A randomized, double-blind, placebo-controlled, multicenter Phase II clinical trial of fruquintinib in patients with metastatic colorectal cancer (mCRC)

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INTRODUCTION

Fruquintinib is a novel, potent and highly selective oral small molecule VEGF receptor inhibitor. In a Phase 1b study (ASCO 2014 #126686), fruquintinib administered at 5mg once daily in cycles of three weeks on and one week off (3/1 wk) was well tolerated and demonstrated encouraging preliminary clinical efficacy in mCRC patients.

OBJECTIVES

To evaluate the efficacy and safety of Fruquintinib in the treatment of patients with metastatic CRC who have progressed after metastatic CRC second line or above standard chemotherapy.

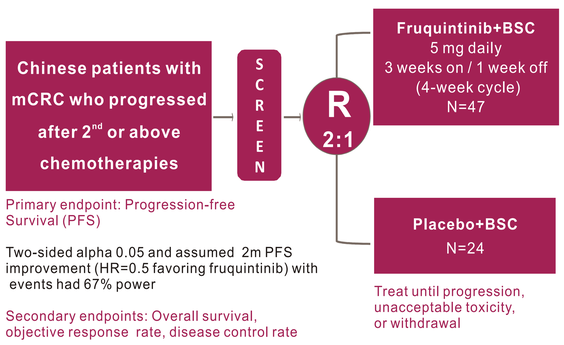
KEY INCLUSION CRITERIA

- Pathologically proven mCRC
- Measurable or non-measurable disease (RECIST* v 1.1)
- Failed or non-tolerable to >2 prior CRC treatment regimens in which included fluoropyrimidine, oxaliplatin, and irinotecan#
- Prior exposure to anti-VEGF or anti-EGFR therapies allowed
- ECOG performance status 0 or 1

* RECIST, response evaluation criteria in solid tumors

Progression during or within 3 months after the last administration of approved standard therapies including fluoropyrimidine, oxaliplatin and irinotecan or during or within 6 months after completing adjuvant oxaliplatin-based therapy; if progression >6 months after completing adjuvant oxaliplatin must have been retreated with oxaliplatin-based therapy.

STUDY DESIGN (NCT 02196688)



Primary endpoint: Progression-free Survival (PFS)

Two-sided alpha 0.05 and assumed 2m PFS improvement (HR=0.5 favoring fruquintinib) with events had 67% power

Secondary endpoints: Overall survival, objective response rate, disease control rate

Treat until progression, unacceptable toxicity, or withdrawal

ASSESSMENTS

Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03

Tumor Response was assessed by Response Evaluation Criteria In Solid Tumors (RECIST) criteria, version 1.1

The primary endpoint (PFS) was evaluated by investigator and independent reviewer.

RESULTS

◆PATIENTS

- A total of 71 patients enrolled in the Phase 2 mCRC trial, 47 in the fruquintinib arm and 24 in the placebo arm, respectively.
- Patient baseline characteristics were similar between the two treatment arms. (Tab.1)
- The median fruquintinib exposure was 84 days (range: 13-188) whereas the median was 21 (range: 19,191) days in the placebo arm.

Tab.1 Baseline Characteristics, ITT

		Fruquintinib N=47	Placebo N=24
Age in yr	median (range)	50(25,69)	54(38,70)
Sex, n (%)	Male Female	35(74.5) 12(25.5)	17(70.8) 7(29.2)
ECOG PS, n (%)	0 1	6 (12.8) 41 (87.2)	5 (20.8) 19 (79.2)
Duration from 1st metastasis diagnosis to randomization, n(%)	<18 months >=18 months	20 (42.6) 27 (57.4)	14 (58.3) 10 (41.7)
Previous lines of chemotherapy, n (%)	=2 >=3	12 (25.5) 35 (74.5)	7 (29.2) 17 (70.8)
Prior EGFR inhibitor use, n(%)	Yes No	11 (23.4) 36 (76.6)	5 (20.8) 19 (79.2)
Prior VEGF inhibitor use, n (%)	Yes No Missing	15 (31.9) 29 (61.7) 3 (6.4)	7 (29.2) 17 (70.8) 0
Liver metastasis, n (%)	Yes No	29 (61.7) 18 (38.3)	17 (70.8) 7 (29.2)
Metastatic site, n (%)	Single Multiple	2 (4.3) 45 (95.7)	2 (8.3) 22 (91.7)
Primary site, n (%)	Colon Rectal	24 (51.1) 23 (48.9)	13 (54.2) 11 (45.8)

◆PRIMARY ENDPOINT- PFS(Fig. 1-3)

- mPFS = 4.7 months (fruquintinib) vs. 1.0 month (placebo)
- Hazard Ratio (HR) = 0.30 (p<0.001)

◆OS (Fig.4)

- Deaths: 22 (fruquintinib) vs. 15 (placebo)
- mOS = 7.6 months (fruquintinib) vs. 5.5 months (placebo)

◆TUMOR RESPONSE (Tab.2)

- Disease Control Rate (DCR) = 68.1% (fruquintinib) vs. 20.8% (placebo), p<0.001.

Fig1. Kaplan-Meier Plots of Progression-Free Survival (Inv.)

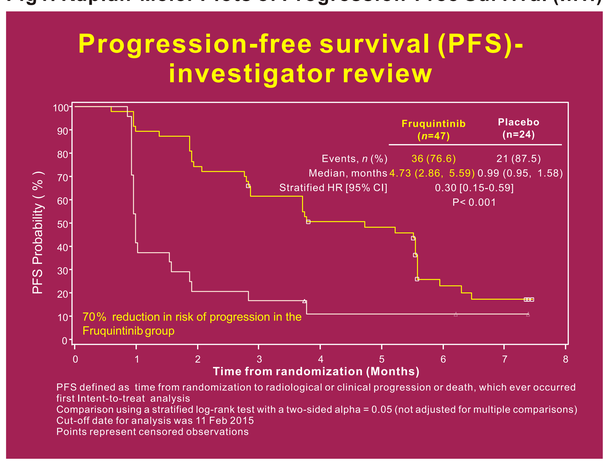


Fig2. Kaplan-Meier Plots of Progression-Free Survival (Ind.)

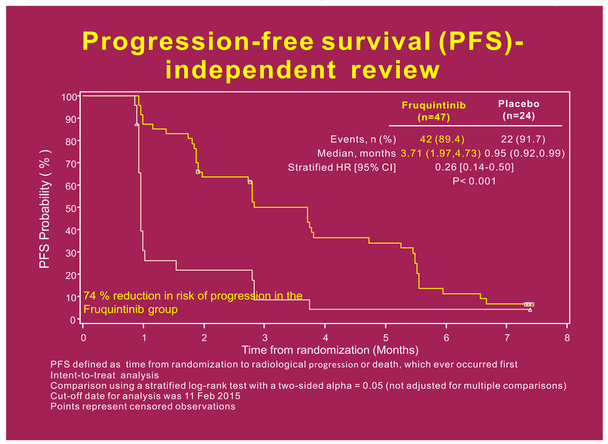


Fig3. PFS Subgroup Analyses (Investigator Review)

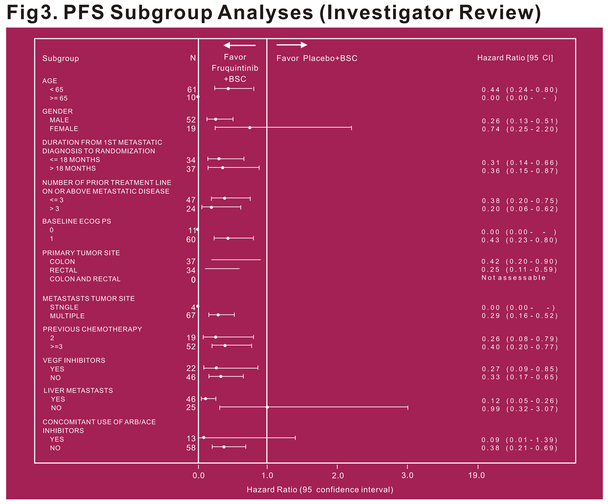
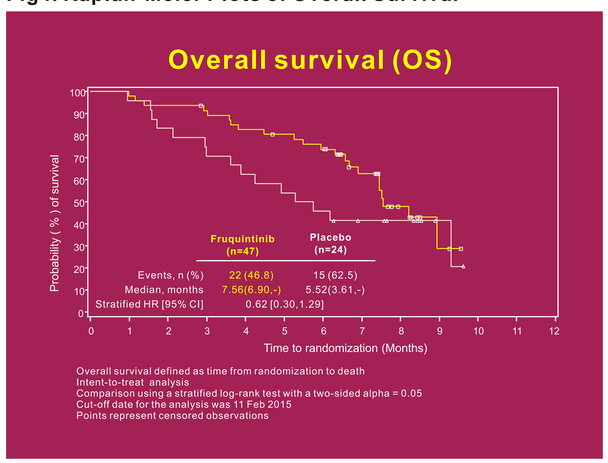


Fig4. Kaplan-Meier Plots of Overall Survival



Tab.2 Tumor Response, ITT results

n (%)	Fruquintinib n=47	Placebo n=24
Complete response (CR)	0	0
Partial response (PR)	1 (2.1)	0
Stable disease (SD)*	31 (66.0)	5 (20.8)
Progressive disease (PD)	12 (25.5)	17 (70.8)
Not evaluable/not assessed	2 (4.3)	1 (4.2)
Disease control rate (DCR)**	68.1%	20.8%
Group Difference and 95% CI Stratified MH Test P-value	47.25 (26.24, 68.27) < 0.001	

*: SD>=8 weeks
**: one non-CR/non-PD was counted in DCR

◆SAFETY OVERVIEW (Tab.3)

- The 5 most common fruquintinib treatment-related adverse events (AEs): hand-foot syndrome (61.7%), hypertension (51.4%), dysphonia (46.8%), proteinuria (44.7%) and AST elevation (27.7%).

Tab.3 Overview of AE（regardless of drug causality）

Patients, %	Fruquintinib n=47	Placebo n=24
TEAEs		
Any grade	47 (100.0)	20 (83.3)
Grade 3	28 (59.6)	2 (8.3)
Grade 4	0	2 (8.3)
Grade 5	3 (6.4)	2 (8.3)
Serious*	12 (25.5)	5 (20.8)
Leading to dose Interruption	14 (29.8)	4 (16.7)
Leading to dose reduction	13 (27.7)	0
Leading to treatment discontinuation	6 (12.8)	3 (12.5)

Safety was evaluated in all randomized patients who received =1 dose of study drug
TEAEs worst grade according to NCI-CTCAE v 4.0
*Serious TEAE defined as an event that resulted in death, was life threatening, required hospitalization, resulted in significant disability, or was a congenital anomaly

Tab.4 The Most Frequent Related TEAEs

Preferred Terms	Fruquintinib(n=47)		Placebo (n=24)	
	Total n(%)	Grade >=3 n(%)	Total n(%)	Grade >=3 n(%)
PPE*	29(61.7)	7(14.9)	2(8.3)	0
Dysphonia	22(46.8)	0	2(8.3)	0
Hypertension	21(44.7)	11(23.7)	3(12.5)	0
Proteinuria	21(44.7)	1(2.1)	5(20.8)	0
AST increased	13(27.7)	1(2.1)	3(12.5)	1(4.2)
TSH increased	11(23.4)	0	1(4.2)	0
Diarrhea	12(25.5)	1(2.1)	3(12.5)	0
Stomatitis	11(23.4)	0	1(4.2)	0
Fatigue	11(23.4)	2(4.3)	1(4.2)	0
Malaise	9(19.1)	0	2(8.3)	0
Decreased appetite	9(19.1)	0	4(16.7)	0
Nail discolouration	9(19.1)	0	0	0
ALT increased	9(19.1)	0	1(4.2)	0

*PPE: palmar-plantar erythrodysesthesia

CONCLUSION

◆Fruquintinib 5mg 3/1 wk treatment demonstrated superior PFS in patients with metastatic CRC as compared with placebo.

◆Fruquintinib was well tolerated and the safety profile appeared to be consistent with that of the TKI class.

◆Further confirmatory clinical studies are warranted.