4.0 Chemistry/Manufacturing Controls

Paclitaxel is a marketed drug; the chemistry and manufacturing controls have been previously reviewed and approved. The sponsor submitted an Environmental Assessment, which will be reviewed by the Chemistry Reviewer, Josephine Jee, Ph.D.

5.0 Animal Pharmacology/Toxicology

Paclitaxel is a marketed drug; the preclinical pharmacology has been previously reviewed by Margaret Brower, Ph.D. and approved.

6.0 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Paclitaxel is a marketed drug; the clinical pharmacology has been previously reviewed by Margaret Brower, Ph.D. and approved.

7.0 Relevant Human Experience/Literature Review

Because the sponsor submitted a published literature review as part of the application, the reviewer's literature review and discussion in the context of the NDA will be presented in section 11.0.

8.0 Summary of Clinical Studies

8.1 Pivotal trials

The sponsor submitted one pivotal trial in this sNDA: CA 139-022 or GOG 111. This study was a prospective multicenter randomized trial of cyclophosphamide and cisplatin versus paclitaxel and cisplatin as first-line therapy of advanced stage ovarian cancer. This trial is reviewed in detail.

The sponsor describes the generation of the database for this study. The GOG required the submission of a series of reporting forms, GOG internal forms, documents from patient records, and representative pathology and cytology slides that were centrally reviewed. Data was extracted from these records in order to generate the GOG database. The contents of the GOG database are as follows:

Patient demographics
Patient pre-treatment characteristics
Surgical measurements from initial and second-look laparotomies

Dosing data per course
Clinical and pathologic response with dates
Date of clinical recurrence
Date of death or last known follow up
Worst on-study toxicity as CTC grade for 18 toxicity groupings
GOG evaluation of patient eligibility, response, protocol violations

This data was transferred to BMS. The sponsor then created its own database from the source documents to include all available information. Examples of additional data included in the BMS database are all adverse events (the GOG database included only AEs felt by the investigators to be related to study drug) and all tumor assessments (the GOG required only 1-2 measurable indicator lesions). The sponsor expanded the limited number of GOG adverse event categories in order to allow better assessment of events such as infection, febrile episodes, cardiovascular events, peripheral neuropathy, arthralgia/myalgia, and gastrointestinal events.

BMS performed an audit of documents on randomly selected patients. The records of 97 patients treated at 19 different sites were examined and were used to create a database with the same structure as the BMS database. The database created on the 97 patients from documents derived from the study sites was compared to the database generated from the GOG database for the same 97 patients. The comparison of the audited and GOG databases will be discussed in the Efficacy section, section 9.5. Where a discrepancy in pathology review between the study site and the GOG existed, the central GOG review was used.

8.2 Supportive trials

Supportive information for this application includes a literature review of both randomized and non-randomized trials of paclitaxel as first-line therapy in ovarian cancer. These studies are listed in the following tables and the relevant trials are reviewed in section 11.0.

Table 1. Summary of published randomized trials of paclitaxel as first-line therapy for ovarian cancer.

Study Number	Institution/ Group	Therapy	Taxol Dose and Schedule	Number of patients	Efficacy
CA 139-209	EORTC/ Intergroup	PT v. PC	175 mg/m^2 over 3 hours	680	*PFS*: 16.6 v. 12 months *OS*: 35 v. 25 months* *cResponse*: 57% v. 43% *pCR*: 3% v. 0%
CA 139-057	GOG-132	PT v. T v. P	135 mg/m^2 over 24 hours with P; 200 mg/m^2 over 24 hours as single agent	648	*PFS*: 14.1 v. 11.4 v. 16.4 months *OS*: 26.6 v. 26.0 v. 30.2 months *cResponse*: 67.2% v. 42.0% v. 67.2% *pCR*: 22% v. 6% v. 14.5%
CISCATAX.18	Neijt (Dutch/ Danish/ Swiss)	T/CBDCA v. PT	175 mg/m^2 over 3 hours in both arms	211	NA
	duBois (AGO)	T/CBDCA v. PT	185 mg/m^2 over 3 hours (both arms)	660	NA
ICON3	Medical Research Council	T/CBDCA v. CBDCA or CAP	175 mg/m^2 over 3 hours	2000	NA

cResponse= clinical partial and complete response in the subset of patients with measurable disease
pCR = pathologic complete response (on the subset of patients with a clinical CR who underwent second-look laparotomy)
PT= cisplatin and paclitaxel; PC=cisplatin and cyclophosphamide; T=paclitaxel; P=cisplatin; CBDCA=carboplatin
* ASCO 1998 abstract

Table 2. Published non-randomized trials of paclitaxel as first-line therapy for ovarian cancer (cited by BMS). [Table adapted from sponsor's tables 1 and 6, volume 6, pps. 39, 44]

Study Number	Institution	Ovarian pts/ Total pts	FIGO Stage II/III/IV	Debulking: optimal/ suboptimal/ none	Response rate: All pts/Eval. Pts (ovarian pts)
Taxol Alone					
CA 139-093*	NorthWest Thames	33/33	--/--/33	--/--/33	36%/48%
CA 139-090*	Scandinavian	27/27	--/27/--	--/27/--	52%/61%
Taxol/Cisplatin					
CA 139-010	Johns Hopkins (sequential use)	6/44	--/6 (III + IV)	--/6/--	83%/100%
CA 139-070	NCIC-CTG	29/29	4/21/3	11/16/2	31%/82%
	Cleveland Clinic	19/35	19 (advanced)	--/--/--	NA (pilot for toxicity)
Taxol/Carboplatin					
CA 139-073 GOG 9202	Fox Chase	39/39	39 (advanced)	--/--/--	46%/75%
CA 139-099	ECC Amsterdam	36/36	-- 24/12	--/--/--	53%/70%
CA 139-238*	Newcastle	11/11	4/6/1	7/4/--	27%/75%
CA 139-178*	Inst. Roussy	40/40	--/40 (III + IV)	--/--/--	NA
CA 139-179*	KAO Germany	14/14	14 (advanced)	--/--/--	NA
23-93.015*	KAO Germany	15/15	15 (advanced)	--/--/--	NA
CA 139-091	Velindre H.	30/30	30 (advanced)	--/--/--	53%/73%
36-93.031	U. Milan	27/27	--/25/2	13/14/--	63%/81%
36-93.017*	S. Orsola H.	9/9	--/9 (III + IV)	--/--/--	NA
Baker-Norton	M.D.	14/14	--/--/--	--/--/--	NA

Study Number	Institution	Ovarian pts/ Total pts	FIGO Stage II/III/IV	Debulking: optimal/ suboptimal/ none	Response rate: All pts/Eval. Pts (ovarian pts)
Three Drugs					
CA 139-061	NCI-Med. Branch	13/13	1/5/6	3/9/--	69%/75%
	Salpetriere	14/14	--/10/4	--/6/8	64%/82%
B-W/ Amgen	M.D. Anderson	23/26	23 (advanced)	--/23/--	65%/88%
High Dose					
CA 139-146	U. North Carolina	2/26	--/2/--	--/2/--	100%/100%
CA 139-121	Memorial	16/16	1/11/4	6/10/--	81%/100%

* Accrual continuing and or interim analysis on a patient subset

8.3 Ongoing trials

Ongoing studies in ovarian cancer, including trials sponsored by BMS and investigator-initiated trials, are summarized in the following table:

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

9.0 CA139-022/GOG 111: Phase III randomized study of cyclophosphamide and cisplatin versus Taxol and cisplatin in patients with suboptimal Stage III and Stage IV epithelial ovarian carcinoma

Trial Accrual Dates: April 13, 1990 to March 2, 1992
Data Cutoff: March 30, 1995

9.1 Rationale and objectives

Ovarian carcinoma is diagnosed in 26,800 women in the United States yearly, with a similar incidence in other countries around the world (Parker SL, Tong T, Bolden BA, Wingo PA. CA:Cancer J. for Clin. 47[1]: 5-27, 1997). The disease is usually diagnosed at an advanced stage, and few women are cured despite the high activity of platinum-based regimens. Standard therapy has consisted of either cisplatin or carboplatin in combination with cyclophosphamide. Although initial response rates are 60-70%, responses are not durable. The median survival of these advanced stage patients is 18-24 months, and the 5-year survival is 10-20%. The activity of paclitaxel in ovarian cancer led to its approval by the FDA for use in patients who had failed first-line or subsequent chemotherapy for the treatment of metastatic carcinoma of the ovary.

Preclinical evidence of synergy between paclitaxel and cisplatin, evidence of non-overlapping toxicity seen in pilot clinical trials, paclitaxel's novel mechanism of action (microtubule stabilization) and the activity seen with this compound in pre-treated ovarian cancer patients led to the current study, which tested this combination as first-line therapy of advanced stage ovarian cancer.

The objectives of this trial were:

- To determine response rate, response duration, and survival in suboptimal Stage III and Stage IV ovarian cancer treated with two different platinum-based combination chemotherapy regimens [amended less than a month after the study opened to determine progression-free survival as the primary endpoint, survival as the secondary endpoint, and response as the tertiary endpoint]
- To evaluate the relative activity of a new combination, cisplatin/taxol, as compared to the standard regimen, cisplatin/cyclophosphamide
- To further evaluate the toxicities of the new combination of cisplatin/taxol in this larger patient population
- To compare the relative toxicities of the two regimens
- To compare the therapeutic index of the two regimens

Reviewer Comment:

1. Endpoints should be prospectively defined. However, the change in the primary endpoint with recalculation of the sample size at a time point when few patients had been entered on trial should not affect the results. A MS Access query indicated that 9 patients had been entered on study at the time the amendment was made.

9.2 Design

This trial was a randomized controlled multicenter open-label Phase III trial in chemotherapy-naive suboptimal Stage III and Stage IV ovarian cancer patients who had undergone optimal surgery for ovarian cancer. The study was conducted by the GOG in 86 hospitals affiliated with its member institutions in the United States. Patients were stratified by measurable or non-measurable disease and then randomized to receive either cisplatin paclitaxel (PT) or cisplatin/cyclophosphamide (PC). Randomization was performed centrally by the GOG office and was balanced within and across GOG centers. The regimens were as follows:

Cisplatin 75 mg/m^2 IV at 1 mg/minute Day 1
Cyclophosphamide 750 mg m^2 IV bolus Day 1 The drugs may be given together

OR

Paclitaxel 135 mg/m^2 as a 24 hour continuous infusion Day 1
Cisplatin 75 mg/m^2 IV Day 2

Both regimens were given every 21 days for a total of 6 cycles.

Patients randomized to receive PT were premedicated with dexamethasone 20 mg po 14 and 7 hours prior to the paclitaxel infusion, benadryl 50 mg IV 30 minutes prior to paclitaxel, and ranitidine or its generic equivalent 50 mg IV 30 minutes prior to paclitaxel. The dexamethasone was given IV in patients with active emesis from bowel dysfunction. The paclitaxel was mixed in 4 aliquots, each administered over 6 hours for stability reasons. Patients had continuous cardiac monitoring during the taxol infusion, which could be discontinued after 2 cycles if no cardiac toxicity was observed; the protocol was later amended to require cardiac monitoring for all cycles based on reports of ventricular tachycardia.

All patients had a baseline postoperative abdominal-pelvic CT scan prior to study entry; patients with measurable disease were restaged every 2 cycles. Patients with a complete clinical response at the conclusion of their assigned therapy and all patients with non-measurable disease were required to undergo a second-look laparotomy within 8 weeks of the last cycle of chemotherapy. The protocol was later amended to exempt patients with CA-125 values of greater than 100 from the second-look laparotomy. Patients were required to complete a 21 item self-report questionnaire and a 5 item nurse-administered neurologic assessment prior to the first cycle and 4-6 weeks after the last cycle of therapy. As noted below, the time points for these assessments were changed in protocol amendments. A summary of all the required study parameters is attached in Appendix A.

Dose reductions in cisplatin were not permitted. Renal or neurologic toxicity mandated a treatment delay, but not a dose reduction. Cyclophosphamide or paclitaxel could be dose-reduced to 500 or 110 mg/m^2 respectively for grade 4 nadir hematologic toxicity (except grade 4 anemia). In the subsequent cycles, the drugs were given at the starting dose unless there was persistent grade 3-4 adverse effects. Paclitaxel was discontinued for AV block but not for asymptomatic sinus bradycardia.

Patients were removed from study for :

- Grade IV hematologic toxicity requiring a treatment delay of > 6 weeks
- Persistent creatinine elevation ≥ 2.0 mg/dl for more than 6 weeks
- Grade IV non-hematologic toxicity requiring a treatment delay of > 6 weeks
- Grade III-IV peripheral neuropathy requiring a treatment delay of > 6 weeks

The protocol was amended 15 times, including 1 amendment made prior to patient accrual and 1 amendment for closure of accrual, with multiple changes per amendment. Most of the amendments corrected typographical and grammatical errors or clarified statements in the consent form. The changes are summarized below:

April 11, 1990	Correction of typographical errors (prior to patient accrual)
April 20, 1990	Clarification of one sentence in the consent form
May 11, 1990	1. Patients with non-measurable disease and a CA-125 > 100 despite a complete clinical response were not required to undergo a second-look

laparotomy.
2. An audiogram was required pre-treatment.
3. The statistical section was changed. The primary endpoint was altered from frequency and duration of complete response to progression-free interval. Response was listed as the third endpoint. The median time to progression with a cisplatin-based regimen was assumed to be 10.3 months for women with measurable disease and 14.4 months for women with non-measurable disease. Median survival estimates were unchanged from those in the original protocol. A clinically significant difference was considered to be an increase in the TTP by 40% or more. A sample size of 360 patients was calculated to provide an 84.6% chance of detecting a treatment effect of this magnitude. The new calculations provided an 82.7% chance of detecting a 40% increase in the median survival after 24 months of follow up, and an 80% chance to detect a 19% increase in complete responses due to taxol. Plans for an interim analysis were also outlined: the analysis will be performed when there are 50 failures in the PC group, expected after 2/3 of the sample size is accrued. If the progression-free interval is greater among PC patients, the study would be stopped early, with a loss in power of 3%. If the progression-free interval is greater among PT patients with a p=0.005, the study will be stopped early with an increase in type I error of 0.5%.
4. Solution preparation standards were updated.

August 24, 1990

1. The ovarian cancer surgical procedure and second-look laparotomy sections were revised.
2. Taxol drug stability data were updated.
3. A postoperative abdominal CT scan was not required if the measurable disease was present outside the abdomen, pelvis, or retroperitoneum.
3. Cytology slides from malignant pleural effusions were required for submission.

January 4, 1991

The Neurologic Assessment procedure was limited to 6 study sites.

February 8, 1991

All patients randomized to PT were required to undergo cardiac monitoring on all cycles because of reports of ventricular tachycardia.

April 5, 1991

1. Two additional study sites were added to the Neurologic Assessment list.
2. Additional timepoints were added for the Neurologic Assessment: prior to cycle 3 and after a negative second-look laparotomy.
3. Patients with non-measurable disease were required to undergo a postoperative pelvic examination and abdominal CT scan.

June 10, 1991	Demographic data was collected with the Neurologic Assessment.
July 29, 1991	Holter monitoring was instituted for a subset of patients, 70 on each arm.
August 9, 1991	A ninth site was added for Neurologic Assessment.
September 27, 1991	These changes were retrospective to July 29, 1991. Neurologic Assessments were added at the 3 and 6 month follow up visits.
February 21, 1992	Protocol closed to accrual as of March 2, 1992.
May 22, 1992	Taxol stability data were updated.
November 25, 1992	A study pathologist was named as a principal investigator.
June 3, 1994	Paclitaxel information was updated and new information about adverse events was added to the consent form.

Reviewer Comment:

1. The trial was open-label. However, conducting a double-blinded study with these drugs was not possible because of the complexity of the ancillary procedures required. For example, patients on PC would have been required to undergo a prolonged hospitalization, taken either the same paclitaxel premedication or placebo premedication, etc. This approach was not feasible or ethical.

2. Stratification was performed for measurable versus evaluable disease and by GOG center but not for other factors. This approach is reasonable: there is little prognostic difference between suboptimal Stage III and Stage IV patients, and all patients were required to have good performance status, the most important prognostic factor. Stratification by measurability of disease allowed calculation of response rates. Stratification by GOG center was designed to maximize the comparability of results across the country. One potential drawback: each center was frequently comprised of a main hospital and several smaller hospitals. Thus, there may have been intracenter variations in treatment according to subcenter. However, the large number of hospitals (86) precluded further stratification. Randomization should offset any bias.

3. The nurse-administered assessment evaluated neurotoxicity alone. As defined in the original protocol, the 21 item self-administered inventory was designed to measure neurotoxicity, but the first 8 questions could address either peripheral neuropathy or general quality of life issues. The quality of life measures are limited by the non-blinded nature of the study. In addition, the time points initially chosen were baseline and the conclusion of chemotherapy. The endpoint will cause bias in the results, since patients who complete 6 cycles of chemotherapy with a partial or complete response are likely to have significantly different results than patients who stopped therapy because of progressive disease or chemotherapy-related toxicity. The choice of an intermediate endpoint, such as after cycle 4, would give a more accurate comparison of the two groups. The addition of the cycle 3 time point as well as the timepoints during follow-

up addressed this limitation. However, because of the timing of the amendments, these data will be limited by missing timepoints and the limited number of sampled sites.

4. Stringent criteria to maintain dosing were included in the protocol.

5. The addition of increased cardiac monitoring allowed for a better delineation of paclitaxel-related arrhythmia; the voluntary Holter monitoring in both treatment arms allows a comparison to untreated patients with comparable medical problems. The requirement for monitoring during all paclitaxel cycles was due to literature reports of ventricular arrhythmias. A MS Access query of cardiovascular adverse events revealed premature ventricular contractions: 1 patient had an asymptomatic 4-beat run of ventricular tachycardia. No significant occurrences of ventricular tachycardia were noted.

6. Although CA-125 has not been accepted as a surrogate marker of patient benefit, an elevated value is likely to be associated with persistent disease. It is appropriate to spare these patients the morbidity of the second-look laparotomy procedure.

7. The statistical section was changed early in the course of the study, less than a month after the study opened to accrual. The endpoint was changed from response rate to time to progression, an endpoint associated with patient benefit. The trial retained the statistical power to detect a meaningful difference in response, TOP, and survival. This amendment should not influence the outcome of the study. A MS Access query was performed to ascertain the number of patients entered on study prior to the statistical amendment. Between 4/13/90 and 5/11/90, 9 patients were entered on study and began treatment. This small number is unlikely to introduce bias.

9.3 Eligibility, enrollment, and demographic/baseline characteristics

9.3.1 Inclusion/exclusion criteria

9.3.1.a Inclusion criteria

- Patients with established ovarian epithelial cancer, suboptimal (> 1cm in diameter) Stage III and Stage IV. All patients must have optimal surgery for ovarian cancer, with at least an exploratory laparotomy and appropriate tissue submitted for histologic examination. A TAH BSO should be performed when appropriate
- One of the following pathologic subtypes: serous, mucinous, clear cell, or endometrioid adenocarcinoma, undifferentiated carcinoma, mixed epithelial carcinoma
- Measurable or non-measurable disease, but patients with measurable disease are preferred. To qualify as measurable disease, lesions must measure at least 3 cm on CT; patients are required to have restaging every 2 cycles
- Must have cytologic confirmation that a pleural effusion is malignant, if entry is based on this site
- Must be entered within 6 weeks of staging surgery
- Adequate bone marrow, renal, and hepatic function
- GOG PS 0, 1, 2 [Reviewer note: GOG PS = ECOG PS]

9.3.1.b Exclusion criteria

- Borderline carcinoma, "probably malignant", or a pathologic subtype not listed above
- Optimally debulked Stage III patients
- Previous cancer chemotherapy of any type or radiation therapy
- Septicemia, severe infection, acute hepatitis, or severe gastrointestinal bleeding
- History of cardiac arrhythmia or patients on anti-arrhythmic medication
- Inability to complete the study or the required follow up
- Unclassified cases of ovarian cancer (unable to verify tumor arising from ovarian tissue)
- Prior history of malignancy other than non-melanoma skin cancer

9.3.2 Enrollment, removal from study, protocol violations

9.3.2.a Enrollment

Four hundred ten patients were randomized on study, 196 to PT and 214 to PC. Two hundred forty patients had measurable disease, 113 on PT and 127 on PC. Twenty-one of these patients were inevaluable, 11 on PT and 10 on PC, for the following reasons: 6 patients on each arm had the wrong primary, 5 patients (randomization not given: completed therapy but had inadequate tumor evaluations performed, and 4 patients requested to go off study prior to completing therapy (randomization not given: . Of the 177 with non-measurable disease, 87 were randomized to receive PT and 90 to receive PC.

Several patients were incorrectly stratified: 1 patient on each arm was incorrectly stratified as measurable disease; 4 patients on PC and 5 patients on PT were incorrectly stratified as non-measurable disease. The sponsor noted that 113 patients on PT actually had measurable disease, as did 127 patients on PC. One patient on the PC arm never received treatment she died of a postoperative pulmonary embolus prior to cycle 1.

Reviewer Comment:

1. There are unequal numbers of patients on the two treatment arms. Randomization logs were available for 43 of the 86 hospitals and probably represent the 43 official GOG centers, each with several subsites. The sponsor was asked to clarify this point. In a Response to FDA Request for Information (RFRI) dated 12/22/97, the sponsor confirmed that patients were stratified by GOG center, not by subcenter. Patients were randomized consecutively by center, regardless of the subcenter that contributed the patient. On FDA review, the logs were filled in correctly, in chronologic order, without skipping assignments, and without gaps. The imbalance is probably due to the stratification for measurable and non-measurable disease and because some centers accrued only 1 or 2 patients. For example, of the 43 logs provided, 5 centers entered patients with measurable disease only and 4 centers entered patients with non-measurable disease only. Eleven centers entered 2 patients each, and 24 centers entered 1 patient each.

2. The number of patients incorrectly stratified totaled 11, representing 3% of the study population. The errors were equally distributed between the two arms and should not affect the outcome of the study.

3. The sponsor corrects the number of patients with measurable disease and uses actual,

not randomized, measurability in the response analyses. As randomized, 109 patients on PT and 124 patients on PC were considered to have measurable disease. Although not a true intent-to-treat analysis, this correction is acceptable.

4. The number of inevaluable patients with measurable disease is 21/240, or 8.8%. This rate is acceptable for a study of this design in this disease. Again, inevaluable patients were equally distributed between the two arms.

5. The sponsor indicates that 5 patients were inevaluable on the measurable disease stratum because they had inadequate tumor evaluations performed. These patients, according to review of their case report forms, had a baseline CT scan and had no further radiographic evaluations. All 5 underwent a second-look laparotomy. Thus, these patients were inevaluable for clinical response, but should be evaluable for pathologic response, time to progression, and survival.

9.3.2.b Removal from study

Patients were removed from study for the reasons summarized in the following table:

Table 4. Removal from study (modified from sponsor table 23, volume 3. page 87)

Reason off study	**Number of patients (%)**		
	Cisplatin/Taxol	Cisplatin/Cyclophos-phamide	Total
Completed treatment	168 (86)	165 (77)	333 (81)
Drug-related toxicity:	11 (6)	15 (7)	26 (6)
Renal	2	4	6
Ototoxicity	--	5	5
Hypersensitivity	5	--	5
Hematologic	--	4	4
Polyneuropathy	1	--	1
Emesis	--	1	1
Seizures	--	1	1
Cardiac	1	--	1
Cutaneous	1	--	1
Infection	1	--	1
Disease progression	5 (3)	20 (9)	25 (6)
Death:	6 (3)	5 (2)	11 (3)
Disease progression	2	--	2
Treatment complication	1	3	4
Intercurrent disease	3	2	5
Patient request	4 (2)	7 (3)	11 (3)
Wrong primary tumor	1 (1)	1 (<1)	2 (<2)
Never treated	--	1 (<1)	1 (<1)
Cerebrovascular accident	1 (1)	--	1 (<1)

Reviewer Comment:

1. There are no drug discontinuations for hypersensitivity to cisplatin listed here. However, in sponsor Table 18, volume 3, page 81, one patient experienced a hypersensitivity reaction to cisplatin on the sixth and final cycle, with premature discontinuation of therapy.

2. Patient developed heart block during cycle 6 after 4.5 hours of the taxol infusion. This patient received the full dose of cisplatin and was considered to have completed therapy, according to the sponsor. This patient is not the patient reported as off-study for cardiac adverse event. The patient removed for cardiac reasons was patient who had ECG changes consistent with silent ischemia.

3. The narratives for the patients removed from study were reviewed. Although patient (PC) is listed as removed from study due to renal toxicity, the narrative reports only a grade 1 creatinine elevation at study discontinuation. Her concomitant problems included grade IV leukopenia and granulocytopenia, grade III nausea and vomiting, grade III symptomatic pericardial effusion, grade II bilateral pleural effusions, thrombocytopenia (grade not given), and grade I hypokalemia. None of her toxicities met the off-study criteria, although it is appropriate from a clinical standpoint to remove her because of multiple severe toxicities. With significant pericardial and pleural effusions, the patient may have had progressive disease. There is no significant difference in the incidence of renal toxicity (any or severe) between the two arms, even after removal of this patient.

4. The cutaneous toxicity consisted of Stevens-Johnson syndrome secondary to vancomycin in a patient treated with PT who developed neutropenic sepsis. The sponsor has conservatively attributed it to study therapy, although it was probably due to antibiotic therapy.

5. The patient removed due to neurotoxicity had grade II neurotoxicity recorded. Grade III or greater neurotoxicity was required for removal from study.

9.3.2.c Protocol violations

Three hundred seventy patients were eligible. Forty patients did not meet all of the eligibility criteria, and were equally distributed between the two arms (20 on PT and 20 on PC). These violations are as follows:

Table 5. Summary of major and minor protocol violations (modified from sponsor table 7, volume 3, page 67 and Table 10, page 70)

Protocol Violation	**Number of patients, Cisplatin-taxol**	**Number of patients, Cisplatin-cyclophosphamide**
Major violations:		
Diagnosis other than ovarian cancer	8	10
History prior malignancy		2 (breast)
Optimally debulked	1	
Wrong stage	1 (stage IB)	
Minor violations:		
No baseline AST	5	3
No baseline bilirubin	2	1
No baseline platelet count	0	1
Elevated AST	4	3
Elevated creatinine	1	1
Low white blood cell count	0	1
Low platelet count	1	0
Wrong cell type:	Total = 8	Total = 10
Ovarian--low malignant potential	1	1
Unknown primary	3	4
Primary peritoneal	1	2
Gastrointestinal	2	1
Endometrial/ovarian	1	1
Endometrial	0	1

Reviewer Comment:

1. Because of the equal distribution of the protocol violations, both major and minor, between the two arms, the study results are unlikely to be significantly affected.

2. Other protocol violations include some of the removal-from-study decisions; one example is given in Reviewer Comments 3 and 5 following section 9.3.2.b. Some patients were removed by investigators who believed it was in the patient's best interest rather than according to study criteria. However, the number of patients removed in this fashion was small, affected both arms, and is unlikely to significantly affect the study results.

9.3.3 Patient demographics and baseline characteristics; tumor characteristics

9.3.3.a Patient characteristics

The median age in each arm was 59 years. Eighty-four percent of patients had a performance status of 0 or 1; 16% had a PS of 2. There was no significant difference in the distribution of performance status between arms. The extent of pretreatment procedures was comparable in the two treatment arms.

No patient had received prior hormonal therapy, radiation therapy, or chemotherapy for cancer treatment. All patients had undergone at least 1 laparotomy prior to protocol entry. Forty-one patients had been optimally debulked (6 randomized to PT, 8 randomized to PC with no residual tumor; 15 and 12 respectively with <1cm residual tumor). All of these optimally debulked patients, except the one noted in the protocol violations, had Stage IV disease. There was no significant difference in the amount of residual tumor between the two arms.

In terms of laboratory tests, 48% of patients in each arm had grade 1-2 anemia at baseline, probably due to extent of disease and prior surgery. Hematology parameters were balanced between the two arms. Forty-three percent of patients on each arm had at least 1 abnormal liver function test at baseline, most commonly an elevated alkaline phosphatase (34% PT, 37% PC). The majority of the elevations were grade 1 and were not significantly different between the two arms. Five percent of PT patients and 6% of PC patients had grade 1 creatinine elevations and 1% in each arm had grade 2 creatinine elevations. Again, these differences were not significant.

9.3.3.b Tumor characteristics

Sixty-six percent of patients had Stage III disease and 34% had Stage IV disease. The diagnosis of ovarian carcinoma was confirmed on central pathology review in 96% of patients; serous adenocarcinoma was the most common type, representing 74% of PT patients and 64% of PC patients (p=0.025). The other cell types were evenly distributed between the two arms, as was the distribution of histologic grade.

9.3.3.c Extent and type of disease

Two hundred forty patients had measurable disease, 113 on PT and 127 on PC; 170 had non-measurable disease (83 on PT and 87 on PC). The most common sites of disease in the patients with measurable disease, considering all measurable and non-measurable lesions, were the pelvis (103 patients, 43%), the abdomen (81 patients, 34%), pleural effusions (62 patients,

26%), liver (51 patients; 21%), ascites (49 patients, 20%), lymph nodes (40 patients, 17%), lung (18 patients, 8%), skin/soft tissue/other (11 patients, 5%), and bone (2 patients, 1%). The distribution of disease sites was comparable in the two treatment arms. A median of 1 measurable site per patient was identified for evaluation of tumor response. This lesion measured 2-5 cm in size in 65% of patients with measurable disease (61% PT, 68% PC). Twenty-six percent of these patients had a lesion between 5 and 10 cm (28% PT, 24% PC), and 3% of patients had a lesion greater than 10 cm (2% PT, 4% PC). There was no significant difference in the number or size of indicator lesions between the two chemotherapy arms. A CT scan was used to assess response in 70% of patients with measurable disease; physical examination was used alone in 16% of patients, a different imaging modality in 3%, and the procedure used was not reported in 11% of patients. Again, these differences in method of assessment were not significantly different between the two arms.

Reviewer Comment:

1. The sponsor lists the actual measurability of the patients, rather than their randomized (intent-to-treat) status. The randomized numbers were 109 patients with measurable disease on PT and 124 on PC.

2. There were more patients with the serous cell type on PT than on PC. However, histologic subtype is not a significant prognostic factor, and this imbalance should not affect the study outcome. [Reference: Ozols RF, Rubin SC, Dembo AJ, and Robboy S. Epithelial Ovarian Cancer. In Hoskins WJ, Perez CA, Young RC (eds): Principles and Practice of Gynecologic Oncology, page 748. Philadelphia, J.B. Lippincott, 1992.] Also, this factor was not identified in adjusted analyses by the FDA statistician as a significant prognostic factor.

9.3.4 On-study therapy

One patient randomized to PC died prior to treatment. A total of 1074 cycles of PT were given to 196 patients; 1145 cycles of PC were administered to 213 patients. The range of cycles per patient was one to 6; the median number of courses in each arm was 6. In the PT arm, 85.7% of patients received 6 cycles; in the PC arm, 77.9% received the planned 6 cycles.

9.3.4.a Dose reductions

There was a significant difference in the incidence of dose reductions between the two arms: 27% incidence of dose-reduction overall for paclitaxel and 21% for cyclophosphamide ($p=0.003$). The predominant reason for dose reduction in both arms was hematologic toxicity: 275 of the 288 paclitaxel dose reductions, and 238 of the 244 cyclophosphamide dose reductions. In the PT arm, 5 patients had dose reductions in paclitaxel because of hypersensitivity reactions, 1 because of cardiac arrhythmia, 5 because of physician decision, and 2 because of dosing error. In the PC arm, 6 patients had dose reductions because of a dosing error. The need for dose-reductions increased with the number of cycles: on course 1, 3% of patients received a decreased dose of paclitaxel and <1% received a decreased dose of cyclophosphamide. At cycle 6, these values were 39% and 30% respectively.

The protocol did not permit dose-reductions for cisplatin, only treatment delays.

However, 10 patients on PT received 12 cycles of chemotherapy with a reduced dose of cisplatin. The reasons for dose reduction included a hypersensitivity reaction (1 cycle), 5 cycles in which cisplatin was not given because of removal from study for a paclitaxel hypersensitivity reaction, 2 cycles for neurotoxicity, 3 cycles because of a dosing error, and 1 cycle in which no documentation could be found that cisplatin was administered. On the PC arm, 13 cycles in 9 patients were given with reduced doses of cisplatin. The reasons for dose reduction included grade 4 neutropenia (1 cycle, in which both cyclophosphamide and cisplatin were reduced), neurotoxicity in 2 cycles, ototoxicity in 1 cycle, a dosing error in 4 cycles, and no explanation in 5 cycles.

9.3.4.b Treatment delays

All cycles after cycle 1 were analyzed for delays in study therapy and included 878 cycles of PT and 932 cycles of PC. Treatment delays occurred in 21% of courses of PT compared to 55% of courses of PC ($p < 0.001$). The median number of days to the next course was 21 days for PT compared to 28 days for PC ($p<0.001$). Fewer than 5% of PT cycles were delayed more than 7 days, compared to 13% for PC. The reason for treatment delay in the PC arm was delayed hematologic recovery in 356 of the 932 cycles (38%), compared to 41 of 878 cycles delayed for hematologic parameters in the PT arm (5%).

9.3.4.c Dose-intensity

Dose-intensity was calculated for each study drug individually as the cumulative dose in mg/m^2 given to each patient divided by the duration of treatment in weeks. The treatment duration was defined as the day of first study therapy to 3 weeks after the last study therapy. The relative dose intensity was the received dose intensity divided by the scheduled or planned dose-intensity in mg m^2/wk multiplied by 100. Patients were also grouped by their relative dose-intensity as having received <80, 80-90, or > 90% of the planned dose intensity. The results are summarized in the following table:

Table 6. Dose-intensity (sponsor table 22, volume 3, page 86)

	ARM A (N=196)		ARM B (N= 213)	
	Paclitaxel	Cisplatin	Cyclophosphamide	Cisplatin
Cumulative dose per patient (mg/m^2):				
Median	756	448	4212	448
Range				
Planned dose intensity ($mg/m^2/wk$)	45	25	250	25
Delivered dose intensity ($mg/m^2/wk$)				
Median	41	24	204	21
Range				
Relative dose intensity--% of scheduled dose [no.pts (%)]				
≥ 90%	102 (52)	142 (72)	70 (33)	88 (41)
80-90%	64 (33)	40 (20)	51 (24)	65 (31)
< 80%	30 (15)	14 (7)	92 (43)	60 (28)

The difference between the delivered dose-intensity of paclitaxel on the PT arm and the delivered dose-intensity of cyclophosphamide on the PC arm was statistically significant, with a p value of <0.001. The delivered dose-intensity of cisplatin on the two arms was also significantly different ($p < 0.001$): patients received a higher dose-intensity of cisplatin on the PT arm than on the PC arm.

Reviewer Comment:

Dose-intensity (DI) has been shown preclinically and retrospectively to be important in the treatment of ovarian cancer. Dose-intensity is calculated as the dose per unit time; therefore,

both total dose and treatment interval are important determinants of DI. While the incidence of dose reductions is significantly greater for PT than PC (27% compared to 21%), the absolute difference clinically is small (6%). Similarly, reductions in cisplatin dose were similar in the two arms. In contrast, more than twice as many courses of PC were delayed compared to PT. Consistent one-week delays may affect efficacy. In addition, lengthening the course of therapy by 1 week per cycle may have an adverse effect on quality of life. These data demonstrate a higher dose intensity for both paclitaxel and cisplatin on the PT arm, and lower dose intensity for both cyclophosphamide and cisplatin on the PC arm.

9.3.5 Subsequent therapy

The majority of patients received subsequent therapy, including chemotherapy, radiation therapy, immunotherapy, and hormonal therapy. Eighty percent of patients treated with PT received subsequent therapy, as did 73% of the PC patients. There was no significant difference between the two groups in the number of patients who received any of these modalities, nor in the number of subsequent regimens. Patients treated initially with PC were most likely to receive paclitaxel as subsequent therapy (38% of the patients on this arm); other common drugs included carboplatin, cisplatin, and altretamine. Paclitaxel was used as second-line therapy in 19 of these patients. On the PT arm, patients most commonly received carboplatin (47%), followed by cyclophosphamide, altretamine, and cisplatin. Forty-three patients on the PT arm received a second paclitaxel-containing regimen; 14 of these received it as second-line therapy.

Reviewer Comment:

A significant percentage of patients on PC received paclitaxel after disease progression, although only 9% received paclitaxel as second line therapy. Despite a 38% cross-over rate, a significant survival advantage for PT was observed.

9.4 Endpoints/statistical considerations

9.4.1 Endpoints

The endpoints included objective response in patients with measurable disease. Response was defined differently than in most oncology trials:

Complete clinical response:	Disappearance of all gross disease for 3 weeks
Partial response:	50% or greater reduction in the product obtained from measurement of each lesions for at least 3 weeks
Progressive disease:	50% or greater increase in the product from any lesion documented within 6 weeks of study entry or the appearance of any new lesion within 8 weeks of entry into study

The following parameter was used to define pathologic response:

Complete pathologic response:	Pathologic confirmation of complete response at second-look laparotomy

The sponsor added the following categories:

Microscopic disease only:	Absence of all gross residual disease at second-look surgery, but positive blind biopsies
Residual disease:	Gross residual disease at second-look surgery

The protocol did not further specify other definitions or other response parameters. In the analysis, the sponsor added the following points.

Tumor markers, such as CA-125, were not used to assess response. The GOG response criteria were followed; however, the response data in this application reflect the judgement of BMS physicians, not the GOG assessment.

The sponsor included the following categories for patients with measurable disease:

Inevaluable:	Patients who did not have ovarian cancer as determined by the GOG review
	Patients who did not have reassessment of tumor lesions which were measurable at baseline
Early death or early toxicity:	Patients who died on study prior to reassessment of tumor lesions
	Patients who went off study due to serious AE related to study therapy prior to reassessment of tumor lesions

The sponsor added the following categories for patients with non-measurable disease:

Never treated:	Patients who were randomized but never treated
Wrong primary:	Patients who were randomized but determined on GOG central review to have the wrong primary tumor or cell type
Early death or early toxicity:	Patients who died on study prior to the third course
	Patients who went off study due to serious AE related to study therapy prior to the third course
Progressive disease:	Patients with new lesions or clear progression prior to the third course
No measurable disease:	Patients with non-measurable disease who received at least 3 cycles of therapy

Patients were assigned to these categories; if more than one applied, the first on the above list was used.