A Phase 2 Study of the Oral Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) Inhibitor, Rivoceranib, for Recurrent or Metastatic (R/M) Adenoid Cystic Carcinoma (ACC)

Presented at ASCO® 2022
Abstract # 6020

Hyunseok Kang,[1] Myung-Ju Ahn,[2] Jameel Muzaffar,[3] Bhumsuk Keam,[4] Daniel W. Bowles,[5] Deborah J. Wong,[6] Alan Ho,[7] Sung-Bae Kim,[8] Francis Worden,[9] Tak Yun,[10] Amit Pande,[11] Suha Sari,[11] Maureen G. Conlan,[11] Glenn J. Hanna,[12]

[1]University of California, San Francisco (UCSF) – Medical Center, San Francisco, CA; [2]Samsung Medical Center, Seoul, Korea, Republic of; [3]Moffitt Cancer Center, Tampa, FL; [4]Seoul National University Hospital, Seoul, Korea, Republic of; [5]University of Colorado Denver, Aurora, CO; [6]University of California, Los Angeles (UCLA), Los Angeles, CA; [7]Memorial Sloan Kettering Cancer Center, New York, NY; [8]Asan Medical Center, Seoul, Korea, Republic of; [9]University of Michigan, Ann Arbor, MI; [10]National Cancer Center, Goyang, Korea, Republic of; [11]Elevar Therapeutics, Salt Lake City, UT; [12]Dana-Farber Cancer Institute, Boston, MA

INTRODUCTION

- Adenoid cystic carcinoma (ACC) is a rare tumor that arises from secretory glands, most commonly salivary glands,[1] and there are currently no approved systemic treatments available for use in patients with recurrent/metastatic (R/M) ACC.
- Median survival duration in patients with R/M ACC is 17 years but 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]
- VEGF is widely expressed in ACC and is associated with metastasis and poor survival.[3-5]
- Multi-tyrosine kinase inhibitors (TKIs) of VEGFR1-3 have been studied as systemic treatment for ACC.
  - Prolonged PFS was observed with axitinib compared to placebo (10.8 months versus 2.8 months; P<0.001) in patients with TKI-naïve disease.[6]
  - Single-arm, single-center studies of lenvatinib demonstrated ORRs of 11.5%[7] and 15.6%[8] and median PFS durations of 9.1 months[7] and 17.5 months[8] in predominantly TKI-naïve patients. These latter results led to inclusion of lenvatinib in treatment guidelines[9] despite a post-hoc analysis that revealed event-free survival of 8.2 months.[8] In addition, 54% of patients discontinued lenvatinib due to drug toxicity.
- Rivoceranib is an orally administered TKI that is a potent and selective inhibitor of VEGFR2.[10,11] VEGFR2 represents the primary VEGFR for regulation of angiogenesis, mitogenic signaling, and vascular permeability.[12]
- We hypothesized that potently and selectively targeting VEGFR2 with rivoceranib may result in an effective treatment option for R/M ACC with a more limited adverse effect profile than observed with multi-TKI inhibition.

METHODS

- RM-202 is 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 or unacceptable toxicity[b]**

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

[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, and 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 by RECIST v1.1 occurring within the 6 months prior to study entry, which was defined as ≥20% increase in radiologically or clinically measurable lesions or appearance of new lesions
- Presence of at least one measurable target lesion evaluable by 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 blinded independent review committee (BIRC)

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

Exploratory:
- Disease control rate (DCR)[a] by investigator and BIRC
- ORR based on the CHOI criteria[13] evaluated by BIRC[b]

[a]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.
[b]Exploratory evaluation of ORR by BIRC was added as investigators observed reduction in tumor density on rivoceranib treatment without changes in tumor lesion diameter.

RESULTS

PATIENTS

- N=80 were enrolled between January 2020 and May 2021 at 11 sites in the United States and Korea (**Table 1**).
- At the time of the current analysis, 11 patients (13.8%) were continuing to receive study drug.
  - The primary reasons for discontinuing study drug were disease progression (n=39 [48.8%]; n=37 [46.3%] per RECIST v1.1 and n=2 [2.5%] per clinical progression) and adverse events (AEs; n=16 [20.0%]).

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, n (%)	74 (92.5)
Sites of metastases, n (%)	
Lung	69 (86.3)
Liver	25 (31.3)
Bone	20 (25.0)
Lymph nodes	20 (25.0)
Pleura	14 (17.5)
Prior surgery/radiotherapy, n (%)	71 (88.8) / 77 (96.3)
Prior systemic therapy, n (%)	49 (61.3)
Median number of lines (range)	1.0 (0, 8)
≥3 lines	16 (20.0)
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.

EFFICACY/RESPONSE ENDPOINTS

- A confirmed partial response per RECIST v1.1 was observed in 11 patients per investigator assessment resulting in an ORR of 15.1% and in 7 patients per BIRC assessment for an ORR of 9.6% (**Table 2, Figure 2, Figure 3**). Median time to response by Investigator was 57.0 days (range: 50-276)
- The DCR per RECIST v1.1 was 64.4% per investigator and 65.8% per BIRC.
- A partial response per CHOI criteria was observed in 31 patients (50.8% [95% CI, 37.7–63.9]) as assessed by BIRC.[13]
- The change in sum of target lesions for the 6-month period prior to enrollment and the first 6 months on study treatment are shown in **Figure 4**.

Table 2: Response per RECIST v1.1 Assessed by Investigator and Blinded Independent Review Committee in the Efficacy Evaluable Population[a] and by Prior VEGFRi Treatment

	Total n=73		VEGFRi-naïve n=60		VEGFRi-treated n=13	
	Investigator	BIRC	Investigator	BIRC	Investigator	BIRC
ORR,[b] n (%) (95% CI)[c]	11 (15.1) (7.8–25.4)	7 (9.6) (3.9–18.8)	11 (18.3) (9.5–30.4)	5 (8.3) (2.8–18.4)	0 (0) (0–24.7)	2 (15.4) (1.9–45.4)
Best overall response, n (%)						
CR	0	0	0	0	0	0
PR	11 (15.1)	7 (9.6)	11 (18.3)	5 (8.3)	0	2 (15.4)
SD	54 (74.0)	61 (83.6)	43 (71.7)	51 (85.0)	11 (84.6)	10 (76.9)
PD	8 (11.0)	4 (5.5)	6 (10.0)	3 (5.0)	2 (15.4)	1 (7.7)
Median DOR, months (IQR)	14.9 (11.9–17.3)	7.2 (5.5–8.3)	14.9 (11.9–17.3)	7.9 (5.4–8.3)	NE (NE–NE)	6.3 (5.5–7.1)
DCR,[d] n (%) (95% CI)[c]	47 (64.4) (52.3–75.3)	48 (65.8) (53.7–76.5)	37 (61.7) (48.2–73.9)	39 (65.0) (51.6–76.9)	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; IQR, interquartile range; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

Figure 2: Maximum Change in Sum of Target Lesions Assessed by Investigator in the Efficacy Evaluable Population

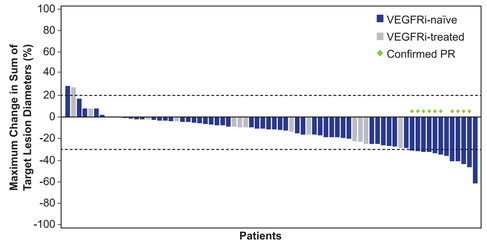


Figure 3: Duration of Treatment

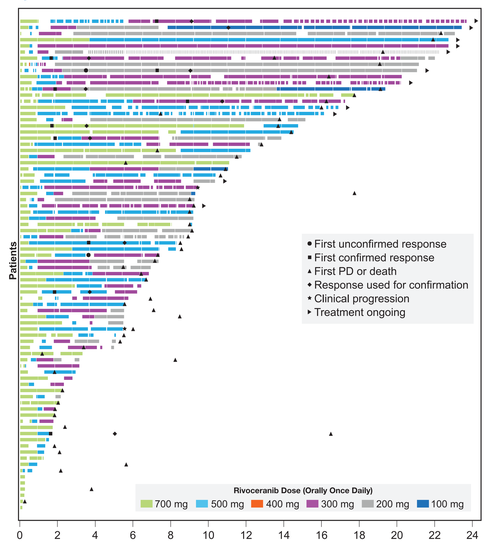


Figure 4: Change in Sum of Target Lesions for the 6-month Period Prior to Enrollment and the First 6 Months on Study per RECIST v1.1 Assessed by Investigator in the Efficacy Evaluable Population

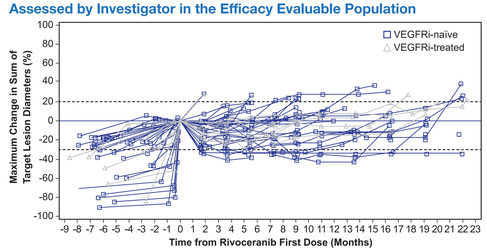
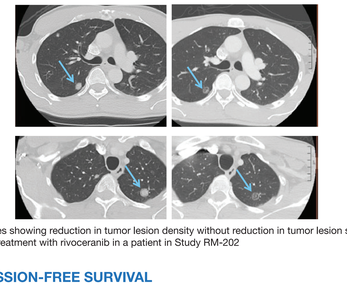


Figure 5: Response per CHOI Response Criteria by BIRC

	Total N=60	VEGFRi-naïve N=48	VEGFRi-treated N=12
ORR, n (%)[a] (95% CI)[b]	31 (51.7) (38.4-64.8)	25 (52.1) (37.2-66.7)	6 (50.0) (21.1-78.9)
Best overall response, n (%)			
CR	0	0	0
PR	31 (51.7)	25 (52.1)	6 (50.0)
SD	25 (41.7)	20 (41.7)	5 (41.7)
PD	4 (6.7)	3 (6.3)	1 (8.3)
Median DoR, months (IQR)	14.8 (7.2, 20.2)	14.8 (7.2, 20.2)	12.2 (12.2, NE)
DCR, n (%)[c] (95% CI)[b]	37 (61.7) (48.2-73.9)	29 (60.4) (45.3-74.2)	8 (66.7) (34.9-90.1)

[a]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.
[b]Calculated using the Clopper-Pearson method.
[c]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.
CHOI criteria population includes all eligible patients treated with ≥1 dose of rivoceranib who have contrast-enhanced CT tumor assessments at baseline and post-baseline timepoints.



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 in Study RM-202

PROGRESSION-FREE SURVIVAL

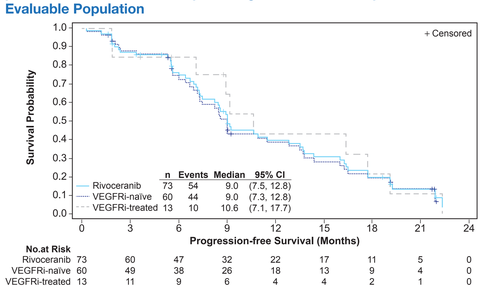
- At the time of data cut-off, patients were followed for a median of 19.5 months (range, 1.9 - 23.7).
- Median PFS per RECIST v1.1 was 9.0 months per investigator, and 9.2 months per BIRC in the overall population, and was consistent regardless of prior VEGFRi treatment (**Table 3, Figure 6**).

Table 3: Progression-free Survival per RECIST v1.1 Assessed by Investigator and Blinded Independent Review Committee in the Efficacy Evaluable Population and According to Prior VEGFR Inhibitor Treatment

	Total n=73		VEGFRi-naïve n=60		VEGFRi-treated n=13	
	Investigator	BIRC	Investigator	BIRC	Investigator	BIRC
Median PFS, mo (95% CI)	9.0 (7.5–12.8)	9.2 (8.0, 12.9)	9.0 (7.3–12.8)	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	76.3 (64.2–84.8)	80.8 (68.5–88.6)	74.5 (60.7–84.1)	80.3 (66.3–88.9)	84.6 (51.2–95.9)	83.1 (47.2–95.5)
12-mo	39.7 (27.4–51.6)	38.2 (25.0–51.3)	38.7 (25.5–51.8)	40.4 (25.6–54.6)	43.0 (13.8–69.8)	26.0 (4.3–56.2)
Median TTP, mo (95% CI)	9.1 (8.5–13.8)	9.3 (8.5–13.6)	9.0 (7.3–13.5)	10.8 (8.5–13.8)	16.4 (8.9–19.1)	8.9 (5.3–12.9)

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 Efficacy Evaluable Population



SURVIVAL

- Median OS has not been reached in the overall population (**Table 4**).

Table 4: Overall Survival in the Intention-to-treat Population and According to Prior VEGFR Inhibitor Treatment

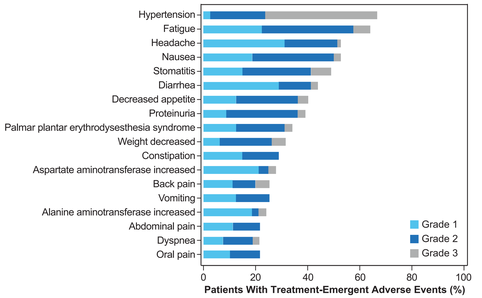
	Total n=80	VEGFRi-naïve n=66	VEGFRi-treated n=14
Median OS, mo (95% CI)	NE	NE	17.5 (10.0, NE)
OS landmark analyses, % (95% CI)			
12-mo	74.5 (62.5–83.1)	77.4 (64.2–86.2)	62.9 (32.3–82.6)
18-mo	61.7 (48.3–72.5)	66.0 (51.1–77.3)	45.8 (18.3–69.9)

OS, overall survival

SAFETY

- All patients received at least 1 dose of study drug and were analyzed for safety.
- An adverse event (AE) of any grade was observed in all patients. Treatment-emergent adverse events in ≥20% of patients are shown in **Figure 7**.
- Grade ≥3 AEs were observed in 64 patients (80.0%).
  - The most common Grade ≥3 AEs were hypertension, stomatitis, anemia, and fatigue.
  - Four patients experienced a fatal adverse event; these events consisted of epistaxis in two patients and acute respiratory failure in two patients.
- Sixteen patients (20.0%) discontinued rivoceranib due to an AE.
- The median duration of treatment was 31.1 weeks (range, 0.6–103.0).
- The median actual dose intensity was 421.0 mg/day. The relative dose intensity was 60.1%.
- Overall, 68 patients (85.0%) required one or more dose modifications (reduction or interruption) due to an adverse event. The median time to first dose reduction was 4.1 weeks (range, 1–40).

Figure 7: Treatment-Emergent Adverse Events in ≥ 20% of Patients



Note: Any grade treatment-emergent adverse events in ≥20% of patients by MedDRA preferred term

CONCLUSIONS

- RM-202 is the largest multicenter trial of VEGFR TKI therapy in patients with R/M ACC, the first trial to require progression within 6 months prior to the trial, solely per RECIST v1.1, and the first trial to report ORR using BIRC.
- In patients with R/M ACC, more than half of whom had received prior systemic therapy, rivoceranib demonstrated:
  - Investigator-assessed ORR of 15.1%, median DOR 14.9 months, median PFS of 9 months, and disease control for ≥3 months in over 60% of patients, regardless of prior VEGFRi therapy.
  - BICR-assessed ORR of 9.6%, median DOR 7.2 months, and a DCR of 64.4%
  - CHOI-assessed ORR of 51.7%, median DOR 14.8 months, and a DCR of 61.7%
- The change in sum of target lesions for the 6-month period prior to enrollment and the first 6 months on study demonstrates the efficacy of rivoceranib in this progressing population.
- The safety profile of rivoceranib was manageable, with an AE profile consistent with other VEGFR TKIs.
- These promising data warrant continued investigation of rivoceranib, including further dose optimization, as a potential new treatment option for patients with R/M ACC.

REFERENCES: **1.** Dillon PM, et al. *Head Neck*. 2016;38:620-627; **2.** Hanna GJ, et al. *Oral Oncol*. 2020;106:104690; **3.** Park S, et al. *Cancer Res Treat*. 2016;48:518-526; **4.** Zhang J, et al. *BMC Cancer*. 2007;7:95; **5.** Zhang J, et al. *Clin Cancer Res*. 2005;11:7334-7343; **6.** Kang EJ, et al. *Clin Cancer Res*. 2021;27:5272-5279; **7.** Locati LD, et al. *Cancer*. 2020;126:1888-1894; **8.** Tchekmedyian V, et al. *J Clin Oncol*. 2019;37:1529-1537; **9.** National Comprehensive Cancer Network. Accessed April 5, 2022. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf; **10.** Sachar M, et al. *Fundam Clin Pharmacol*. 2021;35:485-495; **11.** Sachar M, et al. *Fundam Clin Pharmacol*. 2022;36:171-181; **12.** Shaik F, et al. *Biomolecules*. 2020;10:1673; **13.** Choi H, et al, *J Clin Oncol*. 2007;25:1753-1759.

ACKNOWLEDGEMENTS: This study was funded by Elevar Therapeutics. Mark Phillips, PharmD and Laura Evans, PharmD of Phillips Gilmore Oncology Communications Inc. provided professional assistance with poster preparation. Financial support for writing and editorial services was provided by Elevar Therapeutics.

CONTACT FOR POSTER INFORMATION/QUESTIONS: medicalinformation@elevartherapeutics.com