CLINICAL INVESTIGATION

Bevacizumab in the treatment of epithelial ovarian carcinoma

In recent years, inhibitors of angiogenesis have become a focus of clinical trials aimed at expanding treatment options for women afflicted with epithelial ovarian cancer (EOC). Bevacizumab, a VEGF inhibitor, has been well studied in multiple solid tumors, suggesting progression-free and overall survival benefits. In EOC, bevacizumab has been the subject of many trials with results indicating a progression-free survival benefit in a variety of settings. The addition of bevacizumab to the EOC armamentarium, however, is not without risk. This article provides a rationale for targeting angiogenesis and discusses pivotal trials evaluating the utility of bevacizumab in EOC. Current research is evaluating optimal dosing duration, benefit of bevacizumab beyond progression, biomarkers to direct anti-angiogenic therapy and patient reported outcomes.

Keywords: antiangiogenic agents • bevacizumab • ovarian carcinoma

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Angiogenesis is an integral element in normal ovarian physiology as well as the pathogenesis of epithelial ovarian carcinoma (EOC) [1,2]. The regulation of angiogenesis is complex and not yet completely elucidated; however, multiple pathways, genes and epigenetic phenomena have been implicated. In normal physiology, a delicate balance exists between pro- and anti-angiogenic factors; in EOC, this balance is skewed towards a pro-angiogenic environment with dysregulation of the normal pathways and cellular interactions. Without an expanding blood supply, tumors are limited in their ability to grow and metastasize [2]. VEGF is one of the most potent pro-angiogenic growth factors [3] and, thus, key in the development and metastasis of EOC.

In addition to oncogene and tumor suppressor mutations, the cell microenvironment is an important factor in VEGF expression; stimuli such as hypoxia, oxidative stress and the cytokine/growth factor milieu all contribute to increase VEGF expression [2]. Upon binding to one of three different VEGF receptors (VEGFR-1, -2, -3), phosphorylation of the receptor occurs with subsequent activation of downstream pathways involved in endothelial cell proliferation [4]. Multiple solid tumors, including EOC, express VEGF and its receptors [3]. As biomarkers are sought to better predict response to therapy for patients with EOC, several studies have demonstrated that high preoperative or prechemotherapy serum VEGF levels have correlated with tumor grade and disease stage [5] and may be prognostic for overall survival [5,6]. *In vitro* experiments have shown increased VEGF expression by endothelial cells after treatment with carboplatin, suggesting a need for VEGF inhibition as part of cancer treatment [7]. Several anti-angiogenic therapies target the VEGF pathway including monoclonal antibodies, decoy receptors and tyrosine kinase inhibitors. The most extensively studied and commonly used anti-VEGF therapy is bevacizumab. To date four randomized controlled Phase III trials evaluating bevacizumab in the treatment of newly diagnosed and recurrent EOC have yielded improved progression-free survival (PFS) (Tables 1 & 2) [8–11].

Pharmacology (pharmacokinetics)

Bevacizumab is a recombinant monoclonal antibody directed against all isoforms of

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Table 1. Completed Phase III trials of bevacizumab in epithelial ovarian carcinoma: first-line setting.

Trial	Setting	Regimen	RR (%)	SD (%)	PFS (months)	OS (months)	Grade 3/4 adverse events	Ref.
Perren *et al.* (ICON 7; n = 1528)	Advanced/high risk; new diagnosis	CP ± B (7.5 mg/kg) q3w → B maintenance (12 cycles)	48 vs 67	NR	19.0 vs 17.3	45.5 vs 44.6[†]	Neutropenia (G3–5, n = 117); HTN (G3–5, n = 46); thrombolic events (G3–5, n = 51); wound healing (G3-5, n = 10)	[10]
Burger *et al.* (GOG 218; n = 1816)	New diagnosis; suboptimally debulked stage III or any stage IV	CP ± B (15 mg/kg) q3w → ± B maintenance (16 cycles)	NR	NR	14.1 vs 11.2 vs 10.3	39.7 vs 38.7 vs 39.3	Bevacizumab-containing groups vs placebo: HTN (G≥2, 239 vs 43); GI event[‡] (G≥2, 33 vs 7); proteinuria (14 vs 4); reversible posterior leukoencephalopathy (2 vs 0)	[11]
Chan *et al.* (GOG 262; n = 692)	New diagnosis, suboptimally debulked stage II–IV	Carboplatin + paclitaxel (q1w or q3w) ± B (15 mg/kg) q3w → ± B maintenance until PD	NR	NR	15[§]	NR	Neutropenia (n = 530); anemia (n = 178); neuropathy (n = 149)[¶]	[12]

[†]Restricted mean survival time.
[‡]Includes gastrointestinal perforation, fistula, necrosis or anastomotic leak.
[§]In subset receiving bevacizumab; no difference in median PFS between q3w and weekly paclitaxel.
[¶]Includes study patients not receiving bevacizumab.
B: Bevacizumab; CP: Carboplatin/paclitaxel; GOG: Gynecologic Oncology Group; HTN: Hypertension; ICON: International Collaboration on Ovarian Neoplasms; NR: Not reported; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; q3w: Every 3 weeks; RR: Response rate; SD: Stable disease rate.

VEGF. Interacting with VEGF extracellularly, bevacizumab inhibits the ability of VEGF to bind primarily to VEGFR-1 and -2 with resultant effects on endothelial cell permeability, proliferation and release of various proteases from the vascular bed [2].

Gordon and colleagues performed the first Phase I trial of single-agent bevacizumab (known then as rhuMAb VEGF) in patients with metastatic cancer. Bevacizumab was administered by a 90-min intravenous infusion at doses from 0.1 to 10.0 mg/kg on days 0, 28, 35 and 42. Patients underwent pharmacokinetic sampling, as well as assessments for antibody development and serial VEGF levels. A total of 25 patients were treated on this initial study. No dose-limiting toxicities were identified and doses ranging up to 10 mg/kg were safely administered. The predominant grade 1 and 2 adverse events (AEs) included asthenia, headache and nausea. Hypertension (HTN) was rare, but mild increases (10–15 mmHg) in systolic and diastolic pressures were noted in the 3 and 10 mg/kg dosing cohorts. There were three episodes of hemorrhage that, at the time, were felt to be tumor-related and not secondary to bevacizumab. Serum total VEGF levels were increased, possibly secondary to increased VEGF formation and/or decreased VEGF clearance caused by complex formation between VEGF and bevacizumab. However, serum-free VEGF levels were decreased with bevacizumab doses greater than or equal to 3.0 mg/kg. While there were no objective responses, 12 patients had stable disease and none developed antibodies against bevacizumab [13].

The pharmacokinetic evaluation revealed a half-life of approximately 21 days at doses greater than or equal to 0.3 mg/kg. After multiple weekly doses a slight accumulation of bevacizumab was noted [13]. Further evaluation has confirmed the initial pharmacokinetic assessment. In addition, the predicted time to steady state concentration is approximately 100 days. Drug clearance is affected by gender, patient weight and tumor burden; however, no difference in efficacy has been noted [14]. Drug clearance has not yet been elucidated, however, the involvement of the reticulo-endothelial system has been suggested [15].

Bevacizumab has also been studied in combination with cytotoxic agents in the Phase I setting. A total of 12 patients received bevacizumab with one of three regimens: doxorubicin, fluorouracil or carboplatin/paclitaxel. No synergistic toxicities were noted [16]. The results of these initial studies led to the evaluation of bevacizumab either alone or in combination with chemotherapeutic agents in a variety of malignancies.

In metastatic colorectal cancer, a pivotal Phase III trial showed a 4.7-month increase in median overall

Table 2. Completed Phase III trials of bevacizumab in epithelial ovarian carcinoma: recurrent setting.

Trial	Setting	Regimen	RR (%)	SD (%)	PFS (months)	OS (months)	Grade 3/4 adverse events	Ref.
Aghajanian *et al.* (OCEANS; n = 484)	Recurrent, platinum sensitive	Gemcitabine + carboplatin ± B → B maintenance until PD	78.5 (PR) vs 57.4	NR	12.4 vs 8.4	35.5 vs 29.9	HTN (17.4 vs <1%); proteinuria (8.5 vs <1%); GIP†	[8]
Pujade-Lauraine *et al.* (AURELIA n = 361)	Platinum resistant	PLD or topotecan or paclitaxel ± B (10 mg/kg q2w or 15mg/kg q3w)	30.9 vs 12.6	NR	6.7 vs 3.4	16.6 vs 13.3	TE(5 vs 4); RPL (n = 1); HTN (≥G2, 20 vs 7); proteinuria (≥G2, 11 vs 1); GIP (≥G2, 2 vs 0)	[9]

†Two GIP occurred in patients after discontinuation of study treatment.
B: Bevacizumab; GIP: Gastrointestinal perforation; HTN: Hypertension; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; q2w: Every 2 weeks; q3w: Every 3 weeks; RPL: Reversible posterior leukoencephalopathy; RR: Response rate; SD: Stable disease rate; TE: Thromboembolism.

survival (OS) in patients receiving bevacizumab with chemotherapy compared with those receiving chemotherapy alone [17]; US FDA approval for this indication followed in 2004 [18]. Subsequently, the FDA has approved bevacizumab for use in multiple other solid tumors, including glioblastoma, non-small-cell lung cancer and metastatic renal cancer [19]. Given success in these other tumors, as well as promising preclinical data, there was considerable interest in evaluating bevacizumab in EOC.

For the remainder of this review we will focus primarily on the use of bevacizumab in EOC.

Initial experience in EOC

Bevacizumab has been studied as a therapeutic option in first-line as well as recurrent platinum-sensitive and resistant (defined as persistent/progressive disease while receiving a platinum-based regimen or recurrence within 6 months of receiving such a regimen) settings (Tables 1–4). Thirteen Phase I trials of bevacizumab have either been completed or are currently ongoing in patients with EOC, some with promising results that have lead to larger, randomized studies in a variety of settings [20]. The initial Phase II study of bevacizumab was conducted by the Gynecologic Oncology Group (GOG; GOG170D) [21]. The rationale for evaluating bevacizumab in EOC was based on preclinical data indicating associations between VEGF overexpression and tumor angiogenesis, production of ascites and metastasis [21] in addition to emerging evidence of antitumor activity in Phase I clinical trials. The study enrolled 62 patients with persistent or recurrent EOC. Participants in GOG 170D received bevacizumab at 15 mg/kg every 21 days (q21d) until progression. The overall response rate (ORR) was 21%, while 40.3% of patients remained progression free at 6 months (PFS_{6mo}). The median PFS was 4.7 months (interquartile range (IQR) 2.7, 12.9) with a 17 month median OS (IQR 9.1, 32.4). Grade 3 HTN was present in 9.7% of study participants while 3.2% of patients developed venous thromboembolism (VTE) and 1.6% experienced grade 4 proteinuria. There were no gastrointestinal perforations (GIP). Two patients (3.2%) discontinued the study for AEs [21].

Another pivotal Phase II study (AVF 2949) involved bevacizumab in women with platinum-resistant disease who had progressed within 3 months of receiving topotecan or pegylated liposomal doxorubicin (PLD) [27]. While this study demonstrated antitumor activity (median PFS was 4.4 months; 16% PR), the study was closed early given an alarmingly high number of GIPs (11.5%). All five patients who experienced a GIP had radiologic evidence of bowel involvement prior to entering the study and had each received three chemotherapy regimens prior to study entry [27]. The findings of this trial helped identify patients who are at high risk for GIP and in whom bevacizumab should be avoided or used with caution. The antitumor activity seen in GOG170D [21] and AVF 2949 [27] prompted the development of additional Phase II and III trials evaluating bevacizumab in both the first-line and recurrent disease settings.

Garcia and colleagues conducted one of the first Phase II trials of bevacizumab in combination with chemotherapy in EOC [28]. Bevacizumab, 10 mg/kg every 2 weeks (q2w), with low dose metronomic oral cyclophosphamide, 50 mg/d, was administered to women with recurrent EOC and ≤2 prior regimens. A total of 24% (95% CI: 15–36%) of patients achieved a PR [28], higher than that reported by Burger *et al.* or Cannistra *et al.* [21,27]. Mean time to progression was

Table 3. Completed Phase II trials of bevacizumab in epithelial ovarian carcinoma: first line setting.

Trial	Setting	Regimen	RR (%)	SD (%)	PFS (months)	OS (months)	Grade 3/4 adverse events	Ref.
Micha *et al.* (n = 20)	New diagnosis advanced EOC/PPC/FTC	B (15 mg/kg) + CP	30 (CR) 50 (PR)	5	NR	NR	Neutropenia (G3, 25%; G4, 65%); HTN (G3, 10%); neuropathy (G3, 5%)	[22]
Penson *et al.* (n = 62)	New diagnosis EOC/PPC/FTC; ≥ stage IC	CP + B (15 mg/kg) (cycle 2–6) q3w → B maintenance (1 year)	21 (CR) 55 (PR)	21	29.8	NR	HTN(G3, n = 5); musculoskeletal pain (G3, n = 3); proteinuria (G3, n = 2); metabolic (G3, n = 2); thrombocytopenia (G3, n = 1; G4, n = 1)†	[23]
Konner *et al.* (n = 41)	New diagnosis, optimally debulked stage II–III EOC/PPC/FTC	B (15mg/kg) + IV paclitaxel (D1) + IP cisplatin (D2) + IP paclitaxel (D8) → B maintenance (17 cycles)	NR	NR	28.6	NR	Neutropenia (G3, n = 9; G4, n = 5); anemia (G3, n = 6); nausea/vomiting (G3, n = 5); HTN (G3, n = 5); bowel obstruction (G3, n = 3); GIP (G5, n = 1)	[24]
Gonzalez-Martin *et al.* (OCTAVIA; n = 189)	New diagnosis advanced or high risk EOC/PPC/FTC	B (7.5 mg/kg) + weekly paclitaxel + carboplatin q3w	85	NR	23.7	NR	Neutropenia (59.3%); anemia (7.9%); thrombocytopenia (7.4%); thromboembolus (6.3%); HTN(4.2%)	[25]
Herzog *et al.* (TEACO; n = 132)	Chemo-naive EOC/PPC/FTC (stages IB–IV)	Docetaxel + oxaliplatin q3w (6 cycles) + B (15 mg/kg; 1 year)	33 (CR) 29 (PR)	33	NR	NR	Neutropenia (39%); leukopenia (11%); HTN (9%); fatigue (7%); sensory neuropathy (1.3%)	[26]

†In 55 patients with measurable disease.

B: Bevacizumab; CP: Carboplatin/paclitaxel; GIP: Gastrointestinal perforation; HTN: Hypertension; IP: Intraperitoneal; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; q3w: Every 3 weeks; RR: Response rate; SD: Stable disease rate.

Table 4. Completed Phase II trials of bevacizumab in epithelial ovarian carcinoma: recurrent setting.

Trial	Setting	Regimen	RR (%)	SD (%)	PFS (months)	OS (months)	Grade 3/4 AEs	Ref.
Burger *et al.* GOG170D (n = 62)	Recurrent/persistent†	B (15 mg/kg) q3w	21	52	4.7	17	Gr3: HTN (n = 6); venous TE (n = 1) Gr 4: proteinuria, venous TE (n = 1 each)	[21]
Cannistra *et al.* (n = 53)	Platinum resistant; PLD or topotecan in last 3 months	B (15 mg/kg) q3w	15.9 (PR)	61.4	4.4	10.7	GIP (n = 5); HTN (n = 4); abdominal pain, fatigue (n = 2 each)	[27]
Garcia *et al.* (n = 70)	Recurrent†	B (10 mg/kg) + cyclophosphamide	24 (PR)	63	7.2 (TTP)	16.9	Gr3: HTN (n = 11); proteinuria (n = 3)	[28]
Nimeiri *et al.* (n = 13)	Recurrent†	B (15 mg/kg) + erlotinib	15	54	4.1	11	N/V(n = 3); GIP, diarrhea (n = 2); anemia (n = 1)	[29]
Chambers *et al.* (n = 56)	Recurrent or persistent platinum resistant	B (10 mg/kg) + erlotinib	23.1	25.6	4	NR	Gr3: diarrhea (n = 5); fatigue (n = 4); HTN (n = 3); Gr 4: nasal septal perforation (n = 2); MI (n = 1)	[30]
Sanchez-Munoz *et al.* (n = 38)	Recurrent†	B (10 mg/kg) + cyclophosphamide	8 (CR) 32 (PR)	8	4.5	10.7	HTN (n = 2); anemia; arterial TE; dyspnea; hematuria; GI fistula (n = 1 each)	[31]
Horowitz *et al.* (n = 19)	Recurrent, platinum sensitive	B(10 mg/kg) + oxaliplatin + gemcitabine q28d	68	31	37 weeks	112 weeks	Gr3: Neutropenia (n = 5); neuropathy fatigue (n = 3 each), N/V (n = 2) Gr 4: TE (n = 1)	[32]
Kudoh *et al.* (n = 30)	Recurrent/persistent†	B (2 g/kg) + PLD qw	7 (CR) 27 (PR)	40	6	NR	Gr3: PPE (n = 1); GIP (n = 1)	[33]
McGonigle *et al.* (n = 40)	Recurrent/persistent platinum resistant	B (10 mg/kg) + topotecan q28d	25 (PR)	35	7.8	16.6	HTN (20%); neutropenia (18%); metabolic (15%); bowel obstruction (10%); cardiac (8%)	[34]
Verschraegen *et al.* (n = 46)	Recurrent/persistent platinum resistant	PLD + B (15 mg/kg) (cycle 2 to PD)	30	56	6.6	33.2	PPE (n = 13); HTN (n = 13); headache (n = 5); CNS disturbance (n = 1)	[35]
del Carmen *et al.* (n = 54)	Recurrent, platinum sensitive	B (10 mg/kg) + PLD/ carboplatin q28d	15 (CR) 57 (PR)	20	13.9	NR	Neutropenia (17%); proteinuria (11%); HTN (11%); PPE (7.4%); GIP (2%)	[36]
Wenham *et al.* (n = 27)	Recurrent, platinum resistant (<12 months)	B (15mg/kg) + docetaxel q3w	5 (CR) 53 (PR)	37	NR	NR	Gr3:neutropenia (15%); infection (7%)	[37]
Tillmanns *et al.* (n = 48)	Recurrent, platinum resistant	B (10 mg/kg) D1,8 q21d + ABP qw	46 (PR)	31	8.3	16.5	NR; 10% of all AEs were G3/4	[38]
Hagemann *et al.* (n = 34)	Recurrent/persistent†	B (15 mg/kg) + pemetrexed q28d	41 (PR)	53	7.9	25.7	Hematologic (53%); GI (G3, 12%)	[39]

†Includes both platinum-sensitive and platinum-resistant disease.

ABP: Albumin-bound paclitaxel; AE: Adverse event; B: Bevacizumab; CR: Complete response; GIP: Gastrointestinal perforation; HTN: Hypertension; MI: Myocardial infarction; NR: Not reported; N/V: Nausea and vomiting; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PLD: Pegylated liposomal doxorubicin; PPE: Palmar–plantar erythrodysesthesia; PR: Partial response; q3w: Every 3 weeks; RR: Response rate; SD: Stable disease rate; TE: Thromboembolism; TTP: Time to progression.

7.2 months with a PFS_{6mo} of 56%. The most common bevacizumab-related toxicities were HTN (39% all grades, 15.7% ≥grade 3) and proteinuria (44% all grades, 4.3% ≥grade 3) [28].

First-line setting

Given the preliminary Phase II single agent data reported in the GOG170D [21] and AVF 2949 [27] trials as well as results from Phase II and III trials in patients with metastatic colorectal cancer and non-small-cell lung cancer (NSCLC) [40,41], there was tremendous interest in investigating bevacizumab in combination with standard chemotherapy in women with newly diagnosed EOC.

Phase II

Several Phase II trials were conducted using bevacizumab in the first-line setting (Table 3) [22–26]. Penson *et al.* reported 58% of chemo-naive patients receiving carboplatin/paclitaxel with upfront and maintenance bevacizumab (15 mg/kg) were progression free at 36 months with a median PFS of 29.8 months (95%, 17.3 not yet reached). The majority of study participants had been diagnosed with advanced disease (69% stage III, 21% stage IV) and underwent optimal cytoreduction (79%). Two pulmonary emboli and two GIPs (each 3.2%) were reported during the chemotherapy phase of treatment [23].

Table 5. Bevacizumab and epithelial ovarian carcinoma: active Phase III trials.

Trial	Phase	Number of patients†	Setting	Regimen	Primary objective
NCT01239732	III	1000	Advanced; new diagnosis or recurrent, chemo-naive	Carboplatin + paclitaxel (q3w or qw) × 4–8 cycles + B (5 mg/kg) × 36 or PD	AE
NCT01081262‡	III	332	New diagnosis stage II–IV or recurrent stage I mucinous	Arm 1: CP q3w × six cycles Arm 2: oxaliplatin + capecitabine (D1–14) q3w × six cycles Arm 3: Arm 1 + B (six cycles) → B maintenance (12 cycles) Arm 4: Arm 2 + B × six cycles → B maintenance × 12	OS
NCT01462890‡	III	800	Advanced; new diagnosis	CP + B q3w × six cycles → maintenance B × 16 or 38 cycles	PFS
NCT00262847‡	III	1873	New diagnosis, stage III (suboptimally debulked) or stage IV	CP ± B (Cycles 2–6) → ± B maintenance (cycles 7–22)	PFS
NCT00951496‡ (GOG 252)	III	1500	New diagnosis stage II–IV after debulking surgery	Arm I: CP + B (cycles 2–6) → B maintenance (cycle 7–22) Arm 2: iv. paclitaxel + ip. carboplatin + B → B maintenance (cycle 7–22) Arm 3: iv. paclitaxel + ip. cisplatin + ip. paclitaxel → B maintenance (cycle 7–22)	PFS
NCT01802749‡ (MITO16/MANGO2b)	III	400	Recurrent, platinum sensitive	Arm 1: PLD + carboplatin ± B(10 mg/kg) q2w Arm 2: Gemcitabine + carboplatin q4w ± B (15 mg/kg) q3w; Arm 3: CP ± B (15 mg/kg) q3w	PFS
NCT01837251‡	III	654	Recurrent, platinum resistant	Control: B (15 mg/kg) gemcitabine, carboplatin q3w → B maintenance (15 mg/kg) to PD Experimental: B (10 mg/kg) q2w + PLD + carboplatin q4w → B (15 mg/kg) maintenance to PD	PFS

†Estimated enrollment.
‡Indicates a randomized trial.
AE: Adverse event; B: Bevacizumab; CP: Carboplatin/paclitaxel; ip.: Intraperitoneal; iv.: Intravenous; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PLD: Pegylated liposomal doxorubicin; q2w: Every 2 weeks; q3w: Every 3 weeks; q4w: Every 4 weeks.

Foregoing maintenance bevacizumab, Micha *et al.* reported an ORR of 80% in patients with newly diagnosed EOC, primary peritoneal carcinoma (PPC) or fallopian tube carcinoma (FTC) receiving a standard carboplatin/paclitaxel backbone with upfront bevacizumab (15 mg/kg). Neither GIP nor VTE were reported [22]. A lower dose of bevacizumab (7.5 mg/kg) was studied as upfront and maintenance therapy in combination with carboplatin and weekly paclitaxel in the OCTAVIA trial, the largest Phase II trial of bevacizumab in EOC to date [25]. Overall RR was 84.6% with a median PFS of 23.7 months (95% CI: 19.8–26.4). The most common nonhematologic grade 3 or 4 AEs included peripheral neuropathy (5.3%), thromboembolic event (6.3% total; VTE 4.8%, arterial emboli 1.6%) and HTN (4.2%) [25].

Other studies have incorporated bevacizumab into upfront regimens in different ways. In a trial of 41 patients with optimally debulked, advanced stage EOC, bevacizumab was added to a regimen of intravenous/intraperitoneal paclitaxel and cisplatin with subsequent bevacizumab maintenance [24]. 73% of patients completed all six cycles of initial therapy. Estimated median PFS was 28.6 months (95% CI: 19.1–38.9), although 7% experienced grade 3 small bowel obstructions and one patient died after a rectosigmoid anastomotic dehiscence [24]. A trial of oxaliplatin and docetaxel with concurrent and maintenance bevacizumab as first-line treatment of advanced EOC reported a median PFS of 16.3 months (95% CI: 12.6–19.6) and a median OS of 47.2 months (95% CI: 34.1–NA). The most common grade 3/4 AEs include neutropenia (42.4%) and HTN (8.3%). Five pulmonary embolus (3.8%) and one GIP (0.76%) were reported [26].

Phase III

Large Phase III trials have been conducted to investigate the role of bevacizumab in the management of EOC. Both ICON 7 and GOG 218 evaluated bevacizumab as an addition to standard chemotherapy in an upfront setting [10,11]. GOG 218 was a three-arm, placebo-controlled, double-blinded study of paclitaxel/carboplatin with and without upfront or maintenance bevacizumab in nearly 1900 women. Study participants had FIGO stage III or IV disease and macroscopic residual tumor after primary debulking surgery [11]. Patients were randomized to paclitaxel (175 mg/m^2), carboplatin (AUC 6) plus placebo (arm 1), standard chemotherapy plus bevacizumab (15 mg/kg; cycles 2–6) followed by placebo maintenance (arm 2) or standard chemotherapy plus upfront and maintenance bevacizumab (cycles 2–22; arm 3). Median PFS was improved by approximately 4 months in arm 3 compared with arm 1 (14.1 vs 10.3). No significant improvement in PFS was noted for women receiving concurrent bevacizumab without maintenance dosing (11.2 vs 10.3 months). The hazard ratio of progression/death was statistically significant between those receiving bevacizumab upfront and throughout (arm 3) compared with standard chemotherapy alone (arm 1; HR: 0.717; 95% CI: 0.625–0.824; p < 0.001) [11]. Although no differences in OS were noted in either of the bevacizumab containing regimens compared with chemotherapy alone [11], an exploratory analysis of OS by disease status showed a 7.8 month increase in median OS for patients with stage IV disease (40.6 vs 32.8; HR: 0.72; 95% Cl; 0.53–0.97) [42].

A follow-up quality of life (QOL) analysis of patients enrolled in GOG 218 was performed using a validated QOL tool with assessments during the course of therapy as well as 6 months after completion. Significantly lower QOL was reported for patients in both of the bevacizumab containing regimens compared with those receiving placebo. These differences, however, remained significant only through cycle 7 [43].

ICON-7 had similar aims, adding bevacizumab to a backbone regimen of intravenous carboplatin/paclitaxel in a front-line setting, although using a lower bevacizumab dose of 7.5mg/kg [10]. Unlike GOG 218, ICON-7 was a two-arm, open-label study that identified progression using radiologic, clinical and/or symptomatic markers. Asymptomatic, isolated elevations in CA-125 were not included. Over 1500 patients with early, high-risk disease or advanced EOC, PPC or FTC were randomized to receive one of two regimens. The control arm consisted of carboplatin (AUC 5 or 6) with paclitaxel (175 mg/m^2) q3w for six cycles, while the experimental group received the same chemotherapy with concomitant bevacizumab (five or six cycles) followed by up to 12 cycles of bevacizumab maintenance therapy. Median PFS was 17.3 months in the control arm compared with 19.0 months in the bevacizumab-containing arm (HR: 0.81; 95% CI: 0.70–0.94; p = 0.004). Patients at highest risk of progression (FIGO stage IV disease or FIGO stage III with >1.0 cm residual tumor at time of debulking) experienced the greatest benefit. These high-risk patients randomized to bevacizumab experienced a 5.4 month increase in median PFS (HR: 0.68; 95% CI: 0.55–0.85; p < 0.001) [10]. No global improvement in OS was noted overall; however, in the high-risk group, a 4.8 month increase in median overall survival (log rank p = 0.03, P-H test 0.007) favoring bevacizumab therapy was achieved [44]. Overall grade 3 or 4 AEs in the bevacizumab versus control group included HTN (6 vs <1%), GIP (1 vs <1%), thromboembolic event (7 vs 3%) and neutropenia (17 vs 15%) [10].

A subsequent QOL analysis of ICON 7 participants was also performed. Overall, the mean QOL improved as measured from baseline to week 18, although the mean score was higher at week 54 for women in the standard chemotherapy group compared with those receiving bevacizumab (76.1 vs 69.1; difference: seven points; $p < 0.0001$). Notably, women receiving bevacizumab were more likely to return surveys (66 vs 51%). Initially defined as a ten-point difference, a clinically meaningful result was later stratified to small (4–7-point) or moderate (10–15 point)-difference. Although several factors

Table 6. Bevacizumab and epithelial ovarian carcinoma: active Phase II trials.

Trial	Phase	Patients (n)†	Setting	Regimen	Primary objective
NCT02022917	II	27	Advanced; new diagnosis not amenable to PDS	Platinum + paclitaxel → IDS → CP + B (15 mg/kg; 6 cycles) + maintenance B (17 cycles)	AE
NCT01097746	II	30	Advanced; new diagnosis	Carboplatin + paclitaxel qw + B (15 mg/kg) (cycle 2–6)	Treatment success‡
NCT01847677§	II	66	New diagnosis; planned IDS	CP ± B (15 mg/kg) q3w × four cycles → IDS → CP + B (15 mg/kg) (cycle 5–7) → maintenance B	CRR
NCT00520013§	II	60	Advanced; new diagnosis, prior PDS	CP q3w × six cycles + B q3w (cycle 2–6) → B maintenance ± erlotinib qd × 1 year	PFS, toxicity
NCT01739218§	II	99	Unresectable stage IIIC/IV	Carboplatin (cycle 1–8) + paclitaxel q3w (cycle 1–4; then qw or q3w cycle 5–8) ± B (15 mg/kg) q3w (cycle 1–3) → B maintenance (cycle 6–26)	Complete resection rate after IDS
NCT00886691§ (GOG 186G)	II	150	Recurrent/persistent; platinum free <12m	B q2w ± everolimus daily	PFS, AE, RR
NCT00436215	II	74	Recurrent, platinum resistant	B (5 mg/kg) q2w + sorafenib (M–F)	CRR
NCT00545792	II	20	Recurrent pelvic-confined GYN cancer	B (10 mg/kg) q2w × 3 + pelvic radiation	Toxicity rate
NCT00744718	II	30	Recurrent, platinum resistant, £ 3 regimens	B (10 mg/kg) q3w + carboplatin q5w	PFS
NCT01091259	II	35	Recurrent¶	B (15 mg/kg) + irinotecan q3w to PD	6-months PFS
NCT01838538	II	54	Malignant ascites	CP q3w × 6 + HIPEC cisplatin q2w × 4 ± B after HIPEC	RR
NCT01031381	II	50	Recurrent¶	Everolimus qd + B q2w	PFS
NCT01735071§	II	74	First recurrence; platinum sensitive	Arm 1: B (15 mg/kg) + trabectedin q3w to PD; arm 2: B(10 mg/kg) q2w + carboplatin + trabectedin × six cycles → maintenance B (15 mg/kg) + trabectedin to PD	PFS
NCT01305213§	II	110	Recurrent or persistent	B ± fosbretabulin tromethamine q21d	PFS

†Estimated enrollment.
‡Defined as a patient completing at least 4 cycles of combination therapy regardless of delay or dose modification.
§Indicates a randomized trial.
¶Include platinum-sensitive and -resistant disease.
AE: adverse event; B: Bevacizumab; CP: Carboplatin/paclitaxel; (C)RR: (Complete) response rate; HIPEC: Hyperthermic intraperitoneal chemotherapy; IDS: Interval debulking surgery; PD: Progressive disease; PDS: Primary debulking surgery; PFS: Progression-free survival; PLD: Pegylated liposomal doxorubicin.

achieved statistical significance, the largest between group point difference was 6.1, suggesting only a small effect [45].

With recent data suggesting improved PFS and OS with dose dense (dd) paclitaxel [31], GOG 262 compares weekly versus q3w of paclitaxel with carboplatin treatment with and without concurrent and maintenance bevacizumab in stage II–IV EOC [12]. Given the option, the majority of patients chose to receive bevacizumab during their course of treatment (dd: 84.1%; q3w: 83.5%). With a median follow up of 25 months, no difference in PFS was seen in the overall cohort, although a subgroup analysis (stratifying patients by bevacizumab status) suggested a 4-month median PFS benefit in those receiving weekly paclitaxel without bevacizumab (HR: 0.596; 95% CI: 0.369–0.958; p = 0.033). No benefit was seen for patients receiving bevacizumab with this more intense regimen (HR: 1.058; 95% CI: 0.86–1.31; p = 0.6). Interestingly, the median PFS of the almost 16% receiving dd paclitaxel without bevacizumab was nearly equivalent to that of the cohort receiving standard chemotherapy with bevacizumab (14.2 vs 14.92 months) [12].

Several ongoing Phase II and III trials are evaluating the utility of bevacizumab in the first-line management of EOC (Tables 5 & 6). GOG 252 compares the use of bevacizumab with intravenous or intraperitoneal chemotherapy in upfront management of stage II–IV EOC, PPC or FTC (NCT00951496). Another study aims to determine the optimal duration of consolidative bevacizumab after treatment with carboplatin and paclitaxel (NCT01462890). Clinical and biological prognostic factors are also being investigated in patients receiving bevacizumab in the first-line setting (NCT01706120). Results of these large-scale studies are eagerly anticipated.

Recurrent epithelial ovarian cancer

Phase II

Given the majority of patients with ovarian cancer will experience a recurrence of their disease, multiple studies have focused on the use of bevacizumab in the recurrent setting (Tables 2 & 4) [21,27–30,32–39,46]. In one study, 30% of platinum resistant patients treated with PLD and bevacizumab experienced a response, although the same percentage did not tolerate the protocol dosing of bevacizumab (15 mg/kg, q21d) [35]. Another study of heavily pretreated patients with EOC used weekly bevacizumab (2 mg/kg) with PLD, achieving a 33% ORR [33].

Taxanes have also been investigated in combination with bevacizumab with ORRs at or above 50%. In one study, bevacizumab with docetaxel achieved a response in nearly 60% of patients with a 4.8 month median duration of response [37]. Another Phase II trial revealed an ORR of 50% in patients receiving weekly albumin-bound paclitaxel with bevacizumab with less than 10% of patients experiencing grade 3 or 4 HTN [38]. Bevacizumab has also been evaluated in combination with several other chemotherapeutic agents including cyclophosphamide [28,32], oxaliplatin/gemcitabine [46], PLD/carboplatin [36], pemetrexed [39] and topotecan [34].

It is difficult to fully delineate the benefit of bevacizumab in combination with chemotherapy in several of these studies given the non-randomized study design and lack of contemporary comparative arm.

Phase III

Phase III trials have evaluated the efficacy of chemotherapy combined with bevacizumab in both the platinum-sensitive and resistant settings (Table 2) [8,9]. Bevacizumab was evaluated in the management of recurrent, platinum-sensitive disease in the OCEANS trial. Patients received carboplatin (AUC 4) with gemcitabine (1000 mg/m^2, day 1 and 8) ± bevacizumab (15 mg/kg) q3w followed by bevacizumab or placebo maintenance until progression [8]. With a superior ORR (78.5 vs 57.4%, HR 0.534; p < 0.0001), bevacizumab prolonged the median PFS by 4 months (12.4 vs 8.4; HR: 0.484; 95% CI: 0.388–0.605; p < 0.0001) [8]. The final analysis demonstrates there was no OS benefit to the addition of bevacizumab (HR: 0.952; 95% CI: 0.771–1.176), although a high percentage of patients received post-progression treatment regimens (91.3% placebo, 88.8% bevacizumab) and 44% of patients, randomized to placebo, received bevacizumab in subsequent courses of therapy [47]. Both factors likely have an impact on OS results.

The AURELIA trial evaluated investigators' choice standard of care chemotherapy (PLD, topotecan or weekly paclitaxel) with and without bevacizumab in women with recurrent, platinum-resistant EOC [9]. Given the GIP experience in other studies, women who had received >2 prior regimens, had a history of bowel obstruction or had evidence of rectosigmoid involvement were excluded from participation. Bevacizumab was dosed 10 mg/kg q2w or 15 mg/kg q3w with treatment continuing until progression. At this point, those not receiving bevacizumab were allowed to cross over to bevacizumab monotherapy [9]. Patients randomized to bevacizumab plus chemotherapy (BEV-CT) received a median of six cycles compared with three in the patients randomized to chemotherapy alone (CT). While a significant PFS (HR: 0.48; 95% CI: 0.38–0.60; p < 0.001) and RR (30.9 vs 12.6%; p < 0.001) benefit was seen in those receiving bevacizumab, no significant OS improvement was attributed to the bevacizumab-

containing regimen (HR: 0.85; 95% CI: 0.66–1.08, 2-sided log rank p = 0.174) [9]. Important to consider, 40% of patients randomized to CT crossed over to bevacizumab monotherapy at time of progression, receiving a median 4.5 cycles [48]. This significant crossover must be considered when evaluating these results as it has the potential to mask an OS benefit. Exploratory OS subgroup analyses support the use of weekly paclitaxel with bevacizumab (22.4 vs 13.2 months; HR: 0.65; 95% CI: 0.42–1.02) compared with PLD (13.7 vs 14.1 months; HR: 0.91; 95% CI: 0.62–1.36) or topotecan (13.8 vs 13.3 months; HR: 1.09; 95% CI: 0.72–1.67) [48]. Grade 3 or greater AEs occurred in 58 versus 54% in the BEV-CT and CT groups, respectively [49]. While HTN, proteinuria and neuropathy were more common in the BEV-CT group, the CT group experienced higher incidences of dyspnea, vomiting, abdominal pain and fatigue – disease-related symptoms likely indicating inferior disease control [49]. A follow up QOL analysis indicated the addition of bevacizumab resulted in a greater number of patients with a ≥15% improvement in abdominal/GI symptoms (21.9 vs 9.3%, 12.7% difference; 95% CI: 4.4–20.9; p = 0.002) [50].

The role of bevacizumab after disease progression has been evaluated in other solid tumors [51,52] and now is gaining an audience in EOC. MITO16/MANGO2b (NCT01802749) evaluates continuation or reinstitution of bevacizumab at disease progression in patients previously receiving a bevacizumab-containing first-line regimen. GOG 213 (NCT00565851) is also evaluating bevacizumab in the recurrent setting, using carboplatinum/paclitaxel or gemcitabine with and without bevacizumab followed by secondary cytoreduction for platinum-sensitive disease. The PRECISION trial is focusing on patient-reported symptoms and QOL in women under observation or receiving bevacizumab as maintenance therapy for a platinum-sensitive first recurrence of EOC, PPC or FTC (NCT01422265). Several other observational studies are currently ongoing to evaluate clinical experience with bevacizumab [53].

AES

Phase III studies of bevacizumab in both the upfront and recurrent EOC setting show activity in these populations and suggest a PFS benefit [8–11]. Overall, bevacizumab is well tolerated in most patients with most AEs mild in severity. Many AEs are a result of disruption of VEGF activity in normal physiology. HTN, whether new onset or exacerbation of existing disease, is the most commonly reported AE attributed to bevacizumab [54]. In Phase III EOC trials, rates of ≥grade 2 HTN in patients treated with bevacizumab range from 16.5 to 22.9%, with the highest level seen in patients receiving upfront and maintenance bevacizumab in GOG 218 [9–11]. Although treatment strategies have not yet been defined, Randall *et al.* suggest initiating anti-hypertensive therapy for grade 2 HTN or escalating chosen therapy for grade 3 HTN with the caveat of holding bevacizumab for patients with symptomatic HTN. Bevacizumab should be permanently discontinued for grade 4 HTN [54]. Although the precise mechanism of bevacizumab-induced HTN is unknown, several hypotheses exist, including VEGF inhibition causing decreased nitrous oxide and subsequent vasoconstriction [55], or decreases in capillary density resulting in increases in systemic vascular resistance [56].

Despite occurring in bevacizumab-treated patients with a variety of solid tumors, the premature termination of the Cannistra trial brought significant attention to GIPs and ovarian cancer. A meta-analysis of 12,294 patients from 17 randomized controlled trials (RCT) reported a GIP incidence of 0.9% in those receiving bevacizumab [57]. Another meta-analysis of fatal AEs (FAE) in RCTs reported an overall incidence of 2.9% in those treated with bevacizumab; hemorrhage (23.5%), neutropenia (12.2%) and GIP (7.1%) were the most common causes of death [58]. Again, questions remain as to the precise mechanism behind this increased risk, but studies suggest intestinal wall disruption as tumors regress, impaired healing after surgery or inadequate blood flow due to vasoconstriction [59]. Other AEs associated with bevacizumab include proteinuria, reversible posterior leukoencephalopathy, osteonecrosis of the jaw, VTE and ineffective wound healing/necrotizing fasciitis [14].

Cost–effectiveness

Given improvements in PFS without persistent OS benefits, a significant question surrounds the cost–effectiveness of bevacizumab in the management of EOC. A cost–effectiveness analysis of patients enrolled in GOG-218 reported that each progression-free life year gained came at a cost of US$401,088 [60]. More recently, a QOL-adjusted cost–effectiveness analysis of GOG-218 data demonstrated an incremental cost–effectiveness ratio (ICER) of $757,939 per quality-adjusted progression-free year (QA-PFY) for the bevacizumab-throughout group compared with the standard chemotherapy arm. In their models, adjusting for QOL increased ICERs by more than $100,000/QA-PFY for bevacizumab-containing arms, suggesting the incorporation of prospectively collected QOL data can have a significant impact on cost–effectiveness analyses of these larger trials. In addition, when OS was used as an effective endpoint instead of PFS, bevacizumab-throughout had an ICER of

$2,467,745/QA life year compared with CT [61]. Chan and colleagues modeled the cost–effectiveness of bevacizumab based on ICON7 data [62]. Previously mentioned, an OS benefit was seen for a high-risk cohort of women with EOC (suboptimally debulked stage III disease and stage IV disease) in ICON7 [10]. Chan *et al.* subsequently reported an ICER of $167,771 per life year saved in this particular population [62]. Alternatively, Barnett *et al.* assessed the cost–effectiveness of biomarker-directed bevacizumab therapy [63] using a genetic single nucleotide polymorphism (SNP) previously reported to predict bevacizumab response in patients with renal and pancreatic cancer [64]. This SNP (found in VEGFR-1) was significantly associated with both OS (HR: 2.1; 95% CI: 1.45–3.06; p = 0.00014) and PFS (HR: 1.89; 95% CI: 1.31–2.71; p = 0.00081) in patients with metastatic pancreatic cancer and PFS (HR: 1.81; 1.08–3.05; p = 0.033) in those with metastatic renal cell carcinoma [64]. SNP-directed treatment resulted in an ICER of $129,000/QA life year; a number closer to the $100,000 typically used as the standard threshold for determining cost–effectiveness [63]. Investigators continue to actively search for biomarkers to direct therapy and assess response for women with EOC. Currently accepted markers for assessing response to treatment in EOC, such as CA125, may not be as reliable when anti-angiogenic therapy is utilized [37,65]. A SNP analysis and evaluation of plasma angiogenic growth factors from patients treated on GOG218 is ongoing. Promising biomarkers will need to be validated further in prospective trials as integrated, and ultimately integral, biomarkers before they can be utilized to direct therapy. Integrated refers to markers that have been identified in preexisting studies and are being validated and hypothetically tested for use in future trials. In contrast, integral markers are essential to the design of the trial, and must be performed in real time as they utilized to determine eligibility, stratification, disease monitoring and/or study endpoints [66].

Conclusion

The Phase III trials of bevacizumab (GOG 218, ICON7, OCEANS and AURELIA) indicate that concurrent and maintenance therapy may have a role in the treatment of women with advanced and recurrent ovarian cancer [8–11]. These trials have demonstrated that bevacizumab-throughout conferred consistent PFS benefits, and in select patients, improved OS. Controversy exists regarding timing of bevacizumab administration; some advocating for use in the first-line setting and others withholding bevacizumab until recurrence. The current data does not inform this issue. Our practice is to have a risk–benefit discussion of bevacizumab with patients to review efficacy, the unique AE profile, additional treatment time and financial considerations as an integral part of treatment planning. This comprehensive approach provides valuable information that allows patients to understand the risks and benefits, or 'trade-offs', of bevacizumab therapy while promoting personalized treatment decisions.

Additional studies are ongoing to evaluate optimal dosing duration, the benefit of bevacizumab beyond progression; and biomarkers to direct anti-angiogenic therapy. With the emerging evidence of other promising anti-angiogenic agents, including tyrosine kinase inhibitors and novel therapeutics (poly [ADP-ribose] polymerase inhibitors), additional research must be performed to ascertain how these agents should be used (alone, in combination with bevacizumab, or sequentially). However, as of yet, no FDA approval has been granted for the use of bevacizumab (or any other anti-angiogenic therapy) in EOC, in part due to the lack of demonstrable OS benefit of these agents. Several previous trials showing OS benefits in EOC had limited therapy crossover, perhaps allowing for this transparent OS advantage [67]. In Europe, however, the European Union Committee for Medicinal Products for Human Use (CHMP) has recently recommended approval for the use of bevacizumab in combination with chemotherapy for the treatment of platinum-resistant EOC [68]. For now, given the unique adverse effect profile, increased cost and additional treatment time, a risk–benefit discussion of bevacizumab, including financial considerations, is an integral part of treatment planning in the management of EOC. Not to be overlooked, patient preferences are also an important consideration during clinical decision-making.

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Executive summary

- Angiogenesis is a prime target for epithelial ovarian cancer (EOC) therapies given *in vitro* and clinical data.
- Bevacizumab is a recombinant monoclonal antibody against VEGF and has been studied in multiple solid tumors, including EOC as a single agent and in combination with chemotherapy.
- In EOC, many Phase II and III studies have been performed with consistent progression-free survival benefits and in select patients improved overall survival.
- Although uncommon, severe adverse events associated with bevacizumab include gastrointestinal perforations, encephalopathy, thromboembolic events and hemorrhage.
- The cost–effectiveness of bevacizumab is actively being studied; biomarker-directed therapy may help to reduce treatment-related costs.

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