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Phase II study of biweekly cetuximab in combination with irinotecan as second-line treatment in patients with platinum-resistant gastro-oesophageal cancer

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Abstract *Background:* The purpose of this phase II trial was to evaluate the efficacy and safety of cetuximab and irinotecan as second-line treatment in patients with gastro-oesophageal adenocarcinoma.
Patients and methods: Patients with failure to first-line platinum-based chemotherapy received cetuximab 500 mg/m^2 and irinotecan 180 mg/m^2 every second week until disease progression. Toxicity was evaluated according to The Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v. 3.0. Antitumour activity was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) v. 1.0.
Results: Sixty-three patients were enrolled, median age was 60 years, median performance status was 1 (0–1), 35 patients had two or more organs involved. The median number of courses was 5 (range 1–25). Response rate was 11% (6 partial response (PR)) and 37% had stable disease. Median progression free survival was 2.8 months and overall survival (OS) was 6.1 months. Grade 3–4 toxicity included: diarrhoea (6%), fatigue (5%), vomiting (5%) and neutropenia (16%). Two patients developed febrile neutropenia. Forty-six patients (73%) had developed grade 1–2 skin rash. Patients developing skin rash had a prolonged survival with an OS at 7.1 months.
Conclusions: The combination of cetuximab and irinotecan is active as second-line therapy in patients with gastro-oesophageal cancer. Cetuximab induced skin rash was associated with prolonged survival.

1. Introduction

Gastro-oesophageal cancer (GEC) is the fourth most common cancer and the second most common cause of

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cancer related death worldwide.[1,2] In patients with recurrent, advanced or metastatic GEC randomised trials have provided evidence that systemic chemotherapy palliates symptoms and significantly improves survival (OS) and quality of life.[3,4] Historically, patients with adenocarcinoma of the GEC have been treated as a single entity in regard to the efficacy and toxicity of chemotherapy.[5] At present there are several standards of first-line chemotherapy in GEC. Two cornerstones are 5-fluorouracil (5-FU) and platinum derivatives that are widely accepted as the 'drugs of choice' in the first-line setting, obtaining response rates (RR) of 25–40%. Although many patients primarily respond to first-line treatment, the median OS is still less than one year after diagnosis.[6–9] Beyond progression on first-line therapy patients have a dismal prognosis. Some patients are however still in a good performance status (PS), leading to interest in an effective and tolerable second-line treatment. Irinotecan has proven activity in GEC patients both as a single agent and in combination with other modalities. In the second-line setting irinotecan as a single agent has achieved RR of 16–20% in advanced GEC patients.[10,11] Presently, two randomised phase III studies have demonstrated a prolonged OS in favour of irinotecan compared to best supportive care (BSC).[12,13] Based on these studies irinotecan can be considered as a relevant treatment option in the second-line setting.

Recently, an increased understanding of the molecular basis of cancer has led to the development of specific *molecular-targeted* agents. The epidermal growth factor receptor (EGFR) has been found to be over-expressed in 10–63% of gastric cancers.[14] EGFR over-expression is associated with tumour progression and poor prognosis in GEC patients, providing the rational for targeting this receptor in GEC.[15]

The anti-EGFR monoclonal antibody, cetuximab is usually administered weekly, but pharmacokinetic studies in patients with metastatic colorectal cancer (mCRC) have demonstrated no major differences between cetuximab 250 mg/m^2 weekly versus 500 mg/m^2 every second week.[16–18] Furthermore a simplified administration with only two hospital visits per month is more desirable for patients with severe disease. In the first-line setting the combination of chemotherapy and cetuximab has demonstrated promising results in GEC patients leading to interest in second-line use. Two phase II trials have investigated salvage therapy with cetuximab as a single agent. Both trials concluded that cetuximab seemed to have a minimal activity in pre-treated GEC patients.[19,20] Based on results from the two above mentioned trials cetuximab as a single agent is not a relevant treatment option as second-line therapy in GEC patients. In this phase II trial we therefore investigated the biweekly combination of cetuximab and irinotecan in order to evaluate efficacy and toxicity.

2. Materials and methods

2.1. Patient selection

The study included patients with histological confirmed, evaluable or non-evaluable, non-resectable or metastatic adenocarcinoma of the lower oesophagus, oesophageal-junction or stomach. All patients had received prior platinum-based chemotherapy and demonstrated progressive disease after or during previous treatment. The eligibility requirements included a PS of 0–1; age >18 years and a life expectancy of at least 12 weeks. Preclinical laboratory parameters included an adequate bone marrow function (neutrophils $>1.5 \times 10^9$/L, platelets $>100 \times 10^9$/L); adequate hepatic function (serum bilirubin $<1.5 \times$ upper normal limit (UNL), in case of liver metastases, there were no upper limit for transaminases). Patients were ineligible if they had severe medical illnesses or another active malignancy. Females were not included if they were pregnant or lactating. The study was approved by the local ethics committee and the Danish Health Authority and written informed consent was obtained from all patients before study entry, according to the Helsinki declaration.

2.2. Treatment

Irinotecan 180 mg/m^2 and cetuximab 500 mg/m^2 was administered on day 1 every second week.[21] The first course of cetuximab was infused in 120 min followed 1 h later by irinotecan. Subsequent courses of cetuximab were infused in 60 min, immediately followed by irinotecan as a 30 min infusion. Patients received premedication with antihistamine (e.g. 2 mg clemastine i.v.) to minimise the risk of infusion-related reactions associated with cetuximab. Before cetuximab infusion patients also received antiemetic with oral prednisolone 100 mg and oral ondansetrone 8 mg $\times$ 2. Treatment continued until disease progression, patient refusal or unacceptable toxicity.

2.3. Evaluation of toxicity and dose adjustment

Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE). In case of NCI-CTCAE grade 3 or 4, the dose of irinotecan was reduced by 25% in the subsequent treatment cycles. If patients developed skin rash (acneiform) grade 3 the dose of cetuximab was postponed until recovery to grade $\leqslant 2$. In case of recurrent episodes of skin rash grade 3, the dose of cetuximab was reduced 20% in the subsequent treatment cycles. Patients developing skin rash, any grade, were offered tetracycline in order to reduce symptoms and risk of infection.

2.4. Study assessments

Assessment of medical history, physical examination, evaluation of PS, complete blood count and biochemical tests were performed before study entry and prior to each course. All patients had a computed tomography of the thorax and abdomen performed at baseline and every 8 weeks. Response rate was assessed by the investigator in collaboration with radiologists affiliated to the hospital according to Response Evaluation Criteria in Solid Tumours (RECIST) v. 1.0. After they completed therapy patients without documented disease progression were followed every 2 months with clinical and radiological evaluation. Blood samples regarding tumour biology were analysed at baseline, before every fourth cycle and at disease progression.

2.5. Statistical considerations

The primary end point of the present study was to evaluate the RR of irinotecan and cetuximab every second week. The purpose of the trial was to detect an RR of at least 15% compared to a minimal, clinically meaningful RR of 5%. A two-stage optimal design proposed by Simon was used for this trial, with 90% power to accept the hypothesis and 5% significance to reject the hypothesis. Fifty-five patients with evaluable disease were required. Assuming a drop-out rate of approximately 10% a total of 61 patients needed to be accrued. Secondary end points were to evaluate progression-free survival (PFS) and OS in all patients. Actuarial survival duration was determined using the Kaplan–Meier method. PFS was calculated as the period from inclusion to the first observation of radiological, clinical disease progression or death of any cause. OS was calculated as the period from inclusion until death of any cause. Comparison of OS was made with log-rank test. Data were updated on October 2011. Non-parametric statistics were applied. The statistical data were recorded and analysed in a Medlog® database. All analyses were done on an intention-to-treat population.

2.6. Patient characteristics

Between January 2009 and August 2010, a total of 63 patients were enrolled in the current study. The clinical characteristics of the patients are summarised in Table 1. Median age was 60 years (range 35–80) and the majority of the patients were males (86%). The location of the primary tumour was oesophagus in 16 patients, gastro-oesophageal-junction in 34 and stomach in 13. Twenty-eight patients (44%) had three or more metastatic sites involved at baseline. All patients were in a good PS with 28 (44%) patients in PS 0 and 35 (56%) patients in PS 1. Sixteen patients (25%) had recurrent disease after curative resection. All patients had received prior platinum-based two or three drugs' combination chemotherapy. Among patients who received curative resection seven patients had received perioperative chemotherapy with carboplatin or oxaliplatin in a three drug combination with capecitabine and docetaxel/epirubicin. Only one patient had a disease free period over 6 months and received first-line palliative therapy with platin-based chemotherapy before cetuximab and irinotecan. First-line chemotherapy is summarised in Table 1. Twenty-four patients had progression during first-line chemotherapy or within 2 months after having received the last course. Eleven patients had a treatment free interval over 6 months.

Table 1
Baseline characteristics.

Number of patients	63
Age,	60
Median; years	(range 35–80)
Male/female	54/9
PS, *n* (%)	
0	28 (44)
1	35 (56)
Primary tumour site, n (%)	
Oesophagus	16 (25)
Gastro-oesophageal-junction	34 (54)
Stomach	13 (21)
Primary resected, n (%)	
Yes	16 (25)
No	47 (75)
Platin in first-line	63 (100)
Number of metastatic sites, n (%)	
1–2	35 (56)
$\geqslant 3$	28 (44)
Median TTP under first-line CT (range)	7.3 months (2.3–31) months
Prior treatment	
Epirubicin, oxaliplatin,capecitabine	21 (33)
Carboplatin, docetaxel, capecitabine	33 (52)
Oxaliplatin, capecitabine	7 (11)
5-FU, leukovorin, oxaliplatin	1 (2)
Docetaxel, oxaliplatin, capecitabine	1 (2)

PS performance status, TTP time to progression, CT chemotherapy.

2.7. Safety

In general treatment was well tolerated; worst CTCAE toxicities are listed in Table 2. Haematological toxicities grade 3–4 were; neutropenia (11%) and febrile neutropenia (2%). Non-haematological toxicities were mainly grade 1–2; fatigue (86%), diarrhoea (47%), nausea (54%), vomiting (33%) and skin rash (73%). No patients developed grade 3 skin rash, which might be explained by instant onset of tetracycline at the very first sight of rash. Only four patients (6%) had diarrhoea grades 3–4. One patient had an allergic reaction grade 4 during the first infusion of cetuximab and was subsequently withdrawn from the protocol and switched to other treatment, but is included in the survival analysis.

Table 2
Worst adverse events per patient.

	Grade 1 + 2 *n* (%)	Grade 3–4 *n* (%)	Grade 5 *n* (%)
Haematological toxicity			
Anaemia	50 (83)	0	0
Thrombocytopenia	3 (5)	0	0
Neutropenia	5 (8)	7 (11)	0
Febrile neutropenia	–	1 (2)	0
Non-haematological toxicity			
Diarrhoea	29 (47)	4 (6)	0
Nausea	34 (54)	2 (3)	0
Vomiting	22 (33)	3 (5)	0
Fatigue	54 (86)	3 (5)	0
Skin rash	46 (73)	0	0
Nail toxicity	23 (36)	0	0
Alopecia	31 (50)	0	–
Pneumonia	0	0	1 (2)
Surgical complications	0	0	1 (2)

2.8. Response to therapy and survival

A total of 453 treatment cycles were administered to 63 patients, with a median of five (range 1–25) cycles per patient Table 3. Fifty-four patients were evaluable for response since nine patients had non-measurable disease at baseline. Six patients, (oesophagus in three, gastro-oesophageal-junction in two and stomach in one) had partial response (PR) giving an overall RR of 11% and 19 (37%) patients had stable disease after 4 courses, giving a disease control rate of 48%. All 63 patients were included in the survival analysis giving a progression-free survival (PFS) of 2.8 months (Confidence interval 1.8–3.5) and a median OS of 6.1 months (CI 4.5–7.1) Fig. 1. The 1-year survival rate was 17% and three patients are still alive.

3. Discussion

A large proportion of GEC patients initially respond to first-line chemotherapy, but when patients eventually develop disease progression, the administration of second-line chemotherapy is still a question of debate. Many GEC patients are in an excellent PS at the time of progression and in these patients it is more or less a common practice to offer second-line therapy. It is estimated that up to 30–40% of GEC patients receive second-line treatment after failure to first-line therapy.[22–24] Previously there has been a lack of evidence for the benefit associated with second-line therapy in GEC patients. A small randomised phase III trial including 40 patients investigated irinotecan as a single agent versus BSC. The trial was terminated early due to slow accrual but demonstrated an improvement in OS for patients receiving irinotecan (4.1 versus 2.4 months).[12] Recently another phase III trial evaluating irinotecan or docetaxel versus BSC also demonstrated the benefit of second-line chemotherapy in GEC patients with an OS of (5.1 versus 3.8 months).[13] Several phase II trials have investigated the benefit of second-line therapy using different drugs and combinations. Promising agents such as taxanes, platin derivates and irinotecan have been tested.[10,25–27] However, in Denmark GEC patients are treated with either taxanes or platin derivates in the first-line setting, and because of cumulative toxicity, primarily peripheral neuropathy, these drugs are not an option beyond progression.[28,29] The administration of cetuximab in combination with chemotherapy has obtained promising results in chemo-naïve GEC patients. So far six published phase II trials Table 4 have investigated different combinations of chemotherapy with cetuximab obtaining RR of 40–60%, PFS of 5–9 months and OS of 9–16 months.[30–35] Presently two ongoing randomised phase III trials evaluate the efficacy of adding monoclonal EGFR inhibitors to chemotherapy in the first-line setting, the REAL III trial: Oxaliplatin/epirubicin/capecitabine versus oxaliplatin/epirubicin/capecitabine plus panitumumab (ClinicalTraial.gov identifier: NCT00824785) and the EXPAND trial: Cisplatin/capecitabine versus cisplatin/capecitabine plus cetuximab (ClinicalTrials.gov identifier: NCT00678535). Unfortunately limited results are available for the benefit of cetuximab as salvage therapy in GEC patients. (Table 4). As a single agent in the second-line setting two phase II trials have evaluated cetuximab. Gold et al. administered cetuximab in 55 patients every week. One patient obtained response, PFS and OS were 1.8 months and OS 4 months, respectively, but the trial failed to meet its primary endpoint of a median OS of 6 months.[19] Another phase II trial reported similar results with an RR of 3% a PFS at 1.6 months and an OS of 3.1 months, concluding cetuximab administered as a single agent has minimal clinically activity as salvage therapy in pre-treated GEC patients.[20] Stein et al. evaluated irinotecan and cetuximab every week in 13 heavily pretreated patients. Patients had received two or more previous lines of palliative chemotherapy and were in PS 0–2. Five patients obtained PR but survival data were

Table 3
Efficacy of cetuximab and irinotecan as second-line therapy.

	n (%)
Measurable disease	54 (86)
Non-measurable disease	9 (14)
Number of courses	
Total	453
Median	5 (range 1–25)
Response rate	
PR	6 (11)
SD	19 (37)
Median PFS	2.8 months (Confidence interval 1.8–3.5)
Median OS	6.1 months (CI 4.5–7.1)

CR complete response, PR partial response, SD stable disease, PFS progression-free survival, OS overall survival.

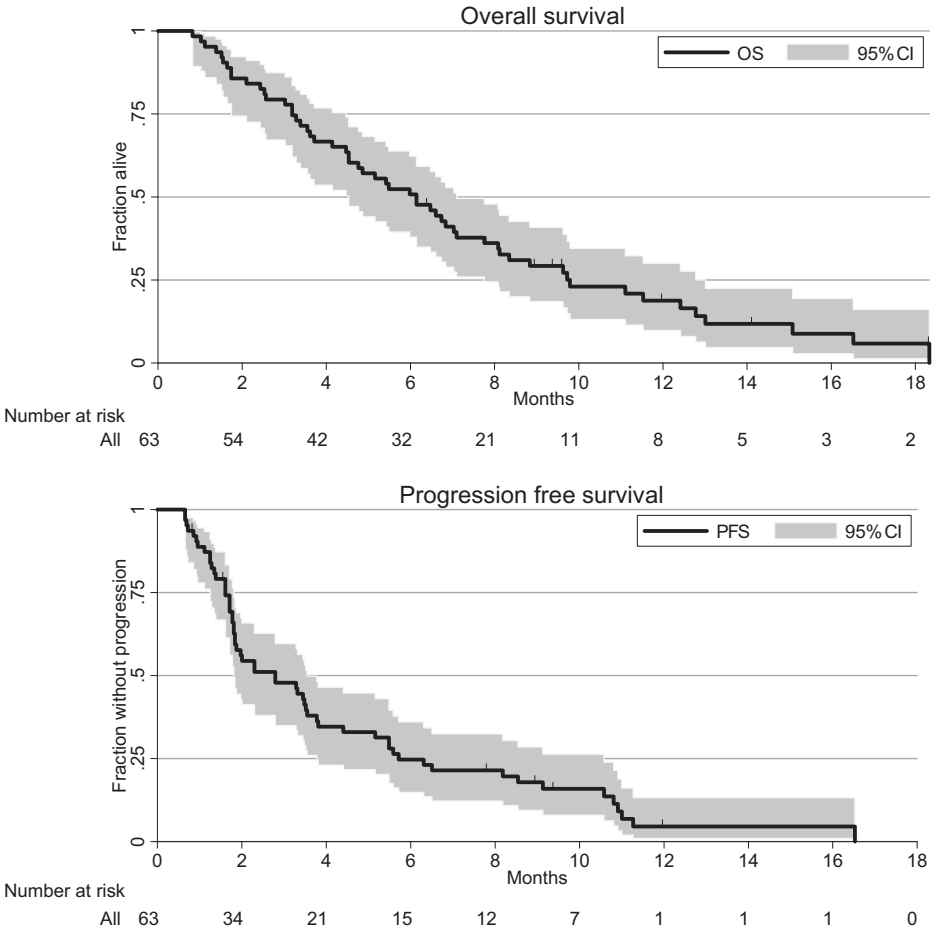

Fig. 1. Overall survival and progression free survival. Kaplan–Meier curves of overall survival (median 6.1 months) and progression free survival (median 2.8 months).

Table 4
Cetuximab in gastro-oesophageal cancer.

Trial	*n*	Regime	Response rates (%)	Progression-free survival (months)	Overall survival (months)	Rash (%)
First-line therapy with chemotherapy and cetuximab						
Pinto et al.[30]	38	5-FU/iri/cetux	44	8	(Estimated) 16	82
Pinto et al.[31]	72	Oxaliplatin/docetaxel/ cetuximab	41	5	9	71
Moehler et al.[32]	49	Iri/5-FU/cetux	46	9	16.5	58
Kim et al.[33]	44	Oxa/cap/cetux	52	6.5	11.8	77
Han et al.[34]	38	Oxa/5-FU/cetux	50	5.5	9.9	85
Lordick et al.[35]	52	Oxa/5-FU/cetux	65	7.6	9.5	89
Salvage therapy with cetuximab						
Gold et al.[19]	55	Cetux	5	1.8	4	42
Chan et al.[20]	35	Cetux	3	1.6	3.1	77
Stein et al.[36]	13	Iri/cetux	38	2.6	3.4	23[a]
Park et al.[37]	32	Iri/5-FU/cetux	6	1.7	3.2	50
Schønnemann et al.[38]	50	Iri/5-FU	14	3.3	5.5	67

Iri irinotecan, Oxa oxaliplatin, Cetux cetuximab, Rash developing rash all grades.
[a] Only grade 3 reported.

similar to those obtained with cetuximab as a single agent.[36] Park et al. performed a retrospective analysis in 32 GEC patients in PS 1–3 receiving second-line therapy with cetuximab and irinotecan-based chemotherapy. Disease control rate was 28.6% and PFS and OS 2.6 and 3.4 months, respectively.[37]

The primary endpoint of our phase II trial was not achieved with an RR at 11% but, with six patients having PR it clearly indicates that a proportion of the patients benefit from second-line therapy with biweekly cetuximab and irinotecan. This is also supported by our survival data with a PFS of 2.8 months and an OS at 6.1 months. Recently we published an analysis of 50 GEC patients treated with biweekly cetuximab and irinotecan as compassionate use. In this series six patients (12%) were in PS 2. We found a comparable RR at 14%, a PFS at 3.3 months but a slightly shorter OS at 5.5 months.[38] In our retrospective study we found that PS 2 was a very strong prognostic factor significantly associated to short survival with a Hazard ratio (HR) at 10.3. Also PS 1 was significantly associated to short survival with a (HR) at 2.4. As a consequence of this we decided to exclude patients in PS 2 in the present phase II trial. Analysis of the present study confirmed a correlation between PS and outcome (median OS of 4.4 months (CI 3.0–6.0) and 7.1 months (CI 6.1–9.6) $P = 0.05$) for patients with PS 1 and PS 0, respectively. As in other trials using EGFR inhibitors, an explorative analysis of our data demonstrated a prolonged survival for patients developing skin-rash. In the present phase II study patients without rash had a median OS of only 3.0 months (CI 1.5–4.5) compared to a median OS of 7.0 months (CI 5.4–9.6) for patients with any-rash ($P = 0.0001$), Fig. 2. The significant prolonged survival in patients developing skin rash retained even after eliminating patients with early progression (within 2 months) and patients having received less than two courses of therapy (median OS of 3.1 months (CI 2.0–4.5) and 8.0 months (CI 6.0–9.8) $P = 0.000$). In a variety of other primaries; mCRC, squamous cell carcinoma of the head and neck, non-small-cell lung cancer and pancreatic cancer; EGFR induced skin rash has also been observed. The pathogenesis of cetuximab-induced rash still remains unclear. EGFR is expressed on epidermal keratinocytes and other skin cells. The monoclonal antibody cetuximab binds to the extracellular domain of

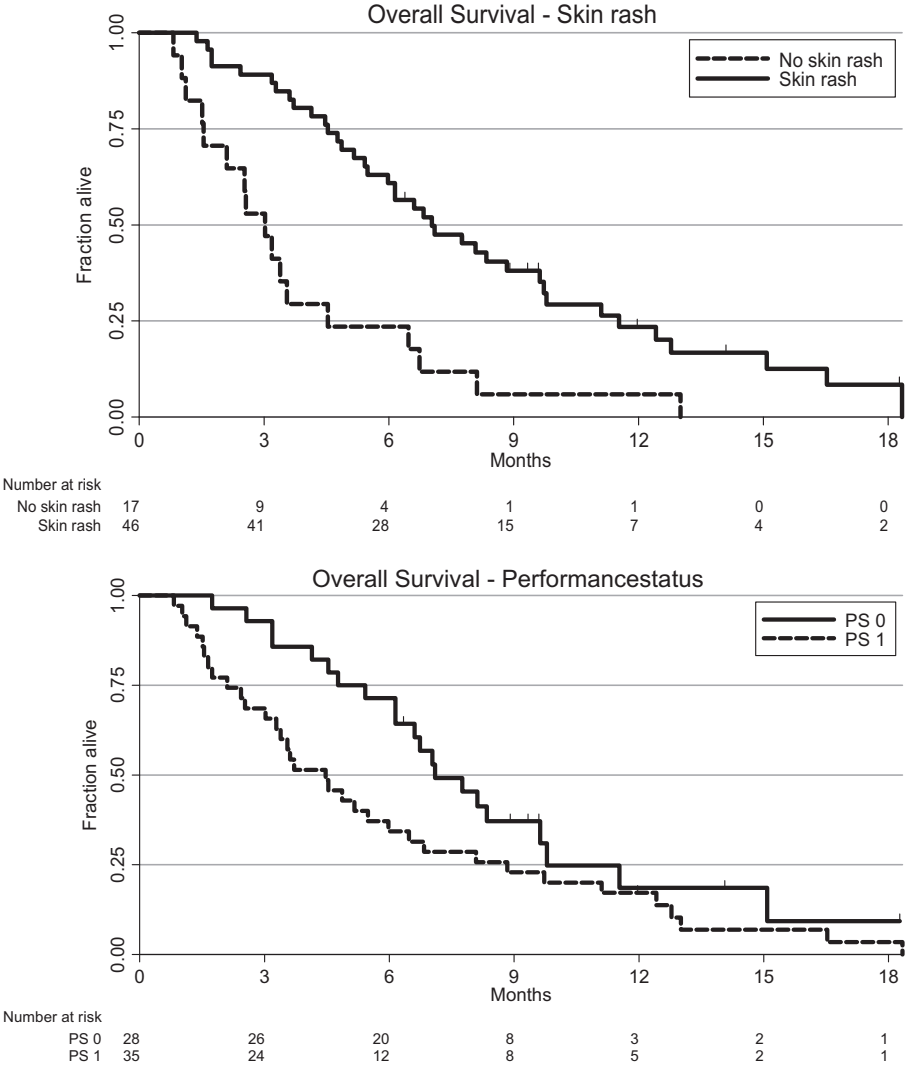

Fig. 2. Overall survival according to skin rash and performance status. A. Kaplan–Meier curves of overall survival according to skin rash (7.0 versus 3.0 months). B. Kaplan–Meier curves of overall survival according to performance status (7.1 versus 4.4 months)

EGFR leading to an inhibition of the EGFR signal transduction in the epidermal and follicular epithelium. This inhibition might explain the cutaneous adverse effect seen in the use of cetuximab. In several clinical trials the development of skin rash has been associated with an improved outcome. One might speculate that skin rash reflects major blocking of EFGR, which in turn seems to favour tumour regression. So far nothing has been concluded about selecting patients for EGFR inhibitor treatment on the basis of skin rash in any cancer diseases.

In conclusion the primary endpoint of this phase II trial was not fully reached, but six patients (11%) obtained PR. In general the combination of biweekly irinotecan and cetuximab was a convenient and well tolerated regimen in the out-patient setting. Explorative analysis of the study suggested that GEC patients in a good PS and patients developing skin rash might benefit the most from the drug combination. Large-scale prospective trials are needed to confirm whether starting and/or continuing cetuximab with chemotherapy in these patients could be based on PS as a prognostic factor and skin rash during early treatment period as a predictive factor.

Conflict of interest statement

P. Pfeiffer is conducting research sponsored by Merck Serono and Roche. P. Pfeiffer is also a member of the speakers' bureau for Merck Serono and Roche. All other authors have declared no conflict of interest.

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