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A prospective randomised phase-II trial with gemcitabine versus gemcitabine plus sunitinib in advanced pancreatic cancer

A study of the CESAR Central European Society for Anticancer Drug Research–EWIV

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Abstract ***Background:*** Pancreatic ductal adenocarcinoma (PDAC) is one of the most common malignant tumours and is still associated with a poor prognosis in advanced disease. To improve the standard therapy with gemcitabine, we initiated a prospective randomised

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Sunitinib
Combination

phase-II trial with gemcitabine (GEM) versus gemcitabine plus sunitinib (SUNGEM) based on data of *in vitro* trials and phase-I data for the combination treatment. The rational of adding sunitinib was its putative antiangiogenic mechanism of action.

Methods: A total of 106 eligible patients with locally advanced, unresectable or metastatic PDAC without previous system therapy were randomised to receive GEM at a dosage of 1.000 mg/m^2 d1, 8, 15 q28 versus a combination of SUNGEM at a dosage of GEM 1.000 mg/m^2 d1 + 8 and sunitinib 50 mg p.o. d1–14, q21d. The primary end-point was progression free survival (PFS), secondary end-points were overall survival (OS), toxicity and overall response rate (ORR).

Results: The confirmatory analysis of PFS was based on the intend-to-treat (ITT) population ($N = 106$). The median PFS was 13.3 weeks (95% confidence interval (95%-CI): 10.4–18.1 weeks) for GEM and 11.6 weeks for SUNGEM (95%-CI: 7.0–18.0 weeks; $p = 0.78$ one-sided log-rank). The ORR was 6.1% (95%-CI: 0.7–20.2%) for GEM and for 7.1% (95%-CI: 0.9–23.5%) for SUNGEM ($p = 0.87$). The median time to progression (TTP) was 14.0 weeks (95%-CI: 12.4–22.3 weeks) for GEM and 18.0 weeks (95%-CI: 11.3–19.3 weeks) for SUNGEM ($p = 0.60$; two-sided log-rank). The median OS was 36.7 weeks (95%-CI: 20.6–49.0 weeks) for the GEM arm and 30.4 weeks (95%-CI: 18.1–37.6 weeks) for the SUNGEM ($p = 0.78$, one-sided log-rank). In regard to toxicities, suspected SAEs were reported in 53.7% in the GEM arm and 71.2% in the SUNGEM arm. Grade 3 and 4 neutropenia was statistically significantly higher in the SUNGEM arm with 48.1% versus 27.8% in the GEM arm ($p = 0.045$, two sided log-rank).

Conclusions: The combination SUNGEM was not sufficient superior in locally advanced or metastatic PDAC compared to GEM alone in regard to efficacy but was associated with more toxicity.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading causes of cancer deaths worldwide [1]. The median age at diagnose is 70 years for men and 76 years for women with a lifetime risk of 1.5% for both genders [1]. Only 10–20% of pancreatic cancer patients can be resected with curative intention at the time of diagnosis [2]. Most patients with pancreatic cancer are diagnosed with locally advanced stage or metastatic disease. Approximately 50% of new pancreatic cancer cases are diagnosed with metastatic disease. Despite some progress in systemic therapies, the outcome in advanced stages is rather poor with a 5-year survival of about 5–10% only. The main back bone agent is still gemcitabine, but meanwhile the combination FOLFIRINOX demonstrated some superiority to gemcitabine alone [4]. Additionally, the combination of gemcitabine with nab-paclitaxel improved overall survival (OS) from 6.7 to 8.5 months [3]. However, there is still a medical need for new therapeutic options.

Pancreatic cancer is a result of multiple genetic alterations for example activation of the K-Ras or BRAF oncogenes, as well as inactivation of the tumour-suppressor genes DPC4, CDKN2A and TP53 [5]. Additionally, down-regulation of STAT3 signalling has been shown to induce apoptosis but also to promote anti-apoptotic gene expression in human pancreatic cancer cells [6–8]. Moreover, an increased activation of the PI3K/AKT-pathway has been detected in about half of pancreatic cancers [9,10]. Recently, Georgiadou et al. [11] could demonstrate that vascular endothelial growth factor (VEGF) and Id-1 overexpression in PDAC were found to be associated with high microvessel density and was associated with a worse outcome in terms of patient survival. Additionally, curcumin has been shown to inhibit the growth of PDAC cell lines *in vitro* and in a mouse model by inhibiting various intracellular pathways including nuclear factor kappa B (NFkB), which is involved in angiogenesis [12,13]. Therefore, the potential of anti-angiogenic active VEGF directed multi tyrosine-kinase-inhibitors (TKI) such as the receptor TKI sunitinib should be assessed for improving the outcome in PDAC. Sunitinib is well established in the treatment of metastatic renal cell cancer and gastrointestinal stromal tumours (GIST) [14,15].

Based on the phase-I data of phase-I trials [16,17] regarding the combination of gemcitabine and sunitinib in advanced solid tumours, we initiated a prospective randomised phase-II trial comparing gemcitabine and sunitinib (SUNGEM) with gemcitabine (GEM) alone in locally advanced or metastatic PDAC.

2. Patients and Methods

2.1. Inclusion and exclusion criteria

Eligible patients were at least 18 year old with a histologically or cytologically confirmed metastatic or locally advanced pancreatic adenocarcinoma.

Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate haematologic, hepatic and renal function, a normal electrocardiogram (ECG) without QT prolongation (corrected QT (QTc) < 450 ms) as well as a measurable disease with at least one uni-dimensionally measurable target lesion by CT-scan or MRI according to Response Evaluation Criteria in Solid Tumors (RECIST) [18].

Exclusion criteria included a resectable pancreatic cancer, previous chemotherapy for adjuvant or metastatic disease, any investigational drug within the 30 days before inclusion, prior use of sunitinib or other multitarget tyrosine kinase inhibitor, pregnancy or lactation period, patients unwilling to use a medically acceptable method of contraception from the start of treatment up to 6 month after end of treatment, clinically symptomatic brain or meningeal metastases (known or suspected), cardiac arrhythmias requiring antiarrhythmics (excluding beta blockers or digoxin), history of a cardiac event within the past 6 months, uncontrolled severe hypertension, other acute or subacute vascular events, a previous malignancy in the last 5 years except basal cell cancer of the skin, pre-invasive cancer of the cervix or superficial bladder tumour, patients with seizure or epileptic disorder as well as patients with other significant diseases.

The study was conducted in accordance with the standards of each site's independent ethics committees, principles of good clinical practice (GCP) and performed in accordance with the Declaration of Helsinki Guidelines. Informed consent was obtained from each patient prior to inclusion in the study.

2.2. Study design

Prospective randomised open-label controlled phase II-study of gemcitabine (GEM) versus gemcitabine plus sunitinib (SUNGEM) in the treatment of patients with advanced, unresectable or metastatic pancreatic ductal adenocarcinoma cancer (PDAC).

2.3. Treatment

Patients were randomly assigned to one of two treatment regimens: gemcitabine alone (GEM, control) and gemcitabine plus sunitinib (SUNGEM). The GEM group received a 30-min infusion of 1.000 mg/m^2 gemcitabine on days 1, 8 and 15 of a 28 day cycle. Patients treated with gemcitabine + sunitinib (SUNGEM) received sunitinib 50 mg/day in cycles of 3 weeks with a 2 weeks on/1 week off schedule, added to gemcitabine therapy (1.000 mg/m^2) given on days 1 and 8 of a 21 day cycle. This schedule was based on the toxicity data of a phase-I trial [16,17].

Dose modification had to be performed in case of haematological toxicity Common Terminology Criteria of Adverse Events (CTCAE) grade ⩾ 3 with a duration of neutropenia >7 days or neutropenic fever or CTCAE grade 4 thrombocytopenia or anaemia. If neutropenia grade 3 occured prior to gemcitabine administration, the full dose of gemcitabine was given, followed by three doses of subcutaneously administered granulocyte-colony stimulating factor (G-CSF). Any non-haematological toxicity CTCAE grade 3 (except for fever, chills and flulike symptoms or alopecia, liver transaminase elevations, inadequately treated diarrhoea, nausea and vomiting and tolerable rash) and haematological toxicity CTCAE grade ⩾ 3 in case of duration of neutropenia >7 days or neutropenic fever or CTCAE grade 4 thrombocytopenia or anaemia, led to a dose reduction of sunitinib to 37.5 mg/day. In case of QT-prolongation to >450 ms or drug related arrhythmias, sunitinib was to be reduced to 37.5 mg/day or the therapy was to be temporarily interrupted until QTc returned to <450 ms, and the patient was to be followed by ECG controls in close intervals. Once a patient has had a dose reduction for toxicity, the dose was not allowed to be reescalated.

Treatment was stopped in case of unacceptable toxicities, disease progression, patient's withdrawal of consent or investigator's decision.

2.4. Patient evaluation

Screening assessments were to be completed within 28 days prior to first treatment including medical history, physical examination, concomitant medication, ECOG performance status, vital signs, haematology, clinical chemistry, baseline electrocardiogram, echocardiography and pregnancy test if indicated.

Safety was assessed throughout the study by physical examination, 12-lead electrocardiograms, vital signs measurements and clinical laboratory tests. Patients were monitored for adverse events (AEs) throughout the whole study. Physical examination was performed at day 1 of each treatment cycle. The frequency, severity and relationship to treatment for AEs that occurred during study treatment and up to 30 days after the last administration of the study drug were evaluated.

Adverse events were assessed according to the Common Terminology Criteria of Adverse Events (CTCAE) version 3.0. All patients who received at least one dose of study drug were included in the safety analyses.

Disease assessment was performed within 14 days before the first administration of study drugs, 6 and 12 weeks after start of treatment and every 8 weeks thereafter until disease progression. In addition, whenever tumour progression was suspected, a tumour assessment was performed. All patients completing at least 8 weeks under treatment according to the protocol and for whom at least one staging was performed within 8–12 weeks after initiation of treatment were evaluable for response. Response was evaluated according to

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RECIST (Response Evaluation Criteria in Solid Tumors) version 1.0 [18]. Patients who developed early tumour progression prior to response evaluation irrespective of study treatment were considered to be progressive on study.

2.5. Study objectives and statistical analysis

The trial was designed as a one-stage randomised non-blinded phase II trial to show sufficient superiority of SUNGEM over the standard treatment arm GEM in PFS as the primary end-point. Assuming a median PFS of 3 months in the standard GEM arm, a clinical relevant difference of 2 months, an accrual time at minimum of 1 year, a follow-up time of 6 months, 10% type I error, 80% power, 5% loss of follow-up and 10% drop-out, sample size calculation yielded a total of at least 96 patients (ie 48 per arm).

The primary end-point of PFS was calculated from date of randomisation to the date of the occurrence of progression or treatment related death whatever occurs first. For the calculation of PFS, date of occurrence of progression was taken as the date of last time when the patient was confirmed as progression-free. The confirmatory analysis of the primary end-point was performed using a one-sided logrank test at a significance level of 10% and was based on the ITT population. Secondary analyses of the primary end-point were performed using Kaplan–Meier method and exploratory two-sided tests of difference in PFS rates between the two treatment arms.

Secondary end-points were the characterisation of safety and efficacy outcome in the experimental SUNGEM arm in comparison to the GEM arm:

- safety assessment according to reported SAEs by CTCAE v3.0,
- progression free survival for 12 weeks (PFS12),
- objective response (OR) according to RECIST criteria,
- time-to-progression (TTP) according to RECIST criteria,
- overall survival (OS).

The secondary end-point of TTP was calculated from date of randomisation to the date of the occurrence of progression or disease-or treatment related death whatever occurs first. For the calculation of TTP, date of occurrence of progression was taken as the date of progression or death. TTP and OS were analysed using censored failure times with the Kaplan–Meier method, logrank test and exploratory two-sided tests of difference in TTP rates between the two treatment arms. Cox proportional hazard ratios were calculated for different subgroups (ECOG, age and extent of disease).

Overall response rate (ORR) was calculated as ratio of the number of patients with confirmed response between 8 and 24 weeks over the number of patients evaluable for tumour response within the 8 and 24 weeks after start of treatment. ORR rates were reported together with exact 95% confidence intervals (95%-CI) based on the Farrington–Manning score statistic.

Safety analysis was based on the safety population ($N = 106$) and included all randomised patients which received the study medication at least once. Adverse events, suspected events (defined as AEs whose relationship to study medication was rated as 'definite', 'probable' or 'possible') and SAEs were described by summarising tables subdivided by treatment regimen and indicating the percent of patients reporting each event at least once. Differences in occurrence between both treatment arms were analysed using two-sided exact Fisher test. Laboratory parameters, vital signs and electrocardiograms were summarised by time point and treatment regimen.

All statistical tests for secondary end-points were interpreted descriptively and explanatorily and no formal statistical conclusions were drawn. If not otherwise specified all p-values reported were based on two-sided tests and statistical significance is judged on the level of 0.05. No imputation methods for missing values were applied.

Biometric analyses were performed according to the Standard Operating Procedures (SOPs) of CESAR–EWIV using the statistical package SAS for Windows Version 9.3 (SAS Institute Inc, North Carolina) [19].

3. Results

3.1. Patient characteristics

In this multicenter study a total of 118 patients were recruited by 12 institutions starting on April 16, 2008 (1st patient in), and February 6, 2012 (last patient out). Of in total 118 screened patients, 113 patients were randomised (95.8%) and five patients had screening failures (4.2%). Seven (6.2%) of the 113 randomised patients did not receive any study medication (GEM: 3; SUNGEM: 4) while 106 patients (93.8%) received the study medication at least once and according to the study protocol represented the ITT population.

The median age of the intend-to-treat (ITT) population of 57 male (53.8%) and 49 female patients (46.2%) was 62.9 years (range 38.5–86.4 years). In both treatment groups, approximately one half had an ECOG performance status 0 and one half had an ECOG performance status 1. In 58 (54.7%) of the 106 patients the pancreatic tumour was located at the pancreas head and in 47 patients (44.3%) in the body or tail of the pancreas and in one patient the data were not available. The majority of patients ($n = 76$, 71.7%) had metastatic cancer, a total of 23 patients (21.7%) had locally advanced cancer and seven patients (6.6%) had both, locally

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Table 1
Patients' demographic data.

	Total ($N = 106$)	Gemcitabine (GEM) ($N = 54$)	Gemcitabine plus sunitinib (SUNGEM) ($N = 52$)	p-Value
Gender				
Male	57 (53.8%)	28 (51.9%)	29 (55.8%)	0.69*
Female	49 (46.2%)	26 (48.1%)	23 (44.2%)	
Age in years (median, range)	63.3 (38.5–86.4)	66.5 (43.2–86.4)	61.2 (38.5–82.4)	0.18*
Eastern Cooperative Oncology Group Performance Status (ECOG PS)				
0	47 (44.3%)	23 (42.6%)	24 (46.2%)	
1	59 (55.7%)	31 (57.4%)	28 (53.8%)	0.71*
Location of primary				
Head of pancreas	58 (54.7%)	32 (59.3%)	26 (50.0%)	0.18**
Body and tail	44 (41.5%)	21 (38.9%)	23 (44.2%)	
Head and body	3 (2.8%)	0 (0.0%)	3 (5.8%)	
Unknown	1 (0.9%)	1 (1.9%)	0 (0.0%)	
M-status at diagnosis				
Unknown	12 (11.3%)	9 (16.7%)	3 (5.8%)	0.06*
M0	17 (16.0%)	11 (20.4%)	6 (11.5%)	
M1	77 (72.6%)	34 (63.0%)	43 (82.7%)	
Time since 1st diagnosis in weeks (median, range)	2.3 (0.0–261.6)	2.4 (0.3–91.9)	2.2 (0.0–261.6)	0.81***
Tumour status at inclusion				
Locally advanced	23 (21.7%)	13 (24.1%)	10 (19.2%)	0.75**
Metastatic	76 (71.7%)	37 (68.5%)	39 (75.0%)	
Loc. advanced/metastatic	7 (6.6%)	4 (7.4%)	3 (5.8%)	
M-status at inclusion				
Unknown	7 (6.6%)	5 (9.3%)	2 (3.8%)	0.53**
M0	10 (9.4%)	4 (7.4%)	6 (11.5%)	
M1	89 (84.0%)	45 (83.3%)	44 (84.6%)	

* Chi square.
** Fisher exact test.
*** Wilcoxon.

advanced and metastatic cancer. The most frequently UICC status was 'IV' in 89 (84.0%) patients. The patients' baseline was well balanced between both treatment arms (Table 1).

Out of 106 patients, 98 (92.5%) patients terminated the study prematurely whereas eight (7.5%) patients terminated the study due to study closure.

3.2. Exposure

The median number of cycles was 4 for both treatment arms with a range of 1–12 cycles in the GEM arm and 1–15 cycles in the SUNGEM arm. The duration of one therapy cycle was 28 days for GEM and only 21 days for SUNGEM as described above. The distribution of administered cycles of the study drug is presented in Table 2.

Duration of treatment was calculated from the date of the first administration of gemcitabine to the date of last administration of gemcitabine or the last intake of sunitinib, whatever occurred later. Median duration of treatment was similar with 15.7 weeks (range: 0.0–52.6 weeks) for GEM and 15.5 weeks (range: 0.1–52.0 weeks) for SUNGEM (Table 3).

For gemcitabine, a total of 1.524 treatment days were recorded. A dose modification of gemcitabine was documented for 83 treatment days (SUNGEM: 36 out of 817 therapy days; GEM: 47 out of 707 therapy days). Out of the 106 patients of the safety population, 41 patients (38.7%) had at least one dose modification of gemcitabine during the study. For sunitinib, a total of 277 therapy cycles were recorded and a dose

Table 2
Administered cycles of study drug (the duration of a cycle was 28 days for gemcitabine (GEM) and 21 days for gemcitabine plus sunitinib (SUNGEM)).

Number of cycles	GEM ($N = 54$)	SUNGEM ($N = 52$)
1	9 (17%)	5 (10%)
2	10 (19%)	15 (29%)
3	6 (11%)	5 (10%)
4	8 (15%)	6 (12%)
5	3 (6%)	0 (0%)
6	6 (11%)	4 (8%)
7	2 (4%)	4 (8%)
8	4 (7%)	1 (2%)
9	1 (2%)	2 (4%)
10	2 (4%)	1 (2%)
11	0 (0%)	1 (2%)
12	3 (6%)	4 (8%)
13	0 (0%)	1 (2%)
14	0 (0%)	2 (%)
15	0 (0%)	1 (2%)

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Table 3
Duration of treatment.

Duration of treatment (weeks)	Gemcitabine (GEM) ($N = 54$)	Gemcitabine plus sunitinib (SUNGEM) ($N = 52$)
Mean	15.7	15.5
Standard Deviation (SD)	13.60	13.99
Median	12.4	10.9
Min	0.0	0.1
Max	52.6	52.0

modification was documented for 80 therapy cycles. Of the 52 patients of the safety population, 36 patients (69.2%) had at least one dose modification of sunitinib. In case of grade 3 neutropenia G-CSF (neutropenia) had to be administered additionally. G-CSF was administered in a total of 49 cycles out of the 518 therapy cycles (GEM: 18 out of 241 cycles; SUNGEM: 31 out of 277 cycles).

3.3. Efficacy

According to the study protocol patients were only evaluable for clinical response after treatment for at least 8 weeks and at least one staging performed within 8–12 weeks after start of treatment or earlier proof of progression of disease before. Out of 106 patients 40 patients did not receive the study medication for at least 8 weeks and one patient was not eligible for response. Out of the remaining 65 patients, four patients had no tumour lesion assessment within the time given. Therefore a total of 61 patients were evaluable for response (GEM 33; SUNGEM 28). Best response was assessed over a time period between a minimum of 8 weeks and a maximum of 2 years after randomisation depending on time under treatment.

3.4. Survival data

The primary objective of this study was to evaluate the superiority of the experimental arm SUNGEM versus GEM in regard to progression-free survival (PFS). The median PFS was not different with 13.3 weeks (95%-CI: 7.0–18.0 weeks) in the GEM arm and 11.6 weeks (95%-CI: 10.4–18.1 weeks) in the SUNGEM arm ($p = 0.60$; one-sided log-rank) (Fig. 1; Table 4). The PFS rates in the SUNGEM arm and the GEM arm were not statistically significantly different at the 10% significance level at 6 months ($p = 0.58$; one-sided log-rank) and at 12 months ($p = 0.75$; one sided log-rank).

A total of 97 of 106 patients (91.5%) were documented with PD or death [GEM: 48 of 54 (88.9%); SUNGEM 49 of 52 (94.2%)]. There was no statistically significant difference in TTP. The median time to progression (TTP) was 14.0 weeks (95%-CI: 12.4–22.3 weeks) for GEM and 18.0 weeks (95%-CI: 11.3–19.3 weeks) for SUNGEM ($p = 0.60$). The forest plot did not demonstrate any significant difference in TTP between subpopulations of patients allocated to GEM or SUNGEM (Fig. 2).

Eighty-five of 106 patients (80.2%) died [GEM: 40/54 (74.1%); SUNGEM: 45/52 (86.5%)]. The life-table-analysis (Kaplan-Meier) for overall survival (OS) is presented per treatment group of the total patient population in Fig. 3.

The median OS was 36.7 weeks (95%-CI: 20.6–49.0 weeks) in the GEM arm and 30.4 weeks (95%-CI: 18.1–37.6 weeks) in the SUNGEM arm. The OS was not statistically significantly different ($p = 0.78$, one-sided log-rank; $p = 0.44$ two-sided log-rank). The OS rate at 6 months was 60.9% (95%-CI: 45.7–73.1%) in the GEM arm and 52.5% (95%-CI: 37.6–65.4%) in the SUNGEM arm ($p = 0.80$) and at 12 months 28.1%

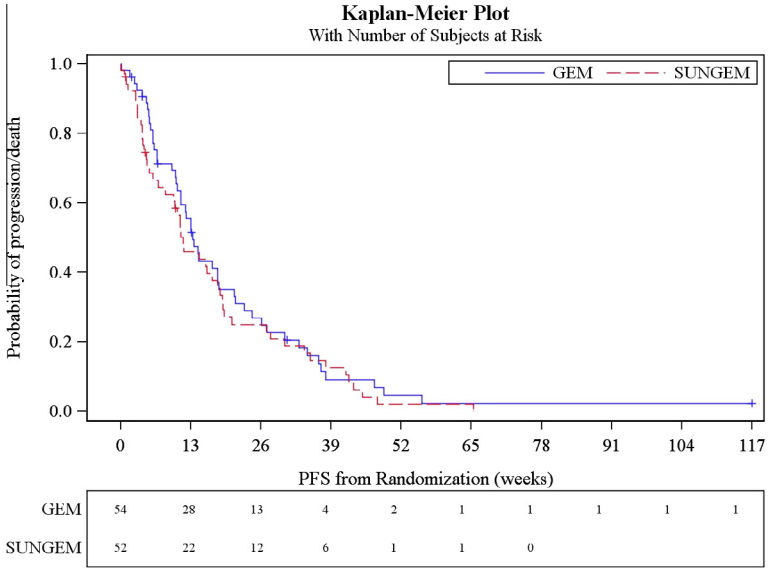

Fig. 1. Kaplan–Meier plot for progression free survival (PFS).

Table 4
Best overall response and survival data in the intent-to-treat population.

	Total	Gemcitabine (GEM)	Gemcitabine plus sunitinib (SUNGEM)	*p*-Value
Response	$N = 61$	$N = 33$	$N = 28$	
Partial remission (PR)	4 (6.6%)	2 (6.1%)	2 (7.1%)	0.61*
Stable disease (SD)	39 (63.9%)	20 (60.6%)	19 (67.9%)	
Progressive disease (PD)	17 (27.9%)	11 (33.3%)	6 (21.4%)	
not evaluable (NE)	1 (1.6%)	0 (0.0%)	1 (3.6%)	
Survival data	$N = 106$	$N = 54$	$N = 52$	
Progression free survival (PFS) (weeks)	13	13.3	11.6	0.78**
(median, 95%-confidence interval (CI))	(10.4–17.0)	(10.4–18.1)	(7.0–18.0)	
Time to progression (TTP) (weeks)	15.1	14	18	0.60**
(median, 95%-CI)	[12.6–19.0]	[12.4–22.3]	[11.3–19.3]	
Overall survival (OS) (weeks)	32.1	36.7	30.4	0.78**
(median, 95%-CI)	(22.0–37.9)	(20.6–49.0)	(18.1–37.6)	

* Fisher exact test.
** One-sided log-rank.

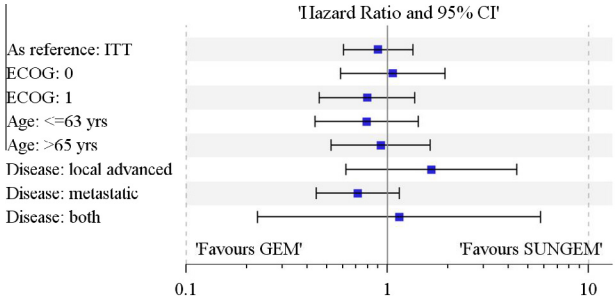

Fig. 2. Time to progression (TTP): Comparison between gemcitabine plus sunitinib (SUNGEM) and gemcitabine (GEM) in subgroups.

(95%-CI: 15.5–42.2%) versus 24.4% (95%-CI: 17.5–35.7%) ($p = 0.65$).

3.5. Response

Of the 61 for response evaluable patients, none had a confirmed complete remission (CR). There were partial remissions (PR) in four patients (6.6%) (GEM two patients; SUNGEM two patients). In addition, in another patient PR was not confirmed. Therefore this patient was considered to have stable disease (SD). All four patients with PR achieved the best response between 8 and 24 weeks after start of treatment. For both treatment arms, the majority of patients achieved SD as the best response. There was no statistical difference between both treatment arms. Details are listed in Table 4.

3.6. Safety and tolerability

Out of the 106 patients of the safety population, a total of 66 patients (62.3%) had at least one suspected SAE (GEM: 29 out of 54 patients (53.7%); SUNGEM: 37 out of 52 patients (71.2%)). Out of the 1507 AEs in total, 174 AEs were considered as SAEs (GEM: 77; SUNGEM: 97). The incidence of SAEs per patient

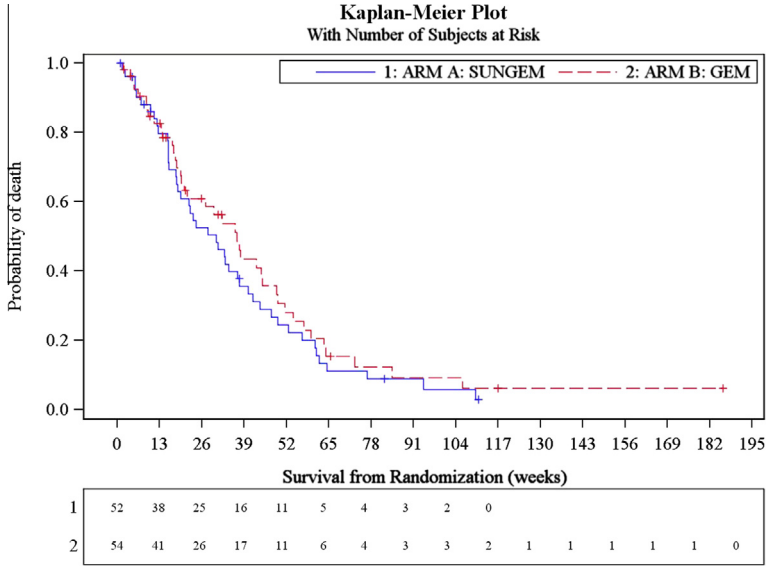

Fig. 3. Life-table-analysis (Kaplan–Meier) for overall survival.

Table 5
Major adverse events (all grades).

Adverse event	Total $N = 106$		Gemcitabine (GEM) $N = 54$		Gemcitabine plus sunitinib (SUNGEM) $N = 52$		p-Value
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	
Anaemia	15 (14.2%)	8 (7.5%)	7 (13.0%)	3 (5.6%)	8 (15.4%)	5 (9.6%)	0.78
Leucopenia	13 (12.3%)	9 (8.5%)	4 (7.4%)	2 (3.7%)	9 (17.3%)	7 (13.5%)	0.15
Neutropenia	39 (36.8%)	37 (34.9%)	15 (27.8%)	13 (24.1%)	25 (48.1%)	24 (46.2%)	0.045
Thrombocytopenia	26 (24.5%)	14 (13.2%)	13 (24.1%)	5 (9.3%)	13 (25.0%)	9 (17.3%)	1.00
Nausea	43 (40.6%)	5 (4.7%)	20 (37.0%)	3 (5.6%)	23 (44.2%)	2 (3.8%)	0.55
Fatigue	41 (38.7%)	11 (10.4%)	18 (33.1%)	4 (7.4%)	23 (44.2%)	7 (13.5%)	0.32
Diarrhoea	24 (22.2%)	0 (0.0%)	8 (14.8%)	0 (0.0%)	16 (30.8%)	0 (0.0%)	0.06
Vomiting	31 (29.2%)	6 (5.7%)	13 (14.1%)	4 (7.4%)	18 (34.6%)	2 (3.8%)	0.29
Pyrexia	18 (17.0%)	0 (0.0%)	7 (13.0%)	0 (0.0%)	11 (21.2%)	0 (0.0%)	0.31

was higher in the SUNGEM group, but did not reach statistical significance ($p = 0.07$, Table 5). The most common treatment-suspected AEs reported were nausea (40.6%), fatigue (38.7%), neutropenia (36.8%), vomiting (29.2%), thrombocytopenia (24.5%), diarrhoea (22.6%), pyrexia (17.0%), decreased appetite (15.1%), anaemia (14.2%), leukopenia (12.3%), constipation (10.4%), peripheral oedema (8.5%) and dysgeusia (8.5%) in the safety population ($N = 106$). The majority of treatment-suspected AEs were of grade 1 or 2 (Table 5). Grade 3 and 4 neutropenia was significantly higher in the SUNGEM arm with 44.2% versus 24.1% in the GEM arm ($p = 0.04$).

Discontinuation of treatment was due to disease progression in the majority of patients (46.2% for both arms) (GEM 50%; SUNGEM 42.3%), followed by adverse events in 13 patients (15.4% for both arms) (GEM 9.3%; SUNGEM 15.4%) and withdrawal of consent in 12 patients (11.3% for both arms) (GEM 13.0%; SUNGEM 9.6%). A total of 86 death were documented (81.1% of the safety population) of which 83 (96.5%) were caused by progression of the underlying disease. In the SUNGEM arm one patient died due to a multiple organ dysfunction syndrome, one patient due to a cardiac shock and one patient due to a bronchopneumonia.

4. Discussion

Locally advanced or metastatic PDAC is still associated with a poor prognosis and in recent years only limited progress has been made to improve its outcome [3,4]. The discovery of co-expression of VEGF and PDGF as a potential therapeutic target for pancreatic carcinoma has raised hope for new treatment options [20–23]. Inhibition of VEGF or VEGFR has shown to inhibit pancreatic tumour cell growth *in vitro* and in mouse models [21–23] and therapeutic concepts including TKIs in the treatment strategies of pancreatic cancer have been discussed [24–28]. Preliminary data of a phase-I trial suggested that bevacizumab, a VEGF-neutralising antibody, combined with standard chemo- and radiation therapy may be active in pancreatic cancer [27]. However, multiple therapeutic concepts with neutralising monoclonal antibodies and TKIs as monotherapy or in combination with gemcitabine have been disappointing [29].

Sunitinib represents an attractive drug for inhibiting multiple targets and shows potential activity against the desmoplastic stromal matrix which is fundamental for the development of pancreatic cancer [21]. This study demonstrated that sunitinib can be safely administered in combination with gemcitabine. In regard to the dose limiting toxicities of the phase-I data combining gemcitabine with sunitinib [16,17], the schedule for the SUNGEM arm had to be modified by administering gemcitabine on days 1 + 8 only and sunitinib for days 1-14 repeating this schedule every 3 weeks. The most common AEs experienced by patients receiving the combination of gemcitabine and sunitinib were consistent with the known safety profile of each agent individually. The most frequently reported treatment-related AEs were nausea, followed by fatigue and neutropenia. In the current study the median PFS and OS were 13.0 and 32.1 weeks, respectively. Despite the lower dose intensity of gemcitabine in the SUNGEM arm (667 mg/m^2/week) compared to the GEM arm (750 mg/m^2/week) SUNGEM caused significantly more neutropenia than GEM. Combination chemotherapy is a major strategy for improving therapeutic efficacy. However, addition of a second effective drug may result in a dose reduction of the standard drug and may limit a potential improvement of the clinical outcome.

The clinical activity was characterised by two patients with a partial objective response in each arm. Additionally, 20 patients allocated to GEM and 19 patients allocated to SUNGEM had stable disease as the best response including 18 patients in whom the duration of stable disease ranged from nine to 15 treatment cycles. The rate of patients with clinical benefit was slightly but not significantly higher in the SUNGEM arm (75.0% versus 66.7%) and did not translate into a better OS. In addition, some patients in our study received subsequent antitumour therapies such as docetaxel or local treatment of liver metastases after 1st line

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therapy, so that more comprehensive treatment may improve TTP and OS as well.

The only significant prognostic factor at a 5% significance level in the univariate Cox-regression of the TTP-dataset was the disease status at baseline (local advanced versus metastatic, $p = 0.04$). Patients with only locally advanced disease had a lower hazard of progression/death compared to patients with metastatic disease. However, univariate stratified analysis did not reveal any significant difference in the ECOG, age or extent of disease within the PFS and OS-dataset.

The median age of the study population in the current study was lower than the age at onset of pancreatic cancer internationally reported. Hence, it might be argued that the tested potency of SUNGEM cannot be a pointer for potency when used in an older cohort of pancreatic cancer patients with an ECOG status of 2.

O'Reilly et al. [30] demonstrated that sunitinib monotherapy after failure of gemcitabine had a limited efficacy as well, but the median time of treatment was rather low with one cycle sunitinib only. Furthermore, our study results are in accordance with the lack of improving clinical outcome by combining gemcitabine with the VEGFR inhibitors sorafenib [31–33] and axitinib [34–36] in 1st line. There was only a slightly higher ORR for the combination of gemcitabine with axitinib in comparison to gemcitabine but without any improvement in OS.

In summary, our study demonstrates that SUNGEM does not provide an advantage over GEM in any of the subgroups as it has more toxic side-effects than GEM without improving the clinical efficacy and can therefore not be recommended for patients with locally advanced or metastatic PDAC. In conclusion, our data together with those of Gonçalves et al. [33] with respect to sorafenib and Spano et al. [35] and Kindler et al [36] with respect to axitinib demonstrate, that the combination of VEGFR targeting tyrosine kinase inhibitors with gemcitabine does not seem to be an effective treatment approach in locally advanced or metastatic PDAC.

Conflict of interest statement

None declared.

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References

[1] Eheman C, Henley SJ, Ballard-Barbash R, et al. Report to the Nation on the status of cancer, 1975–2008, featuring cancers associated with excess weight and lack of sufficient physical activity. Cancer 2012;118(9):2338–66.
[2] Hackert T, Büchler MW, Werner J. Current state of surgical management of pancreatic cancer. Cancers (Basel) 2011;3(1):1253–73.
[3] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817–25.
[4] Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691–703.
[5] Feldmann G, Beaty R, Hruban R, Maitra A. Molecular genetics of pancreatic intraepithelial neoplasia. J Hepatobiliary Pancreat Surg 2007;14:224–32.
[6] Glienke W, Hausmann E, Bergmann L. Targeting STAT3 signaling in pancreatic cancer promotes antiapoptotic gene expression. Pancreas 2011;40(2):323–4.
[7] Glienke W, Hausmann E, Bergmann L. Downregulation of STAT3 signaling induces apoptosis but also promotes anti-apoptotic gene expression in human pancreatic cancer cell lines. Tumour Biol 2011;32(3):493–500.
[8] Mackenzie GG, Huang L, Alston N, Ouyang N, Vrankova K, Mattheolabakis G, et al. Targeting mitochondrial STAT3 with the novel phospho-valproic acid (MDC-1112) inhibits pancreatic cancer growth in mice. PLoS One 2013;8(5):e61532.
[9] Delbaldo C, Albert S, Dreyer C, Sablin MP, Serova M, Raymond E, et al. Predictive biomarkers for the activity of mammalian target of rapamycin (mTOR) inhibitors. Rev Targ Oncol 2011;6(2):119–24.
[10] Asano T. The PI3-kinase/Akt signaling pathway is activated due to aberrant Pten expression and targets transcription factor NF-kappaB and c-Myc in pancreatic cancer cells. Oncogene 2004;23:8571–80.
[11] Georgiadou D, Sergentanis TN, Sakellariou S, et al. VEGF and Id-1 in pancreatic adenocarcinoma: Prognostic significance and impact on angiogenesis. Eur J Surg Oncol 2014;40:1331–7.
[12] Glienke W, Maute L, Wicht J, Bergmann L. Curcumin inhibits constitutive STAT3 phosphorylation in human pancreatic cancer cell lines and downregulation of survivin/BIRC5 gene expression. Cancer Invest 2010;28(2):166–71.
[13] Bimonte S, Barbieri A, Palma G, et al. Curcumin inhibits tumor growth and angiogenesis in an orthotopic mouse model of human pancreatic cancer. Biomed Res Int 2013;2013:810423.
[14] Motzer RJ, Figlin RA, Hutson TE, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.
[15] Younus J, Verma S, Franek J, et al. Sunitinib malate for gastrointestinal stromal tumour in imatinib mesylate-resistant patients: recommendations and evidence. Curr Oncol 2010;17(4):4–10.
[16] Brell JM, Krishnamurthi SS, Rath L. Phase I trial of sunitinib and gemcitabine in patients with advanced solid tumors. Cancer Chemother Pharmacol 2012;70(4):547–53.
[17] Michaelson MD, Zhu AX, Ryan DP, McDermott DF, Shapiro GI, Tye L, et al. Sunitinib in combination with gemcitabine for advanced solid tumours: a phase I dose-finding study. Br J Cancer 2013;108(7):1393–401.
[18] Duffaud F, Therasse P. New guidelines to evaluate the response to treatment in solid tumors. Bull Cancer 2000;87(12):881–6.
[19] SOP 02: Evaluation and selection of a clinical trial proposal for CESAR. Onkologie 2003;26(Suppl. 6):5–10 [No authors listed].
[20] Fujimoto K, Hosotani R, Wada M, et al. Expression of two angiogenic factors, vascular endothelial growth factor and platelet-derived endothelial cell growth factor in human pancreatic cancer, and its relationship to angiogenesis. Eur J Cancer 1998;34(9):1439–47.
[21] Yokoi K, Sasaki T, Bucana CD, et al. Simultaneous inhibition of EGFR, VEGFR, and platelet-derived growth factor receptor signaling combined with gemcitabine produces therapy of human

pancreatic carcinoma and prolongs survival in an orthotopic nude mouse model. Cancer Res 2005;65(22):10371–80.
[22] Buchler P, Reber HA, Ullrich A, et al. Pancreatic cancer growth is inhibited by blockade of VEGF-RII. Surgery 2003;134(5):772–82.
[23] Wey JS, Fan F, Gray MJ, et al. Vascular endothelial growth factor receptor-1 promotes migration and invasion in pancreatic carcinoma cell lines. Cancer 2005;104(2):427–38.
[24] El Fitori J, Su Y, Buchler P, et al. PKC 412 small-molecule tyrosine kinase inhibitor: single-compound therapy for pancreatic cancer. Cancer 2007;110(7):1457–68.
[25] Kleespies A, Jauch KW, Bruns CJ. Tyrosine kinase inhibitors and gemcitabine: new treatment options in pancreatic cancer? Drug Resist Update 2006;9(1–2):1–18.
[26] Cabebe E, Fisher GA. Clinical trials of VEGF receptor tyrosine kinase inhibitors in pancreatic cancer. Expert Opin Investig Drugs 2007;16(4):467–76 [Review].
[27] Crane CH, Ellis LM, Abbruzzese JL, et al. Phase I trial evaluating the safety of bevacizumab with concurrent radiotherapy and capecitabine in locally advanced pancreatic cancer. J Clin Oncol 2006;24(7):1145–51.
[28] Awasthi N, Yen PL, Schwarz MA, et al. The efficacy of a novel, dual PI3K/mTOR inhibitor NVP-BEZ235 to enhance chemotherapy and antiangiogenic response in pancreatic cancer. J Cell Biochem 2012;113:784–91.
[29] Ko AH, Youssoufian H, Gurtler J, et al. A phase II randomized study of cetuximab and bevacizumab alone or in combination with gemcitabine as first-line therapy for metastatic pancreatic adenocarcinoma. Invest New Drugs 2012;30(4):1597–606.
[30] O'Reilly EM, Niedzwiecki D, Hall M, Hollis D, Bekaii-Saab T, Pluard T, et al. A Cancer and Leukemia Group B phase II study of sunitinib malate in patients with previously treated metastatic pancreatic adenocarcinoma (CALGB 80603). Oncologist 2010;15(12):1310–9.
[31] Scheulen ME, Mross K, Dittrich C, Hochhaus A, Morant R, Köberle D et al. (2005) Phase II study of first line sorafenib (BAY 43-9006) in patients with locally advanced and/or metastatic pancreatic cancer – a study of the Central European Society for Anticancer Drug Research–EWIV (CESAR). AACR-NCI-EORTC international conference "Molecular targets and cancer therapeutics; discovery, biology, and clinical applications", Philadelphia, PA, 14–18 November, 2005, Proceedings, p. 116.
[32] El-Khoueiry B, Ramanathan RK, Yang DY, Zhang W, Shibata S, Wright JJ, et al. A randomized phase II of gemcitabine and sorafenib versus sorafenib alone in patients with metastatic pancreatic cancer. Invest New Drugs 2011. http://dx.doi.org/10.11007/s10637-011-9658-9.
[33] Gonçalves A, Viret F, François E, Dahan L, Perrier H, Lamy R, et al. BAYPAN study: A double-blind, phase III randomized trial of gemcitabine plus sorafenib versus gemcitabine plus placebo in patients with advanced pancreatic cancer. J Clin Oncol 2011;29(Suppl.):4028.
[34] Spano JP, Moore MJ, Pithavala YK, Ricart AD, Kim S, Rixe O. Phase I study of axitinib (AG-013736) in combination with gemcitabine in patients with advanced pancreatic cancer. Invest New Drugs 2012;30(4):1531–9.
[35] Spano JP, Chodkiewicz C, Maurel J, Wong R, Wasan H, Barone C, et al. Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. Lancet 2008;371(9630):2101–8.
[36] Kindler HL, Ioka T, Richel DJ, Bennouna J, Létourneau R, Okusaka T, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. Lancet Oncol 2011;12(3):256–62.

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