A phase I study of erlotinib in combination with gemcitabine and radiation in locally advanced, non-operable pancreatic adenocarcinoma

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Purpose: To determine the maximum tolerated dose (MTD) of erlotinib when administered concurrently with twice weekly gemcitabine and radiation therapy (RT) for locally advanced pancreatic cancer, assess the safety and toxicity profile of this combination and secondarily evaluate response, time to tumor progression and overall survival.

Methods: Patients with untreated locally advanced pancreatic cancer were treated with daily erlotinib in combination with gemcitabine 40 mg/m²/30 min twice weekly and RT delivered at 180 cGy/day in 28 fractions over 5.5 weeks for a total of 5040 cGy. Erlotinib was dose escalated in successive cohorts (100 mg, 125 mg). When the MTD was determined, the cohort was expanded to better define toxicity and preliminarily efficacy. All patients were surgically staged. After chemoradiation, patients received maintenance weekly gemcitabine 1000 mg/m² on days 1 and 8 of a 21 day cycle and daily erlotinib for four cycles.

Results: Three patients were treated at dose level 1 (erlotinib 100 mg) without limiting toxicity. Two of six patients at dose level 2 (erlotinib 125 mg) had dose-limiting toxicities, neutropenia and thrombocytopenia, causing dose delay and elevated liver enzymes. The MTD for erlotinib in combination with twice weekly gemcitabine-based chemoradiation was 100 mg/day. Eleven additional patients were treated at dose level 1. All twenty patients were assessable for toxicity. Seventeen patients were assessable for response. The partial response rate was 35% and 53% had stable disease. The median survival for all patients was 18.7 months.

Conclusion: In combination with fixed dose gemcitabine at 40 mg/m² twice weekly and radiation at 180 cGy/day, the MTD of erlotinib was found to be 100 mg/day. This is a relatively well tolerated, biologically active combination in a poor prognostic cancer.

Key words: chemoradiation, erlotinib, gemcitabine, pancreas cancer, phase I

introduction

Adenocarcinoma of the pancreas is the fourth leading cause of cancer-related mortality in the USA. This disease has an extremely poor prognosis, with an overall 5 year survival of <5% [1]. For patients who present with locally advanced, unresectable disease (~40% [2]), combined chemoradiotherapy is an accepted standard approach, although increasingly the timing of radiotherapy remains controversial. Earlier studies have focused on the role of 5-flourouracil (5-FU) as a radiation sensitizer [3] as proposed by Heidelberger et al. [4] in 1958. In recent times, gemcitabine has supplanted 5-FU as the major systemic drug in the management of pancreas cancer based on the results of a prospective randomized clinical trial [5], and efforts have focused on incorporating it into a chemoradiation schedule [6–9].

Epidermal growth factor receptor (EGFR) and its ligands, Epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-alpha), are important in cell proliferation, as well as motility, adhesion, invasion, survival and angiogenesis [10]. Pancreatic cancers contain high levels of EGFR overexpression [11, 12]. Erlotinib, also known as OSI-774 (Tarceva™) is an orally bioavailable EGFR tyrosine inhibitor. Additive effects have been observed with gemcitabine and erlotinib in animal models [13]. A recent randomized phase III trial of 569 patients with untreated inoperable pancreatic cancer demonstrated a small but significant survival benefit for the combination of gemcitabine and erlotinib versus...
gemcitabine alone [14]. This was the first trial to show a survival benefit for any combination therapy in pancreas cancer and led to Food and Drug Administration (FDA) approval of this combination in the front-line therapy of pancreas cancer in 2005.

The aim of this phase I study was to determine the maximum tolerated dose (MTD) of erlotinib when administered concurrently with twice weekly gemcitabine and radiation therapy (RT) for locally advanced pancreatic cancer, assess the safety and toxicity profile of this combination and secondarily evaluate response, time to tumor progression and overall survival (OS).

**patients and methods**

**eligibility criteria**

Patients with histologically confirmed, newly diagnosed, locally advanced nonmetastatic adenocarcinoma of the pancreas were eligible for entry onto this study. Metastases were required to be excluded by diagnostic laparoscopy or exploratory laparotomy in all patients. Additional inclusion criteria were as follows: No prior chemotherapy or radiation for pancreas cancer; Age >18 years; ECOG performance status (PS) zero to two; Life expectancy of >12 weeks; Adequate organ and marrow function; Patients of child-bearing potential were required to use adequate contraception (hormonal or barrier method of birth control) before study entry and for the duration of study participation; Ability to understand and willingness to sign a written informed consent document; Measurable or assessable disease was required. Patients were excluded if they had received prior chemotherapy or radiotherapy for pancreas cancer, had an active intercurrent illness or gastrointestinal disease or pathology that limited chemotherapy or radiotherapy for pancreas cancer, had an active intercurrent illness or gastrointestinal disease or pathology that limited chemotherapy or radiotherapy for pancreas cancer, or had an active intercurrent illness or gastrointestinal disease or pathology that limited chemotherapy or radiotherapy for pancreas cancer. Patients were excluded if they had received prior chemotherapy or radiation for pancreas cancer, had an active intercurrent illness or gastrointestinal disease or pathology that limited chemotherapy or radiotherapy for pancreas cancer, or had an active intercurrent illness or gastrointestinal disease or pathology that limited chemotherapy or radiotherapy for pancreas cancer.

**screening evaluations/pretreatment assessment**

All patients signed an informed consent document before study enrollment. Patients underwent a complete history and physical examination. A complete blood count, including differential and platelet count, chemistry panel, including, electrolytes, blood urea nitrogen, creatinine, glucose, bilirubin, aspartate aminotransferase (AST), alkaline phosphatase, albumin, total protein, calcium, phosphorus and lactate dehydrogenase, carcinoembryonic antigen, Ca19-9, coagulation profile including International Normalised Ratio, were obtained. A baseline urinalysis was carried out. For females of child-bearing potential, a serum or urine pregnancy test was carried out. All the above tests were conducted within 7 days of enrollment. An electrocardiogram (EKG) within the previous 6 months of enrollment was necessary (unless any interval cardiac history, when a new electrocardiogram EKG was obtained within 4 weeks of initiation of therapy). A chest X-ray and either a computed tomography scan (CT) abdomen/pelvis or with oral/IV contrast (5 mm cuts through the pancreas) or a magnetic resonance imaging of the abdomen and pelvis with gadolinium, were required within 21 days of study enrollment. Tumor paraffin block was collected and assayed for confirmation of diagnosis and for correlative immunohistochemical studies, where available. Additional tissue, if available, was snap frozen for additional biologic correlates.

**agent administration**

All treatment was administered on an outpatient basis. There were two parts to this study: (i) Combination chemotherapy, radiation and erlotinib; (ii) Maintenance chemotherapy and erlotinib. Once the MTD was determined for erlotinib in combination with gemcitabine and radiation, an additional 11 patients were treated at the MTD to better define toxicity and response.

**combined chemoradiation.** Patients began treatment on day 1 with radiation and erlotinib. Gemcitabine was dosed at 40 mg/m²/30 min on a twice weekly either Monday/Thursday or Tuesday/Friday schedule beginning on day 1 or day 2 at the treating physician’s discretion.

**radiation technical details.** The intent of the treatment was to deliver 50.4 Gy to the tumor and the primary draining lymph nodes. Patients were placed supine, immobilized and underwent simulation with a CT simulator. In general the field borders were the following (whichever field was the largest):

AP/PA Fields: (i) superior: inlet of the diaphragm or 2 cm above the celiac axis or 2 cm above the gross tumor volume (GTV); (ii) inferior: L3/4 interspace or 2 cm below the GTV; (iii) lateral: the edge of the transverse processes to include the paraaortic nodes or 2 cm beyond the GTV;

Lateral Fields: (i) superior and inferior: same as AP/PA; (ii) anterior: included the paraaortic nodes and 2 cm beyond the GTV;

(iii) posterior: include at least half of the vertebral bodies while blocking the spinal cord.

CT based treatment planning was carried out and the dose was prescribed to the isodose line which covered the GTV with a 1 cm margin. Dose-limiting structures included spinal cord (45 Gy), kidney (at least 50% of the total volume received <18 Gy) and liver (at least 40% of the total volume received <30 Gy). Treatment was delivered with a 15 MV linear accelerator with multileaf collimators. Patients received 1.8 Gy/day, 5 days/week and had weekly port films for field verification.

Erlotinib was self-administered orally daily continuously throughout the radiation period. Erlotinib was dose-escalated in successive patient cohorts starting at 100 mg/day (see study design section and also Table 3).

**maintenance chemotherapy.** For patients who did not demonstrate any evidence of extra-pancreatic tumor progression maintenance therapy was administered with gemcitabine and erlotinib commencing ~4 weeks, but not later than 7 weeks, after completion of radiation. Patients received gemcitabine administered by i.v. infusion at a dose of 1000 mg/m² >30 minutes, on days 1 and 8 of each 21 day cycle for a total of four cycles. Starting on day 1, erlotinib was given orally at a fixed dose of 100 mg/day for four cycles. Radiologic restaging was carried out at week 6 and 12. For patients who tolerated maintenance therapy well and in whom no evidence of disease progression was evident at 12 weeks, the option to continue protocol therapy was allowed with the same protocol maintenance treatment criteria and assessment scan intervals observed.

**study design/end points**

This is a phase 1 clinical trial studying the effect of adding erlotinib to gemcitabine and radiation in patients with locally advanced resectable pancreatic adenocarcinoma. The principal objective of the study was to determine the MTD of erlotinib that can be added to a gemcitabine–radiation combination. The secondary objectives were to assess toxicity, response rate, time to tumor progression and OS in this patient population. The tertiary objective was to study a panel of markers before treatment in both normal and tumor tissues. The correlative study results (including kras and EGFR status, mutation analysis and gene copy number, with correlation to clinical outcome) will be reported in a later publication. For the primary tumor end points, descriptive statistics were employed to document the toxic effects and/or side-effects at each dose level. For tumor response measurements, response data for each patient were recorded.
Response rate was estimated using the binomial probability and exact 95% confidence intervals (CIs) were provided. Time to progression and OS curves were estimated using Kaplan–Meier methodology. Time to progression was determined as being the time elapsed from the date of study enrollment to documentation of clear-cut progression of disease. OS was dated from the time of study enrollment to the date of death.

Three dose levels were considered: 100 mg/day, 125 mg/day and 150 mg/day. Three patients were enrolled per each cohort at each dose level to a maximum erlotinib dose of 150 mg/day. If dose-limiting toxicity (DLT) was observed in one of three patients the cohort was expanded to six patients. Patients enrolled at a given dose level were observed for DLT until 2 weeks following completion of combination chemoradiotherapy before accrual began in the next cohort, hence the observation period per cohort was a minimum of 8 weeks. The MTD was defined as an erlotinib dose of 150 mg/day or one dose level below the cohort in which we observed DLT in 2 of 3 or 2 of 6 patients. Once the MTD was determined an expanded cohort of patients were treated at the MTD to better assess tolerability and preliminarily to assess efficacy of the regimen.

At the completion of combined modality therapy, patients underwent a 4-week break during which no gemcitabine, erlotinib or radiation was administered. Patients were radiologically restaged between 3 and 4 weeks following completion of radiation. Those with stable or responsive disease and acceptable treatment tolerance continued on the maintenance phase of the study.

The MTD of erlotinib was based on the development of DLTs. DLT’s were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 3.0 (http://ctep.info.nih.gov/reporting/ctc_v30.html), and were defined as any of the following: grade 4 thrombocytopenia (platelets < 25 000/\(\mu l\)), grade 3 neutropenia (absolute neutrophil count (ANC) < 1000/\(\mu l\)) lasting ≥ 4 days, neutropenic fever (fever > 38.1°C and ANC < 1000/\(\mu l\)), grade 3 or 4 diarrhea or gastrointestinal bleeding. Any other grade 3 or 4 toxicity, excluding rash, that in the opinion of the Principal Investigator was possibly, probably or definitely related to the combination of erlotinib, gemcitabine and radiation. Grade IV fatigue was dose limiting if lasting >7 days. Any toxicity-related treatment interruptions that resulted in a 2 week or greater delay in completing chemoradiation was also adjudicated as dose limiting. This was a phase I open label, nonrandomized, Cancer Therapy Evaluation Program-supported study.

results

Patient characteristics

Patient demographics are shown in Table 2. Twenty–one patients were enrolled from 3 June 2003 to 24 March 2005. The cut-off point for data analysis was 15 January 2007. Of these 21, 17 were assessable for having completed all protocol therapy, three were assessable for toxicity alone due to incomplete treatment and one patient was withdrawn before receiving treatment due to an elevated alanine aminotransferase (ALT). This latter patient was not included in any of the study end point analyses.

Determination of MTD

Three patients were enrolled to cohort 1 at dose level 1 (100 mg erlotinib), (see Tables 1 and 3). No DLT was observed. A further cohort of three patients was enrolled at dose level 2 (125 mg erlotinib). One of these three patients experienced DLT (platelets and neutropenia). This cohort was therefore expanded to six patients. One patient from the expanded cohort experienced grade 3 elevation’s in AST and ALT which were possibly related to therapy and therefore adjudicated as DLT. All of the six patients treated at erlotinib 125 mg experienced delays in treatment because of toxicity and four required a dose reduction of gemcitabine. One of these patients was hospitalized for recurrent fevers and hypotension which were possibly related to treatment and was removed from protocol. No patient was treated at dose level 3, erlotinib 150 mg. The MTD was therefore defined as erlotinib 100 mg/day, along with gemcitabine 40 mg/m²/twice weekly and 180 Gy/day radiation.

Once the MTD was determined, a further 11 patients were enrolled at this dose as part of an expanded cohort to further define toxicity and assess response. Five of these patients experienced treatment delays and two were removed from protocol due to excessive toxicity, one patient because of persistent thrombocytopenia and the other for diarrhea with weight loss and electrolyte abnormalities. In total, four patients required a dose reduction of gemcitabine during this portion of the study, see Tables 3 and 4 for a summary of DLT’s and grade 3–4 toxic effects encountered during chemoradiation.

toxic effects during maintenance therapy

In total, 17 patients completed chemoradiotherapy. Fourteen of these patients proceeded to the maintenance portion of the study. Two patients had developed evidence of progressive disease and were removed from protocol. One patient, upon

<p>| Table 1. Dose levels of erlotinib during combined chemoradiation |
|--------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Dose level</th>
<th>Erlotinib (mg)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>75</td>
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<tr>
<td>2</td>
<td>100</td>
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<tr>
<td>3</td>
<td>125</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
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<table>
<thead>
<tr>
<th>Table 2. Patient characteristics</th>
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<tr>
<td>Characteristics</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>ECOG PS</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>Laparoscopy/exploratory laparotomy</td>
</tr>
</tbody>
</table>

*A total of 21 patients were enrolled. One patient after completing registration had an elevated alanine aminotransferase and was therefore ineligible to receive protocol treatment.

ECOG, Eastern Cooperative Oncology Group; PS, performance status.
completion of chemoradiotherapy, was deemed potentially resectable after a restaging CT scan. This patient was removed from protocol (but included in the analysis) and proceeded to have an R0 pancreaticoduodenectomy for T3, N1, M0 and American Joint Committee on Cancer stage II-B disease. There was one grade 5 toxicity occurrence during this portion of the study. In this instance the patient had completed the combination chemoradiotherapy portion of therapy with one treatment delay due to neutropenia. He had completed two cycles of maintenance therapy and had demonstrated a partial response (PR) to treatment. On the day before his third cycle of maintenance therapy the patient was hospitalized with an acute gastrointestinal bleed. An esophagoduodenoscopy revealed gastric and duodenal ulceration secondary to invasion of tumor. The patient died shortly afterwards. An attribution to treatment cannot be excluded.

There were no grade 4 toxic effects in the maintenance portion of the study (see table 5). Four patients required a dose reduction of gemcitabine and one required a dose reduction of erlotinib. Eleven patients completed the maintenance portion. Four of these opted to continue extra treatment per protocol option, and the number of extra cycles ranged from 1 to 22.

Table 3. DLTs during chemoradiation

<table>
<thead>
<tr>
<th>Dose level</th>
<th>N</th>
<th>Number of DLTs</th>
<th>DLT specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Erlotinib 100 mg)</td>
<td>3</td>
<td>3a</td>
<td>Neutropenia, hypokalemia, hyponatremia (n = 1);</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diarrhea (n = 2)</td>
</tr>
<tr>
<td>2 (Erlotinib 125 mg)</td>
<td>3+3</td>
<td>1+1</td>
<td>Neutropenia; platelets (n = 1); liver enzymes (n = 1)</td>
</tr>
</tbody>
</table>

*Eleven patients were enrolled as part of an expanded cohort once the MTD had been established, to better characterize toxicity and efficacy.

These toxic effects occurred during the expanded portion of the study, and therefore are not true DLT’s, however they did satisfy DLT criteria which pertained to the dose escalation portion.

*One patient developed recurrent neutropenia and thrombocytopenia which, although did not satisfy strict definition of DLT, necessitated multiple treatment interruptions and prolongation of chemoradiation beyond 8 weeks. The protocol was amended to include treatment delay ≥2 weeks as a DLT.

Grade 3 elevation in alanine and aspartate aminotransferase.
DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

efficacy

Seventeen patients were evaluated for response to therapy, time to progression and OS. The median follow-up time was 18 months (range 3–27). Eleven patients completed all protocol therapy. Response determination was the best response identified post chemoradiation therapy or on completion of the 12 weeks of maintenance therapy, according to Response Evaluation Criteria In Solid Tumors criteria. Six (35%) patients had a PR to treatment (exact 95% CI 14% to 62%). Nine patients (53%) had stable disease as their best response. In total, four patients exhibited local disease failure in the pancreas at 4, 4, 19 and 22 months. Two of these patients had progression of disease on protocol therapy and two had subsequent progression after initially having stable disease as a best response. The median survival duration for the seventeen patients was 18.7 months (95% CI 13.3–24.8) (Figure 2). The median time to tumor progression was 13 months (95% CI 4.8–17.8) (Figure 1).

discussion

Combination concurrent chemotherapy and RT for locally advanced unresectable pancreas cancer is a widely employed standard approach. Gemcitabine has superceded 5-FU as the standard therapy for metastatic pancreatic cancer and is FDA approved for first-line treatment of patients with locally advanced (nonresectable stage II or stage III) or metastatic (stage IV) adenocarcinoma of the pancreas. Gemcitabine has been shown to be a potent radiosensitizer in human colorectal, pancreatic and other solid tumor cell lines [15–17]. A phase I study has shown that a twice-weekly dosing schedule of gemcitabine 40 mg/m² with concurrent radiation is feasible and well tolerated [18]. This dose was adopted by the Cancer and Leukaemia Group B for a phase II study [19] in which patients...
received maintenance gemcitabine upon completion of the chemoradiotherapy with a median OS of 8.2 months. Some studies have also attempted to incorporate even higher doses of gemcitabine into a combined chemoradiation approach with success [8, 20, 21].

Pancreatic cancers contain high levels of EGFR overexpression [12]. EGFR and its ligands EGF and TGF-alpha are important in cell proliferation, as well as motility, adhesion, invasion, survival and angiogenesis [10]. In non-small-cell lung cancer (NSCLC) a specific subpopulation exists that harbour somatic mutations in the EGFR. This appears to account for /C24 10% of NSCLC cases although the proportion varies according to the population studied [22–24]. The occurrence of these mutations correlates with an exquisite sensitivity to inhibition of the EGFR tyrosine kinase with gefitinib or erlotinib in the majority of cases [25–27]. Erlotinib has been shown by Shepherd et al. [28] to prolong survival in patients who had been enrolled on a study of erlotinib and capecitabine as second-line therapy and who had sufficient clinical response to remain on study for at least 100 days. Two of 55 (3.6%) were found to have EGFR mutations, both from the five patients who had demonstrated nonprogression of disease on erlotinib and capecitabine. While none of the 50 unselected pancreas cancer patients’ specimens were found to have EGFR mutations, the authors state that technical factors relating to an excessive stromal component to, and lack of microdissection of, the specimens may have resulted in lower sensitivity for detection of mutations.

A common criticism of clinical trials in pancreatic cancer is that patients with stage III and stage IV disease are often grouped together, rendering interpretation of survival data more difficult and potentially obscuring a survival advantage in genuine stage III patients. A strength of our study is that all the patients were surgically staged and therefore the population is homogenous. Although the primary end point was not survival and recognizing the limitations of interpreting survival data in selected good PS patients conducted in single-institution phase I studies, the median OS of 18.7 months, is nonetheless, striking.

### Table 4. All grade 3 or 4 toxicity during chemoradiation

<table>
<thead>
<tr>
<th>Dose level</th>
<th>N</th>
<th>Hematologic (number/%)</th>
<th>Non-hematologic (number/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Erlotinib 100 mg)</td>
<td>14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Lymphopenia 14 (100%)</td>
<td>Fatigue 1 (7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Platelets 3 (21%)</td>
<td>Diarrhea 3 (21%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neutropenia 3 (21%)</td>
<td>Rash&lt;sup&gt;b&lt;/sup&gt; 2 (14%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anemia 1 (7%)</td>
<td>–</td>
</tr>
<tr>
<td>2 (Erlotinib 125 mg)</td>
<td>6</td>
<td>Lymphopenia 6 (100%)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Platelets 2 (33%)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neutropenia 3 (50%)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anemia 1 (17%)</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup>This number comprises of the three patients from the initial dose escalation part of the study and 11 patients from the expanded cohort of patients treated at the MTD.

<sup>b</sup>There were in addition three episodes of grade 2 rash.

MTD, maximum tolerated dose.

### Table 5. Grade 3 and 4 toxicity during maintenance therapy

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Hematologic</th>
<th>Non-hematologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib 100 mg/day + gemcitabine</td>
<td>14</td>
<td>Lymphopenia 8 (57%)</td>
<td>Fatigue 1 (7%)</td>
</tr>
<tr>
<td>1000 mg/m²</td>
<td></td>
<td>Neutropenia 3 (21%)</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup>This number comprises of the three patients from the initial dose escalation part of the study and 11 patients from the expanded cohort of patients treated at the MTD.

<sup>b</sup>There were in addition three episodes of grade 2 rash.

MTD, maximum tolerated dose.
This phase I study investigated the combination of erlotinib, an EGFR inhibitor with gemcitabine-based chemoradiation. This is one of the first studies reporting on this combination in pancreatic cancer. Ianniti et al. [32] conducted a phase I study of erlotinib in combination with gemcitabine, paclitaxel and radiation, followed by maintenance erlotinib in locally advanced pancreatic cancer. The majority of the patients on that study (14 of 17) were surgically staged. The MTD determined was erlotinib 50 mg/day and the median survival was 14 months.

In conclusion, in association with fixed dose gemcitabine at 40 mg/m² twice-weekly and radiation at 180 cGy/day, respectively, the MTD of erlotinib was found to be 100 mg/day. The results of the correlative studies should provide some further insights into the mechanistic understanding of the role of EGFR therapy in pancreas adenocarcinoma. This is a relatively well-tolerated, biologically active combination in a poor prognostic cancer. The encouraging results are worthy of further development in pancreas cancer, in an adjuvant or neo-adjuvant setting and provide a further building block for treatment of locoregionally advanced disease.

**References**