A phase Ib study of cetuximab combined with fruquintinib in the previously treated RAS/BRAF wild-type metastatic colorectal cancer: the preliminary result of CEFRU study

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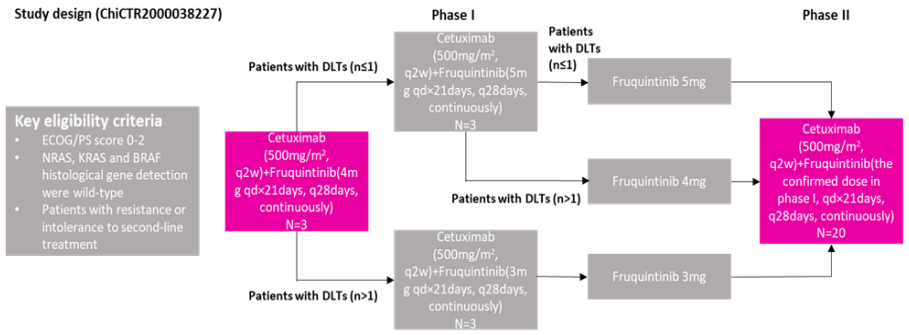
INTODUCTION

The standard third-line treatment of metastatic colorectal cancer (mCRC) is Regorafenib, Fruquintinib, or TAS-102. However, the efficacy was not satisfied. We conducted a phase Ib/IIa clinical study to evaluate the safety and efficacy of Fruquintinib combined with cetuximab in mCRC (TPS151, 2021 ASCO GI). This time we reported the results of phase Ib dose-escalation study.

METHODS

This is a single-center, non-random, prospective, dose-escalation (3 + 3 design), exploratory study. Eligible patients were diagnosed with advanced RAS/BRAF wild-type colorectal cancer and had received at least two prior treatment regimens. The starting dose of Fruquintinib was 4 mg once daily (qd) in a 28-day cycle (3 weeks on/1 week off) plus Cetuximab. If tolerable, Fruquintinib was escalated to 5 mg. If not tolerable, the Fruquintinib dose was reduced to 3 mg. The dose of Cetuximab is 500mg/m^2 every two weeks. 6-9 patients were involved in this study. Adverse events (AEs) were graded according to NCI-CTCAE v4.0. Drug limiting toxicities(DLTs) were evaluated in cycle 1. The response was assessed using RECIST v1.1 q8 wks. The purpose was to confirm the safety and to recommend the dose in phase II study (RP2D).



RESULTS

As of Feb 2021, 7 patients were enrolled. Three patients received Fruquintinib 4 mg and 4 received Fruquintinib 5 mg. One DLTs of grade 3 acneiform rash was observed in 1/3 patients at the 4 mg dose. Two DLTs with grade 3 hypertension and two DLTs with grade 3 proteinuria were confirmed at the 5 mg dose level in 3/4 patients. The RP2D was confirmed as Fruquintinib 4 mg QD (3 weeks on/1 week off) plus Cetuximab 500mg/m^2 every two weeks.

SAFETY

The most common treatment-related AEs were hypertension (3/7), proteinuria (3/7), acneiform rash (3/7), creatinine elevation (2/7), hypoproteinemia (2/7）, hemorrhinia (2/7) ,fatigue (2/7), anemia (2/7), elevated alkaline phosphatase(2/7), elevated aspartic transaminase (1/7) and dry skin (1/7) . Evaluation in 7 treated patients showed 4 cases were stable disease (SD) and 3 cases were progressive disease (PD)

Table 2. DLT in the phase Ib

Fruquintinib Dosing regimen	No. of pts enrolled	No. of pts with DLTs[a]
4mg	3	1 (grade 3 acneiform)
5mg	4	3 (2 with grade 3 hypertension and 2 with grade 3 proteinuria)

a: CTCAE grade for all DLTs was grade 3.

CONCLUSION

Cetuximab combined with Fruquintinib showed acceptable anti-tumor activity in CRC with resistance to at least two prior treatment regimens. No unexpected toxicities were observed.

No conflicts of interest to declare

Table1. Baseline characteristics

Characteristics	n or median (range)
Age, years, median (range)	62 (43–73)
Gender, n	
Female	5
Male	2
ECOG performance status, n	
0	2
1	5
Primary site	
Left ride	6 （ 2,rectal cancer; 2,sigmoid colon cancer; 1,descending colon cancer; 1, splenic flexure of colon cancer）
Right side	1 （1 ascending colon carcer）
Previous treatment, n	
Surgery	7
Radiotherapy	1
Systemic therapy	
Fluorouracil	7
Oxaliplatin	7
Irinotecan	7
Bevacizumab	6
Anti-EGFR antibody (cetuximab or panitumumab)	4
Median previous chemotherapy regimens, n (range)	3 (2–6)
Metastatic sites at screening, n	
1–2	3
≥3	4