



Original Article

Phase 1/2a Study of Rivoceranib, a Selective VEGFR-2 Angiogenesis Inhibitor, in Patients with Advanced Solid Tumors

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Purpose This study aimed to report the results from an early-phase study of rivoceranib, an oral tyrosine kinase inhibitor highly selective for vascular endothelial growth factor receptor 2, in patients with advanced solid tumors.

Materials and Methods In this open-label, single-arm, dose-escalating, multicenter three-part phase 1/2a trial, patients had advanced solid tumors refractory to conventional therapy. Part 1 evaluated the safety and pharmacokinetics of five ascending once-daily doses of rivoceranib from 81 mg to 685 mg. Part 2 evaluated the safety and antitumor activity of once-daily rivoceranib 685 mg. Part 3 was conducted later, due to lack of maximum tolerated dose determination in part 1, to evaluate the safety and preliminary efficacy of once-daily rivoceranib 805 mg in patients with unresectable or advanced gastric cancer.

Results A total of 61 patients were enrolled in parts 1 (n=25), 2 (n=30), and 3 (n=6). In parts 1 and 2, patients were white (45.5%) or Asian (54.5%), and 65.6% were male. The most common grade ≥ 3 adverse events were hypertension (32.7%), hyponatremia (10.9%), and hypophosphatemia (10.9%). The objective response rate (ORR) was 15.2%. In part 3, dose-limiting toxicities occurred in two out of six patients: grade 3 febrile neutropenia decreased appetite, and fatigue. The ORR was 33%.

Conclusion The recommended phase 2 dose of rivoceranib was determined to be 685 mg once daily, which showed adequate efficacy with a manageable safety profile (NCT01497704 and NCT02711969).

Key words Apatinib, Rivoceranib, Stomach neoplasms, Solid tumors

Introduction

Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) play a key role in regulating physiological homeostasis and pathogenesis [1]. Vascular angiogenesis and pathogenesis are induced by VEGF binding to VEGFR-2, which mediates vascular permeability, endothelial cell proliferation, migration, invasion, and survival [2]. VEGFR-2 is regarded as the most sensitive target for endothelial cell growth that directly controls tumor angiogenesis [3]. VEGFR-2 has been shown to specifically promote solid tumor cell proliferation and invasion *in vitro*, as well as accelerated tumor growth *in vivo* [4]. Higher VEGFR-2 expression in gastric tumors is associated with aggressiveness and poorer prognosis [4].

Advanced gastric cancer that has progressed following first-line standard-of-care platinum-fluoropyrimidine chemotherapy has a poor prognosis with median overall survival of approximately 4 to 5 months [5-7]. In the second-line setting, other chemotherapy regimens such as docetaxel have been proven effective compared to best supportive care [6,7].

In addition, ramucirumab has been proven effective either as a monotherapy versus best supportive care in the REGARD trial [5] or in combination with chemotherapy (paclitaxel) versus chemotherapy alone in the RAINBOW trial [8]. These two trials indicated that VEGFR-2 inhibition with tyrosine kinase inhibitors (TKIs) may be effective in gastric cancer.

In patients for whom chemotherapy is not appropriate, ramucirumab monotherapy represents the only non-cytotoxic treatment option for human epidermal growth factor receptor 2–negative tumors without targeted mutations or deficient mismatch repair and is the only VEGFR-2 targeted agent approved outside of China in this setting [9]. In addition, ramucirumab requires administration by intravenous infusion. No orally administered VEGFR-2 TKIs are approved for the treatment of advanced gastric cancer outside of China. Further treatment options are needed for this patient population.

Rivoceranib (apatinib, YN968D1) is an orally administered, highly potent inhibitor of VEGFR-2, with activity in treating various solid tumors, including gastric cancer [10]. Rivoceranib is approved in China under the name of apatinib for

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the third-line treatment of advanced gastric cancer. Herein, we report the findings of a phase 1/2a dose escalation study evaluating the safety, preliminary efficacy, pharmacokinetics, and pharmacodynamics of rivoceranib in Asian and white patients with advanced solid tumors or gastric cancer.

Materials and Methods

1. Study design

This open-label, single-arm study consists of three parts: part 1 was planned to escalate rivoceranib dose; part 2 was planned to increase the number of patients at a dose of either the maximum tolerated dose (MTD) identified in part 1 or the highest evaluated dose; and part 3 was later initiated to evaluate a higher dose(s) than the highest dose in part 1 because the MTD was not reached in part 1. Part 3 was terminated per protocol due to intolerability of the first higher dose than the highest dose evaluated in part 1.

Parts 1 and 2 were conducted at two sites in the United States and South Korea. Part 3 was conducted at a single center in South Korea.

This study was conducted in accordance with the principles set forth in the Declaration of Helsinki, including all amendments up to and including the 1996 revision, the Guidelines of the International Council on Harmonization (ICH) on Good Clinical Practice (CPMP/ICH/135/95), privacy regulations, and other applicable regulatory requirements. The protocol was reviewed by institutional review boards or ethics committees at each institution. All patients provided written informed consent.

2. Patients

Patients eligible for parts 1 and 2 were men and women aged 18 years or older with a solid malignant tumor that was refractory to conventional therapy, or the patient did not tolerate conventional therapy. In part 1, patients could have any solid malignant tumor. In part 2, patients could have non-small cell lung cancer, colorectal cancer, renal cell carcinoma, gastric cancer, gastrointestinal stromal tumor, or triple-negative breast cancer. Patients eligible for part 3 were men and women aged 19 years or older with histologically proven adenocarcinoma of the stomach or gastric junction. In all parts, eligible patients had measurable disease defined by Response Evaluation Criteria in Solid Tumors ver. 1.1 (RECIST v1.1), and an Eastern Cooperative Oncology Group Performance Status (ECOG) ≤ 2 . Complete eligibility criteria for all parts are listed in the Supplementary Material.

3. Treatment

For part 1 patients received five ascending single doses of oral rivoceranib: 81 mg, 201 mg, 403 mg, 604 mg, and 685 mg (administered as 100 mg, 250 mg, 500 mg, 750 mg, and 850 mg rivoceranib mesylate, respectively). Each dose was followed by a 7-day evaluation period. Part 1 was conducted as a sequential evaluation of three patients per dose cohort. If the initial dose was well-tolerated, the patient returned on day 8 $\pm$ 2 to receive a 28-day course of that same dose level of rivoceranib administered daily. In part 2, patients received multiple consecutive doses of 685 mg of rivoceranib if no MTD was determined in part 1. Patients continued treatment with rivoceranib for 28-day cycles of therapy until disease progression, intolerable adverse events (AEs), or withdrawal of consent.

In part 3, patients received oral rivoceranib 805 mg once daily (administered as rivoceranib mesylate 1,000 mg).

Dose modification or dose interruption was allowed for any potentially significant drug-related AE or for scheduled procedures, such as surgery or radiation therapy.

4. Study assessments

At screening and/or baseline for each part, patients underwent echocardiogram, electrocardiogram (ECG), complete blood count, comprehensive metabolic panel, urinalysis, coagulation parameter assessment, and serum tumor marker assessment.

Adverse events, complete blood count, comprehensive metabolic panel, and urinalysis were evaluated on days 1-3 (part 1), days 1-2 (part 2), day 1 (part 3) and at regular intervals through follow-up. The MTD was defined as the dose level below that which ≥ 2 dose-limiting toxicities (DLTs) among six patients were experienced. ECG was performed on the first and last day of dosing (after 28 days) and at the follow-up visit (day 42) in part 1; on days 2, 56 and 62 in part 2; and day 1 of cycle 1, then weekly during the first cycle, days 1 and 15 of cycle 2, day 1 of subsequent cycles, and at end of treatment in part 3, and at the end of study in all parts. Pharmacokinetic assessments are described below. In parts 1 and 2, tumors were assessed at baseline and after completion of two 28-day cycles of treatment. For patients who continued therapy after the first two 28-day cycles, imaging studies may have been repeated to assess objective response after every two additional 28-day treatment periods. Serum tumor markers were evaluated whether the changes were ≥ 2 times the upper limit of normal at baseline on the last day of dosing after two 28-day cycles, day 56 in part 2, and at the final study visit. In part 3, tumor response was assessed after the first 28-day cycle of treatment and at the final study visit.

DLTs were defined as any of the following events that were assessed by the investigator as probably or possibly related

Table 1. Parts 1 and 2: patient characteristics

Characteristic	Part 1					Part 2
	81 mg (n=5)	201 mg (n=9)	403 mg (n=4)	604 mg (n=4)	685 mg (n=3)	685 mg (n=30)
Age (yr)	53 (34-73)	61 (36-75)	74 (47-76)	62 (33-71)	70 (52-75)	56.5 (32-82)
Male sex	2 (40.0)	7 (77.8)	2 (50.0)	3 (75.0)	1 (33.3)	21 (70.0)
Race						
White	5 (100)	7 (77.8)	2 (50.0)	3 (75.0)	1 (33.3)	7 (23.3)
Asian	0	2 (22.2)	2 (50.0)	1 (25.0)	2 (66.7)	23 (76.7)
ECOG PS						
0	1 (20.0)	1 (11.1)	1 (25.0)	2 (50.0)	1 (33.3)	2 (6.7)
1	3 (60.0)	8 (88.9)	3 (75.0)	2 (50.0)	1 (33.3)	25 (83.3)
2	1 (20.0)	0	0	0	1 (33.3)	3 (10.0)
Tumor type						
Gastric	0	2	2	1	2	15
CRC	3	0	0	0	1	9
Neuroendocrine	0	0	1	2	0	2
NSCLC	0	0	0	0	0	3
Mesothelioma	0	1	0	0	0	1
RCC	0	2	0	0	0	0
Chondrosarcoma	0	1	0	1	0	0
Bronchoalveolar	0	1	0	0	0	0
Cervical	1	0	0	0	0	0
Pancreas	1	0	0	0	0	0
Serous papillary ovarian	0	0	1	0	0	0
Soft tissue sarcoma	0	1	0	0	0	0
Small bowel carcinoid	0	1	0	0	0	0
Prior chemotherapy regimens	4 (1-5) (n=5)	2.5 (1-6) (n=8)	2.5 (2-7) (n=4)	3 (2-4) (n=3)	6 (2-8) (n=3)	3 (1-8) (n=29)

Values are presented as median (range) or number (%). CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.

to rivoceranib: any grade 4 event, grade 3 febrile neutropenia, grade 3 hematologic toxicity with duration > 7 days, or grade 3 non-hematologic toxicity including grade 3 nausea, vomiting, and diarrhea that continued despite optimal medical management. Adverse event severity was graded with Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.03. Tumors were assessed using an appropriate imaging technique per RECIST v1.1.

5. Endpoints

The primary endpoint of the initial study (parts 1 and 2) was safety during the first 28-day cycle of therapy following the initiation of multiple dosing of rivoceranib. Secondary endpoints included pharmacokinetic profiles of rivoceranib after single and multiple doses, pharmacodynamic endpoints, objective response rate (ORR), and disease control rate (DCR) defined as complete response plus partial response plus stable disease as the best overall response. The

primary endpoint of part 3 was to observe DLTs. Secondary endpoints included safety, preliminary antitumor efficacy, and the pharmacokinetic profile of rivoceranib at the 805 mg dose level.

6. Pharmacokinetics

In all parts, blood samples for determination of plasma pharmacokinetic profiles of rivoceranib were collected. In part 1, blood samples were collected and analyzed for the rivoceranib concentration prior to dosing on day 1, at regular intervals during the first day following the initial dose, and 24 and 48 hours after dosing (S1 Table). In the multiple dosing period of part 1, plasma samples were collected immediately prior to dosing on days 8, 15, 22, and 35. Plasma samples were also collected in regular intervals after the last dose of rivoceranib on day 35. In part 2, a single pharmacokinetic sample was collected prior to dosing on days 2, 8, 15, 29, 43, and 56 and at 3-5 hours after dosing on days 1 and 56. In part

Table 2. Parts 1 and 2: adverse events

Adverse event	Part 1					Part 2	Total (n=55)
	81 mg (n=5)	201 mg (n=9)	403 mg (n=4)	604 mg (n=4)	685 mg (n=3)	685 mg (n=30)	
Any adverse event	5 (100)	9 (100)	4 (100)	4 (100)	3 (100)	30 (100)	55 (100)
DLTs	0	1 (11.1)	0	0	0	0	1 (1.81)
SAEs	4 (80.0)	5 (55.6)	3 (75.0)	3 (75.0)	0	19 (60.0)	34 (61.8)
Deaths	1 (20.0)	0	0	2 (50.0)	0	10 (33.3)	13 (23.6)
AEs leading to study drug discontinuation	2 (40.0)	2 (22.2)	1 (25.0)	2 (50.0)	0	9 (30.0)	16 (29.1)
AEs leading to dose reduction	0	0	0	0	1 (33.3)	7 (23.3)	8 (14.5)
Most common grade ≥ 3 adverse events^{a)} ($\geq 5\%$ of all patients)							
Hypertension	1 (20.0)	3 (33.3)	2 (50.0)	1 (25.0)	0	11 (36.7)	18 (32.7)
Hyponatremia	0	1 (11.1)	0	1 (25.0)	1 (33.3)	3 (10.0)	6 (10.9)
Hypophosphatemia	0	1 (11.1)	0	1 (25.0)	1 (33.3)	3 (10.0)	6 (10.9)
Cancer progression	0	1 (11.1)	0	1 (25.0)	0	2 (6.7)	4 (7.3)
Palmar-plantar erythrodysesthesia syndrome	0	0	0	0	1 (33.3)	3 (10.0)	4 (7.3)
Blood bilirubin increased	0	0	0	0	0	4 (13.3)	4 (7.3)
Hypocalcemia	0	1 (11.1)	0	0	0	2 (6.7)	3 (5.5)
Hypokalemia	0	0	0	0	0	3 (10.0)	3 (5.5)
Syncope	0	2 (22.2)	0	0	0	1 (3.3)	3 (5.5)
Dyspnea	1 (20.0)	0	0	0	0	2 (6.7)	3 (5.5)

Values are presented as number (%). AE, adverse event; DLT, dose-limiting toxicity; SAE, serious adverse event. ^{a)}Grade 5 events consisted of gastric obstruction (n=1), acute cholangitis (n=1), anal abscess (n=1), cancer progression (n=3), tumor hemorrhage (n=1), acute renal failure (n=1), dyspnea (n=1), pleuritic pain (n=1), and pneumonitis (n=2). All patients were receiving 685 mg except one patient with cancer progression (604 mg) and two patients with pneumonitis (81 mg and 685 mg).

3, blood samples were collected before and after dosing on days 1, 8 and 15. Plasma concentrations of rivoceranib and its metabolites (M1-1, M1-2, M1-6, and M9-2) were analyzed.

7. Pharmacodynamics

In parts 1 and 2, pharmacodynamic assessments included plasma concentrations of VEGF, phosphatidylinositol-glycan biosynthesis class F-protein (PIGF), soluble Flt-1 (sVEGFR-1), soluble VEGFR-2 (sVEGFR-2), soluble VEGFR-3 (sVEGFR-3), Tie 2, and vascular cell adhesion molecule 1. All patients were also evaluated at screening for single nucleotide polymorphisms that may provide genotypes that correlate with response to VEGFR-2 inhibition therapy. Levels of VEGF were evaluated at baseline, on day 35 in part 1, on day 56 in part 2, and after each subsequent two 28-day cycles of therapy and at the final study visit. Pharmacodynamic parameters were not assessed in part 3.

8. Statistical methods

The planned sample size for the initial study was 48 patients (up to 18 in part 1 and 30 in part 2). Safety was analyzed in patients who received ≥ 1 dose of rivoceranib. Patients who discontinued treatment prior to the DLT evalu-

ation period were replaced per dose escalation rules in this study. Efficacy was analyzed in patients who had imaging scans taken and completed the study visits through the final day of dosing (every two 28-day cycles of therapy). All statistical analyses were performed using the SAS ver. 9.1.3 (SAS Institute Inc., Cary, NC).

In part 3, six patients were to be enrolled. Safety and efficacy were evaluated in all patients who received at least one dose of rivoceranib.

Results

A total of 25 patients were enrolled in part 1 and 30 patients were enrolled in part 2. All patients were either white (45.5%) or Asian (54.5%) (Table 1). Most patients were male (65.5%). The most common tumor types were gastric cancer (n=20) and colorectal cancer (n=10). In part 1, the numbers of patients enrolled and treated in each rivoceranib dose cohort were as follows: 81 mg (n=5), 201 mg (n=9), 403 mg (n=4), 604 mg (n=4), and 685 mg (n=3). In part 2, all 30 patients received at least one dose of rivoceranib 685 mg. In part 3, six patients were enrolled and received at least one dose of study drug.

Table 3. Parts 1 and 2: tumor responses

Best overall response ^{a)}	Part 1					Part 2	All patients
	81 mg (n=3)	201 mg (n=5)	403 mg (n=4)	604 mg (n=3)	685 mg (n=3)	685 mg (n=28)	(n=46)
ORR ^{b)}	0	2 (40.0)	1 (25.0)	0	1 (33.3)	3 (10.7)	7 (15.2)
PR	0	2 (40.0)	1 (25.0)	0	1 (33.3)	3 (10.7)	7 (15.2)
SD	0	2 (40.0)	3 (75.0)	2 (66.7)	1 (33.3)	24 (85.7)	32 (69.6)
PD	3 (100)	1 (20.0)	0	1 (33.3)	1 (33.3)	1 (3.6)	7 (15.2)
DCR ^{c)}	0	4 (80.0)	4 (100)	2 (66.7)	2 (66.7)	27 (96.4)	39 (84.5)

CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. ^{a)}Best overall response assessed following continuation therapy, ^{b)}ORR=CR+PR, ^{c)}DCR=CR+PR+stable disease as the best overall response.

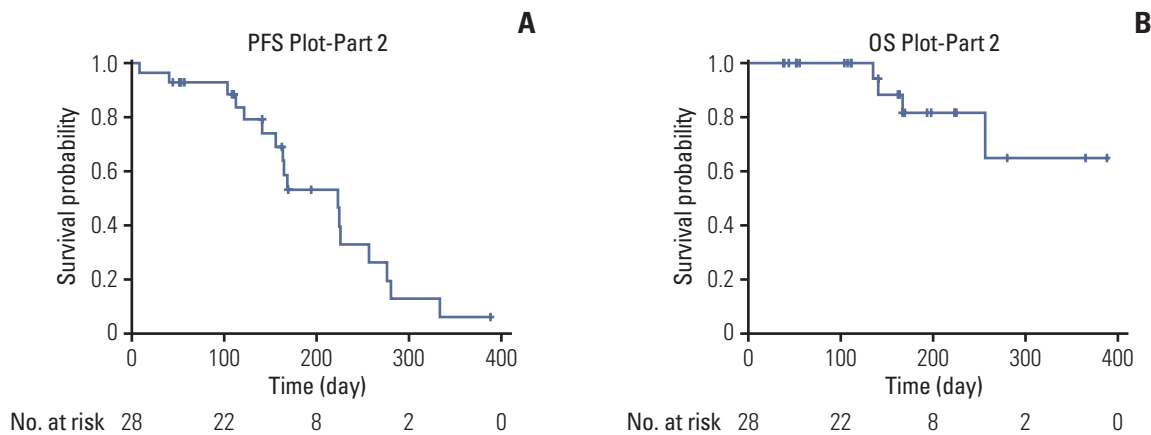


Fig. 1. Parts 1 and 2 combined. Kaplan-Meier estimates of progression-free survival (PFS) (A) and overall survival (OS) (B) in the efficacy analysis set.

All patients in part 3 were male, Asian, and had gastric cancer (S2 Table).

1. Safety

Drug exposure was based on patient-reported compliance. In parts 1 and 2 combined, the average compliance, calculated as the ratio of the total dose received to the total dose planned over all cycles of therapy, was 83.8% (range, 12.5% to 204.1%). One patient had >100% compliance due to a dose increase from the originally planned dose. For part 2 alone in which all patients received 685 mg, average compliance was 80.3% (range, 50.0% to 100%).

In parts 1 and 2, an AE of any grade was observed in all patients (Table 2, S3 Table). The most common grade ≥ 3 AEs included hypertension (32.7%), hyponatremia (10.9%), and hypophosphatemia (10.9%). The most common treatment-related grade ≥ 3 AEs included hypertension (32.7%), palmar-plantar erythrodysesthesia (7.3%), hypokalemia (5.5%), and hypophosphatemia (5.5%) (S4 Table). Two grade 4 treat-

ment-related AEs occurred (malignant hypertension and hyponatremia), both of which resolved upon interruption or withdrawal of study drug. One grade 5 treatment-related AE occurred, consisting of tumor hemorrhage in a patient receiving the 685 mg dose in part 2. AEs leading to study drug discontinuation were reported in 16 patients (29.1%) (S5 Table). Those occurring in >1 patient were fatigue (n=2), pneumonitis (n=2), gastric tumor bleeding (n=2), and disease progression (n=2). Thirteen deaths (23.6%) occurred among patients enrolled in parts 1 (n=3) and 2 (n=10); three deaths were associated with cancer progression.

In part 3, two patients experienced DLTs with the 805 mg dose, all of which were grade 3 severity and resolved: one patient had febrile neutropenia and one patient developed decreased appetite and fatigue. Four patients experienced serious AEs consisting of the following events: cholecystitis (n=2), acute cholecystitis (n=1), decreased appetite (n=1), fatigue (n=1), febrile neutropenia (n=1), gastric ulcer (n=1), and intracardiac thrombus (n=1).

2. Efficacy

In parts 1 and 2 combined, 46 patients were evaluable for efficacy. Nine patients were not included in the efficacy evaluation due to AE (n=3), death (n=3), disease progression (n=2), or withdrawal due to physician decision (n=1). The ORR was 15.2% (7 of 46 evaluable patients); the ORR for part 2 was 10.7% (3 of 28 evaluable patients). Responses were observed at various dose levels: 201 mg (n=2), 403 mg (n=1), 685 mg (n=1) for part 1 and 685 mg (n=3) for part 2 (Table 3). The DCR was 96.4% in part 2. Median progression-free survival (PFS) ranged from 1.9 months to 9.4 months across dose levels in part 1 and was 7.3 months in part 2 (Fig. 1A, part 2). Median overall survival was not reached (Fig. 1B, part 2). Kaplan-Meier plots of PFS and overall survival for part 2 are shown in Fig. 1.

In part 3, three out of the six patients were excluded from the efficacy analysis due to the occurrence of a serious AE and DLT before the first efficacy evaluation. Of the three remaining patients, one experienced a partial response, resulting in an ORR of 33%. One patient had progressive disease at the first efficacy evaluation (8 weeks) and the remaining patient had stable disease at the first efficacy evaluation and progressive disease at the second efficacy evaluation (16 weeks).

3. Pharmacokinetics

The pharmacokinetic parameters for parts 1 and 2 are detailed in the Supplementary Material (S6 and S7 Tables). Briefly, following single-dose administration of 81 mg to 685 mg of rivoceranib, maximum concentration (C_{max}) increased with increasing dose and ranged from 80.4 ng/mL to 595 ng/mL. Median time to peak concentration (T_{max}) was consistent across doses and ranged from 1.98 hours to 4.03 hours. Median half-life ($T_{1/2}$) showed an inconsistent trend across doses and ranged from 6.57 hours to 13.9 hours. Mean area under the curve from time 0 to 24 hours (AUC_{0-24}) increased with increasing dose, ranging from 515 hr·ng/mL to 5,400 hr·ng/mL. Mean AUC from time 0 to infinity ($AUC_{0-\infty}$) also increased with increasing dose, ranging from 604 hr·ng/mL to 7,350 hr·ng/mL.

Following multiple-dose administration of 81 mg to 685 mg of rivoceranib, mean C_{max} variability across dose levels decreased on day 35 (mean CV% of xx%) compared to day 1 (mean CV% of yy%). Mean C_{max} ranged from 77.1 ng/mL to 647 ng/mL. Median T_{max} was consistent across doses, which was comparable to single-dose administration, with levels ranging from 2.00 hours to 4.00 hours. Mean $T_{1/2}$ again demonstrated an inconsistent trend across doses, with levels ranging from 8.69 hours to 27.2 hours. Estimates for $AUC_{0-\infty}$ are not adequate as the plasma concentration time curve was only characterized up to 24 hours post-dose. Mean apparent oral clearance (CL/F) did not show a clear trend with dose.

Rivoceranib and metabolite concentrations in part 3 can be found in the appendix (S8 Table).

4. Pharmacodynamics

In part 2, from baseline to day 56, plasma levels of soluble VEGFR (sVEGFR)-1 (Flt-1) decreased by 20%; sVEGFR-2 decreased by 37%; sVEGFR-3 decreased by 73%; VEGF increased by 43%; PIGF increased approximately 5-fold; soluble vascular cell adhesion molecule-1 increased by 13%, and angiotensin-1 receptor (TIE2) increased by 4% (S9 Table). The numbers of patients in each dose level of part 1 were too small to draw conclusions with respect to pharmacodynamics and pharmacodynamics were not assessed in part 3.

Discussion

Rivoceranib dosed from 81 to 685 mg was generally well-tolerated, with most AEs similar to those seen in prior studies. Rivoceranib showed promising antitumor efficacy, with an ORR of 15.2% in all patients and 12.1% in patients who received 685 mg (i.e., 4/33). A median PFS of 7.3 months and DCR of 96.4% were achieved in part 2. Part 3 demonstrated DLTs in two out of six patients receiving rivoceranib 805 mg evaluated for efficacy. Based on these results, the recommended phase 2 dose from this study was proposed as 685 mg once daily.

Ramucirumab is currently the only VEGFR2 antibody approved for treatment of advanced gastric cancer outside of China. The efficacy results we observed with rivoceranib appeared to be favorable when viewed in context of the pivotal ramucirumab trial. The phase 3 REGARD trial evaluated ramucirumab monotherapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma previously treated with one line of therapy (n=355) [5]. In the REGARD trial, ramucirumab demonstrated a median PFS of 2.1 months versus 1.3 months with placebo and the ORR was 3% in both arms. In the REGARD trial, the rate of grade ≥ 3 hypertension was 8%. In our study, the most common treatment-related grade ≥ 3 AE of hypertension occurred in 32.7% of patients, indicating a need to remain vigilant in managing this side effect. Note that anti-VEGFR therapy-related AEs (e.g., hypertension) due to rivoceranib may be easier to manage compared to those due to ramucirumab because of a relatively shorter half-life of rivoceranib (~15 days vs. < 14 hours).

A strength of our trial was that it was the first study to evaluate rivoceranib in Asian and white patients, which provides pharmacokinetic, pharmacodynamic, safety, and efficacy data in populations not previously studied. Nevertheless, further evaluation in broader patient populations

will be required in future studies to fully characterize these aspects of rivoceranib. This phase 1/2a study was intentionally small to carefully evaluate the safety of rivoceranib in these patient populations. As such, this study is limited in sample size and larger controlled studies are needed to confirm the safety and efficacy of rivoceranib in patients with advanced gastric cancer.

Based on the results of this early study, rivoceranib 685 mg represents a candidate for future investigation in patients with malignant solid tumors including non-small cell lung cancer, colorectal cancer, gastric cancer, neuroendocrine tumor, or mesothelioma. There are currently no orally administered VEGFR2 TKIs approved for the treatment of advanced gastric cancer outside of China. An oral treatment option would increase convenience and decrease costs for both patients and health systems. Further investigation of rivoceranib is underway for the treatment of multiple tumor types, including gastric cancer, hepatocellular carcinoma, adenoid cystic carcinoma, and colorectal cancer [11-14].

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (<https://www.e-crt.org>).

Ethical Statement

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. The protocol was reviewed by institutional review boards (IRB_00054643) or ethics committees at each institution. All patients provided written informed consent.

Author Contributions

Conceived and designed the analysis: Park CH, Jang S, McGinn A.

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Conflicts of Interest

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