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ORIGINAL ARTICLE

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Abstract

Background. Patients with upper gastrointestinal cancers have a poor prognosis and only few treatment options. The epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) are valid targets in many solid tumours, and they have synergistic effects in preclinical studies. *Methods.* In this multi-center phase II trial patients with chemoresistant, metastatic upper gastrointestinal cancer were treated with erlotinib (150 mg daily) and bevacizumab (10 mg/kg every two weeks). Primary endpoint was overall response rate (ORR). Secondary endpoints were progression free survival (PFS), overall survival (OS), toxicity and biomarker correlates. Plasma samples were analysed for EGFR and angiogenesis related markers using quantitative immunoassays. *Results.* One hundred and two patients were enrolled in the trial between June 2006 and October 2007. The most common toxicities were skin reaction, diarrhoea, and fatigue. ORR was 6%, median PFS was 2.2 months, and OS 4.3 months. Low concentration of urokinase plasminogen activator receptor (uPAR) domain I was correlated to longer PFS and OS. *Discussion.* The combination of erlotinib and bevacizumab is well tolerated, however, with low clinical activity in patients with chemoresistant UGI cancer. Some patients do benefit from the therapy, and uPAR forms are potential biomarkers in these patients.

Malignancies in the upper gastrointestinal tract (oesophagus, gastroesophageal junction [GEJ], stomach, biliary tract, and pancreas) are amongst the most aggressive cancers and there only exist few treatment options. Patients often have significant comorbidity and cancer related symptoms resulting in decreased quality of life. New targeted treatments that delay disease progression while reducing toxicity would therefore represent a significant advance.

The epidermal growth factor receptor (EGFR) signalling pathway plays a key role in the development and growth of some tumours, and targeting of this has activity in several tumour types, including pancreatic cancer [1]. Erlotinib is a tyrosine kinase inhibitor targeting the EGFR pathway. Kras mutations are predictive of no benefit of EGFR targeted therapy in colorectal cancer and non-small cell lung cancer (NSCLC) [2], and EGFR mutations are predictive of response to EGFR targeted therapy in NSCLC [3]. These predictive markers are investigated in tumour tissue, which can be challenging to obtain in patients with UGI cancers. No blood based predictive markers are in clinical use.

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Vascular endothelial growth factor (VEGF) is a potent angiogenic growth factor in both benign and malignant angiogenesis [4]. VEGF is a recognised therapeutic target in oncology and therapy targeting the VEGF pathway has proven effect in several tumour types [5]. Bevacizumab is a monoclonal antibody binding VEGF, and thus inhibiting angiogenesis. There exist no predictive markers of response to VEGF-targeted therapies [5].

Preclinical data suggest an interaction between EGFR and VEGF pathways. Acquired resistance to EGFR-targeted therapy has in vivo been reverted with addition of anti-VEGF therapy [6], and EGFR signalling induces angiogenesis [7]. This has led to great expectations to the combination of therapies against these targets.

In this phase II trial with prospectively planned evaluation of biomarkers, we treated patients with erlotinib and bevacizumab. Different angiogenic growth factors, soluble receptors and components of the urokinase plasminogen activator system were investigated as possible predictors of response and survival in the trial. As previously described, sensitivity to some targeted therapies are not solely determined by the histology of the tumour [8]. Biological features may be shared by tumours with an origin usually not sensitive to such therapy [8]. We therefore hypothesised that some tumours, regardless of histology, would share some common biological features that would make them susceptible to this combination therapy. Therefore, we included patients with different upper gastrointestinal cancers in this trial and measured biomarkers in plasma in order to discover markers capable of identifying patients benefitting from the therapy. These markers could be used in future trials for the selection of patients and monitoring of response to this combination therapy.

Methods

Patient eligibility criteria. The study population consisted of patients with histologically or cytologically confirmed, metastatic or locally advanced carcinoma of the upper gastrointestinal tract progressing after standard therapy and no other treatment options available. Patients were further required to have measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST 1.0); age 18 or older; Eastern Cooperative Oncology Group performance status (PS) of 0–2; life expectancy of at least three months; and adequate renal function (EDTA clearance ≥ 45 ml/min), hepatic function (serum bilirubin ≤ 1.5 times the upper limit of normal [ULN] and transaminases ≤ 3 times ULN), bone marrow function (leukocytes $> 3.0 \times 10^9$; neutrophil $> 1.5 \times 10^9$ per l; platelets $> 100 \times 10^9$ per l), and coagulation parameters. No prior therapy with EGFR or VEGF targeting agents was allowed.

Patients were excluded if they had other malignancies (other than basal cell or squamous cell carcinoma of the skin); uncontrolled intracranial metastasis; uncontrolled hypertension; severe infection; major thromboembolic events within the last six months; or major surgery, radiotherapy, or systemic anticancer treatment within four weeks before enrolment. Participating centres included the University Hospitals in Copenhagen, Odense and Aarhus. This study was approved by the local ethical committee, and all patients provided informed, written consent. Inclusion in the biomarker study with multiple extra blood samples required a separate written consent.

Study design. This was an investigator-initiated, single armed, open-label, multicenter phase II trial. The primary objective was to determine response rate (complete or partial) according to RECIST criteria. Secondary end points included toxicity, OS, PFS, and biomarker endpoints. After amendment, the primary endpoint was changed to clinical benefit rate (CR + PR + SD). Erlotinib was administered orally at a dose of 150 mg daily and bevacizumab at a dose of 10 mg/kg i.v. every two weeks. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE v3.0) every two weeks during treatment. For any grade 3 or 4 erlotinib-related toxicity or medically concerning grade 2 non-hematological toxicity, erlotinib was held until symptoms resolved to grade 1 or less and then reinstituted at a reduced dose. The daily dose of erlotinib was reduced in 50 mg/day decrements. For any grade 3 or 4 bevacizumab-related toxicity, bevacizumab was held until symptoms resolved to grade 2 or less, while erlotinib was continued. No dose modification of bevacizumab was allowed. Patients with treatment interruption of more than 14 days went off study. Response was evaluated with computed tomography (CT)-scans according to the RECIST criteria every eight weeks. Patients with confirmed complete remission (CR), partial remission (PR), or stable disease (SD) continued treatment until disease progression, unacceptable toxicity, or withdrawal of patient consent.

As the study evolved it became clear that response evaluation was difficult in this group of patients who often previously had undergone surgery or received radiotherapy. Initially, the primary endpoint was response rate. As the treatment was non-cytotoxic and more often resulted in SD than response, the primary endpoint was later amended to disease control (DC) rate, defined as the rate of CR, PR, and SD.

Biomarker analysis. The biomarker study was prospectively planned and biology driven. Blood samples were collected at baseline, before treatment, on days 8, 15, 21, and 28 and along with every CT-scan evaluation (every eight weeks). Plasma was handled according to standardised methods. Blood samples were drawn into EDTA coated tubes and kept on ice until they, within 30 min, were centrifuged at 3000 g for 30 min at 4°C and stored at −80°C until assayed. Plasma samples were analysed with solid phase sandwich type enzyme linked immunoassays (ELISA) for soluble EGFR (sEGFR; Siemens Medical Solutions Diagnostics, Ballerup, Denmark), soluble vascular endothelial growth factor receptor 2 (sVEGFR-2), and basic fibroblast growth factor (bFGF; R&D systems, Abingdon, UK); with time-resolved fluorescence immunoassays (TR-FIA) for plasminogen activator inhibitor 1 (PAI-1; constructed as PAI-1 ELISA from Monozymes, Hørsholm, Denmark but with Europium labelled detection antibody and fluorescence detection system), intact and cleaved forms of urokinase plasminogen activator receptor [uPAR (I), uPAR (I–III), and uPAR (I–III) + (II–III)] [9]; and with electrochemiluminescence immunoassay (ECLIA) for placental growth factor (PlGF; Roche Diagnostics, Rotkreuz, Switzerland). Before application on patient material, assays were validated as previously described [10]. Samples were run in duplicates and appropriate quality controls were applied. Samples were blinded until statistical analysis was conducted.

Predefined correlative endpoints included progression-free survival (PFS), overall survival (OS) and response according to the RECIST criteria. Due to low number of responders, high frequency of SD, and the nature of the targeted therapies used in this trial, we chose to include DC as the primary correlative endpoint.

Statistical analysis. According to the primary study protocol there was a planned accrual of 28 evaluable patients for the first stage of this two stage phase II study. If four or more patients had a response, another 35 evaluable patients should be enrolled, with an option to include additional 63 evaluable patients (a total of 126 evaluable patients) depending on response in subpopulations according to biomarker data or tumour type. The therapy was accepted as having relevant activity if an overall response rate of 20% was reached.

After amendment to the competent authorities it was decided to continue to the second phase even though only 2/28 patients achieved PR. Furthermore, disease control rate was added as a primary endpoint.

With long-lasting SD it was anticipated that this biomarker driven study could have statistical power to identify correlative biomarkers for clinical benefit.

OS was defined as the time from entry into the trial until death from any cause. PFS was defined as the time from entry into the trial until disease progression or death from any cause.

Activity and safety analyses included all patients receiving at least one dose of study drugs. The number and proportion of patients with an objective response and those with disease control were summarised with the corresponding 95% confidence interval (CI). Time-to-event endpoints were summarised using the Kaplan-Meier method. For biomarker analysis, univariate models were first done to assess the effect of age, gender, diagnosis, PS, and log-transformed (base 2) plasma marker levels on OS and PFS. Keeping the statistical significant variables, multivariate Cox regression analysis of log-transformed biomarkers was then done to assess the effect on PFS and OS. The effect of biomarkers on DC was assessed by logistic regression. All p-values are two sided and a $p < 0.05$ was considered statistically significant. Patients with missing baseline samples were excluded from the biomarker analysis. Patients with missing values for one or more biomarker analysis due to insufficient material were excluded from the biomarker analysis in question. The study was registered with clinicaltrials.gov number NCT00350753.

Results

Patient demographics

In the first stage 28 evaluable patients were included. Two patients had PR, but many patients with long lasting SD had a minor response (defined as unconfirmed PR or tumour regression of less than 30%). There was at that time no other treatment option for these patients, neither standard nor experimental, and it was therefore decided to proceed to stage two. This was approved by the health authorities and the local ethical committee. In stage one and two a total of 65 patients were included. Due to low toxicity and based on subgroup analysis of response, minor responses and stable disease, the trial included additional patients with biliary tract cancer and PS < 2. This was approved by the health authorities and the local ethical committee. A total of 102 patients were included from June 2006 until October 2007. Baseline plasma samples were available in 66 patients – initial enrolment into the plasma marker study was poor due to logistic problems. The baseline characteristics are summarised in Table I. Five patients were not treated due to screening failure (three patients), deterioration of PS before initiation of treatment (one patient), and

detection of uncontrolled brain metastasis prior to initiation of therapy (one patient). The median age of treated patients was 61 years (range 25–78 years). All patients had received prior chemotherapy, 13 patients had received radiotherapy.

Efficacy

Of the 102 treated patients, six patients (6%) had PR as best response and 41 (40%) SD, corresponding to a DC rate of 46%. Twenty-nine patients (28%) had progressive diseases (PD), and 26 (26%) were not evaluable (NE). No patients had complete remission. This corresponds to an overall response rate of 6% (95%CI: 2–12%). Hence, the pre-specified endpoint was not met. The 26 not evaluable patients went off study prior to the first evaluation, many due to death before first evaluation (21 patients), others due to prolonged withhold of one or more study medication due to toxicity (three patients) or other cause (two patients). The six patients with response were two with biliary tract cancer, two with pancreatic cancer, one with gastric cancer, and one with squamous cell carcinoma of oesophagus. Median PFS was 2.2 months (95%CI: 1.8–3.4; Figure 1), OS was 4.3 months (95% CI: 3.1–6.4; Figure 2). There was no

Table I. Demographics of the study population and of the biomarker sub-population.

	Entire population	Biomarker population
N	102	66
Median age (min-max)	61 (25–78)	60 (25–78)
Gender (%)		
Male	66 (65%)	45 (68%)
Female	36 (35%)	21 (32%)
Performance status (%)		
0	36 (35%)	23 (35%)
1	48 (47%)	34 (51%)
2	18 (18%)	9 (14%)
Diagnosis (%)		
Oesophageal cancer	7 (7%)	4 (6%)
GEJ cancer	25 (25%)	18 (27%)
Gastric cancer	12 (12%)	9 (14%)
Pancreatic cancer	42 (42%)	26 (39%)
Biliary tract cancer	16 (16%)	9 (14%)
Previous therapy (%)		
COG	15 (15%)	9 (14%)
Gemcitabine	42 (41%)	26 (39%)
Taxane-based	16 (16%)	10 (15%)
Antracyclin-based	12 (12%)	10 (15%)
CapOx	12 (12%)	8 (12%)
Other	5 (5%)	3 (5%)

COG, capecitabine, oxaliplatin, and gemcitabine; CapOx, capecitabine and oxaliplatin.

significant difference in survival between tumour types (Table II), but patients with PS 0 had significantly longer OS and PFS than patients with PS 1 or PS 2 (Table III). Twenty-five percent of patients survived more than 9.2 months (95%CI: 7.5–10.6 months).

Adverse events

The most common toxicities were skin reaction, diarrhoea, weight loss, nausea, vomiting, fatigue, and hypertension (Table IV). Two patients had thromboembolic event, including one patient with deep vein thrombosis treated with low-molecular weight heparin without complications, and one patient with stroke, treated conservatively. This patient progressed and died shortly after. Two patients had grade 3/4 bleeding; one patient with gastric cancer experienced bleeding from the tumour. One patient with pancreatic cancer experienced low blood count and was treated with transfusion on suspicion of gastrointestinal bleeding. Skin toxicity and hypertension was generally manageable and grade 3/4 was uncommon.

Biomarkers

Plasma was available in 66 of the 102 treated patients (65 patients had sufficient plasma for detection of all biomarkers). Demographics of these patients are listed in Table I. PS was identified as the only baseline patient characteristic being significantly correlated to PFS and OS in multivariate and univariate analysis and was used in the multivariate model. Low plasma uPAR(I) was correlated to longer PFS (HR: 1.8, 95%CI: 1.1–2.7, p = 0.001; Figure 3, Table V) and OS (HR: 2.0, 95%CI: 1.2–3.3, p = 0.001; Figure 4, Table V), and low uPAR (I–III) + (II–III) was correlated to DC (OR: 0.3, 95%CI: 0.1–0.8, p = 0.021, Table V). This was also significant in univariate models. sVEGFR-2 was significantly correlated to longer PFS (HR: 0.7, 95%CI: 0.5–1.0, p = 0.041, Table V) in a multivariate analysis but was not significant in a univariate analysis. None of the other baseline biomarkers correlated with DC, PFS, or OS in univariate or multivariate analysis (Table V). In order to create a suggestive model for use in future trials, we conducted a post-hoc analysis using the high quartile of uPAR(I) as cut point which resulted in a model with HR of 2.7 (95%CI: 1.4–5.1, p = 0.001).

Plasma PlGF concentration increased in most patients after initiation of treatment. Plasma PlGF increased significantly after one week of therapy (p = 0.0001) and the elevated levels were maintained
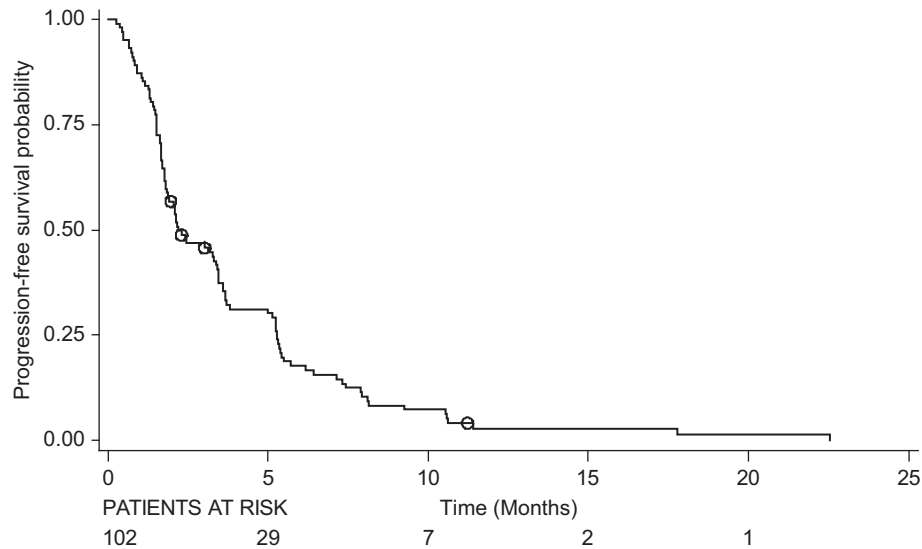
Figure 1. Progression free survival in all treated patients. Median PFS: 2.2 months (95%CI: 1.8–3.4). Circle denotes censored observation.

Discussion

To our knowledge, this is the first phase II trial to combine an EGFR inhibitor with an anti-angiogenic agent in patients with UGI cancers in an approach, where patients with different cancer diagnosis were treated in one trial. The expected determinant of efficacy was not the histology but the biological characteristics of the tumour. This was based on preclinical data suggesting that tumours sensitive to targeted agents may be distributed across histologically different cancer types [8].

Generally the therapy was well tolerated. With an overall response rate of 6% (95%CI: 2–12%), the primary endpoint was not met. The median PFS was 2.2 months (95%CI: 1.8–3.4), OS was 4.3 months (95% CI: 3.1–6.4), and DC rate was 46%. In multivariate and univariate analysis, low plasma concentrations of uPAR(I) was correlated to longer OS and PFS and low uPAR(I–III) + (II–III) was correlated to DC, while sVEGFR-2 was correlated to PFS in multivariate analysis only. The results

at least during the first eight weeks of therapy. None of the other markers changed significantly during treatment.
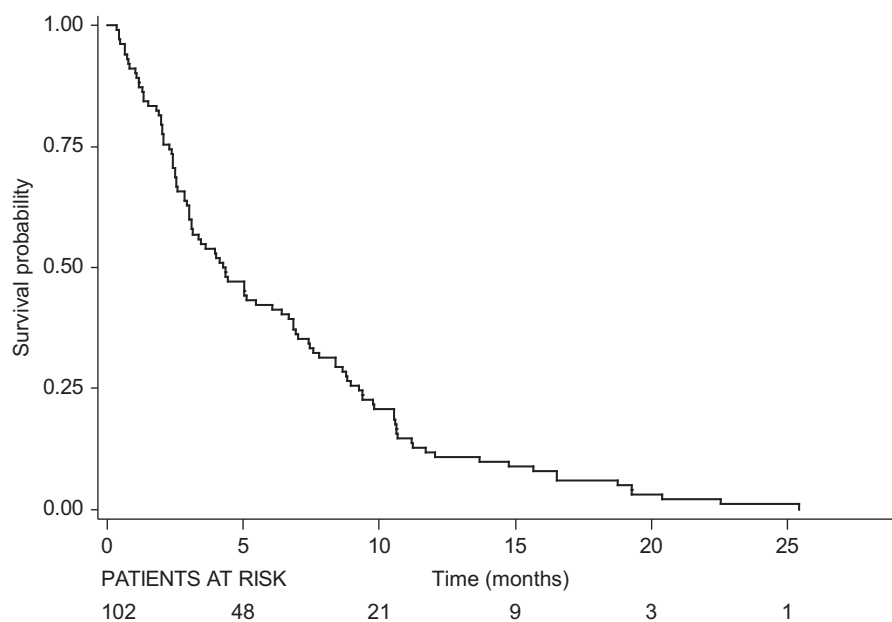

Figure 2. Overall survival. Median OS: 4.3 months (95%CI: 3.1–6.4).

Table II. Median overall and progression free survival according to tumour type. There is no significant difference in overall and progression-free survival between different tumour types.

Diagnosis	OS (months) [95%CI]	PFS (months) [95%CI]
Biliary tract cancer	5.3 [2.3–6.9]	2.8 [1.6–5.3]
Pancreatic cancer	3.4 [2.6–5.1]	2.0 [1.6–3.3]
GEJ cancer	7.0 [3.0–9.2]	3.1 [1.8–5.0]
Gastric cancer	2.4 [1.3–7.5]	2.1 [1.3–5.3]
Oesophageal cancer	7.4 [2.0–13.7]	3.6 [2.0–7.4]

from the present trial do not support the use of erlotinib in combination with bevacizumab in an unselected population of patients with advanced, chemo-refractory UGI cancers. However, 25% of the patients were alive after nine months, some patients indeed did respond, and some patients did have prolonged stable disease. These patients were distributed evenly between the diagnoses. In addition, more than 50% did not benefit from the therapy (26% not evaluable and 28% PD). This supports our approach, in which biomarkers were essential endpoints in the trial, in order to discriminate between those with clinical benefit and those without.

Erlotinib has shown to improve median survival in pancreatic cancer patients when added to gemcitabine by only 14 days [1]. The addition of bevacizumab to this regimen did not improve OS in patients with pancreatic cancer [11].

The promising preclinical synergy between EGFR-targeted and anti-angiogenic therapies has been confirmed by several phase II trials in patients

Table III. Correlations between patient characteristics and overall and progression-free survival.

	OS		PFS	
	HR [95%CI]	p	HR [95%CI]	p
Diagnosis		0.577		0.957
Biliary tract cancer	0.9 [0.5–1.6]	0.722	0.9 [0.5–1.7]	0.827
Oesophageal cancer	0.8 [0.4–2.0]	0.702	0.8 [0.3–1.8]	0.544
GEJ cancer	0.8 [0.5–1.3]	0.313	0.9 [0.6–1.6]	0.806
Gastric cancer	1.4 [0.7–2.6]	0.331	1.1 [0.6–2.1]	0.740
Pancreatic cancer	1		1	
Age	1.0 [0.8–1.2]	0.906	0.9 [0.8–1.2]	0.580
PS		0.002		0.0007
PS 0	1		1	
PS I	2.1 [1.3–3.2]	0.002	1.9 [1.2–3.1]	0.005
PS II	2.4 [1.4–4.4]	0.003	3.2 [1.7–5.9]	0.0003
Gender F vs M	1.3 [0.9–2.0]	0.191	1.3 [0.9–2.0]	0.207

Table IV. Toxicity in all 102 treated patients.

	CTC grade	
	1/2	3/4
Proteinuria	17	0
Nausea	31	0
Vomiting	27	1
Diarrhoea	41	1
Skin reaction	60	5
Fatigue	39	12
Neutropenia	5	0
Thrombocytopenia	4	0
Infection	18	7
Bleeding	17	2
Thrombosis	2	3
Hypertension	27	2
Anorexia	13	4
Stomatitis	9	0
Weight loss	29	2
Total	394	49

with non-small cell lung cancer, colorectal cancer, hepatocellular carcinoma, head and neck cancer, and cancer of unknown primary [12–17], whereas other clinical trials could not confirm this synergy in patients with mesothelioma, non-small cell lung cancer, pancreatic cancer, renal cell carcinoma, ovarian cancer, and breast cancer [11,18–23]. In a previous phase II trial of erlotinib and bevacizumab in patients with biliary tract cancer, Lubner et al. found response in 12% of treated patients [24]. In the present trial, patients with biliary tract cancer included a number of patients with minor response and two patients with partial remission.

In phase III trials of chemotherapy and bevacizumab +/− an anti-EGFR monoclonal antibody, patients with colorectal cancer treated with anti-EGFR therapy had inferior PFS compared to patients only treated with chemotherapy plus bevacizumab alone [25,26]. This negative interaction between the EGFR and VEGF-pathway has been discussed previously [27] and may partly explain why we did not find the combination of erlotinib and bevacizumab to be active in UGI cancers.

In UGI cancers, acquisition of tissue for biomarker detection is often troublesome; biomarkers detected in plasma would therefore represent a significant progress. We investigated plasma markers chosen on the basis of their importance in EGFR signalling or angiogenesis. The uPA system and its most important inhibitor, PAI-1, are central for the extracellular matrix degradation necessary for angiogenesis and metastasis [28,29]. We chose to investigate this system due to substantial data on its importance in EGFR signalling and angiogenesis
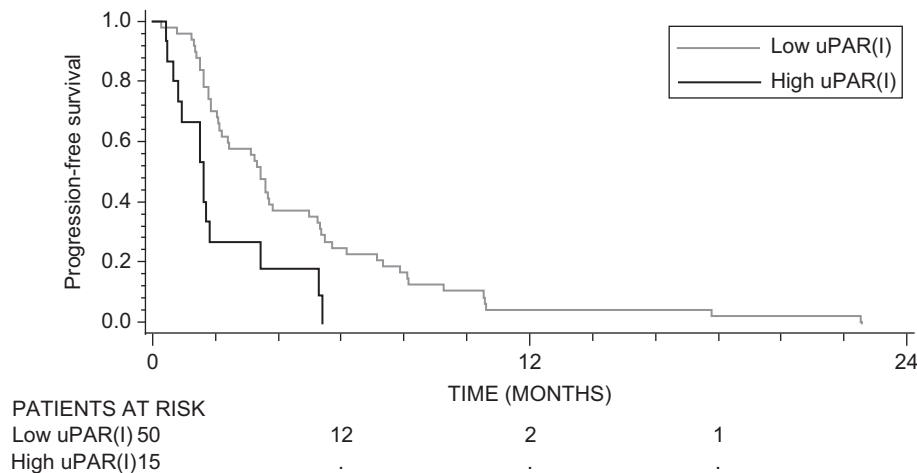
Figure 3. Progression free survival in patients with high uPAR(I) (in the higher quartile) compared to patients with low uPAR(I) (in the lower quartile and inter-quartile range). Hazard ratio for this model: 2.6 (95%CI: 1.4–4.9), p = 0.002.

[28,30]. Furthermore, it is established that uPAR and uPAR cleavage products are prognostic markers in several tumour types [31–34]. We identified uPAR (I) as a plasma marker correlated to survival in the present trial. Patients with low baseline levels of uPAR (I) had significantly longer PFS and OS in both univariate and multivariate analysis, making uPAR(I) an independent predictive or prognostic marker. PlGF and bFGF were investigated due to their importance in angiogenesis. They are both potent angiogenic growth factors, but did not correlate to response or survival [4]. VEGFR-2 is the main receptor of VEGF and sVEGFR-2 is the soluble, extracellular domain of VEGFR-2 [35]. sEGFR is the soluble, extracellular domain of the EGFR [36]. The release mechanism of these receptors is still uncertain. They may be released upon receptor activation [35,36] and could therefore be surrogate marker of receptor activity or be alternative

splice variants released from tumour cells with high expression of the intact receptor, and could thus act as surrogate marker of tumour cell expression of the receptors [35,37]. None of these soluble receptors were predictive in univariate models, but high sVEGFR-2 was significantly correlated to longer PFS in multivariate analysis where uPAR(I) and PS was included. This may reflect the biologic interaction between uPAR and VEGFR-2 [28], but this is speculative.

Whether the predictive values of these markers are specific for patients treated with erlotinib in combination with bevacizumab or they are prognostic markers in all patients with UGI cancer, cannot be concluded from the present study and needs further investigation.

Many patients in the present trial had early progression or death and the fact that 26 patients were not evaluable, reflects that this population was heav-
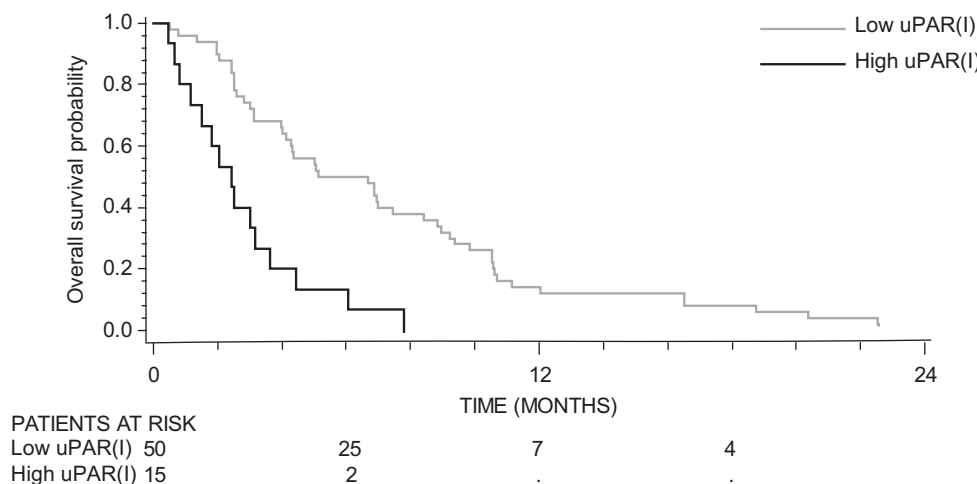

Figure 4. Overall survival in patients with high uPAR(I) (in the higher quartile) compared to patients with low uPAR(I) (in the lower quartile and inter-quartile range). Hazard ratio for this model: 3.6 (95%CI: 1.9–6.7), p < 0.0001.

Table V. Correlations between plasma markers and PFS, OS, and DCR in multivariate analysis.

	PFS		OS		DCR	
	HR [95%CI]	p	HR [95%CI]	p	OR	p
bFGF	1.1 [0.8–1.4]	0.654	1.0 [0.8–1.3]	0.930	0.8 [0.4–1.4]	0.416
PAI-1	1.0 [0.8–1.3]	0.814	1.2 [0.9–1.5]	0.232	1.1 [0.6–1.8]	0.817
PlGF	1.2 [0.8–1.9]	0.343	1.1 [0.8–1.7]	0.512	0.7 [0.3–1.6]	0.369
sVEGFR-2	0.7 [0.5–1.0]	0.041	0.7 [0.5–1.0]	0.082	1.4 [0.5–3.4]	0.499
sEGFR	0.8 [0.5–1.3]	0.371	0.7 [0.4–1.1]	0.109	1.3 [0.4–4.2]	0.631
uPAR (I–III)	0.9 [0.5–1.5]	0.723	1.0 [0.6–1.7]	0.953	1.3 [0.3–4.8]	0.733
uPAR (I–III) + (II–III)	0.8 [0.4–1.6]	0.595	1.1 [0.6–2.1]	0.695	0.3 [0.1–0.8]	0.021
uPAR (I)	1.8 [1.1–2.7]	0.001	2.0 [1.2–3.3]	0.001	1.0 [0.4–2.4]	0.986

DCR, disease control rate (CR+PR+SD); bFGF, basic fibroblast growth factor; PAI-1, plasminogen activator inhibitor 1; PlGF, placental growth factor; sVEGFR-2, soluble vascular endothelial growth factor 2; sEGFR, soluble epidermal growth factor receptor; uPAR, urokinase activator receptor; uPAR (I–III), intact uPAR; uPAR (I–III)+(II–III), intact + cleaved uPAR; uPAR (I), uPAR domain I.

ily pre-treated and with a poor prognosis. This stresses the importance of patient selection. Performance status was a strong predictor of OS and PFS and by only including patients in good performance status in early phase II trials in similar populations, the problem of early progression would be minimised. Furthermore, if the role of uPAR (I) as predictor of PFS and OS is not restricted to patients treated with erlotinib and bevacizumab, it could be suggested that future trials could benefit from only including patients with low uPAR (I). This, however, needs validation in larger cohorts.

Overall, the combination of erlotinib and bevacizumab was well tolerated and toxicity was manageable. The limited efficacy does not support further investigation of this combination as second line therapy in unselected patients with UGI cancers. The interaction between sVEGFR-2 and uPAR(I) and their potential predictive value warrants further preclinical and clinical evaluation. With a significant correlation to PFS and OS, the predictive value of uPAR(I) should be further investigated in patients treated with erlotinib and bevacizumab.

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