Phase 1b/2 Open-label Study to Evaluate the Safety, Tolerability, and Efficacy of Rivoceranib plus Trifluridine/Tipiracil in Patients with Previously Treated Metastatic Colorectal Cancer

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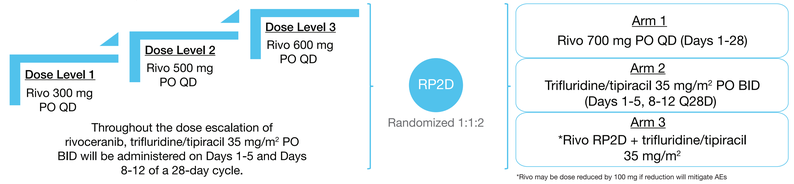
BACKGROUND

- Colorectal cancer (CRC) is the third most frequent cancer with approximately 25% of patients presenting with metastases at initial diagnosis and 50% developing metastases during their disease course.[1,2,3]
- First-line treatment of metastatic CRC (mCRC) involves treatment with 5-fluorouracil (5-FU) and either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) used in combination with a monoclonal antibody (mAb) against vascular endothelial growth factor receptors (VEGFR) or epidermal growth factor receptor (EGFR).[3]
- In patients refractory to an irinotecan-based regimen, second-line treatment must consist of an oxaliplatin-containing combination (FOLFOX and CAPOX). In patients refractory to FOLFOX or CAPOX, an irinotecan-based regimen is proposed as second-line treatment.[3]
- Trifluridine/tipiracil is an oral combination approved for third-line treatment of mCRC based on demonstrated efficacy in 5-FU-refractory patients.[4]
- Rivoceranib is a novel oral tyrosine kinase inhibitor that potently and selectively inhibits VEGFR-2 and has been shown to enhance the efficacy of chemotherapy.[5]
- This multicenter, open-label, phase 1b/2 trial (NCT04073615) is evaluating the safety, tolerability, and efficacy of rivoceranib monotherapy, trifluridine/tipiracil monotherapy and the combination of rivoceranib and trifluridine/tipiracil in patients with mCRC. Herein, we present results from the phase 1b portion of the trial.

METHODS

- In phase 1b of the study, a 3+3+3 dose-escalation was conducted to identify the recommended phase 2 dose (RP2D) of rivoceranib to be used in combination trifluridine/tipiracil. The phase 2 portion will evaluate rivoceranib monotherapy, trifluridine/tipiracil monotherapy, and the rivoceranib RP2D in combination with trifluridine/tipiracil in patients with mCRC.

Figure 1: Study Schema



*Rivo may be dose reduced by 100 mg if reduction will mitigate AEs

DL, dose level; DLT, dose limiting toxicity; mCRC, metastatic colorectal cancer; Rivo, rivoceranib; PO, by mouth; Q28D, every 28 days; QD, once daily; RP2D, recommended phase 2 dose.

Key Inclusion Criteria

- Men or women ≥ 18 years of age
- Histologically or cytologically confirmed diagnosis of mCRC
- Failure to respond or be intolerant of ≥2 prior regimens of standard anti-cancer treatments (study treatment must be 3rd line or greater for mCRC)
  - Subjects who had received adjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant chemotherapy would be considered as 1 prior line of therapy
- Progressed based on imaging during or within 3 months of the last administration of most recent therapy
- Measurable disease as defined by RECIST v1.1
- ECOG performance status of 0 or 1

ECOG, Eastern Cooperative Oncology Group; mCRC, metastatic colorectal cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Endpoints

Phase 1b

Primary:
- Incidence of DLTs during first 28-day cycle
- Safety

Secondary:
- Overall survival
- Additional safety assessments

Phase 2

Primary:
- Progression free survival[a]

Secondary:
- Overall survival
- Overall response rate[a]
- Duration of response[a]
- Time to progression[a]
- Disease control rate[a]
- Safety

[a]Per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by investigator assessment.
DLT, dose limiting toxicity.

RESULTS

PATIENTS

- As of July 2023, 29 patients received treatment with rivoceranib 300 mg (n=7), 400 mg (n=7), 500 mg (n=8), and 600 mg (n=7) in phase 1b.

Table 1: Baseline Characteristics (Intent-to-Treat Population)

Characteristic	Rivoceranib (N=29)
Median age, years (range)	54.0 (30, 80)
Male, n (%)	16 (55.2)
Race, n (%)	
Asian	1 (3.4)
Black or African American	1 (3.4)
White	25 (86.2)
Native Hawaiian or Other Pacific Islander	0
Other	2 (6.9)
ECOG PS 0, n (%)	16 (55.2)
Prior systemic therapy, n (%)	29 (100.0)
Previous number of lines (range)	(1,6)
Prior monoclonal antibody	
Bevacizumab	28 (96.6)
Panitumumab	12 (41.4)
Cetuximab	5 (17.2)
Bevacizumab biosimilar	2 (6.9)
Ipilimumab	1 (3.4)
Nivolumab	1 (3.4)
Ramucirumab	1 (3.4)
Prior chemotherapy	29 (100.0)

ECOG PS, Eastern Cooperative Oncology Group performance status; VEGFR, Vascular endothelial growth factor receptor.

SAFETY

- Seven patients experienced dose-limiting toxicities (DLTs) at various rivoceranib dose levels: 300 mg (n=1), 500 mg (n=2), 600 mg (n=4). No DLTs occurred at the rivoceranib 400 mg dose level (**Table 2**).

Table 2: Dose Limiting Toxicities During the First 28-Day Cycle (Safety Population)

DLT, n (%)	300 mg (n=7)	400 mg (n=7)	500 mg (n=8)	600 mg (n=7)	Total (N=29)
Any DLT	1 (14.3)	0	2 (25.0)	4 (57.1)	7 (24.1)
Neutropenia	0	0	1 (12.5)	1 (14.3)	2 (6.9)
Thrombocytopenia	1 (14.3)	0	0	0	1 (3.4)
Diarrhea	0	0	0	1 (14.3)	1 (3.4)
Nausea	0	0	1 (12.5)	0	1 (3.4)
Fatigue	0	0	0	2 (28.6)	2 (6.9)
Asthenia	0	0	0	1 (14.3)	1 (3.4)
Ventricular arrhythmia	1 (14.3)	0	0	0	1 (3.4)
Lymphocyte count decreased	1 (14.3)	0	0	0	1 (3.4)
Decreased appetite	0	0	0	1 (14.3)	1 (3.4)
Proteinuria	0	0	0	1 (14.3)	1 (3.4)
Hypertension	0	0	1 (12.5)	0	1 (3.4)

- The most common treatment-emergent adverse events (TEAEs) related to the combination of rivoceranib and trifluridine/tipiracil were nausea, vomiting, and diarrhea (**Table 3**).
- The most common grade ≥ 3 TEAEs related to the combination of rivoceranib and trifluridine/tipiracil were neutropenia, hypertension, and leukopenia (**Table 4**).
- No grade 5 TEAEs related to the combination of rivoceranib and trifluridine/tipiracil occurred.

DLT, dose level toxicity

Table 3: Most Common (>20%) TEAEs Related to the Combination of Rivoceranib and Trifluridine/Tipiracil: All Patients

Event, n (%)	300 mg (n=7)	400 mg (n=7)	500 mg (n=8)	600 mg (n=7)	Total (N=29)
Nausea	5 (71.4)	5 (71.4)	5 (62.5)	5 (71.4)	20 (69.0)
Fatigue	5 (71.4)	5 (71.4)	5 (62.5)	5 (71.4)	20 (69.0)
Neutropenia	3 (42.9)	4 (57.1)	3 (37.5)	4 (57.1)	14 (48.3)
Diarrhea	3 (42.9)	2 (28.6)	4 (50.0)	3 (42.9)	12 (41.4)
Hypertension	2 (28.6)	1 (14.3)	6 (75.0)	3 (42.9)	12 (41.4)
Vomiting	2 (28.6)	4 (57.1)	4 (50.0)	1 (14.3)	11 (37.9)
Decreased appetite	2 (28.6)	3 (42.9)	3 (37.5)	3 (42.9)	11 (37.9)
Leukopenia	1 (14.3)	2 (28.6)	0	4 (57.1)	7 (24.1)
Proteinuria	0	0	2 (25.0)	4 (57.1)	6 (20.7)

TEAEs, treatment-emergent adverse events

Table 4: Most Common (>10%) Grade ≥3 TEAEs Related to the Combination of Rivoceranib and Trifluridine/Tipiracil

Event, n (%)	300 mg (n=7)	400 mg (n=7)	500 mg (n=8)	600 mg (n=7)	Total (N=29)
Neutrophil count decreased	3 (42.9)	3 (42.9)	3 (37.5)	4 (57.1)	13 (44.8)
Hypertension	1 (14.3)	1 (14.3)	3 (37.5)	2 (28.6)	7 (24.1)
White blood cell count decreased	1 (14.3)	1 (14.3)	0	2 (28.6)	4 (13.8)
Fatigue	0	1 (14.3)	2 (25.0)	0	3 (10.3)
Neutropenia	0	1 (14.3)	1 (12.5)	1 (14.3)	3 (10.3)

TEAEs, treatment-emergent adverse events

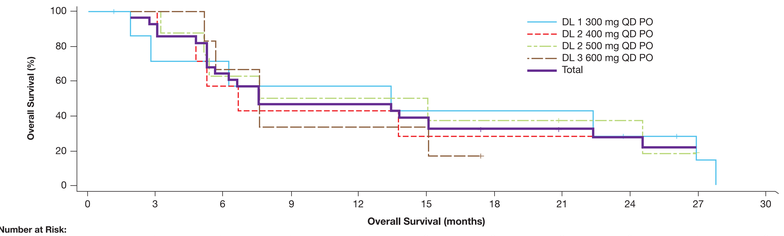
EFFICACY

- Median overall survival (mOS) at rivoceranib 300 mg and 500 mg dose levels were 13.4 months and 11.3 months, respectively (**Table 5**).
- mOS at the rivoceranib 400 mg dose level was 6.7 months with a 12-month OS rate of 42.9% (**Table 5, Figure 2**).

Table 5: Efficacy Results (Intent-to-Treat Population)

	300 mg (n=7)	400 mg (n=7)	500 mg (n=8)	600 mg (n=7)	Total (N=29)
ORR, n (%)	0	0	1 (12.5)	0	1 (3.4)
BOR per RECIST v1.1					
PR, n (%)	0	0	1 (12.5)	0	1 (3.4)
SD, n (%)	4 (57.1)	5 (71.4)	4 (50.0)	1 (14.3)	14 (48.3)
PD, n (%)	2 (28.6)	1 (14.3)	3 (37.5)	4 (57.1)	10 (34.5)
NE, n (%)	1 (14.3)	1 (14.3)	0	2 (28.6)	4 (13.8)
mPFS, mo (95% CI)	3.9 (0.9, 8.3)	4.2 (1.8, NE)	3.6 (1.8, 14.6)	2.1 (1.2, NE)	3.5 (1.9, 6.0)
mOS, mo (95% CI)	13.4 (1.9, 26.9)	6.7 (3.1, NE)	11.3 (3.3, NE)	7.6 (5.2, NE)	7.6 (5.4, 15.1)
12 mo OS rate, % (95% CI)	57.1 (17.2, 83.7)	42.9 (9.8, 73.4)	50.0 (15.2, 77.5)	33.3 (4.6, 67.6)	46.4 (27.6, 63.3)

Figure 2: Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population)



Number at Risk:											
DL 1 300 mg QD PO	7	5	5	4	4	3	3	3	2	1	0
DL 2 400 mg QD PO	7	7	4	3	3	2	2	2	1	0	0
DL 2 500 mg QD PO	8	8	5	4	4	4	3	2	2	0	0
DL 3 600 mg QD PO	7	6	4	2	2	2	0	0	0	0	0
Total	29	26	18	13	13	11	8	7	5	1	0

DL, dose level

CONCLUSIONS

- Two patients experienced DLTs at rivoceranib 500 mg (dose level 2), and no patients experienced DLTs at the de-escalated dose of rivoceranib 400mg.
- Rivoceranib 400 mg PO QD is the RP2D to be used in combination with trifluridine/tipiracil 35 mg/m² PO BID in the phase 2 portion of the trial.
- Phase 2 will evaluate rivoceranib monotherapy, trifluridine/tipiracil monotherapy, and the rivoceranib 400 mg in combination with trifluridine/tipiracil in patients with mCRC.

DLTs, dose-limiting toxicities

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DISCLOSURES: Cathy Eng reports consulting/advisory roles for GlaxoSmithKline, Natera, Janssen Oncology, Merck Serono, Elevation Oncology, Seagen, Pfizer, Abbvie, Hookipa Biotech, Takeda. Cheol Hee Park, Xianzhang Meng, and Seong Jang report employment and stock options with Elevar Therapeutics.

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