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# A phase II study of erlotinib in gemcitabine refractory advanced pancreatic cancer

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**Abstract** ***Background:*** Erlotinib induced skin toxicity has been associated with clinical benefit in several tumour types. This phase II study evaluated the efficacy of erlotinib, dose escalated to rash, in patients with advanced pancreatic cancer previously treated with gemcitabine.
***Methods:*** Erlotinib was given at an initial dose of 150 mg/day, and the dose was escalated by 50 mg every 2 weeks (to a maximum of 300 mg/day) until >grade 1 rash or other dose limiting toxicities occurred. Erlotinib pharmacokinetics were performed, and baseline tumour tissue was collected for mutational analysis and epidermal growth factor receptor (EGFR) expression. The primary end-point was the disease control rate (objective response and stable disease >8 weeks).
***Results:*** Fifty-one patients were accrued, and 49 received treatment. Dose-escalation to 200–300 mg of erlotinib was possible in 9/49 (18%) patients. The most common ⩾grade 3 adverse events included fatigue (6%), rash (4%) and diarrhoea (4%). Thirty-seven patients were evaluable for response, and the best response was stable disease in 12 patients (32% (95% confidence interval (CI) 17–47%)). Disease control was observed in nine patients (24% (95% CI: 10–38%)). Median survival was 3.8 months, and 6 month overall survival rate was 32% (95% CI 19–47%). Mutational analysis and EGFR expression were performed on 29 patients, with 93% having *KRAS* mutations, none having *EGFR* mutations, and 86% expressing EGFR. Neither *KRAS* mutational status nor EGFR expression was associated with survival.
***Conclusions:*** Erlotinib dose escalated to rash was well tolerated but not associated with significant efficacy in non-selected patients with advanced pancreatic cancer.


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## 1. Introduction

Pancreatic cancer continues to be one of the leading causes of cancer related death [1]. Despite recent advances in therapy, median survival remains poor and the majority of patients survive for less than 1-year [2]. Gemcitabine has been regarded as the standard backbone of systemic therapy for advanced pancreatic cancer based upon a 1997 trial comparing gemcitabine versus fluorouracil that demonstrated an improvement in median and 1-year survival [3]. More recent data suggest that FOLFIRINOX (fluorouracil, irinotecan, and oxaliplatin) or a combination of gemcitabine and nab-paclitaxel [33] may be a preferable first line options in patients with good performance status [2]. Once patients have progressed on gemcitabine-based chemotherapy, there is limited evidence that further systemic therapy provides meaningful benefit. Most phase II studies in this setting have noted median progression free survival in the range of 2 to 4 months, and few responses [4–12,14], although one trial demonstrated a modest survival benefit from treatment with fluorouracil and oxaliplatin [13]. Given the lack of effective therapies, new treatment options are urgently needed.

Erlotinib (Tarceva®) is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. EGFR is known to be frequently overexpressed in pancreatic tumours [15–17], and to be associated with worse prognosis [16,17]. There is pre-clinical evidence for an anti-tumour effect of erlotinib in pancreatic cancer [18,19]. A phase III study comparing gemcitabine and erlotinib versus gemcitabine alone (NCIC Clinical Trials Group (CTG) PA.3) demonstrated a modest but significant survival advantage for the combination [20]. A small phase II study was also conducted assessing the combination of capecitabine and erlotinib in the gemcitabine-refractory setting, and demonstrated a response rate of 10% and median survival of 6.5 months [4].

Subgroup analysis of the NCIC CTG PA.3 trial demonstrated that the presence of an erlotinib induced rash was associated with a significantly higher likelihood of achieving disease control, and appeared to be associated with improved survival (hazard ratio: 0.74) [20]. Studies of erlotinib in other tumour types have also demonstrated an association between rash and clinical benefit [21–23]. Chen and colleagues examined the correlation between erlotinib minimum steady state concentration (Cmin) and severity of skin rash and noted that patients without a rash had a significantly lower steady state concentration compared to patients with a rash [24]. Thus, intrapatient dose escalation to rash may be a strategy to increase erlotinib efficacy. It is also possible that molecular factors such as *KRAS* and *EGFR* mutational status may predict for EGFR tyrosine kinase efficacy in pancreatic cancer, as has been noted for non-small cell lung cancer [25,26].

To assess the safety, efficacy and feasibility of this treatment strategy, the Princess Margaret Hospital Phase II consortium undertook a phase II study of erlotinib dose escalated to rash in patients with advanced gemcitabine refractory pancreatic cancer. In addition, mutational profiling and EGFR expression were conducted in patients with archived tissue suitable for analysis to assess mutational profiles predictive of erlotinib efficacy.

## 2. Methods

### 2.1. Patient selection

Eligible patients had locally advanced or metastatic pancreatic cancer and had received prior treatment with gemcitabine. Patients were required to be Eastern Cooperative Oncology Group (ECOG) performance status 0–2, an absolute granulocyte count $\geqslant 1.5 \times 10^9$/L, platelet count $\geqslant 100 \times 10^9$/L, normal serum creatinine and bilirubin $\leqslant 1.5 \times$ the upper limit of normal (ULN). Aspartate aminotransferase (AST) and alanine transaminase (ALT) were required to be $\leqslant 2.0 \times$ the ULN, unless liver metastases were present ($\leqslant 5 \times$ ULN). Patients were required to have measurable disease using Response Evaluation Criteria in Solid Tumours [RECIST 1.0] [27]. Exclusion criteria included concurrent other malignancies and serious medical conditions that would impair the ability of the patient to receive protocol treatment. The institutional review boards of the participating institutions approved the study, and all patients provided written informed consent.

### 2.2. Study design

This phase II study of erlotinib (NCT Registration ID: 00497224) was conducted using a two-stage Simon design, with the primary end-point being disease control rate (objective response plus prolonged stable disease >8 weeks). The study was funded by OSI pharmaceuticals.

Erlotinib was initially administered orally at 150 mg daily on a continuous basis. Study treatment was administered as 28-day cycles. Every 2 weeks for the first two cycles, patients were assessed for toxicity and the presence of rash. Patients who experienced adverse events necessitating dose reduction continued on the reduced dose of erlotinib with no dose escalation. Dose escalation was performed in patients who met all of the following criteria: absence of an erlotinib induced rash; $\leqslant$grade 1 diarrhoea; absence of a dose reduction during cycle 1 for toxicity. Patients that did not meet the criteria for dose reduction or dose escalation continued on the present dose of erlotinib. Patients who did not develop a rash had the erlotinib dose increased by 50 mg every 2 weeks as long as they met the criteria