



Adverse event costs of systemic therapies for metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy and biologics in the US

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Aim: The objective of this study was to compare adverse event (AE) management costs for fruquintinib, regorafenib, trifluridine/tipiracil (T/T) and trifluridine/tipiracil+bevacizumab (T/T+bev) for patients with metastatic colorectal cancer (mCRC) previously treated with at least two prior lines of therapy from the US commercial and Medicare payer perspectives. **Materials & methods:** A cost-consequence model was developed to calculate the per-patient and per-patient-per-month (PPPM) AE costs using rates of grade 3/4 AEs with incidence $\geq 5\%$ in clinical trials, event-specific management costs and duration treatment. Anchored comparisons of AE costs were calculated using a difference-in-differences approach with best supportive care (BSC) as a common reference. AE rates and treatment duration were obtained from clinical trials: FRESCO and FRESCO-2 (fruquintinib), RECOURSE (T/T), CORRECT (regorafenib) and SUNLIGHT (T/T, T/T+bev). AE management costs for the commercial and Medicare perspectives were obtained from publicly available sources. **Results:** From the commercial perspective, the AE costs (presented as per-patient, PPPM) were: \$4015, \$1091 for fruquintinib (FRESCO); \$4253, \$1390 for fruquintinib (FRESCO-2); \$17,110, \$11,104 for T/T (RECOURSE); \$9851, \$4691 for T/T (SUNLIGHT); \$8199, \$4823 for regorafenib; and \$11,620, \$2324 for T/T+bev. These results were consistent in anchored comparisons: the difference-in-difference for fruquintinib based on FRESCO was -\$1929 versus regorafenib and -\$11,427 versus T/T; for fruquintinib based on FRESCO-2 was -\$2257 versus regorafenib and -\$11,756 versus T/T. Across all analyses, results were consistent from the Medicare perspective. **Conclusion:** Fruquintinib was associated with lower AE management costs compared with regorafenib, T/T and T/T+bev for patients with previously treated mCRC. This evidence has direct implications for treatment, formulary and pathways decision-making in this patient population.

Plain language summary: What is this article about?: Fruquintinib, regorafenib, trifluridine/tipiracil (T/T) and trifluridine/tipiracil plus bevacizumab (T/T+bev) have demonstrated survival benefits versus best supportive care for the treatment of metastatic colorectal cancer (mCRC) that has progressed following prior lines of therapy. However, there is limited evidence on their relative safety profiles and respective adverse event (AE)-related cost burden. This study estimates the costs of grade 3/4 AEs related to these therapies based on clinical trial data.

What were the results?: The analysis found that fruquintinib was associated with a lower cost of managing AEs compared with the other therapies in previously treated patients with mCRC. A key cost-driver is the management of grade 3/4 hematologic AEs, which had the highest reported rates with T/T and T/T+bev compared with regorafenib or fruquintinib.

What do the results mean?: The cost implications of AEs associated with different treatments should be considered during treatment selection and formulary decision-making.

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Keywords: adverse events • colorectal cancer • costs • formulary decision-making • healthcare resource use • health economics • Medicare • pharmacoeconomics

Colorectal cancer (CRC) is the fourth most common cancer type and the second leading cause of cancer deaths in the US, accounting for more than 153,000 cases and 56,000 deaths in 2023 [1,2]. CRC is often diagnosed at an advanced stage, with 21–23% of patients in the US diagnosed with metastatic CRC (mCRC) [2,3]. Additionally, up to half of patients with localized disease eventually develop metastases [4]. The prognosis for patients with mCRC is very poor, with the Surveillance, Epidemiology and End Results Program and Centers for Disease Control and Prevention reporting a 5-year relative survival rate in the US of <16% for patients with distant metastases, compared with 5-year survival rates ranging from 71 to 91% in patients with localized and regional CRC [2,5].

The burden associated with mCRC necessitates an effective treatment that prolongs survival while maintaining quality of life [6,7]. However, as mCRC is a heterogeneous disease with multiple pathogenic origins and various disease characteristics, multiple treatment options are needed in the mCRC treatment armamentarium to address individual patient needs [8,9]. Other factors, such as patient age and fitness, comorbidities and drug toxicity, must also be considered in treatment selection and may limit treatment options for certain patients [10].

First-line treatment of mCRC typically consists of a chemotherapy regimen based on fluoropyrimidine, oxaliplatin and/or irinotecan, with or without therapies targeting vascular endothelial growth factor receptors (VEGFRs) or epidermal growth factor receptors (EGFRs) [11–14]. However, most patients will progress following first-line treatment [11]. The presence of various biological determinants in some patients, including rat sarcoma proto-oncogene (*RAS*) mutations or deficient mismatch repair/microsatellite instability mutational status, may additionally influence treatment strategy [11].

Patients with mCRC are exposed to numerous cytotoxic agents during their lines of therapy, which often have substantial treatment-related toxicities [12,13,15–18]. Until recently, patients who have been previously treated with chemotherapy, anti-VEGF therapy, and/or anti-EGFR therapy (if *RAS* wild type) had only regorafenib and trifluridine/tipiracil (T/T) ± bevacizumab as recommended treatment options [13,14]. Safety concerns have been associated with each of these treatments. Regorafenib has a boxed warning for severe hepatotoxicity in the US FDA Prescribing Information, and hand-foot skin reaction has been a frequently reported treatment-related and high-grade adverse event (AE) in clinical trials [17,19,20]. T/T is associated with high rates of myelosuppression, which can be severe and potentially life-threatening [18,21,22]. T/T + bevacizumab (T/T+bev) led to higher rates of grade ≥3 neutropenia than T/T alone, and almost a third of patients required treatment with granulocyte-colony stimulating factor in the SUNLIGHT phase III trial [23]. Furthermore, bevacizumab must be administered via an intravenous (IV) infusion over 30 to 90 min and is associated with infusion-related reactions [24].

Fruquintinib was recently approved by the US FDA (8 November 2023) for adult patients with mCRC who received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type and medically appropriate, an anti-EGFR therapy [25]. The most common grade 3/4 AE was hypertension [26,27], and most common AEs (incidence >20%) were hypertension, palmar-plantar erythrodysesthesia, proteinuria, dysphonia, abdominal pain, diarrhea and asthenia [25].

Despite the widely varying AE profiles of the treatment options available for patients with previously treated mCRC, there is limited evidence on the relative safety profiles and AE-related cost burden associated with these treatments. A recent study by Howe *et al.* comparing randomized trials of patients with mCRC previously treated with at least two prior lines of therapy showed lower treatment exposure-adjusted AE rates associated with grade 3/4 AEs with fruquintinib treatment compared with other treatment options [28]. This study aimed to evaluate the costs associated with managing grade 3/4 AEs related to systemic therapies in this patient population.

Table 1. Key overview of clinical trials.

Trial	Treatment	n	Median DoT (months)	Median follow-up (months)	Ref.
FRESCO	Fruquintinib + BSC	278	3.7	13.3	[26,29–31]
	Placebo + BSC	138	1.8	13.2	
FRESCO-2	Fruquintinib + BSC	461	3.1	11.3	[32]
	Placebo + BSC	230	1.8	11.2	
CORRECT	Regorafenib + BSC	505	1.7	NR	[17]
	Placebo + BSC	255	1.6	NR	
RECOURSE	T/T + BSC	534	1.54	NR	[18,33–36]
	Placebo + BSC	266	1.31	NR	
SUNLIGHT	T/T	246	2.1	13.6	[23,37]
	T/T+bev	246	5.0	14.2	

BSC: Supportive care; DoT: Duration of treatment; NR: Not reported; RAS: Rat sarcoma proto-oncogene; T/T: Trifluridine/tipiracil; T/T + bev: Trifluridine/tipiracil + bevacizumab; VEGF: Vascular endothelial growth factor.

Methods

Overall approach

The costs of AE management were estimated from a third-party payer perspective using the rates of grade 3/4 AEs occurring in $\geq 5\%$ of participants as reported in international phase III randomized clinical trials of fruquintinib, regorafenib, T/T, T/T+bev and best supportive care (BSC) and the respective AE management costs from public databases. For each AE, the cost was estimated as the AE rate multiplied by the corresponding cost of AE management. The AE cost per patient was estimated over the course of treatment for each therapy as the sum over all AEs included for cost estimation, as follows:

$$(\text{AE}_1 \text{ rate} \times \text{AE}_1 \text{ cost}) + (\text{AE}_2 \text{ rate} \times \text{AE}_2 \text{ cost}) + \dots + (\text{AE}_n \text{ rate} \times \text{AE}_n \text{ cost})$$

Because AEs occurred throughout the treatment course and the duration of treatment (DOT) was different for each therapy, per-patient-per-month (PPPM) AE costs were also calculated as the per-patient AE costs divided by the median DOT (in months) of the corresponding treatment.

In addition, anchored comparisons on AE costs were calculated between the different systemic therapies using a difference-in-differences approach with BSC as a common reference group. First, the incremental AE management costs for each systemic therapy versus BSC from the same clinical trial were calculated as mean per-patient AE costs of systemic treatment – mean per-patient AE costs of BSC. Anchored comparisons for fruquintinib versus each comparator were calculated as: (Incremental AE management cost of fruquintinib) – (Incremental AE management cost of comparator). Because there was no BSC arm in the SUNLIGHT trial, the AE burden for T/T+bev cannot be anchored to BSC.

Inputs & data sources

AE Rates & DOT

AE rates and DOT were obtained from international phase III randomized clinical trials. Specifically, data from the following trials were used as these are the clinical studies included in the US FDA Prescribing Information for each treatment: fruquintinib, FRESCO (NCT02314819) and FRESCO-2 (NCT04322539); T/T, RECOURSE (NCT01607957) and SUNLIGHT (NCT04737187); regorafenib, CORRECT (NCT01103323); T/T+bev, SUNLIGHT (NCT04737187) [19,22,25]. The treatments included fruquintinib (5 mg once daily [QD], orally [PO], 3 weeks on/1 week off) in FRESCO (n = 278) and FRESCO-2 (n = 456), T/T (35 mg/m² twice daily [BID], PO, days 1–5 and 8–12) in RECOURSE (n = 533) and SUNLIGHT (n = 246) [18,23], regorafenib (160 mg QD, PO, 3 weeks on/1 week off) in CORRECT (n = 500) [17] and with T/T+bev (T/T 35 mg/m² BID, PO, days 1–5 and 8–12 + bev 5 mg/kg QD, IV, days 1 and 15) in SUNLIGHT (n = 246) [23]. For all aforementioned trials, except SUNLIGHT, both treatment or placebo were given in combination with BSC [19,22,25]. An overview of the clinical trials included is presented in Table 1; more detailed study characteristics and baseline characteristics for each trial can be found in Supplementary Table 1 and 2.

Table 2. Unit cost of adverse events (per event).

	Medicare [39]		Commercial [40] [§]	
	DRG code	Mean cost	CCSR code	Mean cost
Anemia	811–812	\$7571.50	BLD003	\$14,587.64
Asthenia	947–948	\$6109.69	SYM007	\$14,586.58
Diarrhea	391–392	\$6319.82	SYM006	\$9286.89
Fatigue [†]	947–948	\$6109.69	SYM007	\$14,586.58
Hand foot syndrome/palmar-plantar erythrodysesthesia	606–607	\$7231.39	SKN002	\$13,658.63
Hypertension	304–305	\$6000.46	CIR008	\$9925.65
Leukopenia	814–816	\$9135.48	BLD007	\$20,350.23
Neutropenia	808–810	\$10,779.63	BLD007	\$20,350.23
Rash	606–607	\$7231.39	SYM014	\$8829.28
Thrombocytopenia	813	\$10,735.85	BLD006	\$19,497.50
	HCPCS code [42]	Mean cost	HCPCS code [43]	Mean cost
Increased alanine aminotransferase [‡]	99214	\$128.43	99214	\$221.00
Increased alkaline phosphatase level [‡]	99214	\$128.43	99214	\$221.00
Increased aspartate aminotransferase [‡]	99214	\$128.43	99214	\$221.00
Increased total bilirubin [‡]	99214	\$128.43	99214	\$221.00

[†] The management cost associated with fatigue was assumed to be the same as asthenia due to lack of data for fatigue.
[‡] The HCPCS Code 99214: Medical Oncologist Outpatient consultation – follow-up; office or other outpatient visit for the evaluation and management of an established patient, moderate level of medical decision making. 30–39 min of total time is spent on the date of the encounter.
[§] Costs of AE management for the commercial perspective were inflated from 2020 to 2023 US dollars using a factor of 1.059 from the medical care component of the Consumer Price Index [41].
 AE: Adverse event; CCSR: Clinical classifications software refined; DRG: Diagnosis related group; HCPCS: Healthcare common procedure coding system.

AE reporting procedures were largely consistent across the phase III randomized clinical trials included in the analysis [17,18,23,26,38]. AEs were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, and AE rates were estimated as the proportion of patients in a treatment arm who experienced at least one event of the AE during the study period. Across all treatments, grade 3/4 AEs occurring in $\geq 5\%$ for any treatment included: anemia, asthenia, diarrhea, fatigue, hand foot syndrome, hypertension, leukopenia, neutropenia, rash, thrombocytopenia and laboratory abnormalities (increased alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase and total bilirubin). The most frequently reported grade 3/4 AEs ($>15\%$) with fruquintinib were hypertension (16.5%) and with regorafenib were hand foot syndrome/palmar-plantar erythrodysesthesia (16.6%) and fatigue (15.4%). Both T/T and T/T+bev had high rates of hematologic grade 3/4 AEs, most notably neutropenia (43.1 and 36.0%, respectively); grade 3/4 anemia (15.9%) and leukopenia (14.6%) were also reported with T/T. Rates of grade 3/4 AEs that occurred in $\geq 5\%$ of patients treated with fruquintinib (FRESCO and FRESCO-2), regorafenib (CORRECT), T/T (RECOURSE and SUNLIGHT) or T/T+bev (SUNLIGHT) are presented in Figure 1.

DOT was based on the reported median treatment duration for every treatment and BSC in each trial (Table 1) [17,18,23,26,38]. The reported median treatment duration was selected instead of the mean treatment duration, as only the median was reported for all the treatments; the mean treatment duration was not reported for T/T and T/T+bev in the SUNLIGHT trial [37].

Unit Cost of AEs

For laboratory abnormalities, for both the Medicare and commercial perspectives, the cost of a specialist visit was used based on a medical oncologist outpatient follow-up consultation for the evaluation and management of an established patient and moderate level of medical decision making (Table 2) [39,40]. The unit costs of management for the other AEs were obtained from the 2020 Healthcare Cost and Utilization Project for the commercial perspective and the FY2023 Medicare Acute Inpatient Prospective Payment System Fee Schedule for the Medicare perspective, based on the associated average hospital charged amount identified based on inpatient management diagnosis-related group codes (Table 2) [39,40]. The costs of AE management for the commercial perspective were inflated from 2020 to 2023 US dollars using a factor of 1.059 from the medical care component of the Consumer

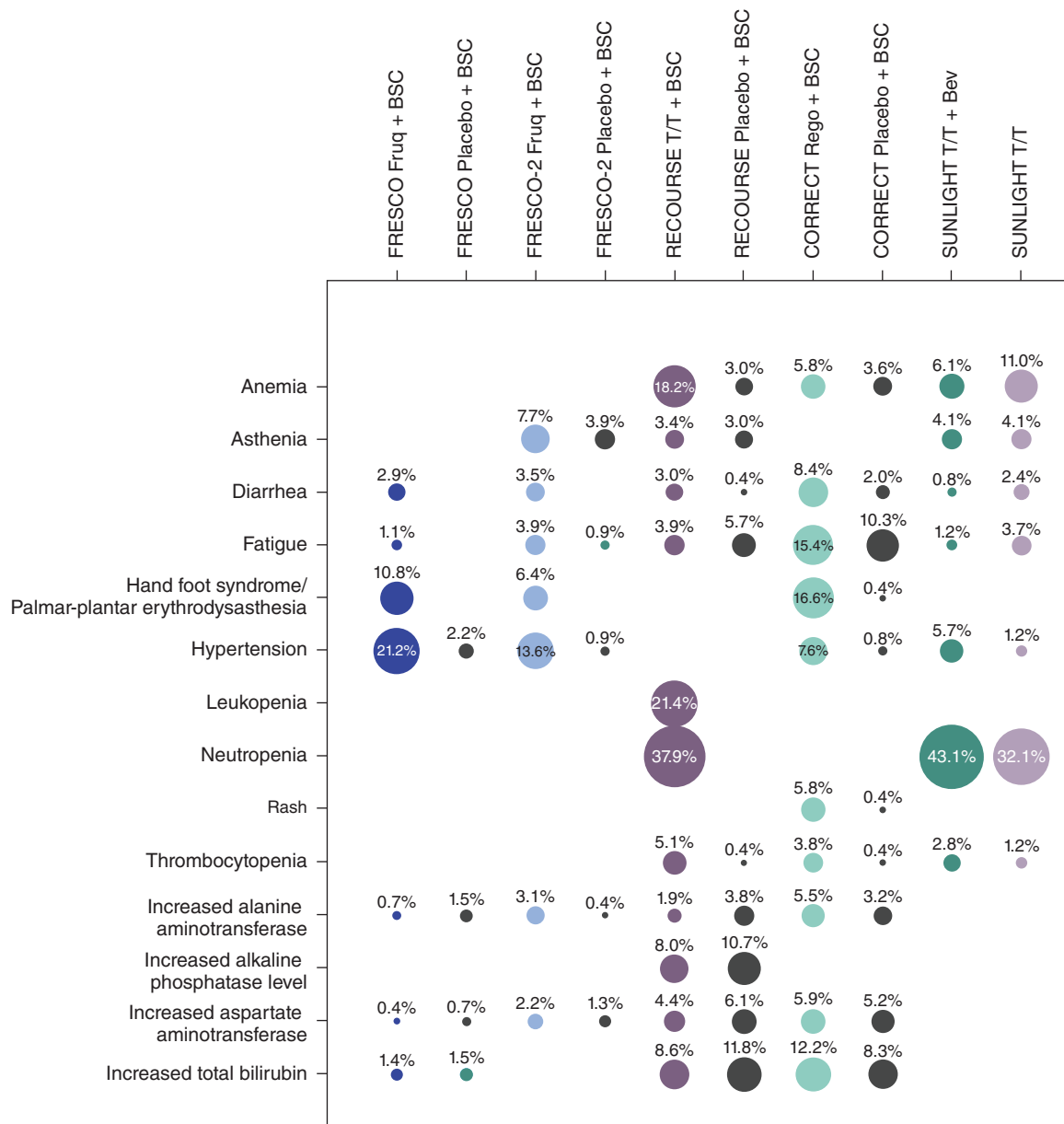


Figure 1. Rate of grade 3/4 adverse events occurring in $\geq 5\%$ of patients in FRESKO-2, FRESKO, RECURSE, CORRECT and SUNLIGHT.

AE: Adverse event; BSC: Best supportive care; Fruq: Fruquintinib; Rego: Regorafenib; T/T: Trifluridine/tipiracil; T/T + Bev: trifluridine/tipiracil + bevacizumab.

Price Index [41]. Additional details on how the management cost for each event was derived for both the commercial and Medicare perspectives is provided in [Supplementary Table 3 and 4](#).

Results

AE management costs are shown in [Table 3](#). The estimated management costs of grade 3/4 AEs of fruquintinib were lower compared with regorafenib, T/T and TT+bev, when considering costs either per-patient over the course of treatment or PPPM adjusted for median DOT, as shown in [Figure 2A & B](#). From the commercial perspective, the lowest per-patient (and PPPM) AE management costs were for fruquintinib, at \$4015 (\$1091) based on AE rates in the FRESKO trial and \$4253 (\$1,390) in the FRESKO-2 trial. The highest AE management costs were associated with T/T, at \$17,110 (\$11,104) based on the RECURSE trial and \$9851 (\$4691) based on the SUNLIGHT

Table 3. AE management costs.										
	FRESCO		FRESCO-2		RECOURSE		CORRECT		SUNLIGHT	
	Fruq + BSC	Placebo + BSC	Fruq + BSC	Placebo + BSC	T/T + BSC	Placebo + BSC	Rego + BSC	Placebo + BSC	T/T+ Bev	T/T
Per-patient over the course of treatment										
Commercial	\$4015	\$227	\$4253	\$793	\$17,110	\$1894	\$8199	\$2483	\$11,620	\$9851
Medicare	\$2307	\$137	\$2216	\$349	\$8630	\$868	\$4425	\$1191	\$6125	\$5122
PPPM, adjusted for median DOT										
Commercial	\$1091	\$123	\$1390	\$431	\$11,104	\$1445	\$4823	\$1552	\$2324	\$4691
Medicare	\$627	\$74	\$724	\$190	\$5601	\$662	\$2603	\$744	\$1225	\$2439
BSC: Best supportive care; DOT: Duration of treatment; Fruq: Fruquintinib; PPPM: Per patient per month; Rego: Regorafenib; T/T: Trifluridine/tipiracil; T/T + bev: Trifluridine/tipiracil + bevacizumab.										

Table 4. Anchor-based comparison of grade 3/4 AE costs with placebo + BSC as the common comparator.				
	Fruquintinib + BSC (FRESCO)	Fruquintinib + BSC (FRESCO-2)	T/T + BSC (RECOURSE)	Regorafenib + BSC (CORRECT)
Difference vs placebo + BSC				
Commercial	\$3788	\$3460	\$15,216	\$5717
Medicare	\$2170	\$1866	\$7762	\$3235
Difference-in-differences (based on FRESCO for fruquintinib + BSC)				
Commercial			-\$11,427	-\$1929
Medicare			-\$5592	-\$1065
Difference-in-differences (based on FRESCO-2 for fruquintinib + BSC)				
Commercial			-\$11,756	-\$2257
Medicare			-\$5896	-\$1368
AE: Adverse event; BSC: Best supportive care; T/T: Trifluridine/tipiracil.				

trial. Regorafenib and TT+bev had AE management costs between the AE management costs of T/T based on SUNLIGHT and RECOURSE. From the Medicare perspective, results were generally consistent. Per-patient (and PPPM) AE management costs for fruquintinib were \$2307 (\$627) based on FRESCO and \$2216 (\$724) based on FRESCO-2. Regorafenib-related AE management costs were \$4425 (\$2603). Finally, T/T per-patient and (PPPM) AE management costs were \$8630 (\$5601) based on RECOURSE and \$5122 (\$2439) based on SUNLIGHT, while costs for T/T+bev were \$6125 (\$1225).

These results were also consistent in anchored comparisons using placebo + BSC as a common comparator. Using the difference-in-differences method, we quantified the difference between the incremental AE management cost of fruquintinib versus the incremental AE management cost of regorafenib and of T/T in RECOURSE (Table 4). Fruquintinib had the lowest incremental cost of AE management compared with regorafenib and T/T in RECOURSE. T/T+bev was not included in this analysis due to the absence of a placebo + BSC arm in the SUNLIGHT trial. From a commercial perspective, AE cost differences for fruquintinib (FRESCO) versus the other therapies were estimated at -\$1929 versus regorafenib and -\$11,427 versus T/T. Using AE rates in FRESCO-2, cost differences for fruquintinib versus the other therapies were estimated at -\$2257 versus regorafenib and -\$11,756 versus T/T. From the Medicare perspective, cost differences for fruquintinib based on FRESCO were estimated at -\$1065 versus regorafenib and -\$5592 versus T/T. Against FRESCO-2 fruquintinib AEs, cost differences were -\$1368 versus regorafenib and -\$5896 versus T/T.

Discussion

This study compared the US costs of grade 3/4 AE management associated with fruquintinib, regorafenib, T/T and T/T+bev, using data from pivotal clinical trials. AE management costs were estimated using AE rates observed in the treatments' clinical studies included in their US FDA Prescribing Information and the costs of AE management in the US. The results indicate that fruquintinib was associated with lower AE management costs from both a Commercial and Medicare perspective. These findings suggest that the AE profile of fruquintinib translates to a lower AE management cost burden compared with regorafenib, T/T and T/T+bev.

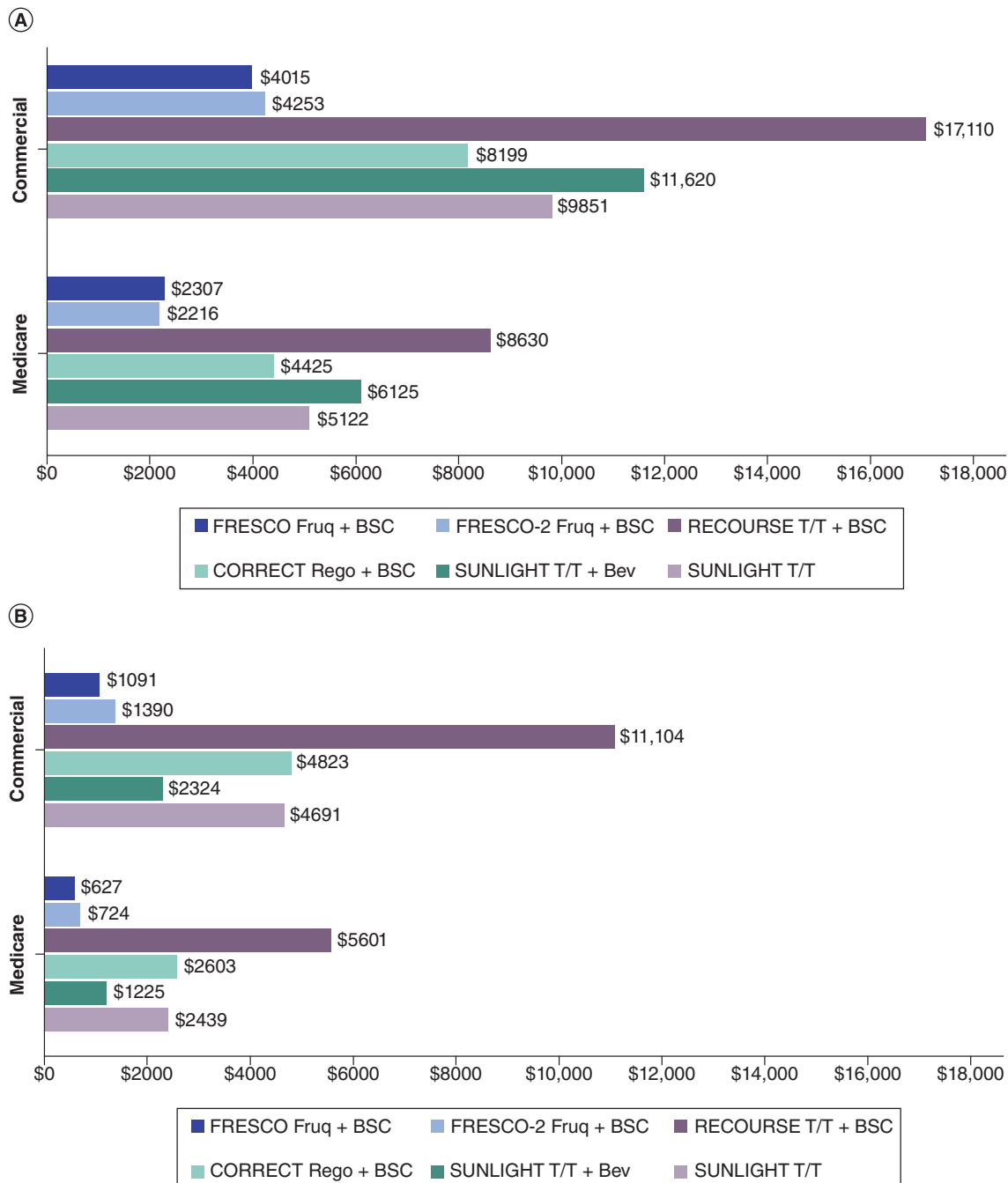


Figure 2. Commercial and Medicare per-patient adverse event management costs and per patient per month for grade 3/4 adverse events in FRESCO, FRESCO-2, RECOURSE, CORRECT and SUNLIGHT. (A) Per-patient over the course of treatment. (B) PPPM adjusted for median DOT.

AE: Adverse event; DOT: Duration of treatment; Fruq: Fruquintinib; PPPM: Per patient per month; Rego: Regorafenib; T/T: Trifluridine/tipiracil; T/T + bev: Trifluridine/tipiracil + bevacizumab.

In the RECOURSE and SUNLIGHT studies, T/T was associated with high rates of myelosuppression, which can be severe and potentially life-threatening [18,21,22]. AE costs were higher for T/T in RECOURSE than in SUNLIGHT given higher rates of AEs for T/T in RECOURSE. This may be due to RECOURSE and SUNLIGHT being conducted and published at least 8 years apart; thus, prior to the SUNLIGHT trial clinicians had real-world experience with T/T which could have led to improved management of T/T and its associated AEs. Compared with T/T and T/T+bev, the lower overall AE costs of fruquintinib are mainly attributable to the lower

rate of hematological AEs. No hematologic AEs of grade 3/4 were reported with fruquintinib in the FRESCO or FRESCO-2 studies [26,27]. Targeted inhibition of VEGFRs with limited off-target activity with fruquintinib has demonstrated a well-tolerated safety profile characterized by manageable AEs [26,38]: in clinical trials, fruquintinib treatment was associated with low rates of grade ≥ 3 AEs for hepatotoxicity, myelosuppression, gastrointestinal hemorrhage or perforation, or neutropenia, compared with higher rates for treatment with regorafenib, T/T and T/T+bev [21–23].

DOT to calculate the PPPM AE costs was based on the reported median treatment duration for every treatment and BSC in each trial [17,18,23,26,38]. This was because only the median was reported for all the treatments and the mean treatment duration was not reported for T/T and T/T+bev in the SUNLIGHT trial. The reported mean DOT in months were: 4.93 and 4.04 for fruquintinib in FRESCO and FRESCO-2, respectively [26,38]; 2.80 for regorafenib in CORRECT [17]; and 2.92 for T/T in RECURSE [18]. Using the mean DOT to adjust the per-patient AE costs, the PPPM AE costs remained lower for fruquintinib versus regorafenib and T/T from the commercial and Medicare perspectives. From the commercial perspective, PPPM AE costs, adjusted for mean DOT were \$814 and \$1053 for fruquintinib based on FRESCO and FRESCO-2, respectively, \$2928 for regorafenib and \$5858 for T/T based on RECURSE. From the Medicare perspective, PPPM AE costs adjusted for mean DOT were \$468 and \$548 for fruquintinib based on FRESCO and FRESCO-2, respectively, \$1580 for regorafenib and \$2955 for T/T based on RECURSE.

The anchored comparisons on AE costs used a difference-in-differences approach with placebo + BSC as a common reference group. FRESCO, FRESCO-2, RECURSE and CORRECT used placebo + BSC as the control arm which was typically defined in the protocol as care required to manage symptoms such as pain, infection, and/or gastrointestinal events (Table 1) [17,18,26,38]. Based on the definitions of supportive care in the trial protocols, there was no information to indicate that BSC differed substantially across trials supporting the anchored comparisons of this study.

Limitations

With the exception of laboratory abnormalities, AE management costs were estimated based on inpatient costs for grade 3 and 4 AEs. It should be noted that costs associated with grade 3 or 4 AEs which occurred at an incidence of $< 5\%$, costs associated with grade 1 or 2 AEs, and costs incurred in outpatient settings were not considered in the AE cost estimation. However, this approach is supported by the fact that inpatient costs are the main driver of AE management and that grade 3/4 AEs commonly require treatments/procedures in the inpatient setting.

Additionally, this study evaluated the AE burden of treatments based on the AE rates reported in randomized clinical trials. Cross-trial comparisons may be potentially confounded by different trial designs and the nuances of the various study populations. In particular, FRESCO-2 was conducted during the global COVID-19 pandemic, and had a more heavily pretreated population relative to the other trials included in this study [17,18,26,38]. Furthermore, patient characteristics and AEs reported in clinical trials may differ from real-world clinical practice, which may limit the generalizability of this study. As real-world use of fruquintinib develops, these analyses should be revisited in the future to confirm the findings.

Conclusion

This study was conducted to better understand the relative safety profiles and AE-related cost burden associated with systemic therapies approved for the treatment of mCRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy and if RAS wild-type, an anti-EGFR therapy. This study demonstrates that fruquintinib has a lower costs associated with the management of grade 3/4 AEs versus regorafenib, T/T and T/T+bev for the treatment of mCRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy and if RAS wild-type, an anti-EGFR therapy in the US, both from a commercial and Medicare perspective. The observed AE management cost benefits for fruquintinib are driven by the lower rates of grade 3/4 AEs compared with regorafenib, T/T and T/T+bev. A key cost-driver is the management of grade 3/4 hematologic AEs, which had the highest reported rates with T/T and T/T+bev compared with regorafenib or fruquintinib. Fruquintinib had no reported grade 3/4 hematologic AEs in FRESCO or FRESCO-2. The cost implications of AEs associated with different treatments should be considered during treatment selection and formulary decision-making.

Summary points

- Systemic therapies such as fruquintinib, regorafenib, trifluridine/tipiracil (T/T) and trifluridine/tipiracil+bevacizumab (T/T+bev) have demonstrated survival benefits versus best supportive care (BSC) in patients with metastatic colorectal cancer (mCRC) previously treated with at least two prior lines of systemic therapy, but there is limited evidence on their relative safety profiles and adverse event (AE)-related cost burden.
- A cost-consequence model was developed to calculate the per-patient and per-patient-per-month (PPPM) AE costs using rates of grade 3/4 AEs with incidence $\geq 5\%$ in clinical trials, the corresponding costs of AE management and the duration of each treatment.
- The estimated management costs of grade 3/4 AEs of fruquintinib were lower compared with regorafenib, T/T and TT+bev, when considering costs either per-patient over the course of treatment or PPPM adjusted for median DOT.
- These findings were consistent across the commercial and Medicare perspectives.
- These results were also consistent in anchored comparisons using placebo + BSC as a common comparator with fruquintinib having the lowest incremental cost of AE management over placebo + BSC compared with regorafenib and T/T.
- The observed AE management cost benefits for fruquintinib are driven by the lower rates of grade 3/4 AEs compared with regorafenib, T/T and T/T+bev.
- A key cost-driver is the management of grade 3/4 hematologic AEs, which had the highest reported rates with T/T and T/T+bev compared with regorafenib or fruquintinib.
- The cost implications of AEs associated with different treatments should be considered during treatment selection and formulary decision-making.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/ce-2024-0084>

Author contributions

VF Paly and L Hernandez made substantial contributions to the conception and design of the work, as well as data analysis. All authors made substantial contributions to the interpretation of the data for the work. All authors also had final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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