CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-262/S-026, 027, 028

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#: 20-262/SE1-026

Applicant: Bristol-Myers Squibb

Name of Drug: Taxol(paclitaxel)

Indication: Primary treatment of ovarian cancer

Documents Reviewed: Vols. 3 - 12 of submission dated October 7, 1998

Medical Officer: Susan Honig, M.D.

Statistical Issue:

(I) Covariate adjustment in logistic and Cox regression

The selection of potential prognostic factors among efficacy variables was inconsistent. Residual diameter was selected as a potential prognostic factor using TTP and survival. Residual diameter was not selected as a prognostic factor using the objective response endpoint. Liver function was selected as a potential prognostic factor using objective response. It was not selected using either TTP or survival. The treatment effect was statistically significant between the two treatment groups in favor of Taxol for the TTP and survival endpoints. The treatment effect was statistically significant in patients with small residual diameter favoring the Taxol arm and not statistically significant in patients with large residual diameter for the TTP endpoint. The treatment effect was statistically significant in patients with small residual diameter favoring the Taxol arm and marginally statistically significant in patients with large residual diameter for the survival endpoint.

In Section 1 we give a brief background on Taxol. Section 2 contains a description of the pivotal study CA139-022. Section 3 contains the efficacy results and this reviewer's comments. Section 4 contains the conclusions regarding this application. An Appendix is included at the end of this review with tables and graphs regarding some of the efficacy endpoints.

I. Background

In this NDA the sponsor seeks approval of Taxol in combination with Cisplatin for the treatment of patients with advanced ovarian cancer. Taxol will be administered at a dose of 135 mg/m2 as a 24 hour infusion followed by Cisplatin on day 2 at a dose of 75 mg/m2.

II. Description of Study

Protocol CA139-022:

Study Design:
Study CA139-022 "was a prospective multicenter, open label,. randomized phase III trial comparing TAXOL/Cisplatin versus Cyclophosphamide/Cisplatin in patients with previously untreated, advanced ovarian cancer [in patients with suboptimal Stage III and Stage IV ovarian cancer]." The study was stratified by institution and clinical measurability of disease.

Number of Patients:
Four hundred and ten patients were randomized into the trial (196 in the treatment arm, 213 in the control arm). One patient in the cyclophosphamide died before receiving a study medication.

Diagnosis and Eligibility:
Women with pathologically verified FIGO Stage III epithelial ovarian cancer after suboptimal surgery (>1 cm residual mass) or FIGO stage IV disease are eligible. They could have clinically measurable or nonmeasurable disease with no previous chemotherapy or radiation for ovarian cancer.

Dose, Route, and Schedule:
Both the standard and experimental therapies were repeated every 21 days or when hematologic and non-hematologic recovery was documented. Dose reductions based on Grade IV hematologic toxicity were required for both treatment arms.

Treatment of duration:
Patients received a total of six cycles of therapy unless there was progression of disease or toxicity.

Efficacy Variables:
The primary endpoint of this study was time to progression, and the secondary endpoints were response rates, duration of clinical

and pathological response, and survival. This study was powered (n=360) "to detect an increase of 40% in the median time to progression based on a median of 10.3 months and 14.4 months for patients with measurable and non-measurable disease respectively" with 84.6% of power at one-sided 0.05 type I error.

III. Efficacy Results and Comments:

Tumor Response:

Reviewer's Table 3.1 shows the number of patients in each treatment group with respect to measurable disease. In the Taxol/Cisplatin group, 113 (57.7%) patients had measurable disease and 83 (42.3%) patients had non-measurable disease. In the Cyclophosphamide/Cisplatin group, 127 (59.3%)patients had measurable disease and 87 (40.7%) patients had non-measurable disease.

Reviewer's Table 3.1: Sample Size with respect to Measurability

	Taxol/ Cisplatin	Cyclophosphamide/ Cisplatin
Measurable	113 (102, 11)*	127 (117, 10)**
Non-Measurable	83	87
Total	196	214

*102 and 117 are the number of evaluable patients in Taxol/Cisplatin and Cyclophosphamide/Cisplatin groups, respectively.
**11 and 10 are the number of unevaluable patients in Taxol/Cisplatin and Cyclophosphamide/Cisplatin groups, respectively.

Reviewer's Table 3.2 shows the number of responders (both complete and partial responders) among patients with measurable disease in each treatment group.

Reviewer's Table 3.2: Number of Responders in Each Treatment Group (Measurable Patients)

	Taxol/ Cisplatin	Cyclophosphamide/ Cisplatin
# of Responders	68	64
Complete	40	32
Partial	28	32

Reviewer's Table 3.3 shows the overall and complete response rates in each treatment group among measurable patients. The difference in the overall response or complete response rates between the two treatment groups was not statistically significant at the 0.05 level.

Reviewer's Table 3.3: Response Rate in Each Treatment Group (All Measurable Patients)

	Taxol/ Cisplatin (N=113)	Cyclophosphamide/ Cisplatin (N=127)
Overall Response Rate	60.2% (95% CI: 50.5% - 69.3%)	50.4% (95% CI: 41.4% - 59.4%)
	P-value*:0.153	
Complete Response Rate	35.4% (95% CI: 26.6% - 45.0%)	25.2% (95% CI: 17.9% - 33.7%)
	P-value*:0.092	

*P-values were derived by Fisher's two tailed exact test.

Reviewer's Table 3.4 shows the overall and complete response rates in each treatment group among both measurable and evaluable patients. Neither difference was statistically significant at the 0.05 level.

Reviewer's Table 3.4: Response Rate in Each Treatment Group (All Measurable and Evaluable Patients)

	Taxol/ Cisplatin (N=102)	Cyclophosphamide/ Cisplatin (N=117)
Overall Response Rate	66.7% (95% CI: 56.6% - 75.7%)	54.7% (95% CI: 45.2% - 63.9%)
	P-value*:0.074	
Complete Response Rate	39.2% (95% CI: 29.7% - 49.4%)	27.4% (95% CI: 19.5% - 36.4%)
	P-value*:0.083	

*P-values were derived by Fisher's two tailed exact test.

The sponsor investigated the effect of potential prognostic factors on the response rate such as age, performance status, stage, residual tumor diameter, histological grade, cell type, and baseline liver function. This reviewer confirmed the results

presented on sponsor's Table 25. The sponsor performed univariate analysis for each factor (sponsor's Table 26). Among these factors, liver function was found to be a potential prognostic factor. This reviewer confirmed this result. The sponsor also applied a stepwise procedure without including treatment in the model to identify potential prognostic factors. Only liver function was found to be statistically significant.

Reviewer's Table 3.5 shows the results from logistic regression analysis adjusting for liver function, which confirms the sponsor's results. The treatment effect of Taxol/Cisplatin over Cyclophosphamide/Cisplatin was not statistically significant at the 0.05 level.

Reviewer's Table 3.5: Results from logistic regression analysis of objective response adjusting for liver function (All Measurable Patients)

	Odds Ratio	95%CI	p-value
Trt effect*	1.486	0.887 - 2.490	0.133

Trt effect* is the treatment effect of Taxol/Cisplatin over Cyclophosphamide/Cisplatin.

This reviewer applied stepwise logistic regression to select possible prognostic factors without including treatment in the model **for the complete responders** among all measurable patients. Two potential prognostic factors, liver function and residual tumor diameter, were selected. Reviewer's Table 3.6 shows this result.

Reviewer's Table 3.6: Results from logistic regression analysis of complete responders adjusting for liver function and residual tumor diameter (All Measurable Patients)

	Odds Ratio	95%CI	p-value
Trt effect*	1.779	1.000 - 3.164	0.050

Trt effect* is the treatment effect of Taxol/Cisplatin over Cyclophosphamide/Cisplatin.

The treatment effect of Taxol/Cisplatin over Cyclophosphamide/Cisplatin with respect to complete response rate among measurable disease patients was found to be marginally statistically significant (P-value = 0.05).

Reviewer's Table 3.7 summarizes the results from logistic regression of objective response adjusting for liver function and

of complete response adjusting for residual diameter. The treatment effect is statistically significant in complete responders after adjusting for residual diameter in both cases (measurable and, measurable and evaluable disease).

Reviewer's Table 3.7: Results from Logistic Regression Adjusting for Potential Prognostic Factor(s) in Measurable, and Measurable/Evaluable Disease Patients

MEASURABLE DISEASE (N=240)				
Overall Response Rate				
	Odds Ratio	95%CI	p-value	Prognostic Factor(s)
Trt Effect	1.486	0.887 - 2.490	0.133	liver function
Complete Response Rate				
	Odds Ratio	95%CI	p-value	Prognostic Factor(s)*
Trt Effect	1.807	1.019 - 3.206	0.043	Dia1**
MEASURABLE and EVALUABLE (n=219)				
Overall Response Rate				
	Odds Ratio	95%CI	p-value	Prognostic Factor(s)
Trt Effect	1.656	0.956 - 2.869	0.072	none
Complete Response Rate				
	Odds Ratio	95%CI	p-value	Prognostic Factor(s)
Trt Effect	1.923	1.069 - 3.461	0.0292	Dia1

*Liver function and residual diameter were found to be possible prognostic factors. This reviewer selected only residual diameter after putting treatment as factor in the model.
**Dia1 stands for a residual diameter (<=5 cm vs. > 5 cm).

This reviewer investigated the effect of the residual diameter variable on the complete response rate. Reviewer's APPENDICES 1,2 and 3 summarize the results. The sponsor applied a 5 cm cut-off criteria to dichotomize the continuous variable of residual diameter. Notice from reviewer's Appendix 1, the sample size was not well balanced between the two categories within each treatment group for the 5 cm cut-off. Hence, this reviewer applied also a 4 cm and a 3 cm cut-off criteria.

The complete response rate was statistically significantly different between the two treatment groups in the lower residual diameter category for measurable and measurable/evaluable patients across the three cut-off criteria. The complete response rate was not statistically significantly different between the two treatment groups in the upper residual diameter category for measurable and evaluable/measurable patients across the three cut-off criteria. Therefore, this reviewer consider the residual diameter variable as an effect modifier, indicating that the magnitude of the treatment effect depended on the size of the residual diameter (the treatment effect was not consistent across the residual diameter categories but it was higher in the Taxol arm than the control).

The same analyses were applied to the overall response rate using the same three cut-off criteria. The residual diameter variable was not found to be an effect modifier.

Time to Progression:

Time to progression (TTP) was calculated in two ways: in Method 1, the duration was calculated "from the day of randomization until the date that clinical evidence of recurrence or progressive disease was first reported. Patients who did not progress were censored at their last date of follow-up. Patients who died of disease and for whom a date of progression was not available were considered to have progressed on the day of their death." In Method 2, patients were considered to be censored "at the time of any therapy following removal from the study, but prior to clinical evidence of recurrence or progression."

Reviewer's Table 3.8 summarizes the results derived by Method 1. This reviewer confirmed the sponsor's results. The relative risk favoring the Taxol treatment was statistically significant.

Reviewer's Table 3.8:Summary of Time to Progression Data (Method 1)

	Taxol/ Cisplatin	Cyclophosphamide/ Cisplatin
Total Patients	196	214
# of Events	163 (83%)	191 (89%)
# of Censored	33 (17%)	23 (11%)
Median Time (months) 95% CI	16.7 14.7 - 19.7	13.0 11.5 - 14.7
Logrank Test: p=0.0006 Relative Risk with 95%CI: 0.695 (0.563 - 0.858)		

Reviewer's Table 3.9 summarizes the results of Method 2. This reviewer confirmed the sponsor's results. The relative risk was statistically significant favoring the Taxol treatment.

Reviewer's Table 3.9:Summary of Time to Progression Data (Method 2)

	Taxol/ Cisplatin	Cyclophosphamide/ Cisplatin
Total Patients	196	214
# of Events	70 (36%)	98 (46%)
# of Censored	126 (64%)	116 (54%)
Median Time (months) 95% CI	16.6 13.9 - 21.0	13.4 10.3 - 16.6
Logrank Test: p=0.0163 Relative Risk with 95%CI: 0.687 (0.505 - 0.935)		

The sponsor investigated the effect of possible prognostic factors on time to progression using Method 1. This reviewer confirmed the results shown in sponsor's Table 32 except for the p-value comparing TTP for non-measurable to measurable patients. This reviewer obtained p=0.0267 for the non-measurable vs measurable variable in a univariate analysis, instead of p=0.009 reported in Sponsor's Table 32.

Reviewer's Table 3.10 shows the result from Cox regression adjusting for the non-measurable vs measurable variable. This

result was slightly different from the one reported by the sponsor (Sponsor's Table 33).

Reviewer's Table 3.10: Final Cox Regression Model for Time to Progression

Factor	Relative Risk	95% CI	P-Value
Treatment	0.697	0.565 - 0.861	0.0008

This reviewer investigated the effect of the residual diameter factor on time to progression. Reviewer's APPENDICES 4,5, and 6 summarize the results. In reviewer's APPENDIX 4, the effect of this variable was investigated in measurable patients across three cut-off criteria. In two criteria (<= 4cm vs. > 4cm and <= 3 cm vs. > 3cm), the relative risk favoring the Taxol treatment was found to be statistically significant in the lower categories, and not to be statistically significant in the upper categories. The magnitude of the relative risk in the lower categories (<= 4 cm or <= 3cm) and the higher categories (> 4 cm or > 3 cm) was about the same and less than 1. This indicated that the residual diameter variable was an effect modifier. In the 5 cm cut off criterion the residual diameter variable found to be an effect modifier, but the direction of the magnitude of the relative risk was opposite, i.e., in the higher category the effect of the Taxol treatment was more favorable than that in the lower category (> 5 cm vs. <= 5cm).

Reviewer's APPENDIX 5 shows the results of the non-measurable patients across the three cut-off criteria. This reviewer observed the same phenomenon in these patients as before. That is, the relative risk favoring the Taxol treatment was statistically significant in the lower category across the three cut-off points and was not statistically significant in the higher category across the three cut-off points. The direction of the magnitude of the relative risk in both categories (lower vs higher) was the same, i.e., <1. Therefore, this reviewer consider the residual diameter variable as an effect modifier in non-measurable disease patients.

Reviewer's APPENDIX 6 shows the results in all patients across the three cut-off criteria. The results were similar as in measurable and non-measurable disease patients. Again, this reviewer determined the residual diameter variable to be an effect modifier. We observe that the treatment effect was statistically significant in the lower stratum favoring the Taxol

arm and that the treatment effect in the upper stratum was not statistically significant.

Survival:

Survival time was calculated "from the day of randomization to death. Otherwise, survival was censored at the last day the patient was known to be alive".

Reviewer's Table 3.11 summarizes the survival analysis results. This reviewer confirmed the sponsor's results. The relative risk favoring the Taxol treatment was statistically significant using the logrank test.

Reviewer's Table 3.11: Summary of Survival Data

	Taxol/ Cisplatin	Cyclophosphamide/ Cisplatin
Total Patients	196	214
# of Deaths	114 (58%)	152 (71%)
# of Censored	82 (42%)	62 (29%)
Median Time (months) 95% CI	35.2 29.6 - 39.6	24.2 20.6 - 29.0
Logrank Test: p=0.0002 Relative Risk with 95%CI: 0.630 (0.494 - 0.805)		

The sponsor investigated the effect of possible baseline prognostic factors on survival time. Three approaches were examined: a univariate, forward selection, and stepwise selection. This reviewer confirmed the sponsor's results reported in Tables 36 and 37. The residual diameter variable was selected as a potential prognostic factor from these approaches.

This reviewer investigated the effect of the residual diameter variable on patients' survival. Reviewer's Appendices 7, 8, and 9 summarize results within each strata. A stratified logrank test across the three different cut-off criteria (<= 5 cm vs. > 5 cm, <= 4 cm vs. > 4 cm, and <= 3 cm vs. > 3 cm) is also included.

Reviewer's APPENDIX 7 shows the results using the 5 cm cut-off criterion. The treatment effect (relative risk) favoring the Taxol treatment was statistically significant and marginally

significant in the lower and upper strata, respectively. Reviewer's Figures 1 and 2 show the Kaplan-Meier curves for survival in the lower stratum (<= 5 cm) and in the upper stratum (> 5 cm). Notice that the sample size in each stratum was not balanced equally.

Reviewer's APPENDIX 8 shows the results using the 4 cm cut-off criterion. The treatment effect (relative risk) was statistically significant in the lower stratum favoring the Taxol treatment and not statistically significant in the upper stratum. The relative risk was less than 1 in both strata. Reviewer's Figures 3 and 4 show the treatment effect in each stratum.

Reviewer's APPENDIX 9 shows the results using the 3 cm cut-off criterion. We observed a similar treatment effect as in the 4 cm cut-off criterion. Reviewer's Figures 5 and 6 show the treatment effect in each stratum.

Considering these results from the three different cut-off criteria, we see that the treatment effect was statistically significant in the lower stratum favoring the Taxol arm and that the treatment effect in the upper stratum was marginally statistically significant or not statistically significant across the three criteria. The estimated relative risk in both strata was less than 1 across all three categories. Therefore, this reviewer considered the residual diameter to be an effect modifier.

IV. Conclusion:

Three endpoints, tumor response rate, time to progression, and survival time, were investigated in this review. This reviewer found that the treatment difference between the two arms favored the Taxol treatment with respect to complete response, time to progression, and survival (Reviewer's Tables 3.7, 3.8, 3.9, and 3.11)

This reviewer investigated the effect of potential prognostic factors on the three endpoints by a univariate analysis, forward and stepwise logistic and Cox regression analyses. This reviewer confirmed the results reported by the sponsor.

This reviewer investigated the effect of the selected prognostic factor of residual diameter in all three endpoints and applied different cut-off criteria for sensitivity analyses (<= 3 cm vs. > 3 cm, <= 4 cm vs. > 4 cm, and <= 5cm vs. > 5 cm). In all three

endpoints, this reviewer observed that there existed a larger treatment effect in the lower stratum of the Taxol treatment group and a small treatment effect in the upper stratum using the three different cut-off criteria. Therefore, this reviewer concluded that the residual diameter was an effect modifier. This indicates that we could expect a stronger treatment effect in the Taxol treatment arm if most of the tumor is removed at operation.

This reviewer believes that treatment with Taxol is effective in this population.

/S/

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Mathematical Statistician

Concur: Dr. Koutsoukos
Dr. Chi

4/3/98

04/03/98

cc:
NDA#20-262/SE1-026
HFD-150 / Division File
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HFD-710 / Dr. Chi
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HFD-710 / Dr. Takeuchi
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Takeuchi / 02-26-98/ WP6.1 - Taxol_Review
This review consists of 13 pages of text, 9 Appendices (Appendix 1-9) and 6 Figures (Figures 1-6).

Reviewer's APPENDIX 1: Complete Response Rate in Measurable and Measurable/Evaluable Patients for Each Residual Diameter Category (<= 5 cm vs > 5cm)

Measurable Patients (N=240)				
Residual Diameter				
	<= 5 cm		> 5 cm	
	Taxol	Cys*	Taxol	Cys*
Responders (30.0%)	32 (45.7%)	26 (29.2%)	8 (18.6%)	6 (15.8%)
Nonresponders (70.0%)	38 (52.3%)	63 (70.3%)	35 (81.4%)	32 (84.2%)
	Odds Ratio: 2.04 95% CI:(1.06 - 3.94) p = 0.033		Odds Ratio: 1.22 95% CI: (0.38 - 3.89) p = 0.738	
Measurable and Evaluable Patients (N=219)				
Residual Diameter				
	<= 5 cm		> 5 cm	
	Taxol	Cys*	Taxol	Cys*
Responders (32.9%)	32 (50.0%)	26 (31.0%)	8 (21.1%)	6 (18.2%)
Nonresponders (67.1%)	32 (50.0%)	58 (69.0%)	30 (78.9%)	27 (81.8%)
	Odds Ratio: 2.231 95% CI: (1.14 - 4.37) p = 0.020		Odds Ratio: 1.200 95% CI: (0.37 - 3.91) p = 0.76	

*: Cys stands for Cyclophosphamide/Cisplatin

Reviewer's APPENDIX 2: Complete Response Rate in Measurable and Measurable/Evaluable Patients for Each Residual Diameter Category (<= 4 cm vs > 4cm)

Measurable Patients (N=240)				
Residual Diameter				
	<= 4 cm		> 4 cm	
	Taxol	Cys*	Taxol	Cys*
Responders (30.0%)	25 (43.1%)	18 (26.9%)	15 (30.0%)	14 (23.3%)
Nonresponders (70.0%)	33 (56.9%)	49 (73.1%)	40 (70.0%)	46 (76.7%)
	Odds Ratio: 2.06 95% CI:(0.91 - 4.37) p = 0.0584		Odds Ratio: 1.23 95% CI: (0.53 - 2.87) p = 0.627	
Measurable and Evaluable Patients (N=219)				
Residual Diameter				
	<= 4 cm		> 4 cm	
	Taxol	Cys*	Taxol	Cys*
Responders (32.9%)	25 (46.3%)	18 (28.6%)	15 (31.3%)	14 (25.9%)
Nonresponders (67.1%)	29 (53.7%)	45 (71.4%)	33 (68.7%)	40 (74.1%)
	Odds Ratio: 2.155 95% CI: (1.00 - 4.63) p = 0.049		Odds Ratio: 1.299 95% CI: (0.55 - 3.08) p = 0.55	

*: Cys stands for Cyclophosphamide/cisplatin

Reviewer's APPENDIX 3: Complete Response Rate in Measurable and Measurable/Evaluable Patients for Each Residual Diameter Category (<= 3 cm vs > 3cm)

Measurable Patients (N=240)				
Residual Diameter				
	<= 3 cm		> 3 cm	
	Taxol	Cys*	Taxol	Cys*
Responders (30.0%)	21 (44.7%)	10 (22.2%)	19 (28.8%)	22 (26.8%)
Nonresponders (70.0%)	26 (55.3%)	35 (77.8%)	47 (71.2%)	60 (73.2%)
	Odds Ratio: 3.06 95% CI:(1.21 - 7.73) p = 0.0185		Odds Ratio: 1.14 95% CI: (0.55 - 2.40) p = 0.720	
Measurable and Evaluable Patients (N=219)				
Residual Diameter				
	<= 3 cm		> 3 cm	
	Taxol	Cys*	Taxol	Cys*
Responder (32.9%)	21 (48.8%)	10 (23.8%)	19 (32.2%)	22 (29.3%)
Nonresponder (67.1%)	22 (51.2%)	32 (76.2%)	40 (67.8%)	53 (70.7%)
	Odds Ratio: 2.83 95% CI: (1.14 - 7.01) p = 0.025		Odds Ratio: 1.10 95% CI: (0.54 - 2.27) p = 0.79	

*: Cys stands for Cyclophosphamide/cisplatin

Reviewer's APPENDIX 4: Relative Risk Rate in Time to Progression for Measurable Disease Patients for Each Residual Diameter Category

Measurable Disease Patients (N=240)					
Dia1=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
159	141	18	0.784	0.561 - 1.097	0.156
Dia1=1					
81	72	9	0.571	0.354 - 0.920	0.0214
Dia2=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
125	113	12	0.670	0.459 - 0.978	0.0380
Dia2=1					
115	100	15	0.755	0.509 - 1.120	0.163
Dia3=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
92	82	10	0.631	0.404 - 0.983	0.042
Dia3=1					
148	131	17	0.771	0.546 - 1.090	0.141

RR: Relative risk (Taxol vs the control)
Dia1: <= 5 cm vs > 5 cm
Dia2: <= 4 cm vs > 4 cm
Dia3: <= 3 cm vs > 3 cm

Reviewer's APPENDIX 5: Relative Risk Rate in Time to Progression in Non-measurable Disease Patients for Each Residual Diameter Category

Non-measurable Disease Patients (N=170)					
Dia1=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
140	113	27	0.672	0.463 - 0.975	0.0364
Dia1=1					
30	28	2	0.824	0.371 - 1.832	0.635
Dia2=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
129	104	25	0.639	0.433 - 0.941	0.0233
Dia2=1					
41	37	4	0.814	0.418 - 1.607	0.562
Dia3=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
118	95	23	0.611	0.407 - 0.918	0.0177
Dia3=1					
52	46	6	0.808	0.448 - 1.460	0.481

RR: Relative risk (Taxol vs the control)
Dia1: <= 5 cm vs > 5 cm
Dia2: <= 4 cm vs > 4 cm
Dia3: <= 3 cm vs > 3 cm

Reviewer's APPENDIX 6: Relative Risk Rate in Time to Progression for Each Residual Diameter Category Including All Patients

Dia1=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
299	254	45	0.714	0.557 - 0.915	0.0078
Dia1=1					
111	100	11	0.625	0.417 - 0.935	0.021
Dia2=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
254	217	37	0.643	0.491 - 0.842	0.0013
Dia2=1					
156	137	19	0.792	0.565 - 1.110	0.176
Dia3=0					
Total	**Event**	**Censored**	**RR**	**95%CI**	**P-value**
210	177	33	0.618	0.458 - 0.834	0.0016
Dia3=1					
200	177	23	0.795	0.591 - 1.071	0.131

RR: Relative risk (Taxol vs the control)
Dia1: <= 5 cm vs > 5 cm
Dia2: <= 4 cm vs > 4 cm
Dia3: <= 3 cm vs > 3 cm

Reviewer's Appendix 7 : Summary of Survival Analysis with Respect to the Residual Diameter Variable (<= 5 cm vs > 5 cm)

	<=5 cm			> 5 cm		
	Total SS	Failure	Censored	Total SS	Failure	Censored
Cyclo*	156	108	48	58	44	14
Taxol	143	78	65	53	36	17
Total	299	186	113	111	80	31
	Median (Month)	95% CI		Median	95%CI	
Cyclo*	24.80	22.28 - 31.15		17.80	13.83 - 28.98	
Taxol	37.91	34.33 - 47.74		24.61	19.09 - 37.52	
Relative Risk	0.610			0.665		
95% CI	0.455 - 0.817			0.424 - 1.043		
p-value	0.0009			0.0758		
p-value (logrank)	0.0008			0.0738		
	Stratified Logrank: Test of Homogeneity: p=0.0035 combined p-value**:0.0002					

*Cyclo stands for cyclophosphamide/cisplatin treatment.
**Combined p-value was obtained using the stratified logrank test. A homegeneity test indicates heterogeneity of the treatment effect between strata, which implies that we should not combine the two categories.

Reviewer's Appendix 8 : Summary of Survival Analysis with Respect to the Residual Diameter variable (<= 4 cm vs > 4 cm)

	<=4 cm			> 4 cm		
	Total SS	Failure	Censored	Total SS	Failure	Censored
Cyclo*	129	91	38	85	61	24
Taxol	125	66	59	71	48	23
Total	254	157	97	156	109	47
	Median (Month)	95%CI		Median (Month)	95%CI	
Cyclo*	24.80	21.19 - 31.15		23.06	16.00 - 29.60	
Taxol	38.80	35.08 - 48.00		26.81	21.68 - 37.26	
Relative Risk	0.552			0.781		
95% CI	0.401 - 0.760			0.534 - 1.142		
p-value	0.0003			0.201		
p-value (logrank)	0.0002			0.200		
	Stratified Logrank: Test of Homogeneity: p=0.0162 combined p-value**:0.0003					

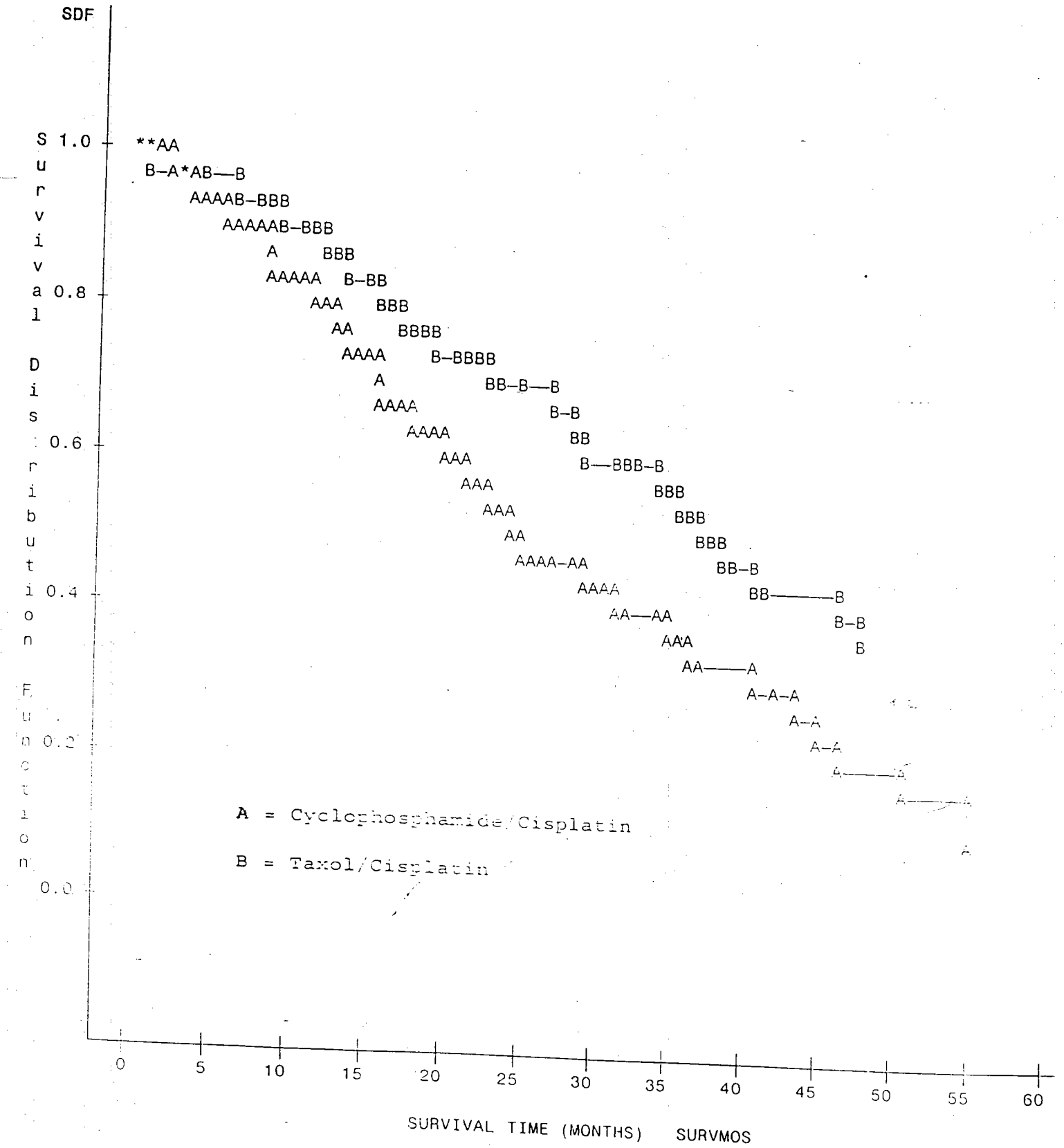
*Cyclo stands for cyclophosphamide/cisplatin treatment.
**Combined p-value was obtained using the stratified logrank test. A homegeneity test indicates heterogeneity of the treatment effect between strata, which implies that we should not combine the two categories.

Reviewer's Appendix 9 : Summary of Survival Analysis with Respect to the Residual Diameter variable (<= 3 cm vs > 3 cm)

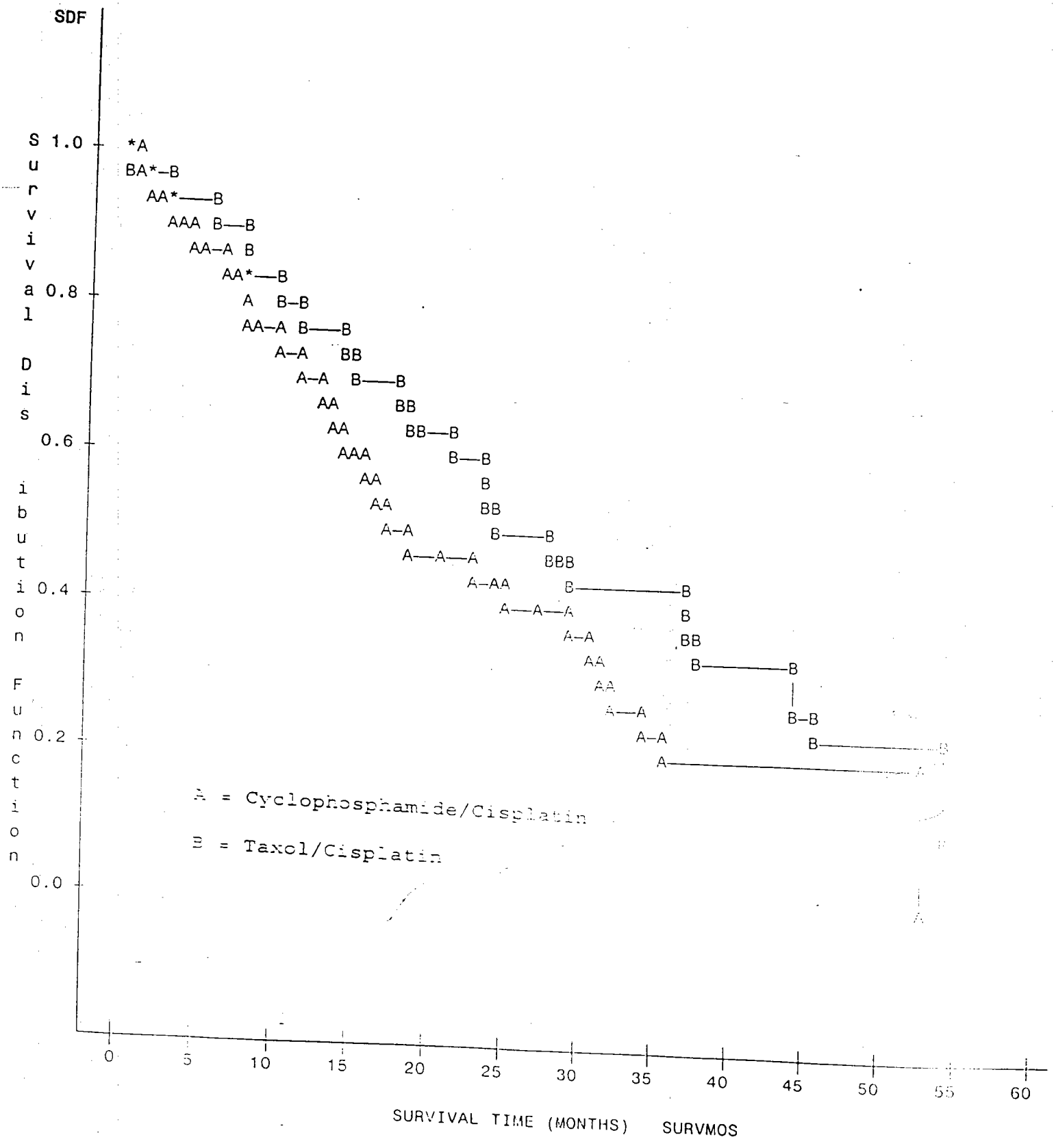
	<=3 cm			> 3 cm		
	Total SS	Failure	Censored	Total SS	Failure	Censored
Cyclo*	103	72	31	111	80	31
Taxol	107	56	51	89	58	31
Total	210	128	82	200	138	62
	Median (Month)	95%CI		Median (Month)	95%CI	
Cyclo*	25.30	21.19 - 31.15		23.06	16.99 - 29.60	
Taxol	38.60	35.02 - .		28.94	23.89 - 37.52	
Trt.Effect	0.551			0.741		
95% CI	0.388 - 0.784			0.528 - 1.041		
p-value	0.0009			0.0837		
p-value (logrank)	0.0008			0.0825		
	Stratified Logrank: Homogeneity: p=0.0147 combined p-value**: 0.0004					

*Cyclo stands for cyclophosphamide/cisplatin treatment.
**Combined p-value was obtained using the stratified logrank test. A homegeneity test indicates heterogeneity of the treatment effect between strata, which implies that we should not combine the two categories.

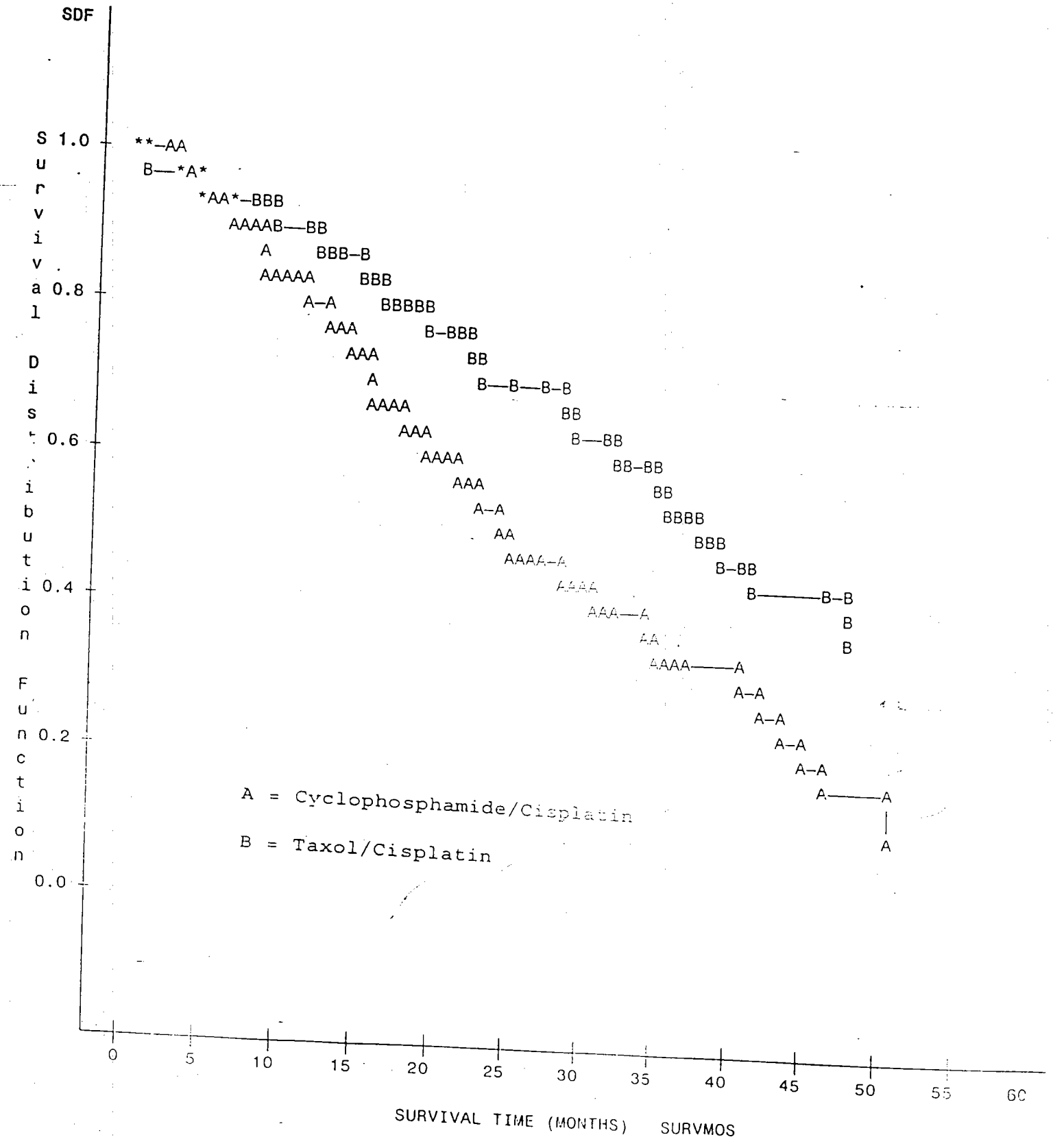
Reviewer's Figure 1: Kaplan-Meier Curves for <= 5 cm Residual Diameter



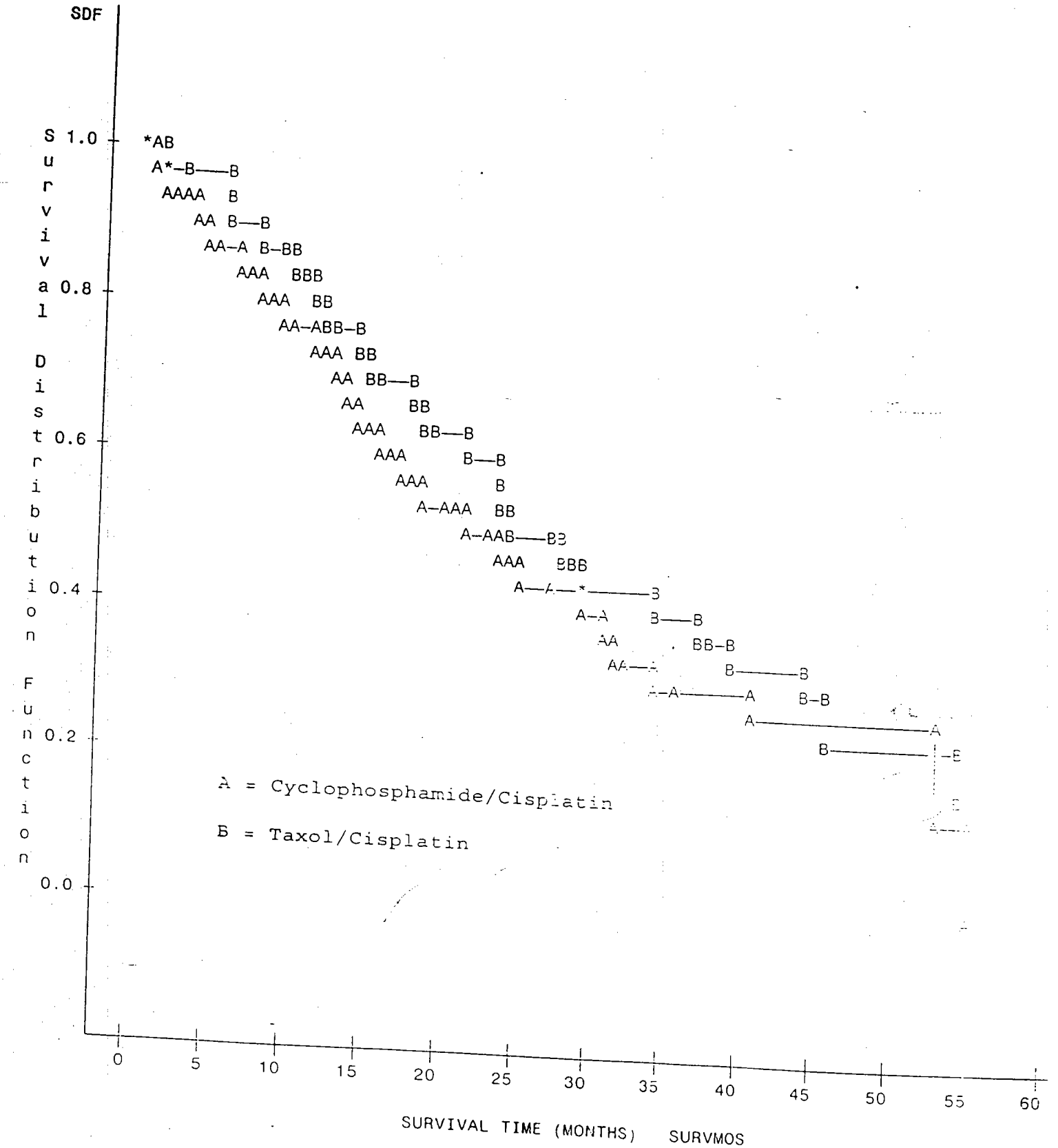
Reviewer's Figure 2: Kaplan-Meier Curves for > 5 cm Residual Diameter



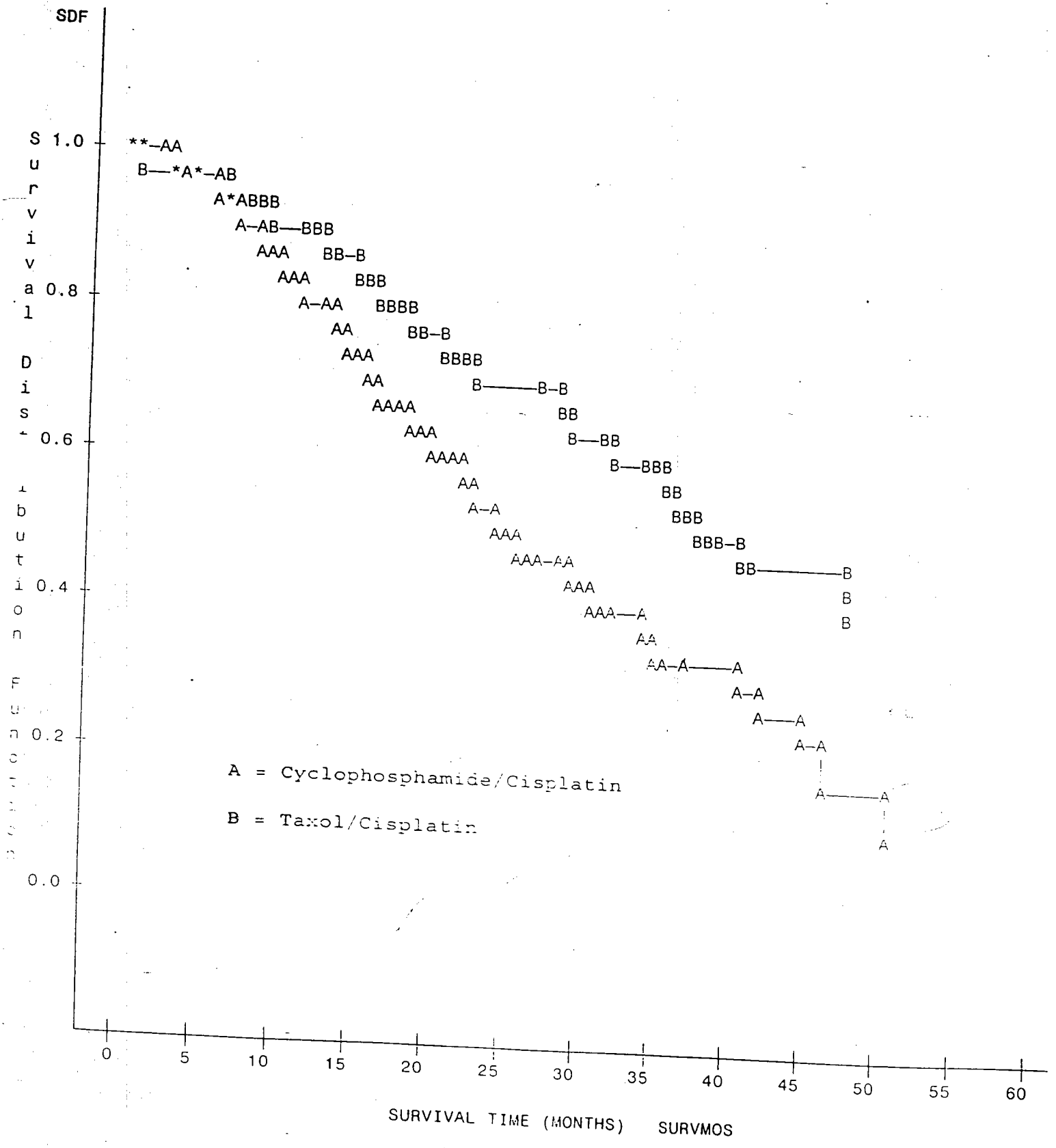
Reviewer's Figure 3: Kaplan-Meier Curves for <= 4 cm Residual Diameter



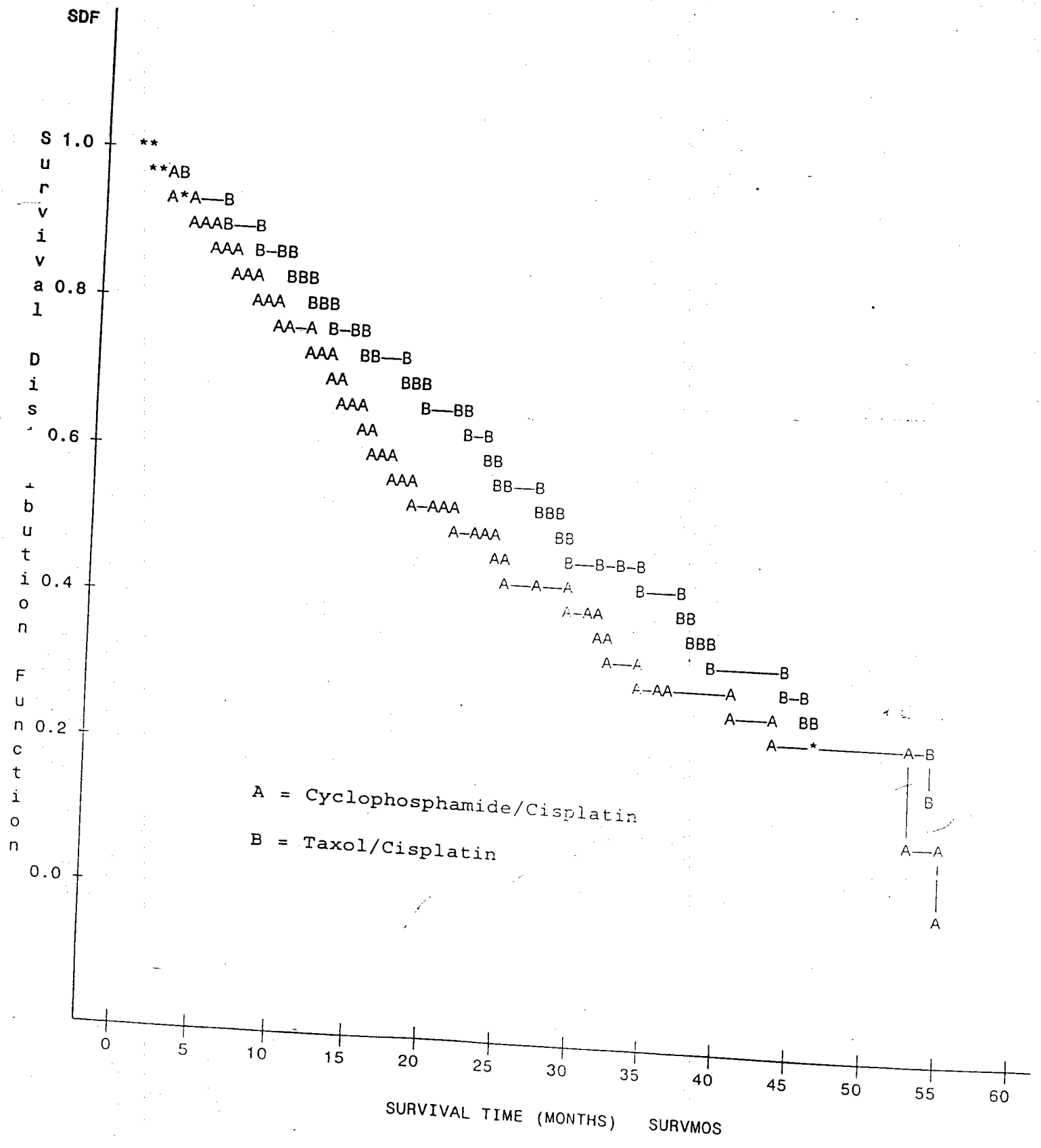
Reviewer's Figure 4: Kaplan-Meier Curves for > 4 cm Residual Diameter



Reviewer's Figure 5: Kaplan-Meier Curves for <= 3 cm Residual Diameter



Reviewer's Figure 6: Kaplan-Meier Curves for > 3 cm Residual Diameter



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-262/S-026, 027, 028

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

SPILLMAN

FEB - 3 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

sNDA: 20-262/026 Submission Date: October 7, 1997

Paclitaxel (Taxol®) Injection: 30 mg/5 mL and 100 mg/16.7 mL Multidose Vials.

Sponsor: Bristol-Myers Squibb
Wallingford, CT

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: Efficacy Supplement

BACKGROUND

This efficacy supplement to NDA 20-262 is for the use of Taxol® /cisplatin combination in patients with advanced ovarian cancer. Taxol® as monotherapy is currently approved for the treatment of metastatic carcinoma of the ovary after failure of the first-line or subsequent chemotherapy and for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Approval for this supplemental NDA is based on data from one randomized, multicenter, Phase III trial (CA139-022) comparing the efficacy/safey of Taxol® /cisplatin combination with a standard combination of cyclophosphamide/cisplatin in patients with advanced ovarian cancer (n=410). The experimental therapy (i.e.,Taxol® /cisplatin) consists of 135 mg/m^2 paclitaxel infused over 24 hours followed by 75 mg/m^2 cisplatin infused at a rate of 1 mg/minute. The standard therapy (i.e., cyclophosphamide/ cisplatin) consists of 75 mg/m^2 cisplatin infused at a rate of 1 mg /minute and concomitant intravenous administration of 750 mg/m^2 cyclophosphamide (See Attachment 1).

This submission contains no additional information on the pharmacokinetics of paclitaxel. The potential for drug interaction between paclitaxel and cisplatin has been studied before and the result of 33 % decrease in paclitaxel clearance when it was administered following cisplatin is incorporated in the current package insert for Taxol® (See Attachment 2).

COMMENTS:

1. The sponsor is requested to submit the study report/results of the effect of hepatic dysfunction on paclitaxel disposition to the Agency for review.

sponsor response sent 3.10.98

2. The revised labeling statement on page 3:

should remain the same as the original statement in current package insert:

RECOMMENDATION:

Please forward Comments 1 and 2 to the sponsor.

/S/

Reviewer: Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT /S/ 2/3/98

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

cc: sNDA: 20-262/024
HFD-150/Division file
HFD-150/Spillman, Williams, Honig
HFD-850/Lesko
HFD-860/Malinowski, Mehta, Rahman, Ibrahim
CDR (B. Murphy)

Attachment 1

TAXOL Protocol CA139-022

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

SUMMARY

Title of Study: Phase III Randomized Study of Cyclophosphamide (NSC 26271) and Cisplatin (NSC 119875) versus TAXOL (NSC 125973) and Cisplatin (NSC 119875) in Patients with Suboptimal Stage III and Stage IV Epithelial Ovarian Carcinoma. Gynecologic Oncology Group Protocol No. 111. Bristol-Myers Squibb Protocol No. CA139-022.

Investigator, Location of Trial: Multicentric trial conducted by the Gynecologic Oncology Group involving 86 institutions in the United States of America. Principal Investigator, William P. McGuire, M.D.

Publication: McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, Clarke-Pearson DL, Davidson M. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with Stage III and Stage IV ovarian cancer. New England Journal of Medicine, 1996; 334 (1), 1-6.

McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Look KY, and Davidson M. TAXOL and cisplatin (TP) improves outcome in advanced ovarian cancer (AOC) as compared to cytoxan and cisplatin (CP). Proceedings of ASCO 1995; 14 (Abstract #771).

McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, Partridge EE, et al. A phase III trial comparing cisplatin/cytoxan (PC) and cisplatin/TAXOL (PT) in advanced ovarian cancer (AOC) Proceedings of ASCO 1993; 12 (Abstract #808).

Study Period: Patients were accrued from April 13, 1990 to March 2, 1992.

Clinical Phase: Phase III

Objectives: The present study was undertaken to compare, in a randomized setting, the objective response rate, time to progression, survival, and the incidence and severity of adverse events of TAXOL/cisplatin with a standard regimen in patients with suboptimal Stage III and Stage IV ovarian cancer.

Study Design: This was a prospective multicentric study of two platinum-based chemotherapy regimens, a standard regimen with cyclophosphamide and an experimental regimen with TAXOL. Treatments were randomly assigned with equal probability after stratification according to institution and the clinical measurability of disease. The study

was conducted by the Gynecologic Oncology Group under the IND of the National Cancer Institute, USA.

Number of Patients: Four hundred ten patients were randomized into the trial. One patient in the cyclophosphamide died before receiving study medication.

Diagnosis and Eligibility: Women with pathologically verified FIGO Stage III epithelial ovarian cancer after suboptimal surgery (> 1 cm residual mass) or FIGO Stage IV disease were eligible. They could have clinically measurable or nonmeasurable disease. Eligibility also required no previous chemotherapy or radiation for ovarian cancer.

Test Product Formulation: TAXOL was supplied by the National Cancer Institute as a concentrated sterile solution, 6 mg/ml in a 5 ml ampule (30 mg/ampule) in polyoxyethylated castor oil (Cremophor® EL) 50% and dehydrated alcohol USP 50%.

Dose, Route, Schedule and Sequence of Administration: The standard therapy consisted of an intravenous infusion of cisplatin, 75 mg/m², given at a rate of approximately 1 mg/minute and the concomitant administration of cyclophosphamide, 750 mg/m² intravenously. The experimental therapy consisted of TAXOL, 135 mg/m², administered as a continuous intravenous infusion over 24 hours followed by an intravenous infusion of cisplatin, 75 mg/m² at a rate of 1 mg/minute. Prior to each TAXOL administration patients were premedicated with a 3-drug regimen consisting of an orally administered steroid followed by intravenous injections of H_1 and H_2 antihistamines. Both the standard and experimental therapies were repeated every 21 days or when hematologic and non-hematologic recovery was documented. Dose reductions based on Grade IV hematologic toxicity were required for cyclophosphamide and TAXOL. No reduction in the cisplatin dose was planned. Lot numbers of TAXOL used for this study were: LIF 19, 89-219, 89-220R, 90-214R, 90-232, 90-236, 90-241, 90-241A, 91-216, S91G044M, S91J048M (Mayaguez lot H1F29), S91J048M-C.

Treatment Duration: Patients were to receive a total of six cycles of therapy unless there was progression of disease or toxicity. Patients who were clinically free of disease were then scheduled for a second look surgery.

Statistical Considerations: The study was powered (n=360) to detect an increase of 40% in the median time to progression based on a median of 10.3 months and 14.4 months for patients with measurable and non-measurable disease respectively. This sample size was also sufficient to detect a 19% increase in clinical complete response rate in the experimental arm, based on a 30% complete response rate among patients with measurable disease treated with cyclophosphamide and cisplatin.

Criteria for Evaluation: The critical endpoints consisted of: tumor response, based on shrinkage of measurable or evaluable lesions, pathological response, duration of clinical and pathological response, time to progression, and survival. Patients were also monitored for adverse reactions. Performance status and ancillary neurologic assessment were used as indicators of quality of life.

Patient Characteristics: The diagnosis of invasive ovarian carcinoma was confirmed in 392 patients (96%), with serous adenocarcinoma in 74% of patients in the TAXOL arm and 64% in the cyclophosphamide arm ($p = 0.025$). All other pretreatment characteristics were well balanced between the two arms. The median age across both arms was 59 years. Performance status was ≤ 1 at entry in 84% of the patients. At the time of initial surgery, Stage III and Stage IV disease was noted in 271 patients (66%) and 138 patients (34%), respectively. For the 240 patients with measurable disease, the most common sites of disease were pelvis (43%) and abdomen (34%). CT scans were used in 70% of the patients to evaluate tumor responses. Pleural effusions (51%) and ascites (38%) were the most common disease sites in the 170 patients with nonmeasurable disease.

Number of Courses Administered, Dose Reductions, Dose Delays and Dose Intensity: There were 1074 courses of TAXOL/cisplatin administered to 196 patients; and 1145 courses of cyclophosphamide/cisplatin were given to 213 patients. The median number of courses administered in both arms was six (range, 1-6 courses). The overall frequency of dose reductions was 28% and 22% for the TAXOL and cyclophosphamide arms, respectively ($p = 0.003$). However, treatment delays were less frequent in the TAXOL arm, 21% of courses, compared to 55% of courses in the cyclophosphamide arm ($p < 0.001$). In the TAXOL arm the median number of days to the next course was 21 days and in the cyclophosphamide arm 28 days. Hematologic toxicity (neutropenia) was the principal reason for dose reductions and delays. Overall, dose reductions and delays resulted in a significantly reduced treatment intensity for the cyclophosphamide arm as compared to the TAXOL arm ($p < 0.001$).

Efficacy: Two hundred and forty patients had measurable disease and were included in the analysis of clinical response. All 410 randomized patients were included in the analysis of pathological response, time to progression and survival.

Clinical response: In the TAXOL arm there were 40 complete responses (35%) and 28 partial responses (25%) for an overall clinical response rate of 60% (68/113). In the cyclophosphamide arm, 32 patients achieved a complete response (25%) and 32 patients had a partial response (25%) for an overall clinical response rate of 50% (64/127). There was no statistically significant difference between the treatment arms in overall clinical response ($p = 0.153$) or complete clinical response ($p = 0.092$). After adjustment for a number of potential prognostic factors using logistic regression, no factor had a

statistically significant effect on the likelihood of achieving a clinical response.

Time-to response: The median time to clinical response for patients receiving the combination of TAXOL/cisplatin was 7.9 weeks versus 8.6 weeks for patients receiving cyclophosphamide/cisplatin.

Duration of response: The median duration of response for clinical responders was 15.8 months for patients on the TAXOL arm and 16.4 for patients on the cyclophosphamide arm. For complete responders, the median duration was 14.9 months on the TAXOL arm and 15.7 on the cyclophosphamide arm.

Pathological response: In the TAXOL arm there were 42 pathological complete responses (21%) and 25 patients with microscopic residual disease (13%) for a pathological response rate of 34% (67/196). In the cyclophosphamide arm, 35 patients achieved a pathological complete response (16%) and eight patients had microscopic residual disease (4%) for a pathological response rate of 20% (43/214). The difference between the two arms was statistically significant for pathological response including microscopic residual disease ($p = 0.001$), but not for complete pathological response ($p = 0.196$). An analysis of prognostic factors revealed that only disease stage seemed to have an impact on pathological response. After adjustment for this selected factor and stratum using logistic regression, the treatment effect was unchanged.

Duration of pathological response: The median duration of pathological response for patients who had achieved a pathological complete response or had residual microscopic disease was 28.5 months in the TAXOL arm and 17.5 months in the cyclophosphamide arm. For pathological complete responders, the median duration was 32.2 months on the TAXOL arm and 16.5 on the cyclophosphamide arm.

Time to progression: Disease had progressed in 354 patients, 163/196 (83%) on the TAXOL arm and 191/214 (89%) on the cyclophosphamide arm. Time to progression or median duration of disease control was 16.6 months for patients in the TAXOL arm as compared to the median duration of 13.0 months in the cyclophosphamide arm. This difference was statistically significant ($p = 0.0008$). The difference observed in time to progression in the TAXOL arm corresponds to a reduction in the risk of tumor progression by 30%. After adjusting for selected prognostic factors and for stratum using Cox regression, the treatment differences remained significant ($p = 0.001$).

Survival: A total of 266 patients, 114/196 (58%) on the TAXOL arm and 152/214 (71%) on the cyclophosphamide arm, had died at the time of analysis. The median survival for those on the TAXOL arm was 35.5 months and for those on the cyclophosphamide arm 24.2 months. This difference was statistically significant ($p = 0.0002$). The analysis of

prognostic factors revealed that only the residual tumor diameter had an impact on survival. After adjustment for this selected factor and stratum using Cox regression, the treatment effect remained significant ($p = 0.0002$).

Safety Results: Clinical signs and symptoms on study as well as hemograms and serum chemistries were used to determine safety. A total of 409 patients were evaluable for safety: 196 patients on the TAXOL arm and 213 patients on the cyclophosphamide/ cisplatin arm. Adverse events resulted in the discontinuation of 27 patients from the study, 12 patients in the TAXOL arm and 15 on the cyclophosphamide arm. Ten patients died within 30 days of the last study dose, six on the TAXOL and four on the cyclophosphamide arm. Three patients died as a result of treatment complications, one patient on the TAXOL arm and two on the cyclophosphamide arm.

Neutropenia (worst course) was almost universally observed in the TAXOL/cisplatin arm (96% of the patients) but was usually of short duration (< 7 days) and without clinical consequences in most cases. In the cyclophosphamide arm neutropenia was seen in 92% of the patients. CTC Grade III/IV neutropenia was seen in 92% of the patients in the TAXOL arm and 80% of the patients who received cyclophosphamide ($p = 0.001$). In the TAXOL arm, there were 54 episodes of infections reported in 41 patients (5% of the courses); there were 46 infectious episodes reported in 32 patients (4% of the courses) in the cyclophosphamide arm. Febrile neutropenia occurred in 35 courses in the TAXOL arm compared to nine courses in the cyclophosphamide arm ($p < 0.001$).

Anemia was observed in 87% of the patients at a similar frequency in both arms and was mostly Grade I or II.

Thrombocytopenia was less frequently observed than neutropenia and occurred at a similar frequency in both the TAXOL and cyclophosphamide arms ($p = 0.434$) for the worst course. For the worst course of therapy, 26% of TAXOL treated patients experienced thrombocytopenia (10% Grade III/IV) and 30% of patients who had received cyclophosphamide had thrombocytopenia (9% Grade III/IV).

Peripheral neuropathy, mostly Grade I or II, was observed in 25% of patients treated with TAXOL/cisplatin and 20% of patients treated with cyclophosphamide/cisplatin ($p = 0.282$). Grade III peripheral neuropathy developed in five TAXOL treated patients.

Arthralgia/myalgia was reported in 9% of patients treated in the TAXOL arm and 2% of the patients in the cyclophosphamide arm ($p = 0.002$). One TAXOL treated patient had Grade III symptoms.

Hypersensitivity/allergic reactions were observed in 15 patients (8%) on the TAXOL arm and three patients (1%) on the cyclophosphamide ($p = 0.003$). Six patients (3%) on the TAXOL arm had study drug infusions discontinued for hypersensitivity reactions.

Nausea and vomiting occurred frequently in both arms and was generally mild to moderate in severity. Grade III/IV nausea and vomiting was reported in 10% of the patients in the TAXOL arm and 11% in the cyclophosphamide arm.

Liver function tests were frequently abnormal but there was no difference between the two treatment arms.

Cardiovascular events occurred in 27 % of patients in the TAXOL arm and 7% in the cyclophosphamide arm ($p = 0.001$). Most were Grade I and II events detected during continuous cardiac monitoring required for patients receiving TAXOL. There was no difference between the two arms in the incidence of Grade III/IV events.

Renal function was evaluated using serum creatinine results. Grade I and II elevations were common on this study with no significant differences between the two treatment arms.

Other signs and symptoms were uncommon and were generally mild to moderate. Two symptoms occurred in more than 10% of patients on either arm. *Alopecia* was reported in 107 patients in the TAXOL arm (55%) and 79 patients in the cyclophosphamide arm (37%; $p < 0.001$). *Asthenia* was noted in 33 patients in the TAXOL arm (17%) and in 21 patients in the cyclophosphamide arm (10%; $p = 0.041$).

Quality of Life: Among patients who had both a baseline performance status and at least one performance status reported on treatment, there was no significant difference between the two arms in time or number of courses to deterioration of performance status. A neurologic assessment was performed on a subset of patients and only at selected sites by the Gynecologic Oncology Group. This consisted of a patient self-report questionnaire and a nurse administered neurologic assessment. There was a trend for a worse total score in the patients treated in the TAXOL arm as compared to baseline and as compared to the cyclophosphamide arm. As the data originated from a subset of patients using a non-validated instrument no formal comparison was made.

Conclusion: In this randomized Phase III trial in patients with untreated advanced ovarian cancer, TAXOL was shown to achieve superior clinical and pathological response rates, improved time to progression and prolonged survival time when compared to standard therapy. The 11.3 months increase in median survival is a significant improvement in treatment for this patient population.

This trial revealed that combining TAXOL and cisplatin does not reduce the ability to deliver full doses of cisplatin. Overlapping toxicities did not necessitate dose reductions or delays of cisplatin. The dose intensity of the TAXOL/cisplatin arm was significantly higher than that of the cyclophosphamide/cisplatin arm.

The safety profile of TAXOL single-agent is well documented from both clinical trials and marketed use of the drug. In this trial, the TAXOL combination was associated with an increased frequency of severe neutropenia compared to the standard arm which was easily managed and had no impact on the timing of dose administration. There was no difference between the two arms in the overall incidence of peripheral neurotoxicity, although there was a higher incidence of severe peripheral neurotoxicity on the TAXOL/cisplatin arm. Severe cardiac events were not different between the two arms. Fever, alopecia, asthenia, arthralgia/myalgia and allergic reactions were also more frequent in the TAXOL arm. Severe events were rare and occurred on both arms at the same frequency.

This randomized phase III trial provides unquestionable evidence of superiority for a TAXOL-based regimen over standard therapy. Therefore, the administration of TAXOL, given a dose of 135 mg/m^2 over 24 hours in combination with cisplatin 75 mg/m^2, should be recommended for the primary treatment of patients with advanced carcinoma of the ovary.

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