Supplementary Material

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

Contents

Investigators

# Subjects enrolled	PI Full Name	Site Name	Country
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6	Dr. Daniel Bowles	University of Colorado Denver	United States
6	Dr. Deborah Jean Lee Wong	University of California, Los Angeles (UCLA)	United States
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4	Dr. Sung-Bae Kim	Asan Medical Center	South Korea
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Supplemental Methods

Eligibility Criteria

Inclusion Criteria

Disease Related

1. Histologically or cytologically confirmed metastatic/recurrent adenoid cystic carcinoma (ACC) not amenable to potentially curative surgery or radiotherapy
2. Evidence of disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1·1
   Disease progression was defined as one of the following occurring within the 6 months prior to study entry:
   a. At least a 20% increase in radiologically or clinically measurable lesions
   b. Appearance of any new lesions
3. Presence of at least one measurable target lesion that was evaluable by RECIST v1·1
4. Patients were eligible if central nervous system (CNS) metastases had been treated and patients had neurologically returned to baseline or were neurologically stable in the opinion of investigator (except for residual signs or symptoms related to the CNS treatment) for at least 4 weeks prior to first dose of study drug administration. In addition, patients had to be either off corticosteroids, or on a stable dose or decreasing dose of <20 mg daily prednisone or prednisone equivalent.
   Only patients with a known history or indication of CNS disease were required to have CNS imaging prior to study entry

Laboratory

5. Adequate organ and marrow function within 14 days prior to the first dose of rivoceranib administration, defined as:
   a. Absolute neutrophil count ≥1500/μL
   b. Platelet count ≥100,000/μL
   c. Serum bilirubin ≤1·5×upper limit of normal (ULN)
   d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3·0×ULN (≤5·0×ULN, if with liver metastasis)
   e. Estimated creatinine clearance >50 mL/min (Cockcroft-Gault)
   f. Partial thromboplastin time (PTT), prothrombin time (PT) and international normalized ratio (INR) ≤1·5×ULN
   g. Hemoglobin ≥9·0 g/dL
6. Urinary protein <2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine or urine protein/creatinine ratio had to be collected and had to demonstrate <2 g of protein in 24 hours

Demographic

7. Men and women ≥18 years of age (or age of majority, if higher per local regulations)
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Ethical/Other

9. The ability to understand and the willingness to sign a written informed consent
10. Female patients who were of non-reproductive potential (i.e. post-menopausal by history – no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR

history of bilateral oophorectomy). Female patients of childbearing potential had to have a negative serum pregnancy test within 72 hours prior to the first dose of rivoceranib
11. Male and female patients of reproductive potential who agreed to use both a highly effective method of birth control (e.g. implants, injectables, combined oral contraceptives, some intrauterine devices, complete abstinence, or sterilized partner) and a barrier method (e.g. condoms, cervical ring, sponge, etc.) during the period of therapy and for 30 days after the final dose of rivoceranib. Female patients should have also refrained from breastfeeding and egg donation and males should had refrained from sperm donation throughout this period
12. QTc interval <480 milliseconds (ms) (National Cancer Institute Common Terminology Criteria for Adverse Events grade 1) using Fredericia's QT correction formula

Exclusion Criteria

Disease Related
1. Previous treatment with rivoceranib
2. Known hypersensitivity to rivoceranib or components of the formulation
3. Packed red blood cell transfusion or erythropoietin therapy within 14 days prior to the first dose of rivoceranib administration
4. History of another malignancy within 3 years prior to enrollment. A patient with the following malignancies was eligible for this study if surgically and medically treated and, in the opinion of the investigator, they did not pose a significant risk to life expectancy or were not likely to recur within 3 years:
   a. Carcinoma of the skin without melanomatous features
   b. Curatively treated cervical carcinoma in situ
   c. Bladder tumors considered superficial such as noninvasive (T1a) and carcinoma *in situ* (Tis)
   d. Thyroid papillary cancer with prior treatment
   e. Prostate cancer that had been surgically or medically treated
5. Prior chemotherapy, radiation therapy or major surgery within 4 weeks prior to rivoceranib administration or presence of any nonhealing wound (procedures such as catheter placement were not considered to be major surgery). Prior immunotherapy within 12 weeks prior to first dose of study drug. Palliative radiotherapy to non-target lesions within 2 weeks prior to rivoceranib administration or biopsy any time prior to rivoceranib administration was permitted
6. Prior tyrosine kinase inhibitor therapy targeting vascular endothelial growth factor receptor (VEGFR), within 5 half-lives prior to rivoceranib administration
7. Patients who had not recovered to ≤ grade 1 from prior tyrosine kinase inhibitor-related adverse events
8. History of uncontrolled hypertension based on investigator's clinical judgement (consistent blood pressure readings ≥140/90 mmHg and/or change in antihypertensive medication within 7 days prior to rivoceranib administration)
9. History of severe adverse events including uncontrolled hypertension or other common anti-angiogenesis class drug effects (e.g. ramucirumab) that may have indicated a higher risk to the safety of the subject if provided further anti-angiogenesis treatment, in the investigator's opinion
10. History of vascular disease including arterial or venous embolic events (pulmonary embolism), other than hypertension, within the last 3 months prior to treatment with rivoceranib (e.g. hypertensive crisis, hypertensive encephalopathy, stroke or transient ischemic attack [TIA], or significant peripheral vascular diseases) that, in the investigator's opinion, may pose a risk to the subject on VEGF inhibitor therapy.
11. History of bleeding diathesis or clinically significant bleeding within 14 days prior to treatment with rivoceranib

12. History of clinically significant thrombosis within 3 months prior to treatment with rivoceranib that, in the investigator's opinion, may have placed the patient at risk of side effects from anti-angiogenesis products
13. Therapy with systemic anticoagulant or antithrombotic agents within 7 days prior to treatment with rivoceranib that in the investigator's opinion could have interfered with clotting. The maximum allowable daily dose of aspirin was 325 mg
14. Gastrointestinal malabsorption, or any other condition that in the opinion of the investigator might have affected the absorption of rivoceranib
15. History of clinically significant glomerulonephritis, biopsy-proven tubulointerstitial nephritis, crystal nephropathy, or other renal insufficiencies
16. An uncontrolled intercurrent illness including, but not limited to any of the following:
   a. Ongoing or active infection (including minor localized infections) requiring oral or intravenous treatment
   b. Symptomatic class 3 or 4 congestive heart failure, defined as a clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood
   c. Unstable angina pectoris
   d. Cardiac arrhythmia
   e. Any other illness or condition that the treating investigator felt would interfere with study compliance or would compromise the subject's safety or study endpoints

Ethical/Other
17. A female subject who was pregnant or breast-feeding
18. Psychiatric illness/social situations that would limit compliance with study requirements
19. History of drug or alcohol abuse within past 5 years
20. Known seropositive requiring anti-viral therapy for human immunodeficiency virus (HIV) infection
21. Known seropositive requiring anti-viral therapy for hepatitis B virus (HBV) infection OR evidence of active hepatitis B infection by detectable viral load if the antibody tests were positive
   A patient with a positive hepatitis B core antibody (HBcAb) and an undetectable surface antigen and negative hepatitis B DNA test (e.g., polymerase chain reaction [PCR] test) could be enrolled
22. Known seropositive requiring anti-viral therapy for hepatitis C virus (HCV) infection OR patients with positive hepatitis C virus antibody
   A patient with positive anti-HCV and an undetectable/negative hepatitis C RNA test could be enrolled
23. Participation in another clinical study with any investigational medication or product administered within ≤28 days prior to first dose of rivoceranib
24. Patients unable or unwilling to discontinue excluded medications for at least 5 half-lives prior to first dose of study drug

Assessments

Urinalysis

Urinalysis included the following:

- Specific gravity
- Glucose, protein, occult blood, by dipstick
- Microscopic examination (if blood or protein is abnormal)

Choi Criteria

Choi criteria responses were defined as follows: [Choi 2007]

- Complete response was defined as disappearance of all lesions and no appearance of new lesions.
- Partial response was defined as a decrease in tumor size of ≥10% or a decrease in tumor density (Hounsfield unit) of ≥15% on computed tomography scan; no new lesions; and no obvious progression of nonmeasurable disease.
- Stable disease was defined as a response that did not meet the criteria for complete response, partial response, or progressive disease and no symptomatic deterioration was observed that was attributed to tumor progression.
- Progressive disease was defined as an increase in tumor size of ≥10% and tumor changes did not meet the criteria of partial response by tumor density (Hounsfield unit) on computed tomography; presence of new lesions; or presence of new intratumoral nodules or increase in the size of the existing intratumoral nodules

Size of tumors was measured as the sum of the longest diameters of target lesions as defined in Response Evaluation Criteria in Solid Tumors. [Eisenhauer 2009]

Intensive Pharmacokinetic Sampling Times on Cycle 1 Day 1 and Cycle 1 Day 15

Visit	**Time Point**
Cycle 1, day 1	Predose (<30 min predose)
	1 h ± 15 min
	2 h ± 15 min
	3 h ± 15 min
	4 h ± 30 min
	6 h ± 30 min
	8 h ± 30 min
	10 h ± 30 min
	12 h ± 60 min
	16 h ± 60 min
	24 h ± 2 h
Cycle 1/day 15	Predose (<30 min predose)
	1 h ± 15 min
	2 h ± 15 min
	3 h ± 15 min
	4 h ± 30 min
	6 h ± 30 min

	8 h ± 30 min
	10 h ± 30 min
	12 h ± 60 min
	16 h ± 60 min
	24 h ± 2 h

Pharmacokinetic Analysis

Following a single 700 mg dose of rivoceranib on cycle (C) 1 day (D) 1, rivoceranib median time to maximum plasma concentration (t_{max}) was 2.5 hours post dose and mean (standard deviation) elimination half-life was 7.5 (1.1) hours. The geometric mean (%CV) maximum plasma concentration (C_{max}) and area under plasma concentration-time profile for the first 24 hours (AUC_{0-24}) was 909 (107%) ng/mL and 7180 (101%) ng×h/mL, respectively. The mean accumulation ratios based on C_{max} and AUC_{0-24} (C1D15/C1D1) were 2.42 and 2.94, respectively. Though large inter-subject variability (i.e., >100%) in rivoceranib C_{max} and AUC_{0-24} was observed, the pharmacokinetic systemic exposure observed from this study is generally consistent with what has been observed from prior rivoceranib studies.[1,2]

1. Sachar M, Park CH, Pesco-Koplowitz L, Koplowitz B, McGinn A. Absence of ethnic difference on single-dose pharmacokinetics of rivoceranib between healthy male Caucasian, Japanese, and Chinese subjects. Fundam Clin Pharmacol 35:485–495, 2021

2. Sachar M, Park CH, Pesco-Koplowitz L, Koplowitz B, McGinn A. Effect of food intake on the pharmacokinetics of rivoceranib in healthy subjects. Fundam Clin Pharmacol 36:171–181, 2022

Biomarker Analysis

Of the 62 patients with available *MYB* and *MYB-L1* gene testing results, 23 patients (37.1%) had *MYB* translocations and 6 (9.7%) had *MYB-L1* translocations. Among 56 efficacy-evaluable patients with *MYB* or *MYBL1* translocations and response, there were no notable differences in ORR based on the presence or absence of translocations in either *MYB* (17.4% and 18.2%, respectively) or *MYB-L1* (16.7% and 18.0%, respectively). The median DOR was 17.3 months in each subgroup (*MYB* or *MYB-L1* responders). Patients with *MYB* translocations had a median PFS of 13.5 months, while patients with *MYB-L1* translocations had a median PFS of 13.8 months. Of the 27 patients with available *NOTCH1* mutation status, 2 patients (7.4%) had *NOTCH1* mutation detected and neither demonstrated a disease response (one had SD).