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Gemcitabine and nab-paclitaxel combined with afatinib in metastatic pancreatic cancer – Results of a phase 1b clinical trial

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ABSTRACT

Purpose: The combination of gemcitabine/nab-paclitaxel is an established standard treatment in the first-line treatment of metastatic ductal adenocarcinoma of the pancreas (mPDAC). Afatinib, an oral second-generation pan ErbB family tyrosine kinase inhibitor, has shown promising pre-clinical signs in the treatment of pancreatic cancer. The aim of this phase 1b trial was to determine the maximum tolerated dose (MTD) of afatinib in combination with gemcitabine/nab-paclitaxel in patients with mPDAC.

Methods: Treatment naïve patients (≥18 years) with histologically proven mPDAC and good performance status (ECOG 0/1) were enrolled to receive gemcitabine/nab-paclitaxel in combination with afatinib. Treatment was continued until disease progression, or unacceptable toxicity. The primary endpoint MTD was determined using a 3 + 3 design. Treatment started at dose level 0 with intravenous gemcitabine/nab-paclitaxel 1000 mg/m^2 / 125 mg/m^2 (day 1, 8, 15 of a 28-day cycle) + oral afatinib 30 mg daily. At dose level + 1 afatinib was increased to 40 mg. Secondary endpoints included safety parameters and exploratory endpoints evaluated treatment efficacy.

Results: Twelve patients were included in this trial, and 11 patients were treated and analysed in the safety and full analysis set (FAS). At dose level 0 the first three patients did not experience a dose-limiting toxicity (DLT). At dose leve (DL) + 1 two patients experienced a DLT. Accordingly, enrolment continued at DL 0 with three more patients, of which one experienced DLT (skin rash ≥ CTCAE grade 3). Seven patients (63.6%) experienced at least one treatment-emergent serious adverse event (TESAE), with four patients (36.4%) experiencing TESAEs grade 3–5 related to the study medication. In the FAS, the objective response rate (ORR) was 36.4%, median progression-free survival (PFS) was 3.5 months and median overall survival in nine evaluable patients was 7.5 months.

Conclusions: In this phase 1b clinical trial, the MTD of gemcitabine/nab-paclitaxel (1000 mg/m^2 / 125 mg/m^2) and afatinib (30 mg) was established. In a cohort of 11 patients, the combination showed an acceptable safety profile.

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1. Introduction

Pancreatic cancer still is associated with a dismal prognosis and most patients are diagnosed in an advanced metastatic stage [1]. In patients with good performance status, first-line palliative treatment is performed with combination therapy using either FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) or gemcitabine/nab-paclitaxel. Those regimens have shown survival benefits and improved quality of life, but treatment efficacy remains limited with poor overall survival times [2,3]. Despite increased understanding of the tumor biology, translation into more effective clinical treatments has been challenging.

Epidermal growth factor receptor (*EGFR*) overexpression is frequently observed in pancreatic cancer. Pre-clinical data indicate that ErbB signaling might play a role in tumor growth [4-6]. Therefore, targeting EGFR with a tyrosine kinase inhibitor (TKI) may exhibit therapeutic activity in (a subset of) patients with mPDAC. When combined with gemcitabine, the oral EGFR inhibitor erlotinib modestly improved overall survival over a combination with placebo (6.24 vs. 5.91 months, HR 0.82 (95% CI, 0.69 to 0.99; p = 0.038) [7]. It must be acknowledged however, that the net gain of 11 days in median overall survival in the full study population, albeit statistically significant, was of limited clinical relevance. The RASH trial evaluated first-line treatment with erlotinib plus gemcitabine. Patients developing rash were continued on treatment, while patients without rash were switched to FOLFIRINOX. Clinical outcome of rash-positive patients receiving gemcitabine/erlotinib was comparable to that previously reported for FOLFIRINOX in the first-line setting [8]. As of now, erlotinib, in combination with gemcitabine, is the only TKI approved for treatment of pancreatic cancer in the first-line setting [9].

Afatinib, a second-generation TKI, irreversibly inhibits the Pan-ErbB family and is approved as single-agent therapy of locally advanced and metastatic, TKI-naïve non-small cell lung cancer (NSCLC) harboring EGFR-mutations and squamous NSCLC progressive under or after platinum-based chemotherapy [10,11]. Preclinical studies in human pancreatic tumor cells showed that afatinib inhibited the growth of all seven human pancreatic cell lines tested and was also effective in blocking EGF-induced phosphorylation of tyrosine, EGFR, MAPK, and AKT, whereas erlotinib did only inhibit the growth of two of the tested human pancreatic cell lines and had no effect in the other cell lines tested [12–14]. Clinical assessment of afatinib in combination with gemcitabine/nab-paclitaxel has not been performed thus far. In the randomized, open label phase 2 ACCEPT study of the Arbeitsgemeinschaft Internistische Onkologie (AIO), patients with mPDAC were treated 2:1 with the combination of afatinib plus gemcitabine or gemcitabine alone. The addition of afatinib to gemcitabine did not induce additional clinical benefit [15]. The phase 1b study AFFECT was designed to further investigate the therapeutic potential of afatinib in combination with the more effective combination of gemcitabine/nab-paclitaxel.

2. Methods

2.1. Patients

Key inclusion criteria were age above 18 and below 75 years, ECOG performance status 0 or 1, and a histologically (not cytologically) confirmed diagnosis of metastatic pancreatic ductal adenocarcinoma (PDAC). At the time of enrolment, at least one unidimensional measurable tumor lesion was required. No previous palliative chemotherapy or ErbB family-directed therapy (e.g., erlotinib, cetuximab, trastuzumab) for PDAC was allowed. Complete eligibility criteria are shown in the supplements (Suppl. Table 1).

Table 1
Patient baseline characteristics.

Characteristics	N = 12 (100%)
Sex	
Male	11 (91.7)
Female	1 (8.3)
Ethnicity	
Caucasian	12 (100)
Median age	57
Range	46 – 73
ECOG performance score	
0	7 (58.3)
1	5 (41.7)
Histopathological subtype	
Adenocarcinoma	12 (100)
Primary tumor location	
Head	4
Body	2
Tail	2
Head + Body	1
Body + Tail	3
CA-19-9 (U/ml)	
Min	2.6
Max	2013.76
Metastatic Site	
Liver	9 (75.0)
Lung	3 (25.0)
Peritoneum	2 (16.7)
Gallbladder	1 (8.3)
Spleen	1 (8.3)
First follow-up treatment after end of study	11 (100)
5-FU, Folinic acid, Irinotecan	2 (18.2)
5-FU, Folinic acid, Irinotecan, Oxaliplatin	2 (18.2)
Gemcitabine, nab-Paclitaxel	2 (18.2)
5-FU, Folinic acid, nal-Irinotecan	1 (9.1)
5-FU, Folinic acid, Oxaliplatin	1 (9.1)
No further anticancer treatment	3 (27.3)
Study treatment	
Yes	11 (91,7)
No	1 (8.3)
Safety Set	11 (100)
Full analysis set	11 (100)
MTD set	9 (81.8)
Per protocol set	6 (54.5)

3. Trial design and endpoints

The multicenter, open-label phase 1b trial AFFECT was performed in treatment-naïve patients with metastatic PDAC (NCT0297514).

Afatinib was given orally once daily, with the first cohort starting at dose level 0 (start level) with 30 mg. Gemcitabine (1000 mg/m^2) and nab-paclitaxel (125 mg/m^2) were given intravenously at standard doses on days 1, 8, and 15 of a 28-day cycle (Suppl. Table 2).

The primary objective was to identify the MTD of afatinib in combination with gemcitabine/nab-paclitaxel. To determine the MTD, a "3 + 3" design was used (see section sample size calculation). For the purposes of determining the MTD, the following patients were evaluated: patients experiencing a DLT in Cycle 1 before start of Cycle 2 or having received at least 80% of the afatinib dose and 60% of the nab-paclitaxel and gemcitabine dose of their respective dose level in Cycle 1 without experiencing a DLT. DLT was defined as toxicities which is at least possibly related to any of the study drugs afatinib and/or nab-paclitaxel and/or gemcitabine. DLT criteria are listed in supplement Table 3. Secondary objectives and explorative objectives were evaluation of safety and efficacy, respectively. Treatment was continued until disease progression, if no DLT was detected, unacceptable toxicity, physician's decision or withdrawal of consent. Here, we report the results of the safety and efficacy of afatinib in combination with gemcitabine/nab-paclitaxel. Safety endpoints included duration of treatment as well as type, incidence, and severity of the adverse events graded according to the NCT CTCAE version 4.03. Efficacy endpoints include overall response, progression-free survival, and overall survival.

Table 2
Adverse events in the safety population.

Adverse Event	Any grade	Grade ≥ 3
(Full safety set)	**N (%)**	**N (%)**
Any	11 (100)	9 (81.8)
Blood and lymphatic disorder	6 (54.5)	2 (18.2)
Anemia	1 (9.1)	1 (9.1)
Leukopenia	3 (27.3)	–
Neutropenia	3 (27.3)	1 (9.1)
Thrombocytopenia	3 (27.3)	–
Cardiac disorder	1 (9.1)	–
Myocardial infarction	1 (9.1)	–
Eye disorder	2 (18.2)	–
Dry eye	1 (9.1)	–
Macular edema	1 (9.1)	–
Xeropthalmia	1 (9.1)	–
Gastrointestinal disorder	7 (63.6)	3 (27.3)
Abdominal pain	1 (9.1)	–
Anal fissure	1 (9.1)	–
Constipation	1 (9.1)	–
Ileus	1 (9.1)	–
Diarrhea	6 (54.5)	2 (18.2)
Dry mouth	2 (18.2)	–
Duodenal perforation	1 (9.1)	1 (9.1)
Dyspepsia	1 (9.1)	–
Enlarged uvula	1 (9.1)	–
Nausea	4 (36.4)	–
Vomiting	6 (54.5)	–
Dry lips	1 (9.1)	–
General disorder	9 (81.8)	3 (27.3)
Catheter thrombosis	1 (9.1)	–
Chills	2 (18.2)	–
Fatigue	7 (63.6)	1 (9.1)
Mucosal inflammation	4 (36.4)	–
Edema	3 (27.3)	–
Pain	4 (36.4)	1 (9.1)
Pyrexia	4 (36.4)	1 (9.1)
Hepatobiliary disorder	1 (9.1)	1 (9.1)
Cholangitis	1 (9.1)	1 (9.1)
Hyperbilirubinemia	1 (9.1)	–
Infections	7 (63.6)	4 (36.4)
C. diff Colitis	1 (9.1)	1 (9.1)
Device related infection	1 (9.1)	1 (9.1)
Infection	4 (36.4)	1 (9.1)
Nasopharyngitis	1 (9.1)	–
Oral Candiasis	1 (9.1)	–
Pulmonary mycosis	1 (9.1)	1 (9.1)
Rhinitis	1 (9.1)	–
Sepsis	1 (9.1)	1 (9.1)
Urinary Tract infection	1 (9.1)	1 (9.1)
Urosepsis	1 (9.1)	1 (9.1)
Investigations	2 (18.2)	1 (9.1)
ALT increased	1 (9.1)	–
AST increased	1 (9.1)	–
AP increased	1 (9.1)	–
Bilirubin increased	1 (9.1)	–
GammaGT increased	1 (9.1)	1 (9.1)
Weight decreased	1 (9.1)	–
Hypergylcemia	1 (9.1)	–
Musculoskeletal and connective tissue disorder	3 (27.3)	–
Joint swelling	1 (9.1)	–
Myalgia	1 (9.1)	–
Pain in Extremities	1 (9.1)	–
Nervous System disorder	4 (36.4)	–
Dysgeusia	2 (18.2)	–
Headache	1 (9.1)	–
Paresthesia	4 (36.4)	–
Peripheral sensory neuropathy	1 (9.1)	–
Restless leg Syndrome	1 (9.1)	–
Renal and urinary disorder	2 (18.2)	1 (9.1)
Acute kidney injury	1 (9.1)	–
Proteinuria	1 (9.1)	1 (9.1)
Respirator and thoracic disorder	1 (9.1)	1 (9.1)
Epistaxis	1 (9.1)	–
Pneumothorax	1 (9.1)	1 (9.1)
Skin and subcutaneous disorder	10 (90.9)	2 (18.2)
Alopecia	8 (72.7)	–
Dry skin	4 (36.4)	–
Psoriasis	1 (9.1)	–
Rash	10 (90.9)	2 (18.2)
Skin fissures	1 (9.1)	–
Vascular disorder	2 (18.2)	1 (9.1)
Embolism	1 (9.1)	1 (9.1)
Vein thrombosis	1 (9.1)	—

Table 3
TESAEs.

Patient	Dose Level	TESAE	Grade CTCAE	Treatment related
1	0	Ileus	2	no
		Macular edema	2	no
2	0	no TESAE	-	-
3	0	Port thrombosis	2	no
4	1	Diarrhea	3	yes
		Embolism	3	no
		Pneumothorax	3	no
		Deep vein thrombosis	3	no
5	1	Urinary tract infection	3	no
		Urosepsis	4	yes
		C. diff colitis	5	no
6	1	Fatigue	3	yes
		Aplasia	3	yes
		Pulmonary mycosis	3	yes
		Sepsis	5	no
		Duodenal perforation	3	unknown
7	0	no TESAE	-	-
8	0	no TESAE	-	-
10	0	no TESAE	-	-
11	0	Cholangitis	3	no
12	0	Fever	3	yes
		Infection	3	yes

All patients who received at least one dose of study medication with afatinib, nab-paclitaxel and gemcitabine were included in the full analysis population (FAS), they also represented the safety population.

4. Assessment

Staging and tumor assessment were performed with either contrast-enhanced computed tomography scan or magnetic resonance imaging of the chest, abdomen, and pelvis at baseline and after every second treatment cycle, preferably in week 4 of every second cycle. Tumor assessment was performed according to RECIST version 1.1 [16]. The severity of adverse events was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 [17].

4.1. Safety evaluation

Safety data included exposure to study drugs afatinib, nab-paclitaxel, and gemcitabine (dose level and frequency of application per cycle; treatment duration), type, incidence and severity of adverse events/ serious adverse events, laboratory parameters, and ECOG score.

Safety parameters and specific events were stratified by System Organ Class, MedDRA Preferred Term, CTCAE grade and causality.

If any dose-limiting toxicities occurred during the first cycle, study treatment with afatinib and gemcitabine/nab-paclitaxel had to be discontinued. Otherwise, dose modifications were implemented according to the protocol. In case of occurrence of interstitial lung disease (ILD) all study drugs afatinib, gemcitabine, and nab-paclitaxel were to be discontinued permanently.

5. Trial oversight

The AFFECT trial was a national German study and was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonization and the principles of the Declaration of Helsinki (EudraCT-Nr: 2015–004065-86). Regulatory and institutional authorities at each site approved the protocol and amendments (project-ID: 303–16 fed). Official sponsor was the Klinikum der Universität München, Großhadern and the coordinating investigator Prof. Dr. Volker Heinemann. Written consent was obtained from all the patients. The trial is an investigator-initiated trial (IIT) and was designed by the investigator and was conducted in collaboration with the CRO ClinAssess GmbH. The data were collected by the investigators and analyzed centrally by statisticians employed by ClinAssess GmbH. Data safety boards were held regularly by the coordinating investigator and study coordinators along with the CRO ClinAssess GmbH.

6. Statistical analysis

6.1. Statistical methodology

In general, the recorded baseline, efficacy, and safety data were analyzed using standard descriptive methods. For continuous data, distribution parameters (mean, standard deviation, minimum, median, and maximum) were computed. For categorical data, frequency counts were given. Regarding response rates, patients in whom the respective response criteria were not met were evaluated as non-responders.

Time-to-event data (progression–free survival, overall survival) was evaluated according to Kaplan-Meier. Median time to event as well as estimates for the proportion of patients not having reached the event after appropriate times was calculated. The starting point was day 1 of the first cycle with application of the study drugs. Patients for whom no event was documented were censored with the last date at which it was known that the respective event had not been reached. Missing data was not replaced.

All results described in the following have been drawn from double-entered data in the clinical database set up by X-act Cologne. The analysis was realized according to the SAP (version 1.0, dated 02.01.2020) and performed using SAS® version 9.4.

6.1.1. Sample size calculation

A "3 + 3" design using a modified Fibonacci sequence with cohorts of up to 6 evaluable patients per dose level was used in this phase 1b trial [18]. It was estimated that a maximum of 18 patients was needed to determine the MTD of afatinib in combination with gemcitabine/nab-paclitaxel.

7. Results

7.1. Trial population

Between 12th of December 2016 and 18th of March 2019, 12 patients were enrolled in the AFFECT trial from three different centers. Eleven patients received at least one dose of the study drug. Eight patients were treated in dose level 0, three patients in dose level + 1, and one patient did not receive study treatment. Baseline characteristics are shown in Table 1. Data cut-off was 2nd of March 2020. Due to temporary safety concerns, study accrual was halted on 22nd of August 2017. As no causal relationship to investigational medicinal product (IMP) was determined after thorough assessment by the investigator team, recruitment re-started on 17th of November 2017.

8. Maximum tolerated dose (MTD) and dose limiting toxicity

At dose level 0 (start level), the first three patients did not experience a dose limiting toxicity (DLT). Two further patients at DL0 were not eligible for MTD analysis as afatinib was reduced < 80% during the first cycle. Accordingly, enrollment continued at dose level + 1; two patients experienced a dose limiting toxicity (DLT: diarrhea ≥ CTCAE grade 3 and urosepsis), while one patient finished the first cycle without a DLT (Suppl. Table 4). Two patients of the dose level + 1 cohort died from infectious complications: Multiorgan failure due to septic shock on grounds of clostridium difficile colitis (DLT: urosepsis) and sepsis after duodenal perforation due to stent dislocation (not treatment related). This led to an intermittent hold of this trial. After meticulous analysis, both events leading to the deaths were evaluated not be directly related to the study drugs. Enrolment then continued at dose level 0 with three more patients, of whom one experienced a DLT (skin rash ≥ CTCAE grade 3, only DLT at DL0). MDT was subsequently determined at dose level 0.

9. Safety

9.1. Duration of treatment

At dose level + 1, owing to DLTs, median duration of treatment was 0.5 months (range 0.4 – 1.3 months).

At dose level 0, median duration of treatment was 4.4 months (range 0.3 – 8.5 months). Overall, median duration of treatment was 3.5 months. Maximum number of treatment cycles at dose level 0 was 8, while the patients treated at dose level + 1 received only one or two treatment cycles. (Suppl. Table 5).

Reason for treatment discontinuation at dose level 0 (n = 8) were disease progression in 6 Patients (75%), adverse event in one patient (hyperbilirubinemia), and other medical reason in one patient (very good treatment response with subsequent resection). It is to note, that in the last patient a DLT (skin rash) occurred. However, upon a non-life-threatening DLT, excellent treatment response, explicit patient wish and treating physicians decision, the patient was continued on treatment with dose-reduced afatinib. Severity of skin rash reduced to CTCAE grade 2 in subsequent cycles. Patient further went on to undergo tumor resection because auf great treatment response. Treatment discontinuation at dose level + 1 resulted from two DLT (diarrhea CTCA grade 3 and urosepsis) and one death (not treatment related).

Dose reductions of study medication are shown in Supplement Table 6.

9.1.1. Adverse events

All patients treated experienced at least one treatment-emergent adverse event (TEAE). Overall, the most common adverse events of all grades were skin and subcutaneous reactions with occurrence in 90.9% of patients, gastrointestinal events with 63.6%, fatigue, and infectious

Table 4
Efficacy of afatinib in combination with gemcitabine and nab-Paclitaxel.

Treatment response – full analysis set (N = 11)	**N (%)**
PR	4 (36.4)
SD	1 (9.1)
PD	2 (18.2)
Not evaluable	4 (36.4)
ORR	
Full analysis set (N = 11)	4 (36.4)
Dose level 0 (N = 8)	4 (50)
Dose level + 1 (N = 3)	0 (0)
Per protocol set (N = 6)	4 (66.7)
DCR	
Full analysis set (N = 11)	5 (45.5)
Dose level 0 (N = 8)	5 (62.5)
Dose level + 1 (N = 3)	0 (0)
Per protocol set (N = 6)	5 (83.3)
Median PFS – full analysis set (in months)	**3.5**
Range	0.6 – 15.7
Median OS at database lock – full analysis set (in months)	**7.5**
Range	0.6 – (>11.6)

complications with 63.6%, and hematological events with 54.5%. Adverse events are listed in Table 2. Two DLTs occurred at dose level + 1 (diarrhea ≥ CTCAE grade 3 and urosepsis).

Ten out of eleven patients (90.9%) experienced at least one TEAE related to the study medication. Nine out of eleven patients (81.8%) experienced a grade 3–5 TEAE, and in eight patients (72.7%) at least one TEAE was related to the study medication. In 63.3% (n = 7), 54.5% (n = 6) and 45.5% (n = 5) either nab-paclitaxel, gemcitabine or afatinib, respectively, had to be reduced or intermittently paused due to TEAEs (Suppl. Table 7).

7 patients (63.6%) experienced at least one serious TEAE (TESAE), four patients (36.4%) experienced a TESAE related to the study medication. Five patients (45,5%) experienced a grade 3–5 TESAE and four patients (36.4%) experienced a grade 3–4 TESAE related to the study

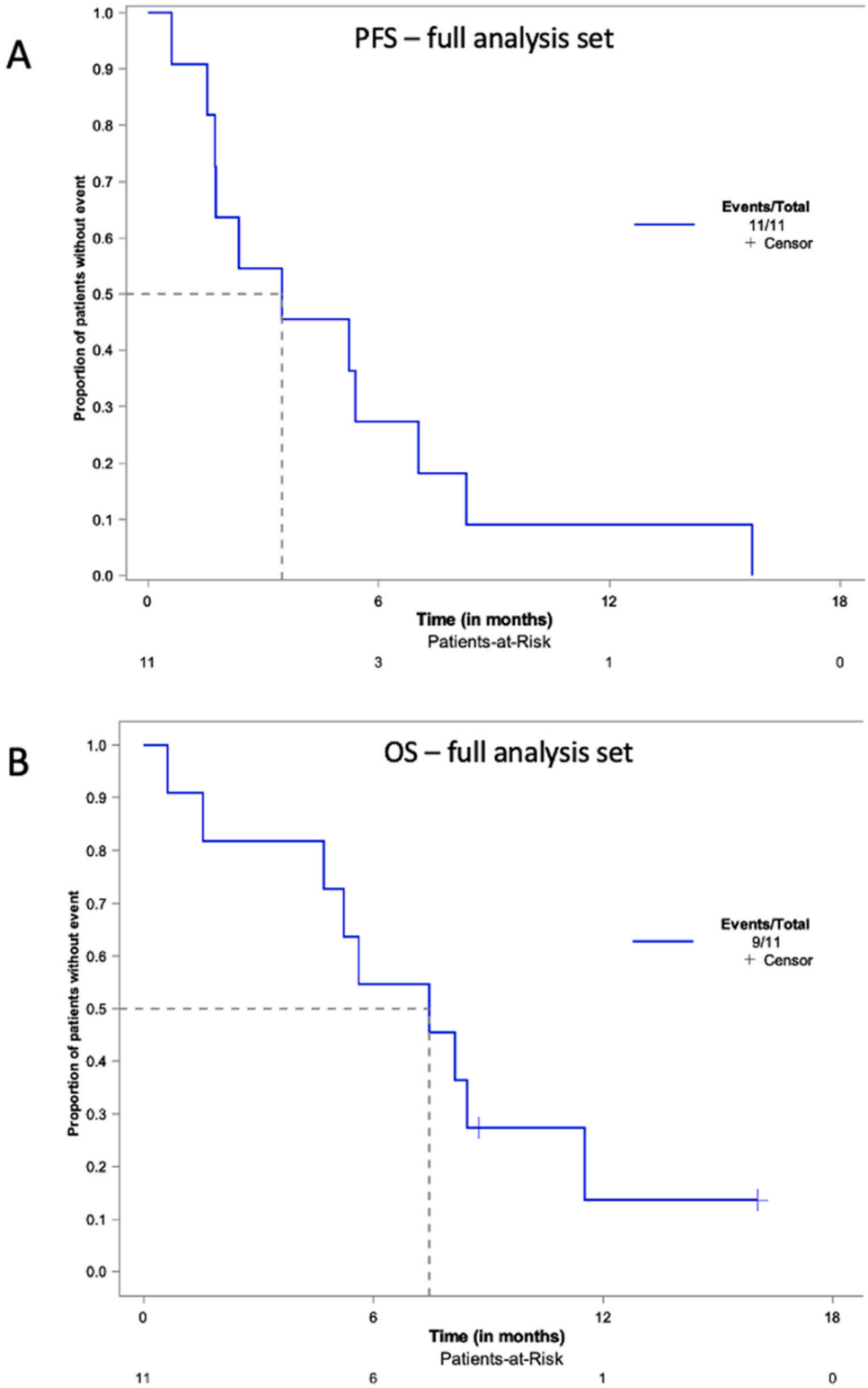

Fig. 1. Kaplan-Meier-Curves for median PFS (A) and median OS (B) of the full analysis set.

medication (Table 3). Two patients (18.2%) experienced a grade 5 toxicity at dose level + 1 (Table 3, Suppl. Table 5) which were not related to study medication. Both cases resulted from infectious complications: Multiorgan failure due to septic shock and clostridium difficile colitis.

Not all TESAE were declared as DLTs. For patient 6 and 12 TESAEs were not declared as DLT defining events, as event did not occur within the first cycle. For Patient 4 and 5 all DLTs occurring within the first treatment cycle were reported as DLTs (see section MTD and DLT).

9.1.2. *Efficacy*

Response assessment was available for seven of eleven patients. The overall response rate (ORR) was 36.4%, with one additional patient achieving stable disease (SD) as best response. ORR in the dose level 0 was 50%, and in dose level + 1 was 0%. Overall disease control rate (DCR) was 45.5% (Table 4). Median progression free survival in the study population was 3.5 months (range 0.6 – 15.7 months) and at database lock median overall survival for the patients analyzed was 7.5 months (range 0.6 – 11.6 months, Table 4 and Figure 1). One patient responded significantly and further went on to undergo tumor resection. Molecular profile of that tumor demonstrated a *KRAS G12C* mutation and a *CDKN2A/B* loss. Clinical courses of all treated patients are illustrated in a swimmer's plot (Figure 2).

10. Discussion

In this phase 1b study, we aimed to explore the potential application of afatinib in combination with gemcitabine/nab-paclitaxel in treatment-naïve patients with mPDAC. In a previous analysis, the ACCEPT phase 2 trial had compared the combination of afatinib and gemcitabine versus gemcitabine alone and showed no improvement in survival by addition of the TKI [15]. As a further extension of this work, the AFFECT phase 1b study investigated the addition of afatinib to first-line chemotherapy with gemcitabine/nab-paclitaxel.

The primary goal of the study was to define the MTD for this combination therapy. At dose level 0, patients received an intravenous starting dose of gemcitabine 1000 mg/m^2 plus nab-paclitaxel 125 mg/m^2 in combination with a daily oral afatinib dose of 30 mg. At this dose level, only one patient had a DLT with skin rash. Most common adverse events were as expected hematological and gastrointestinal toxicities, fatigue, and infectious complications, as well as skin reactions. At dose level + 1, two of three patients experienced DLTs; one patient died from septic shock and the other patient experienced CTCAE grad 3 diarrhea.

When two patients died in the DL + 1 cohort, recruitment was halted intermittently, and thorough analyses of both cases were conducted. It became clear that none of the cases were directly related to the study medication. One patient had shown response to treatment but had secondary dislocation of a tumor stent leading to gastrointestinal perforation. The second death was attributed to an infection with Clostridium difficile colitis following an antibiotic treatment of urosepsis which emerged during neutropenia. The serious adverse event, Clostridium difficile colitis, was not assessed as related to the IMP by the investigators, as well as the coordinating investigator. Subsequently, enrolment on the study was re-started. Though no causal relationship to IMP was determined, study centers were instructed to draw special attention to infectious events.

Exploratory analysis of treatment efficacy showed an ORR of 36.4% and a DCR of 45.5%. These rates compare favorably to those previously reported from the randomized MPACT trial [2]. The exploratory survival analysis showed a relatively lower PFS and OS than reported in the MPACT or the FOLFIRINOX trial with 3.5 and 7.5 months, respectively [2,3]. In this context, it certainly needs to be acknowledged that our data are based on an exploratory analysis of a very small cohort and that cross-trial comparisons may only lead to hypothetical assumptions. Anecdotally, one patient experienced exceptional treatment response and underwent tumor resection. At the last follow up 16 months after start of treatment, the patient was reported to be alive. While outcome data appear to be interesting, it is not possible to draw a conclusion with regard to the clinical efficacy of this drug combination. Rash positivity during erlotinib treatment in mPDAC has been reported to correlate with an improved clinical benefit [8,19]. Due to small sample size, a correlation of rash and clinical outcome was not performed in the AFFECT cohort.

Unfortunately, we do not have the molecular pathology data of all patients. Data was not systematically collected at that time.

In summary, afatinib shows acceptable safety when the oral TKI is given at a daily dose of 30 mg in combination with standard doses of gemcitabine/nab-paclitaxel. Higher doses of afatinib were not tolerated

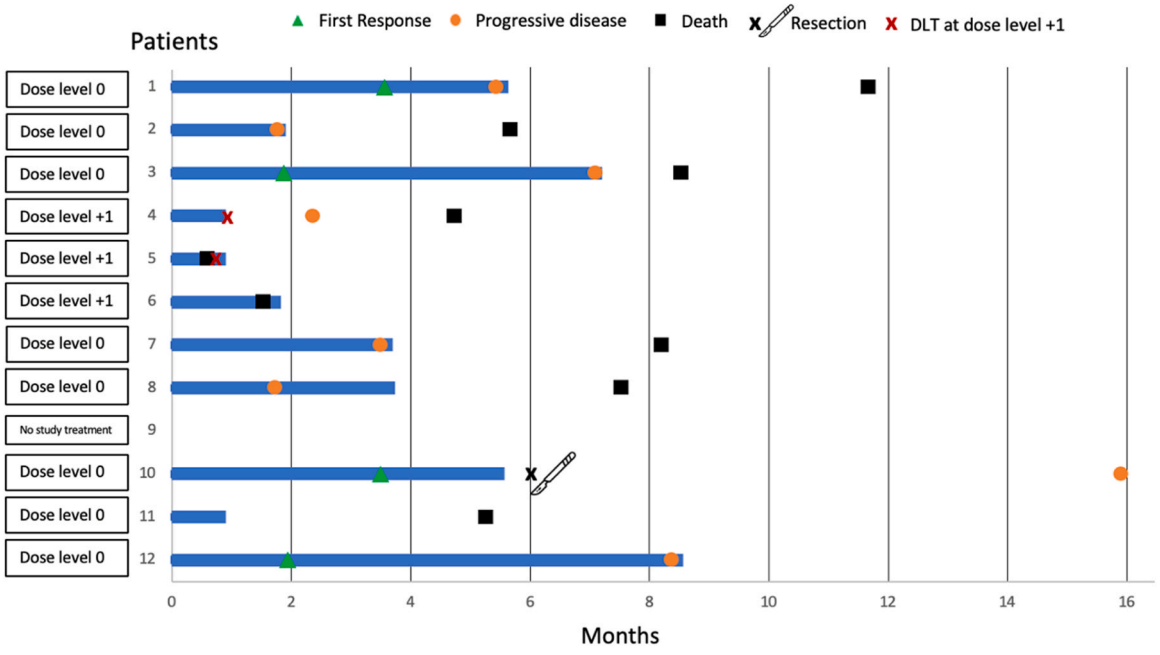

Fig. 2. Swimmer's plot of all treated patients.

well. Two deaths occurring during therapy were not related to treatment. Since mPDAC still has poor survival, innovative treatment regimens are necessary to improve patient outcome. Further studies are needed to establish the clinical impact. Exploratory translational projects are ongoing to assess potential underlying mechanism of favorable response to the experimental combination of afatinib, gemcitabine and nab-paclitaxel.

11. Statements & declarations

11.1. Ethics approval

The AFFECT trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonization and the principles of the Declaration of Helsinki (EudraCT-Nr: 2015–004065-86). Regulatory and institutional authorities at each site approved the protocol and amendments (project-ID: 303–16 fed).

Informed consent was obtained from all individual participants included in the study.

Authors' contributions

All authors wrote the manuscript, reviewed the complete draft and approved the final version of the paper.

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Declaration of Competing Interest

DZ reported receiving honoraria from AstraZeneca, receiving research funding for the institution from Milteny and travel as well as accommodation expenses from AstraZeneca and Amgen. CBW has received honoraria from Amgen, Bayer, BMS, Chugai, Celgene, Falk, GSK, MSD, Merck, Janssen, Ipsen, Roche, Servier, SIRTeX, and Taiho; served on advisory boards for Bayer, BMS, Celgene, Janssen, MSD, Servier, Shire/Baxalta, Rafael Pharmaceuticals, RedHill, and Roche; has received travel support by Bayer, Celgene, Janssen, RedHill, Roche, Servier, and Taiho and research grants (institutional) by Roche. MQ, DTW, FK, KH and MB report no conflict of interest. SW reported being employee of ClinAssess GmbH KD has received travel support from Servier, GSK, and BMS, as well as honoraria from AstraZeneca. LW received honoraria for scientific presentations from Roche and Servier and travel accommodation expenses from Amgen. MH reported receiving travel support from Servier and honoraria for scientific presentations from Falk Foundation. SB had a consulting and advisory role for Celgene, Servier, Incyte, Fresenius, Janssen-Cilag, AstraZeneca, MSD, and BMS, and received honoraria for scientific presentations from Roche, Celgene, Servier, and MSD. VH received honoraria for talks and advisory board role for Merck, Amgen, Roche, Sanofi, Servier, Pfizer, Pierre-Fabre, AstraZeneca, BMS; MSD, Novartis, Terumo, On- cosil, NORDIC, Seagen, GSK. Research funding from Merck, Amgen, Roche, Sanofi, Boehringer-Ingelheim, SIRTEX, Servier. VP reported receiving travel support from Nordic Pharma.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113926.

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