Introduction: Previously published results from a randomized phase III study of pemetrexed plus cisplatin in patients with malignant pleural mesothelioma (MPM) demonstrated a significant survival benefit and higher response rate compared with cisplatin. Although pemetrexed was under review by regulatory agencies, an International Expanded Access Program (EAP) provided more than 3000 mesothelioma patients with access to single-agent pemetrexed or pemetrexed in combination with cisplatin or carboplatin in 13 countries. This manuscript reports the safety and efficacy data from the nonrandomized open-label study in chemo naïve patients receiving pemetrexed plus platinum under the EAP.

Methods: Patients with histologically confirmed MPM, not amenable to curative surgery, received pemetrexed 500 mg/m² in combination with either cisplatin 75 mg/m² or carboplatin AUC 5, once every 21 days with standard premedication. Efficacy data were recorded at the end of study participation. Results: A total of 1704 chemo naïve patients received pemetrexed plus cisplatin (n = 843) or pemetrexed plus carboplatin (n = 861) and were evaluated for safety. The efficacy evaluable population consisted of 745 patients in the pemetrexed plus cisplatin group and 752 patients in the pemetrexed plus carboplatin group for whom physician-reported tumor response was available. The pemetrexed plus cisplatin group demonstrated a response rate of 26.3% compared with 21.7% for the pemetrexed plus carboplatin group, with similar 1-year survival rates (63.1% versus 64.0%) and median time to progressive disease (7 months versus 6.9 months). The most common grade 3/4 hematologic toxicity was neutropenia in 23.9% for the pemetrexed plus cisplatin group and 36.1% of the pemetrexed plus carboplatin group.

Conclusion: This large EAP confirmed the activity of pemetrexed plus cisplatin and pemetrexed plus carboplatin in chemo naïve patients with MPM, demonstrating clinically similar time to progressive disease and 1-year survival rates.

Key Words: Cisplatin, Carboplatin, Expanded access program, Malignant pleural mesothelioma, Pemetrexed.
Pemetrexed Plus Platinums in Mesothelioma

Patients and Methods

Patients

Patients at least 18 years of age with a histologically proven diagnosis of mesothelioma who were not candidates for curative surgery were enrolled under this International EAP. Informed consent was obtained before enrollment. Patients had to be clinically staged using the International Mesothelioma Interest Group Tumor Nodes Metastasis staging criteria. Measurable lesions were not required for enrollment. Patients could have been chemonaive, or may have received one or more lines of prior chemotherapy for malignant mesothelioma. Patients were required to have a performance status \( \geq 70 \) on the Karnofsky scale (after any palliative measures, including pleural drainage, had occurred). Patients were required to have adequate bone marrow reserve [absolute neutrophil count (ANC) \( \geq 1.5 \times 10^9 \text{/liter} \), platelets \( \geq 100 \times 10^9 \text{/liter} \), and hemoglobin \( \geq 9 \text{g/dl} \)], hepatic function [bilirubin \( \leq 1.5 \text{times the upper limit of normal (ULN)} \), alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase \( \leq 3.0 \times \text{ULN} \) (alkaline phosphatase, AST, and alanine transaminase \( 5 \times \text{ULN} \) if liver had tumor involvement]), and normal renal function (calculated creatinine clearance \( \geq 45 \text{ml/min} \) based on the standard Cockcroft and Gault formula. Prior pleurodesis was allowed. Pregnant women were not eligible, and all men and women of reproductive potential were required to use an approved method of birth control. Patients with serious concomitant disorders incompatible with the study were excluded at the investigator’s decision.

Treatment Plan

Under the International EAP, mesothelioma patients received one of the three treatment options. The primary treatment option was pemetrexed plus cisplatin. Patients who were unable to tolerate the cisplatin regimen received either pemetrexed plus carboplatin or single-agent pemetrexed. Patient assignments were nonrandomized and based on individual investigator decisions that considered the clinical status and therapy goals of both the patient and physician. In this report, we describe the findings from 1704 chemonaive patients with MPM who received either pemetrexed plus cisplatin or pemetrexed plus carboplatin.

Pemetrexed Plus Cisplatin Group

Pemetrexed was administered at the dose of 500 mg/m\(^2\) as a 10-minute intravenous infusion, diluted in 100 ml normal saline. Approximately 30 minutes after the administration of pemetrexed, cisplatin was administered intravenously at 75 mg/m\(^2\) over 2 hours. Both drugs were administered on day 1 of a 21-day cycle.

Pemetrexed Plus Carboplatin Group

Pemetrexed was administered at the dose of 500 mg/m\(^2\) as a 10-minute intravenous infusion, diluted in 100 ml normal saline. Approximately 30 minutes after the administration of pemetrexed, carboplatin AUC 5 was administered intravenously over 30 minutes. Both drugs were administered on day 1 of a 21-day cycle.

Folic acid supplementation, 350 \( \mu \text{g} \) to 600 \( \mu \text{g} \) or equivalent, was given orally daily beginning approximately 1 to 2 weeks prior to the first dose of pemetrexed and continuing daily until at least 3 weeks after the last pemetrexed dose was given. A vitamin \( B_{12} \) injection, 1000 \( \mu \text{g} \), was administered intramuscularly approximately 1 to 2 weeks prior to the first dose of pemetrexed, and was repeated approximately every 9 weeks until the patient discontinued from the EAP. Additionally, dexamethasone 4 mg (or an equivalent corticosteroid) was given orally twice per day on the day before, the day of, and the day after each dose of pemetrexed to reduce the risk of severe skin rash. Study therapy was allowed to continue until there was evidence of progressive disease, the...
Dose Adjustments

Dose adjustments at the start of a subsequent cycle of therapy were based on platelet and neutrophil nadir (lowest value) counts from the preceding cycle of therapy (ANC had to be $\geq 1.5 \times 10^9$/liter and platelets $\geq 100 \times 10^9$/liter before the start of any cycle). Dose delays up to 42 days were permitted for recovery from study-drug toxicity. Upon recovery, treatment was resumed from the preceding cycle of therapy at 100% of the previous dose for an ANC $\geq 0.5 \times 10^9$/liter and platelets $\geq 50 \times 10^9$/liter, at 75% of the previous dose for an ANC $< 0.5 \times 10^9$/liter and platelets $\geq 50 \times 10^9$/liter, or at 50% of the previous dose for platelets $< 50 \times 10^9$/liter. Any patient requiring three dose reductions was discontinued from the study. In the event of diarrhea requiring hospitalization (or at least grade 3), treatment was delayed until diarrhea had resolved before proceeding. Treatment was resumed at 75% of the previous dose level. For other nonhematologic events greater than or equal to grade 3 (with the exception of grade 3 transaminase elevations), treatment was delayed until resolution was less than or equal to the patient’s baseline CTCAE grade before proceeding.

Efficacy Assessments

Patients’ tumor response was assessed preferably using the Response Evaluation Criteria in Solid Tumors. The Southwest Oncology Group criteria or the World Health Organization criteria were also acceptable for response evaluation. The best overall response status was determined when the patient completed or discontinued from the study. Overall tumor response rate was defined as the number of patients with documented partial response or complete response divided by the number of patients qualified for tumor response analysis (evaluable patients). TTPD was estimated in months from the date of the first dose to the date of the first documentation of progressive disease. Survival status was collected when the patient completed therapy and at one follow-up visit 30 days after study completion. Survival time was estimated in months from the date of the first dose to the date of death.

Safety Assessments

Safety was assessed by physical examination and clinical laboratory tests. Patients were rated for adverse events before each cycle using the Common Terminology Criteria for Adverse Events (CTCAE) scale, version 2. However, only myelosuppression data were collected in the clinical trial.

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**FIGURE 1.** Patients with pleural mesothelioma who enrolled in the pemetrexed International Expanded Access Program. EAP, expanded access program; N, sample size; n, number of patients. The highlighted boxes are the patient population described in detail in this manuscript.
disposition. Serious adverse events (SAEs) were reported by the investigators to the sponsor’s global safety surveillance system, and were monitored by the Eli Lilly clinical research physician.

**Statistical Methods**

A summary of statistics was provided. Missing data were not considered in the efficacy or safety analysis. Only the available data in each cycle were summarized. The investigator-assessed best overall tumor response was summarized with proportion and 95% confidence intervals (CI). TTPD and survival time were calculated using Kaplan-Meier estimates. Patients who discontinued or for whom no observation was available were censored. The log-rank test was conducted to compare the treatment groups.

All subjects who received at least one dose of the study drug were classified as the safety population. All patients who were in the safety population and who had at least one tumor response observation after baseline were classified as the evaluable efficacy population.

**RESULTS**

**Baseline Characteristics and Patient Disposition**

A total of 3142 patients with MPM was entered into the International EAP; 2074 were chemonaive and 1011 were previously treated (Figure 1). The first patient was assigned to therapy on November 6, 2002 and the last patient completed therapy on October 19, 2006. The present report focuses on the subset of 1704 chemonaive patients who were able to tolerate combination chemotherapy with either pemetrexed plus cisplatin or pemetrexed plus carboplatin. Results for other patient subgroups have been described previously.11,18 Of the 1704 chemonaive patients, 843 patients received pemetrexed plus cisplatin and 861 patients received pemetrexed plus carboplatin and constituted the safety population. Tumor response data were available for 745 evaluable patients in the pemetrexed plus cisplatin group and for 752 evaluable patients in the pemetrexed plus carboplatin group.

The baseline patient demographics and characteristics are presented in Table 1. In the pemetrexed plus cisplatin group, the median age was 62 years (range, 24.0–78.0 years), 85.3% of patients were male, 98.9% were Caucasian, and 86.8% of patients had a Karnofsky performance status ≥80. In the pemetrexed plus carboplatin group, the median age was 66 years (range, 35.0–89.0 years), 80.5% of patients were male, 99.9% were Caucasian, and 85.8% of patients had a Karnofsky performance status ≥80. Nine patients (1.1%) in the pemetrexed plus carboplatin group had a performance status <70, which was a protocol violation.

The main reasons for study discontinuation in the pemetrexed plus cisplatin group were objective tumor progression (19.9%), clinical disease progression (5.8%), patient-physician perception (22.5%), and other (12.6%). The main reasons for study discontinuation in the pemetrexed plus carboplatin group were objective tumor progression (20.7%), patient-physician perception (16.3%), and clinical disease progression (7.9%). Three patients (0.3%) in the pemetrexed plus carboplatin group discontinued from the study because of death from study-drug toxicity.

**Treatment**

A median of five cycles (range, 1–26 cycles) was delivered to the patients in the pemetrexed plus cisplatin group, and a median of six cycles (range, 1–35 cycles) to the patients in the pemetrexed plus carboplatin group. In the pemetrexed plus cisplatin group, 405 (48%) patients completed six cycles of treatment and in the pemetrexed plus carboplatin group, 452 (52.5%) patients completed six cycles. At least 47 patients in each group received 10 treatment cycles, and at least five patients in each group received 20 treatment cycles. The relative dose intensity (the percentage of dose delivered compared with the planned dose of a drug) was high for pemetrexed and cisplatin. In the pemetrexed plus cisplatin group, 95.0 and 94.9% of pemetrexed and cisplatin doses were delivered unadjusted. The relative dose intensities were 98.7% and 97.1%, respectively. In the pemetrexed plus carboplatin group, 91.3 and 91.2% of pemetrexed and carboplatin doses were delivered unadjusted. Although the relative dose intensity for pemetrexed was 97.1%, the relative dose intensity for carboplatin could not be calculated because the details regarding the creatinine clearance level were not captured.

![Table 1. Baseline Demographics and Patient Characteristics](image-url)
Efficacy

In the pemetrexed plus cisplatin group, the overall response rate for 745 patients evaluable for response was 26.3%, consisting of 15 (2.0%) complete responses and 181 (24.3%) partial responses. In addition, 383 patients (51.4%) had stable disease as their best tumor response and 139 (18.7%) had progressive disease. In the pemetrexed plus carboplatin group, the overall response rate for 752 patients evaluable for response was 21.7%, consisting of 7 (0.9%) complete responses and 156 (20.7%) partial responses. In addition, 407 patients (54.1%) had stable disease as their best response and 158 (21.0%) had progressive disease (Table 2).

The median TTPD in the pemetrexed plus cisplatin group was 7 months and the median TTPD in the pemetrexed plus carboplatin group was 6.9 months (Figure 2). The median overall survival could not be estimated due to the high censoring rates of 89% for the pemetrexed plus cisplatin group and 87.1% for the pemetrexed plus carboplatin group. However, the 1-year survival rate for pemetrexed plus cisplatin and pemetrexed plus carboplatin was 63.1 and 64.0%, respectively (Table 3), and Kaplan-Meier survival curves were estimated (Figure 3).

As per an intent-to-treat analysis, survival was evaluated in all treated patients who received pemetrexed plus cisplatin (n = 843) or pemetrexed plus carboplatin (n = 861). Median survival times and CIs could not be estimated, however, due to the high censoring rates (>84%). However, for all treated patients, the 1-year survival rate was 60.5% (95% CI, 50.1–71.0) for the pemetrexed plus cisplatin group and 62.8% (95% CI, 53.5–72.0) for the pemetrexed plus carboplatin group. Thus the survival results in treated patients did not differ considerably from the findings in the efficacy evaluable populations.

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**TABLE 2.** Best Overall Response Rate in Chemonaive Patients with Malignant Pleural Mesothelioma (Evaluable Patients Only)

<table>
<thead>
<tr>
<th>Response</th>
<th>Pemetrexed + Cisplatin (n = 745)</th>
<th>Pemetrexed + Carboplatin (n = 752)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response, n (%)</td>
<td>15 (2.0)</td>
<td>7 (0.9)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>181 (24.3)</td>
<td>156 (20.7)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>383 (51.4)</td>
<td>407 (54.1)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>139 (18.7)</td>
<td>158 (21.0)</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>27 (3.6)</td>
<td>24 (3.2)</td>
</tr>
<tr>
<td>Overall response rate, %</td>
<td>26.3</td>
<td>21.7</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(23.2, 29.6)</td>
<td>(18.8, 24.8)</td>
</tr>
<tr>
<td>Disease control rate (responder + stable disease), %</td>
<td>77.7</td>
<td>75.8</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(74.6, 80.7)</td>
<td>(72.6, 78.8)</td>
</tr>
</tbody>
</table>

CI, confidence interval; n, number of patients.

**TABLE 3.** Time to Progressive Disease and Survival in Chemonaive Patients with Malignant Pleural Mesothelioma (Efficacy Evaluable Population)

<table>
<thead>
<tr>
<th>Event</th>
<th>Pemetrexed + Cisplatin (n = 745)</th>
<th>Pemetrexed + Carboplatin (n = 752)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTPD, mo</td>
<td>7.0 (95% CI)</td>
<td>6.9 (95% CI)</td>
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<tr>
<td>Median survival, mo</td>
<td>NA*</td>
<td>NA*</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(6.7, 8.3)</td>
<td>(6.6, 7.7)</td>
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<tr>
<td>1-yr survival rate, %</td>
<td>63.1</td>
<td>64.0</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(50.7, 75.5)</td>
<td>(53.3, 74.6)</td>
</tr>
<tr>
<td>Censoring rate, %</td>
<td>89.0</td>
<td>87.1</td>
</tr>
</tbody>
</table>

CI, confidence interval; TTPD, time to progressive disease; n = number of patients; NA, not available. *Not estimable.

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**FIGURE 2.** Kaplan-Meier analysis of time to progressive disease (months) in chemonaive evaluable patients with malignant pleural mesothelioma who received pemetrexed plus cisplatin (n = 745) or pemetrexed plus carboplatin (n = 752).
Safety

A total of 843 patients in the pemetrexed plus cisplatin group and 861 patients in the pemetrexed plus carboplatin group were qualified for the safety analysis. Only myelosuppression data were collected. The CTCAE grade 3 and 4 toxicities observed in each treatment group are summarized in Table 4. In the pemetrexed plus cisplatin group, the most commonly reported CTCAE grade 3/4 hematologic toxicities were neutropenia (23.9%) and leukopenia (13.1%). In the pemetrexed plus carboplatin group, the most commonly reported CTCAE grade 3 and 4 toxicities were neutropenia (36.1%), leukopenia (21.0%), anemia (14.3%), and thrombocytopenia (14.3%).

Based on safety data from the Lilly Safety System database, SAEs for the patient population described in this manuscript included hematologic events, febrile neutropenia, nausea, and vomiting. SAEs observed in ≥1% of the patients in the pemetrexed plus cisplatin group were nausea (3.3%), vomiting (2.3%), anemia (1.4%), and neutropenia (1.2%). SAEs in the pemetrexed plus carboplatin group were anemia (4.5%), vomiting (3.4%), nausea (2.7%), neutropenia (1.9%), pancytopenia (1.9%), thrombocytopenia (1.6%), and febrile neutropenia (1.2%). During the study, a total of seven deaths were considered by the investigators as possibly related to study-drug toxicity. Two of these deaths occurred in the pemetrexed plus cisplatin group (both due to neutropenic sepsis), and five deaths occurred in the pemetrexed plus carboplatin group (one each due to septic shock, renal tubular necrosis, diarrhea, pancytopenia, and neutropenia). During follow-up, two additional deaths were observed in the pemetrexed plus carboplatin group (one each due to circulatory collapse and septic shock).

DISCUSSION

Pemetrexed-based combinations with platinum analogs have shown promising activity in patients with MPM (Table 5). This multicenter, nonrandomized, open-label study describes the largest group of chemo-naïve patients reported to date who were provided access to combination therapy with pemetrexed plus cisplatin (n = 843) or pemetrexed plus carboplatin (n = 861) under the International EAP in Europe. Of the patients evaluable for the efficacy analysis, the patients treated with pemetrexed plus cisplatin and pemetrexed plus carboplatin experienced overall response rates of 26.3 and 21.7%, respectively, with comparable median TTPD (7 months versus 6.9 months) and 1-year survival rates (63.1 versus 64.0%, respectively). Although Kaplan-Meier survival estimates are presented (Figure 3), these data should be interpreted with caution given the very high censoring rates (87–89%). In a similar EAP in the United States, reported previously by Obasaju et al., chemo-naïve patients with MPM who were treated with the same dosing schedule of peme-
etrexed plus cisplatin (n = 709) demonstrated a response rate of 20.8% and a 1-year survival rate of 45.9%. In the present study, the overall response rate and 1-year survival rate observed in European patients was found to be slightly higher as compared with the US patients. Additionally, the overall disease control rate was also higher in the present study (77.7 vs 68.3%). We have compared both EAPs to explain the observed differences in response rates. Regarding the patient characteristics, the lower median age (62 versus 70 years) appeared to be in favor of the current International EAP.

In contrast, Vogelzang et al. reported a higher response rate of approximately 41% in patients treated with pemetrexed plus cisplatin in their Phase III study. However, for patients receiving pemetrexed plus cisplatin, the 1-year survival rate was somewhat lower in the trial reported by Vogelzang et al. than that observed in this EAP (50.3 versus 63.1%).

The response rates observed in the present study are within the range of other cisplatin-based combination therapies in MPM. Cisplatin-based combinations with doxorubicin, mitomycin, etoposide, cyclophosphamide, vinblastine, and raltitrexed resulted in 24 to 26% response rates. In a phase III study reported by Vogelzang et al., a higher response rate of 41.3% was reported for pemetrexed plus cisplatin combination therapy. The combination of doxorubicin, cisplatin, bleomycin, and mitomycin produced a response rate of 44% in one study; however, other investigators have been unable to reproduce it.

Other studies similarly demonstrated efficacy with pemetrexed plus carboplatin in MPM. Phase I and II trials of carboplatin in combination with pemetrexed resulted in higher response rates (19–32%) with prolonged survival (13–15 months) (Table 5). In this study, the response rate with pemetrexed plus carboplatin was in the same range (21.7%), with a 1-year survival rate in a significant number of patients (64%). Manegold et al. reported on chemo naïve patients in this EAP who were considered unsuitable for combination chemotherapy and therefore received single-agent pemetrexed. Although the overall response rate appeared lower for chemo naïve patients who received single-agent therapy (10.5%; 95% CI, 7.0–15.0%), it is striking that the 1-year survival rates were more similar (58.6%, 95% CI, 43.3–73.8%) for patients treated with single-agent pemetrexed versus 63.1 and 64% (Table 3) for patients receiving combination therapy.11

In this EAP, the overall response rate, median TTPD, and 1-year survival rate did not differ considerably between the two treatment groups. Under the EAP, the first treatment choice was pemetrexed in combination with cisplatin, thus it is presumed that patients who received pemetrexed and carboplatin in this study were most likely not suitable to receive the cisplatin-based regimen. The higher median age of 66 years in the pemetrexed plus carboplatin group supports this argument. It is noteworthy that these patients could tolerate the carboplatin-based combination very well, as reflected by a higher median number of treatment cycles.

The hematologic toxicity concurred with the phase III study of pemetrexed plus cisplatin in MPM, and was moderate in both treatment groups. The CTCAE grade 3/4 hematologic toxicities and SAEs appeared to be higher in the pemetrexed plus carboplatin group. Because this is not a randomized trial, however, it is unclear to what extent this difference is linked to carboplatin toxicity or to baseline differences in the patient groups. Toxic deaths rates were 0.2% for the pemetrexed plus cisplatin group and 0.6% for the pemetrexed plus carboplatin group.

The results presented here should be interpreted in the context of the limitations associated with the operation of a large EAP. Patients were not randomized to treatment groups and this study was not intended to provide a rigorous comparison of pemetrexed plus cisplatin versus pemetrexed plus carboplatin in MPM. Patients treated with pemetrexed plus carboplatin tended to have poorer clinical status because it was a secondary treatment option for individuals who likely could not tolerate cisplatin. In addition, the protocol allowed physicians to use discretion in evaluating response (Response Evaluation Criteria in Solid Tumors, Southwest Oncology Group, and World Health Organization criteria were allowed), which may have resulted in inconsistencies in the interpretation of individual patient results. Despite these limitations, the findings are significant because they reflect standard clinical oncology practice. Results are derived from a large and diverse patient group from multiple countries. Patient selection was minimal as enrollment criteria were less

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Phase</th>
<th>No. of Patients</th>
<th>Response Rate (%)</th>
<th>Median TTPD (mo)</th>
<th>Median Survival (mo)</th>
<th>1-yr Survival Rate (%)</th>
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<td>12.1</td>
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<td>6.9</td>
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<td>10.2</td>
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TTPD, time to progressive disease; EAP, expanded access program; NE, not estimated; NA, not available.

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stringent than those of a typical randomized trial. Still, the present International EAP confirmed the activity of pemetrexed plus cisplatin, and the hematologic toxicity concurred with the earlier phase III findings. The carboplatin plus pemetrexed group showed similar efficacy as seen with pemetrexed plus cisplatin, and may be a possible choice for patients who are not suitable for cisplatin-based chemotherapy.

ACKNOWLEDGMENTS

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