Phase 1/1b trial of fruquintinib in patients with advanced solid tumors: preliminary results of the dose expansion cohorts in refractory metastatic colorectal cancer

Arvind Dasari, MD, MS[1], Joleen M Hubbard, MD[2], Cathy Eng, MD[3], Heather Yeckes-Rodin, MD[4], Stacey M. Ukrainskyj, BSN[5], Zhao Yang, PhD[5], William R. Schelman, MD, PhD[5], Marek Kania, MD, MBA[5], Tanios S. Bekaii-Saab, MD[6]

[1]MD Anderson Cancer Center, Houston, TX, USA, [2]Department of Oncology, Mayo Clinic, Rochester, MN, USA; [3]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [4]Hematology Oncology Associates of the Treasure Coast, Port St. Lucie, FL, USA; [5]Clinical Development Department, HUTCHMED International, Florham Park, NJ, USA; [6]Medical Oncology Department, Mayo Clinic Cancer Center, Phoenix, AZ, USA

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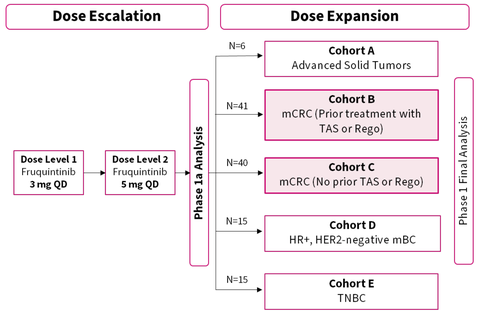
INTRODUCTION

- 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]
- Based on the results of the randomized, placebo-controlled Phase III FRESCO trial (NCT02314819) in patients with refractory mCRC (3rd line or greater), fruquintinib was approved in China in September 2018.[2] Results (fruquintinib arm vs placebo arm) showed:
  - mOS: 9.3 vs 6.6 months (HR=0.65, p<0.001) (Primary Endpoint)
  - mPFS: 3.7 vs. 1.8 months (HR=0.26, p<0.001)
- Here we report the preliminary efficacy and safety of fruquintinib in 2 cohorts of patients with refractory mCRC in and an ongoing Phase 1/1b study being conducted in the US.

STUDY DESIGN

- This is a Phase 1/1b dose escalation and expansion study investigating the safety, efficacy and pharmacokinetics (PK) of fruquintinib in US patients (NCT03251378) (Figure 1).
- The primary endpoint in the dose expansion portion was investigator-assessed progression-free survival (PFS), and the secondary endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DoR), OS and safety.
- Eligible patients must have had ECOG PS 0-1, adequate organ function, and measurable disease per RECIST v1.1. In addition:
  - Patients in Cohort B had progressed on all standard therapies and must have progressed on, or had intolerable toxicity to, TAS-102 [TAS] and/or regorafenib [Rego]).
  - Patients in Cohort C had progressed on, or had intolerable toxicity to, at least 2 prior regimens of standard chemotherapy, but must not have received TAS or Rego.
- Patients received fruquintinib 5 mg orally daily on a 3 weeks on/1 week off regimen, with a cycle length of 28 days.
- Tumor assessments were performed per RECIST v1.1.
- Data cutoff for analyses was 03 September 2021.

Figure 1: Study Schema



HER2=human epidermal growth factor 2; HR+=hormone receptor positive; mBC=metastatic breast cancer; mCRC=metastatic colorectal cancer; QD=once a day; Rego=regorafenib; TAS=TAS-102; TNBC=triple negative breast cancer

RESULTS

Table 1: Demographics and Baseline Characteristics (Safety Analysis Set)

	Cohort B (N=41)	Cohort C (N=40)
Age group, n (%)		
<65 years	27 (65.9)	30 (75.0)
≥65 years	14 (34.1)	10 (25.0)
Gender, n (%)		
Male	21 (51.2)	24 (60.0)
Female	20 (48.8)	16 (40.0)
Race, n (%)		
Caucasian	33 (80.5)	33 (82.5)
African American	4 (9.8)	4 (10.0)
Asian	1 (2.4)	3 (7.5)
Other	3 (7.3)	0
Baseline ECOG PS, n (%)		
0	15 (36.6)	18 (45.0)
1	26 (63.4)	22 (55.0)
Prior therapies, median (range)	5 (3-9)*	4 (1-10)
Prior TAS-102 or Regorafenib, n (%)		
TAS-102	19 (46.3)	-
Regorafenib	8 (19.5)	-
Both TAS-102 and Regorafenib	14 (34.1)	-

ECOG PS= Eastern Cooperative Oncology Group performance status
*2 patients in Cohort B did not receive prior bevacizumab

- Patients in the Safety Analysis Set received ≥1 dose of study drug.
- 22 patients (6 patients in Cohort B and 16 patients in Cohort C) are ongoing in the study.
- Patient disposition: Primary reasons for discontinuation in Cohort B versus (vs) Cohort C were death or progressive disease [30 (73.2%) vs 20 (50%)], withdrawal of patient consent, loss to follow-up [5 (12.2%) vs 2 (5%)].

Table 2: Efficacy Analysis

	Cohort B (N=41)	Cohort C (N=40)
Best overall response		
Complete response, n (%)	0	0
Partial response, n (%)	1 (2.4)	2 (5.0)
Stable disease, n (%)	27 (65.9)	21 (52.5)
Progressive disease, n (%)	10 (24.4)	12 (30.0)
Not estimable, n (%)	3 (7.3)	2 (5.0)
Not available, n (%)+	0	3 (7.5)
Objective Response Rate, n (%)	1 (2.4)	2 (5.0)
Disease Control Rate, n (%)	28 (68.3)	23 (57.5)
Progression-free survival		
Months, median (95% CI)	4.67 (2.76, 5.32)	3.71 (2.00, 5.52)
Overall survival		
Months, median (95% CI)	10.68 (6.74, 11.73)	9.26 (5.16, NE)

+No post-dose tumor assessment was conducted
CI=confidence interval

Table 3: Overview of Treatment-Emergent Adverse Events

	Cohort B (N=41)	Cohort C (N=40)
Any TEAE, n (%)	41 (100)	40 (100)
Any TEAE of Grade ≥3, n (%)	34 (82.9)	27 (67.5)
Any TEAE leading to death, n (%)	1 (2.4)*	0 (0)
Any TEAE leading to dose interruption or reduction, n (%)	30 (73.2)	26 (65.0)
Any TEAE leading to discontinuation, n (%)	4 (9.8)	5 (12.5)

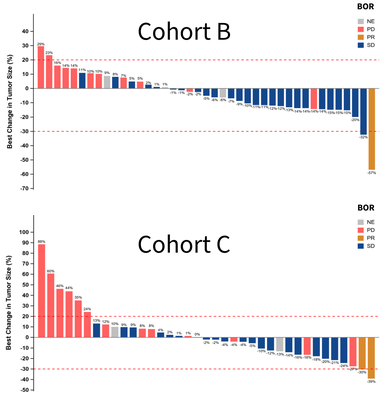
TEAEs (in >2.5% of patients) leading to dose discontinuation include abdominal pain; leading to dose interruption include increased blood bilirubin, fatigue, proteinuria, hypertension, hyponatremia, and hand foot syndrome; leading to dose reduction include fatigue, hypertension, proteinuria, hypertriglyceridemia, and hand foot syndrome.
*Decline in general condition related to PD resulted in 1 patient death

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

Cohort B (N=41)			Cohort C (N=40)		
Preferred Term	Any grade, n (%)	Grade ≥3, n (%)	Preferred Term	Any grade, n (%)	Grade ≥3, n (%)
Any TEAE	41 (100)	34 (82.9)	Any TEAE	39 (97.5)	27 (67.5)
Fatigue	22 (53.7)	2 (4.9)	Hypertension	30 (75.0)	8 (20.0)
Proteinuria	21 (51.2)	1 (2.4)	Proteinuria	16 (40.0)	0
Hypertension	20 (48.8)	13 (31.7)	Myalgia	13 (32.5)	0
Diarrhea	17 (41.5)	2 (4.9)	Fatigue	12 (30.0)	1 (2.5)
Decreased appetite	14 (34.1)	0	Hypertriglyceridemia	11 (27.5)	2 (5.0)
Blood ALP increase	12 (29.3)	3 (7.3)	Hyponatremia	11 (27.5)	3 (7.5)
Dysphonia	12 (29.3)	0	Hypothyroidism	11 (27.5)	0
Hyponatremia	12 (29.3)	7 (17.1)	Blood ALP increase	10 (25.0)	3 (7.5)
Hand foot syndrome	12 (29.3)	3 (7.3)	Decreased appetite	10 (25.0)	0
Constipation	11 (26.8)	0	Abdominal pain	9 (22.5)	3 (7.5)
Headache	11 (26.8)	0	ALT increased	9 (22.5)	2 (5.0)
Nausea	11 (26.8)	1 (2.4)	AST increased	9 (22.5)	1 (2.5)
Abdominal pain	10 (24.4)	4 (9.8)	Blood bilirubin increased	9 (22.5)	2 (5.0)
AST increase	10 (24.4)	2 (4.9)	Dysphonia	9 (22.5)	0
Urinary tract infection	10 (24.4)	3 (7.3)	Hyperglycaemia	9 (22.5)	1 (2.5)
INR increase	9 (22.0)	0	Hand foot syndrome	9 (22.5)	1 (2.5)
Hypertriglyceridemia	8 (19.5)	0	aPTT prolonged	8 (20.0)	0
Stomatitis	8 (19.5)	1 (2.4)	Lymphocyte count decreased	8 (20.0)	3 (7.5)
Weight decrease	8 (19.5)	0	Arthralgia	7 (17.5)	0
aPTT time prolonged	7 (17.1)	2 (4.9)	Constipation	6 (15.0)	0
Arthralgia	7 (17.1)	0	Dyspnea	6 (15.0)	1 (2.5)
Cough	7 (17.1)	0	Headache	6 (15.0)	0
Hypothyroidism	7 (17.1)	0	Insomnia	6 (15.0)	0
Lymphocyte count decrease	7 (17.1)	2 (4.9)	Nausea	6 (15.0)	0
Vomiting	7 (17.1)	1 (2.4)			

ALP=alkaline phosphatase; ALT= alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=Aspartate aminotransferase; INR=international normalized ratio; TEAE=treatment emergent adverse event

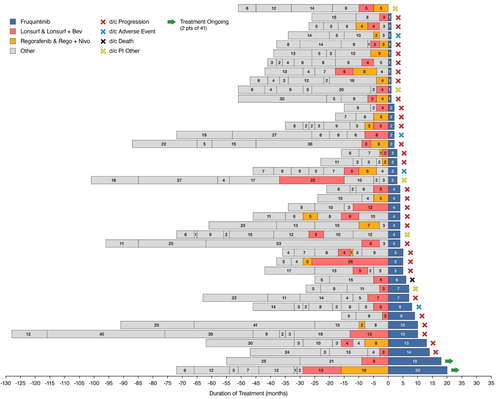
Figure 2: Waterfall Plot for Target Lesions



BOR=best overall response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease

- Waterfall plots show best percentage change from baseline in patients treated with fruquintinib and who had at least 1 post-baseline scan.

Figure 3: Prior Anti-Cancer Therapies and Duration of Treatment (Cohort B)



Bev=bevacizumab; d/c=discontinued; Nivo=nivolumab

- The median duration (weeks) (min, max) of treatment was 19.29 (3.0, 86.9) for Cohort B and 14.14 (1.1, 63.1) for Cohort C.
- In Cohort B, the median duration of prior therapy was 13.9 weeks for TAS-102 and 11.5 weeks for regorafenib.

CONCLUSIONS

- **Fruquintinib was generally well-tolerated with evidence of anti-tumor activity in heavily pre-treated patients with refractory mCRC.**
  - **The safety profile in heavily pre-treated patients in both cohorts was consistent with what has been previously reported.**
  - **The disease control rate of 68.3% in Cohort B and 57.5% in Cohort C was consistent with that seen in FRESCO.**
- **Enrollment is ongoing in patients with metastatic breast cancer.**
- **Fruquintinib is being further investigated in refractory mCRC (progressed on, or were intolerant, to TAS-102 or regorafenib) in the global Phase 3 FRESCO-2 study (NCT04322539).**

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