

# Oncology Briefings

## Progress With Vascular Endothelial Growth Factor/ Vascular Endothelial Growth Factor Receptor Agents in Advanced or Persistent Ovarian Cancer

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### Introduction

Ovarian cancer is the most clinically challenging of all the gynecologic malignancies, with > 15,000 deaths and 21,000 new diagnoses estimated in the United States in 2008.<sup>1</sup> The majority of ovarian cancers are epithelial in origin; initial therapy for patients with epithelial ovarian cancer (EOC) is cytoreduction and surgical staging followed by chemotherapy in most cases. Standard chemotherapy consists of 6 cycles of paclitaxel 175 mg/m<sup>2</sup> over 3 hours plus carboplatin at an area under the curve (AUC) of 5.0-7.5 every 3 weeks. Despite high response rates (RRs) with initial chemotherapy, most patients will relapse and, eventually, develop platinum-resistant disease.

Patients who relapse after a platinum-free interval of  $\geq 6$  months are considered platinum sensitive and can receive platinum-based therapy at relapse until development of platinum-resistant disease, defined as a disease-free interval of < 6 months. Treatment options for patients with platinum-resistant disease are limited, but oxaliplatin, pegylated liposomal doxorubicin, topotecan, gemcitabine, paclitaxel, docetaxel, etoposide, and gemcitabine/cisplatin have demonstrated activity in this setting.<sup>2-8</sup> In patients with platinum-resistant ovarian cancer, RRs tend to be low, highlighting the need for improved therapeutic targets and strategies for these patients.

### Antiangiogenic Therapy

Targeting the tumor microenvironment, specifically the angiogenic cascade, is an effective approach to the treatment of many solid tumors. The vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) axis is an especially appealing target because of its central role in regulating tumor angiogenesis. Increased tumor angiogenesis measured by microvessel density has been demonstrated to correlate with decreased survival in patients with ovarian cancer.<sup>9-11</sup> Antiangiogenic strategies employed in cancer therapy include blocking VEGF-VEGFR interactions with monoclonal antibodies (MoAbs) and inhibiting VEGFR activation with small-molecule tyrosine kinase inhibitors (TKIs).

### Treatment With Anti-Vascular Endothelial Growth Factor Agents

Bevacizumab is a humanized MoAb that targets VEGF and inhibits VEGF-VEGFR binding. Most solid tumors, including ovarian cancer, overexpress VEGF, making bevacizumab a potential therapeutic option in ovarian cancer.<sup>12</sup> A retrospective analysis of single-agent bevacizumab as salvage therapy for patients with heavily pretreated advanced EOC reported an RR of 16%.<sup>13</sup>

Two prospective phase II trials have confirmed the single-agent efficacy of bevacizumab, reporting responses in 13 (21%) and 7 (16%) patients (Table 1).<sup>14,15</sup> In a trial conducted by Dr. Burger and colleagues, patients with persistent/recurrent EOC or primary peritoneal cancer (PPC) received bevacizumab 15 mg/kg every 3 weeks.<sup>14</sup> Of the 62 evaluable patients, 13 (21%) achieved a response, with a complete response (CR) in 2 patients and a partial response (PR) in 11 patients. Stable disease (SD) was seen in 32 patients. The 6-month progression-free survival (PFS) rate was 40%; median PFS and overall survival (OS) were 4.7 months and 16.9 months, respectively. Hypertension was observed in 14 patients, including 6 with grade 3 hypertension, and grade

**Table 1** Prospective Phase II Trials of Single-Agent Bevacizumab in Persistent/Recurrent Ovarian Cancer

	Number of Patients	
	Burger <sup>14</sup> (n = 62)	Cannistra <sup>15</sup> (n = 44)
<b>Number of Prior Regimens</b>	1/2	2/3
<b>Efficacy</b>		
Response	13	7
Complete response	2	0
Partial response	11	7
Median progression-free survival	4.7 months	4.4 months
Median overall survival	16.9 months	10.7 months
<b>Adverse Events</b>		
Grade 3 hypertension	6	4
Deep vein thrombosis	2*	1†
Gastrointestinal perforations	0	5
Bowel obstruction	0	5
Grade 4 proteinuria	1	0
Deaths due to adverse events	0	4

\* Grade 3/4

† Serious adverse event

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This article includes discussion of investigational and/or unlabeled uses of drugs, including the use of oxaliplatin, gemcitabine, topotecan, docetaxel, etoposide, bevacizumab, aflibercept (VEGF Trap), cediranib, sorafenib, and vandetanib in ovarian cancer.

Table 2	Prospective Phase II Trials of Bevacizumab/Chemotherapy in Advanced Ovarian Cancer			
	Number of Patients			
	Micha <sup>19</sup> (n = 18)	Chura <sup>20</sup> (n = 15)	Garcia <sup>21</sup> (n = 70)	McGonigle <sup>22</sup> (n = 24)
<b>Setting</b>	First-line	Recurrent	Recurrent	Recurrent
<b>Efficacy</b>				
Response	16	8	17	6
Complete response	6	2	0	0
Partial response	10	6	17	6
Median overall survival	NR	NR	16.9 months	11.7 months
<b>Adverse Events</b>				
Grade 3 hypertension	2	0	11	5
Gastrointestinal perforations	0	0	3	0
Grade 3 proteinuria	NR	1*	3	1

\* Grade 2  
Abbreviation: NR = not reported

3/4 deep vein thrombosis was observed in 2 patients. No instances of gastrointestinal (GI) perforation were reported. A trial conducted by Dr. Cannistra and colleagues evaluated bevacizumab 15 mg/kg every 3 weeks in patients with platinum-resistant EOC or peritoneal serous cancer.<sup>15</sup> Of the 44 patients enrolled, 7 achieved a PR, and 27 had SD. Median PFS and OS were 4.4 months and 10.7 months, respectively. Hypertension was observed in 14 patients, including 4 with grade 3 hypertension. Notably, GI perforations and bowel obstructions occurred in 5 patients each; the trial was terminated before meeting its primary accrual endpoints due to bowel toxicity.

Bevacizumab/chemotherapy has also yielded high overall RRs (ORRs) in patients with advanced ovarian cancer. Three retrospective analyses have reported ORRs of 35%-78% with bevacizumab in combination with various chemotherapy regimens.<sup>16-18</sup> A prospective phase II trial evaluated first-line paclitaxel/carboplatin/bevacizumab in patients with advanced EOC, PPC, or fallopian tube cancer (Table 2).<sup>19</sup> Of the 18 evaluable patients, 6 achieved a CR, and 10 achieved a PR. Grade 3 hypertension was reported in 2 patients. There were no incidences of GI perforations, bowel obstructions, or wound-healing complications.

Three other prospective phase II trials have also reported high ORRs with bevacizumab/chemotherapy in patients with recurrent ovarian cancer (Table 2).<sup>20-22</sup> In a trial of bevacizumab 10 mg/kg every 2 weeks plus cyclophosphamide 50 mg/day, 2 CRs and 6 PRs were noted in the 15 treated patients, who had received a median of 8 previous lines of chemotherapy; SD was noted in 3 patients.<sup>20</sup> There were no reports of GI perforations in these heavily pretreated patients. In another trial of bevacizumab 10 mg/kg every 2 weeks (weekly for the first 3 weeks) plus cyclophosphamide 50 mg/day, 17 PRs were noted in the 70 patients; SD was noted in 44 patients.<sup>21</sup> Median OS was 16.9 months. Hypertension was reported in 39% of the patients, proteinuria in 44% of the patients, and GI perforations in 3 patients. An interim analysis of a trial of bevacizumab 10 mg/kg every 2 weeks plus topotecan 4 mg/m<sup>2</sup>/week in 24 evaluable patients reported a PR in 6 patients and SD in 7 patients.<sup>22</sup> Adverse events included hypertension in 7 patients, including 5 with grade 3 hypertension; proteinuria in 2 patients, including 1 with grade 3 proteinuria; and grade 3/4 bowel obstruction in 3 patients.

It remains to be seen if bevacizumab/chemotherapy is superior to either bevacizumab or chemotherapy alone. Several ongoing phase III trials are evaluating chemotherapy doublets alone or in combination with bevacizumab in

Table 3	Phase II Trials of Novel Antiangiogenic Agents in Recurrent Ovarian Cancer: Efficacy			
	Number of Patients			
	Aflibercept (VEGF Trap) <sup>27</sup> (n = 162)	Cediranib <sup>28</sup> (n = 32)	Sorafenib <sup>29</sup> (n = 59)	Sorafenib/ Gemcitabine <sup>30</sup> (n = 33)
<b>Response</b>	13	6	2	2
Complete response	0	0	0	0
Partial response	13	6	2	2
<b>Median Overall Survival</b>	NR	NR	NR	13.0 months
<b>Grade 3/4 Adverse Events</b>	<b>(n = 162)</b>	<b>(n = 33)</b>	<b>(n = 59)</b>	<b>(n = 38)</b>
Neutropenia	NR	0	NR	11
Thrombocytopenia	1 <sup>†</sup>	0	NR	8
Hypertension	18%*	14 <sup>‡</sup>	NR	3
Proteinuria	7%*	0	NR	NR
All-grade gastrointestinal perforations	2 <sup>†</sup>	0	NR	NR
Rash	NR	NR	12	NR
Hand-foot syndrome	NR	0	NR	8

\* Except where indicated  
<sup>†</sup> Treatment-related serious adverse event  
<sup>‡</sup> Grade 3  
 Abbreviations: NR = not reported; VEGF = vascular endothelial growth factor

patients with recurrent as well as newly diagnosed ovarian cancer.<sup>23-26</sup> The OCEANS trial is evaluating carboplatin/gemcitabine alone or in combination with bevacizumab in patients with platinum-sensitive recurrent ovarian cancer, PPC, or fallopian tube cancer.<sup>23</sup> The Gynecologic Oncology Group (GOG) 213 trial is evaluating paclitaxel/carboplatin alone or in combination with bevacizumab followed by maintenance bevacizumab and secondary cytoreductive surgery in patients with platinum-sensitive recurrent EOC, PPC, or fallopian tube cancer.<sup>24</sup> The GOG 218 trial is evaluating paclitaxel/carboplatin alone or in combination with bevacizumab with or without maintenance bevacizumab in patients with untreated advanced-stage EOC, PPC, or fallopian tube cancer.<sup>25</sup> The Medical Research Council ICON-7 trial is evaluating bevacizumab combination therapy in untreated patients with EOC, PPC, or fallopian tube cancer.<sup>26</sup>

The major adverse events associated with bevacizumab in ovarian cancer are hypertension, thrombosis, and proteinuria, which occur at rates similar to those observed in other solid tumors.<sup>12</sup> However, GI perforations occur at a higher rate in patients with ovarian cancer compared to those with other cancers, especially in the trial in heavily pretreated patients conducted by Dr. Cannistra and colleagues.<sup>15</sup> Further study will help identify the etiology of this complication, and more experience in patients with less heavily pretreated disease could decrease the incidence of this adverse event.

### Treatment With Other Antiangiogenic Agents

Aflibercept (VEGF Trap) is another anti-VEGF agent that is under investigation in patients with ovarian cancer. Several phase II and III clinical trials are under way in patients with advanced ovarian cancer. Preliminary results from an ongoing phase II trial reported a radiologic PR in 13 of the 162 evaluable patients (Table 3).<sup>27</sup> All of the responding patients had received prior platinum and taxane therapy. Treatment-related serious adverse events included hypertension in 5 patients, GI perforation in 2 patients, and thrombocytopenia and proteinuria in 1 patient each. The most frequent grade 3/4 adverse events were hypertension (18%), proteinuria (7%), and headache (4%).

Several VEGFR TKIs are also under investigation in patients with recurrent ovarian cancer, including cediranib, sorafenib, and vandetanib. Preliminary results from a phase II trial of single-agent cediranib, a VEGFR-1, -2, and -3 and c-Kit TKI, reported a PR in 6 of the 32 patients, with SD occurring in 4 patients (Table 3).<sup>28</sup> Grade 3 hypertension was noted in 14 patients, grade 3 hypothyroidism was noted in 1 patient, and there were no reports of GI perforations or grade 3/4 hematologic toxicity. The ongoing phase III ICON-6 trial is evaluating paclitaxel/carboplatin/cediranib in patients with platinum-sensitive recurrent ovarian cancer.

Sorafenib is a multitargeted TKI that targets Raf, VEGFR, platelet-derived growth factor receptor, FLT-3, and c-Kit. Results from a phase II trial of single-agent sorafenib in patients with persistent/recurrent EOC or PPC demonstrated a PR in 2 of the 59 evaluable patients, with SD in 20 patients (Table 3).<sup>29</sup> The most common grade 3/4 adverse event was rash in 12 patients. Another phase II trial evaluated sorafenib/gemcitabine in patients with recurrent ovarian cancer.<sup>30</sup> Of the 33 evaluable patients, 2 achieved a PR, and 25 had SD (Table 3). Median OS was 13.0 months. The most common grade 3/4 adverse events in the 38 evaluable patients were lymphopenia in 12 patients (28%), neutropenia in 11 patients (26%), thrombocytopenia in 8 patients (19%), and hand-foot syndrome in 8 patients (19%).

## Conclusion

Although many targeted agents have been evaluated in patients with advanced ovarian cancer, antiangiogenic strategies have demonstrated the most clinical activity to date. The activity of single-agent anti-VEGF MoAbs in ovarian cancer has been surprising given their limited single-agent activity in most other solid tumors. Early results indicate that the addition of chemotherapy builds upon the single-agent efficacy seen with antiangiogenic agents. Continued evaluation in randomized clinical trials will further elucidate the role of these agents in the management of advanced or persistent ovarian cancer.

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