Pazopanib plus cetuximab in recurrent or metastatic head and neck squamous cell carcinoma: an open-label, phase 1b and expansion study

Douglas Adkins, Paul Mehan, Jessica Ley, Marilyn J Siegel, Barry A Siegel, Farrokh Dehdashti, Xuntian Jiang, Noha N Salama, Kathryn Trinkaus, Peter Oppelt

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Division of Medical Oncology (Prof D Adkins MD, P Mehan MD, J Ley BS, P Oppelt MD), **Alvin J Siteman Cancer Center** (Prof D Adkins, Prof M J Siegel MD, Prof B A Siegel MD, Prof F Dehdashti MD, K Trinkaus PhD), **Mallinckrodt Institute of Radiology,** (Prof M J Siegel, Prof B A Siegel, Prof F Dehdashti), **Metabolomics Facility** (X Jiang PhD), **and Siteman Cancer Center, Biostatistics Shared Resource** (K Trinkaus), **Washington University School of Medicine, St Louis, MO, USA; Department of Pharmaceutical and Administrative Sciences, St Louis College of Pharmacy, St Louis, MO, USA** (N N Salama PhD); **and Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Cairo, Egypt** (N N Salama)

Correspondence to: Prof Douglas Adkins, Washington University School of Medicine, Division of Medical Oncology, St Louis, MO 63110, USA
dadkins@wustl.edu

Summary

Background Angiogenesis is a hallmark of head and neck squamous cell carcinoma (HNSCC), and a mechanism of resistance to EGFR inhibition. We investigated the safety and potential activity of pazopanib, an angiogenesis inhibitor, plus cetuximab, an EGFR inhibitor, in patients with recurrent or metastatic HNSCC.

Methods We did an open-label, single-centre, dose-escalation phase 1b trial using a standard 3+3 design, followed by an expansion cohort phase. Eligible participants were patients with histologically or cytologically confirmed recurrent or metastatic HNSCC, aged at least 18 years, had measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and an Eastern Cooperative Oncology Group performance status of 0–1. During dose escalation, pazopanib oral suspension was administered daily in 8-week cycles at doses of 200 mg/day, 400 mg/day, 600 mg/day, or 800 mg/day, with cetuximab given intravenously once per week (400 mg/m² first dose and 250 mg/m² in consecutive cycles). The primary endpoint was to determine the maximum tolerated dose or recommended phase 2 dose of pazopanib in combination with cetuximab. Analyses were done per protocol. This trial is registered with ClinicalTrials.gov, number NCT01716416, and it is ongoing but closed to accrual.

Findings Between June 5, 2013, and April 4, 2017, we enrolled 22 patients into the phase 1b, dose-escalation phase of the trial. A maximum tolerated dose of pazopanib in combination with cetuximab was not reached. Single dose-limiting toxic events (all grade 3) during dose escalation occurred with pazopanib 400 mg/day (neutropenia with infection), 600 mg/day (proteinuria), and 800 mg/day (fatigue). The established recommended phase 2 dose for the combination was 800 mg/day of pazopanib during cycles of 8 weeks each, plus cetuximab 400 mg/m² on day 1 of cycle 1, then cetuximab 250 mg/m² weekly. A further nine patients were enrolled into the expansion cohort and treated with the established recommended phase 2 dose. The most common (grade 3–4) adverse events for all patients were hypertension (ten [32%] of 31), lymphocyte count decrease (seven [23%]), and dysphagia (seven [23%]). There were no treatment-related deaths. 11 (35%; 95% CI 19·2–54·6) of 31 patients achieved an overall response, as assessed by the investigator; two (6%) had a complete response and nine (29%) a partial response. Tumour responses were also observed in six (55%) of 11 patients with platinum-naive and cetuximab-naive disease, three (25%) of 12 patients with cetuximab-resistant disease, and five (28%) of 18 patients with platinum-resistant disease.

Interpretation Pazopanib oral suspension at a dose of 800 mg/day was feasible to administer in combination with standard weekly cetuximab for patients with recurrent or metastatic HNSCC. Encouraging preliminary antitumour activity was observed with this combination therapy and warrants further validation in randomised trials.

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Introduction

Activation of EGFR is common in head and neck squamous cell carcinoma (HNSCC).[1] Clinical trials showed improvement in overall survival when cetuximab, an EGFR inhibitor, was added to definitive radiotherapy or palliative chemotherapy.[2,3] However, the clinical benefit of cetuximab in recurrent or metastatic HNSCC was modest, with a median time to progression of only 70 days when given as monotherapy[4] and a prolongation of median overall survival by 2·7 months when added to chemotherapy.[3]

VEGF and fibroblast growth factor (FGF) are key inducers of angiogenesis, a hallmark of cancer.[5] VEGF expression is upregulated by hypoxia and oncogene signalling, which are common events in HNSCC,[6] as is expression of the VEGF receptors 1 and 3.[7,8] Amplification of the FGF receptor 1, mutations of the FGF receptors 2 and 3, and activation of FGF receptor gene fusions also occur in HNSCC.[9–11] Gene-expression profiling identified that hypoxic signalling not only was enriched in the basal subtype of human tumour samples but also was present in varying proportions across all subtypes.[12,13] In normoxic

Research in context

Evidence before this study

We searched PubMed for clinical trials published in English from Jan 1, 2000, to Jan 1, 2012, with the terms "angiogenesis", "cetuximab", and "head and neck cancer". No items were found. Cetuximab—an EGFR inhibitor—improved overall survival in first-line recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) when added to palliative chemotherapy, but had a modest clinical benefit. Pazopanib inhibits angiogenesis by acting on VEGF, platelet-derived growth factor, and FGF receptors. We did a phase 1b and expansion study to determine the safety of pazopanib with standard doses of cetuximab in patients with recurrent or metastatic HNSCC.

Added value of this study

This study showed that pazopanib 800 mg/day in combination with cetuximab was feasible, safe, and should be the recommended dose for phase 2 trials. In patients with platinum-resistant HNSCC, the number who achieved a robust, durable, tumour response, the median time to progression, and the median number who survived were better than expected with cetuximab monotherapy. In cetuximab-resistant HNSCC, similar activity was observed with pazopanib plus cetuximab. Pharmacokinetic endpoints at steady state with the suspension formulation of pazopanib were similar to published results with the oral tablet. The results of this study support the hypothesis that angiogenesis has an important role in HNSCC, and inhibition of angiogenesis is a relevant therapeutic strategy in this disease.

Implications of all the available evidence

To our knowledge, this is the first clinical study to combine pazopanib, an angiogenesis inhibitor, with cetuximab, an EGFR inhibitor, for treatment of resistant or metastatic HNSCC. The results of this trial support further studies to assess angiogenesis inhibitors in combination with targeted drugs in HNSCC. Other reports have linked angiogenesis to resistance to immunotherapy, and the results of this trial might inform development of studies of combinations of angiogenesis and PD-1 inhibitors in HNSCC.

conditions in human tumour samples, EGFR signalling promoted the expression of genes associated with angiogenesis.[14] Upregulation of VEGF is also a mechanism of resistance to EGFR inhibition in HNSCC.[15] The findings from previous studies support angiogenesis as being a hallmark of HNSCC and predict the potential benefit of angiogenesis inhibitors for treatment of this disease.[11–13,16–19] However, few clinical trials have assessed angiogenesis inhibitors in recurrent or metastatic HNSCC. In one study, sunitinib and sorafenib (inhibitors of tyrosine kinase including VEGF receptors) showed modest activity when used as monotherapy in patients with recurrent or metastatic HNSCC in a single-arm study.[20,21] In another study in patients with recurrent or metastatic HNSCC,[22] seven (15%) of 48 patients achieved a tumour response with bevacizumab, a monoclonal antibody that targets VEGF, combined with erlotinib or cetuximab.[23] Findings from the ECOG1305 phase 3 trial of first-line treatment for recurrent or metastatic disease showed an improvement of progression-free survival and overall survival with the addition of bevacizumab to chemotherapy.[24]

Pazopanib targets angiogenesis by inhibition of the VEGF receptors 1, 2, and 3, the platelet-derived growth factor (PDGF) receptors α and β, and FGF receptors 1 and 3. Adverse events associated with pazopanib include fatigue, diarrhoea, anorexia, nausea, hypertension, and increased biomarkers of liver damage. The recommended dose of pazopanib in tablet form is 800 mg/day for advanced renal cell carcinoma. Pazopanib can be given as a suspension formulation; however, this formulation increased the area under the curve $(AUC)_{(0–72\ h)}$ by 33% and the maximum plasma concentration (C_{max}) by 29%, and decreased the time taken to reach C_{max} by 50% (T_{max}).[25] We postulated it would be feasible to combine pazopanib with cetuximab in patients with resistant or metastatic HNSCC, and did a phase 1b and expansion study to investigate the safety of pazopanib plus fixed doses of cetuximab in this patient population.

Methods

Study design and participants

We did a phase 1b, open-label, single-centre trial using a standard 3+3 design followed by an expansion cohort study.

Eligible participants were patients aged at least 18 years with histologically or cytologically confirmed, recurrent (defined as an unresectable recurrence in an irradiated site) or metastatic HNSCC; measurable disease, or assessable disease in the dose-finding cohort only, defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Participants were not permitted to have received an EGFR tyrosine kinase inhibitor (TKI) or EGFR-specific monoclonal antibody for recurrent or metastatic disease in the expansion cohort, but previous therapy for recurrent or metastatic disease was allowed in the dose-finding cohort. Other inclusion criteria were an adequate bone marrow and organ function, urine protein-to-creatinine (UPC) ratio of less than 1, and a QTc of less than 480 ms.

Key exclusion criteria included use of CYP3A4 inhibitors within 14 days of protocol treatment start, or having had radiotherapy, minor surgery, or tumour embolisation during this period. The complete list of inclusion and exclusion criteria are in the protocol (appendix pp 4–69).

See Online for appendix

Tests required to determine eligibility included a complete blood count, metabolic panel, thyroid function, coagulation panel, electrocardiogram (ECG), echocardiogram, and CT scans. The protocol was reviewed and approved by the Institutional Review Board of Washington University School of Medicine, and patients provided written informed consent to participate. Independent data monitoring was done by the Protocol Review and Monitoring Committee (PRMC) of Washington University.

Procedures

In the dose-escalation phase, increasing doses of pazopanib were tested with a fixed dose of cetuximab. Pazopanib was administered daily on an 8-week cycle with weekly cetuximab. Pazopanib doses were started at 200 mg/day, then increased to 400 mg/day, 600 mg/day, and 800 mg/day (the maximum dose). A tablet is the current standard formulation to administer pazopanib. However, because of frequent dysphagia and requirement for gastrostomy in these patients, we chose to test a suspension formulation in this study. Pazopanib was given orally or via gastrostomy on an empty stomach. Intrapatient dose escalation was not permitted. Cetuximab was given intravenously at 400 mg/m² on day 1 of cycle 1, then 250 mg/m² weekly thereafter.

Three patients were enrolled per dose, expanded to six patients if one patient of the first three developed a dose-limiting toxic event. If none of the three patients given a specific dose developed a dose-limiting toxic event, the dose was increased in the next cohort of patients; but if at least two of six patients given a specific dose developed a dose-limiting toxic event, the dose immediately below was considered the maximum tolerated dose. Both dose-limiting toxicities and the maximum tolerated dose were assessed during cycle 1 of treatment. Dose escalation proceeded until either the maximum tolerated dose or the maximum dose level was reached. If a maximum tolerated dose was not established at the highest dose, this was to be considered as the recommended phase 2 dose of pazopanib given with cetuximab. At least six patients were to be enrolled at the recommended phase 2 dose of pazopanib. All patients were assessable for toxic effects.

After cycle 1, criteria to initiate subsequent cycles included a platelet count of at least 50 000 per µL, a UPC ratio of less than 3, and recovery of non-haematological toxicities to less than grade 1. If these conditions were not met, pazopanib administration was delayed by 1 week but cetuximab was continued. If after a 1-week delay toxicities recovered, pazopanib was resumed. If toxicities had not recovered after 2 weeks' delay, pazopanib was discontinued.

Once the recommended phase 2 dose of combination therapy was determined, nine patients were enrolled into an expansion cohort for pharmacokinetic studies and assessments of activity and adverse events. Pharmacokinetic assessment was done during cycle 1. Because of drug shortages, pazopanib suspension formulation was switched to tablets after cycle 1 for five of nine patients in the expansion cohort. Adverse events were monitored every 2 weeks during cycle 1 and then monthly, and were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Thyroxine, thyroid-stimulating hormone, UPC, and ECG data were assessed every cycle.

Pazopanib doses were adjusted for specific grades of adverse events. The lowest dose of pazopanib permitted was 200 mg every other day. Doses were held as needed for resolution of adverse events, and those omitted for an adverse event were not replaced. Based on the worst treatment-related adverse event in the previous cycle, a stepwise decrease in pazopanib dose by 200 mg/day was recommended for the following events: systolic blood pressure higher than 170 mm Hg, diastolic blood pressure higher than 110 mm Hg, a UPC ratio greater than 3, 24-h urine protein of at least 3 g, grade 2 haemorrhage, grade 3 thrombosis, grade 3–4 thrombocytopenia, or any other non-haematological toxic event of grade 2–3. Pazopanib was held until improvement to grade 1 or less for increased alanine aminotransferase (ALT) to at least eight times the upper limit of normal (ULN) with a total bilirubin concentration of less than twice the ULN. Pazopanib was discontinued for refractory hypertension, a persistent UPC ratio of more than 3 or 24-h protein of at least 3 g, grade 3–4 haemorrhage, grade 4 thrombosis, QTc of at least 500 ms, increased ALT to more than three times the ULN with a total bilirubin concentration of at least twice the ULN or with hypersensitivity symptoms, grade 3–4 palmar-plantar erythrodysaesthesia, or other grade 4 adverse events. Cetuximab dose was adjusted for adverse events based on package insert guidelines.

Tumour response assessments were done after every cycle by contrast-enhanced neck and chest CT scan. RECIST version 1.1 criteria were used to determine tumour response (ie, complete response, partial response, stable disease, or progression) and were assessed by the principal investigator. Treatment was continued until disease progression, death, severe adverse events (ie, intolerable), or patient withdrawal. Cetuximab-resistant disease and platinum-resistant disease were defined at study enrolment as progression that occurred on cetuximab or platinum agents, respectively, given to treat resistant or metastatic HNSCC.

Metabolic tumour responses were assessed by PET or CT with ^{18}F-fluorodeoxyglucose (FDG-PET/CT) at baseline and after cycle 1, using methods and metabolic tumour response criteria previously described.[26] In oropharyngeal squamous cell carcinoma, *p16* expression (a surrogate marker of HPV) was assessed by immunohistochemistry using a cutoff where less than 50% of

p16-positive tumour cells was defined as negative and more than 50% was defined as positive.

In the expansion cohort, 20 mL of blood was collected for pharmacokinetic assessments at cycle 1 day 15 before pazopanib administration and at 1 h, 2 h, 3 h, 4 h, 6 h, and 24 h after pazopanib administration. Drug concentrations reached steady-state after 2 weeks of pazopanib, and thus the data collected from this timepoint represent the pharmacokinetic profile at steady state. In the pharmacokinetic analysis of pazopanib, the eight-point standard curve samples with a linear range of 0·2–200·0 µg/mL were prepared in blank human plasma. Protein precipitation was used to extract pazopanib from 50 µL of standard curve and study human plasma samples in the presence of d3-pazopanib as internal standard. The extracts were analysed with liquid chromatography-tandem mass spectrometry (LC-MS). The standard curve samples were prepared in duplicate and run at the beginning and the end of LC-MS. Pazopanib and d3-pazopanib were separated from interferences on an XBridge C8 (3×50 mm, 3·5 µm) column (Waters Corporation. Milford, MA, USA), and detected with 4000QTRAP mass spectrometer.

Outcomes

The primary endpoint was the maximum tolerated dose of combined pazopanib suspension plus cetuximab therapy, defined as the highest dose of pazopanib with a fixed dose of cetuximab that resulted in one or fewer dose-limiting toxicity events in six patients. Haematological dose-limiting toxicities were defined as any of the following attributed to pazopanib: grade 4 neutropenia or thrombocytopenia for more than 5 days, grade 3 or 4 neutropenia with infection, or grade 3 or 4 thrombocytopenia with bleeding. Non-haematological dose-limiting toxicities were defined as grade 3 or 4 toxicity attributed to pazopanib with the following exceptions: suboptimally treated nausea, vomiting, or diarrhoea; grade 3 hypertension controlled with medication; grade 3 proteinuria that improved to less than grade 1 with interruption of pazopanib; grade 3 venous thrombosis; or anorexia.

Secondary endpoints were the pharmacokinetics of the combination at the maximum tolerated dose or recommended phase 2 dose, adverse events assessment, overall tumour response (the proportion of patients with a partial or complete response from the start of treatment until disease progression), the correlation between overall metabolic tumour response and anatomic tumour response, and estimation of the best tumour response after combination therapy.

In the expansion cohort, prespecified exploratory objectives were measurement of expression of p-VEGF receptors, p-PDGF receptors, p-c-kit and p-EGFR by immunohistochemistry on pretreatment and post-cycle 1 tumour tissue. Post-hoc analyses presented here were overall survival (defined as the time from start of treatment to death) and time to progression (time from treatment initiation until disease progression).

Statistical analysis

Based on the 3+3 design, we calculated that up to 24 patients could be enrolled in our phase 1b study based on four dose levels at which up to six patients per dose level could be enrolled. Nine patients were enrolled in the expansion cohort (a budgetary restriction). All patients who received at least one dose of study treatment were assessable for toxicity. Adverse events and serious adverse events occurring during each 8-week interval were summarised by individual patients, dose, type, and grade.

All patients who completed cycle 1 were evaluable for tumour response, unless the patient was removed from the study because of adverse events without undergoing a disease assessment before cycle 2. We assessed activity of pazopanib plus cetuximab by calculating the proportions of patients who achieved a tumour response, disease control (ie, complete response, partial response, and stable disease), or a metabolic response after cycle 1 of therapy. Association of dose with tumour response was explored using an ordinal test for trend (Jonckheere's test) and concordance coefficients (Kendall's tau and Somers' D). Tumour response and metabolic response were compared with a κ coefficient. Cumulative incidence of disease progression was compared by study arm using Fine-Gray's subdistribution hazard method and Gray's test; death without disease progression was considered a competing risk for this analysis. A post-hoc assessment of overall survival and time to progression were estimated in a Kaplan-Meier analysis. CIs for proportions are exact binomial CIs. The quartiles for overall survival and time to progression are the 25th and 75th percentiles calculated directly from data. CIs for median times are from Kaplan-Meier models.

For the pharmacokinetic analyses, the observed mean (SD) drug plasma concentrations were plotted using SigmaPlot version 12.5. Non-compartmental analysis was used to assess pazopanib pharmacokinetics for each participant. At steady-state, the area under the curve during a dosing interval ($AUC_{0\text{-}24h}$) was calculated using the linear trapezoidal rule. The elimination rate constant (Kel) was calculated by regression of the data displaying monoexponential decline in the elimination phase. The steady-state levels at the minimum plasma concentration of pazopanib (C_{min}) were used to mathematically estimate the corresponding apparent steady-state volume of distribution (Vz/F), assuming complete absorption of the dose and prevalence of pure first order elimination at this point of the profile. Steady-state oral clearance (Cl/F) was calculated using Kel and steady-state Vz/F estimates. All statistical analyses were done using SAS version 9.4 and STAT version 14.2. Data processing was done with Analyst 1.5.2 (AB Sciex).

This trial is registered with ClinicalTrials.gov, number NCT01716416.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between June 5, 2013, and April 4, 2017, we enrolled 22 patients into the phase 1b, dose-escalation phase of the trial and nine patients into the expansion cohort once the recommended phase 2 dose was established. Because of required enrolment breaks between dose levels to monitor for dose-limiting toxic events and intermittent lack of study drug availability, trial enrolment did not conclude until April 4, 2017. The cutoff for data analyses presented here was Nov 15, 2017.

	Phase 1b (n=22)	Expansion cohort (n=9)
Age (years)		
Median	59	59
Range	43–72	38–63
Sex		
Male	17 (77%)	8 (89%)
Female	5 (23%)	1 (11%)
Race		
White	16 (73%)	8 (89%)
African-American	6 (27%)	1 (11%)
ECOG performance status		
0	13 (59%)	5 (56%)
1	9 (41%)	4 (44%)
Smoking history		
Yes	16 (73%)	7 (78%)
No	6 (27%)	2 (22%)
Primary site of tumour		
Oropharynx	6 (27%)*	3 (33%)†
Oral cavity	8 (36%)	2 (22%)
Hypopharynx	4 (18%)	2 (22%)
Larynx	3 (14%)	2 (22%)
Nasopharynx	1 (5%)	0
Site of recurrence		
Local or regional	2 (9%)	2 (22%)
Distant	11 (50%)	3 (33%)
Distant and local or regional	9 (41%)	4 (44%)
Previous therapy for recurrent or metastatic HNSCC		
Cetuximab resistant‡	12 (55)	0
Platinum resistant‡	14 (64)	4 (44)
Cetuximab and platinum resistant‡	10 (45)	0
Number of lines of previous therapy for recurrent or metastatic HNSCC		
≥2	9 (41)	1 (11)
1	8 (36)	4 (44)
0	5 (23)	4 (44)

Data are mean (SD), range, or n (%), unless stated otherwise. ECOG=Eastern Cooperative Oncology Group. HNSCC=head and neck squamous cell carcinoma. *Five patients were positive for *p16* expression. †Three patients were positive for *p16* expression. ‡In total, 31 patients were enrolled.

Table 1: **Baseline characteristics of all enrolled patients**

Most patients were smokers with human papilloma virus (HPV)-unrelated HNSCC (as measured by positive *p16* expression) and had received previous therapies for resistant or metastatic disease (table 1). 19 patients (61%) received pazopanib suspension orally and 12 (39%) via gastrostomy. No participants received immunotherapy before enrolment.

During the phase 1b trial, three patients were assigned to pazopanib 200 mg/day, six to 400 mg/day, seven to 600 mg/day, and six to 800 mg/day (all patients received the same fixed dose of cetuximab). The maximum tolerated dose of pazopanib was not reached. During cycle 1 of combination treatment, single dose-limiting toxic events (all grade 3) occurred with pazopanib 400 mg/day (neutropenia with infection), 600 mg/day (proteinuria), and 800 mg/day (fatigue; appendix p 2). The established recommended phase 2 dose for the combination was 800 mg/day of pazopanib during one cycle every 8 weeks, plus 400 mg/m² of cetuximab on day 1 of cycle 1, then 250 mg/m² of cetuximab every week thereafter.

The most common (grade 3–4) adverse events for all patients regardless of attribution to study drug were hypertension (ten [32%] of 31), lymphocyte count decrease (seven [23%]), and dysphagia (seven [23%]; table 2). The most frequent adverse events attributable to pazopanib that occurred at each dose and during all cycles of therapy are in the appendix (p 3). The most common grade 3 adverse events attributable to pazopanib were hypertension, anaemia, fatigue, hypoalbuminaemia, and venous thromboembolism. There were no treatment-related deaths, and no grade 4 adverse events were attributable to pazopanib. Adverse events attributable to cetuximab included hypersensitivity or infusion reactions (four [14%]), rash (23 [73%]), paronychia (ten [32%]), and hypomagnesaemia (13 [42%]).

Of 56 possible doses, the median delivered dose of pazopanib per patient during cycle 1 of treatment (administered number of doses divided by scheduled number of doses) was 56 doses of 200 mg/day (100%; range 100–100), 55 doses of 400 mg/day (98%; 79–100), 54 doses of 600 mg/day (96%; 14–100), and 52 doses of 800 mg/day (93%; 36–100). Some pazopanib doses were not administered because of disease progression (two patients [9%]), adverse events (five patients [23%]), or missed doses (five patients [23%]). During subsequent cycles, intrapatient dose reduction of pazopanib occurred in one (5%) patient because of fatigue or anorexia.

The median delivered dose of cetuximab per patient during cycle 1 of treatment was eight (100%) of eight doses with all doses of pazopanib (percentage

	Grades 1 and 2*				Grade 3				Grade 4			
	200 mg/day (n=3)	400 mg/day (n=6)	600 mg/day (n=7)	800 mg/day (n=15)	200 mg/day (n=3)	400 mg/day (n=6)	600 mg/day (n=7)	800 mg/day (n=15)	200 mg/day (n=3)	400 mg/day (n=6)	600 mg/day (n=7)	800 mg/day (n=15)
Haematological toxicities												
Anaemia	1 (33%)	5 (83%)	5 (71%)	13 (87%)	1 (33%)	1 (17%)	2 (29%)	2 (13%)	..	..	..	..
Lymphocyte count decrease	1 (33%)	5 (83%)	2 (29%)	10 (67%)	2 (67%)	..	3 (43%)	2 (13%)	..	..	1 (14%)	
Neutrophil count decreased	..	..	..	..	..	1 (17%)	1 (14%)	..	..	..	..	..
Platelet count decreased	..	2 (33%)	3 (43%)	6 (40%)	..	..	..	..	..	..	..	..
White blood cell decreased	1 (33%)	2 (33%)	3 (43%)	6 (40%)	..	..	1 (14%)	..	..	..	..	..
Non-haematological toxicities												
Myocardial infarction	..	..	..	..	..	..	1 (14%)	..	..	..	..	..
Hypothyroidism	..	..	5 (71%)	8 (53%)	..	..	..	..	..	..	..	..
Anorexia	..	1 (17%)	3 (43%)	3 (20%)	..	..	1 (14%)	1 (7%)	..	..	..	..
Colitis	..	..	..	..	..	..	..	1 (7%)	..	..	..	..
Constipation	2 (67%)	1 (17%)	1 (14%)	5 (33%)	..	..	..	..	..	..	..	..
Diarrhoea	1 (33%)	1 (17%)	3 (43%)	8 (53%)	..	1 (17%)	..	..	..	..	..	..
Dehydration	..	..	..	..	..	..	..	2 (13%)	..	..	..	..
Dry mouth	1 (33%)	1 (17%)	2 (29%)	8 (53%)	..	..	..	..	..	..	..	..
Dysphagia	..	..	1 (14%)	3 (20%)	1 (33%)	2 (33%)	2 (29%)	2 (13%)	..	..	..	..
Mucositis oral	..	..	..	..	..	..	..	1 (7%)	..	..	..	..
Nausea	..	2 (33%)	6 (86%)	9 (60%)	..	..	..	1 (7%)	..	..	..	..
Oral haemorrhage	..	..	..	..	..	..	..	1 (7%)	..	..	..	..
Oral cavity fistula	..	..	..	..	..	..	..	1 (7%)	..	..	..	..
Small intestinal perforation	..	..	..	..	..	..	..	..	..	..	..	1 (7%)
Vomiting	..	1 (17%)	2 (29%)	3 (20%)	..	..	..	..	..	..	..	..
Oedema limbs	..	4 (67%)		2 (13%)	..	..	1 (14%)	..	..	..	..	..
Fatigue	1 (33%)	2 (33%)	4 (57%)	9 (60%)	..	..	2 (29%)	2 (13%)	..	..	..	..
Infusion-related reaction	1 (33%)	1 (17%)	1 (14%)	2 (13%)	..	..	..	..	..	..	..	..
Bone infection	..	..	..	..	..	..	1 (14%)	..	..	..	..	..
Catheter-related infection	..	..	..	..	..	..	..	1 (7%)	..	..	..	..
Lung infection	..	..	..	..	..	1 (17%)	..	..	..	..	..	..
Paronychia	1 (33%)	2 (33%)		6 (40%)	1 (33%)	..	..	..	..	..	..	..
Skin infection	..	..	..	..	1 (33%)	..	..	..	..	..	..	..
Tracheal haemorrhage	..	..	..	..	1 (33%)	..	..	..	..	..	..	..
Alanine aminotransferase increased	1 (33%)	3 (50%)	3 (43%)	7 (47%)	..	..	..	1 (7%)	..	..	..	..
Alkaline phosphatase increased	1 (33%)	3 (50%)	3 (43%)	5 (33%)	..	..	..	..	..	..	..	..
Aspartate aminotransferase increased	2 (67%)	4 (67%)	4 (57%)	4 (27%)	..	..	..	1 (7%)	..	..	..	..
Blood bilirubin increased	..	1 (17%)	2 (29%)	3 (20%)	..	..	..	..	..	..	..	..
Creatinine increased	..	1 (17%)	1 (14%)	5 (33%)	1 (33%)	..	..	..	..	..	..	..
Hypercalcaemia	1 (33%)	3 (50%)	2 (29%)	2 (13%)	..	..	..	..	..	..	..	..
Hyperglycaemia	1 (33%)	1 (17%)	1 (14%)	3 (20%)	..	..	1 (14%)	1 (7%)	..	..	..	..

(Table 2 continues on next page)

	Grades 1 and 2*				Grade 3				Grade 4			
	200 mg/day (n=3)	400 mg/day (n=6)	600 mg/day (n=7)	800 mg/day (n=15)	200 mg/day (n=3)	400 mg/day (n=6)	600 mg/day (n=7)	800 mg/day (n=15)	200 mg/day (n=3)	400 mg/day (n=6)	600 mg/day (n=7)	800 mg/day (n=15)
(Continued from previous page)												
Hyperkalaemia	..	..	..	..	..	..	..	1 (7%)	..	..	..	..
Hypernatraemia	1 (33%)	2 (33%)	1 (14%)	..	..	..	1 (14%)	..	..	..	..	..
Hypoalbuminaemia	1 (33%)	3 (50%)	5 (71%)	6 (40%)	1 (33%)	1 (17%)	1 (14%)	1 (7%)	..	..	..	..
Hypocalcaemia	1 (33%)	3 (50%)	3 (43%)	4 (27%)	..	1 (17%)	1 (14%)	1 (7%)	..	..	..	1 (7%)
Hypoglycaemia	1 (33%)	1 (17%)	..	..	..	..	..	..	..	..	..	..
Hypokalaemia	..	2 (33%)	3 (43%)	6 (40%)	..	1 (17%)	2 (29%)	..	..	..	..	1 (7%)
Hypomagnesaemia	..	5 (83%)	1 (14%)	5 (33%)	..	..	1 (14%)	1 (7%)	..	..	..	..
Hyponatraemia	2 (67%)	2 (33%)	3 (43%)	7 (47%)	..	1 (17%)	1 (14%)	1 (7%)	..	..	..	..
Hypophosphataemia	..	1 (17%)		6 (40%)	1 (33%)	1 (17%)	2 (29%)	..	..	..	..	..
Dizziness	1 (33%)	1 (17%)	2 (29%)	4 (27%)	..	..	..	..	..	..	..	..
Headache	1 (33%)	1 (17%)	2 (29%)	2 (13%)	..	..	..	..	..	..	..	..
Peripheral sensory neuropathy	..	3 (50%)	1 (14%)	2 (13%)	..	..	..	..	..	..	..	..
Haematuria	..	..	3 (43%)	1 (7%)	..	..	..	..	..	..	..	..
Proteinuria	..	..	..	..	..	..	1 (14%)	..	..	..	..	..
Renal calculi	..	..	..	..	..	..	1 (14%)	1 (7%)	..	..	..	..
Dyspnoea	..	..	2 (29%)	6 (40%)	..	..	3 (43%)	1 (7%)	..	..	..	..
Pharyngeal fistula	..	..	..	..	..	..	1 (14%)	..	..	..	..	..
Pleural effusion	..	..	..	..	..	..	1 (14%)	..	..	..	..	..
Pneumothorax	..	..	..	..	..	..	..	..	..	..	1 (14%)	..
Dry skin	3 (100%)	..	3 (43%)	6 (40%)	..	..	..	..	..	..	..	..
Rash acneiform	3 (100%)	4 (67%)	2 (29%)	13 (87%)	..	..	1 (14%)	2 (13%)	..	..	..	..
Skin induration	1 (33%)	..	..	4 (27%)	..	..	..	..	..	..	..	..
Hypertension	1 (33%)	3 (50%)	3 (43%)	9 (60%)	1 (33%)	3 (50%)	3 (43%)	3 (20%)	..	..	..	..
Hypotension	2 (67%)	1 (17%)	..	2 (13%)	..	..	1 (14%)	..	..	..	..	..
Thromboembolic event	..	..	..	..	1 (33%)	..	..	1 (7%)	..	..	..	..

Data are n (%) of patients with adverse events that occurred during all cycles of treatment and in all patients (all 31 patients received at least one dose of treatment and were included in the safety population) regardless of attribution to study drugs. All patients received pazopanib at the indicated doses plus weekly cetuximab. No deaths occurred. *Reported if frequency ≥10%; all grade 3–4 adverse events are shown.

Table 2: **Adverse events per grade and dose received in all patients**

ranges with pazopanib 200 mg/day, 400 mg/day, 600 mg/day, and 800 mg/day were 100–100, 88–100, 13–100, and 100–100, respectively). Some doses of cetuximab were not administered because of disease progression (two patients [9%]). Intrapatient dose reductions of cetuximab did not occur.

In the expansion cohort, nine patients were treated with the combination therapy at the recommended phase 2 dose. The median number of doses of pazopanib delivered per patient during cycle 1 was 54 of 56 doses (96%; range 63–100) and of cetuximab was eight of eight doses (100%; range 88–100). Some pazopanib doses were not administered because of adverse events (four patients [44%]) or missed doses (one patient [11%]). Adverse events in the expansion cohort were similar to those in the phase 1b cohort (appendix, p 3).

Pharmacokinetic analysis was done for seven patients (78%) in the expansion cohort (two patients declined to take part in pharmacokinetic analyses). The route of pazopanib administration was oral in five patients and via gastrostomy in two. Compliance with administration of study drug was confirmed by patient-reported diaries and cross-checked with the bottles of suspension returned by the patient. In the seven patients, the median delivered dose of pazopanib per patient during cycle 1 was 54 of 56 doses (96%; range 63–100). Mean (SD) observed drug plasma concentrations are in figure 1. Non-compartmental analysis was used to assess pazopanib pharmacokinetics for each participant (table 3). Steady-state C_{max} and T_{max} were determined from data for all seven patients. Other pharmacokinetic parameters were calculated using the profiles of four or five patients (table 3). Biomarker analyses were not available because only three patients underwent pretreatment biopsies and one underwent a post-treatment tumour biopsy.

In total, 11 (35%) of 31 patients achieved an objective response (95% CI 19·2–54·6). Overall, the best tumour response was a complete response in two (6%) of 31 patients, a partial response in nine (29%), stable disease in 14 (45%), and progressive disease in six (19%). 19 (61%)

of 31 patients had measureable decrease in their target lesion, and 12 (39%) achieved a decrease of at least 30% (figure 2). Of 15 patients treated with the recommended phase 2 dose for the combination, seven (47%) achieved an objective response (two [13%] complete response, five [33%] partial response; 95% CI 21·3–73·4). Tumour responses were also achieved by three (25%) of 12 patients with cetuximab-resistant HNSCC, five (28%) of 18 with platinum-resistant HNSCC, six (55%) of 11 with platinum-naive and cetuximab-naive HNSCC, three (38%) of eight with HPV-related oropharyngeal squamous cell carcinoma, and eight (35%) of 23 with HPV-unrelated HNSCC. A metabolic tumour response to cycle 1 of pazopanib plus cetuximab occurred in 20 (77·0%; 95% CI 56·4–91·0) of 26 assessable patients, two complete metabolic responses and 18 partial metabolic responses. Stable or progressive metabolic disease occurred in two (8%) and four (15%) patients, respectively. Tumour response by RECIST version 1.1 was associated with pazopanib dose (table 4; concordance coefficients: Somers' D 0·34, 95% CI 0·03–0·65; Jonckheere-Terpstra test p=0·03). No correlation was observed between pazopanib dose and metabolic tumour response (data not shown) or between tumour response by RECIST version 1.1 and metabolic tumour response (κ coefficient 0·09, 95% CI –0·15 to 0·33).

Cavitation of tumour lesions, all in pulmonary metastases, was observed in 12 (39%) of 31 patients, ten with disease control (four with partial responses and six with stable disease) and two with progressive disease. 11 of these cavitations were asymptomatic, detected by routine imaging. One patient developed a bronchopleural fistula. A post-hoc assessment of all 31 patients showed the median time to progression, represented inversely as cumulative incidence of progression, was 5·3 months (95% CI 3·7–7·2; figure 3). Median time to progression in patients with cetuximab-resistant HNSCC was 5·0 months (95% CI 3·5–7·2), in patients with platinum-resistant HNSCC was 4·6 months (3·4–7·2), and in patients with platinum-naive and cetuximab-naive disease was 6·3 months (3·7–13·7). Median follow-up for these post-hoc analyses was 9·5 months for all patients, 9·4 months for cetuximab-resistant disease, 9·3 months for platinum-resistant disease, and 11·6 months for platinum-naive and cetuximab-naive disease. Median time to progression was 5·5 months (IQR 1·8–7·6) in the eight patients with HPV-related oropharyngeal squamous cell carcinoma and 3·7 months (IQR 3·4–7·2) in the 23 patients with HPV-unrelated HNSCC. Median follow-up was 11·2 months (IQR 7·2–16·8) in the eight patients with HPV-related oropharyngeal squamous cell carcinoma and 9·3 months (5·5–15·6) in the 23 patients with HPV-unrelated HNSCC.

A post-hoc assessment of all 31 patients showed the median overall survival for all patients was 9·5 months (95% CI 8·1–13·9; figure 4). Median overall survival for cetuximab-resistant disease was 9·4 months (5·3–18·8), for platinum-resistant disease was 9·3 months (7·3–18·8), and for platinum-naive and cetuximab-naive disease was 11·6 months (5·5–25·1). At last follow-up (Nov 15, 2017), four patients were alive and one was on study treatment. 23 patients died due to disease progression; one due to comorbidity, and three from an unknown cause of death.

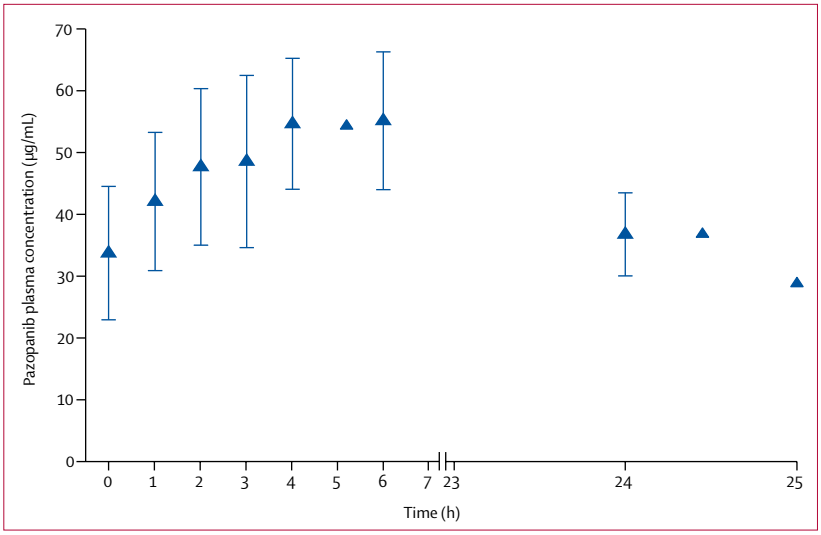


Figure 1: **Pazopanib plasma concentration in the dose expansion cohort**
Triangles represent the mean and error bars the SD. Triangles without error bars represent single patient samples. Only the nine patients included in the dose expansion cohort are included in this analysis.

	Mean (SD)	Median	Range	Number of observations
C_{max}, steady state (µg/mL)	51·0 (13·9)	57·6	31·7–66·6	7
T_{max}, steady state (h)	3·3 (1·4)	3·0	2·0–6·0	7
C_{min}, steady state (µg/mL)	35·9 (5·5)	36·8	28·8–41·5	5
$AUC_{0\text{-}24\,h}$, steady state (h × mg/L)	1080·7 (144·9)	1114·2	877·6–1216·7	4
K_e (per h)	0·02 (0·01)	0·02	0·02–0·03	4
$T_{1/2}$ (h)	31·9 (6·4)	33·0	23·1–38·5	4
Clearance steady state/bioavailability (L/h)	0·74 (0·13)	0·7	0·6–0·9	4
V_z, steady state bioavailability (L/kg)	0·7 (0·1)	0·7	0·6–0·8	4

Pharmacokinetics analyses were done in the nine patients recruited in the dose expansion phase who received the recommended phase 2 dose of combination therapy. All patients received pazopanib at the indicated doses plus weekly cetuximab. C_{max}=maximum plasma concentration. T_{max}=time to reach the maximum plasma concentration. C_{min}=minimum concentration. AUC=area under the curve. K_e=elimination rate constant. $T_{1/2}$=half-life. V_z=volume of distribution.

Table 3: **Pazopanib pharmacokinetics in the dose expansion cohort**

Discussion

The findings of this trial establish the feasibility of administering the novel combination of pazopanib and cetuximab to patients with resistant or metastatic HNSCC. To our knowledge, this is the first clinical study to combine pazopanib, an angiogenesis inhibitor, with cetuximab, an EGFR inhibitor. The recommended phase 2 dose of pazopanib suspension formulation was 800 mg/day, in combination with standard doses of weekly cetuximab. Higher doses of pazopanib were not assessed because tumour responses were seen across the four doses tested, even in cetuximab-resistant disease. Additionally, the dose approved by the US Food and Drug

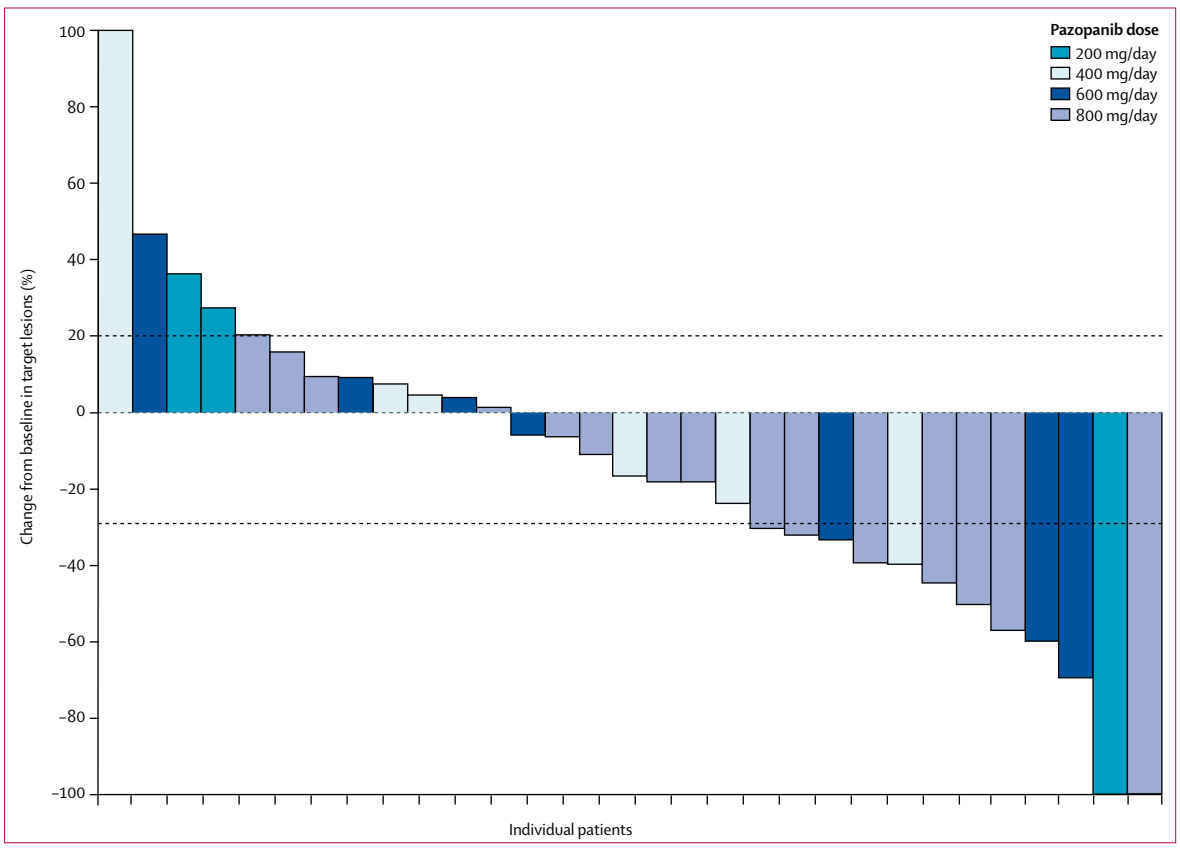


Figure 2: **Best response achieved in all enrolled patients (n=31)**
The dotted line at 20% is the threshold used to define progression by RECIST. The dotted line at –30% is the threshold used to define partial response by RECIST.

	Number of patients	Complete response plus partial response	Disease control (complete response plus partial response plus stable disease)
200 mg/day	3	1 (33%)	1 (33%)
400 mg/day	6	1 (17%)	4 (67%)
600 mg/day	7	2 (29%)	6 (86%)
800 mg/day	15	7 (47%)	14 (93%)

Data are n (%) of patients who achieved a response with differing doses of pazopanib. All patients received pazopanib at the indicated doses plus weekly cetuximab.

Table 4: **Best tumour response per dose in all enrolled patients**

Administration of pazopanib tablets given as monotherapy for advanced renal cell carcinoma is 800 mg/day.

Adverse events attributable to pazopanib were different to those attributable to cetuximab. In this trial, the non-overlapping adverse events of the combination were well tolerated. Dose-limiting toxic events attributed to pazopanib included neutropenia, proteinuria, and fatigue. The most common grade 3 adverse events attributable to pazopanib across all cycles were hypertension, anaemia, fatigue, hypoalbuminaemia, neutropenia, and diarrhoea. Grade 4 adverse events or treatment-related deaths did not occur. Grade 3 fistula and venous thromboembolism occurred in two and three patients, respectively; however, the contribution of pazopanib to these adverse events is difficult to determine because both might be due to the actual disease or other causes. The adverse events typical with cetuximab treatment (eg, rash and infusion reactions)[26] were not altered by coadministration of pazopanib.

We chose a suspension formulation of pazopanib for this trial because this formulation would be easier to administer to patients with resistant or metastatic HNSCC who have difficulties swallowing larger tablets or can only take medications via gastrostomy. A previous study[25] showed that the suspension formulation of pazopanib increased the $AUC_{(0–72\ h)}$ and C_{max}, probably due to an increased extent of oral absorption compared with the tablet formulation. We anticipated that differences in pharmacokinetics between the suspension and tablet formulations of pazopanib would result in reduced tolerance of the highest doses of the suspension in our phase 1b trial because of excess adverse events. However, 800 mg/day of pazopanib suspension was tolerable when given with cetuximab. This finding might be attributable to the similarity between the pharmacokinetic parameters (AUC_{0-24}, C_{max}, T_{max}, C_{min}, and $T_{1/2}$) with the 800 mg/day

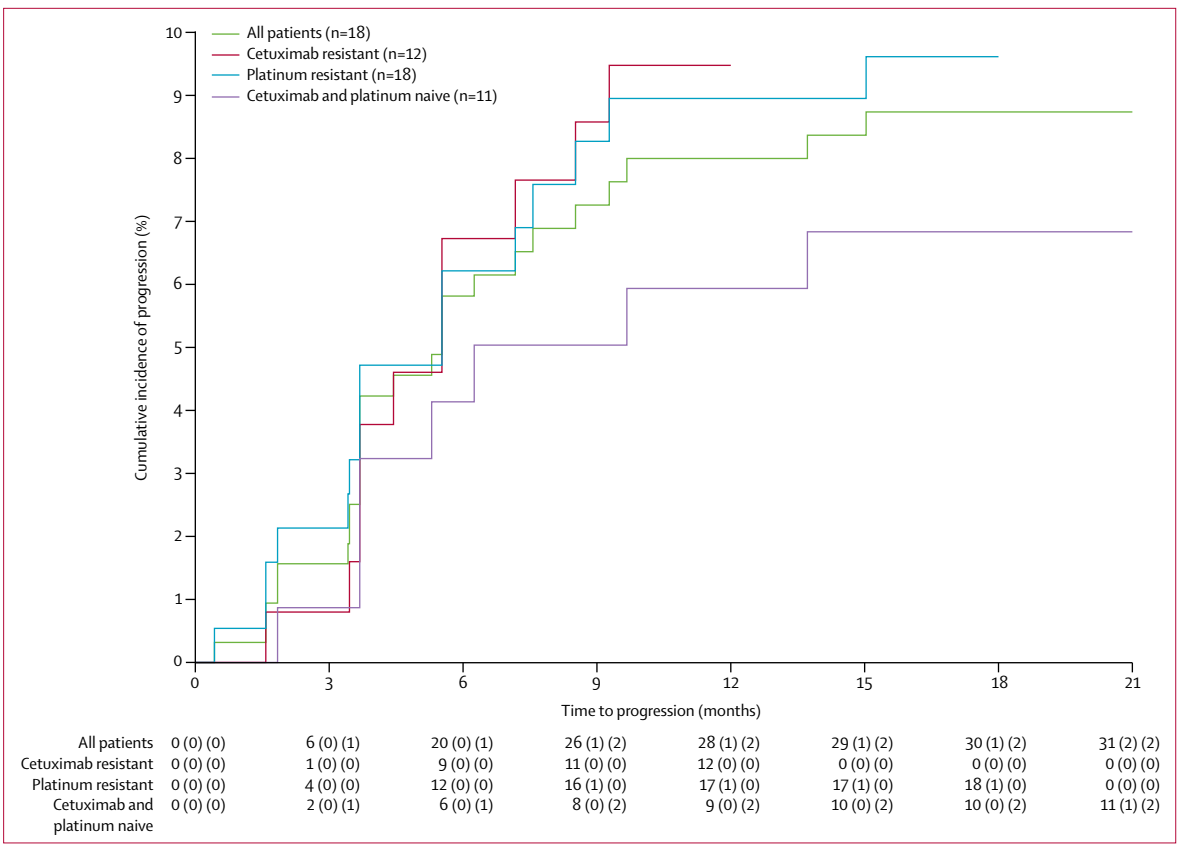


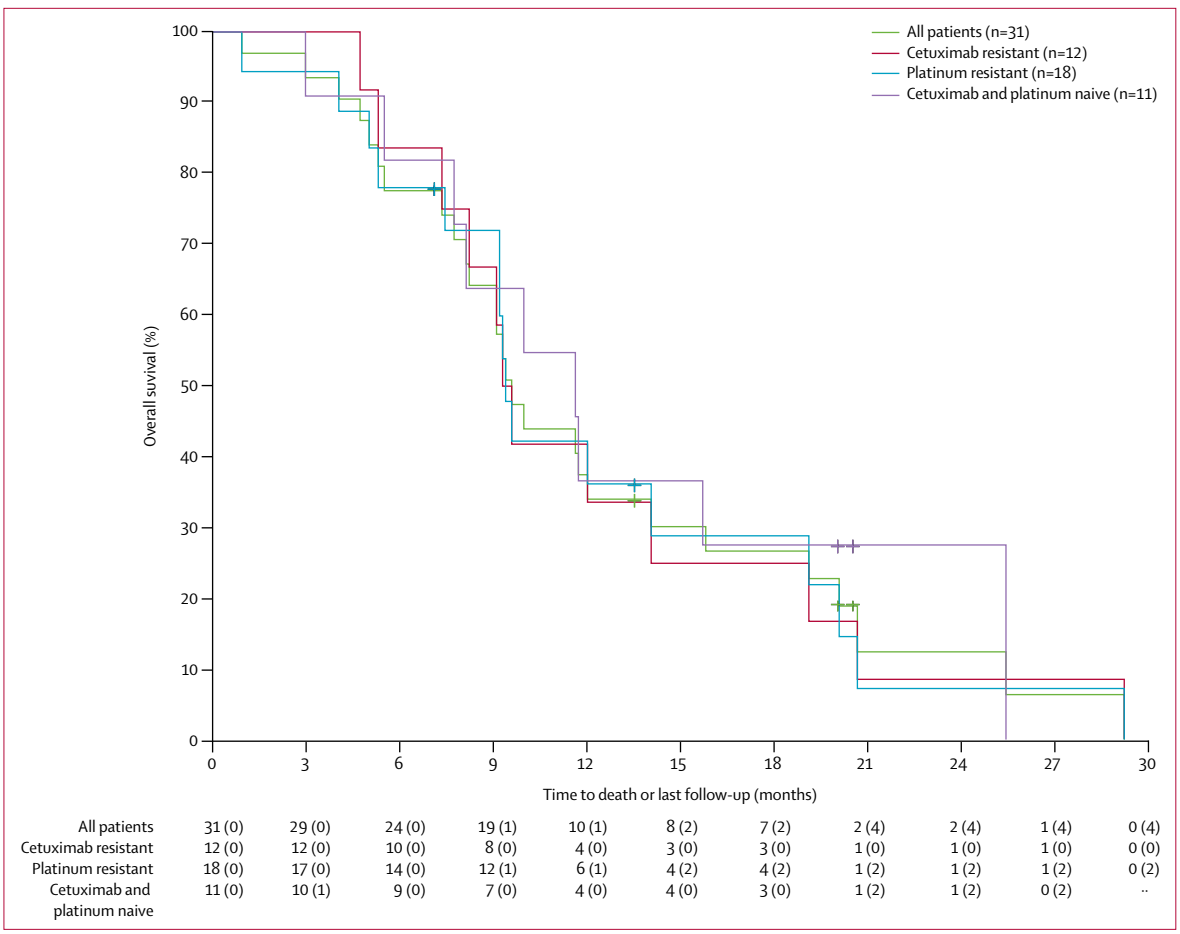
Figure 3: **Post-hoc analysis of time to progression in all enrolled patients**
Data are represented as cumulative incidence of progression to account for patients who died without disease progression: number of patients at risk who progressed (number censored), (number of patients with competing risk).

dose of the suspension formulation in our trial and those reported in the scientific literature with the 800 mg/day dose of the tablet.[27] The reasons for these discordant results are unclear, but might relate to the potential effect of differences in suspension preparation, patient characteristics, fat content of diet, and drug interactions on the pharmacokinetics of pazopanib.

The combination of pazopanib and cetuximab showed substantial antitumour activity in patients with platinum-naive and cetuximab-naive HNSCC, cetuximab-resistant HNSCC, and platinum-resistant HNSCC. Although cross-trial comparisons might be done with caution, in previous studies the overall tumour response with cetuximab monotherapy in patients with platinum-resistant HNSCC was 13% (95% CI 7–21) and median time to progression was 70 days.[4] Although this trial was not powered to detect differences in activity, the preliminary antitumour activity of pazopanib plus cetuximab observed seems to improve when compared to previously reported results with other agents that target angiogenesis. Seven (47%) of 15 patients treated with the recommended phase 2 dose of pazopanib and cetuximab achieved a tumour response. By contrast, in a previous study,[22] only seven (15%) of 48 patients treated with bevacizumab combined with erlotinib or cetuximab achieved a tumour response.[23] These differences in antitumour activity might be due to bevacizumab targeting only the VEGF ligand, whereas pazopanib targets several tyrosine-kinase receptors (VEGF receptors 1, 2, and 3; PDGF receptors α and β; and FGF receptors 1 and 3) that are important in angiogenesis. Differences in patient and tumour characteristics across studies might also be relevant factors for the differences in antitumour activity.

One prospective trial has assessed pazopanib monotherapy in patients with HNSCC.[28] 55% of patients with nasopharyngeal cancer achieved disease control with a pazopanib tablet formulation of 800 mg/day. Dynamic contrast-enhanced CT showed reductions in tumour blood flow consistent with an antiangiogenic effect. Also, a case report described an FGF receptor-mutated oral squamous cell carcinoma that responded to pazopanib monotherapy.[29]

We observed an unusual pattern of tumour response to pazopanib plus cetuximab in patients with HNSCC. Cavitation of tumour lesions developed in 12 (39%) of 31 patients and occurred only in pulmonary metastases. Most cases were asymptomatic and occurred in patients with disease control. Cavitation in pulmonary metastases has been observed previously in patients with



All patients	31 (0)	29 (0)	24 (0)	19 (1)	10 (1)	8 (2)	7 (2)	2 (4)	2 (4)	1 (4)	0 (4)
Cetuximab resistant	12 (0)	12 (0)	10 (0)	8 (0)	4 (0)	3 (0)	3 (0)	1 (0)	1 (0)	1 (0)	0 (0)
Platinum resistant	18 (0)	17 (0)	14 (0)	12 (1)	6 (1)	4 (2)	4 (2)	1 (2)	1 (2)	1 (2)	0 (2)
Cetuximab and platinum naive	11 (0)	10 (1)	9 (0)	7 (0)	4 (0)	4 (0)	3 (0)	1 (2)	1 (2)	0 (2)	..

Figure 4: **Post-hoc analysis of overall survival in all enrolled patients**
Data are number of patients at risk (number censored).

nasopharyngeal carcinoma treated with pazopanib,[28] and reported in 24% of patients with lung cancer treated with an angiogenesis inhibitor, but not in patients treated with chemotherapy alone.[30] As in our study, nearly all cases of tumour cavitation occurred in pulmonary lesions, and cavitation of tumour lesions might be a class effect of angiogenesis inhibitors.

Our trial had limitations. The small number of patients treated did not allow for detection of rare adverse events or adverse events specific to certain populations. For example, in a previous study, an Asian population of patients treated with pazopanib tablets had plasma drug concentrations at least 20% higher than those reported in white populations;[28] higher drug concentrations might increase adverse events. Additionally, the preliminary activity for this combination observed requires confirmation in larger and more homogeneous patient datasets.

In conclusion, this phase 1b and expansion study showed the combination of pazopanib and cetuximab to be tolerable and feasible to be administered to patients with resistant or metastatic HNSCC. The dose of pazopanib suspension formulation recommended for phase 2 trials is 800 mg/day in one cycle of 8 weeks' duration, in combination with standard weekly cetuximab. Encouraging preliminary antitumour activity was observed with this combination therapy, even in patients with cetuximab-resistant or platinum-resistant HNSCC; these results warrant further validation in randomised trials.

Contributors

DA and PM designed the study. DA and JL prepared the initial draft of the report. MJS, BAS, and FD provided radiological interpretation. XJ did the pharmacokinetic testing. NNS did the pharmacokinetic testing and analysed the pharmacokinetic data. KT did the statistical analysis. PM, DA, JL, and PO acquired the data. All authors contributed to subsequent manuscript drafts and agreed with the submission of the manuscript for publication.

Declaration of interests

DA reports research funding from Novartis, GlaxoSmithKline, Celgene, Pfizer, Merck, AstraZeneca, Celldex, Gliknik, and Biothera, and has participated on advisory boards for Pfizer and Merck. All other authors declare no competing interests.

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