A Retrospective Non-Interventional Study on First Line Treatment for Patients with $BRAF^{V600E}$ Mutant Metastatic Colorectal Cancer (mCRC)

Final Version 2.0

12 March 2020

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SIGNATURE PAGE

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

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5-FU	5-fluorouracil
ADR	Adverse Drug Reaction
AE	Adverse Event
BMI	Body Mass Index
BRAF	B- Raf proto-oncogene
$BRAF^{V600E}$	BRAF residue 600
CI	Confidence Interval
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EMR	Electronic Medical Records
EQ-5D	European Quality of Life-5 Dimensions Questionnaire
ERK	Extracellular Signal-regulated Kinase
EU GDPR	European Union General Data Protection Regulation
FAS	Full Analysis Set
FOLFOX	5-fluorouracil, leucovorin, oxaliplatin
FOLFIRI	5-fluorouracil, leucovorin, irinotecan
FOLFOXIRI	5-fluorouracil, leucovorin, oxaliplatin, irinotecan
GDPR	General Data Protection Regulation
GPP	Good Pharmacoepidemiological Practices
GVP	Good Pharmacovigilance Practices
HR	Hazard Ratio
HR-QoL	Health-related Quality of Life
ICD-10	International Classification of Diseases 10^{th} Revision
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
KM	Kaplan-Meier
KRAS	Kirsten Rat Sarcoma Viral Oncogene
LOT	Line of Treatment
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen Activated Protein Kinase
MSI	Microsatellite Instability
MMR	Mismatch Repair
NCCN	National Comprehensive Cancer Network Panel
NIS	Non-interventional Study
NLM	Neutrophil-to-lymphocyte ratio
NRAS	Neuroblastoma RAS viral oncogene homolog
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFM	Pierre Fabre Medicament
PFS	Progression Free Survival
PIK3CA	Phosphatidylinositol 3-Kinase Catalytic Subunit
PR	Partial Response
PROs	Patient-reported Outcomes
PT	Preferred Term
PV	Pharmacovigilance
QC	Quality Control
SACT	Systemic Anti-Cancer Therapy
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Class
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TNM	Tumor, Node, Metastasis
VEGF	Vascular Endothelial Growth Factor
WT	Wild Type

PROTOCOL SYNOPSIS

Background

Colorectal cancer (CRC) is the third most common cancer in men and women worldwide with an estimated 1.4 million cases and 694,000 deaths in 2012; the majority of cases occur in the developed countries.[1] About one-quarter of the patients with CRC have metastatic disease at the time of initial diagnosis and half of the patients develop metastatic disease following their initial diagnosis.[2]

First line treatment in patients with metastatic CRC (mCRC) includes a combination of chemotherapy regimens and biological agents.[3 4] Systemic anticancer therapy (SACT) is the main treatment option where combination chemotherapy remains the consensus standard of care. First line chemotherapy options include: 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX); 5-FU, leucovorin, and irinotecan (FOLFIRI); and capecitabine plus oxaliplatin.[2] Bevacizumab, an anti-vascular endothelial growth factor (anti-VEGF) agent, when given in combination with chemotherapy has shown to significantly improve overall survival (OS) compared to chemotherapy alone.[5 6] The survival benefit was retained in patients who continued using bevacizumab as a combination therapy, beyond first line progression.[7] Other biological agents such as cetuximab and panitumumab, both of which are epidermal growth factor receptor (EGFR) monoclonal antibodies, have demonstrated benefits in survival, progression free survival (PFS) and response rate when used as first-line treatment of patients with wild-type Kirsten Rat Sarcoma Viral Oncogene (KRASwt) tumors in combination with FOLFIRI and FOLFOX when compared to chemotherapy alone, but not with other oxaliplatin-based regimens such as FLOX (combination of fluorouracil, leucovorin and oxaliplatin) and CAPOX (combination of capecitabine and oxaliplatin).[8]

Approximately 10% of CRC patients have B-Raf proto-oncogene (BRAF) mutation,[9] which is a marker of poor prognosis.[10] Metastatic colorectal cancer patients with BRAF^{V6000E} mutation have median OS of 10 to 15 months compared to 21 to 35 months for patients with BRAF wild-type (BRAFwt) tumors.[11-13] Considering the prognostic importance of BRAF^{V6000E} mutation, the European Society of Medical Oncology has recommended assessment of BRAF mutation status alongside RAS gene mutation status in mCRC patients.[2]

To date, there is no agent specifically indicated for patients with BRAF^{V600E} mutant mCRC. Limited data from unplanned retrospective analyses of patients receiving first-line treatment have produced inconclusive results.[3] Because RAS and BRAF^{V600E} mutations are almost always mutually exclusive, BRAF^{V600E} mutant mCRC patients are typically treated with standard-of-care regimens for KRASwt tumors, i.e., either oxaliplatin- or irinotecan-based SACT, with or without bevacizumab (anti-VEGF antibody) or cetuximab (anti-EGFR antibody) but with substantially poorer outcomes than patients without BRAFwt tumors. A retrospective study reported no differences in PFS irrespective of whether oxaliplatin- or irinotecan-based chemotherapy was administered in the first-line setting in patients with BRAF mutant CRC (6.4 versus 5.4 months; P=0.99).[14] There is insufficient evidence to conclude that BRAF is a predictive biomarker for irinotecan or oxaliplatin, as patients benefit regardless of their mutational status.

In the Phase III study TRIBE, BRAF-mutated mCRC patients treated with the combination of 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab showed a trend towards improved OS with 19.0 months compared with 10.7 months (hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.24–1.20) and PFS (HR 0.57, 95% CI 0.27–1.23) compared with FOLFIRI plus bevacizumab among the 28 patients with BRAF mutation.[15 16] FOLFOXIRI plus bevacizumab, however, significantly increases the incidence of grade 3 or grade 4 adverse events (AEs) in mCRC patients compared to FOLFIRI plus bevacizumab.[17]

Rationale

The presence of a BRAF^{V600E} mutation is considered a marker of poor prognosis in patients with mCRC, and findings from clinical trials have largely remained inconclusive regarding the efficacy of first line treatments for BRAF-mutant mCRC patients. In the absence of targeted/specific treatment for BRAF-mutant mCRC, treatment practices can vary based on local practices and guidelines. There is, therefore, an unmet need to document the current practices for first-line treatment of BRAF-mutant mCRC, and their effectiveness and safety in a real-world setting.

This real-world, multicenter non-interventional study (NIS) will describe the treatment patterns, effectiveness and safety of current treatment regimens in BRAF^{V600E} mutant mCRC patients in Europe, with the aim to put the clinical study findings of the ongoing Phase 2, single-arm, open label trial (ANCHOR) into context of the current treatment landscape excluding investigational therapies. Additionally, the NIS output may be used to support future health technology assessment submissions and publications.

Objectives

Primary objective

To describe first line treatment patterns in BRAF^{V600E} mutant mCRC patients.

Secondary objectives

1. To describe baseline demographic and clinical profile of BRAF^{V600E} mutant mCRC patients receiving first-line treatment, overall and by treatment regimen
2. To describe PFS in BRAF^{V600E} mutant mCRC patients receiving first-line treatment, overall and by treatment regimen
3. To describe OS in BRAF^{V600E} mutant mCRC patients receiving first-line treatment, overall and by treatment regimen
4. To describe treatment response in BRAF^{V600E} mutant mCRC patients receiving first-line treatment, overall and by treatment regimen
5. To describe treatment duration (i.e., time to treatment cessation) in BRAF^{V600E} mutant mCRC patients receiving first-line treatment, overall and by treatment regimen
6. To describe BRAF mutation testing procedure and timing in regards with the first-line treatment in BRAF^{V600E} mutant mCRC patients
7. To describe the frequency of relevant AEs in BRAF^{V600E} mutant mCRC patients receiving first-line treatment, overall and by treatment regimen

Exploratory objectives

1. To describe the reason(s) for treatment discontinuation or switch in BRAF^{V600E} mutant mCRC patients starting first-line treatment
2. To describe the treatment(s) received, by line of treatment (LOT), after first progression in BRAF^{V600E} mutant mCRC patients

Study design

This retrospective, multi-center longitudinal study on BRAF^{V600E} mutant mCRC patients will be conducted in Europe to characterize the first-line treatment patterns. All BRAF^{V600E} mutant patients having initiated a first-line treatment for mCRC between January 1st, 2016 and December 31st, 2018 (both days inclusive) with drugs registred for mCRC in respective country will be eligible to participate. Thus the observation period is earlier than the date of inclusion of the patient in the study. The study will not provide or recommend any treatment or procedure; all decisions regarding treatment are made at the sole discretion of the treating physician in accordance with their usual practices and all eligible patients will be considered for enrollment.

The target countries for patient enrollment will include Germany, France, Italy, UK, Spain, Belgium, Austria and the Netherlands. Approximately 300 adult patients (≥18 years) from a mix of academic and non-academic sites (up to 65 sites) will be enrolled.

In order to obtain a representative sample of real-world patients undergoing treatment for BRAF^{V600E} mutant mCRC, an evidence-based approach will be adapted to (1) find and select sites within a country that meet the right criteria for success and representability (taking into account various site-level factors such as center type [public/private, academic/non-academic], center size, center practice, etc.), and (2) identify and mitigate risks that could impact patient enrollment. A strategy plan for site selection will be created before site enrolement to ensure site representativeness, and will describe all processes related to the representativity survey. The site survey will be conducted prior site selection.

Patient data will be collected from the date of the start of first-line treatment for mCRC until the end of the observation period (date of death or last day of study observation period for patients alive at the time of data abstraction). Patients lost to follow-up will be censored at the date of their last available medical record.

For eligible patients, relevant data will be abstracted from their medical records and entered into a centrally-designed electronic case report form (eCRF). The data will be anonymized during the entry into the eCRF by using an algorithm which generates a random patient number without any indication of the patient, centre or country. This anonymization will be maintained in the database used for statistical analysis.

Study population

Patients diagnosed with BRAF^{V600E} mutant mCRC (determined by local laboratory result) in the target countries and initiating first line treatment between January 1st, 2016 and December 31st, 2018 (both days inclusive) will be eligible for enrollment into the study.

The following inclusion and exclusion criteria will be applied:

Inclusion criteria

Patients will be eligible for inclusion if they fulfil all the following criteria:

- Male or female aged ≥18 years at diagnosis for mCRC
- Diagnosis of histologically or cytologically confirmed CRC that is metastatic and unresectable
- Presence of BRAF^{V600E} mutation in tumor tissue, as determined by a local assay
- Initiated first-line treatment with drugs registered for mCRC in the respective country at the time of treatment between January 1st, 2016 and December 31st, 2018 (both days inclusive)
- Provision of informed consent or non-opposition to the patient (or next-of-kin, if applicable) for the use of data, according to local regulations

Exclusion criteria

Patients will be excluded from the study if they fulfil any of the following criteria:

- Patients with another concomitant tumor (or neoplasm) at the time of diagnosis*
- Patients participating in interventional trials on investigational drugs at the time of initiation of first-line treatment

* Except for non-metastatic non-melanoma skin cancers, or in situ or benign neoplasms; a cancer will be considered concomitant if it occurs within 5 years of mCRC diagnosis.

For patients who fulfil the eligibility criteria, but do not participate in the study (non-consent or opposition, non-inclusion because of patient selection process), a screening log will be maintained (subject to local regulations) to record the reason for non-participation, gender, age at diagnosis, first line treatments received (if available) and survival status.

Patient selection process

In each participating center, all eligible patients will be identified and assigned a random number. Data will be abstracted consecutively. If necessary applicable by local regulations, written informed consent from patient or next of kin (for patients alive at the time of data abstraction and for dead patients, if required by local regulations) will be obtained prior to data abstraction. If consent is needed and not provided, the reason will be noted in a screening log.

Data collection/data sources

The source of collected data will be all elements that can constitute a reliable source of patient-level information and that are available at the site. This includes data available in the patient medical charts (e.g., consultation notes, discharge summaries, laboratory test results, recorded prescription data and any other documentation of communication with other health care providers). The site investigator will be responsible for ensuring that all the required data is collected and entered into the eCRF.

The exposure of interest will be the first line SACT (monotherapy, doublet chemotherapy, or triplet chemotherapy with or without a targeted therapy [either VEGF inhibitor or EGFR inhibitor]) for the treatment of BRAF^{V600E} mutant mCRC.

The following key data items will be collected, where available:

- Patient demographic and clinical characteristics
  - Age, gender, weight, height, body mass index at mCRC diagnosis
  - Date of diagnosis of CRC and mCRC
  - Performance status using Eastern Cooperative Oncology Group score at at mCRC diagnosis
  - Comorbidities at mCRC diagnosis
  - Tumor/node/metastasis stage (I, II, III, IV) at the time of initial diagnosis of CRC
  - Histology at the time of initial diagnosis of CRC: adenocarcinoma, other carcinoma

  - Location of the primary tumor at the time of initial diagnosis of CRC: colon left-sided, colon right-sided, colon transverse, rectum, unknown
  - Tests and diagnosis collected at mCRC diagnosis or during follow-up
    - Tumor Biomarker Assessments: BRAF on tumor sample or ctDNA (including date of ordering test and date of test result); RAS; MSI (microsatellite instability); MMR (mismatch repair)
    - Blood biomarker assessments: C-reactive protein; CEA; CA 19-9
  - Biological parameters
    - Other selected routine laboratory tests at at mCRC diagnosis
  - Metastasis
    - Location: Liver, lung, lymph nodes, bone, peritoneum, central nervous system, other locations, unknown
    - Number of metastatic sites

- Treatment history at mCRC diagnosis and during follow-up
  - Prior medications/therapies/procedures for treatment of CRC
  - Treatment for mCRC
    - LOT (to be derived using a data-driven approach if disease progression is poorly documented in the patient medical record)
    - SACT medications (chemotherapies and targeted therapies): monotherapy, doublet therapy or triplet therapy; name of the agent(s); start date and end date
    - Treatment alteration (e.g., switch, discontinuation, dose reduction): dates and reasons for treatment alteration
    - Maintenance therapy (if any) of first-line treatment: name of agent(s); start date and stop date
  - Treatment response (as recorded in patient medical record by the treating physician) of first-line treatment of mCRC: type of response: complete response (CR), partial response (PR), progressive disease (PD); date recorded
  - Date of documented progression
  - Date of death or last patient visit date; cause of death (if patient died)

- Safety data
  - Relevant AEs reported during the follow-up period. Relevant AEs are defined as AEs leading to first-line treatment switch, dose adaptation or discontinuation, or leading to death.

The data collection schedule is presented in Table 4.

All relevant AE data will be extracted from medical records and mapped into the Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class (SOC) and preferred term (PT).

Data management and quality assurance

A data management plan will be created before the start of data collection and will describe all functions, processes, and specifications for data collection, cleaning and validation to ensure that the data are as clean and accurate as possible when presented for analysis. Data collection and validation procedures will be detailed in appropriate operational documents.

A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented. Data quality control (QC) will be performed remotely and at the site level, where permissible according to local regulations, by qualified designated personnel under professional secrecy.

All medical data will be confidential. Pierre Fabre Medicament (PFM), as the Sponsor of the study and data controller, is responsible for the processing of personal data in accordance with the provisions of Regulation 2016/679/EU of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and the free movement of such data (GDPR), the data collected being for research purposes in the field of health, the legal basis of the processing being the legitimate interest of the data controller.

Safety

Within the timeframe of study documentation/data collection, Pierre Fabre has not registered any drug used for the treatment of mCRC, therefore no Pierre Fabre-owned drug was authorized for use within clinical routine treatment for mCRC or BRAF^{V600E}-mutant mCRC. Moreover, patients treated in the frame of interventional clinical studies for mCRC and patients treated with concomitant systemic therapies for cancers other than mCRC, will be excluded. Therefore, this NIS is not expected to generate any safety reports with regard to Pierre Fabre-owned drugs within the frame of the eligibility criteria.

Irrespective of this retrospective anonymized data retrieval, the participating physicians will be reminded of their general reporting obligations with regard to adverse drug reactions concerning any Pierre Fabre product or drugs of other manufacturers in accordance with the respective national law and regulations.

Study endpoints

Primary endpoint

First-line SACT treatment patterns in BRAF^{V600E} mutant mCRC patients, described by:

- Agent or combination of agents received
- Duration of treatment
- Maintenance therapy (if any)

The first-line SACT regimen(s) will be described from the time of treatment initiation (for mCRC) until the time of first documented disease progression or treatment discontinuation, whichever is earlier.

LOT definition will be connected to treatment progression. The LOT will be defined using a data-driven algorithm; in the Statistical Analysis Plan (SAP) an algorithm for LOT definition will be specified, which will consider the specific treatment(s) received (stop and start dates), progression, tumor response (as recorded in the patient medical record, including date), documented reasons for discontinuation of treatments and gap(s) between subsequent treatment regimens, and will be further elaborated in the protocol and the SAP.

Secondary endpoints

1. Description of demographic and clinical profile of patients at the time of treatment initiation (for mCRC)
2. PFS, defined as the length of time between initiation of first-line treatment for mCRC and the first documented disease progression (if disease progression is not well documented in patient's medical record, then start of subsequent LOT may be considered as proxy for disease progression) or death (whichever is earlier)
3. OS, defined as the time between first-line treatment initiation (for mCRC) and death (due to any cause)
4. ORR, defined as CR or PR, described at the end of firstline treatment for mCRC
5. Time to treatment cessation, defined as the length of time between initiation of first-line treatment for mCRC and documented disease progression (or start of subsequent LOT, if disease progression is not well documented in patient medical record), treatment discontinuation or switch to another treatment (defined as change from one treatment regimen to another treatment regimen, e.g., change from FOLFOX-based regimen to FOLFIRI or irinotecan-based regimen)
6. Time to BRAF mutation testing since mCRC diagnosis and since first-line treatment for mCRC, and description of testing procedures
7. Frequency of relevant AEsduring first-line treatment for mCRC. Relevant AEs are defined as AEs leading to first-line treatment switch, dose adaptation or discontinuation, or leading to death.

Exploratory endpoint(s)

1. Description of reasons for treatment discontinuation or switch at the end of first-line treatment for mCRC
2. Second (and subsequent) line treatment patterns in BRAF^{V600E} mutant mCRC patients, defined as treatments received after disease progression following first line treatment, and described by:
   - Agent or combination of agents received
   - Duration of treatment

Statistical considerations

Sample size

The primary objective of this NIS is to assess the treatment patterns of $BRAF^{V600E}$ mutant mCRC patients. The sample size was determined based on the precision with which the primary objective could be achieved. Precision estimates (95% [CIs) were calculated around percentages ranging from 1% to 20% for sample sizes ranging from 200 to 1000. The range of proportions was determined based on projected estimates of patient share as per different regimens in first-line of therapy in UK, Germany, France, Spain, and Italy using Oncology Dynamics data which projected proportions of different lines of therapy between 1% to 21%. A sample size of 300 patients will be able to measure treatment regimens prescribed to 5%, 10%, and 20% patients with a precision of ±2.5% (95% CI: 2.5% to 7.5%), ±3.4% (95% CI: 6.6% to 13.4%) and ±4.5% (95% CI: 15.5% to 24.5%), respectively. This was considered adequate to meet the descriptive objectives of this study. Further details are provided in section 3.5.

Statistical analyses

Statistical analyses will be fully described in a written SAP. The study endpoints will be analyzed overall, by country and by predefined subgroup(s) of interest (e.g., age, gender, primary tumor location, number of metastatic organs). Analyses will be descriptive in nature, as no hypothesis will be tested. In general, missing data will not be imputed (except for dates) and the data will be analyzed according to the complete case approach.

The treatment patterns of patients, baseline demographic and clinical characteristics, time to BRAF mutation testing and description of testing procedures, and reasons for treatment discontinuation will be described using summary statistics. Categorical variables will be summarized by frequencies and percentages. Continuous variables will be summarized by descriptive statistics (mean, and standard deviation, median, 25^{th} and 75^{th} percentiles, minimum and maximum). The number of missing observations for each variable will also be reported. Relevant AEs will be coded by MedDRA and summarized as SOC and PT.

Time-to-event data (PFS, OS, time to treatment cessation) will be evaluated using Kaplan-Meier survival curves. Median survival estimates will be reported along with the 25^{th} and 75^{th} percentiles, and corresponding 95% CIs. Cox regression analysis may be performed to adjust for predefined (baseline) covariates.

Objective response rate (best overall response of CR or PR) will be summarized using frequency tables with their associated 95% CIs. Logistic regression may be used to adjust for predefined (baseline) covariates.

Ethical and regulatory considerations

This study will be conducted under the guidelines of good pharmacoepidemiology practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, the European Union General Data Protection Regulation (EU GDPR) and any applicable national guidelines.

Consistent with local regulations and prior to enrollment of patients at a given site, the study protocol will be submitted together with its associated documents (e.g., informed consent form [ICF]) to the responsible IRB/IEC for its review. Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations.

The data will be anonymized during the entry into the eCRF by using an algorithm which generates a random patient number without any indication of the patient, centre or country. This anonymization will be maintained in the database used for statistical analysis. The patient will be informed of this data collection according to applicable regulations.

1 BACKGROUND AND RATIONALE

Globally, colorectal cancer (CRC) is the third most common cancer in men and women, with an estimated 1.4 million new cases and 694,000 deaths in 2012; the majority of which occur in developed countries. In Europe, CRC is the second most common cancer, with an estimated 447,136 new cases and 214,855 deaths in 2012.[1] Approximately one-quarter of patients with CRC have metastatic disease at the time of initial diagnosis and half of the patients develop metastatic disease following their initial diagnosis.[2]

Metastases in CRC can be synchronous (detected prior/during surgery of the primary tumor or within 3 to 12 months following initial intervention) or metachronous (discovered more than 1 year after surgical resection of the primary tumor). Synchronous metastases are usually associated with a locally advanced CRC following a greater metastatic burden and a poor outcome.[18] The most frequently involved organs in metastatic CRC (mCRC) are the liver, peritoneum, lungs, bone and brain. The liver is often the single site of metastasis in CRC at the time of initial diagnosis (20% to 25% of cases) or after resection of the primary tumor (40% of cases).[19] Peritoneal metastases are detected in 4% to 19% of patients after surgical resection of the primary tumor, and have survival rates of 5-24 months.[20] Lung metastases occur in 10% to 30% of patients at 5-60 months after resection of the primary tumor.[21] The incidence of bone metastases in CRC varies from 6% to 10%, with a median time of detection of 11-21 months after resection of the primary tumor.[22] Brain metastases occur in 2% to 12% of CRC patients during the course of the disease, with a median survival rate ranging from 2.8 to 6 months without surgery and from 6 to 10 months after metastatic resection.[23] Recent research suggests that certain gene mutations, such as Kirsten Rat Sarcoma Viral Oncogene (KRAS), B-Raf proto-oncogene (BRAF), phosphatidylinositol 3-kinase catalytic subunit (PIK3CA), and Neuroblastoma RAS viral oncogene homolog (NRAS) oncogenes, may affect the metastatic behavior of tumors and the patterns of metastatic spread.

Treatment options for mCRC patients

First-line treatment in patients with mCRC includes a combination of chemotherapy regimens and biological agents.[3] [4] Systemic anti-cancer therapy (SACT) is the main treatment option where combination chemotherapy remains the consensus standard of care. Current guidelines advocate the doublet combinations with oxaliplatin (5-fluorouracil [5-FU], leucovorin, and oxaliplatin [FOLFOX]) or irinotecan (5-FU, leucovorin, and irinotecan [FOLFIRI]) based regimens.[2] These regimens are shown to be superior to combination of 5-FU and folinic acid alone.[24]

Targeted therapy, including vascular endothelial growth factor (VEGF) inhibitor benvacizumab or epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab and panitumumab), is currently recommended by clinical guidelines as selective addition to the chemotherapy regimens, taking into account patient's RAS status.[2] Bevacizumab, when given in combination with chemotherapy has shown to significantly improve overall survival (OS) compared to chemotherapy alone.[5] [6] The survival benefit was retained in patients who continued using bevacizumab as a combination therapy, beyond first-line progression.[7] Other biological agents such as cetuximab and panitumumab, both of which are EGFR monoclonal antibodies, have demonstrated benefits in survival, progression free survival (PFS) and response rate when used as first-line treatment of patients with wild-type KRAS (KRASwt) tumors in combination with FOLFIRI and FOLFOX when compared to chemotherapy alone, but not with other oxaliplatin-based regimens such as FLOX

(combination of fluorouracil, leucovorin and oxaliplatin) and CAPOX (combination of capecitabine and oxaliplatin) .[3 8]

B-Raf proto-oncogene mutant colorectal cancer

BRAF encodes a serine/threonine protein kinase belonging to the RAS/RAF/mitogen activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) kinase pathway that has been implicated in pathophysiology proliferation, invasion, and metastasis in CRC.[25] Approximately 5% to 15% of CRC patients have a mutation in the BRAF gene resulting in a valine-to-glutamate change at the residue 600 (V600E), which is nearly always mutually exclusive with the RAS mutation.[6 9 26 27] Multiple clinical trials suggest that BRAF mutation is a poor prognostic factor for mCRC.[10 12 28 29]

Metastatic CRC patients with BRAF mutation have median OS of 10 to 15 months compared to 21 to 35 months for patients with BRAF wild-type (BRAFwt) tumors.[11-13] Patients with BRAF mutation have more adverse histologic features, such as lymphatic invasion, mean number of lymph node metastases, perineural invasion, and high tumor budding.[30] Studies suggest that BRAF mutant mCRC is less likely to present liver-limited metastasis and is associated with increased incidence of peritoneal and distant lymph node involvement.[12 29 31 32] This pattern of metastatic spread in BRAF mutant mCRC may contribute to the poor outcomes.[12 33]

Considering the prognostic importance of BRAF mutation, the European Society of Medical Oncology and the National Comprehensive Cancer Network panel have recommended assessment of BRAF mutation status alongside RAS gene mutation status in mCRC patients.[2 34]

Treatment options for BRAF mutant mCRC patients

To date, there is no agent specifically indicated for patients with BRAF mutant mCRC. Limited data from unplanned retrospective analysis of patients receiving first-line treatment have produced inconclusive results.[3] Because RAS and BRAF^{V600E} mutations are almost always mutually exclusive, BRAF mutant mCRC patients are typically treated with standard of care regimens for KRASwt tumors, i.e., either oxaliplatin- or irinotecan-based SACT, with or without bevacizumab (anti-VEGF antibody) or cetuximab (anti-EGFR antibody) but with substantially poorer outcomes than patients with BRAFwt tumors.

A retrospective study reported no differences in PFS irrespective of whether oxaliplatin- or irinotecan-based chemotherapy was administered in the first-line setting in patients with BRAF mutant CRC (6.4 versus 5.4 months; P=0.99).[14] There is insufficient evidence to conclude that BRAF is a predictive biomarker for irinotecan or oxaliplatin, as patients benefit regardless of their mutational status.

With regards to targeted agents, in a post-hoc analysis of a Phase 3 trial comparing bevacizumab-based chemotherapy with chemotherapy alone, it was reported that BRAF mutation status predicted poor survival overall but had no impact on bevacizumab benefit.[35] BRAF mutation status predictive value for response and benefit from EGFR-directed treatments, such as cetuximab, remain controversial.

Limited data from unplanned retrospective subset analyses of subjects with mCRC treated in the first-line setting suggest that, although a BRAF^{V600E} mutation confers a poor prognosis regardless of

treatment, subjects with disease characterized by this mutation may receive some benefit from the addition of cetuximab to front-line therapy.[13 36]

Retrospective analyses of recent trials have suggested that *BRAF* mutations are not predictive of outcome with EGFR-directed therapies[37] in certain settings whereas other analyses have suggested that cetuximab and panitumumab are most active in subjects with *BRAF*wt mCRC[26 38]. In a recent meta-analysis of 7 randomized controlled trials in which subjects received panitumumab or cetuximab in different lines of therapy, and with a range of background chemotherapy, no significant interaction was noted between the benefits of anti-EGFR therapy (measured as OS and PFS) and the presence of BRAF mutations. These results suggest that anti-EGFR therapy may have benefit for subjects with BRAF^{V600E} CRC.

In a retrospective analysis of the FIRE-3 trial data, the combination of cetuximab plus FOLFIRI, was shown to significantly improve the overall response rate (ORR) in patients with BRAF-mutated mCRC compared to bevacizumab plus FOLFIRI (52% versus 40%), although no difference in PFS or OS was noticed.[39]

In the Phase III study TRIBE, BRAF-mutated mCRC patients treated with 5-FU, leucovorin, irinotecan (FOLFOXIRI) plus bevacizumab showed a trend towards improved OS with 19.0 months compared with 10.7 months (hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.24–1.20) and PFS (HR 0.57, 95% CI 0.27–1.23) compared with FOLFIRI plus bevacizumab among the 28 patients with BRAF mutation.[16] FOLFOXIRI plus bevacizumab, however, significantly increases the incidence of grade 3 or grade 4 adverse events (AEs) in mCRC patients compared to FOLFIRI plus bevacizumab.[17]

Novel combination approaches

BRAF-mutated mCRC is resistant to single-agent RAF inhibitor, such as vemurafenib, with a low ORR of around 5%.[40 41] Dual BRAF plus MEK inhibition does not provide substantial activity either.[42]

A 35% response rate observed in a Phase Ib study combining vemurafenib with irinotecan and cetuximab in patients with BRAF-mutated metastatic colorectal cancer and advanced cancers led the Southwest Oncology Group to set up a randomized controlled trial in BRAF^{V600E} mutant mCRC, evaluating irinotecan plus cetuximab with or without vemurafenib.[43] Median PFS was 4.4 vs 2.0 months (HR 0.42; 95% CI 0.26–0.55; P<0.001) and response rates were 16 vs 4% (P=0.09) while 67% achieved disease control, compared to 22% for the three-drug regimen versus the two-drug regimen. Safety was regarded as manageable however neutropenia, anemia and nausea occurred more frequently in the arm that included vemurafenib.[44]

Cancer cells with BRAF mutations are highly dependent on MEK/ERK signaling. Recent studies have focused on novel targeted therapy combinations to produce more durable responses to BRAF inhibitor. An in vitro study suggested that the combination of BRAF and EGFR could produce sustained suppression of MEK-dependent activation of mitogen activated protein kinase signaling and overcome EGFR-driven resistance.[45] Preliminary results from several clinical trials evaluating the combination of BRAF and EGFR inhibitors suggest response rates ranging from 4% to 23%.[32 42 46-49]

The Phase III BEACON CRC, is a randomized, open label, 3-arm study with the objective to evaluate the combination of encorafenib, and cetuximab with or without binimetinib vs FOLFIRI, or irinotecan plus cetuximab as controls, in patients with BRAF^{V600E} mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting.
In this randomized clinical trial, 665 patients with BRAF V600E–mutant metastatic colorectal cancer that had progressed after one or two prior regimens in the metastatic setting were randomized to receive encorafenib/binimetinib/cetuximab, encorafenib/cetuximab, or the investigator's choice of irinotecan or leucovorin, fluorouracil, and irinotecan (FOLFIRI) and cetuximab.
The treatment combination resulted in a median overall survival of 9.0 months (95% confidence interval [CI] = 8.0–11.4 months) in patients treated with the triplet compared to 5.4 months (95% CI = 4.8–6.6 months) for the control regimens (hazard ratio = 0.52, 95% CI = 0.39–0.70; P < .0001). The objective response rate for the targeted triplet therapy was 26%, compared to 2% for the controls. The triplet combination was generally well tolerated with no unexpected toxicities. Grade 3 or higher adverse events were seen in 58% of patients on triplet treatment, 50% of those in the doublet group, and 61% of those in the standard therapy group.
[50]

Data from the BEACON CRC trial are being used to support regulatory approval of the triplet combination in BRAF V600E–mutant metastatic colorectal cancer, and BRAF inhibitor–based treatment has recently been included as a treatment option in the National Comprehensive Cancer Network© (NCCN©) Guidelines for colon and rectal cancers in the United States.
In light of the early clinical data of the Phase III BEACON CRC study, a Phase II, open label, single-arm, multi-center study, the ANCHOR CRC study, is currently ongoing to evaluate the antitumor activity of the Triplet combination of encorafenib, binimetinib and cetuximab by assessing the confirmed ORR in adult subjects with previously untreated BRAF^{V600E} mutant mCRC, where a total of 90 subjects will be enrolled and the study treatment will be administered in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy or death. After discontinuation of the study treatment, subjects will be followed for survival until 1 year after the start of the treatment of the last subject enrolled.

STUDY RATIONALE

The presence of a BRAF^{V600E} mutation is considered a marker of poor prognosis in patients with mCRC, and findings from clinical trials have largely remained inconclusive regarding the efficacy of first-line treatment options for BRAF^{V600E} mutant mCRC patients. In the absence of a targeted/specific treatment for BRAF^{V600E} mutant mCRC, treatment practices can vary based on local practices and guidelines. There is, therefore, an unmet need to document the current practices for first-line treatment of BRAF^{V600E} mutant mCRC, and their effectiveness and safety in a real-world setting.

This real-world, multicenter, non-interventional study (NIS) will describe the treatment patterns, effectiveness and safety of current treatment regimens of BRAF^{V600E} mutant mCRC patients in Europe, with the aim to put the clinical study findings of the ongoing Phase 2, single-arm, open label trial (ANCHOR) into context of the current treatment landscape excluding investigational therapies. Additionally, the NIS output may be used to support future health technology assessment submissions and publications.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective is to describe first-line treatment patterns in BRAF^{V600E} mutant mCRC patients.

2.2 SECONDARY OBJECTIVES

The secondary objectives are:

1. To describe the baseline demographic and clinical profiles of BRAF^{V600E} mutant mCRC patients receiving first-line treatment, overall and by treatment regimen
2. To describe PFS in BRAF^{V600E} mutant mCRC patients receiving first-line treatment, overall and by treatment regimen
3. To describe OS in BRAF^{V600E} mutant mCRC patients receiving first-line treatment, overall and by treatment regimen
4. To describe treatment response in BRAF^{V600E} mutant mCRC patients receiving first-line treatment, overall and by treatment regimen
5. To describe treatment duration (i.e., time from treatment initiation to treatment cessation) in BRAF^{V600E} mutant mCRC patients receiving first-line treatment, overall and by treatment regimen
6. To describe BRAF mutation testing procedure and timing in regards with the first-line treatment in BRAF^{V600E} mutant mCRC patients
7. To describe the frequency of relevant AEs in BRAFV600E mutant mCRC patients receiving first-line treatment, overall and by treatment regimen. Relevant AEs are defined as AEs leading to first-line treatment switch, dose adaptation or discontinuation, or leading to death.

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives are:

1. To describe the reason(s) for treatment discontinuation or switch in BRAF^{V600E} mutant mCRC patients starting first-line treatment
2. To describe the treatment(s) received, by line of treatment (LOT), after first progression in BRAF^{V600E} mutant mCRC patients

3 RESEARCH METHODS

3.1 STUDY DESIGN

This retrospective, multicenter longitudinal study will be conducted in Europe to characterize the treatment patterns, effectiveness and safety of current treatment regimens in BRAF^{V600E} mutant mCRC patients. The observation period is earlier than the date of inclusion of the patient in the study and the study will not provide or recommend any treatment or procedure; patients will continue to be treated as per the routine practice.
For eligible patients, relevant data will be abstracted from their medical records and entered into a centrally-designed electronic case report form (eCRF) in anonymized form. No additional clinic visits

or examinations, laboratory tests or procedures are mandated or recommended as part of this study. Treatment patterns, effectiveness and safety outcomes will be collected using data generated as part of the routine clinical practice.

This multicenter, non-interventional study entails review of medical records of adult patients who initiated first-line treatment for mCRC between January 1st, 2016 and December 31st, 2018 (both dates inclusive) and with a diagnosis of BRAF^{V600E} mutant mCRC discovered a priori or a posteriori to first-line treatment initiation. The target countries for patient enrollment will include Germany, France, Italy, UK, Spain, Belgium, Austria and the Netherlands. Approximately 300 adult patients (≥18 years) from a mix of academic and non-academic sites will be enrolled.

In order to obtain a representative sample of real-world patients undergoing treatment for BRAF^{V600E} mutant mCRC in Europe, an evidence-based approach will be adapted to (1) find and select sites within a country that meet the right criteria for success and for representability (taking into account various site-level factors such as center type [public/private, academic/non-academic], center size, center practice, etc.), and (2) identify and mitigate risks that could impact patient enrollment. A strategy plan for site selection will be created to ensure site representativeness, and will describe all processes related to the representativity survey. The site survey involving a large number of centers managing CRC patients will be conducted prior site selection.

A Scientific Committee will regularly oversee the conduct of the study to provide scientific advice and guidance with regard to the study methodology, study results and related communication.

3.2 POPULATIONS

3.2.1 Source population (if applicable)

Not applicable.

3.2.2 Study population

The study population will include mCRC patients harboring a BRAF^{V600E} mutation determined by a local assay.at any time during the disease management, residing in one of the target countries (see Section 3.1 for target countries) and initiating first-line treatment between January 1st, 2016 and December 31st, 2018 (both days inclusive).

3.2.2.1 Inclusion criteria

Patients will be eligible for inclusion if they fulfil all of the following criteria:

- Male or female aged ≥18 years at diagnosis of mCRC
- Diagnosis of histologically or cytologically confirmed CRC that is metastatic and unresectable
- Presence of BRAF^{V600E} mutation in tumor tissue, as confirmed by a local assay

- Initiated first-line treatment with drugs registered for mCRC in the respective country at the time of treatment between January 1st, 2016 and December 31st, 2018 (both days inclusive)
- Provision of informed consent or non-opposition to the patient (or next of kin, if applicable) for the use of data, according to local regulations

3.2.2.2 Exclusion criteria

Patients will be excluded from the study if they fulfil any of the following criteria:

- Patients with another concomitant cancer at the time of diagnosis*
- Patients participating in interventional trials on investigational drugs at the time of initiation of first-line treatment

* Except for non-metastatic non-melanoma skin cancers, or in situ or benign neoplasms; a cancer will be considered concomitant if it occurs within 5 years of mCRC diagnosis.

For patients who fulfil the eligibility criteria, but do not participate in the study (non-consent, non-inclusion because of patient selection process), a screening log will be maintained (subject to local regulations) to record the reason for non-participation, gender, age at diagnosis (pre-defined categories), first line treatments received (if available) and survival status.

3.2.3 Participants recruitment and follow-up

3.2.3.1 Participant selection process

In each participating center, all eligible patients' medical records will be identified. The following steps will be followed for patient selection:

- Participating sites (wherever feasible) will be asked to list exhaustively all eligible patients in an pseudonymized way
- The pseudonymized patient list will then be given a number of enrollment
- Medical records will be abstracted by the site staff until reaching the targeted number of patients per site or reaching the end of the list
- The patient will be informed of this data collection according to applicable regulations. If the patient has opposed to data collection, the reason will be noted and the next record from the enrollment list will be identified.

3.2.3.2 Participant data collection

Patients data will be collected from the start of first-line treatment for mCRC until the end of the observation period (date of death or last day of study observation period, ie. January 31st, 2020). Patients lost to follow-up will be censored at the date of their last available medical record or the date when they were last known to be alive. The data will be anonymized during the entry into the eCRF by using an algorithm which generates a random patient number without any indication of the patient, centre or country. This anonymization will be maintained in the database used for statistical analysis.

3.3 STUDY OUTCOMES

3.3.1 Primary endpoint

The primary endpoints are first-line SACT treatment patterns in BRAF^{V600E} mutant mCRC patients, described by:

- Agent or combination of agents received
- Duration of treatment
- Maintenance therapy (if any)

The first-line SACT regimen(s) will be described from the time of treatment initiation (for mCRC) until the time of first documented disease progression, treatment discontinuation or switch, whichever is earlier.

LOT definition will be connected to treatment progression. The LOT will be defined using a data-driven approach. In the SAP an algorithm for LOT definition will be specified, which will consider the specific treatment(s) received (stop and start dates), progression (as recorded in the patient medical record, including date), documented reasons for discontinuation of treatments and gap(s) between subsequent treatment regimens.

3.3.2 Secondary endpoints

1. Description of the demographic and clinical profile of patients at the time of treatment initiation (for mCRC)
2. PFS, defined as the length of time between initiation of first-line treatment for mCRC and the first documented disease progression (if disease progression is not well documented in a patient's medical record, then the start of the subsequent LOT may be considered as proxy for disease progression) or death (whichever is earlier)
3. OS, defined as the length of time between first-line treatment initiation (for mCRC) and death (due to any cause)
4. ORR, defined as complete response (CR) or partial response (PR), described at the end of first-line treatment for mCRC
5. Time to treatment cessation, defined as the length of time between initiation of firstline treatment for mCRC and documented disease progression (or start of subsequent LOT, if disease progression is not well documented in the patient medical record), treatment discontinuation or switch to another treatment (defined as change from 1 treatment regimen to another treatment regimen, e.g. change from FOLFOX-based regimen to FOLFIRI or irinotecan-based regimen)
6. Time to BRAF mutation testing since mCRC diagnosis and since first-line treatment for mCRC, and description of testing procedures
7. Frequency of relevant AEs during first-line treatment for mCRC. Relevant AEs are defined as AEs leading to first-line treatment switch, dose adaptation or discontinuation, or leading to death.

3.3.3 Exploratory endpoints

1. Description of reasons for treatment discontinuation or switch at the end of first-line treatment for mCRC
2. Second (and subsequent) line treatment patterns in BRAFV^{600E} mutant mCRC patients, defined as treatments received after disease progression following first-line treatment, and described by:
    - Agent or combination of agents received
    - Duration of treatment

3.3.4 Exposure definition and measurement

This is a NIS of real-world treatment practices in the adult BRAF^{V600E} mutant mCRC patient population. This protocol does not recommend the use of any specific treatments, and no study medication will be provided as part of participation in the study.

The exposure of interest will be the first-line SACT (monotherapy, doublet therapy, or triplet therapy with or without a targeted therapy [either VEGF inhibitor or EGFR inhibitor]) for the treatment of BRAF^{V600E} mutant mCRC. Treatment patterns will be described by LOT.

Line of therapy will be defined as follows:

- First LOT: the start of first LOT will be defined as the first administration of SACT therapy after diagnosis of mCRC to the date of first documented disease progression
- Second and subsequent LOTs: mCRC treatment(s) received on or after the date of documented disease progression following previous LOT to the date of documented disease progression on or after the current LOT
- In the absence of information on disease progression, an algorithm will be specified in the SAP based on the specific treatment(s) received (stop and start dates), progression (as recorded in the patient medical record, including date), documented reasons for discontinuation of treatments and gap(s) between subsequent treatment regimens.

The exposure variables of interest are described in Table 1.

Table 1 Study Exposure

Exposure	Definition and Measurements
Systemic anti-cancer therapy (SACT)[1] for mCRC	• Details on SACT (by LOT) o LOT[2] (e.g., first, second, third, etc.) o Type of treatment[3] (i.e., monotherapy, doublet therapy, triplet therapy) o Agents used ▪ Chemotherapy regimens (e.g., FOLFOX, FOLFIRI, FOLFOXIRI) ▪ Targeted agents (e.g., benvacizumab, cetuximab, panitumumab) ▪ Duration of treatment: start date and stop date o Date of documented progression o Dates and reasons for treatment alteration (e.g., switch, discontinuation, dose escalation/reduction) o Maintenance therapy (if any) of first line treatment: name of agent(s); start date and stop date • Treatment response (as recorded in patient medical record by the treating physician) of first-line treatment of mCRC: type of response (CR, PR, PD); date recorded

[1] All SACT treatments received/prescribed for mCRC will be captured.
[2] LOT will be defined algorithmically, using a data-driven approach if disease progression is not well documented in the patient medical record. Details will be specified in the SAP.
[3] This will be a derived field, based on the SACT treatments received/prescribed.
CR: complete response; FOLFOX:5-fluorouracil (5-FU), leucovorin, and oxaliplatin; FOLFIRI: 5-FU, leucovorin, and irinotecan; FOLFOXIRI: 5-FU, leucovorin, oxaliplatin, irinotecan; LOT: line of therapy; mCRC: metastatic colorectal cancer; PD: progressive disease; PR: partial response; SACT: systemic anti-cancer therapy

3.3.5 Outcome variables and measurements

Outcomes of interest are OS, PFS, and ORR of mCRC treatment. The study outcomes definitions and measurements are described in Table 2.

Table 2 Study Outcomes

Outcome	Definition and Measurement(s)
Progression free survival (PFS)	• PFS is defined as follows: o In patients where disease progression is well documented in medical record: length of time from start of first LOT to documented disease progression or death due to any cause, whichever occurs first. o In patients where disease progression is not well documented in medical record: length of time from start of first LOT to subsequent LOT[1] or death due to any cause, whichever occurs first. • PFS will be calculated from the start date of LOT to the date of first documented disease progression (or start of subsequent LOT, as applicable) or date of death. • Patients with no disease progression (or death) will be censored at the earliest of: date of last medical record entry or last day of the observation period. • Disease progression will be considered present if best response to treatment is PD; and absent if best response to treatment is CR or PR.
Overall survival (OS)	• OS is defined as the length of time from first-line treatment initiation (for mCRC) to death (due to any cause). • OS will be calculated from the date of first-line treatment initiation fto the date of death.

Outcome	Definition and Measurement(s)
	• If patients are confirmed to be alive, they will be censored at the earliest of: date of last medical record entry or last day of the observation period.
Overall response rate (ORR)	• ORR is defined as the number and percentage of patients whose tumor shrinks or disappears after first-line treatment (as available in the medial records from the time of treatment initiation until the first documented disease progression[1]). • ORR will be expressed as the number and percentage of patients with best response= CR or PR. The denominator will be total number of treated patients with no missing information for best response (patients with NE will be included in the denominator).
Time to treatment cessation	• Time to treatment cessation is defined as the length of time between initiation of first-line treatment and documented disease progression (or start of subsequent LOT, if disease progression is not well documented in patient medical record), treatment discontinuation or switch to another treatment (defined as change from 1 treatment regimen to another). • Time to treatment cessation will be calculated from the date of initiation of LOT to the date of disease progression, treatment discontinuation or switch. • Patients with no disease progression, treatment discontinuation or switch to another treatment will be censored at the earliest of: date of last medical record entry, last day of the observation period or date of death.
Relevant Adverse events	• Information on relevant AEs during the study period will be collected based on information available in the patient medical records. • Relevant AEs will be mapped into the (MedDRA) and grouped by SOC and PT. Relevant AEs are defined as AEs leading to first-line treatment switch, dose adaptation or discontinuation, or leading to death.
Cause of death (for deceased patients)	• The primary cause of death will be recorded as available in the medical record (cancer-related, non-cancer related, unknown/missing).
Reasons for treatment discontinuation or switch	• Reasons for treatment alteration, defined as treatment interruptions, switches and discontinuation, will be collected at the end of each treatment, based on information available in the patient medical records.

[1] For patients in whom disease progression is not well documented, the start date of subsequent LOT will be considered instead of the date of disease progression. Detailed derivation of LOT will be provided in the SAP.
CR: complete response; ICD-10: International Classification of Diseases 10th Revision; mCRC: metastatic colorectal cancer; MedDRA: Medical Dictionary for Regulatory Activities; LOT: line of therapy; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression free survival; PR: partial response; PT: preferred term; SOC: system organ class.

3.3.6 Confounding variables

Multivariable analysis will be performed adjusting for baseline covariates in this study. Covariates of interest include patient demographics and clinical profile, and treatment history of CRC, which will be assessed before or at the time of mCRC diagnosis. The baseline covariates are summarized in Table 3.

Table 3 Study Covariates

Covariates	Definition
Age	Age in completed years at the time of first-line treatment for mCRC (will be computed from the date of birth and date of diagnosis of mCRC)
Gender	Male, female
Weight	Weight in kilograms
Height	Height in centimeters

Covariates	Definition
BMI (kg/m^2)	Calculated using weight and height values BMI categories: <18.5, 18.5 - <25, 25 - <30, 30 - <35, ≥35 and unknown/missing
Tests/investigations related to mCRC diagnosis/treatment	• Records (along with the relevant test dates) of the radiologic, histologic and laboratory tests during the time of diagnosis and follow-up will be extracted based on available information in patient medical records. o Tumor Biomarker Assessments (tumor sample or ctDNA): BRAF; RAS; MSI; MMR o Blood biomarker assessments: C-reactive protein; carcinoembryonic antigen; carbohydrate antigen 19-9
TNM stage at initial diagnosis	• Tumor/node/metastasis (TNM) stage (I, II, III, IV) at the time of initial diagnosis of CRC will be abstracted based on available information in patient medical records.
Histology and location of the primary tumor at initial diagnosis	• Histology at the time of initial diagnosis of CRC will be abstracted based on available information in patient medical records: o Adenocarcinoma o Other carcinoma • Location of the primary tumor: o colon left o colon right o colon transverse o rectum
Metastasis status	Metastasis status will be abstracted based on available information in patient medical records: o Synchronous or Metachronous o Location: Liver, lungs, lymph nodes, bone, peritoneum, CNS, other location(s), unknown o Number of metastatic sites
Treatment history	Prior medications/therapies for CRC (where available in patient medical records): • Radiation therapy: site of radiation, start and stop date, intent • Chemoradiation: concurrent or sequential, regimen, start and stop date • Surgery: date, location, intent
Comorbidity profile	Comorbidities of interest: ischemic cardiac disorder, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, diabetes mellitus with end-organ damage, moderate or severe renal disease, moderate or severe liver disease, rheumatic or connective tissue disease, acquired immunodeficiency syndrome (AIDS), treated hypertension, heart rhythm disorder, others

Covariates	Definition
Performance status	• Performance status will be evaluated by ECOG: o 0=Fully active, able to carry on all pre-disease performance without restriction o 1=Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work o 2=Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours o 3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours o 4=Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair ECOG performance status will be collected at mCRC diagnosis
Biological parameters	• Routine laboratory tests at the mCRC diagnosis

BMI: body mass index; BRAF: B-Raf proto-oncogene; CNS: central nervous system; CRC: colorectal cancer; CRP: C-reactive protein; ctDNA: Circulating tumor DNA; ECOG: Eastern Cooperative Oncology Group; LOT: line of therapy; mCRC: metastatic colorectal cancer; MSI: microsatellite instability; MMR: mismatch repair; TNM: Tumor, Node, Metastasis.

3.4 DATA SOURCES AND COLLECTION

The source of collected data will be all elements that can constitute a reliable source of patient-level information and that are available at the site. This includes data available in the patients' medical charts (e.g., consultation notes, discharge summaries, laboratory test results, recorded prescription data and any other documentation of communication with other health care providers). The site investigator will be responsible for ensuring that all the required data is collected and entered into the eCRF.

The data collection schedule is presented in Table 4.

Table 4 Data Collection Schedule

Data collection	Date of enrollment/Data abstraction	Data at CRC/mCRC diagnosis/Initiation of first-line treatment	Data at observational period [3]	Discontinuation
Informed consent [1] at NIS entry [2], where applicable	X			
Demographics (age at diagnosis, gender, weight, height)		X [4,]		
Diagnosis details (date of diagnosis of CRC and mCRC, TNM stage, histology, primary tumor location)		X [4,5]		
Performance status: ECOG		X [4]		
Comorbidities		X [4]		
Metastasis details (location, number of metastatic sites)		X [4]		
Test (tumor and blood biomarker assessment, radiological tests, colonoscopy, other laboratory tests)		X [6]	X [6]	
Local BRAF mutation testing (specimen type, date of specimen collected/received, date of results reported, and results with test type/name)		X [6]		
Prior medications/therapies/procedures for treatment of CRC		X		
Systemic anti-cancer therapies for mCRC (agent name(s), start date and stop date, duration and number of treatment cycles, maintenance)			X [7]	
Treatment alteration (e.g., switch, discontinuation, dose reduction); dates and reasons for treatment alteration			X [8]	
Treatment response for each line of treatment treatment: type of response (CR, PR, PD); date recorded			X	
Survival status and date of death (if applicable)			X	
Cause of death (if applicable)			X	
Relevant AEs		X [8]	X [8]	X [8]

1. Informed consent should be obtained prior to any data collection from the patient (or the patient's legally authorized representative), where required by local regulations.
2. Reason for non-participation, gender, age at diagnosis, first line treatments received (if available) and survival status will be collected in the NIS screening log for patients who will not consent to participate in this study, if local regulation permits.
3. Observational period: patients will be followed from the start of first-line treatment for mCRC and followed until the end of the observation period. Patients lost to follow-up will be censored at the date of their last available medical record or the date when they were last known to be alive.
4. Data to be collected at the time of mCRC diagnosis.
5. Data to be collected at the time of initial diagnosis of mCRC/CRC.
6. Information on routine laboratory tests will be collected at the time of mCRC diagnosis; information on other tests (including BRAF mutation) and assessments can be captured throughout the observation period.
7. Data on number of treatment cycles and maintenance therapy to be collected for first-line therapy only.
8. Data to be collected for first-line therapy only.

AE: adverse event; CR: complete response; CRC: colorectal cancer; ECOG: Eastern Cooperative Oncology Group; mCRC: metastatic colorectal cancer; NIS: non-interventional study; PD: progressive disease; PR: partial response; TNM: Tumor, Node, Metastasis.

3.5 STUDY SIZE

The primary objective of this NIS is to assess the treatment patterns of $BRAF^{V600E}$ mutant mCRC patients. The sample size was determined based on the precision with which the primary objective could be achieved. Precision estimates were calculated around percentages ranging from 1% to 20% for sample sizes ranging from 200 to 1000 (Table 5). The range of proportions was determined based on projected estimates of patient share as per different regimens in first-line therapy in the UK, Germany, France, Spain, and Italy using Oncology Dynamics data which projected proportions of different lines of therapy between 1% to 21%.

Table 5 Precision estimates for a range of proportions and cohort sizes

Proportion	Sample size								
	200	300	400	500	600	700	800	900	1000
1%	±1.38%	±1.13%	±0.98%	±0.87%	±0.80%	±0.74%	±0.69%	±0.65%	±0.62%
5%	±3.02%	±2.47%	±2.14%	±1.91%	±1.74%	±1.61%	±1.51%	±1.42%	±1.35%
10%	±4.16%	±3.39%	±2.94%	±2.63%	±2.40%	±2.22%	±2.08%	±1.96%	±1.86%
15%	±4.95%	±4.04%	±3.50%	±3.13%	±2.86%	±2.64%	±2.47%	±2.33%	±2.21%
20%	±5.54%	±4.53%	±3.92%	±3.51%	±3.20%	±2.96%	±2.77%	±2.61%	±2.48%

A sample size of 300 patients will be able to measure treatment regimens prescribed to 5%, 10%, and 20% patients with a precision of ± 2.5%, ± 3.4%, and ± 4.5%, respectively. This was considered adequate to meet the descriptive objectives of this study.

3.6 Personal data mapping

With regards to the EU Reg n°2016/679 on protection of personal data :

- all collected data are entered pseudonymously into the eCRF and will be anonymized during the database lock.
- the storage place during the study is predefined as follow: electronic data capture (EDC) of the CLINFILE company, servers located in France at the HDS-certified hosting provider, Cegedim.
- the data will be stored during the whole study duration in EDC. At the end of the study, CLINFILE will transfer the anonymized database onto a media support (CD/DVD) and then delete the database from Cegedim's servers. The sponsor will archived the media support during 10 years after the database transfer.

3.7 DATA MANAGEMENT

All medical data will be confidential. According to the European Union General Data Protection Regulation 2016/679, sponsoring pharmaceutical company acting as data controller will ensure information of the patients about the use of their health data in completely anonymized form. He will also inform the patient that the local care team will keep an identification record of their data entry for a short period of time only and that it will not be possible to exercise their rights laid down in the GDPR (notably article 15-20) after anonymization by destruction of this record.

All data will be collected and entered directly into the EDC system in an anonymyzed way. All participating sites will have access to the data entered regarding the individual site's own enrolled patients. All sites will be fully trained on using the on-line EDC, including eCRF completion guidelines and help files. Sites will be responsible for entering extracted patient data into a secure online EDC database via the eCRF. Investigators and data entry staff will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or by the study coordinator, as appropriate. In all cases, the eCRF should be reviewed, electronically signed and dated by the Principal Investigator. All changes or corrections to eCRFs will be documented in an audit trail and an adequate explanation for such changes or corrections will be required. The data will be anonymized during the entry into the eCRF by using an algorithm which generates a random patient number without any indication of the patient, centre or country. In order to ensure data quality, an enrollment record will be maintained at the site until the eCRFs have been remotely monitored and validated. Upon database lock, the enrollement record will be destroyed by the care team, rendering the data completely anonymous.
A data management plan, aligned with the study design, will be created before the start of data collection and will describe all functions, processes, and specifications for data collection, cleaning and validation to ensure that the data are as clean and accurate as possible when presented for analysis.

3.8 DATA ANALYSIS

3.8.1 General considerations

All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA). Statistical analyses will be fully described in a written Statistical Analysis Plan (SAP), which will be prepared before database lock. The SAP will detail the most appropriate statistical methodology and analyses to be performed in accordance with the study design and objectives.
The Full Analysis Set (FAS) containing all patients who fulfil the eligibility criteria, will be used for this study. If a patient withdraws consent, the patient's data collected before the consent withdrawal will remain in the dataset. Patients in the FAS will also be included in the safety analysis set.

The study endpoints will be analyzed overall, by country and by pre-defined subgroup(s) of interest (e.g., age, gender, primary tumor location, number of metastatic organs). Further details will be provided in the SAP.

Analyses will be descriptive in nature, as no hypothesis will be tested. Data will be analyzed according to the complete case approach, where patients with missing data for relevant variable(s) will be excluded.

Categorical variables will be summarized by frequencies and percentages. Continuous variables will be summarized by descriptive statistics (mean, and standard deviation, median, 25th and 75th percentiles, minimum and maximum). The number of missing observations for each variable will also be reported.

3.8.2 Primary analyses

The first-line treatment patterns of patients, including the regimen received, duration of treatment, maintenance therapy (if any), and concomitant medications/therapies received, will be summarized using descriptive statistics. Ninety-five percent CIs will be calculated for point estimates, but no statistical adjustments will be made for multiple comparisons.

3.8.3 Secondary analyses

- **Demographic and clinical profile**

Demographics and baseline clinical characteristics of patients (as outlined in Table 3) will be summarized using descriptive statistics.

- **Progression free survival**

Progression free survival is defined in Table 2. This will be assessed for first-line treatments and described graphically by Kaplan-Meier (KM) survival curves. Median PFS, 25th and 75th percentiles, and corresponding 95% CI will be reported. Cox regression analysis may be performed to adjust for predefined (baseline) covariates and HR and 95% CIs reported.

- **Overall survival**

Overall survival is defined in Table 2. This will be described graphically by KM survival curves and median OS, 25th and 75th percentiles, and correspondent 95% CI reported. Cox regression analysis may be performed to adjust for predefined (baseline) covariates; HRs and 95% CIs will be reported.

- **Treatment response**

The category of objective response following treatment (CR, PR, and PD) will be summarized by first-line SACT treatments (monotherapy, doublet therapy, triplet therapy) and by treatment regimens using frequency tables with their associated 95% CIs. Additionally, ORR is defined in Table 2. Logistic regression may be used to adjust for predefined (baseline) covariates; odds ratios with 95% CIs will be reported.

- **Treatment duration (time to treatment cessation)**

Time to treatment cessation (defined in Table 2) will be assessed for first-line SACT treatments. This will be described graphically by KM survival curves. Cox regression may be used to adjust for pre-defined (baseline) covariates; HRs and 95% CIs will be reported.

- **BRAF Mutation testing**

Time from metastatic diagnosis to BRAF mutation testing will be assessed in addition to the time from testing to first-line treatment, and all testing procedures will be summarized using descriptive statistics.

- **Safety analyses**

The number and percentage of patients who have at least one of the relevant AE during first-line treatment will be summarized.Clopper-Pearson (Exact) 95% CIs for the proportion will be constructed around the point estimate of the incidence. Tables with counts and frequencies of relevant AEs will be provided and summarized by MedDRA SOC and PT.

3.8.4 Exploratory analyses

- **Reason(s) for treatment alteration**

The reasons for treatment alteration (dose change, interruptions, switches, discontinuation), as recorded in patient medical records, will be described using descriptive statistics.

- **Treatment patterns for second (and subsequent) LOT**

Second- (and subsequent-) line treatment patterns, in the subset of patients who progress beyond first-line treatment, will be analyzed based on the methods described in primary analysis (Section 3.8.2).

3.8.5 Missing data

Due to the nature of the study, missing data (i.e., data that are not collected or documented in the patient's medical record or EMR) may be observed for some variables. In general, missing data will not be imputed (except for dates) and the data will be analyzed according to complete case approach. Partial dates will be imputed using the rules described in the SAP.

3.9 QUALITY CONTROL

A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented. Data quality control (QC) will be performed remotely and, where permissible according to local regulations, at the site level by qualified designated personnel under professional secrecy. The extent and nature of monitoring will be decided during the study planning based on design, complexity, number of subjects, number of sites, etc.

During a site initiation call, the monitor will provide training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. In order to ensure the integrity of the data, eCRFs will be remotely monitored and, where permissible according to local regulations, sites will be randomly visited for quality control. Site quality control, if performed, will be performed by the contractor to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study.

The monitor will close out each site after the last patient's final data collection is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and frequency of monitoring visits will be described in the study monitoring plan. Monitor contact details for each participating site will be maintained in the Investigator Site File.

In most cases, the source documents are contained in the patient's medical record and data collected on the eCRFs must match the data in the medical records. All original source documentation is expected to be stored at the site for the longest possible time required by locally applicable regulations.

Representatives of the Sponsor's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File and the completed eCRFs. Patients' original medical records will only be examined if permitted by locally applicable regulations. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating patients, a record of sent patient information letters or all original signed informed consent forms, if applicable. After the database lock, however the connection between patient identity and collected data will be destroyed. Copies of all CRFs, source documents and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports) should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the study and this should be updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 10 years after completing the participation in the study or as per local regulations, whichever is longer. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the Sponsor.

3.10 STUDY MANAGEMENT

3.10.1 Sponsor

Pierre Fabre Médicament will serve as the Sponsor of this study. It is the responsibility of Pierre Fabre to ensure proper oversight of the contract research organization (CRO) conducting protocol development, implementation and monitoring of the study and compliance with all applicable regulatory guidelines and laws.

3.10.2 CRO responsible for the management of the study

Clinact will serve as the CRO of this study. It is the responsibility of Clinact to develop the statistical analysis plan and clinical study reports, manage recruitment, training, monitoring, management of sites, EDC and data management and analysis under guidance, input, review, and approval of Pierre Fabre.

3.10.3 Scientific Committee (SC)

A scientific committee will be established before the study initiation. Three experts, including 2 clinicians and 1 methodologist, will serve as members on this committee over the study period. The role of this committee will be (i) to validate the study documents (i.e. protocol & CRF), (ii) to validate the survey results and site selection, (iii) to validate study results and interpretation, and (iv) to be involved in the communication and publication plan.
Three main meetings are planned during the study and remote meetings will be planned during the study conduct. More information regarding the roles and responsibilities of the SC , the timing of meetings, methods of providing information, frequency and format of meetings, will be detailed in the Charter.

3.11 LIMITATIONS OF THE RESEARCH METHODS

3.11.1 Selection bias

Selection bias may arise if the study sample differs substantively from the underlying target population of patients with $BRAF^{V600E}$ mutant mCRC. To minimize selection bias, the eligibility criteria are selected to be as broad as possible, andall patients meeting the selection criteria will be enrolled consecutively.. Furthermore, to the extent possible, patients will be recruited from a diverse pool of clinical sites. Finally, where applicable, minimal de-identified information, including the

reason for non-participation, will be collected for patients who are not enrolled in the study to assess whether there may have any systematic differences between participant and non-participants.

3.11.2 Information bias

Inaccurate assessment of study variables may occur in observational research, especially in medical chart review studies. To minimize information bias, clear definitions of the variables of interest will be provided to ensure accurate assessment of the desired data elements, and detailed eCRF completion guidelines will be provided to the site staff to ensure accurate entry of data into the EDC. The eCRFs will include programmable edits to identify missing, out of range, illogical, or potentially erroneous data. All eCRFs will be completed by trained site personnel. In addition, routine monitoring will be conducted and source data verification may be performed to ensure the quality of the data collected.

3.11.3 Follow-up bias

Follow-up bias may occur when differences exist between study participants and patients lost to follow-up or discontinued. The study will be operationalized in such a way to minimize patient loss to follow-up through careful procedures that are minimally burdensome for the patients and the sites.

4 PROTECTION OF HUMAN SUBJECTS AND LOCAL REGULATORY ASPECTS

4.1 ETHICS

To ensure the quality and integrity of research, this study will be conducted under the guidelines of good pharmacoepidemiology practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, the EU General Data Protection Regulation (GDPR) and any applicable national guidelines.

The investigator will be responsible for ensuring that the observational study will be performed in accordance with the protocol, and applicable regulatory and country-specific requirements.

4.2 INDEPENDENT ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD (IEC/IRB)

Consistent with local regulations and prior to enrollment of patients at a given site, the study protocol will be submitted together with its associated documents (e.g., ICF) to the responsible institutional review board (IRB)/independent ethics committee (IEC) for its review. Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the study in accordance with local regulations and requirements.

This study will be undertaken only after the IRB/IEC have given full approval of the final protocol, the ICF and applicable recruiting materials, and the Sponsor had received a copy of this approval.

4.3 PATIENT INFORMATION

For the patients who are alive at the time of data collection, information of the patient about use of their health data in completely anonymized form will be ensured by either sending an information letter or, if required, presenting an ICF, which must be signed by the patient (or the patient's next of kin) before his or her participation in the study. The patient will also be informed that the local care team will keep a record of their data entry for a short period of time only and that it will not be possible to exercise their rights laid down in the GDPR (notably article 15-20) after anonymization by destruction of this record. For deceased patients, a waiver of informed consent/authorization will be requested from the relevant IRB/IEC, where applicable and in accordance with national regulations, for the collection of anonymized data.

4.4 PRIVACY OF PERSONAL DATA

Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients, physicians, hospital sites or even countries. Medical record abstraction will only be performed after receiving the approval from an IRB/IEC or equivalent, as applicable by national regulations. At no time during the study will the Sponsor receive patients' identifying information, except when it is required by regulations in case of reporting AEs.

In order to maintain patient confidentiality, each patient will be randomly assigned a unique patient identifier upon study enrollment which will guarantee anonymisation of the collected data from the moment of data entry. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications or in any other disclosures, except where required by law. In accordance with local regulations in each of the countries, patients will be informed about data handling procedures and asked for their consent, if applicable by national regulations. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data.

4.4.1 Personal data protection

Pierre Fabre Medicament (PFM) as Sponsor of the study and data controller is responsible for the processing of personal data in accordance with the provisions of Regulation 2016/679/EU of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and the free movement of such data (GDPR), the data collected being for research purposes in the field of health, the legal basis of the processing being the legitimate interest of the data controller.

5 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

5.1 TRAINING

Not applicable.

5.2 REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

5.2.1 Definitions

Adverse event (AE); synonym: Adverse experience

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment [Dir 2001/20/EC Art 2(m)].

An AE can, therefore, be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction; synonyms: ADR, suspected adverse (drug) reaction, adverse effect, undesirable effect

A response to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art 1(11)].

Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated by the healthcare professional or consumer as primary source, it meets the definition of an adverse reaction. Therefore, all spontaneous reports notified by healthcare professionals or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the primary source specifically state that they believe the event to be unrelated or that a causal relationship can be excluded.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure [DIR 2001/83/EC Art 101(1)]. Use outside the marketing authorization includes off label use, overdose, misuse, abuse and medication errors.

Serious adverse reaction

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect is considered a serious adverse reaction [DIR 2001/83/EC Art 1(12)].

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (ICH-E2D Guideline).

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction. Misuse of a medicinal product can occur from situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.

Overdose

Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgement should always be applied.

Abuse

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)].

Medication error

Are unintentional errors in the prescribing, dispensing or administration of a medicine while under the control of a healthcare professional, patient or consumer. They are the most common single preventable cause of AEs in medication practice.

Occupational exposure

For the purpose of reporting cases of suspected adverse reactions, an exposure to a medicinal product as a result of one's professional or non-professional occupation.

5.2.2 Reporting

Within the timeframe of study documentation/data collection, Pierre Fabre has not registered any drug used for the treatment of mCRC, therefore no Pierre Fabre-owned drug was authorized for use within clinical routine treatment for mCRC or BRAFV600E-mutant mCRC. Moreover, patients treated in the frame of interventional clinical studies for mCRC and patients treated with concomitant systemic therapies for cancers other than mCRC, will be excluded. Therefore, this NIS is not expected to generate any safety reports with regard to Pierre Fabre-owned drugs within the frame of the eligibility criteria.

Irrespective of this retrospective anonymized data retrieval, the participating physicians will be reminded of their general reporting obligations with regard to adverse drug reactions concerning any Pierre Fabre product or drugs of other manufacturers in accordance with the respective national law and regulations.

5.2.3 Reconciliation

Non applicable.

6 TIMELINES

The planned timelines for this study are listed as below in Table 6.

Table 6 Study timelines

Milestone	Planned date
Final protocol	March 12th, 2020
Start of data entry	April 2020
End of observation period	January 31st, 2020
Database lock	November 2020
Final report delivered	December 2020

7 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS (IF APPLICABLE)

Pierre Fabre is responsible for any presentation and/or publication arising from this study. The study results must be submitted to the review of Pierre Fabre before publication.

Any publication of the results from this study must be consistent with the Pierre Fabre's publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010.

All reporting will be consistent with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Initiative checklist.

8 REGULATORY CONSIDERATIONS

8.1 CONFIDENTIALITY

The subject matter and aim of the study, all information, data relating to the study or any product studied provided to the contractor and/or their collaborators during the term of this agreement and all results of the study (hereinafter collectively called the "Information") will be maintained confidential for an unlimited time period by the contractor and/or their collaborators.

In addition, all Information shall not be used by the contractor for any other purpose than the one described in this Agreement.

The above obligations shall, however, not apply to:

- Information which at the time of disclosure to the contractor is part of the public knowledge,
- Information, which, after disclosure, becomes part of the public knowledge through no fault of the contractor

- Information which the contractor can establish by competent proof was in its possession prior to disclosure hereunder and was not acquired from PFM, directly or indirectly under a secrecy obligation
- Information which is subsequently obtained lawfully from a third party without any secrecy obligation and was not acquired by such third party from PFM, directly or indirectly under a secrecy obligation.

No publication or communication relating to the study or the results thereof, in written or oral form, shall be made by the contractor and/or their collaborators, without PFM's prior written consent.

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10 APPENDICES

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