



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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KEYWORDS

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Skin rash

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 $\geq 40\%$.

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).

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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 $\leq 1.5 \times$ 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

FOLFIRINOX, i.e. ECOG performance status of 0–1, a serum bilirubin level of ≤ 1.5 ULN and no history of clinically significant cardiac disease within 12 months before study entry. Written informed consent was obtained from each patient before any study-specific procedure was performed. The study was approved by ethical committees in all participating German centres and was conducted according to the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization and relevant German and European laws. The study was registered at clinicaltrials.gov (trial identifier: NCT0172948) and Eudra-CT (Eudra-CT number 2011-005471-17).

All patients received gemcitabine (1000 mg/m² intravenously over 30 min weekly) and erlotinib (100 mg daily) for 4 weeks within a run-in phase. Further treatment was dependent on the appearance of skin rash within the run-in phase: patients developing an erlotinib-associated exanthema of grade 1–4 assessed by the local investigator according to the Common Terminology Criteria for Adverse Events (CTCAE, v4.0) continued with gem/erlotinib until progression or unacceptable toxicity (arm A). Patients who did not show any erlotinib-associated skin rash were switched to subsequent treatment with FOLFIRINOX (arm B; oxaliplatin 85 mg/m² intravenously over 2 h followed by leucovorin 400 mg/m² intravenously over 2 h and irinotecan at a dose of 180 mg/m² intravenously over 2 h followed by 5-fluorouracil at a dose of 400 mg/m² as intravenous bolus and subsequently given as a 46-h continuous intravenous infusion, repeated every 2 weeks).

Toxicity was assessed at every study visit according to the CTCAE v4.0. Quality of life was evaluated at baseline and every 4 weeks thereafter according to the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire QLQ-C30. Treatment responses (according to Response Evaluation Criteria in Solid Tumours, version 1.1) by computed tomography or magnetic resonance imaging scan were repeated every 8 weeks in arm A (gem/erlotinib) and for the first time after two cycles of FOLFIRINOX (week 9) and every 8 weeks thereafter in arm B.

2.2. Statistical analyses

Primary study end-point of this prospective, non-randomised, multicentre phase II AIO trial was the 1-year survival rate of patients selected according to the criteria defined by Conroy et al. for FOLFIRINOX developing skin rash during treatment with gem/erlotinib. A 1-year survival rate of $\geq 40\%$ was assumed, comparable to the efficacy data published for FOLFIRINOX. Assuming 70% of patients developing skin rash, a number of 130 evaluable patients were necessary to achieve a total number of 90 patients for the primary study end-point. Twenty patients were expected to be non-evaluable or to show early disease progression, summing up to a total

number of 150 patients to be included in the study. For null hypothesis (H_0), a 1-year survival rate $\leq 25\%$ within a two-sided test (significance level 0.05, power 83%) was assigned. Secondary end-points included overall survival (OS), progression-free survival (PFS), tumour response, safety and quality of life in rash-positive and rash-negative patients.

Response and survival rates were compared by Fisher's exact test; in addition, odds ratios were indicated. The comparison of scores (EORTC QLQ-C30) between treatment groups was conducted by the rank-sum test of Wilcoxon. PFS, OS and time to definite deterioration of quality of scores (EORTC QLQ-C30) were analysed according to the Kaplan–Meier method and expressed as medians; differences between treatment groups were assessed using log-rank tests. Survival-based analyses were also performed by Cox regression and expressed as hazard ratios (HRs) with confidence intervals (CIs). The primary end-point was analysed confirmatively with the two-sided 95% CI (exact method). All other comparisons were performed exploratively with a two-sided alpha of 5%. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

Between July 2012 and July 2015, 150 patients were included into the trial in 20 German centres. The trial flow is illustrated in the CONSORT diagram in Fig. 1. Five patients terminated the study before treatment start. Clinical baseline characteristics of the 145 patients that define the 'intention to treat' and safety population are listed in Table 1. One patient was excluded from the efficacy analyses for violation of inclusion criteria. At the end of the 4-week run-in phase, 90 patients (76.9%) were classified as 'rash-positive' (allocated to arm A), whereas 27 patients (23.1%) were considered 'rash-negative' (allocated to arm B). These 117 patients were available for efficacy analyses according to the primary study end-point. One patient did, however, not continue treatment with gem/erlotinib in arm A. At the time of the final analysis in August 2017, 101/117 patients had died (86.3%): 77 (85.5%) in arm A and 24 (88.9%) in arm B. Twenty-seven patients (18.6%) terminated the study treatment before the end of the run-in phase. For those, physician's decision and tumour progression were the most common reasons ($n = 6$, 22.2% respectively), followed by patient's wish and death from any cause ($n = 5$, 18.5%, respectively), adverse events ($n = 3$, 11.1%) and other reasons ($n = 2$, 7.4%). After the end of run-in phase, median treatment duration was 3.7 months for gem/erlotinib and 3.0 months for FOLFIRINOX.

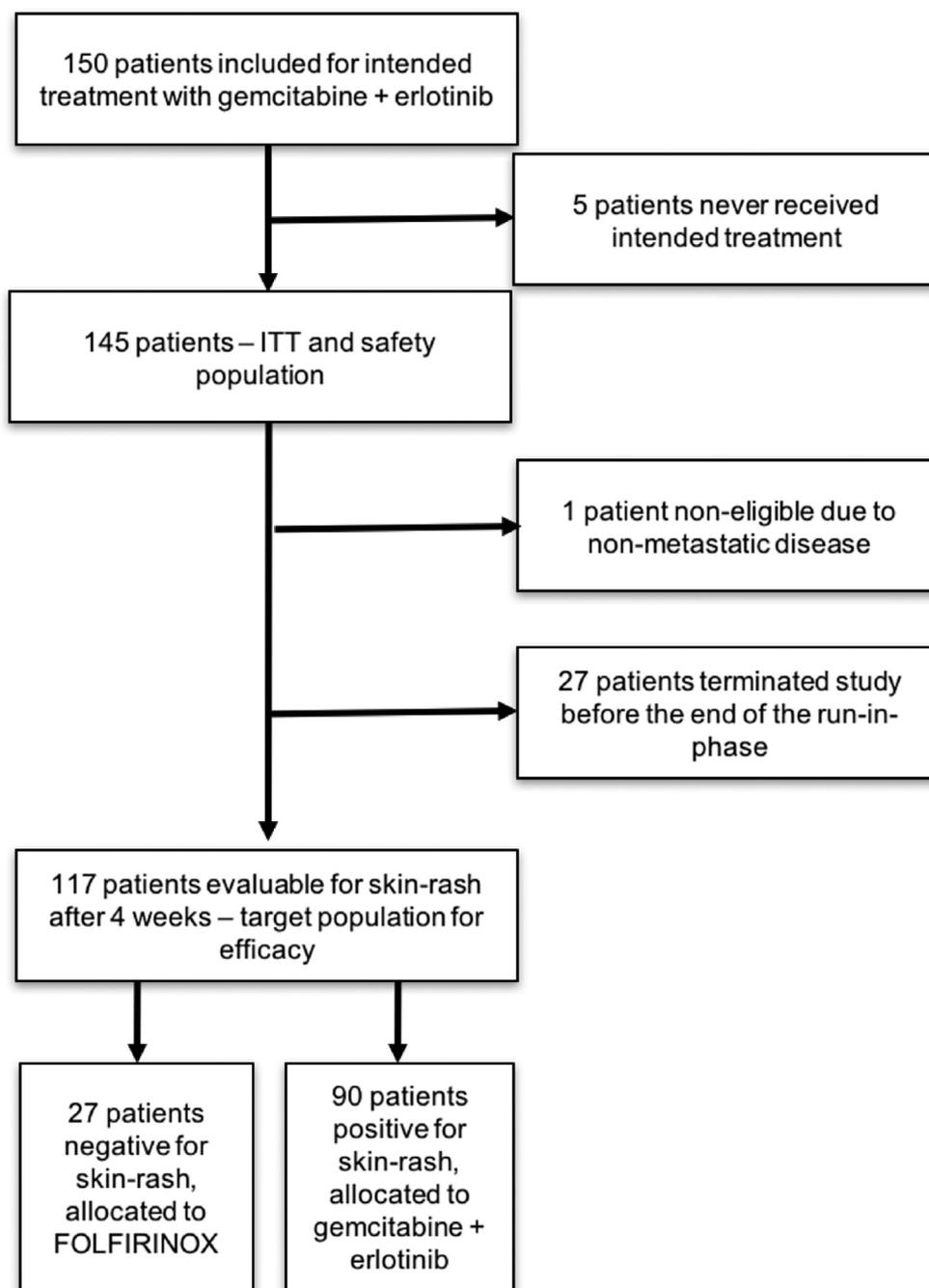


Fig. 1. CONSORT diagram. ITT, intention to treat.

3.2. Efficacy and safety

The 1-year survival rate for patients treated with gem/erlotinib developing skin rash of any grade during a 4-week run-in phase ($n = 90$) was 40.0% (95% CI 29.8–50.9) and therefore, reached the primary study end-point (Table 2). The 1-year survival rate of patients negative for skin rash ($n = 27$), who were switched to FOLFIRINOX, was 48.1% (95% CI 28.7–68.1). The corresponding median OS times were 10.1 months in arm A and 10.9 months in arm B (see Fig. 2a). PFS was estimated with 3.8 months in arm A

versus 6.6 months in arm B (Fig. 2b). The objective response rate was 23.3% for gem/erlotinib versus 33.3% for patients who continued with FOLFIRINOX. There were no significant differences in terms of efficacy between arm A and arm B, although the analyses only have explorative character as the study was not designed for a direct comparison between the two treatment strategies. The safety profiles of gem/erlotinib and FOLFIRINOX were within the expected range of the individual study drugs; details on toxicity data within the safety population are summarised in Table 3.

Table 1
Patient baseline characteristics (n = 145).

Parameter	n	%
Age (years)		
Median	62.3	
Range	24–75	
Gender		
Male	87	60
Female	58	40
Primary tumour location		
Head	66	46
Body	25	17
Tail	40	28
Diverse locations	14	10
Localisation of metastases		
Liver	119	83
Lung	36	25
Other	78	54
ECOG Performance Status		
0	88	61
1	57	39
Previous treatment		
Previous surgery	12	8.3
Previous adjuvant therapy	4	2.8

ECOG, Eastern Cooperative Oncology Group.

3.3. Follow-up and salvage therapy

Of the 90 patients deemed rash-positive at the end of the run-in phase (target population), 62% of the patients received further treatment after failure of gem/erlotinib. In 41.8% of cases, FOLFOX was used, followed by FOLFIRINOX in 34.5% of patients, gemcitabine plus nab-paclitaxel in 10.9%, nab-paclitaxel alone in 3.6%, as well as single-agent capecitabine, 5-FU/folinic acid, gemcitabine plus oxaliplatin and FOLFIRI in 1.8% each, respectively. Salvage therapies after FOLFIRINOX were applied in 59.2% of patients. These consisted in gemcitabine plus nab-paclitaxel in 75% of patients and in gemcitabine alone in 25% of cases.

3.4. Quality of life analyses

At baseline, 92.2% of completed QLQ-C30 questionnaires were available ($n = 84$ in the gem/erlotinib group, $n = 23$ in the FOLFIRINOX group). Patients who turned out to be negative for skin rash and were consecutively treated with FOLFIRINOX reported a significantly worse global health status (QL-2) score (median 50.0 versus 41.7 points, $p = 0.004$), physical functioning (PF-2) score (median 86.7 versus 80.0 points, $p = 0.021$), emotional functioning score (median 58.3 versus 41.7 points, $p = 0.003$) and cognitive functioning score (median 83.3 versus 66.7 points, $p = 0.008$). These patients furthermore reported a higher burden of symptoms specifically regarding fatigue (median 55.6 versus 33.3 points, $p = 0.003$) and pain (66.7 versus 33.3 points, $p = 0.005$).

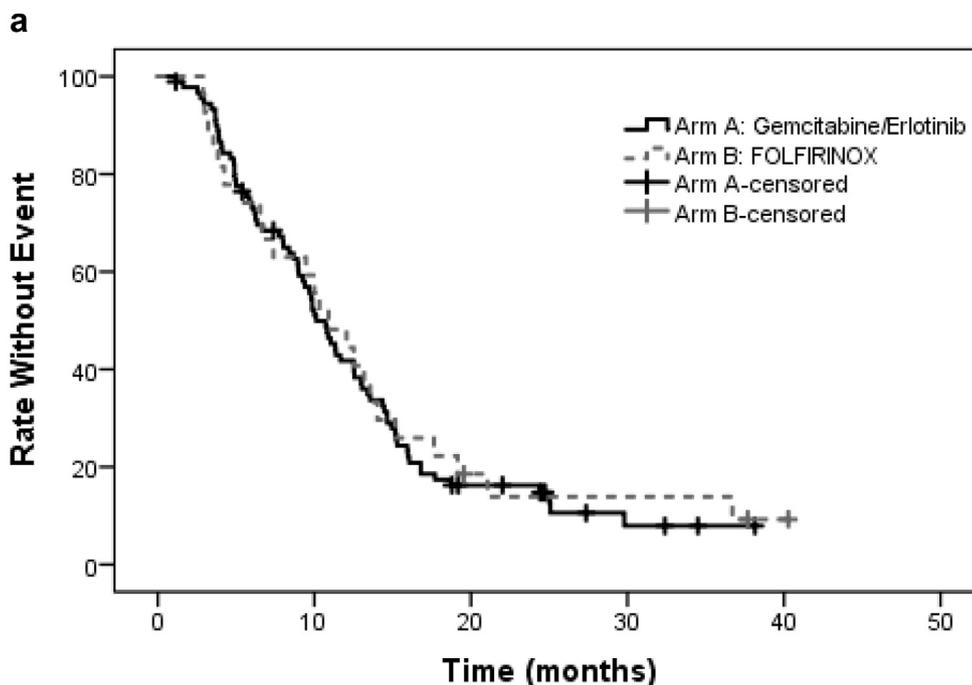
For the longitudinal analysis, at least one further questionnaire was available from 92.2% of patients ($n = 84$ in the gem/erlotinib group, $n = 23$ in the FOLFIRINOX group). The items were evaluated concerning differences in minimum/maximum during study therapy, minimal and maximal improvement/deterioration from baseline and time to definitive deterioration ≥ 10 and 20 points. Patients treated with FOLFIRINOX experienced a higher maximum relief from pain (median -25.0 points versus -16.7 points, $p = 0.049$) and a lower median deterioration of pain (0 points versus $+16.7$ points, $p = 0.012$). A significantly lower proportion of patients reached the end-point ‘time to definitive deterioration of pain ≥ 20 scores’ (10.0% versus 41.8%); the median was ‘not reached’ in the FOLFIRINOX group versus 5.6 months in the gem/erlotinib group (HR 0.22, 95% CI 0.05–0.90, $p = 0.021$). Comparably, a lower proportion of patients in the FOLFIRINOX group (20.0% versus 43.6%) reached the end-point ‘time to definitive deterioration ≥ 20 points for the global health status—QL2’, although the median time was not significantly different (‘not reached’ versus 5.2 months, HR 0.46, 95% CI 0.16–1.30, $p = 0.133$). All other items of

Table 2
Efficacy end-points.

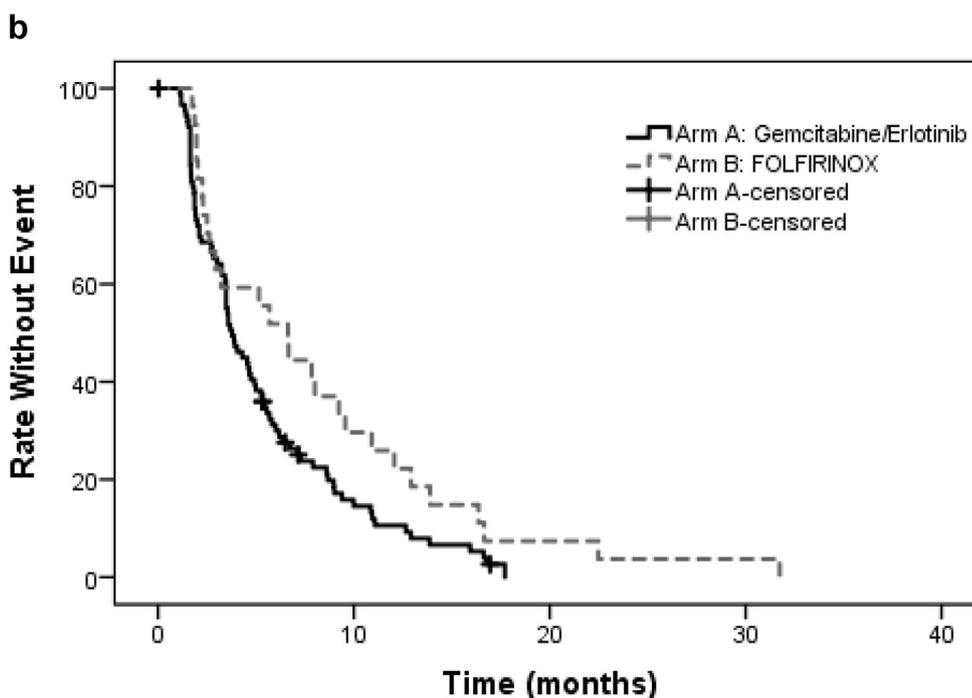
Efficacy variable	Gem/erlotinib $n = 90$	FOLFIRINOX $n = 27$	HR/OR (95% CI)	p -value
1-year survival rate no. (% [95% CI])	36 (40.0 [29.8–50.9])	13 (48.1 [28.7–68.1])	0.72 (0.30–1.71) ^a	0.51 ^a
Overall response rate (ORR) no. (%)	21 (23.3)	9 (33.3)	0.61 (0.24–1.55) ^a	0.32 ^a
Progression free survival (PFS), months	3.8	6.6	0.64 (0.41–1.01) ^a	0.05 ^a
Overall survival (OS), months	10.1	10.9	0.93 (0.59–1.48) ^a	0.76 ^a
OS according to grades of rash, no., months				
Grade 1	$n = 37$; 10.7			
Grade 2	$n = 42$; 10.1			
Grade 3	$n = 11$; 11.3			0.85 ^a

HR, hazard ratio; CI, confidence interval; OR, odds ratio.

^a Explorative analysis.



Overall survival: 10.1 vs. 10.9 months



Progression-free survival: 3.8 vs. 6.6 months

Fig. 2. Overall survival and progression-free survival.

the QLQ-C30 questionnaire did not show significant differences in the longitudinal analysis.

4. Discussion

The primary study end-point, a 1-year survival rate of $\geq 40\%$ for pre-selected mPDAC patients showing skin

rash during treatment with gem/erlotinib, was reached, with a median OS of 10.1 months. These data are within the range of the effectiveness previously reported for FOLFIRINOX by Conroy et al. [11], with a 1-year survival rate of 48.4% and a median survival time of 11.1 months, and are obviously beyond the numbers reported for the pivotal PA.3 trial by Moore et al. with a

Table 3
Toxicity.

Toxicity event	Gem/erlotinib <i>n</i> = 145						FOLFIRINOX <i>n</i> = 28				
	Grade— <i>n</i> (%)						Grade— <i>n</i> (%)				
	1	2	3	4	5	All	1	2	3	4	All
Anaemia	65 (45)	52 (36)	17 (12)	2 (1)		136 (94)	13 (46)	9 (32)	3 (11)	1 (4)	26 (93)
Thrombocytopenia	66 (46)	21 (15)	9 (6)			96 (66)	13 (46)	1 (4)			14 (50)
Neutropenia	1 (1)	8 (6)	27 (19)	4 (3)		40 (28)	2 (7)	3 (11)	1 (4)	2 (7)	8 (29)
Febrile neutropenia			2 (1)			2 (1)			1 (4)		1 (4)
Infections	10 (7)	16 (11)	28 (19)		1 (1)	55 (38)	2 (7)	1 (4)	3 (11)		6 (21)
Nausea	50 (35)	27 (19)	7 (5)			84 (58)	11 (39)	7 (25)	5 (18)		23 (82)
Vomiting	23 (16)	9 (6)	8 (6)			40 (28)	4 (14)	6 (21)	3 (11)		13 (46)
Elevation of liver enzymes (ALT ^a)	65 (45)	28 (19)	23 (16)	2 (1)		118 (81)	16 (57)	2 (7)	2 (7)		20 (71)
Mucositis/stomatitis	20 (14)	4 (3)	2 (1)			26 (18)	6 (21)	2 (7)			8 (29)
Diarrhoea	46 (32)	11 (8)	2 (1)	1 (1)		60 (41.0)	8 (29)	6 (21)			14 (50)
Pneumonitis			1 (1)			1 (1)					0 (0)
Sensory neuropathy	12 (8)	5 (3)	1 (1)			18 (12)	6 (22)	9 (32)	2 (7)		16 (57)
Skin rash	40 (28)	43 (30)	11 (8)			94 (65)	2 ^b (7)				2 ^b (7)

^a Alanine aminotransferase.

^b Documented as ‘associated to erlotinib’ after the end of run-in-phase.

1-year survival rate of 23% and a median OS of 6.24 months for PDAC patients treated with gem/erlotinib [7]. The observation that occurrence of skin rash during treatment with erlotinib might be predictive for better OS in advanced PDAC has been reported by several groups [7,9,10]. However, all these reports evaluated skin rash in a retrospective setting.

The only prospective approach was the Spanish ‘Pan-tar’ trial by Aranda et al. evaluating the efficacy of gem/erlotinib in 153 patients with locally advanced or mPDAC. Patients were divided by the appearance of skin rash \geq grade 2 (25% of patients) versus grade 1/no skin rash (75% of patients). A clear advantage in terms of efficacy was found for the rash \geq grade 2 group with a median OS of 11 months versus 5 months, a PFS of 6 months versus 3 months and an objective response rate of 21% versus 7% [12]. However, setting the cut-off for a skin rash \geq grade 2 has led to a relatively small group of only 38 patients showing a significant rash (25%). Furthermore, as the grades of skin rash were defined by the percentage of affected body surface area and were determined by the respective local investigator, allocating patients to a grade of rash sometimes seems difficult and rather arbitrary in clinical practice. We therefore chose a more reliable approach in our trial in characterising groups by skin rash of any grade versus no rash. The fact that patients must have shown skin rash during a pre-defined induction period (first 4 weeks) and were subsequently classified as rash-positive or rash-negative furthermore reduced the ‘guarantee-time bias’ to a minimum, meaning that we avoided classifying patients as rash-positive at a late time point while other patients would not reach that time point [13]. Multiple factors have previously been discussed why some patients develop skin rash and others do not. A higher incidence of skin rash was described for patients aged <65 years and with better performance status [7,14].

Several authors discussed pharmacological and especially pharmacodynamic population-based varieties leading to different levels of erlotinib and its active agents in patient plasma and therefore influencing efficacy and toxicity [15–17]. More recently, Noll et al. described an ‘exocrine-like subtype’ of PDAC with higher activity of cytochrome P450-3A5 leading to resistance against small-molecule inhibitors such as erlotinib and also paclitaxel [18]. Other hypotheses on the appearance of skin rash were based on polymorphisms in the EGFR gene [19] or special HLA-types [20]. However, to date, there is no other predictive factor for the efficacy of erlotinib than skin rash.

Patients who were negative for skin rash and subsequently switched to FOLFIRINOX showed an OS of 10.9 months in the study presented here. This is remarkable as these patients had formally been reported to have an extremely poor prognosis with median OS times of 3.3–4.8 months only [7,9,10]. Although the analyses for arm B only have an explorative character due to the study design, FOLFIRINOX for rash-negative patients appears to be more effective than gem/erlotinib in rash-positive patients in terms of PFS (6.6 versus 3.8 months) and overall response rate (33.3 versus 23.3%). Furthermore, rash-negative patients had a lower quality of life and higher symptom burden in several items according to the QLQ-C30 questionnaire at baseline. During the intensified treatment with FOLFIRINOX, these patients did not show a worsening in quality of life, but in contrast, a remarkable higher relief in terms of pain compared with patients who continued gem/erlotinib was reported. A significant difference in haematological toxicity and especially febrile neutropenia could not be detected between the treatment regimens (as far as comparable); there was only—as expected—a higher rate of adverse events in terms of nausea/vomiting and sensory neuropathy for FOLFIRINOX. As reported for the

PRODIGE4/ACCORD 11 trial [21], patients' quality of life improved during the intensified FOLFIRINOX treatment in our study as well.

Considering the relatively small difference in OS in comparison to the obvious gap in PFS and objective response in arm A and arm B, we took a close look at the subsequent treatment regimens. In both arms, a further treatment line was applied in around 60% of patients, mainly consisting of 5-FU-based protocols after gem/erlotinib and of gemcitabine plus nab-paclitaxel or single-agent gemcitabine after FOLFIRINOX. In arm A, FOLFIRINOX consisting of all agents was given to 20 patients (22%), to 19 patients in second-line and to one patient even in the fourth-line setting. Furthermore, 18 patients (20%) received the combination of gemcitabine plus nab-paclitaxel, six in second-line, 11 in third-line and one within the fourth-line setting, with a major share of patients receiving this combination in the third-line after failure of FOLFIRINOX in the second-line. The relatively high rate of salvage treatment certainly contributed to the rather favourable outcome of rash-positive patients treated with gem/erlotinib in first-line, but is certainly not the main factor.

A limitation of the present investigation is that because of the adaptive approach, the study was not powered for a direct comparison between treatment arms. Comparative analyses regarding efficacy, quality of life and toxicity, therefore, have only explorative character. Although it was possible to achieve an OS beyond 10 months for the selected rash-positive population, it needs to be kept in mind that 27 patients left the trial before the end of the run-in phase was reached. These patients had a dismal 1-year survival rate of only 14% (OS 3.6 months). However, the 145 patients within the safety population still had an OS of 9.7 months.

5. Conclusions

First-line chemotherapy with gem/erlotinib was applied to rash-positive mPDAC patients deemed to be fit for intensive combination chemotherapy and achieved a 1-year survival rate comparable to that previously reported for FOLFIRINOX. For patients who emerged to be rash-negative, FOLFIRINOX was a successful treatment option.

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Conflict of interest statement

Michael Haas has received honoraria from Celgene, research funding from Boehringer Ingelheim and Roche

(Institution) and travel and accommodation expenses from Boehringer Ingelheim. Ludwig Fischer von Weikersthal is a consultant or advisor for Roche and received honoraria from Pfizer and travel and accommodation expenses from Amgen, Pfizer and Roche. Anke C. Reinacher-Schick is a consultant or advisor for Amgen, Baxalta, Merck Serono, Pfizer, Roche, Sanofi and Servier and received honoraria from Amgen, Baxalta, Celgene, Merck Serono, Pfizer, Roche and Sanofi and research funding from Celgene, Roche and Sanofi. Volker Heinemann is a consultant or advisor for Amgen, Baxalta, Boehringer Ingelheim, Celgene, Merck, Roche, Sanofi and Sirtex Medical and received honoraria from Amgen, Baxalta, Celgene, Merck, Roche, Sanofi and Sirtex Medical, research funding from Amgen, Bayer, Boehringer Ingelheim, Celgene, IntegraGen, Merck, Roche, Sanofi, Sirtex Medical and Taiho Pharmaceutical and travel and accommodation expenses from Amgen, Baxalta, Merck, Roche and Sirtex Medical. Stefan H. Boeck is a consultant or advisor for Baxalta and Celgene and received honoraria from Celgene, research funding from Celgene, Clovis Oncology and Roche and travel and accommodation expenses from Celgene and Roche. The other authors have no conflict of interest to disclose.

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