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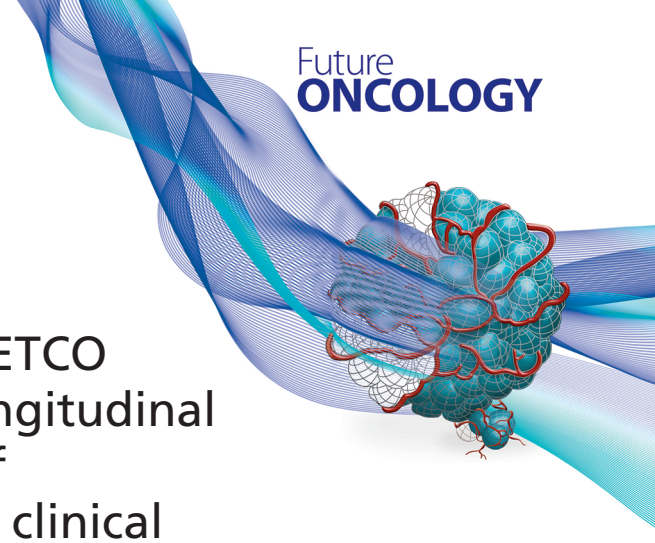
Clinical Trial Protocol

Future ONCOLOGY



Rationale and design of the PROMETCO study: a real-world, prospective, longitudinal cohort on the continuum of care of metastatic colorectal cancer from a clinical and patient perspective

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The PROMETCO study is collecting real-world data on metastatic colorectal cancer (mCRC) patients with two progressions. This international, prospective, longitudinal, observational cohort study is collecting data on mCRC patients with two disease progressions since diagnosis and receiving subsequent treatment. Objectives include overall survival, treatment patterns, effectiveness and safety and patient-reported outcomes using the EuroQol 5-level, 5-dimensional questionnaire, the Brief Fatigue Inventory and a modified version of the ACCEPTance by the Patients of their Treatment (ACCEPT©) questionnaire. Data are collected retrospectively and prospectively up to 18 months. As of 13 October 2021, 544 patients from 18 countries had been enrolled. To the authors' knowledge, PROMETCO is the first international, real-world study of the continuum of care of mCRC patients in this setting.

Trial registration number: NCT03935763 (ClinicalTrials.gov)

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Keywords: continuum of care • metastatic colorectal cancer • patient-reported outcomes • real-world evidence • study design • survival • treatment patterns

Background

In patients with metastatic colorectal cancer (mCRC), the main treatment goals include disease control and prolonging of survival, if possible [1], but these goals must be balanced with considerations for treatment-related toxicities and patient quality of life (QoL) [1,2]. Treatment options for patients with mCRC include several chemotherapeutic and targeted agents [3]. According to the 2016 European Society for Medical Oncology (ESMO) and the 2021 National Comprehensive Cancer Network guidelines, several sequential regimens and treatments are recommended according to molecular abnormalities, age, performance status and comorbidities. For patients with microsatellite stable tumors, a range of chemotherapeutic regimens may be used first-line, with or without targeted therapy, depending on the patient's tumor mutation status [1,4], while pembrolizumab is now the recommended first-line therapy for patients with microsatellite instability high (MSI-H)/mismatch repair deficient (dMMR) mCRC [5]. After first-line therapy, patients may receive alternative chemotherapy regimens, depending on previous treatments received and mutation status, such as encorafenib plus cetuximab in patients with *BRAF* V600E-mutated mCRC [6].

Future Medicine

Two treatment options – trifluridine/tipiracil and regorafenib – are approved and indicated for patients who have progressed through all standard therapies, including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents in *RAS* wild-type tumors [1,7]. Other options include re-challenge with previously used agents [1] and best supportive care [7]; however, these options often have limited effectiveness and have not been evaluated in phase 3 trials.

In RECOURSE and CORRECT, two randomized, double-blind, phase 3 trials, both trifluridine/tipiracil and regorafenib significantly improved overall survival (OS) and progression-free survival (PFS) compared with placebo, but with markedly different toxicity profiles [2,8,9]. The most common adverse events (AEs) with trifluridine/tipiracil were hematological [9], while the most common AEs with regorafenib were non-hematological [8]. Patient QoL deteriorated in both groups in CORRECT [8,10]. While QoL was not assessed in RECOURSE, *post hoc* analyses demonstrated clinically meaningful improvements in quality survival time [11,12].

Treatment guidelines are based on evidence from randomized clinical trials. In real-life clinical practice, actual prescribing patterns may be different, and previous experience and beliefs, treatment availability and reimbursement may play a role in treatment decisions, leading to a departure from evidence-based medicine. Furthermore, it is increasingly recognized that patient-reported outcomes (PROs), which to date have not been used consistently in randomized clinical trials, are a valuable tool and may inform researchers on how a therapy will perform in real-life clinical practice and on patients' perspectives on their therapy and condition, without this information being filtered by the physician [13–15]. It is currently unclear how agents are used in clinical practice in patients with mCRC who have progressed twice with available therapies from diagnosis of metastatic disease, as there are limited real-world data on OS, treatment patterns, effectiveness, safety and QoL in such patients. While several real-world studies have been conducted, they recruited patients treated with specific agents (i.e., were product-oriented) and were limited to a single country [16–24].

Here the authors outline the design of an international, real-world study in which clinical data and PROs will be collected on patients with mCRC who have progressed twice with available therapies and are initiating subsequent therapy. The aim of this study is to provide valuable real-world data on treatment patterns in a well-defined cohort of patients with mCRC (i.e., those who are fit enough and willing to receive a third-line treatment). The aims are to identify, outside the clinical trial setting, which patients receive treatment after two progressions and the treatments they receive and to evaluate the impact of treatment on QoL, as well as any key differences in treatment patterns and outcomes between countries the management of mCRC throughout the continuum of care, addressing current gaps in knowledge, including real-world OS and other broader patient- and disease-related questions.

Materials & methods

PROMETCO study design

PROMETCO (a real-world evidence prospective cohort study in the management of metastatic colorectal cancer: a clinical and patient perspective; NCT03935763) is a prospective, longitudinal, observational cohort study collecting data on patients with mCRC who have had two disease progressions since the first diagnosis of metastatic disease and who are willing to receive subsequent treatment (Figure 1). Approximately 1000 patients will be enrolled at 125 sites in 18 countries (Argentina, Austria, Belgium, Croatia, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, The Netherlands, Portugal, Slovenia, Spain, Sweden, Switzerland and the Uk). Patient recruitment, which began in March 2019, is ongoing. Treatment decisions will be made by each patient's treating physician according to local standard medical practice.

The study is being conducted according to the principles of the Declaration of Helsinki, the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology 2016 and the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. All patients must provide written informed consent, the documents of which were reviewed by the patient advocacy group Digestive Cancer Europe (DICE) before enrollment commenced. The study protocol was approved by the ethics committees of participating centers.

Objectives

The objectives of this study are to describe, in a real-world setting, the OS, treatment patterns throughout the continuum of care, effectiveness and safety of mCRC treatments; the reasons for changes/discontinuation of treatment; adherence to local and ESMO treatment guidelines; healthcare resource utilization in patients with

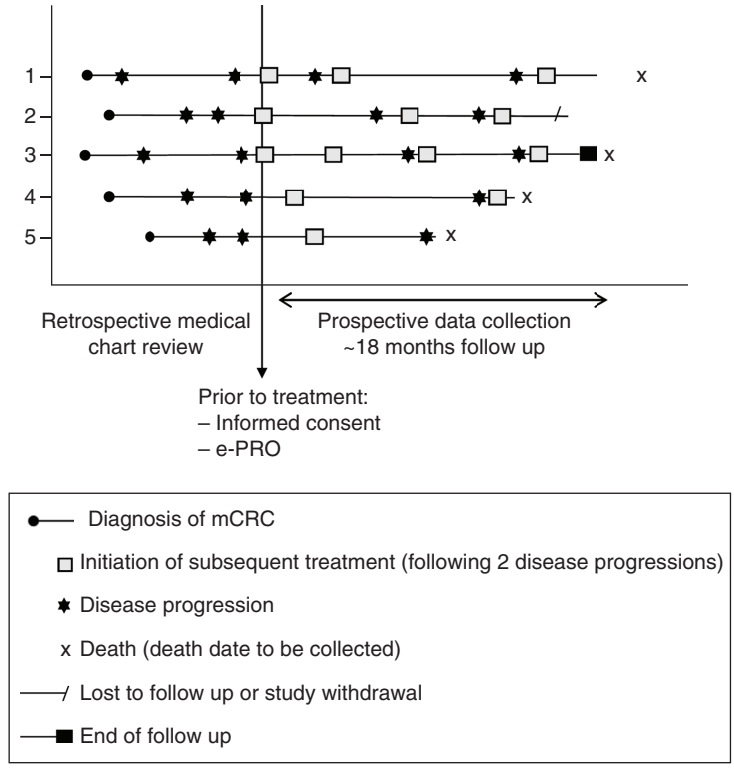

Figure 1. PROMETCO study design.
Patients are eligible for enrollment upon the initiation of subsequent treatment following two disease progressions. Numbers 1 to 5 each represent a unique patient example for potential inclusion in the study.
e-PRO: Electronic patient-reported outcome form; mCRC: Metastatic colorectal cancer.

mCRC; and PROs (including but not limited to QoL). The study will also identify any differences between countries in patient characteristics (including molecular characteristics), treatment patterns and outcomes.

Eligibility criteria

To be included in the study, patients must be aged ≥18 years, have had two disease progressions since the first diagnosis of metastasis that led to the first systemic treatment and be willing to receive subsequent treatment. Patients are excluded if they are currently receiving treatment for another cancer, currently participating in an investigational clinical trial or do not have the ability or mental capacity to participate.

Evaluations

At enrollment, data on patient demographic and clinical characteristics, treatment from mCRC diagnosis, medical history, concomitant diseases and medical resource utilization are obtained retrospectively through a medical chart review using electronic case report forms (eCRFs) and the ClinInfo electronic data capture system (Figure 1). Prospective data are then collected using the same eCRFs in conjunction with regularly scheduled follow-up visits according to local standard medical practices (Table 1) for up to 18 months from study entry. There is no fixed schedule for the follow-up visits.

Effectiveness outcomes include response to treatment (response, disease progression or stable disease assessed using the local medical standard assessments), date of response, OS and PFS. To assess OS, the date of death will be captured even if it is after the 18-month follow-up period. During the follow-up period, data on safety are being collected and reported to the appropriate local authorities. Data on healthcare resource utilization are also being collected, including concomitant medication, hospitalizations and emergency room and outpatient visits.

At enrollment and each follow-up visit, patients complete three questionnaires using an electronic PRO platform installed on a dedicated site-based tablet device. These questionnaires are the EuroQol 5-level, 5-dimensional questionnaire (EQ-5D-5L), which assesses five aspects of patient health – mobility, self-care, usual activities, pain/discomfort and anxiety/depression – using a 5-level scale (no problems, slight problems, moderate problems, severe problems and extreme problems) [25]; the nine-item Brief Fatigue Inventory (BFI), which measures fatigue in terms of severity and interference with daily life, on 10-point scales [26]; and a modified version of the ACCEPTance by the Patients of their Treatment (ACCEPT©) questionnaire [27], which measures a patient's acceptance of a

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Table 1. Schedule for retrospective and prospective data collection.

	Enrollment visit	Prospective visits	After 18 months
Demographic and clinical characteristics			
Date of birth, sex, socioeconomic factors	X		
Height	X		
Weight	X		
Smoking status	X		
Comorbidities (Charlson Comorbidity Index)	X	X	
Performance status (ECOG)	X	X	
Disease characteristics			
Diagnosis date	X		
CRC stage at diagnosis	X		
Molecular testing/status (*RAS, BRAF, MSI*/*MMS* phenotype)	X		
Primary tumor			
Sidedness	X		
Surgery/radiotherapy	X		
Metastases			
Date of first (only metachronous)	X		
Resection (including date)	X	X	
Site, number, synchronous/metachronous	X	X	
mCRC treatment characteristics			
Systemic treatments received	X	X	
Start/end dates (or note if ongoing)	X	X	
Dose and schedule		X	
Adjustments and reasons		X	
Discontinuation and reasons	X	X	
Treatment setting (outpatient/hospital)	X	X	
Reasons for initiation (patient/tumor-related)		X	
Local treatment of metastases (surgery/radiotherapy/other)	X	X	
Effectiveness			
Response to treatment	X	X	
Date of documented response	X	X	
Method of assessing response	X	X	
Safety/tolerability			
AEs		X	
Clinical progression (date and AEs related to)		X	
Abnormal blood test results	X	X	
Resource utilization			
Hospitalizations (dates, reasons, duration, treatments/procedures)		X	
Emergency room visits		X	
Outpatient visits		X	
Hospice care		X	
Concomitant medications		X	
End of study			
Date		X	X[†]
Reasons (lost to follow-up/withdrawal/death)		X	X[†]
Date of death		X	X[†]
Patient survey			
EQ-5D-5L	X	X	
Brief fatigue inventory	X	X	
ACCEPT© questionnaire	X	X	

[†]For patients who are alive after the 18-month follow-up.
ACCEPT: ACCEPTance by the Patients of Their Treatment; AEs: Adverse events; CRC: Colorectal cancer; ECOG: Eastern Cooperative Oncology Group; EQ-5D-5L: EuroQol 5-level, 5-dimensional questionnaire; mCRC: Metastatic colorectal cancer; MSI: Microsatellite instability; MSS: Microsatellite stability.

treatment and was refined by patients from DICE with the patient experience in mind and validated by the questionnaire owner. The decision to use these three questionnaires was guided by DICE.

Statistical analyses

Descriptive statistics will be employed to address the study objectives. Continuous variables will be summarized using mean, standard deviation, median and range. Categorical variables will be reported as number and percentage of patients. PFS and OS will be summarized using Kaplan-Meier survival analysis. The relationship between survival end points and different independent variables at enrollment will be analyzed using a Cox regression model. For each PRO instrument, data will be summarized by individual item, subscale and total score. QoL data will be reported for the overall study population and by the number of previous treatments.

Preliminary results

As of 13 October 2021, 544 patients from 18 countries have been enrolled, and 89% of sites were recruiting patients.

Discussion

Randomized clinical trials, on which treatment guidelines are based [1], only include selected patients; therefore, it remains unknown whether the results can be generalized to the entire patient population. It is also unclear how the recommended agents are being used in clinical practice. Physicians' previous experience or beliefs likely affect treatment decisions, causing actual prescribing patterns to differ from evidence-based recommendations. The treatment landscape for mCRC has been changing rapidly recently, with increasing use of molecular testing/biomarker assessment and targeted therapies [28]. As a result, patients may receive first- or second-line agents in clinical practice (e.g., pembrolizumab, encorafenib + cetuximab) that were not available when the phase 3 studies for later-line treatments were conducted. Thus, the treatment history of patients in the former randomized trials may not be comparable to the treatment history of real-world patients, and this may impact subsequent treatment choices and outcomes. Furthermore, treatment availability and reimbursement vary between countries [29]. Real-world studies can address these issues and contribute to the understanding of treatment effectiveness and safety, disease and treatment patterns and patient behaviors in everyday clinical practice, thus establishing a broad picture of a medication's place in the treatment of a specific disease [30–33]. Real-world studies also often include patients who have poor performance status or comorbid conditions, meaning they are normally excluded from randomized, controlled trials. To avoid these drawbacks, the PROMETCO exclusion criteria are minimal and non-stringent.

After progressing through standard guideline-recommended chemotherapy options, many patients with mCRC are still suitable and willing candidates for further treatment [2]. The two treatments approved in this patient population (regorafenib and trifluridine/tipiracil) provide similar survival benefits [8,9,19,34,35], so other considerations become important in determining the appropriate treatment, such as toxicity and QoL [2].

Another consideration is the optimal sequencing of treatment options, but this has not been established for regorafenib and trifluridine/tipiracil. Results of an observational study conducted in France suggest that there is no difference in terms of the best treatment sequence [36]; however, the outcomes of a randomized, open-label, phase 2 study investigating the feasibility, efficacy and safety of regorafenib followed upon disease progression by trifluridine/tipiracil versus trifluridine/tipiracil followed by regorafenib, which started enrolling patients in November 2020 [37], will be needed to confirm these findings. In the absence of solid data to support either option, the sequencing strategy is often determined by the toxicity profiles of these drugs, patient comorbidities and drug availability or reimbursement considerations.

PROMETCO is the first international study that will prospectively collect data for a large number of patients receiving any treatment for mCRC after two disease progressions. It has been designed to avoid many of the limitations of real-world studies, but some are inherent in studies of this nature. The main limitation is that, because there are no randomized groups and the patient population will be very heterogeneous, between-group comparisons will need to be made with caution. This study will also be subject to bias and confounding factors, particularly in the collection of retrospective data; however, the authors hope to overcome some of these limitations by also collecting data prospectively. Furthermore, the fact that the PROMETCO study includes only patients willing to receive a subsequent treatment – third line – will mean that the population is homogeneous in this regard. Such homogeneity could be a confounding factor, though how a patient's willingness to proceed with treatment could influence the study results is not known.

Conclusion

The international, prospective, observational PROMETCO study aims to collect real-world data on 1000 patients with mCRC who have had two disease progressions since their first diagnosis of metastatic disease and who are willing to receive further treatment. This will be the first international, real-world study to investigate the continuum of care in this patient population, and the first to collect data on all patients regardless of which treatment they are receiving. PROMETCO is expected to provide valuable real-world data on the continuum of care and management of mCRC in this patient population, including OS and other effectiveness, safety and PRO data, as well as some insight into the differences among local standard medical practices in countries. The first outcome results of the PROMETCO study are expected in 2024.

Summary points

- The main treatment goals in patients with metastatic colorectal cancer include disease control and prolonging of survival, if possible, which are balanced against considerations for treatment-related toxicities and quality of life.
- For patients who have progressed through all standard therapies, there are two approved treatment options – trifluridine/tipiracil and regorafenib – as well as re-challenge and best supportive care.
- Data from real-world studies are limited to patients treated with specific agents (i.e., product-oriented) or living in a single country (i.e., country-specific).
- PROMETCO fills this gap insofar as it is an international, prospective, longitudinal, observational cohort study collecting real-world data on metastatic colorectal cancer patients with two disease progressions since diagnosis and receiving subsequent treatment.
- The main objectives of PROMETCO are to collect data on overall survival, treatment patterns, effectiveness and safety and quality of life.
- Quality of life (patient-reported outcomes) will be evaluated using the EuroQol 5-level, 5-dimensional questionnaire, the Brief Fatigue Inventory and a modified ACCEPTance by the Patients of their Treatment questionnaire.
- Data will be collected retrospectively and prospectively up to 18 months for approximately 1000 patients enrolled at 125 sites in 18 countries.
- A strong feature of PROMETCO is that key trial documents were reviewed by the patient advocacy group Digestive Cancer Europe before enrollment commenced.
- PROMETCO will be the first international, real-world study to investigate the continuum of care in this patient population, and the first to collect data on all patients regardless of which treatment they are receiving.

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