Document title	**AMENDED CLINICAL STUDY PROTOCOL**
Study official title	An open-label, randomised, phase III study comparing trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory metastatic colorectal cancer (SUNLIGHT study)
Study brief title	Phase III study of trifluridine/tipiracil in combination with bevacizumab vs trifluridine/tipiracil single agent in patients with refractory metastatic colorectal cancer
Study public title	A study of trifluridine/tipiracil and bevacizumab in patients with resistant colorectal cancer that has spread (metastatic)
Test drug code	Trifluridine/tipiracil (also known as S 95005 or TAS-102)
Indication(s)	Refractory metastatic colorectal cancer
Development phase	Phase III
Protocol code	CL3-95005-007
EudraCT Number	2020-001976-14
Universal Trial Number	Not applicable
Investigational New Drug Application Number	CCI
Sponsor	Institut de Recherches Internationales Servier (I.R.I.S.) (outside the U.S.) Taiho Oncology, Inc. (TOI) (in the U.S.)
International Coordinator	PPD
Date of the document	30 December 2020
Version of the document	Final version
Version number	2.0

Substantial Amendment(s) integrated

No	Final version date	Countries concerned
1.0	30 Dec 2020	ALL

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VERSION LIST

Protocol No	Substantial amendment No	Final version date	Countries concerned	Nature of modifications
1.0	NA	10 June 2020	ALL	Not Applicable
1.1	NA	12 Oct 2020	FRA	See Appendix 9
1.2	NA	05 Nov 2020	ITA, DNK, DEU	See Appendix 10
2.0	1	30 Dec 2020	ALL	- This multinational study will be conducted under the sponsorship of Taiho Oncology, Inc. (TOI) for sites in the U.S. - New exclusion criteria for patients with uncontrolled hypertension, patients with history of any life-threatening VEGF related adverse event and patients with proteinuria - Clarification on the inclusion criteria 4 - Clarification on the definition of the end of study. - Change of the time window to perform the tumour assessment - Baseline ECG obtained prior to patient signed ICF may be used if the date of ECG is within 28 days of randomisation. - Clarification in the IMP management section - Clarification in the reasons for discontinuation and restart of treatment period, in case of COVID-19 infection. - Clarification on follow-up procedures in case of withdrawal of consent. - Clarification on the certification of the scales to be used during the study. - Correction of the definition of overdose. - Clarification in the section 8.7 Definition of Events requiring an immediate notification (ERIN) - Clarification on the reporting of fatal events occurring between ICF signature and IMP administration

				- Minor precisions in statistical and safety parts of the protocol. - Minor modifications in section 14. Data handling included archiving of patient's data from 15 years to 25 years. - Clarifications on data sharing section - Addition of US Product Information in appendix 7

SYNOPSIS

Name of the sponsor: *I.R.I.S. (outside U.S.)/TOI (in U.S.)*	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: S 95005 / TAS-102	**Volume:**	
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Title of study: An open-label, randomised, phase III study comparing trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory metastatic colorectal cancer

Protocol No.: CL3-95005-007

Study Brief Title: Phase III study of trifluridine/tipiracil in combination with bevacizumab vs trifluridine/tipiracil single agent in patients with refractory metastatic colorectal cancer

Study Public Title*:* A study of trifluridine/tipiracil and bevacizumab in patients with resistant colorectal cancer that has spread (metastatic)

Steering Committee Chairman: PPD

Study centre(s):
Total number of countries: approximately 10-12
Total number of centres: approximately 100-110

Study period: - Study duration for the patient: approximately 4 months of treatment + follow-up period for survival - Study initiation date (planned date of first visit first patient): approximately Q4 2020 - Study completion date (19 months after the first IMP intake of the last patient randomised): approximately Q2 2023	**Study development phase:** Phase III

Objectives / Endpoints:

Primary

- To demonstrate the superiority of trifluridine/tipiracil in combination with bevacizumab over trifluridine/tipiracil monotherapy in terms of Overall Survival (OS) in patients with refractory metastatic colorectal cancer (mCRC).

Secondary

- Progression-free survival (PFS)
- Overall response rate (ORR)
- Disease control rate (DCR)
- Safety and tolerability
- Quality of life (QoL)

Methodology:
This is an international, open-label, controlled two-arm, randomised phase III comparison study evaluating the efficacy and safety of trifluridine/tipiracil in combination with bevacizumab versus trifluridine/tipiracil monotherapy in patients with refractory mCRC.

Patients will be randomly assigned in a (1:1) ratio to receive trifluridine/tipiracil plus bevacizumab (experimental arm) or trifluridine/tipiracil as monotherapy (control arm). Randomisation will take place once the consented patient has completed all the necessary baseline procedures and deemed eligible for study entry. Treatment assignment will be done centrally via an Interactive Web Response System (IWRS) stratified by:

- Geographic region (North America, European Union, Rest of the World)
- Time since diagnosis of first metastasis (<18 months, ≥18 months)
- RAS status (wild type, mutant)

Number of included patients:
Planned: 490 patients (245 patients in the trifluridine/tipiracil + bevacizumab arm and 245 patients in the trifluridine/tipiracil monotherapy arm).

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Number of primary events:
Expected: 331 events (deaths) are required for the main analysis.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

Demographic characteristics

1. Male or female patient aged ≥18 years old at the time of ICF signature (or legal age depending on local country regulation)

Medical and therapeutic criteria

2. Has histologically confirmed unresectable adenocarcinoma of the colon or rectum (all other histological types are excluded)
3. RAS status must have been previously determined (mutant or wild-type) based on local assessment of tumour biopsy
   Wild type is defined as KRAS (exon 2, 3 and 4) and NRAS (exon 2, 3 and 4) wild type.
   Mutant is defined as at least KRAS or NRAS mutant (any exon, any mutation).
4. Has received a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer and had demonstrated progressive disease or intolerance to their last regimen
   - Prior treatment regimens for the treatment of advanced colorectal cancer must have included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and/or an anti-EGFR monoclonal antibody for RAS wild-type patients
   - Patients who have received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant/neoadjuvant chemotherapy can count the adjuvant/neoadjuvant therapy as one regimen of chemotherapy for advanced disease
5. Has measurable or non-measurable disease as defined by RECIST version 1.1
6. Is able to swallow oral tablets
7. Estimated life expectancy ≥12 weeks
8. Has an Eastern Cooperative Oncology Group (ECOG) performance status ≤1. ECOG should remain ≤1 during all the screening period (from screening visit to randomisation) (Appendix 2).
9. Has adequate organ function as defined by the following laboratory values obtained within 7 days prior to randomisation:
   - Absolute neutrophil count ≥1.5 x 10^9/L
   - Haemoglobin ≥9 g/dL. In case of blood transfusion, the haemoglobin assessment must be performed 2 weeks or more after the transfusion.
   - Platelet count ≥100 x 10^9/L
   - Creatinine clearance ≥50 mL/min, assessed using the Cockcroft & Gault formula (Appendix 4)
   - Total serum bilirubin <1.5 x upper limit of normal (ULN) (unless Gilbert disease confirmed)
   - Aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT) ≤ 2.5 x ULN (unless if liver function abnormalities are due to underlying liver metastasis, AST (SGOT) and ALT (SGPT) ≤ 5 x ULN)
   - Adequate coagulation function for all patients. For patients receiving anti-coagulant therapy (except platelet antiaggregates) the adequate therapeutic levels of INR should be confirmed
10. Female of childbearing potential (as defined in Section 5.3) must have been tested negative in a serum pregnancy test within 7 days prior to randomisation
11. Female of childbearing potential (as defined in Section 5.3) and males with partners of childbearing potential must agree to use a highly effective method of birth control (as described in Section 5.3), as well as their partners lasting at least 6 months after the last dose of IMP

Informed consent

12. Has provided written informed consent obtained prior to any study-specific procedure as described in Section 13.3.

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Exclusion criteria

General criteria

13. More than 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer
14. In the investigator's opinion, the patient is unlikely to be compliant with the oral medication regimen or the requirements of the study for scheduled evaluations
15. Pregnancy, lactating female or possibility of becoming pregnant during the study
16. Participation in another interventional study within 4 weeks prior to randomisation. Participation in study follow-up part without IMP administration, non-interventional registry or epidemiological study is allowed
17. Patients currently receiving or having received anticancer therapies within 4 weeks prior to randomisation
18. Already randomised in this study

Medical and therapeutic criteria

19. Has not recovered from clinically relevant non-hematologic CTCAE grade ≥ 3 toxicity of previous anticancer therapy prior to randomisation (excluding alopecia, and skin pigmentation)
20. Has symptomatic central nervous system metastases that are neurologically unstable or requiring increasing doses of steroids to control CNS disease
21. Had major surgery within 4 weeks prior to randomisation (the surgical incision should be fully healed prior to study drug administration), or has not recovered from side effects of previous surgery, or patient that may require major surgery during the study
22. In the investigator's opinion, patient with chronic gastrointestinal disorders that might significantly interfere with proper absorption of the study treatments
23. Has hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
24. Has severe or uncontrolled active acute or chronic infection
25. Has active or history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.
26. Known Hepatitis B Virus infection determined as HBsAg positive and / or known Hepatitis C Virus infection determined as detection of HCV RNA in serum or plasma by a sensitive quantitative molecular method
27. Known carriers of HIV antibodies
28. In the investigator's opinion, uncontrolled diabetes mellitus even under treatment

29a. Confirmed uncontrolled arterial hypertension (defined as systolic blood pressure ≥ 150 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg) or uncontrolled or symptomatic arrhythmia

30. Deep arterial thromboembolic events including cerebrovascular accident or myocardial infarction within the last 6 months prior to randomisation
31. Severe/unstable angina, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV (Appendix 3)
32. Drainage for ascites, pleural effusion or pericardial fluid within 4 weeks prior to randomisation
33. Other malignancies including those which were radically treated and for which the remission period at the time of screening is less than five years. Exemptions for this minimally required duration of remission period may be applied for carcinoma in situ of the cervix and basal cell skin cancer that are deemed to be cured by adequate treatment
34. Treatment with systemic immunosuppressive therapy (except steroids given in prophylactic setting or at a chronic low dose [≤20 mg/day prednisone equivalent])
35. Prior radiotherapy if completed less than 4 weeks before randomisation, except if provided as a short course for symptoms palliation only. Tumour lesions if previously irradiated may not be chosen as target lesions for response evaluation

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36. In the investigator's opinion, any clinically significant medical condition (e.g. organ dysfunction) or laboratory abnormality likely to jeopardize the patient's safety or to interfere with the conduct of the study

Criteria related to trifluridine/tipiracil administration

37. Has previously received trifluridine/tipiracil
38. History of allergic reactions attributed to compounds of similar composition to trifluridine/tipiracil or any of its excipients
39. Any contraindication present in the EU Product Information of trifluridine/tipiracil (Appendix 7)

Criteria related to bevacizumab administration

40. History of allergic reactions or hypersensitivity to bevacizumab or any of its excipients
41. History of hypersensitivity to Chinese Hamster Ovary cell products or other recombinant human or humanised antibodies
42. Serious non-healing wound, non-healing ulcer or non-healing bone fracture
43. Deep venous thromboembolic event within 4 weeks prior to randomisation
44. Known coagulopathy that increases risk of bleeding, bleeding diatheses. Any other haemorrhage/bleeding event CTCAE grade ≥ 3 within 4 weeks prior to randomisation
45. Any contraindication present in the EU Product Information of bevacizumab (Appendix 7)
46. History of any life-threatening VEGF-related adverse event
47. Proteinuria ≥ 1 g/24 hours or 2+ by dipstick.

For concomitant medication, refer to Section 6.3

Test drug: trifluridine/tipiracil + bevacizumab
Trifluridine/tipiracil (35 mg/m²/dose) will be administered orally twice a day (BID), within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest; with bevacizumab (5 mg/kg, IV) administered every 2 weeks (Day 1 and Day 15).
This treatment cycle will be repeated every 4 weeks.

Comparator: trifluridine/tipiracil
Trifluridine/tipiracil (35 mg/m²/dose) will be administered orally BID, within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest.
This treatment cycle will be repeated every 4 weeks.

Duration of treatment:
Active treatment period:
Patients will be treated until they meet a discontinuation criterion as described in the Section 5.6.1. Patients will be on treatment as long as they continue trifluridine/tipiracil. Bevacizumab monotherapy is not allowed.

Follow-up period:
After the withdrawal visit, all treated patients will be followed every 8 weeks:

- for tumour assessment (unless patient had discontinued study treatments for radiologic disease progression or withdrawal of consent) until radiologic progression regardless of initiation of a new anticancer therapy,
- for survival status until death or until end of the study is reached (whichever occur first).

If a patient is still receiving study medication at the end of the study, please see Section 6.5 for procedures to be followed.

Criteria for evaluation:
Efficacy measurements:
Tumour assessments will be performed as per RECIST version 1.1 (Eisenhauer, 2009) at baseline and then every 2 cycles from C1D1 until radiologic progression or end of study.

Safety measurements:
Standard safety monitoring will be performed and adverse events (AEs) will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Event Requiring

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Immediate Notification (ERIN) will be reported up to 30 calendar days after the last IMPs intake and the serious AEs related to the research will be reported without any time delay. Records of any change or addition of a new concomitant treatment at each visit.

Other measurements:
Quality of life assessments will be performed at baseline, at each cycle and at withdrawal visit using EORTC QLQ-C30 (Appendix 5) and EQ-5D-5L (Appendix 6) questionnaires.

Data Safety Monitoring Board:
An independent Data Safety Monitoring Board (DSMB) will periodically review and evaluate the safety data for patient safety, study conduct and progress and will recommend continuation, discontinuation, or study modification. The detailed composition, role, and organization of the DSMB are specified in a separate DSMB charter

Specific COVID-19 situation
In case of highly suspected COVID-19 infection (based on typical symptoms or typical chest CT scan images) or confirmed COVID-19 infection (based on positive COVID-19 biological testing), the study treatment(s) should be immediately interrupted.
The study treatment(s) could be restarted if patient is asymptomatic and a period of at least 15 days after the diagnosis has been respected with or without new testing (in case of new testing, the result should be negative).

Contractual signatories	
I, the undersigned, have read the foregoing protocol and the "Participant information and consent form" document attached to the protocol and agree to conduct the study in compliance with such documents, Good Clinical Practice and the applicable regulatory requirements. **INVESTIGATOR:**	
NAME	
CENTER NUMBER	
DATE	
SIGNATURE	
SPONSOR'S MEDICALLY RESPONSIBLE PERSON	
NAME	
DATE	
SIGNATURE	
PPD **OR DESIGNEE:**	
NAME	PPD
DATE	
SIGNATURE	PPD

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List of abbreviations

AE	:	Adverse Event
ALT	:	Alanine aminotransferase
AST	:	Aspartate aminotransferase
bid	:	bis in die (twice a day)
BRAF	:	v-Raf murine sarcoma viral oncogene homolog B
BSA	:	Body Surface Area
BSC	:	Best supportive care
BUN	:	Blood urea nitrogen
CA	:	Competent Authorities
CEA	:	Carcinoembryonic antigen
CI	:	Confidence Interval
cm	:	Centimetre
CMP	:	Clinical Monitoring Plan
CR	:	Complete response
CRC	:	Colorectal Cancer
CT	:	Computerized tomography
CTCAE	:	Common terminology criteria for adverse events
CV	:	Curriculum Vitae
DCR	:	Disease control rate
DNA	:	Deoxyribonucleic acid
DSMB	:	Data Safety Monitoring board
EEA	:	European Economic Area
ECG	:	ElectroCardioGram
ECOG	:	Eastern Cooperative Oncology Group
e-CRF	:	Electronic Case Report Form
EGFR	:	Epidermal growth factor receptor
EMA	:	European medicine agency
EORTC	:	European organisation for research and treatment of cancer
e-PRO	:	Electronic Patient Reported Outcome
ERIN	:	Event Requiring Immediate Notification
FAS	:	Full Analysis Set
FDA	:	Food and Drug Administration
FTD	:	Trifluridine
g	:	Gram
G/L	:	Giga (109) per litre
GCP	:	Good Clinical Practice
G-CSF	:	Granulocyte colony-stimulating factor
GGT	:	Gamma-Glutamyl Transferase (Gamma-Glutamyl Transpeptidase)
HIV	:	Human Immunodeficiency Virus
HR	:	Hazard Ratio
I.R.I.S.	:	Institut de Recherches Internationales Servier
ICF	:	Informed consent form
ICH	:	International Council for Harmonisation
IEC	:	Independent Ethics Committee
IMP	:	Investigational Medicinal Product: a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial (test drug / reference product)

INR	:	International normalized ratio
IRB	:	Institutional Review Board
IV	:	IntraVenous (route)
IWRS	:	Interactive web response system
kg	:	kilogram
KRAS	:	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
L	:	Litre
LDH	:	Lactate DeHydrogenase
mCRC	:	Metastatic colorectal cancer
MedDRA	:	Medical Dictionary for Regulatory Activities
mg	:	Milligram
min	:	Minute
mL	:	Millilitre
mm	:	Millimetre
MMR	:	Mismatch repair
MRI	:	Magnetic resonance imaging
MSI	:	Microsatellite instability
MSS	:	Microsatellite stable
NCCN	:	National comprehensive cancer network
NCI-CTCAE	:	National Cancer Institute - Common Terminology Criteria for Adverse Events
ng	:	nanogram
NS	:	Not statistically Significant
NYHA	:	New York Heart Association
ORR	:	Overall response rate
OS	:	Overall Survival
PET	:	Positron emission tomography
PD	:	Progression disease
PFS	:	Progression free survival
PPS	:	Per Protocol Set
PR	:	Partial response
PS	:	Performance status
QoL	:	Quality of life
RAS	:	Rat sarcoma viral oncogene homolog
RECIST	:	Response evaluation criteria in solid tumours
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SD	:	Stable disease
SGOT	:	Serum glutamo-oxalaczetique transaminase
SGPT	:	Serum glutamo-pyruvate transaminase
SS	:	Safety Set
TOI	:	Taiho Oncology, Inc.
TP	:	thymidine phosphorylase
TPI	:	Tipiracil hydrochloride
ULN	:	Upper Limit of reference range
VEGF	:	Vascular endothelial growth factor
WBC	:	White Blood Cells
WHO	:	World Health Organization
βHCG	:	Beta human chorionic gonadotropin

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

Non sponsor parties, sponsor parties and Contract Research Organisation responsible for local management of the study are described in a separate document entitled Administrative part of clinical study protocol.

The list of investigators for each country is given in separate documents attached to the protocol and entitled "Investigators list for *[name of the country]*".

The composition and role of the supervisory committees are described in Sections 8.10 and 12.4.

2. BACKGROUND INFORMATION

2.1. Overview of disease pathogenesis, epidemiology and current treatment

Over 1.8 million new colorectal cancer (CRC) cases and 881,000 deaths was estimated to occur in 2018, accounting for about 1 in 10 cancer cases and deaths. Worldwide, CRC is the third most common cancer in terms of incidence but second in terms of mortality. There is a wide geographical variation in incidence across the world; incidence rates vary with 8-fold and 6-fold by world region. The highest rates are found in Europe (e.g., in Hungary, Slovenia, Slovakia, the Netherlands, and Norway), in Australia/New Zealand, Northern America, and Eastern Asia (Japan and the Republic of Korea, Singapore [in females]) (Globocan, 2018).

Approximately 25% of patients present with metastases at initial diagnosis and almost 50% of patients with CRC will develop metastases, contributing to the high mortality rates reported for CRC (Ayez, 2011) (Van Cutsem, 2010).
The overall prognosis of patients with metastatic CRC (mCRC) has improved significantly in the past decades, and the average survival is 30 months nowadays (Formica, 2015). Although some patients with mCRC can be cured through surgical and ablative techniques, the disease remains incurable in most cases and there is clearly a need for new therapeutic approaches.

In patients with unresectable disease, chemotherapy is the mainstay of treatment. Various combinations of the drugs may be used for the treatment of these patients at some point during the duration of their disease (Van Cutsem, 2014) (NCCN, 2019). The choice of chemotherapy is based upon the consideration of the goals of therapy, the type and timing of prior therapies, and the differing toxicity profiles of the constituent drugs. Historically, a combined regimen containing a fluoropyrimidine formed the backbone of chemotherapy for decades. However, the introduction of monoclonal antibodies targeting VEGF receptor and the use of EGFR inhibitors for a subset of mCRC patients with RAS wild-type tumours, have shown to improve clinical outcomes when combined with chemotherapy (Baldus, 2010).

An increasing number of patients with mCRC can receive 3 or more lines of therapy (Bekaii-Saab, 2018). Treatments in this setting include regorafenib (a multitargeted tyrosine kinase inhibitor), trifluridine/tipiracil, antibodies that target EGFR for patients with RAS wild-type tumours (if no prior exposure), and, where approved, anti-programmed cell death protein 1 inhibitors for patients with microsatellite instability-high mCRC (Van Cutsem, 2014) (NCCN, 2019). Clinical trials of emerging agents, new treatment combinations, and novel therapies are still needed to continue the efforts to improve outcomes for patients with mCRC.VanCutsem2014a

2.2. Trifluridine/tipiracil

Detailed information on the nonclinical and clinical experience with trifluridine/tipiracil is provided in the Investigator's Brochure.

2.2.1. Mechanism of action of trifluridine/tipiracil

Trifludirine/tipiracil, also known as S 95005 or TAS-102 is a combination of an anti-neoplastic thymidine-based nucleoside analogue, trifluridine (FTD), and the thymidine phosphorylase inhibitor, tipiracil hydrochloride (TPI), at a molar ratio 1:0.5, formulated as two dosage strengths of 15 mg/6.14 mg and 20 mg/8.19 mg immediate release film coated tablets.

Following uptake into cancer cells, FTD is phosphorylated by thymidine kinase, further metabolized in cells to a deoxyribonucleic acid (DNA) substrate, and incorporated directly into

DNA, thereby interfering with DNA function to prevent cell proliferation. When orally administered, FTD is rapidly degraded to an inactive form by thymidine phosphorylase (TP). Co-administration of TPI, an inhibitor of TP, with FTD prevents the rapid degradation of FTD, resulting in a significant increase in systemic exposure to FTD.

The antitumour effect was highly correlated with the amount of FTD incorporation into tumour DNA, and FTD was preferentially incorporated into DNA of tumour tissues as compared to that of normal tissues. FTD was markedly incorporated into DNA compared with fluoropyrimidines and other nucleoside analogues. Divided daily dosing enhanced the amounts of FTD incorporation into DNA and its antitumour effect.

This mechanism of action of trifluridine/tipiracil differentiates it from conventional fluoropyrimidines, which are uracil-based, and for which the primary mode of action is thymidylate synthase inhibition. In nonclinical studies, trifluridine/tipiracil demonstrated antitumour activity against both 5-FU sensitive and resistant colorectal cancer cell lines.

2.2.2. Clinical data of trifluridine/tipiracil in refractory mCRC (RECOURSE study)

Trifluridine/tipiracil was approved as monotherapy for the treatment of adult patients with advanced mCRC based on the results from RECOURSE study.

In this phase III, multinational, randomised, double-blind study (Mayer, 2015), the efficacy and safety of trifluridine/tipiracil (35 mg/m² twice daily [BID] on days 1–5 and 8–12 every 28 days) plus best supportive care (BSC) was compared to placebo plus BSC in patients with histologically confirmed mCRC, who had received prior treatment fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy when appropriate. The primary efficacy endpoint was overall survival (OS), and the supportive secondary endpoint was progression-free survival (PFS).

A total of 800 patients were randomised (2:1) to receive trifluridine/tipiracil (n=534) or placebo (n=266). Patients were stratified by KRAS status (wild-type, mutant); time since diagnosis of first metastasis (<18 months, ≥18 months); and geographic region (Japan, Western [United States, European Union and Australia]).
The median OS (mOS) was 7.1 months for the trifluridine/tipiracil group versus 5.3 months for the placebo group with a hazard ratio (HR) of 0.68 (95% confidence interval [CI]: 0.58, 0.81; p<0.0001). Results for PFS supported the OS results with a statistically significant improvement for trifluridine/tipiracil compared to placebo (HR=0.48, 95% CI: 0.41, 0.57, p<0.0001); median PFS (mPFS) was 2.0 months for the trifluridine/tipiracil group versus 1.7 months for the placebo group.
In general, results for OS consistently favoured trifluridine/tipiracil across the stratification groups and other pre-specified subgroups including age (<65 vs ≥65 years) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1). Among all randomised patients, 60.6% had received a fluoropyrimidine-containing regimen as their last regimen prior to randomisation, and 93.8% of those patients were refractory to fluoropyrimidine. Among these refractory patients, risk reduction in OS with trifluridine/tipiracil remained favourable and statistically significant (HR=0.75).
Among the population evaluable for tumour response (502, trifluridine/tipiracil; 258, placebo) there was no difference between the treatment groups with respect to overall response rate (ORR) (8 patients with partial response in the trifluridine/tipiracil group; 1 patient with complete response in the placebo group). However, there was a substantial difference in the percentage of patients with best overall response of stable disease (42.4%, trifluridine/tipiracil;

15.9%, placebo) leading to a significant difference in disease control rate (DCR) between the trifluridine/tipiracil and placebo groups (27.7%, 95% CI: [21.5, 34.0]; p<0.0001).
In addition, a statistically significant 34% risk reduction in worsening ECOG performance status (time to ECOG performance status ≥2) was observed for trifluridine/tipiracil compared to placebo, suggesting that quality of life (QoL) was maintained while on trifluridine/tipiracil treatment.

The most common adverse events (AE) associated with trifluridine/tipiracil treatment were bone marrow and gastrointestinal toxicities. Among the 533 patients who received trifluridine/tipiracil, 38% had neutropenia of grade ≥3, 4% had febrile neutropenia and 18% experienced anaemia of grade ≥3. These events were generally manageable with reductions in dose, delays in cycle initiation and occasional use of granulocyte colony-stimulating factor (G-CSF). Only 3 patients discontinued treatment due to hematologic AEs, and there was one treatment-related death due to neutropenia-related infection. Events of nausea, decreased appetite, diarrhoea and vomiting related to treatment were common in the trifluridine/tipiracil group (20.1% to 39.4%); however, these AEs were rarely grade 3 or 4. The incidence of stomatitis among patients receiving trifluridine/tipiracil was 7.9%; grade 3 or 4 events of stomatitis were rare (0.4%). In addition, hand-foot syndrome was reported in only 2.3% of patients receiving trifluridine/tipiracil (all grade 1 or 2), which was the same percentage reported in the placebo arm.

As of the cut-off date, the average number of weeks of exposure was 12.7 weeks in trifluridine/tipiracil group and 6.8 weeks in placebo group (median of 6.7 weeks and 5.7 weeks, respectively). In the trifluridine/tipiracil group, 53 (9.9%) patients had a single dose reduction, 18 (3.4%) patients had 2 reductions, and 2 (0.4%) patients had 3 reductions (up to 3 dose reductions allowed per protocol).

2.3. Trifluridine/tipiracil in combination with bevacizumab

2.3.1. Non-clinical data

The antitumour effects of trifluridine/tipiracil in combination with bevacizumab were assessed using mice bearing human SW48 (KRAS wild type cell lines) or HCT116 (KRAS mutant cell lines) colorectal carcinoma xenograft (Tsukihara, 2015). Trifluridine/tipiracil and bevacizumab alone inhibited tumour growth. Combined trifluridine/tipiracil and bevacizumab treatment had superior antitumour activity compared to either drug alone, and had no significant effect on the body weight compared to trifluridine/tipiracil monotherapy. Moreover, phosphorylated trifluridine levels were increased when trifluridine/tipiracil was combined with bevacizumab suggesting that bevacizumab increases trifluridine accumulation in tumour DNA.

2.3.2. Clinical data

Trifluridine/tipiracil in combination with bevacizumab for mCRC refractory to standard therapies has previously been evaluated in two separate clinical studies.

2.3.2.1. Phase I/II C-TASK FORCE study

The C-TASK FORCE is an Investigator Initiated phase I/II study of trifluridine/tipiracil in combination with bevacizumab for mCRC refractory to standard therapies conducted in Japanese patients (Kuboki, 2017).

Twenty-five patients were enrolled from February to July 2014 (phase I-part, n=6; phase II-part, n=19). The recommended phase II dose was determined to be trifluridine/tipiracil

35 mg/m²/dose BID on days 1-5 and days 8-12 in combination with bevacizumab 5 mg/kg on days 1 and 15, every 4 weeks.

The centrally assessed PFS rate at 16 weeks in 21 patients in the primary analysis was 42.9% (80% CI: 27.8, 59.0%). The mPFS centrally assessed in the 21 patients was: 3.7 months (95% CI: 2.0, 5.4). For all 25 patients enrolled, the investigator-assessed PFS at 16 weeks was 60% (95% CI: 39, 79) and mPFS by investigator assessment was 5.6 months (95% CI: 3.4, 7.6). The mOS (at final cut-off date for analysis) was 11.4 months (95% CI: 7.6, 13.9).

The most common grade ≥3 AEs above 10% were neutropenia 18 (72%), leukopenia 11 (44%), anemia 4 (16%), febrile neutropenia 4 (16%) and thrombocytopenia 3 (12%). Twenty-two patients (88%) required a treatment delay, 6 patients (24%) required at least one dose reduction (primarily due to neutropenia), and there were no treatment-related deaths. In addition, the incidence of hand-foot syndrome among patients treated with trifluridine/tipiracil (2.3%) is lower than that commonly observed with fluoropyrimidines including capecitabine.

2.3.2.2. Phase II, the Danish trial

The Danish trial is an Investigator Initiated, open-label, randomised, phase II study of trifluridine/tipiracil in combination with bevacizumab for mCRC refractory to standard therapies conducted in Denmark (Pfeiffer, 2020). Patients were enrolled and randomly assigned (1:1) to receive trifluridine/tipiracil (35 mg/m² BID on days 1–5 and 8–12 every 28 days) alone or combined with bevacizumab (5 mg/kg on days 1 and 15) until progression, unacceptable toxicity, or patient decision to withdraw. Randomisation was stratified by institution and RAS mutation status. The primary endpoint was investigator-evaluated PFS.

From August 2017 to October 2018, 93 patients were enrolled and randomly assigned to trifluridine/tipiracil (n=47) or trifluridine/tipiracil plus bevacizumab (n=46). The mPFS was 2.6 months (95% CI: 1.6, 3.5) in the trifluridine/tipiracil group versus 4.6 months (3.5, 6.5) in the trifluridine/tipiracil plus bevacizumab group (HR 0.45 [95% CI: 0.29, 0.72]; p=0.0015).

The most frequent grade ≥3 AEs was neutropenia (18 [38%] of 47 in the trifluridine/tipiracil monotherapy group vs 31 [67%] of 46 in the trifluridine/tipiracil plus bevacizumab group). Serious AEs were observed in 21 (45%) patients in the trifluridine/tipiracil group and 19 (41%) in the trifluridine/tipiracil plus bevacizumab group. Treatment-related serious AEs in the trifluridine/tipiracil monotherapy group were (one patient for each) vomiting, obstipation, febrile neutropenia, and vomiting, and in the trifluridine/tipiracil plus bevacizumab group were febrile neutropenia (three patients) and diarrhoea (one patient). No deaths were deemed treatment related.

2.4. Study design and selection of dose

2.4.1. Study design

This present study is designed as an international, open-label, controlled two-arm, randomised phase III comparison study evaluating the efficacy and safety of trifluridine/tipiracil in combination with bevacizumab versus trifluridine/tipiracil monotherapy in patients with refractory mCRC.

Due to the difference between the two arms in term of bevacizumab injection (1 vs 0), this study must be performed in open-label.

This study aims to demonstrate superior efficacy of trifluridine/tipiracil in combination with bevacizumab through a reduction in the risk of death compared to trifluridine/tipiracil monotherapy.

OS is the primary endpoint of the study as recommended by European medicines agency (EMA) guideline on the evaluation of anticancer medicinal products in man (EMA, 2017) and by Food and Drug Administration (FDA) guideline on the clinical trial endpoints for the approval of cancer drugs and biologics guidance for industry (FDA, 2018).

The study will be conducted in compliance with the protocol, Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki (Appendix 1) and the applicable regulatory requirements.

2.4.2. Selection of dose regimens

The recommended starting dose of trifluridine/tipiracil is 35 mg/m²/dose BID as long as benefit is observed or until unacceptable toxicity occurs (Appendix 7).

A bevacizumab regimen of 5 mg/kg is a recommended dose for use in combination with fluoropyrimidine-based regimens for treatment of mCRC (Appendix 7).

2.4.2.1. Experimental arm

Trifluridine/tipiracil will be administered orally BID, within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest, with bevacizumab administered IV every 2 weeks (day 1 and day 15). This treatment cycle will be repeated every 4 weeks.

2.4.2.2. Control arm

Trifluridine/tipiracil will be administered orally BID, within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest. This treatment cycle will be repeated every 4 weeks.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Primary objective

The primary objective is to demonstrate the superiority of trifluridine/tipiracil in combination with bevacizumab over trifluridine/tipiracil monotherapy in terms of OS in patients with refractory mCRC.

3.2. Secondary objectives

Secondary objectives are to estimate the effect of trifluridine/tipiracil in combination with bevacizumab versus trifluridine/tipiracil monotherapy in terms of PFS, ORR, and DCR in patients with refractory mCRC. Other secondary objectives are to compare the safety and tolerance, and the impact on QoL of trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory mCRC.

3.3. Endpoints

3.3.1. Primary endpoint

OS is defined as the observed time elapsed between the date of randomisation and the date of death due to any cause.

3.3.2. Secondary endpoints

- PFS is based on investigator judgement and defined as the time elapsed between the randomisation and the date of radiologic tumour progression (according to RECIST version 1.1 (Eisenhauer, 2009) or death from any cause.
- ORR is defined as the proportion of patients with objective evidence of complete response (CR) or partial response (PR) according to RECIST version 1.1 criteria and using investigator's tumour assessment.
- DCR is defined as the proportion of patients with objective evidence of CR or PR or stable disease (SD) according to RECIST version 1.1 criteria and using investigator's tumour assessment.
- Safety and tolerability are assessed by the incidence of AEs, laboratory tests (haematology, biochemistry, coagulation and urinalysis), physical examination and ECOG PS (Appendix 2), vital signs (blood pressure, heart rate, body temperature and body weight), ECG parameters and time to ECOG PS deterioration to ≥2 since randomisation.
- QoL is assessed by two questionnaires EORTC QLQ-C30 and EQ-5D-5L (Appendix 5 and Appendix 6).

4. STUDY DESIGN

4.1. Investigational Plan

4.1.1. Study plan

This is an international, open-label, controlled two-arm, randomised phase III study evaluating the efficacy and safety of trifluridine/tipiracil in combination with bevacizumab versus trifluridine/tipiracil monotherapy in patients with refractory mCRC.

The analysis will be done after 331 events are reported. In order to observe this number of events, 490 patients will be randomised (1:1) to receive trifluridine/tipiracil in combination with bevacizumab (experimental arm) or trifluridine/tipiracil monotherapy (control arm).

Considering the anticipated rapid enrolment and event accumulation in this population, there is no planned interim analysis for efficacy or futility.

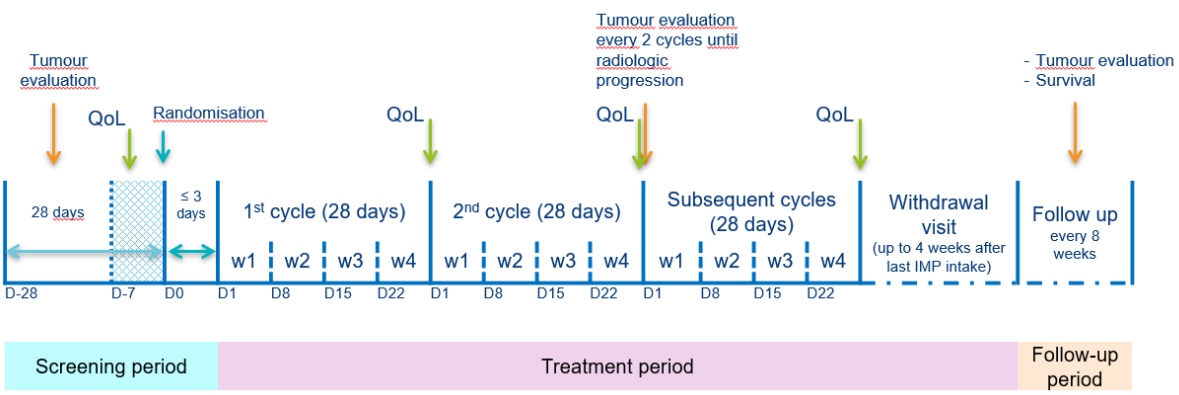
Randomisation will take place once the consented patient has completed all the necessary baseline procedures and is deemed eligible for study entry. The stratification factors will be:

- geographic region (North America, European Union, Rest of the World),
- time since diagnosis of first metastasis (<18 months, ≥18 months),
- RAS status (wild-type, mutant).

For more details about the statistical analyses and the sample size calculation please refer to the Section 10.

The study plan is shown in Figure (4.1.1) 1.

Figure (4.1.1) 1 - Study plan



The study start is defined as the date of the first visit of the first patient.

The study will be divided into the following periods for each patient:

- **Screening visit (up to 28 days prior to randomisation):** to obtain informed consent.
- **Screening period/Inclusion:** to check the eligibility of the patient to be included and randomised in the study.
- **Randomisation:** patients will be randomly assigned to one of the two treatment arms:
  - Trifluridine/tipiracil in combination with bevacizumab: trifluridine/tipiracil (starting dose at 35 mg/m^2/dose) will be administered orally BID for 5 days on/2 days off, for 2 weeks, followed by a 14-day rest, with bevacizumab (5 mg/kg) administered IV every 2 weeks (day 1 and day 15).
    This treatment cycle will be repeated every 4 weeks.
  - Trifluridine/tipiracil: trifluridine/tipiracil (starting dose at 35 mg/m^2/dose) will be administered orally BID for 5 days on/2 days off, for 2 weeks, followed by a 14-day rest.
    This treatment cycle will be repeated every 4 weeks.
- **Treatment period:** randomised patients should receive the first dose of study treatments (day 1 of cycle 1) within 3 days after randomisation.
  Patients will be treated until they meet a discontinuation criterion as described in Section 5.6.1. Patients will be considered on treatment as long as the patients continue with trifluridine/tipiracil. Bevacizumab monotherapy is not allowed.
- **Withdrawal visit:** within 4 weeks following the date of IMPs withdrawal and prior to the start of a new anticancer therapy.
- **Follow-up period:** after the withdrawal visit, a follow-up will be done every 8 weeks as described in Section 5.6.2 until death or end of study.

The end of study will occur 19 months after the first IMP intake of the last patient randomised and is defined as the date of the last follow-up of the last patient (including a contact phone) or the date of the last contact attempt if the last patient is declared lost to follow-up.

If some patients are still receiving study treatments when the end of study is met, please see Section 6.5 for procedures to be followed.

Due to the exceptional circumstances in relation to the coronavirus disease pandemic, the sponsor, in accordance with competent regulatory authority's guidelines, could decide to implement precautionary measures during the study to ensure patients safety, while maintaining compliance with GCP and study data integrity. These precautionary measures will remain in effect only for the duration of national public health emergency.

4.1.2. Investigation schedule

Table (4.1.2) 1 and Table (4.1.2) 2 describe the efficacy, safety and other assessments performed during the study.

The study schedule must be followed, however, under special conditions, (e.g., bank holidays, weekends…), a window of +/- 3 days (from planned CXD1) is allowed for the start of a new treatment cycle and a window of +/- 7 days (from planned CXD1) is allowed for tumour assessment and follow-up visits, as long as the proper order is maintained.

For further practical details, methods of measurement are provided in Sections 7, 8 and 9.

The approximate total volume of blood collected per patient for the screening period and per cycle during the study will be 40 mL.

Table (4.1.2) 1 - Investigation schedule of trifluridine/tipiracil and bevacizumab arm

Procedure	Screening visit / Screening period / Inclusion		Randomisation	On-Treatment period					Withdrawal visit	Follow-up period
				CYCLE 1 (28 days)		SUBSEQUENT CYCLES (28 days)				
				Day of Cycle		Day of Cycle		Every 2 cycles	within 4 weeks after ttt withdrawal and before new anticancer ttt	Every 8 weeks, until death or end of study
	≤ 28 days prior randomisation	≤ 7 days prior randomisation	≤ 3 days prior C1D1	1	15	1	15			
Sign informed consent form[1]	X									
Inclusion / exclusion criteria	X									
Medical history	X									
IWRS[2]	X		X	X	X	X	X		X	
Efficacy measurements										
Tumour measurements[3]	X							X	X	X
Survival status[4]				→	→	→	→	→	→	X
Safety measurements										
Baseline signs & symptoms and height		X								
ECG[15]	X								X	
Pregnancy testing		X[5]							X[6]	
ECOG Performance Status		X[7]		X[9]		X[11]			X	
Physical examination		X		X[9]	X[10]	X[11]	X[12]		X	
Vital signs and weight		X		X[9]	X[10]	X[11]	X[12]		X	
Haematology		X[8]		X[9]	X[10]	X[11]	X[12]		X	
Biochemistry		X[8]		X[9]	X[10]	X[11]			X	
Coagulation		X[8]		X[9]		X[11]			X	
Urinalysis		X		X[9]	X[10]	X[11]			X	
Concomitant treatments	X	→		→	→	→	→	→	→	X[13]
AE assessment	X	→		→	→	→	→	→	→	→
Other measurements										
Quality of Life assessment[14]		X				X (prior to any procedure)			X	
IMPs										
Trifluridine/tipiracil intake				D1 to D5 and D8 to D12		D1 to D5 and D8 to D12				
Bevacizumab IV administration				X	X	X	X			

1. Sign Informed Consent Form (ICF): written informed consent must be obtained during the screening visit, prior to the performance of any study procedure.
2. IWRS: to obtain patient's number at screening, randomisation of patient, allocation and re-allocation of therapeutic units (other visits) and to register the end of treatment for a patient at withdrawal visit.
3. Tumour measurements: tumour assessments should be performed according to RECIST version 1.1. The same method of assessment and the same technique must be used for all evaluations. At each time point, obtain imaging-based evaluation of the chest, abdomen, and pelvis at a minimum (other localisations if clinically indicated) and clinical examination.
    a. Baseline: tumour assessment will be done within 28 days prior to randomisation. Images obtained prior to patient signed ICF may be used if the date of the images is within 28 days of randomisation and if in line with methods and techniques that will be used during study.
    b. Treatment period: tumour assessments will be done every 2 cycles from C1D1
    c. Withdrawal visit: tumour assessments will be performed only if not performed within previous 8 weeks. Every effort should be made to perform the end of treatment tumour assessments prior to the start of new anticancer therapy.
    d. Follow-up period: unless patient had discontinued study treatments for radiologic disease progression or withdrawal of consent, obtain tumour assessments within 8 weeks after the last previous tumour assessment and then every 8 weeks until documentation of radiologic disease progression, regardless of initiation of a new anticancer therapy.
4. Survival status: obtain survival status (alive/dead) at scheduled 8-week intervals until patient death or end of the study. The information can be obtained remotely by using various wired and wireless telecommunication technologies including but not limited to telephone, internet and shared electronic medical records..
5. Pregnancy testing at screening period: with serum βHCG test only. Note: more frequent pregnancy tests should be performed if required by local law.
6. Pregnancy testing at withdrawal: only if not performed within the previous 4 weeks (with serum βHCG or highly sensitive urine test).
7. ECOG Performance Status during the screening period: the patient's performance status must remain 0 or 1 during the screening period and at the time of randomisation for the patient to remain eligible.
8. Laboratory tests (haematology, biochemistry, coagulation) during screening period: an assessment performed by the study site's certified laboratory as per routine clinical practice, on samples collected before ICF signature is acceptable and may not be repeated, only if the assessment is fully satisfying study protocol criteria in terms of completeness and time schedule.
9. Study procedures prior to the first study treatments administration: to be done by the study site's certified laboratory at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1.
10. Study procedures at C1D15: obtain within 48 hours prior to bevacizumab administration.
11. Study procedures at day 1 of subsequent cycles ≥2: obtain within 48 hours prior to day 1 study treatments administration. Verify that patients with toxicities have met resumption criteria prior to administering study treatments.
12. Study procedures at day 15 of subsequent cycles ≥2: obtain within 48 hours prior to bevacizumab administration (not mandatory in case of permanent discontinuation of bevacizumab).
13. Concomitant medications during follow-up period: only anticancer therapies will be collected.
14. Quality of life: EORTC QLQ-C30 and EQ-5D-5L will be performed at baseline, every cycle (prior to any study procedure) and at withdrawal visit.
15. ECG during screening period: ECG obtained prior to patient signed ICF may be used if the date of the ECG is within 28 days of randomisation.

Table (4.1.2) 2 - Investigation schedule of trifluridine/tipiracil monotherapy arm

Procedure	Screening visit / Screening period / Inclusion		Randomisation	On-Treatment period				Withdrawal visit	Follow-up period
				CYCLE 1 (28 days)		SUBSEQUENT CYCLES (28 days)			
				Day of Cycle		Day of Cycle	Every 2 cycles	within 4 weeks after ttt withdrawal and before new anticancer ttt	Every 8 weeks, until death or end of study
	≤ 28 days prior randomisation	≤ 7 days prior randomisation	≤ 3 days prior C1D1	1	15	1			
Sign informed consent form[1]	X								
Inclusion / exclusion criteria	X								
Medical history	X								
IWRS[2]	X		X	X		X		X	
Efficacy measurements									
Tumour measurements[3]	X						X	X	X
Survival status[4]				→	→	→	→	→	X
Safety measurements									
Baseline signs & symptoms and height		X							
ECG[13]	X							X	
Pregnancy testing		X[5]						X[6]	
ECOG Performance Status		X[7]		X[9]		X[10]		X	
Physical examination		X		X[9]	X	X[10]		X	
Vital signs and weight		X		X[9]	X	X[10]		X	
Haematology		X[8]		X[9]	X	X[10]		X	
Biochemistry		X[8]		X[9]	X	X[10]		X	
Coagulation		X[8]		X[9]		X[10]		X	
Urinalysis		X		X[9]	X	X[10]		X	
Concomitant treatments	X	→		→	→	→	→	→	X[11]
AE assessment	X	→		→	→	→	→	→	→
Other measurements									
Quality of Life assessment[12]		X				X (prior to any procedure)		X	
IMPs									
Trifluridine/tipiracil intake				D1 to D5 and D8 to D12		D1 to D5 and D8 to D12			

1. Sign Informed Consent Form (ICF): written informed consent must be obtained during the screening visit, prior to the performance of any study procedure.
2. IWRS: to obtain patient's number at screening, randomisation of patient, allocation and re-allocation of therapeutic units (other visits) and to register the end of treatment for a patient at withdrawal visit.
3. Tumour measurements: tumour assessments should be performed according to RECIST version 1.1. The same method of assessment and the same technique must be used for all evaluations. At each time point, obtain imaging-based evaluation of the chest, abdomen, and pelvis at a minimum (other localisations if clinically indicated) and clinical examination.
    a. Baseline: tumour assessment will be done within 28 days prior to randomisation. Images obtained prior to patient signed ICF may be used if the date of the images is within 28 days of randomisation and if in line with methods and techniques that will be used during study.
    b. Treatment period: tumour assessments will be done every 2 cycles from C1D1
    c. Withdrawal visit: tumour assessments will be performed only if not performed within previous 8 weeks. Every effort should be made to perform the end of treatment tumour assessments prior to the start of new anticancer therapy.
    d. Follow-up period: unless patient had discontinued study treatments for radiologic disease progression or withdrawal of consent, obtain tumour assessments within 8 weeks after the last previous tumour assessment and then every 8 weeks until documentation of radiologic disease progression, regardless of initiation of a new anticancer therapy.
4. Survival status: obtain survival status (alive/dead) at scheduled 8-week intervals until patient death or end of the study. The information can be obtained remotely by using various telecommunication technologies including but not limited to telephone, internet and shared electronic medical records.
5. Pregnancy testing at screening period: with serum βHCG test only. Note: more frequent pregnancy tests should be performed if required by local law.
6. Pregnancy testing at withdrawal: only if not performed within the previous 4 weeks (with serum βHCG or highly sensitive urine test).
7. ECOG Performance Status during the screening period: the patient's performance status must remain 0 or 1 during the screening period and at the time of randomisation for the patient to remain eligible.
8. Laboratory tests (haematology, biochemistry, coagulation) during screening period: an assessment performed by the study site's certified laboratory as per routine clinical practice, on samples collected before ICF signature is acceptable and may not be repeated, only if the assessment is fully satisfying study protocol criteria in terms of completeness and time schedule.
9. Study procedures prior to the first study treatments administration: to be done by the study site's certified laboratory at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1.
10. Study procedures at day 1 of subsequent cycles ≥2: obtain within 48 hours prior to day 1 study treatments administration. Verify that patients with toxicities have met resumption criteria prior to administering study treatments.
11. Concomitant medications during follow-up period: only anticancer therapies will be collected.
12. Quality of life: EORTC QLQ-C30 and EQ-5D-5L will be performed at baseline, every cycle (prior to any study procedure) and at withdrawal visit.
13 ECG during screening period: ECG obtained prior to patient signed ICF may be used if the date of the ECG is within 28 days of randomisation.

4.2. Measures to minimise bias

The following measures will be taken in order to minimise bias:

- Stratification by geographic region (North America, European Union, Rest of the World), the time since diagnosis of first metastasis (<18 months, ≥18 months) and RAS status (wild type, mutant).
- Randomisation, allocation, reallocation and dose adjustment will be centralised by IWRS.
- The QoL questionnaires (EORTC QLQ-C30 and EQ-5D-5L) will be completed by the patient, independently of the study personnel, at the beginning of each visit and prior to any study procedure. These questionnaires will be completed in the local language using an electronic device (e-PRO). In case the patient is not able to use the e-PRO, a caregiver (not a medical/investigator staff) will be allowed to read the questions to the patient and to collect the answer without any interpretation of the questions and the answers. The objective is to enhance the validity of QoL data by reducing missing data and improving the completion rate. Completion of paper versions of the QoL questionnaires is not allowed by the protocol.
- Strategic sponsor personnel will not have access to the arms of treatment. This will be detailed in a separate document.

4.3. Study products and blinding systems

4.3.1. Products administered

Trifluridine/tipiracil and bevacizumab will be supplied by Les Laboratoires Servier Industrie (Gidy, France) or a subcontracted company. The bevacizumab to be used in the U.S. will be sourcing from Genentech, Inc.

Table (4.3.1) 1 and Table (4.3.1) 2 provide a description of the study treatments.

Table (4.3.1) 1 - Description of trifluridine/tipiracil

	Trifluridine/tipiracil 15 mg	**Trifluridine/tipiracil 20 mg**
Pharmaceutical form	Immediate-release film-coated tablet	Immediate-release film-coated tablet
Unit dosage	15 mg	20 mg
Appearance, colour	White round tablet	Pale-red round tablet
Composition	15 mg trifluridine and 7,065 mg tipiracil hydrochloride Lactose monohydrate	20 mg trifluridine and 9,42 mg tipiracil hydrochloride Lactose monohydrate

Table (4.3.1) 2 - Description of bevacizumab

	Bevacizumab 4 ml	**Bevacizumab 16 ml**
Pharmaceutical form	Concentrate for solution for infusion	Concentrate for solution for infusion
Unit dosage	100 mg of bevacizumab	400 mg of bevacizumab
Appearance, colour	Clear to slightly opalescent, colourless to pale brown liquid.	Clear to slightly opalescent, colourless to pale brown liquid.
Composition	Each ml of concentrate contains 25 mg of bevacizumab	Each ml of concentrate contains 25 mg of bevacizumab

Table (4.3.1) 3 and Table (4.3.1) 4 provide a description of the packaging of the study treatments.

Table (4.3.1) 3 - Description of the packaging of trifluridine/tipiracil

	Trifluridine/tipiracil 15 mg	**Trifluridine/tipiracil 20 mg**
Number of units of the pharmaceutical form per primary packaging	1 card of 2 blisters of 10 tablets	1 card of 2 blisters of 10 tablets
Number of primary packaging per secondary packaging	1 aluminium foil pouch "S 95005 15" of 1 card with desiccant	1 aluminium foil pouch "S 95005 20" of 1 card with desiccant

Table (4.3.1) 4 - Description of the packaging of bevacizumab

	Bevacizumab 4 ml	**Bevacizumab 16 ml**
Number of units of the pharmaceutical form per primary packaging	1 vial containing 100 mg of bevacizumab	1 vial containing 400 mg of bevacizumab
Number of primary packaging per secondary packaging	1 vial per small box "Bevacizumab 4"	1 vial per small box "Bevacizumab 16"

The labelling of packages complies with the regulatory requirements of each country involved in the study.

4.3.2. IMP management

In this study, the IMPs are trifluridine/tipiracil and bevacizumab.

The IMPs will be sent by Les Laboratoires Servier Industrie (Gidy, France) (except for bevacizumab to be used in the U.S.) either directly to the study sites or to sub-distribution centres or to local pharmacies depending on the geographic areas and the local regulatory requirements. Bevacizumab to be used in the U.S. will be sent from a subcontracted company located in the U.S. directly to the U.S. study sites.

The investigator and/or the pharmacist of the study site should only use the IMPs provided for the patients involved in the study.

The investigator and/or pharmacist of the study site is responsible for:
- IMPs receipt and storage according to the local procedures and requirements,
- IMPs temperature monitoring,
- IMPs dispensing according to treatment arm assigned by the IWRS,
- maintaining records of IMPs inventory at study site,
- IMPs collection for destruction.

Storage

The IMPs should be stored in a secure area with restricted access. For specific storage conditions, please refer to the Product Information (Appendix 7).

The investigator and/or pharmacist of the study site will record temperature storage daily using CCI "Therapeutic Unit temperature log sheet - centre" (recording Min-Max temperature every working day) or an equivalent document.

In case of temperature deviation, the investigator and/or pharmacist should immediately:

- block the IWRS for the concerned IMPs and place them in quarantine,
- alert the sponsor monitor and forward all required information,
- put in place an adequate corrective/preventive action after the first temperature deviation occurs, in order to avoid recurrence.

IMPs management will be verified on a regular basis by the study monitor.

The investigator and/or the pharmacist of the study site and/or a designated person from their study team must complete in real time all the documents provided by the sponsor concerning IMPs management (therapeutic unit tracking form or an equivalent document…). Therapeutic unit tracking form, or an equivalent document, is the source document to fulfil.

All defects or deterioration of IMPs or of their packaging, including complaints set out by a patient (change of taste, appearance…) are to be reported to the sponsor monitor, or to the IWRS.

Destruction of the IMPs

Destruction of the IMPs is the responsibility of the sponsor and/or of the investigator and/or the pharmacist of the study site.

Remaining treatments (used and unused IMPs, except for used vials of bevacizumab) will subsequently be collected and stored according to the local procedures and requirements, by the person responsible for the IMPs management.

A certificated of destruction will be performed according to standard modalities for that class of product and the attestation must be sent to the sponsor. The practical procedures for destruction of unused IMPs will be defined by the sponsor and adapted to the study site. IMPs collection and destruction form will be completed before the shipment of IMPs to destruction. Destruction of IMPs may be possible (after drug accountability and sponsor authorization) when the product has been used, has expired or after at least the last visit of the last treated patient.

For bevacizumab, used vials will be collected and destroyed according to local procedure by the study site at the time of preparation/administration along with other wastes. Thus, accountability and recovery by monitor are not applicable for used vials of bevacizumab.

In case of batch recall

In the event of anticipated return of IMPs to the sponsor (i.e., batch recall), the sponsor will prepare a notification letter for the investigator and/or pharmacist of the study site. On letter receipt, the investigator and/or the pharmacist will have to identify the patients in possession of the IMPs at the moment the incident becomes known, by using, among other tools, the therapeutic unit tracking form, or an equivalent document, and will contact them immediately.

4.3.2.1. Trifluridine/tipiracil

Trifluridine/tipiracil tablets should not be sucked, chewed, crushed or kept in mouth. Direct contact of the powder from tablets containing trifluridine/tipiracil with the skin or mucous membranes should be avoided. If such contact occurs, immediately begin wash with soap and running water for minimum 15 minutes.

The patient must be instructed in the handling of study medication as follows:

- To store the study medication at room temperature,
- To keep study medication in a safe place and out of reach of children,
- To take study medication within 1 hour after completing a meal (morning and evening meals) with a glass of water,
- To make every effort to take doses on schedule,
- To remove from the study medication kit, only the number of tablets needed at the time of dosing and not to remove doses in advance of the next scheduled dosing,
- To wash their hands after handling study medication,
- To report any missed doses to the investigator. If doses are missed or held, the patient should not make up for missed doses,
- If the patient vomits after taking study medication, the patient should not take another dose,
- To bring all used and unused study medication kits to the study site at each visit.

4.3.2.2. Bevacizumab

Bevacizumab will be provided as commercially available product with clinical labelling. For handling conditions and cleaning procedures instructions, please refer to the Product Information (Appendix 7).

4.3.3. Management of blinding systems

Not applicable.

4.4. Discontinuation of the study

4.4.1. Premature discontinuation of the study or temporary halt

This study may be temporarily halted or prematurely discontinued at any time for any sufficient reasonable cause. After having informed the International Coordinator, the sponsor or the Data Safety Monitoring Board (DSMB) or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or the Competent Authorities (CA) may terminate the study before its scheduled term. The IRB/IECs and CA will be informed according to local regulations.

If the study is prematurely discontinued, the ongoing patients should be seen as soon as possible, and the assessments described in Section 5.6 should be performed.

Under some circumstances, the investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests.

In case of temporary halt, the study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, International Coordinator, the DSMB, the IRB/IEC and CA.

4.4.2. Discontinuation of the study in the event of objective reached

Not applicable.

4.5. Source data

Source data and source documents of the study site should be clearly identified in a specific, detailed and signed document before the beginning of the study.

- Patient's medical file (*e.g.*, ECG report, clinical laboratory examinations reports, tumour assessment reports and all other patient's examinations results) will be considered as source document,
- Therapeutic unit tracking form, or an equivalent document,
- e-PRO service provider's database will be considered as source data.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1. Inclusion criteria

5.1.1. Demographic characteristics

1. Male or female patient aged ≥18 years old at the time of ICF signature (or legal age depending on local country regulation)

5.1.2. Medical and therapeutic criteria

2. Has histologically confirmed unresectable adenocarcinoma of the colon or rectum (all other histological types are excluded).
3. RAS status must have been previously determined (mutant or wild-type) based on local assessment of tumour biopsy
   Wild type is defined as KRAS (exon 2, 3 and 4) and NRAS (exon 2, 3 and 4) wild type.
   Mutant is defined as at least KRAS or NRAS mutant (any exon, any mutation).

4a. Has received a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer and had demonstrated progressive disease or intolerance to their last regimen
   - Prior treatment regimens for the treatment of advanced colorectal cancer must have included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and/or an anti-EGFR monoclonal antibody for RAS wild-type patients
   - Patients who have received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant/neoadjuvant chemotherapy can count the adjuvant/neoadjuvant therapy as one regimen of chemotherapy for advanced disease

5. Has measurable or non-measurable disease as defined by RECIST version 1.1
6. Is able to swallow oral tablets
7. Estimated life expectancy ≥12 weeks
8. Has an Eastern Cooperative Oncology Group (ECOG) performance status ≤1. ECOG should remain ≤1 during all the screening period (from screening visit to randomisation) (Appendix 2).
9. Has adequate organ function as defined by the following laboratory values obtained within 7 days prior to randomisation:
   - Absolute neutrophil count ≥1.5 x 10^9/L
   - Haemoglobin ≥9 g/dL. In case of blood transfusion, the haemoglobin assessment must be performed 2 weeks or more after the transfusion.
   - Platelet count ≥100 x 10^9/L
   - Creatinine clearance ≥50 mL/min, assessed using the Cockcroft & Gault formula (Appendix 4)
   - Total serum bilirubin <1.5 x upper limit of normal (ULN) (unless Gilbert disease confirmed)
   - Aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT) ≤ 2.5 x ULN (unless if liver function abnormalities are due to underlying liver metastasis, AST (SGOT) and ALT (SGPT) ≤ 5 x ULN)
   - Adequate coagulation function for all patients. For patients receiving anti-coagulant therapy (except platelet antiaggregates) the adequate therapeutic levels of INR should be confirmed

10. Female of childbearing potential (as defined in Section 5.3) must have been tested negative in a serum pregnancy test within 7 days prior to randomisation
11. Female of childbearing potential (as defined in Section 5.3) and males with partners of childbearing potential must agree to use a highly effective method of birth control (as described in Section 5.3, as well as their partners lasting at least 6 months after the last dose of IMP

5.1.3. Informed consent

12. Has provided written informed consent obtained prior to any study-specific procedure as described in Section 13.3.

5.2. Exclusion criteria

5.2.1. General criteria

13. More than 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer
14. In the investigator's opinion, the patient is unlikely to be compliant with the oral medication regimen or the requirements of the study for scheduled evaluations
15. Pregnancy, lactating female, or possibility of becoming pregnant during the study
16. Participation in another interventional study within 4 weeks prior to randomisation. Participation in study follow-up part without IMP administration, non-interventional registry or epidemiological study is allowed
17. Patients currently receiving or having received anticancer therapies within 4 weeks prior to randomisation
18. Already randomised in this study

5.2.2. Medical and therapeutic criteria

19. Has not recovered from clinically relevant non-hematologic CTCAE grade ≥ 3 toxicity of previous anticancer therapy prior to randomisation (excluding alopecia, and skin pigmentation)
20. Has symptomatic central nervous system metastases that are neurologically unstable or requiring increasing doses of steroids to control CNS disease
21. Had major surgery within 4 weeks prior to randomisation (the surgical incision should be fully healed prior to study drug administration), or has not recovered from side effects of previous surgery, or patient that may require major surgery during the study
22. In the investigator's opinion, patient with chronic gastrointestinal disorders that might significantly interfere with proper absorption of the study treatments
23. Has hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
24. Has severe or uncontrolled active acute or chronic infection
25. Has active or history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.
26. Known Hepatitis B Virus infection determined as HBsAg positive and / or known Hepatitis C Virus infection determined as detection of HCV RNA in serum or plasma by a sensitive quantitative molecular method
27. Known carriers of HIV antibodies
28. In the investigator's opinion, uncontrolled diabetes mellitus even under treatment

29a. Confirmed uncontrolled arterial hypertension (defined as systolic blood pressure ≥ 150 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg) or uncontrolled or symptomatic arrhythmia
30. Deep arterial thromboembolic events including cerebrovascular accident or myocardial infarction within the last 6 months prior to randomisation
31. Severe/unstable angina, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV (Appendix 3)
32. Drainage for ascites, pleural effusion or pericardial fluid within 4 weeks prior to randomisation
33. Other malignancies including those which were radically treated and for which the remission period at the time of screening is less than five years. Exemptions for this minimally required duration of remission period may be applied for carcinoma in situ of the cervix and basal cell skin cancer that are deemed to be cured by adequate treatment
34. Treatment with systemic immunosuppressive therapy (except steroids given in prophylactic setting or at a chronic low dose [≤20 mg/day prednisone equivalent])
35. Prior radiotherapy if completed less than 4 weeks before randomisation, except if provided as a short course for symptoms palliation only. Tumour lesions if previously irradiated may not be chosen as target lesions for response evaluation
36. In the investigator's opinion, any clinically significant medical condition (e.g. organ dysfunction) or laboratory abnormality likely to jeopardize the patient's safety or to interfere with the conduct of the study

Criteria related to trifluridine/tipiracil administration

37. Has previously received trifluridine/tipiracil
38. History of allergic reactions attributed to compounds of similar composition to trifluridine/tipiracil or any of its excipients
39. Any contraindication present in the EU Product Information of trifluridine/tipiracil (Appendix 7)

Criteria related to bevacizumab administration

40. History of allergic reactions or hypersensitivity to bevacizumab or any of its excipients
41. History of hypersensitivity to Chinese Hamster Ovary cell products or other recombinant human or humanised antibodies
42. Serious non-healing wound, non-healing ulcer or non-healing bone fracture
43. Deep venous thromboembolic event within 4 weeks prior to randomisation
44. Known coagulopathy that increases risk of bleeding, bleeding diatheses. Any other haemorrhage/bleeding event CTCAE grade ≥ 3 within 4 weeks prior to randomisation
45. Any contraindication present in the EU Product Information of bevacizumab (Appendix 7)
46. History of any life-threatening VEGF-related adverse event
47. Proteinuria ≥ 1 g/24 hours or 2+ by dipstick.

For concomitant medication, refer to Section 6.3.

5.3. Definition of women of childbearing potential and contraception methods

Women of childbearing Potential

A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include

hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Highly effective contraception methods for the study
Highly effective methods of birth control refer to those which result in a low failure rate (i.e. less than 1% per year), when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception when associated with inhibition of ovulation (oral, injectable, implantable), some intra uterine devices, intrauterine hormone-releasing system, true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient), bilateral tubal occlusion, male sterilization (vasectomy).

Women using hormonal contraceptive must also use a barrier method i.e. condom or occlusive cap (diaphragm or cervical/vault caps)

5.4. Retest management during screening period

A patient who has a laboratory result(s) that does not satisfy the entrance criteria may have the test(s) repeated providing that the investigator judges it relevant according to the patient previous results, or medical history and if s/he considers laboratory abnormalities are likely to be transient. Results of the test(s) repeated should be obtained within the allowed screening period. In this case the patient will not be required to sign another informed consent, and the original patient number assigned by the investigator will be used.

In any case, the last result available for each parameter must be considered for the patient inclusion.

5.5. Additional information recorded at the inclusion visit

Not applicable

5.6. Participant withdrawal

5.6.1. Withdrawal criteria

Information to be collected during the last visit is given in Section 5.6.2. These follow-up modalities are used to ensure the efficacy and safety evaluation of all patients who received the IMPs.

Patient will be on treatment as long as the patient continues with trifluridine/tipiracil. Bevacizumab monotherapy is not allowed.

Pregnancy (see Section 8.9.2.3) and **End of study** (as defined in Section 4.1.1). will lead to **premature study discontinuation**.

The reasons for discontinuation of treatment period are:
- **Adverse events** incompatible with continuation of the study treatments according to the judgment of the investigator, including no recovery in safety parameters or according to the following predefined criteria:
  - A maximum dose delay >28 days from the scheduled start date of the next cycle

  - Need for more than 3 dose reductions of trifluridine/tipiracil (maximum of 3 dose reductions allowed as described in Section 8.11.1)
- **Protocol deviation** if it interferes with the study evaluations and/or if it jeopardises patient's safety, e.g. any medical event requiring administration of an unauthorised concomitant treatment (see Section 6.3)
- **Radiologic progressive disease** documented by CT-scan or MRI
- **Clinical progressive disease** manifested by symptomatic deterioration
- **Non-medical reason** (to be carefully described) e.g. consent withdrawal, patient's removal
- **Other, physician decision** (for medical reasons that cannot be included in any of the criteria listed above)

5.6.2. Procedure

Upon discontinuation of study treatments, the investigator must:

- Notify the sponsor monitor immediately,
- Register the end of treatment for the patient in the IWRS,
- Complete the e-CRF, specifying the reason for the study patient's withdrawal. If there are several reasons, the investigator must indicate the main reason. The investigator should document the discontinuation in the corresponding medical file.

A withdrawal visit should take place within 4 weeks after the date of IMP withdrawal and prior to the start of a new anticancer therapy.

In the case of discontinuation due to an AE (event requiring immediate notification [ERIN] or not), the investigator must make every effort to collect the information relating to the outcome of the event. If necessary, the information will be collected afterwards (see Section 8.9.2.2). This information is recorded in that part of the e-CRF form which concerns adverse events. If the investigator cannot collect the information from a visit, s/he must collect it from the doctor ensuring the follow-up of the patient.

In the case of discontinuation due to an ERIN, please refer to Section 8.7.

Follow-up period:

After the withdrawal visit, a follow-up will be done every 8 weeks:

- for tumour assessment (unless patient had discontinued study treatments for radiologic disease progression or withdrawal of consent) until radiologic progression regardless of initiation of a new anticancer therapy,
- for survival status until death or the end of the study (whichever occur first). This follow-up can be done remotely by using various telecommunication technologies including but not limited to phone, internet and shared electronic medical records.

Patients are at any time free to discontinue their participation in the study. If patients wish to withdraw their consent to treatment period (i.e. both study treatments and study assessments), they will be asked if they are willing to continue with Follow-up period for survival status (which can be done by phone). If patients wish to withdraw their consent to further participation in the study entirely (treatment period and follow-up period), this should be clearly documented in the patient notes and in the clinical study database.

During the follow-up period, the patient can participate to another clinical study.

A patient is considered discontinued from follow-up period only if one of the following occurs:

- Patient dies,
- At the end of study or if study is terminated by the sponsor or CA.

The dispositions to be taken after IMPs discontinuation are described in Section 6.5.

5.6.3. Lost to follow-up

When the investigator has no news of the patient, s/he must make every effort to contact him/her or a person around him/her (phone calls, letters including registered ones…), to establish the reason for the discontinuation of IMPs and to suggest the patient comes to a withdrawal visit. If all these attempts to contact the patient fail, the investigator can then declare the patient "lost to follow-up". The investigator should document all these attempts in the corresponding medical file.

6. TREATMENT OF PARTICIPANTS

6.1. IMPs administered

The study site will login to the IWRS at the beginning of each treatment cycle to record the given cycle number, the patient's height (screening period only) and weight for calculation of the patient's body surface area (BSA) to obtain the recommended trifluridine/tipiracil dosage. In addition, the IWRS will use the patient's weight to calculate the correct dosage of bevacizumab.

In the experimental arm (trifluridine/tipiracil in combination with bevacizumab), study site will have to connect also to login to the IWRS at D15 of each treatment cycle for bevacizumab administration.

The BSA will be calculated by the IWRS using the following DuBois formula (all BSA calculations are rounded to 2 decimal places) (Du Bois, 1916):
BSA (m^2) = ([Body Weight (kg)]$^{0.425}$ x [Height (cm)]$^{0.725}$) x 0.007184.

The study sites are required to use:
- scales for patient's weight measurement having a valid calibration or a maintenance certificate,
- the BSA calculation provided by the IWRS when determining trifluridine/tipiracil (even if it differs from the BSA provided by the site software),
- the trifluridine/tipiracil and bevacizumab doses calculated by the IWRS (even if it differs from the doses provided by study site's software).

For treatment dose adaptations due to toxicities, please refer to Section 8.11.

Specific COVID-19 situation:

In case of highly suspected COVID-19 infection (based on typical symptoms or typical chest CT scan images) or confirmed COVID-19 infection (based on positive COVID-19 biological testing), the study treatment(s) should be immediately interrupted.

The study treatment(s) could be restarted if patient is asymptomatic and a period of at least 15 days after the diagnosis has been respected with or without new testing (in case of new testing, the result should be negative).

6.1.1. Trifluridine/tipiracil plus bevacizumab arm

Each treatment cycle will be 28 days in duration. One treatment cycle consists of the following:
- Days 1-5: oral intake of trifluridine/tipiracil and bevacizumab IV infusion on day 1
- Days 6 -7: rest
- Days 8-12: oral intake of trifluridine/tipiracil
- Days 13-14: rest
- Day 15: bevacizumab IV infusion
- Days 16-28: rest

6.1.2. Trifluridine/tipiracil monotherapy arm

Each treatment cycle will be 28 days in duration. One treatment cycle consists of the following:

- Days 1-5: oral intake of trifluridine/tipiracil
- Days 6 -7: rest
- Days 8-12: oral intake of trifluridine/tipiracil
- Days 13-28: rest

6.1.3. Trifluridine/tipiracil administration

- Trifluridine/tipiracil dosage is calculated according to BSA. Table (6.1.3) 1 shows the number of tablets that are needed per calculated BSA for a dose of 35 mg/m². Table (6.1.3) 2 shows the number of tablets that are needed per calculated BSA for a reduced dose (30 mg/m², 25 mg/m² and 20 mg/m²).
- If at the beginning of the new treatment cycle, a patient's body weight decreases by ≥10% from baseline, the IWRS will recalculate the patient's BSA and provide the study site with the adjusted trifluridine/tipiracil dosage.
- In case of change of dose level, the IWRS will provide the study site with the adjusted trifluridine/tipiracil dosage.
- No increase in trifluridine/tipiracil dose due to increase in BSA is permitted.
- Trifluridine/tipiracil should be taken with a glass of water within 1 hour after completion of morning and evening meals.
- Trifluridine/tipiracil should only be given on days 1 through 5 and days 8 through 12 of each cycle. If doses are missed or held on those days, the patient should not make up for missed doses. Extension of study treatment into days 6 to 7 or into the rest period (days 13 through 28) is not permitted.
- Any missed doses reported by the patient should be recorded in the e-CRF.

Table (6.1.3) 1 - Number of tablets of trifluridine/tipiracil per dose (standard dose) according to body surface area

Trifluridine/tipiracil Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose (2x daily)	
				15 mg/6.14 mg	20 mg/8.19 mg
35 mg/m²	< 1.07	35	70	1	1
	1.07 - 1.22	40	80	0	2
	1.23 - 1.37	45	90	3	0
	1.38 - 1.52	50	100	2	1
	1.53 - 1.68	55	110	1	2
	1.69 - 1.83	60	120	0	3
	1.84 - 1.98	65	130	3	1
	1.99 - 2.14	70	140	2	2
	2.15 - 2.29	75	150	1	3
	≥2.30	80	160	0	4

BSA=body surface area (calculate to 2 decimal places)

Table (6.1.3) 2 - Number of tablets of trifluridine/tipiracil per dose (reduced dose) according to body surface area

Trifluridine/tipiracil Dose (2x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose (2x daily)	
				15 mg/6.14 mg	20 mg/8.19 mg
Level 1 Dose reduction: From 35 mg/m² to 30 mg/m²					
30 mg/m²	< 1.09	30	60	2	0
	1.09 - 1.24	35	70	1	1
	1.25 - 1.39	40	80	0	2
	1.40 - 1.54	45	90	3	0
	1.55 - 1.69	50	100	2	1
	1.70 - 1.94	55	110	1	2
	1.95 - 2.09	60	120	0	3
	2.10 - 2.28	65	130	3	1
	≥ 2.29	70	140	2	2
Level 2 Dose Reduction: From 30 mg/m² to 25 mg/m²					
25 mg/m²	< 1.10	25[a]	50[a]	2 (PM) [a]	1 (AM) [a]
	1.10 - 1.29	30	60	2	0
	1.30 - 1.49	35	70	1	1
	1.50 - 1.69	40	80	0	2
	1.70 - 1.89	45	90	3	0
	1.90 - 2.09	50	100	2	1
	2.10 - 2.29	55	110	1	2
	≥ 2.30	60	120	0	3
Level 3 Dose Reduction: From 25 mg/m² to 20 mg/m²					
20 mg/m²	< 1.14	20	40	0	1
	1.14 – 1.34	25[a]	50[a]	2 (PM)[a]	1 (AM)[a]
	1.35 – 1.59	30	60	2	0
	1.60 – 1.94	35	70	1	1
	1.95 – 2.09	40	80	0	2
	2.10 – 2.34	45	90	3	0
	≥ 2.35	50	100	2	1

a At a total daily dose of 50 mg, patients should take 1 x 20 mg/8.19 mg tablet in the morning and 2 x 15 mg/6.14 mg tablets in the evening. BSA=body surface area (calculate to 2 decimal places)

6.1.4. Bevacizumab administration

At each visit, the IWRS will provide the study site with the adjusted bevacizumab dosage based on the patient's actual weight. The study site can round this dose at the nearest 0.5 mL. Refer to the Product Information (Appendix 7) for instructions regarding administration of bevacizumab. If there is a medical condition developed that requires bevacizumab to be permanently withdrawn the patient may continue with trifluridine/tipiracil alone.

Bevacizumab should not be administrated alone in case of dose delay due to trifluridine/tipiracil toxicities. The cycle will be delayed, and bevacizumab will be restarted at the same time of trifluridine/tipiracil.

6.2. IMPs dispensing

The treatment arm will be allocated *via* IWRS using a central randomisation (1:1) to trifluridine/tipiracil in combination with bevacizumab or trifluridine/tipiracil monotherapy with stratification by the geographic region (North America, European Union, Rest of the World), the time since diagnosis of first metastasis (<18 months, ≥18 months) and the RAS status (wild type, mutant).

A connection to the IWRS should be performed at each concerned visit to know the allocated kit number(s) to be dispensed to the patient (please see details in IWRS manual).

The detachable portion of the label on the IMP box must be stuck by the investigator on study treatment label collection form or on the prescription form when the study treatments are dispensed by a pharmacist.

6.3. Previous and concomitant treatments

6.3.1. Prohibited treatments

6.3.1.1. Before the study

Patients are not permitted to receive:

- Previous investigational or anticancer therapy for mCRC within 4 weeks prior to randomisation,
- Treatment with systemic immunosuppressive therapy (except steroids given in prophylactic setting or at a chronic low dose [≤20 mg/day prednisone equivalent]),
- Radiotherapy in the last 4 weeks prior to randomisation (except if provided as a short course for symptoms palliation only).

6.3.1.2. During the study treatment period

Patients are not permitted to receive:

- Any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers, or endocrine therapy,
- Treatment with systemic immunosuppressive therapy (except steroids given in prophylactic setting or at a chronic low dose [≤20 mg/day prednisone equivalent] or short-term administration of steroids at daily doses higher than authorized by the protocol in situations of acute care management).

For other precautions of use and interactions of concomitant treatment with bevacizumab please refer to Product Information (Appendix 7).

6.3.2. Authorised treatments

- Palliative radiotherapy is permitted. As far as possible, the irradiation of target lesions must be avoided. Pre-clinical data showed that trifluridine/tipiracil is a radiosensitizer, but no clinical data are available for the concomitant treatment with trifluridine/tipiracil and radiotherapy, so caution is required, and close monitoring of patients is needed.
- It is strongly recommended that patients treated with anti-vitamin K treatment will be switch to low molecular weight heparin.
- Warning for patients receiving trifluridine/tipiracil:
  Caution is required when using drugs that are human thymidine kinase substrates, *e.g.*, zidovudine. Such drugs, if used concomitantly with trifluridine/tipiracil, may compete with the effector, trifluridine, for activation via thymidine kinases. Therefore, when using antiviral drugs that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral agent, and consider switching to an alternative antiviral agent that is not a human thymidine kinase substrate, such as lamivudine, didanosine and abacavir.

6.4. IMP compliance

The number of trifluridine/tipiracil tablets dispensed and returned by the patient is to be counted by the investigator or a designated person from his/her team and recorded in the e-CRF and therapeutic unit tracking form, or an equivalent document.

If the patient did not bring back all blisters dispensed at the previous visit, the investigator must estimate the number of trifluridine/tipiracil tablets taken by the patient since the previous visit, by questioning him/her.

In case of missed dose, the patient must indicate the reason to the investigator.

The compliance will be assessed from the method described above and from the questioning of the patient at the beginning of each cycle.

6.5. Discontinuation of the IMP

After the discontinuation of the IMPs, patient's treatment is left to the physician's discretion.

After completion of the study (see Section 4.1.1 for end of study definition), patients currently being treated will be offered the option to continue the treatments outside of the study.

The sponsor will be responsible for the IMPs dispensing to the patients who are eligible to continue the treatments. The IMPs will be not assigned through IWRS, and IMPs will be manually assigned to patients by the investigator and/or pharmacist of the study site, based on the patient's BSA at the time of study completion.

Specific rules may be followed in some countries according to local regulation.

7. ASSESSMENT OF EFFICACY

7.1. Efficacy measurements

Efficacy measurements performed during the study are indicated in Table (4.1.2) 1 and Table (4.1.2) 2.

7.2. Methods and measurement times

7.2.1. Measurement times

Tumour assessments/imaging of the chest, abdomen, and pelvis at a minimum (other localisations if clinically indicated) will be obtained at each time point listed below for all patients:

- Baseline within 28 days prior to randomisation.
  Note: Images obtained prior to patient signed ICF may be used if the date of the images is within 28 days of randomisation and if in line with methods and techniques that will be used during study
- Every 2 cycles from C1D1 until radiologic progression is documented (including at the withdrawal visit if not done in the previous 8 weeks).
- For patients who were withdrawn for reasons other than radiologic disease progression or consent withdrawal, every 8 weeks during the follow up period until the patient experienced radiologic progression, regardless of the initiation of a new anticancer therapy.

Note: If the investigator determines that a patient develops clinical progression manifested by symptomatic deterioration but not supported by radiologic evidence of progression, the patient should stop study treatments. Symptoms of clinical progression must be documented in the patient's source documents and in AE form. Tumour assessments will continue every 8 weeks until a radiologic progression is documented.

7.2.2. Method of imaging

- The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.
- Images must be acquired of the chest, abdomen and pelvis at a minimum (other localisations if clinically indicated) at each time point.
- Only CT or MRI must be used for tumour measurement (see specific cases below).
- Contrast enhanced CT is the preferred method for tumour assessments. If contrast agent is contraindicated in a patient, obtain at least a non-contrast chest CT and enhanced magnetic resonance imaging (MRI) of the abdomen and pelvis.

Specific cases:

- If new lesions are identified by ultrasound in the course of the study, a confirmation by CT or MRI is needed.
- Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging

evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- In case of PET CT-scan, the CT portion of the PET–CT can be used for RECIST measurements.

7.2.3. Tumour definitions

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as describe in Sections 7.2.3.1, 7.2.3.2, and 7.2.3.3.

7.2.3.1. Measurable lesions

- Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT-scan with a CT-scan slice thickness no greater than 5 mm (when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness),
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable),
- To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT-scan (CT-scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

7.2.3.2. Non-measurable lesions

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions.
- Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
- All non-measurable lesions can only be selected as non-target lesions.

7.2.3.3. Special considerations regarding lesion measurability

- Bone lesions:
  - Bone scan, PET-scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions,
  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above,
  - Blastic bone lesions are non-measurable.
- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts,
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if

noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

- Lesions with prior local treatment: tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

7.2.4. Documentation of "target" and "non-target" lesions

7.2.4.1. Target lesions

- When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then, only the short axis is added into the sum.
- The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

Specific situations:

- Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.
- While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (*e.g.* 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT-scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. In this case a value must be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.
- When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.
- An option of 'Not Assessable' for a lesion will only apply to lesions that that cannot be read due to technical reasons, for example:
  - CT artefact.
  - Patient positioning where the lesions are obstructed or cannot be seen.

- Lesion that may not be seen in their entirety due to CT slice thickness.

7.2.4.2. Non-target lesions

- Non-target lesions include all non-measurable lesions and measurable lesions that have not been selected as target lesions.
- Lymph nodes that have a short axis <10 mm are considered non-pathological and should not be recorded.
- All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, but their presence, absence, or unequivocal progression should be followed throughout the study.

For additional guidance refer to RECIST 1.1. (Eisenhauer, 2009) and RECIST 1.1: Update and clarification (Schwartz, 2016).

7.2.5. Response criteria

On-site assessments will include the assessment of:
- Target and non-target tumour responses.
- New lesions if any
- Overall response.

The above assessments will be made as per the time points identified in Section 4.1.2.

7.2.5.1. Target and Non-target Response Assessments

The definition of responses for Target and Non-target lesions is presented in Table (7.2.5.1) 1 and Table (7.2.5.1) 2 respectively.

Table (7.2.5.1) 1 – Target lesions response definitions

TARGET LESIONS

Lesions Response	**Definition**
Complete Response (CR)	The disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Definitive new lesion presence also indicates progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameters while on study.

Table (7.2.5.1) 2 – Non-target lesions response definitions

NON-TARGET LESIONS

Lesions Response	**Definition**
Complete Response (CR)	The disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological morphologically (*i.e.*, <10 mm in short axis in size).
Non-CR/Non-PD	A persistence of ≥1 non-target lesion(s) and/or maintenance of tumour marker level above the normal limits (not reaching the extent of 'unequivocal progression).
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions (see definition below). (Note: the appearance of one or more new lesions is also considered progression).

When the patient has measurable disease and non-measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

Tumour markers alone cannot be used to assess objective tumour response. If CEA level is initially above the upper normal limit, however, it must normalise for a patient to be considered in complete response.

For additional guidance refer to RECIST 1.1. (Eisenhauer, 2009) and RECIST 1.1: Update and clarification (Schwartz, 2016).

7.2.5.2. New lesions

- The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: *i.e.* not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.
- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
- For new lesions discovered by FDG-PET scan please refers to RECIST 1.1 (Eisenhauer, 2009).

7.2.5.3. Overall Response Assessment

Assessments will be based on the definitions provided in Table (7.2.5.3) 1.

Table (7.2.5.3) 1 - Time point response for patients with target (±non-target) disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD or Not all evaluated	No	PR
PR	Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

7.2.6. Best Overall Response Assessment

The best overall response as per RECIST 1.1 is the best response recorded from the start of the study treatment until the end of treatment.

In this study, the minimum time from baseline to assess a response of "stable disease" is 6 weeks.

8. ASSESSMENT OF SAFETY

All AEs and other situations relevant to the safety of the patients must be followed up, fully and precisely documented in order to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical study.

8.1. Specification of safety parameters

Safety measurements performed during the study are indicated in Table (4.1.2) 1 and Table (4.1.2) 2.

8.2. Methods and measurement times

8.2.1. Electrocardiogram (ECG)

Perform a 12-lead resting ECG at the time points listed below. Patients should be in a supine position for at least 10 min before recording.

- Within 28 days prior to randomisation. ECG obtained prior to patient signed ICF may be used if the date is within 28 days of randomisation.
- Withdrawal visit.

8.2.2. ECOG Performance Status

Obtain an ECOG performance status score (Appendix 2) at the following time points:

- Within 7 days prior to randomisation.
- At C1D1 prior to study treatments administration only if there is more than 7 days since screening assessment.
  Note: ECOG must remain 0 or 1 during the baseline period and at the time of randomisation for the patient to remain eligible.
- Beginning with cycle 2, and for all subsequent cycles, obtain within 48 hours prior to study treatments administration.
- Withdrawal visit.

8.2.3. Height, Vital Signs, Weight

Obtain the patient's height within 7 days prior to randomisation.

Collect the patient's vital signs (blood pressure, heart rate, body temperature) and body weight at the following time point:

- Within 7 days prior to randomisation.
- At C1D1 prior to study treatments administration only if there is more than 7 days since screening assessment.
- At C1D15.
- Beginning with cycle 2, and for all subsequent cycles,
  - At D1, obtain within 48 hours prior to study treatments administration,
  - At D15 (only for patients in the trifluridine/tipiracil with bevacizumab arm), obtain within 48 hours prior to bevacizumab administration.
    (not mandatory in case of permanent discontinuation of bevacizumab).
- Withdrawal visit.

Obtain all the vital signs in a position that is consistent for all time points for each patient. Blood pressure should be measured with the patient in supine position.

When measuring blood pressure, particular care should be taken to:
- take measurements after at least 5 minutes rest,
- use a cuff appropriate to arm width and place the cuff at heart level.

For weight measurement, only scales with a valid calibration or maintenance certificate must be used throughout the study.

8.2.4. Physical Examination

Perform a complete physical examination at the following time points:
- Within 7 days prior to randomisation.
- At C1D1 prior to study treatments administration only if there is more than 7 days since screening assessment.
- At C1D15.
- Beginning with cycle 2, and for all subsequent cycles,
  - At D1, obtain within 48 hours prior to study treatments administration,
  - At D15 (only for patients in the trifluridine/tipiracil with bevacizumab arm), obtain within 48 hours prior to bevacizumab administration.
    (not mandatory in case of permanent discontinuation of bevacizumab).
- Withdrawal visit.

8.2.5. Clinical Laboratory Evaluations

Laboratory tests will be collected and analysed by the study site's certified laboratory during screening period and at C1D1 only if there is more than 7 days since screening assessment. In all cases, the full validated set of normal ranges values will be collected, as well as any update in these values during the study and must be documented on the corresponding page of the e-CRF.
It's preferable for all biochemistry blood samplings to be taken in fasting conditions except if the patient's general health status does not permit it.

Laboratory tests are to be performed as required per protocol. All laboratory values that are out of the normal range are to be evaluated for their clinical significance before exposing the patient to the next dose of study medication.

Any laboratory abnormality that has a clinical impact on the patient, *e.g.*, results in delay of study medications dosing, study discontinuation, requires treatment due to abnormal values, or is considered by the investigator to be medically important, must be reported as an AE, unless it is considered a supporting analysis to a clinical diagnosis that is already reported as an AE.

All laboratory data will be analysed using NCI-CTCAE grade criteria (version 5.0).

Repeat the evaluation of any clinically significant laboratory test, as clinically indicated, until the value returns to the baseline level or clinically stabilises, or until another treatment is given.

8.2.5.1. Haematology

Collect sample for haematological assessments at the following time points and when clinically indicated:

- Within 7 days prior to randomisation.
- At C1D1 prior to study treatments administration only if there is more than 7 days since screening assessment.

Note: For screening and pre-dose C1D1, an assessment performed by the study site's certified laboratory as per routine clinical practice, on samples collected before ICF signature, is acceptable and may not be repeated, only if the assessment is fully satisfying study protocol criteria in terms of completeness and time schedule.

- At C1D15
  Note: for patients in the trifluridine/tipiracil with bevacizumab arm, obtain within 48 hours prior to bevacizumab administration,
- Beginning with cycle 2, and for all subsequent cycles,
  - At D1, obtain within 48 hours prior to study treatments administration,
  - At D15 (only for patients in the trifluridine/tipiracil with bevacizumab arm), obtain within 48 hours prior to bevacizumab administration.
    (not mandatory in case of permanent discontinuation of bevacizumab).
- Withdrawal visit.

Measure the following haematology parameters: haemoglobin, red blood cell count, white blood cell (WBC) count and differential count (neutrophils, lymphocytes), platelets.

Note: for neutrophils and lymphocytes, parameters must be available in absolute value (not in percentage of WBC).

8.2.5.2. Biochemistry

Collect sample at the following time points for biochemistry assessments:

- Within 7 days prior to randomisation.
- At C1D1 prior to study treatments administration only if there is more than 7 days since screening assessment.

Note: For screening and pre-dose C1D1, an assessment performed by the study site's certified laboratory as per routine clinical practice, on samples collected before ICF signature, is acceptable and may not be repeated, only if the assessment is fully satisfying study protocol criteria in terms of completeness and time points.

- At C1D15
  Note: for patients in the trifluridine/tipiracil with bevacizumab arm, obtain within 48 hours prior to bevacizumab administration,
- Beginning with cycle 2, and for all subsequent cycles,
  - At D1, obtain within 48 hours prior to study treatments administration
- Withdrawal visit.

Measure the following serum chemistry parameters: albumin, ionogram (sodium, potassium, chloride, total calcium, magnesium, phosphate), blood urea nitrogen (BUN), serum creatinine, glucose, AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, total bilirubin (in case of elevation in total bilirubin, fractionation (direct/indirect) should be performed), LDH.

Note: If BUN is not available, use the following conversion:

Table (8.2.5.2) 1 - Correspondence between urea and BUN values

BUN (mmol/L) = UREA (mmol/L)
BUN (mg/dL) = UREA (mg/dL) x 0,467
BUN (mg/dL) = UREA (mmol/L) / 0,3571

8.2.5.3. Coagulation

Collect sample at the following time points for International normalized ratio (INR):
- Within 7 days prior to randomisation.
- At C1D1 prior to study treatments administration only if there is more than 7 days since screening assessment.

Note: For screening and pre-dose C1D1, an assessment performed by the study site's certified laboratory as per routine clinical practice, on samples collected before ICF signature, is acceptable and may not be repeated, only if the assessment is fully satisfying study protocol criteria in terms of completeness and time points.
- Beginning with cycle 2, and for all subsequent cycles,
  - At D1, obtain within 48 hours prior to study treatments administration
- Withdrawal visit.

8.2.5.4. Urinalysis

Collect urine samples for qualitative analysis of proteinuria at the following time points:
- Within 7 days prior to randomisation.
- At C1D1 prior to study treatments administration only if there is more than 7 days since screening assessment.
- At C1D15
  Note: for patients in the trifluridine/tipiracil with bevacizumab arm, obtain within 48 hours prior to bevacizumab administration,
- Beginning with cycle 2, and for all subsequent cycles,
  - At D1, obtain within 48 hours prior to study treatments administration
- Withdrawal visit.

If dipstick proteinuria ≥ 2+, a 24 hours-collection urine is required, and quantitative assessment of proteinuria will be performed.

Note: If only quantitative proteinuria is done by the study site, the correspondence between quantitative and qualitative values must be clearly described.
If no correspondence is available, please use the one in the table below:

Table (8.2.5.4) 1 - Correspondence between qualitative and quantitative proteinuria values

- Negative < 10 mg/dL	- 2+ [100 – 300[mg/dL
- Trace [10-30] mg/dL	- 3+ [300-1000] mg/dL
- 1+ [30 – 100] mg/dL	- 4+ > 1000 mg/dL

8.2.5.5. Pregnancy Testing

If the patient is female of childbearing potential, perform pregnancy testing with serum beta-human chorionic gonadotropin (β-HCG) or highly sensitive urine test (except during screening period), at the following time points and record the date, time, and test results in the patient's source documents:

- Within 7 days prior to randomisation (only serum test).
- Withdrawal visit (if not performed within previous 4 weeks).

Note: more frequent pregnancy tests should be performed if required by local law.

8.3. Definition of Adverse events

An AE is defined as any untoward medical occurrence in a subject participating in a clinical study, whether or not there is a causal relationship with the study treatments and/or experimental procedures, occurring or detected from the date the patient signs the information and consent form, irrespective of the period of the study (periods without administration of the study treatments are also concerned).

An adverse event can therefore be:

- any unfavourable and unintended sign (including an abnormal finding from an additional examination such as lab tests, X-rays, ECG, …) which is deemed clinically relevant by the investigator,
- any symptom or disease,
- any worsening during the study of a symptom or a disease already present when the patient entered the study (increase in frequency and/or intensity), including the studied pathology,

and detected during a study visit or at an additional examination or occurred since the previous study visit (including relevant event reported in patient's diary or safety evaluation scale).

Of note:

- Any **hospitalisation for administration of anti-tumoural treatment and/or associated protocol (during or after the study) or other care measures for cancer (e.g. overnight hospital stay to receive a blood or platelets transfusion), for social reasons, educational purpose** (e.g. learning of diabetes management by the patient) or routine check-up should not be considered as an adverse event and **should not be reported in the e-CRF**.
- The following procedures, whether planned before the study or not, whether leading to a hospitalisation or not, **should not be reported in the e-CRF and kept in the source data (or patient file):**
  - therapeutic procedures related to a non-aggravated medical history (e.g. cataract extraction not due to an aggravation of the cataract during the study, haemodialysis sessions related to a renal insufficiency not aggravated during the study),
  - prophylactic procedures (e.g. sterilisation, wisdom teeth removal),
  - comfort procedures (e.g. cosmetic surgery),
  - control procedures of a pre-existing condition without aggravation (e.g. colonoscopy to control the remission of colon cancer).

8.4. Definition of Serious adverse events

Any adverse event that at, any dose:
- results in death,
- is life-threatening [(1)],
- requires inpatient hospitalization or prolongation of existing hospitalization,
- is medically significant [(2)],
- results in persistent or significant disability/incapacity [(3)],
- is a congenital anomaly/birth defect [(4)].

[(1)] Life-threatening in this context refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[(2)] Any event that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardise the participant or might require intervention to prevent one of these outcomes (for example: oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalisation, or development of drug dependence or drug abuse). The investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to sponsor.

[(3)] Disability/incapacity in this context refers to any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

[(4)] Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

8.5. Definition of Overdose

This refers to any intake of a quantity of IMP or a product other than the IMP taken as part of the protocol (NIMP) which is above the maximum dose recommended in the study protocol, independently of the occurrence of any adverse event.

The quantity should be considered per administration or cumulatively regarding the maximum dose recommended in the study protocol. An overdose with trifluridine/tipiracil is defined as taking a dose beyond the recommended dose in one day or beyond the recommended total dose in each cycle (i.e., 35 mg/m²/dose or >160 mg/day for trifluridine/tipiracil).

There is no known antidote available in case of trifluridine/tipiracil overdose. Overdose should be managed aggressively with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

For bevacizumab: please refer to Product Information (Appendix 7) for overdose management information.

8.6. Definition of Adverse event of special interest

Not applicable.

8.7. Definition of Events requiring an immediate notification (ERIN)

An event must be **notified immediately** (i.e. without delay and **within 24 hours following knowledge** at the latest) to the sponsor if it is:

- a serious adverse event,
- an overdose of the study treatments even if asymptomatic,
- any intake of the study treatments by a person around the patient,
- a pregnancy,
- any events of COVID-19.

8.8. Classification of an adverse event (seriousness, severity, causality, expectedness)

It is important that the investigator gives his/her own opinion regarding the **seriousness**, the **intensity** of the event as well as the **cause-effect relationship** between an adverse event and the study treatments. This evaluation must be assessed by the investigator and reported in the AE form. In addition, the sponsor will be responsible for the evaluation the **expectedness** of the event (See Section 8.9.3).

The Seriousness should be evaluated according to international guidance (see definition Section 8.3, in accordance with ICH Topic E2A and DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April).

The severity of all AEs will be graded according to the NCI-CTCAE on a five-point scale (Grade 1 to 5):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL[1].
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

The causal relationship to the study treatments, to the experimental procedures or to disease progression must be assessed when reporting the AE in the AE form. Cases ticked "related" by the investigator or judged by the sponsor as having a reasonable suspected causal relationship to the study treatments (AE linked to the mechanism of action of the study treatments…), will be considered as Suspected Adverse Drug Reaction. In general, if a relationship between AE and drug is at least reasonably possible (i.e. the relationship cannot be ruled out) it is to be considered as "related".

[1] Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden".

8.9. Reporting procedures

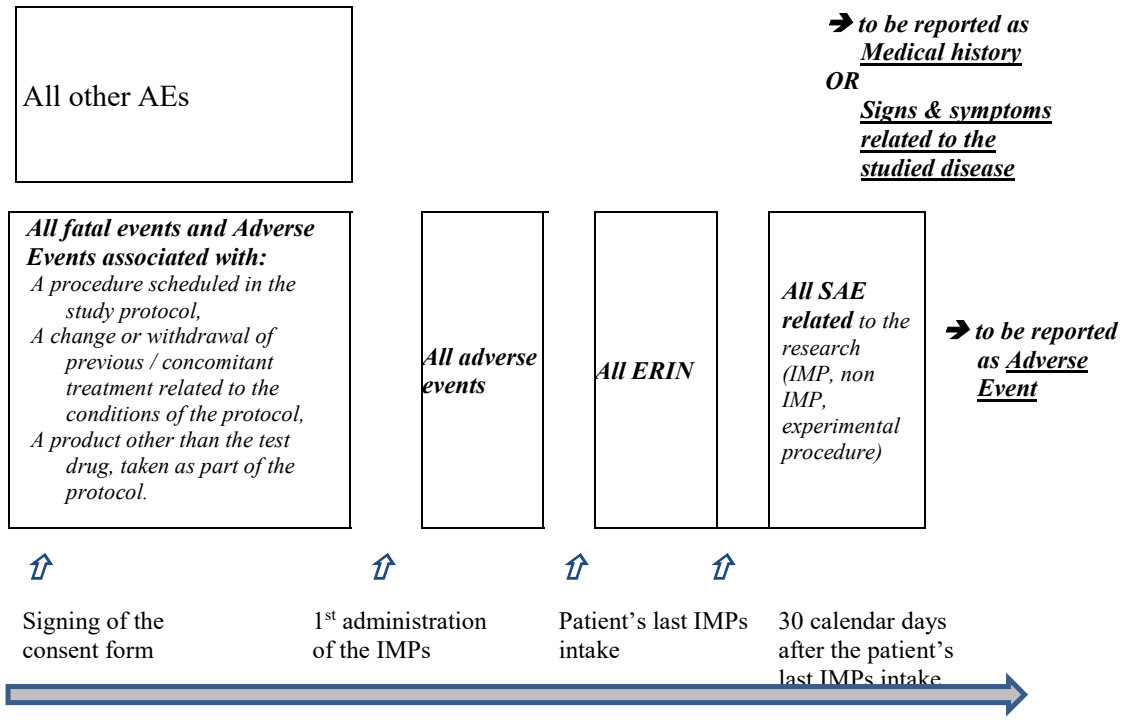
8.9.1. Time frame for AE reporting

Any event meeting the above mentioned definitions (see Sections 8.3 to 8.7) must be reported to the sponsor on an adverse event form if it occurred:

- before the first intake of the IMPs, **for event associated with any procedure/condition required by the study protocol**: procedure (exercise test, MRI, etc.), change or withdrawal of previous/concomitant treatment relating to the conditions of the protocol or a product other than the test drug, taken as part of the protocol (NIMP),
- at any time after the first intake of the IMPs up to the patient's last IMPs intake for all events,
- up to 30 calendar days after the patient's last IMPs intake for all ERIN, regardless of the supposed role of the research (IMP, NIMP, or experimental procedure),
- irrespective of the time of onset after the end of the study in case of serious adverse event related to the research (IMP, NIMP or experimental procedure).

Of note, events occurring between the signature of the ICF and the first study treatments administration for which the investigator does not consider an association with any procedure/condition required by the study protocol must be reported as medical history or as signs or symptoms related to the studied disease in the dedicated form of the e-CRF. Fatal event, related or not to the research, occurring between ICF signature and first IMP intake, should be reported on AE form.

Figure (8.9.1) 1 - Rules for AE reporting



8.9.2. Responsibilities of the investigator

For any adverse event and special situation mentioned above the investigator must:

- **Note in the patient's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the patient or a third person, …) and any other relevant information which he/she has learned of the event,
- **Assess** the event in terms of seriousness, intensity and causality,
- **Report the event to the sponsor** using the AE form (in case of ERIN, the reporting should be done immediately),
- **Document** the event with additional useful information,
- Ensure the **follow-up** of the event,
- **Fulfil his/her regulatory obligations** to the CA and/or to the IRB/IEC, in accordance with local regulations.

Moreover, the investigator must report to the sponsor and/or to the IRB/IEC and/or to the CA in accordance with the local regulation, any new information that might materially influence the benefit-risk assessment of the study treatments or that would be sufficient to consider changes in the study treatments administration or in the overall conduct of the clinical investigation.

8.9.2.1. Documentation of the event

The investigator must ensure that all events are well documented. In particular for ERIN, he/she should provide the sponsor, as they become available, with anonymized copies of the documents which provide additional useful information, such as hospital admission reports, reports of further consultations, laboratory test reports, reports of other examinations aiding diagnosis, or the autopsy report, if autopsy is performed.

8.9.2.2. Follow-up of adverse events

The investigator must ensure that follow-up of the patient is appropriate to the nature of the event, and that it continues until resolution if deemed necessary.

Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an AE already reported must be written up in a new complete evaluation of the event documented on the "Adverse event" page previously created for the event.

If the AE has not resolved at the patient's final visit, the patient must be followed up suitably and any information on the outcome of the event will be noted on the "Adverse Event" page previously created for the event.

If the follow-up of the patient is not done by the investigator him/herself (hospitalisation, followed by a specialist or the patient's general practitioner, …), the investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of the patient.

8.9.2.3. Special situations (pregnancy, overdoses, intake of IMP by a person around the patient)

Pregnancy

If a female patient in the study becomes pregnant, the investigator must:
- stop immediately the study treatments,
- report it on an "Adverse Event" page as well as on the specific paper pregnancy form (1st page) to be notified immediately (ERIN),
- contribute to the follow-up of this pregnancy and provide the sponsor with information concerning this follow-up (notably using the 2nd page of the specific paper pregnancy form).
- If the partner of a patient becomes pregnant during the course of the study, the pregnancy should not be reported in the e-CRF. The investigator should **immediately** contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

Overdose of IMP
- In case of overdose, the investigator should report it on an "Adverse Event" page to be notified immediately (ERIN).
- Overdose should be followed-up to ensure that the information is as complete as possible with regards to:
  - dose details (number of units, duration…) and, if multiple overdoses, details regarding other medicinal products or substance,
  - context of occurrence, i.e. intentional (suicide attempt, other reason) or accidental (error in prescription, administration, dispensing, dosage),
  - related signs and symptoms ("No related adverse events" to be reported otherwise),
  - outcome.

Intake of IMP by a person around the patient

This event should not be reported in the e-CRF. The investigator should immediately contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

8.9.2.4. Recording methods in the e-CRF

AE must be documented on the "Adverse Event" page of the e-CRF.

In case of chronic disease:
- if the disease is known when the patient enters in the study, only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an adverse event,
- if the disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the "Adverse Event" page previously created for the eventwhich will clearly describe the diagnosis.

8.9.2.5. Procedure for an event requiring an immediate notification

In case of an event requiring an immediate notification, the investigator must:

- **Immediately** after being informed of this event, **fill in** the **patient's medical file** as well as the **"Adverse Event" page** of the e-CRF according to the general instructions available in the e-CRF, without waiting for the results of the clinical outcome or of additional investigations. When data will be submitted into INFORM, an e-mail will be immediately and automatically sent to the sponsor.
- Provide the sponsor (person designated in the contact details provided in the investigator's study file), as they become available, with anonymized copies of the documents which provide additional useful information,
- Fulfil his/her regulatory obligations to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.

If an adverse event initially non-serious worsens and becomes a serious adverse event, this must be reported **immediately** on an "Adverse event" page of the e-CRF.

In case the e-CRF is unavailable when the investigator was informed of the ERIN, he/she should:

- **Immediately** fill in a paper "Adverse event" page:
  - For serious event on a paper "Adverse event – Initial information" page,
  - For event initially non-serious on a paper "Adverse event – Initial information" page, and the worsening leading to seriousness on a paper "Adverse event – Additional information" page,
- Immediately send them by fax or by e-mail to the person(s) designated in the contact details provided in the investigator's study file or outside working hours, the 24-hour phone line
- As soon as the e-CRF becomes available, the investigator should enter these data in the "Adverse Event" page of the e-CRF.

8.9.3. Responsibilities of the sponsor

In accordance with international guidance, the assessment of the seriousness and the causality of adverse events are usually made by the investigator but falls also under sponsor's duties, who is responsible for ensuring that all suspected unexpected serious adverse reactions are reported to Competent Authorities and Ethics Committees.

The sponsor will review the seriousness of the adverse events and the causality of (at least) the serious adverse events, whether reported by the investigator or upgraded by the sponsor. The causality and the seriousness may be upgraded (but never downgraded). Anonymized copies of documents providing useful information such as reports of further consultations, laboratory tests reports, reports of other examination aiding diagnosis may be asked for the event assessment. If the assessments of the investigator and the sponsor are different, both will be reported in the clinical study report.

In addition, the sponsor is responsible for determining whether an AE is **expected or unexpected**. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IMP.

Independently of the regulatory obligations of the investigator, the sponsor must report the pharmacovigilance data and any new safety finding likely to affect the benefit /risk balance of the product, required in ICH GCP guidelines and local regulations, to the appropriate

Authorities, to all the investigators involved and to the trial subjects involved - through the investigators - as mentioned in Section 13.4.

The concerned authorities will be notified as soon as possible by the sponsor of the DSMB recommendations if any, where relevant for the safety of subjects (i.e. modification or termination of the study).

8.10. Responsibilities of Data Safety Monitoring Committee

As described in Section 12.4, the DSMB is an independent group of experts which provides expertise and recommendations to the International Coordinator and sponsor.

In accordance with the charter and the rules for functioning, the DSMB is responsible for reviewing the safety data on a regular basis and providing written recommendations to the International Coordinator and the sponsor regarding the conduct of the study.

8.11. Management of treatment dose adaptations due to toxicities

For patients who have experienced a dosing modification, reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's source documents and recorded in the e-CRF.

General rules:

- Before starting a new treatment cycle, toxicity must have resolved as specified in the Sections 8.11.1 and 8.11.2.
- Treatment interruptions are regarded as lost treatment days and missed doses should not be replaced; the planned treatment schedule should be maintained.

8.11.1. Trifluridine/tipiracil

All toxicities related to trifluridine/tipiracil must have resolved to grade 1 or baseline before the start of a new treatment cycle.

In the event of haematological and/or non-haematological toxicities, rules for trifluridine/tipiracil dose interruption and resumption are provided in Table (8.11.1) 1; rules for dose modifications are provided in Table (8.11.1) 2 and Table (8.11.1) 3.

A new treatment cycle with trifluridine/tipiracil can be started only if neutrophils count is ≥1.5 x 10^9/L and platelets count is ≥75 x 10^9/L.

Table (8.11.1) 1 - Dose interruption and resumption criteria for haematological toxicities related to myelosuppression

Parameter	Interruption criteria*	Resumption criteria**
Neutrophils	$<0.5 \times 10^9$/L	$\geqslant 1.5 \times 10^9$/L
Platelets	$<50 \times 10^9$/L	$\geqslant 75 \times 10^9$/L

* Interruption criteria apply only during active treatment intake period (i.e., D1-5 and D8-12) based on an unscheduled laboratory assessment.

**Resumption criteria apply to the start of the next cycle for all patients regardless of whether or not the interruption criteria were met.

Table (8.11.1) 2 - Recommended dose modifications in case of haematological adverse event related to myelosuppression

Adverse event related to myelosuppression	Recommended dose modifications
Febrile neutropenia	- Don't start a new treatment cycle until the resumption criteria are met (Table (8.11.1) 1). - When resuming dosing, decrease the dose level by 5 mg/m² from the previous dose level (Table (6.1.3) 2). - Dose reductions are permitted to a minimum dose of 20 mg/m²/dose twice daily. - Do not increase dose after it has been reduced.
CTCAE Grade 4 neutropenia count $<0.5 \times 10^9$/L that results in more than 1 week's delay in start of next cycle.	
CTCAE Grade 4 thrombocytopenia $<25 \times 10^9$/L that results in more than 1 week's delay in start of next cycle.	

Table (8.11.1) 3 - Recommended dose modifications in case of non-haematological adverse event related to trifluridine/tipiracil

Adverse event related to trifluridine/tipiracil	Recommended dose modifications
CTCAE non-hematologic grade 3 or 4 adverse reaction; except for grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhoea responsive to antidiarrheal medicinal products.	- Don't start a new treatment cycle until toxicity resolves to grade 1 or baseline. - When resuming dosing, decrease the dose level by 5 mg/m² from the previous dose level (Table (6.1.3) 2). - Dose reductions are permitted to a minimum dose of 20 mg/m²/dose twice daily. - Do not increase dose after it has been reduced.

If the patient recovers from toxicities requiring treatment interruption:
- during the 2-week active treatment intake period of a cycle (treatment D1-D12)
  - if no dose reduction is required, trifluridine/tipiracil may be resumed during that cycle. Missed doses must not be caught up
  - if a dose reduction is required, trifluridine/tipiracil should be resumed at the start of the next treatment cycle at the appropriate dose level.
- during the rest period (D13-28):
  - start the next cycle on schedule at the appropriate trifluridine/tipiracil dose level.

If the toxicities do not resolve during the given cycle to grade 1 or baseline, the start of the next cycle must be delayed for a maximum of 28 days from the scheduled start date of the next cycle. If more than 28 days are needed to recover, the patient will be withdrawn from treatment as described in the Section 5.6.1.

8.11.2. Bevacizumab

Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended as described in the Product Information (Appendix 7). If there is a medical condition developed that requires bevacizumab to be permanently withdrawn, the patient may continue with trifluridine/tipiracil alone.

Bevacizumab should not be administrated alone in case of dose delay due to trifluridine/tipiracil toxicities. The cycle will be delayed, and bevacizumab will be restarted at the same time of trifluridine/tipiracil.

8.12. Recommendations regarding treatment of toxicities

8.12.1. Management of nausea and vomiting

Trifluridine/tipiracil has emetogenic potential.

- A single antiemetic agent, such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, such as metoclopramide may be considered for prophylaxis.
- If a patient experiences acute or delayed nausea or vomiting due to trifluridine/tipiracil, it is advised that, at the next cycle, a higher antiemetic regimen may be given.
- In case a patient experiences of anticipatory nausea and vomiting, benzodiazepines are recommended.

(Roila, 2016), (Hesketh, 2016)

8.12.2. Management of diarrhoea

Educate both patients and patients' families regarding the potential seriousness of chemotherapy-induced diarrhoea. Instruct patients to immediately contact the study site staff at the first sign of loose stool. The patient should be instructed to record the number of stools and report symptoms indicating a complicated diarrhoea (see list below).
Educate the patient regarding the dietary measures to be taken in case of diarrhoea.
Provide patients with loperamide (or other standard antidiarrheal therapy) and instruct the patient on how to use it at the first sign of diarrhoea.
Monitor the patient's fluid and electrolyte balance, with appropriate intervention as clinically indicated with fluids and electrolyte replacement (Benson III, 2004).

<u>Mild to moderate diarrhoea (grade 1 or 2 according to NCT-CTCAE without complications):</u>

- It is recommended to start dietary modifications and standard antidiarrheal therapy for example loperamide at an initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool (not to exceed 16 mg/day).
- If diarrhoea resolves with antidiarrheal therapy, the dietary modifications should be continued (with a gradually addition of solid foods). Antidiarrheal therapy may be discontinued when the patient has been diarrhoea-free for at least 12 hours.
- If diarrhoea persists for more than 24 hours, the dose of antidiarrheal therapy should be increased (for loperamide increase to 2 mg every 2 hours), and oral antibiotics may be started as prophylaxis for infection.
- If diarrhoea has not resolved after 48 hours on initial treatment, the patient should be started on a second-line antidiarrheal agent.

<u>Complicated diarrhoea:</u>

- Any grade 3 or 4 diarrhoea is classified as "complicated". In addition, grade 1 or 2 diarrhoea and at least one of the following symptoms are also considered as complicated:
  - fever, sepsis, moderate to severe cramping,
  - grade 2 nausea/vomiting,
  - decreased performance status,
  - neutropenia,
  - frank bleeding,
  - dehydration
- Aggressive management of complicated cases should involve
  - intravenous (IV) fluids;

  - octreotide at a starting dose of 100 to 150 µg SC tid or IV (25 to 50 µg/h) if the patient is severely dehydrated, with dose escalation up to 500 µg until diarrhoea is controlled,
  - administration of antibiotics (e.g., fluoroquinolone).
- Stool work-up (evaluation for blood, faecal leukocytes, C difficile, Salmonella, E coli, Campylobacter, and infectious colitis), complete blood count, and electrolyte profile should be performed.
- Continue intervention as described until the patient has been diarrhoea-free for 24 hours.

8.12.3. Management of mucosal injury

Mucositis refers to mucosal damage secondary to cancer therapy occurring in the oral cavity; pharyngeal, laryngeal, and oesophageal regions; and other areas of the gastrointestinal tract. Oral mucositis presents as erythema and/or ulceration of the oral mucosa. Gastrointestinal mucositis presents with debilitating symptoms such as pain, nausea/vomiting, and diarrhoea.

Prevention and education of the patient:

- The patient must be appropriately educated about oral complications before treatment and be advised to have regular dental examinations and inform the health care professional at first signs and symptoms of oral complications. Sources of trauma (e.g. sharp edges and ill-fitting prostheses) should be eliminated and painful stimuli such as hot foods and drinks and hard, sharp, or spicy foods should be avoided.
- Sodium bicarbonate mouthwash can be used to rinse the mouth (4 to 6 times a day) as long as the patient is treated by bevacizumab.

Treatment of mucositis:

- 0.5% doxepin mouthwash and transdermal fentanyl may be used to treat pain due to oral mucositis.
- For bevacizumab-related stomatitis:
  - The frequency of use of sodium bicarbonate containing mouthwash can be increased, if necessary, up to each hour to treat stomatitis.
  - Sugarless chewing gum or candy, salivary substitutes or sialagogues should be considered to treat oral dryness.
  - Adequate pain management, e.g. anaesthetic mouthwashes (viscous lidocaine 2%), coating agents, or systemic analgesics following the WHO pain management ladder may be provided.
  - Coating agents, topical analgesic or anti-inflammatory agents, topical anaesthetics, and alternative mouthwashes may be considered.

(Lalla, 2014), (Peterson, 2015)

8.12.4. Management of febrile neutropenia and anaemia

Administer hematologic support as medically indicated (*e.g.*, blood transfusions, granulocyte colony-stimulating factor [G-CSF], erythropoietin, etc.) according to the institutional site standards.

If there are no standard procedures for the use of growth factors, follow Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update, available at http://www.instituteforquality.org/practice-guidelines; or the European Organization for Research and Treatment of Cancer (EORTC) update to 2010 guidelines for the use of G-CSF, available at http://www.eortc.org/investigators-area/eortc-guidelines.

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

9.1. Assessments done at baseline

9.1.1. Assessments related to inclusion criteria.

9.1.1.1. Informed consent

Obtain signed and dated ICF from the patient during the screening visit prior to the implementation of study procedures required by the protocol. Please refers to Section 13.3.

9.1.1.2. Histological/Cytological Confirmation

Histological confirmation of adenocarcinoma of the colon or rectum should be documented in the patient's source documents. The pathology report should be available in the patient's source documents.

9.1.1.3. RAS status

RAS status will be collected in the e-CRF and must have been determined based on local assessment of tumour biopsy and documented in the patient's source documents.

9.1.2. Assessments not related to inclusion criteria.

9.1.2.1. Patient Numbering

Once the patient has signed ICF, the study site will connect to the IWRS for patient's registration and to obtain a patient's number (see the IWRS manual for details). Each patient will be assigned a unique patient number. This patient number will be maintained throughout the study and will not be reassigned. Patients who withdraw consent or discontinue from the study after being assigned a patient number will retain their initial number.

9.1.2.2. Demography

Collect demography data (age, sex, ethnic origin).

9.1.2.3. Medical history

Obtain a complete medical history.
Of note, events occurring between the signature of the ICF and the first study treatments administration for which the investigator does not consider an association with any procedure/condition required by the study protocol must be reported as medical history in the dedicated form of the e-CRF.

9.1.2.4. Previous surgery, radiotherapy and treatments related to the colorectal cancer

Collect previous surgery, radiotherapy and treatments related to the colorectal cancer.

9.1.2.5. Baseline Signs and Symptoms

Signs and symptoms related to the colorectal cancer present following ICF signature and before the first study treatments administration should be recorded in the patient's source documents.

9.1.2.6. Primary tumour localisation

The localisation of the primary tumour will be collected in the e-CRF if available.

Note: the localisation is defined in the table below:

Table (9.1.2.6) 1 - Primary tumour localisation

Right		Left	
- Cecum	- Hepatic flexure	- Splenic flexure	- Rectosigmoid segment
- Appendix	- Transverse colon	- Descending colon	
- Ascending colon		- Sigmoid colon	- Rectum

In the case the patient presents multiple tumours in both sides, the disease will be considered as "right-sided".

9.1.2.7. BRAF status and MMR/MSI status

BRAF status and MMR/MSI status will be collected in the e-CRF if available.

9.2. Measurement of drug concentration

Not applicable.

9.3. Pharmacodynamics measurements

Not applicable.

9.4. Assessment of biomarkers

Not applicable.

9.5. Quality of Life

EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30) (Appendix 5) and 5Q-5D-5L (Appendix 6) will be completed by the patient on an e-PRO, independently of the study personnel at the following time points, at the beginning of each visit:

- Within 7 days prior to randomisation (baseline),
- Every cycle, prior to any study procedure,
- Withdrawal visit.

Patients will be provided with specific instructions in order to be comfortable with the tablet and enhance the quality of the data. In case the patient is not able to use e-PRO, a caregiver (not a medical/investigator staff) will be allowed to read the questions to the patient and to collect the answer without any interpretation of the questions and the answers. Data entered by the patient will be sent to a central database via a secured transfer.

10. STATISTICS

10.1. Statistical analysis

Statistical analysis will be produced by the Center of Excellence Methodology and Data Valorisation.

A Statistical Analysis Plan (SAP), and associated templates for Tables, Listings and Graphs, will be written and completed before database lock. These specifications will detail the implementation of all the planned statistical analyses in accordance with the main characteristics stated in the protocol.

10.1.1. Analysis sets / Treatment groups

10.1.1.1. Analysis sets

- **Full Analysis Set (FAS):**

In accordance with the intention-to-treat principle and the section 5.2.1 of ICH E9 guideline, all patients to whom a therapeutic unit was randomly assigned using IWRS. Patients in the FAS will be analysed in the arm they were assigned by randomization.

- **Safety Set (SS):**

All patients having taken at least one dose of IMPs. Patients will be analyzed according to the treatment actually received.

10.1.1.2. Treatment groups

Treatment groups considered for the analysis will be the following:

- Trifluridine/tipiracil + bevacizumab
- Trifluridine/tipiracil

10.1.2. Statistical methods

10.1.2.1. General considerations

The following descriptive statistics will be provided depending on the nature of considered data:

- **Qualitative data**: number of observed values, number and percentage of patients per class.
- **Quantitative data**: number of observed values, mean and standard deviation, median, first and third quartiles, minimum and maximum.
- **Survival data** (time to event occurrence or to censoring): total number of patients, total number and percentage of patients having an event overall and by level of adjustment qualitative variable, number of patients at risk, number of patients with censored data, number of patients with event of interest.

10.1.2.2. Disposition and baseline characteristics

The patients' disposition and baseline characteristics will be described in the FAS by treatment arms and overall.

The number of patients in each study population and the reasons for exclusion, along with any randomization and/or stratification errors will be summarized as well as the disposition of

patients, including reasons for discontinuation and protocol deviations at baseline and during study.

Characteristics of patients including demography, characteristics of the disease at diagnosis and study entry, medical history, prior therapy and concomitant medication at baseline will be summarised.

10.1.2.3. Treatments of patients

Extent of exposure and treatment compliance, as well as concomitant medication during treatment period will be described in the SS. Extent of exposure includes number of cycles, cumulative dose, dose intensity, relative dose intensity, dose modifications.

The follow-up duration will be calculated overall and in each arm with the reverse Kaplan-Meier method.

The non-study cancer treatment after study treatment discontinuation will be summarized. Any use of non-study cancer treatment during the study treatment period will also be presented as protocol deviation.

10.1.2.4. Efficacy analysis

Primary objective
The primary objective is to demonstrate the superiority of trifluridine/tipiracil in combination with bevacizumab over trifluridine/tipiracil monotherapy in terms of OS in patients with refractory mCRC.

Secondary objectives
Secondary objectives are to estimate the effect of trifluridine/tipiracil in combination with bevacizumab versus trifluridine/tipiracil monotherapy in terms of PFS, ORR, and DCR in patients with refractory mCRC.

Other secondary objectives are to compare the safety and tolerance, and the impact on quality of life (QoL) of trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory mCRC.

Intercurrent events
During the study the following intercurrent events could occur:

- Administration of further anti-cancer therapy
- Treatment discontinuation
- Treatment switch (from trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy and from trifluridine/tipiracil monotherapy to trifluridine/tipiracil in combination with bevacizumab)

Estimands of interest

The attributes *treatment* and *population* will be the same for all estimands of interest:

- Treatment: Trifluridine/tipiracil + bevacizumab vs trifluridine/tipiracil monotherapy.
- Population: Full Analysis Set (FAS).

The following estimands will be studied:

Estimand	Variable	Population level summary	Handling IEs
Primary estimand: effect of the randomized treatments on the survival duration in all subjects regardless of whether or not intercurrent events occur	OS	HR	Treatment policy strategy
Effect of the randomized treatments on the survival duration in all subjects before patients receive further anti-cancer therapy	OS	HR	While on treatment strategy
Effect of the randomized treatments on progression-free survival in all subjects regardless of whether or not intercurrent events occur	PFS	HR	Treatment policy strategy
Effect of the randomized treatments on response in all subjects before modification of randomized treatment	ORR DCR	Risk difference	While on treatment strategy

With:

- OS: overall survival defined as the observed time elapsed between the date of randomization and the date of death due to any cause
- PFS: progression-free survival based on investigator judgement and defined as the time elapsed between the randomization and the date of radiologic tumour progression (according to RECIST version 1.1 (Eisenhauer, 2009) or death from any cause.
- ORR: overall response rate defined as the proportion of patients with objective evidence of complete response (CR) or partial response (PR) according to RECIST version 1.1 criteria and using investigator's tumour assessment,
- DCR: disease control rate defined as the proportion of patients with objective evidence of CR or PR or stable disease (SD) according to RECIST version 1.1 criteria and using investigator's tumour assessment.

Estimands and the way for handling IEs will be detailed in the following paragraphs.

10.1.2.4.1. Primary estimand based on the OS

As explained before, the primary estimand of interest is the effect of the randomized treatments on the survival duration in all subjects regardless of whether or not intercurrent events occur (treatment policy strategy). The motivation for this choice is to assess the efficacy of the trifluridine/tipiracil in combination with bevacizumab compared to trifluridine/tipiracil monotherapy under the ITT principle (intercurrent events are considered to be part of the treatments being compared).
All data collected during the trial regardless of occurrence of an IE will be used. This is aligned with the treatment policy strategy.

10.1.2.4.1.1. Primary analysis

The distribution of OS will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (stratification factors based on IWRS data). OS for each arm will be summarized using Kaplan Meier curves and further characterized in terms of the median and survival probabilities at 6, 12 and 18 months along with the corresponding 2-sided 95% CI for the estimates.
The hazard ratio of OS with its 95% confidence interval will be estimated with a stratified Cox proportional hazard model (stratification factors based on IWRS data).

For missing data (not linked to intercurrent events), i.e. patients without documentation of death (lost to follow-up, withdrawal of consent, administrative end of study), the OS will be censored on the last contact date the patient was known to be alive or the cut-off date, whichever is earlier.

10.1.2.4.1.2. Sensitivity analyses

As sensitivity analyses, the following analyses will be done:

- The proportional hazards assumption will be checked. If relevant, other statistical method could be used.
- The distribution of OS will be compared between the treatment groups using an unstratified log-rank test and the hazard ratio (together with associated 95% CI) resulting from an unstratified Cox model will be presented.
- OS analysis excluding patients not fulfilling one of the following criteria:
  - Has histologically confirmed unresectable adenocarcinoma of the colon or rectum
  - Has received a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer and had demonstrated progressive disease or intolerance to their last regimen
  - Has measurable or non-measurable metastatic lesion(s) as defined by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1
  - Has an Eastern Cooperative Oncology Group (ECOG) performance status ≤1
  - More than 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer
  - Has previously received trifluridine/tipiracil
  - Does not currently received or has not received anticancer therapies within 4 weeks prior to randomisation

Other sensitivity analyses will be defined in the SAP if necessary.

10.1.2.4.1.3. Supplementary analyses

Subgroup analyses

OS subgroup analyses are planned to further explore the homogeneity of the treatment effect across patient subsets. Depending on the sample size, the following subgroups will be examined: region (North America, European Union, Rest of the World), time since diagnosis of 1st metastasis (<18, ≥18 months), RAS (wild, mutant), location of primary disease (right, left), ECOG performance status (0, 1), gender (female, male), age (<70, ≥70 years), prior

surgical resection (yes, no), number of metastatic sites (1-2, ≥3), neutrophils to lymphocytes ratio (NLR<3, NLR≥3), number of prior regimens, BRAF (wild, mutant) and MSI status (MSI-H, MSS/MSI-L), prior bevacizumab (yes, no), subsequent regorafenib (yes, no).

An unstratified Cox-regression model with treatment arm as predictor variable will be fitted separately for each subgroup category. The hazard ratio for treatment along with the associated 95% confidence interval will be provided.

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10.1.2.4.2. Additional estimand based on OS

The other estimand based on OS is defined in order to assess the effect of the randomized treatments on the survival time in all subjects before patients receive further anti-cancer therapy (while on treatment strategy). The aim of this estimand is to evaluate the effect of the study treatment without a potential effect of another therapy

The use of data post intercurrent events will be different according to the IE:

- For IE "administration of further anti-cancer therapy" and "treatment switch": data obtained post IE will not be used for the analysis. OS will be censored at the time of administration of further anti-cancer therapy.
- For IE "treatment discontinuation": time of death for any cause after treatment discontinuation will be taken into account.

These strategies are aligned with this estimand.

The distribution of OS will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (stratification factors based on IWRS data).

For missing data (not linked to intercurrent events), i.e. patients without documentation of death (lost to follow-up, withdrawal of consent, administrative end of study), the OS will be censored on the last contact date the patient was known to be alive or the cut-off date, whichever is earlier.

Other estimands will be defined in the SAP if necessary.

10.1.2.4.3. Secondary estimands based on PFS, ORR, and DCR

Secondary estimand based on PFS

Important secondary estimands of interest is the effect of the randomized treatments on progression-free survival in all subjects regardless of whether or not intercurrent events occur (treatment policy strategy).

All data collected during the trial regardless of occurrence of an IE will be used. This is aligned with the estimand and the treatment policy strategy.

The following analyses will be done as primary analyses:

- The distribution of PFS will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (stratification factors based on IWRS data).
- PFS for each arm will be summarized using Kaplan Meier curves and further characterized in terms of the median and survival probabilities at 3, 6, 9 and 12 months along with the corresponding 2-sided 95% CI for the estimates.
- The hazard ratio of PFS with its 95% confidence interval will be estimated with a stratified Cox proportional hazard model (stratification factors based on IWRS data).

PFS is identified as the key secondary variable. A hierarchical testing strategy, where PFS is to be statistically evaluated and interpreted only if the primary efficacy estimand OS is significantly different between the 2 treatment groups, will be used to control the overall type-I error rate.

The following analyses will be done as sensitivity analyses:

- The distribution of PFS will be also compared between the treatment groups using an unstratified log-rank test and the hazard ratio (together with associated 95% CI) resulting from an unstratified Cox model will be presented.
- An analysis that considers clinical progression and administration of further anti-cancer therapy as PFS events in addition to the radiological progression or death.

For missing data (not linked to intercurrent events), i.e. patients who were lost to follow-up or who have withdrawn their consent without radiological progression or reached the time point of analysis without a known record of death or radiological progression, the PFS will be censored at the date of last evaluable tumour assessment or the cut-off date, whichever is earlier.

The same subgroup analyses as used for the primary estimand will be done for PFS.

Secondary estimands based on ORR and DCR

Other secondary estimand of interest are the effect of the randomized treatments on response in all subjects before modification of randomized treatment.

Responses recorded after intercurrent event will be excluded. This is aligned with the estimand and the treatment while on treatment strategy.

The following analyses will be done:

- ORR based on the investigator's tumour assessment will be compared in the FAS between treatment arms using Fisher's exact test and 2-sided 95% Clopper-Pearson CIs. A 2-sided 95% CI for the difference in ORR between the two treatment arms will also be provided based on the normal approximation. If a stratified analysis is required a Cochran-Mantel-Haenszel (CMH) test will be used. A 2-sided 95% CI for the difference in ORR between the two treatment arms will also be provided based on the normal approximation.
- DCR based on the investigator's tumour assessment will be compared in the FAS between treatment arms using Fisher's exact test and 2-sided 95% Clopper-Pearson CIs. A 2-sided 95% CI for the difference in DCR between the two treatment arms will also be provided based on the normal approximation. If a stratified analysis is required a Cochran-Mantel-Haenszel (CMH) test will be used. A 2-sided 95% CI for the difference in DCR between the two treatment arms will also be provided based on the normal approximation.

As supplementary analysis, ORR and DCR will be evaluated on population evaluable for tumour response.

For missing data (not linked to intercurrent events), an unfavourable outcome will be taken into account.

10.1.2.5. Quality of Life analysis

Endpoints:

- EORTC QLQ-C30 questionnaire
- EORTC EQ-5D-5L questionnaire

Analysis:

- EORTC QLQ-C30:

Patients from the FAS should have completed at least one questionnaire item at baseline and during the study period will be analysis in the arm they were assigned by randomization.

The raw QoL data will be scored according to the EORTC scoring manual and the change in score from baseline in the global health status (GHS) scale is identified as the primary QoL variable of interest.

The completion and compliance rates will be summarised by treatment group for each scheduled assessment timepoints.

The completion rate is defined as the rate of patients who completed the QoL instrument among patients of FAS.

The compliance rate is defined as the rate of patients who completed the QoL instrument among patients still on treatment at each visit.

Baseline values and changes in scores from baseline (GHS and each sub-scale score) will be summarized at each scheduled assessment time point by descriptive.

A repeated-measures mixed-effects model (SAS PROC MIXED) that includes terms for treatment arms, baseline stratification factors, baseline sub-scale score and time of visit will be used to compare the two treatment groups with respect to changes from baseline in the 3 sub-scales scores longitudinally over time (GHS, functional scale and symptoms scale).

Time to definitive ≥10 points deterioration from baseline in the GHS and in each sub-scale, will be compared between the two treatment arms in the FAS using the stratified log-rank test at a 2-sided 5% level of significance (strata based on IWRS data). Death will be considered to be a deterioration event of QoL. Patients receiving any further anti-neoplastic therapy before definitive worsening will be censored at the date of their last QoL assessment before starting this therapy. Patients that have not worsened as of the cutoff date for the analysis will be censored at the date of their last assessment (questionnaire) before the cutoff. Patients without evaluable questionnaire at baseline will be censored at their randomization date + 1 day. The distributions will be described using Kaplan-Meier curves including the median time to definitive 10 points deterioration.

- EORTC EQ-5D-5L:

EQ-5D-5L assessment will be considered non-evaluable when responses are missing for one or more of the dimensions. Patients from the FAS with an evaluable EQ-5D-5L assessment at baseline and at least one evaluable assessment post baseline will be analysed in the arm they were assigned by randomization.

The dimensional 5-level system will be converted into a single index utility score: the utility index will be derived according to Euroqol specific country algorithms.

The completion and compliance rates will be summarised by treatment group for each scheduled assessment timepoints.

The completion rate is defined as the rate of patients with evaluable EQ-5D-5L assessment among patients of FAS.

The compliance rate is defined as the rate of patients with evaluable EQ-5D-5L assessment among patients still on treatment at each visit.

A breakdown table to include the proportions of reported problems at baseline versus each scheduled assessment timepoint will be presented in each dimension of EQ-5D-5L by treatment arms.

Baseline values and changes in score from baseline in EQ-5D-5L VAS and EQ-5D-5L health utility index will be presented by treatment arms at each scheduled assessment timepoint by descriptive statistics (N, mean/proportion median, SD, Q1, Q3).

A repeated-measures mixed-effects model (SAS PROC MIXED) that includes terms for treatment, baseline stratification factors, baseline score and time of visit will be used to compare the two treatment groups with respect to changes from baseline in the EQ-5D-5L VAS and EQ-5D-5L health utility index.

10.1.2.6. Safety analysis

All patients included in the Safety set (SS) will be evaluated by treatment arms unless otherwise specified.

10.1.2.6.1. Adverse events

Number of events, number and percentage of patients reporting at least one event, presented by primary system organ class and/or preferred term (depending on the analysis), will be provided for serious adverse events and emergent adverse events over the study and treatment periods, respectively.

Emergent adverse events will be described according to the seriousness, the intensity, the relationship, the action taken regarding the IMP, the requirement of added therapy, the outcome and the time to onset.

Of note, the seriousness and the relationship to the IMP of the adverse event correspond to the investigator opinion or, in case of events upgraded by the sponsor for seriousness or for causality in case of SAE, to the sponsor opinion.

10.1.2.6.2. Clinical laboratory evaluation

For haematological, biochemistry, urinary and coagulation parameters, descriptive statistics on value at baseline, on value at each post-baseline visit under treatment, on last post-baseline value under treatment and, on change from baseline to last post-baseline value under treatment will be provided.

For all clinical laboratory parameters (except urinary parameters), the following analysis will be performed:
Laboratory parameters classified (number and percentage of patients in each class) according to these reference ranges and using shift tables from baseline to the worst (high and/or low) values under treatment.

10.1.2.6.3. Vital signs, clinical examination and other observations related to safety

10.1.2.6.3.1. Vital signs and clinical examination

Vital signs and clinical examination will be described, in terms of value at baseline, value at each post-baseline visit under treatment and last post-baseline value under treatment; as well as in terms of change from baseline to each post baseline visit under treatment and to last post-baseline value under treatment.

Time to ECOG performance status worsening will be analyzed in the FAS using Kaplan-Meier methodology and compared between treatment groups with a stratified logrank test (strata based on IWRS data). To be considered as a worsening, the ECOG PS must be increased by at least one category and to at least a minimal PS value of 2. Patients without ECOG PS worsening will be censored at the last recorded ECOG PS assessment.

10.1.2.6.3.2. Electrocardiogram

ECG parameters will be described, in terms of value at baseline, value at each post-baseline visit under treatment and last post-baseline value under treatment; as well as, for quantitative endpoints, in terms of change from baseline to each post baseline visit under treatment and to last post-baseline value under treatment. Moreover values and changes form baseline of corrected QT interval will be described in classes, considering thresholds defined in ICH E14 (i.e., ≤ 450,] 450; 480],] 480; 500] and > 500 ms for values, and ≤ 30,] 30; 60] and > 60 ms for changes).

10.1.2.7. Biomarkers analysis

Not applicable.

10.1.2.8. Interim analysis

Not applicable.

10.2. Determination of sample size

Calculations are done with EAST 6.4 software.

A maximum of 331 events (deaths for any cause) will be required for the primary analysis to detect a hazard ratio of 0.70 with 90% power using a log-rank test at one-sided cumulative 2.5% level of significance. Based on the data from the RECOURSE study (Mayer, 2015), the median duration of OS in the control group is expected to be around 7.1 months. A hazard ratio of 0.70 translates into 3 months increase of the median OS in the experimental arm (10.1 months) compared to the control arm. Based on the assumption that enrolment will continue for approximately 12 months, and that about 5%/year of the subjects will drop out, a total of 490 patients randomized in a 1:1 ratio will be needed to observe the 331th OS events approximately 9 months after the last patient randomization.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator will allow the monitors, the persons responsible for the audit, the representatives of the IRB/IEC, and of the CA to have direct access to source data / documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study monitoring

Study site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with Good Clinical Practice (GCP), and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the structure mentioned in Section 1.

Details of study site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

12.1.1. Before the study

The investigator will allow the monitor to visit the study site and facilities where the study will take place in order to ensure compliance with the protocol requirements.

12.1.2. During the study

The investigator will allow the monitor to:
- review of the study site's processes and procedures,
- verify appropriate clinical investigator supervision of study site staff and third-party vendors,
- inspect the study site, the facilities and the material used for the study,
- meet all members of his/her team involved in the study,
- consult the documents relevant to the study,
- have access to the e-CRF (i.e. access to an analogic phone line or his/her computer) and/or to the e-PRO service provider's database to check that they been filled out correctly,
- check that the e-CRF and e-PRO have been filled out correctly,
- directly access source documents for comparison of data therein with the data in the e-CRF and the e-PRO service provider's database,
- verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The monitoring will be carried out at regular intervals, depending on the recruitment rate and / or the investigation schedule, and arranged between the investigator and monitor.

All information dealt with during these visits will be treated as strictly confidential.

12.2. Computerised medical file

If computerised medical files are used, and if the computer system allows, no change made in the medical files by the investigator should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information (i.e. audit trail). The investigator will save data at regular intervals.

The investigator must guarantee the integrity of the study data in the medical files by implementing security measures to prevent unauthorised access to the data and to the computer system.

If the computerised medical files are considered as not validated by the sponsor, the investigator undertakes:

- at the start of the study, to print the medical files of all patients allowing a reliable verification of the study criteria (e.g. medical history/previous treatments/ characteristics of the studied disease documented within the period of time defined by the study protocol),
- during the study, to print in real time each data entry and each data change.

The investigator will personally sign, date and give the number of pages on the first or last page of each print-out. At each visit by the monitor, the investigator will provide all the print-outs of the medical files of the patients. The monitor will personally sign and date the first (or last) page then initial all pages in each paper print-out.

If the computer system allows the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the medical files of the patients and the records of the changes made. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

If the computerised medical files are considered as validated by the sponsor, the investigator undertakes to give access to the monitor to the computerised medical files of all patients. If the monitor cannot access to the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the records of the changes made to the medical files of the patients. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

The investigator undertakes to keep:

- all medical file print-outs signed and dated by him/her and by the monitor when the computer system is considered as not validated by the sponsor,
- if the computer system used allows changes to be made, the print-outs of the audit trail when the computer system is considered as not validated by the sponsor or when the monitor cannot access to the audit trail in the computer system,
- all original source-documents (originals of specific examinations, informed consent forms, therapeutic unit tracking form...).

12.3. Audit - Inspection

The investigator should be informed that an audit may be carried out during or after the end of the study.

The investigator should be informed that the CA may also carry out an inspection in the facilities of the sponsor and/or the study site(s). The sponsor will inform the investigators concerned immediately upon notification of a pending study centres inspection. Likewise, the investigator will inform the sponsor of any pending inspection.

The investigator must allow the representatives of the CA and persons responsible for the audit:
- to inspect the site, facilities and material used for the study,
- to meet all members of his/her team involved in the study,
- to have direct access to study data and source documents,
- to consult all the documents relevant to the study.

If the computerised medical file is considered as not validated, the investigator undertakes to provide all the source-documents and the print-outs of the medical files of the patients and, if the computer system used allows, the record of the changes made during the study.

If the computerised medical file is considered as validated, the investigator undertakes to:
- give access to the representatives of the CA and persons responsible for the audit to the computerised medical files of all patients,
- provide the print-outs of the changes made during the study, if the tracking of the changes made to the medical files cannot be accessed in the computer.

12.4. Supervisory committees

The DSMB will comprise of medical oncologist and statisticians, all independent from the sponsor and investigative sites and selected as to avoid conflict of interest and having experience in randomised clinical trials in oncology involving a DSMB.

The primary objective of this DSMB is to provide independent safety monitoring comparing safety between ~~the~~ both study arms.

A DSMB charter will be written to establish well-defined standard operating procedures including meeting proceedings and structure, data assessments, documentation and record keeping, process for DSMB recommendations, and regulatory reporting as applicable. The charter will be written with procedures ensuring the minimization of bias.

DSMB recommendations will be forwarded to the IRB/IEC/CA only if relevant for the safety of patients.

13. ETHICS

13.1. Institutional Review Board(s)/Independent Ethics Committee(s)

The study protocol, the "Participant information and consent form" document, the list of investigators, the insurance certificate, the trifluridine/tipiracil Investigator's Brochure, the Product Information of bevacizumab will be submitted to IRB(s)/IEC(s) by the investigator(s) or the national coordinator(s) or the sponsor in accordance with local regulations.

The study will not start in a centre before written approval by corresponding IRB/IEC(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved has been obtained.

13.2. Study conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 (Appendix 1), with the GCP and with the applicable regulatory requirements.

13.3. Participant information and informed consent

In any case, the patient (and/or his/her legal representative, when required) must be informed that he/she is entitled to be informed about the outcome of the study by the investigator.

The investigator or a person designated by him/her is required to collect written consent from each patient before his/her participation in the study. Prior to this, the investigator or his/her delegate must inform each patient of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the IMPs.

The patient will be provided with an information and consent form in clear, simple language. He/she must be allowed ample time to inquire about details of the study and to decide whether or not to participate in the study.

One, or two if required by local regulation, original information and consent form(s)must be completed, dated and signed personally by the participant and by the person responsible for collecting the informed consent.

If the patient is unable to read, an impartial witness should be present during the entire informed consent discussion. The patient must give consent orally and, if capable of doing so, complete, sign and personally date the information and consent form. The witness must then complete, sign and date the form together with the person responsible for collecting the informed consent.

The patient will be given one signed copy (or original if required by local regulation) of the information and consent form. A signed original will be kept by the investigator.

A copy of the information and consent form in the language(s) of the country is given in the "Participant information and consent form" document attached to the protocol.

13.4. Modification of the information and consent form

Any change to the information and consent form constitutes an amendment to this document and must be submitted for approval to the IRB/IEC(s), and if applicable to the CA.

A copy of the new version of the information and consent form in the language(s) of the country will be given in the amendment to the "Participant Information and consent form".

Such amendments may only be implemented after written approval of the IRB/IEC has been obtained and compliance with the local regulatory requirements, except for an amendment required to eliminate an immediate risk to the study patients.

Each patient affected by the amendment or an independent witness must complete, date and sign one, or two if required by local regulation, originals of the new version of the information and consent form together with the person who conducted the informed consent. He/she will receive one signed copy (or original, if required by local regulation) of the amendment to the information and consent form. The signed original(s) will be kept by the investigator.

14. DATA HANDLING AND RECORD KEEPING

14.1. Study data

A 21 CFR Part 11-compliant electronic data capture system is going to be used for this study. An e-CRF is designed to record the data required by the protocol and collected by the investigator.

The e-CRF will be produced by I.R.I.S. in compliance with its specifications. The investigator or a designated person from his/her team will be trained for the use of the e-CRF by the sponsor or Sponsor's representatives.

Data entry at the investigator's site will be performed by the investigator or by the designated person from his/her team after completion of the patient's Medical File.

Upon entry, data will be transmitted via the Internet from the study centre to the study database.

The investigator or the designated person from his/her team agrees to complete the e-CRF, at each patient visit, and all other documents provided by the sponsor (e.g. documents relating to the study treatments management…).

Data recorded directly on e-CRF and considered as source data (see Section 4.5) must be collected immediately in the e-CRF. The other e-CRF forms must be completed as soon as possible following each visit.

All corrections of data on the e-CRF must be made by the investigator or by the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded using the audit trail feature of INFORM software, including date, reason for modification and identification of the person who has made the change.

In order to ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the investigator's sites, the sponsor or third parties.

Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible.

Data can be frozen during the study after their validation. However, the investigator has the possibility to modify a data if deemed via a request to the sponsor.

After the last visit of the patient, the investigator or co-investigator must attest the authenticity of the data collected in the e-CRF by entering his/her user name and password.

After the data base lock, the investigator or an authorized member of his/her team will have to download from the e-CRF an electronic file containing patient data from his/her centre for archiving it in the study file (see Section 14.3).

14.2. Data management

Data are collected via an e-CRF and stored in a secured database.

For data collected on the e-CRF, the Clinical Data Management of I.R.I.S. is responsible for data processing including data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. An electronic data clarification form is sent to the investigator who is required to respond to the query and make any necessary changes to the data.

For data transferred from e-PRO, the Clinical Data Management of I.R.I.S. is responsible for data transfer: e-PRO provider provides electronic transfer of computerised data to the Clinical Data Management of I.R.I.S. Data are transferred according to a transfer protocol issued by the I.R.I.S. data manager.

For data transferred from IWRS, the Data & Clinical Logistics of I.R.I.S. is responsible for data transfer: IWRS provider provides electronic transfer of computerised data to the Data & Clinical Logistics of I.R.I.S. Data are transferred according to a transfer protocol issued by the I.R.I.S. data manager.

The Medical Data Department of I.R.I.S. is responsible for data coding including:
- medical / surgical history, adverse events and procedures using MedDRA,
- medications using World Health Organization, Drug Dictionary (WHO-Drug).

The coding process is described in a specification manual.

The investigator ascertains he/she will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its representatives monitoring the study, if any, to request approval of a protocol deviation, as no deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC it cannot be implemented. All important protocol deviations will be recorded and reported in the clinical study report.

When data validation is achieved, a reviewof the data is performed according to the sponsor standard operating procedure. When the database has been declared to be complete and accurate, it will be locked, and the study treatments codes will be unblinded and made available for data analysis.

14.3. Archiving

The investigator will keep all information relevant to the study for at least 25 years after the end of the study, or more if specified by the local regulation.

At the end of the study, the investigator or an authorized member of his/her team will download an electronic copy of each participant's data from the e-CRF and should keep it in a reliable, secure and durable location. The file includes all data and comments reported in the e-CRF, the history of all queries and signatures and the full audit trail reports.

The file must include appropriate restrictions (password protection) and adequate protection from loss, physical damage or deterioration for the duration of the archiving period.

16. OWNERSHIP OF THE RESULTS – DATA SHARING POLICY AND PUBLICATION POLICY

I.R.I.S. and TOI, acting as the study sponsor, assume full responsibilities relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit.

I.R.I.S. and TOI will ensure that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Any project of publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end shall be submitted to the sponsor. in accordance with the guidelines set forth in the applicable publication policy or financial agreement.

The investigator, who submitted the project, shall take the sponsor's comments into due consideration.

As the study is a multicentre one, the first publication must be performed only with data collected from several study sites and analysed under the responsibility of I.R.I.S. and TOI. The investigator commits himself not to publishing or communicating data collected in only one centre or part of the centres before the publication of the complete results of the study, unless prior written agreement from the other investigators and I.R.I.S. and TOI has been provided.

The publication policy will be defined in a separate document

Data Sharing Policy is available at https://clinicaltrials.servier.com/data-request-portal/. Researchers can ask for a study protocol, patient-level and/or study-level clinical trial data including clinical study report.

They can ask for all interventional clinical studies:

- submitted for new medicines and new indications approved after 1 January 2014 in the European Economic Area (EEA) or the United States.

- Where Servier or an affiliate are the Marketing Authorization Holders. The date of the first Marketing Authorization of the new medicine (or the new indication) in one of the EEA Member States will be considered within this scope.

In addition, Servier's data sharing policy includes all interventional clinical studies in patients:

- sponsored by Servier,
- with a first patient enrolled as of 1 January 2004 onwards,
- for New Chemical Entity or New Biological Entity (new pharmaceutical form excluded) for which development has been terminated before any Marketing authorization (MA) approval.

The datasets generated and/or analysed during the current study will be available upon request from clinicaltrials.servier.com after the Marketing Authorisation has been granted.

Summary results and a lay summary will be published on clinicaltrials.servier.com within 12 months after the end of the study.

The results will be submitted for publication in scientific literature within 18 months after the end of the study.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the sponsor and the investigators

17.1.1. Persons to inform

In accordance with local regulations, the investigator and/or the sponsor will inform, the Director of the medical institution, the pharmacist involved in the study and the Director of the analysis laboratory.

With the agreement of the patient, the investigator will inform the patient's general practitioner about his/her patient's participation in a clinical study.

17.1.2. Substantial protocol amendment and amended protocol

If the protocol must be altered after it has been signed, the modification or substantial amendment must be discussed and approved by and approved by the International Coordinator and the sponsor.

The substantial protocol amendment must be drafted in accordance with the sponsor standard operating procedure and an amended protocol must be signed by both parties. Both documents must be kept with the initial protocol.

All substantial amendments and corresponding amended protocols must be sent by the investigator(s) or the coordinator(s) or the sponsor, in accordance with local regulations, to the IRB/IEC that examined the initial protocol. They can only be implemented after a favourable opinion of the IRB/IEC has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, except for a measure required to eliminate an immediate risk to the study patients.

When the submission is performed by the investigator or the International Coordinator, the latter must transmit a copy of IRB/IEC's new written opinion to the sponsor, immediately upon receipt.

Furthermore, the substantial amendment and amended protocol are to be submitted to the CA in accordance with local regulations.

17.1.3. Final study report

The study report(s) will be drafted by Centre of Excellence Methodology and Data Valorisation of I.R.I.S. in compliance with I.R.I.S. standard operating procedure.

The sponsor's representative and International Coordinator must mutually agree on the final version. One copy of the final report must be dated and signed by the International Coordinator and by sponsor's representatives.

If the clinical trial is still on-going but ended in the European countries, the statistical analysis will not be relevant before the end of the study worldwide. Therefore, the clinical study report, the summary of the results of the clinical trial together with a summary that is understandable to a layperson will be submitted where applicable within 1 year after the end of the clinical trial worldwide.

17.2. Concerning the sponsor

This multinational study will be conducted under the sponsorship of I.R.I.S (in all countries except the United States) and TOI in the United States.

The sponsor undertakes to:

- supply the investigator with adequate and sufficient information concerning the study treatments administered during the study to enable him/her to carry out the study,
- supply the investigator with the trifluridine/tipiracil Investigator's brochure,
- supply the investigator with the bevacizumab Product Information, the one best suited to ensure patient safety, and any potential updated version during the study:
  - for the test drug if marketed, to be appended to Investigator's brochure (Section 4. Guidance for the investigator
  - for all reference products used in the study
- obtain any authorisation to perform the study and/or import licence for the study treatments administered that may be required by the local authorities before the beginning of the study,
- provide the International Coordinatorannually, or with another frequency defined by the local regulations, with a document describing study progress which is to be sent to the IRB/IEC(s).
- take all the necessary precautions to maintain the safety of the processed data, in particular their confidentiality, their integrity and their availability, by assessing risks identified concerning personal data protection. The following measures will be implemented (non exhaustive):
  - Management of authorisation to access to personal data (e-CRF)
  - Identification and authentication measures before accessing personal data (e-CRF)
  - Traceability measures for the access to and modification of personal data (e-CRF)
  - Secured data transfer
  - Time limit for storing personal data
- handle any security breach by implementing an internal committee (including CISO, DPO, communication department…) in order to qualify the security incident (Information systems, nature and number of personal data impacted), to define an action plan for corrective actions and to notify to relevant person (authority and/or if needed individuals).

17.3. Concerning the investigator

17.3.1. Confidentiality - Use of information

All documents and information given to the investigator by the sponsor with respect to trifluridine/tipiracil and study CL3-95005-007 are strictly confidential.

The investigator expressly agrees that data on his/her professional and clinical experience is collected by the sponsor on paper and computer and stored for its sole use relating to its activities as the sponsor of clinical trials, in accordance with GCP.

He/she has a right to access, modify, and delete his/her own personal data by applying to the sponsor.

In case patient wants to exercise his/her rights regarding personal data protection, he/she will contact the investigator. The investigator will forward the request to the sponsor (Appendix 8).

The investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the sponsor. The clinical study protocol given to the investigator may be used by him/her or his/her colleagues to obtain the informed consent of study patients. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorisation of the sponsor.

The investigator must not disclose any information without the prior written consent from I.R.I.S. and/or TOI, except to the representatives of the CA, and only at their request. In the latter case, the investigator commits himself/herself to informing I.R.I.S. and/or TOI. prior to disclosure of information to these authorities.

A patient screening log and a full identification and enrolment list of each patient will be completed and kept in a safe place by the investigator who should agree to provide access on site to the auditor and/or the representatives of the CA. The information will be treated in compliance with professional secrecy.

The patient screening log must be completed from the moment the investigator checks that a patient could potentially take part in the study (by assessment of patient medical history during a visit or by examination of the medical file).

17.3.2. Organisation of the centre

Every person to whom the investigator delegates under his/her responsibility a part of the follow-up of the study (co-investigator, nurse…) and any other person involved in the study for this centre (cardiologist, pharmacist…) must figure in the "Organisation of centre" document.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the site.

17.3.3. Documentation supplied to the sponsor

The investigator undertakes before the study begins:

- to provide his/her dated and signed English Curriculum Vitae (CV) (maximum 2 pages) or to complete in English the CV form provided by the sponsor and to send it to the sponsor, together with that of his/her co-investigator(s),
- to provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the parameters measured,
- to provide any other document required by local regulation,
- to send a copy of the IRB/IEC's opinion with details of its composition and the qualifications of its constituent members.

The CVs of other members of the team involved in the study (if possible, in English) will be collected during the course of the study (at least, members involved in the patients' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

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19. APPENDICES

Appendix 1: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into

consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: Patient performance status

Status Karnofsky	**Grade**	**Status ECOG* - ZUBROD / WHO**
Normal, no complaints; no evidence of disease.	100	
	0	Fully active, able to carry on all pre-disease performance without restriction.
Able to carry on normal activity; minor signs or symptoms of disease.	90	
Normal activity with efforts; some signs or symptoms of disease.	80	
	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.
Cares for self; unable to carry on normal activity or to do active work.	70	
Requires occasional assistance, but is able to care for most of his personal needs.	60	
	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
Requires considerable assistance and frequent medical care.	50	
Disabled; requires special care and assistance.	40	
	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
Severely disabled; hospital admission is indicated although death not imminent.	30	
Very sick; hospital admission necessary; Active supportive treatment necessary.	20	
	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
Moribund; fatal processes progressing rapidly.	10	
Dead	0 5	Dead

* As published in Oken M.M., Creech R.H., Tormey D.C., Horton J., Davis T.E., McFadden E.T., Carbone P.P. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 3: New York Heart Association (NYHA) classification

The Stages of Heart Failure NYHA Classification

In order to determine the best course of therapy, physicians often assess the stage of heart failure according to the NYHA functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 4: Cockroft formula (Cockroft et al., 1976)

CreatClear [mL/min] = ((140 – Age [years]) / SerumCreat [µmol/L]) * Weight [kg]* Sex

Male = 1.23
Female = 1.04

Ref : Cockcroft DW., et al. "Prediction of creatinine clearance from serum creatinine." Nephron, 1976: 31-41.

Appendix 5: EORCT QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

As published in Aaronson NK., et al. "The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology." Journal of the national cancer institute, 1993: 365-376

Appendix 6: EQ-5D-5L

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

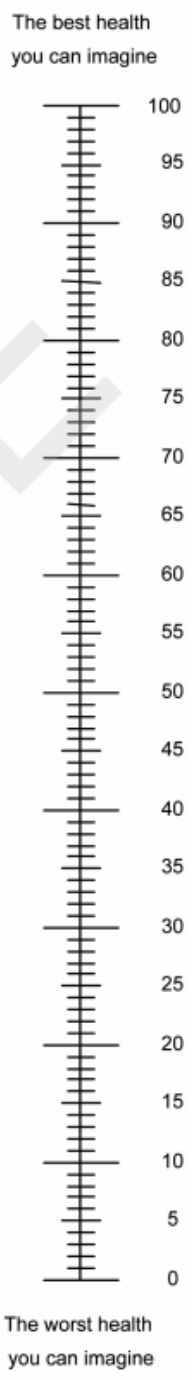
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



As published in Van Reenen M., et al. EQ-5D-5L User guide Version 2.1. 2015

Appendix 7: Link to trifluridine/tipiracil and bevacizumab Product Information

For contraindication of bevacizumab and trifluridine/tipiracil (exclusion criteria n°39 and 45)

All the sites, regardless of location, must refer to the EU Product Information of the corresponding drug available on the EMA website (see links below).

For topics not linked to contraindication of bevacizumab and trifluridine/tipiracil

EMA: applicable for all countries outside the U.S

Trifluridine/tipiracil (Lonsurf®):
https://ema.europa.eu/en/medicines/human/EPAR/lonsurf

Bevacizumab (Avastin®):
https://ema.europa.eu/en/medicines/human/EPAR/avastin

US FDA: applicable for the U.S.

Trifluridine/tipiracil (Lonsurf®):
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207981s009lbl.pdf

Bevacizumab (Avastin®):
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125085s336lbl.pdf

Appendix 8: DATA PROTECTION / GDPR (General Data Protection Regulation of 27 April 2016 n°2016/679)

INSTRUCTIONS TO INVESTIGATOR FOR HANDLING DATA RIGHTS REQUESTS

In the framework of a research study/clinical trial, a participant to the study may exercise his/her rights, i.e. may ask I.R.I.S. (as data controller) for:

- access to his/her data
- rectification of inaccurate/incomplete information
- restriction of processing of data
- objection to processing of data
- data portability (receiving his/her data in a readable format)

In accordance with the Informed Consent Form and information notice provided to participant, we requested participant to contact you first for exercising their rights.

Request for exercise of rights:

- has to be a **written** one (either originating from an (e)-mail from a participant or from request expressed orally to you and put in written)
- has to be sent **by you** by e-mail or by mail **to** I.R.I.S. (as data controller) to central address CCI [redacted] or local Servier address as mentioned in ICF/information notice provided/available

DO **Instructions to be followed by you**	**DON'T** **What you should not do**
E-mail title: Data protection rights	Do not forward participant e-mail (if applicable)
Study name/number	
Participant number	**No information regarding participant identity**: No participant's name, e-mail address, participant's signature
As soon as possible without exceeding a week	

I.R.I.S. and INVESTIGATOR responsibilities

GDPR requirement:
It is mandatory for I.R.I.S. as data controller to provide an answer to participant/volunteer within 1 month following the request (article 12 of GDPR)
Clinical trials requirements:
It is prohibited for I.R.I.S. as a sponsor to know the identity of the participants/volunteer participating to studies

	I.R.I.S. responsability	**Investigator responsability**
Forward/inform I.R.I.S. of the request		YES
Timelines	Answer within 1 month once expressed by the participant	Request: transmitted to I.R.I.S. as soon as expressed by the participant Answer: transmitted by you to participant as soon as sent by I.R.I.S.
Answer the request	YES	