European Journal of Cancer (2014) **50**, 1909–1915

Available at www.sciencedirect.com

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

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Received 5 December 2013; received in revised form 21 March 2014; accepted 2 April 2014
Available online 21 May 2014

KEYWORDS
Pancreatic cancer
Erlotinib
Phase II

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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http://dx.doi.org/10.1016/j.ejca.2014.04.008
0959-8049/

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

for dose escalation. Once a patient developed a rash, dose escalation was stopped and they were to continue on the same dose of erlotinib unless they meet criteria for dose reduction.

Baseline radiological investigations were performed within 28 days prior to study treatment. Radiological assessments for tumour measurements were conducted every 8 weeks. Study treatment continued until unacceptable toxicity, patient request or progression.

2.3. Dose modifications

2.3.1. Non-haematological toxicity

For grade 2 toxicity not immediately resolving with symptomatic treatment, erlotinib was held until the toxicity improved to ⩽grade 1 and then resumed without dose reduction. On second occurrence, the dose was reduced by 50 mg. For grade 3 toxicity, erlotinib was withheld until ⩽grade 1 and then resumed at a 50 mg dose reduction. For grade 4 toxicity protocol, therapy was discontinued.

2.3.2. Haematological toxicity

For grade 4 neutropenia, grade 3 or 4 thrombocytopenia or febrile neutropenia, erlotinib was held until the adverse event resolved to ⩽grade 2. If that adverse event was felt by the investigator to be possibly, probably or definitely related to erlotinib, the dose was reduced by 50 mg/day. If it was thought to be unlikely to be related, or unrelated, no dose reduction was required. If the adverse event persisted for >14 days, therapy was discontinued.

2.4. Erlotinib steady state concentrations

Erlotinib pharmacokinetics were assessed on cycle 1 day 1 (prior to first dose), cycle 1 day 15 (prior to study dose) and cycle 2 day 1 (prior to study dose). In patients that underwent dose escalation, one addition sample was to be taken on cycle 2 day 22 (pre dose).

Plasma concentrations of erlotinib were quantitated with validated high-performance liquid chromatography (HPLC)-tandem mass spectrometry methods. Pharmacokinetic parameters were calculated by non-compartmental methods using the WinNonlin Version 5.1 (Pharsight Corp., Mountain View, CA). Pharmacokinetic variables were analysed with descriptive statistics. Post-hoc analyses of the relationships between smoking status (assessed by baseline questionnaire) and erlotinib pharmacokinetic levels, and toxicity were undertaken.

2.5. Mutational analysis and EGFR expression

Mutation assessment was performed on archived tissue using the Sequenom® system (using the OncoCarta panel v1.0). This a sequencing system that screens for mutations in genes commonly mutated in cancers including *KRAS*, *EGFR*, *BRAF*, *NRAS* and *HRAS*, and can detect *KRAS* mutations in codons 12, 13 and 61. In addition, sequencing analysis was also performed by Sanger sequencing® to detect *KRAS* mutations in codons 12 or 13. A post hoc analysis of the relationship between *KRAS* mutational status and survival was undertaken.

2.6. EGFR immunohistochemistry

Available archival formalin-fixed paraffin embedded tissue blocks were assessed for EGFR expression by immunohistochemistry. Staining was performed using the EGFR pharmDx kit (Dako Inc, Mississauga, ON, Canada) according to the manufacturer's protocols. Slide evaluation was performed independently by two pathologists using light microscopy and the final scores reflect a consensus score. Cases were considered positive if they showed any IHC staining of tumour cell membrane whether complete or incomplete above the background level [28]. Positive and negative control cell lines were included in each run. A post hoc analysis of the relationship between EGFR expression and survival was performed.

2.7. Statistical methods

The primary end-point was the disease control rate (objective response and prolonged stable disease >8 weeks). Secondary end-points included overall survival (defined as time from randomisation to death from any cause), time to progression (defined as time from randomisation to progression by RECIST 1.0), duration of response or stable disease, progression-free survival and toxicity. The optimal Simon two-stage phase II design was used [29], with the treatment determined to be inactive if the disease control rate was at most 10% and active if it was at least 30%. In stage I, 18 patients were to be accrued, and if three patients responded or had prolonged stable disease then the study would proceed to stage II. In stage II, 17 further patients were to be enrolled, and if seven or more patients of the total of 35 met the criteria for disease control the primary end-point would be met. The one-sided α was 0.05, and power 0.90. A minimum of 8 weeks of follow up was required for patients to be evaluable for disease control rate. Standard descriptive statistics were used to summarise the patient characteristics and toxicity. Kaplan–Meier method was performed to estimate time to progression and overall survival in the overall cohort, and also in subgroups based on mutational status and presence or absence or rash, with exploratory comparisons performed using the log-rank test.

2.8. Role of the funding source

OSI pharmaceutical had no role in the study design, data collection and interpretation or manuscript preparation.

3. Results

Fifty-one patients were accrued over 23 months from November 2006 until October 2008, and 49 received treatment (Table 1). Two patients never received treatment, one due to withdrawal of consent prior to treatment and one due to symptomatic deterioration prior to study enrolment. The median number of cycles administered was two (range of 1–15). Thirty-three patients came off study due to progressive disease, two patients died while on study, ten patients withdrew consent, three patients came off due to toxicity (diarrhoea; myocardial ischaemia and fracture; thrombosis and lower gastrointestinal haemorrhage) and one patient was non-compliant with study protocol. One patient was subsequently found to have a tumour more in keeping with neuroendocrine then ductal adenocarcinoma on further pathology review, therefore this patient was excluded from the efficacy analysis. The median follow up was 3.3 months, and as of the last follow up 35 patients had progressed and 40 patients had died.

Dose-escalation to 200–300 mg of erlotinib was possible in 10 (20%) patients. The best response was stable disease in 12/37 evaluable patients (32%). Disease control (stable disease >8 weeks) was observed in 9/37 evaluable patients (24%). The observed disease control rate surpassed the Simon criteria for a positive trial, but at 24% it was less than the 30% disease control rate that was pre-defined to represent relevant activity of the drug.

All patients who received treatment, except for the one patient with neuroendocrine pathology, were included in the survival analysis. The median time to progression was 1.61 months (95% confidence interval (CI): 1.58–2.10) (Fig. 1), with a 6 month progression free rate of 10% (95% CI: 3–24%). Median overall survival was 3.78 months (Fig. 2), with a 6 month survival rate of 32% (95% CI: 19–47%).

All patients who received treatment were included in the toxicity analysis. Adverse events are listed in Table 2. The most common treatment related adverse events of any grade included rash (88%), diarrhoea (49%) and fatigue (49%). Grade 3 or greater treatment related adverse events at least possibly related to erlotinib included fatigue (6%), rash (4%) and diarrhoea (4%) (Table 2). There were no grade 4 or 5 toxicities noted. Dose reductions were required in two patients.

Table 1
Patient demographics.

Characteristic	Enrolled patients ($n = 51$)
Age, years	
Median	62
Range	37–79
Gender	
Male	25
Female	26
ECOG performance status	
0	3
1	38
2	10
Stage	
Locally advanced	6
Metastatic	45
Prior therapy	
Chemotherapy in adjuvant setting	23
Chemotherapy in metastatic setting	32
Radiation therapy	8
Histology	
Adenocarcinoma	50
Neuroendocrine*	1

* This patient was excluded from the efficacy analysis.

3.1. Mutational analysis and EGFR expression

Archived tissue suitable for analyses was available for 29 patients, and mutational analysis was performed using the Sequenom® OncoCarta panel v1.0. Ninety-three percent (27/29) of patients had *KRAS* mutations (one of which had a *KRAS* and *PI3K* mutation, and another that had a *KRAS* and *HRAS* mutation). *KRAS* mutations were confirmed using Sanger sequencing®. Seven percent (2/29) of patients were *KRAS* wild type. None of the patients had an *EGFR* mutation. EGFR expression was performed by immunohistochemistry, and 86% (25/29) of patients had EGFR expression.

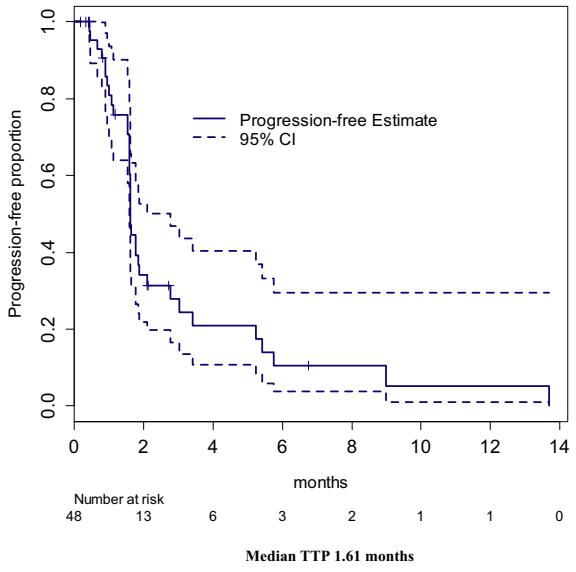

Fig. 1. Kaplan–Meier curve of time to progression (TTP).

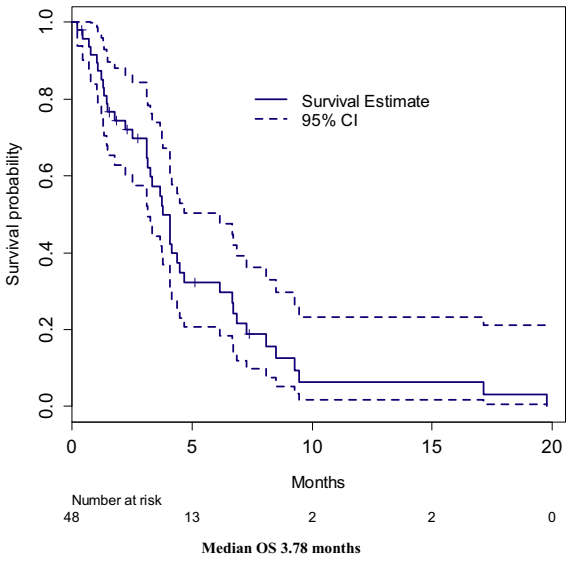

Fig. 2. Kaplan–Meier curve of overall survival (OS).

Table 2
Possibly related grade 3 adverse events.

Adverse event (grade 3)	Erlotinib ($n = 49$)* n (%)
Non-haematological	
Fatigue	3 (6)
Rash	2 (4)
Diarrhoea	2 (4)
Lower gastrointestinal haemorrhage	1 (2)
Cecal perforation	1 (2)
Renal failure	1 (2)
Haematological	
Anaemia	2 (4)
Lymphopenia	2 (4)
Decrease in albumin	2 (4)
Elevation in alkaline phosphatase (ALP)	1 (2)
Elevation in aspartate aminotransferase (AST)	1 (2)
Elevation in bilirubin	1 (2)
Hypokalaemia	1 (2)
Elevation in international normalized ratio (INR)	1 (2)

* Two patients were enrolled but did not receive treatment.

Survival data were available for 28/29 patients (one patient did not receive treatment). There was no difference in overall survival comparing *KRAS* mutant versus *KRAS* wild type patients ($p = 0.6$), nor for the EGFR positive versus negative patients ($p = 0.6$).

3.2. Skin rash

Of the patients evaluable for rash, 16 patients developed a grade 2 or 3 rash and 32 patients had a grade 0 or 1 rash. There was a correlation between rash and disease control, with 7/15 (47%) of evaluable patients with grade 2 or 3 rash having SD >8 weeks versus 2/22 (9%) of patients with grade 0 or 1 rash ($p = 0.017$). There was no difference in survival based on rash with a median overall survival of 3.9 months for patients who developed grade 2 or 3 rash versus 3.8 months for patients with grade 0 or 1 rash ($p = 0.12$). In addition no differences in median time to progression by degree of rash was noted ($p = 0.25$).

3.3. Steady state erlotinib concentrations

Pharmacokinetic data for erlotinib were available for 31 patients. The mean erlotinib Cmin on day 14 was 1179 ± 791 ng/ml. The mean day 14 Cmin of the main active metabolite or erlotinib (OSI-420) was 151 ± 166 ng/ml.

3.3.1. Erlotinib pharmacokinetics by smoking status

Smoking status was obtained in 46 patients, 16 were never smokers (NS), 25 were past smokers (PS) and five were current smokers (CS). Pharmacokinetic data were available for 30 patients with known smoking status. The mean erlotinib Cmin on day 14 in CS, PS and NS was 517, 1008 and 1862 ng/ml respectively ($p = 0.01$ for CS versus NS). The mean Cmin of OSI-420 on day 14 in CS, PS and NS was 55, 123, and 256 ng/ml respectively ($p = 0.01$ for CS versus NS). Cycle 1 $\geqslant$grade 2 diarrhoea occurred in 0/5 (0%) CS, 5/25 (20%) PS and 3/16 (19%) NS ($p = 0.55$ for CS versus NS). Cycle 1 $\geqslant$grade 2 rash occurred in 0/5 (0%) CS, 7/25 (28%) PS and 5/16 (31%) NS ($p = 0.28$ for CS versus NS).

4. Discussion

Improving survival with systemic therapy for metastatic pancreatic cancer remains a challenge, especially in the gemcitabine refractory setting. There is strong rationale, based on both pre-clinical and clinical data, that targeting the EGFR pathway with erlotinib may have an anti-tumour effect in pancreatic cancer [18–20]. The results of this multi-institutional phase II study reveal that erlotinib dose escalated to rash is feasible and generally well tolerated, but is associated with minimal efficacy in non-selected patients in the gemcitabine refractory setting.

Erlotinib as a single agent has been shown to be effective in non-small cell lung cancer (NSCLC), and recent work has demonstrated that this effect is limited to patients who possess *EGFR* mutations (exon 19 deletion or exon 21 L858R mutation) [25,26]. Data from NSCLC have also shown that patients with *KRAS* mutations, which are relatively uncommon in NSCLC compared with pancreatic cancer, have significantly decreased benefit from EGFR tyrosine kinase inhibitors [26]. In addition, evidence from the colorectal cancer literature has convincingly demonstrated that patients with *KRAS* mutations do not benefit from EGFR targeted therapy [30,31].

The frequency of *KRAS* mutations in pancreatic cancer is known to be high, while the frequency of *EGFR* mutations is low. In this study, mutational analysis was conducted on 29 patients, 27 (93%) of which were *KRAS* mutant. Of the 29 patients analysed, none possessed *EGFR* mutations. There was no difference in outcomes seen when comparing patients with *KRAS* mutations versus *KRAS* wild type, but given the small number of *KRAS* wild type patients the conclusions that can be made from this are limited. In addition, EGFR expression was not found to be associated with survival, but this analysis is also limited by the sample size.

The impact of *KRAS* mutations and *EGFR* gene copy number on erlotinib efficacy in pancreatic cancer was previously assessed in the NCIC CTG PA.3 study [32]. The role of *KRAS* mutational status on treatment effect was analysed for 117 patients, and the results indicated a non-significant trend toward a greater benefit from the erlotinib and gemcitabine combination in *KRAS* wild type patients (hazard ratio 0.66 versus 1.07, interaction $p = 0.38$). EGFR gene copy number using fluorescence in situ hybridisation was assessed for 100 patients and appeared to be of no predictive value. Whether *KRAS* wild type and/or *EGFR* mutant pancreatic cancers derive a greater benefit from erlotinib is yet to be determined, but given the high prevalence of *KRAS* mutations, and low prevalence of *EGFR* mutations in pancreatic cancer, patients with these tumour profiles represent a significant minority of all pancreatic cancer patients.

There are increasing data suggesting that rash may be a clinical predictive marker to EGFR inhibitor therapy [20–23,33]. This effect has been demonstrated with both EGFR tyrosine kinase inhibitors and anti-EGFR monoclonal antibodies. In this study we found that degree of rash did appear to correlate with rates of disease control, but this did not translate to differences in time to progression or overall survival. These comparisons were limited by the small sample size. In the phase II RACHEL (BO21128) study patients received 4 weeks of gemcitabine and erlotinib (100 mg/day), and after the run-in period if grade 2 or greater rash was not observed they were randomised to either ongoing treatment with gemcitabine and standard dose erlotinib, or erlotinib dose escalated to rash [34]. Consistent with the results of our study, the RACHEL results did not demonstrate an efficacy benefit from the erlotinib dose escalation to rash strategy.

We conducted a post hoc analysis to assess for a relationship between smoking status and erlotinib steady state levels, as previous studies performed in lung cancer [35–37] have demonstrated that cigarette smoking leads to lower erlotinib levels, possibly due to induction of the CYP1A1 pathway [35,37–39]. Our results also indicate this effect, as current smokers had significantly lower erlotinib and OSI-420 (the main active metabolite) levels then never smokers. In addition, current smokers had a trend toward less toxicity then never smokers. These results add to the body of literature demonstrating an effect of smoking of erlotinib levels, and the concept of alternate dosing of erlotinib in active smokers should be explored further.

This is the largest study to date of single agent erlotinib in advanced pancreatic cancer. The off label use of erlotinib in this setting is currently considered by some clinicians. The results of our study importantly show that in the unselected population the use of single agent erlotinib is of minimal clinical benefit. Whether other molecular markers can predict for a subset of patients that would benefit from single agent erlotinib is yet to be fully elucidated.

In summary, dose escalation of erlotinib to rash is feasible, but it is not associated with significant efficacy in non-selected patients with advanced pancreatic cancer resistant to gemcitabine.

Conflict of interest statement

Dr. Renouf has received honoraria and travel grants from Roche. Dr. Tsao has received research funding and honoraria from Roche. None of the other authors have any conflicts of interest to declare.

Acknowledgements

This study was funded by OSI Pharmaceuticals. OSI did not contribute to the data analysis, interpretation or manuscript writing.

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