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Clinical Trial

Excessive toxicity of cabozantinib in a phase II study in patients with recurrent and/or metastatic salivary gland cancer

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Abstract ***Aim:*** Because the tyrosine kinases c-MET and vascular endothelial growth factor receptors (VEGFR) are often overexpressed in salivary gland cancer (SGC), this study evaluated the efficacy and safety of cabozantinib in patients with recurrent/metastatic (R/M) SGC. ***Patients and methods:*** A single-centre phase II study was conducted. Patients with immunohistochemical c-MET-positive R/M SGC were included in three cohorts: adenoid cystic carcinoma (ACC); salivary duct carcinoma (SDC) and other miscellaneous SGCs. No prior systemic treatments were required. Patients started cabozantinib 60 mg once daily. The

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Tyrosine kinase inhibitor

primary outcome was the objective response rate (ORR). Secondary outcomes included survival, safety and quality of life. Per Simon-two-stage design, depending on efficacy, a maximum of 43 patients would be included.

Results: In total, 25 patients were included until premature closure owing to severe toxicity. Six patients (24%) had grade 3–5 wound complications, occurring at a median of 7.1 months on cabozantinib treatment (range 2.1–12.6). Remarkably, four of these six patients developed this complication in the area prior exposed to high-dose radiotherapy. Other grade ≥3 adverse events in >1 patient were hypertension (20%), diarrhoea (8%) and dehydration (8%).

Twenty-one patients were evaluable for response; 1/15 ACC (ORR: 7%); 1/4 SDC and 0/2 patients with other miscellaneous SGC responded. Median progression-free survival was 9.4 months (95% confidence interval [CI] 7.4–11.4 months), 7.2 months (95%CI 0.0–15.1) and 6.9 months (95%CI 0.0–15.1), respectively.

Conclusion: This study showed too many severe cabozantinib-associated wound complications in patients with SGC, especially in prior irradiated areas. Therefore, the study closed prematurely. The efficacy in the limited number of evaluable patients was low to moderate.

Trial registration: This trial was registered on ClinicalTrials.gov: NCT03729297.

1. Introduction

Salivary gland cancer (SGC) is a rare cancer with an annual incidence of 0.5–2 cases per 100.000 persons. Twenty-two different subtypes are recognised with their own clinical behaviour and prognosis [1,2]. Primary treatment consists of a tumour resection, frequently combined with a neck dissection and postoperative radiotherapy. However, rates of locoregional recurrence and distant metastases (R/M) are high in certain subtypes; especially in adenoid cystic carcinoma (ACC) and salivary duct carcinoma (SDC) [3]. In patients with R/M ACC, chemotherapy remains the cornerstone of treatment, with a response rate of 25% of cyclophosphamide plus doxorubicin plus cisplatin [4]. Recently, several phase II trials explored the efficacy of antiangiogenic tyrosine kinase inhibitors (TKIs) in patients with ACC. Lenvatinib showed a response rate of 16% in 32 patients with ACC [5], and apatinib showed the most promising results, with a response rate of 47% in 59 patients with ACC [6].

For patients with R/M SDC, androgen deprivation therapy and human epidermal growth factor receptor 2 (HER2)-targeted therapies are well-established for patients with androgen receptor-positive (78–96%) and HER2-positive (29–46%) SDC, with response rates of 42% and 70%, respectively [7–9]. Although these treatment options altered the prognosis in subgroups of patients with SGC, new treatment options are needed to substantially improve the prognosis of patients with R/M SGC.

Cabozantinib is a TKI that targets among others c-MET and vascular endothelial growth factor receptor 2 (VEGFR2) and is registered for patients with R/M medullary thyroid carcinoma, renal cell carcinoma and hepatocellular carcinoma [10–12]. c-MET expression has been shown in approximately 53–67% of ACC tumours and 40–50% of SDC tumours [13–16]. Furthermore, VEGFR expression is seen in 76% of ACC tumours [17], and trials with angiogenesis inhibitors in patients with ACC showed promising results (as listed previously). The aim of this phase II trial was to evaluate the efficacy and safety of cabozantinib in patients with R/M SGC with c-MET expression.

1.1. Patients and methods

1.1.1. Patients, treatment and assessments

Patients with locally advanced, recurrent and/or metastatic SGC were included in three cohorts: ACC; SDC and other miscellaneous SGCs. Main inclusion criteria included immunohistochemical c-MET expression (H-score ≥10/300) and measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 [18]. There was no limit on the number of prior anticancer treatments. Objective growth or complaints owing to the disease were required before inclusion in the ACC and the other miscellaneous SGC cohort but not for the SDC cohort because of its aggressive natural behaviour. Additional criteria are listed in the Appendix.

Participants were treated with a starting dose of cabozantinib tablets 60 mg once daily (OD). In case of grade ≥3 (hypertension excepted) or intolerable grade 2 adverse events, treatment was temporally interrupted. Subsequently, the dosage was reduced to 40 mg OD or 20 mg OD (minimal dose). Cabozantinib treatment was

discontinued at disease progression or in case of unacceptable toxicity.

Patients were monitored regularly (Supplementary table 1). Tumour imaging consisted of magnetic resonance (MR) scanning of the primary tumour (in case of local recurrence) and computed tomography (CT) scan of the neck, chest and abdomen. Tumour imaging was performed every 8 weeks during the first year of treatment and thereafter every 12 weeks. Tumour response was assessed as per RECIST version 1.1. Toxicity was scored as per the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0. Furthermore, quality of life was measured as per validated questionnaires (e.g. core quality of life questionnaire [QLQ-C30]), and cabozantinib trough concentration levels were measured, details and results of these outcomes are listed in the Appendix (Supplementary table 3/Supplementary figure 2). This study was approved by the local medical ethics committee.

1.2. Study end-points and statistical analysis

The primary end-point consisted of the objective response rate (ORR), defined as the proportion of patients with a complete (CR) or partial response (PR) as the best response. Secondary end-points included progression-free survival (PFS), overall survival (OS), clinical benefit rate (CR + PR + stable disease [SD] $\geq$6 months) and safety. Only patients with a treatment duration of $\geq$8 weeks were considered evaluable for response. All patients who started cabozantinib treatment were included in the toxicity analysis, PFS and OS.

A Simon two-stage design was used for the ACC and SDC cohort, with a null hypothesis of at most 5% response rate and an alternative hypothesis of at least 25% response rate (α: 0.05, power: 80%). The first stage consisted of nine patients per cohort. In case of at least one response in the first stage, the cohort would be expanded to 17 patients. If $>$ 2 of 17 patients had a response, the null hypothesis would be rejected. A maximum of nine patients would be included in the other SGC cohort.

Kaplan–Meier methods were used for assessment of the OS and PFS. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp, Armonk, New York).

2. Results

The study started in September 2018 and was closed prematurely owing to toxicity on 6th of November 2019. In total, 32 patients were screened for eligibility and 25 patients enrolled in the study. Reasons for ineligibility were rapid clinical deterioration (n = 3), comorbidity (n = 2), secondary malignancy (n = 1) and abnormal liver function (n = 1).

2.1. Patient characteristics

In total, 17 patients with ACC, 5 patients with SDC and 3 patients with other miscellaneous SGC subtypes (carcinoma ex pleomorphic adenoma n = 1, acinic cell carcinoma n = 1 and mucoepidermoid carcinoma n = 1) were included in the study. Most patients (n = 17) were treated for distant metastatic disease (68%), three patients (12%) were treated for local recurrent disease only, and five patients (20%) had both local recurrent disease and distant metastases. Baseline patient characteristics per cohort are listed in Table 1.

2.2. Safety

In total, six patients developed grade $\geq$3 wound complications. Four of these patients developed this complication in the area previously exposed to high-dose radiotherapy (dose $\geq$66 Gy in most patients); of these, one patient developed a tracheoesophageal fistula which resulted in death. Another patient with a pre-existing small fistula in the neck developed severe ulcerating wounds that covered a large part of the neck. After cessation of cabozantinib, the wound slowly healed over a time course of one year, see Fig. 1. One patient developed anal fistula with abscesses which required surgical drainage (after high-dose tailbone radiation), and in one patient with a sore throat, imaging showed pharyngeal ulceration. Details can be found in Table 2. The time between radiotherapy and the start of cabozantinib ranged from 10.5 to 93.1 months. In addition, two patients developed wound complications without prior radiotherapy; in one patient, a small pre-existing salivary gland fistula increased in size, and one patient required surgery for perforated appendicitis. These complications occurred at a median of 7.1 months on cabozantinib treatment (range 2.1–12.6). Two of these patients had a pre-existing fistula at the site of the wound complication, see Table 2. These severe wound complications were the reason for the premature closing of the study.

Other frequently observed adverse events included: fatigue; elevated liver enzymes; hand-foot syndrome; diarrhoea and anorexia; further details can be found in Table 3 and supplementary table 2.

2.3. Efficacy

In total, 15/17 patients with ACC, 4/5 patients with SDC and 2/3 patients with other miscellaneous SGC were eligible for response assessment (treatment

Table 1
Baseline patient characteristics.

	ACC (n = 17) No. of pts (%)[a]	SDC (n = 5) No. of pts (%)[a]	Other SGC (n = 3) No. of pts (%)[a]
Gender			
Male	8 (47)	3 (60)	1 (33)
Female	9 (53)	2 (40)	2 (67)
Age, median (range)	56 (49–71)	54 (51–71)	65 (64–72)
ECOG PS			
0	9 (53)	2 (40)	0 (0)
1	8 (47)	3 (60)	3 (100)
Primary site			
Parotid gland	4 (24)	5 (100)	3 (100)
Submandibular gland	3 (18)	0 (0)	0 (0)
Sublingual gland	0 (0)	0 (0)	0 (0)
Minor salivary gland	4 (24)	0 (0)	0 (0)
Other[b]	6 (35)	0 (0)	0 (0)
Disease distribution			
Locoregional disease	3 (18)	0 (0)	0 (0)
Locoregional and metastatic disease	3 (18)	2 (40)	0 (0)
Metastatic disease	11 (65)	3 (60)	3 (100)
Sites of metastatic disease			
Lung	12 (71)	3 (60)	2 (67)
Pleural	7 (41)	0 (0)	0 (0)
Liver	5 (29)	0 (0)	0 (0)
Bone	5 (29)	1 (20)	2 (67)
Distant lymph nodes	5 (29)	1 (20)	3 (100)
Other	6 (35)	1 (20)	2 (67)
Prior treatments			
Surgery			
Tumour resection	14 (82)	2 (40)	2 (67)
Lymph node neck dissection	5 (29)	3 (60)	1 (33)
Radiotherapy			
Postoperative	11 (65)	3 (60)	2 (67)
Primary treatment[c]	3 (18)	1 (20)	1 (33)
Palliative	6 (35)	2 (40)	3 (100)
Systemic therapy			
Adjuvant	0 (0)	2 (40)	0 (0)
ADT	–	2 (40)	–
Palliative	4 (24)	3 (60)	1 (33)
Median number of prior lines (range)	1 (1–3)	4 (2–5)	1 (–)
ADT	0 (0)	2 (40)	0 (0)
Anti-HER-2[d]	0 (0)	3 (100)	0 (0)
Chemotherapy	4 (24)	1 (20)	0 (0)
Other	2 (12)	0 (0)	1 (33)
c-MET expression, median H-score (range)	110 (20–300)	60 (25–120)	15 (10–180)

ACC, adenoid cystic carcinoma; ADT, androgen deprivation therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HER-2, Human epidermal growth factor receptor 2; pts, patients; SDC, salivary duct carcinoma; SGC, salivary gland cancer.

[a] Values are numbers and percentages, unless indicated otherwise.

[b] Other includes nasal cavity (n = 1), breast (n = 1), trachea (n = 1), sphenoid sinus (n = 1), pterygopalatine fossa (n = 1) and nasopharynx (n = 1).

[c] Patients who received radiotherapy as primary treatment (when the primary tumour was inoperable). A complete radiotherapy overview is presented in supplementary table 4.

[d] All three patients with SDC received multiple lines of HER2-targeted therapy: first-line trastuzumab ± pertuzumab combined with chemotherapy (most often docetaxel), followed by second-line: ado-trastuzumab emtansine.

duration of ≥8 weeks). The ORR was 7% (1/15 patients) in the ACC cohort; furthermore, 1/4 patients with SDC and 0/2 patients with other miscellaneous SGC responded. One ACC patient achieved a PR after 25 weeks on cabozantinib, and the duration of response was 32 weeks. One SDC patient achieved a PR after 9 weeks on cabozantinib with progressive disease at 40 weeks on treatment. All other assessable patients achieved SD as the best response (Table 4). Fig. 2 shows the maximum percentage change in tumour size from baseline, most evaluable patients showed a decrease in target lesion diameter on cabozantinib treatment. Of the four non-evaluable patients, one patient ended treatment <8 weeks owing to side-effects of cabozantinib, and three patients were on treatment <8 weeks and had to stop owing to the closing of the study. Details on the duration of treatment and treatment modifications are listed in Table 4. The median follow-up was 14.2 months. The median PFS for the ACC, SDC and other miscellaneous SGC cohorts were 9.4 months (95% CI 7.4–11.4 months), 7.2 months (95% CI 0.0–15.1 months) and 6.9 months (95% CI 0.0–15.1), respectively. The median OS for the ACC, SDC and other miscellaneous SGC cohorts were 27.5 months (95% CI 15.7–39.4), 14.2 months (95% CI 0.0–28.5) and 15.1 (insufficient events for 95% CI), respectively. Survival plots can be found in Fig. 2.

2.4. Correlation c-MET expression and treatment response

There was no significant relation between these variables (Spearman's rho correlation coefficient: 0.119, p = 0.6). A scatter plot of these variables is presented in supplementary figure 1.

3. Discussion

This study showed that cabozantinib led to considerable toxicity in patients with SGC. Apart from expected adverse events such as hand-foot syndrome and gastrointestinal side-effects, a remarkable high number of severe wound complications were observed. In total, six patients (24%) had grade ≥3 wound complications. This included a tracheoesophageal fistula which resulted in death and a life-threatening ulcerating wound in the neck (Fig. 1). These severe wound complications are possibly the result of prior tissue damage owing to several previous treatments (e.g. surgery and radiotherapy, often combined as primary treatment, and in some cases, prior systemic therapy) in combination with the antiangiogenic effects of cabozantinib.

Especially prior radiotherapy was considered a major risk factor for the occurrence of wound complications in this study, because four of these six patients developed these complications in previously irradiated areas. These

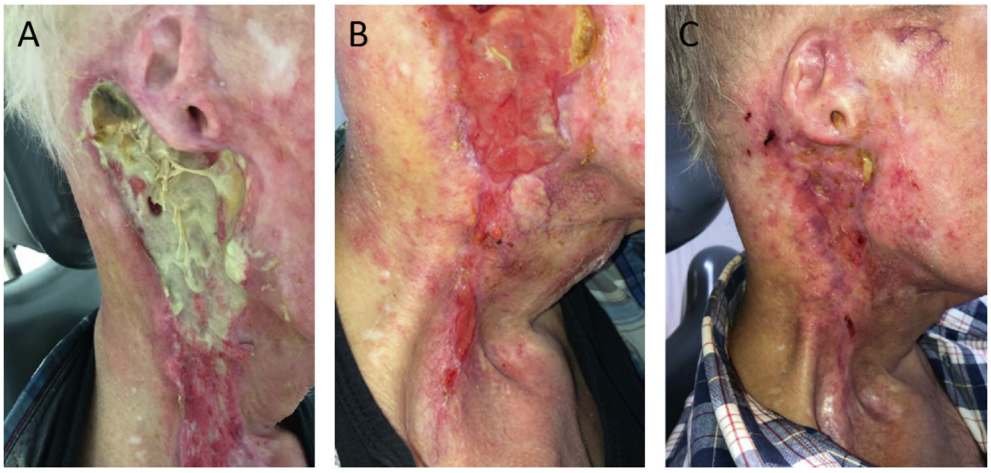

Fig. 1. Ulcerative wound in the neck during cabozantinib treatment; wound at 24 weeks on cabozantinib treatment (A), 3 months after treatment cessation (B), 1 year after treatment cessation (C). Shown with permission from the patient.

wound complications occurred even when the radiotherapy was given several years before the start of cabozantinib. Comparable toxicity was observed in a phase II study of cabozantinib in patients with Merkel cell carcinoma, which was closed prematurely owing to the toxicity and lack of responses [19]. Of eight included patients, two (25%) developed non-healing ulcers and tumour skin fistula. The report did not associate these adverse to previous radiotherapy. Remarkably, in the phase III studies of cabozantinib [10–12,20,21], wound complications do not seem to be a major issue: they were not described in the prostate cancer and renal cell carcinoma studies [20–22], the study in patients with hepatocellular carcinoma only reported on one grade 5 bronchoesophageal fistula [10], and the study in medullary thyroid carcinoma reported on wound complications, gastrointestinal fistula and other fistula in 1.9%, 0.9% and 3.7% of the patients, respectively [12]. According to cabozantinib drug registration reports, fistula/perforations occurred in 1–4% of patients treated with cabozantinib, and wound complications occurred in 2% [23,24]. A possible explanation for this discrepancy is that all patients with SGC in this study were exposed to radiotherapy, often in high-dose (see supplementary table

Table 2
Wound complications grade ≥3 related to cabozantinib treatment.

Adverse event	CTCAE Grade	Pre-existing complications	Recurrent or metastatic tumour at site of AE	Time between start of cabozantinib treatment and occurrence of AE	Relevant prior radiotherapy (dose)	Time between radiotherapy and start of cabozantinib treatment	Prior systemic therapies
Tracheoesophageal fistula	Grade 5	–	No	7.8 months	Local recurrence (70 Gy)	51.1 months	CAP (cyclophosphamide + doxorubicin + cisplatin)
Ulcerating wound	Grade 4	Pre-existing small fistula in the neck area	Yes	5.3 months	Postoperative radiotherapy (66 Gy)	89.0 months	Goserelin + bicalutamide
Anal fistula and abscess	Grade 3	–	No	2.1 months	Bone metastasis tailbone (39 Gy) (because of oligometastases)	10.5 months	–
Pharyngeal ulceration	Grade 3	–	Yes	12.6 months	Primary tumour (70 Gy)	93.1 months	Cisplatin
Salivary gland fistula (cutaneous)	Grade 3	Pre-existing small salivary gland fistula	Yes	7.8 months	–	–	–
Perforated appendicitis	Grade 3	–	No	6.4 months	–	–	Paclitaxel with bevacizumab

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

Table 3
Adverse events probably related to cabozantinib treatment.

Adverse event	Any grade no. of pts (%)	Grade 3 no. of pts (%)	Grade 4 no. of pts (%)	Grade 5 no. of pts (%)
Fatigue	22 (88)	0	0	0
ALAT increased	17 (68)	1 (4)	0	0
Hand-foot syndrome	16 (64)	1 (4)	0	0
ASAT increased	15 (60)	0	0	0
Diarrhoea	15 (60)	2 (8)	0	0
Dysgeusia	15 (60)	0	0	0
ALP increased	12 (48)	0	0	0
Anorexia	12 (48)	1 (4)	0	0
Hypophosphatemia	12 (48)	0	0	0
Mucositis oral	12 (48)	0	0	0
Weight loss	11 (44)	1 (4)	0	0
Hypertension	10 (40)	5 (20)	0	0
Nausea	10 (40)	1 (4)	0	0
Platelet count decreased	10 (40)	1 (4)	0	0
Dry mouth	9 (36)	0	0	0
Dry skin	9 (36)	0	0	0
Dyspepsia	9 (36)	0	0	0
Hoarseness	9 (36)	0	0	0
Alopecia	8 (32)	0	0	0
Dyspnoea	8 (32)	0	0	0
Headache	8 (32)	0	0	0
Constipation	7 (28)	0	0	0
Muscle cramp	6 (24)	0	0	0
Vomiting	6 (24)	1 (4)	0	0
Anaemia	5 (20)	0	0	0
Blood bilirubin increased	5 (20)	0	0	0
Hair colour changes	5 (20)	0	0	0
Oral pain	5 (20)	0	0	0
GGT increased	3 (12)	1 (4)	0	0
Skin ulceration	3 (12)	0	1 (4)	0
Hypokalaemia	3 (12)	1 (4)	0	0
Dehydration	2 (8)	2 (8)	0	0
Pharyngeal mucositis	2 (8)	1 (4)	0	0
Anal fistula	1 (4)	1 (4)	0	0
Appendicitis perforated	1 (4)	1 (4)	0	0
Lung infection	1 (4)	1 (4)	0	0
Myositis	1 (4)	1 (4)	0	0
Salivary gland fistula	1 (4)	1 (4)	0	0
Tracheal fistula	1 (4)	0	0	1 (4)

ALAT, alanine aminotransferase; ALP, alkaline phosphatase; ASAT, aspartate aminotransferase; GGT, Gamma-glutamyltransferase; pts, patients.
Table lists treatment-related adverse events that occurred in 20% or more of the patients (any grade) and any grade 3, 4 or 5 events reported in a patient, regardless of frequency.
Adverse events were graded as per National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Patients were counted once at the highest grade for each adverse event.

4 for details). This is not the case for most patients with renal cell, hepatocellular and prostate cancer, in these cancers, radiotherapy is given less frequently, and if used, it will often be administered at a lower dose. A review on adverse events of anti-VEGF drugs stated that especially in head and neck cancer, prior radiotherapy is a risk factor for fistula formation [25], which is likely owing to the high dose of radiotherapy.

In studies with other VEGFR TKIs in patients with SGC, lower rates of wound complications were observed. One of 32 patients treated with lenvatinib had an oral cutaneous fistula, and one tracheal fistula occurred in 14 patients treated with sunitinib [5,26]. Both reports mentioned that the fistula arose in previously irradiated areas. In addition, one of 32 patients treated with sorafenib had a grade 4 skin ulceration [27]. Other studies in patients with SGC with VEGFR inhibitors, such as axitinib or sorafenib, did not mention the development of wounds or fistulas [28–32]. Thus, wound complications also occurred in other VEGFR-

Table 4
Cabozantinib treatment and efficacy.

	ACC (n = 17) no. of patients (%)[a]	SDC (n = 5) n o. of patients (%)[a]	Other SGC (n = 3) no. of patients (%)[a]
Treatment			
Median duration on treatment, months (range)	5.7 (0.8–12.8)	5.7 (1.1–8.5)	6.6 (0.7–7.6)
Median time to first treatment modification[b], months (range)	0.9 (0.5–2.0)	1.0 (0.3–5.3)	0.7 (0.5–0.7)
Reasons for first treatment modification†			
Side-effects	15 (88)	3 (60)	2 (67)
Other	0	1 (20)	1 (33)
Premature closing study	2 (12)	1 (20)	0
Efficacy			
Evaluable patients[c]	15 (88)	4 (80)	2 (67)
CR	0	0	0
PR	1 (7)	1 (25)	0
SD	14 (93)	3 (75)	2 (100)
≥6 months[d]	10 (67)	2 (50)	2 (100)
PD	0	0	0
ORR	7%	25%	0%
CBR	73%	75%	100%
Median PFS, months (95% CI)	9.4 (7.4–11.4)	7.2 (0.0–15.1)	6.9 (0.0–15.1)
Median OS, months (95% CI)	27.5 (15.7–39.4)	14.2 (0.0–28.5)	15.1[e]

ACC, adenoid cystic carcinoma; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SDC, salivary duct carcinoma; SGC, salivary gland cancer.

[a] Values are numbers and percentages, unless indicated otherwise.
[b] Treatment modification is defined as dose reduction, treatment interruption or discontinuation of treatment.
[c] Only patients who were on treatment ≥8 weeks were considered evaluable.
[d] These numbers are affected by the premature closure of the study.
[e] Insufficient events for 95% CI.

TKI studies in patients with SGC but seemingly at a lower rate than in this study. Because the other VEGFR-TKI SGC studies consisted of patient populations with similar disease distributions (e.g. locoregional recurrence and/or metastatic disease) and comparable rates of prior radiotherapy exposure, these factors are unlikely to account for the difference in wound complications. We consider the difference in the other tyrosine kinase targets of the different VEGFR-TKIs as the most plausible explanation. Although sorafenib, lenvatinib, sunitinib, and cabozantinib all inhibit VEGFRs, each TKI has its own target profile. Cabozantinib distinguishes itself from the other TKIs through inhibition of c-MET and AXL. Both MET and AXL are tyrosine kinases that are involved in wound healing [33,34]. Inhibition of these targets by cabozantinib, especially in areas with prior tissue atrophy, fibrosis and vascular damage as a result of previous radiotherapy and/or surgery, might be the most plausible hypothesis for the high toxicity observed in this study.

Because the study was closed prematurely owing to toxicity, efficacy of cabozantinib could only be determined based on the 25 included patients, of which, 21 patients were considered evaluable (cabozantinib ≥8 weeks). ORRs were 7%, 25% and 0% for the ACC, SDC and other miscellaneous SGC subtype cohorts, respectively.

Based on preclinical data, cabozantinib can inhibit both c-MET-positive tumours, as well as c-MET-negative tumours, by inhibition of other cancer-specific targets, such as AXL, RET and KIT. In mouse models, improved cabozantinib efficacy was correlated with c-MET expression [35]. Therefore, we assumed that tumours with high c-MET expression might respond better to cabozantinib treatment. However, we did not find a significant correlation between c-MET expression and treatment response. Prior studies in patients with renal cell carcinoma, breast carcinoma and cholangiocarcinoma also did not find a correlation between c-MET levels and treatment response [22,36,37].

Limitations of this study include the small sample size and the single-arm design. We describe a possible relation between cabozantinib treatment and prior radiotherapy for patients who developed severe wound complications; however, statistics could not be performed to support or reject this relation owing to the small sample size.

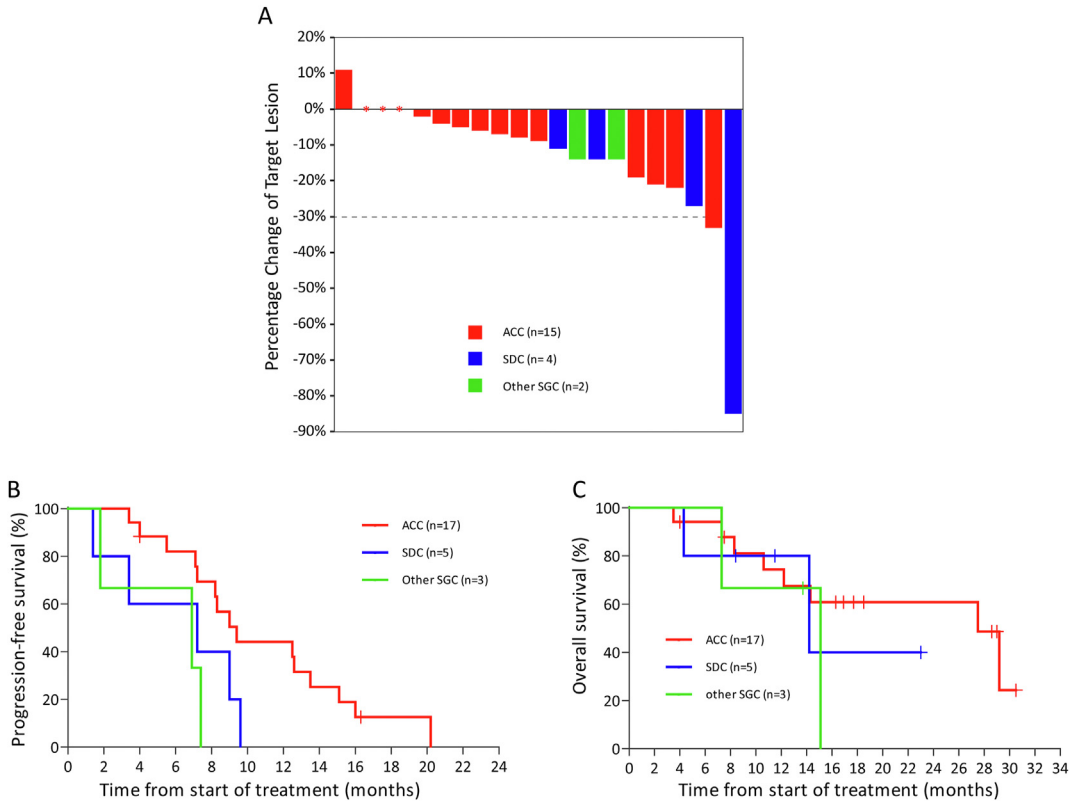

Fig. 2. Treatment efficacy; waterfall plot of evaluable patients (A), Kaplan-Meier plots of progression-free survival (B), and overall survival (C)*.
*Only evaluable patients (treatment duration of ≥8 weeks) are presented in the waterfall plot. All included patients are included in the PFS and OS Kaplan-Meier plots. The plus signs on the Kaplan-Meter plots indicates censored data.

4. Conclusion

This phase II study showed limited efficacy in patients with R/M SGC and was ended prematurely owing to severe wound complications, especially in prior irradiated areas. Therefore, cabozantinib is not recommended in SGC, and caution is suggested when prescribing cabozantinib to patients previously exposed to high-dose radiotherapy.

Presentation of preliminary data

Preliminary data of this manuscript were presented at ASCO 2020. Abstract ID 6529.

Author contributions

WvB: conceptualisation; data curation; formal analysis; investigation; methodology; project administration; validation; visualisation; roles/writing - original draft; writing - review and editing. MU: data curation; formal analysis; investigation; methodology; resources; validation; visualisation; roles/writing - original draft; writing - review and editing. SK: conceptualisation; formal analysis; investigation; writing - review and editing. TD: writing - review and editing. SW: conceptualisation; investigation; writing - review and editing. MJ: conceptualisation; formal analysis; methodology; writing - review and editing. SP: investigation; writing - review and editing. AvE: conceptualisation; formal analysis; investigation; methodology; writing - review and editing. CvH: conceptualisation; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; validation; visualisation; roles/writing - original draft; writing - review and editing.

Conflict of interest statement

WvB reported no conflict of interest to declare. MU reported no conflict of interest to declare. SK reported no conflict of interest to declare. TD reported no conflict of interest to declare. SW receives research funding from BMS, MSD, Pfizer, Roche, Nextcure, AstraZeneca, Bayer and Lily. MJ reported no conflict of interest to declare. SP reported no conflict of interest to declare. AvE reported no conflict of interest to declare. CvH: Advisory (institution): Bayer, Bristol-Myers Squibb, Ipsen, MSD and Regeneron. Research grant

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Appendix A. Supplementary data

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