Oncologic Drugs Advisory Committee
Briefing Document

Gemzar® (gemcitabine HCl)

Recurrent Ovarian Cancer

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Division of Drug Oncology Products

Answers That Matter.

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1. Executive Summary

The Oncologic Drugs Advisory Committee has been requested to evaluate the supplemental New Drug Application (sNDA) for Gemzar® (gemcitabine) in recurrent ovarian cancer. The Sponsor believes there are adequate data to support the approval of this sNDA based on the demonstrated efficacy and safety of Gemzar in combination with carboplatin in Study JHQJ/AGO-OVAR 2.5. Gemzar plus carboplatin offers patients clinically significant and statistically persuasive improvement in progression-free survival (hazard ratio [HR], 0.72; log-rank p=0.0038), which indicates a 28% reduced risk of progression. The median progression-free survival on the Gemzar plus carboplatin arm was 8.6 months compared with 5.8 months for carboplatin treatment, representing a 48% increase in median progression-free survival for Gemzar plus carboplatin treated patients. Multiple sensitivity analyses and consistency of results in key subgroups confirm the robustness of the primary progression-free survival analysis. Importantly, improvement in progression-free survival allowed patients to maintain a longer period without a decline in quality of life (QoL) and a longer time without the need for further treatment to control disease. In addition, this combination demonstrated statistically significant improvements in overall response rate (47.2% Gemzar plus carboplatin arm versus 30.9% carboplatin arm) and complete response rate (14.6% versus 6.2%).

Gemzar plus carboplatin was well tolerated, as evidenced by the infrequent occurrence of Grade 3 and 4 nonlaboratory toxicities, the comparatively low frequency of study discontinuations due to adverse events in the Gemzar plus carboplatin arm, and the low percentage of patients on the combination arm who required a dose reduction of Gemzar. Motor and sensory neuropathy was infrequent in patients treated with Gemzar plus carboplatin, and the combination did not exacerbate preexisting neurotoxicity. While the combination was associated with a higher incidence of hematologic toxicities, clinically relevant sequelae were infrequent.

The efficacy and safety of Gemzar was further supported in two Phase 2 trials of Gemzar plus carboplatin and six Phase 2 trials of Gemzar monotherapy. Based on the activity demonstrated in these studies, Gemzar has been incorporated into the treatment armamentarium of gynecologic oncologists for treatment of patients with recurrent ovarian cancer.

Introduction

Gemzar is a well established cytotoxic agent with approvals in several solid tumor malignancies. Since its first approval in 1995, Gemzar has been used in many countries throughout the world for indications of non-small cell lung cancer (NSCLC), pancreatic cancer, bladder cancer, breast cancer, and ovarian cancer. To date, it is estimated that over 1.3 million patients have been treated with Gemzar, and over 8000 patients in Lilly-sponsored studies have received Gemzar.

The first US Food and Drug Administration (FDA) approval for Gemzar was granted on 15 May 1996 as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas and for patients previously treated with 5-fluorouracil (5-FU). Gemzar in combination with cisplatin was approved for the treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) NSCLC on 25 August 1998. Gemzar in combination with paclitaxel was approved on 19 May 2004 for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated. Gemzar has received foreign approvals for indications including NSCLC and pancreatic, breast, ovarian, bladder, and cervical cancers. The Sponsor is now seeking full approval for Gemzar in combination with carboplatin for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy, based on the pivotal Study JHQJ/AGO-OVAR 2.5 and several supporting studies indicating the activity of Gemzar in ovarian cancer. Study JHQJ/AGO-OVAR 2.5 was conducted by an internationally recognized cooperative group specializing in the treatment of gynecologic malignancies.

The 1998 Guidance for Industry - FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products encourages submission of sNDAs because many registered anticancer drugs are commonly used for malignant diseases that are not listed in the product label. The goal of the guidance is to provide full prescribing information for a product, which would include all clinical indications for which adequate data are available to establish the product's safety and effectiveness. In addition, FDA offers sponsors guidance on submitting alternative sources of data, such as data obtained from experienced, independent cancer clinical trials organizations. Submission of this sNDA is consistent with the goals of the guidance.

Product Rationale

In the preclinical setting, Gemzar, a pyrimidine antimetabolite, exhibits cell-phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. In preclinical tests, Gemzar exhibited antitumor activity against the M5 ovarian carcinoma model (95% to 100% inhibition) (Hertel et al. 1996).

In the clinical setting, Gemzar is a well-established cytotoxic agent, with activity as a single agent in ovarian cancer and a manageable toxicity profile. Responses have been observed in patients with platinum-refractory or bulky disease. Three open-label, nonrandomized, Phase 2 studies assessed the efficacy of Gemzar as a single-agent treatment in patients with recurrent ovarian cancer (Lund et al. 1994, 1995; Friedlander et al. 1998; von Minckwitz et al. 1999). Data from these trials showed response rates of 14% to 22%, and complete responses were observed in two of these trials. Additional Phase 2 studies of Gemzar monotherapy in the recurrent setting confirmed this activity,

with response rates ranging from 11% to 18% (Shapiro et al. 1996; Silver and Piver 1999; Coenen et al. 2000; Markman et al. 2001; see Appendix 1).

The Gemzar plus carboplatin combination therapy demonstrated notable activity, with an expected and manageable toxicity profile in patients with recurrent ovarian cancer, suggesting further development of this combination was warranted. The Gemzar plus carboplatin dose was determined in the dose-finding study, Study AGO-OVAR 2.4/O026 (du Bois et al. 2001) and was used in the pivotal Phase 3 study, Study JHQJ/AGO-OVAR 2.5. Study B9E-MC-JHRW (JHRW), a Phase 2 study, demonstrated similar results, as shown in Table 1 below.

Table 1. Phase 2 Studies of Gemzar plus Carboplatin

Study	Design	ORR (%)	Median PFS (mo)	Median Survival (mo)
AGO-OVAR 2.4 (O026)	Phase 1/2	62.5	10.0	22.5
JHRW	Phase 2	62.5	9.6	26.9

Abbreviations: ORR = overall response rate; PFS = progression-free survival.
Sources: du Bois et al. 2001; Kose et al. 2005.

In addition to the activity seen in ovarian cancer, Gemzar plus platinum combinations have been extensively studied in various solid tumors, including NSCLC, breast, bladder, pancreatic, and cervical cancers; the safety and efficacy of these combinations have been well characterized.

Unmet Medical Need

Ovarian cancer is the second-most common gynecological malignancy worldwide: in 2000, an estimated 192,000 new cases were diagnosed, and an estimated 114,000 women died from the disease (Parkin et al. 2001). In the United States, estimates for 2005 indicated that 22,000 new cases would be diagnosed, and over 16,000 women would die from the disease (Jemal et al. 2005). Age-adjusted annual incidence and death rates have remained relatively constant over the last 50 years; however, 5-year survival rates have significantly improved: from 37% (1974 to 1976) to 44% (1995 to 2002).

The current standard of therapy in the initial treatment of ovarian cancer is debulking surgery, followed by three to six cycles of carboplatin plus paclitaxel. The success rate of this primary standard therapy is approximately 30%. Up to 70% of the patients do not achieve complete responses in the primary therapy, or a relapse occurs after differing lengths of disease-free intervals. Should relapse or progression after the primary standard therapy occur, curative therapy is rarely a realistic option for patients with recurrent ovarian cancer. In these cases, the second-line therapy is mainly palliative. Length of the therapy-free interval is an important prognostic factor and influences the choice of secondary therapy (Markman et al. 1991). Based on the classification of Markman and Hoskins (1992) and modified by du Bois (1996), patients can be differentiated into three groups: those who have not received the standard (platinum) therapy, those with

platinum-refractory disease (relapsed while on platinum therapy), and those with platinum-sensitive disease (relapsed >6 months after platinum therapy).

Throughout the course of their treatment, patients with ovarian cancer receive multiple lines of therapy. Treatment options for patients with recurrent ovarian cancer depend on the length of time between completion of platinum-based therapy and disease recurrence (platinum resistant versus platinum sensitive).

In the platinum-resistant population, FDA-approved therapies have shown moderate response, ranging from 13% to 22% (Hycamtin package insert 2003; Taxol package insert 2003; Doxil package insert 2005). Lower response rates are seen in patients resistant to both a platinum and paclitaxel. The choice of agent depends on any residual toxicities from first-line therapy, performance status, and comorbid conditions of the patient.

The standard of care for patients with platinum-sensitive disease is re-treatment with platinum monotherapy, with response rates ranging from 25% to 55% (Gore et al. 1990; Bolis et al. 2001). Until now, the only treatment that improved upon this standard was carboplatin plus paclitaxel. However, because of the widespread use of carboplatin plus paclitaxel therapy in the first-line setting, readministration of this combination is not desirable for many patients with recurrent disease because of a history of neuropathy or likely exacerbation of persistent neuropathy.

Neurotoxicity is a debilitating residual toxicity that has been reported in up to 30% of patients following carboplatin plus taxane regimens (Vasey et al. 2004). Regardless of grade, neurotoxicity is an important clinical complication, and may be irreversible. Even patients with mild (Grade 1) neurotoxicity typically experience weakness or paresthesia. Patients with moderate (Grade 2) neurotoxicity have significant weakness or paresthesia that interferes with functional activity. Patients with higher grades may have debilitating toxicity, such as paralysis. The existence or history of neurotoxicity limits subsequent therapy, as these patients are typically more prone to neurotoxicity exacerbation. New treatment options that improve efficacy without worsening toxicities are needed for this patient population.

Progression-Free Survival

In late 2003, FDA initiated a Project on Endpoints for Approval. The acceptance of progression-free survival as a measure of clinical benefit is disease-specific, as noted in the FDA Draft Guidance for Industry on Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics. Thus far, progression-free survival has been recognized as a measure of clinical benefit in patients with lung and colorectal cancers. The Sponsor met with FDA to discuss the potential registration of Gemzar plus carboplatin in recurrent ovarian cancer, and the regulatory acceptance of progression-free survival in ovarian cancer was discussed with FDA in December 2004, prior to this sNDA submission.

The Sponsor believes that progression-free survival is an appropriate and valid endpoint for measuring clinical benefit in patients with recurrent ovarian cancer. For patients with recurrent ovarian cancer, a primary treatment goal is delaying disease progression, because progression is associated with death, increased symptoms, decreased QoL, and more therapy resulting in more toxicity. In clinical trial design, progression-free survival has the advantage of being assessable before the introduction of additional therapies, and represents efficacy of only the study therapy. In addition, progression-free survival includes both antitumor activity and survival; and allows for more rapid identification of active treatments than overall survival.

The Third International Ovarian Cancer Consensus Conference (Thigpen et al. 2005) recognizes progression-free survival as an important endpoint for the management of ovarian cancer and assessment of new treatments in ovarian cancer. The International Consensus Conference statements were developed by the Gynecological Cancer Intergroup (GCIG), which includes representatives from four continents and most global study groups performing trials in gynecologic oncology.

Clinical Efficacy

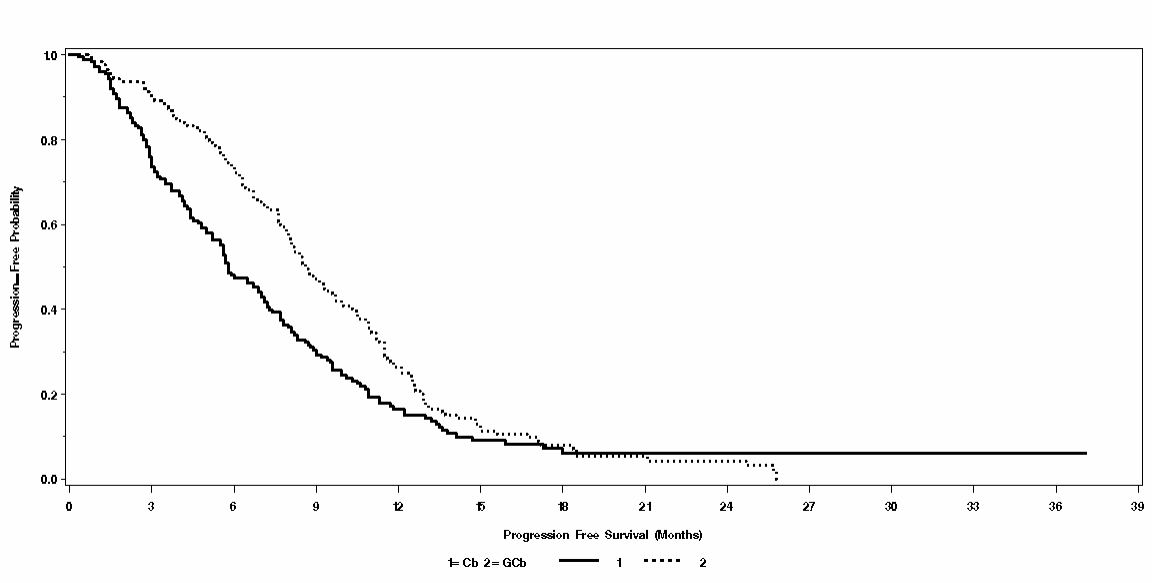
The efficacy of Gemzar in combination with carboplatin for the treatment of patients with recurrent ovarian cancer has been demonstrated in Study JHQJ/AGO-OVAR 2.5, a 356-patient, randomized, multicenter, Phase 3 trial conducted by the Arbeitsgemeinschaft Gynaekologische Onkologie, Studiengruppe Ovarialkarzinom (AGO-OVAR) in conjunction with two other cooperative groups (the National Cancer Institute of Canada-Clinical Trials Group [NCIC-CTG] and the European Organisation for the Research and Treatment of Cancer [EORTC]). AGO-OVAR is a well-established European cooperative group specializing in gynecologic malignancies and is a member of GCIG. The study principal investigator, Dr. Jacobus Pfisterer, is the current chair of the GCIG.

Patients were randomized on a one-to-one basis to receive Gemzar (1000 mg/m^2 on Days 1 and 8 of a 21-day cycle) plus carboplatin area under the curve (AUC) 4 on Day 1 or single-agent carboplatin AUC 5 on Day 1. The primary analysis was time to progressive disease (TtPD) in the intent-to-treat (ITT) population. Time to progressive disease was defined according to Southwest Oncology Group (SWOG) criteria (Green and Weiss 1992) as the time from the date of randomization to the date of disease progression or death from any cause, and is consistent with what is now known as progression-free survival; the term progression-free survival is used in this document.

Patients on both treatment arms presented with poor prognostic factors: approximately 80% of patients on each treatment arm had a platinum-free interval of <24 months, approximately 68% on each treatment arm received prior treatment with a carboplatin-plus-paclitaxel combination, nearly all the patients (94%) had measurable disease, and most patients (≥84% on either treatment arm) had Stage III or IV disease.

In the ITT population, Gemzar plus carboplatin demonstrated a statistically significant improvement in the primary endpoint of progression-free survival compared with

carboplatin monotherapy, p=0.0038 (HR, 0.72; 95% confidence interval [CI], 0.57 to 0.90). This indicates a 28% reduced risk of progression (see Figure 1) for patients treated with Gemzar plus carboplatin compared with carboplatin monotherapy. Median progression-free survival on the Gemzar plus carboplatin arm was 8.6 months compared with 5.8 months for carboplatin treatment, representing a 48% increase in progression-free survival for Gemzar plus carboplatin-treated patients. Multiple sensitivity analyses and consistency of results in key subgroups confirm the robustness of the primary analysis of progression-free survival.



Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin.
Source: Gemzar package insert 2005.

Figure 1. **Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier curve of progression-free survival in Gemzar plus carboplatin versus carboplatin in ovarian cancer.**

The overall response rate was significantly higher in the Gemzar plus carboplatin treated group compared with carboplatin alone (47.2% versus 30.9%). More complete responses were achieved in the Gemzar plus carboplatin arm as well (14.6% versus 6.2%, p=0.0092).

The estimate of median overall survival was 18 months for Gemzar plus carboplatin-treated patients and 17.3 months for carboplatin-treated patients. The estimate of the overall HR was 0.98 (95% CI, 0.78 to 1.24; log-rank test p=0.8977). The protocol-specified multiple regression analysis of survival included three significant covariates: total tumor size, platinum-free interval, and performance status. The resulting adjusted survival HR was 0.86. A multiple imputation (MI) analysis performed to account for baseline data that were not available for 30 patients provides a more robust estimate of

the adjusted treatment group HR. The results of the MI analysis were consistent with the protocol-specified analysis, with an HR of 0.92. The high utilization of postdiscontinuation chemotherapy (approximately 75% of patients in each treatment group received at least one additional line of chemotherapy) is a confounding factor when interpreting survival results.

In Study JHQJ/AGO-OVAR 2.5, patient reported outcomes (PRO) were collected (utilizing the QLQ-C30 and QLQ-OV28 scales) until patients discontinued protocol chemotherapy (not necessarily until progressive disease). Within-arm PRO improvements were similar in each treatment arm; however, global QoL improvements were maintained only on the Gemzar plus carboplatin arm. Based on between-arm analyses, the majority of ovarian-specific scales showed numerically better outcomes for the Gemzar plus carboplatin arm compared with the carboplatin arm, primarily driven by symptomatic patients. Further exploratory analyses were conducted to assess the association between the increased progression-free survival time with measures of patient well-being. These analyses included: time to 10-point QoL improvement, time to 10-point global QoL worsening, event-free interval, and treatment-free interval. Patients treated with Gemzar plus carboplatin had a longer period without a decline in QoL and a longer time without the need for further treatment to control disease.

Clinical Safety

Gemzar plus carboplatin combination had a manageable and predictable toxicity profile in patients with recurrent ovarian cancer that had relapsed at least 6 months after completion of first-line, platinum-based therapy. The tolerability of this regimen was evidenced by the infrequent occurrence of Grade 3 and Grade 4 nonlaboratory toxicities and the comparatively low frequency of discontinuations due to adverse events on the Gemzar plus carboplatin arm versus carboplatin alone. The combination was associated with higher incidence of hematologic toxicities, but clinically relevant sequelae were infrequent. No instances of Grade 4 febrile neutropenia or Grade 4 infection with Grade 3 or 4 neutropenia were reported in either treatment arm. Motor and sensory neuropathy was infrequent in patients treated with Gemzar plus carboplatin, and the combination did not exacerbate preexisting neurotoxicity. An equal number of deaths occurred on study or within 30 days of study drug administration (5 deaths in each arm).

There were more blood product transfusions on the Gemzar plus carboplatin arm, though less than half of these patients were transfused for Grade 3 or 4 toxicities. The use of erythropoietin and colony-stimulating growth factors was low, although more patients on the Gemzar plus carboplatin arm received these agents. According to local practice, more patients received blood transfusions, rather than erythropoietin, which are more commonly prescribed in the United States for the management of patients with anemia. Dose adjustments were infrequent, with neutropenia and thrombocytopenia being the most common reasons for dose reductions in both arms. Hospital admissions were numerically higher on the Gemzar plus carboplatin arm, for social reasons or drug

administration. Hospitalizations due to adverse events were slightly numerically higher on the Gemzar plus carboplatin arm.

Benefit/Risk Evaluation

Improvement in the treatment of patients with advanced cancers remains unassociated with cure; thus, palliative therapy must offer efficacy that is clinically relevant, toxicity that is predictable and manageable, and QoL that is not compromised by treatment. For patients with recurrent ovarian cancer, treatment with Gemzar plus carboplatin is more likely than carboplatin monotherapy to result in a longer time without disease progression or death (that is, a longer progression-free survival time) and a decrease in tumor burden.

In Study JHQJ/AGO-OVAR 2.5, Gemzar plus carboplatin offers patients clinically significant and statistically persuasive improvements in progression-free survival (HR=0.72, log-rank p=0.0038), overall response rate (47.2% Gemzar plus carboplatin arm versus 30.9% carboplatin arm), and complete response rates (14.6% versus 6.2%). In addition, sensitivity analyses demonstrated the robustness of the progression-free survival endpoint.

Because Study JHQJ/AGO-OVAR 2.5 was not designed to determine differences in overall survival, further conclusions about survival are limited. The sample size was determined by hypothesized treatment differences in progression-free survival rather than overall survival, which would have required approximately 350 patients to detect a 41% improvement in progression-free survival. The availability and activity of other active agents administered as postdiscontinuation therapy hamper the ability to determine the true treatment effect on survival. The HR for overall survival of 0.98 (95% CI, 0.78 to 1.24), and the adjusted HR, provide consistent evidence of no detriment to patients treated with Gemzar plus carboplatin.

Patients treated with Gemzar plus carboplatin had a longer period without a decline in QoL and a longer time without the need for further treatment to control disease.

In addition, toxicity was predictable and manageable for the combination. Notably, significant clinical toxicities—those with which patients become symptomatic—were limited in frequency. In addition, motor and sensory neuropathy was infrequent in patients treated with Gemzar plus carboplatin, and the combination did not exacerbate preexisting neurotoxicity. The rate of neurotoxicity observed in Study JHQJ/AGO-OVAR 2.5 was considerably lower than that observed in studies incorporating paclitaxel in treatment of recurrent ovarian cancer (Connelly et al. 1996; Parmar et al. 2003). Thus, the combination of Gemzar plus carboplatin is a valuable treatment option for patients with ovarian cancer recurring after taxane-plus-platinum-based therapy.

The Sponsor believes that Gemzar plus carboplatin therapy offers a favorable benefit/risk profile that makes the combination a valuable treatment option for patients with advanced ovarian cancer that recurs at least 6 months after completion of first-line, platinum-based therapy.

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2. Introduction

2.1. Background

Gemzar (gemcitabine) received approval in the United States by FDA on 15 May 1996 as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas and for patients previously treated with 5-fluorouracil (5-FU). The approval was based on positive data from Study B9E-MC-JHAY (JHAY) (Burris and Storniolo 1997), a single-blind, two-arm, randomized, controlled study of Gemzar 1000 mg/m^2 versus 5-FU 600 mg/m^2.

Gemzar also has approved indications in the United States for use in other tumor types as part of combination therapy. The combination of Gemzar plus cisplatin is indicated for treatment of advanced stage non-small cell lung cancer (NSCLC), based on Study B9E-MC-JHEX, a pivotal Phase 3 trial described by Sandler and associates (2000). In addition, the combination of Gemzar with paclitaxel is indicated for treatment of patients with metastatic breast cancer (Study B9E-MC-JHQG). Results from these studies are given in Section 3.3 of this document.

The focus of this sNDA is on the use of Gemzar in combination with carboplatin for the treatment of patients with recurrent epithelial ovarian carcinoma who have relapsed at least 6 months following platinum-based therapy. The pivotal Phase 3 clinical study, Study JHQJ/AGO-OVAR 2.5, was conducted by AGO-OVAR in conjunction with two other cooperative groups (the National Cancer Institute of Canada-Clinical Trials Group [NCIC-CTG] and the European Organisation for the Research and Treatment of Cancer [EORTC]) in 101 study centers in 12 countries. Study B9E-MC-JHQJ/AGO-OVAR 2.5 is described in detail in the following sections of this document.

Submission of this sNDA is consistent with the FDA Guidance on New Treatment Indications. This guidance was motivated by the fact that many registered anticancer drugs are commonly used for malignant diseases that are not listed in the product label. The guidance notes that the type and quantity of data needed to support claims of effectiveness and safety in a supplemental marketing application depend on what is already known about the product. This guidance does not imply a lesser proof of efficacy for previously approved agents, but recognizes the need to minimize barriers to the submission of supplemental applications for new uses of approved products in the treatment of cancer. Furthermore, the guidance states that product labeling is intended to provide full prescribing information for a product and should include all clinical indications for which adequate data are available to establish the product's safety and effectiveness. The guidance also lists that alternative sources of data supporting applications include data from independent cancer clinical trial organizations.

2.2. Indication Sought and Treatment Regimen

Gemzar in combination with carboplatin is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma who have relapsed at least 6 months following platinum-based therapy.

The dosing regimen for the treatment of advanced ovarian cancer is Gemzar 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion, plus carboplatin area under the curve (AUC) 4 administered after Gemzar on Day 1. The doses of Gemzar (1000 mg/m^2) and carboplatin (AUC 4) were selected based on results from the dose-finding study, Study O026/AGO-OVAR 2.4 (du Bois et al. 2001).

2.3. Recurrent Ovarian Cancer and Current Treatment Options

Ovarian cancer is the second-most common gynecological malignancy worldwide: in 2000, an estimated 192,000 new cases were diagnosed and an estimated 114,000 women died from the disease (Parkin et al. 2001). In the United States, estimates for 2005 indicated that 22,220 new cases would be diagnosed, and 16,210 women would die from the disease (Jemal et al. 2005). Age-adjusted annual incidence and death rates have remained relatively constant over the last 50 years; however, 5-year survival rates have significantly improved: from 37% (1974 to 1976) to 44% (1995 to 2002).

The majority of patients with ovarian cancer present with Stage III or IV disease. The current standard of therapy in the initial treatment of ovarian cancer is debulking surgery, followed by three to six cycles of carboplatin plus paclitaxel. The success rate of this primary standard therapy is approximately 30%. Up to 70% of the patients do not achieve complete responses in the primary therapy, or a relapse occurs after differing lengths of disease-free intervals.

Following first-line therapy, ovarian cancer patients are followed up periodically with clinical examination. During evaluation, clinicians look for the following symptoms and signs of recurrent or progressive disease: abdominal discomfort and bloating, gastrointestinal and urinary tract symptoms, ascites, and pelvic masses. Unfortunately, early detection of relapsed ovarian cancer has not been consistently shown to improve patient outcome, presumably because relapsed disease is generally disseminated and thus incurable. In carefully selected patients (for example, those relapsing >12 months after completion of first-line therapy), secondary cytoreductive surgery has been associated with improved survival in a few small studies (Ozols et al. 2001).

If relapse or progression after the primary standard therapy occurs, curative therapy is rarely a realistic option for patients with recurrent ovarian cancer. In these cases, the second-line therapy is mainly palliative. Length of the therapy-free interval influences the choice of secondary therapy and is of prognostic importance for the ongoing course of the illness (Markman et al. 1991). Based on the classification of Markman and Hoskins (1992) and modified by du Bois (1996), these patients can be differentiated into three groups:

- No prior standard (platinum) therapy: for patients with no primary standard therapy (for example, platinum), application of a therapy containing platinum is recommended.
- Platinum-refractory: patients who progress while undergoing primary platinum-containing therapy or who experience a relapse within 6 months after the primary therapy.
- Platinum-sensitive: patients who have recurrent ovarian carcinoma after a response to the primary therapy and who show a disease-free interval of more than 6 months.

Approximately 20% to 30% of patients developing recurrent ovarian cancer have platinum-resistant disease. When re-treated with platinum agents, patients with platinum-resistant ovarian cancer typically demonstrate response rates of approximately 10% (Markman and Hoskins 1992). The limited activity of platinum has led to the development of non-platinum agents for platinum-resistant ovarian cancer. The most recent FDA-approved agents include paclitaxel, topotecan, and pegylated liposomal doxorubicin. The majority of the data for registration were from Phase 2 trials, with overall response rates ranging from 13% to 22%, and median time to progression ranging from 2.6 to 4.4 months (Table 2). Collectively, only two randomized controlled trials were included in the submissions: topotecan was compared with paclitaxel in 226 patients, and pegylated liposomal doxorubicin was compared with topotecan in 474 patients (Table 3). There were no statistical differences between response rates and time to progression in either of these trials.

Gemzar monotherapy has demonstrated similar activity in recurrent ovarian cancer patients in several Phase 2 trials, with overall response rates ranging from 8% to 22% and time to progression ranging from 1.9 to 3.6 months (see Table 2 and Appendix 1). More recently, a randomized trial of pegylated liposomal doxorubicin versus Gemzar in second or third line treatment of platinum-resistant ovarian cancer was reported. As shown in Table 3, the efficacy was similar with regard to response rates (Gemzar 6.1%, pegylated liposomal doxorubicin 8.4%) and time to progression (Gemzar 3.6 months, and pegylated liposomal doxorubicin 3.0 months; Mutch et al. 2005).

Table 2. Efficacy Results of Select Single-Agent Chemotherapies in Ovarian Cancer

	PLD	Topotecan	Paclitaxel	Gemzar
Patient Population	Platinum-resistant	Platinum-resistant, Platinum-recurrent[a]	Platinum-recurrent[a]	Platinum-recurrent[a]
N	145	223	499	204
Number studies/Phase	3 Ph 2	1 Ph 2 , 1 Ph 3	2 Ph 2, 1 Ph 3	6 Ph 2
ORR, %	13 – 22[b]	14 – 21	13 – 22	8 – 22[b]
Median TtPD, mo	3.7[c]	2.6 - 4.4	2.8 - 4.4	1.9 -3.6

Abbreviations: N = total number of patients who received investigational drug; ORR = overall response rate; Ph = phase; PLD = pegylated liposomal doxorubicin; TtPD = time to progressive disease.

[a] Includes patients with recurrent disease after platinum-containing regimen or not responsive to a platinum-containing regimen.

[b] Does not include an outlier study in which no responders were reported.

[c] Combined data from all three studies.

Sources: Appendix 1; Doxil package insert, 2005; Hycamtin package insert, 2003; Taxol package insert, 2003.

Table 3. Efficacy Results from Three Single-Agent Comparison Studies in Ovarian Cancer

	Topotecan vs Paclitaxel		PLD vs Topotecan		Gemzar vs PLD	
Patient Population	Platinum recurrent		Platinum recurrent		Platinum resistant	
N	112	114	239	235	99	96
ORR, %	21.0	14.0	19.7	17.0	6.1	8.4
Median TtPD, mo	4.4	3.4	4.1	4.2	3.6	3.0
Median OS, mo	14.7	12.3	14.4	13.7	NA	NA

Abbreviations: N = number of patients; NA = not available; ORR = overall response rate; OS = overall survival; PLD = pegylated liposomal doxorubicin; TtPD = time to progressive disease; vs = versus.

Sources: Doxil package insert, 2005; Hycamtin package insert, 2003; Mutch et al. 2005 ; Taxol package insert, 2003.

Approximately 70% to 80% of patients developing recurrent ovarian cancer have platinum-sensitive disease. The degree of sensitivity is related to the length of the platinum-free interval. Patients with platinum-sensitive ovarian cancer with a platinum-free interval of less than 1 year have lower response rates than patients with longer platinum-free intervals (Markman et al. 1991). When re-treated with platinum agents, 25% to 55% of patients with platinum-sensitive disease demonstrate tumor response (Gore et al. 1990; Bolis et al. 2001; Armstrong 2002). The increased activity seen with the platinum agents has made re-treatment with platinum agents, either alone or in combination with other agents, the standard of care. The treatment options for patients with recurrent ovarian cancer depend on the length of time between completion of platinum-based therapy and disease recurrence; any residual toxicities from first-line therapy; performance status; and comorbid conditions. The widespread use of

platinum/taxane therapy in first-line setting increases subsequent neurotoxicity, and therefore limits the readministration of a taxane. Following initial therapy, 75% to 80% of patients report Grade 1 through 4 neurotoxicity (du Bois et al. 2003; Vasey et al. 2004), 30% of patients have Grade 2 or higher neurosensory toxicity, and 7% of patients have Grade 2 or higher neuromotor toxicity.

Neurotoxicity is an important clinical complication for patients with recurrent ovarian cancer, regardless of grade, and may be irreversible. Even patients with mild (Grade 1) neurotoxicity typically experience weakness or paresthesia. Patients with moderate (Grade 2) neurotoxicity have significant weakness or paresthesia that interferes with functional activity. Patients with higher grades may have debilitating toxicity such as paralysis. The existence or history of neurotoxicity limits subsequent therapy, as these patients are typically more prone to neurotoxicity exacerbation.

In clinical practice in the United States, the following treatment options are approved for the treatment of recurrent ovarian cancer: cisplatin, carboplatin, altretamine, paclitaxel, topotecan, and pegylated liposomal doxorubicin. There have been no new approvals in ovarian cancer since 1999.

2.3.1. Regulatory History of Approvals in Ovarian Cancer

The FDA has approved six drugs for the treatment of ovarian cancer that has recurred after initial or subsequent chemotherapy. Five of the six drugs were new chemical entities (NCEs): cisplatin (1978), carboplatin (1989), altretamine (1990), paclitaxel (1992), and topotecan (1996). One drug, pegylated liposomal doxorubicin (1999) received approval of a supplemental application for ovarian cancer. In each of the six approvals, the treatment regimen approved was monotherapy.

Regular approval was granted in all but one instance; pegylated liposomal doxorubicin initially received accelerated approval, and was subsequently granted full approval based on data from a randomized Phase 3 study of pegylated liposomal doxorubicin versus topotecan. The primary basis of approval for all of six agents was response rate, with additional endpoints providing supportive data.

Response rate is considered a surrogate endpoint reasonably likely to predict clinical benefit in recurrent ovarian cancer, and thus suitable for accelerated approval consideration. Complete response, however, is recognized as a clinical benefit for patients rather than as a surrogate endpoint (Johnson et al. 2003). The regular approvals granted on the basis of response rate (and in some cases, complete responses), were primarily a reflection of the regulatory standards at the time, as accelerated approval was not an option prior to 1992. Nonetheless, no initial drug approvals in recurrent ovarian cancer have demonstrated a survival advantage over an accepted (community or regulatory) standard of treatment. FDA consulted the Oncologic Drugs Advisory Committee (ODAC) for advice on the approval packages for each application, with the exception of the approval of cisplatin in 1978. The approvals were made primarily on the basis of response rates observed in noncontrolled studies. Topotecan was approved on

the basis of response rate supported by TtPD and survival data (not statistically significant) from a randomized study. The currently approved regimens are all single-agent therapy and have modest response rates.

Progression-free survival is a more robust endpoint than response rate for determining efficacy and clinical benefit of a new therapy. Progression-free survival, defined as the time from the date of randomization to the date of disease progression or death from any cause, accounts for activity measured in responding and stable tumors. In addition, when there is a long time between progression and death, and active agents are available for subsequent treatment, the potential for postdiscontinuation therapy to confound survival results makes progression-free survival a more reliable endpoint to estimate the true treatment effect of a drug. Progression-free survival also accounts for duration of effectiveness. The clinical benefit shown in Study JHQJ/AGO-OVAR 2.5 is evidenced by the statistically significant improvements in progression-free survival, overall response, and complete response, and by the manageable safety profile of the combination.

2.3.2. Combination Therapy for Platinum-Sensitive Patients

Recently, the International Collaborative Ovarian Neoplasm (ICON) and AGO-OVAR collaborators published the results of three parallel trials (United Kingdom [UK], Italy, AGO-OVAR), collectively known in the literature as ICON4. In these trials, patients with platinum-sensitive ovarian cancer (recurring 6 months after platinum-based therapy) were randomized to receive conventional platinum-based (mainly platinum monotherapy) or paclitaxel plus platinum-based therapy (ICON and AGO-OVAR 2003). Eligibility criteria differed among the protocols by the following: prior taxane exposure, requirements for diagnosis of relapse, presence of measurable disease, and number of prior regimens allowed. The primary outcome of the pooled studies was overall survival. Secondary outcomes were progression-free survival, response rate, quality of life (QoL) via the EORTC QLQ-30 instrument, and safety.

With regard to overall survival, paclitaxel plus platinum-based therapy was superior to conventional platinum-based therapy (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69 to 0.97; p=0.02). Progression-free survival was also superior in the paclitaxel plus platinum-based therapy arm (HR, 0.76; 95% CI, 0.66 to 0.89; p=0.0004). Median progression-free survival was 12 months for paclitaxel plus platinum-based therapy and 9 months for conventional platinum-based therapy (95% CI for the difference, 1 to 4). Response rates were not significantly improved, with an overall response rate of 66% and 54%, respectively (p=0.06); independent review of response rate was not performed. Quality-of-life analyses showed no clear indication that one regimen was worse for functional ability, symptomatic experience, or global health status. Hematologic toxicities (not otherwise specified) were more common in the conventional platinum group than in the platinum plus paclitaxel group (46% versus 29%, respectively) but Grade ≥2 neurotoxicity (1% and 20%) and alopecia (25% and 86%) occurred more frequently in the platinum-paclitaxel group.

This important proof-of-concept analysis demonstrates that platinum combination therapy is superior to conventional platinum-based (mainly platinum monotherapy) in the treatment of patients with platinum-sensitive, recurrent ovarian cancer. It is noteworthy that approximately only one third of the ICON4 patients received a taxane in first-line therapy; thus, the trial data may underestimate the true frequency of neurotoxicity when paclitaxel plus platinum therapy is readministered to patients previously exposed to platinum plus a taxane. This is an important clinical consideration, given the widespread use of platinum plus taxane therapy in the first-line setting, where neurotoxicity following first-line, platinum plus taxane therapy can be demonstrated in 40% to 60% of patients at 1 year, and in 4% to 17% of patients at 2 years (du Bois et al. 2003). Thus, while ICON4 demonstrates that combination therapy is superior to conventional platinum-based therapy, readministration of platinum-paclitaxel is not feasible or desirable in a significant proportion of patients with platinum-sensitive, recurrent ovarian cancer due to residual neurotoxicity.

Of note, AGO-OVAR investigators discontinued their participation in ICON4 early and closed AGO-OVAR 2.2 protocol (which required prior platinum plus paclitaxel therapy) because of the frequent occurrence of neurotoxicity with readministration of paclitaxel plus platinum therapy in their patients. AGO-OVAR was interested in developing an effective platinum doublet therapy without additional neurotoxicity, which led to the development of the alternative combination of Gemzar plus carboplatin in platinum-sensitive patients in OVAR 2.4 (AGO-OVAR Phase 1/2 study of Gemzar plus carboplatin; Lilly study identifier O026) and OVAR 2.5 (AGO-OVAR Phase 3 pivotal trial comparing Gemzar plus carboplatin with carboplatin monotherapy in patients with platinum-sensitive, recurrent ovarian cancer; Lilly study identifier JHQJ).

2.4. Role of Progression-Free Survival

In late 2003, FDA initiated a Project on Endpoints for Approval. The acceptance of progression-free survival as a measure of clinical benefit is disease-specific, as noted in the FDA Draft Guidance for Industry on Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics. Thus far, progression-free survival has been recognized as a measure of clinical benefit in patients with lung and colorectal cancers. The use of progression-free survival as a measure of clinical benefit in recurrent ovarian cancer is a subject of discussion for review of this application.

The Sponsor believes that the primary endpoint of progression-free survival, in conjunction with an increased overall response rate and a favorable safety profile, is an appropriate and valid indicator of clinical benefit in patients with recurrent ovarian cancer.

For patients with recurrent ovarian cancer, delaying disease progression is a primary treatment goal because progression is associated with death, increased symptoms, and decreased QoL. In clinical trial design, progression-free survival has the advantage of being assessed before the introduction of additional therapies, provided that the protocol

requires documentation of progression before allowing subsequent treatment. This is important, as patients with platinum-sensitive ovarian cancer will typically receive numerous lines of chemotherapy. Progression-free survival represents efficacy of only the study therapy, includes both antitumor activity and survival, and allows for more rapid identification of active treatments than overall survival. Thus, improvement in overall and complete response can be evaluated separately for benefit to a patient.

Progression-free survival has an advantage over overall survival as an endpoint because the results are not confounded by postdiscontinuation therapy. The impact of subsequent chemotherapy on overall survival data can be evaluated in the most recently approved ovarian cancer agent, pegylated liposomal doxorubicin, which was compare with topotecan in a Phase 3 setting. The primary endpoint of this study was progression-free survival. Progression-free survival was similar between arms, with a median of 17.6 weeks on the pegylated liposomal doxorubicin arm versus 18.1 weeks for topotecan ($p=0.617$). An updated survival analysis, not adjusted for multiple comparisons, showed an increase in overall survival in patients treated with pegylated liposomal doxorubicin (median 61.92 weeks), as compared with topotecan (median 58.9 weeks) ($p=0.05$). The survival advantage was due to an improvement seen mainly in the platinum-sensitive subgroup. Separation in the survival curve occurred after the majority of patients experienced disease progression. The lack of superiority of progression-free survival and the timing of the improvement in overall survival bring into question the impact of postdiscontinuation chemotherapy with a platinum agent. Unfortunately, postdiscontinuation therapy data needed to appropriately answer this question were not collected.

In addition, the Third International Ovarian Cancer Consensus Conference (Thigpen et al. 2005) recognizes progression-free survival as an important endpoint for the management of ovarian cancer and for assessment of new treatments in ovarian cancer. The International Consensus Conference statements were developed by the GCIG, which includes representatives from four continents and most global study groups performing trials in gynecologic oncology.

2.5. The AGO-OVAR and Lilly Collaboration

AGO-OVAR (Arbeitsgemeinschaft Gynaekologische Onkologie, Studiengruppe Ovarialkarzinom) was founded in 1993 and is a well-established European cooperative group, with over 300 sites, specializing in gynecological malignancies. AGO-OVAR is a member of the GCIG, an organization of 15 international cooperative group for clinical trials for gynecologic cancers. AGO-OVAR is internationally recognized for clinical trials. They have performed eight randomized Phase 3 trials to date. Results from AGO-OVAR studies have been validated by other cooperative groups. Specifically, results from AGO-OVAR's randomized Phase 3 study, OVAR 3 (carboplatin plus paclitaxel versus cisplatin plus paclitaxel as first-line treatment in patients with ovarian cancer; du Bois et al. 2003) were similar to results from the Gynecologic Oncology Group's

GOG158 study which compared carboplatin plus paclitaxel versus cisplatin plus paclitaxel.

The current GCIG chair, Jacobus Pfisterer, MD, PhD, Professor of Gynecology and Obstetrics at the University of Kiel, was the principal investigator for Study JHQJ/AGO-OVAR 2.5. Dr. Pfisterer has been a member of the AGO-OVAR since 1996 and has served as one of its co-chairman since 1999.

Recently the ICON and AGO-OVAR collaborators published the results of three parallel trials, collectively known in the literature as ICON4. In these trials, patients with ovarian cancer recurring 6 months after platinum-based therapy (platinum sensitive) were randomized to receive conventional platinum-based therapy or paclitaxel plus platinum-based therapy (ICON and AGO-OVAR 2003). AGO-OVAR investigators discontinued their participation in ICON4 early (closed Study AGO-OVAR 2.2) because of the frequent occurrence of neurotoxicity with readministration of paclitaxel-platinum therapy in their patients (the vast majority of whom received first-line, paclitaxel-platinum therapy, consistent with clinical practice in Germany).

AGO-OVAR's continued interest in the possible utility of platinum-doublet therapy in platinum-sensitive patients led to the development of the alternative combination of Gemzar plus carboplatin in two studies:

- AGO-OVAR 2.4 (Lilly study identifier B9E-SB-O026): a Phase 1/2 trial which demonstrated safety and efficacy of Gemzar plus carboplatin with low incidence of neurotoxicity. This dose-finding study was considered by AGO-OVAR to be the basis for the Phase 3 Study JHQJ/AGO-OVAR 2.5.
- AGO-OVAR 2.5 (Lilly study identifier B9E-MC-JHQJ): a Phase 3 study in platinum-sensitive patients comparing Gemzar plus carboplatin with carboplatin monotherapy, using progression-free survival as the primary endpoint. AGO-OVAR 2.5 replaced the closed study, AGO-OVAR 2.2. This pivotal study is the basis for this submission.

Study JHQJ/AGO-OVAR 2.5 was funded by Lilly, who was also responsible for data analysis and reporting for the purpose of registering the Gemzar plus carboplatin combination for the treatment of patients with recurrent ovarian cancer. The Lilly clinical research physician and the Lilly statistician were responsible for the appropriate conduct of an internal review process for both the final study report and any study-related material to be authorized for publication by Lilly. The major statistical analyses were defined jointly by Lilly and AGO-OVAR. AGO-OVAR managed the data and did not present or otherwise share trial data with investigators prior to final database lock.

3. Gemzar

3.1. Gemzar in Ovarian Cancer

3.1.1. Gemzar Monotherapy in Ovarian Cancer

As a monotherapy in the clinical setting, Gemzar is a well-established cytotoxic agent, with activity as a single agent in ovarian cancer and a manageable toxicity profile.

Six Lilly-sponsored multicenter studies of single-agent Gemzar were conducted in patients with recurrent ovarian cancer: Study E007 (Lund et al. 1994, 1995; Underhill et al. 2001 [extension portion]), Study JHBU, Study 0026 (von Minckwitz et al. 1999), Study 0027 (Friedlander et al. 1998), Study JHAJ, and Study JHFH (Kudelka et al. 1999) (see Appendix 1). Data from these trials showed response rates of 14% to 22% and complete responses were observed in two of these trials. All were Phase 2, open-label, single-arm studies administering Gemzar on Days 1, 8, and 15 every 28 days. Five of these six studies administered Gemzar at doses ranging from 800 to 1250 mg/m^2; the dose of Study JHFH was significantly higher (2000 mg/m^2). Objectives of these studies were to determine the objective tumor response rate and to characterize the toxicity of Gemzar in this patient population. In previously treated patients, Gemzar monotherapy yielded response rates ranging from 8% to 21.6% (Studies E007, JHBU, 0026, 0027, and JHFH); four complete responses were observed. In the extension portion of Study E007, in previously untreated patients with ovarian cancer, Gemzar monotherapy yielded a response rate of 18%; one complete response was observed. Study JHAJ was an outlier study in which no responders were seen among the 21 patients enrolled. This may be explained by the characteristics of the study population. This trial included only heavily pretreated patients who had received at least two prior treatment regimens.

Additional Phase 2 studies (published in the literature) of Gemzar monotherapy in the recurrent setting have confirmed the activity, with response rates ranging from 11% to 18% (Shapiro et al. 1996; Silver and Piver 1999; Coenen et al. 2000; Markman et al. 2001; see Appendix 1). More recently, results from a randomized trial of Gemzar in comparison to pegylated liposomal doxorubicin in second or third line treatment of platinum-resistant ovarian cancer were reported. The trial demonstrated similar overall response rates (6.1% versus 8.3%, not significant) and TtPD (3.6 months versus 3 months, not significant).

3.1.2. Gemzar plus Carboplatin in Ovarian Cancer

Clinical activity of the combination of Gemzar plus carboplatin in patients with recurrent ovarian cancer has been evaluated in three published studies. In two of the studies (Soh and Ho 1999; Orlando et al. 2000), Gemzar 1000 mg/m^2 was administered on Days 1, 8, and 15, with carboplatin AUC 4 or 5, on Day 1 of a 28-day cycle. The overall response rates in the two trials were 42.8% and 69%, respectively, showing the activity of Gemzar plus carboplatin combination in patients with recurrent ovarian cancer. In the third study,

Gemzar 1000 mg/m^2 was administered on Days 1 and 8, with carboplatin AUC 5 on Day 1 of a 21-day cycle (Papadimitriou et al. 2004). Overall response rate was 40.5% for the entire study population; response rates were lower in patients whose disease relapsed <12 months from completion of first-line treatment (27%) than in those whose disease relapsed ≥12 months from completion of first-line treatment (56%).

The activity of Gemzar (800 mg/m^2 on Days 1 and/or 8) in combination with carboplatin (AUC 5 on Day 1) and paclitaxel (135 to 175 mg/m^2 on Day 1) every 21 days has been evaluated as first-line therapy following cytoreductive surgery in ovarian cancer patients in three studies (Look et al. 2004; Micha et al. 2004; du Bois et al. 2005). Response rates of 71% to 91% were observed, again demonstrating the consistent antitumor effects of Gemzar in the treatment of patients with ovarian cancer.

In addition, Gemzar plus platinum combinations have been extensively studied in various solid tumors, including NSCLC, breast, bladder, pancreatic, and cervical cancers; the safety and efficacy of these combinations have been well characterized.

3.2. Clinical Pharmacokinetics

The following points summarize the key pharmacokinetic findings of single-agent Gemzar in patients with ovarian cancer and the pharmacokinetics of Gemzar and carboplatin in patients with NSCLC:

- The pharmacokinetics of Gemzar in advanced epithelial ovarian cancer patients were not different from the pharmacokinetics characterized in female patients with ovarian cancer and NSCLC (Studies B9E-UT-O026 and B9E-FP-O027, respectively).
- Gemzar and carboplatin pharmacokinetics were not altered when the drugs were given in combination and were independent of the infusion sequence (Studies B9E-BP-O022 and B9E-MC-JHET).
- Previous treatment with chemotherapeutic agents did not appear to alter the pharmacokinetics of Gemzar or the inactive metabolite, 2',2'-difluorodeoxyuridine (dFdU), in epithelial ovarian cancer patients (Study B9E-MC-JHBU).

Because the pharmacokinetics of Gemzar are not different between the two cancer types, and there is no interaction between Gemzar and carboplatin in NSCLC patients, by inference, no differences in the pharmacokinetics are expected when administering this combination in patients with ovarian cancer.

3.3. Clinical Background

Since its first approval in 1995, Gemzar has been used in many countries throughout the world for indications of NSCLC, pancreatic cancer, bladder cancer, breast cancer, and ovarian cancer. To date, it is estimated that over 1.3 million patients have been treated with Gemzar, and over 8000 patients in Lilly-sponsored studies have received Gemzar.

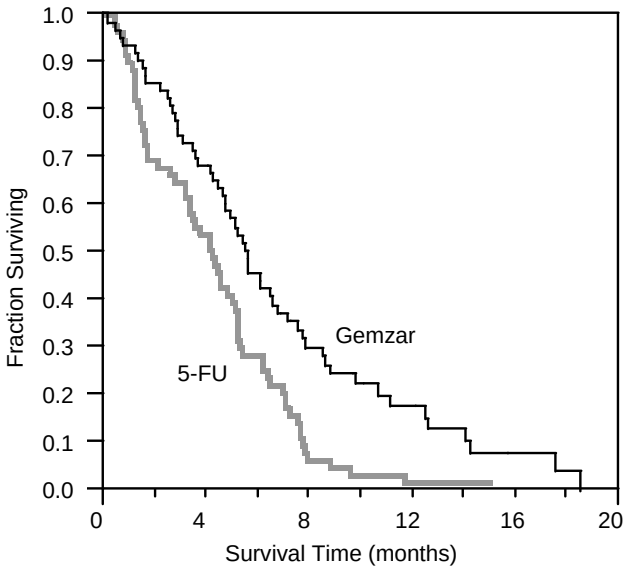
Gemzar was granted FDA approval in 1996 for the first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Study B9E-MC-JHAY (JHAY) helped establish single-agent Gemzar as the standard of care in pancreatic cancer. Study JHAY was a single-blind, two-arm, randomized, controlled Phase 3 trial of Gemzar versus 5-FU in 126 chemotherapy-naive patients with advanced carcinoma of the pancreas and was designed to establish an advantage in clinical benefit for patients treated with Gemzar over those treated with 5-FU. The efficacy results are shown in Table 4 and Figure 2 below. The principal nonlaboratory toxicities encountered in this study for Gemzar-treated patients included nausea and vomiting, fever, and rash. World Health Organization (WHO) Grade 3 and 4 toxicities were infrequent for both groups. This trial demonstrated a statistically significant advantage of Gemzar over 5-FU on two traditional oncology endpoints, survival and TtPD. This study also demonstrated that Gemzar provided a significant (marked and sustained) clinical benefit advantage over 5-FU for chemotherapy-naive patients with advanced or metastatic pancreatic carcinoma.

Table 4. Efficacy Results Gemzar in Pancreas Cancer Study JHAY

	Gemzar N=63	**5-FU N=63**	
Clinical Benefit Response, %	22.2	4.8	p=0.004
Median Survival, mo	5.7	4.2	p=0.0009
Median TtPD, mo	2.1	0.9	p=0.0013

Abbreviations: mo = months; N = number of patients; TtPD = time to progressive disease; TtTF = time to treatment failure.

Source: Gemzar package insert, 2005.



Source: Gemzar package insert, 2005.

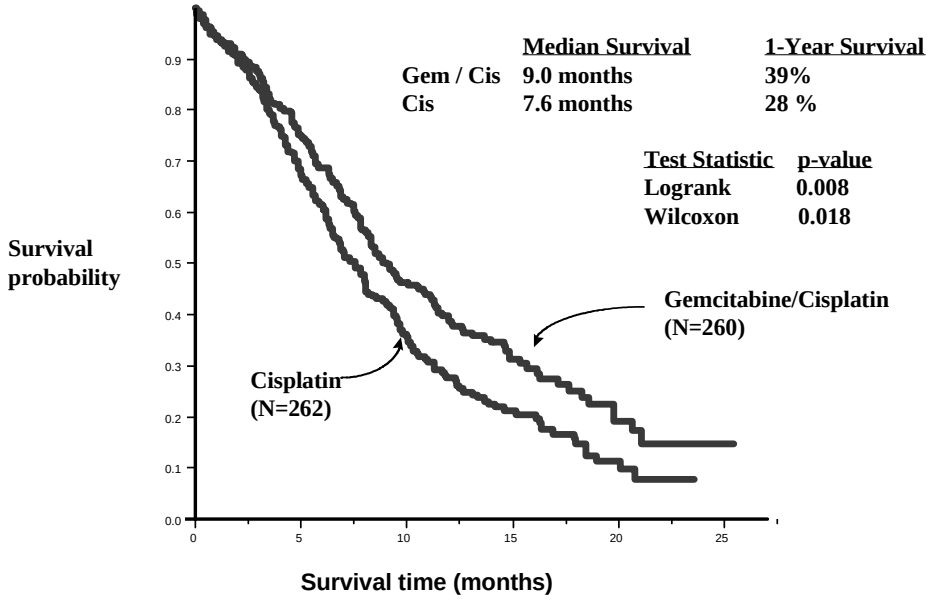
Figure 2. **Study JHAY Kaplan-Meier estimates of survival - Gemzar versus 5-Fluorouracil in a randomized trial as first-line palliative therapy in patients with carcinoma of the pancreas.**

The second FDA approval for Gemzar was granted on 25 August 1998 for NSCLC. Gemzar is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) NSCLC. Study B9E-MC-JHEX (JHEX) was an open-label, randomized, Phase 3 trial designed to compare the survival of patients with Stage III (A and B) or IV metastatic NSCLC treated with the combination of Gemzar plus cisplatin to that of patients treated with cisplatin alone. The efficacy results are shown in Table 5 and Figure 3 below. Toxicity was predominantly hematologic and was more pronounced in the combination arm, with Grade 4 neutropenia occurring in 35.3% of patients compared with 1.2% of patients on the cisplatin monotherapy arm. The incidence of neutropenic fever was <5% in both arms. Grade 4 thrombocytopenia occurred in 25.4% of patients on the combination arm compared with 0.8% of patients on the cisplatin monotherapy arm. No serious hemorrhagic events related to thrombocytopenia were reported for either arm.

Table 5. Efficacy Results Gemzar in Non-Small Cell Lung Cancer Study JHEX

	Gemzar plus Cisplatin N=260	Cisplatin N=262	
Median Survival, mo	9.0	7.6	Log rank p=0.008
1-Year Survival, %	39	28	
Median TtPD, mo	5.2	3.7	Log rank p=0.009
Objective Response Rate, %	26	10	Fisher Exact p<0.0001

Abbreviations: mo = months; N = number of patients; TtPD = time to progressive disease.
Source: Gemzar package insert, 2005.



Source: Gemzar package insert, 2005.

Figure 3. Study JHEX Kaplan-Meier estimates of survival - Gemzar plus cisplatin versus cisplatin therapy in patients with NSCLC.

The third FDA approval for Gemzar was granted on 19 May 2004 for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated. The primary registration study, Study B9E-MC-JHQG (JHQG), was a randomized, open-label, Phase 3 study of Gemzar plus paclitaxel versus paclitaxel in patients with unresectable, locally recurrent or metastatic breast cancer. The addition of Gemzar to paclitaxel resulted in statistically significant improvement in time to documented disease progression and overall response rate compared with monotherapy

with paclitaxel, shown in Table 6 and Figure 4 below. Further, there was a consistent trend toward improved survival for patients treated with Gemzar plus paclitaxel chemotherapy, based on an interim survival analysis. The following are the clinically relevant adverse events that occurred in >1% and <10% (all grades) of patients on either arm with the incidences of Grade 3 and 4 adverse events (Gemzar plus paclitaxel versus paclitaxel) in parentheses: febrile neutropenia (5.0% versus 1.2%), infection (0.8% versus 0.8%), dyspnea (1.9% versus 0%), and allergic reaction/hypersensitivity (0% versus 0.8%).

Table 6. Efficacy Results Gemzar in Metastatic Breast Cancer Study JHQG

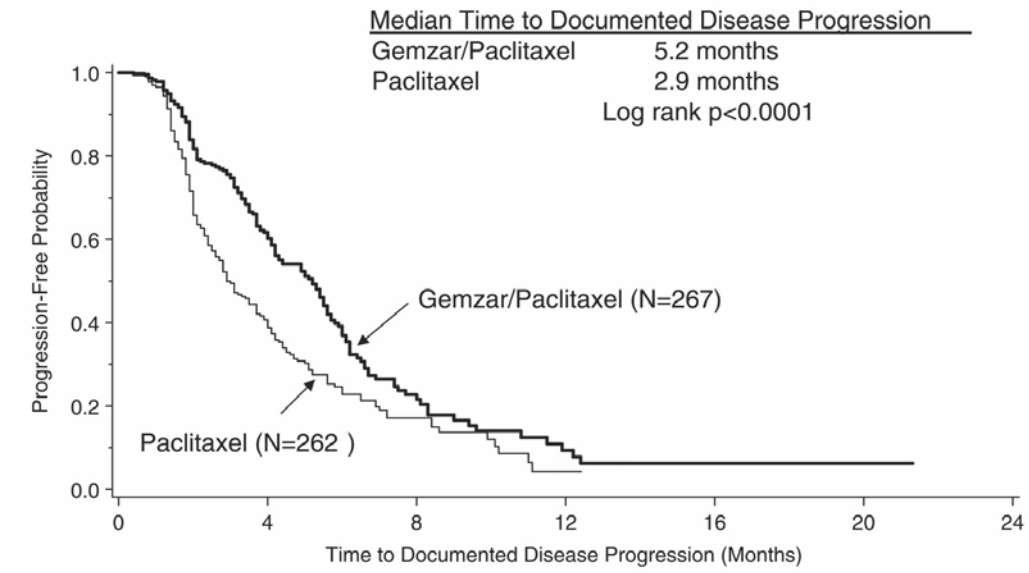
	Gemzar/Paclitaxel N=267	**Paclitaxel N=262**	
Time to Documented Disease Progression[a]			
Median (95%, CI), months	5.2 (4.2 - 5.6)	2.9 (2.6 - 3.7)	
Hazard Ratio (95%, CI)	0.650 (0.524 - 0.805)		p<0.0001[b]
Overall Response Rate[a] (95%, CI)	40.8% (34.9 - 46.7)	22.1% (17.1 - 27.2)	p<0.0001

Abbreviations: CI = confidence interval; N = number of patients.

[a] These represent reconciliation of investigator and Independent Review Committee assessments according to a predefined algorithm.

[b] Log-rank p-value.

Source: Gemzar package insert, 2005.



Source: Gemzar package insert, 2005.

Figure 4. Study JHQG Kaplan-Meier estimates of time to documented disease progression - Gemzar plus paclitaxel versus paclitaxel therapy in patients with breast cancer.

The sNDA for Gemzar in ovarian cancer is supported by the pivotal Phase 3 study, JHQJ/AGO-OVAR 2.5, and two supportive studies, Study O026/AGO-OVAR 2.4 and Study JHRW:

- Study O026/AGO-OVAR 2.4 was a Phase 1/2 that determined the dose-dependent and dose-limiting toxicity (DLT) of Gemzar 800 to 1200 mg/m^2 administered on Days 1 and 8, plus carboplatin AUC 4 or 5 administered after Gemzar on Day 1, of a 21-day cycle (du Bois et al. 2001). The efficacy results are shown in Table 7. At all dose levels, Grade 3 and 4 laboratory toxicities (regardless of relationship to study drug) were primarily hematologic, consisting of neutropenia in 68% of patients, thrombocytopenia in 52%, and anemia in 20%. Thrombocytopenia was the DLT of the combination. The recommended dose was Gemzar at 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle, plus carboplatin at 4 AUC on Day 1 following Gemzar.
- Study JHRW was a Phase 2 study that assessed the efficacy of Gemzar 1000 mg/m^2, administered on Days 1 and 8, plus carboplatin AUC 4, administered after Gemzar on Day 1, of a 21-day cycle. The efficacy results are shown in Table 7. The primary toxicities were hematologic, consisting of neutropenia in 80% of patients, thrombocytopenia in 17.5%, and anemia in 15%. No Grade 4 nonlaboratory toxicities were reported during the study, and the only Grade 3 nonlaboratory toxicity (creatinine) occurred in 1 patient.

Table 7. Phase 2 Studies of Gemzar plus Carboplatin

Study	Design	ORR (%)	Median PFS (mo)	Median Survival (mo)
AGO-OVAR 2.4 (O026)	Phase 1/2	62.5	10.0	22.5
JHRW	Phase 2	62.5	9.6	26.9

Abbreviations: mo = months; ORR = overall response rate; PFS = progression-free survival.
Sources: du Bois et al. 2001, Kose et al. 2005.

Study B9E-MC-JHQJ/AGO-OVAR 2.5, described in detail in Section 4, had first patient enrollment on 29 September 1999. This study was conducted by AGO-OVAR in conjunction with NCIC-CTG and EORTC. Refer to Section 2.5 for details regarding AGO-OVAR.

4. Efficacy of Gemzar in Recurrent Ovarian Cancer

4.1. Summary of Efficacy Claims

The results of Study JHQJ/AGO-OVAR 2.5 demonstrate that Gemzar plus carboplatin provides statistically and clinically significant improvement in progression-free survival for patients with recurrent epithelial ovarian carcinoma who have relapsed at least 6 months following platinum-based therapy.

Progression-free survival, based on the ITT population, was calculated when at least 300 randomized patients had disease progression or death due to any cause (initial database lock 28 February 2003, final database lock 15 February 2005). The HR for progression-free survival in the Gemzar plus carboplatin arm, relative to the carboplatin monotherapy arm, was 0.72 (95% CI, 0.57 to 0.90; log-rank p-value=0.0038), demonstrating that Gemzar plus carboplatin yielded a 39% improvement in progression-free survival compared with carboplatin alone (Figure 7). The analysis adjusted for significant prognostic factors (median tumor burden and platinum-free interval [PFI]), and the result was also highly statistically significant (HR, 0.70; 95% CI, 0.55 to 0.88, Wald's p=0.0023). In addition, the overall response rate was significantly higher in the Gemzar plus carboplatin treated group compared with carboplatin alone (47.2% versus 30.9%). There were more complete responses achieved in the Gemzar plus carboplatin arm as well (14.6% versus 6.2%, p=0.0092).

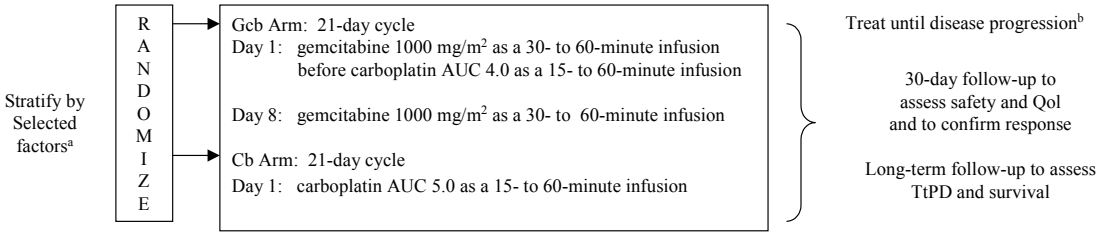
4.2. Design of Study JHQJ/AGO-OVAR 2.5

Study JHQJ/AGO-OVAR 2.5 was an open-label, randomized, Phase 3 study of Gemzar plus carboplatin in patients with advanced epithelial ovarian cancer who had failed first-line platinum-containing therapy at least 6 months after treatment discontinuation. The study, conducted in 12 countries at 101 investigational centers, was sponsored by AGO-OVAR in collaboration with two other cooperative groups, NCIC-CTG and EORTC GCG.

Patients were randomized according to the following stratification factors: progression-free time (6 to 12 months versus >12 months), type of first-line platinum regimen (platinum-paclitaxel versus platinum-nonpaclitaxel), and presence of bidimensionally measurable disease (yes versus no).

Patients were randomized in a 1:1 ratio to receive Gemzar plus carboplatin or carboplatin monotherapy. In the combination therapy arm, Gemzar 1000 mg/m^2 was administered intravenously once each week for 2 weeks (Days 1 and 8) plus carboplatin AUC 4 on Day 1 after Gemzar, followed by a week of rest. The monotherapy arm received carboplatin AUC 5 on Day 1 every 3 weeks. Patients were to receive a maximum of 6 cycles; however, at the discretion of the investigator, selected patients could receive up to 8 cycles. Treatment could continue until disease progression (PD) or unacceptable toxicity. Study drug administration could be delayed or doses reduced for toxicity. Dose

escalation was not permitted. Figure 5 illustrates the study design of Study JHQJ/AGO-OVAR 2.5.



Abbreviations: AUC=area under the curve; Cb = carboplatin; GCb = Gemzar plus carboplatin; Qol = quality of life; TtPD = time to progressive disease.
[a] Stratification factors were progression-free time, type of first-line chemotherapy, and presence of bidimensionally measurable disease.
[b] Patients could discontinue before progression if the protocol-defined treatment was reached (6 cycles, with an additional 2 at the discretion of the investigators), if intolerable toxicity occurred, or at the discretion of the physician, patient, or sponsor.
Source: Figure JHQJ.9.1.

Figure 5. Study design for Phase 3 Study JHQJ/AGO-OVAR 2.5.

Key eligibility criteria included the following:

[1] Histologically proven ovarian cancer with evidence of recurrence or progression, which was not amenable to curative surgery or radiotherapy.

[2] Failed first-line platinum-containing therapy after 6 months of treatment discontinuation (even if the first-line therapy included maintenance treatment).

[3] Documented lesion as evidenced by appropriate computerized tomography (CT), magnetic resonance imaging (MRI) scan, chest x-ray, or ultrasound. Physical examination was allowed for lymph nodes and skin metastases. A physical gynecological examination of well-defined palpable tumor lesions was also permitted. Patients must have had evaluable disease outside of any previously irradiated area.

[4] Previous hormonal therapy or radiotherapy (limited to the small pelvis) must have been terminated at least 3 weeks before study drug administration.

[5] Females ≥18 years of age.

[6] Performance status of 0 to 2 on the Eastern Cooperative Oncology Group (ECOG) scale.

[7] Estimated life expectancy of at least 12 weeks.

[8] Adequate bone marrow reserve: neutrophils ≥1.5 × 109/L and platelets ≥100 × 109/L.

[9] Ability to understand the nature of the study and to give written informed consent.

The primary efficacy endpoint of the study was progression-free survival. All randomized patients were evaluated for progression-free survival, as well as the secondary endpoints of overall survival, response rate, duration of response, and QoL. The distribution of progression-free survival was estimated using the Kaplan-Meier method (Kaplan and Meier 1958). The log-rank chi-square test was used to compare distribution of the endpoint between treatment arms. Tumor measurements were evaluated using modified criteria from the Southwest Oncology Group (SWOG) (Green and Weiss 1992). Quality of life was measured using the EORTC QLQ-C30 (version 3.0), a reliable and valid cancer-specific instrument, and the QLQ-OV28, an ovarian cancer-specific module (Aaronson et al. 1993, Cull et al. 2001). Patients completed these instruments no more than 2 weeks before enrolling into the study and again before every therapy cycle. Questionnaires were completed until patients discontinued protocol chemotherapy (not necessarily until progressive disease). Changes from baseline QLQ-C30 and OV28 scores were compared within treatment arms and between arms using paired t-test and analysis of variance (ANOVA). Scores were summarized at baseline and for each cycle, including the mean, standard deviation, median, minimum, and maximum. An exploratory mixed effects analysis was also performed on all randomized patients who completed a baseline and at least one postbaseline QoL questionnaire.

Safety analyses included assessment of laboratory and nonlaboratory toxicity using the National Cancer Institute Common Toxicity Criteria (CTC) Grading System (Version 2.0; NCI 1998), adverse events, and number of blood transfusions required. Clinical history and physical examination were performed prior to study start and were used as baseline data to monitor patient safety during the trial. Patients were required to return for assessment 30 days after the last on-study visit (Visit 101). At Visit 101, the toxicity rating using the CTC scale, hematology, chemistry, and QoL was collected. Lesion measurements were required at this 30-day postdiscontinuation visit only if necessary to confirm responses. After Visit 101, patients were to be assessed approximately every 3 months for the first two years of follow-up. This assessment included lesion measurements; however, measurements were not captured on the case report forms.

The protocol for Study JHQJ/AGO-OVAR 2.5 was approved internally on 08 February 1999 and had two protocol amendments. The first protocol amendment, approved internally on 30 July 1999 and prior to patient enrollment, changed the carboplatin dosage in the experimental arm from AUC 5 to AUC 4, based upon the results of the Phase 1/2 study, Study O026/AGO-OVAR 2.4, and added an interim safety analysis.

The second protocol amendment, approved internally on 06 July 2001, increased the number of patients to be enrolled from 250 to 350 when it was determined from the Study O026/AGO-OVAR 2.4 data that the median TtPD of Gemzar plus carboplatin therapy in platinum-sensitive patients was approximately 8.5 months rather than the projected 9 months, revising the assumptions to have an 85% power to show a 41% improvement. Additional clarifications of eligibility criteria and dose modifications for thrombocytopenia were also made.

4.2.1. Safety Assessment

One planned safety interim analysis was performed when 60 patients (approximately 30 in each arm) had completed at least three cycles of therapy. This interim analysis was conducted by a data monitoring board. The reporting database for this interim analysis was validated and locked on 01 March 2001. The purpose of the interim analysis was to assess the safety of the combination therapy. Efficacy was not assessed for the interim analysis. No formal statistical comparisons were performed. There were no safety issues identified in the interim analysis and the recommendation was to continue the study without changes. The interim analysis results were not shared with study investigators.

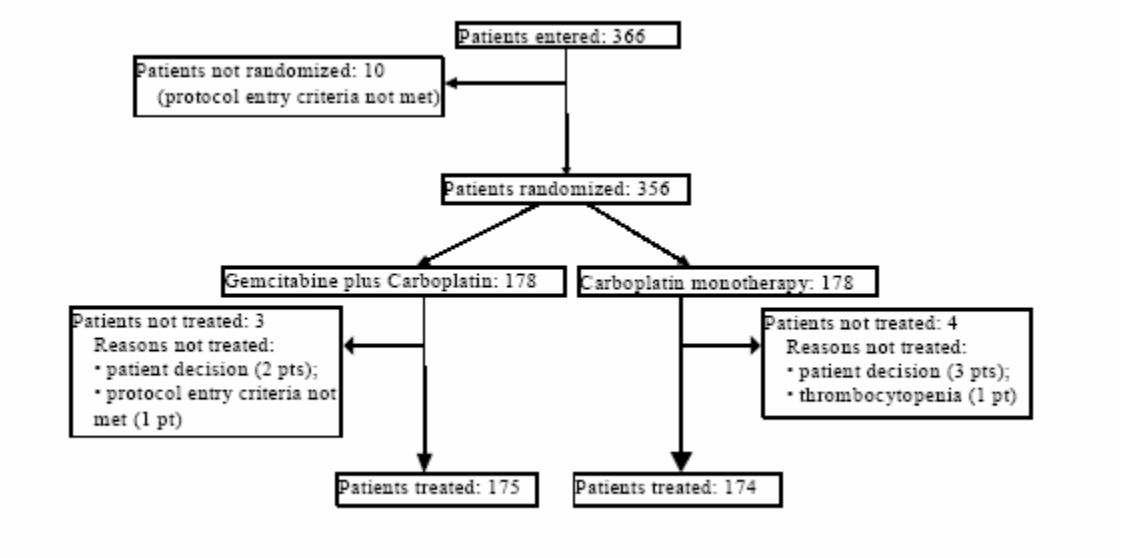
4.2.2. Study Endpoint

The data cut-off point for the analysis of the primary endpoint of progression-free survival was 28 February 2003. The final reporting database was locked on 24 March 2003. The data cut-off point for the update of postdiscontinuation chemotherapy, as well as updated survival date for this sNDA, was 15 February 2005.

4.3. Results from Study JHQJ/AGO-OVAR 2.5

4.3.1. Patient Disposition

A total of 356 patients with advanced epithelial ovarian cancer who failed first-line platinum-containing therapy at least 6 months after treatment discontinuation were randomized into this global study, and 349 received at least one dose of study drug. The first patient was randomized on 29 September 1999. The last patient was randomized on 26 April 2002, and the last patient completed the treatment phase on 10 October 2002. Figure 6 presents a flowchart of patient disposition for the entire study.



Abbreviation: pt(s) = patient(s).
Sources: Table JHQJ.14.1, Table JHQJ.10.1.

Figure 6. Patient disposition.

4.3.2. Patient Characteristics

Overall, the treatment arms were well balanced for patient characteristics. As shown below in Table 8, patients on both treatment arms presented with poor prognostic factors: approximately 40% of patients on each treatment arm had a PFI of <12 months, approximately 68% on each treatment arm had received prior treatment with a carboplatin-plus-paclitaxel combination, and most patients (≥84% on either treatment arm) had Stage III or IV disease. The grades of differentiation were well balanced between treatment arms. Nearly half of the patients on each treatment arm (44% on the Gemzar plus carboplatin arm, 49% on the carboplatin arm) had poorly differentiated disease, which represented a poor prognostic factor for these patients overall.

Of note, only 1% of patients in either treatment arm had been treated with prior carboplatin monotherapy; all other patients had received combination chemotherapy with two or more agents. More patients on the Gemzar plus carboplatin arm than on the carboplatin arm presented with secondary conditions of anemia, ascites (including malignant ascites), neuropathy, fatigue, anorexia, and pleural effusion, suggesting that patients randomized to the Gemzar plus carboplatin arm could have been slightly more symptomatic at baseline (see Table 9).

Table 8. Summary of Patient and Baseline Disease Characteristics Study JHQJ/AGO-OVAR 2.5

	GCb Arm (N=178)	Cb Arm (N=178)
Origin, n (%)		
Caucasian	127 (71.3)	126 (70.8)
Western Asian	34 (19.1)	37 (20.8)
East/Southeast Asian	12 (6.7)	12 (6.7)
Hispanic	2 (1.1)	3 (1.7)
Other	3 (1.7)	0
Age, years		
Mean	58.1	56.5
Median	59.0	58.0
Range	36 to 78	21 to 81
Diagnosis/histology, n (%)		
Epithelial, ovary	177 (99.4)	177 (99.4)
Adenocarcinoma NOS	0	1 (0.6)
Epithelial, fallopian	1 (0.6)	0
Grade of differentiation, n (%)		
Well differentiated	15 (8.4)	13 (7.3)
Moderately differentiated	51 (28.7)	49 (27.5)
Poorly differentiated	78 (43.8)	88 (49.4)
Undifferentiated	10 (5.6)	7 (3.9)
Unknown	24 (13.5)	21 (11.8)
FIGO Stage (at initial diagnosis), n (%)		
Stage I	14 (7.9)	10 (5.6)
Stage II	14 (7.9)	11 (6.2)
Stage III	123 (69.1)	134 (75.3)
Stage IV	27 (15.2)	22 (12.4)
Unspecified	0	1 (0.6)
First-line Platinum-based Therapy, n (%)	178 (100)	178 (100)
Platinum monotherapy	2 (1.1)	2 (1.1)
Platinum and paclitaxel	122 (68.5)	120 (67.4)
Platinum and docetaxel	3 (1.7)	7 (3.9)
Platinum and nontaxane combinations	51 (28.7)	49 (27.5)
Platinum-free interval, n (%)		
6 to 12 months	71 (39.9)	71 (39.9)
>12 months	105 (59.0)	106 (59.6)

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin; n = number of patients; N = total study population; NOS = not otherwise specified; FIGO = Federation of International Gynecology and Obstetrics.

Sources: Table JHQJ.11.2, Table JHQJ.11.3.

Table 9. Secondary Conditions Reported in at Least 10% of Patients, n (%) Study JHQJ/AGO-OVAR 2.5

MedDRA Preferred Term[a]	GCb Arm (N=178)	Cb Arm (N=178)
Patients with at least 1 condition	151 (84.8)	147 (82.6)
Anemia NOS	52 (29.2)	42 (23.6)
Ascites	45 (25.3)	24 (13.5)
Neuropathy NOS	38 (21.3)	29 (16.3)
Abdominal pain NOS	32 (18.0)	38 (21.3)
Hypertension NOS	32 (18.0)	25 (14.0)
Constipation	27 (15.2)	27 (15.2)
Fatigue	23 (12.9)	15 (8.4)
Nausea	18 (10.1)	18 (10.1)

Abbreviations: Cb = carboplatin; GCb = gemcitabine plus carboplatin; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients; N = number of patients who received at least one dose of study drug; NOS = not otherwise specified.

[a] Events were coded using MedDRA Version 5.1.

Source: Table JHQJ.11.9.

4.3.3. Methods of Disease Assessment

In Study JHQJ/AGO-OVAR 2.5, the investigators were instructed to determine PD as either objective progression or clinical progression, based on SWOG criteria (Green and Weiss 1992). Objective progression was defined as a 50% or 10 cm^2 increase (whichever was smaller) in the sum of the products of all measurable lesions, or the development of a new lesion, as determined by radiological and/or physical examination. Clinical progression included worsening ascites or pleural effusion, or performance status decline of two levels.

As shown in Table 10, the majority of disease progressions, both while on treatment and off treatment, were determined based on objective evidence; thus, any tendency on the part of the investigator to overestimate or underestimate progression dates was minimized.

Table 10. Method of Determining Progressive Disease Patients on and off Treatment Study JHQJ/AGO-OVAR 2.5

	Number (%) of Patients			
	On Treatment		Off Treatment	
Method of Determining PD	GCb Arm (N=35)	Cb Arm (N=70)	GCb Arm (N=117)[a]	Cb Arm (N=80)[b]
Objective progression	34 (97.1)	63 (90)	92 (78.6)	66 (82.5)
Clinical progression	1 (2.9)	7 (10)	28 (23.9)	16 (20)

Abbreviations: Cb = carboplatin; GCb = gemcitabine plus carboplatin; N = number of patients who progressed during study treatment; PD = progressive disease.

[a] In the GCb Arm, N=117, but Patients 1003, 4571, and 7151 are counted twice: all 3 patients had both larger or new lesions and deteriorating condition as the basis of progressive disease. Therefore, adding the number of patients in the categories of death, larger or new lesions, and deteriorating condition results in a total of 120 patients.

[b] In the Cb Arm, N=80, but Patients 1061 and 1153 are counted twice: both patients had larger or new lesions and deteriorating condition as the basis of progressive disease. Therefore, adding the number of patients in the categories of death, larger or new lesions, and deteriorating condition results in a total of 82 patients.

Source: ah200401a.

Variations between the Gemzar plus carboplatin and carboplatin treatment arms were minimized by assessing patients in both arms at regularly scheduled visits, at the same intervals, and during both the treatment and follow-up phases of the study. During the treatment phase, patients were assessed clinically every 3 weeks and objectively every 6 weeks. The 6-week interval between objective assessments is appropriate in a study of recurrent ovarian cancer patients because longer intervals between assessments could yield less accurate estimations of TtPD. Assessments continued to be performed at regular intervals in both treatment arms during the follow-up phase of the study. The interval between the date of PD and the date of the previous tumor assessment was calculated to determine adherence with the assessment schedule while on study and off. Adherence to disease assessment and the study schedule was demonstrated equally in both arms while on study and off study. No systematic tendency on the part of the investigators to overestimate or underestimate dates of PD was observed.

Table 11 presents the time intervals from the date of the previous tumor assessment to the date of PD while on and off study therapy, respectively.

Table 11. Summary Statistics for Time Interval from Previous Tumor Assessment to Date of Progressive Disease Patients on and off Treatment Study JHQJ/AGO-OVAR 2.5

	Time Interval (weeks)			
	On Treatment[a]		Off Treatment[b]	
Summary Statistic	GCb Arm (N=35)	Cb Arm (N=70)	GCb Arm (N=117)	Cb Arm (N=80)
25th percentile	5.7	5.2	4.8	4.3
Median	6.1	6.5	7.8	7.4
75th percentile	7.8	7.8	10.4	10.4

Abbreviations: Cb = carboplatin; GCb = gemcitabine plus carboplatin; N = number of patients who progressed while on study treatment.

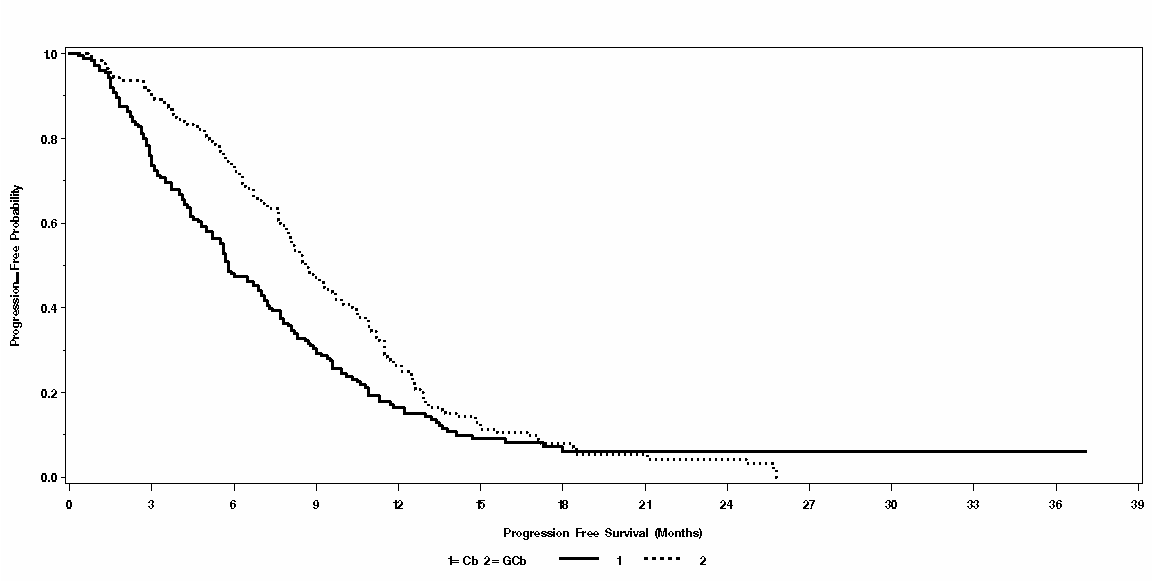
[a] For disease progression identified during study treatment, the interval was measured as the time between the date of the previous tumor assessment and the date of progressive disease.

[b] For disease progressions identified at the first off-study visit (Visit 101), the interval was measured as the time from the last on-study tumor assessment date to the progression date documented in Visit 101. For progressions identified beyond Visit 101, the interval was measured as the time between the previous visit date and the date of progressive disease.

Sources: ah200401a, js2006016.

4.3.4. Progression-Free Survival

Progression-free survival was statistically significantly better in the Gemzar plus carboplatin arm versus the carboplatin arm (log-rank p=0.0038). The estimate of the overall HR was 0.72 (95% CI, 0.57 to 0.90), which provides statistically significant evidence of an advantage for patients in the Gemzar plus carboplatin arm. The median progression-free survival was 8.6 months (95% CI, 8.0 to 9.7 months) on the Gemzar plus carboplatin arm and 5.8 months (95% CI, 5.2 to 7.1 months) on the carboplatin arm. Figure 7 presents the Kaplan-Meier distribution of progression-free survival for randomized patients in Study JHQJ/AGO-OVAR 2.5.



Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin.
Source: Figure JHQJ.11.1.

Figure 7. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates of progression-free survival.

The plot in Figure 7 demonstrates a separation of the curves from the first scheduled assessment of disease after baseline (that is, approximately 1.5 to 2 months after randomization), indicating an apparent treatment effect after the first cycle of Gemzar plus carboplatin.

A protocol-specified multiple regression analysis was conducted to obtain an adjusted HR for progression-free survival. The effect of the following prespecified baseline covariates on progression-free survival was analyzed: age (>60 years versus ≤60 years); ECOG performance status (1 or 2 versus 0); prior paclitaxel therapy (no versus yes); total tumor size (>18.7cm^2 versus ≤18.7cm^2); disease status (evaluable versus bidimensionally measured); and platinum-free interval (>12 months versus 6 to 12 months). The baseline factors that were significant, based on both univariate and multiple regression analyses, were platinum-free interval and total tumor size. Adjusting for these two prognostic factors, the Gemzar plus carboplatin versus carboplatin HR was 0.70 (95% CI, 0.55 to 0.88).

4.3.5. Robustness Analyses for Progression-free Survival

The robustness of statistically significant result for progression-free survival was evaluated in two ways: 1) sensitivity analyses were conducted to investigate the impact of various event and censoring mechanisms for progressive disease; 2) subgroup analyses of progression-free survival were conducted across key subgroups to investigate the internal consistency of the primary result. This robustness evaluation does not

introduce a multiplicity or inflated Type I error concern because primary endpoint (progression-free survival) was statistically significant. The purpose of these analyses is to explore whether the assumptions or decisions made in this study have a major impact on the positive progression-free survival result.

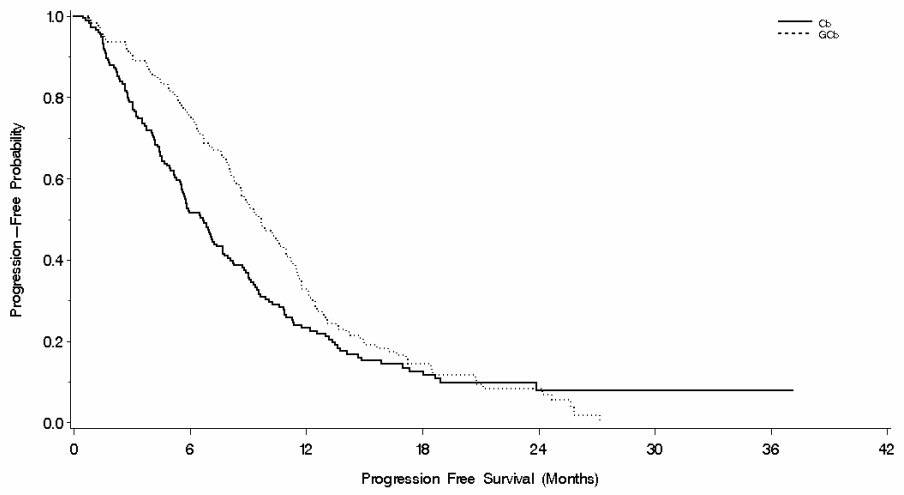
Following external expert advice, sensitivity analyses were performed to evaluate the impact of clinical progressions, objective progressions that occurred without recorded lesion measurements, missed scheduled disease assessments, and alternative censoring mechanisms. The details of these sensitivity analyses and results are summarized below.

Sensitivity Analysis 1 (SA1)

This endpoint permits a sensitivity analysis that assesses the impact of clinical (subjective) progressions. The difference between SA1 and our primary progression-free survival endpoint is that clinical progressions were not included as events nor did they effect the censoring times (ignored). For patients who had a clinical progression, SA1 was the time from randomization to death and for surviving patients was censored at the last visit. The events included in SA1 were:

- objective progression determined by the investigator
- deaths.

The Kaplan-Meier curve for SA1 is shown in Figure 8 and numerical results are in Table 12.



Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin.
Source: az200601a.

Figure 8. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates for Sensitivity Analysis 1.

Sensitivity Analysis 2 (SA2)

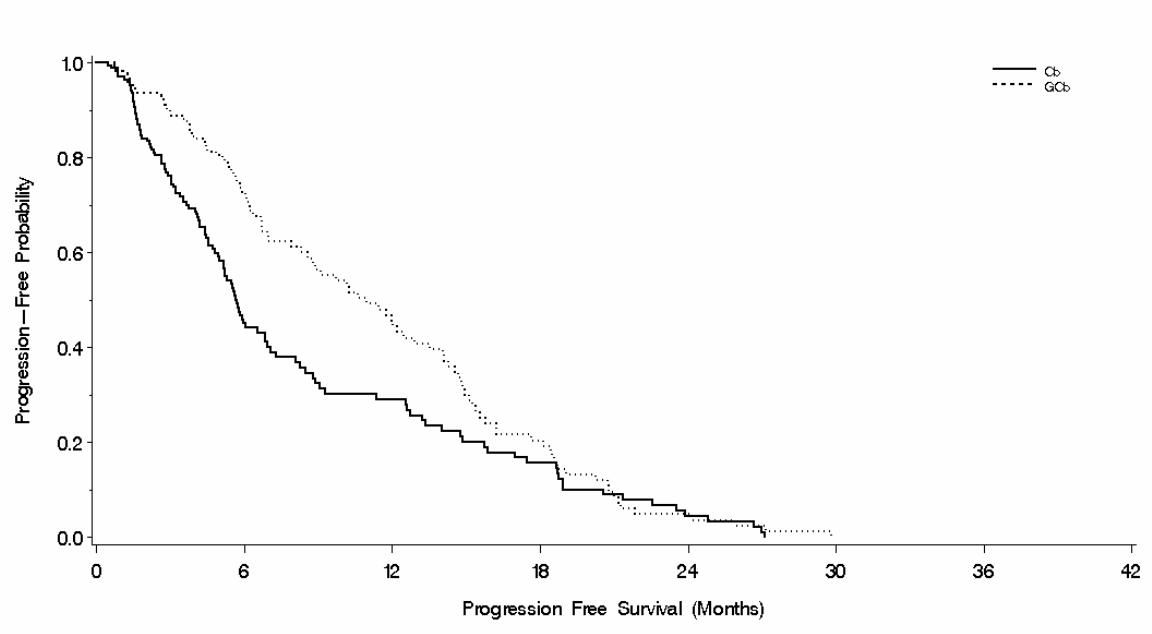
This endpoint permits a sensitivity analysis that assesses the impact of clinical (subjective) progressions and objective progression without lesion measurements captured on the clinical report form (CRF). The events included in SA2 were:

- objective progressions for which lesion measurements were captured on the CRF
- deaths.

Clinical progressions and objective progressions without documentation were ignored in SA2. For patients without documented objective progression and not known to have died as of the data cutoff date, SA2 was censored at the date of the last progression-free objective assessment.

Additionally, objective progressions with documentation following a missed or incomplete scheduled assessment were back-dated to the date of the missed or incomplete scheduled assessment. Back-dating was used as a conservative approach to determining progression, as the progression may have occurred at the time of the missed assessment.

The Kaplan-Meier curve for SA2 is shown in Figure 9 and numerical results are in Table 12.



Source: az200601a.

Figure 9. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates for Sensitivity Analysis 2.

Sensitivity Analysis 3 (SA3)

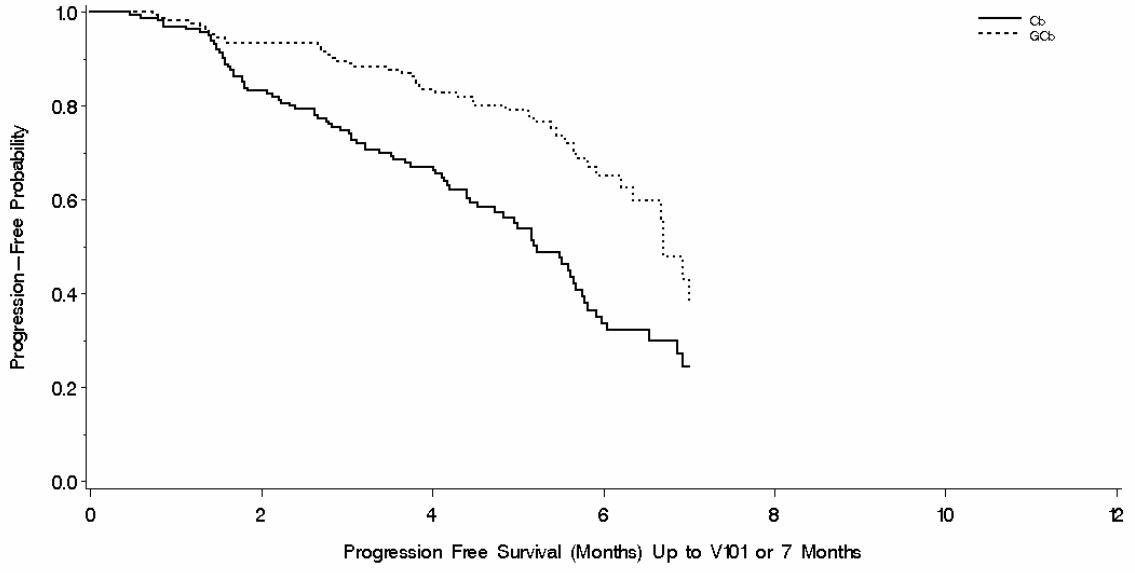
This endpoint reflects the interval of time during which patients were receiving study therapy, and received frequent assessments. The events considered in SA3 were only those events that occurred within the earliest of 7 months from randomization and the Visit 101 date. The events included in SA3 were:

- objective progressions (with lesion measurements captured on the CRF)
- deaths.

Clinical progressions and objective progressions without documentation were ignored in SA3. For patients without documented objective progression and not known to have died as of the data cutoff date, SA3 was censored at the date of the last progression-free objective assessment occurring within the earliest of 7 months from randomization and the Visit 101 date.

Additionally, objective progressions with documentation following a missed or incomplete scheduled assessment were back-dated to the date of the missed or incomplete scheduled assessment. Back-dating was used as a conservative approach to determining progression, as the progression may have occurred at the time of the missed assessment.

The Kaplan-Meier curve for SA3 is shown in Figure 10 and Table 12 lists numerical results.



Source: az200601a.

Figure 10. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates for Sensitivity Analysis 3.

A summary of the sensitivity analyses is presented in Table 12.

Table 12. Results from Sensitivity Analyses for Progression-Free Survival

Sensitivity Analysis	Censoring Mechanism	HR (95% CI) LR p-value	GCb Arm Median, months (95% CI)	Cb Arm Median, months (95% CI)
SA1: Ignore clinical progressions.	Last visit	0.76 (0.60-0.95) 0.0157	9.7 (8.6-10.9) E=148	6.7 (5.6-7.7) E=149
SA2: Ignore clinical progressions and objective progressions without documentation. Back-date objective progressions following missed/ incomplete assessments.	Last progression-free objective assessment	0.65 (0.50-0.85) 0.0013	11.0 (8.6-13.5) E=103	5.7 (5.2-6.9) E=123
SA3: Include objective progressions with lesion measurements and deaths within the earliest of 7 months or Visit 101. Back-date objective progressions following missed/ incomplete assessments.	Last progression-free objective assessment	0.45 (0.32-0.64) <0.0001	6.7 (6.3-NE) E=47	5.2 (4.7-5.7) E=84

Abbreviations: Cb = carboplatin; E = events; CI = confidence interval; GCb = Gemzar plus carboplatin; HR = hazard ratio; LR = log-rank; NE=non-estimable; SA = sensitivity analyses.
Source: az200601a.

All three sensitivity analyses were statistically significant in favor of the Gemzar plus carboplatin arm. These results demonstrated that patients whose progression events were based on clinical measures, or who progressed objectively but without recorded lesions measurements, did not unduly influence or affect the conclusion of the primary progression-free survival result. In addition to the sensitivity analyses summarized in Table 12, the sponsor conducted other sensitivity analyses which were previously submitted to the Agency (see Appendix 2). These results also supported the primary progression-free survival result.

In order to evaluate the internal consistency of the progression-free survival results based this single pivotal trial, subgroup analyses were conducted across baseline covariates that were pre-specified in the statistical analysis plan. These were the factors thought to be potentially important prognostic factors in ovarian cancer patients and were age, ECOG performance status, prior platinum therapy, tumor size, disease status, and duration of PFI. Note that these factors include the three stratification factors for the study (prior platinum therapy, PFI, and disease status at baseline). Per FDA requirements, origin was also included as a factor to define subgroup analyses.

All subgroups were analyzed using Cox (1972) proportional hazard model. In order to estimate the treatment HRs for each subgroup, a model was fit separately for each subgroup, which included treatment as the only cofactor. In addition, for each factor, a model was fit including treatment, factor, and the factor by treatment interaction as sources of variations. From this model the interaction term p-value was determined. Table 13 provides the results of these subgroup analyses.

Table 13. Internal Consistency Across Progression-Free Survival Study JHQJ/AGO-OVAR 2.5

Subgroup		GCb Arm events/total N	Cb Arm events/total N	HR (95% CI)	Interaction p-Value
Age	≤60 y	80/94	83/99	0.74 (0.54-1.01)	0.8552
	>60 y	76/84	72/79	0.70 (0.51-0.97)	
ECOG Performance Status	0	70/83	82/93	0.69 (0.50-0.95)	0.7392
	1 or 2	82/90	72/81	0.73 (0.53-1.01)	
Platinum-free Interval	6 to 12 mo	65/71	63/71	0.69 (0.49-0.98)	0.7500
	>12 mo	89/105	91/106	0.72 (0.54-0.97)	
Prior Paclitaxel Treatment	Yes	108/122	107/120	0.61 (0.47-0.80)	0.0704
	No	48/56	48/58	0.91 (0.61-1.36)	
Bidimensional Disease	Yes	145/163	149/170	0.72 (0.58-0.91)	0.2861
	No	10/14	4/5	0.35 (0.10-1.17)	
Total Tumor Area[a]	≤18.7cm^2	76/87	66/81	0.84 (0.60-1.17)	0.1636
	>18.7cm^2	69/77	84/90	0.60 (0.43-0.83)	
Caucasian	Yes	113/127	110/126	0.74 (0.57-0.97)	0.5421
	No	43/51	45/52	0.65 (0.42-0.99)	

Abbreviations: Cb = carboplatin; CI = confidence interval; GCb = Gemzar plus carboplatin; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; mo = months; N = number of patients with data; y = years.

[a] Median tumor burden size was 18.7 cm^2 in Study JHQJ/AGO-OVAR 2.5.

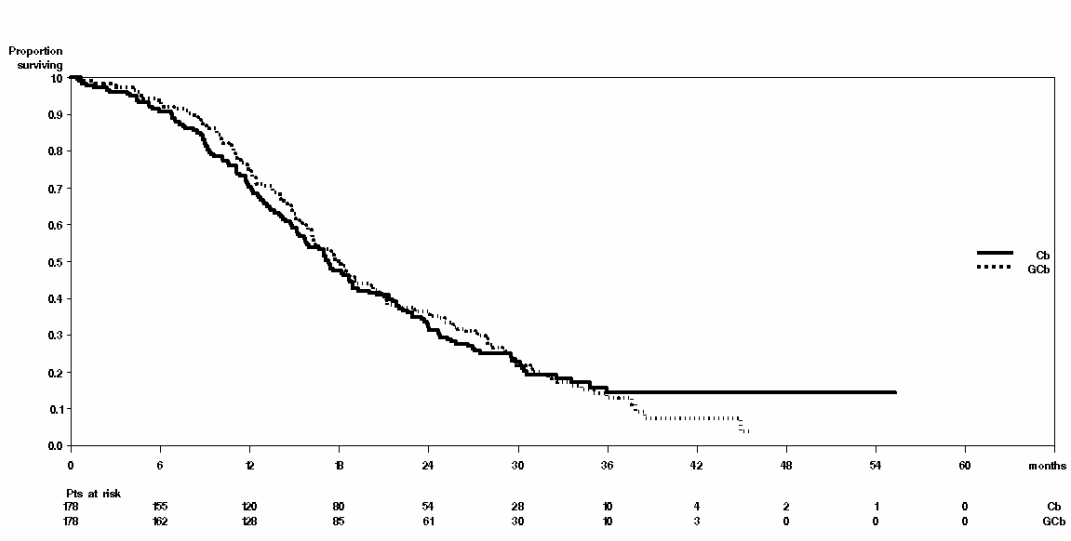
Source: az200504a.

All progression-free survival HRs for these key subgroups were <1, providing strong evidence of the internal consistency of the Gemzar plus carboplatin combination benefit over carboplatin monotherapy. The interaction p-values were all nonsignificant at the 0.05 level.

The analyses presented in this section indicate that the results for the primary study endpoint of progression-free survival are reliable and internally consistent.

4.3.6. Overall Survival

The estimate of median overall survival was 18 months (95% CI, 16.2 to 20.3 months) for Gemzar plus carboplatin-treated patients with 18.5% censoring, and 17.3 months (95% CI, 15.2 to 19.3 months) for carboplatin-treated patients with 22.5% censoring (log-rank test p=0.8977). The estimate of the overall HR was 0.98 (95% CI, 0.78 to 1.24). Figure 11 presents the Kaplan-Meier estimates of overall survival.



Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin.
Source: az200504a.

Figure 11. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates of overall survival.

The effect of the following prespecified baseline covariates on overall survival was conducted: age (>60 years versus ≤60 years); ECOG performance status (1 or 2 versus 0); prior paclitaxel therapy (no versus yes); total tumor size (>18.7 cm^2 versus ≤18.7 cm^2); disease status (evaluable versus bidimensionally measured); and platinum-free interval (>12 months versus 6 to 12 months).

Table 14 presents the effect of these individual covariates on overall survival.

Table 14. Effect of Individual Covariates on Overall Survival Study JHQJ/AGO-OVAR 2.5

Baseline Covariate	HR (95% CI)[a]	p-Value[a]
Age >60 years vs ≤60 years	0.96 (0.76-1.21)	0.7224
ECOG Performance Status 1 or 2 vs 0	**1.48 (1.17-1.88)**	**0.0011**
Prior Paclitaxel Therapy no vs yes	**1.32 (1.02-1.70)**	**0.0313**
Total Tumor Size >18.7cm^2 vs ≤18.7cm^{2,b}	**1.85 (1.45-2.37)**	**<0.0001**
Disease Status evaluable vs bidimensionally measured[c]	0.96 (0.57-1.61)	0.8612
Platinum-free Interval >12 months versus 6 to 12 months	**0.61 (0.48-0.77)**	**<0.0001**

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; vs = versus.

[a] Bold = statistically significant at the 0.05 level.

[b] Median tumor burden size was 18.7 cm^2 in Study JHQJ/AGO-OVAR 2.5.

[c] Evaluable refers to patients who were not bidimensionally measured.

Source: az200504b.

The protocol-specified multiple regression analysis for overall survival resulted in a final model that included ECOG performance status (1 or 2 versus 0), median tumor area (larger versus smaller), and platinum-free interval (>12 months versus 6 to 12 months) as significant prognostic factors. The adjusted treatment HR of Gemzar plus carboplatin over carboplatin was 0.86 (95% CI, 0.67 to 1.10). However, 30 patients had a missing value for at least one of these baseline prognostic factors totaling 37 missing values. Consequently, these patients were not included in the protocol-specified adjusted survival analysis, resulting in an adjusted HR based on a subset of 326 patients. The difference between the unadjusted survival HR (0.98) and the protocol-specified adjusted HR (0.86) may be attributed to both prognostic adjustment and an artifact of the subsetting effect. An MI analysis was conducted to account for the unavailable baseline data which provided a more robust estimate of the adjusted treatment group HR. The results of the MI analysis based on all 356 patients are summarized in Table 15.

Table 15. Final Results for Multiple Regression Survival Analysis Using Multiple Imputation Study JHQJ/AGO-OVAR 2.5 All Patients (N=356)

Baseline Covariate	HR (95% CI)	p-Value
Treatment Group GCb vs Cb	0.917 (0.724-1.163)	0.4760
ECOG Performance Status 1 or 2 vs 0	1.307 (1.015-1.684)	0.0383
Total Tumor Size >18.7cm^2 vs ≤18.7cm^{2,a}	1.640 (1.267-2.123)	0.0002
Platinum-free Interval >12 months vs 6 to 12 months	0.646 (0.506-0.823)	0.0005

Abbreviations: Cb = carboplatin; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; GCb = Gemzar plus carboplatin; HR = hazard ratio; vs = versus.

[a] Median tumor burden size was 18.7 cm^2 in Study JHQJ/AGO-OVAR 2.5.

Source: az200601a.

The unadjusted HR for overall survival (0.98), the protocol-specified adjusted HR (0.86), and the MI adjusted HR (0.92) provide consistent evidence of no survival detriment due to Gemzar plus carboplatin.

4.3.6.1. Postdiscontinuation Therapy

The use of postdiscontinuation therapy was prospectively planned to be collected in Study JHQJ/AGO-OVAR 2.5, though information on specific agents was not collected. Table 16 presents the number of patients who received postdiscontinuation therapy.

Table 16. Patients Who Received Postdiscontinuation Therapy, n (%) Study JHQJ/AGO-OVAR 2.5

Postdiscontinuation Therapy	GCb Arm N=178	Cb Arm N=178
Chemotherapy	135 (75.8)	129 (72.5)
1 line	29 (16.3)	24 (13.5)
2 lines	22 (12.4)	28 (15.7)
3 or more lines	17 (9.6)	19 (10.7)
Unspecified number of lines	67 (37.6)	58 (32.6)
Hormonal or immunotherapy or biological	35 (19.7)	32 (18.0)
Radiation	9 (5.1)	17 (9.6)
Other therapy – not specified	28 (15.7)	27 (15.2)
No postdiscontinuation therapy reported	29 (16.3)	38 (21.3)

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin; N = number of randomized patients.

Source: az200504b.

A variety of treatment modalities were utilized in the poststudy setting in Study JHQJ/AGO-OVAR 2.5. The frequencies of postdiscontinuation therapy was similar on

both arms, with greater than 70% of patients receiving at least one additional line of chemotherapy, and nearly 20% receiving hormonal/immunotherapy. The use of combination therapy did not preclude patients from receiving postdiscontinuation chemotherapy; Gemzar plus carboplatin-treated patients received postdiscontinuation chemotherapy with similar frequency as carboplatin-treated patients. The effect of crossover treatments could not be reliably assessed as specific information of the agents utilized was not collected.

4.3.7. Response Rate

In Study JHQJ/AGO-OVAR 2.5, overall best study response rate was assessed by the investigator utilizing SWOG criteria. As shown in Table 17, the investigator-assessed response rate for the 356 randomized patients was significantly higher on the Gemzar plus carboplatin arm compared with the carboplatin arm (47.2% versus 30.9%; chi-square p=0.0016). There were twice as many complete responses (CRs), according to investigator assessment, on the Gemzar plus carboplatin arm compared with the carboplatin arm (14.6% versus 6.2%; chi-square p=0.0092).

Table 17. Summary of Overall Best Study Response Investigator-Assessed Response Rate Study JHQJ/AGO-OVAR 2.5

	GCb Arm N=178 % (n) (95% CI)	**Cb Arm N=178 % (n) (95% CI)**
Complete response	14.6 (26) (9.4 to 19.8)	6.2 (11) (2.6 to 9.7)
Partial response	30.3 (54) (23.6 to 37.1)	24.2 (43) (17.9 to 30.4)
PRNM	2.2 (4) (0.1 to 4.4)	0.6 (1) (0 to 1.7)
Total responders	47.2 (84) (39.9 to 54.5)	30.9 (55) (24.1 to 37.7)
Stable disease	38.2 (68) (31.1 to 45.3)	38.8 (69) (31.6 to 45.9)
Progressive disease	7.9 (14) (3.9 to 11.8)	16.3 (29) (10.9 to 21.7)
Not evaluable	1.7 (3) (0 to 3.6)	5.1 (9) (1.8 to 8.3)
Not done	5.1 (9) (1.8 to 8.3)	9.0 (16) (4.8 to 13.2)

Abbreviations: Cb = carboplatin; CI = confidence interval; GCb = Gemzar plus carboplatin; n = number of patients with response; N = number of randomized patients; PRNM = partial response in nonmeasurable disease.

Source: Table JHQJ.11.17.

4.3.7.1. Duration of Response

As shown in Table 18, there was a numerically longer median duration of response on the Gemzar plus carboplatin arm compared with the carboplatin arm (median 8.4 versus 7.3 months; log-rank p=0.2511). Nine (10.7%) patients on the Gemzar plus carboplatin patients and 6 (10.9%) on the carboplatin arm were censored for duration of response. The HR was 0.81 (95% CI, 0.56 to 1.16).

Table 18. Summary Statistics for Duration of Response Investigator-Assessed Data Patients with CR, PR, or PRNM Study JHQJ/AGO-OVAR 2.5

Parameter	GCb Arm (N=84)	Cb Arm (N=55)
Patients censored, n (%)	9 (10.7)	6 (10.9)
Patients with events, n	75	49
Median duration of response, months	8.4	7.3
(95% CI)	(7.6 to 9.6)	(5.9 to 8.2)
Log-rank test p value	p=0.2511	
HR (95% CI)	0.81 (0.56 to 1.16)	
% of responders who had not progressed at 6 months	66.7	59.5
(95% CI)	(56.6 to 76.8)	(46.5 to 72.6)
Estimated treatment difference at 6 months	7.1	
(95% CI); chi-square p-value	(-9.4 to 23.6); p=0.3970	

Abbreviations: Cb = carboplatin; CI = confidence interval; CR = complete response; GCb = Gemzar plus carboplatin; HR = hazard ratio; n = number of patients; N = total number of patients with tumor response as per the investigator; PR = partial response; PRNM = partial response in nonmeasurable.
Sources: Table JHQJ.11.21, Table JHQJ.11.22.

4.3.7.2 Robustness Analysis for Response Rate

An independent review of response in Study JHQJ/AGO-OVAR 2.5 was performed for the subgroup of patients that used CT scans for response evaluation to assess the potential for investigator bias given the open-label design of the study and substantiate the activity of Gemzar. This is consistent with the European Regulatory guidance that recommends an independent assessment in open-label studies when response is used as an endpoint. The independent review panel consisted of 3 radiologists external to Lilly and AGO-OVAR. The reviewers were provided radiologic imaging for patients with baseline and one postbaseline radiologic assessment. It was an independent read on the radiologic scans available. The reviewers were blinded to the investigators' response assessments and patient's treatment arm. The independent reviewers were provided the protocol for response assessment criteria. In contrast to the investigator assessment documenting all lesions and physical exam measurements, the independent review panel identified and followed only a limited number of target lesions. This was considered appropriate for the purposes of the independent review of response. Patients with only physical examination

or ultrasound were excluded from this independent review. In this study, 222 of 356 randomized patients had images available for review.

The results of the independent review were compared with the investigator review to assess for any evidence of overt bias in response assessment. The percent of patients downgraded in the independent review was essentially the same as the percent upgraded. This pattern was also observed when reviewing concordance by treatment arm. These results suggest no evidence of investigator bias (Table 19).

Table 19. Concordance of Tumor Responses Investigator Assessed versus Independently Reviewed Data Study JHQJ/AGO-OVAR 2.5

	Independently Reviewed					
	All Patients N=222		GCb Arm N=121		Cb Arm N=101	
Investigator Assessed	**R**	**NR**	**R**	**NR**	**R**	**NR**
R	66	25	39	17	27	8
NR	26	105	17	48	9	57

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin; N = number of patients; NR = nonresponder; R = responder.
Sources: az200504a, ah200401a.

For the 222 patient independently-reviewed cohort, the investigator-assessed and the independently reviewed response rates were nearly identical (Table 20). These results demonstrated that the estimate of response for Gemzar was reliable and consistent between the investigator and independent reviewer regardless of methodology used. There was no statistically significant difference in independently reviewed response rates between the Gemzar plus carboplatin arm and the carboplatin arm in Study JHQJ/AGO-OVAR 2.5 (p=0.1091). The lack of statistical significance was related to the smaller number of patients eligible for independent review and the smaller difference of response rate between arms in this subset of patients as compared to the ITT population.

Table 20. Response Rate in Independently Reviewed Cohort Investigator Assessed versus Independently Reviewed Data Study JHQJ/AGO-OVAR 2.5

	Investigator Assessed	Independently Reviewed
GCb Arm, N=121		
Response Rate	46.3%	46.3%
CR/PR	15/41	11/45
Cb Arm, N=101		
Response Rate	34.7%	35.6%
CR/PR	4/31	4/32
p-value	0.0794	0.1091

Abbreviations: Cb = carboplatin; CR = complete response ; GCb = Gemzar plus carboplatin; PR = partial response.
Sources: ah200304b, js200601b.

4.3.8. Patient Reported Outcomes and Patient Benefit

4.3.8.1. Patient Reported Outcomes

The EORTC QLQ-C30 and QLQ-OV28 instruments were used to measure PROs regarding QoL. QLQ-C30 is a cancer-specific QoL instrument, and scales/items are scored 0 to 100. There are five functional scales and one Global QoL scale for which higher scores represent better QoL. There are eight symptom scale/items and a financial impact item for which lower scores represent lower symptomatology or distress. Although the QLQ-C30 is a general cancer instrument, it has been validated for use in ovarian cancer patients as well (Groenvold et al. 1997). The QLQ-OV28 is an ovarian cancer instrument, with seven symptom scales scored 0 to 100. For all QLQ-OV28 scales, lower scores represent lower symptomatology or distress. If a validated translation of the QoL questionnaires was available, patients were expected to complete the questionnaires at baseline, at the end of each cycle of therapy (prior to the next cycle of therapy or at study discontinuation), and at the 30-day poststudy visit. Patients were treated for a planned 6 cycles of therapy, rather than to disease progression. In Study JHQJ/AGO-OVAR 2.5, the questionnaire-completion compliance rates were high, 153 patients (86%) in the Gemzar plus carboplatin arm and 150 patients (84.3%) in the carboplatin arm filled out a questionnaire at baseline and at least one postbaseline visit during the treatment period.

The sensitivity of the PRO tools to detect treatment differences may have been reduced, because patients may have stopped completing questionnaires prior to showing disease symptoms. This is because, per protocol, patients were not required to complete questionnaires after discontinuation. When patients discontinued study treatment for reasons other than disease progression (approximately 70%), completion of the final questionnaire likely preceded degradation of symptoms. In general, major degradation of symptoms follows disease progression. Therefore, when patients discontinued due to progression (approximately 30%), major degradation of symptoms may not have been

reflected in the responses to the questionnaires. Because patients in Study JHQJ/AGO-OVAR 2.5 were not required to complete questionnaires after discontinuation, PRO results did not reflect the period of time when patients were most symptomatic, thus the sensitivity of the tools may have been compromised.

Table 21 summarizes changes over time within each treatment arm for each item from the QLQ-C30 and QLQ-OV28 scales. Within-arm improvements in these scales were similar in each treatment arm; however, Global QoL improvements were maintained only on the Gemzar plus carboplatin arm.

Table 21. Summary of Statistically Significant Changes Over Time within Each Treatment Arm for QoL Scales/Items (Cycles 1 through 6)

QoL Scale/Item	GCb Arm (N=154)	Cb Arm (N=152)
QLQ-C30		
Global QoL	Improved	Stable
Function Scales:		
Physical functioning	Stable	Stable
Role functioning	Stable	Stable
Cognitive functioning	Stable	Stable
Emotional functioning	Improved	Improved
Social functioning	Stable	Stable
Symptom Scales:		
Fatigue	Stable	Stable
Nausea/vomiting	Worsened[a]	Worsened[a]
Pain	Improved	Improved
Dyspnea	Stable	Stable
Sleep disturbance	Improved	Improved
Appetite loss	Improved	Improved
Constipation	Stable	Stable
Diarrhea	Stable	Stable
Financial impact	Stable	Stable
QLQ-OV28		
Abdominal/GI symptoms	Improved	Improved
Peripheral neuropathy	Worsened	Worsened
Other chemotherapy side effects	Worsened	Worsened
Hormonal symptoms	Stable	Stable
Body image	Stable	Stable
Attitude to disease and treatment	Improved	Improved
Sexual functioning	Stable	Stable

Abbreviations: Cb = carboplatin monotherapy; GCb = gemcitabine plus carboplatin combination therapy; GI = gastrointestinal; N = total population size; QoL = quality of life.

[a] Cycles 1 and 2 only, then stable.

Source: SQOLSTAT.

Per the statistical analysis plan, these scales were further analyzed using repeated measures analysis techniques. These analyses focused on nine scales thought to be most relevant to ovarian cancer patients due to frequency of occurrence and potential impact on patient well being. These included six scales from QLQ-C30 (fatigue, nausea/vomiting, appetite loss, dyspnea, diarrhea, and constipation) and two scales from QLQ-OV28 (abdominal/GI pain and "other chemotherapy side effects") (Cull et al. 2001; Ozols et al. 2001). Additionally, Global QoL was included in this analysis.

Table 22 shows treatment group means for the key ovarian specific scales. There was no statistical treatment difference between these scales.

Table 22. Results from Repeated Measures Analysis Ovarian-Specific Scales from QLQ-C30 and OV28 Study JHQJ/AGO-OVAR 2.5

Scale	GCb Arm Mean[a]	Cb Arm Mean[a]
Global QoL[b]	61.2	59.0
Symptom Scales[c]:		
Fatigue	40.2	39.8
Nausea/Vomiting	16.6	14.3
Dyspnea	23.3	23.4
Appetite Loss	21.6	20.4
Constipation	22.1	24.6
Diarrhea	9.0	8.8
Abdominal/GI Pain	24.5	26.5
Other Chemo Side Effects	23.2	20.3

Abbreviations: Cb = carboplatin monotherapy; GCb = gemcitabine plus carboplatin combination therapy; GI = gastrointestinal; QoL = quality of life.

[a] Treatment group marginal means averaged over 6 cycles.

[b] Higher scores represent better QoL.

[c] Lower scores represent lower symptomatology or distress.

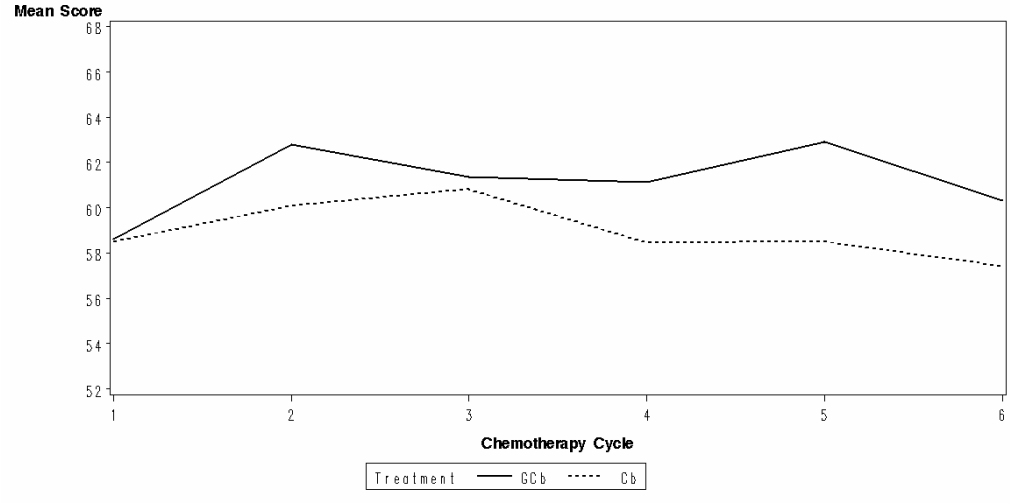
Source: az200504a.

Overall summary items are useful to assess the general well being of a patient. Although there is no total score for the QLQ-C30 or QLQ-OV28, the QLQ-C30 includes a key validated global scale (Global QoL). Global QoL is a composite of the following QLQ-C30 questions:

- "How would you rate your *overall health* during the past week?" (Question 29)
- "How would you rate your *overall QoL* during the past week?" (Question 30).

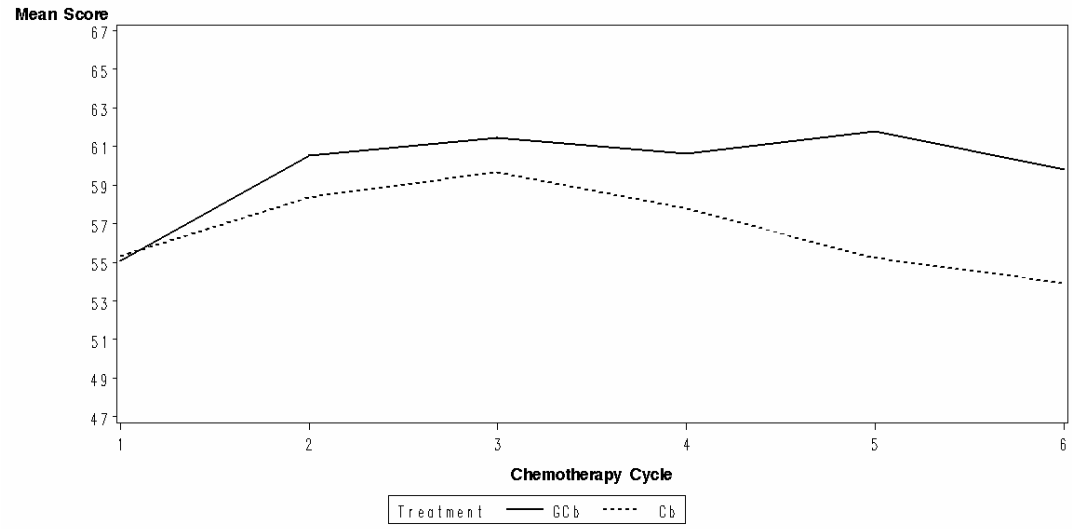
Global QoL may be the best indicator of general well being as it is a composite of items focusing on both overall health and QoL, and is the focus of the PRO results in this section.

Cycle specific results from the repeated measures analysis are presented for Global QoL. The analyses were conducted for all patients (Figure 12 and Appendix 3), symptomatic patients (Figure 13 and Appendix 3), and asymptomatic patients (Appendix 3).



Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin.
Source: js200601b.

Figure 12. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates of Global QoL scores for all patients.



Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin.
Source: js200601b.

Figure 13. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates of Global QoL scores for symptomatic patients.

There were no major between arm differences for the individual ovarian-specific scales, suggesting no detriment for PROs associated with the Gemzar plus carboplatin combination. However, there were numerical trends favoring the Gemzar combination for Global QoL, which were driven by the symptomatic patients. In addition, there was no detriment in Global QoL in the asymptomatic patients.

4.3.8.2. Patient Benefit

Gemzar plus carboplatin demonstrates statistically significant improvements in progression-free survival, overall response rate, and complete response rate over carboplatin monotherapy. Progression-free survival has been recognized by FDA as a measure of clinical benefit in patients with lung and colorectal cancers. In ovarian cancer, FDA has recognized complete response as a clinical benefit. However, progression-free survival is not currently recognized by the FDA as clinical benefit endpoint in ovarian cancer trials. At the initiation of this trial, progression-free survival was considered by AGO-OVAR and the Sponsor to be an appropriate endpoint to establish the safety and efficacy of an experimental treatment in this disease setting. Benefits of progression-free survival to the patients were considered to be self-evident. While it is beyond the scope of this trial to formally validate progression-free survival as a clinical benefit, the Sponsor explored the relationship between improvement in progression-free survival and other measures considered to be reflective of patient well-being.

Since planning and starting this study, the role of PROs has become increasingly emphasized. The evolution of this work has resulted in more sophisticated analyses to interpret patient reported outcome data. This includes AUC and 10-point improvement or degradation. In addition, measures were assessed that reflect the durability of disease control during a chemotherapy-free interval. The goal of this investigation was to understand whether patients report or perceive benefit from a treatment. The analyses, presented below, were exploratory, and not intended to represent additional claims.

Area under the curve is an alternative method of assessing patient reported outcomes, which is equivalent to the total health-related QoL experienced by the patient on a given scale/item (Jordhoy et al. 2001). The advantages of this approach are three-fold: 1) it is a summary measure that avoids the need for multiple statistical comparisons; 2) it reflects both early and continuous treatment effects; and 3) it takes into account potential unequal time periods between assessments (Fairclough et al. 1998; Jordhoy et al. 2001). In essence, AUC is a two dimensional measurement that reflects both quality and quantity of life. For Study JHQJ/AGO-OVAR 2.5, AUC was calculated over a 126 day period (6 cycles x 21 days/cycle). Results for the ovarian-specific scales are shown in Table 23 below.

Table 23. AUC Results Ovarian-Specific Scales Study JHQJ/AGO-OVAR 2.5

Scale	GCb Arm AUC Mean[a] (N)[b]	Cb Arm AUC Mean[a] (N)[b]	Difference (SE)	p-Value
Global QoL	6375.22 (151)	5841.07 (147)	534.15 (272.32)	0.0508
Symptom Scales:				
Fatigue	6201.41 (152)	5862.99 (152)	338.41 (312.93)	0.2804
Nausea/vomiting	8755.15 (152)	8397.79 (151)	357.36 (316.13)	0.2592
Dyspnea	8127.96 (152)	7467.33 (150)	660.63 (342.50)	0.0547
Diarrhea	9591.06 (151)	9005.33 (150)	585.73 (333.10)	0.0797
Appetite Loss	8037.31 (151)	7636.87 (151)	400.44 (356.67)	0.2625
Constipation	7910.02 (153)	7353.84 (152)	556.18 (380.26)	0.1446
Abdominal Pain	7642.86 (121)	7006.93 (118)	635.93 (336.92)	0.0603
Other Chemo Side Effects	8101.41 (121)	7823.15 (115)	278.26 (314.70)	0.3775

Abbreviations: AUC = area under the curve; Cb = carboplatin; GCb = gemcitabine plus carboplatin; N = number of patients included in the analysis; QoL = quality of life; SE=Standard Error.

[a] Higher scores represent better QoL.

[b] Patients were included in the analysis if they had a baseline and at least one postbaseline observation.

Source: az200504a.

The results indicate that there were no significant treatment differences at the 0.05 level for any of the scales/items relevant to ovarian cancer. However, average AUC scores were higher in the Gemzar plus carboplatin arm than the carboplatin arm for all nine ovarian-specific scales/items suggesting that Gemzar plus carboplatin patients generally experienced more and longer-lasting improvements in QoL than carboplatin patients. In fact, Global QoL AUC score was borderline significant ($p=0.0508$) as well as several other scales (dyspnea, diarrhea, and abdominal pain, $p<0.08$). As shown in Appendix 3, 12 of the 13 remaining scales showed numerical results favoring Gemzar plus carboplatin.

While it remains a matter of debate as to how large of a change in QoL scores is required to be clinically meaningful, a change of 5 to 10 points has been demonstrated to be perceptible to patients (and thus presumably clinically meaningful) in a variety of diseases (including several cancers) (Osoba et al. 2005). As a 5-point change may be so sensitive as to yield more "false positives," a cut-off point of ≥10 points has been

recommended to identify those patients who have experienced improved QoL outcomes. Thus, analyses were conducted to determine the proportion of patients with a ≥10-point improvement in the Global QoL score. Additionally, to evaluate the onset of symptom improvement (or worsening), time from randomization to ≥10-point improvement (or ≥10-point worsening) was analyzed using Kaplan-Meier techniques.

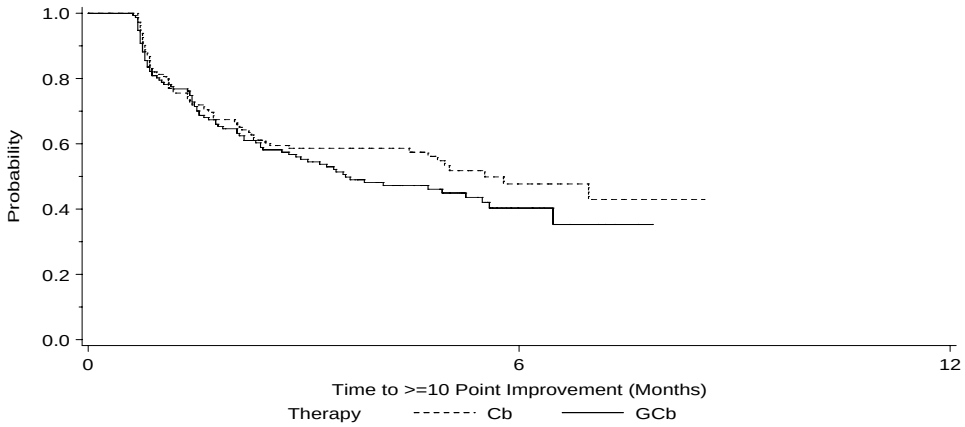
As presented in Table 24, the Gemzar plus carboplatin arm had a greater proportion of patients that improved by ≥10 points than the carboplatin arm for all scales/items relevant to ovarian cancer patients except nausea/vomiting and other chemotherapy side effects.

Table 24. Proportion of Patients that Improved by at Least 10-points at any Cycle
Ovarian-Specific Scales
Study JHQJ/AGO-OVAR 2.5

	% (Number of Patients That Improved/ Total Number of Patients)	
Scale	**GCb Arm**	**Cb Arm**
Global QoL	53.9% (82/152)	44.2% (65/147)
Symptom Scales:		
Fatigue	58.2% (89/153)	55.3% (84/152)
Dyspnea	35.9% (55/153)	30.7% (46/150)
Constipation	33.8% (52/154)	30.3% (46/152)
Nausea/vomiting	28.8% (44/153)	31.8% (48/151)
Diarrhea	14.5% (22/152)	10.7% (16/150)
Appetite Loss	49.3% (75/152)	35.8% (54/151)
Abdominal Pain	54.1% (66/122)	43.7% (52/119)
Other Chemo Side Effects	25.4% (31/122)	25.9% (30/116)

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin, QoL = quality of life.
Source: az200504a.

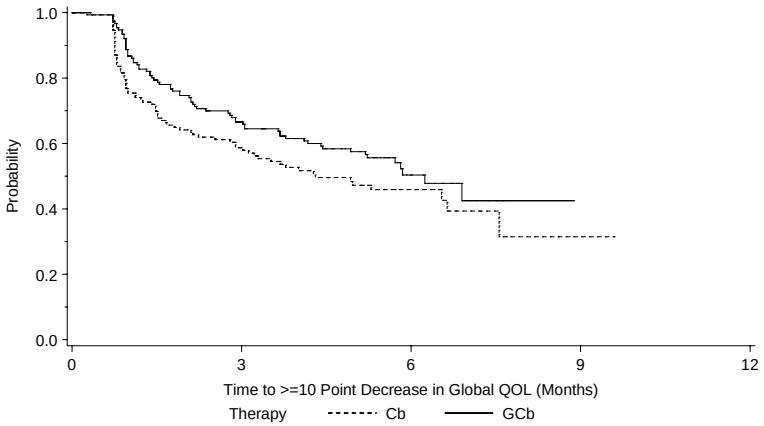
To assess the onset of improved Global QoL scores in Study JHQJ/AGO-OVAR 2.5, the median time from randomization to a ≥10-point improvement in the Global QoL score was estimated for each treatment arm. Patients who never reported a ≥10-point improvement in the Global QoL score were censored at the date of the last completed QoL questionnaire. The median time to ≥10-point improvement was 3.6 months (95% CI, 2.7 to 5.6 months) in the Gemzar plus carboplatin arm with 46.1% censoring compared with 5.5 months (95% CI, 4.5 to not evaluable [NE] months) with 55.8% censoring, log-rank p=0.2284, suggesting that Gemzar plus carboplatin-treated patients may experience a shorter time to improvement in Global QoL than carboplatin-treated patients (Figure 14).



Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin.
Source: az200504a.

Figure 14. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates of time to 10-point or greater improvement in Global QoL score.

Similarly, to assess the onset of worsening of Global QoL, the median time from randomization to a ≥10-point worsening in the Global QoL score was estimated for each treatment arm. Patients who never reported a ≥10-point worsening in the Global QoL score were censored at the date of the last completed QoL questionnaire. The median time to ≥10-point worsening was 6.2 months (95% CI, 4.9 to NE months) in the Gemzar plus carboplatin arm with 61.2% censoring compared with 4.3 months (95% CI, 3.0 to 7.6 months) with 57.9% censoring, log-rank p=0.0838. These results suggest that Gemzar plus carboplatin-treated patients may experience a longer period of time until worsening of Global QoL than carboplatin-treated patients (Figure 15).

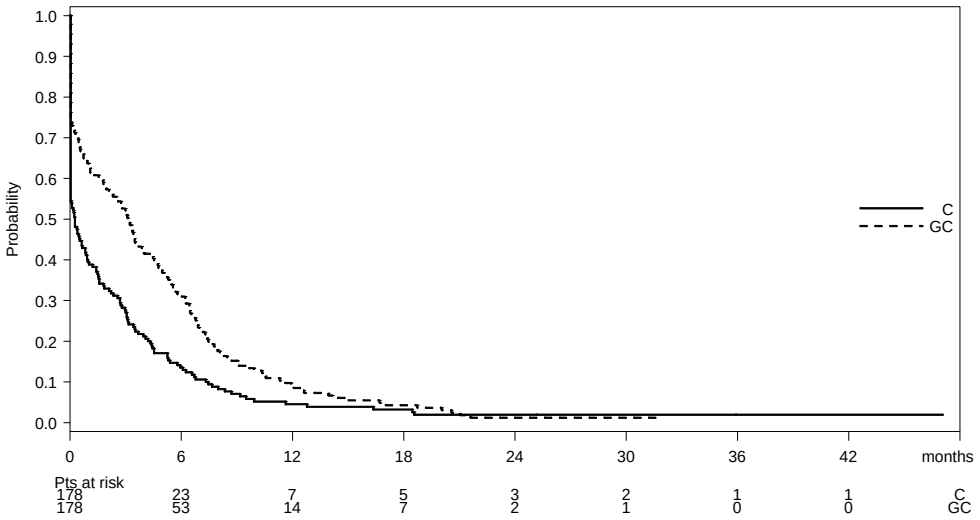


Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin.
Source: az200504a.

Figure 15. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates of time to 10-point or greater worsening in Global QoL score.

Study JHQJ/AGO-OVAR 2.5 was prospectively designed for six cycles of chemotherapy administered every 21 days, with an additional two cycles allowed in selected patients. Patients received a median number of six cycles on both arms of the study, for a median treatment interval of 126 days (approximately 4 months).

The length of time a patient is off of chemotherapy while disease is under control ("event free"), is an important aspect of clinical benefit for patients. This is a benefit to patients because it is a time they are alive, have their disease under control, and are not enduring chemotherapy. In order to assess the event-free interval, an analysis was conducted on the time from discontinuation to postdiscontinuation chemotherapy, death, or disease progression (Figure 16).



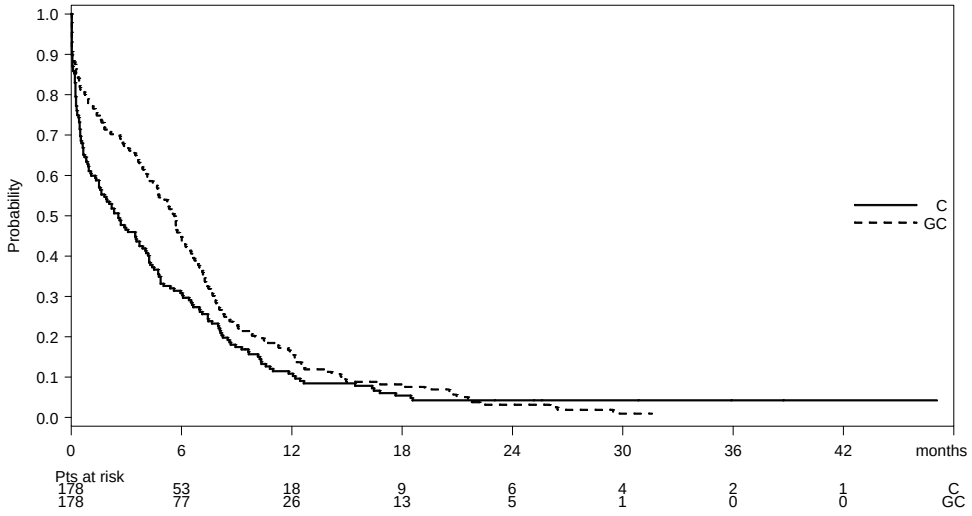
Abbreviations: Cb = carboplatin; GC = Gemzar plus carboplatin.
Source: js200601b.

Figure 16. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates of time from discontinuation to postdiscontinuation chemotherapy, death, or disease progression.

Patients treated with Gemzar plus carboplatin had longer event-free duration than carboplatin monotherapy (median Gemzar plus carboplatin 3.12 months [censoring rate: 4.5%] versus carboplatin 0.26 months [censoring rate: 4.5%]; HR, 0.63; 95% CI, 0.50 to 0.80). This corresponds to an approximate 3 month improvement in the median event-free time after a patient has completed protocol-specified therapy in favor of the Gemzar combination.

Another important aspect of clinical benefit for patients is the length of time from second-line therapy discontinuation to the beginning of third-line therapy ("treatment-free interval"). Patients with recurrent cancer are concerned with the amount of

disruption in their daily lives when faced with cancer treatment, including the amount of time spent going to the clinic to receive chemotherapy. To explore whether the statistically significant improvement in progression-free survival translates to a treatment-free interval difference, time from treatment discontinuation to the beginning of third-line therapy or death was analyzed. In this analysis, PD was ignored (Figure 17).



Abbreviations: Cb = carboplatin; GC = Gemzar plus carboplatin.
Source: js200601b.

Figure 17. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates of time from discontinuation to postdiscontinuation chemotherapy or death.

Patients treated with Gemzar plus carboplatin had a longer treatment-free interval than carboplatin monotherapy (median Gemzar plus carboplatin 5.6 months [censoring rate: 5.1%] versus carboplatin 2.6 months [censoring rate: 7.3%]; HR, 0.80; 95% CI, 0.64 to 0.99). As with the event-free interval, the treatment-free interval was approximately 3 months longer in the Gemzar combination arm.

4.3.8.3. Patient Reported Outcomes and Patient Benefit Conclusions

As there is no summation score for the QLQ-C30 or QLQ-OV28 instruments, the composite "Global QoL" scale from QLQ-C30 (consisting of items focusing on both overall health and QoL), may be the best indicator of general well being and was used to assess the overall impact of treatment on QoL.

The validity of this choice was supported by the internal consistency in the functional and symptomatic scales. The majority of scales (QLQ-C30 and QLQ-OV28) showed better outcomes for the Gemzar plus carboplatin arm compared with the carboplatin arm, as analyzed by AUC and percentage of patients with 10-point improvement.

Patients in the Gemzar plus carboplatin arm experienced a longer time to a worsening event after treatment discontinuation. In addition, these patients had a longer treatment-free interval.

In summary, patients on the Gemzar plus carboplatin arm experienced improved QoL sooner, a delayed time to QoL worsening, and a longer time to progression, death, or subsequent chemotherapy.

4.4. Efficacy Conclusions

Study JHQJ/AGO-OVAR 2.5 demonstrated statistically significant improvement in the primary endpoint of progression-free survival (p=0.0038; HR, 0.72). Multiple sensitivity analyses confirmed the primary analysis results, indicating that progression-free survival was statistically convincing and internally consistent. In addition, there was a statistically significant improvement in overall and complete response rates. The investigator-assessed and the independently reviewed response rates were nearly identical, showing that the estimate of response for Gemzar was reliable and consistent between the investigator and independent reviewer. There was no evidence of investigator bias, measurement intervals were similar, and there was a high concordance between investigator and independent assessment. There was no statistically significant difference in overall survival, however this study was not designed or powered to detect differences in this secondary endpoint.

In conclusion, Gemzar plus carboplatin demonstrated internally consistent and statistically persuasive efficacy in the primary endpoint of progression-free survival, in conjunction with increased overall and complete response rates. The efficacy was further supported by a trend towards an improvement in QoL, delay to deterioration of Global QoL, and a longer treatment-free interval.

5. Safety of Gemzar

Since its first approval in 1995, Gemzar has been used in many countries throughout the world for indications of NSCLC, pancreatic cancer, bladder cancer, breast cancer, and ovarian cancer. To date, it is estimated that over 1.3 million patients have been treated with Gemzar, and over 8000 patients in Lilly-sponsored studies have received Gemzar.

Gemzar, as a single agent, has shown a favorable safety profile in a large number of patients in the dose range of 800 to 1250 mg/m^2 when given as a 30-minute infusion, weekly for 2 or 3 weeks, followed by 1 week of rest.

5.1. Summary of Safety

The dose of Gemzar (1000 mg/m^2) used in Study JHQJ/AGO-OVAR 2.5 was based on the dose-finding Phase 1/2 Study O026 (du Bois et al. 2001).

Overall, the toxicity profile of Gemzar plus carboplatin is predictable and consistent with the toxicity profiles of each compound as a monotherapy, and with the profile observed in previous studies of Gemzar plus carboplatin. Neutropenia, anemia, leukopenia, and thrombocytopenia are the most common CTC laboratory toxicities. Common nonlaboratory toxicities include nausea, alopecia, vomiting, fatigue, constipation, and sensory neuropathy.

In clinical practice, hematological toxicities and clinically significant sequelae can be minimized by ensuring at the start of each cycle that the patient is not treated unless:

- absolute neutrophil count (ANC) is at least 1.5×10^9/L
- platelet count is at least 100×10^9/L
- nonhematological toxicities have resolved to ≤Grade 2.

Gemzar dosage adjustments for hematological toxicity within a cycle of treatment are based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, Gemzar dosage should be given at 50% dose if ANC is between 1000 to 1500 x 10^9/L or a platelet count between 75 to 100 x 10^9/L. Gemzar was held for lower levels of neutrophils and platelets. For severe (Grade 3 or 4) nonhematological toxicity, other than nausea/vomiting, therapy with Gemzar should be held or decreased by 50%, according to the judgment of the treating physician. For carboplatin dosage adjustments, the manufacturer's prescribing information should be consulted. Dose adjustments for Gemzar in combination with carboplatin for subsequent cycles are based upon observed toxicity.

In general, manifestations of myelosuppression (such as neutropenia) are the most common toxicities when Gemzar plus carboplatin is administered to recurrent ovarian cancer patients previously treated with platinum-based therapy.

5.2. Safety Results from Study JHQJ/AGO-OVAR 2.5

5.2.1. Overall Exposure

The median number of cycles completed was the same on both treatment arms: six cycles, which was the standard length of chemotherapy treatment. Patients on the combination therapy arm received 96.2% of the planned mean dose of carboplatin and 75.6% of the planned mean dose of Gemzar; dose adjustments of Gemzar on Day 8 were the primary cause of the lower planned mean dose. The weekly mean dose of Gemzar administered on Day 1 of each cycle was 92.8% of the planned weekly mean dose, and was 63.4% on Day 8 of each cycle. Patients on the carboplatin arm received 98.2% of the planned mean dose of carboplatin.

Table 25 provides a summary of patient disposition for the 356 randomized patients, by reason for discontinuation of study drug therapy. Figure 6 in Section 4.3.1 shows the disposition of patients entered into Study JHQJ/AGO-OVAR 2.5 and shows the reasons why 7 patients were randomized but not treated.

Table 25. Summary of Patient Disposition by Reason for Discontinuation, Randomized Patients, n (%) Study JHQJ/AGO-OVAR 2.5

Reason for Discontinuation	GCb Arm (N=178)	Cb Arm (N=178)
Protocol Completed	114 (64.0)	82 (46.1)
Adverse Event	19 (10.7)	18 (10.1)
Satisfactory Response		
Patient Perception	1 (0.6)	0
Physician Perception	1 (0.6)	2 (1.1)
Patient and Physician Perception	0	2 (1.1)
Patient Moved	2 (1.1)	0
Personal Conflict or Other Patient Decision	10 (5.6)	13 (7.3)
Protocol Entry Criteria Not Met	3 (1.7)	2 (1.1)
Clinical Relapse	1 (0.6)	2 (1.1)
Lack of Efficacy		
Progressive Disease	19 (10.7)	49 (27.5)
Stable Disease	4 (2.2)	4 (2.2)
Death from Study Disease	2 (1.1)	2 (1.1)
Protocol Violation	0	1 (0.6)
Death Due to Other Causes	2 (1.1)	1 (0.6)

Abbreviations: GCb = Gemzar plus carboplatin; Cb = carboplatin; N = number of patients.
Source: Table JHQJ.10.1.

5.2.2. Dose Modification and Discontinuation

On the Gemzar plus carboplatin arm, 10.4% of Gemzar doses were reduced, and 13.7% were omitted; 1.8% of carboplatin doses were reduced, and 0.2% were omitted. Approximately one third of cycles on the Gemzar plus carboplatin arm were delayed (33%, 314/961 total cycles completed). On the carboplatin arm, 3.8% of carboplatin doses were reduced, none were omitted, and 27% of cycles were delayed (236/888 total cycles completed).

The frequency of discontinuation due to adverse events, regardless of relationship to study drug, was similar for the Gemzar plus carboplatin and carboplatin arms (10.9% and 9.8%, respectively). The percentage of patients discontinuing treatment because of adverse events or on-study deaths was the same on both treatment arms. Six patients discontinued treatment because of serious adverse events (SAEs), 2 on the Gemzar plus carboplatin arm and 4 on the carboplatin arm. Four of these patients discontinued treatment because of drug-related SAEs (1 with neutropenia, Gemzar plus carboplatin arm; 1 with syncope, carboplatin arm; 2 with drug hypersensitivity, carboplatin arm). In addition, 24 patients (13 on the Gemzar plus carboplatin arm and 11 on the carboplatin arm) discontinued because of drug-related nonserious adverse events. Neutropenia was the most common non-serious adverse event leading to study discontinuation in both arms of Study JHQJ/AGO-OVAR 2.5. More patients on the carboplatin arm (51/178, 29%) discontinued study treatment with progressive disease or clinical relapse than did those on the Gemzar plus carboplatin arm (20/178, 11%).

5.2.3. Treatment-Emergent Adverse Events

The adverse event profile of Gemzar plus carboplatin therapy in Study JHRW was consistent with that observed in Study JHQJ/AGO-OVAR 2.5. Nearly 100% of patients in both studies reported treatment-emergent adverse events (TEAEs). The most common TEAEs in both studies were those of hematologic or gastrointestinal etiology, as well as fatigue. In most cases, these events were considered possibly related to study drugs. In Study JHQJ/AGO-OVAR 2.5, hematologic events occurred at a higher incidence rate on the Gemzar plus carboplatin arm compared with the carboplatin arm. The incidence of drug-related gastrointestinal events was also higher on the Gemzar plus carboplatin arm. Drug-related neuropathy occurred at a similar incidence rate on both treatment arms. Table 26 summarizes all TEAEs and those possibly related to study drugs, by preferred term and organized by system organ class, in Study JHQJ/AGO-OVAR 2.5.

**Table 26. Summary of TEAEs, by System Organ Class, n (%)
Study JHQJ/AGO-OVAR 2.5**

	All TEAEs		TEAEs Possibly Related to Study Drug[b]	
System Organ Class MedDRA Preferred Term	**GCb Arm (N=175)**	**Cb Arm (N=174)**	**GCb Arm (N=175)**	**Cb Arm (N=174)**
Patients with at least one event	172 (98.3)	170 (97.7)	172 (98.3)	165 (94.8)
Blood and Lymphatic System Disorders				
Anemia NOS	151 (86.8)	130 (75.1)	149 (85.1)	120 (69.0)
Leukopenia NOS	151 (86.8)	121 (69.5)	150 (85.7)	116 (66.7)
Neutropenia	158 (90.3)	101 (58.0)	158 (90.3)	98 (56.3)
Thrombocytopenia	137 (78.3)	99 (56.9)	137 (78.3)	99 (56.9)
General Disorders				
Fatigue	66 (37.7)	53 (30.5)	60 (34.3)	44 (25.3)
Pyrexia	35 (20.0)	18 (10.3)	14 (8.0)	5 (2.9)
Skin and Subcutaneous Tissue Disorders				
Alopecia	86 (49.1)	30 (17.2)	85 (48.6)	30 (17.2)
Gastrointestinal Disorders				
Constipation	74 (42.3)	65 (37.4)	49 (28.0)	40 (23.0)
Diarrhea NOS	43 (24.6)	23 (13.2)	24 (13.7)	12 (6.9)
Nausea	120 (68.6)	105 (60.3)	117 (66.9)	98 (56.3)
Vomiting NOS	80 (45.7)	63 (36.2)	73 (41.7)	57 (32.8)
Nervous System Disorders				
Neuropathy NOS	53 (30.3)	56 (32.2)	49 (28.0)	49 (28.2)

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients; N = number of patients who received at least one dose of study drug; NOS = not otherwise specified; TEAEs = treatment-emergent adverse events.

[a] Summaries of TEAEs are displayed using a cut-off point of occurring in ≥20% of randomized patients on either treatment arm in Study JHQJ/AGO-OVAR 2.5.

[b] Relatedness as assessed by the investigator.

Source: Table JHQJ.12.18.

5.2.4. Deaths due to Adverse Events, and Other Serious Adverse Events

Table 27 presents an overview of adverse events reported during Study JHQJ/AGO-OVAR 2.5.

Table 27. Overview of Adverse Events, n (%)
Study JHQJ/AGO-OVAR 2.5

Adverse Events	GCb Arm[a] (N=175)	Cb Arm[a] (N=174)
Treatment-emergent adverse events		
All	172 (98.3)	170 (97.7)
Possibly related to study drug[b]	172 (98.3)	165 (94.8)
Deaths		
On-study (during treatment period)	4 (2.3)[c]	3 (1.7)
Within 30-day poststudy follow-up	1 (0.6)	2 (1.1)
Serious adverse events		
All	49 (28.0)	37 (21.3)
Possibly related to study drug[b]	29 (16.6)	17 (9.8)
Serious, unexpected, reportable adverse events	1 (0.6)	2 (1.1)
Adverse events resulting in discontinuation		
All	19 (10.9)	17 (9.8)
Possibly related to study drug[b]	14 (8.0)	14 (8.0)

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin; n = number of patients; N = number of patients who received at least one dose of study drug.

[a] Patients may be counted in more than one category.

[b] Relatedness as assessed by the investigator.

[c] One death was attributed to drug-related sepsis.

Source: Table JHQJ.12.17.

5.2.4.1. Deaths

In Study JHQJ/AGO-OVAR 2.5, the occurrence of death on study or within 30 days of study drug administration was low in both treatment arms, and most deaths were attributed to disease progression. Ten deaths were reported on study or within 30 days of study drug administration (5 deaths in each arm). Seven deaths occurred on study treatment, and 3 deaths occurred within 30 days of study drug administration. Of the 7 deaths that occurred on study, 4 deaths were attributed to disease progression (2 deaths in each arm). Of the remaining 3 deaths that occurred on study, 1 patient on the Gemzar plus carboplatin arm died from sepsis, which was considered possibly related to study drug, 1 patient on the Gemzar plus carboplatin arm died of cardiopulmonary arrest, which was considered to be secondary to disease progression, and 1 patient on the carboplatin arm died of bronchial aspiration, which was attributed to an overdose of triazolam. Of the 3 deaths that occurred within the 30 days of study drug administration (1 on the Gemzar plus carboplatin arm and 2 on the carboplatin arm), all were attributed to disease progression; thus, none of these deaths were attributed to the study drugs.

5.2.4.2. Other Serious Adverse Events

The majority of drug-related SAEs with Gemzar plus carboplatin therapy were hematologic in nature. Drug-related SAEs were more common in the Gemzar plus carboplatin arm than in the carboplatin arm (16.6% and 9.8%, respectively). There were

no SAEs that were considered unexpected for Gemzar. The following serious adverse events, possibly related to Gemzar plus carboplatin therapy occurred in only 1 patient each: asthenia, drug hypersensitivity reaction, dyspnea NOS, epistaxis, fatigue, flushing, general physical health deterioration, pyrexia, sepsis NOS, and thrombosis. The following serious adverse events, possibly related to carboplatin therapy, occurred in only 1 patient each: elevated ALT, elevated AST, high output cardiac failure, colitis NOS, elevated GGT, hyperkalemia, leukopenia NOS, edema NOS, syncope, and vomiting NOS.

Serious, unexpected, reportable adverse events (SURs) were those events that were unexpected, reported to a regulatory agency in an expedited manner, and considered related to a study drug (either by the investigator or by the Lilly physician, reviewing the study data). Unexpected means that the event is not listed in the currently approved Clinical Investigator's Brochure (Lilly 2005) (within similar extent of severity), or in other reference safety information according to company procedures.

In Study JHQJ/AGO-OVAR 2.5, 3 patients (1 on the Gemzar plus carboplatin arm and 2 on the carboplatin arm) had SURs during the study. Hypoxia, light-headedness, and cough were reported for 1 patient on the Gemzar plus carboplatin arm; all events were considered SURs for carboplatin, not for Gemzar. On the carboplatin arm, 1 patient reported SURs of colitis and bacteriuria, and another patient reported a SUR of high output cardiac failure.

Table 28 summarizes SAEs reported in ≥2 randomized and treated patients in Study JHQJ/AGO-OVAR 2.5; all events and those possibly related to study drug are displayed by MedDRA preferred term and according to system organ class.

Table 28. Summary of Serious Adverse Events, n (%)
Study JHQJ/AGO-OVAR 2.5

	SAEs Reported in ≥2 Patients		SAEs Possibly Related to Study Drug[a]	
System Organ Class MedDRA Preferred Term	**GCb Arm (N=175)[b]**	**Cb Arm (N=174)[b]**	**GCb Arm (N=175)[b]**	**Cb Arm (N=174)[b]**
Patients with at least 1 event[a]	49 (28.0)	37 (21.3)	29 (16.6)	17 (9.8)
Blood and Lymphatic System Disorders				
Anemia	9 (5.1)	4 (2.3)	9 (5.1)	4 (2.3)
Febrile neutropenia	2 (1.1)	0	2 (1.1)	0
Leukopenia NOS	4 (2.3)	1 (0.6)	4 (2.3)	1 (0.6)
Neutropenia	4 (2.3)	1 (0.6)	4 (2.3)	1 (0.6)
Pancytopenia	4 (2.3)	0	4 (2.3)	0
Thrombocytopenia	9 (5.1)	7 (4.0)	9 (5.1)	7 (4.0)
Cardiac Disorders				
Deep vein thrombosis	0	4 (2.3)	0	0
Pulmonary embolism	2 (1.1)	0	0	0
Thrombosis	2 (1.1)	0	1 (0.6)	0
General Disorders				
Ascites	2 (1.1)	1 (0.6)	0	0
Asthenia	3 (1.7)	0	1 (0.6)	0
Fatigue	2 (1.1)	0	1 (0.6)	0
General physical health deterioration	2 (1.1)	1 (0.6)	1 (0.6)	0
Pyrexia	2 (1.1)	2 (1.1)	1 (0.6)	0
Gastrointestinal Disorders				
Abdominal pain lower	2 (1.1)	0	0	0
Abdominal pain NOS	6 (3.4)	4 (2.3)	1 (0.6)	0
Abdominal pain upper	2 (1.1)	0	1 (0.6)	0
Constipation	3 (1.7)	1 (0.6)	0	0
Gastritis	0	0	0	0
Ileus paralytic	0	0	0	0
Intestinal obstruction NOS	1 (0.6)	3 (1.7)	0	0
Nausea	8 (4.6)	3 (1.7)	4 (2.3)	2 (1.1)
Subileus	3 (1.7)	2 (1.1)	0	0
Vomiting NOS	7 (4.0)	4 (2.3)	4 (2.3)	1 (0.6)
Hepatobiliary Disorders				
ALT increased	0	2 (1.1)	0	1 (0.6)
AST increased	0	2 (1.1)	0	1 (0.6)
GGT increased	0	2 (1.1)	0	1 (0.6)
Ocular icterus	0	2 (1.1)	0	0
Immune System Disorders				
Anaphylactic reaction	0	2 (1.1)	0	2 (1.1)
Drug hypersensitivity	1 (0.6)	4 (2.3)	1 (0.6)	4 (2.3)

(continued)

**Table 28. Summary of Serious Adverse Events, n (%)
Study JHQJ/AGO-OVAR 2.5 (concluded)**

	SAEs Reported in ≥2 Patients		SAEs Possibly Related to Study Drug[a]	
System Organ Class MedDRA Preferred Term	GCb Arm (N=175)[b]	Cb Arm (N=174)[b]	GCb Arm (N=175)[b]	Cb Arm (N=174)[b]
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea NOS	3 (1.7)	2 (1.1)	1 (0.6)	2 (1.1)
Renal and Urinary Disorders				
Pyelonephritis	0	0	0	0

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; Cb = carboplatin; GCb = Gemzar plus carboplatin; GGT = γ–glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients; N = number of patients who received at least one dose of study drug; NOS = not otherwise specified; SAE = serious adverse event.

[a] Relatedness as assessed by the investigator.

[b] Patients may be counted in more than one SAE category.

Source: Table JHQJ.12.23.

5.2.5. Hospitalizations

Hospitalizations were numerically higher on the Gemzar plus carboplatin arm than the carboplatin arm (47.8% versus 37.6%, respectively). It is important to note that hospitalization due to social (nonmedical) reasons were more common on the Gemzar plus carboplatin arm (28 of 85 [(32.9%] patients who were hospitalized) than on the carboplatin arm (16 of 67 [23.9%] patients). Although study therapy in both arms can be easily administered in the outpatient setting in the United States, study drug administration was the reason for hospitalization in over half of all hospitalized patients from each treatment arm. Also, approximately one third of hospitalized patients on each treatment arm were admitted for study procedures, all of which can generally be performed in the outpatient setting. The frequency of hospitalizations for social reasons, administration of outpatient therapy, and performance of outpatient study procedures presumably reflect the various local practices in this global randomized study. There were slightly more hospitalizations due to adverse events in the Gemzar plus carboplatin arm than on the carboplatin arm (24.7% versus 18% patients, p=0.155).

5.2.6. Clinical Laboratory and Nonlaboratory Evaluations

In Study JHQJ/AGO-OVAR 2.5, the adverse event profile appeared to be manageable, with the events noted in this study being consistent with the adverse event profile of Gemzar plus cisplatin therapy as approved for the treatment of non-small cell lung cancer and bladder cancer. The most frequent CTC Grade 3 and 4 laboratory toxicities (regardless of relationship to study drug) were primarily hematologic and were more prevalent on the Gemzar plus carboplatin arm compared with the carboplatin arm (neutropenia: 70.3% versus 12%; thrombocytopenia: 34.9% versus 11.4%; and anemia: 28% versus 10.9%). This result is to be expected with a combination therapy compared

with monotherapy treatment. It is noteworthy that the clinical sequelae resulting from these hematologic toxicities were not markedly different between treatment arms.

Less than 5% of patients on either treatment arm reported Grade 3 or 4 nonlaboratory toxicity possibly related to study drug. The most commonly reported nonlaboratory toxicities were gastrointestinal events, including constipation, nausea, and vomiting, none of which caused discontinuation from the study. The incidence of neuropathy, hemorrhagic events, and infection (including febrile neutropenia) was limited and similar for both treatment arms. In Study JHQJ/AGO-OVAR 2.5, 67 (18.8%) of patients reported neuropathy not otherwise specified (NOS) as a secondary condition at baseline: 38 (21.3%) patients on the Gemzar plus carboplatin arm and 29 (16.3%) on the carboplatin arm. On the Gemzar plus carboplatin arm, 5 (13.2%) of the 38 patients with neuropathy at baseline reported a worsening in severity during the study. All 5 patients had mild (Grade 1) neuropathy at baseline, and the majority of these patients reported a moderate (Grade 2) increase in severity during the study. Similarly, on the carboplatin arm, both the percentage of patients with baseline neuropathy (13.8%) and the magnitude of worsening in severity of neuropathy during the study (no Grade 4 events reported) were low. No more than 1 patient on either treatment arm reported Grade 3 or 4 hepatobiliary, renal, or metabolic toxicities. Patients on the Gemzar plus carboplatin arm had higher rates of blood transfusions compared with patients on the carboplatin arm (40% versus 16.1%). Among the 70 patients on the Gemzar plus carboplatin arm who had blood transfusions, 40 (57.1%) received transfusions of platelets, red blood cells, or whole blood for Grade 3 or 4 anemia or thrombocytopenia. Among the 27 (15.5%) patients on the carboplatin arm who had blood transfusions, 12 (6.9%) received transfusions of platelets, red blood cells, or whole blood for Grade 3 or 4 anemia or thrombocytopenia. Patients on the Gemzar plus carboplatin arm had more frequent use of granulocyte growth factors (23.6% versus 10.1%). The protocol for Study JHQJ/AGO-OVAR 2.5 did not provide guidelines for the use of hematopoietic growth factors or transfusions for management of hematologic toxicity, and use of growth factors and transfusions appeared to vary according to the geographic region.

Investigators were requested to assess the causality of any adverse event experienced by a patient and to grade it using the CTC rating scale, Version 2.0 (NCI 1998). Table 29 and Table 30 present selected maximum CTC Grade 3 or 4 laboratory and nonlaboratory toxicities (regardless of relatedness to study therapy), respectively, occurring in treated patients in Study JHQJ/AGO-OVAR 2.5.

Table 29. Selected Grade 3/4 Hematological Toxicities and Growth Factor Usage Regardless of Causality Study JHQJ/AGO-OVAR 2.5

	Percentage of Patients			
	GCb Arm (N=175)		Cb Arm (N=174)	
	Grade 3	Grade 4	Grade 3	Grade 4
Hemoglobin[a]	22.3	5.7	8.6	2.3
Neutrophils[a]	41.7	28.6	10.9	1.1
Platelets[a]	30.3	4.6	10.3	1.1
Hemorrhage	1.8	0.6	0	1.1
Febrile neutropenia	1.1	0	0	0
Infection with G3/4 neutropenia	0	0	0.6	0
Infection without neutropenia	1.1	0.6	0.6	0
G-CSF / GM-CSF	23.6		10.1	
Epoetin / Erythropoietin	7.3		3.9	

Abbreviations: Cb = carboplatin; G = grade; G-CSF = granulocyte-colony stimulating factor; GCb = Gemzar plus carboplatin; GM-CSF = granulocyte macrophage-colony stimulating factor.

a Statistically significantly higher.

Source: az200504a.

Table 30. Selected Grade 3/4 Nonlaboratory Toxicities Regardless of Causality Study JHQJ/AGO-OVAR 2.5

	Percentage of Patients			
	GCb Arm (N=175)		Cb Arm (N=174)	
	Grade 3	Grade 4	Grade 3	Grade 4
Neuropathy – sensory	1.1	0	2.3	0
Neuropathy – motor	1.1	0	0.6	0
Nausea [a]	6.3	0	2.9	0
Fatigue	2.9	0.6	5.2	0
Vomiting[a]	5.7	0	2.3	0.6
Diarrhea[a]	3.4	0	0.6	0
Anorexia	1.1	0	0	0
Stomatitis/pharyngitis	0.6	0	0	0
Constipation[a]	6.3	1.1	2.9	0

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin.

[a] Statistically significantly higher.

Source: az200504a.

5.3. Safety Conclusions

Overall, the results of Study JHQJ/AGO-OVAR 2.5 showed that Gemzar was well tolerated when administered in combination with carboplatin in patients with advanced ovarian cancer who had relapsed at least 6 months after completion of platinum-based

therapy. Tolerability of the combination is evidenced by the infrequent occurrence of Grade 3 and 4 nonlaboratory toxicities, the comparatively low frequency of study discontinuations due to adverse events in the Gemzar plus carboplatin arm, and the low percentage of patients on the combination arm who required a dose reduction of Gemzar (10.4%), and infrequent Grade 3/4 neurotoxicity (neurosensory 1.1% and neuromotor 1.1%).

As expected, patients treated with Gemzar plus carboplatin experienced higher frequencies of Grades 3/4 anemia, neutropenia, and thrombocytopenia, though the incidence of clinical sequelae such as infection, febrile neutropenia, and hemorrhage was infrequent. There was a higher incidence of transfusions on the Gemzar plus carboplatin arm, though typical usage of erythropoietin, according to US guidelines, would have likely decreased the rate. Importantly, there was a low rate of neurotoxicity in patients treated with Gemzar plus carboplatin, and the combination did not exacerbate preexisting neuropathy. The overall toxicity profile of Gemzar plus carboplatin in patients with advanced ovarian cancer was manageable, predictable, and consistent with the toxicity profiles of each compound as a monotherapy, as well as with the profile observed in previous studies of Gemzar plus carboplatin.

6. Benefit/Risk Summary

Improvement in the treatment of patients with advanced cancers remains unassociated with cure, thus, palliative therapy must offer efficacy that is clinically relevant, toxicity that is predictable and manageable, and QoL that is not compromised by treatment. For patients with platinum-sensitive recurrent ovarian cancer, treatment with Gemzar plus carboplatin is more likely to result in a longer time without disease progression or death (that is, a longer progression-free survival), in comparison to the standard of care, carboplatin monotherapy. In addition, the combination is more likely to decrease tumor burden and to yield symptom control through tumor shrinkage (higher response rates), and a longer period of disease remission (longer progression-free survival and response duration).

Because Study JHQJ/AGO-OVAR 2.5 was not designed to determine differences in overall survival, limited conclusions about survival can be drawn. The size of the study was determined by estimated treatment differences in progression-free survival, which requires approximately 350 patients to detect a 41% improvement in progression-free survival with 85% power. The availability and activity of other active agents administered as postdiscontinuation therapy may hamper the ability to determine the true treatment effect on survival (ten Bokkel Huinink et al. 2004). In this study, it was not practical to standardize postdiscontinuation therapy, as treatment needed to be individualized for each patient. The specific type of postdiscontinuation therapy that patients received was not collected; therefore, the effect of crossover could not be determined. However, there was a high incidence of postdiscontinuation therapy (75% of patients), which could have confounded the survival results. The HR for overall survival (0.98), as well as the adjusted HR (0.92), provides consistent evidence of no detriment to patients treated with Gemzar plus carboplatin.

The Sponsor believes there is adequate data to support the approval of this sNDA based on the demonstrated efficacy and safety of Gemzar in combination with carboplatin in Study JHQJ/AGO-OVAR 2.5. Gemzar plus carboplatin offers patients clinically significant and statistically persuasive improvements in progression-free survival (HR, 0.72; log-rank p=0.0038), which indicates a 28% reduced risk of progression. The median progression-free survival on the Gemzar plus carboplatin arm was 8.6 months compared with 5.8 months for carboplatin treatment representing a 48% increase in median progression-free survival for the Gemzar plus carboplatin treated patients. Multiple sensitivity analyses and consistency of results in key subgroups confirm the robustness of the primary progression-free survival analysis. In addition, this combination demonstrated statistically significant improvements in overall response rate (47.2% Gemzar plus carboplatin arm versus 30.9% carboplatin arm) and complete response rates (14.6% versus 6.2%). Overall, patients on the Gemzar plus carboplatin arm experienced improved QoL sooner, a delayed time to QoL worsening, and a longer time to progression, death, or subsequent chemotherapy.

Gemzar plus carboplatin was well tolerated as evidenced by the infrequent occurrence of Grade 3 and 4 nonlaboratory toxicities, the comparatively low frequency of study discontinuations due to adverse events in the Gemzar plus carboplatin arm, and the low percentage of patients on the combination arm who required a dose reduction of Gemzar. While the combination was associated with a higher incidence of hematologic toxicities, clinically relevant sequelae were infrequent. The rate of neurotoxicity observed in Study JHQJ/AGO-OVAR 2.5 was considerably lower than that observed in studies incorporating paclitaxel for treatment of recurrent ovarian cancer (Connelly et al. 1996; Parmar et al. 2003).

The standard of care for patients with platinum-sensitive disease is re-treatment with platinum monotherapy. Until now, the only treatment that improved upon this standard was carboplatin plus paclitaxel. However, because of the widespread use of carboplatin plus paclitaxel therapy in the first-line setting in the United States, readministration of this combination is not desirable for many patients with platinum-sensitive recurrent disease because of a history of neuropathy or likely exacerbation of persistent neuropathy. New treatment options that improve efficacy without worsening toxicities are needed for this platinum-sensitive patient population.

The Sponsor believes that Gemzar plus carboplatin therapy provides improvements in progression-free survival, in conjunction with increased overall and complete response rates and a favorable safety profile. The favorable benefit/risk profile of Gemzar plus carboplatin make it a valuable treatment option for patients with advanced ovarian cancer that recurs at least 6 months after completion of first-line, platinum-based therapy.

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8. Appendices

Appendix 1: Efficacy Results from Studies of Gemzar in the Literature

Table App.1.1 presents a summary of the efficacy results of the studies of Gemzar monotherapy in patients with recurrent ovarian cancer.

Four Phase 2 studies reported in the literature assessed Gemzar as single-agent treatment in previously treated patients (Shapiro et al. 1996; Silver and Piver 1999; Coenen et al. 2000; Markman et al. 2001). Table App.1.2 presents efficacy results for these studies.

Table App.1.1. Efficacy Results for Gemzar Monotherapy in Recurrent Ovarian Cancer Phase 2 Studies E007, JHAJ, JHBU, 0027, 0026, and JHFH

Efficacy Endpoint	E007 Main Portion (Lund et al. 1994, 1995)	E007 Extension Portion (Underhill et al. 2001)	JHAJ	JHBU	0027 (Friedlander et al. 1998)	0026 (von Minckwitz et al. 1999)	JHFH (Kudelka et al. 1999)
Dose[a], mg/m2	800	1250	800	1000	1200	1250	2000
Patients entered	51	35	21	26	38	40	28
Patients qualified for efficacy analysis	37	33	21	25	36	38	25
Response rate 95% CI Pts with CR/PR/SD	21.6% (8/37) 9.8% to 38.2% 0/8/12	18.0% (6/33) 7.0% to 36.0% 1/5/3	0	8.0% (2/25) 1% to 26% 0/2/8	14% (5/36) 4.7% to 29.5% 2/3/17	18.4% (7/38) 7.7% to 34.4% 2/5/not available	16% (4/25) not available 0/4/7
Duration of response Median Range	not assessed	not assessed	not assessed	5.4 mo 3.7 to 7.1 mo	10.6 mo 3.2 to 14.0 mo	9.3 mo 5.0 to 15.4 mo	not assessed
Median TtPD 95% CI	3.6 mo 2.5 to 4.5 mo	not assessed	not assessed	1.9 mo 1.8 to 3.6 mo	3.0 mo 1.7 to 4.4 mo	3.6 mo 2.0 to 4.9 mo	not assessed
Median OS 95% CI	7.8 mo 6.2 to 11.3 mo	not assessed	not assessed	13.9 mo 3.8 to 14.2 mo	7.0 mo 5.6 to 13.6 mo	8.5 mo 6.2 to 12.6 mo	not assessed

Abbreviations: CI = confidence interval; CR = complete response; OS = overall survival; PR = partial response; Pts = patients; SD = stable disease; TtPD = time to progressive disease.

[a] Gemzar was administered on Days 1, 8, and 15 of a 28-day cycle.

Sources: Synopses E007, JHAJ, JHBU, 0027, 0026, and JHFH.

Table App.1.2. Efficacy Results for Gemzar Monotherapy in Recurrent Ovarian Cancer Phase 2 Studies in the Literature

	Silver and Piver 1999	Coenen et al. 2000	Shapiro et al. 1996	Markman et al. 2001
Dose[a], mg/m^2	800	1000	1000	1250[b]
Patients entered	27	22	38	37
Patients qualified for efficacy analysis	27	22	31	34
Response rate Pts with CR/PR/SD	11% (3/27) 0/3/14	14% (3/22) 0/3/9	13% (4/31)[c] 0/4/6	18% (6/34)[d] not reported
Median TtPD, months Range	5.0 2 to 16[e]	not reported	not reported	not reported
Median survival, months	not reported	not reported	9.0	not reported

Abbreviations: CR = complete response; PR = partial response; Pts = patients; SD = stable disease; TtPD = time to progressive disease.

[a] Gemzar was administered on Days 1, 8, and 15 of a 28-day cycle.

[b] Gemzar 1250 mg/m^2 was reduced to 1000 mg/m^2.

[c] Partial response as evidenced by a ≥50% decline CA-125 level.

[d] Two patients had a response as evidenced by a decline in CA-125.

[e] Reported as progression-free interval for patients with stable disease.

Appendix 2: Previously Submitted Analyses of TtTF, TtOPD, and TtPD101M

Following discussions with FDA in March 2005, three unplanned sensitivity analyses were performed to confirm the robustness of the statistically significant result obtained with the primary analysis, and were presented in the sNDA. These analyses included: time to treatment failure (TtTF), which assessed the impact of early discontinuation; time to objective progressive disease (TtOPD) and time to progressive disease through Visit 101 (TtPD101M), which assessed the impact of various censoring scenarios on progression-free survival.

Time to treatment failure was defined as the time from the date of enrollment to the earliest date of any of the following events: early study discontinuation for any reason, the first observation of disease progression, or death from any cause. Time to treatment failure was censored at the date of the last postdiscontinuation follow-up visit for patients who had not discontinued treatment early, who were still alive, and who had not progressed. As shown in Table App.2.1, patients on the Gemzar plus carboplatin arm had a significantly longer time to treatment failure compared with patients on the carboplatin arm (log-rank p-value=0.0070). The HR was 0.74 (95% CI, 0.60 to 0.92).

Table App.2.1. Summary Statistics and Comparison by Treatment Arm for Time to Treatment Failure Study JHQJ/AGO-OVAR 2.5

Efficacy Endpoint	GCb Arm (N=178)	Cb Arm (N=178)
Patients censored, n (%)	10 (5.6)	11 (6.2)
Patients with event (PD, discontinuation or death), n	168	167
Median TtTF, months (95% CI)	7.0 (5.8 to 8.1)	4.8 (4.1 to 5.6)
Log-rank test p value HR (95% CI)	p=0.0070 0.74 (0.60 to 0.92)	
% of patients event-free for TtTF at 6 months[a] (95% CI)	55.1% (47.8 to 62.4%)	38.1% (31.0 to 45.3%)
Estimated treatment difference at 6 months (95% CI); chi-square p-value	16.9% (6.7 to 27.1%); p=0.0012	

Abbreviations: Cb = carboplatin; CI = confidence interval; GCb = Gemzar plus carboplatin; HR = hazard ratio; n = number of patients; N = total study population; PD = progressive disease; TtTF = time to treatment failure.

[a] Time-to-treatment failure criteria = progression, death, or study discontinuation due to adverse event.

Sources: Table JHQJ.11.15, Table JHQJ.11.16.

The majority of patients had objective evidence of disease progression: 90% of patients during the treatment phase, and 80% of patients with objective progressive disease during the follow-up phase. Time to objective progressive disease was performed as a sensitivity analysis, and was defined as the time from the date of randomization to the

date of objective disease progression including death from study disease. For patients without objectively determined disease, time to objective progressive disease was censored at the date of the last objective progression-free disease assessment. For patients who received postdiscontinuation chemotherapy before objectively determined disease progression, time to objective progressive disease was censored at the date of first postdiscontinuation chemotherapy. The HR for time to objective progressive disease was 0.54 (95% CI, 0.41 to 0.71; log-rank p-value <0.0001). The median time to objective progressive disease was 8.8 months (95% CI, 8.0 to 9.7 months) with a censoring rate of 37.6% for the Gemzar plus carboplatin arm and 5.8 months (95% CI, 5.2 to 6.9 months) with a censoring rate of 34.3% for the carboplatin arm. Table App.2.2 demonstrates that the advantage of Gemzar plus carboplatin over carboplatin for time to objective progressive disease remains consistent and statistically significant when clinical progressions and death from reasons other than disease progression are censored.

To evaluate whether missing scans or incomplete sets of scans may have affected the results of progression-free survival, and to evaluate if there was a bias in radiologic assessment in favor of either arm, an alternative censoring of progression-free survival was performed. Time to progressive disease, censoring for missing scans, incomplete scans, or incomplete sets of scans (TtPD101M) was conducted as a second sensitivity analysis. Patients who were still alive at Visit 101 and who did not have disease progression were censored at Visit 101. Patients who missed a scan while being treated but were found to progress on the next scheduled scan were censored on the date of the last progression-free assessment. As poststudy scans were not required except to confirm response, the analysis of TtPD101M focuses on the period of time where the scans were required. The number of missing or incomplete scans were well balanced between the arms (Gemzar plus carboplatin: 47.8% [85/178] versus carboplatin: 43.3% [77/178]). The HR for TtPD101M was 0.47 (95% CI, 0.32 to 0.68; log-rank p-value <0.0001). The median TtPD101M for the Gemzar plus carboplatin arm was 6.9 months (95% CI, 6.3 to NE) with a censoring rate of 74.2% and 5.6 months (95% CI, 5.0 to 5.9 months) with censoring rate of 57.3% for the carboplatin arm. Table App.2.2 demonstrates that the advantage of Gemzar plus carboplatin over carboplatin is maintained with a stricter enforcement of lesion measurements applied; no observational bias appears to favor either arm. The censoring is high, but the trend and consistent results further demonstrate the robustness of the primary endpoint.

Table App.2.2. Summary Statistics and Comparison by Treatment Arm for Sensitivity Analyses of Progression-free Survival Study JHQJ/AGO-OVAR 2.5

	GCb Arm Median, months (censoring)	Cb Arm Median, months (censoring)	p-value (HR)
PFS	8.6 (12.4%)	5.8 (12.9%)	0.0038 (0.72)
TtOPD	8.8 (37.6%)	5.8 (34.3%)	<0.0001 (0.54)
TtPD101M	6.9 (74.2%)	5.6 (57.3%)	<0.0001 (0.47)
TtTF	7.0 (5.6%)	4.8 (6.2%)	0.0070 (0.74)

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin; PFS = progression-free survival; TtOPD = time to objective progressive disease; TtPD101M = time to progressive disease through Visit 101; TtTF = time to treatment failure.

Source: az200504a.

Appendix 3: Patient Reported Outcomes and Patient Benefit

Table App.3.1. Results from the Analysis of Global QoL Study JHQJ/AGO-OVAR 2.5 All Patients

Cycle	Therapy	N	Mean[a]	SE	P-value
1	GCb	144	58.6095	1.5176	0.9618
	Cb	143	58.5060	1.5403	
2	GCb	140	62.7793	1.5404	0.2227
	Cb	135	60.0861	1.5792	
3	GCb	133	61.3664	1.5621	0.8042
	Cb	124	60.8071	1.6259	
4	GCb	131	61.1196	1.5709	0.2531
	Cb	104	58.4577	1.7167	
5	GCb	112	62.9180	1.6643	0.0697
	Cb	96	58.4873	1.7832	
6	GCb	90	60.3208	1.7735	0.2794
	Cb	65	57.4230	2.0052	

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin; N = number of patients; SE = standard error.

[a] Mean = model based treatment group mean from repeated measures analysis

Source: az200504a.

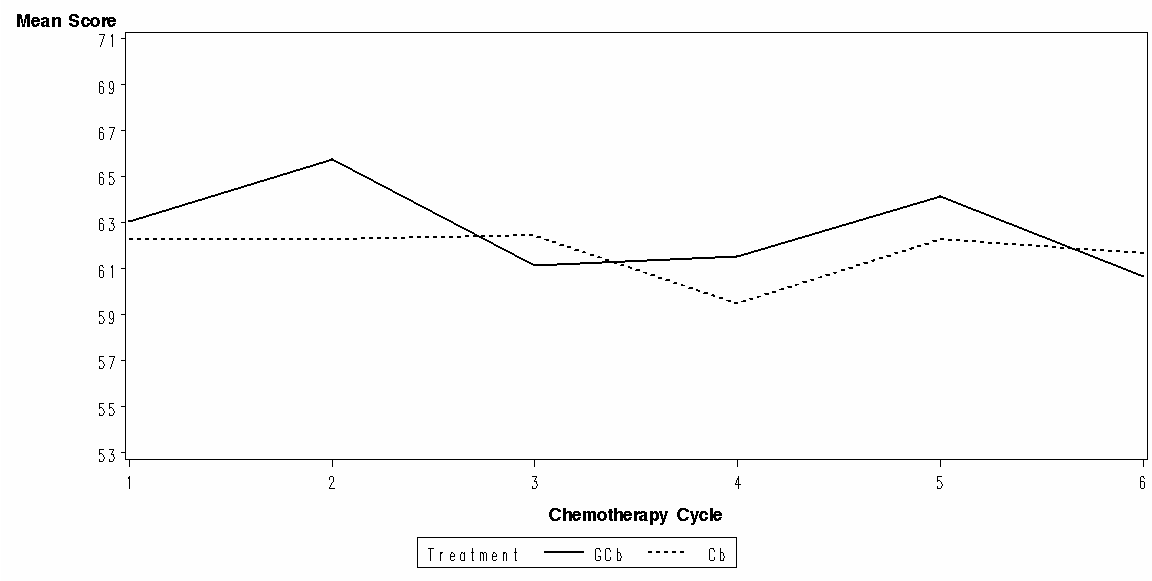
Table App.3.2. Results from the Analysis of Global QoL Study JHQJ/AGO-OVAR 2.5 Symptomatic Patients

Cycle	Therapy	N	Mean[a]	SE	P-value
1	GCb	80	55.0648	1.8953	0.9238
	Cb	76	55.3271	1.9789	
2	GCb	80	60.5222	1.8983	0.4314
	Cb	74	58.3445	2.0083	
3	GCb	76	61.4362	1.9411	0.5288
	Cb	67	59.6365	2.0921	
4	GCb	75	60.6333	1.9426	0.3294
	Cb	57	57.7741	2.1893	
5	GCb	69	61.7949	2.0161	0.0337
	Cb	49	55.2011	2.3494	
6	GCb	54	59.8166	2.1717	0.0836
	Cb	35	53.9028	2.6310	

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin; N = number of patients; SE = standard error.

[a] Mean = model based treatment group mean from repeated measures analysis

Source: az200504a.



Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin.
Source: js200601b.

Figure App.3.1. Study JHQJ/AGO-OVAR 2.5 Kaplan-Meier estimates of Global QoL scores for asymptomatic patients.

Table App.3.3. Results from the Analysis of Global QoL Asymptomatic Patients Study JHQJ/AGO-OVAR 2.5

Cycle	Therapy	N	Mean[a]	SE	P-value
1	GCb	64	63.0472	2.4394	0.8226
	Cb	67	62.2804	2.3936	
2	GCb	60	65.7253	2.5126	0.3299
	Cb	61	62.2809	2.4793	
3	GCb	57	61.1353	2.5244	0.7116
	Cb	57	62.4555	2.5221	
4	GCb	56	61.5450	2.5527	0.5821
	Cb	47	59.5040	2.6857	
5	GCb	43	64.1292	2.7846	0.6321
	Cb	47	62.2691	2.7043	
6	GCb	36	60.6672	2.9286	0.8175
	Cb	30	61.6430	3.0467	

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin; N = number of patients; SE = standard error.

[a] Mean = model based treatment group mean from repeated measures analysis

Source: js200601b.

Table App.3.4. AUC Results
All Other Scales
Study JHQJ/AGO-OVAR 2.5

All Other Scales	GCb Arm AUC Mean (N)[a]	Cb Arm AUC Mean (N)[a]	Difference (SE)	p-Value
Insomnia	7081.59 (153)	6555.17 (150)	526.42 (352.08)	0.1359
Pain	8131.14 (152)	7335.15 (151)	795.99 (336.96)	0.0188
Financial Impact	7916.67 (149)	7517.38 (151)	399.28 (442.20)	0.3673
Physical Functioning	7737.79 (149)	7405.31 (150)	332.48 (305.72)	0.2777
Role Functioning	6986.19 (149)	6618.64 (150)	367.55 (355.65)	0.3022
Cognitive Functioning	8516.94 (152)	7925.05 (152)	591.89 (330.87)	0.0746
Emotional Functioning	6878.77 (151)	6380.62 (152)	498.15 (313.97)	0.1136
Social Functioning	7219.73 (151)	7115.19 (152)	104.54 (359.55)	0.7714
Peripheral Neuropathy	7740.05 (122)	6803.83 (113)	936.22 (396.07)	0.0189
Hormonal Symptoms	8159.82 (123)	7583.91 116)	575.92 (404.85)	0.1562
Body Image	7437.74 (120)	6976.63 (115)	461.11 (417.92)	0.2710
Attitude to disease/ treatment	4530.99 (122)	4654.87 (114)	-123.89 (367.34)	0.7362
Sexual Functioning	1361.09 (100)	1124.04 (101)	237.05 (266.62)	0.3750

Abbreviations: AUC = area under the curve; Cb = carboplatin; GCb = gemcitabine plus carboplatin; N = number of patients included in the analysis; SE = Standard Error.

a patients were included in the analysis if they had a baseline and at least one postbaseline observation.

Source: az200504a.

Table App.3.5. Proportion of Patients that Improved by at Least 10-points at any Cycle
All Other Scales
Study JHQJ/AGO-OVAR 2.5

	% (Number of Patients That Improved/ Total Number of Patients)	
All Other Scales	**GCb Arm**	**Cb Arm**
Pain	54.9% (84/153)	58.9% (89/151)
Sleep Disturbance	51.9% (80/154)	50.0% (75/150)
Financial Impact	26.0% (39/150)	27.8% (42/151)
Physical Functioning	34.7% (52/150)	33.3% (50/150)
Role Functioning	45.3% (68/150)	42.0% (63/150)
Cognitive Functioning	42.5% (65/153)	32.9% (50/152)
Emotional Functioning	54.6% (83/152)	59.2% (90/152)
Social Functioning	40.8% (62/152)	42.1% (64/152)
Peripheral Neuropathy	33.3% (41/123)	34.2% (39/114)
Hormonal Symptoms	41.1% (51/124)	43.6% (51/117)
Body Image	39.7% (48/121)	51.7% (60/116)
Attitude to disease/treatment	74.8% (92/123)	71.1% (81/114)
Sexual Functioning	23.5% (24/102)	20.6% (21/102)

Abbreviations: Cb = carboplatin; GCb = Gemzar plus carboplatin.
Source: az200504a.