

## Recurrent Epithelial Ovarian Cancer

Patients with recurrent epithelial ovarian cancer can be treated with a number of different treatment options that are generally selected based on time since last platinum therapy and other patient and treatment regimen characteristics. Patients with platinum-resistant cancer are usually treated with single-agent chemotherapy with paclitaxel, topotecan, pegylated liposomal doxorubicin (PLD) (Topotecan versus Paclitaxel study, Doxil Study 30-49, Gemcitabine versus PLD study), or these selected agents in combination with trabectedin or bevacizumab (OVA-301, AURELIA). Patients with platinum-sensitive cancer are generally treated with multiagent regimens, including platinum + paclitaxel (ICON4/AGO-OVAR2.2), carboplatin + PLD (CALYPSO), or carboplatin + gemcitabine (AGO-OVAR, NCIG CTG, EORTC GCG trial) with or without bevacizumab (OCEANS).

### **Topotecan Versus Paclitaxel (ten Bokkel, JCO 1997)**

#### REFERENCE

- ten Bokkel Huinick W, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol.* 1997;15(6):2183-2193. PMID: 9196130. (ten Bokkel Huinink et al. 1997)

#### TRIAL SPONSOR

- Supported by a grant from SmithKline Beecham Pharmaceuticals, Collegeville, PA

## RATIONALE FOR TRIAL

- Standard front-line therapy at this time is cyclophosphamide combined with a platinum analogue, but the majority of patients relapse and die of progressive disease (Neijt et al. 1991; Cannistra 1993; Ozols 1994; McGuire et al. 1996).
- In small phase II studies of patients with recurrent disease, second-line agents have yielded response rates ranging from 8% to 26%. Treatment options include:
  - Hexamethylmelamine (Vergote et al. 1992).
  - Ifosfamide (Baker et al. 1993).
  - Etoposide (Baker et al. 1993; Hoskins and Swenerton 1994).
- There is an urgent need to develop new treatment strategies with non-cross-resistant chemotherapy in recurrent ovarian cancer.
- Paclitaxel has been studied in recurrent ovarian cancer.
  - Response rates range from 22% to 37% in small, nonrandomized studies (McGuire et al. 1989; Einzig et al. 1992; Thigpen et al. 1994).
  - In a large, randomized, international study evaluating 2 different doses (175 mg/m<sup>2</sup> vs 135 mg/m<sup>2</sup>) and 2 different dosing schedules (3 hours vs 24 hours), responses confirmed by independent review ranged from 14% to 24% (Eisenhauer et al. 1994). At the approved dose of 175 mg/m<sup>2</sup> over 3 hours every 21 days, the response rate was 15%.
  - In the front-line setting, cisplatin and paclitaxel were found to be superior to cisplatin and cyclophosphamide (McGuire et al. 1996; Piccart et al. 2000).
- Topotecan (Hycamtin) has been studied.
  - Water-soluble, semisynthetic analogue of camptothecin, an alkaloid antitumor agent isolated from the *Camptotheca acuminata* tree from South China.
  - Inhibits topoisomerase I, an enzyme that binds to double-stranded DNA and leads to a single-strand break in front of the replication fork and relieves DNA torsion caused by replication.
  - Topotecan and other camptothecin analogues bind to the topoisomerase I–DNA complex and interfere with the process of DNA breakage and resealing. This blocks the progress of the replication fork and results in DNA breaks and cell death (Hertzberg et al. 1989; Hsiang et al. 1989).

- Preclinical data suggest that topotecan could be given intermittently over multiple days (Houghton et al. 1992).
- Three phase I studies concluded the maximum tolerated dose is 1.5 mg/m<sup>2</sup>/d on 5 consecutive days in a 21-day cycle without the use of growth factor support. The dose-limiting toxicity was myelosuppression (Rowinsky et al. 1992; Saltz et al. 1993; Verweij et al. 1993).
- Phase II studies demonstrate response rates ranging from 14% to 25% in recurrent ovarian cancer (abstract: Armstrong et al. 1995).
- This was a phase III study designed to compare the efficacy and toxicity of topotecan (1.5 mg/m<sup>2</sup> intravenous [IV] over 30 minutes on 5 consecutive days every 21 days) to paclitaxel (175 mg/m<sup>2</sup> IV over 3 hours every 21 days) in patients with recurrent ovarian cancer who progressed after 1 platinum-based chemotherapy regimen.

#### PATIENT POPULATION

- N=235 enrolled, 226 included in the intent-to-treat analysis.
- Stage III/IV, histologically confirmed epithelial ovarian carcinoma.
- Failed first-line therapy with a platinum-based chemotherapy regimen.
- Measurable disease—at least 1 bidimensionally measurable lesion on computed tomography (CT) or magnetic resonance imaging (MRI) scan, ultrasound, or physical exam.
- At least 4 weeks from prior surgery, hormonal therapy, radiotherapy or chemotherapy, and initiation of study drug.
- Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ .
- Adequate bone marrow function: white blood cells (WBC)  $\geq 3500/\mu\text{L}$ , neutrophil count  $\geq 1000/\mu\text{L}$ , and platelet count  $\geq 100,000/\mu\text{L}$ .
- Normal liver function: bilirubin  $\leq 2.0$  mg/dL.
- Normal renal function: creatinine level  $\leq 1.5$  mg/dL or creatinine clearance  $> 60$  mL/min.
- Ineligible:
  - More than 1 prior chemotherapy regimen.
  - Prior topotecan or paclitaxel.

#### TREATMENT DETAILS

##### *Arm 1: Topotecan*

- Premedications: none initially, but antiemetics could be added as indicated.
- Starting dose: 1.5 mg/m<sup>2</sup> IV over 30 minutes for 5 consecutive days every 21 days.

- Dose reduction for toxicity to minimum dose of 1.0 mg/m<sup>2</sup>/d.
- Due to the limited experience with topotecan in this population, dose could also be escalated to 2.0 mg/m<sup>2</sup>/d.
- Treatment withdrawn for >2-week delay at the minimum dose due to medication or toxicity.

#### *Arm 2: Paclitaxel*

- Premedications: dexamethasone, H<sub>1</sub> receptor antagonist, H<sub>2</sub> receptor antagonist.
- Starting dose: 175 mg/m<sup>2</sup> IV over 3 hours every 21 days.
- Dose reduction for toxicity to minimum dose of 135 mg/m<sup>2</sup>.
- Treatment withdrawn for >2-week delay at the minimum dose due to medication or toxicity.

#### *Supportive Measures*

- To maintain dose-intensity and a 21-day treatment cycle, prophylactic granulocyte colony-stimulating factor (G-CSF) could be added starting with second cycle of therapy (on day 6 following topotecan or on day 2 following paclitaxel) if the patient experienced any of the following:
  - Grade 4 neutropenia with fever or infection.
  - Grade 4 neutropenia that lasted more than 7 days.
  - Grade 3 neutropenia that required a delay in treatment.

#### *Duration of Treatment Depended on Response*

- Patients with a complete response (CR) or partial response (PR) could continue treatment until progression or for 6 months past the maximum response.
- Patients with progression were removed from the study.
- Patients with best response of stable disease after 6 courses could be removed from the study or switched to the alternate regimen.

#### ASSESSMENTS

- Responses were determined by the World Health Organization (WHO) criteria.
  - All responses required independent review and confirmation by a radiologist blinded to treatment regimen.
  - CR was defined as the complete disappearance of all measurable and assessable disease on 2 separate scans at least 4 weeks apart.
  - PR was defined as a 50% reduction in the sum of products of the perpendicular diameters of all measurable lesions for at least 4 weeks and no new lesions or progression of assessable disease.

- Progressive disease (PD) was defined as a 25% increase in a single measurable lesion, reappearance of measurable disease, worsening of assessable disease, or the development of a new metastatic lesion.
- Stable disease (SD) was any measurement not fulfilling the criteria for response or progression and lasting at least 8 weeks.
- Nonassessable disease was defined as nonmeasurable lesions with an elevated cancer antigen (CA125) tumor marker.
- Toxicities measured by the National Cancer Institute (NCI) Common Toxicity Criteria (CTC).

#### ENDPOINTS

- Response rate.
- Duration of response measured from time of initial documented response to first sign of disease progression.
- Time to progression measured from time of first study drug administration to documented progression or initiation of third-line therapy.
- Time to response measured from time of first study drug administration to initial response.
- Survival measured from time of first study drug administration to death.

#### STATISTICAL CONSIDERATIONS

##### *Stratification Factors*

- Age: <65 or  $\geq$ 65 years.
- Ascites: present or absent.
- Response to prior platinum-based therapy: resistant, early, interim, or late relapse (van der Burg et al. 1991; Markman et al. 1992).
  - Resistant disease defined as not having response to initial chemotherapy or having an initial PR or CR and then progressing while still on therapy.
  - Early relapse defined as CR or PR and relapse within 3 months.
  - Interim relapse defined as CR or PR and relapse within 3 to 6 months.
  - Late relapse defined as CR or PR and relapse more than 6 months after chemotherapy. This group is recognized as potentially platinum sensitive and responsive to reintroduction of platinum therapy.

##### *Statistical Tests*

- Kaplan-Meier estimates were obtained for each efficacy end point and presented in life-table format over 4-week intervals.

**Table 5.1** Results of Topotecan Versus Paclitaxel Trials

Treatment arm	Topotecan N=112	Paclitaxel N=114	Statistics
<b>Patient characteristics</b>			
Median age (range)	59.2 (29-85)	58.3 (29-79)	
Relapse <6 months	54%	52%	
Prior chemotherapy			
Cyclophosphamide	66.0%	69.0%	
Carboplatin	55.0%	61.0%	
Cisplatin	54.0%	51.0%	
Epirubicin	8.0%	5.3%	
Doxorubicin	8.1%	9.6%	
Etoposide	1.8%	0.9%	
Other	0%-1.8%	0%-1.8%	
Tumor diameter			
<5 cm	48.2%	46.5%	
≥5 cm	50.0%	51.8%	
Serous	51.8%	51.8%	
Endometrioid	8.9%	13.2%	
Mucinous	5.4%	5.3%	
Undifferentiated	16.1%	7.0%	
Other	17.9%	22.8%	
Grade 1	5.0%	7.0%	
Grade 2	20.5%	25.4%	
Grade 3	50.0%	43.9%	
Grade 4	8.9%	10.5%	
Unknown grade	15.2%	13.2%	
<b>Treatment delivery</b>			
Target dose maintained	90%	98%	
Median dose intensity	2.3 mg/m <sup>2</sup> /wk	56.3 mg/m <sup>2</sup> /wk	
Treatment on schedule	77%	92%	
Delays beyond 7 days	5%	3%	
<b>Efficacy</b>			
Overall response rate	20.5%	13.2%	NS
CR	4.5%	2.6%	
PR	16.1%	10.5%	
Duration of response	32.1 weeks	19.7 weeks	RR 0.42, NS
Time to progression	23.1 weeks	14.0 weeks	RR 0.58, <i>P</i> = .002
Time to response	9 weeks	6 weeks	RR 0.48, <i>P</i> = .041
Median OS	61 weeks	43 weeks	RR 1.21, NS

*(continued)*

**Table 5.1** Results of Topotecan Versus Paclitaxel Trials*(continued)*

Treatment arm	Topotecan N=112	Paclitaxel N=114	Statistics
<b>Toxicity</b>			
Greater with topotecan			
G4 neutropenia	79%	23%	$P < .01$
G4 thrombocytopenia	25%	2%	$P < .01$
G4 anemia	4%	3%	NS
Infection	15%	4%	
Sepsis	5%	2%	
G-CSF prophylaxis	23%	3%	
G-CSF treatment	7%	1%	
Platelet transfusions	3%	0%	
Blood transfusions	27%	4%	
Nausea	63.5%	44.8%	
Vomiting	41.1%	30.8%	
Fever	28.6%	17.7%	
Greater with paclitaxel			
Alopecia	75.9%	93.0%	
Arthralgia	6.4%	31.5%	
Myalgia	3.6%	28.0%	
Neuropathy	0.9%	15.8%	

CR, complete response; G-CSF, granulocyte colony-stimulating factor; NS, not significant; OS, overall survival; PR, partial response; RR, relative risk.

- Cox regression was used to compare time-to-event outcomes.
- A model that included treatment and the 3 stratification covariates was used to compare treatment effects.
- Hazards ratios (HRs) with 95% confidence intervals (CIs) were reported.

#### CONCLUSION OF TRIAL

- Compared to paclitaxel, topotecan has a higher response rate and longer time to progression in patients with recurrent epithelial ovarian cancer.

#### COMMENTS

- Choice of paclitaxel as the comparison arm was based on prior studies suggesting response rates of 22% to 37% with paclitaxel in patients who had not responded to first-line platinum (McGuire et al. 1989; Einzig et al. 1992; Thigpen et al. 1994). The regimen of 175 mg/m<sup>2</sup> over 3 hours was chosen due to ease of administration, less toxicity,

and no other regimen with proven greater efficacy (Eisenhauer et al. 1994).

- Topotecan toxicities:
  - 79% had grade 4 neutropenia.
  - 25% had grade 4 thrombocytopenia.
  - Hematologic toxicity was short duration and noncumulative (lack of progressively lower hematologic nadirs on subsequent rounds of therapy).
  - Dose reductions and use of G-CSF resulted in effective prevention of significant clinical sequelae from hematologic toxicities.
  - Only 5.4% had grade 3 diarrhea and no one had grade 4 diarrhea. Incidence of diarrhea is lower with topotecan compared to other topoisomerase I inhibitors.
  - There were no dose-limiting nonhematologic toxicities in this study.
- Topotecan appears to be at least as active as paclitaxel in this paclitaxel-naïve population, but paclitaxel is better tolerated.

### **Doxil Study 30-49 (Gordon, JCO 2001; Gordon, Gyn Onc 2004)**

#### REFERENCES

- Gordon AN, et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol*. 2001;19(14):3312-3322. PMID: 11454878. (Gordon et al. 2001)
- Gordon AN, et al. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. *Gynecol Oncol*. 2004;95(1):1-8. PMID: 15385103. (Gordon et al. 2004)

#### TRIAL SPONSOR

- ALZA Corp, Mountain View, CA

#### RATIONALE FOR TRIAL

- Patients with recurrent ovarian cancer are treated with the goals of palliation and optimization of quality of life as the probability of cure is remote.



- Treatment options that lack cross-resistance to front-line therapies of platinum and paclitaxel (McGuire et al. 1996) are needed for recurrent or refractory disease.
  - Options include topotecan, oral etoposide, and gemcitabine (Shapiro et al. 1996; Bookman et al. 1998; Rose et al. 1998a).
  - At the time of this trial, topotecan is the only approved agent for recurrent ovarian cancer. Topotecan has response rates that range from 13% to 33% depending on platinum sensitivity (Kudelka et al. 1996; Swisher et al. 1997; Bookman et al. 1998; McGuire et al. 2000).
- Pegylated liposomal doxorubicin (PLD).
  - Received Food and Drug Administration (FDA) approval in June 1999 for use on patients with disease refractory to paclitaxel and platinum-based chemotherapy.
  - Encapsulation of doxorubicin in pegylated liposomes decreases the toxicities attributed to high peak levels of doxorubicin (nausea, vomiting, cardiotoxicity) (Gordon et al. 2000), alters the pharmacokinetic profile of doxorubicin, and enhances the therapeutic benefit.
  - Compared to doxorubicin, PLD has a smaller volume of distribution, a larger area under the curve (AUC), slower clearance, and longer elimination half-life of approximately 55 hours (Greene et al. 1983; Eksborg et al. 1986).
  - Pegylated liposomes are small (approximately 100 nm in diameter), which allows them to pass through endothelial gaps and leaky membranes in tumors (Jain 1987; Dvorak et al. 1988).
  - A phase II study using PLD in patients with platinum-resistant and refractory ovarian cancers demonstrated overall response rates of 16.9% and 18.3% in the overall and refractory populations with median times to progression of 19.3 weeks and 17 weeks, respectively. Toxicities included stomatitis, palmar-plantar erythrodysesthesia (PPE), and skin lesions and were easily managed with dosing modifications (Gordon et al. 2000).
- Given the promising results of PLD in phase I/II studies, this trial was performed to compare PLD to topotecan in patients with recurrent epithelial ovarian cancer.

#### PATIENT POPULATION

- N=481 randomized, 474 at least partially treated.
- Enrollment from May 1997 to March 1999 from 104 sites in the United States and Europe.

*Inclusion Criteria*

- Age  $\geq 18$  years.
- Measurable or measurable and assessable disease.
  - Measurable defined as bidimensionally measurable lesion(s) by plain x-ray with at least 1 diameter  $\geq 0.5$  cm or by CT, MRI, or other imaging scan with both diameters  $\geq 2$  cm.
  - Assessable diseased defined as unidimensionally measurable lesion(s), mass(es) with margins not clearly defined, lesion(s) with both diameters  $\leq 0.5$  cm, lesion(s) with diameter smaller than the distance between cuts, palpable lesion(s) with either diameter  $\leq 2$  cm, malignant ascites, or pleural effusion with CA125  $\geq 100$  U/mL in the absence of cirrhosis.
- Recurrence after first-line platinum-based chemotherapy.
- Adequate bone marrow function (platelets  $\geq 100,000/\text{mm}^3$ , hemoglobin  $\geq 9$  g/dL, absolute neutrophil count  $\geq 1500$  cells/ $\text{mm}^3$ ).
- Adequate renal function (serum creatinine  $\leq 2.5$  mg/dL).
- Adequate liver function (aspartate aminotransferase [AST]  $\leq 2$  times the upper limit of normal, alkaline phosphatase  $\leq 2$  times the upper limit of normal, bilirubin equal to or greater than the upper limit of normal).
- Adequate cardiac function (left ventricular ejection fraction [LVEF]  $\geq 50\%$  or the institutional normal).
- Karnofsky performance status  $\geq 60\%$ .
- Disease-free period of  $>5$  years from prior malignancies (excluding curatively treated basal cell carcinoma, squamous cell carcinoma of the skin, carcinoma in situ of the cervix).

*Exclusion Criteria*

- Pregnant or breastfeeding.
- Life expectancy of  $\leq 3$  months.
- Prior radiation therapy to greater than one-third of hematopoietic sites.
- History of cardiac disease that met the criteria for class 2 or higher by the New York State Heart Association Classification system.
- Uncontrolled systemic infection.
- Receipt of investigational agent within 30 days of first dose of study drug.
- Prior PLD or topotecan therapy.
- Receipt of chemotherapy within 29 days of first dose of study drug (or within 42 days for nitrosurea or mitomycin).
- Concurrent use of investigational or antineoplastic agents during the study.

## TREATMENT DETAILS

*Arm 1: Pegylated Liposomal Doxorubicin (PLD).*

- 50 mg/m<sup>2</sup> IV over 1 hour every 28 days.
- Dose modifications for PPE, hematologic toxicity, elevated bilirubin, or stomatitis (Gordon et al. 2000).
- Dose reduced by 25% for all other grade 3 and 4 events until resolution to grade 2 or lower.
- Prophylactic cytokine administration not recommended during first cycle of drug but allowed in subsequent cycles for any grade 4 neutropenia >7 days or failure of absolute neutrophil count (ANC) to recover within 22 days or febrile neutropenia.
- Treatment continued for up to 1 year in the absence of disease progression or evidence for sustained clinical benefit.
- Patients who completed 6 months of PLD were considered to have completed the protocol.

*Arm 2: Topotecan*

- 1.5 mg/m<sup>2</sup>/d IV over 30 minutes daily on days 1 to 5 every 21 days.
- G-CSF could be administered from day 6 at the discretion of the treating physician for severe neutropenia. Prophylactic cytokine administration not recommended during first cycle of drug but allowed in subsequent cycles for any grade 4 neutropenia >7 days or failure of ANC to recover within 22 days or febrile neutropenia.
- For severe neutropenia during a cycle, dose was reduced by 0.25 mg/m<sup>2</sup> for subsequent courses.
- For moderate renal impairment (creatinine clearance 20-39 mL/min), dose reduction to 0.75 mg/m<sup>2</sup> recommended. No dose adjustment needed for mild renal impairment (creatinine clearance 40-60 mL/min).
- Treatment continued for up to 1 year in the absence of disease progression or evidence for sustained clinical benefit.
- Patients who completed 8 cycles of topotecan were considered to have completed the protocol.

*Treatment Discontinuation*

- Disease progression.
- Serious or intolerable adverse events precluding further treatment.
- Inability to tolerate study drug despite dose modification.
- LVEF <45% or a 20% decrease from baseline.
- Patient's decision to withdraw from participation.
- Need for radiation treatment.

## ASSESSMENTS

- Radiographic imaging (chest x-ray, CT, or MRI) at baseline and every 8 weeks.
- Response based on objective tumor measurements.
  - CR defined as complete disappearance of all measurable and assessable disease, no new lesions, and no disease-related symptoms. CR confirmed at least 4 weeks later by imaging to confirm the response.
  - PR documented in patients with  $\geq 50\%$  decrease in sum of the products of bidimensional perpendicular diameters of all measurable lesions; no progression of assessable disease and no new lesions. PR confirmed at least 4 weeks later by imaging to confirm the response.
  - PD in patients with  $\geq 50\%$  increase in the sum of bidimensionally measured lesions over the smallest sum obtained at best response; reappearance of any lesion that had disappeared; clear worsening of any assessable disease; failure to return for evaluation because of death or deteriorating condition; appearance of any new lesion or site.
  - SD in any patient that did not meet criteria for CR, PR, or PD.
- LVEF by multiple gated acquisition scan or echocardiogram at baseline and 4 weeks after the last dose of study drug for all patients; after every 2 cycles of PLD after cumulative dose  $>300$  mg/m<sup>2</sup>.
- Physical examination, chemistries, and CA125 at baseline and before every cycle.
- Complete blood count performed weekly.
- Toxicity assessed by the National Cancer Institute Common Toxicity Criteria (grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening).
- Quality of life assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) (Aronson et al. 1993) at baseline, during every cycle, and 4 weeks after the last treatment dose.
  - Includes 6 domains (physical functioning, role functioning, cognitive functioning, emotional functional, social functioning, and global quality of life) and 8 symptoms scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea).
  - Twelve weeks was the first study time point when quality of life (QOL) could be assessed at the same time for the 2 groups. Less than 50% of patients were completing questionnaires by this time point (approximately 100 patients in each arm available for assessment).

The main reasons for discontinuation were disease progression and death.

#### ENDPOINTS

- Time to progression (primary endpoint).
- Overall survival.
- Response rate.
- Time to response.
- Duration of response.
- Safety and toxicity.

#### STATISTICAL CONSIDERATIONS

##### *Stratification Factors*

- Platinum sensitivity.
- Presence or absence of bulky disease (defined as tumor mass >5 cm).

##### *Sample Size*

- In total, 350 patients allowed 80% probability that the 95% 1-sided confidence limit of the hazard ratio of topotecan to PLD would not fall below 0.757 (80% power to demonstrate statistical equivalence between the 2 groups). Based on 2 additional mitigating factors, the trial was designed to enroll 460 patients, depending on the accessibility rate.
- Two interim analyses were planned, requiring enrollment of approximately 5% more patients.
- It was anticipated that 20% of patients might not be assessable for efficacy endpoints.

##### *Statistical Tests*

- Cochran-Mantel-Haenszel test used to compare baseline differences for categorical data, adjusting for platinum sensitivity and bulky disease.
- Three-way analysis of variance was used to compare continuous variables with effects for treatment, platinum sensitivity, bulky disease, and all 2-way interactions involving the treatment group.
- Kaplan-Meier method used to estimate PFS and OS rates.
- Stratified log-rank test used to compare survival between treatment arms.
- Cochran-Mantel-Haenszel use to compare response rates, stratified by platinum sensitivity and bulky disease.
- Quality-adjusted time without symptoms and toxicity used to evaluate the impact of treatment on both length and quality of life (Gelber et al. 1995).

**Table 5.2** Results of Doxil Study 30-49

Treatment arm	PLD N=239	Topotecan N=235	Statistics
<b>Patient characteristics</b>			
Median age (range)	60 (27-87)	60 (25-85)	
Time from prior chemotherapy, median (range)	7 months (0.9-82.1)	6.7 months (0.5-109.6)	
Initial stage	5%	6%	
Stage I	5%	3%	
Stage II	73%	70%	
Stage III	17%	20%	
Stage IV			
Histology	Not reported	Not reported	
Grade	Not reported	Not reported	
Sum of lesions (cm <sup>3</sup> ), median (range)	20 (1-441)	20 (1-296)	
Platinum sensitive	46%	47%	
Platinum refractory	54%	53%	
Bulky disease present	46%	47%	
Bulky disease absent	54%	53%	
Prior platinum/taxane	74%	72%	
<b>Treatment delivery</b>			
Total number of dosing cycles	1164	1349	
Cumulative dose, mg/m <sup>2</sup>	200 (47-1301)	36 (3-165)	
Mean cycle dose, mg/m <sup>2</sup>	50 (34-58)	7 (3-10)	
Mean cycle length, days	30 (27-56)	24 (20-38)	
<b>Efficacy</b>			
2001 publication			
CR+PR	19.7%	17.0%	NS
SD	32.2%	40.4%	NS
Median PFS	16.1 weeks	17.0 weeks	NS
Platinum sensitive	28.9 weeks	23.3 weeks	<i>P</i> = .037
Platinum resistant	9.1 weeks	13.6 weeks	NS
Median OS	60 weeks	56.7 weeks	NS
Platinum sensitive	108.0 weeks	71.1 weeks	<i>P</i> = .008
Platinum resistant	35.6 weeks	41.3 weeks	NS
2004 publication			
Median OS	62.7 weeks	59.7 weeks	HR 1.21 (95% CI, 1.00-1.48)
Platinum sensitive	107.9 weeks	70.1 weeks	HR 1.43 (95% CI, 1.07-1.92)

*(continued)*

**Table 5.2** Results of Doxil Study 30-49*(continued)*

Treatment arm	PLD N=239	Topotecan N=235	Statistics
Platinum resistant	Not reported	Not reported	HR 1.06 (95% CI, 0.82-1.39)
<b>Toxicity</b>			
Worse with PLD			
Any grade PPE	49%	1%	<i>P</i> < .001
Any grade stomatitis	40%	15%	<i>P</i> < .001
Worse with topotecan			
G3/4 neutropenia	12%	77%	<i>P</i> < .001
G3/4 anemia	5%	28%	<i>P</i> < .001
G3/4 thrombocytopenia	1%	34%	<i>P</i> < .001
G3/4 leukopenia	10%	50%	<i>P</i> < .001
Alopecia	16%	49%	<i>P</i> = .007
G-CSF	4.6%	29.1%	
Erythropoietin	6.3%	23.1%	
Blood transfusions	14.9%	57.8%	
Dosing modifications	57.3%	78.3%	
Sepsis	N=0	N=9 (3.8%)	
Treatment-related deaths	N=0	N=3	

CI, confidence interval; CR, complete response; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; NS, not significant; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PPE, palmar-plantar erythrodysesthesia; PR, partial response; SD, stable disease.

#### CONCLUSION OF TRIAL

- PLD has comparable efficacy, a favorable safety profile, and convenient dosing, which supports its role as a treatment option in patients with recurrent ovarian cancer. Long-term follow-up demonstrates a survival benefit to PLD compared to topotecan, which is most pronounced among patients with platinum-sensitive recurrent disease.

#### COMMENTS FROM 2001 STUDY

- There was no evidence of a relationship between cumulative PLD dose and change in LVEF.
- Sixty-one patients received cumulative dose >300 mg/m<sup>2</sup> PLD.
  - Three of 61 had ≥20% decrease in LVEF.
  - Three of 61 had postbaseline LVEF <45% (2 started study with LVEF <45%).
  - No patients had clinical signs or symptoms of congestive heart failure.
- Fourteen patients received cumulative dose >450 mg/m<sup>2</sup> PLD.

- At 12 weeks, there were no differences in quality of life between the 2 groups.
- Treatment options for recurrent ovarian cancer are limited and response rates are modest.
- Intravenous chemotherapy.
  - Ifosfamide: 20% (Sutton et al. 1989).
  - Hexamethylmelamine: 14% (Vergote et al. 1992).
  - Oral etoposide: 26% (Hoskins and Swenerton 1994).
  - Gemcitabine: 19% (Lund et al. 1994; Friedlander et al. 1998).
  - Vinorelbine: 20% (Bajetta et al. 1996).
- Intraperitoneal chemotherapy.
- Hormonal therapy.
- Secondary cytoreductive surgery.
- Radiotherapy.
- High-dose chemotherapy with stem cell support.
- In the recurrent setting, combination chemotherapy has not proven to be more effective but is associated with higher toxicity. Median survival times are limited, ranging from 6 to 16 months (Bajetta et al. 1996; ten Bokkel Huinink et al. 1997; Bookman et al. 1998). Palliation and quality of life are important priorities in this setting.
- Overall, PFS and OS were similar between the 2 groups, but in subgroup analysis, PLD was superior to topotecan in PFS and OS among platinum-sensitive patients.
  - Data on subsequent therapies were not collected, but topotecan was commercially available at the time while PLD was not yet approved.
  - PLD was associated with less marrow toxicity and may have allowed more subsequent doses of marrow-toxic drugs.
  - PLD may prevent the development of multidrug resistance (Oudard et al. 1991; Thierry et al. 1992).
- Topotecan administration was associated with more grade 4 hematologic toxicities, including fatal toxicities. Grade 4 neutropenia has been observed in 79% to 94% of patients treated with topotecan in other trials (Swisher et al. 1997; ten Bokkel Huinink et al. 1997; Bookman et al. 1998).
- PLD was generally well tolerated in this trial.
  - The most common treatment-related adverse events were stomatitis and PPE.
  - Only 5.3% of dose modifications were due to stomatitis.



- PPE is a cutaneous reaction typically involving the palms of the hands and soles of the feet.
  - PPE typically begins with a 3- to 5-day period of paresthesias followed by edema and erythema and possibly with severe pain and cracking of the skin.
  - Discontinuation of therapy results in desquamation followed by reepithelialization of the affected areas.
  - PPE can be prevented and managed by early recognition and dose modification (decreasing the dose or lengthening the dosing interval) (Uziely et al. 1995; Lopez et al. 1999; Gordon et al. 2000).
  - Topical dimethyl sulfoxide or pyridoxine have been used to manage PPE (Vail et al. 1998; Lopez et al. 1999), although there is no definitive evidence that pharmacologic therapy is effective.
  - PPE typically develops 1 to 3 weeks after repeated dosing of PLD (Gabizon and Muggia 1997).
  - The long half-life and small liposomes of PLD are theorized to result in accumulation of the drug in the skin (Gabizon and Muggia 1997).
  - The primary approach to preventing PPE includes observation for early signs.
- The tolerability of PLD makes it a good candidate treatment for long-term use.
- The lack of hematologic toxicity makes PLD a candidate for combined treatment with other agents.
- PLD is dosed less frequently than other drugs, which makes it more convenient for administration.
- PLD has a favorable safety profile and overall comparable efficacy, making it a good candidate treatment for patients who have progressed after front-line platinum-containing chemotherapy.

#### COMMENTS FROM 2004 STUDY

- Comparison of this study to ICON4 (Parmar et al. 2003).
  - In patients with platinum-sensitive disease, median OS was 107.9 weeks with PLD in this study compared to 116 weeks (29 months) with combination platinum/taxane in ICON4.
  - In ICON4, approximately 40% of patients received prior taxane therapy. In this study, 73% of patients received prior taxane.
  - In ICON4, almost 75% of patients had a platinum-free interval of >12 months, compared to 23% of patients in this study. The probability

of response increases with increasing treatment-free intervals (Gore et al. 1990; Markman et al. 1991).

- Results of this analysis as well as the convenience in administration (1-hour infusion every 28 days) and the safety profile suggest that PLD is the treatment of choice among nonplatinum agents for patients with recurrent ovarian cancer, particularly in those with platinum-sensitive disease.

### **ICON4/AGO-OVAR 2.2 (Parmar, Lancet 2003)**

#### REFERENCE

- Parmar MK, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet*. 2003;361(9375):2099-106. PMID: 12826431. (Parmar et al. 2003)

#### TRIAL SPONSORS

- ICON4 was coordinated by the Instituto Mario Negri, Milan, Italy (IRFMN) and the Medical Research Council's Clinical Trials Unit, London, UK (MRC CTU)
- Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) 2.2 was coordinated by AGO, Karlsruhe, Germany

#### RATIONALE FOR TRIAL

- At the time of ovarian cancer relapse, the probability of response to retreatment is based on the platinum-free interval (Markman et al. 1991).
  - Patients with platinum-sensitive disease (relapse >6 months from last platinum therapy) would generally be retreated with another platinum agent.
  - Patients with platinum-resistant disease (relapse <6 months from last platinum therapy) rarely respond to further platinum therapy and would be treated with an alternative agent such as paclitaxel.
- It is not known whether the addition of paclitaxel to platinum therapy for platinum-sensitive relapse would improve outcomes. Paclitaxel has a different mode of action from platinum drugs. In observational studies, the combination has been reported to have response rates of up to 90% (Rose et al. 1998b; Dizon et al. 2002).

- This trial is a randomized controlled trial to evaluate the efficacy of paclitaxel plus platinum versus platinum alone in patients with platinum-sensitive relapsed ovarian cancer.

#### PATIENT POPULATION

- N=802.
- Enrolled between January 1996 and March 2002 from 119 hospitals in 5 countries to 1 of 3 protocols, each of which had slightly different eligibility criteria.
- One trial coordinated by the MRC CTU for hospitals in the United Kingdom, Norway, and Switzerland.
  - Allowed to have more than 1 line of prior chemotherapy, which included platinum plus or minus paclitaxel.
  - Measurable disease was not required.
  - Diagnosis of relapsed disease could be based on CA125 elevation alone.
- One trial coordinated by the IRFMN in Italy.
  - Only 1 prior line of chemotherapy, which was platinum plus or minus paclitaxel.
  - Measurable disease was required.
- One trial coordinated by the AGO.
  - Only 1 prior line of chemotherapy, which must have been cisplatin plus paclitaxel or carboplatin plus paclitaxel.
  - Measurable disease was not required.
- Epithelial ovarian cancer requiring chemotherapy.
- Previously received platinum-based chemotherapy with relapse more than 6 months from last platinum (>12 months for the Italian ICON4 group).
- No concomitant or prior malignant disease likely to interfere with treatment or outcomes.

#### TREATMENT DETAILS

##### *Arm 1: Conventional Platinum-Based Chemotherapy*

- Carboplatin.
  - Dose based on area under the curve (AUC) method of Calvert (Calvert et al. 1989) with a minimum of 5 (glomerular filtration rate [GFR]+25). GFR was determined by a radioisotope method or 24-hour urine collection.

- If GFR was assessed by the Cockcroft formula, the dose was a minimum of 6 (GFR + 25).
- Cisplatin.
  - Minimum dose of 75 mg/m<sup>2</sup> if given as single agent.
  - Minimum dose of 50 mg/m<sup>2</sup> if given in combination with other agents.
  - Protocol treatments included carboplatin, CAP (cyclophosphamide, Adriamycin, cisplatin), carboplatin + cisplatin, cisplatin + doxorubicin, cisplatin alone, and carboplatin + nontaxane.

#### *Arm 2: Paclitaxel + Platinum*

- ICON4 protocol: paclitaxel 175 mg/m<sup>2</sup> IV over 3 hours followed by carboplatin or cisplatin as dosed above.
- AGO protocol: paclitaxel 185 mg/m<sup>2</sup> IV over 3 hours followed by carboplatin or cisplatin as dosed above.
- Protocol treatments included paclitaxel + carboplatin, paclitaxel + cisplatin, paclitaxel + carboplatin + cisplatin, and paclitaxel alone.

#### ASSESSMENTS BASED ON PROTOCOL

- MRC protocol (ICON4)—assigned at least 6 cycles.
- IRFMN protocol (ICON4)—assigned at least 3 cycles, further 3 cycles based on results of response assessment.
- AGO protocol—assigned 6 to 8 cycles with response assessments done after second and fourth cycles.
- Quality of life collected for MRC and AGO protocols on slightly different schedules.

#### ENDPOINTS

- Overall survival (primary endpoint).
- Progression-free survival.
  - Elevated CA125 in the absence of radiologic evidence of disease was not considered progression.
- Quality of life.

#### STATISTICAL CONSIDERATIONS

##### *Stratification Factors*

- Stratification for ICON4 protocol included center, age, last chemotherapy received, time since completion of last chemotherapy, and intended platinum treatment. Platinum treatment had to be specified before randomization.

- Stratification for the AGO protocol included time since completion of last chemotherapy and whether the patient underwent secondary debulking surgery.

### *Sample Size*

- Original was based on the assumption that the 2-year survival would be around 5% for the control group and would increase by 5% to 10% in the experimental group. Accrual target of 800 patients was set to detect this difference with 95% power at the 5% significance level, corresponding to a hazard ratio of 0.77.
- In 2001, the data monitoring and ethics committee noted the 2-year survival in the control group was much higher than originally predicted at approximately 50%. In the revised calculation, accrual of 800 patients would allow detection of an 11% difference in 2-year survival (from 50% to 61%) with 90% power at the 5% significance level, corresponding to a hazard ratio of 0.71.

### *Statistical Tests*

- Kaplan-Meier curves for overall and progression-free survival.
- Mantel-Cox log rank test to compare survival.
- $\chi^2$  to test for differences in effect size in different subgroups.
- Mann-Whitney nonparametric test used to compare quality-of-life measures: worst score and area under the curve for the first 6 months.

### CONCLUSION OF TRIAL

- Paclitaxel plus platinum chemotherapy improves survival and progression-free survival in patients with platinum-sensitive recurrent ovarian cancer compared to conventional platinum-based chemotherapy alone. The benefit is seen even in the subset of patients who received prior front-line treatment with paclitaxel and platinum.

### COMMENTS

- There was no evidence that the effect of combination treatment was any different in the subgroup of patients that had received prior paclitaxel+platinum (about 40% of the population).
- Differences in subsequent treatment at the time of progression: 31% in the conventional treatment arm received paclitaxel; 8% in the paclitaxel+platinum arm received further taxane-based treatment.
- Myelosuppression was greater in the conventional platinum chemotherapy arm, supporting prior reports suggesting a myeloprotective effect of paclitaxel (van Warmerdam et al. 1997).

**Table 5.3** Results of ICON4/AGO-OVAR 2.2

Treatment arm	Platinum N=410	Paclitaxel+ platinum N=392	Statistics
<b>Patient characteristics</b>			
Median age	59.2	60.0	
Time from prior chemotherapy			
6-12 months	27%	23%	
≥12 months	73%	77%	
No. of prior chemotherapies			
1	93%	90%	
2	6%	6%	
3 or more	1%	4%	
Last chemotherapy			
Paclitaxel/carboplatin	34%	34%	
Carboplatin	31%	30%	
CAP	18%	16%	
Paclitaxel/cisplatin	5%	7%	
Other platinum	10%	11%	
Other nonplatinum	1%	3%	
Intended platinum			
Carboplatin	83%	85%	
Cisplatin	17%	15%	
Stage	Not stated	Not stated	
Histology	Not stated	Not stated	
<b>Treatment delivery</b>			
Received ≥6 cycles	66%	79%	
Received <6 cycles	30%	19%	
<b>Efficacy</b>			
2-year OS	50%	57%	
Median OS	24 months	29 months	HR 0.82 (95% CI, 0.69-0.97)
1-year PFS	40%	50%	
Median PFS	9 months	12 months	HR 0.76 (95% CI, 0.66, 0.89)
CR or PR	54%	66%	<i>P</i> = .06
<b>Toxicity</b>			
Worse with platinum			
Hematologic	46%	29%	
G2-4 nausea/vomiting	40%	35%	
Worse with combo			
G2-4 neurologic	1%	20%	
Alopecia	25%	86%	
No difference			
Infection	14%	17%	
Renal	9%	8%	
G2-3 mucositis	6%	7%	

CAP, cyclophosphamide + Adriamycin/doxorubicin + cisplatin; CI, confidence interval; CR, complete response; HR, hazard ratio; PFS, progression-free survival; PR, partial response; OS, overall survival.

## **AGO-OVAR, NCIC CTG, EORTC GCG Trial (Pfisterer, JCO 2006)**

### REFERENCE

- Pfisterer J, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol.* 2006;24(29):4699-4707. PMID: 16966687. (Pfisterer et al. 2006a)

### TRIAL SPONSOR

- Gynecologic Cancer Intergroup
  - AGO-OVAR
  - National Cancer Institute of Canada Clinical Trials Group
  - European Organisation for Research and Treatment of Cancer (EORTC) Gynecologic Cancer Group

### RATIONALE FOR TRIAL

- The majority of patients with ovarian cancer relapse and die within 5 years. Patients with recurrence are classified as having platinum-sensitive or platinum-resistant disease based on the time interval from last therapy to recurrence (Gore et al. 1990; Markman et al. 1991).
- For patients with platinum-sensitive disease, standard therapy is retreatment with a single-agent platinum compound, and carboplatin is the drug of choice due to its favorable therapeutic profile.
- The ICON4/AGO-OVAR2.2 was a pooled analysis of 3 randomized controlled trials that demonstrated that retreatment with platinum and taxane results in superior PFS and OS compared to treatment with platinum alone in patients with platinum-sensitive recurrent ovarian cancer (Parmar et al. 2003). Global quality of life did not differ between the arms, but 20% of patients treated with platinum/taxane experienced grade 2 to 4 neurotoxicity compared to 1% of patients receiving platinum alone. This may underestimate the true incidence of neurotoxicity as many patients had not received taxane in the first-line setting. The OVAR2.2 portion of the study had been discontinued early due to concern that retreatment with paclitaxel would lead to excessive neuropathy. A large proportion of potentially eligible patients could not be entered due to persisting neurotoxicity from first-line therapy.

- In the AGO-OVAR study evaluating first-line cisplatin/paclitaxel vs carboplatin/paclitaxel, 83% and 75% of patients developed grade 1 to 4 neurotoxicity that slowly resolved (du Bois et al. 2003). However, 20% of patients continued to have persistent neuropathy for 2 or more years.
- These data underscore the need for an alternative platinum-based combination with less risk of neuropathy.
- Gemcitabine is a nucleoside analogue that has single-agent activity in phase II studies of recurrent ovarian cancer, including in patients who have received prior platinum and/or taxane (Lund et al. 1994; Lund and Neijt 1996; Shapiro et al. 1996).
- The AGO-OVAR group conducted a phase I/II study of carboplatin plus gemcitabine in patients with platinum-sensitive recurrent ovarian cancer to identify recommended doses. This trial demonstrated a high response rate of 62.5% and acceptable toxicity (du Bois et al. 2001).
- This trial is a phase III investigation comparing the efficacy of carboplatin and gemcitabine against carboplatin alone in patients with platinum-sensitive recurrent ovarian cancer.

#### PATIENT POPULATION

- N=366 enrolled.
- Enrolled between September 1999 and April 2002.
- Recurrent ovarian cancer at least 6 months from completion of first-line platinum-based chemotherapy.
- Measurable or assessable lesions per Southwest Oncology Group criteria (Green and Weiss 1992).
- ECOG performance status of 0, 1, or 2.
- Adequate bone marrow reserve and renal function.
  - ANC  $\geq$ 1500/ $\mu$ L.
  - Platelets  $\geq$ 100,000/ $\mu$ L.
  - Estimated glomerular filtration rate >50 mL/min.
- No serious concomitant systemic disorders incompatible with the study.
- Estimated life expectancy of 12 weeks or longer.

#### TREATMENT DETAILS

##### *Arm 1: Standard Chemotherapy*

- Carboplatin AUC 5 mg/mL/min IV on day 1.

##### *Arm 2: Experimental Chemotherapy*

- Gemcitabine plus carboplatin (du Bois et al. 2001).



- Gemcitabine 1000 mg/m<sup>2</sup> IV on days 1 and 8.
- Carboplatin AUC 4 mg/mL/min IV on day 1.

### *Dosing Details*

- Carboplatin dosed by Calvert formula (Calvert et al. 1989). AUC calculation was based on GFR calculation based on the formula of Jelliffe (Jelliffe 1973).
- Patients received treatment every 21 days for 6 cycles with the option to receive a maximum of 10 cycles at the investigator's discretion. Treatment was discontinued for progressive disease or unacceptable toxicity.

### *Dose Modifications*

- Treatment could be postponed for a maximum of 2 weeks for toxicity, including ANC  $\leq 1500/\mu\text{L}$  and platelets  $\leq 100,000/\mu\text{L}$ . Longer toxicity-related delays resulted in treatment discontinuation.
- For ANC 1000 to 1500/ $\mu\text{L}$  or platelets 75,000 to 100,000/ $\mu\text{L}$ , gemcitabine day 8 reduced 50%.
- For ANC  $\leq 1000/\mu\text{L}$  or platelets  $\leq 75,000/\mu\text{L}$ , gemcitabine day 8 omitted.
- For G3 nonhematologic toxicities (excluding nausea and vomiting), dose modifications or study discontinuation were at the investigator's discretion.
- For toxicity-related treatment delays of  $>1$  week, ANC 500/ $\mu\text{L}$  for more than 5 days or ANC  $<100/\mu\text{L}$  for more than 3 days, febrile neutropenia, platelets  $<25,000/\mu\text{L}$ , and grade 3 or 4 nonhematologic toxicities (other than nausea or vomiting), successive dose reductions by 1 dose level.
- Carboplatin dose reductions.
  - Dose level 1: carboplatin AUC 4.
  - If additional dose reductions required, patients were discontinued.
- Gemcitabine plus carboplatin.
  - Dose level 1: gemcitabine 800 mg/m<sup>2</sup>.
  - Dose level 2: omission of day 8 gemcitabine.

### ASSESSMENTS

- Baseline assessment: medical history, physical examination, blood counts, chemistries, and radiologic studies to establish tumor burden.
- Blood counts were obtained on days 1 and 8 of each cycle.
- Quality of life was assessed by the EORTC QLQ-C30 and QLQ-OV28, version 2 (Aaronson et al. 1993; Greimel et al. 2003).
  - QOL assessed within 2 weeks before enrollment, before each cycle.

- Toxicity was assessed before each cycle and 30 days after last treatment.
- Patient assessment was performed before random assignment, before each cycle during treatment, and every 2 to 3 months after treatment for at least 2 years.
  - Progressive disease was based on clinical and/or radiologic evaluation.
  - Progressive disease was not based on CA125 elevation alone.

#### ENDPOINTS

- PFS, defined as time from date of randomization to date of disease progression or death from any cause (primary endpoint).
- Duration of response was measured from date of first response to date of disease progression or death due to any cause.
- Overall survival was measured from the date of random assignment to the date of death from any cause.
- Response was measured according to Southwest Oncology Group criteria (Green and Weiss 1992).
- Quality of life.
- Toxicity, graded according to the National Cancer Institute Common Toxicity Criteria version 2 (Trotti et al. 2000).

#### STATISTICAL CONSIDERATIONS

##### *Stratification Factors*

- Platinum-free interval (6-12 months vs  $\geq 12$  months).
- First-line therapy (platinum/paclitaxel vs other platinum-based therapy).
- Bidimensionally measurable disease (yes vs no).

##### *Sample Size*

- Target enrollment was 350 patients. Based on historical data, it was expected that between 300 and 350 patients with disease progression would be observed. Based on the AGO-OVAR phase I/II study (du Bois et al. 2001), the expected median PFS for gemcitabine and carboplatin was 8.5 months compared to a median PFS for carboplatin alone of 6 months. The constant HR was 0.71 with a significance level of .05; the study had 85% power using the log-rank comparison of PFS.
- The study was not powered to detect differences in OS. To detect a 25% improvement of 25% (assuming an HR of 0.8), power would have been 55% with an  $\alpha$  of 0.05 and 352 deaths.

**Table 5.4** Results of AGO-OVAR, NCIC, CTG EORTC GCG Trial

Treatment arm	Carboplatin N=178	Carboplatin+ gemcitabine N=178	Statistics
<b>Patient characteristics</b>			
Median age (range)	58 (21-81)	59 (36-78)	
Time from prior chemotherapy			
<6 months	0%	0.6%	
6-12 months	39.9%	39.9%	
≥12 months	60.1%	59.6%	
Prior platinum/taxane	71.3%	70.2%	
Stage IA-IIA	7.9%	9.0%	
Stage IIB-IIIB	19.1%	21.4%	
Stage IIIC	60.1%	54.5%	
Stage IV	12.4%	15.2%	
Histology	Not specified	Not specified	
Grade 1	7.3%	8.4%	
Grade 2	27.5%	28.7%	
Grade 3	49.4%	43.8%	
Undifferentiated	3.9%	5.6%	
Unknown grade	11.8%	13.5%	
<b>Treatment delivery</b>			
% planned carboplatin	98.2%	96.2%	
% planned gemcitabine day 1		92.8%	
% planned gemcitabine day 8		63.4%	
D/C for heme toxicity	4.0%	5.1%	
<b>Efficacy</b>			
Overall response	30.9%	47.2%	<i>P</i> =.0016
Complete response	6.2%	14.6%	
Partial response	24.7%	32.6%	
Stable disease	38.8%	38.2%	
Progressive disease	16.3%	7.9%	
Median PFS	5.8 months	8.6 months	HR 0.72 (95% CI, 0.58-0.90)
Median OS	17.3 months	18.0 months	HR 0.96, NS
Median DOR	7.3 months	8.4 months	<i>P</i> =NS
<b>Toxicity</b>			
Worse in carboplatin/gemcitabine			
G3/4 anemia	8.0%	27.4%	<i>P</i> <.001
G3/4 neutropenia	12.0%	70.3%	<i>P</i> <.001
G3/4 thrombocytopenia	11.4%	34.9%	<i>P</i> <.001

**Table 5.4** Results of AGO-OVAR, NCIC, CTG EORTC GCG Trial (continued)

Treatment arm	Carboplatin N=178	Carboplatin+ gemcitabine N=178	Statistics
No difference			
Febrile neutropenia	0%	1.1%	NS
G1-4 neuropathy, motor	4.0%	6.3%	NS
G1-4 neuropathy, sensory	26.9%	29.7%	NS
G1/2 alopecia	17.8%	49.2%	

CI, confidence interval; D/C, discontinue; DOR, duration of response; HR, hazard ratio; NS, not significant; PFS, progression-free survival.

### Statistical Tests

- Kaplan-Meier estimations were used for time-to-event parameters.
- Log rank  $\chi^2$  tests used to compare the distribution between groups.
- Univariate Cox models were fitted for each covariate and PFS.
  - Covariates included age ( $\leq 60$  vs  $>60$  years), performance status (0 vs 1-2), prior platinum therapy (platinum plus nonpaclitaxel vs platinum plus paclitaxel), disease status (bidimensionally measurable vs assessable), and duration of platinum-free interval (6-12 months vs  $>12$  months).
- Unadjusted normal approximation for the difference of 2 binomial proportions used to compare response rates.
- Paired  $t$  test and analysis of variance (ANOVA) were used to analyze changes in QLQ-C30 and QLQ-OV38 baseline scores within and between arms.

### CONCLUSION OF TRIAL

- Gemcitabine and carboplatin significantly improve PFS and response rate without worsening quality of life in patients with platinum-sensitive ovarian cancer.

### COMMENTS

- In the Cox proportional hazards model, the improved PFS was maintained in patients who had received prior platinum-taxane as first-line therapy and in patients with a short platinum-free interval of less than 12 months.
- Quality of life did not differ between treatment arms.

- Postprogression therapy: no major differences between carboplatin or carboplatin/gemcitabine.
  - Platinum: 23% vs 29%.
  - Topotecan: 21% vs 29%.
  - Anthracyclines: 18% vs 15%.
  - Etoposide: 4% vs 12%.
  - Alkylating agents: 20% vs 12%.
  - Taxanes: 7% vs 1%.
  - Gemcitabine: 6% vs 0%.
- Because epithelial ovarian cancer often behaves like a chronic illness, there is an urgent need to identify active platinum-based combinations that do not have the same cumulative neurotoxicity of platinum and taxane.
- Carboplatin and gemcitabine are feasible and increase progression-free survival and response rates in patients with platinum-sensitive ovarian cancer, irrespective of factors such as prior taxane exposure and platinum-free interval.
- This study did not show a benefit to OS, but it was not designed or powered to do so. Because the OS outcome reflects all treatments administered and not just the treatment received during a trial, PFS has been considered an important endpoint in ovarian cancer patients.
- Carboplatin and gemcitabine were associated with greater hematologic toxicity, but it was tolerable and associated with infrequent sequelae such as febrile neutropenia and no detrimental effect to quality of life.
- Compared to treatment with taxanes, carboplatin and gemcitabine were associated with a better toxicity profile with less neuropathy and alopecia. This treatment combination represents a treatment option for patients with platinum-sensitive ovarian cancer recurrence.

### **Gemcitabine Versus PLD (Mutch, JCO 2007)**

#### REFERENCE

- Mutch DG, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. *J Clin Oncol*. 2007;25(19):2811-2818. PMID: 17602086. (Mutch et al. 2007)

#### TRIAL SPONSOR

- Eli Lilly & Co.

## RATIONALE FOR TRIAL

- There are limited treatment options for patients with platinum-resistant ovarian cancer that has progressed within 6 months of prior platinum treatment.
  - These patients are typically treated sequentially with single-agent regimens, including topotecan, gemcitabine, and pegylated liposomal doxorubicin (PLD).
  - Treatment choice depends on possibility of efficacy, cumulative adverse effects, and optimal sequencing of agents.
- PLD is approved by the US Food and Drug Administration (FDA) for use in patients with progressive or recurrent ovarian cancer after platinum-based chemotherapy. Single-agent PLD has equivalent efficacy and safety to topotecan (Gordon et al. 2001) and is commonly used in patients with platinum-resistant ovarian cancer.
- Gemcitabine has been extensively studied in phase II studies as a single agent (Lund and Neijt 1996; Friedlander et al. 1998; D'Agostino et al. 2003; Markman et al. 2003b) and in combination regimens (Greggi et al. 2001; Goff et al. 2003; Rose et al. 2003; Raspagliesi et al. 2004; Tewari et al. 2004; Ferrandina et al. 2005; Rose 2005) and is active and generally well tolerated.
- This phase III trial was designed to compare the efficacy and safety of gemcitabine to PLD in patients with platinum-resistant recurrent ovarian cancer.

## PATIENT POPULATION

- N = 195 randomized.
- Patients enrolled between July 2002 and May 2004 from 44 independent sites in the United States.

*Inclusion Criteria*

- Age  $\geq 18$  years.
- Documented pathologic diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.
- Prior platinum-based chemotherapy.
- No more than 2 prior regimens.
- Platinum resistance was based on the most recent exposure to a platinum-containing regimen and was defined as progressive disease within 6 months of completing therapy.
- Measurable disease (Therasse et al. 2000) or CA125  $\geq 100$  U/mL.

- Zubrod performance status of 0 to 2.
- Adequate bone marrow reserve and hepatic and neurologic function.

#### *Exclusion Criteria*

- Prior radiation to the breast, head, or neck within the past 3 years.
- Any prior abdominal or pelvic radiation therapy.
- Tumors of low malignant potential.
- Prior PLD or gemcitabine treatment.
- Tamoxifen use (concurrent low-dose corticosteroid or hormone replacement therapy was allowed).

#### TREATMENT DETAILS

##### *Arm 1*

- PLD 50 mg/m<sup>2</sup> IV over 60 minutes on day 1 every 28 days.
- Treatment continued until progressive disease or unacceptable toxicity.

##### *Arm 2*

- Gemcitabine 1000 mg/m<sup>2</sup> IV over 30 to 60 minutes on days 1 and 8 every 21 days.
- Treatment continued until progressive disease or unacceptable toxicity.

#### *Crossover to Other Therapy Allowed*

- At progressive disease.
- At toxicity requiring withdrawal after reversal to grade 1 or less.
- At a cumulative PLD dose of 500 mg/m<sup>2</sup>.

#### *Dose Modifications*

- Dose/cycle delay or reduction.
- Cytokines were allowed for neutropenia >7 days or febrile neutropenia.
- Dose adjustments were based on ANC counts, platelets, and nonhematologic toxicities.
- Therapy could be resumed after toxicities resolved to grade 2 or less.

#### ASSESSMENTS

- Patients allowed with measurable and/or assessable disease.
- CT scan evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Therasse et al. 2000).
  - Baseline within 28 days of enrollment.
  - Gemcitabine: CT before every fourth 21-day cycle.
  - PLD: CT before every third 28-day cycle.
- CA125 assessable disease.
  - Progression defined by Rustin criteria (Rustin et al. 2001).

- Quality of life assessed by Functional Assessment of Cancer Therapy–Ovarian (FACT-O) (Basen-Engquist et al. 2001).
- Safety evaluated using the National Cancer Institute Common Toxicity Criteria, version 2.0.

#### ENDPOINTS

- PFS, defined as time from random assignment to PD or death (primary endpoint).
- OS.
- Disease control rate (DCR), defined as percentage of patients with confirmed complete response, partial response, or stable disease.

#### STATISTICAL CONSIDERATIONS

##### *Sample Size*

- Calculation was based on Freedman’s method (Freedman 1982). Assuming a constant hazard ratio of 0.625, 148 events (progressions or death) were needed to have 80% power to detect a difference between the treatment arms with a 2-sided  $\alpha$  of .05.

##### *Statistical Tests*

- Log-rank test to compare PFS between the 2 arms.
- Kaplan-Meier method (Kaplan and Meier 1958) to estimate survival curves.
- Multiple Cox regression model to explore the impact of prognostic factors on survival.
- Descriptive statistics for quality-of-life data.
- Two-sided Fisher’s exact test to compare incidences of toxicities.

#### CONCLUSION OF TRIAL

- Although this was not designed as an equivalency trial, gemcitabine seemed to have a comparable therapeutic index to pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer, and single-agent gemcitabine could be considered an acceptable treatment alternative.

#### COMMENTS

- Impact of prognostic factors on survival.
  - Stepwise Cox regression model ( $P = .20$  for entry,  $P = .10$  to stay), including age, number of prior chemotherapies, number of prior platinum regimens, response to prior platinum therapy, disease



**Table 5.5** Results of Gemcitabine Versus PLD

Treatment arm	Gemcitabine N=99	PLD N=96	Statistics
<b>Patient characteristics</b>			
Median age (range)	59 (38-85)	62 (28-83)	
Time from prior chemotherapy	3.5 months	4.3 months	
No. of prior chemotherapies			
1	60.6%	67.7%	
2	39.4%	32.3%	
Response to platinum			
Response: CR+PR	46.5%	45.8%	
Nonresponse: SD+PD	53.5%	54.2%	
Measurable disease	65.7%	62.5%	
CA125 only	34.3%	37.5%	
Stage	Not reported	Not reported	
Histology	Not reported	Not reported	
Grade	Not reported	Not reported	
<b>Treatment delivery</b>			
Median No. of cycles (range)	4 (1-21)	3 (1-13)	
Median No. of doses	8	3	
Mean dose intensity	90.8%	92.4%	
% cycles with reduction	14.5%	9.0%	
Crossover	N=64 (PLD)	N=66 (gemcitabine)	
<b>Efficacy</b>			
Median PFS	3.6 months	3.1 months	NS
Median OS	12.7 months	13.5 months	NS
Median time to failure	2.7 months	2.5 months	NS
ORR, initial treatment	6.1%	8.3%	NS
SD, initial treatment	54.5%	38.5%	
DCR, initial treatment	60.6%	46.9%	<i>P</i> =.63
ORR, crossover	7.6%	4.7%	NS
DCR, crossover	63.6%	45.3%	<i>P</i> =.52
<b>Toxicity—initial treatment</b>			
	Gemcitabine (N=99)	PLD (N=96)	
Higher with gemcitabine			
Grade 2-4 constipation	25	9	<i>P</i> =.004
Grade 2-4 nausea/vomiting	28	12	<i>P</i> =.008
Grade 2-4 fatigue	36	23	<i>P</i> =.043
Grade 3-4 neutropenia	38	18	<i>P</i> =.003
Higher with PLD			
Grade 2-3 PPE	0	19	<i>P</i> <.0001
Grade 2-3 mucositis	3	15	<i>P</i> =.003

**Table 5.5** Results of Gemcitabine Versus PLD*(continued)*

Treatment arm	Gemcitabine N=99	PLD N=96	Statistics
<b>No difference</b>			
Grade 2-4 dyspnea	20	10	NS
Grade 2-4 neuropathy	3	8	NS
Grade 2-4 rash	5	5	NS
Grade 3-4 thrombocytopenia	6	5	NS
Grade 3-4 anemia	3	2	NS
Febrile neutropenia	4	4	NS
<b>Toxicity—crossover treatment</b>			
	PLD (N=64)	Gemcitabine (N=66)	
Grade 2-4 fatigue	22	38	<i>P</i> = .009
Grade 2-3 PPE	11	13	NS
Grade 3-4 neutropenia	12	27	<i>P</i> = .007
Febrile neutropenia	7	3	NS

CA125, cancer antigen 125; CR, complete response; DCR, disease control rate; NS, not significant; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PPE, palmar-plantar erythrodysesthesia; PR, partial response; SD, stable disease.

measurability at baseline, and baseline CA125 and baseline Zubrod performance status.

- PFS: only baseline CA125 was a significant predictor. Patients with a higher than median CA125 level had a higher risk of progression and death.
- OS: both baseline CA125 and performance status were significant prognostic factors.
- Quality-of-life analysis.
  - Study was not able to examine changes in QOL from baseline to study end.
  - Post hoc analysis of baseline QOL and treatment outcome demonstrated that higher baseline FACT-O scores were associated with lower hazard for death (HR, 0.54; *P*= .003).
- Identification of agents active against platinum-resistant ovarian cancer is a priority.
  - Second-line agents should lack cross-resistance.
  - Second-line agents should have a favorable toxicity profile due to the palliative nature of therapy.
- Limited number of randomized studies evaluating single agents in platinum-resistant ovarian cancer (ten Bokkel Huinink et al. 1997; Piccart et al. 2000; Bolis et al. 2001; Gordon et al. 2001; du Bois et al.

2002; Gore et al. 2002; Rosenberg et al. 2002; Buda et al. 2004; ten Bokkel Huinink et al. 2004) have shown no statistically significant differences in therapeutic index with the exception of treatments considered nonstandard, including treosulfan and luteinizing hormone-releasing hormone analogues (du Bois et al. 2002).

- ten Bokkel phase III study suggested that topotecan and paclitaxel are equivalent, but this was in patients who did not receive prior taxane therapy (ten Bokkel Huinink et al. 2004).
- Largest randomized phase III trial in this patient population compared topotecan and PLD (Gordon et al. 2001). There was no survival benefit to either agent. Only 74% of patients treated with PLD received prior taxane therapy. Patients receiving topotecan had significantly more grade 3 and 4 hematologic toxicity.
- This study demonstrates comparable efficacy between gemcitabine and PLD with response rates in line with prior studies evaluating PLD (Gordon et al. 2000; Gordon et al. 2001) and gemcitabine (Lund and Neijt 1996; Friedlander et al. 1998; D'Agostino et al. 2003; Markman et al. 2003b; Rose et al. 2003; Rose 2005).
- Gemcitabine trends toward a higher rate of stable disease, an important efficacy measure in platinum-resistant patients.
- There were no differences in PFS or OS in this study. OS should be interpreted with caution due to the crossover study design. Furthermore, this trial was not designed as an equivalency trial, and so caution must be exercised in interpreting the results.
- Toxicity.
  - Twenty percent of patients who crossed over from PLD to gemcitabine experienced PPE during gemcitabine administration. Based on the timing of this toxicity, much of this is attributed to latent or delayed toxicity from initial PLD administration.
  - A phase II study reported lower rates of grade 2 PPE (12%) when dosing PLD at 40 mg/m<sup>2</sup> every 28 days (Markman et al. 2000). No grade 3 or 4 events were observed. However, the median number of cycles was 2 (range, 1-12 cycles), and 12% of patients had dose adjustments.
- This is the second largest population of platinum-resistant ovarian cancer patients studied in a phase III randomized trial. This trial includes almost exclusively patients previously treated with platinum and taxane and therefore reflects current clinical practice patterns.
- Gemcitabine is an option to consider for taxane-pretreated platinum-resistant ovarian cancer patients.

**OVA-301 (Monk, JCO 2010)**

## REFERENCE

- Monk BJ, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. *J Clin Oncol.* 2010;28(19):3107-3114. PMID: 20516432. (Monk et al. 2010)

## TRIAL SPONSORS

- Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ
- PharmaMar, Madrid, Spain

## RATIONALE FOR TRIAL

- Recurrent ovarian cancer is a clinical challenge with limited numbers of compounds with clinical activity. The only approved drugs by the US FDA are carboplatin, cisplatin, paclitaxel, altretamine, topotecan, PLD, and gemcitabine (in combination with carboplatin).
- Clinical trials to identify new agents for recurrent ovarian cancer have been hampered by several factors, including
  - Slow accrual.
  - Nonstandardized endpoint reporting (CA125, tumor response, progression-free survival, overall survival).
  - The FDA partnered with the American Society of Clinical Oncology (ASCO) and the American Association for Cancer Research (AACR) in 2006 to evaluate surrogate endpoints for ovarian cancer and concluded that PFS might be an acceptable endpoint (Bast et al. 2007). The panel posed the question as to what degree of PFS improvement would be clinically meaningful and recommended that studies should also be designed to evaluate the OS outcome.
- Trabectedin is a synthetically produced antineoplastic agent that was originally isolated from the marine tunicate *Ecteinascidia turbinata*.
  - Trabectedin exerts its antineoplastic effect by binding to the minor groove of DNA, bending DNA toward the major groove, disrupting transcription, and leading to G<sub>2</sub>-M cycle arrest and apoptosis (Carter and Keam 2007).
  - Trabectedin is more effective in cells that have a functioning transcription-coupled nucleotide excision repair system.

- This compound has encouraging single-agent activity in recurrent ovarian cancer and is tolerable (Sessa et al. 2005; Krasner et al. 2007; von Mehren et al. 2008).
- In vitro studies demonstrate synergy between trabectedin and pegylated liposomal doxorubicin (Takahashi et al. 2001; Meco et al. 2003).
- This phase III randomized multicenter trial was performed to assess the efficacy of PLD vs PLD plus trabectedin in patients with relapsed ovarian cancer.

#### PATIENT POPULATION

- N=672 enrolled.
- Enrolled between April 2005 and May 2007 from 124 centers in 21 countries.

#### *Inclusion Criteria*

- Age  $\geq 18$  years.
- Histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.
- One prior platinum-based chemotherapy regimen only followed by persistence, recurrence, or progression.
  - Platinum resistant: platinum-free interval (PFI)  $< 6$  months.
  - Platinum sensitive: PFI  $\geq 6$  months.
- Measurable disease by RECIST.
- ECOG performance status  $\leq 2$ .
- Adequate bone marrow function: hemoglobin  $\geq 9$  g/dL, ANC  $\geq 1500/\mu\text{L}$ , platelets  $\geq 100,000/\mu\text{L}$ .
- Adequate renal function: serum creatinine  $\leq 1.5$  mg/dL or creatinine clearance  $\geq 60$  mL/min.
- Creatine phosphokinase less than or equal to upper limit of normal (ULN).
- Adequate liver function: total bilirubin  $\leq 1.5 \times$  ULN, direct bilirubin less than or equal to ULN, total alkaline phosphatase (ALP)  $\leq 1.5 \times$  ULN, AST and alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN.
- Adequate cardiac function: LVEF within institutional limits.
- Interval between prior treatment and study initiation.
  - $\geq 4$  weeks for radiation or experimental therapy.
  - $\geq 2$  weeks for hormonal therapy.
  - $\geq 3$  weeks for chemotherapy or biologic therapy.

*Exclusion Criteria*

- Platinum refractory—disease progression during front-line therapy.
- Women of childbearing potential and not using adequate contraception.

## TREATMENT DETAILS

*Stratification Factors*

- ECOG performance status (0 to 1 vs 2).
- Platinum sensitivity (sensitive vs resistant).

*Arm 1: PLD*

- Treatment on day 1 of a 4-week cycle.
- PLD 50 mg/m<sup>2</sup> IV over 90 minutes.
- Maximum of 2 dose reductions allowed.
- PLD could be reduced to 37.5 mg/m<sup>2</sup>, then to 28 mg/m<sup>2</sup>.

*Arm 2: PLD+ Trabectedin*

- Treatment on day 1 of a 3-week cycle.
- IV dexamethasone 20 mg (or equivalent) (Donald et al. 2003) 30 minutes prior to treatment.
- PLD 30 mg/m<sup>2</sup> IV over 90 minutes.
- Trabectedin 1.1 mg/m<sup>2</sup> IV over 3 hours through a central venous catheter.
- Maximum of 2 dose reductions for each drug allowed.
- Trabectedin could be reduced to 0.9 mg/m<sup>2</sup>, then to 0.75 mg/m<sup>2</sup>.
- PLD could be reduced to 25 mg/m<sup>2</sup>, then to 20 mg/m<sup>2</sup>.

*Additional Treatment Details*

- Treatment continued until disease progression or confirmation of complete response and could be continued for 2 or more cycles beyond confirmed CR.
- Colony-stimulating factors were permitted after cycle 1 per ASCO guidelines (Smith et al. 2006).
- Additional antiemetics could be added per the investigator's discretion.

*Dose Reductions*

- One level for neutrophils <500/μL with temperature ≥38.5°C or infection.
- One level for neutrophils <500/μL lasting >5 days.
- One level for platelets ≤25,000/μL.
- One level for grade ≥3 nausea/vomiting (despite adequate treatment).

- PLD reduction for stomatitis.
- PLD reduction for first occurrence of hand-foot syndrome (HFS) and day 15 transaminase elevation.
- Trabectedin reduction for first occurrence of grade  $\geq 2$  ALP elevation.
- PLD reduction for grade  $\geq 1$  HFS after first occurrence of grade 3 to 4 HFS.
- Trabectedin reduction of conjugated bilirubin more than ULN.
- Trabectedin reduction for second occurrence of grade  $\geq 1$  ALP elevation.
- One level reduction of both drugs if grade  $\geq 3$  transaminase elevations on day 15 recovered to grade 1 or less by day 1 of the next cycle or within 3 weeks after that date.
- Both drugs terminated if grade  $\geq 3$  transaminase elevations on day 15 and no recovery to grade 1 or less by day 1 of the next cycle or within 3 weeks.

#### ASSESSMENTS

- Disease assessments at screening and every 8 weeks thereafter.
  - Independent radiology review by RECIST criteria (Therasse et al. 2000).
  - Secondary analyses of PFS based on independent oncologist and investigator's assessments.
  - Both independent radiologists and oncologists were blinded to treatment assignment.
- Evaluation of LVEF.
  - Every 2 cycles for patients with cardiac history or total cumulative anthracycline dose more than 360 mg/m<sup>2</sup>.
  - At treatment discontinuation for all patients.
- Complete blood count (CBC) and chemistries every week.
- Safety evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.
- Quality-of-life questionnaires at screening, day 1 of each cycle, and at treatment end.
  - EORTC QLQ-C30 (Aaronson et al. 1993).
  - EORTC QLQ-OV28 (ovarian cancer module) (Greimel et al. 2003).

#### ENDPOINTS

- PFS (primary endpoint).
- OS.

- Overall response rate (ORR; response maintained  $\geq 4$  weeks by RECIST).
- Duration of response (date from first documentation of response to date of progression or death).
- Safety.
- QOL.

#### STATISTICAL CONSIDERATIONS

##### *Sample Size*

- In total, 650 patients were to be enrolled over 2 years and 415 PFS events were required to test a statistical difference assuming a median PFS of 16 weeks for PLD and 22 weeks for trabectedin/PLD with 90% power and 2-sided  $\alpha$  of .05.
- OS analysis was to be performed when 520 deaths were observed to allow for testing of a statistical difference assuming a median OS of 63 weeks for PLD and 83 weeks for PLD/trabectedin with 90% power and a 2-sided  $\alpha$  of .05.
- In December 2006, after the FDA/ASCO/AACR public workshop evaluating endpoints for ovarian cancer clinical trials (Bast et al. 2007), the endpoints were changed to a single primary endpoint of PFS. OS was made a secondary endpoint. Sample size remained unchanged. This occurred when 440 subjects had been enrolled and before central radiology review.

##### *Statistical Tests*

- Kaplan-Meier method was used to estimate survival.
- The log-rank test was used to compare survival.
- The stratified log-rank test was used to compare PFS between treatment arms while adjusting for ECOG PS and platinum sensitivity (Kaplan and Meier 1958).
- A Cox proportional hazards model was used to compare treatment arms while adjusting by prognostic factors as a secondary analysis (Cox 1972).

#### CONCLUSION OF TRIAL

- Trabectedin combined with PLD improves PFS compared to PLD alone with acceptable toxicity in patients with recurrent ovarian cancer.



**Table 5.6** Results of OVA-301

Treatment arm	PLD N=335	PLD/ trabectedin N=337	Statistics
<b>Patient characteristics</b>			
Median age (range)	58 (27-87)	56 (26-82)	
Time from prior chemotherapy			
<6 months	35%	35%	
6-12 months	28%	37%	
≥12 months	37%	29%	
Prior taxane	81%	80%	
Prior consolidation chemotherapy	10%	8%	
Serous	69%	67%	
Endometrioid	5%	7%	
Mucinous	1%	1%	
Clear cell	5%	4%	
Other	21%	21%	
Grade 1	3%	5%	
Grade 2	18%	17%	
Grade 3	52%	52%	
Unknown grade	27%	25%	
<b>Treatment delivery</b>			
Median cumulative trabectedin dose (range)	NA	5.6 mg/m <sup>2</sup> (1-23)	
Median cumulative PLD dose (range)	216 mg/m <sup>2</sup> (3-1061)	154.4 mg/m <sup>2</sup> (15-630)	
<b>Efficacy</b>			
Median PFS	5.8 months	7.3 months	HR 0.79 (95% CI, 0.64-0.96)
Platinum sensitive	7.5 months	9.2 months	HR 0.73 (95% CI, 0.56-0.95)
Platinum resistant	3.7 months	4.0 months	NS
Overall survival	Immature	Immature	
<b>Toxicity</b>			
More common with PLD/T			
Grade 3/4 neutropenia	22.4%	62.7%	
Grade 3/4 ALT elevations	0.3%	30.9%	
Colony-stimulating factors	17%	42%	
Congestive heart failure	N=1	N=6	
More common with PLD			
Hand-foot syndrome	19.7%	3.9%	
Mucosal inflammation	5.8%	2.1%	
Stomatitis	5.1%	0.9%	

**Table 5.6** Results of OVA-301*(continued)*

Treatment arm	PLD N=335	PLD/ trabectedin N=337	Statistics
Death during treatment	N=8	N=11	
Progressive disease	N=6	N=6	
Adverse event	N=1	N=5	
Unknown cause	N=1	N=0	

ALT, alanine aminotransferase; CI, confidence interval; HR, hazard ratio; NA, not applicable; NS, not significant; PFS, progression-free survival; OS, overall survival; PLD, pegylated liposomal doxorubicin; PLD-T, pegylated liposomal doxorubicin+trabectedin.

#### COMMENTS

- Incidence of dose reductions was similar between arms.
- Cycle delays were more common with PLD/trabectedin.
  - Drug-related adverse events were the most common reason for cycle delay in both arms.
  - HFS was most common reason for treatment termination or dose adjustment for PLD alone.
  - Neutropenia was most common reason for treatment termination or dose adjustment for PLD/trabectedin.
- Treatment effect with PLD/trabectedin was seen across different subgroups.
- OS data are immature at the time of publication.
- ORR was higher with trabectedin/PLD (Appendix Table A2 in manuscript),  $P=.008$ .
- Response duration did not differ between arms.
- Duration of disease stabilization was improved with the combination,  $P=.0106$ .
- Proportion of patients receiving subsequent ovarian cancer therapy was similar in both groups.
- There were no differences in quality of life using mixed-effects models to predict baseline and follow-up scores as a function of treatment, days after baseline and interaction between treatment and days after baseline.
- Toxicities.
  - The criteria for Hy's law (concurrent increase in both transaminases and bilirubin) (Temple 2006), which predicts severe liver toxicity, were met for 3 patients (0.9%) receiving PLD/trabectedin. Liver toxicity resolved in all 3 cases and was never severe.

- Nonplatinum monotherapy.
  - Preferred treatment for patients with platinum-resistant disease.
  - Also considered in patients with platinum-sensitive disease as a potential means of increasing the benefit of subsequent platinum-based treatment.
- Prior to this trial, 4 positive randomized phase III trials in second-line treatment of recurrent ovarian cancer have led to regulatory approval of a drug or a change in treatment paradigm.
  - Topotecan vs paclitaxel trial demonstrated efficacy of topotecan (ten Bokkel Huinink et al. 1997).
  - Topotecan vs PLD trial demonstrated improved efficacy, conventional dosing, and a favorable safety profile for PLD, supporting regulatory approval for PLD for both platinum-resistant and platinum-sensitive ovarian cancer (Gordon et al. 2001; Gordon et al. 2004).
  - ICON4/AGO-OVA 2.2 trial comparing single-agent platinum to platinum + paclitaxel demonstrated prolonged PFS and OS for combination therapy (Parmar et al. 2003).
  - AGO-OVAR, NCIC CTG, and EORTC GCG trials comparing carboplatin to carboplatin + gemcitabine showed improvement in PFS with the combination treatment (Pfisterer et al. 2006a).
- This current trial differs from these prior trials in that it combines nonplatinum agents and demonstrates superiority in PFS with the combination regimen.
- Because most women with recurrent ovarian cancer die of their disease, measures such as quality of life, convenience, and safety are as important as efficacy in evaluating a regimen.
  - Findings of this trial and others demonstrate that doublets are more toxic than monotherapies, and this must be weighed in the benefit-risk ratio when choosing a therapy.

### **CALYPSO (Pujade-Lauraine, JCO 2010) Caelyx in Platinum Sensitive Ovarian Patients**

#### REFERENCE

- Pujade-Lauraine E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol.* 2010;28(20):3323-3329. PMID: 20498395. (Pujade-Lauraine et al. 2010)

## TRIAL SPONSORS

- Gynecologic Cancer Intergroup Trial of Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO)
  - Arbeitsgemeinschaft Gynakologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR)
  - Nordic Society Gynecologic Oncology (NSGO)
  - Australia New Zealand Gynaecological Oncology Group (ANZGOG)
  - National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG)
  - Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Austria
  - European Organisation for Research and Treatment of Cancer (EORTC)
  - Multicenter Italian Trials in Ovarian Cancer (MITO)
  - Mario Negri Gynecologic Oncology (MaNGO)

## RATIONALE FOR TRIAL

- A pooled analysis of 3 randomized controlled trials from AGO-OVAR and ICON showed improved PFS and OS in patients with platinum-sensitive recurrent ovarian cancer treated with paclitaxel and carboplatin compared to platinum alone (Parmar et al. 2003). A GEICO phase II study demonstrated a significant improvement in time to tumor progression in patients treated with paclitaxel and carboplatin compared to carboplatin alone (Gonzalez-Martin et al. 2005).
- Retreatment with paclitaxel and carboplatin is limited by the risk of cumulative peripheral neuropathy. In addition, grade 2 alopecia (total hair loss) occurs in 80% of patients.
- Carboplatin and gemcitabine improve PFS and response rates in platinum-sensitive recurrent ovarian cancer, but OS is not improved compared to carboplatin alone in a phase III trial (Pfisterer et al. 2006a). Hematologic toxicities are greater. There remains a need for other active carboplatin combinations.
- PLD is an active drug against ovarian cancer in the second-line setting (Gordon et al. 2001; Gordon et al. 2004; Ferrandina et al. 2008). PLD has equivalent to superior activity in this setting compared to other agents such as paclitaxel or gemcitabine (ten Bokkel Huinink et al. 1997; Ferrandina et al. 2008).
- A phase II study showed the combination of PLD 30 mg/m<sup>2</sup> followed by carboplatin AUC 5 every 4 weeks is safe and efficacious with a high

response rate of 63% and median PFS and OS of 9.4 months and 32.0 months, respectively (Ferrero et al. 2007).

- This phase III trial was designed to compare the efficacy of PLD/ carboplatin every 4 weeks vs standard paclitaxel and carboplatin every 3 weeks.

#### PATIENT POPULATION

- N=976 enrolled.
- Enrollment from April 2005 to September 2007.
- Cancer of ovary, fallopian tube, or extra-ovarian papillary serous tumor with disease progression >6 months after receiving first- or second-line platinum-based chemotherapy.
- Prior taxane therapy was required.
- Measurable disease according to RECIST or CA125 assessable disease according to Gynecologic Cancer InterGroup criteria or histologic proven relapse (Therasse et al. 2000; Vergote et al. 2000).
- ECOG performance status of 0, 1, or 2.
- Life expectancy of at least 12 weeks.
- Adequate bone marrow, renal, and hepatic function.
- Exclusion: preexisting more than grade 1 neuropathy.

#### TREATMENT DETAILS

##### *Arm 1: Paclitaxel and Carboplatin*

- Paclitaxel 175 mg/m<sup>2</sup> IV on day 1.
- Carboplatin AUC 5 IV on day 1 based on Calvert formula using glomerular filtration rate calculated from serum creatinine values by Cockcroft and Gault method (Cockcroft and Gault 1976).
- Treatment administered every 3 weeks for 6 courses in the absence of unacceptable toxicity or disease progression.
- In the event of partial response or stable disease, patients were allowed to stay on treatment until disease progression.

##### *Arm 2: Pegylated Liposomal Doxorubicin and Carboplatin*

- PLD 30 mg/m<sup>2</sup> IV on day 1.
- Carboplatin AUC 5 IV.
- Treatment administered every 4 weeks for 6 courses in the absence of unacceptable toxicity or disease progression.
- In the event of partial response or stable disease, patients were allowed to stay on treatment until disease progression.

*Treatment Plan and Dose Modification*

- All patients received antiemetics, including a serotonin antagonist and a corticosteroid. Patients receiving paclitaxel received premedications to prevent hypersensitivity reactions.
- Guidelines for dose delay and reduction are in the appendix of the manuscript (Smith et al. 2006).

## ASSESSMENTS

- Baseline:
  - History and physical examination, including a gynecologic examination, laboratory studies including CA125, radiographic imaging (CT scan, ultrasound, MRI, or site-specific radiography) within 4 weeks of study entry.
  - Baseline electrocardiogram (ECG) for patients receiving paclitaxel.
  - Baseline left ventricular ejection fraction by ECG or multigated angiography for patients receiving PLD.
- Before each cycle:
  - Clinical, hematologic, and biochemical assessments, including evaluation for toxic events as assessed by the NCI CTCAE.
  - For patients receiving PLD, a left ventricular ejection fraction measurement was performed before each course of therapy if cumulative anthracycline dose was  $>450 \text{ mg/m}^2$ .
- At 3 month intervals during treatment:
  - CA125.
  - Quality-of-life evaluations by EORTC QLQ C30 version 3.0 and OV-28 version 1 (Aaronson et al. 1993; Greimel et al. 2003).
- Follow-up after treatment discontinuation:
  - Clinical examination, including gynecologic examination, CA125, and adverse event evaluation every 3 months for 2 years and every 6 months thereafter for 5 years.
  - Quality-of-life evaluation every 3 months for 1 year from the date of enrollment.
- Definition of disease progression was based on RECIST and GCIG modifications and included clinical or imaging signs of any new lesions, increase in measurable and/or nonmeasurable tumor defined by RECIST, CA-125 elevation defined by GCIG criteria, health status deterioration attributable to disease, and death of any cause before progression was diagnosed (Therasse et al. 2000; Vergote et al. 2000).

## ENDPOINTS

- PFS (primary endpoint).

## STATISTICAL CONSIDERATIONS

*Stratification Factors*

- Patients stratified by therapy-free interval (6-12 vs >12 months), measurable disease (yes vs no), center.
- Based on method of random assignment, a slight imbalance in treatment allocation was observed but treatment arms were well balanced for baseline characteristics and stratification factors.

*Sample Size*

- Designed as a 2-arm parallel noninferiority trial. Calculations were based on the results of ICON4/AGO-OAR 2-2, which showed a 23% relative benefit for PFS and OS favoring paclitaxel and carboplatin (Parmar et al. 2003). A sample size of 898 evaluable patients with 745 progressions was estimated for a noninferiority margin with an HR of 1.23 at 15 months or a 7.9% absolute difference at 12 months with 90% power and a 1-sided confidence interval of 95%.

*Statistical Tests*

- Cox proportional hazards were used to calculate hazard ratios for survival.
- Kaplan-Meier curves and the log-rank test were used to compare survival curves.
- $\chi^2$  and Wilcoxon rank-sum tests were used as appropriate for toxicity comparisons.

## CONCLUSION OF TRIAL

- Pegylated liposomal doxorubicin and carboplatin were associated with a statistically significant improvement in PFS and lower toxicity compared to paclitaxel and carboplatin in patients with platinum-sensitive ovarian cancer.

## COMMENTS

- This is one of the largest trials to be conducted in relapsed/recurrent ovarian cancer to date.
- In addition to demonstrating an improvement in PFS, CD (carboplatin and PLD) produced less severe toxicities, including less carboplatin hypersensitivity reactions and less peripheral neuropathy and less alopecia compared to CP (carboplatin and paclitaxel).

**Table 5.7** Results of CALYPSO

Treatment arm	Paclitaxel and carboplatin (CP) N=507	PLD and carboplatin (CD) N=466	Statistics
<b>Patient characteristics</b>			
Median age (range)	61 (27-82)	60.5 (24-82)	
Time from prior chemotherapy			
<6 months	0%	0%	
6-12 months	36.1%	35%	
≥12 months	63.9%	65%	
No. of prior chemotherapies			
1	82.6%	87.6%	
Carboplatin	98.1%	96.8%	
Taxane	96.7%	97.1%	
2	17.3%	12.4%	
Stage I/II	13.0%	12.3%	
Stage III/IV	84.2%	85.8%	
Serous	72.2%	71.7%	
Endometrioid	6.9%	8.2%	
Mucinous	1.6%	1.9%	
Clear cell	2.6%	3.0%	
Other	16.7%	15.2%	
Grade 1	4.5%	6.2%	
Grade 2	25.2%	21.5%	
Grade 3	53.3%	55.1%	
Unknown grade	17.0%	17.2%	
Measurable disease	63.3%	60.3%	
Tumor size >5 cm	17.7%	19.1%	
Surgery for this relapse	19.6%	18.7%	
<b>Treatment delivery</b>			
Completed 6 cycles	77%	85%	<i>P</i> <.001
Completed 9 cycles	7%	8%	
Median duration of treatment	16 weeks	21 weeks	
Delay >7 days	5%	7%	
D/C for toxicity	15%	6%	<i>P</i> <.001
<b>Efficacy</b>			
Median PFS	9.4 months	11.3 months	HR 0.82 (95% CI, 0.72-0.94)
Progression by RECIST	80%	79%	
Progression by CA125	20%	21%	

*(continued)*



**Table 5.7** Results of CALYPSO*(continued)*

Treatment arm	Paclitaxel and carboplatin (CP) N=507	PLD and carboplatin (CD) N=466	Statistics
<b>Toxicity</b>			
Deaths during protocol	N=1	N=5	
Worse with CP			
G3/4 nonheme toxicity	36.8%	28.4%	<i>P</i> <.001
≥G2 neurosensory	26.9%	4.9%	<i>P</i> <.001
≥G2 arthralgia/myalgia	19.2%	4.0%	<i>P</i> <.001
Allergic/hypersensitivity	18.8%	5.6%	<i>P</i> <.001
Alopecia	83.6%	7%	<i>P</i> <.001
G3/4 neutropenia	45.7%	35.2%	<i>P</i> <.01
Worse with CD			
Hand-foot syndrome, PPE	2.2%	12%	<i>P</i> <.001
G3/4 thrombocytopenia	6.2%	15.9%	<i>P</i> <.001
≥G2 mucositis	7.0%	13.9%	<i>P</i> <.001
≥G2 nausea	24.2%	35.2%	<i>P</i> <.001
≥G2 vomiting	15.6%	22.5%	<i>P</i> <.001

CA125, cancer antigen 125; CI, confidence interval; D/C, discontinue; G, grade; HR, hazard ratio; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PPE, palmar-plantar erythrodysesthesia; RECIST, Response Evaluation Criteria in Solid Tumors.

- Toxicities of CD included a greater degree of mucositis, nausea, vomiting, and PPE. These side effects were generally short term and manageable.
- The addition of PLD to carboplatin appears to reduce the risk of hypersensitivity reactions (HSR) to carboplatin. The rate of HSR with carboplatin retreatment alone is 23% (Alberts et al. 2008a). The mechanism for this reduced effect is unknown.
- This trial was designed to be a noninferiority trial but actually demonstrated superiority of CD over CP. Testing for superiority in the setting on noninferiority is considered acceptable.
- PFS is considered a valid endpoint for recurrent platinum-sensitive ovarian cancer (du Bois et al. 2005b; Bast et al. 2007). PFS reflects tumor shrinkage and disease stabilization effects and is not confounded by the impact of subsequent treatment as the OS endpoint can be.
- Aside from treatment arm, other covariates that predicted improved PFS included therapy-free interval >12 months (HR, 0.56; 95% CI, 0.48-0.65), lack of measurable disease, and CA125 <100.

- Possible explanations for improved PFS with carboplatin and PLD:
  - Carboplatin appears to enhance the activity of PLD. CD has superior OS to carboplatin alone in platinum-sensitive ovarian cancer in a small randomized controlled trial (26 vs 18 months,  $P=.02$ ) (Alberts et al. 2008a).
  - Duration of therapy was longer with CD (21 vs 16 weeks) because the interval between cycles was longer (4 vs 3 weeks) and because of lower toxicity-related treatment discontinuations. The time from end of treatment to progression was almost similar between arms (6.7 months for CD, 5.9 months for CP).

## **OCEANS (Aghajanian, JCO 2012)**

### REFERENCE

- Aghajanian C, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2012;30(17):2039-2045. PMID: 22529265. (Aghajanian et al. 2012)

### TRIAL SPONSOR

- Genentech, South San Francisco, CA

### RATIONALE FOR TRIAL

- Patients with platinum-sensitive recurrent ovarian cancer (relapse  $\geq 6$  months from initial platinum-based therapy) are usually retreated with platinum-based chemotherapy (Parmar et al. 2003; Pfisterer et al. 2006a; Pujade-Lauraine et al. 2010).
- The combination of gemcitabine and carboplatin (GC) was approved for use in platinum-sensitive ovarian cancer in 2004 in Europe and in 2006 in the United States based on an intergroup (AGO-OVAR/NCIC-CTG/EORTC) phase III study (Pfisterer et al. 2006a). Compared to carboplatin alone, the combination of gemcitabine with carboplatin improved progression-free survival from 5.8 months to 8.6 months (HR, 0.72; 95% CI, 0.58-0.90;  $P=.0031$ ) (Pfisterer et al. 2006a).
- Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF-A) and has demonstrated activity in phase II studies in recurrent ovarian cancer.

- GOG 170D treated 62 patients who had received 1 to 2 prior regimens (platinum sensitive or platinum resistant) with single-agent bevacizumab at 15 mg/kg every 3 weeks and showed an objective response rate of 21% and a median duration of response of 10.3 months. Forty percent of patients were progression free at 6 months (Burger et al. 2007).
- In a single-arm study evaluating bevacizumab with metronomic cyclophosphamide, 70 patients who had received 1 to 3 prior regimens (platinum sensitive or platinum resistant) demonstrated a 24% objective response rate and 56% of patients were progression free at 6 months (Garcia et al. 2008). Four patients (5.7%) had a gastrointestinal (GI) perforation or fistula.
- Forty-four patients with platinum-refractory or platinum-resistant ovarian cancer, recurrence after 2 to 3 prior regimens, and progression during or within 3 months of topotecan or pegylated liposomal doxorubicin showed a response rate of 15.9%, and 27.8% of patients were progression free at 6 months (Cannistra et al. 2007). While single-agent bevacizumab was active in this heavily pretreated population, there were 5 GI perforations (11%), leading to early closure of this study.
- Based on data demonstrating efficacy of bevacizumab in recurrent ovarian cancer, OCEANS (Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease) was designed as a randomized, double-blind, phase III trial to compare GC to GC+bevacizumab in patients with platinum-sensitive ovarian cancer.

#### PATIENT POPULATION

- N=484 randomized.
- Enrollment from April 2007 to January 2010.

#### *Inclusion Criteria*

- Recurrent ovarian cancer with disease progression  $\geq 6$  months after completion of front-line platinum-based chemotherapy.
- Measurable disease according to RECIST version 1.0 (Therasse et al. 2000).
- ECOG status of 0 or 1 (Oken et al. 1982).
- Life expectancy of at least 12 weeks.
- Adequate bone marrow, coagulation, renal, and hepatic function.

*Exclusion Criteria*

- Prior chemotherapy for recurrent ovarian cancer.
- Prior treatment with bevacizumab or other VEGF pathway-targeted therapy.
- Other malignancies within 5 years (unless low risk of recurrence).
- History of abdominal fistula, GI perforation, or intra-abdominal abscess.
- Clinical signs or symptoms of GI obstruction.
- Requirement for parenteral hydration or nutrition.
- Nonhealing wound, ulcer, or bone fracture.
- Bleeding diatheses or significant coagulopathy.
- Known central nervous system (CNS) disease (except for treated brain metastases).
- Clinically significant cardiovascular disease.
- Major surgical procedure within 28 days of enrollment or anticipated surgery during course of study.

## TREATMENT DETAILS

- Dosing matched to AGO-OVAR-NCIC CTG-EORTC trial (Pfisterer et al. 2006).

*Arm 1: Gemcitabine + Carboplatin + Placebo (GC+PL).*

- Gemcitabine 1000 mg/m<sup>2</sup> on days 1 and 8.
- Carboplatin area under the curve 4 mg/mL/min on day 1 based on the Calvert formula.
- Placebo on day 1 or each cycle, administered before GC.
- Cycles repeated every 21 days.

*Arm 2: Gemcitabine + Carboplatin + Bevacizumab (GC+BV).*

- Gemcitabine 1000 mg/m<sup>2</sup> on days 1 and 8.
- Carboplatin area under the curve 4 mg/mL/min on day 1 based on the Calvert formula.
- Bevacizumab 15 mg/kg IV on day 1 or each cycle, administered before GC.
- Cycles repeated every 21 days.

*Additional Treatment Details*

- Patients received 6 cycles but were allowed to receive up to 10 cycles if continued response was seen.

- After completion of GC, placebo or bevacizumab was continued until progressive disease or unacceptable toxicity.

#### *Treatment Modifications*

- Day 1 treatment held if ANC <1500, hemoglobin <8.5, or platelets <100,000 within 24 hours of scheduled treatment.
- Cycles could be delayed for a maximum of 3 weeks until minimum values achieved.
- Day 8 gemcitabine dose modifications were made per the package insert.
- Bevacizumab or placebo could be held for toxicity for a maximum of 6 weeks. Beyond 6 weeks, bevacizumab was discontinued.
- If a component of therapy was discontinued for toxicity, the other components could still be administered per protocol.

#### ASSESSMENTS

- CT scan every 9 weeks from day 1 of cycle 1, regardless of treatment delay or discontinuation. Radiologic evaluation was done according to RECIST 1.0.
- Progression could be determined clinically but not by CA125 elevation alone.
- Toxicity was graded according to the CTCAE version 3.0.
- Patients were observed for adverse events for 30 days after treatment discontinuation and survival every 3 months until death.

#### ENDPOINTS

- PFS, as determined by investigators (primary endpoint).
- Overall response rate.
- Overall survival.
- Duration of response.

#### STATISTICAL CONSIDERATIONS

##### *Stratification Factors*

- Time from last platinum treatment to recurrence (6-12 months, >12 months).
- Cytoreductive surgery for recurrence (yes, no).

##### *Sample Size*

- Approximately 317 progression events were required to detect a PFS HR of 0.73 in favor of the bevacizumab arm with a 2-sided  $\alpha$  of .05 and 80% power.

*Statistical Tests*

- Kaplan-Meier test (Kaplan and Meier 1958) was used to estimate the median PFS and duration of response (DOR) for each treatment group.
- The Brookmeyer-Crowley method (Brookmeyer and Crowley 1982) was used to construct 95% confidence intervals for median values.
- The Cox regression model was used to estimate the stratified HR.
- A 2-sided stratified log-rank test was used to compare between groups..
- The Cochran-Mantel-Haenszel test was used to compare response rates.
- Efficacy analyses were performed on the intent-to-treat population.
- Safety analyses were performed on all patients who received at least 1 partial dose of any part of protocol treatment.
- Study was blinded, but patients could be unblinded at time of progression at the request of the investigator.

*Additional Statistical Considerations*

- Trial was initiated as a phase II study with extensive safety reviews focused on GI toxicity.
- After approximately 20 patients were accrued to each arm and no perforations were reported after >10 weeks of follow-up, the trial was converted to a phase III trial.

## CONCLUSION OF TRIAL

- Gemcitabine, carboplatin (GC)+bevacizumab administered until progression extends progression-free survival compared to GC in patients with platinum-sensitive recurrent ovarian cancer.

## COMMENTS

- This is the first randomized phase III study to demonstrate a positive outcome for the addition of a biologic therapy to standard chemotherapy in platinum-sensitive recurrent ovarian cancer.
  - Improvement in PFS.
  - Improvement in ORR.
  - Improvement in DOR.
  - No difference in OS, but data are immature at the time of publication.
  - No new safety concerns, no reports of GI perforation during treatment.
- Subgroup analyses all supported the primary analysis. PFS was superior with bevacizumab for subcategories of age, ECOG performance status, platinum-free interval, and cytoreductive surgery status.

**Table 5.8** Results of OCEANS

Treatment arm	GC+PL N=242	GC+BV N=242	Statistics
<b>Patient characteristics</b>			
Median age (range)	61 (28-86)	60 (38-87)	
Time from prior chemotherapy			
6-12 months	42%	41%	
≥12 months	58%	59%	
Serous	83.5%	78.1%	
Endometrioid	6.6%	5.4%	
Mucinous	0.4%	1.2%	
Clear cell	2.5%	3.7%	
Other	7.0%	11.6%	
Second cytoreduction			
Yes	10%	12%	
No	90%	88%	
<b>Treatment delivery</b>			
Median No. of chemotherapies (range)	6 (1-10)	6 (1-10)	
Median No. of PL or BV (range)	10 (1-36)	12 (1-43)	
Treatment D/C, progression	66.1%	43.0%	
Treatment D/C, HTN	0%	3.6%	
Treatment D/C, proteinuria	0%	2.4%	
Subsequent cancer therapy	88%	84%	
Subsequent bevacizumab	31%	15%	
<b>Efficacy</b>			
Median PFS	8.4 months	12.4 months	HR 0.48 (95% CI, 0.38-0.61)
Overall RR	57.4%	78.5%	$P < .0001$
Duration of response	7.4 months	10.4 months	HR 0.53 (95% CI, 0.41-0.70)
Median OS (immature data)	35.2 months	33.3 months	
<b>Toxicity</b>			
Serious adverse events	24.9%	34.8%	
G3-5 toxicity	82.4%	89.5%	
≥G3 hypertension	0.4%	17.4%	
≥G3 proteinuria	0.9%	8.5%	
RPLS	0%	1.2%	

BV, bevacizumab; CI, confidence interval; D/C, discontinue; GC+BV, gemcitabine and carboplatin+bevacizumab; GC+PL, gemcitabine and carboplatin+placebo; HR, hazard ratio; HTN, hypertension; OS, overall survival; PFS, progression-free survival; PL, placebo; RPLS, reversible posterior leukoencephalopathy syndrome; RR, response rate.

- The overall response rate was 21% higher in the BV arm. The majority of responses were partial responses.
- There was no difference in overall survival, but the data are immature at the time of publication. There was a high degree of data censoring beyond 18 months, and the median OS was longer than expected in both arms.
- Toxicity comments.
  - Proteinuria tended to develop after more extended bevacizumab treatment and was monitored using urine protein-to-creatinine ratio measurements. The median time to development of grade 3 or higher proteinuria was 26.5 months.
  - Three cases of reversible posterior leukoencephalopathy syndrome were reported in the bevacizumab arm: 2 cases were confirmed by magnetic resonance imaging.
  - No GI perforations occurred during study treatment or within the 30-day safety period. Two GI perforations occurred in the bevacizumab arm after the safety period, both at 69 days after study drug discontinuation. Patient 1 received 34 cycles of bevacizumab and developed small bowel obstruction and gastric ulcer perforation at 69 days. Patient 2 received 39 cycles of bevacizumab and developed intestinal perforation at 69 days after study drug discontinuation and after receipt of 1 dose of pegylated liposomal doxorubicin off study.
  - The rates of neutropenia and febrile neutropenia were similar in both arms.
- As ovarian cancer becomes a chronic illness, treatments that prolong PFS and time without cytotoxic chemotherapy are clinically relevant.
- Limitations of OCEANS:
  - Lack of quality-of-life data.
  - Lack of specimen collection for biomarker analysis.
- Strengths of OCEANS:
  - Robustness of primary endpoint with strict adherence to RECIST-defined progression and its supportive independent review committee (IRC) analysis and the schedule of assessments.
  - The 4-month improved PFS is well above the frequency of radiologic assessments (every 9 weeks) (Panageas et al. 2007; Dancey et al. 2009).
- Platinum-based doublets are accepted as the best treatment option for platinum-sensitive recurrent ovarian cancer (ROC) based on ICON4,



AGO-OVAR-NCIC CTG-EORTC, and CALYPSO (Caelyx in Platinum Sensitive Ovarian Patients) trials (Parmar et al. 2003; Pfisterer et al. 2006a; Pujade-Lauraine et al. 2010). Data from OCEANS suggest that the addition of bevacizumab to the GC doublet improves outcomes.

- ICON4 and CALYPSO differ from OCEANS based on inclusion of nonmeasurable and CA125-evaluable disease, allowed length of cytotoxic chemotherapy, assessment modalities, assessment intervals and method to determine progression. These factors influence survival.

## **AURELIA (Pujade-Lauraine, JCO 2014)**

### REFERENCE

- Pujade-Lauraine E, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32(13):1302-1308. PMID: 24637997. (Pujade-Lauraine et al. 2014)

### TRIAL SPONSOR

- Written on behalf of the European Network of Gynaecological Oncological Trial Groups (ENGOT)–Gynecologic Cancer Intergroup (GCIg) investigators
- Sponsored by F. Hoffmann-La Roche (Basel, Switzerland), which also provided third-party writing assistance

### RATIONALE FOR TRIAL

- Approximately 25% of patients with advanced ovarian cancer have first relapse within 6 months of primary platinum-based chemotherapy and are classified as having platinum-resistant disease. Almost all patients with recurrent ovarian cancer eventually develop platinum resistance.
- The most active single agents for platinum-resistant disease are PLD, paclitaxel, and topotecan (Gordon et al. 2001; Buda et al. 2004; Mutch et al. 2007; Vergote et al. 2009).
- Median overall survival is approximately 12 months for platinum-resistant ovarian cancer (Naumann and Coleman 2011).
- Combined chemotherapy appears to increase toxicity without improving efficacy (Buda et al. 2004; Sehouli et al. 2008; Lortholary et al. 2012).

- An alternative treatment strategy is to combine single-agent chemotherapy with a biologic therapy.
- Bevacizumab.
  - Is a monoclonal antibody that targets all isoforms of VEGF-A.
  - Has activity in platinum-resistant ovarian cancer as a monotherapy (Burger et al. 2007; Cannistra et al. 2007) and combined with chemotherapy (Garcia et al. 2008; McGonigle et al. 2011).
- AURELIA (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) is a randomized trial evaluating the combination of bevacizumab and chemotherapy in platinum-resistant ovarian cancer.

#### PATIENT POPULATION

- N = 361 enrolled.
- Enrolled between October 2009 and April 2011.
- Histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- Measurable disease by RECIST version 1.0 or assessable by GCIG CA-125 response criteria.
- Progression within 6 months of completing  $\geq 4$  cycles of platinum-based therapy.

#### *Inclusion Criteria*

- Age  $\geq 18$  years.
- ECOG performance status  $\leq 2$ .
- Adequate liver, renal, and bone marrow function.

#### *Exclusion Criteria.*

- Strict exclusion criteria were defined to reduce the risk of GI perforation, which was a concern in patients with heavily pretreated ovarian cancer (Cannistra et al. 2007).
- More than 2 prior anticancer regimens.
- Refractory disease (progression during previous platinum-containing therapy).
- Risk factors for bowel complications.
  - History of bowel obstruction (including subocclusive disease) related to disease.
  - History of abdominal fistula.
  - History of GI perforation.
  - History of intra-abdominal abscess.

- Evidence of rectosigmoid involvement by pelvic examination.
- Bowel involvement seen on computed tomography.
- Clinical symptoms of bowel obstruction.
- Prior radiotherapy to the pelvis or abdomen.
- Surgery (including open biopsy) within 4 weeks of study therapy (within 24 hours if a minor surgical procedure).
- Anticipated need for major surgery during study treatment.
- Current or recent treatment with another investigational drug within 30 days of first study dose.
- Untreated CNS symptoms or symptomatic CNS metastasis.
- History or evidence of thrombotic or hemorrhagic disorders within 6 months before first study treatment.
- Uncontrolled hypertension.
- Active clinically significant cardiovascular disease.
- Nonhealing wound, ulcer, or bone fracture.

#### TREATMENT DETAILS

##### *Standard Chemotherapy Selection*

- Investigator choice of single-agent chemotherapy with appropriate premedications.
  - Paclitaxel 80 mg/m<sup>2</sup> IV on days 1, 8, 15, and 22 every 4 weeks.
  - PLD 40 mg/m<sup>2</sup> IV on day 1 every 4 weeks.
  - Topotecan 4 mg/m<sup>2</sup> IV on days 1, 8, and 15 every 4 weeks.
  - Topotecan 1.25 mg/m<sup>2</sup> IV on days 1 to 5 every 3 weeks.
- After chemotherapy regimen was selected, patients were randomized to chemotherapy vs chemotherapy plus bevacizumab.
- Chemotherapy and bevacizumab were continued until disease progression, unacceptable toxicity, or withdrawal of consent.
- Investigator selection of chemotherapy was evenly distributed due to capping of the cohorts.
  - PLD, n=126, complete accrual in October 2010.
  - Paclitaxel, n=115, complete accrual in April 2011.
  - Topotecan, n=120, complete accrual in April 2011.

##### *Arm 1: Chemotherapy Alone (CT)*

##### *Arm 2: Chemotherapy Plus Bevacizumab (BEV-CT)*

- Bevacizumab 10 mg/kg every 2 weeks or
- Bevacizumab 15 mg/kg every 3 weeks for patients receiving topotecan every 3 weeks.

*Drug Discontinuation*

- For patients receiving BEV-CT, if 1 agent was discontinued for toxicity, the other could be continued as a single agent.
- Bevacizumab was discontinued for any grade GI perforation.

*Dose Reductions.*

- Bevacizumab dose reductions were not allowed.
- Chemotherapy dose modification guidelines were according to standard clinical practice.

*Crossovers*

- Patients assigned to CT could cross over to single-agent bevacizumab 15 mg/kg every 3 weeks on clear evidence for progression after a careful risk-benefit assessment.
- Patients assigned to BEV-CT received standard-of-care treatment without bevacizumab at progression.

## ASSESSMENTS

- Imaging studies.
  - At baseline and every 8 weeks (or every 9 weeks for patients receiving topotecan every 3 weeks), using the same technique. Computed tomography and magnetic resonance imaging (in case of contrast allergy) were the preferred imaging modalities.
  - Responses were confirmed by computed tomography scan at least 4 weeks after the first response.
- Follow-up: patients were observed for survival for  $\geq 12$  months.
- Safety: assessed before each cycle and within 30 days of completing treatment.
- Adverse events: graded according to the NCI CTCAE (version 3.0).

## ENDPOINTS

- Investigator-assessed PFS by RECIST—defined as the interval between randomization and first radiologically documented disease progression or death (primary endpoint).
- ORR by RECIST (version 1.0) alone, GCIG CA-125 criteria alone, or both criteria combined.
- OS.
- Safety.
- Tolerability.
- Quality of life.

## STATISTICAL CONSIDERATIONS.

*Stratification Factors*

- Selected chemotherapy (PLD vs paclitaxel vs topotecan).
- Prior antiangiogenic therapy (yes vs no).
- Platinum-free interval (<3 months vs 3-6 months).

*Sample Size*

- Initially, a sample size of 300 patients was planned so that 228 progression events would provide 80% power with a 1-sided log-rank test at an  $\alpha$  of .05, assuming a hazard ratio of 0.72 corresponding to a median PFS of 4.0 months with CT vs 5.56 months with BEV-CT.
- The sample size was increased to 332 patients to provide 80% power to detect a PFS HR of 0.70 with a 2-sided log-rank test with an  $\alpha$  of 0.05 after 247 events, assuming a median PFS of 4.0 months with CT and 5.7 months with BEV-CT.
- The independent data monitoring committee (IDMC) recommended the sample size be increased to  $\geq 360$  patients with a primary analysis planned after 290 PFS events based on an HR of 0.72 and 80% power.

*Statistical Tests*

- Unstratified 2-sided log-rank test used to compare PFS between the 2 treatment arms.
- Stratified 2-sided log-rank test was used for the post hoc analysis.
- Exploratory analyses of safety and efficacy were prespecified for the subgroup of patients with ascites at baseline.
- Post hoc analyses were performed to determine the proportion of patients undergoing paracentesis during study therapy.

## CONCLUSION OF TRIAL

- In patients with platinum-resistant ovarian cancer, the addition of bevacizumab to chemotherapy significantly improves PFS and ORR. OS is not improved, and no new safety signals for bevacizumab have been observed. This should be considered a standard treatment option for platinum-resistant ovarian cancer.

## COMMENTS

- This is the first randomized phase III trial to demonstrate a PFS advantage with combined therapy compared to single-agent therapy.
  - The benefit to PFS was seen across all subgroup analyses.

**Table 5.9** Results of AURELIA

Treatment arm	Chemotherapy alone N=182	Chemotherapy plus bevacizumab N=179	Statistics
<b>Patient characteristics</b>			
Median age (range)	61 (25-84)	62 (25-80)	
<3 months, prior chemotherapy	25%	28%	
Two prior chemotherapies	43%	40%	
Prior antiangiogenic	8%	7%	
Serous/adenocarcinoma	84%	87%	
Endometrioid	5%	5%	
Clear cell	7%	2%	
Grade 1	5%	6%	
Grade 2	26%	30%	
Grade 3	58%	53%	
Unknown grade	11%	12%	
Measurable disease	79%	80%	
Ascites	30%	33%	
<b>Treatment delivery</b>			
Median duration	3 cycles (range 1-17)	6 cycles (range 1-24)	
<b>Efficacy</b>			
Median PFS	3.4 months	6.7 months	HR 0.48 (95% CI, 0.38-0.60)
ORR	12.6%	30.9%	<i>P</i> <.001
ORR, RECIST alone	11.8%	27.3%	<i>P</i> =.001
ORR, GCIG CA125 alone	11.6%	31.8%	<i>P</i> <.001
Median OS	13.3 months	16.6 months	HR 0.85 (95% CI, 0.66, 1.08)
Required paracentesis	17%	2%	
<b>Toxicity</b>			
AE, special interest	40.3%	57.0%	
≥G2 hypertension	7%	20%	
≥G2 proteinuria	0%	2%	
≥G2 GI perforation	0%	2%	
≥G2 fistula, abscess	0%	2%	
Arterial thrombosis	0%	2%	
Venous thrombosis	4%	3%	

AE, adverse event; CA125, cancer antigen 125; CI, confidence interval; GCIG, Gynecologic Cancer InterGroup; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

- Chemotherapy exposure was greater in the BEV-CT arm, reflecting the longer PFS.
- The trial was not powered to detect a difference in OS, and crossover to bevacizumab was allowed.
  - At the time of data cutoff for OS analysis, 40% of patients in the CT arm had crossed over to receive bevacizumab after progression on CT alone.
- The addition of bevacizumab appears to improve the control of ascites.
- The 2.2% rate of GI perforation is lower than previously reported (Cannistra et al. 2007; Simpkins et al. 2007).
  - Strict exclusion criteria were used to ensure high-risk patients were not enrolled.
- Safety of bevacizumab.
  - Higher rates of grade  $\geq 2$  hypertension and proteinuria.
  - No new safety signals.
  - The higher cumulative incidence of peripheral neuropathy and HFS in the bevacizumab-containing arm likely reflects the longer chemotherapy exposure and longer PFS.
- The AURELIA results add to the literature demonstrating improved PFS with the addition of bevacizumab to chemotherapy.
  - GOG 218 (Burger et al. 2011).
  - ICON7 (Perren et al. 2011).
  - OCEANS (Aghajanian et al. 2012).
- The utility of bevacizumab use after relapse and front-line bevacizumab containing therapy is unknown.
  - In AURELIA, only 7% of patients received prior antiangiogenic therapy, so no conclusions can be drawn from this study.
  - In colorectal cancer, survival is improved with second-line bevacizumab use (Bennouna et al. 2013).
- Criticisms of trial.
  - Potential for bias as PFS was determined by investigators.
  - No third arm with bevacizumab alone.
- Patient-reported outcomes are described in an accompanying article (Stockler et al. 2014).