Targeting Angiogenesis
Taming the Medusa of Ovarian Cancer

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INTRODUCTION

Epithelial ovarian cancer (EOC), the fifth leading cause of cancer death among North American women, is the most lethal gynecologic cancer. More than 70% of women present with advanced disease. Even with aggressive surgery and chemotherapy, most recur and the 5-year survival rates remain at less than 50%. Cytotoxic combinations are toxic and benefit transient, leading to interest in biologic/cytotoxic

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KEYWORDS

• Angiogenesis • Ovarian cancer • Maintenance
• Vascular endothelial growth factor (VEGF) • Bevacizumab

KEY POINTS

• The process of new blood vessel formation from a preexisting vascular network is angiogenesis.
• Angiogenesis is mediated by a multitude of cooperative pathways. Drugs targeting different arms of angiogenic networks are in clinical development.
• Antiangiogenic agents have activity alone and in combination with chemotherapy across all stages of ovarian cancer.
• Predictive biomarkers remain elusive, but stratification of patients with respect to DNA repair defects and immune context are of interest for future evaluation.
• High priority areas of investigation include the role of continued antiangiogenic therapy postprogression, and the development of rational combinations with agents targeting DNA repair (namely poly(adenosine diphosphate)-ribose polymerase inhibitors) and immune checkpoint inhibitors.
combinations targeting non–cross-resistant pathways with nonoverlapping toxicities. One interesting focus of novel drug development is the tumoral microenvironment, with the best investigated thus far being the tumor vasculature. In this review, we summarize the current status and future directions of antiangiogenic therapy in EOC.

THE TUMORAL MICROENVIRONMENT

Tumors are complex, heterogenous structures—epithelial cells having undergone malignant transformation coexist with stromal and inflammatory cells, in an intricate extracellular matrix. Adding further complexity is the unrestrained cellular proliferation pathognomonic of malignant growth, which promotes an environment where demand quickly outstrips supply. This imbalance of resources forces molecular adaptation to facilitate the increased delivery of oxygen and nutrients, or enable survival despite the hostile circumstances. Only those malignant clones with the capacity to adapt and thrive continue to populate the evolving tumor, in a malignant Darwinian survival of the fittest.\textsuperscript{1}

FOCUS ON ANGIOGENESIS

Vasculogenesis or the de novo formation of a primitive vascular network, occurs primarily in embryogenesis. Once a vascular system is established, endothelial cells become quiescent; they are long lived, with only a small percentage undergoing cell division at a time. Distinct from vasculogenesis, angiogenesis is the sprouting of new vessels from preexisting ones. Its role in normal physiology is limited, because the equilibrium between activating and inhibitory angiogenic factors favors quiescence. This balance is disrupted as an early step in tumorigenic adaptation through the angiogenic switch.\textsuperscript{2} Precipitated by stimuli like tumor hypoxia, the angiogenic switch leads to the release of nitric oxide and other proangiogenic factors (Table 1). This angiogenic cascade (Table 2) enables a growing tumor to meet its ever-increasing metabolic demands, but may also facilitate metastatic dissemination.\textsuperscript{3}

RATIONALE OF ANGIOGENESIS AS A THERAPEUTIC TARGET IN EPITHELIAL OVARIAN CANCER

Pathophysiologic angiogenesis is a critical driver of nonmalignant conditions (autoimmunity and proliferative retinopathy), where antiangiogenics are already in therapeutic use.\textsuperscript{4,5} Malignant angiogenesis in tumors produces immature blood vessels, uniquely sensitive to the activity of antiangiogenics.\textsuperscript{6} This relative tumor selectivity and the potential applicability across cancer types, provide good rationale to develop antiangiogenics as anticancer therapies. A number of agents are now available, with some already established as standard therapies.\textsuperscript{7} A subset has been evaluated in the context of EOC and are described in Table 3.

Angiogenesis is vital to the normal physiology of the female gynecologic tracts.\textsuperscript{8} Studies demonstrating poor clinical outcome in ovarian cancer patients with high VEGF expression or microvessel density suggest that the same pathways are hijacked by malignant programs to facilitate tumorigenesis in these organs.\textsuperscript{9,10} Platelet-derived growth factor receptor and vascular endothelial growth factor (VEGF) receptor-2 have been implicated in the emergence of platinum resistance\textsuperscript{11} and high circulating VEGF after primary surgery correlates with lower survival.\textsuperscript{12} Such data, suggesting a relevance of angiogenesis in promoting more aggressive EOC biology, provide a strong rationale to evaluate antiangiogenics in this disease.
Early signal-seeking studies involved small, heterogeneous groups of patients. Efficacy was observed across the spectrum of EOC, as a single agent and in combination with chemotherapy, but there were concerns regarding perforation/fistula risk. Subsequent trials focused on defining the relevance of antiangiogenic therapy across different populations of EOC, incorporating strategies to mitigate toxicity risks. Outlined below are the phase III studies that guide the current use of antiangiogenics in EOC (Table 4).

### Front Line

ICON-7 randomized patients after primary surgery to carboplatin/paclitaxel followed by bevacizumab (BV) maintenance or chemotherapy alone. A 2-month nonsignificant improvement in the primary outcome of progression-free survival (PFS) was observed, with nonproportional hazards suggesting changing efficacy of BV over time (maximal efficacy at 12 months, with 15% improvement in PFS). A “high-risk” subgroup, which was defined retrospectively (FIGO IV or suboptimally debulked FIGO III) had a 5-month improvement in PFS with BV (10.5 months vs 15.9 months; hazard ratio...
small numbers of patients with clear cell or low-grade histology, or high-risk stage I to IIA disease, preclude definitive conclusions regarding efficacy of BV in these subgroups.16

Table 2
Steps of angiogenesis

<table>
<thead>
<tr>
<th>Step</th>
<th>Factors Involved</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial cell stimulation and activation</td>
<td>NO, VEGF</td>
<td>NO → vasodilation and release of VEGF; VEGF → increased vascular permeability and deposition of matrix for sprouting endothelial cells</td>
</tr>
<tr>
<td>Basement Membrane degradation</td>
<td>MMP, Urokinase bFGF, VEGF, IGF-1, Ang1</td>
<td>MMP activation → release of growth factors from the extracellular matrix → amplification of angiogenic signal. Attachment of endothelial cells and pericytes to ECM loosens to allow endothelial cells to migrate into ECM to form new blood vessels</td>
</tr>
<tr>
<td>Endothelial cell proliferation and migration</td>
<td>VEGF, Ang1, FGF Integrins, ephrins</td>
<td>Proliferating endothelial cells associate in a columns/cords to protrude into extracellular space. Cords develop lumen to become vessels</td>
</tr>
<tr>
<td>Reconstitution of basement membrane and maturation</td>
<td>PDGF, Ang1</td>
<td>Growth factors promote recruitment of support cells (pericytes and smooth muscle cells) to provide stability and foster further endothelial cell proliferation</td>
</tr>
</tbody>
</table>

Abbreviations: bFGF, basic fibroblast growth factor; ECM, extracellular matrix; FGF, fibroblast growth factor; IGF-1, insulin-like growth factor 1; NO, nitric oxide; VEGF, vascular endothelial growth factor.

Table 3
Classes of antiangiogenic drugs including mechanisms of action

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Drug Info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies (intravenous)</td>
<td></td>
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<tr>
<td>Bevacizumab (Avastin)</td>
<td>VEGF-A</td>
<td>Humanized anti-VEGF-A monoclonal antibody</td>
</tr>
<tr>
<td>Fusion proteins (intravenous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aflibercept</td>
<td>VEGF-A, B; PIGF</td>
<td>Fusion protein consisting of extracellular domains of VEGFR-1, -2. Functions as a decoy receptor binding VEGF and PIGF</td>
</tr>
<tr>
<td>Trebananib</td>
<td>Ang-1, Ang-2</td>
<td>Fusion protein that binds to Ang-1, 2 interrupting association with Tie-2 receptor</td>
</tr>
<tr>
<td>Small molecule inhibitors (oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cediranib</td>
<td>VEGFR-1,2,3</td>
<td>ATP competitive tyrosine kinase inhibitor; specific anti-VEGF activity</td>
</tr>
<tr>
<td>PZ (Votrient)</td>
<td>VEGFR, PDGFR, c-kit</td>
<td>Multitargeted receptor tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>Nindetanib (Ofev; Vargatef)</td>
<td>VEGFR, FGFR, PDGFR</td>
<td>Multitargeted receptor tyrosine kinase inhibitor</td>
</tr>
</tbody>
</table>

Abbreviations: FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
A parallel placebo-controlled trial, GOG-218, evaluated the question of concurrent antiangiogenic therapy with chemotherapy (BV initiation) as opposed to both concurrent and maintenance therapy (BV throughout) versus chemotherapy alone. The primary outcome of PFS was improved in the BV-throughout arm compared with chemotherapy alone (14.1 months vs 10.3 months; \( P < .0001 \)) but not with BV initiation. The median overall survival (OS) was just under 40 months with no differences across arms with the caveat that study was unblinded after PFS reporting, allowing for cross-over. Quality of life (QoL) assessment demonstrated a small detriment during chemotherapy that did not persist into maintenance therapy.\(^{17} \) In the cohort of grade 1 to 2 cancers (20%), PFS outcome was significantly improved with BV maintenance.

AGO-OVAR12 was a placebo-controlled study that demonstrated a small improvement in the primary outcome of PFS (17.2 months vs 16.6 months; HR, 0.84; \( P = .024 \)) with nintedanib. There was no QoL benefit and no OS advantage, but the median OS in whole population was impressive, averaging 62 months.\(^{18} \) Approximately 70% patients had serous histology and less than 10% had low-grade disease, but efficacy by histology was not reported. A post hoc analysis evaluated outcome by ICON7–defined risk group. Contrary to the results of ICON7, benefit was preferentially observed in the non–high-risk subgroup.\(^{19} \) Given that this was not a prespecified analysis, the findings are challenging to interpret and might speak to regimen toxicity or consistency of target inhibition; however, these are hypothetical at this juncture.

AGO-OVAR16 evaluated pazopanib in women who had completed 5 or more cycles of platinum-taxane with no progression, a highly selected population with chemosensitive disease. It also included women receiving neoadjuvant chemotherapy (28%). Women randomized to pazopanib (\(<24 \) months) had a median PFS of 17.9 months (vs 12.3 months for placebo; HR, 0.77, \( P = .0021 \)) with no improvement in OS or QoL.\(^{20} \)

Recurrent Disease, Platinum Sensitive

Women with platinum-sensitive recurrence of EOC are rechallenged with platinum-based doublets. Although initial responses are good, the median PFS averages 6 to 11 months and the majority require another line of therapy within 1 year.\(^{21–23} \) The physical and emotional challenges of short treatment-free intervals are significant, leading to interest in approaches that might extend that time. There have now been 3 large studies evaluating antiangiogenic strategies combined with platinum doublets.

OCEANS randomized women with platinum-sensitive recurrence of EOC to carboplatin/gemcitabine with BV or placebo. There was an improvement in the primary endpoint of investigator-assessed PFS from 8.4 to 12.4 months (HR, 0.48; 95% confidence interval, 0.39–0.61) with BV. Benefit was observed across all subgroups, and was striking in patients with less than a 12-month platinum-free interval, echoing results of ICON7, where greater benefit with BV was observed with increasing disease severity. Approximately 30% of BV-treated patients (vs 9% on chemotherapy alone) remained free of disease progression at 12 months. As expected, the majority went on to receive subsequent anticancer therapy at progression, including 30% patients receiving BV.\(^{24} \)

GOG-0213 evaluated carboplatin/paclitaxel with or without BV (15 mg/kg). There was a second randomization to secondary surgery and this aspect of study is still maturing. The median PFS improved from 10.4 to 13.8 months with the addition of BV (HR, 0.61; \( P < .0001 \)) with a higher percentage of objective responses (78% vs 59%; \( P < .0001 \)), including a near doubling of complete responses. There was no initial difference in OS, but a repeat analysis correcting for platinum-free interval
misclassification affecting patient stratification demonstrated a significant OS benefit with BV (HR, 0.823; \( P = .0447 \)).

ICON-6 studied cediranib, with patients randomized to receive either (1) placebo followed by placebo maintenance, (2) cediranib followed by placebo maintenance, or (3) cediranib throughout platinum-based chemotherapy. There were setbacks with AstraZeneca’s decision to abort development of cediranib while the study was only partly accrued and the study was redesigned for a primary endpoint of PFS. Ultimately, median PFS was 8.7 months for group 1, 9.9 months for group 2, and 11.0 months for group 3, with a significant benefit of cediranib throughout treatment.

**Recurrent, Platinum Resistant**

Patients with platinum-resistant disease have a particularly poor prognosis. Standard of care is single-agent cytotoxic therapy but outcomes are poor, with median PFS of 3 months and an average OS less than 1 year. Results of doublet cytotoxic regimens have been disappointing leading to interest in cytotoxic/biologic combinations with better therapeutic ratios.

AURELIA was an open-labeled randomized evaluation of 3 chemotherapy regimens alone or with BV, which demonstrated an improvement in primary endpoint of PFS from 3.4 to 6.7 months (HR, 0.48; 95% confidence interval, 0.38–0.60), as well as secondary endpoint of response rate (from 13% to 31%; \( P < .01 \)). The lack of improvement in the OS is not surprising given that 40% patients crossed over to receive BV. There was a decrease in the requirement for paracenteses, and a trend to improved OS with BV in women with ascites at baseline. In addition, QoL evaluations demonstrated improvement in patient reported gastrointestinal/abdominal symptoms.

The evaluation of trebananib was anticipated with enthusiasm given its distinct mechanism targeting Ang/Tie2. TRINOVA-1 evaluated the addition of trebananib to weekly paclitaxel in platinum-resistant and partially platinum-sensitive EOC (platinum-free interval of 6–12 months). Approximately 80% of women had 1 to 2 prior lines of chemotherapy (<10% had prior antiangiogenic). The median PFS was improved (from 5.4 to 7.4 months; HR, 0.70; \( P < .001 \)). Although there was no OS improvement overall, in the subgroup with malignant ascites median OS improved from 12.3 to 14.5 months (HR, 0.72; \( P = .011 \)).

TRINOVA-2 evaluated the addition of trebananib to pegylated liposomal doxorubicin. Although the secondary endpoints of response rate and duration of response were significantly improved with trebananib, the primary endpoint of PFS was not.

**TOXICITY**

Toxicities associated with antiangiogenics are well-described. The most common class effects include hypertension, proteinuria, bleeding, and thromboembolism, and the rare but serious complication of perforation/fistula. The tyrosine kinase inhibitors (TKIs) are additionally associated with diarrhea, nausea, and fatigue, likely off-target effects. Trebananib, targeting the angioipoietin pathway, has a toxicity profile distinct from VEGF-targeting agents, with edema, pleural effusions, and weight gain.

**Hypertension and Proteinuria**

Hypertension is the most common toxicity observed with antiangiogenics. First-line studies reported on similar rates of significant (grade 2 or higher) hypertension: in ICON7, 18% with BV versus 2% without and in GOG-218, 23% in those receiving BV throughout versus 7%. On OCEANS, grade 3 or higher hypertension occurred in 17% patients on BV (vs <1%) and was the reason for treatment discontinuation in
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment Arms</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG-218 (BV)</td>
<td>Stage III-IV (n = 1873)</td>
<td>1. Carb/Tax/BV × 6 → BV × 22 cycles</td>
<td>14.1 vs 11.2 vs 10.3 (1) vs (3): (HR, 0.717; P &lt; .001)</td>
<td>39.3 vs 38.7 vs 39.7 (HR, 0.915; P = .45)</td>
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<tr>
<td></td>
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<td>2. Carb/Tax/BV × 6 → Pl × 22 cycles</td>
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<td>3. Carb/Tax/Pl × 6 → Pl × 22 cycles</td>
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<tr>
<td>ICON-7 (BV)</td>
<td>Stage I-IV n = 1528</td>
<td>1. Carb/Tax × 6 → BV × 12 cycles</td>
<td>19.0 vs 17.3 (HR, 0.81; P = .004)</td>
<td>45.5 vs 44.6 (NS)</td>
</tr>
<tr>
<td></td>
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<td>2. Carb/Tax × 6</td>
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<tr>
<td>ROSiA (BV)</td>
<td>single-arm study n = 1021</td>
<td>Carb/Tax/Bev → BV × 36 cycles</td>
<td>25.5 mo</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>*Neoadjuvant allowed</td>
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<tr>
<td>AGO-OVAR16 (PZ)</td>
<td>Stages II-IV (n = 940)</td>
<td>1. PZ × 24 mo</td>
<td>17.9 vs 12.3 (HR, 0.77; P = .0021)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>*Enrollment after ≥5 cycles platinum-Tax chemotherapy</td>
<td>2. Pl × 24 mo</td>
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<tr>
<td>AGO-OVAR12 (Nin)</td>
<td>Stage IIB-IV (n = 1366)</td>
<td>1. Carb/Tax/Nin × 6 → Nin × 40 wk</td>
<td>17.2 vs 16.6 (HR, 0.84; P = .024)</td>
<td>NR</td>
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<tr>
<td></td>
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<td>2. Carb/Tax/Pl × 6 → Pl</td>
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<tr>
<td>Recurrent: platinum sensitive</td>
<td>OCEANS (BV) &gt;6 mo PFI after first line (58% &gt;12 mo) (n = 484)</td>
<td>1. Carb/Gem/BV → BV</td>
<td>12.4 vs 8.4 (HR, 0.48; P &lt; .0001)</td>
<td>33.6 vs 35.3 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Carb/Gem/Pl → Pl</td>
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<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment Arms</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG-213 (BV)</td>
<td>&gt;6 mo PFI (70% &gt;12 mo) (n = 674)</td>
<td>1. Carb/Tax/BV</td>
<td>13.8 vs 10.4 (HR, 0.61; P &lt; .0001)</td>
<td>42.2 vs 37.3 (HR, 0.83; NS)</td>
</tr>
<tr>
<td></td>
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<td>2. Carb/Tax</td>
<td>Study included a second</td>
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<td>randomization to secondary</td>
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<td>debulking surgery</td>
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<tr>
<td>ICON-6 (Ced)</td>
<td>&gt;6 mo PFI (67% &gt;12 mo) (n = 456)</td>
<td>1. Chemo/Pl → Pl × 18 mo</td>
<td>8.7 vs 9.9 vs 11.0 (1) vs (3): (HR, 0.56; P &lt; .0001)</td>
<td>26.3 vs 21.0 (HR, 0.77; NS)</td>
</tr>
<tr>
<td></td>
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<td>2. Chemo/Ced → Pl × 18 mo</td>
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<td></td>
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<td>3. Chemo/Ced → Ced × 18 mo</td>
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<tr>
<td>Recurrent: platinum resistant</td>
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<tr>
<td>AURELIA (BV)</td>
<td>≤2 prior lines (n = 361)</td>
<td>** Chemotherapy (3 different</td>
<td>6.7 vs 3.4 (HR, 0.48; P &lt; .001)</td>
<td>16.6 vs 13.3 (HR, 0.85; NS)</td>
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<tr>
<td></td>
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<td>backbones) with or without BV</td>
<td></td>
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<tr>
<td>TRINOVA-1</td>
<td>(trebananib: Tb)</td>
<td>Platinum resistant and platinum</td>
<td>7.4 vs 5.4 (HR, 0.70; P &lt; .001)</td>
<td>19.3 vs 18.3 (HR, 0.95; NS)</td>
</tr>
<tr>
<td></td>
<td>(trebananib: Tb)</td>
<td>sensitive (PFI 6–12 mo) (n = 919)</td>
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<tr>
<td></td>
<td></td>
<td>1. Weekly Tax/Tb</td>
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<td>2. Weekly Tax/Pl</td>
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<tr>
<td>TRINOVA-2</td>
<td>(trebananib: Tb)</td>
<td>Platinum resistant and platinum</td>
<td>7.4 vs 5.4 (HR, 0.70; P &lt; .001)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>(trebananib: Tb)</td>
<td>sensitive (PFI 6–12 mo) (n = 223)</td>
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<td></td>
<td></td>
<td>1. PLD/Tb</td>
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<td>2. PLD/Pl</td>
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Drug Doses by Study: GOG-218: carboplatin (AUC 5); paclitaxel (175 mg/m²); bevacizumab (BV: 15 mg/kg). ICON-7: carboplatin (AUC 5 or 6); paclitaxel (175 mg/m²); bevacizumab (BV: 7.5 mg/kg). ROSiA: carboplatin (AUC 5 or 6); paclitaxel (175 mg/m²); bevacizumab (BV: 15 mg/kg OR 7.5 mg/kg, investigator choice). AGO-12: carboplatin (AUC 5 or 6)/paclitaxel (175 mg/m²); nintedanib (200 mg twice daily); maintenance 120 wk. AGO-16: pazopanib (800 mg one daily). OCEANS: carboplatin (AUC 4); gemcitabine (1000 mg/m²); bevacizumab (BV: 15 mg/kg). GOG-213: carboplatin (AUC 5)/paclitaxel (175 mg/m²); bevacizumab (BV: 15 mg/kg). ICON-6: any platinum-based (preference for Carbo/Gem); cediranib (20 mg once daily).

**Abbreviations: BV, bevacizumab; Carb, carboplatin; Ced, cediranib; Gem, gemcitabine; HR, hazard ratio; Nin, nintedanib; NR, not reported; NS, not significant; OS, overall survival; PFS, progression-free survival; Pl, placebo; PLD, pegylated liposomal doxorubicin; PFI, platinum-free interval; PZ, pazopanib; Tax, paclitaxel (taxol); Tb, trebananib; wkly tax, dose-dense (weekly) taxol.

**AURELIA: paclitaxel (80 mg/m²), PLD (40 mg/m²) or topotecan (4 mg/m² or 1.25 mg/m²) alone or in combination with BV (10 mg/kg). TRINOVA-1: paclitaxel (80 mg/m²), trebananib (15 mg/kg). TRINOVA-2: PLD (50 mg/m²); trebananib (15 mg/kg).
3.6% of patients. Three cases of reversible posterior leukoencephalopathy syndrome were reported in BV-treated patients. AURELIA also documented 1 patient (of 179) with reversible posterior leukoencephalopathy syndrome in the BV-treated cohort. The severity of hypertension associated with reversible posterior leukoencephalopathy syndrome was not reported.

In AGO-OVA12, hypertension (all grades) was documented in 14% of patients on nintedanib versus 6% on placebo. Rates were higher in AGO-OVA16, grade 3 or greater hypertension was observed in 31% of patients on pazopanib versus 6% on placebo. Hypertension was the most common reason for dose reduction and treatment discontinuation related to pazopanib and 1 patient died of complications of reversible posterior leukoencephalopathy syndrome. The risk of hypertension on trebananib is lower (7% vs 4% in placebo).

Although proteinuria has been observed at higher rates in patients receiving antiangiogenic agents, severe events (grade 3 or higher) were uncommon (<5%) and associated with longer duration of therapy.

Gastrointestinal Toxicity Including Gastrointestinal Perforation/Fistula

After initial studies raised concerns regarding gastrointestinal perforation/fistula (GIPF) risk, subsequent trials used strategies to mitigate these, which were ultimately acceptable. In GOG-218, GIPF events occurred twice as commonly in BV-treated patients, but less than 3% of all study patients were affected. Rates in ICON-7 were lower, with GIPF occurring in 10 BV-treated patients (vs 3 chemotherapy only), or less than 1% of all patients. This difference is interesting given the lower dose of BV prescribed in ICON-7. In patients with recurrent disease, OCEANS had 4 patients with GIPF/abscess on BV (vs 1 in chemotherapy only) and in AURELIA GIPF events affected 2% of patients on BV (vs 0% in the chemotherapy-only group).

The increased GIPF risk with antiangiogenic TKIs is lower than that observed with BV. In AGO-OVAR12, events were observed in 2% of patients treated with nintedanib versus 1% on placebo. Risk related to trebananib was 2% (vs 1% on placebo).

Diarrhea in patients on TKIs is common (affecting ≤50% of patients), with severe toxicity (≥ Grade3) affecting 8% of patients on pazopanib and 11% of patients on cediranib (vs 1% of patients on placebo respectively).

Bleeding and Thromboembolism

The risk of bleeding/thromboembolism is generally low. in ICON7, although bleeding rates were higher with BV, events were mostly mucocutaneous and grade 3 or higher bleeds occurred in less than 1% of patients on both arms. In GOG-218, grade 3 or higher bleeding occurred in 2% on BV (vs <1%); importantly, 2 of 608 patients treated with BV maintenance suffered a central nervous system bleed. In AURELIA, bleeding complications affected less than 1% in both groups. Risk with the TKIs were also low—bleeding events on cediranib were exclusively grade 2 or lower; rates with nintedanib and pazopanib were not reported.

Thrombotic events (arterial and venous; grade 3 or higher) occurred in 7% of BV-treated patients (vs 3% on chemotherapy alone) in ICON-7. In GOG-218, venous thrombotic events occurred in 6% to 7% of patients and arterial events affected less than 1% patients in all arms. In AURELIA, the frequency of thrombotic events was similar in BV-treated or BV-untreated patients, but arterial events (rate of 2%) occurred exclusively in patients on BV. Thrombotic event rates on the TKIs angiokinases were similar, with rates of less than 3% with both nintedanib and cediranib.
Trebananib was not associated with an increased risk of bleeding/thrombotic events.\textsuperscript{35,36}

**PREDICTIVE BIOMARKERS**

Multiple lines of evidence now demonstrate benefit of antiangiogenics in EOC. Unfortunately, the ability to identify patients likely to respond or experience toxicity is limited. There remains a critical need to define robust biomarkers given the clinical and financial toxicity of these agents.

**Clinical**

Foremost among potential clinical biomarkers, is the phenomena of treatment-related hypertension. With inhibition of VEGF signaling promoting vasoconstriction and increased vascular resistance, it has been hypothesized that early hypertension could serve as a pharmacodynamic marker of on-target activity. Small studies have been encouraging, including one in lung cancer patients,\textsuperscript{40} but a large metaanalysis has not confirmed a link with hypertension and prognosis or treatment effect.\textsuperscript{41} Small studies in gynecologic oncology patients do not support a correlation.\textsuperscript{42}

**Molecular**

Various molecular markers have been explored for their potential to indicate a reliance on angiogenic pathways. The catalog of these studies is extensive and has been reviewed elsewhere.\textsuperscript{43} Unfortunately, observations are inconsistent, complicated by the challenges of distinguishing prognostic from predictive values of markers in single-arm, retrospective, studies.\textsuperscript{44} Still, a few high priority markers have been identified for validation. Elegant correlative work incorporated into some of the trials described previously, provide important insights into tumor biology and mechanisms of treatment resistance and response in the context of antiangiogenic therapy.

Both ICON-7 and GOG-218 investigated circulating biomarkers. None of the markers studied in GOG-218 were predictive of response,\textsuperscript{45} but multiplex enzyme-linked immunosorbent assay analysis in ICON-7 identified Tie2 as a vascular progression marker.\textsuperscript{46} This finding provokes interesting hypotheses about the use of trebananib after BV progression.

GOG-218 correlative studies also included an evaluation of VEGF-A, VEGF receptor-2, neuropilin-1, MET, and microvessel density in tumor samples. Among these, only microvessel density demonstrated a predictive value with respect to benefit to BV.\textsuperscript{44}

Given the complexity of angiogenesis, focus has shifted to an interrogation of pathways over single markers. Along those lines, gene expression profiling can define a subgroup characterized by the upregulation of immune genes and repression of angiogenic genes, and with an overall superior prognosis. A 63-gene signature defining this immune subset of patients was applied to a cohort of 283 ICON7 patient samples; 44% of patients were profiled as immune and seemed to experience a survival detriment with BV (HR, 1.73; \( P = .048 \)). The remaining patients with proangiogenic profiles had a trend toward a higher median PFS with BV.\textsuperscript{47} These results, albeit intriguing, await validation in other datasets.

Another interesting analysis from AGO-OVAR16 demonstrated clinically significant germline BRCA1/2 mutations in 15% of patients. As expected, outcomes were superior to that of noncarriers (a median PFS of 30 months vs 14 months in the placebo cohort). Interestingly, improvements in PFS related to pazopanib seemed to be limited to the BRCA wild-type patients (median PFS of 11.9 months vs 16.6 months; HR, 0.68,
SUMMARY AND FUTURE DIRECTIONS

Antiangiogenic targeting has clear efficacy across the spectrum of EOC. As per recent consensus statements defining clinically relevant outcomes in EOC, the improvements observed across the various trials are clinically meaningful and current data suggest that almost all women with advanced EOC should receive an antiangiogenic at some point in their disease trajectory. Current evidence favors the use of BV amongst anti-angiogenics evaluated thus far and the increased risk of GIPF associated with more extensive disease supports its use at relatively early timepoints to minimize these risks. Benefit of continuing/rechallenging with BV after progression has been demonstrated in colorectal cancer, but remains unclear in EOC. The less impressive clinical efficacy, partnered with the greater toxicity of the angiokinases, raises doubts as to how these agents will factor into the evolving landscape. One interesting avenue for exploration would be role of these post-BV progression.

Regarding front-line BV, a number of pragmatic questions remain, including optimal dose and the timing and duration of treatment. The lesser toxicity observed in ICON7 provides support for the use of a lower dose. More important, the diminishing gains observed after the completion of maintenance therapy suggests a longer duration of maintenance might be of greater benefit. The experience of the ROSiA trial, through which a similar patient population to ICON7 received up to 24 months of BV, provides reassurance that extending BV maintenance is safe. The median PFS of 25.5 months, albeit within a single-arm study, is impressive and also supports longer durations of maintenance.

A few patient subgroups remain poorly studied, namely platinum-refractory disease and carcinosarcoma. These cohorts have a particularly poor prognosis, for which the potential benefit of antiangiogenic remains undefined.

There is enthusiasm that the promising results observed to date are but the beginning of a new era in the treatment of EOC. The relevance of VEGF in promoting tumoral immune privilege provides rationale for combining VEGF-directed therapies with immune-modulation and the observation of augmented cytotoxic T-cell responses at the preclinical level has now led to the initiation of several trials in this space. Further, a potential synergy between antiangiogenics and agents targeting DNA repair (namely, poly[adenosine diphosphate]-ribose polymerase inhibitors) has been suggested based on the induction of tumoral microenvironment-related DNA repair vulnerabilities, leading to yet another high priority biologic doublet that has entered clinical evaluation. Still, amid the excitement surrounding these novel approaches, we remain cognizant that not all patients will derive benefit. The data from genomic profiling has demonstrated real potential to improve on patient stratification for clinical trials, but given the role of the tumoral microenvironment in driving some of these molecular vulnerabilities it is critical that future profiling efforts incorporate microenvironmental profiling with genomic approaches.

REFERENCES


