

**Advances in the Management of Ovarian Cancer:**  
Highlights from the 2010 American Society of Clinical  
Oncology Annual Meeting

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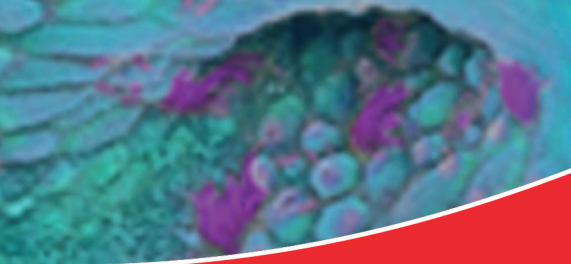
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# Advances in the Management of Ovarian Cancer: Highlights from the 2010 American Society of Clinical Oncology Annual Meeting

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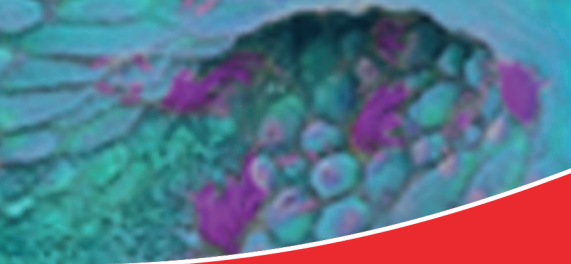
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### **Target Audience**

The intended audience for this initiative includes gynecologic oncologists, medical oncologists, surgical oncologists, and oncology specialty pharmacists caring for patients with ovarian cancer.

### **Learning Objectives**

Upon completion of this educational activity, participants should be better able to:

- Recognize biologic pathways of significance in ovarian cancer pathogenesis and resistance
- Examine current treatment options in the management of ovarian cancer
- Propose an appropriate regimen for patients with either newly diagnosed or relapsed and recurrent ovarian cancer
- Discuss toxicity prevention, identification, and management strategies for patients receiving therapy for ovarian cancer

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## Introduction

The 2010 Annual Meeting of the American Society of Clinical Oncology brought together over 30,000 clinicians and healthcare professionals in Chicago, Illinois June 4-8. Advances in the treatment and management of ovarian cancer discussed included expanded use of novel therapeutics, innovative risk assessment modalities and predictive markers, and new treatment agents and regimens.

## Plenary Proceedings

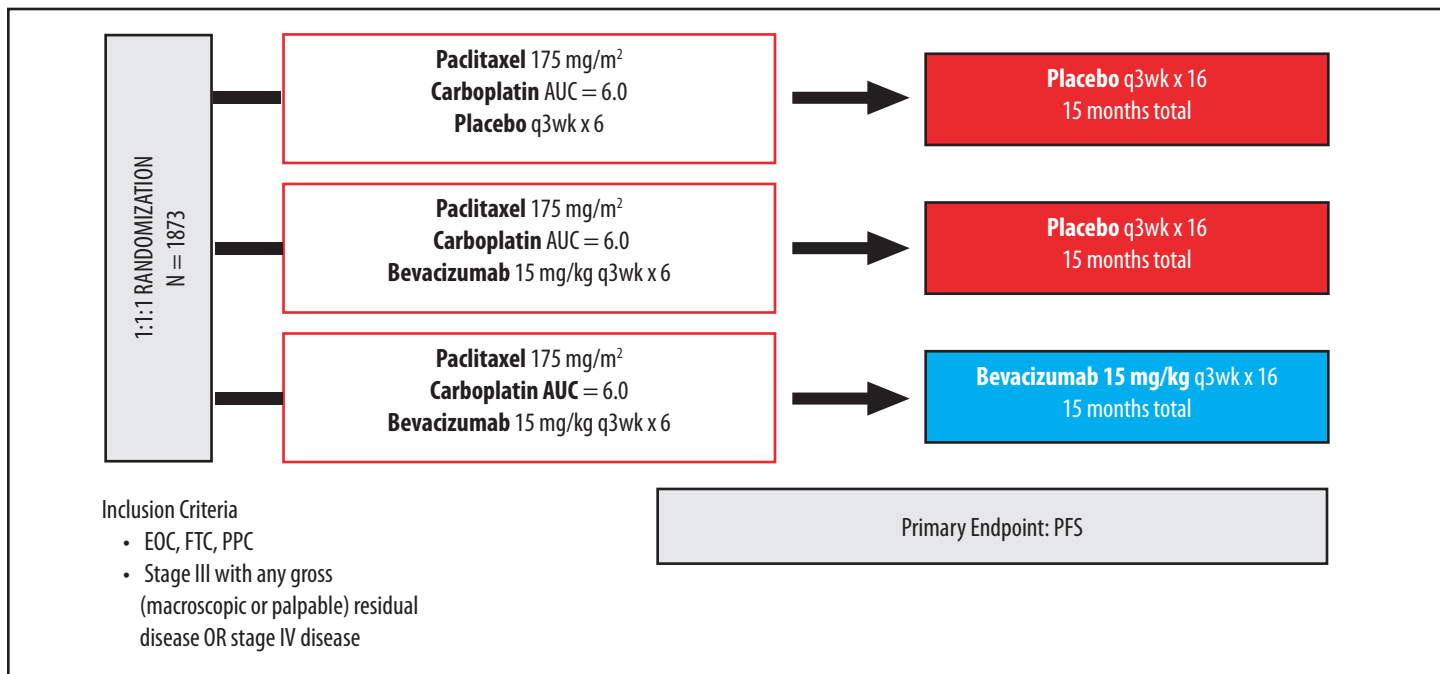
Building on the phase II single-agent experience of bevacizumab in ovarian cancer, Dr Robert Burger, Fox Chase Cancer Center, Philadelphia, PA presented outcomes from Gynecologic Oncology Group (GOG)-0218, a phase III trial evaluating bevacizumab-containing regimens as the primary treatment of advanced epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), and primary peritoneal cancer (PPC) as compared to standard chemotherapy alone.<sup>1</sup> A total of 1873 patients from 336 sites across 4 countries were stratified by prognostic factors and randomized (1:1:1) into 3 study arms. **Figure 1.**

- **Arm A (CP):** carboplatin/paclitaxel/placebo (cycles 1-6)/followed by placebo maintenance (cycles 7-22)
- **Arm B (CP + BEV):** carboplatin/paclitaxel/bevacizumab (cycles 2-6) followed by placebo maintenance (cycles 7-22)
- **Arm C (CP + BEV → BEV):** carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance (cycles 7-22)

Infusions were administered on day 1 of a 21-day cycle and patients received 22 cycles of therapy unless treatment was discontinued due to disease progression, unacceptable toxicity, or patient choice. While the original study design included overall survival (OS) as the primary outcome measure, the study was amended to measure progression-free survival (PFS) of each experimental arm (B or C) compared to the control arm (A) as the primary endpoint.

Eligible patients had newly diagnosed, previously untreated, stage III or IV EOC, PPC, or FTC following abdominal surgery for staging and tumor debulking. Baseline characteristics are presented in **Table 1.**

**Figure 1. GOG-0218 Schema**





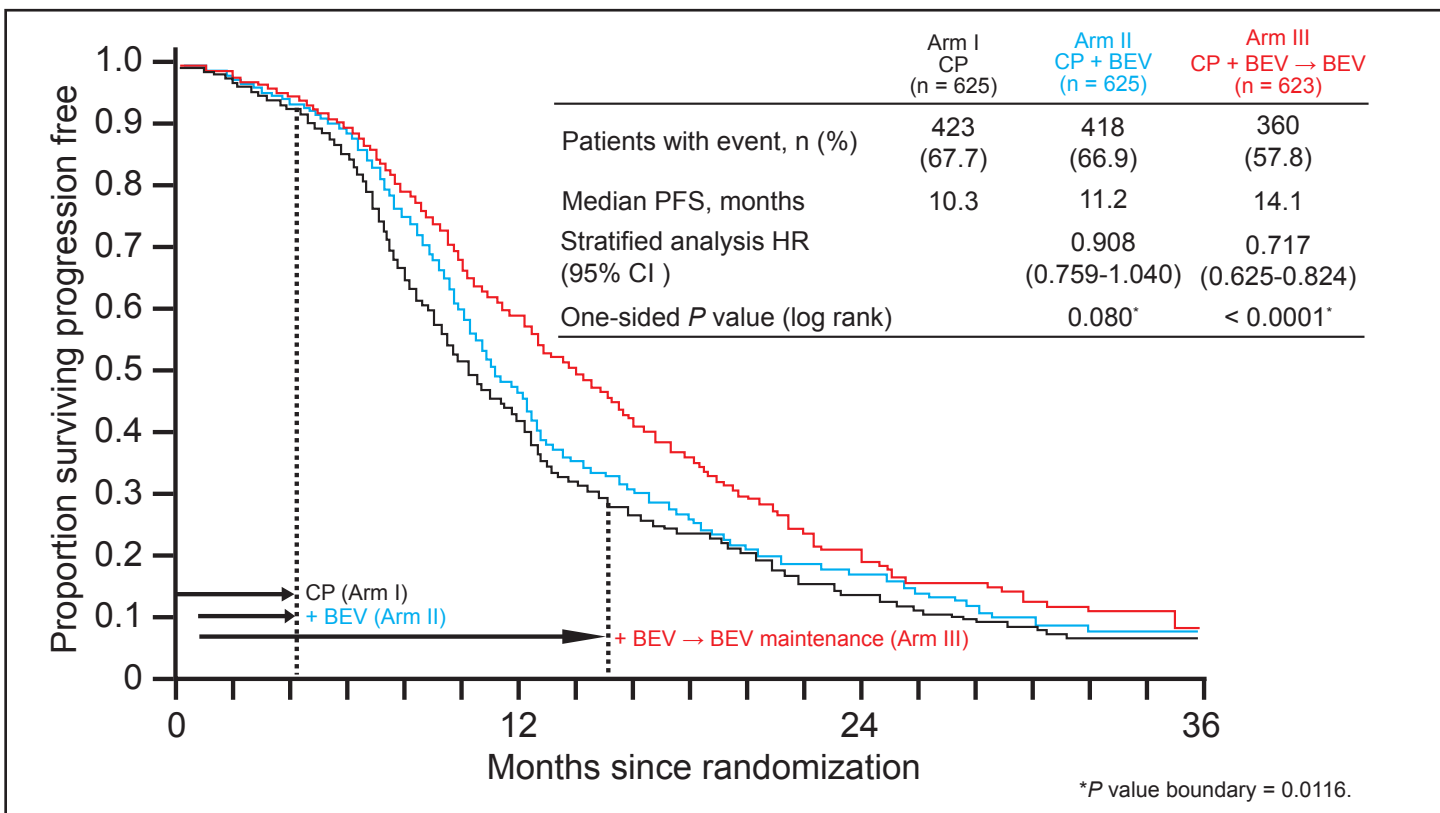
**Table 1. Baseline Characteristics**

	CP (n = 625)	CP + BEV (n = 625)	CP + BEV → BEV (n = 623)
Median age, years	60	60	60
Suboptimally debulked stage III disease	41%	41%	39%
Stage IV disease	25%	26%	27%
Median number of cycles with bevacizumab or placebo (range)	11 (0-22)	12 (0-22)	14 (0-21)
On treatment at time of analysis	14%	13%	19%
Completed treatment regimen	16%	17%	24%
Experienced disease progression while on treatment	48%	42%	26%

While there was no significant difference in median PFS between CP (10.3 months) and CP + BEV (11.2 months), CP + BEV → BEV (14.1 months) demonstrated significantly longer median PFS as compared to CP alone ( $P < 0.0001$ ).

**Figure 2.**

**Figure 2. Progression-Free Survival**



Relative to CP, the hazard ratio of first progression or death for CP + BEV was 0.908 (95% CI: 0.795-1.04,  $P = 0.16$ ) and for CP + BEV → BEV was 0.717 (95% CI: 0.625-0.824,  $P < 0.0001$ ). All PFS subanalyses conducted favored CP + BEV → BEV over CP. At the time of PFS analysis, there appeared no significant difference in the median OS between CP (39.3 months), CP + BEV (38.7 months), or CP + BEV → BEV (39.7 months), although events had occurred in only 24% of enrollees. **Figure 3.**

When censored for CA-125 determined progression, the median PFS in the CP arm was 12.0 months and 18.0 months in the CP + BEV → BEV arm for an absolute difference of 6.0 months, (HR 0.645,  $P < 0.001$ ). All 3 treatment arms were generally well tolerated and selected adverse events (AEs) at cycle 2 are presented in **Table 2.**

Figure 3. Overall Survival

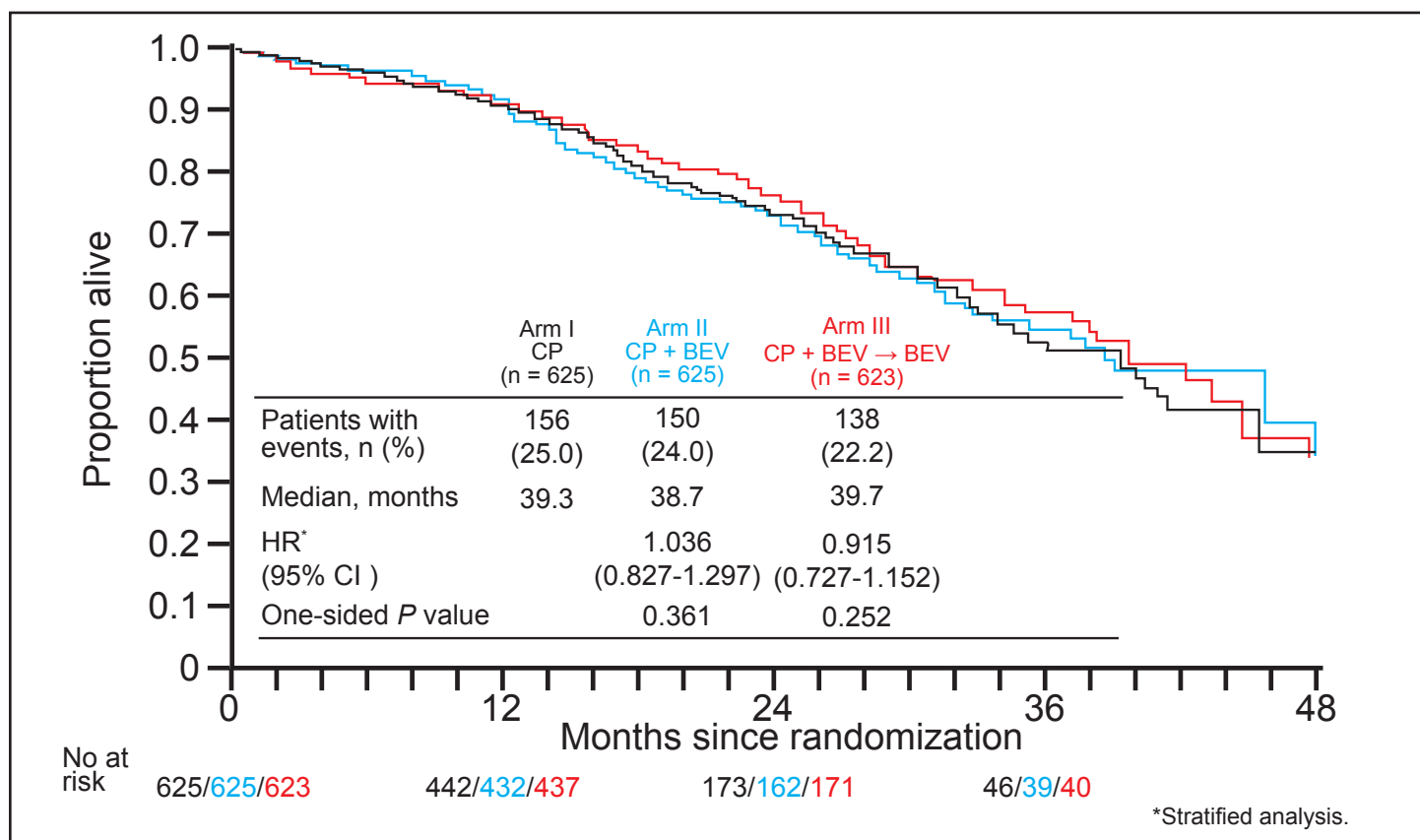


Table 2. Selected Adverse Events Between Cycle 2 and the Date of Last Treatment

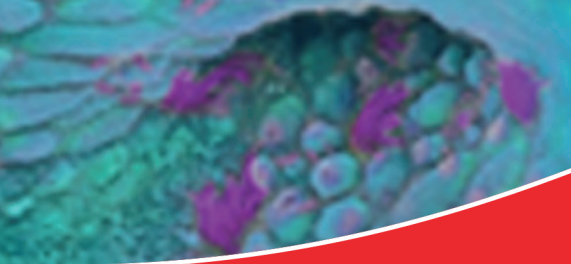
	CP (n = 601)	CP + BEV (n = 607)	CT + BEV → BEV (n = 608)	P Value
≥ Grade 2 Gastrointestinal events	1.2%	2.8%	2.6%	NS
≥ Grade 3 Hypertension	1.7%	5.9%	10.4%	< 0.05
≥ Grade 3 Proteinuria	0.7%	0.7%	1.6%	NS
≥ Grade 2 Pain	41.7%	41.5%	47.1%	< 0.05
Venous thromboembolic event	5.8%	5.3%	6.9%	NS
Arterial thromboembolic event	0.8%	0.7%	0.7%	NS
Reversible posterior leukoencephalopathy syndrome (RPLS)	0%	0.2%	0.2%	NS
≥ Grade 4 Neutropenia	57.7%	63.3%	63.3%	NS
Febrile neutropenia	3.5%	4.9%	4.3%	NS

NS = non-significant.

In summary, GOG-0218 met its primary objective; determining CP + BEV → BEV maintenance prolonged PFS as compared to CP alone. However, the combination of CP + BEV did not improve PFS as compared to CP alone. This study has identified bevacizumab as the first targeted antiangiogenic agent to demonstrate in a phase III investigation both a tolerable safety profile and PFS benefit when used with first-line chemotherapy and continued as single-agent maintenance in patients with advanced ovarian cancer.

**Editor Discussion**

According to Drs Robert Coleman and Judith Wolf of The University of Texas, MD Anderson Cancer Center, Houston, TX, the results of this landmark study are provocative but raise several additional questions.



For instance:

- Why was there no benefit in adding bevacizumab to chemotherapy without maintenance? A corollary question is whether chemotherapy followed by maintenance biological therapy could be just as effective?
- Since OS, although immature at the moment, appears to be similar among the arms, could the same overall benefit to patients be achieved by withholding bevacizumab until recurrence?
- Will previous exposure to bevacizumab impact subsequent angiogenesis-based therapy and will these tumors have a more aggressive phenotype?
- Is there a way to prospectively identify in whom the therapy would be most effective in this strategy?
- Or, could OS be more favorably impacted by a longer maintenance prescription of bevacizumab?

Fortunately, many of these questions are the subject of ongoing clinical trials. Dr Wolf adds, GOG-0218 should be interpreted in light of a previous GOG trial (GOG-178) comparing 3 vs 12 months of monthly paclitaxel maintenance, which showed a 7-month improvement in PFS with no improvement in OS. The question of paclitaxel as maintenance is also being evaluated in the current GOG-0212 trial. Additional information on GOG-0212 can be found at <http://www.cancer.gov/clinicaltrials/GOG-0212>.

## Risk Assessment and Therapeutic Prediction

### *Risk of Ovarian Cancer Algorithm (ROCA)*

Ovarian cancer is the most lethal gynecologic cancer and the 4th leading cause of death among women in the United States (US). The estimated prevalence of ovarian cancer in postmenopausal women is 1:2500. Despite the profound mortality associated with the disease, there remains no effective screening method for the early detection of ovarian cancer within the general population. Dr Karen Lu of The University of Texas, MD Anderson Cancer Center, Houston, TX, presented the results of a single-arm, prospective,

multicenter screening study that evaluated the utility of the Risk of Ovarian Cancer Algorithm (ROCA) among postmenopausal women in the US.<sup>2</sup> ROCA is a personalized algorithm that estimates risk of ovarian cancer based on a patient's age, baseline CA-125, and change in CA-125 over time.

The study enrolled 3252 postmenopausal women age 50-74 with no significant family history of breast or ovarian cancer. Patients received a baseline CA-125 blood test and were re-tested annually. Patients who were estimated to have low risk were triaged to the next annual CA-125, patients with intermediate risk received a repeat CA-125 at 3 months, and patients at high risk were referred for transvaginal sonography (TVS) and results were evaluated by a gynecologic oncologist.

The average annual risk estimate by ROCA for this population was 92.6% normal, 6.5% intermediate, and 0.5% high. Cumulatively 85 women (2.6%) were referred for TVS and gynecologic oncology consultation. From these 85, 8 (9.4% of referrals) underwent surgery, where 3 invasive ovarian cancers (2 stage 1C and stage IIB), 2 borderline ovarian tumors, and 3 benign ovarian tumors were identified. The resulting positive predictive value (PPV) was 37.5% (95% CI 8.5%-75.5%) with a specificity of 99.9% (95% CI 99.5%-99.9%).

In this study, ROCA demonstrated high specificity with few false positives among postmenopausal women with no significant family history of breast or ovarian cancer. All of the cancers identified in the trial were high-grade serous and early stage offering promise that the strategy, when expanded in a larger population base, could affect the natural history of the disease. The PPV observed in this trial was remarkably similar to the preliminary results of an earlier prevalence report from the ongoing UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) study using the same Bayesian-based ROCA triage tool in one arm of the 202,638 patient

3-armed randomized controlled screening trial in women meeting the same eligibility criteria as the current study. The presence of a control group in the UKCTOCS study enables a formal assessment of screening healthy menopausal women at average risk for ovarian cancer on disease-specific mortality. These highly anticipated results are due in 2014.

### **Gene Expression Profile That Correlates With Treatment Responsiveness**

Dr Panagiotis Konstantinopoulos of Beth Israel Deaconess Medical Center, Boston, MA presented results from a study evaluating a gene expression profile for “BRCA-ness”.<sup>3</sup> The BRCA phenotype describes ovarian tumors that are highly responsive to platinum-based therapy in the first-line setting and at relapse, are associated with long treatment-free intervals between relapse, improved OS, and usually, but not always, of serous histology. More recently, BRCA tumors have been found sensitive to PARP inhibition due to an underlying defect in homologous recombination (HR). It has been suggested that PARP inhibition may also be a useful therapeutic strategy for the treatment of patients with sporadic cancers that harbor the BRCA phenotype. In order to better identify such patients, Konstantinopoulos et al defined a gene expression profile of BRCA-ness that correlates with responsiveness to platinum-based therapy and PARP inhibitors.

A microarray data set, which included 61 patients with pathologically confirmed EOC, including 18 with germline BRCA1 mutations, 16 with germline BRCA2 mutations, and 27 without either mutation (sporadic tumors), was used to develop the profile. A 60-gene expression signature was identified that classified samples as non-BRCA-like (NBL) and BRCA-like (BL). The NBL profile cohort was enriched for platinum resistance while the BL profile cohort was enriched for platinum sensitivity. The BL profile was associated with in vitro PARP inhibitor responsiveness. There also was an association with PARP inhibitor responsiveness and radiation-induced RAD51 foci formation (a surrogate of HR) in Capan-1 cell line clones.

The BRCA-ness profile was validated in an independent cohort of 70 untreated patients (35 patients with sporadic EOC who had been sequenced for BRCA1/2 and found to be wild type and 35 patients with sporadic EOC who had not received BRCA sequencing). The profile designated 20/70 (29%) of the validation cohort patients as BL (8/35 [23%] of the sequence-negative cohort and 12/35 [34%] of the non-sequenced cohort) and 50/70 (71%) as NBL.

When the gene-signature was applied to the independent cohort, patients with the BL profile had improved disease-free survival (DFS) (34 months vs 15 months,  $P < 0.013$ ) and OS (72 months vs 41 months,  $P < 0.006$ ) compared to patients with the NBL profile. The BRCA-ness profile maintained independent prognostic value in multivariate analysis.

In this study, the BRCA-ness profile correlated with responsiveness to platinum compounds and in vitro response to PARP inhibitors and identified a subset of patients with sporadic tumors who experienced improved outcome. Upon further investigation and validation, use of this profile may ultimately permit identification of sporadic EOC patients who may benefit from PARP inhibitor therapy.

### **Front-Line Therapy**

#### **Gemcitabine or Paclitaxel Plus Carboplatin Followed by Elective Paclitaxel Consolidation**

While carboplatin/paclitaxel may be considered the most common first-line treatment for ovarian cancer, a number of additional agents are being evaluated for safety and efficacy in this setting. Dr Michael Teneriello, US Oncology, The Woodlands, TX, presented the final safety and efficacy report from a phase III trial comparing 6 cycles of gemcitabine 1,000 mg/m<sup>2</sup>/carboplatin AUC 5 (GC) to 6 cycles of paclitaxel 175 mg/m<sup>2</sup>/carboplatin AUC 6 (PC) as induction therapy followed by elective consolidation with paclitaxel (135 mg/m<sup>2</sup>) in patients with stage IC-IV EOC.<sup>4</sup> This open-label, multicenter, randomized trial

enrolled 919 patients. The primary endpoint was PFS, however, the trial was stopped early after an ad hoc futility analysis indicated a low probability of a positive PFS result in the experimental arm.

Baseline characteristics were balanced across treatment arms, with a median age of 61 years. Efficacy outcomes are presented in **Table 3**. There was no significant difference in PFS between GC and PC. Although median OS significantly favored PC, statistical significance was lost after adjusting for significant covariates. There was no significant difference in OS between patients receiving crossover therapy with P and patients receiving crossover therapy with G. Overall, there was no difference in PFS for induction, crossover, or consolidation. Both treatments were well tolerated, with grade 3/4 anemia occurring more often in patients receiving GC (27.4%) than in patients receiving PC (7.6%) ( $P < 0.0001$ ).

**Table 3. Efficacy Outcomes**

	GC	PC	P Value
Overall Response Rate	67.6%	71%	0.771
Median PFS	20.0 months	22.2 months	0.199
Median OS	43.8 months	57.3 months	0.013
Patients Achieving CR	GC followed by P Consolidation	PC followed by P Consolidation	P Value
Median OS	56.1 months	Not reached	0.035

While PFS was similar between GC and PC, OS analysis was limited by study design and high censorship. The question of utility of paclitaxel consolidation could not be answered. The authors concluded that GC does not offer an advantage over standard of care PC for first-line chemotherapy in advanced ovarian cancer. However, in patients with significant pre-existing neuropathy the GC regimen may be another option for therapy.

#### **Intraperitoneal Carboplatin and Paclitaxel With Intravenous Bevacizumab**

Dr Carolyn Krasner of Massachusetts General Hospital, Gillette Center for Women's Cancer, Boston, MA

presented the results from a pilot study that evaluated a combination bevacizumab regimen, in this case, carboplatin (AUC 6 on day 1) and paclitaxel (60 mg/m<sup>2</sup> on days 1, 8, 15) given by IV in cycle 1 followed by intraperitoneal (IP) carboplatin/paclitaxel and IV bevacizumab (15 mg/kg) commencing day 8, cycle 2 for an additional 5, 21-day cycles.<sup>5</sup>

A total of 40 patients were enrolled with 34 completing all 6 cycles of treatment. No patient experienced progressive disease and toxicity was generally mild with no bowel perforations, febrile neutropenia, grade 3/4 neuropathy, hypertension, proteinuria, renal complications, or delayed wound healing. No major additive toxicity was observed with the addition of bevacizumab. Grade 3/4 toxicities included neutropenia (25%), fatigue (15%), platelets (12%), nausea (10%), abdominal pain (8%), and thrombosis (5%).

Pharmacokinetic results demonstrated that the addition of bevacizumab increased the systemic uptake of paclitaxel administered via the peritoneal cavity. In conclusion, the regimen appeared feasible for additional study and without unanticipated additional toxicity signals. Phase III trials of IP regimens in addition to bevacizumab are ongoing including GOG-0252. Additional information on GOG-0252 can be found at <http://www.cancer.gov/clinicaltrials/ft-GOG-0252>.

#### **Recurrent Disease**

The goal of second-line treatment for recurrent disease is 3-fold, palliation of symptoms, preservation of quality-of-life, and prolongation of PFS. However, at this time, the median PFS among patients with recurrent platinum-sensitive disease is less than 1 year. In an attempt to improve outcomes, several new therapies are under evaluation for the treatment of recurrent ovarian cancer.

#### **Novel Biologics**

##### **AMG-386**

There are several key regulators within the VEGF pathway that may prove to be potential therapeutic targets. Dr Beth Karlan of Cedars-Sinai Medical Center,

Los Angeles, CA, presented outcomes from a phase II study with AMG-386 combined with weekly paclitaxel in patients with recurrent ovarian cancer.<sup>6</sup>

AMG-386 is a first-in-class, investigational peptide-Fc fusion protein “peptibody” that inhibits angiogenesis by neutralizing the interaction between the Tie2 receptor and angiopoietin 1 and 2. A total of 161 patients with recurrent EOC, FTC, or PPC who had received ≤ 3 prior treatments, ≥ 1 of which was platinum-based, were randomized to receive paclitaxel (80 mg/m<sup>2</sup> IV qwk, 3 on/1 off) and AMG-386 (10 mg/kg IV qwk; Arm A), AMG-386 (3 mg/kg IV qwk; Arm B), or placebo (Arm C) until disease progression or unacceptable toxicity. The primary endpoint was PFS.

Baseline characteristics were well balanced across treatment arms with a median age of 59 (Arm A), 60 (Arm B), and 62 years (Arm C). Efficacy outcomes are presented in **Table 4**. The median PFS was 7.2 months (Arm A), 5.7 months (Arm B), and 4.6 months (Arm C) (HR: 0.76, 80% CI: 0.59-0.98, *P* = 0.17, for treatment vs placebo). However, considering the arms independently revealed a positive assessment for trend (*P* = 0.037). While the greater benefit was observed with the higher dose in the general population, in subanalyses, patients with relapsed or refractory disease received the greatest benefit.

**Table 4. Efficacy Outcomes**

	Arm A (AMG-386 10 mg/kg + paclitaxel) (n = 53)	Arm B (AMG-386 3 mg/kg + paclitaxel) (n = 53)	Arm C (placebo + paclitaxel) (n = 55)
Median PFS, (80% CI)	7.2 months (5.6-7.5)	5.7 months (5.2-7.8)	4.6 months (2.0-5.5)
HR* (80% CI)	0.76 (0.57-1.02) <i>P</i> = 0.23	0.75 (0.56-1.00) <i>P</i> = 0.21	
vs Arm C	0.76 (80% CI: 0.59-0.98), <i>P</i> = 0.17		
ORR (CR + PR), %	37	19	27
CA-125 response, %	71	58	28

\*Stratified by prior anti-VEGF therapy, progression on or within 6 months of last chemotherapy regimen.

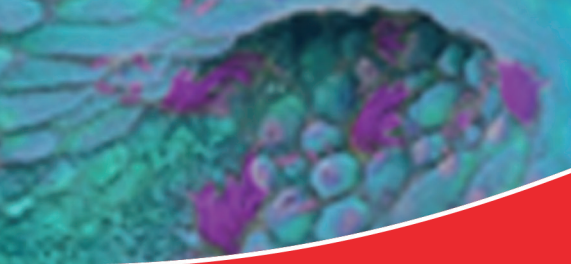
AMG-386 was well tolerated and notable AEs included peripheral edema (Arm A/B/C, 71%/ 51%/29%; ≥ G3, 4/6/4%), hypokalemia (21%/15%/5%; ≥ G3, 12%/11%/4%), thromboembolic events (arterial, 2%/2%/0%, all ≥ G3; venous, 8%/8%/11%; ≥ G3, 6%/6%/9%), and hypertension (8%/8%/5%, no grade 3). No bowel perforations occurred among AMG-386 treated patients and no deaths were considered treatment related. AMG-386 binding antibodies were observed in 3.3% of patients, none of which were neutralizing antibodies.

This study demonstrated the antitumor activity of AMG-386 when combined with weekly paclitaxel and the authors recommend a further phase III study with AMG-386. Since dose-limiting toxicity was not observed at the doses evaluated in this trial, further investigation at 15 mg/kg is being pursued.

#### **Farletuzumab**

Farletuzumab (MORAb-003) is a humanized monoclonal antibody to the folate-α receptor. The folate-α receptor is known to be overexpressed in greater than 90% of ovarian cancers, but is largely absent from normal tissue. Dr Allen J. White of South Texas Oncology and Hematology, San Antonio, TX, presented the final results from a phase II study evaluating the efficacy and safety of farletuzumab in platinum-sensitive relapsed ovarian cancer.<sup>7</sup>

A total of 54 patients with platinum-sensitive EOC in first relapse received weekly farletuzumab either as a single agent (SA) or in combination with carboplatin (AUC 5-6) and a taxane (paclitaxel or docetaxel [P/D]) q21 days for 6 cycles, followed by farletuzumab maintenance. Of these, 28 patients with asymptomatic CA-125 relapse received SA farletuzumab. Patients could receive P/D plus farletuzumab after SA. The remaining 26 patients with symptomatic relapse entered the combination arm directly. Twenty-one patients entered the combination arm after SA treatment. The primary endpoints were normalization of CA-125 and objective response rate (ORR).



Among 25 patients receiving SA farletuzumab available for efficacy analysis, 13 had no change in CA-125 and 5 had a significant decrease in CA-125. At day 43, 75% of these patients had no change or a significant decrease in CA-125. At week 9, by RECIST criteria, 40% of patients had stable disease (SD). Among the 44 patients receiving combination treatment available for efficacy analysis, CA-125 normalized in 39 patients (89%), including 9 (21%) with a CA-125 second response equal to or greater than the first response.

There was an unexpectedly high response rate among patients with a first progression-free interval of < 12 months, comparable to patients with a first progression-free interval of  $\geq$  12 months. Overall, PFS was 35% at 6 to < 12 months, 30% at  $\geq$  12 to < 18 months, and 36% at  $\geq$  18 months. The median PFS by CA-125 was 11 months. Response rate by RECIST (n = 43) included 7% complete response (CR) and 63% partial response (PR) for an ORR of 70%. The disease control rate (DCR) (CR + PR + SD) was 93%.

Farletuzumab was generally well tolerated with infrequent grade 1 and grade 2 reactions. No added toxicity was observed with the combination regimen. A total of 5 serious adverse events (SAEs) were noted in 3 patients. In the SA arm, 8 grade 3 events were recorded among 5 patients and 13 grade 3 events among 6 patients were recorded in the combination arm.

Preliminary data from this study indicated that farletuzumab in combination with a carboplatin plus a taxane may increase objective response and provide duration of second remission equal to or longer than first remission. The authors suggest that given these results, single-agent farletuzumab may stabilize disease, though this warrants further study, and randomized clinical trials in platinum-sensitive and platinum-resistant disease are ongoing.

## Novel Cytotoxics

### ***Trabectedin Plus Pegylated Liposomal Doxorubicin (PLD) vs PLD Alone***

Trabectedin, a tetrahydroisoquinoline alkaloid first approved for the treatment of soft tissue sarcoma, has been evaluated for its potential to extend the platinum-free interval (PFI) in patients with recurrent ovarian cancer. Dr Andres Poveda of the Instituto Valenciano de Oncologia, Valencia, Spain reported results from a subanalysis of partially platinum-sensitive patients from the phase III study (OVA-301) comparing trabectedin and pegylated liposomal doxorubicin (PLD), a non-platinum-based treatment regimen, to PLD alone.<sup>8</sup>

OVA-301 demonstrated a significant improvement in PFS and response rate with combination treatment (trabectedin + PLD) in this patient population with ovarian cancer progressing after 1 prior platinum-based regimen.<sup>9</sup> Among 672 patients, 214 (32%) were partially platinum-sensitive. Baseline characteristics of the subanalysis cohort were balanced and consistent with those of the overall study population. Patients received a median of 6 cycles of trabectedin + PLD or 5 cycles of PLD alone, with 40% and 24% completing the 7-cycle regimen. Response rate, PFS, and OS significantly favored combination treatment. **Table 5.** For comparison, the response rate for platinum-resistant patients on independent review was 13.4% in the trabectedin + PLD arm and 12.2% in the PLD arm,  $P = 0.848$ . Progression-free survival for patients in OVA-301 with platinum-resistant disease was 4.0 months for the trabectedin + PLD arm vs 3.7 months for the PLD arm,  $P = 0.754$ .<sup>9</sup>

The proportion of patients receiving subsequent platinum therapy was similar between both treatment arms. However, there was a significant delay in the administration of subsequent platinum therapy with combination treatment (median 15.3 months vs 11.6 months; HR 0.60,  $P = 0.0093$ ). The safety profile within this cohort was consistent with that of the overall study population and with the known toxicities of each agent with no new or unexpected toxicities observed.

**Table 5. Efficacy Outcomes of Partially Platinum-Sensitive Patients**

	Trabectedin + PLD (n = 123)	PLD (n = 91)	P Value
Response rate	33%	15%	0.0041
Median PFS	7.4 months	5.5 months	0.0152
Median OS	20.7 months	17.2 months	0.0090
Survival from start of subsequent platinum therapy until death	11.0 months	9.2 months	0.2480

This study demonstrated that within a partially platinum-sensitive cohort, combination therapy with the nonplatinum-based trabectedin + PLD may significantly improve response rate, PFS, and OS, as well as delay time to subsequent platinum therapy.

#### ***Nab-Paclitaxel***

Another nonplatinum-based regimen, nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) was evaluated in patients with recurrent EOC, FTC, or PPC in a phase II study reported by Dr Robert Coleman, MD Anderson Cancer Center, Houston, TX.<sup>10</sup> Enrolled patients had persistent (n = 5) or progressed disease within 6 months of completion (n = 42) of primary platinum and taxane-based chemotherapy. All patients were required to have measurable disease, no prior therapy for recurrent disease, and GOG performance status of ≤ 2. Patients received *nab*-paclitaxel 100 mg/m<sup>2</sup> on days 1, 8, 15 of a 28-day schedule. The primary endpoint was RECIST response rate.

Fifty-one patients were enrolled of whom 47 were evaluable. The median age was 59 (range 34-78) years, primary site ovary 87%, serous histology 72%, and high-grade 81%. All patients had one prior chemotherapy regimen and prior surgery. The median time from front-line therapy completion to registration was 3 weeks. Partial response was confirmed in 11 patients (23%) and 17 patients (36%) had SD.

The median PFS was 4.5 months (95% CI 2.1-6.7); OS was 17.4 months (95% CI 12.5-not estimable). Seventeen patients (36%) had PFS > 6 months.

There were no grade 4 AEs. Grade 3 AEs included neutropenia (6), anemia (3), GI (2), metabolic (2), pain (2), and leukopenia (1). Neurotoxicity was documented as grade 2 (5) and grade 3 (1).

The authors concluded that *nab*-paclitaxel appears to be both efficacious and tolerable in this cohort of highly refractory ovarian cancer patients previously treated with paclitaxel. Additional investigation of *nab*-paclitaxel in this setting is warranted.

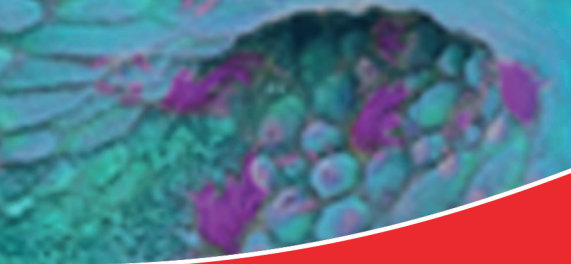
Another phase II study of *nab*-paclitaxel was reported by Dr Todd Tillmanns of The West Clinic, Memphis, TN. Forty-eight patients with recurrent, platinum-resistant ovarian cancer received *nab*-paclitaxel 100 mg/m<sup>2</sup> IV on days 1, 8, 15 with bevacizumab 10 mg/kg IV given on days 1 and 15 every 28 days, and were treated until progression.<sup>11</sup>

The median PFS, with 37 of 48 patients having experienced disease progression or death, was 8 months, (95% CI 7-10 months). The median OS was 18 months, (95% CI 15-23 months). The best overall response included 3 CR (6%), 20 PR (42%), 14 SD (29%), and 8 progressive disease (17%).

The most common hematological toxicities were neutropenia (2.6%) and anemia (2.4%) and the most common nonhematological toxicities were nausea (3.8%), nosebleed (3.8%), neuropathy (2.8%), and infection (1.6%). Bowel obstruction occurred in 5 patients (10.4%), which will require additional investigation as the combination moves forward. Given these promising results the authors recommend further prospective trials with *nab*-paclitaxel + bevacizumab in patients with platinum-resistant ovarian cancer.

#### ***Voreloxin***

Voreloxin is a quinolone derivative selective for topoisomerase II that causes site-selective double-strand DNA damage. Dr Hal Hirte, Juravinski Cancer Center, Hamilton, Ontario, Canada, presented the final results from a phase II study comparing 3 schedules



of single-agent voreloxin in women with primary or secondary platinum-resistant ovarian cancer.<sup>12</sup>

A total of 137 women with platinum-resistant (progression within 6 months) EOC, FC, or PPC with a performance status (PS) of 0-1 who had received 1-3 prior platinum-based regimens and ≤ 1 other treatment regimens were randomized to receive voreloxin at 48 mg/m<sup>2</sup> q3wk (Arm A), 60 mg/m<sup>2</sup> q4wk (Arm B), or 75 mg/m<sup>2</sup> q4wk (Arm C) for up to 6 cycles followed by treatment extension. The primary endpoint was objective response by PFS.

Baseline characteristics were well balanced between treatment arms with a median age just over 60 years, the majority of tumors being serous, and a median number of prior treatments of 3 (range: 1-8). Objective response included 1 CR and 6 PRs (Arm A), 1 CR and 3 PRs (Arm B), and 3 PRs (Arm C). The ORR was 11%, 11%, and 9%, for Arms A, B, and C, respectively. The ORR was 9% (n = 44) for patients with prior PLD treatment failure. The DCR (CR + PR + SD for ≥ 12 wks) at 12 weeks was 48% (Arm A), 54% (Arm B), and 57% (Arm C), including 64% in prior PLD failures. The median PFS was 83 days, 85 days, and 110 days for Arms A, B, and C, respectively. Overall, PFS favored Arm B over Arm A (*P* = 0.03). There was no significant difference between Arm C and Arm A (*P* = 0.08) and Arm B and Arm C (*P* = 0.75). At least 50% of patients had some reduction in tumor volume. A total of 25% of patients continued with treatment extension after cycle 6.

Dose reduction or delay was observed in 38% (Arm A), 19% (Arm B), and 35% (Arm C) of patients. No clinical signs or symptoms of congestive heart failure were seen in patients completing multiple cycles. Hematologic toxicity was as expected and reversible with standard of care. Selected AEs are presented in **Table 6**.

**Table 6. Selected Adverse Events**

	Arm A 48 mg (n = 65)	Arm B 60 mg (n = 37)	Arm C 75 mg (n = 35)
Neutropenia	22%	16%	51%
Febrile neutropenia	9%	5%	29%
Anemia	18%	19%	9%
Fatigue	23%	11%	20%

Voreloxin is a first-in-class quinolone derivative shown to be effective and well tolerated in this highly pretreated population, including patients with PLD failure. While the safety profile was consistent across doses, the febrile neutropenia incidence increased at 75 mg/m<sup>2</sup> and the authors conclude that clinical activity is optimal at 60 mg/m<sup>2</sup> based on efficacy and safety outcomes. The data support continued development of voreloxin in ovarian cancer.

#### **NKTR-102**

NKTR-102 is a topoisomerase I inhibitor irinotecan-polymer conjugate. This open-label phase II study, presented by Dr Ignance Vergote of University Hospital Leuven, Leuven, Belgium, evaluated response by GCIg, RECIST, and CA-125 (50% decline in CA-125) among 71 patients with platinum-resistant or refractory ovarian cancer following treatment with NKTR-102.<sup>13</sup> Patients with ECOG PS 0-1, adequate renal, hepatic, and marrow function, and who had not received prior treatment with irinotecan or topotecan were randomized to receive NKTR-102 145 mg/m<sup>2</sup> every 2 weeks (n = 36) or 145 mg/m<sup>2</sup> every 3 weeks (n = 35). The primary endpoint was GCIg response rate.

The median age was 61 years, with approximately half of patients having ECOG PS 0, and 86% of patients with serous disease. Of the 71 patients randomized, 42 were platinum-resistant and 27 were platinum-refractory. Response rates are presented in **Table 7**. The median time to first 50% decline in CA-125 was 31 days. Neither the number of prior platinum-based lines of therapy nor prior PLD was found to affect outcome.

While only 3 patients demonstrated early progression according to RECIST criteria, response was observed to be rapid among responders. The median progression-free interval from previous therapy was just 4 weeks and the median PFS while on NKTR-102 was 18 weeks, with many patient events still being censored.

**Table 7. Response Rates With NKTR-102**

	NKTR-102 145 mg/m <sup>2</sup> q 2 weeks (n = 36)	NKTR-102 145 mg/m <sup>2</sup> q 3 weeks (n = 35)
GCIG response rates (confirmed and unconfirmed) based on composite RECIST/CA-125 data	47%	41%
RECIST response (confirmed and unconfirmed)	27%	22%
CA-125 response rate	61%	52%

Common related grade 3/4 toxicities (q2wk/q3wk schedules) were diarrhea (22%/11%), dehydration (14%/6%), hypokalemia (14%/6%), fatigue (6%/11%), nausea (14%/3%), and neutropenia (8%/9%). One patient each died due to neutropenic sepsis and pre-renal azotemia.

Single-agent NKTR-102 demonstrated significant anti-tumor activity in this patient population based upon both GCIG and RECIST criteria. NKTR-102 was well tolerated and the 145 mg/m<sup>2</sup> every 3-week schedule is recommended by the authors due to the low incidence of diarrhea. Phase III studies with NKTR-102 q3wk are planned.

**PRECEDENT Study**

As previously stated, the folate receptor is found on > 90% of EOC. EC145, a conjugate of folic acid and desacetylvinblastine hydrazide, targets the folate receptor and may offer a nonplatinum-based regimen for women with platinum-resistant ovarian cancer. In a poster presentation, Dr Robert Naumann of the Blumenthal Cancer Center, Carolinas Medical Center, Charlotte, NC, presented the planned interim analysis from a phase II study (EC-FV-04) comparing PLD

(50 mg/m<sup>2</sup> IV q4wk) with or without EC145 (2.5 mg IV weeks 1 and 3) in patients with platinum-resistant ovarian cancer.<sup>14</sup>

A total of 91 patients were randomized (2:1) and baseline characteristics were similar across treatment arms. Progression-free survival significantly favored EC145 + PLD (24.0 weeks) as compared to PLD alone (11.7 weeks) (HR 0.497, *P* = 0.014). There was no statistically significant difference in OS with combination treatment (HR 0.425, *P* = 0.064), although the analysis is preliminary and limited by censoring. **(Figures 4 and 5.)**

Response rates are presented in **Table 8**. There was no significant difference between study arms with regard to total AEs, SAEs, or the number of patients reporting ≥ 1 treatment-emergent drug-related SAEs resulting in discontinuation.

**Table 8. Response Rates**

RECIST Confirmed Response to Treatment	EC145/PLD (n = 54)	PLD (n = 27)
CR	0 (0%)	0 (0%)
PR	9 (16.7%)	4 (14.8%)
SD	33 (61.1%)	12 (44.4%)
PD	12 (22.2%)	11 (40.7%)
DCR	42 (77.8%)	16 (59.2%)

These interim data support EC145 + PLD as the first nonplatinum-based combination regimen to show statistically significant delay in PFS for women with platinum-resistant ovarian cancer. The final analysis and results are expected in 2011.

Another phase II study evaluated the utility of EC20, an imaging agent based on the same folate-receptor antibody conjugate as EC145, to identify women with advanced platinum-resistant ovarian cancer who may benefit from treatment with EC145. In a poster presentation, Dr James Symanowski of the Nevada Cancer Institute, Las Vegas, NV, presented the results



Figure 4. PRECEDENT PFS

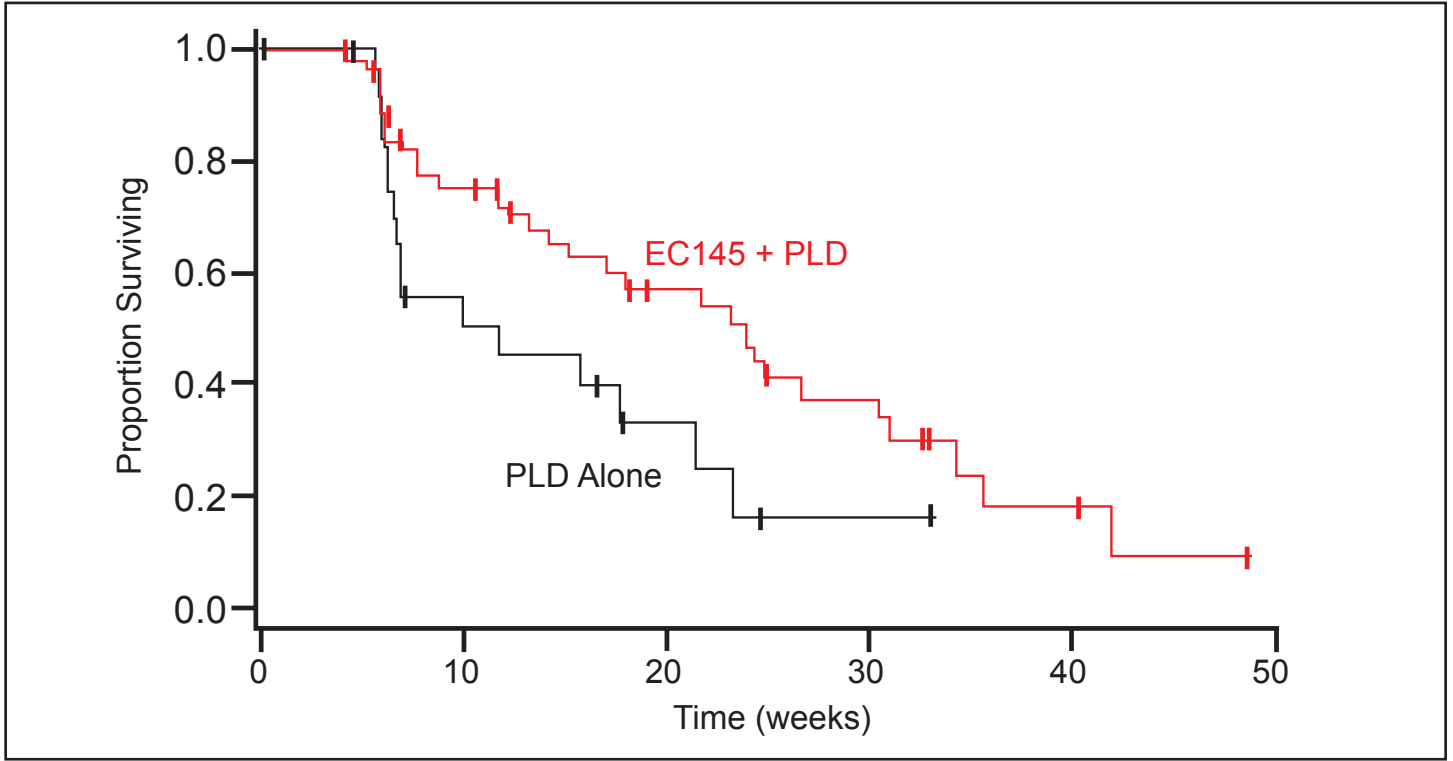
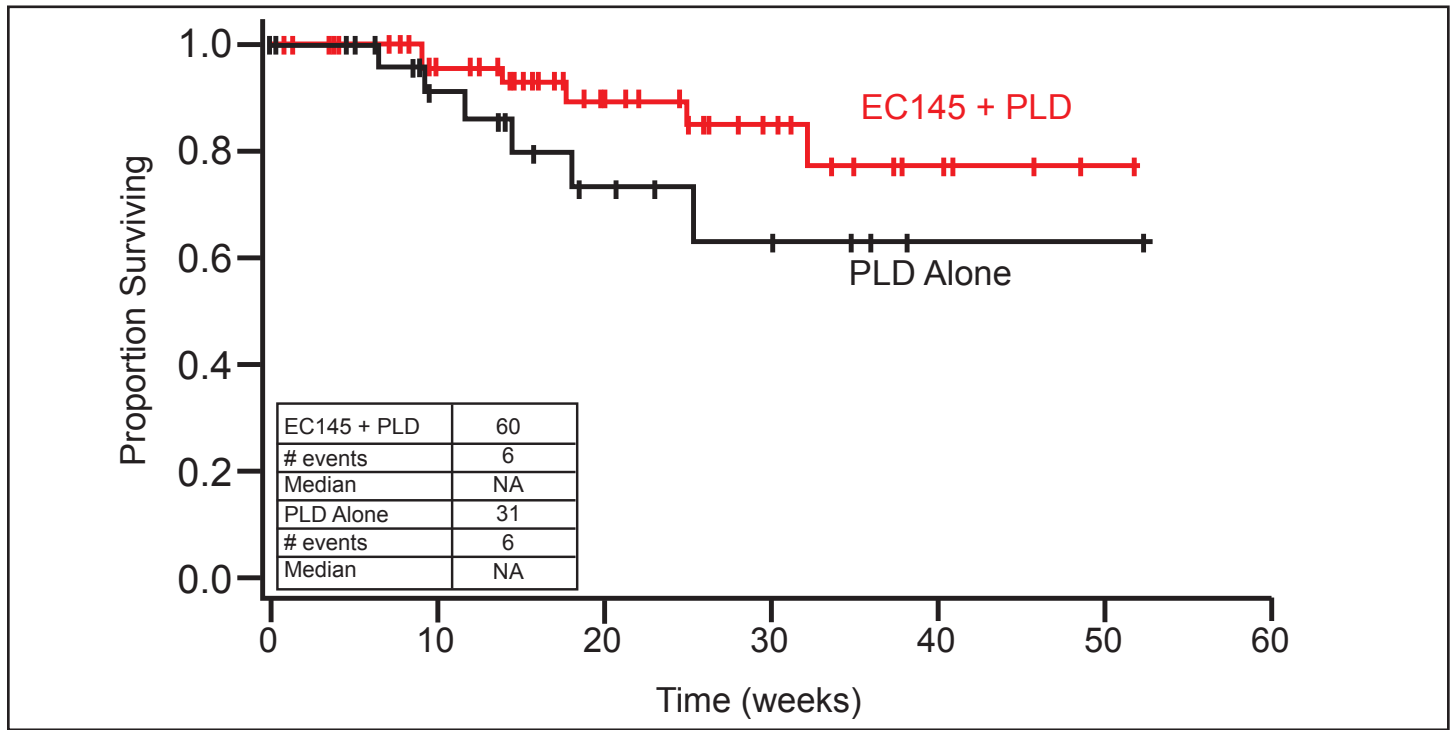


Figure 5. OS Data



from NCT00507741.<sup>15</sup> A total of 45 patients with 216 lesions received 0.5 mg folic acid followed by a 1-2 mL injection of 0.1 mg EC20 labeled with 20-25 mCi of technetium-99m. Patients received planar imaging 1-2 hours following injection and SPECT images were obtained. EC20 uptake for each tumor was classified as positive or negative, after which patients received EC145 therapy.

Among 145 evaluable lesions, EC20(+) lesions had a greater probability of response compared to EC20(-) lesions ( $P = 0.0022$ ). In the patient analysis, DCR increased with EC20 positivity. **Table 9.** In a subgroup analysis of less heavily treated patients (failed  $\leq 3$  prior therapies), the DCR for the EC20(++) group was 86% compared to 50% and 0% in the EC20(+) and EC20(-) groups, respectively. There was a strong trend for improved survival in the EC20(++) subgroup (HR 0.46,  $P = 0.071$ ), with a median OS of 63.4 weeks (EC20[++] vs 23.1 weeks (EC20[+] and EC20[-]) combined).

**Table 9. Patient-Specific Analysis (All Eligible Patients)**

Response to Treatment	All eligible patients N = 45	EC20(++) 100% positive lesions (n = 14)	EC20(+) 1-99% positive lesions (n = 25)	EC20(-) 0% positive lesions (n = 6)
CR/PR	2 (4%)	1 (7%)	1 (4%)	0 (0%)
SD	17 (38%)	7 (50%)	8 (32%)	2 (33%)
PD	26 (58%)	6 (43%)	16 (64%)	4 (67%)
DCR	19 (42%)	8 (57%)	9 (36%)	2 (33%)

The authors conclude that these results suggest that use of the folate receptor-targeted EC20 imaging identifies patients with advanced ovarian cancer who are most likely to benefit from therapy with folate receptor-targeted EC145. Several folate receptor-targeted therapies are in clinical development.

### Maintenance Therapy

Dr Paul Sabbatini of Memorial Sloan-Kettering Cancer Center, New York, NY presented preliminary results from a randomized, double-blind, placebo-controlled trial of abagovomab, a murine monoclonal anti-

idiotypic antibody against CA-125 (MIMOSA Trial).<sup>16</sup> In this phase III trial patients with stage III/IV ovarian cancer in CR after platinum/taxane-based post-first-line chemotherapy were randomized (2:1) to receive abagovomab (2 mg) or placebo administered as a 1 mL sc q2wk for 5 weeks (induction) followed by q4wk (maintenance) until recurrence or for up to 21 months. The primary endpoint was PFS.

A total of 888 patients were randomized with baseline characteristics similar across treatment arms. At a mean exposure of 12.8 months, 19 potentially treatment-related SAEs had been reported, with 14.3% of patients discontinuing due to an AE, 2.1% of which were potentially treatment related. The most frequent nonserious AEs included injections site reaction and fatigue. The most recent data safety monitoring board (DSMB) review (October 2009) found no safety issues and recommended study continuation. Preliminary blinded immunologic results showed 70% (week 10), 72% (week 22), and 70% (week 58) of overall patients were positive for Ab3 while 53% (week 10) and 67% (weeks 22 and week 58) were positive for human anti-murine antibody (HAMA).

These preliminary results confirm that abagovomab, given as repeated monthly sc administrations, is safe and induces a measurable immune response comparable to previous studies. Final efficacy data are expected in early 2011.

### Summary

Several important studies relevant to the treatment and management of ovarian cancer were presented at the 2010 ASCO Annual Meeting. Assessment algorithms to better identify those patients with ovarian cancer and those who will benefit from specific treatments are on the horizon, updated regimens for the front-line treatment of ovarian cancer promise improved PFS, and novel therapeutics have the potential to improve outcomes among patients with recurrent disease.

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