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ORIGINAL ARTICLE

Gemcitabine combined with the monoclonal antibody nimotuzumab is an active first-line regimen in *KRAS* wildtype patients with locally advanced or metastatic pancreatic cancer: a multicenter, randomized phase IIb study

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Background: This randomized study was designed to investigate the superiority of gemcitabine (gem) plus nimotuzumab (nimo), an anti-epidermal growth factor receptor monoclonal antibody, compared with gem plus placebo as first-line therapy in patients with advanced pancreatic cancer.

Patients and methods: Patients with previously untreated, unresectable, locally advanced or metastatic pancreatic cancer were randomly assigned to receive gem: 1000 mg/m^2, 30-min i.v. once weekly (d1, 8, 15; q29) and nimo: fixed dose of 400 mg once weekly as a 30-min infusion, or gem plus placebo, until progression or unacceptable toxicity. The primary end point was overall survival (OS), secondary end points included time to progression, overall response rate, safety and quality of life.

Results: A total of 192 patients were randomized, with 186 of them being assessable for efficacy and safety (average age 63.6 years). One-year OS/progression-free survival (PFS) was 34%/22% for gem plus nimo compared with 19%/10% for gem plus placebo (HR = 0.69; $P = 0.03$/HR = 0.68; $P = 0.02$). Median OS/PFS was 8.6/5.1 months for gem plus nimo versus 6.0/3.4 mo in the gem plus placebo group (HR = 0.69; $P = 0.0341$/HR = 0.68; $P = 0.0163$), with very few grade 3/4 toxicities. *KRAS* wildtype patients experienced a significantly better OS than those with *KRAS* mutations (11.6 versus 5.6 months, $P = 0.03$).

Conclusion: This randomized study showed that nimo in combination with gem is safe and well tolerated. The 1-year OS and PFS rates for the entire population were significantly improved. Especially, those patients with *KRAS* wildtype seem to benefit. The study was registered as protocol ID OSAG101-PCS07, NCT00561990 and EudraCT 2007-000338-38.

Key words: gemcitabine, nimotuzumab, *KRAS* wildtype, pancreatic cancer, EGFR inhibitor

Introduction

Pancreatic cancer is nearly always fatal, with a 5-year survival rate below 5% [1]. Since most patients present with advanced disease, palliative chemotherapy remains the treatment of choice [2, 3]. With standard gemcitabine (gem), median survival in patients with advanced disease is under 6 months [4]. The combination of gem with numerous cytotoxic and targeted agents did not generally lead to a survival benefit. Recent meta-analyses in patients with metastatic pancreatic cancer indicate improvements in overall survival (OS) and progression-free survival (PFS) for some combination therapies [5, 6] as 5-fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX) or nab-paclitaxel plus gem [7, 8].

In terms of targeted therapies, only erlotinib, an inhibitor of the epidermal growth factor receptor (EGFR), added to gem showed a marginal survival benefit of 2 weeks [9].

Enhanced EGFR expression occurs in both primary and metastatic pancreatic cancer in about 30%–70% of the patients [10], although no obvious impact of EGFR expression on survival rates was observed [9]. The combination of cetuximab with gem failed to be more effective than gem alone [11].

Nimotuzumab (nimo) is a humanized IgG1 monoclonal antibody against the extracellular domain of EGFR that mediates anti-tumor effects by its capacity to inhibit proliferation, survival and angiogenesis [12, 13]. In contrast to other EGFR inhibitors, nimo has a very low toxicity profile, which was demonstrated in previous phase I/II studies [13, 14]. An explanation for the low incidence of skin rash has emerged from several experimental studies. Antibodies with an intermediate affinity for EGFR have a higher ratio of accumulation in tissues with higher EGFR expression levels (i.e. tumors) when compared with healthy tissues [15]. In contrast to cetuximab, the binding properties of nimotuzumab were strongly dependent on the EGFR expression levels of tumor cells [13]. These findings support a greater benefit of nimotuzumab in EGFR overexpressing tumors [18, 19].

Safety, efficacy and pharmacokinetics of nimo have already been examined in a phase II trial of patients with locally advanced or metastatic pancreatic cancer. The dose of 400 mg was defined for further clinical development because of pharmacokinetic limitations. Six out of the 36 patients assessable for response showed stable disease (median PFS 19.2 weeks). The only treatment-related adverse event was rash CTC grade 1 in 5 patients [16], apart from constitutional symptoms possibly related to the underlying disease. This randomized, placebo-controlled study analyzes the efficacy and safety of nimo in combination with gem for the first-line treatment patients with advanced or metastatic pancreatic cancer.

Patients and methods

Study design

This multi-institutional, placebo-controlled, randomized phase IIb trial was sponsored by Oncoscience AG, Wedel, Germany, with patients included into the trial between 2007 and 2011. Data were collected by the sponsor and were analyzed by a bio-statistician (CRM Biometrics GmbH, Rheinbach, Germany). An independent data and safety monitoring committee reviewed efficacy and safety data. The study was done in accordance with the Declaration of Helsinki. All patients gave their written informed consent. The institutional ethic committees at each site reviewed and approved the protocol. The study sponsor had no role in the study design, analysis, interpretation, writing, or the decision to submit for publication. The senior author had full access to all study data and final responsibility for the publication.

Patients

Chemotherapy-naïve patients with locally advanced or metastatic pancreatic cancer were eligible for this multi-institutional, randomized trial if they had histologically or cytologically confirmed locally advanced or metastatic adenocarcinoma of the pancreas not amenable to curative radiotherapy or surgery. Patients with measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 and sufficient organ functions were evaluated by the respective laboratory and imaging tests, and physical examinations. Patients had to be at least 18 years of age, with a Karnofsky performance score (KPS) $\geq$70%, and an estimated life expectancy of at least 12 weeks. Patients were excluded if they had any prior anticancer chemotherapy including adjuvant gem for pancreatic cancer, any investigational agent received concurrently or within the last 30 days, major surgery within the previous 3 weeks, symptomatic brain or leptomeningeal metastases, previous or concurrent malignancy other than pancreatic cancer, uncontrolled ascites, or other clinically significant co-morbidities.

Randomization and treatment

Eligible patients were randomly assigned to both gem and nimo or to gem and placebo, double-blinded in a one-to-one ratio. Randomization was carried out centrally ensuring equal distribution of patients on the basis of measurable lesions (locally advanced only versus metastatic disease). Briefly, patients received gem 1000 mg/m^2 (i.v., 30-min infusion) once weekly for 3 weeks, followed by a 1-week rest; and either additional nimo 400 mg fixed dose weekly or placebo, both administered i.v. as a 30-min infusion. Treatment was continued until death, progressive disease, unacceptable toxicity, patient's refusal or investigator's decision. Physical examinations, hematologic and biochemical tests were carried out at weekly intervals in both treatment groups. All adverse events were monitored according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) for Adverse Events (version 3.0). Treatment responses (according to RECIST version 1.0) were assessed by CT/MRI in week 8, 16, 24 and thereafter every 8 weeks until disease progression. Quality of life (QoL) was assessed using the EORTC QLQ C30 at baseline and 6, 12, 24, 48 and 72 weeks thereafter.

The primary end point was OS, secondary end points were PFS, overall response rate (ORR), duration of response (DR) and QoL, pain measurement (pain intensity, analgesic consumption) and safety (adverse events, clinical laboratory assessments).

Statistical analyses

The population for all analyses was defined based on the full-analysis (FAS) population that was defined as all patients, excluding patients who withdrew informed consent before any study specific treatment started, or patients about whom it became known a maximum of 4 weeks after randomization that major in/exclusion criteria were violated. Briefly, the primary end point OS was assessed in a confirmatory statistical analysis based on a two-sided statistical hypothesis test, determined from the date of randomization until death or last date of follow-up [17]. A two-sided log-rank test for equality of survival curves was used at a 5% significance level. Additionally, a one-sided log-rank test at a significance level of 5% for superiority was carried out as secondary analysis. The secondary end point time to tumor progression (TTP) was measured from the date of randomization to the occurrence of progression or death or to the last date of observation without progression or to death when relation to progression could be excluded. According to this definition, TTP corresponded to PFS commonly used for

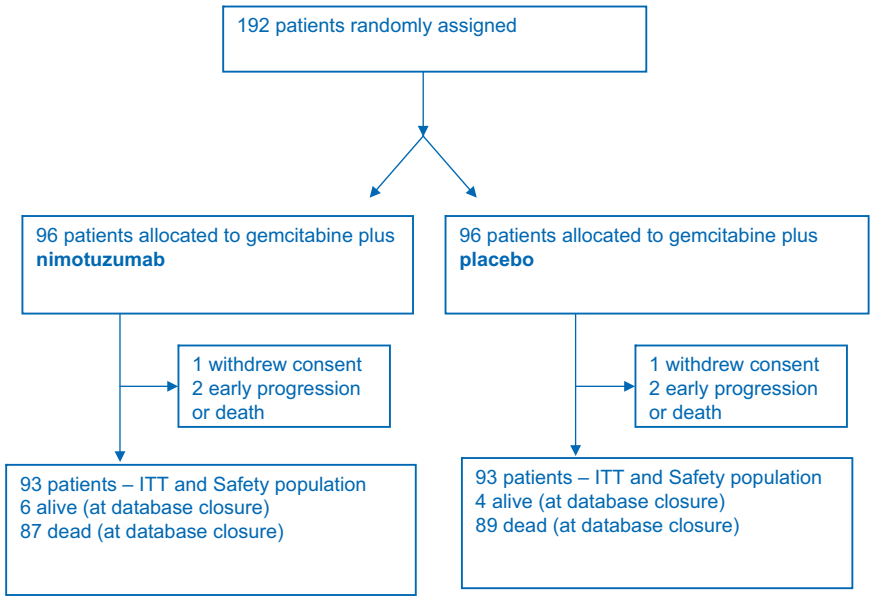

Figure 1. Overall survival (FAS population, T=1 year).

clinical trials. PFS and OS were described using the Kaplan–Meier method. Correspondingly, 95% confidence intervals were calculated for the median and specified survival rates (6 and 12 months). Further evaluation was carried out using Cox's regression model. All other analyses were carried out with an explorative aim. An increase in OS by 3 months or an increase in PFS by 2 months was to be considered as clinically relevant.

Results

Patients

A total of 192 patients with locally advanced or metastatic pancreatic cancer were enrolled from 16 study centers in Germany, Turkey, and Switzerland and randomly assigned to either gem plus nimo (n = 96 patients) or to gem plus placebo (n = 96 patients) (see Figure 1, CONSORT diagram). Demographic and clinical characteristics at baseline as well as *KRAS* status and EGFR-expression are shown in Table 1.

Study treatment

The median duration of treatment was 4 cycles (range 1–21) in the nimo plus gem group, each lasting 28 days, and 3 cycles (range 1–22) in the gem plus placebo group. (The main reason for treatment discontinuation was disease progression.)

Observation time

The observation time of 1 year was chosen in order to define identical conditions of analysis for all patients, especially in order to avoid interactions through second-line treatments, which 71% of all study patients received. Furthermore, 72% of the patients died during the first year; 63% in the gem plus nimo group and 80% in the gem plus placebo group. Hence, by this high number of events, the application of the log-rank tests for the observation time T = 1 year is used to provide the relevant results for the comparison of the OS and PFS rates, respectively.

Table 1. Patient baseline characteristics

Randomized: 192 patients ITT group=186 patients			**Nimotuzumab experimental arm *n*=93**	**Placebo control arm *n*=93**
Sex	Male	*n* (%)	61 (65.6%)	55 (59.1%)
	female		32 (34.4%)	38 (40.9%)
Age (years)	Mean		64.0	63.2
	SD		10.03	10.07
Pancreatic cancer			*n* =93	*n* =93
Only locally advanced			24 (25.8%)	16 (17.2%)
Metastatic (or: locally advanced and metastatic)			69 (74.2%)	78 (83.9%)
Karnofsky index			*n*=93	*n*=93
Missing			1 (1.1%)	0 (0.0%)
70			8 (8.6%)	6 (6.5%)
80			22 (23.7%)	20 (21.5%)
90			43 (46.2%)	38 (40.9%)
100			19 (20.4%)	29 (31.2%)
KRAS status			*n* =49	*n* =48
Wildtype			13 (26.5%)	20 (41.7%)
Mutation G12A (G35C)			1 (2.0%)	1 (2.1%)
Mutation G12D (G35A)			21 (42.7%)	13 (27.1%)
Mutation G12R (G34C)			4 (8.2%)	2 (4.1%)
Mutation G12S (G34A)			–	1 (2.1%)
Mutation G12V (G35T)			10 (20.4%)	11 (22.9%)
EGFR expression			*n* =48	*n* =48
–			30 (62.5%)	25 (52.1%)
+			7 (14.6%)	11 (22.9%)
++			4 (8.3%)	4 (8.3%)
+++			7 (14.6%)	8 (16.7%)

Overall survival

OS was measured in the FAS-population as described above. The Kaplan–Meier curve for OS for the FAS-population with

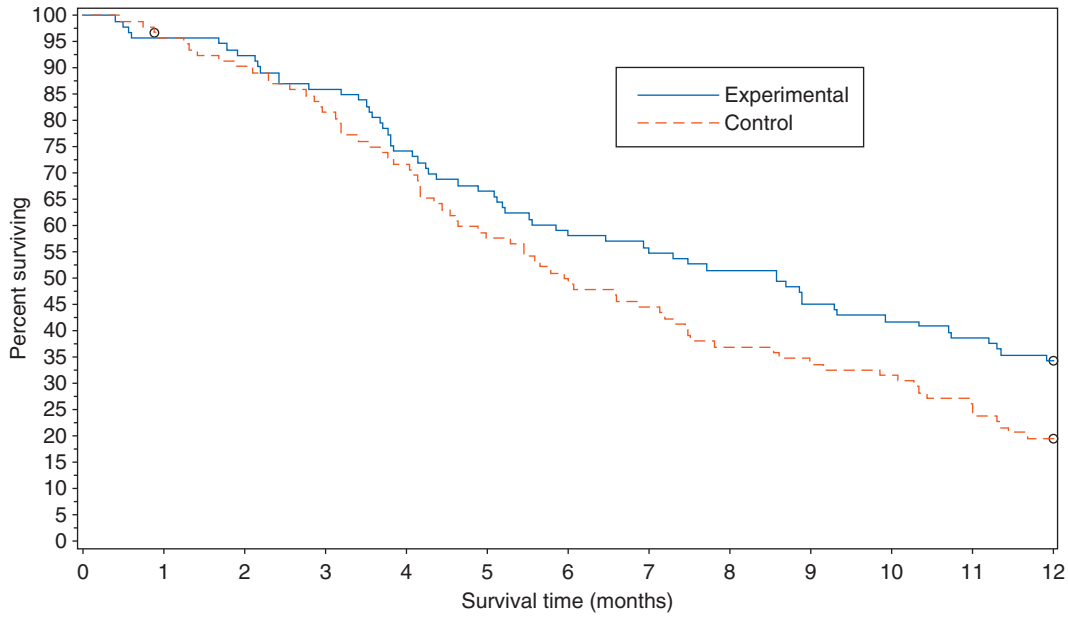

Figure 2. Overall survival (FAS population, $T = 1$ year).

administrative censoring at 12 months is presented in Figure 2. Median OS was 8.6 months for gem plus nimo (95% CI 5.8–10.7) and 6.0 months for gem plus placebo (95% CI 4.6–7.5), hazard ratio 0.69, $P = 0.03$. In addition, the OS rate after 12 months was significantly higher with gem plus nimo compared with gem plus placebo (34% versus 19%, $P = 0.03$). At 18 months, OS rates were 17% versus 9% for gem plus nimo and gem plus + placebo, respectively ($P = 0.07$), suggesting maximal efficacy of the nimotuzumab combination between 6 and 18 months after randomization (Table 2).

Progression-free survival

The median PFS was 5.1 months (95% CI 3.7–6.8) for gem plus nimo versus 3.4 months (95% CI 2.5–4.0) for gem plus placebo (hazard ratio 0.68; $P = 0.02$). The rate of PFS at 1-year was 22% in the gem plus nimo group, when compared with 10% in the gem plus placebo group (Figure 3).

Response rates

The objective response rates were not different among the treatment groups (partial response rate 8.6% for each group). However, the rate of disease control (confirmed response or stable disease for $\geq$16 weeks) was 63% in the gemcitabine + nimotuzumab group and 52% in the gemcitabine + placebo group (Table 2).

Subgroup analyses

Locally advanced versus metastatic patients. Patients with locally advanced disease usually have a better prognosis compared with patients showing metastatic disease. We therefore analyzed them separately. No difference was seen in OS and PFS rates between the two treatment arms for patients with locally advanced disease only. Metastatic patients treated with gem plus nimo had a 12-mo survival benefit (26.1% versus 14.5% with gem plus placebo) ($P = 0.04$). Similar results were obtained for PFS rates ($P = 0.02$) (Table 2).

Molecular biomarkers. Tissue sample of 97 patients were available. A total of 49 patients in the gem plus nimo group and 48 patients in the gem plus placebo group underwent molecular analyses by real-time PCR (LightCycler®) for *KRAS* mutations and EGFR-expression. Patients with *KRAS* wildtype had an OS benefit at 12 months ($P = 0.026$) in the gem plus + nimo group compared with the gem plus placebo group, whereas results for EGFR-overexpression just reach statistical significance (Table 2).

Adverse events and QoL

Common adverse events across both treatment groups were generally grade 1–2. Hematologic adverse events were very similar for both groups, with thrombocytopenia and leukopenia grade being slightly more frequent in the experimental arm (see supplementary Table S1, available at *Annals of Oncology* online). Here, the most frequent non-hematologic adverse events were fatigue (21.5% of patients, one patient grade 3), pyrexia (in 16.1%), chills (in 11.8%) and rash (in 15.1%, two patients grade 3). In addition, the proportion of patients with at least one serious adverse event was comparable across the two treatment groups (58.1% for gem plus nimo versus 65.6% for gem plus placebo). Quality-of-life assessments did not show statistically significant differences in both treatment arms (data not shown).

Discussion

This randomized study showed that in the entire study population, gem combined with nimo is safe and well tolerated with a significantly improved overall and PFS at 12 months. Even at 18 months, OS rates are still superior for the combination treatment, but did not reach statistical significance anymore. This is most likely due to the high number of events during the first 12 months. Moreover, survival benefit beyond 12 months was probably confounded by second-line therapies (more than 40% per arm), as patients were allowed to switch over to any further

Table 2. Overall survival, progression-free survival and response rates in the intent-to-treat population

Efficacy variable	Nimotuzumab plus gemcitabine (*n*=93)	Placebo plus gemcitabine (*n*=93)	Hazard ratio (95% CI)[a]	*P* value
Overall survival				
Median overall survival—months (95% CI)	8.6 (5.8–10.7)	6.0 (4.6–7.5)	0.69 (0.49–0.98)	0.0341
Survival rate—% (95% CI)				
12 months	34	19	0.69 (0.49–0.98)	0.0341
18 months	17	9	0.75 (0.55–1.02)	0.068
Overall survival rate 12 months—% (95% CI)				
Locally advanced	58.3 (36.4–75.0)	43.8 (19.8–65.6)	0.68 (0.28–1.67)	0.18
Metastatic	26.1 (16.4–36.8)	14.5 (7.7–23.3)	0.69 (0.47–1.03)	0.04
Overall survival rate 12 months—% (95% CI)	*n*=49	*n*=48		
KRAS wildtype	53.8 (26.7–80.9)	15.8 (0.0–32.3)	0.32 (0.13–0.84)	0.026
KRAS any mutation	27.8 (13.1–42.4)	17.9 (3.7–32.0)	0.86 (0.49–1.50)	0.390
Overall survival rate 12 months—% (95% CI)	*n*=48	*n*=48		
EGFR normal expression	32.4 (18.2–47.5)	20.0 (8.8–34.5)	0.66 (0.36–1.21)	0.11
EGFR overexpression	36.4 (11.2–62.7)	8.3 (0.5–31.1)	0.75 (0.35–1.56)	0.045
Progression-free survival				
Median progression-free survival—months (95% CI)	5.3 (3.8–7.0)	3.6 (2.6–4.5)	0.71 (0.52–1.02)	0.0524
Rate of progression-free survival—% (95% CI)				
12 months	22	10	0.71 (0.49–1.01)	0.0523
Response				
Rate of disease control[b]				
No. of patients (%)	59	48		
Best response—no. (%)				
Partial response	8 (8.6%)	8 (8.6%)		
Stable disease	51 (54.8%)	40 (43.0%)		
Progressive disease	23 (24.7%)	27 (29.0%)		
Not assessable for response[c]	11 (11.8%)	18 (19.4%)		
Progression-free survival rate 12 months—% (95% CI)				
Locally advanced	37.5 (19.0–56.0)	33.3 (12.2–56.4)	0.87 (0.40–1.92)	0.40
Metastatic	17.2 (9.2–27.3)	5.7 (1.8–12.8)	0.65 (0.44–0.96)	0.02

[a]The hazard ratio for death is provided for overall survival, and the hazard ratio for progression or death is provided for progression-free survival, with a hazard ratio of < 1 favoring the nimotuzumab-gemcitabine group.
[b]Disease control included confirmed complete response, confirmed partial response, and stable disease for 16 weeks or more.
[c]Patients who did not have an assessment after the baseline visit.

non-study treatment of disease progression. Because no standard second-line therapy was defined in pancreatic cancer patients, we did not perform further analysis on this issue. In our study, median OS was improved by 2.6 months in the gem + nimo group, with gem monotherapy being the standard treatment at the time of study initiation and being still an option for patients in reduced overall condition or suffering from co-morbidities. Within the protocol, we considered a 2-month increase in PFS as clinically significant, which was just missed, while a 3.6-month increase in OS can be considered as clinically relevant. However, the published median OS for pancreatic cancer treated with gem (6–7 months) in two large phase III trials fits well with what we could confirm in our patient cohort. At the time of study design, neither nab-paclitaxel nor FOLFIRINOX were standards of therapy yet. A large, randomized phase III study of nab-paclitaxel plus gem versus gem led to a median improvement in OS of 1.8 months [8]. The phase 2–3 trial of FOLFIRINOX versus gem also showed an improvement in median survival by 4.3 months [7]. Adverse events of grade 3 or higher in 46% of FOLFIRINOX-treated patients suggest that this regimen is an option only for patients with a good performance status [7].

In contrast, the safety profile for the gem plus nimo combination was favorable and comparable with the placebo arm. Chills, fatigue und pyrexia were slightly more frequent for the gem plus nimo group. Nimotuzumab was not associated with additional hematologic adverse events and only 15% of the patients experienced skin toxicity, mostly grade 1–2. Patients with significant co-morbidities are usually not candidates for more toxic regimens like those mentioned above. Molecular targeted drugs have been extensively evaluated in pancreatic cancer, but the EGFR inhibitor erlotinib was the only compound showing a minor increase in survival when combined with gem [9]. Cetuximab, another anti-EGFR monoclonal antibody, failed to improve survival in a randomized trial, however, without stratification to *KRAS* status [11].

The reported frequency of *KRAS*-WT in pancreatic cancer is ~10%–30%, and in our study the percentage is considerable

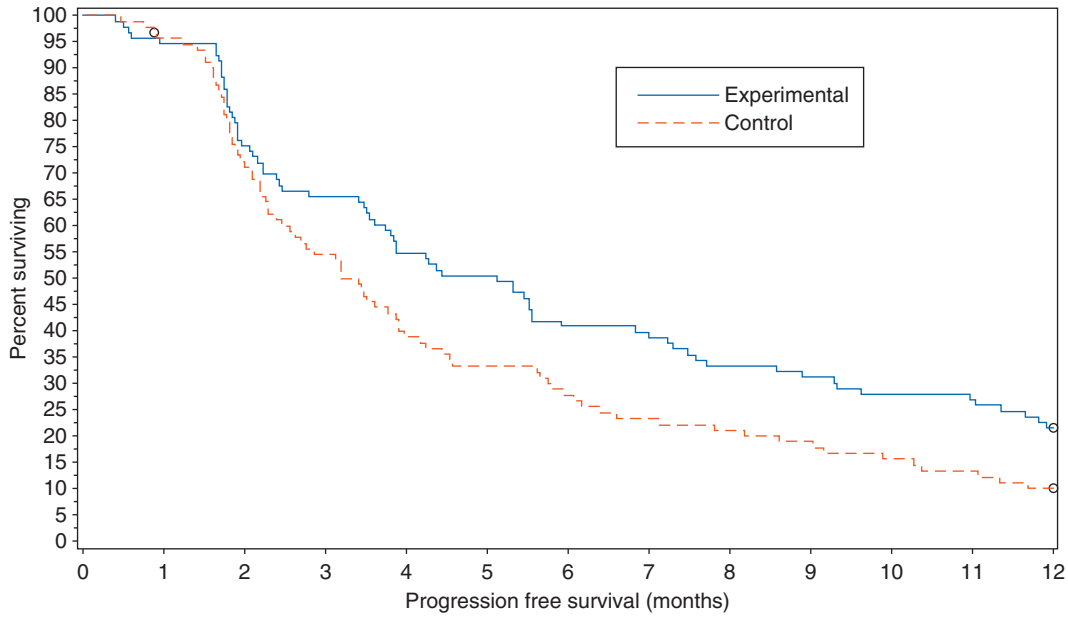

Figure 3. Progression-free survival.

higher than expected, probably due to sample-size or sample selection bias (i.e. PCR out of peritumoral inflammatory tissue). However, these potential confounding factors may lead to a higher *KRAS*-WT rate, which makes the survival advantage for those patients even more remarkable. It is well documented, that anti-EGFR-Abs failed in tumors with *KRAS*-mutations. Therefore, as expected, OS rates of patients with *KRAS* wildtype in the nimotuzumab group were significantly better compared with patients with *KRAS* mutations, consistent with cetuximab studies in colorectal cancer [19]. A phase II adjuvant trial in pancreatic cancer trial recently had shown a trend toward better survival in cetuximab-treated *KRAS* wildtype patients [20]. We therefore suggest antibody-based anti-EGFR-strategies in preselected *RAS-WT* pancreatic cancer patients for future clinical trials.

Many agents that have shown promising results in phase II trials in pancreatic cancer eventually failed in phase III trials. Therefore, a limitation of this study is that the total number of patients is not powered for a regular phase III study. Nevertheless, this randomized study showed a significant improvement in PFS and OS using gem in combination with nimo. A randomized phase III trial is planned to evaluate its benefit in *KRAS* wildtype patients, with extended biomarker analysis to investigate the molecular biology in this patient cohort.

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Disclosure

DR is employee of the sponsoring company; all remaining authors have declared no conflicts of interest.

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