

Multicenter phase II trial to investigate safety and efficacy of gemcitabine combined with cetuximab as adjuvant therapy in pancreatic cancer (ATIP)

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Background: To investigate whether addition of cetuximab to standard adjuvant chemotherapy with gemcitabine improves outcome in pancreatic cancer, specifically whether the rate of disease-free survival (DFS) at 18 months (primary end point) exceeds the previously reported 35% of gemcitabine alone.

Patients and methods: Prospective, open-label, multicenter, nonrandomized phase II study in 76 patients with R0- or R1-resected ductal adenocarcinoma of the pancreas included between October 2006 and November 2008. Gemcitabine and cetuximab were administered for 24 weeks. Secondary end points included overall survival (OS) and toxic effect.

Results: Seventy-three patients received cetuximab. Median DFS was 10.0 [95% confidence interval (CI) 8.9–13.6] months and the DFS rate at month 18 of 27.1% (16.7%–37.6%) was inferior to 35%. Median OS was 22.4 (18.2–27.9) months. Subgroup analyses revealed a nonsignificant increase in DFS for patients with versus without skin toxic effect $\geq$ grade 2 (median 14.7 versus 8.3 months, $P = 0.073$) and wild-type versus mutated K-Ras (median 11.5 versus 9.3 months, $P = 0.57$). Grade 3/4 toxic effects included neutropenia (11.0%), thrombopenia (7%), skin toxic effect (7%) and allergic reactions (7%).

Conclusion: Addition of cetuximab to adjuvant gemcitabine does not seem to improve DFS or OS of unstratified pancreatic cancer patients. Trends for improved DFS in patients with wild-type K-Ras and skin toxic effect remain to be confirmed.

Key words: adjuvant chemotherapy, cetuximab, gemcitabine, pancreatic cancer

Introduction

Only 10%–20% of pancreatic cancer patients can be resected with curative intention at the time of diagnosis. The 5-year survival of patients with resected pancreatic adenocarcinoma is ~14% for patients without any type of adjuvant or neoadjuvant therapy [1].

To improve this situation, many cancer centers in the United States consider adjuvant chemoradiotherapy as standard of care. In Europe, adjuvant chemotherapy is usually preferred over radiochemotherapy as adjuvant treatment. Among others, this

is based on data from the ESPAC-1 trial showing that chemoradiotherapy was associated with reduced survival when compared with chemotherapy or observation, whereas 5-fluorouracil (5-FU)-based chemotherapy significantly prolonged survival [2]. The German CONKO-001-study group evaluated gemcitabine versus observation for adjuvant treatment and showed a significantly improved disease-free and overall survival [3]. Although the ESPAC-3 trial reported equal efficacy of adjuvant gemcitabine and 5-FU [4], gemcitabine has a more favorable toxic effect profile and is considered as standard for adjuvant treatment in pancreatic cancer.

The addition of targeted agents has been evaluated both in palliative and adjuvant treatment of pancreatic cancer, among them antibodies directed against the epidermal growth

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factor-receptor (EGF-R). In pancreatic cancer, the EGF receptor is overexpressed in a large fraction of the tumors and is associated with an aggressive disease and poor prognosis [5]. The monoclonal antibody cetuximab inhibits tumor growth in pancreatic cancer cell lines and shows additive effects to chemotherapy with gemcitabine [6]. Before the commencement of our trial first results of a small phase II study had demonstrated promising results with 12.2% partial remissions and stable disease in 63.4% of patients with advanced pancreatic cancer [7].

Based on these data, we initiated the ATIP trial as multicenter trial of the German AIO (Arbeitsgemeinschaft Internistische Onkologie) to evaluate the combination of gemcitabine and cetuximab as adjuvant treatment of pancreatic cancer in a phase-II single-arm trial.

methods

patient population

Between October 2006 and November 2008, patients with R0- or R1-resected ductal adenocarcinoma of the pancreas were recruited within 8 weeks after surgery at eight university hospitals and two academic teaching hospitals in Germany. The inclusion and exclusion criteria are provided as supplementary Table S1, available at *Annals of Oncology* online.

statistical design and analysis

This trial was designed as an open-label, phase-II, nonrandomized multicentric trial. The primary aim was to determine whether cetuximab in combination with gemcitabine leads to an increased disease-free survival (DFS) when compared with the results of gemcitabine alone reported, e.g. by the German CONKO-001 trial [3] for the adjuvant treatment of patients with pancreatic cancer. The patient population and the treatment protocol of our ATIP trial and the CONKO-001 trial are well comparable (supplementary Table S2, available at *Annals of Oncology* online).

Kaplan–Meier estimates of probabilities for DFS and overall survival (OS) were provided with point-wise two-sided 95% Greenwood confidence intervals. Following intention-to-treat principles with slight modification, we included all patients receiving at least one application of trial medication for the primary efficacy and safety analysis.

The primary efficacy analysis consisted of an evaluation of the rate of patients with DFS at month 18 after registration (primary end point) for which the reported DFS rate of adjuvant gemcitabine alone is 35%. Owing to the pilot character of this phase II trial, for statistical testing of the primary objective, the null-hypothesis '18-months DFS equals 35%' was tested at a significance level of 5% against the one-sided alternative hypothesis '18 months DFS exceeds 35%', corresponding to a two-sided 90% Greenwood confidence interval. Assuming a loss to follow-up rate of at most 10%, the sample size of 73 patients was pre-specified in the study protocol in order to power with 80% a DFS rate of 50% at 18 months.

The study was approved by the ethical committees of all participating centers. The study registration number is NCT00395252 (clinicalTrials.gov, Identifier).

study treatment

Eligible patients received adjuvant treatment with cetuximab and gemcitabine as follows: A cetuximab loading dose of 400 mg/m² was administered over 2 h on day 1, followed by weekly administrations of 250 mg/m² over 1 h for a total of up to 24 weeks. Gemcitabine was administered over 30 min at a dose of 1000 mg/m² on days 1, 8 and 15 one h after the

application of cetuximab, followed by a one-week rest of gemcitabine.

Treatment courses of gemcitabine were repeated on day 29 and a total of six treatment courses of 4 weeks were scheduled.

Secondary end points were overall survival, quality of life and incidence of adverse events. Efficacy was measured by assessment of a possible disease recurrence at end of treatment and during follow-up every 3 months until month 18. For assessment of recurrence, spiral computer tomography (CT) or magnet resonance imaging (MRI) were used. Recurrence was defined either clinically or by imaging. In case of clinically evident, recurrence such as subclavicular lymph nodes or skin metastasis or any palpable mass cytological or histological proof was required.

Toxic effect was recorded weekly using the NCI-CTC version 3.0.

Moreover, quality of life was reported using the questionnaire 'QLQ-C30' of the European Organization for Research and Treatment of Cancer (EORTC).

dose modifications and delay of treatment

Gemcitabine was given without dose modification or delay if neutrophils were $>1.0 \times 10^9/l$ and platelets $>100 \times 10^9/l$ and any other nonhematological toxic effect was $<$ grade 2. Cetuximab was administered without dose modification and delay in the absence of skin toxic effect $>$ grade 2. The dose reduction regimens for gemcitabine and cetuximab are given as supplementary Table S3, available at *Annals of Oncology* online.

discontinuation of treatment

Patient treatment was terminated during the study for any of the following reasons: Serious or life-threatening adverse event, a delay of treatment with cetuximab for more than 2 consecutive weeks, failure to comply with the dosing, evaluations, or other requirements of the study, patient's request, pregnancy, recurrence of disease, drug-related toxic effects not alleviated by consecutive dose modifications or at the investigator's discretion.

K-Ras mutation status

Tumor DNA was extracted after microdissection of tumor cells from histological sections of paraffin-embedded tissue. K-Ras point mutations in codons 12 and 13 were analyzed with a high-resolution melting assay [8].

results

enrollment and patient characteristics

Between October 2006 and November 2008, 76 patients were enrolled. Patient characteristics are summarized in supplementary Table S2, available at *Annals of Oncology* online: Mean age was 62.7 years, 42 patients (55.3%) were male. Patients (89.5%) had an ECOG-performance status of 0 or 1.

Forty-seven of 68 (69.1%) patients had a mutation in codon 12 or 13 of the K-Ras oncogene. Histopathological evaluation of the resected specimens documented 22.4% R1-resections. The UICC tumor formula for the majority of patients was T3 (85.5%) and N1 (71.1%). Only two tumors were well differentiated (G1, 2.6%), whereas the majority displayed G2 or G3 differentiation.

Seventy-three patients received at least one infusion of cetuximab. These patients constitute the basis for the efficacy and safety analysis (supplementary Figure S1, available at *Annals of Oncology* online). The remaining three patients also did not receive gemcitabine as study treatment and follow-up stopped early (one patient was lost to follow-up immediately after inclusion; one patient relapsed before the start of treatment

and one patient had a delay between surgery and start of treatment of more than 8 weeks). Overall, 52 of 73 patients receive one or more post study treatments (supplementary Table S4, available at *Annals of Oncology* online).

efficacy

Median DFS was 10.0 (8.9–13.6) months and the DFS rate at 18 months was 27.1% (16.7%–37.6%) thus failing to demonstrate superiority over 35% ($P = 0.930$, Figure 1A), which is the DFS reported for adjuvant gemcitabine. Median OS was 22.4 (18.2–27.9) months (Figure 1B). Subgroup analyses (Table 1) revealed no statistical significant differences, but showed the following trends: patients with R0-resection had a longer DFS (11.5 versus 8.1 months, $P = 0.67$) and OS (24.1 versus 15.0 months, $P = 0.50$) than R1-resected patients ($N = 16$ only). Also, in nodal-negative patients DFS (25.8 versus 9.1 months, $P = 0.082$) and OS (33.8 versus 21.5 months, $P = 0.096$) were longer than in nodal-positive patients. T stage (T1/2 versus T3/4) apparently had less influence on DFS (8.5 versus 10.2 months) and OS (24.6 versus 21.5 months).

Wild-type K-Ras patients had a median DFS of 11.5 months compared with 9.3 months ($P = 0.57$) in patients with a codon 12 or 13 K-Ras-mutation (Table 1 and supplementary Figure S3, available at *Annals of Oncology* online). In the same way, OS was not significantly different (21.5 versus 24.0 months, $P = 0.18$) and the observed trend in favor of mutated K-Ras suggests that the K-Ras mutational status had no major effect on DFS and OS.

DFS in patients with skin toxic effect $\geq$ grade 2 after one cycle of therapy (Table 1 and supplementary Figure S2, available at *Annals of Oncology* online) tended to be longer than in patients with a skin toxic effect of grade 0 or 1 (14.7 versus 8.3 months, $P = 0.073$); however, this observation failed to reach statistical significance. In the same way, the presence or absence of skin toxic effect was not associated with significant differences in overall survival (22.7 versus 20.6 months, $P = 0.19$, Table 1 and supplementary Figure S2, available at *Annals of Oncology* online). The serum levels of CA19-9 before the start of adjuvant treatment had no influence on DFS or OS (Table 1 and supplementary Table S2, available at *Annals of Oncology* online).

In 61 patients, the site of recurrence was known. Twelve (20%) patients had local recurrence and 49 patients had distant metastases (80%). Main sites of distal recurrence were the liver (23 patients, 47%) and the lung (15, 31%).

Fifty percent of the patients ($N = 37$) had a treatment delay of 7 days or more. Twenty-nine patients (39.7%) never had a treatment delay of more than 6 days. Seven patients received only one single treatment application.

toxic effect

Seventy (95.9%) of the 73 patients with at least one infusion of cetuximab received at least one infusion of gemcitabine. 64.4% of the patients ($N = 47$) received six treatment courses of gemcitabine, 78.1% of the patients ($N = 57$) received at least four courses of gemcitabine and 65.8% of the patients ($N = 48$) received all six cycles of cetuximab. 78.1% of the patients ($n = 57$) received at least four courses of cetuximab. The reasons

for treatment discontinuation were tumor relapse (8.2%), toxic effect (11.0%), patient withdrawal (6.9%), death (2.7%) and other reasons (11.0%).

Only three grade 4 toxic effects occurred (supplementary Table S5, available at *Annals of Oncology* online) in three patients experiencing thrombocytopenia (4%). Most grade 3 toxic effects were hematologic toxic effects (18%) comprising eight patients with leucopenia (11%), three with anemia (4%) and two with thrombopenia (3%). The main nonhematologic grade 3 toxic effects were skin toxic effect and allergic reactions, five patients (7%) each.

quality of life

Before the start of therapy, in 68 (93.2%) of the 73 treated patients, an ECOG status was available and 54 (74%) completed the quality-of-life questionnaire before therapy. The ECOG status was 0 or 1 in 60 patients (88.2%) and the global health status measured with the EORTC-QLQ-C30 questionnaire was $52.8\% \pm 20.7\%$.

Seventy (95.9%) of the treated patients survived the treatment phase lasting about 6 months with intended six courses of gemcitabine and cetuximab. One patient died shortly afterwards. At the end of the treatment phase, the ECOG status was documented in 40 patients (57.1% of 70 patients alive), and was 0 or 1 in 35 (87.5%). The quality-of-life questionnaire was completed by 34 patients (48.6% of patients alive), presenting with a global health status of $56.6\% \pm 23.1\%$.

Pre-post changes or differences during the intended treatment phase could be assessed in 38 patients (54.3% of the patients alive) and 30 patients (42.9%) for ECOG status and quality of life, respectively. ECOG status was unchanged, improved or worsened in 21, 4 or 13 patients (55.3%, 10.5% and 34.2%), respectively. The global health status of the patients alive showed a nonsignificant increase from $55.8 (\pm 20.2)\%$ before $56.9 (\pm 22.4)\%$ after treatment.

discussion

Adjuvant therapy for resected pancreatic adenocarcinoma is now established as standard of care. Studies using gemcitabine or 5-fluorouracil (5-FU)-based adjuvant chemotherapies reproducibly report doubling of DFS to 13–14 months and 5-year OS to 20%–25% [3, 4]. The present trial was designed in the aftermath of the CONKO-001 trial [3] which established gemcitabine as the standard of care in adjuvant treatment of pancreatic cancer in Europe, and had the aim to further improve the efficacy of adjuvant gemcitabine by adding cetuximab.

The study populations in our trial and the German CONKO-001 trial are comparable and reflect the situation in German high-volume-centers for resectable pancreatic cancer (supplementary Table S2, available at *Annals of Oncology* online). Thus, comparison of the results of our trial and the CONKO-001 trial allows to appraise the effect of adding cetuximab to gemcitabine for adjuvant treatment of ductal adenocarcinoma of the pancreas.

The primary end point of our trial was DFS at month 18 (DFS 18) which was 27.1%, and thus failed to be superior to the

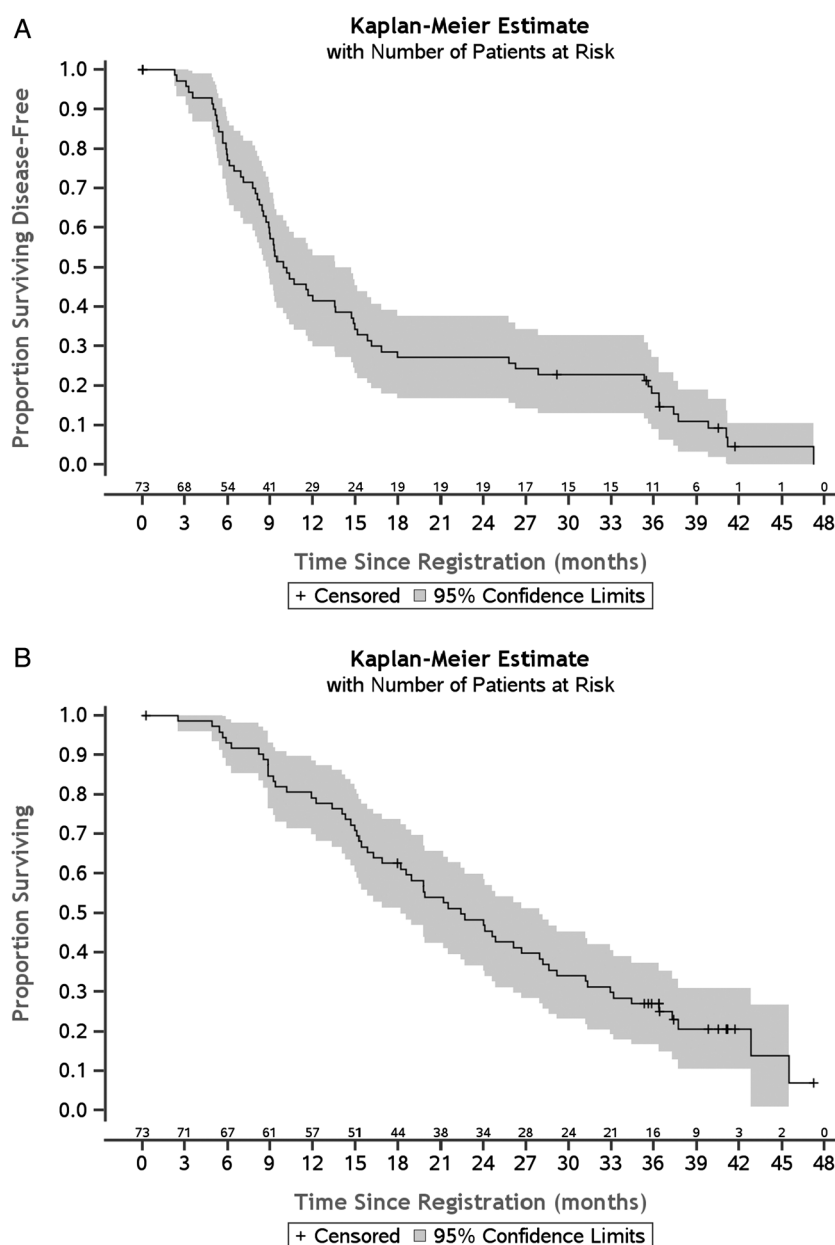


Figure 1. Disease-free (A) and overall survival (B) Kaplan-Meier estimates of probabilities for disease-free survival (DFS) and overall survival (OS). For the intention-to-treat analysis, we included all patients that received at least one application of trial medication.

reported 35% for gemcitabine alone initially defined as null hypothesis. The values observed for median DFS (10.0 months) and for median OS (22.4 months) are comparable to the ones observed in the CONKO-001 trial with adjuvant gemcitabine alone (DFS 13.4 months, OS: 21.7 months) [3]. Differences to results reported in the CONKO-001 trial were only observed for subgroups with small patient numbers such as the DFS of R1-patients (8.1 months for $N = 16$ versus 15.8 months in CONKO-001) and the median OS of T1/2-patients (24.6 months for $N = 9$ versus 48.2 months in CONKO-001). However, no substantial conclusions are possible since the patient numbers in these subgroups were too small.

When compared with the CONKO-001 trial, toxic effect and quality of life were not relevantly influenced by adding

cetuximab. Additional grade-3 toxic effects were only observed for skin toxic effect (7%) and allergic reaction (7%). Overall, our trial suggests that addition of cetuximab to adjuvant gemcitabine does not provide any additional benefit to the unstratified population of patients receiving potentially curative surgery for pancreatic ductal adenocarcinoma.

As for other tumors such as colorectal cancer resistance to palliative treatment with cetuximab has been associated with the presence of K-Ras mutations [9], we carried out a mutation analysis of K-Ras codons 12 and 13.

In ductal adenocarcinoma of the pancreas, K-Ras mutations have historically been reported to be detected in 30% of early neoplasms with the frequency rising to nearly 100% in advanced PDAC [10].

Table 1. Disease-free survival (DFS) and overall survival (OS) (N = 73, median in months)

Subgroup	N	DFS	OS
R0	57	11.5	24.1
R1	16	8.1	15.0
T stage			
T1-2	9	8.5	24.6
T3-4	64	10.2	21.5
N stage			
N0	18	25.8	33.8
N1-2	54	9.1	21.5
K-Ras status			
Wild-type	21	11.5	21.5
Mutated	45	9.3	24.0
Skin toxic effect			
Grade 0/1	32	8.3	20.6
≥Grade 2	23	14.7	22.7
CA 19-9 pretreatment			
≤37 U/ml	44	9.3	22.5
>37 U/ml	28	10.3	19.9

In our study population, the rate of patients with K-Ras codon 12 and 13 mutations was 69%, which is lower than the historically reported data, but similar to other recently reported data. Among others, 121 of 173 (69.9%) PDAC patients had K-Ras mutations in the German AIO- PK0104 trial [11].

In the subgroup analyses of the ATIP trial, K-Ras-wild-type patients appeared to have a longer median DFS (11.5 months) but no longer OS (21.5 months) than patients with a codon 12 or 13 K-Ras-mutation (DFS: 9.3 months, OS: 24.0 months). However, results were not statistically significant which may be due to the small sample size of the individual subgroups. Only a randomized study sufficiently powered for both, patients with and without K-Ras mutations will answer the question whether the K-Ras mutation status has an influence on the response to treatment with cetuximab. Currently, it remains unclear for pancreatic cancer whether K-Ras is a predictive marker for anti-EGFR treatments or rather a prognostic biomarker. A recent *post hoc* analysis of the K-Ras status in the above mentioned AIO-PK0104 trial [11] indicates that wild-type K-Ras patients have an improved survival that was not dependent on concomitant erlotinib treatment, which would favor a role as prognostic biomarker [12]. In our study, it appeared that patients experiencing a rash ≥grade 2 after 1 course of therapy showed a nonsignificant trend to a longer DFS. Thus, in the same way as in the palliative situation when treating with gemcitabine plus erlotinib [13], the appearance of a skin rash could serve as a predictive parameter that may help in patient stratification. However, this hypothesis needs to be tested in a randomized, sufficiently powered trial.

In conclusion, in the same way as recently shown for the palliative situation [14], addition of cetuximab to gemcitabine does not seem to improve DFS or OS in the adjuvant treatment of pancreatic cancer patients. As the ATIP trial was done in a comparable setting, design and patient population as CONKO-001 and could not demonstrate any benefit, we suggest that no phase III trial in an unstratified population should be started to

further test this adjuvant regimen. However, our subgroup analyses though showing only non-significant trends towards improved DFS suggest that it may be reasonable to perform a trial with a patient population stratified according to the appearance of a skin rash and the K-Ras mutational status.

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disclosure

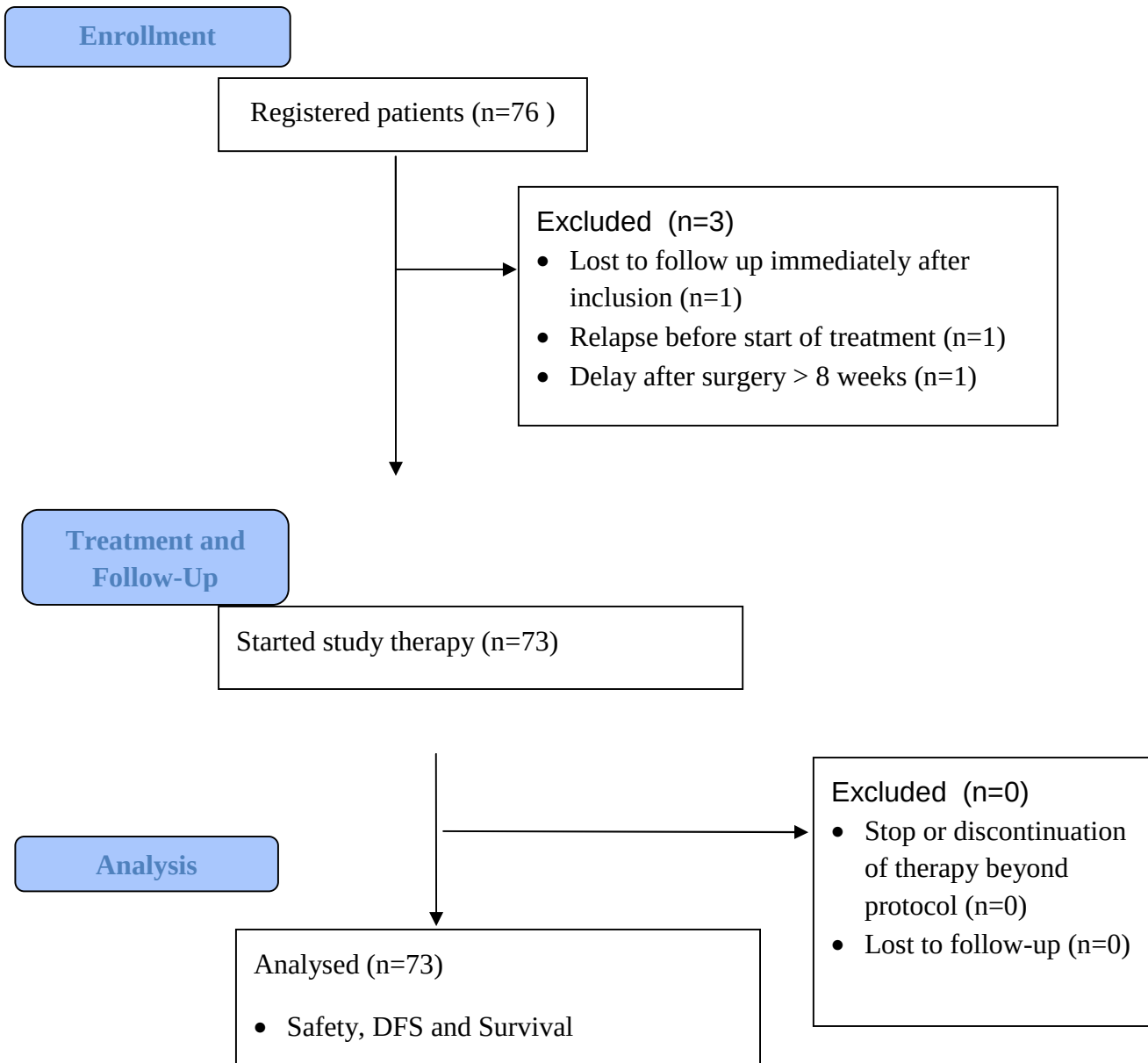
Drugs were provided by Merck KGaA. Merck KGaA has reviewed the publication, the views and opinions described in the publication do not necessarily reflect those of Merck KGaA. Merck KGaA had not influence on the analysis and interpretation of the study results. HF received honorary and was expert testimony of Roche. He got also congress travel support of Roche and Merck KGaA. RH received honorary and research funding of Merck KGaA. All remaining authors have declared no conflicts of interest.

references

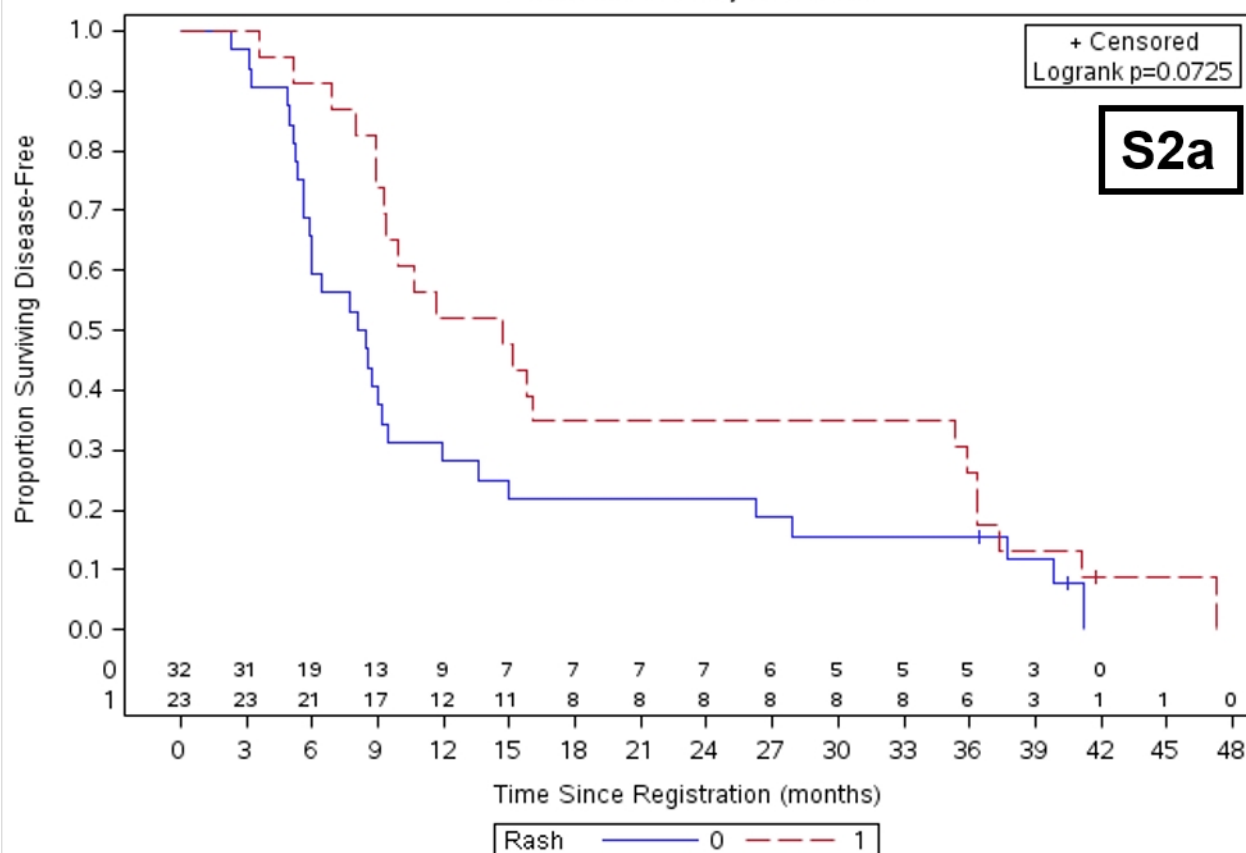
- Jemal A, Siegel R, Xu J et al. Cancer statistics, 2010. *CA Cancer J Clin* 2010; 60(5): 277–300.
- Neoptolemos JP, Stocken DD, Friess H et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; 350(12): 1200–1210.
- Oettle H, Post S, Neuhaus P et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007; 297(3): 267–277.
- Neoptolemos JP, Stocken DD, Bassi C et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010; 304(10): 1073–1081.
- Valsecchi ME, McDonald M, Brody JB et al. Epidermal growth factor receptor and insulinlike growth factor 1 receptor expression predict poor survival in pancreatic ductal adenocarcinoma. *Cancer* 2012; 118(14): 3484–3493.
- Graham J, Muhsin M, Kirkpatrick P. Cetuximab. *Nat Rev Drug Discov* 2004; 3(7): 549–550.
- Xiong HQ, Rosenberg A, LoBuglio A et al. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II trial. *J Clin Oncol* 2004; 22(13): 2610–2616.
- Do H, Krypuy M, Mitchell PL et al. High resolution melting analysis for rapid and sensitive EGFR and KRAS mutation detection in formalin fixed paraffin embedded biopsies. *BMC Cancer* 2008; 8: 142.
- Van Cutsem E, Kohne CH, Lang I et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 2011; 29(15): 2011–2019.
- Rozenblum E, Schutte M, Goggins M et al. Tumor-suppressive pathways in pancreatic carcinoma. *Cancer Res* 1997; 57(9): 1731–1734.

11. Heinemann V, Vehling-Kaiser U, Walschmidt D et al. Gemcitabine plus erlotinib followed by capecitabine versus capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomised phase 3 trial of the 'Arbeitsgemeinschaft Internistische Onkologie' (AIO-PK0104). *Gut* 2013; 62: 751–759.
12. Boeck S, Jung A, Rüdiger P et al. KRAS mutation status is not predictive for objective response to anti-EGFR treatment with erlotinib in patients with advanced pancreatic cancer. *J Gastroenterol* 2013; 48: 544–548.
13. Moore MJ, Goldstein D, Hamm J et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; 25(15): 1960–1966.
14. Philip PA, Benedetti J, Corless CL et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol* 2010; 28(22): 3605–3610.

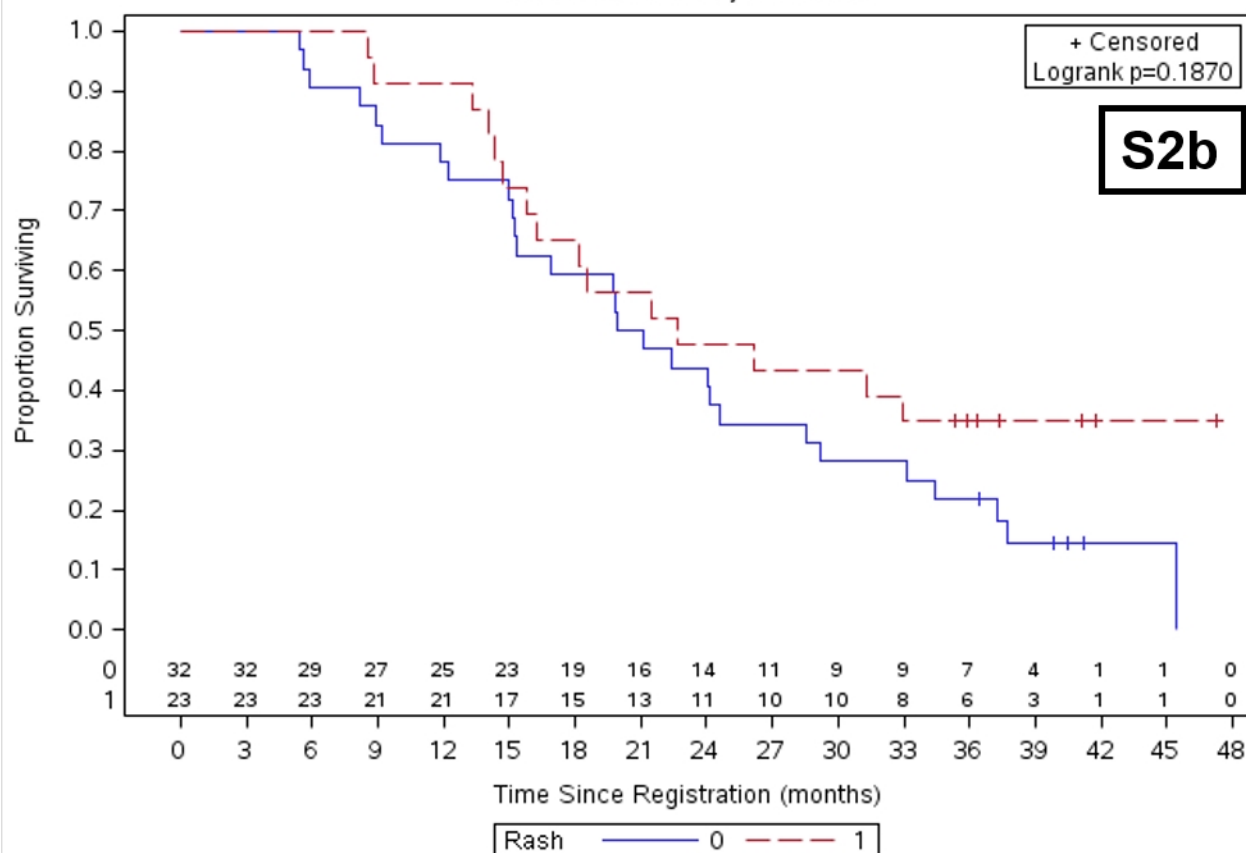
Supplementary figure 1: CONSORT 2010 Flow Diagram



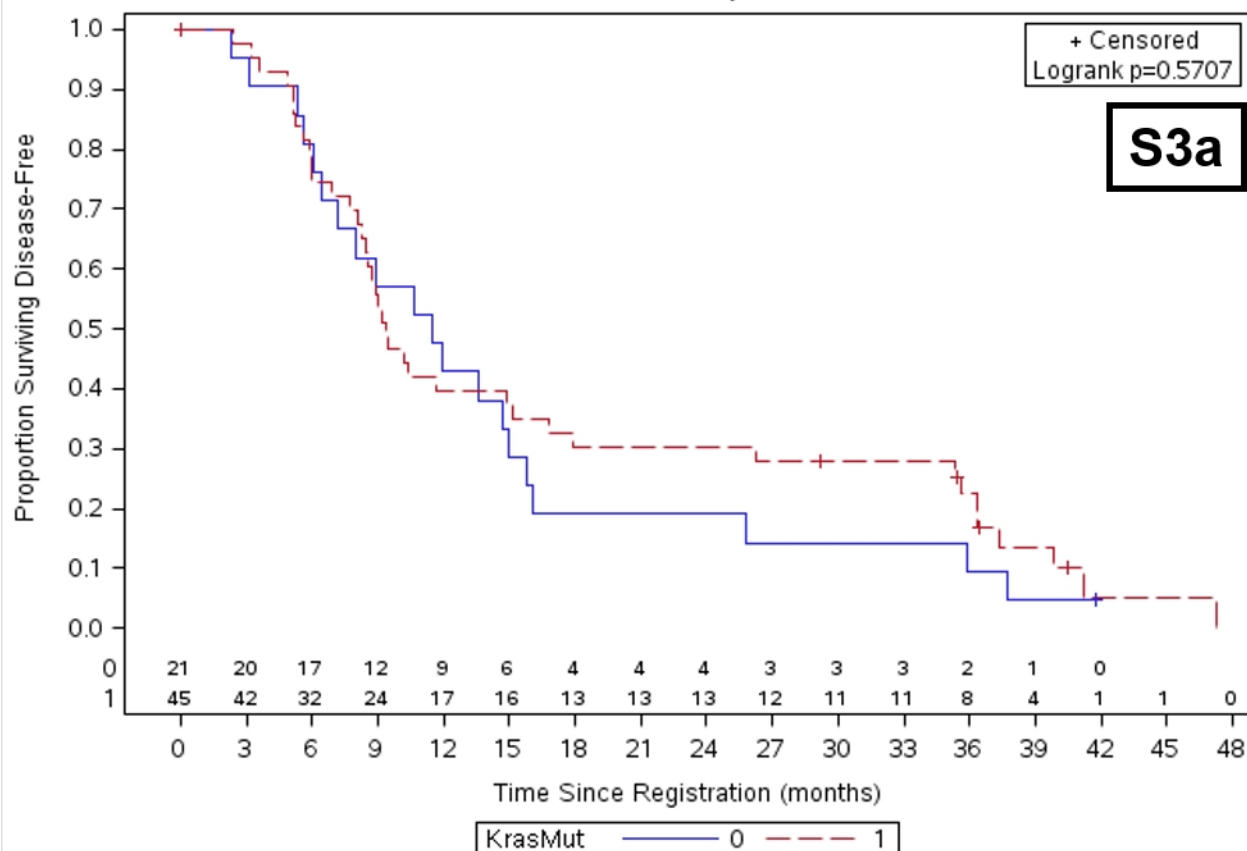
Kaplan-Meier Estimates
With Number of Subjects at Risk



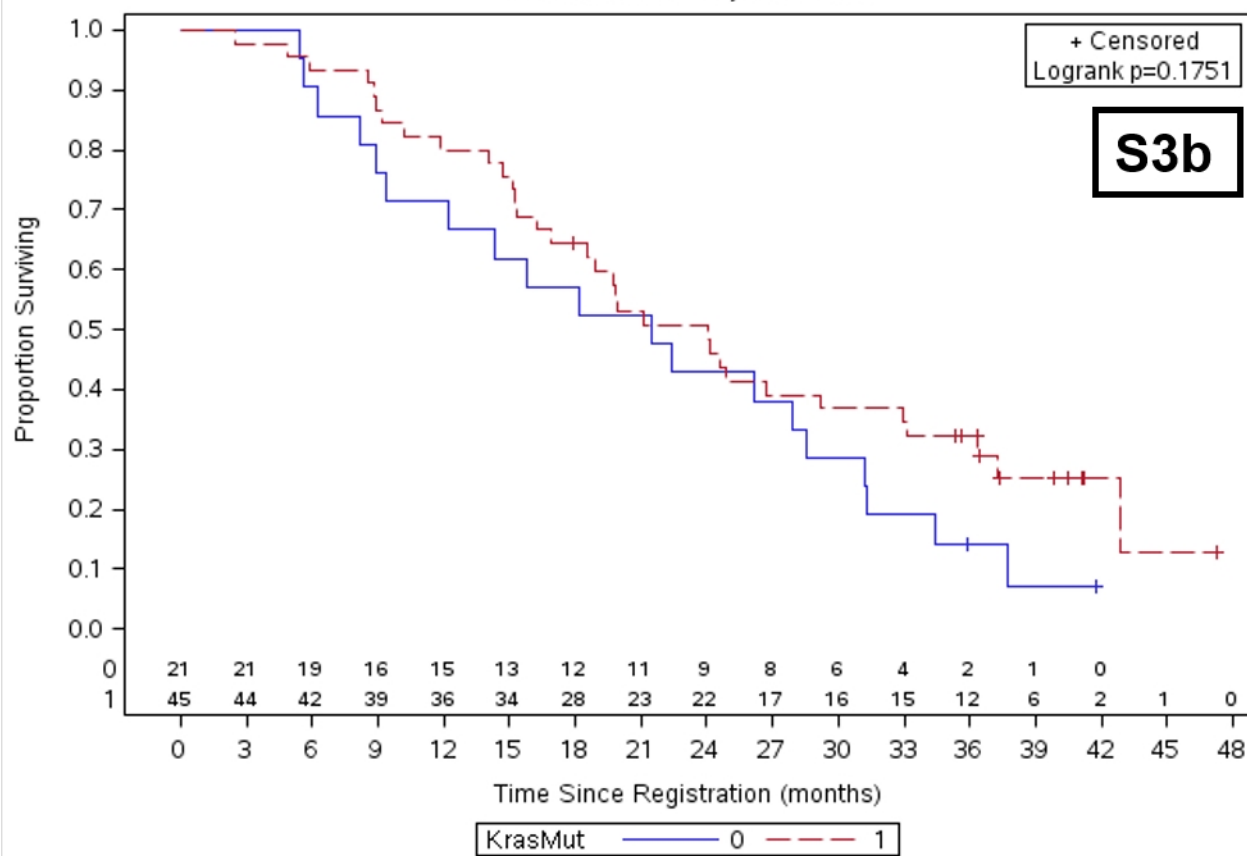
Kaplan-Meier Estimates
With Number of Subjects at Risk



Kaplan-Meier Estimates
With Number of Subjects at Risk



Kaplan-Meier Estimates
With Number of Subjects at Risk



Supplementary table 1:

Inclusion criteria:

- R0 or R1 resected ductal adenocarcinoma of the pancreas
- Signed written informed consent
- age ≥ 18 years
- estimated life expectancy > 12 weeks
- ECOG performance status ≤ 2
- absence of metastases

Exclusion criteria:

- Women of child bearing potential (WOCP) who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and follow-up to 4 weeks after the study, women who are pregnant or breastfeeding, women with a positive pregnancy test on enrolment or prior to study drug administration.
- Patients who had received any prior oncological treatment for pancreatic cancer.
- Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent.
- Any concurrent malignancy other than non-melanoma skin cancer, or carcinoma in situ of the cervix. (Patients with a previous malignancy but without evidence of disease for > 5 years will be allowed to enter the trial).
- Inadequate hematologic function (neutrophils count (ANC) $< 1,500/\text{mm}^3$, platelet count $< 100,000/\text{mm}^3$ and/or hemoglobin $< 9 \text{ g/dL}$).
- Inadequate hepatic function defined by the upper limit of normal (ULN), AST and ALT levels > 5 times the ULN.
- Serum bilirubine > 1.5 times the ULN.
- Inadequate renal function defined by a serum creatinine > 1.5 times the ULN.

- Prior cetuximab or other therapy that targets the EGF pathway.
- Prior antibody therapy.
- Any known allergic reaction against cetuximab.
- Any concurrent chronic systemic immune therapy, radiation therapy, hormonal therapy (except for physiological replacement), or any other investigational agents.
- HIV infection.
- Having participated in another clinical trial of medical or radiotherapeutic oncological treatment as following the German regulations (clinical trials according to Arzneimittelgesetz/AMG) in the preceeding 30 days.

Supplementary table 2: Patient characteristics (N=76), mean or number (%) and comparison with the CONKO-001-trial (gemcitabine group)

Variable	CONKO-001	ATIP
Age, years	62 (median)	62.7 (mean)
Height, cm mean	n.k.	170.9
Weight, kg mean	n.k.	71.3
BSA, m ² mean	n.k.	1.82
Time from resection to start of treatment (days, median)	36 (28-43)	30 (20-70)
	N (%)	N (%)
Performance status	Karnofsky performance status (median): 80%	ECOG ECOG 0: 25 (33) ECOG 1: 43 (57) ECOG 2: 8 (11)
Sex male female	105 (59) 74 (41)	42 (55) 34 (45)
K-Ras mutation	n.k.	47/68 (69)
R1-Resection	34(19)	17 (22)
T-stage T1 T2 T3	7 (4) 18 (10) 146 (82)	2 (3) 7 (9) 65 (86)
N-stage N0 N1 N2	52 (29) 126 (70) 1 (1)	21 (28) 54 (71) 1 (1)
Grading G1 G2 G3 unknown	10 (6) 103 (58) 63 (35) 3 (2)	2 (3) 44 (58) 28 (37) 2 (3)
CA 19-9 pretreatment ≤ 37 U/ml > 37 U/ml	n.k	44 28

Supplementary table 3:

Dose reduction regimens:

Gemcitabine was given without dose modification if neutrophils were $>1.0 \times 10^9/\text{L}$ and platelets $>100 \times 10^9/\text{L}$ and any other non-hematological toxicity was less than grade 2. The dose of gemcitabine was reduced to 75% of the original dose when neutrophils dropped to $<1.0 \times 10^9/\text{L}$, platelet counts dropped to $<100 \times 10^9/\text{L}$ or when a non-hematological grade 2- or 3-toxicity occurred. In case of neutropenia $<0.5 \times 10^9/\text{L}$ or low platelet count $<50 \times 10^9/\text{L}$ or further non-hematologic grade 2-3 toxicity therapy was delayed for one week and continued with a dose reduced to 75%. In case the therapy had to be delayed for more than 2 weeks, the patient had to be withdrawn from the study treatment.

In the event of skin toxicity a special dose reduction regimen of **cetuximab** had to be used: for grade 3 toxicities, infusion was delayed for 1 week. The drug had to be re-administered when the level of toxicity dropped to ≤ 2 . The dose had to be reduced to $200 \text{ mg}/\text{m}^2$ after the second recurrence and to $150 \text{ mg}/\text{m}^2$ after the 3rd recurrence. Cetuximab had to be discontinued at the 4th occurrence of grade 3 toxicity or after a delay of more than 2 consecutive weeks.

Supplementary table 4a: Post study treatments

Therapy	Number of therapies
Gemcitabine	20
Gemcitabine+erlotinib	16
5-FU+ Folinic acid +Oxaliplatin	13
Gemcitabine+ capecitabine	5
Capecitabine+Oxaliplatin	5
Gemcitabine+oxaliplatin	4
Capecitabine	4
Erlotinib	4
Capecitabine+Irinotecan	2
5-FU+Folinic acid	2
Mitomycin C+capecitabine	2
Surgery	2
Docetaxel+Oxaliplatin	1
5-FU+ Folinic acid +Irinotecan	1
DTIC	1
Taxol+Carboplatin	1
Doxorubicin	1
Topotecan	1
FOLFIRINOX	1
Gemcitabine+RAD001	1
Radiotherapy	1

Supplementary table 4b: Number of post study treatments

Number of secondary treatments	Number of patients
1	28
2	14
3	8
4	2

Supplementary table 5: Toxicity (N=73): N (%)

N=73	Any grade>0	Grade≥2	Grade 3	Grade 4
Hematologic				
Hemoglobin	67 (92)	26 (36)	3 (4)	0 (0)
Leucocytes	62 (85)	39 (53)	8 (11)	0 (0)
Platelets	43 (59)	7 (10)	2 (3)	3 (4)
Skin toxicity	64 (88)	45 (62)	5 (7)	0 (0)
Allergic reaction	7 (10)	5 (7)	5 (7)	0 (0)
Others				
Nausea/Vomiting	33 (45)	10 (14)	0 (0)	0 (0)
Diarrhea	26 (36)	12 (16)	0 (0)	0 (0)
Edema	17 (23)	8 (11)	1 (3)	0 (0)