CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-509/S029

Trade Name: Gemzar

Generic Name: Gemcitabine

Sponsor: Eli Lilly

Approval Date: May 19, 2004

Indications: For the first line treatment of patients with metastatic breast cancer.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-509/S029

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
Pharmacology Review(s)	X
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-509/S029

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-509/S-029

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Thierry Kern
U.S. Regulatory Affairs, Oncology

Dear Mr. Kern:

Please refer to your supplemental new drug application dated December 17, 2004, received December 18, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gemzar® (gemcitabine HCl) for Injection.

We acknowledge receipt of your submissions dated January 28 and 29, February 19, March 15 and 25, April 8, May 12 and 13, 2004.

This supplemental new drug application provides for the use of Gemzar® (gemcitabine HCl) for Injection in combination with paclitaxel for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "**FPL for approved supplement NDA 20-509/S-029**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment as agreed in the facsimile dated May 19, 2004. The commitment, along with the completion date agreed upon, is listed below.

> Complete study B9E-MC-JHQG (Multi-center, Phase 3 Study of Gemcitabine Plus Paclitaxel Versus Paclitaxel in Patients with Unresectable, Locally Recurrent or Metastatic Breast Cancer). Submit the final analysis of overall survival when the protocol specified number of

deaths for the final analysis have occurred. This analysis should be submitted within 6 months of the date of the last death.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.8(b)(2)(vii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report",** or **"Postmarketing Study Correspondence."**

All application for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Oncology Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising and Communcation, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
5/19/04 02:15:50 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-509/S029

LABELING

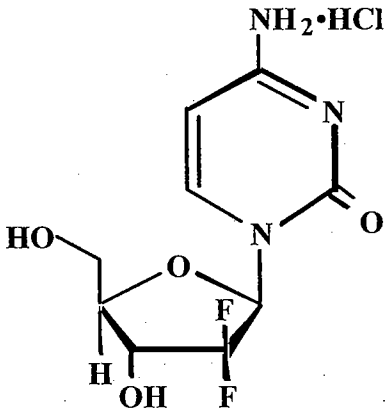
A 3.0 NL 4061 AMP

GEMZAR®
(GEMCITABINE HCl)
FOR INJECTION

DESCRIPTION

Gemzar® (gemcitabine HCl) is a nucleoside analogue that exhibits antitumor activity. Gemcitabine HCl is 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-isomer).

The structural formula is as follows:



The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4$ • HCl. It has a molecular weight of 299.66.

Gemcitabine HCl is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

CLINICAL PHARMACOLOGY

Gemcitabine 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. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin *in vitro*. No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. *In vivo*, gemcitabine showed activity in combination with cisplatin against the LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520 xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure to gemcitabine 4 hours before cisplatin produced the greatest interaction.

Human Pharmacokinetics — Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m^2/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2′-deoxy-2′,2′-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma. Gemcitabine plasma protein binding is negligible.

The pharmacokinetics of gemcitabine were examined in 353 patients, about 2/3 men, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusions (70 to 285 minutes). The total Gemzar dose varied from 500 to 3600 mg/m^2.

Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Clearance was affected by age and gender. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 1 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 1: Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance Men (L/hr/m^2)	Clearance Women (L/hr/m^2)	Half-Life[a] Men (min)	Half-Life[a] Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

[a] Half-life for patients receiving a short infusion (<70 min).

Gemcitabine half-life for short infusions ranged from 32 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes, indicating that gemcitabine, after short infusions, is not extensively distributed into tissues. For long infusions, the volume of distribution rose to 370 L/m^2, reflecting slow equilibration of gemcitabine within the tissue compartment.

The maximum plasma concentrations of dFdU (inactive metabolite) were achieved up to 30 minutes after discontinuation of the infusions and the metabolite is excreted in urine without undergoing further biotransformation. The metabolite did not accumulate with weekly dosing,

but its elimination is dependent on renal excretion, and could accumulate with decreased renal function.

The effects of significant renal or hepatic insufficiency on the disposition of gemcitabine have not been assessed.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

Drug Interactions — When Gemzar (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2. The clearance of cisplatin in the same study was reported to be 3.94 mL/min/m^2 with a corresponding half-life of 134 hours (*see Drug Interactions under* **PRECAUTIONS**).

CLINICAL STUDIES

Breast Cancer — Data from a multi-national, randomized Phase 3 study (529 patients) support the use of Gemzar in combination with paclitaxel for treatment of breast cancer patients who have received prior adjuvant/neoadjuvant anthracycline chemotherapy unless clinically contraindicated. Gemzar 1250 mg/m^2 was administered on Days 1 and 8 of a 21-day cycle with paclitaxel 175 mg/m^2 administered prior to Gemzar on Day 1 of each cycle. Single-agent paclitaxel 175 mg/m^2 was administered on Day 1 of each 21-day cycle as the control arm.

The addition of Gemzar to paclitaxel resulted in statistically significant improvement in time to documented disease progression and overall response rate compared to monotherapy with paclitaxel as shown in Table 2 and Figure 1. Further, there was a strong trend toward improved survival for the group given Gemzar based on an interim survival analysis.

Table 2: Gemzar Plus Paclitaxel Versus Paclitaxel in Breast Cancer

	Gemzar/Paclitaxel	Paclitaxel	
Number of patients	267	262	
Median age, years Range	53 26 to 83	52 26 to 75	
Metastatic disease	97.0%	96.9%	
Baseline KPS[a] ≥90	70.4%	74.4%	
Number of tumor sites 1-2 ≥3	 56.6% 43.4%	 58.8% 41.2%	
Visceral disease	73.4%	72.9%	
Prior anthracycline	96.6%	95.8%	
Time to Documented Disease Progression[b]			p<0.0001
Median (95%, C.I.), months	5.2 (4.2, 5.6)	2.9 (2.6, 3.7)	
Hazard Ratio (95% C.I.)	0.650 (0.524, 0.805)		p<0.0001
Overall Response Rate[b] (95%, C.I.)	40.8% (34.9, 46.7)	22.1% (17.1, 27.2)	p<0.0001

[a] Karnofsky Performance Status.

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

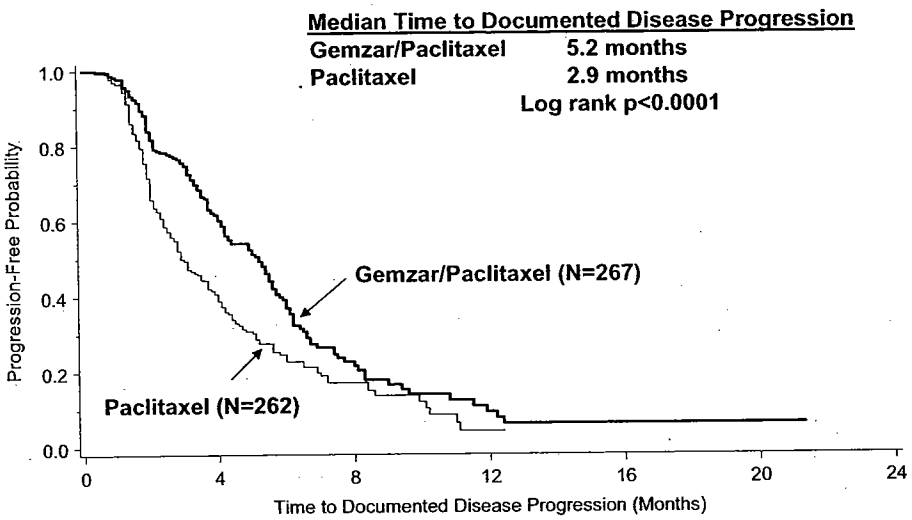


Figure 1: Kaplan-Meier Curve of Time to Documented Disease Progression in Gemzar plus Paclitaxel versus Paclitaxel Breast Cancer Study (N=529).

Non-Small Cell Lung Cancer (NSCLC) — Data from 2 randomized clinical studies (657 patients) support the use of Gemzar in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC.

Gemzar plus cisplatin versus cisplatin: This study was conducted in Europe, the US, and Canada in 522 patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received prior chemotherapy. Gemzar 1000 mg/m^2 was administered on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m^2 administered on Day 1 of each cycle. Single-agent cisplatin 100 mg/m^2 was administered on Day 1 of each 28-day cycle. The primary endpoint was survival. Patient demographics are shown in Table 3. An imbalance with regard to histology was observed with 48% of patients on the cisplatin arm and 37% of patients on the Gemzar plus cisplatin arm having adenocarcinoma.

The Kaplan-Meier survival curve is shown in Figure 2. Median survival time on the Gemzar plus cisplatin arm was 9.0 months compared to 7.6 months on the single-agent cisplatin arm (Logrank p=0.008, two-sided). Median time to disease progression was 5.2 months on the Gemzar plus cisplatin arm compared to 3.7 months on the cisplatin arm (Logrank p=0.009, two-sided). The objective response rate on the Gemzar plus cisplatin arm was 26% compared to 10% with cisplatin (Fisher's Exact p<0.0001, two-sided). No difference between treatment arms with regard to duration of response was observed.

Gemzar plus cisplatin versus etoposide plus cisplatin: A second, multi-center, study in Stage IIIB or IV NSCLC randomized 135 patients to Gemzar 1250 mg/m^2 on Days 1 and 8, and cisplatin 100 mg/m^2 on Day 1 of a 21-day cycle or to etoposide 100 mg/m^2 I.V. on Days 1, 2, and 3 and cisplatin 100 mg/m^2 on Day 1 on a 21-day cycle (Table 3).

There was no significant difference in survival between the two treatment arms (Logrank p=0.18, two-sided). The median survival was 8.7 months for the Gemzar plus cisplatin arm versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for the Gemzar plus cisplatin arm was 5.0 months compared to 4.1 months on the etoposide plus

cisplatin arm (Logrank p=0.015, two-sided). The objective response rate for the Gemzar plus cisplatin arm was 33% compared to 14% on the etoposide plus cisplatin arm (Fisher's Exact p=0.01, two-sided).

Quality of Life (QOL): QOL was a secondary endpoint in both randomized studies. In the Gemzar plus cisplatin versus cisplatin study, QOL was measured using the FACT-L, which assessed physical, social, emotional and functional well-being, and lung cancer symptoms. In the study of Gemzar plus cisplatin versus etoposide plus cisplatin, QOL was measured using the EORTC QLQ-C30 and LC13, which assessed physical and psychological functioning and symptoms related to both lung cancer and its treatment. In both studies no significant differences were observed in QOL between the Gemzar plus cisplatin arm and the comparator arm.

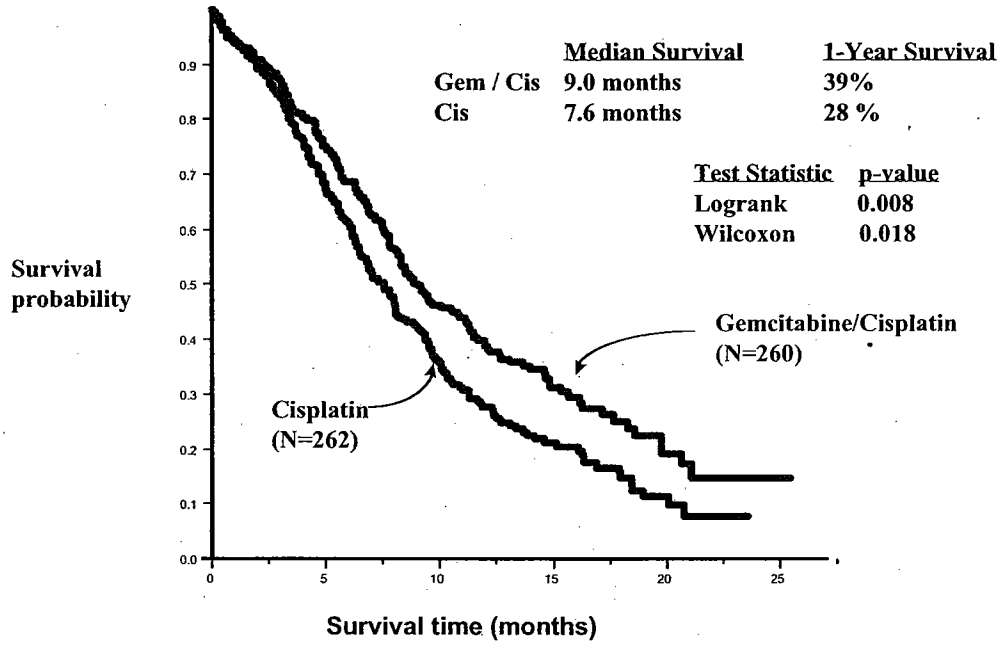


Figure 2: Kaplan-Meier Survival Curve in Gemzar plus Cisplatin versus Cisplatin NSCLC Study (N=522).

Table 3: Randomized Trials of Combination Therapy with Gemzar plus Cisplatin in NSCLC

Trial	28-day Schedule[a]			21-day Schedule[b]		
Treatment Arm	Gemzar/ Cisplatin	Cisplatin		Gemzar/ Cisplatin	Cisplatin/ Etoposide	
Number of patients	260	262		69	66	
Male	182	186		64	61	
Female	78	76		5	5	
Median age, years	62	63		58	60	
Range	36 to 88	35 to 79		33 to 76	35 to 75	
Stage IIIA	7%	7%		N/A	N/A	
Stage IIIB	26%	23%		48%	52%	
Stage IV	67%	70%		52%	49%	
Baseline KPS[c] 70 to 80	41%	44%		45%	52%	
Baseline KPS[c] 90 to 100	57%	55%		55%	49%	
Survival			p=0.008			p=0.18
Median, months	9.0	7.6		8.7	7.0	
(95%, C.I.) months	8.2, 11.0	6.6, 8.8		7.8, 10.1	6.0, 9.7	
Time to Disease Progression			p=0.009			p=0.015
Median, months	5.2	3.7		5.0	4.1	
(95%, C.I.) months	4.2, 5.7	3.0, 4.3		4.2, 6.4	2.4, 4.5	
Tumor Response	26%	10%	p<0.0001[d]	33%	14%	p=0.01[d]

[a] 28-day schedule — Gemzar plus cisplatin: Gemzar 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin 100 mg/m^2 on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m^2 on Day 1 every 28 days.

[b] 21-day schedule — Gemzar plus cisplatin: Gemzar 1250 mg/m^2 on Days 1 and 8 and cisplatin 100 mg/m^2 on Day 1 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m^2 on Day 1 and I.V. etoposide 100 mg/m^2 on Days 1, 2, and 3 every 21 days.

[c] Karnofsky Performance Status.

[d] p-value for tumor response was calculated using the two-sided Fisher's exact test for difference in binomial proportions. All other p-values were calculated using the Logrank test for difference in overall time to an event.

N/A Not applicable.

Pancreatic Cancer — Data from 2 clinical trials evaluated the use of Gemzar in patients with locally advanced or metastatic pancreatic cancer. The first trial compared Gemzar to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial studied the use of Gemzar in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of Gemzar was administered intravenously at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with Gemzar. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

The primary efficacy parameter in these studies was "clinical benefit response," which is a measure of clinical improvement based on analgesic consumption, pain intensity, performance status, and weight change. Definitions for improvement in these variables were formulated prospectively during the design of the 2 trials. A patient was considered a clinical benefit responder if either:

i) the patient showed a ≥50% reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a 20-point or greater improvement in performance status (Karnofsky Performance Scale) for a period of at least 4 consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as 4 consecutive weeks with either any increase in pain intensity or analgesic consumption or a 20-point decrease in performance status occurring during the first 12 weeks of therapy.

OR:

ii) the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain (≥7% increase maintained for ≥4 weeks) not due to fluid accumulation.

The first study was a multi-center (17 sites in US and Canada), prospective, single-blinded, two-arm, randomized, comparison of Gemzar and 5-FU in patients with locally advanced or metastatic pancreatic cancer who had received no prior treatment with chemotherapy. 5-FU was administered intravenously at a weekly dose of 600 mg/m^2 for 30 minutes. The results from this randomized trial are shown in Table 4. Patients treated with Gemzar had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to 5-FU. The Kaplan-Meier curve for survival is shown in Figure 3. No confirmed objective tumor responses were observed with either treatment.

Table 4: Gemzar Versus 5-FU in Pancreatic Cancer

	Gemzar	5-FU	
Number of patients	63	63	
Male	34	34	
Female	29	29	
Median age	62 years	61 years	
Range	37 to 79	36 to 77	
Stage IV disease	71.4%	76.2%	
Baseline KPS[a] ≤70	69.8%	68.3%	

Clinical benefit response	22.2% (N[c]=14)	4.8% (N=3)	p=0.004
Survival			p=0.0009
Median	5.7 months	4.2 months	
6-month probability[b]	(N=30) 46%	(N=19) 29%	
9-month probability[b]	(N=14) 24%	(N=4) 5%	
1-year probability[b]	(N=9) 18%	(N=2) 2%	
Range	0.2 to 18.6 months	0.4 to 15.1+ months	
95% C.I. of the median	4.7 to 6.9 months	3.1 to 5.1 months	
Time to Disease Progression			p=0.0013
Median	2.1 months	0.9 months	
Range	0.1+ to 9.4 months	0.1 to 12.0+ months	
95% C.I. of the median	1.9 to 3.4 months	0.9 to 1.1 months	

[a] Karnofsky Performance Status.
[b] Kaplan-Meier estimates.
[c] N=number of patients.
+ No progression at last visit; remains alive.
The p-value for clinical benefit response was calculated using the two-sided test for difference in binomial proportions. All other p-values were calculated using the Logrank test for difference in overall time to an event.

Clinical benefit response was achieved by 14 patients treated with Gemzar and 3 patients treated with 5-FU. One patient on the Gemzar arm showed improvement in all 3 primary parameters (pain intensity, analgesic consumption, and performance status). Eleven patients on the Gemzar arm and 2 patients on the 5-FU arm showed improvement in analgesic consumption and/or pain intensity with stable performance status. Two patients on the Gemzar arm showed improvement in analgesic consumption or pain intensity with improvement in performance status. One patient on the 5-FU arm was stable with regard to pain intensity and analgesic consumption with improvement in performance status. No patient on either arm achieved a clinical benefit response based on weight gain.

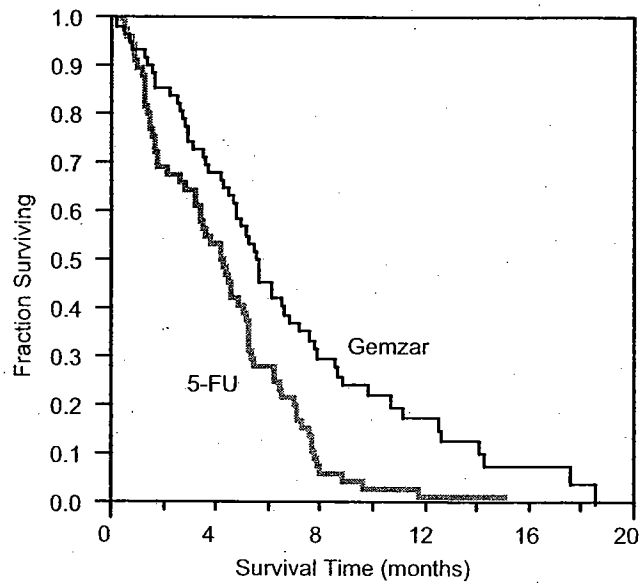


Figure 3: Kaplan-Meier Survival Curve.

The second trial was a multi-center (17 US and Canadian centers), open-label study of Gemzar in 63 patients with advanced pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. The study showed a clinical benefit response rate of 27% and median survival of 3.9 months.

Other Clinical Studies — When Gemzar was administered more frequently than once weekly or with infusions longer than 60 minutes, increased toxicity was observed. Results of a Phase 1 study of Gemzar to assess the maximum tolerated dose (MTD) on a daily x 5 schedule showed that patients developed significant hypotension and severe flu-like symptoms that were intolerable at doses above 10 mg/m^2. The incidence and severity of these events were dose-related. Other Phase 1 studies using a twice-weekly schedule reached MTDs of only 65 mg/m^2 (30-minute infusion) and 150 mg/m^2 (5-minute bolus). The dose-limiting toxicities were thrombocytopenia and flu-like symptoms, particularly asthenia. In a Phase 1 study to assess the maximum tolerated infusion time, clinically significant toxicity, defined as myelosuppression, was seen with weekly doses of 300 mg/m^2 at or above a 270-minute infusion time. The half-life of gemcitabine is influenced by the length of the infusion (*see* **CLINICAL PHARMACOLOGY**) and the toxicity appears to be increased if Gemzar is administered more frequently than once weekly or with infusions longer than 60 minutes (*see* **WARNINGS**).

INDICATIONS AND USAGE

Therapeutic Indications

Breast Cancer — Gemzar in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

Non-Small Cell Lung Cancer — 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) non-small cell lung cancer.

Pancreatic Cancer — Gemzar is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients previously treated with 5-FU.

CONTRAINDICATION

Gemzar is contraindicated in those patients with a known hypersensitivity to the drug (*see Allergic under* **ADVERSE REACTIONS**).

WARNINGS

Caution — Prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing have been shown to increase toxicity (*see* **CLINICAL STUDIES**).

Hematology — Gemzar can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, and anemia (*see* **ADVERSE REACTIONS**), and myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy. *See* **DOSAGE AND ADMINISTRATION** for recommended dose adjustments.

Pulmonary — Pulmonary toxicity has been reported with the use of Gemzar. In cases of severe lung toxicity, Gemzar therapy should be discontinued immediately and appropriate supportive care measures instituted (*see Pulmonary under* **Single-Agent Use** *and under* **Post-marketing experience** in **ADVERSE REACTIONS** section).

Renal — Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of Gemzar. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal

failure leading to death were due to HUS (*see Renal under* **Single-Agent Use** *and under* **Post-marketing experience** in **ADVERSE REACTIONS** section).

Hepatic — Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs (*see Hepatic under* **Single-Agent Use** *and under* **Post-marketing experience** in **ADVERSE REACTIONS** section).

Pregnancy — Pregnancy Category D. Gemzar can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. There are no studies of Gemzar in pregnant women. If Gemzar is used during pregnancy, or if the patient becomes pregnant while taking Gemzar, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General — Patients receiving therapy with Gemzar should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced. There was a greater tendency in women, especially older women, not to proceed to the next cycle.

Laboratory Tests — Patients receiving Gemzar should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. Suspension or modification of therapy should be considered when marrow suppression is detected (*see* **DOSAGE AND ADMINISTRATION**).

Laboratory evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter (*see* **WARNINGS**).

Carcinogenesis, Mutagenesis, Impairment of Fertility — Long-term animal studies to evaluate the carcinogenic potential of Gemzar have not been conducted. Gemcitabine induced forward mutations *in vitro* in a mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, *in vivo* sister chromatid exchange, and *in vitro* chromosomal aberration assays, and did not cause unscheduled DNA synthesis *in vitro*. Gemcitabine I.P. doses of 0.5 mg/kg/day (about 1/700 the human dose on a mg/m^2 basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice, fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day I.V. (about 1/200 the human dose on a mg/m^2 basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day I.V. (about 1/1300 the human dose on a mg/m^2 basis).

Pregnancy — Category D. *See* **WARNINGS**.

Nursing Mothers — It is not known whether Gemzar or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from Gemzar in nursing infants, the mother should be warned and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the potential risk to the infant.

Elderly Patients — Gemzar clearance is affected by age (*see* **CLINICAL PHARMACOLOGY**). There is no evidence, however, that unusual dose adjustments, (i.e., other than those already recommended in the **DOSAGE AND ADMINISTRATION** section) are necessary in patients over 65, and in general, adverse reaction rates in the single-agent safety database of 979 patients were similar in patients above and below 65. Grade 3/4 thrombocytopenia was more common in the elderly.

Gender — Gemzar clearance is affected by gender (*see* **CLINICAL PHARMACOLOGY**). In the single-agent safety database (N=979 patients), however, there is no evidence that unusual dose adjustments (i.e., other than those already recommended in the **DOSAGE AND ADMINISTRATION** section) are necessary in women. In general, in single-agent studies of Gemzar, adverse reaction rates were similar in men and women, but women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia.

Pediatric Patients — Gemzar has not been studied in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

Patients with Renal or Hepatic Impairment — Gemzar should be used with caution in patients with preexisting renal impairment or hepatic insufficiency. Gemzar has not been studied in patients with significant renal or hepatic impairment.

Drug Interactions — No specific drug interaction studies have been conducted. For information on the pharmacokinetics of Gemzar and cisplatin in combination, *see Drug Interactions under* **CLINICAL PHARMACOLOGY** section.

Radiation Therapy — Safe and effective regimens for the administration of Gemzar with therapeutic doses of radiation have not yet been determined.

ADVERSE REACTIONS

Gemzar has been used in a wide variety of malignancies, both as a single-agent and in combination with other cytotoxic drugs.

Single-Agent Use: Myelosuppression is the principal dose-limiting toxicity with Gemzar therapy. Dosage adjustments for hematologic toxicity are frequently needed and are described in the **DOSAGE AND ADMINISTRATION** section.

The data in Table 5 are based on 979 patients receiving Gemzar as a single-agent administered weekly as a 30-minute infusion for treatment of a wide variety of malignancies. The Gemzar starting doses ranged from 800 to 1250 mg/m^2. Data are also shown for the subset of patients with pancreatic cancer treated in 5 clinical studies. The frequency of all grades and severe (WHO Grade 3 or 4) adverse events were generally similar in the single-agent safety database of 979 patients and the subset of patients with pancreatic cancer. Adverse reactions reported in the single-agent safety database resulted in discontinuation of Gemzar therapy in about 10% of patients. In the comparative trial in pancreatic cancer, the discontinuation rate for adverse reactions was 14.3% for the gemcitabine arm and 4.8% for the 5-FU arm.

All WHO-graded laboratory events are listed in Table 5, regardless of causality. Non-laboratory adverse events listed in Table 5 or discussed below were those reported, regardless of causality, for at least 10% of all patients, except the categories of Extravasation, Allergic, and Cardiovascular and certain specific events under the Renal, Pulmonary, and Infection categories. Table 6 presents the data from the comparative trial of Gemzar and 5-FU in pancreatic cancer for the same adverse events as those in Table 5, regardless of incidence.

Table 5: Selected WHO-Graded Adverse Events in Patients Receiving Single-Agent Gemzar
WHO Grades (% incidence)

	All Patients[a]			Pancreatic Cancer Patients[b]			Discontinuations (%)[c]
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Patients
Laboratory[d]							
Hematologic							
Anemia	68	7	1	73	8	2	<1
Leukopenia	62	9	<1	64	8	1	<1
Neutropenia	63	19	6	61	17	7	-
Thrombocytopenia	24	4	1	36	7	<1	<1
Hepatic							<1
ALT	68	8	2	72	10	1	
AST	67	6	2	78	12	5	
Alkaline Phosphatase	55	7	2	77	16	4	
Bilirubin	13	2	<1	26	6	2	
Renal							<1
Proteinuria	45	<1	0	32	<1	0	
Hematuria	35	<1	0	23	0	0	
BUN	16	0	0	15	0	0	
Creatinine	8	<1	0	6	0	0	
Non-laboratory[e]							
Nausea and Vomiting	69	13	1	71	10	2	<1
Pain	48	9	<1	42	6	<1	<1
Fever	41	2	0	38	2	0	<1
Rash	30	<1	0	28	<1	0	<1
Dyspnea	23	3	<1	10	0	<1	<1
Constipation	23	1	<1	31	3	<1	0
Diarrhea	19	1	0	30	3	0	0
Hemorrhage	17	<1	<1	4	2	<1	<1
Infection	16	1	<1	10	2	<1	<1
Alopecia	15	<1	0	16	0	0	0
Stomatitis	11	<1	0	10	<1	0	<1
Somnolence	11	<1	<1	11	2	<1	<1
Paresthesias	10	<1	0	10	<1	0	0

Grade based on criteria from the World Health Organization (WHO).

[a] N=699-974; all patients with laboratory or non-laboratory data.

[b] N=161-241; all pancreatic cancer patients with laboratory or non-laboratory data.

[c] N=979.

[d] Regardless of causality.

[e] Table includes non-laboratory data with incidence for all patients ≥10%. For approximately 60% of the patients, non-laboratory events were graded only if assessed to be possibly drug-related.

Table 6: Selected WHO-Graded Adverse Events from Comparative Trial of Gemzar and 5-FU in Pancreatic Cancer

WHO Grades (% incidence)

	Gemzar[a]			5-FU[b]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[c]						
Hematologic						
Anemia	65	7	3	45	0	0
Leukopenia	71	10	0	15	2	0
Neutropenia	62	19	7	18	2	3
Thrombocytopenia	47	10	0	15	2	0
Hepatic						
ALT	72	8	2	38	0	0
AST	72	10	2	52	2	0
Alkaline Phosphatase	71	16	0	64	10	3
Bilirubin	16	2	2	25	6	3
Renal						
Proteinuria	10	0	0	2	0	0
Hematuria	13	0	0	0	0	0
BUN	8	0	0	10	0	0
Creatinine	2	0	0	0	0	0
Non-laboratory[d]						
Nausea and Vomiting	64	10	3	58	5	0
Pain	10	2	0	7	0	0
Fever	30	0	0	16	0	0
Rash	24	0	0	13	0	0
Dyspnea	6	0	0	3	0	0
Constipation	10	3	0	11	2	0
Diarrhea	24	2	0	31	5	0
Hemorrhage	0	0	0	2	0	0
Infection	8	0	0	3	2	0
Alopecia	18	0	0	16	0	0
Stomatitis	14	0	0	15	0	0
Somnolence	5	2	0	7	2	0
Paresthesias	2	0	0	2	0	0

Grade based on criteria from the World Health Organization (WHO).

[a] N=58-63; all Gemzar patients with laboratory or non-laboratory data.

[b] N=61-63; all 5-FU patients with laboratory or non-laboratory data.

[c] Regardless of causality.

[d] Non-laboratory events were graded only if assessed to be possibly drug-related.

Hematologic — In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity with Gemzar, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was

reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during Gemzar therapy and dosage modified or suspended according to the degree of hematologic toxicity (*see* **DOSAGE AND ADMINISTRATION**).

Gastrointestinal — Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

Hepatic — In clinical trials, Gemzar was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs (*see Hepatic under* **Post-marketing experience**).

Renal — In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving Gemzar in clinical trials. Four patients developed HUS on Gemzar therapy, 2 immediately post-therapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemzar therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required (*see Renal under* **Post-marketing experience**).

Fever — The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash — Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

Pulmonary — In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar (*see Pulmonary under* **Post-marketing experience**). The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

Edema — Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

Flu-like Symptoms — "Flu syndrome" was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection — Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

Alopecia — Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity — There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Extravasation — Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemzar is not a vesicant.

Allergic — Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemzar should not be administered to patients with a known hypersensitivity to this drug (*see* **CONTRAINDICATION**).

Cardiovascular — During clinical trials, 2% of patients discontinued therapy with Gemzar due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior history of cardiovascular disease (*see Cardiovascular under* **Post-marketing experience**).

Combination Use in Non-Small Cell Lung Cancer: In the Gemzar plus cisplatin vs. cisplatin study, dose adjustments occurred with 35% of Gemzar injections and 17% of cisplatin injections on the combination arm, versus 6% on the cisplatin-only arm. Dose adjustments were required in greater than 90% of patients on the combination, versus 16% on cisplatin. Study discontinuations for possibly drug-related adverse events occurred in 15% of patients on the combination arm and 8% of patients on the cisplatin arm. With a median of 4 cycles of Gemzar plus cisplatin treatment, 94 of 262 patients (36%) experienced a total of 149 hospitalizations due to possibly treatment-related adverse events. With a median of 2 cycles of cisplatin treatment, 61 of 260 patients (23%) experienced 78 hospitalizations due to possibly treatment-related adverse events.

In the Gemzar plus cisplatin vs. etoposide plus cisplatin study, dose adjustments occurred with 20% of Gemzar injections and 16% of cisplatin injections in the Gemzar plus cisplatin arm compared with 20% of etoposide injections and 15% of cisplatin injections in the etoposide plus cisplatin arm. With a median of 5 cycles of Gemzar plus cisplatin treatment, 15 of 69 patients (22%) experienced 15 hospitalizations due to possibly treatment-related adverse events. With a median of 4 cycles of etoposide plus cisplatin treatment, 18 of 66 patients (27%) experienced 22 hospitalizations due to possibly treatment-related adverse events. In patients who completed more than one cycle, dose adjustments were reported in 81% of the Gemzar plus cisplatin patients, compared with 68% on the etoposide plus cisplatin arm. Study discontinuations for possibly drug-related adverse events occurred in 14% of patients on the Gemzar plus cisplatin arm and in 8% of patients on the etoposide plus cisplatin arm. The incidence of myelosuppression was increased in frequency with Gemzar plus cisplatin treatment (~90%) compared to that with the Gemzar monotherapy (~60%). With combination therapy Gemzar dosage adjustments for hematologic toxicity were required more often while cisplatin dose adjustments were less frequently required.

Table 7 presents the safety data from the Gemzar plus cisplatin vs. cisplatin study in non-small cell lung cancer. The NCI Common Toxicity Criteria (CTC) were used. The two-drug combination was more myelosuppressive with 4 (1.5%) possibly treatment-related deaths, including 3 resulting from myelosuppression with infection and 1 case of renal failure associated with pancytopenia and infection. No deaths due to treatment were reported on the cisplatin arm. Nine cases of febrile neutropenia were reported on the combination therapy arm compared to 2 on the cisplatin arm. More patients required RBC and platelet transfusions on the Gemzar plus cisplatin arm.

Myelosuppression occurred more frequently on the combination arm, and in 4 possibly treatment-related deaths myelosuppression was observed. Sepsis was reported in 4% of patients on the Gemzar plus cisplatin arm compared to 1% on the cisplatin arm. Platelet transfusions were required in 21% of patients on the combination arm and <1% of patients on the cisplatin arm. Hemorrhagic events occurred in 14% of patients on the combination arm and 4% on the cisplatin arm. However, severe hemorrhagic events were rare. Red blood cell transfusions were required in 39% of the patients on the Gemzar plus cisplatin arm, versus 13% on the cisplatin arm. The data suggest cumulative anemia with continued Gemzar plus cisplatin use.

Nausea and vomiting despite the use of antiemetics occurred slightly more often with Gemzar plus cisplatin therapy (78%) than with cisplatin alone (71%). In studies with single-agent

Gemzar, a lower incidence of nausea and vomiting (58% to 69%) was reported. Renal function abnormalities, hypomagnesemia, neuromotor, neurocortical, and neurocerebellar toxicity occurred more often with Gemzar plus cisplatin than with cisplatin monotherapy. Neurohearing toxicity was similar on both arms.

Cardiac dysrrhythmias of Grade 3 or greater were reported in 7 (3%) patients treated with Gemzar plus cisplatin compared to one (<1%) Grade 3 dysrrhythmia reported with cisplatin therapy. Hypomagnesemia and hypokalemia were associated with one Grade 4 arrhythmia on the Gemzar plus cisplatin combination arm.

Table 8 presents data from the randomized study of Gemzar plus cisplatin versus etoposide plus cisplatin in 135 patients with NSCLC for the same WHO-graded adverse events as those in Table 6. One death (1.5%) was reported on the Gemzar plus cisplatin arm due to febrile neutropenia associated with renal failure which was possibly treatment-related. No deaths related to treatment occurred on the etoposide plus cisplatin arm. The overall incidence of Grade 4 neutropenia on the Gemzar plus cisplatin arm was less than on the etoposide plus cisplatin arm (28% vs. 56%). Sepsis was experienced by 2% of patients on both treatment arms. Grade 3 anemia and Grade 3/4 thrombocytopenia were more common on the Gemzar plus cisplatin arm. RBC transfusions were given to 29% of the patients who received Gemzar plus cisplatin vs. 21% of patients who received etoposide plus cisplatin. Platelet transfusions were given to 3% of the patients who received Gemzar plus cisplatin vs. 8% of patients who received etoposide plus cisplatin. Grade 3/4 nausea and vomiting were also more common on the Gemzar plus cisplatin arm. On the Gemzar plus cisplatin arm, 7% of participants were hospitalized due to febrile neutropenia compared to 12% on the etoposide plus cisplatin arm. More than twice as many patients had dose reductions or omissions of a scheduled dose of Gemzar as compared to etoposide, which may explain the differences in the incidence of neutropenia and febrile neutropenia between treatment arms. Flu syndrome was reported by 3% of patients on the Gemzar plus cisplatin arm with none reported on the comparator arm. Eight patients (12%) on the Gemzar plus cisplatin arm reported edema compared to 1 patient (2%) on the etoposide plus cisplatin arm.

Table 7: Selected CTC-Graded Adverse Events from Comparative Trial of Gemzar plus Cisplatin versus Single-Agent Cisplatin in NSCLC

CTC Grades (% incidence)

	Gemzar plus Cisplatin[a]			Cisplatin[b]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[c]						
Hematologic						
Anemia	89	22	3	67	6	1
RBC Transfusion[d]	39			13		
Leukopenia	82	35	11	25	2	1
Neutropenia	79	22	35	20	3	1
Thrombocytopenia	85	25	25	13	3	1
Platelet Transfusions[d]	21			<1		
Lymphocytes	75	25	18	51	12	5
Hepatic						
Transaminase	22	2	1	10	1	0
Alkaline Phosphatase	19	1	0	13	0	0
Renal						

Proteinuria	23	0	0	18	0	0
Hematuria	15	0	0	13	0	0
Creatinine	38	4	<1	31	2	<1
Other Laboratory						
Hyperglycemia	30	4	0	23	3	0
Hypomagnesemia	30	4	3	17	2	0
Hypocalcemia	18	2	0	7	0	<1
Non-laboratory[e]						
Nausea	93	25	2	87	20	<1
Vomiting	78	11	12	71	10	9
Alopecia	53	1	0	33	0	0
Neuro Motor	35	12	0	15	3	0
Constipation	28	3	0	21	0	0
Neuro Hearing	25	6	0	21	6	0
Diarrhea	24	2	2	13	0	0
Neuro Sensory	23	1	0	18	1	0
Infection	18	3	2	12	1	0
Fever	16	0	0	5	0	0
Neuro Cortical	16	3	1	9	1	0
Neuro Mood	16	1	0	10	1	0
Local	15	0	0	6	0	0
Neuro Headache	14	0	0	7	0	0
Stomatitis	14	1	0	5	0	0
Hemorrhage	14	1	0	4	0	0
Dyspnea	12	4	3	11	3	2
Hypotension	12	1	0	7	1	0
Rash	11	0	0	3	0	0

Grade based on Common Toxicity Criteria (CTC). Table includes data for adverse events with incidence ≥10% in either arm.

[a] N=217-253; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[b] N=213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[c] Regardless of causality.

[d] Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events.

[e] Non-laboratory events were graded only if assessed to be possibly drug-related.

Table 8: Selected WHO-Graded Adverse Events from Comparative Trial of Gemzar plus Cisplatin versus Etoposide plus Cisplatin in NSCLC

WHO Grades (% incidence)

	Gemzar plus Cisplatin[a]			Etoposide plus Cisplatin[b]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[c]						
Hematologic						
Anemia	88	22	0	77	13	2
RBC Transfusions[d]	29			21		
Leukopenia	86	26	3	87	36	7
Neutropenia	88	36	28	87	20	56
Thrombocytopenia	81	39	16	45	8	5
Platelet Transfusions[d]	3			8		
Hepatic						
ALT	6	0	0	12	0	0
AST	3	0	0	11	0	0
Alkaline Phosphatase	16	0	0	11	0	0
Bilirubin	0	0	0	0	0	0
Renal						
Proteinuria	12	0	0	5	0	0
Hematuria	22	0	0	10	0	0
BUN	6	0	0	4	0	0
Creatinine	2	0	0	2	0	0
Non-laboratory[e,f]						
Nausea and Vomiting	96	35	4	86	19	7
Fever	6	0	0	3	0	0
Rash	10	0	0	3	0	0
Dyspnea	1	0	1	3	0	0
Constipation	17	0	0	15	0	0
Diarrhea	14	1	1	13	0	2
Hemorrhage	9	0	3	3	0	3
Infection	28	3	1	21	8	0
Alopecia	77	13	0	92	51	0
Stomatitis	20	4	0	18	2	0
Somnolence	3	0	0	3	2	0
Paresthesias	38	0	0	16	2	0

Grade based on criteria from the World Health Organization (WHO).

[a] N=67-69; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1250 mg/m^2 on Days 1 and 8 and cisplatin at 100 mg/m^2 on Day 1 every 21 days.

[b] N=57-63; all cisplatin plus etoposide patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m^2 on Day 1 and I.V. etoposide at 100 mg/m^2 on Days 1, 2, and 3 every 21 days.

[c] Regardless of causality.

[d] Percent of patients receiving transfusions. Percent transfusions are not WHO-graded events.

[e] Non-laboratory events were graded only if assessed to be possibly drug-related.

[f] Pain data were not collected.

Combination Use in Breast Cancer: In the Gemzar plus paclitaxel versus paclitaxel study, dose reductions occurred with 8% of Gemzar injections and 5% of paclitaxel injections on the combination arm, versus 2% on the paclitaxel arm. On the combination arm, 7% of Gemzar doses were omitted and <1% of paclitaxel doses were omitted, compared to <1% of paclitaxel doses on the paclitaxel arm. A total of 18 patients (7%) on the Gemzar plus paclitaxel arm and 12 (5%) on the paclitaxel arm discontinued the study because of adverse events. There were two deaths on study or within 30 days after study drug discontinuation that were possibly drug-related, one on each arm.

Table 9 presents the safety data occurrences of ≥10% (all grades) from the Gemzar plus paclitaxel versus paclitaxel study in breast cancer.

Table 9: Adverse Events from Comparative Trial of Gemzar plus Paclitaxel versus Single-Agent Paclitaxel in Breast Cancer[a]

CTC Grades (% incidence)

	Gemzar plus Paclitaxel (N=262)			Paclitaxel (N=259)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[b]						
Hematologic						
Anemia	69	6	1	51	3	<1
Neutropenia	69	31	17	31	4	7
Thrombocytopenia	26	5	<1	7	<1	<1
Leukopenia	21	10	1	12	2	0
Hepatobiliary						
ALT	18	5	<1	6	<1	0
AST	16	2	0	5	<1	0
Non-laboratory[c]						
Alopecia	90	14	4	92	19	3
Neuropathy-sensory	64	5	<1	58	3	0
Nausea	50	1	0	31	2	0
Fatigue	40	6	<1	28	1	<1
Myalgia	33	4	0	33	3	<1
Vomiting	29	2	0	15	2	0
Arthralgia	24	3	0	22	2	<1
Diarrhea	20	3	0	13	2	0
Anorexia	17	0	0	12	<1	0
Neuropathy-motor	15	2	<1	10	<1	0
Stomatitis/pharyngitis	13	1	<1	8	<1	0
Fever	13	<1	0	3	0	0
Constipation	11	<1	0	12	0	0
Bone pain	11	2	0	10	<1	0
Pain-other	11	<1	0	8	<1	0
Rash/desquamation	11	<1	<1	5	0	0

[a] Grade based on Common Toxicity Criteria (CTC) Version 2.0 (all grades ≥10%).
[b] Regardless of causality.
[c] Non-laboratory events were graded only if assessed to be possibly drug-related.

The following are the clinically relevant adverse events that occurred in >1% and <10% (all grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse events (Gemzar plus paclitaxel versus paclitaxel): 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%).

No differences in the incidence of laboratory and non-laboratory events were observed in patients 65 years or older, as compared to patients younger than 65.

Post-marketing experience: The following adverse events have been identified during post-approval use of Gemzar. These events have occurred after Gemzar single-agent use and Gemzar in combination with other cytotoxic agents. Decisions to include these events are based on the seriousness of the event, frequency of reporting, or potential causal connection to Gemzar.

Cardiovascular — Congestive heart failure and myocardial infarction have been reported very rarely with the use of Gemzar. Arrhythmias, predominantly supraventricular in nature, have been reported very rarely.

Vascular Disorders — Vascular toxicity reported with Gemzar includes clinical signs of vasculitis, which has been reported very rarely. Gangrene has also been reported very rarely.

Skin — Cellulitis and non-serious injection site reactions in the absence of extravasation have been rarely reported.

Hepatic — Serious hepatotoxicity including liver failure and death has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs.

Pulmonary — Parenchymal toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported rarely following one or more doses of Gemzar administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last Gemzar dose. Respiratory failure and death occurred very rarely in some patients despite discontinuation of therapy.

Renal — Hemolytic-Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of Gemzar. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.

OVERDOSAGE

There is no known antidote for overdoses of Gemzar. Myelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m^2 was administered by I.V. infusion over 30 minutes every 2 weeks to several patients in a Phase 1 study. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

DOSAGE AND ADMINISTRATION

Gemzar is for intravenous use only.

Adults

Single-Agent Use:

Pancreatic Cancer — Gemzar should be administered by intravenous infusion at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates

reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

Dose Modifications — Dosage adjustment is based upon the degree of hematologic toxicity experienced by the patient (*see* **WARNINGS**). Clearance in women and the elderly is reduced and women were somewhat less able to progress to subsequent cycles (*see Human Pharmacokinetics under* **CLINICAL PHARMACOLOGY** *and* **PRECAUTIONS**).

Patients receiving Gemzar should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 10.

Table 10: Dosage Reduction Guidelines

Absolute granulocyte count ($\times 10^6$/L)		Platelet count ($\times 10^6$/L)	% of full dose
≥1000	and	≥100,000	100
500-999	or	50,000-99,000	75
<500	or	<50,000	Hold

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemzar should be administered with caution in patients with evidence of significant renal or hepatic impairment.

Patients treated with Gemzar who complete an entire cycle of therapy may have the dose for subsequent cycles increased by 25%, provided that the absolute granulocyte count (AGC) and platelet nadirs exceed 1500 x 10^6/L and 100,000 x 10^6/L, respectively, and if non-hematologic toxicity has not been greater than WHO Grade 1. If patients tolerate the subsequent course of Gemzar at the increased dose, the dose for the next cycle can be further increased by 20%, provided again that the AGC and platelet nadirs exceed 1500 x 10^6/L and 100,000 x 10^6/L, respectively, and that non-hematologic toxicity has not been greater than WHO Grade 1.

Combination Use:

Non-Small Cell Lung Cancer — Two schedules have been investigated and the optimum schedule has not been determined (*see* **CLINICAL STUDIES**). With the 4-week schedule, Gemzar should be administered intravenously at 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m^2 on Day 1 after the infusion of Gemzar. With the 3-week schedule, Gemzar should be administered intravenously at 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m^2 should be administered intravenously after the infusion of Gemzar on Day 1. See prescribing information for cisplatin administration and hydration guidelines.

Dose Modifications — Dosage adjustments for hematologic toxicity may be required for Gemzar and for cisplatin. Gemzar dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving Gemzar should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 10. For cisplatin dosage adjustment, see manufacturer's prescribing information.

In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemzar plus cisplatin should be held or decreased by 50% depending on the judgment of the treating physician. During combination therapy with cisplatin, serum creatinine, serum potassium, serum calcium, and serum magnesium should be carefully

monitored (Grade 3/4 serum creatinine toxicity for Gemzar plus cisplatin was 5% versus 2% for cisplatin alone).

Breast Cancer — Gemzar should be administered intravenously at a dose of 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m^2 on Day 1 as a 3-hour intravenous infusion before Gemzar administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count ≥1500 x 10^6/L and a platelet count ≥100,000 x 10^6/L prior to each cycle.

Dose Modifications — Gemzar dosage adjustments for hematological toxicity is based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, Gemzar dosage should be modified according to the guidelines in Table 11.

Table 11: Day 8 Dosage Reduction Guidelines for Gemzar in Combination with Paclitaxel

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
≥1200	and	>75,000	100
1000-1199	or	50,000-75,000	75
700-999	and	≥50,000	50
<700	or	<50,000	Hold

In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemzar should be held or decreased by 50% depending on the judgment of the treating physician. For paclitaxel dosage adjustment, see manufacturer's prescribing information.

Gemzar may be administered on an outpatient basis.

Instructions for Use/Handling — The recommended diluent for reconstitution of Gemzar is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemzar upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

Reconstituted Gemzar is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

When prepared as directed, Gemzar solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F) [*See* USP]. Discard unused portion. Solutions of reconstituted Gemzar should not be refrigerated, as crystallization may occur.

The compatibility of Gemzar with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

Unopened vials of Gemzar are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) [*See* USP].

Caution should be exercised in handling and preparing Gemzar solutions. The use of gloves is recommended. If Gemzar solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Although acute dermal irritation has not been observed in animal studies, 2 of 3 rabbits exhibited drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Vials:

200 mg white, lyophilized powder in a 10-mL size sterile single use vial (No. 7501)
NDC 0002-7501-01

1 g white, lyophilized powder in a 50-mL size sterile single use vial (No. 7502)
NDC 0002-7502-01

Store at controlled room temperature (20° to 25°C) (68° to 77°F). The USP has defined controlled room temperature as "A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses."

REFERENCES

1. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. US Government Printing Office, Washington, DC 20402.
2. Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. *JAMA* 1985;253:1590.
3. National Study Commission on Cytotoxic Exposure — Recommendations for handling cytotoxic agents, 1987. Available from Louis P Jeffrey, ScD, Director of Pharmacy Services, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Aust* 1983;1:426.
5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. *CA* 1983;33(Sept/Oct):258.
6. American Society of Hospital Pharmacists: Technical assistance bulletin on handling cytotoxic drugs in hospitals. *Am J Hosp Pharm* 1990;47:1033.
7. Controlling Occupational Exposure to Hazardous Drugs, OSHA Work Practice Guidelines. *Am J Health-Sys Pharm* 1996;53:1669-1685.
8. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburg, PA: Oncology Nursing Society; 1999:32-41.

Literature revised Month dd, yyyy

Eli Lilly and Company
Indianapolis, IN 46285, USA

A 3.0 NL 4061 AMP PRINTED IN USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-509/S029

MEDICAL REVIEW

Clinical Review

Application #	**NDA 20-509 S 029**
Drug Name	
Medical Reviewer	**Martin H. Cohen, M.D.**
Medical Team Leader	**John R Johnson, M.D.**
Documents reviewed	**NDA # N20509** **Incoming Document Type: SE1** **Sequence Number: 029** **Supplement Modification Type:** **Letter Date: 12/17/2003** **EDR \\CDSESUB1\ N20509\ S029\2003-12-17**

CLINICAL REVIEW

Table of Contents

Table of Tables

Table of Figures

Clinical Review for NDA 20-509 S029

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The clinical reviewer of the Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA recommends regular approval of sNDA 20-509. Study JHQG (pivotal trial) demonstrated consistent superiority of treatment with gemzar plus paclitaxel over paclitaxel alone as evidenced by increased response rate (41% versus 22%, $p<0.0001$), prolonged time to documented tumor progression (median 5.2 months (4.2, 5.6) versus 2.9 months (2.6, 3.7); log rank $p <0.001$) and overall survival (analysis performed with 29% of patients censored; median survival 18.6 months versus 15.8 months; log rank $p=0.0489$. At the interim survival analysis with approximately 35% of patients censored the median survival was 18.5 months versus 15.8 months; hazard ratio 0.78 [95% CI 0.63 to 0.96], log rank $p=0.0182$.

Treatment with gemzar plus paclitaxel was tolerable and relatively safe. The toxicity profile with the combination therapy was consistent with those of gemcitabine and paclitaxel as single agents, and no new trends or safety concerns were observed.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The sponsor will be required to continue follow-up of patients enrolled in trial JHQG to obtain long duration survival data.

II. Smmary of Clinical Findings

A. Brief Overview of Clinical Program

The following studies were submitted

1. A pivotal Phase 3 trial, Trial JHQG Gemzar+paclitaxel vs paclitaxel in adjuvant/ neoadjuvant anthracycline pretreated metastatic breast cancer (MBC).

2. Four published phase 2 gemzar+paclitaxel studies in MBC

3. One phase 1 gemzar+paclitaxel study in MBC

4. Twelve phase 2 gemzar monotherapy studies for MBC

The response rates of gemzar+paclitaxel in the published phase 2 studies ranged from 39% to 69%. Median time to progression varied from 5.4 to 9.0 months. Response rates and TTP of other approved MBC regimens (paclitaxel, docetaxel, and capecitabine plus docetaxel are either comparable to, or less than, the reported gemzar+paclitaxel results.

B. Efficacy

Study JHQG (pivotal trial) demonstrated consistent superiority of treatment with gemzar plus paclitaxel over paclitaxel alone as evidenced by increased response rate, prolonged time to documented tumor progression and increased overall survival. The observed p-value of their April 2004 updated overall survival is 0.0489.

C. Safety

Safety data provided by the sponsor was reviewed.

The toxicity profile with gemzar plus paclitaxel was consistent with those of gemcitabine and paclitaxel as single agents, and no new trends or safety concerns were observed.

D. Dosing

Gemzar 1250 mg/m^2 was administered intravenously over 30 minutes on Days 1 and 8 of a 21-day cycle and paclitaxel 175 mg/m^2 was administered intravenously over 3 hours on Day 1 before the infusion of Gemzar. Single-agent paclitaxel 175 mg/m^2 was administered intravenously over 3 hours on Day 1 of each 21-day cycle as the control arm.

E. Special Populations

Pediatrics - Gemzar has not been studied in pediatric patients.

Elderly - Gemzar clearance is affected by age. There is no evidence, however, that unusual dose adjustments are necessary in patients over 65, and in general, adverse reaction rates in the single-agent safety database of 979 patients were similar in patients above and below 65. Grade 3/4 thrombocytopenia was more common in the elderly.

Gender – The pivotal study was conducted in female patients. It is known, however, that Gemzar clearance is affected by gender with more rapid Gemzar clearance in males. There is no evidence, however, that unusual dose adjustments

are necessary in women. In general, in single-agent studies of gemcitabine, adverse reaction rates were similar in men and women, but women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia.

Race/Ethnicity - There was no significant effect of race/ethnicity on either efficacy or safety results.

Renal or Hepatic Impairment - Gemzar should be used with caution in patients with preexisting renal impairment or hepatic insufficiency. Gemzar has not been studied in patients with significant renal or hepatic impairment

Pregnancy - Category D. Gemzar can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays.

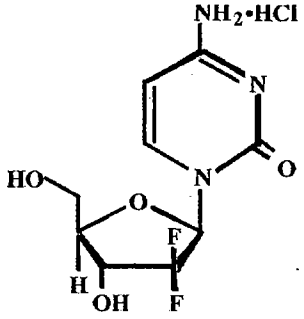
Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (b-isomer). The empirical formula for gemcitabine HCl is C 9 H 11 F 2 N 3 O 4 • HCl. It has a molecular weight of 299.66. Gemcitabine HCl is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents. The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. The structural formula is depicted in **Figure 1**.

Figure 1: Gemcitabine structural formula



Proprietary Name: **Gemzar**

Applicant: **Eli Lilly and Company**

Drug Class: **Antimetabolite**

Current Indication:

Non-Small Cell Lung Cancer — 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) non-small cell lung cancer. *Pancreatic Cancer* — Gemzar is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients previously treated with 5-FU.

Proposed Indication: Above, plus

Breast Cancer — Gemzar is indicated in combination with paclitaxel for the first-line treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy.

Dosage and Administration:

Current Label: *Non-Small Cell Lung Cancer* — Two schedules have been investigated and the optimum schedule has not been determined. With the 4-week schedule, Gemzar should be administered intravenously at 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m^2 on Day 1 after the infusion of Gemzar. With the 3-week schedule, Gemzar should be administered intravenously at 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m^2 should be administered intravenously after the infusion of

Gemzar on Day 1. See prescribing information for cisplatin administration and hydration guidelines.

Proposed Label:

Breast Cancer — Gemzar should be administered intravenously at a dose of 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered [redacted]

B. State of Armamentarium for Indication(s)

Hormones, chemotherapy drugs and biologics are approved for the proposed indication.

Specific chemotherapy drugs commonly used to treat metastatic breast cancer include taxanes (paclitaxel, docetaxel), cyclophosphamide, 5-FU, doxorubicin, methotrexate, thiotepa, vinblastine, and capecitabine. Biologics include trastuzumab. Approved treatments include doxorubicin, 5-FU, paclitaxel, docetaxel, capecitabine and capecitabine plus docetaxel.

C. Important Milestones in Product Development

Table 1: Milestones in Product Development

Event	Date
EOP2 Meeting	Sept. 30, 1998
ODAC Meeting on breast cancer endpoints	June 7, 1999
Initial protocol submitted to IND	August 6, 1999
First study patient enrolled	August 11, 1999
Protocol amendment A (Change of primary endpoint from PFS to OS) submitted	Sept. 9, 1999
Protocol amendment B (PK Change) submitted	March 3, 2001
Protocol amendment C (Addition of 26 patients) submitted	Jan. 4, 2002
Database lock for interim safety	Feb. 16, 2001
Last study patient enrolled	April 2, 2002
Database lock for TtDPD	August 1, 2002
Pre-NDA meeting	May 8, 2003
Pre-NDA meeting	Sept. 16, 2003
Database lock for interim survival	Sept 17, 2003
NDA submission	Dec. 17, 2003

D. Other Relevant Information

Gemzar is currently approved in the U.S. for pancreatic cancer and, with cisplatin, for the first-line treatment of NSCLC.

It is approved outside of the U.S. for the treatment of bladder cancer, ovarian cancer and breast cancer.

E. Important Issues with Pharmacologically Related Agents

None

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Clinical Pharmacology and Biopharmaceutics

See prior NDA reviews

B. Statistics

See statistical review

C. Chemistry

No chemistry review was conducted for this supplemental NDA as there were no new data submitted.

D. Animal Pharmacology and Toxicology

No animal pharmacology and toxicology review was conducted for this supplemental NDA as there were no new data submitted.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Sponsor's analysis of pharmacokinetic data suggested that combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel compared to single-agent administration. Sponsor claimed that the mean gemzar clearance as monotherapy was 76.3 L/h/m2 and combined with paclitaxel it was 71.3 L/h/m2. Similarly the mean paclitaxel clearance as monotherapy was 7.43 L/h/m2 and combined with gemzar it was 7.28L/h/m2.

Hepatic and Renal Impairment:

The effects of significant renal or hepatic insufficiency on the disposition of gemcitabine have not been assessed.

Special Populations:

Table 2 (sponsor) shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 2: Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance Men ($L/hr/m^2$)	Clearance Women ($L/hr/m^2$)	Half-Life[a] Men (min)	Half-Life[a] Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

[a]Half-life for patients receiving a short infusion (<70 min).

B. Pharmacodynamics

No pharmacodynamic review was conducted for this supplemental NDA as there were no new data submitted.

IV. Description of Clinical Data and Sources

A. Overall Data

EDR submissions of December 17, 2003 and January 29, 2004

B. Table Listing the Submitted Clinical Trials

Table 3: Submitted clinical trials

Study phase	Protocol(s)
Phase 3	Trial JHQG Gemzar+paclitaxel vs paclitaxel in adjuvant/ neoadjuvant anthracycline pretreated metastatic breast cancer (MBC).
Phase 2	Gemzar+paclitaxel study in MBC
Phase 2	Four published gemzar+paclitaxel studies in MBC
Phase 1	Gemzar+paclitaxel study
Phase 2	Twelve gemzar monotherapy studies for MBC

C. Postmarketing Experience

Approximately 965,000 patients have received Gemzar between 1996 and the present.

D. Literature Review

Submitted phase 2 gemzar combination chemotherapy and monotherapy trials were reviewed.

V. Clinical Review Methods

A. How the Review was Conducted

The efficacy review is based primarily on analysis of data submitted as SAS transport files for one multicenter trial Protocol B9E- MC- JHQG "A Phase 3 Study of Gemcitabine Plus Paclitaxel Versus Paclitaxel in Patients with Unresectable, Locally Recurrent or Metastatic Breast Cancer".

Tumor measurements were provided in the on-study and post-study site involvement tables. Tumor measurements by the investigator and by an independent panel of experts were included. The panel of experts did not evaluate bone scans. Therefore, for patients with bone metastases tumor measurements by the investigator were evaluated to determine treatment response and time to progression. For patients without bone metastases tumor measurements by the independent physician group were evaluated. Reported dates of progression that were not supported by tumor measurements or by the occurrence of new lesions were not accepted. Patients who had not progressed were censored on the last date that a full assessment for progression was performed.

If there was a disagreement between the FDA reviewer and Lilly as to response status or in the date of progression or censoring the patient was reviewed again by both the sponsor and the FDA. Correspondence regarding these reviews occurred on several occasions including February 3, 2004, February 24, 2004, March 4, 2004 and March 22 and 23, 2004. There was a meeting with Lilly to go over data discrepancies on February 10, 2004. All disputes were satisfactorily resolved.

B. Overview of Materials Consulted in Review

See above.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI on-site audit was used to audit sponsors data quality, integrity and analysis

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Yes

E. Evaluation of Financial Disclosure

The sponsor has submitted certification that they have not entered into any financial arrangement with any of the clinical investigators who participated in Protocol B9E- MC- JHQG "A Phase 3 Study of Gemcitabine Plus Paclitaxel Versus Paclitaxel in Patients with Unresectable, Locally Recurrent or Metastatic Breast Cancer" . This certification was signed on 11/11/03 by Binh Nguyen, M.D., Ph.D., Regulatory Medical Director.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Sufficient data was submitted to allow for independent evaluation of study results. Study JHQG (pivotal trial) demonstrated consistent superiority of treatment with gemzar plus paclitaxel over paclitaxel alone as evidenced by increased response rate (41% versus 22%, $p<0.0001$), prolonged time to documented tumor progression (median 5.2 months versus 2.9 months; log rank $p <0.001$) and overall survival (analysis with less than 30% of patients censored; median survival 18.6 months versus 15.8 months; log rank $p=0.0489$; Final survival analysis was to be performed at the $p=0.03$ level).

B. General Approach to Review of the Efficacy of the Drug

Individual patient data provided by the sponsor were analyzed to confirm sponsor's reported results and analyses.

C. Detailed Review of Trials by Indication

The efficacy review is based primarily on one multicenter trial Protocol B9E-MC- JHQG "A Phase 3 Study of Gemcitabine Plus Paclitaxel Versus Paclitaxel in Patients with Unresectable, Locally Recurrent or Metastatic Breast Cancer"

1. Protocol Review

The phase 3 study protocol (B9E-MC-JHQG) is provided in the appendix.

The protocol was approved by Lilly on 14 June 1999. There were three amendments to the protocol. In addition, there were two addenda to the protocol: addendum (1) affected all investigational sites in Taiwan, and addendum (2) affected all investigational sites in France. Notable changes to the protocol specified by the amendments and addenda are detailed below.

Amendment (a), approved on 7 September 1999, consisted of the following changes:

• As per FDA request, the primary efficacy endpoint of the study was changed from progression- free survival (PFS) to overall survival. The term progression- free survival was changed to time to documented progression of disease (TtDPD). Furthermore, the definition of TtDPD was revised to exclude death due to any cause as an endpoint for this parameter. As a result of the change in primary endpoint, a planned interim analysis was added and significance levels for the interim and final analyses were specified accordingly. Final analysis will be performed after 440 patients have died. The original definition of PFS was retained to allow for analysis of that endpoint as well.

• As per FDA request, the randomization scheme was changed with the addition of the stratification factor prior hormonal therapy (yes or no) and the stratification factor for time to disease progression was changed from " Disease progression during previous chemotherapy (Yes versus No)" to " Disease progression from prior adjuvant chemotherapy ($\leq$ 6 months or > 6 months)".

• As per FDA request, clarifications were provided for the following: bimonthly radiological evaluations were performed only on areas positive for disease at baseline, and WHO criteria for the measurability of a tumor in measurable and nonmeasurable disease were used.

• A $\pm$ 7 days window of time was added to the every- 8- week interval for performing imaging scans. This provided some flexibility for the multiple sites participating in this study.

• The health outcomes analysis section was revised to specify the populations to be analyzed.

• The time interval between administration of paclitaxel and gemcitabine was lowered from 30 minutes to as close to 10 minutes as possible; pharmacokinetic sampling times were adjusted accordingly.

Amendment (b), approved on 14 February 2001, consisted of the following changes:

• As per FDA request, two additional blood samples for pharmacokinetic analysis of paclitaxel were added to both treatment arms. This extended the sampling time from 28 hours to 72 hours from the end of the infusion and enabled capture of a minimum of three half- lives of paclitaxel.

• To comply with European regulatory requirements, the individual responsible for signing the final clinical study report was changed from the Sponsor's medical officer to the coordinating investigator.

• It was clarified that the hazard ratio corresponds approximately to a 33% increase in TtDPD and overall survival only under specific conditions (that is, under exponential distribution for time to progression and overall survival).

Amendment (c), approved on 16 October 2001, consisted of the following change:

• The sample size was increased from 500 patients to approximately 526 patients following the discovery that some patients with positive bone scans at baseline did

not have repeat bone scans performed as required. The decision to allow enrollment of additional patients was made because the missing bone scan data could impact the TtDPD endpoint.

Addendum (1), approved in 1999, allowed investigational sites in Taiwan to use local laboratories to assay blood chemistries because of the high costs associated with transporting blood specimens to a central laboratory.

In order to comply with local regulations in France, Addendum (2), approved in 2001, required that patients must have terminated radiation therapy at least 4 weeks prior to enrollment in a study administering gemcitabine, a potent radiosensitizer.

The following is a listing of the principal investigators and the corresponding participating institutions.

2. List of investigators

Argentina

Investigator Number: 40 Claudio I. Bagnes, MD
Hospital Dr Tornu Ex Combatientes de Malvinas 3002 Ciudad de Buenos Aires 1427

Investigator Number: 41 Luis E. Fein, MD
Centro de Oncologia Rosario Boulevard 1085 Rosario Santa Fe 2000

Investigator Number: 42 Silvia Jovtis
Complejo Medico Churruca Visca Uspallata 3400 Ciudad de Buenos Aires 1425

Investigator Number: 43 Alberto M. Luchina, MD
Centro Oncologico de Excelencia Calle 508 Entre 16 Y 18 Gonnet, Buenos Aires 1897

Investigator Number: 46 Cristina M. Nasurdi, MD
Hospital Provincial de Rosario Alem 1450 Santa Fe Rosario 2000

Investigator Number: 47 Mario F. Bruno, MD
Hospital General de Agudos, " Dr Teodoro Alvarez" Aranguren 2701 Capitol Federal Buenos Aires 1406

Brazil

Investigator Number: 2 Jeferson Vinholes, MD
Santa Casa Rua Annes Dias, 285 Porto Alegre Rio Grande do Sul 90020- 090

Investigator Number: 3 Carlos H. Barrios, MD
Hospital Sao Lucas – Puc Centro de Pesquisa em Oncologia Sala 321 Av Ipiranga 6690 Porto Alegre RS 90610- 000

Investigator Number: 4 Celia Tosello
Oliveira Instituto Brasileiro de Controle do Cancer Setor de Quimioterapia Av Alcantara Machado, 2576 Sao Paulo Sp 03102- 002

Investigator Number: 5 Manoel Odorico Moraes, PhD
Instituto do Cancer do Ceara – Ufce Rua Cel Nunes de Melo 1127 Caixa Postal 3157 Fortaleza CE 60431- 970

Canada

Investigator Number: 851 Martin Elliott Blackstein, MD
Mount Sinai Hospital Suite 1223 600 University Avenue Toronto, Ontario M5G 1X5

Investigator Number: 855 Raynald Simard
Complexe Hospitalier de la Sagamie 305 St. Vallier Chicoutimi Quebec G7H 5H6

Chile

Investigator Number: 44 Francisco Orlandi Jorquera, MD
Clinica Santa Maria A. Santa Maria 0410 Santiago de Chile

Investigator Number: 48 Jose Miguel Reyes Vidal, MD
Clinicas Las Condes La Fontecilla 441 Las Condes Santiago

Czech Republic

Investigator Number: 10 Lubos Petruzelka, MD
Vfn A 1 Lf Univerzity Karlovy U Nemocnice 2 Praha 2 128 08

Investigator Number: 11 Milan Kuta, MD
Nemocnice Chomutov Kochova 1185 Chomutov 43001

Investigator Number: 12 Pavel Vodvarka, MD
Fakultni Nemocnice S Poliklinikou Tr 17 Listopadu 1790 Ostrava- Poruba 708 52

Investigator Number: 13 Rostislav Vyzula, MD
Masaryk University Jihlavska 20 Brno 639 00

France

Investigator Number: 301 Gilles Romieu, MD
Centre Val d'Aurelle 208 Rue des Apothicaïres- Parc Euromedecine Montpellier 34298

Investigator Number: 302 Phillippe Chollet,
PR Crlc Jean Perrin 58 Rue Montalembert BP 392 Clermont Ferrand 63011 Cede

Investigator Number: 303 Daniel Serin, MD
Clinique Sainte Catherine Chemin du Lavarin BP 846 Avignon Cedex 2 84082

Investigator Number: 304 Thierry Petit
Centre Paul Strauss 3 Rue de la Porte de l' Hopital Strasbourg Cedex 67085

Germany

Investigator Number: 401 Gunter von Minckwitz
Klinikum der Johann Wolfgang Goethe- Universitat Frankfurt Theodor- Stern- Kai 7 Frankfurt D- 60596

Investigator Number: 402 Georg- Peter Breitbach, MD
Krankenhaus Neunkirchen Ggmbh Brunnenstrasse 20 Neunkirchen D- 66538

Investigator Number: 403 Andreas du Bois, MD
Hsk- Dr- Horst- Schmidt- Kliniken- Klinikum der Stadt Wiesbaden Ludwig-Erhard- Strasse 100 Wiesbaden D- 65199

Investigator Number: 404 Klaus Gutschow, MD
Klinik Bad Trissl- Onkologische Klinik, Gynakologie II Bad- Trissl- Strasse 73 Oberaudorf D- 83080

Investigator Number: 405 Bernhardt Heinrich, MD
Hamatologisch- Onkologische Praxis Augsburg Halderstrasse 29 Augsburg D-86150

Investigator Number: 406 Wolfram Jaeger, MD
Klinik fur Frauenheilkunde der Universitat Erlangen- Nurnberg Universitatsstrasse 21- 23 Erlangen D- 91054

Investigator Number: 408 Guenter Morack, MD
Klinikum Buch Krankenhausbetriestet von Berlin Pankow Karowerstrasse 11 Berlin, D- 13125

Investigator Number: 409 Carsten Oberhoff, MD
Universitatsklinikum Essen Hufelandstrasse 55 Essen, D- 45147

Investigator Number: 413 Wolfgang Dornoff, MD
Krankenanstalt Mutterhaus der Borromaerinnen Feldstrasse 16 Trier D- 54290

Hungary

Investigator Number: 20
Tibor Lobl Fovarosi Onkormanyzat Peterfy Sandor Utcai Korhaza Peterfy Sandor Utca 8- 20 Budapest 1076

Investigator Number: 21 Tamas Pinter, MD
Petz Aladar Megyei Korhaz Onkologiai Osztaly Vasvari Pal Utca 2- 4 Gyor 9023

Investigator Number: 22 Mikols Szucs, MD
Bacs- Kiskun Megyei Korhaz Nyiri Utca 38 Kecskemet 6000

India

Investigator Number: 650 Shilin Shukla, MD
Gujarat Cancer and Research Institute Department of Medical Oncology Civil Hospital Campus, Asarwa Ahmedabad Gujarat 380016

Investigator Number: 651 Shona Nag, MD
Inlaks and Budhrani Hospital Department of Oncology 7- 9 Koregaon Park Pune 411001

Investigator Number: 652 Asha Kapadia, MD
Pd Hinduja National Hospital and Research Center Department of Oncology Veer Savarkar Marg, Mahim Mumbai Maharashtra 400016

Investigator Number: 653 Jagdev S. Sekhon, MD
Dayanand Medical College and Hospital Department of Medical Oncology Tagore Garden, Civil Lines Ludhiana, Punjab 141001

Investigator Number: 654 Pramod K. Julka, MD
All India Institute of Medical Sciences Department of Radiation Oncology Ansari Nagar New Delhi 110 029

Italy

Investigator Number: 503 Graziella Pinotti, MD
Ospedale di Circolo e Fondazione Macchi Viale le Borri 57 Varese 21100

Investigator Number: 504 Salvatore Siena, MD
Ospedale Niguarda ca'Granda Piazza Ospedale Maggiore, 3 Milano 20100

Investigator Number: 505 Alberto Zaniboni, MD
Casa di Cura Poliambulanza Via Bissolati 57 Brescia 25124

Investigator Number: 506 Pier Franco Conte, MD
Ospedale Santa Chiara di Pisa Via Roma 67 Pisa 56100

Investigator Number: 507 Vinicio Fosser, MD
Ospedale S. Bartolo Viale Ridolfi, 37 Vicenza 30100

Mexico

Investigator Number: 801 German Calderillo Ruiz
Instituto Nacional de Cancerologia Division de Educacion para la Salud Avenue San Fernando 22 Mexico City Tlalpan 14000

Peru

Investigator Number: 60 Luis Mas Lopez
Hospital Nacional Almanzor Aguinaga Asenjo Plaza de la Seguridad Chiclayo

Investigator Number: 61 Fernando Salas Sanchez
Hospital Nac Guillermo Almenara Irigoyen Avenida Grau N 800 la Victoria Lima 13

Poland

Investigator Number: 30 Anna Pluzanska
Klinika Chemioterapii, Regionalny Osrodek Onkologiczny Ul Paderewskiego 4 Lodz 94 509

Investigator Number: 31 Marek Pawlicki, MD
Center of Oncology Ul Garncarska 11 Krakow 31- 115

Investigator Number: 34 Beata Utracka- Hutka, MD
Centrum Onkologii, Klinika Chemioterapii Wybrzeza Armii Krajowej 15 Gliwice 44- 100

Russian Federation

Investigator Number: 750 Avgust M. Garin, MD
Blokhin Cancer Research Center Department of Clinical Pharmacology and Chemotherapy 22nd Floor Kashirskoye Sh 24 Moscow 115478

Investigator Number: 751 Mikhail R. Lichinitser, MD
Blokhin Cancer Research Center Department of Combined Therapy 18th Floor Kashirskoye Sh 24 Moscow 115478

Investigator Number: 752 Vera A. Gorbunova, MD
Blokhin Cancer Research Center Department of Chemotherapy 19th Floor
Kashirskoye Sh 24 Moscow 115478

Slovakia

Investigator Number: 14 Miriam Drahokoupilova Narodny
Onkologicky Ustav Klenova 1 Bratislava 833 10

South Africa

Investigator Number: 51 Anne Gudgeon, MBChB PO Box 18171 Wynberg
Hospital Wynberg 7824

Investigator Number: 53 Louis Goedhals, MBChB, MMed
National Hospital Department of Oncotherapy Private Bag X20598 Bloemfontein
9300

Investigator Number: 54 Johann Petrus Jordaan, MBChB,
MMed Addington Hospital Erskin Terrace, South Beach Durban 4001

Spain

Investigator Number: 601 Juan Miguel Gil Gil, MD
Hospital Duran I Reynals Avda Castelldefels, KM 2.7 Barcelona 08907

Investigator Number: 602 Antonio Cussac Llombart, MD
Instituto Valenciano de Oncologia Profesor Beltran Baguena 19 Valencia 46009

Investigator Number: 603 Pedro M. Aramburo, MD, PhD
Hospital Ruber Internacional La Maso 38 Madrid 28034

Taiwan, Province of China

Investigator Number: 701 Chih- Hsin Yang, MD
National Taiwan University Hospital 7 Chung- Shang South Road Taipei 10016

Investigator Number: 702 Cheng- Hsu Wang, MD
Chang Gung Memorial Hospital Linkou 5, Fu- Shing Street, Kuei- Shan Tao- Yuan
Kuei- Shan 333

Investigator Number: 703 Wing- Yiu Lui, MD
Taipei Veterans General Hospital 201 Section 2, Shih- Pai Road Taipei 112

Investigator Number: 705 Hong- Tai Chang, MD
Kaohsiung Veterans General Hospital 386 Ta- Chung 1st Road Kaohsiung 813

Investigator Number: 706 Hwei- Chung Wang, MD
China Medical College Hospital 2 Yuh- Der Street Taichung 404

Investigator Number: 707 Ming- Feng Hou, MD
Kaohsiung Medical University Chung- Ho Memorial Hospital 100 Shih Chuan First Road Kao- Hsiung ROC 807

United States

Investigator Number: 101 Joyce O'Shaughnessy, MD US Oncology Research, Inc. 5th Floor Collins 4144 North Central Expressway Dallas, Texas 75204

Investigator Number: 107 Robert Gordon, MD
Polyclinic Medical Center Pinnacle Health Regional Cancer Center 2601 North 3rd Street Harrisburg, Pennsylvania 17110

Investigator Number: 109 Katherine H. Tkaczuk, MD
University of Maryland School ofMedicine 22 South Greene Street Baltimore, Maryland 21201

Investigator Number: 113 John A. Ellerton, MD
Southern Nevada Cancer Research Foundation Suite D- 29 601 South Rancho Drive Las Vegas, Nevada 89106

Investigator Number: 115 Paul G. Montgomery, MD
Mountain State Tumor Institute 100 East Idaho Street Boise, Idaho 83712

Investigator Number: 128 Robert B. Cooper, MD
Clinical Research Center of Western Connecticut Attn Sue Coatsworth, RN, OCN CCRC Suite 303 16 Hospital Avenue Danbury, Connecticut 16810

Investigator Number: 130 John R. Eckardt, MD
St. John's Mercy Medical Center Arch Medical Group, LLC Division of Oncology/ Hematology 189- C 621 South New Ballas Road St. Louis, Missouri 63141

Investigator Number: 133 Mark F. Kozloff, MD
Monroe Medical Associates Suite 309 71 West 156th Street Harvey, Illinois 60429

Investigator Number: 144 Marcia Browne
New England Hematology Oncology 65 Walnut Street Wellesley, Maine 02481

Investigator Number 153: Peter D. Eisenberg, MD
Marin Oncology Associates Suite 200 1350 South Eliseo Drive Greenbrae, California 94904

Investigator Number: 155 Mark Graham
University of North Carolina 3009 Old Clinical Building Chapel Hill, North Carolina 27599

Investigator Number: 158 Michael Stipanov, MD
Memorial Hospital Suite 200 Suzanne Stephens 2525 DeSales Avenue Chattanooga, Tennessee 37404

Investigator Number: 160 L. Wayne Keiser, MD
Redwood Regional Oncology Center Suite 100 3555 Round Barn Circle Santa Rosa, California 95403

Investigator Number: 162 Timothy Webb Genesis Cancer Center Suite 303 One Mercy Lane Hot Springs, Arkansas 71913

Investigator Number: 170 John H. Ward
University of Utah School ofMedicine Department of Hematology/ Oncology Room 4C- 416 50 North Medical Drive Salt Lake City, Utah 84132

Investigator Number: 176 Dennie V. Jones
University of Texas Medical Branch at Galveston 301 University Boulevard Galveston, Texas 77555

Investigator Number: 179 Kendrith M. Rowland
Carle Cancer Center 602 West University Avenue Urbana, Illinois, 61801

Investigator Number: 181 Robert O. Kerr, MD
Southwest Regional Cancer Center Lab Suite B-1 711 West 38th Street Austin, Texas 78705

Investigator Number: 192 Naftali Bechar, MD
Indiana Community Cancer Center Inc 115 West 19th Street Indianapolis, Indiana 46202

Investigator Number: 193 Furhan Yunus, MD
The Boston Baskin Cancer Group Suite 800 1331 Union Avenue Memphis, Tennessee 38104

Investigator Number: 194 Michael Schuetz, MD
Milwaukee Medical Clinic Advanced Health Care 3003 West Good Hope Road Milwaukee, Wisconsin 53209

Investigator Number: 199 David A. Rinaldi, MD
Louisiana Oncology Associates Suite 200 501 West St. Mary Boulevard Lafayette, Louisiana 70506

Investigator Number: 200 James Liebmann, MD
New Mexico Oncology Hematology Consult 612 Encino Place NE Albuquerque, New Mexico 87109

Investigator Number: 203 Michael J. Nissenblatt, MD
Impath Physicians Network 11th Floor 400 Kelby Street Fort Lee, NJ 07024

Investigator Number: 207 Robyn Young, MD
Scott and White Memorial Hospital and Clinic Center for Cancer Prevention and Care 2401 South 31st Street Temple, Texas 76508

Investigator Number: 208 Graydon Harker, MD
Intermountain Hematology and Oncology Associates Suite 30 1250 East 3900 South Salt Lake City, Utah 84124

Investigator Number: 211 Piyapong Vongkovit, MD
Northwestern Carolina Oncology Hematology 225 18th Street, Southeast Hickory, North Carolina 28603

Investigator Number: 214 Charles Maurer, MD
Heme- Onc Associates of Fredericksburg, Inc 231 Park Hill Drive Fredericksburg, Virginia 22401

Investigator Number: 215 Ajit S. Desai, MD Albert Einstein Medical Center Cancer Center, 1st Floor 5501 Old York Road Philadelphia, Pennsylvania 19141

Investigator Number: 218 Brian F. Issell
Cancer Research Center of Hawaii 1236 Lauhala Street Honolulu, Hawaii 96813

Investigator Number: 222 Mark Woodson, MD
Midwest Hematology Oncology Consultants, Ltd. 11125 Dunn Road St. Louis, Missouri 63136

Investigator Number: 223 Ashis Chakrabarti
Hope Center 3702 South 4th Street Terre Haute, Indiana 47802

3. Efficacy summary

Study design of Protocol B9E- MC- JHQG is provided in **Figure 2.**

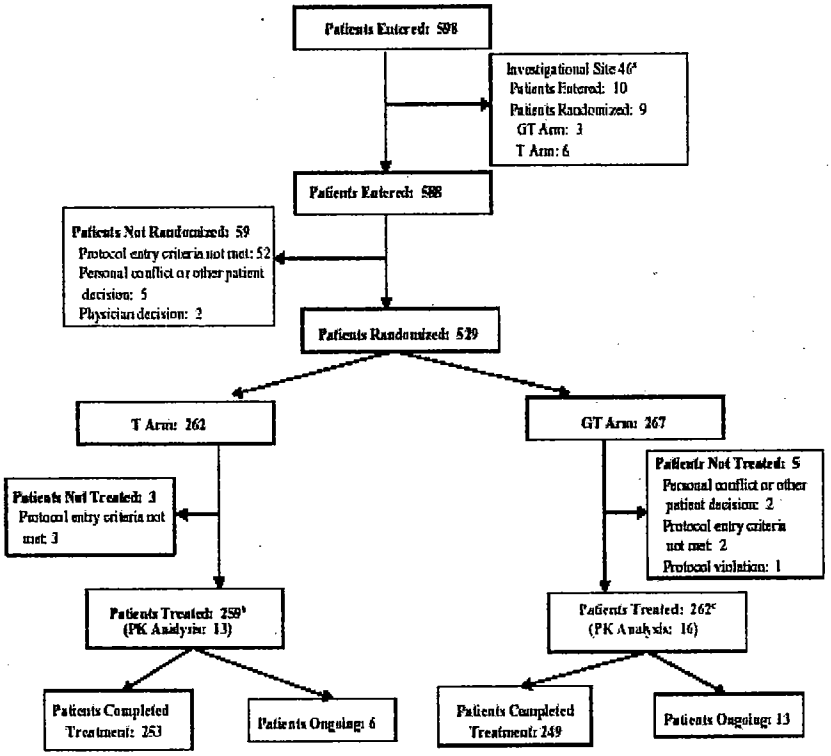
Figure 2: Study design for Protocol B9E- MC- JHQG.

PRE-THERAPY	Females ≥18 years old with unresectable, locally recurrent or metastatic breast cancer who have received adjuvant anthracycline-containing chemotherapy and have KPS ≥70 and adequate organ function and bone marrow reserve	
	Baseline CT scan of chest and abdomen; nuclear medicine bone scan	
	RANDOMIZE	
DURING THERAPY	Arm A: Paclitaxel 175 mg/m^2 (Day 1, q21 days) Gemcitabine 1250 mg/m^2 (Days 1 and 8, q21 days)	Arm B: Paclitaxel 175 mg/m^2 (Day 1, q21 days)
	Treatment continues until the disease progresses, intolerable toxicity develops, or other relevant reason for discontinuation of treatment occurs	
POST-THERAPY	30-day post-therapy follow-up visit to assess safety and confirm response	
	Bimonthly follow-up for patients without confirmed disease progression (by radiologic or physical exam) q2 months after 30-day follow-up until progression	
	Long-term follow-up for patients with confirmed disease progression (by radiologic or physical exam) in 4-month intervals after 30-day follow-up	

A total of 598 patients with unresectable, locally recurrent or metastatic breast cancer were entered into this study conducted at 98 investigational sites globally. The first patient was randomized on 11 August 1999, and the last patient was randomized on 02 April 2002.

Figure 3 presents the disposition of all patients who were entered into the study.

Figure 3: Patient Disposition



Abbreviations: GT = gemcitabine plus paclitaxel; PK = pharmacokinetic; T =paclitaxel.
a Patients were not included in the interim analyses of efficacy and safety presented in this clinical study report. These 10 patients were entered at Investigational Site 46, in Argentina. One of these patients (Patient 46-470) died of study disease prior to randomization; thus, 9 patients were randomized. Three of these patients were treated on the gemcitabine plus paclitaxel combination arm (GT Arm), and 6 patients were treated on the paclitaxel monotherapy arm (T Arm). However, during a routine monitoring visit regarding other Lilly clinical trials, it was discovered that the principal investigator had significant findings that led to questions about the integrity of the data for all patients at that investigational site. There were observations of noncompliance of investigator obligations, as set forth by local regulations, good clinical practice (GCP), and Lilly policies and procedures for participating investigators in clinical trials. Therefore, this investigational site was terminated in June 2002.
b Patient 602-6026 was randomized to the T Arm by the clinical trial study management system (CT-SMS), but received GT therapy. She was reported on the case report form (CRF) as randomized to the T Arm and is reported in the locked database on the T Arm.
c Patient 53-531 was randomized to the T Arm by the CT-SMS, but received GT therapy. She was reported on the CRF as randomized to the GT Arm and is reported in the locked database on the GT Arm.

Table 4 summarizes the reasons for study discontinuation for all entered and randomized patients.

Table 4: Study discontinuation reasons

Reason For Discontinuation	Taxol (N=262) n	(%)	Gem/Tax (N=267) n	(%)
Adverse event	12	(4.6)	18	(6.7)
Death	2	(0.8)	10	(3.8)
Satisfactory response, patient perception	3	(1.1)	9	(3.4)
Satisfactory response, physician perception	9	(3.4)	15	(5.6)
Satisfactory response, patient & physician perception	22	(8.4)	43	(16.1)
Unable to contact patient (lost to follow-up)	1	(0.4)	2	(0.7)
Personal conflict or other patient decision	23	(8.8)	22	(8.2)
Protocol entry criteria not met	5	(1.9)	3	(1.1)
Clinical relapse	16	(6.1)	8	(3.0)
Lack of efficacy, progressive disease	145	(55.3)	100	(37.5)
Lack of efficacy, stable disease	4	(1.5)	8	(3.0)
Physician decision	10	(3.8)	12	(4.5)
Protocol Violation	4	(1.5)	4	(1.5)
Patients continuing	6	(2.3)	13	(4.9)

Table 5 provides a summary of baseline patient demographic characteristics for all randomized patients. Overall, the two treatment arms were well balanced for all baseline demographics and disease characteristics.

Table 5: Demographics

Variable	ALL (N=529)	Taxol (N=262)	Gem/Tax (N=267)
Origin: No. (%)			
African Descent	13 (2.5)	5 (1.9)	8 (3.0)
Western Asian	78 (14.7)	39 (14.9)	39 (14.6)
Caucasian	316 (59.7)	159 (60.7)	157 (58.8)
East/Southeast A	25 (4.7)	12 (4.6)	13 (4.9)
Hispanic	90 (17.0)	43 (16.4)	47 (17.6)
Other	7 (1.3)	4 (1.5)	3 (1.1)
Age:			
Mean	52.81	52.77	52.85
Median	53.00	52.00	53.00
Range	26-83	26-75	26-83
Height cm.: (Visit 1)			
Mean	158.54	158.50	158.58
Median	159.00	160.00	159.00
Range.	124-185	124-185	135-182
Weight kg.: (Visit: 1)			
No. Patients	524	258	266
Mean	69.26	69.42	69.12
Median	68.00	68.00	67.54
Range.	36-159	36-159	37-122
Unspecified	5	4	1

Table 6 summarizes the baseline disease characteristics for all randomized patients, and **Table 7** summarizes tumor burden at baseline for all randomized patients. Overall, the two treatment arms were well balanced for all baseline disease characteristics and baseline tumor burden sites.

Table 6: Baseline disease characteristics

Variable	ALL (N=529)	Taxol (N=262)	Gem/Tax (N=267)
Diagnosis/Histology (Visit: 1)			
Breast	41 (7.8)	22 (8.4)	19 (7.1)
Ductal Breast	438 (82.8)	212 (80.9)	226 (84.6)
Lobular Breast	39 (7.4)	21 (8.0)	18 (6.7)
Tubular Br Ca	2 (0.4)	1 (0.4)	1 (0.4)
Medullary Br Ca	1 (0.2)	1 (0.4)	0
Mucinous Br Ca	6 (1.1)	3 (1.1)	3 (1.1)
Breast papillary	1 (0.2)	1 (0.4)	0
Adeno, pleura	1 (0.2)	1 (0.4)	0
Grade of Differentiation (Visit: 1)			
No. Patients	529	262	267
Well Differentiated	23 (4.3)	16 (6.1)	7 (2.6)
Moderately Differentiated	158 (29.9)	72 (27.5)	86 (32.2)
Poorly Differentiated	128 (24.2)	63 (24.0)	65 (24.3)
Undifferentiated	20 (3.8)	11 (4.2)	9 (3.4)
Unknown	200 (37.8)	100 (38.2)	100 (37.5)
Stage at Entry (Visit: 1)			
Metastatic	513 (97.0)	254 (96.9)	259 (97.0)
Unresectable, locally adv.	16 (3.0)	8 (3.1)	8 (3.0)
Estrogen Receptor (Visit: 1)			
Not Done	35 (6.6)	15 (5.7)	20 (7.5)
Positive	165 (31.2)	80 (30.5)	85 (31.8)
Negative	195 (36.9)	103 (39.3)	92 (34.5)
Intermediate	7 (1.3)	4 (1.5)	3 (1.1)
Unknown	127 (24.0)	60 (22.9)	67 (25.1)
Progesterone Receptor (Visit: 1)			
Not Done (N)	42 (7.9)	18 (6.9)	24 (9.0)
Positive	134 (25.3)	71 (27.1)	63 (23.6)
Negative	198 (37.4)	105 (40.1)	93 (34.8)
Intermediate (I)	6 (1.1)	0	6 (2.2)
Unknown (U)	149 (28.2)	68 (26.0)	81 (30.3)
Estrogen & Progesterone Receptors Combined (Visit: 1)			
++	102 (19.3)	50 (19.1)	52 (19.5)
+-	46 (8.7)	23 (8.8)	23 (8.6)
-+	30 (5.7)	19 (7.3)	11 (4.1)
--	148 (28.0)	81 (30.9)	67 (25.1)
NN	35 (6.6)	15 (5.7)	20 (7.5)
UU	127 (24.0)	60 (22.9)	67 (25.1)
+N or U	14 (2.7)	7 (2.7)	7 (2.6)
-N or U	14 (2.7)	3 (1.1)	11 (4.1)
I+	2 (0.4)	2 (0.8)	0
I-	4 (0.8)	1 (0.4)	3 (1.1)
IN	1 (0.2)	1 (0.4)	0
+I	3 (0.6)	0	3 (1.1)
-I	3 (0.6)	0	3 (1.1)

Menopausal Status (Visit: 1)			
Pre-Menopausal	74 (14.1)	33 (12.6)	41 (15.5)
Post-Menopausal	409 (77.8)	206 (78.9)	203 (76.6)
Peri-Menopausal	39 (7.4)	19 (7.3)	20 (7.5)
Unknown	4 (0.8)	3 (1.1)	1 (0.4)
Unspecified	3	1	2
Performance Status (Visit: 1)			
100	194 (36.7)	95 (36.3)	99 (37.1)
90	189 (35.7)	100 (38.2)	89 (33.3)
80	94 (17.8)	36 (13.7)	58 (21.7)
70	48 (9.1)	29 (11.1)	19 (7.1)
60	2 (0.4)	1 (0.4)	1 (0.4)
Unknown	2 (0.4)	1 (0.4)	1 (0.4)

Table 7: Baseline tumor burden

	Number of Patients (%)	
	T Arm (N=262)	GT Arm (N=267)
Number of tumor burden sites		
1	63 (24.0%)	65 (24.3%)
2	91 (34.7%)	86 (32.2%)
3	60 (22.9%)	59 (22.1%)
4	24 (9.2%)	37 (13.9%)
≥5	24 (9.2%)	20 (7.5%)
Tumor burden site[a]		
Visceral[b]	191 (72.9%)	196 (73.4%)
Lung[c]	134 (51.1%)	145 (54.3%)
Liver	102 (38.9%)	103 (38.6%)
Other[d]	17 (6.5%)	13 (4.9%)
Nonvisceral only	71 (27.1%)	71 (26.6%)
Tumor burden size[e]		
Mean	35.8 cm^2	36.0 cm^2
Standard deviation	63.2 cm^2	101.3 cm^2
Median	15.5 cm^2	12.9 cm^2
Range	1.0 – 447.5 cm^2	1.0 – 1353.0 cm^2

a Patients may be counted in more than one category.
b Includes patients with visceral +/- nonvisceral tumor burden sites.
c Includes pleural effusion, pleura, and pleural fluid.
d Other visceral sites considered: ascites, ovary, abdomen, spleen, adrenal, uterus, pericardial fluid, eye, bone marrow, peritoneum, omentum, diaphragm, trachea, suprarenal gland, and perirenal.
e Includes all measurable visceral and nonvisceral tumor areas as measured and followed by the investigator.

Study patients were also well balanced between treatment groups in stratification factors listed below **(Table 8).**

Table 8: Stratification Factors - Randomized Patients

Stratification Factors		T Arm (N=262)	GT Arm (N=267)
Karnofsky Performance Status	High (90)	195	188
	Low (80)	66	78
Prior anthracycline in adjuvant/neoadjuvant setting	No	15	11
	Yes	247	256
Prior hormonal therapy	No	132	129
	Yes	130	138
Presence of visceral metastases	No	71	71
	Yes	191	196
Disease progression with prior adjuvant chemotherapy[c]	≤ 6 months	51	51
	> 6 months	210	215

Table 9 presents a summary of the time from diagnosis of disease to randomization into this study.

Table 9: Time from Diagnosis to Randomization (Months)

	T Arm (N=262)	GT Arm (N=267)
Mean	43.4	41.4
Median	29.0	34.3
Range	3.7-270.7	2.3-228.2

Table 10 summarizes prior therapy received by study patients.

Table 10: Prior Therapy

Patients with Therapy Type	Taxol (N=262) n (%)	Gem/Tax (N=267) n (%)
Prior Surgery	260 (99.2)	265 (99.3)
Prior Radiotherapy	184 (70.2)	177 (66.3)
Prior Immunotherapy	2 (0.8)	1 (0.4)
Prior Hormonal Therapy	130 (49.6)	138 (51.7)
Prior Chemotherapy	260 (99.2)	267 (100)
Adjuvant Setting	230 (87.8)	228 (85.4)
One Line of Therapy	195 (74.4)	186 (69.7)
Two Lines of Therapy	31 (11.8)	41 (15.4)
Three or More Lines	4 (1.5)	1 (0.4)
Neoadjuvant Setting	61 (23.3)	78 (29.2)
One Line of Therapy	53 (20.2)	72 (27.0)
Two Lines of Therapy	8 (3.1)	4 (1.5)
Three or More Lines	0	2 (0.7)
Metastatic Setting	4 (1.5)	1 (0.4)
One Line of Therapy	4 (1.5)	1 (0.4)
Two Lines of Therapy	1 (0.4)	0

As stated in the inclusion and exclusion criteria defined in the protocol, patients were required to have received one anthracycline-based chemotherapy regimen in the adjuvant/neoadjuvant setting. A non-anthracycline-based regimen in the adjuvant/neoadjuvant setting was required if use of an anthracycline was clinically contraindicated. Twenty patients did not receive an anthracycline. Reason for a non-anthracycline based regimen are summarized in **Table 11**.

Table 11: Reason for a Non-Anthracycline Based Regimen

Reason for Non-Anthracycline Regimen	T Arm (N=11)	GT Arm (N=9)
Medically contraindicated, reason not specified	3	2
Medically contraindicated because of cardiac complications	6	6
Anthracyclines not widely available	1	0
Unknown reason	1	1

4. Reviewer Conclusions regarding patient comparability

Baseline demographics, disease characteristics, tumor burden, time from primary diagnosis, prior therapies, and randomization stratification factors were well balanced between treatment groups.

5. Efficacy Results

The primary objective of this study was to compare overall survival between patients treated with gemcitabine plus paclitaxel combination therapy (GT Arm) and those treated with paclitaxel monotherapy (T Arm). Secondary objectives included comparisons of time to documented disease progression (TtDPD), progression-free survival (PFS), response rates, duration of response, health outcomes (changes in disease-related symptoms and quality of life), toxicities, and pharmacokinetics. It was agreed that TtDPD might serve as an endpoint for accelerated approval.

Overall Survival - Second Interim Analysis

The updated survival analysis (April 12, 2004), performed when censoring was 28.7%, used a dataset locked on 26 February 2004, with a data cut-off date of 30 January 2004. Survival analyses were performed using both the randomized population (RT) and the ITT population. There is a single patient difference between the ITT analyses and the RT analysis. One patient randomized to the T Arm received GT combination therapy in error. Therefore, for survival analyses based on the ITT population, this patient was placed on the T Arm.

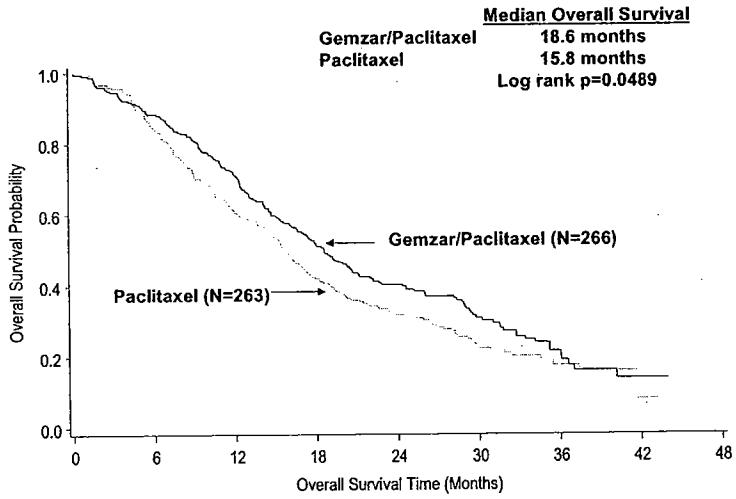
Distribution of overall survival was estimated using the Kaplan-Meier Method. **Table 12** provides summary statistics for overall survival using the 2/26/04 locked database.

Table 12: Summary Survival Statistics (Months)

	T Arm (N=262)	GT Arm (N=267)
Patients censored, n (%)	68 (26.0)	84 (31.5)
Median (95% CI)	15.8 (14.4, 17.4)	18.6 (16.6, 20.7)
12-Months survival probability (95% CI)	60.6 (54.6, 66.6)	71.1 (65.6, 76.7)

Figure 4 presents the Kaplan-Meier plot of survival for randomized patients.

Figure 4: Survival



Post-study chemotherapy

At the time of data cut-off, post-study data had been received from 415 patients. **Table 13** summarizes the number of patients receiving various numbers of lines of post-study chemotherapy. Reporting percentages are based on the entire randomized population.

Table 13: Post-Study Chemotherapy

	T Arm N=262	GT Arm N=267
Total number of patients receiving post-study chemotherapy	129	118
Patients with 1 line chemotherapy	63 (24.0%)	57 (21.3%)
Patients with 2 lines of chemotherapy	29 (11.1%)	22 (8.2%)
Patients with ≥3 lines of chemotherapy	37 (14.1%)	39 (14.6%)

Time to documented progression of disease (TtDPD)

Time to documented progression of disease (TtDPD) was defined as the time from the date of randomization to the first date of documented PD. Time to documented progression of disease was censored at the last visit date for patients who had not had documented PD. Progression dates of the sponsor and FDA reviewer were jointly reconciled so that there is complete agreement among the two parties as to the date of progression or censoring at the last complete follow-up.

Tables 14 and 15 provides summary statistics for TtDPD. The analysis was performed using reconciled dates of progression and censoring.

Table 14: Time to Documented Progressive Disease (Months)

	T Arm (N=263)	GT Arm (N=266)
Patients censored, n (%)	80 (30.4)	110 (41.4)
Median (95% CI)	2.9 (2.6, 3.7)	5.2 (4.2, 5.6)

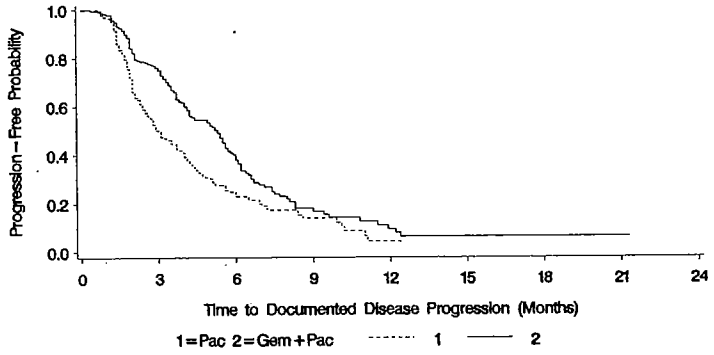
Abbreviations: TtDPD = time to documented progressive disease; T = paclitaxel monotherapy; GT = gemcitabine plus paclitaxel; N = number of randomized patients within each arm; CI = confidence interval.

Table 15: Comparisons – Time to Documented Progressive Disease

	Estimated Difference (95% CI)	p-Value
Log-Rank		<0.0001
Hazard ratio	0.648 (0.523, 0.803)	<0.0001
6-month difference %	14.5 (5.2, 23.7)	0.0021

The distribution of TtDPD was estimated using the Kaplan Meier method (**Figure 5**)

Figure 5: Time to Documented Progressive Disease



Response Rate

Table 16 summarizes the ITT analysis of tumor response rate, after reconciliation.

Table 16: Summary of Reconciled Best Tumor Response

Reconciled Response	T Arm (N=263)	GT Arm (N=266)
Total responders (CR+PR)	59 (22.1%) 95% CI [17.1%, 27.2%]	108 (40.8%) 95% CI [34.9%, 46.7%]

Abbreviations: T = paclitaxel monotherapy; GT = gemcitabine plus paclitaxel; N = number of randomized patients within each arm; CI = confidence interval; CR = complete response; PR = partial response.

Response rate was statistically significant in favor of the GT Arm versus the T Arm ($p<0.0001$).

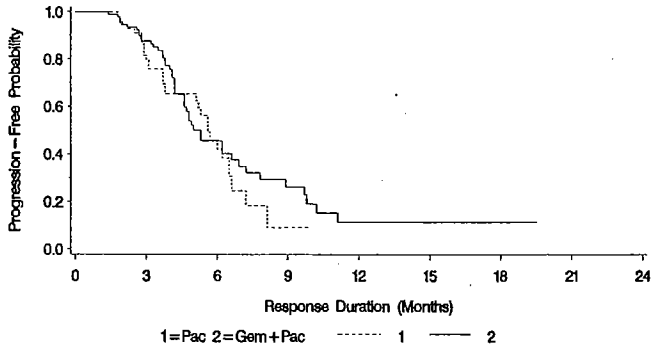
Response Duration

Table 17 presents summary statistics for duration of response defined as duration between date of response and date of disease progression. The distribution of duration of response was estimated using the Kaplan Meier Method (**Figure 6** below). The response duration was similar between two treatment arms.

Table 17: Duration of Response

	T Arm (N=59)	GT Arm (N=108)
Censoring, n (%)	28 (47.5)	59 (56.2)
50th percentile (median) (95% CI)	5.6 (5.1, 6.5)	5.0 (4.6, 6.9)

Figure 6: Duration of response (Kaplan Meier-ITT analysis)



Results of 4 phase 2 trials of gemzar plus paclitaxel are summarized in **Table 18**.

Table 18: Phase 2 gemzar+paclitaxel trials

Study	No. Patients	Time to progression	Response rate
S024 (Lilly)	40	7.2 months	40
Colomer R 2000	43	NR	68
Delfino C 2003	45	11 months	67
Sanchez-Rovira 1999	41	7.8 months	40

E. Efficacy Conclusions

Study JHQG (pivotal trial) demonstrated consistent superiority of treatment with gemzar plus paclitaxel over paclitaxel alone as evidenced by increased response rate (41% versus 22%, p<0.0001), prolonged time to documented tumor progression (median 5.2 months versus 2.9 months; log rank p <0.001) and overall survival (interim analysis with approximately 35% of patients censored; median survival 18.5 months versus 15.8 months; hazard ratio 0.78 [95% CI, 0.63 to 0.96], log rank p=0.0182). An updated survival analysis(analysis performed with 29% of patients censored) showed a median survival of 18.6 months versus 15.8 months; log rank p=0.0489. Activity of gemzar plus paclitaxel is supported by the results of 4 phase 2 trials. overall survival;

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

As expected, from Gemzar and paclitaxel monotherapy studies Grade 3 and 4 toxicities were primarily hematologic. There were more Grade 3 and 4 hematologic toxicities reported on the GT Arm compared with the T Arm. These included neutropenia (48.5% versus 10.8%), anemia (6.9% versus 2.3%), and thrombocytopenia (5.7% versus 0.0%). There were more red blood cell and/or whole blood transfusions (10.3% versus 3.9%) and febrile neutropenia (5.0% versus 1.2%) on the GT Arm compared with the T Arm; however, there was not an increased incidence of infections or hemorrhagic events. Grade 3 and 4 liver enzyme elevation occurred in 5.3% of the patients on the GT Arm and in 1.9% of the patients on the T Arm. Other Grade 3 and 4 laboratory toxicities were minimal.

Grade 3 and 4 non-laboratory toxicities were more common on the GT Arm compared with the T Arm. These included fatigue (6.5% versus 1.5%), dyspnea or hypoxia (1.9% versus 0.8%) and neuropathy (6.1% versus 3.5%). Some patients on the GT Arm reported the onset of neuropathy earlier compared with the T Arm. Five patients on the GT Arm and 2 patients on the T Arm discontinued the study because of Grade 3 or 4 neuropathies.

There was one death on each treatment arm due to drug-related toxicity.

Serious adverse events (SAEs) considered possibly related to study drug were reported in 10.7% of patients on the GT Arm and in 7.7% of patients on the T arm. Febrile neutropenia was the most common drug-related SAE on the GT arm (3.1%), and myalgia was the most common on the T Arm (1.9%). Serious adverse events caused study discontinuation in 5 (1.9%) patients on the GT arm and in 4 (1.5%) patients on the T Arm.

Overall, the adverse events, serious and nonserious, were manageable. No new safety concerns were observed during this study.

B. Description of Patient Exposure

Of the 267 patients randomized to the gemcitabine plus paclitaxel combination therapy (GT Arm), 262 patients received treatment. Of the 262 patients randomized to the paclitaxel monotherapy treatment arm (T Arm), 259 patients received treatment.

Overall, 516 patients completed at least one cycle of therapy, yielding a total of 2911 cycles completed during the course of the study. Of the 262 treated patients on the GT Arm, 260 completed at least one cycle of therapy, yielding a total of 1537 cycles completed. Two patients on the GT Arm did not complete one cycle: Patient 30-310 died from a pulmonary embolism following administration of GT combination therapy on Day 1 and Patient 503-5028 was discontinued from the

study after administration of GT combination therapy on Day 1 because of elevation of aspartate and alanine aminotransferase levels outside of protocol-defined ranges.

Of the 259 treated patients on the T Arm, 256 patients completed at least one cycle of therapy, yielding a total of 1374 cycles completed. Three patients on the T Arm did not complete one cycle: 2 patients discontinued the study because of drug hypersensitivity following small infusions of paclitaxel on Day 1 of Cycle 1, and 1 patient was determined to have been previously treated with fluorouracil, epirubicin, and cyclophosphamide (FEC) for metastatic breast cancer and was discontinued from the study because of a violation of protocol entry criteria.

Table 19 summarizes the number of cycles given for randomized patients treated on the GT Arm and T Arm, respectively

Table 19: Patient Exposure

Number of Given Cycles	GT n=267	T n= 262
	5 (1.9)	3 (1.1)
No Drug Given	2 (0.7)	3 (1.1)
0	11 (4.1)	19 (7.3)
1	22 (8.2)	25 (9.5)
2	26 (9.7)	43 (16.4)
3	19 (7.1)	18 (6.9)
4	38 (14.2)	28 (10.7)
5	59 (22.1)	51 (19.5)
6	23 (8.6)	20 (7.6)
7	23 (8.6)	21 (8.0)
8	13 (4.9)	5 (1.9)
9	6 (2.2)	7 (2.7)
10	7 (2.6)	6 (2.3)
11	5 (1.9)	7 (2.7)
12	2 (0.7)	3 (1.1)
13	2 (0.7)	1 (0.4)
14	1 (0.4)	2 (0.8)
16	1 (0.4)	
17	1 (0.4)	
18	1 (0.4)	
20	1 (0.4)	
	Mean 5.8 Median 6.0 Standard Dev. 3.2 Minimum 0.0 Maximum 20.0	Mean 5.2 Median 5.0 Standard Dev. 3.1 Minimum 0.0 Maximum 16.0

Table 20 presents the mean dose intensities per week of gemcitabine and paclitaxel for randomized patients on the GT Arm, and of paclitaxel for randomized patients on the T Arm. Overall, patients on the GT Arm received 85.0% of the planned mean dose of gemcitabine, with 97.0% of gemcitabine doses on Day 1 administered. A total of 96.2% of the planned mean dose of paclitaxel was administered to patients on the GT Arm. Patients on the T Arm received 99.7% of the planned mean dose of paclitaxel.

Table 20: Dose Intensities of Study Drugs

Study Drug	Number of Patients	Dose Intensity Planned Mean Dose per Patient ($mg/m^2/wk$)	Dose Intensity Actual Mean Dose per Patient ($mg/m^2/wk$)	Percent of Planned Mean Dose (actual/planned)
GT Arm				
Gemcitabine	262	833.3	708.4	85.0%
Paclitaxel	262	58.3	56.1	96.2%
T Arm				
Paclitaxel	259	58.3	58.1	99.7%

C. Methods and Specific Findings of Safety Review

Safety assessments consisted of monitoring and recording all adverse events (AEs) and SAEs (with their severity and relationship to study drug), the regular monitoring of hematology, and blood chemistry, regular measurement of vital signs, the performance of physical examinations and documentation of all concomitant medications and therapies.

Table 21 presents all Grade 3 and/or Grade 4 nonlaboratory CTC toxicities (by treatment arm) occurring in randomized patients who received treatment.

Table 21: Grade 3 and/or Grade 4 non-laboratory CTC toxicities

	T Arm (N=259)		GT Arm (N=262)	
Nonlaboratory CTC Toxicity	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Allergy/Immunology				
Allergic reaction/hypersensitivity	2 (0.8)	0	0	0
Vasculitis	0	0	0	1 (0.4)
Other allergy/immunology	0	0	1 (0.4)	0
CardiovascularArrhythmia				
Sinus tachycardia	1 (0.4)	0	0	0
Ventricular arrhythmia	0	0	1 (0.4)	0
Cardiovascular General				
Edema	0	0	1 (0.4)	0
Thrombosis/embolism	0	0	1 (0.4)	0
Constitutional Symptoms				
Fatigue	3 (1.2)	1 (0.4)	15 (5.7)	2 (0.8)
Fever	0	0	2 (0.8)	0
Sweating	0	0	1 (0.4)	0
Dermatology/Skin				
Alopecia[c]	48 (18.5)	9 (3.5)	36 (13.7)	10 (3.8)
Rash/desquamation	0	0	1 (0.4)	1 (0.4)
Wound-infectious	1 (0.4)	0	0	0
Gastrointestinal/Hepatobiliary				
Anorexia	2 (0.8)	0	0	0
Colitis	1 (0.4)	0	0	0
Constipation	0	0	2 (0.8)	0
Dehydration	2 (0.8)	0	1 (0.4)	0
Diarrhea	5 (1.9)	0	8 (3.1)	0
Nausea	4 (1.5)	0	3 (1.1)	0
Dysphagia, esophagitis, odynophagia	0	1 (0.4)	0	0
Stomatitis/pharyngitis	2 (0.8)	0	3 (1.1)	1 (0.4)
Vomiting	5 (1.9)	0	5 (1.9)	0
Other gastrointestinal	1 (0.4)	0	0	0
Other hepatic	2 (0.8)	0	0	0
Infection/Febrile neutropenia				
Febrile neutropenia	3 (1.2)	0	12 (4.6)	1 (0.4)
Infection with unknown ANC	0	0	1 (0.4)	0
Infection without neutropenia	1 (0.4)	0	0	0
Infection/febrile neutropenia-other	0	1 (0.4)	1 (0.4)	0
Musculoskeletal				
Muscle weakness	1 (0.4)	0	0	0
Other musculoskeletal	0	0	1 (0.4)	0
Neurology				
Insomnia	0	0	1 (0.4)	0
Mood alteration-anxiety agitation	0	0	1 (0.4)	0
Motor neuropathy	2 (0.8)	0	6 (2.3)	1 (0.4)
Sensory neuropathy	9 (3.5)	0	14 (5.3)	1 (0.4)
Syncope	1 (0.4)	0	1 (0.4)	0
Other neurology	0	0	2 (0.8)	0
Other ocular/visual	0	1 (0.4)	0	0

continued

	Number (%) of Patients			
	T Arm (N=259)		GT Arm (N=262)	
Nonlaboratory CTC Toxicity	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Pain				
Abdominal pain or cramping	1 (0.4)	0	2 (0.8)	0
Arthralgia	5 (1.9)	2 (0.8)	7 (2.7)	0
Bone pain	2 (0.8)	0	4 (1.5)	0
Chest pain	2 (0.8)	0	0	0
Headache	1 (0.4)	0	0	0
Myalgia	9 (3.5)	2 (0.8)	10 (3.8)	0
Neuropathic pain	1 (0.4)	0	1 (0.4)	0
Other pain	1 (0.4)	0	2 (0.8)	0
Pulmonary				
Dyspnea	0	0	4 (1.5)	1 (0.4)
Hypoxia	2 (0.8)	0	0	0
Renal/Genito-Urinary				
Vaginitis	0	0	1 (0.4)	0

Notable Grade 2 CTC non-laboratory toxicities are described below.

On the GT Arm, 9 patients reported Grade 2 dyspnea (on exertion), 2 patients reported Grade 2 cranial neuropathy, 16 patients reported Grade 2 motor neuropathy, and 50 patients reported Grade 2 sensory neuropathy.

On the T Arm, 1 patient had Grade 2 cardiovascular toxicity, described as orthostatic hypotension, 6 patients reported Grade 2 motor neuropathy, 46 patients reported Grade 2 sensory neuropathy, and 1 patient reported Grade 2 dyspnea.

Adverse Events

The incidence of adverse events on both treatment arms for this study was consistent with the adverse event profiles of gemcitabine and paclitaxel. **Table 22** presents a summary by treatment arm of all TEAEs occurring in at least 10.0% of randomized and treated patients.

Table 22: TEAEs occurring in at least 10.0% of treated patients.

	Number (%) of Patients	
TEAEs in Preferred Term	**T Arm (N=259)**	**GT Arm (N=262)**
Alopecia	234 (90.3%)	232 (88.5%)
Neuropathy NOS	156 (60.2%)	167 (63.7%)
Hemoglobin decreased	107 (41.3%)	166 (63.4%)
Neutrophil count decreased	79 (30.5%)	182 (69.5%)
Nausea	89 (34.4%)	129 (49.2%)
Myalgia	86 (33.2%)	86 (32.8%)
Arthralgia	64 (24.7%)	76 (29.0%)
Vomiting NOS	55 (21.2%)	83 (31.7%)
Fatigue	58 (22.4%)	7 5 (28.6%)
Diarrhea NOS	46 (17.8%)	63 (24.0%)
Pyrexia	34 (13.1%)	69 (26.3%)
Constipation	44 (17.0%)	56 (21.4%)
Dyspnea	34 (13.1%)	61 (23.3%)
Platelet count decreased	18 (6.9%)	67 (25.6%)
Anorexia	37 (14.3%)	50 (19.1%)
Cough	37 (14.3%)	46 (17.6%)
Bone pain	39 (15.1%)	36 (13.7%)
Headache NOS	33 (12.7%)	44 (16.8%)
Abdominal pain NOS	25 (9.7%)	33 (12.6%)
Alanine aminotransferase increased	15 (5.8%)	42 (16.0%)
Asthenia	24 (9.3%)	30 (11.5%)

Serious Adverse Events

Table 23 provides a complete summary of all SAEs. Seventy (26.7%) patients on the GT Arm and 43 (16.6%) patients on the T Arm reported at least one SAE, regardless of relationship to study drug. Pyrexia, the most common SAE on the GT Arm, was reported in 11 (4.2%) patients. Vomiting, the most common SAE on the T Arm, was reported in 6 (2.3%) patients.

Table 23: SAEs

Organ Categories Preferred Term	Number (%) of Patients[a] T Arm (N=259)	 GT Arm (N=262)
Cardiovascular Arrhythmia		
Tachycardia NOS	1 (0.4%)	0
Ventricular arrhythmia NOS	0	1 (0.4%)
Vascular		
Deep venous thrombosis NOS	1 (0.4%)	3 (1.1%)
Constitutional symptoms		
Pyrexia	2 (0.8%)	11 (4.2%)
Malaise	0	1 (0.4%)
Asthenia	1 (0.4%)	3 (1.1%)
Syncope	0	2 (0.8%)
Weakness	2 (0.8%)	1 (0.4%)
Dermatology/Skin		
Cellulitis	2 (0.8%)	3 (1.1%)
Exfoliative dermatitis	0	1 (0.4%)
Gastrointestinal		
Constipation	0	2 (0.8%)
Dehydration	5 (1.9%)	2 (0.8%)
Diarrhea	1 (0.4%)	1 (0.4%)
Enterocolitis	1 (0.4%)	0
Gastroenteritis	0	1 (0.4%)
Loose stools	1 (0.4%)	0
Esophagitis	1 (0.4%)	0
Oral candidias	2 (0.8%)	0
Mucosal inflammation	1 (0.4%)	0
Nausea	4 (1.5%)	4 (1.5%)
Stomatitis	0	1 (0.4%)
Vomiting NOS	6 (2.3%)	7 (2.7%)
Ascites	1 (0.4%)	1 (0.4%)
Hematologic		
Neutropenia	4 (1.5%)	6 (2.3%)
Anemia	4 (1.5%)	5 (1.9%)
Thrombocytopenia	1 (0.4%)	2 (0.8%)
Leukopenia NOS	0	1 (0.4%)
Hepatic		
AST increased	1 (0.4%)	1 (0.4%)
ALT increased	1 (0.4%)	1 (0.4%)
ALP increased, NOS	1 (0.4%)	0
Bilirubin increased	1 (0.4%)	0
Hepatic necrosis	1 (0.4%)	0
Hepatitis B	0	1 (0.4%)

continued

Organ Categories Preferred Term	Number (%) of Patients T Arm (N=259)	 GT Arm (N=262)
Infection/Febrile Neutropenia		
Febrile neutropenia	2 (0.8%)	8 (3.1%)
Panophthalmitis	1 (0.4%)	0
Sepsis	2 (0.8%)	0
C-reactive protein increase	0	1 (0.4%)
Metabolic		
Hyperglycemia	2 (0.8%)	1 (0.4%)
Hypokalemia	1 (0.4%)	0
Pain		
Abdominal pain	2 (0.8%)	1 (0.4%)
Arthralgia	2 (0.8%)	1 (0.4%)
Back pain	0	2 (0.8%)
Bone pain	0	3 (1.1%)
Chest pain	1 (0.4%)	1 (0.4%)
Myalgia	5 (1.9%)	0
Pulmonary		
Dyspnea NOS	4 (1.5%)	8 (3.1%)
Pneumonia	1 (0.4%)	3 (1.1%)
Hypoxia	1 (0.4%)	0
Renal		
Renal impairment NOS	1 (0.4%)	0

Laboratory Toxicities

Table 24 presents all Grade 3 and/or Grade 4 laboratory CTC toxicities occurring in randomized patients who received treatment. As expected with chemotherapy treatment, Grade 3 and 4 laboratory toxicities were primarily hematologic, including neutropenia, anemia, and thrombocytopenia. There was a statistically significant increase in the incidences of these Grade 3 and 4 hematologic toxicities on the GT Arm compared with the T Arm ($p<0.05$ for all).

Table 24: Laboratory Grade 3/4 Toxicities

	Number (%) of Patients			
	T Arm (N=259)		GT Arm (N=262)	
Laboratory CTC Toxicity	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematologic				
Hemoglobin	5 (1.9)	1 (0.4)	15 (5.7)	3 (1.1)
Leukocytes	4 (1.5)	0	25 (9.5)	3 (1.1)
Lymphopenia	2 (0.8)	0	3 (1.1)	0
Neutrophils/granulocytes	11 (4.2)	17 (6.6)	82 (31.3)	45 (17.2)
Platelets	0	0	14 (5.3)	1 (0.4)
Hepatobiliary				
Alkaline phosphatase	2 (0.8)	0	0	0
Bilirubin	2 (0.8)	0	0	0
GGT	1 (0.4)	1 (0.4)	1 (0.4)	0
SGOT (AST)	2 (0.8)	0	5 (1.9)	0
SGPT (ALT)	1 (0.4)	0	13 (5.0)	0
Metabolic				
Hypercalcemia	1 (0.4)	0	0	0
Hypercholesterolemia	1 (0.4)	0	0	0
Hyperglycemia	3 (1.2)	0	1 (0.4)	0
Hypokalemia	1 (0.4)	0	0	0
Hypomagnesemia	1 (0.4)	0	0	0

One patient on the GT Arm reported Grade 3 hyperglycemia. On the T Arm, Grade 3 hyperglycemia occurred in 3 patients, and Grade 3 hypercalcemia, hypokalemia, and hypomagnesia each occurred in 1 patient. The maximum renal-related laboratory toxicities on the GT Arm were three Grade 1 creatinine elevations. The maximum renal related laboratory toxicities on the T Arm were two Grade 2 creatinine elevations.

Transfusions

Table 25 provides a summary of randomized patients who received whole blood and/or packed red blood cell (RBC) transfusions while on study. A total of 37 patients received at least one transfusion: 10.3% (27/262) of patients on the GT Arm and 3.9% (10/259) of patients on the T Arm.

One patient on each treatment arm received a platelet transfusion. Patient 650-6505, on the GT Arm, received both an RBC and a platelet transfusion. Patient 54-547, on the T Arm, received several platelet transfusions and RBC transfusions, and was hospitalized with thrombocytopenia with bleeding due to a possibly disseminated blood marrow infiltration.

Table 25: Blood Transfusions

Type of Transfusion*	Taxol (N=262) N (%)	Gem/Tax (N=267) N (%)
Platelet Transfusions	1 (0.4)	1 (0.4)
Red Blood Cell Transfusions	9 (3.4)	22 (8.2)
Whole Blood Cell Transfusions	1 (0.4)	5 (1.9)

* Patients could have received more than one type of transfusion

Erythropoetin was used on both treatment arms: 21 (8.0%) patients on the GT Arm and 9 (3.5%) patients on the T Arm received epoetin alfa, erythropoietin, or erythropoietin human. The use of granulocyte colony-stimulating factor (G-CSF or granulocyte/ macrophage colony-stimulating factor [GM-CSF]) was more frequent on the GT Arm than on the T Arm: 20 (7.6%) patients on the GT Arm, compared with 3 (1.2%) patients on the T Arm, received filgrastim and/or sargramostim. Fifteen patients on the GT Arm and 2 patients on the T Arm received filgrastim or sargramostim as treatment; 5 patients on the GT Arm and 1 patient on the T Arm received filgrastim or sargramostim as prophylaxis.

Deaths

There were 12 deaths on study: ten (3.8%) on the GT Arm, 8 disease related, and two (0.8%) on the T Arm, 2 disease related. The other two deaths on the GT arm were due to asthenia (1) and traffic accident (1)

There were eight additional deaths during the 30-day follow-up period, after administration of the last dose of study drug: two (0.8%) on the GT Arm and six (2.3%) on the T Arm. All patients, except for 1 patient on the T Arm, died of progression of study disease. Patient 401-4002 on the T Arm died of septicemia, with ophthalmitis and a possible brain abscess.

D. Adequacy of Safety Testing

Safety testing was adequate. There is considerable experience with both drugs used in this study. There were no new safety concerns.

F. Summary of Critical Safety Findings and Limitations of Data

See section VII A.

VIII. Dosing, Regimen, and Administration Issues

Gemzar has been widely used for several years for treatment of a wide variety of malignancies. It is most often administered intravenously, as a 30-minute infusion, on days 1 and 8 of a 21-day treatment cycle. Doses ranged from 800 to

1250 mg/m^2. Myelosuppression is the principal dose-limiting toxicity. Dosage adjustments for hematologic toxicity are frequently needed.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The study was conducted in female patients. It is known, however, that Gemzar clearance is affected by gender with more rapid Gemzar clearance in males. There is no evidence, however, that unusual dose adjustments are necessary in women. In general, in single-agent studies of gemcitabine, adverse reaction rates were similar in men and women, but women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

1. Age

Gemzar clearance is affected by age. There is no evidence, however, that unusual dose adjustments are necessary in patients over 65, and in general, adverse reaction rates in the single-agent safety database of 979 patients were similar in patients above and below 65. Grade 3/4 thrombocytopenia was more common in the elderly.

2. Race/Ethnicity

There was no significant effect of race/ethnicity on either efficacy or safety results.

C. Evaluation of Pediatric Program

Gemzar has not been studied in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

D. Comments on Data Available or Needed in Other Populations

1. Renal or Hepatic Impairment

Gemzar should be used with caution in patients with preexisting renal impairment or hepatic insufficiency. Gemzar has not been studied in patients with significant renal or hepatic impairment.

2. Pregnancy

Pregnancy Category D. Gemzar can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays.

X. Conclusions and Recommendations

A. Conclusions

Sufficient data were submitted to allow for independent evaluation of study results. Study JHQG (pivotal trial) demonstrated consistent superiority of treatment with gemzar plus paclitaxel over paclitaxel alone as evidenced by increased response rate (41% versus 22%, p<0.0001), prolonged time to documented tumor progression (median 5.2 months versus 2.9 months; log rank p <0.001) and overall survival (interim analysis with approximately 35% of patients censored; median survival 18.5 months versus 15.8 months; hazard ratio 0.78 [95% CI, 0.63 to 0.96], log rank p=0.0182). An updated survival analysis was submitted in April 2004. In that analysis, performed with 29% of patients censored, median survival was 18.6 months (GT) versus 15.8 months (T); log rank p=0.0489.

As expected, from Gemzar and paclitaxel monotherapy studies Grade 3 and 4 toxicities were primarily hematologic. There were more Grade 3 and 4 hematologic toxicities (neutropenia, anemia and thrombocytopenia) reported on the GT Arm compared with the T Arm. There were more red blood cell and/or whole blood transfusions and febrile neutropenia on the GT Arm compared with the T Arm. Grade 3 and 4 liver enzyme elevation occurred in 5.3% of the patients on the GT Arm and in 1.9% of the patients on the T Arm.

Grade 3 and 4 non-laboratory toxicities were more common on the GT Arm compared with the T Arm. These included fatigue, dyspnea or hypoxia and neuropathy. Five patients on the GT Arm and 2 patients on the T Arm discontinued the study because of Grade 3 or 4 neuropathies.

Serious adverse events (SAEs) considered possibly related to study drug were reported in 10.7% of patients on the GT Arm and in 7.7% of patients on the T arm. Febrile neutropenia was the most common drug-related SAE on the GT arm (3.1%), and myalgia was the most common on the T Arm (1.9%). Serious adverse events caused study discontinuation in 5 (1.9%) patients on the GT arm and in 4 (1.5%) patients on the T Arm.

Overall, the adverse events, serious and nonserious, were manageable. No new safety concerns were observed during this study.

B. Recommendations

Regular Approval

Binding phase 4 commitments

The sponsor will be required to continue follow-up of patients enrolled in trial JHQG to obtain mature survival data.

XI. Appendix: Protocol B9E- MC- JHQG

Title: Phase 3 Study of Gemcitabine Plus Paclitaxel Versus Paclitaxel in Patients with Unresectable, Locally Recurrent or Metastatic Breast Cancer

Protocol Approved by Lilly: 14 June 1999 Amendment (a) Approved by Lilly: 7 September 1999 Amendment (b) Approved by Lilly: 14 February 2001 Amendment (c) Approved by Lilly: 16 October 2001

1. Introduction

Breast Cancer

Worldwide, breast cancer is the third most frequent cancer (796,000 cases in 1990) and is by far the most common malignancy of women (21% of all new cases). Breast cancer ranks as the fifth most common cause of death from cancer overall, and it is still the leading cause of cancer mortality in women (314,000 annual deaths represent 14.1% of cancer deaths in females; Parkin et al. 1999).

Incidence rates are high in all the developed areas of the world, with the highest age standardized incidence in the United States (87.1 cases per 100,000; Parkin et al. 1999). In the United States, the estimated number of new cases of breast cancer for 1998 is 180,300 (178,700 for women and 1600 for men), and the estimated number of deaths is 43,900 for both sexes. Breast cancer is second only to lung cancer as the most common cause of death from cancer in women in the United States (American Cancer Society 1998).

A meta- analysis of over 75,000 patients has shown that in selected subgroups of patients, chemotherapy given in the adjuvant setting can yield meaningful improvements in both time to progression of disease and overall survival (Early Breast Trialists Collaborative Group 1992). Unfortunately, a large proportion of patients develop metastatic disease and require chemotherapy to palliate symptoms and improve quality of life (Harris et al. 1997). The anthracyclines are among the most active agents used in the treatment of advanced breast cancer, and

doxorubicin and epirubicin can achieve response rates of around 20% to 40% (when used as single agents) and up to 60% (as part of combination regimens in the first- line setting) (Mouridsen 1992). The potential for cardiac toxicity from anthracycline treatment has led to the development of related compounds such as the anthracenedione mitoxantrone, which has been shown to be a useful alternative in the treatment of advanced breast cancer (Chabner and Myers 1993).

More recently, taxanes have shown promise in the treatment of metastatic breast cancer. Women treated with paclitaxel monotherapy have achieved overall response rates of 30% to 57% in Phase 2 and 3 studies (Nabholtz et al. 1996; Seidman et al. 1995; Holmes et al. 1991; Reichman et al. 1993), whereas docetaxel monotherapy has found overall response rates in 50% to 72% in first-line therapy (Marty et al. 1997). In addition, combinations of paclitaxel and doxorubicin have been reported to yield complete response rates of 41% and objective response rates in the region of 90%, albeit in the first- line setting and confounded by the incidence of cardiac toxicities (Gianni et al. 1995). A pivotal Phase 3 study conducted by the Eastern Cooperative Oncology Group (Sledge et al. 1997) compared doxorubicin, paclitaxel and the combination of doxorubicin and paclitaxel as first- line therapy for patients with recurrent or metastatic breast cancer. Single agent doxorubicin and paclitaxel demonstrated equivalent therapeutic activity (overall response rates 34% and 33%, respectively). The combination arm resulted in improved response rates (46%). Despite this, combination therapy did not differ from single agent therapy with regard to median survival. The promising overall responses seen in patients treated with taxanes has led to the pursuit of other combinations of taxanes with novel agents for the treatment of metastatic breast cancer.

1.2. Gemcitabine

Pre-clinical Information Gemcitabine (difluorodeoxycytidine), an analog of cytosine arabinoside (ara- C), is a pyrimidine antimetabolite (Hertel et al. 1988). The mechanism of action of gemcitabine has been well characterized. Gemcitabine is deaminated by deoxycytidine deaminase to difluorodeoxyuridine or activated by deoxycytidine kinase to difluorodeoxycytidine monophosphate (dFdCMP). Difluorodeoxyuridine is inactive, while dFdCMP is further metabolized to difluorodeoxycytidine diphosphate (dFdCDP) and difluorodeoxycytidine triphosphate (dFdCTP), which, when incorporated into DNA, results in chain termination. In comparison to ara- C incorporation into DNA, dFdCTP is less readily excised from DNA by DNA exonuclease. Thus, dFdCTP accumulates intracellularly to a greater degree than ara- C. This may account, in part, for its different spectrum of preclinical and clinical activity. In addition, gemcitabine inhibits ribonucleotide reductase, an enzyme that produces deoxynucleotides that are required for DNA synthesis. Gemcitabine is active in a variety of murine solid tumors and leukemias, as well as several human tumor xenografts (Hertel et al. 1990).

Overview

Gemcitabine has now undergone considerable testing for various malignancies and has exhibited activity in non- small cell lung cancer (NSCLC), pancreatic cancer, bladder cancer, advanced breast carcinoma, and cisplatin- refractory ovarian carcinoma (Lilly 1998; Lund et al. 1993; Guchelaar et al. 1996; Hansen 1996; Hui and Reitz, 1997). Data from several Phase 2 studies suggest that gemcitabine is active as a single agent or in combination with paclitaxel in the treatment of solid tumors.

Initial Phase 1 and Phase 2 Data

Initial Phase 1 studies using a short infusion schedule, in which gemcitabine was given weekly for 3 weeks followed by 1 week of rest, established 790 mg/m2/ week as the maximum tolerated dose (MTD). Dose- limiting toxicity (DLT) was myelosuppression, with thrombocytopenia being more significant than granulocytopenia (Abbruzzese et al. 1991). More recent Phase 1 and 2 trials have established 1250 mg/ m2/ week as a well tolerated dose (Fosella et al. 1993; Abbruzzese et al. 1993; Casper et al. 1991). Principal toxicities reported were hematologic, including World Health Organization (WHO) Grade 4 neutropenia and thrombocytopenia occurring rarely; reversible elevation in hepatic transaminases; proteinuria; mild skin rash with and without pruritus; and nausea and vomiting. A recent review of 201 patients treated with 1250 mg/ m2/ week who had not received prior chemotherapy revealed the following toxicity profile (WHO Grades 3 and 4): neutropenia, reversible elevation in hepatic transaminases, proteinuria, nausea and vomiting, mild skin rash and pruritus (Tonato 1993).

Data from Phase 2 studies of gemcitabine in the treatment of breast and bladder cancer indicate that dose reductions and omissions are more common on Day 15 compared to Days 1 and 8 of a 28- day cycle (Lilly 1998). Therefore, a 21- day cycle will be used in the current study, with dose administration on Days 1 and 8 followed by a week of rest.

Phase 2 Data in Breast Cancer

In a Phase 2 study of patients with locally advanced or metastatic breast cancer, gemcitabine was administered at 800 mg/ m2/ week for 3 out of 4 weeks. Among the 40 patients determined to be evaluable, 14 were chemotherapy naïve, 7 received adjuvant therapy, and 19 received one prior chemotherapy regimen for metastatic disease. Twenty- nine patients had received prior cytotoxic therapy, and 29 patients had received prior hormonal therapy. The overall objective response rate was 25%, comprising 3 complete responses (CRs) and 7 partial responses (PRs) of at least 4 weeks duration (95% confidence interval between 12.7% and 41.2%). All responses were independently validated by an external oncology review board. Responses were observed early in treatment, with a median time to response of 1.9 months. The median survival for the 40 evaluable patients was 11.5 months. Responses were seen in soft tissue (breast and lymph glands) as well as liver metastases. The mean number of completed cycles was

2.7. Overall, the regimen was well tolerated. Four patients were withdrawn during chemotherapy because of pulmonary toxicity, prolonged myelosuppression, or fatigue. Only 3patients suffered WHO Grade 3 or 4 hematological toxicity. Although transient elevation of liver transaminases occurred, only 3% of all treatment courses were associated with WHO Grade 3 or 4 toxicity, which did not affect treatment. Nausea and vomiting was mild (Carmichael et al. 1995a; Carmichael et al. 1995b).

In a second Phase 2 study, patients with metastatic breast cancer were treated weekly with gemcitabine at 1200 mg/ m2/ week for 3 out of 4 weeks. Thirty- nine patients were enrolled, with 35 evaluable for response. Over the course of therapy, patients received a mean number of 5.4 completed cycles. Among evaluable patients, 1 CR and 10 PRs were observed, yielding an overall response rate of 31.4% (95% confidence interval between 16.9% and 49.3%). The time- to-event data among evaluable patients included an estimated median survival of 21.1 months, a median duration of response of 11.3 months, and a median time to progression of disease of 5.1 months. The most commonly reported toxicities included neutropenia (10 patients with Grade 3), thrombocytopenia (2 patients with Grade 3), nausea/ vomiting (4 patients with Grade 3) and dyspnea (1 patient with Grade 4). One patient had Grade 4 infection (Lilly 1998).

In another Phase 2 study performed in France, gemcitabine monotherapy was studied in 47 patients with metastatic breast cancer. Patients were eligible for treatment if they had previously received and responded to at least one prior chemotherapy regimen with an anthracycline or anthracenedione for metastatic disease, and had relapsed at least 6 months after the first response. Of 47 patients entered, 41 were considered evaluable. In addition, 11 patients (23.4%) received prior adjuvant chemotherapy. All 47 patients received prior chemotherapy for metastatic disease; 10 patients (21.3%) had also been treated with a second- line chemotherapy for metastatic disease. Gemcitabine, at a dosage of 1200 mg/ m2, was administered as a 30- minute intravenous infusion once a week for 3 weeks followed by 1 week of rest; this cycle was repeated every 4 weeks. Over the course of therapy, the mean number of completed cycles administered was 3.8 and the median dosage of gemcitabine delivered was 1006 mg/ m2. There were 4 CRs and 8 PRs, for an overall response rate of 29.3% (95% confidence interval between 16.1% and 45.5%) in this heavily chemotherapy pretreated population. Among evaluable patients, the median response duration was 8.1 months and median time to progression of disease was 4.2 months. The median survival duration for the 41 evaluable patients was 19.4 months. The treatment was well tolerated. Grade 3 and 4 neutropenia was seen in 13 patients and 1 patient, respectively. Other toxicities included thrombocytopenia (3 patients with Grade 3), nausea/ vomiting (4 patients with Grade 3), and allergic reaction, cutaneous reaction, and fever (each in 1 patient with Grade 3) (Lilly 1998).

1.3. Paclitaxel

Pre- Clinical Information

Paclitaxel is a mitotic spindle poison that promotes microtubular aggregation and interferes with essential cellular functions such as mitosis, cell transport, and cell motility (Rothenberg 1993; Rowinsky et al. 1990). Unlike most other antineoplastic agents, paclitaxel has little effect on DNA, RNA, or protein synthesis (Schiff et al. 1979). Its unique mechanism of action has translated into a broad spectrum of antitumor activity in vitro and in vivo against some drug-resistant tumor types, including the MX- 1 mammary tumor, P388 leukemia, LNCaP prostate cancer, Lewis lung tumor, Walker 256 carcinosarcoma, sarcoma 180, and B16 melanoma.

Phase 1 Data

The vast majority of clinical experience with paclitaxel has been obtained using a once every 3 weeks dosing schedule (Rowinsky et al. 1990). The recommended dose of paclitaxel for the treatment of solid tumors was 135 to 250 mg/ m2 by 24-hour infusion every 3 weeks. In an attempt to determine the safety of a shorter infusion of paclitaxel, a randomized study was conducted in Europe and Canada to assess the infusion time of paclitaxel in refractory ovarian cancer patients. Patients (total 407) were treated with either 135 or 175 mg/ m2 of paclitaxel as a 3- or 24- hour infusion (Eisenhauer et al. 1994). All patients received pre-medication to avoid hypersensitivity reactions. Response rates were not greatly affected by dose or infusion length. The overall response rates were between 16 to 20%. However, a difference was seen in the toxicity profile, with an increase in sensory neuropathy, neutropenia, and myalgia in the higher dose group. In addition to dosage, the duration of infusion was important, as the 3- hour infusion was associated with significantly less neutropenia and fewer episodes of febrile neutropenia than a 24- hour infusion. The patients receiving the shorter infusion time rarely suffered dose reductions or delay. Hypersensitivity symptoms were not affected by either dose or infusion time. In conclusion, a 3- hour infusion of paclitaxel, 135 to 175 mg/ m2 can be safely administered by outpatient treatment using a once every 3 weeks dosing schedule, following adequate premedication (Eisenhauer et al. 1994).

Phase 2 and Phase 3 Data

Data from 83 patients accrued in three Phase 2 open- label studies and from 471 patients enrolled in a Phase 3 randomized study support the use of paclitaxel in patients with metastatic breast cancer. Two Phase 2 studies were conducted in 53 patients previously treated with a maximum of one prior chemotherapeutic regimen. Paclitaxel was administered in these two trials as a 24- hour infusion at initial doses of 250 mg/ m2 (with G- CSF or support) or 200 mg/ m2. The response rates were 56% (95% confidence interval between 35% to 76%) and 62% (95% confidence interval between 41% to 80%), respectively (Holmes et al. 1991; Reichman et al. 1993). The third Phase 2 trial was conducted in extensively pretreated patients who had failed anthracycline therapy and who had received a minimum of two chemotherapy regimens for the treatment of mestastatic disease.

These patients were administered paclitaxel at a dosage of 200 mg/ m2 as a 24-hour infusion with G- CSF support. Nine of 30 patients achieved a PR, for a response rate of 30% (95% confidence interval between 15% to 50%; Seidman et al. 1995).

The Phase 3 multicenter trial was conducted in patients previously treated with one or two regimens of chemotherapy. Patients were randomized to receive paclitaxel at a dose of either 175 mg/ m2 or 135 mg/ m2 given as a three- hour infusion. In the 471 patients enrolled, 60% had symptomatic disease with impaired performance status at study entry, and 73% had visceral metastases. These patients had failed prior chemotherapy either in the adjuvant setting (30%), the metastatic setting (39%), or both (31%). Sixty- seven per cent of the patients had been previously exposed to anthracyclines and 23% of the patients had disease considered resistant to this class of agents. The overall response rate for the 454 evaluable patients was 26% (95% confidence interval between 22% to 30%), with 17 CRs and 99 PRs. The median duration of response, measured from the first day of treatment, was 8.1 months (range: 3.4 to18.1+ months). Overall for the 471 patients, the median time to progression was 3.5 months (range: 0.03 to 17.1 months). Median survival was 11.7 months (range: 0 to 18.9 months). For the 458 patients who received single- agent paclitaxel in the Phase 3 second- line carcinoma study, myelosuppression and peripheral neuropathy were the most common adverse events; these two adverse events were dose related. One severe hypersensitivity reaction was observed at the dose of 135 mg/ m2 (Nabholtz et al. 1996).

Paclitaxel has been widely investigated in metastatic breast cancer. Sledge (1997) reported that single- agent paclitaxel was as efficacious as single- agent doxorubicin, with no significant survival difference compared to the combination of doxorubicin plus paclitaxel in subjects with metastatic breast cancer.

1.4. Combination Therapy Data

Preliminary results from a Phase 1 study have established an appropriate regimen for the combination of gemcitabine and paclitaxel. The study examined gemcitabine at dosages of 1000 to 1250 mg/ m2, in combination with paclitaxel at dosages of 135, 150, or 175 mg/ m2. Gemcitabine was administered on Days 1 and 8, and paclitaxel was administered on Day 1 of a 21- day cycle. This study included 39 patients qualified per protocol with recurrent or progressive ovarian cancer. Eighteen patients were treated with 1000 mg/ m2 of gemcitabine; of these 18 patients, 6 each received paclitaxel at dose levels of 135, 150, and 175 mg/ m2, respectively. Twenty- one patients were treated with 1250 mg/ m2 of gemcitabine; of these 21 patients, paclitaxel was administered at dose levels of 150 and 175 mg/ m2 in 12 and 9 patients, respectively. The combination of gemcitabine and paclitaxel was well tolerated at all dose levels; dose escalation was stopped at gemcitabine 1250 mg/ m2 and paclitaxel 175 mg/ m2. Maximum tolerated dose (MTD) was not reached. The combination of gemcitabine and paclitaxel was effective, with an overall response rate of 38.5%. Two patients

experienced CR, and 13 patients achieved PR. Three discontinuations were noted during the study. Two of these discontinuations (uremia and elevated liver function tests, respectively) occurred at the dose combination of gemcitabine 1000 mg/ m2 plus paclitaxel 175 mg/ m2; the third discontinuation (peripheral vascular disorder) occurred at the dose level of gemcitabine 1250 mg/ m2 plus paclitaxel 175 mg/ m2. The most frequent toxicities seen in this trial were hematologic. Overall, 38.5% and 33.3% of patients had WHO Grade 4 and Grade 3 neutropenia, respectively. In addition, 2.6% and 12.8% of patients had Grade 4 and Grade 3 thrombocytopenia, respectively. Only 2.6% of patients experienced Grade 3 anemia, and no patients experienced Grade 4 anemia. Toxicities noted were primarily laboratory abnormalities. No patients experienced either Grade 3 or Grade 4 fever. A Grade 3 infection was seen in 7.7% of patients; no patients had a Grade 4 infection. There were no Grade 4 pulmonary toxicities; 2.6% of patients experienced a Grade 3 toxicity (Lilly 1998).

Gemcitabine and paclitaxel combinations have been established (Pedersen 1997; Dombernowsky et al. 1998). In these combinations, no major unpredicted toxicity has been observed, and the dose- limiting toxicities are of hematologic origin, with neutropenia being the most common. The combination has not resulted in any outstanding clinically significant toxicity, such as neutropenic fever or hemorrhage. In addition, Sanchez- Rovira et al. (1998) conducted a study of patients with breast cancer treated with prior aggressive chemotherapy, using a 28- day cycle, with gemcitabine administered at 2500 mg/ m2 on Days 1 and 15 and paclitaxel administered at 135 mg/ m2 on Days 1 and 15. Forty- one patients had received prior anthracycline- based treatment, and 9 had received prior paclitaxel for metastatic disease. Current preliminary data on 54 evaluable patients reveal 10 CRs and 15 PRs, for an overall response rate of 46% (Sanchez-Rovira, personal communication). The hematologic toxicity was moderate, and the nonhematologic toxicities included mild nausea and peripheral neuropathy (Sanchez- Rovira et al. 1998). Thus, the combination of gemcitabine and paclitaxel has demonstrated efficacy in patients with metastatic breast cancer and deserves further exploration to determine its use in the treatment of metastatic breast cancer.

1.5. Overall Survival and Time to Progression of Disease as Study Endpoints

Patients with metastatic breast cancer are incurable using conventional therapy with antitumoral hormonal drugs or cytostatic agents. The median survival from diagnosis of metastatic disease to death is reported to be approximately 3 years (Harris et al. 1997). While newer cytostatic agents have impacted tumor shrinkage, no significant increases in overall survival have been demonstrated (Sledge et al. 1997). One reason for this result may be that breast cancer has a longer disease time span than NSCLC or ovarian cancer, allowing for administration of multiple therapies with different modalities. These therapies confound overall survival regardless of whether the treatment is a first- line cytostatic agent or a subsequent treatment.

Using a primary endpoint of overall survival in a trial comparing two different cytostatic combinations in the treatment of metastatic breast cancer requires a large Phase 3 study to detect a clinically significant difference. The advantages with such an endpoint are that it is technically easy to monitor and it is not dependent on monitoring tumor status. However, since patients with breast cancer typically receive 3 or more lines of chemotherapy, it is unlikely that survival can be prolonged in a clinically meaningful way by adding a new chemotherapeutic agent to one line of a multiple- line therapy. A decrease in overall survival is unacceptable, despite any positive effects a chemotherapeutic agent may have on other endpoints, such as tumor shrinkage, duration of response, progression- free interval, treatment toxicity, or quality of life. Thus, overall survival becomes a meaningful primary endpoint.

A more specific instrument — if closely monitored — is time to progression of disease. This endpoint reflects the impact of a specific treatment modality on the disease at a given time period and is probably not confounded by any prior treatments or by subsequent therapies. Time to progression of disease also represents an important clinical achievement for patients with metastatic breast cancer. Using an endpoint of time to progression of disease in a trial comparing two different cytostatic combinations in the treatment of metastatic breast cancer requires a large Phase 3 study to detect a clinically significant difference. Patients should be closely monitored, with follow- up visits every other month, to ensure the collection of post-therapy data on time to progression of disease and to avoid an unnecessarily high proportion of censoring. Thus, overall survival and time to progressive disease become major and complementary endpoints when analyzing a randomized, Phase 3 trial in metastatic breast cancer, if the trial has been sized appropriately to detect clinically meaningful changes.

1.6. Study Rationale

This Phase 3 randomized clinical trial, comparing overall survival between gemcitabine plus paclitaxel versus paclitaxel alone in patients with unresectable, locally recurrent or metastatic breast cancer, is designed as a pivotal registration study based on the following points:

- single- agent activity of paclitaxel and gemcitabine in metastatic breast cancer
- encouraging Phase 2 data of the combination
- current data regarding the use of active single agents as first- line therapy with no significant difference in survival
- clinical interest in the unique mechanisms of action and favorable toxicity profiles of the gemcitabine plus paclitaxel combination.

2. Objectives

Primary Objective

The primary objective of this study is to compare overall survival between those patients with unresectable, locally recurrent or metastatic breast cancer who are treated with gemcitabine plus paclitaxel to those patients treated with paclitaxel monotherapy. Patients will have relapsed after receiving adjuvant/ neoadjuvant chemotherapy containing an anthracycline, unless clinically contraindicated.

Secondary Objectives

The secondary objectives of this study are the following:

- Compare the following between regimens:
  - — Time to documented progression of disease.
  - — Progression- free survival.
  - — Response rates.
  - — Duration of response.
- Characterize changes in performance status, patient- reported pain, and disease-related symptoms in each arm.
- Characterize the nature of the toxicities experienced in each arm.
- Characterize gemcitabine and paclitaxel pharmacokinetics.

The efficacy endpoints are defined in Section 3.9.1.3.

3. Investigational Plan

3.1. Summary of Study Design

This is a Phase 3, randomized study of gemcitabine plus paclitaxel versus paclitaxel in patients with unresectable, locally recurrent or metastatic breast cancer. Patients will be randomized to either of the following two arms:

Arm A: On Day 1, paclitaxel (175 mg/ m2) administered intravenously over approximately 3 hours followed by gemcitabine (1250 mg/ m2) administered as a 30- minute intravenous infusion (maximum infusion time of 60 minutes). On Day 8, gemcitabine (1250 mg/ m2) administered as a 30- minute intravenous infusion (maximum infusion time of 60 minutes).

Arm B: Single- agent paclitaxel 175 mg/ m2 administered intravenously over approximately 3 hours on Day 1 every 21 days.

Patients will be treated until documented progressive disease or until intolerable toxicity develops. Follow- up will be conducted as presented in the following figure. Treatment may be stopped at any time at the discretion of the treating physician or the patient. An overview of the study design is presented in Figure 1.

Figure 1. Illustration of study design for Protocol B9E- MC- JHQG.

PRE-THERAPY	Females ≥18 years old with unresectable, locally recurrent or metastatic breast cancer who have received adjuvant anthracycline-containing chemotherapy and have KPS ≥70 and adequate organ function and bone marrow reserve (Section 3.4.2)
	Baseline CT scan of chest and abdomen; nuclear medicine bone scan (Section 3.9.1.1)
DURING THERAPY	RANDOMIZE
	Arm A: Paclitaxel 175 mg/m^2 (Day 1, q21 days) Gemcitabine 1250 mg/m^2 (Days 1 and 8, q21 days)
	Arm B: Paclitaxel 175 mg/m^2 (Day 1, q21 days)
	Treatment continues until the disease progresses, intolerable toxicity develops, or another relevant reason for discontinuation of treatment occurs (Section 3.5)
POST-THERAPY	30-day post-therapy follow-up visit to assess safety and confirm response (Section 3.9.6.1)
	Bimonthly follow-up for patients without confirmed disease progression (by radiologic or physical exam) q2 months after 30-day follow-up until progression (Section 3.9.6.2)
	Long-term follow-up for patients with confirmed disease progression (by radiologic or physical exam) in 4-month intervals after 30-day follow-up (Section 3.9.6.3)

Data will be collected for pharmacokinetics analysis from 24 patients at selected sites (identified in their site- specific letter of agreement), using data from 12 evaluable patients from each treatment arm.

3.2 Discussion of Design and Control

A randomized, two- arm trial with a comparator control is appropriate for the objectives of this study. See Section 3.6.1 for details of the randomization procedure.

3.3. Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical study.

The names, titles, and institutions of the investigators are listed in the Contacts for Protocol B9E- MC- JHQG provided with this protocol.

If investigators are added after the study has been approved by Lilly, an ethical or institutional review board, or a regulatory agency, these additions will not be considered changes to the protocol; however, the Contacts for Protocol B9E- MC-JHQG will be updated to provide this information.

3.3.1. Final Report Signature

The coordinating investigator — who may be the principal investigator or the investigator who enrolls the greatest number of evaluable patients — will sign the final clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report. If the coordinating investigator is unable to fulfill this function, the investigator who enrolls the next greatest number of evaluable patients will serve as the coordinating investigator and will sign the final clinical study report.

3.4. Study Population

3.4.1. Entry Procedures

An informed consent will be obtained from each patient after the nature of the study is explained.

3.4.2. Criteria for Enrollment

Enter The act of obtaining informed consent for participation in a clinical study from patients deemed eligible to participate in the clinical study. Patients entered into a study are those who sign the informed consent document directly or through their legal representatives.

Enroll The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.

3.4.2.1. Inclusion Criteria

Patients may be included in the study only if they meet all of the following criteria:

[1] Patients will have histologic or cytologic diagnosis of breast cancer with evidence of unresectable, locally recurrent, or metastatic disease. Lesions should not be amenable to surgery or radiation of curative intent.

[2] Female patients of at least 18 years of age.

[3] Patients will have relapsed after [a] receiving one adjuvant/ neoadjuvant chemotherapy containing an anthracycline, unless [b] clinically contraindicated.

Before entry into this study, patients must have recovered from the toxic effects of prior therapy.

[a] Treatment with an anthracycline- based chemotherapy regimen in the adjuvant/ neoadjuvant setting with subsequent disease relapse.

OR

[b] Treatment with one non- anthracycline- based regimen in the adjuvant/ neoadjuvant setting if use of an anthracycline was clinically contraindicated (for example, due to low ejection fraction).

[4] Prior treatment with humanized anti- HER2 antibody is allowed.

[5] Clinically measurable disease, defined as bidimensionally measurable lesions with clearly defined margins on imaging studies or physical examination. Ultrasound is not an acceptable method to document tumor measurements for this study. One indicator lesion serving as measurable disease must be at least 1 cm by 1 cm, as defined by computed tomography (CT) scan, magnetic resonance imaging (MRI), or x- ray, or at least 2 cm by 2 cm as defined by physical examination.

[6] Measurable disease that is outside a previously irradiated area.

[7] Radiation must be terminated at least 2 weeks prior to enrollment. Patients must have recovered from the toxic effects of prior therapy.

[8] Performance status of 70 or higher on the Karnofsky Performance Scale

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

[10] Adequate bone marrow reserve: absolute granulocyte count (AGC) $\geq 1.5 \times$ 109/ L, platelets $\geq 100 \times$ 109/ L, and hemoglobin ≥ 9.0 g/ dL.

[11] Adequate liver function (bilirubin ≤ 1.5 times the upper limit of normal [ULN]); alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2 times the ULN (Venook et al. 1998).

[12] Calcium ≤ 1.2 times the ULN.

[13] Adequate renal function (creatinine ≤ 1.5 times the ULN).

[14] Antitumoral hormonal treatment terminated prior to enrollment (up to date of randomization).

[15] Bisphosphonate therapy is allowed; however, therapy can neither be stopped nor started within 4 weeks prior to enrollment.

[16] Patient compliance and geographic proximity that allow for adequate follow-up.

[17] Informed consent from patient.

[18] Utilization of approved contraceptive method (for example, intrauterine device [IUD], birth control pills, or barrier device) for women of childbearing potential during and for 3 months after stopping treatment in this study.

3.4.2.2. **Exclusion Criteria**
Patients will be excluded from the study for any of the following reasons:

[19] Previous therapy with gemcitabine or a taxane.

[20] Previous chemotherapy for metastatic breast cancer.

[21] Inflammatory breast cancer without evidence of metastatic disease.

[22] Active cardiac disease not controlled by therapy and/ or myocardial infarction within the preceding 6 months.

[23] Known or suspected brain metastases/ recurrence requiring steroid or radiation treatment.

[24] Active infection (at the discretion of the investigator).

[25] Serious concomitant systemic disorders (including uncontrolled diabetes mellitus) incompatible with the study (at the discretion of the investigator).

[26] Second primary malignancy (except in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin or squamous cell carcinoma of the skin with no relapse in the past 5 years).

[27] Bone metastases, pleural effusion, or ascites as the only site of disease.

[28] Bone marrow transplantation or autologous stem cell infusion following high- dose chemotherapy for adjuvant or metastatic disease.

[29] Radiation of greater than 20% of total bone marrow producing areas

[30] Concurrent administration of radiation therapy, chemotherapy, hormonal therapy, or immunotherapy (including humanized anti- HER2 antibody).

[31] History of hypersensitivity reactions with drugs formulated in Cremophor® EL (polyoxyethylated castor oil).

[32] Treatment with a drug within the last 30 days that has not received regulatory approval at the time of study entry.

[33] Presence of severe psychiatric disease.

[34] Pregnant or breast feeding.

3.4.2.3. Violation of Criteria for Enrollment
The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be discontinued from the study and Lilly or designee must be contacted. Such individuals can remain in the study only if there are ethical reasons to have them continue. In these cases, the investigator must obtain approval from the Lilly clinical research physician for the study participant to continue in the study.

3.4.3. Disease Diagnostic Criteria
Patients must have a histologic or cytologic diagnosis of breast cancer with evidence of unresectable, locally recurrent or metastatic (M1) disease, as staged by the American Joint Committee on Cancer

3.5. Discontinuations
A patient will be discontinued from the study under the following circumstances.
• If there is evidence of progressive disease.
• If the attending physician thinks a change of therapy would be in the best interest of the patient.
• If the patient requests discontinuation.
• If the drug exhibits unacceptable toxicity.
• If a patient becomes pregnant or fails to use adequate birth control (for those patients who are able to conceive).
• If Lilly uses its discretion as the sponsor to discontinue the patient.

3.6. Dosage and Administration

3.6.1. Patient Assignment
Patients will be randomized to receive gemcitabine plus paclitaxel or paclitaxel alone in this parallel, open- label trial. Randomization will be balanced between treatment arms according to the following factors:
• Karnofsky Performance Status (Low [70 to 80] versus High [90 to 100]).
• Prior anthracycline therapy in the adjuvant setting (Yes versus Contraindicated).
• Prior hormonal therapy (Yes versus No).
• Presence of visceral metastases (Yes versus No). Visceral metastases is defined as any metastases to the major organs excluding bone, skin, soft tissue, and lymph nodes.

• Disease progression with prior adjuvant chemotherapy (≤6 months versus > 6 months).
• Investigational center (by center).

The algorithm of Pocock and Simon (1975), using a probability factor of 0.75, will be applied to balance the treatment arms for these factors.

3.6.2. Materials and Supplies

3.6.2.1. Gemcitabine

Gemcitabine is supplied in a sterile form for intravenous use only. Vials of Gemzar . contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/ or sodium hydroxide may have been added for pH adjustment.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200 mg vial or 25 mL to the 1 g vial. These dilutions each yield a gemcitabine concentration of 38 mg/ mL which includes accounting for the displacement volume of the lyophilized powder. Complete removal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. Reconstituted Gemzar is a clear, colorless to light strawcolorless solution. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

When prepared as directed, Gemzar solutions are stable for 25 hours at controlled room temperature (20 ° to 25 ° C or 68 ° to 77 ° F). Discared unused portion. Solutions of reconstituted Gemzar should not be refrigerated as crystallization may occur. Unopened vials of Gemzar are stable until the expiration date indicated on the package when stored at a controlled room temperature.

3.6.2.2. Paclitaxel

Paclitaxel (Taxol) is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Paclitaxel is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor . EL (polyoxyethylated castor oil) and 49.7% (v/ v) dehydrated alcohol USP. Contact of the undiluted concentrate with plasticized chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. Solutions should preferably be prepared and stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene- lined administration sets.

The contents of the vial must be diluted as required before use. Dilutions should be mixed as closely as possible to the start time of each infusion, as paclitaxel is known to be stable up to 27 hours in solution. Paclitaxel should be administered

as a continuous infusion in normal saline or 5% dextrose, and a concentration of 1.2 mg/ mL should not be exceeded. The full calculated dose of paclitaxel will be diluted in a minimum of 500 mL and a maximum of 1000 mL of normal saline or 5% dextrose as close as possible to the beginning of the infusion.

Upon preparation, solutions may show haziness; this is attributable to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through intravenous tubing containing an in-line (0.22- μ m) filter.

3.6.3. Dosage Administration

In the combination treatment arm, paclitaxel (175 mg/ m2) will be administered on Day 1 over approximately 3 hours as an intravenous infusion, followed by gemcitabine (1250 mg/ m2) as a 30- minute intravenous infusion (maximum infusion time of 60 minutes) in a 21- day cycle. On Day 8, gemcitabine (1250 mg/ m2) will be administered as a 30- minute intravenous infusion (maximum infusion time of 60 minutes) in a 21- day cycle.

On the comparator arm, paclitaxel (175 mg/ m2) will be administered on Day 1 as a 3- hour intravenous infusion every 21 days.

The number of cycles administered on each treatment arm will vary per patient, as treatment will continue until the disease progresses, intolerable toxicity develops, or another relevant reason for discontinuation of treatment occurs (see Section 3.5).

Antiemetics should be given according to institutional guidelines and must be appropriately documented.

To prevent severe hypersensitivity reactions, all patients must be premedicated to the administration of paclitaxel (see Table 1).

Table 1. Recommended Paclitaxel Premedications

Agent	Dose	Route	Duration
Dexamethasone	20 mg	Oral or Intravenous	12 and 6 hours prior to paclitaxel 30 minutes prior to paclitaxel
Diphenhydramine	50 mg	Intravenous	30 to 60 minutes prior to paclitaxel
Cimetidine or	300 mg or	Intravenous	30 to 60 minutes prior to paclitaxel
Ranitidine or	50 mg or	Intravenous	30 to 60 minutes prior to paclitaxel
Nizatidine	150 mg	Oral or	60 minutes prior to paclitaxel
	100 mg	Intravenous	30 to 60 minutes prior to paclitaxel

NOTE: Premedication can be given according to institutional guidelines and must be appropriately documented (alternative compounds of the same classes are allowed for premedication). Oral versus intravenous administration of dexamethasone will be at the discretion of the investigator.

For patients participating in the pharmacokinetic analysis at selected sites, start and stop times of the infusions and volume administered must be recorded on the appropriate form.

3.6.3.1. Dosage Adjustments Within a Cycle

Patients must have an absolute granulocyte count (AGC) of ≥1.5 × 109/ L and a platelet count of ≥100 × 109/ L prior to starting a cycle on Day 1 (hematology assessed on the day of therapy, or up to 2 days prior to therapy). Tables JHQG. 2 and JHQG. 3 present appropriate gemcitabine dose adjustments within a cycle for hematologic and nonhematologic toxicities, respectively.

Table JHQG. 2. Day 8 Hematologic Toxicities Within a Cycle

Total AGC ($\times 10^9$/L)		Platelets ($\times 10^9$/L)	Percent of Day 1 Gemcitabine Dose
≥1.2	and	>75	100
1.0 - <1.2	or	50 - 75	75
0.7 - <1.0	and	≥50	50
<0.7	or	<50	Hold[a]

a treatment may be reinstated on Day 1 of the next cycle.

Table 3. Day 8 Nonhematologic Toxicities Within a Cycle

CTC Grade	Percent of Day 1 Gemcitabine Dose
0 - 2 (and Grade 3 nausea/vomiting and alopecia)	100
3 (except nausea/vomiting and alopecia)	50 or Hold[a]
4	Hold[a]

a This decision will depend upon the type of nonhematologic toxicity seen and which course is medically most sound in the judgment of the physician-investigator. Treatment may be reinstated on Day 1 of the next cycle.

3.6.3.2. Dose Adjustments for Subsequent Cycles
The following guidelines should be followed:

• Hematologic toxicity: Patients who experienced sustained Grade 4 febrile neutropenia, required gemcitabine dose omission on Day 8, or had a prolonged delay of the start of the next cycle (= 2 weeks), should receive 75% of the starting dose of the previous cycle. This should apply to patients on either arm. For Day 8 dosing, gemcitabine will be administered at the same dose as Day 1.

• Nonhematologic toxicity: Table JHQG. 4 provides guidelines for subsequent dosing of gemcitabine and/ or paclitaxel following the worst CTC grade of toxicity demonstrated in the previous cycle.

• Selected nonhematologic toxicities: Table 5 provides guidelines for subsequent dosing of paclitaxel for Grade 3 fatigue and Grades 2 and 3 neurotoxicities.

• Subsequent dose escalation to the protocol- defined dose will be allowed for hematologic or nonhematologic toxicity, providing that the patient tolerates the doses given at the 75% reduction level.

Table 4. Day 1 Nonhematologic Toxicities For Subsequent Cycles (Excluding Fatigue and Neurologic Toxicites)

CTC Grade	Percent of Protocol-Defined Dose Gemcitabine and/or Paclitaxel
0 - 2 (and Grade 3 nausea/vomiting and alopecia)	100
3 (except nausea/vomiting and alopecia)	75
4	50 or Hold[a]

a This decision will depend upon the type of nonhematologic toxicity seen and which course is medically most sound in the judgment of the physician-investigator.

Appropriate dose adjustments of paclitaxel on Day 1, because of selected nonhematologic toxicities, are presented in Table 5.

CTC Grade	Percent of Protocol-Defined Dose Paclitaxel
Grade 3 fatigue	
First occurrence	75
If persistent	50
If persistent	Hold[b]
Grade 2 neurotoxicity	
First occurrence	75
If persistent	50
If persistent	Hold[b]
Grade 3 neurotoxicity	
Any occurrence	Hold[b]
Recovery to Grade ≤1[c]	Reinstitute at 50[d]
No recovery to Grade ≤1[c]	Discontinue

a Toxicities specific to paclitaxel; refer to Tables 3 and 4 for gemcitabine nonhematologic toxicities
b Hold therapy until symptoms resolve to ≤Grade 1 toxicity. Discontinue paclitaxel therapy if symptoms do no resolve within 6 weeks.
c Within 2 cycles (6 weeks).
d Dosage can be escalated at the discretion of the physician- investigator.

Patients on the combination arm who discontinue paclitaxel because of a hypersensitivity reaction to paclitaxel should continue gemcitabine chemotherapy.

Doses held due to toxicity or missed will not be given at a later time. If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient. If the second (Day 8) dose is held or missed, the cycle will start at Day 22 after 2 weeks of rest. Doses held due to toxicity will not be administered.

A patient who cannot be administered drug for 6 weeks from time of last treatment must be discontinued from the study unless approved by Lilly.

3.6.4. Compliance

Gemcitabine plus paclitaxel, or paclitaxel alone, will be intravenously administered only at the investigational sites. As a result, patient compliance monitoring is ensured. Patients who return for follow- up visits will receive study

drug unless they are encountering toxicity problems or their disease has progressed.

3.7. Blinding

This is an open- label, randomized study; therefore, the identity of the treatment will be known to the investigator, patient, and sponsor.

3.8. Concomitant Therapy

No other chemotherapy, immunotherapy (including humanized anti- HER2 antibodies), hormonal therapy (excluding contraceptives and replacement steroids), radiation therapy, or experimental medications will be permitted while the patients are on the study. Any disease progression requiring other forms of specific antitumor therapy will be cause for discontinuation in this study.

Patients are not allowed to start or stop bisphosphonate therapy within 4 weeks of enrollment. For the purposes of this study, hypercalcemia requiring bisphosphonate therapy may be an indicator of progressive disease, which should be confirmed by imaging study or physical exam.

Patients should receive full supportive care. Patients may receive growth factors for hematologic toxicity as clinically indicated. Patients should receive prophylactic antiemetics per investigator discretion and institutional practice. Steroids are allowed for use as an antiemetic and for premedication. These therapies will be recorded in the case report form.

3.9. Efficacy, Pharmacokinetic, and Safety Evaluations

Study procedures and their timing are summarized in the Schedule of Events, See next page.

	Baseline	Cycle 1 (3 weeks)		Cycle 2 (3 weeks)		Cycle 3 and following (3 weeks each)		30-Day Follow-Up (Visit 101)	Bimonthly Follow-Up	Long-Term Follow-Up
Visit Day		1	8	1	8	1	8			
Informed consent signed	X									
Premedication for paclitaxel[a]		X		X		X				
Gemcitabine and		X	X	X	X	X	X			
Paclitaxel therapy[b]		X		X		X				
Paclitaxel therapy[b]		X		X		X				
Physical exam and medical history	X[c]			X[f]		X[f]				
Weight	X[c]			X[f]		X[f]				
Height	X[c]									
Pregnancy test	X[d]									
Vital signs		X	X	X	X	X	X			
Chemistry	X[d]			X[f]		X[f]		X		
Hematology	X[d]		X	X	X	X	X	X		
Chest x-ray	X[e]									
ECG	X[e]									

[a] = see Table JHQG.1 (Section 3.6.3) for timing of premedication.
[b] = treatment continues until the disease progresses, intolerable toxicity develops, or another relevant reason for discontinuation occurs.
[c] = to be performed no more than 1 week before enrollment.
[d] = to be performed no more than 2 weeks before enrollment.
[e] = to be performed no more than 4 weeks before enrollment.
[f] = to be performed before the start of the cycle.

Assessment Performed	Baseline	Cycle 1 (3 weeks)		Cycle 2 (3 weeks)		Cycle 3 and following (3 weeks each)		30-Day Follow-Up (Visit 101)	Bimonthly Follow-Up	Long-Term Follow-Up
Visit Day		1	8	1	8	1	8			
Tumor measurement										
by physical exam	X[c]			X			X	X[l]	X[m]	
by required imaging studies										
CT scan chest/abdomen	X[e]						X[h]	X[l]	X[m]	
Nuclear bone scan	X[e]						X[h]	X[l]	X[m]	
Performance status	X[c]			X[f]		X[f]		X	X	X
BPI/Rotterdam Symptom Checklist	X[g]			X[i]		X[i]		X		
Analgesic level	X[c]			X[f]		X[f]		X		
Physician-assessed DRS	X[c]									
CTC toxicity grading				X[f]		X[f]		X		
Adverse events, as applicable		X		X		X		X		
Transfusions required		X		X					X	X
Post-study follow-up information										
Pharmacokinetic sampling[j]		X	X[k]							

Abbreviations: BPI = Brief Pain Inventory; DRS = disease-related symptoms; CTC = Common Toxicity Criteria.

[c] = to be performed no more than 1 week before enrollment.

[e] = to be performed no more than 4 weeks before enrollment.

[f] = to be performed before the start of the cycle.

[g] = to be performed after the ICD is signed but before randomization.

[h] = if positive at baseline, repeat every 8 weeks ±7 days; for patients with negative baseline bone scan, repeat if symptoms of progressive disease develop.

[i] = completed by the patient before chemotherapy is administered.

[j] = to be performed at selected sites; see Attachment JHQG.5.

[k] = for the combination arm only.

[l] = to confirm response or document disease progression.

[m] = for documentation of disease progression.

Appears This Way
On Original

Appears This Way
On Original

3.9.1. Efficacy

3.9.1.1. Timing of Efficacy Measures

No more than 4 weeks before enrolling into the study, each patient must be assessed by the following imaging studies for tumor measurement (NOTE: Ultrasound is not an acceptable method to document tumor measurements for this study):

• CT scan for chest and abdomen (preferred) or MRI (acceptable in lieu of CT scan). All sites of disease identified by these imaging studies are to be documented in the appropriate CRF modules.
• Nuclear medicine bone scan.

The disease and health outcomes status of each patient will be assessed with the following procedures:

• No more than 4 weeks before enrolling into the study:

— Chest x- ray and ECG.

• No more than 1 week before enrolling into the study:

— Medical history and physical examination, including measurements of height and weight.

— Evaluation of performance status (Karnofsky scale).

— Tumor measurement of palpable or visual lesions.

— Brief Pain Inventory (BPI).

— Analgesic level

— Physician- assessed disease- related symptoms.

— Rotterdam Symptom Checklist (RSCL).

At the stated intervals during the study, efficacy will be examined in each patient by the following evaluations:
• Every 8 weeks ± 7 days: - Imaging studies that were positive for disease at baseline must be measured by the same technique throughout the study.

• Before every therapy cycle:
- Limited medical history and physical examination, including tumor measurements of lesions that are measurable by physical examination.

- Weight measurements.
- Performance status evaluation.
- BPI.
- Analgesic level.
- RSCL.

• A CR or PR must be confirmed no less than 4 weeks after the first observance of the response.

• Repeat bone scans if necessary for evidence of disease progression.

• At the 30- day post- therapy visit (Visit 101):
- Date of disease progression.
- Date of death.
- Response assessment (only if necessary for confirmation). NOTE: response assessment at follow- up will apply only to responders who discontinue treatment for reasons other than disease progression.
- Performance status.
- BPI. - Analgesic level.
- RSCL. - Chemistry and hematology assessments.
- CTC toxicity ratings.
-

• At bimonthly follow- up assessments (every 2 months; see Section 3.9.6.2):
- Date of disease progression.
- Date of death.
- Post- therapy treatment (surgery, chemotherapy, and radiotherapy).
- Performance status.
- Details of other chemotherapy during follow- up (only at last follow- up visit).
- Duration of response to post- therapy treatment (only at last follow- up visit).

• At long- term follow- up assessments (every 4 months; see Section 3.9.6.3):
- Date of disease progression.
- Date of death.
- Post- therapy treatment (surgery, chemotherapy, and radiotherapy).
- Performance status.
- Details of other chemotherapy during follow- up (only at last follow- up visit).
- Duration of response to post- therapy treatment (only at last follow- up visit).

3.9.1.2. Efficacy Criteria (WHO criteria)
Tumor markers will not be assessed.

Eligibility for the study requires that at least one indicator lesion must measure 1 cm by 1 cm by appropriate imaging studies or must measure 2 cm by 2 cm by physical examination (see Inclusion Criteria [5]). Evaluation of other lesions is defined below.

A panel of independent experts may evaluate the best response to treatment with gemcitabine plus paclitaxel or paclitaxel monotherapy by applying standard oncologic criteria. Using this standard criteria, the measurability of a tumor is defined as follows:

Disease Status

• Bidimensionally measurable: tumor measurements will be recorded in centimeters using a ruler or calipers and consist of the diameter of the widest portions of the tumor and the greatest diameter perpendicular to that line. For those organs with multiple metastases at least three lesions should be monitored (modified WHO).

• Unidimensionally measurable disease: for those lesions where only one dimension is measurable — record that single dimension.

• Nonmeasurable disease: the following manifestations are not considered measurable:
- lesions in previously irradiated fields.
- ascites.
- bone metastases.
- pleural effusions.
- abdominal masses that can be palpated but not measured.

Definitions of Objective Response

The same assessment method used to determine the disease status at baseline must be used consistently for efficacy evaluation throughout the study. A CR or PR must be confirmed no less than 4 weeks after the first observance of the response. Lesions will be evaluated using the following standard WHO criteria (WHO Handbook 1979).

Measurable disease

• Complete response (CR): The disappearance of all known disease, determined by two observations not less than 4 weeks apart.
• Partial response (PR): At least a 50% decrease in the sum of the area of the lesions that have been measured to determine the effect of therapy by two observations not less than 4 weeks apart. In addition, there may be no appearance of new lesions or progression of any lesion.
• Stable disease (SD): A 50% decrease in the sum of the area cannot be established, nor is a 25% increase in the size of one or more measurable lesions demonstrated.
• Progressive disease (PD): At least a 25% increase in the area of at least one measurable lesion or the appearance of new lesions.

Nonmeasurable disease

• Complete response (CR): The complete disappearance of all known disease for at least 4 weeks.

• Partial response (PR): Estimated decrease in the sum of the area of at least 50% for at least 4 weeks.

• Stable disease (SD): No significant change for at least 4 weeks. This includes estimated decrease of less than 50% and lesions with estimated increase of less than 25%.

• Progressive disease (PD): Appearance of any new lesion not previously identified, or estimated increase of at least 25% in one or more lesions; appearance of any new lesions noted on bone scan will be considered PD.

Determination of Overall Response in Solid Tumors

If both measurable and nonmeasurable disease are present in a given patient, the result of each should be recorded separately. Note that an overall assessment of response involves all parameters.

In patients with measurable disease, the poorest response designation shall prevail. Stable disease in nonmeasurable lesions will not detract from a PR in measurable lesions but will reduce a CR in measurable lesions to PR overall.

3.9.1.3. Definition of Efficacy Measures

Overall survival time is defined as the time from the date of randomization to the date of death from any cause. Survival time will be censored at the date of last post- therapy follow- up visit for patients who are still alive.

Time to documented progression of disease is defined as the time from the date of randomization to the first date of documented progressive disease. Time to documented progression of disease will be censored at the date of the last post-therapy follow- up visit for patients who have not had documented progressive disease.

Progression- free survival time is defined as the time from the date of randomization to the first date of documented progressive disease or death from any cause. Progression-free survival time will be censored at the date of the last post- therapy follow- up visit for patients who are still alive and who have not had documented progressive disease.

Among patients exhibiting a best study response of PR or CR, the duration of response is measured from the date of randomization to the first date of documented progressive disease. Duration of response will be censored at the date

of the last post- therapy followup visit for responders who have not had documented progressive disease.

Among patients exhibiting a best study response of CR, the duration of complete response is measured from the date the CR was documented until the first date of documented progressive disease. Duration of complete response will be censored at the date of the last post- therapy follow- up visit for complete responders who have not had documented progressive disease.

3.9.2. Pharmacokinetics

Plasma samples will be collected from 24 patients at selected sites (12 evaluable patients per treatment arm) for pharmacokinetic evaluation and will be assayed by a validated HPLC method for gemcitabine, its deaminated metabolite (deoxydifluorouridine, dFdU), and paclitaxel.

3.9.3. Health Outcomes Measures

Brief Pain Inventory (BPI; Attachment JHQG. 6), analgesic level (Attachment JHQG. 7), and the RSCL (Attachment JHQG. 8) for each patient will be assessed at the following times:

- No more than 1 week before enrolling into the study
- Before every therapy cycle
- At the 30- day post- therapy visit (Visit 101)

Physician- assessed disease- related symptoms will be assessed only at baseline (no more than 1 week before enrollment).

The Brief Pain Inventory (BPI) is a valid and reliable instrument developed to assess chronic pain and its impact on quality of life (Daut et al. 1983; Cleeland 1991; Cleeland et al. 1994; Larue et al. 1995; Cleeland et al. 1996). It has been translated and validated from English into French, German, Italian, Spanish, Chinese, and Vietnamese. Only patients for whom there is a validated translation in her native language will complete the BPI.

The RSCL is a valid and reliable instrument to measure psychological and physical distress of cancer patients (de Haes et al. 1990). It has been translated and validated from Dutch into English and Italian (de Haes et al. 1990; Paci 1992). In addition, it has been translated into Czech, French, German, Hungarian, Portuguese, and Spanish (de Haes and Olschewski 1998). Only patients for whom there is a translation in her native language will complete the RSCL.

3.9.4. Safety

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for appropriate medical care of patients during the study.

The investigator remains responsible to follow, through an appropriate health care option, adverse events that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event resolves or is explained. Frequency of follow- up for these events is left to the discretion of the investigator.

3.9.4.1. Safety Measures

Safety will be assessed through clinical adverse events and CTC laboratory and nonlaboratory toxicities, as described in Sections 3.9.4.2 through 3.9.4.3.

3.9.4.2. Clinical Adverse Events

Lilly has standards for reporting adverse events that are to be followed, regardless of applicable regulatory requirements that may be less stringent. For purposes of collecting and evaluating all information about Lilly drugs used in clinical trials, a clinical trial adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, without regard to the possibility of a causal relationship. Cases of pregnancy should be reported for tracking purposes. Lack of drug effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish drug effect.

Adverse events will be collected after the patient has been enrolled. If a patient experiences an adverse event after the informed consent document is signed (entry) but prior to assignment to treatment (enrollment), the event will NOT be reported unless the investigator feels that the event may have been caused by a protocol procedure.

Prior to enrollment, study site personnel will note the occurrence and nature of each patient's medical condition(s). During the study, site personnel will again note any change in the condition(s) and/ or the occurrence and nature of any adverse events.

Events leading to the clinical outcome of death because of progressive disease will be included as part of the safety and efficacy analyses for this study, and will not be recorded as adverse events unless the investigator believes the event may have been caused by the study drug.

3.9.4.2.1. Adverse Event Reporting Requirements
All adverse events occurring after enrollment must be reported to Lilly or designee on the clinical report form.

In addition, study site personnel must report to Lilly or designee immediately, by telephone, any serious adverse event.

If a patient's dosage is reduced or treatment is discontinued as a result of significant laboratory abnormality, inadequate response to treatment, or any other adverse event, study site personnel must clearly document the circumstances and data leading to any such dosage reduction or discontinuation of treatment, using the clinical report form.

In cases where the investigator notices an unanticipated benefit to the patient, study site personnel should enter " unanticipated benefit" with the actual event term (for example, the complete actual term would be " unanticipated benefit — sleeping longer").

3.9.4.2.2. Serious Adverse Events
Study site personnel must report immediately by telephone to Lilly or designee any adverse event from this study that results in one of the following outcomes, or is significant for any other reason:
- death
- initial or prolonged inpatient hospitalization
- a life- threatening experience (that is, immediate risk of dying)
- severe or permanent disability
- cancer (other than cancers diagnosed prior to enrollment in studies involving patients with cancer)
- congenital anomaly.

Recommendations for reporting serious adverse events are presented in Attachment JHQG. 4.

Study- specific clinical outcomes of death because of disease progression are exempt from serious adverse event reporting, unless the investigator deems them related to use of the study drug. Hospitalization for study drug administration is not a serious adverse event.

Serious adverse events will be collected after the patient has received the first infusion of study drug. If a patient suffers a serious adverse event after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event has been caused by a protocol procedure.

Patients should be closely followed for adverse events while receiving study drug and for 30 days after the last dose of study drug in order to detect delayed

toxicity. Serious adverse events occurring after a patient is discontinued from the study will NOT be reported unless the investigator feels that the event may have been caused by the study drug or a protocol procedure.

3.9.4.3. Clinical Laboratory Tests

The timing of laboratory assessments is presented in this section as well as in the Schedule of Events.

No more than 2 weeks before enrolling into the study, each patient will be assessed with the following tests:

- Hematology: hemoglobin, WBC, platelets, lymphocytes, monocytes, and neutrophils.
- Blood chemistries: bilirubin, alkaline phosphatase, ALT, AST, creatinine, calcium, non- fasting glucose, total protein, albumin, sodium, and potassium.
- Pregnancy testing (for pre- and perimenopausal patients).

During therapy, the patients will be assessed as follows:

- The types of transfusions that are required will be recorded at every cycle.
- For patients on the gemcitabine plus paclitaxel arm, hematology samples will be collected on Days 1 and 8 prior to the start of each infusion (collection up to 2 days prior to infusion is allowed). For patients on the paclitaxel monotherapy arm, hematology samples will be collected on Day 1 prior to the start of the infusion and on Day 8 (collection up to 2 days prior to Days 1 and 8 is allowed).
- Blood chemistries will be measured prior to the start of each cycle (samples that are drawn up to 2 days prior to infusion are allowed).
- Vital signs (blood pressure, pulse rate, and temperature) will be taken on days of treatment.
- A toxicity rating, using the NCI CTC scale, will be recorded at the end of each cycle (see the CTC Investigator Guide, Version 2.0, supplied with the clinical report form; NCI 1998).

A central laboratory ——— will assay the blood chemistry and manage the pharmacokinetic samples. Hematology and pregnancy testing (if applicable) will be assayed at a local laboratory. Enrollment or dose adjustment may be based on chemistry results from a local laboratory; however, an additional specimen must be collected and sent to ——— for use in the safety analysis. Investigators must document their review of each laboratory report by signing and dating each report. Pharmacokinetic results will not be reported directly to the investigator.

3.9.5. Safety Monitoring

The Lilly clinical research physician will monitor safety data throughout the course of the study.

3.9.6. Post- Therapy Follow- Up

Patients will undergo post- therapy follow- up in one or more of 3 stages: 30- day post-therapy visit (Visit 101), bimonthly follow- up, and long- term follow- up. Criteria defining the appropriate follow- up for each patient are identified in the respective sections below.

3.9.6.1. 30- Day Post- Therapy Visit (Visit 101)
For all patients, Visit 101 will occur no sooner than 30 days after completion of the last treatment cycle. Data to be collected at Visit 101 are as follows:

- Date of disease progression (progression detected using the same technique that was used at baseline and throughout the study), if progression occurs by the time of the 30- day assessment.
- Date of death.
- Confirmation of response using the same technique that was used at baseline and throughout the study. NOTE: response assessment at follow- up will apply only to responders who discontinue treatment for reasons other than disease progression.
- Performance status.
- BPI, analgesic level, and RSCL.
- Chemistry and hematology assessments.
- CTC toxicity ratings.
- Report of post- therapy adverse events, including:
  - Any study drug- related adverse events in the intervening period.
  - Outcome of any residual toxicities at the time of discontinuation of treatment.

Any adverse events and/ or residual toxicities should be followed regularly (at the discretion of the investigator, but generally no less than every 30 days) until these adverse events and/ or residual toxicities resolve or have stabilized.

3.9.6.2. Bimonthly Follow-Up
For patients without confirmed progressive disease by the 30- day post- therapy visit (Visit 101) — that is, patients who discontinued treatment because of intolerable toxicity or other relevant reasons — follow- up assessments will be performed every 2 months until progressive disease is documented (for a maximum of 30 months after the patient's date of randomization, or 24 months after randomization of the last patient, whichever occurs sooner). Disease progression must be determined by the same assessment method used at baseline. Patients with measurable or evaluable progressive disease by Visit 101 will undergo only long- term follow- up (Section 3.9.6.3).

Data to be collected during bimonthly follow- up assessments are as follows:

- Date of disease progression (progression detected using the same technique that was used at baseline and throughout the study).
- Date of death.

• Post- therapy treatment (surgery, chemotherapy, and radiotherapy; reported at each follow- up assessment).
• Performance status.
• Details of other chemotherapy during follow- up (including humanized anti-HER2 antibody; reported only at the final follow- up visit).
• Duration of response to post- therapy treatment (reported only at the final follow- up visit).

3.9.6.3. Long- Term Follow-Up
Patients with confirmed progressive disease will be included in the long- term follow- up assessment, which will be conducted at 4- month intervals (for a minimum of 24 months after randomization of the last patient), until at least 440 deaths have been observed, to collect patient survival data.

Data to be collected during long- term follow- up assessments are as follows:

• Date of death.
• Post- therapy treatment (surgery, chemotherapy, and radiotherapy; reported at each follow- up assessment).
• Performance status.
• Details of other chemotherapy during follow- up (including humanized anti-HER2 antibody; reported only at the final follow- up visit).
• Duration of response to post- therapy treatment (reported only at the final follow- up visit).

3.9.7. Appropriateness and Consistency of Measurements
All efficacy and safety assessments used in these studies are standard for an oncology study. Collection of BPI and RSCL data from the patient will not interfere with the routine collection of adverse event and concomitant medication data reported by the patient, nor will the sources of data be required to agree.

3.10. Study Extensions
There are no extensions to this study.

3.11. Quality Control and Quality Assurance
To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

• Provide instructional material to the study sites, as appropriate.
• Sponsor a start- up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the clinical report forms, and study procedures.
• Make periodic visits to the study site.
• Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/ or fax.

• Review and evaluate clinical report form data and use standard computer edits to detect errors in data collection.
• Conduct quality review of database.

In addition, Lilly or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly Medical Quality Assurance (MQA) and/ or regulatory agencies at any time. Investigators will be given notice before an MQA audit occurs.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. Investigator files will identify if any clinical report form entries are source data. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and/ or applicable ethical review boards with direct access to original source documents.

The investigator has the responsibility of explaining the correct use of the investigational agent(s) to site personnel, ensuring that instructions are followed properly, and maintaining accurate records of study drug dispensing and collection.

4. Data Analysis Methods

4.1. Sample Size

Approximately 526 patients will be enrolled in this study. There are 2 planned interim analyses and one final analysis. The first interim analysis will not include efficacy endpoints or any formal statistical comparisons, and thus the sample size is based on efficacy analyses for the second interim and final analyses.

At the time of the second interim analysis, survival data will most likely be immature; thus, the second interim analysis will consider time to documented progression of disease as primary. Using a 2.8% significance level for the second interim analysis, the sample size will provide approximately a 75% chance of finding a significant difference in time to documented progression of disease between regimens. This probability assumes a hazard ratio of 0.75 with 20% censoring (ie, approximately 400 progressions observed; Freedman 1982). The hazard ratio corresponds approximately to a 33% increase in time to documented progression of disease, under exponential distribution for time to progression.

Using a 3% significance level for the final analysis, the sample size will provide approximately an 80% chance of finding a significant difference in overall survival time between regimens. This probability assumes a hazard ratio of 0.75 with 12% censoring (ie, approximately 440 deaths observed; Freedman 1982).

The hazard ratio corresponds approximately to a 33% increase in overall survival time, under exponential distribution for time to overall survival.

4.2. General Considerations.

In each of the analyses, confidence intervals for all parameters to be estimated will be constructed using a 95% level. One interim analysis will be performed 6 months after enrollment of the 50th patient on the gemcitabine plus paclitaxel arm. This first interim analysis will not include efficacy endpoints, and no formal statistical comparisons will be performed. The second interim analysis will be performed after enrollment of the last patient. Formal statistical comparisons in the second interim analysis will be performed at a significance level of 0.028. The final analysis will occur approximately after 440 of the enrolled patients have died. Formal statistical comparisons in the final analysis will be performed at a significance level of 0.03. These significance levels of 0.028 and 0.03 were chosen based on the following assumptions:

• Two primary efficacy comparisons (the second interim and final analyses) will be made using the log- rank test.

• The two log- rank statistics (when suitably standardized) follow an approximate bivariate normal distribution with a correlation of 0.7.

Under these assumptions, the overall alpha level is approximately 0.05. The estimated correlation of 0.7 appears reasonable, given an anticipated high degree of stochastic dependence between the second interim and final analyses.

The interpretation of study results will be the responsibility of the Lilly clinical research physician and the Lilly statistician. The clinical research physician and the statistician will also be 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.

4.3. Data to be Analyzed

All patients who receive at least 1 dose of gemcitabine or paclitaxel will be evaluated for safety. All enrolled patients meeting the following criteria will be evaluated for efficacy:

• Histologic or cytologic diagnosis of unresectable, locally recurrent or metastatic breast cancer.

• No concurrent systemic chemotherapy.

For the pharmacokinetics analysis, patients from selected sites who had evaluable samples collected at the times specified in Tables JHQG. 5.1 through JHQG. 5.3 (Attachment JHQG. 5) on Days 1 through 4 and 8 of Cycle 1 (as applicable, per treatment arm) will be included.

4.4. Patient Disposition

A detailed description of patient disposition will be provided. This description will include:

- A definition of patient qualification.
- A summary of data on patient discontinuation.
- A summary of data on overall qualification status of all patients.
- An account of all identified protocol variations.

All patients entered in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins will be specified.

4.5. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics.
- Baseline disease characteristics.
- Pre- existing conditions.
- Historical illness.
- Prior therapies.
- Concomitant drugs.

Other patient characteristics will be summarized as deemed appropriate.

4.6. Efficacy Analyses

- Analyses will be performed on the observed distributions of overall survival time, time to documented progression of disease, progression- free survival time, and duration of response. The log- rank test will be used for comparisons between regimens for each of these endpoints. Additional supporting analyses will include Kaplan- Meier (1958) estimation by regimen.
- Overall survival rates at 12 and 18 months and progression- free rates at 6 months will be compared between regimens. These rates will be estimated using the Kaplan- Meier method and compared based on a normal approximation for the difference of the rates.
- Tumor response rates will be compared between regimens using an unadjusted normal approximation for the difference of two binomial proportions. The tumor response rate (for each arm) is defined as follows:

Response Rate = Number of Responders/Number of patients qualified for efficacy analysis

4.7. Safety Analyses

All patients who are treated with gemcitabine plus paclitaxel or paclitaxel monotherapy will be evaluated for safety. Safety analyses will include the following:

- Summaries of the number of blood transfusions required.

• Summaries of the adverse event rates and laboratory changes.
• Summaries of the number of CTC toxicity grades for laboratory and nonlaboratory parameters.

4.8. Subgroup Analyses

No specific subgroup analyses are planned. Exploratory analyses may be conducted to identify and assess the relevance of possible prognostic factors.

4.9. Interim Analyses

One interim analysis will be performed 6 months after enrollment of the 50th patient on the gemcitabine plus paclitaxel arm. The purpose of this interim analysis is to assess the safety of the combination therapy. This analysis will not include efficacy endpoints, and no formal statistical comparisons will be performed.

A second interim analysis will be performed after enrollment of the last patient. The purpose of this interim analysis is to make an assessment of both the safety and efficacy of the two therapies. Formal statistical comparisons in this analysis will be performed at a significance level of 0.028.

Only the data monitoring board is authorized to review completely unblinded interim efficacy and safety analyses and, if necessary, to disseminate those results. The data monitoring board will disseminate interim results in a manner that will minimize bias. Study sites will not receive information about interim results unless investigators need to know these results for the safety of their patients.

4.10. Pharmacokinetic/ Pharmacodynamic Analyses

Patients will be sequentially enrolled in this study until data for 12 evaluable patients per arm are collected for pharmacokinetic analysis, and have completed all chemotherapy required on Days 1 and 8 for gemcitabine plus paclitaxel and Day 1 for paclitaxel monotherapy.

Assuming that the within- patient variability of gemcitabine clearance is 30%, a sample size of 12 patients gives approximately 80% power to detect (at the 5% significance level) that 1 treatment is 25% lower than the other with respect to clearance.

Based on a 30% coefficient of variation for the between- patient variability in paclitaxel clearance, a sample size of 12 patients per arm provides 80% power to detect approximately a 35% difference in mean clearance for a 2- sided test procedure at the 5% significance level.

Gemcitabine and paclitaxel concentration- time data from 24 evaluable patients (12 on each treatment arm) will be analyzed by a conventional methodology. Area under concentration- time curve, systemic clearance, distribution volumes, and

terminal elimination half- life will be estimated from the concentration data. Gemcitabine concentrations (in combination with paclitaxel) collected on Day 1 of Cycle 1 will be compared to gemcitabine concentrations (without paclitaxel) collected on Day 8 of Cycle 1. Paclitaxel concentrations (in combination with gemcitabine) collected on Day 1 of Cycle 1 will be compared to paclitaxel monotherapy concentrations on Day 1 of Cycle 1.

4.11. Health Outcomes Analyses

Health outcomes will be measured through BPI and the RSCL, as well as performance status and analgesic level. Only those patients for whom a validated translation of the BPI and RSCL is available will complete these instruments; these patients will comprise the intent- to- treat populations defined in this section.

For patient- reported pain, analyses will be performed on both an intent- to- treat population and a subset population that includes only those patients who are symptomatic at baseline. The following will be compared between treatment arms:

• BPI " pain worst" score for six cycles of treatment plus a final assessment 30 days after the patient goes off treatment. The " pain worst" variable from each time point will be analyzed using a mixed effects analysis of variance model. Of interest is a significant time- by- group interaction for " pain worst," addressing whether or not treatment group profiles for pain intensity are different over time (from randomization through the last assessment 30- day post- treatment status).
• Mean BPI score for the seven pain interference items by treatment arm between randomization and the final assessment. This analysis judges the effect of pain on sleep, work, social activity, relations with others, walking and other physical activity, and mood.

Analgesic level will be documented but not used to predict pain scores or to adjust pain scores. Data from a study of patients with metastatic prostate cancer found that pain report and analgesic consumption change in the same direction (Collins et al. 1993). Data from bone marrow transplant patients with oral mucositis indicate that reports of pain and analgesic use were highly positively correlated (Donaldson 1989). Given the high correlation between the two variables, it would be counter- productive to use both in the same analysis.

Analgesic level will be summarized for each treatment arm.

For the RSCL, descriptive analyses will be performed on an intent- to- treat population for the following scales: physical symptom distress level, psychological distress level, activity level impairment, and overall valuation of life. Additionally, descriptive analyses of 9 specific symptoms will be performed on a subset population that includes only those patients who are symptomatic at

baseline. Physician- assessed disease- related symptoms at baseline will be used to determine which patients are symptomatic. The 9 symptoms to be analyzed are lack of appetite, tiredness, depressed mood, lack of energy, low back pain, nausea, difficulty sleeping, abdominal aches, and shortness of breath.

Changes from baseline in performance status will also be compared between treatment arms.

5. Informed Consent, Ethical Review, and Regulatory Considerations

5.1. Informed Consent

The informed consent document will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient is entered into the study.

The investigator is responsible to see that informed consent is obtained from each patient or legal representative and to obtain the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.

5.2. Ethical Review

Where appropriate, the institutional review board must approve the protocol and informed consent document, agree to monitor the conduct of the study, and review the study conduct periodically. The investigator will provide Lilly with documentation that the institutional review board has approved the study before the study may begin.

In addition, the investigator must provide the following documentation.
• The institutional review board's annual re-approval of the protocol, where appropriate.
• The institutional review board's approvals of any revisions to the informed consent document or amendments to the protocol.

5.3. Regulatory Considerations

This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represents the greater protection of the individual.

After reading the protocol, each investigator will sign two protocol signature pages and return one of the signed pages to a Lilly representative (see Protocol Attachment JHQG. 11).

6. References

Abbruzzese JL, Grunewald R, Weeks EA, et al. 1991. Phase I clinical, plasma, and cellular pharmacology study of gemcitabine. J Clin Oncol 9: 491- 498.

Abbruzzese JL, Gravel D, Terassoff P, Raber M, Plunkett W. 1993. Pharmacologically directed strategy for dose intensification of gemcitabine: a Phase I trial (abstract). Proc AACR 34: 375.

American Cancer Society (brochure). 1998. Cancer facts and figures. New York: National Media Office.

Carmichael J, Possinger K, Phillip P, Beykirch M, Kerr H, Walling J, Harris A. 1995a. Advanced breast cancer: A Phase II trial with gemcitabine. J Clin Oncol 13(11): 2731- 2736.

Carmichael J, Possinger K, Phillip P, Beykirch M, Kerr H, Walling J, Harris A. 1995b. Gemcitabine: a Phase II study in patients with advanced breast cancer (abstract). Proc Am Soc Clin Oncol 12(29): 64.

Casper ES, Green MR, Brown DP, et al. 1991. Phase II trial of gemcitabine in patients with pancreatic cancer. Proc ASCO 10: 440.

Chabner BA, Myers CE. 1993. Antitumor antibiotics - anthracyclines. In: DeVita VT, Hellman S, Resenberg SA, editors. Cancer: principles and practice of oncology. 4th ed. Philadelphia: J. B. Lippincott Co. p 376- 381.

Cleeland CS. 1991. Pain Assessment in Cancer. In: Osoba D, editor, Effect of Cancer on Quality of Life. Boca Raton: CRC Press. p 293- 305.

Cleeland CS, Gonin R, Hatfield AK, et al. 1994. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 330: 592- 596.

Cleeland CS, Nakamura Y, Mendoza TR, Edwards KR, Douglas J, Serlin RC. 1996. Dimensions of the impact of cancer pain in a four country sample: New information from multidimensional scaling. Pain 67: 267- 273

Collins E, Eary JF, Donaldson G, et al. 1993. Samarium- 153- EDTMP in hormone refractory prostate carcinoma: A phase I/ II clinical trial. J Nuclear Med 34: 1839- 1844.

Daut RL, Cleeland CS, Flanery RC. 1983. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain 17: 197- 210.

de Haes JC, van Knippenberg FC, Neijt JP. 1990. Measuring psychological and physical distress in cancer patients: Structure and application of the Rotterdam Symptom Checklist. Br J Ca 62(6): 1034- 1038.

de Haes JCJM, Olschewski M. 1998. Quality of life assessment in a cross-cultural context: Use of the Rotterdam Symptom Checklist in a multinational randomised trial comparing CMF and Zoladex (Goserlin) treatment in early breast cancer. Ann Oncol 9: 745- 750.

Dombernowsky P, Giaccone G, Sandler A, Schwartsmann G. 1998. Gemcitabine and paclitaxel combinations in non- small cell lung cancer. Semin Oncol 25(4) Suppl 9: 44- 50.

Donaldson GW. The determining role of theory in measurement practice. In: CR Chapman, JD Loeser (eds.), Advances in pain research and therapy: Issues in pain measurement. Vol. 12. New York: Raven Press, 1989, pp. 17- 35.

Early Breast Trialists Collaborative Group. 1992. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. Lancet 339: 1- 15, 71-85.

Eisenhauer E, ten Bokkel Huinink WW, Swenerton K, et al. 1994. European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: High- dose versus low- dose and long versus short infusion. J Clin Oncol 12(12) L 2654-2666.

Fosella FV, Lippman S, Pang A, et al. 1993. Phase I/ II study of gemcitabine by 30 minute weekly intravenous infusion x 3 weeks every 4 weeks for non- small cell lung cancer. Proc ASCO 12: 326.

Freedman, LS. 1982. Tables of the number of patients required in clinical trials using the log- rank test. Statistics in Medicine 1: 121- 129.

Gianni L, Munzone E, Capri G, et al. 1995. Paclitaxel in metastatic breast cancer: A trial of two doses by a 3 hour infusion in patients with disease recurrence after prior therapy with anthracyclines. JNCI 87: 1169- 1175.

Guchelaar HJ, Richel DJ, Van Knapen A. 1996. Clinical toxicological and pharmacological aspects of gemcitabine. Cancer Treatment Reviews 22(1): 15-31.

Hansen HH. 1996. Gemcitabine - a review [meeting abstract]. Ann Oncol 7(1 Suppl): 29.

Harris J, Morrow M, Norton L. 1997. Malignant tumors of the breast. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer: Principles and practice of oncology. 5th ed. Philadelphia: Lippincott- Raven Co. p 1557- 1616.

Hertel LW, Boder GB, Kroin JS, et al. 1990. Evaluation of the antitumor activity of gemcitabine (2', 2'- difluoro- 2'- deoxycytidine). Cancer Res 50: 4417- 4422.

Hertel LW, Kroin JS, Misner JW, et al. 1988. Synthesis of 2- deoxy- 2', 2'- difluoro- D- ribose and 2- deoxy- 2', 2'- difluoro- D- ribofuranosyl nucleosides. J Org Chem 53: 2406- 2409.

Holmes FA, Walters RS, Theriault RL, et al. 1991. Phase II trial of paclitaxel, an active drug in the treatment of metastatic breast cancer. J Natl. Cancer Inst 83: 1797- 1805.

Hui YF, Reitz J. 1997. Gemcitabine: A cytidine analogue active against solid tumors. American Journal of Health: System Pharmacy 54(2): 162- 170.

Kaplan EL, Meier P. 1958. Nonparametric estimation of incomplete observations. JASA 53: 457- 481.

Larue F, Colleau S, Brasseur L, Cleeland C. 1995. Multicentre study of cancer pain and its treatment in France. Brit Med J 310: 1034- 1037.

[Lilly] Eli Lilly and Company, Lilly Research Laboratories. 1998. Unpublished data. On file.

Lund B, Hansen OP, Theilade K, et al. 1993. Phase II study of gemcitabine in previously platinum treated ovarian cancer patients. Proc ASCO 12: 262.

MartyM, Extra JM, Cottu PH, Espie M. 1997. Prospects with docetaxel in the treatment of patients with breast cancer. Eur J of Cancer 33 Suppl 7: 26- 29.

Mouridsen HT. 1992. Systemic therapy of advanced breast cancer. Drugs 44 Suppl 4: 17- 28.

Nabholtz JM, Gelmon K, Bontenbal M, et al. 1996. Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol 14(6): 1858- 1867.

[NCI] National Cancer Institute. 1998. Cancer Therapy Evaluation Program (CTEP). Available from: Division of Cancer Treatment and Diagnosis (DCTD) via the INTERNET at ctep. info. nih. gov.

Paci E. 1992. Assessment of validity and clinical application in an Italian version of the Rotterdam Symptom Checklist. Qual Life Res 1: 129- 134.

Parkin DM, Pisani P, Ferlay J. 1999. Global Cancer Statistics. CA — A Cancer Journal for Clinicians. 49(1): 49.

Pedersen A. 1997. Phase I studies of gemcitabine combined with carboplatin or paclitaxel. Semin Oncol 24(2): Suppl 7: 64- 68.

Pocock S. J. and Simon R. 1975. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 31: 103- 115.

Reichman BS, Seidman AD, Crown JPA, et al. 1993. Paclitaxel and recombinant human granulocyte colony- stimulating factor as initial chemotherapy for metastatic breast cancer. J Clin Oncol 11: 1943- 1951.

Rothenberg ML. 1993. Taxol, Taxotere and other new taxanes. Curr Opin Invest Drugs 2: 1269- 1977.

Rowinsky EK, Cazanave LA, Donehower RC. 1990. Taxol: a novel investigational antimicrotubule agent. J Nat'l Cancer Inst 82: 1247- 1259.

Sanchez- Rovira P, Medina MB, Mohedano N, et al. 1998. Results from a Phase II study of gemcitabine in combination with paclitaxel in metastatic breast cancer. ESMO Proceedings Abstract # 77P.

Sanchez- Rovira P. 1999. Results from a Phase II study of gemcitabine in combination with paclitaxel in metastatic breast cancer. Personal communication on preliminary data.

Schiff PB, Fant J, Horwitz SB. 1979. Promotion of microtubule assembly in vitro by Taxol. Nature 22: 665- 667.

Seidman AD, Reichman BS, Crown JPA, et al. 1995. Paclitaxel as second and subsequent therapy for metastatic breast cancer: activity independent of prior anthracycline response. J Clin Oncol 13: 1152- 1159.

Sledge GW Jr, Neuberg D, Ingle J, Martino S, Wood W. 1997. Phase III trial of doxorubicin (A) vs paclitaxel (T) vs doxorubicin + paclitaxel (A + T) as first- line therapy for metastatic breast cancer (MBC): An intergroup trial (meeting abstract). Proc Annu Meet Am Soc Clin Oncol 16: 2A.

Sledge GW Jr. 1997. Phase III trial of doxorubicin vs paclitaxel vs doxorubicin + paclitaxel as first- line therapy for metastatic breast cancer: An intergroup trial (transcript of oral presentation). Proc Annu Meet Am Soc Clin Oncol.

Tonato M. 1993. Gemcitabine safety overview. In: Gemcitabine: Novel combination of efficacy and tolerability. Proc Eur Cont Clin Oncol 7 Satellite Symposium. Jerusalem, Israel. p 14- 16.

Venook AP, Egorin MJ, Rosner GL, et al. 1998. Phase I and pharmacokinetic trial of paclitaxel in patients with hepatic dysfunction: Cancer and Leukemia Group B 9264. J Clin Oncol 16(5): 1811- 1819.

[WHO Handbook] The WHO Handbook for Reporting Results of Cancer Treatment. 1979. Geneva, Switzerland: World Health Organization, 48.

Karnofsky Performance Status Scale

Activity Status	Point	Description
Normal Activity	100	Normal, with no complaints or evidence of disease
	90	Able to carry on normal activity but with minor signs or symptoms of disease present
	80	Normal activity but requiring effort; signs and symptoms of disease more prominent
Self-Care	70	Able to care for self, but unable to work or carry on other normal activities
	60	Able to care for most needs but requires occasional assistance
	50	Considerable assistance required, along with frequent medical care; some self-care still possible
Incapacitated	40	Disabled and requiring special care and assistance
	30	Severely disabled; hospitalization required but death from disease not imminent
	20	Extremely ill; supportive treatment, hospitalized care required
	10	Imminent death
	0	Dead

American Joint Committee on Cancer Staging Criteria for Breast Cancer

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0-2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Primary Tumor (T):
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no tumor
T1 Tumor 2 cm or less in greatest dimension
T1a 0.5 cm or less in greatest dimension
T1b More than 0.5 cm but not more than 1 cm in greatest dimension
T1c More than 1 cm but not more than 2 cm in greatest dimension
T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3 Tumor more than 5 cm in greatest dimension
T4 Tumor of any size with direct extension to chest wall or skin
T4a Extension to chest wall
T4b Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c Both (T4a and T4b)
T4d Inflammatory carcinoma
Note: Paget's disease associated with a tumor is classified according to the size of the tumor.
Regional Lymph Nodes (N):
NX Regional lymph nodes cannot be assessed (for example, previously removed)
N0 No regional lymph node metastasis
N1 Metastasis to movable ipsilateral axillary lymph node(s)
N2 Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures
N3 Metastasis to ipsilateral internal mammary lymph node(s)
Distant Metastasis (M):
M0 No distant metastasis
M1 Distant metastasis (includes metastasis to ipsilateral supraclavicular lymph node[s])

Pharmacokinetic Sampling Information

Pharmacokinetic sampling will be performed at selected sites; these sites are identified in their site-specific letter of agreement. Blood samples will be collected for measurement of gemcitabine, dFdU and paclitaxel concentrations from 12 evaluable patients in the gemcitabine plus paclitaxel arm and 12 evaluable patients in the paclitaxel monotherapy arm.

Blood samples must be collected from the arm opposite to the infusion line. If a heparin lock is used, a minimum of 1 mL of whole blood should be withdrawn and discarded prior to each collection to ensure that the heparin does not contaminate the specimen.

Samples will be collected, processed, and shipped as instructed on the central laboratory requisition. Exact infusion start and stop times (actual clock readings), as well as infusion parameters (concentration of dose solution, total volume delivered, and flow rate settings) for each dose corresponding to pharmacokinetic sampling, will be recorded on the central laboratory requisition. The type of pump used for the infusion will be recorded in the comments section of the laboratory requisition.

In order to compare pharmacokinetics across patients,
- each infusion duration should be as close to 3 hours for paclitaxel and 30 minutes for gemcitabine as practical, and
- gemcitabine should be administered as close to 10 minutes after termination of the paclitaxel infusion as possible. The total volume of blood collected from patients in the gemcitabine plus paclitaxel arm is approximately 215 mL; the total volume of blood collected from patients in the paclitaxel monotherapy arm is approximately 105 mL.

Serial blood samples for both gemcitabine and paclitaxel will be collected from each pharmacokinetic patient in Cycle 1 only at the times listed in Tables JHQG.5.1 through 5.3. It is essential to collect all samples at the specified times on Days 1 through 4 and 8 (as applicable). The exact time of each blood sample collection must be accurately recorded on the requisition (based on the same clock used to record infusion times).

Blood Sampling Collection Times for Patients Participating in the Pharmacokinetic Evaluation: Gemcitabine Plus Paclitaxel on Days 1 through 4, Cycle 1

Sample	Day	Collection times relative to start of paclitaxel infusion	G	P
1	1	0 min (immediately prior to start of paclitaxel infusion)	X	X
2	1	1 hr 30 min		X
3	1	3 hr (immediately prior to end of paclitaxel infusion)		X*
4	1	3 hr 5 min		X
5	1	3 hr 10 min (paclitaxel samples collected immediately prior to start of gemcitabine infusion)		X
6	1	3 hr 25 min	X	X
7	1	3 hr 40 min (immediately prior to end of gemcitabine infusion)	X*	X
8	1	3 hr 45 min	X	
9	1	3 hr 55 min	X	
10	1	4 hr 10 min	X	X
11	1	4 hr 40 min	X	
12	1	5 hr 10 min	X	X
13	1	6 hr		X
14	1	8 hr		X
15	1	10-12 hr		X
16	2	22-26 hr		X
17	2	28-32 hr		X
18	3	46-50 hr		X
19	4	70-74 hr		X

* If for any reason the gemcitabine or paclitaxel infusion is stopped early, then a PK sample must be drawn immediately. Subsequent blood samples must be drawn as scheduled above.

Blood Sampling Collection Times for Patients Participating in the Pharmacokinetic Evaluation: Gemcitabine on Day 8, Cycle 1

Sample	Day	Collection times relative to start of gemcitabine infusion	G
1	8	0 min (immediately prior to start of gemcitabine infusion)	X
2	8	15 min	X
3	8	30 min (immediately prior to end of gemcitabine infusion)	X*
4	8	35 min	X
5	8	45 min	X
6	8	1 hr	X
7	8	1 hr 30 min	X
8	8	2 hr	X

G = gemcitabine/dFdU
* If for any reason the gemcitabine infusion is stopped early, then a PK sample must be drawn immediately. Subsequent blood samples must be drawn as scheduled above.

Blood Sampling Collection Times for Patients Participating in the Pharmacokinetic Evaluation: Paclitaxel Monotherapy on Days 1 through 4, Cycle 1

Sample	Day	Collection times relative to start of paclitaxel infusion	P
1	1	0 min (immediately prior to start of paclitaxel infusion)	X
2	1	1 hr 30 min	X
3	1	3 hr (immediately prior to end of paclitaxel infusion)	X*
4	1	3 hr 5 min	X
5	1	3 hr 15 min	X
6	1	3 hr 30 min	X
7	1	4 hr	X
8	1	4 hr 45 min	X
9	1	6 hr	X
10	1	8 hr	X
11	1	10-12 hr	X
12	2	22-26 hr	X
13	2	28-32 hr	X
14	3	46-50 hr	X
15	4	70-74 hr	X

P = paclitaxel

* If for any reason the paclitaxel infusion is stopped early, then a PK sample must be drawn immediately.

Subsequent blood samples must be drawn as scheduled above.

B1. Brief Pain Inventory (Short Form)

Study ID#_____ Hospital#_____

Do not write above this line

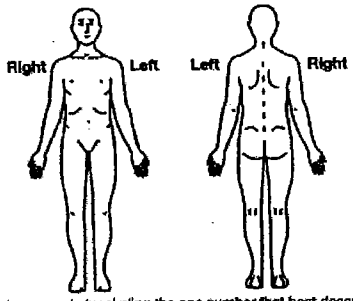
Date: ___/___/___

Time:_____

Name:_____
Last First Middle Initial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today? 1. Yes 2. No

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its worst in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its least in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on the **average**.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

6) Please rate your pain by circling the one number that tells how much pain you have **right now.**

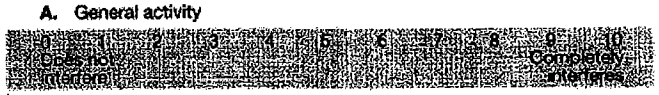
7) What treatments or medications are you receiving for your pain?

---

8) In the past 24 hours, how much **relief** have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

9) Circle the one number that describes how, during the past 24 hours, **pain has interfered** with your:

A. General activity

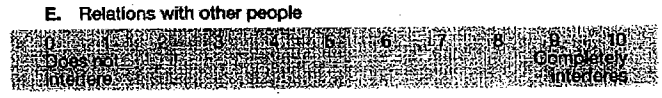


B. Mood

C. Walking ability

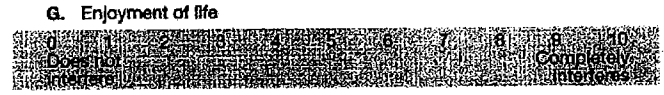
D. Normal work (includes both work outside the home and housework)

E. Relations with other people



F. Sleep

G. Enjoyment of life



Source: Pain Research Group, Department of Neurology, University of Wisconsin-Madison. Used with permission. May be duplicated and used in clinical practice.

Scale for Use of Analgesics for Pain

Codes Description
0 = No analgesia
1 = Aspirin, paracetamol (acetaminophen), NSAIDs
2 = Codeine, dextropropoxyphene, pentazocine, oxycodone
3 = Oral morphine, methadone, transdermal fentanyl
4 = Parenteral opiates
5 = Neurosurgical procedures (blocks)

Rotterdam Symptom Checklist

For the symptoms mentioned, indicate to what extent you have been bothered by it, by circling the answer most applicable to you. The questions are related to the past week.

In this questionnaire you will be asked about your symptoms. Would you please, for all Have you, during the past week, been bothered by

lack of appetite	not at all	a little	quite a bit	very much
irritability	not at all	a little	quite a bit	very much
tiredness	not at all	a little	quite a bit	very much
worrying	not at all	a little	quite a bit	very much
sore muscles	not at all	a little	quite a bit	very much
depressed mood	not at all	a little	quite a bit	very much
lack of energy	not at all	a little	quite a bit	very much
low back pain	not at all	a little	quite a bit	very much
nervousness	not at all	a little	quite a bit	very much
nausea	not at all	a little	quite a bit	very much
despairing about the future	not at all	a little	quite a bit	very much
difficulty sleeping	not at all	a little	quite a bit	very much
headaches	not at all	a little	quite a bit	very much
vomiting	not at all	a little	quite a bit	very much
dizziness	not at all	a little	quite a bit	very much
decreased sexual interest	not at all	a little	quite a bit	very much
tension	not at all	a little	quite a bit	very much
abdominal (stomach) aches	not at all	a little	quite a bit	very much
anxiety	not at all	a little	quite a bit	very much
constipation	not at all	a little	quite a bit	very much
diarrhoea	not at all	a little	quite a bit	very much
acid indigestion	not at all	a little	quite a bit	very much
shivering	not at all	a little	quite a bit	very much
tingling hands or feet	not at all	a little	quite a bit	very much
difficulty concentrating	not at all	a little	quite a bit	very much
sore mouth/pain when swallowing	not at all	a little	quite a bit	very much
loss of hair	not at all	a little	quite a bit	very much
burning/sore eyes	not at all	a little	quite a bit	very much
shortness of breath	not at all	a little	quite a bit	very much
dry mouth	not at all	a little	quite a bit	very much

A number of activities are listed below. We do not want to know whether you actually do these, but only whether you are able to perform them presently. Would you please mark the answer that applies most to your condition of the past week.

	Unable	only with help	without help, with difficulty	without help
care for myself (wash etc.)				
walk about the house				
light housework/household jobs				
climb stairs				
heavy housework/household jobs				
walk out of doors				
go shopping				
go to work				

All things considered, how would you describe your quality of life during the past week?

- excellent
- good
- moderately good
- neither good nor bad
- rather poor
- poor
- extremely poor

Would you please check whether you answered all questions?

Thank you for your help.

Patient Number:

Reference:

de Haes JC, van Knippenberg FC, Neijt JP. 1990. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. Br J Ca 62(6):1034-1038.

Appears This Way
On Original

Appears This Way
On Original

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Martin Cohen
5/19/04 11:26:00 AM
MEDICAL OFFICER

John Johnson
5/19/04 12:22:46 PM
MEDICAL OFFICER
See also my Clinical team Leader Review dated 5/19/04

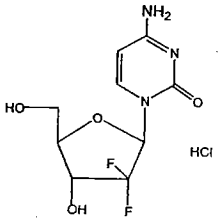
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-509/S029

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION HFD-150 DODP		2. NDA NUMBER 20-509
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S)
6. NAME OF DRUG Gemzar	7. NONPROPRIETARY NAME Gemcitabine HCl for Injection	SE1-029 | 12-17-2003
8. SUPPLEMENT PROVIDES FOR: a new indication for breast cancer.		9. AMENDMENTS DATES BC 5-13-2004
10. PHARMACOLOGICAL CATEGORY Antineoplastic	11. HOW DISPENSED RX √ OTC	12. RELATED IND/NDA/DMF None
13. DOSAGE FORM(S) Lyophilized powder	14. POTENCY 200mg/vial, 1g/vial	
15. CHEMICAL NAME AND STRUCTURE  2'-Deoxy-2',2'-difluorocytidine monohydrochloride (β isomer), $C_9H_{11}F_2N_3O_4.HCl$		16. RECORDS AND REPORTS CURRENT YES √ NO REVIEWED YES √ NO

17. COMMENTS

In this efficacy supplement, the applicant proposed to treat breast cancer using gemcitabine HCl and paclitaxel.

The drug product gemcitabine is an approved anticancer drug in US for use in pancreatic cancer and non small cell lung cancer. Since the discharge of water from sewage treatment facilities in the United States is about 4.07×10^{13} L per year, categorical exclusions apply to active pharmaceutical ingredients that are used in amounts less than 40,700 kg per year (1 ppb = 40,700 kg/4.07×10^{13} L). The total annual use of gemcitabine in the United States will be far less than 40,000 kg per year. This environment assessment indicated that very large margins ———— of safety exist for aquatic organisms that might be exposed to theoretical environmental concentrations of gemcitabine.

Since no manufacturing and control changes have been proposed including drug description and how to supply in the Package Insert and the annual drug production is below 40,700 kg, the claim for categorical exclusions from filing an environmental assessment under CFR 25.31 (b) for gemcitabine is found to be acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval is recommended from standard point of chemistry, manufacturing, and control.

19. REVIEWER

NAM	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.		5-14-2004

DISTRIBUTION	ORIGINAL JACKET	DIVISION FILE	Reviewer: C.Liang HFD-150	CSO: P. Garvey HFD-150	Chemistry Team Leader: Nallaperum Chidambaram HFD-150

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chengyi Liang
5/18/04 11:07:57 AM
CHEMIST

Nallaperumal Chidambaram
5/18/04 05:28:59 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-509/S029

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA /Serial Number:	20-509/SE1/Sn029
Drug Name:	Gemzar (Gemcitabine)
Applicant:	Eli Lilly and Company
Indication(s):	Metastatic Breast Cancer
Date(s):	Submission Date: December 17, 2003
	PDUFA Date: June 17, 2004
	Review Completion Date: May 14, 2004
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I (HFD-710)
Statistical Reviewer:	Rajeshwari Sridhara, Ph.D.
Concurring Reviewer:	Kooros Mahjoob, Ph.D., Acting Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Martin Cohen, M.D. & John Johnson, M.D.
Project Manager:	Ms. Patricia Garvey
Keywords:	Active control/superiority, log-rank test, Cox regression

Table of Contents

1 Executive Summary

1.1 Conclusions and Recommendations

In this reviewer's opinion the study results from a single, randomized, multicenter, open-label, phase III trial support the claim of efficacy based on time to documented progression of disease of the combination of gemcitabine + paclitaxel for patients with nonresectable, locally recurrent, metastatic breast cancer. Whether the endpoint and the size of the effect on this endpoint are adequate for approval is a clinical decision. The interim result of the overall survival analysis suggests a trend in favor of the combination arm. The results of the final analysis of overall survival are not available at this time to confirm superiority of gemcitabine + paclitaxel.

1.2 Brief Overview of Clinical Studies

The sponsor has submitted results of the planned interim analysis from the one phase III, randomized, controlled, open-label clinical trial (registration trial B9E-MC-JHQG, referred as JHQG here after) comparing gemcitabine plus paclitaxel versus paclitaxel in patients with unresectable, locally recurrent or metastatic breast cancer. The sponsor has also provided supportive efficacy data from a phase II, single arm study (B9E-MC-S024).

Study JHQG was a phase III, randomized, open-label, comparative international study in patients with unresectable, locally recurrent or metastatic breast cancer conducted in 529 patients from 98 study centers in 19 countries. Females $\geq$ 18 years old with unresectable, locally recurrent or metastatic breast cancer who have received adjuvant anthracycline-containing chemotherapy and have KPS $\geq$ 70 and adequate organ function and bone marrow reserve, were randomized (1:1) to receive either gemcitabine + paclitaxel or paclitaxel alone.

1.3 Statistical Issues and Findings

This NDA submission is to support administration of gemcitabine with paclitaxel for patients with nonresectable, locally recurrent, metastatic breast cancer. In this NDA submission, study JHQG is the only randomized pivotal study conducted to establish efficacy and safety. This study enrolled a total of 529 patients with 262 patients who received paclitaxel alone and 267 patients who received gemcitabine + paclitaxel. The primary efficacy endpoint of this study was survival. The applicant has submitted this application claiming efficacy based on time to documented progression of disease and is seeking accelerated approval. There was a statistically significant difference between the two treatment arms with

respect to time to documented progression of disease in the ITT population (log-rank test, P-value < 0.0001).

Statistical Issues:

1. This application was submitted based on the interim analysis of the secondary endpoint time to documented progression of disease.
2. At the time of application, the total number of (440) required for the final analysis of overall survival data was not reached.

Findings:

The protocol specified primary analysis was unadjusted log-rank test in the intent-to-treat (ITT) population to compare overall survival between the two treatment arms. The protocol also specified primary analysis at the interim look based on time to documented progression of disease with proper adjustment for overall type I error rate. The current submission is based on the time to documented progression of diseases analysis. This study demonstrates efficacy based on time to documented progression of disease as presented in the following Table A.

Table A: Primary Efficacy Time to Documented Progression of Disease Analysis in as Treated Population

Treatment	Number of Events	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
T	182/262	**2.9** (2.6, 3.7)	0.646 (0.522, 0.801)	**< 0.0001**
GT	157/267	**5.2** (4.2, 5.6)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test

2 Introduction

2.1 Overview

Breast cancer is the most common cancer among women in terms of the number of new cases of cancer reported annually. In Western countries 30% - 40% of patients with breast cancer develop metastatic disease. The development of metastatic disease is usually the cause of death from breast cancer. Chemotherapy is the treatment of choice for patients who have failed hormonal therapy, or are hormone-receptor negative, or have visceral metastases. Chemotherapy agents approved for the treatment of metastatic breast cancer include doxorubicin, epirubicin, docetaxel, and paclitaxel. These agents can be administered as single agents or as combination. Paclitaxel, a taxane, is approved for single-agent use in the treatment of metastatic breast cancer in patients who have failed, or are not candidates for, standard anthracycline-containing therapy. The standard dose of paclitaxel is 175 mg/m2 administered as a 3-hour infusion once every 3 weeks. The reported median time to progressive disease with the standard dose of paclitaxel is approximately 4 months in patients with metastatic breast cancer with prior anthracycline exposure.

2.1.1 Background

Gemcitabine HCL (gemzar) is approved in combination with cisplatin for the treatment of advanced non-small cell lung cancer and is approved as a single agent for the treatment of advanced pancreatic cancer. Single agent gemcitabine has demonstrated activity and tolerability when used as treatment in metastatic breast cancer.

The sponsor has submitted results of the planned interim analysis from the one phase III, randomized, controlled, open-label clinical trial (registration trial B9E-MC-JHQG, referred as JHQG here after) comparing gemcitabine plus paclitaxel versus paclitaxel in patients with unresectable, locally recurrent or metastatic breast cancer. The sponsor has also provided supportive efficacy data from a phase II, single arm study (B9E-MC-S024, referred as S024 hereafter). The main focus of this review will be on results from Study JHQG.

2.1.2 Statistical Issues

1. This application was submitted based on the interim analysis of the secondary endpoint time to documented progression of disease.
2. At the time of application, the total number of (440) required for the final analysis of overall survival data was not reached.

2.2 Data Sources

Data used for review is from the electronic submission received on 12/17/03. The network path is \\Cdsesub1\n20509\S_029\2003-12-17\CLINSTAT\breast ca\control. Specifically, datasets from Study JHQG were reviewed (\\Cdsesub1\n20509\S_029\2003-12-17\CRT\datasets\JHQG, \\Cdsesub1\n20509\S_029\2004-03-15\CRT\Datasets and \\Cdsesub1\n20509\S_029\2004-04-08\CRT\Stats).

3 Statistical Evaluation

3.1 Evaluation of Efficacy

The sponsor has submitted efficacy results from the following two studies:

a) Study S024: First-line therapy with gemcitabine and paclitaxel in locally recurrent or metastatic breast cancer: A phase II study. This is a non-randomized, open-label single arm study conducted in 40 patients from 4 centers (6 investigators), to evaluate the safety and efficacy of gemcitabine with paclitaxel in patients with metastatic breast cancer.
b) Study JHQG: A phase III study of gemcitabine plus paclitaxel versus paclitaxel in patients with unresectable, locally recurrent or metastatic breast cancer. This was a randomized, open-label, comparative study conducted in 529 patients from 98 study centers (in 19 countries), to evaluate safety and efficacy of gemcitabine with paclitaxel compared to paclitaxel alone in patients with metastatic breast cancer.

Reviewer's Comment:

Study S024 is a non-randomized, single arm, open-label study and as such can not evaluate efficacy based on overall survival or time to disease progression. Therefore, this review will focus only on the randomized Study JHQG and particularly on the efficacy aspect of this study.

3.1.1 Study JHQG

Study JHQG was a multicenter international study conducted in patients with advanced breast cancer. This study was initiated on August 11, 1999 and the last patient was enrolled on April 2, 2002. The data cut-off date for the efficacy analysis based on the planned interim analysis submitted in the original submission (submission date 12/17/03) was July 10, 2002.

3.1.1.7.2 Primary Efficacy Analyses

Primary efficacy analysis in this submission is TtDPD based on the planned interim analysis of the data. Regarding overall survival which is the primary efficacy endpoint of the trial, 377 of the 440 deaths have occurred as of 30 January 2004. A final analysis of survival will be conducted in future by the applicant when the planned 440 deaths have occurred. As specified in the protocol, comparing TtDPD between T and GT, in the ITT population using unadjusted log-rank test is presented in Tables 2 (same as reported by the sponsor), 3 & 4. There were a total of 339/538 patients who had events (documented progression of disease) at the time of analysis. The Kaplan-Meier curves for the ITT population are illustrated in Figure 1. Kaplan-Meier curves for the ITT population based on the interim survival analysis (Tables 5, 6, & 7) are illustrated in Figure 2.

Table 2: Primary Efficacy Time to Documented Progression of Disease Analysis in as Treated Population

Treatment	Number of Events	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
T	182/262	**2.9** (2.6, 3.7)	0.646	**< 0.0001**
GT	157/267	**5.2** (4.2, 5.6)	(0.522, 0.801)	

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test.

Table 3: Primary Efficacy Time to Documented Progression of Disease Analysis in as Randomized Population

Treatment	Number of Events	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
T	183/262	**3.0** (2.6, 3.7)	0.645	**< 0.0001**
GT	156/267	**5.3** (4.2, 5.7)	(0.520, 0.799)	

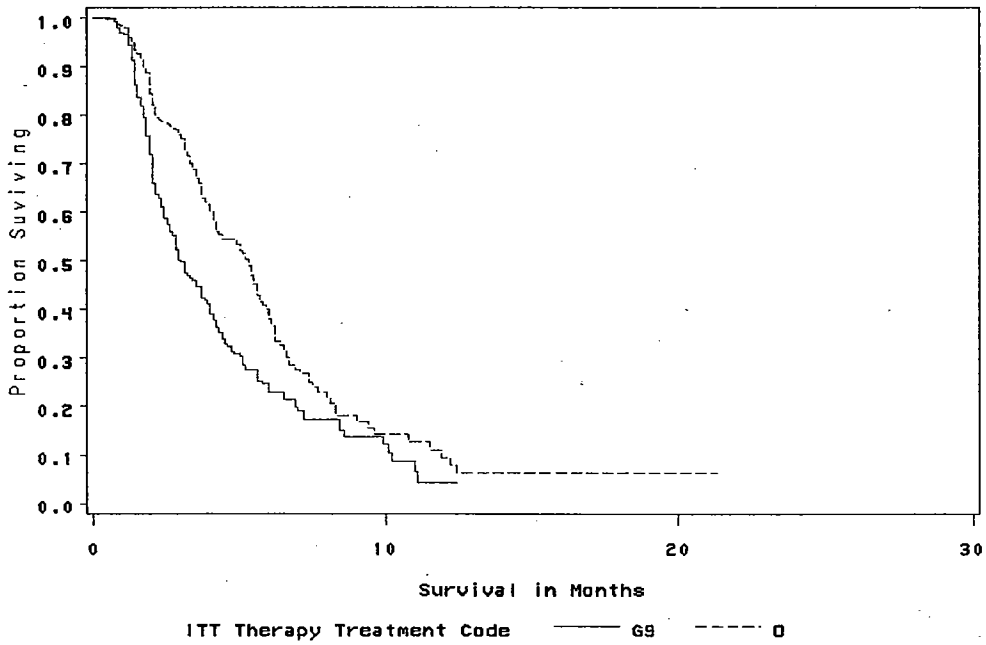
[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test.

Table 4: Primary Efficacy Time to Documented Progression of Disease Analysis Excluding Patient # 531*

Treatment	Number of Events	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
T	182/262	**2.9** (2.6, 3.7)	0.645	**< 0.0001**
GT	156/266	**5.3** (4.2, 5.7)	(0.520, 0.800)	

*: This patient was treated in GT arm but the randomization code was T; [1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test.

Figure 1: Kaplan-Meier Time to Documented Progression of Disease Curves in the ITT Population



(G9 = Taxol, O = Gemzar + Taxol)

Table 5: Interim Survival Analysis in the Population as Treated

Treatment	Number of Events	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
T	194/262	**15.8** (14.4, 17.4)	0.823 (0.673, 1.008)	**0.0592**
GT	183/267	**18.6** (16.5, 20.7)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test.

Table 6: Interim Survival Analysis in the Population as Randomized

Treatment	Number of Events	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
T	195/262	**15.8** (14.4, 17.4)	0.817 (0.667, 1.000)	**0.0489**
GT	182/267	**18.6** (16.6, 20.7)		

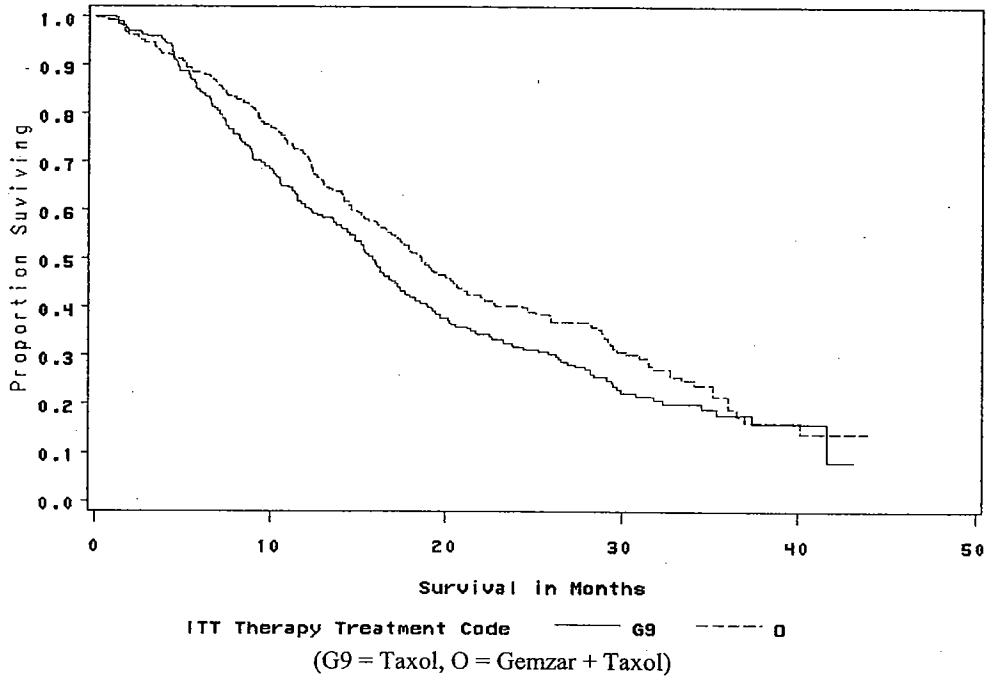
[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test.

Table 7: Interim Survival Analysis Excluding Patient # 531*

Treatment	Number of Events	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
T	194/262	**15.8** (14.4, 17.4)	0.820 (0.669, 1.004)	**0.0538**
GT	182/266	**18.6** (16.6, 20.7)		

*: This patient was treated in GT arm but the randomization code was T; [1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test.

Figure 2: Kaplan-Meier Survival Curves in the ITT Population (Interim Analysis)



(G9 = Taxol, O = Gemzar + Taxol)

Reviewer's Comments:

1. The final analysis of the time to documented progression of disease demonstrates superiority of the combination GT over T with respect to TtDPD (Tables 2, 3 & 4 and Figure 1).
2. The applicant in their submission had originally claimed that the medians were 3.5 months (95% CI: 2.9, 4.0) in T arm and 5.4 months (95% CI: 4.6, 6.1) in GT arm (HR=0.734, P-value=0.0015 with 441 progression events observed). However, the results presented in the Table 2 and Figure 1 are based on the consensus reached by the Medical Reviewer and the applicant (please refer to clinical review of this application for further details on this progression event resolution).
3. The applicant has submitted two sets of treatment codes (THERTRTC (as treated) and TRTCITT(per randomization code)) assigned to the patients at randomization. Depending on the treatment code used to define the treatment arm, the p-value is above or below 0.05 as presented in Tables 5 & 6. There was only one patient (# 531) in whom the two treatment codes

were not the same, i.e., this patient was assigned to T alone arm, but was documented and treated in GT arm. If this patient data is excluded from the analysis then the p-value is 0.0538 as presented in Table 7.

4. Results of the interim survival analysis suggest a trend in favor of GT arm.

3.1.1.7.3 Exploratory Covariate Adjusted TtDPD Analyses

The applicant has conducted a supportive covariate adjusted analysis using Cox model. The results of FDA analysis are as detailed in Table 8 below.

Table 8: Cox's Proportional Hazard Model Adjusting for Covariates in the ITT Population using the Time to Documented Progression of Disease Data (Excluding Patient # 531)

Covariates	Hazard Ratio	95% C.I.	P-value[1]
Treatment (GT/T)	0.639	0.514, 0.795	< 0.0001
Age	0.986	0.976, 0.997	0.0145
KPS	0.861	0.673, 1.102	0.2344
Number of Tumor Sites	1.127	1.040, 1.220	0.0034
Hormone Receptor Status: Negative	1.256	0.943, 1.673	0.1186
Unknown	1.142	0.862, 1.514	0.3552
Visceral Metastases	1.481	1.124, 1.950	0.0052
Prior Radiotherapy	1.163	0.912, 1.482	0.2230
Prior Hormonal Therapy	0.858	0.676, 1.088	0.2070
Prior Anthracycline Therapy in Adjuvant Setting	1.029	0.759, 1.396	0.8531
Time from Diagnosis to Randomization	0.993	0.947, 1.040	0.7573

[1]: P-values not adjusted for multiplicity

Reviewer's Comments:

The adjusted analysis supports the primary unadjusted analysis.

3.1.1.7.4 Secondary Efficacy Analyses

The protocol specified secondary endpoints included objective response (complete response (CR) and partial response (PR)) and duration of response among responders. The applicant had submitted investigator determined responses and independent reviewer responses. The results presented in the Table 9 below are the responses reconciled after review by the Medical Reviewer with the applicant (please refer to clinical review of this application for details on reconciliation of evaluation of response).

Objective Response Rate

Table 9: Objective Response Rate by Treatment Arm

Response Category	T (N=262)		GT (N=267)	
	# of Responders	95% CI	# of Responders	95% CI
CR	6 (2.3%)	(0.08, 4.9)	10 (3.7%)	(1.8, 6.8)
PR	52 (19.9%)	(15.2, 25.2)	99 (37.1%)	(31.3, 43.2)
ORR = CR + PR	58 (22.1%)	(17.3, 27.7)	109 (40.8%)	(34.9, 47.0)
P-value	< 0.0001			
Odds-Ratio	0.412 (95% CI: 0.282, 0.602)			

Reviewer's Comments:

1. The reconciled overall response rate (ORR) in the GT arm was significantly larger compared T alone arm as presented in Table 5.
2. The investigator assessed ORR in the T alone arm was 49/262(18.7%; 9 CR and 40 PR) and in the GT arm was 93/267 (34.8%; 14 CR and 79 PR).
3. The independent reviewer assessed ORR in the T alone arm was 29/262 (11.1%; 1 CR and 28 PR) and in the GT arm was 65/267 (24.3%; 6 CR and 59 PR).

Table 6: Duration of Response* in Responders

Duration in Months	T (N = 58)	GT (N = 106[1])
Mean[2] (S.D.)	4.3 (1.9)	4.3 (2.9)
Median[2] (Range)	3.9 (0.9- 9.9)	3.6 (0.1 to 19.5)
KM Estimate of Median (95% CI)	5.7 (5.1, 6.5)	5.0 (4.6, 6.9)
Proportion Censored	28/58	59/109
P-value (log-rank test)	0.5804	

*: Duration measured from date of response to progression (per FDA definition); [1]: 3 patients who had PR and did not have documented progression date were not included in this analysis; [2]: Censoring was ignored in this computation

Reviewer's Comment:

There was no difference in the duration of response between the two treatment arms.

Health Outcomes: Brief Pain Inventory and Analgesic Level

The applicant has reported that 151 patients on the GT arm and 150 patients on the T arm completed at least one brief pain inventory (BPI). A total of 231 patients (43.7%) did not complete the BPI because of lack of validated translations and 7 patients did not complete the BPI for other reasons. There was no statistically significant difference in the rating of worst pain between the two treatment arms. There was also no difference in the pattern of change between the two treatment arms.

3.2 Evaluation of Safety

Please refer to Clinical Review of this application for safety evaluation.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

Efficacy by gender was not analyzed since all the patients in the study were females. Efficacy by age (< 65 years vs. ≥ 65 years was analyzed by conducting exploratory TtDPD and survival analyses. The results of these analyses are presented in Tables 11 and 12. Efficacy by ethnic origin with respect to time to documented progression of disease and overall survival (Caucasian and Non-Caucasian) are presented in Tables 13 and 14.

Table 11: Exploratory Time to Documented Progression of Disease Analysis by Age Group (Excluding Patient # 531)

Age Group	Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
< 65 yrs	T	160/220	2.9 (2.4, 3.7)	0.656 (0.521, 0.825)	0.0002
	GT	135/228	5.2 (4.2, 5.6)		
≥ 65 yrs	T	22/42	3.5 (2.5, 5.1)	0.610 (0.332, 1.121)	0.1046
	GT	21/38	5.4 (3.7, 11.5)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T;
[3]: unadjusted log-rank test and not adjusted for multiple analyses.

Table 12: Exploratory Survival Analysis by Age Group (Excluding Patient # 531)

Age Group	Treatment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
< 65 yrs	T	163/220	15.6 (13.6, 17.2)	0.872 (0.700, 1.085)	0.2185
	GT	159/228	17.3 (14.6, 19.9)		
≥ 65 yrs	T	31/42	19.4 (13.6, 25.3)	0.555 (0.322, 0.958)	0.0317
	GT	23/38	28.8 (19.2, 33.4)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test and not adjusted for multiple analyses.

Table 13: Exploratory Time to Documented Progression of Disease Analysis by Gender (Excluding Patient # 531)

Origin	Treat-ment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
Caucasians	T	115/159	2.8 (2.4, 3.7)	0.555 (0.423, 0.728)	< 0.0001
	GT	98/157	5.1 (4.2, 5.7)		
Non-Caucasians	T	67/103	3.2 (2.7, 4.5)	0.799 (0.562, 1.137)	0.2055
	GT	58/109	5.4 (3.7, 6.2)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test and not adjusted for multiple analyses.

Table 14: Exploratory Survival Analysis by Gender (Excluding Patient # 531)

Origin	Treat-ment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
Caucasians	T	123/159	15.4 (12.6, 17.4)	0.668 (0.514, 0.868)	0.0023
	GT	104/157	20.3 (17.9, 26.0)		
Non-Caucasians	T	71/103	16.4 (14.0, 19.2)	1.135 (0.822, 1.567)	0.4414
	GT	78/109	16.5 (13.0, 20.2)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test and not adjusted for multiple analyses.

Reviewer's Comments:

1. The treatment effect appears to be similar in younger (< 65 years) and older (≥ 65 years) patients.
2. The treatment effect appears to be similar in Caucasians and Non-Caucasians.

4.2 Other Special/Subgroup Populations

Effect by hormone receptor status was evaluated by conducting an exploratory time to documented progression of disease and survival analysis. The results of this analysis are presented in Tables 15 & 16.

Table 15: Exploratory Time to Documented Progression of Disease Analysis by Receptor Status (Excluding patient # 531)

Receptor Status	Treat-ment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
Positive	T	67/103	2.9 (2.3, 3.9)	0.565 (0.394, 0.811)	0.0015
	GT	57/102	6.0 (5.3, 6.6)		
Negative	T	66/84	3.1 (2.4, 3.7)	0.602 (0.419, 0.866)	0.0050
	GT	54/78	4.4 (3.5, 6.0)		
Unknown	T	49/75	3.5 (2.1, 4.8)	0.825 (0.547, 1.247)	0.3556
	GT	45/86	4.3 (3.7, 5.5)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test and not adjusted for multiple analyses.

Table 16: Exploratory Survival Analysis by Receptor Status (Excluding patient # 531)

Receptor Status	Treat-ment	Number of Deaths	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
Positive	T	67/103	18.9 (15.3, 25.3)	0.853 (0.604, 1.204)	0.3656
	GT	63/102	24.6 (17.9, 28.8)		
Negative	T	70/84	15.6 (11.5, 17.9)	0.782 (0.550, 1.112)	0.1702
	GT	56/78	17.6 (14.5, 21.1)		
Unknown	T	57/75	13.0 (10.2, 16.7)	0.822 (0.573, 1.179)	0.2857
	GT	63/86	15.6 (12.2, 20.4)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test and not adjusted for multiple analyses.

Reviewer's Comments:

The treatment effect appears to be similar in all the hormone receptor status category.

5 Summary and Conclusions

This NDA submission is to support administration of gemcitabine with paclitaxel for patients with nonresectable, locally recurrent, metastatic breast cancer. In this NDA submission, study JHQG is the only randomized pivotal study conducted to establish efficacy and safety. This study enrolled a total of 529 patients with 262 patients who received paclitaxel alone and 267 patients who received gemcitabine + paclitaxel. The primary efficacy endpoint of this study was survival. The applicant has submitted this application claiming efficacy based on time to documented progression of disease and is seeking accelerated approval. There was a statistically significant difference between the two treatment arms with respect to time to documented progression of disease in the ITT population (log-rank test, P-value < 0.0001).

5.1 Statistical Issues and Collective Evidence

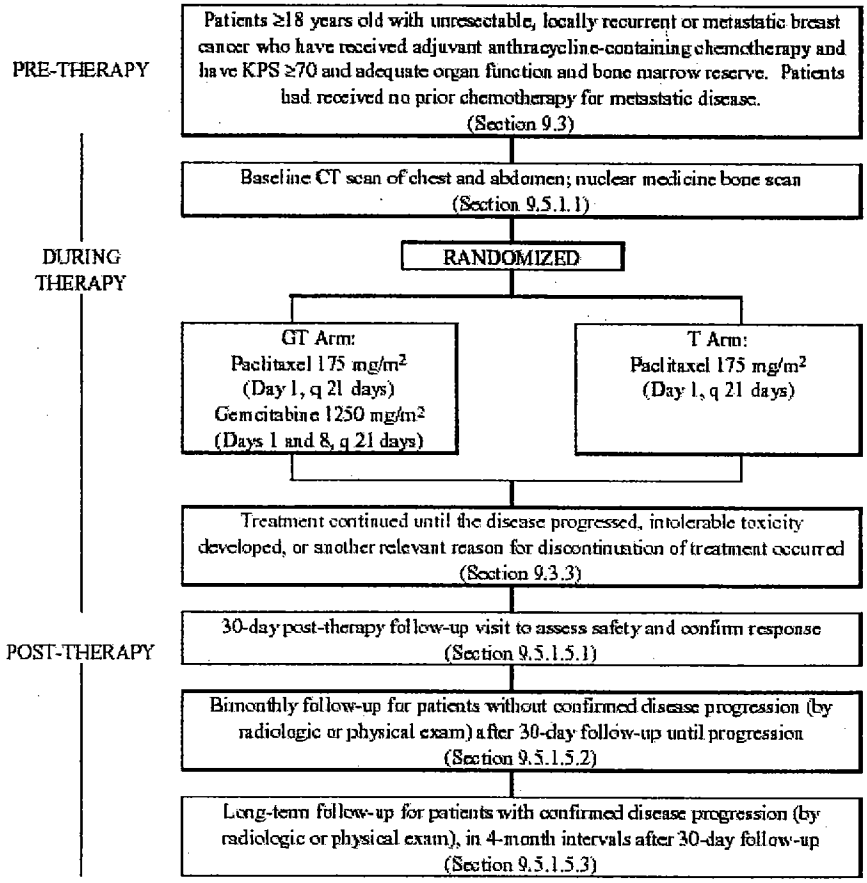
1. This application was submitted based on the interim analysis of the secondary endpoint time to documented progression of disease.
2. The results of the one randomized open-label study conducted in patients with metastatic breast cancer demonstrates claim of efficacy in the combination GT arm based on time to documented progression of disease (HR=0.645, log-rank test p-value < 0.0001).
3. The primary endpoint of the study is overall survival. At the time of this application a final analysis of the overall survival has not been completed as the planned number of events (440 deaths) has not been reached. The interim results of survival analysis suggest a trend in favor of the combination arm.
4. The overall response rate was significantly higher in the combination arm.

5.2 Conclusions and Recommendations

In this reviewer's opinion the study results from a single, randomized, multicenter, open-label, phase III trial support the claim of efficacy based on time to documented progression of disease of the combination of gemcitabine + paclitaxel for patients with nonresectable, locally recurrent, metastatic breast cancer. Whether the endpoint and the size of the effect on this endpoint are adequate for approval is a clinical decision. The interim result of the overall survival analysis suggests a trend in favor of the combination arm. The results of the final analysis of overall survival are not available at this time to confirm superiority of gemcitabine + paclitaxel.

APPENDICES

Appendix 1: Study Design Schema (extracted from Applicant's report)



Appendix 2: Randomization

Protocol B9E-MC-JHQG

Randomization and Stratification

To achieve a high probability of balance between treatment arms with respect to certain baseline prognostic variables, this study will randomize patients using the algorithm of Pocock and Simon (1975). To illustrate the algorithm, this attachment presents a hypothetical example of patient assignment, balancing for the factors specified in Section 3.6.1 and listed below. (To simplify the illustration of how the algorithm works, this example assumes the use of only four investigational centers.) The following table provides a list of the prognostic factors and levels for each one used in this example.

Definition of Randomization Factors

Prognostic Factor	Abbreviation	Levels
Karnofsky Performance Status	KPS	Low (70-80), High (90-100)
Prior anthracycline therapy	PA	Yes, Contraindicated
Prior hormonal therapy	HTx	Yes, No
Presence of visceral metastases	VMETS	Yes, No
Disease progression with prior adjuvant chemotherapy	PD/PAC	≤6 months, >6 months
Investigational center	IC	C1, C2, C3, C4

The following hypothetical example demonstrates the supposition that 30 patients have been enrolled, with 18 assigned to the gemcitabine/paclitaxel [GT] combination and 12 assigned to paclitaxel [T] monotherapy. The following set of tables lists the number of patients by factor level assigned to each regimen, summarizing the entire history of the randomization for these first 30 patients.

Hypothetical Example of Randomization History (First 30 patients)

IC	GT	T
C1	3	4
C2	5	2
C3	6	4
C4	4	2

PA	GT	T
Adjuvant/ Neo-	18	12
Contraind	0	0

KPS	GT	T
Low (70-80)	7	5
High (90-100)	11	7

HTx	GT	T
Yes	15	11
No	3	1

PD/PAC	GT	T
≤6 months	7	6
>6 months	11	6

VMETS	GT	T
Yes	11	3
No	7	9

Given the supposition that the 31st patient presents with the following factor levels—center C3, KPS = 70, prior adjuvant/neoadjuvant anthracycline therapy, no visceral metastases, prior hormonal therapy, and progression ≤6 months with previous adjuvant chemotherapy—the following logic applies:

The algorithm defines the amount of imbalance between treatment arms (with respect to the 31st patient's levels) as the sum of the absolute differences between arms for each factor. The two tables presented below show the amounts of imbalance (for this patient's combination of levels) for assigning this patient to each of the two treatments. If the patient were assigned to the combination regimen, the overall measure of imbalance would be 21, as shown in the first table. If the patient were assigned to paclitaxel monotherapy, the overall measure of imbalance would be 13, as shown in the second table. These measures indicate that the treatment arms would be more balanced with respect to these 6 factors if the patient were assigned to paclitaxel monotherapy.

Measure of Imbalance for Assignment to the Combination Arm

Factor Levels	GT	T	Absolute Difference
Center C3	7	4	3
Low KPS	8	5	3
PA	19	12	7
Prior HTx	16	11	5
No VMETS	8	9	1
PD ≤6 months with PAC	8	6	2
Total			21

Measure of Imbalance for Assignment to the Monotherapy Arm

Factor Levels	GT	T	Absolute Difference
Center C3	6	5	1
Low KPS	7	6	1
PA	18	13	5
Prior HTx	15	12	3
No VMETS	7	10	3
PD ≤6 months with PAC	7	7	0
Total			13

Allocation Rule

Assignment of patients to treatments in this study follows the method of Pocock and Simon (1975), applied using a probability component of 0.75. The treatment allocation

resulting in the smaller overall measure of imbalance (as in the tables above) is performed with probability p=0.75. In this example, the 31st patient will be assigned to paclitaxel with probability 0.75 or gemcitabine/paclitaxel with probability p=0.25. This allocation scheme focuses on achieving an approximate balance with respect to the predefined factors, but this allocation scheme also includes a random component that tends to balance arms generally with respect to any other prognostic factors.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Rajeshwari Sridhara, Ph.D.
Date:

Concurring Reviewer: Kooros Mahjoob, Ph.D.,
Acting Director, Division of Biometrics
Date:

cc:
HFD-150/P. Garvey
HFD-150/M. Cohen
HFD-150/J. Johnson
HFD-710/R. Sridhara
HFD-710/K. Mahjoob
HFD-700/S. Dubey
HFD-700/C. Anello

c:\NDA\allos\20509_statrev_RS.doc

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rajeshwari Sridhara
5/14/04 04:51:18 PM
BIOMETRICS

Kooros Mahjoob
5/15/04 05:15:39 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-509/S029
Administrative/Correspondence

Debarment Certification

NDA Application No.: 20-509

Drug Name: **Gemzar**

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Debasish F. Roychowdhury, M.D., hereby certifies that it did not knowingly and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: D. Roychowdhury
Debasish F. Roychowdhury, M.D.

Title: Director, U.S. Regulatory Affairs

Date: November 12, 2003

See Note to File on Disqualification

JHQG Disqualification of Investigator
Note to File

At the time Study JHQG was initiated, Lilly was not aware of any investigators or sub-investigators who had been debarred by the FDA.

In December 2001, Lilly became aware that investigator #113 (Dr. John Ellerton) at Southern Nevada Cancer Research Foundation was using a sub-investigator _____ that was listed on FDA's Disqualified/Totally Restricted List for clinical investigators. Lilly reported this incident to FDA's DSI on December 18, 2001 and halted further enrollment from this site. The study report discusses how the data were handled (See protocol violations).

In June 2002, Lilly became aware that investigator #46 (Dr. Nasurdi) at an Argentina investigational site was found to have significant GCP violations. Lilly terminated this investigator from the trial. Patients were transferred to another treating oncologist but data were not utilized in Study JHQG. The final study report discusses how the data were not used from Site #46. This site was also listed in the protocol violations section of the report.

D. Roychf

Debasish Roychowdhury, MD
Director, U.S. Regulatory Affairs
Eli Lilly and Co.

PEDIATRIC PAGE

NDA/BLA # : 20-509 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** 029

Stamp Date: December 18, 2003 **Action Date:** June 18, 2004

HFD -150 **Trade and generic names/dosage form:** Gemzar (gemcitabine HCl) injection

Applicant: Lilly **Therapeutic Class:** Cytotoxic

Indication(s) previously approved: pancreatic cancer ; non-small cell lung cancer

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: for use with paclitaxel for unresectable, locally recurrent, or metastatic breast cancer

Is there a full waiver for this indication (check one)?

■ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
X **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.**	**yr.**	**Tanner Stage**	
Max	**kg**	**mo.**	**yr.**	**Tanner Stage**	

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA
HFD-960/Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 10-14-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dotti Pease
2/12/04 12:02:39 PM

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-509 sNDA

NAME OF APPLICANT / NDA HOLDER
Eli Lilly and Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
GEMZAR

ACTIVE INGREDIENT(S)	STRENGTH(S)
gemcitabine	Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl

DOSAGE FORM
sterile lyophilized powder for intravanous infusion

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,808,614	2/28/1989	5/15/2010

d. Name of Patent Owner	Address *(of Patent Owner)*	
Eli Lilly and Company	P.O. Box 6288	
	City/State: Indianapolis, IN	
	ZIP Code: 46206-6288	FAX Number *(if available)*: 317-276-3861
	Telephone Number: 317-276-2958	E-Mail Address *(if available)*: patents@lilly.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
General Patent Counsel, Eli Lilly and Company	P.O. Box 6288	
	City/State: Indianapolis, IN	
	ZIP Code: 46206-6288	FAX Number *(if available)*: 317-276-3861
	Telephone Number: 317-376-2958	E-Mail Address *(if available)*: patents@lilly.com

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
EAMcGraw	9-30-2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☒ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Elizabeth A. McGraw	
Address P.O. Box 6288	City/State Indianapolis, IN
ZIP Code 46206-6288	Telephone Number 317-277-7443
FAX Number *(if available)* 317-276-3861	E-Mail Address *(if available)* patents@lilly.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-509 sNDA

NAME OF APPLICANT / NDA HOLDER
Eli Lilly and Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
GEMZAR

ACTIVE INGREDIENT(S)
gemcitabine

STRENGTH(S)
Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl

DOSAGE FORM
sterile lyophilized powder for intravanous infusion

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

or each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,464,826

b. Issue Date of Patent
11/7/1995

c. Expiration Date of Patent
11/7/2012

d. Name of Patent Owner
Eli Lilly and Company

Address *(of Patent Owner)*
P.O. Box 6288

City/State
Indianapolis, IN

ZIP Code
46206-6288

FAX Number *(if available)*
317-276-3861

Telephone Number
317-276-2958

E-Mail Address *(if available)*
patents@lilly.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

General Patent Counsel,
Eli Lilly and Company

Address *(of agent or representative named in 1.e.)*
P.O. Box 6288

City/State
Indianapolis, IN

ZIP Code
46206-6288

FAX Number *(if available)*
317-276-3861

Telephone Number
317-376-2958

E-Mail Address *(if available)*
patents@lilly.com

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2 Drug Substance (Active Ingredient)

.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

Drug Product (Composition/Formulation)

.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2	Patent Claim Number *(as listed in the patent)* 1	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Breast Cancer — Gemzar is indicated in combination with paclitaxel for the first-line treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy.	

4.2	Patent Claim Number *(as listed in the patent)* 2	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Breast Cancer — Gemzar is indicated in combination with paclitaxel for the first-line treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy.	

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
6	☒ Yes ☐ No
.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Breast Cancer — Gemzar is indicated in combination with paclitaxel for the first-line treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy.

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
7	☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Breast Cancer — Gemzar is indicated in combination with paclitaxel for the first-line treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

Appears This Way
On Original

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
EA McGraw	9-30-2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☒ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Elizabeth A. McGraw	
Address P.O. Box 6288	City/State Indianapolis, IN
ZIP Code 46206-6288	Telephone Number 317-277-7443
FAX Number *(if available)* 317-276-3861	E-Mail Address *(if available)* patents@lilly.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

ITEM 14: PATENT CERTIFICATION

NDA 20-509
GEMZAR
(gemcitabine hydrochloride)

Eli Lilly and Company (Lilly) claims a three year period of exclusivity for the use of gemcitabine hydrochloride in the treatment which is sought in this supplemental NDA, as provided by 21 C.F.R. 314.108(b)(5).

Clinical trials conducted which are essential to approval of this supplemental NDA include:

(B9E-MC-JHQG)

As required by 21 C.F.R. 314.50(j)(4), Lilly certifies that to the best of Lilly's knowledge:

1. each of the above clinical investigations included in this supplemental NDA meets the definition of "new clinical investigation" as set forth in 21 C.F.R. 314.108(a);

2. the above clinical investigations are "essential to approval" of this supplemental NDA. Lilly, through its employees and others, have electronically searched the Scientific literature via Mbase, Medline, Cancerlit, Derwent, Biosys, and SciResearch and has discovered a number of publicly available reports relevant to the use of gemcitabine hydrochloride in the treatment which is sought in this supplemental NDA. This supplemental NDA contains a complete bibliography of these publicly available reports.

3. In Lilly's opinion, the publicly available reports are insufficient to support the approval of this application for a number of reasons, for example:

   a. most of the reports are not "adequate and well-controlled trials" as required by 314.126. The majority are Phase 1 or Phase 2 non-randomized studies;
   b. those reports meeting the "adequate and well-controlled trial" definition are the Lilly-conducted studies being submitted as essential to approval;
   c. according to 314.50(f)(1) and (2), publications alone are insufficient for approval. Case report tabulations and case report forms must be provided for "A and W-C" trials.

In Lilly's opinion, and to the best of Lilly's knowledge, the publicly available reports do not provide a sufficient basis for the approval of the conditions for which Lilly is seeking approval without reference to the new clinical investigations in this application.

4. the above clinical investigations were each conducted or sponsored by Lilly. Lilly was the sponsor named in the Form FDA-1571 of IND number IND 29,653 under which the new clinical investigation(s) that is essential to the approval of this application was conducted.

Elizabeth Beaird

Debasish F. Roychowdhury, M.D.
Director, US Regulatory Affairs

November 13, 2003
Date

Appears This Way
On Original

EXCLUSIVITY SUMMARY FOR NDA # 20-509 SUPPL # 029

Trade Name: Gemzar® for Injection Generic Name: gemcitabine HCl

Applicant Name: Eli Lilly and Company HFD# 150

Approval Date: May 19, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES / **X** / NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) - SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / **X** / NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES / **X** / NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO / **X** /

If the answer to the above question is YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO / **X** /

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / **X** / NO /___/

If "yes," identify the approved drug product(s) containing the

active moiety, and, if known, the NDA #(s).

NDA# 20-509 Gemzar

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO / **X** /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than

bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / **X** / NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / **X** / NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / **X** / NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO / **X** /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

B9E-MC-JHQG

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support

the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO / **X** /

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO / **X** /

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

B9E-MC-JHQG _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50

percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 29,653 YES / X / ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____ _____
Patty Garvey, R.Ph. Date
Regulatory Project Manager

_____ _____
Richard Pazdur, M.D. Date
Signature of Division Director

Form OGD-011347 Revised 05/10/2004

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
5/19/04 02:04:55 PM

MEETING MINUTES

MEETING DATE: May 8, 2003 **TIME:** 3:00 pm **LOCATION:**WOC2/rm 3004

IND: 29,653 **Meeting Request Submission Date:** 3-3-03; sn942
FDA Response Date: 3-13-03
Briefing Document Submission Date: 4-4-03; sn951

DRUG: Gemzar® (gemcitabine HCl, LY188011)

SPONSOR/APPLICANT: Eli Lilly & Company

TYPE of MEETING:

1. Pre-sNDA

2. **Proposed Indications (from briefing package):**
   Gemzar, in combination with paclitaxel, is indicated [redacted] patients with locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy.[redacted]

FDA PARTICIPANTS:

	Grant Williams, M.D.	--	Deputy Director, Division of Oncology Drug Products
	John Johnson, M.D.	--	Medical Team Leader
	Martin Cohen, M.D.	--	Medical Reviewer
	Ning Li, Ph.D.	--	Statistical Reviewer
	Anne Zajicek, M.D., Pharm.D.	--	Clinical Pharmacology & Biopharmaceutics Reviewer
	Patty Garvey, R.Ph.	--	Project Manager
At pre-meeting:	Richard Pazdur, M.D.	--	Director, Division of Oncology Drug Products

INDUSTRY PARTICIPANTS:

Norma Ascroft, Pharm.D.	--	Regulatory Research Scientist
Allen Melemed, M.D.	--	Sr. Clinical Research Physician
Binh Nguyen, M.D., Ph.D.	--	Medical Director
Patrick Peterson, Ph.D.	--	Sr. Statistician
Debasish Roychowdhury, M.D.	--	US Regulatory Affairs Director
Brian Stuglik	--	Director of Oncology Operations
Jun Wu, M.D.	--	Assistant Sr. Statistician

BACKGROUND:

Lilly previously submitted a concise summary of study results based on the interim analysis in the form of the European Expert Report in the December 5, 2002 submission, serial no. 917. Lilly initiated the global, randomized, phase 3 clinical trial of Gemzar plus paclitaxel versus paclitaxel in patients with unresectable, locally recurrent or metastatic breast cancer in September 1999 (September 9, 1999, serial no. 714; March 23, 2001, serial no. 800; and January 4, 2002, serial no. 851) with overall survival as the primary endpoint

and time to documented progression of disease (TtDPD) as a secondary endpoint. The protocol states TtDPD would be the primary endpoint for the interim analysis. The trial has completed enrollment. The study's planned interim datalock for safety and efficacy occurred August 1, 2002. As of August 1, 2002, only 19 patients remained on treatment and of the 529 patients, 411 patients had progressive disease, as determined by the investigators.

MEETING OBJECTIVES (from briefing document):

To discuss a possible submission based on the Study JHQG interim study results. If the FDA is acceptable to a possible submission to the U.S., additional discussions may be needed regarding the specifics of a NDA package.

QUESTION for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:

NOTE: Lilly received the Division's comments via facsimile on May 6, 2003.

During the course of the meeting, there were additional agreements between the Division and Lilly. These agreements are italicized under the discussion section.

---

1. Does FDA agree the process in which Lilly followed the endpoint of time to documented progressive disease (TtDPD), including the blinded independent review, meets the rigor for evaluating this endpoint for a labeled indication in metastatic breast cancer?

   FDA: **The FDA agrees with eliminating tumor progressions based only on symptoms and death without documented progression as events in the TTP analysis.**

   The protocol is not clear on the frequency of tumor assessments during therapy. Apparently tumor assessments were done every 2 months after therapy was completed.

   The FDA does not agree with basing tumor progression on a single new bone scan lesion.

   Apparently only sites of known disease were followed during the study for assessment of tumor progression. This would miss new sites of disease elsewhere which are a frequent determinant for tumor progression.

2. Based on the risk-benefit ratio in study JHQG (significance in response rate, TtDPD, progression-free survival, and acceptable toxicity profile and positive trends in disease-related symptoms), does FDA agree the data are acceptable for filing for full approval of Gemzar in combination with paclitaxel for the treatment of metastatic breast cancer?

FDA: The Gemzar SNDA is acceptable for filing. However, approvability is questionable. You should study the transcript of the June 1999 ODAC meeting before deciding whether to file the application.

We note that the modest reported increase in median TTP of 1.9 months (5.4 mo vs 3.5 mo) is generally not reflected in a favorable effect on the various QOL assessments. Grade 3 or 4 toxicity was also higher on the Gemzar treatment arm.

Generally a minimum of two adequate and well-controlled studies are required for approval. Is there a second adequate and well-controlled study?

Please explain why survival data will not be available until 2005. It appears that 88% of the patients must be dead before the survival analysis can be done. This is an unusually high required proportion of deaths and will significantly delay the survival analysis. Most of the patients will be dead long before 2005.

First patient randomized	**August 1999**
Last patient randomized	**April 2002**
Data cut-off study report	**July 2002**
Patients on Rx at cut-off	**19**
Progression 424/529 patients	**80%**

Discussion: FDA agreed that one study could be sufficient for approval. The sponsor was directed to refer to the efficacy guidelines on approvability based on one study.

3. Does FDA agree TtDPD, as evaluated in JHQG, is a valid surrogate for overall survival in allowing for an approval based on the surrogate of TtDPD results, knowing that the analysis for overall survival will be available in the future?

FDA: The FDA has considered this issue on innumerable occasions, including consultations with the ODAC, the most recent in June 1999. For patients with initial treatment of advanced metastatic breast cancer the ODAC was quite clear that TTP is not a validated surrogate that could be used for standard full approval. TTP could be the basis for accelerated approval if the magnitude of the effect is sufficiently large and statistically persuasive and if the methodology for assessing progression is acceptable. The FDA is not aware of any recent information that would change this position. Again you should read the transcript to access whether the ODAC would consider the results of your study adequate for accelerated approval, particularly regarding the magnitude of the effect on TTP.

Discussion: FDA requested that if the sponsor uses interim analysis for survival then the sponsor should specify in advance 75% of planned events (440 events) and provide data from DMB directly to the FDA before or during the review. The data provided directly from DMB will ensure blinding to the sponsor. The results of the interim analysis of survival should not be submitted to the FDA unless a sNDA has been submitted.

No additional alpha penalty will be incurred due to the single interim survival analysis at 75% of planned events.

ACTION ITEMS:

The sponsor will provide a proposal on the process of providing the interim data to be filed.

There were no unresolved issues. The meeting concluded at 4:20 p.m.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Project Manager

Concurrence Chair:

{See appended electronic signature page}

Martin Cohen, M.D.
Medical Officer

Concurrence: M.Cohen/5-21-03
J. Johnson/5-21-03

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Martin Cohen
6/6/03 09:09:57 AM

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Thierry Kern – Eli Lilly & Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-9254	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	May 19, 2004
Re:	NDA 20-509/S-029 Gemzar		

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Thierry,

Please refer to your sNDA 20-509/S-029 Gemzar – breast cancer indication. The following postmarketing commitment has been revised with a new due date of 6 months instead of the 4 months as previously indicated in our facsimile dated May 19, 2004. The new due dated is based on your verbal agreement to our facsimile.

- Complete study B9E-MC-JHQG (Multi-center, Phase 3 Study of Gemcitabine Plus Paclitaxel Versus Paclitaxel in Patients with Unresectable, Locally Recurrent or Metastatic Breast Cancer). Submit the final analysis of overall survival when the protocol specified number of deaths for the final analysis have occurred. The analysis should be submitted within 6 months of the date of the last death.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
5/19/04 01:51:29 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Thierry Kern – Eli Lilly & Company	**From:** Patty Garvey, R.Ph.
Fax: 317-276-1652	**Fax:** (301) 594-0498
Phone: 317-276-9254	**Phone:** (301) 594-5766
Pages (including cover): 1	**Date:** May 10, 2004
Re: NDA 20-509/S-029 Gemzar	

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

● **Comments:**

Thierry,

Please refer to your sNDA 20-509/S-029 Gemzar – breast cancer indication. The following is a request from the statistical reviewer.

1. Using your dataset srvfinal, percentage of patients with adjuvant anthracycline therapy is close to 70%. You have reported this as approximately 96%. Please clarify.

2. In your dataset respdur2, some of the response durations are recorded as negative. Please clarify.

3. Survival analysis using treatment code, thertrtc (from patdemog dataset), gives an unadjusted log-rank p-value = 0.06. Please clarify.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
5/10/04 12:35:34 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Thierry Kern – Eli Lilly & Company	**From:** Patty Garvey, R.Ph.
Fax: 317-276-1652	**Fax:** (301) 594-0498
Phone: 317-276-9254	**Phone:** (301) 594-5766
Pages (including cover): 1	**Date:** May 7, 2004
Re: NDA 20-509/S-029 Gemzar	

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Thierry,

Please refer to your sNDA 20-509/S-029 Gemzar – breast cancer indication. The following is a request from the statistical reviewer.

> We are trying to verify your Table JHQG 11.11. You have identified data source as SPRTHER. I believe this dataset has not been submitted. It would be very helpful if you can direct us to where we can find this data.
>
> Also regarding prior therapy and other baseline characteristics, if you have and can e-mail an analysis dataset - one record per patient - for all demographic and baseline characteristics it would be very helpful in speeding the review process.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
5/7/04 12:30:27 PM
CSO

MEMORANDUM OF TELECON

DATE: May 7, 2004

APPLICATION NUMBER: sNDA 20-509/S-029, Gemzar® (gemcitabine HCl) for Injection

BETWEEN:

Name: Paolo Paoletti, M.D., Vice President Medical Oncology
Edmundo Muniz, M.D., Executive Director Oncology
Jun Wu, M.D., Senior Statistician
Debasish Roychowdhury, M.D., Director Regulatory Affairs
Anne White, Director Clinical Operation
Patrick Peterson, Ph.D., Senior Statistician
Binh Nguyen, M.D., Medical Director
Allen Melemed, M.D., Senior Clinical Physician
Thierry Kern, Senior Regulatory Scientist
John Worzalla, Senior Regulatory Scientist

Representing: Eli Lilly and Company

AND

Name: Richard Pazdur, M.D., Director, Division of Oncology Drug Products
Rajeshwari Sridhara, Ph.D., Statistical Reviewer
Patty Garvey, R.Ph., Regulatory Project Manager

Representing: Division of Oncology Drug Products, HFD-150

SUBJECT: Statistical analysis

BACKGROUND:

Eli Lilly submitted a NDA 20-509 for Gemzar for a new proposed indication on December 17, 2003. The proposed indication is as follows: "Gemzar is indicated in combination with

The following summarizes the pre-NDA meeting dates with the DODP during the clinical investigations of gemcitabine under IND 29,653 regarding submission of an NDA for breast cancer.

May 8, 2003 Pre-NDA: agreement of initial filing of the application for possible accelerated approval and format for the sNDA.

September 16, 2003 Pre-NDA: agreement on proceeding with interim analysis and agreement on overall survival significance level.

November 21, 2003 Pre-NDA meeting scheduled for November 26, 2003 was cancelled upon the Lilly's request. They received the FDA's responses to their questions on November 21, 2003 and were satisfied with the FDA's responses.

SUMMARY:

FDA indicated that there was a statistical analysis plan. According to the statistical analysis plan, Lilly had indicated that they would conduct the survival analysis at a significance level of 0.03. However, in the submission Lilly conduct the survival analysis at a significance level of 0.05. The FDA had a problem with Lilly changed their statistical analysis plan.

The FDA does see a positive trend in survival however FDA requested that Lilly submit the mature survival data when it is completed.

At this time, FDA would give the sNDA an accelerated approval based on time to progression (or time to documented progressive disease [TtDPD]). Therefore, FDA requested that Lilly remove the survival data and curve in the proposed labeling since the planned analysis is incomplete. Lilly agreed to FDA proposal and request.

Lilly inquired if FDA has any concerns with Lilly presenting their clinical findings at the 2004 American Society Clinical Oncology meeting. FDA stated that these scientific presentations are outside of FDA regulatory jurisdiction.

ACTION ITEMS:

1. Lilly agreed to submit mature survival data when it is completed as a sNDA. The FDA agreed to elevate the mature survival data submission to be at 0.05.

2. Lilly will submit revised labeling to remove the survival data on May 10, 2004.

3. Lilly will submit the datasets that was requested by the FDA statistician in the facsimile dated May 7, 2004 as soon as possible.

Richard Pazdur, M.D.
Director, Division of Oncology Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
5/17/04 02:45:43 PM
CSO

Richard Pazdur
5/17/04 03:06:22 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-509/S029

Lilly and Company
Attention: Norma Ascroft, Pharm.D.
U.S. Regulatory Affairs-Oncology
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Ascroft:

Please refer to your December 17, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gemzar (gemcitabine HCl).

We also refer to your submissions dated January 28 and 29, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 16, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dotti Pease
2/12/04 11:16:40 AM

MINUTES OF FILING MEETING

DATE: February 11, 2004 **TIME:** 1:00 **ROOM:** B

NDA#: 20-509/S029 **DRUG:** Gemzar for breast cancer

ATTENDEES:

Richard Pazdur, M.D., Dir., DODP	John Johnson, M.D., Med. TL, DODP
Martin Cohen, M.D., Med. Rev., DODP	Jennifer Lowe, M.D., Fellow
Raji Sridhara, Ph.D., Acting Stat. TL	Brian Booth, Ph.D., Biopharm, DODP
Hasmukh Patel, Ph.D., Dep. Dir., DNDCI	Dotti Pease, PM

BACKGROUND: Lilly had given their NDA presentation on February 3, 2004 for this supplement which proposes Gemzar/paclitaxel for first line breast cancer. The primary endpoint is survival, and the survival update will be submitted with the 120 day safety update (@end of April). This is a completely electronic sNDA - reviewers report no problems accessing their data.

1. **Discipline reports**
   a. Medical - fileable
   b. Statistical - fileable
   c. Pharmacology/Toxicology - not applicable
   d. Biopharmaceutics - fileable
   e. Chemistry - fileable

2. **Identify Consults** -
   a. Medical
      - DSI - clinical inspections requested.
   b. Chemistry
      - EA/FONSI - Chengyi will incorporate into his review

4. **Set Division Goals:**
   a. Priority / PDUFA date P = June 18, 2004
   b. ODAC ? NO
   c. Timing preference for team meetings: monthly
   d. Target date for first completed reviews: 5-18-04
   e. Target date for first labeling reviews: discuss at next meeting
   f. Div sign-off

5. **Action Items-** PM - Ack ltr and FG letter - **DP**
   schedule monthly team meetings - **DP/PG**
   do Pediatric Page - **DP**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dotti Pease
2/12/04 11:38:59 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-509/S029

PRIOR APPROVAL SUPPLEMENT

Lilly and Company
Attention: Norma Ascroft, Pharm.D.
U.S. Regulatory Affairs-Oncology
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Ascroft:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Gemzar (gemcitabine HCl)

NDA Number: 20-509

Supplement number: 029

Review Priority Classification: Priority (P)

Date of supplement: December 17, 2003

Date of receipt: December 18, 2003

This supplemental application proposes the following change: additional indication of combination with paclitaxel for the first-line treatment of patients with unresectable, locally recurrent, or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 16, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 18, 2004.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and research
Division of Oncology Drug Products, HFD-150
Attention: Document Room 3067
1451 Rockville Pike
Rockville, Maryland 20852

If you have any question, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dotti Pease
2/12/04 09:48:26 AM

INTERNAL MEETING MINUTES

MEETING DATE: November 21, 2003 **TIME:** 12:00 pm **LOCATION:** WOC2/rm 2064

IND: 29,653

Meeting Request Submission Date: 10-8-03; sn 999
FDA Response Date: 10-16-03
Briefing Document Submission Date: 10-24-03; sn A04

DRUG: Gemzar® (gemcitabine HCl, LY188011)

SPONSOR/APPLICANT: Eli Lilly & Company

TYPE of MEETING:

1. Pre-sNDA (3rd)

2. **Proposed Indications (from briefing package):**
   Gemzar, in combination with paclitaxel, ———————————
   patients with locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. ———————————
   ———————————

FDA PARTICIPANTS:

Grant Williams, M.D.	--	Deputy Director, Division of Oncology Drug Products
John Johnson, M.D.	--	Medical Team Leader
Martin Cohen, M.D.	--	Medical Reviewer
Ning Li, Ph.D.	--	Statistical Reviewer
Patty Garvey, R.Ph.	--	Project Manager

BACKGROUND:

Lilly previously submitted a concise summary of study results based on the interim analysis in the form of the European Expert Report in the December 5, 2002 submission, serial no. 917. Lilly initiated the global, randomized, phase 3 clinical trial of Gemzar plus paclitaxel versus paclitaxel in patients with unresectable, locally recurrent or metastatic breast cancer in September 1999 (September 9, 1999, serial no. 714; March 23, 2001, serial no. 800; and January 4, 2002, serial no. 851) with overall survival as the primary endpoint and time to documented progression of disease (TtDPD) as a secondary endpoint. The protocol states TtDPD would be the primary endpoint for the interim analysis. The trial has completed enrollment. The study's planned interim datalock for safety and efficacy occurred August 1, 2002. As of August 1, 2002, only 19 patients remained on treatment and of the 529 patients, 411 patients had progressive disease, as determined by the investigators.

On May 8, 2003, Lilly and FDA discussed the possibility of a submission for an accelerated approval based on Study JHQG interim analysis of time to documented progressive disease (TtDPD) with the follow-up of overall survival (JHQG's primary objective). Safety was a secondary endpoint also evaluated in this trial.

On September 16, 2003, Lilly met with the FDA to discuss their plan to submit a sNDA based on the interim analysis results from Study JHQG, and will perform an interim survival analysis of the Phase 3 Study JHQG. Following the sNDA submission, Lilly also proposes to provide a comprehensive update of safety data from the cut-off date of the above interim analysis of TtDPD (July 10, 2002) to the proposed cut-off date.

MEETING OBJECTIVES (from meeting request document):

To discuss the affect of the interim survival analysis for filing of a sNDA for the proposed indication.

QUESTION for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:

NOTE: Lilly received the Division's comments via facsimile on November 21, 2003.

On November 24, 2003, Dr. Norma Ascroft, Lilly Regulatory Scientist, contacted Ms. Garvey to cancel the meeting scheduled on November 26. 2003. Dr. Ascroft indicated that the FDA addressed Lilly's questions and a meeting was no longer necessary.

---

1. The interim analysis determined an estimated median survival time of 18.5 months (95% confidence interval [CI], 16.50 to 21.20 months) on the gemcitabine plus paclitaxel combination (GT) arm, compared with 15.8 months (95% CI, 14.40 to 17.40 months) on the paclitaxel monotherapy (T) arm. The hazard ratio [HR] for GT was 0.78 (95% CI, 0.63 to 0.96); log-rank p=0.0182. The treatment benefit of GT became more apparent when adjusting for the significant covariates, with an HR of 0.74 (95% CI, 0.598 to 0.0915); p=0.0055. Given the significant advantages in favor of the GT Arm in time to documented progressive disease (TtDPD; log-ran p=0.0013; HR 0.73; 95% CI, 0.61 to 0.89), progression-free survival (PFS); log-rank p+0.0021; HR 0.749, 95% CI, 0.621 to 0.903), and overall response rate (39.3% versus 25.6%; p=0.0007) and the improvement seen at the interim survival analysis (overall censor rate of 35.16%), would the FDA Division of Oncology Drug Products consider granting a full approval for Gemzar in metastatic breast cancer upon validation of the interim survival analyses by the FDA?

   FDA: No. The overall censor rate for the interim survival analysis was 35%; 30% for the T arm and 40% for the GT arm. More mature data is sought.

   a) If FDA does not agree with the above, Lilly would consider providing updated survival data to the FDA at an agreed designated time point during the review as the **final survival analysis endpoint** (for example, at approximately 25% censoring-similar to the final analysis for capecitabine + docetaxel). This would not be considered a major amendment to the submission. Would the FDA agree with this approach for full approach?

      FDA: Yes.

2. Given the importance of the interim survival data, and the low risk of bias, Lilly plans to present the results of the interim survival analysis (for example, at the 2004 annual meeting of the American Society of Clinical Oncology [ASCO]). Does the FDA have any concerns regarding Lilly's plans of sharing these interim survival data with the oncology academic community?

   FDA: At the time the abstract is to be presented more mature survival data will be available. The abstract should state that current survival data are preliminary.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Project Manager

Concurrence Chair:

{See appended electronic signature page}

Martin Cohen, M.D.
Medical Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Martin Cohen
12/9/03 03:33:55 PM

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Thierry Kern – Eli Lilly & Company	**From:** Patty Garvey, R.Ph.
Fax: 317-276-1652	**Fax:** (301) 594-0498
Phone: 317-276-9254	**Phone:** (301) 594-5766
Pages (including cover): 1	**Date:** March 23, 2004
Re: NDA 20-509/S-029 Gemzar – submission dated 3-15-04	

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Thierry,

Please refer to NDA 20-509/S-029 Gemzar – breast cancer indication – submission dated March 15, 2004. Thank you for your prompt response regarding reconciliation of TTP/censor dates and response rate and duration.

We have gone through the former. Our dates now differ for only 4 patients.

Patient	FDA Prog or censor date	Lilly Prog or censor date
601	2/28/02	6/10/02
606	3/26/02	6/10/02
2541	6/14/00	8/10/00
5024	3/6/01	5/14/01

Please review and, if necessary, revise your tables and figures.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
3/23/04 04:08:15 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Thierry Kern – Eli Lilly & Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-276-9254	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	March 24, 2004
Re:	NDA 20-509/S-029 Gemzar – submission dated 3-15-04		

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Thierry,

Please refer to NDA 20-509/S-029 Gemzar – breast cancer indication – submission dated March 15, 2004.

We agree with the reconciled list of PR's and CR's. We agree with response durations with the exception of patients 601 and 606 where we still differ on dates of progression.

Please review and, if necessary, revise your tables and figures.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
3/24/04 03:57:59 PM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Norma Ascroft, Lilly
Fax: 317 276-1652

FROM: Dotti Pease, Project Manager
Phone: **(301) 594-5742**

Total number of pages, including cover sheet 7

Date: 3-2-04

COMMENTS: Re: NDA 20-509/S029, here are more tables from Dr. Cohen. The 3rd column is Dr. Cohen's censor dates; the 4th column is Lilly's censor dates; and the 5th column is the reason why Dr. Cohen chose his date.
Dotti

FDA v Lilly Differences Query1 in Responders

3/2/2004

SDY	CTPAT	PROGDTN	Censor da	Resp FDA	Resp Lilly	THEI	Explanation
42	422	7/28/2000		PR		O	OK
42	425		5/23/2002	CR		G9	OK
42	427		4/19/2002	PR		O	OK
47	471	2/15/2001			PR	G9	NO
48	484		6/10/2002		PR	G9	NO Use L (bone)
51	511	7/11/2000			PR	G9	NO Unconfirm P06 ND
60	602		6/12/2002		PR	G9	NO <50%
101	1011		3/13/2001	PR		G9	YES 6/19/00&3/13/01
101	1035	7/16/2001			PR	O	NO Bone use L, L02 ND
101	1038	6/6/2001		PR		G9	OK
200	2501	10/4/2000		PR		O	OK Use L, p<1.0
223	3021	8/15/2001		PR		G9	OK Use L Bone,
408	4146	3/6/2002		PR		G9	OK, P03 OK
602	6036		12/3/2001		PR	O	NO Use L bone, L04 ND
706	7054	1/22/2002		PR		O	YES

FDA analyses
Remove 4 G9 responders - Lilly response
Remove 2 O responders - Lilly responses
Add 4 O responders - FDA response
Add 5 G9 responders - FDA responses

Net
Add 2 O responders (PR's)
Add 1 G9 responder (CR)

SDYII	CTPA	Censor date FI	Censor date Lil	Explanation
2	21	6/6/2000		
2	32	8/1/2001		
3	41	9/23/2000		
3	44	8/16/2000		
3	45	10/5/2000		
3	47	3/23/2001	4/17/2001	Last tumor measurements (LTM)
3	49	11/26/2001	1/16/2002	LTM
3	50	1/3/2002	5/6/2002	LTM
3	51	3/6/2002	5/27/2002	LTM
4	62	4/18/2001		
4	66	3/13/2002	5/15/2002	
4	70	3/27/2002	7/4/2002	
5	84	6/21/2002		
10	101	10/23/2000		
10	102	8/2/2001		
11	123	8/28/2000		
13	161	8/2/2000		
14	183	2/20/2001		
14	184	6/13/2001		
20	201	1/31/2001		
20	204	8/15/2001		
21	221	7/26/2001		
21	223	12/27/2001		
30	304	11/14/2000	1/10/2001	LTM
30	305	11/27/2000	5/16/2001	LTM
30	308	8/22/2000		
30	310	1/26/2001		
30	311	5/25/2001		
30	313	6/19/2001	8/31/2001	OK
31	322	1/28/2000	2/18/2001	LTM
31	325	8/17/2000	6/18/2001	LTM
31	328	12/27/2000	4/24/2001	LTM
31	343	2/15/2001	10/8/2001	LTM
31	345	6/26/2001	9/11/2001	LTM
31	346	6/29/2001		
31	348	6/29/2002		
34	361	3/16/2001	5/6/2002	LTM
34	366	10/18/2001	6/28/2002	LTM
34	368	9/3/2001		
34	369	1/31/2002	5/9/2002	LTM
40	400	6/12/2000	8/25/2000	LTM
41	412	10/6/2000	~~5/5/2001~~	7 months between evaluations
41	414	8/24/2000		
41	416	6/27/2001		
42	423	1/4/2001	9/22/2001	LTM
42	424	4/18/2002	6/21/2002	LTM
42	425	5/23/2002		
42	426	11/15/2001	4/15/2002	LTM

SDYI	CTPA	Censor date FI	Censor date Li	Explanation
42	427	4/19/2002	7/4/2002	LTM
47	473	12/19/2001		
47	474	3/25/2002	6/27/2002	LTM
47	475	3/25/2002	6/27/2002	LTM
48	482	6/7/2002		
48	484	6/10/2002		
48	485	5/6/2002	7/9/2002	OK
48	486	5/10/2002		
48	488	6/21/2002		
48	489	7/8/2002		
48	490	7/2/2002		
51	514	2/7/2002		
51	515	12/19/2001	3/14/2002	LTM
54	547	4/11/2001		
54	548	8/7/2001		
54	549	11/26/2001	6/6/2002	LTM
54	555	11/6/2001	6/6/2002	LTM
54	558	12/24/2001	2/28/2002	LTM
54	560	7/4/2002		
54	561	12/12/2001	1/24/2002	LTM
54	563	1/21/2002		
48	591	5/30/2002	6/21/2002	LTM
48	592	6/24/2002		
48	594	7/10/2002		
48	595	6/12/2002	7/3/2002	LTM
60	601	2/28/2002		
60	602	6/12/2002		
60	603	6/5/2002		
60	606	3/26/2002		
61	621	6/27/2002		
61	622	5/28/2002		
61	625	6/18/2002		
61	627	5/22/2002		
61	629	6/27/2002		
101	1001	6/5/2000	~~8/28/2000~~	Last complete tumor meas(LCTM)L01-2 ND
101	1003	6/15/2000	~~5/2/2001~~	LTM
101	1004	2/8/2000	~~1/29/2001~~	Next exam almost 1 year later
101	1007	2/23/2000		
101	1011	3/13/2001	6/14/2001	LTM
101	1017	2/23/2001	8/14/2001	LCTM P01 ND
101	1018	12/19/2000	6/3/2001	LTM
101	1023	6/17/2001	6/21/2002	OK
101	1028	9/28/2000		
101	1034	6/19/2001	3/21/2002	LTM
101	1045	5/23/2002	7/9/2002	LTM
109	1242	3/12/2001		
130	1421	11/28/2000	3/14/2001	3.5 mo between measurements
133	1481	2/14/2000		

SDYID	CTPA	Censor date FI	Censor date Li	Explanation
162	1964	1/11/2002		
194	2081	12/21/2000		
179	2183	7/20/2000		
192	2444	5/9/2002	6/25/2002	LTM
193	2461	12/3/1999		
199	2481	3/13/2000		
115	2661	10/13/2000		
203	2781	10/23/2001	5/16/2002	LCTM L01 ND
208	2874	3/11/2002		
211	2891	7/30/2001		
222	3011	10/23/2001	3/25/2002	LCTM L01 ND
301	3503	12/28/2001		
301	3507	7/3/2002		
301	3509	5/15/2002		
401	4002	3/27/2000	5/18/2000	LTM
402	4024	2/21/2002	5/6/2002	LTM
403	4042	3/2/2001	2/28/2002	LTM
403	4043	10/6/2000		
403	4045	5/8/2001	7/3/2001	LTM
403	4046	2/12/2001		
405	4081	4/30/2001		
405	4082	1/22/2001		
405	4083	6/6/2001		
406	4102	12/20/1999		
413	4224	8/31/2001	10/23/2001	LTM
503	5021	5/23/2000	9/18/2000	LCTM P02,3 ND
503	5022	8/8/2000	10/18/2001	LCTM L02 ND
503	5025	4/19/2001	6/5/2002	LTM
503	5028	11/26/2001	1/26/2002	LTM
504	5031	11/7/2000		
504	5034	11/30/2000		
504	5035	9/11/2001	6/27/2002	LTM
504	5037	11/7/2001		
505	5044	3/26/2001		
505	5048	11/21/2001	2/19/2002	LTM
507	5061	7/24/2001	6/18/2002	LTM
602	6023	9/25/2000		
602	6026	5/12/2000		
602	6028	4/19/2001	7/10/2001	LTM
602	6032	4/3/2001		
602	6033	9/10/2001		
602	6036	12/3/2001	6/18/2002	LCTM bone scan ND
650	6503	12/6/2000	2/16/2001	LTM
650	6507	4/20/2001	8/20/2001	4 month interval between evaluations
651	6522	1/10/2001	7/21/2001	6.5 month interval between evaluations
651	6526	3/23/2001		
651	6527	11/22/2000		
651	6529	1/1/2001		

SDYID	CTPA	Censor date FD	Censor date Lil	Explanation
651	6536	8/13/2001		
651	6537	1/3/2002		
652	6540	9/19/2000	9/21/2000	randomization date
653	6560	7/17/2001		
653	6561	11/7/2000	12/30/2000	LTM
653	6566	6/19/2001		
653	6568	5/21/2001	3/7/2001	OK
653	6570	1/7/2002		
653	6573	5/27/2002		
653	6574	11/28/2001		
654	6583	2/8/2001	5/16/2002	LTM
654	6590	5/2/2001		
654	6592	1/12/2002	4/24/2002	LTM
654	6594	11/27/2001	6/1/2002	LCTM
651	6600	9/5/2001	11/21/2001	OK Progession 11/21/2001
651	6603	10/8/2001	11/6/2001	LTM
651	6604	1/30/2002		
651	6609	4/1/2002	6/29/2002	Last eval of L06; Prog 6/8/02 if agreeable
701	7001	5/25/2000		
701	7003	10/2/2001	4/16/2002	LTM
702	7012	2/5/2001		
703	7022	2/13/2001		
703	7028	9/10/2001		
703	7029	4/9/2002	6/21/2002	LTM
705	7041	2/20/2002	6/19/2002	LTM
706	7052	7/13/2001	9/27/2001	LTM
706	7053	6/19/2002		
707	7061	2/9/2001		
750	7501	4/18/2001	10/19/2001	OK Prog 10/19/01
750	7504	9/11/2001		
750	7505	4/19/2002	5/28/2002	LTM
750	7506	5/13/2002	6/28/2002	LTM
750	7509	4/29/2002	7/10/2002	LTM
750	7510	6/4/2002		
751	7528	6/25/2002	7/16/2002	6/25/02 LTM
752	7542	10/30/2001	12/25/2001	LTM
752	7548	5/15/2002		
752	7549	2/19/2002	6/10/2002	LTM
801	8004	7/7/2000		
801	8006	8/2/2000	12/12/2000	8/2/00 LCTM, L09 ND
801	8007	1/12/2001	6/5/2001	1/12/01 LTM
801	8014	3/8/2001		
801	8017	4/16/2001		
801	8018	4/10/2001		
801	8022	11/26/2001	6/17/2002	LCTM, L08ND
851	8510	11/21/2000	2/8/2001	LTM
851	8511	1/22/2001		
851	8513	5/23/2002		

SDYID	CTPA	Censor date FI	Censor date Li	Explanation
851	8514	5/23/2002		
851	8515	4/11/2002	6/20/2002	LCTM, L03 ND

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
3/3/04 02:11:03 PM
CSO
Sent to sponsor via facsimile on March 2, 2004

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Norma Ascroft, Pharm.D. – Eli Lilly & Company	**From:** Patty Garvey, R.Ph.
Fax: 317-276-1652	**Fax:** (301) 594-0498
Phone: 317-277-2308	**Phone:** (301) 594-5766
Pages (including cover): 13	**Date:** February 25, 2004
Re: NDA 20-509/S-029 Gemzar – submission dated 12-18-03	

☐ **Urgent** ■ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Norma,

Please refer to NDA 20-509/S-029 Gemzar – breast cancer indication – submission dated December 18, 2003. The following is the data table from the medical officer with his latest progression and censor dates for the NDA. The response agreement column refers to the investigation response assessment.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Project Manager
Division of Oncology Drug Products

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
2	21		6/6/2000		y	
2	22	3/13/2001		CR	y	y
2	23	2/28/2001			y	y
2	24	1/31/2001			y	
2	25	6/14/2001		PR	y	y
2	28	10/22/2001		PR	y	y
2	29	9/26/2001			y	n
2	30	2/5/2002		PR	y	y
2	32		8/1/2001		y	
2	34	5/15/2002		PR	y	y
2	36	1/22/2002			y	
2	37	2/13/2002			y	
3	41		9/23/2000	PR	n	n
3	42	1/19/2000			y	
3	43	8/2/2000			y	
3	44		8/16/2000		n	n
3	45		10/5/2000		n	n
3	47		3/23/2001		n	
3	48	5/24/2001			y	
3	49		11/26/2001	PR	n	y
3	50		1/3/2002	PR	n	y
3	51		3/6/2002		n	
3	52	5/7/2002			y	
4	61	11/28/2001		PR	y	y
4	62		4/18/2001		n	
4	63	12/5/2001			y	
4	64	8/22/2001			y	
4	65	3/5/2002			y	
4	66		3/13/2002		n	
4	67	11/23/2001			y	y
4	68	2/15/2002			y	y
4	69	10/31/2001			y	
4	70		3/27/2002	PR	n	y
4	71	2/15/2002			y	
5	81	11/28/2001			y	
5	82	2/21/2002			y	y
5	84		6/21/2002	PR	y	y
10	100	9/19/2000			y	
10	101		10/23/2000		n	y
10	102		8/2/2001	CR	n	y
10	103	5/3/2002		PR	y	y
11	121	2/1/2000			y	
11	122	7/12/2000			y	
11	123		8/28/2000		n	
12	141	11/22/2000			y	
12	142	7/1/2001		PR	y	y
12	143	11/9/2001			y	
12	144	6/25/2002		PR	y	y

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
13	161		8/2/2000	PR	n	y
13	162	6/21/2000			y	
13	163	12/21/2000			y	
13	164	11/21/2001			y	y
14	181	6/26/2000			y	
14	182	10/10/2000			y	
14	183		2/20/2001		n	n
14	184		6/13/2001		n	
14	185	1/14/2002		PR	y	y
14	186	2/28/2002			y	
14	187	3/20/2002			y	
20	200	11/10/2000			y	
20	201		1/31/2001		y	
20	202	1/9/2001			y	
20	203	11/12/2001			y	
20	204		8/15/2001		y	
20	205	11/19/2001			y	
20	206	12/13/2001			y	
21	221		7/26/2001	PR	n	y
21	222	7/11/2001			y	
21	223		12/27/2001	PR	n	y
30	300	5/24/2000		PR	y	y
30	301	5/12/2000			y	
30	303	8/11/2000			y	
30	304		11/14/2000	PR	n	y
30	305		11/27/2000	CR	n	y
30	306	9/14/2000			y	
30	307	11/28/2000			y	
30	308		8/22/2000		n	n
30	309	3/19/2001			y	
30	310		1/26/2001		y	
30	311		5/25/2001	PR	n	y
30	312	5/14/2001			y	
30	313		6/19/2001		n	
30	315	9/5/2001			y	
30	316	8/31/2001			y	
30	317	11/21/2001			y	
31	321	4/11/2000		PR	y	y
31	322		1/27/2000		n	
31	323	8/1/2000		PR	y	y
31	324	9/22/2000		CR	y	y
31	325		8/17/2000	CR	n	y
31	326	7/18/2000			y	
31	327	12/13/2000		PR	y	y
31	328		12/27/2000	PR	n	y
31	329	10/25/2000			y	
31	342	2/15/2001		CR	y	y
31	343		2/15/2001	PR	n	y

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
31	345		6/26/2001	PR	n	y
31	346		6/29/2001		y	y
31	347	2/14/2002			y	
31	348		6/29/2002		y	
31	349	4/2/2002			y	
34	361		3/16/2001		n	
34	362	3/14/2001			y	
34	363	3/14/2001			y	
34	365	3/30/2001			y	
34	366		10/18/2001	CR	n	y
34	367	8/21/2001			y	
34	368		9/3/2001	PR	n	y
34	369		1/31/2002		n	
34	370	1/4/2002		PR	y	y
40	400		6/12/2000		n	
41	411	6/20/2000			y	
41	412		10/6/2000	CR	n	y
41	413	9/13/2000			y	
41	414		8/24/2000		y	
41	415	11/20/2001		PR	y	y
41	416		6/27/2001	PR	n	y
41	417	9/3/2001			y	
41	418	10/9/2001			y	
41	419	12/11/2001			y	
41	420	10/25/2001			y	
42	421	9/4/2000		PR	y	y
42	422	7/28/2000		PR	y	y
42	423		1/4/2001	PR	n	y
42	424		4/18/2002	CR	n	y
42	425		5/23/2002	CR	n	y
42	426		11/15/2001		n	
42	427		4/19/2002	PR	n	y
43	431	5/9/2000			y	
44	441	8/22/2000			y	
44	442	10/25/2000			y	
44	443	6/14/2001			y	
44	444	9/12/2001			y	
44	445	9/17/2001			y	
47	471	2/15/2001			y	n
47	472	4/30/2001		PR	y	y
47	473		12/19/2001	PR	n	y
47	474		3/25/2002	CR	n	y
47	475		3/25/2002	PR	n	y
48	481	11/23/2001			y	
48	482		6/7/2002	PR	n	y
48	483	11/21/2001			y	
48	484		6/10/2002		n	
48	485		5/6/2002	PR	n	n

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
48	486		5/10/2002	PR	n	n
48	487	2/5/2002			y	
48	488		6/21/2002	PR	y	n
48	489		7/8/2002		y	
48	490		7/2/2002		y	
51	511	7/11/2000			y	n
51	512	4/25/2001		CR	y	y
51	513	3/22/2001			y	
51	514		2/7/2002		n	
51	515		12/19/2001	PR	n	y
53	531	7/24/2001		PR	y	y
53	532	2/20/2002		PR	y	y
53	533	9/5/2001			y	
54	541	7/3/2001			y	y
54	542	8/29/2001		PR	y	y
54	543	5/15/2001			y	
54	546	6/13/2001			y	
54	547		4/11/2001		y	
54	548		8/7/2001		n	y
54	549		11/27/2001	PR	n	y
54	550	8/14/2001			y	
54	551	4/30/2002		PR	y	y
54	552	10/9/2001		PR	y	y
54	553	8/23/2001			y	
54	555		11/6/2001		n	
54	556	11/6/2001			y	
54	558		10/31/2001		n	
54	560		7/4/2002	PR	y	n
54	561		12/12/2001		n	
54	562	2/21/2002			y	
54	563		1/21/2002		n	
54	564	3/27/2002			y	
54	566	4/30/2002			y	
48	591		5/9/2002	PR	n	n
48	592		6/24/2002	PR	y	n
48	593	6/14/2002		PR	y	y
48	594		7/10/2002	PR	y	n
48	595		5/28/2002		n	
60	600	4/23/2002			y	y
60	601		2/28/2002	PR	n	y
60	602		6/12/2002		y	n
60	603		6/5/2002	PR	n	y
60	606		3/26/2002	PR	n	y
61	621		6/27/2002	CR	n	y
61	622		5/28/2002	PR	n	y
61	625		6/18/2002	PR	n	y
61	626	3/21/2002			y	
61	627		5/22/2002	PR	n	y

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
61	629		6/27/2002	PR	n	n
101	1001		6/5/2000	PR	n	n
101	1002	2/3/2000		PR	y	n
101	1003		6/15/2000	CR	n	y
101	1004		2/8/2000		n	
101	1005	3/27/2000			y	
101	1006	3/23/2000			y	
101	1007		2/23/2000		n	
101	1008	9/19/2000		PR	y	y
101	1009	8/18/2000			y	n
101	1010	7/6/2000			y	
101	1011		3/13/2001	PR	n	n
101	1012	8/18/2000			y	
101	1013	10/19/2000			y	y
101	1014	10/2/2000			y	y
101	1015	7/18/2000			y	
101	1016	7/20/2000			y	
101	1017		2/23/2001	PR	n	y
101	1018		12/19/2000		n	
101	1019	9/13/2000			y	y
101	1020	10/16/2000			y	
101	1021	10/26/2000			y	
101	1022	11/20/2000			y	
101	1023		6/17/2001	CR	n	y
101	1024	4/5/2001		PR	y	y
101	1025	12/6/2000			y	
101	1026	2/15/2001			y	y
101	1027	11/17/2000			y	
101	1028		9/28/2000		n	
101	1029	4/9/2001		PR	y	n
101	1030	12/14/2000			y	
101	1031	1/30/2001			y	
101	1032	3/9/2001			y	
101	1033	2/20/2001			y	
101	1034		6/19/2001	PR	n	y
101	1035	7/16/2001			y	n
101	1037	5/14/2001			y	
101	1038	6/6/2001		PR	y	n
101	1039	10/18/2001			y	
101	1040	11/19/2001		PR	y	y
101	1041	7/25/2001			y	
101	1042	10/11/2001			y	y
101	1044	11/26/2001			y	
101	1045		5/23/2002		n	
101	1046	5/6/2002		PR	y	n
101	1047	3/19/2002			y	
107	1201	7/6/2001		PR	y	y
107	1202	11/9/2001			y	

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
109	1241	7/19/2001		CR	n	y
109	1242		3/12/2001		n	
128	1381	1/4/2001			y	
130	1421		11/28/2000		n	
130	1422	2/14/2001		PR	y	y
133	1481		2/14/2000		n	
153	1781	6/2/2000			y	
155	1821	8/30/2001		PR	n	y
158	1881	11/16/2000			y	
160	1922	7/27/2001		PR	n	y
162	1962	6/12/2000			y	
162	1963	1/7/2000			n	y
162	1964		1/11/2002	PR	n	y
194	2081		12/21/2000		n	
176	2121	5/31/2000			y	y
179	2181	3/29/2000		PR	y	y
179	2182	1/19/2000			y	
179	2183		7/20/2000	PR	n	y
179	2184	6/18/2001		PR	y	y
179	2187	3/22/2001			y	
179	2188	5/9/2002			y	
181	2221	1/19/2000			y	
192	2443	9/10/2001			y	
192	2444		5/9/2002	PR	n	y
193	2461		12/3/1999		y	
193	2463	6/5/2000			y	y
199	2481		3/13/2000	PR	n	y
199	2482	6/21/2001			y	
199	2483	9/17/2001		PR	y	y
200	2501	10/4/2000		PR	y	n
200	2502	10/12/2000			y	
113	2541	6/14/2000			n	
113	2542	3/26/2001			y	
144	2601	5/22/2000			n	
170	2621	7/25/2001			y	
115	2661		10/13/2000	PR	n	y
203	2781		10/23/2001		n	
207	2842	9/14/2001			y	
208	2871	4/9/2001			y	
208	2872	6/13/2001			y	
208	2873	11/19/2001			y	y
208	2874		3/11/2002		n	
211	2891		7/30/2001		n	y
214	2921	8/29/2001			y	
215	2931	6/25/2001			y	
215	2932	1/16/2002			y	
218	2961	1/2/2002			y	
222	3011		10/23/2001	PR	n	y

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
223	3021	8/15/2001		PR	y	y
301	3501	5/15/2001			y	
301	3502	9/19/2001			y	
301	3503		12/28/2001	PR	n	y
301	3504	11/28/2001			y	
301	3505	1/16/2002			y	
301	3506	5/2/2002		PR	y	y
301	3507		7/3/2002	PR	n	y
301	3508	2/4/2002			y	
301	3509		5/15/2002	PR	n	y
302	3511	3/5/2002		PR	y	y
303	3521	7/6/2001			y	
304	3531	9/25/2001			y	
304	3532	12/14/2001			y	
304	3533	11/5/2001			y	
401	4001	3/1/2000			y	
401	4002		3/27/2000		n	
402	4021	4/19/2000		PR	y	y
402	4022	3/29/2001			y	
402	4023	1/23/2001			y	n
402	4024		2/21/2002	PR	n	y
403	4041	2/15/2001		PR	n	y
403	4042		3/2/2001	PR	n	y
403	4043		10/6/2000		n	n
403	4044	2/7/2001			y	
403	4045		5/8/2001	PR	n	y
403	4046		2/12/2001		y	
403	4047	1/16/2002			y	y
403	4048	3/6/2002			y	
403	4049	3/12/2002			y	
404	4061	1/11/2001			y	
405	4081		4/30/2001	PR	n	y
405	4082		1/22/2001		n	n
405	4083		6/6/2001		n	
406	4101	11/5/1999			y	
406	4102		12/20/1999		n	
406	4103	11/9/2000			y	
408	4141	3/27/2000			y	
408	4142	11/8/2000			y	
408	4143	4/3/2001			y	
408	4144	7/27/2001			y	
408	4145	9/10/2001			y	
408	4146	3/6/2002		PR	y	n
409	4161	7/6/2000			y	
409	4162	7/24/2000			y	
409	4163	2/14/2001			y	
413	4221	11/20/2000			y	y
413	4222	8/6/2001			y	y

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
413	4223	8/2/2001		PR	y	y
413	4224		8/31/2001		n	
413	4225	1/21/2002			y	
503	5021		5/23/2000		y	
503	5022		8/8/2000	PR	n	y
503	5023	9/26/2000			y	
503	5024	3/6/2001			n	
503	5025		4/19/2001	CR	n	y
503	5026	9/15/2001			y	
503	5027	12/1/2001			y	
503	5028		11/26/2001		n	
504	5031		11/7/2000	PR	y	y
504	5032	9/25/2000			y	
504	5033	4/6/2001			y	
504	5034		11/30/2000		n	n
504	5035		9/11/2001		n	
504	5036	3/4/2002			y	
504	5037		11/7/2001		n	
505	5041	1/9/2001			y	y
505	5042	2/19/2001			y	
505	5043	10/4/2001		CR	y	n
505	5044		3/26/2001		n	n
505	5045	12/14/2000		PR	y	n
505	5046	2/6/2001			y	
505	5047	5/15/2001			y	
505	5048		11/21/2001		n	
506	5051	8/3/2001			y	
507	5061		7/24/2001	PR	n	y
507	5062	9/12/2001			y	
601	6001	4/18/2000			y	
601	6002	6/11/2001		PR	y	y
602	6021	5/16/2000		PR	y	y
602	6022	4/18/2000			y	
602	6023		9/25/2000	PR	n	y
602	6024	8/11/2000		PR	y	y
602	6025	6/13/2000			y	
602	6026		5/12/2000		n	
602	6027	12/26/2000			y	
602	6028		4/19/2001	CR	n	y
602	6029	4/21/2001			n	
602	6030	4/27/2001			y	
602	6031	8/6/2001			y	y
602	6032		4/3/2001		n	
602	6033		9/10/2001		n	
602	6034	12/20/2001			y	
602	6035	12/17/2001			y	
602	6036		12/3/2001		n	n
602	6037	2/27/2002			y	

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
603	6041	3/7/2001			y	
650	6502	12/6/2000			y	
650	6503		12/6/2000		n	
650	6504	12/6/2000			y	
650	6505	1/19/2001			y	
650	6506	3/16/2001			y	
650	6507		4/20/2001	PR	n	n
650	6508	10/25/2001		PR	y	y
650	6509	5/23/2001			y	y
650	6510	6/13/2001			y	
650	6511	8/2/2001			y	
650	6512	9/25/2001			y	
650	6513	9/11/2001			y	
650	6514	11/12/2001			y	
651	6520	2/26/2001			y	y
651	6522		1/10/2001		n	
651	6523	11/8/2000			y	
651	6525	5/10/2001		PR	y	y
651	6526		3/23/2001	PR	n	n
651	6527		11/22/2000		n	
651	6528	6/7/2001		PR	y	n
651	6529		1/1/2001		n	
651	6530	4/9/2001			y	y
651	6531	5/9/2001		PR	y	y
651	6532	6/5/2001			y	y
651	6533	4/10/2001			y	
651	6534	5/28/2001			y	
651	6535	1/7/2002		PR	y	n
651	6536		8/13/2001		n	n
651	6537		1/3/2002	PR	n	n
651	6538	8/7/2001			y	
651	6539	9/24/2001			y	
652	6540		8/5/2000		n	
653	6560		7/17/2001	PR	n	y
653	6561		11/7/2000		n	
653	6562	3/22/2001			y	
653	6564	3/24/2001			y	
653	6565	8/28/2001		PR	y	y
653	6566		6/19/2001	PR	n	y
653	6567	4/26/2001			y	
653	6568		5/21/2001		n	
653	6569	5/11/2001			y	
653	6570		1/7/2002	CR	n	n
653	6571	9/11/2001			y	
653	6572	10/27/2001			y	
653	6573		5/27/2002	PR	n	y
653	6574		11/28/2001		n	
654	6580	12/21/2000			y	

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
654	6581	3/9/2001			y	y
654	6583		2/8/2001		n	
654	6584	5/18/2001			y	
654	6585	5/15/2001			y	
654	6588	7/18/2001			y	
654	6589	8/13/2001			n	y
654	6590		5/2/2001		n	
654	6591	7/9/2001			y	
654	6592		1/12/2002	PR	n	y
654	6594		11/27/2001		n	
651	6600		9/5/2001		n	
651	6601	10/10/2001			y	
651	6602	11/5/2001			y	
651	6603		10/8/2001		n	
651	6604		1/30/2002	PR	n	y
651	6605	3/13/2002		PR	y	n
651	6606	1/28/2002			y	
651	6607	4/16/2002			y	n
651	6608	3/4/2002			y	
651	6609		4/1/2002	PR	n	y
701	7001		5/25/2000	PR	n	y
701	7002	8/17/2000			y	
701	7003		10/2/2001	PR	n	y
702	7011	9/15/2000			y	
702	7012		2/5/2001		n	n
703	7021	7/13/2001		PR	y	y
703	7022		2/13/2001		n	
703	7023	11/9/2001		PR	y	y
703	7024	5/31/2001			y	
703	7025	5/1/2001			y	
703	7026	9/28/2001			y	n
703	7027	7/9/2001			y	
703	7028		9/10/2001	PR	n	y
703	7029		4/9/2002	PR	n	y
705	7041		2/20/2002	PR	n	y
706	7051	11/12/2001		PR	n	y
706	7052		7/13/2001	PR	n	y
706	7053		6/19/2002	CR	n	y
706	7054	1/22/2002		PR	y	n
707	7061		2/9/2001		n	n
750	7501		4/18/2001		n	n
750	7502	10/8/2001		PR	y	y
750	7503	10/16/2001			n	y
750	7504		9/11/2001		n	
750	7505		4/19/2002	PR	n	y
750	7506		5/13/2002	PR	n	y
750	7507	2/13/2002		PR	y	n
750	7508	2/13/2002			y	

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
750	7509		4/29/2002	PR	n	y
750	7510		6/4/2002	PR	n	n
751	7521	11/20/2001		PR	y	y
751	7522	6/3/2002		PR	y	n
751	7523	3/7/2002		PR	y	y
751	7524	5/21/2002			y	y
751	7525	12/13/2001		PR	y	y
751	7526	2/4/2002		PR	y	y
751	7528		4/26/2002	PR	n	n
751	7529	1/23/2002			y	
751	7530	3/19/2002			y	
752	7541	10/1/2001		PR	y	n
752	7542		10/30/2001	PR	n	y
752	7543	10/2/2001			y	
752	7544	1/10/2002			y	
752	7545	12/10/2001			y	
752	7546	1/4/2002			y	
752	7547	5/15/2002		PR	y	y
752	7548		5/15/2002		n	
752	7549		2/19/2002		n	
801	8001	7/13/2000			y	
801	8002	8/8/2000			n	
801	8004	11/15/2000	7/7/2000		n	n
801	8006	12/12/2000	6/27/2000		n	
801	8007		12/7/2000	PR	n	y
801	8008	12/11/2000			y	
801	8009	10/10/2000			y	
801	8010	2/21/2001			y	
801	8012	3/30/2001			y	
801	8013	6/27/2001		PR	y	y
801	8014		3/8/2001		y	
801	8015	10/25/2001		PR	y	y
801	8016	7/2/2001			n	
801	8017		4/16/2001		y	
801	8018	7/31/2001	4/10/2001		n	
801	8019	7/19/2001			y	
801	8020	8/20/2001			y	
801	8022		11/26/2001	CR	n	y
801	8023	9/24/2001			y	
801	8024	10/26/2001			y	
801	8025	11/22/2001			y	
801	8027	2/18/2002			y	
851	8510		11/21/2000	PR	n	y
851	8511		1/22/2001		n	
851	8512	3/21/2002		PR	y	y
851	8513		5/23/2002		n	
851	8514		5/23/2002		n	
851	8515		4/11/2002		n	

SDYIN	CTPATN	PROGDTN	Censor date	Respons	Prog Agree	Resp Agree
855	8551	6/14/2001			y	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
3/3/04 11:43:56 AM
CSO
Sent to sponsor via facsimile on February 25, 2004

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Norma Ascroft, Lilly
Fax: 317 276-1652

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 13

Date: 3-5-04

COMMENTS: Re: NDA 21-677 (Alimta for NSCLC), here are tables from Dr. Cohen. The 3rd column is progression dates; the 4th column is censor dates; and the 5th column indicates cases where Dr. Cohen changed the progression or censor date.

Dotti for Patty

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
1	DOCETA	7/16/2001	8/27/2001		
11	DOCETA	11/5/2001		3/14/2002	
41	MTA	9/28/2001	12/3/2001		
42	MTA	11/27/2001	1/24/2002		
51	DOCETA	4/9/2001	5/29/2001		
52	DOCETA	4/9/2001	12/19/2001		
53	MTA	4/9/2001	8/20/2001		
54	DOCETA	4/13/2001	7/10/2001		
55	MTA	4/13/2001	8/31/2001		
56	MTA	4/13/2001		5/18/2001	
57	MTA	4/16/2001	10/17/2001		
58	MTA	5/2/2001		9/6/2001	
59	MTA	5/9/2001	6/5/2001		
60	MTA	5/10/2001		6/22/2001	
61	MTA	10/24/2001	12/11/2001		
62	DOCETA	11/14/2001		4/16/2002	
81	MTA	9/19/2001	10/5/2001		
82	DOCETA	8/10/2001	10/29/2001		
84	MTA	9/11/2001		3/21/2002	
85	MTA	11/16/2001	12/28/2001		
86	DOCETA	11/16/2001	3/22/2002		
101	MTA	4/5/2001	6/2/2001		
102	MTA	7/2/2001		11/10/2001	
103	DOCETA	7/19/2001	12/7/2001		
105	DOCETA	9/24/2001	2/5/2002		
111	MTA	6/4/2001	8/29/2001		
112	MTA	6/27/2001	4/10/2002		
115	MTA	8/9/2001		6/24/2002	
117	MTA	9/21/2001	3/14/2002		1
118	MTA	9/28/2001	11/25/2001		
120	DOCETA	11/2/2001		8/18/2002	
121	DOCETA	4/27/2001	6/8/2001		
141	MTA	7/12/2001		7/12/2001	
143	DOCETA	12/3/2001		5/28/2002	
161	DOCETA	5/9/2001	7/18/2001		
171	MTA	3/20/2001	5/2/2001		
172	DOCETA	3/26/2001	5/2/2001		
173	DOCETA	4/5/2001		9/19/2001	
174	DOCETA	4/18/2001		5/25/2001	
176	MTA	10/16/2001		1/5/2002	
178	MTA	12/3/2001	2/22/2002		
201	MTA	4/25/2001	6/1/2001		
202	DOCETA	8/9/2001	9/24/2001		
211	DOCETA	8/31/2001		2/4/2002	
231	DOCETA	3/22/2001	6/29/2001		
261	DOCETA	7/12/2001	8/17/2001		
271	DOCETA	9/10/2001	1/25/2002		
291	MTA	7/23/2001	10/29/2001		1

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
292	DOCETA	7/26/2001		9/27/2001	
301	MTA	12/12/2001		1/24/2002	
311	DOCETA	5/18/2001	6/20/2001		
312	MTA	5/25/2001	10/8/2001		
313	DOCETA	6/15/2001	7/20/2001		
314	DOCETA	11/7/2001		4/24/2002	
321	DOCETA	5/24/2001	7/12/2001		
331	DOCETA	8/8/2001		9/19/2001	1
341	MTA	7/24/2001	10/18/2001		
344	MTA	11/7/2001	12/3/2001		
351	DOCETA	4/30/2001		9/10/2001	
352	DOCETA	5/24/2001	7/10/2001		
353	MTA	8/9/2001	3/13/2002		
354	MTA	9/18/2001		3/29/2002	
355	DOCETA	12/11/2001	3/6/2002		
364	MTA	11/12/2001	1/2/2002		
371	MTA			8/6/2001	
381	DOCETA	8/13/2001	9/21/2001		
391	MTA	7/18/2001	10/18/2001		
392	MTA	8/17/2001	10/1/2001		
394	MTA	8/30/2001	11/23/2001		
396	MTA	10/31/2001	12/18/2001		
402	DOCETA	6/28/2001	8/13/2001		
403	DOCETA	8/8/2001	9/17/2001		
405	MTA	9/4/2001	10/22/2002		
406	MTA	10/17/2001	11/29/2001		
421	DOCETA	9/24/2001	10/10/2001		
441	MTA	11/19/2001	5/13/2002		
481	DOCETA	8/15/2001	11/5/2001		
491	DOCETA	10/23/2001	11/14/2001		
521	DOCETA	7/23/2001	8/28/2001		
522	MTA	9/11/2001	10/25/2001		
523	DOCETA	10/26/2001	11/21/2001		
551	DOCETA	8/28/2001	1/23/2002		
552	MTA	11/16/2001	4/4/2002		
561	MTA	8/9/2001	9/6/2001		
562	MTA	9/5/2001		1/17/2002	
563	DOCETA	10/15/2001	11/8/2001		
564	MTA	10/18/2001		12/5/2001	
565	MTA	10/22/2001		8/22/2002	
566	DOCETA	10/25/2001	11/15/2001		
601	DOCETA	6/7/2001		7/17/2001	
602	DOCETA	6/8/2001		6/9/2001	
606	DOCETA	10/26/2001		12/17/2001	
607	DOCETA	10/30/2001		2/1/2002	
608	MTA	11/5/2001		11/5/2001	
609	MTA	11/26/2001	1/7/2002		
610	DOCETA	12/12/2001	1/28/2002		

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
611	DOCETA	6/14/2001	7/22/2001		
613	DOCETA	6/29/2001		11/7/2001	
614	DOCETA	7/27/2001		11/27/2001	
616	MTA	11/8/2001	6/6/2002		
617	MTA	11/12/2001	1/4/2002		
642	MTA	6/27/2001	12/14/2001		
644	DOCETA	9/27/2001	1/30/2002		
645	MTA	9/28/2001	11/5/2001		
646	DOCETA	10/23/2001		12/5/2001	
647	DOCETA	11/1/2001	12/18/2001		
648	MTA	11/27/2001	1/11/2002		
651	DOCETA	7/12/2001	8/22/2001		
652	DOCETA	9/6/2001	11/6/2001		
721	DOCETA	5/25/2001	12/10/2001		
722	DOCETA	6/4/2001	3/11/2002		
725	DOCETA	6/26/2001	11/14/2001		
726	DOCETA	7/12/2001	11/27/2001		
727	DOCETA	7/16/2001		10/11/2001	
729	MTA	7/27/2001		3/11/2002	
802	MTA	11/26/2001	2/20/2002		
821	DOCETA	9/11/2001	10/17/2001		
831	MTA	8/9/2001		9/21/2001	
880	MTA	11/21/2001	4/29/2002		
1000	DOCETA	5/28/2001	11/26/2001		
1001	MTA	6/4/2001	3/6/2002		
1002	MTA	6/11/2001	7/30/2001		
1003	DOCETA	6/11/2001	7/23/2001		
1004	DOCETA	6/18/2001	1/3/2002		
1005	DOCETA	6/21/2001	8/6/2001		
1006	MTA	6/22/2001	7/27/2001		
1007	DOCETA	7/9/2001	2/20/2002		
1008	MTA	7/9/2001	8/21/2001		
1009	DOCETA	7/9/2001	8/20/2001		
1010	MTA	7/11/2001	8/22/2001		
1041	DOCETA	6/8/2001	7/31/2001		
1045	DOCETA	9/3/2001	9/6/2001		
1051	DOCETA	8/16/2001	12/19/2001		1
1052	DOCETA	9/3/2001		10/22/2001	
1053	MTA	10/10/2001	4/10/2002		
1054	DOCETA	10/23/2001	1/20/2002		
1055	MTA	10/24/2001	3/11/2002		
1056	MTA	1/9/2002	7/10/2002		
1073	MTA	7/27/2001		9/17/2001	
1074	MTA	9/21/2001	2/13/2002		
1076	DOCETA	8/6/2001		11/6/2001	
1077	DOCETA	9/21/2001	3/11/2002		
1079	DOCETA	9/26/2001	12/26/2001		
1080	DOCETA	10/2/2001	10/30/2001		

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
1081	DOCETA	10/1/2001		11/29/2001	
1082	MTA	10/1/2001	8/6/2002		
1088	MTA	10/8/2001	3/26/2002		
1089	MTA	10/18/2001		4/26/2002	
1090	DOCETA	11/5/2001	12/10/2001		
1091	MTA	11/22/2001	2/19/2002		
1092	DOCETA	12/13/2001	1/22/2002		
1300	MTA	7/2/2001	9/28/2001		
1311	MTA	11/6/2001	5/7/2002		
1312	MTA	11/8/2001		2/14/2002	
1321	MTA	11/5/2001	12/25/2001		
1322	MTA	11/19/2001	1/8/2002		
1601	MTA	11/15/2001		3/20/2002	
1602	DOCETA	11/27/2001		4/17/2002	
1603	MTA	11/29/2001		5/15/2002	
1611	MTA	10/29/2001	12/19/2001		
1612	DOCETA	11/21/2001		1/3/2002	1
1614	MTA	1/18/2002		3/11/2002	
2000	DOCETA	5/28/2001	12/13/2001		
2001	MTA	5/24/2001	6/27/2002		
2002	MTA	6/6/2001	7/24/2001		
2003	DOCETA	6/11/2001		11/2/2002	
2004	MTA	6/28/2001	1/29/2002		
2005	MTA	10/15/2001	1/8/2002		
2007	MTA	12/12/2001	2/22/2002		
2008	MTA	12/17/2001	5/24/2002		
2009	DOCETA	1/8/2002	1/18/2002	1/8/2002	
2021	MTA	7/19/2001	10/23/2001		
2022	DOCETA	11/1/2001	12/21/2001		
2024	MTA	1/7/2002	6/19/2002		
2061	DOCETA	1/2/2002	4/13/2002		
2062	DOCETA	1/2/2002		5/15/2002	
2063	MTA	11/30/2001	4/10/2002		
2081	MTA	11/5/2001	12/31/2001		
2083	MTA	12/13/2001	1/28/2002		
2200	DOCETA	5/2/2001		5/2/2001	
2201	DOCETA	5/8/2001	6/14/2001		
2202	MTA	7/3/2001		11/8/2001	
2204	DOCETA	7/20/2001	8/30/2001		
2205	DOCETA	11/2/2001		2/19/2002	
2206	DOCETA	12/10/2001	1/17/2002		
2207	MTA	12/12/2001	4/18/2002		
2209	MTA	12/21/2001	1/22/2002		
2210	MTA	1/4/2002	2/14/2002		
2211	MTA	1/8/2002		2/19/2002	
2241	MTA	6/5/2001	7/6/2001		
2243	MTA	8/3/2001	9/28/2001		
2245	MTA	12/18/2001		12/2/2002	

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
2246	DOCETA	12/20/2001		4/8/2002	
2247	DOCETA	12/24/2001		5/9/2002	
2248	DOCETA	12/24/2001		5/6/2002	
2249	MTA	1/3/2002	6/3/2002		
2251	MTA	1/4/2002		2/18/2002	
2252	DOCETA	1/7/2002	2/15/2002		
3001	DOCETA	6/1/2001		6/1/2001	
3002	DOCETA	6/11/2001		12/5/2001	
3003	MTA	6/25/2001	10/3/2001		
3005	MTA	11/13/2001	2/13/2002		
3016	MTA	6/1/2001	7/25/2001		
3017	DOCETA	10/1/2001		12/12/2001	
3018	DOCETA	10/1/2001		2/19/2002	
3020	DOCETA	10/9/2001	11/20/2001		
3021	DOCETA	10/17/2001		11/27/2001	
3022	DOCETA	2/18/2002	11/26/2001		1
3023	DOCETA	10/25/2001		10/25/2001	
3025	MTA	10/25/2001	2/7/2002		
3026	DOCETA	1/15/2002	4/10/2002		
3031	MTA	10/22/2001		10/22/2001	
3061	MTA	6/12/2001	8/3/2001		
3062	DOCETA	12/5/2001	3/11/2002		
3076	DOCETA	11/19/2001		5/7/2002	
3131	MTA	10/1/2001	2/8/2002		
3146	MTA	11/26/2001	1/10/2002		
3147	DOCETA	12/3/2001		2/20/2002	
3188	DOCETA	1/7/2002	4/8/2002		
3201	DOCETA	10/11/2001		11/28/2001	
3211	MTA	5/2/2001	8/13/2001		
3212	MTA	7/16/2001	11/28/2001		
3213	DOCETA	11/12/2001	1/30/2002		
3221	MTA	7/24/2001		1/16/2002	
3222	DOCETA	12/3/2001	1/17/2002		
3231	DOCETA	5/10/2001	9/5/2001		
3232	MTA	6/29/2001		9/26/2001	
3234	MTA	11/23/2001	4/10/2002		
3241	DOCETA	4/16/2001		7/5/2001	
3242	DOCETA	4/16/2001	5/7/2001		
3243	DOCETA	5/2/2001		7/26/2001	
3244	MTA	5/2/2001	7/26/2001		
3245	DOCETA	6/15/2001		6/15/2001	
3246	MTA	11/12/2001		4/18/2002	
3261	DOCETA	7/10/2001	8/21/2001		
3272	MTA	1/10/2002		3/1/2002	
3283	MTA	5/3/2001		9/11/2001	
3285	MTA	7/13/2001		11/20/2001	
3286	MTA	1/4/2002	3/29/2002		
3292	MTA	5/29/2001		12/21/2001	

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
3293	DOCETA	8/2/2001	10/26/2001		
3294	DOCETA	11/16/2001	12/28/2001		
3295	DOCETA	12/3/2001		1/11/2002	1
3296	DOCETA	1/11/2002	3/8/2002		
3300	DOCETA			2/20/2002	
3301	DOCETA	1/28/2002		1/28/2002	
3312	MTA	1/10/2002	2/25/2002		
3313	DOCETA	1/10/2002	4/2/2002		
3315	DOCETA	1/10/2002	6/4/2002		
3316	DOCETA	1/17/2002		2/25/2002	
3321	MTA	12/7/2001	4/18/2002		
3322	MTA	12/20/2001	2/9/2002		
3323	DOCETA	1/15/2002	2/22/2002		
3324	MTA	1/21/2002		8/30/2002	
3325	MTA	1/30/2002	3/15/2002		
3331	DOCETA	12/31/2001		5/3/2002	
3333	DOCETA	1/25/2002	4/19/2002		
3451	MTA	12/24/2001	3/21/2002		
3452	MTA	1/4/2002		5/20/2002	
3453	DOCETA	1/30/2002	4/2/2002		
3461	MTA	12/31/2001		5/8/2002	
3462	DOCETA	12/26/2001		2/1/2002	
3464	DOCETA	1/14/2002	5/14/2002		
3465	MTA	1/24/2002		7/12/2002	
3511	DOCETA	11/13/2001		2/8/2002	
3512	DOCETA	12/31/2001	1/9/2002	12/31/2002	
4000	MTA	5/25/2001	7/10/2001		
4001	DOCETA	6/5/2001		10/8/2001	
4002	DOCETA	6/27/2001		6/27/2001	
4003	DOCETA	7/11/2001	10/15/2001		
4004	DOCETA	7/20/2001		7/20/2001	
4005	MTA	8/23/2001	10/8/2001		
4006	DOCETA	10/11/2001		2/14/2002	
4007	DOCETA	11/1/2001	12/18/2001		
4021	MTA	4/6/2001	5/25/2001		
4022	MTA	4/9/2001		5/25/2002	
4041	MTA	6/20/2001	10/8/2001		
4042	DOCETA	8/13/2001	9/21/2001		
4043	DOCETA	8/27/2001		10/11/2001	
4044	MTA	10/2/2001	11/22/2001		
4045	DOCETA	11/12/2001		12/27/2001	
4046	MTA	11/13/2001	12/27/2001		
4047	MTA	11/15/2001	1/3/2002		
4048	MTA	12/27/2001		2/14/2002	
4061	DOCETA	7/9/2001		7/9/2001	
4062	DOCETA	8/9/2001		8/9/2001	
4063	DOCETA	9/24/2001		12/27/2001	
4065	DOCETA	10/1/2001		1/2/2002	

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
4081	DOCETA	5/25/2001		6/18/2001	
4082	MTA	6/21/2001	8/8/2001		
4084	MTA	7/9/2001		7/9/2001	
4085	DOCETA	8/9/2001		11/7/2001	
4086	MTA	8/15/2001		8/15/2001	
4088	DOCETA	11/15/2001	12/19/2001		
4089	DOCETA	11/26/2001	1/16/2002		
4090	MTA	12/4/2001	1/18/2002		
4101	DOCETA	6/18/2001		7/31/2001	
4102	MTA	8/16/2001		1/9/2002	
4103	MTA	9/3/2001	12/14/2001		
4104	DOCETA	9/10/2001	10/25/2001		
4105	MTA	9/18/2001		11/1/2001	
4106	DOCETA	1/16/2002		2/17/2002	
4121	MTA	12/27/2001	7/12/2002		
4122	MTA	12/27/2001	3/26/2002		
4123	DOCETA	1/31/2002		3/19/2002	
4141	DOCETA	12/3/2001	12/12/2001		
4161	DOCETA	10/1/2001	11/15/2001		
4162	MTA	10/8/2001		4/4/2002	
4163	MTA	10/10/2001		1/10/2002	
4164	MTA	11/5/2001	3/27/2002		
4165	DOCETA	11/16/2001		4/3/2002	
4166	DOCETA	11/16/2001	4/10/2002		
4167	MTA	11/19/2001		11/19/2001	
4168	DOCETA	11/22/2001	1/17/2002		
4169	DOCETA	12/10/2001		12/10/2001	
4170	DOCETA	12/10/2001		12/10/2001	
4171	MTA	12/19/2001	2/7/2002		
4172	MTA	12/21/2001		12/21/2001	
4173	MTA	1/14/2002		1/14/2002	
4174	MTA	1/14/2002	3/6/2002		
4182	MTA	10/8/2001		10/8/2001	
4183	DOCETA	10/16/2001	11/29/2001		
4184	DOCETA	10/31/2001		3/14/2002	
4185	MTA	10/29/2001		12/12/2001	
4186	DOCETA	11/7/2001		11/7/2001	
4187	DOCETA	11/9/2001		11/9/2001	
4188	DOCETA	11/16/2001	4/15/2002		
4190	DOCETA	12/5/2001		12/5/2001	
4191	MTA	12/10/2001		4/18/2002	
4192	DOCETA	12/14/2001	1/29/2002		
4193	MTA	12/14/2001	2/6/2002		
4194	MTA	12/19/2001	2/18/2002		
4195	MTA	12/27/2001		2/6/2002	
4196	DOCETA	12/27/2001		12/27/2001	
4197	DOCETA	12/21/2001	2/7/2002		
4198	MTA	1/11/2002	3/6/2002		

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
4199	DOCETA	1/18/2002		1/18/2002	
4201	DOCETA	8/14/2001	10/24/2001		1
4202	MTA	8/31/2001	9/27/2001		
4203	MTA	9/25/2001	12/5/2001		
4204	MTA	10/1/2001		10/1/2001	
4205	DOCETA	11/16/2001		11/16/2001	1
4261	DOCETA	6/7/2001		10/15/2001	
4262	DOCETA	6/21/2001		10/25/2001	
4264	MTA	8/1/2001		9/7/2001	
4266	MTA	8/13/2001		1/24/2002	
4267	MTA	11/2/2001	1/28/2002		
4268	MTA	11/16/2001	1/10/2002		
4281	MTA	7/4/2001		11/20/2001	1
4282	DOCETA	8/16/2001	12/19/2001		
4283	DOCETA	9/5/2001	2/21/2002		
4284	DOCETA	10/1/2001	10/26/2001		
4285	DOCETA	10/22/2001		3/13/2002	
4286	MTA	11/7/2001	12/21/2001		
4287	MTA	11/12/2001	2/22/2002		
4288	MTA	11/19/2001	1/7/2002		
4289	MTA	11/23/2001	5/29/2002		
4290	MTA	11/27/2001	1/17/2002		
4291	MTA	12/10/2001	1/18/2002		
4292	DOCETA	1/14/2002	2/6/2002		
5000	MTA	11/27/2001		4/20/2002	
5001	MTA	11/27/2001		4/19/2002	
5002	DOCETA	11/27/2001	3/11/2002		
5003	DOCETA	11/27/2001		1/9/2002	
5004	DOCETA	11/27/2001		5/3/2002	
5006	MTA	12/10/2001	5/5/2002		
5007	DOCETA	12/10/2001		12/10/2001	
5008	DOCETA	12/10/2001		1/22/2002	
5009	MTA	12/10/2001		5/6/2002	
5010	MTA	12/14/2001	1/29/2002		
5011	MTA	12/14/2001		5/6/2002	
5012	DOCETA	12/27/2001		2/15/2002	
5013	MTA	12/21/2001		5/24/2002	
5014	DOCETA	12/31/2001		4/18/2002	
5015	MTA	12/31/2001		5/30/2002	
5016	MTA	12/31/2001	2/19/2002		
5017	DOCETA	12/31/2001	1/18/2002		
5018	DOCETA	12/31/2001	1/23/2002		
5019	MTA	1/9/2002	2/26/2002		
5021	MTA	1/24/2002		3/22/2002	
5040	MTA	12/28/2001	3/20/2002		
5161	DOCETA	1/9/2002	2/26/2002		
5550	MTA	5/23/2001		9/21/2001	
5551	MTA	12/12/2001	1/14/2002		1

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
5570	DOCETA	6/18/2001	10/22/2001		
5572	DOCETA	11/12/2001		11/12/2001	
5573	MTA	12/6/2001	10/23/2002		
5574	DOCETA	12/19/2001	3/28/2002		
5590	MTA	4/17/2001	5/2/2001		
5592	DOCETA	5/4/2001	8/1/2001		
5593	DOCETA	7/2/2001	8/17/2001		
5594	DOCETA	8/1/2001		8/1/2001	
5595	DOCETA	8/3/2001		8/3/2001	
5597	MTA	1/14/2002		4/17/2002	
5601	MTA	6/1/2001		11/16/2001	
5602	DOCETA	11/27/2001		4/4/2002	
5603	DOCETA	12/10/2001		6/14/2002	
5604	MTA	12/17/2001	1/16/2002		
6001	DOCETA	10/9/2001		1/24/2002	
6002	MTA	10/10/2001	12/4/2001		
6003	MTA	10/31/2001	11/19/2001		
6004	DOCETA	11/6/2001	3/14/2002		
6005	DOCETA	11/12/2001	3/14/2002		
6006	DOCETA	12/12/2001		4/18/2002	
6021	MTA	10/15/2001	11/26/2001		
6022	MTA	11/17/2001	12/18/2001		
6023	DOCETA	2/6/2002		4/24/2002	
6061	DOCETA	10/8/2001	12/1/2001		
6062	MTA	12/14/2001		4/12/2002	
6081	MTA	6/25/2001	8/7/2001		
6082	MTA	7/12/2001		7/12/2001	
6083	DOCETA	7/30/2001	9/3/2001		
6086	MTA	12/11/2001		12/11/2001	
6087	DOCETA	12/17/2001	1/23/2002		
6101	MTA	11/14/2001	2/8/2002		
6200	DOCETA	4/24/2001		4/24/2001	
6201	MTA	4/24/2001	7/23/2001		
6202	DOCETA	6/28/2001	8/13/2001		
6203	MTA	6/15/2001	9/13/2001		
6204	DOCETA	6/15/2001		8/27/2001	
6208	DOCETA	11/26/2001		3/18/2002	1
6209	MTA	11/26/2001	1/15/2002		
6210	DOCETA	1/15/2002		5/1/2002	
6224	DOCETA	7/5/2001		8/16/2001	
6225	MTA	8/1/2001	9/5/2001		
6227	DOCETA	11/15/2001		3/28/2002	
6228	DOCETA	11/29/2001		3/11/2002	
6229	MTA	12/6/2001	1/28/2002		
6231	MTA	12/27/2001		12/27/2001	
6232	MTA	1/29/2002	3/11/2002		
6241	DOCETA	5/30/2001		5/30/2001	
6242	MTA	6/5/2001	8/28/2001		

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
6262	MTA	5/7/2001	10/12/2001		
6263	MTA	5/11/2001		5/11/2001	
6264	DOCETA	10/2/2001	4/2/2002		
6268	DOCETA	12/28/2001		4/4/2002	
6269	MTA	1/15/2002		3/5/2002	1
6270	DOCETA	1/25/2002		1/25/2002	
6271	MTA	1/31/2002	7/12/2002		
6282	DOCETA	4/10/2001		8/14/2001	
6283	MTA	5/3/2001		6/23/2001	
6284	DOCETA	5/9/2001		8/3/2001	
6285	MTA	6/18/2001	8/14/2001		
6286	DOCETA	7/31/2001	12/19/2001		
6287	DOCETA	12/3/2001	1/3/2002		
6301	MTA	4/18/2001	9/18/2001		
6304	MTA	12/31/2001	4/1/2002		
6321	MTA	7/16/2001	12/21/2001		
6322	DOCETA	7/25/2001		2/22/2002	
6325	MTA	10/30/2001	12/13/2001		
6328	DOCETA	12/21/2001	2/1/2002		
6329	DOCETA	12/21/2001		6/17/2002	
6330	DOCETA	12/28/2001		5/20/2002	
6341	MTA	4/9/2001	5/23/2001		
6343	DOCETA	6/4/2001	9/19/2001		
6344	MTA	6/11/2001	9/6/2001		
6345	MTA	6/18/2001	7/16/2001		
6346	MTA	7/11/2001		11/19/2001	
6350	MTA	10/1/2001	1/24/2002		
6352	DOCETA	11/26/2001	3/25/2002		
6353	MTA	12/10/2001		1/21/2002	
6355	DOCETA	12/17/2001		12/17/2001	
6356	DOCETA	12/17/2001		4/8/2002	
6357	MTA	12/28/2001	3/25/2002		
6358	MTA	12/28/2001		2/8/2002	
6360	MTA	1/2/2002	2/8/2002		
6600	MTA	11/28/2001	12/26/2001		
6602	DOCETA	12/21/2001	3/22/2002		
6603	DOCETA	12/21/2001		4/23/2002	
6611	DOCETA	11/29/2001	2/16/2002		
6612	DOCETA	11/28/2001	4/2/2002		
6613	DOCETA	12/10/2001		4/16/2002	
6614	MTA	12/10/2001		4/29/2002	
6615	DOCETA	12/10/2001	1/20/2002		
6616	DOCETA	12/17/2001	3/10/2002		
6617	MTA	12/17/2001		5/4/2002	
6618	MTA	1/7/2002		6/8/2002	
6619	DOCETA	1/7/2002	3/30/2002		
6621	MTA	11/28/2001	1/21/2002		
6622	DOCETA	12/19/2001		3/16/2002	

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
6624	DOCETA	12/29/2001	4/3/2002		
6626	MTA	1/10/2002	2/26/2002		
6627	DOCETA	1/17/2002		3/8/2002	
7001	MTA	8/10/2001		8/10/2001	
7002	MTA	12/10/2001		2/7/2002	
7041	MTA	8/16/2001	10/4/2001		
7043	DOCETA	8/16/2001	10/3/2001		
7044	MTA	8/16/2001		10/5/2001	
7045	DOCETA	8/21/2001		11/22/2001	
7046	DOCETA	8/29/2001	10/9/2001		
7047	DOCETA	10/30/2001	12/13/2001		
7048	MTA	10/30/2001		1/2/2002	
7049	DOCETA	11/8/2001	3/27/2002		
7050	MTA	11/12/2001		11/12/2001	
7061	MTA	11/13/2001	1/24/2002		
7062	DOCETA	11/13/2001		2/26/2002	
7065	DOCETA	11/23/2001		1/29/2002	
7121	DOCETA	12/14/2001	3/27/2002		
7200	MTA	8/9/2001	11/5/2001		
7201	DOCETA	10/18/2001	11/21/2001		
7202	DOCETA	10/24/2001		10/24/2001	
7211	MTA	8/2/2001		8/2/2001	
7212	DOCETA	8/9/2001	12/28/2001		
7214	MTA	9/28/2001		9/28/2001	
7215	DOCETA	11/12/2001	12/3/2001		
7216	DOCETA	11/27/2001		1/4/2002	
7217	MTA	12/18/2001	5/2/2002		
7221	MTA	10/9/2001	11/22/2001		
7232	MTA	11/30/2001	1/25/2002		
7700	MTA	6/11/2001	9/4/2001		
7701	DOCETA	6/11/2001		9/3/2001	1
7702	MTA	6/18/2001	11/28/2001		
7703	MTA	12/5/2001	1/24/2002		
7750	DOCETA	5/4/2001	5/29/2001		
7752	DOCETA	7/11/2001	8/21/2001		
7753	MTA	11/5/2001	12/22/2001		
7754	DOCETA	12/19/2001	1/11/2002		
7761	DOCETA	6/21/2001		9/13/2001	
7762	MTA	6/21/2001	7/27/2001		
7763	MTA	6/21/2001		12/7/2001	
7765	MTA	7/20/2001		10/4/2001	
7766	DOCETA	11/8/2001	12/27/2001		
7767	DOCETA	11/27/2001		2/28/2002	
7768	DOCETA	12/13/2001		4/17/2002	
7769	DOCETA	12/13/2001	2/7/2002		
7770	DOCETA	1/9/2002	3/18/2002		
8001	DOCETA	11/13/2001	12/27/2001		
8002	DOCETA	11/28/2001		2/18/2002	

CTPAT	DRUGN	RANDMDTE	PRGRSDT	Censor da	Date chang
8003	DOCETA	12/27/2001	2/6/2002		
8004	MTA	1/24/2002	5/28/2002		
8020	MTA	10/15/2001		11/28/2001	
8023	DOCETA	12/10/2001	1/17/2002		
8060	MTA	12/4/2001		1/25/2002	
8501	DOCETA	6/29/2001		9/24/2001	
8502	MTA	9/26/2001	2/8/2002		
8512	MTA	12/19/2001	1/31/2002		
8513	DOCETA	12/27/2001		4/29/2002	
8521	DOCETA	10/12/2001	11/26/2001		
8522	MTA	10/29/2001	12/7/2001		
8523	DOCETA	1/3/2002		5/15/2002	
8603	DOCETA	1/21/2002	5/29/2002		
8604	MTA	11/12/2001		3/18/2002	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
3/25/04 03:44:42 PM
CSO
Facsimile sent to sponsor on March 5, 2004

CLINICAL TEAM LEADER REVIEW
OF SUPPLEMENTAL NDA

SNDA 20509/SE1/Sn 029

APPLICANT Eli Lilly

DRUG NAME Gemzar (gemcitabine HCL)

SUBMISSION DATE 12/17/03

PDUFA DATE 6/18/04

REVIEW PRIORITY Priority

INDICATION Gemzar in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline containing ———— unless anthracyclines were clinically contraindicated.

CLINICAL EVALUATION

NOTE: All Tables and Figures in this review are copied from the Medical Officer and Statistical Reviews.

Submitted Clinical Trials

Study phase	Protocol(s)
Phase 3	Trial JHQG Gemzar+paclitaxel vs paclitaxel in adjuvant/ neoadjuvant anthracycline pretreated metastatic breast cancer (MBC).
Phase 2	Gemzar+paclitaxel study in MBC
Phase 2	Four published gemzar+paclitaxel studies in MBC
Phase 1	Gemzar+paclitaxel study
Phase 2	Twelve gemzar monotherapy studies for MBC

Results of Phase 2 Gemzar+Paclitaxel Trials

Study	No. Patients	Time to progression	Response rate
S024 (Lilly)	40	7.2 months	40
Colomer R 2000	43	NR	68
Delfino C 2003	45	11 months	67
Sanchez-Rovira 1999	41	7.8 months	40

Phase 3 RCT JHQG

The principal support for the SNDA is from a single randomized clinical trial in 529 patients as described in the following Study design Schema.

Study Design JHQG

PRE-THERAPY	Females □18 years old with unresectable, locally recurrent or metastatic breast cancer who have received adjuvant anthracycline-containing chemotherapy and have KPS □70 and adequate organ function and bone marrow reserve	
	Baseline CT scan of chest and abdomen; nuclear medicine bone scan	
	RANDOMIZE	
DURING THERAPY	Arm A: Paclitaxel 175 mg/m^2 (Day 1, q21 days) Gemcitabine 1250 mg/m^2 (Days 1 and 8, q21 days)	Arm B: Paclitaxel 175 mg/m^2 (Day 1, q21 days)
	Treatment continues until the disease progresses, intolerable toxicity develops, or other relevant reason for discontinuation of treatment occurs	
POST-THERAPY	30-day post-therapy follow-up visit to assess safety and confirm response	
	Bimonthly follow-up for patients without confirmed disease progression (by radiologic or physical exam) q2 months after 30-day follow-up until progression	

Long-term follow-up for patients with confirmed disease progression (by radiologic or physical exam) in 4-month intervals after 30-day follow-up

A total of 598 patients with unresectable, locally recurrent or metastatic breast cancer were entered into this study conducted at 98 investigational sites globally. The first patient was randomized on 11 August 1999, and the last patient was randomized on 02 April 2002.

Demographics

Variable	ALL (N=529)	Taxol (N=262)	Gem/Tax (N=267)
Origin: No. (%)			
African Descent	13 (2.5)	5 (1.9)	8 (3.0)
Western Asian	78 (14.7)	39 (14.9)	39 (14.6)
Caucasian	316 (59.7)	159 (60.7)	157 (58.8)
East/Southeast A	25 (4.7)	12 (4.6)	13 (4.9)
Hispanic	90 (17.0)	43 (16.4)	47 (17.6)
Other	7 (1.3)	4 (1.5)	3 (1.1)
Age:			
Mean	52.81	52.77	52.85
Median	53.00	52.00	53.00
Range	26-83	26-75	26-83
Height cm.: (Visit 1)			
Mean	158.54	158.50	158.58
Median	159.00	160.00	159.00
Range.	124-185	124-185	135-182
Weight kg.: (Visit: 1)			
No. Patients	524	258	266
Mean	69.26	69.42	69.12
Median	68.00	68.00	67.54
Range.	36-159	36-159	37-122
Unspecified	5	4	1

Baseline Disease Characteristics

Variable	ALL (N=529)	Taxol (N=262)	Gem/Tax (N=267)
Diagnosis/Histology (Visit: 1)			
Breast	41 (7.8)	22 (8.4)	19 (7.1)
Ductal Breast	438 (82.8)	212 (80.9)	226 (84.6)
Lobular Breast	39 (7.4)	21 (8.0)	18 (6.7)
Tubular Br Ca	2 (0.4)	1 (0.4)	1 (0.4)
Medullary Br Ca	1 (0.2)	1 (0.4)	0
Mucinous Br Ca	6 (1.1)	3 (1.1)	3 (1.1)
Breast papillary	1 (0.2)	1 (0.4)	0
Adeno, pleura	1 (0.2)	1 (0.4)	0
Grade of Differentiation (Visit: 1)			
No. Patients	529	262	267
Well Differentiated	23 (4.3)	16 (6.1)	7 (2.6)
Moderately Differentiated	158 (29.9)	72 (27.5)	86 (32.2)
Poorly Differentiated	128 (24.2)	63 (24.0)	65 (24.3)
Undifferentiated	20 (3.8)	11 (4.2)	9 (3.4)
Unknown	200 (37.8)	100 (38.2)	100 (37.5)
Stage at Entry (Visit: 1)			
Metastatic	513 (97.0)	254 (96.9)	259 (97.0)
Unresectable, locally adv.	16 (3.0)	8 (3.1)	8 (3.0)
Estrogen Receptor (Visit: 1)			
Not Done	35 (6.6)	15 (5.7)	20 (7.5)
Positive	165 (31.2)	80 (30.5)	85 (31.8)
Negative	195 (36.9)	103 (39.3)	92 (34.5)
Intermediate	7 (1.3)	4 (1.5)	3 (1.1)
Unknown	127 (24.0)	60 (22.9)	67 (25.1)
Progesterone Receptor (Visit: 1)			
Not Done (N)	42 (7.9)	18 (6.9)	24 (9.0)
Positive	134 (25.3)	71 (27.1)	63 (23.6)
Negative	198 (37.4)	105 (40.1)	93 (34.8)
Intermediate (I)	6 (1.1)	0	6 (2.2)
Unknown (U)	149 (28.2)	68 (26.0)	81 (30.3)
Estrogen & Progesterone Receptors Combined (Visit: 1)			
++	102 (19.3)	50 (19.1)	52 (19.5)
+-	46 (8.7)	23 (8.8)	23 (8.6)
-+	30 (5.7)	19 (7.3)	11 (4.1)
--	148 (28.0)	81 (30.9)	67 (25.1)
NN	35 (6.6)	15 (5.7)	20 (7.5)
UU	127 (24.0)	60 (22.9)	67 (25.1)
+N or U	14 (2.7)	7 (2.7)	7 (2.6)

	ALL	Taxol	Gem/Tax
-N or U	14 (2.7)	3 (1.1)	11 (4.1)
I+	2 (0.4)	2 (0.8)	0
I-	4 (0.8)	1 (0.4)	3 (1.1)
IN	1 (0.2)	1 (0.4)	0
+I	3 (0.6)	0	3 (1.1)
-I	3 (0.6)	0	3 (1.1)
Menopausal Status (Visit: 1)			
Pre-Menopausal	74 (14.1)	33 (12.6)	41 (15.5)
Post-Menopausal	409 (77.8)	206 (78.9)	203 (76.6)
Peri-Menopausal	39 (7.4)	19 (7.3)	20 (7.5)
Unknown	4 (0.8)	3 (1.1)	1 (0.4)
Unspecified	3	1	2
Performance Status (Visit: 1)			
100	194 (36.7)	95 (36.3)	99 (37.1)
90	189 (35.7)	100 (38.2)	89 (33.3)
80	94 (17.8)	36 (13.7)	58 (21.7)
70	48 (9.1)	29 (11.1)	19 (7.1)
60	2 (0.4)	1 (0.4)	1 (0.4)
Unknown	2 (0.4)	1 (0.4)	1 (0.4)

Appears This Way
On Original

Baseline Tumor Burden

	Number of Patients (%)	
	T Arm (N=262)	GT Arm (N=267)
Number of tumor burden sites		
1	63 (24.0%)	65 (24.3%)
2	91 (34.7%)	86 (32.2%)
3	60 (22.9%)	59 (22.1%)
4	24 (9.2%)	37 (13.9%)
≥5	24 (9.2%)	20 (7.5%)
Tumor burden site[a]		
Visceral[b]	191 (72.9%)	196 (73.4%)
Lung[c]	134 (51.1%)	145 (54.3%)
Liver	102 (38.9%)	103 (38.6%)
Other[d]	17 (6.5%)	13 (4.9%)
Nonvisceral only	71 (27.1%)	71 (26.6%)
Tumor burden size[e]		
Mean	35.8 cm^2	36.0 cm^2
Standard deviation	63.2 cm^2	101.3 cm^2
Median	15.5 cm^2	12.9 cm^2
Range	1.0 – 447.5 cm^2	1.0 – 1353.0 cm^2

a Patients may be counted in more than one category.
b Includes patients with visceral +/- nonvisceral tumor burden sites.
c Includes pleural effusion, pleura, and pleural fluid.
d Other visceral sites considered: ascites, ovary, abdomen, spleen, adrenal, uterus, pericardial fluid, eye, bone marrow, peritoneum, omentum, diaphragm, trachea, suprarenal gland, and perirenal.
e Includes all measurable visceral and nonvisceral tumor areas as measured and followed by the investigator.

Stratification Factors - Randomized Patients

Stratification Factors		T Arm (N=262)	GT Arm (N=267)
Karnofsky Performance Status	High (90)	195	188
	Low (80)	66	78
Prior anthracycline in	No	15	11
adjuvant/neoadjuvant setting	Yes	247	256
Prior hormonal therapy	No	132	129
	Yes	130	138
Presence of visceral metastases	No	71	71
	Yes	191	196
Disease progression with prior	6 months	51	51
adjuvant chemotherapy[c]	> 6 months	210	215

Time from Diagnosis to Randomization (Months)

	T Arm (N=262)	GT Arm (N=267)
Mean	43.4	41.4
Median	29.0	34.3
Range	3.7-270.7	2.3-228.2

Prior Therapy

Patients with Therapy Type	Taxol (N=262) n (%)	Gem/Tax (N=267) n (%)
Prior Surgery	260 (99.2)	265 (99.3)
Prior Radiotherapy	184 (70.2)	177 (66.3)
Prior Immunotherapy	2 (0.8)	1 (0.4)
Prior Hormonal Therapy	130 (49.6)	138 (51.7)
Prior Chemotherapy	260 (99.2)	267 (100)
Adjuvant Setting	230 (87.8)	228 (85.4)
One Line of Therapy	195 (74.4)	186 (69.7)
Two Lines of Therapy	31 (11.8)	41 (15.4)
Three or More Lines	4 (1.5)	1 (0.4)
Neoadjuvant Setting	61 (23.3)	78 (29.2)
One Line of Therapy	53 (20.2)	72 (27.0)
Two Lines of Therapy	8 (3.1)	4 (1.5)
Three or More Lines	0	2 (0.7)
Metastatic Setting	4 (1.5)	1 (0.4)

Patients with Therapy Type	Taxol (N=262) n (%)	Gem/Tax (N=267) n (%)
One Line of Therapy	4 (1.5)	1 (0.4)
Two Lines of Therapy	1 (0.4)	0

First Interim Survival Analysis
Cut-Off Date 9/17/03
65% Patients Dead

Treatment	Number of Events	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
T	183/262	**15.8** (14.4, 17.4)	0.775 (0.627, 0.959)	**0.0185**
GT	160/267	**18.5** (16.5, 20.7)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test.

Second Interim Survival Analysis in the Population as Treated
Cut-Off Date 2/26/04
71% Patients Dead

Treatment	Number of Events	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
T	194/262	**15.8** (14.4, 17.4)	0.823 (0.673, 1.008)	**0.0592**
GT	183/267	**18.6** (16.5, 20.7)		

[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test.

Second Interim Survival Analysis in the Population as Randomized
Cut-Off Date 2/26/04
71% Patients dead

Treatment	Number of Events	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
T	195/262	**15.8** (14.4, 17.4)	0.817 (0.667, 1.000)	**0.0489**
GT	182/267	**18.6** (16.6, 20.7)		

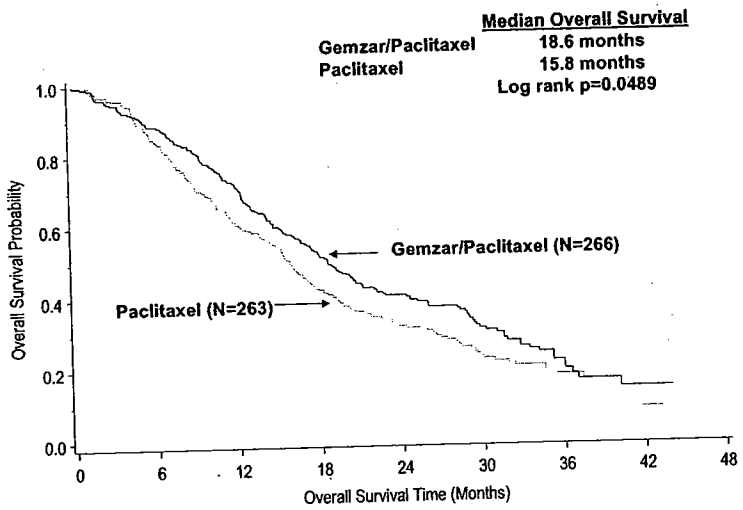
[1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test.

Second Interim Survival Analysis Excluding Patient # 531*
Cut-Off Date 2/26/04
71% Patients Dead

Treatment	Number of Events	Median Survival in Months[1] (95% C.I.)	Hazard Ratio[2] (95% C.I.)	P-value[3]
T	194/262	**15.8** (14.4, 17.4)	0.820 (0.669, 1.004)	**0.0538**
GT	182/266	**18.6** (16.6, 20.7)		

*: This patient was treated in GT arm but the randomization code was T; [1]: Kaplan-Meier Estimates; [2]: Hazard Ratio of GT/ T; [3]: unadjusted log-rank test.

Appears This Way
On Original



Post-Study Chemotherapy

	T Arm N=262	GT Arm N=267
Total number of patients receiving post-study chemotherapy	129	118
Patients with 1 line chemotherapy	63 (24.0%)	57 (21.3%)
Patients with 2 lines of chemotherapy	29 (11.1%)	22 (8.2%)
Patients with □3 lines of chemotherapy	37 (14.1%)	39 (14.6%)
Gemzar	37 (14.1%)	10 (3.75%)

Appears This Way
On Original

Time to Documented Progressive Disease (Months)

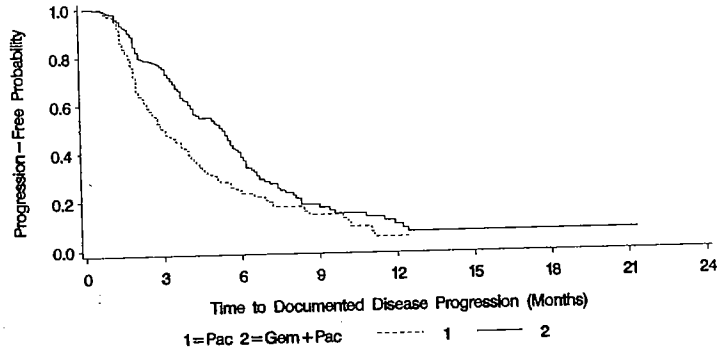
	T Arm (N=263)	GT Arm (N=266)
Patients censored, n (%)	80 (30.4)	110 (41.4)
Median (95% CI)	2.9 (2.6, 3.7)	5.2 (4.2, 5.6)

Abbreviations: TtDPD = time to documented progressive disease; T = paclitaxel monotherapy; GT = gemcitabine plus paclitaxel; N = number of randomized patients within each arm; CI = confidence interval.

Time to Documented Progressive Disease

	Estimated Difference (95% CI)	p-Value
Log-Rank		<0.0001
Hazard ratio	0.648 (0.523, 0.803)	<0.0001
6-month difference %	14.5 (5.2, 23.7)	0.0021

Time to Documented Progressive Disease



Summary of Reconciled Best Tumor Response

Reconciled Response	T Arm (N=263)	GT Arm (N=266)
Total responders (CR+PR)	59 (22.1%) 95% CI [17.4%, 27.5%]	108 (40.8%) 95% CI [34.7%, 46.5%]
Difference in overall response rate (GT-T)	18.2% 95% CI [10.4%, 25.9%]	

Abbreviations: T = paclitaxel monotherapy; GT = gemcitabine plus paclitaxel; N = number of randomized patients within each arm; CI = confidence interval; CR = complete response; PR = partial response.

Response rate was statistically significant in favor of the GT Arm versus the T Arm ($p<0.0001$).

DISCUSSION

This SNDA is recommended for regular approval. The approval recommendation is based primarily on the results of one randomized clinical trial supported by the results of 4 Phase 2 single arm Gemzar/paclitaxel trials and 12 Phase 2 single arm Gemzar trials.

In the randomized trial **on interim analysis** with about 30% of patients still censored the median overall survival on the GT arm is 18.6 months and on the T arm is 15.8 months. The hazard ratio is 0.823 with a stratified Log Rank P value near the 0.05 level. When supported by the clear superiority of the GT arm in Time to Documented Tumor Progression and Objective Tumor response rate along with good objective tumor response rates in the single arm Phase 2 studies, this is sufficient for regular approval of the SNDA. However, this survival P value near the 0.05 level at interim analysis in a single randomized clinical trial is not sufficient to support a survival claim in the labeling at present. The FDA will allow a narrative statement in the Clinical Studies section of the package insert stating that there is a strong survival trend favoring the Gemzar/pacletaxel combination on interim analysis. But the FDA will not permit inclusion of survival curves or specific survival numbers in the package insert until the final survival analysis is submitted.

The question arose whether subsequent treatment might obsure a Gemzar survival advantage. This seems unlikely. Crossover would be the main concern. Only 14% of paclitaxel patients crossed over to Gemzar while 4% of Gemzar/paclitaxel patients received subsequent Gemzar. About 50% of patients in each treatment arm received subsequent chemotherapy.

There was the usual general discussion by the review team regarding whether subsequent therapy may obscure a survival advantage of the test drug. Certainly we continue to see new drugs that increase survival regardless of subsequent therapy. An example is the recently approved application based on a study of Xeloda with or without Taxotere. Xeloda was able to show a clear survival advantage in spite of subsequent therapy. The patient population was very similar to the patient population in the present Gemzar study.

The following general points can be made regarding the issue of whether subsequent therapy can obscure a survival advantage for a test drug.

- The proposal is speculative. There is no way to prove or disprove it in most cases. The assumption of advocates seems to be that if

there is any possibility it might ever occur, we should assume it always occurs. We know it does not occur in all cases as we continue to see new drugs that are successful in prolonging life in breast cancer and other cancers.

- If survival is obscured by subsequent therapy in an occasional case, the survival effect was not very strong. Further this is exactly the result we can expect in real life. Patients taking the drug in question can not expect to live longer than if they do not take it.

RECOMMENDATION

Approval of this SNDA is recommended with labeling changes as specified by the review team (See revised label). There is a Phase 4 commitment to perform and submit the final survival analysis when the protocol required number of deaths has occurred.

John R. Johnson, M.D.
May 19, 2004

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Johnson
5/19/04 01:42:19 PM
MEDICAL OFFICER

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Norma Ascroft
Fax: 317 276-1652

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 13

Date: 2-5-04

COMMENTS: Dr. Cohen's progression dates, censor dates, responders, agreement on progression date and agreement on response.

Dotti

Progression and censor dates

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
2	21		6/6/2000		y	
2	22		12/26/2000	PR	n	n
2	23	02/28/2001			y	n
2	24	01/31/2001			y	
2	25		5/15/2001	PR	n	y
2	28		5/15/2001		n	n
2	29	09/26/2001			y	n
2	30		10/30/2001	PR	n	y
2	32		8/1/2001		y	
2	34		2/14/2002	PR	n	y
2	36		11/1/2001		n	
2	37	02/13/2002			y	
3	41		5/25/2000		n	
3	42	01/19/2000			y	
3	43	08/02/2000			y	
3	44		8/16/2000		n	n
3	45	01/30/2001	10/2/2000		n	n
3	47		3/20/2001		n	
3	48	05/24/2001			y	
3	49		8/14/2001		n	n
3	50		12/4/2001	PR	n	y
3	51		12/17/2001		n	
3	52		4/1/2002		n	
4	61	11/28/2001		PR	y	y
4	62		4/18/2001		n	
4	63	12/05/2001			y	
4	64	08/22/2001			y	
4	65	03/05/2002			y	
4	66		3/13/2002		n	
4	67	11/23/2001			y	
4	68	02/15/2002			y	
4	69	10/31/2001			y	
4	70		3/27/2002	PR	n	y
4	71	02/15/2002			y	
5	81	11/28/2001			y	
5	82	02/21/2002			y	
5	84		6/21/2002	PR	y	y
10	100	09/19/2000			y	
10	101	03/08/2001	10/19/2000		n	
10	102		8/2/2001	CR	n	y
10	103	05/03/2002		PR	y	y
11	121	02/01/2000			y	
11	122	07/12/2000			y	
11	123		8/28/2000		n	
12	141	11/22/2000			y	
12	142	07/01/2001		PR	y	y
12	143	11/09/2001			y	
12	144	06/25/2002		PR	y	y

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
13	161		8/2/2000	PR	n	y
13	162	06/21/2000			y	
13	163	12/21/2000			y	
13	164	11/21/2001			y	
14	181	06/26/2000			y	
14	182	10/10/2000			y	
14	183		2/20/2001		n	n
14	184		6/13/2001		n	
14	185		11/14/2001	PR	n	y
14	186	02/28/2002			y	
14	187	03/20/2002			y	
20	200	11/10/2000			y	
20	201		1/31/2001		y	
20	202	01/09/2001			y	
20	203	11/12/2001			y	
20	204		8/15/2001		y	
20	205	11/19/2001			y	
20	206	12/13/2001			y	
21	221		5/15/2001	PR	n	y
21	222	07/11/2001			y	
21	223		12/27/2001	PR	n	y
30	300		4/26/2000	PR	n	y
30	301	05/12/2000			y	
30	303	08/11/2000			y	
30	304		11/14/2000	PR	n	y
30	305		11/27/2000	CR	n	y
30	306	09/14/2000			y	
30	307	11/28/2000			y	
30	308		8/22/2000		n	n
30	309	03/19/2001			y	
30	310		1/26/2001		y	
30	311		5/25/2001	PR	n	y
30	312	05/14/2001			y	
30	313		6/19/2001		n	
30	315	09/05/2001			y	
30	316	08/31/2001			y	
30	317	11/21/2001			y	
31	321	04/11/2000		PR	y	y
31	322		1/27/2000		n	
31	323	08/01/2000		PR	y	y
31	324		8/8/2000	CR	n	y
31	325		8/17/2000	CR	n	y
31	326	07/18/2000			y	
31	327	12/13/2000		PR	y	y
31	328		11/21/2000		n	n
31	329	10/25/2000			y	
31	342	02/15/2001		CR	y	y
31	343		2/15/2001	PR	n	y

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
31	345		6/26/2001	PR	n	y
31	346		6/29/2001		y	
31	347	02/14/2002			y	
31	348		6/29/2002		y	
31	349	04/02/2002			y	
34	361		3/16/2001		n	
34	362	03/14/2001			y	
34	363	03/14/2001			y	
34	365	03/30/2001			y	
34	366		9/13/2001	PR	n	y
34	367	08/21/2001			y	
34	368		9/3/2001	PR	n	y
34	369		1/31/2002		n	
34	370	01/04/2002			y	
40	400		6/5/2000		n	
41	411	06/20/2000			y	
41	412		8/23/2000	CR	n	y
41	413	09/13/2000			y	
41	414		8/24/2000		y	
41	415		2/26/2001	PR	n	y
41	416		5/2/2001		n	n
41	417	09/03/2001			y	
41	418	10/09/2001			y	
41	419	12/11/2001			y	
41	420	10/25/2001			y	
42	421		8/8/2000	PR	n	y
42	422	07/28/2000			y	
42	423		11/29/2000	PR	n	y
42	424		6/19/2001	PR	n	y
42	425		7/27/2001	PR	n	y
42	426		10/3/2001		n	
42	427		11/9/2001	PR	n	y
43	431	05/09/2000			y	
44	441	8/22/2000			y	
44	442	10/25/2000			y	
44	443	06/14/2001			y	
44	444	09/12/2001			y	
44	445	09/17/2001			y	
47	471	02/15/2001			y	n
47	472	04/30/2001		PR	y	y
47	473		12/19/2001	PR	n	y
47	474		3/25/2002	CR	n	y
47	475		3/25/2002	PR	n	y
48	481	11/23/2001			y	
48	482		6/7/2002	PR	n	y
48	483	11/21/2001			y	
48	484		6/10/2002		n	
48	485		5/6/2002	PR	n	n

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
48	486		5/10/2002	PR	n	n
48	487	02/05/2002			y	
48	488		6/21/2002	PR	y	n
48	489		7/8/2002		y	
48	490		7/2/2002		y	
48	591		5/9/2002	PR	n	
48	592		6/24/2002	PR	y	
48	593	06/14/2002		PR	y	y
48	594		7/10/2002	PR	y	n
48	595		5/28/2002		n	
51	511	07/11/2000			y	n
51	512	04/25/2001		PR	y	y
51	513	03/22/2001			y	
51	514		1/4/2002		n	
51	515		11/14/2001	PR	n	y
53	531	07/24/2001		PR	y	y
53	532	02/20/2002		PR	y	y
53	533	09/05/2001			y	
54	541	07/03/2001			y	
54	542	08/29/2001		PR	y	y
54	543	05/15/2001			y	
54	546	06/13/2001			y	
54	547		4/11/2001		y	
54	548		8/7/2001		n	
54	549		11/27/2001	PR	n	y
54	550	08/14/2001			y	
54	551		2/28/2002	PR	n	y
54	552	10/09/2001			y	n
54	553	08/23/2001			y	
54	555		11/6/2001		n	
54	556	11/06/2001			y	
54	558		10/31/2001		n	
54	560		7/4/2002	PR	y	n
54	561		12/12/2001		n	
54	562	02/21/2002			y	
54	563		1/21/2002		n	
54	564	03/27/2002			y	
54	566	04/30/2002			y	
60	600	04/23/2002			y	
60	601		2/28/2002	PR	n	y
60	602		6/12/2002		y	n
60	603		5/2/2002	PR	n	y
60	606		3/26/2002	PR	n	y
61	621		4/4/2002	CR	n	y
61	622		3/11/2002	PR	n	y
61	625		4/23/2002	PR	n	y
61	626	03/21/2002			y	
61	627		4/17/2002	PR	n	y

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
61	629		5/28/2002	PR	n	y
101	1001		6/5/2000	PR	n	
101	1002	02/03/2000			y	
101	1003		5/3/2000	CR	n	y
101	1004		2/8/2000		n	
101	1005	03/27/2000			y	
101	1006	03/23/2000			y	
101	1007		2/23/2000		n	
101	1008	09/19/2000		PR	y	y
101	1009	08/18/2000			y	n
101	1010	07/06/2000			y	
101	1011		5/4/2000		n	
101	1012	08/18/2000			y	
101	1013	10/19/2000			y	
101	1014	10/02/2000			y	
101	1015	07/18/2000			y	
101	1016	07/20/2000			y	
101	1017		2/23/2001	PR	n	y
101	1018		12/19/2000		n	
101	1019	09/13/2000			y	
101	1020		8/11/2000		n	
101	1021	10/26/2000			y	
101	1022	11/20/2000			y	
101	1023		3/13/2001	CR	n	y
101	1024	04/05/2001		PR	y	y
101	1025	12/06/2000			y	
101	1026	02/15/2001			y	
101	1027	11/17/2000			y	
101	1028		9/28/2000		n	
101	1029	04/09/2001			y	
101	1030	12/14/2000			y	
101	1031	01/30/2001			y	
101	1032	03/09/2001			y	
101	1033	02/20/2001			y	
101	1034		6/19/2001	PR	n	y
101	1035	07/16/2001			y	n
101	1037	05/14/2001			y	
101	1038	06/06/2001			y	
101	1039	10/18/2001			y	
101	1040	11/19/2001		PR	y	y
101	1041	07/25/2001			y	
101	1042	10/11/2001		PR	y	n
101	1044	11/26/2001			y	
101	1045		5/23/2002		n	
101	1046		2/13/2002	PR	n	
101	1047	03/19/2002			y	
107	1201	07/06/2001		PR	y	y
107	1202	11/09/2001			y	

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
109	1241		6/8/2001	CR	n	y
109	1242		2/2/2001		n	
113	2541	06/14/2000			n	
113	2542	03/26/2001			y	
115	2661		10/13/2000	PR	n	y
128	1381	01/04/2001			y	
130	1421		10/4/2000		n	
130	1422		12/15/2000	PR	n	y
133	1481		2/14/2000		n	
144	2601	05/22/2000			n	
153	1781	06/02/2000			y	
155	1821	08/30/2001		PR	n	y
158	1881	11/16/2000			y	
160	1922	07/27/2001		PR	n	y
162	1962	06/12/2000			y	
162	1963	01/07/2000			n	
162	1964		11/8/2001	PR	n	y
170	2621	07/25/2001			y	
176	2121	05/31/2000			y	
179	2181	03/29/2000		PR	y	y
179	2182	01/19/2000			y	
179	2183		7/20/2000	PR	n	y
179	2184	06/18/2001		PR	y	y
179	2187	03/22/2001			y	
179	2188	05/09/2002			y	
181	2221	01/19/2000			y	
192	2443	09/10/2001			y	
192	2444		5/9/2002	PR	n	n
193	2461		12/3/1999		y	
193	2463	06/05/2000			y	
194	2081		12/21/2000		n	
199	2481		3/13/2000	PR	n	y
199	2482	06/21/2001			y	
199	2483	09/17/2001		PR	y	y
200	2501	10/04/2000		PR	y	y
200	2502	10/12/2000			y	
203	2781		10/23/2001		n	
207	2842		7/13/2001		n	
208	2871	04/09/2001			y	
208	2872	06/13/2001			y	
208	2873	11/19/2001			y	
208	2874		3/11/2002		n	
211	2891		7/30/2001		n	
214	2921	08/29/2001			y	
215	2931	06/25/2001			y	
215	2932	01/16/2002			y	
218	2961	01/02/2002			y	
222	3011		10/23/2001	PR	n	y

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
223	3021	08/15/2001			y	n
301	3501	05/15/2001			y	
301	3502	09/19/2001			y	
301	3503		12/28/2001	PR	n	y
301	3504	11/28/2001			y	
301	3505	01/16/2002			y	
301	3506		3/4/2002	PR	n	y
301	3507		4/11/2002	PR	n	y
301	3508	02/04/2002			y	
301	3509		4/8/2002	PR	n	y
302	3511	03/05/2002		PR	y	y
303	3521	07/06/2001			y	
304	3531	09/25/2001			y	
304	3532	12/14/2001			y	
304	3533	11/05/2001			y	
401	4001	03/01/2000			y	
401	4002		3/27/2000		n	
402	4021	04/19/2000			y	n
402	4022	03/29/2001			y	
402	4023	01/23/2001			y	n
402	4024		2/21/2002	PR	n	y
403	4041		12/8/2000	PR	n	y
403	4042		3/2/2001	PR	n	y
403	4043		10/6/2000		n	n
403	4044	02/07/2001			y	
403	4045		4/20/2001		n	n
403	4046		2/12/2001		y	
403	4047	01/16/2002			y	
403	4048	03/06/2002			y	
403	4049	03/12/2002			y	
404	4061		11/2/2000		n	
405	4081		10/19/2000	PR	n	y
405	4082		1/25/2001		n	n
405	4083		6/6/2001		n	
406	4101	11/05/1999			y	
406	4102		9/23/1999		n	
406	4103	11/09/2000			y	
408	4141	03/27/2000			y	
408	4142	11/08/2000			y	
408	4143	04/03/2001			y	
408	4144	07/27/2001			y	
408	4145	09/10/2001			y	
408	4146	03/06/2002			y	
409	4161	07/06/2000			y	
409	4162	07/24/2000			y	
409	4163	02/14/2001			y	
413	4221	11/20/2000			y	
413	4222	08/06/2001			y	

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
413	4223	08/02/2001		PR	y	y
413	4224		8/31/2001		n	
413	4225	01/21/2002			y	
503	5021	09/18/2000	5/23/2000		y	
503	5022		8/8/2000	PR	n	y
503	5023	09/26/2000			y	
503	5024		12/18/2000		n	
503	5025		4/19/2001	CR	n	y
503	5026	09/15/2001			y	
503	5027	12/01/2001			y	
503	5028		11/26/2001		n	
504	5031		11/7/2000	PR	y	y
504	5032	09/25/2000			y	
504	5033		2/1/2001		n	
504	5034		11/29/2000		n	n
504	5035		9/11/2001		n	
504	5036	03/04/2002			y	
504	5037		10/10/2001		n	
505	5041	01/09/2001			y	
505	5042	02/19/2001			y	
505	5043		2/5/2001	PR	n	y
505	5044		3/26/2001	PR	n	y
505	5045	12/14/2000		PR	y	n
505	5046	02/06/2001			y	
505	5047	05/15/2001			y	
505	5048		11/23/2001		n	
506	5051	08/03/2001			y	
507	5061		7/24/2001	PR	n	y
507	5062	09/12/2001			y	
601	6001	04/18/2000			y	
601	6002		4/12/2001	PR	n	y
602	6021	05/16/2000		PR	y	y
602	6022	04/18/2000			y	
602	6023		9/25/2000	PR	n	y
602	6024	08/11/2000		PR	y	y
602	6025	06/13/2000			y	
602	6026		5/12/2000		n	
602	6027	12/26/2000			y	
602	6028		4/19/2001	CR	n	y
602	6029		2/14/2001		n	
602	6030	04/27/2001			y	
602	6031	08/06/2001			y	
602	6032	09/27/2001	4/6/2001		y	
602	6033		9/6/2001		n	
602	6034	12/20/2001			y	
602	6035	12/17/2001			y	
602	6036		11/8/2001		n	n
602	6037	02/27/2002			y	

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
603	6041	03/07/2001			y	
650	6502	12/06/2000			y	
650	6503		12/6/2000		n	
650	6504	12/06/2000			y	
650	6505	01/19/2001			y	
650	6506	03/16/2001			y	
650	6507		4/20/2001	PR	n	y
650	6508		8/16/2001	PR	n	y
650	6509	05/23/2001			y	
650	6510	06/13/2001			y	
650	6511	08/02/2001			y	
650	6512	09/25/2001			y	
650	6513	09/11/2001			y	
650	6514	11/12/2001			y	
651	6520		1/10/2001		n	
651	6522		1/10/2001		n	
651	6523	11/08/2000			y	
651	6525		3/27/2001	PR	n	y
651	6526		11/7/2001		n	
651	6527		11/22/2000		n	
651	6528		5/2/2001	PR	n	n
651	6529		1/1/2001		n	
651	6530		3/9/2001		n	
651	6531	05/09/2001		PR	y	y
651	6532	06/05/2001			y	
651	6533	04/10/2001			y	
651	6534	05/28/2001			y	
651	6535		8/1/2001	PR	n	y
651	6536		6/25/2001		n	n
651	6537		8/14/2001	PR	n	y
651	6538	08/07/2001			y	
651	6539	09/24/2001			y	
651	6600		9/5/2001		n	
651	6601	10/10/2001			y	
651	6602	11/05/2001			y	
651	6603		10/8/2001		n	
651	6604		1/30/2002	PR	n	y
651	6605	03/13/2002		PR	y	n
651	6606	01/28/2002			y	
651	6607	04/16/2002			y	n
651	6608	03/04/2002			y	
651	6609		4/1/2002	PR	n	y
652	6540		8/5/2000		n	
653	6560		3/7/2001	PR	n	y
653	6561		11/7/2000		n	
653	6562	03/22/2001			y	
653	6564	03/24/2001			y	
653	6565		5/28/2001	PR	n	y

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
653	6566		6/19/2001	PR	n	y
653	6567	04/26/2001			y	
653	6568		5/21/2001		n	
653	6569	05/11/2001			y	
653	6570		7/18/2001	PR	n	y
653	6571	09/11/2001			y	
653	6572	10/27/2001			y	
653	6573		2/6/2002	PR	n	y
653	6574		11/28/2001		n	
654	6580	12/21/2000			y	
654	6581	03/09/2001			y	
654	6583		2/8/2001		n	
654	6584	05/18/2001			y	
654	6585	05/15/2001			y	
654	6588	07/18/2001			y	
654	6589		6/6/2001		n	
654	6590		5/2/2001		n	
654	6591	07/09/2001			y	
654	6592		11/19/2001	PR	n	y
654	6594		11/27/2001		n	
701	7001		5/25/2000	PR	n	y
701	7002	08/17/2000			y	
701	7003		8/6/2001		n	n
702	7011	09/15/2000			y	
702	7012		2/5/2001		n	n
703	7021	07/13/2001		PR	y	y
703	7022		2/13/2001		n	
703	7023		5/10/2001	PR	n	y
703	7024	05/31/2001			y	
703	7025	05/01/2001			y	
703	7026	09/28/2001			y	n
703	7027	07/09/2001			y	
703	7028		9/10/2001	PR	n	y
703	7029		10/17/2001	PR	n	y
705	7041		7/26/2001	PR	n	y
706	7051		7/13/2001	PR	n	y
706	7052		7/13/2001	PR	n	y
706	7053		8/30/2001	PR	n	y
706	7054		7/9/2001		n	
707	7061		2/9/2001		n	n
750	7501		4/18/2001		n	n
750	7502	10/08/2001		PR	y	y
750	7503	10/16/2001			n	
750	7504		9/11/2001		n	
750	7505		4/19/2002	PR	n	y
750	7506		5/13/2002	PR	n	y
750	7507	02/13/2002		PR	y	n
750	7508	02/13/2002			y	

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
750	7509		3/12/2002	PR	n	y
750	7510		6/4/2002	PR	n	n
751	7521	11/20/2001		PR	y	y
751	7522	06/03/2002		PR	y	n
751	7523	03/07/2002		PR	y	y
751	7524	05/21/2002			y	
751	7525	12/13/2001		PR	y	y
751	7526		12/28/2001	PR	n	y
751	7528		4/26/2002	PR	n	n
751	7529	01/23/2002			y	
751	7530	03/19/2002			y	
752	7541		8/30/2001	PR	n	y
752	7542		10/30/2001	PR	n	y
752	7543	10/02/2001			y	
752	7544	01/10/2002			y	
752	7545	12/10/2001			y	
752	7546	01/04/2002			y	
752	7547	05/15/2002		PR	y	y
752	7548		3/18/2002		n	
752	7549		2/19/2002		n	
801	8001	07/13/2000			y	
801	8002	08/08/2000			n	
801	8004	11/15/2000	7/7/2000		n	n
801	8006	12/12/2000	6/27/2000		n	
801	8007		12/7/2000	PR	n	y
801	8008	12/11/2000			y	
801	8009	10/10/2000			y	
801	8010	02/21/2001			y	
801	8012	03/30/2001			y	
801	8013	06/27/2001			y	n
801	8014		3/8/2001		y	
801	8015		10/9/2001	PR	n	y
801	8016	07/02/2001			n	
801	8017		4/16/2001		y	
801	8018	07/31/2001	4/10/2001		n	
801	8019	07/19/2001			y	
801	8020	08/20/2001			y	
801	8022		11/26/2001	CR	n	y
801	8023	09/24/2001			y	
801	8024	10/26/2001			y	
801	8025	11/22/2001			y	
801	8027	02/18/2002			y	
851	8510		11/21/2000	PR	n	y
851	8511		1/22/2001		n	
851	8512	03/21/2002		PR	y	y
851	8513		5/23/2002		n	
851	8514		5/23/2002		n	
851	8515		4/11/2002		n	

SDYINVN	CTPATN	PROGDTN	Censor date	Response	Prog Agree	Resp Agree
855	8551		3/19/2001		n	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
3/25/04 03:40:04 PM
CSO
Facsimile sent to sponsor on February 5, 2004

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Wednesday, February 11, 2004 4:04 PM
To: 'Norma Kim Ascroft'
Subject: Medical Reviewer question on Gemzar breast

Based on our discussion yesterday I have started to review post study data. There is a significant discrepancy between information reported in the PSFollowup data base and the post-study site involvement data base.

Unless you can convince me otherwise, if there is no documentation of progression or new lesions in the post-study site-involvement data base, then progression did not occur. The post study follow-up provides no information on which to make an assessment.

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
301-594-5742/301-594-0498 (fax)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dotti Pease
2/12/04 07:24:14 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

c/o Debasish F. Roychowdhury, M.D.
Director, U.S. Regulatory Affairs-Oncology

2. TELEPHONE NUMBER *(Include Area Code)*

(317) 433-6604

3. PRODUCT NAME

Gemzar

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 20-509

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4643

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

[ ] THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

[ ] YES [X] NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
D. Roychf	Debasish F. Roychowdhury, M.D. Director, U.S. Regulatory Affairs	November 12, 2003

FORM FDA 3397 (3/01)

Created by: PSC Media Arts (301) 443-2454 EF

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Garvey
6/21/04 01:27:53 PM

MEETING MINUTES

MEETING DATE: September 16, 2003 **TIME:** 1:30 pm **LOCATION:** WOC3/rm 3004

IND: 29,653

Meeting Request Submission Date: 7-15-03; sn942
FDA Response Date: 7-22-03
Briefing Document Submission Date: 8-13-03; sn982

DRUG: Gemzar® (gemcitabine HCl, LY188011)

SPONSOR/APPLICANT: Eli Lilly & Company

TYPE of MEETING:

1. Pre-sNDA (2^{nd})

2. **Proposed Indications (from briefing package):**
   Gemzar, in combination with paclitaxel, is indicated [redacted]
   patients with locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. [redacted]

FDA PARTICIPANTS:

Grant Williams, M.D.	--	Deputy Director, Division of Oncology Drug Products
Lilia Talarico, M.D.	--	Associate Director, DODP
John Johnson, M.D.	--	Medical Team Leader
Martin Cohen, M.D.	--	Medical Reviewer
Ning Li, Ph.D.	--	Statistical Reviewer
Sophia Abraham, Ph.D.	--	Clinical Pharmacology & Biopharmaceutics Reviewer
Patty Garvey, R.Ph.	--	Project Manager

INDUSTRY PARTICIPANTS:

Norma Ascroft, Pharm.D.	--	Regulatory Research Scientist
Allen Melemed, M.D.	--	Sr. Clinical Research Physician
Jorge Otero, M.D.	--	Medical Director
Debasish Roychowdhury, M.D.	--	US Regulatory Affairs Director
James Symanowski, Ph.D.	--	Sr. Research Scientist, Statistics
Jun Wu, M.D.	--	Assistant Sr. Statistician

BACKGROUND:

Lilly previously submitted a concise summary of study results based on the interim analysis in the form of the European Expert Report in the December 5, 2002 submission, serial no. 917. Lilly initiated the global, randomized, phase 3 clinical trial of Gemzar plus paclitaxel versus paclitaxel in patients with unresectable, locally recurrent or metastatic breast cancer in September 1999 (September 9, 1999, serial no. 714; March 23, 2001, serial no. 800; and January 4, 2002, serial no. 851) with overall survival as the primary endpoint

and time to documented progression of disease (TtDPD) as a secondary endpoint. The protocol states TtDPD would be the primary endpoint for the interim analysis. The trial has completed enrollment. The study's planned interim datalock for safety and efficacy occurred August 1, 2002. As of August 1, 2002, only 19 patients remained on treatment and of the 529 patients, 411 patients had progressive disease, as determined by the investigators.

On May 8, 2003, Lilly and FDA discussed the possibility of a submission for an accelerated approval based on Study JHQG interim analysis of time to documented progressive disease (TtDPD) with the follow-up of overall survival (JHQG's primary objective). Safety was a secondary endpoint also evaluated in this trial.

Lilly plans to submit a sNDA based on the interim analysis results from Study JHQG, and will perform an interim survival analysis of the Phase 3 Study JHQG. Following the sNDA submission, Lilly also proposes to provide a comprehensive update of safety data from the cut-off date of the above interim analysis of TtDPD (July 10, 2002) to the proposed cut-off date.

MEETING OBJECTIVES (from briefing document):

To discuss a possible submission based on the Study JHQG interim study results. If the FDA is acceptable to a possible submission to the U.S., additional discussions may be needed regarding the specifics of a NDA package.

QUESTION for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:

NOTE: Lilly received the Division's comments via facsimile on September 10, 2003.

During the course of the meeting, there were additional agreements between the Division and Lilly. These agreements are *italicized* under the discussion section.

---

1. Does the FDA have comments at this point to the proposed draft USPI for an indication in MBC?

   FDA: No. The data must be reviewed before comments can be made.

2. Does FDA agree with the general outline of the proposed studies for the MBC sNDA?

   FDA: The Agency generally requires two phase 3 trials to support an indication. Be aware that a single randomized trial to support an NDA, the trial must be well designed, flawlessly executed, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.

Yes, your proposed clinical pharmacology studies (Studies JHFV, 0021, 0025, and JHBH) as outlined in the sNDA Table of Contents (Item 6) appear acceptable.

3. Does FDA agree on the proposed format of the NDA and the elements of the CTD, including the e-NDA structure that will include elements of the CTD?

   FDA: Regarding the electronic database:

   An annotated CRF should be submitted showing the database term for each item on the CRF.

   A database dictionary should be provided defining each table and its contents. Also, the column headings in each table should be defined and any codes in the fields should be defined.

   Dates should be in date/time format, i.e. 1/30/2003

4. Does FDA agree that it is acceptable to submit the Summary of Clinical Efficacy and Summary of Clinical Safety sections of the CTD to capture consistencies and inconsistencies across safety and efficacy within the application?

   FDA: Yes.

5. Does FDA agree that the Application Summary will be replaced by the CTD Clinical Overview?

   FDA: Yes.

6. a) Does FDA agree with the interim survival analysis alpha spending approach: 0.0001 for an unblinded comparison?

   FDA: Yes.

   b) Does FDA agree that 0.05 type I error be available for final survival analysis, so that final survival analysis can be done at 0.049983 level?

   FDA: The Division's current standard is that the accelerated and final approval type I error rate be controlled together at 0.05 level, i.e., the two endpoints TTP and Survival share the alpha of 0.05. Hence, the final survival analysis significant level should be set at 0.03 (the alpha left after TTP), as you proposed originally in your protocol.

7. Does FDA agree with the proposal of supplying survival data only in the interim survival analysis and supplying an extended 4-month safety update which would include safety data collected between 10 July 2002 and January 2004?

FDA: Yes.

8. Does FDA agree with the proposal for patient narratives?

FDA: Yes.

9. a) Does FDA agree with submission of the two data sets as defined above?

FDA: Yes.

b) It is Lilly's intention to provide annotated case report forms (CRFs), SAS data sets, and define documents for the Phase 3 pivotal Study JHQG and the main supportive Phase 2 Study S024. Does FDA agree with this?

FDA: Yes.

Discussion: The following proposal was discussed:

- *If JHQG does not show statistical significance at interim at α= 0.028 then overall survival will be tested at 0.03 at the final overall survival analysis*
- *If JHQG does show statistical significance at interim at α=0.028 then overall survival will be tested at α=0.05 at the final analysis*

The FDA will evaluate this proposal.

The FDA will also address what happens to overall survival statistical significance if the sponsor meets the statistical significance of interim (TTP) but does not gain approval?

The sponsor will adjust the SAP after interim survival analysis lock when they hear back from the FDA.

10. Although other clinical pharmacology studies will be included in the submission, Lilly proposes to only include pharmacokinetic data sets for Study JHQG. Does FDA agree with this?

FDA: No. Pharmacokinetic analysis data sets for Study JHQG as well as for all clinical pharmacology studies (Studies JHFV, 0021, 0025, and JHBH) should be included under Item 6 in the sNDA submission.

11. Does FDA agree CRF's for the above patients from study JHQG will be made available upon request?

FDA: Yes.

12. For Study JHQG, scans were collected but were not digitized from the investigative sites by Lilly. As in previous gemcitabine reviews, Lilly proposed that individual patient scans will not be submitted in the application. Does FDA agree with this?

    FDA: Because you are proposing accelerated approval based preliminary on TTP in a single study, we will need to review sample of scans documenting progression. Therefore, the Agency would like to review the scans of all patients with an objective tumor response.

13. Does FDA agree that financial disclosure will be provided for Study JHQG?

    FDA: Yes.

14. Does FDA consider this an indication for a Priority Review?

    FDA: Priority status will be determined at the filing meeting after the initial data review.

15. Lilly will be submitting a waiver for gemcitabine with regard to CFR 314.55 (pediatric investigation) in light of the inapplicable indication of MBC in pediatric population. Does FDA agree with this?

    FDA: Yes.

16. This is Lilly's third sNDA submission for gemcitabine. As in past submissions, Lilly does not plan to submit a new patient insert/leaflet for this indication. Does FDA agree with this?

    FDA: Yes.

17. Can FDA confirm this and provide approximate timing of an ODAC meeting?

    FDA: This will be determined after initial evaluation of submitted trial data.

ACTION ITEMS:

1. The FDA will discuss internal the proposal discussed under question 6(b) and provide comments on the significance for overall survival in which the sponsor is denied accelerated approval, for whatever reason, based on TTPD differences even though significance of the interim is met.

2. Lilly will provide datasets with a converted numberic SAS data variable for each character (i.e. text) data variable.

3. Lilly will provide a list of questions to the FDA regarding the scans, so that these can be discussed with Dr. Cohen and the consulted radiologist.

There were no unresolved issues. The meeting concluded at 2:20 p.m.

ADDENDUM:

After further internal discussion regarding question # 6 (b), the FDA agrees that the alpha of 0.05 be available for final survival analysis regardless of the interim TTP results.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Project Manager

Concurrence Chair:

{See appended electronic signature page}

Martin Cohen, M.D.
Medical Officer

Attachment: Lilly's overhead