# 2. JMHH Synopsis

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# Clinical Study Report Synopsis: Study H3E-MC-JMHH

**Title of Study:** A Phase 1 and 2 Clinical Trial of ALIMTA® (Pemetrexed) in Combination with Carboplatin in Patients with Recurrent Ovarian or Primary Peritoneal Cancer

**Number of Investigators:** This multicenter study included 18 principal investigators.

**Study Centers:** This study was conducted at 18 study centers in 5 countries.

**Publications Based on the Study:** Phase 1 of this study was published (Sehouli et al. 2010).

**Length of Study:**
Date of first patient enrolled: 01 July 2005
Date of last patient completed: 23 February 2010

**Phase of Development:** 1/2

**Objectives:**

The primary objective of the Phase 1 portion of this study was to determine the maximum tolerated dose (MTD) of the combination therapy of pemetrexed and carboplatin when administered to patients with platinum-sensitive recurrent ovarian cancer. The primary objective of the Phase 2 portion of this study was to determine the overall tumor response rate of the combination therapy of pemetrexed and carboplatin when administered to patients with platinum-sensitive recurrent ovarian cancer.

The secondary objectives of the Phase 1 portion of this study were as follows:

- to determine the dose-limiting toxicities (DLTs) of the combination therapy of pemetrexed and carboplatin in patients with platinum-sensitive recurrent ovarian cancer
- to determine the quantitative and qualitative toxicities of pemetrexed in combination with carboplatin
- to determine a recommended dose of the combination therapy of pemetrexed and carboplatin for future Phase 2 studies
- to document the antitumor activity of pemetrexed and carboplatin in patients with platinum-sensitive recurrent ovarian cancer through tumor response assessment

The secondary objectives of the Phase 2 portion of this study were as follows:

- to determine the following time-to-event parameters in patients with platinum-sensitive recurrent ovarian cancer treated with pemetrexed and carboplatin:
  - time to response (TTR)
  - duration of response (DOR)
  - time to objective disease progression (TTP)
  - time to treatment failure (TTF)
  - objective progression-free survival (PFS)
  - overall survival (OS)
- to determine the safety and quantitative and qualitative toxicities of the combination therapy of pemetrexed and carboplatin in patients with platinum-sensitive recurrent ovarian cancer

**Study Design:** This is a Phase 1, open-label, multicenter study of pemetrexed and carboplatin in patients with platinum-sensitive recurrent ovarian or primary peritoneal cancer, followed by a Phase 2, open-label, multicenter study of pemetrexed and carboplatin in patients with platinum-sensitive recurrent ovarian or primary peritoneal cancer.

**Number of Patients**:

Phase 1
Planned: 40
Treated (at least 1 dose): 20
Completed: 20

Phase 2
Planned: 64
Treated (at least 1 dose): 66
Completed: 66

**Diagnosis and Main Criteria for Inclusion:** To be included in the study, patients were required to have a diagnosis of ovarian or primary peritoneal cancer confirmed by histologic evaluation that was platinum-sensitive recurrent and not amenable to curative therapy. Best response to prior platinum-based therapy must have been complete response (CR), partial response (PR), stable disease (SD), or not evaluable due to optimal debulking surgery. Patients enrolling in the Phase 1 portion of the protocol may have had either measurable or nonmeasurable disease as defined by Response Criteria in Solid Tumors (RECIST) guidelines (Therasse et al. 2000). Patients enrolling in the Phase 2 portion of the protocol must have had measurable disease as defined by RECIST guidelines.

Women age 18 years or older who had received no more than 1 line [for patients enrolled through protocol amendment (b)] or 2 lines [for patients enrolled in protocol amendment (c)] of therapy for ovarian or primary peritoneal cancer were eligible to enter the study. Additional requirements included Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, adequate organ function, and life expectancy of at least 24 weeks.

**Test Product, Dose, and Mode of Administration:**

Pemetrexed was administered intravenously (IV) over approximately 10 minutes on Day 1 of a 21-day cycle. Carboplatin was administered IV over approximately 30 minutes on Day 1 of a 21-day cycle, beginning approximately 30 minutes after the end of the pemetrexed infusion. In the Phase 1 portion of the study, patients received pemetrexed dosages of 500 mg/m$^2$, 600 mg/m$^2$, 700 mg/m$^2$, 800 mg/m$^2$, or 900 mg/m$^2$ and carboplatin dosages of 5 AUC (area under the curve) mg/mL min or 6 AUC mg/mL min. Patients received 500 mg/m$^2$ pemetrexed and 6 AUC mg/mL min carboplatin in the Phase 2 portion of the study.

**Reference Therapy, Dose, and Mode of Administration:** Not applicable

**Duration of Treatment:**

Six cycles of therapy. Patients were allowed to receive up to an additional 2 cycles if benefiting from treatment.

**Variables:**

Efficacy: Objective response rate based on the patients' best response (CR or PR); overall survival; objective progression-free survival; time to objective progressive disease (PD); time to treatment failure; time to response (CR or PR); duration of response (CR or PR).

Safety: All patients treated with 1 dose of study drug were evaluated for safety. The safety information is summarized and listed in preferred terms of Medical Dictionary for Regulatory Activities (MedDRA), Version 12.0 and Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

**Statistical Evaluation Methods:**

Efficacy: Kaplan-Meier analyses were performed on the observed distributions of time-to-progressive disease, progression-free survival, duration of overall response, and duration of stable disease.

Safety: Summaries for safety are provided for all patients who received at least 1 dose of study drug. This included CTCAE grades for laboratory and nonlaboratory parameters, treatment-emergent adverse events (TEAEs), and dose adjustments.

**Summary:**

**Phase 1**

The primary objective of the Phase 1 portion, determining the MTD, was not reached. Other studies had shown that there was no advantage of dosing pemetrexed during Phase 2 in excess of 500 mg/m$^2$ (Llombart-Cussac et al. 2007; Cullen et al. 2008; Ohe et al. 2008; Vergote et al. 2008). Additionally, dosing with carboplatin 6 AUC mg/mL·min was selected because this is a standard dose employed in the control arm of a first-line therapy for epithelial ovarian cancer (Bookman 2006) and it was the dose tolerated in the Phase 1 part of this study.

All 20 (100%) patients in Phase 1 experienced TEAEs during the study. Of these, 19 (95.0%) patients experienced TEAEs that were considered by the investigator to be possibly related to study drug. Two serious adverse events (SAEs) were observed in Phase 1, but neither of them were considered to be related to study treatment. Three patients died during Phase 1 after study drug discontinuation. There were no treatment-related deaths in Phase 1. No patients in Phase 1 withdrew from the study due to adverse events (AEs).

Nineteen of the 20 patients in Phase 1 were assessed for response; 17 were analyzed according to the CA-125 response criteria (Vergote et al. 2000) and 2 patients were analyzed by RECIST criteria. By CA-125 criteria, 12 (63.2%; 95% confidence interval [CI]: 41.5%, 84.9%) patients experienced a CR and 4 (21.1%; 95% CI: 2.8%, 39.4%) patients experienced a PR. In the patients that did not experience a response, 1 patient experienced SD and 2 patients experienced PD as their best response. By intent to treat (ITT), the CA 125-defined response rate was estimated to be 80.0% (95% CI: 62.5%, 97.5%).

**Phase 2**

In the 61 patients in the protocol-qualified (PQ) population during Phase 2, 1 (1.6%) patient experienced a CR and 19 (31.1%) patients experienced a PR. The overall response rate was 32.8% (95% CI: 21.3%, 46.0%). Twenty (32.8%) patients experienced SD as their best response, and 21 (34.4%) patients had their best response classified as "unknown." The median time to response was 1.8 (95% CI: 1.4, 2.8) months. The median duration of response was 9.1 (95% CI: 6.9, 10.2) months with censoring rate of 25.0%.

Kaplan-Meier analyses of the PQ population demonstrated that the median progression-free survival time was 9.4 (95% CI: 8.3, 11.1) months with censoring rate of 18.0%. The progression-free survival rates at 6 months and 12 months were 86.0% and 26.0%, respectively. Results of the analysis of time to objective PD were similar to the results of the analysis of objective progression-free survival time. The median time to objective PD was 9.5 (95% CI: 8.3, 11.3) months with a censoring rate of 27.9%. The median time to treatment failure was 7.1 (95% CI: 4.6, 8.5) months with a censoring rate of 9.8%. The probability that the time to treatment failure is at least 6 months is 0.56.

Treatment with pemetrexed was generally well tolerated. A total of 19 (28.8%) patients experienced drug hypersensitivity to carboplatin. Fourteen patients had a change in carboplatin and/or pemetrexed dosing and 5 patients had no change as a result of drug sensitivity. Among these patients, 9 patients had a carboplatin dose reduction and 8 of those patients were subsequently discontinued due to this event. Five patients had their carboplatin dose omitted while continuing to receive pemetrexed.

The most common possibly treatment-related SAEs were anemia, carboplatin hypersensitivity, and vomiting. Twenty patients (30.3%) died during the study. There was 1 drug-related death due to multi-organ failure. The other deaths were due to PD. The most common possibly drug-related TEAEs were nausea, neutropenia, anemia, and fatigue. The primary reasons for pemetrexed dose reduction were thrombocytopenia and neutropenia. In addition, carboplatin hypersensitivity resulted in carboplatin dose reduction and omissions.

**Conclusions:**

**Phase 1**

- Although an MTD was not reached, the combination of pemetrexed (500 mg/m$^2$) and carboplatin (AUC 6) was feasible and sufficiently well tolerated to merit taking the schedule into the Phase 2 component of the trial.

**Phase 2**

- The combination of pemetrexed (500 mg/m$^2$) and carboplatin (AUC 6) demonstrated response rate activity, and progression-free survival duration was commensurate with other available carboplatin based doublets (Parmar et al. 2003; Pfisterer et al. 2006; Pujade-Lauraine et al. 2010) for platinum-sensitive recurrent ovarian cancer. Definitive assessment of relative utility of the carboplatin pemetrexed combination vis-à-vis another carboplatin-based doublet for platinum-sensitive ovarian cancer would require a Phase 3 study.

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