Adverse event costs associated with systemic therapies for metastatic colorectal cancer previously treated with standard therapies and biologics in the United States, Italy, Portugal and Spain

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Luis Hernandez,[1] Victoria Federico Paly,[1] Thihan Padukkavidana,[1] Arvind Dasari,[2] Joleen Hubbard,[3] Tanios Bekaii-Saab,[4] Alberto Sobrero,[5] Elena Elez[6]

[1]Takeda Pharmaceuticals America Inc., Lexington, MA, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]The Mayo Clinic, Rochester, MN, USA; [4]The Mayo Clinic, Phoenix, AZ, USA; [5]Azienda Ospedaliera San Martino, Genoa, Italy; [6]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

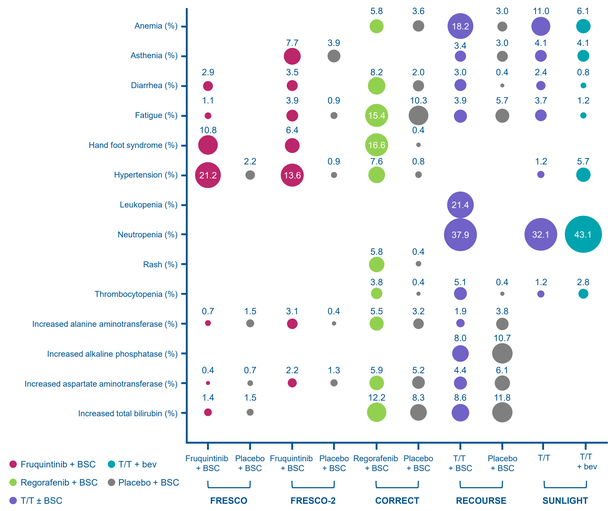
Background & Objective

- Colorectal cancer (CRC) often presents at an advanced stage, with approximately 23% of patients having developed metastatic disease (mCRC) by the time of diagnosis,[1] while up to half of patients with localized CRC at diagnosis eventually develop metastases[2]
- Until recently, regorafenib, trifluridine/tipiracil (T/T), and T/T + bevacizumab (T/T + bev) were the only available treatment options for patients who have been previously treated with chemotherapy, anti-VEGF therapy, and/or anti-EGFR therapy (if *RAS* wild type)[3–5]
  - However, treatment with regorafenib is associated with a high incidence of grade 3/4 hand-foot syndrome,[4] while treatment with T/T is associated with grade 3/4 myelosuppression[5]
- Fruquintinib is a highly selective, oral inhibitor of all three VEGF receptors (VEGFRs -1, -2, and -3) that was approved by the US FDA in 2023 for previously treated mCRC, regardless of biomarker status[6]
  - Fruquintinib is an oral therapy with once-daily dosing that has demonstrated a manageable safety profile in clinical trials; the most common grade 3/4 adverse event (AE) was hypertension[6–8]
- 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 such treatments, which have previously been identified as a driver of healthcare resource use and costs in the US and Europe[9]
- The objective of this analysis is to compare the costs of managing common grade 3/4 AEs (≥5% of patients) associated with fruquintinib, regorafenib, T/T, and T/T + bev in FRESCO,[7] FRESCO-2,[8] CORRECT,[10] RECOURSE,[11] or SUNLIGHT[12] for patients with previously treated mCRC from the payer perspective in the US (Commercial and Medicare), and from the national healthcare perspectives in Italy, Portugal, and Spain

Methods

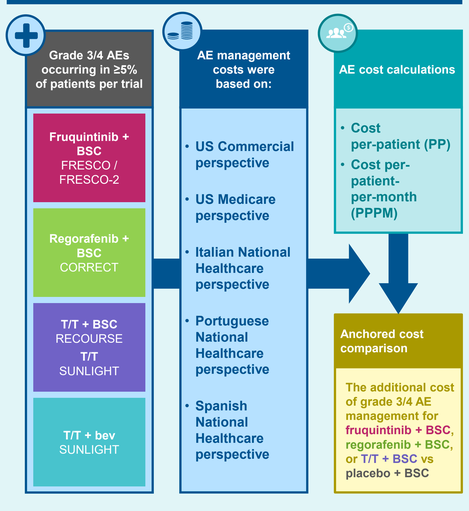
- AE rates (**Figure 1**) and treatment durations were obtained from individual patient data from FRESCO and FRESCO-2 for fruquintinib,[7,8] from CORRECT for regorafenib,[10] from RECOURSE and SUNLIGHT for T/T,[11,12] and from SUNLIGHT for T/T + bev[12]
  - Grade 3/4 AEs that occurred in ≥5% of patients who received any of the four treatments included: anemia, asthenia, diarrhea, fatigue, hand foot syndrome/palmar-plantar erythrodysesthesia, hypertension, leukopenia, neutropenia, rash, thrombocytopenia, and laboratory abnormalities (increased alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and total bilirubin) (**Figure 1**)
- In the US, AE costs were obtained from the 2020 Healthcare Cost and Utilization Project and inflated to 2023 for the Commercial perspective and from the FY 2023 Medicare Acute Inpatient Prospective Payment System Fee Schedule for the Medicaid perspective (**Table 1**)[13,14]
- AE costs for Italy, Portugal, and Spain were obtained from respective Ministry of Health public databases – inflated to 2023, as needed (**Table 1**)[15–17]
- The cost of managing laboratory abnormalities for all countries (and for both US perspectives) was based on the cost of an outpatient follow-up consultation with a medical oncologist (**Table 1**)[18,19]
- For each AE, the cost was predicted as the AE incidence rate multiplied by the corresponding cost of AE management; the total cost of all AEs per-patient was predicted for each therapy as the sum of the management costs of all AEs included for cost estimation
- Per-patient-per-month (PPPM) AE management costs were predicted as the per-patient (PP) AE management cost divided by the median duration of the corresponding treatment reported by each trial in months (**Figure 2**)
  - Median duration of treatment (months) were: 3.68 and 3.06 for fruquintinib + BSC (vs 1.84 for placebo + BSC) in FRESCO and FRESCO-2, 1.70 for regorafenib + BSC (vs 1.60 for placebo + BSC) in CORRECT, 1.54 for T/T + BSC (vs 1.31 for placebo + BSC) in RECOURSE, and 2.10 and 5.00 for T/T and T/T + bev in SUNLIGHT
- Anchored comparisons of AE costs were calculated between treatment with fruquintinib, regorafenib, and T/T (based on RECOURSE only) using a difference-in-differences approach, with placebo + BSC as a common comparator

Figure 1. Rates of grade 3/4 AEs occurring in ≥5% of patients in either FRESCO, FRESCO-2, CORRECT, RECOURSE, or SUNLIGHT

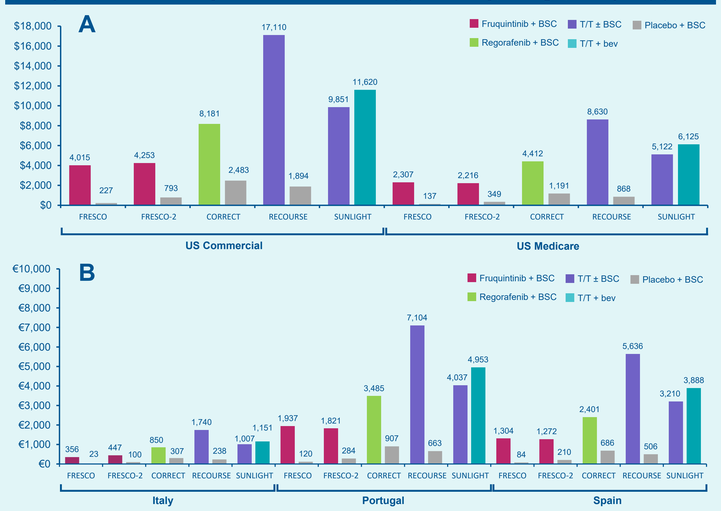


Question What are the management costs of grade 3/4 AEs related to fruquintinib, regorafenib, T/T, and T/T + bev for patients with mCRC previously treated with standard chemotherapy regimens and biologics in the United States, Italy, Portugal and Spain?

Study design



The predicted cost PP (USD and euros) of managing grade 3/4 AEs that occurred in ≥5% of patients enrolled in any of the studies in the US (A) and in Italy, Portugal, and Spain (B)



Key take aways Across the US, Italy, Portugal, and Spain, fruquintinib was associated with lower AE management costs compared with regorafenib, T/T, and T/T + bev for patients with mCRC who previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and biologics; this should be considered in treatment and formulary decision-making.

Table 1. Unit cost of managing AEs (per event) by country

Adverse Event	US				Italy[15§]		Portugal[16]		Spain[17#]	
	Commercial[13†]		Medicare[14]							
	CCSR Code	Mean Cost	DRG Code	Mean Cost	DRG Code	Mean Cost	DRG Code	Mean Cost	DRG Code	Mean Cost
Anemia	BLD003	$14,588	811-812	$7,572	395	€1,806	663	€4,898	663	€4,344
Asthenia	SYM007	$14,587	947-948	$6,110	464	€1,883	663	€4,898	861	€3,655
Diarrhea	SYM006	$9,287	391-392	$6,320	183	€1,033	249	€4,391	249	€3,241
Fatigue*	SYM007	$14,587	947-948	$6,110	464	€1,883	663	€4,898	861	€3,655
Hand foot syndrome	SKN002	$13,659	606-607	$7,231	284	€784	811	€5,930	385	€3,557
Hypertension	CIR008	$9,926	304-305	$6,000	134	€1,037	199	€5,247	199	€3,700
Leukopenia	BLD007	$20,350	814-816	$9,135	399	€1,836	660	€8,856	660	€7,019
Neutropenia	BLD007	$20,350	808-810	$10,780	399	€1,836	660	€8,856	660	€7,019
Rash	SYM014	$8,829	606-607	$7,231	284	€784	811	€5,930	385	€3,557
Thrombocytopenia	BLD006	$19,497	813	$10,736	397	€2,960	661	€8,722	661	€5,975

Adverse Event	Mean Cost[18‡]	Mean Cost[19‡]	Mean Cost[¶]	Mean Cost[¶]	Mean Cost[¶]
Increased alanine aminotransferase	$221	$128	€14	€118	€63
Increased alkaline phosphatase	$221	$128	€14	€118	€63
Increased aspartate aminotransferase	$221	$128	€14	€118	€63
Increased total bilirubin	$221	$128	€14	€118	€63

*The management cost associated with Fatigue was assumed to be the same as Asthenia due to lack of data for Fatigue. †Costs of AE management for the US 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. ‡Cost based on the HCPCS Code 99214: Medical Oncologist Outpatient consultation – Follow-up (an office or other outpatient visit for the evaluation and management of an established patient, with a moderate level of medical decision making required, and lasting 30–39 minutes). §Costs of AE management for Italy were inflated from 2013 to 2023 euros using a factor of 1.078. #Based on the cost of an outpatient follow-up consultation with a medical oncologist. ¶Costs of AE management for Spain were inflated from 2021 to 2023 euros using a factor of 1.016. Note: DRG codes vary by country due to differences in the systems/versions used, as well as country-specific adaptations.
CCSR, Clinical Classifications Software Refined; DRG, Diagnosis Related Group; HCPCS, Healthcare Common Procedure Coding System; N/A, not applicable

Results

- The predicted PP grade 3/4 AE management costs with fruquintinib, regorafenib, T/T, and T/T + bev, for the US (both Commercial and Medicare perspectives) and Italy, Portugal, and Spain, are detailed in the **Summary Panel**
- Across all countries, the predicted PP and PPPM AE management costs of grade 3/4 AEs (based on the median duration of treatment) for fruquintinib were consistently lower compared with regorafenib, T/T, and T/T + bev (**Summary Panel, Figure 2**)
- These results were also consistent in anchored comparisons using placebo + BSC as a common comparator
- Using the difference-in-differences method, fruquintinib demonstrated the lowest incremental cost of management of grade 3/4 AEs in ≥5% of patients[7,8,10–12] relative to placebo + BSC (**Table 2**)

Figure 2: Predicted PPPM cost (USD and euros) of managing grade 3/4 AEs that occurred in ≥5% of patients enrolled in each study in the US (A) and in Italy, Portugal, and Spain (B)

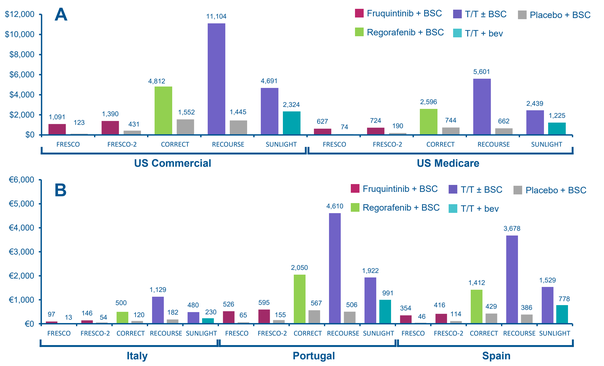


Table 2. Anchor-based comparison of grade 3/4 AE management costs, with placebo + BSC as the common comparator

	Fruquintinib + BSC (FRESCO)	Fruquintinib + BSC (FRESCO-2)	Regorafenib + BSC (CORRECT)	T/T + BSC (RECOURSE)
Difference versus placebo + BSC				
US Commercial	$3,788	$3,460	$5,698	$15,216
US Medicare	$2,170	$1,866	$3,222	$7,762
Italy	€332	€347	€543	€1,501
Portugal	€1,817	€1,537	€2,578	€6,440
Spain	€1,221	€1,062	€1,715	€5,131
Difference-in-differences (FRESCO)				
US Commercial	-	-	-$1,910	-$11,427
US Medicare	-	-	-$1,052	-$5,592
Italy	-	-	-€211	-€1,169
Portugal	-	-	-€761	-€4,623
Spain	-	-	-€494	-€3,910
Difference-in-differences (FRESCO-2)				
US Commercial	-	-	-$2,239	-$11,756
US Medicare	-	-	-$1,356	-$5,896
Italy	-	-	-€196	-€1,155
Portugal	-	-	-€1,041	-€4,903
Spain	-	-	-€653	-€4,068

Limitations

- A limitation of this analysis is that except for laboratory abnormalities, AE management costs were predicted based on inpatient costs for grade 3/4 AEs; therefore, costs associated with grade 1/2 AEs, and costs incurred in outpatient settings, were not included
  - However, inpatient management costs are the main driver of AE management costs overall, as grade 3/4 AEs commonly require management in the inpatient setting
- Another limitation is that 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. Furthermore, patient characteristics and AEs reported in clinical trials may differ from real-world clinical practice, which may limit the generalizability of this study

Conclusions

- In patients with mCRC who were previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and biologics, fruquintinib was associated with lower grade 3/4 AE management costs compared with regorafenib, T/T, and T/T + bev across all countries and payer perspectives analyzed
- The observed AE management cost benefits for fruquintinib are driven by the lower rates of grade 3/4 AEs with fruquintinib compared with regorafenib, T/T, and T/T + bev
- The cost implications of AE management associated with different treatments may be an important consideration for treatment selection and formulary decision-making

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