Expert Commentary on Frequently Asked Questions in Ovarian Cancer:
Unraveling the Risks and Benefits of Antiangiogenic Therapy for Ovarian Cancer Patients
TARGET AUDIENCE
This activity is intended for medical, surgical, and gynecological oncologists; oncology nurses; pharmacists; and healthcare professionals managing and treating patients with ovarian cancer.

PURPOSE
The goal of this activity is to close knowledge, competence, and performance gaps by providing clinicians with a solid understanding of the molecular signaling pathways of agents, as well as the most recent evidence-based data for current and emerging agents and their rationale for use for treating patients with ovarian cancer.

ACTIVITY OVERVIEW
In the United States alone, ovarian cancer is estimated to affect 21,290 new patients in 2015 and cause 14,180 deaths. Approximately 75% of patients are diagnosed at an advanced stage, and the majority of ovarian cancer patients often relapse after chemotherapy treatment. This relapse usually occurs more than 6 months after the end of chemotherapy treatment, leaving the cancer sensitive to another chemotherapy treatment and difficult to manage. In light of these obstacles, researchers are exploring the role of targeted therapies as both monotherapy and in combination approaches to expand the treatment armamentarium for recurrent/resistant ovarian cancer. It is therefore imperative that oncologists are educated on newly available evidence-based data regarding these approaches, and their application to clinical practice so they can provide patients with optimal care.

This activity will provide expert commentary on unanswered questions from the CME-certified grand rounds and webinar series entitled, Unraveling the Risks and Benefits of Antiangiogenic Therapy for Ovarian Cancer Patients.

LEARNING OBJECTIVES
At the conclusion of this activity, participants should be able to:

• Analyze controversial data related to first-line treatment approaches for ovarian cancer
• Discuss clinical data incorporating the use of antiangiogenic agents and PARP inhibitors for treating ovarian cancer
• Integrate recent FDA approvals into the treatment armamentarium for ovarian cancer
• Assess emerging novel targets and agents being studied in clinical trials in ovarian cancer
• Apply evidence-based clinical data of newly approved and emerging treatments to the management of recurrent ovarian cancer

FACULTY
Bradley Monk, MD, FACS, FACOG
Professor
Division Director, Division of Gynecologic Oncology
Vice Chair, Department of Obstetrics and Gynecology
University of Arizona Cancer Center
Creighton University School of Medicine at St. Joseph’s Hospital and Medical Center, a Dignity Health Member
Phoenix
PHYSICIAN CONTINUING MEDICAL EDUCATION

Accreditation Statement
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCMCE) through the joint providership of Postgraduate Institute for Medicine and AXIS Medical Education. The Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation
The Postgraduate Institute for Medicine designates this enduring material for a maximum of 0.75 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

DISCLOSURE OF CONFLICTS OF INTEREST
Postgraduate Institute for Medicine (PIM) requires instructors, planners, managers and other individuals who are in a position to control the content of this activity to disclose any real or apparent conflict of interest (COI) they may have as related to the content of this activity. All identified COI are thoroughly vetted and resolved according to PIM policy. PIM is committed to providing its learners with high quality CME activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

Bradley J. Monk, MD, FACS, FACOG, reported a financial interest/relationship or affiliation in the form of: consulting fee, Boehringer Ingelheim, Genentech - A member of the Roche Group, GlaxoSmithKline, Merck & Co., Inc., and Tesaro, Inc.; speaker's bureau, Genentech - A member of the Roche Group, and Johnson & Johnson Pharmaceutical Research & Development, LLC; contracted research, Amgen, Inc., Array BioPharma, Inc., Eli Lilly and Company, Genentech - A member of the Roche Group, Janssen Pharmaceuticals, Inc. - a pharmaceutical company of Johnson & Johnson, Novartis Pharmaceuticals Corporation, and Tesaro, Inc.

The planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

The following PIM planners and managers, Judi Smelker-Mitchek, RN, BSN, Trace Hutchison, PharmD, Samantha Mattucci, PharmD, CHCP, and Jan Schultz, MSN, RN, CHCP, hereby state that they or their spouse/life partner do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

The following AXIS planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Linda Gracie-King, MS; Deborah Middleton, MS; and Jocelyn Timko, BS, hereby state that they or their spouse/life partner do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

DISCLOSURE OF UNLABELED USE
This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

DISCLAIMER
Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient’s conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer’s product information, and comparison with recommendations of other authorities.

SAFEGUARDS AGAINST COMMERCIAL BIAS
Postgraduate Institute for Medicine and AXIS affirm that the content and format of the CME activities and related materials promote improvements and quality in healthcare and do not promote a specific proprietary business interest of a commercial entity. To this end, Postgraduate Institute for Medicine and AXIS employ several strategies to ensure the absence of commercial bias, including, but not limited to, review of all planned content for CME activities jointly sponsored by Postgraduate Institute for Medicine and AXIS to ensure adherence to the Accreditation Council for Continuing Medical Education’s content validation statements, and resolution of any actual or perceived conflicts of interest that exist. We employ three metrics as we review materials:

1. Fair balance
   a. Recommendations or emphasis must fairly represent and be based on a reasonable and valid interpretation of the information available on the subject matter
   b. No single product or service is overrepresented when other equal competing products or services are available for inclusion

2. Scientific objectivity of studies mentioned in the materials or used as the basis for content

3. Appropriateness of patient care recommendations made to learners

CONTACT INFORMATION
To contact PIM, please visit www.pimed.com.

MEDIA
Internet

METHOD OF PARTICIPATION
Upon successfully completing the post-test with a score of 70% or better and the activity evaluation, your certificate will be made available immediately.

FEE INFORMATION
There is no fee for this educational activity.
Unraveling the Risks and Benefits of Antiangiogenic Therapy for Ovarian Cancer Patients

Bradley J. Monk, MD, FACS, FACOG
University of Arizona Cancer Center-Phoenix

A CME-certified grand rounds and webinar series entitled, Unraveling the Risks and Benefits of Antiangiogenic Therapy for Ovarian Cancer Patients, was held throughout the United States from October 2014 to April 2015. The questions asked by participants during these activities were collected, compiled, and categorized (see Figure 1 below). The questions highlight several areas of clinical focus in the treatment of ovarian cancer and will be addressed as part of this brief analysis.

In our survey, 77% of questions from participants were treatment related, including questions concerning bevacizumab (39%), general treatment (26%), and olaparib (13%). Other questions focused on predictive markers (10%), side effects (7%), cost (3%), and screening (3%). To address these topics, this activity will focus on questions regarding (1) front-line treatment, (2) recurrent disease, (3) antiangiogenic therapy, and (4) poly (ADP-ribose) polymerase (PARP) inhibitors.

Figure 1:

Frequently Asked Questions (N = 31)

Screening, 9%
Cost, 3%
Side effects, 7%
Predictive markers, 13%
General treatments, 20%
Olaparib, 39%
Bevacizumab, 39%

OVARIAN CANCER

Ovarian cancer is the fifth leading cause of death among women in the United States and the leading cause of death from a gynecologic malignancy. In 2015, there are estimated to be over 21,290 women with ovarian cancer and more than 14,180 deaths (Siegel et al, 2015). The high mortality of women with ovarian cancer is thought to be due to the advanced stage of disease at presentation; approximately 75% of patients have stage III to IV disease at diagnosis. In the 1990s, platinum/taxane chemotherapy supplanted cisplatin/cyclophosphamide and became the international standard of care for the first-line treatment of advanced epithelial ovarian cancer (EOC). Despite initial chemo-sensitivity to platinum/taxane combinations, most patients with advanced EOC experience disease relapse after first-line therapy. Thus, more effective therapies are needed to improve response rates and prolong progression-free survival (PFS), thereby improving both the quality and length of life following the diagnosis of advanced EOC (Coleman et al, 2013).

CONTROVERSIES IN FIRST-LINE TREATMENT

Three treatment options have made the first-line therapy of ovarian cancer increasingly vague and controversial. These include intraperitoneal (IP) chemotherapy, dose-dense weekly paclitaxel, and neoadjuvant chemotherapy.

Intraperitoneal Chemotherapy

IP chemotherapy enhances the exposure of high concentrations of cytotoxic agents to tumors in the peritoneal cavity, the primary site of ovarian cancer. Three intergroup trials have demonstrated a survival benefit associated with IP versus intravenous chemotherapy in advanced, low-volume ovarian cancer. The significance of these findings led to a National Cancer Institute clinical alert recommending IP chemotherapy in small volume advanced disease (Trimble et al, 2008). However, the clinical trial reports and National Cancer Institute clinical alert still did not lead to the pervasive use of IP treatment.

The hesitancy of clinicians to use IP therapy is likely attributed to higher toxicity, inconvenience, and catheter complications. In fact, a significant percent (>50%) of patients do not complete the proposed treatment of 6 cycles of IP therapy due to toxicity and other re-
lated complications. Thus, the optimal dose, schedule, and number of cycles of IP chemotherapy necessary to achieve the maximum benefit are not clear. In addition, there are no studies that have determined which patients are more likely to complete the regimen and benefit from IP therapy, such as those with large volume versus small volume residual disease (Coleman et al, 2013; Echarri Gonzalez et al, 2011). However, a recent publication suggested that the benefits of IP therapy are sustained over an extended period.

To determine the long-term survival and associated prognostic factors after IP chemotherapy among patients with advanced ovarian cancer, data from Gynecologic Oncology Group (GOG) protocols 114 and 172 were retrospectively analyzed using Cox proportional hazards regression models. In 876 patients, median follow-up was 10.7 years. Median survival with IP therapy was 61.8 months (95% CI 55.5-69.5), compared with 51.4 months (95% CI 46.0-58.2) for intravenous therapy. IP therapy was associated with a 23% decreased risk of death (adjusted hazard ratio [AHR] 0.77; 95% CI 0.65-0.90; P = .002) and improved overall survival (OS) in those with gross residual (≤1 cm) disease (AHR 0.75; 95% CI 0.62-0.92; P = .006). The risk of death decreased by 12% for each cycle of IP chemotherapy completed (AHR 0.88; 95% CI 0.83-0.94; P < .001). Factors such as clear/mucinous versus serous histology (AHR 2.79; 95% CI 1.83-4.24; P < .001), gross residual versus no visible disease (AHR 1.89; 95% CI 1.48-2.43; P < .001), and fewer versus more cycles of IP chemotherapy (AHR 0.88; 95% CI 0.83-0.94; P < .001) were associated with poorer survival. Younger patients were more likely to complete the IP regimen, with a 5% decrease in probability of completion with each year of age (odds ratio 0.95; 95% CI 0.93-0.96; P < .001). These data provide provocative evidence that IP chemotherapy should be considered among women with small volume residual disease (≤1 cm) after primary debulking surgery (Tewari et al, 2015).

**Dose-Dense Weekly Paclitaxel**

Prior studies have shown that a more dose-dense administration of paclitaxel can enhance its antineoplastic effect by eliciting antiangiogenic and proapoptotic properties. For example, studies showed that weekly paclitaxel therapy improved the survival of patients with early stage or metastatic breast cancer (Seidman et al, 1998; Norton, 2006). In ovarian cancer, Japanese investigators found that dose-dense weekly paclitaxel and carboplatin (ddwT) improved the PFS and OS compared to conventional every-3-week (q3T) treatment (Katsumata et al, 2013). In a European study of weekly paclitaxel combined with weekly carboplatin, the Multicenter Italian Trials in Ovarian Cancer investigators did not find a benefit in weekly therapy over every-3-week treatment; however, paclitaxel was not administered in a dose-dense method (Pignata et al, 2014).

The encouraging clinical trial results from dose-dense paclitaxel and bevacizumab in epithelial ovarian cancer and other cancers led to the design of a current study to determine if dose-dense weekly paclitaxel combined with carboplatin improves PFS over every-3-weeks paclitaxel and carboplatin with or without bevacizumab in primary treatment of ovarian cancer. GOG protocol 262 randomized (1:1) 692 patients with newly diagnosed, previously untreated ovarian cancer to receive either IV paclitaxel 175 mg/m^2 every 3 weeks + carboplatin (area under the curve [AUC] = 6) for 6 cycles versus paclitaxel 80 mg/m^2 weekly + carboplatin (AUC = 6) for 6 cycles. Eighty-four percent opted to receive bevacizumab. In the intent-to-treat analysis; ddwT did not improve PFS over q3T (14.8 vs 14.3 mo; HR 0.97; 95% CI 0.79-1.18). Of those who did not receive bevacizumab (n = 112), ddwT was associated with a 4-month improvement in PFS over q3T (14 vs 10 mo; HR 0.60; 95% CI 0.37-0.96). However, in those who received bevacizumab, ddwT did not prolong PFS over q3T (15 mo for both arms; HR 1.06; 95% CI 0.86-1.31). A test for homogeneity of treatment effect across strata was significant (P = .047). Compared to q3T, ddwT had more grade 3 or worse anemia (40.8% vs 15.7%), more grade 2 or worse sensory neuropathy (25.9% vs 17.8%), but less grade 3 or worse neutropenia (72% vs 83.1%). This study concluded that ddwT does not prolong PFS over q3T in ovarian cancer. However, in patients who do not receive bevacizumab, ddwT increased the duration of PFS (Chan et al, 2013). The results of this trial suggest that ddwT without bevacizumab provides comparable PFS of q3T with bevacizumab and requires confirmation but is hypothesis generating. It is unclear if these results will affect current treatment decisions in clinical practice.
Neoadjuvant Chemotherapy

Although the standard therapeutic strategy for advanced ovarian cancer is maximum primary debulking surgery followed by chemotherapy, a European Organization for Research and Treatment of Cancer (EORTC) prospective randomized trial of 632 patients reported by Vergote and colleagues demonstrated that neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to the standard procedure (Vergote et al, 2010). The HR for death in the group assigned to neoadjuvant chemotherapy followed by interval debulking, as compared with the group assigned to primary debulking surgery followed by chemotherapy, was 0.98 (90% CI 0.84-1.13; P = .01 for noninferiority), and the HR for PFS was 1.01 (90% CI 0.89-1.15). Although postoperative rates of adverse effects and mortality tended to be higher after primary debulking than after interval debulking, this study raised several controversies, particularly regarding the quality of debulking surgery. Importantly, complete resection of all macroscopic disease (at primary or interval surgery) was the strongest independent variable in predicting OS. However, only 41.6% of patients were rendered optimally debulked to 1 cm or less of residual tumor after primary cytoreduction, as compared with 80.6% of patients after interval cytoreduction (Vergote et al, 2010). Based on these results, neoadjuvant chemotherapy may be a reasonable option for significantly malnourished patients and other nonoptimal surgical candidates, but with the significantly lower optimal debulking rates, these data do not demonstrate noninferiority of neoadjuvant chemotherapy in terms of PFS and OS among all women with newly diagnosed advanced ovarian cancer.

Results from the European randomized chemotherapy or upfront surgery noninferiority trial (CHORUS) were presented at the 2013 Annual Meeting of the American Society of Clinical Oncology in the Gynecologic Oncology Track (Kehoe et al, 2013). Eligibility criteria included imaging consistent with FIGO stage 3 to 4 disease, serum cancer antigen 125:carcinoembryonic antigen (CA-125:CEA) >25, anticipated use of carboplatin-based chemotherapy, and acceptable performance status. The primary endpoint was OS. Patients (N = 552) from 76 centers were randomized between 2004 and 2010. No significant differences in either OS or PFS were identified, and the authors concluded that neoadjuvant chemotherapy was noninferior to primary cytoreduction. Within the primary surgery cohort, 16% of subjects were left with no residual disease, and 25% with ≤1 cm residual. In the neoadjuvant cohort, 40% were left with microscopic residual disease and 35% had ≤1 cm gross residual following interval cytoreduction (Kehoe et al, 2013). Similar to the EORTC study, the results of the CHORUS study should also be interpreted with caution given the low microscopic residual disease rate in the primary surgery arm, and identical median surgical times in both arms of 120 minutes. Nevertheless, neoadjuvant chemotherapy is becoming increasingly popular for the infirm and when complete resection (R0) is not deemed feasible.

APPROACH TO RECURRENT DISEASE

As discussed above, although nearly 75% of patients with advanced disease will respond to platinum- and taxane-based combination therapy and enter into remission, most will unfortunately experience disease relapse during the first 3 years of follow-up (Ledermann et al, 2013). Treatment of these patients is typically based on the perceived tumor sensitivity to platinum agents and may include retreatment with platinum-based combination therapy or completely different agents. Some patients may undergo secondary cytoreduction, depending on the clinical scenario. Unlike patients commencing primary therapy for whom the goal is to cure the cancer, and for whom parameters such as toxicity and convenience of chemotherapy schedule are of secondary importance, in the patient population characterized by disease relapse the goals are to control the disease whenever possible.

Importantly, among those with recurrent disease, quality of life as described by tolerability of therapy and ease of administration (eg, oral versus parenteral route, every 21 days versus every 28 days schedule) becomes a primary focus (Ledermann et al, 2013).

The sensitivity of disease to platinum agents may be categorized as platinum sensitive, partially platinum sensitive, platinum resistant, and platinum refractory (Ledermann et al, 2013; Figure 2). It is important to recognize that the 6-month disease-free interval, which separates platinum-resistant disease from the
partially platinum-sensitive disease, and the 12-month
disease-free demarcation, which separates partially
platinum-sensitive disease from platinum-sensitive
disease, are both arbitrary clinical break points that
are not underlined by any known molecular or biologic
mechanisms. In addition, it has become increasingly
clear that platinum sensitivity is not only an important
clinical prognostic factor in this disease, but also a clin-
ical phenomenon that casts a wide net and may be
interchangeable with chemotherapy sensitivity.

Patients who experience disease relapse >12 months
following primary platinum-based therapy have plati-
num-sensitive disease. The therapeutic landscape for
these patients is dominated by re-induction of plati-
num-based chemotherapy (Coleman et al, 2013). The
addition of a second compound to platinum performed
favorably against single-agent platinum in the Inter-
national Collaborative Ovarian Neoplasm 4 (ICON4)
randomized trial (Parmar et al, 2003). Carboplatin
combined with paclitaxel, gemcitabine, or PLD have
emerged as the principle platinum-based chemother-
apy doublets (Coleman et al, 2013). Importantly, the
replacement of paclitaxel with PLD in the CALYPSO
trial proved the noninferiority of the regimen over car-
boblatin plus paclitaxel (Pujade-Lauraine et al, 2010);
interestingly, carboplatin plus PLD was associated
with improved PFS and enhanced therapeutic ratio.
ANTIANGIOGENIC THERAPY

Angiogenesis plays a fundamental role in normal ovarian physiology as well as in the pathogenesis of ovarian cancer, promoting tumor growth and progression through ascites formation and metastatic spread. Vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) are expressed on ovarian cancer cells, and increased VEGF expression has been associated with the development of malignant ascites and tumor progression (Monk et al, 2012). Bevacizumab, a humanized anti-VEGF monoclonal antibody, is the most widely studied antiangiogenesis agent both across tumor types and specifically in EOC, receiving approval by the US Food and Drug Administration (FDA) on November 14, 2014 in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for the treatment of patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (Monk et al, 2012; FDA News Release, 2014a). Preclinical data suggest that prolonged administration of bevacizumab as maintenance therapy after cisplatin-based chemotherapy prolongs survival by inhibiting or delaying disease recurrence in a murine ovarian cancer model (Mabuchi et al, 2008).

In March of 2005, single agent bevacizumab at 15 mg/kg (IV) every 3 weeks was first reported to be active in a case of recurrent high-grade serous ovarian cancer after failing 11th-line cytotoxic chemotherapy and radiation. An objective durable response lasting at least 5 months was documented (Monk et al, 2005). Since then, many case series and phase 2 trials have confirmed these results. For example, the GOG protocol 170-D prospectively studied single agent bevacizumab at this dose and schedule (15 mg/kg IV every 21 days) among 62 women with recurrent ovarian cancer. Thirteen patients (21.0%) had documented responses (2 complete, 11 partial; median response duration, 10 months), and 25 (40.3%) had PFS for at least 6 months. Median PFS and OS were 4.7 and 17 months, respectively. Prior platinum sensitivity, age, number of prior chemotherapeutic regimens, or performance status were not predictive of clinical activity (Burger et al, 2007).

Most recently, 4 randomized phase 3 trials have been performed adding bevacizumab to either front-line chemotherapy (GOG 218 [Burger et al, 2011]) or ICON7 [Perren et al, 2011]) or to chemotherapy in platinum-resistant (AURELIA Trial [Pujoade-Lauraine et al, 2012]) or platinum-sensitive (OCEANS Trial [Aghajanian et al, 2012]) recurrent EOC. Although all 4 studies met their primary endpoints of prolonging PFS (Table 1), only 2 suggested an improvement in OS among unique subsets of patients. In ICON7, among patients at high risk for progression, the benefit of adding bevacizumab was greatest. The estimated median PFS was 10.5 months with standard therapy, as compared with 15.9 months with bevacizumab (HR for progression or death in the bevacizumab group, 0.68; 95% CI 0.55-0.85; \( P \leq .001 \)). Similarly, there were 188 deaths in this group of women with FIGO stage IV disease or FIGO stage III disease and >1.0 cm of residual disease after debulking surgery (109 in the standard-therapy group and 79 in the bevacizumab group) and the median OS was increased from 28.8 months in the standard-therapy group to 36.6 months in the bevacizumab group (HR for death in the bevacizumab group, 0.64; 95% CI 0.48-0.85; \( P = .002 \)) (Perren et al, 2011). In GOG 218, the median OS for FIGO stage IV subjects was increased from 32.8 months in arm 1 (placebo-containing arm) to 40.6 months in arm 3 with the addition of bevacizumab plus maintenance (HR 0.72, 95% CI 0.53-0.97) (Randall et al, 2013).

Unfortunately, there has been concern about toxicity especially bowel perforation (Han et al, 2007), renal dysfunction, and hypertension (Hayman et al, 2012). In addition, the expense and cost effectiveness of bevacizumab has created much controversy (Cohn et al, 2011). Biomarkers and imaging have not consistently been predictive of response (Han et al, 2010; Chase et al, 2012; Gourley et al, 2014) and patient-reported outcomes have not shown improvements in quality of life with the addition of bevacizumab (Monk et al, 2013). Importantly, both AUERLIA and ICON7 were not placebo-controlled trials, creating a potential bias in evaluating both patient-reported outcome and PFS. OCEANS had no patient-reported outcomes at all.

Newer antiangiogenics as well as agents like vascular disrupting agents (VDAs) that target existing blood vessels are in development. Angiopoietin-1 (Ang1) and -2 (Ang2) interact with the Tie2 receptor, which is expressed on endothelial cells, to mediate vascular remodeling in a signaling pathway that is distinct
from the VEGF axis. Ang1 promotes vessel stabilization by increasing endothelial junctions and pericyte coverage; Ang2 blocks Ang1’s blood vessel stabilizing action, increasing angiogenesis and vascularity in tumors (Augustin et al, 2009; Falcon et al, 2009; Scharpfenecker et al, 2005). Trebananib (formerly known as AMG 386) is a peptide-Fc fusion protein (or peptibody) that acts by binding both Ang 1 and Ang2, thus preventing their interaction with the Tie2 receptor. Trebananib has shown antiangiogenesis activity in preclinical models of ovarian cancer, single-agent activity in relapsed ovarian cancer in a phase 1 study, as well as prolongation of PFS in randomized phase 2 and 3 trials in recurrent EOC (Herbst et al, 2009; Karlan et al, 2012; Monk et al, 2014). In contrast to anti-VEGF agents, trebananib has not been associated with an increase in typical class-related anti-VEGF toxicities (Burger et al, 2011). Its most significant toxicity has been reported to be edema (Monk et al, 2014). The results of Trebananib in Ovarian Cancer -1 (TRINOVA-1), a 919 subject randomized placebo-controlled phase 3 trial investigating the addition of trebananib to single-agent weekly paclitaxel in relapsed EOC, showed a PFS improvement of 52% (Cox model HR 0.66; 95% CI 0.56-0.76; P < .001) from a median of 5.4 (95% CI 4.3-5.5) to 7.2 months (95% CI 5.8-7.4) (Monk et al, 2014).

VDAs are distinct from typical antiangiogenics and are ideal candidates to combine with antiangiogenic agents such as bevacizumab. In contrast to angiogenesis agents that target VEGF and angiopoetins, VDAs target existing tumor vascular rather than preventing neovascularization. Tumor vessels can be selectively targeted by VDAs because the newly formed endothelial cells associated with cancer progression lack smooth muscle and pericyte coverage thereby relying more on intracellular tubulin to maintain their flat tube-like shape in vessel walls. VDAs that inhibit cancer-associated endothelial cell tubulin cause the affected endothelial cells to “round up” thereby obstructing tumor-associated blood vessel lumens. This causes vessel collapse and obstruction. Finally, non-tumor-associated blood vessels are relatively resistant to VDAs not only because of increased amounts of endothelial cell smooth muscle, but also because of increased endothelial pericyte coverage, allowing them to maintain their shape when exposed to VDAs (Spear et al, 2011; Mita et al, 2013).

Table 1:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Arms</th>
<th>PFS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 218 First-line EOC</td>
<td>Carboplatin/paclitaxel + placebo, placebo maintenance</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>Carboplatin/paclitaxel + bevacizumab, placebo maintenance</td>
<td>11.6 (HR 0.89; P = .0437)</td>
</tr>
<tr>
<td></td>
<td>Carboplatin/paclitaxel + bevacizumab, bevacizumab maintenance</td>
<td>14.7 (HR 0.70; P &lt; .0001)</td>
</tr>
<tr>
<td>ICON7 First-line EOC</td>
<td>Carboplatin/paclitaxel</td>
<td>17.3</td>
</tr>
<tr>
<td></td>
<td>Carboplatin/paclitaxel + bevacizumab</td>
<td>19.0 (HR 0.81; P = .0041)</td>
</tr>
<tr>
<td>AURELIA Platinum-resistant recurrent EOC</td>
<td>Single-agent chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan)</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Single-agent chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan) + bevacizumab</td>
<td>6.7 (HR 0.48; P &lt; .001)</td>
</tr>
<tr>
<td>OCEANS Platinum-sensitive recurrent EOC</td>
<td>Carboplatin/gemcitabine + placebo</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>Carboplatin/gemcitabine + bevacizumab</td>
<td>12.4 (HR 0.48; P &lt; .0001)</td>
</tr>
</tbody>
</table>
Interestingly, cells on the periphery of solid tumors are also relatively insensitive to VDA-induced vascular shutdown. This resistant peripheral rim of tumor cells contributes to tumor regeneration, metastasis, and ongoing progression after VDA exposure. Conceptually, combining VDAs with antiangiogenesis compounds such as bevacizumab might overcome this “regrowth” phenomenon (Spear et al, 2011; Mita et al, 2013).

Combretastatin A4 (CA4) is a VDA originally isolated from the African bush willow (Combretum caffrum). Fosbretabulin is a water-soluble prodrug of cis-combretastatin A4 (cis-CA4) otherwise known as combretastatin A4 mono tris phosphate (abbreviated in the literature as CA4P). Fosbretabulin is a small molecule that acts as a potent and reversible tubulin depolymerizing agent (Gridelli et al, 2009). Preclinical models have shown that fosbretabulin results in massive acute vascular collapse as early as 2 hours after administration with recovery as soon as 24 hours providing further rationale for combining with bevacizumab. In a phase 1 study of the combination of fosbretabulin plus bevacizumab, the dose-limiting toxicity appeared to be hypertension with the maximum tolerated dose of fosbretabulin being 63 mg/m$^2$ every other week. Importantly, this study showed dynamic contrast enhanced diffusion weighted MRI evidence of profound vascular changes associated with fosbretabulin administration that were only sustained following bevacizumab (Nathan et al, 2012). In a recent randomized phase 2 study in recurrent ovarian cancer, the combination of bevacizumab + fosbretabulin improved PFS compared to bevacizumab alone (HR 0.685; 90% 2-sided CI 0.47-1.00). The proportion responding to bevacizumab was 28.2% (90% CI 16.7-42.3) among 39 patients with measurable disease and 35.7% (90% CI 23.5-49.5) among 42 patients treated with the combination (Monk et al, 2014). Phase 3 trials of this novel non-cytotoxic chemotherapy combination are indicated.

**PARP INHIBITORS**

The most common histologic subtype of EOC is high-grade serous and is characterized by genetic instability and almost universal p53 dysfunction. This phenotype frequently arises as a consequence of defects in the repair of damaged DNA, rendering cancer cells susceptible to DNA-damaging platinum compounds and targeted therapies affecting homologous recombination repair (Ahmed et al, 2010). PARP is a family of proteins involved in the repair of signal single-strand DNA breaks. When cells already deficient in homologous recombination repair are exposed to PARP inhibitors, apoptosis occurs by way of synthetic lethality (Curtin et al, 2013).

Recently, Kaufman et al studied olaparib (400 mg twice daily) in a spectrum of BRCA1/2-associated cancers. Enrollment was restricted to patients with germline BRCA1/2-positive, platinum-resistant recurrent ovarian cancer, breast cancer following 3 or more chemotheraphy regimens, pancreatic cancer with prior gemcitabine treatment, or prostate cancer with progression on hormonal therapy and 1 systemic therapy. In the entire cohort of 298 evaluable patients, the overall response rate was 26.2% overall. The highest responses were reported in patients with prostate (50.0%, 4/8) and ovarian cancer (31.1%, 60/193; 95% CI 24.6-38.1). Only 8 (12.9%; 95% CI 5.7-23.9) of the 62 women with breast cancer experienced objective tumor response by RECIST criteria. Grade 3 or higher adverse events were reported for 54% of patients, with anemia (17%) being most common (Kaufman et al, 2015).

On June 25, 2014, the FDA’s Oncology Drugs Advisory Committee panel members voted 11 to 2 against regulatory approval of olaparib as maintenance therapy for ovarian cancer based on Study 19 (described below) (FDA News Release, 2014b; Ledermann et al, 2012). Additional data from the single arm, open-label phase 2 trial by Kaufman and colleagues was submitted, emphasizing the 31.1% response rate observed in the BRCA-deficient ovarian cancer cohort (Kaufman et al, 2015). These data prompted the FDA to extend the original October 3, 2014 Prescription Drug User Fee Act action date to January 3, 2015. On December 19, 2014, the FDA granted accelerated approval to olaparib as fourth-line therapy for women with BRCA-deficient (germline only) ovarian carcinoma (FDA News Release, 2014c). The ongoing phase 3 randomized study, SOLO 2 (NCT01874353), and its successor SOLO 3 (NCT02282020), are integral to the phase 4 commitment following accelerated approval. FDA approval was done in conjunction with regulatory approval of a companion diagnostic genetic test (BRA-
CAnalysis CDx) that will screen blood from patients with ovarian cancer for mutations in the BRCA genes (gBRCAm). Interestingly, 1 day before regulatory approval in the United States, on December 18, 2014, the European Commission granted marketing authorization for olaparib as a first-line maintenance therapy for adult patients with platinum-sensitive, relapsed BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian, tubal, or peritoneal carcinoma (as reported in Study 19) (Ledermann et al, 2012; Astra-Zeneca News Release, 2014).

In the randomized, double-blind, placebo-controlled, phase 2 Study 19, 265 patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had received 2 or more platinum-based regimens and had had a partial or complete response to their most recent platinum-based regimen were randomized 1:1 to receive either olaparib, at a dose of 400 mg twice daily (n = 136), or placebo (n = 129). In March 2012, data from this interim analysis were published in The New England Journal of Medicine showing an improvement in median PFS of 8.4 months with olaparib compared with 4.8 months with placebo (HR 0.35; 95% CI 0.25-0.49; P < .001) but no significant difference for OS (Ledermann et al, 2012). In a retrospective, preplanned analysis by BRCA mutation status, median PFS was significantly longer in the olaparib group than in the placebo group (11.2 months [95% CI 8.3-not calculable] vs 4.3 months [95% CI 3.0-5.4]; HR 0.18 [0.10-0.31]; P < .0001) for patients with a BRCA mutation. BRCA status was known for 131 (96%) patients in the olaparib group versus 123 (95%) in the placebo group, of whom 74 (56%) versus 62 (50%) had a deleterious or suspected deleterious germline or tumor BRCA mutation. The most common grade 3 or worse adverse events in the olaparib group were fatigue (7% vs 3%) and anemia (5% vs <1%) (Ledermann et al, 2014).

The clinical implications of approving a drug for fourth-line therapy need to be framed in the context of toxicity assessment. This is particularly important in the setting of recurrent disease where quality of life/disease control is the goal. BRCA-deficient patients who were initially platinum sensitive and have become candidates for olaparib therapy are likely to have received 2 lines of platinum-based therapy and a third line of therapy consisting of either one of the AURE-LIA regimens or monotherapy with PLD or topotecan. Olaparib can then be weighed against what they did not receive in third line. Alternatively, in designing a fourth-line chemotherapy regimen, one must consider that the patient will have been treated with platinum-based therapy in the first line, one of the AURELIA regimens in the second line, and either PLD or topotecan (with or without bevacizumab) in the third line. In both examples, toxicity assessment can guide drug selection. As can clearly be seen, olaparib appears to have a more favorable safety profile compared to conventional chemotherapy used in the recurrent setting.

The combination of olaparib (400 mg twice daily) plus bevacizumab (10 mg/kg every 2 weeks) was well tolerated with no dose-limiting toxicities in a phase 1 study involving 12 heavily pretreated patients with solid tumors (Dean et al, 2012). Finally, in a randomized phase 2 study of 90 women with either measurable platinum-sensitive, recurrent, high-grade serous or endometrioid ovarian carcinoma or those with deleterious germline BRCA1/2 mutations were randomized to olaparib 400 mg twice daily or 200 mg twice daily plus the antiangiogenesis orally administered drug, cediranib 30 mg daily. The combination was associated with significantly improved PFS (17.7 vs 9.0 months; HR 0.42; 95% CI 0.23-0.76; P = .005). Grade 3 and 4 fatigue, diarrhea, and hypertension were more common with combination therapy (Liu et al, 2014). This represents another chemotherapy-free alternative for select patients with recurrent disease.

CONCLUSIONS AND LOOKING TOWARD THE FUTURE

With 2 new FDA approvals of targeted agents for EOC in 2014, the future is bright. Angiogenesis and PARP inhibitors are valid targets for the treatment of EOC. Other angiogenesis agents such as those that target Ang1/Ang2 as well as VDAs and novel combinations are in development. Importantly, biosimilars open new opportunities for less expensive medicines.

The next frontier, like many other solid tumors, is immunotherapy. It is now commonly believed that ovarian cancers are immunogenic tumors. A large stepping-stone in the advancement of anti-tumor immune responses in ovarian carcinomas has been the char-
acterization of tumor infiltrating lymphocytes (TILs). Correlation between the presence of TILs and prolonged PFS and OS has been demonstrated in patients with advanced stage ovarian carcinoma. Specifically, the presence of CD8+ TILs has been demonstrated to correlate with increased survival. Conversely, the presence of immunosuppressive regulatory T cells, classified as CD4+/CD25+/FoxP3+ T cells, have been associated with decreased survival. Finally, ovarian cancers express tumor antigens, and patients have demonstrated spontaneous anti-tumor responses, which are specific to these antigens. Antibody-based therapies, immune checkpoint blockade, cancer vaccines, and chimeric antigen receptor-modified T cells have all demonstrated preclinical success and entered clinical testing (Mantia-Smaldone et al, 2012).

Given the cost, potential for toxicity, and finding that only a subset of patients will benefit from these drugs, identification of predictive biomarkers is critical. In addition, there are challenges regarding the optimal drug combination, schedule, timing, and dose of chemotherapeutic agents in ovarian cancer. It is also clear that a substantial number of cases of ovarian cancer will develop resistance to antiangiogenesis and PARP inhibitor therapy. This has led to the urgent investigation of stem cells and mechanisms of drug resistance.
REFERENCES


Han ES, Monk BJ. What is the risk of bowel perforation associated with bevacizumab therapy in ovarian cancer? Gynecol Oncol. 2007;105(1):3-6.


GLOSSARY OF PHARMACEUTICAL AGENTS

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>bevacizumab</td>
<td>Avastin®</td>
</tr>
<tr>
<td>carboplatin</td>
<td>Paraplatin®</td>
</tr>
<tr>
<td>cediranib</td>
<td>Recentin™</td>
</tr>
<tr>
<td>cisplatin</td>
<td>Platinol®</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>Cytoxan® Neosar®</td>
</tr>
<tr>
<td>fosfotubulin (CA4P)</td>
<td>Zybretstat®</td>
</tr>
<tr>
<td>gemcitabine</td>
<td>Gemzar®</td>
</tr>
<tr>
<td>olaparib</td>
<td>Lynparza™</td>
</tr>
<tr>
<td>paclitaxel</td>
<td>Taxol®</td>
</tr>
<tr>
<td>pegylated liposomal doxorubicin</td>
<td>Doxil® Evact™ Lipo-Dox® Caelxy® Doxilen™</td>
</tr>
<tr>
<td>topotecan</td>
<td>Hycamint®</td>
</tr>
<tr>
<td>trabectedin</td>
<td>Yondelis®</td>
</tr>
</tbody>
</table>
About AXIS Medical Education, Inc.

AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, on-demand, and print-based educational activities for healthcare professionals. AXIS delivers convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 25 years of experience in medical meeting planning, logistics, adult learning, and curriculum design/implementation. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities. AXIS employs an experienced team of medical writers, meeting planning and logistics professionals, medical experts, and project managers, all dedicated to meeting the unmet educational needs of healthcare professionals designed to improve patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. AXIS partners with other specialty medical education companies and accredited providers to offer added expertise and assist in expanding access to our educational interventions.

The mission of AXIS is to enhance the knowledge, skills, and performance of healthcare professionals to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led accredited educational programs designed to foster lifelong learning that is applicable to clinical practice.

To learn more and to see our current educational offerings, visit us online at www.AXISMedEd.com.