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Original Research

# Efficacy of gemcitabine plus erlotinib in rash-positive patients with metastatic pancreatic cancer selected according to eligibility for FOLFIRINOX: A prospective phase II study of the 'Arbeitsgemeinschaft Internistische Onkologie'☆

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**Abstract** ***Introduction:*** In metastatic pancreatic ductal adenocarcinoma (mPDAC) treatment, erlotinib is known to be more effective in patients developing skin rash. Treatment with the FOLFIRINOX regimen is only performed in fit patients following defined inclusion criteria. The present study investigates the efficacy of gemcitabine plus erlotinib (gem/erlotinib) in rash-positive patients fit for FOLFIRINOX.
***Patients and methods:*** For this prospective phase II study, 150 patients were recruited in 20 centres. All patients received gem/erlotinib for 4 weeks (run-in phase); the subsequent treatment was determined by the development of skin rash: patients with rash grades 1–4 continued with gem/erlotinib, rash-negative patients were switched to FOLFIRINOX. Primary study end-point was to achieve a 1-year survival rate in rash-positive patients ≥40%.
***Results:*** Ninety patients were deemed positive for skin rash by the end of the run-in phase, showing a 1-year survival rate of 40.0% (95% confidence interval [CI] 29.8–50.9). Median overall survival (OS) was 10.1 months, progression-free survival (PFS) was 3.8 months and overall response rate (ORR) was 23.3%. Patients switched to FOLFIRINOX ($n = 27$) had a 1-year survival rate of 48.1% (95% CI 28.7–68.1), a median OS of 10.9 months, a median PFS of 6.6 months and an ORR of 33.3%. Rash-negative patients had a lower quality of life at baseline but seemed to experience an improved control of pain during FOLFIRINOX.
***Conclusions:*** First-line treatment with gem/erlotinib was effective in fit, rash-positive mPDAC patients achieving a 1-year survival rate comparable to previous reports for FOLFIRINOX. The study was registered at clinicaltrials.gov (NCT0172948) and Eudra-CT (2011-005471-17).


## 1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is increasingly becoming a leading cause of death from gastrointestinal malignancies [1]. In Germany, PDAC is projected to be the second leading cause of cancer death by 2030 [2]. For nearly two decades, gemcitabine has been regarded as a standard of care in advanced PDAC [3]. To date, several combinations of gemcitabine with agents targeting the epidermal growth factor receptor (EGFR) or its downstream pathways were investigated in phase II/III trials, among them cetuximab and lapatinib [4,5]. Very recently, nimotuzumab, a humanised IgG1 antibody against the extracellular domain of EGFR, has demonstrated promising activity combined with gemcitabine in a randomised phase II trial [6]. The only targeted agent approved for treatment of metastatic PDAC (mPDAC) is the small molecule erlotinib. In the pivotal PA.3 trial, patients treated with gemcitabine plus erlotinib (gem/erlotinib) achieved a marginal but statistically significant survival benefit versus gemcitabine plus placebo (6.24 versus 5.91 months, hazard ratio [HR] = 0.82, $p = 0.038$) [7]. In the adjuvant setting, however, the combination of gem/erlotinib failed to provide clinical benefit after R0 resection [8]. In contrast to the rather moderate activity of erlotinib in unselected patients with advanced PDAC, the subgroup of individuals developing skin rash during erlotinib treatment (a known side-effect of drugs targeting the EGFR pathway) evolved to have a considerably improved prognosis with 1-year survival rates beyond 40% [7,9,10].

In 2010, Conroy et al. published the data of the PRODIGE4/ACCORD 11 trial, demonstrating a clear superiority of FOLFIRINOX versus gemcitabine alone (median survival: 11.1 versus 6.8 months) [11]. However, the reported adverse events were higher than for gemcitabine, with a rate of grade 3–4 neutropenia of 45.7%, febrile neutropenia in 5.4% and grade 3–4 diarrhoea in 12.7%. Additionally, only a pre-selected patient population was included into the PRODIGE4/ACCORD 11 trial: main inclusion criteria were for example an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, a serum bilirubin level of ≤1.5 × the upper limit of normal (ULN) and no clinically significant history of cardiac disease.

The primary rationale of the current prospective, multicentre phase II study conducted by the 'Arbeitsgemeinschaft Internistische Onkologie' (AIO), hence, was to assess whether a pre-selected patient population developing skin rash during exposure to gem/erlotinib might experience a comparable survival benefit as reported for FOLFIRINOX. This would subsequently support the option to treat this subgroup of patients with the numerically less toxic regimen of gem/erlotinib.

## 2. Patients and methods

### 2.1. Patient population and study design

Adults between 18 and 75 years with histologically proven mPDAC were eligible for this phase II study if they fulfilled, among others, selection criteria comparable to those previously reported by Conroy et al. for