Reviewer Comments:

1. The same comments about the choice of prognostic factors apply here. The FDA statistical reviewer re-ran the Cox regression analysis without liver function tests as a baseline variable; the results were unchanged and remained significant in favor of PT.

2. Treatment with PT was associated with a statistically significant and clinically impressive improvement in overall survival.

9.5.4 Time to worsening of performance status

Performance status was assessed at each visit and was used as an indication of the quality of life of the patients on study. One hundred eighty-eight of the 196 patients on PT had both a baseline PS score and at least one follow-up PS score recorded on study, and 203 of the 214 PC patients had this data recorded. On the PT arm, 37 of the 188 had a lower PS on study compared to baseline; on the PC arm, 30 of the 203 patients had a lower PS on study compared to baseline. The time to worsening of PS on each arm was calculated and was not significantly different between the two arms ($p=0.060$). Because there was a significant difference in treatment delays between the two arms, the number of courses to worsening of PS was calculated and was again not significantly different ($p=0.231$).

Reviewer Comment:

1. Ninety-six and 95% of the patients on PT and PC respectively had baseline and repeat measures of PS assessed. However, only a small percentage had deterioration in their PS during the course of the study. It is unlikely that this measure is sensitive enough to pick up QOL changes in the specified study population.

9.6 Safety analysis

9.6.1 Adverse events

Four hundred nine patients were evaluable for safety; one patient died prior to receiving any therapy. Twenty-seven patients were discontinued from the study for adverse events: 12 patients on PT and 15 on PC.

Myelotoxicity was common in both arms of the trial. The percent of patients with leukopenia was the same in both arms (82%), as was the percent of patients with individual grades of leukopenia, including severe (grade 3-4) leukopenia.

The most common observed adverse event was neutropenia. Neutropenia was most commonly severe, but of short duration; the sponsor stated that the neutropenia was without clinical consequences. The following table summarizes the incidence and type of this adverse event:

Table 17. Type and incidence of neutropenia (worst course); % (n) (data derived from sponsor table 39, volume 3, page 123; sponsor table 42, volume 3, page 126; sponsor table 43, volume 3, page 126).

Type of Neutropenia	Cisplatin-Taxol N=190	Cisplatin-Cyclophosphamide N=205	P-value
Any	96% patients	92%	0.146
CTC Grade III-IV	92% (175)	80% (163)	0.001
Grade III	11% (21)	22% (45)	
Grade IV	81% (154)	58% (118)	
Infections: Number of patients with infections Number of episodes	 41 patients 54	 32 patients 46	0.123
Febrile neutropenia	35 courses/1074 courses (3.3%)	9 courses/ 1145 (0.8%)	< 0.001

Other myelosuppressive toxicities are summarized in the following table and are expressed in terms of the worst course:

Table 18. Myelosuppression (data derived from sponsor table 40, volume 3, page 124; sponsor table 41, volume 3, page 125)

Adverse myelosuppressive event	Cisplatin-Taxol	Cisplatin-Cyclophosphamide	P-value
Anemia:	n=188	n=207	
Any	88% (165)	86% (178)	0.656
Grade III-IV	13% (24)	9% (19)	0.263
Grade III	10% (18)	8% (16)	
Grade IV	3% (6)	1% (3)	
Anemia (baseline Hb normal):	n=91	n=102	
Any	88% (80)	83% (85)	0.417
Grade III-IV	13% (12)	3% (3)	0.013
Grade III	9% (8)	2% (2)	
Grade IV	4% (4)	1% (1)	
Thrombocytopenia:			
Any	26% (49)	30% (62)	0.434
Grade III-IV	10% (18)	9% (19)	1.000
Grade III	5% (9)	5% (11)	---
Grade IV	5% (9)	4% (8)	---

Thrombocytopenia and anemia were not significantly different between the two arms. However, 49% of the patients in each treatment arm had abnormal baseline hemoglobin values, most likely due to surgery. When the subgroup with normal baseline hemoglobin values was examined, there was a statistically significantly greater incidence of severe anemia in the PT arm. The sponsor suggests that this effect is due to the higher dose-intensity of cisplatin achieved in this arm.

Table 19. Adverse events (worst course) (data from sponsor tables 44-49, p. 129-133, and sponsor table 50, page 135, all in volume 3).

Adverse event	Cisplatin-Taxol	Cisplatin-Cyclophosphamide	P-value
Peripheral neuropathy: Any Grade III-IV	 26% (49) 3% (5)	 20% (43) 0 (0)	 0.286 0.025
Ototoxicity: Any Grade III-IV	 6% (11) 0 (0)	 10% (22) 2% (4)	 0.102 0.124
Arthralgia/myalgia: Any Grade III (no grade IV)	 10% (18) 1% (1)	 2% (4) 0 (0)	 0.002 0.479
Hypersensitivity: Any Grade III-IV	 9% (15) 3% (5)	 <2% (3) 0 (0)	 0.003 0.025
Nausea/vomiting (g.3-4):	10% (19)	11% (23)	0.747
Diarrhea: Any Grade III-IV	 17% (32) 4% (7)	 8% (16) 1% (2)	 0.008 0.094
Liver function tests: Alkaline phosphatase Any Grade III-IV AST Any Grade III-IV Bilirubin Any Grade III-IV	 36% (66) 1% (1) 18% (33) 0 (0) 2% (2) 1% (1)	 33% (67) 1% (3) 13% (26) 0 (0) 1% (2) 0 (0)	 0.668 0.625 0.203 1.000 0.478
Cardiovascular events Any Grade III-IV	 28% (53) 5% (10)	 7% (14) 3% (5)	 0.001 0.188
Creatinine: Any elevation Grade III-IV	 40% (74) 2% (3)	 46% (95) 2% (4)	 0.221 1.000

Adverse event	Cisplatin-Taxol	Cisplatin-Cyclophosphamide	P-value
Alopecia	55% (107)	37% (79)	0.001
Asthenia	17% (33)	10% (21)	0.041

Cardiovascular events were more common in patients on the PT arm (53 patients, or 28%) than in patients on the PC arm (14 patients, or <7%). Grade 3-4 events occurred in 5% of PT patients and <3% of PC patients. The difference in incidence of cardiovascular events is attributed by the sponsor to the requirement for cardiac monitoring in patients who received paclitaxel.

Reviewer Comment:

1. There was a 6.5% discontinuation rate for adverse events. This rate is consistent with the type of therapy and the patient population.

2. The PT arm was associated with a significantly greater incidence of grade III-IV neutropenia than the PC arm (92% v. 80%); however, it should be noted that the rate of neutropenia with PC remains high. Although the sponsor stated the neutropenia was "without clinical consequences" (section 8/10, volume 1, page 122), there was a significantly greater incidence of febrile neutropenia with PT than with PC; it occurred in 35 courses compared to 9 courses. However, only 3 patients (0.7%) in the study died of sepsis, and all received PC (see Reviewer Comments 2 and 3 after section 9.6.3). These data suggest that the neutropenia is unlikely to be associated with irreversible morbidity. Patients presumably were hospitalized for febrile neutropenia, which may decrease the quality of life. However, more PT cycles were delivered on time, indicating that the neutropenia, whether associated with fever or not, was unlikely to interfere with the scheduled administration of drug. The decreased quality of life associated with hospitalization for febrile neutropenia must be weighed against the decreased quality of life that may be associated with treatment delays and a longer period of chemotherapy treatment with PC.

3. The sponsor notes that severe anemia was more likely in patients treated with PT who had a normal baseline hemoglobin; however, the number of patients in this subgroup analysis is small.

4. The majority of detectable cardiovascular events on the PT arm consisted of bradycardia, tachycardia, hypotension, an abnormal ECG, ventricular extrasystoles, unspecified arrhythmia, hypertension, syncope, and atrial fibrillation. While it is likely that monitoring on the PT arm detected more events, it is also likely that paclitaxel was responsible for some or all of the observed events. Bradycardia, for example, is a well-reported side effect of paclitaxel. What is more relevant, however, is how many events were symptomatic. Since most of the events were grade 2 or less, there does not appear to be a clinically meaningful difference in cardiovascular events between the two arms.

5. Other adverse events that were significantly different between the two arms included severe peripheral neuropathy, arthralgia/myalgia, hypersensitivity reactions, diarrhea, and

alopecia. All of the observed events are consistent with the labeled toxicities of paclitaxel; none represent new findings.

6. The reviewer ran multiple MS Access queries and verified the incidence and severity of the adverse events. These queries generally yielded the same results as those reported by the sponsor. In the few cases where the numbers were not the same, they differed by 2-3 patients/events, not a significant difference. The Adverse Event category of "Other" was also reviewed to assess whether significant events had been mistakenly assigned to this category. No mistaken attributions were identified; the majority of events in this category consisted of fatigue. Finally, a query for the incidence of bowel obstruction was run; 4 patients on PC and 2 patients on PT experienced this complication. Bowel obstruction was uncommon and is more likely related to the underlying illness than to the drug therapy.

6. Overall, the significant benefit conveyed by PT therapy outweighs the increased toxicity of this combination.

9.6.2 Neurologic assessment

The Neurologic Assessment was performed on a subset of patients at 9 designated sites. The assessment consisted of 2 parts, the patient self-report form and the nurse-administered questionnaire. The patient self-report form consisted of 21 questions; the first 8 asked general status questions and the rest referred specifically to neurologic signs and symptoms. The response options for questions 1-19 were "not at all", "a little", "quite a bit", and "very much." For the analysis, these responses were coded from "0" (not at all) to "3" (very much). Question 15 ("When holding an object in your hand, are you able to feel its shape?") was scored as "0" (very much) to "3" (not at all) to make these scores consistent numerically with the other questions. Questions 20 and 21 were graphical ("...draw a tight spiral"; "shade in all the places ...where you have...numbness") and were not analyzed.

The second part of the assessment consisted of a 5 question nurse-administered questionnaire. Question 1 was not analyzed, as this question measured the time it took a patient to button a shirt, but did not provide a uniform number of buttons or a uniform button size. In question 2, patients were asked to identify a nickel among a dime, a penny, a paper clip, and a key in a paper bag and were timed. The question was scored on the "time to identify nickel" and on whether or not the patient could identify the nickel. Questions 3-5 used a yes-no format ("Can the patient stand steadily with her feet together with her eyes closed?"; position sense testing in the hand and then in the feet).

Seventy-six patients completed both a baseline and a follow-up neurologic assessment during the course of study, 42 on PT and 34 on PC. The data were collected from 8 different GOG sites and comprised 23-88% of the study population at the respective sites.

For the patient self-assessment, mean total scores with standard deviation were plotted for each arm for baseline values compared to on study, off study, 3 month follow up and 6 month follow up time points. The sponsor analyzed patients with paired data for the two arms at the above timepoints. The number of patients compared was 34 PT/30 PC for baseline/on study; 36 and 22 respectively for baseline/off study; 9 and 11 respectively for baseline/3 month follow up; and 4 and 2 respectively for baseline/6 month follow up. Patients on PT had an elevated mean

total score versus baseline at all time points. There appeared to be a trend towards higher scores in the PT arm compared to the PC arm. However, because this data was derived from a subset of patients with a non-validated instrument, no formal comparison was performed.

In the nurse-administered questionnaire, questions 2-5 showed no difference between the two treatment groups and no difference between baseline assessment and on-study timepoints. The time to identify a nickel was analyzed in the same paired comparison at the same timepoints as for the patient-administered questionnaire. The numbers of patients included were 26 PT/22PC for baseline/on study; 23/14 respectively for baseline/off study; 7/6 respectively for baseline-3 month follow up; and 3/1 respectively for baseline/6 month follow up. There was a trend for an increased time requirement in the PT arm at all timepoints compared to baseline, and an increased time compared to PC. Again, no formal comparison was made.

Reviewer Comment:

1. Nine centers were designated for neurologic testing, but data are reported from only 8 sites. A Request for Information was sent to the sponsor regarding the 9th site. The sponsor noted that the ninth center designated for neurologic testing accrued a total of 3 patients to GOG 111, but received its designation after 1 patient was already on study. Of the two potentially eligible patients, neither had an assessment performed. No data were excluded from analysis.

2. The percent of patients recruited from the designated sites varies widely. A Request for Information was sent to the sponsor asking whether this phenomenon was due to lack of recruitment, or to the time differences in the designation of specific sites. The sponsor replied that the percentages listed in the study report referred to patients who had both a baseline and a follow-up assessment and could be analyzed. The percentage of patients with at least one assessment was higher. Although reasons for non-participation in the neurologic assessment were not listed, the timing of the designation of a study site was a factor.

3. There is a large amount of missing data for both the patient-administered and the nurse-administered questionnaires, as demonstrated by the numbers of patients included in the paired timepoints. The missing data weakens the analysis. The sponsor's descriptive analysis rather than a quantitative analysis is appropriate.

4. Although these data are of poor quality, they suggest that PT was associated with a higher incidence of clinically evident neuropathy, consistent with the formal CTC reporting in section 9.6.1.

9.6.3 Mortality

Ten patients died within 30 days of the last study dose: 6 on PT and 4 on PC. Three deaths were attributed to treatment-related complications, 3 to intercurrent problems, and 4 to progressive disease. The deaths are summarized in the following table:

Table 20. Mortality within 30 days of study treatment (modified from sponsor table 52, volume 3, page 150).

General Cause of Death	Specific Cause of Death	Patient Number	Treatment Arm
Treatment-related complications	Myocardial infarction		Paclitaxel
	Cardiac arrest		Cyclophosphamide
	Sepsis		Cyclophosphamide
Intercurrent problems	Pulmonary embolus		Paclitaxel
	Perforated gastric ulcer		Paclitaxel
	Myocardial infarction		Cyclophosphamide
Disease progression			Paclitaxel
			Paclitaxel
			Paclitaxel
			Cyclophosphamide

Reviewer Comment:

1. Comments from review of the narratives on patients who died of treatment-related complications:

Patient (PT) died of an MI which, on review of the narrative, may have been related to the surgical procedure as well as to the drug therapy. The patient had a history of hypertension and cardiovascular disease and expired 14 days post-operatively and 6 days after cycle 1.

Patient (PC), listed as cardiac arrest, died while septic; blood cultures grew coagulase-negative staph and Candida.

2. Comments from review of the narratives on patients who died of intercurrent problems:

Patient (PT) died of a perforated gastric ulcer after 4 cycles of therapy. It is possible that this complication was related to steroid premedication for paclitaxel. The patient did not receive any concomitant medications, according to a review of the case report form and of the "Concurrent medication" table in the submitted database.

3. Comments from review of the narratives on patients who died of progressive disease:

Patient (PT) suffered an anterior wall MI in the recovery room after her staging laparotomy. Nineteen days later, she began study therapy. At baseline she had bilateral pleural effusions and required oxygen therapy. Treatment was complicated by CHF which responded to therapy. She subsequently died 11 days after cycle 1 with continued effusions and a

low oxygen saturation. It is difficult to assess whether she died of progressive disease or cardiac complications.

Patient (PC) had her death attributed to progressive disease. However, the narrative indicates that she had febrile neutropenia with blood cultures positive for Staph. aureus. Her death is more likely a treatment-related complication.

4. Overall, the number of deaths on or within 30 days of study drug is small, representing 2.4% of the study population. The combination of cisplatin and paclitaxel does not appear to cause excess mortality compared to the standard-therapy arm.

5. Review of the case report forms showed that patient subsequently died of leukemia. While she does not fit the category of death within 30 days, this event should be mentioned. She was randomized to cisplatin and cyclophosphamide and refused further therapy after 3 cycles. She was then treated with carboplatin and cyclophosphamide, carboplatin/cyclophosphamide/etoposide, and hexamethylmelamine. She did not receive paclitaxel; the leukemia is not related to the drug submitted in this sNDA.

9.7 Sponsor's audit results

Audited data were collected on site for 97 patients accrued at 19 of the 86 participating centers; these data were compared to the data transcribed from the GOG primary documents for these same patients. These results are referred to as the "audited database" and the "transcribed database" respectively.

Reviewer Comment:

These results were used for quality control only. All efficacy analyses were performed by the sponsor using the transcribed database (Response to FRFI 12/22/97, BMS).

9.7.1 Study drug audit results

No differences in treatment delays, drug discontinuations, or drug interruptions were identified. Only 1 patient was found to have a dose reduction recorded differently in the audited and transcribed databases. Patient received cyclophosphamide at 750 mg/m^2 for cycles 1-3, with a dose reduction to 500 mg/m^2 for cycles 4-6. The transcribed database listed the dose reduction at cycle 2 instead of cycle 4. No other discrepancies in dose reduction were found.

9.7.2 Efficacy data audit results

9.7.2.a Survival

Survival status and date of death or last follow up were confirmed for 95 of the 97 patients (98%). For 15 patients, additional follow up was obtained. For 6 patients, additional follow up and a later date of death, after database closure, was obtained. For 2 patients (2%), the actual date of death in the audited database differed from the transcribed date by 1 and 2 days respectively. This information is summarized in the following table.

Table 21. Sponsor table 54, volume 3, pages 165-168

Table 54

Survival Dates: Transcription Versus Audit

Patient #	Arm	Transcribed Database		Audited Database		Comments
		Last Alive	Status	Last Alive	Status	
	TAXOL/Cisp	28JUL94	Alive			Confirmed
	Cyclo/Cisp	09NOV92	Dead			Confirmed
	Cyclo/Cisp	05DEC94	Alive			Confirmed
	Cyclo/Cisp	23JAN95	Alive	9OCT95	Alive	Additional follow-up
	Cyclo/Cisp	06MAR93	Dead			Confirmed
	Cyclo/Cisp	06AUG92	Dead			Confirmed
	TAXOL/Cisp	05MAR93	Dead			Confirmed
	TAXOL/Cisp	04NOV92	Dead			Confirmed
	TAXOL/Cisp	21NOV94	Alive	03MAY95	Alive	Additional follow-up
	TAXOL/Cisp	28SEP94	Alive			Confirmed
	TAXOL/Cisp	09AUG94	Alive			Confirmed
	TAXOL/Cisp	13DEC94	Alive	25JUL95	Alive	Additional follow-up
	Cyclo/Cisp	31OCT94	Alive			Confirmed
	Cyclo/Cisp	01AUG94	Alive	15DEC94	Alive	Additional follow-up
	Cyclo/Cisp	20DEC91	Dead			Confirmed
	TAXOL/Cisp	27FEB91	Dead			Confirmed
	Cyclo/Cisp	14DEC93	Dead	16DEC93	Dead	Change in death date (2 days)
	Cyclo/Cisp	23SEP94	Alive			Confirmed
	Cyclo/Cisp	30MAY92	Dead			Confirmed
	TAXOL/Cisp	29APR92	Dead			Confirmed
	TAXOL/Cisp	15MAY92*	Dead			Confirmed
	Cyclo/Cisp	13JUL91	Dead			Confirmed
	Cyclo/Cisp	14MAR92	Dead			Confirmed
	Cyclo/Cisp	19AUG91	Dead			Confirmed
	Cyclo/Cisp	14MAY91	Dead			Confirmed
	TAXOL/Cisp	14FEB95	Alive	26AUG95	Dead	Additional follow-up and date of death
	Cyclo/Cisp	02MAR95	Alive	22AUG95	Alive	Additional follow-up
	Cyclo/Cisp	02SEP93	Dead			Confirmed

Table continues on next page

Table 54

Survival Dates: Transcription Versus Audit

Patient #	Arm	Transcribed Database		Audited Database		Comments
		Last Alive	Status	Last Alive	Status	
Table 54 continued						
	TAXOL/Cisp	16DEC94	Alive			Confirmed
	Cyclo/Cisp	11FEB94	Dead	12FEB94	Dead	Change in death date (1 day)
	Cyclo/Cisp	15NOV92	Dead			Confirmed
	TAXOL/Cisp	13JUN94	Dead			Confirmed
	TAXOL/Cisp	08MAR93	Dead			Confirmed
	TAXOL/Cisp	12JUN94	Dead			Confirmed
	Cyclo/Cisp	19DEC94	Alive	28SEP95	Alive	Additional follow-up
	Cyclo/Cisp	07DEC93	Dead			Confirmed
	Cyclo/Cisp	15JAN94	Dead			Confirmed
	Cyclo/Cisp	02DEC92	Dead			Confirmed
	Cyclo/Cisp	23SEP94	Dead			Confirmed
	TAXOL/Cisp	21DEC91	Dead			Confirmed
	TAXOL/Cisp	18JAN95	Alive			Confirmed
	Cyclo/Cisp	15OCT92	Dead			Confirmed
	TAXOL/Cisp	06MAY94	Alive			Confirmed
	TAXOL/Cisp	01AUG94	Alive	27SEP94	Dead	Additional follow-up and date of death
	TAXOL/Cisp	11FEB91	Dead			Confirmed
	Cyclo/Cisp	13FEB95	Alive			Confirmed
	TAXOL/Cisp	20JUN94	Alive	31JUL95	Alive	Additional follow-up
	TAXOL/Cisp	14JUL94	Alive	15SEP94	Dead	Additional follow-up and date of death
	Cyclo/Cisp	27MAY94	Dead			Confirmed
	TAXOL/Cisp	16AUG91	Dead			Confirmed
	TAXOL/Cisp	05FEB93	Dead			Confirmed
	Cyclo/Cisp	18JAN93	Dead			Confirmed
	TAXOL/Cisp	16AUG94	Alive	01NOV94	Dead	Additional follow-up and date of death
	TAXOL/Cisp	20SEP90	Dead			Confirmed

Table continues on next page

Table 54

Survival Dates: Transcription Versus Audit

Patient #	Arm	Transcribed Database		Audited Database		Comments
		Last Alive	Status	Last Alive	Status	
Table 54 continued						
	Cyclo/Cisp	30MAR92	Dead			Confirmed
	TAXOL/Cisp	23MAR94	Dead			Confirmed
	Cyclo/Cisp	21MAY92	Dead			Confirmed
	TAXOL/Cisp	29JAN92	Dead			Confirmed
	TAXOL/Cisp	24OCT94	Alive	21APR95	Alive	Additional follow-up
	TAXOL/Cisp	12SEP90	Dead			Confirmed
	TAXOL/Cisp	03NOV94	Alive			Confirmed
	Cyclo/Cisp	01AUG92	Dead			Confirmed
	TAXOL/Cisp	15FEB95	Alive	28SEP95	Dead	Additional follow-up and date of death
	Cyclo/Cisp	01NOV91	Alive	15MAY95	Alive	Additional follow-up
	TAXOL/Cisp	02NOV94	Alive	20OCT95	Alive	Additional follow-up
	Cyclo/Cisp	16NOV94	Alive	11SEP95	Alive	Additional follow-up
	TAXOL/Cisp	17OCT94	Alive			Confirmed
	TAXOL/Cisp	29NOV94	Alive			Confirmed
	Cyclo/Cisp	29NOV94	Alive			Confirmed
	Cyclo/Cisp	12FEB92	Dead			Confirmed
	Cyclo/Cisp	30AUG94	Alive			Confirmed
	Cyclo/Cisp	09NOV91	Dead			Confirmed
	TAXOL/Cisp	01SEP94	Dead			Confirmed
	Cyclo/Cisp	24JUL94	Dead			Confirmed
	TAXOL/Cisp	06SEP94	Alive	10JAN95	Alive	Additional follow-up
	TAXOL/Cisp	15MAY92*	Dead			Confirmed
	TAXOL/Cisp	04OCT90	Dead			Confirmed
	Cyclo/Cisp	29APR91	Dead			Confirmed
	Cyclo/Cisp	21MAY93	Dead			Confirmed
	TAXOL/Cisp	24SEP93	Dead			Confirmed
	TAXOL/Cisp	04SEP92	Dead			Confirmed
	TAXOL/Cisp	30JUL93	Dead			Confirmed

Table continues on next page

Table 54

Survival Dates: Transcription Versus Audit

Patient #	Arm	Transcribed Database		Audited Database		Comments
		Last Alive	Status	Last Alive	Status	
Table 54 continued						
	Cyclo/Cisp	07NOV94	Alive	05JUN95	Alive	Additional follow-up
	Cyclo/Cisp	29JAN93	Dead			Confirmed
	TAXOL/Cisp	26JUL93	Dead			Confirmed
	TAXOL/Cisp	05OCT94	Alive			Confirmed
	Cyclo/Cisp	23DEC90	Dead			Confirmed
	TAXOL/Cisp	11MAR94	Dead			Confirmed
	TAXOL/Cisp	19OCT91	Dead			Confirmed
	TAXOL/Cisp	18JAN95	Alive	27JUL95	Dead	Additional follow-up and date of death
	Cyclo/Cisp	04DEC91	Dead			Confirmed
	Cyclo/Cisp	24AUG94	Alive	25APR95	Alive	Additional follow-up
	TAXOL/Cisp	04NOV94	Alive	10MAR95	Alive	Additional follow-up
	Cyclo/Cisp	18JUL93	Dead			Confirmed
	Cyclo/Cisp	27OCT94	Dead			Confirmed
	Cyclo/Cisp	19DEC92	Dead			Confirmed
	TAXOL/Cisp	29NOV92	Dead			Confirmed

* *15 inputted for day of month: actual day unknown*

Reviewer Comment:

1. Information on 13 PT and 8 PC patients was obtained that changed the date of last follow-up or status. Of the 13 PT patients, 6 had died with 2-9 months of additional follow-up. The other 7 were confirmed as alive with an additional 4-13 months of follow-up. The 8 PC patients were confirmed as alive with follow-up ranging from 3 months to 2 years 7 months. Most of the additional follow-up and change in status occurred after the data cut-off point of March 30, 1995. In 5 patients, information was available prior to the cut-off that was not reported in the transcribed database. One patient received PC; her status remained alive, but with 4 additional months of follow up (The other 4 received PT: one remained alive with 4 additional months of follow-up; the other 3 had died prior to the data cut-off. Overall, the number of patients with a change in status is low.

2. The change in the transcribed dates of death for the two patients treated with PC is insignificant, as they were by only 1 and 2 days.

3. Overall, the transcribed database has acceptable accuracy.

9.7.2.b Response data

There were no changes in pathologic documentation of response. For clinical response, 8 patients had their status changed. Two patients on PT and 1 patient on PC were upgraded from non-response to a partial response because of additional tumor measurements found at the audit. Four patients treated with PT who were called a CR in the transcribed database did not have confirmation that all non-measurable baseline lesions were absent. Finally, 1 patient on the PC arm did not have baseline measurable disease that could be confirmed, and she was reassessed as non-measurable. These results are summarized below.

Table 22. Clinical Response: Transcription versus audit (sponsor table 55, volume 3, page 169).

Patient #	Arm	Transcribed Database	Audited Database	Comments
	PC	SD	PR	Additional measurements found
	PT	CR	PR	Non-measurable baseline lesions not reassessed
	PT	Non-measurable	PR	Additional measurements found
	PC	SD	Non-measurable	No measurements found
	PT	CR	PR	Non-measurable baseline lesions not confirmed absent
	PT	Unevaluable	PR	Additional measurements found
	PT	CR	PR	Non-measurable baseline lesions not confirmed absent
	PT	CR	Unevaluable	Non-measurable baseline lesions not confirmed absent

Reviewer Comment:

1. Four patients were upgraded to a CR on the PT arm in the transcribed database, compared to the audited database. However, response rate, while of interest, was not the primary efficacy endpoint. These discrepancies in response will not affect time to progression or survival analyses.

2. The transcribed database differs from the audited database by 8 patients, or 8% (8 of 97). Because of the difficulty of measuring ovarian cancer in general and because of inter-observer variations in assessment, it is not surprising that the response data showed more discordance between the 2 databases than survival.

9.7.2.c Safety data audit results

Overall, there were few significant changes in the safety profiles after the audit. The

sponsor provides details in volume 3, pages 170-181. The differences will be listed in summary form in this review:

Myelotoxicity:
1 patient on PT was found to have grade III leukopenia
1 patient on PC was found not to have grade III leukopenia
Worst-course grade IV neutropenia decreased from 85 to 83% on PT and increased from 65% to 70% for PC
1 additional patient on PC had grade IV thrombocytopenia
3 patients on PC had grade IV anemia (none recorded in transcribed database)

Infections:
Additional mild/moderate infections found in source records--
PT: infections increased from 6 to 20 episodes in 261 cycles
PC: infections increased from 11 to 20 episodes in 249 cycles

No change in grade III-IV infections
Generally skin infections, URI

Fever:
PT: additional 16 cycles with fever
PC: additional 13 cycles with fever

Febrile neutropenia:
PT: additional 11 cycles with febrile neutropenia
PC: additional 6 cycles with febrile neutropenia

Cardiovascular:
PT: 20 additional patients with a cardiovascular event
PC: 5 additional patients with a cardiovascular event
All grade 1-2; included tachycardia (13--10 PT, 3 PC), hypertension (7--5 PT, 2 PC), bradycardia (7--6 PT, 1 PC)), abnormal ECG (3--2 PT, 1 PC), and hypotension (3--PT)

Neurotoxicity:
PT: 9 additional patients with peripheral neuropathy (grade I or unspecified)
PC: 12 additional patients with peripheral neuropathy (3 with grade II)

Ototoxicity:
PT: increase from 3 to 11 patients (grade II or unspecified)
PC: increase from 5 to 11 patients (less than grade III)
Events included hearing loss, tinnitus

Arthralgia/myalgia:
PT: 10 additional patients with this event for a total of 14
PC: 10 additional patients with this event for a total of 10
Transcribed database had no grade III/IV events; audited database showed 1 patient in each arm with grade III arthralgia/myalgia

Hypersensitivity: PT: 2 additional patients identified
PC: 2 additional patients identified
No additional grade III/IV events found

Gastrointestinal: PT: 3 additional patients with grade III nausea/vomiting
PC: 1 additional patient with grade IV nausea/vomiting
1 additional patient with grade III diarrhea
Changes in symptoms:

Nausea/vomiting:	PT: from 71% to 92%
	PC: from 60% to 87%
Diarrhea:	PT: from 8% to 37%
	PC: from 10% to 23%
Anorexia:	PT: from 12% to 37%
	PC: from 8% to 27%

Liver function: No significant changes

Renal function: PT: 1 patient found with grade III creatinine

Reviewer Comment:

1. The audited database shows differences in toxicity assessments compared to the transcribed database, but most of the changes consisted of mild to moderate side effects and were similar for both arms. The incidence of febrile neutropenia and peripheral neuropathy may be underestimated by the transcribed database in both arms, but the relative incidences are likely to be unchanged.

9.8 Subset Analysis by Age and Race

9.8.1 Pretreatment characteristics

Pretreatment characteristics on both arms were well-balanced by race and age with two exceptions. Patients on the PT arm who were younger than age 65 were more likely to have a better performance status (PS 0 for 43% of patients < 65) than older patients (PS 0 in 24%); younger patients on this arm were also more likely to have serous adenocarcinoma (78%) than older patients (68%).

Reviewer Comment:

1. Performance status rather than age is the significant prognostic factor, and the distribution of PS (in contrast to the occurrence of PS 0 specifically) was well-balanced between the two treatment arms, both overall and by age.

2. Pathologic subtype is not a recognized prognostic factor and was not significant in the sponsor's exploratory analyses. This difference should not have influenced outcome in this subgroup.

9.8.2 Survival analysis

The median survival with PT in patients younger than age 65 was 38.8 months, compared with 24.9 months in older patients. The median survival with PC was comparable in younger patients (23.2 months) and older patients (24.8 months). These data with 95% confidence intervals are presented in the following table:

Table 23. Survival by age (sponsor table 68, volume 3, page 184).

	Cisplatin-paclitaxel		Cisplatin-cyclophosphamide	
	< 65 (n=134)	≥ 65 (n=62)	< 65 (n=155)	≥ 65 (n=59)
Median (months)	38.8	24.9	24.8	23.2
95% CI	35.4-48.0	16.5-34.3	20.6-30.4	16.3-31.5

The median survival with PT was longer in white or other non-black race patients (36.7 and 37.0 months respectively) compared with black patients (23.8 months). Similar findings occurred in the PC arm: median survival for whites, 24.8 months; other non-black, 40.8 months; black, 15.8 months. There were few black or other race patients included in the study, which make it difficult to interpret these findings. The following table summarizes the data.

Table 24. Survival by Race (sponsor table 69, volume 3, page 184)

	Cisplatin-Paclitaxel			Cisplatin-Cyclophosphamide		
	White (n=178)	Black (n=14)	Other (n=4)	White (n=187)	Black (n=19)	Other (n=8)
Median (months)	36.7	23.8	37.0	24.8	15.8	40.8
95% CI	29.6-41.5	21.8-37.5	1.0-37.0	21.5	12.8-28.5	8.7-NR

Reviewer Comment:

The sponsor performed the required analyses by age and race. Survival was comparable between the two age groups for PC. PT improved survival in younger women but not older women; PT produced survivals comparable to PC in this age group. Given the small numbers of patients, it is not possible to evaluate the clinical significance of these findings. It would be of interest to evaluate survival by age in other large trials of paclitaxel-cisplatin combinations in order to determine whether this difference persists.

9.8.3 Safety analysis by subset

9.8.3.a Safety by age

The incidence of leukopenia and neutropenia were similar in both age groups. Younger patients treated with PT more likely to have severe neutropenia than older patients treated with PT; older patients treated with PC were more likely to have severe leukopenia and neutropenia than younger patients on that arm. The incidence of thrombocytopenia, anemia, and infection was more frequent in patients aged 65 or older in either arm.

Among non-hematologic toxicities, hypersensitivity reactions were more common in older women treated with PT. Older patients on both arms had a higher incidence of cardiovascular events, peripheral neuropathy, and diarrhea. Nausea and vomiting were less common in older women treated with either regimen. Ototoxicity was more frequent and more severe in older patients treated with PC compared to the other groups. Patients younger than age 65 treated with PT had more alopecia and arthralgia/myalgia than the other treatment groups. Laboratory abnormalities were generally similar between older and younger patients in either treatment group.

Reviewer Comment:

1. Non-hematologic toxicity, ototoxicity, and peripheral neuropathy were more common in older women, consistent with neurologic changes observed with aging.

2. Some of the differential toxicity might have been due to differences in dose intensity. At the reviewer's request, the sponsor provided a dose-intensity analysis by age, summarized in the following table:

Table 25 (sponsor's Attachment 5, RFRI, 12/22/97). Dose intensity (DI) analyzed by age

	Arm A				Arm B			
	< 65 years		> 65 years		< 65 years		> 65 years	
	Taxol (n=134)	Cisplatin (n=134)	Taxol (n=62)	Cisplatin (n=62)	CTX (n=154)	Cisplatin (n=154)	CTX (n=59)	Cisplatin (n=59)
Median cumulative dose/patient ($mg/m^{2)}$	771	447	737	449	4229	448	4099	448
Median DI (mg/m^2/week)	41	24	41	24	205	21	204	21
Relative DI (% pts): % scheduled dose								
>90	54	73	48	71	33	42	32	41
80-90	43	22	34	18	22	28	29	39
>80	19	5	18	11	45	31	39	22

This analysis demonstrates that dose-intensity was comparable between the two age groups, and that dose-intensity was higher with PT than with PC, regardless of age. The observed differences in toxicity patterns are probably due to age differences or small sample sizes rather than to differences in the amount of drug delivered.

9.8.3.b Safety by race

The small number of patients included in the "other" category precluded an analysis of this group compared to white or black patients for toxicity parameters. Overall, any grade of hematologic toxicity was comparable in black and white patients. Grade III-IV hematologic toxicity was less common in blacks than in whites in both treatment arms. Rates of infection were comparable for blacks and whites.

White patients treated with PT had a higher incidence of hypersensitivity reactions than black patients. Ototoxicity was more common in white patients; severe ototoxicity occurred only in white patients treated with PC. White patients treated with PC had more alopecia than all other groups. Patients treated with PT had more asthenia than patients treated with PC; among the PT patients, the incidence was similar in black and white patients. Among PC patients, asthenia was more common in whites than blacks. White patients treated with PT had the

highest incidence of arthralgia/myalgia. Other toxicities were comparable between the races. Laboratory testing demonstrated more liver function abnormalities among white patients; creatinine elevations were more common in black patients.

Reviewer Comment:

This analysis is required in an NDA. However, the small number of non-white patients and the small number of events within each group does not allow meaningful clinical conclusions to be drawn from this data. Overall, there are no obvious differences in safety profile or outcome related to age or race.

9.9 Sponsor summary and conclusions

The GOG 111 study was the first prospective randomized controlled trial of paclitaxel and cisplatin conducted as initial therapy for advanced ovarian cancer. Paclitaxel produced superior pathologic response rates, improved time to progression, and prolonged survival compared to standard therapy. An increase in survival of 11.3 months with Taxol represents a significant improvement over standard therapy and demonstration of clinical benefit. Administration of paclitaxel did not interfere with cisplatin dosing and in fact led to improved dose-intensity. The sponsor also notes that the median survival on the cisplatin-cyclophosphamide arm is consistent with prior published reports; thus, the observed benefit with PT is not due to unexpectedly poor performance of the control arm.

The safety profile of paclitaxel has been documented in both clinical trials and post-marketing use of this drug. The predominant side effect was neutropenia which did not interfere with the timing of dose administration. A greater incidence of anemia and severe peripheral neuropathy was seen with paclitaxel, possibly due to the increased dose intensity with the study combination. The incidence of severe cardiac events was similar in the two arms. Fever, alopecia, asthenia, arthralgia/myalgia, and allergic reactions were more common with paclitaxel. Severe events were rare and occurred with the same frequency on both arms. The numbers of patients who discontinued therapy because of adverse events and patients who died on study were comparable in the two arms.

This study used a 24 hour infusion of paclitaxel because of the timing of the initiation of this study in the development of paclitaxel. A 3 hour infusion might cause less neutropenia but may cause more neurotoxicity.

The sponsor created its own database for analysis. The discrepancies between the GOG database and the BMS database can be summarized as follows: BMS analyzed all randomized patients, while the GOG excluded 24 eligible patients from analysis; and BMS applied WHO criteria for confirmation of clinical response, resulting in a non-significant difference in clinical response, while the GOG reported a superior clinical response rate for the PT arm. Other efficacy and safety results were consistent between the 2 databases. The audit of the primary records showed some discrepancies, but these discrepancies were primarily minor differences that did not impact on the study conclusions.

A review of the literature (section 11.0), particularly a review of the EORTC Intergroup study, supports the findings of GOG 111. The measured TTP in both arms of the Intergroup

study was concordant with that measured in GOG 111; response rates were also comparable. Thus, there is additional published data corroborating the results of the pivotal trial.

Overall, the combination of cisplatin and paclitaxel was more toxic than cisplatin and cyclophosphamide, but resulted in a significant survival advantage for PT. Continued research to define the optimal use of paclitaxel is ongoing. Paclitaxel at a dose of 135 mg/m^2 over 24 hours in conjunction with cisplatin 75 mg/m^2 should be approved for the primary treatment of patients with advanced ovarian carcinoma.

9.10 Reviewer summary and conclusions

GOG 111 was a prospective randomized controlled trial of paclitaxel and cisplatin compared to cyclophosphamide and cisplatin as first line therapy for advanced ovarian cancer. The populations were well-balanced. Progression-free survival was the primary endpoint; survival was the secondary endpoint. The PT arm resulted in a statistically significant prolongation of PFS by 3.6 months and a significant prolongation of OS by 11.3 months. These differences are clinically significant as well and are of striking clinical benefit. No significant differences in clinical response were seen. Overall pathologic response was significantly better with PT, although there was no significant difference in the rate of complete pathologic CR with PT. These results are summarized below:

Table 26. Overall summary of sponsor's results for GOG 111

Efficacy Parameter	Cisplatin-paclitaxel	Cisplatin-cyclophosphamide	p-value
Clinical complete response	40/113 (35%)	32/127 (25%)	0.092
Clinical partial response	28/113 (25%)	32/127 (25%)	
Overall clinical response	68/113 (60%)	64/127 (50%)	0.153
Complete pathologic response	42/196 (21%)	35/214 (16%)	0.196
Microscopic residual disease	25/196 (13%)	8/214 (4%)	
Overall pathologic response rate	67/196 (34%)	43/214 (20%)	0.001
Median progression free survival	16.6 months	13.0 months	0.0008
Median survival	35.5 months	24.2 months	0.0002

It is paradoxical that PT improved PFS and OS without changing the rate of response. However, there was a trend to improved response with PT upon review of the actual response

rates. In addition, it is difficult to fully assess response in ovarian cancer patients because of the intra-abdominal growth pattern of this tumor and concomittant difficulties in accurate serial imaging of tumor masses. Finally, the number of pathologic complete responses was low, decreasing the chance of detecting a significant difference in outcome.

The toxicity of the PT regimen was greater, due either to the side effects of the drugs themselves or to the improved dose-intensity achieved with this regimen compared to PC. The adverse events were consistent with those described in the label for paclitaxel. Despite the increased toxicity, treatment-related mortality on the two arms was comparable.

Overall, this study demonstrates the efficacy of cisplatin and paclitaxel as first-line therapy of ovarian cancer. The striking clinical benefits observed in this study outweigh the increased but reversible toxicity associated with PT, in the opinion of the reviewer.

10.0 Comparison of the Study Report and Published Reports of GOG 111

The GOG 111 study results were presented by McGuire at the American Society of Clinical Oncology meetings in 1993 and 1995 and were published in abstract form in the Proceedings of these meetings (Proc. ASCO 12: page 255, abstract 808, 1993; Proc. ASCO 14: page 275, abstract 771, 1995). The results were published in complete form in a peer-reviewed journal in 1996 (McGuire WP, Hoskins WJ, Brady MF, et al. New Eng. J. Med. 334: 1-6, 1996). The differences and additions between the study report from the sponsor and the published report will be outlined.

Methods:

In the published article, the authors listed additional off-study criteria:

- Cardiac events, with the exception of sinus bradycardia, were reported to the study chairman and were considered a cause for discontinuing therapy
- Severe allergic reaction to paclitaxel

These criteria were not explicitly mentioned in the protocol document.

Reviewer Comment:

Review of the material submitted in the NDA indicates that only 1 patient was removed from study for a cardiac event. Although not explicitly mentioned in the protocol, it is reasonable and medically advisable to remove patients from study for severe allergic reactions to paclitaxel.

Patient evaluability:

As the sponsor noted in the study report, McGuire and colleagues analyzed 386 patients who fulfilled all eligibility criteria. Twenty-four patients were excluded.

Reviewer Comment:

The sponsor states in the NDA that 370 patients were fully eligible. The protocol violations are listed in Table 5. The article by McGuire and colleagues gives the following reasons for ineligibility:

3	Inappropriate stage	(2 per sponsor)
13	Wrong primary	(16 per sponsor)
3	Wrong cell type	(2 per sponsor)
4	History of cancer	(2 per sponsor)
1	Wrong type of surgery	(0 per sponsor)

Despite the differences in assessment of eligibility, the appropriate analysis is the intent-to-treat analysis, which includes all randomized patients. The intent-to-treat analysis was performed by the sponsor but not by the GOG authors.

Dosing:

Eighty-seven percent (160/184)of women randomized to PT completed the planned course of therapy compared to 78% (158/202) of women on PC. Nine women (5%) on PT and 23 (11%) on PC did not complete the treatment program because of disease progression or death. Fifteen women (8%) on PT and 21 on PC (10%) did not complete study therapy because of toxicity or refusal.

The authors reported that there was no difference in the delivered dose of cisplatin.

Reviewer Comment:

1. These values are comparable to those reported by the sponsor.

2. The sponsor also demonstrated that both arms received comparable amounts of cisplatin. However, the sponsor demonstrated a difference in dose-intensity in favor of the PT arm, due primarily to the ability to treat on time.

Toxicity:

Toxicity assessments were collapsed into a smaller number of categories. More toxicity was observed with PT.

Reviewer Comment:

The sponsor provides greater detail about the toxicity profiles in each arm. However, neither the GOG report nor the sponsor's study report noted any new toxicities not previously described for paclitaxel.

Results:

Clinical Response:

Two hundred sixteen women had measurable disease and were evaluable for response. The published response rates were 60% for the PC arm and 73% for the PT arm; the complete response rates were 31% and 51% respectively (p=0.01).

Pathologic response:

Of the 386 women, 24 in each treatment group or a total of 48 refused a second-look laparotomy or had medical contraindications to the procedure. The incidence of negative second-look surgery (pathologic CR) was 20% for PC and 26% for PT, a non-significant difference.

Progression-free survival:

At a median duration of follow up of 37 months, the median progression-free survival for PC was 13 months (95% CI: 11, 15) and for PT was 18 months (95% CI: 16, 21). This difference was significant with a relative risk of 0.7 (95% CI: 0.5-0.8; $p<0.001$).

Overall survival:

The median survival with PC was 24 months (95% CI: 21-30) compared with 38 months for PT (95% CI: 32-44). These figures corresponded to a relative risk of 0.6 in favor of the paclitaxel arm (95% CI, 0.5-0.8; $p<0.001$). McGuire and colleagues stated that additional analyses of survival including the 24 ineligible patients did not significantly alter the results. Analyses of survival in women with and without measurable disease in each group and by stage consistently showed an advantage for the paclitaxel arm (data not shown).

Reviewer Comment:

1. The differences in the efficacy parameters reported by the GOG and the sponsor are listed in the following table:

Table 27. Comparison of study report and published results of GOG 111

Efficacy Parameter	BMS results of GOG 111			Published results of GOG 111		
	Cisplatin-paclitaxel	Cisplatin-CTX	p-value	Cisplatin-paclitaxel	Cisplatin-CTX	p-value
Clinical complete response	40/113 (35%)	32/127 (25%)	0.092	51/100 (51%)	36/116 (31%)	0.01
Clinical partial response	28/113 (25%)	32/127 (25%)		22/100 (22%)	34/116 (29%)	
Overall clinical response	68/113 (60%)	64/127 (50%)	0.153	73/100 (73%)	70/116 (60%)	0.01
Complete pathologic response	42/196 (21%)	35/214 (16%)	0.196	42/ 184 (26%)	35/202 (20%)	NS
Microscopic residual disease	25/196 (13%)	8/214 (4%)		23/184 (14%)	7/202 (4%)	
Overall pathologic response rate	67/196 (34%)	43/214 (20%)	0.001	65/184 (35%)	42/202 (21%)	
Median progression free survival	16.6 months	13.0 months	0.0008	18 months	13 months	<0.001
Median survival	35.5 months	24.2 months	0.0002	38 months	24 months	<0.001

The primary difference between the two sets of data calculations lies in the response assessment. The GOG authors found a statistically significant improvement in clinical complete response and clinical overall response, while the sponsor did not. The sponsor states that the difference in significance level is due to two factors: BMS included all randomized patients, while the GOG included only eligible patients; and BMS required confirmation of response, as mandated by WHO response criteria. The GOG in contrast did not always require confirmation

of response. Overall, the sponsor has applied more stringent criteria in evaluating response.

The results for PFS and OS are comparable between the two groups. The sponsor has reported somewhat shorter durations for these parameters, attributable to the intent-to-treat analysis.

11.0 Literature Review

Paclitaxel was initially approved for use after failure of first-line or subsequent chemotherapy for the treatment of metastatic carcinoma of the ovary. It is also indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy; patients should have received an anthracycline unless clinically contraindicated. Recently, a supplemental NDA was approvable for the use of paclitaxel in the treatment of AIDS-related Kaposi's sarcoma. In addition to these FDA-approved indications, paclitaxel has been used and extensively reported in the literature in other malignant diseases and as part of multidrug regimens. This background section will be limited to a discussion of published literature of paclitaxel as first-line therapy for advanced (stage IIB-IV) ovarian cancer. The primary source for this review was a MedLine search performed by the reviewer; additional documentation from the randomized trials was provided by the sponsor as noted below. The published results of GOG 111 (McGuire WP, Hoskins WJ, Brady MF, et al. NEJM 334: 1-6, 1996; McGuire WP, Hoskins WJ, Brady MF, et al. Semin.Oncol. 24 [1] Suppl 2: S2-13--S2-16, 1997) were discussed in Section 10.0. Two papers based on the results of GOG 111 calculated the cost-effectiveness of therapy with cyclophosphamide-cisplatin in comparison to paclitaxel-cisplatin (Elit LM, Gafni A, and Levine MN. J. Clin. Oncol. 15: 632-9, 1997; McGuire W, Neugut AI, Arikian S, et al. J. Clin. Oncol. 15: 640-45, 1997). Because the FDA does not consider cost in the approval process, these papers will not be reviewed. Finally, only two drug combinations (paclitaxel plus a platinum compound) with standard dosing are reviewed; the literature on paclitaxel as a single agent, as part of a 3- or more drug combination, or as part of a high-dose transplant regimen is not considered. This review includes some but not all trials cited by the sponsor in Tables 1 and 2; it includes several trials not referenced by the sponsor. The response rates cited in this section do not always agree exactly with those listed in Table 2.

11.1 Phase I trials of paclitaxel in combination with cisplatin

Several Phase I trials of paclitaxel in combination with cisplatin have been performed. The **National Cancer Institute of Canada (NCI-C)** conducted a Phase I study of biweekly paclitaxel and cisplatin as first-line therapy for high-risk ovarian cancer patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1 and residual macroscopic disease after laparotomy (Gelmon K, Semin.Oncol. 21[5] suppl 8: 29-33, 1994; Swenerton K, Hoskins P, Stuart G, et al. Ann.Oncol. 7[10]: 1077-9, 1996). The starting dose of paclitaxel was 90 mg/m^2 given over 3 hours, followed by cisplatin at a fixed dose of 60 mg/m^2; paclitaxel was escalated by 10 mg/m^2 in each subsequent dose level. Treatment was repeated every 2 weeks for

a total of 8 cycles. A standard modified Fibonacci Phase I design was used. Twenty-eight eligible patients were entered on study; 16 had measurable disease. The maximum tolerated dose of paclitaxel was 120 mg/m^2, and the observed DLT consisted of granulocytopenia. Of the patients with measurable disease, 7/16 achieved a CR and 3/16 a PR for a total response rate of 63%. The median progression-free survival for the entire group was 12 months. The recommended phase II dose of paclitaxel was 110 mg/m^2 over 3 hours in combination with cisplatin 60 mg/m^2 every 2 weeks.

Investigators at the **Cleveland Clinic** treated 35 women with paclitaxel at 175 mg/m^2 infused over 3 hours followed by cisplatin at 75 mg/m^2 (Connelly E, Markman M, Webster K, et al. Proc. ASCO 14: abstract 777, page 277, 1995). Thirty-one percent of the administered cycles required a dose-reduction in paclitaxel to 135 mg/m^2. Colony stimulating factors were not used routinely. Fourteen of 35 women (40%) developed neuropathy, predominantly grade 1. Sixty-six percent experienced neutropenia. The other observed toxicities included elevated creatinine (2/35 or 6%), allergic reaction (1/35 or 3%), emesis (12/35 or 35%) and total alopecia in all patients. No episodes of febrile neutropenia were observed. No formal response assessments were made. However, 32 of the 35 patients had elevated CA-125 values at baseline. All 32 demonstrated a greater than 50% reduction in the CA-125 level with therapy; 21 patients had a greater than 90% decrease in CA-125. The investigators concluded that this regimen was tolerable, but that the 3 hour paclitaxel infusion produced more neuropathy than the 24 hour infusion.

Mendiola and colleagues presented the results of a Phase I trial of paclitaxel given over 1 hour in combination with cisplatin 80 mg/m^2 given every 21 days in women with untreated stage IIB-IV ovarian cancer (Mendiola C, del Campo JM, Massuti B, et al. Proc. ASCO 16: 359a, abstract 1276, 1997; Cervantes A, Mendiola C, del Campo JM, et al. Semin. Oncol. 24 [5] Suppl 15: S15-40--S15-43, 1997). The starting dose of paclitaxel was 175 mg/m^2; subsequent dose levels for intrapatient dose escalation were 200 and 225 mg/m^2. Sixty-eight women were enrolled in the study. Six patients could not have the dose escalated, 6 women had the dose escalated to 200 mg/m^2, and 45 patients reached the maximum dose of 225 mg/m^2. Of these 45 patients, 11 women received 225 mg/m^2 but subsequently required a dose reduction. Thirty-eight percent of the patients had grade 3-4 neutropenia, but only 1 patient had febrile neutropenia. No grade 3 or 4 thrombocytopenia was observed. Peripheral neuropathy occurred as grade 1 toxicity in 40% of patients, as grade 2 in 43%, and as grade 3 in 9%; this toxicity was dose-limiting. Sixty-seven patients were evaluable for response: 35 had a clinical CR [cCR] (51.4%) and 20 had a PR (29.4%) for a total response rate of 80.8%. Thirty-two of the 35 patients with a cCR underwent a second-look laparotomy, and 20 were confirmed to have a pathologic complete response [pPR] (29.4% of the total population). No time to progression or survival data are available.

These Phase I studies used paclitaxel as a 1-hour or 3-hour infusion rather than a 24 hour infusion, as in the pivotal trial. Cisplatin doses ranged from 60 to 80 mg/m^2, and paclitaxel doses ranged from 110 to 225 mg/m^2. While neutropenia was observed, peripheral neuropathy was the DLT in 2 of these 3 studies. These trials demonstrate the feasibility of administering paclitaxel and cisplatin in these schedules, but do not provide any information about its efficacy relative to the cisplatin-cyclophosphamide combination.