Summary ID# 8426

Clinical Study Summary: Study H3E-MC-JMGV

A Phase 2 Study of Alimta plus Doxorubicin Administered Every 21 Days in Patients with Advanced Breast Cancer

Date summary approved by Lilly: 22 May 2008

Title of Study: A Phase 2 Study of Alimta plus Doxorubicin Administered Every 21 Days in Patients with Advanced Breast Cancer	
Investigators: This multicenter study included 15 principal investigators.	
Study Center(s): This study was conducted at 15 study centers in 7 countries.	
Length of Study: Date first patient enrolled: 19 October 2004 Date last patient completed: 29 October 2007	**Phase of Development:** 2
Objectives: The primary objective was to assess the antitumor activity of pemetrexed plus doxorubicin, as measured by overall tumor response rate, in patients with advanced breast cancer who had not been previously treated with an anthracycline-containing regimen. Secondary objectives were: • To assess time-to-event efficacy variables for pemetrexed plus doxorubicin in this patient population, including: o Time to progressive disease (TtPD) o Progression-free survival (PFS) o Overall survival (OS) • To characterize the quantitative and qualitative laboratory and nonlaboratory data of pemetrexed plus doxorubicin in this patient population.	
Study Design: This was a multicenter, open-label, single-arm trial of pemetrexed plus doxorubicin combination therapy administered every 21 days. The study population included females with advanced breast cancer.	
Number of Patients: Planned: Approximately 70 patients were to be enrolled. Actual Screened/Enrolled: 97 patients were entered; 79 patients were enrolled. Completed: 54 (68.4%) patients completed at least 6 cycles of treatment.	
Diagnosis and Main Criteria for Inclusion: Eligible female patients were required to (1) have histologically- or cytologically-confirmed breast cancer with locally advanced or metastatic disease that was not amenable to local treatment; (2) have at least 1 lesion measuring at least 10 mm long in the longest diameter as determined by spiral computed tomography scan, or at least 20 mm as determined by standard techniques; (3) be chemonaïve or received only neoadjuvant and/or adjuvant chemotherapy; (4) have an	

Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; (5) have adequate bone marrow, hepatic, and renal function; (6) be at least 18 years of age at time of entering the study; and (7) have a life expectancy of at least 12 weeks.

Test Product, Dose, and Mode of Administration: On Day 1 of each 21-day cycle, pemetrexed 500 mg/m^2 was administered as a 10-minute intravenous infusion, followed by doxorubicin 50 mg/m^2 given as a slow intravenous injection. Sites determined the actual doses by calculating the patient's body surface area (BSA) at the beginning of each cycle.

Reference Therapy/Comparator, Dose, and Mode of Administration: Not applicable.

Duration of Treatment: The protocol specified six 21-day cycles, although longer duration was possible at the discretion of the investigator and the sponsor.

Variables

Efficacy: The primary efficacy variable was the overall tumor response rate based on patient's best tumor response across all treatment cycles as determined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Secondary efficacy variables were TtPD, PFS, and OS. Tumors were evaluated for response using radiological and physical assessments.

Safety: Safety variables included numbers and proportions of adverse events (AEs), including treatment-emergent adverse events (TEAEs) and their relationship to study drug, AEs leading to discontinuations, serious adverse events (SAEs) including relationship to study drug, and deaths while on study and within 30 days posttreatment. Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 was used to report maximum intensity of laboratory and nonlaboratory parameters related to study drug. Results of blood transfusions and cardiac function tests were also summarized.

Statistical Methods:

Sample Size: Using a 2-sided Fisher exact test for a single proportion with a 5% level of significance, 68 patients provided a 90% power to detect an overall tumor response rate of 50% with pemetrexed plus doxorubicin. It was assumed that doxorubicin alone would have a 30% tumor response rate, based on a review of the literature. Additional patients were to be enrolled to ensure that at least 68 patients were evaluable for the primary endpoint. Demographics: All patients entered in the study (signed informed consent) were included in the analysis of patient disposition, including qualification, discontinuations, and protocol violations. All treated patients, defined as those who received at least 1 dose of either study drug, defined the enrolled population, which was used for safety analyses. A protocol-qualified (PQ) population was further defined and applied to efficacy analyses. The PQ population consisted of patients who met the following criteria:

- Had a histologic or cytologic diagnosis of breast cancer at baseline, with locally advanced or metastatic disease that was not amenable to local treatment
- Had not received prior chemotherapy for advanced breast cancer at baseline, except for adjuvant or neoadjuvant chemotherapy (prior hormonal therapy was allowed)
- Had measurable disease according to RECIST criteria at baseline
- Had received at least 1 complete cycle of pemetrexed plus doxorubicin

Efficacy: Overall tumor response (complete response [CR] + partial response [PR]) rates and time-to-event (TtPD, PFS, OS) variables were efficacy variables of interest. Descriptive statistics, including Fisher's exact test, were used to analyze response rate. Kaplan-Meier methodology was used to estimate time-to-event parameters. Safety: Summaries and listings of AEs, TEAEs, SAEs, as well as cardiac toxicities were presented. All laboratory and nonlaboratory data of pemetrexed plus doxorubicin were characterized and tabulated for toxicities using CTCAE criteria.

Results:

Patient Disposition: Of the 97 patients who entered the study, 18 were not enrolled due to patient decision (n=3) and not meeting entry criteria (n=15). Seventy-nine patients met the criteria to be included in the safety and PQ populations. The most common reason for discontinuation were having completed the full 6 cycles of treatment (54 patients; 68.4%), followed by progressive disease (16 patients; 20.3%).

Demographics: All 79 patients enrolled were female, with mean (standard deviation [std dev]) age 54.2 (10.11) years. Most patients were Caucasian (50.6%) and the mean (std dev) BSA was 1.7 (0.15) m^2. Over half (41; 51.9%) of patients had ECOG performance status of 0; 35 (44.3%) had an ECOG performance status of 1. Nearly three-fourths (57 patients; 72.2%) of patients had metastatic disease. The majority of patients (69 patients; 87.3%) were diagnosed histologically. The most common pathological diagnosis was ductal breast carcinoma (56; 70.9%), followed by neoplasm metastatic, breast (11; 13.9%), and lobular breast carcinoma (10; 12.7%). Thirty-one patients were estrogen receptor positive and 28 patients were progesterone receptor positive. Of the 33 patients with known HER-2/neu status, 3 patients were HER-2 receptor positive and 30 were HER-2 receptor negative.

Efficacy: (N=79) The overall tumor response rate was 55.7% (95% exact confidence interval [CI]: 44.1%, 66.9%), with 2 patients (2.5%) demonstrating a CR, 42 patients (53.2%) achieving a PR, and 24 patients (30.4%) demonstrating a best response of stable disease. Median (95% CI) TtPD was estimated to be 8.8 (7.0, 14.0) months.

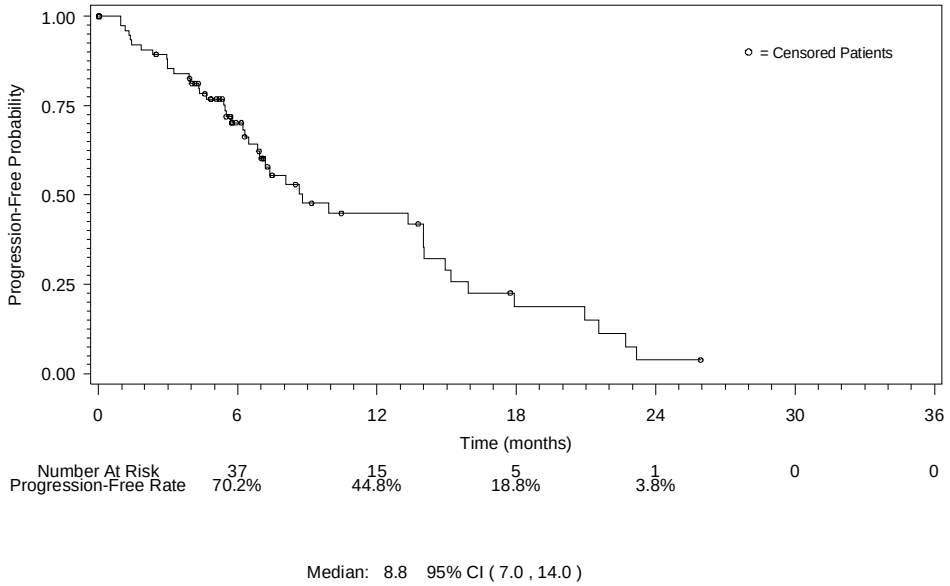

Figure 1. Kaplan-Meier curve for time to objective progressive disease for the protocol-qualified population.

The median (95% CI) for PFS was estimated to be 8.0 (6.5, 13.3) months.

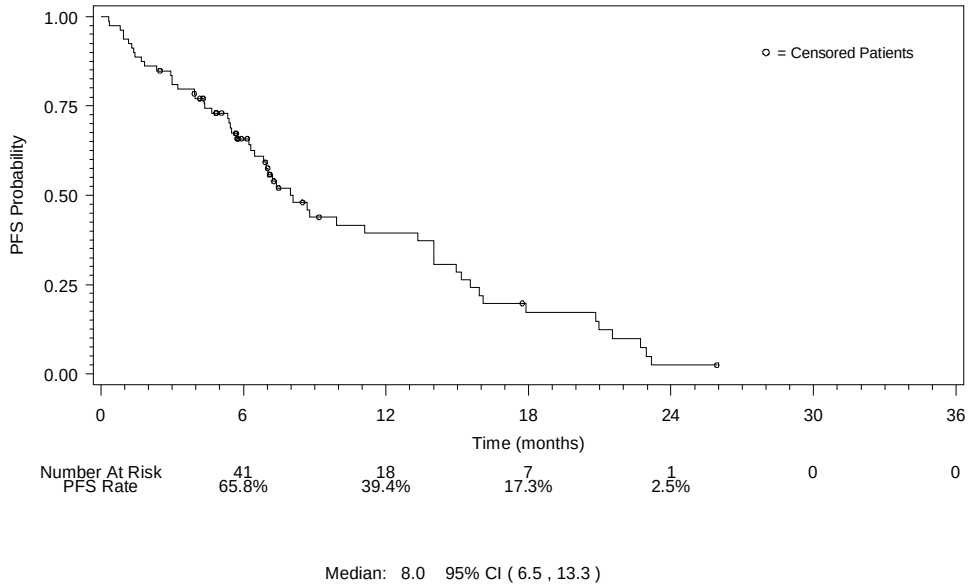

Figure 2. Kaplan-Meier curve for progression-free survival for the protocol-qualified population.

The median OS was not estimable; however, at 24 months after the first dose of study drug, 61.7% (95% CI: 49.7%, 71.6%) of patients were estimated to still be alive.

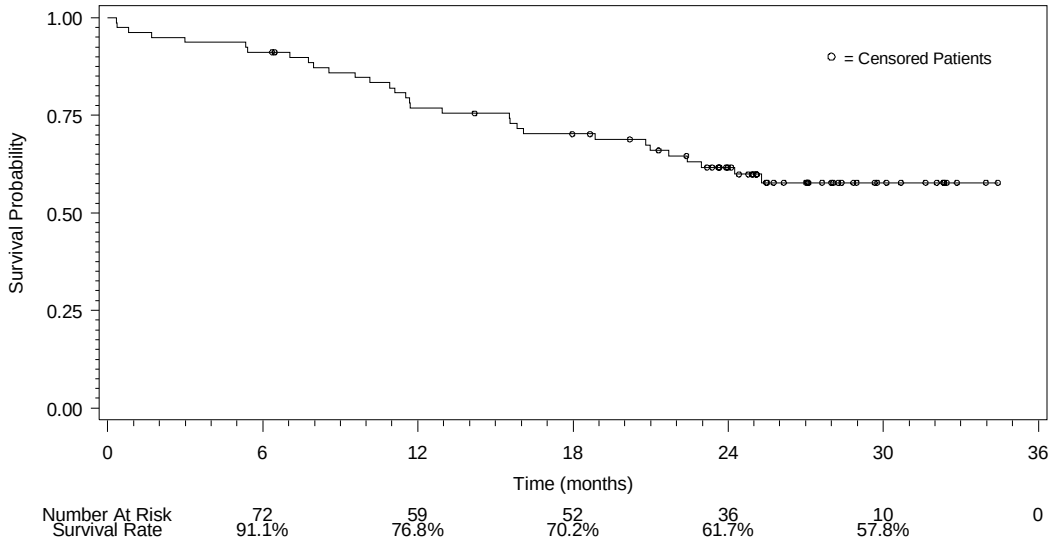

Figure 3. Kaplan-Meier curve for overall survival for the protocol-qualified population.

Safety: (N=79) Five patients died while on study, and 2 of these deaths (one due to diarrhea, one due to pneumonia) were considered by the investigator to be possibly related to study drug. Fourteen patients (17.7%) experienced at least 1 SAE; of these, 7 patients (8.9%) had at least 1 SAE considered by the investigator to be possibly related to study drug. Thirteen patients were hospitalized a total of 17 times due to AEs, and 9 of these hospitalizations were due to study drug-related SAEs. There were 8 discontinuations (including deaths) due to AEs, with 4 of these due to an AE considered possibly related to study drug. There were 67 patients (84.8%) who had at least 1 TEAE related to study drug, with the most common related TEAE (52 patients, 65.8%) in the system organ class of gastrointestinal disorders. Twenty-four (30.4%) patients had CTCAE Grade 3 or higher for laboratory parameters possibly related to study drug. The most frequent possibly related laboratory CTCAE maximum Grade 3 or greater was low neutrophils (19 patients, 24.1%). The most frequent possibly related nonlaboratory CTCAE events for all grades combined were nausea, vomiting, and hair loss (37 patients, 46.8%; 36 patients, 45.6%; and 31 patients, 39.2%; respectively), but the majority of these were maximum Grade 1 or 2. The most commonly possibly related nonlaboratory CTCAE maximum Grade 3 or greater was vomiting (5 patients, 6.3%). Six patients had at least 1 transfusion of packed red blood cells or platelets.

Two cardiac events occurred during the study that were considered by the study investigator to be related to study drugs. One patient experienced a drop in left ventricular ejection fraction (LVEF) from baseline (76%) to postbaseline (28%), and also experienced an SAE of congestive heart failure that required 2 hospitalizations. The investigator considered the SAE to be life-threatening and related to both study drugs. The cardiac event occurred at the end of 6 cycles of study treatment; she did not receive any more study drug after this SAE. Another patient discontinued from the study due to an AE of left ventricular dysfunction. The AE was considered by the study investigator to be related to study drug.

Three (3.8%) and 4 (5.1%) patients had dose reductions for pemetrexed and doxorubicin, respectively. Mean dose intensities were 99.7% and 99.5% of planned doses for pemetrexed and doxorubicin, respectively. The most common reason for cycle delays (59.6% for pemetrexed, 65.1% for doxorubicin) was scheduling conflicts. The median number of cycles was 6. Sixty-five patients (82.3%) went on to receive more therapy after they completed this study.