Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group

Malcolm J. Moore, David Goldstein, John Hamm, Arie Figer, Joel R. Hecht, Steven Gallinger, Heather J. Au, Pawel Murawa, David Walde, Robert A. Wolff, Daniel Campos, Robert Lim, Keyue Ding, Gary Clark, Theodora Voskoglou-Nomikos, Mieke Ptasynski, and Wendy Parulekar

A B S T R A C T

Purpose
Patients with advanced pancreatic cancer have a poor prognosis and there have been no improvements in survival since the introduction of gemcitabine in 1996. Pancreatic tumors often overexpress human epidermal growth factor receptor type 1 (HER1/EGFR) and this is associated with a worse prognosis. We studied the effects of adding the HER1/EGFR-targeted agent erlotinib to gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer.

Patients and Methods
Patients were randomly assigned 1:1 to receive standard gemcitabine plus erlotinib (100 or 150 mg/d orally) or gemcitabine plus placebo in a double-blind, international phase III trial. The primary end point was overall survival.

Results
A total of 569 patients were randomly assigned. Overall survival based on an intent-to-treat analysis was significantly prolonged on the erlotinib/gemcitabine arm with a hazard ratio (HR) of 0.82 (95% CI, 0.69 to 0.99; \( P = 0.038 \), adjusted for stratification factors; median 6.24 months vs 5.91 months). One-year survival was also greater with erlotinib plus gemcitabine (23% vs 17%; \( P = 0.023 \)). Progression-free survival was significantly longer with erlotinib plus gemcitabine with an estimated HR of 0.77 (95% CI, 0.64 to 0.92; \( P = 0.004 \)). Objective response rates were not significantly different between the arms, although more patients on erlotinib had disease stabilization. There was a higher incidence of some adverse events with erlotinib plus gemcitabine, but most were grade 1 or 2.

Conclusion
To our knowledge, this randomized phase III trial is the first to demonstrate statistically significantly improved survival in advanced pancreatic cancer by adding any agent to gemcitabine. The recommended dose of erlotinib with gemcitabine for this indication is 100 mg/d.


INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death with approximately 35,000 new cases and the same number of deaths estimated in North America in 2005.\(^1\) Gemcitabine became the standard treatment for advanced disease 10 years ago after showing superiority over fluorouracil.\(^2\) Since then, eight phase III trials of newer cytotoxic\(^3-8\) or biologic agents\(^9-11\) combined with gemcitabine have not shown any survival improvement compared with gemcitabine alone.

Human epidermal growth factor receptor type 1 (HER1/EGFR) is overexpressed in many pancreatic tumors\(^12,13\) and is associated with poor prognosis and disease progression.\(^14,15\) Blocking HER1/EGFR tyrosine kinase signaling decreases the growth and metastasis of human pancreatic tumor xenografts\(^16\) and improves the anticancer effects of gemcitabine.\(^17\) Erlotinib is an oral HER1/EGFR tyrosine kinase inhibitor currently approved for patients with non–small-cell lung cancer.\(^18\) The present trial was conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) in cooperation with Australasian Gastrointestinal Tumor...
Erlotinib and Gemcitabine in Pancreatic Cancer

Group (AGITG) and investigators in 15 other countries to investigate the effect of erlotinib in combination with gemcitabine on survival in patients with advanced pancreatic cancer. The trial was cosponsored by OSI Pharmaceuticals (Melville, NY).

**PATIENTS AND METHODS**

**Study Design and Treatment**

NCIC CTG PA.3 was a double-blind, placebo-controlled, international, phase III trial of erlotinib (Tarceva; OSI Pharmaceuticals) plus gemcitabine in patients with locally advanced or metastatic pancreatic adenocarcinoma. Patients were stratified by center, performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1 v 2), and stage (locally advanced v metastatic) and randomly assigned in a 1:1 ratio to receive gemcitabine plus either erlotinib or a matched placebo. Gemcitabine 1,000 mg/m² was given by 30-minute intravenous infusion on days 1, 8, 15, 22, 29, 36, and 43 followed by a 1-week rest in cycle one (8 weeks), and on days 1, 8, and 15 in all subsequent 4-week cycles. Erlotinib plus placebo was taken orally at 100 or 150 mg/d until disease progression or unmanageable toxicity. During an initial safety evaluation phase, the tolerability of erlotinib 100 mg/d with gemcitabine was established in selected centers in Canada before general enrollment using this dose. The erlotinib dose was increased to 150 mg/d in a subsequent Canadian cohort to assess the tolerability of this higher dose. Doses of erlotinib or gemcitabine could be reduced or delayed (no more than 20 days) to allow recovery from toxicity.

The primary end point was overall survival. Secondary end points included progression-free survival, response rate, response duration, toxicity, quality of life, and correlation of baseline tumor HER1/EGFR level with outcome. The ethics boards of all institutions approved the protocol and all patients provided written, informed consent. Data were collected, managed, and analyzed at the NCIC CTG central office, and the database was locked from additional changes on September 17, 2004. Follow-up information was updated in June 2005.

**Eligibility Criteria**

Patients had histologic or cytologic evidence of locally advanced or metastatic adenocarcinoma of the pancreas with measurable or assessable disease; ECOG performance status 0, 1, or 2; and adequate hematologic, renal, and hepatic function. Prior radiotherapy for local disease was allowed provided that patients had ECOG performance status 0, 1, or 2; and adequate hematologic, renal, and hepatic function. Prior radiotherapy for local disease was allowed provided disease progression had been documented, and treatment completed at least 4 weeks before random assignment. Prior chemotherapy was not permitted, except for fluorouracil or gemcitabine given concurrently as a radiosensitizer.

**Assessments**

Responses and progression were evaluated using Response Evaluation Criteria in Solid Tumors every 8 weeks. Toxicity was assessed at every visit using the National Cancer Institute Common Toxicity Criteria version 2.0. Quality of life was measured using the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire C30 questionnaire (sites in Canada and United States) every 4 weeks until documentation of progressive disease. HER1/EGFR analysis was conducted on archival tissue by immunohistochemistry using DAKO EGFR Pharm Dx kits (DAKO, Carpinteria, CA). A positive test was defined as ≥ 10% of tumor cells demonstrating membranous staining.

**Statistical Analysis**

Survival analyses were performed on all randomly assigned patients as per the intent-to-treat principle. The trial was powered to detect a hazard ratio (HR) of 0.75 between patients randomly assigned to gemcitabine plus erlotinib or gemcitabine plus placebo. In order to detect the postulated difference with 80% power using a two-sided 5% level test, a minimum of 381 events (deaths) were required for the final analysis. The trial had an initial planned sample size of 800, which would allow an analysis shortly after study closure to accrual. A reduction in sample size to 450 occurred just after the study opened for resource related reasons. This change did not alter the power but necessitated a longer follow-up (estimated to be 18 months after study closure) to achieve the predetermined event rate of 381. Time-to-event variables were estimated using the Kaplan-Meier method, and 95% CIs for median duration by the Brookmeyer and Crowley method. Treatment arms were compared using log-rank tests stratified by performance status, extent of disease, and pain score at baseline. The adjusted HR with 95% CI was used as the primary estimate of the difference between the arms. The effects of potential prognostic factors were assessed using Cox regression. Schoenfeld residual plots were used to check the model assumption for the Cox regression.

A Cochran-Mantel-Haenszel test was used to compare response rates, adjusting for stratification factors at baseline. Fisher’s exact tests were used to compare the toxicities between treatment groups, if appropriate. Patients’ quality of life response distributions were categorized based on change scores from their own baseline, and were analyzed between treatment groups using χ² tests followed by Mantel-Haenszel χ² tests for trend. A change in score of 10 points was defined as clinically relevant.

The association between epidermal growth factor receptor (EGFR) status and treatment outcome was evaluated using a univariate, unadjusted analysis. A Cox regression model with a time-dependent covariate was used to correlate skin rash to time-to-event outcomes, while a logistic regression model was used to correlate tumor response to skin rash and other baseline factors.

**RESULTS**

**Patient Characteristics**

Between October 2001 and January 2003, 569 patients were randomly assigned (285 erlotinib and gemcitabine and 284 placebo and gemcitabine) at 176 centers in 17 countries. Baseline characteristics were well-balanced between the arms (Table 1), except for more females in the erlotinib and gemcitabine arm (52.3% v 43.0%; P = .03). Three patients on the erlotinib and gemcitabine arm and four on the placebo and gemcitabine arm received no treatment. Nineteen patients (10 erlotinib and gemcitabine and nine placebo and gemcitabine) were ineligible because of elevated liver function tests (n = 7), other primary malignancy (n = 5), or other miscellaneous reasons (n = 7). Determination of ineligibility was done before unblinding. All 569 randomly assigned patients were included in an intent-to-treat analyses.

An interim safety analysis of the first 50 patients treated with gemcitabine plus erlotinib 100 mg/d showed no major increase in toxicity. As planned, accrual at 150 mg/d was then opened at selected Canadian centers. The accrual worldwide (at 100 mg) occurred more rapidly than had been anticipated and by the time an evaluation of the safety of the 150-mg cohort was completed, 80% of the planned sample size of 450 had been accrued. Because too few patients would be accrued to the 150-mg cohort to draw definitive conclusions, a decision was made toward the end of the study, before unblinding, to accrue a sufficient number of patients to have 80% power to detect the prespecified HR within the 100-mg cohort.

A data field cutoff date was established when the 381st death was documented in the NCIC CTG database. When all case report forms had been submitted centrally, an additional 63 deaths within the 100-mg cohort were documented before the data field cutoff date, bringing the total to 444 deaths. The results presented are for both dose cohorts combined, except when indicated.

**Survival and Response**

The final analysis was conducted after 486 deaths (239 on erlotinib and gemcitabine and 247 on placebo and gemcitabine). Overall survival was significantly longer in the erlotinib and gemcitabine arm.
with an estimated HR of 0.82 (95% CI, 0.69 to 0.99; \( P = 0.038 \); log-rank test stratified for performance status, extent of disease, and pain score at baseline; Fig 1A). Median survival times were 6.24 months versus 5.91 months for the erlotinib and gemcitabine versus placebo and gemcitabine groups with 1-year survival rates of 23% (95% CI, 18% to 28%) and 17% (95% CI, 12% to 21%), respectively (\( P = 0.023 \)). A multivariate Cox regression analysis showed that erlotinib treatment (HR, 0.82; 95% CI, 0.69 to 0.99; \( P = 0.04 \)) and female sex (\( P = 0.03 \)) were significantly associated with longer overall survival. While there was an imbalance in male:female ratio between the arms, the treatment effect remains significant when adjusted for sex.

Results of subgroup analyses of survival by baseline stratification factors and other factors such as sex, race, pain intensity score, and age are displayed in Figure 2.

Progression-free survival was significantly longer in the erlotinib and gemcitabine arm than the placebo and gemcitabine arm with an estimated HR of 0.77 (95% CI, 0.64 to 0.92; \( P = 0.004 \); log-rank test stratified for performance status, extent of disease, and pain score at baseline; median, 3.75 months vs 3.55 months; Fig 1B).

Five hundred thirty patients had at least one measurable lesion and were assessable for response. The complete plus partial response rate was 8.6% with erlotinib and gemcitabine and 8.0% with placebo and gemcitabine, and the median duration of response was 163 days in both arms. The incidence of stable disease was 48.9% with erlotinib and gemcitabine and 41.2% with placebo and gemcitabine. The overall disease control rate (complete response plus partial response plus stable disease) was 57.5% on erlotinib and gemcitabine and 49.2% on placebo and gemcitabine (\( P = 0.07 \)).

**Toxicity and Dosage Modifications**

Two hundred eighty-two patients on the erlotinib and gemcitabine arm and 280 on the placebo and gemcitabine arm received at least one dose of study medication and were available for assessment of toxicity. Adverse events are summarized in Table 2. Treatment was generally well-tolerated in both arms. Patients receiving erlotinib and gemcitabine experienced higher frequencies of rash, diarrhea, infection, and stomatitis, but these were generally grade 1 or 2. The incidence of other adverse events was similar in both arms.

There were six protocol-related deaths, all in the erlotinib and gemcitabine arm. Two were attributed to treatment complications (interstitial pneumonitis and sepsis) and four were attributed to a combination of cancer and protocol treatment complications (interstitial pneumonitis, sepsis, cerebrovascular accident, and neutropenic sepsis).

A total of eight patients had an interstitial lung disease (ILD)-like syndrome possibly related to therapy, seven receiving erlotinib and gemcitabine and one receiving placebo and gemcitabine.

Hematologic toxicity was balanced between the arms with grade 3/4 neutropenia and thrombocytopenia seen in 24% and 10% of erlotinib and gemcitabine and 27% and 11% of placebo and gemcitabine patients, respectively. Grade 3 or greater elevations of Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Erlotinib and Gemcitabine (n = 285)</th>
<th>Placebo and Gemcitabine (n = 284)</th>
<th>Total (n = 569)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 136 (47.7)</td>
<td>Male 162 (57.0)</td>
<td>Male 298 (52.4)</td>
</tr>
<tr>
<td>Age, years</td>
<td>Median 63.7 (range 37.9-84.4)</td>
<td>Median 64.0 (range 36.1-92.4)</td>
<td>Median 63.9 (range 36.1-92.4)</td>
</tr>
<tr>
<td>ECOG status</td>
<td>0 85 (29.8)</td>
<td>0 85 (29.9)</td>
<td>0 170 (29.9)</td>
</tr>
<tr>
<td></td>
<td>1 145 (50.9)</td>
<td>1 147 (51.8)</td>
<td>1 292 (51.3)</td>
</tr>
<tr>
<td></td>
<td>2 54 (18.9)</td>
<td>2 52 (18.3)</td>
<td>2 106 (18.6)</td>
</tr>
<tr>
<td>Pain intensity (scale 0-100)*</td>
<td>Median 21.3 (range 0-100)</td>
<td>Median 23.4 (range 0-100)</td>
<td>Median 22.2 (range 0-100)</td>
</tr>
<tr>
<td></td>
<td>( \leq 20 ) 131 (46.0)</td>
<td>( \leq 20 ) 127 (44.7)</td>
<td>( \leq 20 )</td>
</tr>
<tr>
<td></td>
<td>( &gt; 20 ) 145 (50.9)</td>
<td>( &gt; 20 ) 151 (53.2)</td>
<td>( &gt; 20 ) 296 (52.0)</td>
</tr>
<tr>
<td>Extent of disease</td>
<td>Locally advanced 67 (23.5)</td>
<td>Locally advanced 71 (25.0)</td>
<td>Locally advanced 138 (24.3)</td>
</tr>
<tr>
<td></td>
<td>Distant metastases 218 (76.5)</td>
<td>Distant metastases 213 (75.0)</td>
<td>Distant metastases 431 (75.7)</td>
</tr>
<tr>
<td></td>
<td>At least one target lesion 268 (94.0)</td>
<td>At least one target lesion 262 (92.3)</td>
<td>At least one target lesion 530 (93.1)</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>Radiotherapy† 22 (7.7)</td>
<td>Radiotherapy† 25 (8.8)</td>
<td>Radiotherapy† 47 (8.3)</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy† 20 (7.0)</td>
<td>Chemotherapy† 25 (8.8)</td>
<td>Chemotherapy† 45 (7.9)</td>
</tr>
<tr>
<td></td>
<td>Prior surgical resection of primary tumor 19 (6.7)</td>
<td>Prior surgical resection of primary tumor 29 (10.2)</td>
<td>Prior surgical resection of primary tumor 48 (8.4)</td>
</tr>
</tbody>
</table>

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

*Pain intensity data were available for 554 patients (276 erlotinib and gemcitabine, 278 placebo and gemcitabine).
†Used as a radiosensitizer only.
and (C) overall survival in the 100-mg cohort. HR, hazard ratio.

AST were seen in 11% and 8% of patients receiving erlotinib and placebo, respectively.

In total, 44 (16%) of 282 patients receiving erlotinib and gemcitabine and 13 (5%) of 280 receiving placebo and gemcitabine had at least one dose reduction of their oral agent. A higher incidence of patients had a dose reduction in the 150-mg/d cohort on the erlotinib and gemcitabine arm than on the placebo and gemcitabine arm (48% vs 8%) compared with the 100-mg/d cohort (13% vs 4%). The dose intensity of gemcitabine was similar in both arms.

Quality of Life

Quality of life analysis was conducted in 376 assessable patients. Questionnaire compliance was similar by treatment group and higher than 64% for each cycle before disease progression. There was no significant difference between the arms in global quality of life or in the individual domains with the exception of worse diarrhea change scores in the erlotinib plus gemcitabine arm (P < .001).

EGFR Analysis

Tumor samples for EGFR analysis were collected from 184 patients of whom 162 had sufficient tumor in the specimen to allow for immunohistochemical analysis. Eighty-six (53%) were classified as EGFR positive and 76 (47%) were EGFR negative. EGFR status was not associated with response or disease stability. In both groups, the HR favored the erlotinib and gemcitabine arm (EGFR positive, n = 86; HR, 0.80; 95% CI, 0.50 to 1.26; for EGFR negative, n = 76; HR, 0.83; 95% CI, 0.51 to 1.34). The overall HR for erlotinib and gemcitabine patients in the 162 patients who had an EGFR analysis done was 0.82 (95% CI, 0.59 to 1.14) and for the 407 who had an unknown EGFR status it was 0.85 (95% CI, 0.69 to 1.05).

Skin Rash and Erlotinib

Of the 282 patients who received erlotinib, 79 had no rash, 102 had grade 1 rash, and 101 had a grade 2 or higher skin rash. Patients younger than 65 (P = .01) and those with a good performance status (P = .03) had a higher likelihood of developing rash. The presence of a rash was associated with a higher likelihood of achieving disease control (P = .05) after controlling other prognostic factors. Cox regression analysis showed that patients survived significantly longer after they developed skin rash (P = .037; HR, 0.74; 95% CI, 0.56 to 0.98). The median survival rates for patients with grade 0, 1, and 2 rash were 5.3, 5.8, and 10.5 months, respectively; and the 1-year survival rates were 16%, 9%, and 43% (P < .001; Fig 3).

**DISCUSSION**

We found that overall survival in patients with advanced pancreatic cancer was significantly improved with erlotinib and gemcitabine compared with placebo plus gemcitabine; the HR of 0.82 represents a 18% reduction in the risk of death, or alternately, an overall 22% improvement in survival. HR is the most appropriate measure of overall and progression-free survival in rapidly progressive diseases such as pancreatic cancer because it encompasses the whole observation period and not just a single point estimate, such as the median. The improvement in median overall survival with erlotinib and gemcitabine is modest (6.24 v 5.91 months) while the 1-year survival rate with erlotinib and gemcitabine is 23% versus 17% with placebo and gemcitabine. The improvement in progression-free survival with a HR of 0.77 supports the beneficial effects of erlotinib. This benefit was achieved without a difference in response rate between the arms. The disease control rate, complete response, partial response, and stable disease combined, was significantly higher with erlotinib plus gemcitabine than placebo plus gemcitabine in the 100-mg cohort (59% v 49.4%; P = .036), but not in the overall study population (57.5% v 49.2%; P = .058).
Most adverse events associated with erlotinib plus gemcitabine treatment in this study were mild-to-moderate, and consistent with previous experience with both agents.2,22,23 Rash was more frequent with erlotinib plus gemcitabine than placebo plus gemcitabine and we did observe an association between rash and a better outcome that has also been seen in other studies of EGFR inhibitors.24-26 This is not explained by patients who stay on treatment longer being at greater risk for rash; analysis was adjusted for this potential bias and the rash related to EGFR tyrosine kinase inhibitors tends to occur early. Potential reasons for this observation could include variability in drug absorption or metabolism; the ability to generate a rash predicting for a more immunocompetent individual; or a pharmacogenetic basis that is seen in both germline and tumor cells. There were more deaths and ILD-like syndromes seen in the gemcitabine plus erlotinib arm. Gemcitabine and EGFR tyrosine kinase inhibitors are both known to cause an ILD-like syndrome in approximately 0.5% to 1.0% of patients, and there is the possibility that there could be a more than additive effect when these agents are combined.27 The incidence seen in this study (2.4%) is higher than in other trials where gemcitabine and erlotinib have been combined. The incidence of ILD in the Tarceva Lung Cancer Evaluation (TALENT) trial which compared gemcitabine and

<table>
<thead>
<tr>
<th>Variable</th>
<th>Erlotinib and Gemcitabine (n = 282)</th>
<th>Placebo and Gemcitabine (n = 280)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>All (n = 100)</td>
<td>Grade 3/4 (n = 62)</td>
</tr>
<tr>
<td>100 mg/d erlotinib and placebo</td>
<td>100 (n = 62)</td>
<td>99 (n = 57)</td>
</tr>
<tr>
<td>Specific toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>56 (n = 9)</td>
<td>41 (n = 2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>89 (n = 4)</td>
<td>86 (n = 3)</td>
</tr>
<tr>
<td>ILD-like syndrome*</td>
<td>2.1 (n = 1)</td>
<td>4 (n = 1)</td>
</tr>
<tr>
<td>Infection (any)</td>
<td>43 (n = 7)</td>
<td>34 (n = 6)</td>
</tr>
<tr>
<td>Rash</td>
<td>72 (n = 12)</td>
<td>29 (n = 5)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>23 (n = 4)</td>
<td>14 (n = 2)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib and placebo</td>
<td>16 (n = 562)</td>
<td>5 (n = 562)</td>
</tr>
<tr>
<td>100 mg (n = 515)</td>
<td>13 (n = 515)</td>
<td>8 (n = 515)</td>
</tr>
<tr>
<td>150 mg (n = 47)</td>
<td>48 (n = 47)</td>
<td>4 (n = 47)</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>47 (n = 58)</td>
<td>58 (n = 58)</td>
</tr>
<tr>
<td>Symptomatic progression</td>
<td>15 (n = 14)</td>
<td>14 (n = 14)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>10 (n = 6)</td>
<td>6 (n = 6)</td>
</tr>
<tr>
<td>Death</td>
<td>9 (n = 8)</td>
<td>8 (n = 8)</td>
</tr>
<tr>
<td>Intercurrent illness</td>
<td>4 (n = 4)</td>
<td>4 (n = 4)</td>
</tr>
<tr>
<td>Refused treatment</td>
<td>8 (n = 6)</td>
<td>6 (n = 6)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (n = 3)</td>
<td>3 (n = 3)</td>
</tr>
<tr>
<td>Still on therapy</td>
<td>4 (n = 1)</td>
<td>1 (n = 1)</td>
</tr>
</tbody>
</table>

Abbreviation: ILD, interstitial lung disease.
*Pneumonitis, pulmonary infiltrate.
cisplatin with or without erlotinib in 1,059 patients with advanced lung cancer was less than 1% and no difference was seen between the treatment arms.28

There is interest in the use of EGFR status of tumors as a predictive factor. In this study using an immunohistochemical analysis on a subset of patients, an obvious impact of EGFR expression on outcome was not seen. The overall rate of EGFR expression observed was 57%, which is lower than has been reported in previous studies.29,30 More recent analyses in lung cancer have suggested that the presence of EGFR mutations or EGFR amplification measured by fluorescence in situ hybridization may be more useful.31,32 However, studies of more than 200 pancreatic tumors did not identify any EGFR mutations. These analyses are also more complex in a combination study where the outcome will be a function of both the chemotherapy and EGFR inhibitor.

The dose of erlotinib as a single agent and in combination studies in non–small-cell lung cancer is 150 mg per day. In this study, we found the dose of 100 mg to be well-tolerated and efficacious in combination with gemcitabine (Fig 1C). There were 23 patients treated at a starting dose of 150 mg of erlotinib of whom 11 required protocol-prescribed dose reductions for toxicity, suggesting that this may be too high a starting dose. The pharmacokinetics of erlotinib has shown significant variability in previous studies with clearance rates and area under the curve varying up to seven-fold.33,34 It is possible that escalation of the dose of erlotinib beyond 100 mg in patients not experiencing toxicity may be useful.

The failure of combination chemotherapy to improve outcomes in pancreatic cancer means we need to look at alternate systemic approaches to this disease. Combinations of gemcitabine with the anti-EGFR monoclonal antibody, cetuximab, and with the anti-vascular endothelial growth factor antibody, bevacizumab, do show promise in phase II studies.29,35 Both approaches are currently in phase III testing versus single-agent gemcitabine in the North American cooperative groups. The recent announcement that the gemcitabine plus bevacizumab trial did not meet its primary end point of improved survival is a reminder of the difficulties of improving outcomes in pancreatic cancer. Other phase II studies are exploring other targeted agents in combination with gemcitabine, or multiple targeted agents in combination with chemotherapy. The recent demonstration of benefit from chemotherapy in the adjuvant setting suggests that studies of erlotinib after surgery for localized disease may also be warranted.36,37

This trial provides proof of principle of targeting HER1/EGFR in pancreatic cancer and shows erlotinib can improve survival when used concurrently with chemotherapy; it also offers a basis for further investigation of targeted agents in this setting. NCIC CTG PA.3 is the first evidence of a survival benefit with an EGFR tyrosine kinase inhibitor in combination with chemotherapcy in any form of cancer. It is also the first phase III trial to demonstrate a significant improvement in survival beyond that seen with gemcitabine alone in pancreatic cancer and is a new treatment option for these patients.

**REFERENCES**

35. Kindler HL, Friberg G, Singh DA et al: A multicenter, double-blind, placebo-controlled randomized phase II trial of gemcitabine/cisplatin (GC) plus bevacizumab (B) or placebo in patients (pts) with malignant mesothelioma (MM). J Clin Oncol 23:8033-8040, 2005

Acknowledgment

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).