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Phase I study to evaluate the safety and efficacy of rivoceranib (apatinib) and nivolumab in patients with unresectable or metastatic cancer

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BACKGROUND

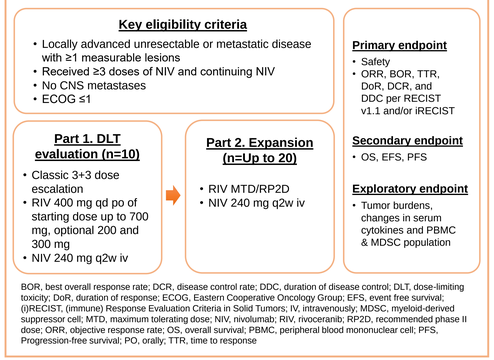
- Recently, clinical activities of anti-angiogenic tyrosine kinase inhibitors (TKIs) combined with immunotherapies have been demonstrated in multiple tumor types.
- Monotherapy of nivolumab (NIV), a PD-1 monoclonal antibody, has not shown a notable tumor response for sarcoma.[1,2]
- Rivoceranib (RIV), also known as apatinib in China, is a highly-selective TKI targeting VEGFR-2.[3]
- In China, based on a Phase III study, apatinib was approved for late-stage gastric cancer in 2014, and investigated for many other tumor types including non-small cell lung cancer and hepatocellular carcinoma.[4]
- Globally, clinical activities of RIV monotherapy is being investigated in a Phase III gastric cancer trial (ANGEL).[5]
- The potential benefit of RIV + NIV combination therapy has been demonstrated in preclinical murine lung carcinoma syngeneic models, in which the combination significantly increased anti-tumor activities of individual therapies.[6]
- Preliminary results of a Phase I study of RIV + NIV in subjects with unresectable / metastatic cancer is presented within this poster.

METHODS

Study Design

- This is an ongoing, open-label, phase I study of RIV + NIV in unresectable or metastatic cancer.
- Subjects who were tolerating at least 3 doses of NIV therapy received RIV in combination with NIV at 240 mg q2w iv.
- Dose-limiting toxicities (DLTs) were assessed during the first cycle for the evaluation of safety and tolerability of the combination therapy in Part 1.
- Once the Recommended Phase II Dose (RP2D) of RIV was determined, additional subjects were enrolled in Part 2.

Figure 1. Study Design of Phase I Study of RIV + NIV in Unresectable or Metastatic Cancer



BOR, best overall response rate; DCR, disease control rate; DDC, duration of disease control; DLT, dose-limiting toxicity; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFS, event free survival; (i)RECIST, (immune) Response Evaluation Criteria in Solid Tumors; IV, intravenously; MDSC, myeloid-derived suppressor cell; MTD, maximum tolerating dose; NIV, nivolumab; RIV, rivoceranib; RP2D, recommended phase II dose; ORR, objective response rate; OS, overall survival; PBMC, peripheral blood mononuclear cell; PFS, Progression-free survival; PO, orally; TTR, time to response

RESULTS

Baseline Characteristics

- 21 subjects were enrolled at the time of data cutoff, Feb 19, 2019.
- 12 subjects (3 in Part 1, and 9 in Part 2) are still undergoing study treatment.
- 9 subjects have discontinued treatment due to disease progression (n=5), adverse events (n=3), and death (n=1).

Table 1. Subject Baseline Characteristics

Parameter	RIV + NIV		
	Part 1 (n=10)	Part 2 (n=11)	Overall (n=21)
Sex, n (%)			
Male	4 (40.0)	6 (54.5)	10 (47.6)
Female	6 (60.0)	5 (45.5)	11 (52.4)
Median age, years (range)	51 (29-76)		
ECOG, n (%)			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	10 (100.0)	11 (100.0)	21 (100.0)
Race, n (%)			
White	8 (80.0)	11 (100.0)	19 (90.5)
Asian	2 (20.0)	0 (0.0)	2 (9.5)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Tumor types, n (%)			
Angiosarcoma	0 (0.0)	1 (9.1)	1 (4.8)
Cholangiosarcoma	1 (10.0)	0 (0.0)	1 (4.8)
Chondrosarcoma	1 (10.0)	2 (18.2)	3 (14.3)
Fibrous histiocytoma	1 (10.0)	0 (0.0)	1 (4.8)
Gastric cancer	1 (10.0)	1 (9.1)	2 (9.5)
Leiomyosarcoma	2 (20.0)	4 (36.4)	6 (28.6)
Liposarcoma	1 (10.0)	1 (9.1)	2 (9.5)
Malignant spindled and epithelioid sarcoma	1 (10.0)	0 (0.0)	1 (4.8)
Cervical cancer (squamous cell carcinoma)	1 (10.0)	0 (0.0)	1 (4.8)
Synovial sarcoma	1 (10.0)	2 (18.2)	3 (14.3)
Prior lines of therapy, n (%)			
≤ 1	2 (20.0)	4 (36.4)	6 (28.6)
2	3 (30.0)	0 (0.0)	3 (14.3)
3	3 (30.0)	4 (36.4)	7 (33.3)
4	2 (20.0)	3 (27.3)	5 (23.8)

ECOG, Eastern Cooperative Oncology Group; NIV, nivolumab; RIV, rivoceranib

Safety

- In the first 3 subjects who received 400 mg RIV starting dose in Part 1, 1 DLT was identified (hypertension) and 1 subject did not complete the DLT period.
- In the next 300 mg RIV dose level, 1 DLT was reported in 6 subjects: 300 mg RIV was determined as the RP2D.
- There was 1 fatal adverse event (pulseless electrical activity) during the study: 1 death was considered unrelated to the study treatments.
- There were no serious adverse events related to the study treatments.

Table 2. Summary of TEAEs

Parameter, n (%)	RIV + NIV		
	Part 1 (n=10)	Part 2 (n=11)	Overall (n=21)
TEAEs	10 (100.0)	11 (100.0)	21 (100.0)
Treatment-related TEAEs	10 (100.0)	8 (72.7)	18 (85.7)
TEAEs ≥ grade 3	5 (50.0)	3 (27.3)	8 (38.1)
Serious AEs	2 (20.0)	1 (9.1)	3 (14.3)
Fatal AEs	1 (10.0)	0 (0.0)	1 (4.8)
Dose modifications			
RIV or NIV dose interruptions due to AEs	6 (60.0)	3 (27.3)	9 (42.9)
RIV dose reductions due to AEs	3 (30.0)	3 (27.3)	6 (28.6)
Discontinuation of RIV or NIV due to AEs	3 (30.0)	1 (9.1)	4 (19.0)

AE, adverse event; NIV, nivolumab; RIV, rivoceranib; TEAE, treatment-emergent adverse event;

Table 3. Most Common TEAEs by Preferred Term and Grade*

Preferred term, n (%)	RIV + NIV (n=21)	
	Any grade	Grade ≥ 3
Hypertension	12 (57.1)	3 (14.3)
Headache	9 (42.9)	2 (9.5)
Blood TSH increased	7 (33.3)	0 (0.0)
Palmar-plantar erythrodysesthesia syndrome	7 (33.3)	0 (0.0)
Abdominal pain	6 (28.6)	2 (9.5)
Back pain	5 (23.8)	1 (4.8)
Nausea	5 (23.8)	0 (0.0)
Urinary tract infection	5 (23.8)	0 (0.0)
Fatigue	5 (23.8)	0 (0.0)
Diarrhea	4 (19.0)	0 (0.0)
Vomiting	4 (19.0)	0 (0.0)
Abdominal pain upper	3 (14.3)	0 (0.0)
Gingival pain	3 (14.3)	0 (0.0)
Lipase increased	2 (9.5)	1 (4.8)
Decreased appetite	2 (9.5)	0 (0.0)
Neutropenia	2 (9.5)	1 (4.8)
Constipation	2 (9.5)	0 (0.0)
Dysuria	2 (9.5)	0 (0.0)
Musculoskeletal stiffness	2 (9.5)	0 (0.0)
Arthralgia	2 (9.5)	0 (0.0)
Oropharyngeal pain	2 (9.5)	0 (0.0)

*Occurring in ≥2 subjects with an any-grade TEAE in the overall subject population.
NIV, nivolumab; RIV, rivoceranib; TEAE, treatment-emergent adverse event; TSH, thyroid-stimulating hormone

Efficacy

- 13 subjects who had at least 2 tumor scan measurements were included in the efficacy analysis set. Investigator assessment by RECIST was used in the following table and figures.
- A summary of tumor response is shown in **Table 4**.
- Tumor size changes from baseline are shown in **Figure 2** and **Figure 3**, respectively.
- An estimate of progression-free survival is shown in **Figure 4**. The median duration of progression-free survival has not been reached.

Table 4. Summary of Tumor Response

Parameter	RIV + NIV		
	Part 1 (n=8)	Part 2 (n=5)	Overall (n=13)
BOR, n (%)			
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	1 (12.5)	0 (0.0)	1 (7.7)
SD	6 (75.0)	4 (80.0)	10 (76.9)
PD	1 (12.5)	1 (20.0)	2 (15.4)
ORR, n (%)	1 (12.5)	0 (0.0)	1 (7.7)
DCR, n (%)	7 (87.5)	4 (80.0)	11 (84.6)

BOR, best overall response; CR, complete response; DCR, disease control rate; NIV, nivolumab; ORR, overall response rate; PD, progressive disease; PR, partial response; RIV, rivoceranib; SD, stable disease

Figure 2. Percentage Change from Baseline to Nadir in Sums of Diameters of Target Lesions

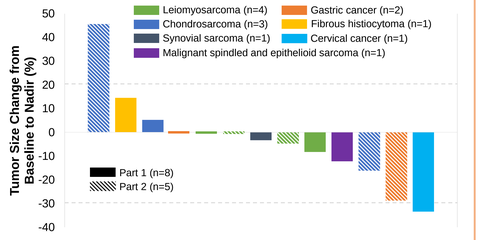


Figure 3. Percentage Change from Baseline in Sums of Diameters of Target Lesions Over Time

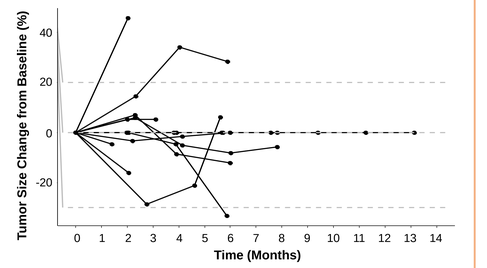
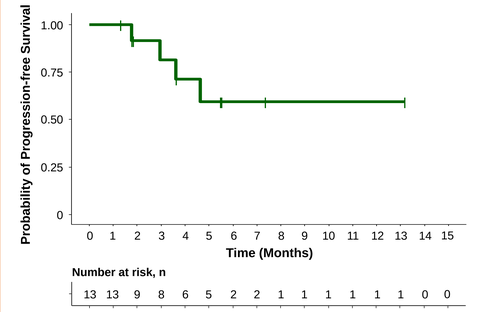


Figure 4. Kaplan-Meier Estimate of Progression-free Survival



CONCLUSIONS

- Preliminary results indicate the potential clinical benefit of a 300 mg of RIV starting dose in combination with 240 mg NIV in unresectable/metastatic solid tumors with a tolerable safety profile.
- Toxicities were manageable with dose modifications of RIV.
- Definite antitumor activity has been observed with the combination and the extent of response will be further investigated in Part 2 expansion period.
- The study will continue to enroll up to 20 subjects in Part 2 expansion period and will focus on Sarcoma subjects including angiosarcoma, leiomyosarcoma, synovial sarcoma, and alveolar soft part sarcoma.

References:

1. L. Pouluzzi, et al. *ASCO 2016.* Abstract #11047.
2. E. Ben-Ami, et al. *Cancer.* 123(17):3285-90, 2017.
3. S. Tian, et al. *Cancer Sci.* 102(7):1374-80, 2011.
4. J. Li, et al. *J Clin Oncol.* 34(13):1448-54, 2016.
5. Y-K. Kang, et al. *ASCO 2017.* Abstract #TPS4138.
6. B. Kim, et al. *AACR 2018.* Abstract #2756.

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