The sponsor added the following category to the pathologic assessment of response:

Unevaluable:	Patients who did not have ovarian cancer

The sponsor added the following categories for patients who did not undergo second-look laparotomy:

Wrong primary:	Patients who were randomized but determined on GOG central review to have the wrong primary tumor or cell type
Death/toxicity:	Patients who died prior to surgery or were removed from study due to toxicity (whether drug-related or not)
Contraindicated:	Patients with a medical contraindication to surgery
Refused:	Patients who met the criteria for second-look surgery but refused
Not reported:	Patients with no explanation why second-look surgery was not performed
Persistent disease:	Clinical evidence of persistent or progressive disease or persistent elevation of CA-125 after completion of study therapy

Again, patients were assigned to one category in a hierarchical fashion.

Although not included in the original protocol, the sponsor calculated the following parameters:

- Duration of clinical response (duration of CR + PR and duration of CR)

Method 1. From the day of first study drug administration until the date clinical progression was noted. Duration of CR was calculated from the day of the CR. Patients who did not progress were censored at their last date of follow up. Patients who died of disease and for whom a progression date was not available were considered to have progressed on the date of their death.

Method 2. Patients were censored at the time of any therapy which was initiated prior to clinical evidence of recurrence or progression. Examples of this therapy included intensification or consolidation therapy after second-look surgery, second-line therapy based on elevated CA-125 alone, or evidence of persistent but not progressive disease at second-look. Patients who did not relapse prior to this analysis were censored at the date of last follow-up.

- Duration of pathological response

This parameter was calculated for patients with a pathologic CR (pCR) and microscopic residual disease (micro) as well as for patients with pCR. The same two methods were used.

- Time to clinical response

This parameter was calculated for CR and PR as the length of time from the first day of treatment until documentation of the best clinical response.

Other prospectively defined endpoints included survival, defined as the length of life from study entry to death; for living patients, from study entry to date of last contact. Progression-free interval was defined in the protocol as date from study entry to the date of reappearance or increasing parameters of disease or to date of last contact. The sponsor calculated this parameter with two methods:

Method 1. Day of randomization until the date clinical evidence of recurrent or progressive disease was first reported. Patients who did not progress were censored at the last date of follow up. Patients who died of disease without a date of progression were considered to have progressed on the day of death.

Method 2. Patients were censored at the time of any therapy following removal from the study but prior to clinical evidence of recurrence or progression.

Finally, the sponsor generated a new parameter, time to worsening of performance status. This endpoint was calculated from the day of randomization until the date of the first worsening in performance status or death on study. All treated patients with assessment at baseline and at "the same time on study" were included.

The neurologic assessments were grouped in the following time categories:

Baseline: Forms completed prior to the first course of therapy
On study: Forms completed prior to course 4, 5, or 6 or at off-study. If more than 1 form per patient was available, the worst evaluation was used
Three months: Forms completed after second-look surgery or 3 months off-treatment
Six months: Forms completed 6 months off-treatment

The analysis of these forms is described in the Efficacy section.

The minimum length of trial to evaluate response was defined as receiving 1 course of therapy and living 3 weeks for a repeat measurement to be performed. The minimum length of trial to evaluate toxicity was defined as receiving 1 course of therapy and receiving any follow-up information for observation of toxicity.

Reviewer Comment:

1. The response criteria are more liberal than the standard oncology criteria: responses need to be maintained for 3 weeks, not 4; 50% increase in disease rather than 25% constitutes progression. However, a one-week difference between duration of CR or PR is unlikely to make a difference, particularly since clinical CRs were required to have pathologic confirmation. Because ovarian cancer is frequently difficult to measure or evaluate on scans, the requirement for 50% increase in disease ensured that patients were not deprived of potentially beneficial therapy.

2. The differences in the GOG and the sponsor's assessment of response will be discussed in the Efficacy section (9.5).

3. Pathologic complete response appears to be the best predictor for long-term disease-free survival. Patients with microscopic residual disease (as opposed to bulk residual disease) have a high rate of relapse. The value of this assessment as an endpoint is unclear. However,

clinically, it permits selection of patients for additional therapy.

4. It is reasonable to categorize patients who did not have ovarian cancer or who did not have reassessment of tumor lesions as inevaluable, but it is important to recognize that the "gold standard" analysis is intent-to-treat. Also, the 5 patients with measurable disease who did not undergo repeat CT evaluation did undergo second-look laparotomy; these patients can still be considered evaluable for pathologic response, time to progression, and survival.

5. Patients with "early death or toxicity", whether with measurable or non-measurable disease, should still be considered in the calculation of progressive disease, if there is evidence of progression at the time they went off study. The sponsor's hierarchy does not include these patients in a PD assessment.

However, an Access query indicates that only two patients developed progressive disease prior to cycle 3. Both had progression shortly after cycle 3 and were taken off study.

6. All patients entered on the trial should be evaluable for toxicity, not only patients who received 1 course of therapy and had follow-up.

7. The sponsor added multiple response parameters calculated by several methods in a post-hoc fashion. This analysis may be biased. The sponsor also classified patients who died of disease without a date of progression as progressing on the date of their death. This method will likely significantly overestimate time to progression in these patients.

8. Two methods were used to calculate response duration and time to progression. The first method uses the conventional method (from the date of first study drug administration until documentation of progressive disease). The second censors patients at the time a new therapy is instituted, prior to objective documentation of progression. This method is not conventionally used. However, because some patients were given consolidation therapy or treated on the basis of rising CA-125 values, this method may decrease the likelihood that a benefit that resulted from a new therapy is mistakenly attributed to the study therapy.

9. The sponsor indicated that patients with a baseline PS assessment and a repeat assessment at "the same time on study" were included. I believe there is a misprint--any patient with 2 PS evaluations was considered, not a population with a baseline PS and a second PS all on the same visit date.

10. Neurologic assessments from cycles 4-6 and off-study were grouped together. Because patients go off-study for different reasons (toxicity versus response), a better analysis might have grouped assessments from cycles 4-5 and separated forms from cycle 6 and off-study timepoints.

11. Although the GOG protocol states that progressive disease was defined in part by the appearance of any new lesion "within 8 weeks of entry into the study", this line is a missprint. A new lesion at any time constituted progressive disease, as confirmed by the sponsor.

9.4.2 Statistical considerations

In the initial protocol, the following calculations were made. Approximately half the patients were anticipated to have measurable disease. Based on data from prior GOG studies, the complete response rate for PC was estimated to be 30%. An improvement of 20% in the complete response rate was deemed to be clinically significant. In order to demonstrate this

benefit, a sample size of 84 evaluable patients with measurable disease per arm was calculated, which would necessitate a total of 336 patients in the trial. The sample size should provide 80% power to detect a 20% difference in the complete response rate with the probability of a type I error at 0.05. It was then estimated that the median survival for PC was 18.5 months for patients with non-measurable disease and 22.5 months for patients with measurable disease. In order to detect a 50% decrease in death rates, follow up for 1 year after study closure was necessary; the sample size allowed an 87% chance of detecting an improvement of this magnitude.

As noted in section 9.2, the statistical section was modified. 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 TOP 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 would be performed when there were 50 failures in the PC group, expected after 2/3 of the sample size is accrued. If the progression-free interval was greater among PC patients, the study would be stopped early, with a loss in power of 3%. If the progression-free interval was greater among PT patients with a p=0.005, the study would be stopped early with an increase in type I error of 0.5%.

Analysis of pretreatment characteristics was performed using Fisher's Exact Test. For ordered or numeric measures, the Kruskal-Wallis test was used. Fisher's Exact Test was also used to compare dose-intensity calculations, the number of patients who received subsequent therapy, and the clinical response rates in the two treatment arms. The Kruskal-Wallis test was used to evaluate the treatment difference in number of subsequent drug regimens and the number of days between courses. The pathologic response rates were compared using the Cochran-Mantel-Haenszel test adjusted for the randomized strata.

An analysis of treatment effect on response rate was performed after adjustment for baseline prognostic factors in a two-stage logistic regression model. The following factors were considered in the initial stage:

Residual tumor diameter	($\leq$ 5 cm versus > 5 cm)
Stage	(III versus IV)
Age	($\leq$ median versus > median)
Site accrual	(0-9 patients versus 10+ patients)
Histologic grade	(1-2 versus 3)
Performance status	(0-1 versus 2)
Liver function tests	(None abnormal versus any abnormal)

In order to remain in the model, a significance level of 0.10 was required in the forward stepwise option. The second stage of the model evaluated the response rate in a logistic

regression model including the factors selected in the first stage, the treatment arm, and the stratum (measurable or non-measurable). For clinical response, stratum was omitted as this parameter was only evaluated in patients with measurable disease. P-values for each potential prognostic factor were calculated for the unadjusted and adjusted analyses. The final model included p values and the odds ratio with 95% confidence intervals.

Time to clinical response was described with summary statistics; the Kruskal-Wallis test was used to assess treatment differences.

Survival was calculated with Method 1 and Method 2 described in section 9.4.1 above and was plotted with Kaplan-Meier curves. The method of Brookmeyer and Crowley was used to calculate the 95% confidence intervals. The logrank test was used to compare treatments stratified by measurable and non-measurable disease.

Adjusted analyses of time to progression and survival were performed using the same forward stepwise Cox regression described for response rate with the same baseline prognostic factors. The forward stepwise model was used to select significant factors; in the final model, these factors were included with treatment arm and stratum. Each potential prognostic factor was tested for its effect on the time to event (adjusted and unadjusted) and the median time to event.

Worsening of performance status, calculated by days from baseline and number of cycles of chemotherapy, was evaluated with Kaplan-Meier curves. Patients who had a recorded baseline PS and also a second PS recorded on study or who died on study were included in this analysis.

Neurologic parameters were assessed with descriptive statistics.

Safety analyses were performed on patients who received at least one dose of study medication. Results were tabulated by frequency by treatment arm on cycle 1 and by worst on-study grade. Incidence rates of major toxicities were calculated and also broken down by grade. Differences in the incidence of events and in the incidence of severe events between treatment arms were evaluated with Fisher's Exact Test.

Reviewer Comment:

1. The analysis stratified by measurability, as specified in the initial protocol document, is considered as the primary analysis by the FDA reviewers. We also rely on an unstratified analysis for TTP and survival. The results of the logistic regression analyses will be reviewed, but are considered as supportive analyses.

2. Ninety-five percent of patients in this trial fit the criteria for inclusion in analysis of time to worsening of PS. However, this analysis will be difficult to interpret, since the timepoints of assessment will differ from patient to patient. Some patients may have had reassessment of PS when they completed all study therapy with a clinical response; others may have been reassessed at the time of progressive disease or removal from study for toxicity, which will bias the assessment.

3. The prognostic factors included in the model are all recognized factors for ovarian cancer except for baseline liver function tests. The reviewer performed a comprehensive MedLine search and reviewed major oncology and gynecologic oncology textbooks and did not find this feature mentioned. In addition, the liver function abnormalities noted in this study were primarily CTC grade 1 and of questionable clinical relevance. The FDA statistician, Massa

Takeuchi, Ph.D. re-ran the program without this factor; results are noted in the Efficacy sections. However, the unadjusted analysis is considered the primary analysis.

9.5 Efficacy analysis

9.5.1 Response

9.5.1.a Clinical response

Two hundred forty patients had measurable disease, 113 randomized to PT and 127 randomized to PC. A total of 21 patients were inevaluable; the reasons are listed in section 9.3.2.a. The sponsor reported response data for all patients, both evaluable and inevaluable, with measurable disease. The response data may be summarized as follows:

Table 7. Complete and partial response rates for GOG 111

Response	Cisplatin-Taxol	Cisplatin-Cyclophosphamide	P-value
Complete response	40/113 (35%)	32/127 (25%)	0.092
Partial response	28/113 (25%)	32/127 (25%)	
Overall response	68/113 (60%)	64/127 (50%)	0.153

If one considers only the 219 evaluable patients (102 on PT and 117 on PC), the complete response rates were 39% and 27% respectively; overall response rates were 67% and 55%. Neither of these differences was statistically significant.

Reviewer Comment:

1. Clinical response rates as reported by the sponsor were not significantly different between the two treatment arms, whether all patients with measurable disease were used or only evaluable measurable patients.

2. The reviewer performed a series of MS Access queries to verify response. All 240 patients with measurable disease were included. The definitions of complete and partial response in the protocol were used, as well as the requirement for a confirmatory measurement. The reviewer accepted evidence of response from a second-look laparotomy as well as subsequent radiographic studies or physical examination as confirmation of response.

Eighty-seven patients had a verified non-surgical response based on the Access algorithm developed by Grant Williams, M.D., Team Leader: 40 on PC and 47 on PT. An additional 21 patients had a negative second-look laparotomy to confirm response: 9 on PC and 12 on PT. The total number of responders based on this preliminary assessment is therefore 49 on PC and 59 on PT, for a total of 108 of 240. On comparing the lists of BMS responders and FDA responders, 4 patients on PC and one patient on PT were noted to have responses documented in the case report forms, although they did not appear on the

list generated by the algorithm. The number of responders by arm is therefore 53 on PC and 60 on PT.

The following patients had discordant results between the FDA and the BMS evaluation:

Table 8. FDA Responders not listed as BMS responders

Patient ID	Treatment Arm	Tumor Evaluation Description	FDA
	PC	Incomplete follow-up; not all lesions assessed	No response
	PC	PR documented at C3 and C5 (excluded because of wrong primary)	PR
	PT	cCR confirmed by CT and by 2nd look lap (excluded because of wrong primary)	CR
	PT	PR confirmed by 4 measurements (excluded because of wrong primary)	PR
	PT	Lesion measured at baseline by CT (area 20 cm^2); PR by PE at C2, C3, C6 and PR documented by 2nd-look lap	PR

The sponsor indicated in the study report that an intent-to-treat analysis of all patients entered on study with measurable disease (240 patients) was performed. Thus, data from patients with the wrong primary should have been analyzed for response. The patient with incomplete follow-up was removed from the list of FDA responders, leaving 52 responders on PC and 60 on PT, or 112 of 240.

The patients with discordant assessments between BMS and the FDA were then reviewed. These results are summarized below.

Table 9. BMS responders not listed as FDA responders: PC arm

Pt No	Tumor Evaluation Description	FDA Judgement
	3 lesions at baseline; 1 measured only at C1,3	Incomplete F/U No response
	1 measurable lesion: area of 12 at C0 to area of 9 at C5	No response
	CR confirmed by PE on review of CRF	Agree with CR
	3 baseline lesions: 1 measured only at baseline, 1 with a single measurement indicating a decrease in size	Incomplete F/U No response
	CR confirmed by PE on review of CRF	Agree with CR
	No second confirmation of CR	No response
	CR confirmed by 2 different modalities (sono, then CT)	Agree with CR
	4 measurable lesions at baseline: 1 measured only at baseline, 1 with 1 measurement after baseline at C4 but not at C6 2 evaluable lesions at baseline: 1 not evaluated again, 1 evaluated at C3 but not confirmed with 2nd measure	Incomplete F/U No response
	No second confirmation of PR	No response
	No second confirmation of CR	No response
	No second confirmation of PR	No response
	No second radiographic confirmation of CR, but pathologic confirmation of PR at second-look laparotomy	Agree with PR
	1 measurable lesion at baseline with no change at C2; no other measurements	No response

Based on this review, 4 additional responders were added to the PC arm, for a total of 56.

Table 10. BMS responders not listed as FDA responders: PT arm

Patient ID	Tumor Evaluation Description	FDA Judgement
	2 meas.lesions at baseline; no PR at C4; PR at end-of-treatment without confirmation No confirmation of resolution of effusion	No response
	1 meas. lesion at baseline: no change at C2; absent C4; no confirmation of response	No response
	Cul-de-sac lesion measurable by PE at baseline; no other measurements recorded. At 2nd-look lap, 0.2 cm disease resected.	Agree with PR
	Meas. lesion at baseline decreased by PE; at C5, new cul-de-sac lesion noted (0.5 cm); decreased at C6 (0.3 cm) and gone at end-of-treatment. At second-look lap, no residual disease in these areas	Agree with PR
	2 meas. lesions and 1 eval. at baseline: incomplete follow-up on the 2 meas. lesions (1 meas. at C3; the other at end-of-treatment); no f/u of eval	Incomplete follow-up: no response
	Baseline meas. lesion absent by PE at C4; no confirmatory exams. 2nd-look lap neg in pelvis	Agree with CR
	No confirmatory measurement of PR (C1,3 only)	No response
	Ratio of area at C3 to baseline=.54; ratio at C5 to baseline = .21	Agree with PR
	PR at C5, but no confirmation; evaluable lesion not evaluated after baseline	No response
	Subhepatic lesion meas. only at baseline; residual .3 cm disease in "abdomen" at 2nd look lap	Incomplete follow-up; no response
	No CT confirmation of CR, but 2nd-look lap negative in that region	Agree with CR
	Baseline lesion not re-measured, but 2nd-look lap showed PR in that area. Bilat pleural effusions increased at C2 and not re-checked	No response; ? progression based on non-evaluable sites

Based on this review, an additional 4 responders were added to the PT arm for a total of 64 (Pt based on subsequent information from the sponsor was already counted on the basis of second-look laparotomy results).

The sponsor was sent the following questions (facsimile 2/6/98); they responded with a submission dated 2/25/98 (not sent by facsmile). The questions are in italics; the sponsor's answers are listed below each question:

(1) If all 240 patients with measurable disease were included in the analysis, why were patients not considered to be responders?

These 3 patients had the wrong primary tumor: although included in the denominator, the sponsor did not consider them to be responders.

Reviewer Comment:

Pt Listed in the CRF as Stage IVA suboptimally resected papillary serous cystadenoma of the ovary; listed as eligible by the GOG reviewer

Pt Primary peritoneal carcinoma

Pt Deemed "wrong primary" because primary ovarian tissue was not biopsied. Operative report indicates that a "massive" unresectable tumor was found which involved all pelvic structures in an indistinguishable mass, with a large omental cake and disease above the liver and ascites. The ascitic fluid and an omental biopsy showed papillary adenocarcinoma with psammoma bodies.

Because all three patients have ovarian cancer as encountered in clinical practice, the reviewer feels it is appropriate to include them in both the numerator and denominator for response.

(2) Patient had a PR confirmed on serial physical examinations. Why does BMS not consider this patient to be a responder?

The sponsor indicated that the patient had the wrong primary, and was not considered as a responder.

Reviewer Comment:

This patients was called the wrong primary by the GOG reviewer because the outside surface of the ovaries was involved, but not the cortex.

The operative note describes tumor throughout the abdomen, involving the peritoneal surface, cul-de-sac, omentum, surface of the colon and appendix, liver, bladder, and ovaries. At the local hospital, 95% of the tumor in the ovaries was described as located on the surface; 5% consisted of microscopic cortical involvement.

Again, this patient clinically had ovarian cancer; the reviewer includes her in both the numerator and denominator for response.

(3) Please review Tables 9 and 10. Can you clarify why BMS considers these patients as responders?

For 9 patients in these tables, there was no disagreement between BMS and FDA.

For 3 patients, BMS agreed with the FDA's assessment of no response:

PC arm:

For 13 patients, BMS feels the clinical evidence supports the assessment of response. Additional narratives were included for review.

Reviewer Comment:

PC arm:

002-018: Lesion 1, measured only at C1 and C3, in question. Baseline size = 4.5 x 7 cm; C3 size = 3.5 x 3.5. No further CT measurements. Sponsor submitted follow-up note from the investigator, who stated that reevaluation showed C3 measurements of 9.0 x 7.0; C5 8.0 x 6.0; end-of-study 7.0 x 5.5. The investigator called the patient a PR. The reviewer reiterates that the inconsistent measurements call into question whether this lesion progressed or not.

Additional physican examinations document the disappearance of the pelvic mass. The reviewer agrees with BMS' assessment of a PR.

One baseline lesion was not measured again; BMS provided 4 additional physical examinations that document disappearance of this lesion. The Medical Treatment Reporting Forms indicate that 2 CT scans showed diminution of the liver lesions. The third area, enlarged lymph node, was not followed by the GOG as an indicator lesion. No CT scans mention this area. BMS calls this patient a PR; the reviewer agrees.

BMS provides a note from the investigator indicating that a CT scan from 4/3/92 (after treatment ended) shows continued improvement in the two baseline lesions in question, providing the confirmatory evaluation. The splenic and other lymph nodes mentioned as baseline were not followed by the GOG; no scans mention increase in the size of these areas. BMS calls this patient a PR; the reviewer agrees.

BMS indicates that on a follow-up form, a CT was performed and showed stable disease; no measurements given. BMS calls this patient a PR; the reviewer agrees.

Additional physical examination findings from the GOG flow sheets are provided to show absence of the measurable lesion. BMS calls this patient a CR; the reviewer agrees.

PT arm:

The GOG follow-up form shows a confirmatory CT. The pleural effusion is not evaluated further, but no mention of an effusion is made, even when the patient subsequently relapsed in the pelvis. BMS calls this patient a PR; the reviewer agrees.

The sponsor states that a confirmatory CT scan was performed 12/18/91 and showed residual pelvic lymph nodes. The patient was admitted for biopsy of these nodes, which were reportedly negative. The follow-up form from the GOG investigator shows that a CT was scheduled. The first page of a discharge summary indicates that the patient was admitted for a biopsy, but no results are given. Subsequent GOG follow-up sheets have a check-mark indicating that the patient is disease-free. No specific documentation is provided.

The reviewer feels that this information is suggestive, but the specifics are lacking. The sponsor was asked to provide the results of the nodal biopsy. The pathology report was sent on 3/10/98 and stated that the aspirate was inadequate for diagnosis. The reviewer therefore did not classify this patient as a responder.

This patient had two measurable lesions at baseline: a cul-de-sac lesion and a right upper lobe lesion. The cul-de-sac lesion measured 8 x 10 cm at baseline, 6 x 8 cm on 11/22/91, and 4 x 5 cm on 12/12/91. The right upper lobe lesion measured 2 x 3 cm at baseline, was absent on 11/22/91, and measured 3 x 1 cm on 3/23/92. The sponsor includes a GOG follow-up form dated 3/1/92, where a pelvic exam was within normal limits. This information confirms the resolution of the cul-de-sac mass. A chest X-ray dated 3/1/92 was marked "abnormal--no change". The sponsor states that this X-ray result supports the complete resolution of the mass. In addition, a pleural effusion was present at baseline. The only additional assessment of the effusion comes from the chest X-ray 3/1/92 was abnormal but without change. The sponsor calls this patient a PR; the reviewer agrees.

The sponsor submitted a GOG follow-up sheet indicating that a second CT now showed a CR. Because a third CT was not performed to document the CR, the patient was deemed a PR by the sponsor; the reviewer agrees.

A pleural effusion was listed as an evaluable lesion at baseline but was not examined further. The sponsor states that the effusion was cytologically negative for malignancy and was therefore not followed. The vaginal apex lesion shrank by 50% on 5/5/92 and was absent on 5/28/92. BMS states that confirmation of the PR was obtained, but not of the CR; the reviewer agrees.

BMS agrees that there is not enough follow-up to document a CR. However, they state the subhepatic lesion was absent at second-look laparotomy and that the presence of a small amount of residual disease should support an assessment of PR. The reviewer agrees--initial lesion size was 2.5 x 2.0 cm and the only residual disease at second-look surgery was 0.3 cm in size.

The FDA reviewer did not assess this patient as a responder because of probable progression based on an increasing pleural effusion. The Medical Treatment Reporting Forms for cycles 4 and 5 note normal chest X-ray results. This information supports an assessment of PR.

(4) The most recent BMS communication (2/2/97, pages 4-5) indicates that confirmation of response was strictly adhered to, and implies that results from a second-look laparotomy were not used to confirm responses. If this statement is correct, then please consider the following list of patients:

**also listed in Tables 9 and 10 above*

These patients had responses confirmed by a negative second-look laparotomy, but did not have documentation of response confirmation by non-surgical means on the case report forms. In a few instances for example), additional tumor measurements were hand-written on the BMS Summary form at the end of the case report form, raising questions about the adequacy of the data. In one instance (patient not only were additional measurements hand-written on the summary form but additional non-evaluable sites were added.

If BMS did not accept second-look laparotomy results as the confirmation of a response, please explain why these patients are considered to be responders.

The sponsor noted that BMS did accept second-look laparotomy results as the confirmation of a response.

3. As a result of the first FDA analysis, the FDA assessment of response shows an overall response rate of 60/113 (53%) for PT and a response rate of 60/127 (47%) for PC. These response rates are lower than those calculated by the sponsor. However, there is no statistically significant difference between the 2 arms, in accordance with the sponsor's statement in the study report.

4. Based on BMS' reply, the FDA assessment of response shows an overall response rate of 70/113 (62%) for PT (CR 40/113 or 35%; PR 30/113 or 27%) and a response rate of 61/127 (48%) for PC (CR 30/127 or 24%; PR 31/127 or 24%).

The sponsor noted a response rate of 68/113 or 60% for PT. The FDA analysis adds 3 patients to the sponsor's calculation (pts excluded because of wrong primary: disagreement between FDA and BMS) and subtracts 1 (pt , inadequate documentation: disagreement between FDA and BMS; sponsor asked to provide additional

documentation).

The sponsor noted a response rate of 64/127 or 50% for PC. The FDA analysis adds one patient to the sponsor's calculation of PC response rate (excluded because of wrong primary: disagreement between FDA and BMS) and subtracts 4 (pt : disagreement between FDA and BMS; and pts : BMS agrees with FDA assessment).

The FDA analysis results in a statistically significant response rate between PT and PC with a p-value of 0.04. The CR rate is at the border of significance, with a p-value of 0.048 with Fisher's exact test and 0.06 with Chi-square and a Yates correction factor. An overall difference in the response assessments of 5 patients changes the result from insignificant to statistically significantly different. These results are probably reflective of the difficulties in assessing response in the ovarian cancer population.

9.5.1.b Response by pre-treatment characteristics

The sponsor identified 7 baseline prognostic factors that might influence outcome. These factors included age, performance status, stage, residual tumor diameter, histologic grade, cell type, and baseline liver function tests. None of the first 6 factors correlated with clinical response. For the 7th factor, response rates in each arm were higher for patients with any abnormal liver function test compared to normal liver function tests (69% versus 53% PT; 54% versus 47% PC). However, the sponsor notes that most patients with abnormal liver function tests had grade 1 elevations of alkaline phosphatase, and that there is no clear pathophysiologic explanation for this observation.

Reviewer Comment:

1. The inclusion of liver function tests in a multivariate analysis is not justified (see Reviewer Comment after section 9.4.2): there is no literature that supports this factor as a prognostic or predictive indicator. Given the fact that the abnormalities were clinically insignificant, the inclusion of abnormal LFTs is questionable.

2. Cell type was included, although there is no clear published data that suggest that the serous subtype conveys a different prognosis. It is reasonable to test whether adjusting for this imbalance alters the results, but should be considered an exploratory analysis only.

3. No baseline patient characteristics were found to be predictive of response.

9.5.1.c Logistic regression for clinical response

The sponsor identified a different set of 7 factors that might influence the likelihood of response. These factors included residual tumor diameter ($\leq$ 5 cm v. > 5 cm), age, stage, performance status, site accrual (less than 10 v. 10 or more patients), histologic grade, and liver function. Fisher's exact test was used to assess the significance of these factors. None were significant except liver function, which yielded a p-value of 0.091. This factor was retained in the stepwise procedure and in the final regression analysis was tested with treatment arm. Neither factor was significant in the final model.

Reviewer Comment:

1. The literature does not support the use of liver function abnormalities in this model. Only 38 patients had elevations of CTC grade 2 or 3, further diminishing the clinical relevance of this factor.

9.5.1.d Time to clinical response

The median time to clinical response was 7.9 weeks for PT compared to 8.6 weeks for PC, not significantly different. For complete responders, the median time to the observation of response was 9.0 weeks for PT and 9.6 weeks for PC (p=0.444).

9.5.1.e Duration of response

At the time of analysis, 55 of the 68 responders to PT (81%) and 56 of the 64 responders to PC (88%) had clinical evidence of progression or recurrence. The median duration of clinical response as calculated in Method 1 (see section 9.4.1, Endpoints) was 15.8 months for PT compared to 16.4 months for patients on PC (p=0.249). These values were 14.9 months and 15.7 months for complete responders, respectively (p=0.779). When Method 2 was used, the duration of response was 21.9 months for PT and 13.8 months for PC, not significantly different (p=0.209). Using Method 2 to calculate duration of complete response gave values of 19.8 months for PT and 12.9 months for PC (p=0.260).

Reviewer Comment:

1. Two methods were used to calculate duration of response. Method 1 is the conventional method: Method 2 attempted to account for the effect of cross-over therapy. Method 2 is likely to induce bias, as patients on PC were more likely to subsequently receive paclitaxel. The response duration for PC was shortened as a result. Method 1 is preferable. However, both methods showed a non-significant difference in response duration between the two arms.

2. Regardless of the methodology used, there were no significant differences in the clinical response rate, time to response, or duration of response between the two arms. No baseline or prognostic factors predictive of a response to therapy could be identified.

3. A MedLine search indicates that the clinical complete and overall response rates for the cisplatin-cyclophosphamide arm are comparable to those reported in the literature for this combination.

9.5.1.f Pathologic response

A total of 341 patients were considered to be evaluable for pathologic response. These characteristics are summarized below:

Table 11. Evaluability for pathologic response (modified from sponsor's table 28, volume 3, page 101)

	Cisplatin-Taxol	Cisplatin-Cyclophosphamide
Evaluable:	n=163	n=178
Second-look laparotomy	122	109
Clinically persistent disease	28	53
Early death/toxicity	13	16
Inevaluable:	n=33	n=36
Wrong primary (surgery performed)	6	3
Refused surgery	20	24
Wrong primary (no surgery)	2	7
Surgery contraindicated	4	1
Reason not given	1	1

Pathologic findings for all patients (evaluable and inevaluable) are summarized in the following table:

Table 12. Pathologic response (modified from sponsor's table 28, volume 3, page 101)

Response	Cisplatin-Taxol	Cisplatin-Cyclophosphamide	P-value
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

If only evaluable patients are considered, the pathologic complete response rate for PT was 26% and 20% for PC (p=0.191). If the pathologic complete response rate plus microscopic residual disease rate is calculated for evaluable patients only, the response rate was 67/163 or 41% for PT

compared to 43/178 or 24% for PC (p=0.001). If these rates are calculated for the entire randomized population, the complete pathologic response rates are 21% (42/196) for PT and 16% (35/214) for PC (p=0.196); overall response rate for the entire population is 34% (67/196) for PT and 20% (43/214) for PC (p=0.001).

Reviewer Comment:

1. The pathologic complete response rate was not significantly different between the evaluable patients nor in the entire randomized population. The pathologic response rates become significant only when microscopic residual disease is included in the definition of response.

2. An Access query to verify the reported pathologic response rates showed 46 pathologic CR for PT and 40 for PC, compared to 42 and 35 respectively as noted in the Study Report. The Access query also showed microscopic residual disease at laparotomy in 27 PT patients and 10 PC patients, compared to 25 and 8 in the Study Report. The sponsor was asked to clarify this point (2/4/98 by facsimile). In a submission dated 2/25/98, the sponsor noted that the fields used in the Access database contained data from investigators and did not always match the central GOG assessment, which was considered as the final interpretation.

9.5.1.g Pathologic response by pretreatment characteristics

The same set of 7 baseline characteristics used to analyze clinical response were applied to pathologic response analysis. Age, performance status, size of residual disease at laparotomy, histologic grade, cell type, and baseline liver function tests were not associated with pathologic response. The stage of disease was significant only for the PT arm: Stage IIIB patients treated with PT had a pathologic response rate of 40% compared to a pathologic response rate of 20% for patients with Stage IV disease. On the PC arm, these response rates were 19% and 22% respectively.

Reviewer Comment:

1. The same comments made earlier about the use of cell type and baseline liver function tests apply here.

2. This exploratory analysis suggests that PT offers an advantage over PC in Stage III patients. This hypothesis will require prospective testing in an independent data set.

9.5.1.h Logistic regression for pathologic response

The 7 factors used in the logistic regression for clinical response as well as stratum were applied in this analysis. Patients with Stage III disease were more likely to respond than patients with Stage IV disease (30% versus 21%). No other factor was significant. This factor was retained at the end of the stepwise selection and was tested with treatment arm and stratum in the final model. In this model, treatment with PT was the only factor significantly associated with pathologic response (p=0.002).

9.5.1.i Duration of pathologic response

The duration of overall pathologic response (complete or microscopic residual) was 28.5

months in the PT arm and 17.5 months in the PC arm. For complete pathologic responders, these values were 32.2 months and 16.5 months respectively when calculated by Method 1. Method 2 yielded a duration of overall pathologic response of 33.0 months for PT and 16.5 months for PC (p=0.167); the numbers for pathologic complete response were 32.9 months compared to 21.2 months. None of these calculated durations was statistically significantly different between the two arms.

Reviewer Comment:

1. Pathologic complete response rate and duration of pathologic response were not significantly different between the two arms. The pathologic response rate was significantly different only when both a complete response and microscopic residual disease were considered.

2. Multivariate analysis suggests that PT may offer an advantage in Stage III disease relative to Stage IV disease. However, this hypothesis requires independent confirmation. If true, it is not clear whether paclitaxel itself offers an advantage in earlier stage disease or whether the higher dose-intensity of cisplatin achieved in this combination offers the advantage.

9.5.2 Time to progression

9.5.2.a Unadjusted analysis

At the analysis time point, 163 of the 196 PT patients had progressive disease (83%) and 191 of the 214 PC patients had progressed (89%). The time to progression was 16.6 months for PT patients and 13.0 months for PC patients (p= 0.0008). This difference is equivalent to a 30% reduction in the risk of tumor progression for PT patients (relative risk 0.698).

Because the protocol did not prohibit maintenance therapy prior to clinical evidence of progression, time to analysis was also calculated with Method 2, where patients were censored at the time of subsequent therapy if this therapy was given prior to clinical progression. In this method, 90 additional PT patients and 93 additional PC patients were censored. In this method, time to progression was 16.6 months for PT and 13.4 months for PC (p=0.016; relative risk 0.686).

Reviewer Comment:

1. Regardless of the method used, treatment with PT resulted in a significantly longer time to progression.

2. The median time to progression observed for the PC arm is comparable to those cited in the literature.

3. This finding represents significant clinical benefit.

4. The reviewer performed an analysis to confirm the reported differences in time to progression. The submitted database did not allow calculation of a progression date from other events for the majority of patients. For example, an Access query using Grant William's algorithm identified patients with a 50% increase in tumor size. However, tumor measurements were only included for the timeframe of chemotherapy administration, and only 11 patients had progression of existing lesions while on treatment according to the algorithm. In response to an FDA Request for Information (1/15/98), BMS supplied a list of progression dates or censoring

dates for each patient (2/2/98). The GOG case report forms were then reviewed for each patient. The BMS case report forms were used as a secondary source, because they contained follow-up information in less detail than the GOG forms. The progression dates were confirmed from the CRF. Dates generated from the PD algorithm were used in preference to those recorded by the sponsor, if a discrepancy existed.

In order to establish a censoring date (ie, patient alive or dead but without documented progression), the following rules were used by the reviewer:

- The censoring date was the last date the patient was examined, not the last date the GOG form was written or the last date of phone contact
- For patients without any documentation of progression, a second analysis was run with a progression date established by a CA-125 > 100 and significantly increased relative to the end-of-treatment value

The following tables were generated:

Table 13. Patients with progressive disease: Discrepancies in date of PD between BMS and FDA

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	6/28/91	10/8/91	Increased disease at second-look laparotomy not documented on on-therapy measurements
	6/3/92	8/28/91	50% increase in disease per algorithm
	2/24/94	2/1/94	Pt called PD because of CA-125, but it increased 2/1/94, not 2/24/91
	2/15/92	12/15/92	Cannot find any data from 2/15/92; CRF lists 12/15/92 as progression date
	2/5/93	8/12/93	CT on 8/12/93 is the first evidence of PD I can find
	6/16/92	9/22/92	September CT scan shows PD; June CT scan read as stable disease
	9/29/92	6/22/92	50% increase in disease per algorithm
	2/15/93	11/26/91	50% increase in disease per algorithm
	9/22/92	4/21/92	CT with progressive disease

Table 14. Patients without progression per sponsor, but PD per FDA

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	6/20/93	6/8/92	CRF states increased disease on physical exam
	4/20/93	7/1/92	CRF states increased disease on physical exam
	7/22/91	6/3/91	CRF states increased disease on physical exam
	10/15/93	10/15/93	Phone report from outside MD stated PD*
	3/2/95	12/2/94	Paracentesis of 8 liters required#
	5/31/94	1/31/91	PD by CT scan
	8/19/91	6/5/91	Increased ascites by PE; none at second-look lap
	12/2/91	5/6/91	CT by local MD showed progression
	4/15/92	1/15/92	Clinical deterioration per local MD report
	2/9/93	9/5/91	Positive biopsy of pelvic mass that increased in size
	12/9/91	11/14/91	New intra-abdominal carcinomatosis at second-look lap
	8/25/94	2/22/94	CT scan showed PD
	9/23/94	6/10/94	CT showed PD
	11/23/94	11/23/94	PE shows new abnormality
	10/20/92	7/30/92	PE shows new vaginal mass (last exam date before death)

Superscripts indicate an additional entry for the same patient in Table 16.

Table 15. Patients without progression: Discrepancies in censoring date between BMS and FDA

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	10/15/91	5/13/91	5/13/91 last documented exam; sponsor's date is a phone report of death from a social worker
	7/9/91	4/15/91	4/15/91 last documented exam; admitted in extremis 7/5/91 with death 7/9/91
	10/24/94	7/13/92	7/13/92 last documented exam; sponsor's date reflects that the patient was alive, but no other information was given
	2/6/95	10/13/93	10/13/93 last documented exam; sponsor's date is a report that a pharmacist filled a prescription for her
	11/6/92	8/25/92	Last documented exam; sponsor's date is a call from the family reporting her death[$]
	4/29/92	5/21/91	Last documented exam; pt then refused f/u. Sponsor's date is a phone report of death
	3/14/92	1/13/92	1/13/92 was date of last exam; sponsor's date is death in hospice[@].
	11/20/92	7/22/92	Last exam date; sponsor has date of death per nursing home
	3/2/95	2/27/95	Last exam date; sponsor has phone report
	2/17/92	11/4/91	Last exam date; sponsor has date of death (DOD) from outside MD from bowel obstruction
	3/1/95	1/13/95	Last exam date; sponsor has DOD from leukemia
	6/24/94	12/7/92	Last exam date; sponsor has DOD from phone call from family, but patient had been lost to follow-up with no intervening exams
	1/22/94	10/21/93	Last exam; sponsor has phone DOD
	4/4/93	3/10/92	Last exam; sponsor has DOD from tumor registry; pt felt to have colon cancer, not ovarian cancer
	6/13/94	5/10/94	Last exam date; sponsor has phone report of

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	11/4/91	3/6/91	Last exam date; sponsor has family phone report of death
	12/20/93	8/1/94	Last MD report 8/1/94; sponsor's date is a phone call
	1/15/94	8/11/93	Last exam; sponsor's date is DOD from medical records
	12/13/94	5/25/94	Last exam; sponsor's date is phone call from son that patient is
	9/15/91	5/27/91	Last exam date; patient then refused f/u. Sponsor has phone report of death
	9/15/92	5/5/92	Last exam date; sponsor's date is DOD in hospice
	5/6/94	10/5/90	Last exam date; no contact with patient afterwards.
	6/25/93	2/19/93	Last exam date; sponsor's date is DOD from LMD
	9/15/92	5/28/92	Last exam date; sponsor's date is phone DOD
	8/16/94	4/7/94	Last exam date; sponsor's date is phone call from pt
	5/25/92	3/12/92	Last exam date; sponsor's date is phone DOD
	8/7/92	4/7/92	Last exam date; sponsor has the date from a form indicating the patient has been lost to follow up
	2/28/93	11/11/92	Last exam date; sponsor has DOD
	2/10/92	8/27/91	Last exam; sponsor has DOD
	8/1/92	5/13/92	Last exam date; sponsor has DOD
	11/2/94	10/21/91	Last exam date; pt lost to follow up; sponsor has phone report
	11/16/94	4/25/94	Last exam date; sponsor has date of a call from a neighbor indicating that patient is well
	3/9/95	6/15/94	Last exam; sponsor's date is from a form indicating phone contact with the patient 2/95

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	10/17/94	4/18/94	Last exam; I cannot find any data corresponding to the date listed by the sponsor
	4/29/93	9/28/92	Last exam; sponsor's date is phone report of DOD
	10/23/92	1/28/92	Last exam; sponsor has DOD
	1/24/92	11/13/91	Last exam; sponsor has DOD
	2/4/92	1/6/92	Last exam; sponsor has DOD
	8/29/94	12/9/93	Last exam; sponsor has phone call from pt
	11/4/94	9/23/94	Last exam; sponsor has phone report
	8/15/92	4/3/92	Last exam date; sponsor has DOD
	11/7/91	9/24/91	Last exam date; sponsor has DOD

Table 16. Patients without progression, but with significant rises in CA-125

Pt ID	BMS date	FDA date	FDA interpretation of CRF
	7/28/95	12/21/93	12/21/93 CA-125 = 212
	10/15/93	12/29/92	CRF states PD; CA-125 was <10; rose to 415, then 1115*
	9/28/94	7/10/93	CA-125 from <7 to 300; stable PE and CT
	3/2/95	11/15/93	CA-125 8298#
	11/6/92	5/28/92	CA-125 from 182 to 390; 8/25/92 = 1860$
	3/14/92	1/13/92	Off study for treatment complications with CA-125 2021 on 10/25/91; CA-125 = 11,100 on 1/13/92@
	12/8/93	1/22/93	CA-125 increased to >100 (no value given) and chemo changed; 10/22/93, CA-125 = 1323
	6/13/94	3/26/93	CA-125 increased to 140!
	9/21/94	3/17/94	CA-125 219 3/17/94
	12/20/93	11/15/93	CA-125 increased to 181^
	8/16/94	4/7/94	Exam/scan negative; CA-125 830
	5/25/92	12/31/91	CA-125 from WNL to 172+
	5/21/92	3/3/92	CA-125 from 1240 to 4520

The above tables were sent to the sponsor for comment on 2/25/98. Specific comments were requested for Tables 13-15; Table 16 was intended as exploratory only.

An analysis of time to progression was first run using the BMS dates and status in JMP. This analysis yielded a TTP of 16.6 months for PT and 13.0 months for PC with a p value of 0.0006. These results correspond to those in the study report.

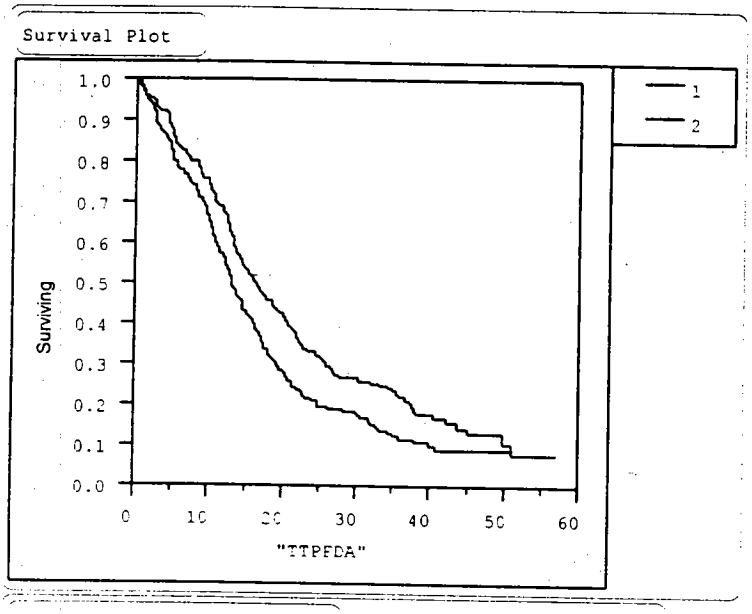
A second analysis was performed using FDA-generated information from tables 13-15 (see below for corrections to data based on sponsor's reply). Median TTP was 16.8 months for PT compared to 13.4 months for PC ($p=0.006$). The curve generated from JMP appears below:

Figure 1. Kaplan-Meier plot of time to progression, FDA analysis

Product-Limit Survival Estimates

Time Variable: "TTPFDA"

Censoring Variable: "DODPstat"



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	7.5304	1	0.0061
Wilcoxon	7.5283	1	0.0061

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Combined

A third analysis was run using progression dates generated from the CA-125 values in table 16, for patients without objective evidence of progression. Time to progression for PC patients was 12.6, compared to 15.5 months for patients treated with PT (p=0.006). This analysis was intended to be an exploratory analysis only. Tumor marker levels are not a proven surrogate endpoint; although rising CA-125 values are probably associated with subsequent relapse/progression, the time lag can be substantial and the value of treating an asymptomatic patient with a rising marker has not been demonstrated.

The sponsor sent a facsimile 3/10/98 that addressed the TTP questions. Tables 13 and 14 were reviewed in detail. Table 15 was not reviewed on a case-by-case basis, as BMS used different rules for assessing progression than the reviewer. These results are summarized below:

Table 13:

Pt	
	BMS agrees with the FDA reviewer
	The FDA reviewer mistakenly wrote "8/28/91" as the progression date; the correct date is 4/22/92. The sponsor prefers the date of 8/28/91, which is the date of exam under anesthesia with biopsy. The reviewer assesses progression on 4/22/92, when physican examination (used to follow the patient throughout the study) documented a 4-fold increase in tumor area.
	BMS agrees with the FDA reviewer
	BMS agrees with the FDA reviewer
	BMS supplied a follow-up form that supports their progression date; FDA reviewer agrees with BMS
	BMS agrees with the FDA reviewer
	The FDA-generated algorithm documented a 50% increase in disease on 6/22/92. However, the disease was initially measured on CT with an end-of-treatment CT that documented significant shrinkage. Interim measurements were based on physical examination and were less accurate, leading to the apparent increase in lesion size. The FDA reviewer agrees with the sponsor
	The FDA-generated algorithm documented a 50% increase in disease on 11/26/91; however, BMS notes that a nodal area increased in size from .7 x .7 cm to 1 x 1 cm as measured on a CT scan. This increase was not classified as PD. FDA reviewer agrees with BMS
	BMS agrees with the FDA reviewer

Table 14:

	BMS agrees with the FDA reviewer
	BMS states that an abnormality on exam was detected 7/1/92, but they do not accept this finding as evidence of progression. They censored the patient for progression on 4/20/93, the date of death. However, the only notes in the record are from these two dates. The note from 7/1/92 indicates that an evaluation was in progress for the PE abnormality. The FDA reviewer, in the absence of other information, assesses progression on 7/1/92, the date a change in the PE was noted by the patient's doctor.
	On 6/3/91, the physician noted "rectal shelf fullness suspicious for recurrence." On that date, the patient had a CA-125 level that increased from 161.8 on 4/18/91 to 2417. The patient was begun on hormonal therapy for recurrence. The FDA reviewer assesses progression on 6/3/91 and not on 7/22/91, which is the next available information and documents the date of death.
	Dates were the same, but sponsor and FDA disagreed about whether or not this patient progressed. The sponsor included her as an event on this date.
	BMS agrees with the FDA reviewer

The FDA assessed progression on 1/31/91 on the basis of increased lung lesions, not pelvic adenopathy. However, on review of the CRF, the lung lesion is measured at 1.5 x 1.5 cm throughout the course of treatment, even though the investigator's note indicated an increase. The sponsor stated that review of the CRF indicates PD on 10/8/91, not 5/31/94; the FDA reviewer agrees with this date.
BMS does not accept "increased abdominal tension attributed to ascitic fluid" as evidence of progression. As the patient had no ascites at second-look laparotomy, the FDA reviewer assesses progression on this date.
The text of the follow-up sheet from 6/4/91 indicates "residual" disease on the CT; the CT is coded as a 3 (abnormal with a change) in the evaluation section of this sheet; and no evidence of recurrence/progression is checked. The data on this sheet are internally inconsistent. The sponsor's assessment of progression on the date of death is accepted.
FDA reviewer agrees with BMS; clinical detioration may have been due to concomittant therapy rather than disease
BMS agrees with the FDA reviewer
BMS agrees with the FDA reviewer
BMS agrees with the FDA reviewer
BMS agrees with the FDA reviewer
The dates are the same. However, the FDA assesses progression on this date based on a change in physical examination described as "vague fullness and thickening...", coded as "abnormal/change" on the follow-up sheet.
FDA reviewer agrees with BMS--reference to vaginal mass based on history, not on exam

For Table 15, the sponsor and the FDA reviewer used different censoring rules. The FDA reviewer's progression dates ranged from 3 days to 3.6 years shorter than the sponsor's and in one case was 7.5 months later than the sponsor's assessed date. The mean difference in date was 7 months. Of the 42 patients listed in Table 15, only 12 had progression dates that differed by less than 3.5 months, the absolute difference in TTP between the two treatment arms demonstrated in GOG 111. It is important to assess whether differences in assessment of TTP can eliminate the advantage seen for PT over PC. Whether the FDA dates or the sponsor's dates are used, the difference persists, supporting the efficacy of cisplatin and paclitaxel over that of cisplatin and cyclophosphamide in the first-line treatment of ovarian cancer.

When TTP was re-run using data corrected from the correspondance with BMS, the following results were obtained: median TTP for PC was 13.4 months; median TTP for PT was 16.8 months; p-value 0.006.

These analyses demonstrate time to progression that is comparable to those submitted in the sponsor's report; in all cases TTP with PT is statistically significantly superior to TTP with PC. The absolute difference between treatment arms is 3.4 months in the FDA analysis, compared to 3.6 months with the sponsor's analysis. This difference remains clinically

significant. The results are robust and demonstrate clinical benefit with PT.

9.5.2.b Cox regression analysis for time to progression

The 7 pretreatment patient characteristics used in the analyses of clinical and pathologic responses and stratum were applied to time to progression. None were significant except stratum. Patients with non-measurable disease had a significantly longer time to progression than patients with measurable disease (16.4 months compared to 13.4 months; p=0.009). This factor and treatment arm were included in the final Cox regression analysis. Both patients with non-measurable disease and patients treated with PT had a significantly reduced risk of disease progression. The relative risk for non-measurable patients was 0.768 (p=0.015) and for PT patients was 0.704 (p=0.001). The median TOP for patients with non-measurable disease treated with PT was 21.3 months, compared to 13.9 months in similar patients treated with PC. For patients with measurable disease, TOP was 14.6 months for PT and 12.0 months for PC (p=0.05).

Cell type was included in this model, despite the lack of evidence for its importance as a prognostic factor, because the incidence of serous adenocarcinoma was imbalanced between the two arms. This factor was not selected in the model and had a minimal impact on the risks presented per the sponsor.

Reviewer Comment:

1. The same comments about the choice of pretreatment variables apply here. The FDA statistical reviewer re-ran the Cox regression analysis without liver function tests included as a potential variable. The results were not different from those described above.
2. Patients with non-measurable disease are likely to have a longer time to progression because of the difficulty of assessing intra-abdominal tumor in ovarian cancer.
3. The subset analysis by stratum supports the advantage for PT seen in the analysis of all randomized patients.

9.5.3 Survival

9.5.3.a Unadjusted analysis

At the analysis time point, 114 of the 196 PT patients had died (58%) compared to 154 of the 214 PC patients (71%). Follow-up time ranged from 28.6-57.2 months for the PT arm and from 9.9 to 56.6 months for the PC arm. In the first 18 months of follow-up, 3 patients on PC were lost to follow-up and were censored from the analysis

The median survival for PT patients was 35.5 months compared to 24.2 months for PC patients (p=0.0002). The calculated relative risk was 0.635 (95% CI 0.497, 0.811), indicating a 36% reduced risk of mortality with PT therapy. By Cox analysis, residual tumor diameter was significant in its impact on survival. After adjustment for this factor, there remained a statistically significant effect of paclitaxel-based therapy.

Reviewer Comment:

1. The survival was significantly better for PT patients than for PC patients. The median survival observed in the PC arm is comparable to that reported in the literature for this combination.

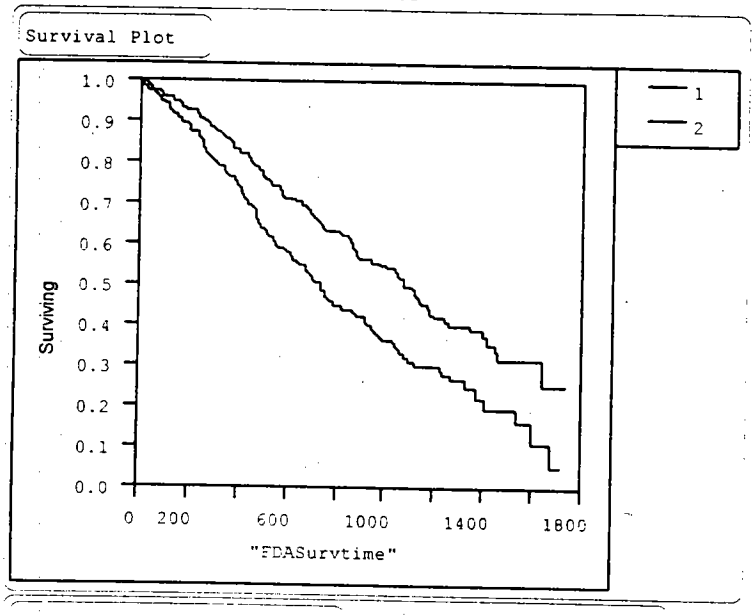
2. The dates of death listed in the database (table "DEATH") were included in the FDA audit. These dates of death were then used in a MS Access query to calculate survival times. The survival times calculated for each patient correlated within 1 day for all 410 patients enrolled in the trial. These calculated survival times (in days) were then exported to JMP and a Kaplan-Meier analysis was performed. The results of this analysis are presented below. Median survival for the PC arm (Arm 1) was 735 days or 24.2 months; median survival for the PT arm (Arm 2) was 1079 days or 35.5 months (see Appendix B for data listings used to derive median survival). The difference was statistically significant with p=0.0002 by the log-rank method or p=0.0003 by the Wilcoxon method. These results are identical to those calculated by the sponsor.

Figure 2. Kaplan-Meier plot of survival, FDA analysis

Product-Limit Survival Estimates

Time Variable: "FDASurvtime"

Censoring Variable: "FDAStatus"



Tests Between Groups

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	13.9455	1	0.0002
Wilcoxon	13.0290	1	0.0003

1

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Combined

9.5.3.b Cox regression analysis for survival

The 7 pretreatment characteristics used to analyze pathologic and clinical response and time to progression were applied to survival. None were significant except small residual diameter ($\leq$ 5 cm) after staging surgery, which was related to survival (p=0.007). In the final Cox regression analysis, this factor was retained with treatment arm and stratum. Both residual tumor diameter and treatment with PT were significant in determining survival. Patients treated with PT had a RR of 0.627 (95% CI 0.491, 0.801); patients with small residual tumor diameter had a RR of 0.682 (95% CI 0.522, 0.891). Patients with small residual disease treated with PT had a median survival of 37.9 months, compared to a median survival of 17.8 months in patients with small residual disease treated with PC (p=0.074). Because of the baseline imbalance in the incidence of serous adenocarcinoma, this factor was tested and was not found to significantly alter the results.