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**Background Information  
Regarding Accelerated Approval of  
DOXIL<sup>®</sup> in Ovarian Cancer**

**Phase IV Commitments**

**DOXIL<sup>®</sup> (doxorubicin HCl liposome injection)  
NDA No. 50-718**

Oncologic Drugs Advisory Committee Meeting  
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# **BACKGROUND INFORMATION REGARDING ACCELERATED APPROVAL OF DOXIL® IN OVARIAN CANCER PHASE IV COMMITMENTS**

## **1. SUMMARY**

DOXIL® (doxorubicin HCl liposome injection) received accelerated approval 28 June 1999 for the treatment of patients with refractory metastatic carcinoma of the ovary. This approval was based on objective tumor response rates observed in three non-randomized phase II trials. Study 30-49 was ongoing at the time of the approval of the ovarian cancer indication and is currently in its follow up phase for an ITT survival analysis. A subsequent phase IV commitment trial conducted by the Southwest Oncology Group is ongoing.

To date, more than 17,000 women in the United States with relapsed or recurrent ovarian cancer have received treatment with this drug product (doxorubicin HCl liposome injection). More than 45 manuscripts have been published regarding the use of doxorubicin HCl liposome injection in the treatment of ovarian carcinoma.

## **2. GENERAL INFORMATION**

**Drug Name:** DOXIL® (doxorubicin HCl liposome injection)

**Indication:** DOXIL is indicated for the treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory disease is defined as disease that has progressed while on treatment, or within 6 months of completing treatment.

This indication is based on objective tumor response rates. No results are available from controlled trials that demonstrate a clinical benefit resulting from this treatment, such as improvement in disease-related symptoms or increased survival.

**Accelerated Approval Date:** 28 June 1999

## **3. INTRODUCTION**

### **3.1. Overview of Ovarian Cancer**

Epithelial ovarian cancer is the most frequent cause of death due to gynecologic malignancies and the fifth most common cause of cancer death

in women. More than 23,100 new cases are diagnosed in the US annually, with approximately 14,000 deaths due to ovarian cancer each year. Ovarian cancer is primarily a disease of post-menopausal women; most cases occur in women between 50 and 75 years of age. The incidence of ovarian cancer increases with age and peaks at a rate of 54 per 100,000 in the 75- to 79-year-old age group. Survival strongly correlates with surgical staging, with 5-year survival rates for stages I, II, III, and IV of 74%, 58%, 30%, and 19%, respectively.<sup>1</sup>

The extent of disease in ovarian cancer patients is generally described as either “early-stage” or “late-stage.” Because early-stage ovarian cancer is generally asymptomatic, 75% to 85% of women are first diagnosed with advanced-stage (Stage III and IV) disease.<sup>2,3</sup> For the initial presentation of advanced-stage disease, the standard of care is combined modality therapy, consisting of aggressive surgical debulking followed by platinum-based combination chemotherapy.<sup>4</sup> Response rates of 60%-80% are reported with carboplatin- or cisplatin-based therapy, with complete responses in 30%-50% of patients.<sup>5</sup> As a result of recent Gynecological Oncology Group (GOG) studies, paclitaxel and platinum-containing therapy is considered to be the current standard of care for advanced-stage ovarian cancer.<sup>6</sup> Median survival with current front-line therapy is 38 months and 5-year survival for patients with Stage III and IV disease is 27%.<sup>7</sup> Despite improvements in both response rates and survival with current combination chemotherapies, first-line therapy with platinum and paclitaxel fails in up to 30% of patients. In addition, 55%-75% of responding patients will relapse within 2 years and a subset of these patients will relapse within 6 months. Consequently, there is an unmet medical need for safe and effective drugs after failure of first-line platinum-based chemotherapy.

Platinum-sensitivity, which is defined by response to first-line platinum-based therapy, is predictive of response to subsequent treatment with a platinum-containing regimen. Disease progression during treatment or relapse within 6 months after the last dose of platinum-based treatment denotes “platinum-refractory” disease. Recurrent disease is potentially “platinum-sensitive” if there is a progression-free interval of greater than 6 months after response to first-line platinum-based chemotherapy. With platinum-sensitive disease, there is a 20%-30% chance of responding to retreatment with platinum-based chemotherapy and similar response to non-platinum regimens is likely. In general, a worse prognosis is associated with disease progression during initial chemotherapy, residual bulky disease after

initial therapy, or recurrent disease within 6 months of the last dose of treatment. Moreover, such tumors are much less likely to respond to subsequent cytotoxic chemotherapy regimens.<sup>8,9</sup>

### **3.2. History of Doxorubicin and DOXIL in Ovarian Cancer Treatment**

Doxorubicin has played an important role in the front-line treatment of epithelial ovarian cancer.<sup>10,11</sup> However, doxorubicin has not had a role as a salvage agent for ovarian cancer after platinum-based chemotherapy; response rates have been low and in this setting, toxicity has been substantial. Myelosuppression is a frequent dose-limiting toxicity, and high cumulative doses of doxorubicin are potentially cardiotoxic. Severe acute nausea and vomiting, stomatitis, and esophagitis associated with doxorubicin also may be dose-limiting. In addition, alopecia typically develops and persists throughout treatment.

In an attempt to improve the anti-tumor activity of doxorubicin and to reduce its toxicity, a new formulation of doxorubicin was developed. DOXIL is a formulation of doxorubicin hydrochloride encapsulated in long-circulating STEALTH<sup>®</sup> liposomes for intravenous administration. DOXIL was designed to enhance the efficacy and reduce the dose-limiting toxicities of doxorubicin by altering the plasma pharmacokinetics and tissue distribution of the drug. Because of the slower plasma clearance of DOXIL relative to conventional doxorubicin, the AUC achieved with DOXIL is 2-3 orders of magnitude larger than the AUC for a similar dose of conventional doxorubicin. In contrast to the triphasic pattern of clearance of conventional doxorubicin (approximate mean half-lives of 12 minutes, 3.3 hours, and 30-40 hours), the biphasic disposition of DOXIL has a short first phase (approximately 5 hours) and a prolonged second phase (approximately 55 hours).<sup>12</sup> Several company-sponsored studies have evaluated the safety and efficacy of DOXIL in patients with ovarian cancer: three non-comparative studies (30-22, 30-47 and 30-47E) and two randomized open-label studies (30-49, comparing DOXIL and topotecan, and 30-57, comparing DOXIL and paclitaxel). The final survival analysis for study 30-49 is ongoing. Table 1 lists the DOXIL ovarian cancer studies that have been completed.

**Table 1:** DOXIL/Caelyx\* Clinical Trials in Ovarian Cancer

Study No.	Design	Treatment, Dose in mg/m <sup>2</sup> , Frequency	No. of pts	Study Endpoints
30-22	Phase II, open label study of efficacy and PK in ovarian cancer	50, every 3 weeks, up to 550 mg/m <sup>2</sup>	35	Response rates, time to and duration of response, TTP, survival
30-47	Phase II, noncomparative, multicenter study of DOXIL/CAELYX for advanced epithelial ovarian carcinoma	50, every 4 weeks for 6 cycles	122	Response rates, time to and duration of response, TTP, survival
30-47E	Phase II, noncomparative, multicenter study of DOXIL/ CAELYX for advanced epithelial ovarian carcinoma (European study sites)	50, every 4 weeks for 6 cycles	62	Response rates, time to and duration of response, TTP, survival
30-49	Phase III, randomized, open-label, DOXIL/ CAELYX versus topotecan HCl for epithelial ovarian carcinoma after failure of first-line, platinum-based chemotherapy	50, every 4 weeks vs. topotecan 1.5 mg/m <sup>2</sup> /day x 5 days, every 3 weeks	474	TTP, response rates, time to and duration of response, QOL, survival
30-57	Phase III, open, DOXIL/ CAELYX vs. Taxol <sup>®</sup> for epithelial ovarian carcinoma	50, every 4 weeks; Taxol <sup>®</sup> 175, every 3 weeks	214	TTP, response rates, time to and duration of response, QOL, survival

\* CAELYX is a registered trade name for doxorubicin HCl liposome injection in certain countries outside the US but is manufactured at the same facility as DOXIL.

**Study 30-22:** In this Phase II clinical trial, DOXIL 50 mg/m<sup>2</sup> was administered at 3-week intervals to 35 patients with ovarian cancer that had relapsed after prior treatment with either platinum- or paclitaxel-based regimens. Objective responses were observed in 9 patients (26%), 7 of which were confirmed by tumor measurements on 2 consecutive computed tomography assessments at least 4 weeks apart. The dose-limiting toxicity, PPE, was successfully managed by increasing the dosing interval from 3 to 4 weeks.<sup>13</sup>

**Study 30-47:** The end-of-planned-treatment analysis for this Phase II study included 122 patients with locally advanced or metastatic epithelial ovarian

carcinoma following failure of at least 2, but not more than 3, prior cytotoxic chemotherapy regimens. In this study, DOXIL 50 mg/m<sup>2</sup> was administered at 4-week intervals for 6 cycles or until disease progression or dose-limiting toxicity occurred. Fifty of the 122 patients were refractory to platinum and paclitaxel (double refractory) and 67 were refractory to platinum, paclitaxel and topotecan (triple refractory). One patient was not treated with DOXIL. Objective responses were reported in 16 patients (1 complete response [CR] and 15 partial responses [PR]).

The median time to response was 106 days (15.1 weeks), with a range of 23 to 230 days (3.3 to 32.9 weeks); the median duration of response was 285 days (40.7 weeks), with a range of 45+ to 338 days (6.4+ to 48.3 weeks). The median time to disease progression was 142 days (20.3 weeks), with a range of 5 to 528+ days (0.7 to 75.4 weeks).<sup>13, 14</sup>

**Study 30-47E:** Sixty-two patients with locally advanced or metastatic epithelial ovarian carcinoma refractory to platinum- and taxane-based chemotherapy were enrolled in this international Phase II study. DOXIL 50 mg/m<sup>2</sup> was administered at 4-week intervals for 6 cycles or until disease progression or dose-limiting toxicity. Thirty-two of the 62 patients were double refractory and 11 were triple refractory. Partial responses were reported in 4 (6.5%) of the 62 patients. At the time of study termination, of the remaining 58 patients 5 (8.6%) had unconfirmed partial responses, 16 (27.6%) had stable disease (SD), 22 (37.9%) had disease progression, and response data was not available for the remaining 15 (25.9%) individuals.

The median time to response was 57 days (8.1 weeks), with a range of 53 to 120 days (7.6 to 17.1 weeks); the median duration of response was 124 days (17.7 weeks), with a range of 114+ to 280 days (16.3+ to 40.0 weeks). Median time to disease progression was 81 days (11.6 weeks), with a range of 1+ day to 399 days (0.1 to 57.0+ weeks).

**Study 30-49:** This Phase III randomized multicenter and multinational study compared the efficacy and safety of DOXIL and topotecan in 474 patients with ovarian cancer that recurred after or didn't respond to first-line, platinum-based chemotherapy. Details of this study are outlined in Section 5.1. Comparable efficacy (overall progression-free survival, overall response, and median overall survival) was reported for the two drugs.<sup>15</sup> Analysis of the platinum-sensitive subset observed a statistically significant benefit in progression-free survival for the DOXIL-treated patients (median 28.9 weeks) compared to those treated with topotecan (median 23.9 weeks),

(P = .037). At the time of publication of the manuscript, overall survival was superior for the DOXIL-treated patients (median 108 weeks) compared to the topotecan-treated individuals (median 71.1 weeks) (P = .008).<sup>15</sup>

**Study 30-57:** This Phase III randomized comparative open-label multicenter study compared DOXIL (50 mg/m<sup>2</sup> every 4-weeks) and paclitaxel (175 mg/m<sup>2</sup> q 3 weeks) in 214 patients with taxane-naïve relapsed ovarian cancer following previous treatment with a platinum-containing regimen. Comparable efficacy was reported for DOXIL and paclitaxel-treated patients, with similar overall progression-free survival rates (DOXIL=21.7 weeks compared to paclitaxel=22.4 weeks); the overall incidence of response was 17.8% for DOXIL-treated patients compared to 22.4% for paclitaxel-treated individuals; and median overall survival was 45.7 weeks for DOXIL-treated patients compared to 56.1 weeks for the paclitaxel-treated patients.<sup>16</sup>

#### **4. REGULATORY HISTORY OF DOXIL IN OVARIAN CANCER INDICATION**

On 28 June 1999, DOXIL was granted accelerated approval under the accelerated approval regulations, 21 CFR Subpart H, for the treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory disease is defined as disease that has progressed while on treatment, or within 6 months of completing treatment. The approval was based on a supplemental New Drug Application submission that also contained preliminary data from the ongoing Sequus/ALZA Study 30-49, “A Phase III Randomized, Open-Label, Comparative Study of DOXIL/CAELYX versus Topotecan HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy.”

As part of this accelerated approval, the Sponsor and the FDA agreed that the Sponsor would provide or perform the following:

1. Complete Sequus/ALZA Study 30-49.
2. Following review and discussion of the 30-49 data, if the results demonstrated convincing superiority of DOXIL over topotecan HCl in either time to progression (TTP) or survival, with a supporting trend demonstrated for the other endpoints, this study would likely fulfill the Phase IV requirement for demonstration of clinical benefit. In this case, it was agreed to submit a supplemental NDA within 6 months after discussing the topline results from this analysis with FDA.
3. If the results of study 30-49 do not demonstrate the clinical benefit of DOXIL, it was agreed that a protocol would be submitted for a study



designed to demonstrate the clinical benefit of DOXIL in patients with ovarian cancer as well as a proposed timetable for completion and submission of the study.

The preliminary results from the first of two planned analyses of Study 30-49 were submitted to the FDA on 13 July 1999. The first analysis, performed after 241 patients had been enrolled in the study, did not reveal a statistically significant difference in overall survival and TTP. The Sponsor agreed to conduct a second analysis (end of planned treatment) as per the protocol by 31 March 2000. This end of planned treatment analysis was based on the results from all patients enrolled as of 3 March 1999 and a database cut-off date of 3 September 1999. On 21 April 2000, the Sponsor submitted a summary of the 30-49 data (end of treatment analysis), which was provided to the FDA for a 29 June 2000 meeting. While there was no overall difference in TTP, there was a statistically significant trend in survival favoring DOXIL in the platinum-sensitive group. It was agreed with the FDA that the Sponsor would continue follow-up of patients from the 30-49 study and perform one additional survival analysis. Based upon the FDA's guidance during the 29 June 2000 meeting, the Sponsor amended the protocol (amendment #3) to include this additional survival analysis.

Pending final survival data for study 30-49, it was agreed with the FDA to implement a second commitment study to fulfill the accelerated approval obligation. The FDA indicated that the new study must demonstrate superiority in the primary endpoint of survival. Protocol SO200/OBI No. DO01-20-0003 "A Phase III Randomized Study of Pegylated Liposomal Doxorubicin Plus Carboplatin Versus Carboplatin in Platinum-Sensitive Patients with Recurrent Epithelial Ovarian or Peritoneal Carcinoma After Failure of Initial Platinum-Based Chemotherapy" was developed with the Southwest Oncology Group (SWOG). On 19 June 2002, the SWOG submitted an Investigational New Drug (IND) application, with cross-reference to the JJPRD IND, to support the conduct of protocol SO200 / OBI No. DO01-20-003. On 30 July 2002, the SWOG IND was in effect. The first patient was enrolled in this study on 30 September 2002.

## **5. DESCRIPTION OF COMMITMENT STUDIES**

### **5.1. Sequus / ALZA Study 30-49**

Study 30-49, "A Phase III Randomized, Open-Label, Comparative Study of DOXIL/CAELYX versus Topotecan HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy"

### **5.1.1. Essentials of Study Design**

This Phase III, randomized, multicenter, open-label study compared DOXIL with topotecan in the treatment of women with histologically proven recurrent epithelial ovarian carcinoma. Up to 460 protocol-eligible patients (in order to obtain 370 evaluable patients) with epithelial ovarian carcinoma following failure of first-line, platinum-based chemotherapy were to be enrolled in this clinical trial.

Patients entering the trial were stratified prospectively for platinum-sensitivity and bulky disease. Protocol-eligible patients, with measurable or measurable and evaluable disease, who had been treated with no more than one prior platinum-based regimen, were randomized to treatment with either a one-hour intravenous infusion of DOXIL 50 mg/m<sup>2</sup> every 4 weeks, or topotecan, 1.5 mg/m<sup>2</sup>/day as a 30 minute infusion for 5 consecutive days every 3 weeks. Patients were to be treated for up to one year, and patients with ongoing clinical benefit could continue study drug upon approval by the Sponsor.

#### **5.1.1.1. Summary of Study Sites**

The study was conducted in 104 study centers in the United States and Europe (47 US and 57 Europe)

#### **5.1.1.2. Patient Population (Eligibility / Exclusion Criteria)**

Patients were to satisfy the following key criteria before entering the study:

- Histologically proven epithelial ovarian carcinoma. Each patient was staged at diagnosis according to FIGO Classification.
- Measurable disease or measurable and evaluable disease.
- Recurrence of disease or disease progression indicating failure of first-line, platinum-based chemotherapy.
- Karnofsky performance status (KPS)  $\geq$  60%.

#### **5.1.1.3. Endpoints**

##### Primary efficacy endpoint

The primary efficacy analysis was comparison of time to progression between the two treatment regimens.

##### Secondary efficacy endpoint

The secondary efficacy analyses included response rates, time to response, duration of response, health-related quality of life, and survival.

#### **5.1.1.4. Treatment Schema**

Patients were randomized to treatment with either DOXIL (50 mg/m<sup>2</sup> IV infusion over 1 hour every 28 days) or Topotecan (1.5 mg/m<sup>2</sup> IV infusion over 30 minutes daily, Days 1-5, 21-day cycle).

#### **5.1.1.5. Efficacy and Safety Monitoring**

Individual sites were monitored at appropriate intervals to assure a satisfactory rate of enrollment, recording of data, and adherence to the protocol. The frequency of monitoring varied depending on enrollment rate and the quality of data collected.

Two planned analyses and a final analysis were specified in the protocol or its amendments. The initial two analyses were to be conducted to evaluate time to progression after 200 and 280 of the evaluable patients were enrolled and all such patients had either experienced disease progression or had been on study for at least 6 months. Enrollment was not discontinued while the analyses were being conducted.

#### **5.1.1.6. Statistical Design**

It was estimated that enrollment of up to 460 patients would be required in order to obtain 370 evaluable patients. Patients entering the trial were stratified prospectively for platinum-sensitivity and bulky disease.

The primary efficacy analysis was comparison of time to progression between the two treatment regimens. The FDA and the Sponsor agreed on 29 June 2000 that the final analysis should focus on survival and the protocol was amended (amendment #3) accordingly. Prior to amendment #3, all patients had been enrolled in the study. The FDA requested that this analysis be performed not at a pre-specified time point, but when a predefined percentage of study subjects had expired or were lost to follow-up. The Sponsor determined that this analysis would be performed when 90% of study subjects reached this endpoint as specified in amendment #3. This final analysis for survival is currently ongoing.

Secondary efficacy analyses included response rates, time to response, duration of response, health-related quality of life, and survival. Statistical analyses were performed on the secondary efficacy parameters for the intent-to-treat (ITT) and the evaluable patient populations.

All statistical tests in these analyses were 2-sided for all variables except the time to progression variable. For all variables, an overall 5% level of significance was used for treatment difference, and 10% level for interaction, with adjustments for the two planned analyses.

The ITT Patient Population was defined as all patients who were randomized and received at least a partial dose of study drug.

The evaluable patient population was defined as all patients who were randomized, met the enrollment criteria, and received at least two cycles of study drug.

#### **5.1.2. Date of Initiation**

Study 30-49 was initiated May 1997.

#### **5.1.3. Accrual**

Enrollment of 481 patients was reached on 3 March 1999. Of the 481 enrolled patients, 474 patients were treated (239 were randomized to treatment with DOXIL and 235 were randomized to treatment with topotecan).

#### **5.1.4. Estimated Timeline for Study Completion**

The Sponsor submitted Amendment #3 to the IND and indicated that the Sponsor would conduct an additional set of survival and progression-free survival analyses when 90% of the 474 patients had either expired or were lost to follow-up. These analyses were to assess whether the survival advantage in the platinum-sensitive group was sustained and to examine the overall survival differences between the two treatment arms. As of December 2002, more than 90% of patients had either expired or were lost to follow-up.

#### **5.1.5. Estimated Timeline for Submission of Study Results**

As noted above, the target number of events was reached in December 2002, and it is expected that results of the final set of survival and progression free survival analyses will be available 1Q 03. The sNDA may be submitted 6 months after the survival endpoint is met but will be dependant on the study results and further discussions with the FDA.

### **5.2. SWOG Study SO200 (OBI Study No.: DO01-20-003)**

Study SO200 / OBI No. DO01-20-003, "A Phase III Randomized Study of Pegylated Liposomal Doxorubicin Plus Carboplatin Versus Carboplatin in

## Platinum-Sensitive Patients with Recurrent Epithelial Ovarian or Peritoneal Carcinoma After Failure of Initial Platinum-Base Chemotherapy”

### **5.2.1. Essentials of Study Design**

This Phase III, randomized, multicenter, open-label study compares the combination of DOXIL and carboplatin with single agent carboplatin in patients with platinum-sensitive recurrent epithelial ovarian or peritoneal carcinoma.

#### **5.2.1.1. Summary of Study Sites**

The study is being conducted as an intergroup study with participation from the following Cooperative Groups or organizations, including:

Southwestern Oncology Group (SWOG)  
Gynecologic Oncology Group (GOG)  
Cancer and Leukemia Group B (CALGB)  
Eastern Cooperative Oncology Group (ECOG)  
North Central Cancer Treatment Group (NCCTG)  
NCI / Cancer Trials Support Unit (CTSU)

#### **5.2.1.2. Patient Population (Eligibility / Exclusion Criteria)**

Patients must satisfy the following key criteria before entering the study:

- Histologically diagnosed disease consistent with epithelial ovarian carcinoma. Primary peritoneal and mixed mullerian tumors are allowed. Borderline ovarian tumors are not allowed.
- Patient must have undergone initial staging laparotomy and must have been surgically staged as FIGO Stage III (A, B, or C) or IV at that time.
- Patient must have recurrence or disease progression with a progression-free and platinum-free interval of 6-24 months after completion of first-line platinum-based chemotherapy (either single agent or combination therapy). Recurrent/progressive disease based solely on CA-125 elevation is allowed, provided it meets the CA-125 progression definition.

#### **5.2.1.3. Endpoints**

##### Primary efficacy endpoint

The primary efficacy endpoint will be a comparison of overall survival between the two treatment groups.

##### Secondary efficacy endpoint

The secondary efficacy endpoint will be progression-free survival and the incidence of confirmed complete response.

### Tertiary efficacy endpoint

The tertiary efficacy endpoint will be time to treatment failure.

#### **5.2.1.4. Treatment Schema**

Patients will be randomized to treatment with either the combination of carboplatin and DOXIL or single agent carboplatin until disease progression or systematic deterioration, unacceptable toxicity or delay in dose of more than 4 weeks. The maximum cumulative dose of DOXIL on this protocol is limited to 600mg/m<sup>2</sup>.

The treatment arms are as follows:

#### ARM 1 (carboplatin and DOXIL)

Carboplatin is to be dosed at AUC = 5 mg/mL IV d 1 every 4 weeks administered over a minimum of 15 minutes prior to infusion of pegylated liposomal doxorubicin, followed by administration of pegylated liposomal doxorubicin at a dose of 30 mg/m<sup>2</sup> IV d 1 every 4 weeks administered over 1 hour.

#### ARM 2 (Single agent carboplatin)

Carboplatin is to be dosed at AUC = 5 mg/mL IV d 1 every 4 weeks.

#### **5.2.1.5. Efficacy and Safety Monitoring**

The study will be conducted under the supervision of SWOG's Data and Safety Monitoring Committee (DSMC). The DSMC will monitor all endpoint data. Toxicity and study summary data will be reported every six months to the SWOG DSMC.

1. An interim analysis will be conducted when one third (125) of the 374 anticipated deaths have been observed on the carboplatin-only arm. The second interim analysis will be performed when approximately two thirds (250) of the anticipated deaths have been observed on the control arm.
2. The Quality Assurance Departments from each Cooperative Group or participating organization will perform audits of their groups' data per NCI and GCP guidelines

#### **5.2.1.6. Statistical Design**

Patients will be randomized equally to the two treatment arms while stratified by disease measurability, number of disease sites and serous histology.

Overall survival (OS) will be analyzed primarily by the stratified log rank test with stratification factors. Progression Free Survival (PFS) will be analyzed by the stratified logrank test in the same manner as for the overall survival. The complete response rates between the two treatment arms will be compared by the Fisher's exact test. To ensure an overall one-sided 0.025 significance level for these two secondary measures, the Holm simultaneous testing procedure will be used.

The other comparison will then be regarded as statistically significant if the corresponding one-sided P value is  $<0.025$ . Time to treatment failure (TTF) will be a tertiary endpoint.

According to the intent-to-treat principle, all eligible patients will be included in the analyses for OS, PFS, TTF, and complete response rate according to the randomized treatment assignment regardless of the actual treatments received.

#### **5.2.2. Date of Initiation**

SWOG activated the study on 15 August 2002. The first IRB approval was obtained in September 2002.

#### **5.2.3. Accrual**

The first patient was enrolled on 30 September 2002.

#### **5.2.4. Estimated Timeline for Study Completion**

Nine hundred eligible patients are targeted for accrual over a period of four and a half years at an accrual rate of 200 patients per year. Patients will be followed for an additional two years until 374 deaths have occurred in the carboplatin single agent arm. This study is estimated to complete accrual in early 2007.

### **6. DIFFICULTIES ENCOUNTERED IN CONDUCT, ACCRUAL, OR COMPLETION OF TRIALS**

As DOXIL is approved for use in the treatment of patients with ovarian cancer, it is challenging to expeditiously conduct clinical trials in this patient population since patients can receive commercially available drug outside of the clinical trial setting. In addition, as of Jan 2003 the NCI PDQ lists 45 studies competing for patients in this limited patient population.

SWOG study SO200 was first proposed to the FDA as a second commitment study on 27 July 2000. Due to the intricacies of working within the cooperative group and NCI/CTSU structure, coupled with the transfer of

clinical responsibilities for DOXIL from ALZA Corporation to Ortho Biotech Products, L.P., there was an unavoidable delay in finalizing the protocol between the SWOG, NCI, FDA and Ortho Biotech.

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