# Erlotinib 150 mg daily plus chemotherapy in advanced pancreatic cancer: an interim safety analysis of a multicenter, randomized, cross-over phase III trial of the 'Arbeitsgemeinschaft Internistische Onkologie'

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**To date, only limited toxicity data are available for the combination of erlotinib with either capecitabine or gemcitabine as front-line therapy for advanced pancreatic cancer. Within a randomized phase III trial, 281 treatment-naive patients were randomly assigned between capecitabine (2000 mg/m$^2$/day, for 14 days, once every 3 weeks) plus erlotinib (150 mg/day, arm A) and gemcitabine (1000 mg/m$^2$ as a 30-min infusion) plus erlotinib (150 mg/day, arm B). In case of treatment failure, patients were crossed over to a second-line treatment with the comparator cytostatic drug without erlotinib. The primary study endpoint was the time to treatment failure of second-line therapy (TTF2). This interim analysis of toxicity contains safety data from the first 127 randomized patients. During first-line therapy, patients received a median number of three treatment cycles (range 0–13) in both the arms. Regarding chemotherapy, a treatment delay was observed in 12% of the cycles in arm A and in 22% of the cycles in arm B. Dose reductions of the cytostatic drug were performed in 18 and 27% of treatment cycles, respectively. Erlotinib dose reductions were performed in 6 and 11% of all cycles. Grade 3/4 hematological toxicity was <10% in both the arms; major grade 3/4 toxicities in arms A and B were diarrhea (9 vs. 7%), skin rash (4 vs. 12%), and hand–foot syndrome (7 vs. 0%). No treatment-related death was observed. In conclusion, this interim safety analysis suggests that treatment with erlotinib 150 mg/day is feasible in combination with capecitabine or gemcitabine.** ***Anti-Cancer Drugs*** **21:94–100 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

**Anti-Cancer Drugs** 2010, **21**:94–100

**Keywords: capecitabine, erlotinib, gemcitabine, pancreatic cancer**

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**Received** 19 June 2009 **Revised form accepted** 23 July 2009

## Introduction

Advanced exocrine pancreatic cancer (PC) still remains a highly malignant disease with a nearly identical annual incidence and mortality rate [1]. Since the nucleoside analog gemcitabine was established as a standard of care for patients with advanced PC (locally advanced and metastatic disease) in 1997, several large phase III trials have been conducted to improve the therapeutic efficacy of systemic therapy for PC [2,3]. Moore *et al.* [4] were the first to demonstrate a statistically significant, but clinically moderate-survival benefit for gemcitabine-based combination therapy (using the oral anti-EGFR tyrosine kinase inhibitor erlotinib) compared with single-agent gemcitabine. Promising efficacy data for combination chemotherapy were also obtained from randomized trials investigating the addition of capecitabine or a platinum analog to standard gemcitabine [5–10]. However, a significant overall survival benefit for one of these

Part of this work was previously presented at the 45th Annual Meeting of the American Society of Clinical Oncology, 29 May – 2 June 2009, Orlando, Florida, USA.

0959-4973 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e32833123ed

combination chemotherapy protocols still has not been proven, although meta-analysis data found evidence for a possible improvement in survival with the use of platinum-containing combination treatment for advanced PC [9,11].

The combination of gemcitabine and erlotinib (100 mg/day) received US regulatory approval from the FDA in November 2005 for first-line treatment of advanced PC. In the European Union, the same gemcitabine/erlotinib regimen was approved in January 2007 – based on a post-hoc subgroup analysis – only for the treatment of metastatic PC. Within the pivotal phase III study ($n = 569$), a small group of patients ($n = 23$) was treated with an increased dose level of erlotinib (150 mg/day). The fact that in this cohort, 11 patients (48%) required protocol-prescribed dose reductions for toxicity led to the recommendation of the 100 mg daily dose for erlotinib in advanced PC [4]. In contrast, the investigated doses of erlotinib in phase III trials for non-small-cell lung cancer (monotherapy and combination therapy) were 150 mg daily [12,13]. In addition, a phase I b clinical trial in patients with nonresectable PC and other advanced solid malignancies found the combination of standard gemcitabine and 150 mg erlotinib daily to be tolerated well [14]. The rationale of combining erlotinib with the oral fluoropyrimidine capecitabine is based on synergistic preclinical data and on efficacy and safety data derived from a single second-line phase II study in gemcitabine-pretreated PC patients [15,16]. Phase II studies investigating a combination of capecitabine and erlotinib in gastrointestinal malignancies used a total dose of 2000 mg/m$^2$/day capecitabine for 14 days (followed by 1 week rest) together with a daily dose of 150 mg erlotinib [16,17]. However, there are only limited safety data available for the capecitabine/erlotinib combination to date and to the best of our knowledge, no study investigating this regimen as a first-line treatment for PC has been presented yet. Especially, the overlapping toxicity profile of capecitabine and erlotinib (with regard to skin and gastrointestinal toxicity) will require an adequate safety evaluation of this all-oral regimen as palliative treatment option for patients with advanced PC.

The primary aim of this interim safety analysis from a multicenter randomized phase III trial was to evaluate the toxicity profiles of the capecitabine plus erlotinib and the gemcitabine plus erlotinib regimen as first-line therapy for advanced PC, with the use of an erlotinib dose of 150 mg daily in both treatment arms.

## Patients and methods

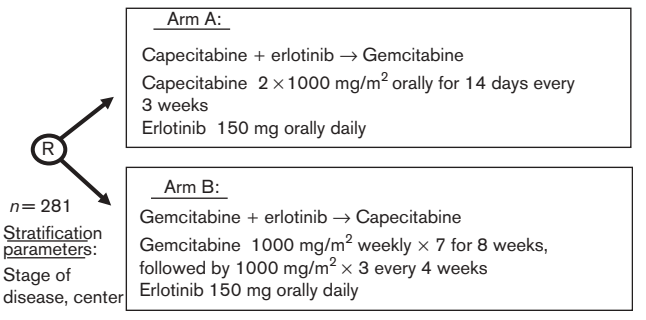
### Patient population

For this phase III trial, male or female patients between 18 and 75 years of age with a histologically confirmed diagnosis of advanced exocrine PC (stage III and IV) were eligible. All patients with previous chemotherapy or radiotherapy were excluded, for study participation a Karnofsky performance status of $\geq 60\%$ was required. Adequate organ function was defined as follows: bone marrow function, absolute neutrophil granulocyte count greater than $1.5 \times 10^9$/l, hemoglobin greater than 8 g/dl, thrombocytes greater than $100 \times 10^9$/l; renal function, serum creatinine $\leq 1.25 \times$ upper limit of normal (ULN), calculated creatinine clearance greater than 30 ml/min; hepatic function, serum bilirubin $\leq 2 \times$ ULN (in case of liver metastasis: $\leq 5 \times$ ULN), aspartate aminotransferase/alanine aminotransferase $\leq 2.5 \times$ ULN (in case of liver metastasis: $\leq 5 \times$ ULN). Exclusion criteria included pregnant or lactating females, women of childbearing potential who lacked a reliable contraceptive method, patients with a history of severe psychiatric disorders, preexisting polyneuropathy, and active infections. Patients who participated in another experimental clinical trial within 4 weeks of the start of treatment were ineligible. The study had approval of the ethics committees in all participating German centers and each patient gave written informed consent before any study-specific procedure. This study was conducted according to the GCP/ICH guidelines and according to the Declaration of Helsinki.

### Study design and treatment

In this prospective, multicenter, cross-over phase III trial, patients were randomized in a 1 : 1 ratio to the two treatment arms, after stratification for stage (locally advanced vs. metastatic disease) and center. Originally, this randomized study was designed to evaluate a sequential treatment of gemcitabine followed by capecitabine versus capecitabine followed by gemcitabine for advanced PC. In case of failure of first-line chemotherapy (e.g. disease progression or toxicity), patients were 'crossed over' to a pre-defined second-line treatment using the cytostatic drug of the comparator treatment arm. After erlotinib received FDA-regulatory approval in the US, the study was amended in March 2006 to include erlotinib in both treatment arms during first-line therapy (Fig. 1).

**Fig. 1**




Study design and treatment protocol after amendment 1.

The primary study objective was a noninferiority comparison of the two treatment arms with regard to time-to-treatment failure after second-line therapy (TTF2). Secondary endpoints included TTF1, objective response (determined by the RECIST), overall survival, CA 19-9 tumor marker response, clinical benefit response, quality of life, and toxicity. This trial was registered at *www.clinicaltrials.gov* (trial identifier: NCT00440167).

After amendment 1, patients randomized to study arm A received first-line therapy with oral capecitabine (1000 mg/m$^2$ twice daily for 2 weeks, followed by 1week rest) and erlotinib (150 mg daily); in case of treatment failure, second-line therapy with single-agent gemcitabine (1000 mg/m$^2$ intravenously over 30 min weekly, similar to that used in the study by Burris *et al.* [3]) was offered to the participating patients. Within treatment arm B, patients received first-line chemotherapy with gemcitabine (1000 mg/m$^2$ intravenously over 30 min weekly, similar to that used in the study by Burris *et al.* [3]) in combination with erlotinib (150 mg daily); in case of treatment failure, second-line therapy with single-agent capecitabine (1000 mg/m$^2$ twice daily for 2 weeks, followed by 1 week rest) was initiated (Fig. 1). In patients with preexisting renal insufficiency (defined by a calculated creatinine clearance of 30–50 ml/min), the capecitabine starting dose was reduced to 75% in both the arms. Treatment continued until disease progression or unacceptable toxicity.

If necessary, protocol-defined dose reductions were performed according to the clinical and laboratory parameters. Supportive treatment (e.g. antiemetic therapy) was administered according to the local standards of the participating centers. Unique, study-specific recommendations for therapy of treatment-associated skin rash and diarrhea were included in the study protocol, and the participating centers were advised to follow these recommendations for optimal supportive therapy.

### Safety evaluation

Pretreatment evaluation included complete history and physical examination, assessment of vital signs, Karnofsky performance status, disease symptoms/quality of life, and a computed tomography scan of the abdomen. Regularly performed laboratory tests included blood counts, creatinine, liver enzymes, total bilirubin, alkaline phosphatase, total protein, albumin, and CA19-9. Toxicity was assessed on day 1 of each treatment cycle and classified according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), Version 2.0.

### Statistical analyses

The main objective of this interim analysis was to evaluate the safety and tolerability of the study treatment, especially with regard to the combination of gemcitabine with erlotinib 150 mg daily and to the combination of capecitabine plus erlotinib for front-line therapy of advanced PC. All toxicity data collected until December 2008 of the first 127 randomized patients (after amendment 1) were taken into account.

## Results

### Patient characteristics

Overall, 328 patients from 46 German centers were randomized in this phase III trial between May 2004 and December 2008. After amendment 1281 patients were randomized since May 2006; all of them received erlotinib during first-line treatment. The first 127 patients of these 281 patients are included in this interim analysis for treatment and safety parameters. Clinical baseline characteristics of these 127 PC patients are summarized in Table 1. The two treatment groups for the current interim toxicity analysis were well balanced with regard to age, stage of disease, and performance status. Most of the included patients suffered from pancreatic adenocarcinoma (95%) and only 8% of study participants underwent previous surgical pancreatic resection.

### Treatment

During first-line therapy, patients received a median number of three treatment cycles (range 0–13) in both the arms; overall 456 first-line treatment cycles were applied (arm A: 218, arm B: 238). In the second-line setting, a median number of two treatment cycles (range 1–7) was applied in both the arms, patients in arm A received 77 second-line chemotherapy cycles and patients in arm B received 50 second-line chemotherapy cycles. At the time of this interim analysis, 98 patients

**Table 1 Characteristics of evaluable patients ($n=127$)**

| | Capecitabine + erlotinib (arm A) | | Gemcitabine + erlotinib (arm B) | |
|---|---|---|---|---|
| Treatment arm | *N* | % | *N* | % |
| Evaluable patients | 60 | | 67 | |
| Age (years) | | | | |
| Median | 66 | | 63 | |
| Range | 44–75 | | 38–75 | |
| Sex | | | | |
| Male | 33 | 55 | 38 | 57 |
| Female | 27 | 45 | 29 | 43 |
| Stage of disease | | | | |
| Locally advanced | 10 | 17 | 12 | 18 |
| Metastatic | 50 | 83 | 55 | 82 |
| Performance status | | | | |
| KPS 60–80% | 20 | 33 | 18 | 27 |
| KPS 90–100% | 32 | 53 | 38 | 57 |
| Missing | 8 | 13 | 11 | 16 |
| Weight loss during 3 months before randomization (kg) | | | | |
| Median | 6.5 | | 5 | |
| Range | 0–45 | | 0–30 | |
| Smoking status | | | | |
| Active smoker | 17 | 28 | 15 | 22 |
| Former smoker | 12 | 20 | 9 | 13 |
| Never smoker | 29 | 48 | 33 | 49 |
| Unknown | 2 | 3 | 10 | 15 |

KPS, Karnofsky performance status.

(77%) had completed first-line therapy and 42 patients (33%) had completed second-line chemotherapy. The main reasons for termination of first-line study treatment were disease progression (51%), tumor-related death (12%), patient refusal (7%), and toxicity (6%). In the second-line treatment arms, most patients discontinued study therapy because of progressive disease (60%), followed by tumor-related death (26%), and patient refusal (5%). Only one of 42 patients (2%) discontinued second-line chemotherapy because of unacceptable toxicity.

### Treatment delay and dose reduction

A detailed analysis of treatment delay and dose reduction of the study medication (separately analyzed with regard to chemotherapy vs. erlotinib treatment, first-line vs. second-line therapy) is summarized in Table 2. In addition, results are grouped by treatment arm (A vs. B) and were calculated on the basis of the number of applied treatment cycles in each arm. In general, dose modifications were rare in both treatment arms, with regard to both the cytotoxic agents and erlotinib (Table 2). On the basis of a per patient analysis, erlotinib dose reductions were performed in 7% of patients treated in arm A and in 14% of patients treated in arm B. In the second-line setting, the number of treatment delays and chemotherapy dose reductions was not increased compared with the data obtained from first-line combination treatment with a cyctotoxic agent (capecitabine or gemcitabine) plus erlotinib.

The main reasons for dose reduction during first-line chemotherapy were myelosuppression [six of 218 cycles (3%) in arm A vs. 53 of 238 cycles (22%) in arm B], hand–foot syndrome (9 vs. 0%) and diarrhea (3 vs. 1%).

**Table 2 Treatment modifications during study therapy (by number of applied treatment cycles)**

| | Capecitabine + erlotinib →gemcitabine (arm A) | | Gemcitabine + erlotinib →capecitabine (arm B) | |
|---|---|---|---|---|
| Treatment arm | No. of cycles | % | No. of cycles | % |
| Treatment delay during first-line chemotherapy | | | | |
| Yes | 25 | 12 | 52 | 22 |
| No | 192 | 88 | 182 | 78 |
| Dose reductions during first-line chemotherapy | | | | |
| Yes | 38 | 18 | 63 | 27 |
| No | 177 | 82 | 170 | 73 |
| Treatment delay during first-line erlotinib therapy | | | | |
| Yes | 25 | 12 | 52 | 22 |
| No | 192 | 88 | 182 | 78 |
| Dose reductions during first-line erlotinib therapy | | | | |
| Yes | 12 | 6 | 24 | 11 |
| No | 201 | 94 | 200 | 89 |
| Treatment delay during second-line chemotherapy | | | | |
| Yes | 27 | 35 | 13 | 28 |
| No | 50 | 65 | 34 | 72 |
| Dose reductions during second-line chemotherapy | | | | |
| Yes | 11 | 15 | 3 | 7 |
| No | 64 | 85 | 43 | 93 |

Regarding erlotinib treatment, the two main reasons for dose reduction were skin rash [eight of 218 cycles (4%) in arm A vs. 11 of 238 cycles (5%) in arm B] and diarrhea (2 vs. 4%). During second-line chemotherapy, dose reductions in patients receiving single-agent gemcitabine (arm A) were mainly related to myelosuppression (seven of 77 cycles, 9%), whereas in patients receiving salvage treatment with single-agent capecitabine (arm B) the main reason for a capecitabine dose reduction was hand–foot syndrome (two of 50 cycles, 4%).

### Safety results

#### *Toxicity during first-line therapy (Table 3)*

Detailed interim toxicity data (hematological and non-hematological toxicity) for both the treatment arms are shown in Table 3. Entire safety data for first-line therapy were available for 56 patients in arm A and for 58 patients in arm B. In the gemcitabine-containing treatment arm, a higher rate of hematological toxicity was observed (grade 3/4: $< 10\%$ in both the arms), gastrointestinal toxicity was comparable between arm A and arm B. Acneiform skin rash (grade 1–4) during erlotinib treatment occurred in more than 60% of study patients in both the arms, with most events being grade 1 or grade 2.

#### *Toxicity during second-line therapy (Table 4)*

The preliminary safety data for second-line chemotherapy are summarized in Table 4. Hematological and nonhematological toxicity data were available for 28 patients (arm A) and 21 patients (arm B). Second-line treatment was also tolerated well; hematological toxicity (mostly grade 1/2) was pronounced in patients receiving salvage chemotherapy with single-agent gemcitabine (arm A).

### Early death

Nine patients in arm A (15%) and eight patients in arm B (12%) died within 60 days after randomization. In arm A, seven of nine patients (78%) died because of PC, one patient because of pulmonary embolism and one patient because of suicide. In treatment arm B, six of eight deaths (75%) were classified as tumor-related, whereas one patient died because of pulmonary embolism and one patient because of sepsis/fever of unknown origin.

## Discussion

On the basis of the landmark trial by Moore *et al.* [4], gemcitabine in combination with the anti-EGFR tyrosine kinase inhibitor erlotinib is regarded as a new treatment option for patients with metastatic PC in the European Union. The safety data obtained in that trial led to a recommended erlotinib dose of 100 mg per day. As a higher dose of erlotinib was regarded safe in non-small-cell lung cancer, we investigated chemotherapy either with capecitabine or gemcitabine in combination with erlotinib 150 mg per day in PC. An interim safety analysis of our multicenter phase III Arbeitsgemeinschaft Internistische Onkologie (AIO) study provides a different

**Table 3 Toxicity results according to NCI-CTC, Version 2.0 (first-line therapy, arm A and arm B)**

| | Percentage of patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Capecitabine + erlotinib (arm A) ($n=56$) Grade | | | | | Gemcitabine + erlotinib (arm B) ($n=58$) Grade | | | | |
| Toxicity | 1 | 2 | 3 | 4 | All | 1 | 2 | 3 | 4 | All |
| Leukocytopenia | 4 | 5 | 0 | 0 | 9 | 31 | 26 | 5 | 0 | 62 |
| Thrombocytopenia | 2 | 0 | 2 | 0 | 4 | 19 | 16 | 3 | 0 | 38 |
| Anemia | 20 | 16 | 5 | 2 | 43 | 19 | 29 | 3 | 3 | 54 |
| Infection | 5 | 9 | 9 | 2 | 25 | 7 | 16 | 16 | 2 | 41 |
| Diarrhea | 27 | 23 | 7 | 2 | 59 | 21 | 19 | 5 | 2 | 47 |
| Nausea | 18 | 34 | 4 | 0 | 56 | 38 | 22 | 3 | 0 | 63 |
| Vomiting | 20 | 14 | 4 | 0 | 38 | 24 | 10 | 2 | 0 | 36 |
| Stomatitis | 29 | 7 | 4 | 0 | 40 | 14 | 7 | 2 | 0 | 23 |
| Skin rash | 36 | 21 | 2 | 2 | 61 | 21 | 33 | 10 | 2 | 66 |
| Hand–foot syndrome | 18 | 7 | 7 | 0 | 32 | 10 | 3 | 0 | 0 | 13 |

**Table 4 Toxicity results according to NCI-CTC, Version 2.0 (second-line therapy, arm A and arm B)**

| | Percentage of patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Gemcitabine (arm A) ($n=28$) Grade | | | | | Capecitabine (arm B) ($n=21$) Grade | | | | |
| Toxicity | 1 | 2 | 3 | 4 | All | 1 | 2 | 3 | 4 | All |
| Leukocytopenia | 21 | 21 | 4 | 0 | 46 | 10 | 5 | 0 | 0 | 15 |
| Thrombocytopenia | 11 | 7 | 4 | 0 | 22 | 0 | 0 | 5 | 0 | 5 |
| Anemia | 18 | 36 | 14 | 0 | 68 | 19 | 14 | 10 | 0 | 43 |
| Infection | 11 | 7 | 14 | 0 | 32 | 5 | 5 | 19 | 5 | 34 |
| Diarrhea | 25 | 11 | 4 | 0 | 40 | 14 | 5 | 0 | 0 | 19 |
| Nausea | 36 | 21 | 0 | 0 | 57 | 5 | 33 | 0 | 0 | 38 |
| Vomiting | 21 | 14 | 4 | 0 | 39 | 5 | 10 | 5 | 0 | 20 |
| Stomatitis | 14 | 0 | 0 | 0 | 14 | 0 | 0 | 5 | 0 | 5 |
| Skin rash | 25 | 11 | 0 | 4 | 40 | 5 | 10 | 0 | 0 | 15 |
| Hand–foot syndrome | 4 | 7 | 0 | 0 | 11 | 14 | 5 | 0 | 0 | 19 |

conclusion than the pivotal study for erlotinib: in 2007, the authors of the pivotal PC trial reported a higher incidence of erlotinib dose reductions (48 vs. 13%) because of toxic events in a subgroup of study patients receiving 150 mg erlotinib daily (vs. the 100 mg/day cohort) [4]; in the current interim toxicity evaluation of our study, a dose reduction of erlotinib during first-line combination therapy was performed in 6% (arm A) and 11% (arm B) of the applied treatment cycles, and in 7% (arm A) and 14% (arm B) of erlotinib-treated patients. Both first-line combination regimens (erlotinib either in combination with capecitabine or gemcitabine) were tolerated well in our patient population and toxicity was manageable. As expected, an increased hematological toxicity was observed in the gemcitabine-containing treatment arm, whereas the incidence of hand–foot skin reactions was more frequent in patients receiving oral capecitabine. Gastrointestinal toxicity was nearly identical between the two treatment arms during first-line therapy, confirming the data from Kulke*et al.* [16], and adding further evidence to the assumption that the addition of erlotinib does not increase gastrointestinal toxicity of capecitabine. We also found no preliminary evidence for an increase in skin toxicity with the combination of capecitabine and erlotinib (Table 3).

As shown in Table 5, the first-line gemcitabine plus erlotinib (150 mg/day) arm in the current AIO study (arm B) does not seem to result in an increased rate of hematological and nonhematological toxicity compared with the gemcitabine plus erlotinib (100 mg/day) arms in the study by Moore *et al.* [4] and the recently published AViTA trial (gemcitabine/erlotinib + placebo arm) [18]. Two phase I clinical trials investigating gemcitabine in combination with erlotinib 150 mg/day also found these regimens to be tolerated well [14,19]. Of note, with the use of erlotinib 150 mg daily (in combination with gemcitabine), we found a slight increase in the rate of grade 3/4 skin rash in our trial compared with the two earlier phase III studies published by Moore *et al.* [4] and Van Cutsem *et al.* [18] (12 vs. 6 vs. 3%; see Table 5). In addition, about 45% of patients treated in arm B developed grade 2–4 skin rash during systemic first-line therapy (compared with 25% in arm A, Table 3), and thus this subgroup of PC patients may – according to the trial by Moore *et al.* [4] – possibly derive most clinical benefit from the anti-EGFR treatment strategy.

During the last years, a significant correlation between the development of skin rash and treatment efficacy has been well established for patients receiving anti-EGFR

**Table 5 Cross-trial comparison of selected toxicity data for the gemcitabine plus erlotinib combination from three randomized phase III trials in advanced pancreatic cancer**

| | Percentage of patients | | | | | |
|---|---|---|---|---|---|---|
| | NCIC-CTG PA.3 [4] Erlotinib 100 mg ($n=282$) | | AViTA [18] Erlotinib 100 mg ($n=287$) | | AIO (current analysis) Erlotinib 150 mg ($n=58$) | |
| | Grade | | Grade | | Grade | |
| Toxicity | 1–2 | 3–4 | 1–2 | 3–4 | 1–2 | 3–4 |
| Neutropenia | NA | 24 | 9 | 17 | 36 | 12 |
| Thrombocytopenia | NA | 10 | 20 | 6 | 35 | 3 |
| Anemia | NA | NA | 24 | 9 | 48 | 7 |
| Infection | 26 | 17 | NA | NA | 22 | 17 |
| Diarrhea | 50 | 6 | 45 | 6 | 40 | 7 |
| Stomatitis | 22 | 1 | NA | NA | 21 | 2 |
| Skin rash | 66 | 6 | 41 | 3 | 53 | 12 |

AIO, Arbeitsgemeinschaft Internistische Onkologie; NA, not available.

agents for the treatment of various tumors, including PC [4,18]. In advanced colorectal cancer, early clinical trials are investigating a 'rash-adapted' dose escalation concept for anti-EGFR agents like the monoclonal antibody cetuximab [20]. In addition, in PC, a prospective randomized phase II clinical trial (the RACHEL study) with an 'erlotinib dose–escalation to rash' concept is currently ongoing [21]; in the experimental study arm, patients who do not develop skin rash (or only grade 1 rash) after 4 weeks of treatment with the standard combination of gemcitabine plus erlotinib 100 mg daily, receive increasing dose levels of erlotinib (up to a maximum of 250 mg/day) until the occurrence of grade 2 skin rash or other dose-limiting toxicities. Our data showed a good tolerability of an erlotinib dose of 150 mg daily in advanced PC, and thus support such a scientific treatment concept.

Furthermore, preliminary evidence also exists that the smoking status may influence a patients' individual erlotinib pharmacokinetics and finally may also affect tolerability and efficacy of erlotinib [22]. In the PC study population reported here, no imbalance between active and former/never smokers in both the treatment arms was observed (Table 1). A detailed subgroup analysis of possible interactions between smoking status and the efficacy and tolerability of an erlotinib-containing first-line regimen is scheduled for the final analysis of this phase III study.

To the best of our knowledge, the AIO multicenter phase III cross-over PC study is the first clinical trial that prospectively included a predefined second-line therapy for each study participant. The currently available data on second-line treatment from this trial are still limited, but preliminary toxicity findings confirm that – in selected PC patients – second-line chemotherapy with either gemcitabine (arm A) or capecitabine (arm B) is feasible and can be administered safely (Table 4). Evidence is increasing that suitable patients with advanced PC may derive significant clinical benefit from salvage chemotherapy after failure of first-line gemcitabine treatment and that fluoropyrimides in combination with oxaliplatin may become a new reference regimen for this patient population [23–26].

In conclusion, the data from this interim safety analysis of a multicenter phase III study in advanced PC suggest that both investigated first-line treatment regimens are tolerated well and that an increased erlotinib dose of 150 mg daily is feasible in combination with cyototoxic agents, for example, capecitabine and gemcitabine, in the treatment of patients with advanced PC.

## Acknowledgements

The authors thank all patients and their families, nurses, study coordinators, and investigators for their ongoing participation in this study.

Research support: Roche, Germany.

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