Phase 1/1b Trial of Fruquintinib in Patients with Advanced Solid Tumors: Preliminary Results of the Dose Expansion Cohort in Refractory mCRC

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Abstract #2217

INTRODUCTION

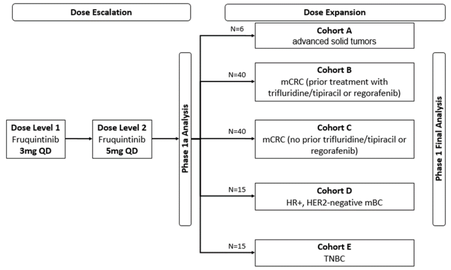
- Fruquintinib (HMPL-013) is a novel, potent and highly selective, oral vascular endothelial growth factor receptor (VEGFR) -1, -2, and -3 tyrosine kinase inhibitor.[1]
- Fruquintinib was approved in China for patients with refractory metastatic colorectal cancer (mCRC) in September 2018 based on results of the FRESCO trial (NCT02314819),[2] a phase 3 study in patients with refractory mCRC in the 3rd line or greater setting. Results showed fruquintinib significantly improved median overall survival (mOS) and median progression-free survival (mPFS) when compared to placebo:
  - mOS: 9.30 vs. 6.57 months (HR=0.65, p<0.001) (Primary Endpoint)
  - mPFS: 3.71 vs. 1.84 months (HR=0.26, p<0.001)
- A phase 1/1b dose-finding study was conducted in the US and is ongoing. Results of the dose escalation portion of this phase 1/1b study were previously reported and confirmed the established RP2D in the US with similar PK characteristics.[3]
- Here we report the efficacy and safety of fruquintinib in an expansion cohort (Cohort B) of the phase 1/1b study, which consists of US patients with advanced, refractory mCRC who progressed on all standard chemotherapies and relevant biologics and also progressed on or were intolerant to TAS-102 and/or regorafenib.

METHODS

- This is an ongoing phase 1/1b, open-label, dose escalation and dose expansion study to determine the safety, tolerability, and preliminary efficacy of fruquintinib in a US patient population (Figure 1).
- The primary objective of the dose escalation portion was to evaluate the safety and efficacy and to determine the RP2D of fruquintinib in US patients with refractory metastatic solid tumors.
- The primary objective of the dose expansion Cohort B was to evaluate the efficacy and safety of fruquintinib in patients with refractory mCRC.
- Eligible patients must have had ECOG PS 0-1; adequate organ function; and measurable disease per RECIST, version 1.1.
- Patients received fruquintinib 5 mg oral daily at a 3 week on/1 week off regimen, with a cycle length of 28 days.
- Adverse events were graded according to CTCAE, version 5.0.
- Tumor assessments were performed per RECIST 1.1.
- Three additional dose expansion cohorts are ongoing to further evaluate the efficacy and safety in patients with: Cohort C) refractory mCRC in the 3L+ setting who had not received either TAS-102 or regorafenib; Cohort D) refractory HR+/HER2- metastatic breast cancer; and Cohort E) refractory triple negative breast cancer (TNBC).
- Data analysis for this presentation was based on a data cut-off of 20 August 2020.

STUDY DESIGN

Figure 1. Study Design



Key Inclusion Criteria for Cohort B:

1) Histologically or cytologically documented adenocarcinoma of the colon or rectum.
2) Progression on all standard chemotherapy, at least 1 anti-VGEF biologic, and, if RAS wild-type, at least 1 anti-EGFR biologic. Patients must also have progressed on or been intolerant to with TAS-102 and/or regorafenib.

Key Exclusion Criteria for Cohort B:

1) Patients with VTE, PE, TIA, stroke or MI <6 months prior to enrollment.
2) GI bleed <3 months prior to enrollment; other bleed or major surgery <60 days prior to enrollment.
3) Systemic anti-neoplastic therapy, or any investigational therapy, within 4 weeks (or 5 half-lives for TKIs) of first dose.

RESULTS

Table 1. Patient Baseline Characteristics

Characteristic	N=34 n (%)
Age, years	
<65	22 (64.7)
≥65	12 (35.3)
Gender	
Male	17 (50.0)
Female	17 (50.0)
Race	
Caucasian	27 (79.4)
African American	3 (8.8)
Hispanic	2 (5.9)
Asian	2 (5.9)
ECOG	
0	14 (41.2)
1	20 (58.8)

Characteristic	N=34 n (%)
Primary Tumor Site	
Colon	26 (76.5)
Rectum	5 (14.7)
Colon and Rectum	3 (8.8)
Prior lines of therapy*	
Median (range)	5 (3-9)
≤3	7 (20.6)
4	10 (29.4)
5	5 (14.7)
≥6#	12 (35.3)
Prior TAS-102 / Regorafenib	
TAS-102	16 (47.1)
Regorafenib	8 (23.5)
Both TAS-102 & Rego	10 (29.4)

* 32 (94.1%) patients received bevacizumab with at least 1 line of therapy, and 11 (32.4) patients received at least 1 anti-EGFR antibody.

5 patients had 6 prior lines; 4 had 7 prior lines; 2 had 8 prior lines; and 1 had 9 prior lines.

EFFICACY

Table 2. Tumor Response

Tumor Assessment	N=31* n (%)
Complete Response	0 (0)
Partial Response	0 (0)
Stable Disease	25 (80.6)
Progressive Disease	6 (8.8)
Objective Response Rate	0 (0)
Disease Control Rate	25 (80.6)

* As of data cut-off, 31 of the 34 patients in Cohort B treated with fruquintinib had a post-baseline scan and received at least 3 months follow up or discontinued treatment early and were evaluable for tumor response (Table 1 and Figure 2).

Figure 2. Waterfall Plot of Best Tumor Response

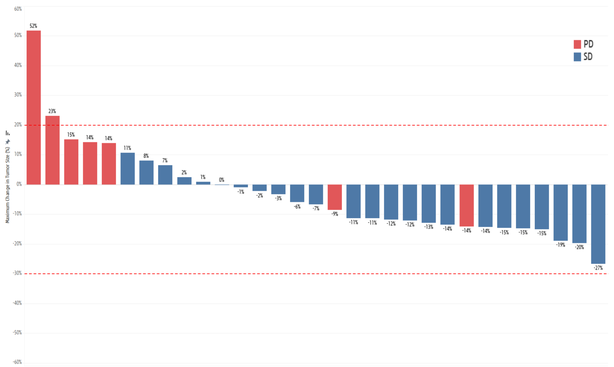
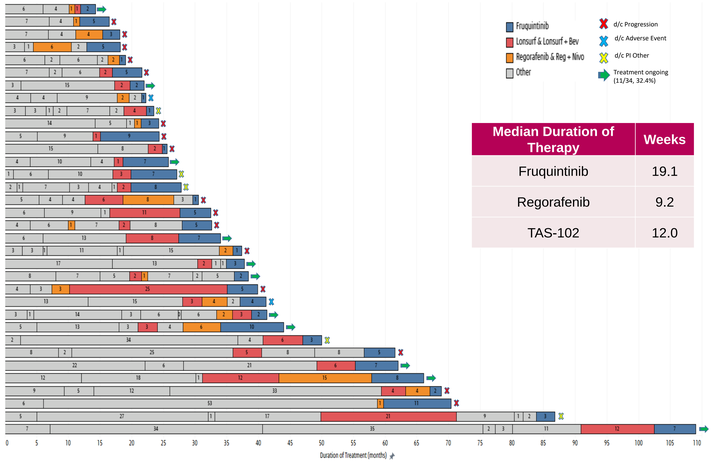


Figure 3. Number of Prior Therapies and Duration of Treatment



Median Duration of Therapy	Weeks
Fruquintinib	19.1
Regorafenib	9.2
TAS-102	12.0

SAFETY

Table 3. Overview of Treatment-Emergent Adverse Events

Overview of TEAEs	Fruquintinib (N=34) n (%)
Any TEAE	34 (100)
Any TEAE of Grade ≥ 3	27 (79.4)
Any TEAE leading to death	0 (0)
Any TEAE leading to dose interruption or reduction†	14 (41.2)
Any TEAE leading to discontinuation‡	3 (8.8)
Any related TEAE	31 (91.2)

† TEAEs resulting in dose delays / reduction were: Hypertension (3 patients); fatigue (2 patients), PPE syndrome (2 patients); Lymphocyte decreased (1 patient), Proteinuria (1 patient), Stomatitis (1 patient), Altered mental status (1 patient).

‡ 1 patient with Biliary obstruction; 1 patient with Bilirubin increase; and 1 patient with Worsening abdominal pain.

Table 4. TEAEs in ≥15% of Patients or ≥5% Grade 3

TEAEs (≥15% or Gr3 ≥5%)	Fruquintinib (N=34) n (%)		
	Grade 1-2	Grade 3-4	Total
Hypertension	5 (14.7)	11 (23.4)	10 (38.5)
Diarrhea	13 (38.2)	2 (5.9)	15 (44.1)
Proteinuria	13 (38.2)	2 (5.9)	15 (44.1)
Fatigue	10 (29.4)	2 (5.9)	12 (35.3)
Headache	11 (32.4)	-	11 (32.4)
PPE syndrome	10 (29.4)	1 (2.9)	11 (32.4)
Dysphonia	10 (29.4)	-	10 (29.4)
Abdominal pain	4 (11.8)	5 (14.7)	9 (26.5)
ALP increased	6 (17.6)	2 (5.9)	8 (23.5)
Constipation	8 (23.5)	-	8 (23.5)
Decreased appetite	8 (23.5)	-	8 (23.5)
Nausea	7 (20.6)	6 (17.6)	8 (23.5)
AST increased	7 (20.6)	-	7 (20.6)
Urinary tract infection	6 (17.6)	1 (2.9)	7 (20.6)
INR increase	6 (17.6)	-	6 (17.6)
Lymphocyte count decreased	5 (14.7)	1 (2.9)	6 (17.6)
Stomatitis	5 (14.7)	1 (2.9)	6 (17.6)
Weight decreased	6 (17.6)	-	6 (17.6)
Hyponatraemia	1 (2.9)	3 (8.8)	4 (11.8)
Pneumonia	-	2 (5.9)	2 (5.9)

CONCLUSIONS

- Fruquintinib was generally well-tolerated with preliminary evidence of anti-cancer activity in patients with heavily pretreated, refractory mCRC.
- The disease control rate in evaluable patients was 80.6%.
- The safety profile was consistent with that seen in the FRESCO trial, and the incidence of ≥Gr3 PPE syndrome was less than that observed with other VEGF TKIs.
- Median duration of treatment was 19.1 weeks, and dose reduction/delay and discontinuation occurred in 41.2% and 8.8% of patients, respectively.
- Enrollment to expanded cohorts in patients with refractory mCRC in the 3L+ setting and in patients with refractory metastatic breast cancer is ongoing.

DISCLOSURES

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