A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer


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Background: This randomized phase III study compared the overall survival (OS) of pemetrexed plus gemcitabine (PG) versus standard gemcitabine (G) in patients with advanced pancreatic cancer.

Patients and methods: Patients with unresectable locally advanced or metastatic pancreatic cancer and no prior systemic therapy (including 5-fluorouracil as a radiosensitizer) were randomized to receive either 1250 mg/m² gemcitabine on days 1 and 8 plus pemetrexed 500 mg/m² after gemcitabine on day 8 (PG arm) of each 21-day cycle, or gemcitabine 1000 mg/m² on days 1, 8 and 15 of each 28-day cycle (G arm).

Results: Five hundred and sixty-five patients with well-balanced baseline characteristics were randomly assigned (283 PG, 282 G). OS was not improved on the PG arm (6.2 months) compared with the G arm (6.3 months) (P = 0.8477). Progression-free survival (3.9 versus 3.3 months; P = 0.1109) and time to treatment failure (3 versus 2.2 months; P = 0.2680) results were similar. Tumor response rate (14.8% versus 7.1%; P = 0.004) was significantly better on the PG arm. Grade 3 or 4 neutropenia (45.1% versus 12.8%), thrombocytopenia (17.9% versus 6.2%), anemia (13.9% versus 2.9%), febrile neutropenia (9.9% versus 0.4%; all P <0.001) and fatigue (15% versus 6.6%; P = 0.002) were significantly more common on the PG arm. Four treatment-related deaths occurred on the PG arm and none in the G arm.

Conclusions: Pemetrexed plus gemcitabine therapy did not improve OS. Single-agent gemcitabine remains the standard of care for advanced pancreatic cancer.

Key words: gemcitabine, pancreatic cancer, pemetrexed, phase III, survival
study was conducted to determine whether this combination of pemetrexed and gemcitabine (PG) would improve overall survival (OS) compared with gemcitabine alone (G) in patients with unresectable, locally advanced or metastatic pancreatic cancer.

Patients and methods

Patient population

Patients at least 18 years of age with histologic or cytologic diagnosis of locally advanced (stage II and III) or metastatic (stage IV) unresectable pancreatic cancer were included in this study. Prior radiation therapy was allowed (except radiation to the whole pelvis) to <25% of bone marrow if completed 4 weeks before study entry; other therapy, including 5-FU as a radiosensitizer, was not allowed. Other inclusion criteria were: at least one bidimensionally measurable lesion with clearly defined margins by computed tomography (CT) or magnetic resonance imaging (MRI); an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; an estimated life expectancy of at least 12 weeks; and adequate bone marrow, renal and hepatic function. Patients with secondary malignancy, except in situ carcinoma of the cervix, adequately treated non-melanomateous skin cancers or other malignancy treated at least 5 years previously with no evidence of recurrence, were excluded. Patients with documented brain metastases, clinically significant pleural effusions and significant weight loss (≥10% body weight in the preceding 6 weeks) were also excluded from the study. Patients who were unable to interrupt non-steroidal anti-inflammatory drugs for a 5- to 8-day period around pemetrexed administration, or those unable to take folic acid or vitamin B12, were ineligible. Patients with serious concomitant systemic disorders that would compromise their ability to complete the study (such as unstable angina pectoris) were also excluded.

Institutional ethical review boards at each institution approved the protocol, and each patient signed an informed consent prior to enrollment. The study was conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki, or the applicable guidelines on good clinical practice.

Study design and sample size

The primary objective of the study was to compare OS between the PG and G treatment groups on an intention-to-treat (ITT) basis. Four hundred and sixty-seven deaths were required to detect a 30% improvement (with 80% power) in OS in the PG arm (assuming a constant hazard ratio of 0.769) compared with the G arm. A total of 520 qualified patients were planned for enrollment into study, allowing for a censoring rate of 12%.

Secondary objectives were comparison of time-to-event efficacy measures including progression-free survival (PFS), time to treatment failure (TTF), duration of response for responders, tumor response rate (RR), effects on health-related quality of life (QoL) and toxicities between the two arms.

Eligible patients were randomly assigned using a centralized, automated randomization procedure to either the PG or G arm. Patient randomization was stratified for stage (II or III versus IV), PS (0 or 1 versus 2), baseline plasma homocysteine level (≥12 versus <12 μmol/L) and institutional center. Patients were balanced with respect to study drug in each stratum for each prognostic factor using the algorithm defined by Pocock and Simon [18]. One interim analysis was to be performed by an independent safety monitoring committee with the sponsor kept blinded to the data.

Treatment plan

Patients on the PG arm received gemcitabine 1250 mg/m² intravenously over ~30 min (maximum of 60 min) on days 1 and 8 followed ~90 minutes later by pemetrexed 500 mg/m² intravenously over ~10 min on day 8 of each 21-day cycle. Patients on the PG arm were to take daily oral folic acid 350–1000 mg (or an equivalent dose in multivitamin preparations) beginning ~1–2 weeks before first dose of pemetrexed in cycle 1 and continuing until 3 weeks after discontinuation from study therapy for pemetrexed-related toxicities, and an intramuscular 1000 mg vitamin B12 injection ~1–2 weeks before the first dose of pemetrexed in cycle 1 and repeated every ~9 weeks until 3 weeks after discontinuation from study therapy [19]. Patients on the PG arm were also to take dexamethasone (4 mg orally twice daily the day before, the day of and the day after pemetrexed) to prevent rash.

Patients on the G arm received gemcitabine 1000 mg/m² intravenously over ~30 min on days 1, 8 and 15 of each 28-day cycle. No vitamin or dexamethasone supplementation was given on the G arm.

Because of the different cycle lengths, patients were to receive a maximum of eight cycles of therapy on the PG arm and six cycles of therapy on the G arm. Additional cycles were permitted only upon approval by the sponsor.

A maximum of two dose reductions were allowed based on nadir counts or clinically significant non-hematological toxicities and dose delays up to 42 days from day 1 of the current cycle were permitted for recovery from adverse events. Granulocyte colony-stimulating factor support was allowed to treat a neutropenic event. Dose escalations were not allowed.

Baseline and treatment assessments

Each patient was assessed by a radiologic imaging study (CT scan or MRI) of the abdomen and other areas affected by pancreatic cancer within 4 weeks before enrollment, at baseline and before every other cycle. Ultrasound and X-ray were not permitted as methods of tumor assessment. The same method of tumor assessment used at baseline was used consistently throughout study. Physical examinations were performed before enrollment and throughout the study to document medical history, tumor measurement of palpable or visual lesions, weight, and ECOG PS. Within 7 days before study enrollment, QoL measurements and laboratory tests were to be performed. CA 19-9 concentrations were not measured.

All ITT patients were included in the time-to-event analyses. The OS time was defined as the time from the date of randomization to the date of death from any cause. Patients alive on the date of the last follow-up visit were censored on that date. PFS was defined as the time from date of randomization to date of disease progression or death from any cause, whichever occurred first. For patients still alive at the time of analysis and who did not have disease progression, PFS was censored at the date of the last follow-up visit. TTF was defined as the time from the date of randomization to date of early discontinuation of treatment, date of disease progression or death from any cause. TTF was censored at date of the last follow-up visit for patients who did not discontinue treatment early, were still alive or did not have disease progression.

Tumor response was assessed by the investigator using the Southwest Oncology Group criteria [20]. Responses were confirmed at least 3 weeks (on the PG arm) or 4 weeks (on the G arm) after the first evidence of response. There was no central radiological review of response data. For patients who exhibited a best study response of complete response (CR) or partial response (PR), the duration of response was measured from date of the first objective status assessment of CR or PR, to date of disease progression or death from any cause. Duration of response was censored at date of last follow-up visit for responders who were still alive and did not have disease progression.

Randomized patients were evaluable for QoL analysis if they completed a baseline and at least one post-baseline QoL questionnaire. Patients completed the EORTC QLQ-C30 questionnaire [21] at least 7 days prior to study enrollment, at the end of each cycle and at all post-study follow-up visits unless the patient received subsequent chemotherapy, radiotherapy or surgery for pancreatic cancer. A baseline and at least one post-baseline measurement of weight and PS were required for analysis of both parameters.
Weight gain was denoted as at least two consecutive monthly observations of a ≥7% increase from baseline. Improvements in PS were denoted as one occurrence of a score better than baseline over at least 28 days (or 21 days, depending on the cycle length).

All patients who received at least one dose of pemetrexed or gemcitabine were evaluable for safety. Toxicity was graded at the beginning of each cycle according to National Cancer Institute Common Toxicity Criteria (NCI CTC), version 2.0. Full blood cell counts and blood chemistries (electrolytes, liver and renal functioning tests) were done each week of therapy in both arms, and additionally on day 15 in the combination arm.

Statistical analyses

All tests of hypotheses were conducted at the α = 0.05 level. Analyses were performed on the observed distributions of OS, PFS, TTF and duration of response. The log-rank test was used for comparisons between treatment arms for each of these endpoints. Additional supporting analyses included Kaplan–Meier estimation by treatment arm for time-to-event end points [22]. For OS, PFS, TTF and duration of response, probabilities at 6, 12, 18 and 24 months were compared between treatment arms. These rates were estimated using the Kaplan–Meier method and compared based on a normal approximation for the difference between rates.

The following pre-specified patient baseline characteristics were analyzed on time-to-event end points using Cox proportional hazards models [23]: ECOG PS (0–1 versus 2); disease stage (II–III versus IV); baseline homocysteine level (continuous variable); investigational center (large versus small); sex (female versus male); race (Caucasian versus non-Caucasian); presence of liver metastasis (yes versus no); and prior resective pancreatic surgery (yes versus no). Factors that showed univariate prognostic significance (P < 0.05) were fitted into a multivariate model to assess prognostic importance in the presence of other prognostic variables. Treatment was then added to the final model to assess its effect when adjusted for the presence of the other important variables.

Tumor response rates were compared between treatment arms using Fisher’s exact test. A logistic regression model was performed to assess the adjusted treatment effect of baseline covariates on tumor response. Each of the baseline covariates was assessed separately.

Each of the scales/items of the EORTC QLQ-C30 was analyzed using a mixed-effects analysis of variance model. This test allowed for missing data expected for QoL assessments [24]. The fixed factors in the model included study therapy, baseline score, cycle number and interaction term for study therapy and cycle number. The variance–covariance matrix used was determined using the maximum Akaike criteria [25]. To implement the variance structure, patients were included in the model as a random effect.

The incidence of adverse events, deaths during treatment or within 30 days of treatment discontinuation, and serious unexpected and reportable events were calculated. P values based on Fisher’s exact test were calculated for selected parameters.

Results

Patient characteristics

A total of 565 patients were randomized (283 PG, 282 G) between October 2001 and February 2003. Overall baseline patient characteristics and prognostic factors were well balanced between treatment arms (Table 1). Median age was 63 years (on both treatment arms) and 57% of patients were male. Most patients (90.6%) had stage IV disease and an ECOG PS of 0–1 (86.2%). Presence of liver metastasis was reported for 179 patients each on the PG and G arms. Previous pancreatic resection had been performed in 9.9% of patients on the PG arm and 13.5% of patients on the G arm.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PG (n = 283) [n (%)]</th>
<th>G (n = 282) [n (%)]</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>171 (60.4)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>112 (39.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median</td>
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</tr>
<tr>
<td></td>
<td>Range</td>
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</tr>
<tr>
<td>ECOG PS</td>
<td>0–1</td>
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</tr>
<tr>
<td></td>
<td>2</td>
<td>30 (11.0)</td>
</tr>
<tr>
<td>Stage</td>
<td>II–III</td>
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</tr>
<tr>
<td></td>
<td>IV</td>
<td>255 (90.1)</td>
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<tr>
<td>Liver metastases</td>
<td>179 (63.3)</td>
<td>179 (63.5)</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian</td>
<td>258 (91.2)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>25 (8.8)</td>
</tr>
<tr>
<td>Homocysteine level</td>
<td>≥12 μmol/l</td>
<td>123 (43.5)</td>
</tr>
<tr>
<td></td>
<td>&lt;12 μmol/l</td>
<td>159 (56.2)</td>
</tr>
</tbody>
</table>

*One patient on the PG arm did not have baseline homocysteine measurements performed.

No baseline characteristics were statistically significantly (P < 0.05) different between the two arms.

PG, pemetrexed plus gemcitabine arm; G, gemcitabine arm; ECOG PS, Eastern Cooperative Oncology Group performance status.

Treatment administered

A total of 546 (273 per treatment arm) patients received at least one dose of study drug(s). Ten patients on the PG arm and nine on the G arm did not receive any study drug(s) due to death from their disease (four PG, two G); inclusion criteria not met (three PG, four G); personal conflict/patient decision (two PG, two G); and adverse event (one PG, one G).

The median number of cycles administered was four (range zero to 22) on the PG arm and three (range zero to 23) on the G arm. Owing to different cycle lengths (3 weeks PG, 4 weeks G), the median duration of treatment was 12 weeks on both treatment arms. The weekly mean doses of gemcitabine and pemetrexed on the PG arm were 690.3 mg/m2 and 136.1 mg/m2, respectively. The weekly mean dose of gemcitabine on the G arm was 647.3 mg/m2, resulting in a similar dose intensity of gemcitabine on both arms (82.8% versus 86.3%). On the PG arm, 3.8% of gemcitabine doses and 7.7% of pemetrexed doses were reduced, most commonly due to neutropenia, and 1.8% of gemcitabine doses and 3.8% of pemetrexed doses were omitted, most commonly due to fatigue. On the G arm, 5.4% of doses.
were reduced and 5% were omitted, mainly due to neutropenia and thrombocytopenia.

At the time of the analyses, 473 (83.7%) patients had died, 92 patients (44 PG, 48 G) were alive, and three patients (two PG, one G) were still receiving therapy. Approximately 34% of patients on the PG arm and 43% on the G arm received second-line chemotherapy.

Efficacy

All 565 randomized patients were included in the ITT population. There was no survival advantage (Figure 1) of PG over G ($P = 0.8477$). The estimated hazard ratio of PG over G was 0.98 [95% confidence interval (CI) 0.82–1.18]. The median OS time was 6.2 months (95% CI 5.4–6.9) on the PG arm and 6.3 months (95% CI 5.4–6.9) on the G arm. The 6-month survival rate was 50.6% on the PG arm and 52.2% on the G arm, and 1-year survival was similar on both arms (21.4% on the PG arm, 20.1% on the G arm).

The analyses of PFS and TTF revealed no significant differences ($P > 0.1$). Median PFS was 3.9 months (95% CI 3.3–4.7) on the PG arm and 3.3 months (95% CI 2.5–3.6) on the G arm. The median TTF was 3 months (95% CI 2.7–3.6) on the PG arm and 2.2 months (95% CI 1.9–2.7) on the G arm.

The RR based on the ITT population was significantly higher in the PG arm (14.8% versus 7.1%; $P = 0.004$). Duration of response was not significantly different (5.8 versus 6.6 months; $P = 0.324$).

Multiple regression analysis

In the univariate and multivariate analyses, a better ECOG PS and absence of liver metastases were the only significant prognostic factors for OS, PFS and TTF. When treatment was added in this final model, there was still no significant difference between the two arms for any time-to-event end point.

QoL analysis

A total of 239 patients on the PG arm and 233 patients on the G arm were evaluable for the QoL analyses from randomization until cycle 6. The compliance rate was >70% for both arms during this time period for analysis. There were no significant cycle-by-treatment interactions ($P < 0.05$) for any scale or symptom parameter (i.e. there were no treatment changes over time). Four of the 15 scales/items showed treatment changes that were significantly ($P < 0.05$) different. Patients on the G arm had a better (lower) financial difficulties score, a better (higher) physical functioning score and a better (higher) cognitive functioning score than patients on the PG arm. Patients on the PG arm had a better (lower) pain score than patients on the G arm. No clear trend was detected with respect to QoL analyses.

PS improvements were confirmed for 11.4% of patients on the PG arm and 9.4% of patients on the G arm. On the PG arm, 10.2% of patients experienced weight gain compared with 5.7% of patients on the G arm. Overall, weight gain, stable weight and weight loss were similar between the two treatment arms.

Toxicity

No safety issues were raised during the interim analysis. All 546 treated patients (PG 273, G 273) were evaluable for safety analysis. A summary of grade 3 and 4 hematological and non-hematological toxicities is presented in Table 2. The total number of all NCI CTC grade 3/4 toxicities was significantly higher on the PG arm as compared with the G arm (75.8% versus 37%; $P < 0.001$). Statistically significantly more treatment-related grade 3 and 4 hematological toxicities were seen on the PG arm: neutropenia (45.1% versus 12.8%), thrombocytopenia (17.9% versus 6.2%), anemia (13.9% versus 2.9%) and febrile

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>NCI CTC grade 3/4</th>
<th>Fisher’s exact $P$ value $^a$</th>
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</thead>
<tbody>
<tr>
<td>PG ($n = 273$)</td>
<td>G ($n = 273$)</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td>173 (63.4)</td>
<td>74 (27.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>123 (45.1)</td>
<td>35 (12.8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>49 (17.9)</td>
<td>17 (6.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>38 (13.9)</td>
<td>8 (2.9)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>27 (9.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Non-hematological</td>
<td>113 (41.4)</td>
<td>48 (17.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>41 (15.0)</td>
<td>18 (6.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (3.3)</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (3.3)</td>
<td>8 (2.9)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>8 (2.9)</td>
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<td>Stomatitis</td>
<td>8 (2.9)</td>
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</tr>
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<td>Diarrhea</td>
<td>8 (2.9)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (2.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Edema</td>
<td>3 (1.1)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (0.7)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

$^a$Two-sided Fisher’s exact test.

NCI CTC, National Cancer Institute Common Toxicity Criteria (version 2.0); PG, pemetrexed plus gemcitabine arm; G, gemcitabine arm.
neutropenia (9.9% versus 0.4%) (all differences $P < 0.001$). Also, there were statistically significantly more incidences of treatment-related fatigue on the PG arm (15% versus 6.6%; $P = 0.002$). No other toxicities were statistically significant between the two treatment arms. On the PG arm, a total of 117 transfusions were reported for 95 (34.8%) patients, compared with a total of 52 transfusions reported for 46 (16.8%) patients on the G arm.

A total of 19 (7%) patients on the PG arm discontinued due to serious adverse events, 14 of which were considered possibly related to study therapy. Seven (2.6%) patients on the G arm discontinued due to serious adverse events, two of which were considered possibly related to study therapy.

There were four (1.4%) treatment-related deaths on the PG arm (two from neutropenic sepsis, and one each from septic shock and renal insufficiency), and no treatment-related deaths on the G arm. All four treatment-related deaths on the PG arm were attributable, at least in part, to febrile neutropenia.

**Discussion**

Over the last 20 years, only limited progress has been made to improve OS for patients with advanced pancreatic cancer [26]. Since the registration study for gemcitabine performed by Burris et al. in 1996, which showed statistically significant improvements in OS and clinical benefit response compared with 5-FU, gemcitabine has become the global standard of care for advanced pancreatic cancer [26–28]. Recent efforts to improve the prognosis of pancreatic cancer have generally included the addition of other drugs to standard gemcitabine therapy. While increases in RR and time to disease progression have been achieved in several studies using this approach, to date no combination has shown a protocol-defined survival advantage compared with gemcitabine monotherapy [5–11].

Despite pemetrexed’s proven antitumor activity in other difficult-to-treat tumors, such as mesothelioma and second-line NSCLC [29, 30], the addition of pemetrexed to gemcitabine in this study failed to improve OS compared with gemcitabine monotherapy in the ITT population. As in other studies, the combination of gemcitabine with other agents did improve RR, yet this improvement ultimately had no impact on OS.

The patient population in this study was typical for a randomized phase III study in pancreatic cancer, and patient characteristics were well balanced between the two arms. Gemcitabine was administered without the 7-week induction period recommended in the package insert. Recent surveys of clinical practice indicate that most patients do not actually receive the 7-week induction period due to early progression, disease-related complications or drug toxicity [31]. Indeed, the omission of the induction period appears to have had a negative impact on gemcitabine’s efficacy in this study, as the median survival time of 6.3 months and 1-year survival rate of 20.1% coincide with results from recently conducted phase III studies [5–11].

The investigator-assessed RR on the PG arm (14.8%) was significantly higher than that on the G arm (7.1%). Because investigators were not blinded to the treatment, the potential for bias cannot be dismissed. However, an independent review of response data was not deemed overly important as the primary end point was OS.

The relatively mild toxicity profile of gemcitabine displayed in other trials was again confirmed in this study [10]. Neutropenia was the most prevalent hematological toxicity reported on the G arm. Other hematological and non-hematological toxicities were generally mild, and rare in frequency. No treatment-related deaths occurred on the G arm.

Not surprisingly, the addition of another cytotoxic molecule (pemetrexed) increased the incidence and severity of chemotherapy-related side-effects. A significantly higher incidence of neutropenia, thrombocytopenia, anemia and febrile neutropenia occurred on the PG arm. All four treatment-related deaths on the PG arm were attributable, at least in part, to febrile neutropenia.

It should be noted that toxicity assessment on the G arm occurred once every week before gemcitabine administration, but not on day 22 of the 4-week schedule, when no treatment was given. In contrast, on the PG arm, blood analyses were carried out every week throughout study. Thus, safety assessment for the PG arm was potentially biased. Patients on the PG arm had blood analyses and toxicity assessments carried out in week 4, when laboratory and non-laboratory side-effects would most likely occur. However, given gemcitabine’s well-known and relatively mild toxicity profile, there appeared to be no justification for patients on the G arm to go to the physician’s office during their week of rest.

In general, non-hematological toxicities were more prevalent on the PG arm, although fatigue was the only non-hematological toxicity that occurred at a significantly higher rate on the PG arm.

Interestingly, the increased incidence of hematological and non-hematological toxicities did not translate into a difference with regard to QoL. There were four subgroups of QoL analysis that were statistically different between the two treatment arms; however, no clear trend in either treatment was identified. No clear detrimental effect of QoL on the PG arm when compared with the G arm could be detected despite the higher toxicity on the combination arm. Overall, QoL was well maintained on both arms. There were also no significant differences in PS and weight, indicating that combination therapy could be safely administered in this patient population.

As has been seen in other recent trials in pancreatic cancer, more patients are being treated with second-line chemotherapy [10]. To date, a clear survival benefit of second-line therapy compared with best supportive care has not been established. With a small percentage of patients having received second-line therapy in this study, it is unlikely that this had an impact on the OS results.

In summary, the combination of pemetrexed and gemcitabine did not improve OS in patients with unresectable locally advanced or metastatic pancreatic cancer. The combination exhibited an increase in toxicity compared with gemcitabine monotherapy. Based on this study, single-agent gemcitabine remains the standard of care for patients with locally advanced or
metastatic pancreatic cancer, and should continue to be used as the comparator in all randomized trials in this patient population.

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