Fruquintinib in Combination with PD-1 Inhibitors in Patients with Refractory Non-MSI-H/pMMR Metastatic Colorectal Cancer: A Real-World Study in China

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Abstract

Background: Fruquintinib, a vascular endothelial growth factor receptor inhibitor, is a new anti-cancer drug independently developed in China to treat refractory metastatic colorectal cancer (mCRC). In Japan, regorafenib in combination with nivolumab has demonstrated promise in patients with refractory mCRC. Here, in a real-world study, we aimed to evaluate the efficacy of fruquintinib plus various programmed death-1 (PD-1) inhibitors after standard treatment in Chinese non- microsatellite instability-high(MSI-H)/mismatch repair proficient mCRC patients.

Methods: Thirty-five patients with refractory mCRC were involved in the study. They were given fruquintinib (3 or 5 mg orally, once daily for 3 weeks followed by 1 week off in 4 week cycles) and a PD-1 inhibitor. Progression free survival (PFS), overall survival (OS), disease control rate (DCR), and objective response rate (ORR) were reviewed and evaluated.

Results: Of the 35 patients, the median age was 54 years (29–85). The ORR was 11.4% (4/35), DCR was 60% (21/35), median PFS was 3.8 months, and median OS was 14.6 months. The duration of response was 3.4 months. The PFS between left and right primary tumors as well as whether lung metastases were present did not differ ($p > 0.05$), which is inconsistent with the REGONIVO study. The multivariate analysis indicated no association of OS benefit in the specified subgroups. No adverse-effect-related deaths were reported.

Conclusions: Fruquintinib in combination with anti-PD-1 was observed to have clinical activity in a small population of patients with heavily pretreated mCRC. The improvements in OS need to be verified using more real-world medical data.

Introduction

Colorectal cancer (CRC) is the fourth most common type of cancer and fifth leading cause of cancer-related deaths in China[1]. Despite improvements in treatments for advanced CRC, the survival of these patients following one or two previous standard lines of therapy remains dismal. Currently, the United States Food and Drug Administration has approved TAS-102 and regorafenib as third line therapies for advanced CRC patients [2, 3]. However, the CONCUR [4] and TERRA studies [5] reported an average progression-free survival (PFS) of three months in Asians. Consequently, attempts were made to improve the survival benefit. In 2019, REGONIVO study [6] demonstrated that nivolumab plus regorafenib led to encouraging activity and manageable safety for patients with late-stage microsatellite stability (MSS) or mismatch repair proficient (pMMR) gastric cancer and CRC. Regorafenib[7] is a novel oral multi-kinase inhibitor that blocks the activity of several protein kinases, including those involved in the regulation of tumor angiogenesis (vascular endothelial growth factor receptor [VEGFR]1, VEGFR2, VEGFR3, and TIE2) and oncogenesis (KIT, RET, RAF1, BRAF, and BRAFV600E). Nivolumab is a human immunoglobulin G(4)-blocking antibody that inhibits the T-cell programmed death-1 (PD-1) checkpoint protein. It has demonstrated encouraging function of tumor control in several cancers whether given alone or in

combination with other agents[8–11]. The combination of a PD-1 inhibitor with angiogenesis agents seems to aid in tumor control, as suggested from the REGONIVO study.

Fruquintinib, an oral multi-kinase inhibitor, is a potent, highly selective small-molecule inhibitor of VEGFR1, VEGFR2, and VEGFR3. Based on the FRESCO study and the 2019 Chinese Society of Clinical Oncology guidelines, it is recommended as a treatment among Chinese metastatic CRC (mCRC) patients who experienced tumor progression following two or more prior chemotherapy regimens[12, 13]. Currently, at least six types of PD-1 inhibitors are available clinically. Data on the efficacy of fruquintinib in combination with anti-PD-1 inhibitors for MSS/pMMR mCRC in a real-world setting have yet to be reported. Here, we sought to further explore, retrospectively in our clinic center, the efficacy profiles of fruquintinib plus PD-1 inhibitors as well as the potential clinical correlates of benefits in patients with metastatic MSS/pMMR CRC that had progressed following second-line or subsequent treatment.

Patients And Methods

Patients in the oncology department of the Chinese PLA General Hospital from January 2019 to August 2021 who progressed to standard chemotherapy were enrolled. The eligibility criteria were: patients with histological or cytological confirmation of adenocarcinoma of the colon or rectum; they had experienced failure of first and second standard therapies such as FOLFOX (fluoropyrimidine and oxaliplatin) or FORFIRI (irinotecan and fluoropyrimidine) with or without bevacizumab or cetuximab; they had at least one non-resectable measurable lesion to evaluate treatment response; and they were administered at least two cycles of treatment. The exclusion criteria included: patients with less than one cycle of treatment, and those with little information on tumor response. This retrospective study was approved by the independent ethics committee of our hospital((NO:S2019-201-01) .

Fruquintinib was given orally once daily in 28-day (D) cycles (21D on/7D off). The PD-1 inhibitor (200 mg pembrolizumab, 3 mg/kg nivolumab, 200 mg sintilimab or camrelizumab, or 240 mg toripalimab was given intravenously once every 3 weeks) on D1. The fruquintinib starting dose was 5 mg; if it was not well tolerated, it was deescalated to 3 or 4 mg in the therapy cycle.

Assessments

Patients were followed up until the cutoff date of August 1, 2021. Tumor evaluation was based on RECIST (version 1.1). The response evaluation included complete response (CR), partial response (PR), stable disease (SD), and progression disease (PD). The objective response rate (ORR) and disease control rate (DCR) were also evaluated. The ORR was calculated as the CR + PR, while the DCR was the CR + PR + SD.

The primary endpoint was PFS, which was defined as the time from treatment to the RECIST-defined disease progression. The second endpoint was the duration of response (DOR), the time from the first

response to disease progression or death from any cause, whichever occurred first. The overall survival (OS) was the time from third line treatment to death from any cause.

Exploratory univariate analyses were performed using the log-rank test, which compared different clinical variables such as tumor location (left versus right side), KRAS status (wild or mutation), liver and lung metastases, and other variables.

Statistical Analysis

SPSS software 18.0 was used for statistical analysis. Objective response and disease control were presented as proportions and comparisons between groups were carried out using the stratified k-square test. Kaplan-Meier curves were used to estimate median OS, PFS, and DOR. Differences between clinic features in PFS and OS were assessed using the log-rank test. The statistical significance level was set to 0.05, and confidence intervals (CIs) were set to 95%.

Results

From January 2019 to August 2021, 35 patients were enrolled in this retrospective study at our hospital's oncology department. Patient clinical characteristics are listed in Table 1. At baseline, the average age was 54 years old (range 29–85), and 77.1% had ECOG performance status (PS) scores of 0/1. 80% of the patients had liver metastases, while 42.9% had lung metastases. The primary tumor site was in the left colon in 77.1% of cases and the right in 22.9%. 88.6% of patients had received bevacizumab prior to treatment. Finally, 23 patients had KRAS mutations, and all patients achieved MSS.

The median number of cycles was 5.0 (range 2–24); four patients had to deescalate fruquintinib from 5 mg to 3 mg. Six patients started fruquintinib at 3 mg; one discontinued the treatment because of an adverse event. 62.8% (22/35) patients received sintilimab plus fruquintinib. Five patients were given pembrolizumab, two patients with nivolumab, and four with camrelizumab.

In terms of response, no patient had a CR. Four patients achieved PRs, and 17 patients had SD. Fourteen achieved PD in accordance with RECIST version 1.1. DCR was 60%, and ORR was 11.4% (Table 2, Fig. 1). The median PFS was 3.8 months (95% CI: 1.8–5.8 months), and the OS was 14.6 months (95% CI: 5.4–23.8 months; Table 2, Figs. 2–3). The median DOR was 3.4 months (Table 2, Fig. 4).

The univariate analysis indicated that the PFS between left versus right primary tumors as well as whether lung metastases were present was not significantly different ($p = 0.396$ and $p = 0.562$, respectively). Neither KRAS mutation nor liver metastases were associated with better PFS or OS (Tables 3–4). The same trends were demonstrated using multivariate analysis.

Discussion

Patients with mCRC will eventually face challenges in its medical management following failure of standard treatment. However, limited choices with good performance still exist in third or further line therapy. Previous studies have found that mCRC patients harboring MSS show little response to immunotherapy [14], likely due to a complex tumor microenvironment that counteracts antitumor immunity via a combination of low antigenic tumor cells and an immunosuppressive tumor microenvironment [15]. However, the REGONIVO study demonstrated promising anticancer activity in mCRC patients with MSS who were administered with a PD-1 inhibitor (nivolumab) and regorafenib; these findings have a profound impact on cancer care for mCRC patients. As of January 2020, three additional antibody therapeutics developed by Chinese companies (tislelizumab, sintilimab, and camrelizumab) became available in China[16]. These compounds are highly selective, fully humanized monoclonal antibodies that block the interaction between PD-1 and its ligands[17]. Based on the REGONIVO combination strategy, our center attempted a similar regime using fruquintinib in combination with various PD-1 inhibitors as a third line therapy for mCRC patients with MSS. We retrospectively reviewed those patients and analyzed the efficacy of their treatments.

We obtained medical records from 35 patients at the time of analysis. Broadly, our therapy regime had efficacy. DCR was 60%, and ORR was 11.4% with four PRs observed. In the REGONIVO study, ORR was observed in 40% of patients; among 50 patients, including 25 CRC and 25 gastric cancers, eight patients had PRs, resulting in an ORR of 33% in MSS CRC patients. By contrast, our response rates were non-superior to the REGONIVO study. Notably, in the North American population, the efficacy of the combination treatment also differed from the Japanese population. More specifically, in the North American version[18] of REGONIVO, five patients (7.1%) out of 70 had a PR, and 22 (31.4%) had SD. The LEAP-005 study[19] (NCT03797326) evaluated the efficacy and safety of lenvatinib plus pembrolizumab in patients with previously treated CRC. They found an ORR of 22% (95% CI: 9–40) and a DCR of 47% in 32 CRC patients. Such discrepancies may be due to the REGONIVO study being a dose-finding and dose-expansion phase 1b trial with an aim of exploring safety and recommended doses. Accordingly, response rates should be verified in further investigations using a larger cohort. Second, the efficacy of the combination treatment varies depending on the specific anti-PD-1 or angiogenesis agent and the population. Third, patients in trials normally have PS scores of 0–1. Real-world studies do not limit PS scores, which means that our study included patients with worse PS scores, which may have affected the treatment responses.

We obtained a median PFS of 3.8 months. This result seems disappointing. The PFS was not superior to that from the REGONIVO study, and much similar to other studies associated with third or subsequent line treatment for mCRC. The PFS in the REGONIVO study was 6.3 months[6], 3.7 months in the FRESCO[20] study, and 2.0 months in the TAS-102 study[5]. We acknowledge the non-superior PFS of fruquintinib and anti-PD-1 treatment in such comparisons. Real world studies are complex, with various factors that reflect actual clinical practice, whereas clinical trials exclude poor condition. Furthermore, although regorafenib and fruquintinib are the same type of oral anti-angiogenesis agents, their underlying mechanisms at the functional site are different. Regorafenib is multi-targeted[7], while fruquintinib is highly selective for

VEGFR1, VEGFR2, and VEGFR3[12]. The molecular properties of PD-1-targeted antibodies are another factor. We acknowledge the limitations in comparing nivolumab and other types of PD-1 antibodies. However, nivolumab and pembrolizumab differ in the extent and spatial location of their binding sites with the flexible PD-1 loops [21]. Based on the available characterization data on anti-PD-1 antibodies, the molecular behavior between nivolumab and other anti-PD-1 antibodies likely differ [22, 23]. We also consider, to some extent, the effect of fruquintinib dose on efficacy. Some patients in our study took fruquintinib at 3 mg due to their tolerance, while the recommended dose on a continuous regimen is 5 mg QD [24, 25]. Therefore, the dose may have affected clinical efficacy.

Notably, the median OS in our study was much higher than in previously reported studies. The OS benefit in our real-world study was 14.6 months, while that of the FRESCO study was 9.3 months, which was the longest OS reported prior to our study. We cannot directly compare the efficacy of our study with the FRESCO or REGONIVO studies; this outcome needs to be confirmed in a larger group.

The PFS in our study appear to be no better than the results from the FRESCO study. Accordingly, we further assessed whether clinical characteristics were correlated with clinical outcome. Gender, tumor location, metastatic organs, and KRAS status did not significantly differ, which was inconsistent with the REGONIVO study. All patients responding in the REGONIVO study [6] were male with lung metastases and had PS scores of 0. Therefore, the results from the REGONIVO study may have been biased by the small sample and need further confirmation in a larger population.

One shortcoming of our study is the limited population and the absence of a side effects profile and data on PD-L1 expression. We did not have sufficient data to calculate a safety profile; what we know is that we found no severe adverse-related deaths. PD-L1 is believed to indicate response to anti-PD-1 antibodies in several tumors[26], However, data are lacking in PD-L1 expression; thus, we were unable to assess PD-L1 as a potential biomarker for CRC patients.

In conclusion, we found that fruquintinib in combination with anti-PD-1 had clinical activity in mCRC refractory to standard chemotherapy. However, this benefit was not observed across all prespecified patient subgroups. Further research is needed to assess OS benefits using a larger group.

Declarations

Ethics approval and consent to participate: This retrospective study was approved by the independent ethics committee of Chinese PLA General Hospital and all the authors consent to participate to the study.

Consent for publication: all the authors had consent for publication.

Availability of data and material: data and material are availability when required

Competing interests: we declare no conflicts of interest.

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Authors' contributions: Miaomiao Gou, Niansong Qian, Yong Zhang are in charge of data collection and writing, Huan Yan and Haiyan Si contribute to data collection, ,Zhikuan Wang and Guanghai Dai come up thoughts.

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Tables

Table 1 Baseline Characteristics of patients(n=35)

Characteristics	No. patients	%
Total	35	
Gender		
Male	24	68.6%
Female	11	31.4%
Age median =54		
<54	16	45.7%
>=54	19	54.3%
ECOG PS		
0-1	27	77.1%
>=2	8	22.9%
Tumor location		
left	27	77.1%
right	8	22.9%
Histological differentiation		
Poorly	2	5.7%
Moderately	31	88.6%
Well	2	5.7%
Kras status		
Wild	12	34.3%
Mutant	23	65.7%
Number of metastatic organs		
<=2	18	51.4%
>2	17	48.6%
Liver metastasis		
Yes	28	80.0%
No	7	20.0%
Lung metastasis		
Yes	15	42.9%

No	20	57.1%
Prior surgery		
Yes	24	68.6%
No	11	31.4%
Prior bevacizumab		
Yes	31	88.6%
No	4	11.4%

Table 2 Response outcome

Outcome	N = 35
ORR (CR+PR),%	11.4%
DCR (CR+PR+SD), %	60.0%
DOR, median, mos	3.4
PFS, median (95% CI), mos	3.8 (1.8 - 5.8)
OS, median (95% CI), mos	14.6 (5.4 - 23.8)

Table 3 Univariate analysis and multivariate analysis of clinical variable for the prediction of progression free survival

Variable		Univariate analysis		Multivariate analysis	
Total		HR	p	HR	p
Gender	Male vs Female	0.924 (0.435 - 1.964)	0.837	0.586 (0.175 - 1.956)	0.384
Age median =54	<54 vs >=54	0.712 (0.351 - 1.446)	0.348	0.504 (0.189 - 1.341)	0.170
ECOG PS	0-1 vs >=2	2.484 (1.032 - 5.978)	0.042	2.760 (0.819 - 9.308)	0.102
Tumor location	Left vs Right	1.428 (0.627 - 3.252)	0.396	1.601 (0.432 - 5.930)	0.481
Histological differentiation	Poorly vs Moderately vs Well	1.780 (0.437 - 7.261)	0.421	1.820 (0.358 - 9.250)	0.470
Kras status	Wild vs Mutant	1.172 (0.556 - 2.472)	0.676	1.627 (0.302 - 8.769)	0.571
Number of metastatic organs	<=2 vs >2	0.905 (0.450 - 1.817)	0.778	0.920 (0.353 - 2.395)	0.864
Liver metastasis	Yes vs No	0.662 (0.283 - 1.548)	0.341	0.592 (0.182 - 1.929)	0.384
Lung metastasis	Yes vs No	1.233 (0.608 - 2.498)	0.562	1.655 (0.565 - 4.852)	0.358
Prior surgery	Yes vs No	1.441 (0.671 - 3.091)	0.349	1.906 (0.466 - 7.791)	0.369
Prior bevacizumab	Yes vs No	0.840 (0.288 - 2.447)	0.749	1.547 (0.359 - 6.670)	0.558

Table 4 Univariate analysis and multivariate analysis of clinical variable for the prediction of overall survival

Variable		Univariate analysis		Multivariate analysis	
Total		HR	p	HR	p
Gender	Male vs Female	0.660 (0.253 - 1.720)	0.395	0.603 (0.118 - 3.071)	0.542
Age median =54	<54 vs >=54	1.387 (0.593 - 3.242)	0.450	1.242 (0.401 - 3.847)	0.707
ECOG PS	0-1 vs >=2	0.639 (0.214 - 1.906)	0.421	0.345 (0.072 - 1.664)	0.185
Tumor location	Left vs Right	0.881 (0.324 - 2.397)	0.804	2.899(0.523 - 16.065)	0.223
Histological differentiation	Poorly vs Moderately vs Well	0.866 (0.265 - 2.833)	0.811	0.739 (0.112 - 4.860)	0.753
Kras status	Wild vs Mutant	0.439 (0.165 - 1.167)	0.099	0.850 (0.133 - 5.439)	0.864
Number of metastatic organs	<=2 vs >2	0.780 (0.334 - 1.822)	0.565	0.673 (0.213 - 2.128)	0.500
Liver metastasis	Yes vs No	0.741 (0.250 - 2.197)	0.589	0.552 (0.115 - 2.648)	0.458
Lung metastasis	Yes vs No	1.608 (0.681 - 3.793)	0.278	1.974 (0.467 - 8.348)	0.355
Prior surgery	Yes vs No	1.823 (0.699 - 4.750)	0.219	1.984 (0.437 - 9.004)	0.375
Prior bevacizumab	Yes vs No	1.166 (0.262 - 5.180)	0.840	1.277 (0.199 - 8.192)	0.796

Figures

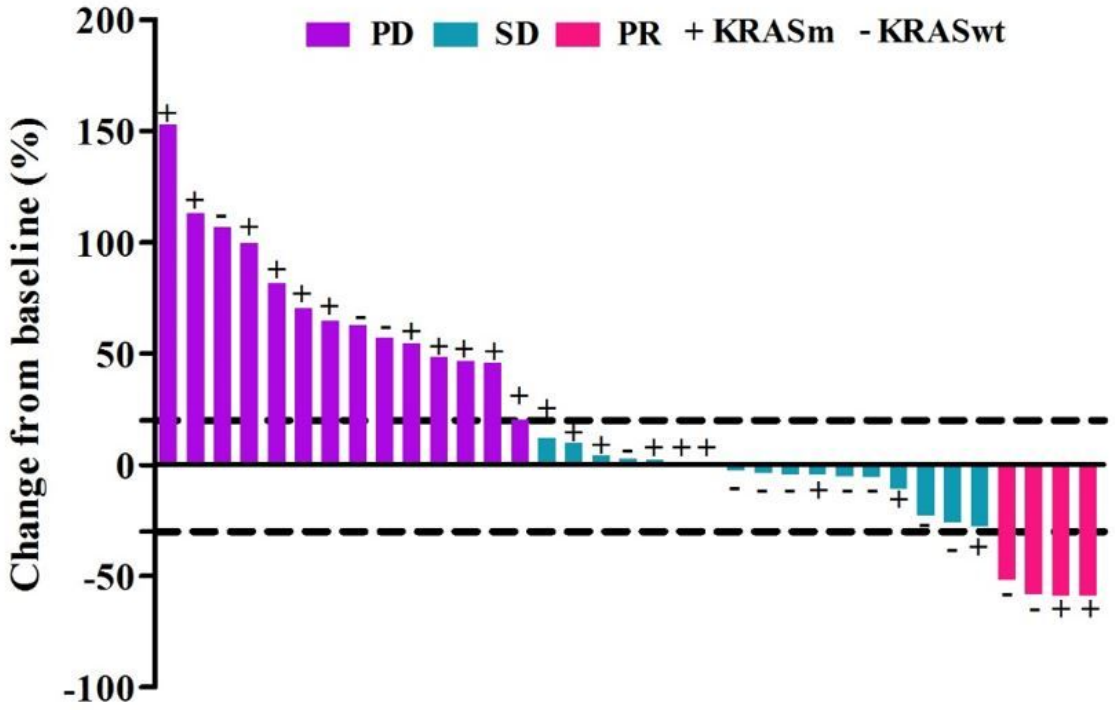

Figure 1

Tumor response in patients treated with fruquintinib plus pd-1 inhibitor with different kras status

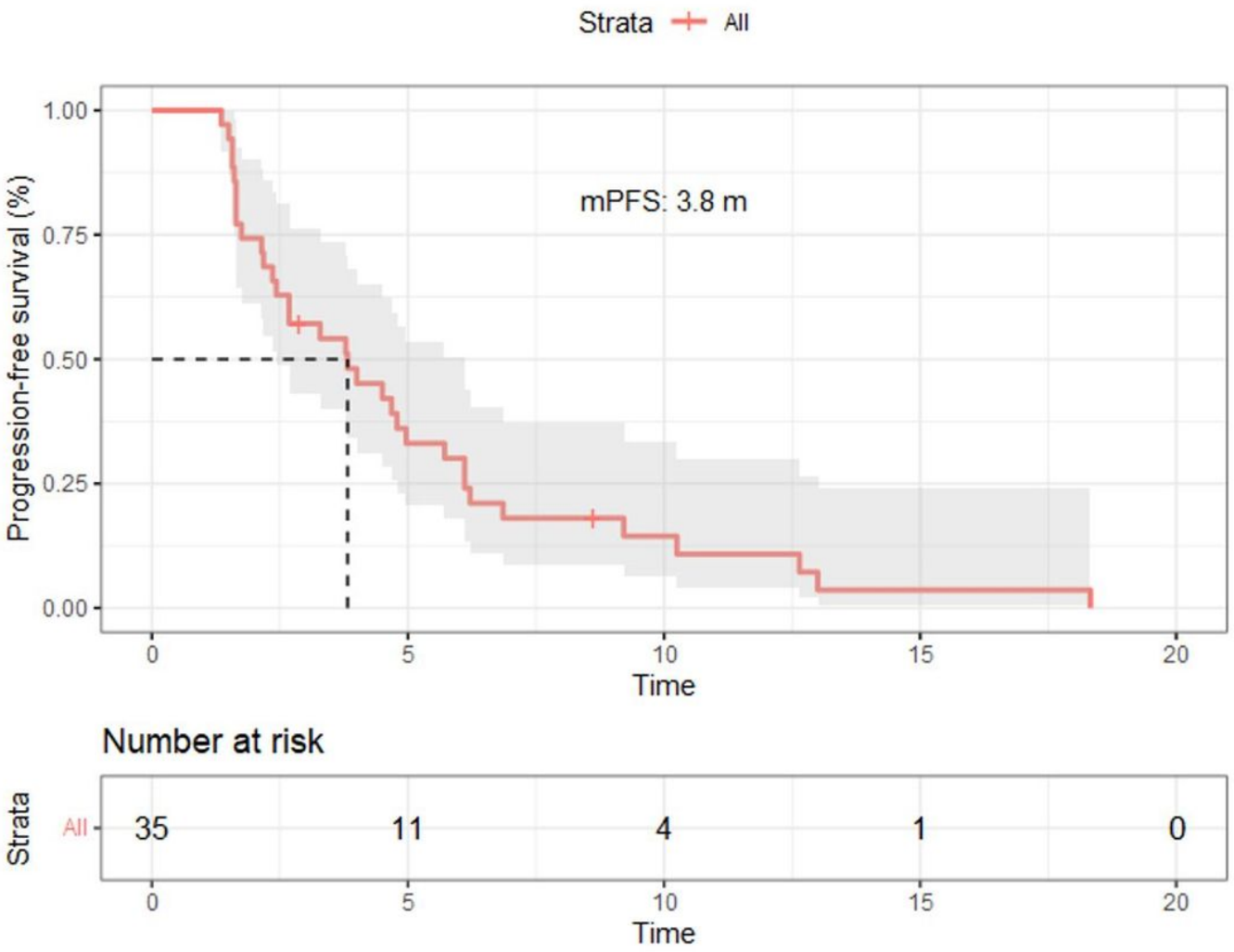

Figure 2

Progression free disease of patients treated with fruquintinib plus pd-1 inhibitor

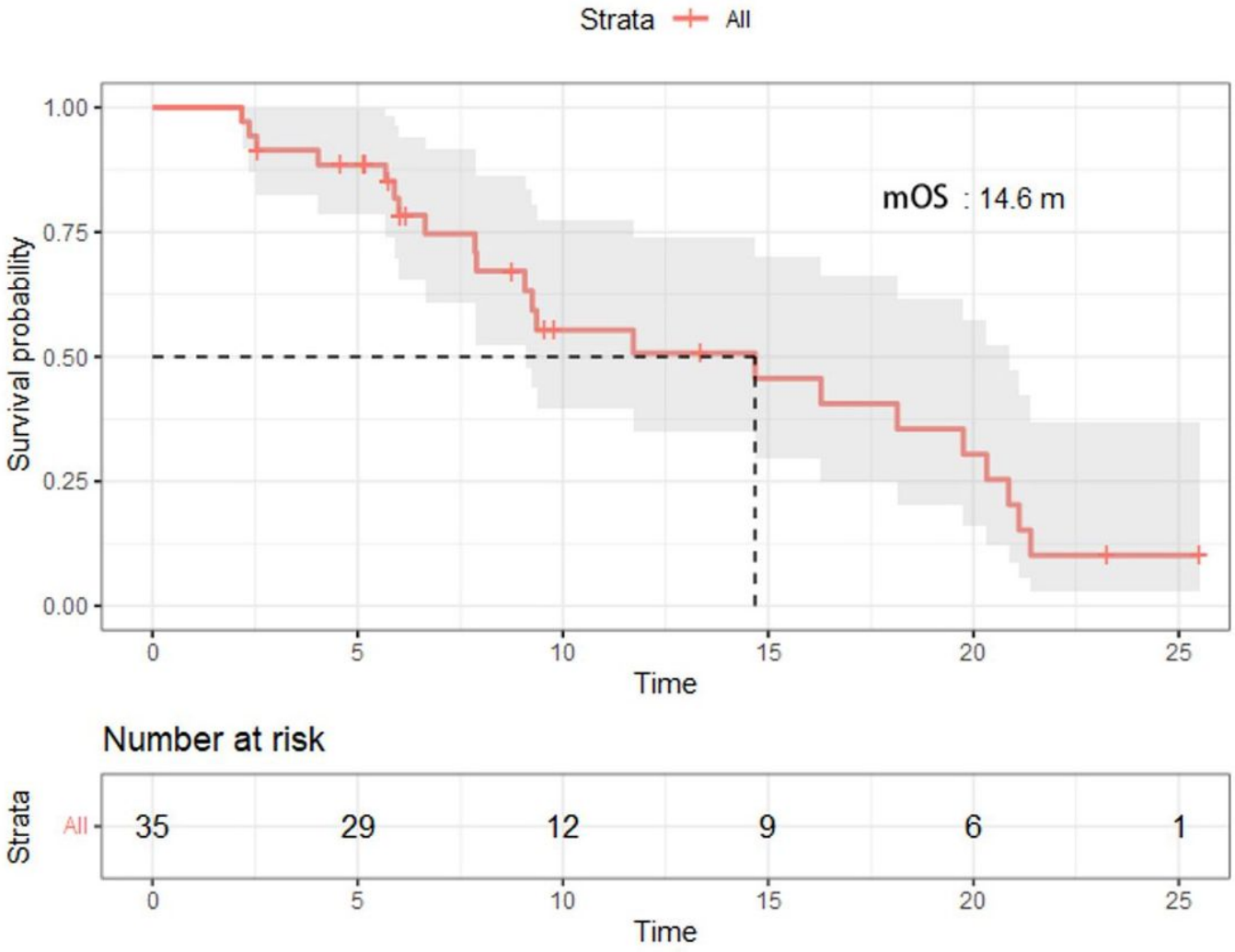

Figure 3

Overall survival of patients treated with fruquintinib plus pd-1 inhibitor

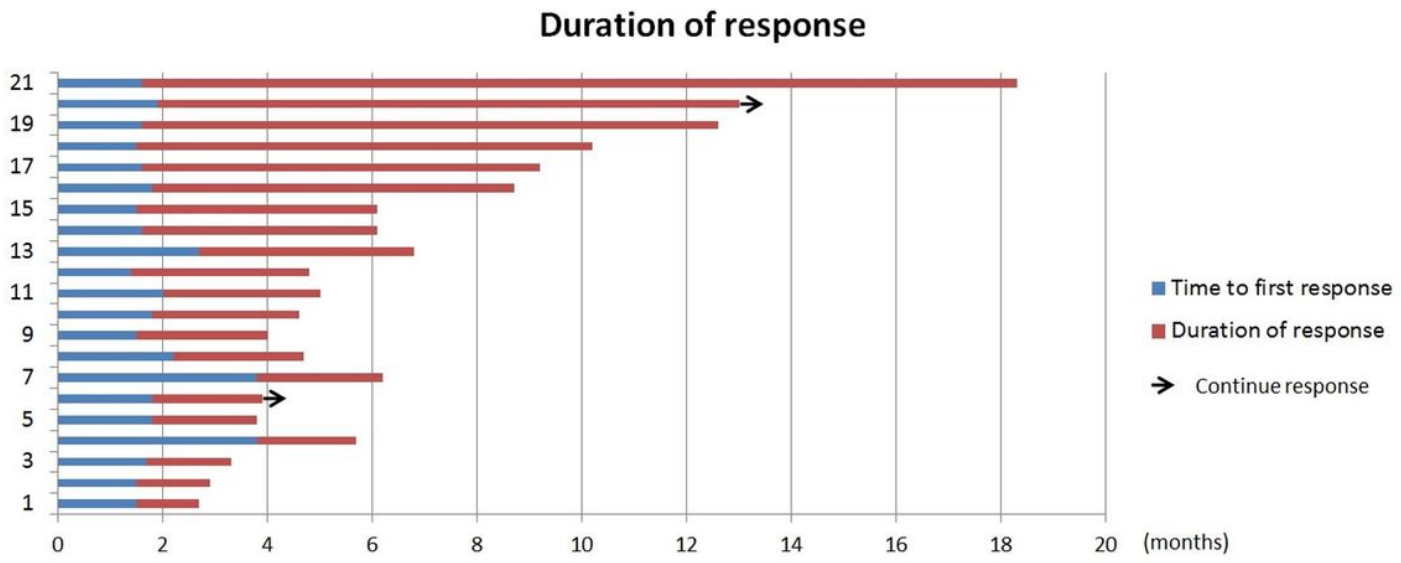

Figure 4

Duration of time of patients treated with fruquintinib plus pd-1 inhibitor