Fruquintinib plus tislelizumab in microsatellite stable metastatic colorectal cancer: Results from a phase 1b/2 study

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Background

- Immuno-oncology (IO) therapies have been approved in the United States and European Union for the treatment of microsatellite instability-high metastatic colorectal cancer (mCRC)[1,2]
- However, in 95% of mCRC cases, tumors are microsatellite stable (MSS);[3] this type of mCRC tends to respond poorly to IO therapy, such as programmed cell death protein-1 (PD-1) inhibitors[4]
- Inhibiting both the vascular endothelial growth factor receptor (VEGFR) and PD-1 pathways may improve efficacy compared with targeting either pathway alone, based on the synergistic effects of modulating the immune microenvironment and activating an antitumor immune response[5,6]
- Fruquintinib is a highly selective oral inhibitor of all three VEGFRs (-1, -2, and -3), that is approved for patients with previously treated mCRC, regardless of biomarker status[7,8]
- Tislelizumab is a humanized, IgG4-variant monoclonal antibody against PD-1, which has been approved for the treatment of different tumor types[9,10]
- Clinical studies have demonstrated the efficacy of several PD-1 and VEGFR pathway inhibitor combinations in various tumor types,[11-14] and preliminary activity has been observed in patients with mCRC[15,16]
- We present results from the MSS mCRC cohort (Cohort D) of a phase 1b/2 study (NCT04577963) evaluating the safety and efficacy of fruquintinib in combination with tislelizumab in patients with advanced solid tumors

Methods

- Adults with MSS mCRC whose disease had progressed on or who were intolerant to two lines of chemotherapy (including fluorouracil, oxaliplatin, and irinotecan) and previous VEGFR/epidermal growth factor receptor inhibitors, as indicated, were enrolled in Cohort D of an open-label, multicenter, nonrandomized trial
- Patients received fruquintinib 5 mg by mouth (PO), once daily (QD) for 3 weeks on/1 week off plus tislelizumab 300 mg intravenously (IV) on Day 1, every four weeks (Q4W) in 28-day cycles until unacceptable toxicity, disease progression, or withdrawal of consent (**Summary Panel**)
- Patients could continue to receive fruquintinib and/or tislelizumab beyond initial investigator-assessed progressive disease (PD), per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), provided patients had investigator-assessed clinical benefit and were tolerating study drug(s)
- The primary endpoint was objective response rate (ORR; complete response [CR] + partial response [PR]) based on best confirmed overall response (BCOR) per RECIST v1.1
  - To be assigned a status of PR or CR, changes in tumor measurements were confirmed by repeat assessments performed no less than 4 weeks after the criteria for response was first met
- Secondary endpoints included disease control rate (DCR; CR + PR + stable disease [SD] for ≥7 weeks), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety
- Tumor evaluation/imaging was conducted at screening, every 8 weeks (±1 week) from cycle 1 Day 1 (C1D1) until disease progression, and ≤7 days (±3 days) after end of treatment (EOT); OS was assessed every 8 weeks (±2 weeks) after EOT
  - Safety assessments were conducted at screening, every week from C1D1 (±1 day for C1 and C2, and ±3 days from C3), ≤7 days (±3 days) after EOT, and 30 days (±1 week) after EOT
- The response-evaluable set included all patients who had a baseline tumor assessment, and either (i) had at least one post-baseline tumor assessment, or (ii) did not have a post-dose tumor assessment but had clinical progression or had died due to disease progression before their first post-baseline tumor scan
  - The safety-analysis set included all enrolled patients who had received at least one dose of fruquintinib or tislelizumab
- No formal hypothesis testing was planned for this study
- A post-hoc subgroup analysis according to the presence or absence of liver metastases at baseline was also conducted

Results

Patients

- From August 9, 2021, to July 25, 2024, 39 patients with MSS mCRC were enrolled and treated across 13 sites in the US
- At baseline, median age was 54.0 years; 27 patients (69.2%) were male, 25 (64.1%) had liver metastases, and 38 (97.4%) had confirmed MSS mCRC (data was missing for one patient); patients were heavily pretreated, with a median (range) of 4 (2–10) prior anticancer medication lines (**Table 1**)

Question

What is the safety and efficacy of fruquintinib in combination with tislelizumab in patients with refractory MSS mCRC?

Study design

Patient eligibility
- Age ≥18 years
- Histologically or cytologically confirmed advanced or metastatic solid tumors
- ECOG PS 0–1
- Adequate organ function

Safety lead-in phase

Recommended phase 2 dose:
- **Fruquintinib**: 5 mg PO, QD, 3 weeks on, 1 week off
- **Tislelizumab**: 300 mg IV, Q4W

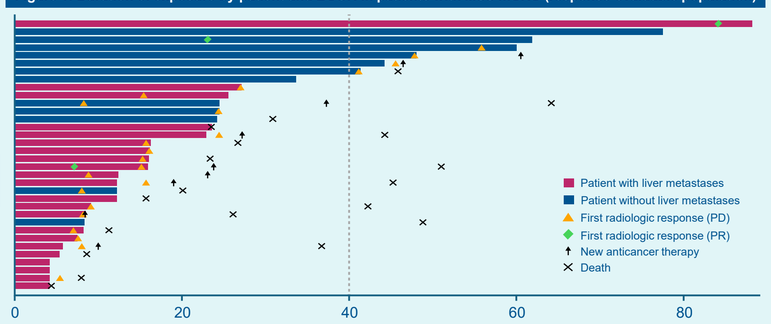
Expansion phase
- **Cohort A**: Triple-negative breast cancer (IO-treated)
- **Cohort B**: Triple-negative breast cancer (IO-naïve)
- **Cohort C**: Endometrial cancer (IO-naïve)
- **Cohort D**: MSS mCRC (IO-naïve)

Treatment until: Unacceptable toxicity or PD or withdrawal of consent

Primary endpoint: ORR
Secondary endpoints included: DCR, DOR, PFS, OS, and safety

Results

Figure 1: Duration of exposure by patient and BCOR in patients with MSS mCRC (response-evaluable population)



Total duration of exposure (days) was calculated from the first dose date of either fruquintinib or tislelizumab in cycle 1 to the earliest date between the last dose date of fruquintinib + 8 days and last dose date of tislelizumab + 28 days, or death date, whichever came earlier if treatment was discontinued, or to the cut-off date if treatment was still ongoing.

- Seven patients in Cohort D (20.6%) had durable clinical benefit on treatment for ≥40 weeks
- In a post-hoc analysis, patients in Cohort D without liver metastases at baseline had a notable improvement in median PFS versus patients with liver metastases (10.5 months vs 3.5 months)
- In Cohort D, the most common TEAEs were fatigue (69.2%), hypertension (33.3%), hypothyroidism (28.2%), and proteinuria (28.2%)
- Nine patients in Cohort D (23.1%) experienced TEAEs leading to study treatment discontinuation

Key conclusions

Fruquintinib plus tislelizumab showed efficacy and tolerability in patients with previously treated MSS mCRC, and safety data were consistent with known profiles of both treatments

Table 1: Baseline demographics and disease characteristics

	MSS mCRC cohort (n=39)
Median age at screening, years (range)	54.0 (37–79)
Age <65 years, n (%)	32 (82.1)
Male, n (%)	27 (69.2)
ECOG PS, n (%)	
0	16 (41.0)
1	23 (59.0)
Primary site at first diagnosis, n (%)	
Colon	25 (64.1)
Rectum	12 (30.8)
Other	2 (5.1)
Liver metastases, n (%)	
Yes	25 (64.1)
MSS at screening, n (%)	38 (97.4)
Median duration of metastatic disease, months (range)	33.5 (2.5–125.3)
Prior anticancer medication lines	
Median (range)	4 (2–10)
<3, n (%)	9 (23.1)
≥3, n (%)	30 (76.9)
Prior oncology treatments, n (%)	
Anticancer medication	39 (100)
Anticancer radiotherapy	16 (41.0)
Anticancer procedures or surgery*	22 (56.4)

*Included colectomy, hepatectomy, ileostomy, lymphadenectomy, proctectomy, liver ablation, colostomy, high frequency ablation, or laparotomy.
ECOG PS, Eastern Cooperative Oncology Group performance status.

Efficacy

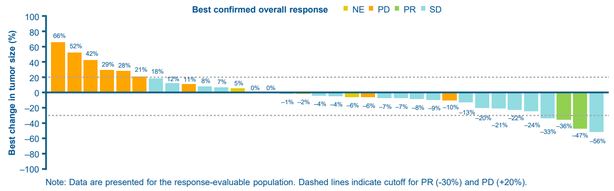
- Overall, 34 patients were evaluable for response; five patients were excluded from the response evaluable analysis set due to the lack of post-baseline tumor assessment
- In the response-evaluable population, confirmed ORR was 5.9% and DCR was 61.8% (**Table 2**)
- Duration of exposure by patient and BCOR is shown in **Figure 1** (**Summary Panel**) and best relative change from baseline in tumor size is shown in **Figure 2**
- Seven patients (20.6%) had durable clinical benefit on treatment for ≥40 weeks (**Figure 1**)
  - Of these seven patients, three were ongoing on treatment at the time of study closure
  - One patient achieved a PR (DOR: 1.8 months) and remained on treatment for 88.1 weeks; this patient also had a CR in a non-target lesion for 3.7 months
  - A second patient also achieved a PR (DOR: 9.1 months) and was on treatment for 61.9 weeks
  - One patient achieved SD and was on treatment for 77.4 weeks
- Confirmed ORR and DCR were higher in patients without liver metastases versus those with liver metastases (**Table 2**)

Table 2: Antitumor response in target lesions (response-evaluable population)

	MSS mCRC cohort (n=34)	Patients with liver metastases at baseline (n=22)	Patients without liver metastases at baseline (n=12)
BCOR, n (%)			
CR	0	0	0
PR	2* (5.9)	1 (4.5)	1 (8.3)
SD†	19‡ (55.9)	10 (45.5)	9 (75.0)
PD	9 (26.5)	7 (31.8)	2 (16.7)
NE§	4 (11.8)	4 (18.2)	0
Confirmed ORR, n (%)	2 (5.9)	1 (4.5)	1 (8.3)
95% CI	0.7–19.7	0.1–22.8	0.2–38.5
DCR, n (%)	21 (61.8)	11 (50.0)	10 (83.3)
95% CI	43.6–77.8	28.2–71.8	51.6–97.9

*One patient had a CR in non-target lesion. †A BCOR of SD was only recorded if a patient was on study for a minimum of 49 days (counted from C1D1). ‡One patient had unconfirmed PR. §NE was defined as having a post-baseline tumor scan, but ≥1 target lesions could not be assessed, or if a response of PR or CR was recorded followed by NE at a subsequent time point, unless the minimum criteria for SD were met.
CI, confidence interval; NE, not evaluable.

Figure 2: Best relative change from baseline in target lesion (response-evaluable population)



Note: Data are presented for the response-evaluable population. Dashed lines indicate cutoff for PR (-30%) and PD (+20%).

- Among all patients (n=39), median PFS was 3.6 months, and median OS was 10.2 months (**Table 3**)
- Median PFS was longer in patients without liver metastases versus those with liver metastases; median OS was not evaluable in patients without liver metastases at baseline (**Table 3**)

Table 3: Summary of PFS and OS

	MSS mCRC cohort (n=39)	Patients with liver metastases at baseline (n=25)	Patients without liver metastases at baseline (n=14)
Median (range) number of prior anticancer medication lines	4 (2–10)	3 (2–9)	4 (2–10)
PFS, months (95% CI)			
Median	3.6 (2.0–5.6)	3.5 (1.8–3.6)	10.5 (1.9–12.8)
OS, months (95% CI)			
Median duration of follow-up	14.3 (7.7–18.3)	10.1 (4.0–NE)	15.7 (7.7–18.3)
Median OS	10.2 (7.1–11.7)	8.3 (5.4–10.2)	NE* (7.1–NE)

*Due to the censoring of nine patients (64.3%) median OS was NE.

Treatment exposure and safety

- In the safety analysis set (n=39), median duration of study treatment exposure was 86 days (approximately 12.3 weeks)
- The most common reasons for discontinuing study treatment were radiological disease progression (51.3%; n=20) and adverse events (AEs) (20.5%; n=8)
- The overall safety profile of the combination of fruquintinib and tislelizumab in patients with MSS mCRC is shown in **Table 4**
  - All patients experienced at least one treatment-emergent AE (TEAE), 30 patients (76.9%) experienced at least one grade ≥3 TEAE, and nine patients (23.1%) experienced TEAEs leading to study treatment discontinuation

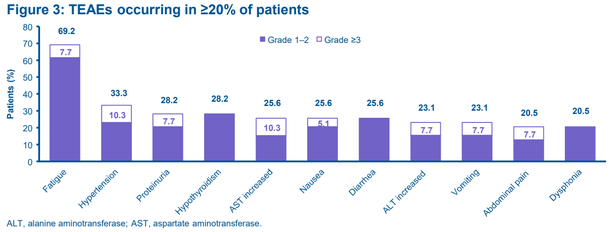
Table 4: Treatment exposure and safety summary

	MSS mCRC cohort (n=39)
Median duration of study treatment exposure, days (range)	86.0 (21.0–617.0)
Median number of treatment cycles (range)	4.0 (1.0–21.0)
Fruquintinib	
Median RDI, % (range)	93.8 (45.7–103.3)
Drug interruption, n (%)	30 (76.9)
Dose reduction, n (%)	9 (23.1)
Tislelizumab	
Median RDI, % (range)	96.6 (73.7–100.9)
Drug interruption, n (%)	5 (12.8)
Patients with any TEAEs, n (%)	39 (100)
Grade ≥3	30 (76.9)
Serious TEAEs	20 (51.3)
Immune-mediated AE	5 (12.8)
All-cause TEAEs leading to fruquintinib dose reduction	8 (20.5)
All-cause TEAEs leading to fruquintinib dose interruption	23 (59.0)
All-cause TEAEs leading to tislelizumab dose interruption	9 (23.1)
All-cause TEAEs leading to fruquintinib and tislelizumab discontinuation	9 (23.1)
All-cause TEAEs leading to death*	4 (10.3)
Fruquintinib-related AEs	33 (84.6)
Tislelizumab-related AEs	33 (84.6)

Note: Tislelizumab dose reductions (or dose increases) were not permitted in this study. *Deaths were due to disease progression (n=2), intestinal obstruction (n=1), and hepatic failure (n=1); all deaths were unrelated to treatment. RDI, relative dose intensity.

- The most common TEAEs in patients with MSS mCRC were fatigue (69.2%; n=27), hypertension (33.3%; n=13), hypothyroidism (28.2%; n=11), and proteinuria (28.2%; n=11) (**Figure 3**)

Figure 3: TEAEs occurring in ≥20% of patients



ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Conclusions

- Fruquintinib plus tislelizumab showed efficacy in patients with previously treated MSS mCRC, with seven patients deriving durable clinical benefit and receiving treatment for ≥40 weeks
- Patients without liver metastases at baseline had improved antitumor responses and a notable improvement in PFS versus those with liver metastases at baseline
- Overall, the combination of fruquintinib and tislelizumab was well tolerated in patients with MSS mCRC, and safety data were consistent with the known profiles of both treatments

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