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# Comparison of Regorafenib, Fruquintinib, and TAS-102 in Previously Treated Patients with Metastatic Colorectal Cancer: A Systematic Review and Network Meta-Analysis of Five Clinical Trials

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Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Background:** This study aimed to conduct a systematic review of the literature to identify key randomized controlled clinical trials (RCTs), followed by network meta-analysis, to compare the efficacy and safety profiles of regorafenib, fruquintinib, and TAS-102 in previously treated patients with metastatic colorectal carcinoma (mCRC).




**Material/Methods:** Systematic literature review was performed using the Medline, Embase, and Cochrane library online databases to identify published randomized controlled trials (RCTs). Hazard ratios (HRs) for progression-free survival (PFS), overall survival (OS), and the odds ratios (ORs) for the objective response rate (ORR), disease control rate (DCR), adverse events (AEs), serious adverse events (SAEs), and fatal adverse events (FAEs) were compared indirectly using network meta-analysis based on a random-effects model.

**Results:** Five RCTs that included 2,604 patients fulfilled the eligibility criteria and were analyzed. Indirect comparisons showed that fruquintinib was associated with significant superiority for PFS (HR, 0.57; 95% CI, 0.34–0.95) and DCR (OR, 1.80; 95% CI, 1.08–3.01) when compared with TAS-102 in patients with mCRC. However, there was no significant difference between OS or ORR between regorafenib, fruquintinib, and TAS-102. Fruquintinib was associated with a significantly higher risk of SAEs when compared with TAS-102 or regorafenib. There was no significant difference in the risk of AEs or FAEs following indirect comparison between fruquintinib, regorafenib, and TAS-102.

**Conclusions:** The findings from network meta-analysis showed that fruquintinib was associated with significant superiority for PFS and DCR compared with TAS-102, but fruquintinib was associated with significantly increased risk for SAEs compared with regorafenib and TAS-102.

**MeSH Keywords:** **Colorectal Neoplasms • Matched-Pair Analysis • Meta-Analysis as Topic**

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## Background

Worldwide, colorectal cancer (CRC) is the third most frequently diagnosed cancer and the third leading cause of cancer death [1]. Treatment strategies that include surgery, radiation therapy, and chemotherapy remain the main treatments for patients with early-stage CRC. Systematic chemotherapy has an established role in palliative treatment, which is focused on the extension of life and improvement in the quality of life [2]. Systemic use of antitumor agents, including fluorouracil (5FU), oxaliplatin, irinotecan, bevacizumab, and cetuximab, have emerged as the primary treatment choices. However, there have been few recent developments in the treatment of patients with advanced and metastatic colorectal carcinoma (mCRC), particularly for patients with mCRC who are resistant to current treatments [3].

Regorafenib, an oral multi-kinase inhibitor, and TAS-102, a novel combined oral formulation of trifluridine (TFT) and the thymidine phosphorylase inhibitor (TPI) tipiracil, have been supported by the findings from randomized controlled trials for the treatment of patients with mCRC who have progressed following at least two previous rounds of standard chemotherapy [4,5]. Both regorafenib and TAS-102 have now been included in clinical guidelines, including the National Comprehensive Cancer Network (NCCN) guidelines, for the management of mCRC [4,5]. Regorafenib is a multi-kinase inhibitor of fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptors (PDGFR), vascular endothelial growth factor receptor (VEGFR), KIT, RET, and BRAF [4]. Regorafenib was approved for clinical use following the positive endpoint results from CORRECT, an international, multicenter, randomized, phase III trial, which showed improved overall survival (OS) compared with placebo in the treatment-refractory population with mCRC, hazard ratio (HR) of 0.77 (95% CI, 0.64–0.94;  $P=0.0052$ ) [4]. Positive results were also reported for TAS-102 from the RECURSE trial, which showed that when compared with placebo, the median OS improved from 5.3 months to 7.1 months, and the HR for patient mortality was 0.68 (95% CI, 0.58–0.81;  $P<0.001$ ) [5]. A more recently published prospective study was undertaken in an Asian population, which also showed that TAS-102 treatment resulted in a significant survival benefit compared with placebo in patients with mCRC that was refractory to standard chemotherapy, with an HR for mortality of 0.79 (95% CI, 0.62–0.99;  $P=0.035$ ), regardless of previous treatment with a biologic [6].

Fruquintinib is a VEGFR inhibitor that inhibits new blood vessel growth associated with tumor proliferation. A phase III, randomized, double-blind, placebo-controlled, multicenter clinical trial was conducted in a Chinese population with refractory mCRC, which showed that treatment with oral fruquintinib resulted in a significant increase in OS compared with placebo, with an HR for mortality of 0.65 (95% CI, 0.51–0.83;  $P<0.001$ ) [7].

However, because of the lack of head-to-head comparative studies of these three compounds, regorafenib, TAS-102, and fruquintinib, no superiority data has been obtained to compare their efficacy and safety in patients with refractory mCRC.

However, two network meta-analysis studies have been recently published that compared the efficacy and safety of regorafenib and TAS-102 [8], and regorafenib and fruquintinib [9] in pretreated patients with refractory mCRC. The lack of comparison data between the three drugs remains a challenge for clinicians who are responsible for treating patients with mCRC. Also, because current RCTs have shown differences in response to treatment in different racial groups, these differences may be a potential source of study bias. For example, the recently published meta-analysis by Jing et al. [9] that compared regorafenib and fruquintinib included three RCTs, including FRESKO (for fruquintinib), CONCUR (for regorafenib), and CORRECT (for regorafenib) [9]. However, only the trial CORRECT was designed as an international RCT that included Caucasian, black, and Asian patients, and the FRESKO and CONCUR RCTs were undertaken only in Asian patients.

Therefore, this study aimed to conduct a systematic review of the literature to identify key RCTs, followed by network meta-analysis, to compare the efficacy and safety profiles of regorafenib, fruquintinib, and TAS-102 in previously treated patients with mCRC.

## Material and Methods

### Literature search

A network meta-analysis was performed following a systematic literature review using the Medline, Embase, and the Cochrane library databases to identify published randomized controlled trials (RCTs) up to March 30<sup>th</sup>, 2019. The literature search terms included 'regorafenib,' 'fruquintinib,' 'TAS-102,' and 'colorectal carcinoma.' The search strategy used to search Medline was as follows: regorafenib OR fruquintinib OR TAS-102. The search procedure was limited to original, published, prospective, randomized, placebo-controlled clinical trials, which had been published in full in the English language. The network meta-analysis was conducted in compliance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

### Inclusion and exclusion criteria

The inclusion criteria were fully published, phase III, prospective, randomized, placebo-controlled clinical trials related to

regorafenib, fruquintinib, or TAS-102 in patients with metastatic colorectal carcinoma (mCRC). The study participants were those who had been evaluated as having disease progression after receiving at least one previous treatment regimen, who were randomly assigned to receive one of the agents (regorafenib, fruquintinib, or TAS-102) compared with placebo treatment in the control group. The studies were required to report the outcomes of objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs).

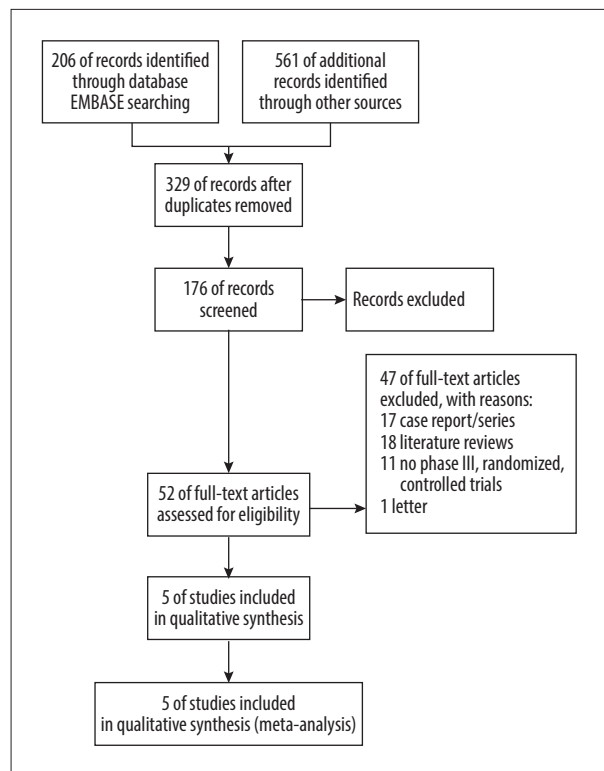
The exclusion criteria included non-controlled or single-arm studies, ongoing clinical trials, meeting abstracts, review articles, letters, meta-analysis data, case reports, commentaries, or publications not in the English language. For repeat publications of the results of the same study reported at different times, the most complete and updated reported publication was selected.

#### Outcome data extraction

The available data from the included studies were extracted independently by two investigators (Chen and Peng), with any differences resolved by consensus between the two reviewers. The essential information extracted from the enrolled studies included the names of the trials, the number of patients, gender, median age, racial distribution, the Eastern Cooperative Oncology Group (ECOG) performance status, the primary site of the tumor, the KRAS status, previous treatment, and whether the patient received anti-EGFR or anti-VEGFR treatment. The length of follow-up and the duration of drug exposure were also identified. The primary outcomes evaluated in the network meta-analysis were PFS (randomized to death, regardless of cause) and OS (randomized to progression to death, regardless of cause). Secondary endpoints included ORR, with patients evaluated as partial response (PR) or complete response (CR) according to the response evaluation criteria in solid tumors (RECIST) criteria version 1.1, DCR, with patients evaluated as PR or CR or stable disease (SD) according to RECIST version 1.1, AEs of any grade, including high grade ( $\geq$ grade 3) serious adverse events (SAEs), and fatal adverse events (FAEs).

#### Quality assessment of included studies

The quality of the included studies was evaluated using the criteria of the Cochrane Collaboration tool to assess the risk of bias of RCTs by the two reviewers (Chen and Peng). The following items were used for the assessment: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other bias, which were presented as a risk of bias graph and a risk of bias summary.



**Figure 1.** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] flow diagram of the study selection procedure.

#### Subgroup analysis

Because of the potential diverse racial distribution in the published RCTs, a network subgroup meta-analysis was performed to compare the efficacy of regorafenib, TAS-102, and fruquintinib in Asian patients with mCRC refractory to previous treatment.

#### Statistical analysis

Data were analyzed with STATA version 13.0 software (StataCorp, College Station, Texas, USA). Three or more interventions were divided into all possible combinations of two intervention tests. Consistency or inconsistency testing was waived because of the absence of a closed-loop in the present network meta-analysis. The intergroup discrepancies for outcomes of PFS and OS were presented with hazard ratios (HRs), and the variance estimates were calculated from the reported confidence intervals (CIs). HRs of PFS and OS were used for indirect comparison with the random-effects model. The ORR, DCR, AEs, SAEs, and FAEs were calculated with the ORs. Indirect comparison of regorafenib, fruquintinib, TAS-102, and placebo, network meta-analysis methods (STATA network) were performed. Based on the surface under the cumulative ranking (SUCRA) curve, the efficacy and safety of the three

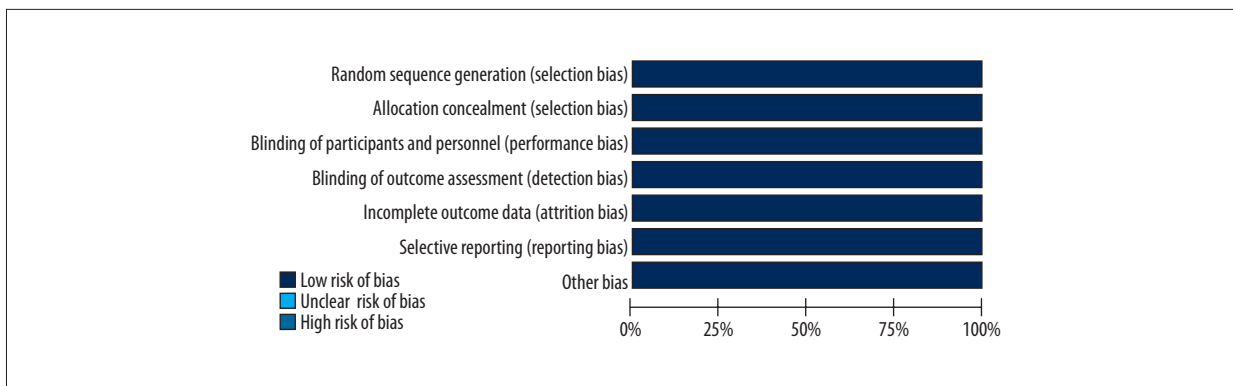


Figure 2. The risk of bias summary showing the reviewers' assessment of the risk of bias for each included study.

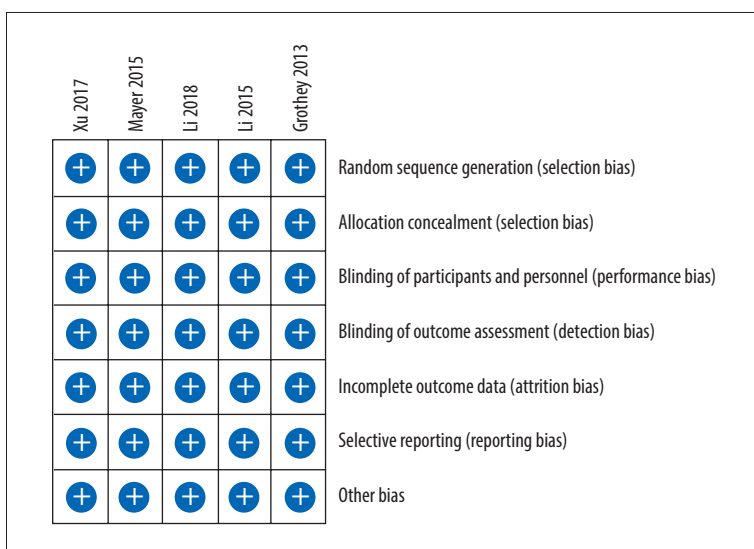


Figure 3. The risk of bias graph showing the reviewers' assessment of the risk of bias presented as percentages for all the included studies.

drug treatments were ranked. Review Manager (RevMan) version 5.3 software (Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for the description of the PRISMA flow diagram [10], risk of bias summary, and risk of bias graph, while the other figures in the present study were developed with STATA version 13.0 software (StataCorp, College Station, Texas, USA). Publication bias of the literature was evaluated using funnel plots.

## Results

### Systematic review of the literature

Figure 1 shows the flow diagram of the study selection [10]. All the included published studies were randomized and placebo-controlled in design and were in accordance with the inclusion criteria of the present study for patients with refractory metastatic colorectal cancer (mCRC). A systematic review of the published literature initially identified 767 potential publications. Following removal of meeting abstracts, duplicated

publications, and studies that were not randomized placebo-controlled trials, the final publications were read and reviewed in full by the investigators.

Five published clinical trials, which included 2,604 patients with refractory mCRC, were considered eligible for meta-analysis [4–7,11]. The published studies included: the CORRECT Trial, of regorafenib monotherapy for previously treated mCRC [4]; the RECOURSE Trial, of TAS-102 for refractory mCRC [5]; the TERRA phase III trial, of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated mCRC [6]; the FRESCO Trial, of the effect of fruquintinib compared with placebo on overall survival (OS) in patients with previously treated mCRC [7]; the CONCUR trial, of regorafenib plus best supportive care versus placebo in Asian patients with previously treated mCRC [11].

### Quality assessment of the included studies

The quality evaluation was conducted using the criteria of the Cochrane Collaboration tool for assessing the risk of bias in

RCTs. All of the five included RCTs satisfied the required items, including random sequence generation, allocation concealment, blinding of the study participants and personnel, and blinding of outcome assessments [4–7,11]. The results of the publication quality assessment are shown in Figures 2 and 3.

### Clinicopathological characteristics of the study population in the five RCTs

The five published RCTs identified, CONCUR [11], CORRECT [4], FRESCO [7], RECOURSE [5], and TERRA [6], which included 2,604 patients, were used in network meta-analysis. All the patients included in these five published RCTs were patients who were refractory to previous drug treatment who had progressed on standard chemotherapy, including oxaliplatin, irinotecan, and 5-fluoropyrimidine (5-FU), and were refractory to targeted agents, including bevacizumab and anti-EGFR treatment in patients with RAS wild-type mCRC.

In the CONCUR trial [11] and the CORRECT trial [4], patients were randomly assigned to receive treatment with regorafenib or placebo at 160 mg once daily with treatment duration from day 1 to day 21 of each of 28 days in a cycle. In the RECOURSE trial [5] and the TERRA trial [6], patients received treatment with TAS-102 or placebo orally administered 35 mg/m<sup>2</sup>/dose in continuous 28-day treatment cycles, with a treatment cycle of TAS-102 or placebo twice per day, for five days a week. In the FRESCO study [7], patients received treatment with fruquintinib (5 mg/day) or placebo, repeated during a 28-day treatment cycle that included three weeks of treatment followed by one week off treatment. All the patients included in the five RCTs received best supportive care and individual treatment until disease progression, death, unacceptable toxicity, withdrawal of consent by the patients, or discontinuation of the treatment by the physician [4–7,11]. The baseline clinicopathological characteristics in all the included RCTs presented in Table 1.

The model of the comparisons developed with the meta-analysis network is shown in Figure 4. All the drugs, including regorafenib, fruquintinib, and TAS-102 were compared separately with placebo. Figure 5 shows the contribution plot of the included publications in the network.

### Comparison of treatment efficacy of regorafenib, fruquintinib, and TAS-102

Direct and indirect comparison of progression-free survival (PFS) for patients with refractory mCRC treated with regorafenib, fruquintinib, and TAS-102 all showed benefit when compared with placebo. For PFS, the hazard ratio (HR) for fruquintinib was 0.26 (95% CI, 0.17–0.41), the HR for regorafenib was 0.41 (95% CI, 0.30–0.57), and the HR for TAS-102 was 0.46 (95%

CI, 0.34–0.61). Also, fruquintinib showed significant superiority when compared with TAS-102 (HR 0.57; 95% CI, 0.34–0.95). No significant difference was found in the indirect comparison between fruquintinib and regorafenib (HR 1.58; 95% CI, 0.93–2.71), or indirect comparison between regorafenib and TAS-102 (HR 0.90; 95% CI, 0.59–1.39). The results of the comparative data for PFS between regorafenib, fruquintinib, and TAS-102 are shown in Figure 6.

Direct and indirect comparison of overall survival (OS) for patients with refractory mCRC treated with regorafenib, fruquintinib, and TAS-102 showed that for all three, patients showed significant clinical benefit when compared with placebo. For OS, the HR for fruquintinib was 0.65 (95% CI, 0.46–0.91), the HR for regorafenib was 0.68 (95% CI, 0.53–0.88), and the HR for TAS-102 was 0.73 (95% CI, 0.58–0.90). However, there was no significant difference in the indirect comparison in the OS between fruquintinib and regorafenib (HR 1.05; 95% CI, 0.69–1.60), in the comparison between regorafenib and TAS-102 (HR 0.94; 95% CI, 0.67–1.32), or in the comparison between fruquintinib and TAS-102 (HR 0.90; 95% CI, 0.60–1.34). The results of the comparative data for OS between regorafenib, fruquintinib, and TAS-102 are shown in Figure 7.

In the indirect analysis of short-term efficacy, including the objective response rate (ORR) and disease control rate (DCR), the only significant difference between regorafenib, fruquintinib, and TAS-102 was identified in the data that compared the DCR between fruquintinib and TAS-102. Fruquintinib showed significant superiority for DCR when compared with TAS-102 (HR 1.80; 95% CI, 1.08–3.01), result of which was showed in Figure 8.

### Network meta-analysis and subgroup analysis

Network meta-analysis and subgroup analysis compared the efficacy parameters of PFS, OS, ORR, and DCR for regorafenib, TAS-102, and fruquintinib in Asian patients in the five RCTs. In this subgroup analysis, fruquintinib still showed significant superiority for PFS when compared with TAS-102 (HR 0.60; 95% CI, 0.43–0.84) (Supplementary Figure 1). However, no significant difference was observed in the indirect comparison for OS, ORR, or DCR between fruquintinib, regorafenib, and TAS-102 (Supplementary Figures 2–4). Therefore, the findings from this study supported the superiority of fruquintinib for PFS in Asian patients with refractory mCRC.

### Comparison of safety outcomes for regorafenib, fruquintinib, and TAS-102

Direct and indirect comparisons of adverse events (AEs), serious adverse events (SAEs), and fatal adverse events (FAEs) were compared for patients with refractory mCRC treated with fruquintinib, regorafenib, TAS-102, and placebo. Regorafenib

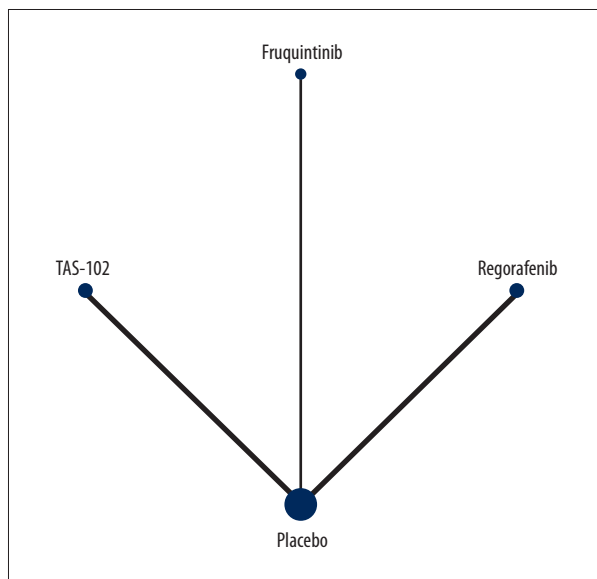
**Table 1.** Baseline characteristics of the five published clinical trials included in the meta-analysis.

	CONCUR		CORRECT		FRESCO		RECOURSE*		TERRA	
	Reg	PLA	Reg	PLA	Fruq	PLA	TAS	PLA	TAS	PLA
Number	136 (%)	68 (%)	505 (%)	255 (%)	278 (%)	138 (%)	534 (%)	266 (%)	271 (%)	135 (%)
Median age (yrs)	57	55.5	61	61	55	57	63	63	58	56
Race										
White	0 (0)	0 (0)	392 (78)	201 (79)	0 (0)	0 (0)	306 (57)	155 (58)	0 (0)	0 (0)
Black	0 (0)	0 (0)	6 (1)	8 (3)	0 (0)	0 (0)	4 (<1)	5 (2)	0 (0)	0 (0)
Asian	136 (100)	68 (100)	76 (15)	35 (14)	278 (100)	138 (100)	184 (34)	94 (35)	271 (100)	135 (100)
Other	0 (0)	0 (0)	31 (6)	11 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gender										
Male	85 (63)	33 (49)	311 (62)	153 (60)	158 (57)	97 (70)	326 (61)	165 (62)	170 (63)	84 (62)
Female	51 (38)	35 (51)	194 (38)	102 (40)	120 (43)	41 (30)	208 (39)	101 (38)	101 (37)	51 (38)
ECOG PS										
0	35 (26)	15 (22)	265 (52)	146 (57)	77 (28)	37 (27)	301 (56)	147 (55)	64 (24)	30 (22)
1	101 (74)	53 (78)	240 (48)	109 (43)	201 (72)	101 (73)	233 (44)	119 (45)	207 (76)	105 (78)
Primary site										
Colon	79 (58)	48 (71)	323 (64)	172 (68)	147 (53)	70 (51)	338 (63)	161 (61)	154 (57)	85 (63)
Rectum	53 (39)	19 (28)	151 (30)	69 (27)	125 (45)	60 (44)	196 (37)	105 (39)	117 (43)	50 (37)
Missing data	4 (3)	1 (1)	30 (6)	14 (5)	6 (2)	7 (5)	0 (0)	0 (0)	0 (0)	0 (0)
KRAS status										
Wild-type	50 (37)	29 (43)	205 (41)	94 (37)	157 (57)	74 (54)	262 (49)	131 (49)	172 (63)	85 (63)
Mutation	46 (34)	18 (26)	273 (54)	157 (62)	NR	NR	272 (51)	135 (51)	99 (37)	50 (37)
Unknown	40 (29)	21 (31)	27 (5)	4 (2)	NR	NR	0 (0)	0 (0)	0 (0)	0 (0)
Prior chemo										
1–2	48 (35)	24 (35)	135 (27)	63 (25)	190 (68)	98 (71)	95 (18)	45 (17)	62 (23)	25 (19)
3	32 (24)	17 (25)	125 (25)	72 (28)	NR	NR	119 (22)	54 (20)	74 (27)	36 (27)
≥4	52 (38)	27 (40)	245 (49)	120 (47)	NR	NR	320 (60)	167 (63)	135 (50)	74 (55)
Prior anti-EGFR										
Yes	48 (36)	29 (43)	219 (43)	107 (42)	40 (14)	19 (14)	278 (52)	144 (54)	71 (26)	42 (32)
No	88 (64)	39 (57)	286 (57)	148 (58)	238 (86)	119 (86)	256 (48)	122 (46)	200 (74)	93 (68)
Prior anti-VEGFR										
Yes	56 (42)	25 (37)	505 (100)	255 (100)	84 (30)	41 (30)	534 (100)	265(99.6)	77 (28)	44 (33)
No	80 (58)	43 (63)	0 (0)	0 (0)	194 (70)	97 (70)	0 (0)	1 (0.4)	194 (72)	91 (67)

**Table 1 continued.** Baseline characteristics of the five published clinical trials included in the meta-analysis.

	CONCUR		CORRECT		FRESCO		RECOURSE*		TERRA	
	Reg	PLA	Reg	PLA	Fruq	PLA	TAS	PLA	TAS	PLA
Drug exposure (months)	2.4 (1.6–5.3)	1.6 (1.1–1.6)	1.7 (1.4–3.7)	1.6 (1.3–1.7)	3.7 (0.1–21.9)	1.8 (0.1–11.1)	1.56 (0.01–18.2)	1.33 (0.01–4.9)	3.48 (NR)	2.04 (NR)
Follow-up (months)	7.4 (4.3–12.2)		NR		13.3	13.2	NR		NR	

The CORRECT Trial, of regorafenib monotherapy for previously treated mCRC [4]; the RECOURSE Trial, of TAS-102 for refractory mCRC [5]; the TERRA phase III trial, of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated mCRC [6]; the FRESCO Trial, of the effect of fruquintinib compared with placebo on OS in patients with previously treated mCRC [7]; the CONCUR trial, of regorafenib plus best supportive care versus placebo in Asian patients with previously treated mCRC [11]; ECOG PS – Eastern Cooperative Oncology Group Performance Status; EGFR – epidermal growth factor receptor; VEGFR – vascular endothelial growth factor receptor; Reg – regorafenib; Fruq – fruquintinib; TAS – TAS-102; NR – not reported; PLA – placebo. \* The RECOURSE Trial [5] enrolled some patients previously treated with regorafenib (17% patients in the TAS-102 group, and 20% patients in the placebo group).



**Figure 4.** Network graph of the comparisons.

showed significantly increased numbers of AEs of all grades when compared with placebo (OR 1.78; 95% CI, 1.16–2.73). Regorafenib also significantly increased high-grade AEs when compared with placebo (OR 3.81; 95% CI, 1.61–9.00). Fruquintinib treatment was associated with significantly increased SAEs when compared with TAS-102 (OR 2.90; 95% CI, 1.37–6.14), and when compared with placebo (OR 2.65; 95% CI, 1.28–5.48). Regorafenib treatment was associated with a significantly lower risk of SAEs comparing with fruquintinib (OR 0.42; 95% CI, 0.20–0.89). There were no significant differences in the other direct or indirect comparisons, with the results shown in Figure 9.

### Publication bias

The funnel plot of the network meta-analysis showed no significant publication bias (Figure 10).

### Discussion

Following a systematic review of the literature, five published randomized placebo-controlled clinical trials (RCTs) were identified, which included 2,604 patients with refractory metastatic colorectal cancer (mCRC) [4–7,11]. The five published RCTs that underwent meta-analysis included the CORRECT Trial, of regorafenib monotherapy for previously treated mCRC [4], the RECOURSE Trial, of TAS-102 for refractory mCRC [5], the TERRA phase III trial, of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated mCRC [6], the FRESCO Trial, of the effect of fruquintinib compared with placebo on overall survival (OS) in patients with previously treated mCRC [7], and the CONCUR trial, of regorafenib plus best supportive care versus placebo in Asian patients with previously treated mCRC [11].

The results of the systematic review and network meta-analysis of the five identified RCTs showed that fruquintinib was associated with significant superiority for progression-free survival (PFS) and disease control rate (DCR) when compared with TAS-102 in patients with refractory mCRC. However, there was no significant difference from the indirect comparison of overall survival (OS) or the objective response rate (ORR) between regorafenib, fruquintinib, and TAS-102. Fruquintinib showed a significantly higher risk of serious adverse events (SAEs) when compared with TAS-102 or regorafenib. However, there were no significant differences in the risk in adverse events (AEs) at any grade, or fatal adverse events (FAEs) in the indirect comparison of fruquintinib, regorafenib, and TAS-102.

		Direct comparisons in the network		
		Fruq vs. PLA	PLA vs. Reg	PLA vs. TAS
Network meta-analysis estimates	Indirect estimates			
	Fruq vs. PLA	100.0		
	PLA vs. Reg		100.0	
	PLA vs. TAS			100.0
	-----			
	Indirect estimates			
Fruq vs. Reg	50.0	50.0		
Fruq vs. TAS	50.0		50.0	
Reg vs. TAS		50.0	50.0	
Entire network		33.3	33.3	33.3
Included studies		1	2	3

Figure 5. Contribution plot of the included publications.

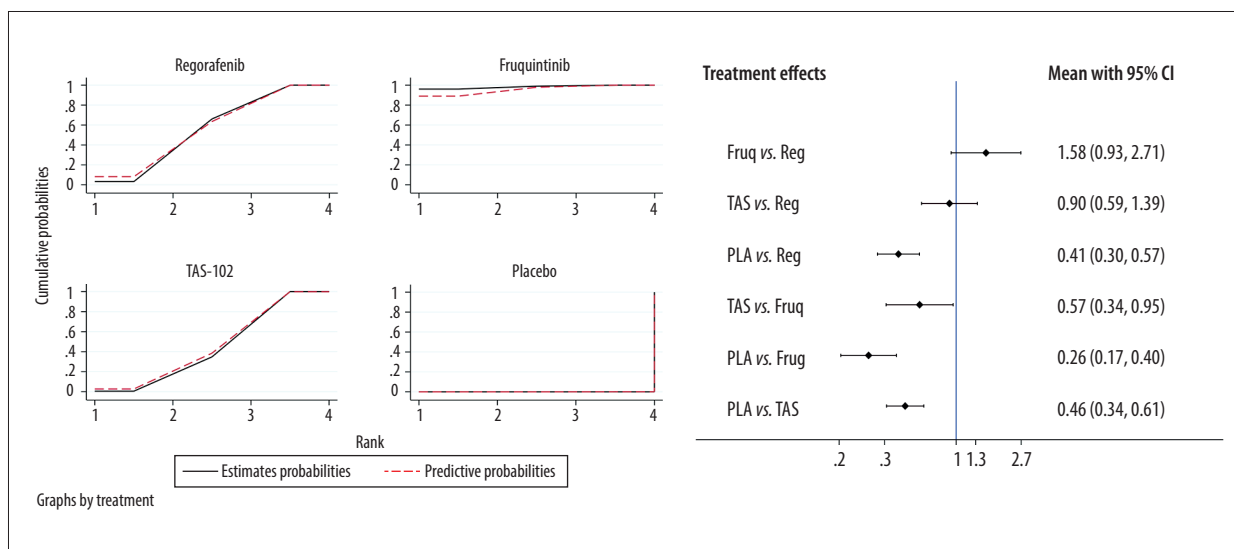


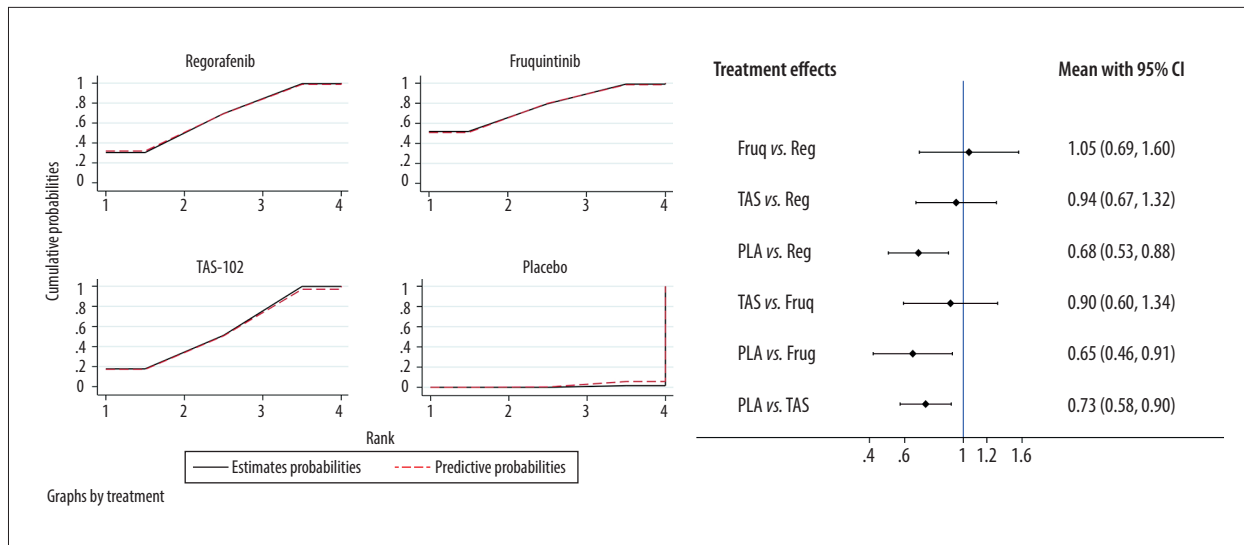
Figure 6. Ranking of the direct and indirect comparisons for progression-free survival (PFS) for Fruq (fruquintinib), Reg (regorafenib), TAS (TAS-102), and PLA (placebo).

In previously treated patients with mCRC, drugs such as fruquintinib, regorafenib, and TAS-102 may be associated with different clinical outcomes due to their different molecular mechanisms. Fruquintinib is a potent, highly selective small-molecule inhibitor of vascular endothelial growth factor receptor-1 (VEGFR-1), VEGFR-2, and VEGFR-3, and is an anti-angiogenic compound. However, regorafenib is a targeted pan-kinase inhibitor for the VEGFR family, and for fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptors (PDGFR), KIT, RET, and BRAF. Regorafenib was designed as salvage therapy in previously treated malignances, including hepatocellular carcinoma (HCC) [12], advanced gastrointestinal stromal tumors (GISTs) [13], and advanced gastric cancer [14]. TAS-102 is an orally administered combination of a thymidine-based nucleic acid analog, trifluridine, and a thymidine phosphorylase

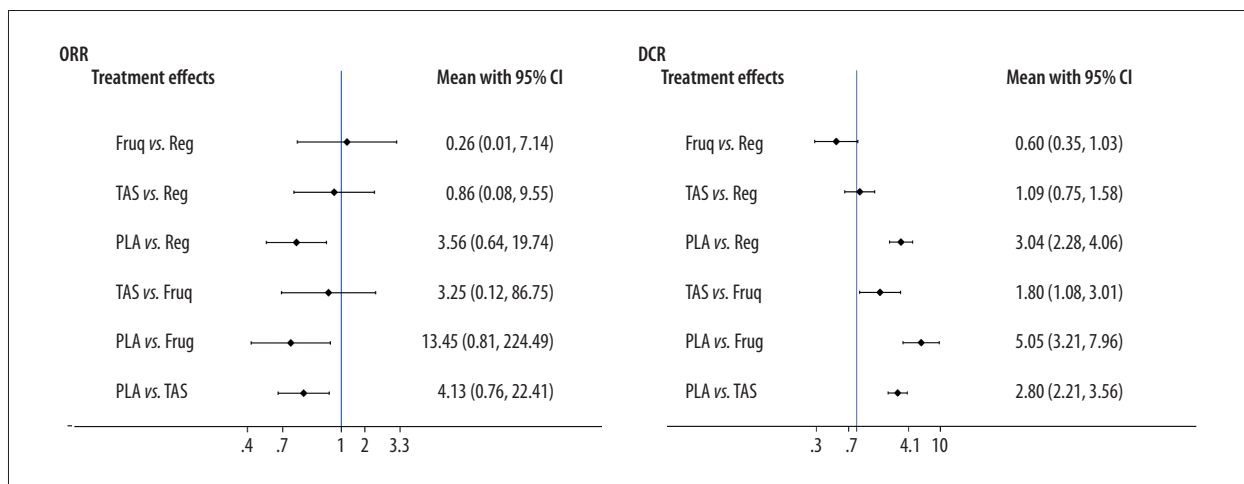
inhibitor, tipiracil hydrochloride and is a chemotherapy agent. Although the mechanism of the anti-tumor effects in the three agents, fruquintinib, regorafenib, and TAS-102 is different, positive outcome data in patients with refractory mCRC was previously demonstrated in RCTs and provided the evidence to support their recommended use in current clinical guidelines [4,7].

In the present study, indirect comparisons of the three drugs showed that fruquintinib demonstrated a significant superiority for PFS when compared with TAS-102, with a similar finding also shown in the indirect comparison of DCR. These improved outcomes suggested that fruquintinib might be a better choice in selected pretreated patients with mCRC. Also, this study showed that the Eastern Cooperative Oncology Group Performance Status (ECOG PS) status of patients included in





**Figure 7.** Ranking of the direct and indirect comparisons of overall survival (OS) between Fruq (fruquintinib), Reg (regorafenib), TAS (TAS-102), and PLA (placebo).



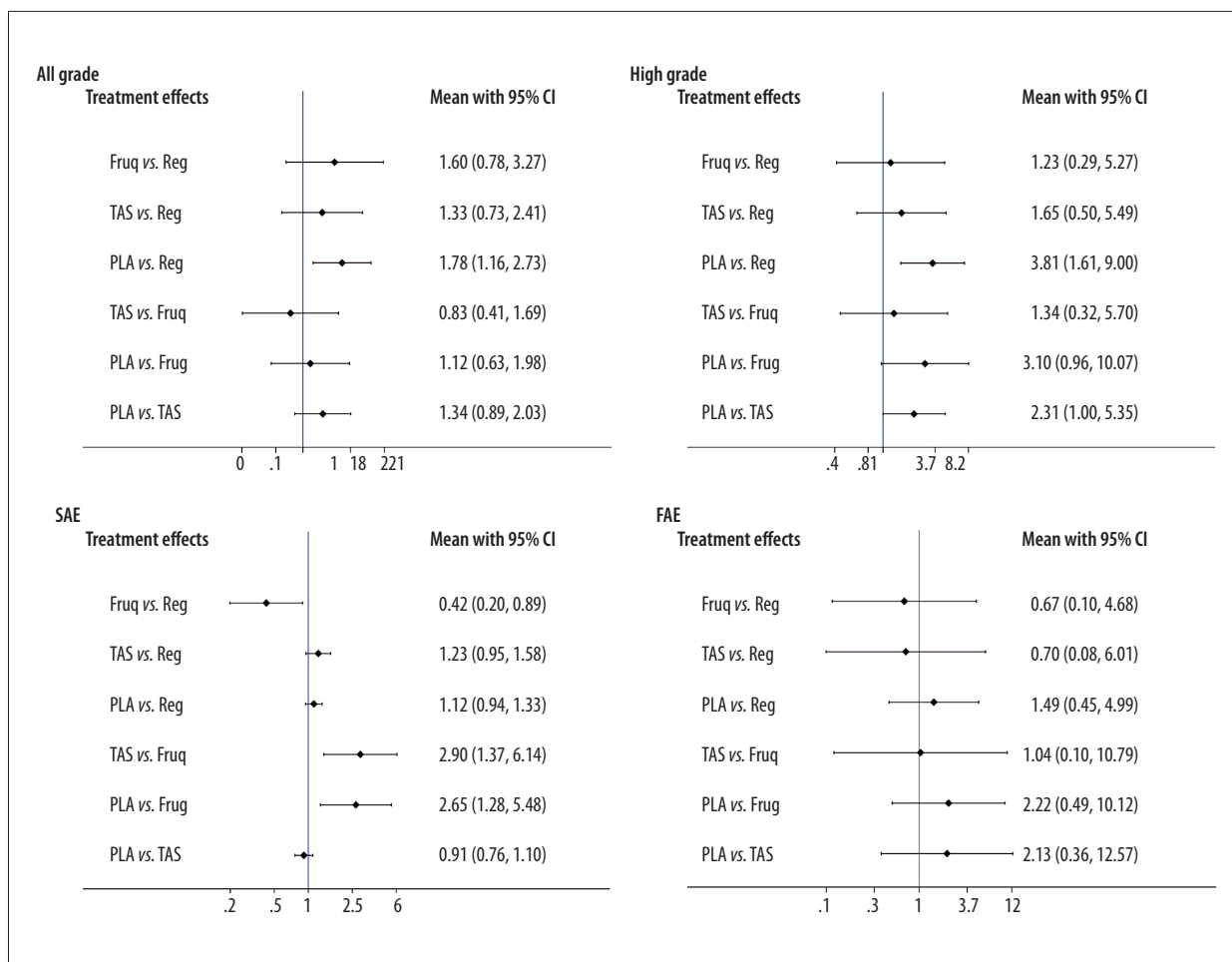
**Figure 8.** Forest plots of the direct and indirect comparisons for objective response rate (ORR) and disease-free survival (DCR) between Fruq (fruquintinib), Reg (regorafenib), TAS (TAS-102), and PLA (placebo).

the CORRECT trial [4] (regorafenib, PS=0; 56.0%) was significantly improved when compared with patients in the FRESCO trial [7] (fruquintinib, PS=0; 27.4%).

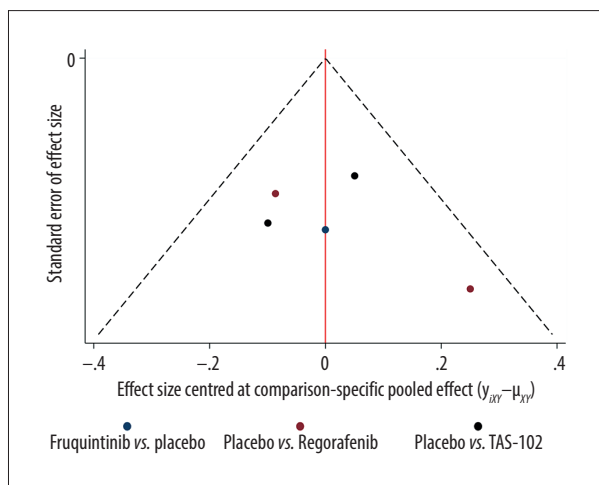
The aim of this study was to independently determine the prognostic value of performance status in cancer patients [15,16], and apply this to patients with refractory mCRC. The findings from this study indicated that fruquintinib might be more effective in the control of refractory mCRC as a further treatment option. Although a significant improvement in OS was not shown from the indirect comparison of fruquintinib and TAS-102, the poorer performance status of patients treated with fruquintinib might have been responsible for this finding. However, definitive recommendations for the choice of

treatment will only be determined by future head-to-head comparative clinical studies to compare fruquintinib and TAS-102.

A finding of interest in this study was the finding that 30% of patients included in the FRESCO trial [7] had previously received anti-VEGFR treatment. The positive results from the effects of treatment with fruquintinib compared with placebo suggested that the further use of anti-VEGFR therapy in further lines of treatment may lead to increased benefits in patients with mCRC, which supports a previously reported finding [17]. The phenomenon was also observed in patients with non-small cell lung cancer (NSCLC) [18]. A similar finding was previously reported for the use of a tyrosine kinase inhibitor (TKI) in a patient with NSCLC who had been resistant to first-line treatment with an EGFR-TKI [19]. The patient subsequently



**Figure 9.** Forest plots of the direct and indirect comparisons for adverse events (AEs) at all grades and high grade, serious adverse events (SAEs), and fatal adverse events (FAEs) between Fruq (fruquintinib), Reg (regorafenib), TAS (TAS-102), and PLA (placebo).



**Figure 10.** Funnel plot for the detection of publication bias.

had a positive response to TKI treatment in further-line therapy [19]. Therefore, re-challenge of previous treatment in the further-line therapy might be of value in selected patients with advanced or metastatic carcinomas, especially in patients with good ECOG PS (PS=0,1). Spatiotemporal heterogeneity of tumor proliferation and differentiation might have a role in this phenomenon. However, the specific mechanism of the positive results associated with drug re-challenge remains to be investigated.

The present study also included network meta-analysis of the indirect comparison between regorafenib and TAS-102. No significant differences were observed between regorafenib and TAS-102 in terms of OS. The results were consistent with the findings from a previously reported meta-analysis [8]. However, the present study was different from previous meta-analysis studies in several ways. Firstly, this study included an analysis of the TERRA trial [6], which investigated TAS-102 and was conducted in an Asian patient population with refractory mCRC.

The CONCUR trial [11], which investigated regorafenib, was conducted in Asian patient population. Inclusion of both trials in the present study may have reduced any analysis bias in the indirect comparison. Secondly, the safety profiles of the indirect comparison of regorafenib and TAS-102 was different in this study and the previously published meta-analysis, which showed that regorafenib resulted in significantly higher toxicity at all grades when compared with TAS-102 [8]. The safety profile outcomes for regorafenib, fruquintinib, and TAS-102 in the present study showed no significant difference in AEs at any grade, SAEs, or FAEs between regorafenib and TAS-102 (Figure 9). This finding may have been due to the addition of the TERRA trial [6].

A further and more recently published meta-analysis compared the efficacy and safety of regorafenib with fruquintinib in pretreated patients with mCRC [9]. The findings showed that fruquintinib showed no significant difference on OS compared with regorafenib, and there was a trend for superiority in PFS of fruquintinib compared with regorafenib, which did not reach statistical significance [9]. In the present study, there was no significant difference in PFS in the indirect comparison of fruquintinib and regorafenib. Also, there was no significant difference in OS in the indirect comparison of fruquintinib with regorafenib, of in PFS or OS in the indirect comparison between fruquintinib and regorafenib. Therefore, in the present meta-analysis, although the inclusion of four RCTs showed similar outcomes for regorafenib, and fruquintinib in patients with refractory mCRC to previous meta-analysis data [8,9], the addition of TAS-102 with the RECURSE trial [5] and the TERRA trial [6] provided more comprehensive data and findings.

In 2018, the findings from a large, retrospective, multicenter, observational study compared the efficacy of regorafenib with fruquintinib (REGOTAS) in pretreated patients with mCRC, using subgroup propensity score analysis [20]. Although there were no differences in OS between regorafenib and TAS-102 (HR, 0.96; 95% CI, 0.78–1.18), adjusted analysis, using a propensity score, showed that regorafenib resulted in improved survival in patients aged <65 years, and fruquintinib improved survival patients aged ≥65 years [20]. Also, the incidence of SAEs and FAEs were similar for regorafenib with fruquintinib [20]. The findings from this previous observational study were consistent with the findings from the present study, which also used an indirect comparison of fruquintinib and regorafenib and showed no significant difference in PFS or OS. However, the present study showed that the incidence of SAEs was reduced in patients treated with regorafenib when compared with fruquintinib, which might indicate that regorafenib may be safer in symptomatic patients with mCRC. The indirect comparison of AEs, SAEs, and FAEs for regorafenib, fruquintinib, and TAS-102

showed that the only significant difference was found for SAEs, and showed that the incidence of SAEs was more common in patients treated with fruquintinib compared with regorafenib, or TAS-102. This is an important finding for clinicians to be aware of who treat patients with mCRC. Otherwise, no differences were found from the indirect comparison in AEs at any grade or FAEs between fruquintinib, regorafenib, and TAS-102.

This study had several limitations. The network meta-analysis identified study heterogeneity, which might be explained by the racial differences in the study populations. The CONCUR trial [11] and the TERRA trial [6] were conducted in patients with mCRC from Asian populations, while the FRESCO trial [7] was conducted only in patients in China. Although a subgroup pooled analysis was performed to compare the efficacy of regorafenib, TAS-102, and fruquintinib in Asian patients with refractory mCRC, future global, multicenter, prospective, randomized studies may still be required. In addition, the type of AEs was not detailed in the presentation of the outcome data. Further studies should be considered to detail the comparisons of toxicities for fruquintinib, regorafenib, and TAS-102. Detailed clinicopathological data that included aspects of past medical history, comorbidities, and other drug treatments were not analyzed in the present study. These demographic and clinicopathological factors may be of interest in future studies. Finally, although there was no significant publication bias shown by the funnel plot, the existence of potential publication bias may not have been excluded.

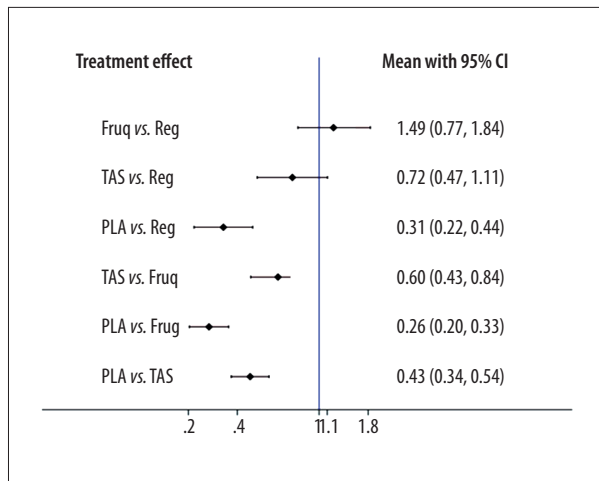
## Conclusions

This study aimed to conduct a systematic review of the literature to identify key randomized controlled clinical trials (RCTs), followed by network meta-analysis, to compare the efficacy and safety profiles of regorafenib, fruquintinib, and TAS-102 in previously treated patients with metastatic colorectal carcinoma (mCRC). The findings showed that fruquintinib was associated with significant superiority for progression-free survival (PFS) and disease control rate (DCR) compared with TAS-102. There was no significant difference in the indirect comparison of overall survival (OS) or objective response rate (ORR) between of regorafenib, fruquintinib, and TAS-102. However, the incidence of serious adverse events (SAEs) was greater in patients treated with fruquintinib compared with regorafenib or TAS-102. These findings have relevance for clinical practice.

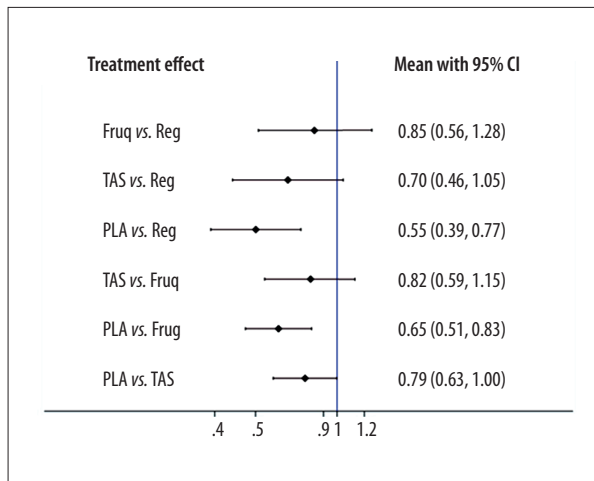
## Conflict of interest

None.

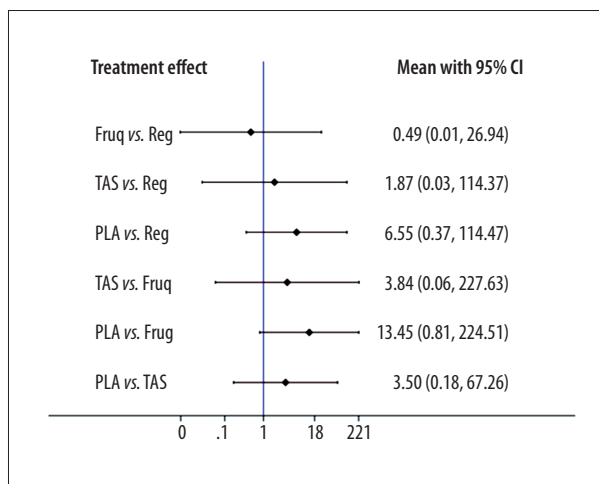
Supplementary Data



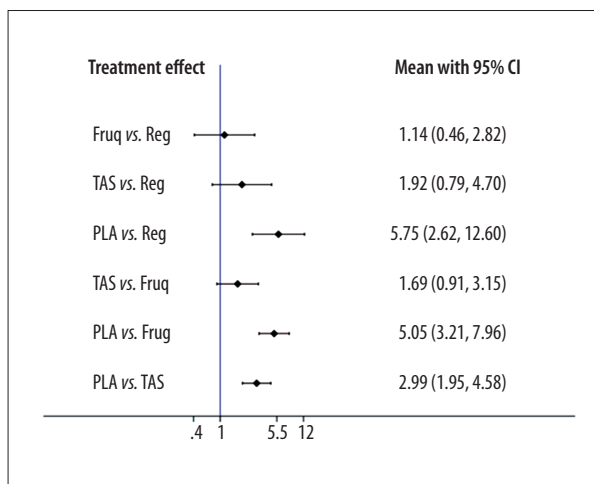
**Supplementary Figure 1.** Indirect comparisons for PFS among Fruq (fruquintinib), Reg (regorafenib), TAS (TAS-102), and PLA (placebo) among trials of FRESCO, TERRA, and CONCUR.



**Supplementary Figure 2.** Indirect comparisons for OS among Fruq (fruquintinib), Reg (regorafenib), TAS (TAS-102), and PLA (placebo) among trials of FRESCO, TERRA, and CONCUR.



**Supplementary Figure 3.** Indirect comparisons for ORR among Fruq (fruquintinib), Reg (regorafenib), TAS (TAS-102), and PLA (placebo) among trials of FRESCO, TERRA, and CONCUR.



**Supplementary Figure 4.** Indirect comparisons for DCR among Fruq (fruquintinib), Reg (regorafenib), TAS (TAS-102), and PLA (placebo) among trials of FRESCO, TERRA, and CONCUR.

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