Summary ID# 9710

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/m^2 (Pem 500) versus pemetrexed 900 mg/m^2 (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/m^2 and the 51 patients who received pemetrexed 900 mg/m^2. 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.

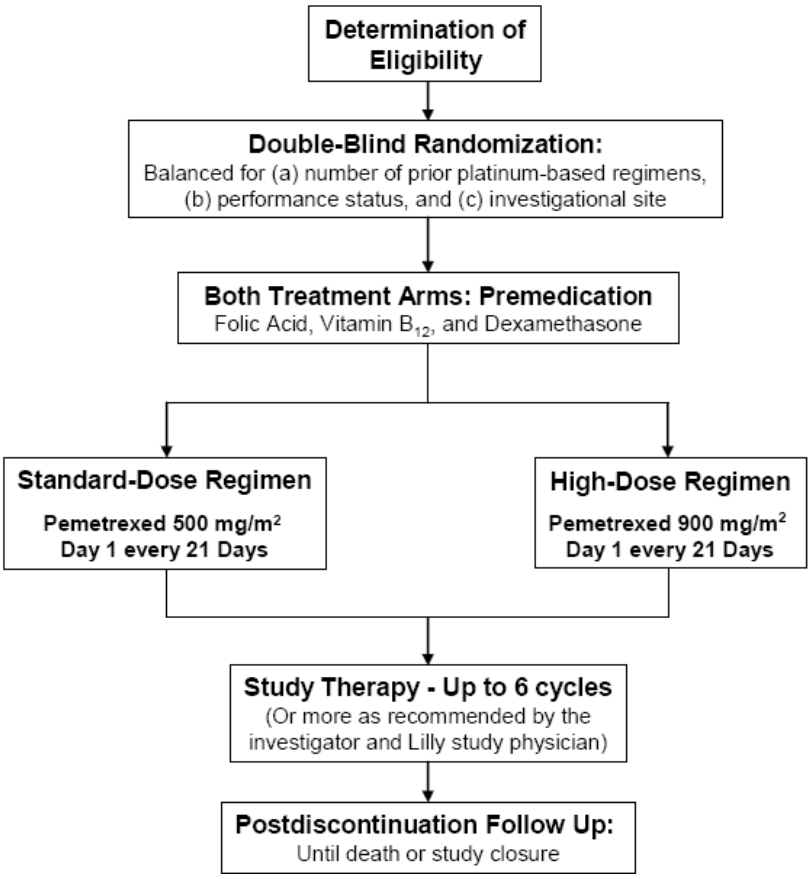


Figure JMHF.1. Study design.

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).

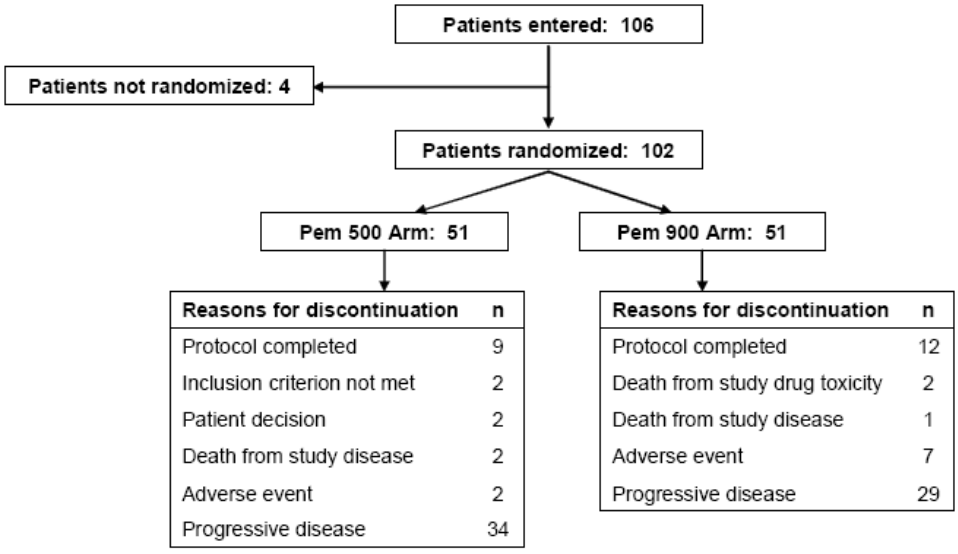
Table JMHF.1. Patient Baseline Disease Characteristics

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/m^2, Pem 900 = Pemetrexed 900 mg/m^2.

Patient Disposition

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



Reasons for discontinuation	n
Protocol completed	9
Inclusion criterion not met	2
Patient decision	2
Death from study disease	2
Adverse event	2
Progressive disease	34

Reasons for discontinuation	n
Protocol completed	12
Death from study drug toxicity	2
Death from study disease	1
Adverse event	7
Progressive disease	29

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

	Number (%) of Patients					
Analysis Population	**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/m^2; Pem 900 = pemetrexed 900 mg/m^2.

[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 conset 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: Pem 500 N=43	Pem 900 N=48	Total N=91	Difference between Arms
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 (%)	4 (9.3)	5 (10.4)	9 (9.9)	0.9864[a]
(95% CI)	(2.59, 22.14)	(3.47, 22.66)	(4.62, 17.95)	

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/m^2 arm; Pem 900 = pemetrexed 900 mg/m^2 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%

CI, 2.37 to 3.22) for Pem 500 Arm and 2.79 months (95% CI, 2.14 to 4.86) for Pem 900 Arm. No statistically significant difference was observed between the two treatment arms.

Time to Treatment Failure

Time to treatment failure (TtTF) was defined as the time from the date of randomization to the date of the first observation of disease progression, death from any cause, or early discontinuation of treatment for any reason.

Forty-three patients on the Pem 500 Arm and 48 patients on the Pem 900 Arm were eligible for this analysis; 1 (2.1%) patient on the Pem 900 Arm was censored. The median TtTF was 2.66 months (95% CI, 2.30 to 2.83) for Pem 500 Arm and 2.46 months (95% CI, 1.87 to 3.25) for Pem 900 Arm. No statistically significant difference was observed between the two treatment arms.

Objective Progression Free Survival

Objective progression free survival (PFS) was defined as the time from the date of randomization to the date of objectively determined PD or death from any cause, whichever occurred first.

Forty-three patients on the Pem 500 Arm and 48 patients on the Pem 900 Arm were eligible for this analysis; 2 (4.7%) patients on the Pem 500 Arm and 2 (4.2%) patients on the Pem 900 Arm were censored. The median PFS was 2.83 months (95% CI, 2.56 to 4.21) for Pem 500 Arm and 2.79 months (95% CI, 2.14 to 4.17) for Pem 900 Arm.. No statistically significant difference was observed between the two treatment arms.

Overall Survival

Overall survival (OS) was defined as the time from the date of randomization to the date of death from any cause. Forty-three patients on the Pem 500 Arm and 48 patients on the Pem 900 Arm were eligible for this analysis; 15 (34.9%) patients on the Pem 500 Arm and 18 (37.5%) patients on the Pem 900 Arm were censored. The median OS was 11.86 months (95% CI, 7.92 to 14.82) for Pem 500 Arm and 10.28 months (95% CI, 7.66 to 14.75) for Pem 900 Arm. No statistically significant difference was observed between the two treatment arms.

Safety

Extent of Exposure

All 98 patients who received at least 1 dose of pemetrexed were evaluated for safety (1 dose = 1 cycle). A total of 195 cycles of therapy was administered to 47 patients on the Pem 500 Arm (median, 4 cycles; standard deviation, 2.03 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.

A total of 188 cycles of therapy was administered to 51 patients on the Pem 900 Arm (median, 3 cycles; standard deviation, 2.09 cycles; range, 1 to 8 cycles). Twelve (23.5%) patients received 6 cycles of therapy, 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. Table JMHF.4 provides a summary of dose administration by cycle for the Pem 500Arm, and Table JMHF.5 provides a summary of dose administration by cycle for the Pem 900 Arm.

Table JMHF.4. Summary of Dose Administration by Cycle Treated Patients Pem 500 Arm

		Number (%) of Patients							
Cycle	N	Doses Administered as Assigned		Cycle Delayed		Doses Reduced		Doses Remaining Reduced[a]	
1	47	47	(100.0)	0		0		0	
2	45	43	(95.6)	4	(8.9)	2	(4.4)	0	
3	36	33	(91.7)	8	(22.2)	1[b]	(2.8)	2[b]	(5.6)
4	28	24	(85.7)	5	(17.9)	1[b]	(3.6)	3[b]	(10.7)
5	16	15	(93.8)	3	(18.8)	0		1	(6.3)
6	13	12	(92.3)	2	(15.4)	0		1	(7.7)
7	4	3	(75.0)	1	(25.0)	0		1	(25.0)
8	3	2	(66.7)	1	(33.3)	0		1	(33.3)
9	1	0		0		0		1	(100.0)
10	1	0		0		0		1	(100.0)
11	1	0		0		0		1	(100.0)

Abbreviations: N = number of treated patients on study therapy at the specified cycle; Pem 500 = pemetrexed 500 mg/m^2.

a This column indicates the number and percentage of patients whose pemetrexed dose was reduced at the previous cycle and remained reduced at the current cycle.

b One patient received a reduced dose at Cycle 2 and continued to receive reduced doses at Cycle 3 and Cycle 4.

Table JMHF.5. Summary of Dose Administration by Cycle Treated Patients Pem 900 Arm

		Number (%) of Patients							
Cycle	N	Doses Administered as Assigned		Cycles Delayed		Doses Reduced		Doses Remaining Reduced[a]	
1	51	51	(100.0)	0		0		0	
2	47	44	(93.6)	11	(23.4)	3	(6.4)	0	
3	29	26	(89.7)	10	(34.5)	2	(6.9)	1	(3.4)
4	20	17	(85.0)	6	(30.0)	2	(10.0)	1	(5.0)
5	18	15	(83.3)	3	(16.7)	2	(11.1)	1	(5.6)
6	16	14	(87.5)	3	(18.8)	0		2	(12.5)
7	4	3	(75.0)	2	(50.0)	0		1	(25.0)
8	3	3	(100.0)	0		0		0	

Abbreviations: N = number of treated patients on study therapy at the specified cycle; Pem 900 = pemetrexed 900 mg/m^2.

[a] This column indicates the number and percentage of patients whose pemetrexed dose was reduced at the previous cycle and remained reduced at the current cycle.

Concomitant Medications

All evaluable patients (Pem 500, 43; Pem 900, 48) had received prior chemotherapy. Approximately 98% of patients in both treatment arms had received carboplatin (Pem 500, 42 [97.7%] patients; Pem 900, 47 [97.9%] patients), and approximately 90% had received paclitaxel (Pem 500, 39 [90.7%]; Pem 900, 43 [89.6%]). Seven (16.3%) patients on the Pem 500 Arm and 5 (10.4%) patients on the Pem 900 Arm had received cisplatin. Seven (16.3%) patients on Pem 500 and 4 (8.3%) patients on Pem 900 had received topotecan. No other chemotherapy drug was reported in more than 3 patients on either treatment arm. Forty-one (95.3%) patients on the Pem 500 Arm and 47 (97.9%) patients on the Pem 900 Arm had also had prior surgery. One patient on each arm had received radiotherapy prior to enrollment in this study.

Table JMHF.6 presents a summary of concomitant drug therapy reported in at least 10% of evaluable patients on either treatment arm.

Table JMHF.6 **Summary of Concomitant Drug Therapy Reported in at least 10% of Evaluable Patients on either Treatment Arm**

	Number (%) of Patients			
	Pem 500		Pem 900	
Drug Name	**N=43**		**N=48**	
Patients with ≥1 drug	43	(100.0)	48	(100.0)
Dexamethasone	41	(95.3)	47	(97.9)
Fortecortin	5	(11.6)	1	(2.1)
B_{12} depot hevert	16	(37.2)	13	(27.1)
Vitamin B_{12}	12	(27.9)	16	(33.3)
Hydroxocobalamin	13	(30.2)	13	(27.1)
Optovite B_{12}	5	(11.6)	7	(14.6)
Paracetamol	13	(30.2)	12	(25.0)
Movicol	10	(23.3)	5	(10.4)
Ciprofloxacin	6	(14.0)	4	(8.3)
Pantozol	6	(14.0)	3	(6.3)
Oramorph	6	(14.0)	1	(2.1)
Cyclizine	5	(11.6)	5	(10.4)
Litican	5	(11.6)	4	(8.3)
Buscopan	5	(11.6)	2	(4.2)
Paspertin	5	(11.6)	0	
Zofran	4	(9.3)	5	(10.4)
Omeprazol	3	(7.0)	6	(12.5)
Ondansetron	3	(7.0)	5	(10.4)
Domperidone	2	(4.7)	7	(14.6)

Abbreviations: N = number of evaluable patients; Pem 500 = pemetrexed 500 mg/m^2 arm; Pem 900 = pemetrexed 900 mg/m^2 arm.

Adverse Events

Table JMHF 7 presents an overview of adverse events reported during the study.

Table JMHF.7. Overview of Adverse Events Treated Patients

	Number (%) of Patients			
	Pem 500		Pem 900	
Adverse Event[a]	N=47		N=51	
Deaths				
On study and within 30 days of last treatment	1	(2.1)	6	(11.8)
Possibly related to study drug	0		2	(3.9)
Serious adverse events				
All	23	(48.9)	23	(45.1)
Possibly related to study drug	8	(17.0)	14	(27.5)
Discontinuations due to adverse events				
All	1	(2.1)	7	(13.7)
Possibly related to study drug	1	(2.1)	5	(9.8)
Treatment-emergent adverse events				
All	46	(97.9)	51	(100.0)
Possibly related to study drug	42	(89.4)	47	(92.2)

Abbreviations: N = number of treated patients; Pem 500 = pemetrexed 500 mg/m^2; Pem 900 = pemetrexed 900 mg/m^2.

[a] No serious, unexpected, reportable events occurred in this study.

Treatment-Emergent Adverse Events

Table JMHF.8 presents a summary of treatment-emergent adverse events (TEAEs) identified by the sponsor in at least 10% of treated patients. On Pem 500 Arm, 46 (97.9%) patients had TEAEs; in 42 (89.4%) patients, the TEAEs were possibly related to study drug, as determined by the investigator. On the Pem 900 Arm, 51 (100.0%) patients had TEAEs; in 47 (92.2%) patients, the TEAEs were possibly related to study drug as determined by the investigator.

Table JMHF.8. Treatment-Emergent Adverse Events Occurring in at least 10% of Treated Patients

	Number (%) of Patients			
	TEAEs		TEAEs Possibly Related to Study Drug	
Event[a]	Pem 500 N=47	Pem 900 N=51	Pem 500 N=47	Pem 900 N=51
Patients with ≥1 TEAE	46 (97.9)	51 (100.0)	42 (89.4)	47 (92.2)
Fatigue	27 (57.4)	26 (51.0)	26 (55.3)	25 (49.0)
Nausea	27 (57.4)	25 (49.0)	23 (48.9)	23 (45.1)
Constipation	23 (48.9)	16 (31.4)	10 (21.3)	9 (17.6)
Vomiting	21 (44.7)	24 (47.1)	13 (27.7)	18 (35.3)
Pyrexia	15 (31.9)	7 (13.7)	10 (21.3)	3 (5.9)
Diarrhoea	13 (27.7)	15 (29.4)	9 (19.1)	6 (11.8)
Anaemia	10 (21.3)	19 (37.3)	8 (17.0)	14 (27.5)
Rash	9 (19.1)	14 (27.5)	9 (19.1)	13 (25.5)
Neutropenia	9 (19.1)	10 (19.6)	8 (17.0)	9 (17.6)
Anorexia	8 (17.0)	12 (23.5)	5 (10.6)	10 (19.6)
Asthenia	7 (14.9)	8 (15.7)	6 (12.8)	7 (13.7)
Leukopenia	6 (12.8)	5 (9.8)	6 (12.8)	5 (9.8)
Thrombocytopenia	4 (8.5)	8 (15.7)	4 (8.5)	7 (13.7)
Pruritus	4 (8.5)	7 (13.7)	3 (6.4)	7 (13.7)
Alopecia	6 (12.8)	3 (5.9)	5 (10.6)	3 (5.9)
Lacrimation increased	2 (4.3)	6 (11.8)	1 (2.1)	6 (11.8)
Headache	8 (17.0)	7 (13.7)	5 (10.6)	1 (2.0)

Abbreviations: N = number of treated patients; MedDRA = Medical Dictionary for Regulatory Activities; Pem 500 = pemetrexed 500 mg/m^2; Pem 900 = pemetrexed 900 mg/m^2; TEAE = treatment-emergent adverse event.

[a] Events are classified according to MedDRA (Version 10.0) preferred term.

Serious Adverse Events

On the Pem 500 Arm, 23 (48.9%) patients experienced a total of 63 serious adverse events (SAEs), and on the Pem 900 Arm, 23 (45.1%) patients experienced a total of 65 SAEs. Table JMHF.9 lists the SAEs experienced by patients treated in this study that were considered related to pemetrexed therapy as determined by the investigator. Eight (17.0%) patients on the Pem 500 Arm experienced a total of 20 SAEs that were possibly related to study drug, 14 (27.5%) patients on the Pem 900 Arm experienced a total of 27 SAEs that were possibly related to study drug.

Table JMHF.9. Serious Adverse Events Possibly Related to Study Drug by MedDRA System Organ Class and Preferred Term Treated Patients

	Number (%) of Patients							
	SAEs				SAEs Possibly Related to Study Drug			
Event[a]	Pem 500 N=47		Pem 900 N=51		Pem 500 N=47		Pem 900 N=51	
Patients with ≥1 SAEs	23	(48.9)	23	(45.1)	8	(17.0)	14	(27.5)
Blood and lymphatic system disorders								
Anaemia	2	(4.3)	2	(3.9)	1	(2.1)	1	(2.0)
Febrile neutropenia	2	(4.3)	2	(3.9)	2	(4.3)	2	(3.9)
Leukopenia	2	(4.3)	2	(3.9)	2	(4.3)	2	(3.9)
Neutropenia	2	(4.3)	2	(3.9)	2	(4.3)	2	(3.9)
Pancytopenia	1	(2.1)	0		1	(2.1)	0	
Thrombocytopenia	1	(2.1)	1	(2.0)	1	(2.1)	1	(2.0)
Cardiac disorders								
Atrial flutter	0		1	(2.0)	0		1	(2.0)
Palpitations	0		1	(2.0)	0		1	(2.0)
Gastrointestinal disorders								
Abdominal pain	0		3	(5.9)	0		1	(2.0)
Diarrhoea	2	(4.3)	2	(3.9)	1	(2.1)	2	(3.9)
Intestinal obstruction[b]	4	(8.5)	1	(2.0)	0		1	(2.0)
Nausea	4	(8.5)	3	(5.9)	2	(4.3)	3	(5.9)
Vomiting	8	(17.0)	8	(15.7)	2	(4.3)	3	(5.9)
General disorders and administration site conditions								
Asthenia	0		2	(3.9)	0		1	(2.0)
Pyrexia	5	(10.6)	1	(2.0)	3	(6.4)	1	(2.0)
Infections and infestations								
Cellulitis	1	(2.1)	1	(2.0)	1	(2.1)	0	
Neutropenic sepsis	0		1[c]	(2.0)	0		1[c]	(2.0)
Pneumonia	0		2	(3.9)	0		1	(2.0)
Sepsis	0		1[c]	(2.0)	0		1[c]	(2.0)
Metabolism and nutrition disorders								
Dehydration	0		2	(3.9)	0		2	(3.9)
Skin and subcutaneous tissue disorders								
Rash maculo-papular	2[d]	(4.3)	0		2[d]	(4.3)	0	

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 10.0); N = number of treated patients; Pem 500 = pemetrexed 500 mg/m^2; Pem 900 = pemetrexed 900 mg/m^2; SAEs = serious adverse events.

[a] Events are classified according to MedDRA (Version 10.0) system organ class and preferred term.

[b] Intestinal obstruction may have indicated disease progression.

[c] Patient was compliant with the protocol's vitamin B_{12} requirement.

[d] One patient with an SAE of rash was not compliant with the protocol's corticosteroid requirement.

Deaths

One (2.1%) patient on the Pem 500 Arm and 3 (5.9%) patients on the Pem 900 Arm died while on study therapy. Three (5.9%) patients on the Pem 900 Arm died within 30 days after the last dose of study therapy. Table JMHF.10 summarizes all deaths that occurred during this study.

Table JMHF.10. Summary of Deaths Treated Patients

Cause of death[a]	Pem 500 (n%) N = 47	Pem 900 (n%) N = 51
Death on study	1 (2.1)	3 (5.9)
Related to study drug		
Neutropenic sepsis	0	1 (2.0)
Sepsis	0	1 (2.0
Due to study disease	1 (2.1)	1 (2.0)
Death within 30 days after last treatment	0	3 (5.9)
Related to study drug	0	0
Due to study disease	0	3 (5.9)

Abbreviations: N = sample size, n = number of patients, Pem 500 = pemetrexed 500 mg/m^2, Pem 900 = Pemetrexed 900 mg/m^2.

Discontinuations Due to Adverse Events

One (2.1%) patient on the Pem 500 Arm discontinued because of an adverse event that was considered to be related to study drug, as determined by the investigator and 7 (13.7%) patients on the Pem 900 Arm discontinued from study therapy because of adverse events. In 5 (9.8%) patients, the events were considered to be related to study drug, as determined by the investigator (Table JMHF.11).

Table JMHF.11. Summary of Discontinuations Due to Adverse Events Treated Patients

Reason for Discontinuation[a]	Pem 500, n (%) N = 47	Pem 900, n (%) N = 51
Serious adverse events related to study drug		
Vomiting	1 (2.1)	0
Abdominal pain	0	1 (2.0)
Serious adverse events not related to study drug		
Anemia	0	1 (2.0)
Non serious adverse events related to study drug		
ALT increased	0	2 (3.9)
Diarrhea	0	1 (2.0)
Blood creatinine increased	0	1 (2.0)
Non serious adverse events not related to study drug		
Creatinine renal clearance decreased	0	1 (2.0)

Abbreviations: N = sample size, n = number of patients, Pem 500 = pemetrexed 500 mg/m^2, Pem 900 = Pemetrexed 900 mg/m^2.

Laboratory and Non Laboratory Toxicities

Table JMHF.12 provides a summary of laboratory and nonlaboratory toxicities, regardless of Common Terminology Criteria (CTC) grade, that were reported in at least 10% of patients on either treatment arm. 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.

Table JMHF.12. Summary of Laboratory and Nonlaboratory Toxicities Reported in at least 10% of Treated Patients on either Treatment Arm

	Number (%) of Patients					
	Pem 500 N=47			Pem 900 N=51		
Event[a]						
Laboratory Parameter	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Hemoglobin	13 (27.7)	3 (6.4)	2 (4.3)	22 (43.1)	6 (11.8)	1 (2.0)
Leukocytes (total WBC)	6 (12.8)	2 (4.3)	1 (2.1)	6 (11.8)	3 (5.9)	2 (3.9)
Neutrophils/granulocytes (ANC/AGC)	8 (17.0)	1 (2.1)	5 (10.6)	10 (19.6)	4 (7.8)	3 (5.9)
Platelets	4 (8.5)	1 (2.1)	1 (2.1)	8 (15.7)	3 (5.9)	3 (5.9)
Nonlaboratory Parameter	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Allergic reaction/hypersensitivity	5 (10.6)	0	0	6 (11.8)	1 (2.0)	0
Anorexia	13 (27.7)	0	0	18 (35.3)	1 (2.0)	0
Ascites (non-malignant)	5 (10.6)	3 (6.4)	0	8 (15.7)	2 (3.9)	0
Constipation	25 (53.2)	0	1 (2.1)	24 (47.1)	0	0
Cough	5 (10.6)	1 (2.1)	0	5 (9.8)	0	0
Dermatology/skin – other	5 (10.6)	0	0	0	0	0
Diarrhea	13 (27.7)	2 (4.3)	0	18 (35.3)	0	0
Distension/bloating, abdominal	6 (12.8)	2 (4.3)	0	1 (2.0)	0	0
Dizziness	6 (12.8)	0	0	6 (11.8)	1 (2.0)	0
Dyspnea (shortness of breath)	11 (23.4)	1 (2.1)	0	6 (11.8)	2 (3.9)	0
Edema: limb	5 (10.6)	0	0	3 (5.9)	1 (2.0)	0
Fatigue (asthenia, lethargy, malaise)	36 (76.6)	3 (6.4)	0	37 (72.5)	8 (15.7)	0
Fever (in the absence of neutropenia)	15 (31.9)	1 (2.1)	0	8 (15.7)	0	0
Gastrointestinal – other	4 (8.5)	0	0	9 (17.6)	1 (2.0)	0
Hair loss/alopecia (scalp or body)	9 (19.1)	0	0	6 (11.8)	0	0
Heartburn/dyspepsia	7 (14.9)	0	0	7 (13.7)	0	0
Hypertension	10 (21.3)	0	0	16 (31.4)	1 (2.0)	0

(Continued)

Table JMHF.12. Summary of Laboratory and Nonlaboratory Toxicities Reported in at least 10% of Treated Patients on either Treatment Arm (Concluded)

Event[a]	Number (%) of Patients					
	Pem 500 N=47			Pem 900 N=51		
Nonlaboratory Parameter (concluded)	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Infection – other	5 (10.6)	1 (2.1)	0	2 (3.9)	0	0
Insomnia	7 (14.9)	1 (2.1)	0	4 (7.8)	0	0
Mood alteration anxiety	5 (10.6)	0	0	3 (5.9)	0	0
Mood alteration depression	6 (12.8)	0	0	8 (15.7)	0	0
Nausea	29 (61.7)	2 (4.3)	0	28 (54.9)	2 (3.9)	1 (2.0)
Neuropathy: sensory	9 (19.1)	0	0	9 (17.6)	0	0
Pain gastrointestinal - abdomen NOS	29 (61.7)	0	0	26 (51.0)	2 (3.9)	0
Pain musculoskeletal - back	6 (12.8)	0	0	4 (7.8)	0	0
Pain neurology - head/headache	11 (23.4)	0	0	7 (13.7)	0	0
Pruritus/itching	5 (10.6)	1 (2.1)[b]	0	8 (15.7)	0	0
Rash/desquamation	12 (25.5)	1 (2.1)	1 (2.1)	15 (29.4)	0	0
Thyroid function, low (hypothyroidism)	4 (8.5)	0	0	9 (17.6)	0	0
Vomiting	23 (48.9)	2 (4.3)	0	26 (51.0)	3 (5.9)	0
Watery eye (epiphora, tearing)	2 (4.3)	0	0	6 (11.8)	0	0

Abbreviations: ANC/AGC = absolute neutrophil count / absolute granulocyte count; N = number of treated patients; NOS = not otherwise specified; Pem 500 = pemetrexed 500 mg/m^2; Pem 900 = pemetrexed 900 mg/m^2; WBC = white blood count.

[a] Severity was graded according to Version 3.0 of the Common Terminology Criteria for Adverse Events scale (NCI 2006).

[b] The patient who had Grade 3 pruritus/itching was not compliant with the protocol's dexamethasone requirement.

Transfusions

Table JMHF.13 provides a summary of the numbers and percentages of patients who received transfusions during the study. Eight (17.0%) patients on the Pem 500 Arm received a total of 9 transfusions, and 15 (29.4%) patients on the Pem 900 Arm received a total of 18 transfusions.

Table JMHF.13. Summary of Transfusions Required Treated Patients

	Number (%) Patients		
Type of Transfusion	Pem 500 N=47	Pem 900 N=51	Total N=98
Patients with ≥1 transfusion	8 (17.0)	15 (29.4)	23 (23.5)
Packed red blood cells	7 (14.9)	13 (25.5)	20 (20.4)
Platelets	1 (2.1)	2 (3.9)	3 (3.1)
Whole blood	1 (2.1)	2 (3.9)	3 (3.1)
Plasma	0 (0.0)	1 (2.0)	1 (1.0)

Abbreviations: N = number of treated patients; Pem 500 = pemetrexed 500 mg/m^2; Pem 900 = pemetrexed 900 mg/m^2.

Translational Research Protocol

Of the 60 randomized patients (30 per treatment arm) entered in the companion translational research study, 27 patients on the Pem 500 Arm and 28 patients on the Pem 900 Arm were evaluable for efficacy. Twenty patients on the Pem 500 Arm and 22 patients on the Pem 900 Arm provided samples for the translational research analyses. For each assay, patients were dichotomized into high- and low-expression subgroups at the point providing the strongest association with each clinical outcome. Key findings are as follows:

Results

Association between Molecular Markers and Efficacy

Table JMHF.14 provides a summary of the associations between markers and efficacy found in this study. Gene expression levels for ERCC1 and RFC1 were statistically significantly associated with differences in more than 1 clinical efficacy measure. Lower levels of RFC1 were also statistically significantly associated with improved best overall response (p=.014) and longer TtTF (p=.008). Lower levels of ERCC1 were significantly associated with increased PFS (p=.049), TtPD (p=.041), and TtTF (p=.028). No protein expression levels were statistically significantly associated with any clinical efficacy measures. No association was identified between any marker and severe toxicity.

Table JMHF.14. Summary of Translational Research Analyses Association between Markers and Efficacy

Marker	Analysis	Dichotomization	p-Value[a]	Odds Ratio[b]	Hazard Ratio[c]
ERCC1	Response	Gene expression	0.096	10.427	
	TtPD	Gene expression	0.041		5.089
	TtTF	Gene expression	0.028		4.110
	PFS	Gene expression	0.049		3.810
FOLRA	TtTF	Gene expression	0.080		3.253
FPGS	Response	Gene expression	0.034	16.549	
	Overall survival	Protein expression	0.082		0.311
GARFT	Response	Gene expression	0.053	14.226	
	TtTF	Gene expression	0.012		4.156
GSTPi	Response	Gene expression	0.021	20.886	
	TtTF	Gene expression	0.058		3.279
	PFS	Gene expression	0.070		3.252
RFC1	Response	Gene expression	0.014	36.674	
	TtTF	Gene expression	0.008		6.280
TP	TtTF	Gene expression	0.060		3.272
	PFS	Gene expression	0.065		2.800
TS[d]	TtPD	Protein expression	0.088		0.274

Abbreviations: ERCC1 = excision repair cross-complementing 1; FOLRA = folate receptor alpha; FPGS = folylpolyglutamate synthase; GARFT = glycinamide ribonucleotide formyl transferase; GSTPi = glutathione S-transferase pi; PFS = progression-free survival; RFC1 = reduced folate carrier 1; TP = thymidine phosphorylase; TS = thymidylate synthase; TtTF = time to treatment failure; TtPD = time to progressive disease.

[a] Asymptotic probability of the observed maximum chi-square statistic under the null hypothesis of no association between the specified efficacy endpoint and marker expression, limiting the search to the central 50% of values. Calculated with the formula of Miller and Siegmund (1982).

[b] Ratio of the odds of a poorer response in the high-expression group versus the odds of a poorer response in the low-expression group.

[c] Ratio of event hazards in the high-expression group versus the low-expression group.

[d] Murine antihuman thymidylate synthase antibody against clone TS106 (Abcam PLC).

References

[NCI] National Cancer Institute. 2006. Common terminology criteria for adverse events v3.0 (CTCAE). Available at http://ctep.cancer.gov/reporting/ctc_v30.html. Accessed 22 August 2007.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP.1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655.

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. 2000. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92(3):205-216.

Vergote I, Rustin GJS, Eisenhauer EA, Kristensen GB, Pujade-Lauraine E, Parmar MKB, Friedlander M, Jakobsen A, Vermorken JB. 2000. Re: new guidelines to evaluate the

response to treatment in solid tumors (ovarian cancer). Gynecologic Cancer Intergroup. J Natl Cancer Inst 92(18):1534-1535.

