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A Phase II Trial of Rivoceranib, an Oral Vascular Endothelial Growth Factor Receptor 2 Inhibitor, for Recurrent or Metastatic Adenoid Cystic Carcinoma

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ABSTRACT

Purpose: This open-label, single-arm, phase II study evaluated the vascular endothelial growth factor receptor 2 (VEGFR2) tyrosine kinase inhibitor (TKI) rivoceranib in patients with recurrent or metastatic (R/M) adenoid cystic carcinoma (ACC).

Patients and Methods: Eligible patients had confirmed disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) with ≥20% increase in radiologically or clinically measurable lesions or appearance of new lesions within the preceding 6 months. Patients received oral rivoceranib 700 mg once daily. Primary outcomes were objective response rate (ORR) by investigator review and by blinded independent review committee (BIRC).

Results: Eighty patients were enrolled and 72 were efficacy evaluable. Seventy-four patients had distant metastases and 49 received prior systemic treatment (14 received VEGFR TKIs). Per investigator and BIRC, respectively, ORR was 15.3% [95% confidence interval (95% CI), 7.9–25.7] and 9.7% (95% CI, 4.0–19.0); median duration of response was 14.9 months (95% CI, 4.9–17.3) and 7.2 months (95% CI, 3.5–8.4); and median progression-free survival was 9.0 months (95% CI, 7.3–11.5) and 9.0 months (95% CI, 7.7–11.5). Grade ≥3 treatment-related adverse events occurred in 56 patients (70.0%); the most common were hypertension (34, 42.5%) and stomatitis (6, 7.5%). Four grade 5 events occurred with one attributed to rivoceranib (epistaxis). Sixty-eight patients (85.0%) had ≥1 dose modifications and 16 patients (20.0%) discontinued rivoceranib for toxicity.

Conclusions: In patients with progressing R/M ACC, rivoceranib demonstrated antitumor activity and a manageable safety profile consistent with other VEGFR TKIs.

Introduction

Adenoid cystic carcinoma (ACC) is a rare tumor that arises from secretory glands, most commonly salivary glands (1). Local and distant recurrence following primary tumor resection and radiation is frequent, with metastases most commonly affecting the lungs, liver, and bone. Recurrent/metastatic (R/M) ACC is generally indolent with median survival exceeding 5 years; however, survival is shortened in those with distant metastases outside of the lungs and in those who require treatment within 3 years of R/M diagnosis (2, 3).

No systemic treatments are approved for use in R/M ACC in the United States or Europe. Cytotoxic chemotherapy typically results in low response rates and is often reserved for symptomatic or rapidly progressive disease (PD; refs. 1, 4). Potential therapeutic targets have emerged in molecular subsets of ACC directed toward *MYB/L1* fusion and *NOTCH*-activating mutations, representing an important area of ongoing research (5). Promising results have been observed in trials investigating multitargeted tyrosine kinase inhibitors (TKI) that inhibit vascular endothelial growth factor receptors (VEGFR). VEGFR is widely expressed in ACC as observed in surgically resected tumor tissue and metastatic ACC cell lines (6–8).

Early studies of multitargeted VEGFR TKIs have demonstrated modest disease control and low response (9–12). Small single-arm studies (13–14) and published real-world data (15) with the use of the pan-VEGFR TKI, lenvatinib, demonstrated median progression-free survival (PFS) and event-free survival (EFS) between 5 and 9 months and overall response rates of 0% to 15.6% in predominantly TKI-naïve patients. In one study, notably, over half of patients discontinued lenvatinib due to drug toxicity (14). A randomized study in R/M ACC demonstrated improved PFS with the pan-VEGFR inhibitor, axitinib, compared with observation (10.8 vs. 2.8 months; $P < 0.001$) in patients naïve to VEGFR TKI therapy (16). Current treatment guidelines include lenvatinib for R/M ACC and axitinib for R/M salivary gland cancers (17), indicating a role for VEGFR inhibition in R/M ACC. However, there remains a need to optimize clinical efficacy and tolerability within this therapeutic class.

Rivoceranib (formerly apatinib) is an orally administered TKI that potently and selectively targets VEGFR2 (18, 19). Compared

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Translational Relevance

Vascular endothelial growth factor receptor (VEGFR) is widely expressed in adenoid cystic carcinoma (ACC). This open-label, multicenter, phase II clinical trial demonstrated antitumor activity with rivoceranib, a selective VEGFR2 tyrosine kinase inhibitor, in patients with recurrent or metastatic ACC that had objective radiographic progression in the preceding 6 months, particularly among VEGFR-naïve patients. The activity was accompanied by a manageable safety profile consistent with other agents in this class. These findings suggest that selective inhibition of VEGFR2 represents a potential treatment for ACC warranting further investigation.

with VEGFR1 and 3, VEGFR2 demonstrates greater kinase activity and represents the primary receptor for regulation of angiogenesis, mitogenic signaling, and vascular permeability (20). A prior study with apatinib for ACC performed in China showed promising results (21). We hypothesized that potently and selectively targeting VEGFR2 with rivoceranib may result in an effective treatment option for R/M ACC with better tolerability compared with pan-VEGFR inhibition. We conducted an international multicenter phase II study, RM-202, to further evaluate the efficacy and safety of rivoceranib in patients with R/M ACC.

Patients and Methods

Study design and patients

RM-202 was a single-arm, open-label, multicenter phase II trial conducted at 11 sites in the United States and South Korea (Supplementary Data). Eligible patients were adults with histologically confirmed R/M ACC (any site of origin) not amenable to curative-intent surgery or radiotherapy. Patients were required to have documented evidence of measurable disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, defined as a ≥20% increase (radiographically or clinically) in measurable lesions or the appearance of new lesions, within 6 months of study entry (as assessed by investigator only). An unlimited number of prior therapies were permitted, including prior VEGFR TKI. Treated central nervous system (CNS) metastases were permitted if patients were stable for four weeks prior to rivoceranib treatment. Palliative radiotherapy to non-target lesions within two weeks of rivoceranib treatment was permitted. Patients had to have adequate organ and bone marrow function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Key exclusion criteria included a history of prior malignancy within three years of study enrollment; prior VEGFR-targeting TKI within five half-lives of rivoceranib administration; chemotherapy, radiotherapy, or major surgery within four weeks of rivoceranib administration (immunotherapy within 12 weeks); and systemic anticoagulation or antithrombotic agents initiated within one week of rivoceranib administration. Patients with nonhealing wounds, a history of vascular disease or thrombosis within the preceding 3 months, history of bleeding diathesis or clinically significant bleeding in the preceding 2 weeks, or uncontrolled hypertension were excluded. Complete eligibility criteria are listed in the Supplementary Data.

The study protocol and associated materials were approved by the institutional review board or ethics committee at each site. The study was conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice. All patients provided written informed consent prior to performance of any screening or study procedures. The study was sponsored by Elevar Therapeutics and is registered with ClinicalTrials.gov (NCT04119453).

Study procedures and assessments

All patients received oral rivoceranib at a starting dose of 700 mg once daily continuously during a 28-day cycle. Patients were instructed to take their dose approximately 1 hour after a meal. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Treatment could be continued beyond progression if the investigator determined the patient was still experiencing clinical benefit and tolerating therapy. However, rivoceranib was to be discontinued if repeat scans between 4 and 8 weeks later demonstrated PD by RECIST, or there was clinical deterioration. Three prespecified dose reductions (to 500 mg, 300 mg, or 200 mg once daily) were permitted for toxicity, with ≤1 dose reduction per cycle. Temporary interruption of rivoceranib dosing was recommended for grade 3–4 treatment-related adverse events (TRAE) with a maximum dose interruption of 21 consecutive days. Prohibited study treatments included other systemic anticancer therapy, radiotherapy other than for palliation of bone metastases, medications that may significantly prolong the QT/QTc interval, and herbal supplements. Medications or food that are strong inducers or inhibitors of cytochrome P450 (CYP)3A4 and 2D6 were to be avoided. Treatment compliance was monitored through documentation of returned, unused rivoceranib or empty unit-dose containers.

At screening, assessments included physical exam, vital signs, ECG, serum chemistries, complete blood count with differential, coagulation parameters, urinalysis (detailed in the Supplementary Data), ECOG performance status, and CT scans with contrast (MRI if iodinated contrast was contraindicated) of the neck, chest, abdomen, and pelvis. Brain imaging was performed if clinically indicated. Vital signs, serum chemistry, hematology, coagulation parameters, urinalysis, ECG, and ECOG performance status were assessed at least once during each cycle (cycle length: 28 days) and at end of treatment. Adverse events (AE) were graded according to the NCI Common Terminology Criteria for AEs, Version 5.0 (CTCAE v5.0). Tumor assessments per RECIST (22) were performed every 8 weeks during the first year of treatment, approximately every 12 weeks thereafter, and at the end of treatment. Objective response [complete response (CR) or partial response (PR)] was confirmed at the next imaging assessment. After end of treatment, patients were followed for survival every 12 weeks; for patients without PD, tumor assessments continued every 12 weeks until PD was documented, or new anticancer therapy was initiated. Patients completed the Functional Assessment of Cancer Therapy (FACT)-G questionnaire at baseline, every 8 to 12 weeks while on treatment, and at the end of treatment.

Archival tumor samples from 62 of 80 (78%) patients were collected and tested for *MYB*/*L1* translocations. Total RNA was extracted from patient samples using the RNeasy DSP FFPE Kit (Qiagen) and quantified using a NanoDrop Lite spectrophotometer (Thermo Fisher Scientific) and a Bioanalyzer (Agilent). Once copy DNA (cDNA) was transcribed and quantified, end-point PCR was performed, followed by a positive control to determine the presence of cDNA and a negative control without cDNA for each sample. For *NOTCH1* mutation status, targeted next-generation sequencing results were available from 27 of 80 (34%) patients as provided by investigators.

Plasma was collected for measurement of rivoceranib concentrations at multiple time points during the study. For pharmacokinetic analyses, intensive blood samples were collected from 10 patients on cycle 1 day 1 (C1D1) and cycle 1 day 15 (C1D15) for measuring plasma concentrations of rivoceranib (detailed in the Supplementary Data).

Outcome measures

The coprimary endpoints were confirmed objective response rate (ORR) per RECIST as assessed by the investigator and by a blinded independent review committee (BIRC) in the efficacy evaluable population. Secondary endpoints were duration of response (DOR) by investigator and BIRC; PFS by BIRC at 6 months, 12 months, and 2 years; time to progression (TTP); overall survival (OS) at 1 and 2 years; and safety and tolerability. PFS was defined as the time from treatment initiation until disease progression, death, or last disease assessment (censored), while TTP was defined as the time from treatment initiation until first PD. Overall survival was defined as the time from treatment until death or last follow-up.

Prospectively evaluated exploratory endpoints were disease control rate (DCR) and ORR based on Choi criteria (23) in the population of patients assessable by Choi criteria (see Supplementary Data) evaluated by the BIRC. DCR was defined as the proportion of patients who achieved a confirmed CR or PR, or stable disease (SD) for ≥3 months from the start of rivoceranib treatment. Additional exploratory endpoints included evaluation of the pharmacokinetics of rivoceranib and tumor molecular correlates of response.

Statistical analysis

A sample size of 72 patients was estimated to achieve 90% power at a 5% significance level to detect the difference between a historical ORR of 10% and a target ORR of 25% to detect the difference of 15% using a two-sided exact binomial test and allowing for a 10% dropout rate. ORR, determined using RECIST criteria, as well as progression, was independently assessed by investigator and by BIRC in the efficacy evaluable population, defined as eligible patients treated with at least one dose of rivoceranib who had at least one post-baseline tumor assessment and were evaluable per RECIST, including those who discontinued due to disease progression. ORR by Choi criteria was assessed by BIRC in the population evaluable by Choi criteria. PFS and OS were evaluated in the intention-to-treat (ITT) population. A 95% confidence interval (CI) was constructed for response data using an exact binomial method. Time-to-event endpoints were summarized using the Kaplan–Meier method. Safety was analyzed among all patients who received at least one dose of rivoceranib. All analyses were conducted in SAS Version 9.3 or higher at a significance level of 0.05.

Data availability

The patient-level data generated from this study are not publicly available due to patient privacy requirements but are available upon reasonable request from the corresponding author. De-identified aggregate study cohort data generated in this study are available within the article and its Supplementary Data files.

Table 1. Baseline characteristics.

	Rivoceranib $N = 80$
Median age, y (range)	54.5 (28–76)
Male, *n* (%)	42 (52.5)
Female, *n* (%)	38 (47.5)
Race or ethnicity, *n* (%)	
White	47 (58.8)
Asian	28 (35.0)
Black or African American	2 (2.5)
Other race	3 (3.8)
Hispanic or Latino	7 (8.8)
ECOG PS, *n* (%)	
0	45 (56.2)
1	35 (43.8)
Primary tumor location, *n* (%)	
Major salivary gland	27 (33.8)
Minor salivary gland	47 (58.8)
Other[a]	6 (7.5)
Stage[b] at study entry, *n* (%)	
II	1 (1.3)
IVA	2 (2.5)
IVB	3 (3.8)
IVC	74 (92.5)
Sites of metastases,[c] *n* (%)	
Lung	69 (86.3)
Liver	25 (31.3)
Lymph nodes (distant)	20 (25.0)
Bone	20 (25.0)
Pleura	14 (17.5)
Peritoneum	7 (8.8)
Kidney	6 (7.5)
Brain	4 (5.0)
Soft tissue	3 (3.8)
Other	9 (11.3)
Genetic alterations, *n/N* (%)[d]	
MYB-NFIB gene fusion	23/62 (37.1)
MYBL1-NFIB gene fusion	6/62 (9.7)
NOTCH1 mutation	2/27 (7.4)
Prior local treatments, *n* (%)	
Surgery	71 (88.8)
Radiotherapy	77 (96.3)
Prior systemic therapy,[e] *n* (%)	49 (61.3)
Median number of lines (range)	1.0 (0, 8)
≥3 lines	16 (20.0)
Prior VEGFR inhibitor[f]	14 (17.5)
Lenvatinib	10 (12.5)
Axitinib	4 (5.0)
Prior chemotherapy	37 (46.3)

[a]Lung ($n = 2$); breast, trachea, Cowper's gland, and intracranial tumor (right temporal region; $n = 1$ each).
[b]Staging was per the American Joint Committee on Cancer.
[c]Total is greater than 100% as the categories are not mutually exclusive.
[d]Based on archival tumor samples.
[e]Excludes chemotherapy given in the adjuvant, neoadjuvant, or maintenance settings.
[f]No patients received >1 line of prior VEGFRi therapy.

Results

Eighty patients were enrolled between January 2020 and May 2021 (Supplementary Fig. S1). Baseline characteristics are detailed in **Table 1**, and study participants appear to adequately represent the broader R/M ACC patient population (Supplementary Table S1). The majority of patients had distant metastatic disease (74, 92.5%) with lung involvement being most common. Forty-nine patients (61.3%) had prior systemic anticancer therapy, and 14 patients (17.5%) had received a prior VEGFR inhibitor (VEGFRi). At data cutoff (February 28, 2022), 11 patients (13.8%) were still receiving rivoceranib and 69 patients (86.3%) had discontinued treatment. The primary reasons for discontinuing rivoceranib were disease progression (39, 48.8%;

including $n = 2$ for clinical progression), AEs (16, 20.0%), consent withdrawal (11, 13.8%), investigator decision (2, 2.5%), and one patient opted to pursue an alternative therapy (1, 1.3%). Treatment was continued beyond disease progression in 18 (22.5%) patients.

Efficacy

The efficacy-evaluable population included 72 patients (90.0%). A confirmed PR was observed in 11 patients per investigator assessment for an ORR of 15.3% (95% CI, 7.9–25.7) and in 7 patients per BIRC assessment for an ORR of 9.7% (95% CI, 4.0–19.0; **Table 2**). Per investigator, median time to response was 1.9 months (range, 1.6–9.1) and median DOR was 14.9 months (95% CI, 4.9–17.3). Per BIRC, median DOR was 7.2 months (95% CI, 3.5–8.4). Responses per *MYB/MYB-L1* translocation and *NOTCH* mutation status are detailed in the Supplementary Data; there was no difference in ORR by MYB/L1 status among evaluable patients, and documented *NOTCH* mutations were uncommon.

The DCR was 65.3% (95% CI, 53.1–76.1) per investigator and 66.7% (95% CI, 54.6–77.3) per BIRC. According to Choi criteria and as assessed by BIRC, PR was observed in 31 of 60 evaluable patients [51.7% (95% CI, 38.4–64.8)] and the DCR was 61.7% (95% CI, 48.2–73.9). Representative CT images showing a reduction in tumor lesion density without reduction in tumor lesion size after two months of treatment are shown in **Fig. 1A**. The maximum change in the sum of target lesions assessed by the investigator is shown in **Fig. 1B** and by the BIRC in Appendix Supplementary Fig. S2. As assessed by investigator, time to response, response confirmation, and duration of response and treatment are shown in **Fig. 1C** and by BIRC per Choi criteria in Supplementary Fig. S3. When compared with the 6 months prior to study enrollment, there was a reduction in tumor progression observed during the 6 months following rivoceranib treatment initiation, with a median maximum change in the sum of target lesion diameters of −7.0 mm (range: −43 to 35) posttreatment versus an increase of +20.5 mm (range: +5 to 180) in the 6 months preceding study treatment (**Fig. 2A** and **B**).

The median follow-up time was 19.5 months (range, 1.9–23.7). Median PFS was 9.0 months (95% CI, 7.3–11.5) per investigator and 9.0 months (95% CI, 7.7–11.5) per BIRC (**Table 2**; **Fig. 2C**; Supplementary Fig. S4). At 12 months, the PFS rate per investigator was 38.0% (95% CI, 26.2–49.7). A total of 26 patients (32.5%) had died at the time of analysis. Median OS has not been reached. At 12 months,

Table 2. Summary of efficacy.

	Total enrolled $N = 80$		VEGFRi-naïve $n = 66$		VEGFRi-treated $n = 14$	
	Investigator	BIRC	Investigator	BIRC	Investigator	BIRC
Response (efficacy-evaluable population[a])						
Evaluable patients, *n*	72	72	59	59	13	13
Objective response, *n* (%, 95% CI)	11 (15.3, 7.9–25.7)	7 (9.7, 4.0– 19.0)	11 (18.6, 9.7–30.9)	5 (8.5, 2.8– 18.7)	0 (0, 0–24.7)	2 (15.4, 1.9– 45.4)
Best overall response, *n* (%)						
Complete response	0	0	0	0	0	0
Partial response	11 (15.3)	7 (9.7)	11 (18.6)	5 (8.5)	0	2 (15.4)
Stable disease	54 (75.0)	61 (84.7)	43 (72.9)	51 (86.4)	11 (84.6)	10 (76.9)
Progressive disease	7 (9.7)	4 (5.6)	5 (8.5)	3 (5.1)	2 (15.4)	1 (7.7)
Disease control rate, *n* (%, 95% CI)	47 (65.3, 53.1–76.1)	48 (66.7, 54.6–77.3)	37 (62.7, 49.1–75.0)	39 (66.1, 52.6–77.9)	10 (76.9, 46.2–95.0)	9 (69.2, 38.6–90.9)
Median duration of response, months (95% CI)	14.9 (4.9–17.3)	7.2 (3.5–8.4)	14.9 (4.9–17.3)	7.9 (3.5–8.4)	NE (NE–NE)	6.3 (5.5–7.1)
Median time to progression, months (95% CI)	9.2 (8.5–13.8)	9.3 (8.5–13.6)	9.0 (7.5–13.7)	10.8 (8.5–13.8)	16.4 (8.9–19.1)	8.9 (5.3–12.9)
Time-to-progression landmark analyses, % (95% CI)						
6 months	77.3 (65.1–85.7)	80.7 (68.5–88.6)	75.6 (61.6–85.1)	80.2 (66.2–88.9)	84.6 (51.2–95.9)	83.1 (47.2–95.5)
9 months	57.8 (44.3–69.2)	57.3 (43.1–69.2)	54.6 (39.8–67.2)	59.3 (43.6–72.0)	70.5 (30.6–90.2)	44.5 (12.0–73.4)
12 months	44.3 (31.1–56.7)	41.0 (27.0–54.4)	41.5 (27.5–54.9)	42.7 (27.2–57.3)	56.4 (18.9–82.1)	29.7 (4.8–61.6)
Progression-free survival (ITT population)						
Evaluable patients, *n*	80	80	66	66	14	14
Median progression-free survival, months (95% CI)	9.0 (7.3–11.5)	9.0 (7.7–11.5)	8.6 (7.2–12.8)	9.2 (7.7–13.7)	9.1 (2.2–17.7)	7.3 (5.3–12.9)
Progression-free survival landmark analyses, % (95% CI)						
6 months	73.1 (61.0–82.0)	77.1 (64.9–85.6)	71.9 (58.2–81.8)	77.3 (63.4–86.5)	78.6 (47.2–92.5)	76.6 (43.3–91.9)
9 months	51.3 (38.7–62.5)	51.1 (37.8–62.9)	49.2 (35.4–61.6)	54.0 (39.2–66.8)	59.9 (27.8–81.4)	35.9 (9.8–63.6)
12 months	38.0 (26.2–49.7)	36.5 (23.9–49.2)	37.4 (24.6–50.2)	38.9 (24.6–52.9)	39.9 (13.0–66.2)	23.9 (4.0–52.9)
Overall survival (ITT population)						
Evaluable patients, *n*	80		66		14	
Median overall survival, months (95% CI)	NE		NE		17.5 (10.0–NE)	
Overall survival landmark analyses, % (95% CI)						
6 months	94.7 (86.4–98.0)		95.1 (85.5–98.4)		92.9 (59.1–99.0)	
9 months	83.5 (72.8–90.3)		83.0 (70.7–90.5)		85.7 (53.9–96.2)	
12 months	74.5 (62.5–83.1)		77.4 (64.2–86.2)		62.9 (32.3–82.6)	
18 months	61.7 (48.3–72.5)		66.0 (51.1–77.3)		45.8 (18.3–69.9)	

Abbreviations: IQR, interquartile range; NE, not estimable.
[a]All patients who received at least one dose of rivoceranib, had at least one postbaseline tumor assessment, and were evaluable per RECIST v1.1.

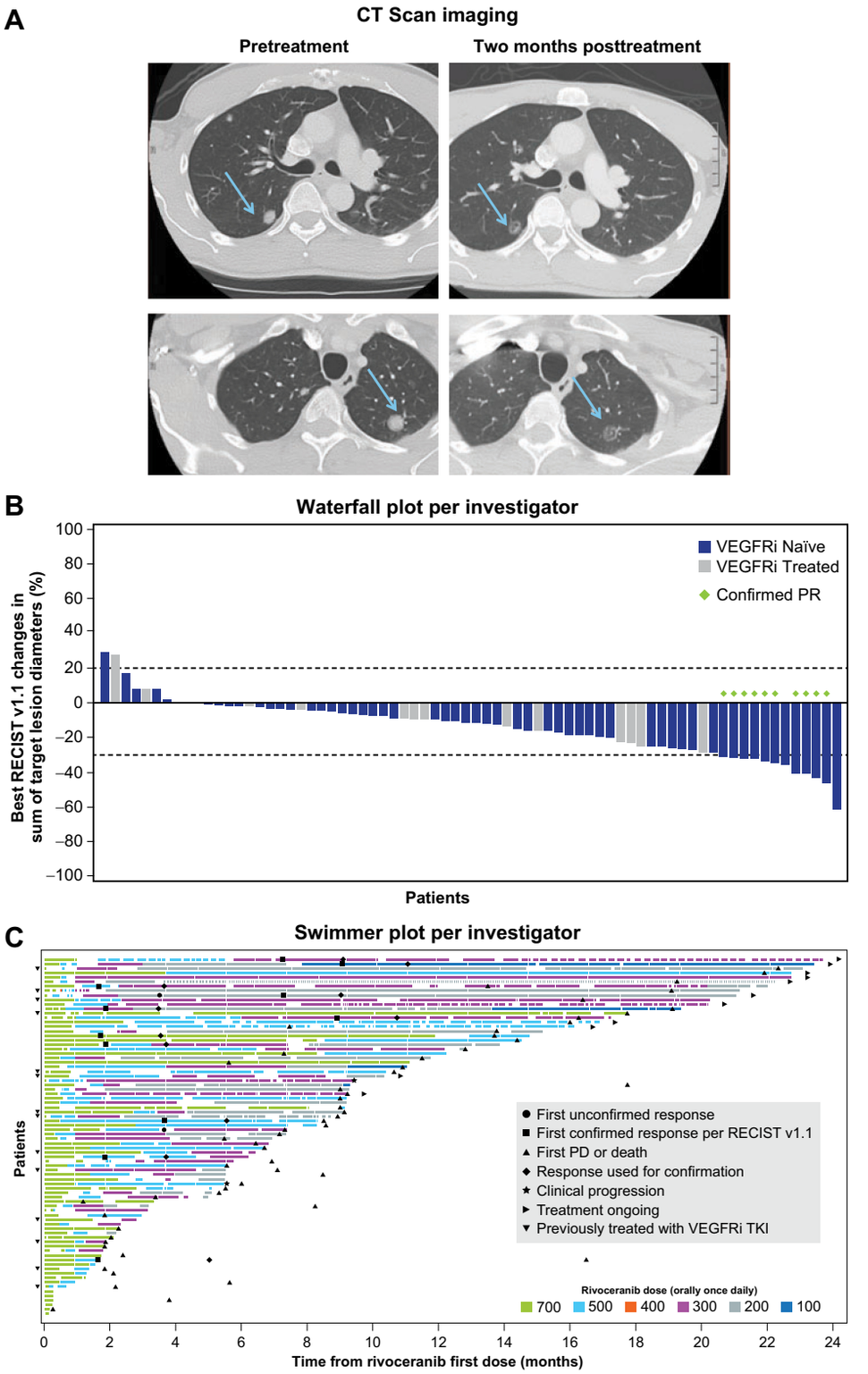

Figure 1.

Imaging, waterfall plot, and swimmer plot depicting tumor responses assessed by investigator in the efficacy-evaluable population. **A,** CT scan images showing reduction in tumor lesion density without reduction in tumor lesion size 2 months after starting treatment with rivoceranib in a patient on study. **B,** Maximum change in sum of target lesions. Each bar represents one patient ($n = 72$). **C,** Duration of treatment in patients with confirmed response. Each bar represents one patient.

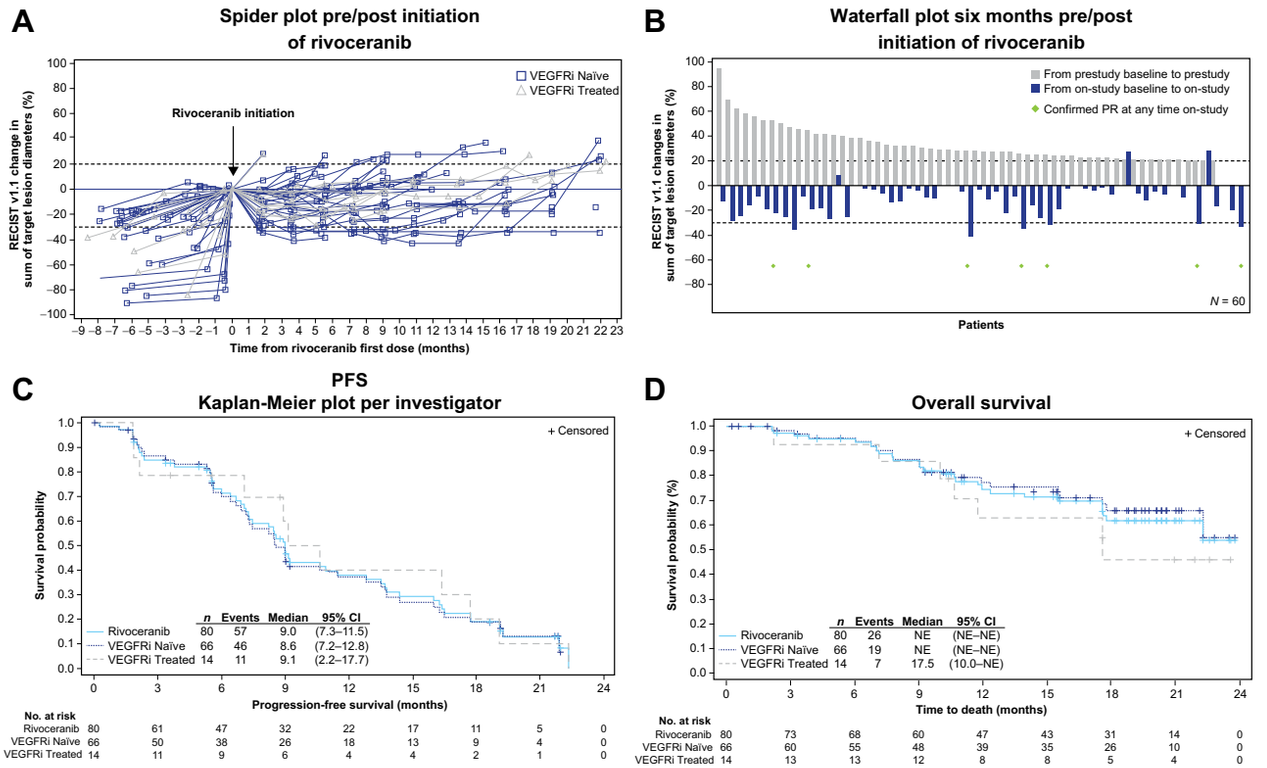

Figure 2.

Spider plot and waterfall plot depicting tumor change prior to and following treatment initiation, and Kaplan–Meier estimates of progression-free and overall survival. Population includes patients who demonstrated a ≥20% increase in measurable lesions prior to study ($n = 60$). **A,** Change in sum of target lesions per investigator prior to and during rivoceranib treatment. Each line represents one patient. **B,** Maximum percent change in sum of target lesion diameters per investigator for 6-month period prior to and the first 6 months on study. **C,** Progression-free survival assessed by investigator in the intention-to-treat population and by prior VEGFRi treatment. **D,** Overall survival in the intention-to-treat population and by prior VEGFRi treatment.

the OS rate was 74.5% (95% CI, 62.5–83.1; **Table 2**; **Fig. 2D**). Data for patients according to prior VEGFRi treatment are presented in **Table 2**.

Safety

All patients received at least one dose of rivoceranib and were evaluated for safety. An AE of any grade was observed in all patients (Supplementary Table S2). Grade ≥3 AEs were observed in 64 patients (80.0%; Supplementary Table S3). The most frequently reported treatment-related AEs were hypertension (52, 65.0%), fatigue (47, 58.8%), and nausea (40, 50.0%; **Table 3**). Grade ≥3 treatment-related AEs were observed in 56 patients (70.0%). The most frequently reported of these AEs were hypertension (34, 42.5%), stomatitis (6, 7.5%), neutropenia (5, 6.3%), and fatigue (4, 5.0%). One event of epistaxis attributed to study drug was fatal. AEs led to dose reduction in 62 patients (77.5%), dose interruption in 69 patients (86.3%), and rivoceranib discontinuation in 16 patients (20.0%). The median duration of treatment was 7.2 months (range, 0.1–23.7). The median actual dose intensity across the study was 397.6 mg/day (range, 121–700). The median time to first dose reduction was 4.1 weeks (range, 1–40; Supplementary Table S4). Dose reduction to the minimum dose of 200 mg was required in 26 patients (32.5%; Supplementary Table S4).

Pharmacokinetic data are detailed in the Supplementary Data.

Discussion

In this R/M ACC population, of whom more than half had received prior systemic anticancer therapy, and all of whom had progressed during the 6 months prior to study entry, rivoceranib demonstrated a durable ORR of 15.3% and median duration of 14.9 months per investigator assessment, and an ORR of 9.7% and median duration of 7.1 months per BIRC which is in line with prior VEGFRi studies where ORR ranged from 0–15.6% (13, 14, 16). Disease control for ≥3 months was achieved in >60% of patients per investigator, regardless of prior VEGFRi therapy. The safety profile of rivoceranib was manageable, reflecting attributable AEs consistent with other VEGFR TKIs.

This study is the largest reported VEGFR TKI therapy trial in patients with R/M ACC and the only reported trial to require progression per RECIST criteria within the 6 months preceding enrollment. These results demonstrate a reduction in the rate of tumor progression following rivoceranib initiation for many patients. Median PFS among studies investigating other VEGFR TKIs were comparable at 9.1–10.8 months (13, 16); however, one study with lenvatinib reported a median PFS of 17.5 months (14) but noted a high number of censored events with a *post hoc* analysis identifying an event-free survival of 8.2 months. Notably, our study aimed to enroll a carefully characterized population that was progressing and in need of treatment. Prior studies of multi-kinase TKIs in R/M ACC have included

Table 3. Treatment-related adverse events[a].

	Rivoceranib $N = 80$, n (%)		
	All grade	Grade 3–4	Grade 5
Hypertension	52 (65.0)	34 (42.5)	0
Fatigue	47 (58.8)	4 (5.0)	0
Nausea	40 (50.0)	2 (2.5)	0
Stomatitis	39 (48.8)	6 (7.5)	0
Proteinuria	31 (38.8)	2 (2.5)	0
Headache	29 (36.3)	0	0
Decreased appetite	29 (36.3)	2 (2.5)	0
Diarrhea	26 (32.5)	1 (1.3)	0
Palmar-plantar erythrodysesthesia syndrome	26 (32.5)	2 (2.5)	0
Aspartate aminotransferase increased	20 (25.0)	2 (2.5)	0
Alanine aminotransferase increased	16 (20.0)	2 (2.5)	0
Oral pain	16 (20.0)	0	0
Vomiting	15 (18.8)	0	0
Weight decreased	15 (18.8)	2 (2.5)	0
Constipation	14 (17.5)	0	0
Platelet count decreased	12 (15.0)	3 (3.8)	0
Rash	11 (13.8)	0	0
Abdominal pain	11 (13.8)	0	0
Gastroesophageal reflux disease	11 (13.8)	0	0
Dysphonia	11 (13.8)	1 (1.3)	0
Blood bilirubin increased	10 (12.5)	0	0
Neutropenia[b]	9 (11.3)	5 (6.3)	0
Dry mouth	9 (11.3)	0	0
Dyspnea	9 (11.3)	1 (1.3)	0
Dizziness	8 (10.0)	0	0
Epistaxis	7 (8.8)	1 (1.3)	1 (1.3)
Anemia	7 (8.8)	3 (3.8)	0
Back pain	5 (6.3)	1 (1.3)	0
Dermatitis acneiform	4 (5.0)	1 (1.3)	0
Hyponatremia	4 (5.0)	1 (1.3)	0
Dehydration	3 (3.8)	1 (1.3)	0
Embolism	2 (2.5)	1 (1.3)	0
Oral cavity fistula	1 (1.3)	1 (1.3)	0
Posterior reversible encephalopathy syndrome	1 (1.3)	1 (1.3)	0
Seizure	1 (1.3)	1 (1.3)	0
Syncope	1 (1.3)	1 (1.3)	0
Lactic acidosis	1 (1.3)	1 (1.3)	0
Malnutrition	1 (1.3)	1 (1.3)	0
Acute kidney injury	1 (1.3)	1 (1.3)	0
Pleuritic pain	1 (1.3)	1 (1.3)	0
Pneumothorax	1 (1.3)	1 (1.3)	0
Normocytic anemia	1 (1.3)	1 (1.3)	0
Tracheo-esophageal fistula	1 (1.3)	1 (1.3)	0
Cholangitis	1 (1.3)	1 (1.3)	0

[a]Treatment-related adverse events of grade 1–2 severity (occurring in ≥10% of patients) and grade 3–5 severity (occurring in any patient).
[b]Term includes neutropenia and decreased neutrophil count.

more modest sample sizes from single institutions, and less rigorous documentation of progression prior to enrollment. In biomarker analysis, patients with *MYB/L1* translocations had similar efficacy outcomes compared with patients without translocations and there were no responses observed among a small number of patients with *NOTCH* mutations. However, the limited number of molecularly categorized patients precludes drawing conclusions based on these exploratory data.

The overall frequency and types of treatment-related AEs observed, including hypertension, stomatitis, and fatigue, were consistent with class effect despite subtle differences across TKIs and VEGFR2 target specificity with rivoceranib. For example, in the randomized trial of axitinib for ACC ($n = 30$ on drug), stomatitis was reported more frequently with axitinib than in the observation arm (43% vs. 3%; ref. 16). Notably, most grade 3 AEs attributed to rivoceranib were not considered clinically serious events. Nonetheless, two patients did experience fatal epistaxis or bleeding events. Both patients had nasal cavity tumors (nasopharynx and paranasal sinuses) such that tumor location, along with prior radiation and surgery, were potential contributing factors to these events. One episode of grade 4 intracranial hemorrhage (1/33, 3%) was observed in a prior trial (14) with lenvatinib, a reminder that life-threatening bleeding is a risk with antiangiogenic agents. These events suggest that patient selection for rivoceranib for treatment of ACC should include avoidance of skull base tumors or those abutting critical vasculature. Most patients required ≥2 dose reductions and actual dose intensity was only 397 mg/day. However, the dose optimization is important given that onset and maintenance of responses were observed even after multiple dose reductions. Rivoceranib and axitnib (16) were discontinued for toxicity in 20% of patients, with higher rates observed for lenvatinib in one study (55%; ref. 14).

Because advanced ACC can exhibit a more indolent disease growth pattern in some patients, and VEGFR TKIs pose toxicity risks, capturing patient-reported quality of life (QoL) data is important. A prior clinical trial of lenvatinib in ACC (13) demonstrated a deterioration in global health and role functioning QoL metrics over time. While the present study collected QoL assessments using the FACT-G questionnaire every 8 weeks for the first year of therapy, every 12 weeks thereafter, and at the end of treatment, these results will be reported separately.

Identification of appropriate endpoints to assess clinical efficacy in R/M ACC with VEGFR TKIs is critical. We observed a DCR at 3 months of 65.3%, and median PFS of 9.0 months in the context of an ORR of 15.3% per investigator assessment (and ORR of 9.7% per BIRC). These data emphasize the importance of disease control and PFS as important endpoints in VEGFR TKI trials—as exemplified by other slow-growing solid tumors such as advanced thyroid cancer (24, 25). Measurement by investigator and BIRC revealed consistent median PFS (9 months with each) and DCR at 3 months (65.3% and 66.7%), although the ORR observed differed (15.3% versus 9.7%, respectively). The discrepancy between investigator and BIRC response (and duration) could be explained by the choice of target lesions measured as numerous metastatic foci often occur in ACC and response assessments could be biased by lesion selection. Furthermore, interpretation of nontarget or new lesions over time can influence reporting of duration of response. Inter-reader variability and differences in training can also be significant, as the proportion of centrally read cases requiring adjudication across oncology trials may be as high as 40% (26). To account for tumor volume loss or cavitary responses observed on CT scans, we performed a prespecified exploratory analysis of response according to Choi criteria (23). This analysis yielded a response rate of 51.7% per Choi criteria with rivoceranib. Some studies have demonstrated more favorable prediction of long-term outcomes using Choi criteria when compared with RECIST, as reported for gastrointestinal stromal tumor and hepatocellular carcinoma (27–29). Further prospective evaluation of VEGFR TKI response using Choi criteria is warranted in ACC given the observation of cavitary imaging responses among patients receiving VEGFR TKIs.

Given the rarity of ACC, as with many studies in this population, limitations of the present trial were the single-arm design, making interpretation of time-related events difficult, and the heterogeneity of the population in terms of primary tumor site, prior therapy exposure, and molecular subtype. An additional limitation of the study was that not all patients had tissue available for biomarker analysis, restricting our ability to draw conclusions from exploratory biomarker data. Strengths were our trial's stringent eligibility requirements, allowance for any number of prior therapies, independent analysis by a BIRC, and the exploration of Choi criteria to assess response. Furthermore, this trial is the largest prospective therapeutic study to date in ACC and was conducted across multiple centers in diverse world geographic regions.

Conclusions

In patients with progressive R/M ACC, rivoceranib demonstrated antitumor activity regardless of prior VEGFR-targeted therapy and was associated with a manageable safety profile consistent with other multitargeted VEGFR TKIs. Further investigation of rivoceranib in a placebo-controlled trial evaluating a time-to-event endpoint is warranted.

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Authors' Contributions

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Note

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