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State of the Science

State of the science: Emerging therapeutic strategies for targeting angiogenesis in ovarian cancer

Ovarian cancer is clinically characterized by advanced stage at presentation, transient chemosensitivity, and stagnant long-term survivorship rates despite a broadening portfolio of "active" therapies [1]. Contemporary treatment standards of newly diagnosed patients dictate timely aggressive surgical cytoreduction followed by paclitaxel and platinum-based chemotherapy. Since "optimal" surgical outcome is no visible residual cancer, most of these favorable prognosis patients completing primary adjuvant chemotherapy will achieve complete clinical response. However, even among patients achieving a pathological complete response (negative reassessment surgery), recurrence rates are high (≥40%), and nearly all will eventually succumb to their disease [2]. Thus, there is a critical need for novel therapeutic agents that are both effective and well tolerated.

An attractive target for therapeutic intervention is the tumor microenvironment, which is theoretically genetically more stable than tumor cells. The tumor microenvironment consists of any cellular components that interact with tumor cells, such as fibroblasts, immune cells, extracellular matrix, pericytes, neoangiogenic endothelial cells, nerves and surrounding blood vessels [3]. Angiogenesis and tumor neovascularization play an essential role in the promotion of tumor growth, metastasis and ascites formation. As such, the development of antiangiogenic agents has been the initial focus of targeted therapy for ovarian cancer.

Currently, the vascular endothelial growth factor (VEGF) pathway is the most widely studied angiogenic pathways in ovarian cancer. Bevacizumab, a monoclonal antibody targeting VEGF, was the first agent to demonstrate encouraging results in the phase II setting. Two front-line phase III trials, the International Collaborative Ovarian Neoplasm Group trial (ICON7) [4] and the Gynecologic Oncology Group trial (GOG218) [5], evaluated the benefit of adding bevacizumab to carboplatin and paclitaxel chemotherapy. While there were several differences between these two trials, including patient eligibility, trial design and dosing of bevacizumab, both showed statistically significant improvements in progression free survival (PFS) but did not extend overall survival (OS). Three randomized phase III trials have evaluated bevacizumab in the recurrent setting. The OCEANS trial evaluated the benefit of adding bevacizumab to carboplatin and gemcitabine in patients with platinum-sensitive disease and showed a 4-month improvement in PFS but no improvement in OS [6]. The AURELIA trial showed that the addition of bevacizumab to several cytotoxic regimens improved the PFS in patients with platinum-resistant disease [7]. Again, there was no improvement in OS, but the results of this trial led to the FDA approval of bevacizumab in combination with chemotherapy for platinum-resistant, recurrent ovarian cancer. GOG213 evaluated the benefit of adding bevacizumab to carboplatin and paclitaxel followed by bevacizumab and secondary cytoreductive surgery in patients with platinum-sensitive disease. The addition of bevacizumab significantly improved PFS. It extended OS (42.2 months vs. 37.3 months) but did not reach statistical significance ($P = 0.056$) [8]. A summary of completed phase III trials with investigational agents targeting angiogenesis is summarized in the Table.

While benefits in PFS have been seen with the addition of bevacizumab to cytotoxic chemotherapy, the lack of improvement in OS, increased toxicity, high cost of bevacizumab therapy, and growing evidence of antiangiogenic escape mechanisms, have led to the targeting of alternative pathways of tumor neovascularization. Adaptive escape from antiangiogenesis therapy and resistance to VEGF may be related to activation or upregulation of alternate proangiogenic pathways within the tumor (angiopoietin 1, Delta-like ligand 4/Notch and microRNAs), immune response such as recruitment of proangiogenic monocytes from the bone marrow (TAMs), induction of hypoxia, and increased pericyte coverage of the tumor vasculature. In addition, there appears to be an immune molecular subgroup of ovarian cancer that has repressed angiogenesis-related gene expression. This subgroup has superior survival, but the addition of bevacizumab to chemotherapy significantly appeared to reduce PFS and OS compared to chemotherapy alone. These data suggest that patient stratification to identify who will benefit from drugs such as bevacizumab should be considered.

Compounds targeting receptor tyrosine kinases have shown promise in early phase trials, with several advancing to Phase III clinical trials. Pazopanib is a small molecule tyrosine kinase inhibitor (TKI) that inhibits VEGFR-1,-2,-3, PDGFR-α and -β, and c-Kit. OVAR16, a phase III trial evaluating pazopanib maintenance after first-line chemotherapy in patients with stage II–IV ovarian cancer, demonstrated a significant improvement in PFS (17.9 months vs. 12.3 months, $p = 0.0021$) [9]. Nintedanib is a TKI that inhibits VEGFR-1,-2,-3, PDGFR-α and -β, and PDGFR-1,-2,-3. OVAR12 was a phase III trial evaluating nintedanib in combination with carboplatin and paclitaxel followed by nintedanib maintenance in the up-front setting. PFS was significantly improved with the addition of nintedanib (17.3 months vs. 16.6 months, $p = 0.024$), and PFS was most improved among patients in the low-risk group with small residual tumors after surgery (20.8 months vs. 27.1 months, $p = 0.005$) [10]. Finally, cediranib, a TKI targeting VEGF-R1,-2 and -3 was studied in platinum sensitive patients in a phase II/III designed multi-arm trial in combination with chemotherapy (paclitaxel/carboplatin, gemicitabine/carboplatin or single agent platinum). The 3-arm, placebo-controlled trial was designed with cediranib

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given concomitantly with chemotherapy (Arm-II) or concomitantly with cediranib maintenance. Significant differences in both PFS and OS were observed (See Table 1) but interpretation is limited based on failure to meet primary accrual targets [11].

The Ang-TIE pathway is of particular interest due to its critical role in blood vessel formation. Ang1 and Ang2 act through binding the cellular receptors Tie-1 and 2 [12]. Ang1 promotes blood vessel stability with decreased permeability. Ang2 functions as an Ang1 antagonist by inducing increased vascular permeability and sprouting angiogenesis [13]. In ovarian cancer, tumor stroma and endothelial cells primarily express Ang2, and elevated levels of Ang2 may decrease the efficacy of anti-VEGF treatment [14]. Trebananib (AMG386) is a peptibody (peptide-FC antibody segment fusion protein) that disrupts the interaction between the Tie 2 receptor and Ang1 and Ang2. Based on promising results from phase I and II studies, the Trebananib in Ovarian Cancer (TRINOVA) program of phase III studies was developed in ovarian cancer. TRINOVA-1 is a randomized phase III trial evaluating weekly paclitaxel with trebananib versus placebo in patients with recurrent disease and showed a statistically significant improvement in PFS in the trebananib arm as compared to the placebo arm (7.2 months vs. 5.4 months; $p < 0.001$) [15]. While not statistically significant, there was a trend toward improved OS in the trebananib arm (19 months vs. 17.3 months in the control arm). TRINOVA-2 is a randomized phase III trial evaluating Pegylated Liposomal Doxorubicin (PLD) plus Trebananib or placebo in patients with platinum resistant disease. The study is active but no longer recruiting patients. TRINOVA-3 is a randomized phase III trial evaluating paclitaxel and carboplatin plus trebananib or placebo followed by trebananib or placebo maintenance for 18 months in the frontline setting. This study was stopped for futility according to the recommendations of an independent data safety monitoring committee.

The Delta-like ligand 4 (Dll4)/Notch signaling pathway is essential for embryonic vascular development and has recently been implicated in tumor angiogenesis [16]. Studies have suggested that VEGF induces Dll4/Notch signaling and Dll4/Notch signaling modulates the VEGF pathway [17]. Alterations in the Notch pathway are prevalent in high-grade serous ovarian cancer and are associated with decreased OS [18]. Dll4 is an endothelium-specific ligand and is strongly expressed in tumor vessels. Targeting Dll4 results in increased tumor vascularity that is non-productive, as evidenced by decreased perfusion and tumor growth [19]. Dll4 was shown to be overexpressed in 72% of ovarian tumors and an independent predictor of poor survival [17]. Tumors of patients responding to anti-VEGF treatment had lower levels of Dll4 than patients with progressive disease. Silencing of Dll4 in ovarian tumor cells and tumor-associated endothelial cells inhibited tumor growth and angiogenesis [17]. Therapeutic agents targeting the

Table 1
Summary of phase III trials using agents targeting angiogenesis in women with ovarian cancer.

Study	Targeting agent	Setting	N	Treatment arm	PFS (Median, months)	PFS-HR (95% CI)	OS (Median, months)	OS-HR (95% CI)
GOG-218 [5]	Bevacizumab	Front-line & maintenance	1873	I: Paclitaxel + Carboplatin + Placebo; Placebo Maintenance	10.3	–	39.3	–
				II: Paclitaxel + Carboplatin + Bevacizumab; Placebo Maintenance	11.2	0.91 (0.8–1.04)	38.7	1.036 (0.83–1.3)
				III: Paclitaxel + Carboplatin + Bevacizumab; Bevacizumab Maintenance	14.1	0.72 (0.63–0.82)	39.7	0.92 (0.73–1.15)
ICON7 [4]	Bevacizumab	Front-line and maintenance	1528	I: Paclitaxel + Carboplatin	17.4	–	58	–
				II: Paclitaxel + Carboplatin + Bevacizumab; Bevacizumab Maintenance	19.8	0.87 (0.77–0.99)	58.6	0.85 (0.69–1.04)
OVAR12 [10]	Nintedanib	Front-line and maintenance	1366	I: Paclitaxel + Carboplatin + Placebo; Placebo Maintenance	16.6	–	Not stated	–
				II: Paclitaxel + Carboplatin + Nintedanib; Nintedanib Maintenance	17.3	0.84 (0.72–0.98)	Not stated	–
OVAR16 [9]	Pazopanib	Maintenance	940	I: Placebo	12.3	–	49*	–
				II: Pazopanib	17.9	0.77 (0.64–0.91)	Not reached	1.08 (0.87–1.33)
AURELIA [7]	Bevacizumab	Recurrent, platinum-resistant	361	I: Chemotherapy (paclitaxel–-weekly, topotecan–-daily x 5 or weekly, PLD)	3.4	–	13.3	–
				II: Chemotherapy + bevacizumab	6.7	0.48 (0.36–0.6)	16.6	0.85 (0.66–1.08)
TRINOVA-I [15]	Trebananib	Recurrent, platinum-resistant/ sensitive	919	I: Paclitaxel–weekly + Placebo	5.4	–	18.3	–
				II: Paclitaxel-weekly + Trebananib	7.2	0.66 (0.57–0.77)	19.3	0.95 (0.81–1.12)
OCEANS [6]	Bevacizumab	Recurrent, platinum-sensitive	484	I: Gemcitabine + Carboplatin + Placebo (combination and maintenance)	8.4	–	32.9	–
				II: Gemcitabine + Carboplatin + Bevacizumab (combination and maintenance)	12.4	0.48 (0.39–0.61)	33.6	0.95 (0.77–1.18)
ICON6 [11]	Cediranib	Recurrent, platinum-sensitive	456	I: Chemotherapy (Paclitaxel or Gemcitabine combination) or Single agent Carboplatin + Placebo; Placebo maintenance	8.7	–	20.3	–
				II: Chemotherapy + Cediranib; Placebo maintenance	10.1	0.67 (0.53–0.87)	Not Stated	–
				III: Chemotherapy + Cediranib; Cediranib maintenance	11.1	0.57 (0.44–0.74)	26.3	0.70 (0.51–0.99)
GOG-213 [8]	Bevacizumab	Recurrent, platinum-sensitive	674	I: Paclitaxel + Carboplatin	10.4	–	37.3	–
				II: Paclitaxel + Carboplatin + Bevacizumab; Bevacizumab maintenance	13.8	0.61 (0.52–0.72)	42.2	0.83 (0.68–1.005)

PFS: Progression-free survival; OS: overall survival; HR: hazard ratios; and * estimated from publication.