For each trial, investigators extracted trial name and year of publication, first author, study design, sample size, center and location, patient characteristics and disease histology, drug dose and schedule, median PFS, median OS, hazard ratios (HR) for PFS and OS along with 95% confidence interval (CI) when available. In the presence of multiple publications or presentations of the same trial, we collected data from the most recent publication with the most complete information. For studies in abstract form only, we included phase 3 randomized controlled trials presented within the past 2 years as oral presentation at either ASCO or ESMO and extracted the data directly from the original slide decks available from the conference library database. We excluded abstracts of phase 2 studies and in poster format. Finally, two reviewers (SLL and LK) performed quality assessments independently for each trial using the Cochrane Collaboration Risk of Bias I (ROB1) tool for randomized controlled trials, with disagreement resolved by discussion and consultation with third reviewer. Bias was assessed as a judgement (high, low, or unclear) for individual elements from the five domains (selection, performance, attrition, reporting, and other [12].

2.3. Statistical analysis

Descriptive statistics were used to describe the different combination treatments employed in the clinical trials for the qualitative analysis, with median PFS and OS measurements reported individually along with their respective 95% CI and/or interquartile range. We stratified studies based on setting (first-line versus recurrent) and phase (randomized phase 3 vs phase 2 vs single-arm). We used R software version 1.2.1335, with the following packages applied: meta, metafor, dmetar, and robvis. For studies with reported hazard ratios (HR) of a two-arm trial, we pooled the HR for PFS and OS using fixed effects model with the inverse variance method and Sidik-Johnkman estimator for tau [2]. To improve consistency, we only evaluated patients with similar characteristics, such as high-risk populations, and used subgroups when necessary to ensure uniform stage and risk status. For results that were taken from a subgroup analysis of a trial, we used the random effects model. For studies with reported median survival and number of events without HR, we calculated the HR and its associated 95% CI manually. We used Chi-squared and Cochrane Q-tests to quantify heterogeneity across studies by computing the I^2 for each endpoint. All 95% CIs were 2-sided and an alpha of less than 5% was considered significant.

3. Results

3.1. Study characteristics and quality assessment

The search strategy identified 35 studies eligible for inclusion in the qualitative analysis (Fig. 1). Among the phase 3 studies, only one abstract was included, the randomized controlled trial MaNGO OV·2B [13], given its significance in assessing bevacizumab re-treatment following prior exposure, availability of sufficient data in the original slide deck, its large sample size and phase 3 design.

Baseline characteristics of included studies are shown in Table 1 (a-d), stratified by phase of study. There were 9 randomized controlled phase 3 studies (4 first-line, 5 recurrent setting), 7 randomized phase 2 studies (2 first-line, 5 recurrent setting), and 19 single-arm phase 2 studies (4 first-line, 15 recurrent setting). Most were multi-centre (13 international, 9 American, 6 European). A total of 7564 patients received bevacizumab out of 10,060 patients included from all studies. The median age ranged from 47 to 67, and 74.5% had high-grade serous histology. The overall risk of bias for randomized phase 2 and 3 studies ($N = 16$) is considered low to moderate, due to many studies being open-label and one study in abstract format (Fig. 2).

3.2. Qualitative synthesis

Efficacy data is summarized in Table 2 (a-c), stratified by study phase. For trials that included pre-defined subgroup analyses, such as high-risk patients in ICON7 [4] and *BRCA* mutation patients in PAOLA-1 [10], the subgroup efficacy data are shown in separate rows.

3.3. First-line Setting

In the first-line setting, the median PFS of advanced stage EOC ranges between 14.1 and 19.9 months for patients receiving combination platinum-based doublet chemotherapy with bevacizumab and maintenance bevacizumab. In comparison, without bevacizumab, median PFS ranges between 10.3 and 17.5 months. The median OS of advanced-stage EOC ranged between 39 and 58 months for combination platinum-based doublet chemotherapy with bevacizumab and maintenance bevacizumab. In comparison, median OS for those treated with chemotherapy alone in the first-line setting ranged between 30.2 and 58.6 months. Of note, many recent trials have not yet reported median OS in either group.

3.4. Recurrent Setting

In the recurrent setting, median PFS and OS for patients treated with bevacizumab combination was variable depending on platinum-sensitivity and number of prior therapies, ranging between 3.4 and 21.1 months for PFS and between 13.3 and 42.2 months for OS. The randomized phase 3 study MaNGO OV·2B [13], which was presented at the 2018 ASCO Annual Scientific Meeting but has yet to be published, shows evidence of significant PFS benefit of 3 months with re-treatment with bevacizumab in patients who have previously received bevacizumab in the first-line setting (HR 0.51), although overall survival was not significant (HR 0.97).

Other combination chemotherapy treatments studied in the recurrent setting include gemcitabine, docetaxel, oxaliplatin, oral metronomic cyclophosphamide, pemetrexed, irinotecan, topotecan, nab-paclitaxel, trabectedin and carboplatin, and mirvetuximab soravtansine. Other than the latter, none of these combinations were associated with improved PFS compared to standard chemotherapy regimen used in recurrent ovarian cancer. Finally, chemotherapy-free regimens evaluated in combination with bevacizumab in the recurrent setting included: PARP inhibitors (niraparib), fosbretabulin (in folate receptor positive patients), everolimus, and nivolumab. Among these, niraparib combined with bevacizumab was associated with significant improvement

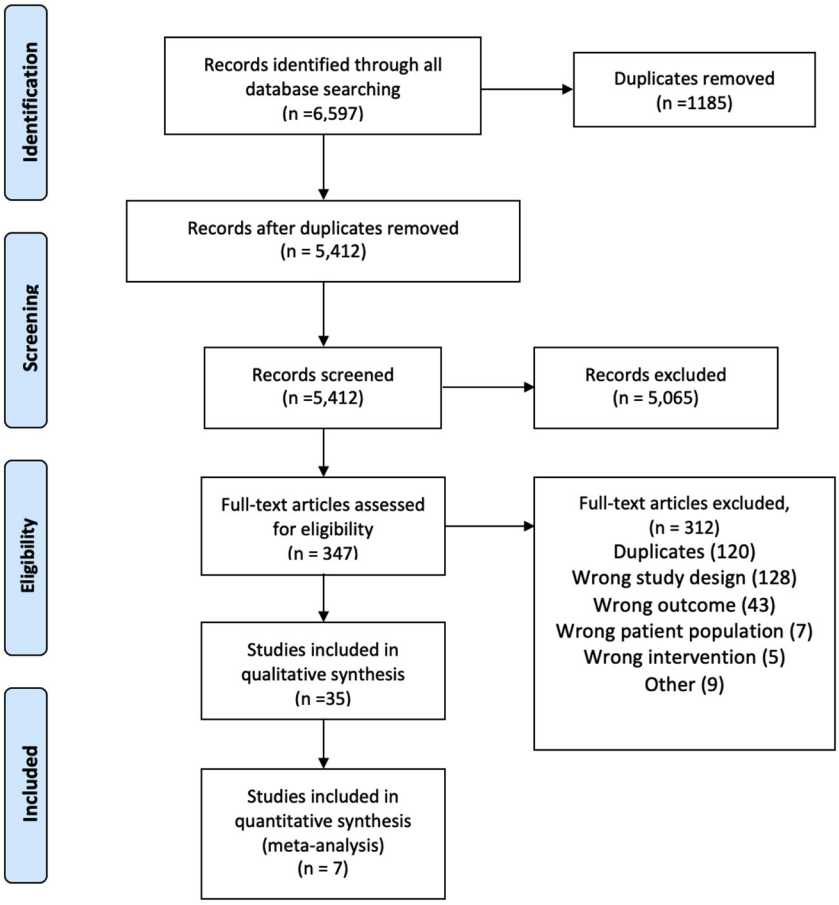

Fig. 1. PRISMA (2009) Flow Diagram.

in PFS compared to niraparib alone in platinum-sensitive recurrent EOC regardless of *BRCA* status.

3.5. Quantitative synthesis

For the meta-analysis, given the heterogeneity in trial design, we only included trials with two arms, one of which involved bevacizumab and the other without. ICON7 high-risk patients were included to ensure homogeneity of interpatient comparison as GOG-218 [5] focused on a population of higher risk similar to ICON7. Of note, GOG-262 [16] was a trial designed to compare standard every 3-week carboplatin and paclitaxel regimen with a dose-dense weekly paclitaxel regimen, and patients could elect to receive bevacizumab, given the changing nature of standard of care treatment. In this trial, 84% of patients chose to receive bevacizumab, and the final analysis was stratified based on receipt of bevacizumab. Therefore, this trial was excluded from the quantitative analysis as both arms received bevacizumab. Based on our inclusion criteria for the meta-analysis, only two randomized phase 2 studies in the first-line setting were included, both evaluating the impact of neoadjuvant chemotherapy with bevacizumab in the context of interval debulking surgery. As both arms in both studies ultimately received subsequent bevacizumab in the adjuvant and maintenance setting, these were also excluded in the meta-analysis.

3.6. Progression-free survival

Forest plots summarizing the PFS results in the first-line setting are presented in Fig. 3. The overall PFS benefit favors bevacizumab combinations. The PFS pooled HR analysis of the ICON7 and GOG-218 in the first-line setting revealed a statistically significant improvement in PFS of chemotherapy combination with bevacizumab compared to chemotherapy alone (pooled HR 0.72, 95% CI 0.65–0.81, $I^2 = 0\%$). Per our methods, we used random-effects model for the first line setting as the population in ICON7 were taken from a subgroup analysis in order to achieve adequate comparison with the other trials and to account for heterogeneity.

In the recurrent setting, pooled analyses of OCEANS [17], GOG-213 [18], MaNGO, AVANOVA2 [22], and AURELIA [7] using fixed-effect models revealed also a statistically significant improvement in PFS of combination bevacizumab compared to regimen without bevacizumab (pooled HR 0.52, 95% CI 0.47–0.58, $I^2 = 63\%$).

3.7. Overall survival

In terms of OS, only ICON7 high-risk populations and GOG-218 were included for adequate comparison in the first-line setting, using random-effects model. The pooled analysis showed no significant improvement in OS for bevacizumab combinations (pooled HR 0.88, 95% CI 0.72–1.06, $I^2 = 84\%$). In the recurrent setting, pooled analyses of OCEANS, GOG-213, MaNGO, and AURELIA showed improvement in OS favoring bevacizumab combination (pooled HR 0.88, 95% CI 0.79–0.99, $I^2 = 0\%$) (see Fig. 4).

3.8. Safety assessment

Toxicity data from 35 studies were reviewed with a specific focus on bevacizumab-specific adverse events. Mean rates of grade ≥ 3 hypertension were 16.5% (range 3–60%), grade ≥ 3 proteinuria 3.16% (range

Table 1
Summary of included studies in meta-analysis. (a) summary of randomized phase 3 trials; (b) summary of randomized phase 2 trials; (c) summary of single-arm phase 2 trials in the first-line setting; (d) summary of single-arm phase 2 trials in the recurrent setting.

(a)

Trial	Patient population	Sample size, arms	Setting	Primary endpoint	Median Age	Histology	Control arm	Intervention arm
First-line setting								
ICON7 [4,14] Perren et al., *NEJM 2011, Lancet Onc 2015.*	FIGO stage I-IIa high risk (clear cell or grade 3) or IIB-IV (70% stage IIIC or IV, 26% residual disease) EOC/PP/FT (90% EOC)	1582 (A) 764 (B) 2 arms	Multicentre international (UK-led)	PFS, OS	57	69% HGSC	C (5-6) + T (175) q3w x 5–6	C (5-6) + T (175) + Bev (15) q3w x 5–6, then mBev (15) q3w x 12
GOG-0218 [5,15] Burger et al., *NEJM 2011, JCO 2019.*	Untreated, incomplete resectable stage III or any stage IV (25% stage IV, 40% residual disease) EOC/PP/FT	1873 (A) 1248 (B) (625 + 623) 3 arms	Multicentre USA, Canada, Japan, South Korea	PFS	60	84% HGSC	C (6) + T (175) + P q3w x 6, then mP q3w x 15	C (6) + T (175) + Bev (15) q3w x 6, then mBev (15) q3w x 15 OR C (6) + T (175) + Bev (15) q3w x 6, then mP q3w x 15
GOG-0262 [16] Chan et al., *NEJM 2016.*	Untreated, incomplete resectable stage III or any stage IV (30% stage IV, 63% residual disease) EOC/PP/FT	692 (A) 580 (B) 2 arms	Multicentre USA, Canada, South Korea	PFS	46% <60	88% HGSC	C (6) + T (175) q3w x 6 + Bev (15) q3w	C (6) + ddT (80) q3w x 6 + Bev (15) q3w
PAOLA-1 [10] Ray-Coquard et al., *NEJM 2019.*	Untreated, stage III-IV HGSC or endometrioid EOC/PP/FT (30% stage IV, 35% residual disease) response to platinum chemotherapy	806 (A) 806 (B) 2 arms	Multicentre Europe	PFS	61	95% HGSC	C + T + Bev (15) q3wk x 6, then mBev (15) x 15 mo + mP x 24 mo	C + T + Bev (15) q3w x 6, then mBev (15) x 15 mo + mOlaparib 300 mg bid x 24 mo
Recurrent setting								
OCEANS [6,17] Aghajanian et al., *JCO 2012, Gyn Onc 2015.*	Platinum-sensitive ROC, <2 prior line therapy, no prior Bev	484 (A) 242 (B) 2 arms	Multicentre, USA	PFS	60	78% HGSC	C (4) + G (1000) + P q3w x 6–10, then mP q3w	C (4) + G (1000) + Bev (15) q3w x 6–10, then mBev q3w
GOG-0213 [18] Coleman et al., *Lancet Onc 2017.*	Platinum-sensitive ROC and prior complete response, includes prior Bev (10%)	674 (A) 377 (B) 2 arms	Multicentre, USA, Japan, South Korea	OS	59.5	81% HGSC	C (5) + T (175) q3w x 6–8	C (5) + T (175) + Bev (15) q3w x 6–8, then mBev (15) q3w
ENGOT OV.18 Intergroup [19] Pfisterer et al., Lancet 2020.	Platinum-sensitive ROC, prior VEGF ok	682 (A) 682 (B) 2 arms	Multicentre Europe	PFS	62	74% HGSC	C (4) + G (1000) + Bev (15) q3w x 6, then mBev (15)	C (5) + D (30) q4w + Bev (10) q2w x 6, then mBev (15)
MITO16B-MaNGO OV2B [13] Pignata et al., *ASCO 2018**	Platinum-sensitive, stage IIIB-IV ROC, received prior Bev in first line	405 (A) 202 (B) 2 arms	Multicentre Europe	PFS	61	79.8% HGSC	C + T/G/D x 6–8	C + T/G/D + Bev (10 or 15) x 6–8
AURELIA [7] Pujade-Lauraine et al., *JCO 2014.* 1.0	Platinum-resistant ROC (<6 mo since last platinum-based chemo), <3 prior lines of therapy	361 (A) 179 (B) 2 arms	Multicentre Europe	PFS	62	87% HGSC/adenocarcinoma	wT (80) q3w or D (40) q4w or topotecan q3-4w	wT (80) q3w or D (40) q4w or topotecan q3–4w + Bev (10 or 15) q2-3w

(b)

Trial	Patient population	Sample size, arm	Setting	Primary endpoint	Median Age	Histology	Control arm	Intervention arm
First-line setting								
ANTHALYA [20] Rouzier et al., *Eur J Can 2016.*	New FIGO stage IIIC-IV EOC/PP/FT (96% HGSC), pre-op	95 (A) 58 (B) 2 arms	Multicentre, France	Complete resection rate	62	95% HGSC	CT x 4 ➔IDS ➔CT + Bev x 4 + mBev (15) x 16	CT + Bev x 4 ➔IDS ➔CT + Bev x 4 + mBev (15) x 16 (No Bev cycle 3–4)
GEICO 1205 [21] Garcia et al., *Int J Gyn Can 2019.*	New FIGO stage IIIC-IV EOC/PP/FT, pre-op	68 (A) 35 (B) 2 arms	Multicentre, Spain	Complete resection rate	63	77% HGSC	CT x 4 ➔IDS ➔CT + Bev x 3 + mBev (15) x 15 mo	CT + Bev x 4 ➔IDS ➔CT + Bev x 3 + mBev (15) x 15 mo (No Bev cycle 3–4)
Recurrent setting								
AVANOVA2 [22]	Platinum-sensitive ROC, unlimited prior	97 (A) 48 (B),	Multi-centre, Europe, USA	PFS	67	HGSC or endometrioid	Niraparib 300 daily	Niraparib 300 daily + Bev (15) q3w

(continued on next page)

Table 1 (*continued*)

(b)

Trial	Patient population	Sample size, arm	Setting	Primary endpoint	Median Age	Histology	Control arm	Intervention arm
Mirza et al., *Lancet Oncol 2019.*	platinum-based line, includes prior Bev	2 arms						
Monk et al., *JCO 2016* [23].	Platinum-sensitive or resistant ROC, up to 3 prior line (1platinum), includes prior 1 L Bev	107 (A) 107 (B) 2 arms	Multicentre, USA	PFS	62% 60–79	85% HGSC	Bev (15) q3w	Bev (15) + Fosbretabulin (30) q3w
Tew et al., *Gyn Oncol 2018* [24].	Platinum sensitive or resistant ROC, <4 prior line, includes prior Bev	150 (A) 150 (B) 2 arms	Multicentre, USA	PFS	63	75% HGSC	Bev (10) q2w + P daily	Bev (10) q2w + everolimus (10) daily
Colombo et al., *Br J Can 2019* [25].	ROC within 6–12 mo of prior platinum-based therapy, <3 prior line, no prior Bev	67 (A) 67 (B) 2 arms	Multicentre, Italy	6 mo PFS	60.8	82% HGSC	Bev (15) + trabectedin (1.1) q3w	Bev (15) q2w + trabectedin (0.8) + C (4) q4w x6, then Bev (15) + trabectedin (1.1) q3w
Liu et al., *JBUON 2019* [26].	Platinum-resistant ROC, no limit to prior line of treatment	86 (A) 43 (B) 2 arms	Single centre, China	ORR	47	51% serous cystadenocarcinoma	Nab-paclitaxel (135–175) daily x 6	Nab-paclitaxel (135–175) daily + Bev (7.5) q3w x 6

1.0

(C)

Trial	Patient population	Sample Size	Setting	Primary endpoint	Median age	Histology	Intervention arm
First-line setting							
RoSiA [27] Oza et al., *Int J Gyn Can 2017.*	New FIGO stage IIB-IV or stage I-IIA grade 3 EOC, after debulking surgery (NACT ok) (77% stage IIIB-IV)	1021	Multicentre, international	Safety	56	73.3% HGSC	C (5, 6) + T (w80 or 175) + Bev (7.5 or 15) q3w x 4–8 post-surgery, then mBev (7.5 or 15) q3w x 24mo
OCTAVIA [28] Gonzalez-Martin et al., *Eur J Can 2013.*	New FIGO stage IIB-IV or stage I-IIA grade 3 EOC, after primary debulking surgery (74% stage IIIC-IV)	189	Multicentre, Europe, UK, Brazil	PFS	55	65% HGSC	C (6) + wT (80) + Bev (7.5) q3w x 6–8, then mBev (7.5) x 17 (or 1 year)
Fleming et al., *Gyn Oncol 2017* [29].	New FIGO stage III-IV EOC/PP/FT, after primary debulking surgery (87% IIIC)	30	Single centre, USA	Tolerability of at least 4 cycles	57	70% HGSC	C (5) + wT (80) + Bev (15) q3w x 6
Herzog et al., *Gyn Oncol 2014* [30].	New FIGO stage IB-IV EOC/PP/FT, after debulking surgery (82% stage IIIC-IV)	132	Multicentre, USA	12mo PFS	58	76% HGSC	Docetaxel (75) + oxaliplatin (85) + Bev (15) q3w x 6, then mBev (15) q3w x 1 year

1.0

(d)

Trial	Patient population	Sample size	Setting	Primary endpoint	Median age	Histology	Intervention arm
Recurrent setting							
Del Carmen et al., *Gyn Oncol 2012* [31].	Platinum-sensitive ROC, <2 prior lines	54	Multicentre, USA	ORR	62.1	NA	C (5) + D (30) + Bev (10 q2w) q4w x max 10
Eisenhauer et al., *Gyn Oncol 2014* [32].	Platinum-sensitive ROC, <2 prior lines	45	2 centres, USA, Italy	PFS, Safety	61	80% HGSC	C (3) + G (1000) + Bev (10 q2w) q4w x 6–24
Horowitz et al., Clin Ov Can 2011 [33].	Platinum-sensitive ROC, <3 prior lines	19	Single centre, USA	PFS	61	58% HGSC	G (1000) + oxaliplatin (65) + Bev (10 q2w) q4w
Matulonis et al., *Gyn Oncol 2012* [34].	Platinum-sensitive or resistant ROC, <3 prior lines	20	Single centre, USA	Safety	64	85% HGSC	Bev (15) q3w, + oral cyclophosphamide (50) daily if progress
Hagemann et al., *Gyn Oncol 2013* [35].	Platinum-sensitive or resistant ROC, <3 prior lines, no prior Bev	34	Single centre, USA	6mo PFS	61.5	70.6% HGSC	Pemetrexed (500) + Bev (15) q3w
Wenham et al., *Gyn Oncol 2013* [36].	ROC within 12 mo of platinum therapy, >4 prior lines, no prior B	41	Multicentre, USA	PFS	58	85.4% HGSC	Docetaxel (40 D1 + 8) + Bev (5) q3w
Musa et al., *Gyn Oncol 2017* [37].	Platinum sensitive or resistant ROC, refractory EOC, no limit to prior lines, includes prior Bev	29	Single centre, USA	PFS	62	NA	Irinotecan (250 or 175) + Bev (15) q3k
Liu et al., *JAMA Oncol 2019* [38].	ROC within 12 mo of prior platinum-based therapy, <4 prior lines, includes prior Bev	38	Single centre, USA	ORR	64	60.5% HGSC	Bev (10 or 5) + nivolumab (5 mg/kg) q2w
McGonigle et al., *Cancer 2011* [39].	Platinum-resistant ROC, <3 prior lines	40	Single centre, USA	PFS	58.6	80% HGSC	Topotecan (4) + Bev (10 q2w) q4w
Tillmanns et al., *Gyn Oncol 2012* [40].	Platinum-resistant ROC, within 6 mo of last platinum course, no Bev	48	Multicentre, USA	6mo PFS	61.6	68.8% HGSC	Nab-paclitaxel (100w) + Bev (10 q2w) q4w
Verschraegen et al., *Ann of Oncol 2012* [41].	Platinum-resistant ROC, <3 prior lines, no prior D or B	46	2 centres, USA	6mo PFS	64	72% HGSC	D (30) + Bev (15) q3w
Ikeda et al., *Int J Gyn Ca 2012* [42].	Platinum-resistant ROC, >1 prior line	19	Single centre, Japan	ORR	58	53% HGSC	G (300) + oxaliplatin (30) + Bev (2) (3w on 1 off) q4w
Liu et al., *Can Chem Pharm 2015* [43].	Platinum-resistant and taxane resistant ROC,	52	Single centre, China	PFS, Safety	55	73% HGSC	Irinotecan (60 qw × 3) + Bev (5 q2w) q4w x 6
FORWARDII [44] O'Malley et al., *GO 2020.*	Platinum-resistant ROC, FRa-positive	66	Multicentre international	ORR	63	95.5% HGSC	Mirvetuximab soravtansine (6) + Bev (15) q3w

Table 1 (*continued*)

(d)

Trial	Patient population	Sample size	Setting	Primary endpoint	Median age	Histology	Intervention arm
Nagao et al., *J Ov Res 2020* [45].	Platinum-resistant ROC, <4 prior lines	19	Single centre, Japan	Completion of 3 cycles	57	63% HGSC	G (1000w) + Bev (115) q3w

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Abbreviations: A: all patients, B: patients with bevacizumab, Bev: bevacizumab (mg/kg), C: Carboplatin (AUC), D: pegylated liposomal doxorubicin, EOC/PP/FT: epithelial ovarian cancer, primary peritoneal, and fallopian tube cancers, G: gemcitabine, HGSC: high grade serous carcinoma, IDS: interval debulking surgery, m: maintenance, mo: months, NACT: neoadjuvant chemotherapy, P: placebo, PFS: progression-free survival, OS: overall survival, q'x'w = every 'x' weeks, ROC: recurrent ovarian cancer, T: paclitaxel (mg/m^2), w: weekly.

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Abbreviations: A: all patients, B: patients with bevacizumab, Bev: bevacizumab (mg/kg), C: Carboplatin (AUC), D: pegylated liposomal doxorubicin, EOC/PP/FT: epithelial ovarian cancer, primary peritoneal, and fallopian tube cancers, FRa: folate receptor a, G: gemcitabine, HGSC: high grade serous carcinoma, IDS: interval debulking surgery, m: maintenance, mo: months, NACT: neoadjuvant chemotherapy, P: placebo, PFS: progression-free survival, ORR: overall response rate, OS: overall survival, q'x'w = every 'x' weeks, ROC: recurrent ovarian cancer, T: paclitaxel (mg/m^2), w: weekly.

0–10.9%), thromboembolic events 2.68% (0–7%), and serious wound issues 1.43% (0–6%). The only adverse event that was consistently reported in all studies was rate of bowel perforation. Among the 7564 patients who received bevacizumab combination treatments, 94 (1.24%; range 0–4.2% from each study) had confirmed bowel perforation.

4. Discussion

In summary, this updated systematic review showed that several new combination treatments have been used in advanced EOC beyond standard chemotherapy for ovarian cancer. These include non-standard chemotherapies such as pemetrexed and irinotecan, PARP inhibitors including olaparib and niraparib, checkpoint inhibitors such as nivolumab, and other targeted therapies such as fosbretabulin and everolimus. Updated PFS and OS results are consistent with prior studies, showing significant improvement in PFS in first-line and recurrent settings but no OS benefit except in first-line high-risk and recurrent settings. Review of toxicity data showed that bevacizumab is generally safe, with a rate of bowel perforation of approximately 1%.

Several potential new targeted therapies were explored, including nivolumab, an immune checkpoint inhibitor, in the recently published study by Liu et al. [38]. Given the short follow-up, OS results are immature. We expect results of larger randomized clinical trials involving immunotherapy in the future, including clear cell carcinoma. Another targeted therapy showing activity was fosbretabulin [23] in folate-receptor positive ovarian cancer. Interestingly, in this study, the efficacy data from the bevacizumab monotherapy control arm demonstrated median PFS and OS comparable to historical controls treated with standard chemotherapy in the platinum-resistant recurrent setting.

In the modern era of targeted therapy, the two major advancements in the systemic treatment of EOC consist of bevacizumab and PARP inhibitors, and consequently these medications have been incorporated into standard practice worldwide across various contexts. As such, more recent studies have focused on combinations of bevacizumab and PARP inhibitors, such as olaparib in PAOLA-1 [10] and niraparib in AVANOVA [22]. These studies suggest that in both the first-line and platinum-sensitive recurrent settings, the combination of PARP inhibitors and bevacizumab significantly improved PFS regardless of *BRCA* status, and benefit is substantially increased in those with known *BRCA* mutations, suggesting synergism between PARP inhibitors and anti-angiogenesis agents. So far, OS data remains immature, thus longer follow-up will be required. Of note, one of the major criticisms of the PAOLA-1 trial is the lack of a control arm with either chemotherapy alone or, more importantly, olaparib and chemotherapy, as both arms in the study received bevacizumab, likely reflecting the assumption that this was standard of care at the time of trial design. In addition,

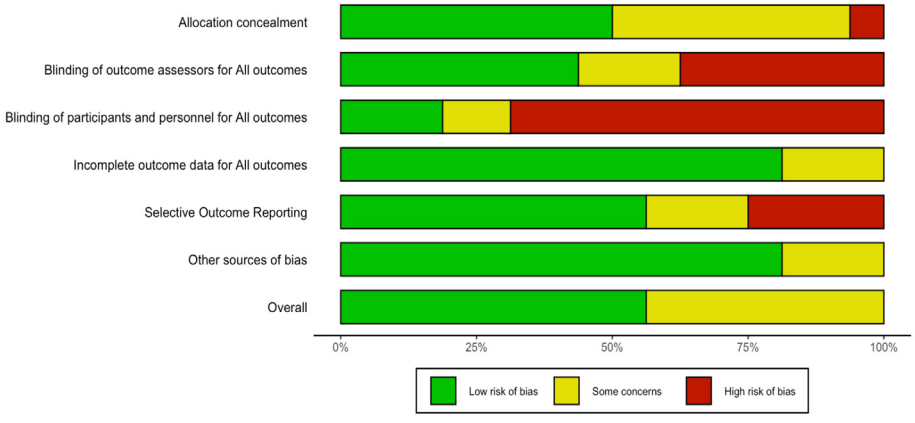

Fig. 2. Risk of Bias Assessment (ROB-1) for randomized clinical trials ($N = 16$).

Table 2
Summary of efficacy data of included studies in meta-analysis. (a) summary of randomized phase 3 trials; (b) summary of randomized phase 2 trials; (c) summary of single-arm phase 2 trials.

(a)

Trial	Arms	Sample size	Patient characteristics	PFS			OS		
				Median (mo)	HR	95% CI	Median (mo)	HR	95% CI
Phase 3 randomized controlled trials									
ICON7	CT	764	Newly diagnosed	17.5	0.93	0.83–1.05	58.6	0.99	0.85–1.14
	CT + Bev + mBev	764		19.9			58.0		
ICON7	CT	254	Newly	10.5	0.73	0.61–0.88	30.2	0.78	0.63–0.97
	CT + Bev + mBev	248	diagnosed	16.0			39.7		
			High risk						
GOG-0218	CT + P + mP	625	Newly diagnosed	10.3	0.717;	0.625–0.824;	41.1	0.96;	0.85–1.09;
	CT + Bev + mBev;	623;	Stage III-IV	14.1;	0.908	0.795–1.040	43.4;	1.06	0.94–1.20
	CT + Bev + mP	625		NR			40.8		
GOG-0262	CT + Bev + mBev	289	Newly diagnosed	14.7	0.99	0.83–1.20	40.2	0.94 (all)	0.72–1.23
	ddCT+Bev + mBev	291	Stage III-IV	14.9			39.0		
GOG-0262	CT + Bev + mBev	298	Newly diagnosed	14.7	0.70	0.625–1.173	NA	NA	NA
	CT	57	Stage III-IV	10.3			NA	NA	NA
GOG-262	ddCT +Bev mBev	291	Newly diagnosed	14.9	0.95	0.690–1.385	NA	NA	NA
	ddCT	55	Stage III-IV	14.2			NA		
PAOLA-1	CT + B + mB + mP0	267	Newly diagnosed	16.6	0.59	0.49–0.72	NA	NA	NA
	CT + B + mB + mOlaparib	537	Stage III-IV	22.1			NA		
PAOLA-1	CT + B + mB + mP	80	Newly diagnosed stage	21.7	0.31	0.20–0.47	NA	NA	NA
	CT + B + mB + mOlaparib	161	III-IV, sBRCA+	37.2			NA		
OCEANS	CG + P + mP	242	Platinum-sensitive ROC	8.4	0.484	0.388–0.605	32.9	0.95	0.77–1.18
	CG + B + mB	242		12.4			33.6		
GOG-0213	CT	337	Platinum-sensitive ROC	10.4	0.628	0.534–0.739	37.3	0.829	0.683–1.005
	CT + Bev + mBev	337		13.8			42.2		
ENGOT OV.18	CG + Bev + mBev	337	Platinum-sensitive ROC,	11.7	0.807	0.681–0.956	28.2	0.833	0.680–1.022
	CD + Bev + mBev	345	prior B (41%)	13.3			33.5		
MaNGO OV2B*	CT/CG/CD	203	Platinum-sensitive ROC,	8.8	0.51	0.41–0.65	27.1	0.97	0.70–1.35
	CT/CG/CD + Bev	202	prior B (100%)	11.8			26.7		
AURELIA	wT/D/topotecan	182	Platinum-resistant ROC, <3 prior line	3.4	0.42	0.32–0.53	13.3	0.85	0.66–1.08

(b)

Trial	Arms	Sample size	Patient characteristics	PFS			OS		
				Median (mo)	HR	95% CI	Median (mo)	HR	95% CI
Phase 2 randomized, first-line setting									
ANTHALYA	NACT	37	Newly diagnosed,	21.2 (95% CI: 14.5–26.7)			NA		
	NACT+B	58	pre-op, stage IIIC-IV	23.5 (95% CI: 18.5–30.6)			NA		
GEICO 1205	NACT	33	Newly diagnosed,	20.1	1.13	0.66–1.93	NA		
	NACT+B	35	pre-op, stage IIIC-IV	20.4			NA		
Phase 2 randomized, recurrent setting									
Tew 2018	Bev + P	75	ROC, <4 prior line (11%	4.5 (95% CI: 3.7–6.0)			17.3 (95% CI: NA)		
	Bev + everolimus	75	prior B, 65% platinum resistant)	5.9 (95% CI: 4.5–7.6)			16.6 95% CI: NA)		
Colombo 2019	Bev + trabectedin	47	ROC (6–12 mo post	9.1 (IQR: 6.7–17.0)			23.2 (IQR: 20.1–31.1)		
	Bev + trabectedin+C	20	platinum), <3 line	21.1 (IQR: 9.8–29.6)			42.6 (IQR: 19.9 – NR)		
AVANOVA2 2019	Niraparib	49	Platinum sensitive ROC,	5.5	0.35	0.21–0.57	NA	NA	NA
	Niraparib + Bev	48	(94% 1–2 prior line, 24% prior Bev)	11.9			NA		
AVANOVA2 2019	Niraparib	18	Platinum sensitive ROC,	9	0.49	0.21–1.15	NA		
	Niraparib + Bev	15	BRCA+	14.4			NA		
Liu 2019	Nab-paclitaxel	43	Platinum-resistant ROC	6.7 (1–14)	P=0.028	NA	12.6 (1–26)	P=0.007	NA
	Nab-paclitaxel + Bev	43		8.9 (1–18)			16.3 (1–29)		
Monk 2016	Bev	53	ROC, <4 prior line, 9.3%	4.8*	0.69	0.47–1.00	22.0	0.85	0.54–1.34
	Fosbretabulin + Bev	54	prior Bev, 25% platinum resistant	7.3			24.6		

(c)

Trial	Arm	Size	Patients	PFS	OS
Phase 2 single arm					
RoSiA	mBev x 24 mo (>15)	1021	Newly diagnosed, post-surgery, IIIC-IV	21.6 (95% CI: 20.6–23.6) High risk: 18.3 (95% CI: 16.8–20.6)	NR
OCTAVIA	CwT + Bev + mBev x 1 yr	189	Newly diagnosed, post-surgery, high risk per ICON7	High risk: 18.1 (95% CI: 16.0–19.6) (all stage: 23.7 (19.8–26.4))	NR
Fleming et al.	CwT + Bev x 6-8a	30	Newly diagnosed, post-surgery, stage III-IV,	16.9 (suboptimal >1 cm) vs 22.4 (optimal R0) (HR 3.75, 95% CI: 1.05–13.34)	29.9 (suboptimal >1 cm) vs NR (optimal R0) (HR 6.02, 95% CI: 0.54–67.11)
Herzog et al.	Docetaxel/oxaliplatin/Bev + mBev	132	Newly diagnosed, post-surgery,	16.3 (95% CI: 12.6–19.6) 12mo PFS: 65.7% (53.4–76.7%)	47.2 (95% CI: 34.1 – NR)
Del Carmen 2012	CD + Bev10 x 10	54	Platinum sensitive ROC, <2 prior lines	13.9 (95% CI: 11.2–16.0)	NA

Table 2 (*continued*)

(c)

Trial	Arm	Size	Patients	PFS	OS
Eisenhauer 2014	CG + Bev10 x 6–24	45	Platinum sensitive ROC, <2 prior lines	13.3 (95% CI: 11.3–15.3)	36.1 (95% CI: 26.7–45.5)
Horowitz 2011	GEMOX+Bev	19	Platinum sensitive ROC, <3 prior lines	36.9 weeks (8.5mo)	112.3 weeks (25.9mo)
Matulonis 2012	Bev+/−oral cyclophosphamide (35% Bev only)	20	ROC, <3 prior line (70% platinum resistant)	8.41 (95% CI: 2.83–15.41)	22.72 (95% CI: 15.44–30.95)
Hagemann 2013	Pemetrexed + Bev	34	ROC, <3 prior lines (35% platinum resistant)	Sensitive: 8.4 (95% CI: 2.8–23.2) Resistant: 6.7 (95% CI: 4.1–9.9) All: 7.9 (95% CI: 4.6–10.9)	Sensitive: 26.5 (95% CI: NA) Resistant: 16.7 (95% CI: NA) All: 25.7 (95% CI: 15.4–29.8)
Wenham 2013	Docetaxel + Bev	41	ROC <12 mo platinum (46% platinum-resistant), <4 lines, no prior B	All: 5.2 (95% CI: 4.4–7.2)	All: 12.4 (95% CI: 0.0–21.9)
Musa 2017	Irinotecan + Bev	29	ROC, any prior lines (45% prior B, 66% platinum resistant)	6.8 (95% CI: 5.1–12.1)	15.4 (95% CI: 11.9–20.4)
Liu 2019	Bev + nivolumab	38	ROC, <4 prior lines (34% prior B, 47% platinum resistant)	9.4 (95% CI: 6.7 – NR) Sensitive: 12.1 (95% CI: 8.4 – NR) Resistant: 7.7 (95% CI: 4.7 – NR)	NA
McGonigle 2011	Topotecan + Bev	40	Platinum-resistant ROC, <3 prior lines	7.8 (95% CI: 3.0–9.4)	16.6 (95% CI: 12.8–22.9)
Tillanns 2012	Nab-paclitaxel + Bev	48	Platinum-resistant ROC, 1–6 prior lines (avg 1.8), no B	8.08 (95% CI: 5.78–10.15)	17.15 (95% CI: 13.57–23.82)
Verschraegen 2012	Caelyx+Bev	46	Platinum-resistant ROC, <3 prior lines	7.8 (95% CI: 6.4–9.7)	33.2 (95% CI: 18–8-NR)
Ikeda 2012	wOxaliplatin+ G + wBev	19	Platinum-resistant ROC	4.5 (2–16+)	NA
Liu 2015	Irinotecan+Bev	52	Platinum-resistant ROC	8.0 (95% CI: 6.78–9.26)	13.8 (95% CI: 1.97–15.63)
FORWARDII	Mirvetuximab soravtansine + Bev	66	Platinum-resistant ROC	6.9 (95% CI: 4.9–8.6)	NA
Nagao 2020	G + Bev	19	Platinum-resistant ROC, <4 lines	5.1 (NA)	21.3 (NA)

* Research published in abstract form only.
* Resistant ($n = 27$): 3.4 v 6.7 m (HR 0.57, $p = 0.01$); Sensitive ($n = 80$): 6.1 v 7.6 m (HR 0.67, 90% CI: 0.43, 1.03).

all patients with a deleterious germline BRCA1 or BRCA2 mutation were eligible for enrollment, regardless of surgical outcome, that is, the presence or absence of residual disease. We know that this is an important consideration for identifying patients who are more likely to respond to bevacizumab, and because only 30% of patients in this study had stage IV disease and most had no evidence of residual disease, we cannot directly use the results of PAOLA-1 to conclude whether bevacizumab improves PFS, as the primary focus of this study was to evaluate PARP inhibitors for those with BRCA mutations. Nonetheless, pre-defined subgroup analyses revealed that regardless of surgical outcome (complete macroscopic vs incomplete resection, presence of residual disease versus no residual disease), the hazard ratio for PFS favors olaparib plus bevacizumab over placebo plus bevacizumab. The tumor HRD status, however, indicates that there is no difference in PFS for HRD-negative or unknown patients receiving olaparib and bevacizumab versus placebo and bevacizumab. Based on the results from this study alone, it is not possible to know whether the addition of bevacizumab has implications for patients based on HRD status. Certainly, testing for homologous recombination repair defects, particularly *BRCA* mutations, is now recommended universally for patients with high-grade serous ovarian carcinoma due to its ramifications on genetic counselling and role in predicting response to PARP inhibitors. While there are no current predictive biomarkers for bevacizumab in EOC, this should continue to be explored further, particularly in the context of combination therapies with other targeted treatments. Ongoing combination studies including bevacizumab in the first-line (NCT03740165, NCT03737643) and recurrent settings (NCT03587311, NCT03353831) are routinely incorporating correlative studies as additional objectives to assist in biomarker discovery and disease understanding.

Furthermore, given the favorable toxicity profile of bevacizumab across the studies included in this review, incorporation of bevacizumab should remain standard of care in selected populations: those with high-risk disease (stage IV and residual disease following debulking surgery) in the first-line setting, and those with recurrent disease. It is worthwhile evaluating current implementation of bevacizumab in ovarian cancer and assess its associated toxicity in real-world patient populations. While many oncologists may be reluctant to prescribe bevacizumab due to risk of bowel perforation, this review suggests the rate of bowel perforation is low.

This review has several strengths. To our knowledge, this is the first comprehensive systematic review of the efficacy of bevacizumab combination therapies in ovarian cancer since 2016 [8]. Similar to previous, there was a statistically significant improvement in PFS for combination chemotherapy and bevacizumab compared to chemotherapy alone in both the first–line high-risk and recurrent settings. In addition, although the individual trials do not demonstrate OS benefit, the pooled analysis in the first-line high-risk setting revealed a trend towards OS benefit favoring bevacizumab combination, and this reached statistical significance in the recurrent setting. One potential explanation for the trend in OS benefit in the first-line setting could be the use of bevacizumab in the recurrent setting. More data is needed to further assess benefits of re-challenge with bevacizumab in those with prior exposure, and to ultimately determine the best timing of utilizing this drug.

There are several limitations to our study. First, heterogeneity among the studies remains a challenge for a more uniform interpretation of results. Subsequent to 2016, many trials now involve bevacizumab in both arms, and the combination arm involves a variety of drugs beyond chemotherapy. In addition, studies such

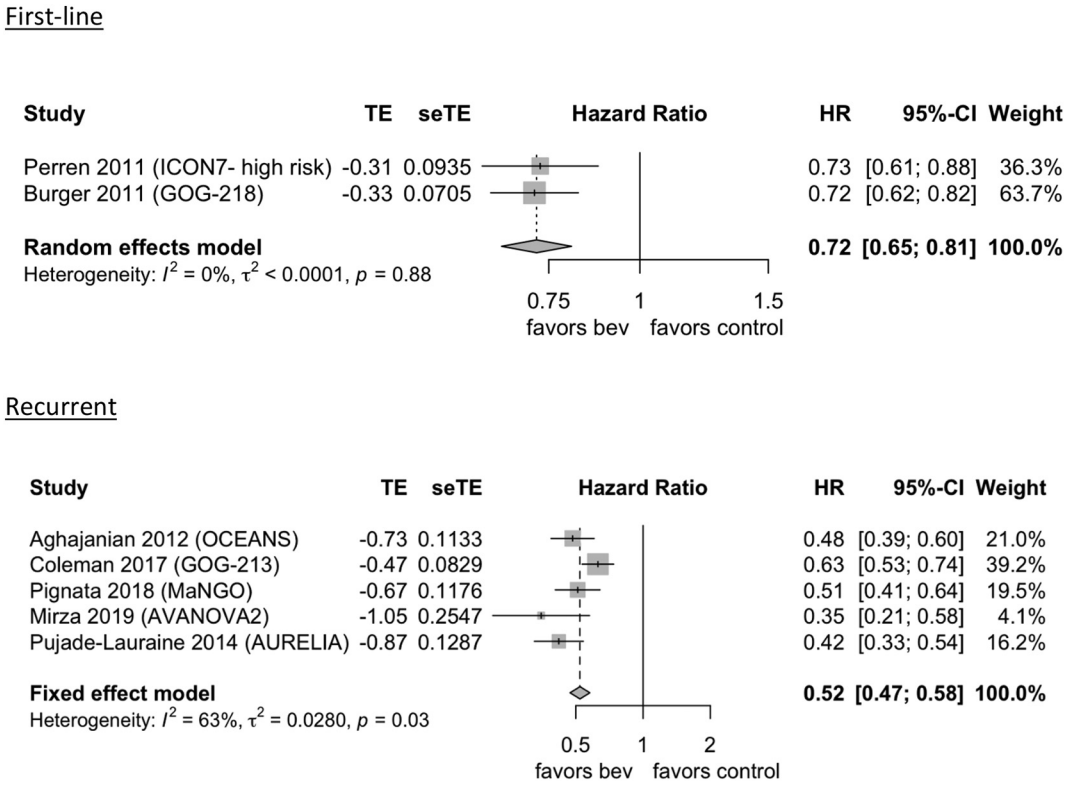

Fig. 3. Meta-analysis of progression-free survival (PFS), stratified based on setting.

as GOG-262 [15] involved the choice to include bevacizumab in both arms and this was not randomized, while others such as PAOLA-1 [10] involved bevacizumab in both arms. This limits the ability to include these studies in quantitative analysis. As such, most of the results from our meta-analysis re-emphasizes findings from prior reviews which included chemotherapy alone as control. It is well known that optimal cytoreductive surgery for epithelial ovarian cancer has prognostic implications, with optimal debulking surgery without residual disease (<1 cm) considered one of the most important positive prognostic factors for survival [46]. As surgical outcomes were not well captured across different studies with different designs and endpoints, we were not able to undertake a sensitivity analysis to assess the impact of surgical outcome in our review. This is reflected even in the randomized phase 3 trials included in the first line setting,

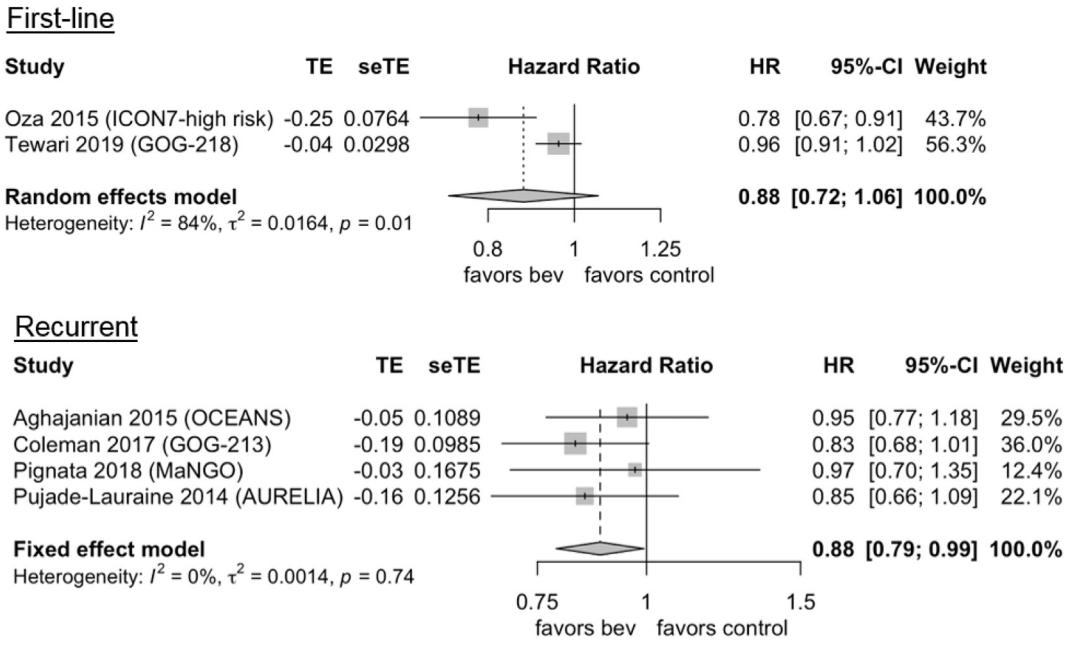

Fig. 4. Meta-analysis of overall survival (OS), stratified based on setting.

where the proportion of gross residual disease varied between 26% and 63% across studies. In the two neoadjuvant trials (ANTHALYA and GEICO 1205), the results regarding the impact of bevacizumab on complete macroscopic resection rate, which was the primary endpoint in both trials, were conflicting, although both indicated that bevacizumab was safe in the neoadjuvant setting. Despite these differences, most large, randomized phase 3 trials had well balanced treatment arms such that patient and surgical characteristics including residual disease would be distributed equally across treatment arms. As such, we believe these findings regarding the clinical benefit of bevacizumab in advanced ovarian cancer remain important, although care should be taken when interpreting the results. Second, several phase 2 studies included did not have efficacy with PFS or OS as their primary endpoint. Instead, overall response rate or complete resection rates were used, thus the secondary endpoints of PFS and OS must be interpreted with caution as studies may not have been powered to interpret efficacy results, although the findings reported are similar across trials. Third, publication bias is not accounted for in the analysis but may be present as in most oncology drug trials. Finally, safety data is not well captured in this review due to the inconsistency in the reporting of adverse events and the variability in toxicity profile of many novel agents. We were able to report the overall rate of bowel perforation as this was the only consistently reported adverse event across trials, which was deemed relatively low (1.24% of the entire cohort receiving bevacizumab). A meta-analysis on safety data is crucial, as the benefits of therapy must always be weighed against the potential risks. Similarly, cost-effectiveness analysis would also be an important objective in future studies.

5. Conclusion

This updated systematic review illustrates the large variety of clinical trials involving bevacizumab in the past decade for ovarian cancer, with a trend towards increased use of targeted therapy combinations such as PARP inhibitors in more recent studies. The meta-analysis confirms the findings of improved PFS in bevacizumab combination therapies as well as improved OS in recurrent settings. Toxicity profile suggests this drug is relatively well-tolerated with very low risk of bowel perforation in the trial setting. As more therapeutic combination studies in EOC incorporate bevacizumab into their treatment arms across various contexts, meta-analyses will need to be updated consistently to summarize the latest information surrounding its ongoing role in the treatment of this life-threatening disease.

Ethics approval and consent to participate

This meta-analysis only used previously published or presented data, and thus no ethics committee approval was sought.

Author contributions

SLL was responsible for the conception, development, analyses, dissemination of the protocol and manuscript writing. SLL and LK were the first and second reviewers respectively, responsible for abstract and full-text screening, and data extraction from included studies. GBF was the third reviewer responsible for resolving discrepancies in study selection. RF and SLL performed the literature search. LW and SLL performed the statistical analyses. SL and MK supervised the conception and development of the study, and provided feedback for the protocol. All authors contributed in reviewing and editing the final manuscript for publication.

Declaration of Competing Interest

The authors have no personal nor financial conflict of interests to disclose. Several of the clinical trials included in this systematic review were conducted at the Princess Margaret Cancer Centre.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.01.028.

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