

Review

Incorporation of anti-angiogenesis therapy in the management of advanced ovarian carcinoma—Mechanistics, review of phase III randomized clinical trials, and regulatory implications



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HIGHLIGHTS

- To date, eight phase 3 randomized trials using anti-angiogenic agents have shown positive results in ovarian cancer.
- Anti-angiogenesis agents active in ovarian carcinoma include monoclonal antibodies as well as drugs that inhibit receptor tyrosine kinases.
- Both vascular endothelial growth factor (VEGF)-dependent and non-VEGF-dependent angiogenic pathways may be targeted in ovarian cancer.

ARTICLE INFO

Article history:

Received 31 October 2013

Accepted 25 November 2013

Available online 3 December 2013

Keywords:

Angiogenesis
Bevacizumab
Pazopanib
Cediranib
Trebananib
Nintedanib

ABSTRACT

Despite survival gains achieved nearly two decades ago with combination platinum- and taxane-based intravenous chemotherapy, overall survival curves have remained relatively unchanged during the 21st century using newer cytotoxic agents. Although combined intravenous–intrapertoneal (IV–IP) chemotherapy is promising, tolerability remains a significant issue. An emphasis has been placed on exploring dose dense schedules and targeted agents. Vascular endothelial growth factor (VEGF) has emerged as an important therapeutic target in several solid tumors including ovarian carcinoma. The monoclonal antibody, bevacizumab, binds VEGF, thus preventing activation of the VEGF receptor (VEGFR) leading to inhibition of tumor angiogenesis. To date eight phase 3 randomized controlled trials incorporating anti-angiogenesis therapy in the treatment of newly diagnosed and recurrent ovarian carcinoma have met their primary endpoints. Four of these trials included bevacizumab and were reported from 2010 to 2012. During 2013, the other four studies were reported, each studying one of the following novel anti-angiogenesis agents: pazopanib, cediranib, trebananib, and nintedanib. Importantly, none of these drugs have been approved by the United States Food and Drug Administration (US FDA) for the treatment of ovarian cancer. The purpose of this review will be to highlight both VEGF-dependent and non-VEGF dependent angiogenic pathways in ovarian cancer and discuss the phase 3 experiences and regulatory implications of targeting the tumor microenvironment with anti-angiogenesis therapy.

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Introduction

Epithelial ovarian cancer (EOC) accounts for 25% of all malignancies affecting the female genital tract, and is the most lethal gynecologic malignancy. In the United States alone, a projected 22,240 new cases will be diagnosed in 2013, with 14,030 deaths [1]. Worldwide, there are 225,000 new cases diagnosed annually and 140,000 deaths. Advanced stage EOC is managed with surgical cytoreduction, followed by platinum- and taxane-based combination chemotherapy on a 21-day schedule [2]. In some centers, chemotherapy is administered via a combined intraperitoneal–intravenous (IV–IP) route. Over the past 12 months, a weekly, dose-dense schedule for paclitaxel has become increasingly popular. Unfortunately, the greatest hurdle is acquired drug resistance leading to recurrent disease through selection of platinum-resistant clones [3]. For patients with platinum-refractory and platinum-resistant tumors, available cytotoxic options are associated with limited responses and clinically insignificant gains in survival.

Importantly, *platinum-resistance* may be a surrogate concept reflecting *chemotherapy-resistance*. Even for those patients with potentially platinum-sensitive disease (relapse 6–12 months following completion of therapy) and those with ‘very’ platinum-sensitive tumors (relapse beyond 12 months), retreatment with platinum is unlikely to result in a durable remission. The development of tolerable and active non-cytotoxic therapies has emerged as a leading priority in ovarian cancer (OC) pharmacologic research programs. Molecular (or biologic) therapies may target specific biomarkers in an enriched population, or those non-specific, ubiquitous, processes found in the cancer microenvironment. Tumor neovascularization and angiogenesis constitute cardinal processes amenable to pharmacologic perturbation.

There are now 8 positive phase 3 randomized clinical trials in EOC involving five unique anti-angiogenesis agents. In this review we discuss the development of anti-angiogenesis therapy and consider the oncologic and regulatory implications of the phase 3 experiences in detail. It should be recognized that despite the remarkable progress that has been gained in this field, to date no anti-angiogenesis drugs approved by the US FDA lists EOC as an indication on the label.

Tumor microenvironment

Platinum resistance is well defined and relies on altered drug metabolism, repair of sub-lethal DNA damage, and inhibition of apoptosis [4,5]. The concept of platinum-sensitive recurrence catalyzed interest in alternate cellular interactions explaining sensitivity with platinum re-challenge, with the tumor microenvironment emerging as an active area of investigation.

Metastatic intra-peritoneal dissemination of OC relies on the ability of floating cells to survive, proliferate and disseminate in the absence of a solid scaffold and vascular structures [6]. These processes are dependent on cytokines, extracellular matrix proteins, growth factors, proteolytic enzymes, and inflammatory cells [4,6–10]. Ultimately, angiogenesis and tumor neovascularization herald cancer growth and dissemination.

Animal models illustrate the ability of intra-peritoneal OC cells to attach to avascular areas, subsequently forming vascular deposits, with rich infiltrates containing lymphocytes, macrophages, fibroblasts, and pericytes [9]. Additional studies have shown that angiogenesis is essential for tumor invasion and metastasis, and is required for tumor growth

beyond 1–2 mm [11,12]. This process requires the recruitment of vasculature, circulating endothelial cells, and pro-angiogenic mediators.

Angiogenesis and discovery of VEGF

In 1939, Ide and Warren were the first to suggest that tumors release specific factors capable of stimulating the growth of blood vessels [13]. In 1971, the American cellular biologist and pediatric surgeon, Moses Judah Folkman (1933–2008, Fig. 1), published his hypothesis in the *New England Journal of Medicine* that tumor growth is angiogenesis dependent and that inhibition of angiogenesis could be therapeutic [14]. This landmark manuscript also introduced the term anti-angiogenesis to mean the prevention of new vessel sprouts from being recruited by a tumor. Folkman's hypothesis predicted that tumors would be unable to grow beyond a microscopic size of 1–2 mm³ without recruitment of new capillary blood vessels. This revolutionary paradigm about cancer has been validated over the years as Folkman and others have isolated the proteins and unraveled the molecular cascade that regulates angiogenesis. From 1980 to 2005, Folkman's laboratory discovered 12 angiogenesis inhibitors. In the 1980s, investigators at Genentech, Inc in South San Francisco and at the University of California San Francisco independently discovered, purified, and sequenced vascular permeability factor which was subsequently named, vascular endothelial growth factor (VEGF) [15].

The Genentech group, led by Napoleone Ferrara, was the first to isolate and clone VEGF [16–20]. All members of the VEGF family of ligands stimulate cellular responses by binding to tyrosine kinase receptors



Fig. 1. Moses Judah Folkman (1933–2008). American cellular biologist and pediatric surgeon who advanced his theory of angiogenesis and anti-angiogenic therapy of cancer.

Table 1
Phase 2 studies of anti-angiogenesis therapy in ovarian carcinoma.

Study	N	Eligibility	Regimen	Grade 3/4 hematologic AEs	Grade 3/4 non-hematologic AEs	RR	Median PFS (months)	Median OS (months)
Burger [44]	62	Persistent or recurrent OC; 2–3 prior CT regimens; GOG PS 0–2	Bevacizumab 15 mg/kg IV q3 weeks	Neutropenia	HTN (10%); GI events (7%)	21% (RECIST criteria)	4.7	17
Cannistra [45]	44	Platinum resistant recurrent OC; 2–3 prior CT regimens; ECOG PS 0–1	Bevacizumab 15 mg/kg IV q3 weeks		GI perforation (11%); SB obstruction (9%); HTN (9%); fatigue (5%)	16% (RECIST criteria)	4.4 (95% CI 3.1–5.5)	10.7
Garcia [46]	70	Recurrent OC; 1–3 prior CT regimens; PS 0–1	Bevacizumab 10 mg/kg IV q2 weeks + C	Lymphopenia	HTN (11%); pain (13%); GI obstruction (5%); hyponatremia (4%); emesis (4%)	24% (RECIST criteria)	6-month PFS, 56%	16.9
Tillmanns [47]	48	Recurrent, platinum resistant OC; ≥1 prior CT regimen; ECOG PS 0–1	Bevacizumab 10 mg/kg IV q2 weeks + Nab-T	Neutropenia, anemia	Bowel obstruction (4%); nausea (4%); nose bleed (4%); bowel obstruction (3.8)	30.8% (RECIST)	8.3	16.5
Gonzalez-Martin [48]	189	Stages 2B–4 or stage 1/2A (clear cell, grade 3) ovarian cancer	Bevacizumab 7.5 mg/kg IV day 1 + T + carboplatin (AUC 6)	Febrile neutropenia (0.5%)	Neuropathy (5%), GIP (0.5%)	84.6% (RECIST)	23.7 (95% CI 19.8–26.4)	NR
Matulonis [49]	47	Recurrent OC; 1–2 prior CT regimens; ECOG PS 0–1	Cediranib 30 mg PO daily		HTN (46%); fatigue (24%); diarrhea (13%); hyponatremia (7%)	30% (RECIST and CA 125)	5.2	NR
Karlán [50]	161	Recurrent OC; 1–3 prior CT regimens; GOG PS 0–1	T + P	Neutropenia	Hypokalemia (15%), neuropathy (10%), dyspnea (9%)	27% (RECIST and CA 125)	4.6 (1.9–6.7)	20.9
			T + AMG 386 (10 mg/kg)			37%	7.2 (5.3–8.1) HR 0.76 (0.49–1.18) p = 0.225	22.5
			T + AMG 386 (3 mg/kg)			19%	5.7 (4.6–8.0) HR 0.75 (0.48–1.17) p = 0.207	20.4
Gotlieb [51]	55	Recurrent OC symptomatic ascites; up to 11 prior CT regimens	Placebo vs. aflibercept 4 mg/kg IV q2 weeks		Dyspnea (20%); fatigue (13%), dehydration (10%), GIP/F (10%); HTN (7%); VTE (7%)	Mean TTRP 55.1 vs. 23.3 days (10.6–53.1) p = 0.0019 RPRR 62.5%	6.3 vs. 7.3 weeks	16 vs. 12.9 weeks HR 1.01 (0.56–1.86)
Colombo [52]	16	Platinum resistant recurrent OC patients requiring 3 or more paracentesis; ECOG PS 0–2	Aflibercept 4 mg/kg IV q2 weeks		HTN (6%); GIP (6%); weight loss (6%); emesis (12.5%); bowel obstruction (31%); edema (12.5%)	31% (CA 125)	59.5 days (41.0–83.0)	92 days (58–NR)
Freidlander [53]	36	Recurrent OC; ≤2 prior CT regimens; ECOG PS 0–1	Pazopanib 800 mg PO daily		ALT elevation (8%); AST elevation (8%); diarrhea (8%)	31% (CA 125)	17% at 6 months (6–33%)	NR
Ledermann [54]	83	Recurrent OC; recent response to 2nd or further line CT; ECOG PS 0–1	Nintedanib 250 mg PO BID or placebo	Neutropenia; thrombocytopenia	ALT elevation (9.3%); GGT elevation (44.2%); anemia (9.3%); fatigue (4.6%); emesis (4.6%)	N/A	16.3% at 36 weeks; HR 0.65 (0.41–1.02; p = 0.06)	HR 0.84 (0.51–1.39; p = 0.51)

HTN = hypertension; CT = chemotherapy; C = cyclophosphamide 50 mg PO daily; Nab-T = nab-paclitaxel 100 mg/m² on days 1, 8 and 15; T = weekly paclitaxel; NR = not reported; GIP = gastrointestinal perforation; P = placebo; TTRP = time to repeat paracentesis; F = fistula; VTE = venous thromboembolism; RPRR = repeat paracentesis response rate; NR = not reached; ECOG = Eastern Cooperative Oncology Group; PS = performance status; N/A = not reported.

on the cell surface causing dimerization and activation through transphosphorylation. The three main subtypes of the vascular endothelial growth factor receptors (VEGFR) are numbered VEGFR-1, VEGFR-2, and VEGFR-3. Typically membrane-bound, the VEGFRs have an extracellular portion consisting of seven immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing the split tyrosine kinase domain. Through alternative splicing, cytoplasmic VEGFRs can also exist.

In 1993, Ferrara’s laboratory reported that anti-VEGF monoclonal antibodies exerted a potent inhibitory effect on the growth of 3 tumor cell lines injected subcutaneously into nude-mice [21]. Interestingly, the antibody had no effects on the cell lines in vitro. Several parallel studies confirmed in vivo growth inhibition, which correlated with decrease tumor microvessel density and inhibition of tumor angiogenesis [21–25]. Ultimately, bevacizumab, a humanized monoclonal antibody directed against VEGF, was synthesized, and used in early proof of concept studies. Bevacizumab neutralizes VEGF-A and blocks its signal transduction through both VEGFR-1 and VEGFR-2, as demonstrated by the inhibition of VEGF-induced cell proliferation, survival permeability, nitric oxide production, migration and tissue factor production.

The first phase I clinical trial assessing the safety, pharmacokinetics and tolerability of bevacizumab was conducted in 1997 [26]. In the United States, bevacizumab gained FDA approval in February of 2004, following a randomized double-blind phase III clinical trial assessing the impact of addition of bevacizumab to irinotecan, 5-fluorouracil, and leucovorin (IFL) in the up-front treatment of patients with unresectable metastatic colorectal cancer [27]. Additional phase III trials were conducted in metastatic non-small cell lung cancer [28], metastatic breast cancer (mBC) [29], renal cell carcinoma, and recurrent glioblastoma multiforme, all of which met their primary endpoints, thus supporting USFDA approval of bevacizumab for these indications

[30]. Although, the accelerated approval of bevacizumab in mBC was ultimately revoked in 2011 because of lack of OS advantage, moving forward, investigators focused their efforts on the anti-angiogenesis terrain of EOC and peritoneal carcinomas.

Targeting angiogenesis pathways

Currently, the VEGF pathway is the most widely studied angiogenic pathway in carcinogenesis, and is comprised of VEGF-A (also known as VEGF) and the two receptor tyrosine kinases, VEGFR1 (Flt-1) and VEGFR2 (Flk-1) (Fig. 2) [19]. Principally, the angiogenic and permeability properties of VEGF are mediated by VEGFR2 binding [19]. Strategies to block the VEGF pathway include ligand binding and sequestration as well as inhibition of the intracytoplasmic tyrosine kinase domain.

The angiopoietin (Ang) pathway is a parallel VEGF-independent pathway with direct effects on the tumor microenvironment and vascular remodeling. Angiopoietin 1 (Ang1) is involved in stabilization of endothelial junctions, while angiopoietin 2 (Ang2) promotes endothelial sprouting; these ligands increase blood vessel density (Fig. 2). To target this pathway, a novel peptibody (trabectedin, formerly AMG 386) has been developed and successfully studied in clinical trials [31].

Fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) have also emerged as targets in the angiogenic cascade. PDGF binding to the PDGF receptor β (PDGFR-β) is essential for pericyte recruitment and blood vessel maturation [32]. The FGF family activates angiogenesis via interaction with FGF receptors 1 and 2 [33]. It is thought that signaling via these alternate pathways (PDGF, FGF) may mediate resistance to VEGF inhibition, supporting a multi-targeted approach [34–38]. In response to receptor–ligand binding, downstream signaling pathways, PI3K-Akt-mTOR and Ras-MEK-Erk, are activated

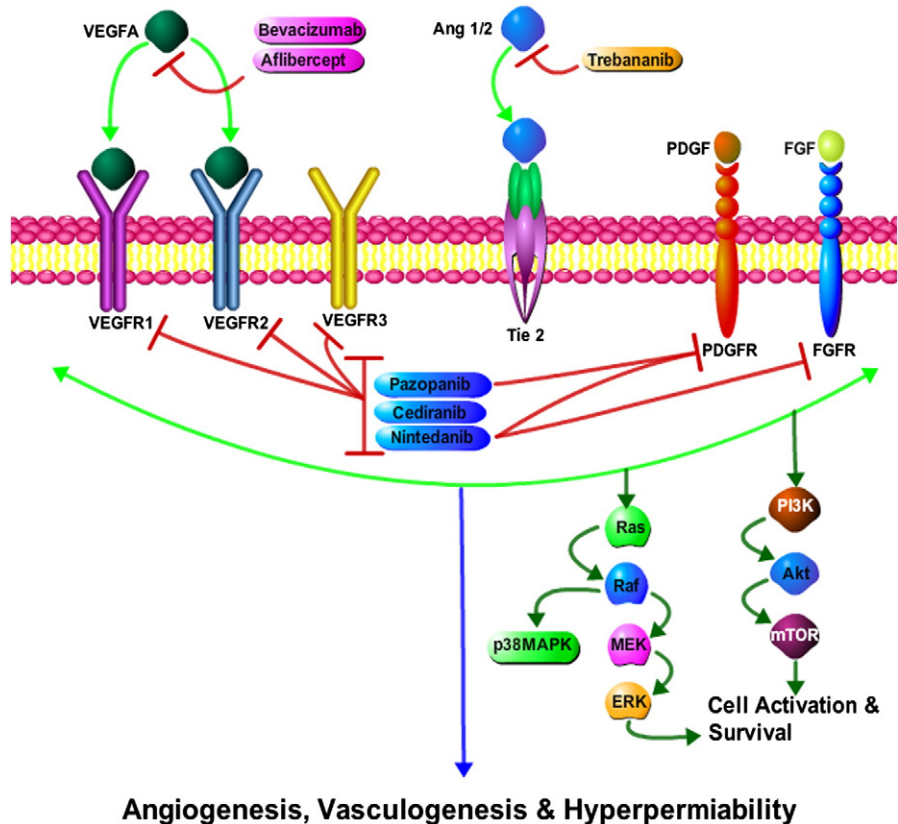


Fig. 2. The angiogenic cascade and anti-angiogenic strategies in ovarian carcinoma. Both VEGF and non-VEGF dependent pathways are noted. Specifically, the general mechanism of action of the anti-angiogenic agents reviewed is depicted. Figure designed by RN Eskander and KS Tewari and created by RN Eskander using Protein Lounge software.

and have been identified as potential targets for drug development [39,40].

Phase 2 studies

The tumor vasculature in EOC is highly disorganized and leaky, with relatively poor blood flow, perpetuating tumor hypoxia, growth factor expression, and potentially interfering with delivery of cytotoxic chemotherapy [41]. Not surprisingly, the first efforts to study anti-angiogenesis therapy in EOC occurred in populations with recurrent disease. Bevacizumab has been the most studied anti-angiogenic agent. The immediate mechanism of action of bevacizumab is to bind and sequester VEGF, depriving the VEGFR of its ligand, inhibiting endothelial, and possibly tumor cell activation and proliferation [42]. In addition to nutrient deprivation, VEGF inhibition has induces vascular normalization and restores normal structure, function, and flow to the disorganized, leaky vessels characteristic of malignant tumors. These changes are hypothesized to result in improved delivery of oxygen, nutrients, and cytotoxic chemotherapy to the tumor [43].

Table 1 details notable phase 2 studies of anti-angiogenesis therapy in EOC [44–54]. Of the 6 molecules studied, 5 have been advanced to the phase 3 arena. These include bevacizumab, pazopanib, cedirinab, trebananib, and nintedanib (formerly BIBF 1120). VEGF-trap (Aflibercept) is a fusion protein that prevents VEGF receptor binding. In contrast to the antibody-based binding strategy used by bevacizumab, VEGF-trap incorporates the second binding domain of the VEGFR-1 receptor and the third domain of the VEGFR-2 receptor [55]. By fusing these extracellular protein sequences to the Fc segment of a human IgG backbone, developers created a chimeric protein with very high VEGF binding affinity, binding all isomers of the VEGF-A family [55,56]. VEGF-trap has been approved in the United States and in Europe for treatment of metastatic colorectal carcinoma and wet macular degeneration. It has been studied in two phase 2 studies involving EOC patients with symptomatic malignant ascites [51,52] (Table 1). In the double-blind, placebo-controlled, parallel-group trial by Gotlieb et al, the mean time to repeat paracentesis (primary endpoint) was significantly longer with VEGF-trap than with placebo (55.1 vs. 23.3 days; difference 31.8 days, 95% CI 10.6–53.1; $p = 0.0019$) [51].

Phase 3 randomized clinical trials 1–4: GOG 218, ICON7, OCEANS, AURELIA (bevacizumab)

Based on the phase 2 experiences of Burger et al. (on behalf of the GOG), Cannistra et al., and Garcia et al., in which response rates (RR) exceeding 20% and 6-month PFS of 40–50% were documented (Table 1), bevacizumab (Avastin) was the first anti-angiogenesis agent to be advanced into the phase 3 randomized trial design for advanced EOC. To date, four pivotal trials have been completed, two in the primary setting and two for patients with recurrent disease (Table 2) [57–66].

Gynecologic Oncology Group (GOG) protocol 218 was a three-arm placebo-controlled study, with all patients receiving carboplatin and paclitaxel [58]. In the first experimental arm, patients were treated with concurrent bevacizumab (15 mg/kg) followed by placebo maintenance (bevacizumab-initiation), while in the second experimental arm, patients received concurrent and maintenance bevacizumab every 21 days for up to 16 doses (bevacizumab-throughout). A total of 1873 women with previously untreated, advanced stage, epithelial ovarian, primary peritoneal and fallopian tube cancer were enrolled at 336 institutions in 4 countries. Of these patients, 34% were optimally cytoreduced, with 40% sub-optimally debulked (residual lesions > 1 cm in diameter), and 26% had stage 4 disease. Of all patients, 19% completed the planned treatment. The median PFS was significantly prolonged in the bevacizumab-throughout arm when compared to chemotherapy alone (14.1 months vs. 10.3 months, $p < 0.0001$). Relative to control, the hazard ratio (HR) for progression or death was 0.717 (95% CI 0.625 to 0.824; $p < 0.001$) with bevacizumab throughout. Maximal

separation of the PFS survival curves for bevacizumab-throughout and the control group occurred at 15 months, with convergence at 24 months, likely indicating crossover to anti-angiogenic therapy in the management of recurrent disease. No significant difference in overall survival (OS) among the three groups was identified.

As part of GOG 218, quality of life (QOL) was evaluated using the Trial Outcome Index of the Functional Assessment of Cancer Therapy-Ovary (FACT-O TOI) survey. Questionnaires were completed before cycles 1, 4, 7, 13 and 22, as well as 6 months after completing the study therapy. The mean FACT-O TOI increased over the duration of the study, indicating improved QOL. During chemotherapy, QOL scores were slightly lower in the bevacizumab initiation and throughout groups relative to control; however, these differences were lost following completion of chemotherapy.

Assessment of adverse events (AE) identified only hypertension (\geq grade 2) as significantly more common in the bevacizumab arms, leading to discontinuation of therapy in 2.4% of subjects. The rates of other AEs including gastrointestinal fistula/perforation, proteinuria (\geq grade 3), neutropenia, thromboembolism, and wound disruptions were similar among the 3 treatment arms.

ICON-7 (International Cooperative Group for Ovarian Neoplasia) was a two-armed trial comparing carboplatin + paclitaxel (six cycles) against carboplatin + paclitaxel + bevacizumab every 3 weeks for 6 cycles, followed by 12 cycles of maintenance bevacizumab. The dose of bevacizumab (7.5 mg/kg) was half of that used in GOG 218 [59]. A total of 1528 women were randomized from 263 clinical sites from Dec. 2006 to Feb. 2009. Eligible patients were stage 1 or 2A (clear cell histology or grade 3) and stages 2B–4, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. Mature PFS data were presented at the 2010 Annual Meeting of the European Society of Medical Oncology (ESMO), with a significant improvement in PFS in the bevacizumab arm relative to control (19 vs. 17.3 months; HR 0.81, 95% CI 0.7–0.94, $p = 0.0041$). In patients at high risk of recurrence (stage 4, stage 3 with residual disease > 1 cm), the benefits of bevacizumab were magnified, with a 5.4 month improvement in PFS. AEs were reported as consistent with previous bevacizumab trials, and included hypertension, proteinuria, thromboembolic events and GI perforations.

Following 714 deaths, mature OS data for ICON-7 was recently presented at the 2013 ESMO Annual Meeting in Amsterdam [60]. There was no significant difference in OS between control and the bevacizumab containing arm (58.6 vs. 58.0 months respectively, HR 0.99, $p = 0.85$). Interestingly, the beneficial effects of bevacizumab in the subset of patients at high risk for progression (stage 4, stage 3 with residual disease > 1 cm) continued, with bevacizumab treatment resulting in a 9.4 month improvement in median OS (30.3 vs. 39.7 months; $p = 0.0072$).

To summarize, GOG 218 and ICON-7 each met their primary endpoint (PFS) concerning the investigational arms in which bevacizumab was incorporated into both the cytotoxic and maintenance phases of treatment. Several noteworthy differences between these studies included eligibility criteria, investigational arms, and drug dosing. In GOG 218, suboptimal FIGO stage 3/4 patients were initially enrolled, and following an amendment, optimally cytoreduced FIGO stage 3 patients were eligible. In ICON-7, patients with high grade or clear cell early stage cancers (stages IA–IIA) were eligible as were patients with FIGO stage 2B and greater. Additionally, GOG 218 was comprised of two investigational arms, a placebo, and a total of 22 cycles of therapy as compared to one investigational arm, no placebo, and a total of 18 cycles of therapy in ICON-7. Furthermore, GOG 218 used a bevacizumab dose of 15 mg/kg as compared to 7.5 mg/kg in ICON-7. Finally, GOG 218 contained a patient reported outcome (PRO) endpoint and ICON-7 was designed to study a high-risk subpopulation characterized by suboptimal surgery and/or stage 4 disease.

The remaining phase III bevacizumab trials were in platinum sensitive and platinum resistant recurrent EOC. OCEANS, an industry sponsored trial, evaluated the efficacy and safety of bevacizumab in the

Table 2
Phase 3 randomized trials of anti-angiogenesis therapy in ovarian carcinoma.

Trial	N	Eligibility	Arms	Grade 3–4 AEs**	1 [†] Endpoint	2 [‡] Endpoint
GOG 218 [57,58]	1873	Incompletely and completely* resected stage 3 or any stage 4; GOG PS 0-2	IV Carboplatin (AUC 5) + IV Paclitaxel (175 mg/m ²) + placebo followed by maintenance placebo Q3 weeks IV Carboplatin (AUC 5) + IV paclitaxel (175 mg/m ²) + IV bevacizumab (15 mg/kg) + placebo maintenance Q3 weeks IV Carboplatin (AUC 5) + IV paclitaxel (175 mg/m ²) + IV bevacizumab (15 mg/kg) + IV bevacizumab (15 mg/kg) maintenance Q3 weeks	HTN; (22.9%) GI events (2.6%); proteinuria (1.6%); VTE (6.7%)	Median PFS 10.3 vs. 11.2 vs. 14.1 mos. HR 0.717; 95% CI 0.625-0.824; p < 0.001	Median OS 39.3 vs. 38.7 vs. 39.7 mos. HR 0.915; 95% CI 0.727-1.15; p = 0.45.
ICON 7 [59,60]	1528	Stage 1-2A (clear cell, grade 3); stage 2B-4; ECOG PS 0-2	IV Carboplatin (AUC 5) + IV paclitaxel (175 mg/m ²) + IV bevacizumab (7.5 mg/kg) + IV bevacizumab (7.5 mg/kg) maintenance Q3 weeks IV Carboplatin (AUC 5) + IV paclitaxel (175 mg/m ²) + IV gemcitabine (1000 mg/m ²) + placebo Q3 weeks IV Carboplatin (AUC 4) + IV gemcitabine (1000 mg/m ²) + IV bevacizumab (15 mg/kg) Q3 weeks	Bleeding (1%); HTN (6%); VTE (4%); GIP (1%); Neutropenia (17%)	Median PFS 17.3 vs. 19.0 mos. HR 0.81; 95% CI 0.70-0.94; p = 0.0041.	Median OS 58.6 vs. 58 mos. HR 0.99; 95% CI 0.85-1.14; p = 0.85.
OCEANS [61]	484	Platinum sensitive recurrent ovarian cancer***; ECOG PS 0-1	IV Carboplatin (AUC 4) + IV gemcitabine (1000 mg/m ²) + placebo Q3 weeks IV Carboplatin (AUC 4) + IV gemcitabine (1000 mg/m ²) + IV bevacizumab (15 mg/kg) Q3 weeks	HTN (17.4%); proteinuria (8.5%); bleeding (5.7%) F/A; (1.6%); VTE (4%)	Median PFS 8.4 vs. 12.4 mos. HR 0.484; 95% CI 0.388-0.605; p < 0.0001.	OS data immature ORR 78.5% vs. 57.4%; p < 0.0001 DOS 10.4 vs. 7.4 months HR 0.534; 95% CI 0.408-0.698.
AURELIA [62,63]	361	Platinum resistant recurrence****; ≤ 2 prior chemotherapy regimens; no e/o rectosigmoid involvement; ECOG PS 0-2	IV Paclitaxel (80 mg/m ²) days 1, 8, 15, 22 Q 4 weeks or IV topotecan (4 mg/m ²) days 1, 8, 15 Q4 weeks or IV PLD (40 mg/m ²) Q4 weeks Chemotherapy as above plus IV Bevacizumab (15 mg/kg) Q3 weeks	HTN (20.1%); proteinuria (12.8%); F/A (2.2%); GIP (1.7%) VTE (3.4%)	Median PFS 3.4 vs. 6.7 mos. HR 0.48; 95% CI 0.36-0.60; p < 0.001.	Median OS 13.3 vs. 16.6 mos. HR 0.85; 95% CI 0.66-1.08; p = 0.174.
AGO-OVAR16 [68]	940	No evidence of progression after surgery and ≥ 5 cycles platinum-taxane therapy, FIGO II-IV	800 mg pazopanib once daily for up to 24 mos Placebo once daily for up to 24 mos	Pazopanib 26% vs placebo 11%; htn, diarrhea, nausea, headache, fatigue, neutropenia	Median PFS 17.9 vs 12.3 mos. HR 0.766; 95% CI 0.64-0.91; p = 0.0021.	First interim analysis (only 189 OS events = 20.1% of population); HR 0.994.
ICON 6 [64]	456	Platinum sensitive recurrence***; ECOG PS 0-1	Chemotherapy (choice of platinum + paclitaxel; platinum + gemcitabine; carboplatin alone Q3 weeks) + PO placebo + continued PO placebo Chemotherapy as above + PO Cedirininib 20 mg daily and maintenance PO placebo Chemotherapy as above + PO cedirininib 20 mg daily + maintenance PO cedirininib 20 mg	HTN (7%); diarrhea (5%); fatigue (20%); voice change (21%); bleeding (25%)	Median PFS ^a 9.4 vs. 12.5 mos. HR 0.57; 95% CI 0.45-0.74; p = 0.024.	Median OS ^b 17.6 vs. 20.3 mos. HR 0.70; 95% CI 0.51-0.99; p = 0.042.
TRINOVA-1 [65]	919	Recurrent ovarian cancer (PFI < 12 mos.); ≤ 3 prior anti-cancer regimens; GOG PS 0-1	IV Paclitaxel days 1, 8, 15 Q4 weeks + IV placebo weekly IV Paclitaxel days 1, 8, 15 Q4 weeks + IV trebananib (15 mg/kg) weekly	Edema (5%), ascites (20%), pleural effusion (13%)	Median PFS 5.4 vs. 7.2 mos. HR 0.66; 95% CI 0.57-0.77; p < 0.001.	ORR 29.8% vs. 38.4% (p = 0.0071) Median OS (interim analysis) 17.3 vs. 19.0 mos. HR 0.86; 95% CI 0.69-1.08; p = 0.19.
AGO-OVAR12/ LUME-Ovar 1 [66]	1366	Advanced stage (FIGO 2B-4) epithelial ovarian cancer; ECOG PS 0-2	Nintenanib 200 mg PO BID + paclitaxel (175 mg/m ²) + carboplatin (AUC 5 or 6) Q3 weeks + nintenanib 200 mg PO BID for up to 120 weeks placebo PO BID + Paclitaxel (175 mg/m ²) + carboplatin (AUC 5 or 6) Q3 weeks + placebo PO BID for up to 120 weeks	Neutropenia (44%); Anemia (14%); Thrombocytopenia (18%); diarrhea (20%); elevated ALT (15%); elevated AST (7%); HTN and fatigue (4%)	Median PFS 17.3 vs. 16.6 mos. HR 0.84; 95% CI 0.72-0.98; p = 0.0239. (RECIST & CA 125)	Not yet mature

N = number; AE = adverse events. PS = performance status; ORR = objective response rate; DOR = duration of response; e/o = evidence of; PLD = pegylated liposomal doxorubicin; PFI = progression free interval.

* = After protocol modification patients with optimally resected stage 3 disease were eligible; PFS = progression free survival; OS = overall survival; QOL = quality of life; HTN = hypertension; GIP = gastrointestinal perforation;

VTE = venous thromboembolism; F/A = fistula/abscess; ECOG = eastern Cooperative Oncology Group.

** Investigational arms.

*** = progression free interval at least 6 months.

**** = progression free interval less than or equal to 6 months.

^a = Maintenance vs. Chemotherapy only arm.

^b = control vs. bevacizumab throughout arms.

^c = control vs. bevacizumab throughout arm.

treatment of patients with recurrent, *platinum sensitive* ovarian cancer [61]. This trial was initiated in response to GOG 170D, which indicated response to single agent bevacizumab in platinum sensitive and platinum refractory disease [44]. Eligible patients were required to have histologically confirmed recurrent ovarian cancer (disease progression ≥ 6 months after completion of front-line platinum based chemotherapy), ECOG PS 0–1, and measurable disease according to RECIST version 1.0. Overall, 484 patients were randomly assigned to carboplatin/gemcitabine + bevacizumab vs. carboplatin/gemcitabine + placebo for 6–10 cycles. Bevacizumab or placebo was then continued until disease progression. Median PFS for the bevacizumab arm was superior to that for the control arm, 12.4 vs. 8.4 months, respectively (HR 0.484, 95% CI 0.388–0.605; $p < .0001$). Addition of bevacizumab significantly improved the objective response rate (ORR) (78.5% vs. 57.4%; $p < .0001$), with the majority being partial responses. At the time of final PFS analysis, the OS data were immature with 141 deaths. An additional analysis was conducted at 235 deaths where the median OS for the placebo arm was 35.2 months and the median OS for the bevacizumab arm was 33.3 months. These data remain immature. Interestingly, evaluation of treatment after disease progression indicated use of bevacizumab in 31% of subjects on the control arm, potentially confounding OS analysis. With respect to toxicity, grade 3 or higher hypertension and proteinuria occurred more frequently in the bevacizumab arm. No cases of GI perforation occurred on study or within the 30-day reporting period. Rates of neutropenia and febrile neutropenia were similar in both arms. Two patients in the bevacizumab arm experienced GI perforation after study treatment discontinuation, and outside the 30-day reporting period. Two deaths were reported on study, one in each treatment arm (acute myocardial infarction, intracranial hemorrhage).

To assess the impact of bevacizumab on oncologic outcome in patients with *platinum resistant* recurrent EOC, AURELIA, an industry sponsored trial was initiated [62,63]. This randomized, open-label phase III clinical trial compared chemotherapy (investigator's choice: weekly paclitaxel, weekly topotecan, liposomal doxorubicin) to chemotherapy plus bevacizumab at a dose of 15 mg/kg. Eligible patients had biopsy proven recurrent epithelial ovarian, primary peritoneal or fallopian tube carcinoma (disease free interval of ≤ 6 months), ≤ 2 prior anticancer regimens, no history of bowel obstruction/abdominal fistula, and no clinical or radiographic evidence of rectosigmoid involvement. Patients were treated to disease progression or unacceptable toxicity, at which point they crossed over to treatment with chemotherapy alone (bevacizumab arm) or bevacizumab alone (chemotherapy alone arm).

A total of 361 subjects were enrolled, with 7% having received prior anti-angiogenic therapy, and 27% having had a disease free interval of < 3 months. Following randomization and treatment on AURELIA, assessment of AEs showed findings consistent with prior bevacizumab containing trials, with 5 subjects (2.7%) experiencing GI perforation on the bevacizumab arm.

The addition of bevacizumab to chemotherapy nearly doubled the median PFS (6.7 vs. 3.4 months; HR 0.48, 95% CI 0.38–0.60; $p < 0.001$), with consistent findings across all subgroups analyzed. Similar to ICON-7, mature OS data were also presented at the 2013 ESMO Annual Meeting, with no significant differences noted between study arms (16.6 vs. 13.3 months; HR 0.85, 95% CI 0.66–1.08, $p = 0.174$) [63]. The study was not powered to detect a statistically significant difference in OS. Additionally, post-progression therapy was not monitored in either arm, with additional confounding by the planned post-progression cross-over to bevacizumab in the chemotherapy alone arm. Overall 72 patients (40%) initially randomized to chemotherapy alone received bevacizumab after documented progression.

In an interesting exploratory sub-group analysis, there was a more pronounced impact on OS when bevacizumab was combined with weekly paclitaxel (13.2 months (paclitaxel alone) vs. 22.4 months (paclitaxel plus bevacizumab); HR 0.65, 95% CI 0.42–1.02). This pronounced effect on OS in the bevacizumab + weekly paclitaxel arm is

consistent with pre-clinical data in orthotopic models of advanced EOC, where metronomic therapy resulted in suppression of tumor vascularity and reduction in micro-vessel density and enhanced the efficacy of alternate anti-vascular drugs [67]. Three additional studies have explored weekly dose dense chemotherapy with bevacizumab. The single arm phase II OCTAVIA study evaluated weekly paclitaxel with q21-day carboplatin and bevacizumab (7.5 mg/kg) in newly diagnosed ovarian cancer. For 189 enrolled patients, median PFS was 23.7 months with 90% completing at least six cycles of therapy (Table 1) [48]. GOG 252 (NCT00951496), a phase 3 randomized 3-arm trial for optimally cytoreduced patients, included bevacizumab (15 mg/kg) in all three arms while testing the efficacy of intraperitoneal carboplatin and weekly, metronomic paclitaxel. The trial completed accrual in November 2011 and data is maturing. Its companion piece for suboptimally debulked patients, GOG 262 (NCT01167712), was a phase 3 randomized trial specifically designed to answer the weekly, dose-dense paclitaxel question in the U.S. population. Incorporation of bevacizumab into either of the trial's two arms was left to the discretion of the treating physician. At the 2013 European Society of Gynaecological Oncology (ESGO) Biennial Meeting in Liverpool, the GOG 262 investigators reported that in the overall study ($n = 692$), weekly dose dense paclitaxel did not significantly increase PFS. These findings are in contrast to the Japanese weekly paclitaxel data and suggest that incorporation of bevacizumab abrogates the benefit observed with dose-dense therapy. This hypothesis is supported by an unplanned subgroup analysis in GOG 262 involving the 112 patients who *did not receive bevacizumab* wherein weekly dose-dense paclitaxel was associated with a 4-month improvement in PFS compared to q21-day paclitaxel (HR 0.596; 95% CI 0.369–0.958; $p = 0.033$).

Unanswered questions concerning bevacizumab include where it should be used (frontline vs. recurrence), as a single agent or in combination, dose, duration, continuation beyond progression, cost-effectiveness, and impact on PROs (i.e. QoL). With respect to the duration of therapy, one potentially important investigational arm not included in any of the studies is a maintenance-only bevacizumab arm. Additionally, in GOG 218, 24–43% of patients could potentially have continued with maintenance therapy beyond 22 cycles, and in ICON-7, 62% of patients could have potentially continued beyond 18 cycles.

Phase 3 randomized clinical trial 5: AGO-OVAR16 (pazopanib)

Pazopanib (Votrient), an oral tyrosine kinase inhibitor, exhibits its anti-angiogenic properties via inhibition of VEGFR, PDGFR and c-Kit signaling. Encouraged by the phase 2 results (Table 1), the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) launched a phase 3 randomized trial of maintenance daily pazopanib (800 mg) vs. placebo for up to two years following primary platinum-based combination chemotherapy for advanced disease (AGO-OVAR16, aka POIZE). At the 2013 Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, du Bois and colleagues reported that the trial had met its primary endpoint with pazopanib maintenance being associated with a significantly increased median PFS (17.9 months vs 12.3 months; HR 0.766, $p = 0.0021$) [68]. An interim analysis containing events from only 20% of patients did not demonstrate any survival benefit (HR 0.994). The most frequently reported grade 3/4 AEs in the pazopanib arm were hypertension, neutropenia, hepatic toxicity, and diarrhea. *The AGO-OVAR16 study represents the first phase 3 trial of pure maintenance therapy in ovarian cancer to complete accrual and meet its primary endpoint.*

Phase 3 randomized clinical trial 6: ICON-6 (cediranib)

Cediranib (Recentin) is a potent oral inhibitor of all 3 VEGFR tyrosine kinases (VEGFR1, 2, 3), with 800–5000 fold selectivity for the VEGFR2. Prior phase 2 studies indicated single agent activity in patients with recurrent EOC (Table 1), catalyzing development and completion of ICON

6, a randomized, double blind, 3-arm phase 3 trial of cediranib in patients with platinum sensitive recurrent ovarian cancer [49,64] (Table 2). Data, presented at the 2013 ESMO annual meeting, indicated a significant improvement in PFS in the cediranib maintenance arm relative to control (12.5 vs. 9.4 months; HR 0.57, 95% CI 0.45–0.74, $p = 0.00001$). Additionally, a 2.7 month improvement in OS was identified in the cediranib plus platinum based chemotherapy followed by maintenance cediranib arm. Although cediranib led to increased OS, there is no evidence to suggest that it is more active than other anti-angiogenesis agents. Post-progression therapy informs post-progression survival and likely is not uniform due to practice patterns and drug availability in different countries. *ICON 6 is the first trial to demonstrate a significant improvement in both PFS and OS using an oral VEGF tyrosine kinase inhibitor in ovarian cancer.* The most common cediranib related AE included diarrhea, nausea and fatigue.

Phase 3 randomized clinical trial 7: TRINOVA-1 (trebananib)

Trebananib (AMG 386) is an anti-angiogenic peptibody, fusing an anti-angiogenic protein to the Fc region of an antibody. This peptibody inhibits Ang1/Ang2 binding to the Tie2 receptor, resulting in inhibition of a parallel angiogenic pathway [31]. Given the promising randomized phase II data by Karlan et al. using trebananib in recurrent disease (Table 1), the phase 3 randomized, double blind trial, TRINOVA-1 (NCT01204749), was developed comparing weekly paclitaxel in combination with trebananib (15 mg/kg) given weekly or placebo in women with recurrent EOC (Table 2). The PFS data was presented at the 2013 ESMO meeting [65]. A total of 919 patients with recurrent ovarian cancer, ≤ 3 prior anti-cancer regimens, a progression free interval of < 12 months and GOG PS 0–1 were enrolled on study over a 2 year period. The study met its primary end-point, with a significant improvement in PFS in the trebananib arm relative to control (7.2 vs. 5.4 months; HR 0.66, 95% CI 0.57–0.77, $p < 0.001$). Although OS data are expected to mature in 2014, an interim analysis with 50% of deaths indicated a non-significant trend in favor of the trebananib arm (19 months vs. 17.3 months; HR 0.86, $p = 0.19$). Importantly, incorporation of trebananib was well tolerated, with reported treatment related AE of edema, ascites and pleural effusions. Traditional anti-VEGF associated toxicities were not common on the trebananib arm. Lastly, QOL was maintained on the study arm without decline in patient reported outcomes during the study period. *The TRINOVA-1 results are intriguing because this is the first phase 3 trial to effectively demonstrate improved PFS using a new anti-angiogenesis strategy in ovarian cancer, one that targets the angiopoietin axis rather than the VEGF pathway.* Currently, TRINOVA-3 (NCT01493505), a prospective, phase 3, randomized, double blind placebo controlled trial is evaluating the impact of adding trebananib to carboplatin and paclitaxel on oncologic outcome in the up front treatment of patients with advanced stage ovarian cancer.

Phase 3 randomized clinical trial 8: AGO-OVAR12/LUME-Ovar 1 (nintedanib)

Nintedanib (Vargatef) is an oral trifunctional angiokinase inhibitor with activity against VEGFR, fibroblast growth factor receptor (FGFR), and platelet derived growth factor receptor (PDGFR). In the AGO-OVAR12/LUME-Ovar 1 phase 3 randomized placebo-controlled trial, postoperative patients with newly diagnosed FIGO stage IIB–IV OC were randomized 2:1 to carboplatin and paclitaxel with and without nintedanib 200 mg twice daily [66]. Monotherapy with nintedanib/placebo was scheduled for up to 120 weeks. A total of 1366 patients were enrolled with approximately 50% of patients in each arm having no macroscopic residual postoperative tumor. At the 2013 ESGO Biennial Meeting, du Bois and colleagues reported that the trial had met its primary endpoint (using combined RESIST v1.1 plus CA-125) with the arm administering nintedanib significantly increasing PFS (HR 0.84; 95% CI 0.72–0.98; $p = 0.0239$). AEs were manageable with

chemotherapy in combination with nintedanib being primarily associated with gastrointestinal toxicity, which led to dose reductions in some patients. *This study is noteworthy for being the first to provide a valid second anti-angiogenesis strategy for newly diagnosed ovarian carcinoma.*

Cost-effectiveness

In our current health care climate, efforts have been directed to control costs while improving patient outcomes. As part of the American Recovery and Reinvestment Act of 2009, the government allocated \$1.1 billion toward comparative effectiveness research, within which falls cost-effectiveness studies. In 2011, Cohn et al. conducted a cost-effectiveness analysis of bevacizumab in the treatment of primary ovarian cancer using a decision analysis program [69]. In the paper the authors determined that, based on preliminary GOG 218 data, the addition of bevacizumab to the adjuvant treatment of patients with ovarian cancer was not effective, with an incremental cost-effectiveness ratio (ICER) per progression free-life year saved (PF-LYS) of \$479,712 in the bevacizumab initiation arm, and \$401,088 in the bevacizumab throughout arm. With variation in drug cost, the authors were able to show that a 75% reduction in drug cost, dramatically decreased the ICER per PF-LYS to a value of \$99,504 in the bevacizumab throughout arm.

In a more recent study, Markov modeling indicated that at a bevacizumab dose of 7.5 mg/kg (ICON 7 dosing), the incorporation of bevacizumab for the treatment of high-risk patients (stage 4 and suboptimally resected stage 3) resulted in an ICER of \$168,000 per quality adjusted life year (QALY) [70]. Additionally, the ICER improves to $< \$100,000$ per QALY when the cost of bevacizumab is reduced by 50%, and to $< \$50,000$ per QALY when the cost is reduced to 25% of the current value.

It should be recognized that cost-effectiveness studies for novel agents cannot be expected to perform in favor of the drug due to high cost during the marketing phase, which in part is required to offset the high expenditure required during drug development and clinical trial phases. Unless the agent can effectively reduce treatment-related toxicities, the new drug will likely be cost-ineffective. However, with time the costs of new therapies are expected to decrease, resulting in improvement in the ICER. During the early days of highly active antiretroviral therapy for acquired immunodeficiency syndrome (AIDS), drug costs appeared prohibitive, but currently protease inhibitors and zidovudine (AZT) are widely distributed in resource poor, impoverished countries in Africa.

Regulatory implications: 8 positive trials, 5 novel agents, and no approved indication

Granted that 4 of the studies were reported in 2013, with 4 other positive pivotal trials encompassing the disease spectrum from newly diagnosed to platinum sensitive and platinum resistant recurrent disease, it is remarkable that we do not have a US FDA indication for anti-angiogenesis therapy in ovarian cancer. Given the high incidence of acquired drug resistance in EOC and lack of effective therapies for recurrent disease, one approach to overcome barriers would be to cite the Orphan Drug Act, which makes provisions for granting special status to a drug or biological product to treat a rare disease or condition. In theory, *orphan drug designation* is intended to support the clinical development of new drugs in diseases affecting less than 200,000 people annually in the United States. This route provides the manufacturer with a 7 year market exclusivity on the indication if the agent is approved, during which time no direct generic competition may occur. The US FDA may provide technical and financial assistance to expedite and optimize drug development in some cases. Two issues stand in the way of FDA approval of bevacizumab for ovarian cancer: the regulatory experience in metastatic breast cancer and the inability to demonstrate an OS benefit in ovarian cancer.

Table 3
Approved indications for anti-angiogenic agents under investigation.

Anti-angiogenesis agent	US FDA	NCCN ovary	European Medicines Agency (EMA)
Bevacizumab (Avastin) [Genentech/Roche]	Metastatic CRC; metastatic RCC; recurrent glioblastoma; metastatic NSCLC	Category 3 (frontline) Category 2B (recurrent, combined with C/G)	Advanced and recurrent OC; metastatic CRC; metastatic RCC; metastatic NSCLC; metastatic BC
VEGF-trap* (Aflibercept) [Regeneron]	Wet age-related macular degeneration	–	Metastatic CRC resistant or progressed after oxaliplatin containing regimen
Pazopanib (Votrient) [GlaxoSmithKline]	Advanced soft tissue sarcoma; advanced RCC	–	Advanced soft tissue sarcoma; advanced RCC
Cediranib (Recentin) [AstraZeneca]	–	–	–
Trebananib (AMG 386) [Amgen]	–	–	–
Nintedanib (Vargatef) [Boehringer Ingelheim]	–	–	–

* = no phase 3 RCT; CRC = colorectal cancer; RCC = renal cell carcinoma; NSCLC = non small cell lung cancer; OC = ovarian cancer; BC = breast cancer; C/G = carboplatin + gemcitabine; NCCN: National Comprehensive Cancer Network.

Regular approval requires substantial evidence of clinical benefit based on prolongation of life, a better life or an established surrogate for either of the above, while *accelerated approval* is designed to hasten the delivery of products appearing to provide a benefit for serious or life-threatening illnesses lacking satisfactory treatments. Because decreasing the time on the market for potentially ineffective therapies is critical, if post-marketing studies fail to demonstrate clinical benefit, or the sponsor fails to perform required post-marketing studies with due diligence, the FDA may withdraw approval, following an open public hearing. In metastatic breast cancer, an Oncology Drugs Advisory Committee (ODAC) was convened in December 2008 and the members voted 5 to 4 against approving bevacizumab. The FDA granted accelerated approval to the drug in early 2009 but ultimately this was revoked in mid-2011 for failure of the sponsor to demonstrate OS benefit.

The question as to whether PFS is an appropriate endpoint in frontline therapeutic trials in ovarian cancer continues to be debated. Certainly, PFS is likely to correlate with OS when a large effect on PFS is seen. The problem arises when small increases in PFS may ultimately be associated with an indeterminate OS due to contamination by cross-over. Although bevacizumab is not approved in the U.S. to be used in frontline therapy for ovarian cancer, it is available for other indications (Table 3), and cross-over from non-bevacizumab arms as well as an inability to control post-progression therapy confound the ability to interpret OS in this disease. Ultimately, in chemosensitive diseases like ovarian carcinoma for which recurrence is generally the rule, post-progression survival (PPS) informs OS. If a significant difference in PFS ultimately results in a significant improvement in PPS, then OS will also be improved. This requires post-trial surveillance to monitor post-progression therapy as is being done in OCEANS.

In the past, notably in GOG protocols 111 and 172, OS was attainable, but the circumstances surrounding those trials were unique. In the mid-1990s before it could be synthesized commercially, paclitaxel was not as readily available off-study. This limited cross-over on GOG 111. On GOG 172, lack of a well-positioned and patent intraperitoneal (IP) catheter limited the ability of patients to cross-over from the non-IP arm to receive combined IV–IP therapy.

Although results from GOG 218 and ICON-7 led to approval of bevacizumab by the European Medicines Agency (EMA) in late 2011 for use in both front-line induction and maintenance therapy for advanced ovarian cancer, Roche has still not filed for approval in the US. This suggests that the FDA has provided guidance that PFS without OS is not salvageable. The National Comprehensive Cancer Network (NCCN) Guidelines have assigned bevacizumab a Category 3 recommendation for use in the first-line indicating substantial disagreement among panel members as to the clinical benefit provided by bevacizumab. Recently, the frontline trial using trebananib (TRINOVA-3) changed its primary endpoint to PFS and reduced its target to 1000 patients.

Currently there are no maintenance therapies approved for ovarian cancer in the U.S., whether cytotoxic or anti-angiogenic. If the mature OS data from the AVO-OVAR16 study continue to be non-significant, pazopanib, is likely to experience the same regulatory fate in ovarian cancer as bevacizumab in the US.

There's a clear signal that anti-angiogenic drugs reduce the likelihood of progression all across the disease spectrum. To paraphrase Carol Aghajanian, study chair of OCEANS, "These studies offer a real-world example of how the precision medicine era of cancer research is paying off in areas where no alternate approved drugs exist." Until regulatory committees accept the value of PFS and acknowledge that pure OS unencumbered by cross-over and post-progression therapy may not be measurable, we are likely to be left with many well-designed positive trials and no indication.

Conflict of interest statement

The authors have no potential conflicts of interest to disclose. Our institution (University of California, Irvine) receives a grant from the Gynecologic Oncology Group to conduct GOG clinical trials and we have enrolled patients onto GOG 218 (discussed in this paper) as well as the current GOG 3001 trial involving trebananib (drug discussed in this paper).

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