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Clinical Study Summary: Study H3E-MC-JMHF

A Randomized, Double-Blind, Phase 2 Study of Two Doses of Pemetrexed in the Treatment of Platinum-Resistant, Epithelial Ovarian or Primary Peritoneal Cancer

Date summary approved by Lilly: 14 December 2007

Brief Summary of Results

This was a multicenter, parallel, double-blind, randomized, Phase 2 study of pemetrexed 500 mg/m² (Pem 500) versus pemetrexed 900 mg/m² (Pem 900) administered every 21 days to patient with platinum-resistant, epithelial ovarian or primary peritoneal cancer. The study consisted of two protocols – the clinical protocol and the translational research protocol. The patients randomized to the clinical protocol may also enter the companion translational research protocol, upon giving their consent. This summary refers to both protocols. The results are as follows:

Clinical Protocol

The primary objective of the clinical protocol was to assess the tumor response rate in patients treated with Pem 500 versus Pem 900.

- One hundred six patients were entered, and 51 patients were randomized to each treatment arm. Four patients on the Pem 500 Arm discontinued without receiving study drug. The safety population included the 47 patients who received pemetrexed 500 mg/m² and the 51 patients who received pemetrexed 900 mg/m². Forty-three patients on the Pem 500 Arm and 48 patients on the Pem 900 Arm were qualified for the efficacy analysis.
- The 2 treatment arms were similar in terms of baseline characteristics, with the exception of platinum-free interval. Numerically more evaluable patients on the Pem 900 Arm had a platinum-free interval of <3 months: 21 (43.8%; N = 48) patients compared with 13 (30.2%; N = 43) patients on the Pem 500 Arm.
- On the Pem 500 Arm, 47 patients received a median of 4 cycles (range, 1 to 11 cycles). Nine (19.1%) patients received the protocol-planned maximum 6 cycles of therapy, and 4 (8.5%) patients received more than 6 cycles. Four (8.5%) patients each required 1 dose reduction, and 15 (31.9%) patients required a total of 24 cycle delays. On the Pem 900 Arm, 51 patients received a median of 3 cycles (range, 1 to 8 cycles). Twelve (23.5%) patients received 6 cycles, and 4 (7.8%) patients received more than 6 cycles. Eight (15.7%) patients required a total of 9 dose reductions, and 21 (41.2%) patients required a total of 35 cycle delays.
- Four (9.3%) patients on the Pem 500 Arm and 5 (10.4%) patients on the Pem 900 Arm had best study response of partial response; there were no complete responses in either arm; the difference in response rate between the two treatment arms was not statistically significant.
- No statistically significant differences between the 2 treatment arms were observed for any secondary efficacy endpoint (time to response, duration of response, time to progressive disease, time to treatment failure, progression free survival and overall survival).
- On the Pem 500 Arm, 46 (97.9%) patients had treatment-emergent adverse events (TEAEs); in 42 (89.4%) patients, the TEAEs were possibly related to study drug. On the Pem 900 Arm, 51 (100.0%) patients had TEAEs; in 47 (92.2%) patients, the TEAEs were possibly related to study drug.
- On Pem 500 Arm, 23 (48.9%) patients had a total of 63 serious adverse events (SAEs); in 8 (17.0%) patients, a total of 20 SAEs were possibly related to study drug. On Pem 900 Arm, 23 (45.1%) patients had a total of 65 SAEs; in 14 (27.5%) patients, a total of 27 SAEs were possibly related to study drug.
- On Pem 500 Arm, 1 (2.1%) patient died of study disease while on study. On Pem 900 Arm, 3 (5.9%) patients died on study, and 3 (5.9%) patients died within 30 days after the last treatment; 2 (3.9%) of the on-study deaths were due to sepsis, and considered possibly related to study drug.

- On the Pem 500 Arm, 1 (2.1%) patient discontinued because of an adverse event that was possibly related to study drug. On the Pem 900 Arm, 7 (13.7%) patients discontinued because of an adverse event; in 5 (9.8%) patients, the event was possibly related to study drug.
- Common Terminology Criteria for adverse events (CTC AE) Grade 3/4 hemoglobin and neutrophils/granulocytes were reported in more than 10% of patients on each treatment arm. Grade 3/4 platelets and fatigue were also reported in more than 10% of patients on the Pem 900 Arm.

Translational Research Protocol

The primary objective of the translational research protocol was to examine the association between molecular markers involved in the cellular transport, activation, and cytotoxic activity of pemetrexed and tumor response. The key results are as follows:

- Sixty randomized patients (30 per treatment arm) entered in the companion translational research study. Twenty patients on the Pem 500 Arm and 22 patients on the Pem 900 Arm provided samples for translational research analyses.
- Analysis of gene expression showed molecular markers ERCC1 and RFC1 to be statistically significantly ($p < .05$) associated with differences in more than 1 clinical efficacy measure. No statistically significant association was observed between protein expression levels and any clinical outcome. No association was identified between any marker and severe toxicity.

Title of Study: A Randomized, Double-Blind, Phase 2 Study of Two Doses of Pemetrexed in the Treatment of Platinum-Resistant, Epithelial Ovarian or Primary Peritoneal Cancer.	
Investigator(s): This multicenter study included 22 principal investigator(s).	
Study Center(s): This study was conducted at 22 study center(s) in 4 countries.	
Length of Study: 20 months Date of first patient enrolled: 13 June 2005 Date of last patient completed: 06 March 2007	Phase of Development: 2
Objectives: Primary Objective: The primary objective was to assess the tumor response rate in patients treated with pemetrexed 500 mg/m ² or 900 mg/m ² . Secondary Objective The secondary objectives were to assess time to response, duration of response, time to objective progressive disease (TtPD), time to treatment failure (TtTF), objective progression-free survival (PFS), overall survival (OS), and safety.	
Study Design: This was a randomized, parallel, double-blind, 2-arm, outpatient study. See Figure JMHF.1)	
Number of Patients: Planned: 100 Randomized/Entered: 51 pemetrexed 500 mg/m ² , 51 pemetrexed 900 mg/m ² Completed protocol-planned 6 cycles: 13 pemetrexed 500 mg/m ² , 16 pemetrexed 900 mg/m ²	
Diagnosis and Main Criteria for Inclusion: Patients were women, age 18 years or older with platinum-resistant epithelial ovarian or primary peritoneal cancer that was not amenable to curative therapy. Histologic confirmation of the original primary tumor was required. Patients had measurable disease or CA-125 greater than 2 times the upper limit of normal and had received 1 or 2 platinum-based chemotherapeutic regimens for management of the primary tumor.	
Test Product, Dose, and Mode of Administration: Pemetrexed 500 mg/m ² or 900 mg/m ² administered intravenously over approximately 10 minutes on Day 1 of a 21-day cycle. Premedication with folic acid, vitamin B12, and prophylactic dexamethasone was required for all patients. Folic Acid: Daily oral folic acid (350 to 1000 µg) was taken beginning approximately 1 to 2 weeks before the first dose of pemetrexed. Folic acid was to continue daily until 3 weeks after the last dose of pemetrexed. Vitamin B12: Vitamin B12 was administered as a 1000-µg intramuscular injection approximately 1 to 2 weeks before the first dose of pemetrexed and repeated approximately every 9 weeks until 3 weeks after the last dose of pemetrexed. Dexamethasone: Dexamethasone (4 mg twice per day) or equivalent was taken orally on the day before, the day of, and the day after each dose of pemetrexed.	
Reference Therapy/Comparator, Dose, and Mode of Administration: None	
Duration of Treatment: 6 cycles. Additional cycles were allowed if recommended by the investigator and the Lilly study physician.	

Variables:

Efficacy: Tumor response rate (response determined according to Response Evaluation Criteria in Solid Tumors [Therasse et al. 2000] and/or criteria proposed by the Gynecologic Cancer Intergroup [Vergote et al. 2000], time to response, duration of response, TtPD, TtTF, objective PFS, and OS).

Safety: Serious and treatment-emergent adverse events (TEAEs) – assessed using the Medical Dictionary for Regulatory Activities (Version 10.0), physical examinations, performance status (Eastern Cooperative Oncology Group [ECOG] scale [Oken et al. 1982]), laboratory and nonlaboratory toxicity (assessed using the Common Terminology Criteria for Adverse Events [CTCAE, Version 3.0; NCI 2006] scale, concomitant medications, and number of blood transfusions).

Evaluation Methods:

Statistical: Response rates and 95% exact binomial confidence intervals were assessed for each dose (Leemis and Trivedi 1996) using SAS (Release 8.2). An exploratory rank analysis of best study response was performed. The Mantel-Haenszel (Mantel and Haenszel 1959) test of row mean score difference was performed to assess the difference in overall tumor regression between the 2 doses.

The following efficacy analyses were also performed: (1) Kaplan-Meier (Kaplan and Meier 1958) analyses of time-to-event variables; (2) planned subgroup analyses of best study response (patients with measurable versus nonmeasurable disease; number of prior platinum-based regimens [1 versus 2]).

Safety analyses were summaries of extent of exposure, the number of transfusions required, TEAEs by severity and relationship to study drug, and laboratory and nonlaboratory toxicity.

Study Design

The study design is represented schematically in Figure JMHF.1.

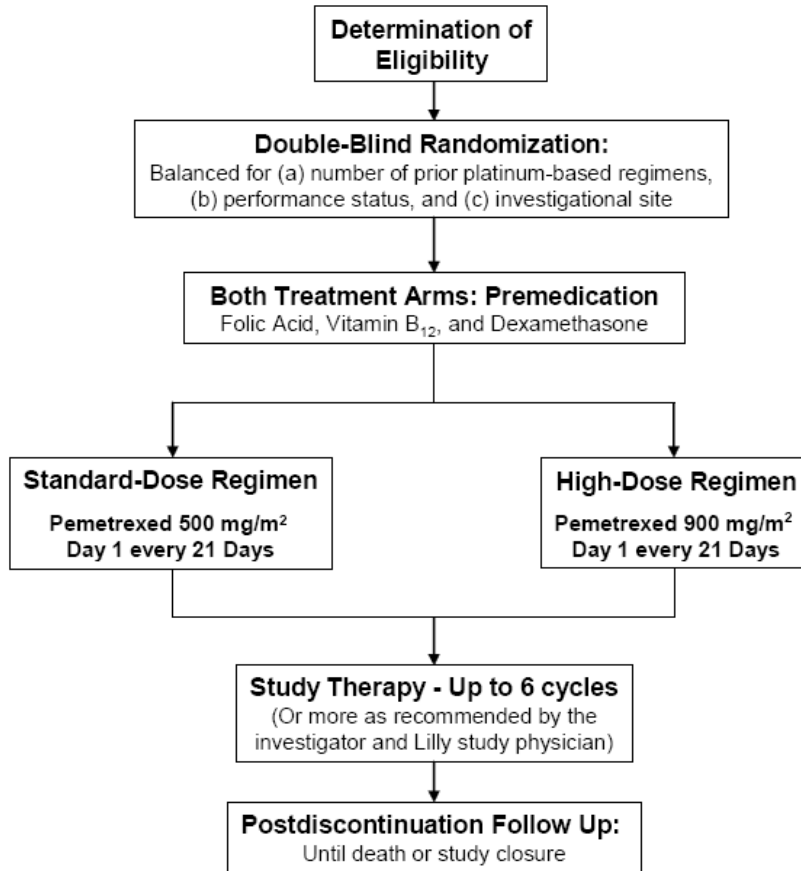


Figure JMHF.1. Study design.

Results:

Patient Demographics

Forty-three patients on the Pem 500 Arm were evaluable for efficacy. The median age was 57.7 years (range, 38.3 to 76.5 years). Forty-two (97.7%) patients were Caucasian, and 1 (2.3%) was of East or Southeast Asian descent. Forty-eight patients on the Pem 900 Arm were evaluable for efficacy. The median age was 63.2 years (range, 29.6 to 78.2 years). Forty-six (95.8%) patients were Caucasian, and 2 (4.2%) were of East or Southeast Asian descent. The 2 treatment arms were numerically well balanced in terms of baseline disease characteristics, except for platinum-free interval (Table JMHF.1).

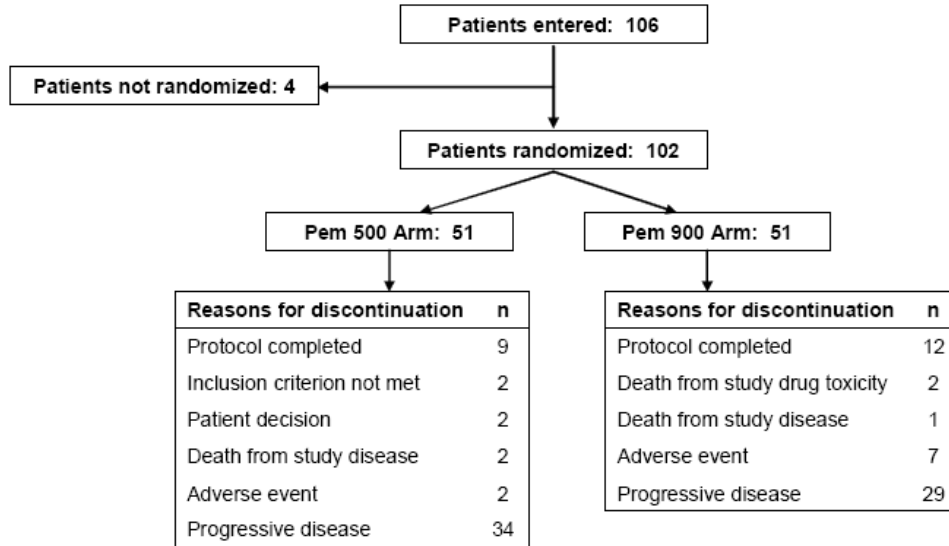
Table JMHF.1. Patient Baseline Disease Characteristics

Parameter	Number (%) of Patients					
	Pem 500 N=43		Pem 900 N=48		Total N=91	
ECOG performance status						
0	13	(30.2)	18	(37.5)	31	(34.1)
1	26	(60.5)	27	(56.3)	53	(58.2)
2	4	(9.3)	3	(6.3)	7	(7.7)
Basis for initial pathological diagnosis						
Histopathological	43	(100.0)	48	(100.0)	91	(100.0)
Pathological diagnosis						
Epithelial ovarian cancer	33	(76.7)	41	(85.4)	74	(81.3)
Primary peritoneal cancer	10	(23.3)	7	(14.6)	17	(18.7)
Measurable disease						
Yes	32	(74.4)	36	(75.0)	68	(74.7)
CA-125 only	11	(25.6)	12	(25.0)	23	(25.3)
Prior platinum-based chemotherapy						
1 regimen	30	(69.8)	31	(64.6)	61	(67.0)
2 regimens	13	(30.2)	17	(35.4)	30	(33.0)
Platinum-free interval						
<3 months	13	(30.2)	21	(43.8)	34	(37.4)
3 to 6 months	30	(69.8)	27	(56.3)	57	(62.6)

Abbreviations: ECOG = Eastern Cooperative Oncology Group, N = number of patients, Pem 500 = pemetrexed 500 mg/m², Pem 900 = Pemetrexed 900 mg/m².

Patient Disposition

Figure JMHF.2 illustrates the patient disposition of all entered patients for both the treatment groups.



Abbreviations: Pem = pemetrexed; n = number of patients.

Figure JMHF.2. Patient disposition.

Table JMHF.2 presents the number of patients randomized, treated (evaluable for safety), and evaluable for the efficacy analyses.

**Table JMHF.2. Summary of Analysis Populations
All Entered Patients**

Analysis Population	Number (%) of Patients		
	Pem 500	Pem 900	Total
Patients entered	-	-	106
Patients randomized	51 (100.0)	51 (100.0)	102 (100.0)
Patients treated ^a	47 (92.2)	51 (100.0)	98 (92.5)
Patients evaluable for efficacy ^b	43 (84.3)	48 (94.1)	91 (85.8)

Abbreviations: Pem 500 = pemetrexed 500 mg/m²; Pem 900 = pemetrexed 900 mg/m².

^a Reasons patients were not treated: 1 patient did not have platinum-resistant disease; 1 patient died of study disease; and 1 patient discontinued because of disease progression. In addition, 1 patient discontinued because of an intestinal obstruction, an event that was incorrectly reported as an adverse event, if a patient did not receive study drug, events that occurred after the informed consent document was signed were to be reported to Lilly only if the event was considered to be related to a protocol procedure. The investigator correctly reported that the intestinal obstruction was not related to study drug.

^b Reasons patients were not evaluable for efficacy: on the Pem 500 Arm, 1 patient did not meet the CA-125 inclusion criterion, 1 patient did not have ovarian or primary peritoneal cancer, and 2 patients did not have platinum-resistant disease. On the Pem 900 Arm, 3 patients did not have platinum-resistant disease.

Reasons for Discontinuations

For both treatment arms, disease progression was the most common reason for early discontinuation (Pem 500: 34 patients [66.7%]; Pem 900: 29 patients [56.9%]) (Figure JMHF.2).

Primary Efficacy Measures

Tumor Response Rate

Response rate was defined as the proportion of patients with complete response (CR) or partial response (PR). Table JMHF.3 presents a summary of the overall best tumor responses among patients evaluable for efficacy. No patients on either treatment arm had a CR. Four patients on the Pem 500 Arm had PRs, for an overall response rate of 9.3% (95% CI, 2.6 to 22.1). Five patients on the Pem 900 Arm had PRs, for an overall response rate of 10.4% (95% CI, 3.5 to 22.7). Fourteen patients on each treatment arm had an overall best study response of stable disease (Pem 500, 32.6% of patients; Pem 900, 29.2% of patients). The difference between the two treatment arms was not statistically significant.

**Table JMHF.3. Summary of Overall Best Study Response
Evaluable Patients**

Best Study Response	Number (%) of Patients			Difference between Arms
	Pem 500 N=43	Pem 900 N=48	Total N=91	
CR, n (%)	0	0	0	NA
PR, n (%)	4 (9.3)	5 (10.4)	9 (9.9)	NA
SD, n (%)	14 (32.6)	14 (29.2)	28 (30.8)	NA
PD, n (%)	21 (48.8)	24 (50.0)	45 (49.5)	NA
Unknown, n (%)	4 (9.3)	5 (10.4)	9 (9.9)	NA
Responders (CR+PR), n (%) (95% CI)	4 (9.3) (2.59, 22.14)	5 (10.4) (3.47, 22.66)	9 (9.9) (4.62, 17.95)	0.9864 ^a

Abbreviations: CI = confidence interval; CR = complete response; n = number of patients; N = number of evaluable patients; NA = not applicable; PD = progressive disease; Pem 500 = pemetrexed 500 mg/m² arm; Pem 900 = pemetrexed 900 mg/m² arm; PR = partial response; SD = stable disease.

^a Fisher exact test p-value.

Secondary Efficacy Measures

Time to Response

Time to response was defined as the time from randomization to the first observation of CR or PR. Four patients on the Pem 500 Arm and 5 patients on the Pem 900 Arm were eligible for this analysis; all 9 eligible patients had an overall best study response of PR. For the Pem 500 Arm, the median time to response was 2.14 months (95% CI, 1.38 to 3.35) and 1.51 months (95% CI, 1.05 to 2.27) for Pem 900 Arm. No statistically significant difference was observed between the two treatment arms.

Duration of Response

Only patients with tumor responses (CR or PR) were included in the analysis of duration of tumor response. Duration of response was defined as the time from the first observation of CR or PR to the earlier of (1) the first observation of progressive disease (PD) or (2) death due to any cause.

Four patients on the Pem 500 Arm and 5 patients on the Pem 900 Arm were eligible for this analysis; all eligible patients had an overall best study response of PR. The median duration of response was 4.04 months (95% CI, 3.06 to 5.98) for Pem 500 Arm and 4.34 months (95% CI, 3.15 to 6.08) for Pem 900 Arm. No statistically significant difference was observed between the two treatment arms.

Time to Objective Progressive Disease

Time to objective progressive disease (TtPD) was defined as the time from the date of randomization to the date of objectively determined PD.

Forty-three patients on the Pem 500 Arm and 48 patients on the Pem 900 Arm were eligible for this analysis; 17 (39.5%) patients on the Pem 500 Arm and 20 (41.7%) patients on the Pem 900 Arm were censored. The median TtPD was 2.76 months (95%

