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Pemetrexed in the treatment of malignant mesothelioma: Results from an expanded access program in Germany

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Summary
An international expanded access program was initiated to provide access to treatment with pemetrexed prior registration and reimbursement for malignant mesothelioma (MM).

Chemonaïve and pretreated patients with inoperable MM of the pleura or peritoneum were eligible. This report describes the results obtained in German centers. Investigators could choose between three treatments: Pemetrexed 500 mg/m^2 alone (P) or in combination with cisplatin 75 mg/m^2 (PC) or carboplatin AUC 5 (PCb).

From November 2002 to June 2004, a total of 567 patients (554 with pleural MM; 41% pretreated) were included. Of 548 evaluable patients with pleural MM, 191 received P, 137 PC and 220 PCb. Patients in the P group were more often pretreated (70%) and had worse performance status compared with the other groups. In the P, PC, and PCb groups overall response

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rate (ORR) was 16%, 24% and 18%, median time to progression (TTP) was 5.5, 8.2, and 6.9 months, and median overall survival (OS) was 8.7, 11.3 and 9.7 months respectively. Efficacy outcomes were better for chemonaïve than for pretreated patients, and P was less hematotoxic than PC or PCb.

Treatment of pleural MM with pemetrexed alone or in combination with platinum was safe and active as first and second-line therapy.

Introduction

Malignant mesothelioma (MM) is an aggressive malignancy arising from the serosal lining of various body cavities.[1–3] Most MMs are pleural mesotheliomas; peritoneal mesothelioma represents approximately 15% to 25% of all mesotheliomas,[1,3] and MMs of the pericardium or tunica vaginalis testis are extremely rare.[4,5] In the majority of cases, the etiology of MM is closely related to chronic asbestos exposure.[6] As a result of the long latency period between first exposure to asbestos and the onset of MM, often exceeding 40 years, the incidence of MM is still increasing worldwide, whereas the rising mortality rate will soon level off in Western Europe.[7] In 2004, a total of 780 newly diagnosed cases were reported to the German Mesothelioma Registry,[8] but the true incidence of MM in Germany is probably higher.

The prognosis of MM remains dismal, with a median survival of 9–12 months.[9] Until recently, the results reported with chemotherapy were disappointing, and no particular regimen was generally accepted as treatment standard.[9]

Pemetrexed is a novel multitargeted antifolate that inhibits thymidylate synthase, dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT) enzymes involved in purine and pyrimidine synthesis. After the efficacy and safety of pemetrexed alone and in combination with cisplatin in the treatment of mesothelioma had been demonstrated,[10,11] a randomized phase III trial was performed in 456 patients with malignant pleural mesothelioma to compare single agent cisplatin with pemetrexed plus cisplatin.[12] Patients treated with the combination had a significantly improved response rate (41% vs. 17%), median time to progression (5.7 vs. 3.9 months) and median overall survival (12.1 vs. 9.3 months) compared with the control group. Based on these results, the pemetrexed plus ciplatin combination was approved by the Food and Drug Administration and the European Medicines Agency (EMEA) for the treatment of inoperable malignant pleural mesothelioma.

Although the treatment results obtained with pemetrexed plus cisplatin are promising, many patients may not be suitable for cisplatin-containing combinations due to comorbidities, poor performance status or advanced age. For these patients, carboplatin-containing combinations or single agent pemetrexed may be attractive treatment options.

Access to pemetrexed was provided in an international Expanded Access Program (EAP) performed in 13 European countries, including 3256 patients with pleural ($n = 3124$) or peritoneal ($n = 113$) mesothelioma.[13,14] Pemetrexed was administered as a single agent or in combination with cisplatin or carboplatin. Here we report the results from the subgroup of German patients, representing 17.4% of the total patient population of the European EAP.

Patients and methods

Patient selection

Patients aged 18 years or more were eligible if they had histologically proven malignant mesothelioma with or without prior treatment and were not candidates for curative surgery. Patients previously treated with pemetrexed were only included if they had responded or received a clinical benefit from treatment. If patients had undergone pleurodesis, a minimum delay of 2 weeks before starting study treatment was recommended to permit resolution of an acute inflammatory response. Patients with adequately treated and stable brain metastases could be enrolled if they did not require corticosteroid therapy. Patients were also required to have adequate bone marrow, hepatic, and renal function defined as absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, hemoglobin ≥ 9 g/dL; bilirubin ≤ 1.5 times the upper limit of normal (ULN), alkaline phosphatase (AP), aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 3.0 \times$ ULN (AP, AST, and ALT $\leq 5 \times$ ULN was acceptable in the case of liver involvement); calculated creatinine clearance (CrCl) ≥ 45 mL/min based on the standard Cockcroft and Gault formula or on measured glomerular filtration rate (GFR) using the appropriate radiolabeled method (^{51}Cr-EDTA or Tc99 m-DTPA). Karnofsky performance status had to be 70 or higher at study entry and after any palliative measures including pleural drainage for pleural effusion were administered. All study candidates were required to provide written informed consent. The study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.

Study design and treatment

The EAP program was a non-randomized, open-label study of pemetrexed in patients with malignant mesothelioma. Patient access to pemetrexed (Alimta®, Lilly Deutschland GmbH, Bad Homburg, Germany) was provided for this indication under the study protocol prior to and during regulatory review for commercial release. Investigators had three treatment options: pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 (PC), single agent pemetrexed 500 mg/m^2 (P), or pemetrexed 500 mg/m^2 plus carboplatin AUC 5 (PCb). Treatment was administered intravenously on day 1 of a 21-day cycle that was repeated until disease progression, inacceptable toxicity or study discontinuation due to patient or investigator decision. The choice of treatment for the individual patient was at the investigator's discretion, considering the patient's clinical status, prior treatment,

and the therapeutic goal. For patients with poor performance status and/or organ dysfunction the use of single agent pemetrexed was encouraged.

Supplementation with folic acid and vitamin B_{12} was given routinely with each treatment regimen, starting about 1–2 weeks prior to the first dose of pemetrexed, and continued throughout treatment. Oral folic acid was given at daily doses of 350–600 μg or equivalent, and 1000-mg doses of vitamin B_{12} were injected intramuscularly approximately every 9 weeks. Oral dexamethasone 4 mg or another corticosteroid at an equivalent dose was given twice daily the day before, the day of administration, and the day after each dose of pemetrexed. Antiemetic prophylaxis was recommended.

Data collection

Assessments included hematologic toxicity graded according to National Cancer Institute Common Toxicity Criteria (NCI CTC), Version 2.0,[15] tumor response (preferably according to RECIST criteria, but Southwest Oncology Group [SWOG] criteria and World Health Organization [WHO] criteria were also allowed),[16] time to progression (TTP), and overall survival (OS). Response was evaluated at study discontinuation, but if a patient had additional tumor response assessments at interim or follow-up visits the best response was chosen for analysis. Safety follow-up was 30 days after completion of treatment or until resolution of any treatment-emergent adverse effect. No formal follow-up for treatment efficacy or death was required.

Statistical analysis

Data evaluations were performed in the safety population and among evaluable patients, as appropriate, and separately for patients with pleural and peritoneal mesothelioma, and for chemonaïve and previously treated patients. The intention-to- treat population included all enrolled patients with malignant mesothelioma, and the safety population included all patients who received at least one dose of the study treatment. For the safety analysis, descriptive methods were used without any formal statistical testing. Overall survival and time to progression were estimated using the Kaplan-Meier method and compared between treatment groups using a log-rank test. Response rates, median survival, median time to progression, and 1-year survival rates are shown with 95% confidence intervals (95% CI). If there was no follow-up visit or if patients discontinued before disease progression or death occurred, these patients were censored. For all data analyses SAS software, Version 8.2, was used.

Results

From November 2002 to June 2004, a total of 567 eligible patients, including 554 with pleural and 13 with peritoneal mesothelioma, were enrolled to the EAP from 14 institutions in Germany. All but 6 patients were assigned to one of the study treatments and received at least one dose of study medication. Thus, the safety population comprised 561 patients. The baseline characteristics of the 548 patients with pleural mesothelioma included in the safety population are shown in Table 1; all characteristics were similar to those of the total European EAP population. The pretreatment status was known from 520 of these patients, of whom 307 (59%) were chemonaïve and 213 (41%) were previously treated. Patients in the P arm had a much worse Karnofsky performance status and had more often received prior treatment compared with those in the PCb or PC arms. Although the number of patients with peritoneal mesothelioma was small ($n = 13$), it was apparent that they were relatively young (median 54 years, range 37–66), and those assigned to treatment with pemetrexed + cisplatin had a better performance status (90 or 100 in 6 of 7 patients)

Table 1 Baseline characteristics of patients with pleural mesothelioma (safety population) by pretreatment status and treatment group.

	Chemonaïve ($n = 307$)	Previously treated ($n = 213$)	Total ($n = 548$)			Overall ($n = 548$)
			PC* ($n = 137$)	*P** ($n = 191$)	PCb* ($n = 220$)	
Age, years						
Median (range)	65 (35–85)	63 (38–81)	63 (38–77)	64 (39–81)	66 (35–85)	65 (35–85)
Male gender, *n* (%)	263 (86)	179 (84)	124 (91)	158 (83)	185 (84)	467 (85)
Caucasian, *n* (%)	306 (100)	213 (100)	136 (99)	191 (100)	220 (100)	547 (100)
Karnofsky PS, *n* (%)						
90–100	193 (63)	110 (52)	94 (69)	81 (42)	149 (68)	324 (59)
70–80	110 (36)	99 (46)	41 (30)	107 (56)	67 (30)	215 (39)
50–60	0 (0)	1 (<1)	0 (0)	1 (1)	0 (0)	1 (<1)
Unknown	4 (1)	3 (1)	2 (1)	2 (1)	4 (2)	8 (1)
Previously treated, *n* (%)	–	–	24/127 (19)	131/187 (70)	58/206 (28)	213/520 (41)
Histology						
Sarcomatoid	24 (8)	12 (6)	9 (7)	13 (7)	16 (7)	38 (7)
Epithelial	206 (67)	155 (73)	91 (66)	132 (69)	159 (72)	382 (70)
Mixed cell	34 (11)	19 (9)	19 (14)	16 (8)	21 (10)	56 (10)
Other	43 (14)	27 (13)	18 (13)	30 (16)	24 (11)	72 (13)

*PC, pemetrexed + cisplatin; P, pemetrexed; PCb, pemetrexed + carboplatin.

than those allocated to single agent pemetrexed or pemetrexed + carboplatin.

Treatment exposure

Overall, patients with pleural mesothelioma received a median of 5 cycles (range, 1–44) of the study treatment, with only minor differences between the treatment arms (PC: 6 [1–44], P: 5 [1–15], PCb: 6 [1–34]). Treatment exposure was comparable in the patient group with peritoneal mesothelioma (median 6 cycles, range 2–35). Overall, one or more dose delays and/or reductions during the course of treatment were required for pemetrexed, cisplatin, and carboplatin in 35%, 26%, and 45% of the patients, respectively. Relative dose intensity was approximately 98% for pemetrexed in all treatment arms, and 95% for cisplatin. The most common reasons for discontinuation of the study included lack of efficacy (30%), tumor progression (29%), or satisfactory response (23%). In the monotherapy arm, treatment tended to be discontinued more often due to progressive disease compared with PCb and PC (38% vs. 28% vs. 19%).

Safety

Hematologic toxicity observed in the patient group with pleural mesothelioma is shown in Table 2. The incidence of grade 3/4 anemia and leukopenia was similar among treatment arms, while grade 3/4 neutropenia and thrombocytopenia was less common in the pemetrexed arm.

Only 3 patients (0.5%) died of adverse events probably or possibly related to study therapy (2 in the P arm with neutropenic sepsis and 1 in the PCb arm with pancytopenia).

Efficacy

Treatment outcome is summarized in Table 3. Twelve patients with peritoneal and 498 patients with pleural mesothelioma were evaluable for response. In the patient group with pleural mesothelioma, there were 3 complete and 90 partial responses, resulting in an overall response rate of 19%. In addition, 280 patients (56%) had stable disease. The highest response rate was achieved in the PC arm (24% [95% CI 17–32%] vs. 16% [95% CI 10–22%] in the P arm vs. 18% [95% CI 13–24%] in the PCb arm), but the difference between the groups was not was not significant.

Response was comparable between chemonaïve patients (20%, 95% CI 15–25%) and previously treated patients (16%, 95% CI 11–22%). Only one (8%) out of 12 evaluable patients with peritoneal mesothelioma achieved a partial response, but 8 (67%) had stable disease.

Median TTP among evaluable patients with pleural mesothelioma was 6.9 months (95% CI 6.2–7.8) in the total population. The longest TTP was achieved in the PC arm, with a median of 8.2 months (95% CI 7.0–8.6) compared with 5.5 months (95% CI 4.9–7.2) in the P arm and 6.9 months (95% CI 5.8–7.6) in the PCb arm; the difference between groups was significant in the log-rank test ($p = 0.004$). Median TTP was 7.6 months (95% CI 6.7–8.3) for chemonaïve patients compared with 5.6 months (95% CI 4.9–6.9) for previously treated patients.

Median OS was 10.1 months (95% CI 8.6–11.6) for all patients with pleural mesothelioma, and 11.3 months (95% CI 7.7 to undetermined) in the PC arm, 8.7 months (95% CI 7.0 to undetermined) in the P arm, and 9.7 months (7.1–10.9) in the PCb arm (Figure 1). The difference in OS between arms was not significant (log-rank $p = 0.606$), but the percentage of censored patients was high in all arms (overall, 78%; range, 77% to 80%). Survival at 1 year was estimated to be 37% (95% CI 24–49%) in the total population, and 42% (95% CI 24–59%) in the PC arm, 42% (95% CI 21–62%) in the P arm, and 18% (0–47%) in the PCb arm. Median OS was 11.6 months (95% CI 9.2 to undetermined) for chemonaïve patients and 8.6 months (6.6–20.4) for previously treated patients with pleural mesothelioma. Survival of patients with peritoneal mesothelioma seemed to be longer; results for this subgroup of patients have been presented in part elsewhere.[17]

Discussion

This report summarizes the results from 561 patients with MM who were treated in German centers as part of an

Table 2 Hematologic toxicity among patients with pleural mesothelioma (safety population) by treatment group.

	PC* ($n = 137$)	P* ($n = 191$)	PCb* ($n = 220$)	Overall ($n = 548$)	p**
Anemia					
n[a]	134	186	216	536	
Grade 3/4, n (%)	21 (16)	37 (20)	43 (20)	101 (19)	0.556
Leukopenia					
n[a]	134	186	216	536	
Grade 3/4, n (%)	30 (22)	28 (15)	47 (22)	105 (20)	0.154
Neutropenia					
n[a]	130	180	212	522	
Grade 3/4, n (%)	37 (29)	28 (16)	78 (37)	143 (27)	<0.001
Thrombopenia					
n[a]	134	186	216	536	
Grade 3/4, n (%)	17 (13)	12 (7)	37 (17)	66 (12)	0.005

*PC, pemetrexed + cisplatin; P, pemetrexed; PCb, pemetrexed + carboplatin.
**χ^2 test.
[a] Designates the total number of patients with available data for a specific toxicity.

Table 3 Response and survival by pretreatment status and treatment group in patients with pleural mesothelioma (safety population).

	Chemonaïve (n = 282)	Previously treated (*n* = 190)	Total (*n* = 498)			
			PC* (n = 130)	P* (n = 161)	PCb* (*n* = 207)	Overall (n = 498)
ORR (CR + PR), % [95% CI]	20 [15–25]	16 [11–22]	24 [17–32]	16 [10–22]	18 [13–24]	19 [15–22]
DCR (CR + PR + SD), % [95% CI]	81 [75–85]	69 [62–75]	80 [72–87]	66 [58–73]	79 [73–84]	75 [71–79]
Median TTP, months [95% CI]	7.6 [6.7–8.3]	5.6 [4.9–6.9]	8.2 [7.0–8.6]	5.5 [4.9–7.2]	6.9 [5.8–7.6]	6.9 [6.2–7.8]
Median OS, months [95% CI]	11.6 [9.2–ud]	8.6 [6.6–20.4]	11.3 [7.7–ud]	8.7 [7.0–ud]	9.7 [7.1–10.9]	10.1 [8.6–11.6]
1-year survival, % [95% CI]	47 [27–66]	38 [22–54]	42 [24–59]	42 [21–62]	18 [0–47]	37 [24–49]

*PC, pemetrexed + cisplatin; P, pemetrexed; PCb, pemetrexed + carboplatin.
95% CI, 95% confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; OS, overall survival; PR, partial response; SD, stable disease; TTP, time to progression; ud, undetermined.

international expanded access program of pemetrexed with or without a platinum agent. All but 13 patients had pleural mesothelioma. Thus, the patient population with pleural mesothelioma constituted the basis of this report. It was shown that all treatment regimens were feasible in routine clinical practice and well tolerated, although patients receiving pemetrexed alone experienced the mildest hematologic toxicity. The difference in TTP between groups was statistically significant and clinically meaningful, with the longest median TTP seen among patients treated with PC (8.2 months). However, this did not translate into a statistically significant difference in overall survival between the treatment groups.

There are some limitations of this trial that are related to the study design and warrant caution in interpreting the results. This study was an Expanded Access Program, therefore there was no control arm. The patients were not randomly assigned to the different treatment arms. Rather, it was left to the discretion of the investigators which chemotherapy regimen they applied, taking into account the clinical status of the individual patient and the intent of therapy. In addition, the high proportion of censored patients limits the accuracy of the survival estimates. Irrespective of these limitations, the study findings clearly demonstrated a favorable safety profile for all chemotherapy options with pemetrexed. Dose intensity of chemotherapy could be maintained as planned in the majority of patients, and only 3 patients (0.5%) died of adverse events probably or possibly related to study therapy.

The differences in baseline characteristics seen among patients of the three treatment groups might reflect the process of clinical decision-making. Single agent treatment with pemetrexed was the preferred choice for previously treated patients with a poor performance status, while most patients treated with pemetrexed/cisplatin or pemetrexed/carboplatin were chemonaïve and physically fit. Despite these important differences at baseline, there was a remarkable similarity between the groups with regard to treatment exposure and outcome measures.

Objective response rates were in the range of 20%, but another 50–60% of the patients had disease stabilization. Thus, between 66% (pemetrexed alone) and 80% (pemetrexed/cisplatin) of the patients benefited from treatment in terms of disease control. The good clinical response was also reflected by a median TTP of 5.5 and 8.2 months, and a median OS of 8.7 and 11.3 months for single agent pemetrexed and pemetrexed/cisplatin, respectively. Outcome for patients treated with pemetrexed/carboplatin was intermediate between the other two groups, but 95% confidence intervals for all outcome measures were overlapping between the treatment groups, and a comparison of the three survival curves using a long-rank test did not show a significant difference. Remarkably, median overall survival of previously treated patients (62% of whom received single agent pemetrexed) was 8.6 months for all treatment groups combined, suggesting good activity of pemetrexed-based second-line therapy. Unfortunately, the type of pretreatment was not available from the EAP database.

This report is one of a series of recently published EAP reports that described clinical experience with pemetrexed alone or in combination with a platinum agent in malignant mesothelioma. The non-US international EAP, part of which was the German population described herein, has already reported results for all chemonaïve patients with pleural mesothelioma receiving treatment with single agent pemetrexed[13] or a pemetrexed-platinum combination.[14] The US EAP differed from the international trial in that only two treatment options were available, either pemetrexed alone or pemetrexed plus cisplatin. The efficacy data from this program indicated that the combination of pemetrexed with a platinum was more effective in terms of higher response and disease control rates and longer median survival, both in chemonaïve and previously treated patients, compared with single agent pemetrexed.[18–20] These data are consistent with our observations suggesting a superiority of PC compared with monotherapy. In chemonaïve patients, the difference in survival between the combination and single agent pemetrexed was significant (10.9 vs. 4.8 months, $P = 0.001$).[19] Although baseline

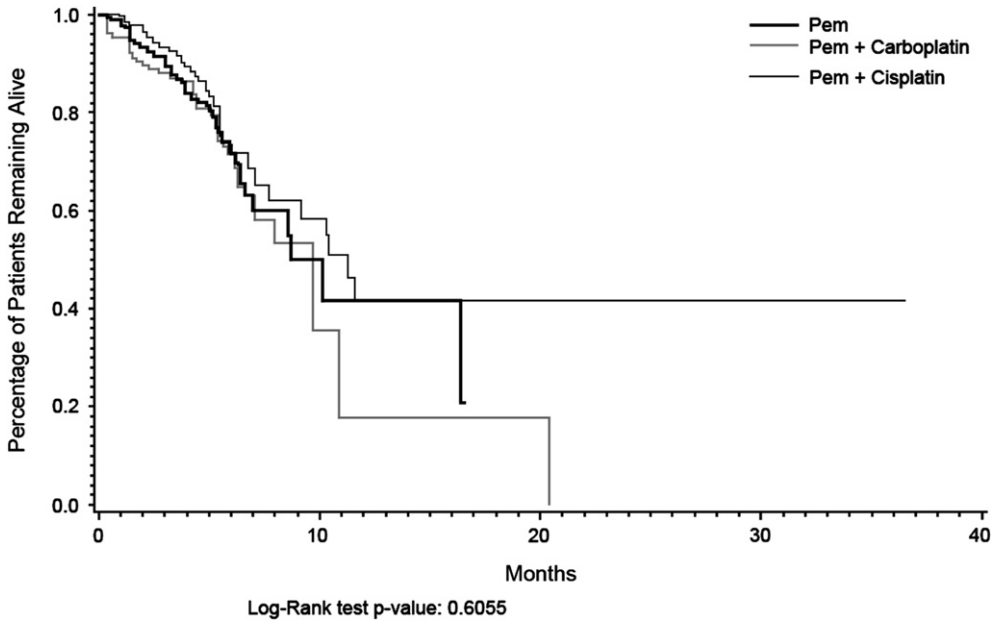

Figure 1 Kaplan-Meier plot of survival time by treatment arm in pleural mesothelioma population in Germany (evaluable population). MTA = pemetrexed.

performance status of the patients was not reported in this publication, it is reasonable to assume that similar to our population, patients treated with single agent pemetrexed were more likely to be in a poorer clinical condition than those offered the platinum combination, thus putting the survival difference into perspective.

While combination chemotherapy with pemetrexed and cisplatin has been established as standard first-line therapy for MM, based on the phase III results reported by Vogelzang et al.,[12] there is accumulating evidence that previously treated patients may also benefit from treatment with pemetrexed. The objective response rate of 16% and the disease control rate (CR + PR + SD) of 69% seen in our study with second-line pemetrexed therapy are in keeping with this concept, and the survival seen in this study, with a median OS of 8.6 months (37 weeks) and a 1-year survival of 38%, indicates second-line treatment offers a clinically meaningful benefit.

A randomized controlled study compared pemetrexed with best supportive care as second-line therapy in 243 patients with pleural mesothelioma.[21] Response rate with pemetrexed was 19%, and median TTP was significantly improved compared with BSC (3.7 vs. 1.5 months; $P = 0.0002$), but median OS was similar in both groups. Sørensen et al.[22] reported on 39 patients who were previously treated with platinum-based chemotherapy without pemetrexed. Second-line therapy consisted of single agent pemetrexed in 28 patients and pemetrexed/carboplatin in 11 patients. Both regimens were similarly effective. Response rate was approximately 20%, median TTP 21 weeks with pemetrexed and 32 weeks with the combination, and median OS approximately 40 weeks for both regimens. Bogaert et al. [23] explored the possibility of pemetrexed maintenance therapy after successful induction with a pemetrexed-based regimen. They found that stable disease was converted to a partial response in 3 of 13 patients receiving maintenance treatment with pemetrexed with or without carboplatin, and progression-free and overall survival in the maintenance group was significantly longer compared with the 14 patients who did not receive maintenance therapy (median TTP, 8.5 vs. 3.4 months; median OS, 17.9 vs. 6.0 months; $P < 0.0001$ for both comparisons).

In conclusion, our results obtained in the German patient population of an international expanded access program are largely consistent with the experience in other EAPs and clinical studies of malignant mesothelioma. It was shown that pemetrexed given alone or in combination with cisplatin or carboplatin is safe and effective as first and second-line therapy in pleural mesothelioma. In particular, single agent pemetrexed could be a valuable treatment option for pretreated patients which may offer substantial clinical benefit. Preliminary evidence suggests that pemetrexed-based chemotherapy has similar activity in peritoneal mesothelioma.[17]

Conflict of Interest Statement

R.A. Stahel, J. von Pawel, M. Karthaus, S. Korfee, C. Eschbach and T.H. Fink have no conflict of interest to declare. M. Serke has received honoraria as a speaker and consultant from Lilly. W.H.-W.Schuette has received honoraria as a speaker from Lilly, Sanofi-Aventis and Merck KGaA and as a consultant from Lilly, M.I. Leschinger is employed by Lilly and has a stock ownership at Lilly. C. Manegold has received honoraria as a speaker and consultant from Merck KGaA, Lilly, Hoffmann-La Roche, Novartis, Amgen, Boehringer Ingelheim, AstraZeneca, Abbott, Pfizer, Sanofi-Aventis. M. Reck has received honoraria as a speaker from Lilly, Hoffmann-La Roche and Merck KGaA and as a consultant from Lilly and Hoffmann-La Roche.

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