Updated Results from a Phase 2 Study of the Oral Vascular Endothelial Growth Factor Receptor 2 Inhibitor, Rivoceranib, for Recurrent or Metastatic Adenoid Cystic Carcinoma

Presented at ASCO® 2023
Abstract # 6040

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BACKGROUND

- Adenoid cystic carcinoma (ACC) is a rare tumor that arises from secretory glands, most commonly salivary glands.[1]
- Median survival duration in patients with recurrent/metastatic (R/M) ACC is 17 years and shortens in those with distant metastases outside of the lungs (8 years) and those who require treatment within 3 years of R/M ACC diagnosis (4 years).[2]
- There are no approved systemic treatments for use in R/M ACC in the United States or Europe.
- At present, vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) represent the mainstay of systemic treatment for ACC. VEGF is widely expressed in ACC and is associated with metastasis and poor survival.[3-5]
- Rivoceranib, an orally administered TKI, is a potent and selective inhibitor of VEGFR2, the primary VEGFR for regulation of angiogenesis, mitogenic signaling, and vascular permeability.[6-8]
- Here we present updated safety and efficacy results from a Phase 2 trial evaluating rivoceranib for R/M ACC.

PATIENTS AND METHODS

- RM-202 was a single-arm, open-label, multicenter phase 2 trial conducted at 11 sites in the United States and Korea (**Figure 1**).

Figure 1: RM-202 Phase 2 Study Schema

Recurrent/Metastatic ACC (N=80)
- Documented disease progression within 6 months of study start
- At least 1 measurable lesion per RECIST v1.1
- ECOG PS 0 or 1
- Adequate organ & marrow function

→ **Rivoceranib 700 mg PO QD in 28-day cycles**
- Pre-planned dose reductions for toxicity[a]

→ **Treatment until progression[b] or unacceptable toxicity**

Tumor assessment (RECIST v1.1) every 8 weeks for first year, then every 12 weeks and at EOT

[a]Rivoceranib dose interruption up to 21 consecutive days was allowed for AEs. Each patient was allowed a total of 3 dose reductions for AEs to 500 mg, 300 mg, or 200 mg QD.
[b]Treatment could be continued beyond progression if the investigator determined the patient was still experiencing clinical benefit and tolerating therapy.
ACC, adenoid cystic carcinoma; AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PO, by mouth; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors

Key Inclusion Criteria

- Histologically or cytologically confirmed R/M ACC not amenable to potentially curative surgery/radiotherapy
- Evidence of disease progression assessed by blinded independent central review (BICR) per RECIST v1.1 occurring within the 6 months prior to study entry, evidenced by ≥20% increase in radiologically or clinically measurable lesions or appearance of new lesions
- Presence of at least one measurable target lesion evaluable by BICR per RECIST v1.1
- Prior VEGFR TKI exposure was permitted if discontinued within 5 half-lives prior to rivoceranib treatment
- ECOG performance status of 0 or 1
- Treated central nervous system (CNS) metastases were permitted if stable for 4 weeks prior to study treatment

Endpoints

Primary:
- Objective response rate (ORR) per RECIST v1.1 as assessed by the investigator and by BICR

Secondary:
- Duration of response (DOR) by investigator and BICR
- Progression-free survival (PFS) at 6 months, 12 months, and 2 years by investigator and BICR
- Time to progression (TTP) by investigator and BICR
- Overall survival (OS) at 1 and 2 years
- Safety

Exploratory:
- Disease control rate (DCR)[a] by investigator and BICR
- ORR per the Choi criteria evaluated by BICR

[a]Disease control rate was defined as the proportion of patients who achieved a complete response, partial response, or stable disease for ≥3 months from the start of study treatment and were confirmed with the same or better response at the immediate next tumor assessment.

RESULTS

PATIENTS AND DRUG EXPOSURE

- As of November 2022, 80 patients (72 evaluable) were enrolled at 11 sites in the United States and Korea (**Table 1**).
- At the time of the current analysis, 6 patients remain on treatment.
- The median duration of treatment was 7.15 months (range, 0.1–32.3).
- The median actual dose intensity was 389.4 mg/day. The relative median dose intensity was 55.6%.

Table 1: Baseline Characteristics of the Overall Population

Characteristics	Rivoceranib N=80
Median age, y (range)	54.5 (28, 76)
Male, n (%)	42 (52.5)
ECOG PS 0, n (%)	45 (56.3)
Primary tumor location, n (%)	
Major salivary gland	27 (33.8)
Minor salivary gland	47 (58.8)
Other	6 (7.5)
Stage IVC at study entry, n (%)	74 (92.5)
Prior surgery/radiotherapy, n (%)	71 (88.8)/77 (96.3)
Prior systemic therapy, n (%)	49 (61.3)
Median number of lines (range)	1 (0,8)
Prior VEGFR inhibitor[a]	14 (17.5)
Lenvatinib	10 (12.5)
Axitinib	4 (5.0)
Prior chemotherapy	37 (46.3)

[a]No patients received >1 line of prior VEGFR inhibitor therapy.

Table 2: Response per RECIST v1.1 in the Overall Efficacy Evaluable Population[a]

	Total (N=72)		VEGFRi-naïve (n=59)		VEGFRi-treated (n=13)	
	Investigator	BICR	Investigator	BICR	Investigator	BICR
ORR,[b] n (%) (95% CI)[c]	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	2 (15.4) (1.9-45.4)
CR	0	0	0	0	0	0
PR	11 (15.3)	7 (9.7)	11 (18.6)	5 (8.5)	0	2 (15.4)
SD	54 (75.0)	61 (84.7)	43 (72.9)	51 (86.4)	11 (84.6)	10 (76.9)
PD	7 (9.7)	4 (5.6)	5 (8.5)	3 (5.1)	2 (15.4)	1 (7.7)
NE	0	0	0	0	0	0
Median DoR, months	14.9	7.2	14.9	7.9	NE	6.3
DCR,[d] n (%) (95% CI)[c]	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)

[a]Efficacy evaluable was defined as patients treated with at least one dose of rivoceranib who have at least one post-baseline tumor assessment.
[b]Patients with a best overall response of PR/CR. Best overall response of PR/CR must be confirmed for inclusion in the numerator of ORR.
[c]Calculated using the Clopper-Pearson method.
[d]Disease control rate was defined as the proportion of patients who achieved a confirmed complete response, confirmed partial response, or stable disease for ≥3 months from the start of study treatment.
CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, overall response rate; PR, partial response; PD, progressive disease; SD, stable disease.

Figure 2: Maximum Change in Sum of Target Lesions Assessed by Investigator in the Efficacy Evaluable Population (N=72)

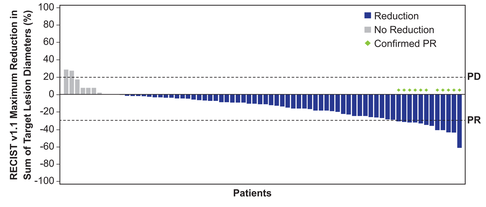


Figure 3: Duration of Treatment in Patients With Confirmed Response Assessed by Investigator per RECIST v1.1

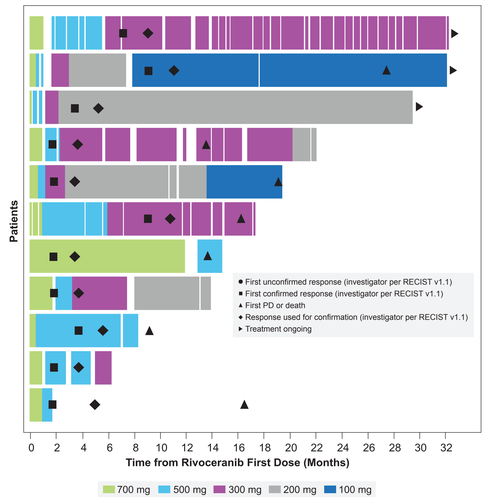


Figure 4: Maximum % Change in Sum of Target Lesion Diameters for 6-month Period Prior to Enrollment and the First 6 Months on Study Assessed by Investigator in the Population With 20% Increase in Measurable Lesions Prior to Study (N=60)

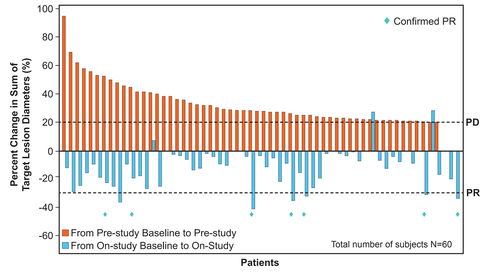
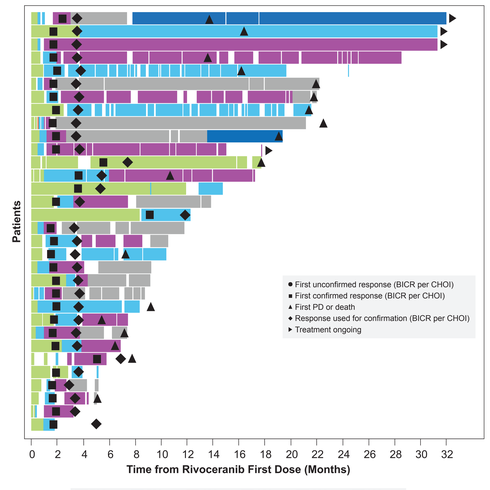


Table 3: Response per Choi Response Criteria by BICR (Choi Criteria Population)

	Total (N=61)	VEGFRi-naïve (n=49)	VEGFRi-treated (n=12)
ORR, n (%) (95% CI)	32 (52.5) (39.3-65.4)	26 (53.1) (38.3-67.5)	6 (50.0) (21.1-78.9)
CR	0	0	0
PR	32 (52.5)	26 (53.1)	6 (50.0)
SD	25 (41.0)	20 (40.8)	5 (41.7)
PD	4 (6.6)	3 (6.1)	1 (8.3)
Median DoR, months (95% CI)	14.3 (11.5-20.2)	14.8 (7.4-20.2)	12.2 (5.7-21.0)
DCR, n (%) (95% CI)	38 (62.3) (49.0-74.4)	30 (61.2) (46.2-74.8)	8 (66.7) (34.9-90.1)

BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 5: Duration of Treatment in Patients With Confirmed Response Assessed by Investigator per Choi Criteria



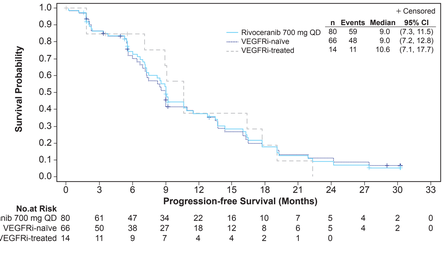
PROGRESSION

Table 4: Progression per RECIST v1.1 in the Overall Efficacy Evaluable Population

	Total (N=72)		VEGFRi-naïve (n=59)		VEGFRi-treated (n=13)	
	Investigator	BICR	Investigator	BICR	Investigator	BICR
Median PFS, mo (95% CI)	9.1 (7.5 -12.8)	9.2 (8.0, 12.9)	9.0 (7.3–13.5)	9.3 (8.0–13.7)	10.6 (7.1–17.7)	8.9 (5.3–12.9)
PFS landmark analyses, % (95% CI)						
6-mo	77.4 (65.3 -85.7)	80.8 (68.5–88.6)	75.8 (61.9-85.2)	80.3 (66.3–88.9)	84.6 (51.2–95.9)	83.1 (47.2–95.5)
12-mo	38.9 (26.7-50.9)	38.6 (25.4–51.6)	39.3 (25.9-52.5)	40.4 (25.6–54.6)	37.6 (11.8-64.0)	31.2 (7.5-59.2)
Median TTP, mo (95% CI)	9.2 (8.5-13.7)	9.3 (8.5–13.6)	9.2 (7.5-13.7)	10.8 (8.5–13.8)	10.6 (8.9-19.1)	8.9 (5.3-13.6)

CI, confidence interval; PFS, progression free survival; TTP, time to progression.

Figure 6: Kaplan-Meier Estimates of Progression-Free Survival per RECIST v1.1 Assessed by Investigator in the Intent-to-Treat Population



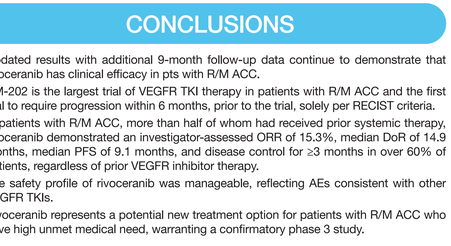
SURVIVAL

Table 5. Overall Survival in the Intention-to-treat Population

	Total (N=80)	VEGFRi-naïve (n=66)	VEGFRi-treated (n=14)
Median OS, mo (95% CI)	25.3 (17.7, NE)	28.3 (17.7, NE)	22.6 (10.6, 31.6)
OS rate at 12-mo, % (90% CI)	74.7 (62.9, 83.3)	76.0 (62.8, 85.0)	69.2 (37.3, 87.2)
OS rate at 18-mo, % (90% CI)	60.2 (47.8, 70.6)	61.8 (48.0, 73)	53.8 (24.8, 76)
OS rate at 24-mo, % (90% CI)	51.8 (39.2, 63.0)	53.5 (39.5, 65.7)	44.9 (17.7, 69.0)

CI, confidence interval; OS, overall survival; NE, not evaluable.

Figure 7: Kaplan-Meier Estimates of Overall Survival in the Intention-to-Treat Population



SAFETY

- All patients received at least 1 dose of study drug and were analyzed for safety.
- The most common (>50%) treatment-emergent adverse events (TEAEs) were hypertension, fatigue, nausea, and headache (**Table 6**).
- Grade ≥3 AEs were observed in 65 patients (81.3%).
  - The most common (>5%) grade ≥3 AEs were hypertension (42.5%), stomatitis (7.5%), anemia (6.3%), and fatigue (6.3%).
  - Four patients experienced a fatal adverse event.
- Eighteen patients (22.5%) discontinued rivoceranib due to an AE.
- Overall, 68 patients (85.0%) required one or more dose modifications (reduction or interruption) due to an AE.
  - Thirty-seven patients (46.3%) required dose reduction and 69 patients (86.3%) required dose interruption due to an AE.

Table 6. Treatment-Emergent Adverse Events (TEAE) in ≥20% of Patients

TEAE	N (%)
Hypertension	53 (66.3)
Fatigue	51 (63.8)
Nausea	43 (53.8)
Headache	42 (52.5)
Stomatitis	39 (48.8)
Diarrhea	35 (43.8)
Decreased appetite	32 (40.0)
Proteinuria	31 (38.8)
Palmar-plantar erythrodysesthesia syndrome	27 (33.8)
Weight decreased	25 (31.3)
Constipation	24 (30.0)
AST increased	22 (27.5)
ALT increased	20 (25.0)
Vomiting	20 (25.0)
Back pain	20 (25.0)
Abdominal pain	17 (21.3)
Oral pain	17 (21.3)
Dyspnea	17 (21.3)

CONCLUSIONS

- Updated results with additional 9-month follow-up data continue to demonstrate that rivoceranib has clinical efficacy in pts with R/M ACC.
- RM-202 is the largest trial of VEGFR TKI therapy in patients with R/M ACC and the first trial to require progression within 6 months, prior to the trial, solely per RECIST criteria.
- In patients with R/M ACC, more than half of whom had received prior systemic therapy, rivoceranib demonstrated an investigator-assessed ORR of 15.3%, median DoR of 14.9 months, median PFS of 9.1 months, and disease control for ≥3 months in over 60% of patients, regardless of prior VEGFR inhibitor therapy.
- The safety profile of rivoceranib was manageable, reflecting AEs consistent with other VEGFR TKIs.
- Rivoceranib represents a potential new treatment option for patients with R/M ACC who have high unmet medical need, warranting a confirmatory phase 3 study.

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ACKNOWLEDGEMENTS: This study was funded by Elevar Therapeutics. The Phillips Group Oncology Communications Inc. provided professional assistance with poster preparation. Financial support for writing and editorial services was provided by Elevar Therapeutics.
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